Quantitative in vivo analysis of ligand-receptor interactions in the Wnt signalling network

Supervisory team:
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Host institution: University of Exeter (Streatham)
CASE partner: Leica Microsystems

Project description:

Cell-cell communication is essential for the regulation of the development and homeostasis of all multicellular organisms. Secreted signals like Wnt signals regulates fundamental processes including cell proliferation and differentiation, cell polarity and migration. Misregulation of this signalling network causes severe diseases e.g. cancer, neurodegenerative diseases, and osteoporosis. Binding of a Wnt ligand with a seven-pass transmembrane Frizzled (Fzd) receptor on the surface of cells is the principal way to activate the Wnt signalling network. 19 different Wnt ligands may bind to 10 different Fzd receptors to specify the nature of the downstream signalling event. Accurate quantification of these interactions in living organisms is crucial to understand signalling specificity, however, due to technical obstacles this was not possible until today.

In collaboration with Leica Microsystems and under the supervision of cell biologists and biophysicists, we will employ correlation spectroscopy to quantify for the first time the effective binding affinities - Kd (effective) - between three Wnt ligands and three different Fzd proteins in vivo, which have important functions in early vertebrate development. The student will apply molecular biological techniques such as mRNA overexpression and CRISPR/Cas9-based knock-out methods, as well as generation of transgenic zebrafish lines to visualize ligands and receptors in zebrafish. Then we will use imaging-based, quantitative measurements of ligand-receptor interaction in the zebrafish gastrula by fluorescence fluctuation techniques. In a collaboration with the R&D unit of Leica, the student will develop and refine Leica's single-molecule detection unit FALCON for its usage in living specimen.

The student selected for this project will develop invaluable skill sets in experimental genetics, in vivo techniques, biophysical methods such as spectroscopy and microscopy, whilst also making a significant contribution to the understanding of the Wnt signalling network. This combined skill set including the interactions with the industrial partner 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 physics will be an optimal environment to conduct these doctoral training studies. The LSI offers unique training opportunities for the PhD student as it allows the student address key problems in life sciences with state-of-the-art equipment in an interdisciplinary environment. The project includes close collaboration with the universities of Cardiff, Bath and Bristol to complement the required skill sets