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Burying the hatchet

Perhaps it was too much to hope that the key players involved in sequencing the ~2.9 billion bases of the draft human genome could have buried their differences before jointly announcing their achievement to the world.

At separate briefings at the BioVision conference in Lyons, France and the London press conference, neither Francis Collins, John Sulston, Mike Dexter, nor Craig Venter could bring themselves to reconcile the two genome efforts—the "public" project funded by NIH, The Wellcome Trust, and government agencies around the world, and the "private" effort funded by the shareholders of Celera Genomics (see p. 191).

At the London press conference, skirmishing between representatives of the public effort and Celera occupied at least half of the question-and-answer session. The Wellcome Trust even issued a four-page press release drawing attention to deficiencies in the Celera sequence: Far from "winning the race," the press release proclaimed, the Celera method "has been found wanting." "It is difficult to escape the conclusion," the release concludes, "that the pure whole genome shotgun has failed as far as generating the sequence of the human genome is concerned."

This is not the language of inclusiveness or conciliation. It is not a form of words that will encourage the general public to think well of scientists from academia or from industry. It sets entirely the wrong tone. This should have been a dignified, propitious, and historic moment. It felt like a wrangle over which genome sequence paper was best or most indispensable; whose genome data the most useful; and whose standards the most appropriate standard for data release.

The chief protagonists seemed unaware that they were participating in a historic moment. This undoubtedly was—and is—a large step for mankind, but one obscured by the small-mindedness of men.

Keeping up appearances

Change, continuing change, inevitable change is a pervasive factor in biotechnology. And so, this issue, which marks the fifth anniversary of *Nature Biotechnology's* relaunch, brings changes in the journal's design intended to improve accessibility of content. Some of these changes are cosmetic; they aim to enhance the appearance, provide a greater feeling of continuity between sections, and embrace a more modern and cleaner layout. Others are more functional; we have introduced design elements to simplify navigation through the journal and ordered sections to provide a better pace of read. Most significantly, we have clearly delineated front-half news and analysis material into Business and Regulatory News, and Research News (we recognize this is a rather artificial distinction, given the interdependence of business and research in biotechnology). A new monthly article on Careers & Recruitment and an expanded classified section in Nature Jobs Biotechnology also starts on p. 285.

A cold dose of medicine

Genomics, of course, will transform traditional empirical medicine into rational treatments for specific pathologies. So with two working drafts of the human genome now officially published, what can we realistically expect from genomic medicine?

The theory goes something like this: Find the genes involved in a disease and identify the encoded proteins. Accumulate information on protein structure and function, elucidate biochemical cascades, and select key control proteins as potential drug targets. Identify compounds that interact with the target and use structural information to refine binding affinity and *in vitro* data/*in silico* prediction to optimize toxicological/pharmacological properties.

That entire process should take about 10 to 15 years (with a following wind). The first step of the approach—identifying novel drug targets—has progressed. Searches of the genome sequence have already revealed at least 30 new disease genes (see p. 207). But as everybody is keen to say these days, this is only a beginning.

Large gaps exist in our understanding of the processes that influence protein diversity and function. Current estimates suggest that at least 10,000 human genes undergo splicing (see p. 136), yet we still know little of this process. Many disease genes are expressed at low levels, and gene expression often shows little or no correlation with changes in the levels of protein anyway.

All this means that we urgently need sensitive and reliable proteomic methods for identifying proteins on a large scale and characterizing post-translational modifications that influence function. Modeling of genetic networks and metabolic engineering also are rudimentary, making elucidation of key points of therapeutic intervention difficult.

There are also many layers of complexity that drug development has to address. There may be hundreds of different variants associated with a single predisposing gene, complicating the design of a single small molecule. How much worse will this problem be for multigenic disorders? Validated protein targets, when found, may not crystallize to allow their structures to be solved. The key proteins of many diseases (e.g., sickle cell anemia) have been known for years, without leading to effective drug treatments. Even when small molecules bind to target proteins, that simple interaction may not reverse the complex perturbations of biological networks that occur in disease.

Most traditional pharmaceuticals combat disease by antagonizing drug targets, thereby ameliorating gain-of-function mutations. Targets uncovered by genomics, on the other hand, are more likely to result in loss-of-function mutations. Addressing those targets will require novel agonist drugs with new chemistries that confer appropriate binding site kinetics and distribution within the body. A recent report "*The Fruits of Genomics*" from Lehman Brothers estimates that the number of drug candidates entering the clinic in the pharma industry will increase by fourfold in the next five years. The productivity of the drug discovery process may, therefore, increase significantly. But the newness of the targets and of the chemistries used for drug candidates will mean significantly higher rates of clinical failure. Thus, genomics will not rapidly improve the efficiency of drug development. In fact, it may make it even more complicated.