Immunosequencing Comes of Age as Researchers Demo Clinical Utility, Aim for FDA-cleared Products

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Premium

NEW YORK (GenomeWeb) – Due to its complexity and variability, the immune repertoire was once thought to be too difficult and costly to sequence to have clinical utility. The tides have now turned, and researchers are increasingly demonstrating that sequencing the immune repertoire can offer valuable insight into various blood cancers, treatment response, and the likelihood of relapse.

Adaptive Biotechnologies, a Fred Hutchinson Cancer Research Center spinout; iRepertoire, a spinout of the HudsonAlpha Institute for Biotechnology; and Sequenta have all been working in the field for the last four years and are developing clinical products.

In November, Sequenta struck an *in vitro* diagnostics deal with Illumina to commercialize a test based on Sequenta's MRD detection and quantification technology. Adaptive Biotechnologies has launched a laboratory-developed test for monitoring MRD in patients with T- and B-cell malignancies, and is looking to launch another one that evaluates tumor-infiltrating lymphocytes. iRepertoire has developed a test called D50 that measures immune diversity.

Meantime, Stanford University spinout Atreca, said recently that it struck a collaboration deal with Janssen Biotech and Johnson & Johnson Innovation to use single-cell sequencing to study autoimmune disorders.

In addition, at this week's American Society of Hematology meeting in San Francisco, researchers presented numerous abstracts demonstrating the clinical utility of immune repertoire sequencing.

"This year feels like the tipping point," Sequenta CEO Tom Willis told GenomeWeb in an interview. There is now a level of acceptance about the technology across clinical sites and even among pharmaceutical companies, he added.

"There is a tremendous opportunity," Adaptive Bio CEO Chad Robins told GenomeWeb. "Nearly all therapeutic areas are related in some context to the adaptive immune system." Earlier this year, Adaptive Bio estimated that the research market for immune profiling in blood-based cancers could reach $390 million by 2018, while the diagnostic market could be $850 million.

Toward FDA clearance

One way companies will tap into the diagnostic market for NGS-based immune profiling is by bringing products through US Food and Drug Administration clearance.

Willis noted that Sequenta is pursuing this through its agreement with Illumina, adding that the earliest a product could be cleared would be in 2016.

"Our desire to have an IVD kit has been there from the start," he said, but until Illumina's MiSeqDx received 510(k) clearance, there was not an appropriate sequencing platform for developing such a kit.

Willis said the first cleared product will test for MRD as a prognostic marker in multiple myeloma. Using MRD as a prognostic measure to predict future disease has been "the principal question we've been taking on in our clinical trials," he said. And studies using Sequenta's technology have shown that "MRD at low levels is indeed extraordinarily predictive."

At the ASH meeting this week, Sequenta and collaborators presented studies comparing sequencing-based testing for MRD to more standard methods like flow cytometry or PCR, and demonstrating that Sequenta's test is more sensitive and provides better prognostic information.

For instance, in a collaboration with researchers from Kanazawa University in Japan, the collaborators compared using Sequenta's LymphoSight platform with allele-specific oligonucleotide PCR for MRD testing. They retrospectively analyzed 109 multiple myeloma patients that received autologous peripheral blood stem cell and had achieved a partial response or better, and found that not only was the LymphoSight platform more sensitive than ASO-PCR, but also that detection of MRD, even at low levels, was predictive of disease progression.

In a separate collaboration with Memorial-Sloan Kettering Cancer Center, the researchers found that in a head-to-head comparison of the LymphoSight platform with flow cytometry, LymphoSight was more sensitive and a finding of no MRD was correlated with better survival. In addition, they also evaluated the ability of LymphoSight to measure MRD from peripheral blood and noted that in patients that had already received treatment, the levels of myeloma clonotypes in blood were very low.

Willis said that aside from using the test to predict disease prognosis, Sequenta is exploring use of the LymphoSight technology to develop a companion diagnostic along with the pharmaceutical company Celgene, which has also invested in Sequenta. "Those uses will require that the CDx be approved alongside the indications of the drug in a pre-market approval," he said.

Adaptive Biotechnologies is also looking to bring products through FDA clearance. Like Sequenta, Adaptive Biotechnologies relies on Illumina's sequencing technology for its assays. Robins said that the firm still has a strong relationship with Illumina despite its IVD agreement with Sequenta, which he noted was not exclusive.

Over the next year, Robins said that Adaptive Bio plans to double in size from its current 90-person team. "We are moving toward becoming a product company," he said. The RUO kit it has launched, ImmunoSeq, will "be the backbone and training ground for IVD kits that will go through the FDA," he said.

Currently, the firm offers a clinical testing service, ClonoSeq, and is working on a second clinical offering, called TILseq (previously called QuanTILfy), which will measure tumor infiltrating lymphocytes in solid tumors. Robins said the company is in "active planning mode" to bring both ClonoSeq and TILseq through FDA clearance in order to sell them as IVD kits.

At the ASH meeting, Adaptive Bio's abstracts demonstrated the utility of ClonoSeq for diagnosing and monitoring MRD in a range of cancers, including acute lymphocytic leukemia, chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and cutaneous T-cell lymphoma.

For instance, the company sequenced bone marrow samples from relapsed B-cell ALL patients as part of a phase I trial for a targeted immunotherapy, which found that MRD-negative patients as measured by ClonoSeq had a better outcome.

In a separate phase II multi-center trial of double induction chemotherapy in ALL patients, run by the Southwest Oncology Group, researchers compared ClonoSeq with flow cytometry for evaluating MRD, and found that when both technologies found MRD, patients had the worst prognosis. But ClonoSeq was also more sensitive than flow cytometry, identifying MRD where flow cytometry could not. Those patients also had significantly worse outcomes than patients that were MRD negative by both ClonoSeq and flow cytometry.

"The data is really compelling" in support of sequencing methods as being superior to flow cytometry, Robins said. "It's a much more accurate and better way to monitor residual disease." And, he added, such studies are the "first step to show that NGS is the way to go."

Immune diversity

iRepertoire is taking a slightly different approach. CEO Jian Han told GenomeWeb that the firm has developed a test it calls D50 for measuring immune diversity. D50 is the number of unique T or B cell clones that account for 50 percent of the total T or B cells. He said the test was developed after studies showed that healthy patients had more diverse immune repertoires.

Han said that iRepertorie collaborated with researchers from France to study cytomegalovirus infection to find that the D50 index decreased upon CMV infection. Additionally, in a separate study of multiple sclerosis, he said that the D50 index went up while patients were being treated, but fell back to the baseline after treatment stopped.

Universal test

While MRD in cancer will likely be the first clinical application of immune sequencing, researchers are now starting to use the technology to also monitor organ transplantation rejection and to study a host of other diseases such as autoimmune disorders, infections, and even complex diseases like type 1 diabetes. Eventually, some researchers think that immune sequencing could serve as the ultimate universal diagnostic.

Sequenta and Adaptive Biotechnologies presented abstracts at ASH this week describing the use of their technology to monitor stem cell transplantation, and Adaptive also presented data for monitoring organ transplantation.

Additionally, Han noted the R10K project, which is being led by the HudsonAlpha Institute, aims to sequence the immune repertoires of 10,000 samples representing 100 diseases with the goal of

identifying disease-specific T- or B-cell receptor sequences to improve diagnosis, prognosis and treatment management.

Already, he said, the group has sequenced over 6,000 samples representing 30 diverse diseases including inflammatory bowel disease, multiple sclerosis, breast cancer, tuberculosis, and colon cancer.

Included in immune repertoires are the complementarity determining regions, or CDRs, which are generated by B cells and T cells. CDRs are incredibly variable and critical to diversity.

Han said that one goal of the R10K project is to develop a disease-specific library that will include shared CDR3s from individuals with a specific disease, and a public library of CDR3s that will include all the diseases' libraries as well as libraries of CDR3s from normal controls.

Han said that iRepertoire is now collaborating with Peter Mannon at the University of Alabama, Birmingham to study 60 IBD patients and 100 controls. So far, he said "almost all IBD patients have significant [sharing index] values with the disease library," while the controls do not. For instance, he said in one patient, 38 percent of the CDR3s overlapped with the public library, while 54 percent overlapped with the disease-specific library.

In a separate study with the University of Hong Kong evaluating the sharing index in breast cancer patients, Han said the group found that it had a specificity of 91.5 percent and a sensitivity of 92 percent.

The idea is that eventually such a tool could be used to diagnose a broad range of diseases by sequencing an individual's immune repertoire and then comparing it to the public library to determine whether the sharing index surpasses some threshold for a specific disease. Immune repertoire sequencing could eventually be the "ultimate diagnostic," Han said.

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