approaches. Breeders wanted the 'physiology' of heredity, not its biometrics.

Before the first decade of the century came to a close, Mendelian heredity had been applied successfully to continuously varying traits, but this did not clear the way for the reconciliation of the opposing sides. The inadequate understanding of the nature of mutation remained. Although estimates of MUTABILITY in the chromosomes of the fruitfly were published in 1919, it was not until 1923 that the idea of mutation as RECURRENT[36] and measurable in the form of a statistical value for a given mutant in a population began to appear in the literature. Until mutation ceased to be considered unpredictable and for the most part saltatory, and so long as mutants were associated with what were considered unimportant or useless characters, there was no way in which Darwinian evolution and Mendelian genetics could come to terms with each other. But Mendelism and horticulture did not have to wait, even though the benefits of Mendelism were only slowly realized.

Robert C. Olby is at the Department of the History and Philosophy of Science, 1017 Cathedral of Learning, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA.
e-mail: olbyr+@pitt.edu

Links

FURTHER INFORMATION Mendelweb | Genetics timeline | Mendel's 1865 paper "Experiments in plant hybridzation." | Galton's 1898 paper "A diagram of heredity." | Bateson's 1899 paper "Hybridization and cross-breeding as a method of scientific investigation." | Bateson's 1900 paper "Problems of heredity as a subject for horticultural investigation." | Bateson's 1902 book "*Mendel's Principles of Heredity, a Defence*" | The Royal Horticultural Society of London | Robert Olby's homepage

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SCIENCE AND SOCIETY

Genomics in the public domain: strategy and policy

Rebecca S. Eisenberg

The public domain has been conspicuous in media accounts of public and private sector initiatives to complete the sequence of the human genome. The issue of whether the human genome will be freely available to the public or privately held as a proprietary resource has captured the attention of the scientific, trade and popular press, the financial markets, and even heads of state. Although some media commentary has framed the issue as a conflict between ethics and greed, strategic considerations go a long way towards explaining the timing and quality of information disclosures on both sides of the public–private divide.

Some descriptions of the relationship between Celera Genomics Corporation and the Human Genome Project have painted a black-and-white picture of a private firm racing to profit from patents while the publicly funded project struggles to keep the genome in the public domain. In fact, both sides of the picture are variegated. Even as it has built a proprietary database and filed patent applications, Celera has repeatedly promised that it will eventually make the raw sequence of the human genome available to scientists free of charge[1], although the timing and details of this commitment are unclear and seem to have shifted. At the same time, although the public sponsors of the Human Genome Project have consistently affirmed the importance of prompt and free public access to raw genomic sequence data (BOX 1), the United States government reportedly holds more patents on DNA sequences than any private firm[2]. Public and private strategies for publication and patenting have overlapped throughout the brief history of genomics research[3]. An important factor contributing to this convergence has been the policy of the United States gov-

ernment, beginning with the passage of the Bayh–Dole Act of 1980, to promote the patenting of government-sponsored research results[4]. This policy has added strategic complexity to decisions concerning public disclosure of research results, as both academic and private institutions have become increasingly mindful of the interaction between the public domain and the patent system. Meanwhile, the increasing scientific significance of private sector research accomplishments has underscored the importance of timely publication of research results in both the public and private sectors.

What motivates these different players to disclose information to the public? How do the missions and priorities of different institutions in the public and private sectors affect the timing and quality of their disclosures?

Reasons for disclosing research results

Scientific recognition and credibility. A perennial motivation for publication of new research results is to stake claim to scientific achievements, thereby triggering recognition. Public disclosure subjects research results to scrutiny, exposing errors and promoting confidence in the validity of the results. It also establishes a priority date for purposes of scientific recognition. These considerations are particularly important for controversial research claims and for disputed claims of scientific priority in a close race.

The goal of scientific recognition undoubtedly motivates both academic and private sector researchers involved in sequencing the human genome. The sponsors of these research efforts depend on access to top scientific talent and cannot afford to ignore the motivations of scientists to achieve recognition in the scientific community. Rivalry for scientific recognition has been aggravated in this particular context by past statements from each side that the other is pursuing a scientific strategy that will not permit satisfactory completion of the job[5,6].

This may be an important reason why Celera, although hoping to profit from selling access to proprietary DNA sequence databases, has nonetheless consistently promised to make the raw sequence of the human genome freely available. Without such public disclosure its claims to priority will be impossible for the scientific community to assess. Researchers have expressed scepticism in the past about the claimed accomplishments of private DNA sequencing firms that do not make their data publicly available[7]. The scientific community gives more credence to claims backed by publicly accessible data than to claims backed only by press release and rumour.

Scientific credibility is also cited by members of the SNP Consortium (BOX 2) as a motivation for making single nucleotide polymorphisms (SNPs) publicly available. The pharmaceutical firms in the SNP Consortium hope to use SNPs as pharmacogenomic markers to develop drugs for which safety and efficacy depend on genotype. Regulatory approval for such products is likely to depend on the reliability of genetic screening tests that predict drug responses of particular patients. Consortium members hope that it will be easier to win approval if the tests use markers that are in the public domain, and are therefore subject to challenge and validation by the scientific community[8].

Publication to the scientific community is inconsistent with long-term secrecy, but it is not inconsistent with patenting. Patent disclosures are made freely available to the public once the patent issues under United States law, and pending patent applications are made public 18 months after their filing dates in most of the world. Even before public disclosure through the patent system, institutions may permit scientists to publish while still preserving patent rights if they coordinate the timing of publication with the filing of patent applications. In most of the world, disclosure of an invention in a publication before patent filing results in a forfeiture of patent rights[9], but United States law permits the filing of a patent application up to one year after publication[10]. So publication of research results is no guarantee that the results are free of intellectual property claims, nor is forfeiture of patent rights a condition for scientific recognition.

Widespread dissemination and use. Apart from concerns about recognition and credibility of research claims, some institutions might choose to disclose DNA sequence information in publicly available databases in order to promote widespread dissemination and use. Free access is particularly important for encouraging users with limited financial resources (such as academic researchers), who might otherwise be unable to gain access to past discoveries for use in future research. In addition to eliminating licence fees, free availability minimizes transaction costs by eliminating the need for owners and users to find each other and negotiate licences.

Apart from advancing the public interest in promoting future research, free access might also advance the financial interests of its champions. For example, the public sponsors of the Human Genome Project are also likely to sponsor future research that makes use of genomic information. If the information is held in proprietary databases or can only be used under the terms of licence agreements, these research sponsors might expect to pay more in the future than they would if the information were in the public domain.

Some private research sponsors might also believe that it serves their financial interests to promote widespread access to DNA sequence information by putting it in the public domain. Life sciences firms that hope to profit from developing and selling new products, such as drugs and crop seeds, might expect to earn more profits sooner by accelerating progress in fundamental biological research, thereby bringing new commercial products into view. Rather than trying to do this fundamental research themselves — an expensive

Box 1 | Bill Clinton and Tony Blair on genome data access

United States President, Bill Clinton and United Kingdom Prime Minister, Tony Blair issued the following statement concerning access to genome sequence data, on the 14 March 2000.

"To realize the full promise of this research, raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere. Unencumbered access to this information will promote discoveries that will reduce the burden of disease, improve health around the world, and enhance the quality of life for all humankind. Intellectual property protection for gene-based inventions will also play an important role in stimulating the development of important new health care products.

We applaud the decision by scientists working on the Human Genome Project to release raw fundamental information about the human DNA sequence and its variants rapidly into the public domain, and we commend other scientists around the world to adopt this policy."

(Photo by Mark Wilson, Newsmakers.)

job at which they have no comparative advantage — they might prefer to let academic scientists do the research with public funds. To the extent that free access facilitates pre-market research in universities, these firms may find their interests aligned with the interests of public research sponsors in promoting free disclosure of DNA sequence information in the public domain. This may explain why Monsanto recently decided to release a rough draft of the rice genome in the public domain[11], and why Merck was willing to invest in university-based research to generate a database of expressed sequence tags (ESTs) for the public domain[12].

Defeating potential patent claims. Another consideration that seems to be motivating public disclosures of genomic information by some institutions in both the public and private sectors is a wish to prevent patenting of DNA sequences. This seems to be one factor driving the requirement that publicly funded investigators deposit all newly identified DNA sequences and mutations in the publicly accessible GenBank database within 24 hours under the 'Bermuda rules' (BOX 3). This accelerated timetable, which makes it difficult for grantees to get patent applications on file before public disclosure, also leads to the prompt creation of 'prior art' that could defeat potential patent claims of others. A subsequent inventor cannot patent something that was already publicly disclosed before the patent claimant discovered it[13].

Of course, the requirement for prompt deposit in the public domain could be justified as a way of giving the scientific community the benefit of free access to as much sequence information as possible as quickly as possible, without invoking an anti-patent motivation. But the Bermuda rules are not the only evidence of an anti-patenting norm for raw DNA sequence information within the Human Genome Project. The National Human Genome Research Institute has explicitly discouraged grantees from pursuing such patents (BOX 4).

Francis Collins (right), director of the National Human Genome Research Institute and Craig Venter, president of Celera Genomics Inc. at a press conference to mark the completion of the first draft of the human genome sequence, 26 June 2000. (Photo by Alex Wong, Newsmakers.)

The creation of prior art may prevent the issuance of patents not only on past discoveries that are publicly disclosed, but also on future discoveries that become obvious in light of past disclosures[14]. This raises the possibility of publishing early research results as a strategic move to pre-empt the patenting of future discoveries by commercial rivals[15,16]. It might even be possible for a firm that is lagging in a race to forestall the patent claims of a swifter rival through publications that enrich the prior art enough to limit what may be patented in the future. This possibility might explain why it is often the laggards rather than the leaders in DNA sequencing races that sing the praises of the public domain. So, for example, when Merck decided to sponsor the Merck Genome Initiative, at least two private firms already had a significant lead over Merck in generating private databases of ESTs[17]. By putting ESTs in the public domain, Merck may have hoped to create prior art that would defeat future patent claims by these or other firms to the corresponding full-length genes, although it now seems unlikely that this strategy will prove successful[18,19]. The creation of patent-defeating prior art is an acknowledged part of the strategy of the SNP Consortium. Again, the SNP Consortium entered the race late, after numerous other private sector SNP discovery efforts were well under way[20]. Under these circumstances, patent-defeating publication may have seemed like the best hope for Consortium members to preserve future access to information that would otherwise become proprietary. But if the patent-defeating goal dominates the goal of prompt dissemination of information, prompt publication in the public domain may not be the best way to proceed.

In fact the SNP Consortium, in contrast to the Merck Genome Initiative and participants in the Human Genome Project that comply with the Bermuda rules, does not publish all of its information as quickly as possible. Instead, it uses a patent law device called a Statutory Invention Registration (SIR) to create prior art while delaying publication (BOX 2).

The mechanism for creating prior art before public release is codified at § 157 of the United States Patent Act. This provision authorizes the United States Patent and Trademark Office (PTO) to publish a patent application that has been converted to a SIR, without examining it for patentability, if the applicant waives the right to receive a patent on the invention within a specified period of time. A SIR has the 'attributes specified for patents', but does not include the right to exclude others from making, using, selling or importing the invention[21]. One attribute of a patent is that it is effective as prior art for purposes of defeating the patent claims of other applicants as of its filing date[22], even though it might not be published for some time thereafter. It is therefore possible to file a patent application describing a discovery, wait a while before converting it to a publicly accessible SIR, and have the SIR count as prior art as of its filing date, even though the disclosure was not yet published on that date. Through the use of this device, the SNP Consortium hopes to create prior art that will prevent subsequent inventors from patenting their newly identified SNPs, while deferring disclosure of the SNPs until after they have been mapped. This strategy for prior art creation combines the benefits of disclosure with the benefits of nondisclosure.

Reasons for withholding results

Institutions in both the public and private sectors may have compelling reasons for withholding research results from disclosure. How these reasons are balanced against the reasons

Box 2 | The SNP Consortium

Members of the SNP Consortium include the Wellcome Trust, APBiotech, AstraZeneca PLC, Aventis, Bayer AG, Bristol-Meyers Squibb Company, F. Hoffmann-LaRoche, Glaxo Wellcome PLC, IBM, Motorola, Novartis, Pfizer Inc., Searle and SmithKline Beecham PLC.

"The SNP Consortium, Ltd. (TSC) has been formed to advance the field of medicine and the development of genetic based diagnostics and therapeutics, through the creation of a high density single nucleotide polymorphism (SNP) map of the human genome. This map will be freely available to all parties (members and non-members) at the same time."

The SNP Consortium candidly describes its intellectual property strategy as follows:

"The overall IP objective is to maximize the number of SNPs the [*sic*] (1) enter the public domain at the earliest possible date, and (2) to be free of third-party encumbrances such that the map can be used by all without financial or other IP obligations. To meet objective (2), the [SNP Consortium] intends to withhold public release of identified SNPs until mapping has been achieved to prevent facilitating the patenting of the same SNPs by third parties. Mapped SNPs will be publicly released quarterly, approximately one quarter after they are identified. The intellectual property plan is intended to maintain the priority dates of discovery of the unmapped SNPs during the period between identification and release, for use as 'prior art'."

Box 3 | The Bermuda rules

The Bermuda rules derive their name from an agreement entered into at the International Strategy Meeting on Human Genome Sequencing held in Bermuda on the 25–28 February 1996, sponsored by the Wellcome Trust[26].

"It was agreed that all human genomic sequence information, generated by centres funded for large-scale human sequencing, should be freely available and in the public domain in order to encourage research and development and to maximise its benefit to society."

The Bermuda rules have been criticized for promoting public disclosure of data that have not been checked for accuracy[27].

for making disclosure will vary depending on the priorities of the institution.

Retaining exclusive access for customers. An obvious reason to withhold commercially valuable information from public disclosure is to preserve its value for sale to paying customers. Nobody wants to pay for something that they can get free. Firms like Incyte Genomics and Human Genome Sciences that seek to profit from selling access to proprietary databases are therefore understandably reluctant to give the same information away free in public databases. Why, then, is Celera promising to make the raw sequence of the human genome freely available? Sometimes limited disclosure of information in the public domain is consistent with selling a proprietary information product that offers further value over the public domain version[23]. Celera's paying customers gain access to sequence data before the public-release version becomes available, as well as getting annotations and proprietary bioinformatics capabilities that will not be released in the public domain.

Avoiding disclosure to rivals. Another reason to withhold information from publication is that public disclosure lets your rivals know exactly what you have accomplished and gives them the benefit of what you have learned so far. This seems to be a concern for both public and private sector researchers involved in sequencing the human genome. Celera has cited concern that competitors will repackage their data and sell it in competition with them to justify restrictions on use of the version of the human genome sequence that they promise to make available free of charge[24]. For their part, some participants in the public sector Human Genome Project feel aggrieved by Celera's inclusion of data that they themselves deposited in GenBank in its claim to have completed the sequence of the human genome. Some scientists are particularly indignant that Celera's publications might include data deposited in GenBank by academic investigators who would not be included as co-authors[25].

In a race to accumulate information, everything one discloses in the public domain becomes available to one's rivals and helps them get ahead. If one side makes its data freely available and the other side keeps its data secret, the rival that relies on secrecy will always know at least as much as the rival that promptly discloses its data.

Sometimes information disclosures will be of more value to the secretive rival than to the disclosing rival because of the cumulative value of combining public data with private data. Suppose, for example, that two rivals, Public University and Private Company, each sequence different portions of the same gene. Suppose further that the patent system offers more generous protection for full-length genes than for gene fragments. (Although the matter is not free from doubt, this seems to be consistent with the position of the PTO as reflected in recently disclosed training materials for patent examiners in applying the written description and utility guidelines.)

If Public University freely discloses its portion of the gene in GenBank, Private Company might add that information to the partial sequence it already has, quickly complete the full-length sequence, and file a patent application that it would not have been in a position to file without the Public University disclosure. So prompt disclosure in the public domain can be treacherous if your ultimate goal is to keep information freely available. Although disclosure creates potentially patent-defeating prior art, it may also enhance the value of complementary private information, and perhaps even make it easier for rivals to get patents.

This may explain why the SNP Consortium defers disclosure of its newly identified SNPs by filing SIRs instead of publishing. As well as delaying additions to the proprietary SNP collections of their rivals, the deferred-disclosure strategy allows the Consortium to conceal from its rivals just what it has accomplished so far, creating uncertainty as to which SNPs are worth patenting and which are already in the prior art. However, the SIR strategy does not make as much information available to the research community as quickly as prompt publication or posting on a website would do, leaving those who need prompt access to SNPs with nowhere to turn but proprietary collections. But as the SIR strategy promises eventual disclosure, those with less urgent needs may be content to wait, knowing that the Consortium's SNPs will soon be freely available.

If the goal of promoting immediate public access dominates the goal of defeating future patent claims, then publication might make more sense than patent filing. This may be one reason why the sponsors of the Human Genome Project, whose overarching mission is to promote research, call on their grantees to deposit their data promptly in GenBank in accordance with the Bermuda rules rather than to file patent applications and defer disclosure pending conversion to SIRs. But the public sector Human Genome Project has paid a price for this policy — it has advanced the competitive position of their private sector rivals in the race to complete the sequence of the human genome, and may have enhanced their patent positions.

"Public disclosure of genomic information advances some interests while harming others, with no simple distinction between the interests of public and private institutions."

Preserving patent rights. A final reason for deferring disclosure of DNA sequence information is to preserve the possibility of obtaining viable patent rights in the future. This

Box 4 | NHGRI policy on release of human genome sequence data

The National Human Genome Research Institute issued the following policy statement on the 7 March 1997.

"In NHGRI's opinion, raw human genomic DNA sequence, in the absence of additional demonstrated biological information, lacks demonstrated specific utility and therefore is an inappropriate material for patent filing. NIH is concerned that patent applications on large blocks of primary human genomic DNA sequence could have a chilling effect on the development of future inventions of useful products…NHGRI will monitor grantee activity in this area to learn whether or not attempts are being made to patent large blocks of primary human genomic DNA sequence."

Box 5 | **European Parliament directive on patenting**

Directive 98/44/EC of the European Parliament and of the Council of the 6 July 1998 on the legal protection of biotechnological inventions, Official Journal L 213, 30/07/1998 p. 0013–0021 Article 5:

- **The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.**
- **An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.**
- **The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.**

concern may motivate some institutions to defer publication in precisely the circumstances that it motivates other institutions to make prompt disclosure. The difference depends on whether they believe that preempting future patents is good or bad. Apart from concern about preserving their own patent rights, public research sponsors and publicly funded research performers may worry that premature public disclosure could prevent them from complying with their mandate under the Bayh–Dole Act to promote technology transfer and product development by patenting research results. Indeed, this concern was cited by former NIH director Bernadine Healy in support of the decision to file patent applications on the first ESTs identified by Craig Venter when he was at NIH[25].

In fact, it does not seem that publication of raw genomic DNA sequence will prevent the issuance of patents on genes that are subsequently found to lie within that sequence under United States law. The situation in Europe is less certain and awaits clarification of national laws in response to a 1998 directive of the European Parliament on the legal protection of biotechnological inventions (BOX 5). Although the patent system has not yet resolved many of the legal issues that will determine what portions of the human genome may be patented, for the time being there seems to be little threat that disclosure of the human genome in the public domain will leave future researchers who identify and characterize genes with nothing left to patent.

Conclusion

Complex and interrelated strategies for endowing the public domain are at work in the field of genomics. These strategies arise out of the varied plans of different institutions for extracting value out of genomic information, complicated by the interplay of the public domain with the patent system. Public disclosure of genomic information advances some interests while harming others, with no simple distinction between the interests of public and private institutions. Understanding these interests might do more to enlighten public policy debates about the importance of the public domain in genomics research than appeals to ethical imperatives.

Rebecca S. Eisenberg is the Robert & Barbara Luciano Professor of Law at the University of Michigan Law School, Ann Arbor, Michigan 48109, USA. e-mail: rse@umich.edu

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Links

COMPANIES Celera | Monsanto | Merck | Incyte |Human Genome Sciences

FURTHER INFORMATION Human Genome Project | Joint statement by Bill Clinton and Tony Blair | The SNP Consortium | The Bermuda rules | National Human Genome Research Institute policy on patenting of human genomic sequence | Interim utility guidelines and written description guidelines for Patent Examiners | European Parliament directive on patenting

OPINION

Evo-devo: the evolution of a new discipline

Rudolf A. Raff

The history of life documented in the fossil record shows that the evolution of complex organisms such as animals and plants has involved marked changes in morphology, and the appearance of new features. However, evolutionary change occurs not by the direct transformation of adult ancestors into adult descendants but rather when developmental processes produce the features of each generation in an evolving lineage. Therefore, evolution cannot be understood without understanding the evolution of development, and how the process of development itself biases or constrains evolution. A revolutionary synthesis of developmental biology and evolution is in progress.

Developmental and evolutionary biology are two disciplines that explore morphological change in organisms over time. However, the processes involved are different. Development is genetically programmed and cyclical. Evolution is non-programmed and contingent. Although a