biotechnology business, but I also pointed out that a composition of matter patent on the product of the gene would have sufficed.

The public Human Genome Project (HGP) was not driven by the desire for gene patents. The business plan for the commercial genome sequencing effort did include patenting of genes as a value generator, but it was not claimed to be the major reason for investment. Binns wonders whether the public HGP would have grown as rapidly without the stimulus of the commercial genome sequence project – probably not. The rapid escalation of the HGP to produce a draft sequence was debated in 1995 but it was considered to be premature [5]; full-scale production sequencing began in March 1999. The announcement of the commercial effort did help to accelerate the flow of funds to the HGP. There was also a reciprocal benefit to the commercial project that was able to incorporate all public sequence data, freely available from the Internet under Bermuda Rules, into their draft sequence. Only the public HGP will produce a finished sequence that will be the definitive version of the human genome sequence and the most useful source in which to search for novel drug targets.

Gene patenting maintaining competitiveness in the EU

I welcome the agreement from Patrick Nef [6] that developing drugs is sufficiently difficult that it is in the public interest that 'companies with exclusive rights on a particular gene target are ready to make them available to others for a reasonable fee'. I hope that we can look to Hoffmann-La Roche to set an example in this regard. Nef doubts that a policy of not granting gene patents in the EU would encourage pharmaceutical R&D in Europe. It would be interesting to know whether other EU pharmaceutical companies share his doubts.

I am not swayed from my argument that a lack of gene patents would not hurt pharmaceutical R&D. I do not think that Nef makes a good case for gene patents being value generators for pharmaceutical companies. Successful, patent-protected products are the only way for a pharmaceutical company to recover the huge costs of drug discovery and development. Freedom to explore any gene target would be assured in the absence of gene patents; secrecy is not a viable option for reasons stated previously. For academia few gene patents prove to have commercial value, whereas investors in biotechnology companies are more impressed by the 'value-added' to gene patents through genuine innovation.

Nef adds to Heinemann's list of grounds on which to challenge gene patents in the future. However, he rightly acknowledges the costly (and I would add complicated) nature of such a challenge in the courts. Nef points to key differences in the practice of granting gene patents in the EU versus the USA. This supports the view that we need a uniform treatment of gene patent applications worldwide.

References

1 Williamson, A.R. (2001) Gene patents: are they socially acceptable monopolies, essential for drug discovery? *Drug Discov. Today* 6, 1092–1093

2 Heinemann, J. (2002) Gene patents: are they socially acceptable monopolies, essential for drug discovery? – Reply. *Drug Discov. Today* 7, 23–24

3 Binns, R. (2002) Gene patents: are they socially acceptable monopolies, essential for drug discovery? – Reply. *Drug Discov. Today* 7, 102–103

4 Williamson, A.R. (2001) Gene patents: socially acceptable monopolies or an unnecessary hindrance to research? *Trends Genet.* 17, 670–673

5 International Human Genome Sequencing Consortium (2001) Initial sequencing and analysis of the human genome. *Nature* 409, 860–921

6 Nef, P. (2002) Gene patents: are they socially acceptable monopolies, essential for drug discovery? – Reply. *Drug Discov. Today* 7, 103–104

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Finding new antibiotics: the power of computational methods ▼

Antibiotics have been highly successful for the treatment of bacterial infections. Their extensive use, however, has led to the rapid evolution of antibiotic resistance. The antibiotics that are currently available act on a relatively small number of cellular processes such as protein synthesis or peptidoglycan biosynthesis. New agents that act on novel gene products within previously untargeted biochemical pathways would circumvent many of the known resistance mechanisms and provide new therapeutic options. How then, can this be accomplished?

An important question to be answered when choosing potential targets is whether the biochemical pathway to be targeted is unique to bacteria and, if so, how widespread is it among bacteria? A biochemical pathway that is common to both bacteria and humans is not ideal because of the potential for side effects. Similarly, the extent of conservation of a biochemical pathway between bacterial species will influence the spectrum of activity of the antibiotic to be designed. The large and rapidly increasing number of available microbial genome sequences is being used to answer these questions and thereby facilitate the identification of new bacterial targets for antibiotic development.

A powerful computational approach that uses bacterial genome sequence information is to compare the identified genes in all bacterial pathogens to determine which genes are shared by various species (see Read *et al.* [1] for a recent review). For example, a comparison of the sequences of the respiratory tract pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neiserria meningitidis* indicated that *S. pneumoniae* has a much greater capacity to utilize sugars than the other

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organisms, suggesting that it occupies a unique microenvironment within the respiratory tract [2]. A further comparison of sequences of respiratory tract bacteria with other pathogens identified genes that are specific to respiratory tract pathogens and genes that are common to many pathogens [1].

This information could be used to select targets based on the desired spectrum of activity. For example, targets could be selected that are specific to particular respiratory tract pathogens to develop focused, narrow spectrum agents. Alternatively, wider spectrum agents could be designed by targeting either pathways common to respiratory tract pathogens in general, or pathways common to all pathogens.

A combination of computational and experimental approaches is another useful means of identifying potential targets for drug development. For example, Freiberg *et al.* [3] used a computational approach to identify a set of novel open reading frames (ORFs) that were found in a wide range of bacterial pathogens including *Escherichia coli*, *Staphylococcus aureus*, *S. pneumoniae* and *Enterococcus faecalis*. A subset of these ORFs were then individually deleted from the *E. coli* genome and the resulting strains were tested for growth in complex medium [3]. In this way, six previously uncharacterized genes were found to be essential for *E. coli* growth. These six gene products represent potential targets for the development of novel broad-spectrum antibiotics.

Another important question when choosing a target protein concerns the function of that protein and how it interacts with other members of a pathway. Defining protein interactions on a genome-wide scale can establish networks of interacting proteins, which in turn can provide important clues about the function of a gene product. Recently, several algorithms have been developed that use genome sequence data to map functional interactions between proteins. These algorithms include the phylogenetic profile [4], domain fusion [5] and gene neighbor methods [6]. These methods have produced complex functional interaction maps for several bacterial species [7]. The results are useful for defining metabolic pathways and, in combination with the genome comparisons described here, can be used to identify novel targets for broad-spectrum antibiotics.

One of the benefits of computational approaches that use genome sequence data is that these methods generally become more robust as additional sequences are added to the databases. The increased power and resolution of the methods will lead to their widespread use which should, in turn, yield new insights to facilitate antibiotic design.

References

1 Read, T.D. *et al.* (2001) Finding drug targets in microbial genomes. *Drug Discov. Today* 6, 887–892

2 Tettelin, H. *et al.* (2001) Complete genome sequence of a virulent isolate of *Streptococcus pneumoniae*. *Science* 293, 498–505

3 Freiberg, C. *et al.* (2001) Identification of novel essential *Escherichia coli* genes conserved among pathogenic bacteria. *J. Mol. Microbiol. Biotechnol.* 3, 483–489

4 Pellegrini, M. *et al.* (1999) Assigning protein functions by comparative genome analysis: Protein phylogenetic profiles. *Proc. Natl. Acad. Sci. U. S. A.* 96, 4285–4288

5 Marcotte, E.M. *et al.* (1999) Detecting protein function and protein–protein interactions from genome sequences. *Science* 285, 751–753

6 Overbeek, R. *et al.* (1999) The use of gene clusters to infer functional coupling. *Proc. Natl. Acad. Sci. U. S. A.* 96, 2896–2901

7 Eisenberg, D. *et al.* (2000) Protein function in the post-genome era. *Nature* 405, 823–826

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