Contribution ID: **6**

Type: **Lecture**

De Novo Nanobody Design

Thursday 25 September 2025 09:00 (1h 30m)

Nanobodies (Nbs) from pre-immune libraries could exhibit deficiencies in biophysical properties, such as stability and affinity, necessitating an optimization step. This can be achieved either in vitro through controlled mutagenesis followed by another round of panning or in silico by proposing variants. This approach, which involves screening multiple single-site variants, may demand extensive experimental efforts. Additionally, negative epistatic effects can occur when combining multiple potentially beneficial single-site variants, where increased affinity variants may negatively impact stability.

Emerging data-driven Machine Learning (ML) approaches are promising in the field of de novo Nb design or redesign, as they can learn multidimensional constraints between protein structure, stability and binding capacity, while explicitly designing protein and non-protein biomolecules at atomic-level resolution.

Anyway, a small amount of data is available for training Nbs-specific methods and available models have been tested and validated mainly in the design of mini-binders of known protein biomarkers. In this workshop session an introduction to these methods and their expected accuracy on published data will be provided, with the possibility to try a couple of them through a Jupiter Notebook run over the internet browser in a simple case study. In the second part there will be a perspective and discussion on adapting such de novo protein design systems for nanobody CDRs (re)design tasks.

Presenter: Dr ORLANDO, Marco (University of Milano-Bicocca, Italy)

Track Classification: In Silico Modelling and Design