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Commentary

21st Century Pharmacovigilance: Intuition, Science, and the Role of Artificial Intelligence

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ABSTRACT

In an environment of real world evidence, patient reported outcomes, expanding expedited and conditional review pathways for the treatment not only for cancers, but for a broad spectrum of serious and life-threatening diseases, we must care more than ever about pharmacovigilance via more regular and creative risk management plans to be sure, but also through a more diligent effort to understand just what "safety and surveillance" is about in the 21st century. At least part of the solution lies with something called "Artificial Intelligence."

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In an environment of real world evidence, patient reported outcomes, expanding expedited and conditional review pathways for the treatment not only for cancers, but for a broad spectrum of serious and life-threatening diseases, we must care more than ever about pharmacovigilance via more regular and creative risk management plans to be sure, but also through a more diligent effort to understand just what "safety and surveillance" is about in the 21st century. At least part of the solution lies with something called "Artificial Intelligence."

According to Dr. Bertalan Mesko, we are experiencing the Fourth Industrial Revolution, which is characterized by a range of new technologies that are fusing the physical, digital and biological worlds, impacting all disciplines, economies and industries, and even challenging ideas about what it means to be human. Healthcare will lead this revolution and artificial intelligence will be one of the major catalysts for change with actionable consequences.

Artificial intelligence has unimaginable potential. Within the next couple of years, it will revolutionize every area of our life, including medicine – and pharmacovigilance.

With the evolution of digital capacity, more and more data is produced and stored in the digital space. The amount of available digital data is growing by a mind-blowing speed, doubling every two years. In 2013, it encompassed 4.4 zettabytes, by 2020 the digital universe – the data we create and copy annually – will reach 44 zettabytes, or 44 trillion gigabytes.

Usually, we make sense of the world around us with the help of rules and processes that build up a system. The world of Big Data is so huge that we will need artificial intelligence (AI) to be able to keep track of it.

In a world increasingly driven by outcomes reporting and Big Data, *more* patient-level information from individual consumers is not always synonymous validated data. Despite the frustrating increase in the signals-to-noise ratio, artificial intelligence is becoming an ever-more significant source of potentially valuable electronically generated health care information.

The broader question is about the future of Real World Evidence. Once considered "junk science," Real World Evidence (clinical outcomes data not collected in conventional randomized controlled trials) is the new star on the precision medicine horizon and will help define the scope and strategies of 21st century pharmacovigilance.

21st century pharmacovigilance isn't just about uncovering, reporting, and addressing adverse events associated with already approved and marketed prescription medicines, rather it can be best described as the systematic monitoring of an "ecosystem" or in the words of the United Kingdom's Medicines and Healthcare Products Regulatory Agency "Monitoring the use of medicines in everyday practice to identify previously

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unrecognized adverse effects or changes in the patterns of adverse effects; Assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use; Providing information to healthcare professionals and patients to optimize safe and effective use of medicines; Monitoring the impact of any action taken."

Ground Zero for a real-world evidence regulatory pathway will be Sentinel, the existing public/private program that uses a variety of databases to track, collect and analyze adverse event reports about drugs, vaccines and medical devices. But the tool set for using this new treasure trove of health care information is nascent and the tasks as are daunting as the opportunities.

Consider biosimilars. A key issue driving the development of 21st century regulatory PV activities is the need for updated post-marketing surveillance of biosimilars. Issues related to the particularities of biologics (sources, process, quality requirements and new safety profiles) require sophisticated new thinking. Fundamentally, all of the players in the pharmacovigilance ecosystem will have problems characterizing biosimilar issues since we don't have an existing, validated predictive models of potential "hot spot" products, base ingredients or suppliers. Consequently, bio similar pharmacovigilance will have to evolve at the same time as new medicines are launched into this space.

Part of the solution to this post-marketing "indetermination" will certainly be strategies spear-headed by tools powered by artificial intelligence, and the first step should be to develop new epidemiological approaches based on a better understanding of the differences between the concepts of "generic" and "biosimilar." We already understand there can be different safety profiles for generics (based on differing bioequivalence ranges, excipient and API sourcing, etc.).

When it comes to biosimilar PV activities, however, variability-induced iatrogenesis concerns, differences between batches by multiple manufacturers, and the elastic definition of "similarity" aren't only questions of "safety profile," but also of "concept."

Artificial intelligence will facilitate what the pharmacovigilance ecosystem lacks today – a coordinated and efficient systems for developing actionable evidence on safety and effectiveness.

Today, the absence of these capabilities significantly impacts the public health by creating obstacles for patients and clinicians to receive the meaningful information they need to make informed decisions, perpetuating unnecessarily long delays and gaps in effective and timely safety communications and recall management, hindering the timely development of new and innovative treatment options, and increasing the overall costs and inefficiency of the healthcare system.

To improve the ability of patients to receive high quality, safe, effective, and timely care, better information via pharmacovigilance must be a priority as the world's many regulatory systems build the capacity to harness electronic health information to improve health, care quality, and safety.

In considering the role artificial intelligence can play in the both the near and long-term future of outcomes centricity, we need to discuss and internalize the concept of *Design Thinking* which requires intense cross examination of the filters used in defining a problem and to revise the potential opportunities before developing strategies and tactics. Design Thinking requires cross-functional insights into a problem by varied perspectives as well as constant and relentless questioning. In Design Thinking *observation* takes center stage. In the "Sciences of the Artificial," Herbert Simon has defined "design thinking" as the "transformation of existing conditions into preferred ones."

Unlike Critical Thinking, which is a process of *analysis*, Design Thinking is a creative process based around the creation of action-oriented ideas.

Artificial intelligence can be a revolutionary tool to develop those action-oriented ideas? And, just for the record, "action-oriented" and "pharmacovigilance" are not mutually exclusive terms.

Consider ISOP'S Special Interest Group, created in 2015 with the goal of designing novel risk minimization methods applied in a risk proportionate manner to specific populations.

In keeping with the theoretical underpinnings of Design Thinking and the practical applications of Artificial Intelligence, this initiative, (also referred to as the Post-Approval Vigilance Program), can more fully and swiftly develop a customizable decision aid yielding multiple levels of stringency to risk minimization interventions, leading to a more efficient, practical, and transparent planning of risk minimization activities.

To quote JM Eisenberg, the former Director of the US Agency for Healthcare Research and Quality, "Globalize the evidence, localize the decision."

There is so much data to utilize: patient medical history records, treatment data – and lately information coming from wearable health trackers and sensors. This huge amount of data must be analyzed not only to provide patients who want to be proactive with better suggestions about lifestyle, but also to serve providers with instructive pieces of information about how to design healthcare based on the needs and habits of patients, and provide regulators not just with more data, but better data *in context*.

We have not yet reached the state of "real" AI, but it is ready to sneak into our lives without any great announcement or fanfares – narrow AI is already in our cars, in Google searches, Amazon suggestions and in many other devices. Apple's Siri, Microsoft's Cortana, Google's OK Google, and Amazon's Echo services extract questions from speech using natural-language processing and then do a limited set of useful things, such as look for a restaurant, get driving directions, find an open slot for a meeting, or run a simple web search.

But can AI usage for adverse event reporting *and prediction* be far behind?

Here's a more worrisome question: Do regulatory agencies have the IT, AI, and human resources chops to suss out the wheat from the chaff? As Dr. Donald Therasse (former VP of Global Patient Safety and Global Medical Affairs at Eli Lilly & Co.) commented at a recent conference, "The fear is not that we will find new information; it's that we would overwhelm our current systems and capacity with poor quality information." These worries beg the question of what staffing levels and training is required to adequately and appropriately handle the 21st century demands for pharmacovigilance data that is usable at a regulatory level.

If you're wondering how global PV professionals from Washington to Delhi will address exponentially increasing amounts of Individual Case Safety Reports (ICSRs), sit back in your seats and consider that artificial intelligence will not only *operate* ICSR processing but also assist in their evaluation – including the direct collection of ICSRs from mobile devices.

Artificial intelligence is already found in several areas in healthcare, from data mining electronic health records to helping design treatment plans, from health assistance to medication management.

Artificial intelligence will have a huge impact on genetics and genomics, helping to identify patterns in huge data sets of information and medical records, looking for mutations and linkages to disease. There are companies out there today inventing a new generation of computational technologies that can tell doctors what will happen within a cell when DNA is altered by genetic variation, whether natural or therapeutic. Imagine the predictive capabilities for pharmacovigilance.

But making knowledge actionable requires the application of proven analytical methods and techniques in order to produce reliable conclusions. Until recently, such analysis was done by experts operating in centers that typically restricted access to data. This "walled garden" approach evolved for several reasons: the imperative to protect the privacy and confidentiality of sensitive medical data; concerns about the negative consequences that could arise from inappropriate, biased, or incompetent analysis; and, the tendency to see data as a competitive asset.

Regardless of the specific reason, the result has been the same: widespread and systemic barriers to data sharing.

If we are to reverse these tendencies and foster a new approach to creating evidence, we must bear in mind that there must be a common approach to how data is presented, reported and analyzed and strict methods for ensuring patient privacy and data security.

Rules of engagement must be transparent and developed through a process that builds consensus across borders and relevant ecosystem stakeholders. To ensure support across a diverse ecosystem that often includes competing priorities and incentives, outputs must be intended for the public good and be readily accessible to all stakeholders at the push of a button.

For any of this to work – and especially in the world of pharmacovigilace, we must view artificial intelligence through the lens of 21st century *interoperability*: the idea that different systems used by different groups of people can be used for a common purpose because those systems share standards and approaches.

What about the most popular current usage of artificial intelligence, mobile apps? According to a new research study fielded between December 2013 and January 2014, 72% of all US adult Rx patients are using mobile applications. That's reality.

A national survey of 2,216 US patients (age 18+ who take at least one prescription medication per day) show that whether you're a Millennial or a member of the Greatest Generation, you're using apps via a smart phone or a tablet.

According to Robert Jamison, PhD, professor of anesthesia and psychiatry at Harvard Medical School and pain psychologist with Brigham and Women's Hospital, mobile medicine is helping chronic pain patients cope with and manage their condition thanks to new smartphone apps, which can track patients from a distance and monitor pain, mood, physical activity, drug side effects, and treatment compliance.

And according to a new report just issued by the Center for Technology and Aging, medical optimization ("med-ops") via information technology is an important element to improving medication-related errors and improving medication adherence among older adults. The report says "widespread use" of technology aimed at this population could save thousands of lives and billions of dollars."

Philip K. Dick wrote, "Reality is that which, when you stop believing in it, doesn't go away."

Will our socio-economic "technology gap" lead to a more pronounced pharmacovigilance gap?" It's an important question. That's why it's crucial we remember

there is no one-size-fits all solutionLet's face it, when it comes to mobile phones, any gap is rather narrow.

But we have to think beyond apps and the role of artificial intelligence has to be front and center.

As the American industrialist Walter O'Malley once opined, "The future is just one damned thing after another." Much depends not just on infrastructure, but also on capabilities, and trust.

The end goal is the same for all stakeholders — ensuring optimal use of resources for healthcare systems; improving access to value-adding medicines for patients; and appropriate reward for innovation. But a key question we must ask ourselves is – will we control the data, or will the data control us?

As management guru W. Edwards Deming once quipped,

"*Change is not required. Survival is not necessary.*"

Artificial Intelligence is here. Ladies and Gentlemen, fasten your seatbelts.

Commentary

Agricultural Biotechnology is Much More Than Herbicide-Tolerant Crops

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ABSTRACT

Herbicide-tolerant genetically engineered (GE) plants have been a lightning rod for activists, who regularly attack them, citing a number of spurious objections. Contrary to their claims, the plants do not contain herbicides; rather they are resistant to the herbicides, in order to make weed control – an essential aspect of farming – more efficient and cost-effective. But molecular genetic engineering applied to crops has made monumental contributions in addition to herbicide-resistance, and these are discussed.

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Tomatoes offer an instructive story about genetic modification. Before plant breeder Alexander Livingston came along in the late 19th century, tomatoes were "small, hollow, tough [and] watery," according to his 1893 tome, Livingston and the Tomato. Since then, tomatoes have undergone astonishing improvements and after more than a century of breeding. Thousands of varieties are grown worldwide after having been modified for many climates and soils and to enhance a variety of desirable traits, including pest-resistance, abiotic stress tolerance, improved nutrition, better taste and delayed ripening. They are an important part of the human diet, supplying minerals, vitamins and phytochemicals, and are the fourth most important commercial crop in the world in terms of net production value, which is estimated at more than $50 billion.

In the 1990's, the techniques of molecular genetic engineering (GE) were first used to create tomatoes with delayed ripening for longer shelf-life (which means less wastage), and although the attempts were technically successful, overall the tomato, dubbed the Flavr Savr, wasn't very good and flopped commercially. Sometimes, however, technology has a way of taking us back to the future, and an article in the journal *Nature* in July 2015 suggests that long shelf-life tomatoes are making a comeback. A group of Anglo-American academic scientists employed genetic engineering techniques to achieve "targeted control of tomato softening, without affecting other aspects of ripening, by silencing a gene" that codes for a single enzyme. The project is still in the early stages but seems promising.

While the use of molecular techniques for the genetic engineering of tomatoes was in suspended animation for decades, there have been monumental breakthroughs in other plants. A subset of these – which have been modified to be herbicide-tolerant – have been a lightning rod for activists, who regularly attack them, citing a number of spurious objections. Contrary to their claims, the plants do not *contain* herbicides; rather they are resistant to the herbicides, in order to make weed control – an essential aspect of farming – more efficient and cost-effective. And although the total amount of herbicides applied may have increased as the result of these herbicide-tolerant, genetically-engineered crops, the overall environmental impact is *smaller* because the herbicides applied (most often glyphosate, or Roundup), have less impact compared to the herbicides they replaced. See the table here for a comparison of the toxicity of glyphosate to other common chemicals.

In addition to the herbicide-tolerant plants that the activists deride and disparage, there are many crop plants that have been genetically engineered for

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unrelated traits. They include both plants with improved agronomic properties — which directly benefit growers primarily – and those that boast properties attractive to consumers. Many of the latter are in the development pipeline, and they are becoming ever more prevalent.

BT-CROPS

Broad spectrum insecticide spraying is effective at controlling insect pests but it also kills beneficial insects. More than 20 years ago agricultural scientists found an ideal way to reduce or eliminate insecticide spraying. A soil bacterium called *Bacillus thuringiensis* (Bt) produces a variety of proteins that are selectively toxic to certain insects but non-toxic to all other animals. Inserting the genes that code for these Bt proteins into crops allows the crops to protect themselves from the insect pests. Over the past twenty years Bt crops have allowed farmers to reduce the amount of broad spectrum insecticide spraying by hundreds of millions of pounds.

Bt crops include corn, cotton and soy. The newest Bt crop, brinjal (eggplant), represents a major agricultural advance. Brinjal requires up to 100 applications of insecticide through the growing season to protect it from a voracious insect pest. Often, subsistence farmers in the developing world have little or no protective equipment. The GE version containing Bt proteins has been a tremendous success in Bangladesh. Growing Bt brinjal dramatically reduced insecticide applications, resulting in less environmental impact, reduced occupational exposure for farmers and improved yields. It is likely that India will soon follow Bangladesh's lead.

Consumers also directly benefit from Bt crops. Every year, scores of packaged food products are recalled from the U.S. market because of the presence of contaminants such as insect parts, toxic molds, bacteria and viruses. Because farming takes place out of doors and in dirt, such contamination is a fact of life. Over the centuries, the main culprits in mass food poisoning have often been mycotoxins, such as ergotamine from ergot or fumonisin from the mold Fusarium. These come from the fungal contamination of unprocessed crops, which is exacerbated when insects attack food crops, opening wounds in the plant that provide an opportunity for pathogen invasion. Once the molds gain a foothold, poor storage conditions also promote their post-harvest growth on grain.

Fumonisin and some other mycotoxins are highly toxic, causing fatal diseases in livestock that eat infected corn and esophageal cancer and neural tube defects in humans. Regulatory agencies such as the U.S. FDA and UK Food Safety Agency have established recommended maximum fumonisin levels in food and feed products made from corn. Unprocessed or lightly processed corn (e.g., corn meal) can have fumonisin levels that exceed recommended levels. In 2003, the UK Food Safety Agency tested six organic corn meal products and 20 conventional (non-organic) corn meal products for fumonisin contamination. All six organic corn meals had elevated levels—from nine to 40 times greater than the recommended levels for human health—and they were voluntarily withdrawn from grocery stores. By contrast, the 20 conventional (i.e., non-organic) products averaged about a quarter of the recommended maximum levels. Research has shown that there is more than 90% reduction of this toxin in Bt corn, so it is difficult to understand why environmental NGO's like Greenpeace actively and relentlessly campaign against these Bt crops.

VIRUS-RESISTANT PAPAYAS

Papaya ring spot virus (PRSV) has caused massive crop damage around the world. The virus was first detected in Hawaii in the 1940's, and by the 1950's, infestations forced farmers to stop growing papayas on Oahu, so production moved to the Puna district of the big island. Soon 95% of all Hawaiian papayas were grown there. In 1992 the virus arrived in Puna and in only a couple years was decimating the $64 million a year industry. By 1991, scientists had developed virus-resistant papaya varieties using molecular genetic engineering techniques that spliced a gene coding for the virus's coat protein into the papaya genome, and today more than 80% of the state's papayas are those varieties.

A dramatic photograph of the unmodified, virus-susceptible papaya trees and the genetically engineered virus-resistant ones growing side by side may be found here. The ones on the left have a marketable yield of approximately nil, while the ones on the right have normal yields.

Papaya-growing countries around the world are developing GE papaya to resist their own specific PRSV strains.

INNATE POTATO AND ARCTIC APPLE

Potatoes are one of the most consumed foods on earth but they suffer from significant losses due to post-harvest bruising. By down-regulating (i.e., turning off) the genes for the enzymes that mediate bruising, at least two companies have developed GE potato varieties that resists bruising, potentially saving over a billion pounds from being wasted annually. "Innate" potatoes from the J.R. Simplot Company are bruise-resistant and contain 50%-70% less asparagine, a chemical that when heated to high temperatures is converted to acrylamide, a presumptive

carcinogen. The advantage of lower levels of a carcinogen is obvious, but the resistance to bruising is important to sustainability because of the potential to decrease waste. Second-generation Innate potatoes contain an additional trait: resistance to the destructive fungus called late blight, which caused the Irish potato famine of the mid-19th century and is still a problem.

Environmentalists take note: Potatoes resistant to bruising and late blight represent major advances in sustainability, because every serving of french fries and every potato chip made from them represents less farmland and water consumption.

Arctic apples are conceptually similar. Using molecular genetic engineering to reduce the level of the enzymes involved in "enzymatic browning"—the unappetizing discoloration that occurs when an apple is cut or bruised–the fruit is highly resistant to browning. The ingenious biology that made this possible – the insertion of genes in the reverse of their normal orientation (antisense) such that the genes that meditate browning are not expressed — is far more precise and predictable than conventional, older techniques that have been employed to create virtually our entire food supply (including even "heirloom" varieties and the overpriced organic stuff). The beauty of this technology is that it can be transferred to any apple variety relatively quickly. Approximately 40 percent of all apples are wasted, so this technology will increase sustainability and should put downward pressure on prices.

CASSAVA

Cassava is a potato-like tuber that is grown primarily in Africa and the Indian subcontinent, and more than 500 million people rely on it for food and income. It grows in poor soil and drought conditions, making it an important crop for millions in the developing world. But cassava has a few problems. It produces cyanide at levels that require extensive treatment before it can be consumed, and it is low in iron, zinc, beta-carotene (the precursor of vitamin A) and protein. Viral diseases have been known to destroy 100% of a farmer's crop. All of these challenges are being addressed with genetic engineering. Field trials in Africa are showing excellent viral resistance, and scientists have been successful at elevating the levels of micronutrients and protein content as well as reducing the cyanide levels by 99%. People in Africa will soon have access to genetically engineered varieties that will help to ensure abundant, healthy cassava crops.

BANANA

More than 90% of current varieties of bananas are derived from cuttings, or clones, of natural mutant bananas which were discovered over 10,000 years ago. Those mutations allow bananas to be sterile and to grow without seeds. For almost a hundred years North America and Europe enjoyed a banana variety called Gros Michel. That ended in the 1950's when fungus virtually wiped out this variety. A different variety, Cavendish, that was resistant to the fungus soon replaced Gros Michel, but it, too, is now threatened by a disease called *Black Sigatoka* that can only be treated by applying massive doses – as many as 50 applications a year — of fungicides. However, that remedy is rapidly losing effectiveness as the fungus becomes more resistant, and the banana could be extinct within the next decade. Current techniques such as conventional cross breeding are limited in scope and effectiveness, but the use of molecular genetic engineering techniques promises to be much more effective.

GOLDEN RICE

Billions of people worldwide get most of their calories and nutrients from rice – and therein lies a problem. Ordinary rice — which itself has been extensively genetically modified over centuries — produces β-carotene, a precursor of vitamin A, in the leaves but not in the grains, where the biosynthetic pathway is turned off during plant development. In "Golden Rice" (GR) — called that because of its golden color — two genes (one from corn, the other from a bacterium) have been inserted into the rice genome by precise molecular techniques of genetic engineering. That modification enables the carotenoid biosynthetic pathway to produce and accumulate β-carotene in the rice grains.

Since a prototype of GR was developed in the year 2000, new lines with ever-higher β-carotene content have been generated, and feeding studies in adult humans have demonstrated that GR is a good source of vitamin A. Why are vitamin A and its precursor, β-carotene, important? Vitamin A is critical for normal vision and also plays a central role in maintaining the integrity of the immune system. The World Health Organization estimates that 250 million preschool children are vitamin A deficient, which causes blindness in 250,000 to 500,000 of them every year. Within 12 months of losing their sight, half die, often from diarrheal diseases or measles.

This ongoing catastrophe is preventable. In theory, the most desirable remedy would be a varied and adequate diet, but this is not always achievable. The reasons are manifold, ranging from traditional preferences to geographical and economic limitations. GR varieties

have the advantage of not creating new dependencies or displacing traditional foods. Moreover, they are sustainable because there is no need for public health infrastructure to provide repeated alternative interventions for fortification or supplementation. GR varieties will be given away at no cost to subsistence farmers in the developing world.

Unfortunately, intense lobbying by anti-genetic engineering environmental groups like Greenpeace has slowed the delivery of this humanitarian product. Recently, more than 110 Nobel Laureates published an open letter to Greenpeace asking them to stop their campaign against Golden Rice. The activists' response was to demean the expertise of the Nobelists.

THE PROMISE OF GENETIC ENGINEERING

Molecular genetic engineering of crop plants besides those engineered to be herbicide-tolerant has already made monumental contributions. A 2016 study by British economists Peter Barfoot and Graham Brookes concluded:

> *The insect-resistant (IR) technology used in cotton and corn has consistently delivered yield gains from reduced pest damage. The average yield gains over the 1996-2014 period across all users of this technology has been +13.1% for insect resistant corn and +17.3% for insect resistant cotton relative to conventional production systems. 2014 was also the second year IR soybeans were grown commercially in South America, where farmers have seen an average of +9.4% yield improvements;*

And as discussed above, genetic engineering of papayas has saved the papaya industry in Hawaii and the Innate potato and similar varieties will avoid wastage and be a huge boost to sustainability. As more products move through the pipeline, GE crops with healthy traits that benefit the consumer, reduce losses to pests and diseases, and lower pesticide use will become more common.

Or perhaps we should qualify that statement by saying that they will become more common *if* excessive, unscientific, technique-based government regulation and the relentless opposition of activists can be kept at bay. As University of California Berkeley agricultural economist David Zilberman has observed, excessive regulation "comes at a cost — it prevents the introduction of beneficial innovation, and eventually lack of innovation is a source of heightened risk" to human health and the environment.

Article

R&D Spending & Success: Key Trends, Issues & Solutions

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ABSTRACT

Debates about rising bio/pharmaceutical prices are often predicated on the presumption that higher product prices are necessary for continuing funding of innovation. Recent trends only partially bear this out. While total spending on bio/pharmaceutical R&D has largely remained constant, costs for clinical trials have consumed a rising proportion of R&D budgets. More spending on clinical trials, however, has not yielded higher trial success rates. Prior to product launch, clinical trials take up most of the financial resources attributed to a product in development, costing on average $75–$100M. While completing a full cycle of pre-clinical and clinical trials can take an average of 7.5 years, the probability of successful filing for marketing a drug after clinical trial testing has never exceeded 13–20%, despite advances in trial design and testing processes. This article discusses key trends in R&D spending and productivity. It then lays out issues that prevent clinical trials from achieving higher success, and presents operational and strategic solutions that can be implemented to improve the effectiveness of increases in R&D spending.

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Bio/pharmaceutical R&D prides itself in making new products for treating afflictions with no cure, developing therapeutic advances that offer significant new benefits, finding better ways to make drugs safer and work more effectively, or devising radical new approaches to how they are administered. Such innovation is costly; industry R&D spending on an annual basis is in excess of $50B. Even companies that only develop one drug spend >$350M on its R&D [1]. Whether and how to fund more R&D is cause for perennial debate. Even more of a cause célèbre is whether more R&D spending has resulted in more innovation.

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R&D INNOVATION & PRICES

One of the most frequent rationales for justifying high and rising prices of biotech and pharmaceutical products in the US is the all too real fact that part of the revenues accruing as such are plowed back into the all too necessary research and development (R&D) activities required to produce genuinely innovative treatments. A supplementary logic argues that when R&D productivity is flat, particularly when a raft of products is losing patent exclusivity, it is but critical to invest more, not less,

in activities that have a reasonable chance of producing innovation that cures or controls hitherto unmanageable afflictions.

Recent trends in pharmaceutical pricing provide some evidence to reflect such rationale. For example, between 2008 and 2015 branded-drug prices increased 127%, compared with an 11% rise in the consumer price index, according to drug-benefits manager Express Scripts Holding Co. Needham & Co. reported in a June 2014 research note there were as many as 50% more drug-price increases during the previous 21/2 years as there were in the prior decade [2]. Between FY2013 and FY2015, hospital inpatient drug spending increased an average 23.4 percent annually, and on a per admission basis, by 38.7 percent. Growth in spending in the hospital inpatient setting exceeded the growth in retail drug spending, which increased by 9.9% during the same time. In a survey of US community hospitals, over 90 percent of responding hospitals reported that recent inpatient drug price increases had a moderate or severe effect on their ability to manage the overall cost of patient care, with one-third of the respondents indicating that the impact was severe [3]. Even the prices of generic products - which do not rely on R&D for product innovation per se - are on the rise. According to a report by Elsevier, between Nov '13 and Nov '14, out of a research sample of 4421 generic drug groups, 222 drug groups increased in price by 100% or more. There are also some extreme cases (17 drug groups) where price increases of more than 1000% were seen [4].[1]

In parallel with such price increases it would seem rational for one to expect substantial changes in R&D spending.

R&D SPENDING TRENDS

A number of studies estimate that it costs between $161M to $2B to bring a pharmaceutical / biotechnology product to market [5]. Other studies have included time costs, i.e. expected returns that investors forego while a drug is in development, and costs for post-approval studies, which bring the total estimated R&D costs incurred to bring one product to market to be between $2.6B & $2.9B [6].

A number of factors impact estimated costs, including molecular complexity of the product in compound form; type, size and number of clinical trials necessary to produce convincing evidence for successful filing, the size and structure of patient segments targeted for obtaining a label that is commercially viable, and the extent to which one or more niches in the range of afflictions likely to be treated is fulfilled by the current standard of care.

Estimates provided by the Pharmaceutical Research & Manufacturers Association (PhRMA) [7] indicate that total R&D spending among its member firms in 2014 was $51.2B compared to $50.7B in 2010 (See Figure 1). Another study estimates that in the US R&D expenditure declined by $12.9B between 2007 & 2012[8]. The average cost to develop a drug among the same firms, however, was estimated to increase from $1B to $2.6B from 2000 to early 2010. In other words, what increase in R&D allocations may have been expected (partly enabled by revenue increases attributed to price increases) would likely have impacted drug development costs, not total R&D expenditures.

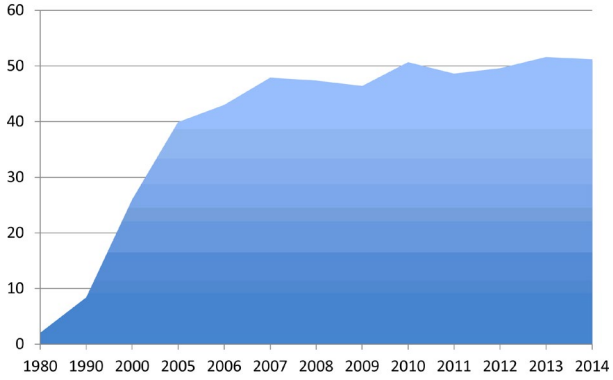
Despite the fact that drug development costs have increased two to three fold in recent years, the rates for successful development of an asset from Phase 1 through regulatory filing and market launch have largely remained same. Estimates of successful development range from 8%[9] to 13-21%[10]. So the key question is what has caused the rapid rise in drug development costs that do not seem to have improved successful development? Based on a number of published studies, it appears that clinical trials are at issue. According to one study, clinical success rates have dropped substantially. It is a lot harder for a compound to clear all phases of clinical testing and come to market. As a result, one report [11] estimates that the internal rate of return (IRR) from R&D spending has dropped in half since 2010, from 10.5 percent to 5.5 percent in 2014.

Apropos it seems reasonable to infer that price increases by themselves would have been unable to create the desired effect of increasing R&D spending and the ensuing sustenance of innovation. Instead most of any increase in funds available for investment would have been used to cover costs that have little to do with innovation.

KEY ISSUES WITH CLINICAL TRIALS

A number of challenges with varying complexity complicate successful execution of clinical trials, thereby increasing drug development costs and limiting the potential to achieve higher success rates commensurate with rising spending levels.

1 Key reasons for generic product price increases include consolidation among generic product manufacturers (leading to fewer manufacturers per generic), supply constraints and shortages due to quality concerns and stricter regulatory oversight



Source: Pharmaceutical Research & Manufacturers of America (PhRMA); Total R&D spend by year among PhRMA members

Figure 1: R&D Costs ($B)

Time & Cost

Longer human life spans throughout the world have meant increasing incidence of chronic and degenerative diseases. Large markets for chronic diseases implicitly present larger opportunities for products that would be administered over longer life cycles. To realize such opportunities, however, such products need to undergo clinical trials that are sufficiently long and powered to represent the addressable patient population over a sufficiently representative time in its life. For example, longer studies are needed to see if safety issues conclusively arise when drugs are taken over a lifetime to manage chronic diseases. It is not uncommon for adverse events not observed in a clinical trial setting to crop up in a product's market life cycle after launch [12]. Longer timelines increase costs and hold the potential to impinge on revenues if and when the product launches in the market after securing approval. Given that every bio/pharmaceutical product has a finite patent life, more time spent in clinical trial testing implies less time to serve patients in the market. Financially, this also implies a lower net present value (NPV) estimate of future earnings. More time in clinical trials also increases the possibility of competition from alternatives developed for the same types of patients. According to one study [13] the average length of time from start of clinical testing to drug marketing is 90.3 months (~7.5 years).

Longer clinical trials do not necessarily mean a drain on resources. If the trial is designed to establish a drug's effectiveness (rather than efficacy alone), the resulting benefits can pay off in the long run. In the increasingly competitive market for chronic drugs, private and public insurers are looking for evidence that shows drug benefits in a real-world setting, covering multiple types of patients not limited to a small core tested in a controlled setting designed to tease out data on efficacy. Additionally, if a drug files for approval on the basis of viable pharmacoeconomic evidence that establishes its value relative to a standard of care, its chances of approval are heightened. Clinical trials designed with foresight that covers critical coverage and reimbursement challenges may involve additional cost and complexity in execution, but can also produce worthwhile results [14].

Global Trials

The benefits of globalization have perversely affected clinical trial complexity and costs, without notable increases in success rates. Multinational clinical studies are now common, accounting for at least 25% of Phase 3 studies. Such studies involve an average of 80% more patients and 25% more procedures per patient than single-study protocols [15]. It stands to reason that enlarging the geographical scope of a clinical trial has very little to do with establishing scientific evidence of clinical safety or efficacy of a bio/pharmaceutical molecule. Rather, it enables such evidence to be developed so it is consistent with local (rather than global) regulatory stipulations. Thus while global studies are costlier, they do not contribute to increasing clinical trial success rates. In lieu of global standards that harmonize requirements for regulatory filing and approval, a piecemeal approach to conducting clinical trials will continue to add needless cost, without expectation of increasing returns.

Specialty Products

The disparity between rising costs and flat success rates also has roots in the rising importance of products meant to treat highly specialized diseases. Products that serve patients treated by specialists are bright spots in the modern biopharmaceutical landscape. They promise substantial benefits in previously under-treated categories like cancer, arthritis, Alzheimer's disease and multiple sclerosis. Approximately 40% of drugs in the pipelines of pharmaceutical companies are specialty drugs. Such drugs are based on large molecules or complex molecular combinations that are typically delivered through injections or infusions. Many specialty drugs are more effective when used in conjunction with molecular testing for biomarkers that improve the quality of treatment selection decisions and the chances of drug success. Complex specialty drugs require careful, controlled assessments over longer time periods compared to traditional small molecule drugs available in pill formulation; with possibilities that adverse events in the real world may well be detected years after the specialty drug is launched. Clinical trials to determine optimal pharmacodynamics, clinical properties and proof paradigms are longer,

more complex in design and more expensive. Safety and efficacy conclusions are less open to generalization, and more subject to differences in individual genetics. The true burden of proof for a novel specialty medication only partially depends on results from company-sponsored clinical trials. It often expands to include demands for outcomes data in a real-world setting. Development timelines for novel specialty products can stretch into decades, contributing to sunk costs [16]. Looking at costs and success rates of specialty drug clinical trials may not provide an adequate perspective on their true value, which may be realized fully only long after they are approved and in the market - fulfilling large, unmet patient needs, with additional positive impact on societal health care and related costs.

Regulatory Improvements

Studies have pointed out that regulatory changes in how clinical trials are designed and conducted will contribute to reducing the gap between rising developmental costs and trial success rates [17]. US regulations for clinical trials were written at a time when the clinical trial enterprise was simpler. As of now, community-based physicians rarely get involved in clinical trials, which are often conducted in academic settings that are intrinsically better set up to follow strict regulations, albeit over longer timeframes. Many clinical trials aim for a larger number of highly specific patient subpopulations, in studies with multiple arms set up to achieve more diverse primary and secondary endpoints. The consequence is that there is more competition for the same patients willing to participate in similar trials. Recruiting patients who meet very specific qualifying criteria is harder, takes longer and is costlier. Further, variations in the type and number of patient segments studied under a trial necessitates more detailed analysis of sub-group characteristics that can have an impact on study conclusions, also adding to time and cost requirements – without impacting trial success rates [18]. An even more serious implication is suggested in [18], which argues that rising clinical trial costs have made the industry as a whole more averse to risk and less willing to take chances on novel medicines.

SOLVING KEY ISSUES

Studies have suggested steps that focus on policy and process improvements to reduce trial costs. These include revamping regulations that allow for simplified enrollment procedures, more efficient and less risk-averse protocols, and more frequent communications between trial sponsors, investigators and regulators. Relying more on e-technology (e.g. mobile data collection & monitoring, electronic health records) will undoubtedly make trial design and execution more efficient. The use of FDA priority vouchers has increased in the recent past, enabling speedier review of trial data for approval decisions [16], thereby reducing the extra time costs that would have been incurred otherwise.

This article's author has designed and executed strategic research projects that streamline decisions about costly clinical trial design choices, enabling critical commercial perspectives to inform a prioritization of multiple trial designs. The projects are driven by principles fundamental to marketing, marketing research, decision modeling and finance [19]. They bring a systematic business framework to bear on clinical trial strategies, making them less prone to uncertainties, combining market considerations and resource requirements with measures of risk and return so smart executive decisions about trial selection, design and execution are enabled.

While details of specific projects vary with considerations such as therapeutic area, drug delivery mechanism, type and number of patient segments and the competitive clinical landscape, broad elements of the framework are designed to collect retrospective and prospective data that, upon analysis, together enable an informed, rational view of alternate clinical trial options, and predict, within manageable levels of statistical error, the financial impact of pursuing one trial over another. Developmental costs can then be allocated rationally under alternate assumptions of trial success rates.

A part of the retrospective database consists of collecting data on past clinical trials in the same or analogous therapeutic area of interest, so prospective costs can be suitably benchmarked. While this does not in itself provide final answers, it sets up the ballpark within which various trial options can be examined in detail. Other parts of this database contain details about trial parameters (such as inclusion / exclusion criteria, subpopulation characteristics, sample sizes and power calculations), expected endpoints and results. Multivariate analyses of this database can provide vital insights about costs, underlying factors and their impact on trial success rates.

A follow up phase of the project involves taking an in-depth, prospective look at the clinical trial options under consideration. A first step typically involves consultative research with development personnel deeply involved in trial design. Key issues of discussion include assessments of timelines, complexity, desired endpoints and technical risk associated with each trial design, as well as a mapping of the strengths, weaknesses, opportunities and threats that are perceived to influence trial outcome. A second step requires in-depth qualitative and quantitative research with potential customers of

	Risk Adjusted NPV	Success Probability
Trial A	$800M	45%
Trial B	$300M	90%
Trial C	$1.2B	50%
Trial D	$3.0B	30%
Trial E	$120M	95%

Figure 2: Example Trial NPV. Numerical estimates are shown for illustration only

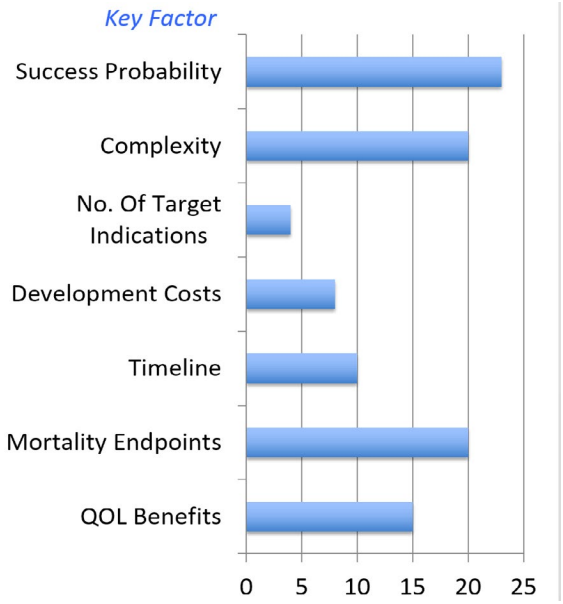


Figure 3: Relative importance of factors in influencing risk-adjusted NPV

the developmental compound who would be influenced by the design and results of each trial option under consideration. Such customers would include clinicians, health technology assessors, managers who make decisions about drug coverage and reimbursement, and, in some situations, patients who have access to clinical trial information and can make use of it to request one drug over another from their health care provider.

An analysis of the comprehensive, combined retrospective and prospective database subsequently yields vital results, such as –

- An understanding of what would drive clinical trial success for the product under consideration, based on first hand insight combined with results of numerical causal modeling (See Figure 2 For Illustration)
- Estimates of the relative importance of trial-defining parameters in shaping trial success, including study design characteristics such as patient subpopulation descriptors, size and power, type of primary and secondary endpoints, the number of target indications and the number of study arms
- Assessment of the impact of study design parameters on study costs, and the relationship between costs and probability of trial success
- An in-depth risk analysis focusing on the key sources of risk, defining a range of values such sources may take and a quantification of net risk under alternate clinical trial descriptions
- Forecasts of the risk-adjusted net present value (rNPV) of each clinical trial option, based on alternate scenarios as described on the basis of its parameters, costs and risks (See Figure 3 For Illustration)
- Estimates of changes in rNPVs as a result of varying key inputs, such as market characteristics, type and number of competitors, trial design characteristics, costs, assumptions about technical success and commercial receptivity to trial outputs.

CONCLUSION

Debates about rising bio/pharmaceutical prices are often predicated on the presumption that higher product prices are necessary for continuing funding of innovation. Recent trends only partially bear this out. While total spending on bio/pharmaceutical R&D has largely remained constant, costs for clinical trials have consumed a rising proportion of R&D budgets. More spending on clinical trials, however, has not yielded higher trial success rates. This article discusses key issues that prevent such success and presents operational and

strategic solutions that can be implemented to improve the effectiveness of increases in R&D spending.

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Article

Analysis of genetically modified food induced international trade law issues

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ABSTRACT

The advantages of genetically modified food are gradually highlighted because of the rapid development of modern transgenic technology. The trade proportion of genetically modified food in international trade products is increasing. Till now, legal regulations concerning the international trade of genetically modified food are still contradictory and conflicting, and a series of initiated legal issues about the international trade of genetically modified food becomes more acute. As a great power of transgenic crops planting, China should fully learn from the trade disputes of genetically modified food, perfect laws such as the safety management, approval and identification of import and export, accelerate the development of transgenic technology, and strengthen the mutual benefit and collaboration of the developing countries, thus to gain a strong competitive position in international trade and maintain the fundamental interests of China better.

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Keywords: genetically modified food, international trade, legal issues, countermeasures

INTRODUCTION

Transgenosis refers to transferring one or more exogenous genes into a specific organism using genetic engineering technology to generate corresponding products such as polypeptide or protein effectively. Food which is produced taking genetically modified organisms as the raw materials is called genetically modified food.[1] As to the laws and regulations about the technical barrier to trade of genetically modified food, there is Cartagena Protocol on Biosafety, TBT Agreement, SPS Agreement, etc. internationally, and countries such as Europe, America, Japan and Russia formulated laws that are applicable to their own conditions. Due to the uncertainty of genetically modified food, relevant law systems about it is conflictive internationally, the recognition and attitude of different countries on genetically modified food is polarized,[2] and the legal issues concerning the international trade of genetically modified food has become more prominent. Scholars from China and other countries have made many studied on it. Pillarisetti JR and Radel K pointed out that, the insufficient rules for genetically modified food in WTO will cause serious and irreversible risks to global organic and bio-dynamic agriculture[3]. Meng Yu,[4] a Chinese scholar, proposed that, the issues involved in genetically modified food are issues concerning a scientific field more than legal issues, there is no unified recognition on genetically modified products currently and WTO has not given positive reply to the problem because the safety of genetically modified products has not been verified scientifically in the current stage, which makes different countries and regions adjust measures to local conditions in the supervision and control of genetically modified products. This study aims at analyzing the current situation and development trend of the international trade of genetically modified food and propose countermeasures which needs to be

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adopted in the current international trade environment for the problems existing in the international trade laws for genetically modified food.

1 THE CONCEPT, ADVANTAGES AND DISADVANTAGES OF GENETICALLY MODIFIED FOOD

1.1 The Concept of Genetically Modified Food

Genetically modified food refers to partially changing the property or function of a specific organism by transferring exogenous genes to the organism using molecular biology methods. Genetically modified food is produced directly or indirectly using transgenic organisms. Genetically modified food can be divided into three categories, plant-based genetically modified food, animal-based genetically modified food and organism-based genetically modified food. Plant-based genetically modified food is the major component of genetically modified food currently, and transgenic soybean, transgenic tomato and transgenic corn are directly or indirectly circulated in market.

The purpose of transgenosis is to make organisms more suitable for using or eating by modifying their properties.

1.2 The Advantages and Disadvantages of Genetically Modified Food

1.2.1 Advantages

- The higher output of genetically modified crops can reduce the input of grain, which is benefit to global grain issues.
- Genetically modified crops are resistant to weeds and drugs, which can reduce the use of insecticide and herbicide compared to traditional crop.
- The development of genetically modified crops enriches biodiversity. Its quality guarantee period is long and moreover taste and flavor are improved to some extent.
- Genetically modified crops can be made into food which can resist diseases and is benefit to health using relevant technologies, which can avoid the waste caused by instability due to the application of grafting and hybridization.

The global planting and trade of genetically modified food can not only solve the problem of global food shortage, but also can realize commercial benefits. Therefore, there is great social values and broad market prospect. However, the safety of genetically modified food has not been definitely confirmed so far, which is induced by the limited recognition of people.[5] Thus, genetically modified food also has obvious disadvantages.

1.2.2 Disadvantages

- It may damage biodiversity, lead to ecological unbalance, and affect ecological environment.
- It may be toxic and cause unexpected risks to human because of its long incubation period.
- It is difficult to take the nutritional components of food into account while possessing the above advantages.

2 THE CHARACTERISTICS AND TREND OF INTERNATIONAL TRADE OF GENETICALLY MODIFIED FOOD

2.1 The Characteristics of the International Trade of Genetically Modified Food

2.1.1 The proportion distribution of genetically modified food

Currently, the planting area of genetically modified crops and the number of countries planting genetically modified crops both increase, while the proportion of traditional crops of same kinds reduces. Moreover, the proportion of genetically modified food among the products involved in international trade is increasing constantly.

As is known, America remains to the first power for the planting of genetically modified crops in the world, with a planting area of 70.9 million hectares (39% of the global planting area). Except America, the other countries which rank in the front places are Brazil, Argentina, India and Canada. The countries mentioned above are all export great powers of genetically modified food in the world; the import countries concentrate on Asia and Europe.

2.1.2 Being marketed and eaten after being processed into foods

Most of the foods abroad contain genetically modified food.[6] In countries such as America, daily food diet such as oatmeal in the breakfast all contains genetically modified components. In China, 80% of soybean oil for marketing is made from genetically modified soybean.

2.1.3 Increasingly prominent trade disputes

Transgenosis related technologies and products are of high risks to cause irreversible damages to the health of human body and environment. Therefore, the international trade issues induced by the safety of genetically modified products have been more and more prominent.

2.2 The Total Volume and Prospect of the International Trade of Genetically Modified Products

There are evidences suggesting that the total economic benefits generated by genetically modified crops from 1996 to 2014 were 150 billion dollars, 76.2 billion from the developed countries (50.7%) and 74.1 billion from the developed countries (49.3%). After the commercialization of genetically modified crops, about 18 million people planted genetically modified crops over the twenty years, and 90% of them were small peasant households from developing countries.

As a result, Chinese farmers gained 17.5 billion dollars benefit and Indian farmers obtained 18.3 billion dollars benefit at least from 1996 to 2014. Besides benefits, at least 50% of insecticide and pesticide spraying are saved due to the weed and insect resistance properties of genetically modified crops, which protect farmers from the damages of insecticide, reduce the intake of pesticide, protect environment, and reduce pollution.

Till 2015, the planting area of genetically modified crops had been more than 3.7 million hectares in China; the crops included genetically modified cotton, pawpaw and poplar, and the planting area of genetically modified crops was 3.7 million hectares. To accelerate the examination and approval of genetically modified crops, China has paid at least 3 billion dollars for the study of self-produced genetically modified seeds.

America has approved the commercialization of genetically modified animals as food, and the first species is salmon.[7] Moreover, Food and Drug Administration (FDA) has approved the first kind of genetically modified animals as a commercial food for consumption in 2015, after twenty years of examination. It is a kind of genetically modified salmon with faster growing speed and is expected to enter into American food chain before 2018.

3 PROBLEMS IN THE LEGAL REGULATIONS OF THE INTERNATIONAL TRADE OF GENETICALLY MODIFIED FOOD

3.1 The Legal Regulations of Genetically Modified Food in International Trade

3.1.1 Legal regulations in the framework of WTO

Agreement on technical barriers to trade

The purpose of the agreement is to standardize the behaviors of members exerting technical trade regulations and measures, guiding members to formulate, adopt and exert reasonable technical trade measures, encourage members to adopt international standards and conformity assessment procedures,[8] and ensure that technical regulations and standards for packaging, labeling and tagging conform to assessment procedures to avoid unnecessary international trade disorders and reduce technical trade barriers.[9]

The agreement on the sanitary and phytosanitary measures

The purposes of the agreement included maintaining the sovereignty of any government to provide proper health protection level and moreover avoid the abuse of the right for the purpose of protectionism and the unnecessary disorders to international trade. [10]

Agreement on trade-related aspects of intellectual property rights (TRIPS)

TRIPS does not specially mention the issues of genes or genetic technology patent.[11] Members can add the following explanation for it: a gene modified by genetic engineering may be new and innovative and can be applied in industry. Obviously, the gene conforms to the conditions related to invention in TRIPS and can be granted with patent as an invention and protected by TRIPS.[12]

3.1.2 Legal regulations outside the framework of WTO

Convention on biological diversity

Its main aim is to protect biodiversity, realize sustainable utilization of biodiversity components and share the

commercial benefits of heritage resources in a fair and reasonable way.[13]

Cartagena protocol on biosafety

The protocol emphasizes on the issue of transboundary movement of living modified organisms which are obtained by modern biotechnology and may produce adverse influence on the protection and sustainable use of biodiversity.[14]

3.2 Problems in Legal Regulations of Genetically Modified Food in International Trade

3.2.1 Different aims of international regulations

Globalization trend strengthens the correlation between different fields in the world and leads to the overlap of international regulations because of the spread of problems in one field to other fields.[15] However, different international regulations have different aims.

WTO system is established for the purpose of free trade, and the content related to environment is based on the value orientation of trade liberalization. It aims at ensuring environment policies won't be the disorder of free trade and realizes the complementarity of trade policy and environment policy. Relevant standards of multilateral environmental agreements aim at environmental protection and health. Environmental issues usually come along with trade expansion, while policies concerning human health and environmental protection often limit the free development of trade.[16] The two aims are conflictive.

3.2.2 Conflicts between specific rules in international standards

The aim difference of international standards leads to conflicts in the form layer, and those differences mainly reflect on detailed content. When a country is a member of WTO and a member or contracting party of other agreements at the same time, performing the obligation of a system may violate the obligation of another system. Different countries perform obligation under different systems may also induce corresponding trade conflicts, for example, WTO rules and Cartagena protocol on Biosafety (Table 1).

3.2.3 The disadvantageous positions of the developing countries in WTO multilateral mechanisms

There is a large gap in the application degrees of WTO multilateral mechanisms by the developing countries and developed countries;[17] the developing countries are far behind the developed countries.

The developed countries and regions such as Europe, America and Japan join WTO earlier than the developing counties, have maturely developed international trade, have fully understood and mastered WTO rules, and collected many materials to cope with trade

Table 1: Similarity and difference of WTO rules and Cartagena protocol on Biosafety

		WTO rules	Cartagena protocol on Biosafety
Similarity		Both of them consider the transboundary movement of pest can threaten the health and safety of human, animals and plants and proper measures must be adopted to ensure human health and biological environment.	
		Both of them realize international trade activities can affect biological environment and emphasize scientific principles, existing scientific evidence and the roles of international standards and international organizations.	
Differences	Basic aims	WTO related agreements mainly aim to promote the development of trade. Though many WTO related agreements mention to consider environmental protection, which is a principle stipulation, it is difficult to operation in reality and WTO has not established specialized agreement of trade and environment.	It aims at preventing the adverse effects of the transboundary movement of genetically modified organisms and their products on biodiversity as well as the risks to human health, with the hope to adopt proper safety measures to ensure environmental and human health while developing and applying modern biotechnology. But it considers little about the development of trade.
	Basic principles and rules	Non-discrimination principle is the footstone of WTO.	Precautionary principle is the most important principle and footstone of Cartagena protocol on Biosafety.

friction that is encountered in WTO multilateral settlement mechanisms. The developing countries seem to be weaker than the developed countries, no matter fund, technology or the familiarity degree of WTO terms.

4 THE COUNTERMEASURES AVAILABLE FOR CHINA IN THE CURRENT INTERNATIONAL TRADE ENVIRONMENT

In view of the current scientific layer, whether genetically modified food is safe is unable to be determined. Moreover, due to the differences of science and technology level, the depth of transgenic technology study and the level of economic development aggravate the divergence of different countries in the international trade of genetically modified food. Therefore, the WTO members are difficult to formulate unified uniform international standards, but only can formulate their own trade standards and policies by themselves.

China has released relevant legal regulations about genetically modified food. Especially in 21 century, China strengthened relevant laws and released Regulations for Agricultural Genetically Modified Organisms Safety Management, Regulations for Agricultural Genetically Modified Organisms Safety Assessment and Management, Regulations for Agricultural Genetically Modified Biological Label Management, Regulations for Agricultural Genetically Modified Organisms Import Safety Management and Regulations for Inward and Outward Genetically Modified Products Inspection and Quarantine Management.[18]

The successful implementation of genetically modified special projects is a symbol which suggests the study level of bioscience and safety in China has stepped to a new and higher step. But at the same time, China may face with potential significant risks brought by the development. It seems that the laws concerning genetically modified food in China have been perfected gradually; however, there are lots of problems. In general, there are problems such as incomprehensive legislation, imperfect system, incoherent procedure and outdated information transmission mechanism; therefore, continuous improvement and perfection are needed.

4.1 Perfecting Genetically Modified Food Labeling Legislation

In China, only soybean, corn, oilseed rape, cotton and beet are approved to be imported as processing raw materials. These foods must obtain the safety certificates. The amount of those foods is much less than the amount of imported food containing genetically modified components that can be flowed in trade. Therefore, we should properly expand and publicly demonstrate more catalogs of the species of genetically modified products which apply identification laws. The current transgenic identification system in China cannot be effectively implemented because of the incomplete legislation, imperfect system and incoherent procedure, which urges the legislation of genetically modified food identification in China to accelerate completion and modification. In the current stage, whether genetically modified food is harmful to human body and environment has not been confirmed yet. The Chinese government should speed up to modify and complete the legislation of genetically modified food identification, positively cope with the genetically modified food disputes in the future, and protect our own benefits when WTO has not been able to solve those disputes in short term.[19]

4.2 Perfecting Inbound Examination and Approval Pattern

European Union requires the country which wants to export genetically modified food to provide enormous research materials, experimental data and even relevant technical report and experimental instruments; only when no security threat is found by European Union related institutions can the application be accepted.[20] But when the application is proposed to China, China is unable to obtain correct test results due to the limited technology, which leads to severe resource loss. China should learn from the experience of European Union and refer to the method when some other products are applied for import approval.

4.3 Establishing Normative Grain Production and Trade Data Interaction System

Currently, the genetically modified food which is developed by China independently can only be supplied to the domestic market, which is because the total amount of

the produced genetically modified food is not enough to satisfy large-amount export but can only satisfy the domestic demand.[21] China should take efforts to carry out researches on the regulations and conventions for the international trade of food, strengthen information flow and transmission system and establish the green barrier warning integrated system for various kinds of food including genetically modified food as well as the crucial grain production and trade data interaction system to timely transmit and share data and improve the precaution ability and rapid response ability of trade units to various green barriers.

4.4 The Developing Countries Make Mutual Benefit and Collaboration

The tolerance of the developing countries to genetically modified food is quite different, but the differences should not be the obstacle for the mutual benefit and collaboration between them.[22] Only when some great powers among the developing countries play the leading role well and improve their positions and speaking rights in the legal regulations for the international trade of genetically modified food can some week counties see hope and join the team. The developed countries will emphasize the requirements of the developing countries and the pattern of the international trade of genetically modified food may tend to be balanced when the developing countries are banded together like strands of a rope.

5 CONCLUSION

The advantages and disadvantages of genetically modified food as a newly sprouted thing cannot be determined in a scientific layer, because there is no evidence suggesting genetically modified food is absolutely harmless. Therefore, the attitudes to genetically modified food around the world are inconsistent, and even WTO is unable to give a definite answer to the issue of genetically modified food trade in the perspective of laws temporarily. A series of legal issues induced by genetically modified food need to be solved by regulations that are formulated by different countries and regions according to their own conditions.

With the improvement of the proportion of genetically modified food in international trade, only when we continuously deep the recognition and exploration on genetically modified food, perfect the law related to genetically modified food, establish normative information interaction system, positively cooperate with the developing countries, and reasonably cope with the disputes generated in the international trade of genetically modified food can the international competition of genetically modified food be improved on the premise of safe and ordered condition.

We should realize that, transgenic technology can bring unpredictable contributions to human being if it develops towards a good direction under the guidance of laws and regulations.

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Review Article

Genetic Diversity Assessment and its Importance on Crop Improvement in Ethiopia: Potentials and Challenges

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ABSTRACT

Genetic diversity assessments of plant play a great role in a predictable area to improve agricultural production and productivity, to solve food uncertainty in developing world. Many breeders has tried to realized that crop with diverge genetic diversity can be assessed, evaluated ,captured and stored in the form of superior plant genetic resources such as gene bank, DNA library to preserve genetic material for long period. However, the conserved genetically diversified plant must be utilized to improve crop production in order to solve future food and nutritional challenges. This paper reviews eight important areas; (i) Gaps in Developing Taxonomy of Ethiopian crops (ii) Monitoring diversity for crop improvement, (iii) Alterations in landscape features, (iv) Significance of Germplasm Conservation of crops, (v) Gap in morphological characterization, (vi) Global perspective of agro biodiversity and molecular evolution, (vii) Emergence of tissue culture technology in Ethiopia (viii) Germplasm improvement. It provides basic enlightenment for plant breeders for better understanding and rapid diversity assessment of crop, for better understanding and utilization of germplasm from gene banks to their applied breeding programs. With the advent of new biotechnological techniques, this process of conventional breeding is now being accelerated and carried out with more precision and speedy manner than the classical breeding techniques by using molecular markers to avoid taxonomic confusion. For sustainable food production, conventional plant breeding research should have integration with molecular marker assisted evaluation of crops genetic diversity and/or cultivar improvement will be achieved. As a result, availability and access to diverse genetic sources will ensure that the global food production network becomes more sustainable. The merit and demerit of the basic morphological characterizations are briefly discussed and their source links were provided to get easy access; thus, it improves the understanding of modern molecular tools and its practical applicability to the breeders.

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Keywords: Ethiopia, genetic diversity, germplasm conservation, molecular marker, crop improvement

INTRODUCTION

The knowledge of genetic diversity has provided a good opportunity for plant breeders, to develop superior crop cultivar with desirable property which is quit suitable for both farmer, consumers, traders for commercial purpose and to Secure food consumption (Narain, 2000). The diversity within crop appears to be high which is confusing for plant breeders to breed that genotype (Cubry *et al*., 2008). So that, it is crucial to study the genetic diversity of plant for further study, genetic improvement and conservation of germplasm for breeding purpose (Desalegn *et al*., 2008). For example, researchers to avoid taxonomic confusion, to depict genetic distance of coffee genotype and to provide basic breeding information for breeders' research has been done using molecular markers, biochemical test and morphological trait (Desalegn *et al*., 2008).

The basic steps in meaningful breeding program are studying the genetic diversity of plant material using

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reliable and accurate means. Comprehensively, to explain the divergence of plant cultivar breeder can use diverse data sets from the morphology of plant, biochemical nature and genetic makeup of the crop (Mostafa, 2011). In order that to determine and characterize the genetic relationship between cultivars using friendly software package aids to generate reliable and useful information for researchers. The fundamental reason for undertaking diversity analysis also stems from the trend of monitoring diversity. The human and material resource to trace poverty has been identified and explained by a strong motive of different econometrics, but it fails to identify basic crop improvement techniques to address food insecurity problem in the world (Baudoin *et al*., 2001).

Genetic diversity assessment plays a pivotal role in crop improvement. It provides information about the evolution of genetic divergence and serves a podium for specific procreation objectives. It identifies parental combinations useful to create segregating progenies with maxim genetic potential for advance selection, as demonstrated by (Barrett and Kidwell, 1998).For example, the genetic diversity of faba bean based on morphological data was investigate to provide meaningful breeding information in Ethiopia (Gemechu Keneni *et al.,* 2005). Commercial varieties of field pea were characterized using IRAP, SSR and RBIP and, they become a good potential planting material source for researchers and breeders to improve its production (Smýkal *et al*., 2008).

In addition diversity analysis is also required for global perspective of agrobiodiversity and molecular evolution. Comparison of various ecotypes, for instance, cultivated and related wild coffees were compared and identified interms of quality (Cubry *et al*., 2008). There have been some molecular studies on estimating the existing genetic diversity among selected enset collections of the country. Birmeta *et al* (2002) did RAPD analysis of genetic diversity among different enset clones from Southern Ethiopia. Absence of gene flow from wild to cultivated enset has also been reported from RAPD-based study made on the wild and cultivated enset gene pools (Birmeta *et al*., 2004). Therefore, molecular characterization of the available germplasm, with a better sampling coverage and the use of informative molecular markers may produce a good estimate of the genetic diversity for utilization in further improvement of the crop and its conservation. The phylogeny obtained from the most recent research is always indicator of the progress of the diversity.

Now a day, plant breeders has tried a lot to increase production and productivity of market oriented, quality, disease resistance, pest resistance, drought resistance and nutracutical crops using characterized planting materials which is as such effective to address food insecurity problem. On the other hand, lack of knowledge about the genetic diversity of domestic crops is jamming the improvement of crop production. Usually, a plant breeder has been waste much resource, time and a lot energy to improve crop production without knowing variability of plant which was little significant in crop improvement (Winter and Kahl, 1995).

Genetic diversity assessment is at juvenile stage due to the presence of limited research in the specific varieties of Ethiopia. Generally, the taxonomic classification and characterization of the varieties is critical for crop improvement even if it is not well developed in Ethiopia. Farmer varieties and their wild type contributed to advancements of the economic sector and agricultural sector of Ethiopia for they are adapted to various agro ecosystems of the country (Negash Almaz, 2001).

Based on the available literature, this paper reviews the importance of taxonomic classification and genetic diversity assessment of Ethiopian crops; Gaps in Developing Taxonomy of Ethiopian crops and minimizing taxonomic confusions, Monitoring diversity for crop improvement, Alterations in landscape features, Significance of Germplasm Conservation, Gap in morphological characterization, Global perspective of agro biodiversity and molecular evolution, Emergence of tissue culture technology in Ethiopia, Germplasm improvement for breeder.

GAPS IN DEVELOPING TAXONOMY OF CROPS IN ETHIOPIA

Taxonomic classification of crops is the primary task before launching ample of projects which could be of breeding experiment or whatever. Obviously, most of the crops are part of global biodiversity. Hence, there is no "taxonomy of crop" specific to Ethiopia. But, the gene pool is not monotonous throughout the globe revealing that there could be specific variety pertinent to Ethiopia. That's why it is always underlined that the taxonomy of Ethiopian crops is at its juvenile stage for the presence of limited research in the specific varieties of Ethiopia.

Generally, the taxonomic classification and characterization of the varieties is not well developed in Ethiopia. Farmer varieties and their wild type contributed to advancements of the economic sector and agricultural sector of Ethiopia for they are adapted to various agro ecosystems of the country (Negash Almaz, 2001). It has been long time since landraces came in to the attention of Ethiopian researchers. Most of the researches were morphological characterizations based on superficial features although there has been encouraging efforts for molecular characterization to know diversity of crop.

Table 1: Genetic diversity assessment and its importance on crop improvement

Crops list	Assessment method	Diversity Assessment for (specific trait)	Reference
Brassica juncea	Biochemical, Morphological markers and SSR	For discriminating genotypes, phenotypic variability, Genetic distance, high seed yield, high oil content together with low amount of glucosinolate in seed meal and low erucic acid	(Singh, Bangari, Singh, & Tewari, 2011); (Vinu *et al*., 2013)
bread wheat	tandemly repeated DNA motifs	For integrative biodiversity indicators such as HT*, that take into account the full range of factors (varietal richness, spatial evenness, between-variety genetic diversity and within-variety genetic diversity)	(Bonneuil *et al*., 2012)
Cassava	SSR marker	Genetic differentiation among accessions from different regions	(Turyagyenda *et al*., 2012)
Common Bean	principal component analysis varimax rotation and method	For improvement of nitrogen fixation ability and seed production	(Golparvar, 2011)
Fenugreek	AFLP analysis	For relationship of accessions from Iraq and Pakistan	(Al-Maamari, Al-Sadi, & Al-Saady, 2014)
Maize	SSR Marker	pro-vitamin A content	(Adeyemo, Menkir, Melaku, & Omidiji, 2011)
Maize	Morphological and molecular methods	Effects of Transgenic Maize in Mexico	(Ellstrand, Raven, Snow, & Solleiro, 2004)
Mango	Multivariate analysis	For genetic divergence, morphological characters and geographical distribution	(Majumder *et al*., 2013)
Naked barley	Agromorphological traits, biochemical and molecular markers	To determine the relationships of genetic distance estimates	(Eshghi, Abrahimpour, Ojaghi, & Salayeva, 2012)
Oilseed rape, lotus, coffee	AFLP, ISSR and SSR markers	TBP (tubulin-based polymorphism), for tubulin proteins and revealed high genetic distances	(Bardini *et al*., 2004); (Havlíčková, Jozová, Rychlá, & Klíma, 2014)
Pea	SSR Markers	For development of true hybrids	(Ahmad, 2012)
physic nut	Morphological and biochemical	For normal toxic and non toxic nature	(Gohil & Pandya, 2008)
Potato	AFLP markers	Geographical differentiation in potato diversity.	(Esfahani, Shiran, & Balali, 2009)
Rice	Molecular markers, SSR	Starch quality, germplasm assessment and utilization of the genetic diversity	(AO *et al*., 2016); (Lin *et al*., 2012); (Li & Zhang, 2002)
Sesame	AFLP	Geographical origins and morphological characteristics	(G. M. Ali, Yasumoto, & Katsuta, 2007)
Shorea Tumbaggia	RAPD	For successful management and preservation of natural populations and conservation of the species	(Sasikala & Kamakshamma, 2015)
Sorghum	Morph-physiological	Assessment for drought tolerant	(M. Ali, Niaz, Abbas, Sabir, & Jabran, 2009)
Sorghum	SSR	Genetic and geographical diversity, for various biotic and abiotic stresses and developing recombinant inbred line	(Kunyuga, 2012);(Madhusudhana, Balakrishna, Rajendrakumar, Seetharama, & Patil, 2012)
sunflower	Dynamic modeling	For assessment whether specific adaptation of cultivars.	(Casadebaig & Trépos, 2014)
Tea	RAPD	Genetic variation among tea clone	(Shefali Boonerjee, M. Nurul Islam, 2013)

Table 1: Continued

Crops list	Assessment method	Diversity Assessment for (specific trait)	Reference
Tobacco	Morphological analysis and ISSR methods	For selecting superior and genetically divergent parents for hybridization to optimize the genetic variation of subsequent generations	(Maryan, Lahiji, & Deylami, 2012)
Tomato	Morphological and molecular marker method	For high yielding tomato accessions	(Sciences, Naz, Zafrullah, Shahzadhi, & Munir, 2013)
wheat	Biochemical, agromorphological and physiological and RAPD Analysis	For endosperm proteins, assessment of parental variability and agronomic traits	(Jan *et al*., 2014) (Chavan & Patil, 2015); (Grewal *et al*., 2007); (Mishra *et al*., 2015); (Pordel-maragheh, 2013)
white clover	AFLP	Accurately quantify individual genetic structuring.	(Khanlou, Vandepitte, Asl, & B, 2011)
Yam	AFLP, SSR and ISSR	Estimate the genetic diversity maintained by traditional farmers	(Nascimento, Rodrigues, Koehler, Gepts, & Veasey, 2013)

Thus, it is high time to scale up the level of research and allot full time engagement in the molecular characterization of landraces. Classification at family, genus and species level of Ethiopian crops is quite advanced for it follows a global trend.

However, classification at subspecies and variety level remains to be a challenge especially when we think of the entire farmer varieties. On farm characterization had been undertaken throughout the development of the Agricultural sector in Ethiopia. Recent advancement in biological science is introducing molecular tools to detect variation at the genetic level. There is a growing concern of molecular characterization research in Ethiopian crops even though it is unsatisfactory.

The taxonomical hierarchy of farmer varieties, wild types, subspecies of crops and others will be completely resolved via the applications of tools of biological science at molecular level. The farmer varieties are given a vernacular or local name. Different ethnic groups may give different name for same crop resulting in confusion (Negash Almaz, 2001). Convergent evolution also complicates taxonomy of Ethiopian crops. Due to similar environmental factors detected in various agroecosystems, crops of different taxonomic group may appear similar morphologically and this has to be resolved. Consequently, the ultimate remedy to find resolution for this confusion lies within the molecular machineries of cell, which are novel tools for they determine a given trait or phenotype, which is a reflection of the genes or alleles hosted in the entire genome (Rohlf., 2002).

POTENTIAL OF MONITORING DIVERSITY FOR CROP IMPROVEMENT

The application of molecular markers for monitoring DNA sequence variation was underlined (Bagali *et al.,* 2010). Monitoring genetic diversity is of paramount importance even if some species of crops are over studied at molecular level in Ethiopia (Table 2). The task of characterization is a continuous process. Anthropogenic and environmental burdens may lead to a decrease in the overall diversity. Crop genetic diversity is threatened due to loss of farmer varieties following a subsequent replacement by selected seed, drought conditions, forest destruction, soil erosion, invasion and other factors. In evolutionary time scale, there could be splitting of species of crops via events of speciation and merging of different species of crops. Sometimes, hybrids are created due to a random cross in the natural population. Frequently, transgenic crops are adopted as a technology. These plants may reproduce with native crops and affect the native allele frequency. Eventually, mutation due to the existence of mutagens may affect allele frequency of native crops if mutation occurs randomly. Thus, it is desirable to undertake monitoring study to avail the most updated taxonomy.

ALTERATIONS IN LANDSCAPE FEATURES

The diversities of the crops are due to landscape variation, climate change, edaphic and other environmental factors. Above all, topography may attribute to minor

Table 2: Application of molecular markers to study the genetic diversity and/or phylogeny of plants from Ethiopia (adopted from Abraham, 2009).

Crops/plants	Marker type used	Reference
African wild rice	SSR	Melaku *et al*., 2013
Anchote	ISSR	Bekele *et al*, 2014
Barley	RFLP	Demisse *et al*., 1998
Brassica carinata	RAPD	Teklewold and Becker, 2006
Coffee	Sequence of part of chloroplast genome	Tesfaye *et al*., 2007
Coffee (cultivated, forest)	RAPD, ISSR, AFLP, SSR	Aga *et al*., 2003, Aga *et al*., 2005, Silvestrini *et al*., 2007.
Endod	AFLP, RAPD	Semagn, 2002
Enset	AFLP, RAPD	Negash *et al*., 2002, Birmeta *et al*., 2002
Ethiopian lenti	Morphological and molecular	Fikiru *et al*., 2010
Guizotia spp.	ITS sequence	Bekele *et al*., 2007
Guizotia spp. (weedy and wild)	AFLP; RAPD	Geleta *et al*., 2007
Hagenia abyssinica	ISSR	Feyissa *et al*., 2007
Highland maize	AFLP	Beyene *et al*., 2006
Linseed	AFLP	Wakjira *et al*., 2005
Mustard	AFLP	Genet *et al*., 2005
potato	SSR	Abebe *et al*., 2004
Sorghum	AFLP, SSR, RAPD, ISSR	Geleta *et al*., 2006, Ayana et al., 2000a; Tadesse & Feyissa, 2013
Sweet sorghum	SSR	Disasa *et al*., 2016
Tef	RFLP, AFLP, SSR, ISSR, EST-SSR, SNP	Bai *et al*., 1999, Bai *et al*., 2000, Yu *et al*., 2006, Yu *et al*., 2007, Zhang et al., 2001
Wheat (tetraploid)	SSR, EST-SSR	Yifru *et al*., 2006, Wang *et al*., 2007
Wild Sorghum	RAPD, ISSR	Ayana *et al*., 2000b; Teshome & Feyissa, 2013
Yam	AFLP	Tamiru *et al*., 2007

AFLP, amplified fragment length polymorphism; RFLP, restriction fragment length polymorphism; RAPD, Random amplified polymorphic DNA; SSR, single sequence repeats; SNP, single nucleotide polymorphism; EST, Expresses sequence tag; ISSR, Intersimple sequence repeats; REP-PCR, repetitive extragenic palindromic PCR; ITS, internal transcribed spacer.

genetic differences detected within same species. The agroecological zones are quite varying. A digital map of the ecosystem is available at this moment (Eticha *et al*., 2010). The articulated lands of Ethiopia with the unique topography created following tectonic movements and numerous geological events attributes to the diverse agroecosystem. The traditional classification like "Dega", "Weyna Dega", "Kola" and the like emanated from altitudinal difference and other factors. All in all, in this unique landscape, various endemic species, farmer varieties and unique ecosystems are harbored and a variety of crops are cultivated. Wild types of various domesticated crops occur. Following the diversity of the crops, much more effort had been attempted to undertake morphological characterizations.

Ethiopia is one of the Vavilov centers meaning centre of origin for various crops. Most probably, the landscape variation attributes for that diversity detected to qualify the country for Vailovian center. Ethiopia is mentioned to be centre of origin for Abyssinian hard wheat, poulard wheat, emmer, Polish wheat, barley, grain sorghum, pearl millet, African millet, cowpea, flax, teff, sesame, castor bean, garden cress, coffee, okra, myrrh and indigo (http://en.wikipedia.org/wiki/Main_Page). There is a continuous change happening to the landscape following a number of intrinsic and extrinsic factors. A typical example is the process of desertification which occurs in dry land and desert habitats. This may contribute to microhabitat variation that may affect crop diversity. For example, the diversity of barely in Ethiopia is quite high for an extended history of cultivation and variant agroecosystems (Eticha *et al*., 2010).

Environmental factors as a varied soil types, altitudinal variation and climatic factors attribute to the diversity of barely manifested in Ethiopia. The morphologically characterized landraces of barley (Ababadhas, Abashewaye, Balame, Butuji, Garbuguracha, Hadho,

Kate, Kitankite, Luka'a, Muga, Samareta, Shamari, Sidamo and Warkina) collected from west showa showed that alteration of landscape feature is the cause for the divergence of barely genotype (Eticha *et al*., 2010). Beside this, 568 SSR markers were developed for molecular characterization of Barley collected from Tunisia, Syria and Danemark to demonstrate the effect of environment on barley species (Chaabane *et al*., 2009).

Barriers may be created following change happening to a land mass. Thus, the diversity detected in the present time will never remain the same given there is a continual variation in landscape. The overall implication of this review is diversity of crops has no limit and there is no time to ascertain that the entire diversity is studied once and for all to support conventional plant breeding.

SIGNIFICANCE OF GERMPLASM CONSERVATION OF CROPS

Intimidation on various crops leads to the urgent need of characterizing the plant to launch appropriate conservation programs for breeding purpose. There is a continual loss of land races. Above all, there is usually underrepresentation of in-situ and ex-situ sites. Even for some species, in-situ and ex-situ conservation approaches may not be commenced. With the aid of molecular markers, ex-situ and in-situ conservation and genetic diversity conservation is possible (Bagali *et al*., 2010). It is common to encounter limited number of accessions in gene bank. As it has been said repeatedly, the Ethiopian crops are under extensive human induced pressure and natural disasters. Preserving species is uneasy before knowing diversity at gene, species and ecosystem/agroecosystem level. A case study on coffee guides to select and conserve populations to encompass maximum genetic diversity instead of conserving the entire population for it is cumbersome and impractical from resource point of view (Alemayehu Teresa, 2007). It has been said that improving and utilizing crops are hindered by insufficient knowledge about the genetic diversity (Negash Almaz 2001). It is critical to investigate the molecular diversity of the crops either to update existing information or initiate establishment of field genebank/community gene bank, botanical garden, green house, preservation in test tube and tissue culture based preservation means.

Gene bank of Ethiopia has collected seeds of the various Ethiopian crops. For instance, germplasm of Ethiopian crops is not necessarily in Ethiopia. There is wild coffee collection in CIRAD, French Guiana (Cubry *et al.,* 2008). These collections may not be characterized well except attempts in morphological level characterization although there have been several attempts of molecular characterization. Local experts usually encounters duplicates, same thing coded as different variety in gene bank. Some accessions in gene bank may not be characterized even at morphological level. During collection, collectors who deposit seed in gene bank might skip critical places endemic to a particular crop. Epigenetic changes may happen to stored and conserved seeds. With the aid of markers, seed mixtures, duplications and genetic drift will be studied. This reveals that undertaking molecular characterization will aid to evaluate the existing status about the existing germplasm.

GAP IN MORPHOLOGICAL CHARACTERIZATION

The Ethiopian agroecosystems which affects the physical appearance of economically important crop is poorly understood. Perhaps, the existing agroecosystem is always under revision. The forest cover, land cover and land use classification is poorly understood though to date, there is positive insight. Thus, scientists who conducted morphological characterization in Ethiopian crops may not undertake intensive allocation of wild crops for knowledge gap in the updated agroecosystem map of Ethiopia. They may visit similar agroecosystems during morphological characterization. This couldn't hood to detect exact crop variation, because the physical appearances of crops are highly sensitive to environmental factor.

For example, current updates of in the science of *coffea arabica* revealed that this species is frequently studied via morphological characterization to resolve fallacies of classical taxonomy but it was not as such informative to classify the botanical base of this species. But, no single researcher is here to continue research about molecular characterization of coffee. Although several authors conducted research on this species, it is never exhaustive and representative of the whole part of the country. It is possible to hypothesize that not all parts of Ethiopian places are studied for their coffee genetic diversity. It is not doubtful to say every scientist visit south west Ethiopia (centre of origin for coffee) to study the molecular ecology of Coffee. But, there could be other places which we need to explore. Even north western Ethiopia, which is not known as coffee endemic area, was identified for coffee collection (Desalegn *et al*., 2008). For example, one may explore the south eastern part of Ethiopia, which seems to lack intensive molecular characterization research of the Hare *coffea,* which is hypothesized to be the source for the Coffee cultivated in Yemen. The former

study might be inadequate calling for further research. It is high time to explore the entire diversity of Ethiopian coffee using molecular markers besides the pre-existing studies. Generally, thus, it is highly likely that there are places in Ethiopia, which are not explored and studied for their crop genetic diversity.

GLOBAL PERSPECTIVE OF AGRO BIODIVERSITY AND MOLECULAR EVOLUTION

Comparison of various ecotypes is the day of the trend. Speciation events could happen some years back in evolutionary time scale. That speciation might happen during segregation of a big land mass that could happen following disasters like continental drift. So, it is good to collect samples from different countries and bioregions for implementing comparative approach of phylogenic study to document global agrobiodiversity and understand pattern of diversity globally. For example, most of the researches about *Coffee* were not studied based on collections from a single country. Coffee collected from France, Uganda and Ethiopia was characterized (Cubry *et al*., 2008). Coffee collected from Brazil, Jamaica, Mexico, Costa Rica, La Réunion, Côte-d'Ivoire, Yemen, Ethiopia and Sudan were characterized using AFLP and SSR (Anthony *et al*. 2002; Moncada and McCouch, 2004). Barely collected from Tunisia, Syria and Denmark were characterized using SSR (Chaabane *et al.,* 2009). In addition collection of *Pisum sativum* from Syrian Arab Republic, Tajikistan, Jordan, Algeria, Tajikistan, Nepal, Turkey, Iran, Greece, Rusian Federation, India, Ethiopia, Germany, United Kingdom, Rusian Federation, Lebanon, Afghanistan, Algeria and Egypt were characterized using SSR markers (Nasiri *et al*., 2009).

Fundamental biology in the area of molecular science is also far from advancement in Ethiopia. Unique genes harbored in the Ethiopian crops must be over studied to increase our understanding about fundamental evolutionary biology. Understanding evolutionary aspects like plant evolution from wild type may enhance future attempts in laboratory evolution, which happens in relatively short period of time. New networks of evolutionary units or an updated phylogenetic tree can be discovered should studies direct towards consideration of samples from different countries. The phylogeny obtained from the most recent research is always indicator of the progress of the diversity. So, it is equally important to trace evolutionary origin of crops and deduce a biologically sensible evolutionary tree/ dendrogram.

EMERGENCE OF TISSUE CULTURE TECHNOLOGY IN ETHIOPIA

Tissue culture is the *in vitro* aseptic culture of cells, tissues, organs or whole plant under controlled nutritional and environmental conditions (Thorpe, 2007) often to produce the clones of plants. The science of plant tissue culture takes its roots from proposal of, Schleiden and Schwann (1838), that cell is the basic unit of all living organisms. Based on this premise, in 1902, Gottlieb Haberlandt, a German physiologist, attempted to culture isolated single palisade cells from leaves in knop's salt solution enriched with sucrose for the first time. Plant tissue culture is done in the countries namely Kenya, Uganda, Tanzania, Ethiopia, Rwanda, Burundi and Democratic Republic of Congo and some projects have already been commercialized (Mtui, 2011). Plant tissue culture technology is the likely opportunity for Ethiopian agricultural system towards improving agricultural yields (Hussain *et al*., 2012).

Advancement in tissue culture calls for molecular characterization. Tissue culture experiments that are conducted at the Ethiopian Institute of Agricultural Research and other places release tissue culture pure lines. For example, Ethiopia has a number of plants generated from a tissue culture experiment. Although the country has no prolonged experience in tissue culture, presently tissue culture experiments are expanding(Seid, 2013). Recently there are many tissue culture protocols developed in majority of crops in Ethiopia (Table 3). And National Agricultural biotechnology Research Center of Ethiopia also launched various tissue culture programs in crops like enset, sweet potato, grape etc. In addition there are some commercial tissue culture laboratories in Ethiopia including Tigray biotechnology institute (TBI) and Amhara tissue culture laboratories. This rapid expansion of the program will be accompanied with release of varieties propagated from tissue culture in the near future.

The objectives of tissue culture experiments, the explants source and the status vary in different crop (Table 3). In most tissue culture experiments like the experiments conducted at EIAR, generating identical progeny is the principal aim, thus, there shouldn't be diverse clones. However, there are variant clones with minor genetic difference due to the existence of somaclonal variation (a variation occurring in plant tissue culture). This variation could be due to point mutation, gene duplication, and chromosomal rearrangement, changes in number of chromosome, transposable element movement and DNA methylation and occur in the nucleus, mitochondria and chloroplast may be contributes by the hormone 2, 4-D (Larkin Philip; Bagali *et al.,*

Table 3: Explants source, main objectives and status of tissue culture protocols developed for some of crops in Ethiopia.

Name	Explants source	Main objective	Status	Reference
Anchote	Shoot tips,	Micropropagation	Completed	Yambo and Feyissa, 2013
Banana	Shoot tips,	Micropropagation, Virus cleaning	Completed and being scaled up	Dugassa and Feyissa, 2011
Black pepper	Shoot tip	Micropropagation	Ongoing and in good progress	
Brassica spp.	Anther	Double haploid line development	completed	Abrha *et al*., 2014
Korarima	Rhizome lateral bud	Micropropagation	Completed	(Tefera & Wannakrairoj, 2004)
Cassava	Meristem	Micropropagation, Factors affecting in vitro propagation, Virus cleaning	completed	Beyene *et al*., 2010; Berhanu and Feyissa, 2013
Citrus	Seed	Micropropagation, virus cleaning	Ongoing and in good progress	
Coffee	Leaf	Micropropagation, *in vitro* disease screening and somatic embryo genesis	Completed and being scaled up.	Ahmed *et al*., 2013
Enset	Shoot tip, zygotic embryos	Micropropagation, disease free, Callus culture and somatic embryogenesis	completed and in good progress for scaling up	Negash *et al*., 2000; Gezahegn and Mekbib, 2016
Garlic	Meristem	Micropropagation, virus cleaning	Initial stage	
Geranium	Shoot tip	Micropropagation	Completed	
Ginger	Rhizome lateral bud	Micropropagation	Completed	Disasa *et al*.,2011
Grapevine	Shoot tip	Micropropagation	Completed	
Hagenia abyssinica	Shoot tip and leaf	Micropropagation	Completed	Feyissa *et al*., 2005
Niger	Anther	*In vitro* regeneration, Double haploid line development	Completed and in good progress for scale up	Disasa *et al*., 2011
Noug	Anther	Embryogenic callus induction and regeneration	Completed	Disasa *et al*., 2010
Pineapple	Shoot tip, Slip	Micropropagation, assess the potential of temporary immersion bioreactor (TIB)	Completed and being scaled up	Ayenew *et al*, 2013
Plectrantus edulis **(Ethiopian dinch*)***	Meristem	Micropropagation	Completed	(Tsegaw & Feyissa, 2014)
Potato	Node	Micropropagation, virus cleaning	Completed and being scaled up	
Sweet potato	Shoot meristem, leaf and petiole	Micropropagation, for production of virus free planting material	Completed	Getu & Feyissa, 2012; Wondimu *et al*., 2012
wheat	unpollinated ovary	Regeneration of plantlets	Completed	Getahun *et al*., 2013
Tef	Floral part & embryo rescue cultures	Double haploid line development & Somatic embryogenesis	Completed and scaling up in good progress	Getahun *et al*., 2012
Yam	Node	Micropropagation	Completed and to be scaled up	Dessalegn *et al*., 2015

2010). It could be created by the various factors during manipulation of a tissue culture. This variation is crucial in germplasm improvement programs like acquiring disease resistant plant. In tissue culture experiments which have aim of generating uniform clones, soma clonal variation is disadvantageous. It may have effect on the genetic composition in occasional cases. During somatic embryogenesis and callus production of cotton using 2, 4-D, variation at DNA level was detected in cell lines based on characterization studies conducted using RAPD and SSR markers (Jin *et al.,* 2008).

GERMPLASM IMPROVEMENT

For instance, studying the genetic diversity of crops using markers have an immense applications to detect genetic variations, identification of cultivar and planning of breeding. Combining the right alleles is of great significance for breeding. Thus, characterization using molecular markers has a considerable importance to design an effective program in breeding. Crop improvement has a value of achieving a desired genetic combination from different lines, selecting specific genotypes from a bunch of genotypes and maintaining and perpetuating the favorite genotype (Clegg *et al*., 1999). Conventional breeding takes long years like 8 and 12 years. It takes much time and relies on the external environment. Shortly, a variety with better yield and rich in nutrition can be produced via marker assisted selection and breeding. Also molecular breeding to investigate biotic and a biotic stress is possible using molecular markers (Bagali *et al.,* 2010).

FUTURE PROSPECTS OF GENETIC DIVERSITY ASSESSMENT OF PLANTS IN ETHIOPIA

Ethiopia is an agrarian country that can have enormous benefit from the applications of biotechnology for increasing its agricultural productivity. The country is at initial stages of research and development in agricultural biotechnology with scattered efforts underway in various public institutions. Research efforts and applications in crop production include plant tissue culture, biofertilizers and biopesticides, molecular markers for disease diagnosis and genetic diversity. Know a day, based on the available genetic diversity research result breeders has been released many improved crop varieties within a short period of time without wasting to much energy to secure food consumption in the country. Its productivity is increased from time to time.

Ethiopian government development strategy recognizes the leading role of agriculture in the economy and stipulates that for the country to record rapid economic prosperity. The strategy identifies information and communication technology and biotechnology as essential tools for genetic diversity assessment and rapid transformation of largely subsistence mode of production to market-oriented production enterprises that ultimately lead to industrialization.

CONCLUSION

Diversity of plant genetic resource is very crucial asset for human kind that Agriculturist should not lost and attention should be given to evaluate the diversity for breeding feature. The production and productivity of crops should be highly supported by modern technology to examine the diversity of planting materials which are increasingly required to be accessible for feeding a burgeoning world population in future. Assessing genetic variability of crops is essential for its further improvement by providing options for the breeders to develop new superior crop varieties and hybrids within a short period of time without wasting too much time, energy and resource. This can be highly achieved by molecular characterization of Plant genetic resource. Molecular markers are central tools for measuring the diversity of plant species. Many important factors are considered when we are going to choose tools for genetic diversity such as Low assay cost, affordable hardware, throughput, convenience, and ease of assay development and automation.

Now it is possible to characterize a large number of genotypes using high throughput molecular marker technologies with limited time and resource which is ensuring speedy and quality of data generated. Many software package are available to evaluate and/or asses molecular diversity which speed up selection of superior varieties for breeding programs and plant breeders to speed up the crop improvement. Therefore, we believe that this paper provides useful and fashionable information for breeders; it improves the understanding of molecular tools for students about molecular characterization and also practical applicability to the researchers.

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Article

A Guide to Time Lag and Time Lag Shortening Strategies in Oncology-Based Drug Development

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ABSTRACT

One of the ongoing challenges for academic, biotech and pharma organizations involved in oncology-related research and development is how to help scientists be more effective in transforming new scientific ideas into products that improve patients' lives. Decreasing the time required between bench work and translational study would allow potential benefits of innovation to reach patients more quickly. In this study, the time required to translate cancer-related biomedical research into clinical practice is examined for the most common cancer cases including breast, lung and prostate cancer. The calculated "time lag" typically of 10 years for new oncology treatments in these areas can create fatal delays in a patient's life. Reasons for the long "time lag" in cancer drug development were examined in detail, and key opinion leaders were interviewed, to formulate suggestions for helping new drugs reach from bench to bed side more quickly.

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Keywords: Time lag, cancer, translational study, technology transfer

INTRODUCTION

Basic biomedical research requires huge amount of financial investment. In 2017, the federal budget will provide $14.6 billion for basic research, $1 billion as an initiative for cancer research, and $33.1 billion for biomedical research (1). However, transforming this investment into an innovation to improve public health takes tremendous amount of time, which causes delays of potential patient benefit.

Cancer is the second leading cause of death in United States. According to the latest statistics, 595,690 American are predicted to die from cancer by the end of 2016, which equals to 1,600 deaths per day (2). Breast cancer will be the most common cancer in women with 246,660 new cases predicted, prostate cancer will be the most common cancer in men with 180,890 new cases predicted, and lung cancer will be the second most common in both women and men with 117,920 new cases predicted in 2016.

On one side of the coin, one might well say that cancer patients race with time for their lives. On the other side of the coin however, despite the tremendous amounts of time and money invested in biomedical research, the translation of basic biological discoveries into clinical applications takes a frustratingly long time. Therefore the "time lag" between basic biomedical research and translation of the resulting innovations into public health improvements deserves more attention (3).

In this study, firstly, the length of time between patent application and approval of a new cancer drug is examined. For this purpose, the three most common cancer types - breast, prostate and lung cancer - were chosen. As part of this study it is clearly important to

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understand the pace of current basic biomedical research and to develop potential solutions to the obstacles and challenges that it faces. With this in mind, in the second part of the study the reasons for this "time lag" in biomedical research are studied and defined in more detail.

METHODS

In the first part of the study, information from the Pharmaprojects® database (produced by Citeline/Informa PLC) was used to calculate time lags of breast, lung and prostate cancer drugs. The time length between patent priority date, date of regulatory filing of the initial application and approval date of the new drug was calculated for each drug, and the average time length was calculated. Patent priority date of a new drug is considered as a publication date, and most of the drugs have patent protection. However, some of the Pharmaprojects® drug profiles did not include patent information, and in those cases the date of the first press release or publication was considered to be the publication date. Drugs without patent, publication or approval dates were eliminated.

In the second part of the study, key opinion leaders were interviewed, including principal investigators, scientists, researchers from National Institutes of Health (NIH), National Cancer Institute (NCI), National Center for Advancing Translational Sciences (NCATS), Yale University, Massachusetts Institute of Technology (MIT), Queen's University School of Medicine, Dentistry and Biomedical Science, Belfast (U.K), and Regeneron Pharmaceuticals. The interviews were performed to better understand the reasons for the lengthy time required for drug discovery or/and the failure of basic biomedical research to reach translational study. Additional background was obtained from relevant published articles and recorded seminars, as well as attendance at the American Association of Cancer Research (AACR) 2016 Annual Conference and translational study-related conferences.

During these interviews, the following questions were discussed;

1. What determines that basic research results are not qualified to continue to translation study?
2. What are possible reasons for the lengthy time required to translate basic research into clinical practice?
3. How could we shorten the time lag in biomedical research?

RESULTS

Time Lag in Breast, Lung and Prostate Cancer Research

The definition of translational research is not as clear as that of basic research or clinical research, and it is described as "a process that transfers basic science findings into clinical application" or "bench to bedside". Translation of basic research findings into medical benefit requires an enormous amount of time and money (4, 5). When we empathize with a patient who has been waiting for a cure to survive, the time that is required for the translation of a drug into clinical application becomes more critical and important than ever. On the other hand, the large investment in basic and clinical biomedical research by the government creates the expectation and pressure to see public health benefits of biomedical research. Due to these obvious reasons, the first part of the study focused on the calculation of time lag in the three most common cancer types including breast, lung and prostate cancer.

In calculating these time lags, two data points were selected for each approved drug. The first data point was the patent priority date or the initial publication date; the second data point was the regulatory approval date for the drug itself. The time lag between these two data points and average time lag for each cancer type were calculated.

As seen in Figure 1, there are currently 44, 36, 24 approved drugs, respectively, for breast cancer, lung cancer and prostate cancer. Some of these drugs could be used for more than one cancer indication. For example, 17 drugs could be used to treat both breast and lung cancer, 4 drugs could be used to treat both breast and prostate cancer and 5 drugs could be used to treat breast, lung and prostate cancer. A total of 130 approved breast, lung, and prostate cancer drugs could potentially have been used for the calculation of time lag. However, drugs without patent priority date/publication date or launched date were excluded from the time lag calculation.

As shown in Figure 2, 97 drugs out of 130 drugs were examined for time lag calculation: 30, 32, 17 approved drugs, respectively for breast cancer, lung cancer and prostate cancer. As seen in Figure 2, 12 drugs could treat breast and lung cancer, 4 drugs could treat both breast and prostate cancer and 5 drugs could treat breast, lung and prostate cancer.

As seen in Figure 3, the average time required to launch a cancer drug was calculated to be 11 years, 10 years and 10.4 years, respectively for breast, lung and prostate cancer. In another study, the time lag for general biomedical research (not just cancer), calculated by

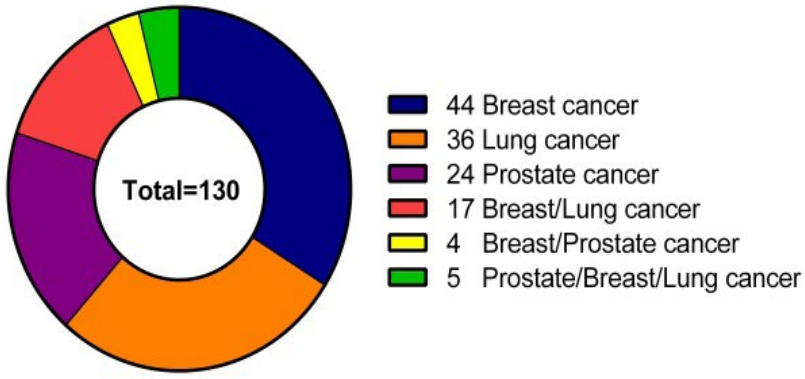

Figure 1: The number of approved drugs for prostate, breast and lung cancer.

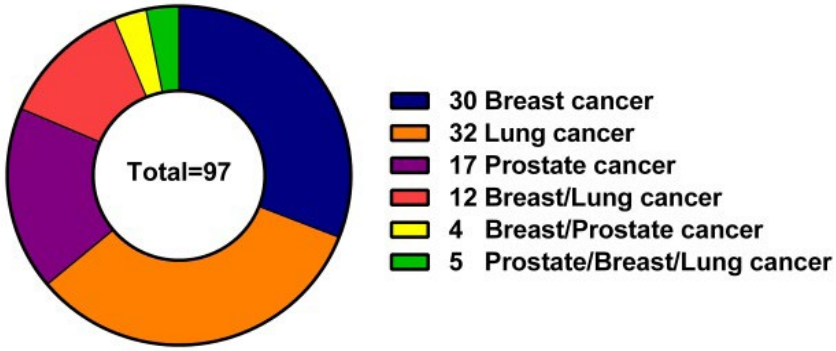

Figure 2: The number of approved drugs that were used to calculate time lag for prostate, breast and lung cancer treatment.

searching publication data of 23 studies, was determined to be 17 years (6). In either instance, this is a frustratingly long time to launch a drug, cancer or otherwise. When we consider the typical conditional 5-year relative survival time for a cancer patient (7), the 10 to 11 year time required for translation of a cancer drug into clinical applications makes for a dramatically heart-breaking and fatal waiting period.

Reasons for the Long "Time Lag" in Breast, Lung and Prostate Cancer Research

Finding the reasons for this "time lag" in new breast, lung and prostate cancer treatments is a multi-dimensional puzzle. These reasons need to be first better defined so that potential solutions can be developed by both the biotechnology industry and the research community. Clearly, the causes for this lengthy "time lag" can be divided into two categories: scientific and non-scientific.

SCIENTIFIC REASONS

Challenges in Reproducible Data Generation

Reproducibility is clearly one of the most important fundamental principles of science research. Reproducibility means that any laboratory could produce the same results for experiments conducted under the same conditions. Reproducible data generation is an issue in oncology research as without reproducibility, a new treatment discovery could easily be dismissed as invalid. There are multiple reasons for reproducibility problems in research studies such as weak experimental design, lack of knowledge by the investigator of basic experimental principles, inappropriate statistical analysis, inappropriate small sample size, other human error related variations, overly complex experimental procedures, and unanticipated changes (especially stability or contamination) in chemical and biological ingredients (8). The main reasons for this "time lag" in oncology related to reproducibility will now be reviewed and discussed in more detail.

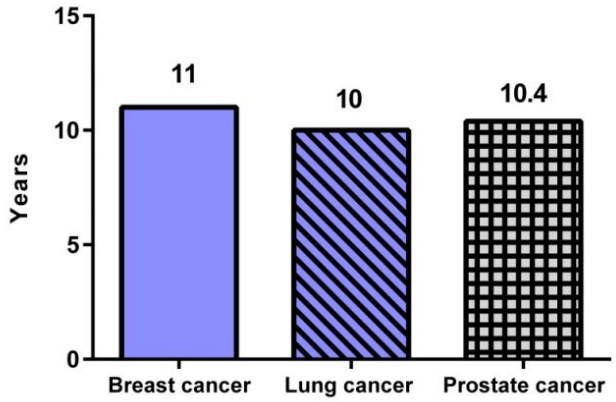

Figure 3: Calculated "*time lag*" of translation of a cancer drug into clinical application for breast, lung and prostate cancer

Vitro-Vivo Model Differences and Mouse Models for Human Disease

Unexplored differences between *in vitro* (working with living cells in a dish) and *in vivo* (working with whole living animal) models of disease could be the source of unreproducible data generation and one biggest challenges in oncology research today. While an *in vitro* study could be the genesis for a novel biomedical discovery and eliminate the cost and complexity of a whole animal study, misidentified, virus or mycoplasma contaminated cells would however lead to unreliable experimental results. When such occurs it means the loss of time in general research progress and more importantly, a delay in the discovery of life-saving drugs (9). To improve reproducibility of an *in vitro* study, cell lines need to be periodically validated for their purity and confirmed authentication (10).

On the other hand, an *in vivo study* usually produces more reliable and reproducible data and early toxicology studies and potential adverse effects for a new drug should include an *in vivo* evaluation. One of reproducibility problems appears in case of switching from an *in vitro* system to an *in vivo* system. Often the activity of a drug compound in *an in vitro* system can be different than in *an in vivo* system due to differences between oral uptake and general absorption (11).

Human xenograft mouse models are considered as a foundation of cancer research, and they have been used for decades in drug development including safety and toxicity testing. *In vivo* study models are expensive and time consuming. Despite successful pre-clinical testing, mouse models often do not lead to successful practice in clinical applications due to their often overlooked historic low translational success and low reproducibility. Besides the examples for cancer, there are many mouse models for other diseases with similar low success rates. Alzheimer disease is another example for well-known but often ineffective or inefficient *in vivo* model systems. Approximately 36 drugs have failed in Alzheimer disease clinical trials, even though they were successful in transgenic mouse and rat models (12, 13). There are also many other reasons for low reproducibility and translational success of *in vivo* studies. One particularly noteworthy case is that of using healthy animals with transplanted tumors for immunological cancer treatment or drug testing. Without considering the entirety of relevant but often complex endogenous factors in cancer progression, studies that focus only on a single factor can generate in unreliable *in vivo* data that will not lead to subsequent successful clinical applications (14, 15, 16, and 17). Other problems are statistically poor experimental design, lack of randomization and replication as well as omitted negative results. Human patient samples, collaborations with tissue bio banks, humanized mouse models and spontaneous cancer mouse models can be considered as alternative approaches in oncology research to prevent animal model-related obstacles or delays (9).

Human Patient Samples

Even though mouse models bring advantages to ease the complexity of biomedical research, their correlation with human cancer pathology and subsequent use to measure the safety and efficiency of chemotherapeutic drugs has significant potential for failure. Taking advantage of human patient samples and tissues from bio banks should thus be in general more relevant for translational studies than mouse models. However, collection and

storage of human patient samples can cause problems themselves in reproducible data generation. For example, freezing human samples could change the protein structure of the samples — later causing reproducibility problems with treatments using fresh human patient samples. Therefore, using fresh human samples could be one of the solutions to generate more reliable data.

NON-SCIENTIFIC REASONS

Competitor Versus Collaborator

Finding cures for a cancer has been a challenging adventure, similar in deed to a "moon shot" and collaboration thus is an inevitable requirement to shorten time lag in such biomedical research. Most of the time, failure in biomedical research can eventually be attributed to lack of fundamental understanding by one or more of participating investigators of the underlying scientific principles of the ongoing research project. Collaboration can bring a steadier pace and effectiveness into an otherwise slowly processing research program. However, the intellectual property (IP) generated from such research and resulting competition to commercialize it can be one of the obstacles to collaboration and research tool sharing in cancer research if not handled properly (18).

Intellectual Property (IP) Challenges for Sharing Research Tools

In the Unites States, the total number of the pharmaceutical and medical field related patents granted between 1964 and 2012 by the U.S. Patent and Trademark Office is 168,435 (19). Both the universities and private companies that own these patents thus potentially have significant control over the biomedical research field due to this increasing amount of patent activity, including those related to research tools. However to minimize future time-lags, it is clear that drug discovery related to cancer research conducted at universities or private companies will need rapid access to state-of-the-art research tools. Unreasonable restrictions or delays in the distribution or use of such tools can stifle new discoveries, thus limiting the development of future biomedical products. In 1997, Harold Varmus, then Director of the National Institutes of Health (and later Director of the National Cancer Institute), established a Working Group to look into the increasing apprehension that intellectual property restrictions might be stifling the broad dissemination of new scientific discoveries and thus limiting future avenues of basic research, drug discovery and product development in all therapeutic areas, not only cancer. Specific areas of concern were raised in the scientific community regarding: problems or delays encountered in the distribution, licensing and use of unique research tools as well as the competing interests of intellectual property owners and research tool users. Case in point was the difficulties in cancer research being encountered due to the so-called "DuPont Oncomouse Patents" originating from Harvard University.

In response, the NIH developed guidance for NIH-funded scientists and their collaborators on tool sharing and tool distribution (whether the tool was patented or not), to facilitate the exchanges of these tools for research discoveries and product development independent of IP status. Now more than sixteen years later, these guidelines have become standard clauses for nearly all funding from government and non-profit agencies so that a proper balance has been achieved to balance the interest in accelerating scientific discovery with that also of facilitating product development for health and patient care. (18, 20).

Public-Private Partnership Challenges

Partnerships in biomedical science optimize the use of available knowledge and resources and speed the progress of biomedical research. Public-private partnerships include at a minimum at least one private and one non-profit organization working together to accelerate translation of a biomedical discovery into public health benefit. Enactment of the Bayh-Dole Act and related legislation by the U.S. Congress beginning in the 1980s marked the start of opportunities for public-private partnerships. One of the good examples for public-private partnerships is the osteoarthritis initiative partnership between the NIH and private industry. This partnership accomplishments included establishing a database of radiological images, relevant biomarkers and physical exams as objective and measurable standards for the progression of this painful and disabling disease – all of which should be helpful in reducing time lag of future biomedical research in this field (21, 22). However, despite the inherent advantages of public-private partnerships, there are still obstacles to be avoided in their use that could otherwise limit their efficient application. It will be critical, for example, to set well-articulated common goals in such a partnership for otherwise further time-lags may result that may adversely affect the outcomes of the research. Thus in a typical academia-pharmaceutical company partnership, academic scientists will likely focus on biochemical and molecular targets of the disease, while on

the other hand pharmaceutical company scientists will focus on the manufacturing and clinical development of the innovative therapy. When not handled properly in advance and then managed effectively during the project, problems in public-private partnerships can result from differing end goals of each partners, unwillingness to share control and resulting financial benefits of a project, or simply differing work cultures – all of which could cause delays in translation of an innovation into a new oncology or other disease therapeutic.

Conclusions and Future Opportunities

Eroom's law indicates that drug discovery is slower and more expensive today than the past decades. As a general trend, the number of new drugs launched per year has been decreasing, however spending in drug development process have been increasing (23). Today we have more advanced technology, more investment in biomedical research and unfortunately seemingly less positive outcomes for drug development. The trend thus appears to be more delays in drug approval, further losses in productivity of pharmaceutical research. In this study, the findings showed that the typical age of a cancer drug is at least 10 years before it ever reaches the patients. For cancer patients 10 year period translates unfortunately to more than a life time of delay. To find solution for delays and to increase productivity in oncology as well as other areas of biomedical research, the problems or roadblocks need to better articulated and understood by all participants so that corrective action can be taken. While drug discovery and clinical testing are themselves inherently difficult, there are both scientific and non-scientific reasons contributing to the time-lag in biomedical research. As described previously scientific reasons include reproducible data generation, inappropriate use of in vitro/vivo models, and variation in human sample collection. Non-scientific reasons can include are poor collaborations among interested parties, lack of sharing of research tools and weak or ineffective public-private partnership arrangements.

Future Opportunity: Establishing Stronger Academia - Industry Connection for Oncology

Besides these problems discussed above, it seems that a general disconnect exists between academia and pharmaceutical companies that also stretches the time lag between bench and bedside. This lack of connectivity between industry and universities at times may be leaving potentially brilliant ideas in the dark. Academics have deep scientific knowledge but suffer from funding problems to pursue their research and typically lack the more applied skills of later stage clinical research, regulatory and production scale-up knowledge. Pharmaceutical companies generally have funding and applied skills, but they are dependent on academics and small biotech companies for fundamental knowledge and novel discoveries. Establishing more stronger and living connections between academia and pharmaceutical companies, thus increasing clinical research knowledge of academic scientists would go far to bring better pace and synergy in biomedical research.

Future Opportunity: Repurposing of FDA Approved Drugs for Oncology Applications

During one of the interviews for this article, a principal investigator from a major university said that time lag in his research to market is only 2-3 years, because his laboratory studies FDA approved drugs for different indications. Using FDA approved drugs for other indications, which means repurposing of a drug would dramatically reduce time lag and overall cost. The more exciting part of repurposing drugs, of course, is that translation of a drug into a new treatment for a patient's benefit will be quicker.

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Legal & Regulatory Update

Intellectual Property Challenges for the Modern Biotechnology Enterprise: An Overview

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ABSTRACT

The paper investigates the IP protection in the field of biotechnology among new innovators. Incompatibilities of the development process in modern biotechnology and the current IP systems are highlighted. Development process in biotechnology is notoriously slow, characterized by long delays in obtaining experimental data and marketing approvals. Initial development stages have been accelerated by the development *in silico*, by the global competition and accessibility of information. Thus, the most valuable part of the innovation (e.g., genetic sequence, protein structure) may be known years before the full experimental data. This significantly increases the risks of losing IP protection due to competing development, espionage, accidental disclosure, urging the premature patenting despite lack of resources to maintain global patents. Moreover, in biotechnology enterprise prohibitive costs of international patenting deplete the limited development resources and adversely affect both patenting and development. Costs are compounded by the increasing complexity of obtaining IP protection. Some of the complexities are recognized and underline multiple legislative interventions in establishing special regulations for biotechnology. The market also adjusted through practices such as evergreening. Unfortunately, legislative and market responses are not serving new innovators and may be contributing to the biotechnology patenting conundrums. The paper suggests that new legal innovation is needed in order to sustain healthy innovation in biotechnology and address the needs of new innovators. Several general and specific features for advancement of the legal protection of biotechnology are proposed for further research and discussion.

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Keywords: biotechnology, intellectual property, patents, innovation

INTRODUCTION

Traditionally, intellectual property (IP) is a mechanism facilitating the preferred position in the market for creative and innovative individual or enterprise. IP worked historically, and contributed to advances in many technological fields, such as chemistry, mechanical and electrical engineering (May, Sell, 2006).

The success of IP has somewhat predisposed it to trouble of trying to protect everything and everywhere. Over the last century, and especially over the last few decades, IP regimes were stretched to cover diverging subject matter – from traditional objects of art (literature, sculpture, painting) to computer software, and from tangible mechanical items to the genetic sequences. Such stretching inevitably produced the fallout in terms of inadequate or overbroad legal protection, costs and complexity. The specifics of biotechnology have triggered the need to craft special provisions and exceptions (including special provisions and exceptions for different biotech subject matter – e.g., microorganisms or genetic sequences). Novelty also caused substantial lag and uncertainties until clarification of the new rules is attained and added to complexity of regulation, making the IP law understandable to the few specialists rather than the innovators themselves – the subjects who are supposed to benefit the IP rights in the first place.

Subject matter of IP protection has inherently diverged in terms of global reach. The value of a poem in most cases is limited by language and national culture, however a novel molecule or a novel way to apply it has inherent global value. IP law has evolved to equally protect both and to allow global legal protection for any subject matter. It also achieved a reasonable unification worldwide. Nevertheless the actual needs of legal

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protection for different subject matter and especially the costs of obtaining worldwide protection and enforcing it have diverged dramatically. For globally valuable technologies the costs are becoming prohibitive. Thus, while IP rights are being touted by the policy makers as the main tool for national innovators and SMEs to break into the global marketplace, the market realities may be different.

Over the last two decades the value of IP has also been questioned on the social front. Multiple social initiatives suggesting anti-innovativeness of the IP rights have emerged (e.g., open source movement) and established themselves as a lasting trends. Criticism on the social effects of the current IP regimes has also resonated in the scholarly literature already for two decades (Foray, 2000; Shiva, 2001; Drahos, Mayne, 2002).

This context provides a framework for the analysis of the legal protection needs for modern biotechnology. The goal of this paper is to examine the specific IP issues (especially patenting problems) arising in modern biotechnology enterprise and to highlight incompatibilities of the existing IP regimes with the needs of the innovators in this field. Legal, policy and industry own responses to biotechnology legal protection problems are also investigated.

GLOBALIZATION ERODES THE VALUE OF IP FOR NON-CORPORATE INNOVATORS?

While abstaining from the social criticism of IP rights, it must be recognized that IP protection is not a virtue *per se*. It is only useful for the IP owner when it is able to deter imitators, copycats and other such market entrants. It is fair to assume that IP is valuable only as much as it is secured (properly registered and maintained in case of inventions), respected by the marketplace and enforced against the infringers (Cychosz, 2004). Thus, the economics of obtaining, maintaining and enforcing IP rights is increasingly the determinant of its value.

Globalization has influenced IP economics in several ways. Most notably it is now an essential necessity to obtain and maintain IP rights in countries, where it was not relevant 20-30 years ago –BRICS countries, Eastern European countries, Mexico (Bird, 2006). Moreover, the timespan to obtain such global IP protection has increased significantly due to exploding volume of patent applications worldwide, increasing wait times at the patent offices, as well as the willful strategies to extend the time before committing to patent application and paying the associated costs.

Parallel to the economic globalization the technological globalization took place over the last 20-30 years. In global society the technological lifecycles are increasingly short. In software and communications technology the technological cycles average 18 months and anything longer than 5 years is extremely uncommon. This acceleration has been caused by technological innovation, market demand and global competition, but also by the absence of regulatory barriers (such as IP rights) for market entry. Accelerated technology cycles require continuous innovation, disallowing reliance on existing IP for market leadership (Bilir, 2013), hence further erodes the value of the IP rights.

The globalization also directly and very significantly decreased the cost of imitation and direct copying, while increasing the rewards the IP ignorance. What once required years and sophisticated technological leadership is now attainable within seconds and may be distributed globally at little cost (Jons, 2010).

As it was noted, globalization, opening of the markets and growing complexity of the IP regimes augmented costs of IP protection. Efforts to simplify and bring down the costs of trans-national IP rights have been relatively modest, and outpaced by the growth in complexity of the international IP regimes and technological change. Piracy and patenting controversies have created perceptions that IP is compromised in the networked society. On top of this, many current innovators, especially in IT field, have a history of ignorance of the IP rights and have been raised on perception that IP rights are contra-innovatory (Naughton, 2014).

Separate issue that deserves separate mention is the increasingly prohibitive costs of patenting. The costs of patenting have exploded since 1980s due to several reasons:

- Globalization (the need to obtain and maintain patent rights in additional jurisdictions (e.g., BRICS));
- The huge inflation of the patent application volume worldwide due to the increased global competition and rush to patent, forcing effort and expense in assessing patentability of technological advances;
- Growing complexity and uncertainty of the patent systems, which requires expensive expertise (e.g., lack of clarity whether the article can be protected by the IP rights and the scope to which it can be protected).

Maintaining or retaining high-quality IP expertise is incompatible with the dominant lean and fast young technology enterprise strategies and therefore

inaccessible for SMEs, startups, individuals and even university development teams. Lack of proper expertise at the filing of the patent application, mainly due to the need to analyze large patent volume and subject matter specific issues, also leads to decrease in patent quality.

Even if patent application and prosecution costs are bearable, few innovators can afford the costs of potential enforcement or litigation (including oppositions) (Kingston, 2000). Only multinational corporations and in some cases public entities have the resources to pursue protection in case of legal challenges, and even less to police the protection of their invention in all jurisdictions, where the patent is applied for or extended (Sichelman, 2014). Even multinationals have limited resources to engage into the enforcement action and litigation. The costs involved in this in most cases are far greater than the potential benefits or even the value of the patent itself. Generally only blockbuster technologies are vigorously defended and pertinent patents carefully enforced. Thus, it must be ascertained that the startup has no realistic chance of litigating and enforcing their rights, especially in foreign jurisdictions, as one author has put it for SMEs patent litigation is "inefficient, ineffective and undesirable" (Kingston, 2000).

The high costs of patenting and discounting of potential litigation/enforcement place the startup and individual innovators in the position where preferred patenting strategies are inaccessible due to cost considerations (Mitchell, 2008). Too early and inappropriately broad filings with ensuing failure to address search and review opinions, extension into one or few jurisdictions, as well as failure to maintain patents are common outcomes. Litigating, policing and enforcement of patents is out of question for SMEs, startups, individuals and even universities (Lanjouw, Schankerman, 2004).

The above comments are generally applicable for any field of technology. What makes biotechnology innovators more cost sensitive is that securing of biotech patenting is economically more risky, suffers from pressure to patent as early as possible (way before any revenue and even before validation of the technology) and drains the development resources needed to validate the technology itself, as it is elaborated further in the paper.

WHAT DEFINES MODERN BIOTECHNOLOGY ENTERPRISE?

In the field of biotechnology the acceleration of technological development is also taking place, albeit mostly in research, rather than market entry. Best example of accelerating technological development in biotechnology is whole genome sequencing, which a decade ago required seven figure expenditures and lasted months. Now the same is possible for just several hundreds of Euros and requires few hours to complete (Ståhl, Lundeberg, 2012). Acceleration of technological development in the field of biotechnology is further facilitated by the unprecedented accessibility of previous research data and information. Global competition, researcher mobility and growing international collaborations also drive the increased speed of the technological development.

On the other hand the regulatory environment for biotechnology has grew in complexity over the last decades. Market access for biotechnological innovation in the fields of human or animal health and nutrition, has been historically very complex, subjected to the need of comprehensive safety testing, multi-stage clinical trials and special regulatory approvals. In the US and Europe many advanced biotechnology innovations (e.g., stem cell research) are further caught in the everlasting debate on the limits of the precautionary principle and ethics. All of this means that market entry even for pre-clinically validated research can be delayed by 7 to 10 years. Because of this lengthy and fastidious process the risks and resources involved in obtaining market approval for biotechnological innovations are immense.

Overall modern biotechnology is experiencing a convergence of fast development techniques at the preclinical stage, however is bound to slow biologic and very bureaucratic processes at the clinical and market approval stages.

Technological development techniques employed for early biotechnological work currently focus on the so called *in silico* methods, that is, the techniques where molecules and their interactions are computer modeled, selected and optimized (Kayser, Warzecha, 2012). After *in silico* modelling the development proceeds to the wet laboratory – to be tested in biological cultures. The computer models used for *in silico* work are rapidly getting increasingly sophisticated, and the technology is already at the stage where rough idea on the biological (genomic or proteomic) target may be converted into viable candidate molecule (e.g., antisense or antibody) within days. Nevertheless the subsequent *in vivo* and *in vitro* development (commonly referred to as "Death Valley" of preclinical development) is notoriously slow. The slowness is primarily due to the intrinsic nature of the biological systems, e.g., in case of *M.tuberculosis* several weeks are required just to grow the bacterial culture in the selective medium, whereas in larger organisms the biological cycles can last years. Huge expense is another factor for *in vitro* and especially *in vivo* pre-clinical development, requiring major expensive infrastructure and specialized staff. The latter may also require regulatory approvals (ethical clearances and approvals for animal model research).

Partially due to recognizing of the clinical development and marketing approval bottlenecks, but mainly in an attempt to rein on the ever increasing healthcare costs, over the last 20 years several legal shortcuts have been introduced for the clinical and market approval stages, which are discussed below.

CHARACTERIZING MODERN BIOTECHNOLOGY INNOVATION

Research on innovation systems conclusively suggests the important role of new innovators for the healthy innovation systems (Block, Keller, 2008). New innovators are critical to innovation, economic growth and job growth (Acs, Audretsch, 1990; Audretsch, Keilbach, Lehmann, 2006; Stangler, Litan, 2009). In the field of biotechnology startups and academic teams contribute outsized part of innovations (Kneller, 2010).

New innovators (biotechnology startups, university research teams) are best characterized as business focused projects developing and attempting to bring to market unverified and pioneering technologies. Another essential characteristic is very limited development resources available. Biotechnology SMEs and startups are especially disadvantaged in this respect, since they need highly expensive infrastructure and reagents, also, relatively more human resources. Note that in many other fields of technology the development costs have gone down to account mostly just the human capital, technological development is facilitated by various accelerator instruments and programs, and normally within 12-18 months the market viability of the technology can be reasonably established at a cost of tens of thousands of Euros (Holzera, Ondrusb, 2011). This is not the case for biotechnology, where such rapid and inexpensive validation is plainly impossible.

The slow technological development cycle in biotechnology means that it is traditionally more reliant on IP protection. Software, computer and communications technologies are so fast to market, that patenting becomes essentially irrelevant. The time needed to obtain international patent protection based on the statutory terms alone is in excess of 2 years. In software, computer and communications technologies this is unacceptably long period. In many cases technology applied for in the patent application two or three years ago would be obsolete by the time the application is granted. Moreover fast changing technologies, such as software, are still stuck in the legal quagmires of subject matter patentability. As a result many software, computer and communications innovators file for patent protection only at a later stages of their evolution, when original technology is validated and outside capital (e.g., venture capital) is injected into the startup (Kravets, 2012). This also means that patenting is not a drag onto the development of the original technology, that is – it is not siphoning financial resources and time, which otherwise would be used for the development and validation of the technology. It is also noteworthy that venture capital available for software industries is larger than the capital available for biotechnology, e.g., in 2013 in the US the software industry claimed 27% of the venture funding, while the life sciences sector (biotech and medical devices combined) accounted for 23% percent of all venture capital dollars invested in 2013 (PWC, 2014).

Overall, the following stages of the development of biotechnological innovations may be identified:

- Discovery and *in silico* stage, where target and complementary molecule are identified (normally 2-6 months (not accounting the underlying basic research));
- Moderate in vitro stage, where initial validation of the target molecule is performed (normally 12-24 months);
- Slow in vivo stage, where secondary validation of the target molecule is performed (normally 24-36 months);
- Very slow clinical stage, where final validation of the target molecule is performed (5-7 years);
- Market approval (1-3 years).

Validation of the technology in development in biotechnology comes only in the clinical stage. The overwhelming majority of biotechnological innovations fail to even succeed in animal models (in vivo stage) and few proceed to clinical trials, where success is also rare. Thus, preclinical biotechnology projects are very high risk enterprises, which also have higher capital needs (especially compared to software projects). Due to these reasons the outside investment into biotech project normally comes after pre-clinical stage and at the beginning of the clinical stage. Moreover, in biotechnology patent portfolio is usually a prerequisite for outside investment (Dutfield, 2009).

FORMAL IP RIGHTS THROUGH VARIOUS STAGES OF BIOTECHNOLOGY INNOVATION

From the perspective of the inventive process, the above described biotechnology development model suggests that essential parts of the invention are known at the earliest stage, and subsequent stages are required in order

to obtain experimental data necessary in order to verify and substantiate the invention.

Increasingly, in the modern biotechnology projects the most valuable part of the technology (e.g., genetic sequence, protein structure) is known years before the experimental data, which enables patenting. At best the patent application may be filed at the end of the in vitro stage, as long as the experimental data is supportive.

This means at least two things: (1) confidentiality is paramount for biotech projects and needs to be sustained for long periods; and that (2) in biotechnology projects patenting process interferes into the development process at the early-middle of the way, and competes for the money/time, which would otherwise be used for further development. This contrasts with the software technology, where patenting process complements the validated development process and happens only after the necessary additional resources for patenting are obtained. Limited patenting resources in SMEs and university biotechnological projects usually means that price rather than quality are the determinants of the patenting – what is available, rather than what is the best, are drawn in the patenting process.

After the patent application is filled, further lengthy development and market approval await the technology. These further steps before the technology reaches market usually consume large part of the available useful patent protection period. Global competition in the marketplace and technological development mean global race to patent – an imperative that patent protection shall be sought at earliest possibility, what is not helpful for the quality of invention (and value of the patents) and is contradictory to the need to maximize the useful patent protection period.

Other IP rights such as copyright are not useful for biotechnology innovations. Publication of the research or other disclosure of the technology, which is normally needed in order to secure copyright protection, generally destroys patenting prospects for the disclosed subject matter, since novelty of the invention is lost.

Interestingly, copyright protection at the theoretical level can be applicable to the nucleotide sequences or amino acid sequences, since such sequences are essentially a text-like code, very similar to the software code (Smith, 1987). Such argument may be especially made with respect to artificially created biological sequences and other synthetic constructs, which do not exist in nature, e.g., fusion proteins, synthetic organisms (Rai, Boyle, 2007). The main disadvantage of the copyright approach is that it is rather weak protection, allowing for numerous exceptions and modifications, as well as not precluding independent creation of the same article, where the rights would co-exist simultaneously. Copyright approach is also prone to disputes on non-protectable elements (e.g., natural sequences) embedded in the useful sequence, similarly to what happened in the software copyright field with the advent of the objective programming and non-textual elements (e.g., graphical user interfaces).

Commercial secret protection is still the most accessible form of legal protection available for SMEs, startups and university teams, on which they rely during the initial stages of development. It needs to be balanced against the risks of competitive development, data leaks or accidental disclosures, as well as espionage risks. Adoption of commercial secret strategy also bars any publication of the research, which normally follows after the patent application, and is required as the part of the validation process for the new technology and its acceptance by the scientific community and marketplace.

Overall, it is evident that the existing IP regimes are not accommodative to the innovative biotechnology projects. The same problems of limited resource allocation and rush to patent are encountered even by university teams, albeit they may be not as vital as in the case of startups and SMEs.

Biotechnology innovators face the trio of innovation challenges – (i) global competition and race to patent; (ii) patenting competing with the development; and (iii) risks of losing IP protection due to competing development, espionage, accidental disclosure, premature patenting or lack of resources to maintain global patents. These challenges commonly predisposes the startup biotechnology patents to suboptimal quality and poorer enforceability, hence obscurity and lack of external licensing interest. It may deter new innovators from patenting or lead to early loss of the patent protection due to non-maintenance or unwillingness to engage in disputes (Frietsch, Neuhäusler, Rothengatter, 2013).

LEGAL AND POLICY RESPONSES TO BIOTECHNOLOGY INNOVATION CHALLENGES

The specifics of intellectual property in biotechnology are increasingly recognized by the government and the industry themselves. In addition to general patenting difficulties and costs, as it was explained biotechnology innovators rather uniquely suffer from extremely lengthy development, validation and market approval terms. Long terms before entering the market minimize the useful patent protection terms, thus, put biotechnological innovations at a disadvantage compared to other technological fields. They also contribute to the exorbitant costs of the innovative medicine.

Many examples of legal and policy responses addressing specific needs of biotechnology come from

the EU. To address the time deficit, in early 1990s the EU introduced a supplementary protection regime that extends the duration of the exclusive pharmaceutical marketing rights. Supplementary protection enters into force after expiry of a patent upon which it is based. It is available for human or veterinary medicaments and plant protection products (e.g., insecticides and herbicides). The justification of supplementary protection regime is to compensate the developer for the long time needed to obtain regulatory approval of these products (i.e., authorization to put these products on the market). The supplementary protection regime is set forth in the Council Regulation (EEC) No 1768/92 of 18 June 1992 (effective as of 2 January 1993). The original regulation is now supplanted by the recodified regulation No 469/2009. Supplementary protection for plant protection products was introduced by the Regulation (EC) No 1610/96 of 23 July 1996 (effective as of 8 February 1997).

The EU Directive 98/44/EC introduced further special rules for patent protection in the field of biotechnology, banning patenting of specific subject matter, but generally enabling patenting of isolated genetic constructs and other isolated biological material. Patentability standards on the latter have been somewhat rigorized by emphasizing the thorough evaluation of patentability (e.g., plain genetic construct without specific useful application can not be patented) and full disclosure requirements.

While the above steps have essentially expanded IP protection available for biotechnological innovation, further regulations followed up with restrictions by introducing broader exceptions and simplified regulatory approach for market authorization of generics and biosimilars.

Regulation No. 726/2004 *On the Community procedures for the marketing authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*, as well as Directive 2004/27/EC *On the Community code relating to medicinal products for human use* introduced exceptions for manufacturing, clinical trials on a bioequivalent of the patented product and application for marketing approval before the patent has expired. On top of the research exception the simplified marketing approval is allowed through abridged marketing authorization procedure. The generic/biosimilar research exception is not a separate exception but rather the liberal interpretation of the historical "experimental use" exception. In most EU countries (19 out of 27) this exception does not limit the permitted acts to marketing authorizations related to generic medicines using the abridged procedure, but extends to any medicines.

Yet another way for marketing approval shortcut is so called orphan drug designations, allowing accelerated approvals of medicines for niche indications. It is especially developing in the US (Cote, 2010).

Non specifically for biotechnology (that is for any patents in any field of technology) there have been attempts to reduce patenting costs. First measures have been introduced at a country and then regional level. Some countries (Italy) have experimented with full abolition of patenting fees. Reduction in costs (and simplification of procedures) has been one of the key arguments for introducing the European Unitary Patent system in the majority of the EU Member States. Similar attempts are being made in the CIS with the so called Eurasian patent system. Unfortunately, these attempts are relatively minor at the global scale and the decrease in patenting fees is not able to compensate for the increases due to escalating complexity or globalization. These attempts may also contribute to further increase in patent application volume, thus indirectly increasing the net costs of filing a patent application.

Another approach aimed at alleviating the general patent cost burden is the governmental policies providing financial support for national and international patenting. It is becoming widespread practice in many developing and even developed countries. Arguably, this approach is contributing to the problem that it tries to resolve by distorting the patenting incentives and not accounting for the quality of underlying inventions.

Many governments also introduced numerous simplifications and incentives for the patenting process at the national level, by enabling electronic filing, very simple provisional patent applications and simplifying the procedures on amending and supplementing patent applications.

Overall, the patent systems worldwide are being increasingly stretched to accommodate novel technologies and globalization, but for biotechnology the changes are especially significant, gradually converting the biotechnology patent regulations into *sui generis* biotechnology legal protection regime.

INDUSTRY OWN RESPONSES TO BIOTECHNOLOGY PATENTING CHALLENGES

The industry has also come up with its own solutions to address the short useful patent protection terms. Creative patenting strategies involving multiple incremental applications on similar or overlapping subject matter, applications on combinations of known substances, applications in different jurisdictions, careful filing and withdrawals of the provisional applications,

as well as lengthening of the intra-patent office process, all aimed to maximize the available patent protection terms, are employed. Such strategies are collectively known as evergreening practices and while profitable for multinationals, they present another challenge for new biotechnology innovation.

Examples of evergreening are most abundant in pharmaceutical industry. A recent and vivid example of evergreening are patents on etanercept (brand name - Enbrel), a biopharmaceutical for treating autoimmune diseases by regulating tumor necrosis factor (cachectin). Original patent application for etanercept (US 5,712,155) was granted in 1998. Original applications for etanercept were filed in 1989 and 1990, which already suggests a patent prosecution terms of more than 8 years. Although original patent on etanercept was set to expire in 2012, at the end of 2011 a new patent application covering etanercept was published and later granted patent by the USPTO (US 8,063,182), extending patent protection for another 16 years past its 2012 expiration date. This "new" patent draws on original patent applications also filed in 1989 and 1990, and re-filed for the US patent in 1995. The original applications were filed and then rejected, modified, resubmitted, opposed, and updated during the course of its prosecution. The end result is very significant gains in useful patent protection term. Both patents provide very similar protection with respect to the active compound but from a different angles - the original patent covers isolated DNA sequence that encodes a polypeptide (protein) having the specific amino acid sequence, while the new patents covers useful ways (known recombinant technologies) of synthesizing the polypeptide (protein) of the same sequence.

Evergreening is not generally illegal in most countries, but is essentially an expert manipulation of the patent system for the purpose of maximizing legal protection and monopoly in the market. Evergreening practices contribute to the growing criticisms of the current patent systems, since they are the source of patent thickets and legal uncertainties. Evergreening patents create a mottle legal landscape where they are protected in some countries, but refused protection in other countries.

Some countries are taking steps at restricting evergreening. In 2013 Indian courts (Novartis AG v. Union of India (UOI) and Ors.; Natco Pharma Ltd. v. UoI & Ors.; M/S Cancer Patients Aid Association v. UoI & Ors., Civil Appeal No. 2706-2716 of 2013) have refused patent protection for modification (mesylate salt) of blockbuster drug imatinib, which was originally patented in free base form in the early 1990s in both the US and Europe (US 5,521,184 and EP 0564409) as N-phenyl-2-pyrimidineamine and its derivatives. The owners of the patent argued that imatinib mesylate salt and the beta crystalline form of imatinib mesylate salt is more than a derivative in that it possess enhanced efficacy due to higher bioavailability relative to the base form. The patentability was refused on lack of evidence of improved therapeutic efficacy relative to known forms of that compound, that is – better efficacy on molecular basis was not substantiated. Properties that do not relate to therapeutic efficacy, such as better bioavailability or improved stability, were deemed irrelevant for the efficacy on molecular basis.

Separately, evergreening practices are criticized for causing significant increases in healthcare costs (Vernaz, et al., 2013) and in some cases leading to unjustified and even immoral profits – especially in the case of imatinib, which contributed to the said anti-evergreening stance by the Indian courts.

While criticism of the certain specific cases of evergreening are well justified, caution must be exerted with respect to making generalizations. The two analyzed examples – etanercept and imatinib – are two very different cases. Etanercept is a complex fusion protein, which currently can be synthesized only through most advanced recombinant biotechnology methods and at low yields, making it unattractive to the generic industry even in countries where it is unprotected. Imatinib, on the other hand, is a small molecule drug, which can be easily synthesized through organic synthesis for the very small fraction of the cost of the patented medicine. Therapeutic success of imatinib was mostly unexpected and accidental, hence the case of imatinib shall not be extended as an example of predominantly abusive patenting in the whole biotechnology industry.

For the purposes of this paper, two negative aspects of evergreening must be emphasized – (1) evergreening is rather exclusive to the few adept players in the patent system; (2) evergreening restricts follow-up innovation. Evergreening involves significant costs and requires special competences and hence is available only to the most resourceful and knowledgeable parties, definitely not to SMEs, startups, individuals or universities. Also, the nature of evergreening suggests that the patents are already secured and maintained for the whole validity period, which makes evergreening irrelevant for the early development stages.

The large biotech industry is also developing marketing approval shortcuts, such as off label prescribing, and adopting corporate strategies (e.g., targeted acquisitions, paying for market non-entry) in order to limit competition after the expiration of the patent rights.

LEGAL INNOVATIONS NEEDED TO HELP NEW INNOVATORS IN BIOTECHNOLOGY

Based on the overview of the field presented in this paper, intellectual property in biotechnology must be clearly recognized as already a field of multiple legal innovations and emerging *sui generis* legal regime.

Long and expensive biotechnology development process, despite recent technological advances, means that biotechnology innovators need some kind of legal protection early in the technological development process and before the technology is even validated. Due to the same reasons, and differently from software or communications technology innovators, biotechnology innovators cannot rely on continuous innovation or market leadership as the ways to protect their development. At the same time, all available traditional legal instruments of intellectual property are poorly adjusted for the needs of the biotechnology innovators.

Further complexity of the current situation lies in the fact that in the field of biotechnology SMEs, startups, individuals and academic development teams are unable to leverage the patent system (Sichelman, 2014), while the adept industry actors are able to manipulate the system for their own interest and pure profit considerations. In other words, the *status quo* is more advantageous to the incumbents and is discriminatory to new innovators. Moreover at the international level it gives preference to the players, who can rely on larger domestic markets (USA, UK, China) where national rights alone are more valuable.

Additionally, it is evident that existing legal protection regime for biotechnology increasingly relies on governmental interventions in both creating new regulations (subject matter, exceptions, etc.), and in government financial and other support for anyone who wants to enter biotechnology industry and secure IP protection internationally.

Unfortunately, the comprehensive picture accounting for needs of the society, industry incumbents and new innovators is not at the heart of most existing regulations and research on legal protection of biotechnological innovations. This paper does not have the ambition to present the proposal for the holistic biotechnology legal protection regime, it only attempts to delineate the issues at stake and especially to highlight the neglected interests of the new innovators – SMEs, startups, individuals and academic teams – which are essential for the healthy and sustainable innovation in biotechnology. As the global competition intensifies, the need to enable the new innovators to play on equal terms in the patent systems is ever more obvious.

The IP systems worldwide are already experimenting with new initiatives aimed to simplify and make them more accessible cost-wise. Interesting examples are expansion of utility models and innovation patents. Although local and compromised, they are specifically designed to be more startup friendly (less expensive). Some countries (Japan) are experimenting further by allowing conversions of utility models into full-fledged patents.

These legal experiments provide a basis for a discussion on the future special biotechnology intellectual property rights system, along with the existing general proposals on the improvement of the patent systems, such as the collective defense proposals (Patent Defense Union) for patent rights (Kingston, 2000; 47-71). Specifically for biotechnology at least the following policy/regulation directions shall be considered in order to answer the challenges in this field:

- Longer term provisional rights, exceeding the currently allowed 12 months (general priority term under the Paris convention);
- Regulation of evergreening – applying the doctrine of equivalents on the parallel or overlapping patent applications by the same parties and/or taking into account the economics of the existing patents;
- Further differentiation of the rules for different fields of biotechnology (e.g., genetic constructs and small molecules).

DISCUSSION

The biggest and growing general problem of international patenting is the prohibitive costs of obtaining worldwide protection and especially the costs of enforcing it. The economics of obtaining and maintaining IP rights is key determinant of its value.

The overview of the field presented in this paper suggests that biotechnology intellectual property is already a field of multiple legal innovations and emerging *sui generis* legal protection regime. Unfortunately, it currently contributes to the complexity of the field, and costs of patenting.

There is growing evidence that patent protection is less valuable to many fields of new technology, but biotechnology development remains strongly reliant on patenting and therefore endures general and specific patenting problems. In addition to unfavorable patenting economics, biotechnology patenting by the startups, SMEs and universities suffers from lack of expertise (poor quality applications), too-early patenting (before any revenue is secured, before validation of the technology),

depletion of the development resources needed to validate the technology itself, as well as short useful patent validity terms. New innovators in biotechnology face the multiple challenges of global competition, race to patent due to competing development, espionage, accidental disclosure, as well as patenting competing with the development. These challenges predisposes such biotechnology patents to suboptimal quality and poor enforceability, hence obscurity and lack of external licensing interest. It may deter new innovators from patenting or lead to early loss of the patent protection due to non-maintenance or unwillingness to engage in disputes.

Legislative responses to address the needs of biotechnology innovators do not address the challenges for new innovators, and hence may be contributing to the biotechnology patenting problems, rather than resolving them. The ways to address patenting limitations developed by the biotech industry themselves (especially evergreening) appear to be controversial to new innovators and even society at large. Thus, sustainability of biotech innovation develops dependency on governmental interventions in both special regulations (subject matter, exceptions, restrictions on evergreening), and in essential government financial support for patenting.

The overview of the intellectual property issues in biotechnology presented in this paper may be helpful to delineate the issues at stake and especially to highlight the neglected interests of the new innovators – startups, SMEs and to lesser extent academic development teams – which are essential for the healthy and sustainable innovation in biotechnology, as well as development of national biotech industries.

Several general and specific proposals for further advancement of the legal protection of biotechnology – such as, enforcement pooling, longer term provisional rights, regulations for evergreening and differentiation of the rules, are suggested for further research and discussion.

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Legal & Regulatory Update

Patenting Genomics Innovations: Post-*Myriad* Challenges and Possibilities

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ABSTRACT

Patenting gene and its nucleotide sequence has been a controversial subject since the release of working draft of the Human Genome Project. A number of US Supreme Court judgments pronounced in the recent past and accordingly revised patent examination strategies of the United States Patent and Trademark Office (USPTO) created a huge confusion in the field of biotechnology. The present article explores the volatile nature of judicial decision-making in modern biotechnology arena and attempts to analyze and gauge the practical impact of the landmark judgment of *Association for Molecular Pathology v. Myriad genetics Inc*. The present article also reveals how the *Myriad* judgment changed the USPTO's long-standing practice of granting patents on isolated DNA molecules and set a new patent-eligibility standard for genes and DNA related innovations. The present article also endeavors to investigate the challenges and possibilities of patenting isolated proteins, sequence homology and protein three-dimensional structure based innovations in post-*Myriad* US patent regime.

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INTRODUCTION

After the release of working draft of the Human Genome Project, the US Patent and Trademark Office (USPTO) received a number of letters from stakeholders including the then NHGRI[1] director Francis Collins arguing a revision of its acceptability norms for gene and DNA sequence related patent applications. In 2001, USPTO issued a guideline raising the bar on patent-eligibility standard for DNA related patent applications stating that identification of gene sequence alone is not patentable, but that discoveries directed to genes isolated from their natural environment might be patentable if they possessed "specific, substantial and credible utility".[2] USPTO specifically clarified in its revised guidelines that even if a gene was discovered from its natural source but "isolated" and "purified" from other molecules naturally associated with it would be patent-eligible as long as the requirements of title 35 of the US code were met. And in such cases questions whether the gene is an invention or discovery will not arise even if the isolated gene in question has a nucleotide sequence similar to its natural counterpart.[3] However, USPTO has always been of the opinion that purified state of synthetic gene is different from those of the naturally occurring compounds hence there is no objection in granting patents for such genes as 'composition of matter' or 'a matter of manufacture'.[4] Patent applications directed to isolated gene never faced unavoidable challenge at the USPTO; however, the scenario dramatically changed in 2013 when the US Supreme Court invalidated three disputed patents of Myriad Genetics Inc. related to BRCA gene. The *Myriad* judgment has not only set a new interpretation standard for §101, but also created

1 The National Human Genome Research Institute (NHGRI) is a division of the National Institute of Health (NIH) originally established as the National Center for Human Genome Research (NCHGR) in 1989 to carry out the International Human Genome Project (HGP).

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2 Federal Register, Pub. L. No. 4, 66 1092–99 (2001)
3 *Id.*
4 *See infra* 16.

an uncertain environment for future patent applications related to genes and DNA molecules. The present article investigates the adverse effect of *Myriad* judgment caused to gene or DNA based future patent applications and possibilities of patenting other genomics innovations in post-*Myriad* American patent regime.

LANDMARK COURT DECISIONS AND CHANGING PATENT-ELIGIBILITY JURISPRUDENCE IN MODERN BIOTECHNOLOGY ARENA

The US Supreme Court Judgement on Gene Patenting and Legal Uncertainity

In patent ecosystem, it is a well-observed phenomenon that even a brilliant discovery or a breakthrough innovation does not by itself is patent-eligible unless they meet the statutory requirements[5]. This fact becomes more prominent when the real world experience of genomic technology is brought to Courts in the form of actual cases. In 2013, a landmark judgment of the US Supreme Court completely changed the scenario of gene patenting in America. The US Supreme Court's ruling on *Association for Molecular Pathology* v. *Myriad genetics, Inc.* altered the USPTO's thirty years old practice of granting patents on isolated genes and DNA molecules[6]. In *Myriad* case, the observation of the US Supreme Court was completely different from the observation once had in *Parke-Davis & Co.* v. *H. K. Mulford Co.*, an age-old landmark case on adrenaline patent dispute. It was then noted by the Supreme Court that compounds "'isolated' from nature are patentable even if it were merely an extracted product without change; there is no rule that such products are not patentable." Surprisingly, the US Supreme Court completely undermined the long history of natural product patenting and relied heavily on the *Mayo v Prometheus*, a process-patent litigation, to decide *Myriad's* disputed patents directed to genomic DNA. The controversial patent dispute between Mayo Collaborative Services and Prometheus Laboratories was related to diagnostic test and method of determining appropriate dose of thiopurine metabolite for the treatment of patients suffering from autoimmune diseases. The US Supreme court held in that patent dispute that giving drugs to patient, measuring metabolites for that drug etc. as claimed in US patent No. 6,355,623 and 6,680,302, were not allowable as they were close to *natural law* exception of the US patent statute. Though the *Prometheus* patent dispute was not entirely relevant for *Myriad*'s human gene patenting issue, however, it influenced the US Supreme Court to a large extend which led to rejection of nine claims directed to genomic DNA of three disputed patents.[7] The Court clarified its position stating that "a naturally occurring DNA segment is a 'product of nature' and not patent eligible merely because it has been isolated". The Supreme Court's decision in *Myriad* is not only an unexpected departure from a long-standing affirmation of isolated DNA patenting but also raises obvious questions regarding the volatile nature of judicial decision-making in the modern biotechnology arena.

In *Myriad* litigation, the US Supreme court set a new paten-eligibility standard applicable for all future patent applications related to gene or DNA sequence. The "new and useful…composition of matter"–requirements as set forth in §101 or claiming naturally occurring phenomena (*natural law*[8] *exception*) will be judged based on the primary enquiry–whether the claimed invention is meant for creating "incentives that lead to creation, invention, and discovery or impeding the flow of information that might permit, indeed spur, invention".[9] In this regard, the US Supreme Court observed that a delicate balance is required to be maintained in order to arrive at a rational conclusion. The Court further clarifies that the synthetic DNA fragments e.g. exons-only DNA fragment or cDNA is patent-eligible like before[10], even if the nucleic acid sequence of the synthetic DNA molecule is similar

5 Funk Brothers Seed Co. v. Kalo Inoculant Co., 333 U.S. 127.

6 The Federal Circuit pointed out in *Myriad* Case that the USPTO has issued patents directed to DNA for almost thirty years. The FC also pointed out that 2,645 patents claiming "isolated DNA" has already been issued by the USPTO.

7 Claims 1,2,5,6 and 7 of US patent No. US 5,747,282; Claim 1 of US patent No. US 5,693,473 directed to BRCA-1 gene and Claims 1, 6 and 7 of US patent No. US 5,837,492 directed to BRCA-2 gene.

8 As described in MPEP §2106, in addition to the terms laws of nature, physical phenomena, and abstract ideas, judicial exceptions have been described using various other terms, including natural phenomena, products of nature, natural products, naturally occurring things, scientific principles, system that depends on human intelligence alone, disembodied concept, mental process and disembodied mathematical algorithms and formulas, for example. The exceptions reflect the judicial view that these fundamental tools of scientific and technological work are not patentable.

9 *12-398 Association for molecular pathology v. Myriad genetics, Inc. (06/13/2013), (us 2013).*

10 *Id.*

to that of the naturally occurring gene codes for the same protein.

Challenges and Possibilities in Genomics Innovations

Though the magnitude of *Myriad* judgment is huge; however, it is not a blanket prohibition for patenting all DNA/gene sequence of human origin or any other origin, but for those DNA/genes that are *merely* "isolated" from natural environment and do not show *markedly different* characteristics (as established in *Diamond v. Chakrabarty* case) in terms of modification in the nucleic acid chain.

Immediately after the *Myriad* judgment, USPTO again changed its examination strategy towards gene-related innovations. According to a memorandum[11] issued by the USPTO on 13th June 2013, patent examiners were instructed to reject all product claims directed to naturally occurring DNA molecule whether it was isolated or not.

Nucleotide sequence-based innovations

DNA sequence information represented by A, T, G, and C alone is not a patent eligible subject matter under the US patents law as it is nothing more than a typical nucleic acid sequence information.[12] However, according to *Myriad* interpretation standard of §101, *markedly different* DNA fragment or gene described by nucleic acid sequence in the form of A, T, G and C is patent-eligible provided they meet the utility requirements as set forth in the current US patent statute.

Similarly, ESTs[13] are also patent-eligible under the current US patents law if they meet the criteria of utility, novelty and non-obviousness. Moreover, the *Myriad* judgment further strengthened the patent-eligibility of EST as the Supreme Court has completely acknowledged patent eligibility of cDNA.[14]

A reasonably favorable environment is also expected for nucleotide homology-based innovations. There is no specific rule in the United States for DNA sequence homology based patent applications and therefore it is most likely that USPTO will continue to assess such patent applications based on their own technical merit. According to general practice, the USPTO accepts homologous DNA sequences (both nature and the degree of homology) of genes or fragments thereof as a patent-eligible subject matter as long as they satisfy other criteria, e.g. sufficiency of disclosure, credible utility etc. The USPTO has a coherent approach for sequence homology related broad claims. Claims reciting whole nucleotide genus is also allowable in a single patent application on the condition that the representative nucleotide species are adequately described in the specification. Though protection of whole nucleotide genus sometimes leads to cross-species patent coverage because of the fact that some homology/percent identity claims encompasses a large number of macromolecule variants which may belong to entirely different species[15] or orthologs; however, USPTO does not raise any unavoidable objection in accepting them. Additionally, DNA homologs are not considered to be non-patentable *merely* because of the reason that the function and utility of the claimed DNA homologs have asserted through bioinformatics method analyzing sequence homology with prior-art nucleic acid sequence found in public databases.[16]

Amino acid sequence-based innovations

USPTO has a non-stringent practice regarding the acceptability of protein homology-based claims. Amino acid sequence disclosed for a single species is considered to be a *representative of the genus* because all member amino acid sequence have at least certain degree of percent identity with the parent genus and therefore obtaining patents on this subject matter does not involve major challenges as long as the description of representative amino acids fulfills enablement requirements stipulated in §112 of U.S.C. 35.

According to recent USPTO guideline[17] issued on March, 2014, claims directed to proteins are close to judicial exceptions i.e. natural phenomena or natural prod-

11 MEMORANDUM from Deputy Commissioner for Patents Examination Policy to Patent Examining Corps, Supreme Court Decision in Association for Molecular Pathology v. Myriad Genetics, Inc. (USPTO Jun. 13, 2013).

12 S*upra note* 2

13 Expressed Sequence Tags (ESTs) are small chain of nucleic acids, generally 200-800 base pair (bp) in length, generated from randomly selected cDNA clones. ESTs are extremely useful for purpose of gene identification and verification of gene prediction. —- *John Parkinson (ed.). Expressed sequence Tags (ESTs): Generation and analysis, vol.533, Humana Press 2009.*

14 *Supra note 9.*

15 Letter from Eli Lilly and Co. to USPTO, COMMENTS OF ELI LILLY AND COMPANY ON THE REVISED INTERIM WRITTEN DESCRIPTION GUIDELINES 132 (USPTO).

16 *supra* note 2, at 1096

17 MEMORANDUM from Deputy Commissioner for Patents Examination Policy to Patent Examining Corps., 2014 Procedure For Subject Matter Eligibility Analysis Of Claims Reciting Or Involving Laws Of Nature/Natural

uct. Therefore, proteins are not patent-eligible under §101 unless they are *significantly different*[18] from the judicial exception regardless of the use of phrases, like "isolated", "recombinant", or "synthetic" etc. in claims reciting a protein. Similar to DNA sequence, amino acid sequence of a protein or peptide alone is not patent-eligible unless it is *markedly different* (in terms of addition, deletion or substitution of amino acid(s)) from the naturally occurring protein molecule[19].

In advent of major breakthroughs in biotechniques, functional genomics products, e.g. therapeutic proteins produced by recombinant DNA (rDNA) technology have been successfully used worldwide including in the USA to treat a wide range of diseases for which there was no cure using pharmaceutical drugs.[20] Proteins/peptides are considered to be potential drug candidate for various practical reasons which include target specificity, non-interference with other biological processes of the human body etc. Because of these useful characteristics, researcher's principle objective always focused on producing synthetic protein/peptide molecules that are structurally (both in terms of amino acid sequence information and three-dimensional conformation) similar to those found in human body[21] for example, Humulin®.[22] Although, these man-made variants of structurally resembling molecules are often confused with the molecules found in nature and contested during prosecution; however, patenting these therapeutic macromolecules should not face any additional challenge in post-*Myriad* US patent regime because of the fact that the Court's observations on isolated genomic DNA will certainly have some limits and will not necessarily be applicable for isolated proteins or peptides and encoding amino acid sequence thereof. Any adverse impact to isolated protein patenting can also be ruled out in view of the *Prometheus* judgment. In *Mayo Collaborative Services v. Prometheus Labs, Inc.*, the Court stated that "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract idea," and "too broad an interpretation of this exclusion principle could eviscerate patent law".[23] In addition to that, in *Myriad*, the Court had no observation regarding patent-eligibility of isolated proteins and USPTO has no specific guidelines in this regard either. Hence, it can be said that isolated proteins/peptides of natural origin or their recombinant variants are still patent-eligible under §101 of the US patent law.

Structural Genomics Innovations

Besides patenting isolated therapeutic proteins and amino acid sequence based innovations, it is also evident that trend of protecting structural genomics innovations has been increased significantly around the world. Three-dimensional structural information of protein is always proved to be crucial; naturally, protection of this spatial information has great value for biotechnology industry. According to a report on the comparative study[24] conducted by trilateral patent offices, inventions that claim protein three-dimensional structural coordinates fall under the category of "information contents" which is further interpreted as nothing more than "mere presentation of information or abstract ideas". Therefore, innovations related to this technological field are not patent-eligible under §101.

However, protein three-dimensional structures represented by spatial arrangements of atoms or structural coordinate data are considered to have technical effect as long as they are used in an *in silico* or bioinformatics screening method to generate chemical compounds. In 1999, USPTO granted a patent in this area for the first time for an invention directed to the use of structural coordinates of interleukin-1β converting enzyme (ICE) and mutants thereof to screen and design potential drug candidate. Since then a number of patents have been granted by the USPTO, e.g. patent No. US6,490,588 and US6,329,184 to name a few for inventions directed to protein three-dimensional structure and their use in structure-based drug design (SBDD).

The patent-eligibility standard has certainly been raised for gene-related innovations in light of a number of

Principles, Natural Phenomena, And/Or Natural Products (USPTO Mar. 4, 2014).

18 *Id.*

19 USPTO, *supra* note 17.

20 Tom Strachan and Andrew Read, Human Molecular Genetics (New York : Garland Science/Taylor & Francis Group, c2011., 4th ed. 2011).

21 *Id.*

22 Humulin® is a polypeptide hormone manufactured by Eli Lilly & Co. from a non-disease-causing laboratory strain of *Escherichia coli* bacteria, is the world's first recombinant DNA drug approved by the FDA. Structurally, this rDNA originated insulin is indistinguishable from pancreatic human insulin designed to save millions of lives around the world suffering from diabetes.

23 10-1150 Mayo collaborative services v. Prometheus laboratories, Inc. (03/20/2012), (US 2012).

24 Trilateral Co-operation between EPO, JPO and USPTO was set up in 1983 with the objectives including improvement of the quality of patent examination process, improving quality of incoming applications, solving common problems related to IPR protection, harmonization in practice between three patent offices etc. — *Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims (2002).*

Supreme Court judgments[25] and revised USPTO guidelines; however, there has been no sign of increase in the number of rejection of patent applications from 2012 until now. Patent prosecution history of post *Myriad* era suggests that, USPTO has been issued patents for genomics innovations after a thorough patent-eligibility assessment under § 101; naturally, that process led to a substantial increase in the issuance of office action until grant.

CONCLUSION

It was initially estimated that the material consequence of the Supreme Court judgment in *Myriad* patent litigation would be far-reaching. However, it seems that the practical impact of this judgment to gene related future patent applications will not be severe as anticipated. The trend of filing patent applications at the USPTO and issued patents in the area of gene or DNA related innovation is still maintaining its usual momentum. Most importantly, no significant irregularity in this regard has been noticed in post-*Myriad* patent regime.

However, in light of revised patent practice of the USPTO chances of obtaining patents is certainly higher for those genomics innovations that are more restricted to non-naturally-occurring nucleotides, such as cDNA or nucleotides of man-made variants. On the other hand, isolated proteins and its recombinant variants including their encoding amino acid sequences should not face any additional challenge at the USPTO as the breadth of *Myriad* judgment is limited to isolated genomic DNA or genes of human origin. Inventions directed to sequence homology or percent identity is likely to be assessed based on their individual technical merits and scope of the invention, like before. Whereas, other genomics innovations, e.g. innovations directed to protein 3D structures and their applications in drug discovery (SBDD) are less susceptible to any direct impact of *Myriad* judgment. Though spatial information of protein itself is far beyond any patent protection; however, protection for the use of such structural information in the production of useful products will continue to be allowable under the useful and credible utility doctrines until any specific guidelines in this regard is issued by the USPTO in contrary to present examination practice.

Finally, it can be said that the Supreme Court decisions and USPTO guidelines issued in various occasions since 2012 certainly elevated the standard of subject matter eligibility of biotechnology innovations. However, the overall patent granting scenario in biotechnology domain has not been changed significantly in post-*Myriad* era except the fact that there has been an increase in the number of office action till the grant of each biotechnology patent application.

25 Supreme Court's ruling on diagnostic method claims (Mayo Collaborative Services v. Prometheus Laboratories, Inc., 566 U.S. ___, 132 S.Ct. 1289 (2012); Supreme Court's rejection of patents directed to isolated genomic DNA segments (Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. ___, 133 S.Ct. 2107 (2013)) and Supreme Court's observation on abstract idea in Alice Corp. v. CLS Bank Int'l, 134 S.Ct. 2347 (2014).

Legal & Regulatory Update

Successful Strategies for Diagnostic Method Patents

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ABSTRACT

This article addresses strategies used to obtain patent protection for diagnostic method patents after the 2012 Mayo decision by the U.S. Supreme Court.

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The U.S. Supreme Court *Mayo* decision in 2012[1] greatly curtailed the ability to obtain broad patent protection in the United States for processes in the field of medical diagnostics and prognostics. See, for example, "US personalized-medicine industry takes hit from Supreme Court"[2] and "Diagnostic patents at risk after Federal Circuit decisions."[3] There are several requirements for obtaining patent protection for an invention in the United States, including novelty,[4] nonobviousness[5] and clarity[6] of the patent application claims. In addition, a patent application must convey that the inventor is in possession of the invention, enable one of ordinary skill in the field to practice the invention, and set forth the best mode of the invention (if known).[6] The statute that specifies the kinds of invention that are patent-eligible is 35 U.S.C. §101, which, as approved by Congress in 1952, states: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." This in turn rests upon Article 1 of the U.S. Constitution, which gave Congress the right "To promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." Nevertheless, 35 U.S.C. §101 has been interpreted by federal courts, and in turn by the Patent Office, in a manner that restricts the ability of inventors to obtain patent protection for new and useful medical diagnostic and prognostic processes.

Historically, judge-made law has long prohibited patents directed to a law of nature, a natural phenomenon, or an abstract idea. For example, one cannot patent gravity or electromagnetism. But, as stated in 1981 by the U.S. Supreme Court: "an application of a law of nature … to a known structure or process may well be deserving of patent protection."[7] In 2012, in a case commonly referred to in shorthand as *Mayo*,[1] a unanimous Supreme Court indicated that something more is required to transform a newly discovered practical application of a law

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of nature into a valid method claim, without providing much guidance as to what that something more has to be. Since the *Mayo* decision,[1] the U.S. Patent Office and lower federal courts have struggled to provide guidance and clarity as to what constitutes an allowable something more. The difficulties of this challenge were reinforced by the U.S. Supreme Court's 2016 decision refusing to hear an appeal on a prenatal diagnostic method patent (U.S. Patent No. US 6,258,540 B1[8]) declared invalid by a lower court. The science behind this diagnostic process was acknowledged by a federal judge as a "groundbreaking" invention. Nevertheless, under the wide-ranging language of the Supreme Court's 2012 *Mayo* decision,[1] the patent was found invalid by the United States Court of Appeals for the Federal Circuit,[9] and the U.S. Supreme Court declined to consider it further.

In May 2016, the U.S. Patent Office issued "Subject Matter Eligibility Examples: Life Sciences"[10] (to supplement previous guidelines which were largely silent on life science methods) taking into account the 2012 *Mayo* decision[1] (and other relevant judicial decisions). The examples included hypothetical processes or methods that could be considered as still patent-eligible. Notably, a straightforward "old style" diagnostic claim - for diagnosing a hypothetical autoimmune disease called "julitis" based on obtaining a plasma sample from a subject and detecting the hypothetical marker JUL-1 in the sample using an anti-JUL-1 antibody, and diagnosing the subject based on the result, *i.e.*, a new and useful process, was deemed not eligible for a patent. Additional analysis and comments on subject matter patent eligibility can be found in online Alerts.[11,12]

In view of these restrictions, we thought that it would be instructive to review strategies that were successful in obtaining patent protection in 2016 for medical diagnostic and prognostic claims.

ANALYSIS

We reviewed 100 U.S. Patents[13] issued in 2016 that included claims directed to diagnostic or prognostic methods and, for comparison, the "old style" claims of 5 patents that issued in 2011 before the *Mayo* decision.[1] For the purposes of analysis, the 2016 issued claims were assigned into one or more of the following eight categories:

OS - *O*ld *S*tyle broad
e.g. A method of diagnosing disease X comprising detecting marker Y in a sample from a subject, wherein the presence of marker Y is indicative of the presence of disease X.

OSN - *O*ld *S*tyle *N*arrow
e.g. A method of diagnosing disease X comprising detecting marker Y in a sample by contacting the sample with an antibody, wherein the presence of marker Y is indicative of the presence of disease X.

MS - *M*ulti-*S*tep
e.g. Claims with at least 5 separate method steps.

SA - *S*pecific *A*gent
e.g. A method of diagnosing disease X comprising detecting marker Y in a sample by contacting the sample with a labelled probe having the nucleotide sequence set forth in SEQ ID NO:1, wherein the presence of marker Y is indicative of the presence of disease X.

SAP - *S*pecific *Ap*paratus
e.g. A method of diagnosing disease X comprising detecting marker Y in a sample by contacting the sample with a labelled probe and measuring binding thereof using dynamic secondary ion mass spectrometry, wherein the presence of marker Y is indicative of the presence of disease X.

DT - *D*iagnose and *T*reat
e.g. A method comprising diagnosing disease X comprising detecting marker Y in a sample from a subject, wherein the presence of marker Y is indicative of the presence of disease X, and treating the diagnosed subject by administering drug B to the subject.

DC - *D*ependent *C*laim
e.g. A method for diagnosing disease X comprising obtaining a sample from a subject and detecting the presence of marker Y in the subject by the method of Claim 1, wherein the presence of marker Y is indicative of the presence of disease X. Claim 1 in this example is directed to an independent patentable method of detecting the presence of marker Y in a sample from a subject.

SA+SAP - Combination of *S*pecific *A*gent and *S*pecific *A*pparatus.

RESULTS

Patents Issued in 2011

The first five 2011 patents reviewed all had broad diagnostic claims issue (OS), where detection of the relevant

Table 1: Categories of diagnostic method claims in 2016 issued patents*

Old Style	Old Style Narrow	Multi-Step	Specific Agent	Specific Agent + Apparatus	Apparatus	Dependent Claim	Diagnose & Treat
1	18	31	56	15	1	16	20

**Numbers total > the 100 patents reviewed since the claims of some patents fell into more than one category*

Table 2: Occurrences of Multiple Categories in diagnostic method claims issued in 2016 issued patents

Old Style Narrow + Multi Step	Multi-Step + Specific Agent	Dep. Claim + Specific Agent	Multi-Step + Specific Apparatus	Multi-Step + Diagnose Treat	Specific Agent + Diagnose Treat
3	9	11	6	5	4

marker in the sample was not limited by a detection method or by the use of a specific agent or apparatus. These claims would previously have offered strong protection to the inventors since they are difficult to "design around."

Patents Issued in 2016

Of the one hundred 2016 patents analyzed, only one patent fell into the Old Style (OS) category (see Table 1). A review of the particular file history for this patent revealed that no 35 U.S.C. §101 rejection had ever been made during the Patent Office examination of the application. Notably, the examining Art Unit was not in Technology Center 1600 ("Biotechnology and Organic Chemistry"), as were the bulk of the remainder of the patents, but rather was Art Unit 2872 ("Optical: Systems and Elements").

Of the remaining 99 patents, most claims (56 patents) were issued listing a specific agent (*e.g.,* a probe with a recited sequence or a specified antibody). The second most common aspect of the issued claims was multiple steps, which we defined as at least 5 or more method steps (31 patents). The third most common successful approach was a two-part claim of diagnosing then treating the diagnosed subject (20 patents). Claims reciting using an agent to detect a disease marker, but where the agent was not narrowly specified (*e.g.*, "a labelled probe" rather than the narrower "a labelled probe having SEQ ID NO:1"), accounted for 18 of the reviewed 2016 patents. Claims requiring a specific apparatus, or a specific agent and apparatus combination, were found in 16 of the patents.

Some patents had claims that fell into more than one of the eight categories listed above (see Table 2). Of these, most combined the specific agent (SA) attribute with another attribute (24 patents). The second most common combination was the multi-step (MS) attribute with another attribute (23 patents). The diagnose and treat (DT) attribute was found in combination with another attribute in 9 patents.

DISCUSSION

Reciting a specific agent (SA) and/or multiple steps (MS) were the most successful strategies for obtaining allowance of diagnostic method claims in the one hundred 2016 issued patents that we reviewed. However, such claims are potentially limiting in that competitors can make trivial changes to "design around" the patent protected method without much effort. Similar concerns apply to the claims reciting specific apparatus (SAP).

Twenty of the 2016 issued patents have claims to a method of diagnosing and treating a subject (DT), a claim type that the USPTO suggests can be patentable in its Subject Matter Eligibility Life Science: Examples.[10] However, one potential problem with this type of claim is that it may give rise to a so-called "divided infringement" claim — *i.e.*, different steps being performed by different entities where, for example, the "wet" steps of the diagnostic procedures are performed by testing laboratories rather than by the physician or hospital that administers treatment. Like patent-eligibility law, the law on divided infringement has also been evolving over recent years. The current standard for showing "divided infringement" requires a showing that performance of all of the steps of the claimed method are attributable to a single entity.[14]

In 16 of the 2016 issued patents, the diagnostic claim was allowed as a dependent claim of an independent process claim (DC). One might speculate that part of such a strategy is to reduce attention to the trigger word "diagnosis" by avoiding it in the independent claim on which the Examiner would be most focused. However, the potential enforceability of such dependent claims must be considered. Can such a claim, even if it was allowed

by the U.S. Patent Office, survive a subject matter ineligibility challenge in the federal courts? In addition, there is the question of whether such a dependent claim properly limits the independent claim. If not, it may be found invalid in court.[15]

CONCLUSIONS

While it is currently difficult to obtain broad claims in the U.S. for diagnostic and prognostic methods, one strategy for protecting diagnostic methods intellectual property could be to cover an invention with one or more narrower claims that are tied to the successful strategies discussed above.

However, it is also worth noting that strategies that were successful in obtaining patent protection in 2016 may no longer be successful at the Patent Office or may not prevail if a patent is challenged in federal court or at the Patent Office Patent Trial and Appeal Board (PTAB) in a post-grant review. As an example of how the Patent Office is continuing to modify its interpretations of its own guidelines, the authors have seen a situation in which an application allowed in 2016 was pulled from issue by the Patent Office in 2017 after the issue fee had been paid, further to an additional review of the allowed diagnostic claims by an internal review panel at the Patent Office. Thus, there is yet to exist a "bright line" for delineating subject matter that is patent eligible under 35 U.S.C. §101. This uncertainty of what is and what is not patent eligible is likely to continue until or unless the U.S. Congress steps in to address the lack of clarity imposed by judge-made exceptions to 35 U.S.C. §101. In January 2017, the Board of Directors of the Intellectual Property Owners Association adopted a resolution supporting legislative amendments to 35 U.S.C. §101.[16] Thus, one strategy for U.S. patent applicants who are negatively affected by current interpretations of judicial exceptions to 35 U.S.C. §101 would be to keep an application pending at the U.S. Patent Office in the event that Congress does make clarifying amendments to 35 U.S.C. §101.

It is also worth noting that in contrast to the situation in the U.S., the European Patent Office (EPO) has not excluded diagnostic or prognostic methods from patentability.[17] While the EPO does have some limitations on such methods (for example, the method cannot be performed on a human being *per se*, but can be performed on a sample previously obtained from a human), broad diagnostic and prognostic claims are still patentable. This disjoint with the U.S. situation represents a setback in the road to global patent harmonization. A global strategy to optimize patent coverage for diagnostic and prognostic inventions should include a variety of narrow scope claims for the U.S. and additional broad scope claims for those foreign countries where wider protection is available.

NOTICE

The views expressed herein are those of the authors and do not necessarily represent those of Amster, Rothstein & Ebenstein, LLP, or its clients. Nothing in this article is to be construed as legal advice or as a substitute for legal advice.

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