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Synthetic Biology and Intellectual Property Rights

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1. Introduction

The pioneering work of Cohen and Boyer in recombinant DNA (deoxyribonucleic acid) technology [1] gave birth to genetic engineering and the biotechnology industry. The related Cohen-Boyer patents [2-4] that protected the technology played a stellar role in the rapid rise of the biotechnology industry [5, 6]. The next landmark was the creation of a bacterial cell controlled by a chemically synthesized genome by Craig Venter and his group in 2010 [7]. More recently, Floyd Romesberg and colleagues in 2014 [8] reported the creation of a semi-synthetic organism with an expanded genetic alphabet that has raised both hope and fear [9]. The new letters in the alphabet are artificially created nucleotides not found in Nature. Along with these breakthroughs, the great promise of CRISPR (clustered regularly interspaced short palindromic repeats), and in particular CRISPR-Cas9 gene editing technology pioneered by Feng Zhang in 2012 [10] as a new way of making precise, targeted changes to the genome of a cell or an organism (see Section 2.3) has set the stage for major advances in synthetic biology, which aims to design and construct new biological parts, novel artificial biological pathways, organisms or devices and systems including the re-design of existing natural biological systems for useful purposes.

Researchers are now focussing on developing tools and methods that would enable them to encode, in artificially created or natural DNA, basic genetic functions in novel combinations by design. The aim is to artificially create biological systems of increasing size, complexity, and tailored functionality. Currently synthesis capabilities far exceed design capabilities in the sense that we know how to build but not yet with clarity what to build [11]. Synthesis capabilities are developing at a pace where DNA synthesis can be automated and the desired DNA produced once the sequence is provided to vendors. This integration of biology and traditional engineering is occurring so rapidly, it appears likely that a couple of decades hence researchers may begin producing synthetic organisms that can produce not only pharmaceutical products but also industrial

products such as bio-fuels on a commercial scale. Possible socio-economic benefits from synthetic biology research is thus enormous, but then so is the possibility of the technology's misuse. The concerns range from bioethical and environmental worries to bio-terrorism, say, by malicious release of genetically engineered viruses targeted at specific ethnic groups. The main concern here is the illegal creation and growth of bio-weapons.

The socio-economic promise of synthetic biology has spurred both public and private investments and made people introspect about its consequences and impact on human society. All players involved in creating and commercialising this knowledge-and-capital intensive emerging technology are obviously deeply interested in knowing how they would gain or lose from the intellectual property (IP) system in place and whether that system needs to be changed, replaced, or abolished from their respective perspective.

DNA as an information carrier gained currency in the 1950s with the discovery of the double-helix structure of cellular DNA by James Watson and Francis Crick in 1953 [12]. Prior to that biologists talked of biological "specificity". In 1953, Watson and Crick noted: "...it therefore seems likely that the precise sequence of the bases is the *code* which carries the genetical *information*..." (Emphasis added) [13]. Now the language of information is pervasive in molecular biology—genes are linear sequences of bases (like letters of an alphabet) that carry information (like words) for the production of proteins (like sentences). The process of going from DNA sequences to proteins we use words like "transcription" and "translation", and we talk of passing genetic "information" from one generation to another. It is rather uncanny that molecular biology can be understood by ignoring chemistry and treating the DNA as a computer program (with enough input data included) in stored memory residing in a computer (the cellular machinery). It is this aspect that bioinformatics exploits. It is analogous to viewing Euclidean geometry not in terms of drawings but in terms of algebra. In our current understanding, DNA is an informational polymer. It is a vast chemical information database that *inter alia* carries the complete set of instructions for making all the proteins a cell will ever need. As Albert Lehninger lyrically put it, understanding the DNA is the study of "the molecular logic of the living state." [14].

The intellectual property (IP) system, as it stands, did not anticipate the convergence of the patenting of information carrying living matter, a knowledge-based global economic system, and the ascendancy of a research-centric and innovative biotechnology industry. Therefore, the IP system is already under great strain because biotechnology related IP has been patched onto an existing patent system in an *ad hoc* manner. For example, in the complex legal maze, intellectual property rights (IPR) related to DNA synthesis, which is at the core of synthetic biology, may be inadvertently infringed by DNA synthesis companies in terms of enforceable trade secret, trademark, copyright or patent laws, simply by constructing DNA sequences for their clients [15].

That the DNA is an information encoded molecule, makes the interpretation of IP laws that much more difficult by judges who are generally ignorant about the deep science that supports biotechnology. Indeed organisms are defined by the information encoded in their genomes, and since the origin of life that information is believed to have been encoded using a two-base-

pair genetic alphabet (A–T and G–C). Recent research has expanded the alphabet to include several man-made unnatural base pairs (UBPs) which can be efficiently PCR-amplified and transcribed in vitro and whose unique mechanism of replication has been characterized. Clearly, the expansion of an organism's genetic alphabet leads us into unknown scientific territory related to DNA replication, gene expression, unknown proteins, DNA repair, etc. [8]. While the core principles of synthetic biology are common to those of well-practised recombinant DNA techniques, the biggest differences lie in the size, scope, accuracy, and speed of genetic changes that can now be accomplished [16]. Note that genetic modification incorporates DNA from one species into another; genome editing introduces new mutations into an organism's own DNA (similar to what Nature does or we do through selective breeding but on an accelerated time scale).

The critical IP issue in synthetic biology is determining, in an equitable manner, the nature of the IP rights to be allocated, to whom they should be allocated and the context in which they should be allocated for the overall socio-economic benefit of society. This chapter therefore briefly introduces synthetic biology and its relevance to human society, the intellectual property it may generate, equitable modes of protecting the generated intellectual property, and suggests changes to patent laws keeping in mind the changing socio-economic circumstances in which it must operate.

This chapter is written for young researchers and students in synthetic biology for whom a basic understanding of IPR issues related to their subject has assumed great importance.

2. Synthetic biology — Its aims and relevance

Synthetic biology is a revolutionary development in life sciences. It is highly multidisciplinary where molecular biology, physical sciences and engineering merge to design and construct new biological parts, novel artificial biological pathways, organisms or devices and systems including the re-design of existing natural biological systems for useful purposes. We may call it bioengineering. It has already produced tumour-seeking microbes for cancer treatment, photosynthetic systems to produce energy, artificial life, etc. Like engineering, it too aims to produce standardized components and connectors, manufacturing and assembly processes, test vehicles and certification processes, etc. to enable production and marketing of increasingly sophisticated and functional systems on a mass scale. In a sense, "Synthetic biology is the engineering of biology: the synthesis of complex, biologically based (or inspired) systems which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures – from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of 'biological systems' in a rational and systematic way." [17].

Enormous expectations rest on future advancements in systems biology as it has the potential to radically change the way we approach key technologies, such as medicine and manufacturing. Current efforts have focused on creating highly generic capabilities (the building

blocks) in the form of bio-tools and bio-processes that can be scaled for industrial application. Given the high intellectual calibre of the synthetic biology research community, it appears inevitable that the scientific knowledge they produce and place in the public domain will quickly be translated into industrial applications of high economic value by equally talented industry researchers. This raises obvious concerns about the ownership and control of generated intellectual property that may lead to high commercial value in a twenty-first century economy that truly belongs to the life sciences. The key enabling technology is DNA synthesis. The workspace includes microbes, mammalian cells, plants, etc. Its applications include therapeutics, energy (e.g., fuels), chemicals, agriculture, etc.

The pioneering paper of Watson and Crick [12] that elucidated the double helix structure of cellular DNA has been hailed as the greatest discovery in biology since Darwin's theory of evolution. In their paper, they showed that the structure was made possible by the unique base pairing of nucleotides guanine (G) with thymine (T), and adenine (A) with cytosine (C), each member of a pair belonging to opposing strands. It is this pairing that allows base pairs to be arbitrarily stacked as a double helix. In a famous understatement, they wrote: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." It was the potential for explaining biological function of DNA that led to the widespread acceptance of the double helix model rather than any compelling structural evidence. The helical structure was not rigorously determined by X-ray crystallography until the late 1970s [18]. Whereas cells were regarded as the basic building blocks of living organisms during the nineteenth century, the Watson and Crick paper [12] shifted attention from cells to DNA molecules in the middle of the twentieth century, when geneticists began to seriously explore the molecular structure of genes.

In his 2013, State of the Union message, President Barack Obama said:

If we want to make the best products, we also have to invest in the best ideas... Every dollar we invested to map the human genome returned \$140 to our economy... Today, our scientists are mapping the human brain to unlock the answers to Alzheimer's... Now is not the time to gut these job-creating investments in science and innovation. Now is the time to reach a level of research and development not seen since the height of the Space Race.¹

On 02 April 2014, President Obama unveiled a bold new research initiative designed to revolutionize our understanding of the human brain.² The BRAIN (Brain Research through Advancing Innovative Neurotechnologies) initiative's ultimate aim is to help researchers find new ways to treat, cure, and even prevent brain disorders, such as Alzheimer's disease, epilepsy, and traumatic brain injury. Undoubtedly, synthetic biology will play a signal role in this initiative and much of the needed basic research will happen in the universities.

¹ See <http://www.whitehouse.gov/the-press-office/2013/02/12/president-barack-obamas-state-union-address>.

² Fact Sheet: BRAIN Initiative, The White House, 02 April 2013, <http://www.whitehouse.gov/the-press-office/2013/04/02/fact-sheet-brain-initiative>

2.1. DNA carries information

DNA is Nature's digital recording medium. The molecular instructions for creating living organisms are encoded in the complex DNA molecule, a portion of which passes from parent to offspring during the reproduction process. Natural DNA is a linear sequence of four types of nucleotides: A, T, G, and C. Each organism's DNA sequence is unique and autobiographical; it determines an organism's unique characteristics, *e.g.*, the colour of a person's eyes, the shape of his nose, his resistance to disease, etc. Other molecules in a biological cell "read" the DNA sequence and set in motion the physical and chemical processes the cell calls for. For example, the vast information carried by the DNA includes the complete set of instructions for making all the proteins a cell will ever need. Over the years biologists have discovered certain tricks for manipulating DNA in a manner similar to manipulating character strings in a text. For example, they can copy DNA fragments using the polymerase chain reaction (PCR) or clone it using a cloning vector; cut DNA using molecular scissors called restriction enzymes; join two complementary DNA strands into a double-stranded molecule in a process called hybridization; and measure the size of DNA fragments without sequencing them using a technique called gel-electrophoresis. The enormous potential of CRISPR genome editing technology lies in its ability to precisely insert DNA into a cell *in vivo*. For example, CRISPR, allows one to snip out mutated DNA and replace it with the correct sequence. It thus offers possible means of treating many genetic disorders [19].

2.2. The extended DNA alphabet

Since the late 1990s, researchers have discovered that DNA construction can be extended beyond the natural bases (C, G, A, and T) to include man-made ones and artificial DNA constructed. An expanded "DNA alphabet" will obviously allow cramming of more information by way of larger variety of coding patterns for a given number of nucleotides comprising a DNA strand, *e.g.* an extended genetic code and thus enable a wider range of applications from precise molecular probes and nano-machines to useful new life forms. [20, 21].

Watson and Crick [12] showed that natural bases form two base pairs (A-T, G-C) as a result of specific hydrogen bonding patterns. The unnatural base pairs created by Romesberg's group [8] too pair stably and selectively in DNA. These new base pairs draw upon unnatural hydrogen-bonding topologies as well as upon shape complementarity and hydrophobic forces as opposed to only hydrogen bonding in natural pairs and are also synthesized with high fidelity by DNA polymerases. Romesberg *et al* have succeeded in creating DNA strands using the two natural base pairs and a third unnatural base pair of their design with high fidelity [8]. In a sense, researchers may well be anticipating and pre-empting evolutionary events that left to themselves would have taken a few million years to occur.

2.3. CRISPR technology

CRISPR technology is a new way of making precise, targeted changes to the genome of a cell or an organism. CRISPRs are often associated with cas genes that code for proteins related to CRISPRs. By inserting a plasmid containing cas genes and specifically designed CRISPRs, an

organism's genome can be cut at any desired location. Since its invention in 2012, the CRISPR/Cas system has been widely used for gene editing (silencing, enhancing or changing specific genes) in basic research. The importance of the CRISPR/Cas adaptive immune system is that it is a prokaryotic immune system that confers resistance to foreign genetic elements such as plasmids and phages and provides a form of acquired immunity. CRISPR spacers recognize and silence these exogenous genetic elements like RNAi in eukaryotic organisms. It is in building the elaborate system of DNA-cutting proteins and guide RNA sequences that requires extensive engineering to function in eukaryotic cells, and to insert new genes where the targeted host DNA is excised. For a quick introduction to CRISPR technology, see [22].

On 15 April 2014, the USPTO issued the first patent (US8697359, CRISPR-Cas systems and methods for altering expression of gene products) to cover CRISPR-Cas9 gene editing technology to Feng Zhang, the sole inventor, just six months after the patent application was filed on 15 October 2013. The patent is assigned to MIT, and the Broad Institute with Broad managing the patent's licensing. The patent claims a modified version of the CRISPR-Cas9 system that is found naturally in bacteria and which microbes use to defend themselves against viruses. The patent, *inter alia*, claims methods for designing and using CRISPR's molecular components. It is widely expected that Broad will adopt a liberal licensing policy that would make the technology available to scientists for research around the world.

CRISPR is already revolutionizing biomedical research because it provides a very efficient way of recreating disease-related mutations in lab animals and cultured cells. It also holds the promise of treating genetic diseases in humans in unprecedented ways, *e.g.*, by directly correcting mutations on a patient's chromosomes. Mental illnesses too may find similar remedies. Since 2012, CRISPR's use in research has spread like wildfire. The chemistry behind the Cas9 protein is still being explored.

2.4. NGS + CRISPR technologies

The first generation DNA sequencing developed in 1975 by Edward Sanger [23] remained the gold-standard for two and a half decades. It was used in the Human Genome Project that cost \$3 billion and 13 years to sequence the human genome and was completed in 2003. In comparison, next-generation sequencing (NGS) use non-Sanger based, high-throughput technologies to sequence millions and billions of DNA strands in parallel, are much faster and cheaper. In fact, an entire genome can be sequenced in a day. And when it is coupled with powerful computational algorithms, say, to answer questions related to mutational spectrum of an organism on a genome-wide scale, we have phenomenal opportunities to understand our biological selves. Targeted sequencing facilitates discovery of disease causing mutations for diagnosis of pathological conditions, and of genes and regulatory elements associated with disease [24, 25]. For trends in DNA sequencing costs, see <http://www.genome.gov/sequencingcosts/>. (In 2014, it was less than \$0.1 per raw mega-base of DNA sequence compared to about \$1k in 2004; during 2007-2010, the cost fell sharply.) NGS is not yet ready for clinical use.

For recent advances in CRISPR-Cas9 technology see [26]. In principle, NGS and CRISPR technology together would allow one to change a genome at will to almost anything one wants and even elicit enough detailed information about disease risks, ancestry

and other traits of a person to determine his identity. Clearly, such advances raise privacy, ethical, legal, and other social issues that are presently barely understood and therefore need careful study. A NIH initiated study in the U.S. [27] notes: “The ongoing evolution of genomic research and health care requires a continuing analysis of the normative underpinnings of beliefs, practices and policies regarding research, health and disease. In addition, as personal genomic information permeates many aspects of society, it has profound implications for how we understand ourselves as individuals and as members of families, communities, and society--and even for how we understand what it means to be human. Long-held beliefs about the continuum between health and disease may be transformed, as will concepts of free will and responsibility.”

3. Intellectual property rights — Its aims and relevance

Forms of intellectual property rights (IPR) are copyright, trademark (including service mark and geographical indication), trade secret, and patent. Depending on the type, government granted rights enable owners to select who may access and use their property and to protect it against infringement. Since the protections granted by a government vary from jurisdiction to jurisdiction, the acquisition, registration, or enforcement of IPR must be pursued or obtained separately in each territory of interest. Intellectual properties, in general, are creative ideas and expressions of the human mind that have commercial value. The owner of an intellectual property can generally transfer (with or without consideration), license (or rent), or mortgage it to third parties. Most exclusive rights are nothing more than the right to sue an infringer. Those wishing to use an intellectual property held by another, must license it from the owner. In many jurisdictions the law places limits on the restrictions the licensor can impose on the licensee.

A *license* results if the IP owner transfers less than all of his IP rights. The party receiving the license is called the licensee. If the license is given to only a single person and pursuant to the terms of the license is not permitted to license others, the license is termed an *exclusive license*. If licenses are given to multiple parties or to one person reserving the right to license it to others at a future date, the license is termed a *nonexclusive license*. In the case of an exclusive license, the owner of the intellectual property cannot make, use, or sell the intellectual property unless he has expressly reserved the right to do so in the license agreement. If all the rights are transferred to someone, it is known as an *assignment*. Variations in the terms of a license agreement are virtually limitless, depending upon the needs, desires, and bargaining positions of the parties involved.

3.1. Copyright

Copyright is an exclusive right conferred by a government on the creator of a work (*e.g.*, original literary, dramatic, musical, artistic works in books, recordings, films, videos, etc.) to exclude others from reproducing it, distributing it to the public, performing it in public, or displaying it in public. Copyright law protects the holder’s right to decide how and where his

material is used, not just the right to earn profits from the work. Copyright protection comes into effect immediately upon the creation of something that can be protected and is 'fixed' in some way, *e.g.*, on paper, on film, on electronic media (including the Internet), etc. It is not necessary to register a copyright or take any official action to obtain it. However, registration is advisable as it strengthens the owners claim to copyright in litigation. The doctrine of fair use allows non-owners of a copyright work to use such work in a limited way without being accused of infringement.

Things that cannot be copyrighted include abstract ideas, procedures, processes, systems, methods of operations, concepts and principles, regardless of how they are expressed, whether it be by words, illustration, or in some three-dimensional form. Of course, the manner in which they are expressed may be copyrighted, but not the labour that goes into creating a work. Unfortunately, the line between copyrighted material and non-copyrightable ideas, wherever it is drawn, will seem arbitrary to many.

3.2. Trademark and other marks

A mark used in trade—trademark, service mark, certification mark, collective mark, geographical indication—is any sign which can distinguish the goods and services, as appropriate, of one trader from those of another. A mark may be words, logos, pictures, shape of a product or container, or a combination of these. (Certain kinds of marks are not permitted, *e.g.*, marks which are immoral, deceptive, or scandalous, national symbols, national flags, etc.) A trademark serves to identify the origin of goods and creates goodwill for the owner; it signifies that all goods bearing the mark come from or are controlled by a single source and are of specified quality.

3.3. Trade secret

It is any device or information that gives an advantage over competitors who do not know about it or do not use it. Its value lies in its secrecy. Its owner is responsible for protecting it (*e.g.*, through non-disclosure agreements, by restricting access, etc.). Infringement of a trade secret is a type of unfair competition. The subject matter of trade secrets usually includes sales methods, distribution methods, consumer profiles and advertising strategies, lists of suppliers and clients, and manufacturing processes. The Coca Cola recipe is a famous example of a trade secret. What information constitutes a trade secret is case specific. Unfair practices related to trade secrets obviously include industrial or commercial espionage, breach of contract, and breach of confidence.

3.4. Patent

A patent is a limited period monopoly property right granted to an inventor for his invention by a Government subject to prescribed conditions, which include that the invention must be novel, nonobvious to those ordinarily skilled in the art, useful, and fully disclosed. Four types of inventions are eligible for such utility patents: process, machine, manufacture, or composition of matter. They are known as statutory subject matter. In exchange of a patent, the inventor

describes the secrets related to the invention, publishing them as per law for all to see, absorb, and improve upon but not infringe. This description must be so clear and detailed as to enable a person skilled in the technologies relevant to the said invention to independently reproduce the invention (enablement requirement) without undue extra-solution activity, such as further research, data gathering, etc. on his part. In fact, this description should leave no doubt that the patent applicant was in possession of the claimed invention at the time of filing his application. Patents may be sought on non-trivial improvements over existing inventions. The life of a granted patent is usually 20 years from the filing date of the first valid patent application claiming the invention.

Patent monopoly differs from market monopoly; a patent is a right to exclude, a right to prevent trespassing. In this sense it is similar to, say, the right to keep one's personal properties free from trespassers. A patent grants its owner the right to exclude others from making, using, selling or offering to sell, and importing the claimed invention in the country of grant; it does not confer any right to practice the invention. This is because in practicing the invention, one may well need complementary patents held by others unwilling to license or there may be other laws, rules or regulations that prevent its practice. Patents are issued only to the first inventor (or group of joint inventors) of an invention who files a legally valid patent application; all others are barred, even if they independently created the invention. Consequently, those other inventors must get a license from the first inventor if they wish to practice the invention. Although grant of patents is subject to country-specific constraints, there is universal agreement among nations that patents seeking pre-emptive monopoly of abstract ideas (e.g., mathematical formulas), laws of nature, natural phenomena, and products of nature are ineligible. What else to exclude from patent monopoly is a national prerogative, largely dependent on government policy related to prevailing socio-economic conditions it must manage, and international treaty obligations.

Two recent rulings by the Supreme Court of the United States (SCOTUS) are of importance to the biotechnology industry since it invokes the dictum that "laws of nature, natural phenomena and abstract ideas" are not patentable. In March 2012, the court ruled against Prometheus Laboratories in California observing that it could not patent metabolite levels to guide drug dosing [28]. Then, in June 2013, the court struck down a patent claim by Myriad Genetics of Utah that linked certain DNA sequences to female breast cancer [29]. It held that a naturally occurring DNA segment is a product of nature and its mere isolation does not make it patentable. However, cDNA may be patentable as it is not a naturally occurring substance. Thus to get a gene patent one will have to show that it is significantly different from any natural gene. However, in a diametrically opposite ruling, the Federal Court of Australia in *D'Arcy v Myriad Genetics Inc.* [2014] FCAFC 115 on 05 September 2014 ruled unanimously that isolated DNA and RNA are patentable subject matter under Australian law (Patents Act 1990 (Cth) s 18(1), Statute of Monopolies s 6). To say the least, this makes gene patenting a complex issue if such patents are sought in multiple countries.

Governments grant patents to human inventors only. Post-grant they may be assigned to people or institutions. A patent granted by a government is enforceable only in the territory it governs. One may, however, seek patents for the same invention from multiple countries.

Patent laws of a country do not over-ride its other laws that might regulate the invention's use. Patent laws of a country may take into account moral, cultural, ethical, social, environmental, or scientific concerns of society. Patent rights may be exercised by the patentee, his heirs or assigns. When a patent expires, the related invention becomes the common heritage of mankind.

Limited period patent monopoly may provide an enormous first mover advantage to an entrepreneur, especially if it involves new technology that could lead to a natural monopoly.

3.5. Traditional knowledge

The World Health Organisation (WHO) defines traditional medicine as [30]:

Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

This knowledge, much of it undocumented and available only to small groups of people through oral transmission from generation to generation, predates molecular biology by centuries and hence belongs to prior art (public domain). Its importance to synthetic biology is that such knowledge may provide promising directions of research in the hunt for exotic genes.

4. IP outputs of synthetic biology and public concerns

Deciphering the working of a cell, leave alone creating an artificial one, is far more than just listing its constituent parts, *e.g.*, listing its genes. We also need to know how the parts connect and operate together, *e.g.*, how genes and proteins interact to, say, form larger modules and circuits analogous to those in electronic systems. More sophisticated conceptual understanding is needed to advance synthetic biology towards rational construction and redesign of biological circuitry. In addition, development of new computer models, computational algorithms and experimental techniques are needed for exploring gene interactions. Already known techniques, such as chemical modification of proteins and splicing and rearrangement of genetic information in the DNA have matured to a level where they can be used to redesign basic molecular interactions and pathways of living cells. Further, the development of machines and methods for rapid synthesis of DNA with specified sequences has made it possible to build wholly synthetic, highly complex collections of genes and even to synthesize living organisms from the genome up. In fact, biology inspired templates for engineering nanostructures is emerging as a dominant research theme.

Notable contributions in synthetic biology include those from Dae-Kyun Ro, *et al*, Production of the antimalarial drug precursor artemisinic acid in engineered yeast, [Nature, 2006] in therapeutics; Marc Gitzinger, *et al*, Controlling transgene expression in subcutaneous implants using a skin lotion containing the apple metabolite phloretin, [PNAS, 2009] in therapeutics;

Shota Atsumi, *et al*, Non-fermentative pathways for synthesis of branched-chain higher alcohols as biofuels, [Nature, 2008] in fuels; Yoon Sung Nam, *et al*, Biologically template photocatalytic nanostructures for sustained light-driven water oxidation, [Nature Nanotechnology, 2010] in solar energy; John E. Dueber, *et al*, Synthetic protein scaffolds provide modular control over metabolic flux, [Nature Biotechnology, 2009] in chemicals; Tae Seok Moon, *et al*, Use of modular, synthetic scaffolds for improved production of glucaric acid in engineered *E. coli*, [Metabolic Engineering, 2010] in chemicals; Michael B. Elowitz & Stanislas Leibler, A synthetic oscillatory network of transcriptional regulators, [Nature, 2000] in biological computing, programmability; Eileen Fung, *et al*, A synthetic gene-metabolic oscillator, [Nature, 2005] in biological computing, programmability; Marcel Tigges, *et al*, A tuneable synthetic mammalian oscillator, [Nature, 2009] in biological computing, programmability; Tai Danino, A synchronized quorum of genetic clocks, [Nature, 2010] in biological computing, programmability; Daniel G. Gibson, *et al*, Creation of a bacterial cell controlled by a chemically synthesized genome, [Science, 2010], in extending the principles of design and construction to whole organisms; Denis A. Malyshev, *et al*, A semi-synthetic organism with an expanded genetic alphabet, [Nature, 2014], in expanding the genetic code to incorporate unnatural nucleotides and base pairing; Cong, L., *et al*, Multiplex Genome Engineering Using CRISPR/Cas Systems, [Science, 2013], in gene editing.

Research efforts in synthetic biology are largely concentrated in the United States and to a substantially lesser degree in the European Union. Currently no country has the necessary framework for coordinating its research activities, fostering a community of researchers, and creating a forum for the establishment of goals, shared tools, and professional standards. Biological research, more than ever, needs to address ethical and safety concerns of society, especially with respect to synthetic biology if the research community is to gain public trust without raising Frankensteinian fears.

In general, perceived safety and investment risks involved in converting proof-of-concept products and processes developed in laboratories and making them market ready are very high and intimately related to the mode of IP dissemination, *e.g.*, open source, patents, IP commons, and private law initiatives. The last is based on contractual agreements that are basically binding among those involved and not on third parties. The open source movement has generally restricted itself to basic research outputs that form the foundation on which subsequent applied research depends. As synthetic biology results move out of research labs and migrate to industry to be integrated into marketable products, altruistic open source initiatives and private profit motive collide. The potential for fierce litigation suddenly arises whose source is the patent system, which has the unenviable task of delicately balancing the need to encourage innovation through grants of limited period monopoly and protect public interest through minimal free-market encroachment.

4.1. The bright side of IP outputs

Due to genetic engineering, modern biotechnology has progressed well beyond simply using natural strains, classic breeding, and strain selection to produce a variety of chemical products. Artemisinin, a critical ingredient in malaria drugs is now pro-

duced from yeast altered through synthetic biology. Rennet, a key processing aid in cheese making, since the 1990s has been made by a microbe altered with insertion of a single bovine gene and is in wide use in the U.S. Algal oil is produced by genetically modifying algae which is now used in making laundry detergent. Synthetic biology techniques are now used to coax bacteria, fungi and other organisms into producing substances they would not otherwise produce. Some of the micro-organisms synthetic biologists create to make ingredients like orange and grapefruit flavourings have passed the muster of the Environmental Protection Agency of the U.S. while the U.S. Food and Drug Administration says the ingredients they produce are “generally recognized as safe”. Some companies also produce food-grade vanillin, resveratrol and citrus flavourings from yeast and other microorganisms via synthetic biology. Yet enough misgivings in public perception exist that companies shy away from admitting that some of their products are created or mediated by artificial organisms made possible by synthetic biology [31]. Nevertheless, synthetic biology continues to tackle far more ambitious goals. Here are some examples.

1. *Three-person IVF*. The Human Fertilization and Embryology Authority in the U.K. that regulates the use of human eggs, sperm, and embryos in treatment and research has assessed two types of in vitro fertilisation (IVF) methods: one that involves removing parental nuclei from a fertilized egg and placing them into a donor embryo from a second woman, and another that moves the nucleus from the mother's egg into a donor egg, which then can be fertilized. The aim is to help women with mitochondrial diseases have healthy babies. The report [32] noted that three-person IVF is expected to be ready for use in preventing the birth of children with mitochondrial disease through assisted conception in about two years. Its use on humans in the U.K. will need Parliamentary approval.
2. *Next generation sequencing*. Fourteen year old Joshua lay in a coma for weeks, his brain swelling with fluid due to an unknown cause. With parental approval, doctors ran a test with an experimental new technology that searched the child's cerebrospinal fluid for pieces of DNA that might belong to the pathogen causing his encephalitis. They were able to pinpoint the cause within 48 hours. The child had been infected with an obscure species of bacteria, which the doctors eradicated within days [33]. The technology although years away from clinical use has raised hopes of powerful diagnostic tools for presently undiagnosable diseases becoming available in the future.
3. *Exome sequencing*. In June 2014, researchers in the *Finding of Rare Disease Genes* (FORGE) project reported analysing 264 rare disorders using exome sequencing and identifying the causal mutations to 146 of them and identifying 67 novel genes [34].
4. *Whole-genome sequencing*. A recent paper in *Nature* [35] has suggested that whole-genome sequencing can diagnose severe intellectual disability in newborns even when standard tests don't. Based on data on 50 patients with severe intellectual disability and their unaffected parents, the genome-wide analysis found 84 novel sequence variations and 8 novel structural variations associated with the disability. Previous gene screens in the same patients had failed to identify disease markers. The results led to a diagnosis of 42 percent of patients studied. Can a synthetic biology remedy be far behind?

5. *Gene editing technology.* In Nature Biotechnology [36] researchers reported the use of CRISPR-Cas9 to alter the genome of the human malaria parasite *Plasmodium falciparum*. This parasite has been difficult to manipulate with existing tools. Researchers were able to specifically disrupt chromosomal loci and generate marker-free, single nucleotide substitutions with high efficiency. They were also able to generate a strain of the protozoan resistant to a key malaria treatment.
6. *Solar energy.* An article in Nature [37] reported that in Caltech's Jorgensen's Lab more than 80 researchers are engaged in using inorganic material (silicon, nickel, iron, etc.) to create artificial photosynthesis. Their goal "is to use sunlight to make hydrogen and other fuels much more efficiently than real leaves ever made biomass." Making fuels using power from the Sun, which is effectively inexhaustible but also carbon-free would be a boon. While not synthetic biology, it is inspired by it.
7. *Genome transfer.* Researchers have found that allopolyploidization can also occur by asexual mechanisms. They have shown that "upon grafting—a mechanism of plant–plant interaction that is widespread in nature—entire nuclear genomes can be transferred between plant cells". They have created a new allopolyploid plant species from an herbaceous species and a woody species in the nightshade family. The new species is fertile and produces fertile progeny [38]. Synthetic biology, in conjunction with a potential asexual mechanism of speciation opens up vast new possibilities for the generation of novel allopolyploid crop species.
8. *De-extinction, reanimation.* Recreating extinct species is no longer far-fetched. Synthetic biology not only makes it feasible to revive them but also improve them by boosting their immunity and fertility, their ability to draw nutrition from available food, and to cope with environmental stress. Just as a new vaccine can reduce demand on medical resources, improved species make for better ecological compatibility and balance. Indeed, George Church is currently modifying genes from an Asian elephant to make them more mammoth-like [39].

4.2. The dark side of IP outputs

New technologies come with unknown risks of using and not using it! They have their share of scary stories and apprehensions. Construction of artificial life that goes well beyond traditional recombinant DNA technology, is both ambitious and ominous. But then modern civilization is the result of past risk taking. With older and mature technologies we gradually found ways of muting their dark side by enacting legislation and creating regulatory bodies.

While possible socio-economic benefits from synthetic biology are enormous, so is the possibility of its misuse. The concerns range from bioethical and environmental worries to bio-terrorism, say, by malicious release of genetically engineered viruses targeted at specific population groups. The main concern is the creation and growth of bio-weapons. They can be created surreptitiously, cheaply, on a mass scale, and released in a variety of inexpensive ways into the environment using a variety of delayed triggering mechanisms that would camouflage their presence. Bio-weapons make the lethality of atomic and nuclear weapons passé.

A panel of life sciences experts in 2003 noted [40]:

- “The effects of some of these engineered biological agents could be worse than any disease known to man.”
- “The genomic revolution is pushing biotechnology into an explosive growth phase. ... [T]he resulting wave front of knowledge will evolve rapidly and be so broad, complex, and widely available to the public that traditional intelligence means for monitoring WMD [weapons of mass destruction] development could prove inadequate to deal with the threat from these advanced biological weapons.”

A decade later, these concerns have become more pronounced. The threat spectrum is diverse and elusive and already impossible to comprehensively defend against. The pace, breadth, and volume of the evolving scientific base in synthetic biology and its easy public accessibility makes the controlled development of bio-weapons a hopeless task.

4.3. The regulatory side of IP outputs

Synthetic biology ingredients are rapidly entering consumer products and food [31]. The legitimate concern of various advocacy groups is that synthetic biology is so new that there are as yet no regulations in place for the creation, use, and disposal of new synthetic organisms or even credible risk assessment methods before such organisms are released in the environment [41, 42]. The fear is that premature, wider, large-scale industrial use of synthetic biology ingredients is likely to cause serious harm to biodiversity and farmers. The fact remains that scientists cannot predict, at this nascent stage of synthetic biology, what new forms of life or attempts to ‘reprogram’ existing organisms, such as yeast and algae, would do to the environment and human life, given that they can now generate millions of new, untested organisms on a mass production scale. The possible effects range from beneficial, benign, to ecological and economic disaster. The core ecological concern is that artificial organisms breed, reproduce, and once released into the environment cannot be recalled. Hence the fear of unintended consequences. Of course, as synthetic biology matures, many equitable solutions are also likely to emerge.

In this ‘good-bad’ debate, the real concern is the regulation of artificially created living organisms rather than the non-living chemical products (bio-fuels, pharmaceuticals, oils, etc.) they produce. For the latter, reasonable regulatory mechanisms exist and they are continuously evolving. Chemistry is much better understood than the biochemistry of life. Therefore, the demand, as is sometimes made, for labelling ingredients as having come from synthetic biology processes in products has no scientific basis. The chemical properties of an ingredient are independent of the process used in making them.

The regulatory aspect of such synthetic biology products as genetically engineered microbes, plants and animals, promises to be a nightmare. Concerns related to environmental, health, and food safety require specialized regulating agencies. R&D advances in synthetic biology have been so rapid and novel that existing regulatory agencies are either unable to cope or find themselves without the authority to review. The sheer variety and increasing complexity of artificial life, many of which can be generated within a short span, makes their risk assess-

ment a great challenge. Not only will the regulators need additional funding to meet increased workload and expertise requirements, but also the legal authority to carry out certain tasks not included in current laws. See, *e.g.*, [16]. Most countries currently lack human, financial, and scientific resources to set up effective regulatory agencies or even frame regulatory policies.

Another major concern is the accidental release of artificial organisms in the environment. In some cases, researchers can design organisms with built-in safety features. For example, by designing organisms that can survive and breed only in an artificially created environment, such as by controlling the chemical sources of energy they have access to or by the reassignment of the stop codon. It was recently discovered that in the standard genetic code the stop codon can undergo recoding in nature. Reassignment of the stop codon has been observed in bacteriophages and bacteria indicating that bacteriophages can infect hosts with a different genetic code. This can lead to phage-host antagonism based on code differences. Its implication in synthetic biology is that the stop codon reassignment may be used as a means to engineer organisms to prevent the exchange of genetic information between engineered and naturally occurring species.

Clearly, synthetic biology requires new methods of risk assessment because it involves exotic biological systems based on an alternative biochemical structure, *e.g.*, genetic code based on novel types of nucleotides, or an enlarged number of base pairs. There is also the risk of synthetic biology skills diffusing into wrong hands (*e.g.*, Do-it-yourself biology, amateurs, and bio-hackers) with time as these skills begin to percolate down the education system.

4.4. The societal side of IP outputs

Since artificially created biological systems will often be expected to interact with natural biological systems, including human societies, there are moral and ethical concerns and the need to develop a rational public–science interface to address those concerns [44]. In particular, what should be the relationship between humans and artificially created living organisms and the moral and legal status of the products, *e.g.*, transgenic humans. Indeed, how would we define human life? What would be the legal status of artificial humans, especially if illegally created? What if they formed their own societies, rules of governance and rules of interaction with natural humans? What if there were to occur a sudden spurt of diversification of the human species, engineered or accidental? Could it lead to the collapse of human society as we know it today and the extinction of natural humans?

Precision editing of DNA will eventually enable us to alter not just individual organisms but also ecosystems. It would then be possible to wipe out diseases like malaria by altering *Anopheles* mosquitoes, which have evolved resistance to anti-malarial drugs and insecticides (a vaccine against malaria has been elusive), by modifying their genome, disabling or hindering their reproductive cycle or building up resistance to parasites through highly heritable genes, and then releasing them throughout the population. However, the accessible nature of the technology, such a “gene drive” could also be used irresponsibly and raise the risks of accidental or even intentional harmful effects [45]. Given the delicate ecological balance needed for human survival, how is responsible behaviour to be integrated with the patent system?

Historically, pioneering technologies have created intense patentability debates [46, 47] that range from conceptual to political. For example, IPR opponents in the past had argued agriculture was not an industry, patents on pharmaceuticals would be unethical, biotechnology is about trying to play God, software and business methods are non-technical, etc. In the 1970s, concerns surfaced about recombinant DNA technology that innocuous microbes could be engineered into human pathogens resistant to then known antibiotics, or enable them to produce toxins, or transform them into cancer causing agents [47]. Fears have since abated. Recombinant DNA technology now dominates research in biology. In synthetic biology, the fears are more in terms of our ability to regulate research and industrial activities so that these activities are carried out safely [16] and the human species preserved.

4.5. The IPR side of IP outputs

In societies that abhor monopoly rights and favour level playing fields of competition, even limited period monopoly creates social tension. Thomas Jefferson (1743–1826), the third President of the United States (1801–1809), the principal author of the Declaration of Independence (1776), a well-known scientist of his time, the initiator of the first U.S. patent system in 1790, and the author of the 1793 Patent Act, had this to say in 1813 in a letter to Isaac McPherson [48]:

Considering the exclusive right to invention as given not of natural right, but for the benefit of society, I know well the difficulty of drawing a line between the things which are worth to the public the embarrassment of an exclusive patent, and those which are not.

The demarcation debate between openness and limited period monopoly may never end. In synthetic biology this debate is complex because it involves the assimilation of a new technology by society and of inventions that were never anticipated to become part of the patent system. Indeed, some of these future inventions may well be bio-robots and bio-computers with the DNA serving as programmable memory. It would require tremendous legislative efforts to equitably deal with such live inventions. However, one expects that bio-weapons, like atomic weapons, would be kept outside the patent system.

5. Look before leaping to patent

Before filing a patent application, ensure that a thorough prior art search is done and in relation to that prior art, map out all possible obvious extensions to the art that are likely to occur to a person of ordinary skill in synthetic biology (*e.g.*, the average post-doc). If your invention goes beyond the obvious extensions, and fulfils the statutory requirements of novelty, non-obviousness and utility then expeditiously file a patent application for your invention ensuring that you fully describe the invention (including the best mode) therein. File a provisional application if necessary to claim priority over other inventors and follow it up in a timely manner with a non-provisional application. Scrupulously follow patent office protocols. Getting a patent is expensive, so a business analysis before filing is prudent.

5.1. Prior art search

Prior art or state-of-the-art is all information, available in any form (including social media), in the public domain. It does not include secret information, *e.g.*, trade secrets or confidential communications. Patentability searches of prior art – to decide whether or not an invention is patentable – especially from the point of view of novelty and non-obviousness are routinely performed by patent examiners. Even then, it is usually prudent to pre-emptively carry out a similar search. *Inter alia*, such a search provides valuable information to the lawyer drafting the patent application. First, it helps him define the prior art and the background of the invention so that he can highlight patentable features of the invention. Second, he will be able to strike a balance between framing too broad or too narrow claims for the invention.

Learn the art of prior art search. Automated searches (*e.g.*, Google scholar) are valuable as a lead-in to conducting a specialized manual search or as a follow-up to locate patents or other prior art after a manual search. If affordable, get a professional search done. Note that no search can guarantee that it is complete or completely accurate. More importantly, only the absence, and not the existence, of novelty of your invention can be established.

5.2. PHOSITA

This legal fictional person (or a team) having ordinary skill in the art, called a PHOSITA who is neither a genius nor a layperson, is considered to possess average skills and knowledge in a particular technical field and hence unlikely to ever become an inventor. He thus serves as a reference for determining by comparison whether an invention is obvious or not. If a PHOSITA is deemed capable of coming up with the invention if required, assuming he/she would make the effort to study relevant prior art, then the particular invention is deemed unpatentable. Note that a “person of ordinary skill is also a person of ordinary creativity, not an automaton.” [49]. Further, “in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.” [49].

The skill profile of a PHOSITA is determined on a case-by-case basis, depending on the level and technological features of the invention. Factors used in profiling include the education level of the inventor, type of problems encountered in the art, known prior art solutions, rapidity with which innovations are made in the art, sophistication of the technology, and education level of active workers in the field. Clearly, a PHOSITA’s profile changes with time as he continuously imbibes new advances in related technologies. A PHOSITA of today, may have been an expert yesterday! This is clearly true in synthetic biology where the PHOSITA will most likely be a researcher with a PhD.

5.3. Novelty, non-obviousness, utility, written description, claims

Only an invention that can be classified as machine, manufacture, process, or composition of matter and further if it is considered novel with respect to prior art, non-obvious to a PHOSITA, and useful to society at the time the patent application (provisional or non-provisional) is filed is eligible for consideration of a patent grant provided the invention is clearly and fully described. Patent prosecution is the process by which a non-provisional patent application is

defended before the patent office. Prosecution begins with the filing of the non-provisional patent application and ends with the final decision on the application by the patent office.

Obviousness creates a 'patent-free' zone around the prior art related to the invention and prevents trivial advances from being patented. Under the doctrine of equivalents, straying into the patent-free zone of a valid patent amounts to infringing the patent. (See Section 6.2.)

The invention must have a useful effect or a purpose meaningful to society else the invention is not patentable. The invention's utility must be specific to the subject matter claimed, credible to a person skilled in the field, and should not require further research to discover it.

The written technical description of the invention should enable a person skilled in the art to reproduce and use the claimed invention without undue research or experimentation beyond those normally expected from such a person. Because the experimentation may be complex for a particular invention it will not become undue if a person of skill in the art typically engages in such complex experimentation. The inventor must point out how his invention differs from prior art. Finally, the non-provisional application must include one or more claims that distinctly spell out specific aspects of the invention which the inventor claims are his intellectual property in need of legal protection. Omitted aspects that could have been claimed are deemed to have been gifted to mankind. Likewise, disclosing the invention by putting it in public use, testing it in public, describing it in a speech in a technical conference, sale of the invention, disclosing the invention to people without a signed non-disclosure agreement with them, discussing it in the social media, etc. before filing a patent application may be construed as placing the invention in the public domain and hence ineligible for a patent.

It must be clear from the written description that the applicant was in possession of the claimed invention at the time of filing. There is no statutory requirement that the inventor disclose why the invention works or how it was developed. Inventors are expected to write their invention using the language and ideas that are accepted in the field of the invention, say, by a PHOSITA. In some countries, it is a statutory requirement that the inventor set forth the best mode contemplated by him of carrying out his invention.

While the written description must be followed by one or more claims through which the inventor points out and distinctly claims aspects of the invention he believes are his original non-obvious contributions, he should not pre-emptively claim ideas, laws of nature or natural phenomena. Each claim must be so drafted that patent examiners and potential infringers can understand what the claimed subject matter is. Writing claims is a specialized art, and should preferably be drafted by a patent attorney. Claims lie at the heart of infringement litigation and they form the most important part of a patent.

A patent is invalid if its claims, read in light of the invention's description and prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention. However, when the invention is novel and non-obvious, words may not exist to describe it so the law allows words to be invented and defined to describe the invention to fill unintended idea gaps in a language.

5.4. Business prudence

Economic viability of a patent depends on the following:

Detectability. Once a patent is granted, the idea and implementation details become public. Hence, to enforce your patent, you must be able to detect infringement easily, otherwise keeping the invention a trade secret may be a better option.

Non-avoidability. If viable alternatives to your invention exist or can be developed within reasonable timeframes and costs, then seeking a patent may be unwarranted.

Business value. Acquiring a patent is both time-consuming and expensive. So weigh the potential benefits that may accrue from a patent against potential risks of not seeking a patent.

Technology obsolescence. Track emerging technologies and technology trends to determine if your invention will become obsolete in the near future.

Since biotechnology patents generally underpin business, it is imperative that patent applications are prepared and prosecuted by experienced patent attorneys and that inventors work closely with them to minimize prosecution hurdles and future litigation possibilities.

6. Look before litigating

Infringement occurs when someone unauthorized makes, uses, offers for sale or sells a patented invention within territories where it is protected, or imports into that territory the patented invention during the term of the patent. Infringement and litigation is mainly about the power to regulate the manner in which patented goods and services are traded, not how people use them. Patent disputes seldom throw up clear-cut good guys and bad guys. Each feuding party is likely to honestly believe its actions are reasonable and lawful. Litigation costs are usually very high, so anticipate spending a million or more U.S. dollars. No infringement occurs outside the term of a patent. Patent offices have no jurisdiction over infringement issues, only designated courts have. The relief sought from courts for infringement may be an injunction to prevent further infringement, and award of damages for past infringement. Alleged infringers, if challenged, are quite likely to counter-challenge by questioning the validity of the disputed patent. While the Government that granted the patent may use the patented invention without permission of the patent owner, it must, nevertheless, compensate the owner.

6.1. Obviousness and obvious-to-try

Obviousness and “obvious to try” are not synonyms. The mere fact that something is “obvious to try” in view of prior art does not automatically imply that the invention resulting therefrom is obvious. This is especially true where the number of things one can obviously try are very many (say tens-of-thousands or millions as can happen with respect to chemical molecules) and the search would amount to finding a needle in a haystack. That is, the prior art does not contain any suggestion or teaching that might

suggest how the invention might be accomplished or any basis for reasonable expectation that beneficial results will accrue by proceeding along the lines taken by an inventor. There are, however, situations where “obvious to try” or “worth a try” may be indicative of obviousness. In *KSR v. Teleflex* [49], the SCOTUS indicated one:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product [is] not of innovation but of ordinary skill and common sense.

6.2. Doctrine of equivalents

The judicially created doctrine of equivalents, universally followed, is a rule of claim interpretation wherein a product or process, although not literally infringing nevertheless infringes if it performs substantially the same function in substantially the same way to obtain the same result as a patented product or process. The doctrine extends patent protection beyond the literal language of the claim.

Literal infringement of a patent, though rare, occurs when the alleged infringing product or process is an obvious near replica. Generally, people try to work around a patented invention by introducing differences and variations they hope will be large enough to beat the doctrine of equivalents. Deciding equivalency is tricky as it must deal with two opposing public policies: (1) the need to provide public notice as to what infringes by requiring clear and distinct claims, and (2) the need to prevent an infringer from avoiding liability by covert means. Of course, one may ask, “What if a device performs substantially the same function in a substantially *different* way to obtain the same result?” This leads us to the reverse doctrine of equivalents (Section 6.3). In determining equivalency, courts may seek expert opinion as to scientific or engineering facts and the decision may well lean on the more believable expert. Note that things that are equivalent for one purpose may not be so for other purposes.

6.3. Reverse doctrine of equivalents

The reverse doctrine of equivalents circumscribes the doctrine of equivalents. The SCOTUS in *Graver Tank* [50] ruled that:

The wholesome realism of this doctrine [of equivalents] is not always applied in favor of a patentee but is sometimes used against him. Thus, where a device is so far changed in principle from a patented article that it performs the same or similar function in a substantially different way, but nevertheless falls within the literal words of the claim, the doctrine of equivalents may be used to restrict the claim and defeat the patentee’s action for infringement. [Citations omitted.]

Thus, where an invention relies on the fundamental concept embodied in a patent but, say, relies on “a significant advance” in technology, the accused device does not infringe by virtue of the reverse doctrine of equivalents. Once a patentee establishes literal infringement, the

burden is on the alleged infringer to establish non-infringement under the reverse doctrine of equivalents.

6.4. Prosecution history estoppel

Estoppel means a bar preventing one from making an allegation or a denial that contradicts what one has previously claimed as the truth. This can happen, *e.g.*, during patent prosecution, if a claim is rejected by the patent examiner citing prior art and the claim is then amended and narrowed to avoid the prior art. In such a case the patentee is barred from asserting the narrowed claim in a broader sense under the doctrine of equivalents or recapture what was surrendered in the amendment. Thus when prosecution history estoppel applies, only literal infringement may be invoked.

6.5. Research exemption

Generally, use of patented inventions in pure research is exempt from infringement liabilities. That is, if the pursuit is no more than “for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry.” [51]. Still caution is warranted as the scope of exemption varies from country to country and whether the research is associated with a commercial goal. If it is, exemption is unlikely. Researchers in synthetic biology need to be very cautious, especially if their research is funded by industry or is likely aimed towards a commercial product. Generally, use of patented inventions in research and tests in preparation for regulatory approval from government bodies is exempt if conducted within a limited period prior to the patent’s expiry. This *e.g.*, allows generic manufacturers to prepare generic drugs in advance without infringing relevant patents.

6.6. Method claims

Unlike product claims, process or method claims are generally problematic in litigation. In the United States where patent litigation is rampant, the SCOTUS has often enough reversed the decisions of the Court of Appeals for the Federal Circuit (CAFC) in patent litigation [52]. In a recent case, *Limelight v. Akamai* [53] the SCOTUS while unanimously overturning the CAFC’s decision, commented, “The Federal Circuit’s analysis fundamentally misunderstands what it means to infringe a method patent. A method patent claims a number of steps; under this Court’s case law, the patent is not infringed unless all the steps are carried out.” It also held that a defendant is not liable for induced infringement if there is no direct infringement. The decision has raised some concerns in the biotech industry since biotech patents often include complicated, multi-step methods. It now appears that the patent system could be gamed by infringers by simply outsourcing part of the process to avoid lawsuits.

6.7. Balancing conflicting requirements

Balancing the requirements for non-obviousness in litigation, with the constraints imposed by the doctrine of equivalents, reverse doctrine of equivalents, and prosecution history estoppel can be tricky because much depends on prior art related to the patent-in-suit, the profile of the

PHOSITA, and exact wordings of the patent's claims. In most cases, the issue involves the expansionary scope of the doctrine of equivalents and whether obvious-to-try is the same as obvious from the perspective of the PHOSITA. Some of the trickiest situations involve the opposing tendencies of the doctrine of equivalents and prosecution history estoppel. Such matters are best left to experienced lawyers.

7. Sundry IP protection issues in biotechnology

In scientific research, openness in sharing foundational research results and tools promptly with the scientific community advances the field more rapidly than otherwise. This requires that synthetic biologists collaboratively create a basic platform where, *e.g.*, standardized biological parts that are safe, ethical, and cost effective are easily accessible to facilitate the development of other inventions needed by society but require an industrial setting, a profit motive, and IPR protection. A shared basic platform will foster less acrimonious market competition. Basic research is curiosity-driven and largely government funded; product development is market-driven and requires huge private funding. The government owns the mint, the private sector does not nor can it crowd-source funds via taxation. IP laws try to bridge this gulf. The task is far from easy as the following two examples indicate.

1. *Galileo seeks IPR.* The Venetian Senate passed the first patent law on March 14, 1474, granting limited duration monopoly for original devices. That same Venice in 1594 granted Galileo a "privilege" (a patent) for 21 years on a machine which he had invented [54] "for raising water and irrigating land with small expense and great convenience," on the condition that it had never before been thought of or made by others. In his petition for the privilege he said, "it not being fit that this invention, which is my own, discovered by me with great labour and expense, be made the common property of everyone" and adding that if he were granted the privilege, "I shall the more attentively apply myself to new inventions for universal benefit." Clearly, even Galileo, the father of modern science, was not willing to divulge his invention only to have it copied for free exploitation by others. Galileo's argument pervades the modern patent system.
2. *The Bayh-Dole Act.* In the late 1970s the U.S. Government realized with shock that while it held title to approximately 28,000 patents (at the time all patents resulting from federal R&D funding at universities were owned by the government), fewer than 5% were licensed to industry for development of commercial products. Literally, results of billions of dollars of federal R&D investment were under-utilized in commerce. The remedy was the Bayh-Dole Act of 1980. It went against prevailing wisdom that patents resulting from tax-payer funded research should belong to taxpayers and availed by industries under non-exclusive licenses. It turned out that without an exclusive license, companies were wary of investing the huge sums required to turn those inventions into marketable products when the resulting products could easily be appropriated by competitors. The business risks were too high. Therefore, under the Act, the government relinquished its ownership rights to future patents arising from federally funded R&D in the universities

and small businesses and turned them over to the fund recipients. It also permitted them to grant exclusive licenses thereby creating the needed incentives for private firms to invest. Many countries have since enacted Bayh-Dole type Acts. About the Act, *The Economist* (December 14, 2002) wrote:

Possibly the most inspired piece of legislation to be enacted in America over the past half-century was the Bayh-Dole act of 1980... More than anything, this single policy measure helped reverse America's precipitous slide into industrial irrelevance.

7.1. Limited period monopoly versus dedicated to the public

The *quid pro quo* of the patenting system is that in exchange for government granted limited period monopoly, the inventor must fully disclose the details of the invention so that further innovation and improvement of the invention by others can continue. On the patent's expiry, the invention falls in the public domain and all patent rights are extinguished. Patent law encourages such inventions where without a patent the incentive to invent products and processes useful to society is unlikely to occur rapidly enough. For example, not having patents may mean not having certain drugs and therapies.

Acquiring patents is expensive; fighting litigation even more so. So the key question in framing a patent system is: "Will concentration of monopoly power in a given technology be detrimental to industrial growth in the long run?" The answer depends on the scale and availability of funding. Only those with deep pockets can afford to acquire a sizable patent portfolio. The second question, "Is the patent office ready to handle this technology?" New technologies that come rapidly to the fore can be a nightmare for any patent office because of lack of examiners, inadequate repository of and access to prior art, inadequate case-law from which they can seek guidance, etc. Not every country has the ability or the resources to cope with such a situation. The third question, "How high should the bar be set for grant of patents in terms of novelty and non-obviousness?" Higher the bar, less will be the cost of enforcing patent law since a great many infringement battles can be eliminated and more inventions will populate the public domain. How the answers to the three questions are dynamically balanced will decide how well the patent system serves society. This balancing act is far from easy given that substantial and rapid technological advancement is not possible if based purely on the innovative capabilities of ordinary people. Only extraordinary people are capable of such feats and many of them require the incentive of government granted and protected privileges in order to be productive, *e.g.*, Galileo. Patents promote trade and commerce and avoid the accumulation of trade secrets.

7.2. Patents common

There is a perennial dilemma: How does one encourage innovation without eroding the vitality of the scientific commons? What is the right balance between philanthropy and profit incen-

tive? Should the balancing be driven by free market mechanisms or government intervention? Reforms in the patent system are undoubtedly warranted but what they should be are unclear.

The biotechnology industry, recognizing these dilemmas, has funded certain initiatives in the past with the clear aim of placing the resulting research output in the public domain in the larger interests of both industry *and* society via patents-information commons. These initiatives sought a balance between the intellectual property system that quarantines new knowledge and information and the goal of science to put them in the public domain expeditiously [55]. For example, to mitigate debilitating competition, like-minded companies have collaborated to create and share IP among themselves to enhance the scale, scope and speed of innovation; used cross-licensing, patent pools, and patent exchanges to lower the cost of exchanging IP; embraced open standards to enhance inter-operability and encourage collaboration; and invested in pre-competitive information-commons to boost their downstream product development. Some well-known examples of pre-competitive information-commons are *Merck Gene Index* (1995), *Merck sponsored project to create patent-free transgenic mice* (1997), *SNP Consortium* (1999), *International HapMap Project* (2002), and *The Genographic Project* (2005).

The National Institutes of Health (NIH) in the U.S. too has been active in creating information commons. Since 1996, all human genomic DNA sequence information that it funds is placed in the public domain. In December 1999, it adopted a general statement of “Principles and Guidelines for Sharing of Biomedical Research Resources”³ that said:

[T]he use of patents and exclusive licenses is not the only, nor in some cases the most appropriate, means of implementing the [Bayh-Dole] Act. Where the subject invention is useful primarily as a research tool, inappropriate licensing practices are likely to thwart rather than promote utilization, commercialization, and public availability.

In the same spirit, the Guidelines encourage unencumbered transfer of unpatentable research tools to other needy researchers. Of course, in view of the Bayh-Dole Act, the Guidelines could not restrain grantees from filing patent applications.

In August 2014, NIH issued a final policy on genomic data sharing that builds on and replaces its earlier policy issued in 2007 in an effort to promote the sharing of data from genome-wide association studies, and through the creation of the database of Genotypes and Phenotypes (dbGaP), a two-tiered system for distributing data. One tier offers open-access with no restriction and the other provides controlled access that can be used only for research purposes consistent with the original informed consent under which the data were collected. This new policy (available at <http://gds.nih.gov/03policy2.html>) will go into effect in January 2015. NIH's preference for open access understandably comes from its top leadership which is typically drawn from academia and the basic research community that sanctifies open access. A survey of deals and business models that highlight the more charitable side of the pharmaceutical and biotechnology industry is available at [56].

³ Available from http://grants.nih.gov/grants/intell-property_64FR72090.pdf.

8. Universities taste entrepreneurship

8.1. Some history

The Bayh-Dole Act spurred U.S. universities to seek patents and facilitated university-industry partnerships that turned universities into engines of economic growth. However, a Bayh-Dole type Act is unlikely to succeed elsewhere as it requires a system of world-class research universities, brilliant research faculty, a continuous stream of brilliant doctoral students and post-docs, and access to substantial funds to create and maintain research infrastructure. In 1980, the U.S. had all these. Even then, only companies with the wherewithal to convert university generated basic research results into marketable end-products benefited most. So far the most successful example has been the bio-medical sector [55]. For example, in FY 2007, top licensing revenue earners included: New York University (approx. \$791.2 million), Columbia University (\$135.6 million), The University of California system (\$97.6 million), Northwestern University (\$85 million), and Wake Forest University (\$71.2 million).⁴ Most of these earnings came from biomedical discoveries, rather than physical sciences. Even in biomedicine, it was often a block-buster patent that strikingly stood out. For example, New York University's largest licensing income came from an undisclosed portion of its worldwide royalty interest in the monoclonal antibody Remicade; it was \$650 million!

Here is another example of IP treasure troves in universities. World-wide the top 10 universities granted U.S. patents in 2012 were: (1) The Regents of University of California (357); (2) Massachusetts Institute of Technology (216); (3) Stanford University (182); (4) Wisconsin Alumni Research Foundation (155); (5) Tsinghua University (149); (6) University of Texas (141); (7) California Institute of Technology (136); (8) National Taiwan University (122); (9) University of Michigan (97); (10) University of Illinois, National Chiao Tung University, and University of Utah Research Foundation (85 each).

To play the IP game on this scale, U.S. universities have had to change dramatically. Since the founding of Harvard University in 1636 when universities provided their students with the requisite classical background and knowledge of leadership and government, the shift to a radically new training-centred curriculum to accommodate mechanical science, agricultural technology, etc. that would complement the new rapidly industrializing economy and the aspirations of the emerging middle class, was remarkable enough. This shift to science-inclusive education helped propel the U.S. economy well into the twentieth century. Post-Bayh-Dole, universities are once again adapting themselves to remain relevant in a global innovation-driven economy, in which researchers are highly mobile, technology obsolescence rates are high, and knowledge acquisition is a continuous requirement. A unique feature of this transition is the birth of the entrepreneurial professor who sets up companies, sometimes taking his graduate students along with him. (Often the same university that does research in science also does research in business management!) Many young professors now routinely

⁴ Ben Butkus, Biomed Dominates Tech Transfer in US; NYU, Columbia, MassGen Tops in Licensing Income, GenomeWeb, January 28, 2009, <http://www.genomeweb.com/biotechtransferweek/biomed-dominates-tech-transfer-us-nyu-columbia-massgen-tops-licensing-income>

acquire managerial skills by participating in multimillion dollar R&D projects. To such academics, university-industry collaboration comes easily. Indeed, they expect and get help from their university in spinning-off start-ups to exploit their research. Such 'commercialization' has not eroded basic research, which continues to fascinate top researchers dreaming of Nobel Prizes. In fact, biomedical researchers strive to find clinical applications of their basic research.

8.2. Technology transfer

The technology transfer process between university and industry is complex because it must contend with two fundamentally different and sometimes opposing cultures of dealing with the profit motive. Universities need to ensure that the process does not unduly compromise their educational and research mission. Bayh-Dole type provisions facilitate technology transfer by giving universities the necessary autonomy and IP ownership rights, which provides greater legal certainty and acts as a strong incentive for industries to collaborate with universities. However, the downside is that universities must involve themselves in hitherto unfamiliar activities, such as creating technology transfer offices, and developing interdisciplinary teams with legal, business, scientific, and licensing expertise. For an informative tutorial on technology transfer in U.S. colleges and universities see [57]. *Inter alia* it discusses "the role technology transfer plays in adding value to the academic and research mission of universities and colleges." Of course, remodelling of universities alone is not enough. An entire ecosystem is required that includes the university system, the intellectual property system, immigration laws, technology transfer offices, venture capitalists, and most importantly, opportunities for researchers to remain mobile—getting gifted people to work in a poor country will therefore be an arduous task.

The corner stone of basic research is insight which begins as tacit knowledge held by researchers. The diffusion of tacit knowledge via university-industry collaboration is crucial for technology transfer and commercial success. This means that star scientists—their accessibility, location, motivation to collaborate at the bench-science level with scientists in industry in converting basic scientific knowledge into commercially viable products and processes—will be crucial in determining the pace at which tacit knowledge is diffused [58, 6]. Graduating students too carry considerable tacit knowledge derived from their faculty mentors with them when they join the biotech industry as employees. Donald Kennedy, a former editor-in-chief of the journal *Science* and President Emeritus of Stanford University, once aptly noted, "Technology transfer is the movement of ideas in people." This movement in biotechnology frequently requires the protective cover of patents to ensure adequate return on investment in commercialization. The biotechnology industry's ascendancy has meant that universities are no longer not-for-profit ivory towers.

A crucial activity of university technology transfer offices is the marketing of their patent portfolios. An outstanding example of marketing is the Cohen-Boyer patents by Stanford University. It was master-minded by Neils Reimers who had an unusual talent for balancing academic values and industries' needs. And the Bayh-Dole Act which Congress passed on December 12, 1980 some ten days after the first Cohen-Boyer patent was granted, was a

godsend. Reimers designed a trail-blazing licensing program. By end of 2001, the three Cohen-Boyer patents had made \$255 million in licensing revenues from licenses granted to 468 companies. More importantly, 2,442 products were developed from the patented technology that included drugs to mitigate the effects of heart disease, anaemia, cancer, HIV-AIDS, diabetes, etc. Remarkably, the patents never faced litigation. Reimers showed that cutting edge university-centred research, patents, and industry collaboration could be integrated into a formidable system that can propel a country's economic agenda, without the university sacrificing its core values [5].

It now appears that CRISPR-Cas9 technology is the new superstar in biotechnology. Zhang's patent (U.S. patent No. 8,697,359) is the first to cover this technology. While the Cohen-Boyer patents survived their terms without litigation, one hopes that Zhang's patent assigned to Broad Institute will be so blessed. Zhang's patent significantly simplifies gene editing compared to other contemporary techniques, *e.g.*, TALEN and zinc fingers. Since Zhang's method allows one to basically reengineer any organism by modifying its own genome, it immediately opens up the possibility of engineering a variety of applications ranging from better agricultural crops (*e.g.*, drought resistant) to bio fuels to disease detection to personalised medicine (*e.g.*, by correcting the causative mutation), and, of course, of better understanding of gene functioning [26]. So, one expected development is the blooming of patent thickets. The financial stake around the CRISPR-Cas9 technology in the private sector is expected to be enormous and with patent thickets the potential for fierce litigation will be high. A likely development is that if exclusive licences do not create hurdles, companies would try to gather as many patent licences as they can to ensure their freedom to pursue their research and commercial goals. This could be an optimal solution for rapidly developing a plethora of products and processes that will in any case need a large number of players to chip in, much like the electronics industry, where there is space for many players to compete against and collaborate with.

8.3. Litigation

While research universities now see a patent portfolio as a potential source of revenue generation, few are enthusiastic or even prepared to enforce their patents, when infringed, through litigation. In the U.S., universities, by law, must participate as plaintiffs in enforcement lawsuits over their *exclusively licensed* patents regardless of a university's effective ability or enthusiasm to do so [59, 60]. Therefore to preserve licensing freedom, patent application preparation and its prosecution must be strategized to discourage litigation. Clearly, universities must maintain excellent technology transfer offices, whose members are not only "licensing and business development professionals" but who also "handle technologies from inception through research"; "handle conflict of interest issues"; close deals with commercial partners, and "then (God forbid)" participate in litigation to protect IP rights [61].

A few recent high profile cases indicate that the brave may sometimes inherit the earth. For example, in the Carnegie Mellon University (CMU) patent lawsuit against Marvell Technology Group, which allegedly appropriated CMU research for a computer chip used in high-speed drives, the jury awarded the university \$1.17 billion in December 2012 [62]. On appeal, Marvell was ordered to pay enhanced penalties of \$1.5 billion

for wilful infringement of CMU patents [63]. In another case, Varian Medical Systems, which allegedly infringed on the University of Pittsburgh patents for a respiratory device, a judge awarded \$85.8 million. Such cases have made other universities wonder if their technology transfer offices should get more aggressive in protecting patents [62]. Once a patent is infringed the alternatives are litigation or an out-of-court settlement. In litigation, the patent will almost certainly be dissected in terms of the doctrine of equivalents, prosecution history estoppel, the subjectively determined profile of the PHOSITA, applicable prior art relative to the patent, clarity of description of the invention, the breadth and narrowness of claims, etc. Litigation results are often uncertain. In the U.S., *e.g.*, some one-third of district court decisions on claim boundaries are reversed on appeal [64], while a large number of CAFC patent decisions have been reversed by the SCOTUS on appeal [52].

A commercially successful patent attracting litigation is a fair possibility because a patent's validity is not guaranteed. Post-grant a patent may be found invalid because of erroneous evaluation of the invention by the patent examiner during prosecution, or because he was simply blindsided by undetected prior art, etc. In addition, one must be prepared to deal with intentional predatory moves by patent trolls and the calculated overreach of some patent owners in asserting patent claims against non-infringing entities. Their general aim is to either drag the target into expensive litigation or force it into licensing agreements under the threat of litigation, which small and medium enterprises can ill afford.

9. Patent law reforms

Since Galileo (1564-1642), science has dramatically affected society. Industry, transportation, communications and medicine have all undergone such revolutionary changes that most mortals today appear to have semi-divine powers compared to pre-seventeenth century denizens of the world. The common man's focus has shifted from seeking divine favours to diligently acquiring human invented technological gadgets and services. Today,

Western industrial technology has transformed the world more than any leader, religion, revolution, or war. Nowadays only a handful of people in the most remote corners of the earth survive with their lives unaltered by industrial products. The conquest of the non-Western world by Western industrial technology still proceeds unabated. [65].

Yet some of these technological and scientific advances, such as genetically engineered plants and animals, human cloning, electronic surveillance, the use of robots, and now the possibility of genetically engineered humans raise serious moral and ethical issues, which demand legislative solutions and hence political intervention. If the track record of politicians, say, in handling problems related to climate change is any indication, we can expect synthetic biology related calamities to inundate us before they act. Their inadequate understanding of synthetic biology and the legislative process driven by one-person-one-vote electoral dynamics in a knowledge-driven society where knowledge creators and knowledgeable people constitute a

miniscule minority creates an anomaly. Intellect-driven legislations require an entirely different legislative process than mass-and-emotion-driven legislations. When laws of Nature and laws of man collide, catastrophe results.

9.1. Challenges

For patents to be an effective tool to promote innovation, they should be scarce and hard to obtain, especially in today's knowledge driven world, where the population of university educated people is far larger than it was several centuries ago when the modern patent system was instituted in England during the rule of Queen Elizabeth (reign: 1558 – 1603). An enormous knowledge gulf separates the PHOSITA of the Elizabethan era and of today. The biggest challenge patent examiners face today is the objective profiling of the modern biotechnology PHOSITA whose profile is prone to rapid changes, sometimes within months.

The second challenge is related to patent seeking researchers whose desire is to seek patents in anticipation that their discoveries will eventually, but during the lifetime of a patent, lead to substantial, if not miraculous, benefits to society that truly touches peoples' lives. The challenge patent examiners face here is, whether or not the applicant is claiming a 'law of Nature', or whether granting a patent will be against the interests of society (*e.g.*, patents on nuclear weapons are banned), such as creating obstacles to further research or advancement of the invention.

The third challenge is fulfilling the need for a new patent system that would minimize litigation. When patent offices are inundated with patent applications in highly competitive cutting-edge technology areas populated with extremely well qualified PHOSITAS, determining overlapping claims among applications is an incredibly demanding task, and therein lies the source of debilitating and fierce future litigations. Current legal systems are visibly deficient in handling such litigations so remedies may lie elsewhere, *e.g.*, in the form of peacemakers among feuding parties.

The fourth challenge is providing adequate scientific research support to the judiciary. It needs a permanent science advisory body to enhance its understanding of the scientific basis on which biotechnology patent claims rest and in creating a plausible PHOSITA profile acceptable to the scientific community on a case-by-case basis. This will substantially simplify and accelerate judicial proceedings in biotechnology patent litigation and lead to greater consistency in judicial decisions. The science advisory body can bring about greater clarity to the vexing question: "When is obvious-to-try the same as obviousness?" in relation to the profiled PHOSITA.

The fifth challenge is integrating introductory IPR courses in science and engineering curricula in universities to bring home to students the paramount economic relevance of their acquired scientific and technical knowledge and skills.

9.2. Questions

The fact that synthetic biology involves the creation of artificial living matter or modification of living matter through human intervention raises important questions related to biosecurity,

biosafety, bioethics, and environmental health and sustainability. Their answers will require consultation with engineers, scientists, attorneys, innovators, teachers, students, policymakers, and ordinary citizens. However, before doing so society must decide how synthetic biology as a scientific discipline is to be handled. That is, establish rules and regulations of ownership, diffusion, and access to the knowledge the discipline generates and accumulates. Concurrently, to further the bio-economy, it must establish global engagement and collaborative models, mentor and nurture young leaders, create next-generation manufacturing facilities, and address standards-related issues. The crucial questions are:

- When do basic research results benefit society most if placed in the public domain as opposed to limited period IP monopoly of those results?
- When it is appropriate for industry to seek private ownership of inventions derived from the results of open innovation?
- When is an open innovation policy in synthetic biology likely to discourage industry from developing commercially viable products and processes?

Johnson [66] notes that synthetic biology needs “public policies and collaborative mechanisms that promote broad and robust pre-competitive openness, sharing, and access” and “strong and robust IPR” to enable “later-stage economic value creation, IPR-enabled commercialization, and market-based investments”. They will indeed help in aligning international investments, in framing lab-to-market policies, and in creating global manufacturing and marketing policies to facilitate global commerce.

9.3. Harmonization

There are serious obstacles to globally harmonizing patent laws [67]. Disparate national laws have caused a number of complicated cross-border IP disputes and multiple infringement suits. For example, software and business method patents are permitted only in some countries. Even when patent laws are similar in two countries, their interpretation by the courts may vary widely. Patent laws operate on the principle of territoriality and the needs of individual nations. Thus in a globalized, knowledge-driven economy, technologically advanced nations support strong patent protection to spur innovation, while the less advanced see it as barriers erected to restrict their access to new goods and dilute their welfare programs. Current national patent laws embody premises and concepts that were shaped by the Industrial Revolution; they are not malleable enough for the knowledge and information-driven age that has given rise to such exotic technologies as nano-technology, information technology, biotechnology, and robotics (and in the future, possibly bio-robotics). Today’s inventor is frequently university educated or a researcher or a member of a large R&D team rather than an artisan or a technician. There is thus an acute need for harmonization of patent law and its enforcement. The assumption is that a uniform legal system would reduce legal uncertainties, cost of litigation, and barriers to trade. Other potential benefits include liberalized technology transfer and increased foreign direct investment from developed countries to the developing and underdeveloped countries and thus raise living standards globally. Ideally, harmoniza-

tion would improve the world's capacity to innovate as a whole, which would be greater than the sum from its parts.

The World Intellectual Property Organization (WIPO) has been leading harmonization efforts. It currently administers the Patent Cooperation Treaty (PCT), the Paris Convention, the Patent Law Treaty, the Budapest Treaty, and the Strasbourg Agreement. However, these are not enough. WIPO's Standing Committee on the Law of Patents (SCP), created in 1998 to spur substantive harmonization efforts, has a wide representation of interested parties. So far, their deliberations have resulted in the Patent Law Treaty in 2000. Its modest aim is to harmonize formal procedures, *e.g.*, related to the filing date for a patent application, the form and content of the application, and representation. During 2001-2006, discussions on framing a Substantive Patent Law Treaty generated enough disagreements that they were put on hold in 2006. The SCP has since focused "on building a technical and legal resource base from which to hold informed discussions in order to develop a work program" while larger issues related to exceptions and limitations to patent rights; technology transfer; quality of patents, including opposition systems; confidentiality of communications between patent advisors and their clients; and patents and health hibernate.

Clearly, a bold experiment in universalising IPR governance and rule of law is sorely needed. Present disparities in IP laws and innovation capabilities among nations have created a "creditors and debtors" relationship where creditors appear to impose conditions that would perpetuate their dominance over debtors via institutions such as the WTO. Biotechnology provides strategic socio-economic advantages to creditor nations because of their research universities. This means that flight of capital and talent to countries with top research universities coupled with their liberal immigration policies for researchers can quickly deplete the talent pool of debtor countries. Of course, smart creditors know that helping debtors improve their circumstances makes for better, amicable, long-term, diversified, and more profitable business. Helping debtor countries build world-class universities would be one such example.

However, for synthetic biology, there is more to IP protection than just utility patents. Products arising from DNA synthesis and construction may also qualify as human authored original "literary work and artistic works" and hence eligible for copyright protection. Further, DNA is an information carrying molecule much like a computer program, which too is copyrightable. Likewise synthetic biology motifs can be used as trademarks and tacit knowledge locked up in a researcher's mind and selectively shared may deserve trade secret protection. And, of course, one can seek design patents for novel DNA designs.

10. Conclusions

The genetic uniqueness of each individual implies the existence of numerous undiscovered non-trivial interactions in the human genome that would make linking individual factors to a disease condition highly complex. These interactions, due to inheritability, must account for

family history to correctly interpret genotyping results to provide personalised medical treatment. Indeed, they must go beyond and ask how a given genome copes with a dynamic environment. The magnitude of this task has propelled the convergence of life sciences with other fields, *e.g.*, physics, chemistry, mathematics, computing, engineering, social sciences, etc. in search of new and innovative solutions. A recent NRC study notes [68]:

The scientific opportunities enabled by convergence—the coming together of insights and approaches from originally distinct fields—will make fundamental contributions in our drive to provide creative solutions to the most difficult problems facing us as a society. This convergence provides power to think beyond usual paradigms and to approach issues informed by many perspectives instead of few.

Synthetic biology makes personalised medicine appear within reach in terms of developing personalized drugs and diagnostics, minimizing adverse drug reactions, and personalising treatments by enabling people to make personalized health decisions. However, to take research results from the lab to the patient's bedside, to the community (translational application) and finally make it accessible to every human on Earth is a colossal endeavour that calls for a very high level of convergence. The time has come for governments to frame policies that would enable the desired convergence. The U.S. government, *e.g.*, is discussing a “modular” policy [69] with public participation. A module, *e.g.*, may include education, basic research, and infrastructure; another that promotes market-oriented innovation through R&D tax credit, intellectual property policies, etc.; and yet another for catalysing breakthroughs in such areas as clean energy, biotechnology, nanotechnology, advanced manufacturing, information technology, and space technologies.

Genomics researchers are the new super-stars of science. A Thomson Reuters report provides a listing of authors who have written multiple highly cited reports and have thereby demonstrated their tremendous influence on ongoing research in their respective fields. Out of the seventeen hottest researchers a dozen belong to genomics [70]. Not surprisingly, the US sits atop the genomics-related patent filings heap, trailed by Europe and Asia, indicating the dominance of the U.S. both in research and its translation. [71]. An enigmatic world order is in the making.

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