

High throughput computational and experimental approaches applied to the study of the pathogen innate/adaptive immune interface.

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I am interested in recruiting students who are interested in combining computational and experimental approaches to solve biological problems. I have worked for many years on the biology of the antigen presenting cell, the cell which forms the interface between invading pathogens and adaptive immunity. My objective is to understand the three way interaction between pathogen, innate immunity and adaptive immunity, and ultimately to exploit this to improve prevention or treatment of disease. Experimental models active in our laboratory include ovarian cancer, tuberculosis, HIV and Herpes simplex virus. To this end we want to exploit new technologies capable of producing ever larger amounts of data, such as high throughput sequencing, expression arrays and proteomics. But these large data sets need dedicated computational approaches which can analyse, organise and ultimately reverse engineer manageable but realistic models from the data.

I would be interested in recruiting a student to work in any of the three following areas :

1. Sequence analysis of the T cell repertoire. Adaptive immunity is based on the ability of our immune system to generate an extraordinary number of different antigen specific receptors (possibly $> 10^{10}$) by a complex process of gene recombination and editing. Advances in high throughput sequencing (using the technology which has driven the Human Genome Project) now allow us to obtain comprehensive snapshots of the repertoire of receptors present in samples of blood or tissue lymphocytes. This has enormous implications both for diagnosis and also for vaccine design. We are developing laboratory and computational tools to optimally exploit these very large data sets, and will use them to study basic features of the evolution of the T cell repertoire in response to vaccination or infection. These studies will be carried out in collaboration with Prof. Paul Kellam and the Sanger Institute.
2. Building gene networks from expression data. We are building up a large collection of gene expression data on human macrophages and dendritic cells, exposed to different pathogens and immune-modulators. We want to identify the key functional gene units within these cells and describe how they are regulated and regulate cellular function. However, the data is high dimensional and very noisy. We are working with colleagues in Computer Sciences to use machine learning tools to identify and validate gene clusters within this growing data set. As part of a joint programme of research with Dr. Mahdad Noursadeghi, a research scientist and Consultant in Infectious Disease at UCL Hospital we will subsequently explore the function of these networks using molecular cell biology tools such as gene transduction and knockdown.

3. Analysing the MHC peptide repertoire. The repertoire of the CD4 T cell response is determined in large part by the number and sequence of the antigen peptides presented by antigen presenting cells. Advances in mass spectroscopy now make it feasible to elute and analyse peptide repertoires from primary antigen presenting cells such as dendritic cells. We are collaborating with proteomics experts at the University of Ghent, Belgium to analyse peptides eluted from dendritic cells, and to explore the role of antigen uptake and antigen processing on the family of peptides presented.