Topic Proposal

Doctoral study program: Life Sciences

Supervisor: Konstantinos Tripsianes, Ph.D.

Topic title[1]: Dishevelled internal affairs in Wnt signaling

Annotation:

Dishevelled (DVL) is the central hub of Wnt signal transduction that integrates and transduces upstream signals through distinct cytoplasmic cascades. Looking at the many DVL faces reported in literature, three salient features underlying its function in signaling can be highlighted: (1) it interacts with more than seventy binding partners, (2) it is heavily phosphorylated at multiple sites by at least eight different kinases, in particular by Ck1ε/δ after Wnt stimulation, and (3) it consistently forms puncta in the cytosol, that are phase-separated self-assemblies also called liquid droplets.

Our working hypothesis is that DVL conformational plasticity mediated by the order-disorder interactions allows the combinatorial integration of phosphorylation input, partners binding, self assembly in droplets, and allosteric coupling, to exquisitely control signal routing. We integrate structural biology (NMR, SAXS, X-ray, MS-HDX) and biophysical techniques (FRET, ITC, BLI) with cellular readouts (TopFlash, BRET) to understand DVL structure, function, and regulation. Candidates can choose among three open questions, that if resolved, will have significant impact on Wnt research.

1) Does disorder provide new contexts to structured domain(s) and, hence, enhance the DVL functional space associated with them?

2) Is there a direction, order or hierarchy in the phosphorylation of individual S/T sites and clusters in DVL?

3) What are the physical behaviors associated with intrinsic disorder and their connection to DVL liquid-liquid phase separation?

Recommended literature:

1. Kravec M. et al. A new mechanism of posttranslational polyglutamylation regulates phase separation and signaling of the Wnt pathway protein Dishevelled. Embo J., 2024.
2. Hanáková K. et al. Comparative phosphorylation map of Dishevelled 3 links phospho-signatures to biological outputs. Cell Commun. Signal., 2019.
3. Harnoš J. et al. Dishevelled-3 conformation dynamics analyzed by FRET-based biosensors reveals a key role of casein kinase 1. Nat. Commun., 2019..

[1] *For each PhD position, there should be one topic proposal. If you wish to fill multiple positions, please prepare a separate topic proposal for each.*

By announcing the topic, the supervisor commits to paying contributions to the PhD candidate during the standard duration of their studies at least to the guaranteed monthly net income of CZK 22,000, as set out in the Rules of Funding for Students of the CEITEC PhD School. (Measure of the Director of CEITEC MU No. 1/2019 effective as of 1 February 2020, Scholarship Programs of the University Institute CEITEC MU – Annex No. 3) until August 2025. The supervisor is also prepared to cover the expected increase of the mandatory candidate income since September 2025 (to the total expected income 1.2 times of the minimum wage in case of the stipend and/or 1.8 times of the minimum wage in case of the salary). The student income will include stipend of 12,000 CZK from NCBR + stipend of 2,500 CZK from CEITEC MU (if any) + contribution of the supervisor (based on the Czech minimal wage and the form of payment.

Research area:
protein research in health, Wnt signalling, structural proteomics, mechanisms of protein function

Keywords:
Wnt signaling, Dishevelled, Casein kinase, interactions, conformations, phosphorylations, dynamics, allostery, NMR, X-ray crystallography, SAXS, FRET, cryo-EM, native MS, MS-HDX.

Funding of the PhD candidate:
GACR 2507

Requirements for candidate:
Biomolecular NMR
Biochemistry
Molecular Cell Biology

Information about the supervisor:
3 PhD students, 35 publications, *h*-index 21

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