VALIDATE Annual Meeting 2018 Programme

6-7th November 2018, The Principal Hotel, York

Tuesday 6th November

0900-1200 (optional additional meetings)	**A** - ECR Networking Session (open to all Associate/Affiliate members)	**Main room**
	B - Data drop-in with Dr Deniz Cizmeci, VALIDATE Research Data Analyst (open to any member who would find this useful)	**Main room**
	C - Pump-priming project mini meetings (for funded project teams to meet up and discuss their projects and next steps if they want to)	**Main room**
	D - Mentor-mentee meetings (opportunity for VALIDATE mentors and mentees connected in rounds 1 and 2 to meet in person, if they would like to)	**Main room**
1000-1200	**E** - Network Management Board Meeting (NMB members only)	**Board room**
1200-1300	*Buffet lunch for all delegates and start of main meeting*	

1300-1310		**Title:** Welcome **Prof Helen McShane**, VALIDATE Co-Director, University of Oxford, UK	**Main room**
1310-1320		**Title:** VALIDATE Data Portal Launch **Dr Deniz Cizmeci**, VALIDATE Research Data Analyst, University of Oxford, UK	**Main room**
1320-1330		**Title:** VALIDATE's first year and what's ahead **Samantha Vermaak**, VALIDATE Network Manager, University of Oxford, UK	**Main room**
1330-1400		**Title:** Vaccine Hesitancy **Prof Heidi Larson**, Professor of Anthropology, Risk and Decision Science, LSHTM, UK	**Main room**

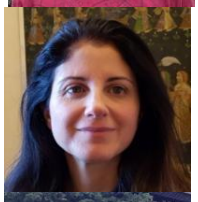
Round 1 pump-priming project talks:

1400-1420 

Title: Natural variation of the bovine lymph node microenvironment and its possible effect on BCG immunogenicity

Dr Lucia Biffar, APHA/University of Oxford, UK

Main room

1420-1440 

Title: Enhancing BCG efficacy: the Social Technology Lab Initiative

Asst Prof Delia Boccia, LSHTM, UK

Main Room

1440-1500 

Title: Establishment of a functional assay panel to evaluate the role of antibodies in defence against melioidosis and tuberculosis

Dr Panjaporn Chaichana, MORU, Thailand

Main Room

1500-1520 *Tea break*

Foyer area

1520-1540 

Title: Overcoming innate immune tolerance in the respiratory tract for optimal vaccine design

Dr Rajko Reljic, SGUL, UK

Main Room

1540-1600 

Title: The effect of BCG vaccination in immune responses against visceral leishmaniasis in a natural (canine) model of infection

Dr Javier Salguero Bodes, PHE, UK

Dr Isadora dos Santos Lima, Oswaldo Cruz Foundation, Brazil

Main Room

1600-1620 

Title: How do functional and metabolic characteristics of trained monocytes affect their anti-bacterial activity?

Asst Prof Steve Smith, LSTHM, UK

Main Room

1620-1630 **Pump-priming grants round 2 turbo talk:**

Main room

Title: In vivo protection studies of chimeric *Burkholderia pseudomallei* antigens presenting multiple epitopes on protein scaffolds and outer membrane vesicles

Dr Louise Gourlay, Università degli Studi di Milano, Italy

1630-1730 Networking session

Main room

1800-1900

Drinks reception

Industry partners showcase, and Early Career Researchers poster session

The Early Career Researchers poster session aims to highlight the work of VALIDATE ECRs, to facilitate networking and the building of new collaborations. Posters will be up from lunchtime on the 6th November, with a poster session over drinks that evening.









Poster presenters:

Dr Panjaporn Chaichana, Post-doctoral researcher, MORU, Thailand

Dr Amanda Gibson, Post-doctoral researcher, Royal Veterinary College, UK

Dr Taniya Kaewarpai, Post-doctoral researcher, Mahidol University, Thailand

Dr Jomien Mouton, VALIDATE Fellow, Post-doctoral researcher, Stellenbosch University, South Africa

Dr Olayinka Osuolale, Post-doctoral researcher, Elizade University, Nigeria

Dr Eduardo Milton Ramos Sanchez, Post-doctoral researcher, Universidade de São Paulo, Brazil

Dr Shraddha Siwakoti, Clinical Microbiologist, B. P Koirala Institute of Health

Dr Isadora dos Santos Lima, Post-doctoral researcher, Oswaldo Cruz Foundation, Brazil

Dr Rachel Tanner, VALIDATE Fellow, Post-doctoral researcher, University of Oxford, UK

Sciences, Nepal

1900+

Conference Dinner

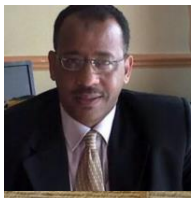
Main room

Wednesday 7th November

0830-0900 *Coffee/tea*

0900-0920 **Round 2 pump-priming project turbo talks continued:** **Main room**

0900-0910



Title: Identification of Leishmania donovani and *Mycobacterium tuberculosis*- derived proteins on the surface of infected macrophages that are associated with ADCC induction

Dr Mohamed Osman, University of York, UK

0910-0920

Title: Vaccines to target people with diabetes: characterising the pathways of immune response to *M. tuberculosis* and *B. pseudomallei* in people with diabetes compared to non-diabetics

Prof Susie Dunachie, University of Oxford

0920-1300 **Ideas Laboratory** **Main room**

This is an exciting facilitated session that will help delegates form new collaborations and pull together innovative pump-priming project ideas ready for VALIDATE's 3rd funding call, which will open in November 2018.
There will be tea and coffee on offer during the session.

1300-1400 *Buffet lunch*

1400 **Conference Ends**

Abstracts

Prof Helen McShane, VALIDATE Co-Director, University of Oxford

Welcome

Helen will open the conference and welcome our delegates to the VALIDATE 2nd Annual Meeting.

Dr Deniz Cizmeci, VALIDATE Research Data Analyst, University of Oxford

VALIDATE Data Portal Launch

Deniz will take members through the new VALIDATE data portal, where members can safely share and access published and unpublished data.

Samantha Vermaak, VALIDATE Network Manager, University of Oxford

VALIDATE's First Year and What's Ahead

Sam will briefly take members through VALIDATE's achievements in our first year, and give an overview of the funding calls and activities planned for year two.

Prof Heidi Larson, Professor of Anthropology, Risk and Decision Science, LSHTM, UK

Vaccine hesitancy

Dr Lucia Biffar, APHA/University of Oxford, UK

Natural variation of the bovine lymph node microenvironment and its possible effect on BCG immunogenicity

Bovine tuberculosis is a disease affecting cattle in the UK and worldwide. It is caused by *Mycobacterium bovis*, a bacterium closely related to the human pathogen *Mycobacterium tuberculosis*. The vaccine routinely used to protect humans against tuberculosis is BCG, a live attenuated vaccine developed from a *Mycobacterium bovis* strain. BCG may also be used as a vaccine against bovine tuberculosis in cattle,

Project funded in round 1 and led by Dr Lucia Biffar (University of Oxford), with Dr Bernardo Villarreal-Ramos (APHA) and Prof Tracy Hussell (University of Manchester)

however, it is currently only administered in experimental studies. The ability of BCG to induce protection varies considerably between different population groups and amongst individuals from 0-80%, both in humans and in cattle. The reasons for this variability still needs to be understood. After administration a vaccine drains to the lymph node closest to the site of injection. In the lymph node immune cells are trained to recognise the target pathogen, thus enabling them to combat the pathogen during future infection. The lymph node microenvironment is made up of different immune cells and the immune molecules (e.g. cytokines) they express. We suggest that a potential factor influencing the variable efficacy of BCG might be natural variation of the lymph node microenvironment between different individuals. The aim of this project is to analyse the lymph node microenvironment in different cows before and after parenteral BCG administration, by measuring the expression of cytokines and analysing the composition of immune cells. Results from this experiment will provide a baseline for future experiments investigating the impact differences in the lymph node microenvironment might have on the protection conferred by BCG. Furthermore, this baseline data will enable us to design experiments seeking to manipulate the lymph node microenvironment with the aim to improve efficacy of BCG. The results may have wider applicability to other diseases for which vaccines have been difficult to develop.

Asst Prof Delia Boccia, LSHTM, UK

Project funded in round 1 and led by Assist Prof Delia Boccia (LSHTM), with Dr Jenn Dowd (KCL), and Assoc Prof Helen Fletcher (LSHTM)

Enhancing BCG efficacy: the Social Technology Lab Initiative

With approximately 2 million deaths every year, tuberculosis (TB) remains the top killer infectious disease in the world. This disturbing figure persists despite the availability of the Bacillus Calmette-Guérin (BCG) vaccine. However, this vaccine has shown largely inconsistent effectiveness across populations with different living standards. This variability has been mainly attributed to biological factors, however they do not fully explain this phenomenon. What is missing in this picture is the understanding of how social determinants may also play a role at influencing individuals' immunity and ultimately BCG efficacy.

The lack of research in this area is paradoxical for at least two reasons: a) TB has been historically described as a disease of poverty, whose epidemiology and control are still largely driven by socioeconomic factors; b) Despite the efforts, there is currently no new, better TB vaccine in the pipeline that may become available reasonably soon. At the same time, mathematical modelling studies seem to suggest that the fight against TB could be significantly enhanced if the current, albeit imperfect, TB vaccine was complemented with socioeconomic interventions addressing extreme poverty.

We argue that combining socioeconomic interventions with BCG administration could enhance the response to BCG among impoverished children. If our hypothesis is correct, this could become an innovative,

alternative model to improve vaccine R&D strategies to TB and other diseases of poverty.

With this grant we aim to assess preliminarily the validity of this interdisciplinary model. Specifically, we will undertake 12 months of formative research to test the scientific appropriateness and feasibility of this approach to TB vaccine R&D. The knowledge so generated will inform a more ambitious scientific proposal to evaluate the actual impact of poverty-reduction strategies on BCG efficacy in a cohort of children in at least two low and middle-income countries.

Dr Panjaporn Chaichana, MORU, Thailand

Project funded in round 1 and led by Dr Panjaporn Chaichana (MORU), with Prof Susanna Dunachie (University of Oxford), and Assoc Prof Helen Fletcher (LSHTM)

Establishment of a functional assay panel to evaluate the role of antibodies in defence against melioidosis and tuberculosis

Melioidosis is an infectious disease and a major cause of death in lower and middle income countries including Thailand. It is caused by a bacterium named *Burkholderia pseudomallei* mostly found in rice paddies. Each year thousands of people living in environments contaminated with the bacteria are infected, and nearly half of them die. The bacterium is classified as a potential bioweapon, and commonly-used antibiotics cannot completely cure the disease.

The symptoms of the disease are more severe and deadly in patients whose immune systems work abnormally, including people with diabetes, renal disease, alcoholism and increased age. Antibody-based strategies are the most promising ways to prevent and treat melioidosis. We wish to identify which types of antibody provide protection against disease and how they work.

B. pseudomallei has some common features with the bacterial cause of tuberculosis: *Mycobacterium tuberculosis*, including the intracellular nature of the bacteria and an overlap in clinical disease such as lung symptoms and abscesses formation. This project will make the most of these similarities by combining experimental expertise in the development of antibody assays to define protective antibody profiles.

First, we plan to develop five tests that measure important actions of antibodies in protection against bacterial infection, which have never been done in the melioidosis field. This will be a collaboration between a Thai scientist and scientists at the London School of Hygiene and Tropical Medicine, who have developed expertise in tuberculosis immunology. Then we will measure and compare the actions of antibodies between patients who survived melioidosis and those who did not survive, to identify significant factors in protective responses. The work on melioidosis will in turn inform the further development of antibody assays for the TB. Results from this study will help develop vaccines and new antibody-based therapies for both diseases.

Overcoming innate immune tolerance in the respiratory tract for optimal vaccine design

Mucosal (i.e. non-injectable) administration is a preferred route of vaccine delivery against pathogens that infect mucosal tissues. *Mycobacterium tuberculosis* (Mtb) enters via the respiratory

Dr Rajko Reljic, SGUL, UK

Project funded in round 1 and led by Dr Rajko Reljic (SGUL) with Prof Tracy Hussell (University of Manchester)

tract and infects lungs. Therefore, mucosal vaccination against tuberculosis would be highly desirable, for both practical reasons of the ease of vaccine delivery but also for enhanced protection, since the vaccine would engage the same immune tissues and mechanisms that the pathogen encounters itself. However, one significant roadblock in a mucosal vaccination strategy is the difficulty in inducing robust immune responses compared to systemic vaccination. This, we believe, is due to the high immune tolerance levels in mucosal tissues and the anti-inflammatory manner in which antigens are removed. For example, the phagocytic activity of lung alveolar macrophages may destroy the vaccine without effectively engaging the adaptive immune response. Another aspect is the removal or degradation of the vaccine by the mucosal fluids. To overcome these obstacles, we will study in detail the role of alveolar macrophages in mucosal vaccination. We will also attempt to bypass the macrophages by targeting novel vaccine constructs to the alveolar epithelium, leading to longer vaccine persistence and better access to the immune cells of the submucosa.


Dr Javier Salguero Bodes, PHE, UK
Dr Isadora dos Santos Lima, Oswaldo Cruz Foundation, Brazil

Project funded in round 1 and led by Dr Javier Salguero (PHE), with Dr Isadora dos Santos Lima (FIOCRUZ), Assoc Prof Daniela Farias Larangeira (UFBA), Dr Deborah Fraga (FIOCRUZ), Dr Geraldo Sá Oliveira (FIOCRUZ), Dr Washington dos-Santos (FIOCRUZ), and Prof Luiz Freitas (FIOCRUZ)

The effect of BCG vaccination in immune responses against visceral leishmaniasis in a natural (canine) model of infection

Visceral leishmaniasis (VL) is the most severe clinical form of leishmaniasis due to frequent complications and the risk of developing into untreated death. It is a zoonosis with high prevalence and wide distribution by the world. In urban areas, the dog is considered the main reservoir of VL due to its close relationship with humans. Canine disease is also considered valuable for the understanding of human disease, since the clinical presentation in both species show similarities.

Several drugs have been used in the treatment of VL; however, some of them are not recommended by the world health organization for use in veterinary medicine, in order to avoid the parasite's resistance to active principles. Immunotherapy involves the use of biological substances or molecules to modulate immune responses in order to achieve prophylactic and / or therapeutic success. Immunotherapy with or without chemotherapy has been used for the treatment of leishmaniasis. Several studies have described that the use of immunotherapy helps to reduce the clinical signs, the dose of drugs and the time of the treatment.

The BCG vaccine is widely used to prevent tuberculosis and originates from attenuated strains of Mycobacterium bovis. The main mechanism of action of BCG induced protection has been described as mediated by Th-1 cells. The BCG vaccine has been studied as a possible immunotherapeutic for the control of leishmaniasis. Studies with murine models have shown that the use of BCG associated with conventional treatment helps to reduce the parasite burden, the severity of clinical manifestations, and helps increasing the resistance of macrophages to infection, also increasing the capacity of these cells to kill the parasite.

The present study aims to evaluate the effects of BCG vaccination administration on the clinical presentation and parasite load of naturally infected dogs from an area endemic for visceral leishmaniasis.

Asst Prof Steve Smith, LSTHM, UK

Project funded in round 1 and led by Asst Prof Steven Smith (LSHTM), with Dr Javier Sanchez (Instituto Politécnico Nacional), Prof Jo Prior (dstl), and Prof Gregory Bancroft (LSHTM)

How do functional and metabolic characteristics of trained monocytes affect their anti-bacterial activity?

The human immune response has two components, the innate and the adaptive responses. This project will investigate the potential of the innate response to contribute to protection against tuberculosis (TB) and melioidosis. TB remains a major global problem being one of the world's leading causes of death from infectious disease. In addition to better drugs and better means of diagnosing TB, we also need a better vaccine. The current vaccine, BCG, is only partially effective and an improved version is needed. However, many novel TB vaccine candidates focus on the adaptive immune response involving T-lymphocytes as this is where immune memory is found which is essential for vaccine-induced protection. We think that an optimal innate response is also essential. It has recently been discovered that the innate response can be "trained" by some vaccines to respond better to later infections. In this project, we aim to investigate this training effect on the innate response to a) determine how best to train innate cells to prevent the growth of the causative organisms of TB and melioidosis; b) characterise these trained innate cells to find which immune molecules are important for their protective effect and how the metabolism (or biochemical energy production pathways) of these cells affects the trained response and c) to investigate why innate cells from different people do not respond in the same way to training – to do this we will look at differences in the DNA of immune cells (termed epigenetic marks) which cause these cells to produce different immune molecules when exposed to the same microorganism. The data produced by this project should help us understand better how different components of the immune response contribute to protection against TB and meliodosis and should aid the design of better vaccination regimes for bacterial diseases.

Dr Louise Gourlay, Università degli Studi di Milano, Italy

Project funded in round 2, and led by Prof Gregory Bancroft (LSHTM), with Assistant Prof Louise Gourlay (University of

In vivo protection studies of chimeric *Burkholderia pseudomallei* antigens presenting multiple epitopes on protein scaffolds and outer membrane vesicles

To develop vaccines against microbes that cause serious infection in humans, we must identify their protein (antigen) components, which activate the lymphocytes of the immune system. Many organisms have too many proteins to test individually; therefore efforts to identify immunoreactive molecules should be highly focused and based on sound scientific rationale. If we know how a protein antigen is structured in three-dimensions, and we know the location and conformation of the immunoreactive portion of the molecule, this information can be used to design an improved, more reactive antigen. This so called structural vaccinology (SV) strategy is proposed by experts

Milan), Prof Martino Bolognesi (University of Milan), Prof Giorgio Colombo (University of Pavia), and Assistant Prof Ganjana Lertmemongkolchai (Khon Kaen University)

in the field to drive the design of future vaccines targeting challenging diseases such as AIDS and cancer.

We applied a SV approach to protein antigens from the bacterial human pathogen *Burkholderia pseudomallei* that causes high mortality in tropical countries; there is no current vaccine to combat this infection, and antibiotic treatment is prolonged and often unsuccessful. In particular, we used antigen 3D-structure information and knowledge of the location of the immunoreactive portions (epitopes) to design new protein antigens. Each protein antigen was specifically engineered, using recombinant DNA technology, to present multiple epitopes from two known antigens that induce partial immune protection. The main aim is to evaluate the ability of these engineered antigens and peptide epitopes to protect mice against melioidosis, when presented on the surface of outer membrane vesicles (OMVs). Many bacteria naturally produce OMVs, which are naturally immunogenic and thus ideal vaccine delivery vessels. The immune response, by both engineered protein antigens and epitopes presented on OMVs, will be compared as a first step towards vaccine development.

Dr Mohamed Osman,
University of York, UK

Project funded in round 2, and led by Dr Mohamed Osman (University of York), with Prof Paul Kaye (University of York), Dr John Pearl (University of Leicester) and Prof Andrea Cooper (University of Leicester)

Identification of Leishmania donovani and *Mycobacterium tuberculosis*- derived proteins on the surface of infected macrophages that are associated with ADCC induction

Leishmaniasis and tuberculosis (TB) are globally important infectious diseases, with a major impact on human health. They are caused by pathogens that have adopted an intracellular lifestyle, living within cells of the immune system called phagocytes. Both diseases have a negative prognosis when associated with HIV infection. No effective vaccines are available, despite intense effort, particularly in the case of TB. Drugs treatment regimens are prolonged which may result in patient non-adherence and increased toxicity, and the emergence of drug resistance and / or an increase in treatment failures is a major threat.

Our understanding of what constitutes protective immunity in TB or leishmaniasis is incomplete and indeed it is possible that immune responses not normally provoked during infection may prove more amenable to manipulation and have greater efficacy than those induced during natural infection. We propose to investigate the potential for a form of immunity which involves the production of antibodies against pathogen-derived molecules expressed on the surface of infected cells and their recognition by “killer cells”. Our hypothesis is that these antibodies will be able to help the killer cells to remove Leishmania and Mycobacterium tuberculosis (Mtb)-infected cells from the body. In this proposal, we will identify pathogen-derived molecules expressed on the surface of infected phagocytes and determine whether they are recognised by pathogen-specific antibodies. This is a critical first step to evaluating whether enhancing this mechanism of immunity will help control disease. This project has the potential to provide new candidate molecules for vaccine development and to promote the development of novel recombinant antibodies that can be used to treat patients. Hence,

this proposal seeks to generate new tools for the fight against leishmaniasis and TB.

Prof Susie Dunachie,
University of Oxford

Project funded in round 2, and led by Associate Prof Susanna Dunachie (University of Oxford), with Assistant Prof Jacqueline Cliff (LSHTM), and Prof Gregory Bancroft (LSHTM)

Vaccines to target people with diabetes: characterising the pathways of immune response to *M. tuberculosis* and *B. pseudomallei* in people with diabetes compared to non-diabetics

A better vaccine is urgently required for tuberculosis (TB), and there is no vaccine at all for the neglected tropical disease melioidosis. Both diseases are caused by bacteria that live inside cells, and there are shared defence mechanisms. People with diabetes are at increased risk of getting ill with TB (three-fold increased risk) and are twelve time more likely to develop melioidosis than non-diabetics. We therefore need to understand why people with diabetes get ill with these bacteria, and how diabetes prevents the body from clearing the infection.

We will combine expertise at the London School of Hygiene and Tropical Medicine, Mahidol- Oxford Tropical Medicine Unit in Bangkok and the University of Oxford, to study the pattern of human immune response to TB and melioidosis in people with and without diabetes. To do this, we will use “transcriptomics” - the big-scale study of the gene readouts from the body’s DNA (“transcripts”) which are instruction messages for protein manufacture carried as ribonucleic acid (RNA). By measuring the pattern of RNA in a person’s blood, we can compare which immune pathways are active in different groups of people. We will identify differences in the pattern of responses in TB patients with and without diabetes, see how they relate to cure from TB, and then compare the results with responses in melioidosis patients with and without diabetes.

We will detect the most important protective immune response pathways which are seen in nondiabetic patients but are lacking in people with diabetes. This will allow us to design better vaccines for TB and melioidosis that work well in people with diabetes, and can also help us develop ways to use medicines at the time of vaccination to boost immune responses in people with diabetes.