2018-05

IC-**3i** International PhD Program

PhD thesis project

2018 Call for application

The tubulin code as a new therapeutic target - from single molecules to organisms

General information

Call	2018-2019
Reference	2018-05-JANKE_MAGIERA
Keyword(s)	Microtubule cytoskeleton, tubulin code, tubulin glutamylation, organelle transport, neurodegeration

Director(s) and team

Thesis director(s)	Carsten Janke
Research team	Regulation of microtubule dynamics and functions
Research department	UMR3348 – Genotoxic stress and Cancer

Description of the PhD thesis project

The tubulin code as a new therapeutic target - from single molecules to organisms

The microtubule cytoskeleton is a complex network that adapts to a huge variety of functions in different cells, and is highly responsive to changing developmental and physiological requirements. We are investigating the tubulin code as a novel way of controlling microtubule functions. We have demonstrated that a posttranslational modification of the microtubules, polyglutamylation, is important for neuronal functions, as the deregulation of this modification leads to neurodegeneration. This could have huge repercussion on our understanding of the molecular mechanisms that underlie, or even initiate neurodegenerative processes long before the typical pathological features can be detected.

In the current project, we will build on our work showing the direct link between deregulated polyglutamylation and neurodegeneration to determine the molecular mechanisms that underlie degeneration using an interdisciplinary approach. The central objective is to determine which transport cargoes are selectively regulated by the polyglutamylation of microtubules in neurons.

For this we will (1) measure the transport parameters of a panel of neuronal transport vesicles in neurons with either increased or decreased polyglutamylation, (2) determine the motor proteins and MAPs involved in the sensitivity of these cargoes to polyglutamylation in vitro (3) determine the organism-level defects of these specific transport defects by investigating the fate of these cargoes in the mouse nervous system of our mouse models with decreased or increased polyglutamylation. As we have already demonstrated that neurodegeneration due to increased polyglutamylation can be avoided by removing enzymes that generate this modification, we will (4) collaborate with an industrial partner with whom we screen large component libraries for inhibitors of polyglutamylases.

International, interdisciplinary & intersectoral aspects of the project

In this project we collaborate with a company in Germany to screen a chemical component library for small-molecule inhibitors of polyglutamylases. Together with clinicians in Germany and Austria, we aim at determining if other neurodegenerative disorders are also linked to alterations in polyglutamylation. The experimental approaches used are highly interdisciplinary. The student will use single-molecule in vitro reconstructions of microtubule assemblies, and correlate the detected alterations in microtubule dynamics and interactions with associated motor proteins and MAPs with observations on the intracellular level in neurons prepared from our mouse models. Mouse models will be characterized with collaborators in the Czech Republic, and compared to clinical findings.

Recent publications

1. Basnet N, Nedozralova H, Crevenna AH, Bodakuntla S, Schlichthaerle T, Taschner M, Cardone G, **Janke C**, Jungmann R, Magiera MM, Biertumpfel C, Mizuno N (2018) Direct induction of microtubule branching by microtubule nucleation factor SSNA1. Nat Cell Biol 20: 1172-1180

2. Magiera MM, Bodakuntla S, Ziak J, Lacomme S, Marques Sousa P, Leboucher S, Hausrat TJ, Bosc C, Andrieux A, Kneussel M, Landry M, Calas A, Balastik M, **Janke C** (2018) Excessive tubulin polyglutamylation causes neurodegeneration and perturbs neuronal transport. EMBO J 37: e100440

3. Magiera MM, Singh P, Gadadhar S, **Janke C** (2018) Tubulin Posttranslational Modifications and Emerging Links to Human Disease. Cell 173: 1323-1327

4. Shashi V*#, Magiera MM*,..., **Janke C**#, Senderek J# (2018) Loss of tubulin deglutamylase CCP1 causes infantile-onset neurodegeneration. EMBO J 37: e100540

5. Silva CG, Peyre E, Adhikari MH, Tielens S, Tanco S, Van Damme P, Magno L, Krusy N, Agirman G, Magiera MM, Kessaris N, Malgrange B, Andrieux A, **Janke C**, Nguyen L (2018) Cell-Intrinsic Control of Interneuron Migration Drives Cortical Morphogenesis. Cell 172: 1063-1078

Expected profile of the candidate

The candidate is expected to have a strong interest in the complexity of biological processes, as well as a solid capacity for independent and creative thinking. The interdisciplinarity of the project requires a desire to perform a challenging, methodologically complex project, and a strong motivation to learn and adapt new methods and approaches. Overall, a background in molecular biology, protein biochemistry, cell biology and imaging are required. The project will be highly intersectoral and involve collaborators with different backgrounds, thus good communication skills are also important.