TB SERS BIOSENSOR

A prototype diagnostic device for rapid, sensitive and direct identification and quantitation of Mycobacterium tuberculosis at point-of-care in low resource settings ("SERS Biosensor")

BACKGROUND

Tuberculosis (TB) is the leading cause of death in Sub-Saharan Africa and South Africa, and globally, 10.4 million new cases are diagnosed annually. It is a stigmatizing disease that marginalizes patients and their families, and the prolonged morbidity and high death rates are economically debilitating. Detection of TB remains a major problem, with a large majority of patients being co-infected with HIV (approximately 60% of the caseload). Currently diagnosis is difficult, with a number of patients being sputum scarce (cannot produce sputum), including 30% of TB-HIV co-infected patients), others being smear negative (low concentration of TB bacilli in the sputum) and the cases of extrapulmonary TB (EPTB) being as high as 50% in HIV co-infection. Current diagnostic tools are expensive (>$10 per test, after subsidy) and have poor sensitivity in HIV infected and smear negative TB patients. Bacterial culture is the most reliable test for diagnosis but is rendered ineffective for Point-of-Care (POC) diagnosis as culture results are slow (approximately 3 weeks minimum) and infrastructure and trained personnel are required. There is, therefore, a need for new low cost, Point-of-Care (POC) diagnostic tools to which a multitude of biological samples can be applied, resulting in a sensitive and specific diagnosis, irrespective of age and HIV status.

TECHNOLOGY DESCRIPTION

The TB SERS Biosensor is a novel, hand-held, battery operated POC TB diagnostic device consisting of aptamer- or antibody-based Surface Enhanced Raman Scattering (SERS) biosensor, integrated with a universal sample preparation module for detection, identification and quantification of intact pathogens and pathogen-derived antigens present in peripheral fluids (sputum, urine and pleural fluids). The SERS technique is notable for its ultra-sensitive, specific and low limit of detection of specific biomolecules, allowing for identification and quantification of these biomolecules at low concentrations. This device will therefore be able to diagnose TB, monitor treatment response in TB patients and potentially also allow for drug resistance typing, all at limits of detection, cost and speed that outperform current TB diagnosis techniques.

VALUE PROPOSITION

The field-portable TB SERS Biosensor is a novel, low cost device that will allow for TB diagnosis, TB drug resistance typing and monitoring of treatment response in TB patients at point of care in low resource settings. SERS assays are rapid, label-free, amplification free and provide for low cost, highly multiplexed detection of many different analyte types on a single chip (protein, lipid, small molecule metabolites, DNA and intact pathogens), allowing for detection from different samples and flexibility for incorporation of novel biomarkers, as these are identified and validated. The diagnostic platform requires minimal resources and will allow for rapid delivery of results, enabling treatment to be prescribed at the point at which care is given, whilst the patient is still present.

CURRENT STATUS

The individual components of the novel SERS-based, multiplexed POC diagnostic device (including highly reproducible nanostructured silver surfaces on to which we immobilized analyte-specific capture agents - DNA aptamers and antibodies) have been developed. These components are integrated to a field-operable, surface tension valve and magnetic bead-based sample preparation device, for identification of intact Mycobacterium tuberculosis bacilli in sputum samples.

We have demonstrated a limit of detection of <20 bacilli in a label-free, amplification free assay that directly detects and positively identifies bacilli (superior to GeneXpert MTB RIF assay). We have also demonstrated that we can use our SERS-based biosensor platform to detect proteins and metabolites at clinically-relevant concentrations and with a reproducibility and linearity that conforms to CLIA specifications.
Evaluation of the clinical sensitivity and specificity of our prototype diagnostic test is currently being completed.

INTELLECTUAL PROPERTY STATUS & PUBLICATIONS

National phase patent applications based on PCT/IB2012/056108 have been filed and granted in USA (US9,518,986), China (CN104,380,105B), Europe EP2773958 (Denmark, Germany, United Kingdom, Sweden and The Netherlands) and South Africa (ZA2014/03386). Brazil and India applications are pending.

- Zhao L, Blackburn J* & Brosseau CL* (2015) Quantitative Detection of Uric Acid by Electrochemical-Surface Enhanced Raman Spectroscopy (E-SERS). Analytical Chemistry 87, 441-7.
- Robinson AM, Zhao L, Yasmin M, Harroun SG, Dendukuri D, Blackburn J*, Brosseau CL* (2015) The development of "Fab-Chips" as low-cost, sensitive surface-enhanced Raman spectroscopy (SERS) substrates for prospective disease diagnosis. Analyst 140, 779-85.
- Karaballi R, Nel A, Blackburn J* & Brosseau CL* (2015) Development of an electrochemical surface-enhanced Raman spectroscopy aptasensor for direct detection of DNA hybridization. Physical Chemistry Chemical Physics 17, 21356-63.
- Alula MT, Krishnan S, Hendricks NR, Karamchand L & Blackburn JM (2017) Identification and quantitation of pathogenic bacteria via in-situ formation of silver nanoparticles on cell walls, and detection via SERS. Microchimica Acta 184, 219-227.

TB SERS BIOSENSOR (CONTINUED)

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- Alula MT, Karamchand L, Hendricks NR, & Blackburn JM (2018) Citrate-capped silver nanoparticles as a probe for sensitive and selective colorimetric and spectrophotometric sensing of creatinine in human urine. Analytica Chimica Acta 1007, 40-49.

OPPORTUNITIES

The University of Cape Town is seeking funding for component integration, prototype development and validation (field testing and clinical accuracy) of the diagnostic platform.

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