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

<u>Open PhD Position</u> at Freie Universität Berlin, offered only to Chinese CSC scholarship candidates 2019

Please Note: this PhD position is only offered to <u>Chinese</u> PhD candidates for the application in the framework of the FUB-CSC PhD Program.

<u>Department/Institute:</u>	Department of Biology, Chemistry, Pharmacy; Institute of Chemistry and Biochemistry
<u>Subject Area:</u>	Gene Regulation, Transcription, Structural Biochemistry
<u>Name of Supervisor:</u>	Prof. Markus C. Wahl, PhD (Mr.)
<u>Number of Open PhD Positions:</u>	2
<u>Type of the PhD Study:</u>	Full-time (4 years)
<u>Project Title:</u>	Structural basis of transcription regulation

PhD Project Description:

In all free-living organisms, transcription is carried out by multi-subunit RNA polymerases (RNAPs). Bacteria harbor a single RNAP that receives regulatory inputs from the substrate DNA, nascent RNA and protein transcription factors[1]. The Escherichia coli RNAP core enzyme has a $\alpha2\beta\beta'\omega$ subunit composition and associates with a σ factor to form a holoenzyme that can initiate transcription at promoters. After promoter escape, σ is replaced by elongation factors NusA and NusG[2], which together with core RNAP form a stable transcription elongation complex. During elongation, E. coli NusA enhances RNAP pausing at specific sites[3], while NusG increases RNA chain elongation rate[4]. Transcription can be terminated via an intrinsic mechanism, elicited by a stable stem-loop structure followed by a stretch of uridine residues in the nascent RNA, which leads to conformational changes in RNAP, destabilization of the DNA:RNA hybrid and release of the transcript[5]. Alternatively, the ρ factor can terminate transcription by engaging nascent RNA via ρ-utilization sequences, translocating on the transcript in 5'-to-3' direction and, upon encounter of RNAP, extracting the transcript[4,6]. NusA facilitates intrinsic termination[5] and can support or counteract ρ-dependent termination depending on the context[6]. NusG can directly contact ρ via its C-terminal domain and supports ρ-dependent termination[4]. Phages can hijack the host transcriptional machinery in diverse ways, and elucidation of such mechanisms also informs about regulatory principles underlying bacterial transcription[7].

We use integrative structural biochemical approaches (including X-ray crystallography, single-particle electron cryo-microscopy and chemical cross-linking/mass spectrometry) and structure-guided mutational analyses to elucidate the functional organization of intact bacterial transcription complexes[8] as well as of individual components and sub-complexes[8,9]. Recently, for example, we have worked out the functional architecture of a processive transcription antitermination complex, comprising RNA polymerase, DNA, RNA bearing a specific regulatory sequence, host transcription factors NusA, NusB, NusE and NusG and the phage protein λN[10,11], revealing how the λN protein can launch a multi-pronged strategy to convert RNA polymerase into a termination-resistant form.

In the course of one of the proposed PhD projects, we plan to investigate the molecular mechanisms underlying other antitermination mechanisms, which depend on cis-acting RNA

elements on the nascent transcript alone or on cis-acting RNA signals in combination with trans-acting proteins. The second project aims at elucidating the molecular bases of factor-dependent and intrinsic termination and the structural basis of co-transcriptional RNA folding1.

References
1. Zhang J, Landick R (2016) A Two-Way Street: Regulatory Interplay between RNA Polymerase and Nascent RNA Structure. Trends Biochem Sci **41**, 293-310.
2. Mooney RA, Davis SE, Peters JM, Rowland JL, Ansari AZ, Landick R (2009) Regulator Trafficking on Bacterial Transcription Units In Vivo. Molecular Cell **33**, 97-108.
3. Yang X, Lewis PJ (2010) The interaction between RNA polymerase and the elongation factor NusA. RNA Biol **7**, 272-275.
4. Tomar SK, Artsimovitch I (2013) NusG-Spt5 proteins-Universal tools for transcription modification and communication. Chem Rev **113**, 8604-8619.
5. Nudler E, Gottesman ME (2002) Transcription termination and anti-termination in E. coli. Genes Cells **7**, 755-768.
6. Ciampi MS (2006) Rho-dependent terminators and transcription termination. Microbiology **152**, 2515-2528.
7. Casjens SR, Hendrix RW (2015) Bacteriophage lambda: Early pioneer and still relevant. Virology **479-480**, 310-330.
8. Burmann BM, Schweimer K, Luo X, Wahl MC, Stitt BL, Gottesman ME, Rosch P (2010) A NusE:NusG complex links transcription and translation. Science **328**, 501-504.
9. 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.
10. Krupp F, Said N, Huang YH, Loll B, Burger J, Mielke T, Spahn CMT, Wahl MC (2018) Molecular Mechanisms of an All-Purpose Transcription Anti-Termination Factor. SSRN, https://ssrn.com/abstract=3231853
11. Said N, Krupp F, Anedchenko E, Santos KF, Dybkov O, Huang YH, Lee CT, Loll B, Behrmann E, Burger J, Mielke T, Loerke J, Urlaub H, Spahn CMT, Weber G, Wahl MC (2017) Structural basis for lambdaN-dependent processive transcription antitermination. Nat Microbiol **2**, 17062.

Language Requirements:

English is the working language in our lab. The doctoral thesis can be written in English or German. Proficiency in German is neither required in the lab nor for the thesis. English requirements: IELTS 6.5 or TOEFL 95 ibt

Academic Requirements:

We welcome applications from students holding a Bachelor's or Master's degree in Biochemistry or a related area of the Molecular Life Sciences. While students typically enter a PhD program with a Master's degree, in principle students can join after their Bachelor's degree. In the latter case, they may have to conduct some additional courses during the first year of the PhD.
Students need to have a strong theoretical background in Biochemistry and Molecular Biology. They need to have basic biochemical and molecular biological laboratory skills. For example, they should have practical experience with molecular cloning, recombinant protein production and protein purification. Additional background in Structural Biology or Bioinformatics is a plus.

Information of the Professor or Research Group Leader:

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Publications: http://www.ncbi.nlm.nih.gov/pubmed/?term=wahl_mc

Hompage: http://www.bcp.fu-berlin.de/en/chemie/biochemie/research-groups/wahl-group/index.html

Please Note: In a first step, the complete application should be submitted to the Beijing Office for evaluation by January 4th, 2019. Please do not contact the professor before. He/she will get in contact with you after having received the complete application via the Beijing Office in January.