

## **Work progress and achievements during the period**

Modelling has concentrated on two aspects of pathogen cell biology related to endosome maturation; the role of phosphoinositides (PIPs) and of Rab5-Rab7. Work on phosphoinositides has focussed on the kinase-phosphatase complex and mathematical models have been developed and used to investigate the effect of these complexes on the shape of the dose-response curves; simulations of inactive kinase-active phosphatases leads to the bump-like response curves reported in the literature. Improvements have been made to the automated modelling approaches, particularly in parameter fitting, which makes them more suitable for tackling problems in systems biology, such as phagocytosis. The improved automated modelling techniques have been used to reconstruct a model of endosome maturation, both from simulated and measured data. Other machine learning methods have been developed, such as predictive clustering trees for clustering time series data, and used to analyse a variety of data related to the phagocytosis of intracellular pathogens.

On the experimental side we have set up high-content and high-throughput screening platforms using cell-based assays, and established high-throughput transfection protocols for efficient knock-down in the various phagocytic cells required for the pathogens we are using. All of these assays are now in place and library screening is underway. We have collected a panel of mycobacterial mutants reported to be attenuated in their ability to block phagosomes-lysosome fusion in murine macrophages, and tested their phenotype in human type 1 and type 2 macrophages. This has highlighted a number of differences between the murine and human systems which is under further investigation using *M. tuberculosis* mutants.