**Department of Respiratory Sciences PhD studentship Project information**

**Funding Source:** Self-Funded

**Proposed project start date**: Open

**Closing date for applications:** Open

**Eligibility:** International students only

**Tuition fee £37,750** (there is no funding for this project)

**Department/School:** Respiratory Sciences

**Supervisors:** Prof Galina Mukamolova

**Project Title:** Investigation of signalling mechanisms that control *Mycobacterium tuberculosis* survival under host-imposed stresses

**Project Description :**

*Mycobacterium* *tuberculosis* (*Mtb*) is a sophisticated pathogen, and it can replicate in eukaryotic cells and survive in infected humans for decades. Mtb forms dormant non-replicating persisters which are very resistant to treatment and difficult to eradicate from patients. Revival of these dormant Mtb is controlled by resuscitation-promoting factors (RPFs), a family of cell wall degrading enzymes. RPFs are produced during resuscitation and growth of Mtb, they are also important for adaptation pf Mtb to host-imposed stresses. However, the precise mechanism regulating expression of RPFs is currently unknown.

This project is aimed to investigate regulatory mechanisms that control RPF expression during adaptation to stress, resuscitation, and growth in macrophages. We will focus on several transcriptional regulators such as MtrA, Lsr2 and Rv0023 and investigate their role in Mtb survival and regulation of RPF expression under nitrosative and oxidative stresses and resuscitation. Post-translational modifications of these regulators and their effect on DNA binding will be also studied.

The following *experimental approaches* will be used in this study:

* Cultivation of Mtb and model mycobacteria
* Cultivation of macrophages and infection studies
* Genetic manipulation and generation of Mtb mutants
* Transcriptomics studies using RNA-Seq and quantitative PCR
* Production of recombinant proteins and kinases assays
* CHIP-Seq and electromobility shit assays.

The student will be trained for work in the C3 containment laboratory. They will learn techniques for cultivation of various organisms, transcriptomics studies (including data analysis) and transferrable skills such as writing papers and grants and presenting results.

**References:**

1. Rosser A, Stover C, Pareek M, Mukamolova GV. (2017) Resuscitation-promoting factors are important determinants of the pathophysiology in *Mycobacterium tuberculosis* infection. *Crit Rev Microbiol* 17:1-10.

# 2. Alqaseer K, Turapov O, Barthe P, Jagatia H, De Visch A, *et al*. (2019) Protein kinase B controls Mycobacterium tuberculosis growth via phosphorylation of the transcriptional regulator Lsr2 at threonine 112. *Mol Microbiol.* 112(6):1847-1862.

3. Bancroft P, Turapov O, Jagatia H, Arnvig K, Mukamolova GV, Green J. (2023). Coupling of Peptidoglycan Synthesis to Central Metabolism in Mycobacteria: Post-transcriptional Control of CwlM by Aconitase. *Cell Rep*. 32(13):108209. doi: 10.1016/j.celrep.2020.108209.

4. Glenn SM, Gap-Gaupool B, Waddell SJ, Bacon J, Crosatti M, Hincks J, KendallSL, Riabova O, Monakhova N, et al (2023) Exposure to nitric oxide drives transition to differential culturability in mycobacteria. (2021). *BioRxiv*, doi: <https://doi.org/10.1101/2021.09.28.462152>.

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**To apply please refer to** [**https://le.ac.uk/study/research-degrees/research-subjects/respiratory-sciences**](https://le.ac.uk/study/research-degrees/research-subjects/respiratory-sciences)

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