



CENTRAL
EUROPEAN INSTITUTE
OF TECHNOLOGY

The Director of Central European Institute of Technology
(CEITEC MU) opens

POSTDOC AND PHD POSITIONS IN STRUCTURAL BIOLOGY OF WNT SIGNALING

Research Group: Protein-DNA interactions

Research Group Leader: Konstantinos Tripsianes, Ph.D.

Description

CEITEC is a scientific centre in the fields of life sciences, advanced materials and technologies whose aim is to establish itself as a recognized centre for basic as well as applied research. CEITEC offers a state-of-the-art infrastructure and great conditions to employ excellent researchers.

Project information:

We will apply structural biology methods in order to gain a mechanistic view of CK1 ϵ action in the Wnt signalling pathways. CK1 ϵ (and redundantly functioning CK1 δ) is a well-established positive regulator of both Wnt/ β -catenin and Wnt/PCP pathway. Dishevelled 3 (DVL3) is a phosphoprotein and a crucial CK1 ϵ target that is required for both canonical Wnt/ β -catenin and non-canonical Wnt/PCP signaling. Wnt-activation stimulates kinase activity, promoting phosphorylation of DVL3 by CK1 ϵ that results in the signal propagation and downstream effects.

CK1 ϵ represents an attractive therapeutic target but currently two key steps in the CK1 ϵ -mediated Wnt signal transduction are unclear: (**PostDoc Project**) how CK1 ϵ gets activated and/or engages target proteins in response to Wnt signal and (**PhD project**) how CK1 ϵ phosphorylates its key substrate DVL and what are the consequences of DVL phosphorylation.

During the preparatory work we have generated an extensive phosphomap of DVL where we compared the action of CK1 ϵ with other known DVL kinases. Out of 80 phospho-sites detected on DVL3 in a cellular system only a minor fraction appeared unique to CK1 ϵ . In addition, we were able to produce full length DVL3 as a substrate for in vitro kinase reactions, which after proteomic analysis gave us a list of Ser/Thr residues directly phosphorylated by CK1 ϵ . Combination of these two approaches identified 10-12 candidate sites distributed across all three DVL3 domains (DIX, PDZ and DEP) and connecting unstructured regions. We have shown for PDZ that NMR is the ideal technique for monitoring protein phosphorylation events in reconstituted kinase reactions. These data represent the basis for the proposed structural and functional validation.

Our preliminary data suggest that we can efficiently apply methods of integrated structural biology to (i) probe the DVL3 conformational landscape using in vitro and in vivo FRET sensors coupled to SAXS and CryoEM, (ii) understand the (auto)phosphorylation regulatory mechanisms of CK1 ϵ , (iii) analyse by NMR the functional consequences of DVL3 phosphorylation and (iv) monitor DVL3 phosphorylation by real-time NMR under controlled cellular conditions.

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Both positions are part of a multidisciplinary project that combines (i) cellular and molecular biology, (ii) proteomic analysis, (iii) **biochemistry and structural biology**, and received generous funding in a very competitive grant scheme.

CEITEC is a vibrant work place with excellent colleagues and infrastructure comparable to the best institutions in Europe for: (i) **cryo-electron microscopy** (Titan Krios with phase plate, Falcon3, and K2 direct electron detectors, Talos Arctica equipped with Falcon3 direct electron detector, Tecnai F20, FIB/SEM Versa3D, and vitrification robot), (ii) **X-ray crystallography** equipped with the BioSAXS arm on the Rigaku diffraction system, (iii) **high-field NMR** (500 MHz, 600 MHz, 2 × 700 MHz, 850 MHz, and 950 MHz equipped with high-sensitivity cryogenically cooled probeheads), (iv) **biointeractions** (SPR, ITC, DSC, MST, DSF, AUC, CD).

Requirements:

- We are looking for highly motivated researchers with a strong background or interest in structural biology.
- Hands-on experience with protein expression and purification is prerequisite.
- Experience with biomolecular NMR is a plus.

Employment Conditions:

Salary that will be based on the candidate's qualifications and experience.

We offer:

- Interesting position in a dynamically expanding research institute
- Background of a recognized and successful institution with supportive and international working environment
- Environment promoting interdisciplinarity and intersectorality of research
- In house core facilities
- Support of administrative departments (including grant office service)
- Support with the relocation process (welcome office service)
- 6 weeks of paid holiday

Anticipated start date:

Beginning of 2019 or upon agreement.

Please send the application (including CV, short statement of research background / interests and the contact information of at least three references) by e-mail to **kostas.tripsianes@ceitec.muni.cz**.

Please quote the "position" in the subject.

Electronic application deadline is: 31st of March 2019

For further information about:

- CEITEC, please visit www.ceitec.eu
- CEITEC Welcome Office, please visit <http://www.ceitec.eu/ceitec-welcome-office/t1137>
- Masaryk University, please visit www.muni.cz

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