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IGRA based diagnosis of infection and prediction of disease

Peter Andersen[1,2]

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Can IGRA assays, used in the highly specific and sensitive quantiFERON and T-spot tests, predict the development of disease in individuals who are infected but currently display no symptoms? High ESAT-6 reactivity may predict disease because ESAT-6 is a marker for bacterial burden. We found that vaccinated cattle for which the vaccine did not offer protection displayed high reactivity to ESAT-6 early in infection; cattle that controlled the infection displayed low ESAT-6 reactivity. By evaluating the response in guinea pigs both vaccinated and not vaccinated with BCG, we found that the animals with a large skin test result (high reactivity) after infection with *Mycobacterium tuberculosis* did not have a long survival time. In mouse vaccination studies ESAT-6 reactivity dropped as the vaccine controlled bacterial activation, which indicates that ESAT-6 reactivity correlates with the dynamics of infection.

For humans, we developed a template to use as a cut-off or conversion model for predicting three possible scenarios for individuals post-exposure. The model, based on IFN-γ levels in response to ESAT-6, delineates three possible reactions: people who control initial bacterial replication and remain ESAT-6 negative; people who fail to control initial replication, but eventually control the infection, becoming ESAT-6 positive and latently infected; people who fail to control replication, become ESAT-6 positive and later develop clinical TB. A large study with serial quantitative IGRA testing is necessary to be able to make a statistically robust ROC curve.

ESAT-6/CFP10 has great value as a predictor of TB disease. In low/meso-endemic regions, ESAT-6/CFP10 predicts progression to disease with higher accuracy than PPD, resulting in more precise targeting, preventive therapy and less treatment. In high endemic regions, the potential for TB prediction may depend on the establishment of a cut-off or QFT conversion that would allow the identification of QFT positive individuals at the highest risk of progression. If longitudinal monitoring of ESAT-6 reactivity levels is used as a biomarker of bacterial replication, it can also be useful as a clinical endpoint, allowing for much shorter clinical trials of both vaccines and novel drugs.

Author details
[1]Infectious Disease Immunology, Statens Serum Institute, Copenhagen, Denmark. [2]Vaccine R&D, Statens Serum Institute, Copenhagen, Denmark.

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Correspondence: PA@ssi.dk
[1]Infectious Disease Immunology, Statens Serum Institute, Copenhagen, Denmark
Full list of author information is available at the end of the article