Principal Supervisor: **Professor Andrew Fry (Leicester)**

Co-supervisor:  
**Dr Mohammed El-Mezgueldi** (Leicester) - expert in biochemical methods  
Collaborator - Prof John Schwabe (Leicester) - expert in acetylation  
Collaborator - Prof Anne Straube (Warwick) - expert in cell migration

PhD project title: **Exploring the role of cortactin phosphorylation in cancer cell division and migration**

University of Registration: **Leicester**

**Project outline**

1. Project outline describing the scientific rationale of the project (max 4,000 characters incl. spaces and returns)

**Background**: Cortactin is an F-actin binding protein that stimulates actin polymerization. It is frequently overexpressed in human cancer and promotes migration and invasion [1]. Cortactin also has a role in regulating cell proliferation and can promote disassembly of the microtubule-based primary cilium upon re-entry of quiescent cells into the cell cycle [2]. The primary cilium is an antennae-like structure that transduces external signals to control proliferation and differentiation, but which must be disassembled for cell division [3].

**Preliminary work**: We have discovered that cortactin is phosphorylated by the cell cycle-regulated Nek6 kinase at four positions in its actin-binding repeats (Figure 1). We therefore wish to first test whether this regulates the ability of cortactin to promote F-actin polymerization [4,5]. Second, as these phosphorylation sites lie close to sites that undergo acetylation and deacetylation of cortactin contributes to cilia disassembly by enhancing cortactin binding to F-actin [6,7], we will investigate potential cross-talk between phosphorylation and acetylation in regulating cortactin function. Finally, we will explore how phosphorylation of cortactin by Nek6 might promote proliferation, migration and invasion of human cancer cells in vivo.

![Figure 1. Domain organization of human cortactin](image)

**Hypothesis and project objectives**: We propose that Nek6 cooperates with cortactin overexpression in human cancer cells to enhance actin polymerization and promote proliferation and metastasis.

This hypothesis will be tested by addressing three mechanistic questions:

- Does Nek6 phosphorylation regulate actin binding, activity or localization of cortactin?
- Is Nek6 regulation of cortactin function dependent on acetylation status of cortactin?
- Does Nek6 cooperate with cortactin to regulate cilia disassembly, cell division, migration and invasion?
References

Relevant BBSRC Strategic Research Priority:
World Class Underpinning Bioscience

Techniques that will be undertaken during the project.

- Cell culture and stable cell line generation
- Expression and purification of recombinant proteins from bacteria
- Generation of engineered proteins with non-hydrolysable modifications
- Biochemical stopped-flow kinetics experiments
- Fixed and time-lapse quantitative confocal microscopy

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