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The promise of proteomics

Analysing the entire set of proteins of an organism is a far bigger challenge than anything in genomics. The technological obstacles and biological complexities require, for now, a steady approach to that necessary goal.

The inside of a cell is a crowded and dynamic place, where proteins are perpetually being created and discarded. Understanding the structures, interactions and functions of all of a cell's or organism's proteins is one of the grand goals of the post-genomic era, and has been given a disciplinary title of its own: proteomics. There are even some who want to develop a human proteome project. Is that premature, or even meaningful?

Proteomics, if defined as the study of many proteins simultaneously in order to understand the function of one restricted state of a cell, remains in its infancy. A pioneering example was published last month (*Nature* **402,** 147–154; 1999). That paper reported that, out of the 2,500 polypeptides in the cytosol of the bacterium *Escherichia coli*, only around 300 proteins use cylindrical (GroEL) molecules as chaperones to ensure that they are correctly folded. The analysis, using two-dimensional gels and database comparisons, positively identified more than 50 of these, and highlighted key structural features that determine these proteins' interactions with, or need for, 'chaperonins'.

As is described in this week's survey of the prospects for proteomics (see page 715), the now well-established two-dimensional-gel approach has many limitations, while the development of the more advanced technologies we can envisage — antibody and protein-array technologies that may deliver fast and parallel quantitative analyses of protein distributions — has a long way to go. Moreover, as the number of proteins identified in a cellular event grows, so too do the demands to validate those identifications and infer the proteins' activities in order to give meaning to the observations. New centres are springing up in many universities, bringing together the skills and technologies required to tackle such challenges. Alongside the embryonic technical state of proteomics, there is, critically, a shortage of people skilled in bioinformatics.

On top of these technical limitations is a more fundamental issue. The number of genes in an individual human, as in any organism, is static and fixed. Given the much larger set of proteins produced by that organism at one time or another throughout its life, the goal of identifying the whole of the human proteome is a far bigger and more complex challenge. Indeed, there is no such thing as 'the' human proteome — it will differ significantly not only between individuals (much more than do their genomes), but also within one individual before and after, say, a millennium party.

So, should funding agencies be pouring money into some global strategy at this point? A boost now risks committing large sums to techniques that may soon be superseded. Moreover, there are already more than enough known molecular systems that need to be targeted in a focused way. Such arguments were initially raised against the Human Genome Project and with hindsight were a distraction. But here and now, with respect to proteomics, they are apt. Collaborations between many centres can add value by concentrating on the proteins involved in aspects of cell function and development selected for their wide relevance across the kingdoms of life or their particular relevance to human health. The fact that the pharmaceutical industry is excited about the dawning prospects of using proteomics to help identify new drug targets, but has yet to invest substantially, reflects the wisdom of a steady approach to the growth of proteome biology.

Cataloguing hundreds of proteins in a life-threatening parasite or an organelle, while technically impressive, is no more than frustratingly tantalizing if some understanding of their activities is not also developed. As submitted papers in proteomics grow in number, *Nature* intends to play its part by insisting on conceptual insights from among the great quantities of information that such work will certainly deliver. Researchers and funding agencies need to beware of hype, but should be conscious of the great potential in this research, and keep themselves abreast of the key techniques and technologies. ■

Gene therapy for the public

The hearings held by the US National Institutes of Health (NIH) last week into problems that have arisen in adenovirus-based gene-therapy trials revealed clear breaches of protocol by some of the field's leading researchers, and inadequacies in the state of experimentation (see page 707). Adenoviruses are one of several types of vectors being tried in clinical gene-therapy studies. The case of Jesse Gelsinger, whose death during a gene-therapy trial led to last week's hearing, reveals how poorly understood are the body's responses to those vectors in particular. But the uncertainties and the violations revealed by the hearing should not halt the pursuit of the adenovirus approach, whose particular advantages include the fact that they can infect non-dividing cells.

Given gene therapy's highly experimental and controversial nature, demanding standards of openness are appropriate. Last week's hearings underscore the desirability of giving the NIH's Recombinant DNA Advisory Committee (RAC) more power to examine adverse events as they arise, thus ensuring a public airing of problems.

The NIH has made commendable efforts to make itself accessible — all RAC meetings are open to the public and their minutes are on the web. Given the controversy of the past few months and the worries and even hostilities that experiments in genetic manipulation can engender, the NIH can usefully go further. It should establish itself as a model provider of readable and easily navigable information, providing on its website a substantial overview of the genetic basis of diseases and the state of understanding of respective gene therapies. Considering the amount of unreliable information offered to the public on the web (see page 722), and especially the interests of those members of the public more directly concerned — patients, for example, or their relatives and dependents — the NIH should use the website routinely to give detailed but well-signposted and comprehensible information on the state of trials, covering progress and problems worldwide. Such a programme of enhanced access requires a small budgetary commitment compared with experimental funds. But it could come to play a major role in sustaining both informed consent and public trust. ■