DANDRITE / Kjeldgaard LECTURE

Therapeutic manipulations of phosphatases and kinases controlling protein quality control systems: From the bench, to the clinic and back.

The deposition of misfolded proteins is a defining feature of many age-dependent human diseases, including the increasingly prevalent neurodegenerative diseases. Why aggregation-prone proteins accumulate in aged cells remains largely unclear. Cells normally strive to ensure that proteins get correctly folded and have powerful and sophisticated mechanisms to maintain protein homeostasis (proteostasis) under adverse conditions. However, with age and in diseases, the cellular defence systems against misfolded proteins are overwhelmed, leading to the accumulation of misfolded proteins with devastating consequences for cells and organism.

In principle, improving the cells' ability to deal with misfolded proteins could represent a generic approach to reduce the pathology in diverse protein misfolding diseases. My lab has identified powerful small drug-like molecules that safely boost a natural defence system against misfolded.
These small molecules inhibit serine/threonine phosphatases controlling the termination of a proteostatic pathway, an interesting finding because phosphatases were previously thought to be undruggable. The inhibitors have demonstrated therapeutic effects in various models of neurodegenerative diseases. This work demonstrates that generic approaches aimed at helping cells to survive protein quality control failures can be useful to prevent protein misfolding diseases, including the devastating neurodegenerative diseases. One of these inhibitors, Sephin1, has passed through favourable Phase 1 clinical trials in 2019 and is being now developed for Charcot-Marie-Tooth disease and amyotrophic lateral sclerosis. In 2011, Guanabenz was found beneficial in a phase 2 clinical trial in ALS, 10 years after we reported its proteostasis-boosting activity.

The work on these inhibitors has perked our interest in serine/threonine phosphatases, a class of very important yet poorly characterized enzymes. In a recent tour de force, we have deployed a combination of approaches to elucidate the mechanism by which an eIF2 phosphatase recruits its large substrate.

Expanding our toolbox, we recently made the unexpected discovery that broadly used ATP-competitive inhibitors of eIF2 kinases can paradoxically increase eIF2 phosphorylation by directly binding to and activating a sister kinase resulting in functional activation of the pathway rather than the intended inhibition. These findings have broad relevance to kinases.

Hosts: Chao Sun (DANDRITE) and Christian Kroun Damgaard (Kjeldgaard).

After the lecture we serve coffee and cake, followed by a chalkboard session for the PhD students (also in 1871-120).

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Date:	**Thursday 7 November 2024**
Time:	**13.00 – 14.00**
Venue:	**Nucleus (1871-120)**
Address:	**Universitetsbyen 81**
	8000 Aarhus C

OPEN TO ALL INTERESTED.

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