Project outline

1. Project outline describing the scientific rationale of the project

*Helicobacter pylori* (HP) is a human-specific bacterium that chronically colonizes the stomachs of 50% of the world’s population. Although most of the infected individuals remain asymptomatic, ~15% develop a number of gastro-duodenal diseases ranging from superficial gastritis and peptic ulcer to gastric cancer and mucosa-associated lymphoid tissue lymphoma. The reasons for such heterogeneity remain unknown, and are likely related to complex interactions involving host and bacterial genetic determinants and environmental factors such as diet.

HP strains are markedly genetically diverse among and within individuals due to their high mutation and recombination rates. HP genomes also show prominent divergence between continents, mirroring the genetic structure in humans. This genetic stratification tracks with human phylogeographic history, and probably reflects geographic isolation and adaptation to genetic differences between ethnic groups. In addition to this macroevolution process, HP has been shown to have a dynamic genome exhibiting within-host variation that evolves over time. This microevolution process typically starts with the transmission of few bacteria from a donor host, followed by population expansion in the new host. This allows the rise of new mutations in their genomes, including adaptive mutations that can rapidly fix in the new population. The size and dynamics of the population within the new host is critical for both the development of immune response and of drug resistance.

Several studies on within-host evolution have shown that recombination plays a pivotal role in genomic diversification of HP, especially in the presence of infection with multiple strains. These studies have started to disclose general patterns of microevolution of HP, but there are still important questions to answer. For instance, how do these mechanisms work to give rise to HP genomes that are more adapted to their ecological niche? Or, if genome diversification leads to phenotypic variation, can it lead to the generation of specific combinations of virulence factors and ultimately disease? Whole-genome sequencing of multiple isolates from a set of individuals will allow to perform a complete analysis of the mechanisms of genomic change and evolution of HP within their host.

We propose an ambitious PhD project that combines microbiological techniques with novel genomics and computational approaches to investigate the patterns of HP evolution in a cohort from the Cape Verde islands in West Africa. Colonized by the Portuguese in the 15th century, Cape Verdeans derived mixed ancestry from Europe and West Africa. Due to the random recombination that occurs over the generations since the first admixture event, present day admixed genomes (both host and HP
genomes) in Cape Verde consist of mosaics of segments with European and African ancestry that are relatively easily to trace computationally. We can explore this property to characterize the history of recombination of HP and its role in the generation of diversification in HP. We are currently following this endemic population to study host-bacterium coevolution and susceptibility to infection.

The specific aims and objectives are:
To characterise the genomic variation of (1) 10 bacterial isolates from each of 10 infected asymptomatic Cape Verdeans, and of (2) 10 infected Cape Verdeans showing indirect signs of gastric mucosa damage (tested in the blood), through whole-genome sequencing using next-generation technologies. To use this data: (1) to infer the haplotypic structure of the isolates in terms of the number of blocks of African and European ancestry and to evaluate the role of admixture in the general population structure of HP; (2) to test for multiple infections; (3) to test for the role of mutation and recombination in generating genomic and phenotypic variation within the host; (4) to identify bacterial loci involved in adaptive responses to immune selection and drug resistance.

Relevance to BBSRC and Approvals

1. How does this project fit within the remit of the BBSRC?

This project lies within BBSRC’s research priority on “Bioscience for health” since it aims to use basic fundamental science to identify critical factors that may pinpoint patients at high risk of developing adverse conditions due to Helicobacter pylori infection. In terms of remit, the work fits within Research Committee B (Plants, microbes, food and sustainability). The study will assemble a unique database that we aim to make public, another strategic research priority of BBSRC.

2. Select the relevant BBSRC Strategic Research Priority:
World Class Underpinning Bioscience

3. How does the project comply with BBSRC’s requirement for multidisciplinarity and new ways of working?

This research combines microbiology with computational biology, genomics, and population and evolutionary genetics approaches and offers to develop a new methodology based on analysis of admixture to study micro-evolutionary patterns of bacterial diversification. This approach will complement molecular and cellular studies of pathogenesis, and will be of special relevance for studies of other bacteria that show divergence among human populations.

4. Please list the techniques that will be undertaken during the project.

The project involves microbial techniques (bacterial isolation and culture, tests for antimicrobial drug susceptibility), molecular genetics (e.g. DNA extraction, DNA library construction, PCR), NGS using paired-end sequencing, and bioinformatics and statistical analyses. The candidate will also have the opportunity to conduct fieldwork in Cape Verde, although this is not really a requirement.