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Commentary

Effective Leadership through Bioentrepreneurship and Bioinnovation

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ABSTRACT

Biotechnology firms need leaders that can lead scientists beyond the science and turn new discoveries into commercially viable products. Bioentrepreneurial leaders are continuous learners; they are adaptable to change and flexible, they are not afraid to take risks, and they challenge existing assumptions with the objective of generating greater value through novel bioinnovative discoveries. Without bioentrepreneurial leadership, many discoveries will not make it to the marketplace. Biotechnology scientists, by nature, tend to work for the greater good and hope that their discoveries will benefit mankind. Yet it is often the hyper focus on addressing the scientific and technical aspects of a problem that leads to difficulties. Scientists do not generally have the necessary skills or mindsets required to meet commercial or monetary milestones to successfully commercialize products. Therefore, bioentrepreneurial leaders must themselves be willing to continuously learn and adapt to a dynamic industry and at the same time they must inspire and motivate employees at all levels of biotechnology firm to also learn and adapt. Creativity and innovative thinking are required at all stages, and across all disciplines in the organization. Only when this happen will the firm succeed with new innovations through product development and commercialization.

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INTRODUCTION

The global population has grown exponentially from 3 billion to 7 billion since 1960, and will reach 9.7 billion by 2050. Scientists struggle to keep pace with the growing need and demand for new medicines, treatments and inventions as they attempt to develop tomorrow's innovations today. However, if scientists are to continue to play a pivotal role in building 21st Century biotechnology firms that address the extremity of known and unforeseen conditions and diseases facing our society, a new form of leadership is required.

For biotechnology firms to successfully commercialize the products and services of the future, they need leaders that can lead scientists beyond the science and turn new discoveries into commercially viable products. Effective future leaders of biotechnology firms need to be "bioentrepreneurial leaders" with an entrepreneurial mindset and a bioinnovation focus.

Bioentrerpreneurial leaders have the ability to effectively change the way business is conducted by creating a vision that inspires the team, utilizes its competencies to identify opportunities, and successfully turns those opportunities into breakthrough commercially viable products.

WHAT IS A BIOENTREPRENEURIAL LEADER?

Bioentrepreneurial leaders are continuous learners; they are adaptable to change and flexible, they are not afraid to take risks, and they challenge existing assumptions

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with the objective of generating greater value through novel bioinnovative discoveries. They are futuristic leaders that can make a difference to the world of science and biotechnology and in doing so motivate scientists to create not just a technology but, a commercially viable opportunity. However, bioentrepreneurial leaders know that to succeed, they must surround themselves with exceptional experts in areas beyond their own skillset and trust those experts to act accordingly. This can be challenging because while they may be trained in the science, they may not have the necessary regulatory or clinical expertise to advance the concept from the laboratory to the market.

True Bioentrepreneurial leaders are characterized by their ability to effectively inspire, motivate, be creative and develop their team. They understand that they must ensure the vision of the organization is known at all levels and must inspire everyone in the firm to want to succeed. Inspiration spurs motivation and the bioentrepreneurial leader recognizes that motivation comes from a variety of sources and this is not the same for everyone. For instance, the bioentrepreneurial leader helps to build a culture that aligns personal goals with firm goals. This means that the leader must allow decisions to be made at all levels of the organization, utilizing the competencies and creativity of workers and empowering them to make decisions. Additionally, the bioentrepreneurial leader needs to create a culture where a certain amount of failure is accepted. Failure can be very difficult for biotech leaders to accept when they have traditionally been successful academically and in research. Innovation will only happen in learning organizations that develops teams which means all members of the firm must be able to continuously learn and embrace new opportunities.

BIOENTREPRENEURSHIP AND BIOINNOVATION

Innovation has been recognized as central to entrepreneurship[1] (Hisrich and Kearney, 2013). For biotechnology firms to bring life-changing drugs, diagnostics, and treatments to market, they must master the regulations, funding, patents, FDA approval processes, combined with the increasingly dynamic, complex and competitive external environment. Bioentrepreneurship and bioinnovation are about discovering new innovations in medicines and treatments, and transforming these innovations in ways that can treat and cure diseases that will significantly improve lives, while also building a more competitive firm. Bioentrepreneurial leaders can champion bioinnovative ideas, provide necessary resources or expertise, and ultimately institutionalize the bioentrepreneurial activity within the firm's system and process. When resources are limited, as is often the case in biotechnology firms due to the extreme cost of developing and commercializing products, workers need to know that the leader will do everything possible to remove obstacles and support innovative thinking. Even when inevitable failure happens, the true bioentrepreneurial leader does not blame, but learns.

BIOINNOVATION THROUGH BIOENTREPRENEURIAL LEADERSHIP

Bioentrepreneurial leadership at all levels is at the core of bioinnovation. This becomes even more fundamental with the increased convergence of different areas of expertise (drugs, IT, diagnostics, biomarkers, surgery, robotics and so forth). Again, successful leaders' of such firms must continuously learn and adapt to highly dynamic situations that are often dissimilar in their leadership needs. For instance, the research laboratory is often highly collaborative and processes are easily changed. The product development and production processes may be highly regulated which means processes once defined may not be easily changed. These leaders' must anticipate disruptive market events and trust their key lieutenants to do their jobs—a task that is often difficult when stakes are high. Bioentrepreneurial leaders instill a strong commitment among the team. In doing so they need to identify the key stages of the innovation process specific to their firm and the necessary competencies and technologies that are required at each stage. Additionally, they must utilize all possible resources to identify each potential opportunity for bioinnovation and take appropriate action to accelerate the science that will give the firm a competitive edge. These resources include:

- *Tangible Assets* (such as plant, equipment, finances and location)
- *Human Assets* (employees, their skills and motivation)
- *Intangible Assets* (such as technology [patents and copyrights], culture and reputation).

It is clear that bioinnovation is not a one-time implementation but rather a continuous process that needs to be supported and facilitated by effective bioentrepreneurial leadership that builds the necessary culture throughout the entire organization. Bioentrepreneurship and bioinnovation must be embedded into the culture of the

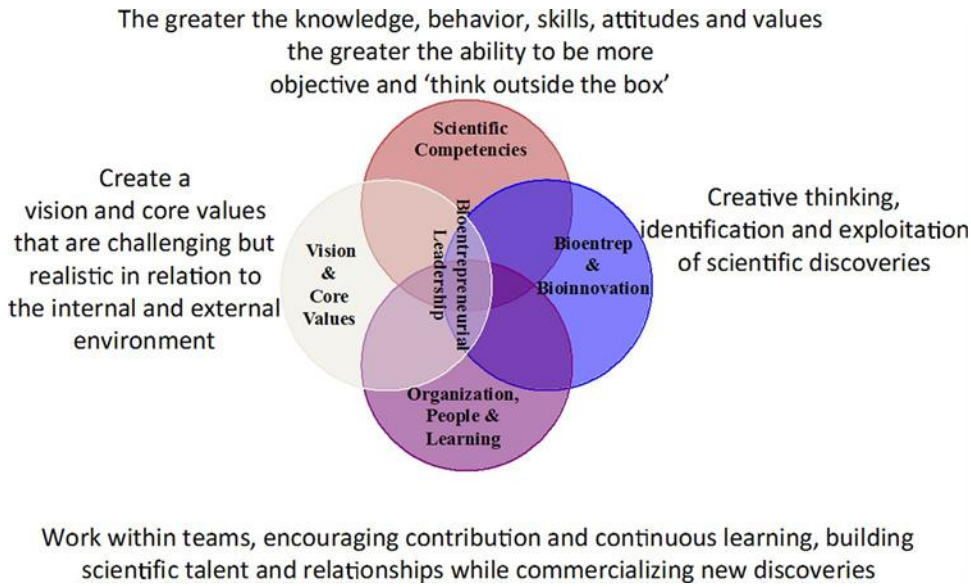

Figure 1: Conceptualizing leadership through bioentrepreneurship and bioinnovation

firm and become the core of 'the way things are done around here'. Bioentrepreneurial leaders recognize the importance of developing and supporting a culture that focuses not only on scientific goals, but also on people and management. This is necessary to create a culture that encourages scientific discovery by eliminating obstacles that inhibit opportunity identification, promotes effective teamwork that utilizes the core scientific competencies of the team, ensures availability of resources and is totally committed to R&D with the objective of commercializing breakthrough scientific discoveries.

As depicted in figure 1, we believe that bioinnovation is manifested through effective bioentrepreneurial leadership. The core role of leader is to continuously learn and adapt and create a shared vision with the whole firm. The leader must utilize the competencies of the team to identify and commercialize new scientific discoveries, in a conducive environment, that supports the team to develop new innovations.

CONCLUSION

Without bioentrepreneurial leadership, many discoveries will not make it to the marketplace. Biotechnology scientists, by nature, tend to work for the greater good and hope that their discoveries will benefit mankind. Yet it is often the hyper focus on addressing the scientific and technical aspects of a problem that leads to difficulties. A dilemma exists, as scientists do not generally have the necessary skills or mindsets required to meet commercial or monetary milestones to successfully commercialize products. Therefore, bioentrepreneurial leaders must themselves be willing to continuously learn and adapt to a dynamic industry and at the same time they must inspire and motivate employees at all levels of biotechnology firm to also learn and adapt. Creativity and innovative thinking are required at all stages, and across all disciplines in the organization. Only when this happen will the firm succeed with new innovations through product development and commercialization.

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Commentary

Patients Suffer While the Science Establishment Resists Innovative Therapies

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ABSTRACT

Human gene therapy has been up to now of a type that affects only the patient being treated; it has not modified sperm or eggs cells or embryos in a way that would constitute "germ line gene therapy" (GLGT) by creating a heritable change and affecting future generations. Preclinical research has progressed almost to the point where GLGT interventions will be possible with a reasonable likelihood of success, but such clinical trials are currently prohibited: NIH's Recombinant DNA Advisory Committee is not permitted even to consider such proposals, and the FDA cannot use appropriated funds to review such trials. Such absolute prohibitions are bad for patients and bad public policy.

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Keywords: gene therapy; germ line gene therapy; somatic cell gene therapy; regulation; genetic disease;

Human gene therapy has been one of the goals of biotechnology since the advent of molecular techniques for genetic modification in the 1970's. There are two distinct conceptual approaches, presenting different kinds of benefits, risks and controversies.

Somatic cell human gene therapy (SHGT) alters genes—either by the editing of genes or the insertion of new ones—in the cells of human subjects, in order to correct conditions present at birth or acquired later in life. (Somatic cells are any cells in the body except eggs or sperm, so modifications in them are not heritable – that is, passed on to offspring.) It can be performed outside the body of the patient (ex vivo), such as by obtaining the patient's cells, modifying and then returning them, or by injecting a virus or some other substance that migrates to a site(s) in the body and modifies the function of a malfunctioning organ.

SHGT has progressed from a proof-of-principle clinical experiment in 1990 to the approval last year of three treatments for serious diseases – two ex vivo treatments (CAR-T therapy) for advanced lymphoma and acute lymphoblastic leukemia, respectively; and for a rare genetic disorder — retinal dystrophy due to a mutation of the RPE65 gene, which causes severe and progressive visual impairment beginning in infancy. SHGT holds promise for afflictions ranging from rare and fatal genetic diseases to Parkinson's; and additional basic research and clinical trials will undoubtedly yield further progress.

Up to now, gene therapy has been of a type that affects only the patient being treated; it has not modified sperm or eggs cells or embryos in a way that would constitute "germ line gene therapy" (GLGT) by creating a heritable change and affecting future generations. But in a proof-of-principle experiment to perform gene editing with a system called CRISPR/Cas9, published in 2015, Chinese researchers reported an unsuccessful attempt to perform germ line gene therapy on embryos that were nonviable and going to be discarded in any case. A firestorm in the scientific community ensued, with some, such as Sangamo BioSciences CEO Edward Lanphier and colleagues in a 2015 commentary, calling for an absolute ban on attempts to treat even lethal diseases with gene editing techniques. Also in that year, Nobel Laureates David Baltimore and Paul Berg and a group of other "interested stakeholders" met to discuss the issue at a conference in Napa, California, and came to similar conclusions: "At present, the potential safety and efficacy issues arising from the use of this technology must

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be thoroughly investigated and understood before any attempts at human engineering are sanctioned, if ever, for clinical testing." *If ever?* Really?

The move toward prohibition gained ground at a December 2015 conference held in Washington under the auspices of national academies of science of the United States, China and the U.K. The attendees called for what amounts to a moratorium on making inheritable changes to the human genome, concluding that it would be "irresponsible to proceed" until the risks were better understood and until there was "broad societal consensus" about such clinical research. These themes were reiterated yet again in a February 22 webinar, "Human Genome Editing: Latest Developments and Advancements" co-hosted by the National Academy of Sciences (NAS), National Academy of Medicine (NAM), and Biotechnology Innovation Organization (BIO).

Those recommendations – coming mainly from people who don't actually treat patients – were the result of the kind of groupthink that dismisses conflicting minority opinions and produces poorly reasoned consensus.

It is unethical to modify normal embryos, but nobody is proposing to do that. For diseases that are genetically dominant, which means an abnormal gene from either parent causes the disease — examples of which include Huntington's Disease, familial hypercholesterolemia, polycystic kidney disease and neurofibromatosis type 1 (the last three of which are relatively common) — one could simply perform pre-implantation genetic diagnosis to identify a normal embryo (the parents' eggs and sperm would produce both affected and unaffected embryos), and then implant it in the uterus, discarding the abnormal ones.

There is no need to manipulate normal embryos. In fact, to perform germline gene therapy it may not even be necessary to manipulate abnormal embryos, because another approach is to generate normal sperm from abnormal ones via tissue culture and gene-editing.

Many of those opposed to germ line gene therapy have waxed nostalgic about a historic meeting of scientists, ethicists and members of the press at Asilomar, California, in 1974, which resulted in a moratorium on recombinant DNA, or gene-splicing, research and, ultimately, highly restrictive, unnecessary research guidelines. They appear to be on the verge of repeating the errors of Asilomar.

What many have forgotten is that at the time, the research community was far from any consensus on the question of whether the existing moratorium or new stringent regulation was necessary. Indeed, many in the scientific community did not regard the Asilomar conference as a success, scientific or intellectual. In fact, the Asilomar cabal misunderstood and exaggerated the potential risks of recombinant DNA technology, modern biotechnology's core technique, and induced NIH to draft and promulgate overly restrictive 'biosafety' guidelines. In the words of historian Jose´ Van Dijck, "In the politicized mood of the 1970s, genetics got annexed as an environmental issue; this new configuration manifested itself in changed images of genetics, genes and geneticists," which were no longer altogether altruistic, or even benign. The modern-day equivalent is political correctness, which obsesses over concepts like inclusiveness, "triggers" and "micro-aggressions."

The NIH's process-based recombinant DNA guidelines, which were, and remain, focused on the use of a single technique instead of on the actual risks of experiments, have plagued genetic engineering research ever since. By assuming from the beginning that recombinant DNA-modified organisms—which were later dubbed "genetically modified organisms" or "GMOs" — were a high-risk category that needed to have regulatory oversight by NIH (which is not a regulatory agency, it should be noted), the NIH guidelines created significant duplication of oversight for many products. Worst of all, they reinforced the misconception that recombinant DNA-modified organisms were a genuine "category." Although NIH gradually pared back the stringency of its guidelines, stultifying process-based approaches to regulation of this *non*-category have remained there and at other federal agencies, including the U.S. EPA, FDA and USDA, and in many foreign countries.

One explanation for much of the excessive regulation of recombinant DNA technology — which later would have adverse consequences for regulations and public perceptions far beyond U.S. borders — resulted from inadequate expertise brought to bear in the initial consultations. At one point, for example, the NIH convened a conference to discuss the possibility that human insulin-producing *E. coli* could colonize the human gut and cause hypoglycemia, immune responses or other problems, but not a single endocrinologist, gastroenterologist or immunologist was invited.

A moratorium on all germ line gene therapy--would be misguided. An appropriate – and, indeed, compelling – application of GLGT would be to correct the debilitating and ultimately lethal sickle-cell anemia, which is marked by atypical hemoglobin molecules that distort red blood cells into a crescent, or sickle, shape. These abnormal blood cells often obstruct small blood vessels, causing frequent infections, pain in the limbs, and damage to various organs, including the lungs, kidneys, spleen and brain.

In genetics terms, sickle-cell anemia is an autosomal recessive disease, which means that a patient inherits a defective hemoglobin gene from both parents, so every one of his or her sets of chromosomes carries a

defective gene. The sickle cell gene bears a mutation in a single nucleotide of DNA, which in turn gives rise to a specific substitution of one amino acid (a valine instead of the glutamic acid found in normal hemoglobin) in a discrete location in the protein chains of hemoglobin. (This elegant, groundbreaking biochemistry was done by Professor Vernon Ingram, my advisor when I was an undergraduate at M.I.T.)

Sickle cell disease is the most common inherited blood disorder in the United States, affecting more than 100,000 patients. What is particularly significant is that unlike genetically dominant afflictions like Huntingdon's disease, *every* offspring of two patients with sickle-cell disease will be afflicted with the disease. Repair of this sort of molecular lesion has been performed successfully in animals for decades, and has become even easier and more reliable with new, highly precise gene-editing techniques – which have been used successfully in mice and monkeys.

However, as discussed by Matthew Porteus and Christina Dann in a 2015 commentary, several technical obstacles currently preclude successful zygote injection in humans, including the fact that "only a fraction of injected zygotes give rise to viable offspring. Tens to hundreds of zygotes would need to be injected and implanted into several surrogate mothers to generate viable, genetically modified offspring." Such an approach would, therefore, with current technology, be neither ethical nor feasible in humans.

Porteus and Dann also warned that that the editing of genomes to correct a disease-causing mutation must not create mutations at other sites, but that reservation has largely been overcome by significant improvements in the precision of gene-editing techniques. They suggest possible alternative approaches to zygote injection that would avoid both of those pitfalls:

> In contrast to the zygote-injection strategy, editing of stem cells that can be propagated *in vitro* enables characterization of the modified stem cells before use in therapy. Spermatogonial stem cells (SSCs) ultimately give rise to haploid sperm. Recent developments in animal models have shown that SSCs can be grown as clones in culture and then transplanted back into the testis to generate sperm. Thus, a potential strategy is to isolate SSCs, use genome editing to precisely correct a disease-causing mutation, perform whole-genome sequencing of clones that have undergone gene correction, and use only the clones that are free from off-target mutations. A related strategy would be to directly generate sperm *in vitro* from edited SSCs to be used for *in vitro* fertilization.

Thus, even though the current state of technology does not permit the therapeutic correction of genetic diseases by means of editing via zygote injection, the two approaches suggested by Porteus and Dann could be attempted now, even for genetically dominant diseases. Certainly further proof-of-concept research should proceed, even if gene-editing of SSCs isn't successful immediately.

Technologies are seldom successful right out of the gate; as they're applied and refined, they improve, sometimes with astonishing rapidity. The first mobile phones and mainframe computers were large, clunky, inefficient and temperamental. When I was a medical student during the 1970's, bone marrow transplants were being performed in only a few institutions and as a last resort, and the success rate was abysmal. But the discovery of potent immunosuppressants and other technical advances improved the success rate markedly; and bone marrow transplants are now routine in many institutions. Some leukemias that were once a death sentence now have cure rates around 90 percent. There are many similar stories in medicine, including open-heart surgery, which was remarkably primitive in its earliest incarnation but which is usually quite routine now.

Interventions that involve germ-line gene therapy should be used sparingly and with scrutiny, to be sure, but we don't need a moratorium. (And at the very least, we must not let skepticism about potential applications that would modify humans interfere with research-based editing of germ cells.)

Ironically, much of the controversy about germ line gene therapy is moot because it cannot be conducted legally in the United States. The FDA is prohibited by statute from evaluating proposals for germ line gene therapy, and Appendix M of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules creates a virtually absolute prohibition on germ line gene therapy:

> RAC [the NIH's Recombinant DNA Advisory Committee] will not at present entertain proposals for germ line alterations but will consider proposals involving somatic cell gene transfer. The purpose of somatic cell gene transfer is to treat an individual patient, e.g., by inserting a properly functioning gene into the subject's somatic cells. Germ line alteration involves a specific attempt to introduce genetic changes into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual's offspring.

As to the scope of its applicability, "Appendix M applies to research conducted at or sponsored by an institution that receives any support for recombinant or synthetic nucleic acid molecule research from NIH," which would appear to rule out germ line gene therapy experiments by researchers at any U.S. academic institution. And given that there is likely to be little interest in germ line therapeutic interventions by companies because of the inability of the FDA to approve clinical trials, public attention and economic considerations, a moratorium is effectively already in place.

Appendix M's prohibition is both puzzling and disturbing. Given that the NIH RAC can reject any proposal for any reason, its unwillingness even to consider an entire category of clinical studies seems unnecessarily intransigent and arbitrary. It's also cruel: Children will die, while potentially life-saving therapies go untested, unproven and delayed indefinitely.

Sound and humane public policy would have the NIH RAC repeal Appendix M and announce its intention to consider carefully crafted human germ line gene therapy proposals that meet the ambient standard for risk-benefit. Ideally, NIH should get out of the business entirely, since FDA and local Institutional Review Boards — not the RAC or NIH officials — have experience with that standard, and they will necessarily be involved, whether or not NIH had a role.

Many maladies have been successfully treated or cured by pushing the frontiers of biotechnology – a stunning recent example of which was reported in the journal *Nature* last November. An experimental gene therapy procedure used to transform and grow sheets of healthy skin saved the life of a 7-year-old boy who suffered from a genetic disease, junctional epidermolysis bullosa, that had blistered and destroyed most of his skin. He was on the verge of death, but two years after the treatment with genetically engineered cells produced by a multi-national team, he has healthy skin and leads a normal life.

Another game-changing biotech innovation almost ready for the clinic is xenotransplantation, the transplanting of animal organs into humans. Improved immunosuppressant drug regimens and increasing numbers of pig lines that have been gene-edited to eliminate antigens that would cause rejection by the human recipient are a potential game-changer. (Interestingly, it involves germ line gene therapy, in order to create breeding lines.) The experiments in which porcine organs have been transplanted into monkeys have been very promising. The availability of animal organs for transplantation into humans will revolutionize our ability to treat organ failure.

If we are eventually to rid families of monstrous genetic diseases, we need to continue the progression toward successful human germ line gene therapy. Mindless, intractable regulation will obstruct that progression.

Article

Turbulence in the Biotechnology Sub-sector of the Western Cape Regional Innovation System

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ABSTRACT

The research was initially designed to complete the study with an investigation of the growth stories of the biotechnology spin-offs from the universities in the study. When it became evident that several of the firms targeted for this in-depth story, were no longer in existence, a more important question became 'why did they fail?' In the search for answers to this question, a tale of turbulence in the sector, and particularly in the environment in which they were to innovate and grow, emerged. This research is novel in that it shows with the aid of the case studies, how a complex series of internal (to the firms) and external factors (in the national and regional innovation systems) combined to lead to the failure of the biotechnology spin-offs. The paper yielded important insights on the unintended consequences of institutional changes. Further, funding for seed and start-up capital remains an obstacle to growth in biotechnology in South Africa. These insights may assist policy makers, technology transfer officers and entrepreneurs in designing and implementing strategies to enhance the development of the biotechnology sector and spin-off creation in general.

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Keywords: university spin-offs (USOs); biotechnology; turbulence; regional innovation system; South Africa

INTRODUCTION

Biotechnology is seen as one of the major growth industries in many countries with applications in different fields, such as health care, agriculture, food and the environment among others.[1–6] Involvement of Small-to-medium size enterprises (SMEs) in the biotechnology sector are the key forces in revealing the biotechnology products and processes to the global marketplace.[3,7] For instance, biotechnology in the United States was pioneered by small biotech firms in the early 1980s.[4] Biotechnology start-up[i] companies require a strong knowledge of the relevant science and a familiarity of business principles, market development and venture capital.[7] Above all else, one of the important factors needed to develop a biotechnology industry in a region is to have a strong entrepreneurial culture meaning that university scientists (researchers) should also look at the commercial exploitation of their results.[8]

Biotechnology spin-off culture in South Africa is much younger than in developed countries. By employing case study methods and with the aid of the three pillars of successful biotechnology commercialisation from the literature, this paper aims to understand the genesis, the characteristics and the trajectories of the biotechnology spin-out companies in Western Cape region, South Africa.

In this paper we are posing the question 'what happened to the university spin-offs and start-ups since their inception?', i.e. we trace their trajectory from genesis to growth, or sadly, their demise. We pursue this question with two broad notions in mind:

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i In this research spin-out firms are also known as "start-up" and "spin-off" firms.

Table 1: Three Pillars of Successful Biotech Commercialisation

Three pillars	Description
Effective management	Effective management is not always a strong point for dedicated scientists who produce technologies. Effectively bringing in the necessary know-how is essential to succeed.
Sufficient capital	Finding adequate capital is often a challenge for scientists who do not have a financial background.
Access to new technology that leads to products	A start-up further needs access to good technology and associated patents in order to produce revenue.

Source: Malazgirt, 2011

a. The essential pillars that underpin growth in biotechnology spin-offs and start-ups (effective management, sufficient capital, and access to technology);
b. The role of institutions and other actors in the Western Cape, aimed at supporting innovation.

The research was initially designed to complete the study[ii] with an investigation of the growth stories of the biotechnology spin-offs from the universities in the study. When it became evident that several of the firms targeted for this in-depth story, were no longer in existence, a more important question became 'why did they fail?' In the search for answers to this question, a tale of turbulence in the sector, and particularly in the environment in which they were to innovate and grow, emerged. Turbulence, in the literature on economics of innovation, refers to entry and exit of firms in an industry or sector.[9-12] In general terms, turbulence also refers to discontinuities and changes that occur in the environment in which the firm operates, especially the institutions in the national and regional innovation systems that have or are supposed to have supportive linkages to the firms. We use the concept of turbulence here in both senses.

The merit of this paper lies in the fact that it draws together many of the useful insights from previous papers and the literature, and with the aid of the case studies, show how a complex series of internal (to the firms) and external factors (in the national and regional innovation systems) combined to lead to the failure of the biotechnology spin-offs.

The rest of the paper is structured as follows. After expanding on the three central requirements (the so-called 'pillars') for success in biotechnology commercialisation, we proceed to the case studies, discussing the methodology and providing the information on the ten biotechnology firms that were initially targeted for in depth study, where after we present the case studies. We derive lessons and policy implications in the discussion section and conclude in the last section.

THE THREE PILLARS OF SUCCESSFUL BIOTECHNOLOGY COMMERCIALISATION

According to the literature, there are three structural elements which are called the "three pillars" that are essential to gain success for a biotechnology start-up company: (i) effective management, (ii) sufficient capital and (iii) access to new technology that leads to products.[6,13–14] (see table 1).

The following section gives brief information about each pillar.

Effective Management

Managerial talents are one of the most fundamental challenges and the weakest pillar in most biotechnology companies. R&D poses difficult managerial challenges because it is the most critical aspect of bringing a product to market and it is costly. Hence, biotechnology firms need a complex range of knowledge, skills and talents.[6,13–16] York et al. (2009)[17] state that such a bio-entrepreneur should have cross-disciplinary knowledge and talents including marketing, the basics of Intellectual Property Rights (IPR), early-stage technology finance, and knowledge of scientific, regulatory and ethical issues. Moreover, bio-entrepreneurs should also

ii In the prior research authors sought to understand the spin-off phenomenon whereby a new firm is created and formed from parent universities. Specifically, the objectives of the paper were to explore the nature and definition of university spin-off firms in the South African context. The authors were further interested in the motivations behind the spin off, the relationships with the parent university post spin off, as well as the most important obstacles that the spin offs faced.

have special communication, emotional and social intelligence skills like self-awareness, self-control, and social awareness.[14] This feature, having technical and commercial skills, is mostly found in biotechnology companies where the biotechnology start-up companies have a dual decision team, with an executive manager (CEO) and a scientific manager (CSO).[18]

Resolving the economic and commercial challenges faced when developing a new product requires a completely different set of skills from conducting research on technology and its application. In this case, a successful management team must encourage scientific staff to work on the one or two products that will lead the company to its success. Frequently, a scientific team has a wide range of potential products; however, most of the time they lack the resources to exploit several products commercially at any given time. On the other hand, established pharmaceutical companies are experimenting with a wide range of technologies and products in order to find that one blockbuster.[6]

Finding appropriate talent is an international problem. A recent report describing the Singapore cluster, for example, noted that their biggest problem is its continued shortage of entrepreneurial scientists and managers.[14] Similarly, Volery et al. (2007)[16] revealed in their research that Switzerland faces several key challenges in management of young biotechnology companies, which include funds management, planning strategies, marketing and sales, IP and administration. Nosella et al. (2006)[4] gave another example from Italy. Managerial skills at university start-ups are mostly lacking in the scientific staff working at the university. Rutherford and Fulop (2006)[19] found a similar lack of expertise in Australian biotechnology start-ups. The authors observed that business awareness of science is low and scientists lack the entrepreneurial skills to commercialise their research. To overcome these problems, Rutherford and Fulop (2006)[19] and Nosella et al. (2006)[4] suggested respectively to train and equip scientists with the necessary commercialisation and managerial skills and to get assistance from TTOs in terms of organisational and financial support. Nosella et al. (2006)[4] suggested another solution that can solve the problem in Italy which is a joint scientific and managerial competency where the founders could be a team of both academic scientists and industry managers.

Sufficient Capital

Capital forms the second pillar of any biotechnology company's struggle, because biotechnology is capital intensive and in many cases requires huge amounts of funding for many years. At the early stages, in many cases, a biotechnology company struggles to have enough funds.[6,13,15–16] The process of bringing a drug into the international market is costly and time consuming. Some experts have pointed out that it takes approximately US$1 billion and additional ten years of research and clinical trials to finally release a drug. Lately over 200 new medical treatments and vaccines have gone through this process which includes products that treat cancer, diabetes, AIDS and other autoimmune disorders.[6]

Therefore, bio-entrepreneurs should spend considerable time on cultivating financial resources for their young companies.[13] Konde (2012)[20] echoes this finding, stating that early stage biotechnology start-up investing is a resource-intensive business, where entrepreneurs need to build strong partnerships with local and global investors, with corporations and government entities.[20]

This is a big problem in developing countries as well as developed countries. Byrd (2002)[21] found that the major problem faced by Canadian biotechnology spin-off companies is access to the capital to develop the company. One of the biggest challenges faced by biotechnology start-ups in Singapore is getting sufficient funding to keep them going. In the high-risk early stage start-ups, companies mostly rely on angel investors.[22] This is also the case for India. The Indian biotech firms mainly rely on private equity (PE) and venture capital (VC) funds. In recent years, Indian start-up biotech companies have been left vulnerable by the decline in early stage funding. Main reason is that the private investors move to later-stage investment strategies, due to the lack of money to invest in new and risky projects.[20]

In both developed and developing countries, governments are the most important funders of the biotechnology sector. In South Africa, a developing country, government support is more important than private investments. Financing for biotechnology in South Africa is strongly government-led, with the BRICs[iii]

iii Biotechnology Regional Innovation Centres (BRICs) was formed in 2002 and served as vehicles for facilitating and supporting biotechnology innovation and commercialisation.[26] Three biotechnology innovation centres were created. These are Cape Biotech Initiative (CBI) in Western Cape, the East Coast Biotechnology Consortium (EcoBio, operating under the trade name of LIFElab) in Kwazulu Natal and Biotechnology Partnership for Africa's Development (BioPAD) in Gauteng province. The BRICs focuses different areas: Cape Biotech and LIFElab focus on human health biotechnology research and development while BioPAD concentrates on biotechnology research and development in agriculture, mining, and environmental applications.[23,27]

(part of the TIA[iv] now) instruments. However, compared to other countries, South Africa is still falling behind in this level of finance. We return to the South African situation in the case study analysis.

Access to Technology

Phenomenal scientific partnerships such as Cohen and Boyer, Kohler and Milstein have set the foundation for the biotechnology industry based on the recombinant DNA and the monoclonal antibody breakthrough technologies, which emerged in the mid-1970s. This is the third essential pillar which most companies are built upon. To this day, most biotechnology companies still look at universities first for sources of new technology. Universities are essential components for discovering new technology, because they are often the most fertile grounds for producing such discoveries. Important policies such as the Bayh–Dole Act and other legislations that encourage academic institutions to license discoveries from research that have been conducted with government funding still continue to fuel and are the backbone of the biotechnology revolution.[13]

An essential component for any biotechnology company, from its inception, is to have a well-defined and well-articulated product focus. Whether the product is directed towards the development of a specific technology or whether it is focused towards a certain disease area, the company still needs to set a clear vision regarding its foundation for future revenues.[13] For biotechnology start-ups it can be a difficult task as they can only focus on one or two avenues of research, hence they are not as successful as big pharmaceutical companies with regards to developing a successful drug to enter the market or even other biotechnological avenues.[6]

The great challenge for any bio-entrepreneur in this time of ubiquitous opportunities is to maintain a rigorous focus on the chosen product and its underlying technology.[13] Having explained the key requirements for successful biotechnology commercialisation, we can now proceed to the empirical work, where we will apply these insights in the South African cases.

iv The DST recently established an agency which is called the Technology Innovation Agency (the TIA) and is a single public agency that was formed from a merger of seven DST-funded organisations, namely, BRICs (Lifelab, BioPAD, Cape Biotech), Plantbio, Tshumisano, the Innovation Fund and AMTS (Advanced Manufacturing Technology Strategy).[28-29] The TIA is involved in several fields, i.e. industrial biotech, agriculture, health, mining, energy, advanced manufacturing technologies and information and communication technologies.[29]

CASE STUDY: THE EVOLUTION OF BIOTECHNOLOGY SPIN-OFFS AND START-UPS

Methodology

Following a literature survey and our initial survey on university spin-offs, we ventured into the field to establish whether our biotechnology spin-offs identified in the survey were still in existence, and whether new ones have been created since. This exploration resulted in ten biotechnology firms being identified, two from the University of the Western Cape, four from the University of Cape Town (UCT) and four from the University of Stellenbosch.

For the purposes of these in-depth case studies, we initially set the criteria that the companies should have been created after 2000 (to be comparable), must be active in biotechnology, and particularly in manufacturing, product development or research. We therefore excluded service-type and consultancy firms (four); one firm that was created in 1997 and closed down in 2007; and a company which was created in 2011. Four companies fitted the criteria. However, when we continued the investigation, we found that more companies had gone under than survived (only one firm still alive). The more important question to pursue, became 'why the failure?'. Two of the companies that failed, were willing to participate in the in-depth interviews. One was from UCT and one from the University of Stellenbosch. To garner the perspective of the supporting agencies in the regional innovation systems, we arranged and conducted interviews with senior staff at the company, at the universities' technology transfer offices[v] and the TIA. The interviews yielded a considerable amount of information, which, as we will show in our analysis, tell a tale of failure that holds important lessons for practitioners and policy makers.

In the next section, we elaborate on the company histories. The companies are coded Company A and B.

Overview of Biotechnology Spin-Off Companies

Company A

Company A, was a University of Stellenbosch pre-start-up company, which at the time of its establishment, represented and opportunity to realise the commercial potential by bringing to market the technologies

v Unfortunately, the TTO at UCT was only willing to confirm that Company B was no longer operational and the founder of the company refused to give any information beyond what is in the public domain.

developed, and capitalising on the research proficiency and extensive knowledge generated at the Institute of Wine Biotechnology (IWBT) at Stellenbosch University.[30–32] This company was officially launched in 2005. It was a biotechnology-based pre-start up with the aim of establishing a sustainable product and technology development process that would combine the research output and intellectual property generated by the IWBT with sound commercialisation and marketing practices.[30–31,33]

To pursue this pioneering initiative, the IWBT appointed a team of five researchers to work only on Company A projects, and a Project Manager to guide the commercialisation and business needs of the venture in 2005. The research staff members at the IWBT assisted the team, each contributing their expertise and knowledge to the Company A projects. There was a Project Leader who is a full Professor in a department at Stellenbosch University.[30]

The company focused on the areas of genetic enhancement technologies, conventional development of unique yeast and bacterial strains, and development of quality control niche service offerings (chemical and microbiological) to the wine industry. Their projects were designed to generate a large number of hybrid and/or recombinant wine yeast strains. Research aimed, amongst others to develop yeast strains that are able to enrich wines with antioxidants and nutritional supplements. Company A also wanted to make the fermentation process more efficient through the production of yeast strains with enhanced levels of key fermentation enzymes, and reducing the reliance on sulphur dioxide during the fermentation process.[30–31,33] These research and technology developments were believed to hold an important strategic advantage for the South African wine industry in the global market. Company A sought to actively commercialise the novel technologies at the IWBT, thus contributing towards the global competitiveness of the South African wine industry.[31]

To initiate the company, funding was obtained from CBI. The venture was in a three year project development phase after which it is envisaged that a private company will be incorporated, representing the commercialisation arm of the Institute for Wine Biotechnology.[30–31,33]

There was much hope that this company would be a successful example for future biotech spin-offs. Scott (2007)[34] reported that a California-based businesswoman noted that biotechnology start-ups could provide a critical kick-start to South Africa's economic growth as well as fight poverty. The example she gave referred to the fledgling Stellenbosch University company, Company A, which was one of fifteen Western Cape "baby biotechs", financially supported by the CBI and designed to commercialise and utilise academic discoveries. Unfortunately, Company A was terminated in 2010. Some of its projects reverted to the IWBT and are pursued there.

Company B

Company B was created in 2006 by a PhD student who developed the technology at the University of Cape Town. It was a start-up biotechnology company developing a production process for the manufacture and marketing of natural products derived from microalgae. The objective of its project was to produce natural astaxanthin from microalgae for the local and international markets using closed system cultivation technology for better process control[35] The astaxanthin project used technology developed at the University of Cape Town by the founder, who also received assistance from the Professor who supervised his PhD research and heads the Centre for Bioprocess Engineering Research (CeBER) in the Department of Chemical Engineering at UCT. The research group at the university provided Company B with inocula (starter algal cultures), maintaining the algal culture to mitigate the risk of contamination at the Upington site, as well as providing routine analytical support.[36]

Company B was incorporated in March 2006 after receiving funding of 3.8 million Rand (~USD 600.000) from the CBI, who funded the start-up operation, linking in with their other algal initiatives in Upington.[35–36] Available funding for this project was used to further develop the technology and to establish a pilot production facility. Company B uses facilities in Upington for its manufacturing and piloting studies where the climatic conditions are favourable to algal growth. Company B was in a three year development phase from 2006 to 2009. After this phase a full scale plant capable of producing up to 2 tons of 100% astaxanthin were to be established. Company B was then in need of a second round of funding to progress to full scale production.[35] Not succeeding in acquiring the needed funds, the company was terminated in 2011.

ANATOMY OF FAILURE IN BIOTECHNOLOGY SPIN-OFFS: AN INTERNAL AND EXTERNAL ENVIRONMENT PERSPECTIVE

Using the insights from the literature discussed earlier in the paper and the information garnered from the interviews, we tabulate the factors linked to the failure by the interviewees in Tables 2 and 3. This allows us to systematically

Table 2: Reasons for termination from different perspectives (Firm, TTO and TIA)

	Managerial skills	Sufficient capital	Technology	Others
COMPANY A				
Firm perspective				
Lack of knowledge and communication	-	-	-	O
Funding	-	O	-	-
New mandate in TIA	-	-	-	O
TTO Perspective				
New mandate in TIA	-	-	-	O
Technology was too far from the market	-	-	O	-
Unclear market	O	-	O	-
Timing	O	O	-	O
Uncertainty in Company	O	-	-	-
Having no leader	O	-	-	-
Conservative market	-	-	O	-
Expectations	-	-	-	O
Freedom	-	-	-	O
Not having a sustainable business plan	O	-	-	-
TIA perspective				
Having no leader	O	-	-	-
Having no commercial products	-	-	O	-
Technology was too far from the market	-	-	O	-
Unclear market	O	-	O	-
Business model	O	-	-	-
Expectations	-	-	-	O
R&D driven	O	-	-	-
COMPANY B				
TIA perspective				
No managerial and technical (engineering) skills	O	-	-	-

Source: Authors' own construction, 2012

identify similarities and differences in the reasons for failure advanced from the different perspectives.

We group the relevant factors for analytical purposes in terms of internal (firm-specific) factors and external (relating to the environment in which they operated, and specifically to the relevant institutions or organizations in the national[vi] and regional[vii] innovation systems (NIS, RIS) respectively).

vi The national innovation system (NIS) approach[37–39] places stress on the role of institutions in a system within a nation state, through their interactions, in supporting the technological development process.

vii Niosi and Banik (2005)[40] proposed that regional innovation system (RIS) are geographical concentrations of interacting organisations (innovative firms, research universities, government laboratories and venture capital firms) designed at the development of a specific technology.

Firm specific factors

Managerial skills and leadership

Out of the three interviews conducted for Company A, only the TTO representative and the senior staff member at the TIA identified managerial factors as contributing to the demise of the company. According to the senior member of staff of the Company A the managers' skills were not such a big problem, because the early challenges were of a scientific and technological nature. She believes the need for business and financial skills would only become critical once the firm became a fully-fledged company. She stated that the company had created a pleasant and healthy working environment where the team, including the founders worked well together. The only hiccup was the fact that they had lost a project manager to another company and had difficulties finding another one. According to senior staff

Table 3: Firm-specific, NIS and RIS explanations for biotechnology spin-off failure

	Firms	NIS/RIS Institutions/Organisations
COMPANY A		
Firm perspective		
Lack of knowledge and communication	-	O
Funding	-	O
New mandate in TIA	-	O
TTO Perspective		
New mandate in TIA	-	O
Technology was too far from the market	O	-
Unclear market	O	-
Timing	O	O
Uncertainty in Company	O	-
Having no leader	O	-
Conservative market	O	-
Expectations	-	O
Freedom	-	O
Not having a sustainable business plan	O	-
TIA perspective		
Having no leader	O	-
Having no commercial products	O	-
Technology was too far from the market	O	-
Unclear market	O	-
Business model	O	-
Expectations	-	O
R&D driven	O	-
COMPANY B		
TIA perspective		
No managerial and technical (engineering) skills	O	-
Limited scalability	O	-

Source: Authors' own construction, 2012

member at Innovus, the TTO at Stellenbosch University, the company did not have a CEO or a clear leader to take the projects further and this resulted in instability and uncertainty. That the company did not have a feasible business plan and disagreed with the funder about it, also complicated matters (more on this below). According to the senior staff member interviewed at the TIA, the right person, with the right leadership and managerial skills, especially to drive the commercialisation and 'hunt money', rather than research output, would have made all the difference. In this interviewee's mind, the business model of chasing revenue from licensing, rather than further commercialisation was not the right one. The company already had something to commercialise, but the focus was too much on R & D, and not commercial products.

The same interviewee also asserted that Company B failed because it had no managerial and technical (engineering) skills.

Insufficient capital

Both companies had funding from the Cape Biotech trust to fund start-up and development costs, but in both instances they were not able to muster enough funding to scale up operations to produce marketable products. From the firm's perspectives, the trouble started when the TIA absorbed Cape Biotech in 2010, with resultant uncertainty and changes (staff turnover, loss of key contacts in Cape Biotech), new business plan investigations and viability studies. The end result was that the TIA concluded that the Company did not fit their mission, and funding was terminated.

The Innovus representative lamented the timing of this upheaval:

> *"Company A needed about four more months of funding to get the desired results that would generate income, but the TIA decided to terminate the venture in November 2010. If they could just have continued for another season, they could have had wonderful results."*

The TIA representative's view was that there were expectations that the company should have commercialised some output from the project by year 3. The TIA position was clear: commercialise or the funding would be stopped. Commercialisation was not forthcoming, so the funding stopped. Company B had, according to the TIA representative:

> *"a brilliant product, for which they had funding, but they could not take the project to the next level, i.e. scale it up, and therefore the TIA decided to terminate the company."*

Technology

For both companies, the nature of the technologies they were trying to turn into marketable products, were such as to require a long lead time and many resources to bring the projects from production in pilot plants to production for large markets. According to the TTO representative as well as the TIA representative, the technology from Company A were still too far from being market ready, and for this reason, it was also unclear precisely which market to target to achieve the best pay-off.

Market-related factors

Both the TTO and TIA representatives identified market-related factors as problematic. Apart from emphasizing the fact that it was not yet possible to target a market for products that are still too far from market-ready (discussed above), the Innovus interviewee also mentioned that the market that Company A chose (wine producers) are still fairly conservative and not likely to adopt genetically modified products. In fact only America and Canada allow genetically modified wines to be sold.

External (NIS, RIS) Factors

Most of the factors in this section have to do with the impact of changes in the institutions supporting the development of the biotechnology sector, and specifically the changes brought by the establishment of the Technology Innovation Agency (the TIA, a national body) in 2010 and the absorption of Cape Biotech (a regional body) into the TIA.

Knowledge and communication gaps

When the TIA took over, much uncertainty was created, with paralyzing effects. The company interviewee opined:

> *"The people appointed to the TIA did not know what was going on and their communication was terrible."*

Almost a year elapsed before they were informed that their funding was terminated.

Discontinuities: from Cape Biotech to TIA

The TTO representative stated that the creation of the TIA resulted in a period of chaos, shifting the focus and mandate from a regional one under Cape Biotech to a national one under the TIA. Also, whereas Cape Biotech understood that biotechnology has a very long lead time before significant revenue is generated; the mindset of the TIA was one that preferred funding companies with products and technologies close to market ready. This is an unfortunate development, in the face of the persistent refrain in the empirical literature and our earlier research, about the long and costly development paths in biotechnology and the lack of venture capital markets in developing economies. On this latter point we elaborate in the next section.

Funding sources in the innovation system

The interviewees indicated that try as they might, the management teams at the biotech start ups under discussion here, could not garner the necessary funds to ensure their survival. Private financing for biotechnology remains severely limited in South Africa. The problem in South Africa is the lack of finance available for seed and start-up companies, the bulk of the capital going into replacement capital, such as management buy-outs and black economic empowerment transactions.[41] Biotechnology companies usually run through multiple rounds of funding in order to achieve maturity. In the USA and European countries there can be as many as six rounds of venture capital funding before a company is self-sustaining or lists on a stock exchange. In South Africa, several fledgling biotechnology companies have received two to three rounds of financing but are facing the 'valley of death' with no means of support.[23,41] Government funds for the biotechnology industry are limited, and South Africa's investment community is immature in biotechnology, with having only one VC in

biotechnology[viii]. Without a change in this funding picture, the efforts that the government has made so far in stimulating biotechnology will be threatened.[23] In addition to the above explanations, Sherwin (2007)[41] notes both the South African government and the private sector need to be realistic about the time frames and the amount of capital that required in developing the biotechnology sector. According to her, this is not a three to five year commitment, but a ten to twenty year commitment at least.

Timing of interventions

According to the interviewees at Company A and the TTO, the timing of the TIA interventions were very unfortunate. They believe that, if allowed to continue to work normally (absent the interruptions by TIA officials) and if they had funding for a few more months, they would have been able to deliver on commercialisation.

Expectations and business perspective of funder

Insights from the TTO interviewee suggest that even before the discontinuity created by the takeover of Cape Biotech by the TIA, Company A and the former were at odds over the appropriate business plan for the company. She observes that Company A did not seem to have the freedom to choose their business model or the line of products that they wanted to pursue. When the funder and the beneficiary are at odds, end goals are complicated and the desired outcomes are not clear. It may result in expectations not being met.

In sum, these factors confirm the main obstacles that biotechnology start-ups face, as identified in the literature. The results further point to useful insights regarding the NIS and RIS. In RIS structure, according to Cooke (2002)[43], to capture the variety of degrees of influence and decision-making authority, the presence or absence, or weaker and stronger relationships amongst the diverse possible kinds of application, exploitation, generation and diffusion elements of specific regions and their degrees of "systemness", one needs to investigate the interactions amongst the constituent parts of the system. Although we have only focused here on biotechnology firms and certain institutions in the RIS, we have learned plenty about the weak points and potential weak points in the system. We highlight the implications of these in the conclusion.

CONCLUSION

In this study, we wanted to trace the growth paths of the biotechnology companies that spun off from universities in the Western Cape. Our efforts to find the spin-offs that were still active in the biotechnology sector, made it clear that a more relevant question to ask, would be 'why do they fail?' rather than 'how did they succeed?'.

With the aid of the three pillars of successful biotechnology commercialisation from the literature, and the information on our case study companies, gathered from interviews with the company, TTO and TIA representatives, we constructed two sets of factors that led to the demise of these firms. These were the internal, or firm-specific factors, and external or NIS/RIS related factors.

Our findings on the firm-specific factors underscore the importance of a diverse set of managerial skills, discussed here. This is an important message for several players in the NIS and RIS, for example educational and training institutions, agencies such as the TIA that must play a supporting role, and Technology Transfer Offices, some of which operate training programmes and incubators for biotechnology entrepreneurs. With respect to the factors related to the RIS and NIS, the following stand out:

- The imperative to be mindful of disruptive effects in the very sector or system that an institutional change is supposed to assist and support. In the case of Cape Biotech and the TIA, the change was clearly turbulent and competence and capacity destroying, rather than enhancing.
- Funding for seed and start-up capital is consistently identified as an obstacle to growth in a promising sector of the economy. The nature of the technology and the longer-term investment horizon required make the sector unattractive for investors with a shorter term perspective. It would now seem that the government agency tasked with promoting growth in the biotechnology sector has adopted the latter view. In addition, the venture capital market in South Africa is underdeveloped and resources scarce. Until this aspect of the innovation system is addressed more effectively, firm formation and innovation in the sector may continue to remain under its potential level.

viii The only private biotechnology Venture Capital was dormant in 2010 due to investing their whole portfolio (information received through interview with a manager at the TIA, 7 November 2012). The Biotech VC firm raised R80 million in funds in 2001. By May 2010, company invested R76 million in total of 8 private equity/venture capital investments and the current (2012) portfolio size was 3.[42]

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Article

Evaluation on National Biotechnology Policy (NBP) 2005: Towards Achieving 20 Global Companies In NBP Phase III

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ABSTRACT

The purpose of this paper is to discuss on the latest progress of the NBP 2005 through selecting significant performance indicators towards the end of policy tenure, which is nurturing 20 global status companies. The research was carried out through qualitative method using verbatim analysis from Focus Group Discussion (FGD) with lead implementing agencies, Bioeconomy Corporation and also supported by desktop research from the statistics provided and literature review. Through this research, general performances in NBP Phase II were examined, as they will influence the strategies execution in the Phase III. Hence, researcher was exploring the global companies in the context of NBP in term of definition, grooming programs, potential and existing companies, characteristics, niches, and other relevant information related. The findings of this research indicated that NBP Phase II showed significant achievements while general information on the global companies been obtained, mostly in 3 main biotechnology sectors the namely agriculture, healthcare and industrial biotechnology due to non- disclosure agreement with the companies. Therefore, this research is very useful, it could possibly benefit policy makers in the future on policy planning, and intervention in science, technology, and innovation related policy. Finally, originality value from this research will unlock possibility for future study to conduct quantitative survey on the respective companies and also other international benchmarking indicators. However, the study was only based on the FGD session, documents analysis, and information given from ministries and agencies officers.

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INTRODUCTION

According to Article 2 from the United Nation Convention on Biological Diversity, biotechnology is the application of living biological systems, organisms and derivatives to modify product or process for a specific use (OECD, 2009). Generally, the sector consists of activities involving research and innovation which spur the economy worldwide. Biotechnology is also referred as the application of modification processes of living organism for specific uses (Dorocki, Slawomir, Bogus, 2014). Biotechnology has emerged as one of the priority focus areas of both private and public sectors worldwide due to its large growth potential and public benefits. Existing biotechnology R&D leverages on decades of life sciences researches and the development of increasingly powerful mechanisms to obtain and utilize biological data.

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BIOTECHNOLOGY POLICY IN MALAYSIA

In April 2005, the Malaysian government launched National Biotechnology Policy (NBP) as forecasting onto new source of wealth. Biotechnology sector has been

identified as new driving force to achieve knowledge based economy. This policy was detailed out to 9 Policy Thrusts for 15 years implementation with the main goal to contribute 5% of Malaysia's Gross Domestic Product (GDP) and creation of 280,000 jobs work force by the end of year 2020 (NBP, 2005). Then, the NBP strategies were divided into three phases with distinguish strategies within each phases: Phase I: Capacity Building (2005-2010), Phase II: Science to Business (2011-2015) and Phase III: Global Presence (2016-2020). Another target set was to produce at least 20 Malaysian global biotechnology companies by the 2020, which the nurturing process will begin in the Phase II.

GLOBAL COMPANY DEFINITION

Currently there is no standard definition for a global company from political science or economic perspective. Based on Iowa State University, Department of Economic, a theory stated that a global company must have owners from many countries while another theory suggested that a global company must have executives of different nationalities. Then this theory suggested companies that sell their products or provide services or have operations in many countries as global companies.

Global company can also identified as a company that affects local communities with its multinational marketing business strategy. Such company integrates its business unit by localizing business strategy and adapting to local cultures. For instance, McDonalds created different menus for different countries depending on the local culture like kebab on flatbread in Israel and hamburgers in United States (Azevedo & Bertrand, 1999).

According to (Huebsch, Russel, Kokemuller, 2017), global company can be defined as an enterprise that operate in one country and trade in other part of the world. They indicated the British East India Company that traded in Asian region between 1500 and 1700 as an example. Therefore, a global company can also defined as a large company that headquartered in one country and has operations in several other countries (Thompson, 2017).

Knight, Madsen and Servais (2004) stated that global companies are companies which less than 20 years of establishment, have internationalized in 3 years of launch and having 25% income from export. In contrast, Chetty & Campbell-Hunt (2004) stated the internationalization years are within 2-8 years and export ratio is 50% (Amzan, 2009).

In general, the common definitions of global companies are the ones present in more than one country, have export trading, and have offices and premises in other countries.

CHARACTERISTICS OF GLOBAL BIOTECHNOLOGY COMPANY WORLDWIDE

In general, top global biotechnology companies are listed on the stock exchange. According to Statista, an online website, top five biotechnology and pharmaceutical companies by market value are Johnson & Johnson, Roche, Pfizer, Novartis and Merck (2017) with more than USD150 billion of market capital in the first quarter of 2017.

Forbes 2016 Global 2000, a listing that measures the performance of companies based on revenue, profits, assets and market value, have found that biotechnology companies are continuously expanding. Johnson and Johnson inched up the rank from number 34 in 2015 to number 32 in 2016 while Pfizer recorded a staggering total sale of USD48.9 billion. Among other companies in the top list are Novartis, Roche, Bayer, Monsanto and also Allergan, a company newly set up in 2010 that manufactures drug and Botox. 25 of the biggest drug and biotechnology companies in the world are from eight countries. 15 companies are based in the US, two in the UK, two in Switzerland, two in Germany and one in Denmark, France, Israel and Japan respectively.

Benchmarking against another country reveals different characteristic too. Canada, for instance, have six criteria of global Canadian biotechnology firms. The criteria include (1) patenting company's inventions to attract venture capital, (2) actively conducting R&D on products, (3) targeting export market for knowledge-intensive product, (4) attracting venture capital, (5) conducting alliances and (6) planning for Initial Public Offering (IPO) (Traoré, 2004).

RESEARCH DESIGN

This study was carried out using qualitative method. This method was chosen because the data required fell under the Non-Disclosure Act and could not be publicly accessed via reports and publications. Qualitative method, however, had opened up the possibility for researcher to gain information from research participants based on their knowledge, experience and expertise.

Focus Group Discussion (FGD) technique was used by the researcher. FGD is a form of interview involving a group of people to obtain opinions, views, perceptions based on their expertise. According to Lederman (1995), participants were purposively selected as a sample from their population for a group interview on a given topic to share their in-depth views. Meanwhile, Burrows & Kendall (1997) introduced the concept of 'applicability' in which the subjects were selected based on their

Table 1: Experts for FGD Session

No.	Participants	Participants Name	Designation
1	1	Pn. Nurdita bt Rasidi	Vice President, Financial Strategy & Corporate Planning, Bioeconomy Corporation Sdn. Bhd.
2	2	En. Shazaril Adri bin Mohd Sharif	Vice President, CEO Office, Bioeconomy Corporation Sdn. Bhd.

knowledge of the subject. The niche of the FGD is a set of data could be generated based on the synergy of group interaction (Rabiee, 2004). Questions were asked in interactive session whereby the participants freely expressed their views and interact with other group members.

The chosen participants are experts in the biotechnology industry in Malaysia. They have been with Bioeconomy Corporation for more than 10 years and experienced in industry development, facilitating entrepreneurs and nurturing companies. They also have full credibility and qualification to answer the prepared questions. Experts for FGD Session as per Table 1 below:

GLOBAL COMPANIES IN MALAYSIA BIOTECHNOLOGY INDUSTRY

Proposed Global Company Definition

Both participants said that there is no definition stated in the NBP document. However for the purpose of NBP Phase III implementation, Bioeconomy Corporation had determined the definition that could be followed. There are two definitions established which are (1) the presence in more than one country, the origin and other countries and (2) some product differentiations to suit that local market.

In this matter, Bioeconomy Corporation also looks into three other possible criteria which are (1) export revenue, (2) office in other country and (3) presence in the foreign stock exchange market. In the context of NBP, a biotechnology company will be considered as a global company when the company meets one of these criteria.

During the FGD session, researcher was informed that this proposed definition was prepared internally by the Bioeconomy Corporation based to the practices in other countries. Besides that, they carry out consultation with SME Corporation as they are involved in the companies' development and the closest agency to be referred in term of company development. However, specific benchmarking and consultations are not clearly stated. Based on that, the proposed definition has been refined and is stringent for NBP context.

Table 2: Public Listed Biotechnology / Holding Companies

No.	Stock Exchange	No. of Companies
1	Kuala Lumpur Stock Exchange	18
2	London Stock Exchange	2
3	Australia Stock Exchange	2
4	Singapore Exchange	1
5	New York Stock Exchange	1
6	India National Stock Exchange	1
Total		25

Malaysian Biotechnology Companies IPO Listing

Currently there are 25 Public Listed Malaysian Biotechnology/Holding Companies in various stocks market with 18 companies are listed in the Kuala Lumpur Stock Exchange (KLSE). The remaining seven companies are listed abroad in five different foreign stock exchanges. Summary of the companies listings based on the stock exchanges is as per Table 2. The summary of the list of Biotechnology companies in stock exchange is depicted in Table 3 below:

In this matter, researcher was informed that some of the big companies were listed just solely because of their holding companies were listed. For instance, IOI Lipid Enzymtec Sdn. Bhd. generated a revenue of RM460 million but IOI Group Bhd. was listed instead. Participant 1 stressed that going for IPO is entirely up to the company's decision and not necessarily because the company wants to go global.

Participant 1 also explained that if a company listed in the KLSE does not generate export revenue, the company cannot be considered as global but only as potential global company. Participant 2 also agreed.

Participant 2 then suggested focusing only on the direct listed companies. Based on Table 3, only two companies: Stemlife Berhad and Malaysian Genomics Resources Centre Berhad, are being listed individually while other companies are only subsidiaries of their respective holding companies. Participant 2 later

Table 3: List of Biotechnology / Holding Companies in Stock Exchange

No.	Listing Bourse	Listed Holding/ Related Company	Biotechnology Company
1	Main Board, KLSE	-	StemLife Berhad
2		Hovid Berhad	Hovid Research Sdn Bhd
3		Genting Plantation Berhad Bhd	ACGT Sdn Bhd
4			Genting GreenTech Sdn Bhd
5		IOI Group Bhd	IOI Palm Biotech Sdn Bhd
6			IOI Lipid Enzymtec Sdn Bhd
7		TMC Life Sciences Bhd	TMC Biotech Sdn Bhd
8		TSH Resources Bhd	TSH Biotech Sdn Bhd
9		Pharmaniaga Bhd	Bio-Collagen Technologies Sdn Bhd
10		Sindora Berhad	GranuLab (M) Sdn Bhd
11			Microwell Bio Solutions Sdn Bhd
12		Kulim (M) Bhd	Kulim Top Plant Sdn Bhd
13		QL Resources Bhd	QL Agribio Sdn Bhd
14	ACE Market, KLSE	-	Malaysian Genomics Resource Centre Bhd
15		Bioalpha Holdings Bhd	Bioalpha R&D Sdn Bhd
16		Sunzen Biotech Bhd	Sunzen Life Sciences Sdn Bhd
17		Innocorp Venture Bhd	KLSMC Stem Cells Sdn Bhd
18		Khazanah Nasional Bhd	Biotropics Malaysia Berhad
19	Australian Securities Exchange	SECOS Group Limited	Cardia Bioplastics (M) Sdn Bhd
20		Holista CollTech Ltd	Holista Biotech Sdn Bhd
21	National Stock Exchange of India	Dr Reddy's Laboratories Limited	Aurigene Discovery Technologies (M) Sdn Bhd
22	AIM Market, London	PureCircle Ltd	PureCircle Sdn Bhd
23		Green & Smart Holdings Plc	Green & Smart Sdn Bhd
24	NYSE, New York	Quintiles Pharma Inc	Quintiles (M) Sdn Bhd
25	Singapore Exchange	Willmar	PGEO Biotech Sdn Bhd

explained that Bioalpha R&D Sdn. Bhd. can be considered as listed as the company is only focusing on one activity and have no other subsidiaries.

Participant 1 then explained further on the companies that met criteria listed and export revenue requirement. The seven IPO subsidiary companies with export revenue are IOI Lipid Enzymtec Sdn. Bhd., QL Agribio Sdn. Bhd., Bioalpha R&D Sdn. Bhd., Sunzen Life Science Sdn. Bhd., Biotropics Malaysia Bhd., Pure Circle Sdn. Bhd. and Quintiles (M) Sdn. Bhd.

Both participants agreed that companies listed in the foreign stock exchanges can also considered as global companies. The other five relevant companies to be included which are Cardia Bioplastics (M) Sdn. Bhd., Holista Biotech Sdn. Bhd., Aurigene Discovery Technologies (M) Sdn. Bhd., Green & Smart Sdn. Bhd. and also PGEO Biotech Sdn. Bhd.

Based on FGD session, IPO listings is not necessarily a method to go global as some biotechnology companies are subsidiaries of listed holding companies. Hence, IPO by individual entity is not a requirement. None of these listed companies can be defined as global in term IPO listing criteria. As a result, there are 12 companies that have already achieved global status in accordance with the requirement. The list of global biotechnology companies are as per Table 4 below:

Table 4: Malaysia Global Biotechnology Companies

No.	Companies	Criteria
1	Bioalpha R&D Sdn. Bhd.	IPO listed and export revenue
2	IOI Lipid Enzymtec Sdn. Bhd.	IPO listed and export revenue
3	QL Agribio Sdn. Bhd.	IPO listed and export revenue
4	Biotropics Malaysia Bhd.	IPO listed and export revenue
5	Pure Circle Sdn. Bhd.	IPO listed and export revenue
6	Sunzen Life Sciences Sdn Bhd	IPO listed and export revenue
7	Quintiles (M) Sdn. Bhd	Foreign IPO listed
8	Cardia Bioplastics (M) Sdn. Bhd	Foreign IPO listed
9	Holista Biotech Sdn. Bhd.,	Foreign IPO listed
10	Aurigene Discovery Technologies (M) Sdn. Bhd	Foreign IPO listed
11	Green & Smart Sdn. Bhd.	Foreign IPO listed
12	PGEO Biotech Sdn. Bhd	Foreign IPO listed

DISCUSSION AND CONCLUSION

Information was gathered in order to propose the definition of global status company in the context of NBP. From FGD session, both participants stated that the definition has four criteria which include the (1) presence in more than one country, the origin and other countries, (2) product differentiations to suit other markets, (3) export revenue and (4) presence in the stock exchange market. At least one of these criteria has to be met.

For criteria (1), this matches the definition proposed by the Iowa State University. Global companies are companies that sell their products or provide services in many countries or have operations in many countries (Huebsch, Russel, Kokemuller, 2017). This is similar to Thompson (2017) definition that stated global company as a large company that has headquarter in one country and operates in several countries (Thompson, 2017).

For criteria (2) on product differentiation for other market, this show similarity with Azevedo & Bertrand (1999) that cites McDonalds as an example for creating different menus for different countries. They indicated a global company as a company that adapt to local communities by having a multinational business and marketing strategy. This company integrates its business unit to focus on marketing strategy depending on different countries (Azevedo & Bertrand, 1999). India's largest biopharmaceutical company, Biocon Limited have different range of products to address the needs of patients from 120 countries (Biocon, 2016).

Meanwhile for criteria (3), one of the main indicators for a global company is to generate profit from export activity. Knight, Madsen and Servais (2004) stated that they have 25% income from export activity while Chetty & Campbell-Hunt (2004) stated that their export ratio are 50% (Amzan, 2009). Based on FGD session, Participant 2 mentioned Sunzen Life Sciences Sdn. Bhd. has generated 25% of export revenue from their total sale.

For criteria (4), presence in the stock exchange market is also a common trait for global companies worldwide. For instance, biotechnology companies are in the top 100 in the world biggest public companies (Forbes, 2017) which consist of Pfizer (no.47), Novartis (no.61), Sanofi (no. 88) and Merck (no.100).

Decision for IPO listing is solely dependent on a company's jurisdiction. Some of the companies will not be looking into IPO as their holding companies are already listed. However, companies that are only listed in Malaysia stock exchange without generating export revenue will only be considered as potential global companies. Meanwhile, companies listed in foreign stock exchange listed companies are established as existing global company.

Hence, based on the proposed definition from Bioeconomy Corporation with four listed criteria, researcher would like to recommend a refined global company definition under NBP as follow:

"A Malaysian Biotechnology Company which fulfilled at least one of the following criteria namely the company's presence in origin and other country, has export revenue, has product differentiation to suit other market or listed in foreign stock exchange"

Otherwise, companies listed in Malaysia stock exchange without having export revenue will be entitled as potential global company status. Later, this proposed definition should be reviewed and tabled to Bioeconomy Advisory Board for further discussion and endorsement. Both participants agreed that 20 global companies will be nurtured in the end of NBP Phase III, year 2020.

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Article

The Marketing of Genetically Modified Food with Direct and Indirect Consumer Benefits: an Analysis of Willingness to Pay

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ABSTRACT

Genetically modified foods have traditionally been marketed as having direct industry benefits. Whereas, consumer benefits of genetically modified foods have been largely indirect, through price reduction. This study explores the marginal effects of differing value propositions on consumers' acceptance and willingness to pay for genetically modified foods among Canadians. Consumers' exposure to genetically food advertisements with industry-oriented benefits lowered both purchase intention and willingness to pay for genetically modified food. Consumers' exposure to non-genetically modified food advertisements with direct consumer benefits increased both purchase intention and willingness to pay. Most noteworthy, consumers' exposure to genetically modified food advertisements with both direct consumer benefits and industry-oriented benefits increased their willingness to pay. These findings provide insight into the future of successful genetically modified food marketing.

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INTRODUCTION

Genetically modified (GM) food for human consumption has been a subject of intense public debate, as well as academic research. Despite the lack of scientific evidence to suggest GM foods are less safe than conventional foods, researchers have shown that consumers are reluctant of fully embracing the technology. For example, Lusk, Kurlander, Roucan, and Taulman[1] conducted a meta-analysis of 25 prior studies on GM food and reported that consumers placed a lower value on GM food relative to non-GM food. More recently, Hess, Lagerkvist, Redekop, and Pakseresht[2] conducted a meta-analysis of 214 relevant studies on the subject matter and concluded consumers responded negatively to GM foods with benefits such as increased food supply, price discounts, or extended shelf life.

Indeed, GM foods have typically been positioned to have direct industry benefits for producers, such as increased supply and prolonged shelf life. The benefits for consumers are mainly indirect, through price reduction.[3] Kaye-Blake, Saunders, and Cagatay[4] termed these industry-oriented GM products as the first generation of GM food (GM1). Giannakas and Yiannaka[5] argue that GM1 food is facing much opposition and negative evaluation because it lacks direct benefits for consumers.

However, it appears that the biotechnology industry has been trying to communicate the direct consumer benefits for some time. For example, in the mid-1990s, Calgene's Flavr Savr™ tomato was approved in the United States and Canada.[6,7] While the original value proposition of the GM tomatoes was industry-oriented, designed to delay ripening, thereby extending its commercial shelf-life, the marketing of the product focused on its enhanced flavour.[6] The

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second generation of GM products (GM2) is poised to create direct benefits for consumers, such as increased nutrition, better taste, and environmental sustainability.[4,8–9] GM2 food has the potential of changing the consumer perception and acceptance of GM food for the better, as well as increase yield for the anticipated population growth.[5] Colson and Hoffman[3] conducted a choice experiment in the US and revealed that American consumers were willing to pay more for GM foods with enhanced nutrition, compared to conventional products. Ison and Kontoleon[10] conducted a survey in the UK and found significant market support for GM2 foods, as a large portion of the British consumers surveyed (33%) were willing to pay a premium for GM products that contained both direct and indirect benefits.

However, there are a number of issues that still require further investigation. First, there are very few actual GM2 food products currently on the market. The vast majority of the studies contained in Hess, Lagerkvist, Redekop, and Pakseresht's[2] meta-analysis have employed scenarios with fictions GM foods. As noted by the authors, consumers are sensitive to how questions are framed in such studies.[2] As a result, it is difficult to delineate true consumer intentions and what portion of the responses were the effects of manipulation treatments. In this study, we intend to measure the marginal effects of the manipulation treatments. Such marginal effects can provide insights into the potential value of future communication and marketing of GM2 foods.

Second, Hess, Lagerkvist, Redekop, and Pakseresht[2] found that there are geographical disparities documented in the extant literature regarding the acceptance of GM1 food. For example, Canadian consumers were more likely to accept GM1 food than Japanese consumers. Dolgopolova and Teuber[11] found that Canadian consumers are likely to pay a lower price premium for health-enhanced foods. Accordingly, it is quite important to investigate the acceptance and willingness-to-pay (WTP) for GM2 food among Canadian consumers.

Third, while Hess, Lagerkvist, Redekop, and Pakseresht[2] found that consumers are largely insensitive to the type of food products in prior studies (mostly GM1 food), Dolgopolova and Teuber[11] argue that consumer responses to health-enhanced foods are product-specific. In this study, we employed three types of fictitious GM2 foods. We chose to include food produced from wheat (bread), canola (canola oil), and soybeans (tofu) as they are prominent Canadian crops.[12] Moreover, all of the mentioned crops have GM varieties approved on the Canadian market.[13]

LITERATURE REVIEW

Factors That Influence Consumer WTP for GM Food

The perceived benefits of GM foods have been shown to be one of the most important factors to predict consumer acceptance.[14,15] The recent research on consumer attitudes toward GM foods has indicated that the types of benefits for GM1 food, such as increased supply and prolonged shelf life, are not appreciated by consumers and are unable to generate price premiums.[2] Several scholars have argued that only direct benefits to consumers can elicit positive consumer attitudes and product evaluations.[3,10]

The perceived risks of GM foods have been shown to negatively influence consumers' WTP.[14–18] Moon and Balasubramanian[16] found that if consumers perceived risks associated with GM foods, they were willing to pay premiums to purchase non-GM foods. Similarly, Chiang, Lin, Fu, and Chen[18] found that the higher the risk perception, the more likely consumers were willing to pay a premium to avoid GM foods. Bukenya and Wright[17] found that consumers that had negative perceptions of GM food safety were willing to pay over 10% more for non-GM food.

Additionally, trust of the institutions involved in developing, regulating, and distributing GM food has also been shown to influence consumer attitudes.[15,19,20] The trust of the institution has been found to be important when assessing perceived risks and benefits.[20] For example, Li, Curtis, McCluskey, and Wahl[19] attributed Chinese consumers' WTP for GM food, in part, to their trust in the government as a food regulator.

A multitude of demographic factors, such as age, gender, and family income have been shown to have direct and indirect influences on consumers' acceptance of, and WTP for, GM food.[14–16]

Based on the findings reported in the extant literature, we present a base model of consumers' WTP for GM food that includes influencing factors such as perceived benefits, perceived risks, trust of institutions, and demographics. This model is similar to what Ison and Kontoleon[10] used in their study. The model can be expressed mathematically as follows:

$$\mathbf{WTP} = \beta_1\mathbf{*(Perceived\ Benefits\ of\ GM\ Food)} + \beta_2\mathbf{*(Perceived\ Risks\ of\ GM\ Food)} + \beta_3\mathbf{*(Perceived\ Trust\ of\ Institutions)} + \beta_4\mathbf{*(Age)} + \beta_5\mathbf{*(Gender)} + \beta_6\mathbf{*(Income)} + \beta_7\mathbf{*(Education)} + \mathit{error}$$

Of course, this paper is not intended to be a replication of Ison and Kontoleon's[10] UK study in the Canada context. We argue that, for better or worse, individual consumers have already accumulated some knowledge about GM food and formulated individual perceptions about GM food. Their attitude will influence their decisions. However, that is not to say that they would not respond to future marketing and communication attempts. Our intention is to detect the marginal effects of the communication treatments, controlling for participants' pre-existing attitudes.

Consumer WTP for GM Food with Additional Communication without Direct Consumer Benefits

Numerous studies have explored consumers' WTP for GM versus non-GM food.[3,14,16–19,21–27] Findings from these studies have been mixed. Product attributes, particularly value propositions, have resulted in differing WTP premiums. For example, when direct consumer benefits of GM food are not presented, consumers often assign a premium to non-GM food or discount GM food.[16–18,22–25]

In Chern, Rickertsen, Tsuboi, and Fu's[22] study of US and Norwegian consumers, a large number of consumers were willing to pay a premium to avoid GM food when no direct consumer benefits were communicated. Specifically, Norwegian consumers were willing to pay a premium of 54% and 67% to avoid GM-fed salmon and GM salmon, respectively. Although slightly less than Norwegian consumers, US consumers were willing to pay a premium of 41% and 53% to avoid GM-fed salmon and GM salmon, respectively. However, when a clear consumer-oriented value proposition was communicated to consumers, the willingness to consume increased significantly.[22] Similarly, Chiang, Lin, Fu, and Chen[18] found Taiwanese consumers were willing to pay a premium of 7% to avoid GM-fed salmon.

Noussair, Robin, and Ruffieux[23] did not communicate a value proposition when they explored French consumers' WTP for food made with GM corn. Their results showed that when participants observed a GM label, WTP decreased by as much as 30%. A second study conducted by Noussair, Robin, and Ruffieux[24] showed that as much as 35% of participants refused to purchase GM biscuits. Moreover, roughly 40% were willing to purchase GM biscuits, but only if they were priced significantly less than the conventional alternative.

Assuming there would be a price premium for non-GM food, Moon and Balasubramanian[16] explored US and UK consumers' WTP for GM cereal with no value proposition. Moon and Balasubramanian[16] found that US consumers were willing to pay less than UK consumers for non-GM cereal. However, both US and UK consumers were willing to pay premiums for non-GM cereal over GM cereal, suggesting a desire to avoid GM food.

In other studies of US consumers, findings support the preference of non-GM food over the GM alternatives. Communicating only industry-oriented benefits but not direct consumer benefits, Huffman, Shogren, Rousu, and Tegene[21] found strong support for the preference of the non-GM potatoes, vegetable oil, and tortilla chips, as consumers were willing to pay a 14% premium for over the GM alternatives. In their second study, Rousu, Huffman, Shogren, and Tegene[25] found that US consumers discounted GM potatoes, vegetable oil, and tortilla chips by 7% to 13% as compared to non-GM food. Similarly, Bukenya and Wright[17] found that US consumers were willing to pay a premium of roughly 20% for non-GM tomatoes over GM tomatoes with industry-oriented value propositions.

There has been strong evidence to support that consumers generally assign a discount to GM food compared to the non-GM counterparts. When consumers have been presented GM foods with various industry-oriented benefits, but without clear direct consumer benefits, they have perceived GM foods as less desirable than non-GM foods. In other words, the marginal value of additional communication of indirect benefits is negative.

$$\textbf{WTP} = \beta_A\text{*(Communicating Industry-Oriented Benefits of GM Food)} + \beta_1\text{*(Perceived Benefits of GM Foods)} + \beta_2\text{*(Perceived Risks of GM Foods)} + \beta_3\text{*(Trust of Institutions)} + \beta_4\text{*(Age)} + \beta_5\text{*(Gender)} + \beta_6\text{*(Income)} + \beta_7\text{*(Education)} + \textit{error}$$

Where βA is expected to be negative

> ***Hypothesis 1***: *When only industry-oriented benefits are presented, consumers will perceive a negative marginal WTP for GM food compared to a conventional alternative.*

Direct Consumer Benefits without Mentioning Genetic Modification

The labelling of GM foods is another controversial issue. Canada currently does not have mandatory GM labelling regulation.[28] As a result, communicating the direct consumer benefits of new and novel

foods without mentioning the fact that they are made with GM ingredients is a real option. While the ethical issue of doing so is questionable, there is no legal requirement to clearly identify GM foods providing there are no safety concerns or nutritional changes.[28] Prior research has suggested that consumers are increasingly conscious about the link between health and diet.[29–31]

As functional foods, or nutrition-enhanced foods, are becoming more popular, scholars have extensively investigated consumers' attitudes, willingness to accept, and WTP for such foods. It has been revealed that health claims on food items positively influence consumers' purchase intentions and WTP for functional foods.[32,33] Consumers' WTP is often influenced by consumers' knowledge about the nutrition enhancements.[34] Moreover, consumers have reacted positively when information on health benefits has been provided.[35] Research has also indicated that consumers seem to prefer simple health statements[36] and well-known healthier options, such as whole grain over fortified white bread.[35] In addition, consumers that insist on organic foods may be less likely to purchase nutrition-enhanced foods.[33] Furthermore, because health attributes are often considered an attribute that is difficult to detect immediately, many scholars argue that effective government regulation and proper labelling would play an important role in helping consumers make informed choices.[37–42]

The body of literature on functional foods and consumer acceptance thereof seems to suggest that consumers are generally willing to pay a premium for direct consumer benefits, such as enhanced nutrition and other health-related benefits. It is highly likely that in the context of GM2 food, a possible strategic option is to solely focus on communicating the direct consumer benefits without mentioning the GM attribute. We would expect that the marginal value of communicating direct consumer benefits is positive.

$$\textbf{WTP} = \beta_B{}^*\textbf{(Communicating Direct Consumer Benefits of Non-GM Food)} + \beta_1{}^*\textbf{(Perceived Benefits of GM Food)} + \beta_2{}^*\textbf{(Perceived Risks of GM Food)} + \beta_3{}^*\textbf{(Trust of Institutions)} + \beta_4{}^*\textbf{(Age)} + \beta_5{}^*\textbf{(Gender)} + \beta_6{}^*\textbf{(Income)} + \beta_7{}^*\textbf{(Education)} + \textbf{\textit{error}}$$

Where β_B is expected to be positive.

> ***Hypothesis 2***: *When direct consumer benefits are presented without mentioning GM, consumers will perceive a positive marginal WTP for the product compared to a conventional alternative.*

Clear Communication of GM Food with both Direct and Indirect Consumer Benefits

Prior studies have found that when clear direct consumer benefits are communicated, results tend to differ. For example, Colson[26] explored US consumers' WTP for antioxidant- and vitamin-enhanced GM produce. The author's findings suggested that US consumers were willing to pay premiums for produce that was enhanced via genetic modification. The author concluded that consumers may be willing to pay a premium for GM-labelled food. Colson and Huffman[3] and Colson, Huffman, and Rousu[27] received similar results and concluded that there may be an incentive for GM labelling. Although these findings suggest that labelled GM food with direct consumer benefits elicit favourable consumer responses, the authors may have overemphasized the importance of the GM labelling at the expense of the direct consumer benefits. A few other studies support the notion that direct consumer benefits result in WTP premiums.[14,19]

Li, Curtis, McCluskey, and Wahl[19] explored Chinese consumers' WTP for vitamin-enhanced GM rice and soybean oil. Li, Curtis, McCluskey, and Wahl[19] found strong support for GM-enhanced food, as nearly 44% of consumers were willing to pay a premium for vitamin-enhanced GM rice and 73% of consumers were willing to pay a premium for vitamin-enhanced GM soybean oil. Unlike Colson's[26] conclusion, Li, Curtis, McCluskey, and Wahl[19] attribute the increased WTP effect as result of the additional consumer health benefits, not its GM properties.

De Steur, Gellynck, Storozhenko, Liqun, Lambert, Van Der Straeten, and Viaene[14] explored consumer acceptance of GM food with health benefits related to neural-tube defects. Neural-tube defects are spinal cord and brain malformations in early human development.[43] Multivitamins with folic acid can reduce the risk of neural-tube defects. Neural-tube defects in the Shanxi Province are among the highest reported cases in the world. De Steur, Gellynck, Storozhenko, Liqun, Lambert, Van Der Straeten, and Viaene[14] explored the acceptance and WTP for GM rice with high folate content in Shanxi Province in China. De Steur, Gellynck, Storozhenko, Liqun, Lambert, Van Der Straeten, and Viaene[14] found that over 60% of consumers were willing to accept GM rice designed to contain folic acid. Moreover, nearly 80% of consumers were willing to pay a premium for GM rice designed to contain folic acid. Specifically, the average premium was 34% for the GM rice as compared to conventional rice. These results demonstrate strong consumer acceptance of and WTP for GM food aimed at reducing the risk of a severe illness.

Table 1: Marketing Messages

	Messages included in treatments		Note
	Industry-Oriented Benefits	Direct Consumer Benefits	
Condition 1	Yes	No	This condition is similar how GM1 food has been typically marketed.
Condition 2	No	Yes	This is similar to how Functional Foods are currently being marketed. Without a mandatory GM labelling regulation, this strategy can be a realistic option for the future marketing of GM2 food.
Condition 3	Yes	Yes	This would be a comprehensive marketing strategy of GM2 food, highlighting both direct and indirect benefits.
	No	No	Having neither direct nor indirect benefit is an unrealistic scenario. Hence, this condition is *not* used in the survey.

These studies suggest that GM foods with clearly communicated and relevant consumer-oriented value propositions may have the potential to change the paradigm, receiving consumer acceptance and even price premiums in the marketplace.

$$\mathbf{WTP = \beta_A{*}(Communicating\ Industry\text{-}Oriented\ Benefits\ of\ GM\ Food) + \beta_B{*}(Communicating\ Direct\ Consumer\ Benefits\ of\ GM\ Food) + \beta_1{*}(Perceived\ Benefits\ of\ GM\ Food) + \beta_2{*}(Perceived\ Risks\ of\ GM\ Food) + \beta_3{*}(Trust\ of\ Institutions) + \beta_4{*}(Age) + \beta_5{*}(Gender) + \beta_6{*}(Income) + \beta_7{*}(Education) + error}$$

Where $\beta_A{*}$ is expected to be negative and $\beta_B{*}$ is expected to be positive.

Hypothesis 3: *When both industry-oriented and direct consumer benefits are presented, consumers will perceive a positive marginal WTP for GM food compared to a conventional alternative.*

METHODOLOGY

We employed online survey questionnaire method. Seven hundred and fifty (750) Canadian individuals over the age of 18 that lived in one of the western Canadian provinces (British Columbia, Alberta, Saskatchewan, and Manitoba) participated in the study.

The survey was experimental in nature. Participants were first asked a series of questions related to their general attitudes toward GM foods, including their perceived benefits of GM foods, perceived risks of GM foods, and trust of institutions in the context of GM foods. Participants were then randomly assigned to one of the three conditions (Table 1).

Each participant was shown three advertisements, one for bread, one for canola oil, and one for tofu. The advertisements in the first condition emphasized that foods were made with GM ingredients and that GM offers a number of industry-oriented value propositions that might indirectly benefit consumers. The benefits presented included higher yield, less pesticide usage, and increased global food supply. The messages contained in this condition were similar to typical messages in current GM food advertisements.

The advertisements in the second condition focused exclusively on the direct consumer benefits, such as better taste and enhanced nutrition. Advertisements in this condition did not mention genetic modification or any indirect benefits. This is similar to how functional foods are currently being marketed.

The advertisements in the third condition promoted both direct and indirect consumer benefits. These advertisements highlighted direct consumer benefits such as enhanced taste and nutrition derived through genetic modification.

After seeing these fictitious advertisements, participants were asked to indicate their intention to purchase (yes or no) and WTP for the products presented, relative to a conventional alternative.

Consumers' WTP for GM foods have been most commonly assessed via survey instruments.[14,16–18,19,22] or experimental auction markets.[3,21,23–27] Surveys have employed the contingent valuation (CV) method of for measuring consumers' WTP. In these studies, the CV method allowed respondents to make valuations of foods by choosing pre-determined price premiums or discounts relative to baseline prices. For example, given the baseline price of a conventional product, survey respondents were asked to assign a predetermined premium or discount for a GM alternative.

In this study, we employed the CV method for assessing consumers' WTP for the delineated foods

under the various conditions. The baseline price for a loaf of conventional bread was $3.00. The participants were asked to indicate how much of premium (or discount) they were willing to pay for the product shown in the advertisement. Similarly, the price for a one-liter bottle of conventional canola oil was set at $5.00 and the one pound package of tofu was set at $2.00. The participants were asked to indicate the premium (or discount) they were willing to pay for the products shown in the advertisements.

All participants also provided demographic information pertaining their gender, age, education, and household income.

RESULTS

Demographics

Of the 750 responses, 377 (50.3%) were female, 367 (48.9%) were male, and three (0.4%) identified themselves as an alternative gender identity. According to Statistics Canada (2015a), there is roughly the same number of males as females in Canada. Therefore, the gender of respondents was fairly representative of the Canadian population. All participants were over 18 years of age. Seven (0.9%) were between the ages of 18 and 25, 98 (13.1%) were between the ages of 26 and 35, 144 (19.2) were between 36 and 45 years of age, 162 (21.6%) were between the ages of 46 and 55, 16 (21.3%) were between the ages of 56 and 65, and 173 (23.1%) were 65 or older. Based on Statistics Canada's[44] population, all age categories in this study were fairly representative of the Canadian population. Per Statistics Canada[45] data, the distribution of respondents was reflective of the population distribution in Western Canadian provinces. Respondents' median household income range was $5,001 to $6,000 per month, similar to the Canadian median household income of $6,379 per month.[46] Overall, the respondent demographics were representative of the Canadian population.

General Attitudes toward GM and WTP

The participants' general attitudes toward GM foods, including their perceived benefits of GM foods, perceived risks of GM foods, and trust of institutions were measured adopting the multi-dimensional scale used in Rodriguez-Entrena, Salazar-Ordonez, and Sayadi's[15] study. Because multiple items were used to measure the factors, we conducted a confirmatory factor analysis to test the dimensionality and loading. Using SPSS Amos, we specified a structural equation model with measurement items to load onto the intended factor and each of the factors to co-vary. The result suggested that the three-factor model fit the data well, with both the comparative fit index (CFI) and the root mean square error of approximation (RMSEA) in the acceptable range (CFI=0.947; RMSEA=0.078). All item-to-factor loadings were above 0.60. Hence, we were satisfied with the convergent validity of the measurement. The items that loaded onto the same factor were averaged to created composite indices for subsequent regression analysis.

As previously stated, our baseline model specifies, as commonly documented in the literature, that consumers' WTP for GM food is influenced by their perceived benefits, perceived risks, perceived trust, and a number of demographic characteristics.

In order to generate confidence in this baseline model, we used general linear regression model in SPSS. First, we ran a regression model with purchase intention as the dependent variable. The result shows that, as expected, consumers' general attitudes toward GM, which already exist in the minds of the consumers prior to the marketing treatments, have significant influences on purchase intentions (Table 2). More specifically, in the bread condition, perceived benefits of GM food had a positive influence (β_1=0.308, p<0.001), perceived risks of GM foods had a negative influence (β_2=-0.214, p<0.001), and the trust of institutions had a positive influence (β_3=0.109, p=0.014) on purchase intention. Education, income, and age were not significant factors. However, gender influence was significant, as women tended to have lower purchase intentions (β_5=-0.075, p=0.021). Similar patterns are observed for the canola oil and tofu categories with minor variations (Table 2). For example, in the tofu condition, perceived trust of institutions was not a significant factor. However, age emerged as a significant predictor, where younger consumers exhibited a higher intention to purchase tofu (β_4=-0.083, p=0.021).

We also tested a model with WTP as the dependent variable. In this model, the dependent variable was actually the contingent, or marginal value of WTP, which was measured by the premium or discounts assigned by participants. In this model, we only selected the cases where the participants had indicated that they were willing to purchase (positive purchase intention). The results indicated that in the bread category, only perceived risks had a significant negative influence on marginal WTP (β_2=-0.169, p<0.001) (Table 3). In the canola oil category, perceived risks (β_2=-0.129, p=0.005), the trust of institutions (β_3=0.129, p=0.029), and household income (β_6=0.089, p=0.046) were significant predictors, while in the tofu category, none of the independent variables had significant influence.

Table 2: Purchase Intentions Baseline Model

Product Category	Bread		Canola Oil		Tofu	
	Standardized Beta	Sig.	Standardized Beta	Sig.	Standardized Beta	Sig.
Perceived Benefits of GM Food	.380	.000	.427	.000	.207	.000
Perceived Risks of GM Food	-.214	.000	-.235	.000	-.125	.001
Trust of Institutions	.109	.014	.118	.006	.003	.959
Gender	-.075	.021	-.088	.005	-.064	.078
Age	-.020	.541	-.039	.199	-.083	.021
Education	.029	.373	.021	.489	.065	.070
Household income	-.012	.708	-.019	.531	-.021	.559
Dependent Variable	Purchase Intention - Bread		Purchase Intention – Canola Oil		Purchase Intention - Tofu	
Model Statistics	Adjusted R^2 = 0.256		Adjusted R^2 = 0.323		Adjusted R^2 = 0.070	

Table 3: WTP Baseline Model

Product Category	Bread		Canola Oil		Tofu	
	Standardized Beta	Sig.	Standardized Beta	Sig.	Standardized Beta	Sig.
Perceived Benefits of GM Food	.092	.120	.030	.610	.114	.133
Perceived Risks of GM Food	-.169	.000	-.129	.005	-.100	.074
Trust of Institutions	.004	.950	.129	.029	.017	.822
Gender	.013	.764	-.006	.900	.092	.100
Education	-.014	.747	-.030	.504	-.084	.137
Household income	.055	.216	.089	.046	.065	.246
Age	.041	.359	.044	.326	.008	.885
Dependent Variable	Marginal WTP for Bread		Marginal WTP for Canola Oil		Marginal WTP for Tofu	
Selection Criterion	Purchase Intention = 1		Purchase Intention = 1		Purchase Intention = 1	
Model Statistics	Adjusted R^2 = 0.024		Adjusted R^2 = 0.026		Adjusted R^2 = 0.016	

Our H1 predicted that, with consumers' general perceptions of GM foods their demographic characteristics, further promotion of genetic modification, and the associated indirect benefits would have a negative influence on consumers' WTP. In order to test this hypothesis, we took the same two-step approach as described above and added the variable of promoting the indirect benefits into the model. The results indicate that the additional promotion of genetic modification and industry-oriented benefits of GM food (indirect consumer benefits) had a significant negative influence on purchase intentions in the bread (β_A=-0.149, p<0.001), canola oil (β_A=-0.152, p<0.001), and tofu (β_A=-0.141, p<0.001) categories. Furthermore, promoting industry-oriented benefits had a significant negative influence on marginal WTP in the bread (β_A=-0.217, p<0.001),canolaoil(β_A=-0.209,p<0.001),andtofu(β_A=-0.163, p<0.001) categories. Hence, H1 was supported.

Our H2 predicted that the promotion of direct consumer benefits without mention of the presence of genetic modification would have a positive influence on consumers' WTP. In order to test this hypothesis, we added the variable of promoting direct consumer benefits into the baseline model. The results indicated that, the promotion of direct consumer benefits with no mention of genetic modification had significant positive influences on purchase intentions in the canola oil (β_B=0.107, p<0.001) and tofu (β_B=0.101, p<0.001) categories, but was not statistically significant in the bread category (β_B=0.061, p=0.056). Moreover, promoting direct consumer benefits had significant positive influence on marginal WTP in the bread (β_B=0.245, p<0.001), canola oil (β_B=0.200, p<0.001), and tofu (β_B=0.160, p=0.003) categories, supporting H2.

Our H3 predicted that when both industry-oriented and direct consumer benefits were promoted they would have unique and significant influences on consumers' WTP. In order to test this hypothesis, we added both variables promoting both the industry-oriented and

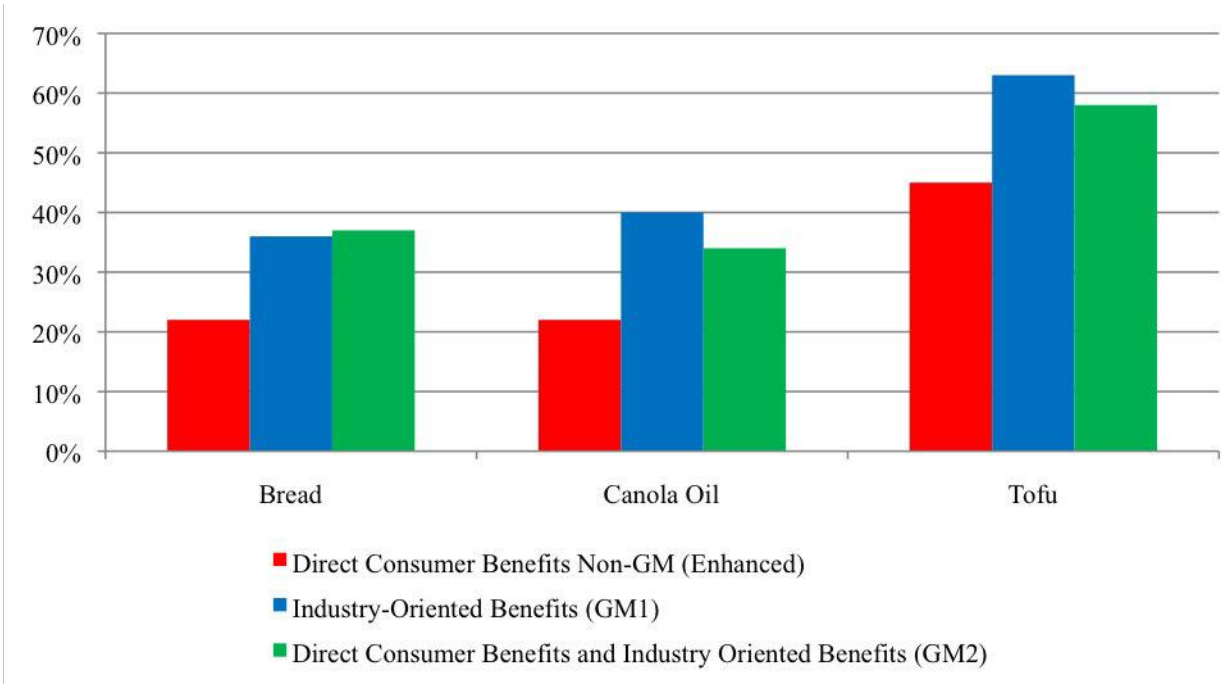

Figure 1: The Non-Purchasing Segment

Table 4: Non-Purchasers ANOVA

Product Category		Sum of Squares	df	Mean Square	F	Sig.
Bread	Between Groups	3.678	2	1.839	8.671	.000
	Within Groups	158.430	747	.212		
	Total	162.108	749			
Canola Oil	Between Groups	4.381	2	2.191	10.303	.000
	Within Groups	158.819	747	.213		
	Total	163.200	749			
Tofu	Between Groups	4.602	2	2.301	9.493	.000
	Within Groups	181.072	747	.242		
	Total	185.675	749			

direct consumer benefits into the baseline model. The results indicated that, the promotion of industry-oriented benefits had a significant negative influence on purchase intentions in the bread (β_A=-0.156, p<0.001), canola oil (β_A=-0.129, p<0.001), and tofu (β_A=-0.114, p=0.005) categories, while the simultaneous promotion of direct consumer benefits had no significant influence on purchase intention in any of the categories. In terms of WTP, the results indicated that, as expected, the promotion of industry-oriented benefits had a negative influence on WTP. But these negative influences were only significant in the bread (β_A=-0.117, p<0.001) and canola (β_A=-0.141, p<0.001) categories, not in the tofu category (β_A=-0.107, p=0.098). The simultaneous promotion of direct consumer benefits had a positive influence on WTP. The influences were significant only in the bread (β_B=0.183, p<0.001) and canola oil (β_B=0.129, p<0.001) categories, but not in the tofu category (β_B=0.101, p=0.108). Therefore, H3 was only partially supported.

Non-Purchasers

There were a substantial number of the participants that were not willing to purchase bread, canola oil, and tofu in all three treatment groups (Figure 1).

ANOVA was conducted in order to compare the percentage of participants not willing to purchase bread, canola oil, and tofu among the three treatment groups. Statistically significant differences were found among bread, canola oil, and tofu non-purchasers (Table 4).

Table 5: Multiple Comparisons of Non-Purchasers

Product Category	(I) GROUP	(J) GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Bread	Enhanced	GM1	-.14562*	.04107	.001	-.2421	-.0492
		GM2	-.14967*	.04107	.001	-.2461	-.0532
	GM1	Enhanced	.14562*	.04107	.001	.0492	.2421
		GM2	-.00405	.04144	.995	-.1014	.0933
	GM2	Enhanced	.14967*	.04107	.001	.0532	.2461
		GM1	.00405	.04144	.995	-.0933	.1014
Canola Oil	Enhanced	GM1	-.18206*	.04113	.000	-.2786	-.0855
		GM2	-.12538*	.04113	.007	-.2220	-.0288
	GM1	Enhanced	.18206*	.04113	.000	.0855	.2786
		GM2	.05668	.04149	.359	-.0408	.1541
	GM2	Enhanced	.12538*	.04113	.007	.0288	.2220
		GM1	-.05668	.04149	.359	-.1541	.0408
Tofu	Enhanced	GM1	-.18627*	.04391	.000	-.2894	-.0831
		GM2	-.12959*	.04391	.009	-.2327	-.0265
	GM1	Enhanced	.18627*	.04391	.000	.0831	.2894
		GM2	.05668	.04430	.407	-.0474	.1607
	GM2	Enhanced	.12959*	.04391	.009	.0265	.2327
		GM1	-.05668	.04430	.407	-.1607	.0474

*. The mean difference is significant at the 0.05 level.

Post-hoc Tukey tests revealed that the percentage of participants not willing to purchase GM food with industry-oriented (GM1) and direct consumer benefits (GM2) were significantly higher than non-GM with consumer benefits (enhanced) (Table 5).

Consumer purchase decisions are influenced by many factors. It was not surprising that some consumers were not willing to purchase bread, canola oil, or tofu. However, it is telling to observe that there were significantly more participants not willing to purchase bread, canola oil, and tofu made with GM ingredients as compared to non-GM bread, canola oil, and tofu with consumer benefits. This suggests that some consumers are unwilling to purchase food based on the presence of GM ingredients. Moreover, the lack of statistical difference between the percentages of participants not willing to purchase GM food with industry-oriented (GM1) versus GM food with direct consumer benefits (GM2) implies that some consumers are not willing to purchase food made with GM ingredients no matter how the advertisers describe the potential benefits.

GM2 Purchasers versus Non-Purchasers

ANOVAs were conducted in order to compare purchasers and non-purchasers of food items containing direct consumer benefits. The results indicate that purchasers versus non-purchasers did not differ significantly in terms of their income or education across all treatment groups. Moreover, there was no significant difference in terms of age among purchasers versus non-purchasers of bread and canola oil. However, the age of tofu purchasers and non-purchasers differed significantly. The results suggested that younger participants were more likely to purchase GM2 tofu. Across all treatment groups, there was a significant difference in terms of gender among purchasers and non-purchasers, with male participants being more willing to purchase GM2 food.

Additional ANOVAs were conducted to explore the differences between purchasers and non-purchasers with respect to their perception of benefits and risks as well as the trust of institutions. The results indicated that, not surprisingly, the groups differ significantly on all three factors and among all treatment groups. The purchasers perceived the benefits as higher, the risks as lower, and information trust as higher than their non-purchasing counterparts.

DISCUSSION

Perceived benefits had a positive, and perceived risks had a negative, influence on consumers' purchase intention. Similarly, perceived benefits and risks had the

same effect on consumers' WTP. This supports previous conclusions conclusion that perceived benefits in consumers' decisions to purchase GM food.[14,15] Moreover, the negative effect of perceived benefits on consumers' decisions to purchase GM food further supports extant literature.[14–18] The trust of institutions also proved to have a positive effect on purchase intentions and WTP. However, this relationship was only found in the bread and canola oil conditions. Although Yee, Traill, Lusk, Jaeger, House, Moore, Morrow, and Valli[20] found trust of institutions to be an important factor in Chinese consumers' WTP, we offer the thought that its magnitude of importance may not universal across products or countries. Nonetheless, the combination of benefits, risks, and trust of institutions are considerations of consumers and impact their purchase intentions and value assigned to GM food.

Our first hypothesis was supported, as consumers' exposure to industry-oriented GM food advertisements lowered both the purchase intention and WTP. This supports previous findings, suggesting consumers generally assign a discount to GM food with indirect benefits. We offer two explanations for these relationships. First, consumers' purchase intentions and WTP may be lowered as they assign little value to the industry-oriented benefits. Secondly, in terms of WTP, consumers may view these industry-oriented benefits as efficiencies that lower costs and therefore demand discounts in the marketplace.

Hypothesis two was also supported, as consumers' exposure to non-GM food advertisements with consumer benefits increased both their purchase intention and WTP. Intuitively this makes sense because direct benefits are presented to consumers in the absence of perceived risk from genetic modification. Logically, products are more appealing to consumers as more benefits are included in the offering.

Hypothesis three was partially supported, as consumers' exposure to GM food advertisements with direct consumer benefits and industry-oriented benefits increased their WTP in the bread and canola oil condition. However, this relationship was not found in the tofu condition. Nevertheless, it can be concluded that adding direct consumer benefits to GM food influences its perceived value. Of our findings, this is the most noteworthy. Our findings suggest that the value proposition, as opposed to solely how the food is made, is fundamental to consumers' WTP. Unlike previous studies that only explored consumers' WTP for GM food with industry-oriented benefits or direct consumer benefits in isolation, this study explores similar foods with differing value propositions. The implications of our study are great, both in terms of adding to the existing literature and GM food marketing.

IMPLICATIONS

Our study has several implications for academia. Our study adds to the growing body of consumer WTP for GM food research. Previous studies have separately explored consumers WTP for GM food with industry-oriented benefits and direct consumers benefits. However, our study is novel as it explores consumers' purchase intention and WTP for GM food with industry-oriented benefits (GM1), direct consumer benefits (GM2), and non-GM food with consumer benefits (functional food), providing evidence that value propositions play an essential role in consumer acceptance of food. Differing from the works of Colson[26] and Colson, Huffman, and Rousu[27], our study finds that the consumer-oriented value proposition, as opposed to the GM-nature of the food, drives consumer willingness to pay. The findings highlight the importance of agricultural biotechnology embracing a market-orientated culture. A major component of a market orientation is to understand the needs of the consumers.[47] As Wilson, Perepelkin, Zhang, and Vachon[48] have revealed, market-oriented biotechnology companies generally outperform non-market oriented counterparts.

Our study's findings have the potential to create significant value for agriculture biotechnology companies. Particularly, our study finds that consumers are willing to accept and pay premiums for GM food that has personally relevant value. The findings offer some support for the notion that changing the value proposition from producer to consumer, may assist in changing the negative connotation associated with GM food. Knowing that feeding the world in 2050 will require leveraging agricultural biotechnology[49] and increased genetic modification in agriculture, it is necessary to gain widespread consumer support. Perhaps creating GM food with direct consumer benefits will play a critical role in gaining such support. Not only does the promotion of direct consumer benefits have the potential to change the paradigm, as shown by this study's data, it may also be a profitable endeavor.

LIMITATIONS

While our study provides significant insight into positioning GM food for consumer acceptance and WTP, several limitations must be delineated. First, although our study was representative of Canadian demographics, it was limited to Western Canada. Second, the range GM foods were limited to bread, canola oil, and tofu. Third, this study was conducted via survey research and not in an actual marketplace setting. Finally, as differences were found among bread, canola oil, and tofu, it may be

of interest to explore other consumer acceptance and WTP for other foods at a national level.

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Study on the Detection of Total Colony in Medical and Health Environment Based on ATP Bioluminescence

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ABSTRACT

In this paper, the application of ATP fluorescence in the detection of colonies in the health environment of hospitals was studied. Firstly, the principle of ATP bioluminescence method was described. Then, ATP bioluminescence and plate count method were used to test the density of the surface of the objects in selected area, taking the time points 2 hours after disinfection as the time nodes. The results showed that the difference between the qualified rate of ATP bioluminescence assay and the plate count method was statistically significant {P<0.01}. Therefore, ATP bioluminescence method was highly correlated with bacterial culture method. The correlation coefficient of pass rate of the two methods was 0.782, which indicated that there was a positive correlation between the two test results. Besides, the detection results showed that ATP bioluminescence method had higher sensitivity than plate counting method. Therefore, ATP bioluminescence method was more suitable for the rapid detection of the colony of hospital health environment, and helps the hospital to better manage its environmental hygiene conditions.

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Key words: colony detection; plate count method; ATP fluorescence method; detection pass rate; correlation analysis

INTRODUCTION

Hospital infection is the main cause of morbidity and mortality. Therefore, the disinfection and inspection of hospital sanitation environment becomes the problem that must be solved. Domestic and foreign scholars have done some researches on environmental microorganism detection. Kiranmai S et al. [1] adopted the fixed plate method for 10 cases of OT treatment room, 4 cases of ICU room and 1 case LR for air sampling. Swabs were collected from different locations and the bacterial species were isolated and identified. It was found that the variation range of CFU of air bacteria in ophthalmic OT was 6-72 CFU/m3. The air rate of the bacterial CFU of ICU varies from 28 to 100 CFU/m3, and is occupied by pollutants such as bacillus, as well as potential pathogens such as klebsiella and pseudomonas. Fungal CFU is also seen in OT and ICU. High levels of microbial contamination suggest regular monitoring and early detection of bacterial contamination levels and prevention of hospital-acquired infections. Komatsu M [2] found that hospitals in Japan often outsourced the testing of environmental microbes, but the reporting period was low, and the value of microbial reports and the quality of nosocomial infection control systems declined. He suggested that the hospital should conduct timely detection of the sanitary environment to prevent bacterial contamination of the environment. In recent years, research on adenosine triphosphate (ATP) has developed rapidly, and some results have been applied to the detection of microorganisms. Cunningham AE et al. [3] found that visual and tactile assessment of food contact surface cleanliness to meet regulatory requirements might not be sufficient. The ATP-B test may be an effective microbiological detection tool that can help facilitate the implementation of more effective food contact surface cleaning operations for food companies. Wu H et al. [4] developed the rapid quantitative detection method of triphosphoric acid (ATP) bioluminescence, using pretreatment technology to eliminate interference and make detection more efficient. Besides, they compared it with

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microscopy and plate counting and determined the feasibility of using ATP bioluminescence detection method for the testing of the total number of bacteria in the probiotic product. In this paper, by compring ATP biofluorescence and plate counting method, the reliability of applying ATP biofluorescence method for the hospital health environment colony detection was verified.

1. ATP BIOLUMINESCENCE REACTION

1.1 The composition of hospital management staff

Adenosine triphosphate (ATP) [5] is a high-energy compound composed of phosphoric acid and adenosine which exists in nearly all biological activity inside cells, involved in the metabolic process of sugar, protein, nucleic acid, providing energy for cellular activities. In the microbial cells that survive the normal life cycle, ATP content is relatively constant. The ATP content of different biological cells is different, but usually maintained at between 10^{-18} ~ 10^{-15}, with the concentration around 10^{-13} mol/L. There is a linear relationship between the concentration of ATP and the number of microorganisms in stock. When cells are damaged or die, the ATP in the cells will be broken down by the enzymes of the cells, which will be lost rapidly and will not affect the detection of the living cells. Using this principle, we can detect the number of bioactive cells by detecting the amount of ATP.

The detection methods of ATP include electrophoresis, isotope tracer method and bioluminescence method [6-8], among which the bioluminescence method is the most simple and effective detection method. ATP fluorescence reaction principle is: Firstly, the cell lysate is used to destroy the cell wall or cell membrane of the active cell, release the ATP substance in the cell, and add fluorescein to the sample. Under the catalysis of magnesium ion and luciferase [9], a complex of fluorescein and AMP (adenosine monophosphate) and pyrophosphate are formed. Then the fluorescein and AMP (adenosine monophosphate) complex reacts with oxygen to make the fluorescein excited. Fluorescein will release photons and produce fluorescence when jumping to the normal state, which is expressed in the following equations.

$$ATP + \text{fluorescein} + \text{luciferase} \xrightarrow{Mg^{2+}} \text{fluorescein} + AMP + \text{pyrophosphate}$$

$$\text{fluorescein} - AMP + O_2 \rightarrow AMP + \text{oxygen fluorescein} + O_2 + \text{photons}$$

ATP concentration CATP has the following relation with luminous intensity [10]:

$$I = I_{\max} \times \frac{CATP}{K_m} + CATP \; I = I_{\max} \times \frac{CATP}{K_m} + CATP$$

Where I_{max} refers to maximum luminous intensity, K_m = 1 x 10^{-4}. When the ATP concentration is far smaller than K_m, the luminous intensity is proportional to the ATP concentration of the sample. Therefore, ATP concentration can be determined by measuring the luminescence intensity of the sample. The amount of ATP in bacteria is roughly the same, which is around 10^{-18} mol. The ATP content in the sample can be derived by measuring the intensity of the light, and the number of bacteria in the sample can be further determined.

2. Detection of bacterial colony in hospital sanitary environment

This paper used the ATP fluorescence spectrometer based on ATP bioluminescence technology to test the hospital environment colonies, and through contrast with plate count method, verify its performance. Below is the arrangement for verification.

2.1 Division and selection of medical and health areas

China's GB15982-2012 "hospital disinfection hygiene standards" divided hospitals into four categories. Class I environment is the operating room and other places that adopt the technology of clean air; Class II environment includes the intensive care area, newborn room, delivery room, protective isolation ward and other areas; Class III environment includes hemodialysis room, mother and infant room, hospital wards, etc .; Class IV environment includes infectious disease outpatient and ward, general out-patient department. While dividing the hospital area, the hygiene standards of the total number of colonies on the surface of the objects and the hand of the medical staff in the four types of areas are also clarified as shown in Table 1. Medical staff disinfection types are divided into surgical hand disinfection and hygiene hand disinfection. As for surgical hand disinfection, it refers to that the medical staff needs to use soap and flowing water to scrub their arms for disinfection before surgery. As for hygiene hand disinfection, it means that the medical staff needs to use soap and flowing water to scrub their arms for disinfection before treatment and nursing operations.

Table 1 Hygiene standards for the total number of colonies on the surface of environmental objects and in the hands of health care workers

Environmental category		Type of hand disinfection	Average number of colonies on the surface of environmental objects and in the hands of health care workers CFU/m^2
Class I environment	Clean operating department	Surgical hand disinfection	≤5.0
	Other clean places		
Class II environment			≤5.0
Class III environment		Hygiene hand disinfection	≤10.0
Class IV environment			≤10.0

This study took 2 representative operation rooms, ICUs, infant rooms, general hospital wards, hemodialysis units, the infectious disease department and the enteric diseases clinic from Beijing No. 309 Hospital and collected samples of the medical staff and the surface of the objects separately. A total of 10 specimens were collected every day in each region, including 5 hand samples from the medical staff, including 2 doctors, 2 nurses and a cleaning staff. The samples of the object surface were collected from bed column, operating platform, storage cabinet inner face, atomizer and the surface of the instrument, which was completed within three days, each performed 2 hours after disinfection.

2.2 Colony detection method

2.2.1 ATP fluorescence detection method

This study adopts the SystemSURE Plus ATP biofluorometer produced by American Hygiena company [11] and the Ultrasnap swab used with the fluorescence instrument [12]. The sampling steps are as follows: First, take out the matching swab and apply it to the hands of the medical staff and object surfaces. Object surface samples were taken within an area of 10cm x 10cm. After smearing was finished, the valve core was bended. Squeeze the swab twice to drop the liquid into the test tube, put the enzyme lysis solution, and shake it gently for 3 times. Insert the test tube after shaking into the test hole of the ATP detector. After 15s, the instrument will reflect the test result. Repeat the test five times, taking the mean of the test data as the experimental data. Data qualified evaluation standard shall be provided by merchants: RLU value ⩽10 means qualified, RLU value greater than 10 and less than or equal to 30 indicates that there is still microbial residue in the detection area, RLU value> 30 means unqualified.

2.2.2 Plate count method

Use a sterile cotton swab to smear the surface of the hands of the medical staff and regional objects respectively. After finishing the smear, rinse the cotton swab with 5 ml of sterile saline and pour the cleaning solution into the conical flask containing the jasmine master. Shake the suspension into bacterium suspension. Use 1ml of sterile Western sample homogenateand dilute it to 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9}. For each dilution, 1 mL sterile pipette or tip was changed. The 1ml sample was absorbed into the sterile plate, and the 15ml AGAR medium was poured into the plate and mixed evenly. After the agar was solidified, the plate was turned over and allowed to incubate at 36 ° C for 48 h [13]. The colony count can be observed by the naked eye, or by means of a magnifying glass. Colony counting unit is colony-formingunits. Plates where the colonies did not spread were selected for counting. If there is no obvious link between colonies on a plate, it can be regarded as a colony count.

2.3 Statistical analysis

In this study, SPSS18.0 software was used to make statistics on the data. Counting data were expressed as the number of samples (a) and pass rate (%) respectively. X^2 and J test were applied. $P<0.05$ indicates that the difference is statistically significant. Pearson correlation analysis was used to analyze the relationship between ATP fluorescence and plate count [14].

3. Sampling test results

3.1 Test results of hygienic qualification rate of object surfaces

As shown in table 2, the hygiene pass rates of Class I environmental objects were 96.7% and 100% respectively by using ATP biofluorescence assay and bacterial plate counting method. The hygiene pass rates of Class II environmental objects were 93.3% and 96.7% respectively; that of Class III environmental objects were 83.3% and 90%; that of Class IV environmental objects were 80% and 90%, respectively. The pass rate of ATP bioluminescence detection was statistically significant (P <0.05) compared with that of plate counting method. The overall detection rate of biofluorescence detection was lower than that of plate counting method.

As shown in table 3, the health pass rates of bed surface were 75.0% and 79.2% respectively using ATP biofluorescence assay and bacterial plate counting method; the hygiene pass rates of operating platform surfaces were 96.8% and 100% respectively; that of the storage cabinet was 91.7% and 100% respectively and that of the atomizer was 91.7% and 95.8% respectively. The pass rate on the surface of instrument was 87.5% and 91.7%. The pass rate of ATP bioluminescence detection was statistically significant (P <0.05) compared with that of plate counting method.

3.2 Hand hygiene test results of medical staff

As shown in table 4, the hygiene pass rates of the surface of Class I environmental objects were 93.3% and 100% respectively using ATP biofluorescence assay and bacterial plate counting method. The hygiene pass rates of Class II environmental object surface were 93.3% and 96.7% respectively, ; The sanitation pass rates on the surface of Class III environmental objects were 76.7% and 90% respectively; the sanitation pass rates on the surface of Class IV environmental objects were 66.7% and 80% respectively. The pass rate of ATP bioluminescence detection of medical staff in hand hygiene was statistically significant (P <0.05) compared with that of plate counting method.

Table 2 Test results of hygienic qualification rate of object surfaces of the two methods

Environment category	Total sample number	ATP bioluminescence detection		Plate count method		P value
		Qualified sample number	Pass rate /%	Qualified sample number	Pass rate /%	
Class I environment	30	29	96.7	30	100.0	<0.05
Class II environment	30	28	93.3	29	96.7	<0.05
Class III environment	30	25	80.0	27	90.0	<0.05
Class IV environment	30	24	80.0	26	86.7	<0.05

Table 3 Health pass rate of the two methods on the surface of five objects

Item	Total sample number	ATP bioluminescence detection		Plate count method		P value
		Qualified sample number	Pass rate /%	Qualified sample number	Pass rate /%	
Bed column	24	18	75.0	19	79.2	<0.05
Operating platform	24	23	96.8	24	100.0	<0.05
Storage locker	24	22	91.7	24	100.0	<0.05
Atomizer	24	22	91.7	23	95.8	<0.05
Instruments	24	21	87.5	22	91.7	<0.05

Table 4 The results of the hygienic qualification rate of the hands of medical staff of the two methods

Environment category	Total sample number	ATP fluorescence detection		Tablet counting method		P value
		Qualified sample number	Qualifying rate/%	Qualified sample number	Qualifying rate/%	
I environment	30	28	93.3	30	100.0	<0.05
II environment	30	28	93.3	29	96.7	<0.05
III environment	30	23	76.7	25	83.3	<0.05
IV environment	30	20	66.7	24	80.0	<0.05

4. Discussion

In the process of hospital diagnosis and treatment, patients may be infected again by age, disease, antibiotics, hospital environment and other factors, which will have adverse effects on the patients' health. However, some factors related to the hospital health environment and the diagnosis and treatment process can be controlled artificially. Sterilizing and cleaning [15] has always been an effective means to eliminate the unstable factors of health environment. Therefore, it is very important to evaluate the cleanliness and safety of hygienic environment after cleaning and disinfection. ATP is widely stored in living cells, which has become a marker of active cell detection [16], and the fluorescence principle of ATP has become an ATP detection direction. In this study, the Pearson correlation coefficient of the qualified rate of ATP bioluminescence detection and the pass rate of the plate count method was r=0.782, indicating that ATP can substitute the plate counting method to play the role of colony detection. Combined with the test results, we can see that the detection accuracy of ATP bioluminescence method is better than that of the plate counting method, which can detect the microorganism in the target area more accurately. Plate count method often requires sampling, dilution, cultivating, counting, calculation steps to detect the colony density in the target area, resulting in a large change of the samples, with 48 hours of cultivation, which greatly affects the accuracy of the test results. In contrast, ATP fluorescence detection method is easier to operate, and has a shorter inspection time, with higher timeliness and better precision.

5. Conclusion

ATP is widely stored in living cells, which has become a marker for active cell detection, and the fluorescence principle of ATP has become an ATP detection direction. In this paper, ATP bioluminescence method and plate counting method were used to detect the colony number and distribution in hospital environment, and the reliability of ATP bioluminescence method was verified. The detection results and Pearson correlation analysis showed that ATP biofluorescence could replace the plate counting method to detect the distribution density of the health colony in the hospital. Compared with the latter, the biofluorescence detection of ATP was more accurate and the operation was simpler, with higher timeliness. With the rapid development of photoelectric technology, the performance of ATP fluorometer will be improved gradually, which will benefit the hospital in assessing the disinfection effectiveness, helping to eliminate the microbial sources and ensure the safety and health of the hospital environment.

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Article

Strategy First, Execution Second: Why Life Science Entrepreneurs Should Adopt a Top-Down Mindset Early

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ABSTRACT

Despite the dedication of the management team and board to a company's success, an often overlooked component is the dynamics of the segment in which the company operates. In an effort to demonstrate the importance of the external view and how segment dynamics are likely to significantly impact the reality of companies, we analyzed recent data between 2015 and 2017 pertaining to financing events, M&A transactions and initial public offerings (IPOs) in three separate sectors: therapeutic devices, oncology therapeutics and antibiotics. The analysis presented will provide management with a valuable estimation of the required capital to achieve value-inflection milestones as well as the anticipated return on investment upon a liquidity event. These examples demonstrate the fundamentally different dynamics of these sectors, which will impact the path to liquidity as well as the probability to closing an exit transaction. For example, we found that therapeutic device companies have to be at or close to regulatory approval prior to an exit. In contrast, the oncology therapeutics segment supports healthy exits across all stages of clinical development. Despite the high unmet need for novel antibiotics, both financing and exits have been limited in this sector. Return on investment is greater upon an M&A transaction versus an IPO. The presented data demonstrates that exit opportunities and return on capital are largely sector-dependent. Thus, savvy management should adopt an external, market-driven evaluation and analysis rather than inward-looking and uniformed biased judgment. Crafting a mature, market-aligned strategy will increase the probability of success.

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INTRODUCTION

Evaluating the prospects of a life science company achieving liquidity and shareholder return is a highly complex endeavor hinging on multiple factors such as the strength of the science, the financibility of the value proposition, the size of the market, and the capability of the managing team. A dominant component, often grossly overlooked by management and Board, is the dynamics of the segment in which the company operates. As previously described[1], it is segment dynamics that often dictates the reality of a company and its path to success or failure.

Executives seldom adopt an objective and a statistical mindset when considering their specific sector dynamics and instead rely on incomplete and limited information. They focus on the specific circumstances of their company and personal past experiences and draw vague plans resulting in an uneducated financing strategy, predictions about valuations, future acquisition price or various other terms. More often than not, management is oblivious to the odds they face and fail to consider the enormous impact of the dynamics of their segment[2]. Decision-makers are thus likely to commit a planning fallacy, where they will be unrealistically close to best-case scenarios and unlikely to remedy their predictions by simply consulting the statistics of similar cases. However, if appropriate benchmarks are chosen,

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the external view is likely to provide a fairly accurate indication on a realistic approximate value for a transaction and likelihood for success.

The base rate is a prediction based on prior data and probabilities, absent of information specific to a particular situation. With regard to financing or merger and acquisition (M&A) transactions, the base rate is the likelihood that a transaction will close without considering the perceived probability of the specific transaction in mind. Unfortunately, base rate neglect is rampant and statistical facts rarely come into consideration. Instead, management tends to make big decisions based on little or no information and leap from little information to big conclusions. In our experience, management will almost always neglect to take the base rate into account and, consequently, decisions–making is unnecessarily exposed to additional risk to closing. It is this base rate that could provide executives and entrepreneurs with an early indication as to their probability of success and should thus be central to their developing strategy.

In an effort to demonstrate the importance of the external view and how segment dynamics are likely to significantly impact the reality of companies, we analyzed recent data in the three-year period between 2015 and 2017 pertaining to financing events, M&A transactions and initial public offerings (IPOs) in three separate sectors: oncology therapeutics, antibiotics and therapeutic devices.

METHODS

Data was collected from Pitchbook from 01/01/2015-12/20/2017. Oncology therapeutics companies were found by searching for "oncology" and "cancer". All companies falling within the therapeutic devices sector were screened. Antibiotic companies were found by searching for "antibiotic" and "anti-infective". In all cases, company descriptions were screened to determine if companies fit the desired sector. Financing encompassed Series A through D. Phase of development was found from ClinicalTrials.gov and company press releases. Outliers were removed via the ROUT method with Q of 1%. Some details on transactions were not always available. Capital to exit and deal size were not always available for all companies, resulting in some exits not included in Figure 5. In particular, smaller M&A deal sizes are not required to be disclosed to shareholders of public companies, resulting in the possible skewing of data to show an average higher deal value. This is particularly a concern in the therapeutic device sector. Exit values are considered the total deal value for M&As. For IPO exit values, market capitalization at 6 month post-IPO was used as this represents the typical lock-up period for investors holding stock post IPO.

RESULTS AND DISCUSSION

The amount of capital required to meet value-inflection milestones, investor appetite and likely path to liquidity is largely sector-dependent. The number of funded companies and total capital raise across three sectors is shown in Figure 1. As expected, the number of companies financed decrease based on series; there are far more early-stage Series A financing compared to Series D (Fig. 1A). This is partially due to exits (M&As and IPOs) and failures, given the diminishing probability of success along the product development cycle. The oncology therapeutics segment dominated in terms of number of companies financed and total capital raised, with almost $6 billion compared to $2 billion for therapeutics devices and a meager $400 million for antibiotics (Fig. 1A and B). Two hundred oncology companies received capital versus 149 therapeutic device companies and only 24 antibiotics companies (Table 1). The large market size and recent advancement of immuno-oncology appear to be enticing investors to participate in the long-term promise of the segment. Interestingly, although the antibiotics segment is expected to reach $57 billion by 2024[3], relatively little capital is deployed in this space. Difficulty in getting clinical approval and obtaining commercial traction due to the large number of generic options is likely cautioning investors[4].

Exit opportunities, comprising of M&As and IPOs, for the three sectors are shown in Figures 2, 3 and 4. It is clear that the oncology segment is highly acquisitive with a high risk tolerance as M&A transactions occurring at all stages, from pre-clinical through FDA approval (Fig. 2A). Acquirers are willing to pay top dollar for oncology assets (Fig. 2B). While there was a significant number of oncology IPOs, most occurred while the most advanced asset was in clinical trials, with very few pre-clinical or FDA-approved assets. Larger exits were observed the further the most advanced asset was in development as acquirers are willing to pay more for de-risked assets (Fig. 2B). It should be noted that there is a large amount of redundancy in the oncology sector as companies contend to develop multiple drugs for similar targets; for example, more than 20 antibodies are currently in development for PD-1 or PD-L1 alone[5] and ClinicalTrials.gov is reporting over 500 combination oncology clinical trials currently active or enrolling. This redundancy will likely result in numerous failures in the coming years as lead products outcompete others. In addition, patient recruitment is becoming a rate limiting factor for these

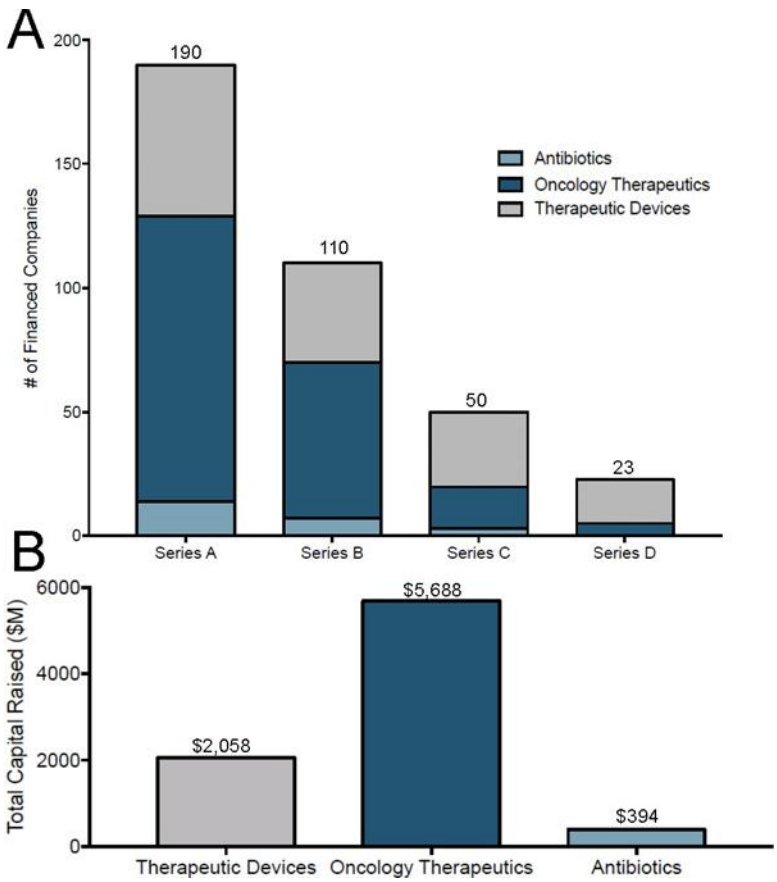

Figure 1: Oncology therapeutics sector dominates in number of financed companies and capital raised compared to tthe therapeutic devices and antibiotic sectors. Number of funded companies is shown, excluding seed, angel and late series (post-Series D) (A). The total amount of capital raised for each sector is shown (B). Data from 01/15-12/17 collected from Pitchbook.

Table 1: Summary of US financing and exit events 2015-2017. Numbers represented as mean ± SEM across all phases of development

	Therapeutic Devices	Oncology Therapeutics	Antibiotics
Number of Financed Companies	149	200	24
Total Capital Raised per Sector ($M)	$2,058	$5,688	$394
Number of M&As	64	49	12
Capital Invested to M&A ($M)	$60 ± 8	$82 ± 15	$182 ± 89
Time to M&A (years)	13 ± 1	9 ± 1	13 ± 3
M&A Deal Size ($M)	$140 ± 23	$1443 ± 743	$205 ± 110
M&A Return on Investment Multiple	8 ± 4	12 ± 3	2 ± 1
Number of IPOs	23	45	5
Capital Invested to IPO ($M)	$94 ± 19	$101 ± 10	$93 ± 12
Time to IPO (years)	13 ± 2	10 ± 1	10 ± 3
Market Cap at 6 months post-IPO ($M)	$133 ± 33	$473 ± 106	$152 ± 22
IPO Return on Investment Multiple	3 ± 1	4 ± 1	2 ± 1

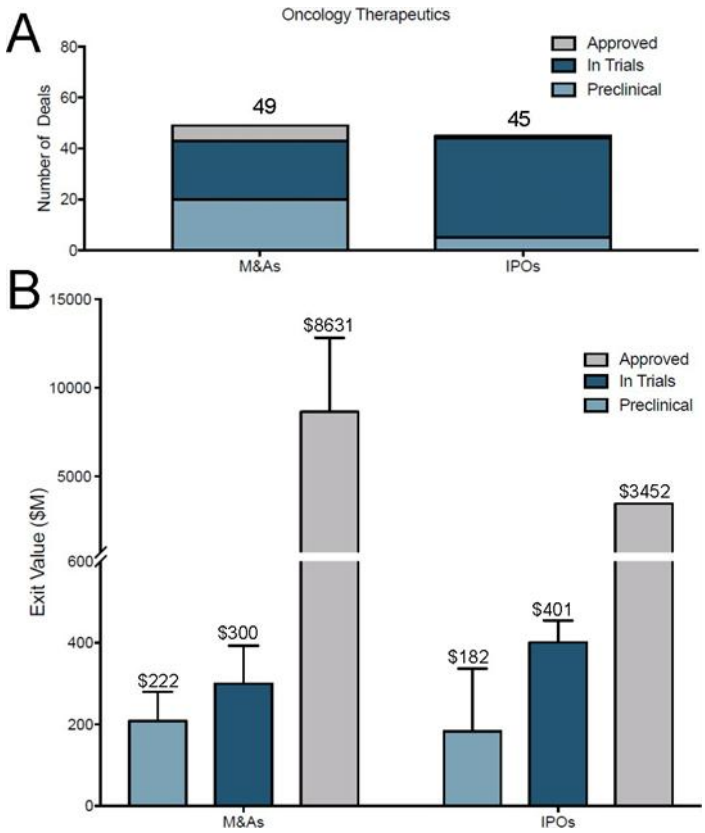

Figure 2: Exit opportunities for the oncology therapeutics sector happen early and often. Number of M&As and IPOs for the oncology therapeutics sector is shown (A). Total M&A deal value and market cap at 6 months post-IPO are shown (B). Note the large number of exits and large deal size, even when the assets are early stage. Data from 01/15-12/17 collected from Pitchbook. Error bars represent SEM.

companies. Therefore, while there is a vast amount of opportunity, the segment is heavily crowded suggesting that management teams should focus on clearly differentiated assets.

In sharp contrast, the antibiotics sector shows little exit opportunity with few M&As or IPOs (Fig. 3). This is due, in part, to a lack of appetite resulting from modest revenues from recently approved antibiotics[4] as well as unfavorable returns to private and public investors (Table 1). Of the limited exits, the majority occurred when the lead candidate was in Phase 3 trials or already approved. This indicates that raising both private and public capital for antibiotic assets is likely to be a challenge and that those companies will experienced heightened risk of undercapitalization. It will thus be wise for management teams in the antibiotics sector to focus on large funds with ample "dry powder" to support the company over the long haul, all the way to approval. Also, early partnerships with strategic players is much needed in this segment to curtail development risk. Indeed, there have been several partnership transactions recently, most notably the $387 million partnership of Roche with WarpDrive Bio to identify new antibiotic targets.

The therapeutic device sector exhibits distinctly different dynamics. While the sector supported healthy M&A activity and IPO opportunities, exits values are substantially lower than oncology or antibiotics (Fig. 4 and Table 1). Transactions typically took place at a late stage of product development where devices were approved (Fig. 4A). Furthermore, 50% of the companies reported revenues at the time of acquisition. There was no statistical difference between M&A deal value between products in trials or approved (Fig. 4B). In addition, it should be noted that those "in trials" had approval imminent (i.e. finishing clinical trials or approval application filed) and the vast majority were cardiovascular therapeutic devices, indicating that this sub-sector allows for slightly earlier and large deal values. The lower valuations of device companies is understandable given the lower capital requirements to bring a device to market compared to a drug. On average, 510(k) and PMA device approval cost $31 million and $94 million[7], respectively, versus a new drug, where cost is typically in excess of

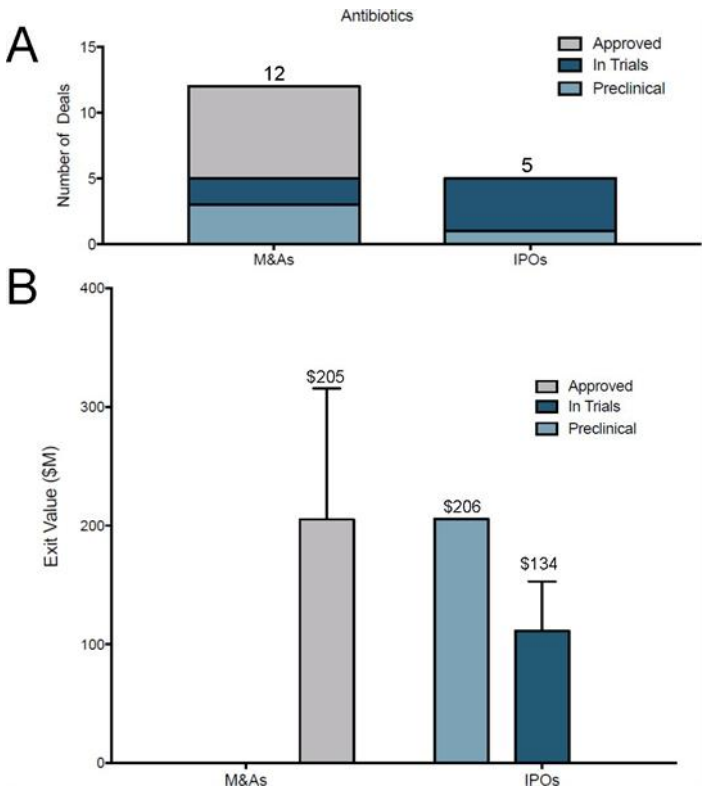

Figure 3: Exit opportunities for the antibiotic sector are limited. Number of M&As and IPOs for the antibiotic sector is shown (A). Total M&A deal value and market cap at 6 months post-IPO are shown (B). Note the limited number of exits and when they did occur, it was usually when the company had an asset approved. Data from 01/15-12/17 collected from Pitchbook. Error bars represent SEM.

$1 billion[6]. Therefore, the reduced capital requirement to achieve return in therapeutic devices, compared to traditional pharmaceutical therapeutics, is reflected in acquisition prices.

Return on investment at various stages of development across the three sectors is illustrated in Figure 5. While oncology therapeutic is a capital-intensive sector requiring large amounts of capital to propel assets through clinical trials, the M&A transaction size supports healthy returns on investment with correlation between invested capital and clinical development and consequently investor appetite (Table 1). Moreover, the oncology sector supports healthy returns at all stage of development as even early pre-clinical assets are attractive to buyers, and represents the best average return on investment. This point is of particular importance to management as it suggests a favorable probability of a successful capital raise (with lower undercapitalization risk) as well as multiple opportunities for a liquidity event across the development path. In contrast, both the antibiotics and therapeutic devices sectors did not support exits of pre-clinical and early clinical assets with most M&A transaction occurring at late clinical development or post-approval (Fig. 3A and 4A). In addition, the average time to exit is shorter in oncology compared to therapeutic devices and antibiotics, providing further incentives to investors (Table 1). Unlike oncology, the antibiotics sector did not demonstrate that return on investment is proportional the amount of capital raised. However, it should be noted that given the relatively few M&As in antibiotics, it is difficult to draw conclusions on potential for return on investment but it is anticipated that returns in this sector are unlikely to be favorable.

Contrary to common belief by many CEOs and Board members, the public market does not seem to provide attractive return on capital for investors in these sectors. While the public market certainly provides an avenue for raising capital as well as liquidity for investors, the M&A route is more attractive as indicated by valuations at exit (Figs. 2B, 3B, 4B) as well as M&A multiples (Table 1). This observation especially holds true for oncology therapeutics (M&A multiple of 12 ± 3 vs. IPO multiple of 4 ± 1) but also for therapeutic devices therapeutics (M&A multiple of 8 ± 4 vs. IPO multiple of 3 ± 1).

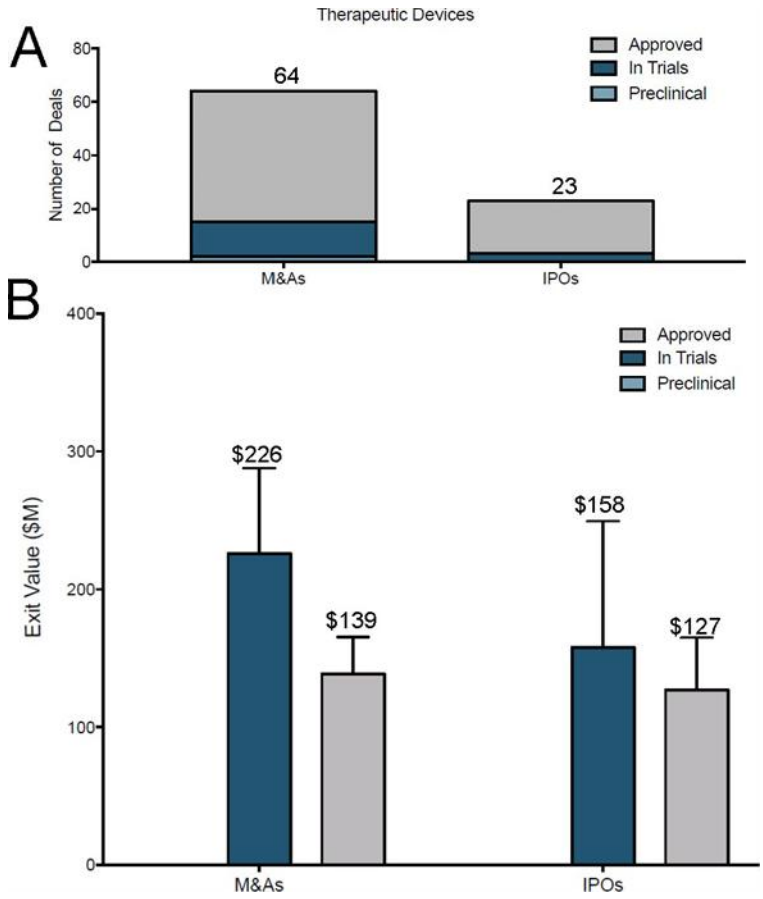

Figure 4: Exit opportunities for the therapeutic devices sector is satisfactory. Number of M&As and IPOs for the therapeutic devices sector is shown (A). Total M&A deal value and market cap at 6 months post-IPO are shown (B). M&A is the preferred route of exit for this sector and primarily occurs when the company has an approved asset. Data from 01/15-12/17 collected from Pitchbook. Error bars represent SEM.

CONCLUSION

So what actionable information can be learned by the adoption of a statistical mindset and a simple reflection on the data? If you are an entrepreneur running a young oncology therapeutics company, provided that the basic science is sound and differentiated, the investment community is likely to support your R&D efforts as substantial amount of capital flows into the segments and M&A returns on capital are lucrative. Moreover, segment dynamics with respect to pharma interest in oncology assets is more likely to allow for multiple exit opportunities along the drug development continuum, which, in turn, would provide a more favorable risk profile for all stakeholders; company, management and investors. The reality of entrepreneurs in the antibiotics segment is markedly different. The risk of undercapitalization is significant and would dictate targeting the limited universe of investors that are not only interested in the segment but also have ample capital to support the company all the way to phase 3 and beyond. As such, management teams of antibiotics companies should focus on large venture firms while avoiding the numerous small or mid-size firm that are highly unlikely to successfully participate in this sector. From a statistical point of view, these dynamics indicate that early discussion with corporate partners to propel product development is key. The required capital to exit in the therapeutic device sector seems favorable compared to antibiotics or oncology therapeutics suggesting appetite by the investment community to participate. However, as most exits take place at later stage of development, mostly post-regulatory approval, CEOs of therapeutics device companies should be cognizant of undercapitalization risk and seek investors that have enough capital to support the company at least through European approval (CE-Mark) as well as engage with corporate venture firms which may have a strategic interest in investing in technologies that would feed into the pipeline of their parent company.

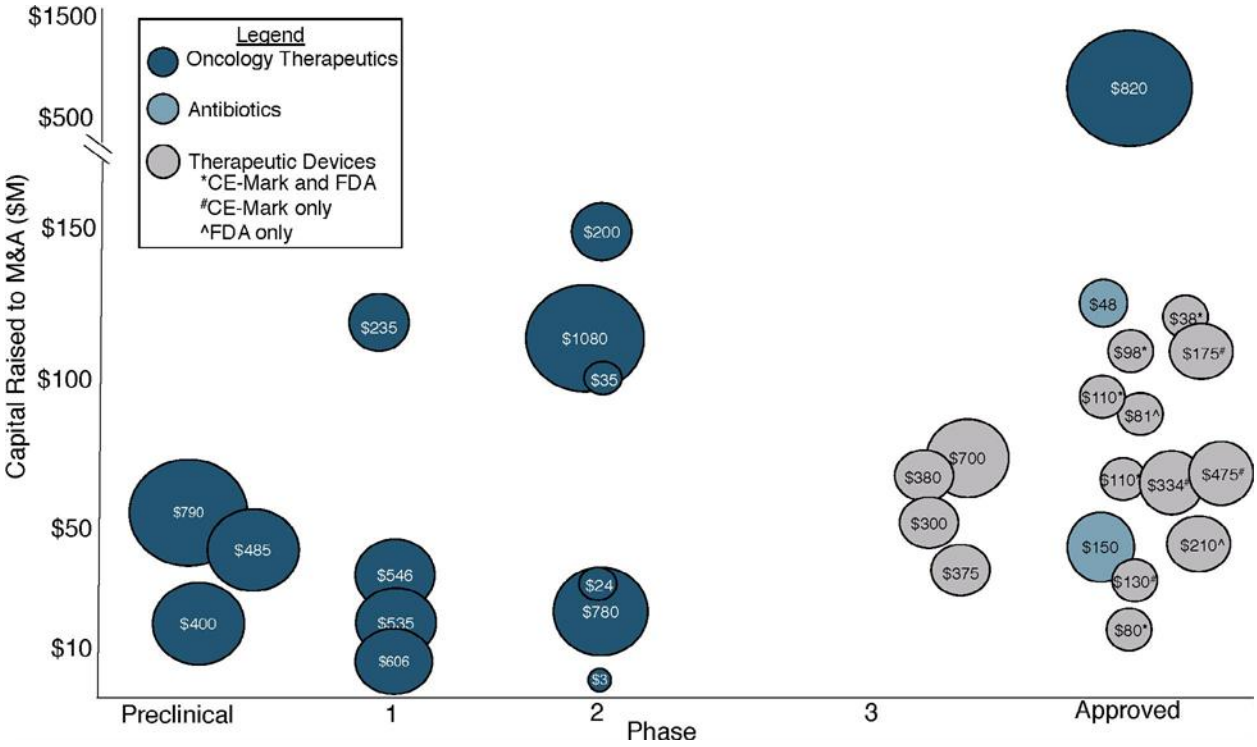

Figure 5: Sector dictates when M&As occur during product development, amount of capital needed to exit, and deal size. Deal size is shown within each circle and size of the circle is relative to M&A deal size. Oncology therapeutic exits happen earlier during product development for larger deal sizes compared to therapeutic devices that are typically approved before an exit or the limited number of exits in antibiotics. Note: M&A of therapeutic devices had completed trials and filed for approval. Data from 01/15-12/17 collected from Pitchbook and press releases.

Management must recognize and adapt to the dynamics of the sector in which it operates. It is imperative to adopt an outwardly, top-down (as opposed to technology-up), market-driven point of view from the outset. This includes developing a clear path to liquidity that is closely aligned with market characteristics or the behavior of investors as well as strategic players in your specific area. Focus on strategy first, execution second. Typically, a market segment will support a defined range of capital requirements, developmental paths and valuation inflections. While outliers do exist, a conservative strategy to follow a similar path to liquidity of the majority of benchmark companies will increase the probability of success. Entrepreneurs who evaluate their prospects based on a narrow, internally focused view, while relying on limited information and personal experience, rather than consulting the statistics of similar cases, are prone to grossly overestimate both their probability and degree of success. Management will thus be wise to avoid an internal myopic view of their company and reflect on external benchmark base rates.

The simple analysis presented here provides the base rates data for various sectors and should provide management with a good estimation as to the required capital to achieve value-add milestones as well as the anticipated return on investment. These examples demonstrate the fundamentally different dynamics of three sectors, which will impact the reality of companies in those sectors. Substituting external formal thinking, market-driven evaluation and analysis for inward-looking and biased judgment can go a long way in crafting a mature business case for your company as well increasing the probability of success.

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Intellectual Property Management

Patenting Bioinformatics Inventions: A Global Perspective

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ABSTRACT

Patenting bioinformatic inventions has become a ride on the rail to the scientists and inventors. Specifically in bioinformatics, drafting an invention in bounds of patentability criteria is one the most critical task for an inventor to protect his invention. As bioinformatics is a budding field of science, patentable subject matter in bioinformatics was not specifically defined by most of the patent offices in the world. In this regard, we have tried to explain patentable subject matter in bioinformatics by classifying bioinformatics into different subject fields. Additionally, we have tried to trace out patentable subject matter for bioinformatic inventions based on country specific patentability standards and granted bioinformatic patents of US, Europe, India, Canada and Australia.

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Keywords: bioinformatics; patentable subject matter; patentability; patents

INTRODUCTION

Bioinformatic scientists and program developers often prefer driving specifically towards patents as an intellectual property right for protecting their inventions in a broad concern [1]. The activity of biological computing has been brought under an umbrella of Bioinformatics. Researchers in the field of bioinformatics perform studies and invent novel approaches in intersection of Omic sciences like Genomics, Proteomics, Transcriptomics, Metabolomics, Metagenomics and Applied sciences like Molecular Biology, Biotechnology, Biochemistry with Mathematics, Engineering, Computer Systems and Computational Biology [2]. In a nutshell, bioinformatics is more focused towards modeling of biological systems and functions; analysis of biological data; generation models based on accumulated data from experiments; study of new data using mathematical models;recognition motifs in the experimental data;predicting functions of genes and proteins and In silico experiment [3].

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PATENTABILITY OF BIOINFORMATICS: A GLOBAL VIEW

In a global scenario, patenting bioinformatic inventions is comparatively different in different countries based on the country specific legal patenting standards towards bioinformatics. In United States (US) bioinformatic patents are considered under utility patents satisfying the major patentable criteria such as novelty, usefulness, non-obvious process, machine, manufacture and composition of matter. United States Patent and Trademark Office (USPTO) had categorized most of the bioinformatic and computer based biological inventions under "inventions implemented in a computer and inventions employing computer-readable media" [4, 5]. In contrast, Article 52 (2) (c) of European Patent Convention states that computer programs are not patent eligible [6]. However, the court decision in 1987 of *VICOM* [7] case

had transformed the things, blooming thoughts towards patenting computer programs in Europe. In support to this, the Enlarged Board of Appeal of the EPO issued on May 12, 2010 in case G 3/08 explained that the subject matter of a claim is not excluded from patentability under Article 52(2) & (3) EPC if the claimed subject matter, taken as a whole and independently of considerations of the prior art, has technical character. Moreover, there was an argument that a general purpose computer, programmed for a special purpose is, however, not excluded from patentability as long as it produces a "technical effect" [8].

India, being the world's largest sourcing destination for the information technology has adapted bioinformatics by merging biology and information technology. In these prospects, bioinformatics is being widely used by pharmaceutical companies for drug discovery and research institutes for analyzing huge chunks of genomic and proteomic datasets in collaboration with multiple information technology companies [9, 10]. As Indian bioinformatic scientists and inventors are busy in protecting their intellectual property by possible intellectual property rights, section 3(k) of Indian Patent Act states that "*a mathematical or business method or a computer programme per se or algorithms are not patentable inventions. Bio-informatics is a relatively young science and has emerged from the combination of information technology and biotechnology. Thus, the determination of patentability of inventions relating to bioinformatics requires special attention vis-a-vis exclusions under Section 3 (k) of the Act*" [11].

Canadian Intellectual Property Office (CIPO) had considered European and US patent law as a model in establishing their patent statutory landscape. Moreover, CIPO has exclusively included a section §17.02.04 for Bioinformatics under Patentable subject matter in Manual of Patent Office Practice (MOPOP) [12]. According to §17.02.04 MOPOP allows CIPO to take the position to exclude claims containing a computer model of a biomolecule which relies on the structural information of the biomolecule. However, computer models of biomolecules can be used in, for example, in silico screening methods. The mere presence of a computer model of a biomolecule in a method does not of itself render the method unpatentable [12].

The field of bioinformatics is not specifically defined in Australian Patent Law. However, it indulges fields like biotechnology, computer programs and business methods which are individually considered as a patentable subject matter (Satisfying the requirements of s18 Act are met). A decade ago, Australian Advisory Council on Intellectual Property (ACIP) has conducted a review on patenting of business systems. In the course of review, Australian Centre for Intellectual Property in Agriculture argued that bioinformatics was not a patentable subject matter as it includes only practical way to analyse large volumes of genomic data and claiming a sequence in a computer reliable medium, aiding patent holders to restrict others in using the computer reliable information [13-15]. However, ACIP did not consider their argument in the review process and as of now bioinformatics in a part is a patentable subject matter in Australia. Section 2.9.2.7 of Patent Manual of Practice and Procedure (PMPP) of Australian Patent Law states that, there are no specific exclusions to inventions that are implemented as computer software or a related product. However, they are only patentable if they meet the requirements for a manner of manufacture and in particular are not mere schemes, abstract ideas or mere information.

PATENTABLE SUBJECT MATTER IN BIOINFORMATICS

As bioinformatics is a blooming science, most of the countries doesn't possess a specific patentable subject matter criteria for patenting bioinformatic inventions. However, most of these country specific patent offices issue bioinformatic patents under closest predefined patentable subject matter criteria and relevant bioinformatic court case readings. In this scenario, we have tried to describe patentable subject matter in bioinformatics of different jurisdictions by classifying bioinformatic inventions. The classification of bioinformatic inventions described in Table 1 is designed based on classes and subclasses of Cooperative Patent Classification (CPC) such as G06F19 (Digital computing or data processing equipment or methods, specially adapted for specific applications), G06F1910 (Bioinformatics, i.e. methods or systems for genetic or protein-related data processing in computational molecular biology) and C12N15 (Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, e.g. plasmids, or their isolation, preparation or purification).

MOLECULAR MODELS

A molecular model visualizes the three dimensional structure. This involves usually proteins or a chemical process, as well as other biomolecules. Furthermore, establishing a biomolecular model using computational methods, algorithms and processes is considered to be an example for bioinformatics. Recently, in silico based techniques such as Computer-Aided Molecular Design

Table 1: A country specific comparative patentability view of bioinformatics inventions

	Australia	US	Europe	India	Canada
Molecular Models	-	-	-	-	-
In silico Screening Methods	+	+	+	+	+
Systems Biology Methods	+	+	+	*	+
Bioinformatic Databases	-	-	-	-	-
Bioinformatic Software	+	+	-	-	+
Biological Sequences	-	+	+	-	+

+ Patentable, -Not Patentable, * Unclear

(CAMD) are being used for the design of novel molecules in different fields. Globally, some patent offices such as Canada and EPO have different prospects in accepting and rejecting the patents claiming for molecular models, as the model itself equates to a graphical presentation of the underlying information [12]. In view of US patent office, molecular models are mere presentations of information which are considered as abstract ideas and are thus neither patentable under US patent law 35 USC §101. However, multiple grated patent records suggest that USPTO allows inventors in patenting methods of constructing molecular models [16]. As, molecular models are not considered as a patentable subject matter in most of the patent offices such as Europe under Article 52(2)(d), India under §3 (d), Canada §17.02.04, international patent applications comprising molecular models have been drafted and claimed in a different way with respect to the country specific patentability criteria[16]. Section 2.9.2.7 of PMPP of Australian Patent Law excluded patentability of molecular models stating that, an invention is not patentable if it is truly a scheme implemented on a generic computer, using standard software and hardware, then the invention will not result in an artificially created state of affairs.

IN SILICO SCREENING METHODS

Identification of ligand molecules in the process of Drug designing assisted by computational systems is considered as in silico screening [17]. Usually this part of research is classified under Computer Aided Drug Designing (CADD) in the process of drug designing [18]. In silico screening methods are treated as patent-eligible subject matter in USPTO, as they produce useful, concrete and tangible results. At the EPO and JPO, the same methods are also eligible for patent protection because they have technical characteristics and their potential for use in drug screening. However, multiple patent offices holds different views on the assessment of novelty and inventive step [19]. In fact, some of the recently granted patents by Canadian Intellectual Property Office (CIPO) details that in silico screening methods are considered as patentable subject matter in Canada [20]. According to our granted patent search analysis within the selected countries, we found that some granted Indian patents has claimed for in silico screening methods as such [21]. Moreover, § 2.9.2.7 of PMPP of Australian Patent Law clearly states that "a computer implemented method" can be patentable. Conversely, under a global comparative overview, acceptance of the in silico screening method patents always depends on the inventor who can draft the claims most precisely claiming only for the in silico screening methods as such.

SYSTEMS BIOLOGY METHODS

The era of Interactome biology has built a path for scientists and inventors to travel towards molecular interaction studies. Biological pathways are the strategic mutual interactions of molecules in a cell leading to establish a specific function [22]. In comparison with the last decade, patents in relation biological pathway based computational methods have been considerably increased [23]. In fact, in silico methods for developing biological pathways are usually considered as a patentable subject matter in US [24, 25]. However, US patent law (§ 101) does not permit the patenting of naturally

occurring biological systems [26]. European patent office has stringent criteria in accepting patents in relation with computational methods related to biological networks. Nevertheless, there have been some patents granted by EPO; covering the subject matter such as systems and methods for inferring biological networks [27]. A recent granted patent provides a view towards patenting systems biological invention in Canada; this patent claims for a method and system for modeling cellular metabolism [28]. In view of this and similar granted patents, systems biological inventions can be considered as a patentable subject matter in Canada. Our granted patent search analysis didn't find any relevant Indian patents in relation to systems biological inventions. Moreover, as per our search, we haven't found any supporting information in relation with the patentability of systems biological inventions in Indian patent office. Even though, there are very few patents granted by IP Australia (IPA) on systems biological inventions [29], IPA actually accepts patents in relation with systems biology, holding that the patent applicant has drafted and claimed for only methods and systems of systems biology satisfying novelty, non-obviousness, utility and other patentability criteria.

BIOINFORMATIC DATABASES

In relation to bioinformatics, a database is a compilation of biological information that can be easily accessed, managed and retrieved. Usually, a database intact is not considered as a patentable subject matter as it is a mere compilation of information. Nevertheless, a database may be provided for a patent protection, if it is not a mere compilation of information but is more likely to be a data processing system that holds a capability of converting a raw data in to a "tangible" outcome [30]. However, USPTO states that a database might not be considered as a patentable subject matter, if the database is merely a "data structure" or "nonfunctional descriptive material" [31]. Europe follows a different path in dealing with databases and their intellectual property rights. Article 52(2)(d) of European Patent Convention in accordance with the patentability of databases explains that any kind of presentation of information shall not be regarded as invention and cannot be considered as a patentable subject matter. However, in Europe databases are usually protected under copyright and *sui generis* right which give a right to protect the compiled information [32]. Section 3 (l) of Indian patent law directly states that Electronic databases are not considered as a patentable subject matter [11]. According to the CIPO, a database to be solely a collection of information, and is consequently considered to be disembodied and not an invention within the meaning of §2 of the Patent Act [33, 34]. In Australia, databases are actually protected under copyright protection [35] and are not considered as a patentable subject matter. However, not all foreign countries recognize copyright in codes, or data banks or tables; and some foreign countries may require some formalities to be met. In a global concern, databases are specifically not considered as a patentable subject matter. Nonetheless, databases are mostly protected under copyright laws of countries specific jurisdictions.

BIOINFORMATIC SOFTWARES

A logical compilation of machine readable instructions that directs system hardware to perform specific functions is considered as Software. Softwares that are specifically concerned towards biological implementations and applications are derived as Bioinformatic Softwares. Most of the countries consider software as a patentable subject matter in regard to their country specific patent laws. In US, in accordance with the Supreme Court and federal circuit statements, "a software program is more than a mere algorithm; the program may be eligible for patent protection" [36-38]. Since then, software does constitute patentable subject matter in US if it produces useful, concrete and tangible outcome. A recent version (July 2015) of USPTO guide lines of subject matter eligibility had shed light on patent eligibility of software patents [39]. In Europe, a computer program claimed "as such" is not a patentable invention [40]. Mere software program listings are considered under copyright protection and are not patentable. Article 52(2)(c) of European Patent Convention states that schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers shall not be considered as inventions [6]. Nevertheless, a patent can be granted for a computer-implemented invention, if it solves a technical problem in a novel and non-obvious manner. With regard to public welfare, India has developed more stringent criteria in accepting patents for computational inventions. According to the section 3(k) of Indian patents Act [11], "Computer programs *per se* and algorithms, mathematical methods" are not considered as patentable subject matter in India. According to CIPO, a computer software program may not be considered as a patentable subject matter as it is viewed as a abstract scheme, plan or set of rules for operating a computer and not to considered as an invention with respect to §2 of Canadian Patent Act [33, 41]. Nonetheless, software can be claimed by directing the claim to a physical memory storing the computer program as a claim to a physical memory falls within the category manufacture [41]. Australian patent law enables a diverse range

of software to gain patent protection. According to the Section 2.9.2.7 of PMPP of Australian Patent Law, software or programs in a machine readable form "causing a computer to operate in an improved or better way" are patentable. However, it should show some industrial application and should not be merely a procedure for solving a given type of mathematical problem which is not considered as a patentable subject matter [42].

BIOLOGICAL SEQUENCES

A biological sequence is a single, continuous extension of molecules in nucleic acid or protein. Section 101 [43] of US patent law permits the patentability of *"composition of matters"* and specifically USPTO has interpreted this to include DNA, RNA, and protein as *compositions* [44]. The things have been clearer after the Supreme Court decision in *Diamond v. Chakrabarty* case [45]. With reference to this case USPTO started granting patents for biological sequences as it is a "composition made by man," where the biological molecule has been isolated and purified from its natural setting [30]. On the flip side, a recent decision by US Supreme Court states "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring" [46]. Our granted patent search and analysis of biological sequence patents of US from 2006 to September 2015 suggest that there was a gradual decrease in granting practice trends from 2010. In connection to this scenario, patent grants on biological sequences had fallen down after 2010 (Supplementary. Fig.1). According to European Patent Convention, a mere discovery of natural substances, such as the sequence or partial sequence of a gene is not patentable. However, if an inventor provides a description of the technical problem they are intended to solve and a technical teaching they move from being a discovery to being a patentable invention [47]. A controversial debate is always active on patenting biological sequences in India. Merely isolated naturally occurring genes are not considered as an invention and are therefore deemed to be not patentable as per sub-section 3(c) of Indian Patent Act. However, patents covering genetic material in the form of cDNA and protein sequences have been granted by Indian Patent Office [48, 49]. §17.02 in Manual of Patent Office Practice of CIPO explains that a nucleic acid sequence or a poly peptide sequence can be considered as a patentable subject matter. Moreover, our granted patent analysis had also revealed some patents granted by CIPO with regard to biological sequences [50, 51]. A recent case decision by Australian high court in D'arcy V Myriad Genetics Inc & Anor case describes that an isolated nucleic acid, coding for a BRCA1 protein, with specific variations from the norm that are indicative of susceptibility to breast cancer and ovarian cancer, was not a "patentable invention" within the meaning of s 18(1)(a) of the Patents Act 1990 [52]. Patents claiming such biological sequences should also specify the use of particular biological material in the specifications of patent. As, if the invention relates to a gene, the specification must disclose a specific use for the gene, such as its use in the diagnosis or treatment of a specific disease, or its use in a specific enzymatic reaction or industrial process [53].

DISCUSSION AND CONCLUSION

In the world of digital life, where most of the day to day human life is conquered by computers, importance of computers and their applications in all the fields of sciences has increased enormously. Bioinformatics is a view of biology with computational prospectus, part of these applications have shortened the timelines of initial stages of drug discovery. In all of this regard, inventions in the field of bioinformatics have been comparatively increased and inventors would like to protect their inventions preferably in the form of patent as an intellectual property. As bioinformatics is a budding field of science, patentability standards and criteria were not specifically defined by most of the patent offices in the world. In this regard, we tried to explain patentable subject matter of bioinformatics based on CPC classification, available bioinformatics patents and traced out country specific patentability standards of bioinformatic inventions in US, Europe, India, Canada and Australia (Table.1). Table 1 provides a comparative overview of patentability of bioinformatic inventions based on patentable subject matter and granted patents in specific classified subjects in different jurisdictions.

According to our country specific comparative patentability view, USPTO seems to be the most liberal patent office opening gates for the inventors. In contrast, Europe and India have almost follow a similar stringent patentability criteria towards patenting bioinformatic inventions. However, some granted patents have cleverly drafted inventions indirectly claiming for the claims which cannot be claimed with regard to the patentable subject matter. Canada and Australia have a similar and neutral view towards patenting bioinformatic inventions. Comparatively, Canadian, Australian and US patent laws almost fall in a similar path in identifying an invention to be patentable subject matter. Satisfying all the patentable criteria, acceptance of a bioinformatic patent application solely depends on the inventors way of cleverly drafting the patent application concerning all the patentability statutory requirements.

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Intellectual Property Management

Patenting Therapeutic Methods: Statutes and Strategies

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ABSTRACT

Patenting medical therapeutic methods has become one of the toughest tasks for inventors and scientists in some jurisdictions where these methods are excluded from patentable subject matter. There are recent amendments by different countries in relation to patentability aspects of Therapeutic methods. In this scenario, analysis of these recent amendments would provide a path for researchers in the field to identify whether their inventions are considered as patentable subject matter. Our analysis sheds some light on different statutes and regulations of major jurisdictions on the patentable subject matter and patentability aspects of therapeutic methods. Furthermore, we have identified that most of the jurisdictions restrict inventors in patenting therapeutic methods. However, some countries such as United States and Australia allow patents related to therapeutic methods. We think adapting different strategies that are provided in this article would help researchers, inventors and patent attorneys in patenting the inventions related to therapeutic methods. Moreover, while applying the provided strategies, it is suggested that inventors should draft the patent claims by keeping a note of different statutes and regulations of countries in which they are interested to file the patent applications.

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INTRODUCTION

A medicine can be a drug or an art of preventing or curing a disease. The management and care of a patient to combat against any disease or disorder is considered as Medical treatment [1]. During early civilizations, Egyptians are the first to have a tradition of properly developed medicine [2]. In the due course of human life, humans started inventing different things and ways for better life and life style. Intellectual property rights specifically patent law has helped inventors to protect their inventions from un-incentivised exploitation. However, questions have been raised that this practice should not restrict the use of inventions related to common need and public health. Here is where the therapeutic methods had come into picture. Therapeutic methods also known as Medical treatment methods are procedures or techniques that are practiced for the treatment of humans or animals effected by a disease or illness. Patenting therapeutic methods has been restricted by most of the

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jurisdictions all over the globe. Nevertheless, some of the jurisdictions around the world allow inventers to patent therapeutic methods.

This article provides a comparative overview of patentability of therapeutic methods in major jurisdictions. Initial sections of the article elucidates the gist of statutes and precedents of specific jurisdictions that allows or excludes the inventions claiming therapeutic methods. In addition, this article sheds some light on possible strategies of patenting therapeutic methods, analyse some jurisdiction specific patents having therapeutic method claims, and examine the way in which inventers had strategically claimed different therapeutic methods. Expert opinion section of this article provides authors suggestions and recommendations on best strategies of patenting therapeutic methods in major jurisdictions followed by a comparative overview of patentability of therapeutic methods.

PATENTABILITY OF THERAPEUTIC METHODS: GLOBAL PERSPECTIVE

Inventions related to medical research are gradually increasing all over the globe. However, most of the inventions related to Medical research are of Medical instruments [3]. Inventions related to therapeutic methods are comparatively less due to the objections raised by most of the jurisdictions regarding patentability. Nevertheless, recent precedents made in some jurisdictions may help increase of patent filings in the field of therapeutic methods.

In United States, therapeutic methods are not excluded from patentability. So, for example, an invention related to treating a disease would be considered patentable in United States. However, according to §35 USC 287(c) [4] the patentee is disabled to enforce his patent rights on a Medical partitioner or a Health care entity in case of any possible infringement. In contrast, Article 53(c) of European Patent Convention [5] expressly excludes methods of medical treatment from patentable subject matter. The article clearly states that "the patents shall not be granted with respect to methods for medically treating human or an animal body through surgical or therapeutic and diagnostic methods practised on the human or animal body".

Australia has completely a different tale with lots of twists and turns in respect to patentability of therapeutic methods. Initially, the Australian Patent Office had a practice of denying patents claiming methods of medical treatment as, this kind of inventions are 'generally inconvenient' and 'essentially non-economic'. However, a verdict [6] delivered by the Australian High Court in the year 1972 against the decision of Commissioner of Patents to decline grant of a patent for a process of treating human hair and nails, eventually directed the Australian Patent Office to narrow its patentability exclusion with regard to methods of medical treatment. Additionally, in the year 1994, a full bench of Federal Court of Australia had considered patentability of methods of medical treatment [7]. Subsequently, in the year 2000, a full bench of Federal Court of Australia had affirmed that therapeutic methods of humans can be considered patentable in Australia [8]. Recently, in support to the previous Federal Court decisions, High court of Australia for the first time held that, a method of medical treatment, precisely, the administration of therapeutic drugs to humans, constitutes patent-eligible subject matter in Australia [9]. Based on all of these case decisions, the Australian Patent Office has revised its stand and opened doors to accept inventions related to process or methods of medical treatment of human body or part of it for patentability.

There are some major jurisdictions, which follows the path of Europe in patentability of methods of medical treatment. Specifically in India, any method or process for medical, surgical, curative, prophylactic or other treatment of human beings or animals is excluded from patentability under Section 3(i) of Indian Patent Act [10]. Similarly, according to Article 25(3) of the Chinese Patent Law [11], an invention can be decline for patent grant if the proposed invention includes any method or process of preventing, relieving or reducing the cause or focus of diseases in order to reinstate the health of a live human or animal or lighten its distresses. For example, if a substance is known, but its use as a pharmaceutical or for a particular method of treatment is not known, then a method of preparation of a pharmaceutical may be claimed, e.g. "the application of compound X for preparation of a pharmaceutical for the treatment of disease Y". Likewise, inventions related to methods of surgery, therapy or diagnosis of humans are not considered to comply with the "Industrial applicability" requirements according to Examination Guidelines for Patent and Utility Model in Japan [12].

Surprisingly, Canadian Patent Act doesn't provide any rules related to patentability or non-patentability of therapeutic methods in Canada. However, a decision delivered in a recent case [13] declines the patentability of therapeutic methods in Canada reasoning that, "granting monopoly over a method of medically treating a patient could affect with physicians' skill and judgment when treating patients". Nevertheless, an invention claiming use of a device or a compound to medically treat a disease or a disorder may be considered patentable in Canada, as long as the claimed invention does not limit the judgement and skill of a physician [14]. Figure 1

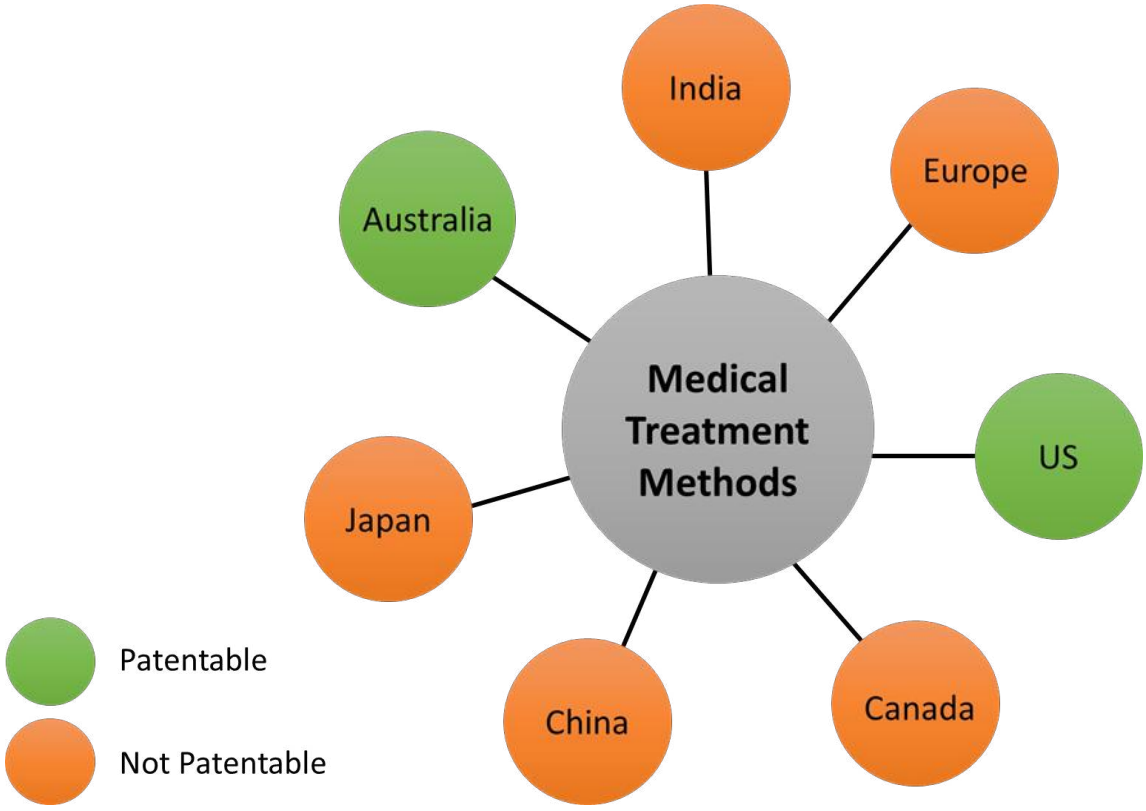

Figure 1: Comparative visualisation of Patentability of Methods of Medical treatment in major jurisdictions

provides a comparative overview of patentability aspects of therapeutic methods in different jurisdictions.

PATENTING STRATEGIES

As most of the jurisdictions restrict patentability of therapeutic methods, inventers adapt different claiming strategies to make their inventions related to therapeutic methods patentable. However, the claiming strategies adapted for patenting medical treatment inventions may vary significantly between jurisdictions.

Specifically, as discussed in the previous section, when the claims once directed to therapeutic methods, those specific claims are considered patentable in jurisdictions such as Australia and United States where the statutes and precedents allow inventors to claim so. On the other hand, the similar kind of therapeutic method claims are excluded from patentability in most of the jurisdictions around the world based on different statutes and precedents. In this scenario, most of the inventers try to protect the therapeutic products and their use. This particularly happens in the case of inventions related to drug compounds where, a first or further therapeutic use may be determined after the discovery of the compound.

Most of the jurisdictions in Asia-Pacific region preclude claims directed to methods of medical treatment. On the other side of coin, such inventions may still be protected using a strategy known as "New use of known compound or product". However, it is recommended that the inventers should check into specific jurisdiction where the "New use of known compound or product" claims are allowed. Adapting this strategy, a therapeutic invention can be claimed using "Swiss-type" claims according to the permissibility.

One of various claim strategies can be applied depending on the jurisdiction and their legal practice to get the inventions related to therapeutic treatment methods patentable. Most of the inventers follow a direct approach to protect their inventions by directing the claims towards methods of medical treatment itself. In this scenario, such claims can be allowed protection only if the claims are directed to (i) use of a new product and/or (ii) comprise steps of new method. Once such claims are drafted, they can be followed by examples describing treatment of a novel disease with the help of known compound or drug and directing methods to new treatment regimes.

Usually, claims which are directed towards therapeutic products are considered patentable but the claims

directed towards treatment using the claimed product are not permissible in some jurisdictions. In this regard, when a new product related to drug or a medical apparatus is developed, protection for the therapeutic use can be typically gained by the way the product is claimed. Nonetheless, mostly the contribution of an invention related to therapeutic treatment may be directed to use. The best example for this kind of cases would be therapeutically active compounds. For example, it can only be possible to demonstrate that a known compound is therapeutically useful only after the discovery of the product. In a similar way, a compound that has disclosure of usefulness for the treatment of specific disease or conditions may later be identified to be effective in treating other disease or conditions. In this scenario, claims directed towards known product, irrespective of its use; may not be considered patentable. However, these specific inventions can be gained protection by applying some other strategies for claiming a new use of known compound/product.

STYLES OF THERAPEUTIC CLAIMS

Patent attorneys and Inventers try to protect therapeutic inventions by adapting different claim types. Specifically, for patenting therapeutic methods in different jurisdictions, inventers try to adapt Swiss-type claims to get the inventions patentable. These Swiss-type claims are first been introduced in Europe and have gradually been adapted for patenting therapeutic methods in other jurisdictions. However, it was not yet clear whether the Swiss-type claims are successful in reflecting the broad scope of therapeutic methods for specific inventions.

In some instances, patent attorneys use Swiss-type claims for claiming different structures. For example, "Use of compound (X) for the manufacture of a drug for (a new therapeutic use)". These styles of claims are usually used to claim a secondary therapeutic use of a product in jurisdictions where therapeutic methods are excluded form patentable subject matter, for example, India. Moreover, Swiss-type claims are also adapted in jurisdictions like Europe for claiming any compound, if that specific compound is useful in a particular way.

For example, let us go through an Australian Patent [15], which covers Swiss-type claim as well as a claim of method of medical treatment.

Claim 1 – Swiss-type

Use of a cabostyril compound of (formula with the structure) or a pharmaceutically acceptable salt or solvate thereof, for the production of a medicament, effective in the treatment of disorders of the central nervous system associated with (the) 5-HT1A receptor subtype

Claim 7 – Method of medical treatment

A method for treating a patient suffering from disorders of the central nervous system associated with (the) 5-HT1A receptor sub-type (detailing about the disorder) comprising administering to said patient a therapeutically effective amount of a carbostyril compound of (formula with the structure) or a pharmaceutically acceptable salt or solvate thereof.

A recent case [16] decision from Australian Federal court held that Swiss-type claims could be suitably classified under method claims. Conversely, the justice did not treat the Swiss-type claims as different form of medical treatment method claims. Instead, the justice had followed the typical Australian style of constructing a claim to identify that the Swiss-type claim was focused on method of manufacturing a drug rather than a medical treatment method. Moreover, this decision had certainly avoided considering whether Swiss-type claims are patentable subject matter in Australian patent law. As therapeutic methods have been recently confirmed to be considered under patentable subject matter by High court of Australia, inventers can now confidently move on to draft methods of medical treatment claims directly rather than trying to reshape them into Swiss-type claims.

EXPERT OPINION

Therapeutic treatment methods are in practice from ancient periods of human life. In this scenario, most of the countries who oppose to provide protection to therapeutic methods believe that, considering therapeutic methods in patentable subject matter would allow monopolisation of inventions essential for human life specifically to public health [5, 10–12]. Moreover, as methods of medical treatment are very closely related to basic public needs, the practice of granting patents to these methods may ignite ethical issues in the future. On the other side of coin, countries who are allowing patents on methods of medical treatment believe that, considering these methods for patentability would obviously enhance innovation and creativeness in the specific subject field. Moreover, countries like United States who is one of the countries accepting medical treatment method patents, has taken clear measures to restrict monopolisation of patents by disabling the enforcement of patents granted on methods of medical treatment [4].

Inventers have adapted different strategies in patenting therapeutic methods in countries where such inventions

are restricted from patentability. Even though, inventers are cleverly drafting the therapeutic method claims, the patent examiners who have experience in examining similar kind of patent would obviously decline the claims that are excluded from the patentable subject matter according to their jurisdiction specific patent law. In some instances, even though such patent is granted with claims related to therapeutic methods, such patents would be challenged and specific claims would be invalidated through post grant opposition procedures. In this scenario, it is suggested that inventers, researchers and scientists who are working on similar research should have a preliminary check and go through the patentable subject matter of specific jurisdictions in which they are interested to file a patent application so that they can at least amend their patent application accordingly before submission. In some instances, this preliminary check would also help inventers to decide not to file an application that would save their application fees and other filing expenses. In this scenario, it is recommended that the researcher or scientist should consult a patent attorney who would help them with a legal advice.

CONCLUSION

It would be evident from our analysis that countries have different stands on accepting and declining patent applications related to methods of medical treatment. Most of the jurisdictions exclude methods of medical treatment from patentable subject matter. However, most of the jurisdictions have some provisions to allow use limited claims to therapeutic compounds, enabling protection for new therapeutic use of known compound. With this regard, the points that should to be considered are, some countries in the Asia-pacific region provide fewer guidance with respect to acceptability of use-related claims to therapeutic compounds except drugs. Comparatively, in jurisdictions like Europe, patent protection is allowed to new use of compound or a composition. Considering the scenario, it is suggested that patent offices may adapt the strategy of United States with regard to patenting therapeutic methods, which at least provides incentives to inventors in the form of a patent grant however, disabling the enforcement of the specific patent rights, which would substantially support the public needs.

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