Project Details	
Project Code	IIAR27Ca Stanton
Title	Optimising immune responses against emerging viruses
Research Theme	Infection, Immunity & Antimicrobial Resistance
Project Type	Wet lab
Summary	Worldwide, viruses that transmit to humans from biting insects account for ~17% of infectious diseases and ~700,000 deaths/yr, with ~4 billion people at risk. Climate change, population density, and deforestation, all increase the chances of outbreaks occurring. Oropouche and Mayaro are endemic in Brazil and frequently spill over into humans, with recent outbreaks leading to cases across Europe and North America. Yet we have no vaccines against them and know very little about which immune responses are optimal to control these pathogens. This PhD aims to address this knowledge gap as the basis for vaccine development against (re)emerging virus threats.
Description	Climate change has accelerated the global spread of insect vectors that transmit viruses, whilst increased human population density and deforestation increases the chances of human contact with infected animals. Outbreaks are predominantly caused by arboviruses, which account for ~17% of infectious diseases and ~700,000 deaths/yr worldwide, with ~4 billion people at risk. The Amazon forest is a megadiverse region and home to the greatest diversity of arboviruses globally. Of ~500 known arboviruses, ~200 are in the Amazon rainforest. Deforestation and rural settlement construction in the Amazon can lead to outbreaks, amongst which Mayaro (MAYV) and Oropouche (OROV) are neglected arboviruses that cause significant disease, with both virus families UKHSA priority pathogens. OROV has caused multiple outbreaks of neglected-febrile illness since 1960, infecting >500,000 people. In 2023-2024, OROV re-emerged in South/Central America and was imported into Europe and America. Disease includes fever, severe headache, myalgia, arthralgia, polyuria, epigastric and retro-ocular pain. ~5% of cases develop signs of CNS infection (e.g., nystagmus, diplopia, loss of balance), or Guillain Barré. Reports imply vertical transmission with congenital abnormalities and fetal loss. MAYV (a togavirus) emerged in the 1950s and has been imported into Europe. It has caused large outbreaks with seroprevalence up to 72%. Infection is associated with acute/chronic arthralgia, chills, arthritis that can persist for years, and neurological complications. Loss of productivity and subsequent economic/public health impact are significant. Despite this, we have no vaccines or immunotherapies, nor any significant understanding of the immune responses that control them. Neutralising antibodies that inhibit cell-free virus entry, are a critical component of immunity, are readily generated using entry glycoproteins as immunogens, and are currently being studied. However, once a virus has established intracellular infection it is protected from these responses. As a result, immune responses that target the infected cell through binding to cell surface viral antigens and recruiting cellular immunity become critical. We have shown that the antigens and the epitopes that induce these activities can differ substantially from those that promote neutralisation. Therefore, as the basis for optimal vaccines

	and immunotherapies against MAYV and OROV, this PhD will characterise the ability of non-neutralising antibodies to promote recruitment of cellular immunity to attack OROV/MAYV infected cells. Question 1 – how does infection change the proteome of the infected cell surface? Our previously developed plasma membrane profiling technology uses cell-surface enrichment and quantitative proteomics to determine which proteins are on the cell surface, and how infection alters protein abundance across the entire proteome during a time course of infection. We used this to identify vaccine/immunotherapeutic targets in SARS-CoV-2 and HCMV, and will now deploy it against OROV/MAYV. As well as identifying therapeutic targets, this will also reveal whether these viruses manipulate cell-surface antigens in order to alter cellular immune responsiveness to the infected cell – for example we found that both SARS-CoV-2 and HCMV inhibit expression of activating ligands for Natural Killer (NK) cells. Such changes increase the activation threshold that antibodies must induce for efficient killing of the virus, and must be accounted for in downstream functional assays. Question 2 – which viral antigens are targets for antibody-induced cellular immune control of the infected cell? Having identified cell surface viral antigens, we will identify potential vaccine/immunotherapeutic targets through expressing each individually in the presence of serum from naturally infected individuals (as a source of antibody - serums will be supplied by collaborators in Brazil), then carrying out established assays for antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Question 3 – can we induce antibodies targeting these antigens/epitopes through vaccination, and are they effective? Co-I Anu Goenka specialises in the use of Tonsil Organoids, which enable vaccination studies to be carried out directly in human tissue. These unique reagents will be used to generate antibodies targeting the antigens and/or epitopes of interest, which can then be tested as in Question 2. Vaccines will be based on our established RNA and Adenovirus platforms, to determine if one is superior for inducing effective responses. We will also compare vaccine-induced responses with those raised against natural infection, since preliminary data indicates that both OROV and MAYV replicate efficiently in Tonsil Organoids.
Can be completed part time?	No
Supervisory Team	
Lead Supervisor	
Name	Professor Richard Stanton
Affiliation	Cardiff
College/Faculty	Life Sciences
Department/School	Medicine
Email Address	Stantonrj@cardiff.ac.uk
Co-Supervisor 1	
Name	Dr Ceri Fielding
Affiliation	Cardiff
College/Faculty	Life Sciences

Department/School	Medicine
Co-Supervisor 2	
Name	Dr Anu Goenka
Affiliation	Bristol
College/Faculty	Cellular and Molecular Medicine
Department/School	Immunology
Co-Supervisor 3	
Name	Professor Eddie Wang
Affiliation	Cardiff
College/Faculty	Life Sciences
Department/School	Medicine