lished in December in patients sicker than they were before. Normal tissue can be damaged by treatment, leaving therapies for cancer, one aspect often gets overlooked: Normal tissue that’s downregulated or absent on tumor cells. To do this, they combined an antigen-recognition domain with signaling domains of CTLA-4 and PD-1. In this context, the checkpoint blockades downstream of these proteins are used for their natural purpose: to ensure that the immune system doesn’t overreact to threats.

Because the checkpoint blockades respond only to an antigen found on normal tissue but not on the tumor, the iCARs can be turned on again if they meet a tumor cell.

“What’s very exciting about the concept is that it’s reversible, mimicking what the normal immune system does, but we’ve twisted it to make it selectively protective for what we want to protect,” says molecular pharmacologist Michel Sadelain, MD, PhD, who led the work.

“I think it’s a wonderful idea,” says Stanley Riddell, MD, an immunologist at the Fred Hutchinson Cancer Research Center in Seattle, WA, who praised the Sloan-Kettering team for experimentally evaluating what others have only talked about. “And I think this does demonstrate in principle that this could work.”

The real challenge will come when the iCARs are tested in the clinic, where T cells will need to be carefully engineered to express both a chimeric antigen receptor and an iCAR in a way that maximizes antitumor activity and minimizes off-target killing. However, current mouse models are not really rigorous enough to adequately test the iCARs, notes Riddell, who is working to improve these models.

“The reason this paper is important is that it provides a new avenue to investigate,” Riddell explains. “As we proceed in identifying new receptors, we can think about how we can combine signaling modules to tune the response to be more selective against the tumor and less against normal tissues.”

Today, there are probably a few thousand PDX models total in academia and industry worldwide, Li estimates. “Particularly this year, PDX models have become a much more favored translational approach,” he says, and the number of models is climbing quickly as major pharmaceutical companies adopt the approach.

“Scalability is very important, and maintaining and annotating the PDX models is a huge investment,” Li notes. Production of PDXs for some types of cancer, including colon and pancreatic cancers, “has become quite an industrialized process,” with the ability to convert patient tissue samples to PDX models at a rate of up to 100% with very good quality, he adds. However, he points out that engineering models of certain other types of cancer, such as breast and prostate, may still prove difficult.

Partially funded by a Chinese central government grant, the center will support translational oncology projects both for SIMM’s drug development pipeline and for other organizations around the world.

Fine-tuning the Effects of T-cell Therapy

In all the excitement around T-cell therapies for cancer, one aspect often gets overlooked: Normal tissue can be damaged by treatment, leaving patients sicker than they were before.

In a proof-of-principle study published in December in Science Translational Medicine, researchers at Memorial Sloan-Kettering Cancer Center in New York, NY, propose a solution (Sci Transl Med 2013;5:215ra172). They have engineered molecules called inhibitory chimeric antigen receptors (iCAR) that can protect normal tissue from the off-target effects of T-cell therapy.

The T-cell therapies do exactly what they’re designed to do—attack tumor cells that express specific antigens on their surface. Unfortunately, there are very few antigens on cancer cells that aren’t also on the surface of normal cells, so T-cell therapies attack them, too.

To stop that attack, the Sloan-Kettering team designed the iCARs to turn off if they encounter a second antigen found on healthy cells that’s downregulated or absent on tumor cells. To do this, they combined an antigen-recognition domain with signaling domains of CTLA-4 and PD-1. In this context, the checkpoint blockades downstream of these proteins are used for their natural purpose: to ensure that the immune system doesn’t overreact to threats.

Because the checkpoint blockades respond only to an antigen found on normal tissue but not on the tumor, the iCARs can be turned on again if they meet a tumor cell.

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FDA OK’s Iclusig’s Return to Market

The U.S. Food and Drug Administration (FDA) has approved new safety measures to reduce the risk of potentially fatal vascular problems that, once in place, will allow Ariad Pharmaceuticals (Cambridge, MA) to resume selling its leukemia drug Iclusig (ponatinib).

On October 31, 2013, the FDA requested that Ariad suspend sales of the drug after standard safety monitoring revealed a significant increase in the number of patients experiencing blood clots and severely narrowed blood vessels compared with the number reported when the drug was approved in December 2012 (Cancer Discov 2014;4:6–7). Ariad complied with the request.

The new measures mean that fewer patients will be candidates for Iclusig. Its use will be limited to adults with T315I-positive chronic, accelerated, or blast phase chronic myeloid leukemia (CML) or T315I-positive, Philadelphia chromosome–positive acute lymphoblastic leukemia (ALL), as well as adults with chronic, accelerated, or blast phase CML or Philadelphia chromosome–positive ALL for whom no other tyrosine kinase inhibitor therapy is indicated.

In addition, Ariad will revise Iclusig’s label to highlight the risk of blood clots and narrowed blood vessels, complications that have occurred in at least 27% of patients who have taken the drug, according to the FDA. The company also will update its medication guide for patients.

Finally, Ariad must undertake a risk evaluation and mitigation strategy, which will include activities such as sending letters to likely prescribers and prominently posting information at scientific meetings, to alert health care professionals to the drug’s risks.

Ariad said that it would start distributing Iclusig again in mid-January, and that it would continue to assess the drug’s dose, efficacy, and toxicity in postmarket investigations.

Dasatinib–Letrozole Gets Split Verdict

Adding dasatinib (Sprycel; Bristol-Myers Squibb) to the aromatase inhibitor letrozole (Femara; Novartis) improved progression-free survival (PFS) in women with estrogen receptor–positive, HER2-negative metastatic breast cancer in a phase II clinical trial, according to results presented on December 12 at the 2013 San Antonio Breast Cancer Symposium in Texas.

However, the combination was no better than letrozole alone when it came to the study’s primary endpoint, a “clinical benefit rate” defined as the sum of those with a complete response, partial response, or stable disease for at least 6 months.

Dasatinib is an approved treatment for chronic myelogenous leukemia and Philadelphia chromosome–positive acute lymphoblastic leukemia. Because dasatinib inhibits a variety of kinases, including the Src family of kinases, which are involved in cell proliferation, investigators are testing it against a wide variety of cancers. Preclinical data suggested that it has therapeutic potential in breast cancer.

In this trial, principal investigator Devchand Paul, DO, PhD, a breast oncologist at Rocky Mountain Cancer Centers in Denver, CO, and at US Oncology Research in The Woodlands, TX, and his colleagues enrolled 120 postmenopausal women with locally recurrent or metastatic breast cancer and randomly assigned them to either letrozole and dasatinib or letrozole alone. The results showed that 71% of the women in the dasatinib–letrozole arm met the clinical benefit rate criteria endpoint compared with 66% of those in the letrozole arm.

About 40% of the patients had received prior adjuvant endocrine therapy, with 85% treated with tamoxifen. Paul says the study was designed with the expectation that more women would have used an aromatase inhibitor as adjuvant therapy. The lack of previous exposure to an aromatase inhibitor may have made letrozole particularly effective as a treatment for metastatic disease, so the addition of dasatinib might not have made much of a difference with respect to the primary endpoint, he says.

However, there was a large difference in PFS between the two study arms: 20.1 months for the women assigned to the dasatinib–letrozole arm versus 9.9 months in the letrozole arm.

Results from previous trials testing the addition of dasatinib to exemestane (Aromasin; Pfizer), another
pCR Proves Valid Surrogate Endpoint


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