nature biotechnology

The quiet revolution

Biotechnology companies face an uphill struggle competing with pharmaceutical giants ruthlessly intent on pursuing those major markets capable of recuperating R&D expenditure. Their only means to outmaneuver pharmaceutical brethren is to provide better quality medicines based on more efficacious and less toxic molecules. Despite the dearth of spectacular examples, one major way in which this could be achieved is through genetics-based 'personalized' medicine. And a spot of crystal gazing suggests that healthcare will soon see the emergence—at least temporarily—of a two-tier system: pharma providing the first pass 'one-size-fits-all' treatments; biotech providing improved treatments targeted at genetically defined patient segments.

Most, if not all, of the major drug developers are now stockpiling DNA, blood or tissue biopsies from patients enrolled in trials. According to San Francisco-based consulting firm Recap (http://www.recap.com/), more than 60 pharma–biotechnology alliances have been struck since the start of 1998 concerning the genetics of drug response. Their purpose, in general, is to find associations between certain types of measurable genetic markers and individuals' different responses to drugs. Some of the specialist companies focus on haplotype (blocks of single nucleotide polymorphisms on chromosomes that tend to be inherited together) identification (*e.g.*, Genaissance Pharmaceuticals, Perlegen Sciences, Curagen and deCODE Genetics), others focus on finding protein biomarkers in serum or tissues (*e.g.*, SurroMed), and yet others provide storage, curation and banking facilities for samples taken from clinical trials (*e.g.*, Ardais, GenVault).

However, most pharma companies are not really doing anything much with the samples or data. Pharma executives remain shackled to their blockbuster model for drugs with greater than $500 million markets. This is because there is no economic incentive for market-dominant companies to subdivide patients into different genetic groups. Companies have concerns that adding a genetic analysis element to a trial will serve only to increase the time and expense of development. And they also largely lack the in-house expertise (or interest) to carry out DNA haplotyping/sequencing or screening for protein biomarkers; hence, the collaborations with specialist biotechnology companies.

The one place where pharma has shown interest—the possibility of using genetic markers to exclude adverse reactions that might kill a drug's market—also looks shaky. In 2001, Bayer was forced to withdraw its cholesterol-lowering statin Baycol from the market because of 100 deaths associated with the drug. Perhaps it could have been possible for Bayer to associate biomarkers in patient samples with the lethal side effects. But 100 deaths is a very small number compared with the number of people given the drug. The clinical trial required to detect such a rare event—even if it were genetically associated and not merely stochastic—would probably turn out to be prohibitively expensive. Furthermore, the error tolerance of the genetic test required to segment such rare events would have to be extraordinarily low. And our present genetic testing technology is simply not sufficiently robust or error free to do this.

On the other hand, those companies content to explore sub-blockbuster opportunities in genetically defined markets have two economic incentives to do so. The first is that it could be much cheaper. Statistical considerations alone dictate that the clinical trials—the largest cost component in drug development—of a highly efficacious medicine will be much lower than those of a marginally efficacious one. If one can exclude poor responders by genetic diagnosis, then fewer patients will need to be trialed to demonstrate a statistically significant improvement over existing therapies. The economics of this are exemplified by Genentech's Herceptin, a monoclonal antibody drug used in the treatment of metastatic breast cancer patients overexpressing the *HER2* marker. In 2002, the drug generated sales of $385 million which, assuming a 40% operating margin, is roughly enough to recuperate the estimated $150 million developmental cost from a single year's sales. Several other prominent biotechnology companies have adopted the same development template. Vertex Pharmaceuticals is collaborating with deCODE Genetics to incorporate genetic profiling into its clinical trials of VX-148, an experimental small molecule for treating psoriasis. And Biogen is teaming up with SurroMed to study the response of multiple sclerosis patients to its Avonex therapy.

The other economic incentive for biotechnology companies to get into genetically defined markets is the prospect of product protection under orphan drug rules. Both the FDA and the European Medicine Evaluation Agency have indicated that genetic markers could in theory be used to define a population of less than 200,000 patients and allow designation as orphan indications. If genetics could be used to define new orphan subtypes of a molecularly heterogeneous disease (breaking hypertension down into 15 different molecularly defined subtypes, for instance), new markets could open.

The bottom line is that personal medicine does not have to wait for regulatory agencies to impose safety or efficacy constraints. The day of genetic tests for avoiding adverse reactions will come, but only when our molecular understanding of drug metabolism and side effects is much more complete. In the meantime, economic incentives can already drive the emergence of genetically defined efficacy. While pharma companies will not proactively segment their existing markets, they will find them being segmented nevertheless—by a biotechnology product that provides better efficacy to this genetically defined group, by another product that works better for another segment, and so on. Not exactly death by a thousand cuts, but death by a thousand SNPs, perhaps. Furthermore, the diagnostic assessment need not be a barrier to a drug's success. It is just as likely to be perceived as an eligibility criterion reinforcing the premium value of the associated drug, a biological platinum card that opens up a world of medical privilege.

Five years ago, personalized medicine was hailed as the next 'revolution' in drug development. The revolution has been a long time coming. But if it is based on economic realities, not regulatory caprice, molecular-defined medicine will indeed prove sustainable and irresistible.