

RESEARCH ETHICS

Declaration of patent applications as financial interests: a survey of practice among authors of papers on molecular biology in *Nature*

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Objectives: To determine whether authors of scientific publications in molecular biology declare patents and other potential financial interests.

Design: Survey of a 6-month sample of papers related to molecular biology in *Nature*.

Methods: The esp@cenet worldwide patent search engine was used to search for patents applied for by the authors of scientific papers in *Nature* that were related to molecular biology and genetics, between January and June 2005.

Results: Of the 79 papers considered, four had declared that certain authors had competing financial interests. Seven papers in which no financial interests were declared had authors with patent applications that were based on the research in the paper or were closely related to it. Another paper had two authors with connections to biotechnology companies that were not disclosed.

Conclusion: Two thirds of the papers in which authors had patent applications or company affiliations that might be considered to be competing financial interests did not disclose them. Failure to disclose such information may have negative implications on the perception of science in society and on its quality if the possible bias is hidden. Journals should make greater efforts to ensure full disclosure, and scientific institutions should consider failure to disclose financial interests as an example of scientific malpractice. Establishing a register of interests for scientists is one way to increase transparency and openness.

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One important dimension in ensuring the quality of scientific research and public confidence in science is that any potential conflicts of interests should be disclosed to enable peer reviewers, journal editors and readers to consider whether any bias has been introduced into the research and its interpretation. In their requirement for biomedical publications, the International Committee of Medical Journal Editors¹ states that interests should be declared “whether or not the individual believes that the relationship affects his or her scientific judgement”. Disclosure of such interests is controlled by the author and, with the exception of employer and patent applications, other forms of possible conflicts of interest are difficult to verify independently. No register of interests exists, for example, in which directorships of companies or consultancies have to be recorded, as for some in public life.

The advent of intellectual property rights in the form of patents on knowledge in the biological sciences, particularly relating to genetics and biotechnology, which at one time may not have been considered to be an invention is one discipline in which the potential for conflicts of interest, has increased.² The increasing scope of patentability, coupled with pressure to gain full commercial potential from scientific advances, has led to researchers in both the public and private sectors being more commonly associated with patent applications. Although this has increased the potential for conflicts of interest because patent applications are in the public domain, it also provides an opportunity for independent scrutiny.

In February 2004, *Nature* published a brief communication,³ which GeneWatch UK discovered as the subject of an earlier patent application that was not disclosed by the authors.⁴ A corrigendum was published 2 weeks later, acknowledging that this should have been given as a competing financial interest.⁵ The research reported here

was undertaken as a systematic study to determine whether such non-disclosure of patent applications is common practice or whether it was an isolated incident.

METHODS

Twenty six issues of *Nature* (7021–7046), published between 1 January and 30 June 2005, were examined. In these issues, 513 scientific peer-reviewed papers were published: 5 reviews, 39 brief communications, 2 progress, 68 articles and 399 letters. Of these, 79 (15.4%) were examined to determine, by using patent searches, whether the authors had properly declared any competing financial interests with regard to patent applications. The papers examined were selected because they covered the disciplines of molecular biology and genetics, including gene structure and function. Of the 79 papers, 15 were articles, 1 was a review and the remaining 63 were letters to *Nature*.

The 79 papers were subdivided according to whether they had declared any competing financial interests. When authors submit papers to *Nature*, they are required to state whether they have, do not have or do not wish to disclose whether they have any competing financial interests. The competing financial interests declaration form is available at: <http://www.nature.com/nature/authors/policy/form.html> (accessed 2 June 2006).

Searches on all the authors of the papers that did not declare competing interests were conducted using the European Patent Office search engine, esp@cenet, and the worldwide database that covers more than 70 countries and regions, including Europe, the USA and Japan. With the advanced search facilities, each of the authors' full names was entered in turn into the field “inventor”. If necessary, the

Abbreviation: PCT, Patent Cooperation Treaty

author's institution was also included in the field "applicant", to narrow the search.

If a search on an author gave a positive result, the patents or patent applications were examined in more detail to determine whether they were based directly on the research published in the papers; were related to it but arising from earlier work; or had no clear link to the published paper. If a commercial company was commonly associated with an author on patent applications, information about the company available on its website was searched to see if there was any formal link, such as adviser or employee.

In cases where a direct link existed between a paper and a patent application, information was gathered on how the paper had been publicised more widely—for example, through its inclusion in the News and Views section of *Nature* or as the subject of a press release from the journal or the author's institute.

RESULTS

Four of the papers examined (two articles and two letters) declared that they had competing financial interests.^{6–9} The authors of the other 75 papers stated that they did not have any financial interests to declare. No authors took up the third option offered by *Nature*, that of choosing not to declare their financial interests. If authors have competing financial interests, they are required to provide details of these. The authors' statement of whether there are any competing financial interests is given at the end of the paper. The details of the nature of the interest are available only on *Nature's* web-based version of the publication.

Of the four papers that declared competing financial interests, three^{6–8} acknowledged that one or more of the authors had links to a biotechnology company. Two stated that patents had been applied for on the research reported in the paper⁷ or on a part of it.⁹

Seven other papers^{10–16} did not disclose that some or all of the authors were the inventors named on patent applications arising from the work or were closely related to it. None were listed as owners or assignees of the patent; their employing institutions were listed:

1. The first of these papers,¹⁰ by researchers in Germany and the USA, was on the development of genetically modified malaria parasites for use in vaccines. The paper was first published online by *Nature* on 5 December 2004 and in the printed version of the journal on 13 January 2005. Between these dates, on 20 December 2004, three of the four authors, Kappe, Matuschewski and Mueller, filed an application under the Patent Cooperation Treaty (PCT), WO 2005/063991, "Live genetically attenuated malaria vaccine". This was not declared as a competing financial interest in the printed version of the journal. An accompanying News and Views article in *Nature* drawing attention to the paper¹⁷ was profiled on the website, SciDev Net, where funding by the Gates Foundation and the National Institutes of Health was mentioned, but not the patent application.¹⁸
2. The second paper¹¹ was on stem cells found in the hearts of newborn rats, mice and humans that can develop into heart cells at a later stage. The research from the University of California, California, USA, relies on the expression of a cell marker, islet 1, to identify the stem cells (which are called islet1+) with the potential to develop in this way. A News and Views article in the same issue of *Nature* drew attention to the paper.¹⁹ In an accompanying press release on Eurekalert,²⁰ one of the authors, Chien, says: "Conceptually, these cells could provide a cell-therapy based approach to pediatric cardiac disease, which is new for cardiology". Neither

the paper nor the press release discloses that five of the authors, Evans, Cai, Moretti, Chien and Laugwitz, filed a PCT application, WO 2004/070013, "Use of Islet 1 as a marker for isolating or generating stem cells", on 2 February 2004. This patent claims the method of using islet1 to identify cardiac stem cells and their culture.

3. The third paper¹² was about bitter taste receptors and showed, by using normal and genetically modified mice, that a class of receptors, T2R, was responsible for bitter taste. Four of the six authors of the paper, Zuker, Ryba, Mueller and Hoon, from the University of California and the National Institutes of Health, had filed a US patent application, US 2005/0048586, "T2R, a novel class of taste receptors", on 7 October 2004. This patent application claims the gene and amino acid sequences of the T2R receptors as well as methods for detecting them and screening compounds that modulate their activity.
4. The fourth paper¹³ was about the pathology of osteoarthritis, which identified a key protein, ADAMTS5, and pointed to a possible new approach to treatment. The authors of this paper all worked for Wyeth Research, Madison, New Jersey, USA, so their institutional affiliation was clear; however, they did not disclose that two of the authors, Morris and Glasson, had filed a PCT application, WO 2005/060456, "Method of treating ADAMTS-5-associated disease", on 8 November 2004. This patent application, which includes on its front page the same diagram used as fig 1a of the paper in *Nature*, describes experiments with transgenic mice (as in the paper) and claims patent protection for the use of compounds to inhibit ADAMTS-5 in several diseases. This approach contrasts with that taken by the authors, where patent applications were declared in addition to employer's name.⁷
5. The fifth paper was a review¹⁴; so the findings themselves were not the subject of a specific patent application. Both authors, Reya and Clevers, however, had patent applications directly relevant to the cell signalling system of stem and cancer cells that the review considered. Reya has patent applications (US 2004/171559 and WO 2003/102215) related to a protein, β -catenin, which was described as a central part of the Wnt signalling system identified as a possible pathway for therapeutic intervention in cancer or stem cell renewal. Clevers had a patent granted (US 5998600) in December 1999 for gene coding for a protein, Tcf, which is associated with the regulation of β -catenin and so is also part of the Wnt signalling system.
6. The sixth paper¹⁵ reported research conducted at the Universities of Sheffield and Newcastle in the UK on DNA repair associated with a protein known as PARP and breast cancer associated with the *BRCA2* gene. The paper describes how inhibitors of PARP can be used to kill breast cancer cells. A News and Views article¹⁸ referred to the paper, although it cautioned that the proposed treatment may also have negative effects. A press release on Eurekalert²² accompanied the paper in which one of the authors, Helleday, claimed that "[PARP inhibitors] could lead to revolutionary new treatments for women with hereditary breast cancer within the next five years or so". It was not disclosed that on 23 July 2004, two of the paper's authors, Curtin and Helleday, had filed a US patent application, US 2005/0143370, "Therapeutic compounds" and that Helleday had filed another PCT application, WO 2005/012524, "Use of RNAi inhibiting PARP activity for the manufacture of a medicament for the treatment of

cancer" on 25 July 2004. Curtin and Helleday's US patent application replicates figs 1a, c, d, e; 2a, b, c; and 3a, b, c, d of their paper in *Nature*. The paper in *Nature* that immediately followed this paper on the same subject⁷ clearly stated that there were competing interests because some of the authors were associated with a biotechnology company and a patent application had been filed.

7. The seventh paper¹⁶ in which authors did not declare a related patent application, reported research into the mechanisms of inflammation and its control. The scientists from the University of California described their research on the role of a protein, IKK α , in limiting the inflammatory response. The paper pointed to possible therapeutic applications of IKK α inhibitors in complicated infections or immunodeficiency. Two of the authors, Karin and Beben, however, are inventors on PCT application, WO 2005/033284, "Compositions and methods for gene expression", filed on 29 September 2004, which claims the gene sequence for IKK α and methods of identifying compounds that affect its activity.
8. The eighth paper,²³ in which competing financial interests seemed to have been omitted from the declaration, was about DNA damage and cellular responses to it in the context of acquired cancers. No directly related patents were discovered, but two of the authors, Sehested and Φ rnthoft, were inventors on unrelated patent applications together with two biotechnology companies. Examination of the websites of the companies showed that Sehested is the Chief Scientific Officer and a cofounder of the Danish biotechnology company, ϕ opoTarget (www.topotarget.com), which describes its focus as "on drugs which target key molecular mechanisms associated with the cell cycle, chromatin control and DNA damage". Φ rnthoft is the Chief Executive Officer and a founder member of another Danish biotechnology company, AROS Applied Biotechnology (www.arosab.com), which undertakes contract research and clinical trials and provides microarray services to the public and private sectors.

DISCUSSION

The research reported here indicates that failure to report competing financial interests in original research published in *Nature* is the norm, not the exception. The 6-month period from January to June 2005 is in no way abnormal in this respect. Only 4 of a possible 12 cases of such possible conflicts were reported while using a conservative standard of selecting papers, where patents that were directly related to the data reported were not disclosed. If the standards adopted by the *Journal of the American Medical Association* had been used,²⁴ which requires declaration of possible financial interests over the past 5 years and the foreseeable future, a larger number of failures to disclose are likely to have been recorded.

This finding confirms and extends other surveys^{25, 26} by considering the publication of non-clinical, basic scientific research. Most concern in the past has centred on applied and clinical research because of the closer relationship between such studies and the corporate sector. This study shows that financial interests are present and under-recorded in basic molecular biological studies. The extent of patenting of knowledge in basic molecular biology was also evident among the authors of papers not among those reported here, many of whom had filed patent applications for earlier work.

The nature of the financial reward due to inventors on patent applications depends on the financial agreements that exist between the inventors, applicants and other parties. In

some cases, there may be direct financial benefit to inventors from promoting the invention. In others, authors may benefit only indirectly (eg, through career advancement or further funding for research).

There has been controversy for some time about how the disclosure of competing financial interests by authors of research published in peer-reviewed journals should be managed.²⁷ An increasing number of journals require authors to declare whether they have any connections that may be perceived to influence their work. In relation to employment and personal financial interests, *Nature* asks the author submitting the manuscript on behalf of all the authors to declare if there are any "Recent (while engaged in the research project), present or anticipated employment by any organization that may gain or lose financially through publication of the paper" and "Stocks or shares in companies that may gain or lose financially through publication; consultation fees or other forms of remuneration from organizations that may gain or lose financially; patents or patent applications whose value may be affected by publication". It offers an additional guideline of disclosing "Any undeclared competing financial interests that could embarrass you were they to become publicly known after your work was published."

Nature is one of the most prestigious journals in the world and is seen as the benchmark of excellent and trustworthy science. A paper published in *Nature* may secure a person's future career and is considered to be an endorsement of the quality of work undertaken. It may probably be a positive indicator of future potential if any applications of the new knowledge are considered likely. Therefore, it would seem particularly important that all patent applications that are directly connected to the work should be disclosed together with any other interests, such as directorships of biotechnology companies, industry funding and consultancies. Failure to disclose such interests will undermine the authority that science can claim from its truthfulness and impartiality.

The results reported here indicate that journals need to take the disclosure of financial interests much more seriously because self-policing is not working. As others have suggested,²⁶ this may include sanctions (such as refusing to publish research from the authors for a certain period), requiring each author to complete more detailed disclosure forms such as those used by the journals published by the *American Thoracic Society*, or scientific societies could establish registers of interests as in other areas of public life. *Nature* and other journals should also summarise the financial interests of authors on the paper itself when these exist and not only in a separated form on a website. Although there may be disagreement on the extent to which financial interests influence the course of research, if they are kept secret it will be impossible to conduct studies to determine objectively what their effect may be.

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Competing interests: SM is the Director of GeneWatch UK, a public interest, not-for-profit organisation that campaigns against patents on discoveries about nature.

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