support for home care and pharmaceuticals, and do all of these things in a practical way. It is a tall order, but it must be done, precisely because of my first point: this is too important to the Canadian people for us not to succeed.

The Hon. Bob Rae served as Premier of Ontario from 1990 to 1995. He is a partner at Goodmans LLP and serves as a trustee of the University Health Network, where he is Chair of the Audit Commitee.

Competing interests: Mr. Rae is a partner in a law firm that acts for a number of companies with an interest in the health care field, as well as governments and professionals.

Correspondence to: *Mr. Bob Rae, Goodmans LLP, 250 Yonge St., Toronto ON M5B 2M6*

Articles to date in this series

Lewis S. The bog, the fog, the future: 5 strategies for renewing federalism in health care. *CMAJ* 2002;166(11): 1421-2.

Maxwell J. Bringing values into health care reform. *CMAJ* 2002;166(12):1543-4.

Suzuki D. Expanding the health care debate. *CMAJ* 2002; 166(13):1678-9.

Bégin M. Renewing medicare. *CMAJ* 2002;167(1):46-7.

Wynne-Jones T. Whose health? Who cares? *CMAJ* 2002; 167(2):156-7.

Occasional essay

Patenting of genetic material: Are the benefits to society being realized?

Donald J. Willison, Stuart M. MacLeod

ß See related article page 256

Patents represent a contract between an inventor and society. By granting time-limited market exclusivity, patents create the potential for inventors to generate high returns on successful innovations. In exchange, the inventor provides a complete description of the invention so that others may build on the technology to create improvements or other breakthrough discoveries. Patent protection of intellectual property is particularly important to inventors in the biotechnology field because of the relatively high fixed cost of research and the ease with which discoveries may be copied. By attracting investment capital for research, patent protection increases the pace of innovation, thus benefiting society.

To qualify for a patent, the invention must be deemed useful, novel and not obvious. The utility criterion requires that a clear application is known. Novelty means that the invention has not been described before in the literature. The criterion of non-obviousness demands creativity on the part of the inventor. For example, the courts in the United Kingdom have ruled, on the grounds of obviousness, that Pfizer's patent on the use of the entire drug class of phosphodiesterase-5 inhibitors for erectile dysfunction was invalid because the knowledge was already in the public domain when the patent was issued.[1]

Although contentious in principle, patenting of life forms is now well established in law. The landmark case identifying the patentability of life forms occurred in 1980, when the US Supreme Court ruled in a 5–4 decision that the genetic modification of a bacterium to break down oil spills was consistent with "a new composition of matter" as defined in the Patent Act of 1793.[2] This decision did not directly address the patentability of genes; however, the courts eventually reasoned that, if whole organisms were patentable, then their components would also be eligible for patent protection. Subsequently, the patenting of isolated gene sequences (but not the human genome) was permitted by the American and European patent offices, provided the applicant could demonstrate utility of the gene sequence. The Canadian Intellectual Property Office has recognized the patentability of isolated genetic sequences, and the status of patents for higher life forms (e.g., the Harvard oncomouse) is currently before the Supreme Court.[3] The Canadian Biotechnology Advisory Council has recently recommended that higher life forms (i.e., plants,

seeds and nonhuman animals) that meet the criteria of utility, novelty and non-obviousness be patentable, subject to certain restrictions.[4]

A wave of new diagnostic and therapeutic inventions is coming to market, based on innovations in genomics and proteomics. Development has been funded in large part through private capital, stimulated by the patenting of genetic materials. As gene-based tests and therapies come to market, practising physicians have an important professional role to play in interpreting the growing debate for their patients and for the general public. Consider the case of Myriad Genetics Laboratories (Myriad) involving the *BRCA1* and *BRCA2* gene patents.

In June 2001 Myriad declared that hospitals in several provinces were violating its patent on a test of genetic susceptibility to breast cancer. Myriad demanded that all testing be conducted in its laboratory in the United States at a cost of about US$2500, almost 5 times what is currently being charged.[5] Although other provinces either stopped using the test or quietly went on as usual, in September 2001 the Ontario government announced that it would challenge private companies' rights to patent genes and to control, and profit from, diagnostic and medical treatments using the patent.[6] To date, Ontario continues to defy Myriad's patent claim[7] and has taken steps toward charting a path that balances societal and commercial interests in the area of genomics.

Genetic patents were intended to benefit society through more rapid access to innovations that would improve the health and well being of society. In this article we review key issues in the patenting of genetic materials and ask whether the intended benefits from patenting of genetic material are actually occurring.

Concerns over patenting of genetic material

Effects on the biotechnology sector

Patenting of genetic material has created a huge market for private investment capital. Indeed, private investment in biotechnology has become an important aspect of Canadian science and industrial policy, supporting Canada's goal of leadership in the information economy.[8,9] The race to decipher the human genome probably finished ahead of schedule because of the entry of private sector funds. How, though, has the patenting of basic discoveries affected the research process and the resulting innovations produced?

Research process

In a survey of over 2100 life scientists, about 20% of respondents reported delays in publication of 6 months or more to allow for patent application, to protect their scientific lead, to slow dissemination of undesired results, to allow time for patent negotiation or to resolve disputes over ownership of intellectual property.[10] Engagement in academic–industry research partnerships and commercialization of university research were significantly associated with publication delays. In another survey, 47% of geneticists who asked other faculty for additional information, data or materials regarding published research reported denial of at least 1 request in the preceding 3 years.[11] In 28% of cases, respondents were unable to replicate published research as a direct result of this refusal to share information. The rate of denial of requests for data was equivalent to that reported by non-geneticists. However, geneticists were more likely to report that the withholding of data impeded progress of their research (58% v. 38% respectively). Thirty-five percent of geneticists felt that data sharing had decreased during the past decade.

Innovations

There are 2 types of innovation: breakthrough discoveries and those that improve on existing technology by creating either a better product or a cheaper product of equivalent quality.

Breakthrough discoveries: Privatization of new tests or therapies can go astray when too many owners hold rights to discoveries.[12] Before 1980, basic discoveries, such as the H_2-receptor responsible for gastric acid secretion, were considered to be in the public domain. (These basic discoveries are often called "upstream discoveries.") Only the specific tests or therapies that harnessed this basic knowledge, such as H_2-receptor antagonists, were patented. (These tests and therapies are commonly called "downstream applications.") Currently, patentable upstream discoveries include genes, gene sequences, gene fragments or expressed sequence tags, the proteins expressed by these genes, and single nucleotide polymorphisms, commonly used in researching genetic diseases. Although the patenting of upstream discoveries has stimulated a huge influx of private investment capital, inventors of downstream applications are likely to cross the boundaries of several patents, necessitating the "stacking" of royalties to patent holders. This could reduce the value of all patents, vastly increase legal costs and actually inhibit innovation. Indeed, Barton[13] noted a 70% increase between 1986 and 1994 in the number of intellectual property lawyers employed per dollar spent on research and development.

Discoveries that improve on an innovation: An excessively broad patent — particularly on an upstream discovery — might block or place severe constraints on the ability of others to develop new tests or therapies that build on the patented invention. This is one of the criticisms directed at Myriad Genetics by Institut Curie and the French government concerning their patent on the *BRCA1* gene.[14]

Effects on society

Research focus

In general, genetic patenting issues mirror those associ-

ated with commercialization of research. Effort is placed disproportionately on discoveries that would maximize profits to the inventor, by targeting large, potentially lucrative markets, rather than on discoveries that would maximize benefit to society. This exacerbates existing disparities in the availability of treatments across socioeconomic and ethnic groups within countries and between developed and developing countries.[15] In addition, research into genetic "solutions" may overshadow research into the roles of less glamorous but important contributors to disease prevention. For example, modifiable behavioural factors, such as obesity, inactivity and smoking, account for over 70% of the cases of stroke and colon cancer, over 80% of coronary artery disease and over 90% of adult-onset diabetes.[16] Ignoring these targets of innovation will result in a narrower and more costly range of solutions than might otherwise occur.

Market control

High licensing fees and royalties may constrain the number of laboratories prepared to provide a particular test. For example, Merz and colleagues[17] found that 30% of laboratories testing for hemochromatosis ceased to develop or provide the test once the patent holder began enforcing its patent. Access to tests is thus reduced, and an environment is created wherein patent holders dictate the conditions under which tests will be performed.[18]

Even more constraining is the refusal to license a product to other laboratories. Although Myriad Laboratories cites quality control as its reason for refusing to license out its *BRCA1* and *BRCA2* tests, this practice also provides Myriad with an expanding exclusive database for researching and patenting new mutations in the 2 genes, potentially extending for years the company's monopoly in this area.

Consumption

Society has limited funds to distribute between health care and other social benefits. The socially optimal amount to be spent on any one therapy takes into account that, beyond a certain point, greater health benefits may be achieved by investing elsewhere. By contrast, the patent holder seeks to maximize sales of its invention. This induces pressures to broaden the pool of patients considered eligible for a test or therapy beyond that which is socially optimal. For example, if one compares Myriad Genetics' indications for its *BRCA* tests with those recommended by an independent academic body, one finds that the latter excludes women without a family history of breast or ovarian cancer, whereas Myriad's guidelines include these lower risk women.[19]

One may argue that individuals deemed ineligible for a particular test or treatment within the public health care system should be allowed to purchase these out-of-pocket. However, this ignores the induced costs to the public system in follow-up to the genetic test itself — costs that may quickly exceed that of the test.[20] Without controls on direct-to-consumer marketing similar to those in place in Canada for pharmaceutical products, potential overconsumption is likely to be exacerbated.

Policy implications

The evidence suggests several areas in which patenting of genetic materials may actually be slowing innovation through delayed publications, increased secrecy, increased transaction costs due to royalty stacking, and excessively broad patents. Researchers themselves will generate some solutions, such as the SNP Consortium — a collaboration of several pharmaceutical firms and the UK Wellcome Trust — that places the commonly used single nucleotide polymorphisms (SNPs) in the public domain.[21] However, there is now no clear delineation between patentable discoveries and those in the public domain. Other solutions may come from regulators. For example, the US Patent Office has recently suggested the use of patent pools, which are a form of cross-licensing agreement between patent holders, allowing for the sharing of technologies in a common field.[22]

The need for patent reform is generally recognized.[23–25] Ontario's report on genetics, testing and gene patenting[26] recommends tightening the existing interpretation of Canada's Patent Act as it relates to biological materials, and it recommends amendments to the act to:

- narrow the scope of gene patents;
- create clear exemptions for experimental and noncommercial clinical use of a patented invention;
- introduce a morality clause, the basis on which a patent may be challenged;
- make provision for a separate ethics review panel;
- create a faster, less expensive dispute-resolution mechanism; and
- permit compulsory licensing of genetic diagnostic and screening tests, giving government authority to require the patent holder to license the test to another firm, under reasonable conditions.

Although necessary, these patent reforms do not address the bias toward producing products that will maximize a return on investment. Federal and provincial governments must ensure adequate, continued funding for research that does not have commercial potential — for example, lifestyle and environmental contributors to health and well being.

Conclusion

A handful of large biotechnology enterprises is emerging from existing small and medium-sized biotechnology firms. As this occurs, it is important that adequate mechanisms be in place to limit the potential for abuse of monopoly power. Federal leadership is needed to clarify interpretation of current patent laws. Ultimately, however, Canada must work in concert with other nations on fundamental reform of these laws to fit societal needs for both innovation and affordable

access to these innovations. This effort will require engagement with all stakeholders, including the medical community and the general public. The national and provincial medical associations have important roles to play as advocates for both patients and physicians to ensure that workable and sustainable approaches are found.

This article has been peer reviewed.

Drs. Willison and MacLeod are with the Department of Clinical Epidemiology and Biostatistics, McMaster University, the Centre for Evaluation of Medicines, St. Joseph's Hospital, and the Father Sean O'Sullivan Research Centre, St. Joseph's Hospital, Hamilton, Ont. Dr. Willison is also with the Centre for Health Economics and Policy Analysis, McMaster University. Dr. MacLeod is also with the Departments of Medicine and Pediatrics, McMaster University.

Competing interests: None declared for Dr. Willison. Dr. MacLeod is Vice-President, Medical Affairs, at Innovus Research Inc., Burlington, Ont., a company specializing in the design and conduct of clinical trials, health policy and health economic studies.

Contributors: Dr. Willison initiated the concept of this article and was the principal author. Dr. MacLeod contributed to the initial design of the article and critically reviewed and revised each draft. Both authors approved the submitted version of the article.

Acknowledgements: We thank Steve Morgan for his helpful comments on an earlier draft of this article.

Dr. Willison holds a Career Scholar Award with the Canadian Institutes of Health Research.

References

1. Viagra patent invalid, says UK court. *Scrip* 2002;2716(Jan 30):6.
2. Crespi RS. An analysis of moral issues affecting patenting inventions in the life sciences: a European perspective. *Sci Eng Ethics* 2000;6(2):157-80.
3. Gold R. Building a better patent law. *Globe and Mail* [Toronto] 2002 May 17;Sect A:7.
4. *Patenting of higher life forms and related issues. Report to the Government of Canada Biotechnology Ministerial Coordinating Committee*. Ottawa: Canadian Biotechnology Advisory Committee; June 2002. Available: www.cbac-cccb.ca/documents/en/E980_IC_IntelProp.pdf (accessed 2002 July 5).
5. Mallan C. Gene test for cancer won't stop. *Toronto Star* 2001 Sep 20;Sect A:3.
6. Mackie R. Harris battles firm over gene patenting. *Globe and Mail* [Toronto] 2001 Sep 20;Sect A:14.
7. Eggertson L. Ontario defies US firm's genetic patent, continues cancer screening. *CMAJ* 2002;166(4):494.
8. Innovation. In: *The speech from the Throne to open the first session of the 37th Parliament of Canada*. Ottawa: Office of the Prime Minister; 2001. Available: www.sft-ddt.gc.ca/sft-ddt/03_e.htm (accessed 2002 July 5).
9. *Achieving excellence: investing in people, knowledge and opportunity. Canada's innovation strategy*. Ottawa: Industry Canada; 2002. Cat no C2-596/2001-1E-1N2. Available: www.innovationstrategy.gc.ca (accessed 2002 July 8).
10. Blumenthal D, Campbell EG, Anderson MS, Causino N, Louis KS. Withholding research results in academic life science. Evidence from a national survey of faculty. *JAMA* 1997;277(15):1224-8.
11. Campbell EG, Clarridge BR, Gokhale M, Birenbaum L, Hilgartner S, Holtzman NA, et al. Data withholding in academic genetics: evidence from a national survey. *JAMA* 2002;287(4):473-80.
12. Heller MA, Eisenberg RS. Can patents deter innovation? The anticommons in biomedical reserach. *Science* 1998;280:698-701.
13. Barton JH. Reforming the patent system. *Science* 2000;287:1933-4.
14. Shulman S. Owning the future: doctors without patents. *Technol Rev* 2001; 104(10):33.
15. Singer PA, Daar AS. Harnessing genomics and biotechnology to improve global health equity. *Science* 2001;294:87-9.
16. Willett WC. Balancing life-style and genomics research for disease prevention. *Science* 2002;296(5568):695-8.
17. Merz JF, Kriss AG, Leonard DG, Cho MK. Diagnostic testing fails the test. *Nature* 2002;415:577-9.
18. Merz JF. Disease gene patents: overcoming unethical constraints on clinical laboratory medicine. *Clin Chem* 1999;45(3):324-30.
19. Caulfield TA, Gold ER. Genetic testing, ethical concerns, and the role of patent law. *Clin Genet* 2000;57:370-5.
20. Miller F, Hurley J, Morgan S, Goeree R, Collins P, Blackhouse G, et al. *Predictive genetic tests and health care costs: final report prepared for the Ontario Ministry of Health and Long-Term Care*. Toronto: Ontario Ministry of Health and Long-Term Care; 2002.
21. Sachidanandam R, Weissman D, Schmidt SC, Kakol JM, Stein LD, Marth G, et al. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* 2001;409(6822):928-33.
22. Clark J, Piccolo J, Stanton B, Tyson K, Critharis M, Kunin S. *Patent pools: a solution to the problem of access in biotechnology patents?* Washington: US Patent and Trademark Office; 2000.
23. Thurow LC. Needed: a new system of intellectual property rights. *Harv Bus Rev* 1997;75(5):95-103.
24. Mooney PR. *The impetus for and potential of alternative mechanisms for the protection of biotechnological innovations.* Prepared for the Canadian Biotechnology Advisory Committee, Project Steering Committee on Intellectual Property and the Patenting of Higher Life Forms; 2001. Available (pdf format): www.cbac-cccb.ca/documents/en/AltMechanisms_Mooney.pdf (accessed 2002 July 5).
25. Gold ER. Moving the gene patent debate forward. *Nat Biotechnol* 2000;18 (12):1319-20.
26. Ontario Provincial Advisory Committee on New Predictive Genetic Technologies. *Genetics, testing and gene patenting: charting new territory in healthcare*. Toronto: Ministry of Health and Long-Term Care; 2002.

Correspondence to: *Dr. Donald J. Willison, Centre for Evaluation of Medicines, 105 Main St. E, Level P1, Hamilton ON L8N 1G6; fax 905 528-7386; willison@mcmaster.ca*