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Intellectual Property Issues in Genomics

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Controversy over intellectual property rights in the results of large-scale cDNA sequencing raises intriguing questions about the roles of the public and private sectors in genomics research, and about who stands to benefit (and who stands to lose) from the private appropriation of genomic information. While the US Patent and Trademark Office has rejected patent applications on cDNA fragments of unknown function from the National Institutes of Health, private firms have pursued three distinct strategies for exploiting unpatented cDNA sequence information: exclusive licensing, non-exclusive licensing and dedication to the public domain.

Intellectual property issues have been unusually conspicuous in the recent history of advances in genomics, even by the standards of the patent-weary genetics and molecular biology communities. Controversy has been particularly acute over intellectual property rights in the results of large-scale human cDNA sequencing. Beginning in 1991 with the filing of patent applications by the National Institutes of Health (NIH) on the first batch of expressed sequence tags (ESTs) from the laboratory of Craig Venter[1], each new development has been met with lively speculation about its strategic significance from an intellectual property perspective. Are cDNA fragments of unknown function patentable, or is further research or characterization necessary before they satisfy standards of patent law[2–9]? Will patents on such fragments promote commercial investment in product development[3,6], or will they interfere with scientific communication and collaboration, and retard the overall research effort[5,7,9]? In the absence of patent rights, how may the owners of

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private cDNA-sequence databases earn a return on their investment, while still permitting other investigators to obtain access to the information on reasonable terms[8,10–12]? What are the rights of those who contribute resources, such as cDNA libraries, that are used to create the databases[13,14], and what are the rights of those who identify sequences of interest out of the mass of information in the databases by formulating appropriate queries[15]? Will the disclosure of ESTs in the public domain preclude patenting of subsequently characterized full-length genes and gene products[3]? And why would a commercial firm invest its own resources in generating an EST database for the public domain[16]?

Two factors have contributed to the fascination with intellectual property issues in genomics research. The first is a perception that some pioneers in large-scale cDNA-sequencing have sought to claim intellectual property rights that reach far beyond their actual achievements to cover the future discoveries of others[17,18]. For example, the controversial NIH patent applications claimed not only the ESTs for which sequences were actually set forth in the specifications, but also the corresponding full-length cDNAs, as well as smaller portions of those full-length cDNAs that might not even include the disclosed ESTs (Ref. 1). More recently, private owners of cDNA-sequence databases have made access to the databases conditional upon agreement in advance to offer either a license or a right of first refusal to any resulting intellectual property rights[10–12]. These efforts to appropriate discoveries that have yet to be made by other researchers raise issues about the fairness and efficiency of the intellectual property system in allocating rewards and incentives along the path of cumulative innovation. These concerns are particularly compelling to research scientists, who have more than just commercial interests at stake in disputes over claims to inventions[19].

The second factor is the counterintuitive alignment of interests in the debate[20,21]. It was a public institution, the NIH, that initially took an aggressive position in favor of patenting discoveries that some representatives of industry thought were unpatentable and should remain unpatented, and it was a major pharmaceutical firm, Merck & Co., that ultimately took upon itself the quasi-governmental function of sponsoring a university-based effort to place comparable information in the public domain[16]. These topsy-turvy positions in the public and private sectors raise intriguing questions about the proper roles of government and industry in genomics research, and about who stands to benefit (and who stands to lose) from the private appropriation of genomic information[22].

Promoting R&D through exclusive rights

Research scientists in public institutions are often troubled by the concept of intellectual property, because they believe that science will advance most rapidly if subsequent researchers enjoy free access to prior knowledge. By contrast, the law of intellectual property rests on an assumption that, without exclusive rights, there will be too little investment in R&D (Ref. 23).

In a commercial setting, a standard argument for intellectual property is that inventions are costly to make in the first place, but cheap and easy to copy once someone else has made them. Firms will, therefore, have very little incentive to invest in research and development unless they have some means of preventing competitors from reaping the benefits of their investment without sharing in the initial risk and cost. One way of excluding competitors is to keep inventions secret, but secrecy is not always feasible and may be socially undesirable.

The patent system provides an alternative strategy for protecting inventions without secrecy. A patent provides the right to exclude others from making, using and selling the invention for a limited term – in most of the world, this is 20 years from the application filing date[24,25]. In order to get a patent, the inventor must disclose the invention fully, so as to enable others to make and use it[26,27]. Within the realm of industrial research, it is plausible that the patent system promotes more disclosure than would occur if secrecy were the only available strategy for excluding competitors from using the discovery. This is less clear in the case of research in the public sector, which is typically published with or without patent protection.

The argument for patenting inventions made in the public sector is a variation on the standard justification for patents in the commercial setting, with emphasis on the post-invention costs and risks involved in taking a new invention out of the laboratory and developing it into a successful commercial product, rather than the pre-invention costs of making the invention in the first place[20,21]. The argument is that the cost of post-invention development typically far exceeds pre-invention research outlays, and firms will be unwilling to make this substantial investment without protection from competition if the product proves successful. Patents thus facilitate the transfer of technology to the private sector by providing exclusive rights to preserve the profit incentives of innovating firms.

Public and private cDNA sequencing

Such an argument was advanced by the NIH while it was pursuing patent rights in the first few thousand ESTs identified by Venter and his colleagues[3,28]. However, the response of the intended beneficiaries of the NIH patents – the US biotechnology and pharmaceutical industries – was less than enthusiastic, suggesting that there may be some limits to the logic of promoting private appropriation of the results of publicly supported research[21]. Perhaps this was an example of the sort of research discovery that might be more effectively exploited – even by industry – if left in the public domain. Ultimately, those particular sequences entered the public domain after the US Patent and Trademark Office rejected the NIH patent claims[29].

The NIH did not continue to support the large-scale cDNA-sequencing effort that Venter and his colleagues had begun in the public sector. Instead, Venter and his group turned down a grant from the US Department of Energy and left the NIH in 1992

to form a non-profit research organization, The Institute for Genomic Research (TIGR; Rockville, MD, USA), with more generous private-sector funding[30]. The same financial backers also formed a for-profit company, Human Genome Sciences (HGS; Rockville, MD, USA), to identify and develop commercial products from the sequence information that TIGR developed[31]. Both organizations were soon engaged in a massive automated cDNA-sequencing effort, creating two, large, privately held databases of sequence information. Meanwhile, another private firm, Incyte Pharmaceuticals (Palo Alto, CA, USA) had also turned its attention to large-scale sequencing of cDNA fragments, creating a competing private database[32].

Non-patent strategies for commercial exploitation of sequence databases

Although the database owners are actively seeking patent protection on their sequences, and have obtained a few patents on sequences encoding identified peptides with disclosed function[33–35], it remains to be seen what, if any, patent rights they will ultimately obtain in sequences for which they cannot yet provide a comparable disclosure[36]. Meanwhile, they have been able to exploit the databases commercially by controlling access to them, in effect, using contracts and trade secrecy to protect their intellectual property.

The viability of contract and trade secrecy strategies for the protection of sequence information may be limited by Merck's entry into the field as sponsor of a competing cDNA-sequencing effort at Washington University (St Louis, MO, USA), the results of which are made immediately available in the public domain[16,22,37]. The commercial value of private databases is likely to decline as the information in the public domain increases; prospective licensees may hesitate to sign restrictive database-access agreements if they expect to find comparable information available in the near future on an unrestricted basis.

There are, however, differences in the information available from the public and private sources; these differences, at least to date, leave the private database owners with something to sell. How long this window of opportunity remains open will depend on whether, and how quickly, comparable information becomes available in the public domain, and on what the private firms do in the interim to maintain their advantage. Although the public-domain database is growing rapidly[38], at this point, the private databases are significantly larger[39]. Owners of the private databases also claim to offer superior products in a number of respects: they have assembled contiguous fragments of cDNA into longer sequences; they provide more-complete annotations for the sequences, including information about expression in different types of tissue; and their sequence information comes with high-powered bioinformatics capabilities and user-friendly software. Inasmuch as all the information that enters the public database also promptly becomes available in the private databases, the public database can never be superior to the private databases. Nevertheless, the free availability of the public database enhances the value of the sequences it includes as a resource for discovery in certain respects. For example, sequences in the public database are being mapped[40], and the mapping information is also promptly made available in the public domain, enhancing the value of the public database sequences to positional cloners[41].

The value of the public database could be limited by the pending patent applications of private database owners. If these applications ripen into issued patents, they could subsequently pre-empt the use of any sequences that they cover, even if those sequences were publicly disclosed prior to issuance of the patents, as long as the patent applicants are able to establish their priority. Because US patent applications are maintained in confidence until a patent is issued[42], it is impossible to determine, at this stage, what sequences have been the subject of patent applications. Therefore, those who make use of sequences obtained from the public database cannot be sure that the sequences will remain in the public domain, and may face a future injunction against continuing use of sequences that are subsequently patented by HGS or Incyte on the basis of previously filed patent applications. Of course, the same uncertainty applies to sequences obtained from the private databases – a sequence obtained by a subscriber to the Incyte database might turn out to be covered by a previously filed HGS patent, for example. Because the Merck initiative got off to a late start, its sequences are more likely to be covered by prior patent applications of the other firms.

Exclusive licensing, non-exclusive licensing, and the public domain

Meanwhile, in the absence of issued patents for all but a few of their sequences, the owners of private databases may be able to convert their current control over access to databases into a valuable proprietary position in subsequent future research discoveries. The actions of HGS, Incyte and Merck show three distinct strategies for exploiting unpatented information: exclusive licensing, non-exclusive licensing and dedication to the public domain. As each of these approaches comes from the private sector, we can assume that each firm believes, rightly or wrongly, that its strategy will maximize the value it obtains from the information. The strategies are quite different, but they are interdependent, and it is still too early to tell how each will pay off. However, we can see how different firms are placing their bets, and we also have some idea of the size of those bets.

Exclusive licensing

HGS has sold a three-year exclusive right of access to its database to SmithKline Beecham (SB) in exchange for US$125 million, to be made in payments over a three-year period, plus royalties on product sales[31,43]. The agreement gives SB a 'right of first refusal' to develop and market protein therapeutic and diagnostic products using the information in the database,

but it does not cover gene therapy or antisense products – HGS has entered into separate collaborative agreements with other research partners for the development of products in these areas[44]. During the three-year period of SB's license, investigators in academic and non-profit institutions may obtain access to portions of the database if they and their institutions sign a Database Access Agreement[45,46] or a Material Transfer Agreement[10,47]. The terms of these agreements vary depending on whether the sequence was identified at TIGR or HGS, and whether it has a counterpart in a public database. Access to HGS sequences that have not yet been disclosed or have been partially disclosed in a public database is permitted only to those who sign a Material Transfer Agreement granting 'a sole and exclusive worldwide right and license' to HGS to develop any resulting products on terms to be negotiated in the future[47]. Academic investigators may obtain access to TIGR sequences that have not yet been disclosed in a public database if their institutions sign a Database Option Agreement granting HGS 'a sole and exclusive option to obtain a sole and exclusive or a non-exclusive worldwide royalty bearing license' to resulting products[41,42]. Sequences that have been disclosed or partially disclosed in a public database are available on less-restricted terms, but even for these sequences, investigators are limited to a specified number of queries that may be recorded, stored and monitored by the Database Manager[46]. No outside investigators may trawl through the database or manipulate its contents at will, and commercial investigators may not obtain access to the database at all.

An obvious advantage of this exclusive-licensing strategy, at least from the perspective of HGS, is that it has generated a lot of revenue. SB placed a very large bet, but we don't yet know how it will pay off. An obvious concern with the exclusive-licensing approach is that restricting access to the database to such a degree may limit the value that is extracted from the information during the term of the exclusive license. Indeed, as the term of SB's exclusive license under the original agreement comes to an end, HGS and SB appear to be departing from their original exclusive licensing strategy in favor of allowing more firms to tap into the database. Within the past year, HGS and SB have entered into collaborative agreements (or, in one case, signed a letter of intent to enter into such an agreement) to allow four additional pharmaceutical firms [Takeda Chemical Industries[48], Merck KGaA (not related to Merck & Co.)[49], Schering Plough and Synthelabo SA (Ref. 59)] to share access to the database, evaluate the information and develop related products. These new collaborators will make total payments of at least US$140 million to HGS and SB over a five-year period, not including milestone payments and royalties. In addition to bringing in new revenue, it is likely that these new agreements will increase the amount that is learned from the database by expanding the universe of investigators who are able to make queries.

Non-exclusive licensing

Incyte has offered non-exclusive licenses, at a considerably cheaper price, to as many firms as will take them, with eight firms having signed up as database subscribers to date. Upjohn (now Pharmacia & Upjohn) and Pfizer have each signed non-exclusive agreements with Incyte, involving payments in the region of US$20–25 million, including amounts for the purchase of Incyte stock, plus royalties on product sales[50]; Novo Nordisk and Hoechst have signed similar agreements on undisclosed financial terms[51,52]; and Abbott Laboratories subsequently signed an agreement that Incyte characterized in a press release as 'the largest financial commitment by a subscriber to date', although these terms include payment for sequencing microbial genomes[53]. When Incyte announced its sixth subscriber, Johnson & Johnson, the accompanying press release claimed that the six subscribers will pay a minimum combined total of US$100 million, excluding contingent payments such as milestones and product royalties[54]. Since that announcement, Incyte has entered into additional agreements with Hoffmann-La Roche[55] and Zeneca[56]. Incyte's subscribers have placed smaller individual bets than SB did but, in the long run, there could be quite a number of subscribers. Although the HGS strategy initially appeared to generate more revenue for the database owner, Incyte's strategy may yet prove to be more lucrative. One might expect that Incyte's window of opportunity for signing up new subscribers would be closing as the Merck-sponsored sequencing effort at Washington University expands the competing public database; however, all but the first of Incyte's subscribers have signed up since Merck announced its competing effort.

From a broader social standpoint, the size of the ultimate payoffs is more interesting than the size of the bets placed. Which approach will yield more discoveries or commercial products? Although the non-exclusive strategy seems more likely to take advantage of the different capabilities of different commercial firms, a drawback of the Incyte approach is that the company has not yet figured out how to make its database available to academic investigators without undermining its value to corporate subscribers. At present, academic investigators may only obtain access to the database by collaborating with one of Incyte's subscribers.

Public domain

The Merck strategy of putting sequence information in the public domain is the newest approach and, at least at first glance, the most puzzling. How does this strategy advance Merck's own interests? By putting the information in the public domain, Merck can generate the information more cheaply – indeed, almost unbelievably cheaply. Merck is placing a very small bet, somewhere under US$10 million[57]; this is a fraction of the amounts spent by Pfizer and Upjohn for their non-exclusive deals with Incyte, and a tiny fraction of the amount spent by SB for its exclusive deal with HGS. By positioning itself as a public benefactor, Merck is able to take advantage of existing infrastructure

at Washington University, previously put in place with public funds, for use in its sequencing effort. Merck has also been able to obtain other inputs at nominal cost that it would have had to pay a premium for if it were trying to assemble a private database[13].

Apart from generating the sequence information more cheaply, Merck claims that it expects to derive more benefit from the information by distributing it widely[58]. As Merck sees it, the sequence information will not yield products for commercial development until further fundamental research is done to elucidate the functions and biological pathways associated with the partially sequenced genes. Merck's comparative advantage does not lie in performing this fundamental research, but rather in developing specific drugs at a later stage in the R&D process. Nothing compels researchers who use the database to bring any potential products to Merck for commercial development, but Merck is confident that its capabilities and resources will allow it to capture an adequate share of resulting products to justify its modest investment in generating the database.

Some observers have suggested a more cynical motivation: that Merck seeks to undermine the value of investments already made in existing sequence databases by its commercial competitors[58]. Putting the information in a public database leaves HGS and Incyte (and their collaborators) dependent on patent rights to protect their proprietary positions in the long run, and Merck may be betting that they won't obtain much in the way of patent rights.

The Merck data may enhance the value of existing databases as a resource for discovery, but it plainly undermines the value of the databases as intellectual property, at least to the extent that they are unprotected by patent rights. This distinction highlights the very different ways in which the sequence information is valued by Merck on the one hand, and HGS and Incyte on the other. From Merck's perspective, cDNA sequences are research tools for use in drug discovery, not products for sale to consumers. For HGS and Incyte, cDNA sequences are, themselves, an immediate source of revenue.

Merck's own strategy for making money does not rely on maintaining a proprietary position in cDNA sequences, so it has little to lose, and possibly something to gain, by putting such sequences in the public domain. Merck does not have any therapeutic protein or DNA diagnostic products that might require proprietary rights in DNA sequences to be commercially viable. Far more important to Merck's commercial position are its proprietary rights in the small molecules that it hopes to develop and sell as pharmaceutical products.

Apart from the question of whether Merck makes any money out of the sequence information that goes into the public domain, it will be interesting to see how other firms and publicly funded investigators put this information to use. Will the non-proprietary character of the information lead commercial firms to shun the data for fear of being unable to exclude competitors from the market for any resulting products, or will the public database be actively and widely exploited? Preliminary indications suggest that as the data come on line they are raising considerable interest, with accessions to GenBank showing a dramatic increase[38]. A large part of this increase has come in the form of anonymous file transfer protocol (ftp) downloads of the entire database, a form of query that is likely to be popular with commercial users who do not want to risk showing their hands to competitors by leaving an electronic record of what it is they are looking for.

Public versus private

These three different approaches highlight striking differences in the interests of different companies in proprietary rights in the human genome: HGS and Incyte may benefit from a strategy that promotes the private appropriation of DNA sequences, whereas Merck may benefit from a strategy that puts these sequences in the public domain. One firm's research tool may be another firm's end product. However, in an important sense, the fact that Merck chooses to put cDNA sequences in the public domain is more instructive than the fact that HGS and Incyte choose to appropriate them as private property. Whenever new property rights come into view, someone will step forward to claim them, and it is unsurprising to hear the claimants assert that private ownership will enhance the public welfare. It is far more uncommon for a private firm to disclaim proprietary rights in the information it generates and to sing the praises of the public domain.

The Merck initiative raises fundamental questions about the boundaries between public and private in research science and product development. Previously, one could give a coherent account of these boundaries in theory, however blurred they may have been in practice: public research tended to focus on the pursuit of fundamental knowledge that was not readily appropriable by a private owner, and that would have the greatest social value if it was widely distributed with no restrictions on its use; by contrast, private research tended to focus on narrower applications of scientific principles that were readily appropriable by innovating firms, and these firms required proprietary rights to make their investments in R&D profitable. Publicly supported research was presumptively placed in the public domain, while privately supported research was typically appropriated as intellectual property.

These boundaries are now more difficult to maintain, particularly in fields of such obvious commercial interest as genomics. Researchers in the public and private sectors are often working on the same problems, whether competitively or collaboratively, and the prevailing wisdom is that institutions performing publicly sponsored research should patent their discoveries to promote commercial development. In this environment, we lack a clear strategy about when it makes sense for the public to sponsor research, and when it makes sense to dedicate new knowledge to the public domain.

When public policy promotes the private appropriation of research results as intellectual property, even when they emerge from public sector research, it is easy to lose sight of the public and private benefits of disseminating information in the public domain. The most obvious of these benefits is that free availability encourages widespread use of information and minimizes transaction costs. Travel on a freeway is both cheaper and faster than travel on a route with numerous tollbooths. Similarly, R&D is cheaper and faster if it uses resources that are freely available than it is if the road to product development requires frequent stops to negotiate licenses for access to prior discoveries. Free roadways can also enhance the value of private property by making it more readily accessible. Thus, free dissemination of information via the Internet helps firms attract customers. A vigorous public domain can supply a meeting place for people, information and ideas that might not come together in the course of more organized, licensed encounters. For fields of research that draw heavily upon work carried out in the public sector and in academia, it is particularly relevant that information in the public domain is accessible to relatively poorly funded users who would otherwise be priced out of the market. Thus, for example, if academic researchers are particularly important to the progress of research in a field, as Merck evidently believes they are for understanding the human genome, then the overall research enterprise could be significantly retarded by property rights that restrict their access to essential resources and information.

If, in fact, ESTs have more social value in the public domain than in the hands of private owners, perhaps government sponsors should have taken upon themselves the burden of supplying this resource to the public, rather than leaving it to the private sector. On the other hand, perhaps the extent of private-sector interest in supporting large-scale cDNA sequencing indicates that this work does not require government funding, and that public resources would be better spent on other projects. The Merck initiative invites the optimistic conclusion that there are limits to how far the government can go wrong – that if the stakes are high enough, someone in the private sector may find it worthwhile to correct for any errors in judgement on the part of the government, and maybe even to pick up the tab. It would, however, be foolish to conclude on the basis of this extraordinary episode that we can rely on the private sector to enrich the public domain while public research institutions pursue patent rights. Perhaps a better lesson to draw, is that we may have underestimated the value, to the private sector as well as to the public sector, of a rich public domain, and that we may need to reconsider the limits of private appropriation of new information as a means of promoting commercial development.

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