AI-Driven Discovery of Modulators of Nucleic-Acid Sensors in Inflammation and Ageing

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Project Description

Nucleic-acid sensing pathways are central components of the innate immune system, responsible for detecting misplaced DNA or RNA as signals of infection or cellular damage. Key sensors such as cGAS, RIG-I, MDA5, AIM2, and selected TLRs initiate potent inflammatory programmes when activated (1). While essential for host defence, inappropriate or chronic activation of these pathways has been directly linked to age-associated inflammation ("inflammageing"), sterile tissue damage, metabolic dysfunction, and multiple age-related diseases. In particular, aberrant cGAS activation by cytosolic or nuclear DNA contributes to senescence, SASP induction, and persistent immune signalling (2). As a result, discovering specific inhibitors or modulators of nucleic-acid sensors may represent a promising strategy to help limit maladaptive inflammation and potentially support healthier ageing.

This PhD project aims to develop an artificial-intelligence-driven platform for the discovery of small-molecule and peptide modulators of nucleic-acid sensors, with an initial focus on cGAS. Recent advances in large language models and generative AI have transformed the landscape of drug discovery, enabling the design and prioritisation of compounds that exploit structural and biochemical features learned from vast protein and chemical datasets (3). We will leverage these approaches to build models capable of generating and ranking candidate binders targeting specific functional surfaces—such as the DNA-binding interface of cGAS, its nucleosome-interaction region, or allosteric pockets that regulate activation. Similar approaches will later be extended to additional RNA and DNA sensors involved in dysregulated innate immune signalling.

The student will construct and refine AI models to:

1. Generate novel compounds (small molecules, peptides, mini-proteins) predicted to modulate nucleic-acid sensors.
2. Screen and prioritise candidates using AI-based scoring of binding affinity, selectivity, stability, and synthetic feasibility.
3. Integrate structural information from high-resolution cGAS-DNA and cGAS-nucleosome complexes to constrain and improve predictions.

Lead compounds identified in silico will then be tested experimentally. Biochemical assays will examine their ability to interfere with cGAS–DNA and cGAS–nucleosome interactions. Promising candidates will be evaluated in cell-based models of senescence, where cGAS–STING activation drives inflammatory cytokine production. This will allow us to determine whether AI-generated molecules can suppress aberrant innate immune activation and dampen the SASP in relevant physiological contexts.

Overall, this project combines AI-based drug discovery, innate immunity, and cellular ageing biology, and will contribute directly to developing targeted anti-inflammatory strategies within our Team Science programme.

References:

1. Kong et al. (2023). Exp. Mol. Med. 55:2320-2331.
2. Zhang et al. (2025). Annu. Rev. Immunol. 43:25.1–25.26.
3. Wang et al. (2025). Nat. Microbiol. 10:2997-3012.