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, bacterial transcription
Name of Supervisor:	Prof. Markus C. Wahl, PhD
Number of open positions:	1
Project title:	Mechanisms of Nus factor-dependent transcription regulation

Project description:

Competition between transcription termination and antitermination constitutes a key mechanism of bacterial gene regulation. This regulatory principle is exemplified by processive antitermination during lytic growth of phage λ (1) or during ribosomal RNA transcription in *Escherichia coli* (2) as well as by premature transcription termination on a phage λ genome evoked by phage HK022 (3). The latter process presumably constitutes a protection mechanism of HK022 against super-infection by phage λ. These transcription antitermination or premature termination processes depend on a signal element on the nascent RNA (the N-utilization, *nut*, site), four host N-utilization substances (NusA, NusB, NusE [equivalent to ribosomal protein S10] and NusG) and, in the case of the phage-induced processes, phage proteins N (λ) or Nun (HK022). The Nus factors and the *nut* site RNA alone or together with one of the phage proteins assemble elaborate ribonucleoprotein complexes on the surface of RNA polymerase (RNAP) that accompany the elongating enzyme by a looping mechanism. We have previously investigated several of the factors involved and some of their complexes structurally und functionally (4-11). However, it is still unknown how the same group of transcription factors (the Nus proteins) together with the same RNA signal element (*nut*) can be sequestered by different phage proteins (λN or HK022 Nun) to render RNAP either termination-resistant or more termination-prone. This project aims at elucidating the molecular mechanisms underlying λN-mediated transcription antitermination and HK022 Nun-mediated transcription termination by structural biochemical approaches. Antitermination complexes (comprising RNAP, the Nus factors, a nut site-containing RNA and phage proteins λN) or termination-prone complexes (containing the same factors and HK022 Nun instead of λN) will be assembled from recombinant components, and their structures will be investigated by electron cryo-microscopy (cryo-EM) and X-ray crystallography. In addition, transcription assays will be set up to monitor the influence of the various factors (wild type or mutant forms) on transcriptiona antitermination and termination. Apart from shedding light onto fundamental regulatory principles of bacterial transcription, the outcome of the proposed work will

provide novel platforms for the development of antimicrobial substances.

References

(1) DeVito J, Das A (1994) Control of transcription processivity in phage lambda: Nus factors strengthen the termination-resistant state of RNA polymerase induced by N antiterminator. *Proc Natl Acad Sci USA* **91**, 8660-8664.

(2) Condon C, Squires C, Squires CL (1995) Control of rRNA transcription in Escherichia coli. *Microbiol Rev* **59**, 623-645.

(3) Robert J *et al.* (1987) The remarkable specificity of a new transcription termination factor suggests that the mechanisms of termination and antitermination are similar. *Cell* **51**, 483-492.

(4) Drögemüller J, Stegmann C, Mandal A, Steiner T, Burmann B, Gottesman ME, Wöhrl BM, Rösch P, Wahl MC, Schweimer K (2013) An auto-inhibited state in the crystal structure of *Thermotoga maritima* NusG. *Structure* **21**, 365-375.

(5) Burmann BM, Schweimer K, Luo X, Wahl MC, Stitt BL, Gottesman ME, Rösch P (2010) A NusE:NusG complex links transcription and translation. *Science* **328**, 501-504.

(6) Burmann BM, Luo X, Rösch P, Wahl MC, Gottesman ME (2009) Fine tuning of the *E. coli* NusB:NusE complex affinity to *boxA* RNA is required for processive antitermination. *Nucleic Acids Res* **38**, 314-326.

(7) Luo X, Hsiao HH, Bubunenko M, Weber G, Court DL, Gottesman ME Urlaub H, Wahl MC (2008) Structural and functional analysis of the *E. coli* NusB-S10 transcription antitermination complex. *Mol Cell* **32**, 791-802.

(8) Bonin I, Robelek R, Benecke H, Urlaub H, Bacher A, Richter G, Wahl MC (2004) Crystal structures of NusB from *Thermotoga maritima* and implications for RNA binding. *Biochem J* **383**, 419-428.

(9) Bonin I, Mühlberger R, Bourenkov GP, Huber R, Bacher A, Richter G, Wahl MC (2004) Structural basis for the interaction of *Escherichia coli* NusA with protein N of phage λ. *Proc Natl Acad Sci USA* **101**, 13762-13767.

(10) Steiner T, Kaiser JT, Marinkovic S, Huber R, Wahl MC (2002) Crystal structures of transcription factor NusG in light of its nucleic acid- and protein-binding activities. *EMBO J* **21**, 4641-4653.

(11) Worbs M, Bourenkov GP, Bartunik HD, Huber R, Wahl MC (2001) An extended RNA binding surface through arrayed S1 and KH domains in transcription factor NusA. *Mol Cell* **7**, 1177-1189.

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:

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.