The Difference between Discovery and Invention in Biomolecules and Biologicals

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I. INTRODUCTION

Inventions based on biological systems are never entirely the result of creative endeavour, as are mechanical or electrical inventions, and most often require the intervention of a biological system either to create or to verify. Biological systems are complicated and their intricacies are often not fully known even after a patent has been filed. Biologically based inventions are the magical equivalent of putting a silk scarf into a hat and pulling out a rabbit, resulting in patent claims to the scarf and the rabbit, the antigen and the antibody, but not to the awesome magical hat.

As with the magic tricks that amaze us, planning and performing the biological transformation to arrive at a truly useful invention requires more effort, knowledge, and creativity than initially apparent to the casual observer. Decisions about which gene to pursue or which protein to characterize after an initial discovery are only the beginning. Although patents have been granted for nucleic acid and amino acid sequences worldwide for near thirty years, it is clear that the patent system deals very poorly with biomolecule and biotechnology based inventions. For one thing, the subject of biomolecule patents are nearly all fragments of pre-existing sequences that were isolated and/or discovered by researchers (for example claims to genes), or the result of exposing biological systems to manipulation (for example claims to antibodies).

The solution to the practical problem of, for example, arresting or arresting the growth of cancer cells, is an invention that it is incumbent upon us to protect. As companies try to patent new isolated biomolecules and biotechnological inventions derived from biological constructs, the issues surrounding what constitutes patentability in biotechnology will become increasingly complex, far more so than those which arise in the small molecule pharmaceutical cases which are currently monopolising the time of Federal Courts.

This article delves into the science of biomolecules and biotechnology and why it is important to provide robust legal protection for this class of inventions within the patent system, and what is at stake if the International patent system fails to do so.

II. THE DIFFERENCE BETWEEN DISCOVERY AND INVENTION

a. The Finder and the Maker

In the fall of 1996, the world of DNA sequencing was very different than it is now. The good race was being carried out in labs all over the world as scientists took part in the greatest project of the day: the sequencing of the human genome. The Human Genome Project was a high priority for the United States Department of Energy and the National Institutes of Health, as it was thought that a sequence of the human genome would be the key to understanding human physiology and disease. On a more spiritual level, many scientists as well as the general public believed that if we could read a human DNA sequence, we would be able to understand the book of life, the set of rules that govern who we are and how we became who we are, individually as well as a species. Like landing on the moon, sequencing the human genome was the next intuitive step in our society's technological advancement and demonstrated our mastery of science. Although we have learned much since the sequence was officially completed in 2003, the genome sequence was not the Rosetta Stone that translated DNA into a clear understanding of what makes you and me. Science, of course, is far more complicated than that.

Consider, for a moment, that your own cells could serve as prior art based on the DNA, RNA, protein and carbohydrate biomolecules contained within them. Would a patent to your entire DNA sequence be valid? What about an naturally occurring protein or fragment of RNA within them? These are ridiculous questions, to be sure, but like the ancient practice of *reductio ad absurdum*, to find the relevant it is often useful to begin by ruling out the absurd.

The United States is presently is wrestling with the question of whether isolated fragments of DNA are patentable in the Myriad Genomics case[1]. (DNA does not occur in isolated fragments in nature.) The Myriad case involves two patents directed to the DNA sequences of breast cancer genes, and the uses thereof in the detection of breast cancer. Since the mid 1990s it has been known that single mutations on the BRCA1 and BRCA2 genes predict increased susceptibility of both women and men to breast cancer[2], both genes which are at issue in Myriad. For an good review on the race for BRCA1 and BRCA2, see Williams-Jones[3]. One Myriad patent[4] issued in Canada without fanfare last year, including claims to a method of determining a person's predisposition to cancer by sequencing that person's particular tumour suppressor gene and comparing it to a known non-mutated wild type. By obtaining a patent on this gene, Myriad has effectively prohibited anyone without a licence from sequencing a particular area of your genome. By analogy, this can be seen as equivalent to prohibiting you from reading a book in your own personal library.

Under the right circumstances, gene sequences must be patentable. The relevant question is, what fraction of your genome is patentable, and under what circumstances? In section 2 of the *Patent Act*, the definition of invention provides the entire scope of patentable subject matter allowed in Canada as follows:

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[1] An excellent review of the ongoing Myriad case: Andrew Cohen, "Nature vs. Nurture: The Continuing Sage of the Gene Patenting Case" *The Atlantic* (3 April 2011), online: The Atlantic <http://www.theatlantic.com/national/archive/2011/04/nature-vs-nurture-the-continuing-sage-of-the-gene-patenting-case/73359/>

[2] D. Ford *et al.*, "Genetic Heterogeneity and Penetrance Analysis of the BRCA1 and BRCA2 Genes in Breast Cancer Families" (1998) 62 Am. J. Hum. Genet. 676-698 at 676.

[3] Bryn Williams-Jones, "History of a Gene Patent: Tracing the Development and Application of Commercial BRCA Testing" (2002) 10 Health L.J. 123-146.

[4] "GERMLINE MUTATIONS IN THE MTS GENE AND METHOD FOR DETECTING PREDISPOSITION TO CANCER AT THE MTS GENE", Can. Patent No. 2162150, PCT Patent Publication WO1995/25813 (17 March 1995).

> "invention" means any new and useful art, process, machine, manufacture, or composition of matter, or any new and useful improvement in any art, process machine, manufacture, or composition of matter;

Section 27(8) of the *Patent Act* provides a statutory restriction on the patenting of "any mere scientific principle or abstract theorem", although it is clear that biomolecules including DNA fall squarely within the "composition of matter" category in the definition of invention and are not a mere scientific principle. With respect to the patentability of DNA as well as other biotechnology-based inventions, simply applying the Sanofi test[5] for anticipation, specifically for the disclosure requirement, is not sufficient.

In mechanical inventions where the components are entirely human-made, it is a fairly simple task to discern whether an invention is new. One may ask: "Is one of the components new?" or, "Is the combination of components assembled in a new way to arrive at an unexpected result?" In the field of biotechnology, however, where many inventions are either isolated from existing biological soups (for example DNA or enzymes) or made using life processes (for example antibodies or artificial organs), the novelty is in the discovery of the biomolecule or bio-system and its utility.

b. <u>What is a Biomolecule</u>

If there is one thing you need to know to understand the basic mechanism of life, it is that DNA, the code of life, is transcribed into RNA, and RNA is translated into protein which constitutes the machinery of the cell. Biomolecules of many different flavours are entering the patent system; the following overview explains the structures of each of the main types to give the reader a deeper understanding of the issues at hand.

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[5] *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61, [2008] 3 S.C.R. 265 [*Sanofi*].

DNA in your cells consists of long, tightly wound double strands that form chromosomes. Each double strand consists of many millions of base, or nucleic acid, pairs, like beads on a very long string. On each chromosome strand can be found multitudes of genes, each a section of DNA that contains the code for a protein or section thereof. When a particular stretch of DNA is unwound, RNA is assembled to match the unwound DNA strand, and the RNA travels to a ribosome where it can be translated into the protein molecule that is encoded by the DNA.

Subject matter that has been found patentable in Canada includes DNA fragments, plasmids (short stretches of circular DNA), RNA of all sorts, small proteins having a molecular weight in the hundreds, large proteins including antibodies with molecular weights in the hundreds of thousands, and methods of use of these biomolecules.

Although we have the capacity to sequence long stretches of DNA, it is often unclear what the exact function of the encoded gene is. The difference between the DNA sequence of two individuals, whether a single base change or deletion, or the insertion of deletion of longer stretches of DNA, can have drastic effects, or no effect at all, depending on where or what the change is. Also, the DNA sequence that codes for a protein usually isn't contiguous, meaning long stretches of bases must be excised prior to translation. In Laurence Hurst's recent column in Nature, he suggests that genetic mutations that look silent, in other words that don't change the protein sequence, may have an effect on how efficiently the mRNA is transcribed, and thus on human phenotype in, for example, Crohn's Disease[6].

Further complication comes when considering that the sequence or chemical structure of a protein is but one component of its nature -- without proper folding, the protein will have no biological function. Some proteins are made up of multiple smaller proteins and do not function

[6] Laurence D. Hurst, "The Sound of Silence" (31 March 2011) 471 Nature 582.

without all of their components; others only function if they are embedded in fatty cell membranes such that their structure when assembled away from the membrane renders them entirely useless. Applying Consolboard[7] to protein biomolecules, for example, doesn't work -- as three dimensional structure of a protein is rarely described in protein patents, there will be many instances where a claimed embodiment will simply not do what the Specification promises it will do.

c. <u>Anticipation and Public Disclosure</u>

In 2008, the law on anticipation in Canada was reconsidered and set out in the Supreme Court decision in Sanofi[8], wherein it was determined that for a disclosure to be considered anticipating, it must both disclose and enable the practice of the invention. In the field of biomolecules, enablement is usually within the common knowledge of the skilled person. There are tomes and textbooks with step-by-step instructions on how to isolate, purify or detect just about any biomolecule. How to manufacture antibodies, isolate proteins and nucleic acid fragements, and how to sequence DNA are among the standard skills of a biological scientists to whom biotechnology patents are directed. Nowadays there are also a multitude of companies where for a pittance and a few days wait can buy you an antibody to any antigen you can dream up.

In the recent Immunex decision of the Patent Appeal Board[9], the Commissioner finally conceded that monoclonal antibodies could be claimed without a working example in the original description, as the methods of making such antibodies were well known to the skilled

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[7] *Consolboard Inc. v. MacMillan Bloedel (Sask.) Ltd.*, [1981] 1 S.C.R. 504 at p. 525.

[8] FIX THIS TO IBID at p.

[9] *Re Immunex Corporation Patent Application* (2010), 89 C.P.R. (4th) 34 (Patent Appeal Board and Commissioner of Patents).

person on the claim date. For patent practitioners who have been trying in vain for years to get claims to monoclonal antibodies for their clients, this is a victory, and perhaps an admission by the Patent Office that the previous decision of Institut Pasteur[10], which they had been using to justify rejection of such antibodies for so long, was very out of date. More and more, the disclosure of the invention in a biotechnology patent is sufficient to support the claims. Enablement in biotechnology is now more a matter of long hours spent following standard protocols in the lab.

It is clear that possessing a particular biomolecule in your cells does not constitute an anticipatory disclosure. By analogy, if a plant is known to have antibiotic properties, an extract of the plant is not patentable since its special property is known. However, the active antibiotic identified and isolated from the plant may be patentable. In the strange UK case of Merrell Dow[11], affirmed by Hughes J in the Abbott Clarithromycin case[12], Lord Hoffman ruled that claims to a compound that existed only in the body were anticipated by public disclosure, even if no one had ever analysed it. Hughes J commented on the Merrell Dow case as follows:

> [72] ...The issue in that case was whether a claimed pharmaceutical had been previously disclosed by use. The previous use was by way of metabolism in the human body, that is, a related but different pharmaceutical composition was swallowed but, in the liver it changed to some extent. It was "metabolized" and became the chemical claimed in the patent at issue. Nobody had conducted an analysis, however, at any previous time as to what if anything was happening in the liver. The "metabolite" itself had not been previously identified. Lord Hoffmann held that there was sufficient anticipation to invalidate the claimed invention. In doing so, he relied on a case in the European Patent Office which held that a patent claiming a process for making flavour concentrates from vegetable or animal substances by extraction with fat solvents under pressure in the presence of water was anticipated by old cookbook recipes for pressure cooking chicken or stews. Nobody knew that flavour concentrates were being extracted but it was being done; hence the claim was anticipated. As he said at

[10] *Re Institut Pasteur Patent Application* (1995), 76 C.P.R. (3d) 206 (Patent Appeal Board and Commissioner of Patents).

[11] *Merrell Dow Pharmaceuticals Inc. v. H.N. Norton & Co.. Ltd.*, (1995), [1996] R.P.C. 76 (H.L.) [*Merrell Dow*].

[12] *Abbott Laboratories v. Canada (Minister of Health)*, 2008FC 1359, [2009] 4 F.C.R. 401 at para. 72 [*Abbott Clarithromycin*]

> page 90 lines 8 and 9 "if the recipe which inevitably produces the substance is part of the state of the art, so is the substance".

Following from Lord Hoffman, it would seem evident that naturally existing biomolecules are anticipated by public disclosure just by the nature of their existence, even if they have never been isolated or analyzed. This may be true if the invention is the biomolecule itself, but as argued above, the invention of the biomolecule is in its identification *and the disclosure of its utility*, not simply the biomolecule itself. To quote the Commissioner, a substance, even if it is novel, it not patentable unless it has a use.[13].

In Baker Petrolite[14], Rothstein J. considered the requirements that would lead to a finding of public disclosure for the purpose of anticipation, paraphrased below. To put the quote into the context of biomolecules, consider the concept of prior sale as a public disclosure:

1. Sale to the public or use by the public alone is insufficient to prove anticipation. To be part of the state of the art, the invention must have been made available to the public.
2. For a prior sale or use to anticipate an invention, it must amount to "enabling disclosure". The disclosure has to be such as to enable the public to make or obtain the invention.
3. The prior sale or use of a chemical product will constitute enabling disclosure to the public if its composition can be discovered through analysis of the product.
4. The analysis must be able to be performed by a person skilled in the art in accordance with known analytical techniques available at the relevant time. The person skilled in the art, using available analytical techniques, must be able to find the invention without the exercise of inventive skill.
5. When reverse engineering is necessary and capable of discovering the invention, an invention becomes available to the public if a product containing the invention is sold to any member of the public who is free to use it as she or he pleases.
6. It is not necessary to demonstrate that a member of the public actually analysed the product that was sold. Thus an anticipating description in a book will invalidate a patent if the book is on a shelf of a library open to the public, **whether or not anybody read the book** and

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[13] *Commissioner of Patents v. Ciba Ltd.*, [1959] S.C.R. 378

[14] *Baker Petrolite Corp. V. Canwell Enviro-Industries Ltd.*, 2002 FCA 158, 211 D.L.R. (4th) 696 at para. 42 [*Baker Petrolite*]

whether or not it was situated in a dark and dusty corner of the library. If the book is available to the public, then the public have the right to make and use the information in the book without hindrance from a monopoly granted by the State. [Emphasis added.]

7. The amount of time and work involved in conducting the analysis is not determinative of whether a skilled person could discover the invention. The relevant consideration, in this respect, is only whether inventive skill was required.

The chemical technology considered in the Baker Petrolite decision was the removal of hydrogen sufide from natural gas (also known as 'sweetening') using a mixture of two commonly available chemicals (monoethanolamine and formaldehyde). The Court decided that as the chemical mixture was available to the skilled person to do with as he pleased, and since the analytical techniques to reverse engineer the two-component mixture were also available to the same skilled person, the unconditional release of the mixture into the public domain prior to the claim date constituted a public disclosure and therefore anticipated the Baker Petrolite patent.

What if the mixture was instead a cell comprised of a multitude of biomolecules, and the analytical techniques to analyse the contents of the cell were readily available and known to the skilled person on the claim date? This is an oversimplification to be sure, but it is important to consider how the exponential increase in complexity between a binary chemical mixture and the biological soup that is the cell changes the inventive concept from the chemical mixture itself (composition of matter and use thereof) to the identification and isolation of a biomolecule with a particular use from an ocean of other biomolecules.

Realigning the inventive concept as such, there is no question that if the subject biomolecule demonstrates its required modicum of utility when isolated from its endogenous biological system, then it has satisfied the requirements of utility, novelty and inventiveness

required for patentability. As stated in the landmark Supreme Court decision of Free World Trust[15]:

> The grant of a patent depends on the inventor giving to the public something it did not have before. If the public already has it, then the inventor gives nothing and is not entitled to anything in return, i.e. a monopoly for a period of years.

An biomolecule isolated from its natural state is something that the public did not have before. Whether or not it existed (and was available for analysis) prior to the claim date as is the case with many proteins and fragments of DNA, or whether its previous existence is unknown as is the case with novel antibodies, the step of isolation and finding of utility launches a biomolecule firmly into the realm of patentable subject matter.

III. PATENT NOT COPYRIGHT IN SEQUENCES

a. The Infinite Monkey Theorem and Evolution

The myth that an army of monkeys typing at random could eventually arrive at the complete works of Shakespeare, termed 'the Infinite Monkey Theorem' is peppered through modern literature[16]. The Monkey Shakespeare Simulator Project ran from July 2003 to 2007 to virtually reproduce random typing of characters on a typewriter in an attempt to demonstrate the mathematical improbability of the infinite Monkey Theorem. After virtually generating more than 10^{35} pages of text (equivalent to 2,737,850 million billion billion billion years of random monkey-typing), the longest string of characters which matched *any* fragment taken from Shakespeare was a mere 24 characters long. Though mathematically not impossible, the improbability of the desired result was soundly demonstrated.

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[15] *Free World Trust v. Électro Santé Inc.*, 2000 SCC 66, [2002] 2 S.C.R. 1024 at para. 13 [*Free World Trust*].

[16] A poignant reflection and mathematical analysis of the Infinite Monkey Theorem is presented in: John D. Barrow, *100 Essential Things You Didn't Know You Didn't Know: Math Explains Your World* (New York: W.W. Norton & Company, 2010) at ch. 3.

In Section 2 of the *Copyright Act*, a "book" is defined as a volume or part or division of a volume, in printed form. Without delving into a treatise on the evolution of written language from hieroglyph to syllabary and the meaning of 'print' as it relates to the meaning of individual letters[17], suffice it to say that as English words are represented by syllabary of representational letters, so can a sequence of nucleic or amino acids represented by a series of letters. Put the sequence into 'printed' or fixed form, whether electronic or on paper, and it can be argued that one has created a book. Overlooking who or what one might consider to be the 'maker' or 'author' of the biological sequence, let us simply agree that the human sequences within us are substantially shared, and are therefore owned by all of us collectively. Insofar as my code may be slightly different from yours, I consider myself the owner and author of my own mutations and the genes that contain them, and you the owner and author of yours. Further, since all the techniques to discover these mutations are fully known to the skilled person and only require time and effort to find rather than ingenuity, my sequence and yours are therefore in the public domain.

In his book on Copyright Law, David Vaver[18] identifies one of the key features of copyright protection as follows:

> Only original work is protected. This stipulation does not mean new work, but simply that the work must originate from the author, cannot be copied, and must involve some minimal intellectual effort.

For a work to be copyrightable it must be original, fixed, and creative. Unless you have an identical twin or clone, and even if you do, no one in the world past, present or future will have the same DNA sequence as you have in every one of your cells. However novel, by any evaluation our resident biomolecules did not originate by any intellectual effort of any human,

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[17] For an imminently readable review of the evolution of the written language, see *Maryanne Wolf, Proust and the Squid (New York: Harper Perennial, 2006).*

[18] David Vaver, *Essentials of Canadian Law – Copyright Law* (Concord, Ontario:Irwin Law, 2000) at 29.

and are therefore not 'original' in the parlance of copyright. Further, our biomolecules required no intellectual effort on our part to create, and many are necessarily copyable by their nature. Regardless, their structure may also be considered to be similar to copyrightable musical score or labanotation (choreographic score), which are instructions for the recreation of a musical or dance performance, respectively, in a similar fashion as a DNA sequence can contain instructions for the creation of a protein.

A review of why DNA sequences are not amenable to copyright protection was discussed by James Silva in 2000[19]. The applicability of copyright protection to DNA was soundly rejected by Silva, nominally because a DNA sequence is not original or creative. To the skilled person with the assistance of accessible and available technology, any sequence in the human genome is available to be read. With respect to chemical compositions as stated Baker Petrolite[20], "if its composition can be discovered through analysis of the product" using techniques known and available to the skilled person on the claim date, then it is considered an enabling public disclosure, even if no one had yet done so."

As discussed above, the invention in a biomolecule is not in its discovery or reverse engineering, but in identifying a particular sequence that has a yet unknown utility. So, a biological sequence is akin to a book on a shelf in a library in a mountain monastery in a faraway land, a book containing a really good secret -- publicly available and fully accessible to the skilled person willing to go out of her way to retrieve it with an unknown location. The invention is in the discovery of the location of the library and the identification of the book.

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[19] James G. Silva Esq. "Copyright Protection of Biotechnology Works: Into the Dustbin of History?" *2000 B.C. Intellectual Property and Technology Forum 012801* (28 January 2000), online: <http://www.bc.edu/bc_org/avp/law/st_org/iptf/articles/content/2000012807.html>.

[20] *Supra* note 14 at para. 24.

The publication of the human genome has turned the inventive work of science into seeking new or altered genes as targets for intervention, figuring out what sequences do, where they begin and end, and how they can be used to beneficial effect.

b. <u>Fair Use</u>

From the infringement perspective, if one or your isolated genes is patented, is your use of that gene in your own body considered fair use? For many reasons, the answer is a resounding yes, in spite of the following:

1. A gene is a small stretch of DNA on a long double strand, however when 'exploited' or used exists as smaller fragments of messenger RNA (mRNA) within the cell, so a claim to an isolated nucleic acid sequence may very well encompass the sequences that your cells transcribe.
2. mRNA can be easily isolated from the cell and sequenced using available techniques known to the skilled person.
3. A person can not control the endogenous use or *exploiter* of his own genetic material.

Similar to copyrighted music, companies like Myriad discussed above would never pursue the individual user for possession or use of their two copies of the patented sequences as it is neither feasible nor profitable. However, should your doctor or medical testing company seek to utilize the gene for the purpose of determining your genotype, you can be sure that Myriad wouldn't miss the opportunity to assert its rights.

During the trial preceding the decision of the Supreme Court of Canada in Monsanto[21], farmer Percy Schmeiser led extensive evidence to demonstrate that he neither intentionally used canola seeds containing the patent protected glyphosate-resistant gene, nor did he want to use the same. Regardless, it was found that Mr. Schmeiser did make use of the Monsanto gene, whether

[21] *Monsanto Canada Inc. Schmeiser*, 2004 SCC 24, [2004] 1 S.C.R. 902 at para. 58 [*Monsanto*].

or not he intended or desired to. In the decision, McLachlin C.J. and Fish J. considered what constitutes determination of "use":

> 1. "Use" or "*exploiter*", in their ordinary dictionary meaning, denote utilization with a view to production or advantage.
>
> 2. The basic principle in determining whether the defendant has "used" a patented invention is whether the inventor has been deprived, in whole or in part, directly or indirectly, of the full enjoyment of the monopoly conferred by the patent.
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> 3. If there is a commercial benefit to be derived from the invention, it belongs to the patent holder.
>
> 4. It is no bar to a finding of infringement that the patented object or process is a part of or composes a broader unpatented structure or process, provided the patented invention is significant or important to the defendant's activities that involve the unpatented structure.
>
> 5. Possession of a patented object or an object incorporating a patented feature may constitute "use" of the object's stand-by or insurance utility and thus constitute infringement.
>
> 6. Possession, at least in commercial circumstances, raises a rebuttable presumption of "use".
>
> 7. While intention is generally irrelevant to determining whether there has been "use" and hence infringement, the absence of intention to employ or gain any advantage from the invention may be relevant to rebutting the presumption of use raised by possession.

The decision in Monsanto was based entirely on exploiter, meaning whether or not Schmeiser made use of the patented gene; the issue of patentability of the gene was considered settled and was intentionally not discussed by the court.

Having regard to the Monsanto decision, there is no question that use of the contents of your own body can not be construed as a commercial gain. Yet, a patented gene is most likely a "significant or important part" of your body, whether or not you fully understand or can control its function. Furthermore, a gene is only the instructions for making the functional component of your cell, namely the protein product of the gene, and is certainly not the only control factor in the production of other associated biomolecules.

With the advent of gene patenting, there are now patented genes present throughout our bodies: they just happened to be incorporated in their natural long double stranded state. Your particular copies of the genes might not be exactly as in the patented sequence listing, but many patents include within their claims that a certain degree of sequence variation, for example a change of up to 30% of the nucleic acids in the sequence may be altered while the patentee retains a monopoly on the variable sequence. In biological terms, a sequence with only 70% of the DNA the same could code for a protein (the ultimate use of most DNA, as far as we know today) that is entirely different than the one coded by the original DNA sequence, albeit with the implicit understanding that the product retains the same utility as the original. To analogize, it would be similar to taking a claim to a motorcycle, swapping out half the parts, and arguing that the original claims also encompass a child's tricycle.

IV. BIOLOGICALS AND JURISPRUDENCE

a. Canadian and International Jurisprudence

The patentability of biomolecules and biologicals was established in the U.S. case of Diamond v. Chakrabarty[22] and the similar Commissioner's decision in the Application of Abitibi Co.[23] These two applications claimed a genetically modified microorganism capable of environmental remediation: Chakrabarty's a bacterium for oil spill cleanup; and Abitibi's a yeast culture mixture for breaking down the sulfite by-products of pulp and paper processing. Chakrabarty took a bacteria which had no innate ability to degrade oil and genetically modified it to insert a plasmid, or circular stretch of DNA, to create a stable bacterium capable of converting hydrocarbons into simple metabolites using enzymes coded for by the plasmid. The origin of the

[22] *Diamond v. Charkrabarty*, 447 U.S. 303 (1980).

[23] *Re Application of Abitibi Co.* (1982), 62 C.P.R. (2d) 81 (Patent Appeal Board and Commissioner of Patents) [*Abitibi*].

plasmid was from a different bacterial genus than that of the host bacteria, and so the combination, he argued, would not normally occur in nature and required the skill and inventive step of the inventors to come into existence, thus rendering the resulting bacterial strain patentable.

In the invention of Abitibi, a microbial culture of five different strains of yeast, all of which were previously known and naturally occurring in sewage, were isolated and found to have utility in the breakdown of waste sulfite liquor when cultured together. In Abitibi, the inventive step was the selection and isolation of the useful yeast strains from sewage, and the application of those strains in a new process. As the yeast strains were not normally found in waste sulfite liquor, the living yeast matter was deemed to be the product of human intervention and ingenuity; the resulting culture with utility in remediation was determined not to be a product of nature, but rather an entirely new culture with improved properties and certain patentability. As stated by the Commissioner in Abitibi[24]:

> Certainly this decision will extend to all micro-organisms, yeasts, moulds, fungi, bacteria, actinomycetes, unicellular algae, cell lines, viruses or protozoa; in fact to all new life forms which are produced en masse as chemical compounds are prepared, and are formed in such large numbers that any measurable quantity will possess uniform properties and characteristics.

In Re Application of Abitibi[25], the Patent Appeals board considered under what circumstances organisms might be considered patentable subject matter:

> The organism, to be claimed, should not of course have existed previously in nature, or in that event the "inventor" did not create it, and his "invention" is old. It must also be useful, in the sense that it carries out some useful known objective, such as separating oil from sand, producing antibiotics or the like. It cannot be a mere laboratory curiosity whose only possible claim to utility is as a starting material for further research. And it must be sufficiently different from known species that it can be said that its creation involved the necessary element of inventive ingenuity.

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[24] ibid., at 89.

[25] *Ibid.*, at 91.

To have utility, the invention must also be operable, controllable, and reproducible, meaning that the subject matter of the invention must be reliably manufacturable such that the desired result must inevitably follow when the invention is put into practice[26]. In the case of Abitibi, not only was the yeast culture easily reproducible, but so was the promised utility. So was the precedent set for the patentability of unicellular organisms, which aligned the Canadian patent system in this respect with United States patent law.

In my memory, the most recent episode in Canadian History where a pro-life lobby came out in force was in 2002 when the Harvard Mouse case was being considered by the Supreme Court. Siding with strange bedfellows as the Sierra Club and Greenpeace, the Canadian Council of Churches and Evangelical Fellowship of Canada emerged to pressure the Supreme Court not to allow a patent on the Harvard oncomouse, thus setting Canada apart from most major International jurisdictions. In the Harvard Mouse case[27], the Supreme Court considered whether the definition of invention in Section 2 of the *Patent Act* encompassed higher life forms within the categories of "manufacture" or "composition of matter". In the decision, the Court reminded us that neither the Commissioner of Patents nor the Supreme Court itself has the discretion independent of the *Patent Act* to consider the public interest when granting or denying a patent, and that the judicial role of the Court is simply to apply the law as provided by Parliament. Accordingly, the question addressed by the Supreme Court was not *whether* higher life forms should be patentable, but whether higher life forms fall within a fair interpretation of the *Patent Act* as passed by Parliament. As stated by Binnie J in his dissenting judgement in paragraph 10:

> The proper question is not whether Parliament intended to include "oncomice" or "higher life forms" or biotechnology generally in patent legislation, but whether

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[26] Canadian Intellectual Property Office, *Manual of Patent Office Practice* (Ottawa: Industry Canada, 2010) at sections 12.08.01-12.08.02.

[27] *Harvard College v. Canada (Commissioner of Patents)*, 2002 SCC 76, [2002] 4 S.C.R. 45 [*Harvard Mouse* or *Harvard*].

> Parliament intended to protect "inventions" that were not anticipated at the time of enactment of the *Patent Act*, or indeed, at any time before the claimed invention.

There is no question of the utility of the oncomouse -- a result of the infection of a mouse embryo with a gene that causes cancer, the resulting oncomouse has greatly assisted researchers in the discovery, development and evaluation of human cancer drugs. As was determined in the Commissioner's decision and not refuted in the courts, the oncomouse invention was undeniably new and non-obvious. Patented in major jurisdictions in Europe including the United Kingdom, Germany and France, as well as in the United States, this Supreme Court decision stands out as an outlier in international patent law.

There is no question that we need to promote the biotechnology offered by the oncomouse. As stated in paragraph 18 of Harvard:

> This is not to suggest that because something is beneficial it is necessarily patentable. As stated, such value judgements have been excluded from the administration of the *Patent Act*. It is to say, however, that the massive investment of the private sector in biotechnical research is exactly the sort of research and innovation that the *Patent Act* was intended to promote.

With the hoopla that came with the oncomouse case, many parties on both sides expected Parliament to take up the issue and amend the *Patent Act* to address new areas of biotechnology that were not be easily addressed by current law. However this did not occur, and the *Patent Act* remains ambiguous with respect to the patentability of the most exciting new areas of biotechnology.

Directive 98/44/EC of the European Parliament on the legal protection of biotechnological inventions (1998) [28] provided an early framework for addressing the inevitable "uncertainty regarding the protection of biotechnological and certain microbiological

[28] EC, *Commission Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions from 30 July 1998,* [1998] O.J. L213/13.

inventions"[29] issues that followed in member states with respect to advances biotechnology. The Directive provides the following guidance with respect to isolated biologicals[30]:

> (16) Whereas patent law must be applied so as to respect the fundamental principles safeguarding the dignity and integrity of the person; whereas it is important to assert the principle that the human body, at any stage in its formation or development, including germ cells, and **the simple discovery of one of its elements or one of its products, including the sequence or partial sequence of a human gene, cannot be patented**; whereas these principles are in line with the criteria of patentability proper to patent law, whereby a mere discovery cannot be patented; [emphasis added]

In spite of the Directive, or perhaps under its umbrella, the European Union has seen fit to patent transgenic animals, as well as naturally occurring gene fragments. Perhaps we should rightly consider whether a similar Directive could be useful in Canada to prevent future conflicts that will certainly arise.

b. What we have to Gain

DNA is a product of nature, and might as a general rule be considered unpatentable as a whole due to the amount of external intervention required to put it to the use that it has evolved to carry out, namely the coding for the protein machinery of biological systems. However, scientists have taken the raw DNA sequence and invented many extraordinarily useful applications that we, as a society, want to encourage as well as protect in an effort to sustain research efforts and fuel our scientific industry. We benefit directly from inventions based on DNA, from the model organisms that simulate human disease for testing new treatments and therapies, to protein therapeutics (e.g. insulin and antibodies) obtained from genetically modified and cultured cells, to high-yielding strains of drought resistant rice (e.g. NERICA). These inventions have the capacity to change and better our world and it is up to us in the legal

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[29] *Ibid.*, at para. 9.

[30] *Ibid.*, at para. 16.

community to ensure that inventors of biotechnology have sufficient protection to enable future research and allow funding for even more ambitious projects.

The creation of genetically modified organisms that model human disease like the mouse which models obesity and the *C. elegans* worm lacking certain signalling molecules that models aging, hold great promise for improving human health. One new model organism is Erika Sasaki's marmosets that express green fluorescent protein (GFP), a protein coded in the DNA of the *Aequorea victoria* jellyfish, in their skin[31]. Small primates, marmosets have a physiology which is far closer to human than the current popular model organisms predominantly used for medical research, namely rats and mice. Although there is nothing particularly helpful to humans in the generating of fluorescent marmosets, the technique used to insert a GFP gene into marmosets at the embroyonic stage bodes well for the future success for insertion of genes into humans, a technology that is really only just beginning to mature. Proving this principle of gene insertion is a promising step forward. With marmosets as an animal model, a technique used to treat or cure a marmoset of a genetic disease stands a reasonable prospect of working in a human.

Laying the ethics of using animals for medical research aside, scientists are slowly homing in on what models are more predictive of similar treatment in humans, and therefore are accelerating the process, we hope, of finding treatments and cures for human disease. For those concerned about animal welfare, improving our animal models means that fewer animals will be required for research, and this can only be good for the animals, as well as research budgets. A leaner budget for one project means that more money can be spent on other biotechnology projects.

[31] Erika Sasaki *et al.*, "Generation of transgenic non-human primates with germline transmission" (2009) 459 Nature 523-528, with an extraordinary photograph on page 524. Work on GFP earned scientists Martin Chalfie, Osamu Shimomura, and Roger Y. Tsien the 2008 Nobel Prize in Chemistry.

I would be remiss not to also mention Craig Venter's new synthetic bacterium[32] , wherein all the DNA in the bacterium was designed and synthesized in the laboratory. This proved that "a complete genetic system be reproduced by chemical synthesis starting with only the digitized DNA sequence contained in a computer"[33]. The resulting synthetic *Mycoplasma mycoides* bacterium was fully capable of reproduction, and to all definitions is a true organism. Although the original genes were synthesized based on pre-existing sequence that the research group determined to be essential to the survival of the bacterium, one can quickly envisage the direction this research is taking -- with a minimum of necessary genes, the synthetic organism can be turned to our uses by adding any gene that we want it to have.

V. THE ROLE OF THE PATENT SYSTEM

a. Public and Private funding for Research -- What we have to Lose

Isolated DNA sequences that are fragments of a naturally occurring sequence, as well as naturally occurring proteins and antibodies and the DNA sequences thereof, have been afforded patent protection worldwide. There are currently 34 monoclonal antibody drugs on the U.S. market[34] which are used to treat diseases ranging from cancer to multiple sclerosis, as well as preventing blood clotting and respiratory syncytial virus (RSV) infections. No small commercial endeavour, the total therapeutic market for monoclonal antibodies in 2010 was 48 billion U.S. dollars[35]. With the hope of prolonging life for metastatic cancer patients, drugs like Trastuzumab

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[32] Daniel G. Gibson *et al.*, "Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome" (2010) 329 Science 52.

[33] *Ibid.*, at 52 column 1.

[34] U.S. Department of Health & Human Services, *US Food and Drug Administration: FDA approved Drug Products*, online: Drugs@FDA <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

[35] Krishan Maggon, "Top Ten Monoclonal Antibodies 2010: Global Market Analysis & Blockbuster mabs" (29 April 2011), Online: Knol: a unit of knowledge <http://knol.google.com/k/krishan-maggon/top-ten-monoclonal-antibodies-2010/3fy5eowy8suq3/143>.

(Herceptin) and Bevacizumab (Avastin) are being widely used with substantial success, despite their steep price tag of upwards of $60,000 USD per year. (The question of how much an additional year of life is worth for a cancer patient has been and still is being debated by medical ethicists in countries with socialized medicine.) Bringing a sequence from discovery or isolation to use as a commercial product for human or animal use takes years of careful experimentation and must be supported by vigorous funding. There is no question that without significant private investment, high price tags and strong patents, these new drugs would never have been brought to market.

Reflecting on the scientific process, Dr. Jennifer Couzin-Frankel had the following to say on the 20th anniversary of the discovery of the Cystic Fibrosis (CF) gene at the Hospital for Sick Children in Toronto[36]:

> "CF offers an object lesson in how difficult it is, and how long it takes, to convert genetic knowledge into treatments. Every CF expert agrees that the gene discovery transformed their understanding of the disease's pathology. But even after so much hard work, not a single therapy based on the CF gene has reached the market."

With the cost of biological research so high and the results unknown, it is near impossible to predict which technologies are going to prove useful (and profitable), and which will only offer more questions than answers. Even the noblest of researchers stretching their funding to the limits often have to be satisfied with a minor contribution to a field, unlike the blockbuster cures and discoveries of the past.

In a recent editorial in Nature Magazine, Matthew Cooper and David Shlaes[37] report that the number of private companies researching novel antibiotics has plummeted from 18 to 4 in the last 21 years. With the decline of research into new antibiotics and the widespread mis-use of

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[36] Jennifer Couzin-Frankel, "The Promise of a Cure: 20 Years and Counting" (2009) 324 Science 1504-1507.

[37] Matthew A. Cooper & David Shlaes, "Fix the antibiotics pipeline." (2011) 472 Science 32.

antibiotics, new resistant strains are emerging worldwide. The World Health Organization (WHO)[38] warns that without new antibiotics drugs, many infectious diseases that used to be treatable with current antibiotics will become untreatable due to antibiotic resistance. Without the discovery of new medicines, the human population could return to a pre-antibiotic era where people begin to die of diseases that are presently curable. Classical antibiotics are not themselves biomolecules, however the newer generation of antibiotics such as the class of aminoglycosides may be considered biomolecules, and are currently used in cases of methicillin-resistant *Staphylococcus aureus* (MSRA) infections which are all too commonly present in hospitals worldwide. Also, many of the technologies required to identify, screen, and test new pharmaceuticals require biomolecule and animal technology that can be protected. The WHO calls upon the world community to invest more into the discovery of new antibiotics, and it is incumbent upon us in the Intellectual Property community to assist with this endeavour by staunchly protecting advances in biotechnology.

The question of legal protection of new or isolated biomolecules is ultimately a question of who will pay for and benefit from our technological advances of the future. If we do not reward and therefore encourage biotechnology innovation within the private sector, the daunting responsibility of inventing new antibiotics, cancer drugs, and environmental remediation techniques will fall to taxpayers. Without the profits of private industry to fuel research, opportunities for scientists will decline and the brightest of the next generation will seek more stable and lucrative employment elsewhere.

It is imperative that biomolecules and biologicals have a strong place within our patent system so that by granting such monopolies and allowing private biotechnology firms to prosper, we can continue to enable the improvement of human health.

Finally, a prosecution case recently passed by my desk that is giving me pause to reconsider the importance of the issues discussed herein and illustrates one conflicts with the patent system certainly soon to come. The invention is a method of processing an organ from a cadaver such that the cells are first removed to leave a solid scaffold, and then the scaffold is re-populated with naturally existing cells to arrive at a semi-synthetic organ suitable for transplant. The scaffold organ may be derived from a common slaughterhouse pig, and can be implanted with human cells matching those of the patient requiring transplant. The Examiner has reiterated an objection under Section 2 of the *Patent Act* that the claimed semi-synthetic organ is unpatentable on the basis that it is manufactured from an organ which is the product of a higher life form. The Examiner is almost certainly right within the confines of the *Patent Act* and jurisprudence and has no authority to challenge the law, but I believe that this invention is the best of human ingenuity and deserves all the protection we can give it. Both the Examiner and I are in a legal bind.