Up the function

"The difference between physiology and functional genomics", quipped Howard Jacob (Medical College, Wisconsin) a few weeks ago at the fifth annual *Nature Genetics* conference*, "is marketing". Indeed, the profusion of grant requests, start-up companies and science conferences touching in one way or another on the notion of 'functional genomics' probably rivals other voguish social trends, such as platform shoes and swept-forward hairstyles. But peel away the hype and the trade-marked logos and one finds a hard core of traditional scientific values, although complemented by innovative technologies designed to elucidate the function of genes on an unprecedented scale and hopefully to harness that information in the application of novel disease therapies.

Although the arduous route to disease gene cloning via mapping and chromosome walking is still paying off with regularity for researchers and companies alike, many suspect there has to be a better way. The 'problem', if that is the right word, was illustrated by Francis Collins (NHGRI) in describing his team's recent success[1] in identifying the gene for multiple endocrine neoplasia type 1. This task consumed years of effort, only to reveal a gene of no known function — at least for the time being. Progress in disease gene identification will of course be accelerated by the exponentially swelling ranks of databases (W. Gilbert, Harvard) such as GenBank and XREF[2], and may soon be complemented by gene-expression databases such as the Cancer Genome Anatomy Project, CGAP (M. Boguski, NCBI)[3,4].

Studies in a variety of model organisms — some well established in the geneticists' arsenal, others up and coming — are providing a fillip to attempts by human geneticists to understand gene function[5]. It is probably unnecessary to compare the pros and cons of one model organism with those of another — although that certainly didn't prevent several speakers at the conference from trying! *Caenorhabditis elegans* ("little people in disguise" — R. Horvitz, MIT) and *Drosophila melanogaster* (G. Rubin, Berkeley) are proving amenable to the study of genetic pathways: by some estimates, the function of the 70,000 or so human genes can be boiled down to about 1,000 biochemical pathways. New methods of chromosome engineering in mice will facilitate more intricate modelling of chromosomal aberrations than single-gene knockouts alone (A. Bradley, Baylor). By comparison, zebrafish genetics is still in its infancy, but the captivating mutants displayed by W. Driever (MGH) certainly support the organism's bid for scaled-up study.

At the other end of the evolutionary scale, genome sequencing undoubtedly breeds success: the yeast genome project was completed last year (A. Goffeau, Lou-

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Ian Wilmut and **Francis Collins** split time at the *Nature Genetics* 'Functional Genomics' conference in Washington DC.

*Functional Genomics: From Genes to Drugs. The 5th International *Nature Genetics* Conference, Washington D.C., 16–17 April 1997.

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

Model organisms and genome databases share centre stage. From left to right, **André Goffeau, Wolfgang Driever** and **Mark Boguski**.

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Peter Goodfellow demonstrates how much his salary has multiplied since joining the pharmaceutical industry.

vain), and the full details are now available in the *Nature* Genome Directory[6]. But even the density of the yeast genome is surpassed by those of micro-organisms such as *Mycoplasma genitalium* and others, which have been completely sequenced at the Institute for Genomic Research (C. Fraser) and elsewhere. Some two thirds of the 470 genes in *M. genitalium* are known genes, and only 20% fail to find a match in the database. In an effort to determine the minimum number of genes required to sustain life in this organism, transposon-tagging experiments already suggest that 75 genes are not essential.

Drug paraphernalia: Many high-tech strategies are being explored to identify and characterize human genes, ranging from differential display to examine genes activated by sheer stress in atherosclerosis (R. Tepper, Millennium) to DNA chips, which tackle everything from expression monitoring and mutation detection to bi-allelic gene mapping (S. Fodor, Affymetrix). Others are extracting as much information as possible from the tissue-specific and developmental expression profile of genes (W. Haseltine, Human Genome Sciences). One of the most original strategies for studying gene function was outlined by D. Beach (Cold Spring Harbor), involving the transfection of retrovirally cloned cDNA libraries into human cells as a prelude to the production of antisense products which inhibit specific cellular functions. Meanwhile, for other prized genes, such as BRCA1, there is the daunting prospect of years' more work ahead to elucidate its cellular function and contribution to carcinogenesis (B. Weber, U. Pennsylvania).

Perhaps the most tantalizing technique of all, although not yet in widespread use, is cloning (I. Wilmut, Roslin Institute), which could offer a host of applications for the pharmaceutical industry in terms of protein production and analysis of animal physiology. Although the pharmaceutical industry has not yet embraced cloning technology, it is fully aware of the potential of genome-based technologies. Many 'collaborations' (or what cynics such as SmithKline Beecham's Peter Goodfellow deride as simply "spending big sums of money") have been struck with smaller genomics companies to stimulate the isolation and analysis of novel genes. Perhaps Goodfellow had in mind the recent liaison between the Whitehead Institute and three commercial partners, Bristol-Myers Squibb, Millennium Pharmaceuticals and Affymetrix, worth $40 million over five years. Commenting on the arrangement, Eric Lander said: "We've put seven years so far into building maps and sequences, telling ourselves that this structural genomic information would help change the world. It's time to take that out for a test drive."[7]

Whether this particular road test, and initiatives like it, will prove successful remains to be seen. Goodfellow, for example, pointed out the significant and disappointing rate at which promising drug candidates in model organisms fail to produce the desired effects in humans. And with the costs of bringing a drug to the marketplace now averaging $500 million, pharmaceutical companies are concluding that "disease prevalence is necessary for drug profitability" (J. Drews, Hoffmann-La Roche). By the time any therapeutically useful drugs resulting from the latest scientific craze are ready to emerge, the term 'functional genomics' will be history in more ways than one.

1. Chandrasekharappa, S.C. *et al. Science* **276**, 404–407 (1997).
2. Bassett, D.E. *et al. Nature Genet.* **15**, 339–344 (1997).
3. Strausberg, R., Dahl, C. & Klausner, R. *Nature Genet.* **15**, 415–416 (1997).
4. Strachan, T., Abitbol, M., Davidson, D. & Beckman, J.S. *Nature Genet.* **16**, 126–132 (1997).
5. Gabor Miklos, G.L. & Rubin, G.M. *Cell* **86**, 521–529 (1996).
6. Mewes, H.W. *Nature* **387** Suppl., 7–8 (1997).
7. Roush, W. *Science* **276**, 891 (1997).