Patenting Genes - Stifling Research and Jeopardising Healthcare

Every day, new patents are filed for discoveries about genetic material – including gene sequences and gene fragments. Whilst the biotechnology industry claims that patent protection on genes is essential to pay for research and development, evidence is emerging which shows that patents are already:

- preventing or hindering development of new or improved medicines and treatments;
- limiting access to healthcare by increasing the cost of diagnostics and treatment for certain diseases;
- exploiting information and materials and inhibiting their free exchange between researchers;
- involving unsuspecting parties in extensive and costly legal battles.

If genetic research is to be of benefit to the public, it is essential that scientists and citizens join forces to bring an end to the practice of patenting genetic material.

In this briefing, we give three examples of how patents on genes are obstructing the progress of science and the development of new or cheaper treatments.

Background

A patent - which may be granted under national or regional laws (such as the European Patent Convention) - is the formal and legal description of an invention and is intended to prevent mechanical inventions or chemical processes from being copied. A patent allows the holder to exclude anyone else from making, using or selling the 'invention' for up to 20 years although this can be extended by clever manoeuvring for up to 30 years or even longer (see the Amgen case below). Since 1980, patents have been increasingly extended to include living organisms, their cells and their genes. Despite objections from some countries - particularly those in the 'developing' world - the US and industry, citing free trade rules, are pushing for all countries to allow patents on genes and living organisms.

However, the trend towards patenting genes is opposed by many scientists, including most of those involved in the Human Genome Project itself, on the grounds that working out a gene sequence and its basic function is a simple process of discovery, not invention. Leading scientists like Dr John Sulston of the Sanger Centre in Cambridge view the patenting of human genes as unethical and an obstacle to the rapid application of genomic information to health problems:

> "*People have to take democratic responsibility for the human genome. It's not something that can be left to the commercial manufacturers, like making motor cars."* [1]

Others have emphasised that increased secrecy between scientists is another negative consequence. For example, Professor Jonathan King of the Massachusetts Institute for Technology has said:

> "*Patent attorneys regularly advise researchers to restrict their presentations to colleagues, don't show your work, don't show your notebook, don't give that talk, so as not to jeopardise the planned patent submissions. This has reversed the half century culture of free and open communication in the scientific communities*." [2]

In addition, studies leading up to the final 'discovery' are often conducted by university researchers and doctors, funded through public money. The 'first past the post' rules for patents let the winner take all whilst the public pays twice – not only for state funded research but also the royalties and inflated drug costs imposed by the patent holding company.

Breast Cancer Diagnostics and Therapeutics - The BRCA 1 and BRCA2 Genes

Approximately 5-10% of breast cancer cases are currently associated with an inherited genetic defect. The case of Myriad Genetics and breast cancer susceptibility genes shows how determined a company can be to enforce

its monopoly control through patents and how this can force up costs and hinder research.

Patent holder:	Myriad Genetics, Inc. (Headquarters: Salt Lake City, Utah, USA)
Product name:	BRACAnalysis (BRCA1/2 DNA testing kit/service)
Patents:	Breast and ovarian cancer susceptibility genes, mutations, related diagnostics and treatment
BRCA1:	e.g. US patents 5709999, 5710001 and 5747282 (granted in 1998)
BRCA2:	e.g. US patents 5837492 (November 1998) and 6033857 (April 2000)

By the end of 2000, Myriad Genetics had been awarded a total of nine US patents on the breast/ovarian cancer susceptibility genes, BRCA1 and BRCA2, and two on another tumour suppresser gene (called p15) as well as patents covering antibodies to the BRCA and p15 proteins. Similar patents have been granted in Canada and Japan and filed in the UK and Europe.

The BRCA1 and BRCA2 patents provide Myriad with exclusive rights to commercialise laboratory testing services, diagnostic test kits and therapeutic products that use the BRCA1/2 DNA sequences. For diseases like breast cancer which are common and may have an inherited component, the economic potential for testing is great. As Peter Meldrum, Myriad's President and CEO says: "*Myriad's substantial and growing portfolio of full-length human disease gene patents is an important and valuable corporate asset for the Company*." [3]

However, despite Myriad's patent claims, the discovery of the first gene for a predisposition to breast cancer (BRCA1) was based on international collaboration and the open exchange of information between groups around the world. Women carrying the gene helped by providing material and by investigating their family histories to provide clues. But as research got closer to isolating the gene, Myriad Genetics moved in and finally claimed a patent on the basis of being the first to complete the identification and sequencing of the gene.

Similarly, much of the work on the second gene (BRCA2) took place in Britain at the Sanger Centre in Cambridge and the Institute of Cancer Research (ICR). Myriad filed its patent application literally hours before the ICR published its discovery of BRCA2 in the journal *Nature* and the ICR still insists it discovered the gene first. This is recognised in the UK where, at least for now, the ICR holds a patent for which it does not charge a licence fee.

In the US, Myriad Genetics has threatened or taken legal action against anyone who markets or performs genetic tests for breast cancer and, as a result, it now has exclusive rights to OncorMed's patents (current and pending) for BRCA1 and BRCA2 genetic testing. US cancer researchers and laboratories have accused Myriad Genetics of using its patents to stifle genetic breast cancer research and restrict women's access to DNA testing[4].

In the UK, the National Health Service has developed its own tests for the breast cancer susceptibility genes but for some time Myriad has been pressuring the NHS to pay royalties for use of their patented gene(s). In March 2000, Myriad had entered into an exclusive European marketing agreement with Rosgen Ltd, based at Roslin in Scotland. Rosgen was to provide commercial screening for known mutations whilst patient samples would be sent to Myriad in Utah for full sequencing. At the end of 2000, the Health Service Directorate warned that: "*If Myriad Genetics is successful in gaining patent protection in the UK, either Myriad Genetics itself, or Rosgen, could choose to take action against NHS laboratories, claiming damages back to the date on which the patent claim was filed (August 1996). It is our understanding that these damages could be substantial*." [5]

Negotiations with the Department of Health concerning royalties and exclusive services failed as Rosgen collapsed in early 2001. Therefore, the NHS remains in an uncertain position and, if Myriad succeeds, could have to pay not only damages but massive cost increases as the following comparison shows:

US costs: Myriad's monopoly means screening for a particular mutation known to occur in a patient's family will cost between £179 ($250) and £357 ($500). Full sequencing of both BRCA genes to check for any mutation that could occur in either gene will cost about £1,714 ($2,400).

UK costs: Scientists at the Central Manchester Healthcare NHS Trust calculated that screening for a particular mutation known to occur in a patient's family costs less than £100 ($140) in their own

laboratories. Full sequencing of both BRCA genes would cost £800 ($1,120) - half the price of Myriad's £1,714 ($2,400)[6].

Anaemia Treatment – The Erythropoietin Gene and Protein

Erythropoietin (EPO) stimulates red blood cell production and is normally produced in the kidney and liver. Because failing kidneys do not produce enough EPO - leading to chronic anaemia - an artificial version of EPO has a huge potential market among a growing number of dialysis patients, estimated to be 220,000 in the US alone. Amgen's patent on the EPO gene has given them a monopoly on its production by exploiting earlier public sector research and strategic manoeuvring has allowed them to extend the patent lifetime to 30 years.

Patent holder:	Amgen – Headquarters in Thousand Oaks, California, US.
Product name:	Epogen - to treat anaemia resulting from kidney failure
Patent:	US patent 4,703,008 "DNA sequences encoding erythropoietin", granted October 1987. Amgen holds a total of five patents on erythropoietin.

The EPO protein was first identified at the University of Chicago by molecular biologist Eugene Goldwasser in 1977 after two decades of government-funded research. However, Amgen won the race for the gene patent in the mid 1980s although it had to go through protracted litigation to win exclusive rights to manufacture its recombinant version of EPO - called Epogen - which is now the most expensive drug in the US Federal Government's Medicare programme.

Whilst its first EPO patents were process patents on isolating and cloning the gene, Amgen took out product patents in the 1990s which claim that it owns the rights to all artificial EPO made from mammalian cells. As a result, the company sued Transkaryotic Therapies (TKT) and Aventis on the grounds that they had infringed its patents by developing a technology to activate the EPO gene in human cells. Even though TKT only used regulatory sequences to activate EPO genes that were already present in the cells - and so consciously avoided the use of any of Amgen's technologies - Amgen won this crucial battle on 19th January 2001 with far-reaching implications for future drug development. If this decision is upheld on appeal, Amgen's strategic timing of its patent applications (the first was granted in 1987 while the last will expire in 2015) will extend its monopoly on Epogen to nearly 30 years, inflating drug costs and stifling competition for much longer than the 17 years for which patents are normally granted[7].

Amgen funded the National Kidney Foundation - a patient advocacy group – to conduct a medical literature research project to provide guidelines aimed at reducing the death rate among US dialysis patients. In 1997, the Foundation recommended raising hematocrit (a measure of red blood cell levels) into the 33 to 36% range, thus necessitating higher dosages of Epogen. Once Amgen had spread the word, doctors started prescribing levels even above 36.

In 1999, total US Epogen sales were approximately $1.8 billion, making it one of the top-selling pharmaceutical products worldwide.

Human Genome Sciences and the Receptor Gene (CCR5) for the AIDS Virus

Human Genome Sciences (HGS) hit the jackpot when others discovered that its patented 'HDGNR10' gene was in fact the gene for a crucial AIDS receptor in human cells. Though HGS did not include this property in its patent claims, it has stated its intent to profit from this discovery as the broad patent covers the gene and all its medical applications.

Patent holder:	Human Genome Sciences, Inc. – Headquarters: Rockville, Maryland, U.S.A.
Patent:	U.S. Patent No. 6,025,154 "Polynucleotides Encoding Human G-Protein Chemokine Receptor HDGNR10," granted in February 2000

When HGS isolated the HDGNR10 gene – later to be known as the CCR5 gene - it concluded that it had found a gene belonging to the family of cell receptors. It filed a patent on the gene believing it to be a

receptor for chemokines, which play a role in inflammatory diseases such as arthritis. HGS had no idea that the receptor was one of the entry points for the HIV virus into human cells. This was discovered by scientists from several academic centres - including the Aaron Diamond AIDS Research Center in New York and the National Institute of Health – who, after painstaking laboratory and research work, found and isolated a protein that the AIDS virus requires to infect cells – the CCR5 receptor. They eventually isolated the gene, knowing that any drug which can block the protein could be used in the fight against AIDS[8].

However, the gene had already been claimed by HGS and, when the patent was granted, the Company announced that: *"HGS receives patent on AIDS virus entry point"*, causing its stock price to soar. Without having contributed to this breakthrough and without even knowing the gene's role in the life cycle of the AIDS virus, HGS has a broad enough patent to cover any use of the gene, thus enabling them to claim royalties and profit through licensing contracts. AIDS researchers globally have expressed their disbelief and outrage over this patent, saying that wherever the patent is valid, *"research would be immediately taxed if it was ever fruitful."* [9]

Furthermore, this patent will have huge implications for the costs of CCR5 based AIDS drugs, as recently highlighted by the legal battle between pharmaceutical companies and the South African Government over drug prices and availability.

Conclusions

These three examples show that patents on genes and gene fragments seriously threaten future medical research. They can stifle research and collaboration and increase prices through patent monopolies, neither of which serve the public interest. A review of gene patents - both granted and pending over the last few years - is long overdue. In particular, the case of the CCR5 gene and AIDS clearly highlights the folly of granting broad patents for all medical applications. The simplest solution is for genes and gene fragments to be made unpatentable – political action is needed now before the companies clean up on gene patents and society is left counting the cost.

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