David Bentley discusses life after the Human Genome Project

Interviewed by Rebecca Lawrence

David Bentley, Head of Human Genetics, The Sanger Centre

How do you see the sequencing of the human genome impacting on drug discovery in the future?

I think the human genome sequence will have an enormous impact on drug discovery in various ways, and will enable a much more rational approach to drug development. The information will undoubtedly lead to the discovery of many new targets for which a variety of new drugs will be developed. However, we must not expect instant discoveries. In the long-term, we can use the genome information to understand the biology of each system properly, which will lead us to all the other components in a particular biochemical pathway, perhaps enabling us to find the optimal target for intervention.

Personalizing medicines is also a very important area, starting with existing drugs that are already on the market. To do this effectively requires the entire genome of the representative individual, and the ability to investigate the variations between individuals and how such variations affect an individual's response to drugs and environmental agents. My hope is that we can tailor existing drugs to bring some very significant improvements in healthcare, and this avenue could deliver results faster than new drug discovery. Much of the groundwork has already been done, and this approach could yield very early returns.

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How do you think we should best tackle the problem of discovering the function of many of these genes?

There is no easy answer to this, but it is an enormous help that through the entire genome sequence we will have the primary sequence of every protein, which itself will provide much information about possible function. If the sequence already matches, or is homologous to, another protein that we know the function of, we can classify proteins into families with specific functions. Of course, every protein has a unique function and so there is more work to be done beyond looking at the sequence.

The most important question to ask, in my view, is what a protein interacts with, and what it binds to, because this is what is specific to that protein and this can be modulated by intervention with a drug. It is also important to know where the protein is because, while some proteins are present on the cell surface and are readily accessible to drugs, other proteins are inside the cell, inevitably creating the additional problem of how to enable a drug to access its target. Such information on protein binding and protein–protein interactions can be found for example using large-scale array approaches. We can narrow the field by selecting the specific targets that are known to be involved; for example concentrating on those that are present on the cell surface.

Where do you see the main bottlenecks in the discovery of new drugs from this information and how do you think we might best overcome them?

From a biologist's point of view, a major bottleneck is finding the right target. One approach is to use genetics to detect particular genes involved in a polygenic (i.e. multifactorial) condition, and separate the effects of the genes on each other from the effects of the environment. This is an area that holds great promise and is where much of the effort is now being directed through SNPs.

Another bottleneck is unravelling a complete biochemical pathway that is associated with a particular disease, and finding the right target within that pathway.

How do you think company strategies in R&D, development and registration should change to accommodate the pharmacogenomics era?

We have to decide how effective and how safe a drug is for every individual in the population. Currently this is done by a lengthy and carefully regulated process, but does not account for possible differences in the genetic background of the individual. Genetic information on the individual can be used to improve the prescription of drugs by tailoring dosage to suit the individual more precisely. It might also be possible to introduce new drugs with the added benefit that the appropriate genetic background for their administration can now be monitored, where this was previously not possible. There is a potential risk in taking this approach, where a drug might appear on the market which is well suited to one person, but could be a health hazard for another – a distinction that would only be revealed by genetic testing. A further implication of this situation is that the drug in question would only be of benefit for part of the population. However, given that we are aware of the risks, personalized medicine has a great future.

My personal view is that most, or all, of human genetic information should not be patented.

Do you think the Human Genome Project will have as significant an impact on drug discovery as was anticipated at the beginning of the project?

I am sure it will be extremely significant. Although there is a lot of work to do in developing drugs and targets using the genome sequence, we have a good idea of how to proceed. Already, many of the questions posed about the value of the Human Genome Project in pharmacogenetics have been answered, and there is great promise in the new avenues of research that are opening up today.

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Do you feel it is ethical to patent human genetic information?
My personal view is that most, or all, of human genetic information should not be patented. However, it is not entirely the patenting process itself that is the problem; it is the way in which patent protection can be used for selectivity. While patenting is a form of publication and provides free access to information, the protection offered can give a selective advantage to some groups, and make it less viable for others to use the same genetic information. I would be happy for every gene to be patented if it was for the benefit of making it freely available, but not if it is for exclusive licences and for profit based on knowledge of the gene sequence itself. Conversely, there is defensive patenting in which gene sequences can be made freely available to all, without restriction, thus levelling the playing field.

I entirely support the idea of protecting proprietary information resulting from novel research using the knowledge gained from discovery of genes and their functions. It is vital that large investments are made in the development of effective diagnostics and drugs. Patents filed on these discoveries are then for the protection of the truly inventive work that goes into using the genomic information.

What is your biggest concern about the current/future research?
I have two fears. One is misuse of genetic information – technology is highly accessible, it can easily be established and is applicable to all genes. There is a danger that use of the technology and information can be motivated by personal gain, leading to incorrect use of the information.

My second fear is that communication to the public of both the benefits and the dangers of genetic knowledge might be either inadequate or misleading. I would like to see the knowledge of genetics brought to the public in a realistic and informative way so that the full potential of the human genome can be realized.

How do you think that scientists can communicate what effect the HGP will really have on therapeutic advances and does the Sanger Centre have any plans to contribute to educating the public on such matters?
We have explored many areas of communication with the public, since the founding of the Sanger Centre. For example, we develop teaching materials and run educational seminars involving a wide range of people from 9 year-olds to family groups, to various professional and academic gatherings. We have also been involved in refresher courses for teachers, and a basic course for sixth-formers, which extends beyond their curriculum.

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There are some excellent examples in other institutions such as the DNA Learning Center at Cold Spring Harbor. The Wellcome Trust runs practical courses at a senior level, provides a comprehensive range of publications aimed at science teachers, and is engaged in an initiative, which tours schools, to present science through drama. We would like to build on what we have learnt, possibly with a more formal programme, and to work more closely with the media and the Internet.

What do you think to the future prediction that in 20 years or more, we will be able to change people's lifetimes and their intelligence, and that this will create a super-race for those that can afford this type of treatment?
Anything is possible and one cannot predict the future. We are talking about things that are of fundamental interest to people. My personal view is that work that touches on creating a super race would be a major abuse of this knowledge and technology. Also, 'for those who could afford it' exemplifies the profiteering use of such technology as opposed to the beneficial use. I very much hope that, given freedom of information and good education, it is a possibility that will be averted.

What lies on the horizon for genomic research over the next five years?
There will be very exciting progress in being able to use the knowledge of the genome and what it contains – it will certainly herald revolutions in medicine, although not all of it in five years. We will always need to be patient, but we will no longer be scratching around in the dark in many areas of research.

We should also not forget that in the next five years, there will be a much greater understanding of many other genomes and how they compare, and this can be used to provide more information on the human genome as well as information on biology in their own right. So far, every genome has been an enormous effort, expensive and slow, and therefore future genomes in the short-term will be drawn from different points in the evolutionary tree to make the most of examining the differences and the similarities. However, genome sequencing is getting easier, not only because the technology is improving, but also because we can now use some genomes as a skeletal framework for building maps of others. In five years, we will definitely see many more genomes, and we will learn a tremendous amount from being able to compare them. We will also ultimately be able to sequence multiple copies of the same genome from different individuals. The possibilities are therefore unlimited, but they have to be affordable and have to be a realistic investment.

The possibilities for the future are unlimited, but they have to be affordable and have to be a realistic investment.

What would you like to have achieved by the end of your career?
I think the promotion of good scientific practice and progress in others is very important. I am concerned with education and with passing on skills and information to others. I would be happy if I had helped the continual learning process of understanding our genome, and how that knowledge interacts with healthcare, the environment and society.

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