CFP-NTD2023 Summaries

850.000 euros | **Molecular dissection of leprosy immunopathology to inform the use of novel therapeutics. Dr Gabriele Pollara - University College London and Hospital for Tropical Diseases, London, United Kingdom.**

Leprosy is a disabling and highly stigmatised neglected tropical disease. More than 200,000 cases are reported to the World Health Organization each year but this number is likely an under-estimate. Leprosy is caused by infection with the bacterium Mycobacterium leprae and can cause a range of clinical symptoms that affect the skin and nerves, leading to pain, numbness, loss of function and permanent deformity. There is effective antibiotic treatment for the initial infection, but despite effective killing of the bacteria, approximately 50% of individuals experience severe inflammatory complications called 'reactions'. Leprosy reactions are not the result of relapsed infection, but are due to the person's immune system causing inflammation which damages the skin, nerves and other organs. There are different ways to classify reactions, but they are all painful and result in nerve damage, which can cause disability. It is not currently possible to predict which individuals will develop leprosy reactions and the specific changes in the immune system responsible for them are unknown.

Large doses of immunosuppressive steroid tablets are the first line treatment to control the severe inflammation of reactions. These steroids need to be taken for many months for a long time and they cause significant adverse effects, including infections, high blood pressure, cataracts, weight gain, diabetes and osteoporosis. Steroids control the inflammation but do not address the underlying immune mediated cause of the reactions. Not all individuals respond well to steroids, and patients often experience deterioration in symptoms and further disability. Therefore, there is an urgent need to 1) predict which patients will develop reactions 2) discover better treatments than steroids to treat the underlying immune dysfunction of the reactions.

The project team will recruit people with leprosy from two world leading centres of leprosy care in Ethiopia and UK, and focuses on the aspects of the immune response that cause leprosy reactions. Small skin biopsies will be taken from skin affected by leprosy and reactions to look whether specific immune genes are more or less active in each type of reaction. This will allow the team to identify the ones most important for causing reactions. The leprosy patients will be followed for up to 2 years. In addition, it will focus on individuals in whom leprosy reactions do not respond well to steroids, so that they can see what kinds of immune responses remain elevated despite steroid treatment.

The project will provide the most detailed analysis of the immune processes associated with the most disabling and hard to treat aspects of leprosy. By discovering immune components associated with reactions, the project could justify treating leprosy patients early before they develop complications from reactions, and to identify new therapies that target aspects of immune responses that are not affected by steroids.

Leprosy (who.int)

849.500 euros | **Development of the first Scabies Rapid Antigen Test System for Point-of-Care. Prof Katja Fischer - QIMR Berghofer Medical Research Institute, Brisbane, Australia.**

Scabies is a highly contagious disease caused by microscopic parasitic mites that live in the upper layers of the skin. The mites are invisible to the naked eye and are easily transmitted between humans. With an estimated 500 million annual cases scabies ranks as one of the commonest skin diseases worldwide and has a higher incidence than melanoma and keratinocyte carcinoma. The scabies mite causes extreme itching, and scratching damages the skin allowing for bacteria to breach this important barrier, giving rise to severe downstream complications.

Scabies is a truly neglected tropical disease, most prevalent in poor and overcrowded populations with limited or no access to health services. The diagnosis of scabies, especially at an early stage, is challenging. There are numerous skin conditions with symptoms very similar to scabies, but no reliable, practical molecular test exists to

differentiate scabies from other disorders. Unrecognized scabies cases are the prime source of ongoing spread and outbreaks. We urgently need a safe and efficient skin sampling method combined with a new generation rapid antigen test (RAT) that can be performed by an untrained user. The projects aims to develop a test that works in principle like a pregnancy test or a covid RAT. The team has identified scabies biomarkers in scabies skin samples that can be detected using this type of technology. They will develop a device that can be used at multiple common infection sites (wrists and hands) or where itching occurs and will then be dipped into a tube with in-house buffer, closed and mixed by shaking. Then a few drops of the sample/buffer solution will be transferred with a supplied dropper to the test strip. Soon after the result can be seen: If two coloured lines appear, the test is positive, which means that the tested person has scabies. If only one line appears, the test was performed correctly and the tested person does not have scabies.

The research team combines scabies molecular biology and innovative diagnostics expertise provided by two research laboratories at high level medical research institutions. They are joined by teams providing the dermatological expertise needed for this project to be successful. The proposed project will deliver a field-trial tested prototype RAT kit for scabies diagnosis and implementation will be streamlined in negotiation with industry to impact as soon as possible on scabies prevalence in endemic regions.

Scabies (who.int)

850.000 euros | **Understanding the link between immune pathology, hypopigmentation and pathogen control in Post kala-azar Dermal Leishmaniasis (PKDL) and Leprosy. Dr. Susanne Nylen - Karolinska Institutet, Stockholm, Sweden.**

The infectious diseases post kala-azar dermal leishmaniasis (PKDL) and leprosy both present with stigmatizing skin disease that can cause ostracization and a major impact on quality of life. The Leishmaniases are a group of neglected tropical diseases (NTDs) caused by >20 species of parasites collectively termed Leishmania. Depending on the infective species and host immune response, infection can result in a wide range of clinical features. The systemic and fatal form called visceral leishmaniasis (VL) or kala-azar can after therapy and recovery sometimes reappear in the skin as a sequel termed PKDL. PKDL presents with different types of skin lesion (a) white patches (macules) or (b) small pimple-like swellings (papules) and/or larger nodules or (c) a combination of macules and papules/nodules (polymorphic PKDL).

Patients with PKDL do not always actively seek treatment, as the macules can be confused with another skin NTD, namely leprosy – a chronic bacterial disease caused by Mycobacterium leprae. The macular variant of PKDL is akin to the tuberculoid form of leprosy, in that both present with loss of skin pigment (melanin), a low pathogen burden, and minimal infiltration of immune cells. Importantly these forms are difficult to treat. On the other hand, the polymorphic variant of PKDL shares similarities with the lepromatous form of leprosy in that both have a high pathogen load, a considerable degree of immune cell infiltration, and respond well to treatment. Since PKDL cases harbour parasites in their skin, they are potential disease reservoirs. Thus, when bitten by the sandflies spreading disease, PKDL patients can contribute to the VL transmission cycle. Thus, it is important to effectively treat PKDL cases, yet the treatments are long-term, coupled with substantial side effects and safer treatments are needed.

Therapies targeting the local immune responses can be a way forward, but such requires an increased understanding of the 'immune landscape'. In the absence of animal models for PKDL and leprosy, knowledge about immune-mediated skin pathogenesis and how this is linked to pathogen control remains limited. Building on partnerships established between clinical and basic researchers we will undertake detailed and high-resolution analyses of skin reactions in PKDL and leprosy to investigate the clinical spectrum of these diseases to delineate the relationship between hypopigmentation and pathogen. The role of adaptive T cell immune response and epithelial cells will be studied to address their impact upon (i) loss of pigmentation and pathogen control in macular PKDL and tuberculoid leprosy and (ii) the failure to control pathogen growth and development of nodular/polymorphic PKDL and lepromatous leprosy (Figure A1). The project envisions that by applying high-resolution and molecular analysis, the combined study of the two diseases will provide detailed information on cell mediated immune and antimicrobial responses operating in the skin. This can enhance understanding of these diseases and their clinical manifestations so as to propose effective therapeutic strategies.

The post Kala-azar dermal leishmaniasis (PKDL) atlas (who.int)