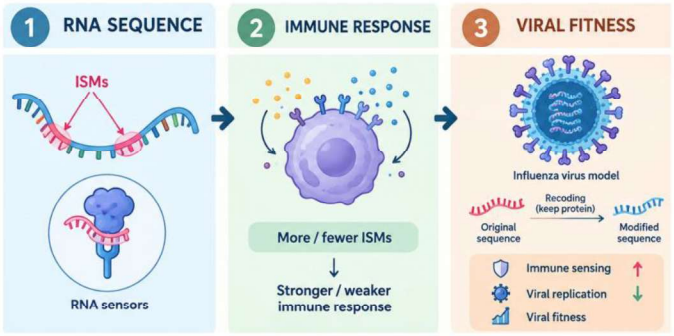
RNA sequence and innate immunity: defining the role of immunostimulatory motifs in viral genomes

Project ID: 3631

Supervisory team

Main supervisor: Dr Jamie Mann (University of Bristol)
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Other supervisors: Dr Behroz Khan (University of Bristol)
Collaborators: Dr Allen Haddrell (University of Bristol), Prof Paul Wigley (University of Bristol), Prof Eric Arts (Western University)

Host institution: University of Bristol



Project description: The problem:RNA sequence influences innate immune activation through immunostimulatory motifs (ISMs), which can activate RNA-sensing pathways. However, the prevalence, and biological consequences of ISMs in important RNA viruses remain poorly understood.Our preliminary proof-of-concept studies using retroviral genomes identified a relationship between ISM prevalence and innate immune activation, providing a strong rationale to investigate whether this represents a broader and exploitable feature of viral RNA biology.This project will investigate ISMs in RNA viruses of veterinary and One Health importance, initially using influenza virus as a model, and translate these findings into rationally engineered viral and therapeutic RNA. The key innovations:1. Establishing ISMs as determinants of viral RNA immunogenicity: Defining how ISM abundance and sequence composition influence innate immune activation, building on preliminary observations in retroviral genomes.2. Engineering viral RNA immunogenicity: Using rational recoding to manipulate ISM content while preserving protein sequence and determining how this alters innate sensing and viral replication fitness.3. Translating viral RNA biology to RNA therapeutics: Applying the resulting design principles to therapeutic RNA to determine how sequence can be optimised to balance innate immune activation and efficient translation. Challenges:RNA recoding can affect multiple properties, including innate sensing, stability, translation and viral replication. Combining computational design, synthetic RNA, reporter assays, primary cells, recombinant viruses and in vivo studies will allow ISM-dependent effects to be distinguished from other consequences of sequence modification. Aim:To define how ISMs in viral RNA regulate innate immune activation and determine how rational RNA recoding can be used to manipulate viral fitness and use these findings to generate next-generation RNA design rules for vaccines and therapeutics. Objectives:Identify and characterise ISM-associated innate immune activation in influenza RNA.Determine how RNA recoding alters IRF/NF-κB activation and responses in primary PBMCs.Establish the effects of recoding on influenza replication fitness and infection in vivo.Translate these findings to RNA therapeutics, determining how RNA sequence can be optimised to balance innate immune activation with translation. The student will gain expertise in molecular virology, RNA biology, innate immunology, computational biology and translational RNA therapeutics, addressing fundamental questions with veterinary and human One Health relevance.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.