Journal of COMMERCIAL BIOTECHNOLOGY

VOLUME 26 I NUMBER 2

RECOGNIZING AND CELEBRATING INNOVATION AND INNOVATORS IN BIOPHARMA

ISSN: 1462-8732 / eISSN 1478-565X
WWW.COMMERCIALBIOTECHNOLOGY.COM

Journal of
COMMERCIAL
BIOTECHNOLOGY
http://CommercialBiotechnology.com

Journal of
COMMERCIAL BIOTECHNOLOGY

VOLUME 26 NUMBER 2 AUGUST 2021

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Journal of Commercial Biotechnology (2021) 26(2), 1. doi: 10.5912/jcb983

From the Editorial Board

Introduction, Rationale and Commentary on Recognizing and Celebrating Innovation in Our Industry

ABSTRACT

This article summarizes our intent and basis for recognition of innovators in our industry, including the criterion that we are using for those organizations selected. Our focus for this year is largely on the Biopharma segment, because of Covid-19 and the positive and significant impact that our industry has made in that regard. We focus on companies across the life cycle from startups ranging to the large multi-national pharma companies.

Journal of Commercial Biotechnology (2021) 26(2), 3–10. doi: 10.5912/jcb985

INTRODUCTION

Our industry, along with US NIH, BARDA, FDA and CDC all deserve credit for their respective contributions over that last year. That has resulted in US and global market introductions of several vaccines along with diagnostics, and therapeutics. Now, almost two-thirds of Americans view the pharma industry positively according to recent Harris Poll surveys. It's a stunning reversal from just one year ago, when only about one-third (32%) rated the industry positively. We also signal our intent for subsequent issues later in 2021 to include recognition for innovation in the areas of Digital Health and in Digital Therapeutics/Diagnostics, to be developed in alliances with universities who are leaders in these fields.

We announced our intent to publish an annual tribute to the innovators in our community in a recent introductory "From the Boardroom" article in J. Commercial Biotechnology titled "What's Coming Next in Transformative Innovation", c. f. Boni et al, J. Commercial Biotechnology, Vol. 25, No. 4, pp 1-3, (2020). In short, our premise is that in our diverse, healthcare-centric industry it is appropriate for us to recognize annually, companies and their leaders who have developed and validated creative business models to facilitate transformative innovation and evolution in our industry. Inspirational, team-based leadership, leading to developing a culture of innovation is a critical part of the success of companies that pursue transformative technologies.

Innovation occurs by the creation and implementation of novel platforms and partnerships/alliances to develop, commercialize and bring to market, multiple emerging and promising innovations driven by "cutting edge" science and technology that enable products and services that serve real and compelling needs. To achieve commercialization of transformative innovations, we most often start with the creation of early-stage organizations, e. g. startups and emerging companies and business models appropriate for these products and services. And, to achieve full commercial potential they leverage alliances and partnerships across the value chain by leveraging open innovation. Over decades that defined the evolution of biotechnology, we have witnessed the emergence of many startup organizations, funded by grants, followed by angel investments, and multiple venture capital rounds. They have also partnered with larger organizations via partnerships to provide funding and access to other parts of the value chain. These larger partners (most often pharma) control more resources, and are "owners" of a larger share of the value chain – on both the customer facing and company facing side of the business model "canvas". See for example our recent article (The "Art of Collaborations": Understanding the Anatomy of Transformative Transactions in Biopharma; JCB Vol. 25, No. 4 (2020), pp. 50–56. These alliances have often, but not always, led to mergers and acquisitions that fill the product pipeline. Subsequent to de-risking and value-added provided by early-stage VC funding, many of these corporate alliances are funded directly by the pharma partner. However, many more are funded by a

corporate sponsored VC fund. For example, in the last few years, the following firms have been most active in this regard: J&J, Pfizer, SR One, Roche, Sanofi, Amgen, AbbVie, Illumina, and GV (Google Ventures).

As a result, we have observed over the last several decades an effective convergence of Pharma and Biotech to create what is now recognized as the Biopharma industry – big pharma, big biotech, and emerging biotech. This trend has also been mirrored in the MedTech industry, and is in a stage of early evolution in Digital Health, Medicine and Therapeutics.

Within the last year, and driven by the Covid-19 pandemic, we have observed unprecedented success in following this model precipitated by extreme and urgent customer need. We have seen efficient and powerful partnerships that have facilitated the development of effective vaccines, therapeutics and diagnostics on a remarkably short time scale. Our industry pursued a path of collaboration between large and smaller entities, both national and international to develop several COVID-19 vaccines and rolled them out to millions in a matter of months! We also saw both diagnostic and therapeutic products developed and brought to market. This is an obvious credit to the many universities, emerging companies and their industry partners across the value chain. And, with a credit to years of prior investment to advance these transformative technologies. Manufacturers also are rightly receiving a lot of credit, and deserve a 'shout out'. Also notable is the role of government funding via NIH and BARDA. But, regulators have also played a key role to provide safe and effective solutions that are currently being rolled out to the world. We have also seen promising technologies such as robotics and artificial intelligence/machine learning (AI/ML) begin to emerge as early stage offerings, albeit at a still early adoption stage. These technologies and business models are expected to evolve and drive innovation in MedTech and digital health, medicine and therapeutics. Many of these are recognized in this volume, but we intend to cover these transformative innovations and innovators in more depth in subsequent issues editions in 2021 and 2022.

In our previous work, we have noted the following simplified business model evolution to capture the transformation in the pharmaceutical industry over the decades. And, we now add Pharma 5.0 to our evolution (stay tuned).

- ***Pharma 1.0*** (1980's and 1990's) – *Focus on Blockbuster Drugs*
  - The Billion Dollar Molecule in Big Pharma
  - Biotechnology industry born with Genentech, Amgen, and a number of others
- ***Pharma 2.0*** (1990's–2000) – *Focus on Portfolio Development*
  - Pharma beginning to partner with and acquire emerging biotech to fill their product portfolios
- ***Pharma 3.0*** (2000–2010) – *Focus on Patient and Payer Centricity. Emergence of the genomic era, and the promise of personalized medicine.*
  - Maturing of strategic alliances as a strategy
  - Enhancement and formalization of outsourcing as CROs moved from "just find me patients "to the entire gamut of resources representing the validation of the concept of the virtual pharma company.
- ***Pharma 4.0*** (current) – *Convergence of 5Ps*
  - 5 P's aligning (patients, physicians, providers, payers, partners)
  - Biopharma partnerships accelerated across the board, and more formal, open innovation executed
- ***Pharma 5.0 (****emerging****)*** – Exploitation and Integration
  - Commercialization, adoption and development of business models to achieve the promise of personalized medicine and appropriate business models for digital health, therapeutics, and diagnostics

In this regard, we focus on innovative companies ranging from promising startups as they progressed thru their emerging and clinical development stages, to the larger pharma companies who often are in need of products to fill their pipelines to fill patient need. As noted above, none of this occurs without leadership (in both the larger pharma companies and in the emerging companies that provide the promising products for the pipeline. Therefore, we also recognize the historic contributions of a small cohort of historical innovation leaders that have stood out to us during the last 30 or 40 years as the industry evolved. Their pioneering leadership drove transformative change and exploited opportunities that set the stage for where we are today. Without them, the industry would not exist and be as productive as has been recently demonstrated with the development and commercialization of vaccines, antibodies, and diagnostic testing to fight the current Covid-19 pandemic. Below we include a brief paragraph for those leaders who have demonstrated exceptional contributions to our industry and recognized by our Editorial Board.

Selection Criteria

Companies from across the life cycle were selected based on the criteria listed below. And, in our editorial opinion, it is essential for these organizations to possess the leadership to have developed and sustained the resources, processes and values (RPV) that they creatively acquire and deploy to support innovation as defined below, at least through the initial stages of capitalization and team formation. The entrepreneurial process model starts with an opportunity, identifies and acquires the required resources, and assembles the team/leadership necessary to pursue and exploit the opportunity. We cite specifically the **following essential elements for companies selected**:

- The organization is built on a business model, that is either disruptive or radical/ transformative, and the opportunity being pursued is sufficient to create new markets and value networks capable of eventually disrupting an existing market and value network, and displacing established market-leading firms, products, and alliances.
- Critical elements of the business model have been validated with resources and processes. Especially the value propositions associated with the patient, physician, provider, and partner components.
- Critical elements of the technology-enabled platform have been validated beyond the laboratory stage, and the company has developed intellectual property that is strongly protected with patents (worldwide) and/or trade secrets
- The organization has been well funded and validated by credible investment sources and/or partners.
- A credible management/leadership team, CEO, and open innovation partnerships are in place to reduce the risk of moving the organization successfully thru the next several value inflection points including clinical validation and payer validation. And, the leadership team has enabled development of a culture of values that encourage innovation.

Our Historic, Leadership Roster of Industry Founders and Leaders

For this, our first year to recognize innovators, we are focusing on our largest industry sector, Biopharma, which is now matured. We do include some emerging innovators in the digital segment, but plan a more in-depth focus on this sector later in 2021 to provide additional coverage of some exciting digital innovations. These issues will focus more exclusively on: 1) digital health/medicine; and, 2) Robotics as an emerging digital solution/ therapeutic.

As noted, the importance of dedicated and inspiring leadership is needed. We have developed the following list of pivotal, industry thought-leaders and pioneers along with highly annotated bio-sketches of each - summarizing their noteworthy achievements and contributions to the industry**.** For our first year, we have developed this list from our Editorial team and Editorial Advisory Board members. In future years we plan to broaden via a survey of an extended network of industry experts.

However, leadership and team building deserves a short perspective on those topics, especially related to transformative innovation. Therefore, we focus briefly on the skill sets and practices of disruptive or transformative innovators. Boni, with Cunningham and Sloat published a recent article in JCB titled "Bridging Theory and Practice for Commercialization and Innovation: A Market-Centered Perspective for Cross-Industry Applications", c. f. JCB Vol. 24, No. 1 (2018), pp 7–36. In that work, we highlighted data that described innovative organizations by aggregating them into three categories: Needs seekers (market pull), market readers (fast followers), and technology drivers (technology push). In our opinion, most frequently it is the needs seekers who build organizations that are successful with transformative innovation. However, most of these leaders are also well trained in and conversant with the enabling technologies, i.e. they are scientifically trained. We also incorporated in that article some key principles that comprise the "innovators DNA", as reported by Dyer, Gregerson and Christensen in their recent classic book titled "The Innovators DNA: Mastering the Five Skills of Disruptive Innovators", c. f. Harvard Business Review press (2011). These authors identify five capabilities (traits or behaviors) demonstrated by the best innovators: (1) **Associating, or associative thinking**: drawing connections between questions, problems, or ideas from other disciplines or unrelated fields; (2) **Questioning**: posing queries that challenge common, or current ways of thinking; (3) **Observing**: "or watching" the behavior of users, customers, suppliers, and competitors to identify new ways of doing things; (4) **Experimenting**:

constructing interactive experiences and provoking unorthodox responses to see what insights emerge (we view this as basically an extension of "the scientific method, i. e. hypothesizing and testing); and, (5) **Networking**: engaging people with different ideas and perspectives. The authors explain how to generate and pursue ideas (or potential opportunities) with these skill sets, collaborate with "delivery-driven" colleagues to implement ideas, and build, collaborative innovation skills throughout the organization that is focused (like a laser) on commercializing, or bringing to market, new and unique products and services.

In selecting our list of individuals for our initial **"JCB Innovators Hall of Fame",** each of the individuals name therein have followed the principles underlying the Innovators DNA. And as a result, they have launched and/or built multiple organizations that brought to market many transformative innovations. Since this is our first year, we are naming the following individuals, some of whom have died, but others are still with us and contributing to innovation in our industry today. While some have been pioneers in the formation of our industry, some have emerged as leaders of new industry segments as the pharma industry has grown and diversified into many new segments.

THE JCB INNOVATORS HALL OF FAME - 2021

David U'Prichard

David was a leader of R&D and well versed in drug discovery in pharma (Beecham Pharmaceuticals, a predecessor of Glaxo Smithkline Beecham – GSK). He also served on many boards and participated as an early stage investor thru Druid Bioscience. This background led to his pioneering leadership to create a very unique organization and concept intended to discover, develop and commercialize drugs while navigating multiple "valleys of death" – the BioMotiv/Harrington project. This is a very novel organization focused on accelerating breakthrough medicines (potentially transformative technologies/ academic discoveries). This organization was designed by David and his collaborators to move them from the laboratory into the clinic and thru the commercialization stages in collaborative partnerships with pharma. We included a description in recent article in our recent special edition; c. f. Boni, "An introductory perspective on emerging, transformational technologies in biopharma: promises, challenges, and impediments"; c. f. Boni, JCB Vol. 25, No.4, pp 21–24 (2020). We also refer the interested reader to the BioMotiv/Harrington website https://www.biomotiv.com/the-harrington-project. David died recently and is missed by our community.

Henri A. Termeer

Henri was a biotechnology executive and entrepreneur who is considered a pioneer in corporate strategy in the biotechnology industry for his tenure as CEO at Genzyme; https://en.wikipedia.org/wiki/Henri_Termeer. He was named as one of the top fifty leaders of thought in orphan drugs and rare diseases in a list published by Terrapin for the World Orphan Drug Congress which included "eminent personalities that have advanced rare disease research." Henri was a biotech pioneer long before anyone knew what biotechs were. He founded Genzyme which is often said to have kick started today's orphan drug biotech M&A frenzy. Henri is definitely a mover/shaker in the biotech world and in the orphan drug space. He will always be known as the guy who figured out how to build a great business by making drugs for rare diseases. An inspiration and pioneer, many of his protégés have since moved on to lead other successful companies in the rare disease and biotech space thanks to his influence." In 1993, Termeer helped bring about the creation of Biotechnology Industry Organization through the merger of two associations created in the 1980s (now Biotechnology Innovation Organization). He later served as BIO's CEO, and served on the BOD of Moderna.

George Rathmann

Rathmann co-founded and served as the first CEO of Amgen, one of the early, pioneering companies in biotechnology. After transitioning the company to leadership by Gordon Binder, he founded and served as CEO of ICOS, a Seattle-based company. ICOS later formed a novel joint venture with Eli Lilly & Co. to commercialize an ICOS discover. This new drug (Cialis) was then taken into clinical studies and commercialized for treating erectile dysfunction and enlarged prostate (benign prostatic hyperplasia) – a competitor to Viagra. While at ICOS, he raised the largest-ever-to-date private offering for a biotechnology company. Rathmann received the first of the Biotechnology Heritage Awards from BIO, in recognition of his career as a scientist and entrepreneur. While leading Amgen, Rathman built and led a team that lasted well beyond his tenure there, and indeed still today is a role model for innovation. For reference, see the book review written by Art Boni and published in JCB in 2009; **"Science lessons: What biotech taught me about management"** written by Gordon Binder and Philip Bashe. Journal of Commercial Biotechnology (2009) 15, 86–91.

Robert S. Langer

Langer is well known in the fields of engineering and science, but is cited here as the founder of "Langer Lab" at MIT. This organization is responsible for over 30 spin off companies; c.f. https://en.wikipedia.org/wiki/Robert_S._Langer. Most of these companies were venture-backed, leveraged MIT inventions for successful commercialization, and incorporated Langer's post docs. To illustrate, we have invented a phrase that we and others in the technology transfer community describe as "the Langer model" for successful technology transfer, i. e. transfer the technology, and the post-docs into the company for seamless commercialization. It really speaks to building a well-balanced team that brings expertise in technology and business together around breakthrough technologies for success.

"He is the most cited engineer in history and 4th most cited individual in any field having authored over 1,500 scientific papers, and is also a prolific entrepreneur, having participated in the founding of over 40 biotechnology companies including Moderna. Langer's research laboratory at MIT is the largest biomedical engineering lab in the world; maintaining over $10 million in annual grants and over 100 researchers. He has been awarded numerous leading prizes in recognition of his work". And for public acknowledgement, Massachusetts innovators-Transforming the world, Langer is featured as "Revolutionary Biomedical Technology through Development of Controlled Drug Delivery Systems".

Robert (Bob) Swanson and Herbert (Herb) Boyer

We profile these co-founders of Genentech together, appropriately since their names are forever intertwined, and that is an appropriate way to profile the combination of science (Boyer), and finance/VC (Swanson) for founding and growing pivotal, transformative organizations: https://en.wikipedia.org/wiki/Robert_A._Swanson. Genentech was a pioneer in the field, and it remains one of the leading biotechnology companies in the world (now operating as a unit of Roche). **Swanson** served as CEO of Genentech from 1976 to 1990, and as chairman from 1990 to 1996. He graduated from MIT, with an undergraduate degree in chemistry and a master of science degree in management. Thanks to the science based courses, and then graduate business courses he took at MIT, he realized that he was particularly interested in two things: organizational development, and the commercialization of innovative ideas. He was fascinated by the potential of recombinant DNA technology, and decided to cold call scientists working on the technology. This led to the partnership with Boyer, who was a professor at the University of California, San Francisco (UCSF). Boyer's scientific expertise and Swanson's business plan convinced the venture capitalists at Kleiner Perkins Caulfield and Byers who funded Genentech. According to Wikipedia, "Robert Swanson's legacy can still be found to this day through the company he cofounded and led. Genentech is still producing drugs and treatments to this day, and some of his policies, such as allowing company scientists to publish, are still in place. Genentech scored many firsts under Swanson's leadership, such as developing the first drug produced via genetic engineering, being the first biotechnology company to go public, and being the first biotechnology company to sell its own drug. All business model innovations. These accomplishments have earned Genentech, Swanson and Boyer, a place in the history of the biotechnology industry. **Herb Boyer**, represented the science: https://en.wikipedia.org/wiki/Herbert_Boyer. Genentech's approach to the first synthesis of insulin won out over Walter Gilbert's approach at Biogen which used whole genes from natural sources. Boyer built his gene from its individual nucleotides. He served as Vice President of Genentech from 1976 until his retirement in 1991. This science/business partnership worked well to create and grow a truly world-class organization that brought together transformative science with business/strategy to create an organization that was distinguished as the first biotechnology IPO. And, of course a stream of innovations, partnerships and financings that led to an innovative partner with the part of the Roche family of companies, and a right to buy that was eventually exercised to make Genentech an integral part of that organization.

Sue Desmond – Hellman, MD

Sue is an American oncologist and biotechnology leader who served as the Chief Executive Officer of the Bill & Melinda Gates Foundation from 2014–2020. Wikipedia. She was previously Chancellor of the University of California, San Francisco (UCSF), the first woman to hold the position, and Arthur and Toni Rembe Rock Distinguished Professor In 1995, she joined Genentech as a clinical scientist; she was named chief medical officer the following year, and in 1999 became executive vice president of development and product operations. From March 2004 through April 2009 she was president of product development, playing a role in the development of two of the first gene-targeted therapies for cancer, Avastin and Herceptin. She left after the company was bought out by Roche Pharmaceuticals.

Marc Levin

Xconomy announced Marc *Levin, co-founder and partner at Third Rock Ventures, with their 2019 Lifetime Achievement Award in Boston*. https://xconomy.com/national/2019/07/31/mark-levin-named-xconomys-2019-lifetime-achievement-award-winner-in-boston/

"Levin built Millennium Pharmaceuticals—inspiring a generation of future executives/entrepreneurs along the way—and also helped reinvent the venture capital market for early stage biotechs by founding Third Rock, where his work has helped bring "a slew" of important new companies and new drugs to market. His efforts have played a key role in making Boston biotech what it is today".

"Levin, who has spent about 40 years in the biotech world—30 of them at venture capital firms—says taking the slow, methodical path is the key to success. Since Third Rock's founding in 2007, the firm has raised $2.7 billion and invested in more than 50 companies, including standouts like Agios, Foundation Medicine, and Bluebird Bio".

Third Rock, Levin says, "spends up to four years finding the right mix of business executives and scientists to tinker with an idea—such as whether a genome scan could identify the best drug for each patient—just to decide if there's enough there to start a company". "One academic with one idea will not be successful, mostly," Levin says in an interview with Xconomy. "We go out and meet all the best people in the world and we [together] develop an R&D plan, a discovery plan, [and reflect on] does this make regulatory and reimbursement sense … we'll spend years on that idea."

"That combination of active networking and recruiting is key to the teams Levin put together both at Third Rock and Millennium Pharmaceuticals, says John Maraganore, currently CEO of biotech Alnylam Pharmaceuticals in Cambridge. "You can have the greatest science and the greatest idea and if you don't have the right people behind it, the likelihood of success is really low," he adds". Note that Millennium and Alnylam are profiled in an mini-case study by S. Rang later in this special edition of JCB.

Alejandro Zaffaroni

Alejandro Zaffaroni was a serial entrepreneur who was responsible for founding several biotechnology companies in Silicon Valley. Products that he was involved in developing include the birth control pill, the nicotine patch, corticosteroids, and the DNA microarray. Wikipedia. "Dr. Zaffaroni was most closely associated with Alza, which developed new ways to administer medicines to increase their effectiveness, reduce side effects and allow people to take pills less frequently. These advances include extended-release tablets, implantable devices and skin patches, like the NicoDerm CQ nicotine patch. Founded in 1968, Alza was acquired by Johnson & Johnson for about $12 billion in 2001. He also co-founded Affymetrix in 1991; the company was a pioneer in developing DNA chips, more formally known as microarrays. Those chips revolutionized genetic studies, allowing many genes to be analyzed at once. They are now widely used in studies aimed at finding genetic variants linked to different diseases".

c.f. https://www.nytimes.com/2014/03/07/business/alejandro-zaffaroni-biotechnology-entrepreneur-dies-at-91.html

The following is included herein for historical reference regarding the origins of Alza, and is abstracted from a 2004 Kansas University News article. It nicely illustrates university ties/technology transfer (well before implementation of the Bayh-Dole Act) to commercial drug development organizations: In 1967, **Takeru Higuchi**, widely recognized as the "Father of Physical Pharmacy" was persuaded to join the KU faculty (he invented the time-release medication capsule, which would release medicine slowly into the bloodstream). New facilities for his research were part of the package. Alejandro Zaffaroni offered Higuchi an enticing prospect - to start a company called Alza in Palo Alto. Higuchi preferred to remain in Lawrence. Therefore, Alza operated out of Lawrence for five years, in the building next door to McCollum laboratories that today bears Higuchi's name. Dipivefrin or Propine® (dipivaloyl epinepdrine) was developed by Takeru Higuchi at Alza/INTERx, with some of the work done at KU. The product was eventually sold through Allergan in Irvine, CA. Higuchi also held the patents through Alza, with much of the work done at KU-on the Alza osmotic drug delivery systems.

William J. Rutter

Bill is an American biochemist who cofounded the early biotechnology company Chiron Corporation together with Edward Penhoet and Pablo DT Valenzuela; Wikipedia. "He is also Founder and Chairman and CEO of Synergenics, LLC, which controls a consortium of companies with different, but complimentary approaches to diagnosis, prevention and treatment on a worldwide basis. Previously, Dr. Rutter was co-founder and chairman of Chiron Corporation, a major biotechnology company which is well known for the development of recombinant DNA-based vaccines,

including Hepatitis B, and for the discovery of Hepatitis C, the first sequencing of the HIV-AIDS virus. Chiron pioneered the development of quantitative DNA-based diagnostic tests measuring viral load, which has played a major role in protecting the blood supply, and also in developing drugs for treatment of these diseases. Chiron was acquired in two stages by Novartis and its antecedent company Ciga-Geigy. Dr. Rutter has served on boards of Novartis and several Biotech companies, including Cytokinetics, Sangamo Biosciences, and Synergenics companies. Dr. Rutter is a member of the National Academy of Sciences and the American Academy of Arts and Sciences. Previously, Dr. Rutter served as Chairman of the Department of Biochemistry and Biophysics at UCSF. His lab made key contributions to biotechnology and recombinant DNA technology, including cloning of the human insulin gene and the production in yeast of a virus-like particle for Hepatitis B, which was eventually used in the manufacture of a Hepatitis B vaccine". https://goldlabfoundation.org/presenters/william-rutter/

Joshua S Boger

Josh Boger, Ph. D is an organic chemist and is considered a pioneer in the field of structure-based rational drug design. Wikipedia. "In 1989, Boger founded Vertex Pharmaceuticals Incorporated. He has served variously as its President, CEO and Chairman of the board. At Vertex, Boger pioneered an approach to structure-based rational drug design that changed the way that drug development occurred. Employees worked in multi-disciplinary teams, combined technologies from biophysics, chemistry and computer science, and applied them to drug discovery and the development of small molecule drugs. As of 2003, Vertex was listed as one of forty worldwide Technology Pioneers by the World Economic Forum, for advancing drug discovery through this approach". Vertex and Berger were also profiled in two books by Barry Werth. "The Billion Dollar Molecule- the quest for the perfect drug" (1994) deals with the early history of Vertex, and the technology/business intersection. "The Antidote Inside the World of New Pharma" (2014) looks at the evolution of Vertex 20 years later.

Frederick Frank

Frederick Frank is an investment banker, with more than 50 years of experience on Wall Street. He is considered the first investment banker to have specialized in the areas of biotechnology, pharmaceuticals, and health care services. As of 2014, Frank became a founder and chair of EVOLUTION Life Science Partners. Wikipedia. He is credited as lead underwriter for over 125 IPOs and as a negotiator in over 75 mergers and acquisitions Frank was chosen as one of the top 100 contributors to biotechnology in 2005". "In the late 1970s, Frank began to work with companies such as Cetus, a company developing industrial applications for Recombinant DNA technology, and Genentech. Frank saw rDNA technology as a "game-changing opportunity. Advised by Frank, Cetus went public on March 1, 1981 with the second-largest IPO in U.S. corporate history. Frank was also instrumental in the Bristol-Myers Squibb merger of 1989 and the Hoffmann-La Roche acquisition of Genentech in 1990. At the time, the merger of an established pharmaceutical company with a younger biotechnology company was highly unusual. It has been described by Frank as a "strategy of convergence".

Stelios Papadopoulos

Stelios has been involved with the biotech and pharma industries for nearly three decades. Papadopoulos retired as Vice Chairman of Cowen & Co., LLC in August 2006 after six years with the firm where, as an investment banker, he focused on the biotech and pharma sectors. Prior to joining Cowen, he spent thirteen years as an investment banker at PaineWebber, Incorporated where he was most recently Chairman of PaineWebber Development Corp., a PaineWebber subsidiary focusing on biotechnology. He joined PaineWebber in April 1987 from Drexel Burnham Lambert where he was a Vice President in the Equity Research Department covering the biotechnology industry. Prior to Drexel, he was a biotechnology analyst at Donaldson, Lufkin & Jenrette. He is a co-founder and chairman of the Board of Directors of both, Exelixis, Inc., and Anadys Pharmaceuticals, Inc.; he is a co-founder and a member of the Board of Directors of Cellzome, Inc. He is Chairman of the Board of Directors of Biogen Idec, Inc., BG Medicine, Inc., Joule Unlimited, Inc. and Regulus Therapeutics, Inc. https://xconomy.com/author/spapadopoulos/

J. Craig Venter

Founded **Celera Genomics**, The Institute for Genomic Research (**TIGR**) and the J. Craig Venter Institute (JCVI), where he currently serves as CEO. He was the co-founder of Human Longevity Inc. and Synthetic Genomics. He is known for leading the first draft sequence of the human genome and assembled the first team to transfect a cell with a synthetic chromosome. While maintaining a strong scientific presence, he has also pursued and enabled others (thru Celera) to pursue the commercial

opportunities enabled by the genomic sequencing, including Illumina, also part of his ecosystem in San Diego.

George M. Church

Dr. Church is a geneticist who has made significant impacts in academia and in translating science into commercial practice. His Wikipedia profile indicates that Church is known for his professional contributions in the sequencing of genomes and interpreting such data, in synthetic biology and genome engineering, and in an emerging area of neuroscience that proposes to map brain activity and establish a "functional connectome." Among these, Church is known for pioneering the specialized fields of personal genomics and synthetic biology. He has co-founded commercial concerns spanning these areas, and others from green and natural products chemistry to infectious agent testing and fuel production, including Knome, LS9, and Joule Unlimited (respectively, human genomics, green chemistry, and solar fuel companies).

His technology transfer and translational impact indicate that Church has co-founded 22 companies, including Veritas Genetics (human genomics, 2014, with Mirza Cifric, Preston Estep, Yining Zhao, Joe Thakuria), Warp Drive Bio (natural products, 2011, with Greg Verdine and James Wells), Alacris (cancer systems therapeutics, 2010, with Hans Lehrach, Bernhard Herrmann, and Shahid Imran), Knome (human genomics, 2007, with Jorge Conde and Sundar Subramaniam),Pathogenica (microbe and viral NGS diagnostics, 2009, with Yemi Adesokan),AbVitro (immunomes, 2010, with Francois Vigneault),Gen9 Bio (synthetic biology, 2009, with Joseph Jacobson and Drew Endy), EnEvolv (Genome Engineering), Joule Unlimited (SolarFuels, 2007, with Noubar Afeyan and David Berry), and LS9 (green chemistry, 2005, with Chris Somerville, Jay Keasling, Vinod Khosla, Noubar Afeyan, and David Berry.He has participated in technology development, licensing patents and advising most of the Next-Generation Sequencing companies, including Complete Genomics, Life Technologies, Illumina, Danaher Corporation, Roche Diagnostics, Pacific Biosciences, Genia, and Nabsys.

Jennifer A. Doudna, Ph. D.

Jennifer is an American biochemist known for her pioneering work in CRISPR gene editing, for which she was awarded the 2020 Nobel Prize in Chemistry along with Emmanuelle Charpentier – Wikipedia. She is the Li Ka Shing Chancellor's Chair Professor in the Department of Chemistry and the Department of Molecular and Cell Biology at the University of California, Berkeley. She has been an investigator with the Howard Hughes Medical Institute since 1997. Outside the scientific community, she has been named one of the *Time* 100 most influential people in 2015 (with Charpentier). She is the founder of multiple companies profiled elsewhere in this volume. She is also profiled in the latest Walter Isaacson book, "The Code Breaker" that is reviewed in an Editorial Commentary later in this volume of JCB.

Dietrich A. Stephan, PhD

Dr. Stephan is an industry veteran who is considered one of the fathers of the field of precision medicine, having trained with the leadership of the Human Genome Project at the NIH and then going on to lead discovery research at the Tran Dietrich A. Stephan, PhD slational Genomics Research Institute and subsequently serve as professor and chairm In parallel, Dr. Stephan has exported an of the Department of Human Genetics at the University of Pittsburgh. Stephan has identified the molecular basis of dozens of genetic diseases and published extensively in top-tier peer-reviewed journals such as Science, the New England Journal of Medicine, Nature Genetics, Proceedings of the National Academy of Sciences and Cell. These fundamental new insights form the basis of new molecular diagnostics and knowledge-based therapies. In parallel, Dr. Stephan has exported his new insights into the market to benefit patients through industry co-development or new company formation. Stephan has founded or co-founded in excess of a dozen biotechnology companies. These companies are usually anchored in first-in-class technologies with transformational potential for impact, and backed by top-tier healthcare investors. For example, Stephan co-founded Navigenics, a personal-genetics testing company, which was among the first direct-to-consumer genomics companies. In 2014, he helped launch Pendulum Therapeutics, a leading gut microbiome-modulation company, and served as its Chairman of the board for many years. Stephan also helped launch Peptilogics, Inc. a deep learning peptide therapeutics development company now funded by Presight Capital and Thiel Capital, and currently serves as its Chairman of the board. Stephan has also advised numerous diagnostics, therapeutics and technology companies such as Genia Technologies, a single-molecule sequencer on a chip which was acquired by Roche and Guardant Health, Inc. a cancer "liquid biopsy" testing company. Stephan has a keen interest in new technologies that arise from the collision of various sectors of innovation and which promise step-function improvements in health for the global population. To this end,

in 2019, he founded NeuBase Therapeutics, Inc., a biotechnology company that can uniquely engage disease-causing genes in the human genome and address all causal mechanisms undergirding rare and common diseases, including cancers. Stephan is currently Chairman and CEO of NeuBase Therapeutics. https://en.wikipedia.org/wiki/Dietrich_Stephan

Laura E. Niklason

Laura E. Niklason is Nicholas Greene Professor of anesthesiology and biomedical engineering at Yale University. She is a member of the National Academy of Engineering and the co-founder of Humacyte and specializes in vascular and lung engineering. Her work on lab-grown lungs was recognized as one of the top 50 most important inventions of 2010 by Time magazine. Wikipedia. The early work was done at Duke and MIT. Durham-based Humacyte, a regenerative medicine company that received start-up support from the North Carolina Biotechnology Center 15 years ago, is going public in a novel deal that will give it a market capitalization of $1.1 billion. Humacyte and Alpha Healthcare Acquisition Corp., a special purpose acquisition company (SPAC) based in New York, have signed a business-combination agreement to take Humacyte public, along with a $175M PIPE financing agreement. Niklason will lead the company, to be listed on the Nasdaq Capital Market

Anne E. Wojcicki

Anne is an American entrepreneur who co-founded and serves as CEO of the personal genomics company 23andMe. The following information is taken from Wikipedia. "As of 2020, she is listed as #93 in *Forbes* list of the World's 100 Most Powerful Women. After her graduation from Yale, Wojcicki worked as a health care consultant at Passport Capital, a San Francisco-based investment fund[6] and at Investor AB.[She was a health care investment analyst for 4 years, overseeing health care investments, focusing on biotechnology companies. Disillusioned by the culture of Wall Street and its attitude towards health care,she quit in 2000, intending to take the MCAT and enroll in medical school. Instead, she decided to focus on research. Wojcicki is best known as the co-founder and CEO of 23andMe, a privately-owned, direct to consumer DNA testing company, which allows for consumers to test for ancestry and health risks. Anne founded the company in 2006 with Linda Avey and Paul Cusenza, with a goal of solving the pain point that a majority of people do not have access to their genetic information, which could provide information on cures for diseases or treatments, especially with the help of Glaxo and their $300 million investment. Anne has expressed interest in "revolutioniz[ing] health care" with DNA testing, as it could provide consumers with sufficient enough information as to predict potential genetic illnesses".

Daphne Koller, Ph. D.

Daphne is an Israeli-American computer scientist. She has been a Professor in the Department of Computer Science at Stanford University and a MacArthur Fellowship recipient. She is one of the founders of Coursera, an online education platform. Her general research area is artificial intelligence and its applications in the biomedical sciences. Koller was featured in a 2004 article by *MIT Technology Review* titled "10 Emerging Technologies That Will Change Your World" concerning the topic of Bayesian machine learning. Daphne is the founder and CEO of Insitro, as described below. Her work in the biomedical sciences is recent but promising. And is featured in our emerging company section.

Glen de Vries

Co-founder and co-CEO of Medidata, the most-used platform for clinical trials around the world. Medidata has powered tens of thousands of clinical trials, with millions of patients and billions of patient records. de Vries has been a driver of Medidata's mission and vision since inception in 1999. Their vision is to "power smarter treatments and healthier people" by transformation with technology, non-traditional thinking, and industry collaboration.

Eric Topol

Eric is a cardiologist, scientist and Founder/Director of the Scripps Research Translational Institute. While serving in largely academic positions he has pioneered and published on his vision to advance the use of digital tools and technologies that have the potential to enable physicians in multiple fields to diagnose, treat and cure. His work and publications have illuminated the potential of digital technologies to be developed by others to pursue them in the private sector. His recent book, "Deep Medicine" is a classic overview of this visionary thinking. https://www.hachettebookgroup.com/titles/eric-topol/deep-medicine/9781541644632/

Alise Reisen, MD

According to John Carroll, "Tectonic Therapeutic isn't your average biotech startup story. For all sorts of reasons. There's your billionaire Harvard scientist and philanthropist who's personally bankrolling much of the operation. The CEO is one of the most prominent women involved in the global drug hunting business". (The Sana website profiles Alise as follows). "Alise was previously President, Global Clinical Development at Celgene Corporation, where she oversaw the development and approval of drugs across their pipeline in oncology, hematology and autoimmune diseases and fibrosis. She currently serves on the board of directors of Homology Medicines and Sharsheret. Alise has extensive early and late clinical development experience working across a broad range of therapeutic areas, including oncology, hematology, rheumatology, dermatology, gastroenterology, pain, respiratory and allergic diseases. She played a leadership role which led to the initial approval of 10 novel medicines and the approval of more than 10 indications for an additional 5 drugs. Alise previously served as Head of Global Clinical Development at EMD Serono. Prior to this, she served as Vice President, Program and Pipeline Leadership, Oncology at Merck and Co. In this capacity, Alise led Merck's Keytruda (anti-PD-1) program and oversaw the initial development and filing activities worldwide for melanoma and non-small cell lung cancer, and the initiation of development plans in 7 additional indications. Prior to Merck, she was a faculty member at Columbia Medical School, and a physician and researcher at Columbia Presbyterian Hospital".

From the Editorial Board

Companies Recognized as Innovators for 2021

ABSTRACT

Our awards are framed into the 4 models or paths to innovation as described by Boni and Joseph, and published in JCB previously in two companion articles, c. f. JCB Vol. 24, No. 4 (2020); "Aligning the Corporation for Transformative Innovation: Introducing Dashboard 2.0", pp 14–22, &"Four Models for Corporate Transformative, Open Innovation", pp. 23-31. The 4 models that we categorized can be summarized: 1) Direct Entrepreneurship; 2) Consortia/Alliances – open innovation partnerships or alignments with Startups & Emerging Companies; 3) External Accelerators; and, 4) Corporate Accelerators.

Journal of Commercial Biotechnology (2021) 26(2), 13–7. doi: 10.5912/jcb986

INTRODUCTION AND OVERVIEW

How did we come up with our list or companies to recognize? For this, our inaugural or first year, each member of the JCB editorial board was asked to provide a list of their candidates. We also included perspectives from other thought leaders in the industry in our networks beyond the Editorial Board, and the Editorial Advisory Board. In subsequent years, we intend to solicit broader input from the community.

As noted, we aggregate the organizations to be recognized into the four quadrants identified in the recent Boni and Joseph articles listed in the Abstract. We recognize that there has been widespread adoption of open innovation/partnering that has occurred in our industry over the last two decades as biotech and pharma have blended into biopharma. So, while these categories provide a useful framework, most larger organizations use a combination of internal and external resources to innovation. Therefore, we include a brief description of each company, and include them in a category that predominantly describes their approach to pursuing innovation. Keep in mind that most organizations in biopharma employ open innovation today so could be listed in multiple categories. So, we note that in the descriptive material for each company, why we are including them for recognition. The organizations that we recognize below clearly demonstrate innovation by bringing truly transformative technologies to market – and in the case of Covid-19 therapeutics, in record time! And, also meeting all of the criteria that we have established for recognition and discussed on the introduction.

CONSORTIA/ALLIANCES – OPEN INNOVATION PARTNERSHIPS OR ALIGNMENTS WITH STARTUPS & EMERGING COMPANIES

Our Consortia/Alliances category is dominated this year by **Covid-19 therapeutics** that were brought to market in alliances between larger pharmaceutical companies in partnership with smaller emerging companies who had been advancing the mRNA and adenovirus technologies previously. These novel solutions were brought to market in about one year time in 2021! A remarkable achievement driven by the Covid-19 pandemic. The very first vaccines for Covid-19 to complete phase 3 testing are an entirely new type: mRNA vaccines. Never before have mRNA vaccines — such as the two-dose Pfizer/BioNTech and Moderna vaccines that have now received emergency use authorization from the FDA — been approved for use in any disease. Adenovirus is one of the viral vectors used by J&J/Janssen in partnership with Novavax. In these viral vector vaccines (that are one dose), a gene unique to the virus being targeted is added to the viral vector. For COVID-19 vaccines, this gene codes for the spike protein, which is only found on the surface of SARS-CoV-2. So, our short list for celebrating and recognizing innovation in this category is highlighted by: **Pfizer/BioNTech; Moderna/Lonza** with funding from BARDA and NIH (and with recently announced a series of supply chain partnerships with IBM, Baxter and Recipharm, and a distribution in Japan partnership with Takeda)**; Johnson & Johnson/Janssen/Novavax**. We note that Novavax received significant funding from the Bill and Melinda Gates Foundation, and this was certainly essential in their pursuit of this project with perseverance over the

years. Right behind this group is **Astra Zeneca/Oxford U with partnerships with IQVIA/Serum Institute of India.** As of this writing they have not yet received Emergency Use Approval from the FDA. While (to our knowledge) vaccines have not been developed previously by AZ, they deserve credit for stepping up and trying it now via the partnerships and alliances.

Additionally, **Roche, with their recent acquisition of Spark Therapeutics** also deserve recognition for advancing the field of **gene therapy**. Once again, after previous pivotal partnerships and acquisition transactions with pioneering biotech companies (Genentech and Foundation Medicine), Roche acquired gene therapy pioneer Spark Therapeutics. Spark had a product already on the market with Luxturna [from Children's Hospital of Philadelphia – CHOP} when they signed the deal with Roche. But, it is apparent that Roche really bought them for their futures. For more details see "The Art of Collaborations: Understanding the Anatomy of Transformative Innovation in Biopharma" by Boni, published in JCB Vol. 25, No. 4, pp 50–56.

One other company pursuing gene therapy also deserves mention and that is BioMarin. After some setbacks in 2020, **BioMarin Pharmaceutical Inc.** announced in January 2021 positive Phase 3 results for adults with severe hemophilia A. Their study met all primary and secondary end points in their one year data set. This followed an unexpected rejection in August 2020. The full one-year results for Roctavian are a positive indicator for the company's pursuit of a new approach for hemophilia. The full one-year results from the study are an important milestone for Roctavian, which was unexpectedly rejected in August 2020 by the Food and Drug Administration after BioMarin had applied for an accelerated approval. The regulator, asked BioMarin for two years of follow-up data. So, stay tuned on this important innovation within the next year. Perseverance in this effort, as with any entrepreneurial pursuit is necessary and laudable.

DIRECT ENTREPRENEURSHIP – FROM PROMISING EARLY STAGE TO MATURE COMPANIES ACROSS THE COMPANY LIFE CYCLE

Many pivotal biopharmaceutical companies emerged in the Boston area and paved the way from innovation since the late 1990's. We highlight four of them. They are **Millennium Pharmaceuticals (since acquired as an operating unit by Takeda), Alnylam Pharmaceuticals, Kymera, and Moderna** (mentioned above for their pioneering mRNA for Covid-19). Their importance and impact it recognized as essential drivers in the Boston/Cambridge innovation ecosystem surrounding MIT and Harvard. Refer to the mini-case study by Sheen Rong in a later section of this issue of JCB for more details on these four companies.

Gilead Sciences, Inc., is an American biopharmaceutical company headquartered in Foster City, California, that focuses on researching and developing antiviral drugs used in the treatment of HIV, hepatitis B, hepatitis C, and influenza, including Harvoni and Sovaldi; c.f. Wikipedia. Also refer to article titled "Lessons from Sovaldi: Fueling Innovation while Ensuring Access" by Daniel S. Levine & Marc. C. Watrous article in JCB, Vol. 25, No.4, pp 10–20 (2020).

Amgen, Inc. has been a biotechnology pioneer since 1980, and has grown to be one of the world's leading independent biotechnology companies. Its products have reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential. We refer the interested reader to the book on the origins of Amgen written by Gordon Binder (who took over as CEO from founding CEO George Rathman). Refer to the book review by Boni, "Science Lessons; What Biotech Taught Me About Business", JCB Vol. 15, No. 1, pp 86-91, January 2009.

Vertex Pharmaceuticals, Inc. is an American biopharmaceutical company founded by Dr. Josh Boger in 1989 and based in Boston, Massachusetts. It was one of the first biotech firms to use an explicit strategy of rational drug design rather than combinatorial chemistry; c.f. Wikipedia. Josh Boger's vision was to prove he could do rational drug design using high-tech approaches like X-ray crystallography and molecular modelling. This was long before pharma companies were willing and able to pursue these transformational technologies.

Regeneron Pharmaceuticals, Inc. is a biotechnology company founded in 1988 and specializes on monoclonal antibody technology. Taken from the Regeneron website: "Regeneron is applying our 30 years of scientific and technology expertise to combat the COVID-19 pandemic. We feel uniquely positioned to face this public health threat given our proprietary *VelociSuite*® technologies and our track record against infectious diseases such as Ebola. We have moved REGEN-COV™ (casirivimab and imdevimab) from discovery to late-stage clinical development and regulatory review in record time".

Eli Lilly and Company is a well know, leading pharmaceutical company founded over 100 years ago. Their antibody combo for Covid-19, reduces hospitalization, & deaths by nearly 90%. This is certainly a noteworthy contribution to the worldwide fight against Covid-19.

Flatiron Health is based in New York City, Flatiron Health is a healthcare technology and services company focused on accelerating cancer **research** and improving patient care. The company's platform enables cancer researchers and care providers to learn from the experience of every patient. Flatiron has emerged and is now a unit of Roche Holding AG.

In the next subsection, we highlight some promising, emerging early stage organizations to look out for in the coming years as the transformative technologies on which they are founded evolve – and appropriate business models and partnerships are implemented! Since CRISPR is currently emerging as a platform technology, 5 emerging CRISPR companies are grouped and listed first. We did not attempt to rank order any of the companies selected.

CRISPR Therapeutics AG

(From Wikipedia) is a Swiss–American biotechnology company. CRISPR Therapeutics was founded in 2013. Two of the co-founders are Emmanuelle Charpentier and Jennifer Doudna who later shared the Nobel Prize in Chemistry in 2020. As part of a working group, they provided the first scientific documentation on the development and use of CRISPR gene editing. The company, CRISPR Therapeutics applies this new technology commercially. In 2016, the company went public on NASDAQ. In August 2016, the company started to operate Casebia Therapeutics as a joint venture with Bayer (who is an investor in CRISPR). In 2019, Casebia Therapeutics came directly under the control of CRISPR Therapeutics.

EDITAS Medicine

(From Wikipedia) is a clinical-stage biotechnology company which is developing therapies based on CRISPR-Cas9 gene editing technology. Editas is based in Cambridge, MA and has facilities in Boulder, Colorado. It was founded in 2013 with funding from Third Rock Ventures, Polaris Partners, and Flagship Ventures; and, licensed CRISPR patents from the Broad Institute's Feng Zhang, patents from Harvard's David Liu and George Church, and patents from Partners Healthcare – MGH's J. Keith Joung. These four were co-founders and scientific advisory board members along with Jennifer Doudna.

Intellia Therapeutics

(From Wikipedia) is a biotechnology company developing biopharmaceuticals using a CRISPR gene-editing system invented by Jennifer Doudna (with colleagues at the University of California, Berkeley, Virginius Siksnys (with colleagues at Vilnius University). The company has partnerships with Novartis and Regeneron. It was backed by Atlas Venture and Novartis.

Scribe Therapeutics, Caribou, Mammoth BioSciences are 3 additional companies co-founded by Jennifer Doudna and are profiled in our editorial commentary in the last section of this special edition so we will not repeat the company descriptions here.

Inscripta

(From LinkedIn). This company is developing the world's first benchtop platform for scalable digital genome engineering. The company's advanced CRISPR-based platform, consisting of an instrument, consumables, software, and assays, offers a fully automated workflow that enables massively parallel, trackable editing of single cells at an unprecedented scale. Inscripta's goal is to empower scientists whose gene editing research is stifled by current technical and licensing limitations. By providing this unique platform and engaging in collaborative business practices, such as making its MAD7™ CRISPR nuclease free for research and development purposes, the company enables scientists to realize a new era of biological discovery. Inscripta is headquartered in Boulder, Colorado, with offices in Pleasanton, California, San Diego, California and Copenhagen, Denmark. Inscripta is backed by an array of leading investors.

Gritstone Oncology

The company with headquarters in Emeryville CA, engages the immune system against cancer, by leveraging their artificial intelligence Gritstone EDGE™ platform, as well as their expertise in cancer genomics. Gritstone is developing multiple immunotherapies designed to direct a robust immune response to neoantigens. They are developing two key classes of tumor-specific neoantigen product candidates to treat patients with cancer.

Abridge AI

The Pittsburgh-based early-stage company's mission is to bring context and understanding to every medical conversation so people can stay on top of their

health. This development stage company is focused on the consumer—and using technology to bridge the gap between patients and clinicians. That attracted their investment partner, since most healthcare entrepreneurs attempt to solve things from the healthcare side. Abridge focuses on building a great user experience for the consumer. See their mini case study in Section 4 for more detail!

FluidForm

FluidForm is an early stage company that aspires to be a world leader in functional human tissue for research, repair, and replacement. Their patented FRESH 3D printing technology has developed in the laboratory of Dr. Adam Feinberg, at Carnegie Mellon University in Pittsburgh, and has been published in Science. The technology to create Fluid Form was licensed from CMU. According to a recent press release, the company's robust pipeline includes development and preclinical programs addressing significant unmet need in human health. These programs include bioprosthetic implantable medical devices, and a new generation of structurally and compositionally complex tissue models to test drug efficacy and cardiotoxicity, with an ultimate focus on tissue and organ replacement. FluidForm is in the Boston area, and recently signed an agreement with Ethicon, Inc., a member of the Johnson & Johnson Medical Devices Companies, to develop 3D Bio printed applications using FluidForm's patented FRESH technology. For more detail on this emerging technology, see a recent JCB publication on commercializing 3D printing technology, including a discussion on commercializing the technology underlying FluidForm's developments, c. f. Thakur, Cabrera, DeCarolis and Boni (Vol. 24, No 1, 2018).

Sherlock Biosciences

Is a Boston, MA based company that (according to their LinkedIn site) aims to disrupt molecular diagnostics with better, faster, affordable tests. Their unique Engineering Biology platforms, place them on the cusp of solving challenges ranging from faster pathogen detection and simpler testing for cancer to improved food safety. They envision a world where their products will enable users to make more effective decisions in any environment, whether in hospitals, industrial settings, the developing world, or at home. Their team and founders include Engineering Biology pioneers with world-leading expertise in CRISPR and Synthetic Biology, diagnostic industry veterans, and disease-area authorities. Together, they provide an unparalleled set of capabilities that are transforming molecular diagnostics in clinical and non-clinical settings. They recently received a grant from the Bill and Melinda Gates Foundation to continue the development of its synthetic biology-based INSPECTR molecular diagnostics platform.

10x Genomics

Is an American biotechnology company headquartered in Pleasanton, CA that designs and manufactures gene sequencing technology used in scientific research. It was founded in 2012 by Serge Saxonov, Ben Hindson, and Kevin Ness. 10x Genomics products have been adopted by researchers around the world including in all of the top 100 global research institutions as ranked by Nature in 2019 based on publications and all of the top 20 global pharmaceutical companies by 2019 research and development spend, and have been cited in over 2,250 research papers on discoveries ranging from oncology to immunology and neuroscience.

NeuBase Therapeutics, Inc.

This early-stage company is built upon a technology platform (PATrOL™) that has reverse-engineered nature's information encoding system to be able to engage misbehaving genes in the human genome and increase, decrease or even edit a gene's functions to resolve the causal defects undergirding rare and common diseases. Almost every human disease is genetically-driven and thus the market opportunity and potential for impact on health are expansive. The chemistry behind the platform has the highest precision of engagement with a genetic sequence in the industry and appears to be biologically and immunologically inert. Precision of target engagement allows discrimination between misbehaving genes with even single-base variation and their normal counterparts – this reducing or eliminating "off-target" engagement which causes side effects. Tolerability is important as chronic, lifelong therapy must not trigger, for example, an immune response or other types of adverse reactions.

Ariel Precision Medicine

We published in our most recent edition on business model challenges associated with transformative technologies, a mini case study published on this company that specializes in augmenting healthcare with human-centered technologies AI technologies, c. f. JCB, Vol. 25,

No. 4, pp 35–40. This article includes a mini-case study that focuses augmented intelligence is being applied to precision medicine.

Molecular Assemblies

This company, based in San Diego is a pioneer with focus on the new frontiers in DNA writing using enzymatic synthesis. Their objective is to make DNA synthesis more cost effective, faster, sustainable, and more accurate. It was also highlighted in JCB, Vol. 25, No. 4, pp 56–62.

Ionis Pharmaceuticals

The company has been a pioneer in antisense oligonucleotides, an area of genetic medicine that acts on modulating RNA. I list the company not only because of its technology, but it is rare success story of a biotech that used a partnering model to advance a broad pipeline. Most companies that have a platform technology start out that way but end up commercializing their own products because the economics of partnerships and changes in partner's management and pipeline needs are usually disastrous for these companies. Ionis has a broad pipeline (40?), many of which are partnered with Big Pharma companies.

BridgeBio

This company finds, develops, and delivers breakthrough medicines for diseases where the mechanism is well-understood. Then develops medicines that target rare genetic diseases at their source. The company bridges advancements in genetic science with a unique entrepreneurial engine required to rapidly create lifesaving medicines for patients with unmet needs. Founded in 2015, the company has built a portfolio of more than 15 transformative drugs ranging from pre-clinical to late-stage development in multiple therapeutic areas including genetic dermatology, oncology, cardiology, neurology, endocrinology, renal disease, and ophthalmology. The BridgeBio model of creating nimble, focused subsidiaries around in-licensed assets creates efficiency and scale. It lets the company distribute shared central resources while remaining hyper-focused on developing therapies for each disease. In just three years, BridgeBio has more than 15 drug programs for 20 genetic diseases. The company has a $10 billion market cap. (For more detail, see mini-case study by Danny Levine elsewhere in this issue of JCB).

Berkeley Lights

Whether it is cells engineered to provide therapeutic benefits or bio manufacturing processes to replace energy-intensive and toxic chemical byproducts of industrial manufacturing, getting the right cell for the job is essential. Berkeley Lights has developed platform technologies that allow researchers to rapidly screen large numbers of cells and analyze them to identify the best cells for their purposes. (For more detail, see mini-case study by Danny Levine elsewhere in this issue of JCB).

Unlearn AI

One of the challenges of conducting clinical trials is finding enough patient to include in a control arm of a study. This can slow the pace of drug development and increase its costs. Unlearn AI is seeking to change that by using its artificial intelligence platform to create digital twins of trial participants that can serve as control arms in studies. This provides a way around many of the barriers to data sharing including privacy and regulatory hurdles as the synthetic data is not actual patient data.

Senti Bio

Is using synthetic biology to build intelligence into cell and gene therapies, altering the way they act depending on the changing biological circumstances they may encounter in the body. Doing so may lead to safer and more effective therapies and address such things as the tumor microenvironment and mechanisms cancer have to grow, spread, and become resistant to treatments. It is engineering a new class of intelligent medicines capable of hitting multiple targets It's focusing on oncology but leveraging the technology in other areas through partnerships. In April 2021, Fierce Biotech reported that "Roche's gene therapy unit Spark Therapeutics entered into a $645 million-plus biobucks pact with Bayer-backed Senti Biosciences for new tech aimed at tweaking next-gen gene therapies. Under the deal, Spark will maneuver Senti Bio's gene circuit tech to drive the development of gene therapy 2.0. specifically directed toward specific cell types in the central nervous system, eye or liver".

Rani Therapeutics

Delivering biologics orally rather than through injection has been an intriguing goal but has proven difficult. Most efforts have focused on finding ways to turn these large protein molecules into formulations where they

would not breakdown along the digestive tract before they can be absorbed and provide a therapeutic benefit. Rani Therapeutics has taken an unusual tact. Rather than reconceiving the biologic, Rani has reconceived the pill itself. The company has developed what it calls a "robotic" pill that carries the therapeutic to the gut where it injects the drug into the wall of the intestines.

Recursion Pharmaceuticals

One of the early and truest AI drug development platforms. They started out with the intent of finding drugs to repurpose for rare diseases, but they have expanded into novel molecules and, through a big dollar collaboration with Takeda, moved into cancer and other areas.

Humacyte

This company is an emerging regenerative medicine company – material drawn from; https://e.endpointsnews.com/t/t-l-msgyd-ctikulijr-k/. (Authored by John Carroll)

> *"Laura Niklason left a prominent position at Yale last fall so she could take charge of her regenerative med biotech at a critical point in its 17-year history. Celebrated by Time and Fortune, and heralded as a leader in the long-running regenerative med technology story in tissue engineering, with roots in the field that go back to her days as a postdoc in Bob Langer's storied lab at MIT, the scientific founder of Humacyte made a career switch that put her in charge of a company with 130 staffers and ongoing late-stage programs that could put them on the threshold of commercialization". Recently, "the scientist-come-CEO is making a swift leap onto Nasdaq, adding $255 million in new financing to the company — on top of about half a billion dollars already raised — through a SPAC led by Rajiv Shukla".*

Insitro

(From LinkedIn). Insitro is a data-driven drug discovery and development company that leverages machine learning and high-throughput biology to transform the way medicines are created to help patients. At Insitro, we are rethinking the entire drug discovery process, from the perspective of machine learning, human genetics, and high-throughput, quantitative biology. Over the past five decades, we have seen the development of new medicines becoming increasingly more difficult and expensive, leaving many patients with significant unmet need. We're embarking on a new approach to drug development – one that leverages machine learning and unique in vitro strategies for modeling disease state and designing new therapeutic interventions. We aim to eliminate key bottlenecks in traditional drug discovery, so we can help more people sooner and at a much lower cost to the patient and the healthcare industry. We believe that by harnessing the power of technology to interrogate and measure human biology, we can have a major impact on many diseases. We invest heavily in cutting edge bioengineering technologies to enable the construction of large-scale, high-quality data sets that are designed specifically to drive machine learning methods. Our first application is to use human genetics, functional genomics, and machine learning to build a new generation of in vitro human cell-derived disease models whose response to perturbation is designed to be predictive of human clinical outcomes. This cannot be done without great people. We are bringing together an outstanding team of people whose expertise spans multiple disciplines – life sciences, machine learning, human genetics, engineering, and drug discovery – and building a unique culture where people from diverse backgrounds work as a single team towards a common goal. Daphne Koller, Ph.D., founder and chief executive officer of Insitro said as part of a recent $400 million financing: "We built out and demonstrated the capabilities of our target discovery platform in our Gilead collaboration in NASH, receiving the first of our operational milestone payments, and put in place an outstanding collaboration with Bristol Myers Squibb in ALS; we also took a big step forward towards moving from targets to medicines through the acquisition of Haystack Sciences, a high throughput chemistry platform that enables ML-driven molecular design; and we recruited Dr. Roger Perlmutter to our board to help guide our drug discovery efforts".

CORPORATE ACCELERATORS

We have previously cited **JLabs** (a Johnson and Johnson entity) for their leadership role in supporting corporate innovation; also, Bayer's **CoLaborator**, and **Illumina's Accelerator**. We also note that Illumina has now extended their 'footprint' internationally (see a mini case study on that organization included in the last section of this volume). Also, refer to the recent Corporate Accelerator Forum survey on innovation approaches being taken in the Covid-10 pandemic. The three organizations are now being highlighted for their leadership roles for identifying and supporting innovation that may be leveraged for corporate purposes, and is definitely worthy of further recognition. We further refer interested readers to a

recent paper written by Diana Joseph, Susan Windham-Bannister, and Mikel Mangold titled "What Corporates Can Do to Help an Innovation Ecosystem Thrive – and, Why They Should Do It"' c. f. our most recent issue, JCB Vol. 26, No. 1 (2021).

EXTERNAL ACCELERATORS

In our previous writings we have recognized several external accelerators that need no further elaboration. However, we recognize Tech Stars, Plug & Play Technology Center and Rock Health. At the current time, we single out Elevate BIO and BioMotiv/Harrington Project for their exceptional business models to advance biopharma innovation.

Elevate BIO

Is a Cambridge, MA organization the acts as a holding company to grow and launch multiple biotech companies focused on cell and gene therapy. In a recent press release, it was reported that ElevateBio also runs what it calls a "BaseCamp" in a 140,000-square-foot mixed-use Waltham building, which serves as the research, development, and manufacturing hub for all of its portfolio companies. Its goal is to provide biotech businesses and researchers an "end-to-end" ecosystem to speed up the development of these therapies. https://www.bostonglobe.com/2021/03/15/business/elevatebio-raises-525-million-fuel-growth-cell-gene-therapy/?s_campaign=8315.

BioMotiv/Harrington Project

https://www.biomotiv.com/the-harrington-project. The Harrington Project for Discovery & Development is a $340 million US and UK initiative to support the discovery and development of therapeutic breakthroughs by physician-scientists. It is a new and powerful model that addresses a set of major challenges in advancing medicine. The Harrington Project for Discovery & Development consists of an aligned set of mission-driven organizations: The Harrington Discovery Institute and BioMotiv. Together, the organizations support prestigious physician-scientists, transform drug development from research institutions, and create a robust biotech development platform for the benefit of patients and society. The Harrington Discovery Institute at University Hospitals in Cleveland, Ohio is a nonprofit initiative that enables physician-scientists to transform their extensive, cross-cutting knowledge derived from real-life practice and research into therapies that improve patients' lives significantly more than the current standard of care. Through annual competitions, the Harrington Discovery Institute selects a group of scholars whose projects are grant funded for advancing their discoveries. It is led by Dr. Jonathan Stamler and guided by a renowned advisory board, all of whom are physician-scientist innovators.

The Innovation Support Center within the Harrington Discovery Institute, also a nonprofit initiative, provides mentorship, resource connections, and business support to assist physician-scientists. Guided by experienced industry and investment professionals, the Innovation Support Center develops relationships between inventors and industry experts to prepare discoveries for advancement to commercialization.

BioMotiv, a for-profit, mission-driven company, is designed to specifically advance breakthrough discoveries into medicines through an innovative business model. We note that this initiative was informed by the late David C. U'Prichard who we have highlighted previously as one of the key figures in driving the emergence of biopharma thru informed investment models. Ref. Dr. U'Prichard in JCB, Vol. 18, No. 2, pp 11-18, and by Boni in JCB, Vol. 25, No. 4, pp 21-24 ("An Introductory Perspective on Emerging, Transformative Technologies in Biopharma; Promises, Challenges, and Impediments").

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Article

Waiving COVID-19 Vaccine Patents: A Bad Idea and a Dangerous Precedent

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ABSTRACT

The Biden Administration believes that suspending COVID-19 vaccine patents will expedite the swift development of high quality "cheap" versions of existing vaccines and hasten the pandemic's end. This view is dangerously wrong. Vaccinating the world is essential, but temporarily waiving patent rights for COVID-19 vaccines (also known as "compulsory licensing") will actually slow their availability to the developing world.

While providing no gain, compulsory licensing promises lots of pain. Waiving patent protection discourages cutting-edge research investments, which in turn produce breakthrough treatments not just for COVID-19, but for other diseases, like cancer. Weakening these protections would be anti-patient and counterproductive.

The reality is that, in order to save the world, we must all work together as partners. The remarkable speed with which we developed diagnostics, therapeutics, and vaccines to combat COVID-19 points to the need for more collaboration, not less. Patents are a foundational principle upon which that success rests.

While the policy of temporarily waiving patents seems fair and humanitarian, the devil is in the details. Such a policy will not result in a single citizen of the developing world getting vaccinated one minute sooner. In fact, the unintended consequences are the reverse. More confusion, lower quality, less transnational cooperation. A triple play of disastrous global proportions.

We cannot negotiate with people who say "What's mine is mine and what's yours is negotiable." – John F. Kennedy

Journal of Commercial Biotechnology (2021) 26(2), 20–25. doi: 10.5912/jcb987

INTRODUCTION

"Temporarily" waiving biopharmaceutical patent rights (also known as "compulsory licensing"[1]) for COVID-19 vaccines is a bad idea – and a dangerous precedent.

When it comes to broadening the availability of vaccines, dispensing with patent protection will actually slow their availability to the developing world — and what does "temporary" really mean? Shunting aside patent and intellectual property rights sends a very dangerous signal to innovator biopharmaceutical companies (and their investors) that the government may not be such a good partner after all.

The claim, by India, South Africa and some high-profile members of civil society (such as Knowledge Ecology International[2]), is that suspending COVID-19 vaccine patents would allow developing countries to manufacture their own "cheap" versions, hastening the end to the pandemic. They're wrong. Dangerously wrong – and entirely unnecessary.

Innovator vaccine developers have been ramping up production for months.[3] It has taken time, industry officials said, because the shots currently available rely on newer technologies like messenger RNA. With the extra output, Pfizer had begun shipping U.S.-produced doses to countries including Mexico and Canada, while Moderna agreed to deliver the COVAXX Initiative doses to supply shots to poor nations.[4]

The companies were also in discussions with the Biden administration about how to get more supplies to the developing world. The industry proposed providing more doses to developing countries at cost or not for profit, said Jeremy Levin, chairman of the Biotechnology Innovation Organization (BIO) and chief executive of Ovid Therapeutics Inc. "These proposals appear to not even have been looked at."[5]

Gutting IP protections won't make COVID-19 vaccines more readily available but it will set a terrible precedent that will chill future medical innovation and hurt those they are most vociferously claiming to assist. *Cui bono?*

Biopharmaceutical research is risky and expensive. For every 5000 molecules developed in the lab, only one successfully advances through lab, animal, and clinical testing and receives regulatory approval.[6] After accounting for all these failures, it costs almost $3 billion, on average, to bring a single medicine to pharmacy shelves.[7]

Biotech investors only take these risks because of strong patent protections.[8] When a startup receives its first patent, the firm's chances of attracting funding from institutional investors—such as venture capitalists—increases 53%, according to a National Bureau of Economic Research working paper.[9] Patents save lives and enhance the value of medicines. As Abraham Lincoln (the only President to ever hold a patent) said, "Patents add the fuel of interest to the passion of genius."[10]

Not surprisingly, nations with strong patent laws (and specifically the United States and the European Union) produce higher volumes of new treatments. The United States has the most robust IP protections, which explains why American scientists develop over half of the new drugs invented globally.[11] Waiving patent protection discourages research and development here in America and around the globe.

Patent protections incentivize firms to make big research investments, which in turn produce breakthrough treatments not just for COVID-19, but for other diseases, like cancer. Weakening these protections would be anti-patient and counterproductive. It wouldn't speed the rollout of existing vaccines, but it would ensure we're less prepared to fight the next phase of the COVID-19 pandemic – not to mention future global public health emergencies. This was precisely the strategy behind the Orphan Drug Act of 1983.[12] This major piece of legislation was the first-of-its-kind for rare diseases and its success has helped to encourage similar legislation in other parts of the world. In the late 1970s and early 1980s, there was growing awareness that very few medical treatments were being developed for people who had diseases affecting small patient populations. The problem was that pharmaceutical companies couldn't expect to recover the investment required to develop treatments for diseases affecting a small number of people. Hence, these diseases came to be known as "orphan" diseases.

The Orphan Drug Act provided pharmaceutical manufacturers with three primary incentives: Federal grants for orphan drug research; a 50% tax credit to defray the cost of clinical trials and; seven years of marketing exclusivity for products approved as orphans. The result? Currently, more than 400 orphan designated drugs are commercially available and close to 1000 drugs are undergoing clinical trials.[13] Incentives work, threats do not and actions have consequences. Incentives drive behavior as do disincentives. One day after President Biden announced his support for a temporary waiver of COVID-19 patent rights, stock prices for innovative biopharmaceutical companies plummeted.

When the power of the healthcare ecosystem (government, biopharmaceutical companies, academia, healthcare providers, logicians and patients) work together as partners, we accomplish miracles at Warp Speed. "Waiving" patents isn't good partnership behavior.

HISTORICALLY, COMPULSORY LICENSING HAS NOT WORKED

Compulsory licensing is legal under international law, but only in limited instances. It allows local companies to produce generic versions of patented medicines in desperate times — such as an infectious disease outbreak. However, India, Brazil, and other nations abuse this policy and allow drug-makers to produce just about any generic without any urgent reason at all, and without the patent owners' permission.[14] "Temporary?" *Caveat emptor.*

Developing countries obviously need COVID-19 vaccines as quickly as possible. But removing IP protections won't accelerate vaccine distribution in these nations. In fact, it could slow it down. In the past, when developing countries have issued compulsory licenses—which effectively allow domestic manufacturers to create knockoff treatments even before drug patents expire—it has taken years for generic manufacturers to receive the drug formulas, work out logistical and payment challenges, and scale up production. In one case, it took

over four years to bring a generic AIDS drug to Rwanda with half that time spent settling a contract between the domestic manufacturer and the patent holder.[15] A valuable lesson learned with direct and immediate application for the COVID-19 patent debate is that patents do not hinder availability, but lack of patent production eviscerates incentives for innovation.

As the late Senator Daniel Patrick Moynihan quipped, "People are entitled to their own opinions, but not to their own facts." Hopefully this reality will result in an open and honest negotiation at the World Trade Organization (WTO) over the next several months, leading up to their Ministerial meeting on November 30th. At the May 6th 2021 WTO General Council meeting, Director General Ngozi Okojo Iweala urged members to begin text-based negotiations of the proposed COVID-19 vaccine waiver.[16]

AREN'T COVID-19 VACCINES "ESSENTIAL?"

Vaccinating the world against COVID-19 is essential. But how has the world fared in addressing the accessibility of other "essential medicines?" Considering its the World Health Organization (WHO) that is driving the policy of pausing COVID-19 vaccine patents, it's worthwhile to examine the impact of that institution's Essential Drug List. The WHO 's Model List of Essential Medicines contains the medications considered to be most effective and safe to meet the most important needs in a health system.[17]

Very few of the 400 or so drugs deemed essential are new, or patented (or ever patented) in the world's poorest countries. In category after category, from aspirin to Zithromax, in almost every case and in almost every country, these medicines have always been (or have been for many years) in the public domain. That is, the medicines are fully open to legal and legitimate generic manufacture. Their availability remains spotty and their quality questionable. Just as the coronavirus mutates to survive and thrive, so to do the purveyors of counterfeit medicines. There is no value at all in vaccines that are not manufactured to the highest standards. Poorer nations must receive the same high-quality vaccines that are available in the West. According to a recent report from the Center for Medicine in the Public Interest, "Not surprisingly, the COVID-19 pandemic has increased the public's exposure to counterfeit medical products."[18] Allowing manufacturers with questionable safety records to produce vaccines that require sophisticated processes, procedures, material and manufacturing is a recipe for disaster.

According to Dr. Michelle McMurry-Heath, the President of BIO, "Handing needy countries a recipe book without the ingredients, safeguards, and sizable workforce needed will not help people waiting for the vaccine. Handing them the blueprint to construct a kitchen that—in optimal conditions—can take a year to build will not help us stop the emergence of dangerous new COVID-19 variants."[19]

Dr. Jeremy Levin reinforces the proposition that, "This is not just a matter of forcibly transferring IP and know-how from America to other nations. There was and is no need to rebuild factories around the world where not only will it take a long time to do so but also the standards and capabilities that exist in America cannot be easily replicated or guaranteed. In the future, this decision will act as a disincentive to companies to respond to the next pandemic."[20]

WHERE DO MEDICINES COME FROM?

Many politicians and pundits mistakenly believe that biopharmaceutical innovation is primarily driven by the National Institutes of Health (NIH). The reality is that the primary engine of drug innovation is private industry. The members of the Pharmaceutical Research and Manufacturers Association (PhRMA) spend in excess of $136 billion on research and development — and these are only some of the larger companies.[21]

Both the NIH and private firms provide research financing to academic institutions. But it is industry that employs most of the scientists that conduct the hands-on development work. Unfortunately, some lawmakers have bought the myth that the NIH is primarily responsible for new medicines.

A study by Bhaven N. Sampat and Frank R. Lichtenberg entitled "What Are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation? "[22] provides a data-driven analysis that gives the National Institutes of Health (NIH) its due—but in the proper frame of reference. Sampat and Lichtenberg studied 478 drugs that were associated with $132.7 billion in prescription drug sales in 2006. Less than 10 percent of these drugs had a public-sector patent. Drugs with public-sector patents accounted for just 2.5 percent of sales, although the indirect impact was higher for drugs granted priority review by the FDA. (Priority Review is given to drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists.[23]) Drugs whose applications cited federally funded research and development or government publications accounted for 27 percent of sales.

Another study in the British Medical Journal also analyzed the topic. Comparable to prior research, the investigators found that the majority of biopharmaceutical research was conducted and funded by the private sector. Despite having excluded vaccines, biologic medicines and gene therapies from their final analysis, a study limitation noted by the authors, the researchers found that 75% of all Food and Drug Administration (FDA) approved drugs between January 2008 and December 2017 were funded and researched by private companies. Only 19% of the approved drugs had origins in publicly supported research and development, and 6% originated in companies that were spun from publicly supported research programs. Thus, 25% of approved medicines benefited from "some" public support. The results were impressive, and indicative of how central private-sector research is to biopharmaceutical innovation.[24]

THE DEBATE OVER REMDESIVIR

Consider remdesivir and the related debate over Bayh/Dole March-in Rights.[25] The recently released Government Accountability Office (GAO) report, Information on *Federal Contributions to Remdesivir*,"[26] considered whether federal patent rights were appropriate, given the federal government's contributions in researching and developing the drug.

The GAO report came in response to stiff political headwinds. In August 2020, citing concerns over pricing and availability of remdesivir, 34 state attorneys general (including present Health and U.S. Human Services Secretary Xavier Bercerra) asked federal officials to exercise the government's march-in rights over the COVID-19 treatment.[27] The attorneys general said Gilead has been "unable to assure a "supply of remdesivir sufficient to alleviate the health and safety needs of the country" amid the COVID-19 pandemic.

The straightforward, unambiguous, and politically inconvenient conclusion of the independent GAO report found that "Federally supported remdesivir research conducted by CDC, DOD, NIH, and NIH-funded universities has not resulted in government patent rights, because, according to agency and university officials, federal contributions to the research did not generate new inventions." The principal investigators at the NIH, who were working on coronavirus research projects, told the GAO they did not consider filing invention disclosures because their work did not involve modifying remdesivir or its parent compound.[28]

It was President Franklin Roosevelt who recognized the vital role of the federal government partnering with "Good old American know-how" to win the Second World War and propel the American Century forward. Decades before Operation Warp Speed forged a partnership to defeat a natural foe, an earlier public/private partnership of industry, academia, and government, the Manhattan Project, proved the value of collaboration in the face of a deadly human enemy.

When it comes to regulated health care technologies specifically, and the anti-COVID-19 armamentarium explicitly, collaboration is a *sine qua non*. One of the most important lessons of the pandemic is that when the health care ecosystem works together, we can achieve amazing things. We are all in this together. Politics is a distraction. Science must be collegial, intramural, and transnational.

BAD POLICY IDEAS HAVE REAL-WORLD CONSEQUENCES

The COVID-19 vaccine debate is not America's first joust with pharmaceutical patents. Senator Bernie Sanders has previously introduced a bill that would replace our current patent system for pharmaceuticals with a "Medical Innovation Prize Fund.[29]

It's not a new idea. The prize model has been used in the past by the old Soviet Union — and it didn't work.[30] The Soviet experience was characterized by low levels of monetary compensation and poor innovative performance. The US experience isn't much better. The federal government paid Robert Goddard (the father of American rocketry) $1,000,000 as compensation for his basic liquid rocket patents.[31] A fair price? Not when you consider that during the remaining life of those patents, US expenditures on liquid-propelled rockets amounted to around $10 billion. This is certainly not what Schumpeter had in mind when he wrote about a "spectacular prize thrown to a small minority of winners." There's a difference between "Creative destruction" and destroying medical innovation.[32]

"Prizes over Patents" legislation would replace a patent system that has allowed the average American lifespan to increase by almost a full decade over the last 50 years[33] with a prize program that has a solid record of complete failure. To borrow an over-used adjective from the world of global climate change – we must protect "sustainable" innovation.

It's important to put the "temporary" COVID-19 vaccine patent waiver in the context of the on-going battle by the global "anti-pharmaceutical patent" lobby. There is a small but vocal and influential public health policy cohort that believes patents are the most significant cause of healthcare disparities worldwide. Their philosophies repeat and reinforce many misunderstandings

relative to the impediments to broader access to medicines. Their ill-considered policy schemes (such as a prize system and a more regular and aggressive use of compulsory licensing practices) reinforce the false narrative of a "Good Guys/Bad Guys" *weltanschauung* that pits the innovative biopharmaceutical industry against the needs of the developing world. This is untrue, unfortunate and counter-productive. There are rarely simple answers to complex questions. The reality is that, in order to save the world, we must all work together as partners. A free-market healthcare paradigm for drug development, although far from perfect, works. A well-appointed armamentarium of COVID-19 diagnostic tools, therapeutics and vaccines – all invented in under one year, speaks to the power of ecosystem teamwork and fair incentives – most importantly patent protection for innovation.

According to a recent article in Health Affairs, "The remarkable speed with which we developed diagnostics, therapeutics, and vaccines to combat COVID-19 points to the need for more collaboration, not less. One of the most important lessons of the pandemic is that when the health care ecosystem works together, we can achieve amazing things."[34] And patents are a foundational principle upon which that success rests.

The Biden Administration has empowered a resurgence in the anti-biopharmaceutical industry, anti-patent, anti-intellectual property debate. Shortly after President Biden signaled his support for waiving COVID-19 vaccine patents, Representative Alexandria Ocasio-Cortez tweeted, "Let's do insulin next"[35] and Senator Sanders commented, "This is exactly the kind of leadership the world needs right now … I also recognize the dedicated work done by activists in communities around the world to put this issue on the global agenda. We are all in this together."[36]

President Biden's support of "temporary" waivers may not end up being so temporary at all if elected officials such as Ocasio-Cortez and Sanders have their way.

Despite this constant negativity from the anti-patent lobby, global production capacity is expanding and accelerating global access is possible. Strengthening the current system that created vaccines and treatments at a record-setting pace is the best way to achieve this important global public health goal. It's time to ask some tough questions: are poorer nations engaged with global manufacturers in negotiating a fair price for vaccines? If not, why not? Have these same developing nations countries thought about partnering with the biopharmaceutical companies to build manufacturing facilities that can legally and safely produce the vaccines — facilities can then be used to manufacture other essential medicines? If we shy away from asking the tough questions, we are unlikely to find the right answers.

While, *prima facie,* the policy to temporarily waive patent rights seems fair and humanitarian (two words regularly used to describe President Biden), the reality is quite different. Such a policy will not result in a single citizen of the developing world getting vaccinated one minute sooner. The anti-patent consortium is, unfortunately, willing to sacrifice the developing world on its own infallible Altar of Altruism, fueled by their dogmatic adversity to free-market principles.

The most empowering relationships are those in which each partner lifts the other to a higher possession of their own being. — Pierre Teilhard de Chardin.

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Article

Book Review of *The Code Breaker: Jennifer Doudna, Gene Editing, and The future of the Human Race*

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ABSTRACT

In this book review and accompanying commentary and Addendum, we focus on 5 principal topics/major themes that are of interest for our readership, with a focus on framing the translation of transformative technology into a platform business model in biopharma. We focus on: 1) the behavioral and personal side of the story of the academic scientist, in this case the principal "code breaker" – Jennifer Doudna; 2) the innovation/technology transfer models, including team building appropriate for successfully translating technology from the academic laboratory into the private sector; 3) the IP considerations needed for broad commercialization and dissemination of pivotal, platform inventions in biopharma; and, 4) framing the issues surrounding the ethical discussion related to use in patients associated with a transformative, gene editing technology like CRISPR. We also include an Addendum that covers, 5) Some pertinent, concluding comments on the importance of high–performance, diverse teams for founding, building, and growing successful biotechnology companies.

Journal of Commercial Biotechnology (2021) 26(2), 26–32. doi: 10.5912/jcb988
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INTRODUCTION

This article is intended to go beyond a traditional book review of the excellent book by Isaacson, who does his usual incredibly insightful and well documented job of writing on innovators like Steve Jobs and Leonardo da Vinci. This book focuses on the scientific creators of an emerging technology, and who also are engaged actively in the commercialization process. To those of us who have worked in technology management and transfer area in top-tier university programs, there is a saying that goes – "you don't transfer the technology, you transfer the people". Truth be told, both are most often ideal. Earlier in this volume, we highlighted a number of scientific innovators who exemplify this statement. The Isaacson book was released in mid-March 2021, and already at the time that this article has been written, several traditional book reviews quickly appeared, and they are cited herein. That speaks to the importance and timeliness of the topic, and also the challenges that remain ahead as the business model evolves over the next years (or decades) ahead. While Isaacson did cover the entire spectrum of academic scientists involved in the pursuit of CRISPR, he chose to focus on one of the innovators (Dr. Jennifer Doudna, the principal code breaker) who were trying to unravel the science of gene editing. The book does a phenomenal job of following the story of Doudna, her academic career, an in-depth discussion on her pursuit of CRISPR with an array of US and international collaborators and competitors, and culminating in the award of a Nobel Prize along with her French partner Emmanuelle Charpentier. However, he also does a great job of bringing in the entire "cast" from around the US and the world who have played essential roles in advancing what was the mystery of the technology. Some have suggested that the title should have been the plural, code breakers, since most usual in the pursuit of science-driven innovation, there were a whole cast of others engaged as teams spread across the globe competed to publish first, but more importantly to patent their potentially breakthrough inventions (with freedom to operate). While good science and engineering is indeed a "team sport", in this case Doudna is clearly the lead code breaker. The book tells this story in great detail and is a great read. And, the science is mostly understandable, even for physical scientists and engineers, as well as non-scientists. However, we note that the focus of J. Commercial Biotechnology readership is not on the transformative science itself (as interesting as that may

be). Therefore, we focus on the translation of that science from the lab into commercial practice – a principal focus of Jennifer Doudna who straddled the academic – private sector part of the commercialization process. Building and leading her team at UC Berkeley in that regard is certainly relevant to setting up the broader topic of commercialization and innovation – translation from lab to patient. We focus on those topics in this commentary.

DISCUSSION

We begin with examining the **traits and behaviors of academic scientists** who pursue transformative science and technology that is of Nobel Prize quality, while in parallel excelling at commercialization. The objective is challenging; and the result worthwhile, with the goal of **technology transfer from academia into the private sector.** Isaacson has many examples in both technology, and biotechnology that are covered nicely in the book as a contrast to the CRISPR story. In the last century, these have ranged from genes (DNA discovery and the Human Genome), and even into the physical sciences that deal with atoms/nuclear technology, and computer chips. Doudna does that very well, and there are lots of quotes that we extract for this article. Most of the others, including Charpentier are largely driven by the science. That is their role in the life cycle of discovery to invention to commercialization to breakthrough applications. In the book, we are also exposed to the Boston-based team at MIT/Harvard/Broad Institute, with Eric Lander, Tom Church, Feng Zhang, et al. who pursued not only prestigious publications, but patents (more on that later), and then to startup companies. The Boston team was well connected to the venture capital/business community. The Berkeley led team, not so much.

We discuss how Dr. Doudna identified doctoral students and post-docs for her lab not only for their scientific **skill**, but for their **will** and **fit** into the culture that she nurtured. Early in her career, she recognized that she really liked pursuing the commercial implications of their collaborative work thru startup companies and has done a few as part of her pursuit to understand and commercialize CRISPR (we discuss them below). So, she stands out as one who learned how to straddle the gap between academia and commercialization. And as usual here, all of us who have gone thru this process "learn from our mistakes" and pivot the next time through the process. There is great material in the book that identifies her as an individual who excels at science, but who definitely keeps her eye on the outside work to take invention from "lab or bench top" to patients. As we discuss later in the article, perhaps she would have benefitted from a more experienced technology transfer/business school partnership along the way. But, we all learn from our experiences, and the book points out many "lessons learned" by Dr. Doudna.

The **topic of innovation** itself is worth discussing, and we have covered the promise of transformative technologies and their business model challenges, c. f., J. Commercial Biotechnology, Vol. 25, No.4 (2020). We refer the interested reader to that volume. Also, consider our "Boot Camp 2.0 volume, that covers all of the topics needed from translation of science into business in a two-day boot camp offered annually in partnership with BIO (the Biotechnology Innovation Organization); J. Commercial Biotechnology, Vol. 24, No.4 (2019). In the case of CRISPR, the technologies are indeed major breakthroughs, and Isaacson likens them by analogy to the 3 great scientific revolutions of our times, e. g. **atoms, bits, and genes** and how the academic and commercial institutions and their leaders participated in those races. And, as a subset, what are the characteristics and behavioral traits of innovators vs 'inventors/professors'. Her "epiphany" upon leaving a tenured position at the University of California, Berkeley for Genentech, and then quickly returning is worthy of note, and we also cover that below.

We believe that innovation is inherently a "team sport", including those innovations originating in academic institutions where the process starts in the university lab. The technology (and the IP) is then "transferred" for commercialization in a NewCo (or licensed directly to larger, established organizations), and then progresses thru the regulatory/reimbursement process, and ends up accessing the market via channels controlled by larger partners in biotech and biopharma. These transitions are discussed in the Isaacson "Code Breaker" book. We believe that for successful commercialization, a strong intellectual property (IP) foundation is required to build a competitive, commercial platform. While we cannot and do not go into great depth, we do cover some of the fundamental concepts below.

Intellectual property (IP) and its issues is of course, is always a critical factor in building any successful tech/biotech based business – especially for a transformative, platform technology like CRISPR. And, that leads to the topic of patents (one form of intellectual property that is essential for commercial practice; vs. trade secrets). Simply put, a **patent** is a title that gives its owner the legal right to exclude others from making, using, or selling an invention for a limited period of years in exchange for publishing an enabling public disclosure of the invention – so it is necessary to be first to invent. In simple terms, the invention must be **new, useful, and non-obvious** (to one skilled in the art). That last caveat is always worthy of discussion, and turns out to have been critical here as is

pointed out in the Isaacson book. We refer the interested reader to 3 articles on IP written by : Kathryn Doyle (pp 32-37), Raymond Miller (pp 38-41), who are two excellent t IP attorneys who talk about this material in our Entrepreneurship Boot Camp at each international BIO meeting since 2005. We also recommend the more recent article by James Jordan (pp 42–47). All of these articles are published in our previous special edition; "Boot Camp 2.0", c. f., J. Commercial Biotechnology, Vol. 24, No.4 (2019). The Jordan article goes beyond IP per se to articulate an IP Pyramid strategy that builds on patents, but also incorporates other factors to build "an impermeable competitive advantage" beyond IP, e. g. proprietary relationships, and proprietary knowledge (these are largely team and partner related). These later factors will become obvious in the discussions on patents and competitive advantage that appear in the Isaacson book.

There is extensive discussion in the Isaacson book on the topic of "the race to invent first" between the Doudna (UC Berkeley) and Zhang (MIT/Harvard/ Broad Institute) groups that are still being resolved. While Doudna was beaten in the "first to file race" by a few weeks by Zhang and Church, Zhang contends in the book that was not obvious that getting the "trifecta" to work in human cells (that lab had extensive expertise in working with human cells). Doudna contends that it is was obvious to her (one skilled in the art), but the expertise in her lab at the time was not primarily in studies associated with human cells. There were extensive discussions among all of the parties, who clearly recognized the fact that for successful commercialization, unification and consolidation of the UC Berkeley, Broad/ Harvard patents, it would be strategically necessary to exploit the full potential of the "CRISPR platform". And we add parenthetically how other industries have handled this issue with broad, cross licensing; e. g. with computer chips, or with non-exclusive licensing. In the post Bayh-Dole era (where universities were granted ownership of government-funded research – licensing proceeds are to be shared with the inventors). Apparently, human behavior got in the way, and Doudna had qualms – "I just did not get a good feeling from Zhang" (there is our previous reference to "trust" as an essential element of an effective team). And, according to Isaacson, the feeling was mutual. While the university made the decision, the principal inventor decided to give an exclusive license of the Berkeley technology to Caribou a startup company that she started with Rachel Haurwitz at the helm. While Haurwitz did have some background in business, Zhang argued that "someone more "seasoned" would be required to move the technology forward. (We would agree that advancing the technology in parallel with advancing the business model is essential for ultimate success; c. f. our discussion on teams at the end of this article). Doudna did quote in the Isaacson book that "if I had to do it over again, I would have licensed it differently". "When you have a platform technology like CRISPR, it is probably a better idea to license in a way that offers it as broadly as possible"; since, neither she, nor the university had experience with licensing a broad, transformative technology. There is a telling quote from Doudna in the Isaacson book. "A couple of people that I trusted at Berkeley were telling me to definitely work with the people in Boston, since they were better at business".

Several other points regarding patenting and IP are worth noting. For those not familiar with licensing of pivotal patents, the Isaacson book points out that Stanford "made $25 million in 25 years for non-exclusive licensing of the Cohen and Boyer patents for recombinant DNA". Indeed, the Association of University Technology Managers (AUTM) was developed to establish and share best practices amongst universities so that the benefits of commercializing government sponsored research and the Bayh Dole Act could be optimized.

One further point relates to a fact that reflects on the astuteness of the Broad Institute with regard to the commercial implications of these fundamental, foundational patents. They chose to take advantage of a provision in patent law to request an expedited review. Isaacson states that "it did not occur to them (at Berkeley) to spend a little extra (money) to have the application expedited". "The US PTO granted the Zhang patent on April 15, 2015, even while the Doudna patent was still being considered". Under US law, when this situation exists, the person whose application is still under review has a right to file for an interference hearing. These battle line were initiated in April 2015, and continued thru lengthy and expensive legal hearings. Isaacson correctly points out that it might have been more expeditious for the Berkeley and Broad teams to work out an arrangement to cross license their respective patents and to share the proceeds. Also keep in mind that in 2013, the USPTO adopted a first to file provision. Isaacson provides a very succinct analogy taken from the cross-licensing agreement between Texas Instruments and Intel, and ends with a quote "don't fight over divvying up the proceeds until you finish robbing the stagecoach".

And last, but not least, there are significant **ethical issues** involved, and they too go unresolved. We anticipate that this debate will go on for years as commercialization of CRISPR proceeds. There are many who advise a cautious approach with a concern about the technology racing ahead of the bioethics legal issues and a full assessment of the long term consequences. Most of the first generation use of CRISPR Cas9 is targeted at diseases that edit some of the body (somatic) cells and make changes that are not inherited. This can be done by ex

vivo or in vivo modalities. In 2019, sickle cell disease was done with an ex vivo treatment in Nashville, under the auspices of CRISPR Therapeutics (that company affiliated with Emmanuelle Charpentier). In the book, Isaacson covers in detail why the ex vivo use of CRISPR is a perfect example for, in our words "a market entry point, for CRISPR". And, it worked!

The next issue is a big one – cost. Since treatments are in excess of $1M, can the healthcare system afford it? And this is a factor that impacts virtually all of the breakthrough, transformative technology biotechnology products. And, kudos to Doudna for the formation of the Innovative Genomics Institute with funding from the Gates Foundation and the NIH. Their first focus was on sickle cell disease. The Chinese have moved on to focus on cancer that is also a significant disease with high treatment costs for emerging technologies. CRISPR is also being used for diagnosis of cancer via a Doudna spinoff company, Mammoth Biosciences. And for treatment of congenital blindness via an in vivo treatment in clinical trials run by Editas (a Zhang et al company).

These early trials are promising, even with the cost issue looming. But, then we have already seen some of the longer-term issues emerge, including the "designer babies" episode in China in 2018 that has initiated ethical discussion that will continue to be debated going forward. As a current resident of Napa, CA, I was surprised to see in Isaacson's book reference to an "Asilomar like" conference organized to discuss the then emerging field of recombinant DNA. This conference was organized by Doudna who invited 18 experts in the emerging field, to discuss the ethical implications of CRISPR – like creating designer/babies.

These will surely take a generation or two as the technology evolves, and the community learns and adapts to this truly transformative technology. We have highlighted some of these from the Isaacson book, but we also refer the interested reader to the following two recent book reviews of the Isaacson book that recently appeared in Foreign Policy and the New York Times.

FROM: FOREIGN POLICY ARTICLE BY MICHAEL HIRSH

https://foreignpolicy.com/2021/04/02/what-is-it-to-be-human-anymore/

In this Foreign Policy article, Michael Hirsh writes that "in the beginning, Doudna was frightened by the implications of what she had created, waking from a nightmare in which she dreamed she had met Adolf Hitler, who pressed her for answers about her technology". "Have we created a toolbox for future Frankensteins?"

Hirsh then writes, "these may be the hardest ethical questions of our time, but they require a book more profound than Isaacson's to address them. Will children, as they age feel that they are becoming obsolete?" Isaacson writes. "Fortunately, these are questions we can ask for amusement, but not for an answer. It will be up to our grandchildren to figure these out."

"In the end, just what Doudna and her colleagues have let out of the lab remains to be seen, and the answers to all these questions might, as Isaacson (and we) says, await another generation or two. They certainly will require another book than this one, as impressive an accomplishment as it is".

FROM: NYT INTERVIEW WITH EZRA KLEIN.

https://www.nytimes.com/2021/04/02/podcasts/ezra-klein-podcast-walter-isaacson-transcript.html?smid=em-share

This very well done and thoughtful interview, and goes well beyond the scope of this article. We highly recommend it for our audience, and include a few key quotes as excerpts below:

EZRA KLEIN

"So, it sounds to me there's almost a ladder of programming complexity here. There's, as you say, a set of conditions that we understand. There is a mistake in the code, and we can look at it. We can look at normal code. We can look at code that has this error in it, and then you say, OK, we're going to just change that little mistake".

"Then there are things where we pretty well understand how it works, like, say, muscle mass. We know there are certain things we can turn on and off because we've watched it happen in people. Then there are things we know people currently have like bipolar disorder or schizophrenia or high IQ, but we don't really know how it works".

"And then I assume there are things that people don't currently have. You bring this up in the book. Like one can imagine in the future us understanding how to give people capabilities they don't currently have through genomic editing. But because we can't currently look at people and see that, we don't know how to do that, that coding. Is that a reasonable way of framing the ladder"?

WALTER ISAACSON

"Absolutely, and the interesting thing about the ladder is we could create new things for human capabilities, maybe even to hear different frequencies or be able to see colors that are off the normal visible spectrum. But the important thing you put your finger on is we say it's not in the wild. In other words, nobody really has it. And so it's far safer to edit the human genome to create a genome that already exists in other people in the wild form. But if you're going to edit something that's never existed before, I think we've got a few decades before we're going to try to cross that line".

EZRA KLEIN

"So, as you gesture towards, we've had the capacity to do some level of genetic editing or changing for some decades now. What did CRISPR add to our capabilities here? What made CRISPR different"?

WALTER ISAACSON

"What made CRISPR different is it's not just recombining DNA or even using the old, clunky tools we used to have that could try to cut DNA and make an edit known as ZFNs or TALENs and things like that. What made it different is that it's easily reprogrammed. You can say, OK, I want to do it right here at this sequence. And so you have this guide RNA, and the guide RNA can just be much more precise, and it can be done much more quickly".

EZRA KLEIN

"Let's say you had unlimited money and few ethical strictures. What could CRISPR actually probably do right now"?

WALTER ISAACSON

"Right now, it's best at single-gene mutations. But if you really had a doctor in a clinic somewhere with no ethical guidelines, certainly there are things that clearly predispose height, for example, or muscle mass, as we talked about with our friend the biohacker. That's just a myostatin regulator".

"And certainly, by the way, if we can make cells so that they aren't sickled in the blood and carry more oxygen, that might make muscle mass or blood or endurance much better. And then obviously, the type of diseases we have — Tay Sachs, muscular dystrophy — you'd edit those out of your children if you wanted to".

SO, WHAT'S COMING NEXT FROM THE DOUDNA LAB?

As a result of the lack of trust between the early, academic pioneers who developed CRISPR and the patents that came out of that, Isaacson discusses the split that occurred when Doudna lost trust and respect for what she refers to as the "gang of men who dominated the biotech and finance world in Boston". She resigned from Editas and went on to found other companies with those whom she respected and trusted. "They were people who do good science, but are more importantly, honorable straight-shooters". As a result, the CRISPR – Cas 9 pioneers ended up in three companies (CRISPR Therapeutics, Editas Medicine, and Intellia Therapeutics).

These have been highlighted in a previous section of this issue of JCB. Herein we highlight that the Doudna team has three additional early stage companies in development pursuing commercialization of the CRISPR technology. They have all closed recent rounds of financing and also entered into key partnerships. They are **Scribe Therapeutics, Caribou, Mammoth BioSciences, and Intellia Therapeutics**.

San Francisco-based **Scribe Therapeutics** is using the CRISPR technology with its next-generation platform for gene editing. The company recently announced a collaboration with Biogen to develop CRISPR-based genetic medicines for neurological diseases, including Amyotrophic Lateral Sclerosis (ALS). The company also recently closed a $20M funding round.

Caribou Biosciences, Inc., a leading clinical-stage CRISPR genome editing biotechnology company, announced today the successful completion of an oversubscribed $115 million Series C financing. Proceeds from the financing will be used to further develop the Company's proprietary, next-generation CRISPR technology platform and to advance the Company's pipeline of wholly-owned allogeneic immune cell therapies for oncology with best-in-class potential. Business Wire reported that Caribou has developed a next-generation CRISPR technology platform with substantial advantages in genome editing specificity and efficiency. The Company's technology platform has fueled a pipeline of allogeneic cell therapies for oncology with best-in-class potential including enhanced persistence of its off-the-shelf cell therapies that is expected to drive the clinical durability of effect in multiple malignancies. Rachel Haurwitz,

former Doudna protégé is President and CEO of the company.

Mammoth Biosciences, a company that uses gene-editing technology Crispr for disease testing, said Thursday that it had raised $45 million in Series B funding to expand into treatments. The round, led by Decheng Capital and including new investor Verily, brings total funding to over $70 million. https://www.forbes.com/sites/leahrosenbaum/2020/01/30/mammoth-biosciences-raises-45-million-to-create-crispr-diagnostic-tests-and-its-tech-is-already-being-used-against-coronavirus/?sh=6be915cf56c9

The South San Francisco-based company, founded in 2017 by *Forbes Under 30* honorees Trevor Martin, Janice Chen, Lucas Harrington and CRISPR pioneer Jennifer Doudna, uses CRISPR as a genetic "search engine" to find disease markers and alert researchers of their presence. They've already partnered with others, such as gene-editing company Horizon Discovery and a UC San Francisco researcher who is creating a rapid diagnostic test to identify people infected with the new coronavirus.

"The company has been one of the most prolific innovators in the overall CRISPR ecosystem," says Ursheet Parikh, an investor at the Mayfield Fund, which also participated in the round. As noted, the technology is already in use for Covid-19 applications. Mammoth has also moved into new lab space on the South San Francisco campus of Verily, Alphabet's life sciences company.

Intellia Therapeutics is a biotechnology company developing biopharmaceuticals using a CRISPR gene-editing system invented by Jennifer Doudna and Virginijus Šikšnys. The company has partnerships with Novartis and Regeneron. Wikipedia.

In closing, it is very clear that CRISPR is being commercialized rapidly in response to ongoing need in the community. Additionally, the impact of Doudna's work is not only advancing the science and technology, but is rapidly leaving the lab to be used for improving the lives and health of patients worldwide.

ADDENDUM – SOME PERTINENT, CONCLUDING COMMENTS ON THE IMPORTANCE OF HIGH –PERFORMANCE TEAMS FOR FOUNDING, BUILDING, AND GROWING SUCCESSFUL BIOTECHNOLOGY COMPANIES

Building teams for advancement of the science and technology is essential for any academic scientist who has aspirations to create new entrepreneur. However, when it is apparent that there is commercial potential, especially of a transformative magnitude any spinoff company has to be started as an independent organization and one with a team formed to advance that technology to several important downstream milestones. While this topic is discussed in the Isaacson book, we believe that it is important to include this Addendum to discuss the topic further.

Our top 10 takeaways on building high-performance teams:

1. While the startup team is small (perhaps two or three people), it needs to include credible technology and business expertise along with a few key advisors and coaches from day one.
2. Build diversity into the team from day one.
3. Note that teams include: Founders with technology and business experience; Advisors/coaches for technology, business, and legal (IP, reimbursement); Directors who bring independent perspective, and also who have fiduciary responsibility.
4. What is required from the team includes: access to people, capital/investors, partners, legal counsel for IP and transactions, experienced advisors/mentors/coaches. (Note that a great team attracts great people, partners, etc.)
5. Team members require competence, commitment, and a common goal or vision – look for skill, will, and fit.
6. Strive to add value and reduce risk incrementally by building and scaling a team across the product life cycle from startup; to development stage; to and through clinical stage; to market entry and growth.
7. As you go through these stages evolve your team thru the "evolution and revolution" that could occur at each transition.
8. Remember that "a startup is a "temporary organization" in search of a scalable, repeatable, profitable business model" – think lean startup.
9. Adopt the Innovator's DNA perspective of questioning, observing, networking, experimenting/testing hypotheses, and use recognize the diverse teams are better suited to use associative thinking that provides 'out of the box' perspective from different disciplines and backgrounds.
10. Failure does occur, but the most likely failure is caused by lack of performance of the team, followed by market/competitive factors, and then the technology itself does is bypassed

by alternatives with alternative performance metrics.

We refer the interested reader to several of our previous publications for a more detailed discussion of the fundamentals of building and leading teams.

1. Boni, Arthur A., Laurie Weingart, and Gergana Todorova, Chapter 7 in "Building, Managing, and Motivating Great Teams", in "Biotechnology Entrepreneurship, Starting, Managing, and Leading Biotech Companies", Academic Press (2020), 2nd Edition (Craig Shimasaki).
2. Boni, Arthur A. "Leading and Managing Teams in Entrepreneurial Organizations, an Experiential Perspective", J. Commercial Biotechnology, Vol. 24, No 4, pp 74–80, (2019).
3. Todorova, Gergana, "Building and Managing Great Teams: An Evidence-Based Approach, J. Commercial Biotechnology, Vol. 24, No. 4, pp 81–85 (2019).

Article

A Note on Corporate Open Innovation: Engagement with Startups

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ABSTRACT

This Note summarizes our findings based on an exploratory and initial global research study of best practices for organizations employing open innovation business model strategies. We utilized an expert interview approach to develop a survey that was taken during the Covid-19 pandemic. It was meant to assess open innovation strategies and tactics, particularly focused on partnering with startups and emerging companies. We worked with a cohort of Corporate Accelerator Forum (CAF) members (as experts), prior to a more extensive survey of corporations concerning their engagement with startups. Our experts included key leadership from Techstars, Bayer CoLaborator, and Illumina Accelerator. We plan a broader, more extensive survey of national and international companies as a follow up. Our results highlight and provide commentary on current industry practices and trends during the Covid-19 pandemic, and have applicability to the biopharma, MedTech, and digital medicine/health markets.

Journal of Commercial Biotechnology (2021) 26(2), 33–3. doi: 10.5912/jcb989

INTRODUCTION

The Corporate Accelerator Forum was founded by Diana Joseph to be an intimate, membership-based group of global corporations and their leaders who pursue an open innovation strategy that incorporates working with startups and growth-stage companies. Their strategy is to identify and source emerging opportunities that might be capable of "driving innovation" in their respective organizations, vs. internal development alone. This approach to innovation is described by Boni and Joseph who have identified the "corporate accelerator model" as one of 4 models to engage in the pursuit of innovation, and is particularly relevant to larger organizations; c. f. Boni and Joseph in J. Commercial Biotechnology [See Boni and Joseph; "Four Models for Corporate Open Innovation", JCB, Vol. 24, No. 4, pp 23–31 (2019); and, "Aligning the Corporation for Transformative Innovation: Introducing Innovation Dashboard", Vol. 24, No. 4, pp. 14–22(2019)]. In Fall 2020, we brought together several organizations in the corporate-startup engagement world to investigate how corporates are currently engaging with startups, and what they see in the near future. They included Techstars, Bayer CoLaborator and Illumina Accelerator. A pilot survey was developed by these experts from our advisory group, and then sent out to other experts in their networks , as well as CAF and IGE companies. We were seeking input from a cohort of informed practitioners to shed light on the landscape. This parallels the methodology suggested by Roberto Verganti in his classic book "Design Driven Innovation" published by Harvard Business School Press in 2009. We received 41 qualified responses from CAF and IGE companies with expertise in innovation, of which 8 (~20%) were in the healthcare/pharmaceutical industry".

This approach was meant to be exploratory and done as a combination of expert interviews combined with the perspectives of a larger cohort.

We covered five areas in the survey, and we offer some key concepts from each in our Summary below.

- **Strategy** – where do corporates place their startup-engagement bets, and why?
- **Tactics** – what are the engagement models in play?
- **Pandemic Impact** – what has changed for corporates and their startup partners or spinoffs?
- **Future /What's Coming Next** – what do corporations foresee next?
- **Demographics –** industry focus, size of organization, 'location' of innovation leaders in their respective organizational hierarchies.

A SHORT SUMMARY OF KEY TAKEAWAYS

A short summary of our findings from the surveys follows in this section. A more detailed report from CAF is available to member companies. If you are interested, please contact the lead author: diana@corporateacceleratorforum.com.

- **Innovation is Important**. Respondents to our survey were self-identified as senior innovation leaders. Nearly one third were directly responsible for P&L and "housed" in departments named as innovation organizations. Ongoing innovation and technical insight were the most-cited reasons for innovation, with much less interest in transformative innovation, culture change, or social impact.
- **Calculated Risk.** Corporates aim to limit both their risk and their expenditures. Over 1/3 of respondents identified their innovation approaches as preferring certainty over risk-taking. Furthermore, they tended to select companies in the risk/cost sweet spot of A-round venture-funded companies, rather than idea-stage projects or more mature companies that would likely be more expensive. They did have an appetite and patience for longer term outcomes.
- **Stay the Course.** More than 60% intended to continue their innovation strategies thru the Covid-19 pandemic; with over 50% expecting an increase, but 20% foreseeing a decrease in the next 12 months. Nearly 50% look to mid-term vs. short or long-term payoff from their partnering.
- **No Corporation is an Island.** In a rapidly changing world, corporates must engage more actively than ever in their innovation ecosystems. Engagement with startups is viewed as a special imperative.

LESSONS AND INSIGHTS FOR CORPORATES IN THE BIOTECH SPACE

- As large, highly-aligned organizations, corporates need to:
  - Draw close to smaller companies' agility and speed. Further, they need to leverage other entities to allow them enhanced insight into what is happening in the ecosystem.
  - Create a clear way for startups to reach you — for example, naming a head of innovation tells them who to contact.
  - Identify where to make "bets", and what models to employ for effective partnering. Partner with VCs for guidance, identification, screening and managing risk.
  - They seek:
    - Companies that already have high quality products, services, and customer interaction.
    - Companies with strong leadership teams and business acumen.
    - Companies amenable to "high-touch engagement" and coaching.

NEXT STEPS

CAF is seeking research sponsors and partners to extend this work in the following ways:

- investigating distinctions between the perspectives of front-line staff, senior leaders, and the startups
- comparing B 2 B and B 2 C companies
- comparing industries and regions
- delving deeper into culture, values, and tools

For more information on our surveys, methods, and results, or to participate in this ongoing research, please contact-diana@dianajoseph.com.

ACKNOWLEDGEMENT

Our thanks to Techstars for their contribution to the survey development and distribution.

Article

Building Technology Enabled Platform Companies in Biopharma – A Perspective on Early-Stage Value Creation from Millennium, Alnylam, Moderna, & Kymera

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ABSTRACT

This paper addresses the topic of building platform-based companies in biopharma. We provide a short literature review on the topic, followed by a discussion of financing growth of platform companies. This is followed by case studies on four pioneering biopharma companies that cover the era of the mid-1990s until today. These companies are all well recognized pioneers and have gone thru their life cycles from founding, to building portfolios of products, to acquisition. Our mini-case studies include Millennium Pharmaceuticals (now a unit of Takeda), Alnylam, Moderna, and Kymera.) These also cover different technology bases for their respective platforms that have emerged during the last two decades since the emergence of the genomics revolution.

Journal of Commercial Biotechnology (2021) 26(2), 36–47. doi: 10.5912/jcb990

1.0 INTRODUCTION AND OBJECTIVE

Drug development is a long journey and the process by itself is actually a continuum of creating value while managing and reducing multiple risks. Since the industry inception with Cetus in 1971, and then the pivotal foundation of Genentech in 1976, followed by Amgen in 1980 the biotech paradigm has evolved significantly from creating startups, and funding the creation of well-established biotech companies, to getting the first product approved by the FDA – most often in partnership with a larger pharma company. Many business models have been described over time with regard to how to employ different business strategies at various development stages[1,2].

As a biotech entrepreneur, many crucial strategic subjects need be reviewed and considered, even before embarking on their company. These include the technology robustness, uniqueness and applicability, how the potential solution addresses the unmet clinical need, the competitive landscape, culture, regulatory hurdles, reimbursement, etc. We suggest that an essential consideration is to determine the type of company they shall choose. In other words, is this a single product company or, is there potential for creating an enabling technology platform company. This paper reviews four landmark technology platform companies created in the past two decades, and all of whom have made significant impact by exploiting a platform strategy. We explore how they established a sustainable value base in their early stage and over time pivoted their platform into a proprietary R&D driven biotech, and ultimately transformed into platform companies that have brought transformative technologies to market. Our objective is to provide the future biotech entrepreneurs (our intended audience) with some insights of strategic value creation in the early stages of technology platform – based companies. The landmark platforms selected in this paper are a genomics company applying world-class technology to drug

1 Gary Pfeffer (2020) Lawton Burns. 'The Biotechnology Sector: Therapeutics', The Business of Healthcare Innovation 3rd edition. Cambridge University Press. pp. 135–149.

2 Craig Shimasaki (2020) 'Understanding Biotechnology Business Models and Managing Risk', *Biotechnology Entrepreneurship 2nd edition*. AP. pp. 163–176.

discovery (Millennium – now a subsidiary of Takeda), RNA interference (Alnylam), mRNA (Moderna), and emerging protein degradation (Kymera). These companies have demonstrated their abilities to innovate around an emerging and transformative technology to build platforms. The science, platform, culture, and leadership, are all absolutely critical in the process of capturing the value creation; however, that is not the theme of this paper. We focus on the elements of business model development that is required to build a platform company – beyond the technology itself.

2.0 TAXONOMY AND DEFINITION

Before we review those landmark companies, it would be important to clarify some key definitions and concepts associated with platform companies and understand how they create value. Platforms have been described in many books and articles, but to some extent conflicts and questions still exist.

2.1 Are you a technology platform company? And which type?

Before we decide if we can build a platform company or not, we must define what constitutes a platform company. It is interesting to notice the differences discussed in two, recent biotechnology books. Millennium Pharmaceuticals was categorized as a subscription business model by Shimasaki, while Pfeffer defined it as a technology platform company[1–2]. Why does this difference exist? Lanza illuminated the criteria with some key questions that a successful platform company needs to answer[3]: 1) whether the technology is broadly applicable to address an industry wide problem, 2) whether the technology provides an alternative to existing processes, and, 3) whether the technology is scalable and offers greater efficiency. Three consecutive yes answers would lead to technology platform company, and Millennium is fully meets these criteria. However, a more instructive question is how to subcategorize the platform company, which probably results in the differences between Shimasaki and Pfeffer. I believe that Steven Holtzman addressed it perspicuously[4]. According to his taxonomy, there are two types of platform companies; product (therapeutic modality) platform companies, and insight platform companies, and the latter includes two subtypes (pathway and target driven, and biology driven). The perception confusion associated with Millennium was that the company did use the service and subscription mode in the initial stage to generate revenues and advance the platform, however, it fully merits a target and pathway – insight driven platform company according to Holtzman (Genus 2 Species A). All the other three companies founded after 2000 and described in this paper actually are product platform companies (Genus 1) in his typology.[4]

To further illuminate the role of the platform in creating and sustaining value and competitive advantage, we highlight some of the recent work published by Boni in this journal and used to screen early stage companies, c. f. "Evolution of the Screening Metaphor: Project, Product, or Platform (JCB, Vol. 24, No. 4, pp 7–13 (2019). This article is a lead article in a special issue titled "Boot Camp 2.0" and used at each annual BIO Entrepreneurship Boot Camp (to assist emerging bio-entrepreneurs to build their potential companies). We include here some materials taken from that paper with permission of the author and the publisher:

> *"Projects are best pursued with commercial partners via licensing arrangements. Products may be pursued using a research and development company business model. Platform is intended to signify creation and growth of a lasting, scalable organization intended to develop and bring multiple disruptive or transformative innovations to market. Which path to the marketplace is appropriate, or even possible will depend on a number of factors. These include: the magnitude of value being created for the market; the competitive set; and, the uniqueness of the solution and its sustainable, competitive advantage that can be created. It is also necessary to determine whether the value captured by the business model that may be constructed could generate sufficient profitability to balance the commercialization risks, while meeting the goals and objectives of the founders, investors and partners over an appropriate time line."*

> *"One definition of* **"Platform"** *is the common foundation (or, technological) ba this paper actually are product se from which one can create a family of products (and services), while targeting different customer segments. e. g. multiple disease states. Platforms are incorporated into business models*

3 Lanza, G. Building today's platform company. Bioent (2009). https://doi.org/10.1038/bioe.2009.6

4 Steven Holtzman, Early-Stage Biotech Value Creation: The Roles of Equity and Partnerships. http://leadershipandbiotechnology.blogspot.com/2018/08/early-stage-biotech-value-creation_15.html

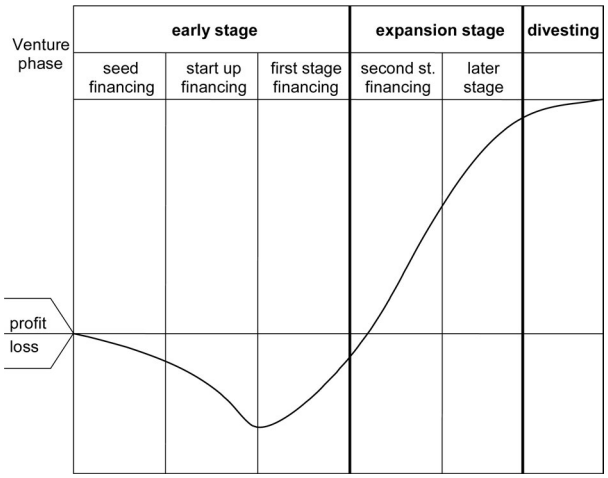

Figure 1: Typical Development phases of high growth companies
Source: Leleux IMD Case[5]

with the potential to create, deliver, and capture more value than a single product or service, and more importantly sustainably. They can also be used to allow multiple parties ("market sides") to transact across the platform. "A multi-sided platform that connects partners, users and payers can create more value for all than just the entity that creates the platform" (a paraphrase of a Bill Gates quote)".

"The platform and its supporting ecosystem and network may be used to build and sustain a market leadership position vs. a single product with a much less powerful network. However, the early-stage company may start from a single product; then grow and dominate multiple market segments by developing a supporting ecosystem and network. Alternately, the organization can start with the vision of creating an industry leading platform, and use the entry product as a step in that direction. However, and depending on the industry and competitive landscape, it may be necessary for the early stage company to join existing networks of power players to provide complementary products or services. In today's innovation landscape, platforms are most often thought of in the context of information technology (IT). However, the concept of a platform has been around for years and evidenced in the product pipeline/portfolio approach taken in the biopharma industry".

2.2 Biotech Valuation Stage

Biotech companies face the need for valuation at various development stages. Leleux described that the possible stages of a high-growth company that include: Seed stage (conceptualizing); Start-up stage (launching); First stage (Developing), Second stage (Accelerating Growth); Later stage (Restructuring for Value Added); and, Exit stage[5].

It is essential to position a technology platform company at different stages because each would reflect specific risks attached to the safety, efficacy, competition, regulation, demand, etc. The amount of money raised at each crucial step needs be justifiable and requires a careful and thorough analysis and rationalization, that will impact the future valuation estimations significantly. An early stage company must carefully evaluate what share they would have to cede to the investors in exchange for the investment, where to allocate its capital, and which project they should push forward to reduce risk and to ultimately achieve higher valuation associated with risk reduction.

In any finance textbook, value is typically defined as the expected future free cash flows discounted at the opportunity cost of capital. Although a variety of valuation methods can be considered, the discounted cash flow approach (DCF) are widely used with the focus on projecting appropriate discount rate and expected cash flow, particularly in the non-listed company.[5] The adjustment of DCF can be roughly based upon the management, quality and uniqueness of the science, market potential, however, the market value could be primarily driven by expectation, i.e. the hope of realized earning potentials from approved drugs. As drug development is a long process and its value creation could take more than a decade to be captured, it is indeed the non-financial indicators that are key to valuation of a biotech

5 Benoit Leleux, Victoria Kemanian, Atul Pahwa, and Katrin Hacki. Venture Valuation AG: The Genedata Assignment. IMD Case: IMD251

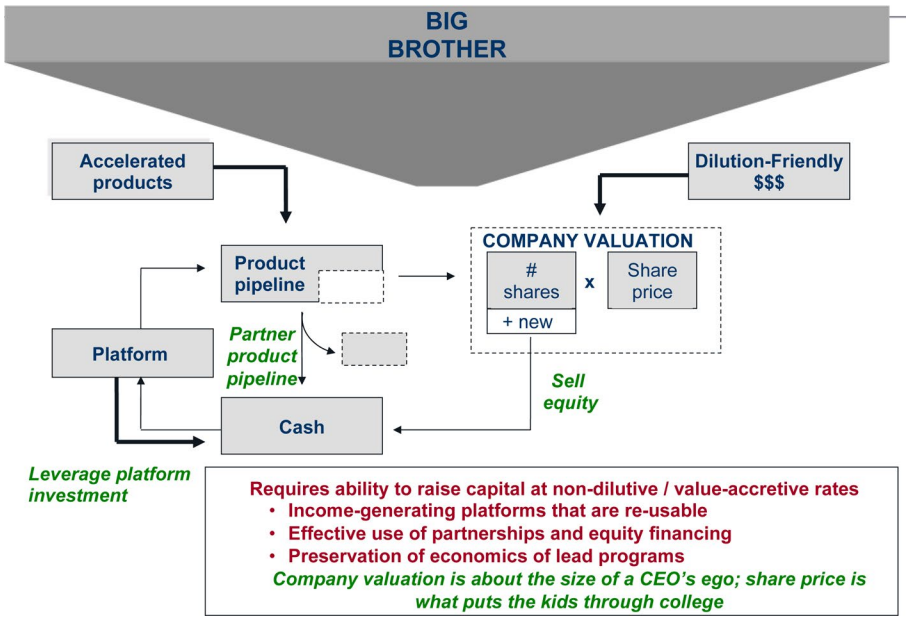

Figure 2: Biotech Value Creation Cycle (Source: Steve Holtzman Blog[4])

company, which may include commencement and completion of milestone trials at different phases, approval of IND, strategic alliance (including marketing, R&D, and manufacturing, etc.), and product launch[6]. Compared with other measurable non-financial indicators, given high inherent risk of drug development, the intense competition in the drug marketplace, forming alliances and partnerships is essential to a platform company's valuation and boost the value creation cycle given its positive impact on investor's risk reduction and pipeline need, and more importantly to meet and exceed the investor's expectation and reinforce their confidence to attain the expected cash flow due to breakthrough discoveries that stemmed from the platform to address the desperately unmet need.

2.3 Biotech Value Creation Cycle

It is indeed a long journey before a biotech company can produce any revenue from product sales, therefore the value to be promoted to the investors is subject to discussion and rationalization amongst the parties. This would include the value at present, which could be technology insight, product potential to a partner company, including the value of perceived futures thru marketing/profiting sharing, etc. Therefore, as Holtzman described, biotech value creation is not about the size or market capital, but predominantly about share price appreciation. The focus of the size of market capital by absorbing too much dilution early would compromise the stakeholder's value. Therefore, when sourcing value accretive capital, any alliances and partnerships need be vigilantly balanced in a manner not to give away the major parcels of future value creation[4].

In the next section, by observing some strategic value creation implementation process in a few paradigm platform companies particularly in their early stages, we would hope to reveal some success secrets during their value creation cycle.

3.0 PLATFORM COMPANY IN BIOTECH – MONOCLONAL ANTIBODIES (MAB) (LATE 1970S TO 1980S)

The discovery of monoclonal antibodies has defined the modern history of biomedicine. In 1983, based on a number of animal studies, the pioneers in mAb believed that a new era of cancer treatment would begin soon. In the following year, the landmark Nobel Prize was awarded to Georges Köhler and César Milstein. In 1996, Rituximab and trastuzumab were approved by the FDA as the first and second therapeutic mAb based cancer treatments[7]. It is worth noting that the first generation of therapeutic

6 McConomy, Bruce & Xu, Bixia. (2004). Value creation in the biotechnology industry. CMA Management. 29–31

7 Robert Oldham and Robert Dillman. Monoclonal Antibodies in Cancer Therapy: 25 Years of Progress. Journal of Clinical Oncology 2008 26:11, 1774–1777

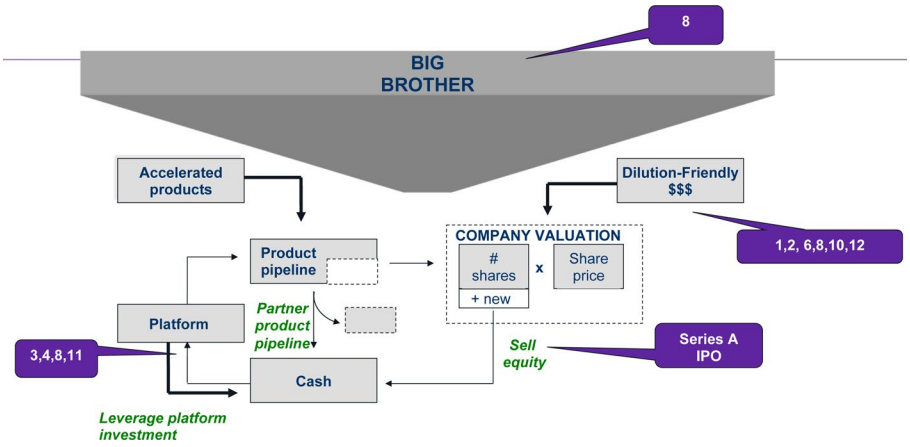

Figure 3: Biotech Early Stage Value Creation Cycle: Millennium Snapshot

modality platform companies such as Genentech were founded with different financing mechanisms from most of what we will discuss in 1990s and later, therefore, their strategic value creation will not be discussed in this paper.

3.1 Millennium Pharmaceuticals – Value Creation via Strategic Alliances (1990s)

Millennium Pharmaceuticals, Inc. was founded in Cambridge, Massachusetts in 1993. Started as a technology platform company with $8.5 million initial VC funding, it went public in 1996 and became one of the most successful biotech companies in the 1990s. It was managed and transformed into a fully integrated biopharma firm in early 2000s prior to being acquired by Takeda pharmaceutical in 2008 at $8.8 billion.

Partnering with big pharmaceutical companies was fundamental to the growth of Millennium in its early stage. By leveraging the timing of the Human Genome Project, enthusiasm, and leadership, they controlled a significant early slice of the genomics pie. The company crafted a series of breakthrough strategic alliances with 8 of the 10 largest pharmaceutical companies in five years after its commencement; including a history of discovery alliances worth $465 million agreement with Bayer, which also sped up their growth through aggressive acquisition strategy to secure their platform advancement, and made the company's market capitalization exceed $4 billion by the end of 1999.

From the very start, the company decided to generate reliable revenue streams very early on. The management team scrutinized various failures of other small biotech firms, which were largely attributed to having narrow platforms, selling off product rights too soon, huge sinking cost of development, and framed a clear strategy to build up a comprehensive technology "platform" that would empower them to develop and sell some of their assets, such as drug targets and later drug leads, to big pharms with hunger for new drug candidates, while preserving the capability to keep a good amount for the firm and retain ownership and IP for further development. Under this strategy, an array of proprietary technologies in the discovery chain, such as proteomics, bioinformatics, high-throughput screening, synthetic chemistry, cheminformatic, as well as molecular biology were assembled and merged into a state of the art "technology platforms,". Partnering with big pharmaceutical companies was a core step in CEO Mark Levin's roadmap. A typical alliance agreement would include that pharmaceutical partner pay Millennium an upfront fee, and milestone payments when a predefined research milestone was achieved and take responsibility for potential downstream drug development and commercialization. The series of alliances and collected about $2 billion in a few years and helped them strengthen technology platform and cultivate its capability of identifying its own drug leads to a variety of therapeutic areas[8,9].

The Table 1 below provided a snapshot of its deal distribution in the value creation cycle. As described in Section 2.1, Millennium was a novel and science insight driven platform company, and the value creation cycle illuminated that product in-incensing is less likely to feature in the value creation cycle. However, their relentless

8 Stefan Thomke. Millennium Pharmaceuticals, Inc. (A) Harvard Business School Case Number: 9-600-038 Rev: August 27, 2001

9 Julie Wulf, Scott Waggoner. Organization and Strategy at Millennium (A) Harvard Business School Case Number: 9-710–415 Rev: April 26, 2010

Table 1: Millennium selected early stage alliances (Source[1,2])

Date	Deal #	Deal Type/Partner	Value(m)	Terms	Role of Millennium
1994	1	Hoffmann-La Roche	$70	Equity investment and fees from partner	Gene/target research focus on Obesity, Type II diabetes
1995	2	Eli Lilly I	$50	Equity investment and fees from partner	Focus on Atherosclerosis & Oncology
1996	3	Astra AB	$60	Up-front Licensing Fees from partner	Focus on Inflammatory respiratory diseaseses
		Eli Lilly II	$30	Up-front Licensing Fees from partner	Extension of previous deal
1997	4	AHP (Wyeth-Ayerst)	$90	Up-front Licensing Fee from partner	Focus on General Nervous System disorders
	5	ChemGemics	$90	Acquisition	Acquisition of lead research capability
	6	Eli Lilly III	$20	Equity investment and mileston fees from partner	Extension of previous deal
	7	Monsanto	$218	Fees from partner	Technology transfer to partner
1998	8	Bayer	$465	Equity investment and Up-front Licensing fees from partner; ownership of targets not retained by Bayer	Gene/target research: Cardiovascular, Oncology, Osteoporosis, Liver fibrosis, hematology, viral infections. 225 targets over 5 y period
1999	9	LeukoSite	$750	Acquisition	Acquisition of lead research capabilities, product development pipeline, and near-market products
	10	Becton Dickinson	$68	Equity investment and fees from partner	Gene/target research
	11	Bristol-Myers Squibb	$32	Fees from partner	Gene/target research
2000	12	Aventis	$450	Equity investment and fees from partner; 50-50 ownership of end products	Full codevelopment of drug;cocommercialization in North America
	13	Cambridge Discovery Chemistry	$50	Acquisition	Acquisition of chemistry capability
2001	14	Abbott Laboratories	$250	Equity investment and fees from partner; 50-50 ownership of end products	Full codevelopment of drug;cocommercialization

1 https://hbr.org/2001/06/mastering-the-value-chain-an-interview-with-mark-levin-of-millennium-pharmaceuticals

2 Michael Watkins and Sarah Matthews, Strategic Deal-making at Millennium Pharmaceutical, HBS Case No. 800-032.

effort of consolidating their platform capabilities helped them secure competitiveness within a short period of time, and the massive non-dilutive investment from big pharma partners had supported their sustainable growth and allowed them to pivot and transform later. As seen in its early stage value creation cycle (Figure 4), their first-mover advantage, the genomics timing, groundbreaking platform nature, the charismatic leadership, as well as aggressive and savvy capital raising had helped them with rapid and remarkable value creation in the early stage, thus impacted the company's valuation significantly.

3.2 Alnylam Pharmaceuticals – Value Creation from the IP Estate (2000s)

Alnylam Pharmaceuticals, Inc. was founded in Cambridge, Massachusetts in 2002 based on the RNA

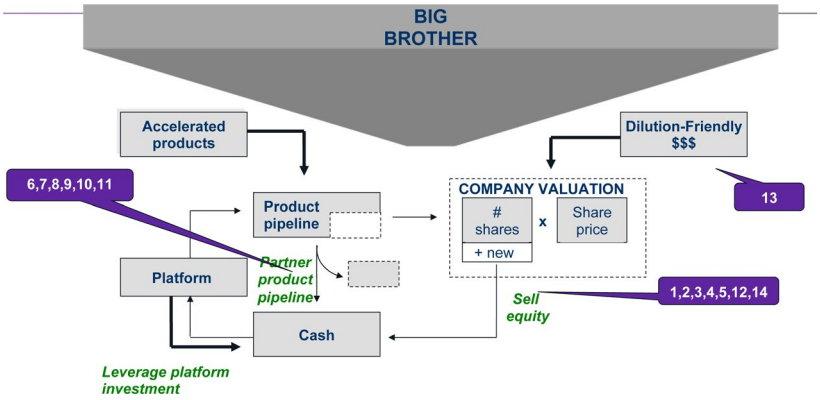

Figure 4: Biotech Early Stage Value Creation Cycle: Alnylam Snapshot

Table 2: Alnylam selected early stage alliances (Source[13,1,2,3])

Date	Deal #	Deal type/Partner	Value(m)	Terms	Business Status/Role of Alynlam
2002.7	1	Series A	$2	Venture Funding	Product Development
2002.8	2	Series B	$15.5	Venture Funding	Generating Revenue
Undefined	3	Series C	$17.5	Venture Funding	Generating Revenue
2004.3	4	Series D	$30	Venture Funding	Generating Revenue
2004.5	5	IPO	$30	Public Investment	Generating Revenue
2005.9	6	PIPE, Novartis	$56.8	Strategic Alliance	Joint discovery of new RNAi therapeutics
2006.10	7	PIPE, Multiple VCs	$24.6	Venture Funding	Generating Revenue
2007.8	8	PIPE, Roche	$331	Strategic Alliance	Providing non-exclusive licenses on RNAi therapeutics
2008.4	9	GSK	$600	Strategic Alliance	Via Regulus, a JV with ISIS, receive milestone payments for each of the four microRNA-targeted therapeutics
2008.5	10	PIPE, Takeda	$1000	Strategic Alliance	Providing non-exclusive access to RNAi therapeutics in the fields of Oncology and metabolic disease
2010.6	11	Sanofi	Up to $750	Strategic Alliance	Via Regulus, a JV with ISIS, receive milestone payments
2012.2	12	2PO	$80.63	Public Investment	Generating Revenue
2014.2	13	PIPE, Genzyme/Sanofi	$1,500.00	12% stake of Alnylam	Acquired Assets of Sirna Therapeutics
2015.1	14	2PO	$432.00	Public Investment	Generating Revenue
2020.4	15	PIPE, Blackstone	$100	Private Equity	Generating Revenue

1 Pitchbook: Alnylam Pharmaceutical

2 Pitchbook: Regulus Therapeutics

3 http://archive.boston.com/business/healthcare/articles/2010/06/28/regulus_makes_750m_deal_with_sanofi_aventis/

interference (RNAi) technology. Starting from $2 million series A funding, it went public in less than two years and was one of the most high-profile therapeutic platform driven biotech companies in the early 2000s. In 2018, the FDA and European EMA approved their first-ever RNAi therapeutic ONPATTRO (patisiran). In 2019, the FDA approved the second product, GIVLAARI (givosiran). At present, their RNAi driven pipeline includes three programs in late-stage clinical development and multiple programs in early-stage clinical development[10].

The RNAi harnesses the technical viability to silence disease-causing genes at the RNA level before translation into protein occurs and the science began to materialize in 2001 when Tom Tuschl discovered the siRNA structure and was able to put the RNA into human cells to show ability to silence genes. People began to consider it a ground-changing technology with potentials for an entirely new therapeutic paradigm on treating many genetically based diseases by targeting a specific gene and silencing it. Alnylam was founded accordingly with aim to be the first mover when RNAi was still far from certain, and the founders all understood it would be a long journey to turn the technology into a therapeutic, and before that enormous investments would be needed.

They had a very explicit strategy at the beginning to consolidate the intellectual property and assemble a patent portfolio (the "patent estate") all together so that anyone who anticipated therapeutic use of RNAi would have to license from them. After thoroughly reviewing the RNAi patent landscape, they identified eight frontier or associate patents in RNAi and negotiated all these different license grants, in agreements with academic institutions where those licenses were being held and secured either ownership or freedom to practice if without full control. By consolidating IP in this manner, they enjoyed pretty much non-competitive benefits, and were able to enhance their value creation by licensing the portfolio selectively and to raise sufficient non-dilutive funding capital from pharma partnerships. One of Alnylam's earliest licensing deals, as an example, was with Novartis in 2005 to target discovering, developing, and commercializing RNAi therapeutics for a defined number of gene targets exclusively selected by Novartis. In July 2007, Alnylam got one of its biggest licensing deals with Roche, providing a non-exclusive license to Alnylam's technology platform for developing RNAi therapeutics. The partnerships with big brothers funneled the money back into R&D to develop the necessary delivery mechanisms for RNAi and supported their ability to develop their own pipeline so as to avoid raising capital from more expensive capital markets. They also provided Alnylam with some grant-back licenses to discoveries from licensees as well as access to other IP platforms from the partners. Licensing therefore worked as a hedge for its own research program and enabled Alnylam to cherry-pick other partners' successful programs and potentially acquire partial ownership. Within 8 years, they raised $950 million, in which only $250 million was in the form of equity to venture capitalists or to the public markets and more than $700 million came from non-dilutive licensing fee (IP estate), which significantly, although indirectly raised their appreciation over the time[11].

As illustrated in its early stage value creation cycle (Figure 4), their first-mover advantage, and groundbreaking product platform nature had driven their progressive value creation in the early stage using balanced partnerships and equity deals, and indirectly impact the company's valuation. After 17 years since inception, their valuation had increased significant attributing to the concept turning into products proved by the FDA.

3.3 Moderna (2010s) – Value Creation before COVID-19 Vaccine

Moderna, Inc. was founded in Cambridge, Massachusetts in 2010. They are pioneering their industry's leadership based on a messenger RNA or mRNA technology platform, the infrastructure to accelerate drug discovery and early development. Their pipeline includes development candidates for mRNA-based vaccines and therapies spanning several therapeutic areas, and currently multiple clinical trials are underway, and its vaccine candidates has aggressively progressed through the clinic, and recently given vaccine approval for the Covid-19 pandemic. In December 2018, Moderna achieved the largest biotech IPO in history, raising US$600 million for 8% of its share since inception[12]. As of Aug 2020, Moderna was valued at $25 billion, and none of its mRNA molecules had yet to enter into large clinical trials.

The concept of mRNA-based therapy is that by injecting mRNA therapeutics to the patient's cells with the genetic code from DNA could get used again, the patient would be able to perform its protein producing function to cure the relevant diseases. Since its start as a private company, Moderna mostly performed in stealth mode with little disclosure of its research. However, they

10 https://www.alnylam.com/

11 Willy Shih, Sen Chai. Alnylam Pharmaceutical: Building Value from the IP Estate. HBS Case. Case number: 9-611-009. Rev July 15, 2013

12 https://fortune.com/2018/12/08/moderna-ipo-biotech-future/

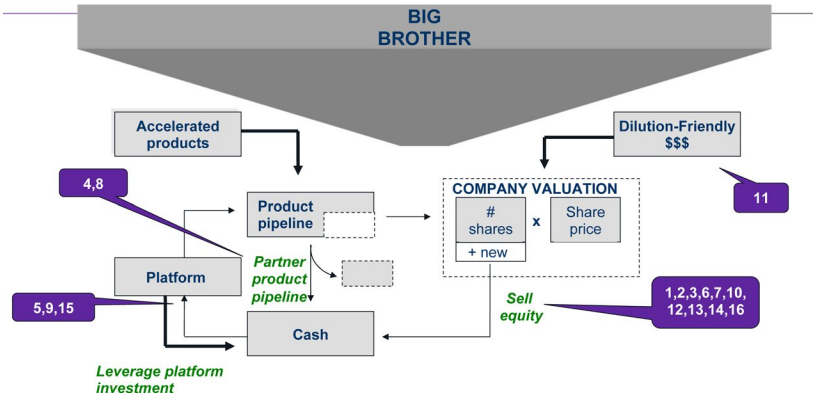

Figure 5: Biotech Early Stage Value Creation Cycle: Moderna Snapshot

Table 3: Moderna selected early stage alliances (Source[1,2])

Date	Deal #	Deal type/Partner	Value(m)	Terms	Business Status/Role of Moderna
2010.10	1	Series A	$2.1	Venture Funding	Generating Revenue
2011.12	2	Series B	$9.2	Venture Funding	Generating Revenue
2012.12	3	Series C	$27.6	Venture Funding	Generating Revenue
2013.3	4	AstraZeneca	$240	Strategic Alliance	Exclusive access to select any target of tis choice in cardiometabolic diseases
2013.10	5	Grant, DARPA	$24.6	Grant Funding	Generating Revenue
2014.1	6	Series D	$135	Venture Funding	Generating Revenue
2015.1	7	Series E	$450	Venture Funding	Generating Revenue
2016.7	8	Vertex	up to $275	Strategic Alliance	milestones plus royalty for CF mRNAi therapeutics
2007.8	9	Grant, Bill &Melinda, BARDA, DARPA	$331	Grant Funding	Generating Revenue, Supporting FIH study
2016.9	10	Series F	$474	Venture Funding	Generating Revenue
2016.10	11	Debt, CIT group	$1,340.00	Debt	Generating Revenue
2018.2	12	Series G	$500	Venture Funding	Generating Revenue
2018.5	13	Series H	$125	Venture Funding	Generating Revenue
2018.12	14	IPO	$604.35	Public Investment	Generating Revenue
2020.4	15	Grant from Biomedical Advanced Research and Development Authority	$483	Grant funding	Accelerating mRNA vaccine candidate against covid-19
2020.5	16	2PO	$1,340.00	Public Investment	Generating Revenue

1 Pitchbook: Moderna Inc.

2 https://www.fiercebiotech.com/biotech/vertex-moderna-pair-to-create-mrna-cystic-fibrosis-treatment

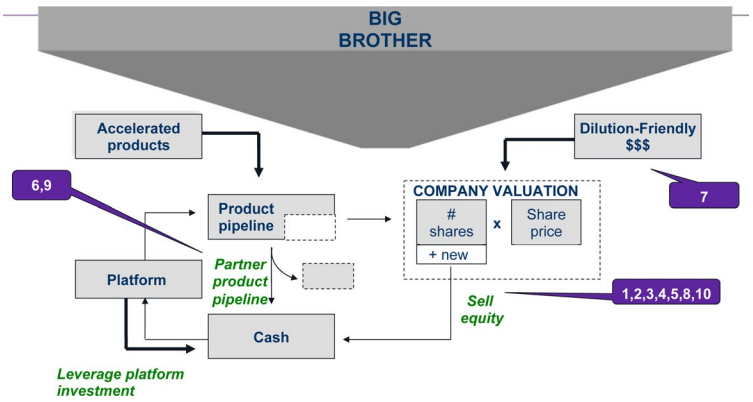

Figure 6: Biotech Early Stage Value Creation Cycle: Kymera Snapshot

quickly built strategic relationships with AstraZeneca, Merck and Vertex Pharmaceuticals, as well as the Defense Advanced Research Projects Agency (DARPA), the Biomedical Advanced Research and Development Authority (BARDA), and the Bill & Melinda Gates Foundation as they are passionate for the potential of its mRNA therapeutics, which could apply to a wide range of diseases from cancer to rare genetic conditions. As an example, in 2013, Moderna and AstraZeneca sealed a five-year exclusive option agreement to discover, develop, and commercialize mRNA for treatments in the areas of cardiovascular, metabolic and renal diseases, and selected targets for cancer. The agreement included a $240 million upfront payment to Moderna and is considered "*one of the largest ever initial payments in a pharmaceutical industry licensing deal that does not involve a drug already being tested in clinical trials*"[13].

As illustrated in its early stage value creation cycle (Figure 5), their initial investment via public investment is heavy. However, driven by the first-mover advantage, Moderna could raise massive non-equity capital in the early stage to complement its venture financing, and the curve at early stage (Figure 1) demonstrated the trend of steep value increasing curve even during expansion stage.

3.4 Kymera – Protein Degrader platform on the horizon (2020s)

Kymera Therapeutics, Inc. was founded in Cambridge, Massachusetts in 2017. Launching from stealth mode as an Atlas Venture backed incubator, Kymera is at the forefront of protein degradation R&D, with many other pioneers such as C4 Therapeutics, Arvinas and Nurix. Kymera has marched forward steadily since then and completed an IPO on August 2020 with a $173.7 million raise. The biotech is focusing research on a serial of lead programs designed to degrade IRAK4, IRAKIMiD and STAT3, respectively. IRAK4 was the star of the Sanofi alliance[14].

Targeted protein degradation, as an emerging therapeutic modality, is dramatically progressing with massive investment in recent years. As part of cellular processes, proteins are specifically recruited to E3 ubiquitin ligases and tagged for destruction with chains of ubiquitin. Compared to inhibition strategies, degradation offers numerous advantages, including the chance for removal of the target protein and consequent ablation of all associated functions. The unique properties of degraders provide opportunities for widely differentiated therapeutics, as well as the chance to tackle pathologies driven targets that were previously considered undruggable[15,16].

According to the definition of technology platform in Section 2.1, indeed, this targeted protein degradation can broadly address industry's problem of shortage in druggable targets, and technology provides an alternative to existing small molecule inhibitors, and technology is very scalable and offer greater efficiency. Although in the early stage, protein degradation technology has

13 https://www.nytimes.com/2013/03/21/business/astrazeneca-to-pay-240-million-to-moderna-therapeutics.html

14 https://www.contractpharma.com/contents/view_breaking-news/2020-07-09/kymera-sanofi-enter-multi-program-strategic-alliance/

15 Chamberlain, P.P., Hamann, L.G. Development of targeted protein degradation therapeutics. Nat Chem Biol 15, 937–944 (2019).

16 Mayor-Ruiz, C., and Winter, G.E. (2019). Identification and characterization of cancer vulnerabilities via targeted protein degradation. Drug Discov. Today. Technol. 31, 81–90.

Table 4: Kymera selected early stage alliances (Source[1,2,3])

Date	Deal #	Deal type/Partner	Value(m)	Terms	Business Status/ Role of Kymera
N/A	1	Seed round	$3	Venture Funding	Startup
N/A	2	Accelerator/Incubator	$3	Venture Funding	Startup
N/A	3	Accelerator/Incubator	$3	Venture Funding	Startup
2017.10	4	Series A, led by Atlas	$30	Venture Funding	Generating Revenue
2018.11	5	Series B	$65	Venture Funding	Generating Revenue
2019.5	6	Vertex (Series B1)	$70	Strategic Alliance	Upfront to discover protein degrader drugs
2019.10	7	Debt from Multiple Debtors	$13.85	Debt Financing	Generating revenue
2020.3	8	Series C	$105.29	Venture Funding	Generating revenue
2020.7	9	Sanofi	$150	Strategic Alliance	Upfront to discover protein degrader drugs
2020.8	10	IPO	$173.7	Public Investment	Generating Revenue

1 Pitchbook: Kymera Therapeutics

2 https://www.fiercebiotech.com/biotech/vertex-pays-kymera-70m-upfront-to-discover-protein-degradation-drugs

3 https://www.fiercebiotech.com/biotech/sanofi-pays-150m-upfront-2b-biobucks-to-tap-protein-degrader-biotech-kymera

become an emerging breakthrough therapeutic modality, and Kymera, as one of the players, are working diligently to solidify its proprietary platform, which is likely to be continually validated from the high-value strategic partnerships with big brothers/partners, like Vertex and Sanofi. As illustrated in its early-stage value creation cycle (Figure 6), their value is driven by the first-mover advantage and leverage of substantial non-equity capital in the early stage right after the seed and start up financing, and the curve at early stage (Figure 1) become shallower and shorter to reach IPO before it could stretch up its profit curve up in the expansion stage.

4.0 CONCLUDING REMARKS

Over the past thirty years, technology platform-based business models evolved significantly in biopharma. Our observations based on four paradigm platform companies in different times suggests that the friendly, development environment of Millennium, as a pioneering "technology-insight" genomics platform company (rather than a therapeutic based platform) had experienced in 1990s, became rare. However, if you decide to build up a therapeutic platform company with aspirations to make sustainable achievement with remarkable valuations, the experience from the present paradigm companies like Alnylam, Moderna, and Kymera are insightful. Actually, the process of early stage strategic value creation from the four companies described above indeed shared a lot more similarities and could shed some light on the future stars of innovative and transformative technology platform driven biotech.

1. The enabling technology platform model is still viable and timeline to an IPO is visibly shortened.
2. To make a paradigm success, the technology platform must be groundbreaking, ideally therapeutic nature, with broad range of application to create multiple product opportunities, in order to ensure the sustainable growth.
3. Platforms must be highly leverageable in order to raise non-dilutive, high-margin capital. Equity and partnerships need be carefully balanced. The quality and quantity of non-dilutive capital deals and partnerships with big brothers/partners in very early stage is a great indicator of valuation.
4. Relentlessly consolidate your platform, and build your own pipeline to keep sustainable competitive advantages.
5. Nowadays, biotech founders and entrepreneur need to work even more intimately with little brothers (early stage VC) in the start-up stage given the heavy funding needed in this period with timely and meaningful deliverables. Note they are very dilution averse and would like

to participate in all private financings until an inflection point.

6. Think about the context and timing when building up your platform company (political, capital market, science maturity). First mover obtains big advantages, so don't wait until science is fully ready, and we believe you will find a chance to adapt, pivot, and transform your company later. Perseverance is important!

ACKNOWLEDGEMENT

I cannot express enough thanks and gratitude to Professor Stephen Sammut at Wharton School and Steven Holtzman for their continued support, mentorship on this paper as a part of my biotech entrepreneurship project. My completion of this work could not have been accomplished without their advice, encouragement, and even meeting during the COVID-19.

Article

Putting Theory into Practice at BridgeBio

Daniel S. Levine

Journal of Commercial Biotechnology (2021) 26(2), 48–51. doi: 10.5912/jcb991

Many drug companies spring from scientific discoveries made in a laboratory. BridgeBio Pharma, though, owes its genesis to the musings of a financial theorist.

MIT Sloan School of Management Professor Andrew Lo began educating himself about the world of cancer therapies when in a four-year period of time he lost six friends and his mother to cancer. As Lo searched for information about potential new treatments for people he cared about, he started to learn about the drug development process, and soon came to view the translational science challenge of moving a potential therapy from discovery to proof of concept—a gulf that's come to be known as the "valley of death"—as being a financial, rather than a scientific, problem. "It occurred to me that finance ends up playing a big role in drug development—often too big a role in my view," said Lo. "That's when I started to think about applying the tools that I was familiar with to this area and to see whether or not it can make a difference."

In a paper Lo coauthored in *Nature Biotechnology* in 2012, he argued that the solution rested in applying portfolio theory to biomedical innovation. The approach to drug development where a so-called "megafund"—a fund of between $5 billion to $15 billion—could invest in a large and diversified range of assets at different stages where the success or failure of any single asset was largely independent from the success or failure of another.[1] Doing so could reduce risk and increase the odds of success. At the same time, he argued for a mix of equity and securitized debt to tap into larger sources of capital to fund a multi-billion portfolio of projects.

Even though the approach might reduce the potential for venture capital-sized returns sought by classic biotech investors, it would open access to nontraditional biotech investors such as pension funds, insurance companies, and large institutions that have a lower appetite for risk but are satisfied with a lower level of return. A simulation for the paper based on new molecular entities to treat cancer from 1990 to 2011 yielded average investment returns of 8.9 to 11.4 percent for equity holders and 5 to 8 percent for research-backed obligation holders.[2]

The paper came at a time when the expiration on patents from blockbuster drugs were delivering a wallop to Big Pharma revenue and R&D productivity was falling as the industry in 2010 found itself spending nearly twice what it spent in 2002 for R&D investment, but yielding roughly the same number of new drugs year after year.

The paper struck a nerve with Neil Kumar, a principal in the venture capital firm Third Rock Ventures. Kumar had taken a finance class with Lo while he was earning his Ph.D. in chemical engineering at MIT. He later attended a conference Lo organized around the themes of the paper and approached his former professor about an idea he had. He wanted to apply the approach Lo advocated to the world of rare disease. As it turned out, Lo had a preprint of another paper he had been working on that applied the model to rare diseases, which he believed was even better suited for such an approach because of a more streamlined development path and incentives established through the Orphan Drug Act.

In 2015, Kumar and a number of other co-founders including Lo, launched BridgeBio, to develop therapies for rare genetic diseases and genetically-defined cancers. The company's name is meant to suggest a bridge across the valley of death. BridgeBio licenses therapeutic candidates from universities and research institutes that are good at innovation but lack the capital and expertise to advance these candidates through clinical development. It may also license an asset from a biopharmaceutical company that abandoned it in development because of a change in strategy, or because it has failed in one indication but BridgeBio sees potential for its use in another.

1 Fernandez, J. M., Stein, R. & Lo, A. Commercializing biomedical research through securitization techniques. *Nature Biotechnology* **30**, 964–975 (2012). https://doi.org/10.1038/nbt.2374

2 ibid

LEAN AND FOCUSED

Biotech companies have long liked to boast about big pipelines that provide them with multiple shots on goal, but the financial reality of the substantial capital needed to move a therapeutic candidate through development to market means the fortunes of smaller companies with multiple product candidates often rise and fall with the success or failure of a lead program. "There's a lot more capital in the world that is scared of taking biotech-like binary risk than there is that wants to take that type of risk," said Kumar.

BridgeBio puts Lo's portfolio theory model into practice. When the company finds an asset it wants to develop, it forms a subsidiary company around that asset and charges the subsidiary with advancing the candidate through the development process. These subsidiary companies operate as lean as possible with specialized scientific talent who are incentivized around the subsidiary's success and provided with enough capital to advance the asset to the next decision point.

The company contends it has among the lowest ratios of headcount to development candidate programs in the industry. As of the end of 2020, the company had 385 full-time employees and 11 part-time employees, 268 of whom are focused on driving research and development programs through its affiliates and 128 of whom work across the company to provide strategic business development, finance, and executive leadership. The company assembles teams of fewer than five people around early-stage assets. That number will increase to about ten people as it finishes preclinical development. Once a program is in the clinic, it will size a team as needed with a focus on the minimum viable number of people needed.

Kumar estimates it takes BridgeBio less than $10 million on average through preclinical development and about $30 million for a gene therapy. Part of the ability to run lean comes from minimizing overhead and fixed costs. The parent company's central team provides certain shared support services and workspaces that limit the fixed infrastructure subsidiaries need. For instance, finance functions reside at the parent level.

And to ensure a scientist's or executives' self-interest or commitment to a program doesn't cloud thinking about whether to advance or kill a program, that decision is left to members of a committee at the parent company whose compensation is not tied to any single program, but rather the success of the total enterprise. They are charged with making dispassionate decisions to maximize the value of the company.

"I disagree with the concept that a group of scientists would kill their own project. If they would, I question their passion for it because there's always some parameter that's available to you—there's always some hope for a program, particularly preclinically," said Kumar. "You need to divorce the people who are working in a very focused way to make a program successful from the people who ultimately are going to shut it down or keep it going. That is a key aspect of BridgeBio."

Today, the company boasts 20 subsidiaries, more than 30 programs in development, with 19 ongoing clinical trials. [3] It got additional validation for the model at the end of February 2021 when the U.S. Food and Drug Administration approved Nulibry for its affiliate Origin Biosciences. Nulibry is the first treatment for the ultra-rare, genetic, metabolic disorder molybdenum cofactor deficiency type A, the first drug approval for the company. BridgeBio acquired Nulibry as a late-stage asset from Alexion Pharmaceuticals in 2018 for undisclosed terms.

BridgeBio raised $348.5 million in an upsized initial public offering in 2019 to help fund its growing pipeline. It was the largest biotech IPO of that year. Part of the argument for the portfolio approach is that by mitigating the risk typically associated with biotech development, a company could access a much broader range of investors and financing instruments, such as convertible debt, to fund translational research. BridgeBio has done that. Most recently it raised nearly $750 million through an offering of convertible notes in February 2021 that pay 2.25 percent interest.

THE CASE FOR RARE GENETIC DISEASES

BridgeBio focuses on rare genetic diseases because these conditions have clear targets for drug development. The indications it pursues can be tied to a specific genetic mutation and pathway that allows it to develop candidates with mechanisms of action that treat the underlying cause of a disease.

"This is a space where innovation has been incredible in terms of understanding the true causal drivers of disease and being able to map from a genetic aberrant to protein dysfunction, to cell signaling, and ultimately to symptomatology. And that is all happening on the back of cheaper and cheaper exome and genome sequencing and better and better availability of data that marries molecular data like genetic data and symptomatic or phenotypic data," said Kumar. "There's a constellation of technologies that allow us to understand these diseases better than we understand diabetes or a common form of heart failure."

3

Kumar said working from a clear understanding of the mechanism of a disease is an "elegant" type problem that is more akin to engineering than biology. If there is a link between an underlying mutation to a gene and its relation to the symptom and progression of a disease, a drug developer has more information to work with than is typical for larger, less defined syndromes. That, he said, increases the probability for success. In fact, the company noted in its registration statement with the U.S. Securities and Exchange Commission that from 2006 to 2015, drug programs for orphan indications had a 2.5 times higher likelihood of successful development from phase 1 to approval than drugs across all indications.[4]

At the same time, Mendelian diseases—those caused by a mutation to a single gene—represent a large unmet medical need. There are more than 7,400 rare Mendelian phenotypes that have been identified. Nevertheless, since the passage of the Orphan Drug Act in 1983, there are approved therapies for only about 5 percent of these conditions.[5] While rare disease drug development has long been encumbered by a lack of understanding of these conditions, advances in sequencing, progress in understanding the molecular basis of diseases, and the availability of long-term retrospective studies that elucidate the connection between genotype to phenotype is changing that.

A BRIDGE PLATFORM

While BridgeBio is agnostic about the modalities of the medicines it develops—its pipeline runs the gamut from small molecules to gene therapy—there are several critical elements the company looks for when it identifies new programs to pursue. In fact, BridgeBio has mapped the known universe of Mendelian diseases and applied a set of 14 criteria to those conditions to identify potential opportunities of interest. From a scientific perspective, those criteria are intended to determine how well described a disease is, the opportunity to target it at its source, and whether there is a clear genotype/phenotype relationship that could enable the design of a drug. It also takes into account business considerations, such as potential commercial viability of a product, intellectual property positions, prospects for favorable pricing and reimbursement, and the potential impact of competition.

To find new opportunities, BridgeBio has a team of scientists who scour public genetic databases to identify potential new targets while a business development team spends its time on the road engaging with technology licensing offices and academics in search of promising programs and new relationships with research centers.

As a reflection of these efforts, the company in April 2021 announced seven separate collaborations with top academic and research institutions around genetic disease and cancers with clear genetic drivers. That increased the total number of such collaborations to 20 for the company. Though the term and focus of each partnership varies, they involve BridgeBio working closely with outside scientists to identify and fund programs that they may choose to license. Among its partnerships include ones with Boston Children's Hospital, Cincinnati Children's Hospital Medical Center, MD Anderson Cancer Center, the University of California San Francisco, and St. Jude Children's Research.

And while the low R&D productivity of the pharmaceutical industry set off a trend many years ago to externalize innovation, Kumar said that for preclinical assets targeting genetic diseases, there is still a lack of capital and interest, particularly in preclinical small molecule programs focused on rare diseases.

"The premise that we started with was that there's a lot of just great innovation that was going untapped. That was something we were living. I didn't need a data set to tell me that there was no one who really wanted to start with stuff that was three years before the clinic," he said.

While there are aspects of the business that have become increasingly competitive, there are broad swaths of therapeutics that BridgeBio pursues where there are few biopharmaceutical players or venture capital interest. That leaves plenty of opportunity particularly at a time when academia has become adept at identifying interesting starting points for drugs.

A NEW PHASE BEGINS

As BridgeBio begins life as a commercial biotech, it has been thinking how to best extend its model from a development company to a commercial company. That in part is complicated by the nature of markets for rare disease therapies and the need to understand the unique characteristics of patient populations and the physicians who serve them.

While its drug Nulibry has been approved to treat MOCD type A, other programs are in late-stage development. In March, BridgeBio subsidiary QED Therapeutics announced a global collaboration and licensing agreement with Helsinn Group to develop and commercialized QED Therapeutics' FGFR1-3 inhibitor infigratinib in oncology and all other indications except for skeletal

4 BridgeBio Pharma Form S-1 Registration Statement, United States Securities and Exchange Commission, May 24, 2019, Page 120. https://investor.bridgebio.com/node/6571/html, accessed May 8, 2021

5 ibid

dysplasias including achondroplasia, a rare genetic condition and the leading cause of dwarfism. The deal provided QED with more than $100 million in upfront payments and the potential to receive a total of more than $2 billion in milestone payments. The FDA is reviewing an application to approve infigratinib as a treatment for cholangiocarcinoma, a bile duct cancer, in patients with an FGFR2 gene fusion rearrangement.

Under the terms of that agreement, QED and Helsinn will co-commercialize infigratinib in oncology indications in the United States and will share profits and losses equally. Helsinn will have exclusive commercialization rights and lead commercialization for infigratinib in non-skeletal dysplasia indications outside of the U.S., excluding China, Hong Kong and Macau, which are covered by BridgeBio's strategic development and commercialization collaboration with LianBio.

"We've thought a great deal about it. It needs to continue to be focused on the level of the disease so that we can market these drugs in a way that is consistent with who we are as a company, which is a rigorous science company," said Kumar. "But that needs to be centralized, so that we can build capabilities in things like patient outreach services, market access, or distribution, so that we can be the best owner of these compounds as they are ultimately commercialized. Scale there is useful, but it's not going to be the traditional call-point scale."

Article

Foundational Tools for Building a New Bioeconomy

Daniel S. Levine

Journal of Commercial Biotechnology (2021) 26(2), 52–54. doi: 10.5912/jcb992

While biotechnology has been transforming the diagnosis and treatment of disease, it has also been altering everything from the production of crops to how we manufacture goods. Berkeley Lights, which sits at the nexus of biotechnology, microfluidics, and information technology, is playing a critical role in enabling the way living cells can be harnessed as microscopic factories to power the emerging bioeconomy.

Berkeley Lights emerged from the lab of Ming Wu, professor of electrical engineering and computer sciences at the University of California, Berkeley. It was founded in 2011 to commercialize so-called optoelectronic positioning, which uses light to move cells. The company, which bills itself as a digital cell biology company, has an automated technology platform to sort, clone, culture, and analyze tens of thousands of single cells at a time on microfluidic chips and capture their individual activity in great detail.

Using the workflows developed by Berkeley Lights, customers can capture a deep understanding of the behavior of individual cells by recording critical data such as relevant phenotypic characteristics and linking that to genetic information and doing so for thousands of cells in parallel. The workflows—automated processes that begin with the importation of cells into Berkeley Light's Beacon system at one end and exporting data at the other—can allow a user to find the best cell for a desired product.

"It's the most magical piece of technology I've ever seen," said John Cumbers, founder of Synbiobeta, an organization that brings together biological engineers, investors, and entrepreneurs interested in synthetic biology. "It allows for predictable, robust, reproducible, biological systems. We haven't had that ever in biology. That's massive."

Berkeley Lights' approach has been to enable functional testing of single cells throughout its various customers' operations by finding opportunities for them to exploit this ability earlier in their product development process. To do that, the company works closely with potential customers to identify challenges they face and find workflows and assays that can address their problems. It also engages with customers through traditional sales of its equipment and consumables. To expand access to small customers, the company in June launched a subscription-based program known as TechAccess. The subscriptions are offered on a one-year, renewable basis and give customers the ability to benefit from the technology without the need for upfront capital expenditures.

At the heart of the Berkeley Lights platform is a postage-stamp sized consumable chip that contains anywhere from 2,000 to 20,000 individual compartments called "nanopens." Through the use of light, the technology moves individual cells into each pen and then can conduct experiments and take measurements on the performance of each cell. The ability to test thousands of cells on a parallel basis reduces the time it takes to complete experiments from weeks or months to days.

"The challenge today is that these cells express genomic information in a bunch of ways that we just can't accurately predict. And because we can't accurately predict it, we need to do functional testing. And that functional testing is hard," said Eric Hobbs, CEO of Berkeley Lights. "It takes a long time and costs a lot of money. We solve that problem by providing a high-throughput, high-resolution functional test to make sure that the cells are making that cell-based protein that our customers need to be made."

FASTER, BETTER, CHEAPER

Consider the way the Berkeley Lights' platform is transforming the process of antibody discovery. Traditionally, drug developers would use hybridoma technology to create a desired antibody. This involves a process in which a scientist would inject a mouse with an antigen, take the B cells from that mouse once an immune response was detected, and fuse the B cells with a myeloma cell—an immortal B cells—to produce a supply of the antibody.

When creating a hybridoma, it takes about eight to 12 weeks before the cells can be functionally characterized.

And, when the fusion process is performed, a large number of cells are lost, which can destroy the genetic diversity of these cells. It can take a few months before a drug developer can determine whether the process yielded any therapeutic candidates.

By contrast, with the Berkeley Lights technology, B cells from the animals can be placed directly into its system and characterized at an individual level. Within eight hours, the system can determine whether there are therapeutic candidates to pursue.

The biotechnology giant Amgen was an early adopter of the Berkeley Lights technology. It said instead of using thousands of cells to derive a single point of data, it can conduct experiments on single cells with thousands of cells on a single chip. "We can actually see how fast the cells are growing, how much antibody they produce, how effectively the antibodies bind to their target and modify the biology," said Philip Tagari, vice president of research for Amgen in a video published by Amgen. "This technology has changed how Amgen develops cell lines and searches for antibodies. Research that used to take weeks or months can be done in hours or days."[1]

He said the technology will allow the company to solve complex problems that are too hard or too expensive to solve with traditional tools and it will allow the company to search for the one in a million cells that can make extraordinary medicines.

The antibody discovery company Genovac, a Berkeley Lights customer, did a comparative study of the Berkeley Lights technology against conventional hybridoma. Using Berkeley Lights' technology, it was able to find ten times more unique antibody therapeutic candidates, did so in a fifth to a tenth of the time, and did so at one twentieth of the cost compared to the hybridoma process.

EXPANDING WORKFLOWS

Though much of Berkeley Lights early focus has been on the use of its technology in the development of antibody therapies and cell therapies, the growing demand for synthetic biology for industrial applications represents a significant area of potential growth. In 2019, Ginkgo Bioworks, which engineers organisms to replace industrial and pharmaceutical applications, entered into a $150 million, multi-year, non-exclusive agreement with Berkeley Lights to incorporate the company's optofluidic platform into Ginkgo Bioworks' automated genetic engineering foundries.

By incorporating the Berkeley Lights platform into core workflows of Ginkgo's automated foundries, the company said scientists are able to observe and manipulate thousands of individual cells, providing unprecedented control over them. Ginkgo expects the collaboration will drive growth in output and efficiency of its foundries and enable new innovation in synthetic biology and its application across numerous industries from food to fragrances.

The company said it expects the technology to more than triple its capacity to measure the performance of cells, increasing the overall speed and efficiency of product delivery to its customers. The ability to measure and observe the performance of individual cells at a microscopic scale will significantly reduce the time needed for data collection. The company also noted that the Berkeley Lights platform provides data richness from single cell analysis that is currently unavailable in data from conventional bulk measurements.

"We're exponentially improving our ability to engineer biology every year and new technologies like Berkeley Lights' platform are essential to maintaining that pace of improvement," he said. "The Berkeley Lights team has already had an incredible impact on pharma—including cell line development and antibody discovery—and we believe this partnership will bring about a step-change in the speed and scale at which we engineer biology for applications across a variety of industries."[2]

Together, the two companies are also expanding the application of Berkeley Lights' optofluidic platforms through the creation of new workflows available beyond those already released for the biopharmaceutical market. While the existing workflows on the Berkeley Lights platform had been primarily focused on mammalian cells for drug discovery and development, the collaboration with Ginkgo Bioworks will allow Berkeley Lights to generate a number of new workflows, leveraging its platform for several organisms including yeast, bacterial, and fungal cells that will enable the development of a broad range of synthetic biology products.

"We are in an era where cell-based products are changing everything from healthcare and biofuels to

1 The Digital Cell Biology Revolution, Amgen, June 13, 2019, https://www.youtube.com/watch?v=98YeqTfjork, accessed May 14, 2021.

2 Ginkgo Bioworks and Berkeley Lights Bring Unprecedented Speed and Scale to Synthetic Biology with $150MM Collaboration, PR Newswire, October 1, 2019, https://www.prnewswire.com/news-releases/ginkgo-bioworks-and-berkeley-lights-bring-unprecedented-speed-and-scale-to-synthetic-biology-with-150mm-collaboration-300928615.html, accessed May 15, 2021.

agriculture and food," said Keith Breinlinger, CTO of Berkeley Lights. "At the same time, using cells to make new, better, and more efficient products is in its nascency. We believe you will see a huge groundswell in this market in the coming years."[3]

INVESTING IN GROWTH

Berkeley Lights went public in 2020 raising $205 million in an upsized IPO that came above its expected range at $22 a share. Though the company is down from its 52-week high of $113.53 per share, it is trading at around twice its offering price and has a market cap in excess of $2.6 billion.

For the year ending December 31, 2020, the company generated revenue of $64.3 million, a 31 percent increase over the $56.7 million generated for the same period the previous year. It posted a $41.6 million loss for the year compared to a $18.3 million loss in 2019. Despite the challenges posed by the COVID-19 pandemic, the company ended the year with an installed base of 75 platforms, a 56 percent increase over 2019. It has not made any forecast about when it expects to turn profitable, although it has provided guidance that it expects to generate revenue of $90 million to $100 million in 2021.

There should be plenty of room for growth. The three areas the company is initially targeting—antibody therapeutics, cell therapy, and synthetic biology—had products sales of $148 billion in 2019 and are expected to grow to more than $250 billion in the next four years. Together, they represent what Berkeley Lights estimates to be an addressable market opportunity of $23 billion.

The expanding demand for cell-based products, the increasing complexity of these products, and the need for greater precision in the assays used to develop them is helping drive growth for the company. At the same time, the emergence of new therapeutic modalities that require precise functional validation, including multi-specific antibodies, cell, and gene therapies using DNA or mRNA therapeutics, is also driving growth opportunities for the company.

The challenge of manufacturing these therapies is also creating an additional opportunity for Berkeley Lights. It is developing workflows that move the functional validation of manufacturing parameters early into the process, giving customers higher predictability of manufacturing yield and throughput. It is also enabling new manufacturing approaches with higher throughput. In 2020, the company released six new workflows, bringing the total number of commercial workflows to eight, one of which allowed it to move into the expanding markets for cell line development and contract development and manufacturing companies.

Though Berkeley Lights offerings are unique, it does compete against more conventional tools from providers who offer equipment and assays on different machines. Nevertheless, its automated workflows that provide integration into a single package for now provides it with a compelling offering that positions it to grow with the market.

"We know that cells are capable of producing the products and product classes that we need. We, in fact, know that cells are better than humans at manufacturing things like proteins that we just simply chemically and synthetically can't produce yet. The fundamental unit alive—the cell—can make these proteins very efficiently," said Hobbs. "We're right on the cusp of creating that future that we desire. It's right in front of us. And what we have to do and understand is how do we find those cells that produce the products we need? And, I do believe that that's through functional tests and I believe Berkeley Lights provides the highest throughput functional tests available in the market today."

3 ibid

Article

Illumina Accelerator: Next-Gen Corporate Accelerator with a Customer-Creation Focus

Diana Joseph
is the CEO of the Corporate Accelerator Forum (CAF), a curated community by and for corporate innovators who work with startups. CAF delivers the tools, practices, examples and relationships that corporates need to unlock open innovation. Diana is a learning scientist, entrepreneur and regular contributor to JCB.

Amanda Cashin
is Co-Founder and Global Head of Illumina For Startups, which is focused solely on creating an innovation ecosystem for the genomics and multi-omics industry by partnering with leading venture capital investors and entrepreneurs to create, launch, and grow genomics startups.

ABSTRACT

We describe the history, design and expansion of Illumina for Startups — a case that represents a company with strong entrepreneurial capacity engaging in open innovation, through a startup accelerator now expanding internationally with different models. This case highlights the strategy and tactical reasoning behind Illumina's approach.

Journal of Commercial Biotechnology (2021) 26(2), 55–61. doi: 10.5912/jcb993
Keywords: Corporate Innovation Startups Accelerator Genomics

I. CONTEXT

In our 2019 paper,[1] *Four Models for Corporate, Transformative, Open Innovation*, Art Boni and Diana Joseph described four different ways that corporates can and should engage with startups, to be selected depending on the corporate's strategic and tactical innovation capacity. Illumina Accelerator represents an elegant example of the Corporate Accelerator, a direct model suitable for companies with strong innovation-oriented cultures and leadership. The Corporate Accelerator model is a well-known approach made famous by companies like Microsoft, Citrix and Telefonica.[2] (Author Diana Joseph led curriculum development for the Citrix Startup Accelerator in the mid 2010's). Traditionally, a startup accelerator has four key traits: A limited timeframe, a cohort, learning support, and a culminating demo day based on pitching the startup's merits to investors. Accelerators often provide startups with resources like funding, space or equipment, and take a small percentage of equity.[3] Corporates were inspired to form their own accelerators by independent programs such as Y Combinator — an accelerator famous for producing "unicorn" companies with relatively small outlays of capital and resources on the accelerator's part.

Corporate accelerators have fluctuated in popularity over time, with programs opening and closing on a regular basis. For example, the Citrix Startup Accelerator opened in 2010 and closed in 2016.

The genomics sequencing company Illumina created its accelerator in 2014 and has only increased its footprint and impact. What has made Illumina Accelerator shine, and how might other corporates benefit from its example? Illumina for Startups is Illumina's way of accelerating innovation in the entrepreneurial community by partnering with leading venture capital investors and entrepreneurs to create, launch and grow genomics startups. Illumina for Startups initiatives include Illumina Accelerator SF Bay Area, founded in 2014; Illumina Accelerator Cambridge, UK, founded in 2020; and Sequoia Capital China Intelligent Healthcare Genomics Incubator, Powered by Illumina, launching Fall 2021. In collaboration with startups and venture capital investors, Illumina for Startups advances breakthrough applications in genomics and multi-omics, including therapeutics, diagnostics, agriculture, synthetic biology, software and direct-to-consumer applications. In this

article, we describe the history, principled design and future of Illumina for Startups, and highlight key lessons to inform corporate decision-making about startup engagement.

II. HISTORY

Illumina Accelerator was founded in 2014 when former CTO Mostafa Ronaghi, a successful serial entrepreneur, successfully made the case for an accelerator to Illumina's leadership team and board. He identified four key motives: Create, grow and stay close to the market. Get exposed to emerging applications. Partner with the brightest entrepreneurs and investors in the field, and obtain an equity stake in emerging companies and generate a financial return.

Illumina's mission is to "improve human health by unlocking the power of the genome," and Illumina recognizes that fulfilling this mission is necessarily a collaborative effort. Illumina has a very specific role to play in the ecosystem — namely, that of a sequencing technology innovation company. The purpose of Illumina Accelerator is to catalyze the startup innovation ecosystem.

Innovation maturity

In *Four Models for Corporate, Transformative, Open Innovation*[1], we argued that corporates need to choose the right open innovation model based on their operational and cultural maturity. As a corporate seeking to innovate with startups, Illumina has the advantage of being close to its entrepreneurial roots. Founding CEO Jay Flatley and other C-suite leaders were entrepreneurs themselves.[4] They were familiar with how startups work, operationally, technically and socially. They were ready as leaders to champion the risks of working with startups. In addition, Illumina's culture fosters entrepreneurial mindsets and behavior, for example in the corporate values below (see Figure 1). Illumina is widely recognized for its breakthrough innovation. "Flatley's Law" is Illumina's answer to "Moore's law" — through Illumina's leadership, size, speed and cost of sequencing machines are improving even faster than the tech industry's standard. In short, Illumina was already mature in its operational, strategic and cultural innovation readiness. When Ronaghi brought forward the accelerator concept, company leadership was very much ready to receive it — by consensus committing resources toward lab space and personnel.

Creating the right team

By the time this approval came through, Ronaghi already had his eye on Amanda Cashin to lead Illumina Accelerator. Cashin, an author of this paper, was a trained PhD-level chemical biologist turned successful corporate investment leader. Her deep ties into the life science investment ecosystem and her entrepreneurial spirit brought her to Ronaghi's attention. They first connected at an industry dinner where Ronaghi was struck by Cashin's breadth of investment experience across life science therapeutics, diagnostics, and research tools as well as her track record of picking winning investments. Technical expertise, business expertise, track record, and network: Clearly Cashin was a great fit for the leadership role. But hiring her was by no means a foregone conclusion.

Overcoming assumptions

Cashin notes: In 2013, when she first heard that Illumina was considering an accelerator, she was skeptical — a position many corporate innovation leaders share. This skepticism is reasonable. As of 2013, many corporate-startup programs had disappeared, including Citrix Startup Accelerator (where author Diana Joseph had led the Accelerator's curriculum function), the Pfizer Incubator[6] and Biogen Idec's.[7,8] Cashin perceived these abandoned vehicles as lacking sustained internal

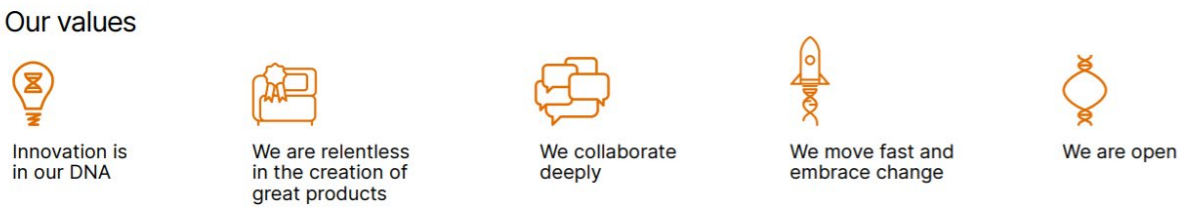

Figure 1 From Illumina (2020) Corporate Social Responsibility Report[5]

support, lacking strategic fit, and worse yet, risking damage to the startups who participated. Cashin was in fact so skeptical that when she received Ronaghi's job posting for a Head of Illumina Accelerator, she forwarded it on to other candidates.

Ronaghi knew Cashin through the San Francisco Bay Area bioscience business community and by reputation, so he reached out to her directly. Over a cup of coffee, Ronaghi and Cashin realized they had a similar vision, and together they could create a sustainable corporate accelerator at Illumina that would be purposefully designed with two important principles in mind:

*__Founder-friendly__. As a recent entrepreneur himself, Ronaghi understood what this meant in practice and was fully committed to centralizing this principle as a foundation in the design of the program.

*__Ecosystem-focused.__ The purpose of Illumina Accelerator is tied to the ecosystem necessary to the company's long-term health — not to any short-term metric.

With these considerations addressed, Amanda joined the team as its founding leader.

Together, CTO Ronaghi and Head of Accelerator Cashin covered bioscience expertise, entrepreneurial experience and bioscience investor background. The team also included a key scientist who could guide experiment design and use of Illumina's sophisticated DNA sequencing instruments to form the original team.

Accomplished track record

Over the past nearly seven years, across two sites, Illumina Accelerator has launched 54 startups who have collectively raised over $1B in venture capital from leading VC firms. Impressively, 93% of the Illumina Accelerator graduates to date have gone on to raise capital. Approximately 56% of Illumina Accelerator startups have a female co-founder, 22% are led by a female CEO. And, 85% of the capital raised by Illumina Accelerator startups was secured by teams with female co-founder(s).

Now reporting to Illumina's current CTO Alex Aravanis, Cashin remains at the helm in leading a talented global team of investment professionals, company builders, genomics experts and ecosystem developers.

III. DESIGN OF ILLUMINA ACCELERATOR

The Illumina Accelerator design is inspired by well-known startup engines in technology and biotechnology, including the classic accelerator Y Combinator and top tier life sciences VCs known for company creation.

What is the design of the startups' journey?

From the standpoint of a startup, the Illumina Accelerator journey looks like this:

*_Application_: A startup finds Illumina Accelerator through a variety of routes. They may already know Illumina Accelerator and its excellent reputation and visibility in the genomics space. In addition, startups are often well connected to Illumina employees and commercial networks, who can help a startup determine if Illumina Accelerator is the right fit for them. And, fellow entrepreneurs and VCs frequently recommend startups to apply to Illumina Accelerator. Startups complete Illumina Accelerator's straightforward four-page application.

*_Selection_: Candidate teams visit Illumina Accelerator in person (during non-pandemic times). This visit serves to demonstrate commitment on the part of the startup and to provide insight into the team and team dynamics – ultimately Illumina Accelerator vets whether the team is VC backable. Illumina Accelerator then selects a non-competitive cohort of three to five startups per site with strong teams who stand to benefit from Illumina's technology and guidance. Notably, the selected startups are pursuing breakthrough genomics ideas downstream or upstream of Illumina's sequencing technology — never in the same space as Illumina.

*_Onboarding_: Selected teams form a partnership with Illumina Accelerator, committing to work onsite for the six-month funding cycle and to provide 8% equity in return for access to space, expertise, Illumina sequencing equipment and consumables, business and technology coaching, as well as potential funding from third-party investors.

*_Residency_: Startup teams move into Illumina Accelerator's site in the San Francisco Bay Area or in Cambridge, UK, which are co-located with Illumina's innovation campuses. During this six-month funding cycle, the Illumina Accelerator team provides weekly coaching and selectively pulls in internal and external experts on an as-needed basis. Startup teams meet a network of sophisticated seed and VC investors along the way, for example during a private investor roundtable that helps kickoff fundraising. Illumina Accelerator intentionally

neither requires nor offers a structured curriculum for startups to follow. By definition, startups thrive in flexible environments and require agency to achieve their vision. The Illumina Accelerator team's role is to guide founders to dream big, stay focused, and pursue the path that makes them successful.

*_Graduation_: Upon completing the six-month funding cycle, the startups have achieved significant business and technical milestones, generated terabases of sequencing data on Illumina's platforms, grown their teams, and raised capital. Graduation is marked with a simple internal celebration.

*_Post-Accelerator_: Once a startup graduates from Illumina Accelerator, it's not the end of the road for the relationship. As a common shareholder in each startup, Illumina Accelerator is incentivized to continue to support and nurture the graduates along their journeys. The graduates continue to draw on the Illumina Accelerator network, including other portfolio founders, investors and industry experts for advice on fundraising, building teams, strategy, and scaling up.

What makes Illumina Accelerator's design founder-friendly?

To attract the best entrepreneurs from across the globe, Illumina Accelerator was intentionally designed to be founder friendly.

*__Interests are aligned__ with the founders and the co-investors in seeking both a financial return (through Illumina's equity stake in each startup) and in making an impact in human health and beyond. By partnering with startups, Illumina has potential financial upside and the startups are helping Illumina achieve its mission of unlocking the power of the genome to improve human health.

*Illumina Accelerator companies are Illumina **customers**, and purposefully not potential acquisition targets to bolster Illumina's pipeline. This strategy sends a clear signal to the market — all participating startups are high-quality and supported by Illumina. Decisions about exit opportunities and investment opportunities are driven by the market, not Illumina.

*Illumina's **brand is enhancing** for its startups. Illumina is a/the leading brand in the genomics sequencing space — Illumina's expertise and presence on the cap table validates the quality of the early stage startup.

*Illumina Accelerator religiously **respects founders' time**. In addition, while Illumina Accelerator very much wants to see interaction between its startups and Illumina employees, they are strict about ensuring that this only happens when it benefits the startups. Typically this kind of contact is pull-only — Illumina Accelerator leaders reach out to arrange contact with Illumina employees when and only when their expertise will benefit a startup. Illumina employees take this role very seriously, for example, Ronaghi himself typically dedicated significant time mentoring companies.[9]

IV. GOING GLOBAL

After working for over 3.5 years and 7 cohorts of startups, the Illumina Accelerator team summed up their findings, and reported them to the C-Suite and Board of Directors. The team felt they were onto something valuable and were ready to expand. Leadership never blinked — they supported the move to go global immediately.

In the background of all of this decision-making, Cashin tapped into the wisdom of non-competitive peers through the Corporate Accelerator Forum (CAF) — Cashin is a founding advisor and sponsor for CAF, co-author Diana Joseph is CEO. This curated community of corporate innovators who work with startups delivers the tools, practices, cases and relationships that corporates need to unlock open innovation. Joseph invited Cashin to bring the "Going Global" challenge to the CAF Annual Meeting in 2019. Acting as a "discussion host," Cashin raised the question of how best to go global to a self-selected group of 10 or so other large organizations with similar startup engagement programs. A key takeaway for Cashin — in each location, determine which elements should be shared with the home-base site, and which can change, balancing efficiency and consistency, with local conditions. In a similar environment like Cambridge, 80% of the framework can match its parent site. In a very different environment like China, perhaps only 20% will match. The team identified a core set of non-negotiable elements, and allowed the rest to adapt as needed for the region.

Cambridge, UK

With the decision to "go global" made, the next question was where, and how. China was a compelling choice given the size of the market and dramatic trends in sequencing activity in the late 2010s. Still, the challenges were significant — distance, cultural and economic differences would have to be considered. In this moment

of possibility, Illumina's commercial leader in Europe, Middle East, and Africa saw the penny drop from her vantage point – the United Kingdom was entering a sweet spot of timing: the United Kingdom had become a global leader in genomics investment, and Cambridge was ripe for new company creation in genomics. The Illumina Accelerator team from San Francisco flew to London and received a warm welcome from VCs, startups and other ecosystem partners. The message: Now is the time for the UK! In 2020, Illumina Accelerator opened its second site, co-located with Illumina's innovation center, in Cambridge — during a pandemic! Generally speaking the UK site followed the Bay Area site's playbook: secure space adjacent to Illumina's innovation campus, secure third-party funding, apply the company creation framework, learn and tune the system cohort by cohort.

Shanghai, China

By starting in Cambridge, Illumina bought itself more time to sort out a model that would make productive sense in China — a very different setting than the SF Bay Area in terms of national culture, entrepreneurial culture and the economy. In January of 2021, Illumina announced the Fall 2021 opening of *Sequoia Capital China Intelligent Healthcare Genomics Incubator, Powered by Illumina*.[10] The genomics incubator in China carries the strengths and relationships of a local world-class partner in Sequoia Capital China and is located in a central innovation district in Shanghai. This approach simultaneously leverages Sequoia's track record in backing companies in China, and Illumina's track record in creating genomics startups. The genomics incubator follows a customized playbook for Greater China: secure a local VC partner that can not only fund the startups but also run the incubator, apply the company creation framework, learn and tune the system cohort by cohort.

Broadened Strategy

Clearly the global expansion demanded a larger staff, new offices and advanced teamwork. To ramp up this new Illumina for Startups model swiftly and smoothly, Cashin brought in Martin Global Leaders who provided team and executive coaching in Q1 2020. This become more complex quickly with the COVID-19 pandemic. From April 2020 to Summer 2021, team coaching addressed six major arenas:

- Build strong trust and working relationships
- Become aligned on objectives and strategy and stakeholder expectations
- Develop standardized processes for expansion
- Help team members support each other dealing with working from home
- Learn tools and protocols for advanced team learning

Martin Global Leaders CEO, Craig Martin comments: "It is remarkable how this team came together powerfully to create a new global operation during a time of great upheaval, while not missing a beat supporting their startups. It's a great example of teamwork that in turn benefits the startups and their ability to bring new innovations to the market."

With a seven-year track record, Illumina for Startups continues to broaden its strategy and double down on the future: Expect to see new models with new partners in new locations, expanding to companies at every stage in the startup lifecycle.

V. CONCLUSION: FIVE KEY QUESTIONS TO ASK IF YOU'RE DESIGNING AN ACCELERATOR

Over the last five years at the Corporate Accelerator Forum, we've studied dozens of corporate-startup engagement engines, from formal accelerators like Illumina Accelerator, to incubators like Bayer CoLaborator, to third-party supported programs such as Techstars and Plug & Play, to internal incubators, to corporate VCs and scouting programs. Based on these investigations, we've come to understand several important lessons this Illumina Accelerator case elegantly reveals.

If you're a corporate innovator eager to work with startups, ask yourself these five questions:

1. *Why do you want to engage with startups?*
Crystal-clear goals will keep you on track in designing, executing and monitoring your program. Is your goal to stay at the cutting edge of your field? To explore new markets? To improve your technology? To be recognized as an innovator? To foster an internal entrepreneurial culture? Each of these goals would drive a different design and a different set of metrics and key resonating stories.
Illumina's goals were crystal clear: to catalyze new market applications for Illumina's technology. Their startup engagement engine was shaped to address this goal by fostering a thriving startup ecosystem and building future customers.

2. *What is your company's appetite for startup engagement*?

What is your company's current capacity for innovation? To what degree are senior leaders prepared to champion innovation and entrepreneurial behavior? Do they themselves have an entrepreneurial track record? How is the culture set to support innovation — for example, are incentives in place to reward risk-taking?

Illumina began with a strong entrepreneurial culture and leadership eager to commit their own time to the project.

3. *What is your plan to maintain alignment with internal stakeholders?*

How will you set expectations at all levels? What metrics and key resonating stories will you use to communicate progress, and how often? A design and metrics tool to consider is the Innovation Dashboard 2.0 — the Dashboard acts as a one-page canvas for making expectations explicit and shared.[11] Illumina Accelerator influenced the development of the dashboard.

Illumina maintains a very strong relationship between Illumina for Startups and the C-Suite, based on personal time spent on a day-to-day basis, as well as regular leadership presentations.

4. *What is your plan to maintain alignment with startups?*

The startup world is small — corporates develop a reputation very quickly. Why will your startups sing your praises? How will you align your incentives with those of the startup founders? How will you ensure that your signals to the market are positive so that even companies you don't acquire are glad they had the experience?

Illumina Accelerator's design is very careful in this regard: Startup partners are upstream or downstream from Illumina's technology, equity aligns incentives on both sides, cohorts in each site are selected to preclude startups that compete with each other, and startup's time is treated as precious.

5. *How will you leverage best practices and prior art?*

Where will you go for advice, stories and examples from the front line of corporate-startup partnership to learn from others' experience?

Amanda Cashin draws on her Corporate Accelerator Forum experience as a regular component of her startup engagement work. A weekly live CAF audio session called Weak Signals allows her to practice forecasting based on small market observations. The bi-weekly public CAF WaterCooler is there when she is looking to expand her network. Bi-weekly private CAF members-only sessions provide ad-hoc consulting. As a Founding Sponsor, Cashin sits on the leadership team to guide the Forum calendar, and therefore her most compelling questions are addressed directly – for example, the "Going Global" session described above. And the CAF Annual Meeting brings together corporate open innovators in a carefully crafted, curated, private conversation where Cashin can speak frankly, and frankly provide feedback to her colleagues in this setting designed for corporate innovators, by corporate innovators.

Answer these five questions as a foundation to selecting the right model, the right goals and the right expectations for your company.

Because Illumina Accelerator had clear answers to the questions above, as well as clear goals and expectations, its designers were able to zero in on a logical key that resolved many of its challenges: They chose to focus the accelerator on Illumina's customers. Customers don't compete with the corporate. Customers understand that when they do better, the corporate does better. Appearing on your customer's cap table is a strong positive signal. Customers' experience informs the corporate about markets. The corporate CFO, CTO, CEO and COO are all on the same page about wanting customers to thrive.

Collaborating with customers is not the only path to a strong and sustainable accelerator design logic — the key is to understand the corporate context and zero in on a design that aligns goals and expectations from the start.

In these dynamic times, corporations do not have the luxury of sitting on the sidelines of innovation. Sticking to the core is more comfortable than doing something new — but it may be even more risky. While we don't know exactly which disruptions will occur, or when, or from where. But we can be certain that *some* disruption will occur that will be material for every organization. The COVID-19 pandemic has made that abundantly clear. As innovation author Adi Mazor Kario[12] says to corporates: Innovation is your insurance policy!

There are as many paths to startup engagement as there are corporates — each organization has its own strategy, ecosystem, strengths, weaknesses, opportunities and threats. The story of Illumina for Startups describes one compelling, logically consistent path to startup engagement that measurably serves both its internal and external stakeholders. What will be your path?

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Article

Abridge: A Mission Driven Approach to Machine Learning for Healthcare Conversation

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ABSTRACT

In this brief case study, we describe an approach to structuring and summarizing information from one of the largest untapped sources of data in healthcare delivery — spoken conversations. Abridge's mission is to shift agency to the people and families at the center of those spoken conversations, using bleeding-edge machine learning and human-centered design. The space of conversation understanding is largely untapped and we will discuss our scientific approaches to business challenges that map to the company's mission of helping everyone better understand and follow through on their healthcare conversations.

Journal of Commercial Biotechnology (2021) 26(2), 62–66. doi: 10.5912/jcb994

INTRODUCTION

Our core thesis is that healthcare is driven by spoken conversations. There are 883.7M [1] spoken doctor-patient conversations every year in the United States. And there are over 2 billion conversations when also accounting for conversations that people have with nurses, pharmacists, care managers, and other healthcare professionals. We believe that the highest leverage care for those with chronic diseases such as diabetes, cardiac disease, and cancer, is delivered via these spoken conversations as opposed to an asynchronous text message or chatbot. In addition, we know that these spoken conversations are actually upstream and less dependent on hegemonic healthcare IT systems such as the Electronic Medical Record.

We founded Abridge with a mission to help people better understand and follow through on those conversations. In addition, and using the same underlying technology, Abridge helps healthcare professionals across Payers, Providers, and Pharma save time in their own professional workflows. That professional value maps to large markets in and of themselves — for example, provider documentation itself is a $4-10B market [2] in the United States. At a broader and more systemic level, technology that can improve the quality of healthcare conversations can address many of the efficiencies and waste in the US healthcare system. That waste on aggregate represents costs of $760–$930B, representing 25% of total healthcare expenditures [3].

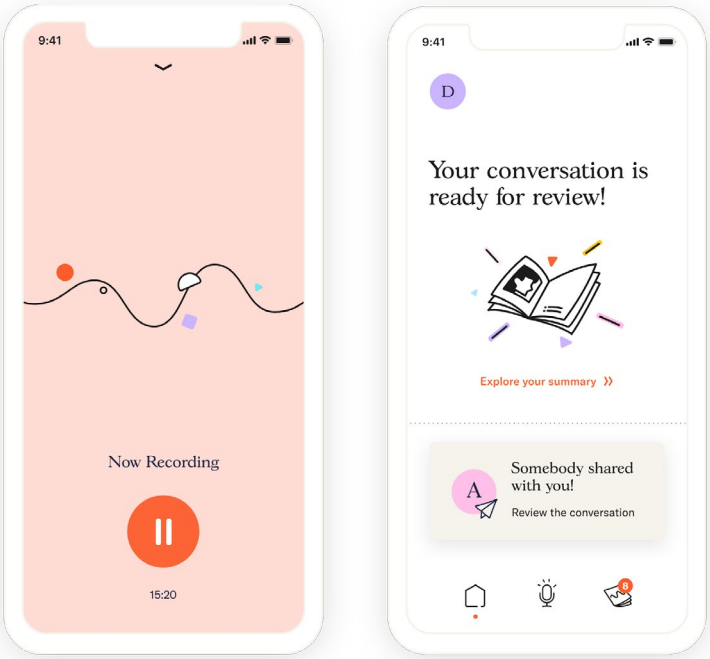
In this case study, we offer a high level description of the end user pain point and solution that we are focused on, and also highlight aspects of the machine learning research that underpin the end user experience we deliver to our users.

PROBLEM AND SOLUTION

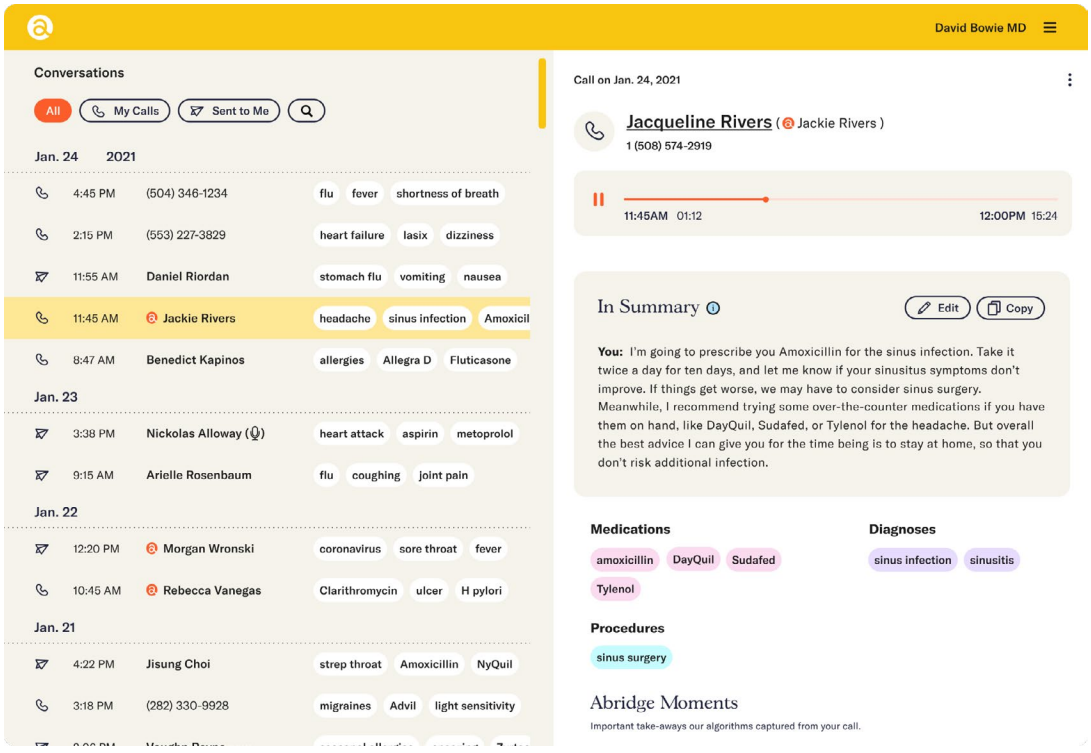
People forget up to 80% of what they hear in medical conversations [4]. In fact, studies show that half of all patients walk away from medical conversations unclear on what they were just told, unless they took notes or had someone accompany them. Poor recall, understanding, and follow-through leads to poor outcomes, especially given that healthcare is powered in large part by these spoken conversations. For example, adherence to care plans can be as low as 50% for chronic disease patients, and poor adherence in diabetes alone costs $25B annually.

Our solution includes a mobile phone application that any person can download to immediately begin recording their health related conversations.

On the healthcare professional side, Abridge can integrate with any modern telemedicine solution and



Abridge App



Abridge Professional Dashboard

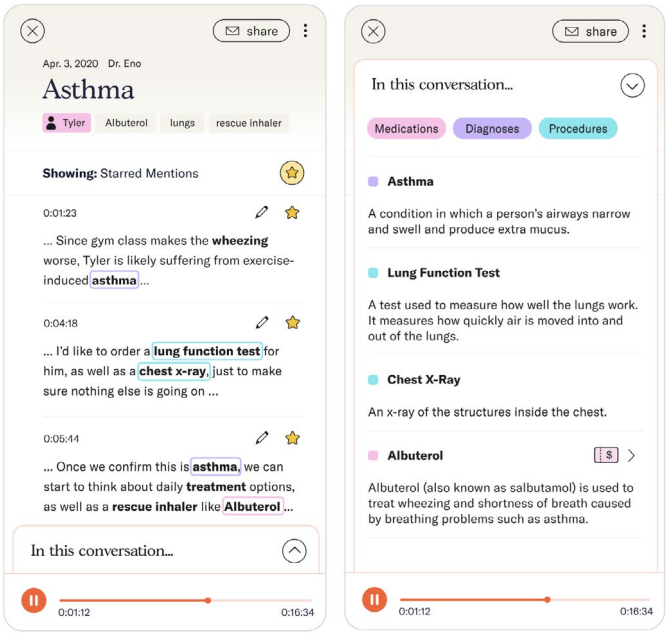
also offers a full stack solution for telephone and video calls. Patients can access those professional – initiated Abridge conversations via the consumer mobile application as above. In this way, when Abridge is a part of the conversation, patients as well as healthcare professionals and their associated enterprise systems can benefit.

POWERED BY ARTIFICIAL INTELLIGENCE

Machine learning powers many of the key features that help patients and healthcare professionals alike derive more value from their conversations. Since inception, the company has invested heavily into Artificial Intelligence challenges that map to the mission of helping people better understand and follow through on their medical conversations. At this time, the company has published 10 papers [5] on spoken medical conversation AI. These papers are centered on challenges around transcribing, summarizing, classifying, and extracting relevant information from medical conversations. In the following sections, we present an overview of some key mission-driven machine learning challenges.

1. Better Understanding:

To help people better understand their medical conversation, our machine learning algorithms transcribe, extract and highlight the key clinical concepts, and define the medical jargon at a consumer reading level. Complex medical terminology, accents, interruptions, overlapping speech, false starts, and filler words like "umm" and "okay" all make it harder for an algorithm to track a conversation correctly [6]. Abridge algorithms need to accurately capture the words in each conversation before they can determine which parts of the conversation are important to people's health. That's why we tackle challenges and contribute to research in Automatic Speech Recognition (ASR), the field of machine learning dedicated to the transcription of speech. We also use machine learning to adapt, or correct, off-the-shelf ASR systems to improve the transcription accuracy of medical terminology. We've trained our algorithms to focus more on medical concepts, and to understand relevant bits of context that might be spread across each conversation [7] [8]. The output of our ASR system — the transcript — is passed through our clinical concept extraction pipeline, which highlights medications, diagnoses, and procedures. Some of these key medical terms are then linked with concise explanations from our trusted content partners, including the National Library of Medicine and the Mayo Clinic.



[On the left] Transcribed medical parts of the conversation with clinical concepts highlighted, [On the right] Definitions curated with help from our trusted partners such as the Mayo Clinic

2. Better Follow through:

To help people better follow through on their care plan, we built a machine learning model [9][10] that can classify utterances from medical conversations according to (i) whether they were more likely spoken by a doctor or patient, and (ii) where they might be classified into specific sections of a doctor's note that a patient would benefit from understanding. We adopted a widely-accepted SOAP Note template that contains:

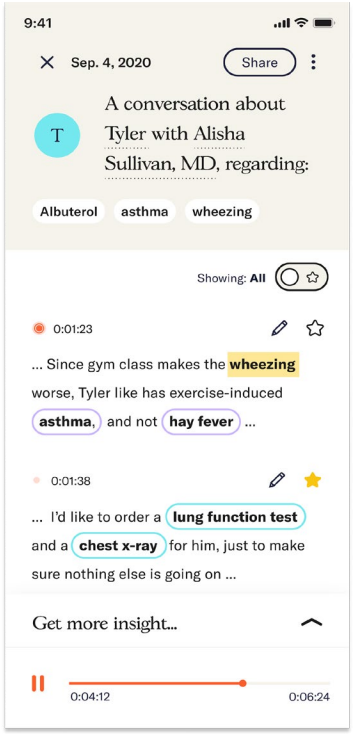
- **Subjective:** The "story" from the patient about why they are visiting.
- **Objective**: The objective record of the doctor's physical examination and review of diagnostic results.
- **Assessment**: A summary of the doctor's decision-making process and diagnoses.
- **Plan**: The doctor's next steps for the patient based upon their Assessment.

Using the above four classes, we formulated a multi-label classification problem and built a classifier that can identify clinically relevant parts of the conversation. For this classifier to perform well on ASR transcripts as input, we also developed a method for mapping human annotations from a clear, high-quality signal (the human transcript) to a noisier signal (the ASR transcript). Training our models on the ASR dataset made our systems more robust to the types of noise injected by ASR systems.

In addition to the above classification work, we also tackled research challenges around extracting structured information from the conversations. We focused primarily on two information extraction challenges so far: 1) Medication Regimen extraction [11] [12] and 2) Appointment extraction [13]. These systems can help our users in medication adherence and in keeping their appointments.

In the medication regimen extraction work, we specifically focus on frequency, route of the medication and any change in the medication's dosage or frequency. For example, given the conversation excerpt and the medication "Fosamax" as shown in the figure below, the model needs to extract the spans "one pill on Monday and one on Thursday", "pill" and "you take" for attributes frequency, route and change, respectively.

In the appointment extraction work, we focus on extracting the appointment reason and time spans from medical conversations as shown in the figure below. The reason span refers to a phrase that corresponds to diagnostics, procedures, follow-ups, and referrals. The time span refers to a phrase that corresponds to the time of the appointment.



Care plan "starred" by our machine learning classifier

DR: Limiting your alcohol consumption is important, so, and, um, so, you know, I would recommend vitamin D[1] to be taken[1]. Have you had Fosamax[2] before?
PT: I think my mum did.
DR: Okay, Fosamax[2], you take[2] one pill[2] on Monday and one on Thursday[2].
DR: Do you use much caffine?
PT: No, none.
DR: Okay, this is[3] Actonel[3] and it's one tablet[3] once a month[3].
DR: Do you get a one month or a three months supply in your prescriptions?

An utterance window from a medical conversation annotated with medications and associated attributes: change, route and frequency

DR: And the thing with angiogram, uh, um, um, we already scheduled, uh, the days I do it is Mondays and on Fridays. That's the best time for me to do the angiogram.
DR: Um, yeah, I, I guess I could make it Monday next week.
DR: Or next, or Friday?
DR: Which one is better for you?
PT: Um, well, it's already - Today is, uh, uh, Tuesday.
DR: Yeah, let's do it as soon as possible.
PT: Okay, let's do it on Monday.

An utterance window from a medical conversation annotated with appointment reasons and time span

CONCLUSION

In this case study, we cover the founding thesis around which we started Abridge and briefly discuss the market, user pain points, and the patient centered solution currently being used across the United States. We specifically focus on the machine learning challenges we've been tackling in our effort to transcribe, classify, extract, and understand the medical conversations exchanged between patients and healthcare professionals. In future editions, we hope to cover regulatory challenges, go-to-market strategy and product adoption.

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Article

A Case Study – NeuBase Therapeutics, Inc.

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ABSTRACT

Please modify abstract to: NeuBase is a genetic medicines platform company that is developing a new type of therapy that is able to drug the human genome to increase, decrease or change gene function with single-base precision and high tolerability to resolve genetic defects that drive most diseases.

Journal of Commercial Biotechnology (2021) 26(2), 67–2. doi: 10.5912/jcb995

DISCUSSION

We are in the midst of a fundamental transformation in the pharmaceutical industry. We are witnessing the shift from an analog mode of drug discovery to a digital mode, accompanied by the efficiencies that come with such shifts – increased performance, scalability and cost reductions.

Since the beginning of the era of modern medicine, drug development efforts have primarily focused on brute force approaches such as screening vast chemical libraries against a disease target to identify those which positively affect the disease process. Thereafter, often years of chemical optimization efforts ensued to maximize potency while minimizing toxicity. High-throughput screening was necessary primarily due to ambiguities in how to engage dynamic structures such as proteins within patient cells to ameliorate disease processes. The time and expense necessary to move from target selection to nominating a candidate for clinical studies essentially made each drug development effort an expensive and bespoke endeavor. As a result, most diseases remain intractable today. Consider this as an analog approach in that we use information represented by continuously variable spatial positions between, for example, a small molecule and its interaction points with proteins to optimize for potency and selectivity.

As a result of the sequencing of the human genome, more than two decades of pathogenic genetic variant discovery efforts and databasing, the establishment of global infrastructure to perform genetic testing of patients and concurrently computational infrastructure and expertise, we have set the stage to be able to address diseases at the genetic level using a digital strategy.

New therapies have emerged as proof-points of this new digital era in the pharmaceutical industry. Gene replacement/activation, gene silencing and gene editing all target misbehaving genes directly, the true root causes of most human diseases, through Watson-Crick base-pairing for binary (at the nucleobase level) target engagement.

NeuBase Therapeutics' platform technology engages genetic targets in a sequence specific manner to increase, decrease or edit gene function to address the majority of causal mechanisms undergirding human diseases in a unifying approach with ultra-high precision of target engagement and a well-tolerated chemistry. The compounds that are produced look conceptually like single stranded short oligonucleotides, but due to the chemistry that is used, they have advantages over other genetic medicines. The "backbone" of the oligo is made of modified peptides, onto which are coupled nucleobases in a sequence that engages a nucleic acid target of interest in a sequence-specific (binary) manner. These are termed peptide-nucleic acids (PNAs). Due to a neutral charged backbone and the resultant high-affinity engagement, the oligos can invade into double-stranded DNA without being repulsed and engage the target with Watson-Crick base pairing (in addition to a variety of other binding modes to fine-tune rescuing gene function). Importantly, the backbone is also rigid which increases the precision of engagement in that even a single mismatch can cause the drug to disengage and seek a perfect match engagement. These two features allow us to drug the *genome* with *single base precision*, to increase gene

expression, decrease expression, or to edit the genome. As the backbone is a polyamide much like a nylon, it is largely biologically inert. These features form the basis for a growing pipeline of therapies at an increasing rate of output that have the cardinal features one would select for an optimal therapeutic modality: in silico design, target-specific engagement without off-target effects and a well tolerated fundamental chemistry to address a variety of single-gene Mendelian diseases, cancer targets and eventually common diseases.

Because the platform can address all three major causes of disease at the genetic level, there is broad set of targets that are under consideration. The single-base precision of engagement also allows a broadened set of therapeutics targets as many diseases are caused by small mutations (such as missense mutations in dominant diseases) that are largely not addressable by other genetic medicine technologies. This precision also has the potential to reduce off-target engagement which may result in adverse events. Finally, as the backbone appears to have minimal inherent toxicities (for example no innate or acquired immune responses seen to date), the potential for broad impact is notable. Conceptually, this has the potential to be a final generation therapeutic modality.

Related to scalability, as with any platform, the promise is that as one becomes conversant with the technology, that it becomes more efficient over time. We have seen hints of this with various first-generation genetic medicines companies. We have witnessed increasing efficiencies internally as we progress with our various programs. For example, our initial programs required manufacturing and screening hundreds of candidate compounds to identify a few hits, whereas now we are able to screen dozens of candidates to achieve high hit rates. Similarly, as the general non-sequence dependent toxicology profiles become predictable and we can focus on off-target effects (OTEs), the promise to anticipate these off-targets engagements potentially enables the Company to eliminate OTEs *a priori* through careful target sequence selection, or to anticipate them in advance and monitor for them proactively to ensure efficient development.

The Company has announced several programs in areas of large unmet need. For example, in RAS-driven tumors. Approximately 30% of all cancers are caused by mutations in an oncogene named *RAS*. The two most common mutations in *KRAS*, G12D and G12V, remain "undruggable". Investigational compounds have been developed by the Company that are able to engage the mutant copy of the *KRAS* gene selectively and slow tumor growth *in vivo*, in some cases illustrating tumor regression. This can be done at the DNA or at the RNA levels, and result in a lack of production of the mutant protein itself. This is a different strategy that is being used to address a less common mutation, G12C at the protein level with small molecules. Digital drug development with single base precision at the genetic levels has opened a new area of opportunity for patients suffering from a wide range of largely intractable tumor types.

NeuBase is a digital drug development company working to deliver on the promise of the Human Genome Project by outputting genetic medicines that address root causality in an ultra-precise manner across a multiplicity of diseases using a scalable platform strategy. The end result, we believe, will be to improve the lives of patients with a wide variety of diseases through moving the industry from an analog to digital mode with increased efficacy and with increased performance related to efficacy and tolerability, scalability of output to impact many more diseases and development cost reductions which may allow healthcare to become sustainable as we as an industry succeed in the coming decades.

Journal of
COMMERCIAL
BIOTECHNOLOGY
http://CommercialBiotechnology.com

PUBLISHER

The *Journal of Commercial Biotechnology* is published quarterly in Washington, DC by thinkBiotech LLC.

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Print ISSN: 1462-8732
Online ISSN: 1478-565X