PhD Program between the Freie Universität Berlin (FUB) and the China Scholarship Council (CSC)

Open PhD position for CSC scholarship candidates 2015

The PhD position is only offered to Chinese PhD candidates for application in the framework of the FU-CSC Program.

Department/Institute:	Department of Biology, Chemistry, Pharmacy / Institute for Chemistry and Biochemistry
Subject area:	Structural biochemistry, molecular biology, pre-mRNA splicing
Name of Supervisor:	Prof. Markus C. Wahl, PhD
Number of open positions:	1
Project title:	Role of the Snu114 G protein in pre-mRNA splicing

Project description:

Precursor messenger RNA (pre-mRNA) splicing and alternative splicing are carried out by a RNA-protein (RNP) molecular machine of stunning complexity, the spliceosome, whose activity intimately hinges on elaborate conformational and compositional dynamics. For each round of splicing, a spliceosome is assembled anew, catalytically activated and, after splicing catalysis, disassembled in an ordered fashion by the stepwise recruitment and release of five small nuclear ribonucleoprotein (snRNP) particles and many non-snRNP splicing factors (1). This process is accompanied by repeated conformational and compositional remodeling of the spliceosome's RNP network with the help of eight highly conserved nucleotide triphosphate-dependent RNA helicases (1,2). The structurally unique RNA helicase, Brr2, in complex with a regulatory scaffold, Prp8, and an eEF2-like G protein, Snu114, forms a remodeling machinery that is part of the U5 snRNP and that mediates spliceosome catalytic activation by disrupting the U4/U6 di-snRNP (1,2). Both Prp8 and Snu114 have been shown to regulate Brr2 helicase activity, presumably to achieve proper timing of spliceosome catalytic activation. Several aspects of Prp8-mediated Brr2 regulation have recently been elucidated (3-6). However, while Snu114 has been shown to regulate the Brr2 RNA helicase dependent on its nucleotide bound state (7), it is unclear how this regulation is achieved on the molecular level. This project aims at investigating the Snu114 G protein alone and in complex with Prp8 and Brr2 by structural biochemical approaches to unravel the mechanisms of Snu114-mediated regulation of Brr2. Techniques will encompass recombinant production of proteins and protein complexes, structural analyses by X-ray crystallography and functional assays such as *in vitro* U4/U6 di-snRNA unwinding, using wild type and mutant Snu114, Brr2 and Prp8.

References

(1) Wahl MC, Will CL, Lührmann R (2009) The spliceosome: Design principles of a highly dynamic molecular RNP machine. *Cell* **136**, 701-718.

(2) Staley JP, Guthrie C (1998) Mechanical devices of the spliceosome: motors,

clocks, springs, and things. *Cell* **92**, 315-326
(3) Mozaffari Jovin S, Wandersleben T, Santos KF, Will CL, Lührmann R, Wahl MC (2014) Novel regulatory principles of the spliceosomal Brr2 RNA helicase and links to retinal disease in humans. *RNA Biol* **11**, 298-312.
(4) Mozaffari Jovin S, Wandersleben T, Santos KF, Will CL, Lührmann R, Wahl MC (2013) Inhibition of RNA helicase Brr2 by the C-terminal tail of the spliceosomal protein Prp8. *Science* **341**, 80-84.
(5) Mozaffari Jovin S, Santos KF, Hsiao HH, Will CL, Urlaub H, Wahl MC, Lührmann R (2012) The Prp8 RNase H-like domain inhibits Brr2-mediated U4/U6 snRNA unwinding by blocking Brr2 loading onto the U4 snRNA. *Genes Dev* **26**, 2422-2434.
(6) Santos KF, Mozaffari Jovin S, Weber G, Pena V, Lührmann R, Wahl MC (2012) Structural basis for functional cooperation between tandem helicase cassettes in Brr2-mediated remodeling of the spliceosome. *Proc Natl Acad Sci USA* **109**, 17418-17423.
(7) Small EC, Leggett SR, Winans AA, Staley JP (2006) The EF-G-like GTPase Snu114p regulates spliceosome dynamics mediated by Brr2p, a DExD/H box ATPase. *Mol Cell* **23**, 389-399

Language requirements:

The doctoral thesis can be written in English or German. English is the working language in our lab. Proficiency in German is not required (neither required in the lab nor for the thesis).

Academic requirements:

A Master's degree in Biochemistry or a related subject area is required to enter the PhD program.

Link to professor and further information:

Prof. Markus C. Wahl, PhD
Homepage: http://www.bcp.fu-berlin.de/en/chemie/biochemie/ag/agwahl
Please note:
In a first step the complete application should submit to the Beijing Office for evaluation by January 4th. Please don't contact the professor before. He will get in contact with you after having received the complete application in January.