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## KEYNOTES

## ABSTRACTS

### THIRD ANNUAL SYMPOSIUM OF THE WEST INDIAN IMMUNOLOGY SOCIETY ON APRIL 29 2023.

#### 1. The curious case of TCR gamma/delta+ T-cells in immune-mediated cardiomyopathy

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T-cells bearing the  $\gamma\delta$  T-cell receptor (TCR) are a minor but highly active cell population in human blood. Performing *in silico* analysis of public transcriptome data from heart tissue of patients with Chagas disease cardiomyopathy (CCC), the most deleterious consequence of human infection with *Trypanosoma cruzi*, we found that  $\gamma\delta$  gene expression is upregulated. We hypothesize that  $\gamma\delta$ + T-cells display characteristics of inflammatory and cytotoxic responses associated CCC. We analysed the expression of cytokines and their receptors, cardiotropic receptors and cytotoxic molecules in circulating CD4+, CD8+ and CD4-CD8- (DN) T-cells, expressing  $\gamma\delta$  and  $\alpha\beta$  TCR, before and after *in vitro* stimulation with *T. cruzi* antigens (TRP), in CCC and asymptomatic indeterminate (IND) Chagas disease patients by multiparameter flow cytometry. We found that expression of TNF was higher in CCC than IND in all T-cell subsets and that its expression was three times higher in  $\gamma\delta$  + than  $\alpha\beta$  + cells. TNF receptor was highly expressed in CD8+ $\gamma\delta$ + in CCC. While CD8+ cells from CCC displayed higher expression of IL-10 than IND, *in vitro* recall with TRP reduced IL-10 expression by those cells from CCC, but not IND. TRP induced expression of IL-10 receptor in  $\alpha\beta$  and  $\gamma\delta$  cells from IND but reduced its expression in CD8+ $\gamma\delta$ + cells from CCC. The ratio TNF/IL-10 receptors was approximately 5 times higher in CD8+ $\gamma\delta$ + cells from CCC than IND, reaffirming the highly inflammatory profile of these cells. CD8+ $\alpha\beta$ + from CCC display higher granzyme and perforin expression than IND, but CD8+ $\gamma\delta$ + cells also express these cytotoxic molecules. DN T-cells display a highly cytotoxic profile in CCC as compared to IND. The expression of cardiotropic receptors was higher in  $\gamma\delta$  + cells from CCC than IND, especially in CD8+ and DN subsets. Further *in silico* analysis showed that upregulation of the  $\gamma\delta$  gene is positively correlated with upregulation of CD8, cytotoxic and cardiotropic genes, as well as inflammatory cytokines in CCC cardiac tissue. CD8+ $\gamma\delta$  cells from CCC display a highly inflammatory profile, cytotoxic potential, and cardiotropic markers, consistent with their presence in the heart, suggesting a potential role as mediators of tissue destruction in CCC. Seeking to verify if pentoxifylline (PTX), a molecule that controls responses mediated by NF- $\kappa$ B transcription factor, particularly TNF, is able to modulate the inflammatory profile of  $\gamma\delta$  + cells,



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we incubated cells from CCC with TRP and PTX and evaluated the expression of the above-mentioned molecules. We observed that PTX reduced the expression of TNF and of TNFR in CD4+ and CD8+  $\square\square$ T-cells, respectively, without altering IL-10 expression. In addition, PTX led to a slight decrease in the frequency of expression of granzymeA+CD107+ in CD8+  $\square\square$ T-cells. This suggests that PTX may be employed to modulate the inflammatory response in CCC patients, opening perspectives for its use as an adjunct immunotherapy.

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## SHORT BIOGRAPHY

Walderez Ornelas Dutra, PhD.

Ph.D. in Biochemistry-Immunology with honors from Federal University of Minas Gerais (UFMG). Fellow at DNAX Research Institute with Robert Coffman, former visiting professor at the Department of Genetics Stanford University and at the Department of Pathology University of Cambridge, UK.

Full Professor at the Department of Morphology, head of the Cell-cell Interactions laboratory (UFMG), studying the cellular and molecular mechanisms underlying of generation of protective or pathogenic immune responses in human tropical neglected diseases, especially Chagas disease, leishmaniasis and rheumatic heart disease. She is currently part of the scientific advisory committee of DNDi, vice-president of the Latin-American Society of Immunology, and is a CNPq 1A fellow. Coordinator of internationally funded projects, she has advised over 50 PhD and MS students, 90% of them women currently working in high education and research institutes in Brazil and abroad.



## 2. Off-target effects of Bacillus Calmette–Guérin (BCG) Vaccine

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The Bacillus Calmette–Guérin (BCG) is a live attenuated form of *Mycobacterium bovis* which was introduced as a vaccine against *Mycobacterium tuberculosis* (MBT) in 1921. Soon after its introduction, the off-target effect of BGC was recognized from epidemiological observations because BCG vaccination resulted in a significant reduction in infant morbidity and mortality that could not have been explained by the reduction in MBT infection alone. Findings from several animal model experiments, human case-cohort studies, and randomized clinical trials supported the early epidemiological reports, in particular in regard to reducing respiratory infections. The nonspecific protection of BCG is not limited to infections alone, but against cancer of certain types and autoimmune diseases as well. Recently, the role of BCG in giving cross-protection against the Covid-19 virus infection has been a focus of several investigations. Although there could be many confounding factors that led to the inconsistent findings from epidemiological observations, and clinical trials; data from animal experiments, in vitro analysis and molecular studies are providing more convincing evidence of the immunological relationship between BCG and the Covid-19 virus. It is possible that more than one immune mechanism may contribute to the heterologous beneficial effects of BGC, however, currently, the largely accepted mechanism is an antigen-independent enhancement of the innate immune system known as “trained innate immunity”. BCG vaccination causes metabolic and epigenetic changes in cells of innate immunity which is mediated by methylation and acetylation of the histone, resulting in enhanced chromatin accessibility resulting in easier transcription of genes important in host defense. Since trained immunity induced by BCG gives cross-protection against a wide range of pathogens as all as noncommunicable diseases there is an increasing interest in enhancing the immunomodulatory activities of BCG. It has been proposed that the wild type of BCG or its genetically modified forms can serve as tools in developing a new generation of broad-spectrum vaccines.



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## SHORT BIOGRAPHY Wezenet Tewodros, PhD

Dr. Wezenet Tewodros is Professor of Microbiology and Immunology and discipline chair. She began her teaching career as a Lecturer at Addis Ababa University in Ethiopia, the same University where she had earned both her BSc. and MSc. degrees in Biology. She earned her PhD in medical microbiology from the Karolinska Institute, Stockholm, Sweden. Dr. Tewodros research interest included molecular epidemiology and pathogenesis of bacterial pathogens and has several publications. In addition to her academic career, she had held academic administration posts of various capacities including the office of the Director of Academic Affairs at the University of Asmara, Eritrea. In 2002, Dr. Tewodros was granted a research fellowship from the Swedish Institute and spent a year as a Visiting Scientist at the Karolinska Institute. She then took on a post doctorate position at the New York Medical College in Valhalla, New York. Since 2005 she has been teaching Microbiology and Immunology at US offshore medical schools in the Caribbean. In 2010, she joined her current position at Trinity School of Medicine, St Vincent and the Grenadines, West Indies.



### 3. Into the eye of the leptospiral cytokine storm

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Leptospirosis is a neglected tropical zoonosis that is both emerging and re-emerging, and affects animals and humans, with humans being accidental hosts. The disease is reportedly more widespread in developing than developed countries, and its re-emergence as a health threat is not only because of the impact of its broad geographical distribution on risk groups but in part due to globalization, climate-based factors, and expansion of urban slums. The ubiquitous aetiology of leptospirosis, general syndromic clinical manifestations and demanding differential diagnosis contribute to its under-reporting and misdiagnosis. This is exacerbated by an inadequate system for disease notification. Predominantly hospital-based surveillance studies report an annual estimate of 1.03 million leptospirosis cases and 58 900 deaths worldwide, which is an estimated small fraction (5 to 15%) of clinical leptospiral infections. Generally, the disease is more pervasive in tropical and subtropical areas, and climatic changes such as high levels of rainfall which instigate flooding, potentially increases the frequency of outbreaks by compounding predisposing risk factors such as inadequate sanitation, poor housing and the complex interactions between the environment and the aetiological agent, *Leptospira spp.*

*Leptospira* are finely coiled, rapidly motile Gram-negative bacteria that span 0.1-0.2  $\mu\text{m}$  in diameter and 6-20  $\mu\text{m}$  in length. *Leptospira* faintly retain Giemsa stain, however, they are aptly stained by silver impregnation techniques, and visible by dark-field and phase contrast microscopy. The bacterial genome consists of two circular chromosomes: C-I, 3,500 - 4,600 kb; C-II, ~350 kb. Leptospiral pathogenesis can be mediated via direct effects by leptospires, or by expression of virulence factors, which are influenced by environmental signals such as temperature or oxidative stress.

Most human infections are mild or asymptomatic. However, 10% of human leptospirosis cases develop into severe forms, including high leptospiraemia, multi-organ injuries, and a dramatically increased mortality rate. The usual presentation of severe leptospirosis includes high fever, chills, headache, severe myalgia, nausea and vomiting. There may be conjunctival suffusion/photophobia, jaundice, abdominal pain, diarrhoea, or a rash. Untreated, leptospirosis may result in kidney failure, cardiopulmonary complications, CNS involvement, and multiple organ failure (Weil's disease). The mortality rate is usually ~10% but can be as high as 30%. The disease may be biphasic, with an anicteric (Acute or septicaemic) phase, characterized by



bacteraemia, and lasts about 1 week, followed by a fulminant (Icteric or Immune) phase, where there is antibody production, and excretion of leptospire in the urine. Given that leptospirosis has protean clinical manifestations, and mimics other diseases, including common viral infections, and bacterial causes of pyrexia of unknown origin, among several others, accurate diagnosis requires a high degree of clinical suspicion and differential diagnosis.

During infection, the triggering of the inflammatory response, especially through the production of cytokines, is essential for the early elimination of pathogens. However, uncontrolled cytokine production (Cytokine storms) can ensue, and pathology begins at local site and spreads via peripheral circulation, resulting in immunoparalysis, sepsis and organ failure. The dysregulated inflammation seen in leptospirosis, is particularly due to the elevated levels of particularly the pro-inflammatory cytokines TNF $\alpha$  and IL-6, anti-inflammatory and immunomodulatory cytokines IL-8 and IL-10, and the chemokines CXCL8/IL-8, ICAM-1 and VCAM. The pro-inflammatory cytokines induce macrophage apoptosis via caspase-3 and -8 dependent pathways, alter sodium channels (which mediate pulmonary damage), increase other interleukins such as IL-6, an important indicator of septic shock. The level of IL-6 correlates with disease severity and is related to clinical bleedings and coagulation. The elevated chemokines are associated with organ damage and poor outcomes. Further, strictly regulated induction of pro-inflammatory cytokines in asymptomatic/mild cases vs delayed and overexpression of these in severe leptospirosis highlight another important difference between the types of leptospirosis cases.

Following the onset of cytokine storm in leptospirosis, the systemic production of IL-10 is considered the hallmark of immune system restoration as IL-10 influences and is important for bacterial clearance. However, its role might be dependent on the stage and severity of the disease. Consequently, elevated IL-10 usually correlates with sepsis and death and suggests immunosuppression. There are also some roles for regulatory cytokines, e.g., IL-4, IL-13 in impaired bacterial clearance and immunoparalysis (fulminant septicemia).

Both leptospiral and viral infections, such as Covid-19 and influenza, produce elevated pro-inflammatory cytokines and cytokine storms. However, the specific cytokine profiles, while overlapping, are different in levels of some cytokines, or might be produced at different times during the disease manifestation. These differences may have implications for the severity and duration of the immune response. Further, co-infection of leptospirosis with viral infections can result in a more severe illness than infection with either pathogen alone, although having similar clinical manifestations. Consequently, early recognition and prompt treatment of co-infections, particularly in areas where both diseases are endemic, are essential to prevent severe complications and reduce the risk of death.

On admission, all patients will benefit from aggressive fluid and electrolyte replacement. Depending on the severity of the disease (and possibility of co-infection with endemic viruses), one of several of the following will be indicated: antibiotics, intravenous fluids, corticosteroids, plasma exchange or plasmapheresis, and immunoglobulin therapy. In some cases, mechanical ventilation, and dialysis. Excellent supportive care is essential for patient survival.



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In summary, cytokine storms play important immunopathogenic roles in severe cases of leptospirosis, which mediate the development of life-threatening outcomes in human leptospirosis. These cytokine storms are also a potentially dangerous complication of co-infection with endemic viruses. Consequently, early recognition and management of severe leptospirosis are critical to prevent a fulminant course and fatal outcome.

## SHORT BIOGRAPHY

PAUL BROWN, PhD

Professor Paul Brown lectures undergraduate and graduate students in Microbiology and Molecular Biology in the Department of Basic Medical Sciences at the University of the West Indies (UWI) at Mona. He has been involved in research in public health related infectious diseases (mainly in Jamaica) for the past 30 years, particularly in infectious diseases as well as in areas of basic medical sciences. An important aspect of his research has been to enhance research capacity and foster collaboration in molecular ecological investigation of leptospirosis in Jamaica. Over the past decades, he has carried out research on molecular detection of *Leptospira* in fatal cases and surface water, and the effect of climatic variables on the incidence and pathogenesis of leptospirosis. He currently serves on the Council on Microbial Sciences of the American Society for Microbiology.



## 4. The Role of The IL-23 In Autoimmunity, Guselkumab In Psoriatic Arthritis

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Psoriasis, Psoriatic arthritis (PsA) and inflammatory bowel disease are all characterized by the pathogenic overproduction of IL-23 at barrier sites, i.e. the skin, the joints and the gut, respectively. This makes IL-23 an attractive target for all three conditions. In psoriatic arthritis the production of IL-23 in the enthesis, synovium, bone and cartilage may be driven by one or a combination of factors, including: Genetic and epigenetic susceptibility contributes to the pathogenesis of PsA, particularly HLA-B38, HLA-B-39 (peripheral) and HLA-B27 (axial PsA). Biomechanical stress has been shown to result in an activation of MAP kinase and p38 kinase which causes a release of pro-inflammatory cytokines, including IL-23. Overproduced IL-23/Th17-related cytokines and Th17 and other innate immune cells from the gut enter the circulation and distribute to the site(s) of inflammation in PsA. Increased production of IL-23 leads to activation of sentinels, amplifiers, and effector cells, leading to the release of cytokines, including IL-17 and IL-22. Activated innate immune cells lead to enthesitis, synovitis, bone loss, and osteoproliferation (structural damage), and bone fusion. IL-17 activates osteoclasts leading to bone loss and inflammation, whereas IL-22 activates osteoblasts associated with osteoproliferation. By specifically binding to the p19 subunit of IL-23, IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab) block downstream signaling pathways and inhibit inflammatory responses. Guselkumab (GUS) a human monoclonal antibody, GUS is currently approved to treat moderate-to-severe PsO and active PsA at a dose of 100 mg given at week 0, 4 and then every 8 weeks. Guselkumab has a proven clinical efficacy, regardless of baseline characteristics in biologic-naïve and patients with prior intolerance or inadequate response to TNF alpha inhibitors. GUS efficacy is comparable to other marketed and agents. Guselkumab has an established and well-preserved safety profile through two years in PsA and 5 years in PsO.





## 5. Immunometabolism: Exploring the impact of macrophages.

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The discipline where immunology and metabolism meet, known as immunometabolism, has become a captivating area of research to uncover the intricate relationship between immune cells and metabolic processes. Macrophages, which are multifunctional guardians of the immune system, play a major role in managing immune reactions and keeping the body's equilibrium. Recent research has illuminated the essential role of macrophages in immunometabolism, uncovering their capacity to detect and respond to metabolic signals, affecting immune operations and tissue remodelling. This research paper provides a comprehensive overview of the multifaceted role of macrophages in immunometabolism, exploring their metabolic plasticity, immunoregulatory functions, and therapeutic implications. Macrophages can adapt to a variety of environmental stimuli thanks to their amazing metabolic flexibility. They can alternate between several metabolic states, such as the conventionally activated (M1) and alternatively activated (M2) phenotypes, each of which is distinguished by a different metabolic signature. While the M2 phenotype promotes oxidative phosphorylation and fatty acid oxidation, boosting anti-inflammatory and tissue repair activities, the M1 phenotype predominantly depends on glycolysis and the pentose phosphate pathway to create energy and maintain pro-inflammatory responses. In view of their ability to adapt their metabolism, macrophages can tailor how they behave dependent on the immunological milieu and metabolic needs of the immediate surroundings. A key component of macrophage-mediated immunometabolism is immunoregulation. Macrophages possess the capacity to detect metabolites, danger signs, and nutrition availability, which can affect immune responses. To control inflammatory processes and cellular fate decisions, they combine metabolic signals with immunological signalling pathways such as the mTOR and AMPK pathways. Chronic inflammation, metabolic diseases, and cancer are just a few of the clinical conditions that can be exacerbated by dysregulated macrophage metabolism. Understanding how macrophages regulate their metabolism therefore offers a special chance for therapeutic approaches. Beyond their direct roles in immunological modulation, macrophages also perform immunometabolic tasks. Through metabolic reprogramming, macrophages actively take part in tissue remodelling, regeneration, and repair processes. By engaging in efferocytosis, the phagocytic clearance of apoptotic cells, and by stimulating tissue repair and remodelling through the production of trophic substances, they aid in the resolution of inflammation. Furthermore, macrophages are essential for maintaining the homeostasis of adipose tissue and controlling energy metabolism, and abnormal macrophage activity can lead to metabolic dysfunction associated with obesity. In addition to obesity there other metabolic conditions in which macrophages play a crucial role. In atherosclerosis, macrophages play a central role in the development of atherosclerotic plaques in blood vessels. They take up oxidized LDL cholesterol, leading to the formation of foam cells, which are a hallmark of early atherosclerotic lesions. Macrophages also secrete pro-inflammatory cytokines and growth factors, promoting plaque progression and destabilization. In Type 2 diabetes mellitus:



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Macrophages contribute to the development of insulin resistance. They accumulate in adipose tissue and secrete inflammatory mediators that interfere with insulin signalling pathways, impairing glucose uptake and utilization by target tissues. In rheumatoid arthritis (RA), macrophages are present in the synovial tissue of affected joints. They contribute to chronic joint inflammation by producing pro-inflammatory cytokines and enzymes that degrade cartilage and bone. Macrophages also interact with other immune cells and perpetuate the inflammatory response in RA. Macrophages are involved in the pathogenesis of metabolic syndrome, a cluster of conditions that increase the risk of cardiovascular disease and type 2 diabetes. In metabolic syndrome, macrophages infiltrate various tissues, including adipose tissue, liver, and blood vessels, promoting inflammation and insulin resistance. Immunometabolism, whilst a young discipline, provides potential therapeutic approaches for the management of several disorders. Immunomodulation and tissue healing are both very susceptible to manipulation of macrophage metabolism. By focusing on metabolic pathways and metabolite availability, one may adjust macrophage polarization and improve immune responses in illnesses including cancer, cancerous tumors, and chronic inflammatory disorders. Additionally, treatment approaches that support healthy macrophage morphologies and functions may be able to reduce the symptoms of metabolic disorders and enhance tissue regeneration. Finally, macrophages are important participants in immunometabolism, dynamically modifying their metabolic profiles to influence immune responses and support tissue homeostasis. The diverse significance of macrophages in health and illness is highlighted by their involvement in tissue remodelling, metabolic plasticity, and immunoregulatory activities. Understanding the molecular processes that underlie macrophage metabolism and their interactions with other immune cells gives up fresh possibilities for therapeutic approaches that may completely alter how different pathological situations are treated. For patients all around the world, further study in this area has the potential to unlock the full potential of macrophage-targeted immunometabolic treatments.