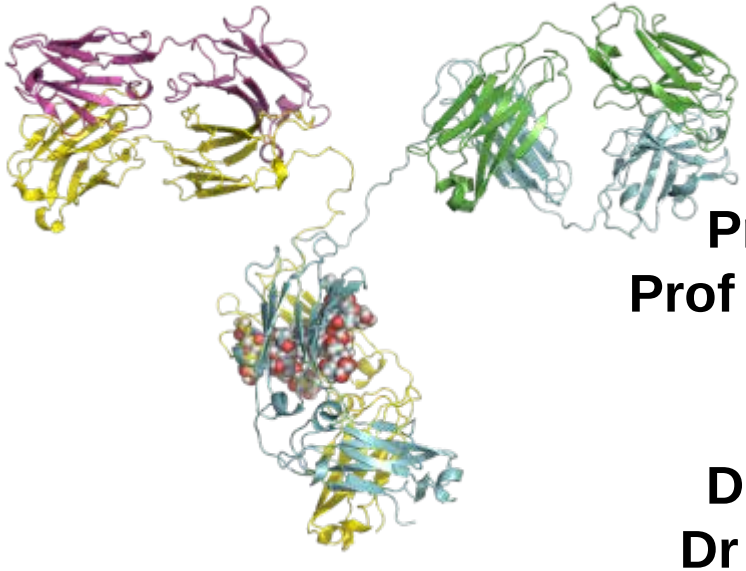
Enabling rapid liquid and freeze-dried formulation design for the manufacture and delivery of novel biopharmaceuticals



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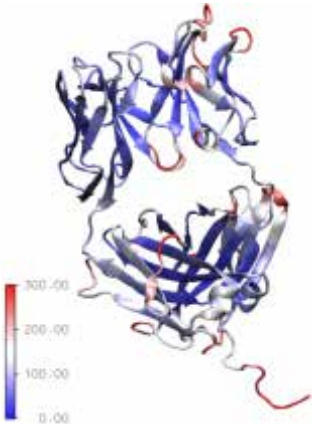


EPSRC EP/N025105/1

Introduction

- ***Biopharmaceuticals market*** *is rapidly growing with reported sales of £197 billion in 2016 (compared with total drug market of £816 billion)*

- *Next generation therapies are increasingly complex and engineered for biological activity at the expense of physical and chemical stability (eg protein fusions, fragments, conjugates with small drug molecules)*

- ***Formulation development of biopharmaceuticals***

  1. *Major challenge: dosage forms are required for clinical trials which fixes formulation at an early stage. Development stages occur early in the therapeutic lifetime when not much material is available*

  2. *Formulations require stability, potency, and ease of delivery to patient*

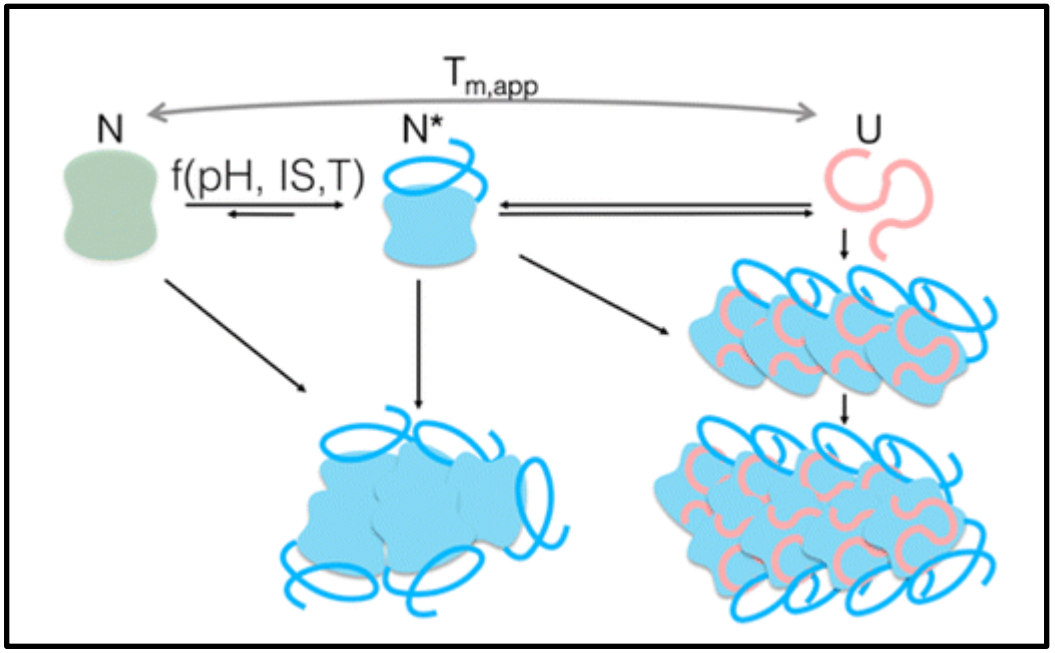
  3. *Chemical and physical degradation pathways compromise stability*

  4. *Many therapeutics are required at high concentrations which leads to increased physical degradation, poor rheological properties, and phase separation*

Protein aggregation

- ***Predicting and controlling aggregation is an outstanding challenge:***

1. *Key intermediates are transient and occur at very low relative populations*
2. *Key steps in aggregation pathways are difficult to isolate*
3. *Multiple mechanisms for aggregate formation and aggregate growth that depend on protein and environmental conditions (solvent properties, temperature)*



- ***Predictive approaches are indirect***

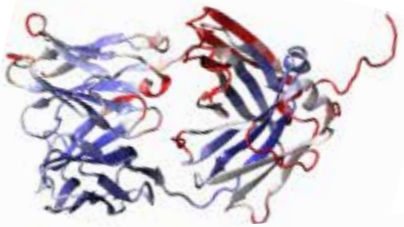
1. *Use surrogate parameters such as unfolding temperature or free energy, colloidal stability (eg aggregation temperatures and protein-protein interaction measurements)*
2. *Accelerated aggregation using Arhenius-type extrapolations*

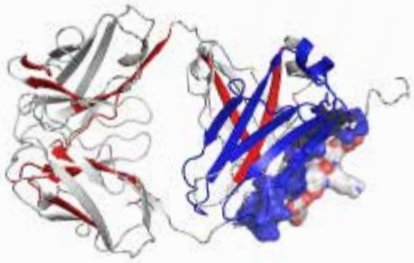
Objectives

O1. Use high-throughput automation to generate a large experimental formulation dataset for protein:excipient combinations, that will include aggregation kinetics, conformational stability, colloidal stability, phase behaviour, and rheology measurements.

O2. Molecular informatics and modelling will improve predictability of formulation attributes and excipient effects

O3. Analytical advances will enable earlier, more sensitive, and lower-volume assessments of formulated protein degradation kinetics.





Understand:

What structural / sequence features underpin aggregation?

- *3 ° / 4 ° conformation?*
- *local dynamics?*
- *global stability?*
- *aggregation (cross-beta) hotspots?*
- *excipient binding interactions?*

Evaluate and Measure:

Do conformational and colloidal stabilities correlate to aggregation rates?

Does forced degradation at high temperature predict shelf-life?

Can alternative methods be developed for predicting aggregation rates?

Ultra-low volume predictive measurements – intrinsic time-resolved fluorescence (IP-TRF).

Can dilute concentration measurements be predictive of concentrated solution properties (phase separation, rheology)

Engineer:

Can we engineer lower aggregation rates?

Can we develop novel (GRAS-based) excipients?

Research team

PDRAS

- John Hales – UCL
- Cheng Zhang – UCL
- Samir Aoudjane - UCL
- Jordan Bye – University of Manchester
- Max Hebditch – University of Manchester

PhD students*

- Nuria Codina – UCL
- Akash Pandya - UCL
- Nikita Vekaria – University of Manchester
- Jas Kalayan – University of Manchester

* Supported by CDT affiliated with EPSRC Centre for Innovative Manufacturing in Emergent macromolecular Therapies

Molecules and Partners to date

Partners and in-kind material

- UCB Pharma - A33 Fab, IgG1, IgG4
- NIBSC – GCSF, TGN1412, Camel Abs
- UCL/Abzena – Domain 1
- Porton Biopharma – recombinant vaccine, erwinase
- Albumedix – HSA, HSA-fusions
- MedImmune – IgG1, IgG4
- Ipsen – Endoneg Dysport
- LGC – HGH
- Arecor – novel excipients

Equipment manufacturers

- Wyatt Technology – plate reader, viscostar