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# Competitors Try Collaboration To Speed Drug Development

**By Margie Patlak**

Sharing data may be a venerable tradition in some research communities, but nobody in the world of drug development expects to collaborate with potential competitors. That situation may be changing, though, according to speakers at a workshop on precompetitive collaboration in cancer research, sponsored by the Institute of Medicine (IOM) last February.

The hope is that such collaborations, just now getting under way and involving both academic and industry researchers, will boost the currently dismal 5% success rate for new anticancer compounds in drug development pipelines.

"People are ready for change—everyone knows we need to work together on a framework that gets us out of the 'one drug, 10 years, and a billion dollars to develop it' paradigm," said Laura Esserman, M.D., director of the Carol Franc Buck Breast Care Center of the University of California, San Francisco.

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One prime example of precompetitive collaboration that the workshop highlighted is the joint preclinical testing by AstraZeneca and Merck of a combination therapy for cancer, for which each company contributed a potential therapeutic agent. Another is the recently begun I-SPY 2 trial, which Esserman leads, that will test compounds and biomarkers from several companies in the same phase II study.

## A Tale of Two Compounds

The AstraZeneca–Merck collaboration got its start in October 2007 at the Dublin airport, when Pearl Huang, Ph.D., vice president of oncology at Merck, bumped into AstraZeneca scientist Paul Smith, Ph.D., after hearing him speak at a meeting about a new MEK inhibitor that AstraZeneca had developed. At the time, Merck didn't have any MEK inhibitors in the pipeline, but the company did have a promising inhibitor for Akt.

MEK plays a key role in one of the most important signaling pathways involved in carcinogenesis; Akt is critical in another. Each pathway can act as a backup pathway for the other: When the MEK pathway is blocked, the Akt pathway can be activated and vice versa.

Huang suspected that Merck's Akt inhibitor would be more effective at stopping cancer growth if an effective MEK inhibitor, which AstraZeneca seemed to already have in hand, also shut down its backup pathway. So she approached Smith and discussed collaborating on a cancer treatment that simultaneously used both inhibitors. AstraZeneca's MEK inhibitor was then in phase II testing and Merck's Akt inhibitor had graduated to phase I. AstraZeneca had Akt inhibitors in development, but none was as far along as Merck's Akt inhibitors. Joining forces to test a combination treatment with the two compounds made sense for the two researchers and their companies.

In addition to sharing costs and expertise in development, a competitive advantage would exist for being the first to come out with the combination, Huang said. "We will sell more of our drug and they will sell more of their drug, if it actually works."

She and Smith also stressed the advantages to patients of a combination being developed more rapidly. "It is the type of collaboration asked for by clinical investigators who wonder why they and their patients have to wait for a single company to combine compounds within their portfolio when there are further-developed agents from other companies," said Smith.

There was just one catch: Such collaborations had never been done so early in the drug development pipeline by two large pharmaceutical companies, according to the two researchers. The project raised many new issues, such as how to share costs, decision rights, and intellectual property and patents that result from the collaboration. If phase III trials prove the two-hit combination therapy's safety and efficacy, another looming issue will be how to coregister with the U.S. Food and Drug Administration a treatment comprising two unregistered drugs.

Laura Esserman, M.D.

All those issues were resolved, except FDA regulation, via a series of meetings that included the scientific collaborators and their company lawyers. The resulting agreement enabled joint preclinical testing of the Merck Akt inhibitor and the AstraZeneca MEK inhibitor but didn't preclude either company's independently testing other, similar combinations with their own MEK or Akt inhibitors. When the collaborative preclinical testing of the MEK–Akt combination showed promising results, the companies agreed to joint phase I testing of the combination therapy, which began in December 2009—record time, according to Huang, for such a complex treatment.

Once the two companies committed to working together, Huang said, developing the testing protocols went smoothly and quickly. Together Merck and AstraZeneca designed preclinical and clinical testing

plans that assessed dose amounts, dose sequencing, and the subpopulations in which to test their combination of compounds. In these plans, the companies agreed to share the costs of such testing as well as the decision making. The agreements also include a conflict resolution process, which so far hasn't been needed. Merck will keep intellectual property rights to its Akt inhibitor, just as AstraZeneca will keep rights to its MEK inhibitor. The inventors will share any intellectual property that results from the collaboration.

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Still unknown is how the FDA will regulate development of the combination therapy. Although combination therapy for cancer is standard, the combinations are usually tested after the registration of at least one drug, so that a new potential treatment is tested with standard therapy. No one has ever coregistered two previously unregistered drugs, according to Huang.

The FDA was unable to verify this assertion, but a spokesperson said that the agency is currently developing general combination guidance for how to codevelop two or more new molecular entities for tuberculosis, cancer, and other serious diseases.

### I-SPY 2 Collaboration

The regulation path that will be taken for compounds tested in the I-SPY 2 trial, by contrast, was largely worked out before the trial began. This phase II multisite trial will be testing, along with standard neoadjuvant chemotherapy, up to a dozen experimental breast cancer drugs from several companies. Simultaneously, it will assess the effectiveness of various biomarkers to predict response to the investigational agents.

The trial will start by testing five new molecular agents. As the trial drops those agents for lack of safety or effectiveness, or as they graduate to phase III testing, new compounds will be seamlessly entered into the trial. So far, four companies, including Pfizer and Abbott Laboratories, have signed on, and twice as many have expressed interest.

Although many participating companies have drugs that target the same pathways, the trial will not compare them directly. "We said we would not compare head-to-head two IGFR inhibitors or two mTOR inhibitors," said UCSF's Esserman, who is principal investigator. Instead, the trial will test drugs by class. "Whoever's drug in a class is farthest along the pipeline goes in first, and we'll make our results rapidly available to the community so we can all learn and move forward," she said.

Usually multiple drugs require multiple trials, each with its own investigational new-drug (IND) application to the FDA. To speed up the process, the Biomarkers Consortium, trial organizers, and the FDA developed a plan by which the Foundation for the National Institutes of Health holds the master IND application. The foundation was chosen because it was seen as a trusted, neutral third party that can sponsor and manage the trial fairly and effectively, said Esserman.

The FDA and relevant internal review boards approved INDs for the initial group of experimental agents before the trial started. The trial will test their replacements by amending the protocol to include approvals by the FDA and the review boards.

Such planning was a major feat and required time-consuming meetings with all the relevant stakeholders, including the FDA, right from the outset, Esserman noted. But this effort should pay off because it eliminates the need for a new protocol each time that the trial adds an agent, and it affords a pathway for rapid development. Esserman said that developing the protocol for I-SPY 2 and launching it took two and a half years.

Managing the intellectual property that will result from the trial remains a formidable challenge that the Foundation for NIH, which will hold the licenses for the new inventions, will tackle. The foundation will return a fair share of royalties (less expenses) to inventing organizations and will manage the patents. Preexisting intellectual property brought to the trial will remain with the original companies.

David Wholley, M.Phil.

Other precompetitive collaborations described at the IOM conference include the Foundation for NIH's Biomarkers Consortium, in which 12 large pharmaceutical companies share their data to better qualify and validate biomarkers that can aid the diagnosis of disease, predict therapeutic response, or improve clinical practice. Founded in 2006 by the NIH, the FDA, and the Pharmaceutical Research and Manufacturers of America, the consortium's first completed project identified a biomarker in diabetes. The project used pooled and blinded preexisting data contributed by four pharmaceutical companies from clinical trials. The data were analyzed under the direction of scientists from industry, government, and academia.

Four companies also recently shared their clinical trial data in an American Society of Clinical Oncology–led effort to assess the minimal data that need to be collected for supplemental new-drug approvals. This effort resulted in a white paper that the FDA is heavily relying on as it develops new guidance on the topic, according to Mark McClellan, M.D., Ph.D., of the Brookings Institution's Engelberg Center for Health Care Reform.

More such precompetitive collaborations are emerging because, according to the Foundation for NIH's David Wholley, M.Phil., who spoke at the IOM conference, "the increasing complexity, amount of data, and downstream effects on regulatory science is leading to the dawning realization that nobody is smarter than everybody."

The workshop was not designed to reach a consensus, but after 2 days of presentations and discussion, it became apparent that major factors driving the interest in collaborations include declining research and development budgets combined with the growing complexity of biomedical research, especially in the cancer arena. Several participants viewed precompetitive collaborations as a means to solve many problems that currently plague drug development.

In a discussion of next steps, participants called for seeking more public and private support and funding for collaborations, as well as publicizing success stories and management plans. It was also suggested that an appropriate authoritative body establish a set of standards for sharing precompetitive materials that could be stipulated in state and federal grants for biomedical research or for electronic medical records. An IOM committee may examine these issues and suggestions further.

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