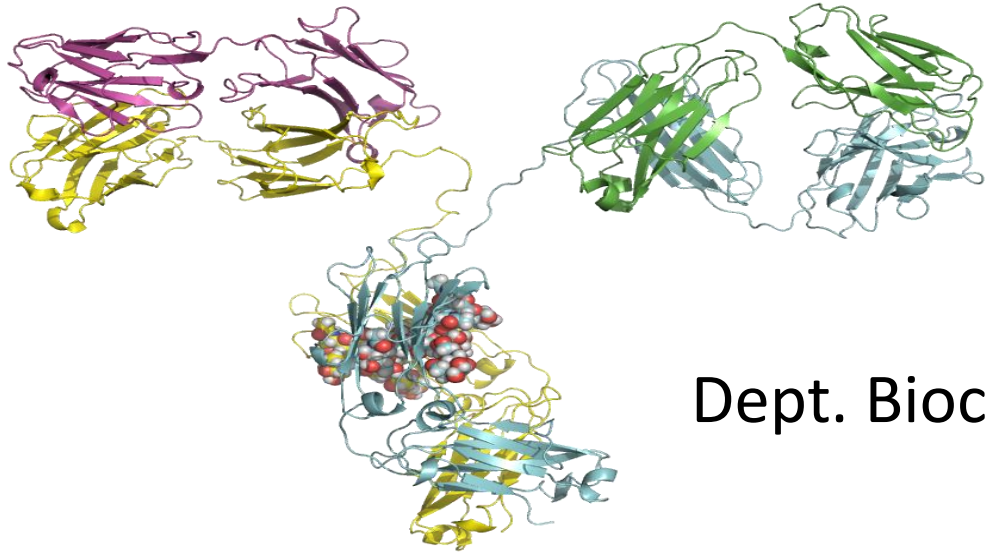
EPSRC CENTRE for Innovative Manufacturing in Emergent Macromolecular Therapies

Analytical challenges in protein formulation



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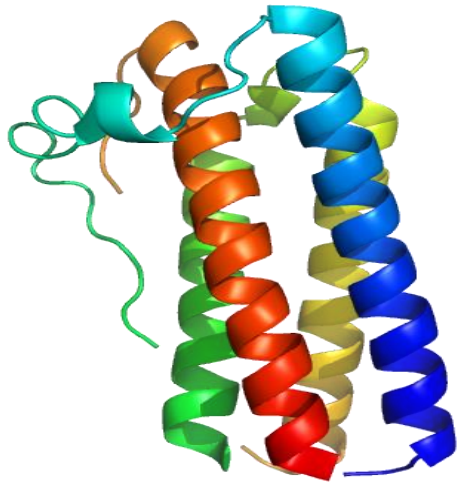

Formulated product evolution

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Higher protein concentration MAb formulations

- stability
- viscosity

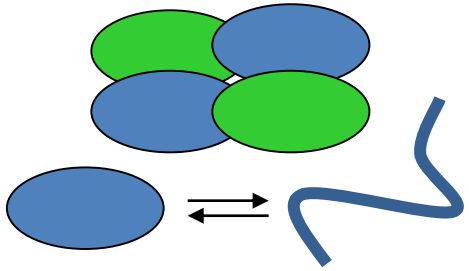
New engineered molecules

- could be inherently less stable than platform Mabs
- new types of (or different ranking of) molecular instability in novel entities?

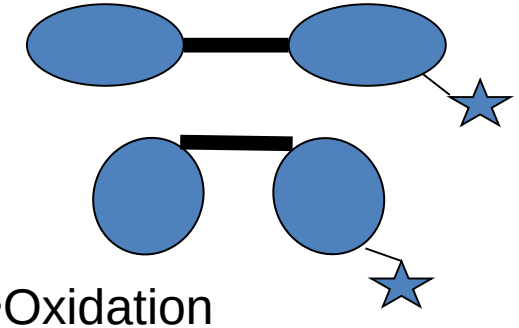
Novel formulation modes

- conjugates
- liposomes
- nanoparticles
- emulsions
- solid state implants
- multi-protein products
- protein-DNA / protein-mRNA / etc

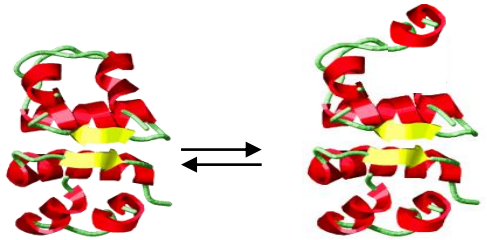
Analytical Capability



- Size
- Subunit composition
- (Un)Folding extent
- Oligomerisation
- Aggregation



- Oxidation
- Deamidation
- Glycosylation
- Conjugation (eg PEG)
- Fragmentation/clipping



N **N***

- Partial unfolding
- Rapid transitions
- Excipient interactions
- Global dynamics

Conformation / aggregation → **Native mass / charge mods** → **Structural dynamics**

CD, Fluorescence, SANS, SAXS, AFFF, AUC, DLS, MALLS, Particle imaging, SEC, HIC, Thermofluor / DSF, SDS-PAGE, RP-HPLC

IEX / CZE-IEX
LCMS

NMR
XRCD
FRET
FCS

Not to mention…..Immunogenicity, Viscosity, Function, *In vivo* half-life

Outputs of July 2012 UCL EPSRC CIM Straw Poll

95% - Characterisation of “Protein Stability”

91% - Characterisation of protein degradation of final dosage form

83% - Characterisation of protein degradation during bioprocess manufacturing

78% - Characterisation of interactions between excipients and proteins

76% - Tools to show that a candidate product is Fit for purpose (i.e. readily manufactured

75% - Low volume screens/assays

73% - High-throughput screens vs accuracy

72% - Predictive tools for formulation excipient selection

70% - Characterisation of <2% contaminants

67% - Characterisation of heterogeneity and phase states in freeze-dried formulations

67% - Analytical methods to complement thermal forced degradation studies

Q1: Challenges to prioritise

- Too little material available at early bioprocess development stages
- Need to screen a large design space
- Formulations are 10-200 mg/ml, Biophysics is 0.01-5 mg/ml
- New degradation pathways with new products
- Compliance / acceptance with regulatory agencies
- Shortage of analytical skills

Q2: Possible solutions to prioritise

- High concentration biophysics / analytics
- Increased throughput
- Low volume/sample measurements
- Gaps in molecular species characterisation
- Applicability to more complex formulations (eg liposomes / emulsions etc)
- Better training of graduates / technicians