Task 1
Sexual Development

Introduction

Plasmodium berghei is used as a rodent model of malaria. It is known that in the lab it can evolve to stop producing sexual stages (Figure 1). We want to try and use this observation to our advantage. If we can understand how the parasite switches to the sexual, transmissible stage, then we might better understand how to prevent this from happening and prevent the spread of malaria.

Several cultures of a transmissible strain were grown continuously in the lab for several months (Figure 2). These all became gametocyte non-producers (GNPs). The genomes of these strains were then sequenced, the data mapped and the variants called. Your first job is to identify the mutations in these strains, which contribute to the GNP phenotype. Our hypothesis is that while each GNP strain will have many mutations compared to the parental strain, **only one gene will have unique mutations in every strain** and this gene will be a key regulator of gametocytogenesis. Luckily there is evidence from earlier work that the gene is located on chromosome 14, so we need only consider that one!

The variant call files for each mutant are available in the data directory. A full explanation is found in a README file in the directory.

Once you have found the gene you can explore its role in gametocytogenesis. We have RNA-seq data from a strain where the gene has been knocked out allowing us to examine how the gene affects the transcriptional landscape of the parasite. Which transcripts are affected by the knockout of this gene? What does this tell us about the importance of the gene in the switch to sexual development? What could this gene list be useful for in future?

Sequencing reads as well as the reference sequence are available in the data directory (please use this rather than download one). There are also files of genome annotation, product descriptions, GO terms and an R script for performing GO term enrichment. A full explanation is found in a README file in the directory.

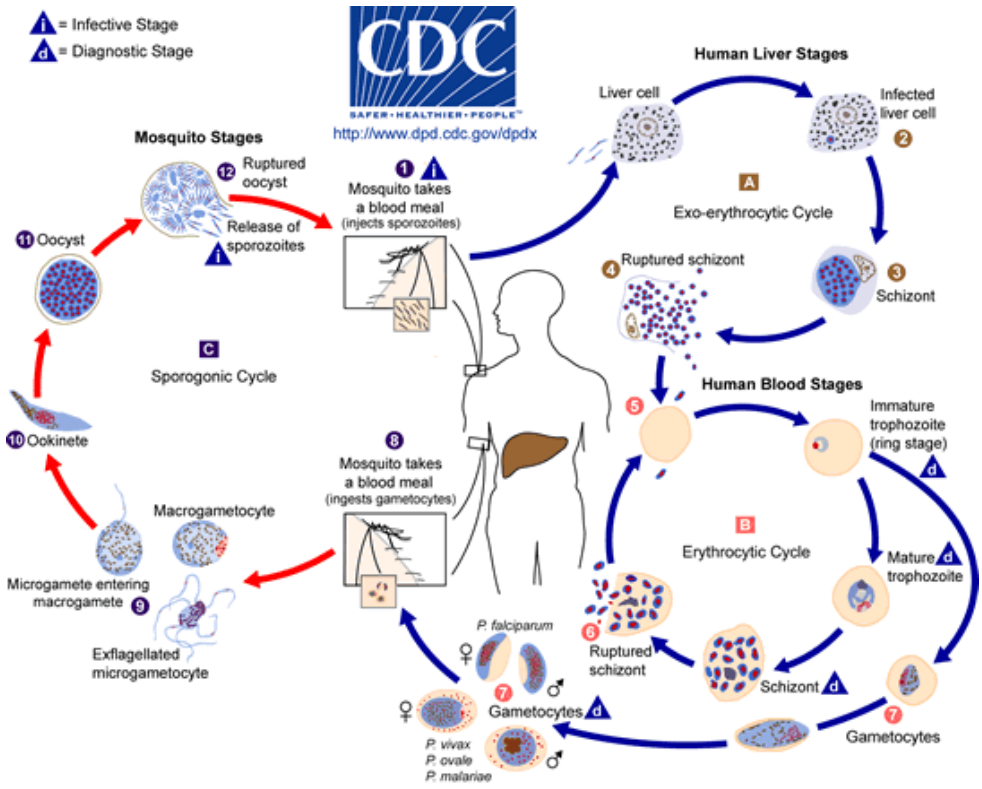

Figure 1. Malaria life cycle. The parasites must produce sexual forms called gametocytes in order to be transmitted from the intermediate mammalian host to the definitive mosquito host.

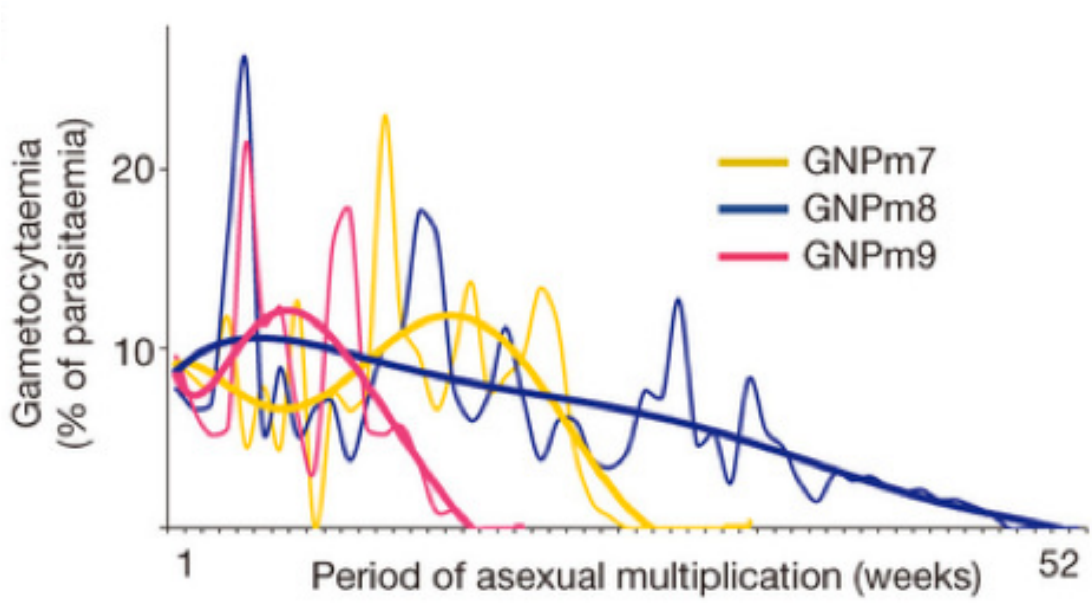

Figure 2. Parasites were passaged continuously in mice until they lost the ability to produce gametocytes. The bold lines show smoothed versions of the real data to even out fluctuations in gametocytemia. GNPm7-9 are different lines of parasites from the same parent which have independently lost the ability to produce gametocytes (transmissible sexual stages).

Summary

To achieve this goal you should:

- View the variant calls in Artemis
- Identify the gene responsible for gametocyte development
- Map the RNA-seq data to the reference
- Confirm the knockout in the mutant samples
- Call differentially expressed genes
- Perform a Gene Ontology enrichment analysis (we have provided an R script to help with this)