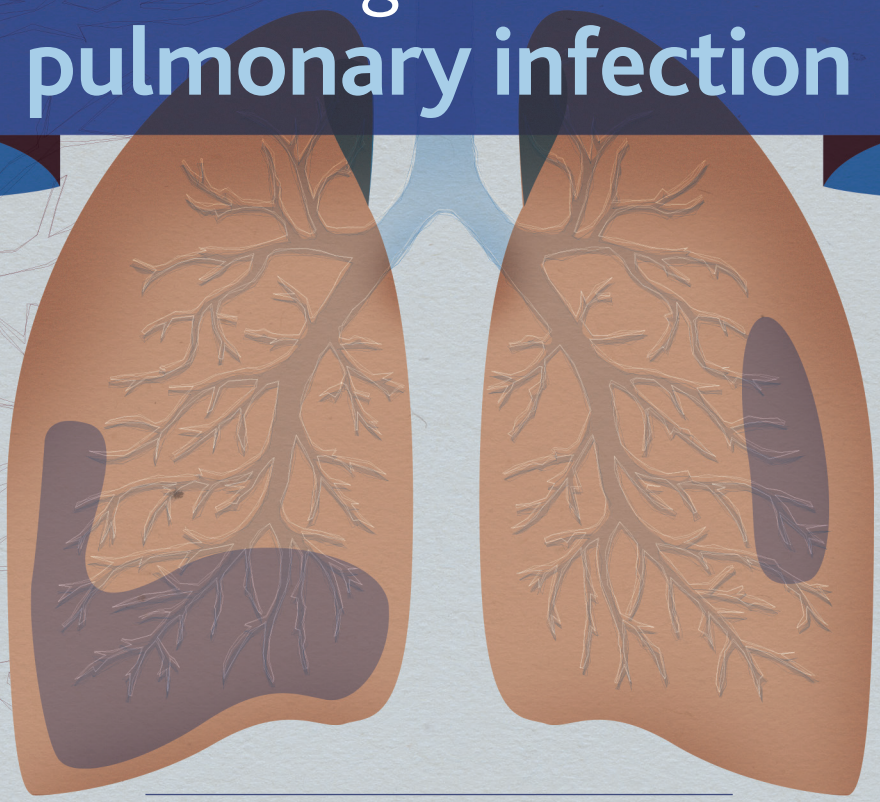
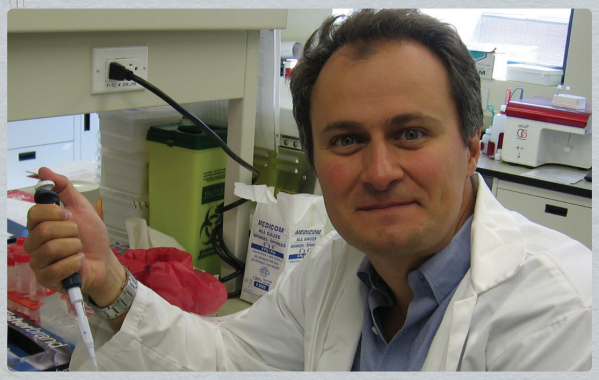
DR MAZIAR DIVANGAHI

Immune regulation against pulmonary infection



For the past 12 years, **Dr Maziar Divangahi** has been searching for new therapeutic avenues in the fight against two infectious lung diseases: influenza and tuberculosis



What are your overarching research interests and objectives?

It is evident that the immune system has evolved to protect us against a variety of pathogens, including viruses (influenza virus), bacteria (*Mycobacterium tuberculosis*) and parasites (tapeworm). The host utilises many different strategies to defend us.

Understanding the innate versus adaptive arms of immunity as well as their communication or regulation is therefore essential for the future development of effective therapies or vaccines. For this reason, I have become very interested in investigating the cellular and molecular mechanisms involved in cross-talk between innate and adaptive immunity, with a special focus on pulmonary infectious diseases.

How did you come to study immunology and pulmonary infectious diseases?

To be honest, it was serendipity that I ever become a scientist in the first place! It all started during my undergraduate studies in immunology at McMaster University, where I accidently came across an opportunity to work in one of the best immunology centres in Canada as a summer student under Drs Jack Gauldie and Zhou Xing. The project was to establish a mouse model of acute pulmonary infection with an opportunistic strain of bacteria (*Pseudomonas aeruginosa*). The experience was so fulfilling that I decided to pursue a career in the investigation of immunity against pulmonary infectious diseases.

I then completed my PhD at McGill University under the supervision of Dr Basil Petrof, where I studied the effects of chronic Pseudomonas lung infection on respiratory muscles (diaphragm). This was followed by three distinguished postdoctoral fellowships: one at McMaster with Dr Xing researching immunity to mycobacteria and viral infection (Adeno and influenza viruses), another at McGill with Dr Marcel Behr studying the role of pattern recognition molecule (Nod-like receptor) in immunity to mycobacterial infection, and finally at Harvard with Drs Heinz Remold and Samuel Behar, investigating the critical role of macrophage fate in immunity to *Mycobacterium tuberculosis* infection.

Could you provide an insight into some of the research methodologies and

technologies that are currently used in your laboratory?

A thorough understanding of host mechanisms that mediate deleterious and protective responses to pulmonary tuberculosis (TB) or influenza infection is expected to provide a foundation for novel therapeutic approaches to reduce morbidity and mortality during infection.

By taking advantage of both novel mice deficient in lipid mediator genes or receptors and selective chemical inhibitors for eicosanoid pathways, we will investigate how loss-of-function is involved in immunity against infection. Moreover, due to the availability of these lipids as pure preparations, we will further study how gain-of-function may affect the immune response to infection.

We hope to effectively address the role of lipid mediators in host defense mechanisms against pulmonary influenza and TB infection by using both genetic and chemical approaches *in vitro* and *in vivo*.

Who have been some of your key collaborators on this most recent line of research?

Working alongside me are investigators with expertise in biosynthesis and biological roles of eicosanoids in inflammation (Dr Powell), lung pathology (Dr Hamid), pulmonary inflammatory diseases (Dr Martin), respiratory physiology (Dr Petrof) and signal transduction (Dr Rousseau).

As an immunologist, my research programme also forms part of a broader collaborative effort led by the McGill International TB Centre, which is currently home to some of North America's leading TB research scientists, including Dr Behr, a molecular mycobacteriologist; Dr Schurr, a geneticist with expertise in human factors that predispose to mycobacterial infections including leprosy and TB; Dr Menzies, a clinical epidemiologist; Dr Madhukar Pai, a TB diagnosis specialist; Dr Reed, a mycobacterial-lipid biologist; and Dr White, a biochemist with expertise in Vitamin D and TB; and many others.

Overall, our project encompasses a tremendous pool of talent including epidemiologists and geneticists from both McGill University and the Université de Montréal. We also collaborate nationally and internationally with experts in macrophage biology (Dr Remold, Harvard University, USA), TB-vaccine (Dr Xing, McMaster University, Canada), the influenza virus (Dr McCullers, St Jude Children's Research Hospital, USA) and prostaglandins (Dr Jakobsson, Karolinska University Hospital Solna, Sweden).

Understanding immunity

Researchers at **McGill University** are seeking to understand the mechanisms of host defense against influenza and *Mycobacterium tuberculosis* to develop a novel generation of therapy and vaccines

THE 1950 VACCINATION efforts against Poliomyelitis are often regarded as one of medicine's biggest successes; and cases of polio have dropped from hundreds of thousands to under a thousand annually. Whilst vaccines have been shown to be truly effective in the fight against a number of human diseases, some bacterial and viral infections are still proving hard to control or eradicate.

Influenza and tuberculosis (TB) are two pulmonary infections that pose a persistent threat to human health. In both diseases, the host's immune system response is known to play a significant part in their development and proliferation. However, a better understanding of the mechanisms behind this response is needed in order to achieve effective treatment. Dr Maziar Divangahi, Assistant Professor at McGill University, has dedicated much of his 12-year career to investigating the cross-talk between innate and adaptive immunity against influenza virus and *Mycobacterium tuberculosis* (*Mtb*), the infectious agent of TB.

ADAPTIVE AND INNATE IMMUNITY

Historically, the human immune system has been broadly characterised into two arms: innate and the adaptive immunity. It was previously thought that the innate immune system constituted the first line of non-specific host defense against an invading pathogen; however, Nobel prizewinning research has shown that immune cells such as macrophages can, in fact, sense microbial infections through specific pathogen recognising molecules such as toll-like receptors.

Further to this, more recent studies have found that other cell types from the innate immune system, such as natural killer cells, have the capacity to become memory cells, which is a historical component of adaptive immunity. "The classical dichotomy between innate and adaptive immunity no longer exists and we need to understand how these two arms of immunity communicate with one another and, most importantly, what key regulatory mechanisms are involved in turning them 'on' or 'off'," explains Divangahi.

TUBERCULOSIS

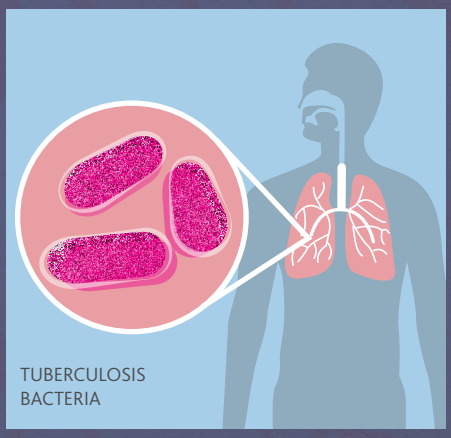
In 2003, a team of scientists uncovered evidence of TB in the spines of Egyptian mummies dating back to 3000–2400 BC, suggesting a longstanding evolutionary relationship with humans. Since then, the causative agent *Mtb*, which was identified and described by Dr Robert Koch in 1882, has defied efforts by scientists to curb the disease. Today, TB remains one of the most deadly human pathogens, killing around 2 million people annually worldwide.

TB is an air-borne disease and the pulmonary immunological response, or lack thereof, in the lung is known to play an integral role in its infectious capabilities. This becomes especially apparent in *Mtb*'s ability to infect healthy individuals, implicating its capacity to avoid, evade and even subvert both the innate and adaptive immunity of patients. Divangahi's lab has been attempting to first understand the cellular and molecular mechanisms of the host's defense against *Mtb*, and to examine the activities of the bacterium's first point-of-contact: alveolar macrophages (Mϕ).

INFECTED ALVEOLAR MACROPHAGES

Mtb has evolved into a facultative intracellular parasite that is able to survive and replicate within Mϕ once phagocytised. Divangahi and his collaborators showed how the balance between the two eicosanoid lipids, prostaglandins (eg. PGE2) and lipoxins (eg. LXA4), plays a vital role in regulating apoptosis and necrosis of infected Mϕ. "Virulent *Mtb* induces necrosis in macrophages, which allows them to escape and spread into other cells," observes Divangahi.

The researchers used mice that were genetically altered so that they were unable to produce PGE2 and LXA4. Once the mice



INTELLIGENCE

IMMUNE REGULATORY ROLE OF HOST LIPID MEDIATORS IN PULMONARY INFECTION

OBJECTIVES

The goals of the research programme are twofold: to investigate the critical regulatory role of the mediators in immune-pathological response of the lung during influenza infection; and to develop a novel vaccine employing a pharmacological approach or recombinant Bacille de Calmette et Guérin (BCG) vaccine as tools to enhance immunity and ultimately protection against pulmonary *Mycobacterium tuberculosis* infection.

KEY COLLABORATORS

Professor Qutayba Hamid; **Professor James Martin**; **Professor Basil Petrof**; **Professor William Powell**; **Dr Simon Rousseau**: Meakins-Christie Laboratories, McGill University, Canada • **Professor Marcel Behr**; **Professor Philippe Gros**; **Dr Dick Menzies**; **Dr Madhukar Pai**; **Dr Michael Reed**; **Professor Erwin Schurr**; **Professor John White**: McGill International TB Centre, Canada • **Dr Jonathan McCullers**, St. Jude Children's Research Hospital, Canada • **Dr Gary Kobinger**, Public Health Agency of Canada • **Professor Zhou Xing**, McMaster University, Canada • **Professor Heinz Remold**, Harvard University, USA • **Dr Per-Johan Jakobsson**, Karolinska University Hospital Solna, Sweden

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DR MAZIAR DIVANGAHI is currently Assistant Professor of Medicine at McGill University, Research Director of the Meakins-Christie Laboratories, associate member of the Department of Microbiology & Immunology and member of McGill International TB Centre. Divangahi has been awarded numerous awards, including the CIHR-New Investigator Award.

were infected with *Mtb*, Divangahi and his colleagues were able to demonstrate that both lipids are essential in regulating Mϕ death modality which is critical to both innate and adaptive immunity to *Mtb*. With these data, the investigators now believe that the balance between eicosanoid lipid mediators plays a critical role in modulating Mϕ survival and thus determining whether the immunological response to *Mtb* is adequately regulated (which is necessary for recovery) or dysregulated.

INFLUENZA

Influenza (commonly known as flu) is a viral infection which can be differentiated into seasonal, pandemic and zoonotic or variant influenza, and can pose a significant risk to human health. Indeed, as recently as 2009, the H1N1 strain (also referred to as 'swine flu') resulted in around 300,000 deaths worldwide. The flu virus evolves much more rapidly than other viruses such as measles, mumps and polio, thus rendering vaccinations ineffective against new strains.

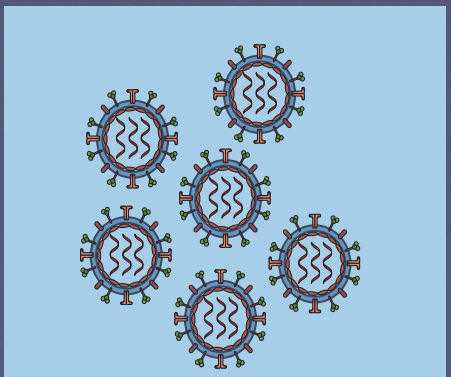
Interestingly, most influenza viral infections do not lead to death; rather, it is a dysregulated host immune system that can cause complications instead of the cytopathic effects of the virus itself. Mϕ are known to be the first immune cells to encounter the influenza pathogen in the distal parts of the lung, and previous studies found that the function of these Mϕ is often paralysed following infection.

Armed with this knowledge, Divangahi's lab is seeking to understand the regulatory role of host-lipid mediators in the immune-pathological response of the lung during an infection. "Inadequate immune responses in either direction – 'too little' or 'too much' – are not beneficial to the host since this provides an opportunity for pathogens to rapidly replicate and cause immunopathology," Divangahi elaborates.

INFLUENZA IMMUNITY

Seeking out regulatory mechanisms that could be exploited to fight the influenza virus, the team was interested in the fact that non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin are often used to manage symptoms of flu. By applying his extensive expertise in eicosanoid biology to the investigations, Divangahi was led to believe that prostaglandins specially PGE2 may play a major regulatory role in immunity to flu.

Based on this hypothesis, using *in vitro* as well as *in vivo* models, the McGill University group demonstrated that the inhibition of this prostaglandin greatly enhances both innate and adaptive immune responses to influenza infection. Thus, in contrast to virulent *Mtb,* which inhibits the production of (PGE2) – important to prevent necrotic cell death – the influenza virus induces PGE2 to suppress immunity to viral infection.



INFLUENZA VIRUS

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Therefore, comparable to *Mtb*, the role of eicosanoids in the regulation of Mϕ survival and function may hold the key to novel vaccination strategies. Moreover, the investigators also showed in a 2010 study that eicosanoid-regulated cell death of infected macrophages can, in turn, modulate the response by acquired immunity cells, namely T cell lymphocytes.

CLINICAL IMPORTANCE OF EICOSANOIDS

In demonstrating that eicosanoids have a part to play in both influenza and TB infection, the researchers are paving the way for clinical investigations into drugs that are already used to target eicosanoid pathways. With regard to TB, for example, Divangahi believes that by employing a novel pharmacological approach and/or recombinant Bacille de Calmette et Guérin (BCG) vaccine, we may be able to increase the levels of apoptosis of infected macrophages and therefore enhance overall immunity and protection against *Mtb*.

A bench-to-bedside approach has always been a driving factor for Divangahi and, with these findings, he believes that his team could now begin to formulate new protection strategies against the two infections: "The eicosanoids appear to play an unexpected role in immunity to TB, flu and possibly more," he reveals. "By taking advantage of current drugs that target these pathways, I hope that we can develop novel therapeutic strategies against these pulmonary infections, which can then be brought into the clinical realm."