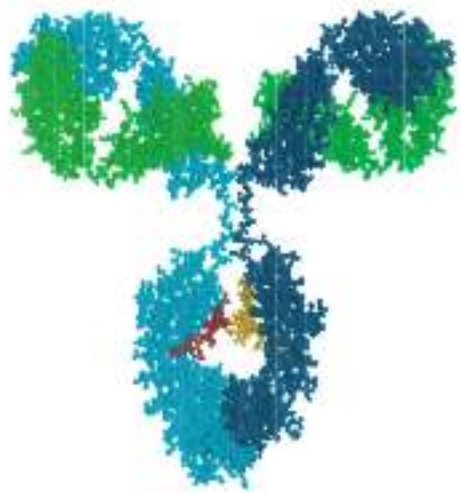
Creative Formulation Approaches to Overcome New and Old Challenges

Bernardo Perez-Ramirez, Ph.D.
Senior Scientific Director, BioFormulations, Global Pharmaceutical Development-Biologics. Genzyme/Sanofi, Framingham, USA

MIBio 2016: Stability of biopharmaceuticals – From molecular interactions to successful products.
9st November 2016, Cripps Court, Magdalene College, Cambridge, UK

SANOFI

ONE PROCESS-ONE PRODUCT: PARADIGM FOR FORMULATION DEVELOPMENT

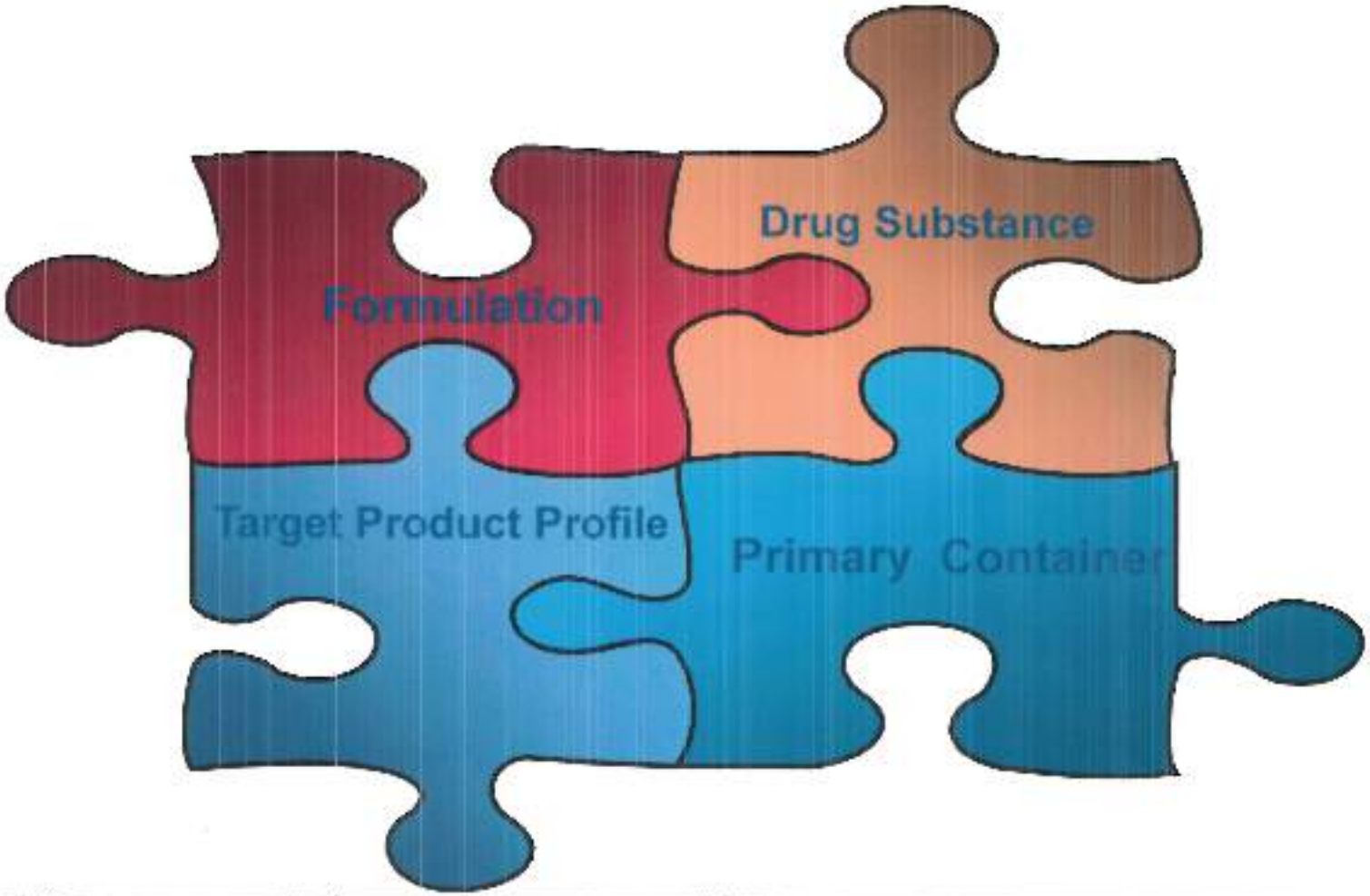


- Biologics are highly complex molecules whose properties are closely related to their **manufacturing process:**
  - Fluctuations in the manufacturing process (e.g., pH, temperature, culture media)
  - Changes in the manufacturing process (e.g., expression system)
  - Batch variability (glycan pattern, oxidation, aggregates)

- For biotechnology medicinal products, small changes of the drug substance production (upstream processing) and purification (downstream processing) can affect the final drug product.

➔ Changes of the manufacturing process during development should be carefully considered from a formulation perspective.

FORMULATION AS PART OF AN INTEGRATED DEVELOPMENT APPROACH



SANOFI

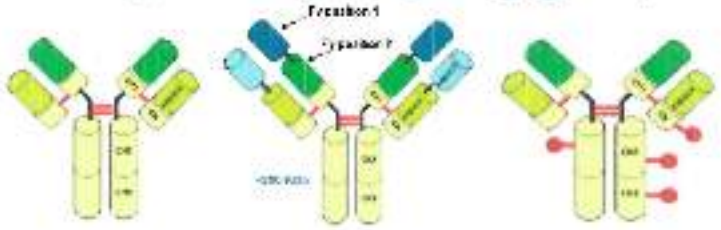
CHALLENGES FACING PROTEIN FORMULATION AND PRODUCT DEVELOPMENT

The formulation development for biologics is constantly changing to reflect the emerging of **new antibody scaffolds**, the **increasing use of subcutaneous injection** (as alternative to iv injection) and the growing **constraints on development timelines** particularly at the early clinical stages.

Intellectual property and freedom to operate: innovators vs. biosimilars

Antibody scaffolds

Monoclonal antibody (mAb), Bi-specific antibody, antibody drug conjugate (ADC)



mAb *bi-spec* *ADC*

Pharmaceutical Form / Drug Device Combination

Concentrate or Powder for solution for infusion, Solution for injection.

PFS, Auto-injector, Large volume device

SANOFI

FORMULATION DEVELOPMENT MUST CONSIDER THE CONVENIENCE TO PATIENTS

- Target Product Profile (TPP) should be defined earlier
  - Can we achieve the TPP?
- Most monoclonal administered by SC route to improve patient convenience
  - Low bioavailability
  - De-risking construct earlier
    - Process not defined
  - Develop ability/device ability

High protein concentrations, small volumes, high viscosity: **CAN WE INCREASE EFFICACY?**

In need of analytical tools (in silico & experimental) to predict protein solution behavior from low to high protein concentration (*more later*)

- The balance between first in human and commercial formulations
  - Platform approaches
  - Robotics and high through put screening (new scaffolds that do not fit platform).

PLATFORM APPROACHES IN FORMULATION DEVELOPMENT: LIQUID FORMULATIONS

- Liquid formulation optimized around a few types of excipients with defined function for stabilizing mAbs
  - *Buffering system and pH*: the pH can affect the degradation pathway (deamidation, isomerization...) and play a key role in long range electrostatic interactions (colloidal aggregation): pH 5.0-7.5 / Acetate, Citrate, Histidine, Tris, Phosphate.
  - *Thermal stabilizers* to improve the stability of mAb upon thermal stress and to increase the shelf life of the drug product: sucrose, glycine, proline, arginine, mannitol, NaCl...
  - *Viscosity reducers* for highly concentrated mAb formulation: arginine, lysine.
  - *Surfactant stabilizers* to prevent the precipitation or aggregation of proteins when agitated (hydrophobic interfaces): polysorbate PS20 or PS80, polyethylene glycol.

LIQUID FORMULATIONS IN COMMERCIAL mAbs DRUG PRODUCTS- *(Warne et al., 2011)*

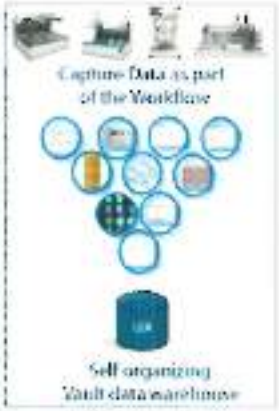
Surfactant: 12 PS80. 4 PS20 / 21 ; **Buffer**: His 9 . / 21 ; **Polyol**: Sucrose 7. Mannitol 3 /21

Product name	Dosage form	Concentration	pH	Formulation
ILARIS® (canakinumab)	Lyophilized	150 mg/mL	NA	82.4 mg/mL sucrose, L-histidine and L-histidine HCl, 0.6 mg/mL polysorbate 80
XOLAIR® (omalizumab)	Lyophilized	125 mg/ml	NA	125 mg/mL omalizumab, 90 mg/mL sucrose, 1.7 mg/mL L-histidine hydrochloride monohydrate, 1.1 mg/mL L-histidine, 0.3 mg/mL polysorbate-20
RAPTIVA® (efalizumab)	Lyophilized	100 mg/mL	~6.2	Approximately 82 mg/mL sucrose, 4.5 mg/mL L-histidine hydrochloride monohydrate, 2.9 mg/mL L-histidine, 2 mg/mL polysorbate-20
SYNAGIS® (palivizumab)	Lyophilized	100 mg/mL	NA	47 mM histidine, 3 mM Glycine, 5.6% mannitol
SIMPONI® (golimumab)	Liquid	100 mg/mL	~5.5	0.88 mg/mL histidine and histidine–HCl monohydrate, 41 mg/mL sorbitol, 0.16 mg/mL polysorbate 80
STELARA® (ustekinumab)	Liquid	90 mg/mL	5.7–6.3	1 mg/mL L-histidine and L-histidine–HCl, 76 mg/mL sucrose, 0.04 mg/mL polysorbate-80
HUMIRA® (adalimumumab)	Liquid	50 mg/mL	~5.2	6.2 mg/mL sodium chloride, 0.86 mg/mL sodium citrate, 1.3 mg/mL citric acid monohydrate, 12 mg/mL mannitol, 1 mg/mL polysorbate 80
CAMPATH® (alemtuzumab)	Liquid	30 mg/mL	NA	8 mg/mL sodium chloride, 1.44 mg/mL dibasic sodium phosphate, 0.2 mg potassium chloride, 0.2 mg/mL monobasic potassium phosphate, 0.1 mg/mL polysorbate 80, 0.0187 mg/mL disodium edetate dihydrate
AVASTIN® (bevacizumab)	Liquid	25 mg/mL	6.2	60 mg/mL trehalose, 5.8 mg/mL sodium phosphate monobasic monohydrate, 1.2 mg/mL sodium phosphate dibasic anhydrous, 0.4 mg/mL polysorbate-20
HERCEPTIN® (trastuzumab)	Lyophilized	21 mg/mL	~6	Approximately 20 mg/mL α,α-trehalose dehydrate, 0.5 mg/mL L-histidine HCl, 0.32 mg/mL L-histidine, 0.09 mg/mL polysorbate-20, 1.1% bacteriostatic water
VECTIBIX® (panitumumab)	Liquid	20 mg/mL	5.6–6.0	5.8 mg/mL sodium chloride, 6.8 mg/mL sodium acetate
RoACTEMRA® (tocilizumab)	Liquid	20 mg/mL	6.5	15 mM phosphate, 70 mg/mL sucrose, 0.5 mg/mL polysorbate 80
ARZERRA® (ofatumumab)	Liquid	20 mg/mL	6.5	8.35 mg/mL sodium citrate, 0.105 citric acid monohydrate, 5.85 mg/mL sodium chloride
SOLIRIS® (eculizumab)	Liquid	10 mg/mL	NA	Chloride, phosphate dibasic, phosphate monobasic, polysorbate-80
LUCENTIS® (ranibizumab)	Liquid	10 mg/mL	5.5	10 mM histidine–HCl, 10% trehalose, 0.01% polysorbate 80
REMICADE® (infliximab)	Lyophilized	10 mg/mL	~7.2	50 mg/mL sucrose, 0.05 mg/mL polysorbate-80, 0.22 mg/mL monobasic sodium phosphate monohydrate, 0.61 mg/mL dibasic sodium phosphate dihydrate
RITUXAN® (rituximab)	Liquid	10 mg/mL	~6.5	9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80
ZENAPAX® (daclizumab)	Liquid	5 mg/mL	~6.9	3.6 mg/mL sodium phosphate monobasic monohydrate, 11 mg/mL sodium phosphate dibasic heptahydrate, 4.6 mg/mL sodium chloride, 0.2 mg/mL polysorbate 80
SIMULECT® (basiliximab)	Lyophilized	4 mg/mL	NA	1.4 monobasic potassium phosphate, 0.20 mg/mL disodium hydrogen phosphate (anhydrous), 0.32 mg/mL sodium chloride, 4 mg/mL sucrose, 16 mg/mL mannitol, 8 mg/mL glycine
ERBITUX® (cetuximab)	Liquid	2 mg/mL	7.0–7.4	8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate
REOPRO® (abciximab)	Liquid	2 mg/mL	pH 7.2	10 mM sodium phosphate, 150 mM sodium chloride, 0.001% polysorbate 80

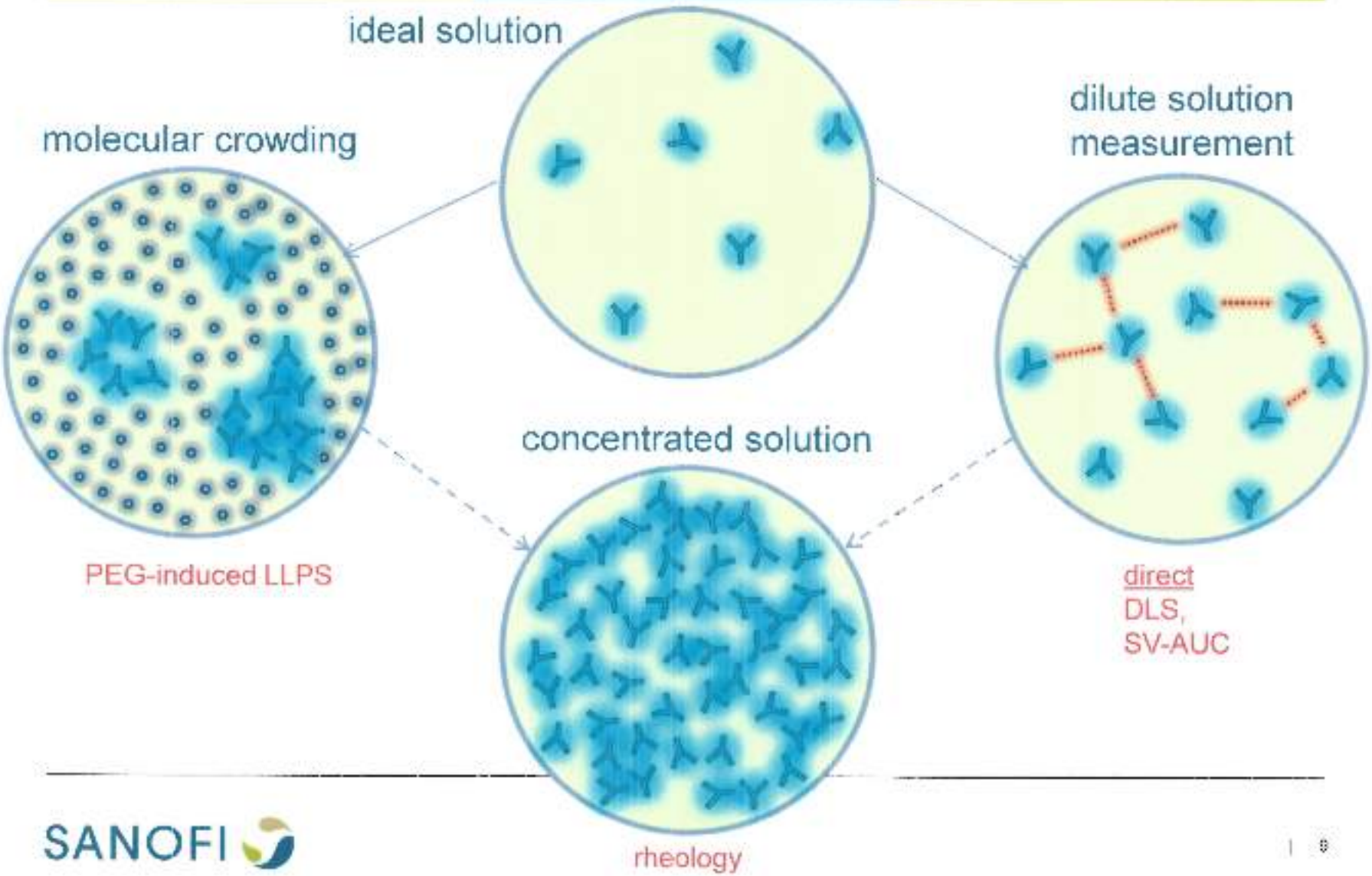
HIGH THROUGHPUT SCREENING (HTS): AUTOMATE SYSTEM

PFO/FOR SCREENING → **STRESSES** → **ANALYSIS** → **Data Mgt**

- PFO/FOR SCREENING: Freeslate Core CM3; pH control; Visual Inspection Station; Bare code mgt
- STRESSES: Shaker; Incubators; -20°C (F/T cycles); 40°C (accelerated condition)
- ANALYSIS: Conform. Stab. (fluo, turbi); Thermal stab. (Tm, Tagg.); Colloidal stab. (B_{22}); Chemical purity
- Data Mgt: LEA software



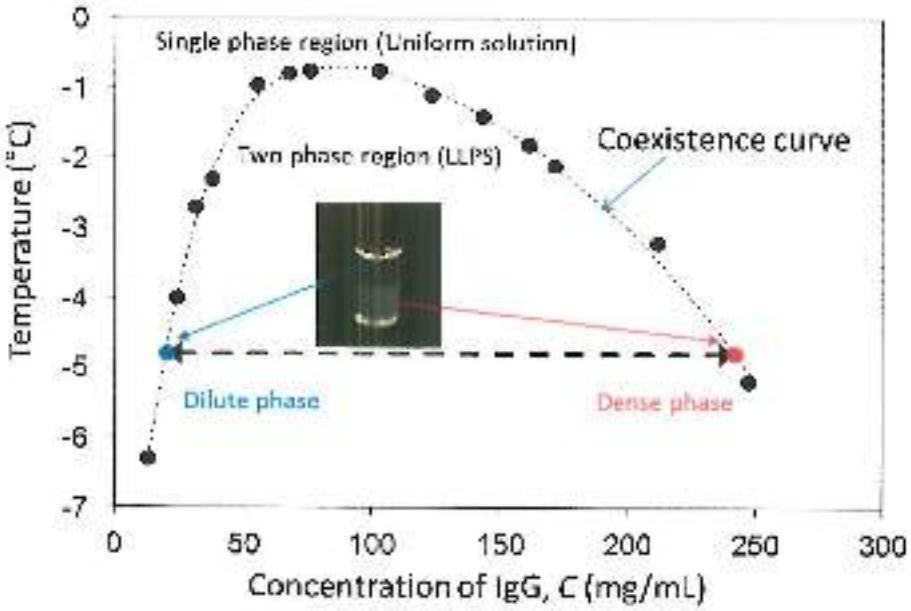
MEASUREMENT OF WEEK PROTEIN SELF NTERACTIONS: SUPPORT DEVELOPABILITY



LIQUID-LIQUID PHASE SEPARATION: DISSECTING THE ENERGETIC OF PROTEIN-PROTEIN INTERACTIONS

- The dense and dilute phases coexisting at a given temperature are in thermodynamic equilibrium and have the same chemical potential.

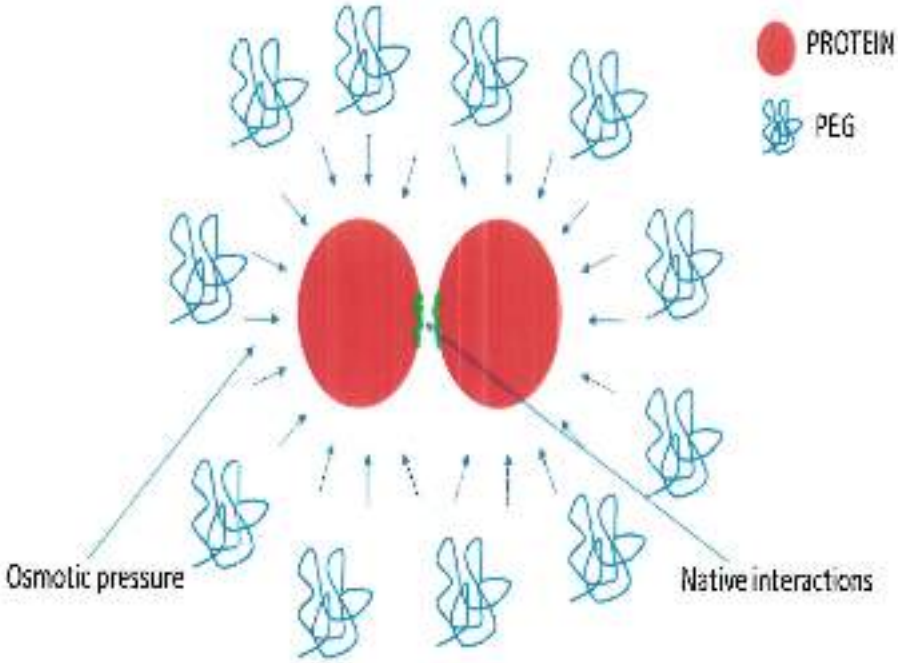
- We can evaluate binding (attraction) energy in the dense phase by measuring protein concentration of the dilute phase.



SANOFI

Wang Y, Latypov RF, et al. (2014) Mol. Pharm. 11, 1391-1402.
Wang Y, Lomakin A, Latypov RF, et al. (2013) J. Chem. Phys. 139, 121904 (doi: 0.1063/1.4811345).
Wang Y, Lomakin A, Latypov RF, et al. (2011) Proc. Natl. Acad. Sci. USA 108, 16606-16611.

LIQUID-LIQUID PHASE SEPARATION: DEPLETION INTERACTION INDUCED BY PEG



When two protein molecules are close enough so that PEG molecules cannot fit in the space between them, the unbalanced local osmotic pressure adds an additional attraction between the two protein molecules.

Native interactions are not affected.

The dense phase (precipitate) mimics a highly concentrated drug product.

$$\Delta G = \Delta G_P(N_P, V) + \Delta G_{PEG}(N_{PEG}, V_{PEG})$$

$$\varepsilon_B = -(KT\, ln(\, \nu_0\, c_1^l) + \Pi_2 . \Delta \nu\,).\, NA/1000$$

Binding energy

Protein mass concentration in the supernatant

Depletion interaction

SANOFI

Wang Y, Latypov RF, et al. (2014) Mol. Pharm. 11, 1391-1402.
Wang Y, Lomakin A, Latypov RF, et al. (2013) J. Chem. Phys. 139, 121904 (doi: 10.1063/1.4811345).
Wang Y, Lomakin A, Latypov RF, et al. (2011) Proc. Natl. Acad. Sci. USA 108, 16606-16611.

Pharmaceutical Stability and Robustness: Looking for a Special Sweet Spot

In need of something that measures the delicate interplay between colloidal properties (solution energetics), conformational properties and solvation thermodynamics

Develop ability/Device ability criteria

AGENDA

14:00 Development of co-formulation of monoclonal antibodies and recombinant human hyaluronidase (rhuPH20)- a case study

Astrid Pappenberger. Group Leader, Senior Scientist, Roche, Switzerland.

14:30 Combining computational approaches and experiments for selecting compounds with the desired properties, applied in particular to the osmolye-like effects on the thermal stability of a monoclonal antibody.

Andreas Bender, Lecturer for molecular informatics and drug design, University of Cambridge, UK.

15:00 Coffee break. Exhibition Posters

15:30 Use of math modelling to understand delivery of biopharmaceuticals to the lung.

Nia Stevens, Investigator, GSK, UK.