

# Research Interests

## Overview

I am interested in developing a quantitative understanding of the dynamics of pathogens and immune responses. The work of my group involves the use of mathematical models and computer simulations. We like nothing better than to validate models by confronting them with experimental data — we try to make testable predictions, and in collaboration with experimentalists conduct the relevant experiments. We work in close collaboration with experimental immunologists, in particular the group of Dr. Rafi Ahmed at Emory. Our three main areas of investigation are:

1. **The dynamics of infections and immune responses**

How do immune systems work? What determines whether an infection is short lived or chronic, and whether it generates lasting immunity? The answers to questions could help us design better vaccines, particularly towards persistent infections such as malaria and HIV.

2. **Linking immunology and epidemiology**

Immunology and epidemiology are traditionally very different fields, yet they are intimately related. We have developed a theoretical framework to connect the within-host dynamics of a pathogen with its transmission characteristics. We have used this framework to understand why pathogens harm their hosts, and under what conditions we expect a pathogen's virulence to change.

3. **The emergence, spread and evolution of infectious diseases**

How do pathogens emerge and spread through host populations? By addressing these general questions we can gain insight into the factors that have led to the emergence of HIV, SARS, and new strains of the influenza virus. This will allow us to predict what factors will be important in the emergence of infectious diseases in the future.

## My choice of one key publication in each of these three areas:

1. R. Antia, V. V. Ganusov, and R. Ahmed. The role of models in understanding CD8(+) T-cell memory. *Nature Reviews Immunology*, 5:101–11, 2005.
2. \* R. Antia, B. R. Levin, and R. M. May. Within-host population-dynamics and the evolution and maintenance of microparasite virulence. *American Naturalist*, 144: 457–472, 1994.
3. R. Antia, R. R. Regoes, J. C. Koella, and C. T. Bergstrom. The role of evolution in the emergence of infectious diseases. *Nature*, 426:658–61, 2003.

\* A more recent publication would be V. V. Ganusov, C. T. Bergstrom, and R. Antia. Within-host population dynamics and the evolution of microparasites in a heterogeneous host population. *Evolution Int J Org Evolution*, 56:213–23, 2002.

## The dynamics of infections and immune responses

How does the immune system work? The first step towards answering this is to qualitatively describe the various components of the system — here, the pathogen and cells and molecules of the immune system. However, infections exhibit complex dynamics that cannot be explained by a taxonomic approach alone. Understanding immune responses requires a quantitative understanding of the interactions between *populations* of pathogens and immune cells. Mathematical models and computer simulations are the tools we use to develop this understanding.

### Design Principles

Immune systems face a daunting challenge. They need to minimize damage from pathogens, without wasting energy and resources or generating autoimmune responses. They must also be robust against sabotage and deception by rapidly evolving pathogens.

How do we search for the ‘design principles’ that immune systems use to satisfy these requirements?

[11–13]

One way is to look for common themes in the immune systems of very different organisms. Until recently it was believed that only vertebrates possessed “adaptive” immune systems capable of specificity and memory, but it is becoming clear that other phyla have rich and complex defenses that exhibit some or all of these properties – such as the RNA silencing pathway in plants and invertebrates.

[7, 12]

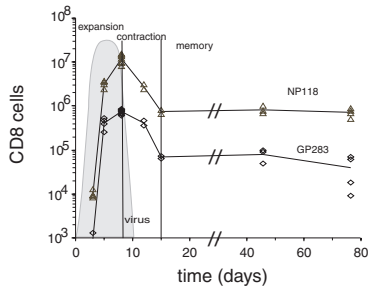
Another way is to infer the general design principles from specific aspects of the immune responses of vertebrates, and we outline our work in this area in more detail below. An example is the ‘programmed’ nature of immune responses — after stimulation, cells capable of effecting an immune response continue to divide largely independently of the presence of the pathogen. We show that while this is an energetically costly strategy, it provides a robust defense against pathogens trying to subvert the generation of immune responses.

Because our work focuses on the immune system of vertebrates we can develop models in close contact with data. We are particularly fortunate to have superb experimental collaborators such as Dr. Rafi Ahmed and Dr. Chris Larsen in the Immunology Program at Emory University, and access to a wealth of quantitative data. Our approach is to start by modeling well-characterized infections of mice and gradually progress to model infections more relevant to human health.

### Acute infections [3, 23, 25]

As a starting point, we study acute infections which are short-lived and generate long-lasting immunity. Most childhood infections fall into this category and are targeted by our most successful vaccines. Particularly useful experimental models are the infection of mice with the lymphocytic choriomeningitis virus (LCMV), and the bacteria *Listeria monocytogenes*. By studying these we aim to understand how immune responses are generated and immunological memory is maintained.

We have focused on CD8 (cytotoxic) T cell responses during acute infections. These cells play a central role by killing cells infected with pathogens such as viruses. There are three phases to the response (Figure 1). During the expansion phase (within a week of infection) the number of CD8 T cells specific for different epitopes of the virus increases from an undetectable level to approximately  $10^6$  to  $10^7$  cells per spleen. This is followed by a contraction phase during which the cell population declines by a factor of between 10 to 100. The final stage is the maintenance of a stable population of cells which confer immunological memory.



**Figure 1: Dynamics of acute infection.** We plot the dynamics of CD8 T cells during acute infections of BALB/c mice with Lymphocytic choriomeningitis virus. The immunodominant (NP 118) and subdominant (GP 283) epitopes are represented by triangles and diamonds respectively. The dynamics of virus is indicated by the shaded area. Data from the laboratory of Rafi Ahmed.

**Estimating parameters**

What processes control these dynamics? To answer this, the first step is to generate quantitative models. We have used these to estimate quantities that cannot be measured directly – for example,

- [14] • the number of naive antigen-specific CD8 T cells prior to infection — a quantity that is below the experimental threshold of detection.
- [19, 26] • the variable division and death rates that underlie the changes in CD8 T cell numbers. We want to disentangle the relative contributions of division and death to the population dynamics of the response, and knowledge of total cell numbers alone only tells us the difference between these quantities.
- [28] • the rate at which CD8 T cells can find and kill infected cells *in vivo*. Experiments allow us to follow populations of labeled target cells following their transfer into immune mice where they are killed by CD8 T cells. We have developed models of the migration and killing processes involved in these experiments and used them to estimate the rate constant for killing of target cells by CD8 T cells.
- [15] • The use of models has also provided insights into the cause of immunodominance — why the immune responses to the different epitopes (such as the NP118 and GP283 responses in Figure 1) have different magnitudes.

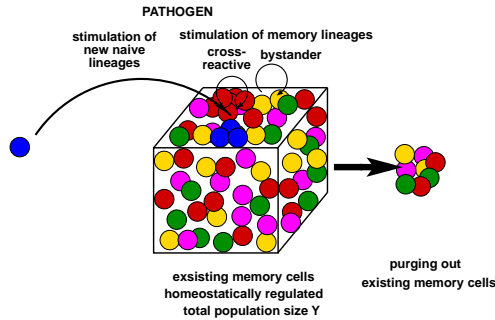
**Testing hypotheses**

Models can also allow us to discriminate between different hypotheses for how the immune system works. The failure of a model to predict experimental observations can be particularly instructive.

- [7] • Conventionally, immune responses have been described in terms of ecological predator-prey models, with the pathogen (the prey) eliciting the proliferation of an immune response (the predator). These models predicted that removal of an epitope from a pathogen should lead to compensatory increases in the responses to other epitopes — and this is not observed. Together with a number of experimental studies this discrepancy led us to develop models for CD8 responses, in which after stimulation, antigen-specific T cells continue to divide in a ‘programmed’, antigen-independent manner. This allowed us to make testable predictions regarding how this program is regulated. This work has given us insights into how the immune system avoids deception by pathogens.
- [9] • By confronting models based on different hypothesis with data we were able to discriminate between two pathways for the origin of memory cells during the primary response. We showed that the experimental data was consistent with a hypothesis in which effector cells differentiate into memory cells during the primary response, and we could reject the hypothesis that effector cells arise by differentiation of memory cells.

[6, 9, 20]

- A major problem in immunology is how the immune system maintains a ‘memory’ of exposure to pathogens and responds faster on reexposure. We have used models to discriminate between different hypotheses for immunological memory (Figure 2). This work led us to a quantitative framework describing the rate at which immunological memory declines. We are currently testing the predictions of our model regarding the loss of memory cells specific for existing pathogens following exposure to new pathogens.



**Figure 2: Longevity of CD8 memory.** *The figure depicts the factors that affect the longevity of different clones of memory cells (shown in different colors) in the memory compartment. Exposure to new pathogens results in the generation of new memory cells as well as the expansion of cross-reactive memory cells and bystander cells. The homeostatic regulation of the size of the memory compartment results in the purging of memory cells. We have used models to examine the effects of all these processes on the longevity of immunological memory.*

## Chronic infections

[1, 2, 5]  
[6, 24]

The most problematic infections, such as HIV, malaria and many others, are those in which the immune system fails to clear the pathogen for an extended period of time. What causes an infection to persist rather than being cleared? This is a particularly important area of research and we have only just begun to work on.

Our approach is to compare (the course of) infections with acute and chronic strains of LCMV. We hope to identify and quantify strain-specific differences in the division and death rates of immune cells. We are particularly interested in using models to develop strategies to enhance the immune response and clear the chronic infection.

## Graft rejection

A transplanted organ or graft, much like a pathogen, is normally recognized as ‘foreign’ and destroyed by CD8 T cells and other components of the immune system. A successfully transplanted organ or graft is analogous to a persisting pathogen. We are exploring this analogy in collaboration with the experimental laboratories of Dr. Chris Larsen and Dr. Rafi Ahmed. In contrast to the LCMV system described above, the aim here is to minimize the immune response and thus allow the graft to persist indefinitely.

## Infectious Diseases

While we can learn a lot of basic immunology by studying infections of mice, for our work to be practically useful it must also be applied to infections of clinical importance such as HIV, tuberculosis and malaria. These are complex diseases, and at present we are a long way from understanding them. However, models can provide answers to carefully chosen questions. As Peter Medawer noted, science is the ‘art of the soluble’.

Thus far we have focused on understanding the dynamics of the initial phase of persistent infections, and particularly on understanding whether the growth of the pathogen is controlled by the immune response or simply the depletion of resources. Our contributions in this area have all involved bringing models into close and potentially risky contact with experimental data.

### *SIV* [27]

In the case of HIV and SIV infection, there has been considerable debate on whether target cell (i.e. resource) limitation is sufficient to control primary infection, or whether specific CD8+ T cell responses are needed. We addressed this question by analyzing data on SIV infections of rhesus macaques. Our results show that target cell limitation alone is not sufficient to bring down the first peak of viremia, and that specific immune CD8+ T cell responses play an important role.

### *malaria* [10]

We are tackling tackled the question of what is responsible for the virulence of acute malaria infections. We have used simple models of the acute stage of the infection together with data from infections with *Plasmodium chabaudi* strains. Our results challenge the widely-held views that the multiplication rate of the parasite in red blood cells (RBC) or the immune response to the parasite determines its virulence (defined as the maximum anemia shortly after infection). We have suggested that the virulence of different strains of malaria is determined by the range of ages of RBC they can infect. We have shown that this hypothesis not only explains the key features of single infections, but can also be used to predict the dynamics of competition between different strains during mixed infections.

## Linking immunology and epidemiology

[4, 18]

Immunology and epidemiology are traditionally very different fields, yet they are intimately linked. Since immune responses play a key role in determining the pathogen numbers within the host, they influence both the degree and the duration of an individual's infectiousness. We have shown how, in principle, it is possible to estimate the epidemiological parameters (namely the basic reproductive number, and the rate constants for transmissibility, recovery and mortality) from the parameters which determine the growth of the pathogen and the immune response.

*Evolution of virulence*

[4, 16–18]

Why do pathogens harm their hosts? The general understanding is that a pathogen must harm its host in order to maximize transmission. We have shown that this trade-off between virulence and transmissibility arises naturally from the immune response of the host. Our results suggest that pathogens should evolve intermediate growth rates and levels of virulence. This is because infections by slower growing pathogens would be cleared by the immune response before they reach a sufficiently high density to achieve much transmission. On the other hand, infections by faster growing pathogens rapidly kill their hosts limiting the time during which transmission can occur. Surprisingly, we find that the optimal level of virulence is very sensitive to many of the details of the interaction between the pathogen and immune system. This suggests that we have to consider the biology of the interactions between each pathogen and its host to understand the evolution of its virulence.

## The emergence, spread and evolution of infectious diseases

*Role of ecological & evolutionary change*

[8, 29]

It is unclear when, where and how novel pathogens such as monkeypox and severe acute respiratory syndrome (SARS), and new strains of the Influenza A virus will cross the barriers that separate their natural reservoirs from human populations and ignite the epidemic spread of novel infectious diseases. New pathogens are believed to emerge from animal reservoirs when ecological changes increase the pathogen's opportunities to enter the human population and to generate subsequent human-to-human transmission. Effective human-to-human transmission requires that the pathogen's basic reproductive number,  $R_0$ , should exceed one, where  $R_0$  is the average number of secondary infections arising from one infected individual in a completely susceptible population. However, an increase in  $R_0$ , even when insufficient to generate an epidemic, nonetheless increases the number of subsequently infected individuals. We have shown that as a consequence of this, the probability of pathogen evolution to  $R_0 > 1$  and subsequent disease emergence can increase markedly. We have subsequently extended this work to take into account heterogeneity in the pathogen and host population.

*antimicrobial resistance*

[21, 22]

We are interested in the emergence of drug resistance in pathogens. Pathogens that evolve resistance to drugs usually have reduced fitness. However, mutations that largely compensate for this reduction in fitness often arise. We are investigating how these compensatory mutations affect population-wide resistance emergence as a function of drug treatment.

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