Stanford Spinout Inflammatix Developing Sepsis Diagnostic Based on Host Immune Response

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NEW YORK (GenomeWeb) – Inflammatix, a startup spawned from a Stanford University research lab, seeks to measure gene expression patterns of a patient's immune response as a way to diagnose infectious disease.

In particular, Inflammatix anticipates that its first product will be a sepsis diagnostic — an 18-gene panel that will be able to tell from a blood sample whether a hospitalized patient has a bacterial, viral, or no infection so that physicians will be able to administer more appropriate treatments earlier.

"There is an enormous number of potential value cases, and certainly one of them is earlier detection of bacterial infection, especially in hospitalized patients," said Inflammatix Cofounder and CEO Tim Sweeney, who developed the gene panel and Inflammatix's discovery method while at Stanford alongside Purvesh Khatri, a cofounder and scientific advisor to the startup.

"The other is … discrimination between bacterial and viral infections … [which] gives a physician more confidence that it's not bacterial, but you are looking at a patient who is sick," Sweeney said. "We think one of the benefits of reporting out those three classes is that it will improve the uptake of the test itself, even if in the vast majority of cases there may not be a specific treatment beyond [potentially] running some viral diagnostics, like culture or a rapid influenza test."

The idea of examining host response to diagnose infectious diseases has been picking up steam in recent years. In February, Seattle-based Immunexpress received 510(k) clearance from the US Food and Drug Administration for Septicyte Lab, an RNA-based blood test that can determine if an infection is the cause of a patient's systemic inflammation. However, this test does not claim to distinguish between viral and bacterial infections.

In addition, over the last several years a team from Duke University School of Medicine has been developing a gene expression assay to determine whether a respiratory infection is viral or bacterial in nature.

Sweeney said that the gene expression analysis approach is particularly promising for sepsis diagnosis.

"Most people have sort of a misconception that sepsis means bacteremia, and really that's not the case," Sweeney said. "Sepsis is a dysregulated immune response to any infection. In particular, we know that the majority of people with acute infections actually don't have … pathogens in their bloodstream."

There is a large and well-established testing industry that focuses on picking out particular pathogens. "But they're fundamentally not serving probably the majority of patients that come through the door in an emergency department who are not going to have detectable

bacteria in their bloodstream, and in fact have inaccessible localized infections," Sweeney said.

Inflammatix's approach to diagnostic development, which Khatri called a "multicohort analysis framework," uses custom informatics algorithms to sift through publicly available datasets from real-world patients to identify candidate biomarkers.

"All the data that that we use is publicly available," Khatri said. "The multicohort analysis framework takes advantage of the biological and technical heterogeneity that exists in publicly available data."

This "discovery cohort" is basically used to identify a transcription signature that is unique to the disease or condition in question. That signature is then tested on a separate validation cohort. "We never allow the same group to be in discovery and validation," Khatri said. "This is truly an independent cohort validation."

The method has already been borne out in several peer-reviewed studies and scientific posters authored by Sweeney, Khatri, and colleagues.

This includes a Science Translational Medicine paper last year describing the discovery and validation of the 18-gene panel — actually a combination of a previously published signature that can discriminate between infection and inflammation, and a seven-gene signature that can distinguish between viral and bacterial infection.

Sweeney and Khatri have also shown how their approach could produce a three-gene expression signature to distinguish latent from non-latent tuberculosis, work that was published in The Lancet Respiratory Medicine in March 2016. And Khatri, who remains a professor of medicine specializing in computational immunology at Stanford, has also collaborated with other researchers to develop a gene expression signature for systemic sclerosis severity, and, most recently, an immune response signature to differentiate malaria from other infections.

Khatri presented the malaria work in a poster at the European Congress of Clinical Microbiology and Infectious Diseases last month in Vienna. Specifically, he and collaborators trawled through data from more than 40 previously published studies representing more than 3,000 blood samples from patients with various infectious diseases. They ultimately found a seven-gene signature indicative of malarial infection, and tested it on a subset of 900 samples from patients with various tropical diseases and malaria, finding that they could discriminate malaria infection with 96 percent accuracy.

Each of these studies has lent further support to Inflammatix's approach, but the company for now is maintaining its focus on sepsis. Inflammatix has an exclusive license to the sepsis biomarkers from Stanford, and it has completed a Series A financing for an undisclosed amount led by Khosla Ventures with participation from the Stanford-StartX fund. Sweeney also said that Inflammatix has secured a Small Business Innovation Research grant for an undisclosed amount from the Defense Advanced Research Projects Agency of the US Department of Defense.

Inflammatix is now using its funding to further validate its gene signature and begin testing it in the clinic.

"There are ongoing non-interventional studies to further confirm biomarker efficacy, and we are also in the planning stages for an interventional diagnostic trial," Sweeney said.

The company has also begun working with an undisclosed partner to develop a device based on real-time PCR — which Sweeney said is the "known and trusted gold standard for gene expression quantitation" — to administer the assay.

"We surveyed the market and identified a small number of potential partners and have chosen to go ahead with a device-side partner as a way of keeping our capital footprint relatively lighter, rather than engaging in full-time device development in addition to assay development," Sweeney said.

Ideally, Khatri noted, this device would have three characteristics: "It would be random-access, multiplex, and have a rapid turnaround time, so results would come back in under an hour," he said. "If you look at the diagnostic space, there are many devices available that satisfy two of these characteristics, but we've done an extensive survey and there is no device that we know of that does all three of these."

Sweeney and Khatri both indicated that the platform would also likely follow the razor-razorblade model that has been followed by many other infectious disease diagnostic manufacturers.

"The technology already exists," Khatri said. "It's now an engineering problem of how you fit it onto one device that satisfies the three criteria."