Published in final edited form as:

Nat Biotechnol. 2007 July ; 25(7): 739–741. doi:10.1038/nbt0707-739.

PATENTS AND TRANSLATIONAL RESEARCH IN GENOMICS:

Issues concerning gene patents may be impeding the translation of laboratory research to clinical use

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The aim of translational research is to take the outcomes and innovations developed within the research context into clinical practice. In the United Kingdom, the importance of this process has been recognized in a recent review of health research funding, undertaken by Sir David Cooksey, which places considerable emphasis on the need to translate the results of basic research along the pathway to new innovations, products or healthcare practices¹. Increasingly, biomedical research within the UK's National Health Service (NHS) and university sectors has a translational goal. In the field of genetics, this is evident in the funding of six Genetics Knowledge Parks to undertake translational genetics programs, and in the Department of Health's Genetics White Paper of June 2003, which promoted the development of new diagnostic tools and set ambitious targets for translation and delivery to patients². One of the barriers to translation in genetics can be the existence of gene patents. A significant proportion of the human genome is the subject of patents in the United States and Europe^{3, 4}, and these patents could potentially impede the use of genes for research, diagnosis and treatment.

The experience of the Oxford Genetics Knowledge Park (OGKP) has demonstrated how some of these impediments can be circumvented. Addressing these problems will help the goals for translational research, as proposed by the Department of Health's White Paper on Genetics and the Cooksey Review, to be realized.

The OGKP was established in 2002 with funding from the Department of Health and the Department of Trade and Industry. Its funding ended in June 2007, although some of its activities are ongoing because some of the genetic tests developed have been adopted into clinical practice or the research has been funded through other sources. The OGKP was a collaboration between the Oxford Radcliffe Hospital NHS Trust (ORHT) and the University of Oxford. The primary purpose of the initiative was to ensure that developments in genetics were translated into clinical use for the benefit of NHS patients. One of the OGKP's major areas of research has been in the development of new genetic diagnostic tests for conditions

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COMPETING INTERESTS STATEMENT

The authors declare no competing financial interests.

known to cause sudden cardiac death (SCD), including hypertrophic and dilated cardiomyopathies (HCM and DCM, respectively) and long QT syndrome (LQT). It is in these studies that some of the issues concerning patents in translational research have come into focus.

The primary aim of the SCD research was to assess whether genetic testing can improve the identification and management of inherited SCD syndromes. A pilot service encompassing mutation detection and cascade screening for known SCD genes is being provided by the Oxford NHS Regional Molecular Genetics Laboratory. The HCM, DCM and LQT tests have been approved by the UK Genetic Testing Network. Referrals are accepted from Regional Genetics Clinics across the UK. To date, over 1,200 patient samples have been received. This pilot service has emerged from a close working relationship between the ORHT Regional Genetics Clinic and Molecular Genetics Laboratory and University of Oxford researchers.

Why are patents important in translational research?

An understanding of the patent landscape is essential in the process of translational research and the development of innovations for clinical use. Patents can have an impact at the research stage, at the point of commercialization, and also when diagnostic tests are used in the clinic⁵. It is essential that researchers are aware of the patents in existence when developing novel diagnostic tests for two reasons. First, the use of technology or tests which infringe valid patents could lead to enforcement action which can be time-consuming and expensive for both parties. Second, researchers may wish to protect the intellectual property arising from their own research, and therefore must understand what existing patents there are, in order to understand how their research may be innovative. The protection of intellectual property in innovations is increasingly important to both academic and NHS institutions, a trend which is reflected in the emphasis on patents in research council funding applications, the RAE (Research Assessment Exercise) and internal university assessment procedures. Such protection is also essential to effectively commercialize an innovation. In the absence of such protection, companies are unlikely to invest in the development of a diagnostic test.

The experience of the OGKP

There are three major issues relating to patents that the OGKP has encountered in its translational program: the research exemption and the extent of its application; the difficulties associated with mapping the patent landscape; and the need for infrastructure support.

The research exemption

One of the areas of uncertainty for the OGKP was whether its translational activities fell within the scope of the research exemption that is found in section 60(5)(b) of the Patents Act UK. This exemption specifies that there will not be an infringement of a patent if the infringing act “is done for experimental purposes relating to the subject-matter of the invention”⁶.

The effect of the research exemption is that researchers can use products and processes that are patented without infringing the patent, and so there is no need to notify the patent holder or pay license fees. However, the activities that are allowed under the exemption are narrow in scope, while at the same time being poorly defined⁷. To fall within the research exemption, an experimental activity must be intended to test a hypothesis relating directly to the patented invention. The scope of the exemption and how it should apply are still in the

process of being developed by the courts, as there are relatively few decisions that have set the limits of the exception⁸. However, in *Monsanto v. Stauffer Chemical*⁹, it was held that the research exemption would cover situations in which experiments are directed to the invention, such as testing whether the product can be made or an article made to work, or experiments to test modifications or improvements to the product.

It is important to understand that the research exemption will apply only to research on the patented invention itself rather than to the use of a patented research tool in the course of the research. This means, for example, that a license is needed for the use of the polymerase chain reaction (PCR), which is now a standard research tool used in all major universities and research laboratories. However, if the purpose of the research were to establish if a modification could be made to improve the PCR process, then this would come under the research exemption and no patent infringement would occur. It should be noted, however, that most research tools are marketed as a kit, bundled with a license. The use of the patented innovation in research is therefore not the only criterion necessary in order for the research exemption to apply. If this were the case, the effect would be to deprive many research tool patents of their value.

In the context of gene patents, it is likely that the following activities will fall within the research exemption:

- Research to determine new functions of a patented gene sequence;
- Verifying the functions of a patented gene sequence;
- Finding new variants such as single nucleotide polymorphisms (SNPs);
- Finding new information related to a gene sequence;
- Research directed at improving a known genetic diagnostic.

The other difficulty in translational research is that the research exemption will not apply to all stages of research. The position in relation to pure laboratory research is relatively clearcut, as investigations to discover new mutations, or develop a new test to identify those mutations, should fall under the exemption. However, as soon as the invention becomes clinically applicable, the research exemption will no longer apply¹⁰. In the OGKP's research, the neat divide between the clinic and the research laboratory is difficult to sustain, as patient samples are used both for diagnosis and for furthering the development of the research. This is relatively common in the case of genetic diagnostics, where the generation of a cohort of samples from patients assists in the identification of further disease-causing mutations, but the results of a single test are also clinically significant for a patient and their family. As this is not purely research, the research exemption is unlikely to provide protection against possible patent infringement.

This dilemma should be faced by all researchers carrying out translational research. However, there is a general belief that all research, even that which crosses the boundary between the laboratory and the clinic, is exempt. We are concerned that this belief may not be based on a clear understanding of the research exemption and how it applies. One of the contributing factors is that, in the UK at least, neither the Parliament (in the original legislation) nor the courts have clearly articulated the scope of the exemption and its application. It is worth noting that the research exemption was drafted at a time when translational research and biotechnology patents were less prevalent.

In practice, patent holders are reluctant to pursue those engaged in academic research for patent infringement, both because of the bad publicity this would generate and because of the unlikelihood of obtaining significant monetary damages for the infringement. This has

resulted in a de facto research exemption, which appears also to operate in jurisdictions without an effective legislative exemption, such as the US and Australia^{11, 12}. However, the reasons for not pursuing patent infringement will disappear as soon as the research has a clinical application, and damages for patent infringement become a realistic prospect.

In the case of the SCD research, the OGKP decided that it was not certain that the research exemption applied, because of the close relationship between the clinic and the laboratory. Therefore, a decision was made to conduct a search of all patents that could possibly impinge on provision of the service at the pilot stage, with a view to negotiating licenses where necessary. This had significant resource implications in terms of time and cost.

Mapping the patent landscape

Another difficulty that the OGKP encountered was mapping the patent landscape to ascertain what existing patents had implications for the OGKP research. Although there are a number of publicly accessible patent databases, identifying patents that researchers may be infringing is not an easy task in genomics. Numerous patents on human genes exist³, and in many cases there are overlapping patents such that a single gene may be the subject of many patents; for example, a patent over the entire sequence, together with patents over various elements of the gene. Furthermore, for genetic diagnostics, there may be multiple disease-causing genes. This complexity means that expert advice may be required, but this can be extremely costly. In the case of the OGKP, the UK Patent Office's Search and Advisory Service provided a cost effective way to map the patent landscape, and showed that there were no valid patents in the UK and EU jurisdictions on the SCD genes being tested. The UK Patent Office's Alert Service can be used to ensure that any changes to this situation are easily identified. It should be noted that although comprehensive, the UK Patent Office's searches are not legally binding and legal advice may also be required.

Moreover, although it is possible to determine the identity of a patent holder from Patent Offices and their search engines, it is not always clear with whom negotiations should be carried out. Overlapping sets of patent rights, or 'patent thickets', may require the negotiation of multiple sets of licenses and incur stacking royalty payments¹³. In many cases, patents are licensed to third parties but the licensing information is often commercial and confidential, and is difficult, time-consuming and costly to trace without legal expertise.

The need for infrastructure support

Patents can therefore create a number of difficulties for translational researchers. It is difficult to decide when it is appropriate and necessary to investigate intellectual property issues and to establish which patents apply and with whom to negotiate licenses, given that this requires a significant investment. Although it may not be necessary to actually negotiate licenses with patent holders until innovative research reaches clinical use, it may then be too late for the investigation of the existing patents impinging on the provision of a clinical service or the commercialization of an invention. Significant effort will have been invested in the research and it is inappropriate, if at this point, it is discovered that appropriate license arrangements cannot be negotiated, or if there is significant delay. Also, a researcher who has not obtained a patent license at this stage will not be in a strong bargaining position to negotiate a competitive license fee.

Research scientists do not have the skills or time to conduct such work, yet the necessary infrastructural support for translational research is not in place. Where translational research is likely to lead to an innovation that can be commercialized, university technology transfer offices or the newly formed NHS Innovation Hubs can conduct due diligence on patents. However, assessment of freedom-to-operate is carried out only for products or services

where there is potential for commercial gain, and thus may need to be undertaken by the individual hospital trusts which will operate the new clinical service. Anecdotal evidence suggests that these difficulties mean that intellectual property issues are essentially ignored until, or sometime well after, an innovation reaches the stage when it enters clinical practice.

Most researchers engaged in translational research do not have the finances or the management and legal expertise to investigate the patents that may have implications for their work. This places them in a dilemma—whether to carry out expensive patent searches when they are not sure that anything will come out of the research, or to wait until the research has progressed further and then wait for the searches to be carried out and licenses negotiated. If translational research is to be supported within the UK, financial support and legal expertise needs to be provided to researchers to ensure that such decisions are made in a way that does not impede the clinical adoption of new diagnostic tests.

Conclusions

In order for the goals of the Cooksey Review for the development of translational research and the plans for diagnostic laboratory genetic testing to be realized, a number of major issues need to be dealt with in regard to patents. There needs to be a clearer definition and awareness of when, and how, the research exemptions apply. There also needs to be more patent and legal support for researchers so that intellectual property rights are not a barrier to research, but just another consideration that can be navigated with ease and knowledge. The experience of the OGKP suggests that exploring patent rights can be a time-consuming and costly experience that has the potential to have a detrimental effect on fledgling research.

For translational research to be effective in the UK and for the partnerships between universities and the NHS to be fully optimized, policies and support mechanisms that promote translational research need to be put in place. We hope that such recommendations will be considered in the implementation of recommendations of the Cooksey Review.

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