Protein aggregation diseases: from molecular biology and structure to clinic and therapy

Organizers: Ronald Buijsen[1], Willeke van Roon-Mom[1], Wim Mandemakers[2], Andrea Conidi[2], Vered Raz[1]

[1] *Human Genetics, Leiden University Medical Center, Leiden*
[2] *Erasmus Medical Center, Rotterdam*

Date: **28-29 November, 2024**
Location: **Erasmus MC, Rotterdam**

Aberrant protein homeostasis can lead to accumulation and aggregation of proteins in insoluble cellular structures. Protein aggregation is a hallmark feature of many common and rare adult neurodegenerative and neuromuscular diseases. Despite the varied genetic causes for the protein aggregation diseases, common molecular mechanisms are involved in the accumulation of protein aggregates leading to common disease mechanisms. Accumulation of proteins and subsequently its aggregation is caused by malfunctioning of protein homeostasis and protein folding machineries. Some diseases, such as polyglutamine or polyalanine disorders are rare and monogenic, while for more common disorders such as Alzheimer and Parkinson, there are multiple known and unknown genetic causes.
This course will discuss the main basic molecular mechanisms regulating protein homeostasis and protein folding that affect protein aggregation, and the structure of fibrils generated by pathogenic protein aggregates. We will discuss research tools and models for protein aggregation, and will discuss genetics, clinics, and therapeutic developments in interactive sessions.

Programme

Day 1, November 28th 2024, Erasmus MC room Ee251 (OWR-72):

Introduction: an overall concept for protein aggregation and pathological conditions, similarities and variations between condition (spectrum of conditions, genetics, causes) and the path to therapeutics.

Morning session:

08:45-09:15 Registration and coffee

09:15-09:30 Introduction to the course

Session 1: Molecular Mechanism regulating protein accumulation and folding: molecular regulators of protein aggregation.

09:30-10:15 Lecture 1: Mitochondrial dysfunction *Pier Mastroberardino (Erasmus MC)*

10:15-11:00 Lecture 2: The UPS *Monique Mulder (LUMC)*

11:00-11:15 coffee and tea break

11:15-12:00 Lecture 3: Chaperones Anne Wentink (Leiden University)

12:00-12:30 Discussion molecular mechanisms *all speakers morning session*

12:30-13:30 Lunch break

Afternoon session:

Session 2: Protein aggregation structure and single molecule dynamics

13:30-14:00 Lecture 4: Aggregation of alpha-synuclein *Steven Roeters*

14:00-14:30 Lecture 5: Imaging the molecular details of protein aggregation with cryoEM *Thom Sharp (Bristol University, UK)*

14:30-15:00 Discussion structure and dynamics

15:00-15:15 coffee and tea break

Session 3: Protein aggregation in disease models and clinics

15:15-15:45 Lecture 6: Clinical description of protein aggregation disorders *Agnita Boon*

15:45-16:15 Lecture 7: Gene hunting protein aggregation disorders *Vincenzo Bonifati*

16:15-16:45 Lecture 8: Disease modeling of protein aggregation disorders *Wim Mandemakers*

16:45-17:15 Discussion disease models and clinics

17:15-18:15 Drinks and networking.

Day 2, November 29 2024, Erasmus MC Ae-406)

***Morning session*:**

Session 4: Translational session - examples of therapeutic developments

09:00-9:45 Lecture 1: Dutch ALS centre, clinics, genetics, disease mechanism, therapeutical approaches and clinical trials. *Pavol Zelina (UMCU)*

9:45-10:15 Lecture 2: Therapy development in the lab *Willeke van Roon-Mom(LUMC)*

10:15-10:30 coffee and tea break

10:30--11:00 Lecture 3: Vectorized antibodies anti-aggregation as potential therapeutics *Vered Raz (LUMC)*

11:00-11:30 Lecture 4: Small molecules therapy *Sabine Schipper-Krom (AMC)*

11:30 – 12:00 Discussion: therapeutic options

12:00-13:00 Lunch break

Afternoon session:

Session 5: Interactive session

13:00-16:00 *interactive session in workgroups (2 hours prep and one hour presentation – 12 minutes per group).*

16:00 drinks