Host-Based Biomarkers for Early Diagnosis of Exposure or Infection

A Novel Host Protein-based Assay and Point-of-care Platform for Rapidly Distinguishing between Bacterial and Viral Infections

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Background: Bacterial and viral infections are often clinically indistinguishable, especially early during infection. This diagnostic uncertainty leads to antibiotic misuse and limits our ability to manage outbreaks. A host-based biomarker test would complement pathogen-based tests as it does not require access to infection site, and has the potential to be insensitive to colonizers and unaffected by pathogen evolution. In a previous 1002-patient study we screened over 600 host proteins to develop a novel signature that integrates the levels of three blood-borne biomarkers: TRAIL, IP-10, and CRP. The resulting 'TIC' signature score indicates the likelihood of bacterial infection. Broad application of the TIC signature requires overcoming two major challenges: (i) double blind clinical validation studies to independently establish test performance; and (ii) development of a rapid (within minutes) and quantitative platform to measure the TIC signature at the point-of-care (POC).

Results: TIC signature performance was demonstrated in 3 independent clinical studies ('Curiosity' - NCT01917461 (n=1002); 'Pathfinder' - NCT01911143 (n=597), and 'Opportunity' - NCT01931254 (n=777)), encompassing over 60 bacterial and viral pathogens, in which it was applied in a wide range of clinical indications including cases when the infection site was not readily accessible, and was shown to be insensitive to colonizers and unaffected by pathogen evolution. Importantly, both Pathfinder and Opportunity were investigator-initiated double blind multicenter studies. Moreover, the TIC signature was observed to be accurate irrespective of time from symptom onset, raising the possibility that it may be applied to detecting early and even pre-symptomatic infections. The TIC signature repeatedly showed significantly better diagnostic performance relative to routine laboratory parameters (e.g., white blood cell count, absolute neutrophil count) and single host proteins (e.g., CRP, PCT, HNL). This superiority is likely attributable to the signature’s combination of both viral- and bacterial-induced biomarkers that participate in different pathways, and compensate for one another's blind spots. A meta-analysis of the three studies yields sensitivity 91% (CI: 87%-94%) and specificity 94% (CI: 92%-96%), with 11% equivocal test results.

A 1st generation ELISA-based test for measuring the TIC signature within two hours (called ImmunoXpert™) was developed and cleared in Europe and Israel. To date, the test has been used in conjunction with clinical assessments and other laboratory findings as an aid to differentiate bacterial from viral infection and guide treatment of >10,000 patients in early stages...
access clinical centers. However, to allow broader impact, a rapid and easy to use version of the test is required. Accordingly, over the past few years we have been developing ImmunoPoC™, a 2nd generation POC platform capable of conducting rapid measurement (within 15 minutes) of the TIC signature, which we are now prototyping together with DTRA. More generally, the new platform will conduct rapid multiplex-protein measurements at the POC with lab quality precision, which has multiple applications.

**Conclusion:** The trilogy of clinical studies establish that the TIC signature accurately distinguishes between bacterial and viral infections. The platform developed jointly with DTRA will enable wider adoption of the TIC signature and potentially promote prudent antibiotic use and improve outbreak management.

Prototyping of the point-of-care platform is being supported by DTRA under contract number HDTRA1-17-C-0011.