Dr Isabel Sada-Ovalle is studying the complex immune response to tuberculosis at a cellular level. Here, she discusses the significance of international collaboration for scientists in developing countries and the impact that prestigious awards have had on her exemplary research career.

Can you provide an insight into your academic background? How did you become interested in immunology?

I obtained my MD degree at the Autonomous University of San Luis Potosí in Mexico. After deciding that I was interested in conducting basic research that focused on human diseases, I went on to complete a Master's degree in Human Physiology at the same university. Subsequently, I moved to Mexico City were I studied for my PhD in Immunology. One of the most important achievements in my early career was receiving the Parker B Francis Award, which was crucial for enabling me to undertake my postdoctoral studies at Harvard Medical School in Boston, USA. The Award was established by Parker B Francis in 1951 to support the development of scholars planning careers in pulmonary research – and to date it has contributed more than US $52 million to the fellowship programme, funding over 770 researchers. A survey of former awardees shows that over 90 per cent are currently employed in universities and teaching hospitals, and that they devote significant portions of their time to research. This award has only been given twice in Mexico and I feel very privileged to have received it. The subsequent accomplishments I have made in basic and translational research have driven my career forward, culminating with the establishment of my own laboratory at Mexico’s National Institute of Respiratory Diseases in November 2010.

In 2010 you received two other prestigious awards; what were they for?

The first award was from the Fundación Miguel Alemán AC, a non-profit organisation that gives annual financial support to the 20 most successful scientists in Mexico City. I received this for my recent work on tuberculosis (TB) immunology. The second award was from the Centers for AIDS Research (CFAR) and the National Institutes of Health (NIH) in the US, for a novel project on HIV-TB coinfection. For the first time in the history of CFAR, the awards were presented in Vienna at the International AIDS Society conference to the 10 most successful scientists in the world.

Could you outline your current professional activities?

I am working on several different projects, all of which are related to the immune response in the lungs. I also teach Basic and Advanced Immunology at the National Autonomous University of Mexico to both Master’s and PhD students. Finally, I have to write up the projects, conduct experiments and mentor my own students in the lab.

What are your plans for the future?

Our long-term goal is to understand the immunological basis for protective immunity to tuberculosis. To achieve this, we are focusing on answering two main research questions: how does the host kill Mycobacterium tuberculosis, and how can we make these mechanisms more efficient?
Respiratory responses

In collaboration with research teams from around the world, scientists at the National Institute of Respiratory Diseases, Mexico, are studying the underlying disease mechanisms of tuberculosis, a prominent threat to global health.

**Mycobacterium tuberculosis** is one of the world’s deadliest human pathogens. It is the bacteria responsible for most cases of tuberculosis (TB), which is only rivaled by HIV as the number one killer among infectious diseases. *M. tuberculosis* has a long and devastating history, causing Europe’s ‘White Plague’ in the 17th and 18th Centuries, in which it infected almost 100 per cent of the European population and caused some 25 per cent of all adult deaths during this period. The pathogen, which primarily affects the lungs, was first identified in 1882 by the Nobel Prize-winning German doctor Robert Koch.

Extensive research since Koch’s initial discovery has built a clearer picture of *M. tuberculosis*. For instance, it is widely accepted that the genus originated over 150 million years ago, possibly in the Horn of Africa, and microscopic analysis has highlighted the incredible resilience of this nonmotile, rod-shaped bacterium. For example, its cell walls are very thick and have an unusual waxy coating due to high lipid content, forming a protective barrier against antibiotics and the host’s immune responses. *M. tuberculosis* is also able to survive within macrophages – the white blood cells that ingest and kill pathogens in the body – by modulating their metabolic activity and thereby preventing its destruction. Additionally, the pathogen’s ability to enter a non-replicating state with reduced metabolic activity means that it can survive for many years.

**Closing the gap**

While scientists today have attained a broad knowledge of the structure and properties of *M. tuberculosis*, this bacterium remains a significant threat to global public health. The disease primarily affects young adults and is most prevalent in low- and middle-income countries, where over 95 per cent of TB deaths occur. Furthermore, the risk of contracting the disease is significantly higher in those who suffer from HIV or other conditions that impair the immune system. Worryingly, although the number of people falling ill with TB is declining – albeit very slowly – increasing numbers of drug-resistant forms of the disease are emerging across the world.

Based in Mexico’s National Institute of Respiratory Diseases, Dr Isabel Sada-Ovalle is a prominent researcher who is committed to the study of the host’s innate immune response to infection by *M. tuberculosis*. She has a strong track record of research excellence and is passionate about engaging in studies that enable scientists from developing and developed countries to work as equal partners to address global health threats. As such, her research activities are rooted in the promotion of human rights, equity, solidarity and democracy. “It is relatively easy for researchers in developed countries to obtain human samples from developing countries, whereas the reverse is far more challenging,” she points out. “However, research should be more focused on helping the people in developing countries and providing the scientists there with better access to training and funding opportunities.”

**Investigating immunity**

It was during her postdoctoral studies at Harvard Medical School, USA, that Sada-Ovalle developed an innovative technique that enabled her to generate a deeper understanding of the complex cellular interactions between *M. tuberculosis* and the host’s immune system. The technique in question was a simple yet physiologically relevant *in vitro* model, which used a reduction in bacterial numbers as an endpoint. Sada-Ovalle’s team in her Laboratory of Integrative Immunology still uses this model in their current research on the body’s immune response to *M. tuberculosis*.

In one key study, Sada-Ovalle and her colleagues tested the hypothesis that macrophage exposure to crystalline silica particles makes them prone to necrosis when infected by the pathogen. Using their *in vitro* model, the researchers were able to describe the effects of macrophage exposure to crystalline silica: “Our data demonstrated that the exposed macrophages are sensitised to cell death by the MAPK kinase-dependent signalling pathway,” Sada-Ovalle explains. “The secretion of pro-inflammatory molecules by *M. tuberculosis*-infected macrophages promoted necrosis – and this deregulation of cell death pathways may favour the release of viable bacilli, thus leading to the progression of TB.”

**Important interactions**

More recently, Sada-Ovalle and her colleagues have concentrated on studying the role of T cell immunoglobulin and mucin domain 3 (Tim3) in regulating immune tolerance, autoimmune responses and antiviral immune invasion. Previous research on Tim3 has firmly established it as a negative regulatory molecule. For instance, the interaction of Tim3 and galectin-9 (Gal-9) – its first ligand – has been shown to induce cell death, while the *in vivo* blockade of this interaction has been shown to increase host autoimmune and the abrogation of tolerance. In addition to this, it is known that Tim-3 promotes T cell exhaustion and that it induces the expansion of myeloid-derived suppressor cells.
Using their in vitro experimental model, Sada-Ovalle and her team made an interesting discovery about the Tim3/Gal-9 interaction. They identified a mechanism through which it mediates the macrophage clearance of intracellular pathogens. For instance, infection with M. tuberculosis induces T cell reactions that in turn trigger the expression of Gal-9. During infection, Tim3+ T cells are transported to the lungs, where they come into contact with Gal-9 expressed in infected alveolar macrophages. It is the subsequent Tim3/Gal-9 reaction that is of most interest to the researchers; it led to the identification of an unknown activating signal via Gal-9 into the infected macrophages, which triggers IL-1 beta secretion. Importantly, this secretion is thought to act in an autocrine way, further activating innate pathways of pathogen clearance.

**DRIVING PROGRESSION**

Sada-Ovalle and the rest of her team are eager to continue carving a deeper understanding of the basis for protective immunity to TB. To this end, the researchers are participating in two forward-thinking studies. Using a cohort of susceptible and multidrug-resistant TB patients, the goal of the first study is to determine the metabolic pathways activated in M. tuberculosis-infected macrophages after antibiotic treatment. The second study – conducted in partnership with the Centers for AIDS Research and the Ragon Institute, USA – is focused on the innate control of intracellular bacterial growth during the coinfection of HIV and TB. Together, the scientists are planning to follow a cohort of HIV-1 patients for at least six months in order to assess their ability to control bacterial replication after they have begun antiretroviral therapy.

Ultimately, the hope is that Sada-Ovalle’s innovative and interweaving research activities will contribute to a more complete understanding of the mechanisms of M. tuberculosis, in turn leading to the development of innovative therapeutic strategies for TB patients. Yet, it is only through the creation of an inclusive and ethical global health framework that this will be achieved. “It is critical to narrow global disparities in basic and clinical research.” Sada-Ovalle asserts. “Indeed, it is only through international research partnerships that we will help disadvantaged groups in developing countries and thus improve global health.”

**INTELLIGENCE**

**PRE-EXPOSURE OF MYCOBACTERIUM TUBERCULOSIS-INFECTED MACROPHAGES TO CRYSTALLINE SILICA IMPAIRS CONTROL OF BACTERIAL GROWTH BY DEREGLATING THE BALANCE BETWEEN APOPTOSIS AND NECROSIS**

**OBJECTIVES**

To investigate the immunological basis for protective immunity to tuberculosis, using innovative techniques to explore the complex cellular interactions between the Mycobacterium tuberculosis bacterium and the host’s immune system.

**KEY COLLABORATORS**

Dr Rogelio Peréz Padille, National Institute of Respiratory Diseases, Mexico
Dr Samuel M Behar, Harvard Medical School, USA

**FUNDING**

National Institute of Respiratory Diseases
National Council for Science and Technology (CONACYT)

**CONTACT**

Dr Isabel Sada-Ovalle
Head, Laboratory of Integrative Immunology
National Institute of Respiratory Diseases
Calzada De Tlalpan 4502
Colonia Sección XVI
Mexico City 14080
Mexico

T +52 55 43 42 0901
E isadamx@gmail.com

www.iner.gob.mx

@isadamx

http://on.fb.me/1ApiGOp

http://google.com/+IsabelSadamx

**ISABEL SADA-OVALLE** completed her MD and MSc at the Autonomous University of San Luis Potosí, Mexico, before pursuing a PhD at the Autonomous National University of Mexico. She then carried out a postdoctorate position at Harvard Medical School, USA. Alongside her research, Sada-Ovalle is on the editorial review board of the journal Neumología y Cirugía de Tórax.

**Devastating deregulation**

Cells in the innate immune system – such as macrophages and dendritic cells – play a vital role in protecting the host against M. tuberculosis. It is their job to sense infections, trigger adaptive immune responses and induce antimicrobial functions once activated. It is therefore unsurprising that the deregulation of macrophage and dendritic cell functions are associated with increased susceptibility to tuberculosis, especially in patients with a compromised immune system, such as those with HIV or cancer.