IN brief

Investor stampede for CARs

Engineered T cells are used as therapy

A cross-country collaboration devoted to adoptive T-cell therapy—considered by some the breakthrough technology of the year—has scored big with investors. In December, Juno Therapeutics of Seattle

raised \$145 million in a series A round, among the largest biotech A rounds ever assembled. A unique structure teams up three clinicians and researchers from Memorial Sloan-Kettering Cancer Center in New York with three from Seattle's Fred Hutchinson Cancer Research Center and the Seattle Children's Research Institute. Collectively, the group has expertise in both engineered and nonengineered approaches to creating autologous T-cell therapies for cancers. "There was this recognition very early on in the discussions about not just the fact that together it was a strong team, but that the experience that the different groups had was highly complementary," says Juno CEO Hans Bishop. Investigators from these groups, as well as groups under the direction of Carl June at the University of Pennsylvania and Steven Rosenberg at the US National Institutes of Health, have wowed the cancer field with response rates in B-cell malignancies using genetically-engineered T cells that target CD19. However, CD19 is a "dream target" admits Juno co-founder Stanley Riddell, of the Fred Hutchinson Cancer Research Center, because people can survive the depletion of normal CD19⁺ B cells. "One of the challenges is to find other such targets," he says. Although CD19 is expressed on healthy nonmalignant B cells as well as on B-cell tumors, people can survive the killing of normal CD19⁺ B cells by the chimeric antigen receptor (CAR)-modified T cell. Unfortunately, thus far, few truly tumor-specific surface proteins that can be targeted by CAR T cells have been identified, so in each case one needs to consider the potential toxicity that would result from simultaneous CAR T-cell attack on healthy tissue. Autologous cell therapy, never a darling of investors, has challenges, both logistical and economic, and engineering T cells has some on top of those. "With CAR T cells, you find the patient, they get it once. So you have no recurring revenue, which is a business model issue," says David Miller of Alpine BioVentures in Seattle. "I think the logistics of that are more difficult than people think," he says. But with the potential to durably 'cure' patients, the technology is seemingly irresistible. "This is really paradigm shifting. This is taking patients who have advanced refractory malignancies, who have failed everything, and putting them into complete remission," says Riddell.

Laura DeFrancesco

Box 1 What use are genetic tests for cancer? AHRQ report questions utility of genetic tests

A draft technology assessment report from the Agency for Healthcare Research & Quality (AHRQ) on the clinical utility of genetic tests for evaluating the risk of cancer recurrence will not have made for comfortable reading for some of the companies whose products were examined. The report, which was open for review from November 26 until December 12, found that of the 11 prognostic tests studied, only around half had evidence supporting their prognostic accuracy or clinical validity. Moreover, the report's authors, who are based at the AHRQ-funded RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center, stated that they "found no evidence to determine whether using the tests leads to improved outcomes for patients."

Neil Barth, chief medical officer of Amsterdam-based molecular diagnostics firm Agendia, concedes the draft report is partly justified. The assessment states that Agendia's MammaPrint array-based test, which employs a 70-gene signature to predict the post-surgical recurrence of breast cancer in early-stage patients, does have prognostic accuracy, but that there is insufficient evidence to conclude that it has any impact on treatment decision-making. The report found moderate evidence that a rival test, Oncotype DX, from Redwood City, California–based Genomic Health, does influence treatment decisions. But Barth says, "There hasn't been any published data by any diagnostic company in this space that has met the definition of level I evidence for clinical utility." Although there is a growing body of evidence suggesting that MammaPrint can help breast cancer patients avoid unnecessary chemotherapy—and pinpoint those who do need chemotherapy—the company still lacks sufficient data from prospective, randomized trials. "When it comes to guidelines inclusion, that's where we get knocked," Barth says. A 6,600-patient prospective study, called Mindact, completed accrual in 2011 and should provide a readout during 2015. In the meantime, Agendia is putting its case to the AHRQ that data reported from a 427-patient prospective, nonrandomized observational study (*Int. J. Cancer* **133**, 929–936, 2013) is "at least at the level of moderate clinical utility in a technical assessment."

The AHRQ, an agency of the US Department of Health and Human Services, is charged with improving healthcare quality by fostering patient-centered outcomes research. The business impact of its assessments may not be hugely important, however. "The AHRQ is not cited by many of the payer technical committees as being a critical analysis," Barth says. "I don't want to be dismissive of it, and we're certainly paying attention to it," he adds.

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For those who want to develop tests on top of the NGS system, the Illumina authorization represents a starting point. "It still leaves the burden on the clinical lab to develop their informatics pipeline," Lubin says. That entails developing the capability to manage the data analysis tasks associated with managing and interpreting large quantities of sequence data. "That takes quite a bit of infrastructure and knowledge—to do it and to maintain it," he says. Illumina is already offering a cloud-based data analysis and management platform, BaseSpace. Lubin speculates that companies specializing in informatics may emerge to focus exclusively on analyzing and interpreting NGS data. "Those kinds of business models may need to develop," he says.

Interpreting genomic variation will remain challenging (Box 1). In the same week as Illumina's milestone approval, the FDA moved to limit the activities of 23andMe, a Mountain View, California–based firm offering single-nucleotide polymorphism genotyping services directly to consumers (*Nat. Biotechnol.* **32**, 1, 2014). NGS-based clinical testing offers far

greater sensitivity and power, but it also must avoid the pitfalls that can arise from false positives or false negatives for certain gene variants.

Illumina's Heath says he expects early adoption to proceed in several areas, including reproductive genetics, cancer, infectious disease, and compatibility testing for blood transfusions and organ transplants. "The barriers tend to be not around the technology per se, but around indications," he says. Testing laboratories need to be confident they will have a market—and that their services will be reimbursed.

For Iris Schrijver, associate professor of pathology at Stanford University School of Medicine, in Stanford, California, looking at the genome in isolation from other aspects of human biology, such as the proteome, the metabolome and the microbiome, will offer limited returns, however. "We're only looking at the alphabet and not at how the words are put together and make a complete story," she says. "By itself, it is a huge step. It's just not the whole story."

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