SORS: The Mutational Landscape of a Prion-like Domain

Objectives

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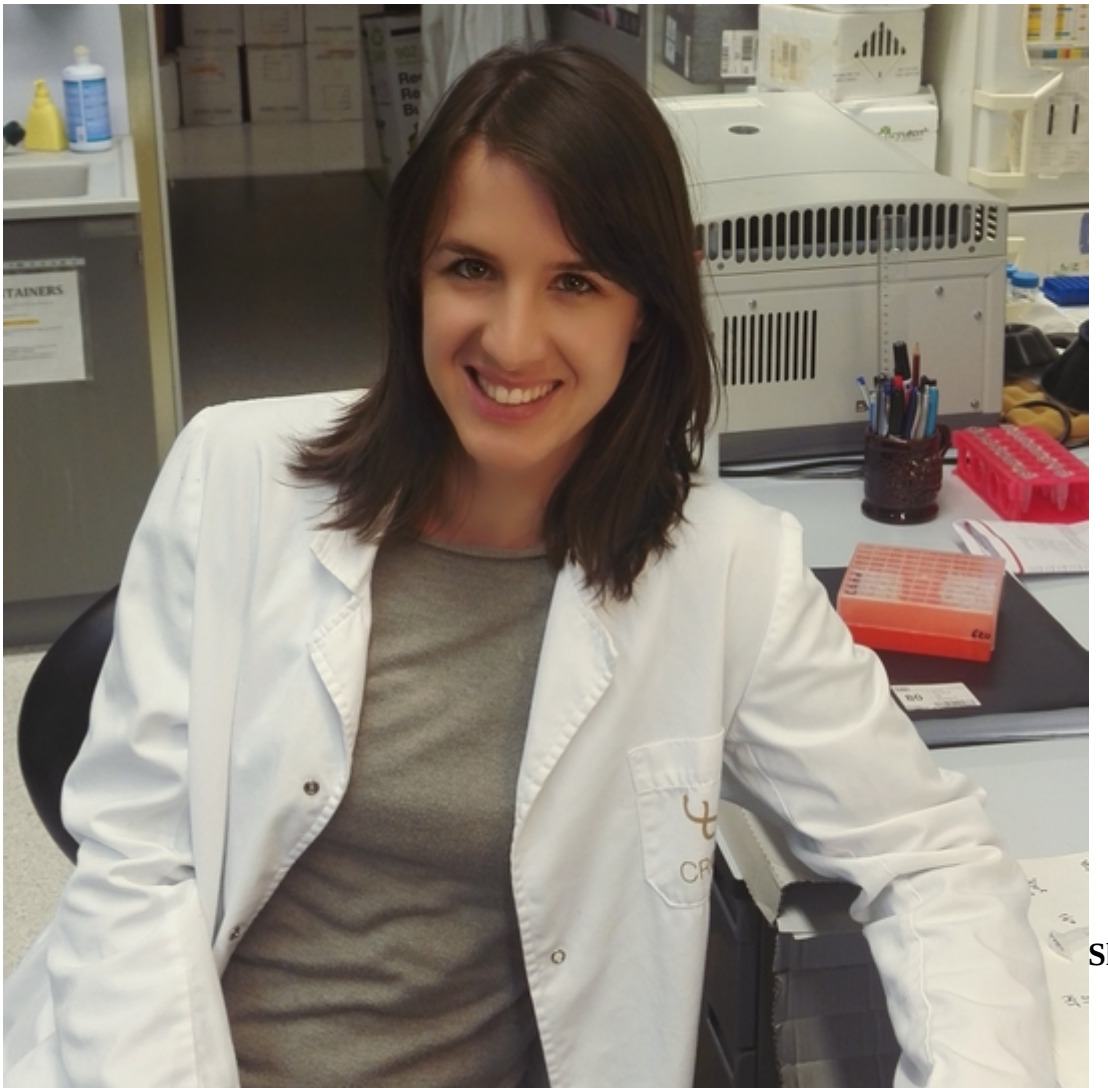
Abstract: At least 70 human RNA-binding proteins contain a prion-like domain (PrLD). PrLDs are low complexity domains which resemble in composition the infectious yeast prions. Mutations in PrLDs are associated to the onset of many neurodegenerative conditions, such as Amyotrophic Lateral Sclerosis (ALS). PrLDs are able to populate multiple physical states: diffuse, liquid de-mixed, insoluble amyloid. Pathological mutations affect these equilibria in ways we cannot yet fully understand, or predict. The TAR DNA binding protein TDP-43 contains a 140 aa long PrLD and forms cytoplasmic aggregates in most cases of ALS. We use Deep Mutational Scanning to understand how sequence determines the toxicity of TDP-43 in a yeast model. I will present the first "genotype-to-phenotype" map of TDP-43 where we quantify the effect of all possible amino acid substitutions in the PrLD on cellular fitness. While allowing us to understand the impact of mutations within low-complexity regions, these data provide the basis to understand by which mechanism protein inclusions drive pathogenesis.



Short bio: Benedetta

Bolognesi graduated in Biotechnology from the University of Pavia, Italy, and carried out her PhD studies with Prof. Chris Dobson, at the department of Chemistry in Cambridge, UK. Here, she focussed on characterizing the biophysical properties of the Amyloid-Beta peptide. For her Post-Doc, Benedetta moved to the CRG, Barcelona, where she studied the ability of proteins to liquid de-mix in response to altered expression levels. She Joined IBEC with a junior group leader position in September 2018. Her lab builds mutational landscapes of intrinsically disordered proteins involved in neurodegeneration.

Speakers

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