CAMO (COMPARING ANIMAL MODELS TO ORGANOIDS) - TESTING MEDICAL COUNTERMEASURES WITH MICROPHYSIOLOGICAL SYSTEMS AND COMPARING TO TRADITIONAL ANIMAL MODELS AND CLINICAL TRAILS

The Development Of Nhp Ex Vivo Tissue Models To Assess Host-pathogen Interactions And Medical Countermeasures

Michelle Nelson Dstl **Rachel Ireland** Dstl

There is a requirement for the development of effective medical countermeasures against biological agents considered to be a threat to operational effectiveness. This involves understanding both the host-response to the pathogen and the effectiveness of medical countermeasures. Much of this research is undertaken in animal models of disease due to the rarity, and therefore lack of opportunities, to study the disease in humans. However, there is a moral and ethical duty to ultimately reduce and replace the use of animals for scientific research. Microphysiological systems (MPS) are being developed for this purpose. The aim of this work was to develop ex vivo tissue models using primary cells obtained from a small, New World Monkey, the common marmoset (Callithrix jacchus). Marmoset models of infectious diseases have been used at Dstl to understand disease caused by a number of bacterial and viral agents, as well as to assess medical countermeasures. Therefore data from the ex vivo models can be directly compared to in vivo data. Lung and bones were extracted from ex-breeder marmosets that were otherwise surplus to requirements. Hematopoietic stem cells were isolated from thigh bones and cultured to produce bone marrow-derived macrophages (BMDMs). Single cell suspensions of lung tissue were prepared and ATII cells isolated following digestion, centrifugation and enrichment. BMDM were used to assess the ability of two antibiotics to control the intracellular growth of B. pseudomallei. A greater reduction in bacterial counts was observed for both antibiotics in the marmoset cell assay compared to a similar assay using J774.2 cells, and was consistent with in vivo data. ATII cells were used to understand the interactions between the ACE2 receptor and SARS-CoV-2 in marmosets. Expression of the human ACE2 receptor, using an Ad5-huACE2 vector, in this model rendered cells permissive to infection. Significantly higher quantities of virus were released from marmoset lung cells expressing the human ACE2 receptor compared to wild-type cultures. This again was consistent with in vivo data. These marmoset ex vivo tissue models described can provide insight into host-pathogen interactions and efficacy of antimicrobials and may be further developed to predict responses in humans.