Immunity to tuberculosis

Could you begin by describing your current research interests?

My longstanding interest is in the pathogenesis and immune response to mycobacterial infection, including *M. leprae* and *M. tuberculosis* (Mtb). Recently, we have concentrated our efforts on understanding the interaction between the host immune response and the metabolic and replication state of the bacilli.

We have also explored the possibility of modulating the immune response using phosphodiesterase E4 (PDE4) inhibitors that reduce the stringency of immune pressure on the organism and improve responsiveness to antibiotics. We hope this approach will be used to improve treatment of patients with TB.

How have your studies into TB progressed as a result of using the rabbit model?

We have characterised a rabbit model of TB latency and reactivation as well as a model of chronic progressive cavitary disease. Because the lesions of the rabbit are so similar to human lesions, we are now able to examine the effect of interventions on disease outcome in rabbits as a surrogate for human TB.

In terms of host/pathogen interaction in the rabbit model, how might your findings be harnessed to determine the most useful candidates to move forward in humans?

Characterising the latency model has allowed us to clearly distinguish growth phase versus control and clearance of infection. This rabbit model will facilitate comparative analysis of the efficacy of new TB drugs in penetrating infected tissues and acting against replicating and non-replicating bacillary populations. This model will also help us to determine whether candidate vaccines can improve control and clearance of infecting bacilli inducing sterilising immunity that is fully protective against Mtb infection. Our chronic progressive TB model will enable us to evaluate candidate vaccines for their ability to reduce disease severity and block cavity formation to restrict the spread of disease from one (infected) individual to another.

What techniques have you employed to develop a spectrum of responses in the rabbit?

We used two clinical isolates of Mtb with differing levels of immunogenicity to model a range of human responses to Mtb infection. In rabbits infected with the more immunogenic strain, Mtb CDC1551, infection induces a protective immune response that essentially drives clearance of the organisms and establishes latency. We showed that this is true latency because immune suppression stimulates the bacilli to resume growth. In contrast, when rabbits are infected with the less immunogenic, more virulent Mtb strain HN878, the immune response fails to control the infection, the bacillary loads remain persistently high in the lungs and the pathology worsens progressively. Ultimately, full-blown cavities are formed, with large numbers of bacilli at the cavity surface. It is these organisms that are likely to spread and infect new hosts.

We can now explore the full range of human like responses to Mtb infection. By direct comparison between the two models, we will understand the nature of the immune response that is protective versus that which fails to control the infection.

In the absence of significant immune suppression or toxic effects, what have your results revealed about the potential of a PDE4 inhibitor in adjunctive immune modulation for patients with TB and/or other inflammatory lung diseases?

PDE4 inhibition gives rise to mild immune modulation in the absence of immune suppression, while maintaining control of Mtb infection. This observation provides proof-of-concept for the potential use of such an intervention in humans with TB. Since an intact immune response is necessary to avoid exacerbation of disease, the targeted effect seen with PDE4 inhibition supports its safe use in a variety of applications. PDE4 inhibition is anti-inflammatory; mild de-activation of macrophages could in principle be used to dampen lung inflammation in other clinical settings, such as asthma and chronic obstructive pulmonary disease as well as fibrotic lung diseases.

Our preliminary results suggest that the PDE4 inhibitor molecule is highly efficacious in improving antibiotic killing of Mtb and might significantly shorten TB treatment. Shortening TB treatment would improve compliance and prevent survival of residual bacilli in the lungs.

Are you encouraged by your findings to date?

Absolutely, we are very optimistic. We have specific models for defining protective immunity versus pathogenic processes. Our rabbit models will facilitate identification of immunologic markers of the full range of host responses to infection, which was not possible previously without good models of TB latency.
TUBERCULOSIS (TB) IS an airborne disease associated with cramped living conditions that, despite being both treatable and preventable, remains at epidemic levels globally. In the past, patients with TB were isolated in sanatoria for containment purposes; now, they are treated with antibiotics and remain in the community. Despite pharmacological advances, however, TB requires costly, long-term medication which the disadvantaged populations that it most often affects cease to take when they start to feel better, often before the disease has been cleared from their lungs. Failure to adhere to treatment, together with inappropriately-prescribed or poor quality drugs has led to development of drug resistance in many strains of Mycobacterium tuberculosis (MtB). Multidrug-resistant (MDR) and extensively drug-resistant (XDR) forms of TB, as well as the prevalence of recurrence, can limit treatment options and increase the burden on healthcare organisations.

The vulnerability of the immune system in HIV-infected individuals means that about 13 per cent of TB cases worldwide arise in people who are HIV-positive, complicating patient management and treatment and adding further to the burden of healthcare. In 2010, about 8.8 million people were reported to have TB and 1.45 million died; among the dead a significant number – 350,000 or so – were also HIV-positive. The co-incidence of TB with HIV and growing resistance of the TB mycobacteria to drugs are currently key issues in the global fight against TB.

THE MAKING OF AN EPIDEMIC
A potential reduction in US Government funding for research into TB and other global health issues will have a major impact on the search for solutions, according to Dr Gilla Kaplan, Professor of Medicine and head of the Laboratory of Mycobacterial Immunity and Pathogenesis at the Public Health Research Institute Centre of the University of Medicine and Dentistry of New Jersey (UMDNJ): “Ultimately it will have a detrimental effect on both the quality of research and the number of well-qualified investigators,” she asserts.

In the 1980s, funding for TB control in the US was severely cut. When there was an outbreak of TB in New York in the 1990s, however, the funds required to curtail the spread of the disease were made available. At the height of the New York epidemic, 3,800 people were infected with MtB and many died; the cost of containment amounted to over $1 billion.

The New York epidemic was triggered by some of the same factors that pertain in South Africa and other countries with high incidences of TB: a significant level of drug-resistant TB already existed and the numbers of HIV-infected individuals with the disease was rising. In South Africa today, in a population of about 50 million, of the 490,000 people who have TB, roughly 128,000 are also HIV-positive. The numbers of TB cases in India (3 million out of a population of 1,225 million) and China (1 million out of a population of 1,340 million) are staggering, but the numbers of patients with co-morbid HIV are, by comparison with South Africa, still relatively low (about 41,450 and 4,540 respectively). In South Africa, the incidence of concomitant HIV and TB is currently continuing to rise; the rate of TB among small children is also a matter of considerable concern.

GROWING KNOWLEDGE OF TB
Kaplan’s chief research interests are immune responses and aspects of the pathogenesis of microbial infections, and she has devoted nearly 20 years of her life to the study of TB. In the mid-1990s, when South African expertise in TB research was limited, her laboratory became a training ground for South African researchers, nurturing more than 25 TB investigators. Now, South African TB expertise is world-class: “South African academic and clinical organisations are among the leading sites for TB research in the world today,” Kaplan reflects. She was also

Clearing the air
About a third of the world’s population is thought to be infected with Mycobacterium tuberculosis, the causative agent of tuberculosis. Collaborative research into immune system responses is seeking to enhance the mechanisms that confer immunity and in so doing, improve the efficacy of treatment for the active disease.
Dr Gilla Kaplan has been leading research into tuberculosis for over 20 years. Current projects in which she is involved span across the research spectrum, from pre-clinical studies using the rabbit model to broader collaborations in global health, largely based in South Africa and the US.

**KEY COLLABORATORS**

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Dr Gilla Kaplan is instrumental in obtaining funding from the Bill and Melinda Gates Foundation for an analysis of the causes of the failure of BCG vaccination in the Western Cape, South Africa.

Currently, Kaplan is involved in a variety of projects, in collaboration with centres of excellence in both the US and South Africa, some involving animal models and some human TB patients: “Our experimental approaches combining iterative patient-based studies and animal models, inform both the design of basic science questions and their application to clinically-relevant problems,” she states. One such study is concerned with the effects of antiretroviral therapy for HIV on TB; another is analysing both host and pathogen characteristics that lead to XDR TB; a further study is focused on the mechanisms that confer protective immunity: “The testing of new candidate vaccines is in its early days and will require much better understanding of the determinants of protective immunity to facilitate selection of the most efficacious vaccines for clinical testing”.

**RABBIT MODEL**

In researching immunity, Kaplan is using newly refined rabbit models to improve understanding of how susceptibility to TB infection is determined, how TB takes hold and how the body responds to drugs during treatment of TB. Two rabbit models, both infected with Mtb clinical isolates, have been established. One is a latent TB model, in which, when the dormant TB bacillus is reactivated, the resulting lesions in the lungs resemble lesion development in immune compromised humans. Kaplan’s laboratory is comparing the immune system responses from this latent TB model with a rabbit model of chronic cavitary disease, to better understand protective immunity and identify means of stopping the spread of Mtb infection.

Having studied mice previously, Kaplan is enthusiastic about this approach and is keen that it will be validated: “We have shown conclusively that the two rabbit models are much more similar to the human manifestations of disease than mouse models,” she asserts. Testing the rabbits with new drugs has revealed the promise of phosphodiesterase E4 inhibitors in strengthening the efficacy of antibiotic treatments in TB. Having obtained proof-of-concept for the approach, Kaplan soon hopes to see the approach tested in humans using a PDE4 inhibitor that is already cleared for human application; if successful, the approach would shorten the time required for therapy and so positively influence patient adherence to prescribed drug treatment.