Institution: University of St Andrews

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Improving tuberculosis treatment and trials using a novel biomarker

1. Summary of the impact (indicative maximum 100 words)

There are 10 million new infections and one million deaths from tuberculosis annually and there is an increase in resistant diseases. Yet there have been no new anti-tuberculosis agents developed for forty years. TB drug development is expensive because of the time taken for the organism to grow and because trials are expensive and the sample size is high. The biomarker and mathematical methods developed at St Andrews address these problems by making preclinical development faster and cheaper and is being used by three commercial companies and eight drug development groups. These methodologies shorten the time taken to complete trials and reduce cost.

2. Underpinning research (indicative maximum 500 words)

The research conducted by Professor Stephen Gillespie, a researcher at University of St Andrews since 2010, has shown that, in human tuberculosis, bacterial load can be used as a critical determinant of treatment outcome[1]. This breaks a crucial logjam in thinking about the design of clinical trials. A key part of such research is being able to plan future trials, yet monitoring clinical trials in real time is extremely difficult, prone to error, costly and slow. Current measures depend on culture of the bacteria, taking a minimum of three months, and a significant component of the bacteria present will not grow although they are viable and can cause disease. This reduces the speed of drug development and adds to the noise in pre-clinical and clinical studies. In 2010 we developed a simple biomarker of cell viability for *M. tuberculosis* (Molecular bacterial load assay MBLA) based on the 16SrRNA gene together with a new RNA extraction control to reduce assay variability through Prof. Gillespie's MRC grant (Rapid Evaluation of Biomarkers for TB grant)[1]. As it uses a single assay in comparison to competing systems that use a multiplicity of immune response measures it is simple to apply in high burden countries. The choice of this target increases the sensitivity of measurement, allows viable but non-culturable organisms to be detected, and is not confounded by the presence of typical mycobacterial cords that reduce accuracy. Importantly, the test takes four hours, potentially reducing the time to a read-out by 98%.

The data derived from this assay are evaluated using a basic model Prof. Gillespie described to follow treatment and in 2012 this was developed into an unique semi-mechanistic model of tuberculosis treatment that uses markers of bacterial load to predict the outcomes of different regimens. This provides a method to input data from pre-clinical and early phase clinical studies to predict the outcome of future trials, allowing pharmaceutical companies or public private partnerships to make go-no-go decisions. The facility that this provides has allowed the development of an effective Multi-arm, Multi-stage TB trial[2]. In the pre-clinical sphere, time taken to measure the number of viable bacilli adds considerably to the length of studies to evaluate novel agents. This technique reduces this process from weeks to minutes.

Thus, the MBL assay has now been developed to be able to specifically detect non-tuberculosis mycobacteria such as *M. smegmatis* and *M. marinum* that are used in pre-clinical phases. This permits pre-clinical experiments to be conducted more rapidly and the results to be available in four hours compared with a minimum of four days presently. This approach has been taken up rapidly by the PreDiCT-TB consortium (an academic industry consortium of 22 members).

3. References to the research (indicative maximum of six references)

The underpinning research for this case study has been published in the leading clinical microbiological, infectious diseases and clinical tuberculosis journals. The quality of the work is exemplified by its use to support the award of a €1.2m to Innovative Medicines Initiative grant (PreDiCT-TB) and a €1.7m grant from the European Developing Country Clinical Trials Partnership (PANBIOME) to the St Andrews research group.

1. Honeyborne I, McHugh TD, Phillips PPJ, *et al.* Molecular Bacterial Load Assay, a Culture-Free Biomarker for Rapid and Accurate Quantification of Sputum Mycobacterium tuberculosis Bacillary Load during Treatment. *J Clin Microbiol* 2011; **49**: 3905–11. doi: 10.1128/JCM.00547-11

2. Phillips PPJ, Gillespie SH, Boeree M, *et al.* Innovative Trial Designs Are Practical Solutions for Improving the Treatment of Tuberculosis. *J Infect Dis* 2012; **205**: S250–7. doi: 10.1093/infdis/jis041

4. Details of the impact (indicative maximum 750 words)

Impact on commercial partnerships development

The research described is of value to the commercial companies, public/ private partnerships that are developing novel regimens and trial designs for TB drug development by speeding development and reducing its cost. Tuberculosis trials are hugely expensive (> $50 million) due to the large number of patients that must be recruited. They are slow because of the time taken to grow the organism in the laboratories supporting the trial. The assays that we have developed directly address this as they take just a few hours in comparison to 42 days of conventional methods[1]. Justin Green of GSK states *"Of real importance, it reduces the time taken to obtain a positive culture from approximately 42 days to just a few hours" [1]*. This means that go-no-go decisions in our adaptive trials paradigm can be made in real time[2]. By quantifying the number of viable organisms there is the potential to reduce the sample size of the trial (http://c-path.org/CPTR.cfm).

In particular, developing an understanding of the role of bacterial load and the relationship between load and cavities has had a major influence on commercial and academic researchers performing and developing clinical trials for tuberculosis (example GATB Consultants meeting) [3]. The MBL assay has now been incorporated into the industry- academic development project funded to develop model-based systems to shorten TB drug development by the Innovative Medicines Initiative in collaboration with GSK, Janssen and Sanofi Aventis [4]. The value of this technique to determine treatment response has been identified in an authoritative review that gives it the highest level of certainty to this statement [5].

Current impact on drug development and trials

The MBL Assay has been taken up rapidly and is being applied to the design of current trials by international researchers in the PanACEA consortium's MAMS phase IIb study of four novel regimens started in March 2013 in South Africa and Tanzania that is recruiting up to 400 patients [2]. From March 2012, its utility is being evaluated in comparison with other commercial assays and a novel assay in development is being funded by a grant from the European Developing Country Clinical trials partnership [4] in collaboration with Pharma company Sequella Incorporated who are providing co-funding, bringing the total funding €1.7m.

Impact of pre and early phase clinical trials

The St Andrews research is being developed and applied as part of our partnership with the pharmaceutical industry and is being taken up by our research collaborators who have been awarded funding via the Innovative Medicines Initiative [4]. Justin Green from the GSK states "*this novel assay that detects live mycobacteria is felt to be an important new tool for commercial drug developers like GSK*" [1].

The CSO of Helperby Therapeutics, a pharmaceutical SME note *"The work of Professor Stephen Gillespie is having considerable impact on the field of tuberculosis. For example, his new assay (MBL) for the measurement of the total quantity of* Mycobacterium tuberculosis *in sputum and other tissues is highly significant. This is because it is becoming clear that conventional culture and microscopy techniques underestimate the bacterial load. Using the Gillespie assay, it is now possible to objectively detect and quantify all the different subpopulations of* M. tuberculosis

including those that are missed by conventional methods. The combination of MBL and modelling is transforming the speed of pre-clinical studies by short circuiting the need for culture and supporting the development of new models. It is possible that one day, the Gillespie technique or one which is based upon it, will replace all conventional methods of detection of M. tuberculosis*."* [2]

Pre-clinical model development

The mathematical model has been used to demonstrate the value of a new more human-like mouse model of tuberculosis treatment and this allows the evaluation of novel drugs more rapidly shortening the duration of the pre-clinical pathway [2]. This model has also been used to test a new mouse treatment model that mimics human disease more closely in an industry academic research partnership. The modified MBL assay for *M. marinum* is being used by an SME, ZF-screens (Holland), in the rapid evaluation of tuberculosis drugs in Zebra fish reducing the costs and allowing drugs to be evaluated more rapidly.

As GSK state "*the Mycobacterial Load [assay] is one of the early success….could now be applied not only to human studies, but also cutting edge animal models*." [1]

By reducing costs and timelines in clinical and pre-clinical tuberculosis drug development research in this way patients benefit with the prospect of new medicines for tuberculosis coming closer.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] Letter GSK, Director Clinical Development Late Stage Corroborating the importance of the tool for commercial drug developers.

[2] Letter from The Chief Scientific Officer and Director Helperby Therapeutics Corroborating the impact on commercial drug developers of this technique in terms speed and accuracy.

[3] GATB Web-site: www.tballiance.org/newscenter/view-brief.php?id=1026 corroborating the importance of bacterial load measurement in reducing sample size of clinical trials

[4] http://www.edctp.org/Newly_signed_grants.500.0.html Confirming the award to University of St Andrews

[5] Wallis et al., Tuberculosis biomarkers discovery: developments needs and challenges *Lancet Infectious Diseases* 2013; 13:363-372 doi: 10.1016/S1473-3099(13)70034-3 an authoritative review that confirms that our assay measures viable count accurately.