Comment

Pharmacogenomics arrives

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It happens all the time: a pharmaceutical or biotechnology company will spend ten years and hundreds of millions of dollars on a drug candidate that looks spectacular in animal models of a disease, only to see it fail during clinical trials, either because of unexpected adverse reactions in a small number of patients or a surprising lack of efficacy. For every drug that is approved, on average more than 6,000 new chemical substances are created. Only seven of these ever end up being tested in humans, and only three make it to Phase III clinical trials, the final step before a drug is approved by the Food and Drug Administration in the US. It takes over a decade and at least several hundred millions of dollars - sometimes close to $1 billion - to get that far, and even then, on average, only one of three candidates will emerge from Phase III and become a marketed drug.

This combination of colossal failure rate with astronomical cost - unique to the pharmaceutical industry - is the main reason new medicines are both expensive and hard to come by. Despite advances in synthetic chemistry, high-throughput screening, and structure-based drug discovery, the number of new drugs approved has remained relatively constant, at about 20-30 per year, for a quarter of a century. As human lifespan increases, the demand for medicines to treat more difficult diseases such as cancer, heart disease, autoimmune disorders and neurodegeneration is likely to cause this meager success rate to decline - which may already be happening, since many big drug firms currently have rather dry pipelines. Such a trend could spell disaster for some of the largest pharmaceutical companies, which have grown so big through mergers that they need historically high returns on investment just to survive. For many of them, only so-called 'blockbuster' drugs - those with projected annual sales in excess of $1 billion a year - are now seen as worth developing.

That would seem to leave much of the field clear to biotechnology, but the enormous cost of taking a drug all the way through Phase III clinical trials means that most small biotech pharmaceutical companies can't manage it without at some point partnering with one of the big firms. Industry experts saw all this coming years ago. In the absence of some transforming technology, it seemed to pose an unsolvable conundrum: how to satisfy an increasing public demand that the wave of exciting biological discoveries from academia and biotech be translated into a vast array of new, cheaper, better medicines, when the cost and time needed to do so was steadily getting worse.

No wonder the genomics revolution was viewed with such hope. Even before the genome of the first free-living organism was sequenced by Fraser, Venter and their associates (Smith *et al.*, *Science* 1995, **269:**538-540), one of the selling points of the human genome project was that it would lead eventually to a new era, the era of pharmacogenomics. The reason so many promising drugs failed so late in the development process - in human trials - it was argued, was that differences in individual human genome sequences led to different profiles of gene expression, especially of isozyme families such as the cytochrome P450 enzymes, which carry out much of the metabolism of foreign substances, like drugs, in the human body. Once these differences could be determined for each patient, it would be possible to predict who would be likely to suffer an adverse reaction to a particular drug. Such people could simply be excluded from clinical trials (and of course from later therapy), and consequently the success rate for drug development would increase markedly.

We've had the human genome sequence for a little while now, and it looks as though we're still some way off being able to exclude from most clinical trials those people who will probably suffer side effects. Toxicity is a complex, often polygenic, process and we need to know more about it in order to link it confidently with genomic information. But two articles that have just appeared this month, in *Science* (Paez *et al.*, *Science* 2004, DOI: 10.1126/science.1099314) and the *New England Journal of Medicine* (Lynch *et al.*, *N Engl J Med* 2004, DOI: 10.1056/NEJMoa040938), make it clear that the era of pharmacogenomics has nevertheless

arrived. If they are any indication, and I think they are, this era will begin not with ruling patients out on the basis of likely toxicity, but rather with ruling them in on the basis of likely efficacy.

Both articles deal with the response of patients with non-small-cell lung cancer (NSCLC), the leading cause of death from cancer worldwide, to a new drug, gefitinib. (Most drugs now have three names: a systematic chemical name, a generic drug name, and a specific product name from the company that first developed them. Thus the non-steroidal anti-inflammatory drug called Advil in the US is Wyeth Pharmaceutical's name for its brand of ibuprofen, which in turn is the generic name for the chemical substance isobutylphenyl propionic acid. Iressa is the product name given to gefitinib by the drug company AstraZeneca.) Gefitinib targeted a molecule that was known to be overexpressed in this cancer, and the drug looked very promising in animal model studies, so it was both surprising and disappointing when it was found in clinical trials that most NSCLC patients had no response to gefitinib at all. Yet a small subset, about 10%, not only responded, but did so spectacularly - a 'Lazarus response', according to one physician, with complete remission even of advanced disease. These patients tended to have certain common characteristics: the majority were nonsmokers and women. Moreover, Japanese patients responded more frequently (about 25%) than did Caucasians. All these data suggested a genetic basis for the efficacy of the drug in such cases.

The authors of both papers started with the same assumption, that the first place to look for allelic variations among patients was the gene for the target. Gefitinib is an inhibitor of the epidermal growth factor receptor protein kinase HER1, or EGFR. It binds to the ATP-binding site in the catalytic domain of the kinase, blocking the enzyme's ability to phosphorylate protein substrates. Both teams of investigators sequenced the *EGFR* gene from tumor samples of both responders and non-responders to the drug. They found that nearly all the responders had heterozygous mutations in their *EGFR* gene, while none of the non-responders did. The mutations, which included both short deletions and single amino-acid substitutions, tended to cluster around the ATP-binding site. Moreover, when the receptor gene was sequenced from a cohort of NSCLC patients who had not been treated with gefitinib, similar mutations were found in about 10% of them, exactly the percentage of responders in the clinical trials. One of the studies even found that female nonsmokers and Japanese patients showed a higher than average incidence of the mutations, also correlating perfectly with the clinical data. Taken together, these data strongly suggested that the favorable response to the drug not only correlated with, but was caused by, the mutated *EGFR* gene.

Heterozygosity of the mutations implied they might produce a gain of function. *In vitro* studies showed that the mutated receptor was indeed more active than the wild-type, which could account for its relatively high incidence in tumors - presumably it confers some survival or growth advantage. The assumption is that the altered ATP-binding site leads to the increased activity, as well as to increased affinity for gefitinib. Enzymological studies will be needed to establish exactly how this occurs and whether it is the whole story. No-one is concerned by the small number of responders who were not found to have EGFR mutations in their tumors; non-small-cell lung carcinomas, like other solid tumors, are probably polyclonal. Presumably, had a different sample of cells been sequenced, mutations would have been observed.

It now seems clear that, for a subset of NSCLC patients, gefitinib promises to be an effective treatment. Screening people who present with this cancer for EGFR mutations in the kinase domain is a trivial task, and ought to be the first step in deciding what therapy to use. But if this is really the dawning of the age of pharmacogenomics, the gefitinib story can't be an isolated case.

Recent data suggests that it is not. A subset of breast cancer patients overexpress a related receptor, HER2, on the surface of their tumor cells. Many of these patients show a good response to trastuzumab (Herceptin), Genentech's monoclonal antibody drug directed against this receptor. Novartis's drug imatinib (Gleevec), which also binds to the ATP-binding site of its target, the Bcr-Abl protein kinase, has shown considerable effectiveness against chronic myelogenous leukemia, a disease in which this kinase is activated by a chromosomal translocation (producing the so-called Philadelphia chromosome). The Bcr-Abl kinase can transform hematopoietic cells and is essential for tumor progression, explaining the efficacy of the drug for this cancer. Interestingly, imatinib also appears to be effective against a subset of gastrointestinal stromal cancers, and responsive tumors have recently been found to contain mutations in the c-Kit protein kinase (Heinrich *et al.*, *J Clin Oncol* 2003, **21:**4342-4349). The hope is now that for many cancers, at least a percentage will have proteins that are essential for tumor progression, either through overexpression or mutation, and that these proteins will form the basis for targeted therapy.

When the first report came out that gefitinib was effective in only a subset of NSCLC patients, science reporters and stock analysts bemoaned the loss of income that AstraZeneca would suffer. Given the pharmaceutical industry's need for blockbuster drugs, it might indeed seem that pharmacogenomics would be little, if any, help, if all it did was drastically reduce the size of the potential market for a given drug. But let's do the sums. In the US alone, 140,000 people are diagnosed each year with NSCLC (the figure is about a million worldwide). If about 10% of these turn out to have gefitinib-responsive tumors, then the US market is on the order of 10,000. Gefitinib is expected to cost about $3,000 per

month per patient, so revenue from sales could reach, theoretically, around $360 million per year. But 10,000 patients per year is the rate of incidence, not prevalence: that many new patients are expected to present with gefitinib-responsive NSCLC each year. And each of them will probably need to take the drug for the rest of their life. So the market for gefitinib should rapidly grow to blockbuster size, even if only the US market is considered. And for any such patients, for some time to come, gefitinib will clearly be the front-line treatment, not one of a host of alternatives as is the case with other forms of cancer. That's a recipe for the kind of profits even the biggest drug company should be happy with.

Pharmacogenomics might turn out to be an even bigger boon to the biotechnology industry. Any biotech company would be thrilled to have a revenue stream of a few hundred million dollars a year: the problem is the cost of getting there. But if clinical trials could be conducted with fewer patients than is now the case, because the likely responders could be identified in advance, and if that also translated into fewer drug failures in late-stage clinical trials, then both the cost and time to gain approval of a new drug could drop substantially, perhaps to the point that even a small company, or a joint venture of several of them, could go it alone. Of course, for that to happen, the problem of adverse reactions would also have to be solved, or at least greatly mitigated. Pharmacogenomics hasn't made an impact on toxicity yet, but give it time. It's only just arrived.