EXHIBIT 2

NOBEL PRIZE FOR DISCOVERIES IN GENETICS

Heritage of humanity

The 2002 Nobel Prize in physiology or medicine was presented this month to John Sulston, Sydney Brenner and H Robert Horvitz for discoveries about the genetic regulation of organ development and programmed cell death. John Sulston is also a principal player in another remarkable scientific endeavour, the human genome project. The entire sequence of the genome will be made public next year, despite many obstructions because of greed over lucrative genetic patents.

by John Sulston

ALTHOUGH the genome is the starting point for human life, we should view it as a source of possibility rather than as a constraint. Many fear that individuals' genetic information will be used against them, and these concerns should be taken seriously. Insurers are pushing for the right to use genetic test results in deciding whether or not to issue policies. If permitted by law, insurers and employers could make genetic testing a prerequisite for issuing policies or offering jobs. We should oppose such discrimination.

And since people continue to suffer from cancer, heart disease, senile dementia and other diseases, newspaper headlines such as "Miraculous gene code could eradicate all disease" will only lead to disappointment.

Still, our recently acquired genetic knowledge is enormously valuable to the twin fields of biology and medical research. That is why it is so important to complete a definitive version of the preliminary human genome sequence – the draft version's release was celebrated worldwide on 26 June 2000 – and to give researchers access to the data without delay. The sequence will be completed sometime next year and should become a permanent scientific archive and reference tool.

The genome will undoubtedly have a huge impact on people's choice of diet and lifestyle. In Western societies this will be a major marketing opportunity: I fear that people will begin choosing restaurants according to their genotype.

In all likelihood we will develop new drug treatments for hard-to-treat diseases over the next decade. For example, Mike Stratton's cancer team at the Sanger Centre is currently screening tumours to see how they differ genetically from normal tissues. In many cases it is still easier to kill a cell than to cure it. Genome information may help drugs find targets on cancer cells and destroy

cells selectively, leading to fewer side-effects and better remission rates.

Genome sequencing is a major step forward for our knowledge of the human body at the molecular level. Yet we are only in the early stages. We still do not know what most of the genes look like, nor do we know when or where they are expressed as proteins. The genome by itself does not provide answers to any of these questions. Nevertheless, the information is available to everyone as a resource tool. The next step is to track down all the genes, determining their significance, their location and how their control signals work.

In November 1995 Stratton's team at the United Kingdom-based Institute of Cancer Research (ICR) found a mutation in one of their breast-cancer gene "families", apparently connected with the BRCA2 gene. The region containing that gene had just been sequenced at the Sanger Institute, and within two weeks the ICR team had not only confirmed the discovery but found five more mutations. Stratton moved fast to publish the findings in the international weekly scientific journal Nature, keeping them secret from his colleagues until the last minute. But despite his efforts, some information reached Utah-based Myriad Genetics Inc in the United States, which then located the gene. Myriad's chief scientific officer, Mark Skolnick, then filed a patent application - on the day before the ICR paper was published.

With the threat of commercialisation looming, the ICR moved to patent the mutations it had discovered. At the same time, Myriad used its own patent applications to claim rights to the BRCA2 gene as well as to the entire BRCA1 gene, which Myriad's scientists were the first to clone. Myriad set up a commercial diagnostic laboratory, and once its patents were granted, the company threatened legal action against any other United States laboratory using either gene for breast cancer screening. This meant that Myriad had the only lab that could perform such screening, at a cost of nearly $2,500 per patient. The company also had the right to grant licences to other labs to carry out simpler procedures at a cost of $200 per test.

One of Myriad's tests focused on a mutation discovered by the ICR affecting the BRCA2 gene, commonly found among Ashkenazi Jews from central and eastern Europe. "The Ashkenazi A mutation was the framework for our original paper," says Professor Stratton. "Myriad is claiming a fee for a mutation that we discovered." As an Ashkenazi Jew, Stratton found this especially galling.

By claiming proprietary rights to the diagnostic tests for the two BRCA genes and

charging for the tests, Myriad is adding to total health-care costs. Even worse, once scientists really understand how the BRCA1 and 2 mutations cause tumours to grow, they might be able to devise new therapies. But because of its patents, Myriad has exclusive marketing rights.

Throughout the formidable task of sequencing the human genome, we were faced with the question of research-related proprietary rights. Although the full impact of Myriad's aggressive approach was unclear in 1995, it was clear where a focus on commercial profit and patents would lead. What was needed was a commitment from the international sequencing community to make all genome information publicly available and not to parcel it out via individual deals between companies and researchers.

How to manage the data?

We decided to hold an international meeting to hammer out a strategy deciding who would do what, and how to manage the data. The UK selected Bermuda, close to the US, as the site of the meeting. This was our introduction to the world of international politics. The meeting was extremely constructive, since it was the first opportunity for researchers to compare notes freely. We were forced to work together because nobody at that time could complete the sequencing alone. Everyone arrived with pieces of paper stating their intentions to sequence a particular region of the genome, and during the meeting we resolved the overlapping claims.

At that time there was no mechanism for loading preliminary data into public databases, which were set up for finished data only. Even in raw form, the human genome sequence data obtained from our machines might prove useful to other researchers seeking to localise genes or to check hypotheses. As we had done with the nematode (1), we made all of our data available electronically from our own sites at the Sanger Institute, so that people could download information and do with it as they saw fit (2). We merely asked them to recognise that the data was preliminary and to acknowledge us as the source in any publications.

The principle of data availability had to be endorsed at the Bermuda meeting or else mutual trust would have been impossible. At first I thought it unlikely that everyone would come to an agreement. Several of those present, including Craig Venter of the Institute for Genomic Research (TIGR) (3), already had links to commercial organisations and might oppose the idea of giving everything away

to the public, with nothing in return. But as I stood at the white board, scribbling away, erasing and rewriting, we eventually came up with a statement. The Wellcome Trust – a medical research charity and the Sanger Institute's main financial backer – still has a photo of that handwritten statement with its three bullet points:

- Automatic release of sequence assemblies larger than 1 kb (preferably within 24 hours).
- Immediate publication of finished annotated sequences.
- Aim to make the entire sequence freely available in the public domain for both research and development in order to maximise benefits to society.

While Bob Waterston of St Louis's Washington University and I were drafting the statement together with our colleagues, another colleague, Michael Morgan, was meeting with representatives from the funding agencies to secure support for our initiative. What I had written on the board, with minor modifications, became known as the Bermuda principles, and these have since served as the benchmark for publicly funded large-scale sequencing projects.

The principles of accessibility and on-the-spot release mean that anyone in the international biological community can use the data and ultimately turn them into new inventions that are eligible for patents. But when the raw sequence is released publicly, it will be unpatentable. It promised well that so many people came to share a vision of the genome sequence as the heritage of humanity, as stated in Article 1 of the universal declaration on the human genome and human rights, which emerged from Unesco's general conference in 1997.

The 20th century saw a split between the sciences and the humanities. Many no longer perceive science as a manifestation of culture. One reason is that science has become increasingly equated with technology; in many quarters technological development represents science's sole purpose. Scientists are encouraged to capitalise on their discoveries commercially, regardless of the social consequences.

A discovery, not an invention

The genome sequence is a discovery, not an invention. Like a mountain or a

river, the genome is a natural phenomenon that existed, if not before us, then at least before we became aware of it. I believe that the Earth is part of the common good; it is better off not owned by anyone, even though we may fence off small parts of it. But if an area proves important because it is especially scenic or is home to some rare species, then it should be protected in the public interest.

To be sure, there will always be arguments concerning the balance between private and public lands and how they should be used. The human genome is an extreme example. We all carry our personal copies of the genome, and each portion of it is unique. You cannot say that you own a gene because you would then own one of my genes as well. And you cannot say that we can share our individual genes because we need every single one of our genes. A patent may not grant literal ownership of a gene but it does specifically bestow the right to prevent others from using that gene for commercial purposes.

Placing legal or proprietary restrictions on genes should be confined strictly to current applications or to inventive steps. Someone else may choose to work on another application and may thus need to have access to the same gene. Inventing human genes is impossible. So every discovery relating to genes - their sequence, functions and everything else - should be placed in the pre-competitive arena. After all, one goal of the patent process is to stimulate competition. The most valuable gene-related applications are often far removed from the first easy steps. So this is a matter of science, not just a matter of principle.

In March 2000 Maryland-based Human Genome Sciences Inc (HGSI), a company set up alongside TIGR in 1992, announced that it had been granted a patent on the CCR5 gene, which encodes a receptor on the surface of cells. When HGSI initially applied for its patent it did not know how this receptor functioned. While the patent was pending, a group of publicly funded researchers at the US National Institutes of Health (NIH) discovered that some people with CCR5 gene defects were resistant to infection with the AIDS virus (HIV). CCR5 appeared to be one of the gateways the virus uses to invade cells. As soon as they found out about the NIH discovery, HGSI confirmed the role of CCR5 through experiments and obtained the patent. HGSI asserted its proprietary rights to use the CCR5 gene for any purpose and then sold licences to several pharmaceutical companies to develop drugs and vaccines.

But who took the inventive step? Was it the company that made a lucky match

with the right gene? Or was it the researchers who determined that HIV-resistant individuals had a defective gene?

William Haseltine, HGSI's chief executive officer, argues that patents stimulate progress in medical research, and that the CCR5 patent may well lead to a new drug or vaccine for HIV. But a survey of researchers at US university labs found that many of them have been deterred from working on particular gene targets, fearing that they might have to pay hefty licence fees (or royalties) to companies or risk lawsuits (4).

The patent question

The US recently clarified its guidelines on granting gene patents to provide a somewhat tighter definition of utility - use must now be "substantial, specific and credible". But the guidelines still allow sequences to be patented since they can be used as probes to detect genes responsible for various diseases. The European patent directive, approved by the European parliament in 1998, states that a sequence or partial sequence of a gene is only eligible for a "composition of matter" patent when it can be replicated outside the human body (in vitro), for example copied in bacteria, as we do for human genome sequencing.

This argument has always seemed absurd to me. The essence of a gene is the information it provides - the sequence. Copying it into another format makes no difference. It is like taking a hardback book written by someone else, publishing it in paperback and then claiming authorship because the binding is different.

The number of applications for gene patents on humans and other organisms has now passed the half-million mark, and several thousand such patents have been granted. Nevertheless, the issue of gene patents remains complex and confused. The US Patent and Trademark Office (USPTO) still maintains that a gene discovery is patentable. Until the recent changes, the USPTO granted patents even for partial gene fragments whose only claimed utility was as gene probes. The European Patent Office remained unconvinced about gene patents until the European Union issued its 1998 biotechnology patent directive, which explicitly permitted the patenting of gene sequences. Several EU member states, including France, are opposed to the EU directive, while other EU members, such as the UK, maintain a more neo-liberal line on patenting so that their biotechnology industries remain competitive with those in the US.

I realised long ago that trying to reach an equitable solution using moral or even legal arguments was doomed to failure. The best way to prevent the sequence being carved up by private interests was to place it within the public domain so that, in patent office jargon, as much as possible became "prior art" and thus unpatentable by others. The international sequencing consortium, while working on the human genome project, succeeded in doing just that with respect to the raw sequence data. Now we are raising the bar by placing as much information as possible about the annotated gene sequence and gene function in the public domain.

Some have proposed drawing a patent line between life and non-life. While agreeing with the concerns, and with the urgent need for a value other than a commercial one to be placed on living things, I think there is no case for this particular line. Because the chasm that previously existed between the biological and the chemical is closing, such a distinction will not be sustainable. We should not be patenting whole life forms, such as transgenic mice or cotton plants - and not just because they are living organisms. A sounder reason is this: we did not invent these organisms, only the specific modification that made the mice susceptible to cancer or the cotton resistant to pests.

The future of biology is strongly tied to that of bioinformatics, a field of research that collects all sorts of biological data, tries to make sense of living organisms in their entirety and then makes predictions. If this data is freely accessible, bioinformatics will allow experimental biologists to complement the work of other researchers and to connect with them. If we wish to move forward with this fascinating endeavour, which will undoubtedly translate into medical advances, the basic data must be freely available for everyone to interpret, change and share, as in the open-source software movement. The situation is too complex for a piecemeal approach, with limited amounts of data released at a time and with a single entity holding the access keys.

The saga of the human genome project proves that publicly financed science is extremely effective because it is so intensely competitive. The project's success also refutes the widespread notion that only private industry is capable of carrying out large-scale research.