A conversation with Professor Valerie Mizrahi, December 16, 2015

Participants

- Valerie Mizrahi, PhD – Director, Institute of Infectious Disease and Molecular Medicine, University of Cape Town
- Lily Kim, PhD – Scientific Advisor, Open Philanthropy Project

Note: These notes were compiled by the Open Philanthropy Project and give an overview of the major points made by Professor Valerie Mizrahi.

Summary

The Open Philanthropy Project spoke with Professor Mizrahi of the University of Cape Town (UCT) as part of its investigation into tuberculosis (TB). Conversation topics included the urgent need to study TB in humans, the power of cohort studies, ways to improve TB research, as well as challenges facing researchers.

Studying tuberculosis in humans

The South African tuberculosis (TB) epidemic is in dire need of an intervention. Implementing existing interventions and diagnostic tools more effectively and on a larger scale will be essential in combating this epidemic, but researchers must also address critical unanswered questions about TB infection and disease in humans.

These questions include:

- Some individuals who are frequently exposed to TB appear never to become infected. Why?
- The majority of individuals who become infected following exposure do not progress to TB disease. Why?
- In addition to the known confounding factors (for example, HIV co-infection), what other factors influence disease progression and how?
- Once researchers better understand disease progression, are there ways they can intervene?

Human studies

Conducting human studies is expensive, slow, and more complicated than using animal models (such as mice).

Animal models play a crucial role in TB research and are constantly being improved and refined to better model TB infection and disease in humans. However, studying the disease in humans is crucial for understanding the natural history of the host-pathogen relationship and for capturing the complexity of TB disease in humans.

TB transmission in humans

In order to intervene in the TB epidemic, it is essential to have a better understanding of the dynamics of TB transmission. We need to learn more about the infectiousness and transmission of TB between humans. Studying infectiousness at the level of the individual patient is a relatively new field, one that researchers at UCT are actively involved in. Knowing when a patient becomes infectious and at what point transmission occurs is particularly important for high-burden countries like South Africa where transmission is rampant.

There has been extensive research on the physiological states of TB bacteria in animal models, in vitro cultures, cell models, and macrophage models, but additional research is needed to connect the work done in models to the stages of exposure, infection, and progression in humans. Questions include:

- When and how are bacteria aerosolized?
- What are the physiological states of the organisms when they are transmitted?
- Is it possible to develop tools for identifying and capturing individual bacilli expelled from patients?

People to talk to

- Robin Wood – Professor of Medicine and director of the Desmond Tutu HIV Centre, University of Cape Town

Cohort studies

Many traditional funders have been reluctant to provide the expensive and sustained investment required to conduct the cohort studies that are needed to understand the progression of TB in humans.

A cohort study conducted by researchers at the University of Cape Town's South African Tuberculosis Vaccine Initiative (SATVI), together with collaborators at the Centre for Infectious Disease Research in Seattle, which is aimed at identifying correlates of risk for developing TB disease, provides a good example of the power of this approach.

In Cape Town and the surrounding areas, the risk of TB infection by early adulthood is over 90 percent. Participants recruited into the cohort were monitored for more than two years to identify those who did and did not develop tuberculosis. Using whole-blood transcriptional profiles, a transcriptional signature that is predictive of the development of TB disease has been identified. Signatures such as this have potential as biomarkers to identify those who are at greatest risk for developing disease, and who would benefit most from therapeutic intervention.

Conducting cohort studies across geographic regions allows researchers to account for complexities arising from both human genetic variation and pathogen variation. The larger the scale, the more powerful the studies are. To advance biomarker research for TB, the US National Institutes of Health, together with governments in disease-endemic countries, are

working together to create a platform for collaborative TB research that addresses this need – the Regional Prospective Observational Research in TB (RePORT) International, which is bringing together research consortia in Indonesia, India, Brazil, and South Africa under a common protocol for data and specimen collection. Initiatives such as this offer exciting prospects.

Identifying biomarkers

Because cohort studies allow researchers to monitor disease progression over time, they could help researchers identify new biomarkers. Identifying early indicators of the disease would be particularly useful.

For example, several studies, including a landmark 2010 study by Anne O'Garra, then based at the UK's NIMR in London, and colleagues, including researchers from the University of Cape Town's Clinical Infectious Disease Research Initiative, identified a whole-blood transcript signature for active TB disease. Signatures such as this have potential as tools for monitoring responses to TB drug treatment.

People to talk to

- Thomas Scriba – Deputy Director of the South African Tuberculosis Vaccine Initiative, University of Cape Town
- Robert J. Wilkinson – Director of the Clinical Infectious Disease Research Initiative, University of Cape Town
- Peter Kim, MD – Deputy Director of the Therapeutics Research Program, Division of AIDS, National Institute for Allergies and Infectious Disease
- Carol Dukes Hamilton, MD – Consulting Professor, Duke University School of Medicine

Improving TB research

Cross-disciplinary research

Tuberculosis research would benefit from attracting technology savvy young investigators from other disciplines, including engineering and the physical sciences.

Imaging tools

Some of the leading TB researchers are working to develop more sensitive imaging tools capable of non-invasively visualizing individual TB bacilli in different physiological states. These tools would allow researchers to monitor how tubercle bacilli respond to the environmental changes that accompany the host response to infection, for example, during granuloma infection. Prof. Mizrahi expects major advances in this field over the next five years.

Genome-scale tools

The field would benefit from a better understanding of how small molecules kill TB bacteria. Genome-scale tools provide a means of enabling researchers to rapidly identify the mechanisms of action of small molecule inhibitors of growth and survival of *Mycobacterium tuberculosis*.

Early diagnosis

By the time a patient is sufficiently ill to develop the symptoms of TB and seek medical care, they might already be transmitting. The ability to make earlier diagnosis would have a major impact on the epidemic. New diagnostic tools are in development, but they are not necessarily for early disease detection.

Biomarkers and drug development

A critical question in TB drug development is how to achieve treatment shortening. Although researchers have many hypotheses, there are no clear answers. Related questions include:

- What are the physiological states of the bacteria in the human host during the course of an infection?
- Researchers suspect there are multiple physiological states; if this is true, what are the implications for treatment-shortening?
- Can we identify compounds that are active against both actively multiplying bacteria, and slowly- or even non-replicating "persister" bacteria, and if so, would this be necessary and sufficient to achieve treatment-shortening?

Drug development is also hampered by the lack of reliable biomarkers for monitoring the impact of new TB drugs and drug regimens. Without biomarkers, researchers in clinical drug trials must wait months after the end of the treatment phase to observe whether the patient becomes sick again. If they do, researchers must then distinguish between relapse (i.e., lack of durable cure of the infection that was treated) and re-infection. TB drug trials can last for years, making them very expensive.

Biomarkers that allow researchers to more rapidly assess new drugs and drug combinations would transform the field, in a manner akin to the transformative impact that the CD4 count and the viral load has had on HIV/AIDS research.

Access to human lung tissue samples

In the development of biomarkers, critical work is being done validating potential biomarkers, but Prof. Mizrahi believes it is equally important to find and apply ways to discover and measure new things.

This is an area of rapid growth, spurred by increasingly powerful 'omics tools such as metabolomics (the study of the composition and abundance of metabolites in a biological system) and transcriptomics (the study of the RNA transcripts produced under specific

circumstances). However, increased access to human lung tissue samples could encourage researchers to think more creatively.

Recently, researchers have pushed for more "site-of-disease"-type research. In TB-endemic countries, lung resections performed on individuals with TB and on those who do not have TB but are undergoing lung resections for other conditions provide an important resource for making new discoveries.

With access to this resource, recent technological advances could facilitate enormous progress. Clues gathered from analyzing TB lesions from human tissue samples can be reverse translated, which will improve animal and other models that are employed in TB research, and thus, accelerate the process.

Other people to talk to

- **Gerhard Walzl** – Professor, Stellenbosch University
- **Adrie J.C. Steyn, PhD** – Investigator, KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH)
- **Keertan Dheda, PhD** – Professor of Respiratory Medicine, University of Cape Town
- **Stefan Kaufmann, PhD** – Director, Immunology Department, Max Planck Institute for Infection Biology

Challenges facing TB researchers

Complexity of TB

One of the greatest challenges facing researchers is the complexity and heterogeneity of TB as a disease in humans. Complicating factors include:

- **Lesions within an individual patient progress independently of each other.** This has been confirmed by JoAnne Flynn (Professor, Department of Microbiology & Molecular Genetics, University of Pittsburgh), Clif Barry (Chief, Tuberculosis Research Section, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases), and colleagues who have pioneered the use of positron emission tomography–computed tomography (PET-CT) imaging to follow the progression from infection to disease in non-human primate models and more recently in humans.
- **TB progresses very slowly and can subvert many of the mechanisms that successfully fight other pathogens.** The disease triggers a robust immune response, which is necessary but insufficient.
- **Infection does not confer immunity.** Individuals who previously had TB can become re-infected.

Technical challenges

TB research must be conducted in laboratories meeting biosafety level 3 (BSL-3) standards. Although access to labs meeting these standards has increased in recent years, studying a

slow-growing pathogen under BSL-3 conditions is complicated, and studying TB at the site of disease is difficult.

Funding challenges

Most countries fund some level of TB research, but there are major funding gaps in all areas of tuberculosis research on the discovery, development and implementation of new tools to control this disease, ranging from basic and translational research, to clinical research and implementation science. In order to achieve the aspirational goal of TB elimination, the entire spectrum of TB research must be supported at a significantly higher level than is currently the case. In this regard, the TB-burdened BRICS countries – Brazil, Russia, India, China and South Africa – have a particularly important role to play as emerging economies.

All Open Philanthropy Project conversations are available at
http://www.openphilanthropy.org/research/conversations