Federal Task Force Seeks Standards for Immunotherapy Biomarker Studies

By Joel B. Finkelstein

Researchers could be learning more from clinical trials of cancer immunotherapy, according to organizers of a workshop who are looking for novel biomarkers that accurately predict response to these treatments.

“The clinical trials of cancer immunotherapies haven’t been terribly successful. The problem so far is that the strategies that have been tried, if not successful clinically, you don’t learn that much from them,” said Peter Lee, M.D., an associate professor of hematology at Stanford University’s School of Medicine and a member of a new Taskforce on Immunotherapy Biomarkers, which is organizing the workshop.

Jointly sponsored by the U.S. Food and Drug Administration and the International Society for the Biological Therapy of Cancer, the task force’s goal is to build on existing consensus within the cancer community to facilitate the discovery and validation of new biomarkers. Agreeing on common research standards and strategies is a key objective.

After a decade of clinical trials of immunotherapy for cancer, the average response rate has generally been low, at around 15% of patients. Given that, researchers should be striving to learn as much as possible from that small group of people who do respond to treatment, said Lee, who is co-chairing the task force’s working group on biomarker discovery.

The low response rate to these treatments can in part be explained by the fact that cancer cells themselves are effective in suppressing immune response.

“If you are trying to induce an immune response to cancer while the cancer cells themselves are trying to shut it off, it’s a
sort of arms race going on inside the body,” said Lee.

However, the absence of unified strategies for either measuring biomarkers or exploring their significance means that researchers have learned too little about the mechanisms of immune response in cancer patients.

The Problems
“We have taken a very reactive approach to identifying biomarkers rather than a proactive one,” said Francesco Marincola, M.D., chief of the infectious disease and immunogenetics section at the National Institutes of Health, the discovery working group’s other cochair, and the driving force behind the task force.

While researchers could be learning more from patients who have a positive response to immunotherapies, they can also learn from a lack of response to treatments, Marincola said. Biological therapies are expensive and often toxic, so finding biomarkers that predict a non-response may be just as important in terms of knowing earlier if a treatment is not working in a patient.

For example, Marincola’s team recently found that high levels of vascular epithelial growth factor predict a nonresponse to therapy with interleukin 2.

“It’s not perfect. What we found was that if levels are high, people will not respond. If it is low, people may or may not respond. … But if you can eliminate 30%–40% of the population from getting this very toxic therapy, it’s useful,” he said.

One problem is that such findings have been difficult to verify. Studies of cancer immunotherapy have been small and inconsistently designed, making it next to impossible to compare results across trials. Marincola cites, for example, the studies of cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies in cancer.

“Nobody has learned anything from all those trials except that there is a lot of toxicity. What is CTLA-4 doing to the tumor, what is really happening in different immunological parameters? Nobody really knows,” he said.

Although such details are missing, there is evidence that there is more to the CTLA-4 picture than is apparent from the trials that have been conducted, said Lisa H. Butterfield, Ph.D., assistant professor of medicine at the University of Pittsburgh and cochair of the task force’s working group on biomarker validation.

“Looked at by classical standards of tumor response criteria, patients seem to progress and, following those rules, they are officially tagged as progressors and yet months later have antitumor effects and long-term survival that would not have been predicted by those criteria,” she said.

“For the field to move forward, instead of small phase I, phase II trials at individual institutions following their own rules, [we should] start to combine data from multiple institutions … and learn at a much faster pace,” said Butterfield. But that can happen only “if people are following the same rules,” she said.

The idea that the task force members are advocating is a simple one, namely, that clinical researchers need to look beyond the traditional endpoints of cancer trials. The interplay of variables in immunotherapy are more complex than in chemotherapy. Simply measuring biomarkers, without striving to understand how they work, is no longer enough.

Possible Solutions
The task force’s two working groups, one focused on facilitating the discovery of new biomarkers and the other on developing standards to validate those biomarkers, consist of dozens of scientists from government, academia, and industry. The group’s first step is the workshop, planned for fall 2009, which will aim to address what consensus around standards already exists within the research community; to publish a report outlining that consensus; and to create a Web site where scientists can easily access that information.

“There has been a lot of work and publications about [sample collection], but when you look for standards [while you’re] sitting in your laboratory trying to make some decisions and start a new clinical trial, it can be difficult to find these things even though the work has already been done,” Butterfield said.

The researcher faces several questions when trying to define these standards: Which tube should the blood be drawn in? What additives should be used? How should the blood be cryopreserved? How long can the blood sit at what temperature before the cells and the proteins in the blood will start to change and no longer provide an accurate snapshot of what was going on in the patient?

“Things that seem very mundane like that can critically impact the data,” Butterfield said. “All of these things have been studied and can be standardized; we just need pull that together and present it in a unified fashion and make it available.”

A paper published by Marincola and colleagues to announce the formation of the task force and the fall workshop, as well as to invite comment from the community, suggests that the collection of this material has at least in part been stymied by “practical, ethical, and financial rationalizations.” The ethical issues inherent in any clinical trial can be magnified in immunotherapy trials, in which often terminally ill patients are asked to submit to many biopsies, blood tests, and invasive exams. The task force intends to address such issues with the help of bioethicists, officials from regulatory agencies, statisticians, and input from the community in general.

They are starting from three basic assumptions. According to their paper published in the December 23 issue of the Journal of Translation Medicine, these are “1) excessive and unnecessary regulatory burdens ultimately result in a disservice.
to present and future patients; 2) studies limited for financial reasons are likely to be more wasteful than well-designed costly studies because they will eventually need to be repeated; 3) the application of training/validation strategies may significantly reduce costs without compromising the scientific yield of well-designed studies.”

**Mandating Strategy?**

Marincola believes that a comprehensive approach to incorporating standard collection procedures is critical enough to warrant imposing them on researchers seeking federal funding or approval.

“My ultimate goal is that we influence the FDA, and maybe the NCI, to require a more programmatic [approach] in the design of clinical protocols,” said Marincola.

He expects some scientists may balk at such a mandate, but he argues that the research community in general can no longer afford to move ahead haphazardly.

“Obviously, you are never going to find a biomarker if you don’t have the materials that are relevant,” he said. “If you want to seriously attack clinical issues, you have to do it systematically and rationally. A study of 20 patients done well is probably worth 1,000 [not done well].”

He and the other task force members see this comprehensive approach becoming even more critical soon. Multiplex assays that combine several biomarkers into a comprehensive profile will eventually offer a much broader picture of response by simultaneously assessing multiple antigens, genes, and signaling pathways.

“That’s where I think the new biomarkers are going to come from, allowing us to predict rather than quantitate. That will yield a much more global picture,” said Butterfield.