Clinical pharmacogenomics: Almost a reality?

Using genomics to drive clinical development is gaining some traction, but it still has obstacles to overcome.

BY DAVID FILMORE

The advantages genetics could bring to clinical development and decision-making, as well as the next steps needed to make it a valid tool in this environment, were underscored in the recent findings of two studies performed by distinct research groups at Harvard Medical School. The studies analyzed tumor samples from lung cancer patients who had taken Iressa (gefitinib), a small-molecule targeted cancer therapy developed by AstraZeneca.

Iressa was approved in the United States in 2003 as a third-line treatment for lung cancer, based on a Phase II study in which 10% of participants had a substantial tumor shrinkage response. But in Phase III randomized trials, the drug caused no survival improvement when added to conventional chemotherapy. So in a minority of patients, Iressa has a dramatic effect, but in many other cases its effect is much less or none. Determining when the drug might be the right one to use has been a difficult task for physicians.

The papers, published in the May issues of *Science* (**2004,** *304,*1497–1500) and *The New England Journal of Medicine* (**2004,** *350,* 2129–2139), reported a strong correlation between certain gene mutations discovered in the kinase domain of Iressa's target, the epidermal growth factor receptor (EGFR), and patient response. The *Science* study also identified a cell line, with one of the EGFR gene mutations found in patients, that showed a dramatic in vitro response to Iressa compared with cell lines without the mutation.

"In our study, all of the patients with responses had mutations, and all of the patients that progressed did not," says William Sellers, assistant professor of medicine at the Dana-Farber Cancer Institute and one of the lead authors of the *Science* paper. On the basis of the results, he is confident that prescribing Iressa, even as a first-line treatment, is now a much more predictable decision.

ASTRAZENECA

"In my mind, there is no doubt that if someone has the mutation, they deserve treatment with Iressa," he says. "If I had the mutation, I would take Iressa alone."

"But if you were the FDA, you probably would like to do a clinical trial," he adds.

However, the pharmaceutical industry is uncertain about the prospects of performing trials in which analyzing safety or efficacy is put in the context of genetic or genomic subgroups or in which patients are initially stratified on the basis of genetic data. The industry may be even more unsure about the outlook for making the resulting data available to regulatory agencies and the public.

"Despite the enthusiasm researchers have for advancing biomedical technology and exploring the human genome, there is little willingness to incorporate pharmacogenomics into clinical trials," says William Evans, St. Jude Children's Research Hospital scientific director.

But signs are emerging that the opportunity for integrating pharmacogenomics, the science of linking genetic determinants to drug response, into the clinic is increasing.

Pharmacogenomics future?

"The future is arriving," asserts Christopher Webster, director of regulatory strategy and intelligence at Millennium Pharmaceuticals, a company founded on the concepts of personalized medicine and pharmacogenomics.

He points to drugs like Genentech's Herceptin (trastuzumab) and ImClone Systems' Erbitux (cetuximab), two monoclonal antibody cancer therapies with associated FDA-approved tests to measure protein receptor levels predictive of patient response. Although these tests are immunohistochemical protein assays and not genetic measurements, they carve out a pathway for the co-development and co-approval of drug products and assays, an essential aspect of pharmacogenomics-based medicine.

By many accounts, overcoming the challenge of carrying out well-designed pharmacogenomics-based clinical trials and using the information to drive drug development and approval are at the heart of making personalized medicine a reality.

Two big reasons industry has been wary of moving ahead too quickly with pharmacogenomics drug development, says Kurt Jarnagin, vice president of biological sciences and chemical genomics at Iconix Pharmaceuticals, is "regulatory uncertainty and legal product liability." Essentially, he says, companies are worried about what the FDA or a trial lawyer might dig out of the data to use against the drug. This reflects an "unknown factor" still associated with genomic information.

Whereas the legal issue remains more of a question mark, targeted discussions ongoing between the FDA and industry since early 2002 have done a lot to flesh out the regulatory uncertainties.

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Recent studies suggest which patients might benefit best when taking the anticancer drug Iressa.

One product of these interactions is the soon-to-be-released final FDA guidance document for submitting pharmacogenomics data. A draft version was published in November 2003. One section of the guidance addresses contexts in which genomics data, preclinical or clinical, might be required for regulatory review, such as when assessment of safety, efficacy, or dose in a submitted drug application is contingent on genetic marker information.

Another component focuses on the types of submissions expected in the nearer term, that is, voluntarily submitted exploratory pharmacogenomics data not slated for regulatory decision-making. The voluntary submission concept, Webster says, came out of calls by industry for a "safe harbor," letting companies submit the data with less concern that it will be put to unintended use and allowing the agency to get more comfortable working with and analyzing pharmacogenomic information.

Following the release of the first draft of the guidance in November 2003, many pharmaceutical and biotechnology companies submitted comments to the FDA regarding the voluntary submission process and the procedure for validating exploratory biomarkers. But how forthcoming the firms will be with genomics data still remains to be seen.

Wyeth has already submitted voluntary genomic data to the FDA, but it was related to an Alzheimer's disease vaccine program that was previously discontinued. Millennium, Webster says, plans on making a voluntary submission regarding one of its drugs in development later this year.

Mathematical problem

Voluntary submissions will provide a mechanism for validating genomic biomarkers as predictive tools in particular disease contexts. The FDA plans to establish an Interdisciplinary Pharmacogenomics Review Group to review the voluntary submissions in relation to each other. And a pharmacogenomics advisory subcommittee will be formed to assess the aggregate data and determine when a correlation between clinical outcomes and a genomic marker is convincing enough to drive clinical and regulatory decision-making.

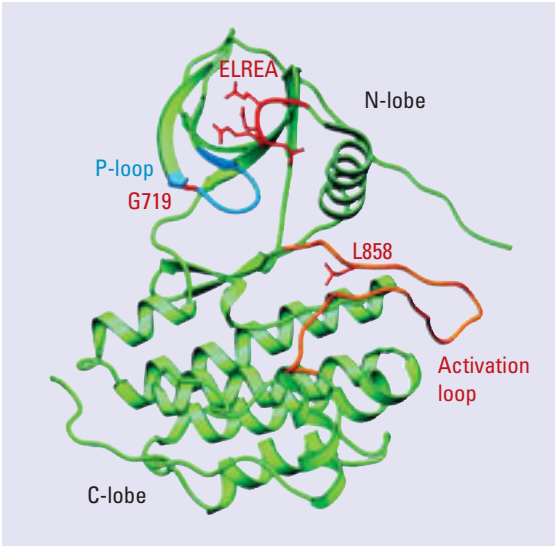
This will not be a straightforward task, according to several at the helms of leading clinical research institutions.

In a recent review paper in *Nature* (**2004,** *429,* 464–468), Evans and St. Jude Hospital colleague Mary Relling, chair of pharmaceutical sciences, point out some of the challenges of conducting definitive clinical pharmacogenomic studies. These include the complexity of multiple genes influencing patient response to a drug or interference in assessing genetic subgroups from nongenetic confounders like drug interactions, diet, and smoking.

Robert Califf, director of the Duke Clinical Research Institute, noted at an FDA Science Board meeting in April that the prospect of multivariable genomics (and burgeoning proteomics) will generate "an enormous mathematical problem" in getting meaningful results from clinical trials. He cited replicated clinical trials that showed a correlation between astrological sign and clinical benefit from aspirin. This "subgroup problem is magnified now that we can measure multiple biomarkers," he said.

"There is not a company on the face of the earth that can do enough experiments to find out what the array of biomarkers is that predicts a beneficial treatment over time, or even toxicity," Califf warned.

Both Evans and Relling, as well as Califf, suggest there is a need for large-scale trials with adequate follow-up, carried out in partnerships between public and private organizations.



Mutations in various positions, colored red, of the epidermal growth factor receptor that were associated with patient response to Iressa. The L858R missense mutation was also detected in a cell line that was particularly sensitive to the drug. (Adapted with permission from Paez, J. G.; et al. *Science* **2004,** *304,*1497–1500. Copyright 2004 AAAS.)

Real trials

Despite the uphill battle, several companies are clearly taking on the challenge of incorporating pharmacogenomics into their clinical development programs.

Many firms, for example, are screening for various mutations in CYP450 drug metabolism enzyme genes such as *CYP2D6*. This is one of a few genetic classes that have consensus as validated biomarkers for predicting whether a patient will have safety or efficacy issues based on over- or undermetabolism of a drug. Roche Diagnostics' November 2003 diagnostic device application submission to the FDA for its Amplichip CYP450 microarray only signals further efforts in this direction.

Industry is also beginning to broaden its clinical genomics focus.

At a conference entitled "Safety Biomarkers" that took place in Washington, DC, in May, Daniel Burns, vice president of discovery genetics at GlaxoSmithKline, discussed several completed or ongoing GSK clinical trials that involved matching particular single nucleotide polymorphisms (SNPs) to drug toxicity responses. One program is for the already marketed HIV drug Ziagen (abacavir). According to Burns, by using microarray technology to screen large swaths of the genome of clinical trial participants, GSK has identified SNP markers for abacavir sensitivity, a side effect that, in situations in which the patient is taken off the drug and then restarted on it, can be fatal.

Another major pharmaceutical company showing signs of incorporating the pharmacogenomics model into clinical trials is Pfizer. The company signed an agreement in January with Perlegen Sciences—a 2000 spin-off of Affymetrix founded to use high-affinity microarrays to screen clinical trial participants for genetic variation—to find SNPs associated with response to drugs for major depression disorder. Perlegen also has similar alliances in other disease areas with Pfizer, AstraZeneca, Eli Lilly, GSK, and Bristol-Myers Squibb.

Like Perlegen, Genaissance Pharmaceuticals is focused on providing services that allow partner companies to put pharmacogenomics to use in clinical studies through its *HAP* technology, which includes a large database of genetic variation and associated informatics tools.

But Genaissance is also conducting its own clinical trials with the pharmacogenomics concept at their core. These include the STRENGTH (Statin Response Examined by Genetic *HAP* Markers) study, which was conducted at 65 sites in the United States to find response markers to the statin class of cholesterol-lowering drugs; and the CARING (Clozapine and Agranulocytosis Relationships Investigated by Genetics) trial, designed to determine patients most likely to develop a life-threatening side effect from the off-patent schizophrenia drug clozapine. Initial results of the STRENGTH study indicating a specific variant of a gene that controls LDL–cholesterol response to statins were announced in March 2003. The work has attracted major statin producers, including Bayer and AstraZeneca, wanting to access the company's data.

By and large, these and other clinical efforts are focused on finding one or several specific genetic variations associated with drug response. The even more statistically taxing effort of correlating global gene expression signatures with response, however, is still predominantly relegated to drug discovery and preclinical activities. But companies like Iconix, Jarnagin says, which has developed a large chemogenomics database linking expression data with drug response, are working to "build bridges" between this data and "improved clinical diagnostics and therapeutics."

Back to Iressa

But what about the simpler case of Iressa? The recent Harvard results suggest a potentially straightforward path relying on a single mutation for predicting drug response. And the prospects for confirming the results in a clinical trial are good, Sellers believes. A quick first step, he says, is to go back and analyze tumor samples from the already completed randomized Phase III trial. "One could very readily ask, by retrospectively analyzing tumors, whether there was a benefit in the trial to patients with mutations."

This is essentially what AstraZeneca is pursuing now, although the analysis is not so clear-cut, says company spokeswoman Mary Lynn Carver. "Based on the patients who have received Iressa to date, we don't know enough about what type of correlation we have," she explains. "It looks like we have a very strong correlation in the

dramatic responders. But in one of those trials [the NEJM study], you had a dramatic responder that did not have a mutation. So you still have some mysteries. Is there more than one mutation we need to be looking for?"

Carver also points out the approximately 30% of patients in the original Phase II trial who didn't have dramatic tumor reductions but did maintain stable disease without substantial progression. "We don't know if those patients have the same mutation, a similar mutation, or anything in common with one another," she says.

MILLENNIUM PHARMACEUTICALS

Millennium's Webster, sitting before a genomic heat map, expressed his confidence in the promise of pharmacogenomics.

AstraZeneca is currently in discussion with both outside and in-house researchers, Carver stresses, but the company is not ready to say for sure whether this finding will lead to new trials or discussions with the FDA about new marketing strategies.

ICONIX PHARMACEUTICALS

Jarnagin, from Iconix Pharmaceuticals, says companies are concerned about "regulatory uncertainty and legal product liability" when submitting genomic data to the FDA.

Another important factor in a company's decision whether to pursue pharmacogenomics in later-stage development is the commonly cited concern that identifying a specific responder group might be bad for business if it limits the drug's market to only that group. Right after the Iressa results were announced, some analysts predicted a significant drop in the drug's market size. Whether this consideration will play a role in AstraZeneca's actions on Iressa or in the actions of Genentech, which, along with OSI Pharmaceuticals and Roche, has completed Phase III trials, which showed positive results, on another EGFR inhibitor for lung cancer called Tarceva (erlotinib HCl), remains to be seen.

Often, Millennium's Webster says, the pharmacogenomics isn't going to be as simple as black and white. "You can have a situation where a drug might bring some benefit to people who don't have the marker but would perhaps bring much more benefit to people who do have the marker." Therefore, the economic affects of pursuing this line of research aren't necessarily predictable. (Although, according to IBM Healthcare and Life Sciences' Carol Kovac, pursuing it is the only sustainable option for companies; see "Closing the loop on information", p 27.)

Generally, Webster believes pharmacogenomics will not be a downer for drugs' market share. "There will still be blockbusters that gross in excess of a billion dollars," he believes. "There will be shifts in the marketplace and shifts in clinical use, but there will still be blockbusters."

"If patients know that they have a much higher likelihood of therapeutic success with a genomically prescribed drug, they will tend to shift in that direction." ■