

Cytoneme-mediated morphogen transport during wound healing and regeneration

Supervisory team:

Main supervisor: Prof Steffen Scholpp (University of Exeter)

Second supervisor: Prof Paul Martin (University of Bristol)

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Host institution: University of Exeter (Streatham/St Luke's)

Project description:

The determination of the cellular fate is one of the most fundamental and classical problems in regeneration. In many tissues, cell fate is determined by morphogen signalling proteins. Two families of morphogens, namely Shh and Wnt - are essential for determining many fundamental aspects such as cell proliferation, differentiation and migration. We and others have shown that the distribution of these morphogens can be facilitated by membrane protrusions - also known as cytonemes. Cytonemes are thin, actin-rich, and transport essential components of the Shh and Wnt signalling pathway between cells (Zhang and Scholpp, 2019; Curr Opin Gen & Dev). Cytonemes are highly dynamic and can form and retract within minutes (Stanganello et al., 2015; Nat Comms). Their emergence is precisely controlled by the cytoneme-producing cell and the extracellular space through which they traverse (Brunt, et al., 2021, Nat Comms). Although there is strong evidence that Wnt3a and Shh cooperate during wound healing, to date, it is unknown how their crosstalk is regulated. Furthermore, the role of cytoneme-mediated transport during wound healing is unclear.

Under the supervision of leading cell and developmental biologists, the student will study Wnt and Shh transport in the regenerating fin in zebrafish. The student will generate transgenic zebrafish lines in which signalling components are fluorescently tagged to investigate cytoneme-based morphogen release by quantitative imaging. We will also use real-time PCR, single-molecule fluorescence in-situ hybridisation, and advanced high-resolution microscopy in the wound to describe signal activation. Finally, the student will interfere with the emergence of cytonemes by using chemical inhibitors and CRISPR/Cas9-based mutations to study their impact on zebrafish wound healing.

The student selected for this project will develop invaluable skill sets in experimental genetics, developmental biology, and high-resolution microscopy, whilst also making a significant contribution to the understanding of a cell fate specification. This combined skill set will make the candidate a highly desirable recruitment prospect for future academic and industrial employers.

The Living Systems Institute (LSI), with complementary expertise in biosciences and high-resolution imaging, will be an optimal environment to conduct these doctoral training studies. The LSI offers unique training opportunities for the PhD student. It allows the student to address key problems in life sciences with state-of-the-art equipment in an interdisciplinary environment. The project includes an extended placement in the lab of Prof Paul Martin (University of Bristol) - an international leading expert in wound healing and signalling biology.