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Aggregation challenges in the formulation development of multi-dose peptide products

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AGGREGATION CHALLENGES IN THE FORMULATION DEVELOPMENT OF PEPTIDE PRODUCTS: KINETICS AND ANALYTICS

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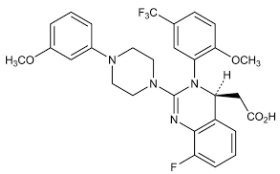
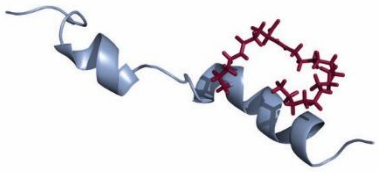
Peptide Therapeutics Constitutes an Unique Modality

Small molecule drugs
< 500 Da

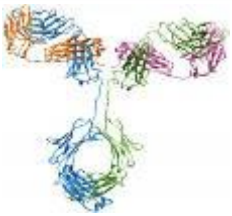
Peptides
5 ~ 40
amino acids

Biologics > 5000 Da
(e.g. cytokines, growth factors, mAbs)
Injectable





Liraglutide



Chemical control and definition

Specificity and half-life

Dosing route

- Peptide products differentiate with other modalities in targets requiring high affinity agonist action, especially those associated with natural hormones.

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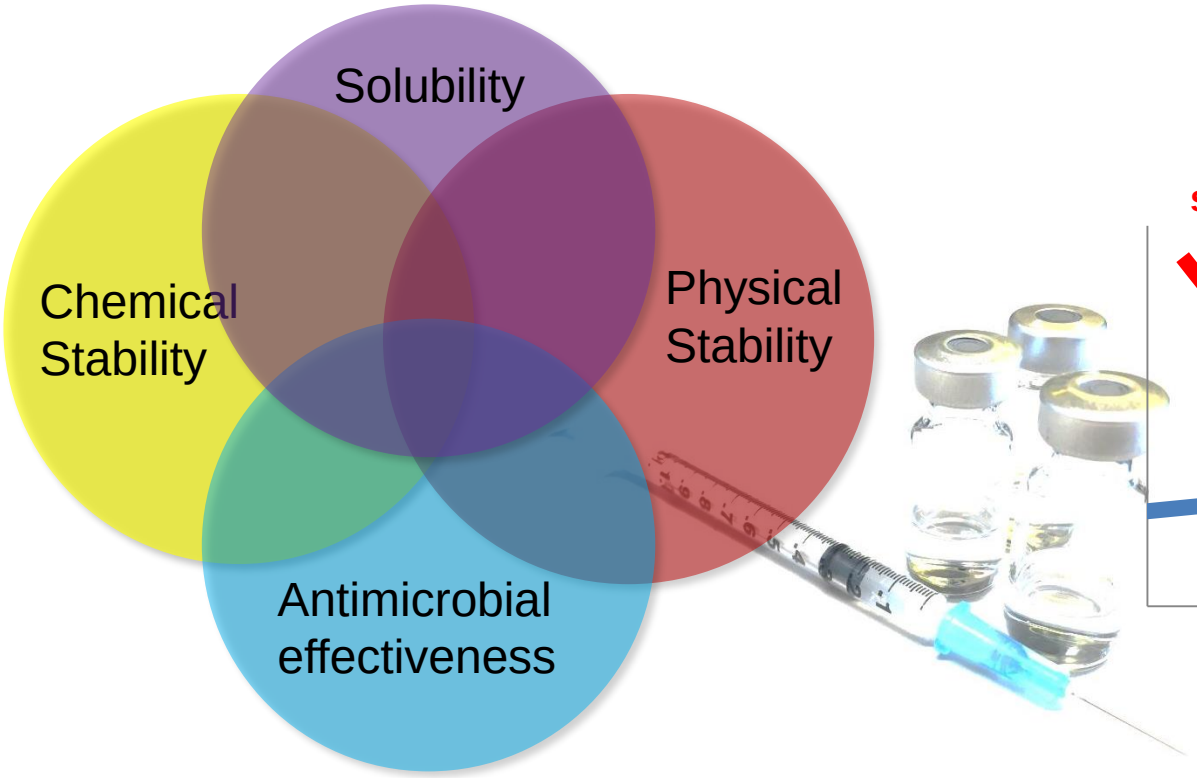
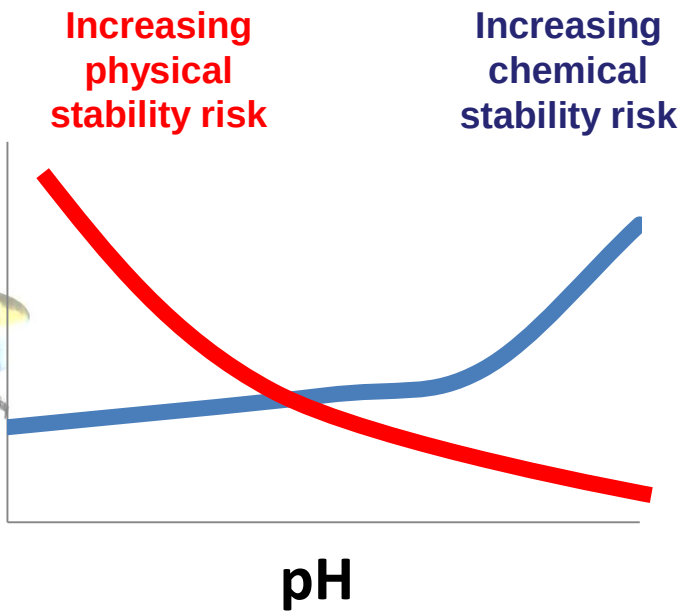
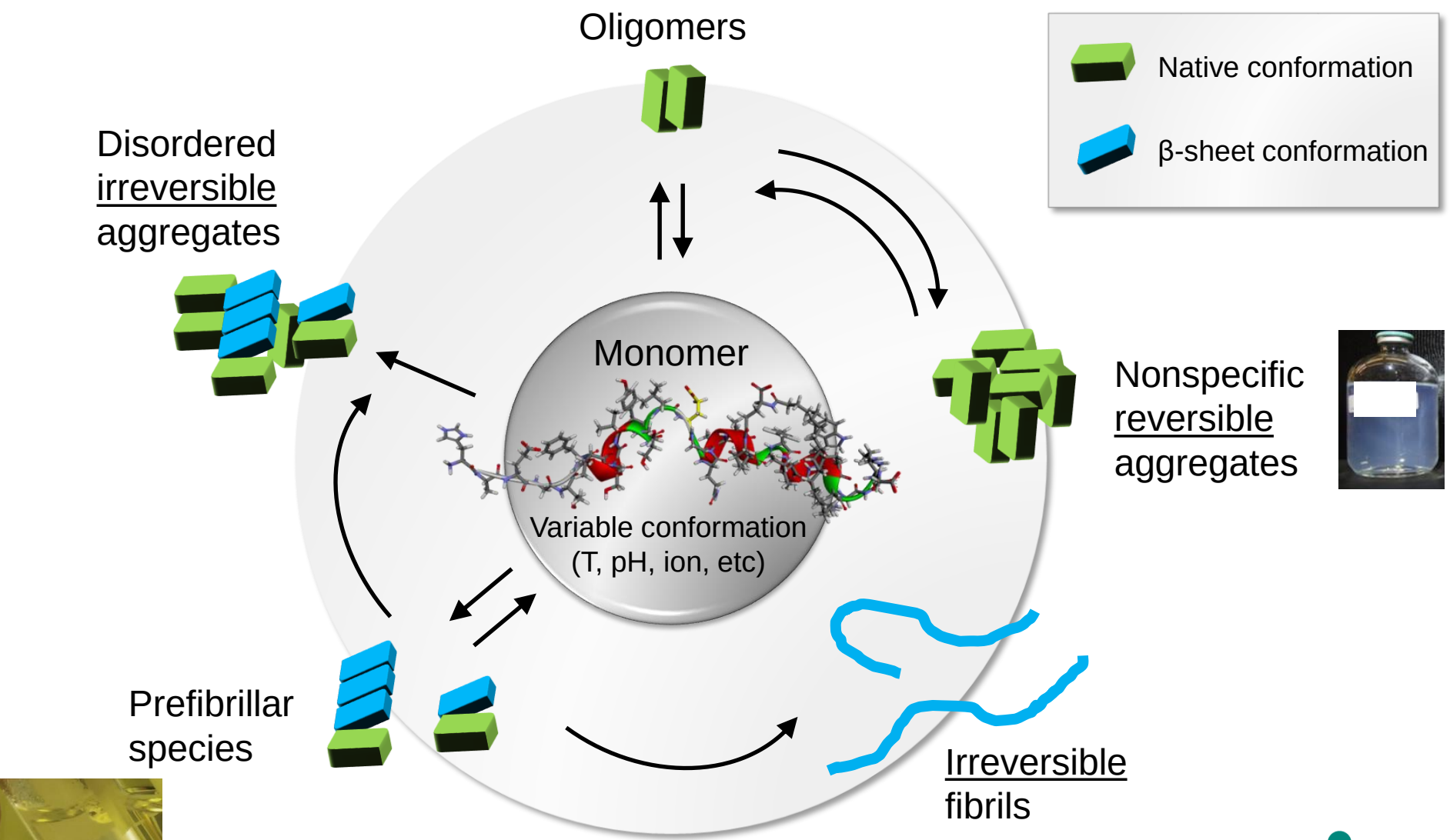
Peptides Present Unique Challenges for Parenteral Formulation Development

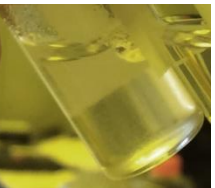
- Formulation goal: bioavailability + **stability** + sterility…
- Peptides typically don't have well ordered structure and therefore chemical and physical stability could be worse than biologics. Daily use product require >18 month 5ºC solution product
- In particular, poor understanding in the developability study for physical stability
- Stability could frequently be the limiting factors in peptide formulation development (e.g. glucagon).



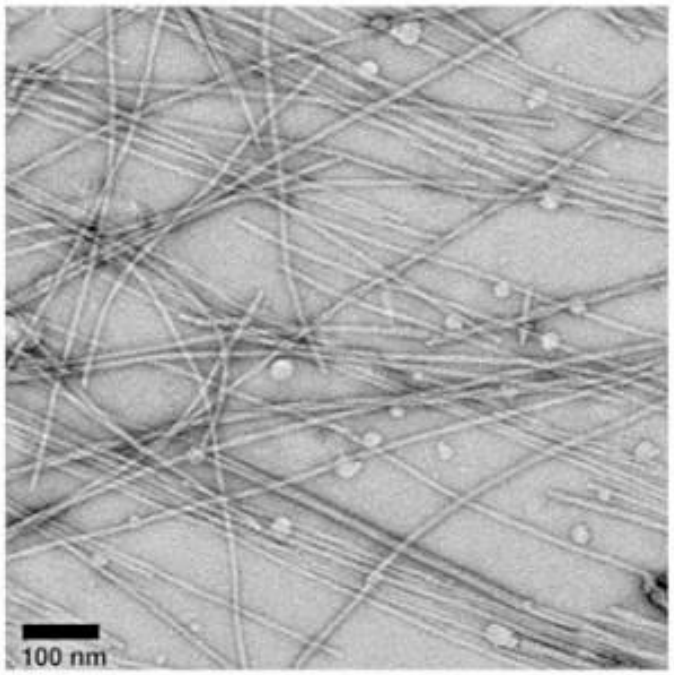


Reversible and Irreversible Aggregation in Synthetic Peptides

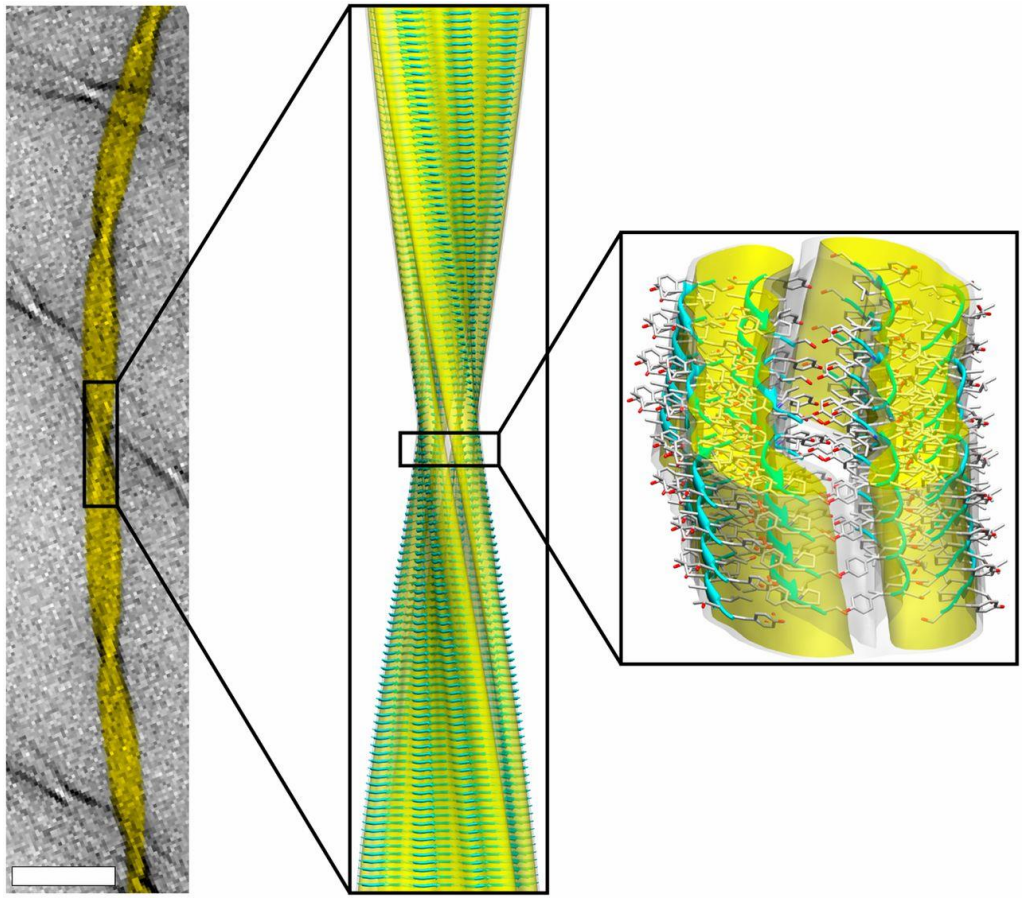




Amyloid Fibrils are Supramolecular Assemblies with Highly Ordered Stacking



Science. 2017 Oct 6;358(6359):116-119



5468–5473 | PNAS | April 2, 2013 | vol. 110 | no. 14

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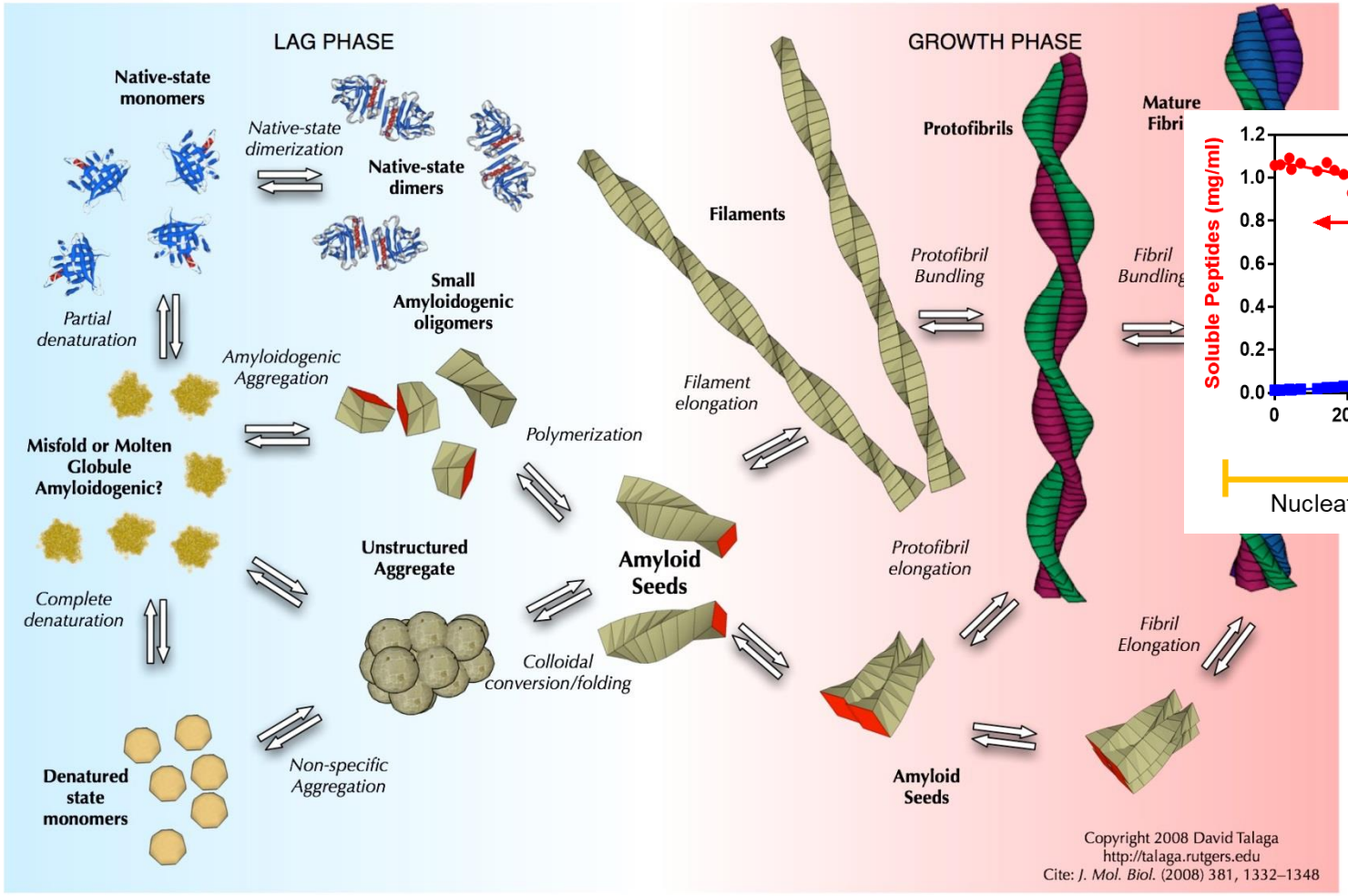
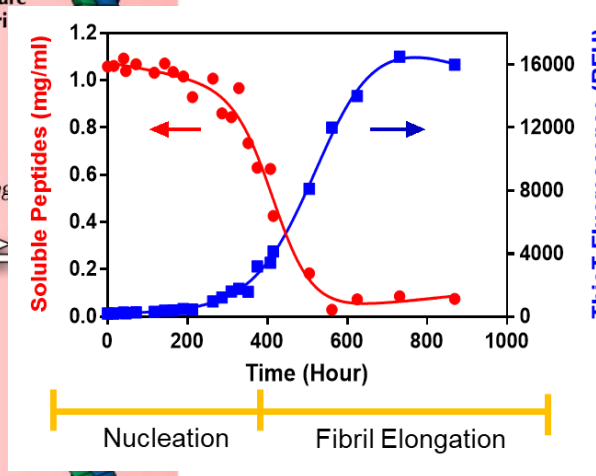
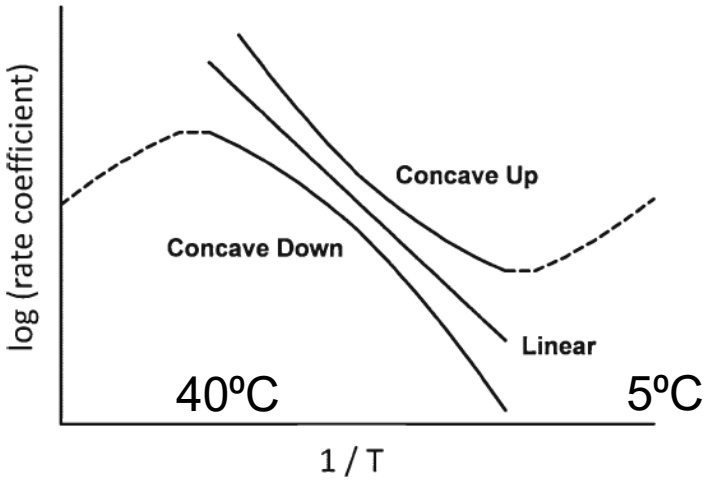
Nucleated Polymerization of Fibril Kinetics



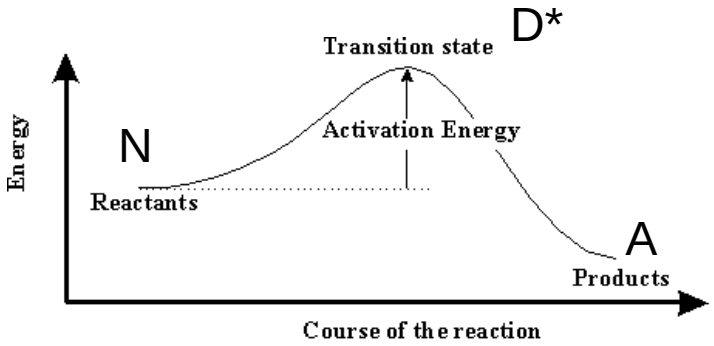


Where is the Gap in the Development Knowledge?

- Is it due to the non-ideal behavior in kinetics between accelerated conditions and real time?



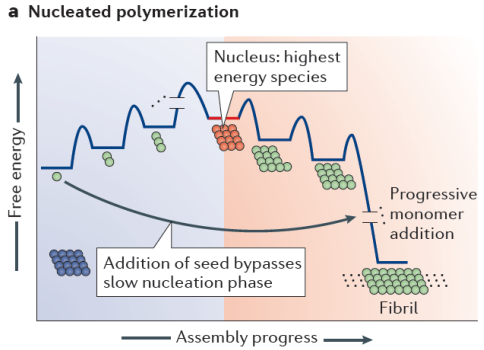
The AAPS Journal, Vol. 15, No. 3, July 2013



$k=A*exp^{(-E_a/R*T)}$

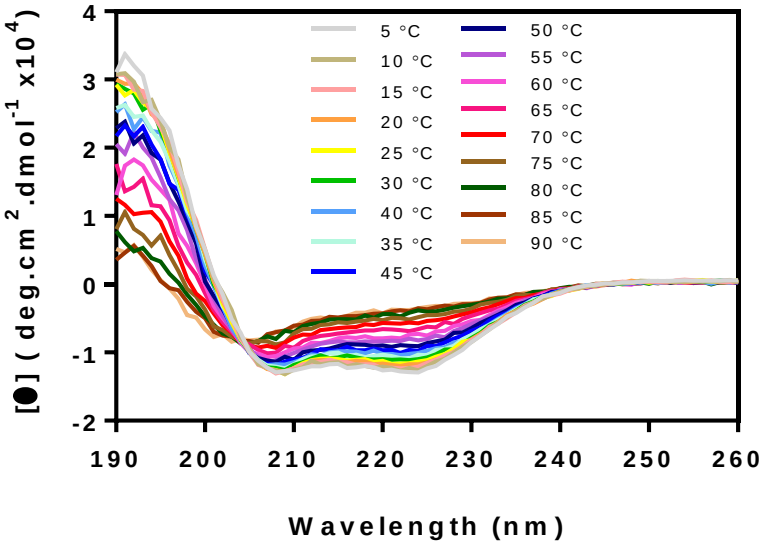
High unfolding energy can contribute to the non-Arrhenius behavior.

- Is it because the how representative the materials are (both benchmarks and peptide A)?
  - Purity
  - Manufacturing method
  - Counterions
  - **Preexisting seeds**
  - ….



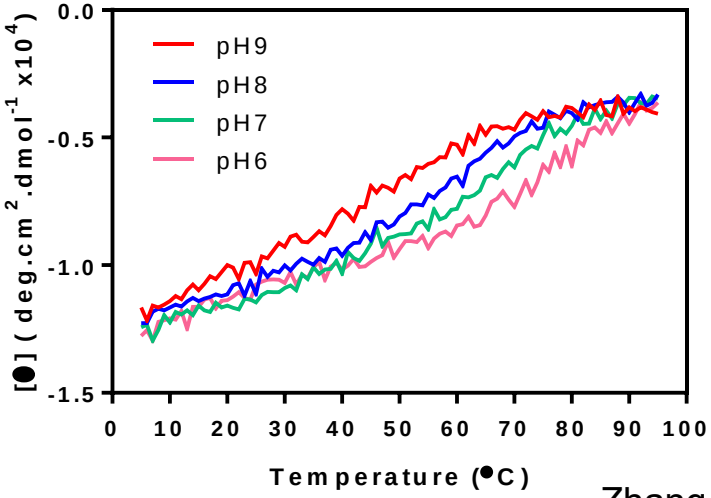
Small Peptides are Conformationally Unstable—Unlike Most Proteins

- **Helical peptides undergo gradual melting upon heating**



Mw 3.8 kDa,
29 residues

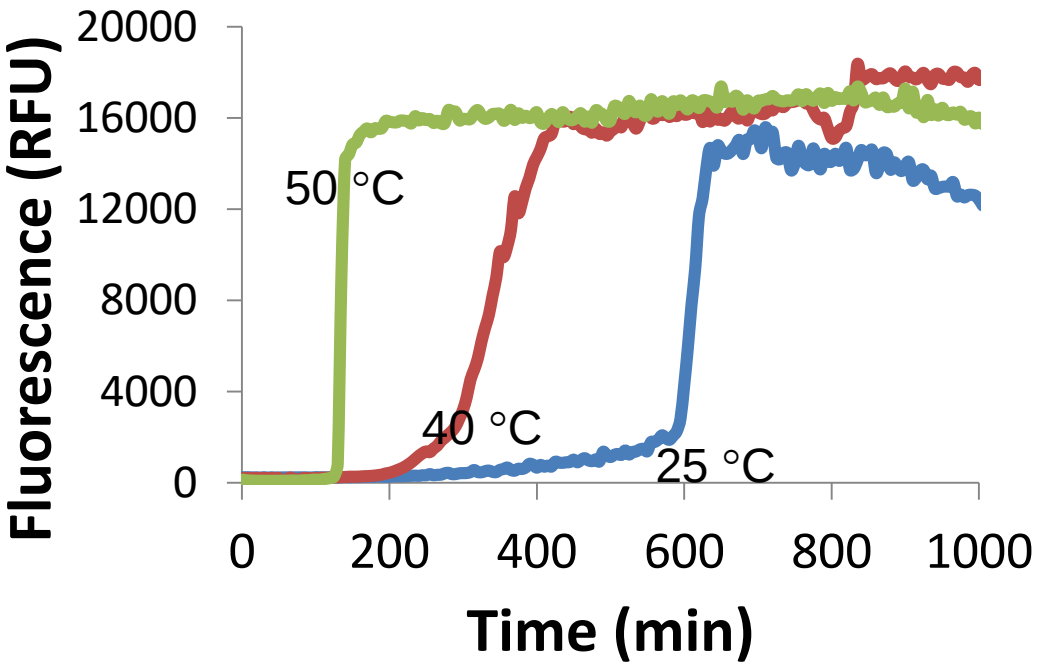
- **Unfolding is of low cooperativity and reversible.**



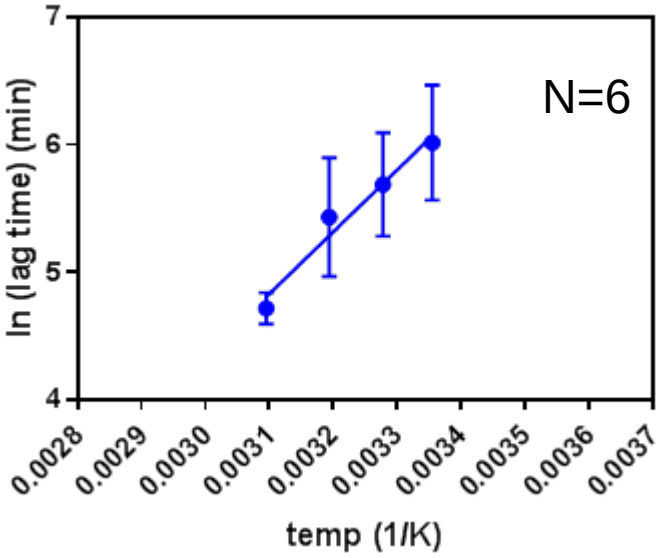
Formulation pH	T_m (°C)	ΔH_m (kcal/mol)	ΔS_m (cal/mol/K)	$\Delta G_{20\,°C}$ (kcal/mol)
pH 6	74.9 ± 1.9	47.7 ± 14.1	137.2 ± 40.5	7.5
pH 7	75.2 ± 2.4	21.2 ± 4.9	60.9 ± 14.0	3.3
pH 8	65.2 ± 0.7	26.2 ± 3.9	77.4 ± 11.4	3.5
pH 9	63.1 ± 1.0	21.5 ± 5.5	64.0 ± 16.4	2.7

Zhang et al. Mol. Pharmaceutics 2018, 15, 5591−5601

Accelerated Study Conditions: Assembly of Peptide Alone Shows Arrhenius Kinetics



$k=A*\exp^{(-E_a/R*T)}$



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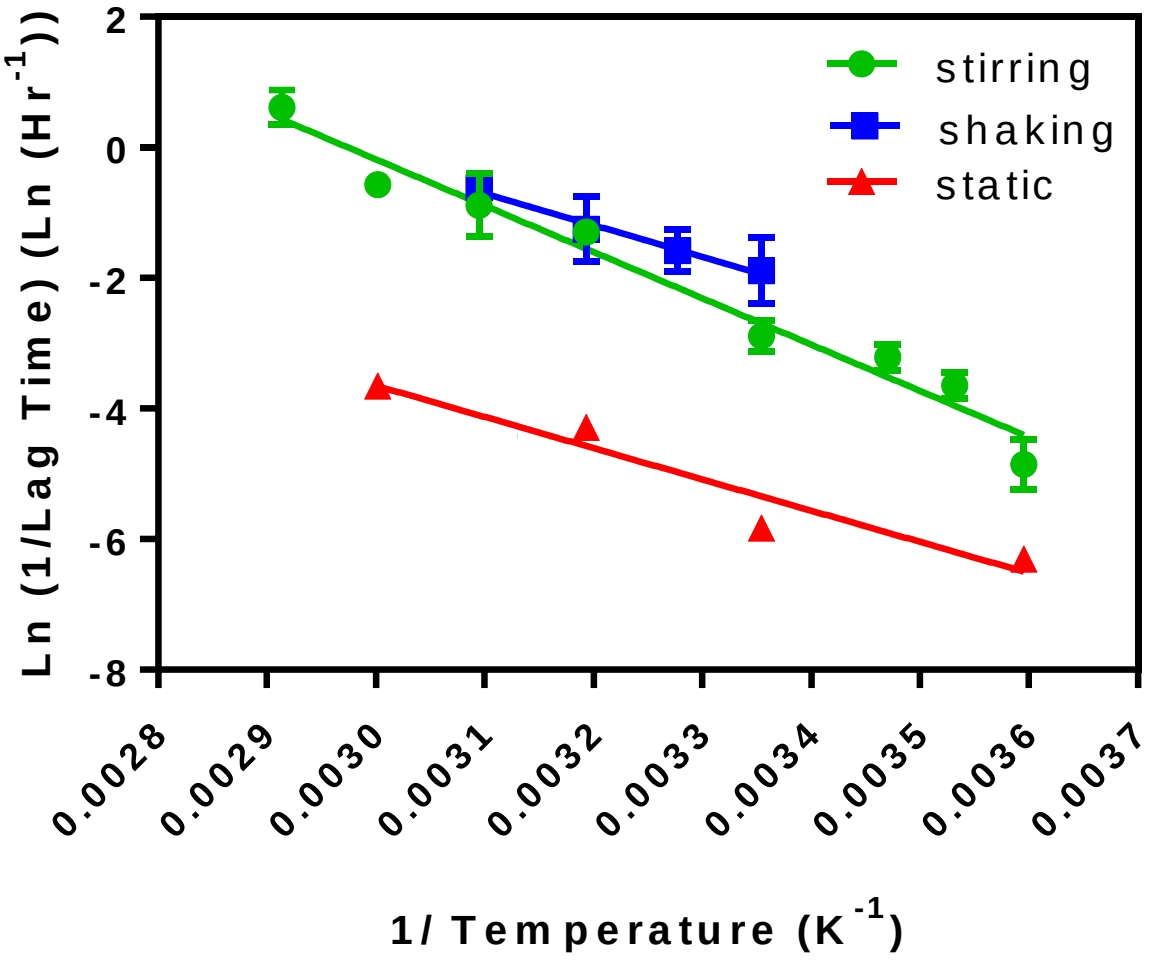
Assembly of Peptide Alone Shows Arrhenius Kinetics: Accelerated vs. Real Time



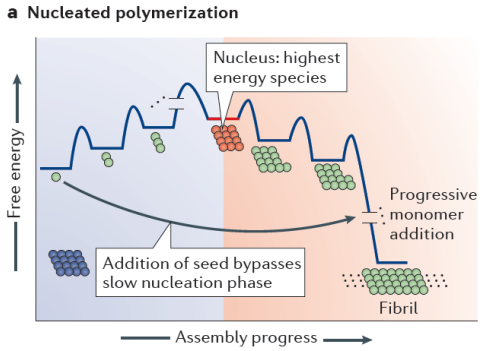
Temp °C
5
10
15
25
40
50
60
70

Zhang et al. Mol. Pharmaceutics 2018, 15, 5591−5601

Can “Seeds” Play a Role in the Kinetics?

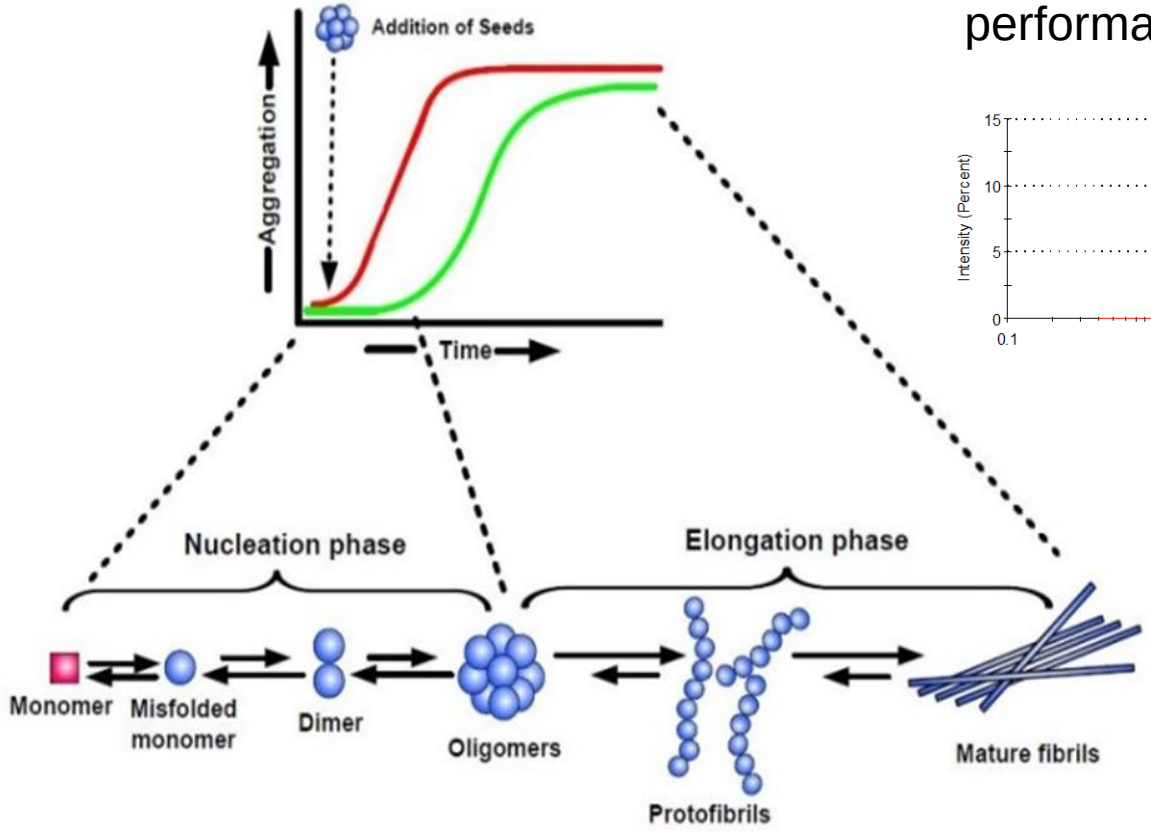
- Peptide alone demonstrates an aggregation kinetics that are Arrhenius in nature. i.e accelerated testing at high T and shear could be used to extrapolate to real time.
- Temperature behavior in kinetics cannot explain the observed effects.

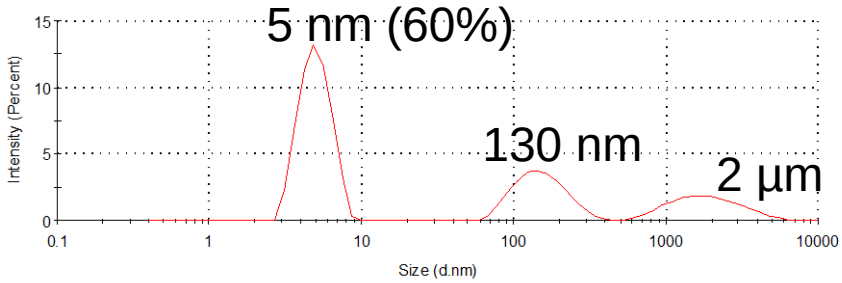
- Is it because the how representative the materials are (both benchmarks and peptide 2)?
  - Purity
  - Manufacturing method
  - counterions
  - **Preexisting seeds**
  - ….



How can Submicron “Seed” Species Influence Product Quality? Can We Detect Them Quantitatively?

- “nucleated polymerization and growth”
- Submicron species appear to serve as nucleus to physical instability
- Will API history influence DP performance?

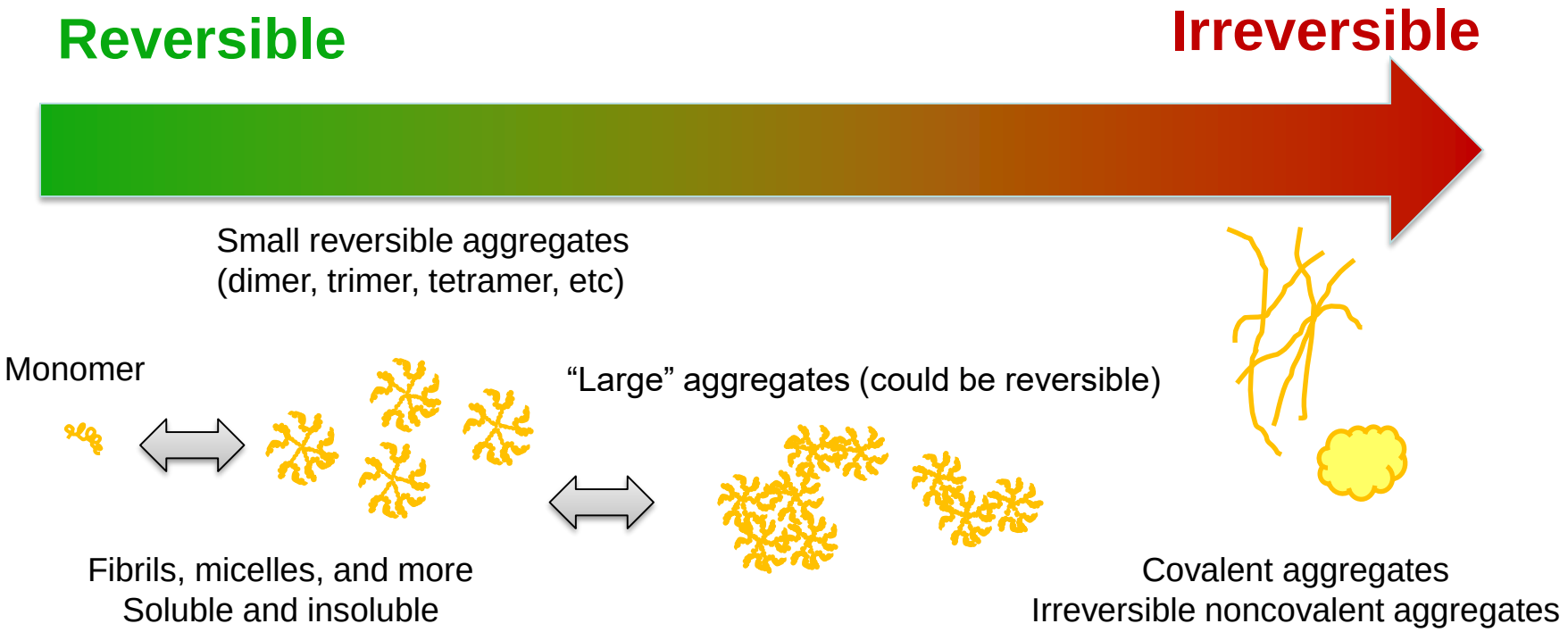




Methods explored for detecting of the “seeds”

- Conventional aggregation control method did not work for these purpose.
- Use of the ThioT kinetic test (i.e, assume the lag time correlate with presence of amount of seeds)
- Can we leverage the use of submicron tools, although may need to differentiate between active vs inactive seeds.

Conclusion



- Peptides are uniquely differentiated from protein and small molecules.
- Aggregation is a significant risk for pharmaceutical development of peptide drug products. Understanding of aggregation pathway is highly important to its development.
- Fibrillation kinetics are highly sensitive to its preparation method, purity, existing of seeds etc. Seamless integration between DS and DP are required.

Acknowledgments

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