OXFORD INTERDISCIPLINARY BIOSCIENCE
Doctoral Training Partnership

Industrial CASE Studentship Advertisement – 2023 Entry

Supervisor(s) names:	Academic supervisors: A/Prof Jelena Bezbradica Mirkovic (primary supervisor), Prof Mark Coles (co-supervisor), Prof Chris Buckley (co-supervisor). Industrial supervisor: Dr. Thomas Hanke, Evotec
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Project Title:	**How chloride channel CLIC5 amplifies inflammatory signalling in fibroblasts-macrophage crosstalk**

Brief description of project:

Tissue resident cells, such as macrophages and fibroblasts communicate with each other to maintain homeostasis and health. Upon infection or injury, they initiate transient inflammatory response with aim to defend, repair and restore health. When this inflammatory response becomes amplified and persistent, it drives tissue damage and pathologic tissue remodelling. We recently identified chloride channel CLIC5 as one of the highest differentially expressed genes in a very destructive tissue resident synovial fibroblast subset found in chronic joint inflammation. When this subset was purified and transferred into heathy joints, it was sufficient to drive tissue damage and bone remodelling. These data suggest that CLIC5 might be a good future target to limit chronic tissue damage, but we know very little about the basic CLIC5 biology. CLIC5 is a member of a larger family of chloride channels that are known to amplify inflammatory signalling downstream of toll-like receptors (TLRs) in macrophages. Fibroblast do not express TLRs, but they do express receptor for inflammatory cytokine interleukin-1 (IL-1R), whose signalling cascade looks almost identical to that of TLRs. In joints, IL-1b is typically produced by activated macrophages. It acts on fibroblasts where we found it induces CLIC5 expression. We thus hypothesise that in inflamed tissues, activated macrophages secrete IL-1b, which acts on IL-1R on fibroblasts to upregulate CLIC5. CLIC5 then further amplifies and sustains IL-1R pro-inflammatory signalling on fibroblasts that drives their pathologic re-programming into a tissue destructive subset. How CLIC5 amplifies inflammatory IL-1R signalling in fibroblasts is unknown and is the question that will be addressed in this project. To address the central hypothesis, we are currently generating CLIC5 deficient and CLIC5 overexpressing fibroblasts, and we have generated a library of new CLIC5 inhibitors, with the help of the industrial partner EVOTEC. With these unique tools we will: 1. Characterise CLIC5 expression and subcellular localisation in resting and activated fibroblasts using 2D cultures or 3D organoid models with resting or activated macrophages; 2. Characterise how biochemically CLIC5 amplifies IL-1R signalling; and 3. Define what tissue destructive functional programmes high CLIC5 expression enables. These are fundamental questions which span the biology of chloride channels, biology of IL-1R signalling and biology of fibroblasts and macrophages in tissues. It is essential to address this knowledge gap before any further disease-intervention studies using CLIC5 inhibitors can be

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planned in mice or humans. Project will benefit from combination of academic, clinical and industrial supervisors that are experts in innate signalling and IL-1R biology (A/Prof Jelena Bezbradica Mirkovic), fibroblast biology (Prof Mark Coles and Prof Chris Buckley) and small molecule drug development, particularly aimed at targeting ion channels (EVOTEC).

Attributes of suitable applicants:

Essential:

-applicant that is enthusiastic, highly collaborative and motivated

Desired, but not essential:

-some experience with immunology/inflammation-focused wet lab project

-some experience with either macrophage or fibroblast signalling work

-some experience with imaging

Funding notes:

This project is funded for four years by the Biotechnology and Biological Sciences Research Council UKRI-BBSRC. UKRI-BBSRC eligibility criteria apply (https://www.ukri.org/files/funding/ukri-training-grant-terms-and-conditions-guidance-pdf/). Successful students will receive a stipend of no less than the standard UKRI stipend rate, currently set at £17,668 per year.

This project is supported through the Oxford Interdisciplinary Bioscience Doctoral Training Partnership (DTP) studentship programme. The student recruited to this project will join a cohort of students enrolled in the DTP's interdisciplinary training programme, and will participate in the training and networking opportunities available through the DTP. For further details, please visit www.biodtp.ox.ac.uk. The DTP and its associated partner organisations aim to create a community that is innovative, inclusive and collaborative, in which everyone feels valued, respected, and supported, and we encourage applications from a diverse range of qualified applicants.