(Fig. 1). Random screening efforts can be focused into highly productive, information-rich campaigns.

One example of this is the elegant work by GlaxoWellcome on gene family targeting within the extended nuclear-receptor gene family[2], including the peroxisome proliferator-activated receptor (PPAR) gene family. 'Data warehousing' gives the opportunity to obtain maximum benefit from these developments. The advent of high-content screening, using, for example, gene expression microarrays, promises to extend this information into the area of absorption, distribution, metabolism and excretion (ADME) toxicology profiling. Substantially *in silico* lead discovery could soon become a reality.

Conclusions

As genomic data increase the supply of potential targets, an alliance of computational chemistry with HTS and combinatorial chemistry is crucial to increase the industry's success rate in lead generation. Although most companies have made all three of these investments, the balance of investment might need review, as might the strategy with which these three technologies are used in concert.

References

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How will pharmacogenetics impact the future of research and development?

'Pharmacogenetics has the potential to radically change the pharmaceutical industry'.

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The increasing cost of drug discovery and development, and marketing of a new chemical entity, is one factor that drives large pharmaceutical companies towards blockbuster drugs. However, a narrow portfolio of medicines can expose companies to risk. If the number of patients suffering from serious adverse events is high enough, then a new wonder drug can be withdrawn from the market, leaving tens of thousands of patients who would have benefited with no access to this drug. Further, this opens up the market to other companies.

Alternatively, a drug for a common disease might only be effective in a small proportion of patients, resulting in restricted approval for use by government 'value' committees. It might also be kept off formularies on cost-effectiveness grounds because the drug might consequently be prescribed for many patients who receive no benefit.

Evolution of pharmacogenetics

Advances in pharmacogenetics will provide opportunities to resolve this problem. Let us consider pharmacogenetics and medicine response profiles (MRPs), which will be developed from these advances as tools that use information from a small fraction of patients' DNA to predict their response to a medicine[1]. It is probable that there will be a rapid evolution in the impact of this technology on research and development, and in the application of this technology to the delivery of healthcare.

First, this technology will be applied to currently marketed medicines that are associated with rare severe adverse events in a small proportion of patients. These proof-of-principle studies will evaluate the technology and potentially enhance the risk:benefit ratio of these medicines. The initial studies of this type are ongoing and will be completed over the next

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few years. Second, if these studies can identify individual patients who are at a higher risk of experiencing adverse events, several changes in medical practice will be required for this technology to assist physicians in identifying patients who are susceptible to relatively rare, serious adverse events.

To identify and develop an MRP, DNA from patients who received the drug and suffered the adverse event, and matched controls who received the drug but did not experience the adverse event, must be available. In the post-marketing environment, MRPs will need to be developed rapidly to positively impact the safety of the medicine. To identify patients who are susceptible to the adverse event, DNA from patients must be analysed before the prescription is filled.

These basic requirements lead to the notion of a repository of DNA samples for new chemical entity surveillance to identify MRPs for rare serious adverse events. DNA samples from patients (or later, standardized whole-genome single nucleotide polymorphism mapping profile information) with physician-reported adverse events could then be immediately assembled, along with matched control DNA samples from patients who did not experience the serious adverse event, and analysed to develop an adverse event-related MRP. Subsequent patients taking the drug would have their DNA tested using the adverse event-related MRP at the time the prescription is issued. If the MRP indicates that the patient is not susceptible to the serious adverse event, the prescription is given. There is nothing mysterious in these requirements, but it would mean simple changes in medical practice and regulatory procedures that currently provide little information to identify individual patients who are susceptible to a particular adverse event.

Acceptance of the technology to predict drug-related adverse events will also provide opportunities to apply pharmacogenetics to predict efficacy responses. Pharmacogenetics could be incorporated into clinical development programs of some drugs so that efficacy MRPs could be developed. By collecting DNA samples in Phase II clinical trials and identifying DNA markers that correlate with defined efficacy parameters, it might be possible to further focus Phase III clinical trials by recruiting only those patients likely to respond. This will make these studies more efficient. In addition, information collected that identifies 'non-responders' in Phase II studies could be used in drug discovery to find new drugs to meet current unmet need in real time, rather than many years after trial-and-error post-marketing. In fact, using genetic and genomic technologies to improve our understanding of variations in a drug candidate's metabolic profile or target before it enters phase II clinical trials will decrease attrition rates overall.

Interestingly, one of the major points of failure in drug development is preclinical toxicology. Regulatory toxicology studies add at least two years to the drug development programs. Designing experiments that provide predictive toxicology information in 1–2 months rather than 1–2 years could increase the efficiency by better utilising those resources that are currently used for longer proscribed toxicology studies. A greater throughput of candidates that are less likely to fail regulated toxicology studies could lower the overall cost of drug development. This greater efficiency will provide opportunities to target diseases that are currently thought to be providing a low level of return on research and development investment.

Market value

The application of pharmacogenetics will not diminish the population of patients in which a drug is effective, but will allow a prediction of patient response. The potential in-market population for a particular medicine can appear to be reduced by the ability to identify those patients that are likely to respond. However, in many cases this is likely to be more than offset by an enhanced product profile of the medicine in the population likely to respond and the ability to more readily demonstrate the value of the medicine in these patients. It should be emphasized that the number of patients who experience rare post-marketing adverse events leading to the withdrawal of a medicine is orders of magnitude less than the size of the efficacy market. A safer drug has major competitive advantages. Safe drugs targeted to patients likely to benefit will be profitable, both for patients and drug companies.

Pharmacogenetics and change

Pharmacogenetics promises to change the way R&D is conducted and the way healthcare is delivered to patients. Before these benefits can be realized, changes in the way the pharmaceutical industry is regulated need to be agreed. It is therefore necessary for there to be partnership in change management of medicine development and delivery systems between industry, government, medical-care providers, and the public. Both regulators and large pharmaceutical companies need to be cognisant of the changing environment and, according to good Darwinian principles, companies must adapt or die.

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