Title
Predicting clinical outcomes from transcriptional trajectories in blood

Title and Research Question
Predicting clinical outcomes from transcriptional trajectories in blood

Methods
Clinical presentation and progression of infectious diseases vary between patients. Transcriptome analysis can be used to distinguish phenotypes across scales from individual cells to whole organisms. A novel approach, termed RNA Velocity, has recently been developed to quantify the transcriptional trajectory of single cells, predicting their future transcriptomic and therefore phenotypic states based on ratios of immature to mature RNA. I hypothesised that this approach could be extended predict the future clinical state of patients.

Results
Methods
RNA sequencing was performed on cultured malaria parasites and blood samples from malaria-infected mice and humans. Transcriptional fate maps were produced using principal component and t-SNE approaches. RNA Velocity predictions were overlaid onto fate maps, indicating the transcriptional trajectory of each sample.
Results
Proof-of-concept was demonstrated in synchronous *Plasmodium vivax* parasites, sampled at regular intervals during their 48-hourr intraerythrocytic cycle. Fate mapping showed expected progression of gene expression over pseudo-time, and RNA Velocity predictions identified the correct transcriptional trajectories through the lifecycle. Current work is now proceeding to use blood transcriptomes from malaria-infected mice, with known outcomes of infection (fatal or resolving), to determine whether RNA Velocity can be used to predict outcome of infection. When the algorithm has been optimised, I will apply it predict outcome in human samples.

Conclusion
Conclusion
RNA-velocity can be used to predict future biological state. Further work will focus on validation in larger human datasets with other infections and known clinical outcomes, and development of a method to quantify how well RNA-Velocity predicts future state. This will also involve the incorporation of feature selection techniques to identify the genes that best predict the future biological states.

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Title

ETIOLOGY AND OUTCOME OF FEBRILE CHILDREN COMING FROM THE TROPICS, A MULTICENTER REVIEW

Title and Research Question

ETIOLOGY AND OUTCOME OF FEBRILE CHILDREN COMING FROM THE TROPICS, A MULTICENTER REVIEW

Methods

Research question: International travelers have grown significantly over last years, as well as imported diseases from tropical areas. Information in pediatric population is scarce. We aim to describe demographic and clinical characteristics of febrile children coming from the tropics.

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Results

Methods: We have already performed a single center retrospective review of patients under 18 years old, presenting at a tertiary hospital and surrounding primary health care centers between July 2002 and July 2018 with a stay in a tropical region during the previous year. Patients were selected from microbiological charts of thick smears for malaria and dengue serologies. We would like to extend this study to various centers in Spain.

Results: Based on our single center data, 188 patients were studied: 52.7% were born in Spain with a median age of 3.0 years old (IQR 1.5-8.0). Main regions of stay were Sub-Saharan Africa (54.8%) and Latin America (29.8%), mostly for visiting their friends and relatives (56.3%), followed by recent arrival migrants (32.4%). The most frequent diagnoses were febrile syndrome without source (56.4%), respiratory condition (15.4%) and acute diarrhea (11.7%).

Conclusion

Around a half (52.1%) were managed as outpatients, but 46.2% were hospitalized and 7.4% were admitted to Intensive Care Unit. No specific diagnosed was achieved in 24% of cases. However, 39 patients (29.7%) were diagnosed of malaria.

Conclusion: Children with fever coming from tropical areas were at risk of severe infectious diseases. A wider perspective of multiple hospitals may enrich representation of different population groups involved.

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Title
Identifying distinct transcriptional states of the malaria parasite in response to the host environment

Title and Research Question
Identifying distinct transcriptional states of the malaria parasite in response to the host environment.

Methods
Reciprocal interactions between host and pathogen may contribute to the outcome of infection. However, it is difficult to separate the constitutive and adaptive components of pathogen behaviour. I aim to determine the variation that occurs in malaria parasite behaviour during progression of infection within the host, and to identify the drivers of this variation, such as changes in the host metabolic environment.

Results
Differential gene expression analysis was used to identify variation in parasite gene expression between the pre-symptomatic and severe stages of infection of C57BL/6 mice with five different rodent malaria parasites *(Plasmodium berghei* ANKA, *Plasmodium begrhei* NK65, *Plasmodium yoelli* (lethal and non lethal) and *Plasmodium chabaudi*). Analyses were adjusted for variation in the mixture of parasite developmental stages based on blood film morphology. The developmental stages were one of Schizonts, Trophozoites, Rings or Gametocytes). Adjusted parasite gene expression was correlated with blood lactate concentrations in the mice. Work is ongoing using data from the Malaria Cell Atlas Project to derive more granular life-cycle stage-specific transcriptional signatures. These signatures will then be incorporated into the analysis to improve the deconvolution of stage mixture.

Conclusion
Prior to adjustment for parasite stage, there were hundreds of significantly differentially expressed genes between early and late stages in *Plasmodium berghei* and *P.yoelli*, many of which were gametocyte-associated genes. After deconvolution, there were significantly differentially expressed genes and some were significantly correlated with blood lactate concentrations.
The data indicates malaria parasites may adapt their gene expression as infection progresses, possibly responding to changes in the host metabolic environment. We will focus on pathway analyses to understand the biological basis of changes in parasite behaviour.

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