Research profile for applicants

Name of DKFZ research division/group:	***Molecular Embryology A050***
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Group homepage: *Visit this website for further information on current research and recent publications.*	***www.dkfz.de/en/mol_embryology/index.php***
Eligibility:	• ***DKFZ Postdoctoral Fellowships***

RESEARCH PROFILE AND PROJECT TOPICS

Project 1: DEVELOPMENT of ROTACs for TARGETED CANCER THERAPY

Proteolysis-targeting chimeras (PROTACs) are a revolutionary technology for therapeutic intervention in oncology, but options to target cell surface proteins and receptors have remain limited. To overcome this, we have recently introduced ROTACs, which are bispecific chimeras utilizing R-spondin (RSPO) as scaffolds to target the degradation of transmembrane proteins, leveraging the specificity for certain transmembrane ligases (Sun et al., 2023).

In this project, you will develop new ROTACs against transmembrane cancer target proteins. You will design ROTACs yourself, produce them as recombinant proteins, and characterize their efficacy against cancer cell lines. You will join a collaborative team that includes a biotech company supporting this research.

This project provides an opportunity for a comprehensive exploration of the development and application of ROTACs in the context of cancer therapeutics, contributing to the evolving landscape of targeted treatment options. The postdoc will also be embedded in a WNT-focused Collaborative Research Center (https://sfb1324.de/).
Applicants should hold a degree in chemistry/biology/life sciences with a background in cell or molecular biology, or biochemistry.

Sun R, Meng Z, Lee H, Offringa R, Niehrs C. (2023) ROTAC's leverage signaling incompetent R-spondin for targeted protein degradation. Cell Chem Biol. 20; 30:739-752.

Project 2: DEVELOPMENT of LEFT-RIGHT ASYMMETRY DURING MOUSE & FROG EMBROGENESIS

Left-right (LR) asymmetry of thoracic and visceral organs, e.g. the left position of the heart, is a chief attribute of many animals. Hence, the embryonic- and evolutionary origins of LR body axis formation are a fundamental question in biology. Mechanistic understanding of LR specification is also medically relevant because LR abnormalities cause organ dysfunction in humans. In most vertebrates, LR body axis formation is regulated during embryogenesis by a cilia-driven leftward fluid flow in the left-right organizer (LRO). A cardinal question is the mechanism whereby leftward flow triggers symmetry breakage. The 'chemosensation' model posits that ciliary flow transports an unknown morphogen towards the left and thereby produces a signaling gradient along the LR axis. However, despite intense research, such a 'sinistralizing' morphogen has remained elusive. In a breakthrough discovery, we identified R-spondin 2 (Rspo2) in Xenopus (frog) embryos as sinistralizing signal and unravel that it acts to inhibit dextralizing FGF signaling. Hence, an anti-FGF/FGF signaling axis governs LR specification in frog (Lee et al., 2024).

This discovery sets the stage to address the central hypothesis, that an FGF/anti-FGF signaling axis is a conserved mechanism for LR patterning in vertebrates and beyond, with three specific Aims. First, we will analyse mouse model systems t embryos to address how conserved FGF/anti-FGF signaling in LR patterning is in vertebrates. Second, to delineate the dextralizing signaling pathway, we will conduct a systematic analysis of the FGF cascade and link it to asymmetric gene expression in Xenopus. Third, we will visualize LR symmetry breakage of FGF signaling by Rspo2 in the Xenopus LRO. This project will allow for fundamental discoveries at the interface of cell signaling and evolutionary developmental biology to unravel how the LR body axis is determined.

Lee H, Camuto CM, Niehrs C. (2024) R-Spondin 2 governs Xenopus left-right body axis formation by establishing an FGF signaling gradient. Nat Commun. 2;15:1003