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

Open PhD Position at Freie Universität Berlin, offered only to Chinese CSC scholarship candidates 2025

Department/Institute: Department of Biology, Chemistry, Pharmacy / Institute of Chemistry and Biochemistry

Subject area: Bacteriophage defense systems, Structural Biochemistry

Name of Supervisor: Prof. Markus C. WAHL, PhD (Mr.)

Number of open PhD positions: 2; full time

Type of the PhD Study: Full time (4 years)

Project title: Molecular mechanisms of bacterial immunity

PhD Project description:

Bacteria and viruses that infect them (bacteriophages) wage a constant evolutionary battle. Phages have evolved diverse molecular machinery to attack their hosts and take over host metabolism to ensure their replication. Bacteria, in turn, have acquired tools to fend off or terminate such attacks. The study of phage infection and replication mechanisms can inspire and inform the development of new antimicrobial strategies, while the identification and characterization of bacterial phage defense systems can lead to the development of powerful molecular biological, genetics and therapeutic tools, as impressively exemplified by the restriction/modification and CRISPR/Cas systems, for instance. Our group is interested in the molecular mechanisms underlying both phage attack and bacterial phage defense systems, with a focus on molecular systems that modulate phage or host gene expression (Fig. 1).[1-3] Numerous novel putative phage defense systems have been identified and in part validated in recent years.[4-6] However, the detailed molecular mechanisms whereby these systems take effect remain largely unknown. The proposed project will contribute to closing this knowledge gap and will involve:

- Validation of putative phage defense systems of interest (expression of putative phage defense systems in model bacteria; phage infection assays)
- Assessment of cellular protein and nucleic acid interactomes of phage defense system components (in-cell cross-linking in combination with protein mass spectrometry; cross-linking/immunoprecipitation in combination with RNA sequencing; chromatin immunoprecipitation in combination with DNA sequencing)

- Recombinant production of phage defense system components and interactors; reconstitution of their functional complexes (molecular cloning, protein production and purification)
- Characterization of putative enzymatic activities of phage defense system components (*in vitro* functional assays)
- Structural analysis of phage defense system components, their interactors and their functional complexes (cryogenic electron microscopy in combination with single-particle analysis; macromolecular crystallography; *in vitro* cross-linking in combination with protein mass spectrometry)
- Structure-informed mutagenesis and test of effects (expression of mutated phage defense systems in model bacteria; phage infection assays)

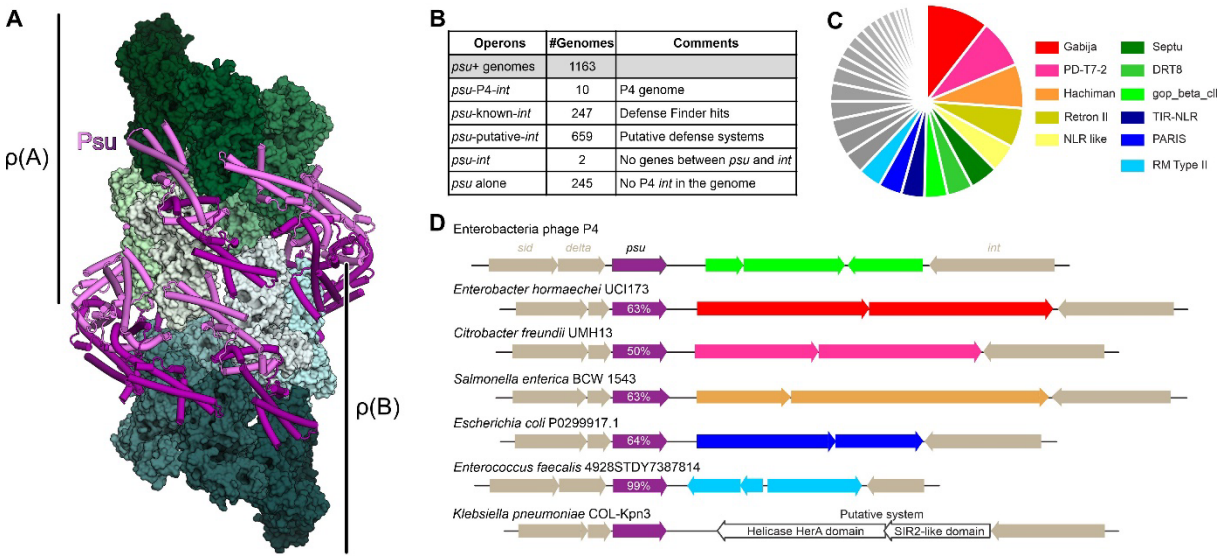

Figure 1. Psu as a marker of anti-phage defense systems. A. Structure of a ρ-Psu complex. Phage P4 capsid protein, Psu, inactivates transcription termination factor, ρ, by forced hyper-oligomerization. Eight Psu dimers (violet and purple) bridge two open ρ rings, ρ(A) and ρ(B), and facilitate expansion of the ρ rings to at least the nonamer stage. **B**. Defense system analysis of *psu*$^+$ genomes. **C**. Psu-like proteins seem to regulate expression of diverse phage defense systems across bacteria. The 37 classes of *psu*-associated defense systems identified by DefenseFinder[4] are shown in a pie chart, with the eleven most abundant defense systems indicated in color. **D**. Examples of *psu*-associated defense system loci; % identity to P4 Psu is shown. The known defense genes are colored as in **C**; a putative defense system with a SIR2-like domain is shown in white. For details see [1].

References

1. Gjorgjevikj D, Kumar N, Wang B, Hilal T, Said N, Loll B, Artsimovitch I, Sen R, Wahl MC (2023) Widespread gene regulator Psu inhibits transcription termination factor ρ by forced hyper-oligomerization. *bioRxiv* **2023**, 546067; doi: 10.1101/2023.06.22.546067
2. Krupp F, Said N, Huang YH, Loll B, Burger J, Mielke T, Spahn CMT, Wahl MC (2019) Structural Basis for the Action of an All-Purpose Transcription Anti-termination Factor. *Mol Cell* **74**, 143-157 e145; doi: 10.1016/j.molcel.2019.01.016
3. 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; doi: 10.1038/nmicrobiol.2017.62

4. Tesson F, Herve A, Mordret E, Touchon M, d'Humieres C, Cury J, Bernheim A (2022) Systematic and quantitative view of the antiviral arsenal of prokaryotes. *Nat Commun* **13**, 2561; doi: 10.1038/s41467-022-30269-9
5. Doron S, Melamed S, Ofir G, Leavitt A, Lopatina A, Keren M, Amitai G, Sorek R (2018) Systematic discovery of antiphage defense systems in the microbial pangenome. *Science* **359**, eaar4120; doi: 10.1126/science.aar4120
6. Millman A, Melamed S, Leavitt A, Doron S, Bernheim A, Hor J, Garb J, Bechon N, Brandis A, Lopatina A, Ofir G, Hochhauser D, Stokar-Avihail A, Tal N, Sharir S, Voichek M, Erez Z, Ferrer JLM, Dar D, Kacen A, Amitai G, Sorek R (2022) An expanded arsenal of immune systems that protect bacteria from phages. *Cell Host Microbe* **30**, 1556-1569 e1555; doi: 10.1016/j.chom.2022.09.017

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 Master's degree in Biochemistry or a related area of the Molecular Life Sciences.
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 (website, awards etc.):

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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 uploaded to the online portal (https://fuberlin.moveon4.de/form/60acfece5d328710e40bdbd5/eng) for evaluation by January 15th, 2025.