NIH Grant to Fund Research on Proteomics, Immunoassay for TB Activation in HIV Patients

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Premium

NEW YORK (GenomeWeb) – The National Institutes of Health has awarded Albert Einstein Medical College researcher Jacqueline Achkar a five-year, $3.7 million grant to develop a protein-based immunoassay to predict tuberculosis progression in HIV patients.

With the funding from the National Institute of Allergy and Infectious Diseases, Achkar will collaborate with several partners to find human protein biomarkers that indicate a latent TB infection is becoming active. The first phase will use mass spectrometry to find candidate biomarkers, which will then be used to create diagnostic and prognostic immunoassays. Specifically, Achkar will evaluate immune response proteins and human antibodies against *Mycobacterium tuberculosis* proteins.

The goal is to build an immunoassay platform that can be easily integrated into routine follow-up care for HIV patients, to find those most likely to benefit from TB medications that have been shown to prevent a latent infection from progressing.

"Simple point-of-care testing needs to be the way to go," Achkar said, adding that a dipstick-style test would be ideal. "None of my research is focused on technology that cannot go on to be a simple test. What the world needs is something very simple, for use in resource-limited settings without any lab infrastructure."

While infection with HIV or TB is usually manageable, the combination of the two diseases is particularly deadly. HIV positive patients are at significant risk for co-infection with TB bacteria and for those with latent infection, the time it takes for the infection to become active tuberculosis is faster than for those patients without HIV, Achkar told GenomeWeb. Approximately 1.5 million HIV-positive people die of TB each year, one-sixth of all TB deaths worldwide.

Certain TB medications can prevent latent infections from progressing and while the World Health Organization advises prophylactic treatment of HIV patients with them, it's not practical to give them to everybody, Achkar said. "If we could measure the [bacteria] activity level in co-infected individuals and determine who is at risk for progression to active TB, we would have a better idea of when to intervene," she said.

While nucleic acid-based detection technology — like Cepheid's US Food and Drug Administration-cleared GeneXpert MTB/RIF test — is advancing quickly, there's a particular need for cheap testing that doesn't depend on advanced laboratory infrastructure.

And it's unlikely to reveal much about which patients are on their way to an active, rather than latent, TB infection.

"Proteins are an indirect marker of *M. tuberculosis* infection activity," Achkar said. "Infection doesn't mean disease." But in patients infected by both HIV and latent TB, the risk of developing an active TB infection is 30 to 60 times greater than the general population and it happens much faster.

While prophylactic treatment can prevent disease, it has its limitations. In addition to side effects, contributing to multi-drug resistance, and interaction with HIV drugs, the protective effect can fade.

"We need to identify biomarkers in HIV-positive people and find those that are at highest risk for developing active infection, and only then go in with targeted prophylactic therapy," Achkar said.

To find biomarkers, Achkar will be using mass spectrometry analysis to find proteins differentially expressed in two populations: co-infected patients who never developed active TB and those that did. She's already obtained samples from two cohorts, one in the US and one in the Republic of South Africa, taken at both the time of diagnosis as well as two years prior. By looking at the two time points, she can see what changes as the bacteria activate.

Working with Montreal-based proteomics services firm Caprion Biosciences, Achkar has already identified a panel of 87 proteins that are different at the time of diagnosis. They published a study last year in *EbioMedicine*.

"What we anticipate finding is that two years prior to diagnosis, the proteins will still be at baseline levels," she said. "Then, over the two years, they will slowly go up."

The mass spec-based proteomics phase will be large-scale and "very expensive," Achkar said. "Then we will narrow it down to candidate proteins and then make monoclonal antibodies to these proteins so we can build immunoassay prototypes. Then these can be easily used on a much more cost-effective basis to validate our findings."

They could also help create a platform for more complicated tests. If Achkar and her colleagues are right, then some biomarkers will begin changing early on in the latency-to-activity transition, and some later. Based on that, algorithmic analysis could help provide a prognosis for whether or not a patient is likely to be developing an active infection.

The grant will also fund development of nucleic acid programmable antibody microarrays, which Achkar will collaborate on with scientists at Arizona State University. "Particularly with antibodies, if two years before diagnosis they are low, and 18 months prior they go up a bit, and then after one year [following diagnosis] they're up even higher, you could say, 'I see there is a development in rising antibody levels,'" she said.

Such a test, if it were available in an easy-to-use, point-of-care format, could be integrated into routine appointments every couple months for patients in regions endemic for TB.

"Mass spec is very expensive, so ultimately you want to get away from [it] for simple tests," Achkar said. "There is a lot of TB diagnostic technology out there and some of it is very fancy, but currently almost everything requires some degree of lab infrastructure." Bacterial culture is the "gold-standard" test, but it requires time and a laboratory. *Mycobacteria* can be identified in sputum with a microscope, but not only does that require an instrument and a technician, it's particularly unsuited for HIV-positive patients, who have fewer *Mycobacteria* in their spit.

Immunoassays have their own caveats, namely specificity, in this case the degree to which a positive result is truly indicative of active TB.

"But that's not a big issue," Achkar said, "TB is often over-treated anyways." The disease is hard enough to diagnose on its own and damaging enough that patients presenting with TB-like symptoms are often treated for it. "If you suspect TB, they might not have it, but you treat it anyways," she said.

High sensitivity and specificity are always the ideal, but she said that for some diseases, it's not always achievable. If you can combine simple techniques like immunoassays or dipsticks to have high sensitivity with moderately good specificity, that's already very helpful," she said.

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