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BUILDING AND LEVERAGING ECOSYSTEMS AND CLUSTERS

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Co-Editors' Preface and Statement

The Impact of the COVID-19 Pandemic on the Content and Logistics of this Special Edition on Building and Leveraging Ecosystems and Clusters

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On March 11, 2020, the World Health Organization (WHO) Director General Dr. Tedros Adhanom Ghebreyesus addressed the global media: "WHO has been assessing this outbreak around the clock and we are deeply concerned both by the alarming levels of spread and severity, and by the alarming levels of inaction. We have therefore made the assessment that COVID-19 can be characterized as a *pandemic*."[1] While the existence, transmissibility, treatment, and potential impact of severe acute respiratory coronavirus SARS-CoV-2 were real questions since the virus was first recognized in December, 2019,[2] much of the media coverage was driven by global public health concerns and international/national political posturing. However, it was a different date that catalyzed commercial biotechnology.

In first few days of January, 2020, Fuhan University Professor Yong-Zhen Zhang's lab at the Shanghai Public Health Clinical Center received a sample from a Wuhan patient suffering from the virus. Some forty hours later, the lab had decoded its complete genome, and soon realized that it shared some 80% of the genome of SARS-CoV, commonly referred to as "SARS", which had been discovered and decoded in 2002. Several days later, on January 11, 2020, University of Sydney Professor Edward Holmes, a colleague of Professor Zhang's, asked if he could release the decoded genome on the Internet.[3] Within minutes, the full genomic sequence of the SARS-CoV-2 coronavirus was released on the open Internet forum, Virological,[4] and deposited in GenBank,[5] the genetic sequence database maintained at the National Center for Biotechnology Information, part of the National Library of Medicine at the National Institutes of Health (NIH). Of importance, GenBank[6] is part of an international collaboration which is comprised of the DNA Data Bank of Japan (DDBJ) and the European Nucleotide Archive (ENA). According to the NIH website, "These three organizations exchange data on a daily basis."[6]

It was at this moment in time, on January 11, 2020, that the bioentrepreneurs of this world, the research scientists in every university and at every institute, and biotechnology companies, large and small, got to work. Now, they had something to work with.

Journals, on the other hand, do not move at such lightning speed. This special edition focuses on "Building and leveraging the innovation ecosystem and clusters: universities, startups, accelerators, alliances, and partnerships", and it has been in planning for nearly a year and half at this writing, well before COVID-19 made its appearance. Known to the editors throughout that period are numerous individual bioenterprises and research efforts, which have pivoted to address some aspect of the COVID challenge, while other efforts have been delayed.

And yet a "pivot" is not a final outcome, nor does a delay necessarily spell failure. This special edition is about the disposition of clusters and innovation ecosystems which entered this time. The articles you will read address capabilities which are *collectively* powerful, as opposed to individually capable. To be sure, it is not a predictor of the status of these innovation ecosystems and clusters in the post-COVID period, but certainly, it is a test. In that way, this is an opportune time to record their potential and to begin to study their resilience.

All signs tell us that this is a period of accelerated and positive innovation within the field of commercial biotechnology, and in many ways, it may be changed forever.

Wherever efforts to address COVID challenges were identified at the time of article submission, they are clearly marked.

Arthur A. Boni

Moira A. Gunn

Co-Editors of A Special Edition of the Journal of Commercial Biotechnology

"Building and leveraging the innovation ecosystem and clusters: universities, startups, accelerators, alliances, and partnerships"
November, 2020

1. World Health Organization. (2020). WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020. Posted March 11, 2020. WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020.
2. World Health Organization. (2020). Pneumonia of unknown cause – China. Posted January 5, 2020. WHO | Pneumonia of unknown cause – China.
3. Campbell, C. (2020). Exclusive: The Chinese Scientist Who Sequenced the First COVID-19 Genome Speaks Out About the Controversies Surrounding His Work, Time, August 24, 2020. Zhang Yongzhen Speaks Out About Controversies Around His Work | Time.
4. Viological.org, (2020). Novel 2019 coronavirus genome – SARS-CoV-2 coronavirus – Virological.
5. GenBank. (2020). Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome (Updated Version). https://www.ncbi.nlm.nih.gov/MN908947.
6. National Institutes of Health/National Library of Medicine/National Center for Biotechnology Information. (2020). GenBank Overview. GenBank Overview (nih.gov).

A "From the Board Room" Perspective by the Special Edition Co-Editors

Introductory Overview to Special Edition – "Building and Leveraging the Innovation Ecosystem and Clusters: Universities, Startups, Accelerators, Alliances, and Partnerships"

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ABSTRACT

This article focuses on the concepts of ecosystems and clusters, with an emphasis on their importance for building vibrant a vibrant and life science/biopharma industry. We illustrate the underlying principles through work published in academic articles and in the popular press. These are highlighted in brief overviews of several mature and emerging ecosystems in the United States, Europe and Australia. The US perspective is based on our own professional life experiences in Boston, Silicon Valley, San Diego, and Pittsburgh, and, with a shorter preview of Philadelphia where we've both done business and have close colleagues. The article ends with a look to the future in a concluding section titled "What's Coming Next". It is our attempt to look at the future of digitally enhanced collaborative innovation. This is based on our observations during the first 9 months of the Covid-19 pandemic, social distancing, and working from a distance. We ask, what is the potential impact of these emerging digital technologies on work and advancement of the agenda in the life sciences industries? Will the pandemic transform or disrupt the borders and mode of collaboration of traditional definitions of ecosystems and clusters as we define them today?

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INTRODUCTION AND OVERVIEW

Previous work has introduced some of the key concepts and definitions underlying Ecosystems and Clusters, and highlight the key ingredients for success. Herein, we use common definitions that have been reduced for simplicity, and applied to innovation with cross industry perspectives. Simply, clusters are industry groupings that originate and grow in the overall environment provided by the ecosystem that pertains to the entire region or city. More precisely:

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- An ***ecosystem*** is a sustainable economic region comprised of a community or critical mass of interacting organizations and individuals that produce goods and services of value to customers. The community attracts capital (monetary and human) and is generally composed of the entire spectrum of parties required to support the creation or products and services and to generate economic value for the firms and for its surrounding community.
- ***Clusters*** are geographic concentrations of firms focused largely on one industry of the overall ecosystem to produce innovations in a market segment. Generally, the firms

in a cluster support a particular industry like biopharma, med tech, digital health, technology, etc. Some also add the term "hub" to delineate the geographical concentration or location within the region, e.g. center of activity of a cluster.

Boni has previously taken an entrepreneurial perspective and suggested that there are three P's required to build and grow successful companies: *People, Processes, and Problems*. This may also be considered as a very simplified, high-level framework to view ecosystems and clusters. The "Problems would relate to specific areas or market segments of biopharma and med tech, or digital health. The Processes include synergistic collaboration between or among multiple parties located in the ecosystem or cluster. And, in the embedded entrepreneurial culture and approach as well as the financial resources required. People, includes the human capital needed inside each company, but also present in the surrounding ecosystem or cluster so that collaborative innovation can occur, and more importantly to reach critical mass. For, example this includes: public sector engagement and leadership of public/private partnerships, research universities and hospitals, a skilled workforce, a culture to support risk taking, and a strong financial sector with strength and diversity across the life cycle from startups thru mature organizations.

Rich Bendis (see his publication in Section Two of this special edition) suggests a short list consisting of the following success factors: 1) Strong Leadership; 2) Significant Industry Engagement; 3) Talent; 4) Access to Capital; 5) Research Assets and Facilities; and, 6) Market and Brand Awareness.

Research universities have been noted as a source of the technologies that fuel innovation. We also note that accelerators, either corporate or independent, have become an important part of the innovation ecosystem development in recent years, e. g. moving technology from the lab towards validation in New Cos. Brad Feld, a co-founder of Techstars is a luminary pioneer in the realm of accelerators having created Techstars first in Boulder, CO and then scaling nationally. His book, ***"Startup Communities: Creating a Great Entrepreneurial Ecosystem in your City"*** highlights some of the important principles for building and sustaining innovation ecosystems cross industry. He highlights the importance of entrepreneurial leadership and of welcoming everyone in the community to engage in "the entire entrepreneurial stack". That is "tech talk" for: first-time entrepreneurs, experienced entrepreneurs, aspiring entrepreneurs, investors (angels, VCs, corporate VCs, mentors, employees of startups, service providers to startups, and anyone else who wants to and needs to be involved, e.g. government, universities, independent accelerators like Techstars, and corporate accelerators like J-Labs. It's bottoms up, not top down. One other piece of advice (that we discuss later) is to have a 20-year time expectation and commitment! We consider Feld's guidance to be great advice for any aspiring region regardless of location on the globe.

Going forward, we blend these perspectives to highlight the following necessary ingredients needed for building strong ecosystems and associated industry clusters in biopharma, med tech and digital health. This perspective is developed based on studies of successful regions that are covered in this Special Edition. In effect, we blend Boni and Bendis to frame the following set of necessary and sufficient conditions for successful development and growth of ecosystems and clusters in cities and regions:

1. They embrace and reward an entrepreneurial culture, and has (or is able to attract) strong leadership in both the public and private sectors, and who work collaboratively with a shared long range vision
2. Has strong universities and world class hospital systems to provide an educated workforce and a source of technologies and spinoffs
3. Attracts people who want to live in the region since it's a great place to live and raise a family – and is affordable
4. Has the ability to grow and/or attract leadership for biopharma, med tech and digital medicine (or health) organizations across the life cycle
5. Home to a full spectrum financial industry for sources of risk capital across the company life cycle to start, grow and build strong industry clusters
6. Has, or is building, one or more world class anchor organizations to serve as role models and attractors
7. Well connected and networked to collaborate with other regions in the US and internationally
8. The region is patient and persistent, and has "the grit" to prevail over the long period required to develop and grow the regional ecosystem and associated clusters

Moira Gunn who is co-editor of this edition pursues this topic later in this volume thru an article that focuses on the more "popular press" perspective on ecosystems and clusters. This article is titled **"Thought Leader Insights on Innovation Ecosystems and Clusters".** Some of the authors covered there include *AnnaLee Saxenian*, "Regional Advantage"; *Leslie Berlin*, the building of Silicon Valley from "Troublemakers"; *Richard Florida* ,"The Creative Class" and, Greg Horowitt "Rainforest".

We recognize that collaborative innovation is (and always will be) a hallmark ingredient of the broad biopharma industry. It is well known that the industry has grown and sustained the innovation pipeline thru partnering and M&A activity. That fact has been discussed in two recent publications by Boni & Joseph (Vol. 24, No. 4 (2019), 14-22, and pp 23-31. The first article is titled "Aligning the Corporation for Transformative Innovation; Introducing Dashboard 2.0; and the second is "Four Models for Corporate Transformative, Open Innovation. In that work, it is pointed out that there are similar parallels in other industries undergoing transformation – for example the recent evolution of autonomous vehicle partnerships and collaborations. In that regard, look to emerging clusters for autonomous vehicles in Silicon Valley and Pittsburgh. Boston, the Bay Area, and San Diego have emerged similarly in the biotech field, attracting pharma partners to complement their strong university and VC systems. Then, in the recent JCB special edition on "The Promises and Business Model challenges on Emerging Transformative Innovations (Vol. 25 No. 4), we go on to reinforce the need for collaboration and partnering by reinforcing the evolution of partnerships between emerging companies (universities, startups, early stage companies and their larger/existing leading to the emergence of the biopharma industry (marrying pharma and biotech).

The "success ingredients" noted above are illustrated in this Special Edition, where we highlight both US, and also in several typical emerging international biopharma/MedTech ecosystems and clusters. We do not specifically discuss the time scale for development of thriving ecosystems because it depends on both initial conditions, internal factors and externalities. An order of magnitude estimate can be obtained by examining the various regions in the US. We would estimate that to be in the 20+ year range. So, we included "patience and grit" to our necessary conditions. We elaborate briefly in a short synopsis below, the differences between an ecosystem and clusters in the last 20+ years, using the California (Bay Area, San Diego) and Boston as prime examples of mature ecosystems. We also point out what has happened in Pittsburgh (a "rust belt" city) and the DC/Maryland/Philadelphia areas, but still adjacent on the Eastern Seaboard). The "Tale of Two Cities" in PA (Philadelphia and Pittsburgh are highlighted. Each of these regions is explored in much greater depth in the papers that appear in Section Two.

AN EDITORIAL, AND PERSONAL "SNAPSHOT" OF SEVERAL ECOSYSTEMS THAT HAVE EVOLVED IN THE UNITED STATES IN THE LATE 20TH AND EARLY 21ST CENTURIES

This section is based on the personal experience of the co – editors from having lived and worked in all of the cities that we highlight in this From the Boardroom perspective. However, we've both done lots of business in Philadelphia, so we augment our personal experience with the input of our editorial board colleague Dennis Gross for an article included on Philadelphia. And for Pittsburgh, from Dennis Yablonsky who led economic development initiatives for the Pittsburgh Region, and then later for the entire Commonwealth of Pennsylvania as Cabinet Secretary of the Department of Community and Economic Development in the Rendell administration. Dennis Abremski and Paul Roben of UCSD also provide a perspective on San Diego the profound impact of UC San Diego on the emergence of San Diego as a great example of an ecosystem that has evolved into the leader in life science and other areas of advanced technology.

CBRE Group, Inc. (Coldwell Banker Richard Ellis) has recently highlighted the top life science clusters (ecosystems) in the United States, c. f. https://www.cbre.com/research-and-reports/US-Life-Sciences-Report-2020. They list the Boston/Cambridge area, the San Francisco Bay Area, San Diego and the Washington DC areas as the three top-tier clusters. Emerging areas include Pittsburgh as number one, followed by Houston and Austin. We highlight some of these below as a preview of more detailed summaries to be detailed later in this volume.

MATURE ECOSYSTEMS

Boston/Cambridge, MA – The "Hub"; historically a strong educational center with a strong economy, and with a historically world class system of higher education. This region also incorporates and a strong financial center, including venture capital, and built economic clustering in defense, technology and computing. The disruption of this computing and tech cluster by the microchip led to the decline and demise of industry stalwarts like Digital Equipment Company (DEC), Wang Laboratories, Computer Vision, and others circa 1990. Most of that shifted to Silicon Valley along with the microchip expertise. However, their regional strengths led to survival and regrowth: e. g., the educational community that is unparalleled with MIT Harvard, Boston College, Boston University, Northeastern, Tufts, etc.); a healthcare

system of world class stature (Mass General, Brigham and Women's, Beth Israel Deaconess, UMass, etc.), and an historical and very strong VC community with affiliated early stage funding vehicles. So, Boston always a "hub", re-developed an ecosystem and affiliated clusters that attracted pharma industry partners, that attracted significant investment capital in biopharma, med tech, robotics, etc. We'd note about a 20+ year transition period to rebuild the ecosystem around a new biopharma cluster adjacent to MIT and Harvard in Cambridge.

San Francisco/Bay Area – The "City by the Bay" has world class core strengths in education and healthcare (Stanford, Berkeley, UC San Francisco), strong VC and investment capital, entrepreneurial leadership and is perhaps the "gold standard" ecosystem with worldwide fame (and attempted emulation by many). The microchip revolution started in Silicon Valley which created a strong technology cluster starting in the 1970s, i. e. the tech-company cluster that currently exists in Silicon Valley, south of the City of San Francisco. And the world-famous Sand Hill Road, home to the most probably the largest concentration of VC firms, that is itself located adjacent to the Stanford University campus that is directly or indirectly responsible for a significant volume of startup activity cross industry. However, more recently, the younger generation preferred to live in the city. That trend, and the emergence of a biopharma cluster surrounding Genentech and UC San Francisco in South Bay led to the creation of a powerful shift to new clusters in the City of San Francisco starting in the early 21st century. That led to an interesting, not so subtle shift where many of the tech companies whose "younger employees preferred the city life" created operations there. This evolution continues with movement to the East Bay and closer proximity to UC Berkeley for both tech and biotech companies who need proximity to the City and Silicon Valley. Then, it spread even further east and north to build up the manufacturing operations required to support biopharma and technology. Of course, the VC system itself has migrated from Sand Hill Road in Menlo Park to cover the entire Bay Area ecosystem, including the City. So, we see multiple ecosystems and clusters that have emerged, and the greater San Francisco area is a "gold standard" for innovation. Critical mass occurred in this region over a similar 20+ year period and has refined and evolved over the next decade or so.

San Diego, CA – "America's finest City" – Traditionally a region with a strong military and aerospace supported economy, known as "America's Finest City" and a great place to live visit, and enjoy an enviable "Mediterranean climate" on the Pacific Ocean. General Dynamics (Astronautics and Convair), General Atomic, Salk Institute, and Scripps Institute of Oceanography were key components of the economy in the 1960-1970-time frame. And that led to a pivotal move – the formation of the now world class UC San Diego with its strong engineering and science programs, medical school and healthcare system. The emergence of this university to top tier US and International status occurred on an unprecedented short time frame. The entrepreneurial community was robust (albeit not in biotech). Science Applications International Corporation (SAIC) emerged as a technology services powerhouse that anchored an emerging, cross-industry technology cluster (the city wa a "unicorn" with a national and global footprint before that term became commonplace in the tech community).

Strong regional leadership recognized the need for change in the 1960's era, and the need for diversifying the economy. Major community initiatives started in the mid to late 1980's to support the development of an innovation ecosystem in San Diego led by a city-wide consortium of private and public sector leaders. UCSD Connect, and Tech Coast Angels emerged. The region worked collaboratively and since the 1990's, the San Diego Convention Center has hosted the annual international BIO meeting several times. That ecosystem is still growing with evolving concentrations or clusters in biopharma and technology. VC investment still lags their "competitor to the north", but a strong early stage investment and angel community has evolved, as has UCSD as a top tier university that attracts a large pool of potential entrepreneurs and innovators. And of course, San Diego is a great place to live and attract the workforce needed to grow the ecosystem. But the region is still waiting for the pivotal "magnet" company in biopharma. J&J located JLabs there as is Biogen Idec is located in Carlsbad in North County. And, Illumina is notable on the diagnostics side. As this paper is being written we find a recent announcement – a life science development firm has unveiled plans to transform eight acres along San Diego's waterfront into a mixed-use hub that could attract leading edge companies to the city. This is a significant investment, potentially signaling that the city may be at a growth inflection point. Most biotech companies are located currently in the Torrey Pines area adjacent to UCSD. https://www.10news.com/news/local-news/san-diego-news/massive-biotech-hub-planned-for-waterfront.

Philadelphia, PA. – A traditional center for the pharmaceutical industry with local anchor companies like Merck, GSK, and others, and with a strong educational/healthcare system at U. Pennsylvania and a strong and diverse base of highly regarded educational institutions like Drexel, and Temple. The region responded to the migration of pharma to other places in the 2000+ era, but retained their healthcare culture and workforce. So, in some respects the region responded more quickly than Pittsburgh with an entrepreneurial community

approach. And continues to emerge since then with emphasis on scientifically driven innovations in healthcare. The region has responded with pride to the recent acquisition of Spark Therapeutics, a gene therapy company by Roche. And note the analogy of Roche's acquisition to that of Genentech as an anchor firm in San Francisco.

PREVIEW OF AN EMERGING ECOSYSTEM IN THE UNITED STATES

Pittsburgh, PA –The "Steel City" was the "capital of the world" for leveraging its natural wealth that was stored underground – coal, limestone and natural gas. And, it capitalized on its network of navigable waterways to facilitate export. A strong industrial, manufacturing culture emerged in the early 1900's, consisting of coal, steel, and glass organizations, and led by an entrepreneurial cohort of industrial leaders, e. g. Carnegie, Mellon, et al. While the founders were entrepreneurial, those who led these mature organizations were less so. And, the entrepreneurial culture "disappeared", as the city became a home for Fortune 500 companies. And, fortunately for the city, for the large concentration of philanthropic Foundations formed from the fortunes of the former "barons of industry". Then crisis came, led by 'foreign competition' in the steel industry. The industrial steel base consolidated, leading to a drain of talent, and an economic collapse in the 1980's. Community leadership did finally come together in the early to mid-90's, led by the Allegheny Conference on Community Development, and multiple strong philanthropic foundations created from the wealth of industry leaders (and they supported entrepreneurial activities). In the early to mid 1990's, these organizations formed a coalition along with Carnegie Mellon University (CMU) and the University of Pittsburgh and its newly emerging medical center (UPMC Health System which has since emerged as an international force). This guiding coalition responded to build a new "meds and eds" economy that is just now being recognized internationally. Currently, we see the emergence of a strong Robotics/AI/ML cluster emerging from Carnegie Mellon. And, a nascent life sciences cluster (along with a very strong medical robotics cluster that serves both the technology and biopharma industries). Slowly, but surely the ecosystem is still evolving to support a large number of companies emerging from both CMU and the University of Pittsburgh. University and Commonwealth of PA funded "accelerators" (Innovation Works/Alpha Lab, Pittsburgh Life Sciences Greenhouse and more recently LifeX) were formed to support early stage companies. Both universities have built top tier technology transfer and entrepreneurial education programs over the last 20+ years.

What is still in development for Pittsburgh? – attracting significant growth capital, and company leadership to grow the new life science, med tech and digital health companies into industry leaders. This would be a precursor to the creation of a few, highly visible "anchor" companies in life sciences and tech e. g. a Genentech in the Bay Area, a Millennium or Moderna in Boston. And, to their partnerships/alliances with global companies in biopharma – companies like Roche, J&J, Merck, Amgen, etc. However, we do note that in Pittsburgh that "missing link" has started in tech with the autonomous vehicle evolution; Argo, Aurora, Aptiv, Uber and Lyft – and their global partnerships with automotive companies like VW, Ford and GM. We note that the UPMC Health System has made a significant investment in forming a venture capital organization thru the UPMC Health System.

NOTE – See expanded, more detailed case studies in later papers in this volume, e. g. Pittsburgh Ecosystem by Dennis Yablonsky, the Philadelphia Ecosystem by Dennis Gross, the Baltimore/Maryland/DC/Philadelphia complex by Bendis, and Darmody, and the Boston/Cambridge Ecosystem by Joseph, Windham-Bannister, and Mangold.

WHAT'S COMING NEXT? – DIGITALLY ENABLED COLLABORATION AND INNOVATION "BEYOND THE BORDERS" OF COMPANIES, ECOSYSTEMS AND CLUSTERS

In this concluding section, we look ahead to the emergence of virtualization and collaboration that has been noted over the last year, but accelerated during the Covid-19 pandemic. Our premise it that this trend of "digital collaboration will continue to proliferate even after Covid-19 has been brought under control. In a sense this might be extend our current world of ecosystems and clusters. That remains to be seen. "Creative destruction a discussed by Schumpeter is underway". As Tom Friedman said in a recent New York Times editorial dated October 21, 2020 quoting Ravi Kumar, CEO of Infosys; "because the pace of technological change, digitization and globalization just keeps accelerating, two things are happening at once: the world is being knit together more tightly than ever — sure, the globalization of goods and people has been slowed by the pandemic and politics, but the globalization of services has soared — and "the half-life of skills is steadily shrinking," said Kumar, meaning that whatever skill you possess today

is being made obsolete faster and faster. So, education is also being disrupted.

So, we included this short summary section developed to highlight a number of potential future opportunities. Some of these emerged earlier and have had limited traction. Others have become apparent in 2020 during the COVID-19 pandemic. Our intent is to provide a provocative summary of "what's coming next?" in our industry. Clearly these disruptions provide opportunities for innovation and extension of the ecosystem and cluster concepts utilized digital methodologies. Additionally, our intent is to use this section as a short preview that may encourage an on-ongoing set of articles and "From the Boardroom" perspectives for publication in subsequent issues of this journal.

In the following section, we start with a short summary of selected and potentially important "editorially noted" trends that have arisen from our observations. Each potential trend is then followed by annotated comments provided by our relationships with experts in these areas, interviews or their comments, and/or extracted from industry reports. **As we mentioned above, we encourage these and other authors to contribute articles on these and other emerging trends and developments.**

"The Virtual Classroom" enables "The on-line Conference" – Over the last decade we have followed and been personally engaged in the creation, evolution and utilization of on-line education and communication platforms. This experience came from our personal experience at Carnegie Mellon University and started nearly 10 years ago coincident with the roll out of on line education programs by Coursera, Udemy, Khan Academy, etc. This hybrid MBA program is currently ranked in the top 3 MBA programs as is at the leading edge of on-line curricula platforms as described below. It would follow that such a platform could be adapted to the creation of virtual conferences, conventions, meetings, etc.

For the MBA program, the Tepper program consists of part time MBA students located throughout the country. There are 3 components: Synchronous Classes held once per week live and on-line; Asynchronous classes for pre-recorded content, that can be completed as convenient for the student; and, Access Weekends held at convenient locations at the beginning of each class/program. The IT platform also permits team meetings since student teams regularly meet to work on collaborative projects as part of their course work. We'll cover that in the next section.

Similar programs are now being rolled out cross campus as on-line education became necessary with Covid-19. We believe that these platforms can be scaled and adapted to provide interaction and collaboration with distributed teams in organizations that have learned that "work from home" is a viable option. Going into the office is often not necessary, especially on a daily basis. Employees can now live in the mid-West and work for organizations located in the larger innovation ecosystems like the San Francisco Bay area, or live in the East Bay and work remotely, but perhaps with a weekly visit to the office. Perhaps this is the new normal and technology can enable these modes of work and education.

"The Virtual Collaborative Team" – As an extension of the on-line education platforms, leveraging, connecting and leading distributed teams remotely located, could lead to the "Zoom era of virtual collaboration", and use of social media to connect, communicate and collaborate, e. g. Facebook, Instagram, etc. But in this case, it is applied to business operations, not education or conferences. Some insights in this regard might follow from one of our colleagues in the Organizational Behavior and Theory group at the Tepper School of Business. Anita Wooley et al. at CMU/Tepper who studies collective intelligence; see recent Wired Article – https://www.wired.co.uk/article/remote-work-collective-intelligence. This article describes "what makes people work well together so that teams become more than the sum of their parts". We urge interested readers to read the entire Wired article. Below, we extract a few quotes from Wired and Wooley.

"Woolley observed that if a group performed well on one task, they tended to perform well on the others. This wasn't predicted by the maximum nor the average intelligence of the team members. Instead, Woolley found a collective intelligence score, "c", with predictive power: when the teams were brought back to the lab to play a video-game simulation, their performance was correlated to their c factor. The study, published in 2010 in the journal *Science*, was one of the first to suggest a metric for collective intelligence".

Competition within a team actually lowered its intelligence. One finding was that teams with more women outperformed male-dominated ones. "You have a benefit to having a majority of women, but you still need some men," she says. "The teams that are consistently more intelligent are gender diverse."

For Woolley, this represents the first sketch of what the productivity software of the future might look like: a facilitator that's running in the background, picking up on the fact that people are good at different things and prompting them when they are available. It's about managing individual skills and the allocation of effort, she says: "The tools help prompt that conversation." We might add, that might well be an analog of the teacher or professor in the "flipped classroom".

"The Virtual Laboratory" – Doing laboratory work in biopharma remotely thru robotics. A few years back some former student who had moved to California to do their doctoral work in San Diego and Palo Alto. After their graduations, D. J. Kleinbaum and Brian Frezza

started Emerald Therapeutics with funding from Peter Theil and the Founders Fund. A great achievement for two young entrepreneurs. Emerald Therapeutics was launched in South San Francisco to pursue "antiviral therapeutics for diseases such as HPV and HIV". During this time, they experienced frustrations with laboratory hardware and software. To simplify laboratory testing, the group wrote centralized management software for the different laboratory machines and a database to store all metadata and results. This may be viewed as a "laboratory operating system" including the ability to directly control instrumentation and manage inventory and procurement. Recognizing the value this type of system presented outside of their own development goals, Kleinbaum and Frezza launched this service in 2014 under the name Emerald Cloud Lab. In 2016, Emerald Cloud Lab and Emerald Therapeutics were spun off from one another, and both are independent corporations. Wikipedia reports that "as of July 2020, Emerald Cloud Lab offered full control of over 150 laboratory instruments, with plans to expand capabilities through 2021".

Having visited ECL and DJ many times over the years, we believe that the potential for the Emerald Cloud Lab solution would appear to be huge and as yet unexplored in full. ECL is still in its early stages of market penetration to innovators and early adopters, but it would seem that the "virtual laboratory" might have a large role in advancing the early stages of drug development with more consistency and capital efficiency – and the drug development company could be located in Oklahoma, Shanghai, Abu Dhabi – or San Diego.

Now, even more recently the robotically-enabled laboratory has seen a new innovation coming along that has significant potential for drug design and manufacturing. At the Lab of Professor Lee Cronin at the University of Glasgow, Professor Cronin have developed software that translates a chemist's words into recipes for molecules that a robot can understand. "Cronin and his colleagues described their machine's capability to produce multiple molecules last year, and now they've taken a second major step toward digitizing chemistry with an accessible way to program with the machine. Their software turns academic papers into "chemputer"-executable programs that researchers can edit without learning to code. This innovation was announced earlier this month in *Science*. The team represents one of dozens of groups spread across academia and industry all racing to bring chemistry into the digital age". These developments could lead to safer drugs, and fuel transformation in the biopharmaceutical industry (and others as well).

"The Virtual Expert Interview" – Many have expounded over the years regarding the importance of obtaining consumer and market insights through questioning, observing, networking and then using associative thinking to vision new products to test their hypotheses, c. f. Dyer, Gregerson and Christensen in The Innovators DNA. So, why not use AI/ML and data mining, as for example has been attempted using IBM Watson? We are aware of two emerging companies founded by close friends and colleagues, both coincidentally located in Pittsburgh and who tapped into the AI/ML expertise at Carnegie Mellon University to do just that. This is another example of using emerging digital technologies to anticipate need, including products and services driven by Covid-21.

We first provide publicly available descriptions of Civic Science and 113 Industries, and then go on to postulate how these solutions could be extended to develop and test products and services in the Covid-19 era and beyond – remotely and digitally!

In 2007, **Civic Science** emerged from the vision of founder and CEO John Dick that market research and opinion-gathering needed a new solution. Consumer and public-oriented businesses that had long relied on traditional polling and survey techniques found those methods were growing tired and less effective in reaching a representative audience. The emergence of social media sharing brought convenience and immediacy of the public's voice to the table, but also inherent biases and untrustworthy information.

Our ambitious goal was to develop a revolutionary new way to connect the real-time opinions of consumers to the decision makers who need that information every day – but to do so with depth, breadth, and reliability.

The company built their first survey website in early 2008 and, through extensive experimentation, database engineering, and software development, created what is now the fastest, most sophisticated, and most democratic survey solution ever invented. Today, we provide software and services to the world's leading brands media companies, and investors, while giving a trusted and powerful voice to all people.

Moving on to **113 Industries**, another Pittsburgh-based early stage company and taken from their website – "It takes some powerful AI technology, Natural Language Processing and even IBM Watson to sift through all the discussions happening across the web and identify high value segments, unarticulated needs and compensating behaviors. This is how we begin forming the foundational insights that go into effective product innovation and brand marketing. Is it technical? Yes. Is it also brilliant? Most definitely".

"All of our data is organic – consumers volunteer the information on forums, blogs, websites, and social media – anywhere public and online. Then, through pattern extraction and a Split-Sample methodology (blind analyses run on split samples of the data), we verify the accuracy and impact of consumer behaviors in the market".

"But when it comes down to it, no one gets humans like humans. That's why we leverage a hand-picked group of strategists with unique backgrounds (everything from material science engineer to psychologists to journalists) to discover the real human story in the data". These would be the "experts or interpreters" as defined by Verganti in his classic book, "Design-Driven Innovation".

Our point in including Civic Science and 113 Industries in this section, is that they both use digital, AI/ML technology to define consumer need and behavior just be monitoring behaviors and needs remotely via web, social media, and other digital means. In a Covid-19 world, why travel to do interviews as products and services are being developed? What is on the minds of people as new drugs and vaccines are being developed? How can the population that does not believe in vaccines be motivated to use them? Or masks!

"THE VIRTUALLY MANAGED CLINICAL TRIAL"

Endpoint news recently reported the Covid-19 motivated efforts of an early-stage, Los Angeles – based company, Science 37, c. g. https://endpts.com/pharma-giants-back-a-leader-in-virtual-clinical-trials-as-covid-19-blights-sites/. The digital platform developed by this company "connects clinical trial participants to researchers via telehealth and a network of home-health nurses. Patients can pick up a cell phone to participate, rather than risking a visit to a clinical site" many of which are operating under restrictions during the pandemic.

"Not all Science 37 trials are fully remote. The company's model allows researchers to opt for a virtual arm to traditional sites. But the pandemic has only exacerbated the need for remote trials". Investors in the recent financing included Novartis, Amgen, Sonofi Ventures, LuxCapital, Redmile Group and PPD.

"The Virtual Doctor's Office" – The emergence of telehealth has been accelerated during Covid-19 pandemic. A quick web search provides a broad definition that is useful:

"Telehealth is the use of communications technologies to provide health care from a distance. These technologies may include computers, cameras, videoconferencing, the Internet, and satellite and wireless communications. Some examples of telehealth include: a "virtual visit" via phone or video; remote monitoring at your home and communication to the provider; use of robotic technology by the provider remotely; alert sensors that communicate distress to the provider.

If you've been examined by a primary care physician or ophthalmologist recently you've probably had a telehealth service.

Conclusions, Extrapolations, and Validations – So, what's coming next? All of the above and more – enabled by entrepreneurs and innovators who anticipate need and leverage technology to find solutions to real opportunities. We predict that digitization and automation will drive the creation of new markets. Recall the definition: market = the job to be done + the executors + the context. In this case, the context has shifted due to the Covid-19 restrictions and constraints in many cases. The jobs to be done and the executors are more invariant. Some of these have been summarized briefly above, but there are many more.

Remote is in, and likely to remain for the near future. Our answer to this opportunity is to leverage technology that has been coming available, but perhaps the timing has not been right. There are many new opportunities coming for those who seek them in our industry.

As this article is being written, McKinsey just issued a new report that contains the responses of 800 executives. This report suggests and supports that a disruptive period of workplace changes lies ahead due to acceleration of automation, digitization, and other trends. See for reference: https://www.mckinsey.com/featured-insights/future-of-work/what-800-executives-envision-for-the-postpandemic-workforce?cid=eml-app.

We predict that ecosystems and clusters will continue to be the building blocks for our industry, but somehow the borders may shift as technology evolves and the workforce and regions adapt to change and opportunity. In this regard, we note recent shifting, and perhaps disruption of some ecosystems. A recent NY Times article by Margaret O'Mara published on Dec. 28, 2020 is titled "Is Silicon Valley Over? Not So Fast". O'Mara states that the obituary for California's tech industry has been written before, and it will be rewritten again and again and again. This is prompted by movement of some tech firms from SV to Texas, e. g. Oracle, Hewlett-Package Enterprise, and Elon Musk himself! Stay tuned in the biopharma, MedTech and digital health segments.

Article

What Corporates Can Do to Help an Innovation Ecosystem Thrive – and Why They Should Do It

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ABSTRACT

Given the pace of change in nearly every aspect of society, transformative innovation is imperative. At the same time transformation is very difficult for large established companies. Open innovation – collaboration with outside entities such as startups — is a powerful tool for exploring both business model and technological innovation. A thriving ecosystem provides a healthy environment in which dramatically different types of entities can find each other and the resources they need to explore and ultimately engage in transformative innovation. Given these benefits, corporates can and should play a role in the creation and growth of thriving ecosystems. We describe the work done to create the life sciences ecosystem in Boston/Cambridge through the eyes of Susan Windham-Bannister who was a central leader in that effort. And we describe in detail both the benefits corporates can enjoy, and the role corporates can play in developing a thriving ecosystem.

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INTRODUCTION: TRANSFORMATIVE INNOVATION REQUIRES A THRIVING ECOSYSTEM

Innovation sounds like something that happens in a flash of insight on the part of a creative individual. In fact, the process of innovation, especially transformative innovation, is long, expensive, fraught with risk, and requires participation from a wide array of stakeholders. Transformative innovation is less about a genius inventor working alone in a laboratory, and more about the physical, social, financial, and informational environment in which inventors can be effective.

We have argued[1] that transformative innovation practice is imperative for large corporates who intend to weather crises and prosper in a dynamic world. Transformative innovation is most likely to occur in thriving ecosystems. For us, thriving ecosystems are environments where ideas routinely reach commercialization and impact. In thriving ecosystems, all key players involved in the process of delivering business impact are **present**; actively **exchanging** goods, services, value and information; and where **pathways** to join in and benefit from these exchanges are clear.

In this paper we describe ecosystems that support transformative innovation, both from a theoretical point of view and through examples. We make the case that large corporates can and should play a significant role in the development, maintenance and growth of thriving ecosystems, and explain how that can be accomplished. And we peer into the future of ecosystems.

Author Diana Joseph of this article is a convener of corporate innovators and brings insight from the work of developing systematic connections among corporate innovators, and between corporate innovators and their external constituents such as startups and non-profits.

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Author Susan Windham-Bannister led ecosystem development in the life sciences for the greater Boston area and played key roles in advising the New York and Los Angeles life sciences ecosystems as well. She brings insight on the development journey and the role that corporates can play in creating a thriving ecosystem. Author Mikel Mangold is a social media connector and innovator with experience in separate corporate incubator, accelerator and venture lab programs. He brings on-the-ground perspective on how corporates engage with their ecosystems.

TRANSFORMATIVE INNOVATION

Transformative innovation usually refers to the introduction of a technology that transforms the way we live and work. Transformative innovation can dramatically disrupt, reshape or eliminate existing business models, paradigms and industries.[2] At the corporate level, fostering transformative innovation means significant architectural change to *both* the business model *and* the technology offered.[3,4] In prior work, Boni and Joseph (2019) observed that the transformative types of innovation required for organizations to thrive in the long-term are extremely difficult for established incumbents to execute, in part because they have existing businesses to maintain[1] and because the costs and risks are significant. However, in a rapidly changing, dynamic world large corporates must place some bets in the transformative arena — no particular existing technology or business model is guaranteed a successful future, so exploration is imperative. Transformational innovation is most likely to emerge in a conducive ecosystem.

INNOVATION ECOSYSTEMS

In a biological ecosystem, organisms function independently in that their behavior is designed to promote their own survival. At the same time, they are deeply *inter*-dependent – their individual survival depends on their mutual interactions and exchanges. Similarly, stakeholders in an innovation ecosystem function independently with their own interests at heart… but, at the same time, they can be more successful if they share and cross-leverage resources and expertise, develop formal relationships and collaborative efforts, and engage with other stakeholders in cross-promotion of the ecosystem.

In the world of innovation, we often use the terms 'cluster' and 'ecosystem' as if they are interchangeable. But a cluster is not enough to support transformative innovation. A cluster is the *inventory* of stakeholders and assets in an innovation community, perhaps including start-ups, well-established companies, workforce, investors, academia, professional services providers, real estate developers, the public sector, technology and infrastructure. But the mere presence of these assets does not mean that they are highly leveraged.

Thriving innovation ecosystems are well-coalesced, collaborative, supportive environments where there is an active exchange across the members of the cluster. This "value exchange" promotes leverage on resources, creates positive feedback loops, supports the translation of ideas into reality, and creates an environment where success breeds further investment which breeds further success.

A thriving ecosystem also contains all or most of the key stakeholders, enabling factors and resources that support transformative innovation. There is no single "magic bullet" that enables transformative innovation to occur – a bevy of the key enabling factors must be present and must interact. As an example, many formal initiatives to accelerate the pace of innovation in a given geography have tended to focus heavily on just one of the enablers of innovation: *infrastructure*, through investments to create low-cost rental space for start-ups. However, rental space by itself is not enough. In the absence of accessible capital, mentoring for entrepreneurs, availability of operating talent, etc., early stage companies can easily fail, be forced to move to a more supportive geography, or (at best) putter along but never scale. And, without an active pipeline of start-up companies to replace those that do fail or leave, real estate developers and real estate landlords will be disinclined to make future investments in additional infrastructure such as new incubating, co-working, accelerating and commercial lab spaces.

Like biological ecosystems, innovation ecosystems generate extensive variation — each new idea represents a variant that might or might not survive and thrive. Ideas arise, are tested, and either grow or fail, all against a backdrop of an ecosystem. A thriving ecosystem fosters ideas, healthy real-world testing (including evidence-based failure) and growth. In an underdeveloped ecosystem, good ideas may not be nurtured, companies that should have failed early may continue to limp along, and overall growth of the life sciences community may be suboptimal. In a thriving ecosystem, stakeholders share an interest in the health of the ecosystem itself and invest time and treasure to create a generative environment.

Competition in thriving ecosystems provides a "productive" tension that weeds out less-promising ideas, reinvests underused or under-leveraged resources, creates leverage opportunities and strengthens "survivors." Because innovation ecosystems facilitate this type of resource, talent and idea exchange they enhance opportunities for transformative innovation to occur.

An ecosystem therefore requires both grand diversity *and* collaboration. When these attributes are present, challenges to the ecosystem can be met by the ecosystem

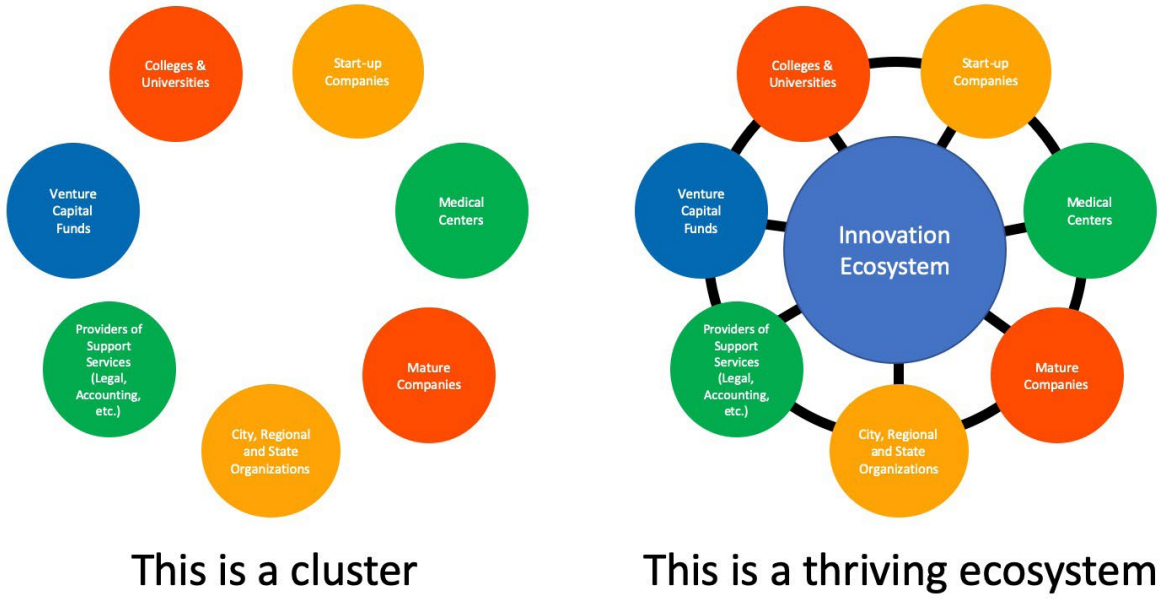

Figure 1: Adapted from Biomedical Growth Strategies, LLC[6] and inspired by the work of Linda Booth Sweeney, Toggle Labs.

as a whole, with flexibility and re-organization. Even in a shock, key elements of a highly collaborative ecosystem can remain connected and operating

Granstrand and Holgersson, based on their review of a broad set of the characteristics of innovation ecosystems, compiled this definition: "An innovation ecosystem is the evolving set of actors, activities, and artifacts, and the institutions and relations, including complementary and substitute relations, that are important for the innovative performance of an actor or a population of actors."[5]

In sum, the assets and stakeholders which define a cluster — organizations, talent and infrastructure — do not by themselves meet the definition of an ecosystem. An ecosystem requires that these institutions, attributes and individuals have relationships, that these relationships are active, producing lively value and resource exchanges and real outcomes. Furthermore, in a thriving ecosystem, these exchange activities result in *emergence,* that is, thriving ecosystems produce behaviors that no individual member or individual pair could possibly produce on their own.

ECOSYSTEM-DEPENDENT REQUIREMENTS FOR TRANSFORMATIVE INNOVATION

In a thriving ecosystem, primary relationships among key individuals at various types of entities relationships massively increase the speed at which information, capital and other resources can be delivered where they are needed. These primary relationships and active resource and produce emergent behaviors conducive to transformative innovation. These behaviors include:

- Win-win scenarios through shared ownership of ecosystem **events** created by diverse players, for example, a venture capital (VC) and a service provider, a corporate host and a university, etc.
- Increased **employment** opportunities. As an outcome of an effective innovation ecosystem, we should see an increase in the number of jobs available, other factors being equal.
- Diverse players across the ecosystem sharing a long-term view. Together, ecosystem players can think more effectively about what comes next, and

how the ecosystem can both shape and accommodate the **future**.

- **Re-mixing and mash-up**. The intersection of different types of experience and expertise is a powerful source of ideation. Facebook occurs when engineering meets university students' social behavior. The iPhone arrives along a path that begins where music meets marketplace development. Modern popular music itself emerged in part from the confluence of African musical composition practice (analogous to software) and European instrument technology (analogous to hardware). New things are very frequently the result of multiple established things coming together. Opportunity for effective mashup is one of the many reasons why diversity of every kind is so important in innovation. Ecosystems invite mashup at the multilayered interfaces between actors.
- Increased customer access and pipelines. At every stage of development, transformative innovation relies on potential **customers**, initial customers, and loyal customers.
- More **accessible supply chains**. Obvious perhaps – transformative innovations need reliable supplies to reach and sustain their impact.
- More accessible **fabrication**, **manufacturing** and **publishing**. Ideas are the spark for transformative innovation. They require fabrication that manifests ideas into tangible reality, and manufacturing (or publication/ syndication) makes that real product (or service) available in the world at scale.
- More accessible and thoughtfully deployed **capital**. Capital, or lack thereof, makes or breaks transformative innovation. Many excellent ideas have languished or perished due to lack of timely capital. Furthermore, too much capital at the wrong time can cause a mediocre or unready idea to take up time and energy that would be better spent elsewhere. A thriving ecosystem includes multiple options for types of capital, timing of capital, and where that capital can be deployed.
- More **accessible Information**. In addition to knowing the fundamentals of the field or fields from which the transformative innovation emerges, innovators need easy access to information, for example, about the legal, social, physical and environmental implications and requirements of their work.
- Better-tuned **regulation**, e.g., zoning. Well-crafted regulations can clarify for entrepreneurs what steps to take and where to go to access customers, produce goods, etc.

With the ingredients of transformative innovation in mind, it's not at all surprising that the World Economic Forum calls for an increase in *collaboration between businesses, academia and the public and third sectors.* In essence, they are calling for the development of thriving ecosystems in order to foster transformative innovation.[7]

CREATING A THRIVING ECOSYSTEM THROUGH INTENTIONAL INVESTMENT: THE BOSTON LIFE SCIENCES STORY

In 2008 then-Governor Deval Patrick, together with the Massachusetts legislature, created a 10-year $1B Life Sciences Initiative to transform Massachusetts from a leading life sciences academic *research* hub to a world leading life sciences *innovation hub,* where new technologies could be translated, developed and commercialized. In 2018, Governor Charles Baker re-capitalized the Initiative for another 5 years at $500M.

The Initiative and its $1.5B fund are administered by a quasi-public authority, the Massachusetts Life Sciences Center (MLSC). The MLSC is funded by the state but governed by a Board of Directors and advised by a Scientific Advisory Board. Susan Windham-Bannister led MLSC as its founding CEO, from the Center's inception in 2008 until 2015.

The broad goals of the Life Sciences Initiative are to:

- ✓ Invest in good science *and* good business
- ✓ Strengthen Massachusetts' global leadership in life sciences
- ✓ Accelerate the commercialization of promising new therapies and technologies
- ✓ Create jobs and drive economic development across the state

The MLSC's strategy for achieving these goals has been to strengthen Massachusetts' "innovation capacity" – the ability to translate promising new technologies into the market on a sustained basis. In other words, to ensure that all the conditions are present in Massachusetts to

support the entire innovation life cycle from bench to bedside, especially a strong ecosystem. Through a strategy to build innovation capacity, investments are used to strengthen the platform that supports the full life cycle of innovation. All stakeholders benefit from and can use that platform; and the strategy leverages the strengths of *both* the public and private sectors

The CEO of a large life sciences corporate that has established a major presence in Massachusetts makes the following observation: "Massachusetts has created an environment where innovation can thrive and where large companies must locate and invest in order to get a look at emerging therapies and rub elbows with a vibrant start-up community."

Innovation capacity depends upon five enablers: Academic culture, entrepreneurial culture (including risk capital), workforce, infrastructure, and crucially: a thriving ecosystem. Dr. Windham-Bannister's first step as CEO was to conduct a situational analysis to identify where there were major gaps in these key enablers of innovation capacity and how these gaps were hindering Boston/Cambridge, with all of its world class research firepower, from operating as a globally recognized life sciences innovation hub. The situational analysis, including interviews with more than 100 key players, was a first step in developing a shared understanding and recognition of mutual goals among key stakeholders in the life sciences community.[6]

This situational analysis provided the basis for setting initial, stakeholder-driven priorities and targets for investment.

- **Enabler: Academic Culture.**
  - *Gap:* Many of the academic research institutions generally were not participating actively in translational research activities, the formation of new companies, or in academic-industry partnerships.
  - *Targeted investments:* Grants to enable academic institutions to hire Entrepreneurs-In-Residence (EIRs); Grants to junior faculty who were interested in translational research; Funding for incubating spaces on university campuses to enable start-up activity.
- **Enabler: Entrepreneurial Culture and Risk Capital.**
  - *Gap:* The greater Boston region received significant amounts of National Institutes of health (NIH) research funding but much less risk capital was flowing into Boston and Cambridge to support entrepreneurship. Entrepreneurial culture also was suboptimal.
  - *Targeted investments:* Funding for business plan competitions at Massachusetts academic institutions to encourage the formation of start-up companies; Formation of a fund for pre-Series "A" companies to support achievement of key funding milestones, attract subsequent (larger) investment; Assistance to large corporates and investors in getting an expedited, "early look" at promising start-ups and new life sciences technology across Massachusetts.
- **Enabler: Workforce.**
  - *Gap:* While the availability of research talent was strong in the region, there was a smaller pool of operating talent — individuals with the skills to raise capital and grow young companies.
  - *Targeted investments*: Funded Internships at start-up companies to provide training experiences and pathways into the industry for entry-level workers; Funded the development of new curricula that supported the development of skills needed by industry; Funded the creation and build-out of new training facilities.
- **Enabler: Infrastructure.**
  - *Gap:* The region needed a larger inventory of incubating, accelerating, convening and commercial (wet and dry) lab spaces. In addition, the region needed "cutting-edge" research spaces to further strengthen new areas of research and translation where Massachusetts had the opportunity to become a center of excellence.
  - *Targeted investments:* Fund cutting edge, shared research spaces; Fund the build-out of commercial lab space and new co-working, accelerating and incubating spaces for start-ups; Fund incubating and "maker" spaces on the campuses of colleges and universities.
- **Enabler: Ecosystem.**
  - *Gap:* The region lacked a well-coalesced relationship network across, which enabled all stakeholders to connect, find needed resources and leverage the existing expertise.

- *Targeted investments:* Fund grants and activities that required collaboration; Cost-share with industry on sponsored research with academia; Fund convening spaces and convening activities; "Connect the dots" across the cluster; Promote a shared vision.

A thriving ecosystem is a dynamic environment. As stakeholders grow, arrive or change, and as new behaviors emerge, the ecosystem shifts, potentially creating new opportunities and challenges. A key responsibility of the MLSC was to monitor and respond to the needs of the ecosystem by expanding its portfolio of programs and investments to better support the ecosystem as it evolved, address emerging gaps and barriers, and enhance emerging strengths and opportunities. Examples include creating funding for "step out" companies (in addition to the funding for Pre-Series A companies), expanding workforce programs that promote greater diversity and inclusion in the life sciences workforce, and creating infrastructure for biomanufacturing.

EVALUATION

The MLSC commissioned independent impact evaluations in 2014 and 2018. Some key findings of these evaluations:[8]

- **Employment**:
  - Massachusetts now ranks #1 in the U.S. in total life sciences employment, controlling for population size.[9]
  - The life sciences sectors have proven to be a major economic engine for the Commonwealth both in terms of its direct job creation and the indirect and induced jobs it has fostered.
  - Growth in the Life Sciences Sector helped bring the Massachusetts' economy out of the recession, when little employment was being generated elsewhere in the state's economy.[10]
- **Venture Capital:**
  - For every dollar of NIH funding, Massachusetts attracts $2.19 of venture investment. As of 2018 the greater Boston area is now second only to the Bay area in VC investment.[11]
  - The Massachusetts biopharma industry raised $2.1 billion in VC investment in the first half of 2020, despite economic uncertainty created by COVID-19.
  - The Initial Public Offering (IPO) market also remained strong, with seven IPOs from Massachusetts biotechnology companies in the first half of 2020, representing 1/3 (33%) of all US-based biotechnology IPOs, and raising an average of $187 million.[12]

CORPORATES AND ECOSYSTEMS

We have argued[1] that open innovation is a required activity for corporates that intend to survive and thrive in the long run. Ecosystems are a powerful, and perhaps required, foundation for open innovation.

At the Corporate Accelerator Forum (CAF), run by Diana Joseph, corporate leaders come together to discuss and jointly investigate challenges and opportunities that emerge from engaging in open innovation with startups. This is in and of itself an ecosystem activity – entities in the same role in different companies and industries are learning from each other in order to benefit themselves and the system. Furthermore, each corporate participant in CAF is involved directly with some group of startups; this link between a corporate and startups can be, we argue, a powerful component of a thriving ecosystem.

Through their work together at CAF, Members have described a variety of ways they benefit from startup engagement. We describe some of these benefits, and then suggest how corporates can get more out of their ecosystems by contributing more.

Corporate innovators have a special role to play in fostering innovation with startups, and special benefits to gain.

Where traditional venture capitalists primarily provide money and relationships, corporations also have specialized technical domain knowledge. Where traditional equipment or lab service providers have space and tools, corporations also have expanded supply chain relationships. Where traditional design and engineering firms have skills, corporations also have customers. Corporate brands and products can be of great value to startups.

Startups bring great value to corporations as well, as generators of financial return on investment (ROI), and perhaps more importantly as idea, technology and market testers. Further, transformative innovation is extremely difficult in a corporate context[1] – startups can explore far more broadly.

Corporations certainly generate ideas and technologies and test them, however, corporations are constrained by a variety of considerations from which startups are generally released. While all idea generators in the biotechnology space must hew to Food and Drug Administration (FDA) regulations and achieve reimbursement outcomes, large public companies are further constrained by

Securities and Exchange Commission (SEC) requirements, large-company Human Resources (HR) obligations and huge numbers of stakeholders in diverse categories (board, employees, vendors, customers, shareholders, etc.), holding diverse and sometimes divergent goals. One important answer to these constraints, as we have previously argued[13] is open innovation. Partnering with other organizations, large and small, allows corporations to enrich their knowledge, resource and talent in ways that are simply not available to a single organization operating alone. Open innovation allows corporates to foster innovation in the broader ecosystem more effectively, and to participate more effectively in idea generation themselves. Corporates can engage with each of the other members in an ecosystem to drive powerful emergent behavior and innovation.

A healthy ecosystem creates multi-directional links between multiple active players and multiple connectors. We briefly describe how corporates can move into this more complex multi-dimensional practice, informed by innovation models described in our prior work.[13]

One-dimensional relationships. In traditional corporate scouting in the absence of a thriving ecosystem, outreach to potential startup partners tends to be outbound. That is, scouts reach out to startups whose profiles appear in industry publications or VC funding lists, or who show up at known events such as a pitch day or meet-up. This outreach activity is valuable and necessary, but it moves along a single familiar vector which is genericized by common use – every corporate and venture scout in the industry is reaching out to the same relatively small set of startups, namely those within easy access or those with a strategic focus on publication. This makes it very difficult for a scout to see a big idea in its early stages, and it means that competition for a "famous" startup's attention is high. This "crowdsourcing" effect also means that energy is poured into a relatively small number of relatively familiar relationships – great ideas and great teams can easily be missed simply because they do not travel in the right (visible) social circles. A thriving ecosystem promotes the discovery of more complex ideas, more diverse founders, and valuable rare finds, because startups and corporates know how to reach each other, and other parties in a position to make introductions know who can benefit by meeting whom.

Attracting attention from startups. In a thriving ecosystem, corporates can create conditions that invite contact from startups, for example, hosting a regular meet-up or maintaining a lively online forum for startups. This two-way communication may improve ability to find startups before the crowd. A more complex approach with innovation benefits in addition to relationships is creating a corporate accelerator – this generates still deeper relationships with startups, and puts the corporate on the radar of other founders in the ecosystem. Depending on the design, a corporate accelerator can access a variety of types of startup partners – not only acquisition targets, but also future customers, suppliers, etc. Corporate accelerators and other direct innovation approaches (corporate incubator, corporate VC, etc.) can also provide ground for strong lasting and supportive relationships between startups, with results such as easier access to talent, company housing, etc.

Adding startup relationships through 3rd parties. Many corporates leverage third parties such and Techstars or Plug and Play to identify relevant startups. This indirect approach[13] provides a one-to-many linkage: Through the 3rd party, the corporate gets access to more startups that are (a) more relevant because of the 3rd party's filtering service, and (b) higher quality because of the 3rd party's development support. These third parties provide clear offerings to the corporate innovation market, and therefore are quite straightforward to engage even for corporates that have not yet developed strong innovation capacity. Like in-house startup accelerators, they also provide a setting for relationships between startups.

Adding relationships with peers. Corporations can form consortia or alliances with others as a pathway to transformative innovation. Consider for example the alliance between the automotive industry in Detroit, high-tech in Silicon Valley, and robotics in Philadelphia[14] — these three types of players come together to propel the development of self-driving cars. Such consortia provide access to a much greater number of relationships with idea-makers in partner corporates, in Universities, and in startups as well as other entities.

Full ecosystem participation. By engaging actively in ecosystems, corporates take advantage of the rich variety of relationships and resource pipelines that emerge in such a setting. For example, Verizon, Kaiser and Wells Fargo sponsor the Alliance for SoCal Innovation's work to develop a broad ecosystem across industries, and across a region from the California-Mexico border to Santa Barbara, and from the Pacific Ocean to the Inland Empire. Through this activity corporates are able to reach respondents for their questions about their own innovations as well as an audience for their innovation work. The ecosystem directly benefits from the corporates, both through the learnings and resources shared by the corporates, and from access to the broader set of relationships that corporates bring to the table (Diana Joseph is a facilitator for this work and Susan Windham-Bannister an expert host). This setting includes corporates and startups and the relationships among them. It also includes many other types of players: Service providers, 3rd party incubators and accelerators, non-profits, government, universities, development agencies and others. The many different types of relationships here increase the opportunity for resources and information to flow to where they are most useful.

The simultaneous presence of all of these relationship types are prerequisite for the emergent outcome effects we expect to see in thriving ecosystems. These entities working together produce common assets, shared infrastructure, new resources, favorable norms and new capacity that no single entity or pair could possibly generate.[15]

HOW CORPORATES CAN FOSTER AND ENHANCE ECOSYSTEMS

At a recent CAF panel[16], Alex Tepper of Techstars highlighted the crucial role that ecosystems play in the success of corporate engagement with startups. Techstars has focused on creating such ecosystems globally, and written about their approach.[17]

The classic entrepreneurial ecosystem in Silicon Valley arose organically and relied on the foundational efforts of corporates who needed each other to move forward. An organic ecosystem takes 25 years at minimum to materialize and comes with significant undesirable side effects. For example, the classic form of venture capital that emerged in Silicon Valley relies heavily on subjective pattern-recognition to select fundable companies. The consequent funding can prop up lower-quality ideas just long enough for an exit, resulting in both painful losses for participants caught up in the process, and painful opportunity costs where the capital might have been more effective. This approach can starve good companies that don't match a familiar pattern. Intentionality can bring better, faster results.

Furthermore, ecosystems that develop without intentionality can miss key players and be less resilient as a result. Consider Detroit when GM faltered, taking rubber, battery and other supplier companies with it. A thriving ecosystem might have had more entrepreneurs and more entrepreneurial behavior that might have allowed the system to flex more effectively. Silicon Valley itself is now seeing significant exodus of capital and expertise. Perhaps a more intentional Silicon Valley ecosystem would be (will be!) able to address the brittleness of baked-in behaviors — for example, by developing more ways to evaluate startups, beyond the traditional patterns.

When players create ecosystems with purpose and discipline, the system can develop faster, and in a healthier way. New York's biotechnology, ecosystem, for example, began with corporates who followed a fairly similar path as Boston/Cambridge – research to identify gaps, creation of enablers, investment. We discuss New York in further detail below.

Imagine an alternative origin story for an ecosystem like biotechnology in Boston/Cambridge – what if the original spark of imagination comes from corporate players, rather than from the state? How might corporates proceed in fostering an ecosystem? What if an alliance of corporates used the Boston example as a manual? Here's how this might look:

I. Identify the gaps around key enablers. This is a research project, essentially. This work could be done by research team made up of investigators from a group of non-competitive companies in a region. Or, it could be done by researchers from a single company in partnership with local non-profits and startups. Or, corporates could sponsor 3rd party research, for example Dr. Windham-Bannister's work in New York.

II. Invest. Corporates have multiple tools for investment, including literal financial investment as in the case of venture capital, as well as the investment of energy, intelligence, advice, "hard" resources such as lab space, influence on other ecosystem players, and more. These investments can serve each of the enablers:
    a. Talent development. For example, SAP employees mentor young women engineers through Technovation[18], and ThermoFischer Scientific sponsors the Bay Area Bioscience Education Community.[19]
    b. Capital for startups – Deploying corporate venture capital in an ecosystem-friendly way is one method. Choosing venture partners who are ecosystem-focused is another.
    c. Incentives for job creation – job creation is a goal generally left to government entities. Even so, corporates have a role to play in the ecosystem – both in hiring on their own behalf, and in engaging with startups who have an opportunity to grow.
    d. Building a culture of entrepreneurship. Corporates can develop entrepreneurial behaviors within the company[20], and they can contribute to entrepreneurial culture in the broader ecosystem. For example, literal entrepreneurs whose companies are acquired might value the opportunity to stay in the entrepreneurial ecosystem by acting as mentors in a corporate accelerator.

e. Shared resources and infrastructure. Corporates can invest together with other entities in the ecosystem to create spaces like QB3, a life science and innovation institute that provides startups with incubation space, guidance, events and relationships. [21]

III. Evaluate. Crucially, thriving ecosystems take their own temperature on a regular basis, and re-tune accordingly. For example, consider an ecosystem where angel investors have been the primary source of capital for very early stage companies. As more investors join that ecosystem and share risk, angel investors may now choose to reduce their risk exposure by targeting companies with more proof points. Overall, this could mean that even as more capital is invested in the region overall, less capital would be available for seeding ideas that need very small amounts of capital, such as step-out companies emerging from the University. A thriving ecosystem would recognize this new gap through regular formative evaluation and could take steps to address it. Imagine a coalition of corporates participating, or even leading, the work to develop the metrics for this kind of health check. An example can be found in Los Angeles where the LA Incubator Network meets regularly to share evaluation metrics.

The MIT D-Lab[15] proposes that vibrant innovation ecosystems depend upon (1) a shared purpose, (2) key actors, resources and contextual elements, and (3) relationships and interconnections between actors, resources and elements. Hoffecker raises an additional consideration: The importance of a backbone organization that can strengthen the system through coordination, information-sharing and facilitation. In Cambridge, MLSC played the role of backbone organization.

Currently in New York, coalitions of corporate actors, through collaborations such as the Partnership Fund for New York City, have taken steps toward the development of a thriving biosciences ecosystem. They have worked with 3rd parties (including Dr. Windham-Bannister) to identify gaps and woo key actors such as VCs to the region. Connections have been forged with city and state government, universities and hospitals. Together, these entities have developed a shared purpose around economic development in the life sciences, and are poised to create a sustainable ecosystem. Time will tell whether these coalitions can form or spin off a backbone organization that will take ongoing responsibility for coordination of the ecosystem. We expect that a backbone organization will be required in order to further awaken the fledgling innovation ecosystem in New York.[11]

Los Angeles, by contrast, has put forward a coordinating backbone organization in Biosciences LA, for which Dr. Windham-Bannister serves on the governing board. As the shape of the ecosystem firms up, we look forward to seeing what might unfold in Los Angeles as corporate players step up to participate actively.

SUMMING UP

In our view, a thriving innovation ecosystem is required to establish the creativity and resiliency required for transformative innovation. Transformative innovation is itself required in order to anticipate and respond to the speed of change — environmental, social, economic and technological change — that is the hallmark of our time. Corporates play a key role in making an ecosystem hum, and the ecosystem gives back by creating a generative environment for new ideas and new innovators to emerge, be tested in the real world, and grow (or be pruned off).

Waiting around for a thriving ecosystem to emerge organically is one approach. It is entirely possible, faster and healthier to create a purposeful ecosystem that produces relationships, pipelines, and pathways for the transfer of resources and information. Through the example of the Massachusetts Life Sciences Center, we outlined a process for creating a thriving ecosystem. In the simplest terms, the process requires: identification of ecosystem gaps, enablement and investment in solutions, and ongoing, iterative, formative evaluation. Corporates can and should participate in the development of thriving ecosystems, building on assets already in place in context. An ecosystem is not merely a collection of actors, it has structure, purpose, and multi-layered connections between actors and resources. A place to start: Forming an organization that can play the role of backbone.

THE FUTURE

We are living in or tightly tied to California – living directly in systems that must re-organize in response to new forces, including a pandemic, new travel and immigration rules, intense refreshed focus on racial justice in the United States, complex electoral politics globally, and global climate change manifesting as massive wildfires that we experience directly in each breath as we write. The year 2020, with the sudden shift to work from home

and the attendant digital transformation, sudden impact on the health care system, education system etc., etc. etc. drives home the need for rapid innovation, going forward. Entrepreneurial ecosystems are critical to the innovation life-cycle, and we have more clarity than ever before about the value of intentional efforts to create and enhance such ecosystems. Partners such as governments, academic institutions, non-profits, young companies and other entities can see the value of participating with corporates in a thriving ecosystem.

The pandemic itself is driving the creation new ecosystems focused on solutions to the pandemic. The pandemic is also driving new formats. Since online work has replaced travel, ecosystems can be global – locality provides much less privilege when even local colleagues are doing most of their collaboration online. While we have focused on regional ecosystems in this paper, industry-based and problem-based global ecosystems can be powerful settings for open innovation as well. This time of intense change will ultimately tell us how ecosystems in places like Silicon Valley, Southern California, New York and Boston manage disruption – what ecosystem features will prove most important in providing the flexibility reorganize effectively in the face of these new forces?

NOTES AND REFERENCES

1. Boni, A. A. & Joseph, D. (2019). Aligning the Corporation for Transformative Innovation: Introducing Innovation Dashboard 2.0. *Journal of Commercial Biotechnology*. **24(4)**.
2. Terwilliger, J. (2015). The Three Levels of Innovation. Creative Realities, Inc., 30 September, https://www.creativerealities.com/innovationist-blog/bid/49954/The-Three-Levels-of-Innovation, accessed 09 November 2020.
3. Pisano, G. (2015). You need an innovation strategy. Harvard Business Review. **93(6)**. pp. 44-54.
4. Boni, A. A. (2018). The Business of Commercialization and Innovation. *J Commercial Biotechnology*. **24(1)**.
5. Granstrand, O. & Holgersson, M. (2020). Innovation ecosystems: A conceptual review and a new definition. Technovation. **90-91**.
6. Windham-Bannister, S. (2016). A new role for government in accelerating life science innovation: The Massachusetts Life Sciences Initiative. Biocat, BioRegion of Catalonia, 28 November, https://www.slideshare.net/biocat/a-new-role-for-government-in-accelerating-life-science-innovation-the-massachusetts-life-sciences-initiative-susan-bannister, accessed 15 November 2020.
7. Timmons, E. (2015). The 4 essential ingredients for innovation. World Economic Forum, 22 January, https://www.weforum.org/agenda/2015/01/innovation-endless-natural-resource/, accessed 23 November 2020.
8. TEConomy Partners, LLC, Mass Economics. (2018). Public-Private Partnerships in Action: The Statewide Impact of the Massachusetts Life Sciences Center on the Life Sciences Ecosystem.
9. MassBio. (2017). Industry Snapshot 2017.
10. Bluestone, B. & Alan, C-M. (2013). Life Sciences Initiative as a Catalyst for Economic Development: The role of the Massachusetts Life Sciences Center. The Boston Foundation.
11. KPMG, Windham-Bannister, S. (2016). New York's Next Big Industry: Commercial Life Sciences. June, https://pfnyc.org/research/new-yorks-next-big-industry-commercial-life-sciences/, accessed 21 November 2020.
12. MassBio. (2020). 2020 MassBio Industry Snapshot.
13. Boni, A. & Joseph, D. (2019). Four Models for Corporate Transformative, Open Innovation. Journal of Commercial Biotechnology. **24**(4).
14. AVCC. About Us. https://www.avcconsortium.org/aboutus, accessed 20 November 2020.
15. Hoffecker, E. (2019). Understanding Innovation Ecosystems: A Framework for Joint Analysis and Action.
16. Tepper, A., Boni, A., Abremski, D. & Joseph, D. (2020). Global Industry Survey of Corporate Engagement with Startups. CAF Fourth Annual Meeting.
17. Feld, B. (2020). The Startup Community Way: Evolving an Entrepreneurial Ecosystem. John Wiley & Sons.
18. SAP.Io. (2020). No Boundaries: Technovation 2020. https://sap.io/noboundaries/, accessed 15 November 2020.
19. Sponsors and Partners. BABEC: Bay Area Bioscience Education Community, http://babec.org/sponsors-and-partners/, accessed 15 November 2020.
20. Ahuja, S. B. (2016). How Intuit Built a Better Support System for Intrapreneurs. Harward Business Review, 05 April, https://hbr.org/2016/04/how-intuit-built-a-better-support-system-for-intrapreneurs?ab=at_articlepage_relatedarticles_horizontal_slot3, accessed 20 November 2020.
21. QB3, Where Startups Get Started. https://qb3.org/, accessed 19 November 2020.

Article

Thought Leader Insights on Innovation Ecosystems And Clusters

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ABSTRACT

This article provides short, "book reviews" and selected comments on recent, popular books that focused on ecosystems and clusters. They include: AnnaLee Saxenian (reflections and lessons from "Regional Advantage"; Leslie Berlin (the building of Silicon Valley from "Troublemakers"); Richard Florida (reflections and extensions of "The Creative Class"); and, Greg Horowitt (lessons from "Rainforest").

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INTRODUCTION

The initial idea for this contribution was simple: Would it be valuable to consider a complement of proven entrepreneurship books for this special issue on innovation ecosystems and clusters? Solid books on entrepreneurship move our thinking, re-orient us in time and space, and give our motivations new life. And the very effort of reading an entire book asks us to think more deeply about the human dynamic of entrepreneurship.

Still, some dismiss general entrepreneurship books as inapplicable to the business of biotechnology, and there is clearly a point to be made here. Intentionally needing to pressure emergent science and/or developing unprecedented, while dependable, technologies does not make for a predictable path to success. With biopharmaceuticals requiring 12-15 years from lab bench to FDA approval and $1B-$2B of funding, or more, to achieve approval, it's difficult to argue that these are not exceptional circumstances. And yet, whether it's biopharmaceuticals, or relatively less resource-intensive efforts, such as biomedical devices, diagnostics, or BioIT analytics-in-the-cloud, or potentially even greater resource-intensive efforts, as is the case for new vaccines. whose development and deployment are potentially changing permanently before our eyes … make no mistake, all of these efforts exist within an entrepreneurial dynamic. Could more general entrepreneurship concepts apply? Do they translate to innovation ecosystems for building biotech enterprises? Or don't they?

Harvard Business School Professor Gary P. Pisano's viewpoint saw no essential differences between the challenges of biotechnology businesses and those of Silicon Valley in the areas of semiconductors, computers, and advanced materials. In his seminal 2006 book, *Science Business*, he states: "The science-based business actively participates in the process of advancing and creating science", emphasizing that each needs to push the boundaries of science to be successful.[1] Whether high tech or high bio, these innovative businesses are intent on creating new and disruptive products, and this requires new science. Tracing the roots of the Silicon Valley electronics industry to the founding of Fairchild Semiconductor in 1957, Dr. Pisano cautioned that this two-decade head start must be considered when attempting to compare the maturity of the two industries. Marking the biotechnology industry's launch of Genentech in 1976, in 2006, he writes: "We are still very much in the learning phase."[1] One benchmark for this perspective might be that at the time of his book's publication, whole genome testing cost $300,000, while today, it costs several hundred dollars.[2] Yet, these specifics beg the question: What hasn't changed? In both high-bio and high-tech? Arguably, the continuous need for evermore groundbreaking science and continuous disruptions in technology.

The shear complexities of the challenges in both fields, and the collective minds required to address them, speak to the necessity of functioning innovation ecosystems and clusters. From concept to every step in the innovation journey, through to market entry and full operation, these ecosystems must be active and working at every level. This starts with individual contributors

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and extends to teams, and groups, and every organizational unit up through the entire enterprise, as well as it positioning within the total ecosystem in which it exists. When considered in these terms, bioenterprise may be no different from any highly innovation-driven enterprise, and the perspectives of general entrepreneurship may provide real value.

The next challenge became "Which books?" To simply pick the bestsellers from last year tends to harvest the trends in current thinking, while selecting books published over time brings other problems. For example, these books reflected the times in which they were written or last revised; changes in technology and advances in science can be disruptive on many levels. And our ability to contrast and compare them is impeded by our own personal experiences, which are set against the backdrops of all the breakthroughs in science or technology which occurred in the interim. And while many start-ups can be traced to one or a few interconnected individuals, we are today experiencing a massive *collective, multi-organization pivot*, due to COVID-19. Recent pre-COVID perspectives may already be outdated, just as perspectives offered prior to ubiquitous mobile technology, DNA-on-demand, and instant global communications may need re-interpretation.

Yet … does entrepreneurship necessarily change? As new scientific or technological capabilities are made possible? It is the unprecedented capability of the individual human brain, and humans working together, which drives innovation in the end. And humans are still humans.

In keeping with this issue's focus on innovation ecosystems and clusters, five best-selling books by five authors are presented here to give the reader some insight into what each offers. Whether a new bioentrepreneur or an experienced one, the challenge before you appears to be in constant flux. Some operate within a sparse innovation ecosystem, either bound by geography or by the lack of the "right" scientific expertise. Others innovate within an ecosystem-rich environment, yet somehow find themselves acting in isolation. And for any entrepreneur, there are those who must create their own innovation ecosystem, among a myriad of other possibilities.

All authors were able to make original contributions to this article. Interviews (either written responses or via Zoom) were conducted with regard to changes which have taken place since publication of their books with authors AnnaLee Saxenian, Victor W. Hwang and Greg Horowitt. Silicon Valley historian Leslie Berlin made the argument for studying history in the innovation context. Richard Florida's 2019 book revision reflects his most up-to-date statistics and insights, yet he added his latest research efforts into the impact of COVID-19 on cities.

THE BOOKS

Author: AnnaLee Saxenian
Professor, School of Information, UC Berkeley
Formerly, Dean, School of Information and Professor, City and Regional Planning

Two Books: *The New Argonauts: Regional Advantage in a Global Economy*[3]
Harvard University Press, 2006

Regional Advantage: Culture and Competition in Silicon Valley and Route 128[4]
Harvard University Press, 1994

UC Berkeley Professor AnnaLee Saxenian has studied the dynamics, limits and potential of innovation regions for decades. In 1994's *Regional Advantage*,[4] Saxenian analyzes and compares the two regions which drove the electronics industry in the 1980's: the long-established Route 128, enabling businesses to centrally arc around Boston, all some 15 miles away, and Silicon Valley, just south of San Francisco, officially the Santa Clara Valley, which prior to the emergence of the electronics boom was the world's largest producer of fruit and fruit-packing. This book can now be read at arm's length: What are the elements that foster innovation? What is the impact of one region massively losing technological resources to another? What can be duplicated, what can be avoided, and what must be grown organically? The deep and unexpected interest which the Japanese showed in this book post-publication recognizes the perceived value of innovation ecosystems and clusters.

In her successor book, 2006's *The New Argonauts*,[3] Professor Saxenian examines the effect of engineers moving to Silicon Valley from all points in the globe and their multi-cultural, multi-regional experience at a time where all technology is global technology. The ecosystem of Silicon Valley became more a reflection of the world's capabilities then a locally-staffed entrepreneurial region. The challenges of transitioning the non-U.S. engineer's experience and expertise back to their home countries is explored, with primary emphasis on China, India, Taiwan and Israel.

Since this time, there has been great interest in the effect and success of "returning entrepreneurs" to their home countries – the so-called "sea turtles", who usually return to the beach where they were born to nest. More recent research includes analyses of success of these home country returns,[5-6] their incorporation with respect to newly-created science parks,[7] and a new (2020) literature review with respect to returning entrepreneurs.[8]

2020 INSIGHTS FROM ANNALEE SAXENIAN:

Professor Saxenian cites three important changes since the publications of both books: corporate size distribution, a backlash against technology companies leading to new regulations, and the US-China business environment. She also provides her perception of the impact of the COVID-19 Pandemic.

Corporate Size Distribution: "With the Internet and the web, the growth of a handful of giant tech corporations that have disrupted the prior patterns of *size distribution*. In the past there were lots of small and mid-sized firms, and big companies rose and fell regularly—but Google, Facebook, and Apple have been dominant for longer and seem positioned to persist due to resources, scale, political clout. They've also undermined competition through acquisitions — and over longer haul could threaten startup ecosystem. (But we're not there yet.)"

Tech Backlash Leading to New Regulations: "[T]he backlash against tech and [the] push for regulation is new—antitrust, privacy protection, risks of misinformation, concerns about addiction, surveillance and control of data, etc. This level of political scrutiny is new."

The US and China: "US-China relations have deteriorated significantly under Trump, threatening patterns of immigration, the transnational communities, investment flows and knowledge exchange that were essential to The New Argonauts. China and the US may come to be separate spheres for internet, technology, and trade."

The Impact of the COVID-19 Pandemic: "With respect to the COVID situation, it seems the pandemic has further strengthened the position of tech giants because they are fully online — so they remain accessible to customers, and work from home doesn't hurt their processes (the way it would in other industries) — at least in short term."

Author: Leslie Berlin
Project Historian, Silicon Valley Archives
Stanford University

Book:
Troublemakers: Silicon Valley's Coming of Age[9]
Simon & Schuster, 2017

Here we get to the personal stories, as only an historian would tell them. A Project Historian with the Silicon Valley Archive at Stanford University, Dr. Berlin interweaves many stories of what might be termed the adolescence of Silicon Valley. Perhaps proving Professor Pisano's insights regarding the intrinsic importance of both the electronic and biotechnology industries to Silicon Valley, Berlin includes the beginnings of Genentech, venture capitalist Bob Swanson, UCSF professor Herb Boyer, Stanford professor Stanley Cohen, and others. The question of what makes intellectual property in the biotech space was a true open question, and it was also a time when venture capitalists were, in a sense, just learning to be venture capitalists in these high risk environments. The result is an insight into how innovation ecosystems are born, reminding us that even the ecosystem itself is a product of innovation. Entrepreneurs will likely see themselves in many of these personalities and situations – biotech and otherwise.

2020 INSIGHTS FROM LESLIE BERLIN:

The Import of Studying the History of Innovation: While Silicon Valley Archive Project Historian Leslie Berlin continues to study, provide comment on, and identify and acquire new Silicon Valley innovation archival material, she clearly states: "With the importance and pace of breakthroughs only continuing to rise, it's more important than ever to study the history of innovation and the people who innovate."

Authors: Victor W. Hwang and Greg Horowitt
Victor W. Huang
Founder & CEO, Right to Start
Former Vice President for Entrepreneurship, Kauffman Foundation
Co-Founder & Former CEO, T2 Venture Capital
Greg Horowitt
Director of Innovation
University of California, San Diego (UCSD)
Co-Founder & Managing Director, T2 Venture Capital

Book:
The Rainforest … The Secret to Building the Next Silicon Valley[10]
Regenwald, 2013

The Rainforest speaks directly to the innovation ecosystem, writ large and small. Authored by two long-time Silicon Valley venture capitalists and entrepreneurs in their own right, it proposes that Silicon Valley – and all innovation ecosystems – might be envisioned as a living and dynamic tropical rainforest. Well considered and insightful, it reminds us that venture capitalists are more than just providers of the funds necessary to bring an enterprise to fruition. Venture capitalists are also coaches, constantly on the lookout for what could go wrong within an enterprise. They also look for what is going right, and why. This includes human behavior and what motivates

us, good vs. less-than-optimal motivations, what makes for a fair vs. unfair deal, and why we should care. The culture of an enterprise as it relates to the larger ecosystem is considered, as well as how to measure the health of something as changeable and organic as a rainforest. Rules and Tools are presented throughout. Not a long read, but a smart one. You might be tempted to scan past the bullet points. Don't. Each bears consideration, and there is that one essential chapter for all: How to Build a Rainforest.

2020 INSIGHTS FROM VICTOR W. HUANG:

The Legacy of Silicon Valley: "*The Rainforest* was inspired by the valley, but the concepts can apply towards prosperity anywhere for anyone in any community. Someone once asked me, 'Is that going to be the greatest legacy that Silicon Valley leaves?' I hope so, because it's not just about an iPhone or a website. It's around a conceptual model of how you create prosperity. That, to me, would be the best legacy. I've seen small towns, rural areas, underserved communities – they've all taken parts of this work, and they've made it their own. There's something about this universality that's really interesting. Especially where there's so much disruption to so many communities, where big companies have done well, and little companies have struggled. We actually think about reinventing an economy, helping lift up the voices that are forgotten from the little innovators and entrepreneurs.

Individuals Innovating from Their Own Homes: "I think what our leadership hasn't fully grasped is that the Internet has changed the ability to create economic value. It used to be, not that long ago, that corporations were corporations, and people were people. You have people now that can do what only large corporations could do [only] a decade or two ago. People have the power to build their own supply chains, their own manufacturing process, their own marketing channels, and to do it in their pajamas from their bedrooms. That was not possible a decade or two ago – now everyone can do it.

Evolving Business Models: "[This calls] into question all of the models around Who's a worker? Who's a company? Who's an employer? Everyone can be a creator. Everyone can be an employer and employee, at the same time. But what does our economic and governance system look like? I think that's the shift we're having to make right now, and it's a great one, because it means we can distribute value creation everywhere. Everyone can find solutions to problems, but we don't teach [how to] do it and we don't help people with it. We don't have a system that's makes it easy to do that. So that's the opportunity now is to really democratize the means of innovation and capitalism for everybody in a way we just haven't done."

Current Technical Tools: "You look at the technological tools now. They're used to actually serve bad ends: To create addiction, to help drive clicks for things that we don't need and to drive want and desire, where we actually don't get value from things. You can actually take those same tools that technology has taught us around how to direct people's attention and apply it now towards actually creating things, building ecosystems, building relationships to drive problem solving. I think there's huge opportunity, but we've got to realign the way we operate our economy to do it."

New Capital Funding Models: "One of the things we did at Kauffman is we actually invested into capital formation. So we actually built a fund to create funds that are innovative, addressing underserved markets. That's actually a lesson you can take from places like Israel. Israel is known for being the most prolific venture capital industry in the world, per capita. What people don't realize is that [its] venture capital industry was built in large part by a government sponsored "fund of funds", that, is a fund that helped create other funds. And that that fund has returned itself, many times over. And it was the model that actually built Latin America's venture capital industry, called the Multilateral Investment Fund, which was modeled off of Israel and has sponsored over 100 funds in Latin America. You can take that same basic model and build capital in all sorts of markets across the US, but no one has done that. There's a huge opportunity to create that kind of mechanism here."

The Impact of the COVID-19 Pandemic: "I think COVID is a great proof point regarding individuals working from home. New businesses are bursting everywhere. We haven't built a system that really recognizes and respects that, and I think that's the opportunity we have right now. We have a real opportunity here to reinvent the economy. Most people don't see it yet … but it's right there."

2020 INSIGHTS FROM GREG HOROWITT:

Thoughts Since the Book's Publication: "Between the time we finished *The Rainforest* and now, I always talk about how the future is going to be in these 'digital' rainforests, as well. A lot of governments, when you talk about innovation, per se, you're seeing places like Singapore and Israel that have dominated in their own way, their innovation landscape is proportionate to their geography. What I've been doing lecturing and writing about is this concept of 'digital' rain forests and how we interact and how we connect our physical bodies to these digital

realities. What are the new tools, and how do we navigate and create impact well beyond our physical limitations."

The Impact of the COVID-19 Pandemic: "One of the hallmarks of true innovation is serendipity. So, when you looked at our book we talked about the engineering process because in the rain forest, it's about the engineering of environments and basically the entering of serendipity. It's about increasing the collisions and randomness. So, even on a campus where we now have to study at home versus being on campus. One of the greatest values of the college experience for many are the social constructs that they develop bumping into one another. It's the bad judgment that gets exercised that eventually leads to better judgment. It's the social experiences, and that's what's being missed. So, innovation, in the time of COVID, is we have to somehow replace that. So some of the new tools can embrace the virtual tools. They're not directly placements, and they never will be, because human beings still need human interaction, which includes social cueing, looking at someone's eyes. It's a very human thing."

Author: Richard Florida
University Professor, School of Cities and Rotman School of Management
University of Toronto
Distinguished Fellow, New York University, Urban Lab

Book:
The Rise of the Creative Class (Paperback, Illustrated)[11]
Basic Books, 2019

Professor Richard Florida has written a number of best-selling books, including *The Flight of the Creative Class*, which projects the global competition for talent. While that may seem to be the most relevant book here, his first book, *The Rise of the Creative Class,* most recently revised in 2019, speaks directly to people working in cities, both in the United States and globally. This particular year for a revision was opportune, as it records the data immediately prior to the COVID-19 pandemic.

While the trend of movement into urban settings has been definitive and substantial until the start of the pandemic, it was instantly disrupted by the requirement to work from home. Where workers will be living in the post-COVID era remains to be seen, the details regarding numerous cities within the United States, the global reach of creative workers, and qualifying the quality of places to live and work remains extremely informative. Has a person who lived in the hip and dense Mission District of San Francisco, but has now moved to a nearby suburb within the San Francisco Bay Area, actually left the region? Suburbs were once viewed as adding commute but, now, reducing density and expense. The habits and needs of the "creative class" within the United States bear significant examination while planning for the post-COVID era.

2020 INSIGHTS FROM RICHARD FLORIDA:

The Impact of the COVID-19 Pandemic: Professor Florida's extensive research on urbanism has pivoted significantly during the COVID-19 Pandemic. He has either personally written or been significantly referenced on this topic in some sixty mainstream publications since March, 2020, as of this writing.

In the October 14, 2020 edition of the *Financial Times*' "From peak city to ghost town: the urban centres hits hardest by COVID-19", footfalls, in terms of the number of people who entered retail or leisure spaces, cited Manhattan, San Francisco and Los Angeles as having 43%, 46% and 70%, respectively, of pre-COVID levels, as measured during the week of October 9th.[12] Among other comments, Dr. Florida provides this insight: "The pandemic is not only going to reshape cities but it's going to reshape suburbs and rural areas"; further, bringing the significant base of digitally-supported workers together in high-rise city towers may be perceived as "the last gasp of the industrial revolution".[12]

Globally, at the other end of the economic spectrum, but also, with no escape from COVID, Professor Florida, with co-author Robert Muggah, published "COVID-19 will hit the developing world's cities hardest. Here's why" in May, 2020 on the World Economic Forum's COVID Action Platform. [13] Considering the impact of infectious disease, specifically COVID-19, the authors point out that "mega-slums are incubators of disease transmission", while "60% of the world's labour force works in the informal economy". [13] This makes "the notion of 'shelter-in-place' preposterous".[13]

With the experience of the COVID-19 Pandemic, such insights demand a larger vision for the biotechnology industry, well beyond those target markets which return investment. Multi-national clinical trials have become routine, even while those markets may not be lucrative for the ultimate product. *ClinicalTrials.gov*, maintained by the U.S. National Library of Medicine at NIH, reports 350,497 clinical trials underway in 219 countries.[14] The successful development of biopharmaceuticals, diagnostics, biomedical devices, etc. may require a greater horizon in the face of pandemic-level infectious disease.

A complete list of media relating to Professor Florida and his work regarding the impact of COVID on urban areas can be found at https://covidcities.com.

REFERENCES

1. Pisano, G. (2006). *Science Business: The Promise, the Reality, and the Future of Biotechnology*. Harvard Business School Press.
2. Brown, K. V. (2019). A $100 Genome Within Reach, Illumina CEO Asks If World Is Ready. Bloomberg. Posted February 27, 2019. Link: https://www.bloomberg.com/news/articles/2019-02-27/a-100-genome-within-reach-illumina-ceo-asks-if-world-is-ready#:~:text=Illumina%20Inc.%20%E2%80%99s%20first%20machines%2C%20introduced%20in%202006%2C,one%20day%20bring%20the%20cost%20close%20to%20%24100.
3. Saxenian, A. (2006). *The New Argonauts: Regional Advantage in a Global Economy*. Harvard University Press.
4. Saxenian, A. (1994). *Regional Advantage: Culture and Competition in Silicon Valley and Route 128*. Harvard University Press.
5. Li, H., Zhang, Y., Li, Y., Zhou, L. A. & Zhang, W. (2012). *Returnees versus locals: who perform better in China's technology entrepreneurship?* Strategic Entrepreneurship Journal. 6 (3):257–272.
6. Qin, F., Wright, M. & Gao, J. (2017). *Are 'sea turtles' slower? Returnee entrepreneurs, venture resources and speed of entrepreneurial entry.* Journal of Business Venturing, 32(6):694-706.
7. Wright, M., Liu, X., Buck, T. & Filatotchev, I. (2008). *Returnee entrepreneurs, science park location choice and performance: an analysis of high-technology SMEs in China*. Enterprise Theory and Practice. 32 (1):131–155.
8. Gruenhagen, J. H., Davidsson, P. & Sawang, S. (2020). *Returnee Entrepreneurs: A Systematic Literature Review, Thematic Analysis, and Research Agenda*. Foundations and Trends in Entrepreneurship. 16:310-392.
9. Berlin, L. (2017). *Troublemakers: Silicon Valley's Coming of Age*. Simon & Schuster.
10. Hwang, V. W. & Horowitt, G. (2013). *The Rainforest … The Secret to Building the Next Silicon Valley.* Regenwald.
11. Florida, R. (2014). *The Rise of the Creative Class: Revisited, Revised and Expanded.* Basic Books.
12. Romel, V. & Burn-Murdoch, J. (2020). "From peak city to ghost town: the urban centres hits hardest by COVID-19". *Financial Times.* October 14, 2020. Link: https://www.ft.com/content/d5b45dba-14dc-443b-8a8c-e9e9bbc3fb9a.
13. Muggah, R. & Florida, R. (2020). "COVID-19 will hit the developing world's cities hardest. Here's why". World Economic Forum's COVID Action Platform. May 27, 2020. Link: https://www.weforum.org/agenda/2020/05/covid-19-will-hit-the-developing-worlds-cities-hardest-heres-why/.
14. ClinicalTrials.gov. (2020). Trends, Charts and Maps. NIH/U.S. National Library of Medicine. December 13, 2020. Link: https://clinicaltrials.gov/ct2/resources/trends#:~:text=Trends%2C%20Charts%2C%20and%20Maps%20ClinicalTrials.gov%20currently%20lists%20359%2C341,2020%2C%20ClinicalTrials.gov%20receives%20about%203.5%20million%20visitors%20monthly.

Article

Creating Communities of Life Science Innovation in the US: History of Critical Factors That Helped the BioHealth Capital Region Emerge

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ABSTRACT

Art is 'I': Science is 'We'

Claude Bernard, French Physiologist, 1813-1878

Background: Advancements in biotechnology are recognized as one of the most important scientific achievements of the 20th Century. The emergence of biotechnology profoundly impacted the health of the world, and the economic vitality of regions where bio clusters and bioresearch parks grew. This article explores some of the historical and policy implications undergirding this development in the United States and the importance of alignment of life science research activity, public policies, and leadership to build place-based communities of biotechnology innovation.

Discussion: The real scientific advances in biotechnology research are beyond the scope of this paper. Instead, this paper will review the growth of team science, the historical factors supporting the growth of the technology sectors with an emphasis on biotech clusters and bioresearch parks, and policies and programs in the 20th Century that helped launch the 21st Bio Century. We conclude with a ranking of the leading biotech clusters in the US, the factors supporting bio clusters, with a case study of the emergence of the multi-jurisdictional BioHealth Capital Region in Maryland, the District of Columbia, and Virginia.

Conclusion: Regions that coordinate life science research at anchor institutions, take advantage of supportive federal policies, spur local bio innovation incentives, and foster private leadership will be those that advance faster and farther in bio health economic development. Beyond the advantages of local economic development, an agile and responsive biohealth cluster can spur global health solutions. The unprecedented speed and international cooperation, as the responses to the need for Covid19 vaccine development, and distribution have demonstrated to the world, can be applied more broadly for other health needs and broadter technology solutions.

Learning from successful case studies of leading regional biohealth clusters, particularly the Capital Region BioHealth cluster, should be of interest to policymakers, public health officials, and economic development practitioners across the United States.

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INTRODUCTION

Technology clusters have been of interest to researchers for many years. Darmody and Bendis participated in a National Research Council Symposium, *Clustering for 21st Century Prosperity,* Washington DC., 2012, which included speakers from the US Small Business Administration (SBA), National Institute for Standards and Technology (NIST), the U.S. Economic Development Administration (EDA) and the State Science and Technology Institute (SSTI). The symposium emphasized the need for sustained investment and coordination of federal, state, and local actors with anchor institutions, including universities, corporate research centers, research parks, hospitals, and others to build effective technology clusters.

In particular, biotechnology clusters offer communities local economic development opportunities and advances in human and animal health worldwide. But not all communities have these advantages. The cost of wet lab space, the presence of anchor universities or hospitals, the need for trained bioscience researchers and technicians, regulatory hurdles, and the longer maturation time for life science innovations necessarily limit world-class growth biohealth regions. Even with these assets, some biohealth clusters will underperform due to a lack of strong biotech alignment.

In terms of biotechnology alignment regionally, public/private innovation intermediaries are a critical factor. BioHealth Innovation (BHI), a public-private partnership life science innovation intermediary, was formed in 2011 in the BioHealth Capital Region to accelerate the growth of life scientists, entrepreneurs, and businesses to the resources, networks, collaborators, and investors they need to grow.

Rich Bendis, the founder of BHI, has identified six factors for strong biohealth alignment in regions:

1. strong leadership,
2. significant industry engagement,
3. talent,
4. access to capital,
5. research assets and facilities, and
6. marketing and brand awareness.

The application of these factors to the BioHealth Capital Region will be explored at the conclusion of this paper. Additionally, the region's response to the COVID-19 Pandemic in attracting research funding for vaccine research and other pandemic responses shines a light on pre-existing networks' importance to respond to unexpected opportunities.

DISCUSSION:

Increasing Importance of Team Science

Science increasingly is collaborative, and the efficiency and effectiveness of science geographically clustered in recognized. This is especially true of bioscience given the increased cost of wet lab facilities, a longer time for maturation of technologies, clinical trial design, government regulatory hurdles, reimbursement strategies, and other factors.

According to the National Research Council:

Ninety percent of all science and engineering publications are authored by two or more individuals. The size of authoring teams has expanded as individual scientists, funders, and universities have sought to investigate multifaceted problems by engaging more individuals. Most articles are now written by 6 to 10 individuals from more than one institution. See, *Enhancing the Effectiveness of Team Science.* Washington, DC: The National Research Council 2015. National Academies Press. https://doi.org/10.17226/19007.

Nearly all Nobel prizes are now awarded to teams. The time of the solo scientist is long past. The last sole winner in Physics, for example, was in 1992. There have been only four sole winners of the Nobel Prize in Medicine since 1973. Research parks and bioclusters historically have helped facilitate connections among scientists and engineers, along with industry, through place-based informal and formal interactions.

Agglomeration Theory

Why do technology firms, including biotech firms, locate near each other? According to Economist Alfred Marshall (1842-1924), firms receive increasing returns from a trinity of agglomeration economies: 1) a local pool of skilled labor, 2) local supplier linkages, and 3) local knowledge spillovers. Marshall famously posited the theory of intellectual spillovers by arguing that in industrial clusters, "the mysteries of the trade become no mystery, but are, as it were, in the air." That is why there are clusters of tech companies in Silicon Valley, auto manufacturers in Detroit, and financial services in New York.

Agglomeration benefits regions and residents by better job matching, higher wages, and more opportunities for civic engagement. Growing clusters in a region and creating a sense of place is the goal for many cities and regions.

Early knowledge clusters and business clusters

Libraries and Universities as Knowledge Centers:
Knowledge clusters are as old as history and started with institutions that recorded knowledge. One of the first knowledge institutions was the library. One of the earliest libraries was formed in the city of Nineveh, located near the current Mosul in Iraq. Over 30,000 clay tablets from the Library of Ashurbanipal have been discovered at Nineveh, probably from the 7th Century BCE. Many other libraries, such as the Great Library of Alexandria in Egypt, followed.

Later, universities became centers of knowledge, such as the University of Bologna (1088), the University of Paris (1150), and the University of Oxford (1167). Much later, universities would become important research centers that helped launch the biotech revolution in the 20th Century.

Considered the first research university in the U.S., Johns Hopkins University would integrate teaching and research, borrowing the concept of graduate education from Germany's Heidelberg University. Later, Johns Hopkins University would create Johns Hopkins Medical School and Hospital, widely noted as one of the world's best medical complexes. The JHU model of graduate education and research would be adopted by research universities across the U.S.

Business Clusters:
In Istanbul, the Grand Bazaar is just one example of ancient meeting places that focused exchange of goods and were precursors to modern cities and business clusters. Long before Starbucks, coffee shops played an important role as business clusters allowing all sorts of classes of people to meet and discuss. In the late 17th century, more than 80 coffee shops in London were centers where businesses and entrepreneurs traded information. The London Stock Exchange (LSE) was founded in Jonathan's coffee shop in 1698 when broker John Casting began posting stocks and commodities' prices, a popular meeting place for businessmen to conduct trades. A similar pattern at Lloyd's Coffee shop in Tower Street in London followed where the underpinning of Lloyd's of London Insurance was formed by posting information about shipping out of England's ports.

The eternal human need for having accessible places where people could gather to share information and knowledge would be replicated in creating bioclusters and bioresearch parks.

Later Policy and Program Developments in the US:

A series of path-breaking private, academic, and government biological research efforts, policy initiatives, entrepreneurial drive, and industry organizations' development helped spur the creation of bio clusters and bioresearch parks in the U.S. in the 19th and 20th centuries.

1862: Land Grant Act and Strong Patents

One of the first federal tech transfer acts was the Land-Grant College Act of 1862 or Morrill Act, which provided grants of federal land to states to finance the establishment of colleges specializing in the agriculture and mechanical arts. Sponsored by Vermont Congressman Justin Morrill (1810-1898), the legislation provided land to the states, the sale of which provided funds to create or support mostly public colleges. (MIT is a Massachusetts land grant university along with the University of Massachusetts. Cornell is the original land grant for the state of New York.) Among other benefits, the legislation spurred the creation of more engineering departments, the 'mechanical arts" that would later benefit the United States in its economic growth.

Abraham Lincoln signed the Land Grant legislation during the Civil War. Abraham Lincoln would also help promote the patent system that would be critical to the launch of the biotech revolution by becoming the only President to be awarded a patent in 1849.

While running for office in 1859, he made his famous comment that the patent system 'secured to the inventor, for a limited time, the exclusive use of his invention; and thereby added the fuel of interest to the fire of genius, in the discovery and production of new and useful things.'

Nearly all observers recognize that strong patent protection available historically in the US has been a mainstay for the growth of biotech companies in the US.

The Land Grant system that Lincoln helped create would benefit the looming biotech revolution by creating agricultural experiment stations—experimental farms—in 1887. Later in 1914, Congress would fund the cooperative extension service whereby trained experts from land grant universities would work with the leading economic sector—agriculture—to provide scientific expertise on improving crop yields and eventually helping the US feed the world. In later years, some of these agricultural experiment stations would be the catalysts for research parks. The portions of the land that universities acquired or the experimental stations would be transformed into research parks and innovation hubs.

Current NIH campus, Bethesda, Maryland

More importantly, the tradition of land grant universities working with their local industry partners through the extension service would continue as new technologies evolved, including information and biotechnologies. This experience would lead many universities to help form biotech spinouts when the technology advances and policy reforms later in the century encouraged this activity, as discussed below. This, in turn, led to the founding of AUTM, an international organization of technology commercialization professionals that has been critical to the advancement of bioscience commercialization activities.

1930: The Ransdell Act and Creation of the National Institutes for Health

The Act changed the name of the federally supported Hygienic Laboratory located in downtown Washington DC to the National Institute of Health. It moved it to its present site in Bethesda, Maryland. The Hygienic Laboratory was originally located on Staten Island as a single room bacteriological lab for sick and disabled sailors. The lab moved to Washington DC in 1891, and its workload increased when Congress passed the Biologics Control Act in 1902 as a result of the need for testing of vaccines for purity and potency, a topic of much interest currently (The FDA would gain this vaccine regulatory authority in 1972 from the NIH).

As improvements in bio health research evolved in the middle part of the 20th Century with the War Against Cancer and other initiatives, Congress increasingly looked to the NIH to supply research-based solutions to health issues facing the nation, creating more NIH institutes and providing more funding to NIH.

The creation of the small one-room hygienic lab originally on Staten Island at the end of the 19th century would, with funding by Congress and US taxpayers, grow by 2000 into the world's largest biomedical institution in Bethesda, Maryland and fund billions of dollars of bioresearch at universities and firms across the country as well as its own researchers on its campus in Maryland. (*See,* Steve Furgenson's history of NIH, in this publication, *infra)*

1945: World War 2 and The Endless Frontier

Seventy-five years ago, Vannevar Bush, an electrical engineer who directed government research during the Second World War, authored *Science—The Endless Frontier.* His report called for a centralized approach to government research, which led to the creation of the National Science Foundation in 1950 and is credited as a path-breaking roadmap for US science policy.

Over the next 75 years, the federal government invested billions of dollars of research through NIH, DOD, Department of Energy, the National Science Foundation, and others, creating the world's leading research universities in the United States based on research funds competed.

1951: World's First Research Park at Stanford University

In 1951, Stanford University, in cooperation with the city of Palo Alto, created the Stanford Industrial Park, with Varian Associates and Hewlett-Packard as early tenants. This is arguably the world's first research park. Stanford University Provost and Dean of Engineering Frederick Terman proposed the park to bring industry closer to Stanford University, emerging as an internationally known research university. Several orchards adjacent to the university formed the research park site, eventually seeding the development of Silicon Valley in the 1960s-1980s.

1958: Growth of the Venture Capital Sector Financing Innovative Companies

In 1958, Congress passed the Small Business Investment Act that allowed the US Small Business Administration (SBA) to license Small Business Investment Companies (SBICs) to help finance and manage small entrepreneurial businesses. This law helped to launch the private equity sector. A later change in 1974 through the Employee Retirement Income Security Act (ERISA), which allowed corporate pension funds to invest in private equity, helped spurt the modern venture capital industry that would provide funding for information technology companies and biotech companies in the 1970s through today.

The angel investing movement, a related way to support start-up firms, would grow, allowing high net worth individuals to invest their funds into private firms and angel investing clubs' growth. Federal Securities and Exchange Commission (SEC) reforms in later years would allow more individuals to take part in private investment that earlier would have required high net worth.

These financing initiatives would help support the growth of the biotech industry in the years following their enactment. Some states and localities would enact bio financing incentives as well, such as the state of Maryland and Montgomery County Maryland bio investment tax credit.

1959: Incubators Launched: Later Emergence of Biotech Incubators

In 1959 the city of Batavia in New York had lost its major industry partner. This Massey-Harris harvester company had a huge warehouse with no corporate tenants willing to take up leasing the entire facility. One of the city's leading business families acquired the space, rebranded it the Batavia Industrial Center, and offered what would become offerings for many technology incubators: short term leases, smaller spaces, shared secretarial service and office supplies, mentoring services, and financing help for companies. It leased space for chicken coops from the nearby Mount Hope Hatchery, creating one of the first incubator spaces in the U.S.

The concept of incubator space and accelerators for start-up companies would grow with organizations such as Y Combinator, and the International Business Innovation Association (iNBIA) would be formed to represent these organizations. iNBIA estimates there are now more than 7,000 incubators worldwide. Specialized biotech incubators with high-cost wet lab space would be launched, such as JLabs, part of Johnson and Johnson Innovation in 13 bio incubator locations worldwide.

1980: Bayh Dole Act, the Cohen Boyer Patent and Genentech Initial Public Offering

In 1980 President Carter signed into law the Patent and Trademark Law Amendment Act, better known as the Bayh-Dole Act. That law gave universities and other organizations the right to take title to intellectual property created with federal research funding. This law gave rise to university technology transfer offices and spurred new drugs and biotech companies.

That same year two investors, Stanley Cohen of Stanford and Herbert Boyer of UCSF were awarded a patent for their work in 1974 studying the process of recombinant DNA, which would be a platform for further bioscience research in the 1980s and beyond. Advances in bioresearch had been taking place decades earlier.

Finally, that year Genentech, a four-year-old company that produced human proteins made by bacteria into which human proteins had been slipped using recombinant DNA, had its public offering on the New York Stock Exchange. Genentech benefited from the venture capital sector advanced by Congress, and many follow-on biotech companies would go public in the months and years after the Genentech filing.

1986: Association of University Research Parks Formed

After its founding, the Stanford Research Park model would be emulated in many places across the U.S. and

increasingly worldwide. University City Science Center, one of the first urban research parks, was formed in 1963 in Philadelphia around the University of Pennsylvania, Drexel, Temple, and others. Research Triangle in North Carolina was growing after a slow start.

In 1986, research park directors from Stanford Research Park, Central Florida Research Park, Arizona State University Research Park, Oakland University, RPI in New York, Texas A&M. Research Triangle Park, and Edmonton Canada Research Park Authority met in Arizona to form the Association of University Research Parks (AURP).

The growth of university tech transfer offices spurred by the Bayh Dole Act, more start-up companies financed by venture and angel capital, and advances in biotech research helped to promote the use of research parks as places to grow university public-private partnerships. Specialized parks in biotechnology were formed in San Diego, Baltimore, Boston, and San Francisco. AURP would form an AURP Bio Health Caucus to represent the unique opportunities and challenges in bio health research, including the higher cost of wet lab facilities, longer maturation time for life science technologies, and clinical trial strategies.

1993: BIO Organization formed: State Affiliates Follow

In 1993 two small bio trade groups—the Industrial Biotechnology Association (IBA) and the Association of Biotechnology Companies (ABC)—merged to form a single organization called the Biotechnology Industry Organization (BIO). Initially uniting 503 biotech companies, the new organization would grow to become the largest bio trade organization representing more than 1,100 biotech firms, research universities, state biotechnology centers in the US, and more than 30 countries. The organization would later rebrand itself as the Biotechnology Innovation Organization.

State organizations related to BIO would be formed to build regional bio clusters, such as Virginia BIO, California Life Science Association, and the Maryland Tech Council. https://www.bio.org/csba These organizations would be critical state-based organizations to advocate on behalf of bio institutions and clusters in their jurisdictions, working on state and local programs to support this sector of the innovation-based economy.

2017: National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL)

In 2017 a $70 million award was made by the National Institute for Standards and Technology (NIST) to create NIIMBL, headquartered at University of Delaware Research Park with a national consortium of university and industry partners. NIIMBL's mission is to accelerate innovation in biopharmaceutical manufacturing, support the development of standards to enable more efficient and manufacturing capabilities, and train a world-leading workforce to support an industry sector supplying medicines worldwide. The Association of University Research Parks (AURP) awarded NIIMBL its COVID19 Excalibur Award for Response and Resiliency in 2020 to coordinate biomanufacturing research during the Pandemic.

NIIMBL is a Manufacturing USA member, a national network of linked manufacturing institutes, and joins BioFab USA of Manchester, New Hampshire and BioMADE (Bio Industrial Manufacturing and Design Ecosystem) of St. Paul Minnesota as other bio-related manufacturing institutes sponsored by NIST and the Department of Defense. With the growing interest of ensuring medical supply lines are robust in the US, more funding of biomanufacturing initiatives is expected in the future.

There are no such things as applied sciences, only applications of science
Louis Pasteur, 1822-1895

COLLABORATIVE RESEARCH IN BIOTECHNOLOGY:

The Organization for Economic Co-operation and Development (OECD) defines biotechnology as "*the application of science and technology to living organisms as well as parts, products, and models thereof, to alter living or nonliving materials for the production of knowledge, goods, and services.*"

Biotechnology companies are often located close to anchor institutions—major universities, hospital systems, and research centers—and can be associated with supportive, more prominent companies interacting with smaller bio enterprises spun out from anchor institutions. Biotech firms are often located in bio parks, such as UMB Bio Park in Baltimore, UCSD in San Diego, California, or Research Triangle Park in North Carolina. Even in downtown Manhattan, high rise office buildings are being repurposed into wet lab space.

Modern biotechnology harnesses cellular and biomolecular processes to develop technologies and produce to improve our lives and our planet's health. Biotechnology includes industrial use of recombinant DNA, cell fusion, and novel bioprocessing techniques. Advances in the biosciences have blurred the boundaries between historically separate disciplines and overlapping with other fields, such as medicine, artificial intelligence, chemistry, informatics, quantum computing, and physics, thereby increasing the need for interdisciplinary research and bringing different industries closer to each other. The biotechnology sector also makes extensive use of external services in R&D—testing, financing, and marketing—which also tend to be located nearby.

Counterintuitively, international connections are also critical to the local growth of bioclusters as much bioscience involves researchers from many countries. Accordingly, proximity to international airports and transportation hubs is an essential element of building robust biotech clusters.

Biotechnology is a science-driven business, which means that clustering often occurs in proximity to crucial knowledge centers, usually universities or public research institutes conducting top-level research. Because this knowledge is often tied to individual researchers or research groups, effective utilization requires close interaction between actors and multilevel partnerships. Also, anchor institutions are now looking at ways to connect with the community, whether it is workforce housing, childcare, biotechnician training programs attracting clients from the local community, and other connecting activities. Specialized labs, such as CGMP (Current Good Manufacturing Practices) that meet FDA regulations are sometimes needed as part of the local bio innovation ecosystem.

WHERE ARE THE LEADERS IN BIOHEALTH? INDUSTRY BIO REGION RANKINGS:

Listed below are recent rankings from Genetic Engineering and Biotech News (GEN), CBRE, and JLL, three of the most respected life science industry observers. There is some variation of the rankings of bio regions depending on how the region is defined— is New Jersey included in New York? for example— and the criteria being measured (NIH grants, amount of wet lab space, number of patents, venture capital, jobs, etc.)

GEN

Genetic Engineering and Biotech (GEN) Ranking

1. Boston-Cambridge
2. San Francisco Bay Area
3. New York/New Jersey
4. BioHealth Capital Region: Md/DC/Va
5. San Diego
6. Greater Philadelphia
7. Los Angeles/Orange County
8. Raleigh/Durham North Carolina
9. Seattle
10. Chicagoland

CBRE

CBRE Ranking

1. Boston-Cambridge
2. San Francisco Bay Area
3. San Diego
4. New Jersey
5. Raleigh/Durham North Carolina
6. DC-Baltimore
7. New York City
8. Philadelphia
9. Los Angles
10. Chicagoland

JLL

JLL Ranking

1. Greater Boston
2. San Francisco Bay Area
3. San Diego Metro Area
4. Maryland (BHCR)
5. Raleigh Durham Metro Area
6. Philadelphia Metro Area

7. New York Metro Area
8. Los Angeles/Orange County
9. Seattle Metro Area
10. New Jersey

The following city snapshots of bio clusters from the East Coast are from *Genetic Engineering News* review of top biotech clusters for 2019 to provide some context of local factors supporting the growth of these clusters:

Boston/Cambridge

Rather than rest on its laurels, the nation's largest biopharma cluster seeks new avenues for growth and thinks it has found one in digital health. Addressing a Massachusetts Biotechnology Council (MassBio) conference on September 9, Gov. Charlie Baker (R) committed the Bay State to advancing digital health by creating a digital health record database, citing McKinsey's estimate the industry will grow to more than $350 billion by 2025. Another new avenue is gene editing: In March, Cambridge-based Beam Therapeutics, co-founded by CRISPR pioneer Feng Zhang, Ph.D., raised $135 million in Series B financing, bringing its total capital raised to $222 million in less than a year. Longtime strengths like top-tier universities and talent have fueled an increasingly robust start-up ecosystem. On September 13, a team of industry veterans and academic researchers—including George Church, Ph.D., of Harvard Medical School—opened Petri, a start-up accelerator offering a 12-month program for translating research ideas into commercial success; its tools include $250,000 or more in capital and access to the team's expertise. However, the region's clogged highways and Massachusetts Bay Transportation Authority—plagued by two train derailments in June—must improve, or biopharma job growth cannot continue, MassBio's Elizabeth Steele told *The Boston Globe*. The region ranks lowest at third in employment with 95,209 jobs (JLL), while MassBio recorded 74,256 biopharma jobs last year. Boston/Cambridge is second in patents (7,935), and leads the nation in lab space (figures range from 30 million [Colliers|Boston] to 23.9 million [JLL]), NIH funding

(5,004 awards totaling $2.627 billion), and VC funding ($6.789 billion in 174 deals).

Greater Philadelphia

University City Science Center plans to join developer Wexford Science + Technology and Chicago real estate investment trust Ventas to develop One uCity Square. The 389,000-square-foot, 13-story office-lab-retail building, is slated for completion in the fourth quarter of 2021. At the center, the new Launch Lane accelerator will begin accepting applications in October; up to 12 start-ups will be accepted early next year. In February, the Science Center welcomed Cranbury, NJ-based Amicus Therapeutics, which is creating a Global Research and Gene Therapy Center of Excellence, bringing 200 jobs to 3675 Market St. The region houses 30+ cell and gene therapy developers, including Spark Therapeutics. The spinout of Children's Hospital of Philadelphia has found a buyer in Roche, but the planned $4.8 billion acquisition had been delayed for months while the companies try to resolve competitiveness concerns raised by the U.S. Federal Trade Commission and U.K. regulators. In suburban Montgomery County, Thomas Jefferson University has opened the $7 million Jefferson Institute for Bioprocessing in collaboration with the Dublin, Ireland-based National Institute for Bioprocessing Research and Training. In Harleysville, PA, Colorcon on September 17 created the $50 million Colorcon Ventures VC fund to invest in companies across manufacturing, the supply chain, and delivery of pharmaceutical products and services. The "City of Brotherly Love" and suburbs remains a consistent sixth in VC ($806 million in 37 deals), NIH funding (2,340 awards totaling $1.108 billion), lab space (10.6 million square feet), but is seventh in patents (1,912) and jobs (54,709 according to JLL; 49,000 according to Select Greater Philadelphia).

New York/New Jersey

Manhattan's lab space inventory should nearly double in two years as another 1.5 million square feet is built, according to commercial real estate firm CBRE. Leading the way is Alexandria Real Estate Equities, now constructing a third building—the 550,000 rentable-square-foot North Tower—at Alexandria Life Science Center-New York City in Manhattan. Across the East River in Long Island City, Alexandria, last year bought The Bindery, a 175,000-square-foot building, for a reported $75 million, then spent $25 million in July for a site across the street. Alexandria also plans to expand its LaunchLabs® accelerator to a second Big Apple location at Columbia University's Lasker Biomedical Research Building. Deerfield Management this month closed on financing to acquire 345 Park Avenue South for conversion into life-sci space, while Larry Silverstein's Silverstein Properties and Taconic Investment Partners have converted 619 West 54th Street into The Hudson Research Center. North of NYC, BioMed Realty, on August 29, plans to renovate two buildings totaling 97,000 square feet for smaller biotechs at Ardsley (NY) Park. In New Jersey, Gov. Phil Murphy (D) enacted a doubling of the

state tax credit for angel investors in July. The Garden State has 60% of the region's jobs, in which the two-state tandem ranks first (127,376, according to JLL). NY-NJ is second in lab space (figures range from 30.33 million square feet [JLL] to roughly 20 million square feet [CBRE]), as well as NIH funding (4,525 awards totaling $2.16 billion). However, the region places fourth in venture capital ($1.512 billion in 40 deals, up 40.5% from a year ago) and fifth in patents (4,539).

BioHealth Capital Region [Maryland/Virginia/Washington, D.C.

The Maryland/Virginia/Washington, DC "BioHealth Capital Region (BHCR)" has won over numerous employers as it strives to grow into a top-three cluster by 2023. Kite, a Gilead Company, chose Maryland's Frederick County to build a 279,000-square-foot manufacturing site for CAR-T therapies, including its marketed Yescarta® (axicabtagene ciloleucel). Also, in April, Paragon Bioservices (since acquired by Catalent) opened a 151,000-square-foot commercial manufacturing center in Harmans, MD. AveXis, a Novartis Company, agreed to use Harmans as a manufacturing site for the recently-approved gene therapy Zolgensma® (onasemnogene abeparvovec-xioi). A month later, Gaithersburg, MD-based Viela Bio filed for a $150 million IPO; the company spun out last year from AstraZeneca, a regional anchor since 2007 when it acquired MedImmune (a name retired in February). French diagnostics developer HalioDx, a Qiagen spinout, opened its first North American lab in Richmond at Virginia Bio+Tech Park, which is partnering with Activation Capital to develop additional space for expansion-stage companies. Regional anchors also include the NIH, FDA, and Johns Hopkins University, which won 40% ($648.971 million) of the region's $1.6 billion (3,272 awards) in NIH extramural funding, ranking it third; the agency also devotes about 10% of its $39.234 billion FY 2019 budget to intramural research. BHCR is third in NIH fund ing (3,272 deals totaling $1.608 billion) and patents (5,367), and fourth in lab space with 22.8 million square feet according to Rockville, MD-based Scheer Partners, which measures the entire region [JLL counts 12.95 million for Northern Virginia/Suburban Maryland/Baltimore). In VC, JLL records $1.229 billion, good for fifth (and better than the $750 million counted by PwC/CB Insights). BHCR's 55,882 jobs (JLL) ranks the region sixth.

Profiles from Genetic Engineering News https://sciencecenter.org/news/top-10-u-s-biopharma-clusters-2

APPLYING SIX FACTORS SUPPORTING GROWTH OF BIO CLUSTERS TO THE BIOHEALTH CAPITAL REGION:

The BioHealth Capital Region (BHCR), comprised of Maryland, Washington, DC, and Virginia, is perhaps a surprising entrant on leading biotech clusters in the US. Unlike Greater Philadelphia, with its ties to Delaware and New Jersey, the DMV (DC, Md, and Virginia) does not have a history of multi-jurisdictional cooperation.

Also, until 2015 the region did not have a recognizable science brand. Still, leaders at Astra Zeneca—a leading biotech company headquartered in the region— and BHI thought it was time to consider new names. Over six months, 150 regional leaders met to evaluate the need for a brand, and *The BioHealth Capital Region* term and brand emerged.

The brand's rationale was that names such as 'biotechnology' and 'life sciences' were too limiting when drug development, biotechnology, medical devices, computing advances, diagnostics, vaccines, healthcare cybersecurity, and other technologies were becoming interdependent on one another. Second, the term 'capital' had a double meaning with the Nation's Capital as the jurisdiction with existing international awareness, coupled with the need for financing 'capital' to grow the industry. Third, 'region' was used to intentionally eliminate artificial state, county, and city boundaries to find ways to work together regionally. Since that time, BioHealth Capital Region has been increasingly accepted locally, nationally, and internationally as a science brand for the area.

With a deep bench of federal labs, universities, and private industry and BioHealth Innovation-a critical intermediary organization to bring jurisdictions together – the BHCR region has jumped two spots in GEN's rankings in the last five years. The region's strengths include more than 800 biohealth companies, proximity to NIH and FDA, a network of bio-oriented research parks and research universities, and a strong bio patent portfolio.

BHI CEO President Rich Bendis has identified six factors critical for success in the BHCR and other regions in the country:

#1: STRONG LEADERSHIP

Strong leadership is always critical to a cluster's development, expansion, and sustained success. A cluster's growth can be spearheaded by various sources, including academia, political leaders, industry, and others.

"I was involved with building the Philadelphia biohealth cluster led by academia with support from the mayor, governor, and industry. The President of the University of Pennsylvania, Judith Rodin, was the primary driving force," stated Bendis.

"Leadership in building a cluster comes in many different flavors," he added. Bendis noted that other major clusters have been led by politicians, technology, talent, and other influencers. As an example, the Boston cluster has largely been driven by technology and talent emerging from Harvard and MIT. According to Bendis, the BHCR cluster has been led by industry, with MedImmune (now AstraZeneca) and other supporting organizations like BHI as the primary driving forces in the cluster's rise to prominence.

"I think the potential to last the longest would be an industry-driven cluster rather than a government one, which is subject to changes in administrations and priorities. It is not necessarily "all for one" when it comes to academic and government cluster leadership. Industry-led clusters have more potential for the stability of vision and action," according to Bendis.

"Industry is a predictable driver of growth. It will always be driven by the market; you have to create products that the market needs, and that will drive the economy," stated Bendis.

About six years ago, Medimmune examined what it needed to do to support its own growth within the region and took the lead, partnering with BHI and other organizations to create a regional brand and the infrastructure it needed to thrive. While AstraZeneca has absorbed the Medimmune brand, multiple companies are emerging as new industry cluster leaders.

AstraZeneca has recommitted to supporting the BHCR cluster, and homegrown companies like Emergent Biosolutions, Macrogenics, United Therapeutics, and Supernus, among others, have grown substantially. What's more, international biohealth companies like GSK, Qiagen, Kite, Autolus, and Janssen (who acquired Beniver) see the value in keeping or establishing a presence in the region.

From an industry leadership standpoint, the BHCR is in a strong position with homegrown companies thriving and international companies increasingly planting roots in the BHCR.

#2: SIGNIFICANT INDUSTRY ENGAGEMENT

Bendis believes that significant industry engagement—above and beyond engagement focused only on a company's benefit—is critical to creating a top-tier biohealth hub. This means an industry-led, industry-funded, and market-driven effort to cluster building and growth.

According to Bendis, government, economic development organizations, associations, and other loosely connected membership organizations are not enough to build a top-tier cluster. Industry must be directly engaged with strong, committed cluster leaders and supported by organizations with experienced professionals with business and entrepreneurial experience. Building an elite biohealth cluster is about bringing various forces together behind industry-driven and funded programs designed to maximize the return on the region's growth assets. Bendis sees the ascension of the BHCR as a product of this type of collaboration.

MedImmune/AZ was the first major industry player, led by Jarrod Borkat, to commit to building the cluster. It took an even bolder step forward when it gave up control, showing they were not purely motivated by self-interest. Over the past five years, dozens of other companies have become more engaged in the region, such as GSK, Emergent BioSolutions, Emmes Corporation, Qiagen, REGENXBIO, and American Gene Technologies (AGT).

AGT's CEO, Jeff Galvin, has become one of the region's most vocal supporters. He invests his time every month to engage in various ways with the ecosystem, from supporting STEM education programs or hosting events for postdocs at their facility to visiting other local companies and even writing about other Gene Therapy companies in Maryland on their blog.

"At BHI, which serves as an innovation intermediary for the region, we contributed to bringing industry, academia, government, and other forces together by helping these groups better manage what we call the three "Cs" of ecosystem building: cash, control, and credit," stated Bendis. "Who gets the cash? Who is in control? And who gets the credit…the cash is really the driving factor. The next is control. Who controls what? The cash, budgets, programs, and venues? Finally, it is credit. Everyone wants credit when someone succeeds. If everyone can understand these drivers and get their egos out of the way, we can succeed together."

Collaboration, the fourth "C," can only be achieved when key influencers decide to work together for the greater good of the biohealth cluster. The spirit of true collaboration for universal benefit is a critical factor in sparking the right kind of industry engagement for cluster growth. Bendis believes in a balanced and measured approach to cluster building and that this collaborative *esprit de coeur* is growing here in the BHCR.

#3: TALENT

Developing, attracting, and retaining life science talent at all levels is another key driver to biohealth cluster success. Each of the top four clusters has a significant and diverse pool of local talent, the strong companies to attract new talent, job mobility potential without relocating, and a desirable lifestyle.

"Scientific talent has never been a problem in the BHCR," stated Bendis. "I've been talking to a number of CEOs at emerging biohealth companies, and they tell me they can generally build their core team with talent from the region—that is to say about 75-80% of the talent they need is right here," added Bendis.

The BHCR has the highest concentration of PhDs and master's Degrees in the life sciences in the world. The region's scientific talent pool exists because of its robust university system and government presence.

However, the region does have its challenges, particularly in the area of finding local sales, marketing, and commercial talent. Because many BHCR companies are pre-market and pre-commercial, these professionals' regional talent pool is less robust than some bioclusters. In addition, Bendis sees a need for more c-level and entrepreneurial talent in the region but does not view this as a major obstacle to its development.

Bendis believes attracting this talent is not too challenging for the BHCR given the number of high-profile companies in the region and its attractive lifestyle. The cost of living in biohealth clusters like Boston, the San Francisco Bay Area, and New York/New Jersey is very high. It is altering migratory talent patterns, putting the BHCR in a strong position for talent acquisition and retention.

"What we are seeing is talent migrating south. The cost of living tends to decrease the further south you go. The BHCR is not the least expensive, but we do offer a great quality of life, outstanding schools, and the security that comes with strong industry, academic, and government opportunities to move jobs if needed," stated Bendis.

Bendis believes talent is one of the BHCR's greatest assets and that the region is well-positioned to build on this key biocluster element.

#4: ACCESS TO CAPITAL

Whether angel investment, seed capital, pre-series A, Series A/B, or non-dilutive funding, access to capital or lack thereof, is a key driver of biocluster development, growth, and sustainability.

Silicon Valley's Sand Hill Road area is the poster child for concentrated venture capital driving growth and innovation. And clusters like Boston, San Francisco, and New York/New Jersey simply have a higher concentration of capital opportunities than the BHCR, though that is starting to change.

"There are a lot of wealthy, high net worth individuals within the BHCR. The venture capital environment is just not as formalized here as it is in other clusters. The people that can fund companies come from lower risk, non-entrepreneurial backgrounds and tend to be reluctant to jump into high risk biohealth investing," stated Bendis. "There seems to be a leadership gap in organizing the many high net worth people able to fund deals."

Access to early-stage capital is a challenge in the BHCR, particularly in the 500K to $5M space.

Regionally, the average round in 2018 was about $14M, up from $11.5M in 2017. These larger funding levels mirror a national trend where venture capital firms are investing higher amounts in fewer companies, thus creating a gap in that early-stage funding strata.

There is good news for start-ups and early-stage companies seeking funding: The region sits at the center of non-dilutive funding opportunities via the Small Business Innovation Research (SBIR) program. $3.5B in SBIR funding is available each year nationally, flowing through 11 agencies. Many SBIR funding opportunities come via the NIH and other entities located in the BHCR. While proximity to agencies with SBIR funding is not a determining factor in who gets selected, companies in the region certainly can benefit from being closer to these agencies.

"SBIRs are the purest form of capital that exists. You don't have to mortgage your house, you don't give up any equity, and you don't have to pay it back," stated Bendis. "We are not yet at our' bodyweight' in the region regarding SBIR funding," added Bendis.

The region has its strengths and weaknesses when it comes to funding. SBIR and non-dilutive opportunities abound while early-stage funding opportunities are growing but remain a challenge. Initiatives like the annual BioHealth Capital Investment Forum, which allowed 95 companies to connect with over 30 investors, including JP Morgan, is a step in the right direction for increasing venture capital opportunities. The second annual BioHealth Capital Investment Forum is scheduled for October 15th and 16th at AstraZeneca.

"If you take a look at our major financings recently, it represents a significant upward trend of attracting new investors from outside the region," stated Bendis.

#5: RESEARCH ASSETS & FACILITIES

A concentration of research assets and available facilities, particularly when it comes to wet lab space, is an

essential building block for a robust bioscience cluster. Strong cluster research assets produce a steady stream of talent and tech transfer opportunities that foster sustainable growth. And ample wet lab space and cutting-edge facilities help this talent bring new technologies to commercialization.

The BHCR has an unrivaled research asset infrastructure already in place. Johns Hopkins University (JHU) and the University System of Maryland (USM) generate $3.5B in combined, annual R&D investment; the NIH's intramural program employs 6,000 scientists and has a $3.5B annual research budget; and the Federal Research R&D investment in 59 Maryland labs—the most labs in any state— totals $12B annually.

From a facilities standpoint, the BHCR is ranked #4 in wet lab space with 22.5M square feet spread across a multitude of centers and institutes across the region. "We are ranked 4th in research, but when you add the 6,000-intramural scientist at NIH, the BHCR annually generates $5.5B in research, and no other cluster even comes close to that," stated Bendis.

#6: MARKETING & BRAND AWARENESS

Having a strong cluster is one thing; national or global awareness of this strength is another. Many top-tier biohealth clusters actively promote their regional brands and have strong brand recognition in the U.S. and across the globe. The BHCR has many strengths, but self-promotion and regional brand evangelism is not yet one of them.

"We are not self-promotional. This is not a marketing-driven cluster. People generally are not as extroverted about promoting their successes publicly," stated Bendis. "Brand awareness is extremely important. If we do not talk about ourselves, if everyone does not become an ambassador for their company and the region, we won't continue to have a strong cluster. We need to deliver the same, consistent BHCR message when we are at conferences and traveling around the country and the globe."

Bendis added that the region has largely adopted the BHCR as its overall brand identity, moving away from the 270 Corridor or DMV names of the past, which were too limited in scope. Bendis stated, "Having forums like the BioHealth Capital Region Forum, which had 1,200 registrants in 2019, our new investor conferences, or a program like BHI's International Soft Landing is an opportunity to sell the BHCR cluster nationally and internationally."

Bendis also feels strongly that BHCR brand promotion needs to happen more frequently and in a more coordinated fashion.

A unified effort at brand promotion is even more critical for the BHCR due to its large geographic area and a lack of geographic density found in other clusters like Cambridge, Massachusetts. Elevating the region's brand awareness and promotional initiatives will help raise the cluster's profile and generate greater connectivity across the diverse and highly dispersed players that call the BHCR home.

The BHCR is making progress across Bendis' 6 key elements that build successful biohealth clusters. The region has remarkable strengths and significant untapped potential that could propel it into the top 3 by 2023. Bendis strongly believes in a thoughtful, measured, and strategic approach to cluster building where a rising tide lifts all boats. "The key is that the GEN bio cluster annual report is based on five indicators, and the region has made progress in 3 out of 5. It's not one thing but rather a combination of things that are coming together; we are not yet #1 in any one indicator, but we've progressed from 6 to 5 to 3 or 4 in some categories," stated Bendis.

"I look at this through the recognition of people outside the region that this is a great place to start or have a business, and it's a good place to seek investments. We have outstanding leadership, a deep and diverse life science talent pool, remarkable assets, and tremendous opportunities for local, regional and international collaboration," stated Bendis.

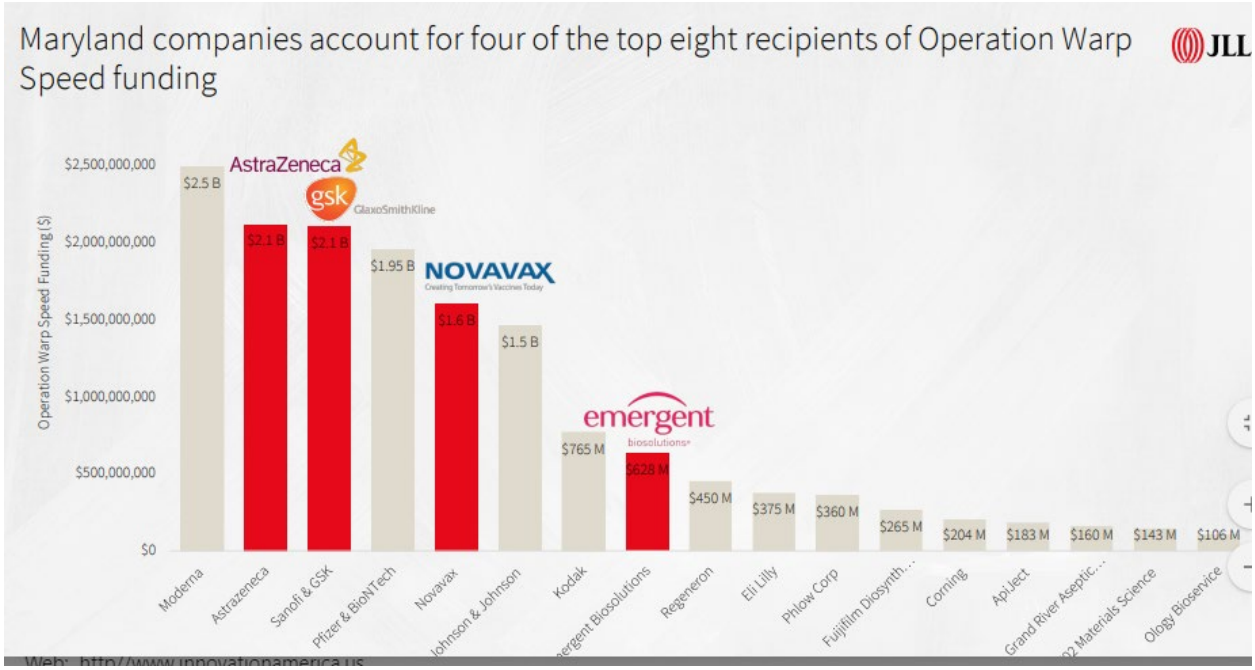
"People and companies are increasingly recognizing the BHCR as a go-to biohealth cluster rather than a drive-through or fly over destination," added Bendis.

THE COVID-19 PANDEMIC IMPACT ON THE BIOHEALTH CAPITAL REGION

While the Pandemic has been devasting to the U.S. and the world, it has had some positive benefits to the BHCR.

The BHCR has been recognized for its unique assets that no other region in the world has, namely the Food and Drug Administration (accelerated approvals), National Institute for Health (research, world-class scientists and funding), NIST, DARPA, BARDA (and its $20 Billion Operation Warp Speed) and the presence of the Director of NIH Institute for Allergies and Infectious Diseases, Dr. Anthony Fauci, who lives in the region.

Astra Zeneca, GSK, Novavax, Emergent BioSolutions, and several other companies have received over $8 billion in funding within the last six months to focus their resources on vaccine, therapeutic and



Source: JLL, Life Sciences in the Mid-Atlantic Region, 2020

diagnostic development as well as vaccine manufacturing. More importantly, several BHCR companies that may have been competitors are now collaborating to fight this dreaded Pandemic. Lastly, the BHCR has become more visible globally due to its importance in addressing this global crisis, as the graph below demonstrates.

CONCLUSION:

The growth of biotech clusters in the United States has been supported by new developments in research and technology supported by scientists working in the private sector, university, and federal labs accompanied by supportive federal, state, and local policies. The COVID-19 Pandemic has shown the incredible speed by which scientists can collaborate with industry and the federal government to create new technologies supporting human health.

Regions can support their bio clusters' growth by taking advantage of existing institutions, aligning talent, technology, leadership, financing options, and creating neutral intermediaries that can bring together regions, regardless of institutional and political jurisdictions. The lessons learned from the BioHealth Capital Region demonstrate that new bio clusters can receive national attention through strategic alignment of existing institutions and creative branding.

With the anticipated successful deployment of a COVID-19 vaccine to the general population in 2021, an 'era of good feelings' for the bioscience industry should result. Without question, new funding for bioscience will likely be available from federal, state, community, foundation, and other resources.

Jurisdictions that take advantage of the biotech revolution through the right leadership and institutional alignment –as the BioHealth Capital Region has done— will be the regions that thrive in the future.

AURP is a global non-profit representing research parks and innovation districts sponsored by universities, federal labs, hospitals, and communities CELEBRATING ITS 35 th ANNIVERSARY IN 2021. The AURP Bio Health Caucus focuses on the unique challenges and opportunities of life science communities of innovation. www.aurp.net

BioHealth Innovation is a public-private partnership serving as an innovation intermediary in the BioHealth Capital Region to advance local technologies, assets, and resources, accelerate innovation and globally connect sectors, industries, communities, and markets. http://www.biohealthinnovation.org/

Article

A Tale in Three Parts: The Success of California's Life Science Clusters

Joe Panetta
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ABSTRACT

With the seventh largest GDP in the world, California has the economic heft of a country. One of the largest drivers of economic growth in California is the life science industry. In fact, it is a cornerstone of California's innovation ecosystem, and is characterized by three distinct geographical clusters. There's San Diego's entrepreneurial energy, Los Angeles' emerging incubators and the Bay Area's unique tech influence. All of these clusters drive growth and distinct opportunities for institutes, universities, businesses and entrepreneurs.

This article focuses on: how did California become a life science powerhouse, and what do each of these regions have to offer to the industry?

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BIOCOM CALIFORNIA: BRIDGE BUILDERS IN THE GOLDEN STATE

Clusters require strong leadership, vision, and an association that moves the industry forward. They require transformative resources, powerful advocacy, access to capital, and essential connections. Biocom California ensures exactly that, accelerating success for life science clusters across the state, providing customized resources and specialized support needed for companies to not only survive – but thrive.

With offices in San Diego, Los Angeles, South San Francisco, Washington, D.C. and Tokyo, Biocom California has built its statewide and global presence to meet the needs of our ever-expanding industry. Biocom California was founded on advocacy, and first and foremost, it is the driving force behind all we do. We speak for the industry in key cities across California, in Sacramento and in Washington, D.C. We work to bring federal research funding to the state, to protect intellectual property that our research institutes and companies create, and better inform public officials about the promise of our industry to Californians.

That said, clusters require more than advocacy work. They need networks. They need connections. So, we build bridges. We create opportunities for like-minded people to connect on issues and topics they care about, whether it's organizing events to connect life science entrepreneurs with venture capitalists, investing in out of the box sources for growing the biotechnology workforce, such as our military veterans-transition program, or curating customized events for Environmental Health and Safety officers. We consider ourselves the leader in creating and activating networks to connect scientists, policymakers, business development executives, CEOs and academics. Together, these components ensure that any cluster – whether it's the size of San Diego or of California – can flourish.

Biocom California represents members of all sizes, from four-person startups to global biopharma companies, so we also help our members on the capital development front. Biocom California connects member companies with venture capital and other sources of funding through programs including angel investing, licensing and partnering opportunities, M&A discussions, research grant insights and one-on-one discussions.

Ensuring the success of any life science cluster also means building connections outside of not only the state, but the country, too. Today, Biocom California has many formal international relationships – including partnerships with organizations in the United Kingdom, France, Australia and Japan. Strategic partnerships with organizations in Asia, Europe and Australia are crucial not only for the global life science ecosystem, but also for California. These partnerships are carefully assessed,

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ensuring that they are always mutually beneficial: we insist on regular interactions, establish a common set of priorities, focus on economic and social good for our countries, and support for public policies and international agreements that lift up the industry and make it competitive. And one last critical element: a clear and passionate focus on the reason that we are all in this business to begin with – the patients. The sole reason our industry exists is to improve human health around the world, and it is these patients who give our work meaning.

GOOD THINGS COME IN THREES

One of Biocom's main missions is focused on communicating the vibrant message of California's life sciences industry, whilst also underlining the individual strengths and opportunities of each geographic hub.

San Francisco Bay Area

The San Francisco Bay Area can be divided into nine micro-clusters, each with differing specializations. It is known as the birthplace of biotechnology, with companies like Genentech serving as the foundation for today's innovation. It's home to world-class universities, including UCSF, UC Berkeley and Stanford, with new discoveries emerging from their research labs every day. While the Bay Area workforce is highly educated and competitive (49.1% have a bachelor's or graduate degree), jobs of all levels are available – even for non-scientists.

According to Biocom California's latest Economic Impact Report databook, the Bay Area's life science industry generated $139.3 billion in economic activity, employed nearly 150,000 people and had an average wage of $172,000 in 2019 alone. The Bay Area is known worldwide for its astonishing creativity and boundary-shattering breakthroughs. The result? A culture of entrepreneurship and innovation, which is evident by its abundant VC firms and the global talent it attracts.

With unrivaled spirit and prosperity, it's no wonder both Silicon Valley and the biotech industry were born in the Bay. The region has become a unique crossover between the tech and life science industries, giving rise to job opportunities at the intersection of both, such as biopharmaceutical manufacturing and medical device development. This intersection has led to the emergence of revolutionary technologies and novel sectors. Take synthetic biology, for example: a burgeoning field addressing long-term sustainability challenges in food, energy and other materials.

San Diego

San Diego has become known for launching some of the best success stories in the life sciences. While the cluster emerged concurrent with the Bay Area's, it has differentiated itself as a leader in cutting-edge technology in genomics, therapeutics and research. As the home of skilled serial entrepreneurs with respected track records, many startups are successfully launched and acquired by larger pharma companies. Take Agouron, a San Diego-based biotech formed in the 1990s that pioneered the first protease-inhibitor drug to treat HIV/AIDS – and was quickly acquired by Pfizer. IDEC pharmaceuticals, the creators of the first monoclonal antibody drug for Non-Hodgkin's lymphoma, experienced similar success after quickly merging with Boston-based Biogen. Today, virtually every large pharma company has some sort of research outpost in San Diego: Eli Lilly, Johnson & Johnson, Merck, and Novartis have footprints in the region, to name just a few.

But San Diego is not just a place for early-stage innovation. In 2019, the industry employed more than 68,000 people with average annual earnings of $130,000, bringing the total economic impact of the region to more than $41 billion. The county is now home to many later-stage commercial entities, including: Dexcom, Nuvasive, Neurocrine, and Acadia Pharmaceuticals, among others.

San Diego is also the worldwide center of the genetic sequencing industry. Illumina is the leading sequencing company in the world, and as a result, has spawned the growth of other regional companies in the analytical, sequencing and personalized medicine arenas.

Los Angeles

The Los Angeles life science industry is significant – and growing by the day. The regional cluster has contributions stemming from a strong academic presence (including California Institute of Technology, University of Southern California, University of California Los Angeles), as well as hospital-focused research institutions such as City of Hope and Cedars-Sinai.

With an increasing number of incubators, accelerators and venture funds scattered across the County, it's quickly becoming a robust ecosystem for scientific innovation – as evidenced by its $44.2 billion economic impact from 2019 and 93,000 employees. It also received the largest amount of new NIH funding of any county in the state last year, a total of more than $1.15 billion in the 2019 fiscal year (also representing 25% of total California NIH awards).

THE LARGEST BIOPHARMA CLUSTER

Broadening our scope once again, I come back to my original question: How did California become a life science powerhouse?

On one hand, the latest generation of new technologies and the convergence of these technologies is a big driver in fueling the state's ecosystem. Big data, artificial intelligence, virtual reality, precision medicine, immuno-oncology, stem cell startups, and digital health all take advantage of the collective power found in these innovative clusters.

Another factor that contributes to successful clusters is the wealth of business and research aptitude. Companies are attracted by the sheer magnitude of talent, funding, relationships, and experience available here. Life science companies in California generate more than $372 billion in annual economic impact, support more than 1.4 million jobs and our organizations received $4.59 billion in funding from the National Institutes of Health – the most of any state.

However, perhaps the most important aspect of California is the spirit of community and collaboration woven throughout each cluster and the state more broadly. This is exactly what Biocom California strives to encourage and exactly the foundation needed to support a successful life science cluster.

Article

Philadelphia And The Delaware Valley: A Geographically Distributed and Expanding Life Science Ecosystem

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Philadelphia has been considered by many to be the birthplace of the modern US pharmaceutical industry with Merck & Co. Inc.'s research division Merck Research Labs [originally called MSDRL] based in West Point and GSK's primary US labs [originally SKF] now based in Collegeville. The City of Philadelphia is also home to two of the oldest medical schools in the US: Perelman School of Medicine at the University of Pennsylvania founded in 1765 and the Sydney Kimmel Medical College [formerly Jefferson Medical College] founded in 1824. The conjunction of those two touch-points along with the other big pharma players, *e.g.*, Johnson & Johnson/Janssen and emerging biotech entities in the wider Delaware Valley region is significant. Also noteworthy is the presence of other research intensive universities such as Drexel University, Temple University, Jefferson University and research institutes such as the Wistar Institute, Fox Chase Cancer Center [associated with Temple University School of Medicine], Lankenau Institute, Monell Chemical Senses Center and the Coriell Institute in Southern New Jersey.

These anchor institutions have led JLL, a commercial real estate, property, and asset management services firm [1] to label Philadelphia as a "New World City". JLL did so as Philadelphia entered the global stage because of its ability to attract young talent and international investors due to its innovative ecosystem fostered by the mix of universities, medical schools, big pharma, and biotech spinouts from local universities. This emerging ecosystem is supported by its ever-expanding skilled talent pool and its increasingly supportive business infrastructure outside of the central business district and recently in the "collar counties" around Philadelphia *e.g.*, Bucks, Chester, Delaware, and Montgomery Counties.

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More importantly there is a depth of mature talent due to the downsizing of big pharma in the Delaware Valley. This downsizing has resulted in a significant number of recently retired or separated scientific and technical staff with extensive experiences especially in the areas of safety toxicology, regulatory affairs, process scale-up, and clinical sciences. Many of the mature members of these pools with deep biopharma knowledge have become the new entrepreneurs of the region in addition to reservoirs of talent start-ups seem more than willing to tap into as a pool of experienced staff and consultants.

JLL in their global map of major cities puts Philadelphia and the Delaware Valley in their Innovators Class with other cities such as Denver, Dublin, Seattle, San Diego, Tel Aviv, Austin, and the Silicon Valley. Cities such as these are usually ranked by their size and gross domestic product, but in the 21st Century such ranking are also influenced by other key metrics such as the talent pool, perceived innovation environment, and the real estate market momentum. One to two years ago, Colliers International felt that the burgeoning field of cell and gene therapy would become a major driver for growth in the region and that its expansion and development would be critical for Philadelphia to become a world class life science cluster (1). In fact, at one point, the marketing catch phrase "Cellicon Valley" was coined to try and capture the emerging spin-offs in the local cell and gene therapy space especially those from CHOP [Children's Hospital of Philadelphia] from where Spark Therapeutics emerged, and recently became part of the Roche "constellation".

A great benchmark to apply towards the success of any research-intensive university-centric ecosystem is their success in attracting National Institutes of Health research grants to support their scientific efforts. Metrics in other research-intensive ecosystems such as dual life science epicenters of Boston/Cambridge, San Francisco

Table 1: Adapted from Colliers International (2).

Institution	2020 YTD	2019	2018	2017	% CHANGE '17->'20
Univ. of Penn	$1,237	$1,200	$1,145	$1,127	9.8%
CHOP	$290	$253	$236	$224	29.5%
Temple Univ.*	$261	$264	$271	$237	10.1%
Jefferson University	$197	$173	$165	$154	27.9%
Drexel University	$119	$99	$106	$102	16.7%
Wistar Institute	$54	$51	$49	$60	-10.0%
Univ. of the Sciences	$4	$2	$2	$2	100.0%
Lankenau Institute	$3	$4	$6	$7	-57.1%
SUM =	$2,165	$2,046	$1,980	$1,913	13.2%

** Includes Fox Chase Cancer Center*

and even San Diego show the relationship between levels of NIH funding at their universities and the continuum of funding that translates into early stage spin-offs and SBIR/STTR funded start-ups founded by university faculty and their students. The NIH has awarded, as noted in Table 1, $2.165 Billion [2020 YTD] in grant funding to the institutions highlighted in this table.

Based upon 2019 full year data, Philadelphia ranks 6th nationally in such funding only behind the Raleigh-Durham area and ahead of the Los Angeles area. The Penn School of Medicine at the University of Pennsylvania, Penn Medicine, Children's Hospital of Philadelphia and the Wistar Institute, part of what Colliers International terms the Philadelphia Institutional Core, alone received over 73% of the NIH grants awarded in 2020 in the Philadelphia cluster. While a trite phrase, Colliers noted that these institutions are the engine that in 2020 stimulates an emerging future pipeline of new cutting-edge start-ups in cell and gene therapy, medtech and novel small molecules design and development. Spin-off start-ups such as Spark from CHOP, doctoral student conceived start-up like Invisible Sentinel [recently acquired by BIoMerieux] or well established CDMOs such as WuXi Biologics represent the future direction for the urban-based life science ecosystem.

Recently, new purpose-built lab facilities are being developed near the Science Center on Market Street by University Place Associates with the Wistar Institute and the Benjamin Franklin Technology Partners as anchor tenants speaks to the importance of "place" in the continuing growth of this urban life science ecosystem though neighborhoods are scattered. Recognizing the possibilities of this urban life science cluster, a new 1.5 million square foot life sciences development will be emerging in the years ahead just east of the University Science Center at the doorstep of Drexel University and marketed as Schuylkill Yards. This will further validate the decision of Roche/Spark to further develop their presence in this new neighborhood in downtown Philadelphia near the institutional research core of the city and its deep pool of talent.

Indeed, Philadelphia has an interesting history in the development of big biopharma and the beginnings of an ever-expanding life science's presence in downtown Philadelphia west of the central business district. One critical area that needs expansion is in funding for start-ups. Significant funding is needed to go beyond what has been termed the 5 F's of funding:

- Founders – Equity stakes
- Family – Loans, Equity, or both
- Friends – Loans, Equity, or both
- Feds – RO1 Grants, SBIR/STTR awards
- Fools – Probably Angels for equity

It is that the final source of funding as represented by Fools which many consider to be represented by Angel funding organizations that is still a bit lacking in the Delaware Valley, especially in Philadelphia proper. There are some firms based in Philadelphia such as Broad Street Angels, Gabriel Investments, Keiretsu Forum Mid-Atlantic Angel Group and Robin Hood Ventures. One local educational institution, the University of Pennsylvania, also started their own angel fund for faculty just a few years ago with an initial $50 million investment. In addition, the University of Pennsylvania renovated the former DuPont Labs near Gray's Ferry south of the city's institutional core and created a 62,000-square foot incubator space called Pennovation and used by faculty and non-university associated entrepreneurs but managed by an outside organization. They have plans in the works to expand the footprint of the existing site.

But the real money in that continuum of funding comes from venture capital or VCs. While they expect a greater ROI and a higher multiple on their return than Angels, plus having a longer horizon than angels for that payback, they too are not that well represented in the immediate Philadelphia ecosystem. One funding opportunity not frequently thought about is corporate venture capital. It was represented in the Delaware Valley by SR-One which was associated with GSK. However, recently GSK has spun them off as separate entity with offices now, not just Philadelphia but London and San Francisco. They have completed their first fund with $500 million and while GSK still is engaged, SR-One is a standalone VC at this stage. Other big pharma firms have VC groups such as the J and J Foundation and the Merck Foundation, but they are not domiciled locally. Closer to home however are the VCs that have grown up in the region either as privately funded operations from partnerships or from Commonwealth-backed funds. The major player in Philadelphia is the Benjamin Franklin Technology Partners [BFTP] with Commonwealth-back seed funds. They have invested in over 350 companies between 2010 and 2019. The next most active VC investor in the region is BioAdvance followed by Robin Hood Ventures and Osage Venture Partners. Funding for BioAdvance was allocated from the Pennsylvania's tobacco industry settlement.

Like its venture funding-base, due to its geography and infrastructure, the urban Philadelphia and the Delaware Valley have been and is still to some extent a decentralized real estate development market for start-ups and established life science entities looking to expand or establish a new base of operations. Basically, it is a region of submarkets and even fractionation of those submarkets [Ranked by size] (1):

- Philadelphia
  - Upper Market Street [University Place]
  - Lower Market Street [University Science Center, Century Therapeutics, Roche/Spark]
  - Lower Schuylkill [Pennovation Works]
  - Institutional Core [Wistar Institute, Penn Medicine, CHOP, Penn School of Medicine]
  - Navy Yard [WuXi, AdaptImmune, Iovance]

- Interstate-476 NE Corridor
- Route 202 Corridor
  - Merck & Co, Inc. [MSD, MRL, MMD]
  - Pennsylvania Biotech Center in Doylestown
  - The Spring House Innovation Center [Former Dow Chemical/Rohm & Haas site]
  - The Discovery Labs in Upper Merion [Former GSK West Campus]
  - Pfizer
  - WuXi Biologics

- PA Turnpike Corridor
  - Johnson & Johnson

- Route 422 Corridor
- Interstate-95 South
- Lehigh Valley [OraSure Technologies]
- Southern New Jersey
  - Coriell Institute

The above list of scattered "neighborhoods", all supporting life science enterprises to one degree or another is both a strength and weakness of the region and is a follow-on to JLL's concept of satellite real estate markets developing. These satellite markets develop as urban epicenters become too expensive and too crowded for early stage firms and even more established entities to partake of the urban ecosystems. The University Science Center and facilities being developed by University Place Associates as noted previously speaks to the importance of place in the continuing growth of this urban though scattered Philadelphia neighborhoods: Neighborhoods chosen for expansion and *de novo* development. However, as with any new establishment focused on entrepreneurs, it will take a while to firmly create the "buzz" that entrepreneurs desire in any new ecosystem and convince them that life and operations in a major city have the advantages they seek. Those senses of buzz are hard to create however, when the ecosystem resides in high rise multitenant or even mid-rise buildings separated by concrete and major roads.

While indeed Philadelphia has tried and succeeded in many instances to attract capital investment by suspending taxes using Keystone Opportunity Zones to attract other commercial ventures. We noted above a move to downtown Philadelphia such as FMC, and there are still issues. More than 20 years ago, far sighted Philadelphia officials looked at the 7.5 million square feet of space occupied by the US Navy at the foot of Broad Street and had visions of a business center that would house mixed use retail, private firms and with the aid of far-sighted firms such as Liberty Property Trust, be developed into a life science neighborhood. Indeed, one of the first tenants as WuXi Biologics in 2003: A firm that has expanded with the addition of three additional labs and buildings for a significant CDMO manufacturing site that now employees over 600 scientists and technicians in their four buildings in

the Navy Yard. Fast forward to the present and other firms planted their flags there such as GSK with their US corporate headquarters, AdaptImmune, Benjamin Franklin Technology Partners, RevZilla and Azalta. The site is now about 95% fully leased and has grown so much that the Navy wants 23 acres back to add to the 200 acres they currently use.

One observation though of recent tenants that have left the Navy Yard is that it is so large that some of the corporate employers may actually be crowding out the start-ups and life science firms that they originally hoped to attract to the site. One former tenant felt that because the site had become so crowded it had really lost its sense of buzz and place that start-ups thrive on [3][4] That tenant's decision was to move from the city to an expanding site in Montgomery County. The site, the Spring House Innovation Park [SHIP], is a repurposing by MRA Group of an abandoned Dow/Rohm & Haas site occupied now by some start-ups, established firms and a bio manufacturing training facility operated by Thomas Jefferson University as part of their academic programs.

As attractive as Philadelphia might be as an urban life sciences hub as noted above, Philadelphia has its weaknesses that have impacted the site choices of some start-ups and expansion plans for established firms. With rapid expansion of sites such as the Navy Yard, a lack of supportive infrastructure as become an issue. Components such as public transportation, quality of life issues, affordable housing and the state of the public schools are key factors. They have impacted siting and desirability of place as decisions many potential hires approach as barriers to entry before making the decision of moving to distributed urban life science clusters in a big city. Competing against Boston casts Philadelphia as not quite serious about being that world class city as projected by JLL. As noted by Joseph Distefano in a recent article in the Philadelphia Inquirer, the city is more interested in a progressive image rather than being a place where firms wish to set-up shop or employ talent that might otherwise go to the life science competition in Boston/Cambridge, San Francisco Bay area or even San Diego [4].

One important consideration for a start-up or even the expansion of an existing enterprise is in that comparison to Boston. It has been noted that Boston has no wage tax. Philadelphia has a wage tax that is levied not only on urban employees who live in the city but at a slightly reduced rate on suburban employees that commute and work in the city. The City also has a business-receipt tax. That makes for an interesting calculus, since for now not only does a start-up have to factor in rent, but differential insurance rates (urban *vs.* suburban), available parking, staff commuting costs and where their potential workforce live but the burden of operational taxes on their firms and their employees. One also must never forget that every recruit is a spousal recruit and that must be considered in a firm's recruiting strategy.

If one looks at that calculus problem, it appears to be addressed recently by firms trying to balance the advantages of being near that intellectual core of the City with the financial advantages of more space and lower operating costs. Even Roche/Spark Therapeutics with their significant ties to CHOP made the interesting decision recently to buy a lab campus for their R&D Center in Glenolden in Delaware County. From an historical standpoint Glenolden, PA is also geographically interesting as the place where Sharp & Dohme had their original labs prior to their merger with Merck & Co. and their move to West Point, PA. More importantly, WuXi Biologics, as successful as they have been in expanding their manufacturing and employee base since 2003 in the Navy Yard complex, has made the strategic decision to expand not in the city but at the repurposed GSK West Campus site now rebranded as the Discovery Labs: 1,000,000 square feet of space gradually being renovated and redeveloped for small and big companies especially in the cell and gene therapy CDMO space. A major selling point for the site is accessibility to major highways, affordable housing, and quality of life issues.

In this era of Covid-19 with is impact on safety, health, and social distancing, established firms and start-up entities are reassessing the proposition of place in their decision-making process. Cities such as Philadelphia are and will remain epicenters for business and especially innovation due to the proximity of the central business district to the intellectual core of the city. Philadelphia however needs to realize its distributed urban life science clusters must experience a transformation for the 21st Century. This transformation is necessary for it to continue to be relevant as a life science epicenter and realize as noted by JLL [1] there is no reversal of the urbanization process: Only new cycles the city can take advantage of will encourage transformation, innovation on all levels and firmly establish a degree of resilience the city and its surrounding counties in the Delaware Valley can take advantage of to improve their competitive advantage and status. It cannot however ignore the revitalization being experienced by its surrounding collar suburbs and their desire to make themselves even more attractive as a place for the expansion of established firms and as a place for start-ups to find their niche and establish themselves in satellite ecosystems. Places that also hope to replicate that vibe and buzz once only reserved for civic centers. What the area cannot forget is that it is not just the City but the entire Delaware Valley region that will now and, in the future, be the

attractant for its growth as a world-class life science hub. The City must figure out a way to balance that growth and attractiveness while at the same time being the engine that drives life science innovation from its enviable intellectual base [5][6].

REFERENCES

1. "Demand and Disruption in Global Cities: JLL and the Business of Cities", 2019.
2. "Converging for Cures: Philadelphia Life Science Market Report". Colliers International 2020.
3. Joseph N. Distefano, "Shift at the Navy Yard", 8 November 2020, *Philadelphia Inquirer*, Pp. H1,H4.
4. Joseph N. Distefano, "Good intentions won't help Phila. Grow",15 November 2020, *Philadelphia Inquirer*, Pp. H1,H2.
5. "Greater Philadelphia's Life Sciences Market" Newmark Knight Frank, September 2019.
6. "Leading Life Science Clusters: The Bio-Boom Intensifies" U.S. Life Sciences Research 2020, CBRE Research.

Article

Transforming Pittsburgh's Economic Ecosystem and Clusters

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INTRODUCTION

The Pittsburgh region's recovery and transformation from an economy dominated by heavy industry to a balanced and diversified economy throughout the region has been documented by many publications during the past decade. Pittsburgh is rightfully viewed as a model for post-industrial transformation and is positioned to provide sustainable careers and a high standard of living for its people. This article will not attempt to tell that broad economic recovery story again, but instead will focus on one important aspect of the story: the rise of Life Sciences/Biotech as one of the key clusters driving the Pittsburgh story. I had the privilege of being at the table for much of the planning and execution that went into the development of this cluster. In this article, I hope to provide a unique view of the key elements of the plan for Life Sciences in the Pittsburgh Region. From my perspective, there were five key elements to the regional strategy that supported the results achieved over the past 20 years. They include: Analysis and Planning, a Targeted local Cluster Development Initiative, Public Policy and Program support from the State, a unique collaboration between the two premier research and educational institutions in the region, and the cooperation and support of existing local economic development organizations. This article will explore each of these five areas and concludes that together they provided a unique and effective strategy for targeted cluster development, and broad-based leadership.

ANALYSIS, PLANNING AND TARGETS

In the early 90s, as it was becoming increasingly apparent that the traditional industries in Pittsburgh would not be able to sustain the region, regional leaders facilitated by the Allegheny Conference began an analysis and targeting initiative. To bring a fresh set of eyes to the problem, Michael Porter and his team from the Harvard Business School were engaged to help with the process. Literally hundreds of leaders from business, academia, philanthropy and government were engaged in a process of analyzing the relative strengths and weaknesses of various segments of the Pittsburgh economy. That analysis was coupled with data on what growth opportunities presented themselves. The result was an identification of five clusters comprising a combination of regional strengths relative to national averages and potential growth opportunities. These clusters included three traditional sectors of the Pittsburgh economy and two potentially new ones. The traditional ones were *advanced manufacturing, energy and financial services*. The two new ones were tech-based and included *information technology and the life sciences/biotech sectors.* The latter two being driven by the large and growing research base occurring at the University of Pittsburgh/UPMC, and Carnegie Mellon University among others.

This planning and targeting initiative led to the development of regional programs, including a group referred to as the Working Together Consortium and the launch of a regional life sciences/biotech cluster initiative which became known as the Pittsburgh Life Sciences Greenhouse.

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PITTSBURGH LIFE SCIENCES GREENHOUSE

In the late 90s, regional leaders came together to work on the development of a regional Life Sciences/ Biotech cluster. Battelle Labs out of Columbus, OH was engaged to do the data analysis and gather input from all the regional stakeholders. The report that came from these efforts concluded that a new regional organization was needed to be the catalyst for the life sciences cluster. At the same time, then Governor Ridge was proposing a unique way to use funding from the national Tobacco Settlement to kick start economic activity in the Life Sciences across the state. Based on the success of the Pittsburgh Digital Greenhouse (PDG) model (a prior cluster development initiative focusing on electronics and robotics), Governor Ridge proposed the creation of three Life Sciences Greenhouses in Philadelphia, Hershey and Pittsburgh using a model similar to the PDG. As a result, the Pittsburgh Life Sciences Greenhouse was created in 2001 to drive the development of the cluster.

The operational plan called for a small, experienced and multi skilled team to build out and execute the plan. This Initial team totaled 10 people and eventually was supplemented with several Executives in Residence to provide leadership, industry related expertise and connections.

Initial funding came from the state in the form of a $33 million commitment to the Pittsburgh Life Sciences Greenhouse. Greenhouse staff, with support from the newly created board, raised additional funds bringing the total funding to $100 million to support the first five years of operations. The bulk of the additional funding came from regional foundations. The Greenhouse business plan called for the development of technology and commercialization in the fields of therapeutics, medical devices, Bio tools, diagnostics and Heath care IT. The overall intent was to accelerate technology commercialization with support for seed and early stage companies, connect those companies to investors and to relocate Life Sciences companies from outside the region. The plan also called for significant funding to go to the universities to enhance our research and translational development capabilities, including packages that would allow the universities to attract additional world-class research faculty to the region. An advisory committee was formed to evaluate proposals and select the ones that best matched promising research with market opportunities and capital thus increasingly the likelihood of commercialization. Funding would also be used to support technology transfer from the universities, including wet labs during the early incubation stages. In addition, early stage funding would be available to translate university research into commercial technology along with pre-seed and seed funds. The plan included a novel Executive in Residence program that would utilize experienced life science executives who were in between assignments to work with the early stage companies to assist them in business planning, fundraising, milestones management etc. Finally, a networking community would be developed to regularly communicate with all involved parties and to provide sharing of best practices across the cluster.

In addition to this targeted regional support, the state provided additional support through two major statewide initiatives. The first was as mentioned before, Governor Ridge proposed (and got approved) a unique use of tobacco settlement funding focused on development of the life sciences industry across the state. In addition to the afore mentioned hundred million dollars allocated for the three greenhouses across the state, $60 million was set aside for venture capital investments in the life sciences and over $20 million a year was set aside to invest in expanding research capabilities at the universities. In 2003, after Governor Rendell's election, he proposed a massive stimulus package designed to jumpstart the state's economy, including significant investments in tech-based economic development. Some of the programs that were eventually approved by the state legislature included an additional $310 million in venture capital investments, a geographically targeted keystone innovation zone program that would establish physical zones adjacent to the universities and special tax credits for companies that established operations there, additional faculty start up attraction package money was also made available and finally a tradable research and development tax credit was implemented. Taken together the state and regional investments that were being made in the development of the Pittsburgh cluster were likely the most significant anywhere in the country.

UNIVERSITY OF PITTSBURGH/ CARNEGIE MELLON UNIVERSITY COLLABORATION

One of the hallmarks of Pittsburgh's overall recovery from the loss of its traditional industrial base, is the collaboration model it uses to address major public policy issues. This began with the advent of the Allegheny Conference, which is still viewed and studied all over the world as a unique model for regional cooperation among businesses, academia, philanthropy and government. This model of cooperation was exemplified once again by a unique collaboration between the leaders and staff of Pitt and CMU.

Part of the basis of this close working relationship in the Life Sciences arena is the natural overlap of research and expertise at the two institutions. The simplest way to explain this is Pitt has deep capabilities in the Bio world and CMUs depth is in the Digital world. The combination of the two brings unique solutions to modern life sciences treatments and patient care. One of the examples of this close working relationship, is the fact that Pitt Chancellor Mark Nordenberg and CMU President Jerry Cohen agreed to co-chair the board of the PLSG. Sharing responsibilities, they led the development of the business plan which was adopted by the board and carried out by staff. Their example also attracted other key leaders from the region to participate, providing the PLSG with a world class set of directors which enhanced the success of the organization. Because of the personal example they set, the message was clear to the research teams, tech transfer organizations and others at their respective institutions that working together to develop this key sector of the region's economy was critically important.

In furtherance of their commitment to working together, an office of strategic economic development was created that reported jointly to Mark and Jerry. During this period, the research base continued to grow and the intensity around tech transfer increased. This stimulus for startup formation, plus the work the PLSG was doing resulted in an increase of startup activity from 2-3 new companies (NewCo's) per year in the Life Sciences to 20-30 achieving, one of the key objectives for the formation of the PLSG.

LOCAL PARTNERS

One of the goals of the PLSG was to create a community of stakeholders in the development of the Life Sciences Cluster in the Pittsburgh region. This need was addressed multiple ways. The first was by partnering with other complementary economic development organizations in the region. The Allegheny Conference and it's marketing arm, the Pittsburgh Regional Alliance were partners from the start. The ACCD was actively involved in the initiation of the PLSG and continued their involvement post opening. They assigned one of their board members to sit on the board of the PLSG to maintain close coordination between the two organization's agendas. In addition, the PRA, whose task is business attraction and retention in the region, works with the PLSG on company attraction activity. Today the greenhouse activities have generated over a dozen existing life science companies moving to the Pittsburgh region to establish operations because of the ongoing momentum being built in the cluster. The second area where cooperation has been ongoing is with other early stage funding organizations in the region. Innovation Works has been a close partner with the PLSG combining their early-stage investment funds with the PLSG's to bring greater depth of funding coverage to promising companies and technologies. In addition, the needs of individual companies can be matched up with local venture capital firms or angel investors, a syndication process that the PLSG executive in residences coordinate. Finally, there has been an ongoing effort to connect with and keep all key stakeholders updated on the goals, progress and issues surrounding the greenhouse mission. This includes regular individual and group interactions with key stakeholders in the research community, healthcare, philanthropy, business and government. This broad attempt to bring together all of the stakeholders allows for ongoing input to the PLSG Staff, including how to improve its execution and how to connect appropriate stakeholders where collaboration will have a benefit. This natural inclination in the Pittsburgh region to work together has been in the DNA of Pittsburgh leadership since the early 1940s and continues to show its benefits in initiatives like the Pittsburgh Life Science Greenhouse.

EARLY STAGE INVESTING

One of the mayor issues highlighted by the Battelle report was the lack of early and growth stage capital available in the region to support fledgling life sciences companies. When the PLSG was formed, Innovation Works (a state sponsored early stage tech investor) was the primary source of these funds and historically has been oversubscribed. A few institutional venture capital firms also were based in Pittsburgh, but the level of investing was not enough to address the growing start up activity. The state's investments in venture capital via the Tobacco settlement and Governor Rendell's stimulus provided a jumpstart and, with private matching money, moved the region forward during the 2000s. UPMC Enterprises, a division of the world class University of Pittsburgh Medical Center was formed to commercialize and invest in promising technologies and has had a positive impact in the region. Unfortunately, in spite of the state's stimulus efforts the region still faces a dearth of venture capital. It is currently estimated that we are receiving only 10% of the venture investing expected based on the level of research activity in the region. And while it is fair to say that the available capital has improved since 2000, it is still the most frequent critique mentioned regarding the development of the cluster and thus is an ongoing issue.

FINAL THOUGHTS

It was not my intent to do an exhaustive data-driven analysis about whether the PLSG achieved its objectives. That is a subject for another article. However, I do have some summary observations I would like to make. My perspective comes from having been the founding CEO of the PLSG, then the Secretary for Community and Economic Development for the Commonwealth of Pennsylvania during the time the state made its stimulus investments in the Life Sciences industry. Finally, I am the retired CEO of the Allegheny Conference, a key partner with the PLSG throughout its history. Overall, I think there is no doubt that the cluster is larger and stronger than it was in 2001. The research base has grown significantly since that time and hundreds of new products have been developed and put into the market that originated from local life sciences research. The rate of startup activity is an order of magnitude larger than 20 years ago and thus the business side of the cluster is larger and more robust. New and exciting complementary organizations now exist including LIFEX that will continue to help drive the growth of the cluster. How much of this can be attributed to the PLSG is debatable, but there is no doubt that the Pittsburgh Region Life Sciences Cluster is better than it was when the PLSG was formed in 2001.

Article

Australian Biotechnology: Promissory Expectations And Ecosystem Performance Far From The Global Superclusters

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ABSTRACT

Australia is an interesting case study of biotechnology ecosystem development. Despite its distance from the US biotechnology superclusters, the country has had high expectations for its potential development into a biotechnology superpower. These expectations have not been met over the last two decades. Despite generous R&D tax incentives and a robust network of public research organizations (PROs), the local biotechnology industry has remained small and weak, without a single 'big biotech' emerging. Cluster analysis over 11 years of all private and public DBFs indicated that the PRO network output failed to translate to the development by the local biotech industry of drug candidates that could attract Big Pharma deals. Analysis of the investor returns over 15 years from all public drug development biotech firms (DDBs) showed that not a single firm produced attractive long-term investor returns and the sector overall generated negative returns for investors. Despite high promissory expectations, favorable government policies and an inflated view of the quality of the country's science output, Australia has failed to create a sustainable biotechnology ecosystem. Some of the reasons are identified and suggestions are offered for changes in government policy that could improve value creation by the local biotech sector.

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INTRODUCTION

Governments worldwide have embraced the idea of biotechnology clusters as essential to building ecosystems with the critical mass needed to foster a robust bioeconomy. The US biotechnology sector is the exemplar of a successful bioeconomy, where the so-called 'superclusters' in the Boston area and San Francisco areas have been central to building critical mass and driving the remarkable growth of the US biotech sector.

In seeking to emulate the US success, other countries have embraced the idea of clusters as a key to building critical mass and creating a sustainable ecosystem. Australia is no exception: In 2001, the Australian Federal Government launched an 'innovation action plan for the future', highlighting biotechnology as a key opportunity area, because of the country's alleged prowess in the life sciences.[1,2]

The optimism was high, as echoed in a *New Scientist* article in 2002: "Once upon a time, Australia was the Cinderella of the commercial biotech world. But now the continent is set to blossom as the belle of the ball."[3] These aspirations were cheered on by the national industry body, AusBiotech, which over the last two decades has consistently proclaimed Australia's international biotechnology leadership, often referring to Australia's disproportionately large number of public biotech firms and the country's high ranking in the *Scientific American* "Worldview Biotechnology Scorecard".[4]

This paper examines whether the promissory expectations for the Australian biotechnology ecosystem have been realized over the last 20 years. It highlights recent studies that have sought to objectively measure the performance of the sector and empirically assesses the efficacy of the government policies and corporate strategies

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aimed at building a successful biotechnology ecosystem in Australia.

PROMISSORY EXPECTATIONS

There is no doubt that the expectations for an Australian biotechnology industry have been high.[5] Since the early 2000s, the rhetoric has been universally celebratory and unrelenting, especially from AusBiotech. The AusBiotech website homepage states[i]:

> *Biotechnology is widely recognised as a "game-changer" and foundation stone of our future. It is anticipated that biotechnology will underpin our economy and provide solutions to disease, climate change, fuel alternatives and food security – in addition to improving our quality of life.*

In a 2016 article, titled 'Australian biotechnology packs a powerful punch',[6] AusBiotech reported that: "Australia is a world-leading location for biotechnology, boasting the largest listed biotechnology sector as a proportion of GDP in the world. It has one of the largest and fastest-growing public markets for biotechnology and yields some of the greatest public revenues across the globe." A 2017 *Industry Position Survey* by AusBiotech[7] stated: "Australia currently has around 100 ASX-listed life sciences companies, with a market capitalisation of $93.74 billion." The consistent message has been that Australia has been successful in creating a vibrant biotechnology ecosystem. Another consistent message from AusBiotech and some State governments has been that Australia is a world biotechnology leader, based on its high ranking in the *Scientific American* "Worldview Scorecard".[4]

From 2009 to 2016, *Scientific American* published its annual Worldview Scorecard of the global biotechnology industry. The 2016 Worldview Scorecard measured the comparative performance of 54 countries with respect to biotechnology activity, based on 27 metrics around: Productivity, Intellectual Property Protection, Intensity, Enterprise Support, Education/Workforce, Foundations, and Policy & Stability. Over the years, the Worldview Scorecard has been cited by governments and industry bodies to promote their biotechnology prowess on the world stage, the attractiveness of their country as a home for biotechnology firms, and the potential for partnering their biotechnology outputs. Australia has been particularly active in this regard[4,8,9]. The Worldview Scorecard has also been used as input to public policy [10,11].

A number of the metrics for the scorecard were derived from public biotechnology company data published each year in *Nature Biotechnology* (NBT). For a number of years, at least until 2016, the NBT datasets included the revenue, market cap and employment numbers for the Australian pharmaceutical firm, CSL. As noted in a recent study and as long recognized by most CEOs in the local biotech sector, CSL is a century-old and previously government-owned pharmaceutical manufacturing business that has low R&D intensity and was never a biotech firm[12]. However, with 2015 revenues of $5.5 billion, a market cap of $36 billion and 14,000 employees, its inclusion in the NBT dataset served to dramatically inflate the numbers for Australia's biotechnology performance and elevate its ranking on the Worldview Scorecard.

From 2016, after a critical review by NBT of their inclusion criteria, CSL was removed from the NBT dataset (along with several other large firms incorrectly classified as biotech firms), reducing Australia's reported 'biotechnology revenues' from $5.7 billion in 2015 to $0.4 billion in 2016, and biotechnology market valuation from $37.8 billion to $2.8 billion. Nevertheless, the historical 'top five' ranking of Australia on the Worldview Scorecard continues to be promoted by AusBiotech[ii] and in news articles about Australian biotechnology.[13]

COLLABORATIONS, CLUSTERS AND NETWORKS

A study in 2008[14] focused on Australia's networks and clusters and questioned whether clusters far from the world superclusters are viable, noting they "are little more than the combination of research institutions and spinout biotechnology firms…[and] there is good reason to question whether the ambitions of regional governments are realistic." In Australia's case, the study identified the 'tyranny of distance' as a major obstacle to the development of the Australian biotechnology ecosystem. It concluded: "regional governments face an immense challenge in creating viable biotechnology clusters far from the world hubs."

A 2010 study[15] compared the clusters in Australia's three largest cities – Melbourne, Sydney and Brisbane – with San Diego, and concluded that the Australian cities lacked many of the features needed for a US-standard biotechnology ecosystem. Specifically, Australian cities suffer from inadequate investment intensity, support a relatively shallow research portfolio, and generate

i <https://www.ausbiotech.org/biotechnology-industry/biotech-is-a-game-changer> accessed October 21, 2020

ii <https://www.ausbiotech.org/biotechnology-industry/fast-facts> accessed October 22, 2020

research outputs of low average quality and low commercial significance.

The most extensive and robust study of Australian biotechnology clusters and networks was only recently completed and published.[16] The design of the study drew heavily upon the landmark research by Powell and colleagues in the US, which mapped the trajectories of US biotech firms, clusters and networks from 1988 to 2002[17-20]. The Australian project similarly mapped the development of all Australian biotechnology firms (public and private), as well as cluster and network formation from 2003 to 2014; 2003 was used as the baseline year because in that year Australian DBFs (dedicated biotechnology firms) overall were approximately the same age, size and scale as the DBFs in the US superclusters in 1988[16]. Like the US study, DBFs were defined as 'independently operated, profit-seeking entities involved in human therapeutic and diagnostic applications of biotechnology' in line with the definitions applied by Powell and colleagues.[17]

The study identified the three critical challenges for biotechnology firms as: access to new knowledge and intellectual property, early-stage fund-raising for the timely development of a viable product, and commercial efforts aimed at bringing a product to market. In the US, firms pursue 'multiconnectivity' to meet these challenges.[17] The Australian study sought to assess the degree to which such mutliconnectivity occurred in Australia and its efficacy in meeting all three challenges. It employed descriptive analyses and data visualizations, as well as statistical modelling. For statistical modelling, the study used three dependent variables, each aligned with these three challenges.

In relation to new knowledge and acquiring a science base, the study used the *number of patent applications* in a given year as a proxy for DBF inventive productivity. While patent applications do not necessarily reflect product development output or commercialization, they are a useful indicator of new knowledge creation.[21] With regard to early-stage fund-raising, whether or not a DBF was able to forge a *risk capital deal* was used as a dependent variable. This was coded as 1 for each year that a DBF secured a deal with a financial partner (or listed on ASX). Finally, with respect to commercialization, *deals with Big Pharma* (in a given year), was used as the dependent variable.

The results showed that collaborations between DBFs and PROs underpinned Australian clusters and domestic networks throughout the period. Indeed, PROs appeared to produce more connectivity in Australian clusters during the period than was the case in the US superclusters during the 1990s[22]. It appeared that the regional science base in Australia generated positive network effects consistent with the experience of the world superclusters and consistent with the opportunity to create the 'virtuous cycle' needed to support a viable biotechnology ecosystem.

In relation to the second challenge, the results showed that provision of early-stage funding for DBFs in Australia was dominated by domestic partnerships with financial entities. These included government funding, such as the Innovation Investment Fund and grants through the federal agency, AusIndustry. The results indicated that ties with Australian PROs, domestic DBF collaborations and financial collaborations positively influenced early-stage funding and thereby confirmed the potential for PROs to be anchor tenants for Australian biotechnology, extending beyond knowledge creation to early-stage funding. In summary, it appeared that the collaboration networks helped Australian DBFs in meeting the second challenge of accessing early-stage funding for development of a viable product. However, it was in the third step – commercialization – that the process came to a dead end.

For the final challenge of commercialization, the focus of the study shifted from domestic to international collaborations, mainly because of the absence of multinational pharmaceutical companies in Australia, apart from CSL. Descriptive and visual analyses showed that as DBFs became more mature, not unexpectedly, they formed relatively more international collaborations, but unlike domestic collaborations, they were thinly spread and gave rise to sparse networks and very few Big Pharma deals. Overall, the local collaborations and networks failed to translate into international network effects necessary for partnering and commercialization.

In summary, Australian PROs served as anchor tenants in meeting the first two challenges. However, in not facilitating the third, they failed as anchor tenants for the development of an effective biotechnology ecosystem in Australia. This finding was consistent with other studies that highlighted the limitations of PROs as anchor tenants.[23,24] As noted by the authors (p. 14):

> *The challenge of securing deals with Big Pharma can partly be understood in terms of the 'tyranny of distance' (Gilding, 2008), but it is much more than this. It requires attention to institutions, facilities and practices that mitigate geographic distance, extending the reach of local and domestic organizations and their absorptive capacity. This might include local observatories (as found in the superclusters), international exchange programs between PROs and Big Pharma (designed to make PROs more robust anchor tenants), or incentive schemes for more mature DBFs to forge collaborations with start-ups (following the example of the superclusters).*

They noted that the public investment, bipartisanship and patience needed to nurture such initiatives were inconsistent with the partisan Australian industry policy climate, short election cycle times and the government's narrow understanding of market failure. The authors concluded[16] (p. 14):

> *In conclusion, our analysis suggests that advocates of the innovation economy – politicians, policymakers, scientists and industry players – have overstated their case for biotechnology as a prospective industry for countries far from the world biotechnology superclusters and Big Pharma. In close connection, the literature on 'territorial knowledge dynamics' is excessively optimistic about the prospects of navigating distant collaborations and combinatorial knowledge across 'multi-location milieu' (Butzin and Widmaier, 2016; Crevoisier and Jeannerat, 2009). Distant collaborations cannot seamlessly substitute for local deficits. Regional public research organizations struggle to catalyze collaborations with diverse partners across the entire value chain. Strategies to build absorptive capacity and embed distant capabilities are poorly understood. Collaborations do not automatically translate into virtuous cycles, and may become dead ends. The ambitions of regional policymakers and industry players have been mostly disappointed. We need a better understanding of network failure in order to fashion new industries far from the world advanced-technology hubs.*

INVESTOR PERFORMANCE

Another recent study examined the effectiveness of the Australian biotechnology ecosystem from the perspective of investor performance over a 15-year period.[12] The study focused on public biotech firms and specifically those involved with drug development, which is by far the dominant application and the historical standard bearer of biotechnology. To distinguish these firms from DBFs, which includes diagnostics firms, the term 'DDB' or drug development biotech was deployed. This term was preferred over 'biopharma', because the latter is a broader term that has been used to embrace large pharmaceutical firms as well as biotech firms, as in the 'biopharma industry'.[25-27] Also 'biopharma' has led to confusion with the term 'biopharmaceutical', which is restricted to biologic drugs that are the product of bioprocessing[28].

According to the study, outside the US, almost all DDBs remain as pre-commercial entities that are consistently loss-making and reliant on ongoing investor funding. Investors invest in these firms for the capital value growth arising from changes in the perceived value of the DDB's pipeline as it progresses candidate drugs towards a pharmaceutical license or sale. In the absence of cash flow from operating profitability, a DDB will not be able to progress its R&D pipeline or even survive without ongoing investor support. This makes investors crucial stakeholders and gives them a substantial 'captaincy' role in firm birth and survival. Therefore, the delivery of long-term investor returns is a relevant measure of the performance of individual DDB firms and crucially important to the health and sustainability of a country's biotech sector, for which the DDB sector is a proxy[12,29].

For public DDB firms, especially in Australia, maintaining investor confidence and securing regular ongoing funding is crucial to building value and survival. In turn, growth in the value of a DDB's share price is crucial to investor confidence. Accordingly, the research sought to answer the question: Do Australian public DDB firms deliver attractive investor returns, consistent with building a robust biotechnology ecosystem that is adequately supported by investors?

The study[12] focused on all 40 public DDB firms that existed (and had a minimum of five years' operation) in Australia from 2003 through 2018. As a principal performance metric, it measured overall sector investor return by treating the portfolio of 40 firms as if it were a venture capital (VC) portfolio and calculated the gross pooled internal rate of return (IRR) over the 15 years.

In addition to overall sector IRR, the study measured the performance of individual firms using a similar IRR calculation, which was equivalent to annualized share price growth. Apart from investor performance, it also collected data on the average levels of cash held by firms and their R&D expenditure (RDE) to assess whether these variables had any predictive value with respect to investor performance for individual firms.

The results showed that the overall sector returns were abysmal: The portfolio lost 51% of the invested principal over the period, representing a sector IRR (annualized loss) of – 6.2%. The individual firm results were equally disappointing: Only nine firms (22.5%) produced a positive investor return over the period, but the highest return was only 8.5%, which was well below investor expected returns for this high-risk sector. The more telling result was that 31 firms (77.5%) produced negative average annual returns, with the vast majority losing more than 80% of their investors' principal over the period[12].

The study also examined whether the results were an artifact of an unusually negative terminal year for the final return calculation, but the opposite was the case: 2018 proved to be a year of modest positive value growth for the sector and choosing any other recent ear for the

Table 1. NBT 2017 data for global biotech industry

Country	Number of public biotech firms	Total MV US$ mill	Total RDE US$ mill
United States	337	878,133	41,153
Australia	43	3,550	261
France	39	19,403	1,301
UK	32	55,968	2,346
Sweden	30	9,276	278
Canada	28	4,152	483
Germany	18	8,280	393
Israel	15	1,736	201
Switzerland	11	5,763	389
Denmark	10	31,019	765
Other countries (21)	63	65,254	1,716
Total	626	1,082,534	49,286

Source: Morrison, C. and Lähteenmäki, R. (2018) Public biotech in 2017 – the numbers.
Nature Biotechnology 36(7):576-84 (supplementary table 1).

terminus actually worsened the results. It was apparent that since the 2008/09 recession, the underlying value of the sector had been in steady decline, with 2018 potentially being a modest silver lining, due to substantial value increases for two firms, one of which was sold in 2018.

Public biotech firm metrics reported by NBT were compared for Australia and other countries. This data is in Table 1, showing countries ranked by the number of public biotech firms.

The US accounts for around half of all biotech firms globally, but an overwhelming 81% of market value and 83% of R&D spend globally. Australia has a relatively large number of public biotech firms for its population, but this is due to the low valuation and listing hurdles for the ASX and the opportunity for expedited listing without the involvement of VCs or institutional funds (discussed below). However, as a result, the public biotech sector is weakly funded and small, based on valuation and RDE. The study concluded that the Australian biotech sector is fundamentally small and weak and any view that Australian biotech 'punches above its weight', at least in the core area of drug development biotech, is groundless[12].

While inadequate commercialization skills, lack of venture capital funding and the 'tyranny of distance'[14,30] have been blamed for Australia's weak biotechnology performance, the study results suggested that the quality of the science underpinning these companies also may be part of the problem. The study observed, however, that regardless of the causes of the poor investor performance, the sector's history of negative investor returns and the absence of a big biotech success story will make it very difficult for Australian biotechnology to attract future private funding.

WHERE TO FOR AUSTRALIAN BIOTECHNOLOGY?

Australia is an interesting case study because it appears to have a lot going for it as a place to build a bioeconomy. Firstly, it has a Federal government with an expressed commitment to growing a world-class biotechnology ecosystem. While government policies and financial support for biotechnology may have waxed and waned over the last 20 years, through its various systems of grants and the tax incentives, the government has been a major investor in Australian biotechnology. In the DDB sector, the amount of the government funding over the last 15 years has been estimated to be around $2 billion, which is almost as much at the total funding from private investors.[12] The R&D tax incentive (RDTI) alone is extremely attractive, in that qualifying RDE receives a 43.5% cash rebate. Effectively, it halves the cost of R&D for Australian biotechnology firms. Australia's commitment to biotechnology has been reinforced by a highly active industry group, AusBiotech, dedicated to promoting the benefits of Australia as a world-leading site for biotechnology innovation, lobbying for favorable government policies, and otherwise fostering industry development.

Another often-cited attraction for Australian biotechnology firms is that Australia is a favorable location for conducting Phase I human trials, because of its expedited CTN (clinical trial notification) system. This compares with the much more burdensome and time-consuming US IND (Investigational New Drug application) process. Combined with a favorable exchange rate, this has led to the proliferation and growth of local CROs (contract clinical research organizations) dedicated to running such trials, mostly for foreign pharmaceutical clients. However, the real benefits of the CTN system for the local biotechnology sector are indeterminate. Also, it should be recognized that while Phase I trials are useful to establish initial human safety and drug pharmacokinetics, it is the more expensive and risky Phase II trials, aimed at establishing dosage, efficacy and safety in patients, that are the real trigger for pharmaceutical deals; and to have deal-making currency, these generally need to be done in the US, under an IND.

Although not often promoted by AusBiotech or the government, another feature of Australia as a location for biotechnology firms is the low barrier to public listing on the ASX, compared with many other jurisdictions including the US. In many ways, an ASX listing provides

a substitute for venture capital for early-stage Australian firms[31]. As such, it represents an attractive mechanism for early-stage funding of technologies that might otherwise not receive VC funding, either due to a lack of VC funding – as is often claimed in Australia – or because the program does not meet the type or quality of program sought by the VCs. Indeed, it has been argued that VCs cherry-pick the highest quality projects and leave the lesser-quality programs to compete for an ASX listing, obtaining their 'venture capital' from less-discerning retail investors.[31] Regardless, there is no doubt that the low listing hurdles in Australia are an advantage for Australian biotechnology firms.

Apart from the initial funding at IPO, an ASX listing opens access to ongoing public funding through institutional placements (referred to as PIPEs in the US), share purchase plans (SPPs) and other public equity sales through brokers and investment bankers. Due to the early-stage of most biotechnology programs at IPO and the relatively modest initial raises, most firms rely on ongoing equity sales to continue to fund their R&D; however, this comes at the cost of shareholder dilution and the negative impact that that has on investor returns.[12]

ASX listing is such an attractive funding mechanism for early-stage projects that it has been exploited by entrepreneurs to fund foreign technologies that have been unable to secure funding in their home countries. For example, the most valuable ASX-listed DDB in 2018 was Clinuvel, which was built on drug technology from the University of Arizona, not an Australian PRO. Indeed, up to a third of all recent DDB ASX listings were based on foreign technology.[12] This must bring into question the quality or accessibility of the output of Australia's much lauded PRO network? It should also cause the Australian Government to question its substantial investment in RDTI (R&D tax incentives) where the firm is simply a vehicle for funding of foreign technology rather than the output of a local PRO.[12]

In addition, many other recent ASX listings have been simple repurposing of existing technology or products, rather than scientific breakthroughs, whether from Australian PROs or not. Possibly the most opportunistic in this regard have been the cannabis-related companies, with 14 of them listing on the ASX in the last several years. Indeed, it is difficult to find any Australian public DDB firms that are exclusively built on Australian PRO drug discovery research.

Ironically, a feature of the Australian biotechnology landscape that has been heavily promoted by the government and AusBiotech is the quality of its PRO research output, with the long-standing and rarely-questioned assertion being that the country "has punched well above its weight in terms of scientific breakthroughs".[6,32] However, one study has suggested otherwise,[15] concluding that Australia's research output is of mediocre quality, compared to a US cluster like San Diego. Another recent study also questions the quality of Australian science as a basis for building a DDB sector.[12]

If Australia does indeed 'punch above its weight', then the science base and network of PROs should provide a solid springboard for a globally-competitive drug discovery ecosystem. However, the cluster study described earlier[16] suggested otherwise and indicated that the activities of the network of Australian PROs fail to translate into commercially-relevant products, at least as measured by Big Pharma deals. The fact that there are few if any public DDBs on the ASX that are primarily built on Australian PRO breakthroughs reinforces this.

Even when the PRO research output is categorically world-class, there may be another cause for the disconnection between PROs and local industrial exploitation. The one major recent drug research breakthrough from an Australian PRO – the research by Walter and Eliza Hall Institute that led to the billion-dollar anti-cancer drug, venetoclax – was licensed directly from the PRO to Big Pharma (Genentech/Roche and AbbVie), at a very early stage and without any local Australian development beyond drug discovery and patenting by the PRO. Ultimately, the PRO sold off its royalty rights to its Big Pharma partners for a relatively modest $325 million, with the funds mostly directed to expansion of the PRO's facilities.[12]

There is no shortage of cancer-focused DDB firms in Australia and had the venetoclax discovery been licensed to one of these companies and clinical-stage value added in Australia prior to its licensing to Big Pharma, there is little doubt that the net present value of the licensing deal would have been in the tens of billions of dollars. More importantly, the country would have created its first home-grown 'big biotech' by now.

The country may have also obtained preferred, low cost access to this important drug. Instead, the PRO circumvented the Australian biotech industry to pocket a small payout, while – egregiously – this expensive cancer drug is now re-imported into Australia and subsidized on the Pharmaceutical Benefits Scheme, with the exorbitant treatment cost borne by Australian taxpayers. Incongruously, this has been celebrated by the PRO and the government as a great victory and a testament to Australian scientific prowess.[iii] The reality is that it was

iii <https://www.wehi.edu.au/news/illuminate-newsletter/september-2017/venetoclax-annoucement#:~:text=The%20Institute%20has%20made%20a,the%20anti%2Dcancer%20treatment%20venetoclax.> accessed October 30 2020.

a squandered opportunity to decisively bolster the DDB sector and pivotally leverage the government's multi-billion dollar investment in grants and tax credits to the biotechnology sector.

Apart from the 'venetoclax syndrome', there may be another insidious cause of the broken bridge between PROs and local industrial realization. During the early 2000s there was considerable interest by various Australian VC groups in funding Australian biotechnology projects. Indeed, Australian VCs backed three firms, which all progressed to listing on the ASX: Pharmaxis, Alchemia and Qrxpharma. Unfortunately all three later crashed emphatically, due to clinical trial or regulatory failures. Since 2010, not a single VC-backed biotech has progressed to listing on the ASX.[12] No doubt the three high-profile failures were dissuasive, but the other factor was the two-year escrow (post-listing) and other constraints imposed by ASX, which made it unattractive for VCs to list portfolio companies on the ASX.

One way or another, VCs moved their focus to private DDB firms, cherry-picking high potential programs from PROs with the goal of a trade sale and explicit avoidance of any projects where the founders wanted to build a sustainable company or list on the ASX[iv]. For example, the VCs backed several private PRO spinouts, such as Hatchtech, Spinfex and Fibrotech, and then on-sold them to pharmaceutical partners at the earliest opportunity, thereby liquidating their investments without an IPO.[12] The overall trade sale values obtained were in the hundreds of millions of dollars, which accrued to the benefit of the small number of high net worth investors in the VC funds (and to some extent the PROs), but like the venetoclax syndrome, the opportunity to contribute to the sustainable development of the DDB sector was squandered.

The venetoclax syndrome and VC cherry-picking are examples of behavior that have led to value leakage rather than value creation in the context of building a robust local biotechnology ecosystem that has any chance of reaching critical mass. The ultimate culprit is the financialized model of biotech funding.[33,34] This model promotes 'value extraction' rather than 'value creation' and the early monetization of drug development programs – typically in trade sales – rather than building a sustainable biotechnology sector. The Australian VCs have explicitly pursued this and the venetoclax syndrome shows that Australian PROs are complicit. The urgency to extract value at the earliest opportunity is a constant brake on growth and leads to leakage of value creation and depletion of the assets needed to reach ecosystem critical mass. In the face of this challenge, a recent study concluded[12]:

> *Potentially, Australia has neither the funding ecosystem nor the technology quality to support a globally-competitive DDB sector that can reach the critical mass needed to spin out one or more big biotech firms, and on which a bioeconomy could be anchored.*

As the author of that conclusion and the self-confessed promoter and perpetrator of value extraction events for public DDBs, I now demur. I believe that if the forces causing the leakage of assets can be understood and tamed through government policy and ASX changes, it may be possible for Australia to reach the critical mass needed to generate its first big biotech and build a world-class bioeconomy.

Key to that goal must be the recognition that the health of the public DDB sector is the key measure of ecosystem success. ASX listing by DDB firms brings with it, not only funding opportunities, but a public profile that drives aspirations for drug breakthroughs, determines investor sentiment, and shapes the country's overall perception of the efficacy of its biotechnology output. Public biotech firms should be vehicles for the 'best of the best' of Australian biotechnology commercialization opportunities – the standard bearers for Australian successful drug development. If the public biotech sector fails then the ecosystem fails. For the last 20 years, it has failed, but it can be salvaged by removing the drivers of value leakage and moving the value creation opportunities into the hands of ASX-listed biotech firms. This may finally give the sector the critical mass it needs to spin out its first big biotech.

Stemming the value leakage would require government policy aimed at ensuring that any drug discovery or development research generated by PROs is offered to Australian DDBs (or used to spinout a new Australian DDB) and that the 'venetoclax syndrome' is never repeated. It would also require policy that prevents Australian VCs from exiting private DDB programs through trade sales, at the same time incentivizing VCs to not only increase their investment in drug development projects (specifically), but also to exit only through ASX listing. Finally, ASX listing of foreign technology should be dissuaded by preclusion of any RDTI for companies that list based principally on foreign technology. Above all, ASX listing must not be viewed solely as a funding mechanism for companies, but as a responsibility to carry the standard for Australian technology and to contribute to a sustainable biotechnology ecosystem, not drive to an early exit.

iv Based on personal communications with VC firms between 2012 and 2016.

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REFERENCES

1. Sharrock, G. About Australia's Future: Geoff Sharrock Questions the depth of Howard's Research Plan. *Arena Magazine*. 2001 (June):13.
2. Australia. Backing Australia's Ability: An Innovation Action Plan for the Future. In: AusInfo, editor. Canberra: Commonwealth of Australia; 2001.
3. Sun, surf and stem cells. *New Scientist*. 2002:54.
4. Ausbiotech. Australian biotechnology innovation jumps to fourth on the world stage <http://www.ausbiotech.org/spotlight/details.asp?id=1133&returnToUrl=/default.asp2015>
5. Petersen, A. & Krisjansen, I. (2015). Assembling 'the bioeconomy': Exploiting the power of the promissory life sciences. *Journal of Sociology* 51(1):28-46.
6. Ausbiotech. Australian biotechnology packs a powerful punch <https://nfmri.org.au/australian-biotechnology-packs-powerful-punch/2016>.
7. Ausbiotech. Biotechnology Industry Position Survey 2017 <https://www.ausbiotech.org/documents/item/2682017>.
8. Dalidakis, P. (2015). Victoria secures Australia's largest biotech conference. Media release by the Victorian State Government, 11 December.
9. Anonymous. (2014). Delegation to BIO stamps Australia as a world leader in biotech. Lab & Life Scientist. <http://labonline.com.au/content/life-scientist/news/delegation-to-bio-stamps-australia-as-a-world-leader-in-biotech-376969364#ixzz4BHcletSC2014>.
10. Rios, M. (2011). China's New Five-Year Plan: How It May Reshape the Country's Biopharmaceutical Industry. Bioprocess International (June 2011, Supplement):8-11.
11. Wood, F. Entrepreneurship in Australia: The missing links. A report prepared for the US Studies Centre, September 2011. <https://core.ac.uk/download/pdf/30678983.pdf>.
12. Molloy, P. Value creation and investor performance of the Australian drug development biotech sector. PhD thesis. Swinburne University of Technology; 2019. <https://researchbank.swinburne.edu.au/file/0a7ee27f-bef3-4a7c-b32d-87e2c3df372f/1/peter_molloy_thesis.pdf>.
13. Nogrady, B. (2018). Australia makes its mark in biotechnology. *Nature* 557(10 May):27-29.
14. Gilding, M. (2008). 'The tyranny of distance': Biotechnology networks and clusters in the antipodes. *Research Policy* 37(6–7):1132-1144.
15. Barlow, T. (2010). Biotechnology clustering, phase II: Landscape analysis. University of Sydney <https://united-states-studies-centre.s3.amazonaws.com/attache/ff/dc/c7/84/35/d2/21/47/53/f7/8d/ef/d9/02/4a/a5/BT4.pdf:>.
16. Gilding, M., Brennecke, J., Bunton, V., Lusher, D., Molloy, P. L. & Codoreanu, A. (2020). Network failure: Biotechnology firms, clusters and collaborations far from the world superclusters. *Research Policy* 49(2):1-17.
17. Powell, W. W., White, D. R., Koput, K. W. & Owen-Smith, J. (2005). Network dynamics and field evolution: The growth of interorganizational collaboration in the life sciences. *American Journal of Sociology* 110(4):1132-1205.
18. Powell, W. W., Koput, K. W. & Smith-Doerr, L. (1996). Interorganizational collaboration and the locus of innovation: Networks of learning in biotechnology. *Administrative Science Quarterly* 41(1):116-145.
19. Powell, W. W., Koput, K. W., Bowie, J. I. & Smith-Doerr, L. (2002). The Spatial Clustering of Science and Capital: Accounting for Biotech Firm-Venture Capital Relationsships. *Regional Studies* 36:291-305.
20. Padgett, J. F. & Powell, W. W. (2012). The Emergence of Organizations and Markets. Princeton: Princeton University Press.
21. Trajtenberg, M. (1990). A penny for your quotes: Patent citations and the value of innovations. *The RAND Journal of Economics* 21(1):172-187.
22. Owen-Smith, J. & Powell, W. W. (2006). Accounting for emergence and novelty in Boston and Bay Area Biotechnology. In: Braunerhjelm P, Feldman M, editors. Cluster genesis: Technology-based industrial development. Oxford: Oxford University Press.

23. Breznitz, S. M. (2013). Cluster Sustainability: The Israeli Life Sciences Industry. *Economic Development Quarterly* 27(1):29-39.

24. Powell, W. W., Packalen, K. & Whittington, K. (2012). Organizational and Institutional Genesis: The Emergence of High-Tech Clusters in the Life Sciences. In: Padgett JF, Powell WW, editors. The Emergence of Organizations and Markets. Princeton NJ: Princeton University Press; p. 434-465.

25. Morrison, C. & Lähteenmäki, R. (2018). Public biotech in 2017 – the numbers. *Nature Biotechnology* 36(7):576-584.

26. Lokko, Y., Heijde, M., Schebesta, K., Scholtès, P., Van Montagu, M. & Giacca, M. (2018). Biotechnology and the bioeconomy—Towards inclusive and sustainable industrial development. *New Biotechnology* 40:5-10.

27. Downs, J. B. & Velamuri, V. K. (2016). Business model innovation opportunities for the biopharmaceutical industry: A systematic review. *Journal of Commercial Biotechnology* 22(3):19-63.

28. Rader, R. A. (2008). (Re)defining biopharmaceutical. *Nature Biotechnology* 26(7):743-751.

29. Hodgson, J. (2006). Private biotech 2004—the numbers. *Nature Biotechnology* 24(6):635-641.

30. Marot, M., Selsky, J., Hart, W. & Reddy, P. (2005). Research Teams in an Australian Biotechnology Field: How Intellectual Property Influences Collaboration. In: Beyerlein MM, Beyerlein ST, Kennedy FA, editors. Collaborative Capital: Creating Intangible Value. Advances in Interdisciplinary Studies of Work Teams. 11: Emerald Group Publishing Limited; p. 1-31.

31. Vitale, M. & Sparling, D. (2004). Australian biotechnology IPOs: Too early, too small? Growth 53(Apr 2004):73-91.

32. Ferris, W. D. (2001). Australia Chooses: Venture Capital and a Future Australia. *Australian Journal of Management* 26(2):45-64.

33. Lazonick, W. (2014). Innovative enterprise and shareholder value. *Law & Financial Markets Review* 8(1):52-64.

34. Lazonick, W. & Tulum, Ö. (2011). US biopharmaceutical finance and the sustainability of the biotech business model. *Research Policy* 40(9):1170-1187.

Article

A New Vision for Europe's Bioeconomy in a Post-COVID World

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INTRODUCTION: THE POST-COVID LANDSCAPE FOR THE EU BIOECONOMY

In response to the COVID-19 global pandemic, the European Commission (EC) provided inclusive leadership, working as a team including EU member (national) officials, biopharmaceutical industry, NGOs, academic researchers and frontline health care personnel – acting with unprecedented collaboration and cohesion. The emergence in early 2020 of the greatest public health threat in a century required new approaches and new collaborations. While the United States failed to provide leadership in 2020, the EU did not disappoint.

While the burdens of COVID-19 were felt within national borders, the Commission's efforts to enhance transparency and cooperation proved critical in terms of assimilation and equitable distribution of healthcare solutions across Europe, e.g., including Personal Protection Equipment (PPE), diagnostic tests, repurposed as well as ongoing evaluation and commercialization of novel therapeutic interventions and vaccines:

> *The devastating impact of COVID-19 in a social, economic and human sense has underlined the critical importance of collaboration as a first principle for success for Europe's biopharmaceutical industry and more broadly for the discovery, development, commercialization, and enhancement of equitable access to novel diagnostics, therapeutics, vaccines to respond to global health threats as well as to respond to the EU's unmet health threats and human needs.*[1]

Through this collaborative effort, time-consuming regulatory processes were streamlined without sacrifice of public safety in the best interests of patients. COVID-19 not only showed what could be done, but what should be done to safeguard the health of Europeans.

Recent launch of a number of novel COVID-19 vaccines give hope for a healthier 2021, even while Europe and the world struggles to contain ongoing COVID-19 infections. Looking ahead to a post-COVID world, the EU's Pharmaceutical Strategy for Europe[2] released November 25, 2020 offers a new vision for vibrant and sustainable growth of the EU biopharmaceutical and appears to have learnt some lessons from managing the COVID – 19 crisis.

EVALUATING THE EU BIOPHARMACEUTICAL STRATEGY

This is the first-ever European comprehensive strategy for the pharmaceutical sector, based on explicit recognition that "the pharmaceutical industry is of key importance for the EU's economy."[3] Biopharmaceuticals remain of central

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1 Recommendations, EU Health Coalition, October 2020, https://www.euhealthcoalition.eu/

2 "A Pharmaceutical Strategy for Europe," published online 25 November 2020, and noting that implementation will notably include proposals for legislation by or before 2022. https://ec.europa.eu/health/human-use/strategy_en

3 A Pharmaceutical Strategy for Europe: Questions and Answers, 25 November 2020 https://ec.europa.eu/

importance for the European bioeconomy,[4] responsible for the lion's share of value creation through research and development of healthcare products that generate social and economic benefit.[5] In a supporting memorandum provided along with the EU Pharmaceutical Strategy, the European Commission notes:

> *In 2019 it invested more than €37 billion in Research and Development (R&D), it is responsible for 800.000 direct jobs and almost 110 billion € in trade surplus. At the same time the EU is the second largest market in the world for pharmaceuticals. The EU's total pharmaceutical spending was around €190 billion in 2018. The overall pharmaceutical sales is even greater when including the medicines used in hospitals.*[6]

For its part, the European Federation of Pharmaceutical Industries and Associations (EFPIA) estimates that Europe's biopharmaceutical sector is valued at nearly €230,000 million, more than doubling the value of the pharmaceutical sector as compared to 2010.[7]

In the context of the COVID-19 pandemic, the critical importance of the innovative biopharmaceutical industry became obvious to the 'man on the street' as country after country went into (repeated) lock-down, without recourse to vaccines or safe and effective therapies. Given the absence of American leadership in 2020, the EU's coordination and encouragement of industry collaboration proved critical. Companies ranging from Fortune-100 to start-up answered the call.

Nearly 20 innovative biopharmaceutical pharma companies focused their R&D capabilities on developing a vaccine to stop the epidemic, with even more companies worked to commercialize faster, better diagnostic tools for COVID-19 detection and effective COVID therapeutics. These companies raced to develop the "magic bullet" of a vaccine or a therapeutic – benefiting from decades of past work and without diminution of good clinical practices (GCP). Development of the Hepatitis B vaccine, for example, took 12 years before full commercial development following decades of primary and translational research.[8] Commercialization of the HPV vaccine took 16 years.[9] Certainly COVID-19 innovators stood on the shoulders of giants; nonetheless, we have seen extraordinary acceleration in development of healthcare solutions brought about by collaborations going beyond biopharma R&D to supply chain solutions, enhancing access to therapies. It is interesting to note that the first vaccine approved by the FDA was the result of a partnership between Pfizer and a small German R&D company BioNTech .

As the world faced a new wave of COVID-19 infections in mid-2020, several companies announced key vaccine development milestones, enabling potential availability of one or more COVID vaccines by year's end. Experts cautioned that even if that was to happen, the vaccine might only be 50% to 70% effective, however by the end of 2020 two vaccines demonstrating 94% to 95% effectiveness (almost unprecedented efficacy) – the vaccine from the Pfizer-BioNTech collaboration and another from Moderna –were authorized for emergency use in the US and UK; approval of AstraZeneca's vaccine developed in collaboration with Oxford University followed days later in early January 2021, with indications that an additional vaccine from Johnson & Johnson could be available as early as February 2021. Other vaccines have been announced by regulatory officials in India, China, and Russia . At the same time, many research collaborations are underway for novel therapeutics to treat COVID-19, including repurposing of approved medications that appear helpful to treat COVID symptoms.[10] Even with approval of several COVID vaccines, ongoing R&D is critical to find better

commission/presscorner/detail/en/qanda_20_2174

4 A decade of EU funded GMO research (2001 – 2010)" European Commission Directorate General for Research and Innovation, Biotechnologies, Agriculture, Food (2010) EUR 24473 (En), 2010, p. 9. (Noting that the bioeconomy: "refers to economic activities relating to the invention, development, production and use of biological products and processes" such as "industrial and pharmaceutical biotechnologies, and includes significant know-how on the health-related aspects of the Bio-Economy.")

5 This is due in part to the policies resulting in exodus of agricultural biotechnology from the EU. See discussion below: Limitations on Advanced Agricultural Technologies in the EU, pp. 69-71.

6 A Pharmaceutical Strategy for Europe: Questions and Answers, 25 November 2020 https://ec.europa.eu/commission/presscorner/detail/en/qanda_20_2174

7 EFPIA Report: The Pharmaceutical Industry in Figures Key Data 2020, p. 5, available online at https://www.efpia.eu/media/554521/efpia_pharmafigures_2020_web.pdf

8 See, e.g., Beasley RP. Development of Hepatitis B Vaccine. *JAMA*. 2009;302(3):322–324. doi:10.1001/jama.2009.1024 https://jamanetwork.com/journals/jama/fullarticle/184248

9 Inglis S, Shaw A, Koenig S. Chapter 11: HPV vaccines: commercial research & development. Vaccine. 2006 Aug 31;24 Suppl 3:S3/99-105. doi: 10.1016/j.vaccine.2006.05.119. Epub 2006 Jun 23. PMID: 16950023. https://pubmed.ncbi.nlm.nih.gov/16950023/ (paywall)

10 For example, dexamethasone, a steroid developed in the late 1950's appears very effective against COVID-19. See **Michelle Roberts** "Coronavirus: Dexamethasone proves first life-saving drug," BBC News online 16 June 2020 https://www.bbc.com/news/health-53061281

therapies and cures for COVID variants, not to mention other urgent healthcare priorities. However size and large R&D budgets do not guarantee success in the search for a COVID vaccine, as three of the largest vaccine companies have struggled to develop a vaccine.

Pillars of the EU Pharmaceutical Strategy

It may be interesting to speculate what would have been included in the EU's Pharmaceutical Strategy if it had been published in January 2020, before the realization that Europe – and the world at large – faced an unprecedented global epidemic from COVID-19.

There are four main pillars to the European Pharmaceutical Strategy:

- Ensuring access *to affordable medicines* for patients and addressing unmet medical needs (e.g. in the areas of antimicrobial resistance, cancer, rare diseases)
- Supporting *competitiveness, innovation sustainability of the EU's pharmaceutical industry* and the development of high quality, safe, effective and greener medicines.
- Enhancing *crisis preparedness and response mechanisms,* diversified and secure supply chains, address medicines shortages
- Ensuring a *strong EU voice in the world* by promoting a high-level quality, efficacy and safety standards.[11]

The accompanying EC Communication provides more a more detailed overview on these pillars, as follows:

> *The Pharmaceutical Strategy for Europe builds on these foundations. It will foster patient access to innovative and affordable medicines. It will support the competitiveness and innovative capacity of the EU's pharmaceutical industry. It will develop the EU open strategic autonomy and ensure robust supply chains so that Europe can provide for its needs, including in times of crisis. And it will ensure a strong EU voice on the global stage. The strategy has four work strands which flow from these objectives. Each strand contains flagship initiatives and flanking measures to ensure the objectives deliver tangible results. Taken together, they will ensure Europe's pharmaceutical policy evolves in line with the green and digital transitions, demographic change and remains relevant given the realities of today and the ambitions of tomorrow, as part of a stronger Health Union.*
>
> *The strategy will also help to deliver other Union objectives. By boosting innovation to address unmet needs, including vaccination against treatable infections that cause cancer, as well as medicines for paediatric and rare cancers, it directly contributes to 'Europe's Beating Cancer Plan'. Together, the Pharmaceutical Strategy and the Cancer Plan will ensure that patients across Europe can access high-quality treatment and new therapies when they need them and ensure the availability and affordability of essential medicines for cancer patients across the EU. The strategy's actions to address access to medicines will also help to meeting EU-level commitments under the UN's sustainable development goals.*
>
> *The strategy is also complementary to the European Green Deal and more particular the Zero Pollution ambition for a toxic-free environment, notably through the impact of pharmaceutical substances on the environment. The pharmaceutical strategy paves a way for the industry to contribute to EU's climate neutrality, with a focus on reducing greenhouse emissions along the value chain. It also contributes to the action plan to implement the European Pillar of Social Rights, the strategic frameworks on achieving a Union of Equality, the upcoming Green Paper on Ageing, the strategy on Shaping Europe's digital future, the European strategy for data, the work on the creation of a European health data space, the European One Health Action Plan against antimicrobial resistance and the new industrial strategy for Europe.*
>
> *Finally, the strategy is of key relevance for non-EU countries as well, in particular in the Western Balkans and the EU's neighbourhood, as candidate countries, potential candidates and DCFTA countries have an obligation to align to the EU acquis of the pharmaceutical legislation.*[12]

The EC announcement of the Pharmaceutical Strategy for Europe and accompanying supporting materials reaffirm the importance of incorporating the

11 A Pharmaceutical Strategy for Europe, 25 November 2020 https://ec.europa.eu/health/human-use/strategy_en

12 Communication from the Commission to the European Parliament, the Council, The European Econoimc and Social Committee and the Committee of the Regions, Pharmaceutical Strategy for Europe Brussels, 25.11.2020 COM (2020) 761 final, https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52020DC0761&from=EN

lessons of COVID-19. just as the proof of the pudding is in the eating, time will tell whether this is indeed the case. In the meantime, it is helpful to highlight what has been learned from the global COVID-10 pandemic and the European experience.

What are the lessons of COVID-19?

- *For Healthcare 'just in time' is too late*

In times of crisis, it is essential that all required resources needed by first responders and patients alike, e.g., Personal Protection Equipment (PPE) supplies, should readily available. The first lesson of COVID-19 is that EC and EU member states need to prioritize healthcare as an investment in public health and not as a cash cow for savings that come at the cost of European patients. Crisis does not come with the lead-time to get essential supplies; next time we must be ready.

- *Transparency, collaboration and meaningful incentives spur meaningful R&D*

For example, over just a few months in 2020, the EU's Innovative Medicines Initiative (IMI) fast-track proposal process attracted 144 proposals, of which fully 120 met IMI requirements. Given the high number of quality applications, IMI increased available funding from €45 to €72 million and selected 8 project for funding.[13] Looking forward, spurring R&D for unmet needs is vital. In particular it is crucial that R&D to address anti-microbial resistance (AMR) will clear action plans. and accountability so that the needed R&D will be done. We also need to see greater transparency over evaluation of the value of innovation to ensure equity of access.

- *Science based, time-sensitive regulation is critical for European Leadership*

Whether we are talking about COVID-19 vaccines and therapies, AMR or new drugs for rare diseases, the patient is waiting. It should not require a global pandemic to ensure that safe and effective new medicines and vaccines are brought to market as quickly as possible. At the same time, regulatory processes should be apolitical and not developed in reaction to pressure-groups without a basis in science. What would the results have been in 2020 if EU policies had undermined vaccine R&D in Europe as they have with regard to GMOs?

- *Integration of EU-wide and national supply chains is essential*

European patients need to be able to rely on supply chain management for healthcare products and associated services, without respect to EU member state boundaries. COVID-19 has shown us how important it is to coordinate supply chain processes both within EU Members boundaries and across the EU.

- Monitoring and Tracking is key to success

We count what matters. Just as the EU success during COVID-19 has stemmed from unprecedented communication and collaboration among stakeholders, the process also relied heavily on monitoring and tracking. The COVID lesson here is the need to work with stakeholders to develop key metrics for monitoring, including annual reports to track progress and possible online or in-person events.

THE WAY FORWARD:

While comprehensive reform of policies adversely affecting the European Bioeconomy may not be in the offing, the EU Biopharmaceutical Strategy offers an important opportunity to reinvent European biopharmaceutical development in a post-COVID, post-Brexit world. Rather than focus on specific elements of the European Strategy, the authors offer the following suggestions for EU policymakers:

- Establish an enabling environment for inclusive consultation

It is essential to take the pulse of key stakeholders – including industry, VCs, civil society, academia, relevant EC Directorates in Brussels and EU member state governments, before framing out an issue and identifying a sustainable policy direction. Soliciting views, investing time to for meaningful consultations with stakeholders and listening carefully to their concerns ensures that relevant issues are aired prior to reaching the decision-making stage. As an additional benefit, the consultation process generally builds trust across the table and strengthens the working relationship between policymakers and stakeholders. The process of gaining agreement may, by necessity, include a great deal of repetitive discussion, e.g., where nothing has been said until everyone has said it.[14] This also accords with the recommendation of

13 IMI announces COVID projects, boosts funding pot to EUR 72 million, 5 December 2020 https://www.imi.europa.eu/news-events/press-releases/imi-announces-covid-projects-boosts-funding-pot-eur-72-million

14 This is a paraphrase of the dictum: "Everything has been said but not everyone has said it yet," attributed to Congressional Representative Morris Udall at the 1968 Democratic National Convention.

the EU Health Coalition,[15] recommendation for establishment of a "multi-stakeholder Forum for Better Access to Health Innovation, covering all aspects of innovation, from disease prevention, therapies, technologies, and supply chains, to improvements in care pathways and healthcare services," and involving all stakeholders – from Member States and regional authorities to patients and civil society, from healthcare professionals to industry."[16]

- Gather Empirical Data

EU biotechnology policy writ large, and the new pharmaceutical strategy, should be based on reality and the actual experiences of stakeholders either at the local, regional or EU Member State level, including the actual experiences of Academic researchers, Industry, Funders, and related non-government stakeholders. There should be a concerted effort to recognize and understand the ground realities by which businesses operate and how investment decisions are actually made, so that appropriate incentives are balanced against necessary regulatory restrictions for the benefit of all stakeholders.

EU policy should similarly look beyond the immediate impact of a policy, e.g., price controls, to gain a better understanding of the broader impact to ensure that adopted policies support job creation, research productivity and sustainable long-term growth. This includes greater transparency around the process of evaluation and pricing, with appropriate reward for innovation based on its value to patients, health systems and society based on agreed principles.

- Adopt Transparent, Science-based Regulatory Processes

EU biotechnology policy should strive for transparency, predictability, consistency, durability and non-discriminatory regulation across areas of technology – including agricultural biotechnology where Europe has essentially lost a generation of industrial development due to the expansive interpretation of the Precautionary Principle – and should also revisit problematic intellectual property policies (e.g., Patent Disclosure, curtailment of Supplemental Patent Certificate terms) that have had a documented chilling effect on products development.

- Identify and Implement Best Practices for Technology Clusters

EU biotechnology policy broadly speaking should reflect best practices in highly innovative, successful biotechnology clusters both within EU Member States and around the globe, taking into account the increasing importance and impact of technology clusters for R&D productivity. The relative success of the UK in attracting investment and growing its bio-cluster may provide insights, as well of course as leading biotech clusters in the United States and Israel.

CONCLUSION

The hard-won lessons of 2020 on the critical value of collaboration and cooperation between stakeholders at all levels hold enormous potential for the successful implementation of the EU pharmaceutical strategy.[17] Drawing on the lessons of COVID-19 collaboration and dialogue to identify the right incentives, EU can revitalize innovative biotechnology in the 21st century, but the EU must recognize the lessons learnt from the COVID19 crisis.

Two questions remain: Does the European Commission's vision for biopharma has focused on the lessons learned from the Covid-19 epidemic? Will the Commission implement the European Pharmaceutical Strategy in a post-COVID world with a focus on collaboration and transparency? How will things be different than before?

ANNEXES:

Status of Europe's Biopharmaceutical Research Enterprise in 2020

Impact of Brexit on the European Bioeconomy

Limitations on Advanced Agricultural Technologies in the EU

15 The EU Health Coalition is currently composed of 33 organizations including patient organizations, EU research-oriented medical societies, healthcare providers, industry organizations as well as regional and local health authorities.

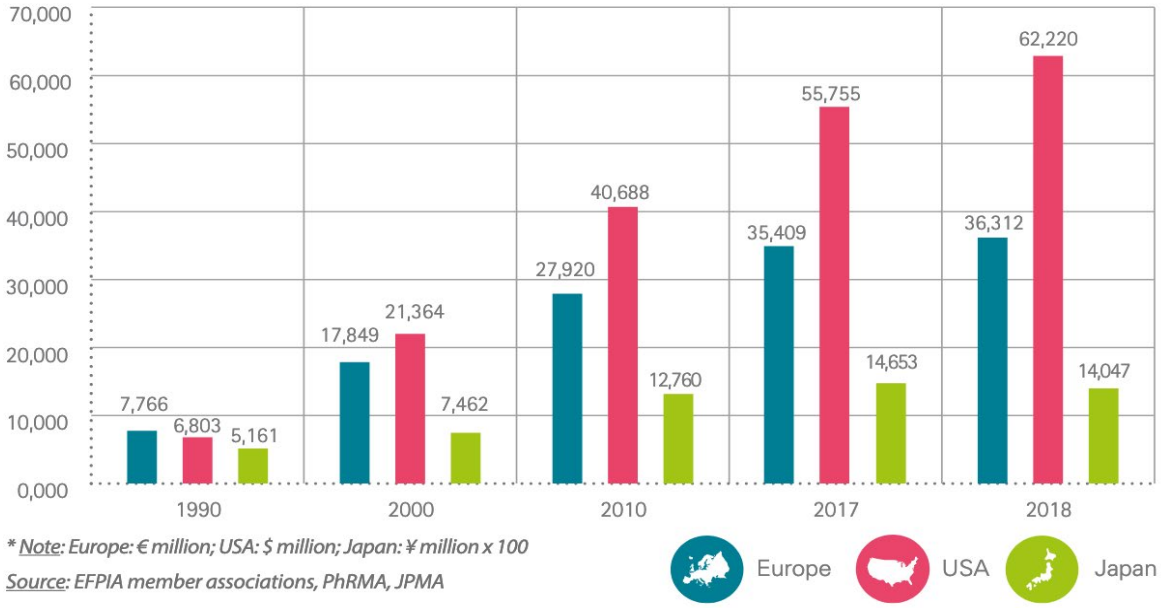
16 "A Shared Vision for the Future of Health in Europe: Lessons Learnt from the COVID-19 Pandemic," EU Health Coalition, October 2020. p. 4, https://www.euhealthcoalition.eu/wp-content/uploads/2020/10/FINAL-lessons-learnt-from-the-COVID-19-pandemic.pdf

17 "A Shared Vision for the Future of Health in Europe: Lessons Learnt from the COVID-19 Pandemic," EU Health Coalition, October 2020. ("The COVID-19 pandemic has also shown us the importance of cooperation between sectors and actors in ensuring our healthcare systems work to their optimum ability in preventing premature deaths.") https://www.euhealthcoalition.eu/wp-content/uploads/2020/10/FINAL-lessons-learnt-from-the-COVID-19-pandemic.pdf

STATUS OF EUROPE'S BIOPHARMACEUTICAL RESEARCH ENTERPRISE IN 2020

Contrasting the fruitful collaboration during the 2020 COVID-19 pandemic with sustained losses of the last three decades demonstrate the lack of sufficient recognition by policy makers in as to the value of inclusive policy development and implementation, including industry as a key stakeholder. Despite year-on-year growth, Europe has been in decline as a commercial R&D destination for a generation. EU biopharmaceutical R&D has long been losing ground to the US, China and India. In 2018, U.S. pharmaceutical R&D spending exceeded $62 billion; dwarfing that of the EU at €36 billion.

PHARMACEUTICAL R&D EXPENDITURE IN EUROPE, USA AND JAPAN (MILLION OF NATIONAL CURRENCY UNITS*), 1990–2018



Note: Europe: € million; USA: $ million; Japan: ¥ million x 100

Source: EFPIA member associations, PhRMA, JPMA

The European Commission has long recognized the need for intervention to enhance European biopharmaceutical productivity,[18] however was in the past unable to identify the right approach to stem erosion of European R&D competitiveness and retake its historically leading role.

The high caliber of European academic research centers is unquestionable: "Europe has world-class research institutions, medical centers, and hospitals that provide a strong basis for sourcing and developing scientific and clinical innovations. The region is home to 16 of the world's top 50 universities for life sciences and publishes roughly the same number of articles in top ten journals as the United States does and three times as many as China."[19]

EU academic research institutions continue to attract ambitious scientists from around the globe: Finland,

18 Nathalie Moll, The EFPIA View (blog), March 1, 2020 https://www.efpia.eu/news-events/the-efpia-view/blog-articles/would-the-last-pharmaceutical-investor-in-europe-please-turn-the-lights-out/ ("In its 1994 Communication on the *Outlines of an Industrial Policy for the Pharmaceutical Sector in the European Community,* the European Commission stated that the pharmaceutical "*industry is a substantial asset for growth and employment in the European Union*" and that "*there are signs that the competitiveness of the Community industry is yielding in comparison with its main competitors.*")

19 Franck Le Deu and Jorge Santos da Silva,"Biotech in Europe: A strong foundation for growth and innovation," McKinsey & Company (August 2019), available online at https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/biotech-in-europe-a-strong-foundation-for-growth-and-innovation.

Sweden, Germany and Switzerland, which are among the world's top science spenders, attract thousands of foreign researchers each year.[20] Fixed-term research positions and training opportunities for non-EU scientists and students are available at universities and research institutes across Europe. European and national funding agencies and academic exchange services, scientific societies and private foundations offer a wide range of support for early-career scientists from around the world. Moreover, visiting scientists generally "find that conditions for science — including funding, training opportunities and access to research facilities and lab reagents — are much better than in their native area."[21]

However, the continuing attraction of Europe for academic researchers has not translated into broader biotechnology success in terms of commercialization of new products and services, and Europe risks becoming the world's research hub while innovative products and processes and the jobs and growth that go with their development, will be found elsewhere."[22] Nathalie Moll, EFPIA Director General, sums up the situation with hard truths: "The sobering reality is that Europe has lost its place as the world's leading driver of medical innovation. Today, 47% of global new treatments are of US origin compared to just 25% emanating from Europe (2014-2018). It represents a complete reversal of the situation just 25 years ago."[23]

Both investment and the number new biotech start-ups are flagging.

> *Further down the innovation chain, European companies were responsible for originating 13 percent of the new drugs produced by biotechs and approved by the US Food and Drug Administration in 2017 and 2018, while US biotechs were responsible for 78 percent. However, Europe's share of new drugs could grow if its biotechs are able to attract more investment; they currently receive only 20 percent of the funding their US counterparts do.*[24]

Despite the political expansion of the EU and a continuing commitment by the European Commission to public funding for high-quality academic research, half of all European biotechnology companies are concentrated in France, Germany and the United Kingdom (UK), and start-up activity in France and Germany has been falling for several years.[25] As a follow-on, the pace of start-up activity in the EU also is adversely affected by the lower growth in R&D spending, given that most new biotech companies are staffed by alumni of global biopharmaceutical companies. The relative decline of European biopharma thus becomes a vicious cycle where the greater success of new companies in Boston, San Diego and San Francisco becomes a siren call to bio-entrepreneurs in Europe. R&D location and incentives, sources of funding and the impact of (and the unintended consequences of) government policies have all contributed to the decline in "D" in Europe. Moreover, the UK biopharmaceutical sector has been an outsize contributor to European biopharmaceutical sector and so the impact of Brexit specifically in this area may be profound.

20 Quirin Schiermeier, "Europe is a top destination for many researchers," 21 May 2019, available online at https://www.nature.com/articles/d41586-019-01570-3

21 Quirin Schiermeier, "Europe is a top destination for many researchers", 21 May 2019, p. 590, available online at https://www.nature.com/articles/d41586-019-01570-3

22 Ernst & Young EuropaBio Biotechnology in Europe Report (2014)

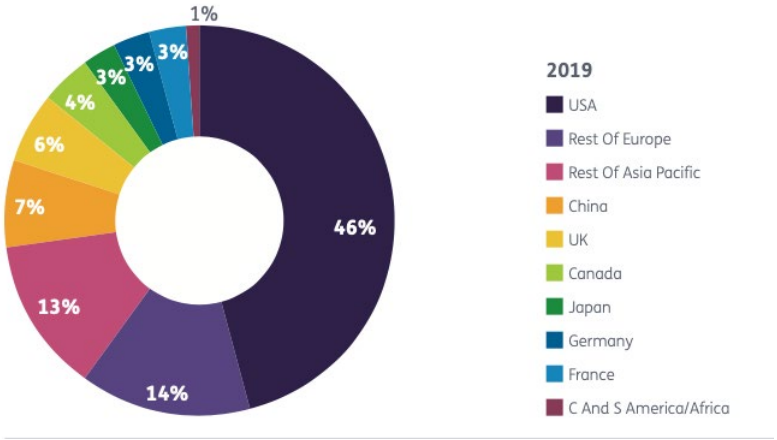
23 Ibid.

24 Franck Le Deu and Jorge Santos da Silva,"Biotech in Europe: A strong foundation for growth and innovation," *McKinsey & Company (August 2019), available online at* https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/biotech-in-europe-a-strong-foundation-for-growth-and-innovation.

25 Franck Le Deu and Jorge Santos da Silva,"Biotech in Europe: A strong foundation for growth and innovation," *McKinsey & Company (August 2019), available online at* https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/biotech-in-europe-a-strong-foundation-for-growth-and-innovation.

IMPACT OF BREXIT ON THE EUROPEAN BIOECONOMY

The UK has been a bright spot for the European biopharmaceuticals sector. This pie chart from 2020 EFPIA report demonstrates that UK R&D equals the total R&D of Germany and France combined, and is nearly a quarter of total EU R&D, in addition to showing the falling share of biopharmaceutical R&D being carried out in Europe broadly.[26]



Within the European Union, the UK represents the single largest biotechnology cluster, and accounting for more than a third of all EU biotechnology companies: "In fact, the United Kingdom has not only played a disproportionate part in multiple technologies and disease areas but also been home to 35 percent of all biotech start-ups in Europe since 2012."[27]

Beyond start-up activity, British biotechnology companies also attracted the lion's share of venture capital and other funding: "According to data from information provider Informa provided to the UK BioIndustry Association, the country's biotech sector attracted ~$870 million in risk capital last year, including $590 million in series B round financings — a record-breaking amount. In 2019, UK biotech attracted nearly three times as much venture capital as the sectors in France or Germany."[28] Among EU members, the United Kingdom has gone its own way in terms of domestic support for biotech, and is the consistent leader in terms of fundraising, "In Europe, the UK has maintained its pre-eminent position – accounting for just over a quarter of total VC funding in 2019."[29] At a time when start-up activity in Germany and France has been decelerating, Brexit will be a great loss to the European bioeconomy.

Loss of the UK biotechnology sector represents a goliath blow to the EU's bioeconomy. In this context, Brexit offers an important opportunity to re-invent and rebuild the European bioeconomy on a solid, sustainable foundation. At the same time the UK understands the importance of continuing scientific connectivity within Europe and has opted to continue to participate in the ongoing EU Horizon 2020 research collaboration program and is likely to contribute financially to participate on an associate basis in 2021 and beyond.[30]

26 Ibid

27 Ibid. (also noting in contrast that "biotech start-up activity in France, Germany, and Sweden has decelerated over the past few years.") See also Mark Terry, "Ranking the Top 10 Biotech Clusters in Europe, Biospace", October 30, 2019, https://www.biospace.com/article/ranking-the-top-10-biotech-clusters-in-europe/ ([T]he UK ranks at the very top in public funding, with 7,981 Horizon 2020 grants and 2,153 biopharma companies according to Bioscience and Health Technology Statistics 2018, which was published in May 2019. It ranks second in biopharma jobs, with about 121,000, and fourth in patents, with 276 granted and 549 applications in 2018."

28 Making the best of Brexit. *Nat Biotechnol* **38,** 249 (2020) https://doi.org/10.1038/s41587-020-0463-x

29 Global and Growing: UK biotech financing in 2019, UK BioIndustry Association (January 2020) https://www.bioindustry.org/uploads/assets/uploaded/cc26cb0f-3097-43f4-9b5a6d0008941b2d.pdf (Presumably 2019 investments have 'baked-in' remaining uncertainties relating to the details of Brexit and serve to underscore VC and other funders preferences for the UK biocluster.)

30 Quirin Schiermeir, "Horizon 2020 by the numbers: how €60 billion was divided up among Europe's scientists," Nature 22 December 2020 https://www.nature.com/articles/d41586-020-03598-2
("UK politicians have repeatedly stated their intention to join Horizon Europe as an 'associated country', which would enable researchers based in the United Kingdom to participate in the same way as those in the EU. There are currently 16 non-EU associated countries, which pay a mandatory contribution to the bloc's research programme in exchange for access to grants.")

LIMITATIONS ON ADVANCED AGRICULTURAL TECHNOLOGIES IN THE EU

Until the 1990's, the U.S. and Europe pursued similar approaches to advanced agricultural technologies, however harmonization of European regulatory processes in the 1990's led to critical differences in evaluation and approval of bio-enhanced or genetically engineered (GE) agricultural products, also known as genetically modified organisms (GMOs). European Union members with more strongly held views against adoption of agro-biotechnology technologies held sway. In the process, science advisors and sectoral experts lost control of the debate, which was driven by highly politicized, emotional populism that proved impossible to address on a rational basis:

> *Genomic studies of the last decade have demonstrated that a genome is not a static entity but a dynamic structure continuously refining its gene pool. So, for a scientist in genetics, the act of splicing to generate a transgenic organism is a modest step when compared to the genomic changes induced by all the 'crosses' and breeding events used in agriculture and husbandry. The molecular biology tools simply add a new precision, speed and reach to this indispensable process of species domestication. So it was a surprise for many scientists to discover that pub – lic opinion did not 'buy into' this line of thought. Some European interest groups even opposed the idea of GM crops with a religious zeal. The Precautionary Principle – which some interpret as saying that, if a course of action carries even a remote chance of irreparable damage, then one should not pursue it, no matter how great the benefits may be – gave Europeans a firm philosophical basis for saying no to GMOs. Political leaders and public servants in the Member States and the EU institutions were ill-prepared for this emotional uproar.*[31]

In sum, EU policy relating to advanced agricultural products and processes ignored all of the science, rigorous regulatory processes implemented by these same policy makers, and global empirical data on the safety of genetically engineering.

Over time the European Commission implemented labeling standards for bio-enhanced products that further demonized agrobiotechnology, where "the real benefits of the technology to agriculture and the environment were lost because consumer values were ignored. And when public acceptance and trust collapsed, serious support for the products evaporated."[32] Not surprisingly, innovative agricultural companies transitioned R&D activities to more receptive venues. While the EU has continued to support academic research,[33] there has been no meaningful progress towards a science-based regulatory process for agrobiotechnology products.

There has been markedly little progress in demystification of genetic modification to address important societal challenges sustainable development in the context of climate change and population growth.

> *Meeting the challenge to 'prove that GM crops are safe!' is not so easy. It looks like a scientific issue, but it isn't. Science can certify the existence of danger, but not its absence. Moreover scientists will continue to question any negative results that surface, and there will certainly be reward and recognition for the person who finds proof of harm. Expert contention that a 100 % GM variety approved for commercialisation is neither more*

31 Marc Van Montagu, Chairman, Institute of Plant Biotechnology for Developing Countries (IPBO) . Ghent University, Belgium "A decade of EU funded GMO research (2001 – 2010)" European Commission Directorate General for Research and Innovation, Biotechnoloies, Agriculture, Food (2010) EUR 24473 (En), 2010, p. 9.*http://www.ipbo.UGent.be http://www.psb.Ugent.be http://www.efb-central.org http://www.pubresreg.org , p. 21 – 22*

32 "Hearts and Minds," Nature Biotechnology, February 2007.

33 "Still, the results and even the existence of GMO biosafety research are often ignored in the public debate on the biosafety of GMOs. As a consequence, the already established strong basis for a science-based discussion on GMO biosafety is not fully explored in Europe or worldwide. In line with the complex public debate on the use of genetic engineering in agriculture and food production, the European Commission has been funding projects supporting science-based political decisions and improving the communication on 'green genetic engineering'." Prof. Dr. Joachim SCHIEMANN, Julius Kühn Institute (JKI) Federal Research Centre for Cultivated Plants, Head of the Institute for Biosafety of Genetically Modified Plants , "A decade of EU funded GMO research (2001 – 2010)" European Commission Directorate General for Research and Innovation, Biotechnologies, Agriculture, Food (2010) EUR 24473 (En), 2010, p 209

nor less of a health or environmental problem than its parent crop will not answer the question.[34]

Sadly, reliance on the Precautionary Principle as a policy making tool for advanced agricultural policies has proven to be a blind alley: "after 25 years of field trials without evidence of harm, fears continue to trigger the Precautionary Principle. But Europeans need to abandon this knowingly one-sided stance and strike a balance between the advantages and disadvantages of the technology on the basis of scientifically sound risk assessment analysis." While facing an intractable political environment, the European Union's own independent research concludes that GMO technologies provide no greater risks to health or the environment than conventional agricultural methods.[35]

Case Study: Stagnation of Italian Advanced Agricultural Technologies

Going back a quarter of a century, Italy led Europe in in agricultural biotechnology with over 250 experimental projects at a national level ranging including olive oil and fruit varieties. Italy's innovative agricultural sector has long since fell prey to internal EU politics over GM agriculture. In 2001, the Italian Ministry of Agriculture banned all agricultural biotechnology research trials. Despite subsequent EU decrees from Brussels that have been less negative over time, Italy has never reversed course; the curtailment of public research funding for agrobiotechnology, hamstringing competitiveness and reducing productivity of Italian companies.

In the absence of domestically produced GM products, like other EU Members, Italy became dependent on imported GM corn and soy. Far from being a GMO-free state, it is now recognized that GE agricultural products are widespread and essential inputs for "Made in Italy" exports, including pasta, regional cheeses, Prosciutto and others.

In 2014 Italian farmers and scientists appealed to Senator for Life and highly respected scientist Elena Cattaneo to weigh in on the issue in favor of science and advancing technology for Italy's struggling agricultural sector. Cattaneo responded positively, calling on Italy to adopt a science-based position favoring GE agriculture:

GE crops are not more risky than non-GE or organic ones. Moreover, the scientific community has clearly expressed the usefulness and safety of GE crops, calling for further research and testing of these products in field trials in Italy. Therefore, the so-called 'precautionary principle' should be abandoned and Member States should allow the cultivation of approved GE crops.[36]

This exchange had little apparent impact. While the EU approved limited cultivation of select GE crops based on scientific consensus, an Italian Inter-ministerial Decree officially banned planting of GE crops in January of 2015. Italy then pressed for a new exception to EU regulations to enable opt-out for non-science reasons. The EU acceded, publishing the Amended Directive in March 2015 (Directive (EU) 2015/412).

Italy's commitment to address 21st century food challenges explicitly includes agricultural biotechnology methods. In February of 2016, the Ministry of Agriculture initiated a three-year €21 Million Sustainable Biotech program for next-generation technologies,[37] seeking benefits of agricultural biotechnology with new GE techniques – and without the old GMO baggage. As Italy's Council for Agricultural Research and Agricultural Economic Analysis (CREA) asserts, this research focuses

34 Marc Van Montagu, Chairman, Institute of Plant Biotechnology for Developing Countries (IPBO) . Ghent University, Belgium "A decade of EU funded GMO research (2001 – 2010)" EC Directorate General for Research and Innovation, *Biotechnoloies, Agriculture, Food (2010) EUR 24473 (En), 2010, p. 9.http://www.ipbo.UGent.be http://www.psb.Ugent.be http://www.efb-central.org http://www.pubresreg.org , p. 21 – 22*

35 Forward, "A decade of EU funded GMO research (2001 – 2010)" EC Directorate General for Research and Innovation, Biotechnologies, Agriculture, Food (2010) EUR 24473 (En), 2010, p. 10. "The main conclusion to be drawn from the efforts of more than 130 research projects, covering a period of more than 25 years of research, and involving more than 500 independent research groups, is that biotechnology, and in particular GMOs, are not *per se* more risky than e.g. conventional plant breeding technologies." https://ec.europa.eu/research/biosociety/pdf/a_decade_of_eu-funded_gmo_research.pdf

36 Ibid, translation curtesy of the USDA Foreign Agricultural Service, p. 18.

37 Omella Bettini, "Italian Agricultural Research System Overview," USDA Foreign Agricultural Service Report, May 8, 2017, noting that: The research focuses on genome editing and cisgenesis. Minister Martina noted, 'These techniques are much different from transgenesis (insertion of a gene from a different gene pool) and will allow Italy to produce crops resistant to climate change and diseases.'" https://apps.fas.usda.gov/newgainapi/api/report/downloadreportbyfilename?filename=Italian%20Agricultural%20Research%20System%20Overview_Rome_Italy_5-24-2017.pdf

on molecular techniques and field plan phenotyping that are "far away from the GMO method."[38] CREA may be right, or Italy may be pouring new wine into old bottles.[39]

Continued political opposition at the local and regional level further complicate prospects for GM agriculture in Italy. Lacking advanced agricultural technologies, Italy has not only lost out on potential avenues for industrial biotechnology – it is unable to meet domestic demand for polenta, becoming a net importer of corn for this staple of Italian cuisine. Italy's loss is Spain's gain – as in other states where farmers are allowed to choose, Spanish farmers are choosing GM corn and now account for 90% of all EU BT corn production.

38 Ibid.

39 The jury is still out on the impact of Italy's research program which was extended in 2018 with an additional €6 million commitment over three years. Omella Bettini, "Italian Agricultural Research System Overview," USDA Foreign Agricultural Service Report, September 12, 2018, https://apps.fas.usda.gov/newgainapi/api/report/downloadreportbyfilename?filename=Agricultural%20Biotechnology%20Annual_Rome_Italy_10-18-2018.pdf

Article

The U.S. National Institutes of Health – Founding A National Biomedical "Innovation Ecosystem"

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ABSTRACT

With its unique system of intramural and extramural research programs, funding for academic and corporate product development, along with its supporting foundations, the National Institutes of Health (NIH) has created a vibrant public "innovation ecosystem" that has changed not only the face of healthcare, but has also led to the creation of the biotech industry in the U.S. Whether your interest in the overall healthcare environment is scientific, medical, educational or commercial, there is something here for you.

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INTRODUCTION

The start of National Institutes of Health (NIH) and thus the origins of its "innovation ecosystem" begins in 1887, when a one-room laboratory was created within the Marine Hospital Service (MHS), predecessor agency to the U.S. Public Health Service (PHS). The MHS itself had been charged by Congress in the 1880s for examining passengers on arriving ships for clinical signs of infectious diseases, especially for the dreaded diseases cholera and yellow fever, in order to prevent epidemics. Joseph J. Kinyoun, a young MHS physician trained in the new bacteriological methods being reported in Europe, was chosen to set up a one-room laboratory in the Marine Hospital at Stapleton, Staten Island, New York (Photo 1). Dr. Kinyoun (in essence the first NIH Director), called this facility a "laboratory of hygiene" to indicate that the laboratory's purpose was to serve the public's health. Within only a few months, Kinyoun had identified the cholera bacillus in suspicious medical cases and used his Zeiss microscope to demonstrate it to his colleagues as confirmation of their clinical diagnoses. In stimulating and assisting other parties for the improvement of healthcare we see the very beginnings of this unique innovation ecosystem around NIH.

Besides being the founding NIH Director, Dr. Kinyoun also focused on what we could call today bioentrepreneurship and technology transfer. In working first as a federal employee and later in the private sector Kinyoun invented and patented multiple industrial disinfecting machines used in quarantine operations such as the "Kinyoun Portable Bed Disinfectors". He also developed the first smallpox immune serum and his "Kinyoun Method" of smallpox vaccination used until the 1960s. The "Kinyoun Stain" that he discovered for TB is still in use today. Late in his career he even worked in pharma for a firm that became a predecessor to Merck.[1] Clearly Kinyoun led by example in founding NIH not only as an institution but also as an innovation ecosystem.

NIH TODAY

Despite his own remarkable vision and activities, Dr. Kinyoun could hardly have imagined the size and scope of the NIH's present programs and the supportive environment for biomedical research and product development that is fostered today. From its humble beginnings

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1 DM Morens and AS Fauci, *mBio*. 2012 Jul-Aug; 3(4): e00139-12.

Photo 1: Dr. Joseph J. Kinyoun, NIH Founder.

as a single laboratory, the NIH has evolved into a comprehensive program of 27 institutes and centers (ICs) that is both national and international in scope.

As a result of the numerous scientific opportunities and funding programs that make up today's NIH, the environment that NIH fosters continues to foster even more significant contributions to human health, new medical products and economic development. The 1986 Federal Technology Transfer Act codified and fostered partnerships between NIH intramural research and private-sector development of new medical products.

Around 90 percent of NIH's $41.7 billion FY 2020 final budget allocation went to more than 300,000 research personnel at over 2,500 universities, medical schools, companies and other research institutions in every state and throughout the world. The remaining 10% of this funding was spent on internal NIH R&D projects (intramural research) carried out by the approximately 6,000 scientists employed by the NIH. Dozens of NIH-supported scientists from around the world have received Nobel Prizes for their groundbreaking achievements in Physiology or Medicine; Chemistry; Physics; and Economic Sciences. To date, 163 NIH supported researchers have been sole or shared recipients of 96 Nobel Prizes. Included here are also individuals who have served as NIH staff scientists in the NIH Intramural Research Program. The 1980 Bayh-Dole Technology Act codified and fostered partnerships between NIH-funded extramural research and private-sector development of new medical products.[2]

As a continuous process, biomedical research and product development requires a supportive environment and an innovative ecosystem. For new research to truly yield new drugs, devices, and reagents, both public and private sector institutions need to use the ecosystem to refine and build upon basic knowledge to enable the development of even better products. Uniquely for NIH, it does not matter whether an idea originates in a supported university laboratory, its own intramural research program, or even in the private sector. Each new medical idea can be evaluated and supported based upon its own scientific and product merits, regardless of its origin. Collaborations, publications and research tool sharing also help ensure that important findings percolate through and invigorate the entire scientific community. For NIH's innovation ecosystem, new findings serve as a building blocks for establishing a deeper understanding of human health and disease and can be supported through a wide variety funding, educational, training and developmental programs.

STRUCTURE OF THE NIH INNOVATION ECOSYSTEM

To truly function as the foundation of an ecosystem, an institution or organization must realistically be able to help stimulate and sustain two primary functions — for biomedicine this would be both new research as well as product development. Most biomedical products have some history of their research and development that can be traced back to basic research institutions with the original research often funded by NIH or other governmental programs. Licensing and technology transfer programs at these federal labs, or other non-profit basic research organizations, then provide a means for getting new inventions to the market for public use and benefit. From a research institution's perspective, this portion of the innovation ecosystem is quite desirable since the public and commercial use of inventions typically come with new recognition of the value of basic research programs at the university or organization that originated it. These inventions also serve as helpful means to attract new R&D resources and partnerships within the ecosystem to these laboratories. Through licensing or other technology-transfer mechanisms, these institutions also receive a "return on investment" whether that

2 https://www.nih.gov/about-nih/what-we-do (accessed October 25, 2020).

is measured in terms of financial, educational or societal parameters, or some combination thereof.

NIH INNOVATION ECOSYSTEM KEYSTONE: BAYH-DOLE AND THE BIRTH OF TECHNOLOGY TRANSFER

Picking up from the momentum of the policies of Presidents John F. Kennedy and Richard Nixon, in 1980 Senators Birch Bayh and Robert Dole enacted legislation that gave universities, nonprofits, and small-businesses the right to own inventions made by their employees for federal government-funded research. The Bayh-Dole Act of 1980 (P.L. 96-517) reversed the presumption of title ownership by NIH in NIH grants and permitted a university, small business, or nonprofit institution to elect and pursue ownership of an invention in preference to the government. The underlying spirit of this important piece of legislation was to maximally utilize the outstanding research at these universities and other recipients for the good of the public who funded the research through their tax dollars and thus setting the stage for explosive growth of a new innovation ecosystem built around government biomedical funding agencies such as NIH.

The ownership right that universities and other funding recipients have to these inventions comes with obligations, but these obligations also stimulated activity in the ecosystem. The primary obligation for these institutions is to actively market and attempt to commercialize the invention, preferably through U.S.-based business enterprises (including start-ups) to benefit the public. Thus, was born the field of "technology transfer" and the establishment and growth of technology-transfer offices (TTOs) now found on every research campus. Prior to Bayh-Dole, 28,000 patents were owned by the U.S. government, less than 5 percent of which were commercialized. Since the enactment of Bayh-Dole, more than 6,500 new companies that were created are still operational, resulting in billions of dollars of direct economic impact within the United States and more than 800 new products put in the market during those years—all based upon NIH or other agency funded research.[3]

Similarly, in the 1980s, federal intramural laboratories, including NIH, were also given a statutory mandate under the Stevenson-Wydler Technology Innovation Act (P.L. 96-480), the Federal Technology Transfer Act (P.L. 99-502), and Executive Order 12591, to ensure that new technologies developed in federal laboratories were similarly transferred to the private sector and commercialized.

Within the innovation ecosystem, NIH and NIH-funded universities have developed a more strategic focus for their technology-transfer activities that is focused on working with entrepreneurs. Maximization of licensing revenue is not the goal of the NIH supported ecosystem. Instead, research organizations find themselves also looking for increasing product launches, company formation and new jobs creation based upon NIH-funded inventiveness, supporting faculty recruitment and retention, enhancing access to follow-on research funding, and in general creating an entrepreneurial culture that will help attract venture investment. The economic development aspects of research are being recognized as a fourth mission for such institutions—going along with education, research, and public service. Entrepreneurs play a key role in this "fourth mission" by establishing companies driven by new research discoveries and thus helping to build out the innovation ecosystem.

ACCESSING TECHNOLOGIES AND COLLABORATIONS IN THE NIH INNOVATIVE ECOSYSTEM

Generally, bioentrepreneurs can directly access NIH-supported research and inventions for product development from three main sources as shown in Table 1. For research funded by grants and contracts from NIH (extramural research), the individual university or small business would control commercial rights. Biomedical research conducted by NIH itself (intramural research program) is licensed directly through the individual IC technology transfer offices or their service centers at NIH.[4] The full spectrum of NIH intramural technology transfer activities is shown in Table 2.

Both NIH and NIH-supported research institutions have a robust research program "pipeline" that provides novel, fundamental research discoveries available for commercial applications. NIH, for instance, as both a large-scale provider and consumer, represents a sort of "supermarket" of research products or tools for its commercial partners and suppliers. Additionally, overall product sales of all types by NIH licensees generally are around $6 billion annually. Most NIH intramural technology transfer activities date from the Federal Technology Transfer Act of 1986 which authorized formal research partnerships with industry and provided incentives for these NIH programs to license technology by allowing the federal laboratory to, for the first

3 https://autm.net/AUTM/media/Surveys-Tools/Documents/AUTM_FY2018_Infographic.pdf (accessed October 25, 2020)

4 https://www.ott.nih.gov/tdcs (Accessed October 25, 2020).

Table 1: Sources for Accessing NIH-Funded Research In The Ecosystem

time, keep its license royalties and share them between the individual inventors and their laboratories or institutes.

Research collaborations or research assistance from NIH or NIH funded institutions can take several forms as these researchers and clinicians can work with industry under different collaborative modalities. For example, research institutions may seek to access technologies developed by industry—an imaging tool, a sequencing platform, or a drug discovered and in development by a company. The technology transfer office then works with companies and clinical partners to memorialize the understanding between the scientists and/or clinicians to allow the collaborations to happen. The key components of these collaboration agreement are terms related to inventions, rights to inventions, confidentiality versus publication, managing conflicts of interest, and finally, indemnification, especially for work involving patient care.

INDUSTRY COLLABORATIONS IN THE NIH INNOVATION ECOSYSTEM

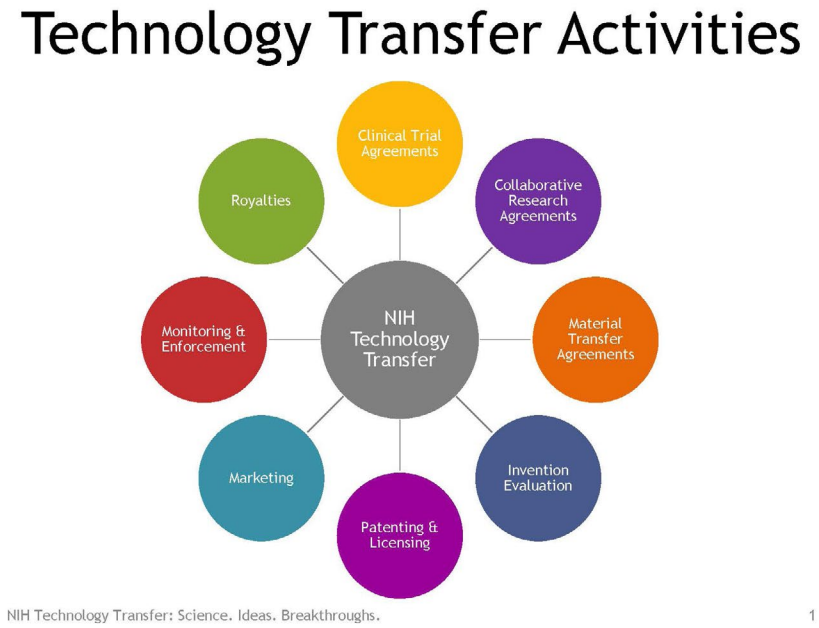
There are several types of research or collaboration-related agreements that biotech companies will commonly encounter in working with NIH and NIH-funded institutions:

Confidential Disclosure/Nondisclosure Agreements (CDA/NDA): Prior to engaging in any collaboration, each party may need to disclose to the other party some proprietary information that if passed on to third parties might be detrimental to the interest of the disclosing party. Such a discussion is a necessary first step to determine the interest in, and the breadth and scope of any potential collaboration. The parties will negotiate a CDA/NDA that ensures the information disclosed is held confidential, is only used for establishing the collaboration, stipulates a term of how long the information needs to be held confidential, and describes the consequences of nonadherence to the terms of the agreement.

Material Transfer Agreement (MTA), Sponsored Research Agreement (SRA), Research Collaboration Agreement (RCA), Clinical Trial Agreement (CTA) and Cooperative Research and Development Agreement (CRADA): Companies, both small and large, typically need to invest a significant research and development funds toward developing drugs or other biomedical products. NIH and NIH-funded research institutions have several programs that are key towards understanding the fundamental biology underlying a wide variety of commercial products. When companies and research institutions seek to collaborate, they often will have very different focuses. A company often is hoping to learn more about their product concept, get mechanistic insights that can be used to position their product better in the marketplace, and have discoveries come out of this collaboration which may improve the usefulness and utility of their eventual product. In the case of collaborations with NIH supported clinical programs, it may also be possible to access to patient samples in addition to the valuable clinical insights the company hopes will guide them through clinical validation of their product whether it be a potential drug, medical device, or diagnostic. The NIH or university investigator are often interested to test various compounds from various companies to build a scientific insight or medical knowledge that will be publishable. It will also be possible under CRADAs or SRAs for the investigator to receive funding support from the company for basic or clinical research programs that may need it.

MTAs and SRAs are agreements that dictate the terms of the transfer of material and/or money from the company to the academic institution. Similarly, at NIH, joint projects with companies for basic research or clinical studies can be formalized as CRADAs or if there no IP options or funding provided then RCAs. Because of their clinical hospitals and centers as well as other networks and facilities, the NIH and at least some of its supported universities can also take some medical discoveries (or

Table 2: Intramural NIH Technology Transfer Ecosystem Activities



those of their partners) into clinical trials through CTAs. A case study about how the Foundation for the National Institutes of Health (FNIH)as an NIH-supporting foundation helps to "fill the collaboration gaps" in the NIH innovation ecosystem is given in Appendix A.

LICENSING TECHNOLOGIES FROM THE NIH INNOVATION ECOSYSTEM

Basic Licensing Principles of University and Federal Laboratories: Compared to technology licensing with corporations, NIH and NIH-supported institutions bring a different focus and perspective to the table when negotiating technology transfer agreements. Because these agreements are used to further overall institutional missions, representatives from such nonprofit institutions consider the public consequences of such licenses as their priority, not the financial terms that may be involved. For example, NIH-funded nonprofit institutions, compared with their peers in industry, have the mandate to make new technology as broadly available as possible. This means that there is a strong preference to limit the scope of a license to only what is needed to develop specific products. Exclusive licenses are quite typical for biomedical products such as vaccines, therapeutics, and others where the underlying technologies require substantial private risk and investment (and a prior public notice and comment period in the Federal Register in the case of NIH laboratories). In their agreements, NIH laboratories and universities would also typically expect to retain the right to permit further research use of the technology whether to be conducted either in the NIH intramural program, universities, or companies. Because the commercial rights granted represent institutional (and public) assets, these agreements have enforceable performance benchmarks to ensure that the public will eventually receive the benefit (through commercialized products) of the research it funded. Regulations governing the license negotiation of federally-owned technologies and their mandated requirements are described in more detail at 37 Code of Federal Regulations (CFR), Part 404, while those for federally-funded technologies can be found at 37 CFR Part 401.

In a license agreement, the academic entity essentially grants rights to a company to make, use, and sell products that were it not for the license, would infringe on the patent rights that the academic center owns and/or controls. In some instances, the academic center also grants the company rights to use technological information/know-how or materials that goes together with the information in the patent application and that is valuable to the company as it hopes to commercialize the technology into products. Licensing is at the heart of operations of a technology transfer office since neither NIH, or NIH-funded universities, function as nonprofits, and do not, and cannot, have a product commercialization arm.

NIH or NIH-funded universities may also not themselves convert inventions into commercial products and processes. They must partner with industry to do that as is also often the case with NIH-funded small businesses under the Small Business Innovation Research (SBIR) programs. Thus, these out-licensing activities are the key for research programs to fulfil the core of the Bayh-Dole Act and other federal mandates of commercializing inventions that arise from NIH funding.

Licensing from NIH & NIH-Funded Laboratories: Commercializing technologies, such as vaccines or drugs, and then marketing them successfully in worldwide markets, cannot be the responsibility or mission of research institutions or government agencies. As is the case with its funded universities, the NIH is not able to commercialize its discoveries even with its considerable size and resources—it relies instead upon partners. Companies with access to the needed expertise financial resources are needed to undertake continued development of these inventions from the NIH or other research institutions into final products. Typically, a royalty-bearing license agreement with the right to sublicense is given to a company from NIH (if NIH-owned) or the university (if university-owned) to use patents, materials, or other assets to bring a therapeutic, vaccine, or other product concept to market. Exclusivity is almost always the norm for the U.S. Food and Drug Administration (FDA)-regulated products due to the risk involved in time, money, and regulatory pathways involved for companies and their investors. Financial terms of the license agreement are negotiable but do typically reflect the nascent, high-risk nature of the discovery. Because the technologies coming from NIH or NIH-funded research are most typically preclinical inventions, most licensees are early-stage companies or start-ups, rather than larger firms who typically want more proven ideas for new products. In addition to the license agreement, there will often be research collaborations between the licensee and the NIH or university to assist with additional work needed on the product technology. When the NIH licensee can sufficiently "de-risk" the technology through its various efforts, these companies then sublicense, partner, or get acquired by larger biotech or pharmaceutical firms for the final, most expensive stages of development with the large company expected to sell the product once it reaches the market.

Start-Ups as Licensing Vehicles in The NIH Innovation Ecosystem: Since the 1980s, federally-funded health research institutions have developed an active but increasingly strategic focus on improving public health through technology-transfer activities. As such, they are particularly interested in working with start-ups and other early-stage companies in the healthcare area that are looking to develop and deliver innovative products. Rather than just seeking a financial return through revenue generation, these institutions are looking to utilize licensing of nascent inventions to increase new company formation, support faculty recruitment and retention, enhance research funding, and create in general a more entrepreneurial culture within the organization, attracting venture investment and development to their specific geographic region (universities) or to the health sector in general (NIH).

The licensing practices for most NIH-funded nonprofit research institutions have changed significantly over time with respect to biomedical inventions.[5] With its ever-increasing consolidation, large pharmaceutical firms are typically no longer looking to directly license early-stage technologies for commercialization, whereas the number of licenses signed with start-ups as well as small – to medium-sized biotechnology companies is on the rise. Indeed, typically around 70 percent of the total licenses are executed with start-ups and small biotech firms. Unlike 20 or so years ago, when all or most of the important medical products based on licenses from university or federal laboratory research came from direct agreements with large pharmaceutical firms, most of the latest success stories tend to be from those originally partnered with biotech or other smaller companies at the time of the original license agreement. Some examples from the NIH licensing program are Kepivance® (a human growth factor used to treat oral sores arising from chemotherapy licensed to Amgen), Velcade® (a small molecule proteasome inhibitor used to treat multiple myeloma from Millennium), Synagis® (a recombinant monoclonal antibody for preventing serious lung disease caused by respiratory syncytial virus in premature infants from MedImmune), Prezista® (an HIV protease inhibitor used to treat drug-resistant AIDS patients from Tibotec) and Taxus Express® (a paclitaxel drug-eluting coronary stent used to prevent restenosis from Angiotech). Although these firms or their successors are all substantive, well-known companies now, at the time the underlying technology was licensed to them, they were not large corporations.

FUNDING IN THE NIH INNOVATION ECOSYSTEM

NIH is well known as the largest public funder of biomedical research in the world and invests more than $37 billion a year with outside institutions to enhance life and reduce illness and disability. This level of funding

5 G Ben-Menachem, S Ferguson, K Balakrishnan, Doing Business With NIH, *Nature Biotechnology* 2006: 24(1):17-20.

supports a strong research ecosystem that has led to breakthroughs and new treatments, helping people live longer, healthier lives, and building the research foundation that drives discovery. NIH offers funding for many types of grants, contracts, and even programs that help repay loans for researchers

While perhaps best known for grants to academic scientists, NIH also provides private sector entities with nondilutive funding through the SBIR (Small Business Innovation Research) and STTR (Small Business Technology Transfer Research) programs.[6] The NIH SBIR program is perhaps the most valuable and stable funding source for new companies and unlike small business loans or convertible notes, SBIR grant funds do not need to be repaid.

Other noteworthy advantages of NIH SBIR programs for small companies include retention by the company of any intellectual property rights from the research funding, receipt of early-stage funding that doesn't impact stock or shares in any way (e.g., no dilution of capital), national recognition for the firm, verification and visibility for the underlying technology and the generation of a leveraging tool that can attract other funding from venture capital or angel investors.

The SBIR program itself was established in 1982 by the Small Business Innovation Development Act to increase the participation of small, high technology firms in federal R&D activities. Under this program, departments and agencies with R&D budgets of $100 million or more are required to set aside 3.2 percent of their R&D budgets to sponsor research at small companies. The STTR program was established by the Small Business Technology Transfer Act of 1992 and requires federal agencies with extramural R&D budgets over $1 billion to administer STTR programs using an annual set-aside of 0.45 percent. In FY 2018 NIH's combined SBIR and STTR grants totaled over $1.059 billion.[7]

The STTR and SBIR programs are similar in that both seek to increase small business participation and private-sector commercialization of technology developed through federal R&D. The SBIR program funds early-stage research and development at small businesses. The unique feature of the STTR program is the requirement for the small business applicant to formally collaborate with a research institution in Phase I and Phase II.

Thus, the SBIR and STTR programs at NIH differ in two major ways. First, under the SBIR program, the principal investigator must have their primary employment with the small business concern at the time of the award and for the duration of the project period. However, under the STTR program, primary employment is not so stipulated. Second, the STTR program requires research partners at universities and other nonprofit research institutions to have a formal collaborative relationship with the small business concern. At least 40 percent of the STTR research project is to be conducted by the small business concern and at least 30 percent of the effort is to be conducted by the single "partnering" research institution.

As a major mechanism at the NIH for achieving the goals of enhancing public health through the commercialization of new technology, the SBIR and STTR grants present an excellent funding source for start-up and other small biotechnology companies. The NIH SBIR and STTR programs themselves are structured in three primary phases: Phase I (feasibility), Phase II (development) and Phase III (commercialization).

In addition to receiving funding through the NIH SBIR and STTR programs, small companies may also be eligible for technical and management assistance programs designed to increase their chances for successful commercialization of the funded technology. These are a key part of the NIH innovation ecosystem and would include:

Niche Assessment Program – For SBIR/STTR Phase I Awardees, this program is designed to help small businesses "jump start" their commercialization efforts by providing market insight and data that can be used to help such companies strategically position their technology in the marketplace. The results of this program can help small businesses develop their commercialization plans for their Phase II application and be exposed to potential commercial partners.

Innovation Corps (I-Corps) at NIH — The I-Corps program provides funding, mentoring, and networking opportunities to help SBIR Phase I awardees commercialize promising biomedical technology. During this 8-week, hands-on program, companies learn how to focus their business plans and get the tools to bring their treatment to market. Program benefits include funding up to $55,000 to cover direct program costs; training from biotech sector experts; expanding professional networks; creating a comprehensive business model; and gaining entrepreneurial skills.

Commercialization Accelerator Program (CAP) – NIH CAP is a nine-month program open to SBIR/STTR Phase II awardees that is well-regarded for its combination of deep domain expertise and access to industry connections, which have resulted in measurable gains and accomplishments by participating companies. Offered since 2004 to address the commercialization objectives of companies across the spectrum of experience and stage, 1000+ companies have participated in the CAP. The program enables participants to establish market and customer relevance, build commercial relationships, and focus on revenue opportunities available to them.

6 https://sbir.nih.gov/ (Accessed October 25, 2020).

7 https://report.nih.gov/nihdatabook/category/8 (Accessed October 25, 2020).

USING NIH BASIC AND CLINICAL RESEARCH ASSISTANCE TO DEVELOP THE INNOVATION ECOSYSTEM

Basic and clinical research assistance from the NIH institutes may also be available to companies or other partners through specialized services such as drug candidate compound screening and preclinical and clinical drug development and testing services, which are offered by several programs. These initiatives are particularly targeted towards developing and enhancing new clinical candidates in the disease or health area of focus at various NIH institutes. The largest and perhaps best-known programs of these types at the NIH are those currently run in the National Cancer Institute (NCI)[8]. The NCI has played an active role in the development of drugs for cancer treatment for over 50 years. This is reflected in the fact that approximately one half of the chemotherapeutic drugs currently used by oncologists for cancer treatments were in some form discovered and/or developed with NCI. The Developmental Therapeutics Program (DTP) promotes all aspects of drug discovery and development before testing in humans (preclinical development) and is a part of the Division of Cancer Treatment and Diagnosis (DCTD). NCI also funds an extensive clinical (human) trials network to ensure that promising agents are tested in humans. NCI's Cancer Therapy Evaluation Program (CTEP), also a part of the DCTD, administers clinical drug development. Compounds can enter at any stage of the development process with either very little or extensive prior testing. Drugs developed through these programs include well-known products such as cisplatin, paclitaxel, and fludarabine.

Beginning in 2012 the NIH established a new center called the National Center for Advancing Translational Sciences (NCATS) that is designed to assist companies with the many costly, time-consuming bottlenecks that exist in translational product development.[9] Working in partnership with both the public and private organizations, NCATS seeks to develop innovative ways to reduce, remove, or bypass such bottlenecks to speed the delivery of new drugs, diagnostics, and medical devices to patients. NCATS is not a drug development company but focuses more on using science to create powerful new tools and technologies that can be adopted widely by translational researchers in all sectors. NCATS-supported programs and projects have also produced numerous tools to help basic and clinical researchers advance translational science.

Programs of note for the NIH innovation ecosystem from NCATS include *Bridging Interventional Development Gaps (BrIDGs)* which enables research collaborations to advance candidate therapeutics for both common and rare diseases into clinical testing; *Clinical and Translational Science Awards (CTSA)* support a national network of medical research institutions that work together to improve the translational research process to get more treatments to more patients more quickly; and *Therapeutics for Rare and Neglected Diseases (TRND)* offers collaborative opportunities to access rare and neglected disease drug-development capabilities, expertise, and clinical/regulatory resources.

There is additional assistance available from other NIH institutes in a variety of disease areas including infectious diseases, drug abuse, and others—many more than can be highlighted here. All in all, such efforts can provide a wide variety of technical assistance (often at modest or no cost) for preclinical and even clinical development of novel therapies or other biomedical products by a variety of partners within the NIH innovation ecosystem.

CONTRACTING OPPORTUNITIES WITH NIH AND NIH-FUNDED INSTITUTIONS

One of the most overlooked opportunities by biomedical-focused companies is the ability to sell products and services to the NIH and NIH-funded centers. Indeed, for start-up companies looking to develop new products used in conducting basic or clinical research, the NIH may be their first customer. With an intramural staff of about 18,000 employees, laboratories in several regions of the country (with the Bethesda campus in Maryland home to the majority), and an annual intramural budget of about $4 billion, the NIH is perhaps the largest individual institutional consumer of bioscience research reagents and instruments in the world. A variety of mechanisms for selling products and services to the NIH are possible, including stocking in government storerooms and general contracting opportunities. Companies that provide products and services to NIH laboratories and programs can not only generate cash flow and revenues to fuel their own R&D, but also begin to demonstrate their commercial acumen to would-be partners and investors. Being a large research organization, the NIH has numerous R&D contracting opportunities. Specific information on such opportunities can be found by visiting the NIH Office of Acquisition Management and Policy website.[10]

8 https://dtp.cancer.gov/ and https://ctep.cancer.gov/ (Accessed October 25, 2020).

9 https://ncats.nih.gov/ (Accessed October 25, 2020).

10 https://oamp.od.nih.gov/ (Accessed October 25, 2020).

The annual NIH Research Festival is also an excellent starting point for companies hoping to sell products to the NIH[11]. This event is held at the Bethesda, Maryland campus and the Frederick, Maryland campus. Part scientific, part social, part informational, and part inspirational, this event draws a variety of small – to medium-sized bioscience firms to exhibit their product and services available to NIH.

TRAINING AND EDUCATION IN THE NIH INNOVATION ECOSYSTEM

In addition to traditional scientific training supported at all educational levels, NIH and NIH-funded universities have set up or have access to educational programs that train scientists and engineers to have a greater appreciation as to the importance of commercialization. These programs are often funded and supported at NIH institute training offices. In addition, the NIH Office of Intramural Training and Education (OITE) provides resources and information to enhance the educational experience of NIH trainees and can assist with finding appropriate workshops, arranging individual career counseling and identifying other NIH resources to meet trainee needs. OITE resources are also available for trainees in the extramural NIH community. Other options for education and training include entrepreneurship centers and small business assistance programs at many universities and such things as the "Advanced Studies in Technology Transfer" program given at the Foundation for Advanced Education in the Sciences (FAES) Graduate School at NIH.[12] A case study on how FAES as an NIH-supporting foundation helps to "fill the educational gaps" in the NIH innovation ecosystem is given in Appendix B.

NIH INNOVATION ECOSYSTEM HAS SPURRED BIOTECHNOLOGY INDUSTRY GROWTH

As previously noted, the economic development potential of biomedical research is being recognized as a fourth mission for research institutions such as the NIH —going along with education, research, and public service. Thus, it is in this "fourth mission" that bioentrepreneurs and NIH find themselves again sharing the common goal of having new companies established based upon developing innovative research discoveries.

The economic importance of licensing and technology transfer has become better recognized in recent years and some of the figures can be quite striking. For example, the overall product sales of all types by licensees of NIH intramural research reported by the NIH Office of Technology Transfer as being around $6 billion annually, the equivalent of mid-tier Fortune 500 companies. Economic development also was the focus of the October 28, 2011 U.S. Presidential Memorandum entitled "Accelerating Technology Transfer and Commercialization of Federal Research in Support of High-Growth Businesses".[13] This directive from the White House recognized the economic aspects of innovation and technology transfer for federal research in the way it fuels economic growth as well as creating new industries, companies, jobs, products and services, and improving the global competitiveness of U.S. industries. The directive requires federal laboratories such as the NIH to support high-growth entrepreneurship by increasing the rate of technology transfer and the economic and societal impact from federal R&D investments. During this period, federal laboratories such as the NIH will be establishing goals and measuring progress towards commercialization, streamlining the technology transfer and commercialization processes, especially for licensing, collaborations, and grants to small companies, and also facilitating the commercialization of new technology and the formation of new start-up firms through local and regional economic development partnerships.

Looking at the university and academic medical center figures reported by the Association of University Technology Managers (AUTM), we find there are similar economic indications for the impact of technology transfer and the initial funding of research from NIH and other federal programs.[14] In 2018 AUTM reported 9,350 new license agreements and new research expenditures of 71.7 billion by reporting universities. In 2018, more than 6,518 start-ups were also still operational from prior years. By the end of 2018, 828 new products had been introduced into the marketplace.

11 https://researchfestival.nih.gov/2019 and http://www.technicalsalesassociation.org/site/ (Accessed October 25, 2020).

12 https://faes.org/content/advanced-studies-in-technology-transfer (Accessed October 25, 2020).

13 https://federallabs.org/about/history (Accessed October 25, 2020).

14 https://autm.net/AUTM/media/SurveyReportsPDF/AUTM_FY2018_US_Licensing_Survey.pdf (Accessed October 25, 2020).

NIH INNOVATION ECOSYSTEM: RESULTS TO DATE

With their leading-edge research programs and focus in the healthcare market, NIH and NIH-funded research programs have an exemplary record in providing opportunities for bioentrepreneurs to develop both high-growth companies and high-growth medical products. Indeed, a preliminary study from 2007 has shown that more than 100 drug and vaccine products approved by the U.S. FDA were based at least in part on technologies directly licensed from university and federal laboratories with federal labs (NIH) providing nearly 20 percent of the total[15]. Further, another study from 2009 has shown that university-licensed products commercialized by industry created at least 279,000 jobs across the United States during a 12-year period and that there was an increasing share of the United States GDP each year attributable to university-licensed products[16]. Additionally, a study published in the *New England Journal of Medicine*[17] in 2011, based upon the earlier 2007 preliminary study, showed the intramural research laboratories at the NIH as by far the largest single nonprofit source of new drugs and vaccines approved by the FDA. Finally, a 2017 study from the National Cancer Institute SBIR Development Center showed that out of 690 awards, 368 (53%) had already resulted in sales. Total cumulative sales were $9.1 billion, which equates to average sales of approximately $24.8 million for each of the 368 awards.[18]

These sales indicate that the impact of the NIH innovation ecosystem is strong and will be increasingly effective and important into the future. Although new knowledge and product development has been a model in showing the value of the NIH innovation ecosystem from NIH and NIH-funded institutions, it is not the entire story. The final tally must include not only the full societal value and economic impact both of new companies, but also more importantly as well as the life-saving or enhancing therapeutics, vaccines, diagnostics, and other biomedical products on the market that have origins in this federally-funded research. This is believed to be the truest measure of an innovation ecosystem as well demonstrating the value and importance of having the growth of the intramural and extramural programs of the NIH since its humble origins in 1887.

CONCLUSIONS

In conclusion, there are also NIH-related programs intended to accelerate and support collaborations intended to foster entrepreneurship to support the commercialization of the inventions and discoveries that come from its laboratories, much like most innovative universities have done as well (c.f. articles included elsewhere in this Special Edition, authored by Moira Gunn at University of San Francisco, and Paul Roben and Dennis Abremski at the University of California, San Diego). We illustrate two significant NIH-related programs that are described in two concluding **Sidebars**: the Foundation for the National Institutes of Health, and the Foundation for Advanced Education in the Sciences.

HELPING NIH FOSTER A SYSTEM OF COLLABORATIONS:

Foundation for the National Institutes of Health (FNIH)

The Foundation for the National Institutes of Health (FNIH) is a 501(c) (3) charitable organization chartered by Congress in 1996 that procures funding and manages alliances with public and private institutions in support of NIH's mission.[19] The FNIH is legally chartered to accept donations from alumni inventors and scientists, philanthropists, and high-wealth individuals to support activities designed to accelerate biomedical research and strategies to fight against diseases in the United States and across the world. FNIH organizes and administers research projects; supports education and training of new researchers; organizes educational events and symposia; and administers a series of funds supporting a wide range of health issues.

15 J Jensen, K Wyler, E London, S Chatterjee, F Murray, M. Rohrbaugh, The Contribution of Public Sector Research to the Discovery of New Drugs. Personal communication of poster at 2007 AUTM Annual Meeting. 2007.

16 https://www.bio.org/sites/default/files/legacy/bioorg/docs/files/BIO_final_report_9_3_09_rev_2_0.pdf (Accessed October 25, 2020).

17 A Stevens, J Jensen J, K Wyller, P Kilgore, S Chatterjee, M. Rohrbaugh, "The Role of Public-Sector Research in the Discovery of Drugs and Vaccines. *New England Journal of Medicine* (2011) 364 535–541.

18 https://sbir.cancer.gov/impact (Accessed October 25, 2020).

19 https://fnih.org/about and https://itif.org/publications/2019/03/04/bayh-dole-acts-vital-importance-us-life-sciences-innovation-system (Accessed October 25, 2020).

Since its founding, it has raised over $1 billion which it has used to support over 600 research programs. FNIH specializes in building public-private partnerships between government, academic, industry, nonprofit, and patient-group researchers in order to conduct research into specific disease states and research areas. Because partnerships have become increasingly important in life-sciences innovation, FNIH is an important convener and facilitator in the NIH innovation ecosystem.

HELPING NIH FOSTER A SYSTEM OF ENTREPRENEURSHIP –

Foundation for Advanced Education in the Sciences (FAES) at NIH

The Foundation for Advanced Education in the Sciences at the NIH (FAES@NIH) has fostered an environment of learning in the sciences since it was established in 1959.[20] The biomedical science focus has expanded to include many courses and programs intended to support the commercialization of the many biomedical innovations being created every day at the NIH. These courses and workshops include areas such as management, valuation of innovation, technology transfer and marketing of biomedical technologies.

The history of the FAES started with 11 NIH scientists seeking to create a more university-like environment for the NIH researchers. Since its beginning, FAES has offered graduate level courses and workshops to thousands of NIH researchers. This continues today, and the educational programming remains open to the general public as well as the NIH. In 2020, FAES registered almost 3,000 students in its nearly 200 courses and workshops.

The programming at FAES is kept affordable because its mission is to offer programming that is accessible by the NIH scientists at all levels. The educational programs are focused on topics that the NIH staff and researchers find relevant. In addition to hard science, one of the key areas is the Department of Technology Transfer, Business and Industry. Students can sign up for a broad selection of core courses including project management, regulatory science, intellectual property, and even courses in how to build a biotech company. FAES Academic Programs has also developed its unique "Advanced Studies Certificate in Technology Transfer" to serve the needs of scientists and engineers who want expertise in patenting, licensing, collaborative agreements, and other fundamental intellectual property transactions. This program culminates in an independent capstone project through which students demonstrate their knowledge of the theory and practice of technology transfer by completing a project of their own design at the NIH, or in their regional community.

FAES also partners with many NIH institutes to offer customized programming to help each institute meet their specific mission. One example is a partnership with the National Center for Advancing Translational Sciences. NCATS underwrites the cost of a course in bench to bedside cancer treatments so students only pay a very modest $60 total tuition. FAES@NIH also partners with several universities so that the courses often transfer and count towards a master's degree. For instance, students interested in data science and bioinformatics may take 15 of the total thirty credits from FAES toward the University of Maryland Baltimore County Master of Professional Science in Data Science.

For decades at FAES, the philosophy has been to 'do for the NIH what the NIH couldn't or can't do for itself.' The current course offerings have all come together to create and support the ecosystem at NIH – one that fosters a culture of community and support to researchers. Beyond just education, though, the FAES has developed services that have grown to include a bookstore, coffee shops, and a social and academic center that houses classrooms and entertainment space. FAES even sponsors a music program for the NIH clinical center that features world-recognized musicians, such as the National Symphony Orchestra. Besides educational programming, FAES also offers support services such as health insurance to almost 4,000 NIH fellows, who otherwise would not have access to affordable health insurance.

When the founders of FAES@NIH created the organization, they could not have imagined the long-lasting impact it would have. Yet, 61 years later, FAES@NIH supports so many areas within the NIH community, including support for an entrepreneurial ecosystem that allows researchers to expand their research beyond the lab by supporting the transfer of their discoveries from the lab to the patients.

20 https://faes.org/ (Accessed October 25, 2020).

Article

Multi-Disciplined Ecosystem-Centric Bioentrepreneurship Education: Case Study – University of San Francisco (USF)

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ABSTRACT

Bioentrepreneurship education has evolved into at least three different types, all of which co-exist: Education 1.0 – In Service of Biotechnology Startups, Education 2.0 – In Service of Biotechnology Innovation Ecosystems, and Education 3.0 – In Collaboration with Biotechnology Innovation Ecosystems. Examples are given at all levels, along with a Case Study of the Bioentrepreneurship (BioE) program at the University of San Francisco (USF). The USF program draws from twelve expertise disciplines described by the Bioenterprise Innovation Expertise Model (BIEM 2.0), those essential disciplines bioenterprise requires to bridge the science/technology discovery/invention through to viable commercial product life cycle. As a result, the USF program reaches graduate students across the university. The utilization of the BIEM 2.0 model throughout the BioE courses is discussed, as well as the incorporation into the curriculum of BioTech Nation interviews with biotechnology industry executives and scientists. Due to the COVID-19 Pandemic and the requirement to move the BioE courses to a remote modality, future plans include the development of a fully online Bioentrepreneurship (BioE) certificate, primarily targeting the California state biotechnology corridor of San Francisco, Los Angeles, Orange County, and San Diego Biotechnology Innovation Ecosystems. Additional new BioE courseware will address the growing sector of Digital Health.

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INTRODUCTION

What builds innovation ecosystems and clusters within the global biotechnology industry? Is it driving more and more scientific breakthroughs? Is it creating new technologies which enable these breakthroughs to become deliverable products? Is it fostering, incubating and funding startups to bridge that expanse? These efforts are undoubtedly key to fueling the engine which drives the commercial biotechnology economy. Does this suggest this is where universities must solely focus?

This paper examines several educational models in which universities may engage with the biotechnology innovation ecosystem. It further provides a Case Study of the University of San Francisco's (USF's) bioentrepreneurship (BioE) program, which serves as an exemplar within one of these educational models, and which can be replicated within other innovation ecosystems, ultimately providing substantial benefit to the ever-evolving biotechnology industry.

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EDUCATION 1.0 – EDUCATION IN SERVICE OF BIOTECHNOLOGY STARTUPS

The central myth of the successful biotechnology startup is that a life scientist makes a breakthrough at the lab bench, meets a daring venture capitalist, and the two

create a stunning biotech company. In other words, Herb Boyer meets Bob Swanson, and the result is Genentech. Adding substance to the myth, Genentech is often mistakenly referred to as the first biotech company. Even the esteemed journal *Nature* made that mistake in 2019, and corrected itself in 2020.[1,2] It seems that Cetus was founded some five years earlier, and that others must also be counted among the bold. That would include Gamma Biologicals and Irvine Scientific.[2] Also lost in the mythological construct – Herb did not "pitch" Bob; Bob went looking for Herb.[3]

Thus, the perception of what entrepreneurship has come to mean today seems to overlook the visionary serendipity of the founding of Genentech and translates itself into a fueled mission which starts with embracing a potential commercial idea from science and/or technology, commencing an indefatigable search for funding, and ultimately proceeding to company startup.

This perception and similar non-biotech founding myths have wended their way into general entrepreneurship education. A case-in-point can be found among the Stanford Center for Professional Development's impressive array of professional education offerings, while also offering credited individual courses, degree programs and certificate opportunities.[4] Its 10-week, online "Idea-to-Market" course enables a "step-by-step guide to prepare your idea for launch", collaboration and networking "with an international cohort of entrepreneurs", and "feedback on your completed pitch deck and presentation from our industry expert mentors".[4]

To be fair, every enterprise has to start somewhere and somehow, but professional education in the biotech startup space is necessarily more complex. First of all, the need for funding is legendary. In biopharmaceuticals, the largest biotech industry sector, a March, 2020 London School of Economics and Political Science study published in *JAMA*, the *Journal of the American Medical Association*, focused on publicly-available data for 355 FDA-approved drugs between 2009 and 2018.[5-6] Accounting for the cost of failed trials, the median capitalized investment to bring a new drug to market was found to be $985 million, while the average was calculated to be $1.3 billion (in 2018 dollars).[6]

This level of investment invites risk, and in the biopharmaceutical space, the failure rate of such endeavors cannot be ignored. A 2018 study published in the journal *CTS (Clinical and Translational Science)* examined pre-clinical studies in the United States, Europe and Japan, and calculated pre-clinical failure rates for biologics at 68.2%.[7] For those drugs which then move on to FDA clinical trials, a recent MIT study published in the journal *Biostatistics* indicated that 86% of all drugs entering FDA clinical fail.[8] And unfortunately, they may not fail quickly.

Even when successful, the time required to develop a new biopharmaceutical is truly remarkable. In 2010, it was estimated at 10 years on average by PhRMA, a consortium of US biopharmaceutical companies, but the elements of these timelines have also been changing over time.[9-10] A 2020 Harvard study published in *JAMA*, the *Journal of the American Medical Association*, examined FDA approvals between 1983 and 2018.[10] It found that biopharmaceuticals benefited from advances in technology, that approvals under the Orphan Drug Act (increased to 41% of all approved drugs), and that 81% of all drugs approved benefited from one or more of these schedule-improving designations: Accelerated Approval, Fast-Track and Priority Review.[10] Still, even with roughly half the drugs now solely requiring only one pivotal trial instead of two, the average time of approval through all clinical trials remains at 8 years.[10]

In the current COVID-19-related climate, the FDA has approved vaccines under emergency use with less than a year for all clinical trial phases.[11] Whether this has an impact on the timelines of future clinical trials remains to be seen. In any event, all commercial biotechnology endeavors require significant investment capital that must be put at risk for many years.

Specialized entrepreneurship education in the biotech startup space recognizes these considerations as the higher level challenge it is. One example with respect to initiating a bioenterprise is the relatively new, ten-week online course from the UCSF Entrepreneurship Center: "Entrepreneurship for Life Science and Healthcare Startups: Master Class Direct from Silicon Valley".[12]

Another example is the annual Biotechnology Entrepreneurship Boot Camp, a two-day intensive created by senior bioentrepreneurship academics from Carnegie Mellon University and Wharton Business School, and supported by industry.[13] It is a part of the annual Biotechnology Innovation Organization (BIO) conference. Having evolved over 15+ years, the boot camp is experiential in nature and today covers Product/Company Assessment and Qualification, Reimbursement and Pricing, Global Regulatory Implications, U,S, Regulatory Planning, Intellectual Property, Board Membership Design, and Entrepreneurial Management Teams. This goes beyond the idea of a single or first pitch for funding and portrays instead the multiple, successive search for funding typically needed. It includes Pre-Seed/Seed Funding Pitches, Early Stage Funding Pitches, and Exit Triggers within the framework of the total capitalization needed by the biotechnology venture over time.[13] Similarly, it starts with qualifying the idea and gaining initial funding, but it quickly moves on to delivering the reality of the total bioenterprise. Future boot camps will be online while the BIO conference retains its temporary digital

format, and will resume on an in-person basis in step with the annual BIO conference.[13]

Degree-oriented university science programs have also sought to incorporate bioentrepreneurship in support of startup ideation, creation and participation upon graduation. At the masters' level, the University of Pretoria's Karl Kunert and Case Western Reserve University's Christopher Cullis encapsulate this philosophy in their editorial, "Universities must teach their budding scientists entrepreneurship".[14] It further points out the opportunity afforded by universities offering Professional Science Masters (PSM) degrees. These PSM degrees require business curriculum and internships as a complement to science and other technical fields; over 40 PSMs in Biotechnology are offered within the United States.[15] In the case of Case Western, its unique PSM degree is decidedly entrepreneurial: a PSM in Entrepreneurial Biotechnology.[16]

From an educational pedagogy standpoint, these examples begin to be a departure from the professional education startup paradigm. While students may well have in mind starting up a bioenterprise, the courses and internships speak for themselves – participation in biotechnology innovation ecosystem. It's arguable that these degree programs actually belong in the next transitional category: Bioentrepreneurship Education 2.0.

EDUCATION 2.0 – EDUCATION IN SERVICE OF BIOTECHNOLOGY INNOVATION ECOSYSTEMS

Many times labelling any activity "2.0" suggests that it replaces "1.0". That is not suggested here. In fact, that which has been identified as Education 1.0 remains much needed, and it will continue to evolve and thrive, as it should. Let us remember that the biotechnology industry, and bioenterprise along with it, is relatively new, measured only in single-digit decades. As any entity matures, more will be recognized about achieving success in the science-to-product cycle.

In fact, participating in any bioenterprise at any level could be considered entrepreneurial, independent of the company founders and the ongoing need for investment funds. Thus, Education 2.0 focuses on the expansive and expanding job of work required by the bioenterprise to achieve success in the science-to-product life cycle. Several examples of Education 2.0 are provided.

Given the premise that the engine of biotechnology begins with breakthroughs in science, and recalling the entrepreneurial points made by Kunert and Cullis, the evolution within bioentrepreneurship education inside academia is evolving.[14] One well-known and innovative construct can be found at the University of California, Davis. UC Davis's Biotechnology program offers a Designated Emphasis in Biotechnology (DEB) to PhD's within 29 STEM doctoral areas.[17] The DEB emphasis seeks to "develop an understanding of the 'business of biotech'", including an internship and requiring a microbiology course taught by a complement of working research scientists from Novozymes' Davis, California R&D facility.[17] This brings graduate students from multiple STEM disciplines directly into the Davis biotechnology innovation ecosystem in a variety of ways. The point for the student is not necessarily to start up a bioenterprise, but rather to find his or her place in it.

Another program somewhat challenges the premise that university biotechnology entrepreneurship degree programs must start with science. Johns Hopkins University's fully online Master of Biotechnology Enterprise and Entrepreneurship appears to prefer applicants to possess a bachelor's degree in the life sciences, or "with a strong background", they may take a single, additional undergraduate course, *Foundations in Bioscience*.[18] A close look at the master's curriculum finds it reminiscent of an MBA-like program within a biotech environment. With most courses including the term "Biotech" in their titles, the core curriculum is familiar: management, leadership, marketing, finance, ethics, regulatory practices, intellectual property, and so on. Students choose electives from over 100 available Johns Hopkins' courses, and there is also an optional concentration in Biotechnology Legal and Regulatory.[19] Since students attend classes entirely online and come from many backgrounds, this university program arguably serves multiple biotechnology ecosystems regionally, nationwide, and worldwide, and in many different ways.

A more regionally-centric program at the University of San Francisco's (USF's) Bioentrepreneurship program reflects elements of each of these in its quest to serve the San Francisco biotechnology innovation ecosystem. It's case study is described subsequently.

WHAT SERVES A BIOTECHNOLOGY INNOVATION ECOSYSTEM?

A central question for any educational program with the intent to serve any innovation ecosystem is: "What serves a biotechnology innovation ecosystem?" And this truly can be answered in many ways. The USF perspective looks first to the nature of the challenge being undertaken by the ecosystem. Gunn's 2013 paper, "An agile, cross-discipline model for developing bio-enterprise professionals", describes the science-to-product

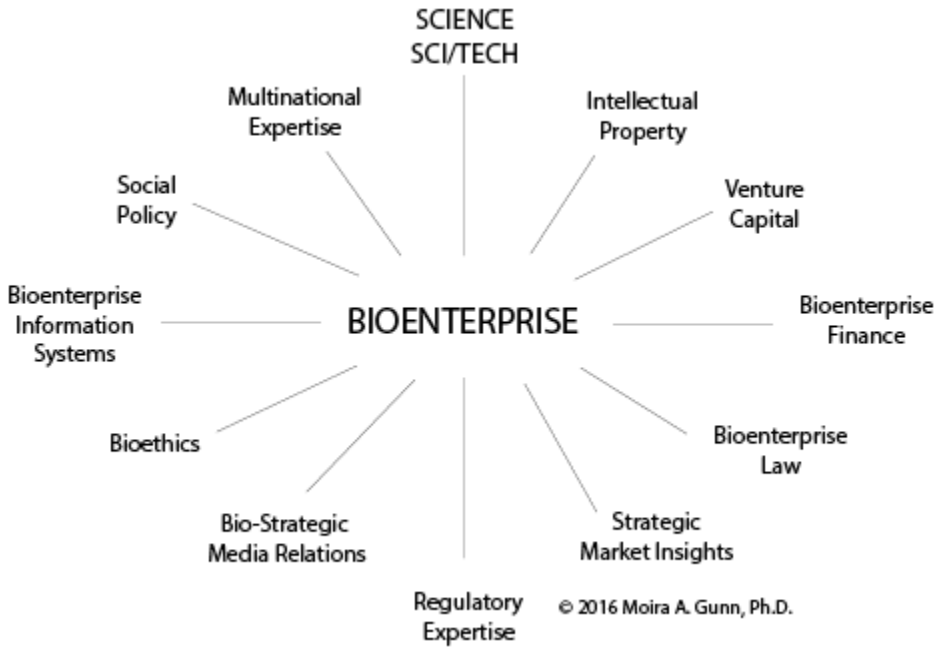

Figure 1. BIEM 2.0 (Bioenterprise Innovation Expertise Model) – Essential Capabilities.

innovation phase of bringing a biopharmaceutical to registered product as follows.[20]

> *"The endeavor carries innate risk. Simply stated, the bioenterprise must drive nascent science to stable, commercially-available and ultimately profitable products and services, an exercise for which success can neither be predicted from the outset, nor at numerous points along the way. Achieving commercial success requires a multi-disciplinary and creative entrepreneurial organization, which can operate within a continually-challenging and unprecedented business context."* [20]

This paper further described the various disciplines required in a Bioenterprise Innovation Expertise Model (BIEM), the result of both observation of success and examination of failure.[20]

> *"Successful bioenterprises were observed to assemble the right expertise at the right time at every turn in the biotechnology innovation life cycle. Agile organizations had an appreciation for a larger spectrum of expertise than did less flexible ones. … While breakthroughs in science are expected, there are also scientific setbacks. The creativity and resilience required to ensure that investment capital is in place goes hand-in-hand with a readiness to construct previously unexplored investment vehicles … How last year's marketplace behaves may be completely different from this year's marketplace – there are competitor's products, a changing regulatory scene, negative and/or positive media, and much, much more. … The Bioenterprise Innovation Expertise Model reflects a dynamic of the expertise needed to address the challenges of bioenterprise, which itself must be both robust and creative, and is frequently called upon to address situations which are arguably unprecedented. Such is the nature of science-business."* [20]

By 2016, the BIEM model evolved to incorporate biomedical devices, which simply added "**SCI/TECH**" to "**SCIENCE**" into a single, combined node reflective of the innovation disciplines. [21] The newly-terms BIEM 2.0 model has remained unchanged since that time. It is depicted in Figure 1.

A priority was made of validating the BIEM 2.0 model, and an effort to assess the BIEM 2.0 model was undertaken in 2016. The relative importance of each of innovation expertise disciplines was directed via questionnaire at 20 biopharmaceutical venture capitalists with an average of 30 years of experience in the biotechnology industry.[21] As a group, their experience represented a substantial portion of the venture capital invested in the successful biologics available today. Along the way, they also experienced many, many failures. All had served on biopharmaceutical company boards, most as board chairs, and significantly, 80% has been CEO's and/or presidents of biopharmaceutical companies. From the Gunn, et al. 2016 paper "The BIEM Verification Study: Experienced Venture Capitalists Assess a Biopharmaceuticals Innovation

Expertise Model" published in the Journal of Commercial Biotechnology" [21]:

> *"20 biopharmaceuticals venture capitalists with 30 years average biotechnology industry experience … rated the innovation expertise disciplines of BIEM 2.0 as to their importance in the scientific discovery through market-ready product innovation phase of biopharmaceutical development. Despite a small sample size, statistically significant insights were produced, verifying the BIEM model. The most important innovation expertise disciplines were intellectual property, science, regulatory expertise, and venture capital, in that order. Further, the strongest correlations linked regulatory expertise and science, and equally so, intellectual property and venture capital."* [21]

With respect to the development of biomedical devices, verification of the BIEM 2.0 model has not been conducted as yet. While the cost to develop and bring a medical device to market is significantly lower than biopharmaceuticals, there are also challenges in defining the biomedical device market itself since categorizing the devices can be somewhat complicated. Are they standalone devices? Are they part of a diagnostic? Are they part of treatment regimen. Do they collect information and store it in the cloud? Is the analysis of the data considered a part of the medical device? Are they meant for commercial use by multiple people? Are they meant to interact with other medical devices and/or other data entities? While biomedical devices require less investment capital and are generally able to reach market on a shorter timeline, there are more dissimilarities between devices than similarities. It became clear that none of the innovation expertise disciplines could be fully eliminated, but that no new disciplines need be considered. Formal verification of the BIEM 2.0 model with respect to biomedical devices is on hold unless and until a workable verification protocol can be developed.

Even so, with biopharmaceuticals and biomedical devices a substantive part of the greater San Francisco Bay Area biotechnology innovation ecosystem, the BIEM 2.0 model is essential USF's BioE courses.

THE SAN FRANCISCO BAY AREA BIOTECHNOLOGY INNOVATION ECOSYSTEM

The University of San Francisco primarily serves the San Francisco Bay Area. This ecosystem is home to some 1,059 biotechnology companies, of which San Francisco proper hosts 144 companies, and South San Francisco hosts 134 companies.[22] The remainder largely ring the San Francisco Bay.[22] The "California Life Sciences Report 2019" places direct employment in the biotech sector in the San Francisco Bay Area at 82,568, outpacing the Southern California ecosystems of Los Angeles County at 57,117, Orange County at 44,957, and San Diego County at 48,430.[23] Taken together, the state of California creates an unparalleled, integrated and larger biotechnology innovation ecosystem, in and of itself.

While primary focus in the San Francisco Bay Area has been in biopharmaceuticals and biomedical devices, there is near meteoric recent growth with respect to venture capital investment in digital health. In 2017, $1.8 Billion was invested in San Francisco, and in 2018, this investment increased to $3.9 Billion.[23] Combining Los Angeles, Orange and San Diego counties over that same time period, digital health venture capital investment was $139 million in 2017 and $288 million in 2018.[23] This shows that 93% of the digital health venture capital investment went to the San Francisco Bay Area in the years 2017 and 2018.[23]

UNIVERSITY OF SAN FRANCISCO (USF) WITHIN THE SAN FRANCISCO BAY AREA BIOTECHNOLOGY INNOVATION ECOSYSTEM

The University of San Francisco (USF) is a private Jesuit university with its main campus in San Francisco, and additional campuses in Downtown San Francisco, Pleasanton, Sacramento, and Orange County. With a Carnegie classification as a Master's focused institution, its academic organization is a College of Arts and Sciences, School of Law, School of Management, School of Education, and School of Nursing and Health Professions. The total student body approaches 10,000 students, of which 4,200 are graduate students.

Viewed as a whole, the university provides graduate education opportunities in all twelve BIEM 2.0 expertise disciplines through master's degrees and graduate degrees, such as MBA in the School of Management and J.D. in the School of Law. Recalling that the breakthrough science which catalyzes the engine of biotechnology are most often found at such nearby institutions as UC San Francisco (UCSF) and Stanford University, USF's profile matches more closely the innovation expertise disciplines identified within Bay Area bioenterprise in the over 80,000 jobs identified within the San Francisco biotechnology innovation ecosystem. With Bioentrepreneurship (BioE) courses available to every graduate student at the university, the ability to serve the

local biotechnology innovation ecosystem is possible on many levels.

CASE STUDY: BIOENTREPRENEURSHIP (BIOE) EDUCATION AT USF

Bioentrepreneurship at USF was first conceived in 2007 as a proposed concentration in the Masters in Information Systems (MSIS). By the time of implementation in 2010, it had expanded to include MBA students and JD/MBA students. In 2012, it became the entrepreneurship portion of the new Professional Science Masters (PSM) in Biotechnology being offered by the College of Arts and Sciences. Other students who have taken advantage of these courses include students from master's degree programs in Professional Communications, Organizational Leadership, Nonprofit Administration, Public Administration, and Nursing. In 2018, Bioentrepreneurship transferred from the School of Management to the College of Arts and Sciences, where it reports to the Dean's Office. Currently, there are 78 students enrolled in the PSM in Biotechnology, including approximately a dozen students with delayed graduation due to COVID-19.

Impact of the COVID-19 Pandemic on Bioentrepreneurship Education at USF

Due to COVID-19 safety precautions, in Spring, 2020, all BioE courses began their transition to remote modality, completing this transition by the end of Spring, 2021. Of necessity, the biotech global study tours were immediately suspended, and an additional course, Biotech's Response to the COVID-19 Pandemic, also in the remote modality, was developed as a replacement. All are more fully described in a subsequent section.

USF Bioentrepreneurship Educational Pedagogy

While the BIEM 2.0 model addresses individual expertise disciplines which come into play over the innovation lifetime of a bioenterprise, they do not operate in isolation. To be effective in the constantly changing dynamic of the innovation phase, individuals from these BIEM disciplines must be able to work together. Thus, the vision of the bioentrerpreneurship educational pedagogy at USF has four requirements:

- The Learning Objectives of all graduate BioE courses are based on the integrated BIEM 2.0 model and its relation to bioenterprise
- All graduate students with a discipline reflected in the BIEM 2.0 model are eligible to take any BioE course
- All BioE course may have a complement of students from any of the BIEM disciplines.
- All presentations and papers must be written/delivered in a manner comprehensible by all BIEM disciplines

At the same time, BioE courses do not teach science, per se, but rather they teach minimalist science to relate those elements of science which relate to the value proposition and risk of the bioenterprise. Furthermore, and particularly challenging for science students, the requirement that all communications be comprehensible by all BIEM disciplines may seem difficult, but the principle behind it is simple and straightforward: All members of an innovation team must be able to communicate and have an appreciation for each other's discipline. Dovetailing with this, every bioenterprise team must also be aware of what may be missing in any effort; having knowledge of the BIEM disciplines can deliver on this challenge.

The BIEM disciplines are incorporated into each type of course in a variety of ways. These can be found with each course type in subsequent sections, and several are described in more detail in Gunn, 2016, "When Science Meets Entrepreneurship: Ensuring Biobusiness Graduate Students Understand the Business of Biotechnology" in the *Journal of Entrepreneurship Education*.[24]

The Bioentrepreneurship (BioE) Courses

All USF Bioentrepreneurship (BioE) courses have been designed to be taken singularly or as a complement within a number of degree programs. The Professional Science Masters (PSM) in Biotechnology program requires a BioE study tour in addition to four BioE core lecture courses. As indicated above, the BioE study tours have been temporarily replaced with a biotech COVID course, which will continue until study tours may be resumed.

BioE Lecture Courses

Lecture courses utilize the BIEM model in several ways. One central example is that each course requires listening to *BioTech Nation* podcasts, a biobusiness interview segment of Gunn's *Tech Nation* program on NPR on SiriusXM and other public radio venues. Students listen

to the interviews and determine which elements of the BIEM model are – and are not – present. For example, an interview with a person from the FDA would not include references to Intellectual Property, which is appropriate. Perhaps, an interview with the founder of a new startup does not give enough information to clarify where a particular product is in the FDA regulatory cycle. All of this provides further material for threaded online Discussion Boards in which the entire class may interact.

The *BioTech Nation* interviews can also be used in a number of contexts. For example, Dr. Gunn's 2005 *BioTech Nation* interview with Elizabeth Holmes, founder and former CEO of now-defunct Theranos, can be used as part of a regulatory course, or a course in biomedical device management, or perhaps a legal/ethical inquiry.[25]

Another element of every BioE course is the individual tracking of a publicly-traded biotech stock. Students select one at that beginning of their first course and there is a set of requirements to follow the stock's movement and news which affects it. This can be relative to the company itself, or the stock market in general, or any number of emergent issues. At the conclusion of each course, students are required to put their daily change tracker on a collective spreadsheet. Questions on the final are directed to this collective spreadsheet. The effect of the COVID-19 pandemic, as well as the U.S. presidential election, made Fall, 2020 an instructive time to participate. Students may elect to keep their stock in the next course, or they may select a new publicly-traded biotech stock.

Global and US Regulatory Affairs

Course Catalog: "Studies US and global regulatory requirements in the biopharmaceutical and biomedical device sectors. Primary focus is on Pre-Clinical development thru Phase IV clinical trials and FDA filing/approval, identifying comparable actions in the EU/Japan, and other significant global markets." [26]

Additional Notes: Each student must prepare a report and deliver a presentation on a Failed Drug (Phase 3 or Phase 4 failures) and a Failed Biomedical Device. All include reason for the failure, potential for failure being avoided, impact on the company, etc.

Legal, Social and Ethical Implications of Biotech

Course Catalog: "Studies the ethical, social and legal impact of biotech, both in the US and globally. Includes HIPAA, GINA, the developed vs. developing world, Supreme Court decisions, national/global intellectual property, the orientation of organized religions, and the potential impact of synthetic biology." [26]

Additional Notes: Each student must debate either a PRO or a CON side to a major bioethical debate, as outlined in Caplan and Arp's "Contemporary Debates in Bioethics." [27]

Bioinnovation Management

Course Catalog: "Develops skills in managing bioentrepreneurship projects in the bioscience and biomedical device fields. Students learn how to be responsive team members as well as communicative team leaders. Also covered is sustaining innovation in organizations and team dynamics." [26]

Additional Notes: In two successive three-week sessions, each student must operate as a team leader. At the same time, each student with be a team member in four other teams. Students learn to create agenda, lead meetings, make reports, and ultimately solve a unique team puzzle with clues distributed among team members. As in science-business, sometimes the clues deliver wrong information, as would happen when a scientific test was ill-structured, sometimes team members are absent or simply don't respond, sometimes the project team leader is absent but the meeting must be conducted in any event with reports to management, etc. Still, the team must continue driving the project forward.

Local, National and Global Biotech

Course Catalog: "Studies the global biotechnology industry, the US biotech landscape, and the impact of the San Francisco Bay Area – the largest biocluster – both nationally and globally. Focuses on the nature of biobusiness and significant bioclusters, while featuring lectures from local biotech professionals." [26]

Additional Notes: Each student must prepare reports and deliver presentations on a San Francisco company (or local site of a multi-site company), a national biocluster, and a global biocluster.

Biotech's Response to the COVID-19 Pandemic (Temporary Replacement Biotech Study Tour) of

Course Catalog: "An overview of the response to the COVID-19 pandemic by the US and global biotech community. Includes potential diagnostics, treatments, vaccine development, and biomedical devices, and reflects the convergence of biobusiness pivots, accelerated scientific research and bioengineering. Topics include accelerated FDA changes, lessons from media coverage, challenges for the CDC, and government response." [26]

Additional Notes: In addition to prepared lectures his course shall be run as a collaborative research seminar. Each student (in two successive sections) shall select a unique global region or country to research. Guest

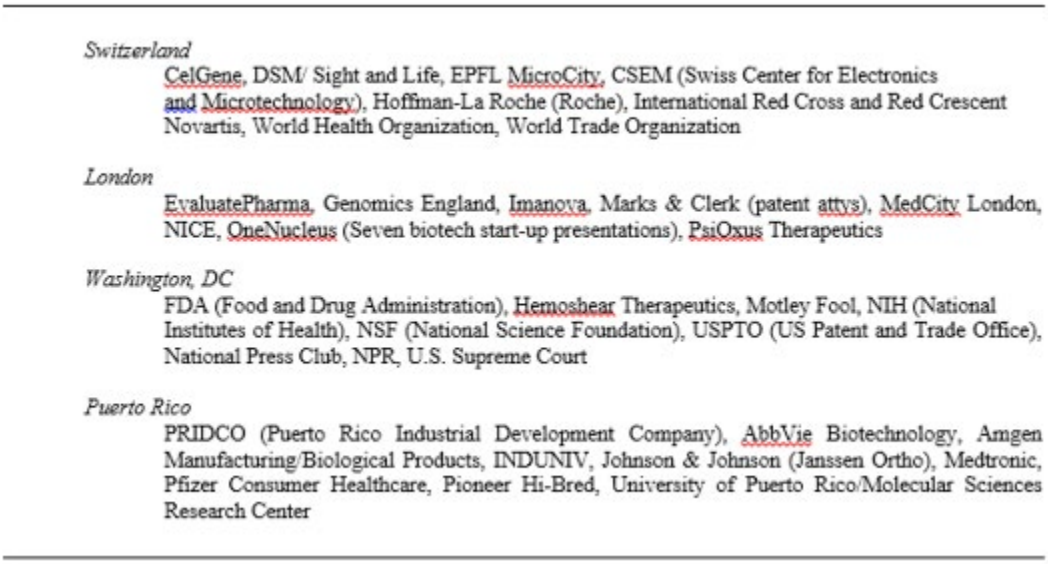

Figure 2. Exemplar BioE Study Tour Site Visits.

lecturers include the Gilead Sciences head of clinical trials for Remdesivir. A number of recent *BioTech Nation* interviews involving corporate COVID pivots will be utilized.

BioE Biotech Study Tours:

Since January, 2011's inaugural study tour to London/Oxford/Cambridge, USF's Bioentrepreneurship (BioE) program has offered multiple one-week BioE study tours. Other venues have included Switzerland, Washington, DC, Montreal, San Diego, Puerto Rico, Australia, and Ireland/Northern Ireland, this last of which was cancelled due to COVID-19.

In addition to a unique project and presentation related to the cluster or ecosystem visited and speaker reports, students are required to keep a personal journal of the study tour, with elements that were encountered in the BIEM 2.0 model. Students are often able to meet *BioTech Nation* guests, whose interviews they have listened to for an earlier course. At the end of the course, a separate BIEM Report must be made, which rewrites the Personal Journal but in terms of each BIEM category.

Exemplar site visits on earlier tours are described in Figure 2.

EDUCATION 3.0 – EDUCATION IN COLLABORATION WITH BIOTECHNOLOGY INNOVATION ECOSYSTEMS

As pointed out with Education 2.0, the concept of Education 3.0 is not a successor. It describes a different university-ecosystem relationship which can be highly productive. To be clear, this is not the prototypical corporate-university relationship which has been familiar for many years. Instead, with highly receptive innovation ecosystems and the ability of a university to have both breadth and depth in bringing forth breakthrough science and building unprecedented technologies, a new dynamic can emerge. Such is described with regard to UC San Diego in the Abremski and Roben article in this same special issue of the *Journal of Commercial Biotechnology*.[28] They demonstrate an "Innovation Ecosystem Virtuous Cycle" over time.[28] At its core, collaborative in nature, it goes beyond the more typical corporation-university liaison, and also reaches back to the university's graduate research and engineering capabilities and the design of programs which support them.

More consideration must be given as to what is tentatively called Education 3.0 in the confines of this paper. All such constructs with value, scale, and thus, this educational model may well evolve in other places in the greater biotechnology industry. Certainly, its initial description by Abremski and Roben reveals an advanced model of education and entrepreneurship within a world-class biotechnology innovation ecosystem. In other words, Education 3.0 presents a new opportunity.

DISCUSSION AND FUTURE DEVELOPMENT

One of the silver linings of the COVID-19 Pandemic was the absolute necessity to deliver bioentrepreneurship courses in a remote modality. It proved that nearly all

of the courses were readily translatable. In fact, some of the teaching tools improved delivery and student experience. As a result, USF's Bioentrepreneurship program is pursuing:

- The development of a fully online Certificate in Bioentrepreneurship
- The development of courseware supportive of the Digital Health sector
- The intention to continue delivering Bioentrepreneurship courses online in the evening with one meeting per week in the Pacific Time Zone
- The participation of enrollees from a larger segment of the biotechnology industry, particularly with California state biotechnology corridor of San Francisco, Los Angeles, Orange County, and San Diego
- The participation of enrollees who have expertise in one or more of the BIEM disciplines, and who wish to join the Biotechnology Industry in the future
- The resumption of BioE study tours visiting global innovation ecosystems in person when that becomes possible

Bioentrepreneurship education and its related educational research has, as yet, no proven set of pathways; it is itself in a formative state. There are no "best practices" at this early date, and all who develop and teach bioentrepreneurship courses of any sort and at any level are truly innovators, themselves. In fact, they are innovating education for an industry that itself is in constant change. Viewing bioentrepreneurship education as an ever-evolving dynamic may yield the clearest perspective.

REFERENCES

1. Lucier, P. (2019). Can marketplace science be trusted? *Nature,* 574(481-485), https://doi.org/10.1038/d41586-019-03172-5.
2. Bains, W. (2020). Genentech was not the first biotech company. *Nature,* 577(622), https://doi.org/10.1038/d41586-020-00187-1.
3. Genentech. (2020). Our Founders. Genentech, A Member of the Roche Group. https://www.gene.com/about-us/leadership/our-founders.
4. Stanford Online. (2020). Idea-to-Market. Stanford Center for Professional Development. Stanford University. Link: https://online.stanford.edu/professional-education/idea-market.
5. Polaris Market Research. (2020). Biotechnology Market Share, Size, Trends & Industry Analysis Report By Application (BioPharmacy, BioServices, BioAgriculture, BioIndustrial, Bioinformatics) Segment Forcast 2020-2026. https://www.polarismarketresearch.com/industry-analysis/biotechnology-market.
6. Wouters, O., McKee, M. & Luyten, J. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA, Journal of the American Medical Association,* 323(9):844-853. https://doi.org/10.1001/jama.2020.1166.
7. Takebe, T., Imai, R. & Ono, S. (2018). The Current Status of Drug Discovery and Development as Originated in the United States Academia: The Influence of Industrial and Academic Collaboration on Drug Discovery and Development. *CTS, Clinical and Translational Science* 11(6):597-606.
8. Wong, C., Siah, K. & Lo, A. (2019). Estimation of clinical trial success rates and related parameters. *Biostatistics,*20(2):273-286. doi:10.1093/biostatistics/kxx069.
9. Van Norman, G. (2016). Drugs, Devices and the FDA: Part 1, An Overview of Approval Processes for Drugs.
10. Darrow, J., Avorn, J. & Kesselheim, A. (2020). FDA Approval and Regulation of Pharmaceuticals, 1983-2018. *JAMA, Journal of the American Medical Association,* 323(2):164-176. https://doi.org/10.1001/jama.2019.20288.
11. FDA. (2020). FDA Takes Additional Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for Second COVID-19 Vaccine: Action Follows Thorough Evaluation of Available Safety, Effectiveness, and Manufacturing Quality Information by FDA Career Scientists, Input from Independent Experts. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-takes-additional-action-fight-against-covid-19-issuing-emergency-use-authorization-second-covid
12. UCSF Innovation Ventures. (2020). Entrepreneurship for Life Science and Healthcare Startups: Master Class Direct from Silicon Valley. University of California, San Francisco. https://innovation.ucsf.edu/global-online-entrepreneurship-class.
13. BIO. (2020). Biotechnology Entrepreneurship Boot Camp. Biotechnology Innovation Organization. https://bootcamp.bio/.
14. Kunert, K. & Cullis, C. (2019). Universities must teach their budding scientists entrepreneurship. *The Conversation.* https://theconversation.com/universities-must-teach-their-budding-scientists-entrepreneurship-121388.

15. Professional Science Masters (PSM). (2020). Program Locator. Professional Science Masters. https://www.professionalsciencemasters.org/program-locator?field_psm_program_name_value=&field_field_of_study_tid=892&field_psm_institution_name_tid=All&field_psm_location_tid=All&field_delivery_method_tid=All.

16. Case Western Reserve University. (2020). Entrepreneurial Biotechnology. Case Western Reserve University. https://case.edu/step/entrepreneurial-biotechnology.

17. UC Davis. (2020). UC Davis Designated Emphasis in Biotechnology (DEB). University of California, Davis. https://deb.ucdavis.edu/program-overview.

18. Johns Hopkins University. (2020). Master of Biotechnology Enterprise and Entrepreneurship. Johns Hopkins University. https://advanced.jhu.edu/academics/graduate/master-biotechnology-enterprise-entrepreneurship/.

19. Johns Hopkins University. (2020). Degree Details and Courses. Johns Hopkins University. https://advanced.jhu.edu/academics/graduate/master-biotechnology-enterprise-entrepreneurship/degree-details-courses/.

20. Gunn, M. A., Dever, J., Tzagarakis-Foster, C., Lorton, P., Kane, K. & Masterson, N. (2013). An agile, cross-discipline model for developing bio-enterprise professionals. *Journal of Commercial Biotechnology*, 19(4):72-87.

21. Gunn, M. A., Masterson, N., Lorton, P. & Baronet, J. (2016). The BIEM Verification Study: Experienced Venture Capitalists Assess a Biopharmaceuticals Innovation Expertise Model. *Journal of Commercial Biotechnology*, 22(2) 50:63, https://doi.org/10.5912/jcb749.

22. BioPharmaGuy. (2020). Biotech Companies in the Bay Area and Northern California. BioPharmaGuy. https://biopharmguy.com/links/company-by-location-northern-california.php.

23. CLSI. (2019). California Life Sciences Industry Report 2019. California Life Sciences Association. https://califesciences.org/wp-content/uploads/2018/11/clsa-2019-california-life-sciences-industry-report.pdf.

24. Gunn, M. (2016). When Science Meets Entrepreneurship: Ensuring Biobusiness Graduate Students Understand the Business of Biotechnology. *Journal of Entrepreneurship Education,* 19(2), 53-77.

25. Gunn, M. (2005). BioTech Nation interview: Moira Gunn interviews Elizabeth Holmes, Founder and CEO, Theranos. *Tech Nation [BioTech Nation].* http://technation.com/2005-elizabeth-holmes—-theranos-interview.html.

26. USF. (2021). University of San Francisco Course Catalog. University of San Francisco.

27. Caplan, A. & Arp, R. (2014). Contemporary Debates in Bioethics. Wiley Blackwell.

28. Abremski, D. & Roben, P. (2020). UC San Diego, The Military and Building a Unique, Diversified Economic Growth Ecosystem. *Journal of Commercial Biotechnology.* XX(x):xx-xx.

Article

UC San Diego, The Military and Building a Unique, Diversified Economic Growth Ecosystem

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ABSTRACT

San Diego's economy, fueled by its innovation ecosystem, has experienced meteoric growth over the past several decades, with the region now ranked amongst the top life sciences clusters in the world. This growth has been inextricably linked to the military presence over the decades and the region has benefited from the symbiotic presence of both the military and private and public sector innovation partners, creating an ecosystem that may be unique in the nation. This unique combination of market forces is turbo-charging the creation of "multi-use" technologies and startups, through regional collaborations and associated programs that align the research discoveries and capabilities of universities, with the strategic needs of the government, while feeding the growth of commercial industry partners and the economy as a whole. One key to the continued competitiveness and success of San Diego will be to strengthen this virtuous cycle, to drive productivity and propagate the impact of the engagement across multiple innovation sectors or clusters.

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A HISTORY OF (LINEAGE OF INTERCONNECTED COLLABORATION)

The origin of the San Diego (technology) and (innovation) cluster can be traced to the establishment of the Marine Biological Association of San Diego by Ellen Browning Scripps in 1903 – this was the precursor to the Scripps Institution of Oceanography, which in 2012 became part of the University of California. Almost 20 years later, in 1922, the United States Naval Base San Diego was established and has become what is now, the largest naval presence in the world. Following WWII, there was enormous growth in the overall defense sector, with the establishment of several leading contractors such as San Diego's own General Dynamics in 1954. In parallel, as the city and surrounding communities grew in population and influence as both a desirable (vacation-retreat) destination and industrial center, a new university was being envisioned by a group of regional influencers, under the leadership of Roger Revelle, Director of The Scripps Institution of Oceanography and a nationally prominent scientist and educator. Armed with a generous gift of 63 acres of land from the City of San Diego coupled with a donation from General Dynamics, UC San Diego was founded on November 18th, 1960 on what was formerly the Navy's Camp Matthews. Herbert York was named the founding Chancellor in 1961 and the first undergraduate students were admitted in 1964. In 1965, the first of UC San Diego's colleges was named Revelle College in honor of Roger Revelle, considered the "father" of the university.

Built on this foundation of collaboration between the public and private sectors, the following decades saw steady growth of technology innovation with the founding of companies such as Linkabit (which gave rise to Qualcomm), by UC San Diego Professor, Irwin Jacobs in 1968, a prime example of next generation leading communications technology consulting contractors, and Hybritech, a pivotal life science company, a groundbreaking biotech company that developed the first blood test for porstate cancer, by UC San Diego Professor Ivor

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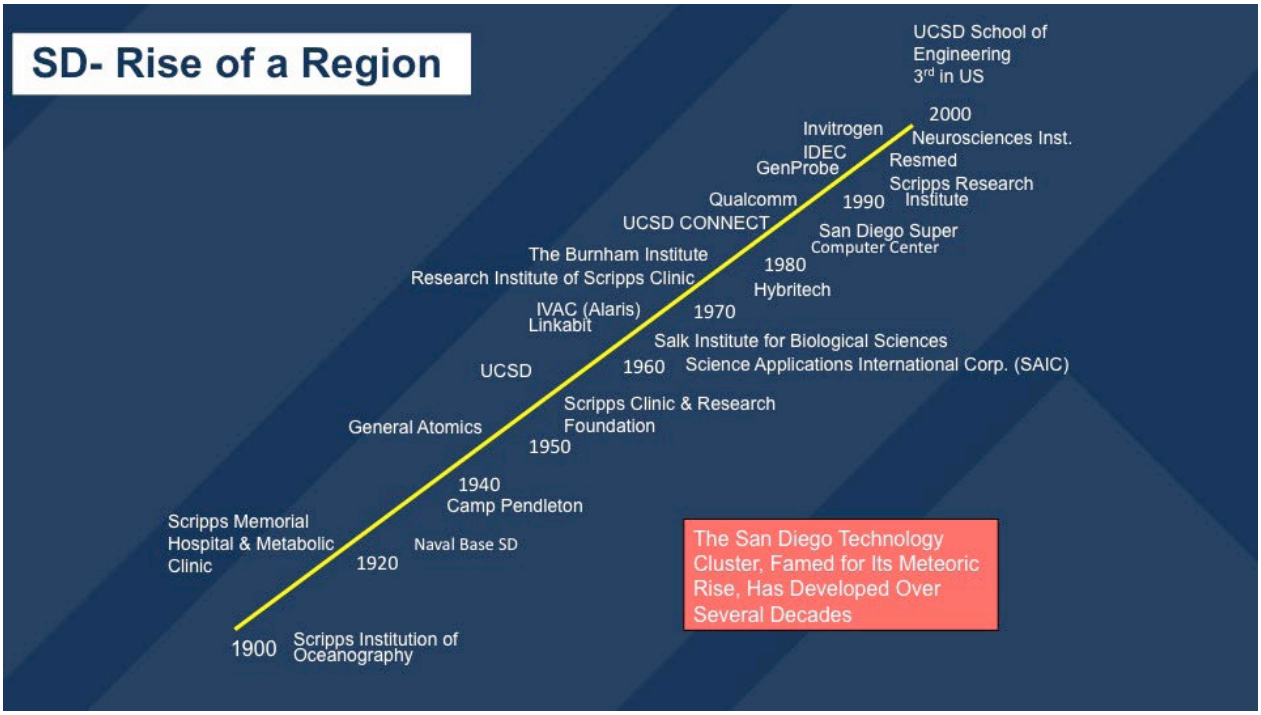


Royston, in 1978. The entrepreneurial ecosystem that currently exists in San Diego can be directly attributed to these innovative and visionary companies and their prolific subsequent spin-outs and acquisitions. Hundreds of startups can trace their origins back to these founders, senior management, and technology leaders who were instrumental in these and other early successes. It is this extremely interconnected lineage that has greatly contributed to the success and uniquely (impactful) degree of entrepreneurship and collaboration that is a core strength of the San Diego Innovation Ecosystem.

WHERE ARE WE NOW? (TODAY'S SAN DIEGO/TWENTY FIRST CENTURY INNOVATION)

Significant Military Infrastructure and Workforce

Today, the greater San Diego region is home to the nation's largest concentration of military personnel with more than 100,000 active duty personnel split roughly evenly between the Navy and the Marine Corps. Equally as important, there are approximately 250,000 military veterans in the region, making up 13% of the population of the county. These veterans are comparatively young and well educated, compared to the national average (35% hold a Bachelor's degree or higher), with training and expertise acquired during their service careers, that are particularly well suited to leadership and entrepreneurship. The combined military presence contributes over $50 billion, or roughly 25% to the regional economy annually.

Growing Innovation Economy

San Diego is known for cutting-edge life science, telecommunications, software, and defense industries and for its significant innovation ecosystem. A 2018 study of San Diego's innovation economy, supported by 80-plus educational and research institutes, reported that 362 new startups were founded in the county that year, resulting in over 1,600 jobs and over $19 billion in payroll, with an average salary of $116,000. 2019 saw the region attract almost $3.5Bn in Venture capital across over 200 deals in biotech, energy, software, defense and other sectors.

Much of this growth has been supported by one of San Diego's most valuable assets – its highly collaborative innovation ecosystem fueled by an interconnected network of support organizations. One of the first among those was Connect San Diego, one of the nation's first statup accelerators, founded in 1985 by the University of California San Diego to bring together people interested in new ventures and furthering individual companies in order to support the overall innovation economy. This revolutionary organization recently merged with San Diego Venture Group, originally founded in 1986 and, together the two have been providing access to mentors, investors and education for the past 35 years.

Biocom, founded in 1995, works on behalf of over 1,300 members to drive public policy, build an enviable network of industry leaders, create access to capital, introduce cutting-edge workforce development and STEM education programs, and create robust value-driven purchasing programs. Other dynamic organizations dedicated to the regional innovation economy include Cleantech San Diego, Startup San Diego and incubators such as Evonexus, Biolabs and Jlabs, to name but a few. These and other organizations contribute to what may be San Diego's greatest strength – its collaborative spirit and willingness to give back to the community by helping those in the ecosystem who need it. Rarely will an entrepreneur find a closed door in San Diego.

The significant assets of the San Diego Region to support innovation have not gone unnoticed: San Diego has been ranked first for concentration of military and defense assets in the world (Brookings Institution) and second among the world's most inventive cities (Forbes 2013). In 2014, Forbes ranked San Diego as the "Best Place to Launch a Startup".

University of California San Diego – Research Engine and Powerhouse

Recognized as a top 15 research university globally, UC San Diego has launched, created, or developed technologies for well over 1,000 companies contributing to an estimated $16.5 billion annual economic impact for California. With an annual spend of $1.5 billion, it is one of the largest research enterprises in the nation, with internationally recognized engineering, science and oceanography programs, medical school and healthcare systems. Initiatives in entrepreneurial education, technology commercialization, and startup acceleration, developed by campus organizations such as the Institute for the Global Entrepreneur, (IGE) (a partnership between the Jacobs School of Engineering and the Rady School of Management), the California Institute for Innovation and Development, and the University-wide Office of Innovation & Commercialization (OIC) support and leverage the university's resources and talent in driving economic and social prosperity in the region. UC San Diego is deeply engaged with regional resources and is working with them to connect the pipeline from university research to innovation to startup creation and accelerate the development and scaling of innovative solutions. Over the past 5 years, through coordinated partnerships across the campus and across the community, the university has doubled the number of startup companies launched into the marketplace.

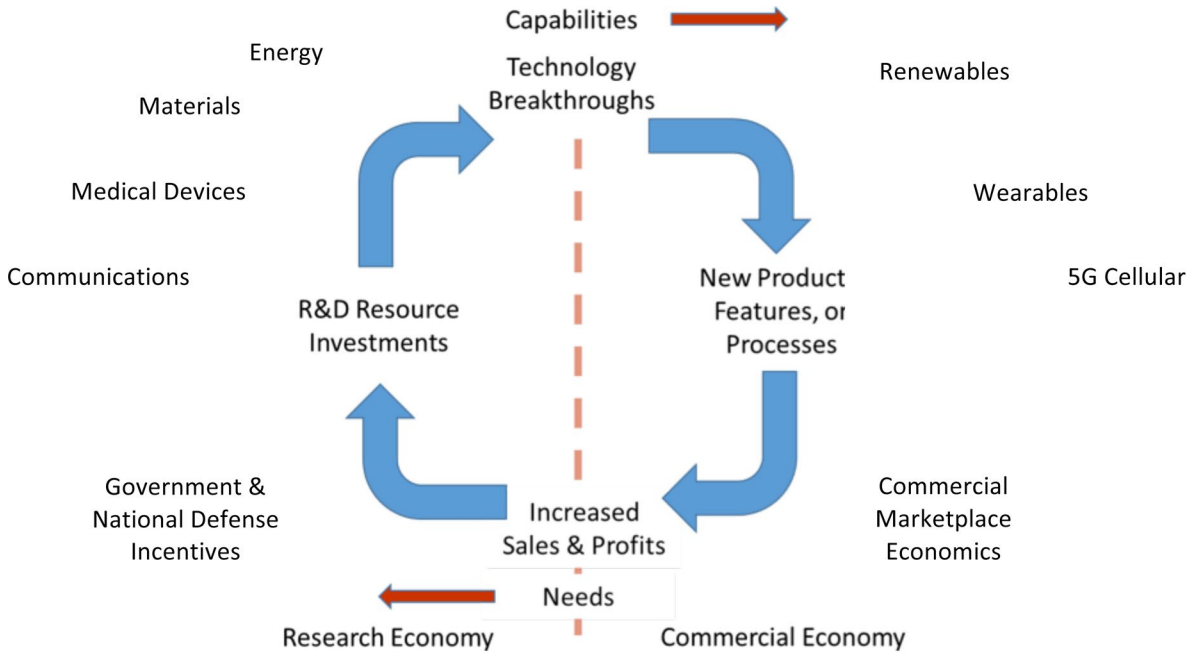
The challenge, which San Diego is uniquely suited for, is to harness these market forces to sustain a vibrant, growing ecosystem.

SAN DIEGO'S PROVEN TRACK RECORD (HOW IT APPLIES TO THE CYCLE & INCENTIVES FOR GROWTH)

An innovation ecosystem can thrive and grow when the resources invested in the research economy (either through private, government, or direct business investment) are replenished by innovation induced profit increases in the commercial economy, See Figure 1. This feedback loop creates a virtuous cycle that matches the capabilities of the research community with the needs of the market. The challenge to creating growth in such a system is figuring out how to turn breakthrough R&D efforts into startups and products that lead to profits.

Traditionally, government agencies have invested heavily in basic fundamental research to act as a catalyst or driver of innovations for the public good. A great example of this are the National Science Foundation's Engineering Research Center (ERC) proof of concept testbeds. The (ERC) program has funded potentially transformative engineering systems and supports the development of associated innovation ecosystems. Originated more than 25 years ago, the program is still going strong and has been successful at developing sustainable ecosystems for a wide variety of impactful technologies in many areas, including energy, communications, and healthcare. It's safe to say that in today's fast-changing technology landscape, one could easily consider the strategic needs of the federal government as a market force. Aligning the incentives of researchers, targeted governmental agencies, and the commercial industry economy, can power the virtuous feedback loop and drive growth. It's a logical progression to extend this cycle to strategic DOD priorities, especially those that overlap with commercial markets – energy/power resilience, healthcare, communications, internet security (both financial and critical infrastructures).

To this end, San Diego is uniquely positioned to sustain this virtuous cycle, and to create and prove the efficacy and impact of such a model. It's possible to grow and sustain such initiatives because three critical market forces are active in San Diego. Home to the largest concentration of military assets in the world, San Diego's regional economy has a robust ecosystem of national security practitioners, academic research organizations, and entrepreneurs in all the major areas of emerging technology. The region is a hotbed of startup companies and a biotechnology and healthcare hub for the nation,



What is an Innovation Ecosystem – Deborah J. Jackson

Figure 1. Innovation Ecosystem Virtuous Cycle.

and the source of many healthcare innovations. San Diego is also one of the nation's strongest regions for higher education and research, with one of the largest R&D workforces. All three ingredients are readily available to actively promote collaborative programs to align research capabilities with targeted government needs and strategic industry partners.

COUPLING ENTREPRENEURIAL EDUCATION, ACCELERATION, AND TECHNOLOGY TRANSFER TO STRATEGIC OBJECTIVES

An effective strategy for developing a pipeline of innovation is to find ways of lowering the perceived risk for entrepreneurs, partners and investors. Through proven entrepreneurial education and focused acceleration programs, researchers can benefit from foundational workforce development and leadership training and collaborate with multi-disciplinary campus resources and industry partners, leveraging their first-hand knowledge of market sectors and the unmet needs that deep tech university-based technologies might potentially address. Such targeted accelerator programs are currently underway on the UC San Diego campus at the IGE. The IGE MedTech Accelerator focuses on technology commercialization and the launching of startups developing medical devices, diagnostics, and therapeutics. The accelerator program is tightly coupled to the newly formed, NIH funded, Device Acceleration Center in the Altman Clinical Translational Research Institute and draws on resources from the School of Medicine, the Galvanizing Engineering and Medicine (GEM) Program and the Accelerating Innovation to Market program, housed within the Office of Innovation and Commercialization. Other targeted sectors under consideration include smart transportation, and 5G/6G Communications.

These programs also address the problems that many startups launched from research labs often encounter – a lack of resources after initial government catalyst sources are exhausted. This gap in resources for technology demonstration and development is commonly known as the Valley of Death. It is within this valley that many potential innovations die for lack of the resources to develop them to a stage where industry or the investor community can recognize their commercial potential. A combination of acceleration and collaboration with follow-on resources, such as connections to manufacturing partners, facilitated by governmental organizations may lower the entry costs for start-ups and raise their probability of success rates. In this context, university research can drive the initial development of innovations, buoyed by government assistance, that have the potential for delivering solutions to strategic problems while simultaneously generating economic growth.

CONNECTING THE DOTS

Entrepreneurial education, focused acceleration, and collaborations form the basis for driving research from the lab to the market. In addition to focusing on the advancement of Medical Technologies, San Diego and smaller sub-regional cities have demonstrated a commitment to host living laboratories and test-beds for innovative, broad based smart city technologies, including advanced communications, and energy distribution systems, combining their assets and capabilities with the major regional Navy and Marine Corps installations to create a connected community with a significant real-world testing and deployment capacity. Additionally, there are several on-going public-private collaborations focused on strategic governmental initiatives that are part of this overall virtuous cycle.

Energy: CEC EPIC Program

Created by the California Public Utilities Commission (CPUC) in December 2011 – to support investments in clean energy technologies that provide benefits to the electricity ratepayers of Pacific Gas and Electric Company (PG&E), San Diego Gas & Electric Company (SDG&E), and Southern California Edison Company (SCE). MCAS Miramar, in partnership with the University of California San Diego (UCSD), was granted $5M from the CEC which funded a 3 MW / 1.5 MWh battery sited next to the microgrid power plant. The battery was installed and incorporated into the microgrid in 2020. The base also modified its existing Area Wide Energy Management System (AWEMS) to enable base wide HVAC load shedding capability.

Data Sciences: National Information Warfare Center (NIWC) Pacific – UC San Diego Fellows Program

This program embeds employees of NIWC in UC San Diego's Halicioglu Data Science Institute to work side-by-side with faculty and students. The goal is to build up more core competencies in the most cutting-edge techniques in data science to bring back to NIWC Pacific, and also work closely on recruitment and interaction with data science students, setting up events like hackathons, and running scenarios using game theory. Building the innovation workforce of the future may be the most impactful and sustainable way to build resilience into our economic and national security supply chains.

Communications: 5G & 5G Enabled Emerging Technologies

In the 2020 Appropriations Bill (more info), Congress funded $5M to pilot and evaluate 5G enabled technology on the "5G Installation Next Network", established by Verizon, utilizing the assets of Marine Corps Air Station Miramar. This collaboration was enabled through a Collaborative Research and Development Agreement between the Department of the Navy and Verizon. The Congressional investment expedited the evaluation of the 5G network and the "enabled" technologies, such as connected autonomous vehicles, digital fortress, drone delivery, and energy connectivity all in pursuit of resilient installations. This effort highlights potential "dual use" technology being developed for commercial applications, while also having implications across national defense. Congressional support along with national interest in expediting U.S. based 5G technology, has alleviated many bureaucratic barriers to adoption across DOD, thereby expediting 5G as a dual use technology as well as the coming tide of emerging tech that will be enabled by 5G.

(PRIMING THE PUMP) – CURRENT INITIATIVES

San Diego National Security Catalyst Program

A first of its kind, a broad-based collaborative effort, coordinating the activities of Homeland Security, US Coast Guard, the Departments of Justice, Interior, Energy, the Center for Disease Control, and other First Responders in addition to the Department of Defense. Its mission is to improve the transition of innovative multi-use-use research and technology to national security users by leveraging San Diego's unique security, technology, business, and university environment and to provide practical, effective policy recommendations to eliminate barriers to innovation and improve national security competitiveness.
Additional goals include:

- Raise national and international awareness of San Diego's rich entrepreneurial environment.
- Increase student exposure to national security agencies and challenges through positive, practical, multi-disciplinary problem solving.

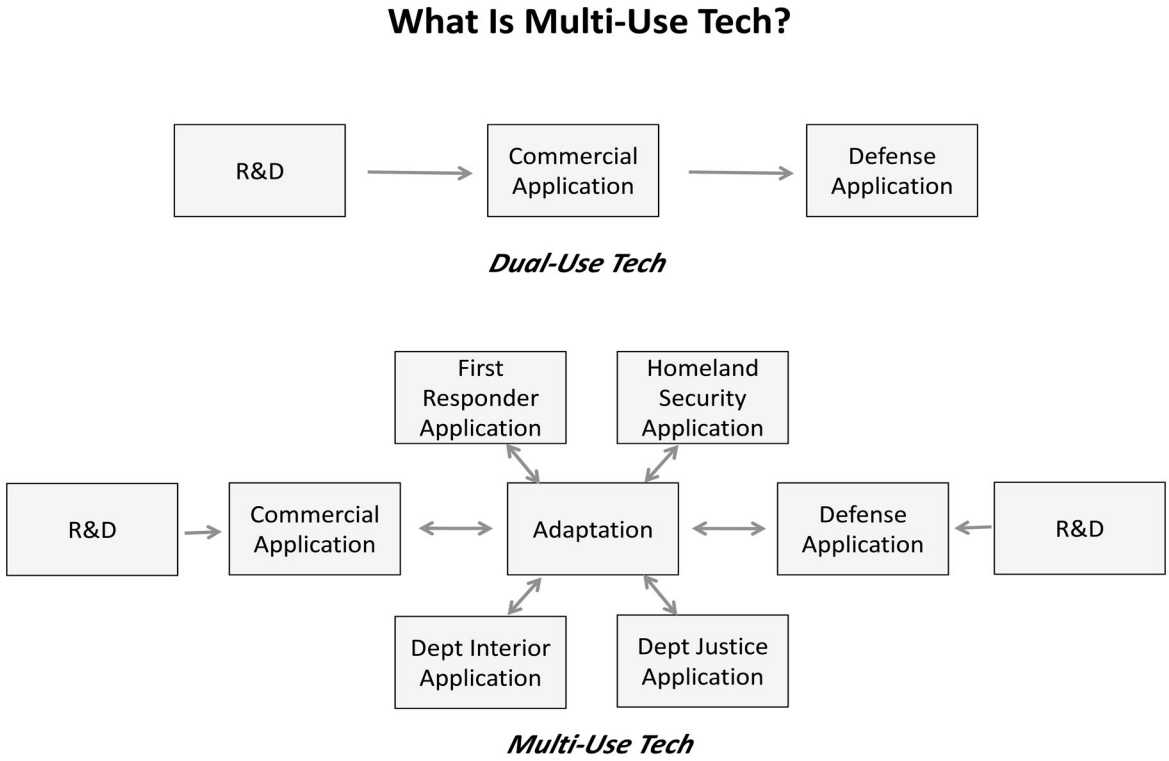


Diagram courtesy of San Diego National Security Catalyst

- Building on collaboration models developed to cope with the challenges of the Covid-19 pandemic to improve the long-term civic resilience of San Diego.

Multi-Use Research & Entrepreneurial Ecosystem Concepts

Multi-Use Startups are a rich source of valuable technology and expertise which, to date, has not been efficiently tapped by the defense sector. Through the efforts of the university and "Catalyst" initiative, a number of startup companies have been meaningfully connected to the national security enterprise, including:

- Regenica Bioscience: Prevention and cure against nerve agent chemical substances
- NeuroTrainer: Human performance (reflexive decision making) improvement
- TruGenomix: Genetic pre-screening for PTSD susceptibility
- EVT: AI-based training, briefing, VI enhancement
- OceanAero: Autonomous SUV/ USV platformsSeaPort Techologies:

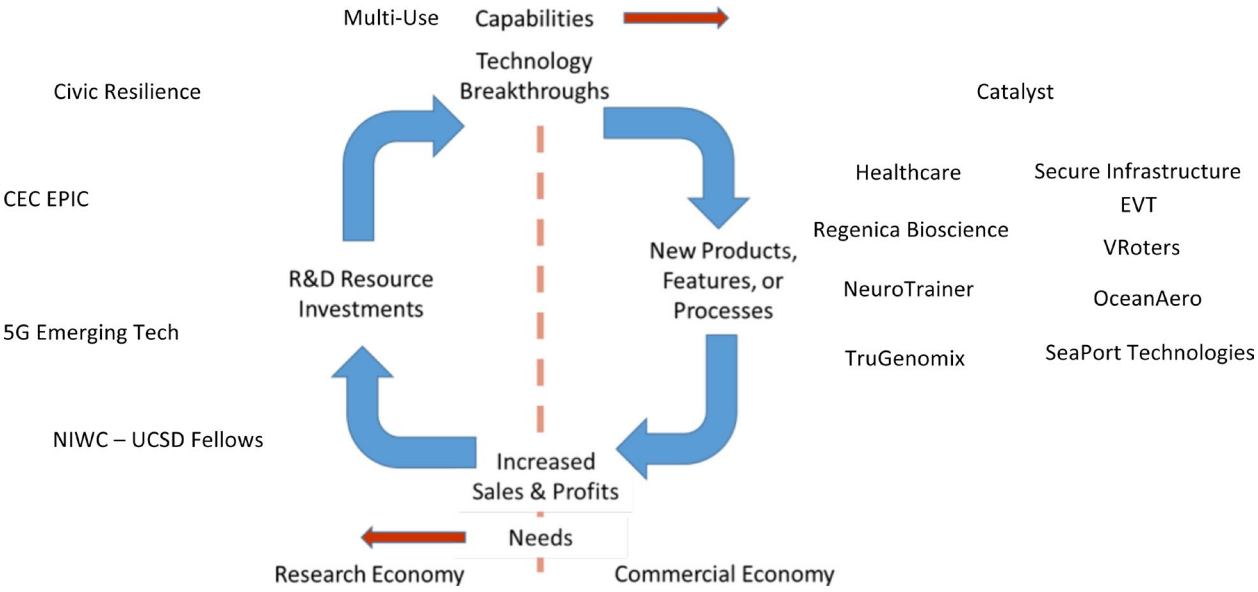
Extreme data security and performance improvement for remote work

Through more integrated efforts, these companies have developed substantial engagements with operators within the national security sector to accelerate the development of technologies that will have value both in the national security and civilian markets.

THE PANDEMIC

The COVID-19 crisis has made at least two things clear: *First*, in a world that is likely to face systemic shocks of increasing intensity, scope and frequency, our society must quickly become more resilient to shocks whether they be natural or man-made in origin; *Second*, the public-private partnerships that blossomed in the crisis, if sustained and more effectively structured, can provide both rapid and effective response in times of crisis, and tremendous value in non-crisis periods through collaborative innovation that accelerates national security and economic development.

While the pandemic has underscored the power competition between nations, this struggle did, of course, predate the crisis. It was already apparent that the United States is at potential risk of losing its technological superiority to foreign government and private-sector



competitors due to insufficient agility to address new threats and slower innovation to generate new ideas in response. This deficit is paired with warranted concern of losing technology to global competitors through both legal and illicit means. Now, more than ever, it is critical that we build resilience into the technology supply chain, which will require a combination of new technologies, policies, and economic models.

The COVID-19 emergency has highlighted the importance of resilience at all levels of our society and the imperative for effective, standing partnerships between government, academia and private industry, to ensure the long-term sustainability of our economy and National Security Complex. Resilience is needed at all levels: an agile "dual use" workforce that continuously cross-trains and collaborates, and can rapidly adapt to crisis situations; agile and persistent partnerships between Federal, State, Local governments with academia and private industry that provide innovation during 'steady state' periods and can very quickly mobilize in response to major challenges; and infrastructure and supply-chains that can quickly respond to disaster situations; and an underlying social fabric that is deliberately strengthened in stability to survive and provide community resilience in times of stress.

RESILIENT INFRASTRUCTURE: CIVIC RESILIENCE PUBLIC-PRIVATE PARTNERSHIP

A robust group of founding partners, including Arizona State University, UC San Diego, NSIN, Naval-X, Marine Corp Installations West, USA Ignite, and others have joined to create a new evolving regional private-public partnership to develop, sustain and organize a coordinated network of regional cluster groups – specializing in the key functions required to strengthen the technological supply chain for both civilian and military purposes.

The objective of the Civic Resilience Partnership is to build a pipeline of expertise around specific problems to strengthen the technological supply chain for both civilian and military purposes in a way that is both deployable across the military and economically sustainable. This approach will strengthen the resilience across respective markets, enhance regional and local economies, and ensure the nation has a dynamic capacity to accelerate technology and create an agile workforce for national and economic security that can be used to rapidly respond in a time of crisis. The Partnership will initially focus on 5G enabled communications and autonomous systems and power resilience with opportunities to expand to Healthcare and Energy resilience. As the partnership evolves, other likely key functional areas of focus will include: Crisis Response, Power & Infrastructure, Homeland Security, Cyber, Logistics & Operations, Fire Fighting & Damage Control.

The overall function is to cultivate an ecosystem that is comprised of capital, research, knowledge, capabilities, policies, incentives, and people that turns ideas into innovations and transforms discoveries into useful technology and products that increase resiliency and protect our national security. Specifically, this will include:

- Operationalize a coordinated network of regional resources that persistently links national security practitioners, State and Local crisis response organizations, academic research organizations, dual-use

companies, entrepreneurs, and related non-profits to provide mutual benefit in normal times and rapid mobilization during crises.
- Strengthen supply-chain resilience, both civilian and defense, by helping small to medium dual-use companies gain access to government or defense contracts while developing products and services that also have a commercial application.
- Cultivate an ecosystem of proactive regional collaboration to transform discoveries into high-growth job creation within industries of the future; and build a more resilient and adaptable workforce through skills training.
- Strengthen regional infrastructure (such as 5G) required for broad-based resilience in the region
- Support research organizations to develop dual-use technologies for transfer to industry partners.

LESSONS LEARNED FOR SUSTAINED GROWTH

San Diego's innovation economy was born and has sustained long-term growth in many respects due to the symbiotic relationship between its military, academic, government, and industry sectors. Over the decades, this relationship has, in part, given rise to one of the most robust and unique innovation clusters in the world.

Leveraging our strengths and the relationships between our military and innovation sectors will be key to ensuring San Diego's continued competitiveness in the future. This will require new, creative and "out-of-the-box" thinking.

Existing models and frameworks for the interactions of these sectors, while helpful in the past, are now outdated and not sufficient to enable each sector to take full advantage of the fast pace of disruptive or transformational innovation in our current markets. New models are needed. We believe the time is right for this.

1. The defense sector has recognized the need for a new approach in the creation of initiatives such as DIU, Naval-X, NSIN and AFWERKS.
2. The academic research sector has displayed a willingness and flexibility in understanding and meeting the needs of the national security sector – particularly in areas of multi-use technologies, where civilian markets are also addressed.
3. The industrial sector is moving faster than either of the other two in the development of disruptive solutions and is eager to develop the defense sector as an additional market.

Military and Economic Growth Innovation Ecosystem Testbed

Taking advantage of all three markets forces that are active in San Diego, in the true spirit of entrepreneurism, we're experimenting, testing, and putting into practice, initiatives such as the Catalyst program to turbo-charge a sustainable virtuous cycle of innovation. A living laboratory / regional testbed is now active in San Diego – aligning the incentives for advancing research based on governmental and defense priorities, while simultaneously creating companies, products, and services that also meet the needs of the commercial economy. We're addressing strategic and tactical supply chain DOD priorities, especially those that overlap with commercial markets – energy/power resilience, healthcare, communications, internet security (financial and critical infrastructure).

Testbed Characteristics

1. Collaborative programs to align research capabilities with targeted government needs and strategic industry partners.
2. A pipeline of intellectual property based innovation filled through Entrepreneurial education for students, faculty, alums, and affiliated startups
3. The creation of Multi-disciplinary advisory working groups, leveraging Medical, Business, Engineering, Data Sciences, Materials, and Supply Chain Expertise
4. Focused Acceleration in key market sectors: Medical Devices, Smart Transportation, Energy, Security
5. Targeted Industry partnerships – Healthcare, Regulatory, Infrastructure
6. Deploying the resources and funding to develop Multi-use companies to solve strategic and tactical DOD problems and while competing successfully in commercial markets.

We are optimistic that these steps will propel, not just San Diego, but other regions across the country, who might test and adapt these concepts and initiatives

in their particular innovation ecosystem. We extend an invitation to additional partners and welcome the opportunity to collaborate with other regional ecosystems toward greater entrepreneurial and economic global competitiveness and success.

Article

Global Alliances to Accelerate Innovation at Plug and Play Technology Center

Alireza Masrour
General Partner, Plug & Play Ventures, Sunnyvale, CA

ABSTRACT

The Plug and Play (PnP) accelerator model is differentiated vs. traditional accelerators in many ways, especially by encouraging cross industry collaboration globally. PnP has developed a global network spanning the value chain from universities to startup companies, to financial partners, to global industry leaders in multiple industries, including life sciences, med tech and digital technologies. Networking activities across the value chain and cross industry encourage associate thinking and collaboration and differentiates PnP vs. other accelerators.

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INTRODUCTION

Plug & Play Technology Center and the P&P Venture group have developed worldwide and industry wide partnerships to enable startups and emerging companies to boost economies via innovative ideas. Startups emerge from various sources ranging from laboratories, universities, and as spinoffs from larger organizations. These organizations benefit from our programs and international networks spanning the value chain and industries.

We note that the acceleration concept evolved from its beginning when Paul Graham of Y-Combinator (YC) and his co-founders invented the concept in March 2005 and now after 15 years, this concept has evolved to virtually every ecosystem and region in the US and soon to be the world, c. f., Jessica Livingston, "Founders at Work: Stories of Startups' Early Days", Apress, 2007).

Initially having all the startups and concepts at the same early stage being together "in a class" helps them to learn from each other and encourages them to get realistic feedback from customers, partners, investors and each other. Additionally, after a few years, you see the benefit for getting the accelerator alumni to come back and help others.

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OVERVIEW OF THE PNP PROGRAM

Our strategy of encouraging cross-stage engagement encourages learning through mentorship at all levels and parts of the value chain, e. g. from fellow founders, mentors, investors, partners, etc. What Plug and Play did to build on the concepts of phenomenal programs like YC is described below. Saeed Amidi, founder of Plug and Play invented a unique form of "Corporate Acceleration" where all the companies across the stages of the value chain formed a global network. The commonality is that they were all seeking proof of concepts (POCs), partnerships, and revenue achieved by partnering with global fortune 1000 companies.

He first realized that when companies at all stages are "in the same room" they benefit more when they all come from the same industries. Accelerators like Rock Health, Illumina, JLabs, and others provide amazing programs for vertically focused companies in the Health/Biopharma vertical. But, while the companies benefit from being at those programs, they obtain "know-how" from only one industry and from one perspective. Saeed asked the question: how could companies in one industry like Biopharma learn from medical device companies or digital health companies? In effect, this cross-industry perspective and experience has been evolved at most universities, where they started with one flagship program focused on one industry, and then soon after developed multi-industry programs that also ranged evolved

from graduate and faculty programs to also incorporate undergraduates, and also

Plug and Play evolved its model to span being vertically focused, to being cross vertical by running over 15 verticals at the same time. One can observe "the magic" happening when you see a Fintech payment company boosting healthcare payment processing, or insurance companies getting partners with medical device companies. As in "real life" you don't silo any industry from others but you can see when they are all at the same location they benefit from the knowledge sharing among each other and also keeping their competition close means the economy and people benefit from a healthy competition, the speed of innovation, better services and more transactions between small to big corporations. So, once again, cross industry collaboration and partnering has been validated. Industries can learn valuable lessons from each other.

PARTNERS, PORTFOLIO, AND SUCCESSES

At Plug and Play, we can partially attribute our growth and success to the prestigious universities and accomplished corporations who we partner with. As mentioned, we hold events alongside our university partners, some of which are Harvard, Stanford, USC, Insead, UCL, St. Gallen, and more. Our list of corporate partners surpasses 400, however, some notable names are WalMart, Tyson, Visa, Ford, Pfizer, Adidas, Airbus, Exxon Mobil, AT&T, to name just a few.

Our portfolio of investments is varied, and has provided us with successes to celebrate, and missteps from which to learn. PayPal , Honey, acquired by Paypal, FiscalNote, Guardant Health and LendingClub who IPO'd, and Dropbox, who also IPO'd are some of our largest exits. A few of our successful investments who are still fundraising are Kustomer, Big ID, and VisbyMedical.

THE NEXT CHAPTER

Now, our next chapter is to develop and implement borderless programs. We believe that talent, and "big ideas" originate from good university grads like ETH in Zurich, Oxford in the UK, to MIT in Cambridge, MA, NUS in Singapore, and Stanford, in our backyard in Silicon Valley to name a few. Capital to finance these ideas at all stages is everywhere. What is missing is a global ecosystem, and Plug and Play is so committed to building this multi-stage, cross vertical and global ecosystem.

Just a few examples to illustrate. Think about a drug discovery company or medical imaging company from Taiwan collaborating with a medical device company from ETH/Switzerland to present a novel innovative idea to Roche, J&J or Sanofi.

The world will be much different after the COVID-19 disaster because everyone in our global economy will learn from tough times about hidden opportunities independent of its location brought in to solve this issue globally during this tough time.

Article

California Tool Works: Assessing the Impact of Life Science Incubators and Accelerators

Matt Gardner
President California Biomanufacturing Center, and California Business Incubation Alliance

ABSTRACT

With the proliferation of types and business models in incubation and acceleration, a landscape survey commenced nearly a decade ago with innovation professionals running accelerators, incubators, corporate innovation teams, venture studios, and maker spaces. The benchmarking continues under the auspices of the California Business Incubation Alliance. For this paper, a selected set of findings specific to biotechnology have been detailed, including best practices, success measures, outcomes, and economic impact. The perspective of entrepreneurs, innovation executives, investors, and the public sector have been taken into account throughout this exercise.

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INTRODUCTION

Matt Gardner is president of the California Biomanufacturing Center, president of the California Business Incubation Alliance, and a board member of InBIA. He has worked on innovation ecosystems for more than two decades.

For the last decade, the California Business Incubation Alliance has worked with hundreds of incubators and accelerators to explore the myriad ways they measure their own short, medium, and long-term impacts. This running dialogue, inside and outside California includes surveys, interviews, focus groups, regular meetings, and analysis of individual incubator and accelerator programs.

Widely regarded as one of the most difficult industries in the world based on barriers to entry, technology risk, and product development timelines, health care – and particularly health technology – requires patient capital and persistent entrepreneurs. In addition, with long lead times and extraordinary regulatory burdens, biotech startups face a gap in typical commercial real estate markets. Biotech startups commonly seek flexible, short-term space in small amounts, and often lack the underwriting and credit worthiness to make significant lease commitments.

Governments, universities, and economic development agencies have found cause to intervene in this market failure for decades, creating subsidized, flexible spaces with the capacity to weather high failure rates. This collaboration is based on a strong alignment of interests, as development in biotechnology generates significant capital investment, including lab-based tenant improvements, and high-skilled jobs with high multiplier effects in regional economies. The first California Tool Works survey identified this intersection of industry specificity and capital intensity through the Gardner-Hamaoui Matrix (Gardner et al, May 2016).[i] As a result, significant emphasis has been placed throughout these surveys on the forms of return on investment that might satisfy both the public and private interests in measuring startup success.

BACKGROUND

The process of creating and building a startup has been commoditized to the point that there are low barriers to

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i Gardner et al, California Tool Works, May 2016, p 58. https://drive.google.com/file/d/0BxOWZxPt8aPFT3k4VTlmaFN6RWs/view?usp=sharing

Figure 1: Number of U.S. Programs by Industry Investment Focus.

establishing a new accelerator. The average accelerator surveyed for California Tool Works injected more than $400,000 annually into its local economy.

As a result, the number of these programs has risen dramatically since 2010.

However, generation of energy, hardware, and life sciences (collectively sometimes referred to as "deep tech") incubators represent a very different level of investment and economic impact. The typical hardware or life sciences incubator requires millions in equipment, in addition to real estate and personnel, to commence operations.

The proliferation of programs has also led to increasing diversity of industry focus among these programs (Figures 1 and 2). Whether this is representative of programs attempting to differentiate themselves or investors directing resources are narrowly targeted industry niches is impossible to determine.

The net result is an increasing diversity of programs available to startups from almost any industry, ranging from the primary economy to manufacturing to the service economy.

The proliferation of programs in software and the digital economy is, at least in part, based on relatively low barriers to entry. Industries such as advanced manufacturing, life sciences, and microelectronics, have barriers to entry for startups and incubators alike.

Because of these barriers to entry, the proportionality of accelerators to incubators reflects the relative ease of entry into fields like software and digital marketing (Figure 2). Two-thirds of the programs in digital marketing, and nearly two-thirds in software, are identified as accelerators.

These definitions, however, remain problematic. SOS Ventures has taken its template from Hax and other acceleration programs and built a wet lab life sciences accelerator. Indie Bio offers the temporary use of wet lab facilities and some of the kinds of shared equipment life sciences startups need.

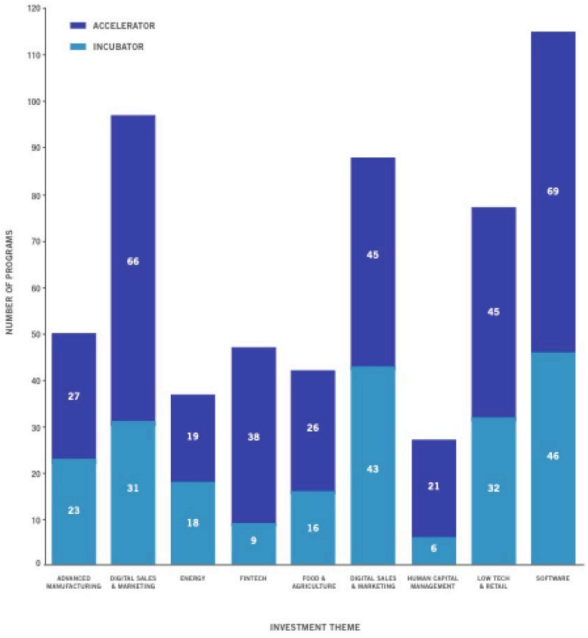

Figure 2: Program Type by Investment Focus.

SHARED RESOURCES, SHARED PROSPERITY

The investment thesis of many accelerators is oriented toward industries with low barriers to entry, including software, mobile, and e-commerce. Correspondingly, accelerators in those industries are more likely to have high volumes of startup throughput and deals. In more capital-intensive industries, such as advanced manufacturing and life sciences, the most active programs tend to specialize, as opposed to attempts to serve all industries.

The Gardner-Hamaoui Matrix is a means of typing incubators and accelerators according to how specific their focus is (X axis) and the richness of their resources (Y axis). Short cohort accelerators providing support to any kind of startup while emphasizing no physical space in favor of a mentor-driven model would fall into the bottom left quadrant as the most general and least resource-intensive programs. Wet lab incubators supporting therapeutic biotechnology companies would fall into the top right quadrant of the most specific, most resource-intensive type of startup support offerings.

In an attempt to classify accelerators by focus and resource intensity, the matrix provides one possible approach to comparing and contrasting incubators and accelerators. Covered incubator and accelerator programs include five main types. While these types do not strictly correspond to the sponsor of that program, they do provide indicators of the source and strategic direction of that program. Types of programs assessed include:

- Corporate
- University
- International
- Independent
- Venture capital affiliated

Dozens of incubators, accelerators, and corporate innovation chiefs were interviewed across the United States for this analysis. There is no universally-accepted definition as to what distinguishes an incubator from an accelerator, even among those who are steeped in their activities. Two experienced open innovation professionals at a recent conference faced a question from the audience: "What's the difference between an incubator and an accelerator?"

"I look at it from a time standpoint. I look at acceleration kind of early on, and then incubation kind of later on," said one person.

"I think of incubators usually working with ground-up technologies, versus accelerators that may be accelerating something that's already established," said the other. "There's a little bit of a grey line."

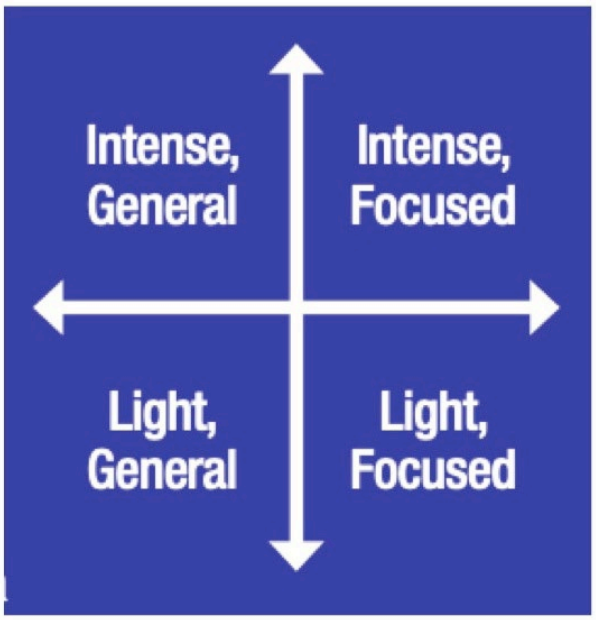

Figure 3: The Gardner-Hamaoui Matrix.

In short, experienced innovation leaders with large budgets for these activities gave the opposite responses in a public setting. For life sciences and other deep technologies defined by hardware, capital expenditure and major barriers to entry, the general guidelines between an incubator and an accelerator seems to have settled on accelerators having shorter, more formal curriculum, and incubators being associated with flexible tenancy. Even these informal lines are routinely challenged and re-shaped as the semester-length accelerator concept culminating in a pitch day has been abandoned by many operators.

Of responses from program managers, 66 percent indicated they invest in the companies they select (Figure 4). While many accelerators invest cash in the companies they select, there is not a direct correlation between programs calling themselves accelerators and the provision of capital. Among the 34 percent of respondents indicating they do not provide capital, roughly 21 percent indicated that they charge a fee, including some equity in companies selected for their program.

The majority of programs are associated with a physical space for startups, even if it is short – term and flexible space (Figure 4). Among those surveyed, 73 percent offered some form of office space, whether relocated headquarters or temporary company housing for participating startups.

Among participating programs, 44 percent offered some combination of shared equipment, prototyping, support with experimentation, and labs (Figure 4). For industries with high barriers to entry, including life sciences, electronics, aerospace, and others, these facilities

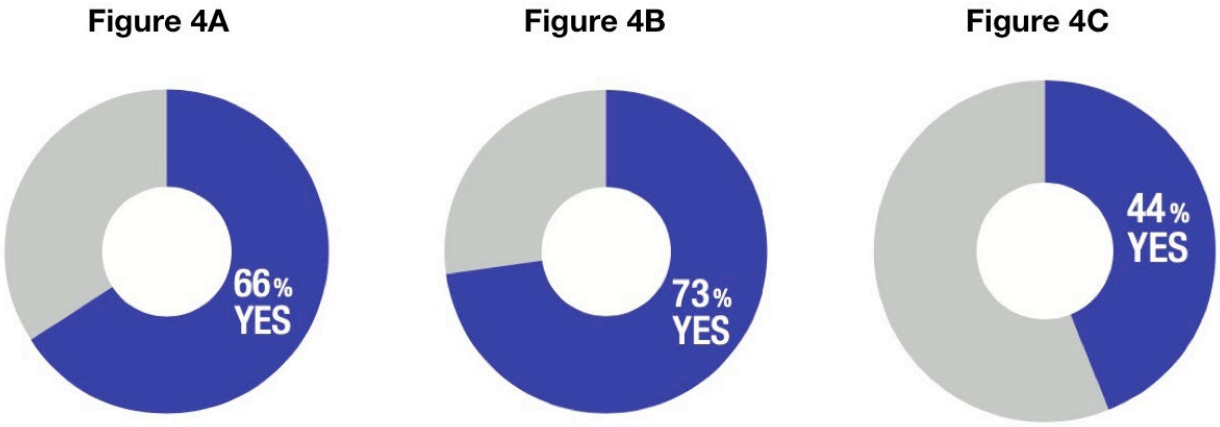

Figure 4: Percent of Programs: (**A**) Investing in Companies Accepted (**B**) With Physical Space Provided to Tenants (**C**) Providing Access to Shared Equipment.

can provide shared resources that would otherwise be totally inaccessible to startups.

The costs of research equipment for startups in biotechnology, Internet-of-Things, or transportation technologies, among other resource-heavy industries, can represent insurmountable and unaffordable conditions of product development absent an incubator to bear the expense.

A growing number of test beds and technology demonstration centers proliferated in the last decade, including for life science companies. The establishment of the California Biomanufacturing Center in 2020 included announcements about new pilot and test bed capabilities for novel equipment and bioprocessing technologies, and this new Center is not alone.[ii]

In adjacent technology industries including energy, smart cities, and IoT, demonstration projects such as Prospect Silicon Valley, GoMentum (at the former Concord Naval Weapons facility), the California Mobility Center, and the California AutoTech Testing and Development Center (at the former Castle Air Force Base) all provide critical test environments for innovators, without requiring massive capital expenditure to re-create such conditions by any individual startup.

EXPLORING NEW BUSINESS MODELS

The path to product approval in the life sciences is long and expensive. Several accelerator programs have taken approaches to product development they hope will be evolutionary steps forward.

ii The author was named founding president of the CBC in October, 2020.

INDIEBIO

IndieBio is an accelerator program in the SOS Ventures portfolio of accelerators. Their approach to developing companies includes a concerted effort to speed development. Part of the investment thesis shaping this approach is that IndieBio selects a range of companies including diagnostics and tools, materials, and other technologies beyond therapeutic biotech. The result is that their investments are strategically dispersed into companies with variations in time to market.

Acceptance into IndieBio is accompanied by cash investment of $50,000 for 8 percent equity in biotech startups followed by a $150,000 convertible note at a 20 percent discount for a total of $250,000 in funding. The five-month program operates in a fully-equipped BSL-1 and BSL-2 lab in downtown San Francisco, the birthplace of the biotechnology industry.

This program is a unique approach combining short-course, fixed-term accelerator programs with curriculum for company founders with the infrastructure that is typically part of a permanent wet lab facility. Investors at Indie Bio hope that a higher throughput of companies and the strategic spread across technologies selected for the program, can generate more promising life sciences companies on a faster track to market.

BREAKOUT LABS

A stand apart from the traditional incubator or accelerator, Breakout Labs offers up to a $350,000 grant for startups, especially in the life sciences, that are too far away from being able to raise funds from for-profit groups and too niche for traditional fundraising. Breakout Labs also

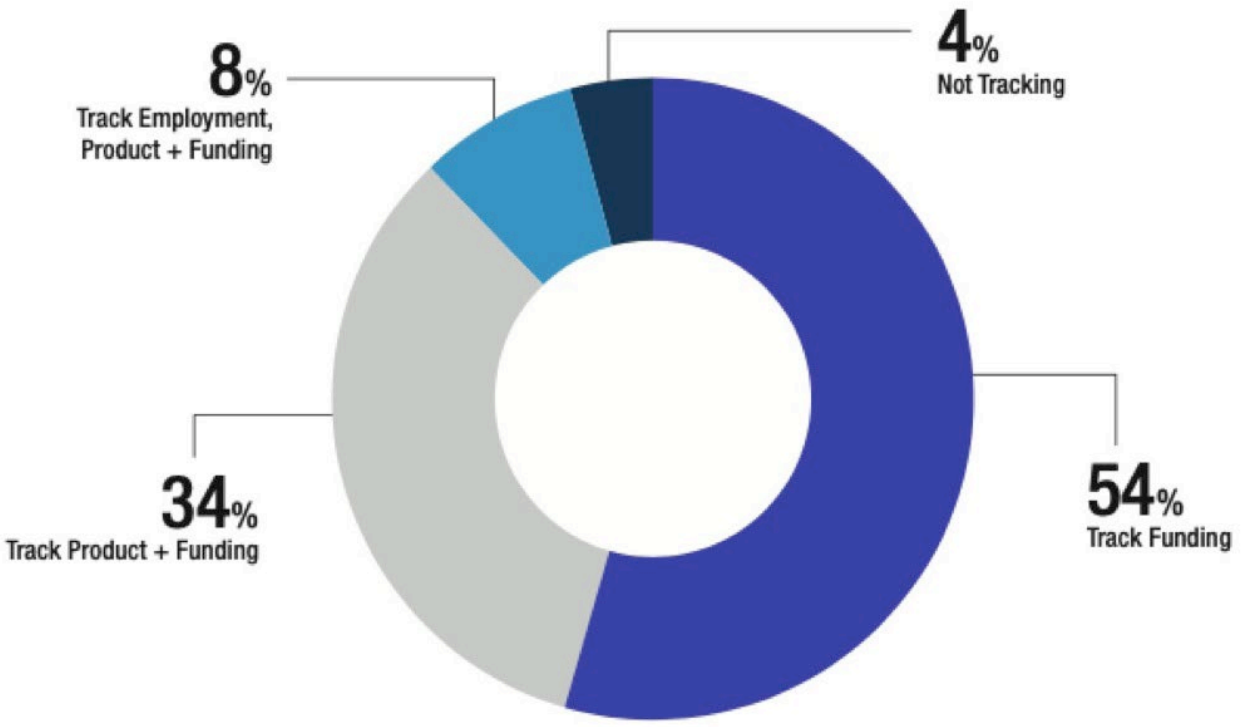

Figure 5: Measurement of Success Factors Tracked by Participating Incubators and Accelerators.

offers a two-year program of networking in the industry, exposure to potential industry partners, and strong press team to assist in generating press and publicity for startups.

Among the many unique features of Breakout Labs, the program offers no space for selected companies, and invests in companies anywhere in the U.S., regardless of location. The recent addition of Breakout Ventures may signify improved strategic value for portfolio companies. The presence of a sidecar fund could provide companies accepted into Breakout Labs with an option for expansion capital with a direct tie to the relationships they already have.

MEASURING OUTCOMES

Perhaps the most important indicator of success of a program from the perspective of entrepreneurs is the ability to raise funds or make exits, whether through some form of public offering, sale of the company, or merger. Outstanding recent examples of biotech capital raising include Perfect Day ($361 million), Pionyr ($275 million), Geltor ($114 million), Soylent ($72 million), and Clara Foods ($56 million). These are just a few examples of the graduates of programs including QB3 at UCSF, IndieBio, and Y-Combinator.[iii]

Funding is only one measure of the success of startup portfolios. Participating companies make other kinds of measurable progress. Some programs track product milestones, employment changes, new markets entered, and more (Figure 5). Almost all responding programs affirmed that they track funding events of portfolio companies, and many go further.

Some 54 percent reported they track funding, and 33 percent track product milestones as well as funding. Eight percent reported that they track both of those for successful graduated companies, as well as the growth or change in headcount of portfolio companies. Only 4 percent indicated that they are not tracking successes of graduated companies.

Incubators and accelerators also drive economic activity by their own direct investments. Operating any of these programs requires space, personnel, and often the kind of capital equipment that is beyond the reach of typical startups. To assess direct investments made by programs, the California Business Incubation Alliance

iii Funding rounds sourced from Crunchbase, discounted not to include pharma partnering dollars in future potential earnings, https://www.crunchbase.com/home.

surveyed approximately 50 programs regarding their annual spending activities.

Among respondents, the average for annual internal spending on staff, space, equipment, and consumables totaled $439,000. Many represented small businesses themselves, with an average of less than ten employees.

Life sciences programs face some measurement challenges in the value of their contributions to entrepreneurs, as well as their own spending to generate economic impact. Programs surveyed for California Tool Works replied that more than $50 million dollars in research equipment had been donated or acquired on a deeply discounted basis from companies making changes or closing. Impacts such as these, representing the strength and connectivity of an entire ecosystem, were beyond measure.

SUMMARY AND CONCLUSIONS

In certain ways, incubators have helped fill the "valley of death" in terms of both capital and product development for life sciences entrepreneurs. By providing subsidized space in smaller floor plates and on more flexible terms than possible in conventional commercial real estate, incubators extend the capital efficiency of and contribute to the survival and potential success of life science startups. The majority of programs directly invest in startups they accept, furthering the contribution.

Meanwhile, the tremendous growth in all accelerator programs in California and nationally has been matched by dramatic growth in programs with a life sciences focus. The California programs surveyed have supported the growth of more than 100 companies which attracted well over $800 million in risk capital in the last five years.

In general, the growth of incubation options represents more opportunity and more variety available to entrepreneurs in need of flexible space to develop their first products. Simultaneously, the public's interest is served by the lasting economic impacts from incubation in research-intensive industries.

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