DDT Vol. 6, No. 6 March 2001

The human medicine project has started: place your bets now

Allen D. Roses, Senior Vice-President, Genetics Research, GlaxoSmithKline, Five Moore Drive – 5616, Research Triangle Park, NC 27709, USA.
tel: +1 919 483 7418, fax: +1 919 315 6013, e-mail: adr69412@gsk.com

So now we have it – the first installments of the Human Genome Project (HGP). Appearing on computer screens all over the world will be two general versions: one from the public consortium[1] and the other of the subscription version from Celera Genomics (Rockville, MD, USA)[2]. There is no denying that this is a major technical feat for humankind. Books will no doubt be written about the many personalities and interactions that brought us to this point[3]. Stories of how scientific influence and power finally convinced governments and investors to support the nobility and utility of this information will provide interesting versions of a single set of facts.

But the sequencing efforts are close to history now and soon scientists all over the world will have the edited, accurate human genome information (as well as mouse, rat and other genomes) at their full disposal on usable databases. Akin to the moment when the first footstep was taken on the moon, we might all view this point in time as a reference to when the next phase of science was recognized. Like Star Trek's *Space: The Final Frontier*, fictional projections of the future impact of the HGP on biology has already received the first wave of hype. However, unless scientists can deliver biological uses for humanity, as opposed to technical feats for humankind, boredom with the next round of finishing touches (ho-hum) on the human and other genomes will erode interest and support. Just ask NASA!

Indeed, the 12 February 2001 issue of *Nature* provides a bewildering set of viewpoints reflecting heterogeneous perspectives on future prospects from the public sequencing effort. The issue of *Science* published contemporaneously presents Celera Genomics' perspectives. The drama and speculations from the sequencing race is entertaining, but the real challenge is making safe and effective medicines. Biology rules, but practical issues prevail.

What now?

Efficient drug discovery and development are two relevant, practical biological uses of genomic information receiving fanfare from the HGP. How does the completion of the human genome, with each gene identified (whether 35,000 or 100,000) lead to treatments and cures for diseases? At the start of the race to sequence the human genome, only a few genes were known and characterized. Now, in this scenario, all the gene sequences are known. Which set of interactive gene products will lead to the early clinical expression of depression, Alzheimer's disease, late-onset diabetes mellitus or other common diseases[4]? How does the inheritance of certain combinations of sequence coding variations (single nucleotide polymorphisms or SNPs) affect the onset of clinically defined diseases that manifest during a person's life[5]? What are the real functions of the introns and the rest of the 'junk' DNA? Most importantly, what innovative applications will identify the disease-relevant genes for targets that should be screened for hits and leads and developed into medicines? The pharmaceutical industry is the principal link between more gene targets and safe, effective medicines. The hype that provided the rationale for investing billions of dollars to sequence the human genome was based on improving our ability to understand and treat disease. It is time to make good on that investment.

The accelerated success of Celera Genomics' private sequencing effort, based on a 'shotgun' DNA fragment-linking strategy that most experts considered impossible, forced the public-funded initiatives to pick up the pace[3]. The hype was the 'race,' the reality was a faster strategy coupled with major advancements in sequencing capacity and computer data crunching.

The clever R&D folks in the pharmaceutical sector who can learn to select and translate genome variations into relevant target screens will accelerate the practical history of the HGP. There are thousands of hypotheses or experiments from academia-based research that provide a rationale for current drug discovery. The quintessential question for pharmaceutical companies is how to select which targets to screen first, in order to increase the proportion of the product pipeline with genetically relevant molecules.

In the real world, the attrition rate of the drug discovery programs must be decreased and the efficiency of the drug development process increased[6]. The decrease in the attrition rate should result from too many good molecules, not too many screens based on variably validated notions. The ability to survive financially demands improvement in the rate of success of medicine discovery and delivery. The current consolidation

 PII: S1359-6446(01)01722-6

in the pharmaceutical industry through mergers and acquisitions alone will not be sufficient, and brings to mind the quip about rearranging the deck chairs on the Titanic. Increasing the pipeline efficiency is key to the pharmaceutical industry for sustained survival.

Whether their priorities are curing horrible illnesses or creating blockbuster products, the first organizations to capitalize on disease-specific gene susceptibilities, and the efficient delivery of chemical screening and clinical development will transform the world of medicine and, along the way, the pharmaceutical industry. As with the rest of scientific history, progress will be based on the changes instituted by a few innovative individuals, not based on surveys of past performances based on stagnant paradigms. Commonly held group-thinking has made the drug research and development process bigger and more expensive, but not, as yet, more efficient.

The possibilities

The genome-sequencing world was changed by a simple innovation coupled with focused technological and computer progress. By analogy, imagine a pharmaceutical world in which:

- The rational selection of disease-specific, genetically associated targets for screening is enabled;
- The preclinical development pipeline is filled with a greater proportion of molecules that will not fail toxicology screens;
- A modernized, regulated clinical development system in place that enables patients who respond efficaciously to an experimental drug in Phase II to be selected by pharmacogenetic medicine response tests for faster and less expensive Phase III trials; and
- A streamlined, regulated surveillance system that is routine, so that medicine response tests of genetic susceptibility for serious adverse events can be rapidly developed to improve the safety of medicines in the post-marketing setting[7].

The anticipated contributions from the human sequencing projects are that the genome information relevant to disease will accelerate the selection and creation of relevant target screens. These disease-related targets will be more efficient at selecting molecules that are effective against disease.

Pharmaceutical companies can be the victims of financial analyses that shape short-term priorities, enlarging capacities and creating shareholder value, thusfar, without significantly increasing the rate of R&D success[6]. Survival and real growth will come as the tools of discovery are made more efficient across a company's pipeline. Scientists will always be enamored with technology, but ordering the march through the human genome information to select useful, disease-specific target screens first is the real goal. A higher proportion of more relevant molecules would accelerate the drug discovery component of delivering innovative medicines to the market. The motivation is immaterial, whether the goal is better medicines, multi-billion dollar products for shareholder returns, or answers to the Zen-like question of 'What will people die from when all diseases are conquered?' (For a hint to a possible answer, bacteria and viruses adapt better than people do, and with less controversy!)

One key to this 'human medicine project' (HMP) lies in understanding the difference between genetics-based target selection and the currently popular target validation[8]. Using genetic evidence-based methods of target selection should reduce the testing of too many hypotheses that are eventually proven wrong[9]. The HMP is a race too. Success in discovery is measured by reducing attrition and improving a product's return on investment. As molecules pass through the development pipelines, choices made in 2001 will undoubtedly play a role in the outcomes of 2015. The organizations that are the most proficient in target selection, once affectionately known as the *Picking the winners project* in the former GlaxoWellcome dialect of pharmaceutical language, will win.

Where could we be?

Here is how the future could look. Insight into a rapid method of target selection that is disease-specific enables the industry to fill and order its earliest pipeline with prioritized targets that are known to be genetically associated or linked with specific diseases. The alternative and currently common 'validation' approach (jumping on a biological hypothesis and spending years and cash to validate molecules identified by the screen work to treat disease) can sometimes work – but is horribly expensive in attrition, time and money. Even if a company can spend the cash, it is still a crapshoot. By contrast, starting with genetically relevant targets will improve the odds of success.

In the game of craps, betting across the whole table and playing only in games with natural odds increases the chances of success. In the drug discovery game, identifying important disease-susceptibility genes and determining their interactions, especially the effect of polymorphic or variant genes on differential metabolism, seems like a good bet. Learning to decipher the metabolic interactions of mutated genes that lead to rarer forms of common diseases also seems like a reasonable bet. Studying protein interactions, skewed by disease-associated variants of the gene, is also worth a gamble. Success can be pure 'dumb luck' or a consistent scientific strategy that produces more trips to the table and more chances to win over time.

There are now a lot of genes out there. Which ones are related to which diseases? Which biological pathways will yield targets for high-throughput screening? Increased efficiency of target selection will successfully identify more relevant molecules for full development. Predictive toxicology will enable a

greater proportion of those molecules to pass through regulated preclinical development. Efficacy pharmacogenetics will add focus to clinical development that will make it faster and less expensive. Safety (adverse event) pharmacogenetics will facilitate prescribing products for the right patients in whom the drugs will have a favorable benefit-to-risk ratio. It might also enable products to stay on the market by improving their safety profile in post-approval use[7]. The genes and the SNP map are now available. The race to apply these genetic dictionaries to write the poetry of life begins now. Start your engines.

References

1 International Human Genome Sequencing Consortium (2001) Initial sequencing and analysis of the human genome. *Nature* http://www.nature.com/genomics/human/

2 Venter, J.C. *et al.* (2001) The sequence of the human genome. *Science* 291,1304–1351

3 Davies, K. (2001) *Cracking the Genome*, The Free Press

4 Roses, A.D. (1998) Alzheimer diseases: a model of gene mutations and susceptibility polymorphisms for complex psychiatric diseases. *Am. J. Med. Genet.* 81, 49–57

5 Saunders, A.M. *et al.* (2000) The role of apolipoprotein E in Alzheimer's disease: pharmacogenomic target selection. *Biochim. Biophys. Acta* 1502, 85–94

6 Lehman Brothers–McKinsey & Co. Joint Study (2001) *The Fruits of Genomics: Drug Pipelines Face Indigestion Until the New Biology Ripens.*

7 Roses, A.D. (2000) Pharmacogenetics: the link between the development of and the practice of medicine. *Nature* 405, 857–865

8 Marton, M.J. *et al.* (1998) Drug target validation and identification of secondary drug target effects using DNA microarrays. *Nat. Med.* 4, 1293–1301

9 Wiley, S.R. (1998) Genomics in the real world. *Curr. Pharm. Des.* 4, 417–422

Is there a future for GMO medicines in New Zealand?

Brian J. Day, Clinical and Regulatory Services Limited, PO Box 480, Pukekohe, New Zealand. tel: +64 9 238 3447, fax: +64 9 238 9239, e-mail: carsl@attglobal.net

In June 2000, a recall of a cholera vaccine was initiated in New Zealand. However, this was not an issue of the safety or effectiveness of the vaccine, but a lack of review of the potential environmental risks. Because the vaccine contained a genetically modified live organism, recent legislation requires approval by an environmental risk management agency. Rather than being just a scientific issue, political grandstanding has created an atmosphere that could hamper the future introduction of genetically modified medicines in New Zealand.

The product recalled is Orochol® Berna, a live, single-dose, oral vaccine for active immunization against cholera (see Box 1). It contains a genetically modified organism (GMO), strain *Vibrio cholerae* CVD I03-HgR, is manufactured by Swiss Serum and Vaccine Institute (Berne, Switzerland) and is registered in several countries. An application was made to the Ministry of Health (MoH) for approval of the product in April 1998. Approval was granted on 2 March 2000. However, the product has been supplied to the New Zealand market since June 1998 under legal exemption. During this period, about 1400 people have used the vaccine.

To fully understand the background to the situation, it is necessary to appreciate the political environment in New Zealand.

Political background

Currently, there is a centre–left Labour coalition government, which was elected in November 1999. This coalition includes the left-wing Alliance party and the Green party. In order for the government to progress legislation, it requires the support of both the Alliance and the Greens. This support comes at a price, with the Greens (who have been a very strong anti-genetic engineering lobby) being in a position to advance its own agenda. The culmination of this pressure was agreement that the Government would initiate a Royal Commission on Genetic Modification. This Commission was also accompanied by a voluntary moratorium that effectively halted applications made under the Hazardous Substances and New Organisms Act 1996 (HSNO) for field testing, import or release of GMOs until after 31 August 2001.

It was provisions of the HSNO Act that resulted in the recall of Orochol Berna. Although drafted in 1996, the Act did not take effect until 28 July 1998, after the filing of the new medicine application with the MoH, and after the product had already been imported and distributed in New Zealand. To add further confusion, only parts of the Act specific to new organisms came into effect at this time, and the sections relating to hazardous substances are still not in effect. It must be said that the Environmental Risk Management

1359-6446/01/$ – see front matter PII: S1359-6446(01)01733-0