The Institute of Clinical Chemistry and Clinical Pharmacology (research group of Prof. Dr. Kathrin Leppek) at the Faculty of Medicine of the Rheinische Friedrich-Wilhelms-University Bonn invites applications for

3 PhD student positions (m/f/d) (65% TV-L E13, 3 years)

Project Title: Transcript-specific translation by the ribosome

The Institute of Clinical Chemistry and Clinical Pharmacology represents the two areas of Clinical Chemistry and Clinical Pharmacology in research and healthcare. The institute includes the Central Laboratory of the University Hospital, the Phase I unit for early clinical trials and 11 scientific working groups. The institute is member of the Cluster of Excellence ImmunoSensation, the Center for Integrated Oncology (CIO) Cologne Bonn and the German Center for Infection Research (DZIF). The research focus is in innate immunity, specifically immune recognition of nucleic acids and tumor immunology.

Lab Description:

Our lab focuses on how regulation of gene expression is directly executed by the ribosome, particularly in the innate immune response. Our lab studies a fundamentally new mode of gene regulation by which ribosomal RNA (rRNA) regions exposed on the outer shell of the ribosome bind to selective transcripts to control mRNA- and species-specific translation. We combine innovative RNA biochemistry and modern RNA-based technology development with model systems ranging from yeast to macrophages. Our ultimate goal is to decipher how rRNA-directed specialized translation shapes gene expression to understand the role of the ribosome in innate immune responses. Bonn is a major centre of immunological research in Germany and our lab is a new, growing, exciting, creative and inclusive place to mentor the next generation of scientists.

Project Description:

Regulation of gene expression, the decision which proteins to make from an identical genome, is essential to specify cell types and tissues. The ribosome, one of life's most ancient molecular machines, has recently been revealed to be an active regulator of gene expression. Ribosomes are not all identical in composition and do not translate all mRNAs equally: ribosomes preferentially translate specific transcripts to diversify gene expression. It is poorly understood how ribosome components, proteins and rRNA, mediate such selectivity. The regulatory capacity of rRNA in translation has long remained unexplored. Ribosomes have dramatically increased in size across eukaryotic evolution, due in part to less conserved sequence insertions called rRNA expansion segments (ESs) that "expand" rRNA on the outer ribosome shell. rRNA ESs neither contribute to nor interfere with rRNA's essential role in peptide-bond formation, so why do they exist? And what do they do?

In several projects, we want to understand how rRNA ESs directly bind to selective transcripts to control mRNA- and species-specific translation (Leppek et al., 2020; Leppek, Byeon et al., 2021), how ribosomes recognize, bind and translate selective mRNAs such that rRNA-mRNA recognition patterns diversify the proteome. Ribosomes have thereby evolved the ability to discriminate which proteins are made in a cell through selective translation via rRNA. We aim to identify and characterize the molecular mechanisms of such ribosome-directed translation. The eukaryotic ribosome contains a multitude of distinct, unexplored ESs that all have different sequence and structure. Thus, there are many open questions about what other potential functions rRNA ESs on ribosomes may have in gene regulation. In particular, we view ribosome-regulation through the lens of the innate immune response of macrophages. In the innate immune response customized translation may underlie dynamic and rapid cellular specification.

We also continue to advance tailored RNA-based technologies such as RNA aptamer-based affinity purification or our recent VELCRO-IP (variable expansion segment-ligand chimeric ribosome-IP) method, a ribosome purification and mRNA-interaction strategy that harnesses the interspecies evolutionary change in rRNA ES sequence to engineer chimeric ribosomes. Beyond, we strive to design and employ ribosome- and RNA-focused technologies to ask hard biological questions and with applications in basic science as well as in RNA therapeutics.

Selected Publications:

- **Leppek K***, Byeon GW*, Kladwang W*, Wayment-Steele HK*, Kerr CH*, Xu AF**, Kim DS**, Topkar VV, Choe C, Rothschild D, Tiu GC, Wellington-Oguri R, Fujii K, Sharma E, Watkins AM, Nicol JJ, Romano J, Tunguz B, Diaz F, Cai H, Guo P, Wu J, Meng F, Shi S, Eterna Participants, Dormitzer PR, Solórzano A, Barna M‡, Das R‡. Combinatorial optimization of mRNA structure, stability, and translation for RNA-based therapeutics. ***Nature Comm***. 2022 Mar;13(1): 1536,1-22.

- **Leppek K***, Byeon GW*, Fujii K, Barna M. VELCRO-IP RNA-seq reveals ribosome expansion segment function in translation genome-wide. ***Cell Reports***, 2021 Jan 19;34(3):108629.
- **Leppek K**, Fujii K, Quade N, Susanto TT, Boehringer D, Lenarčič T, Xue S, Genuth NR, Ban, N, Barna M. Gene- and species-specific Hox mRNA translation by ribosome expansion segments. ***Mol. Cell***, 2020 Dec 17;80(6):980-995.e13.
- **Leppek K**, Das R, Barna M. Functional 5' UTR mRNA structures in eukaryotic translation regulation and how to find them. ***Nat Rev Mol Cell Biol***. 2018 Mar;19(3):158-174.
- **Leppek K** and Stoecklin G. An optimized streptavidin-binding RNA aptamer for purification of ribonucleoprotein complexes identifies novel ARE-binding proteins. ***Nucl Acids Res***. 2014 Jan;42(2):e13.
- **Leppek K**, Schott J, Reitter S, Poetz F, Hammond MC, Stoecklin G. Roquin promotes constitutive mRNA decay via a conserved class of stem-loop recognition motifs. ***Cell***. 2013 May 9;153(4):869-81.

Methods that will be used:

- Molecular Biology/ Biochemistry
- *In vitro* cell culture/ mouse embryonic stem cells/ primary immune cells
- Ribosome profiling/ Polysome profiling/ mRNA translation techniques
- Yeast genetics/ engineering
- CRISPR-based genome editing
- RNA technology development
- RNA structure-function assays/ RNA structure probing
- RNA sequencing/ data analysis
- FACS/ cell sorting
- Mouse genetics (eventually/ in collaboration)

Profile of candidate's qualification:

The candidate (m/f/d) should hold a M.Sc. degree (or equivalent) and be an enthusiastic and highly motivated student who can work independently in a team, and values creativity, innovation and collaboration. The ideal candidate should be excited to join an international research group in a highly dynamic working environment (with English as the main written/spoken language) and should be reliable, responsible and have high scientific standards. The candidate should have a biomedicine, RNA biology, immunology, biology or a biochemical and molecular biology background. Experience in data science and RNA-seq analysis is a plus and willingness to learn computational biology is ideal.

We offer:

- The salary will be according to the German salary scale TV-L
- A "Jobticket" (subsidized public transport) is available
- There is also a possibility to use the day care center
- Supplementary benefits in the public sector (pension plan according to VBL)

The University of Bonn is committed to diversity and equal opportunity. It is certified as a family-friendly university. It aims to increase the proportion of women in areas where women are under-represented and to promote their careers in particular. It therefore urges women with relevant qualifications to apply. Applications will be handled in accordance with the Landesgleichstellungsgesetz (State Equality Act). Applications from suitable individuals with a certified serious disability and those of equal status are particularly welcome.

Application / Contact:

For further details about the application procedure and inquiries, please send an email with your CV, letter of motivation and two contacts of reference in one single pdf file addressed to Prof. Dr. Kathrin Leppek preferably by email as soon as possible and **before 31st August 2022** to:

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