

09 Nov
2022

Wednesday
LECTURE*

MEET & EAT*
Light lunch provided

11.15 am - 12 noon

12.15 - 1.15 pm

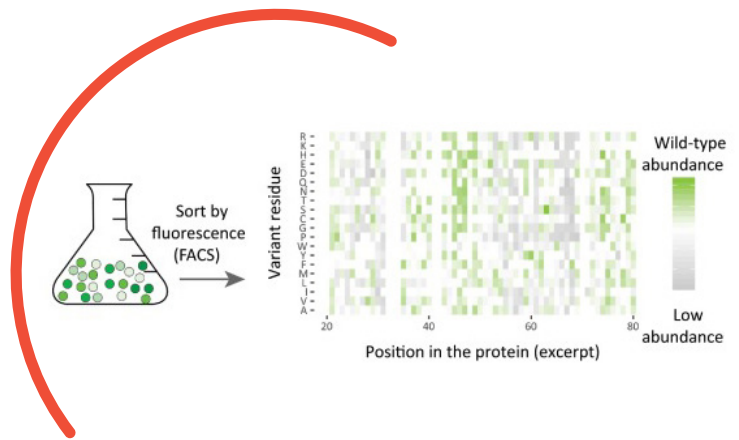


Proteostasis analyzed through deep mutational scanning

ABSTRACT

More than half of disease-causing missense variants are thought to lead to protein degradation, but the molecular mechanism of how these variants are recognized by the cell remains enigmatic. To approach this issue we have applied deep mutational scanning experiments to test the degradation of thousands of missense protein variants in large multiplexed experiments in cultured human cells. We use a model protein where known missense variants result in an autosomal recessive neurodegenerative disorder. The resulting mutational map comprises >99% of all possible single-amino-acid substitution and nonsense variants.

With a few notable exceptions, the majority of the destabilizing mutations are located within the structured domains of the protein, while flexible and disordered linker regions are more tolerant to mutations. The cellular abundance data correlate with the protein's structural stability, evolutionary conservation, and separates known disease-linked variants from harmless variants. Systematic mapping of degradation signals (degrons) shows that inherent primary degrons in the protein largely overlap with regions that are highly sensitive to mutations. The vast majority of low abundant variants are degraded through the ubiquitin-proteasome system and are stabilized at lowered temperatures. In conclusion, in addition to providing a diagnostic tool for rare genetic disorders, deep mutational scanning technologies have the potential to reveal both protein specific and general information on the specificity of the protein quality control network and the ubiquitin-proteasome system. Examples of this will be presented.



SPEAKER

Prof Rasmus Hartmann-Petersen

University of Copenhagen, Denmark

HOSTS:

Department of Infection and Immunity (LIH)
University of Luxembourg

RESPONSIBLE SCIENTISTS:

Gunnar Dittmar / (gunnar.dittmar@lih.lu)
Alexander Skupin / (alexander.skupin@uni.lu)

For any questions regarding the Lecture Series please email:
omics-lecture@lih.lu

***Please note that registration is mandatory by sending an email to
florence.henry@lih.lu**

Location:

University of Luxembourg
CAMPUS BELVAL
Maison du Savoir
Room: 4.510
2, avenue de l'Université
L-4365 Esch-sur-Alzette

Webinar via webex:

JOIN

Event number: 2734 477 0315
Event password: qRx3MyAx65N

Meet & eat:

University of Luxembourg
Campus Belval
Coffee Lounge, 2nd floor, BT1
7, avenue des Hauts-Fourneaux
L-4362 Esch-sur-Alzette