Actiphage® TB blood test finds live mycobacterium tuberculosis in the blood of people with incipient TB

Trial results presented at ECCMID shows potential of Actiphage for risk stratification in those with latent TB

A clinical trial of Actiphage®, a promising new diagnostic for tuberculosis infection, has shown for the first time that live bacteria can be detected in the blood of people with incipient TB infection. Offering almost three times greater specificity than the gold standard IGRA test for this state of latent infection. This ground-breaking clinical trial shows the potential for using Actiphage as a pathogen directed biomarker to identify those with incipient TB, a key WHO research priority.

Nearly a quarter of the world's population has latent tuberculosis infection (LTBI), which is asymptomatic and a reservoir for future disease. A small proportion have incipient TB, defined as a state of higher risk of developing to TB unless treated. However, separating these individuals from everyone else with LTBI is currently problematic.

Research presented at ECCMID 2022 (European Congress of Clinical Microbiology & Infectious Diseases) by researchers from the University of Leicester have shown that Actiphage, a new blood test for *Mycobacterium tuberculosis* (Mtb) can improve identification of those at risk of progressive tuberculosis infection, offering potential for a rapid, non-invasive biomarker for early screening of asymptomatic individuals.

Lead author, Jee Whang Kim of the Leicester Tuberculosis Research Group (LTBRG), presented the findings of the study in the 'hot topics in tuberculosis' session at ECCMID 2022.

Kim explains: "The trial aimed to investigate whether there is an association between the presence of Mycobacterium tuberculosis (Mtb) circulating in the blood of individuals who are otherwise completely well, and evidence of progressive TB infection.

"The results show that by using Actiphage, we were successful in isolating Mtb in the blood of a subset of individuals with latent TB and also in demonstrating an association with radiological and microbiological evidence of progressive TB infection. Compared with IGRA, Actiphage was almost three times more specific at identifying this group.

"To our knowledge, this is also the first time that viable Mtb infection has been isolated in people with a clinical diagnosis of latent TB infection."

Dr Pranab Haldar from the University of Leicester is the lead clinician on the trial; he comments: "Although TB is now second to Covid as the leading cause of death from an infectious disease, the future impact of TB on human health is likely to far exceed the Covid pandemic. TB prevention through identification and treatment of at-risk LTBI is a key long-term strategy for TB control and elimination."

The clinical trial of Actiphage was held at the University Hospitals of Leicester NHS Trust and involved 36 persons that shared a household with 15 patients known to have pulmonary TB.

All the participants were tested with Actiphage, which uses a phage to detect bacteria in blood, and IGRA QuantiFERON-TB Gold plus (QFT), which measures the immune response to infection. The individuals were followed prospectively over 12 months according to whether or not they developed evidence of progressive TB infection based on clinical assessment and highly sensitive imaging with PET-CT scans. Those with evidence of infection related activity on PET-CT had further invasive sampling using bronchoscopic methods.

Dr Haldar explains that the study used imaging and microbiological characteristics to provide a clinic definition of incipient TBI and the health of the participants was monitored after 12 months.

He says: "We define a composite endpoint for incipient TBI based on the state and trajectory of TBI characterised by serial [18F]-fluorodeoxyglucose (18F-FDG) positron emission tomography-computed tomography (PET-CT) and invasive microbiological sampling at sites of high 18F-FDG uptake.

"Using this approach, we describe a subgroup of household contacts with a clinical phenotype of LTBI that express imaging and microbiological characteristics of uncontrolled infection consistent with non-human primate models of progressive TBI. We then compared this with the results from Actiphage and IGRA and found an association between our definition of incipient TB and detection of Mtb in the blood using Actiphage."

Dr Ben Swift, Director of Research and Development at PBD Biotech, developers of Actiphage, comments that Mtb is very slow growing, making traditional culture methods inefficient, and its tough cell wall makes DNA extraction difficult.

He says: "Actiphage uses a specific bacteriophage that infects live Mtb and breaks open the cells to release DNA for detection. The whole testing process can be completed in as little as six hours. Unlike other tests which measure the host's immune response, Actiphage directly detects live mycobacterium."

Dr Haldar agrees: "The results presented at ECCMID 2022 provide early evidence that circulating Mtb in blood is a key pathogenic feature of progressive infection that has also been observed in animal studies.

"Our findings demonstrate the potential utility of Actiphage as a pathogen directed biomarker for improving risk stratification of LTBI that can potentially complement the evolving panel of host-directed immune biomarkers.

"We hope our findings will stimulate further research to develop other pathogen directed biomarkers for this purpose."

The 32nd European Congress of Clinical Microbiology & Infectious Diseases (ECCMID 2022) was held in Lisbon, Portugal on 23-26 April 2022. Jee Whang Kim is to present findings of the study "A novel bacteriophage-based assay stratifies tuberculosis risk in recent household contacts of pulmonary tuberculosis: a prospective observational cohort study" in the 'Hot topics in tuberculosis' session at 13:30 -14:30 on Tuesday 26th April.

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About the NIHR Leicester Biomedical Research Centre (www.leicesterbrc.nihr.ac.uk)

The National Institute for Health Research (NIHR) Leicester Biomedical Research Centre (BRC) is a partnership between University Hospitals of Leicester NHS Trust, the University of Leicester and Loughborough University. It is funded by the National Institute for Health Research (NIHR).

The NIHR Leicester BRC undertakes translational clinical research in priority areas of high disease burden and clinical need. These include cardiovascular disease, respiratory disease, and lifestyle, obesity and physical activity. There is also a cross-cutting theme for precision medicine. The BRC harnesses the power of experimental science to explore and develop ways to help prevent and treat chronic disease. It brings together 70 highly skilled researchers, 30 of which are at the forefront of clinical services delivery. By having scientists working closely with clinicians, the BRC can deliver research that is relevant to patients and the professionals who treat them.

About PBD Biotech (www.pbdbio.com)

PBD Biotech Limited specialises in the use of novel bacteriophage-based technology. The company has developed proprietary, patented technology that can be used to detect the presence of mycobacteria that cause tuberculosis in humans and animals.

This includes human TB – *Mycobacterium tuberculosis* (Mtb) – where the technology has application as a screening tool, as well as Bovine TB – *Mycobacterium bovis* (*m.bovis*) – and *Mycobacterium avium* subsp.*paratuberculosis* (MAP; Johne's Disease), which are significant causes of morbidity and loss of productivity in the agricultural industry.