

PHD studentship opportunity: Determinants of fibroblast diversity and fibroblast-immune cell interaction in inflammatory bowel disease (IBD).



Funding: Science Foundation Ireland/Irish Research Council Pathway Program.

Duration and stipend: 36-48 months, €18,500/year + EU tuition fees.

Project description: Fibroblasts are structural cells with a key role in tissue repair and healing. Recent evidence from studies investigating the composition of the intestinal mucosa during homeostasis and in inflammatory bowel diseases (IBD) have shown the existence of multiple fibroblast phenotypes. Of great interest, a fibroblast with a phenotypic signature that indicates potential homeostatic functions was found in the healthy colon and the abundance of these cells diminished in IBD patients. Conversely, a fibroblast with an inflammatory genetic signature that is virtually absent in the healthy intestinal mucosa emerges in IBD biopsies. Notably, these inflammatory fibroblasts have been also found in intestinal specimens from therapy-resistant IBD patients, where they are suspected to interact with immune cells. However, little is known about the mediators that control pathogenic fibroblast differentiation and the nature and consequences of their interactions with immune cells. To address these gaps in the knowledge, we will: (1) Investigate the molecular mechanisms that control the transition of fibroblasts from homeostatic to inflammatory in IBD; (2) Characterize the environmental factors that define fibroblast diversity in the intestinal tract; And, (3) Evaluate how fibroblasts interact with immune cells, and the cellular responses promoted by this interaction.

Relevant publications on this topic from the principal investigator include: Manresa MC, et al. *Mucosal Immunology* (2022), Manresa MC, et al. *Gastroenterology* (2020), Manresa MC, et al. *Allergy* (2019) and Manresa MC et al *American Journal of Physiology – GI* (2016).

Clinical significance: The progression of chronic inflammatory diseases such as IBD toward complications including ulcerations and fibrosis and the resistance or loss of response of a significant number of patients to currently available therapies, makes IBD difficult to treat. Moreover, complications such as fibrosis, in which fibroblasts are central players, often lead to surgical interventions due to the lack of pharmacologic therapies that can properly address disease progression. The majority of therapies developed to date have the aim of blocking the activation of inflammatory responses at the immune cell level. Our group will take an alternative approach by investigating the mediators that control the activation of structural cells such as fibroblasts and how these cells control inflammatory responses. This may ultimately reveal new molecular targets to treat IBD.

Qualifications / Expertise: The candidate should be highly motivated and passionate about research and have an MSc or BSc (Hons) in Cell and Molecular Biology, Physiology, Pharmacology or a similar relevant area. Candidates in possession of or currently finishing a Master's degree are encouraged to apply. Experience in cell culture, RNA and protein extraction, RT-PCR, Western blot, flow cytometry and/or animal models will be an advantage.

Environment and project details: The successful candidate will integrate in a multidisciplinary team and work closely with the groups of Professor Cormac Taylor and Dr. Eoin Cummins. Our combined expertise in structural cell biology, hypoxia, immunology, cell signalling and translational medicine will give the candidate the opportunity to immerse in a dynamic and collaborative environment. The student's project will fundamentally use *in vitro* models, culturing primary cells and investigating cellular responses by RNA sequencing, RT-PCR, western blot, ELISA and flow cytometry. The candidate will be involved with human biopsy and murine tissue sample handling, preparation and analysis. The student will present work at international conferences and publish peer reviewed manuscripts.

Start Date: No later than August 2022.

To Apply: Informal inquiries should be sent to Dr. Mario Manresa (mario.manresa@ucd.ie). Formal applications will consist of CV, a cover letter and the contact of 2 potential referees.