CRBM external seminar
BIOLuM
Thursday, November 14th at 11:00 am Salle Marcel Dorée

"Enhancing cellular proteostasis as a strategy against misfolded proteins accumulation"

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*Agnieszka Krzyżosiak graduated in Biotechnology from Wroclaw University of Science and Technology, Poland. Agnieszka holds a PhD in Neurosciences, achieved through a prestigious co-tutelle program between the **Université de Strasbourg** and **Wroclaw University of Technology**. She furthered her expertise as a Postdoctoral Researcher in **Dr. Anne Bertolotti's team** at the **MRC Laboratory for Molecular Biology** in Cambridge, UK, where she received both **EMBO** and **HFSP long-term fellowships**.*

*Currently, Agnieszka leads her own research group at the **Łukasiewicz Research Network – PORT Polish Center for Technology Development** in Wroclaw. Her lab focuses on understanding the **molecular mechanisms of neurodegeneration**, with a particular emphasis on preventing protein misfolding in neurodegenerative diseases. Among her notable achievements is the discovery of the **first selective inhibitor of PPP1R15B phosphatase**, which has shown promise in alleviating the symptoms of Huntington's disease. This breakthrough led to the founding of **CamPhos Therapeutics Ltd.**, where Agnieszka gained invaluable experience in translating basic research into commercial applications.*

Abstract

Neurodegenerative diseases (NDDs) are devastating, age-related disorders, which despite substantial efforts remain largely uncurable. The incidence of NDDs rises dramatically in our aging population, which points to an urgent need to tackle these fatal diseases. The deposition of misfolded proteins in a cell is a defining feature of NDDs that points to the deregulation of protein quality control (PQC) pathways in NDDs. With that said, enhancing the PQC systems could serve as an attractive therapeutic strategy. We have validated this concept by identification of PQC-boosting selective phosphatase inhibitors. These eIF2α pathway-targeting small molecules readily crossed the blood-brain barrier and were safe upon chronic administration in vivo. Enhancing cellular proteostasis using those agents prevented the behavioral and molecular deficits in NDD mouse models as well as prevented neurodegenerative phenotypes development in human reprogrammed neurons, derived from patients by direct conversion of fibroblasts, a model retaining the genetic and epigenetic background of the disease. The beneficial effect of boosting PQC was recapitulated upon genetic manipulation of the pathway. This work demonstrates the disease-modifying potential of phosphatase inhibitors and points to the opportunities to identify therapeutic targets in neurodegeneration within the space of the protein quality control that we continue to develop in our laboratory.

Selected publications

1. Krzyzosiak A., Pitera A., Bertolotti A. An Overview of Methods for Detecting eIF2α Phosphorylation and the Integrated Stress Response. (2022) Methods Mol Biol. 2428:3-18.
2. Krzyzosiak A., Podlesny-Drabiniok A., Vaz B., Alvarez R., Rühl R., de Lera AR., Krezel W. Vitamin A5/X controls stress-adaptation and prevents depressive-like behaviors in a mouse model of chronic stress. (2021) Neurobiol Stress. Aug 3;15:100375.
3. Krzyzosiak A., Sigurdardottir A., Luh L., Carrara M., Das I., Schneider K., and Bertolotti A. Target-Based Discovery of an Inhibitor of the Regulatory Phosphatase PPP1R15B. (2018) Cell. Aug 23; 174(5), 1216–1228
4. Niewiadomska-Cimicka A., Krzyżosiak A., Ye T., Podleśny-Drabiniok A., Dembélé D., Dollé P., Krężel W. Genome-wide Analysis of RARβ Transcriptional Targets in Mouse Striatum Links Retinoic Acid Signaling with Huntington's Disease and Other Neurodegenerative Disorders.