CRBM external seminar

Friday Dec 8th 10:00 am Amphithéâtre CNRS

Title: Targeting dipeptide repeat-driven condensation in ALS/FTD

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Peter Tompa is the professor of biochemistry at the VUB (Free University Brussels), and a group leader in both Brussels (at Flanders Institute of Biotechnology, VIB) and Budapest (in the Institute of Enzymology). He is also the founder of NEQ Biosciences, a Boston-based startup targeting intrinsically disordered proteins (IDPs).

He was among the ones founding the IDP field, developing many basic concepts of protein disorder, such as moonlighting, fuzziness, disordered domains, supertertiary structure, multisteric regulation, etc…. Currently, his interest turned to studying the role of structural disorder in liquid-liquid phase separation (LLPS) of proteins in physiology and disease. He published 235 papers and the first monograph of the IDP field "Structure and function of intrinsically disordered proteins" (2009) by Taylor and Francis, Inc.

Abstract: Biomolecular condensation is a process whereby many macromolecules (proteins and RNAs) form non-stoichiometric, functional assemblies. The dominant mechanism of such biomolecular condensation is liquid-liquid phase separation (LLPS), which leads to the formation of membraneless organelles (MLOs), such as the nucleolus and stress granules, in the cell. The proteins involved often have a high proportion of intrinsic structural disorder, which drives LLPS by transient, multivalent interactions. As MLOs play key roles in cell signaling, the misregulation of their formation and dissolution often leads to disease states, "condensatopathies", and asks for the development of condensate-modifying drugs, "c-mods". In my presentation, I will outline the basic mechanisms leading to such disease states, focusing on cancer, viral infections and neurodegeneration. I will then show in detail the pathological impairment of nucleoli and stress granules by dipeptide repeats, poly-GR and poly-PR generated in amyotrophic lateral sclerosis (ALS), and outline that a special FDA-approved drug, polystyrene sulfonate, can counter such pathological effects.

Selected publications:

Tompa, P., Davey, N. E., Gibson, T. J., and Babu, M. M. (2014) A million peptide motifs for the molecular biologist. Mol. Cell 55, 161-169

Sormanni et al. (2017) Simultaneous quantification of protein order and disorder using NMR spectroscopy. Nature Chem. Biol. 13: 339-342

Boeynaems et al. (2017) Phase Separation of C9orf72 Dipeptide Repeats Perturbs Stress Granule Dynamics. Mol. Cell 65: 1044–1055

Korkmazhan, E., Tompa, P. and Dunn, A. R. (2021) The role of ordered cooperative assembly in biomolecular condensates. Nat. Rev. Mol. Cell Biol. 22: 647-648.

Van Nerom, M., et al. (2023) C9orf72-linked arginine-rich dipeptide repeats aggravate pathological phase separation of G3BP1. bioRxiv. https://www.biorxiv.org/content/10.1101/2023.03.31.535023v1