https://doi.org/10.17952/38EPS.2026.O60

Computational/Experimental Symbiosis to Design Functional Supramolecular Peptide Assemblies





38th EPS

European Peptide Symposium



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2026/09/10

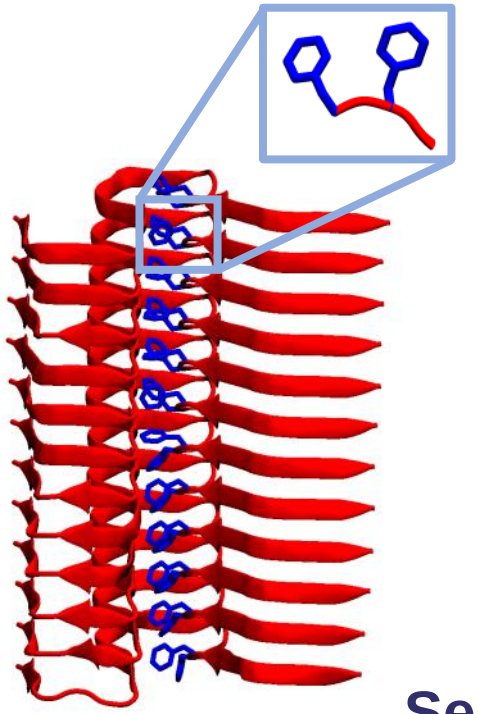

Bordeaux
Donostia / San Sebastián
A Coruña
Gijón
Oviedo
Toulouse
Bilbao
Carcassonne
Santiago de Compostela
Lugo
Vitoria-Gasteiz
Pamplona
León
Perpignan
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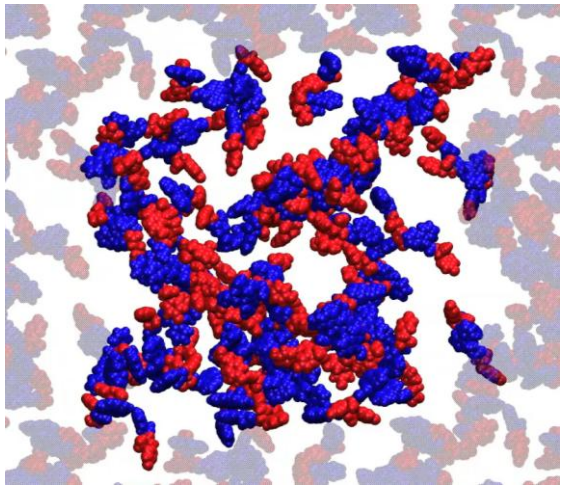
Supramolecular Peptide Assemblies (SPAs)

Inspired by Highly ordered Protein Sections

Short Peptide (n ≤ 10) ► self-assemble

►nanostructures

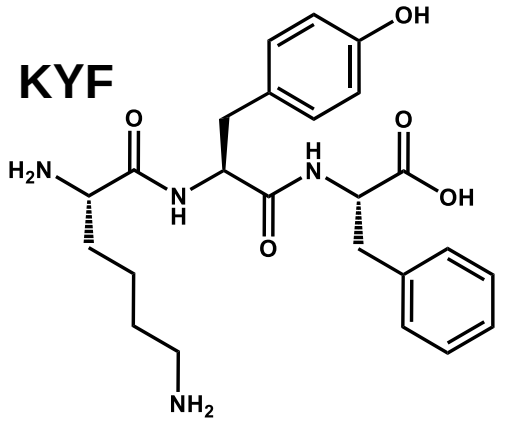




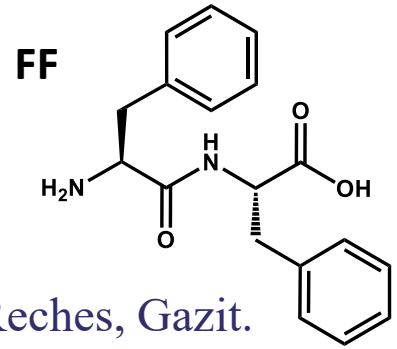
Self-assembly

Spontaneous formation of

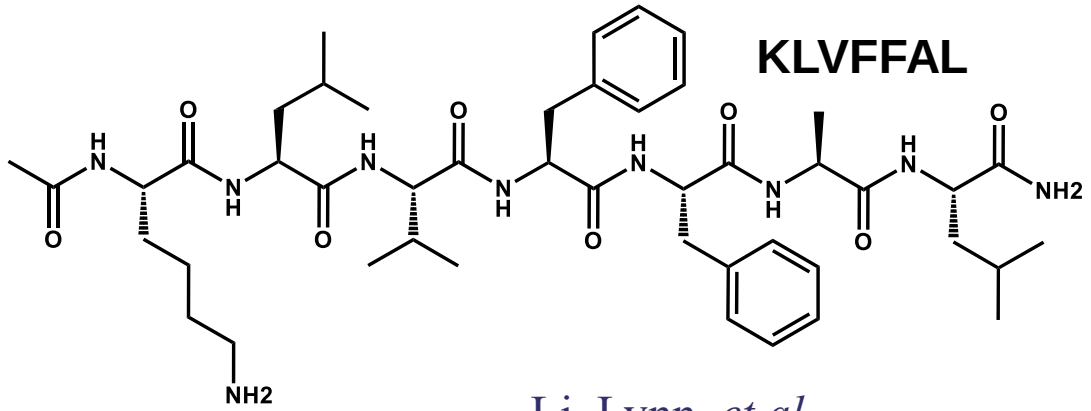
highly ordered nanostructures in solution



Frederix, Tuttle, *et al.*
Nat. Chem. **2015,** *7*, 30

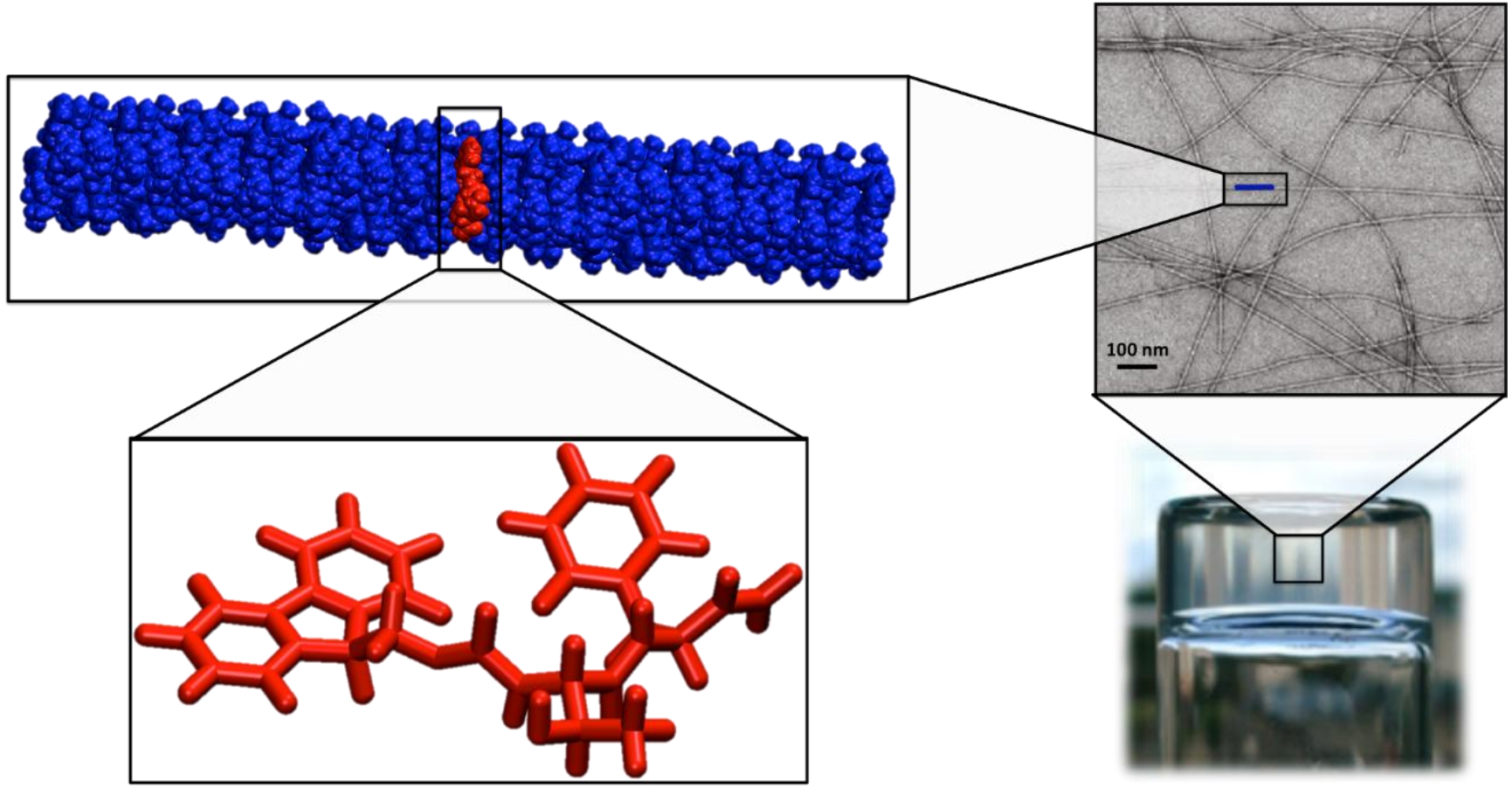


Reches, Gazit.
Science **2003**, *300*, 625



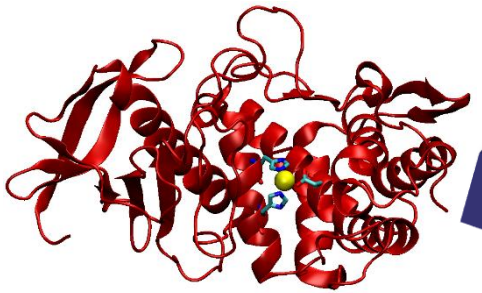
Li, Lynn, *et al.*
J. Am. Chem. Soc. **2016**, *138*, 3579

Supramolecular Peptide Assemblies (SPAs)

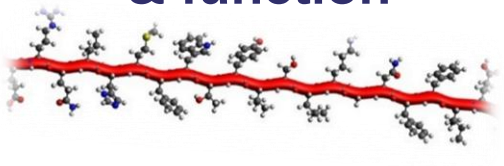


Small Simple Molecules → **Complex Biomaterials**

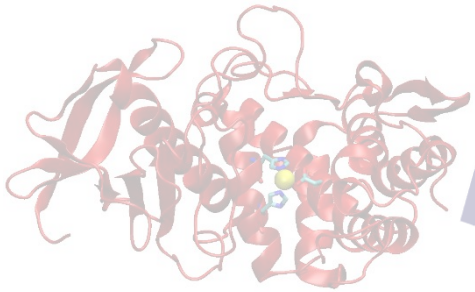
Chemical/Structural/Functional Diversity



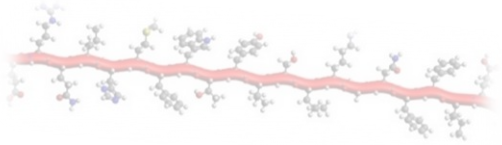
Sequence encodes structure, properties, & function



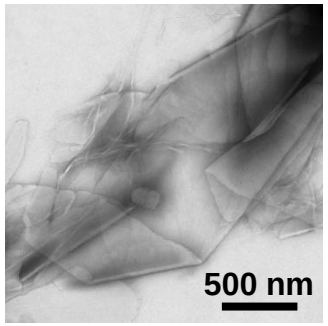
Chemical/Structural/Functional Diversity

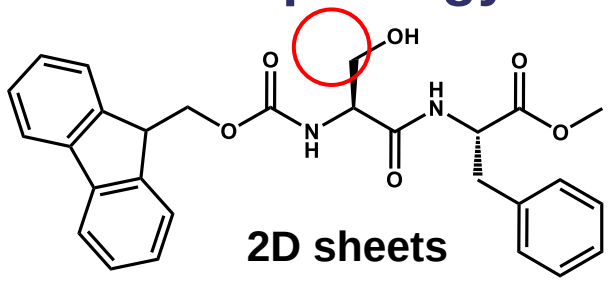


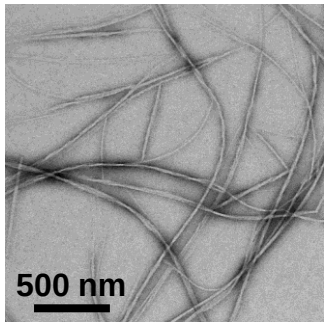
Sequence encodes structure, properties, & function

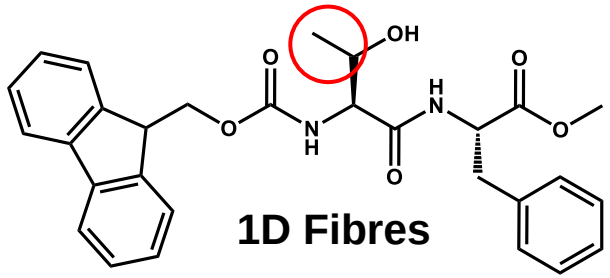


Sequence ↔ Morphology



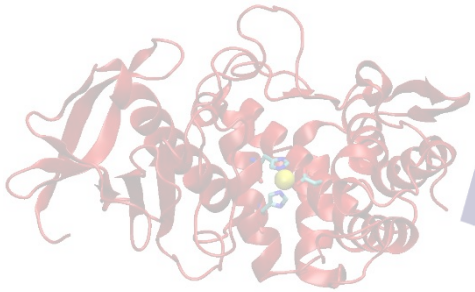




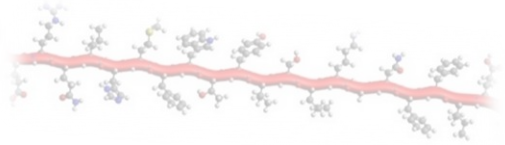


Hughes, Ulijn, *et al. Soft Matter*, **2012**, *8*, 5595

Chemical/Structural/Functional Diversity

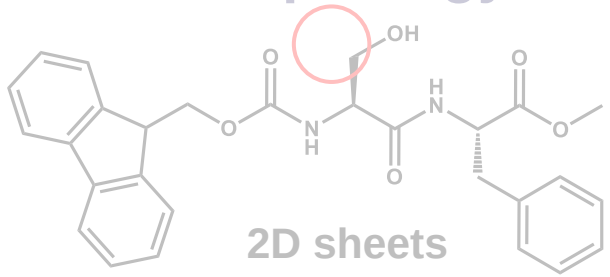


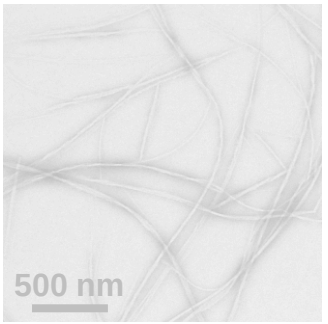
Sequence encodes structure, properties, & function

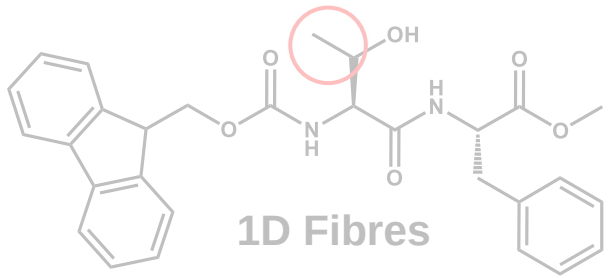


Sequence ↔ Morphology



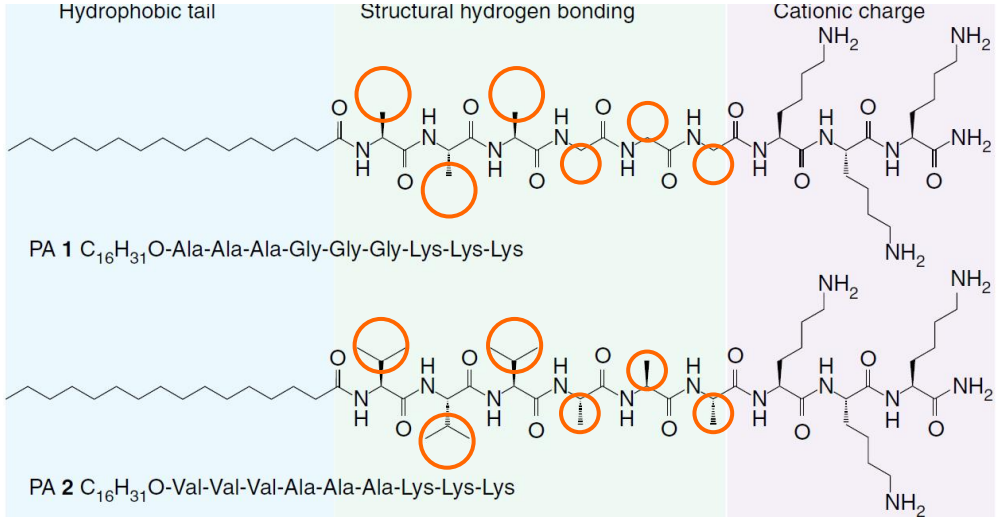


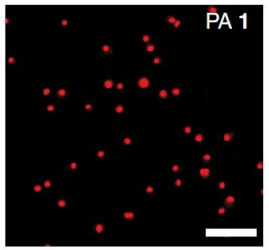


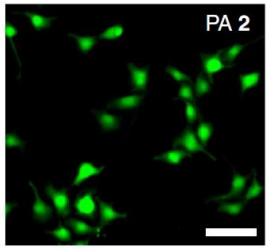


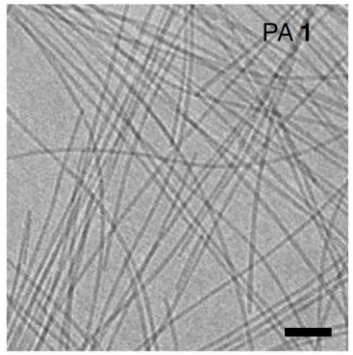
Hughes, Ulijn, *et al. Soft Matter*, **2012**, *8*, 5595

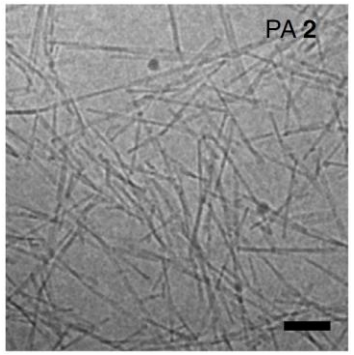
Sequence ↔ Crystallinity ↔ Biocompatibility

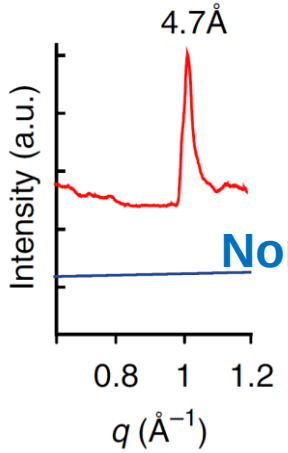












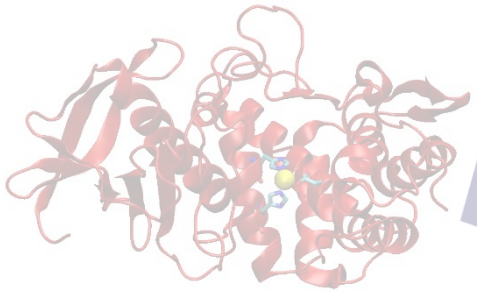
Crystalline

vs

Non-crystalline

Newcomb, Stupp, *et al. Nat. Commun.*, **2014,** *5*, 3321

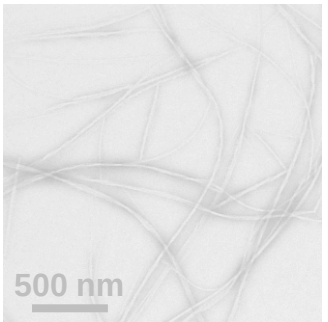
Chemical/Structural/Functional Diversity

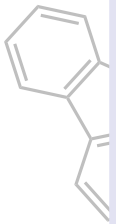


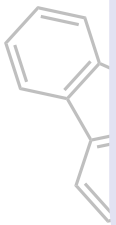
Sequence encodes structure, properties,

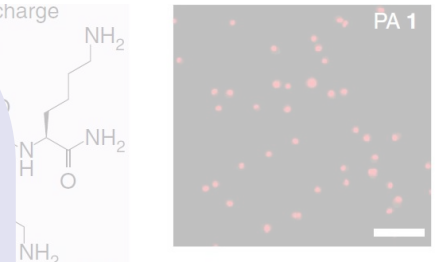
Sequence ↔ Crystallinity ↔ Biocompatibility

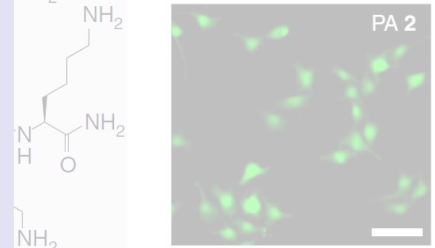


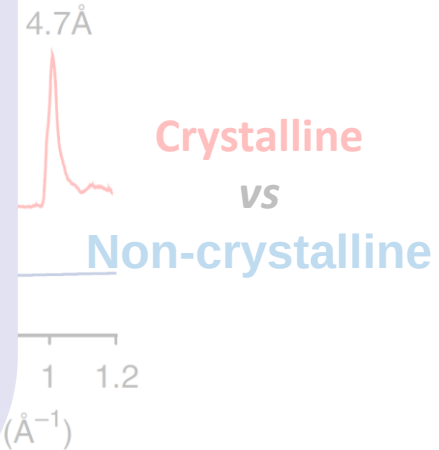








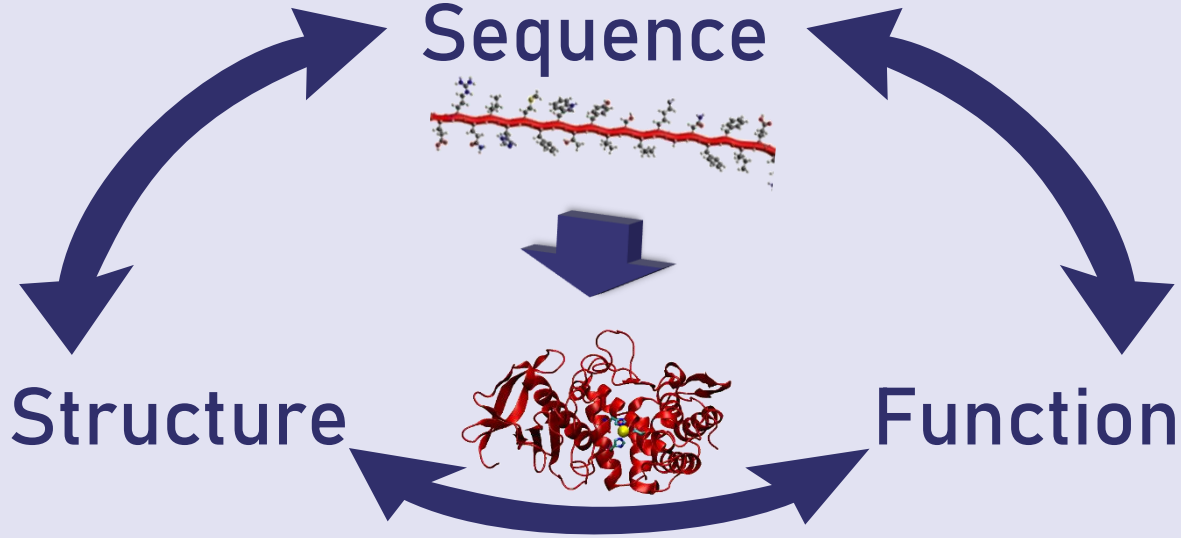




Crystalline

vs

Non-crystalline



Understood?

- ¬ Proteins ☑
- ¬ SPAs ☒

Hughes, Ulijn, *et al. Soft* … *nmun.*, **2014**, *5*, 3321

Experimental Challenges in SPAs

Characterization techniques from Proteins

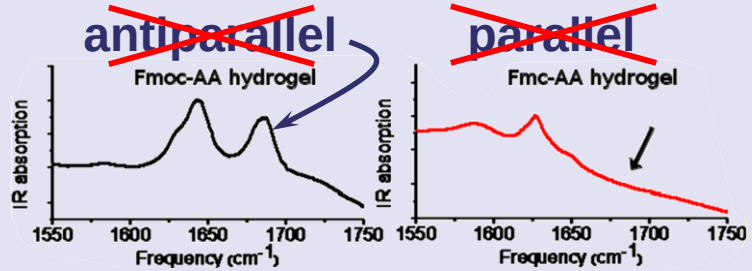
- Same techniques (chemically identical)
- Different interpretation

FT-IR

- Different interpretation

β-sheet:

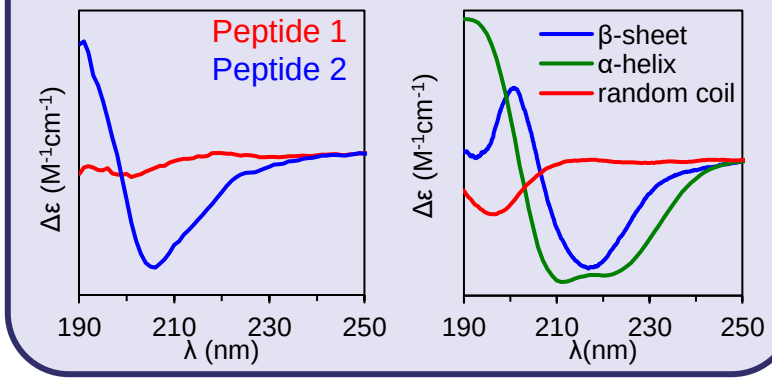
~~antiparallel~~ ~~parallel~~



Sasselli *et al*. *Langmuir*, **2013**, *29*, 9510

Circular Dichroism (CD)

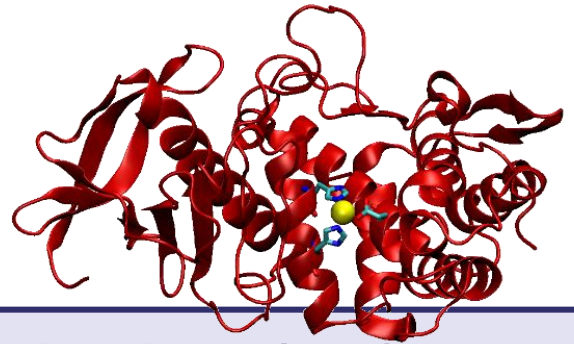
- Non-perfect 2^{ary} structures
- No orientation information

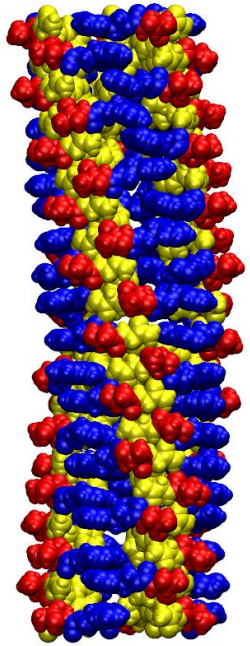


Experimental Challenges in SPAs

Characterization techniques from Proteins

- Same techniques (chemically identical)
- Different interpretation
- *Cannot resolve structure*



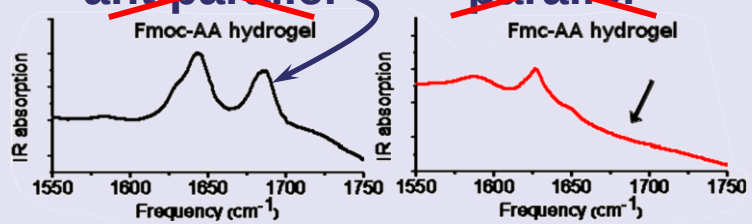


FT-IR

- Different interpretation

β-sheet:

~~antiparallel~~ ~~parallel~~

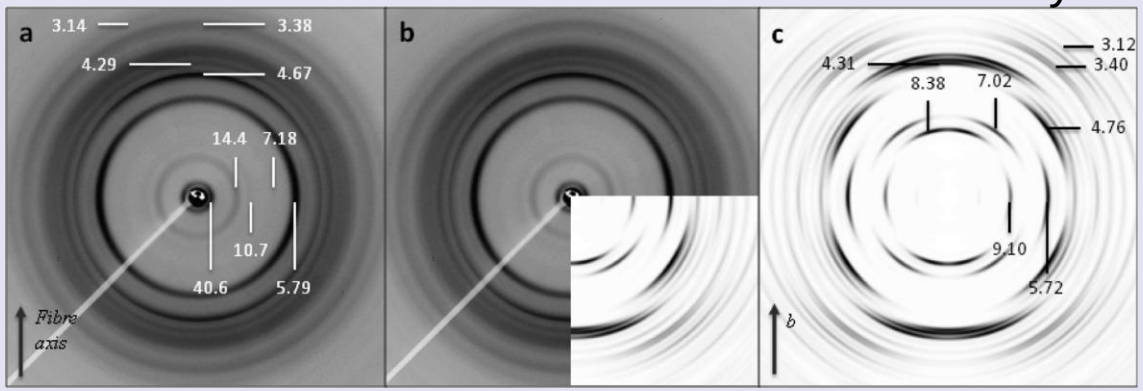


Sasselli *et al. Langmuir*, **2013**, *29*, 9510

Assemblies (1-2D) ≠ Crystals (3D)

Fiber diffraction

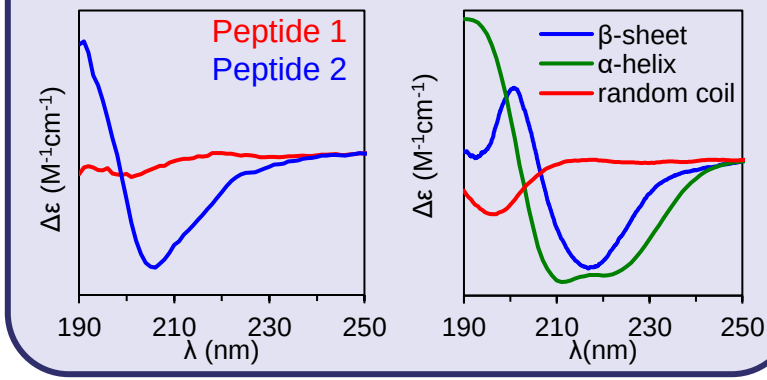
Model from crystal



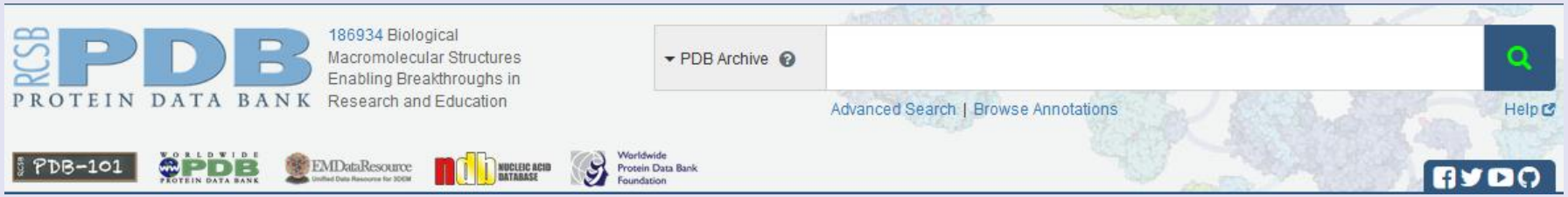
Houton, Adams, *et al. Langmuir*, **2012**, *28*, 9797

Circular Dichroism (CD)

- Non-perfect 2^{ary} structures
- No orientation information

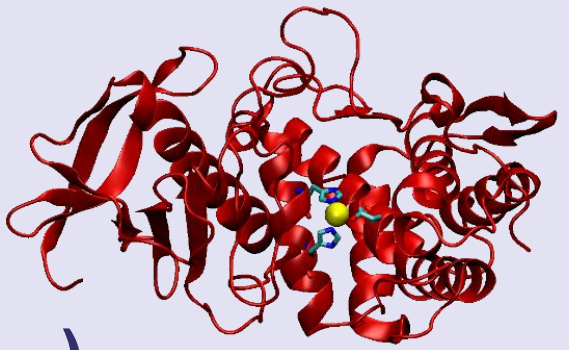


Experimental Challenges in SPAs

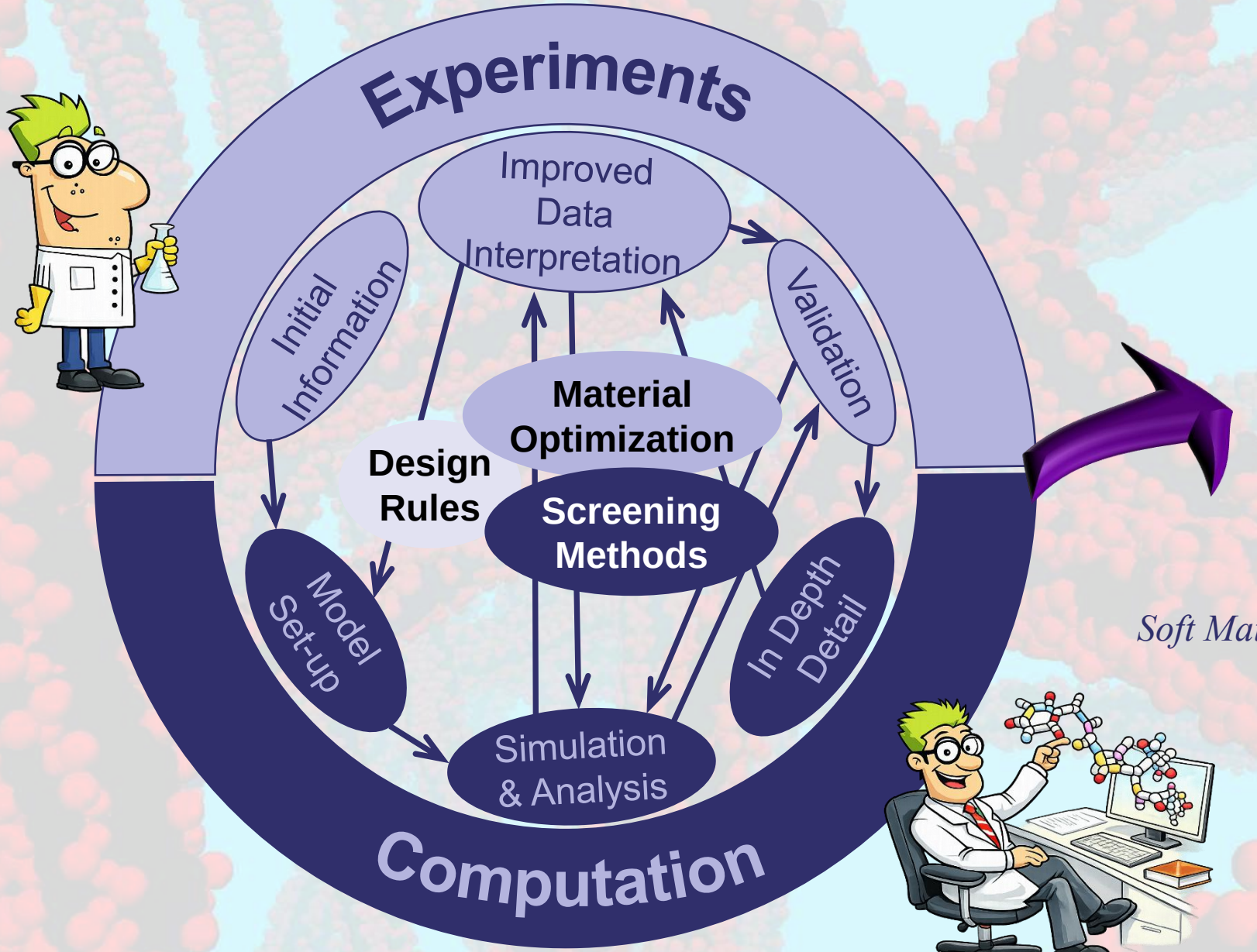


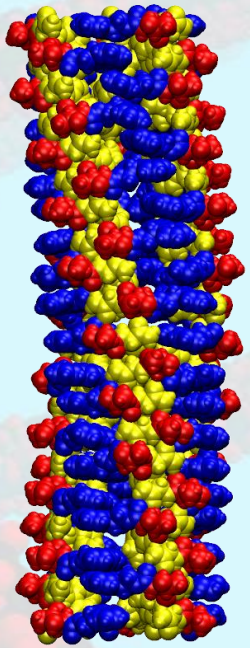
Huge Protein Crystals Databases:

- Structure → resolved with Å resolution
- Benchmarking of:
  - Characterization techniques
  - Computational methods (MD, α-fold…)



Computational/Experimental Symbiosis



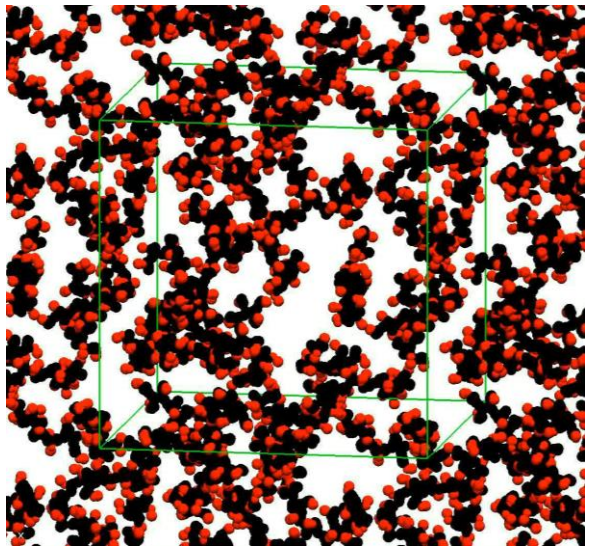


Sasselli, *et al.*
Soft Matter, **2016**, *12*, 8307

CG Self-Assembly Simulation

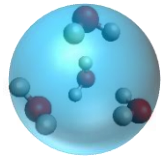
Martini

Reproduce/Predict: Self-assembly from scratch

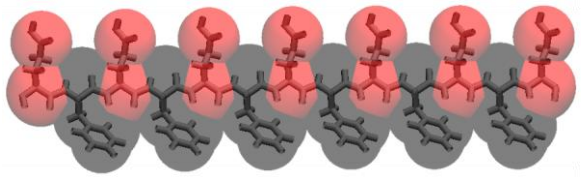


From solution (No input needed)

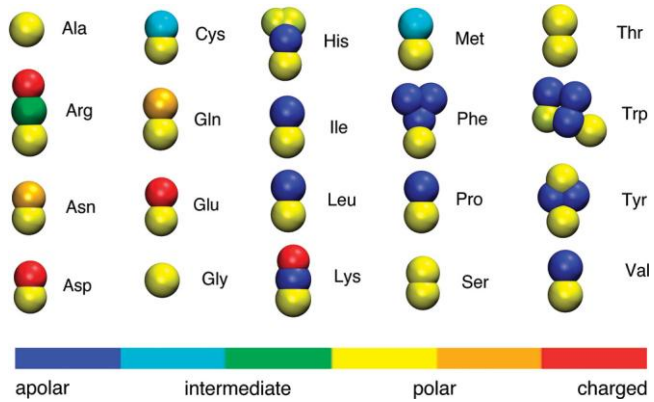
1-4 (1-2) Mapping



1 bead → 12 atoms

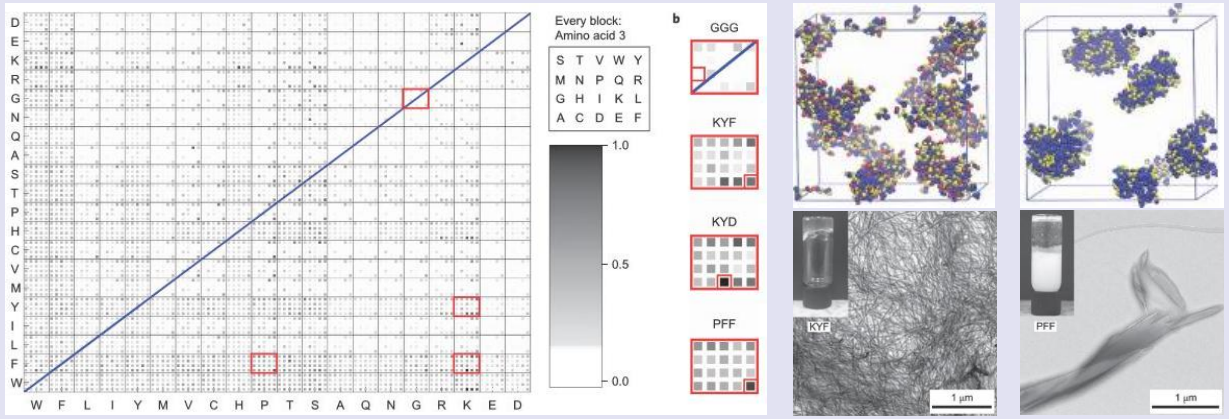


38 beads → 235 atoms



Monticelli, Marrink, *et al. J. Chem. Theory Comput.* **2008**, *4*, 819

Screening of 8000 Tripeptides

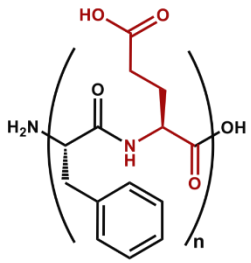


Frederix, Tuttle, *et al. Nature Chem.* **2014**, *7*, 30

Self-assembling Peptide Design

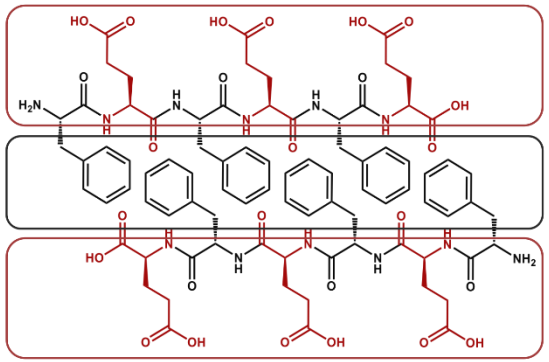


Glutamic acid



Phenylalanine

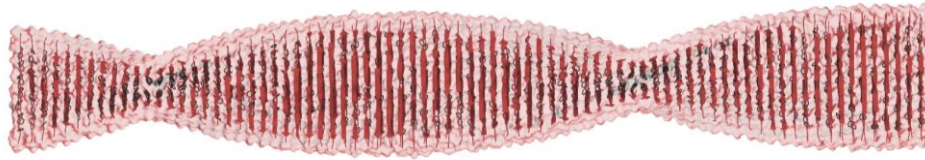
n repetitions

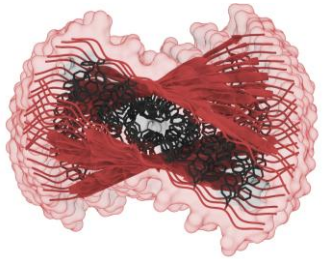


Hydrophilic surface

Hydrophobic core

Hydrophilic surface

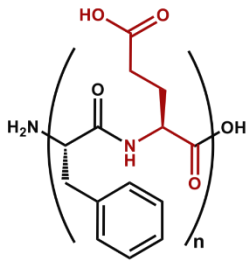




Self-assembling Peptide Design

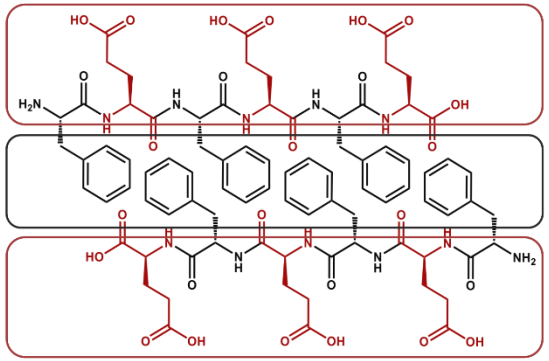


Glutamic acid



Phenylalanine

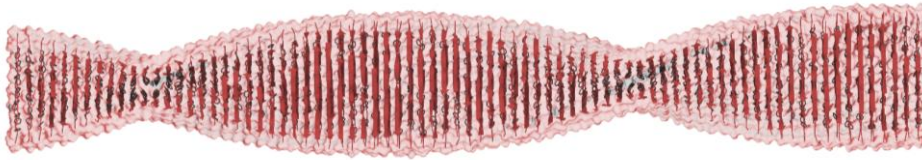
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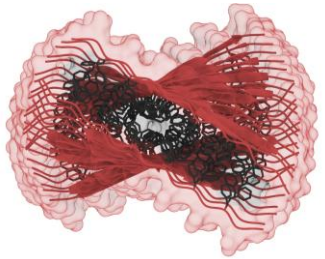


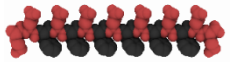
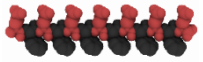
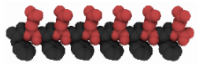
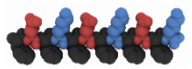
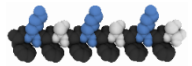
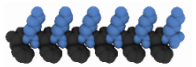
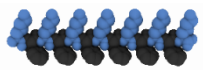
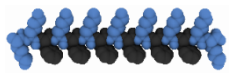
Hydrophilic surface

Hydrophobic core

Hydrophilic surface



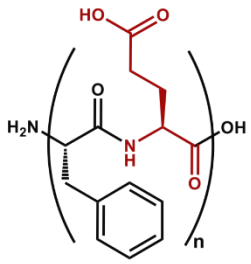


	q	n
	-9	1
	-7	2
	-6	3
	-3	4
	0	5
	+3	6
	+6	7
	+7	8
	+9	

Self-assembling Peptide Design

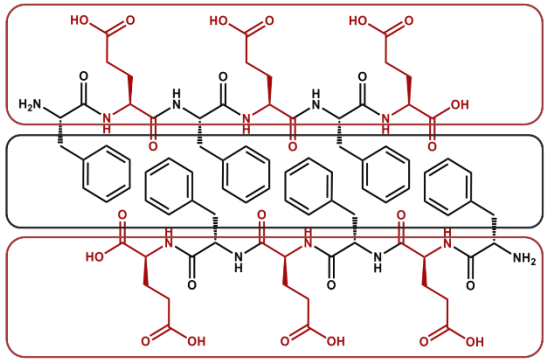


Glutamic acid



Phenylalanine

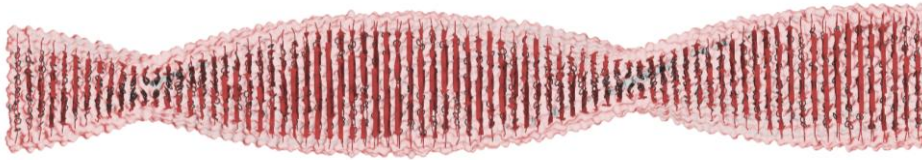
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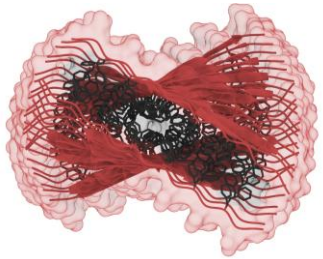


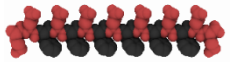
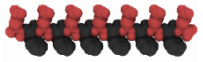
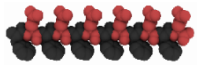
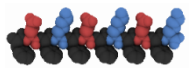
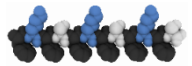
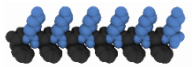
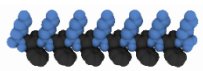
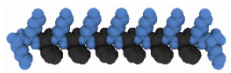
Hydrophilic surface

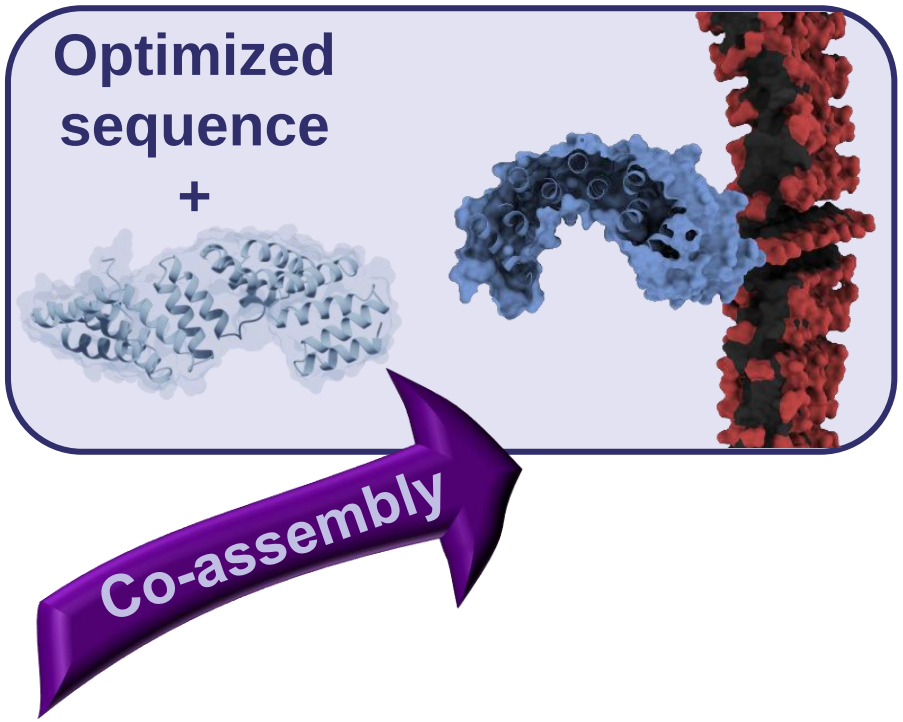
Hydrophobic core

Hydrophilic surface





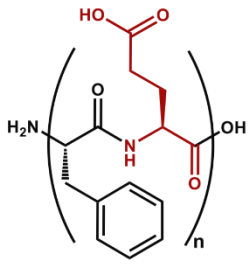
	q	n
	-9	1
	-7	2
	-6	3
	-3	4
	0	5
	+3	6
	+6	7
	+7	8
	+9	



Self-assembling Peptide Design

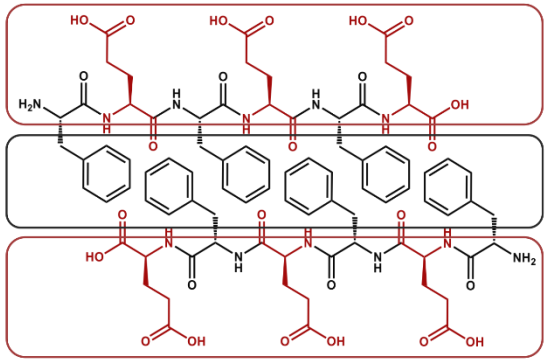


Glutamic acid



Phenylalanine

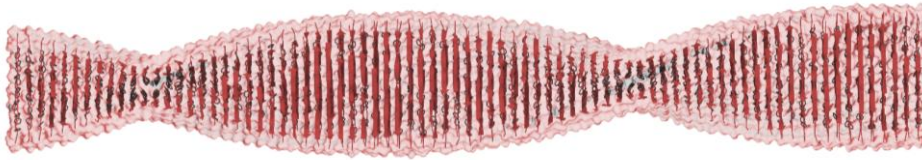
n repetitions

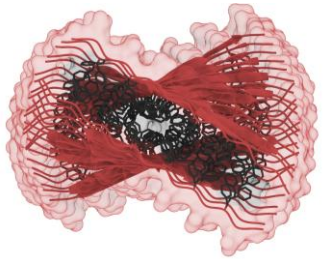


Hydrophilic surface

Hydrophobic core

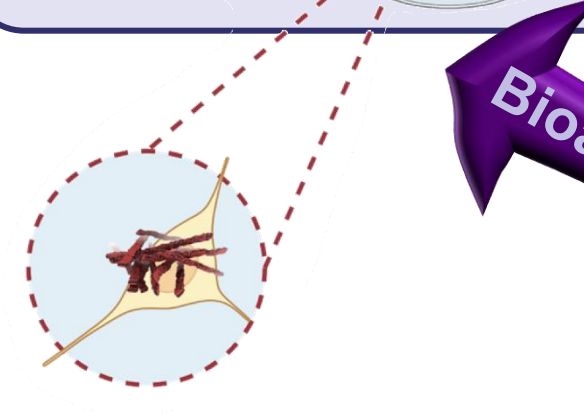
Hydrophilic surface







Library:
-q ⇔ +q

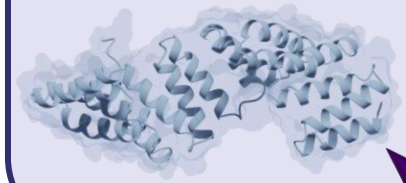


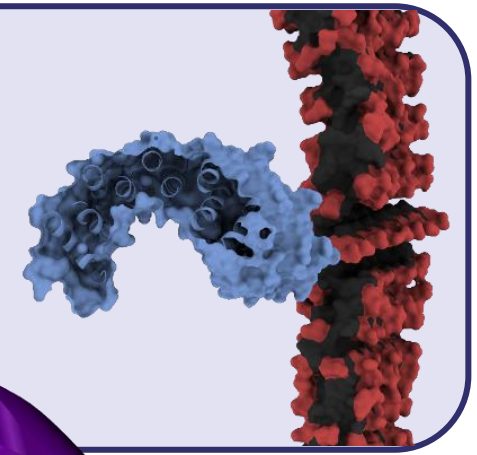
Bioactivity=f(q)

q	n
-9	1
-7	2
-6	3
-3	4
0	5
+3	6
+6	7
+7	8
+9	

Optimized sequence

+



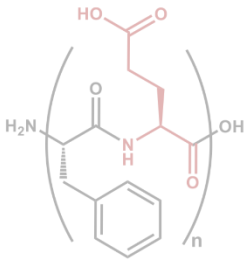


Co-assembly

Self-assembling Peptide Design

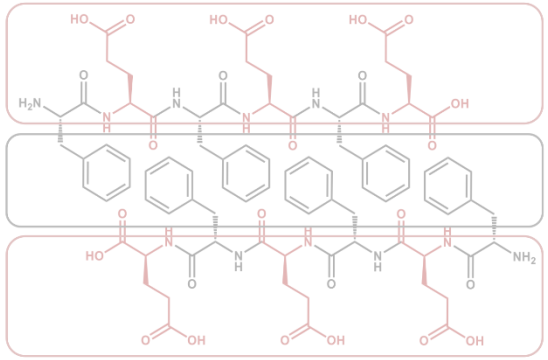


Glutamic acid



Phenylalanine

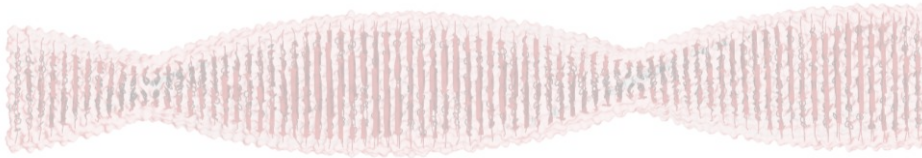
n repetitions

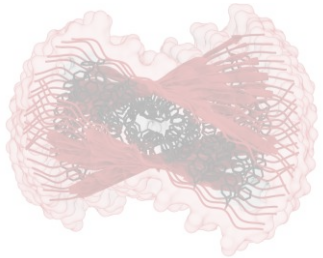


Hydrophilic surface

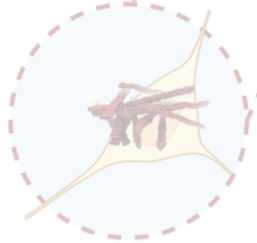
Hydrophobic core

Hydrophilic surface









Bioactivity=f(q)

q	n
-9	1
-7	2
-6	3
-3	4
0	5
+3	6
+6	7
+7	8
+9	



Co-assembly

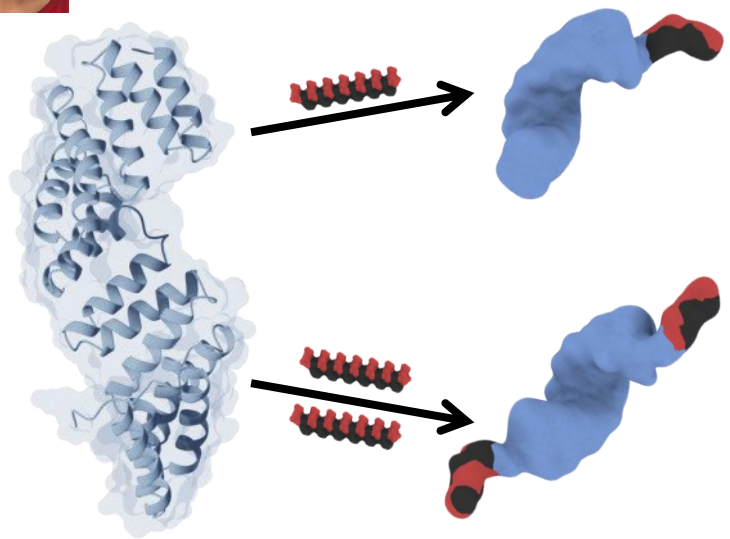
Protein-Peptide Co-assemblies

- **Peptide Assembly:**



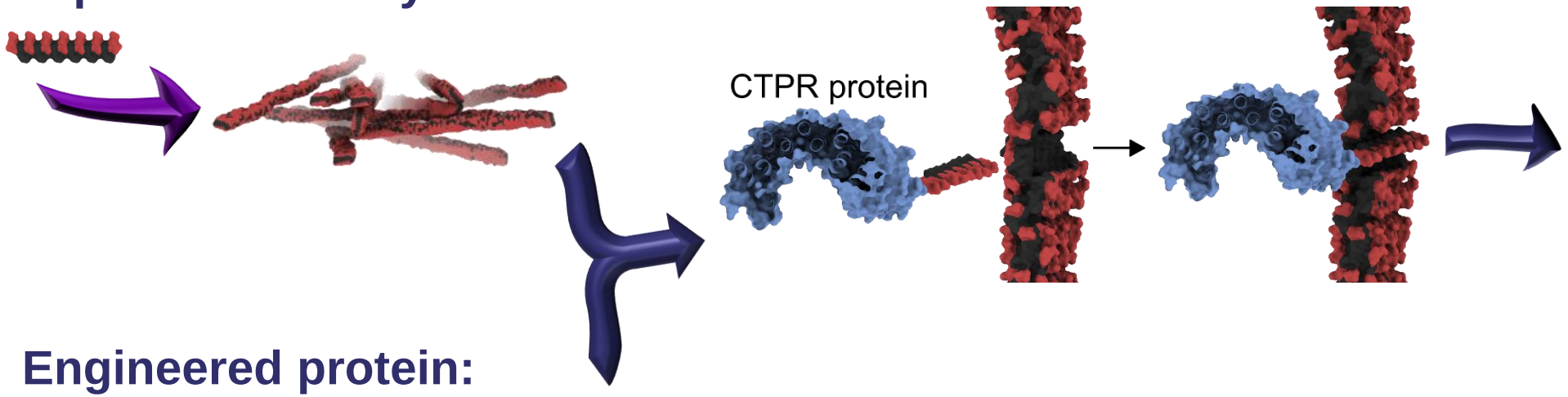
- **Engineered protein:**
  - **CTPR + 1-2 Peptides**
  - **Aitziber L. Cortajarena**

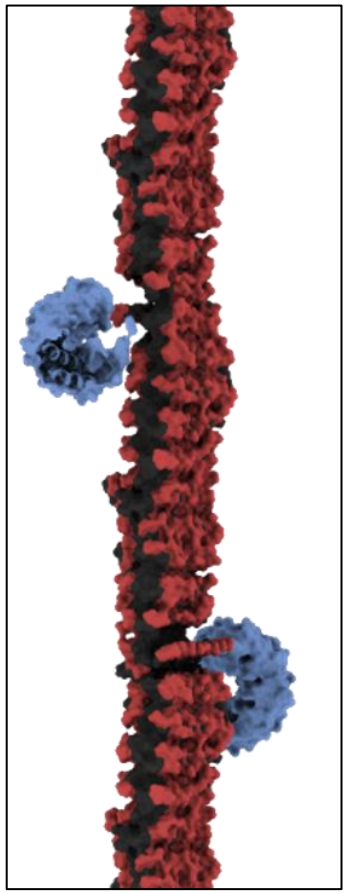




Protein-Peptide Co-assemblies

- **Peptide Assembly:**

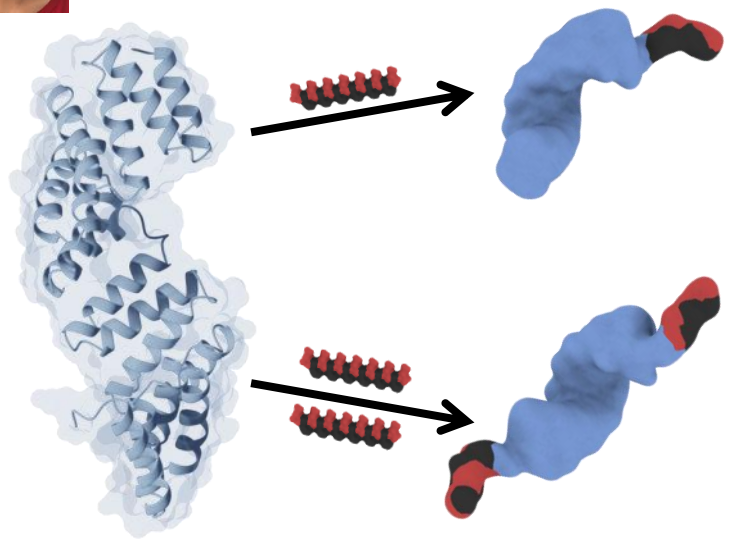




CTPR decorated assemblies

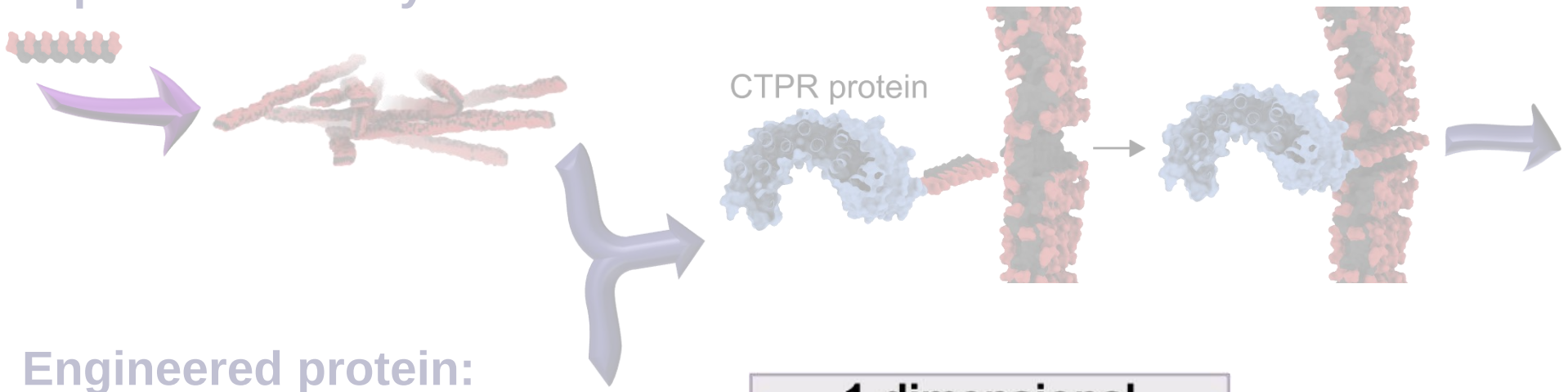
- **Engineered protein:**
  - **CTPR + 1-2 Peptides**
  - **Aitziber L. Cortajarena**





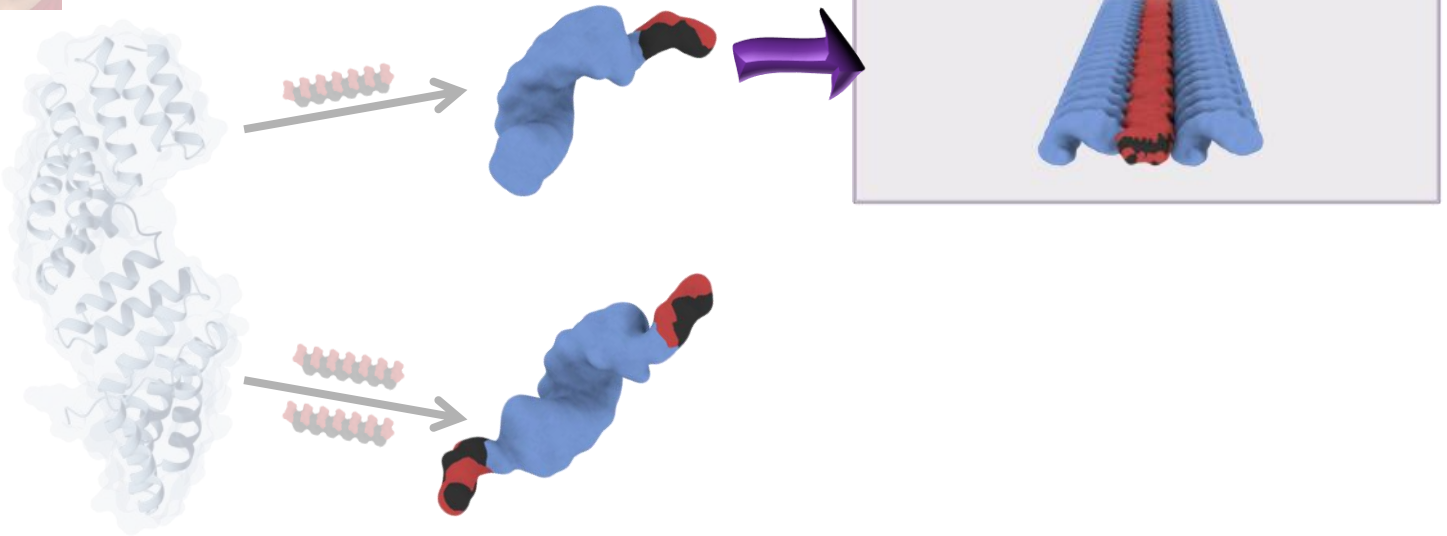
Protein-Peptide Co-assemblies

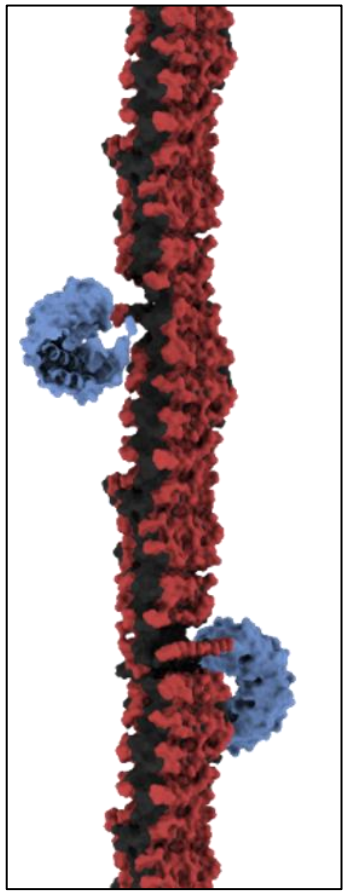
- Peptide Assembly:



- Engineered protein:
  - CTPR + 1-2 Peptides
  - Aitziber L. Cortajarena

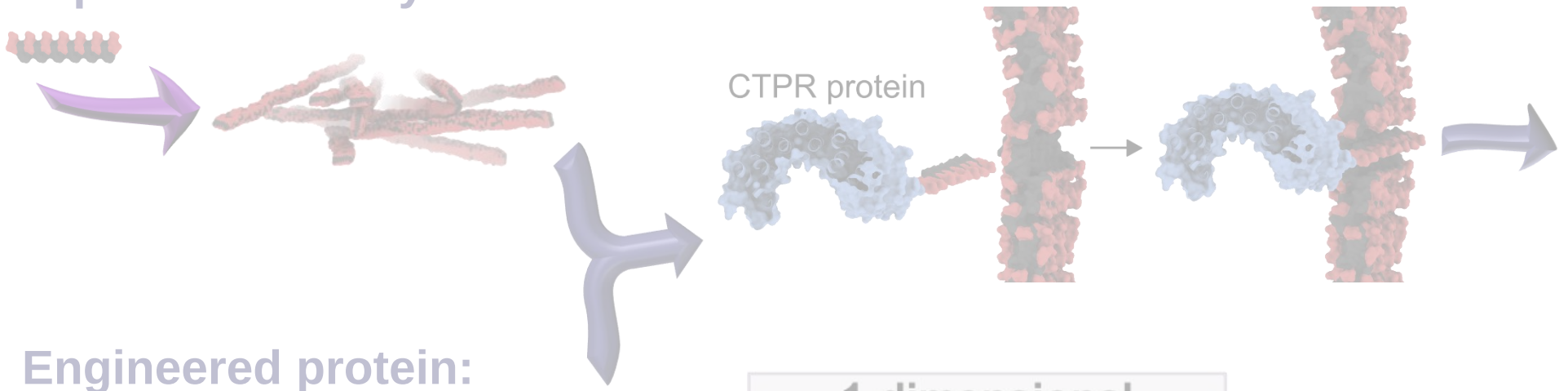


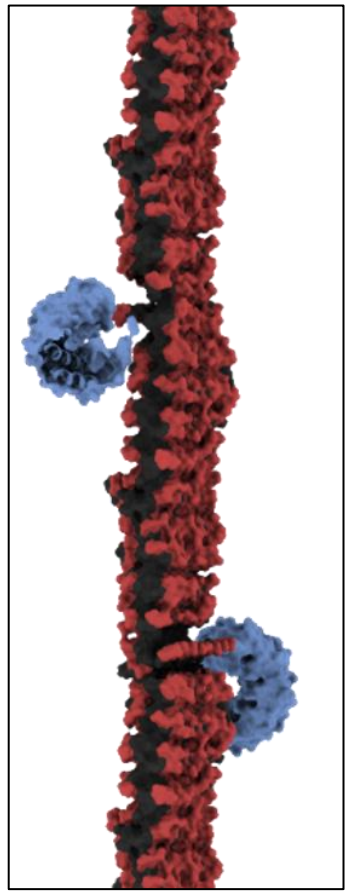




Protein-Peptide Co-assemblies

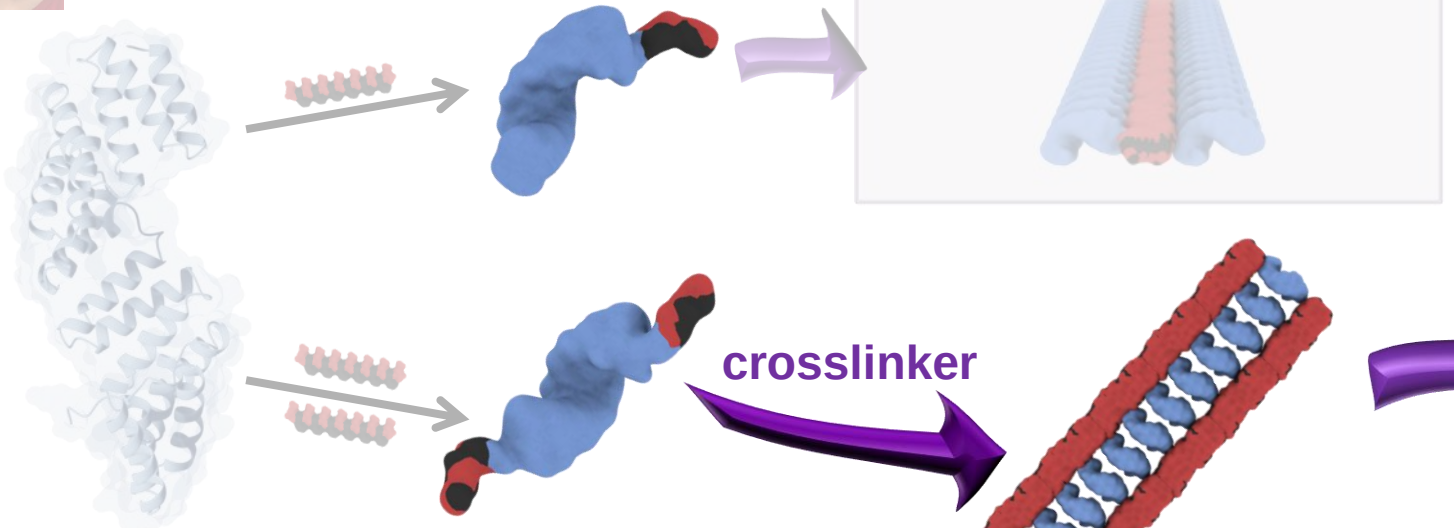
- Peptide Assembly:





- Engineered protein:
  - CTPR + 1-2 Peptides
  - Aitziber L. Cortajarena

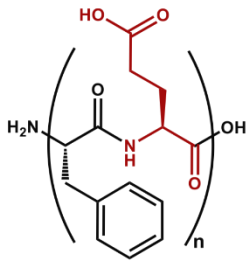




Peptide Self-assembly Optimization

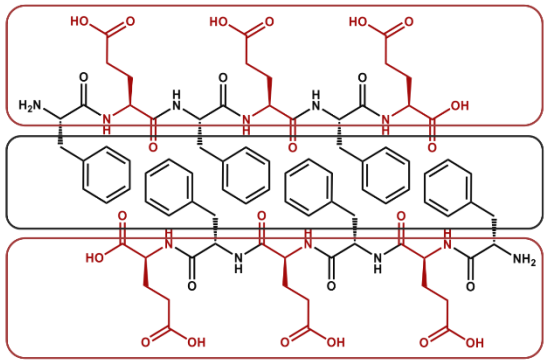


Glutamic acid



Phenylalanine

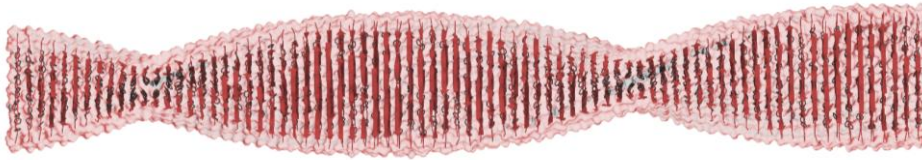
n repetitions

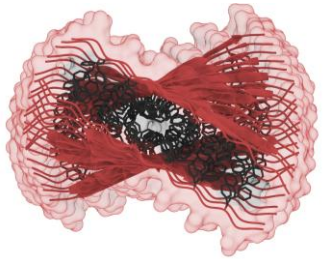


Hydrophilic surface

Hydrophobic core

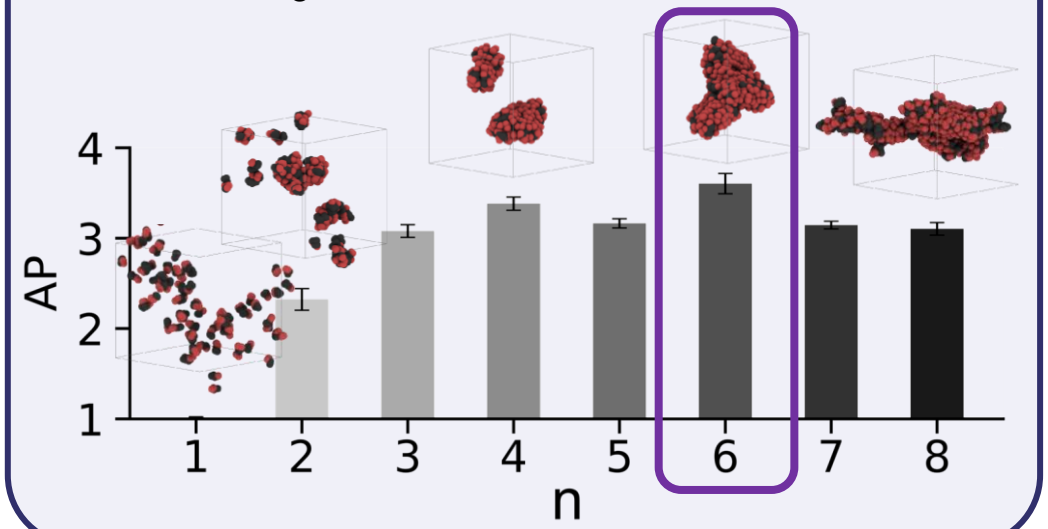
Hydrophilic surface





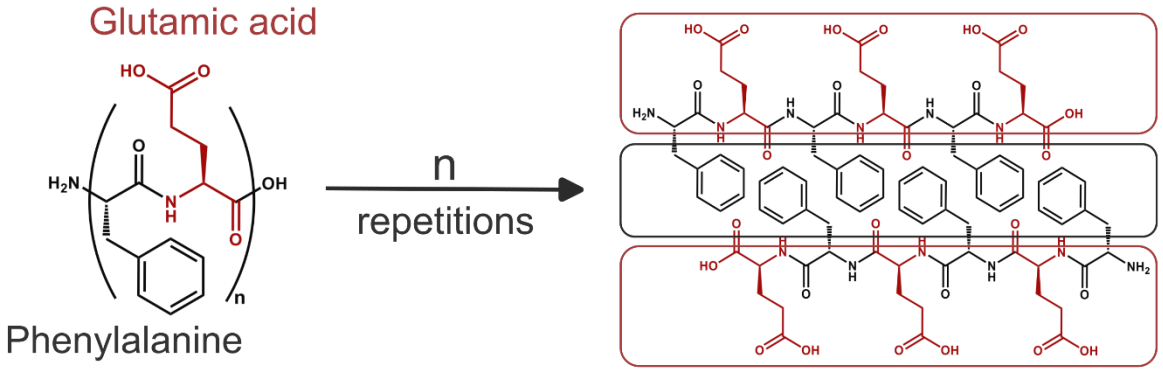
Peptide length optimization:

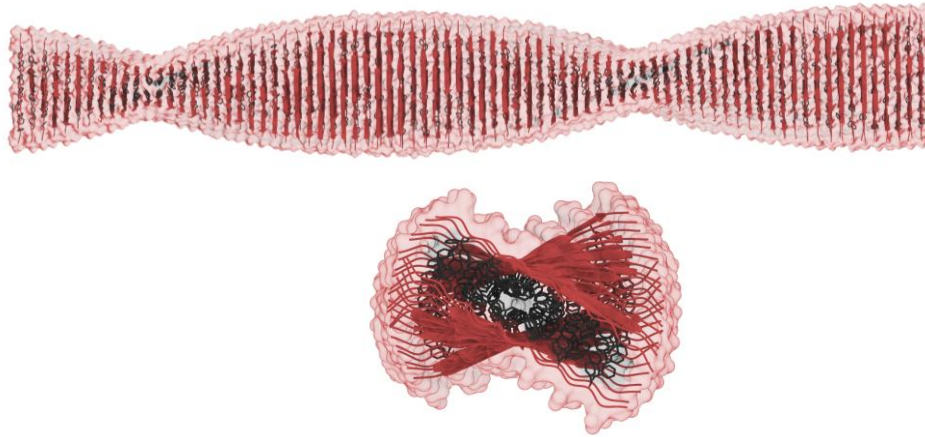
¬ $(FE)_6$



Peptide Self-assembly Optimization

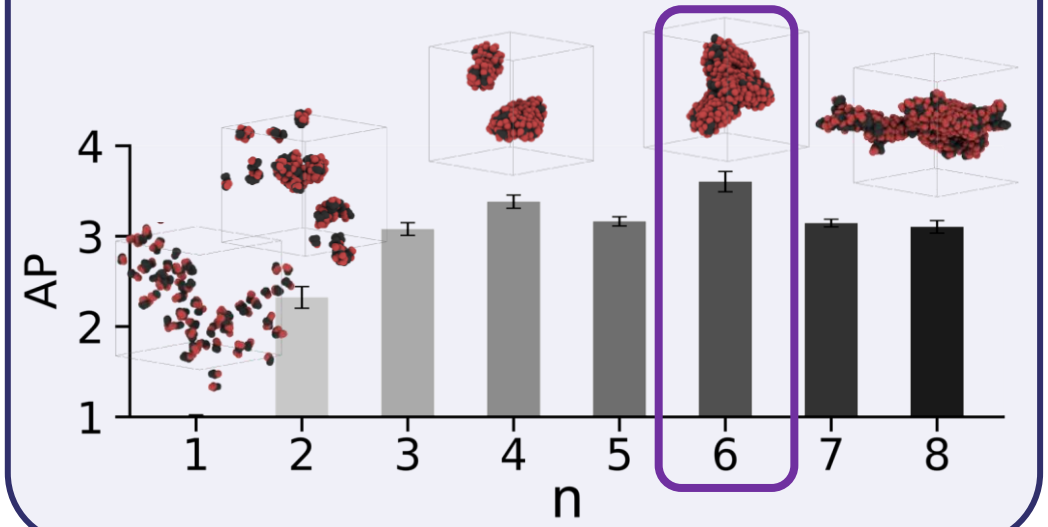
Cortajarena, Sasselli, *et al.*
ACS Nano **2025**, *19*, 16500.





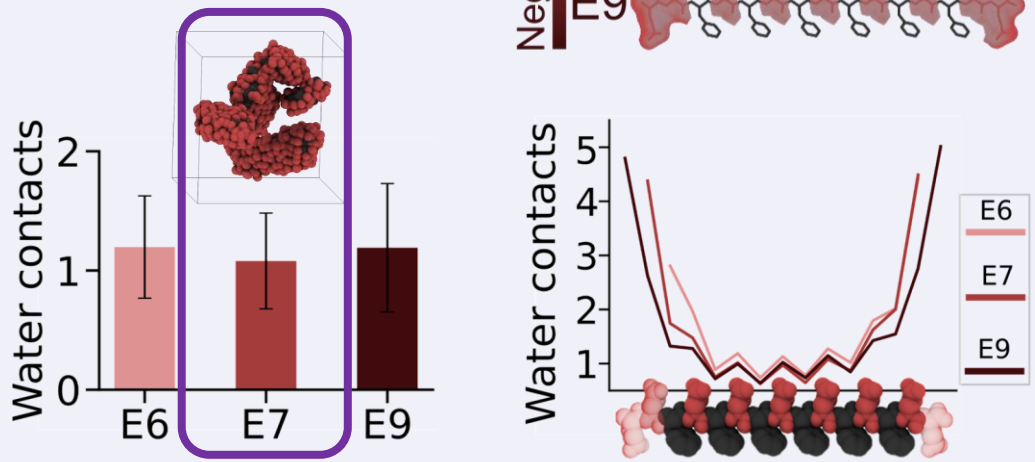
Peptide length optimization:

¬ $(FE)_6$



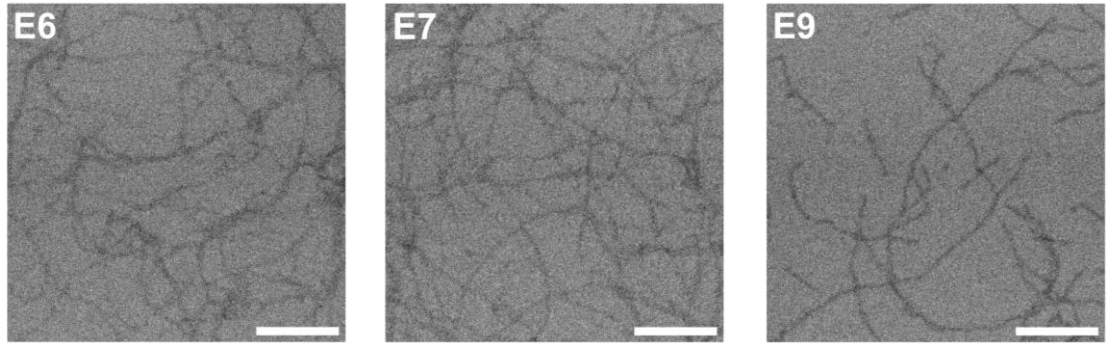
Charge/peptide optimization:

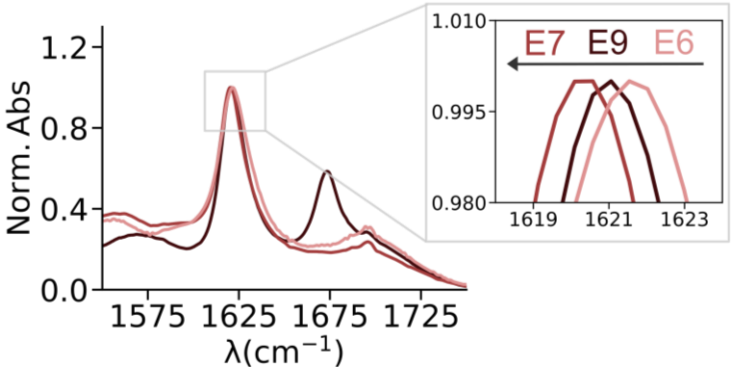
¬ E7 ≡ $E(FE)_6$



Experimental Validation – E7 Selected

Cortajarena, Sasselli, *et al.*
ACS Nano **2025**, *19*, 16500.



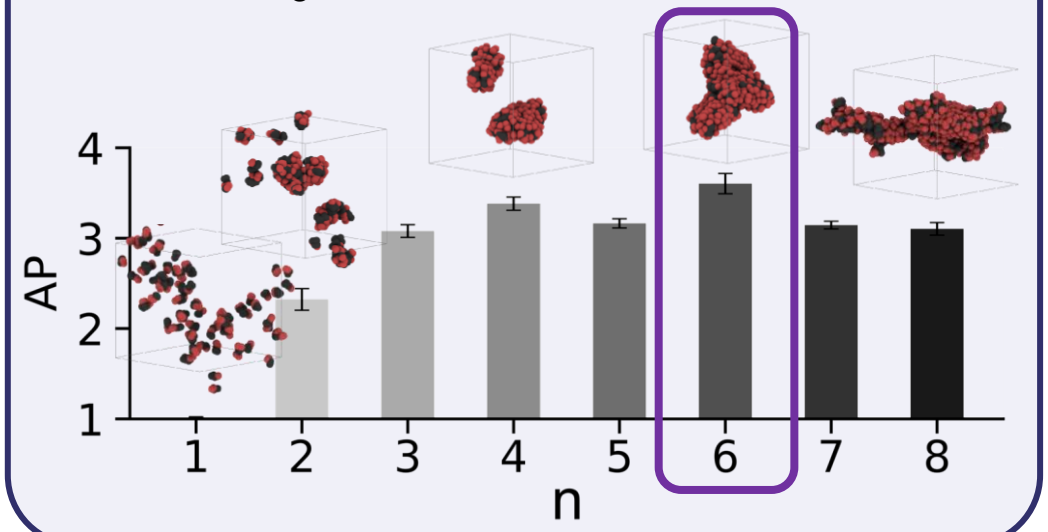


Experimentally:

- ¬ Fiber formation
- ¬ β-sheet:
  E7 > E9 > E6

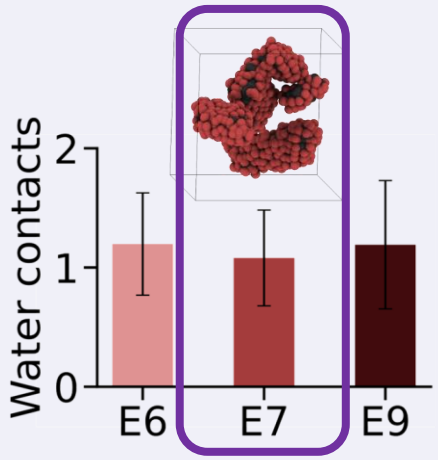
Peptide length optimization:

- ¬ **$(FE)_6$**

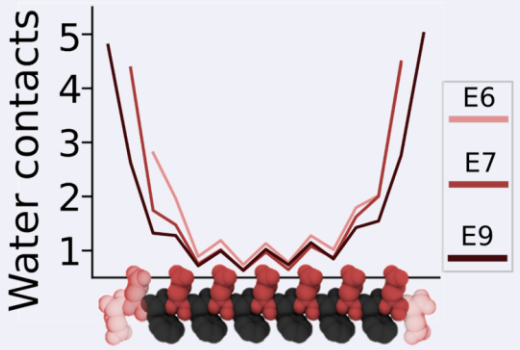


Charge/peptide optimization:

- ¬ **E7 ≡ $E(FE)_6$**

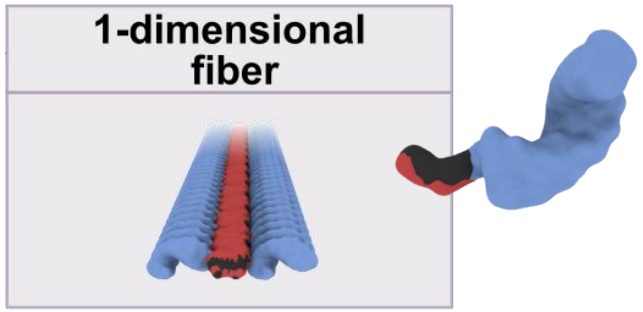




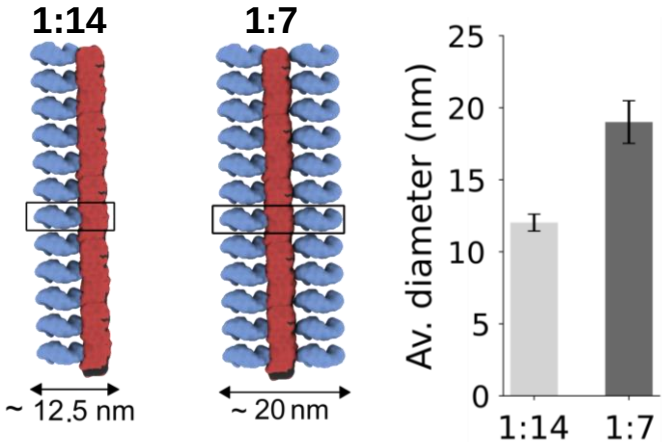


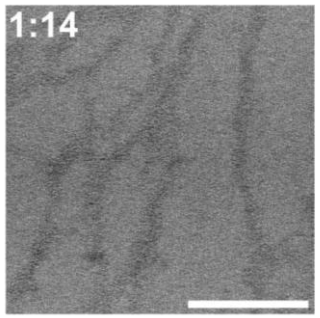
Protein-Peptide Co-assemblies

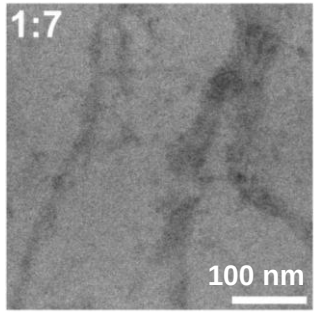
Cortajarena, Sasselli, *et al.*
ACS Nano **2025**, *19*, 16500.



protein:peptide ratio

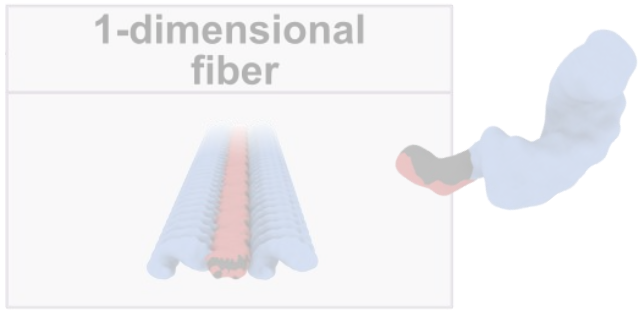


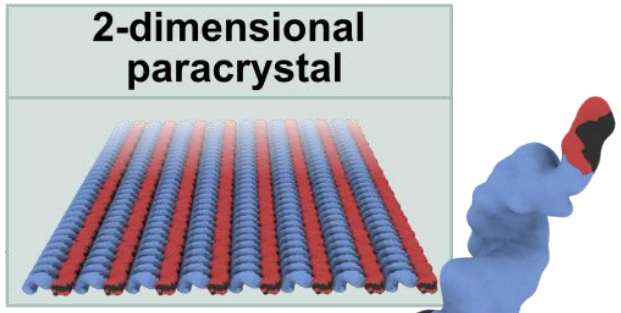


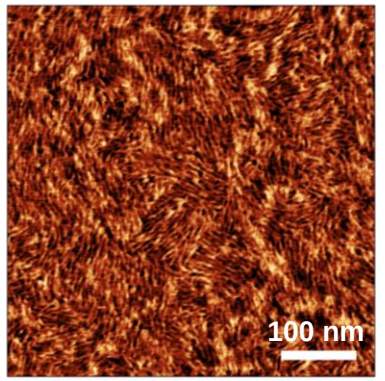


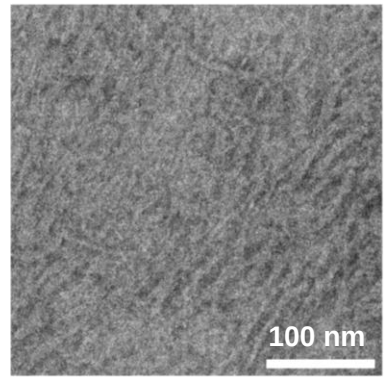
Protein-Peptide Co-assemblies

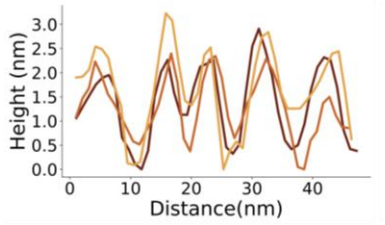
Cortajarena, Sasselli, *et al.*
ACS Nano **2025**, *19*, 16500.

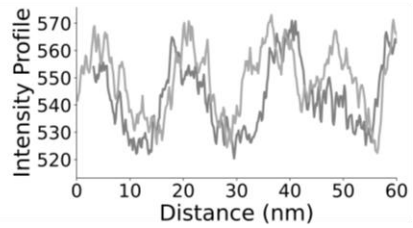




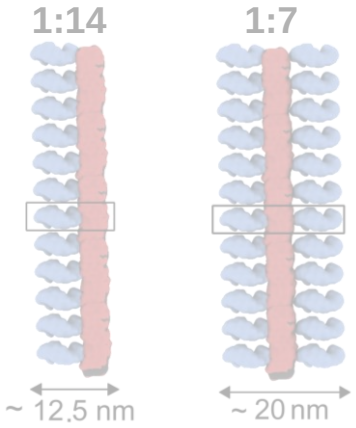


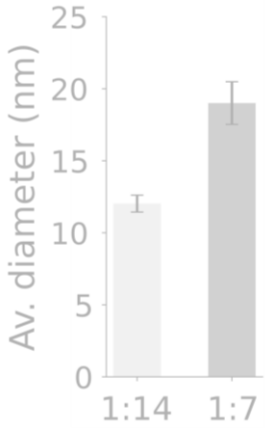


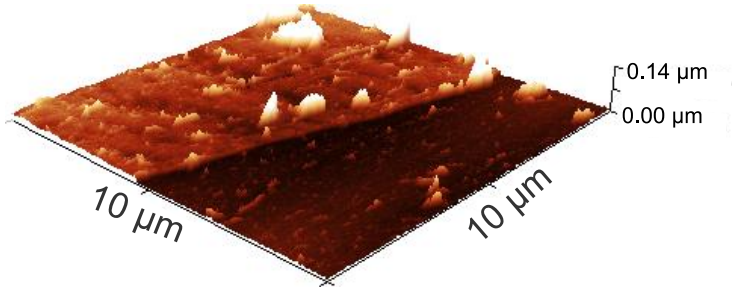


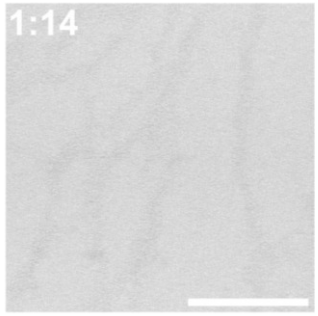


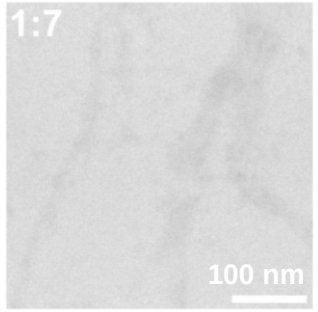
protein:peptide ratio



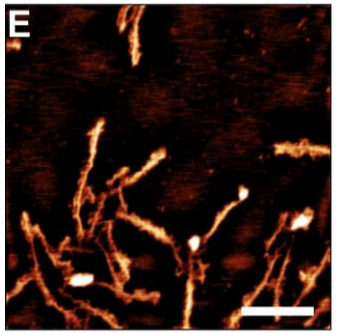






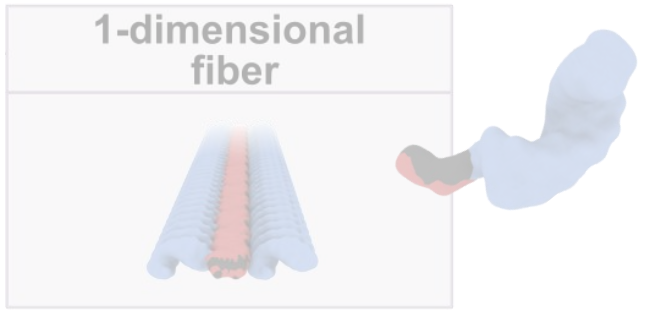


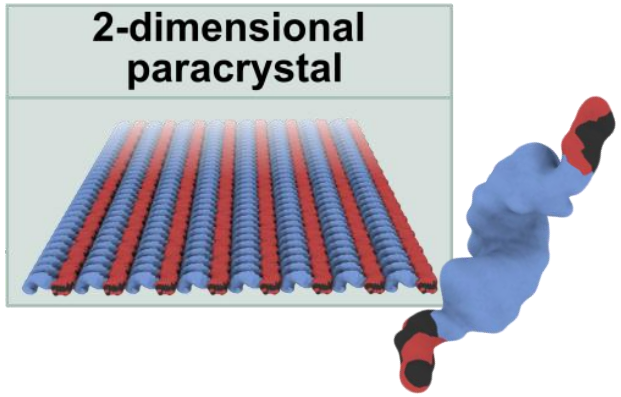
Disassembled control

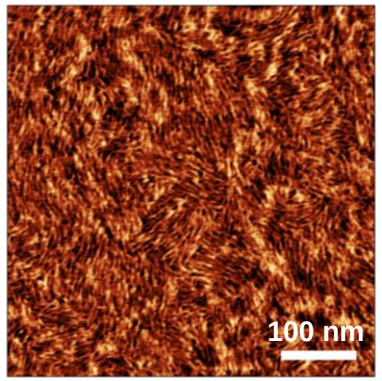


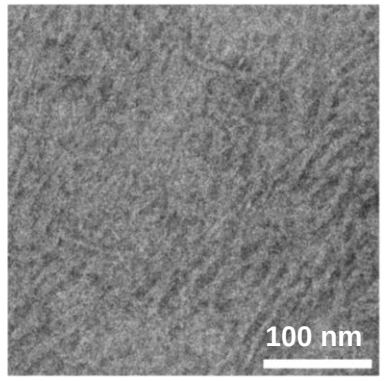
Protein-Peptide Co-assemblies

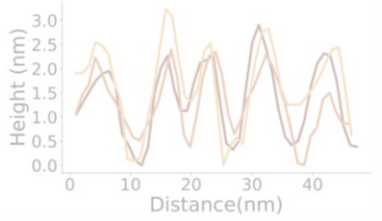
Cortajarena, Sasselli, *et al.*
ACS Nano **2025**, *19*, 16500.

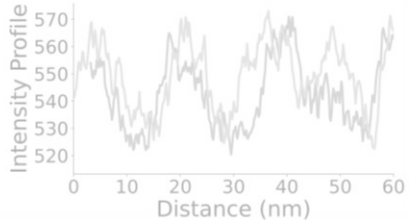




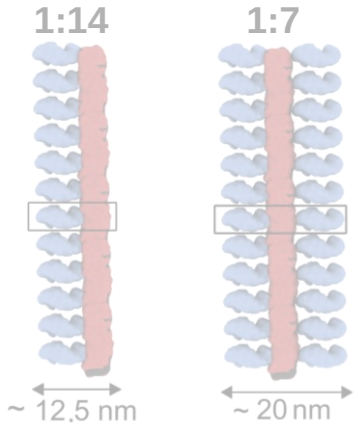


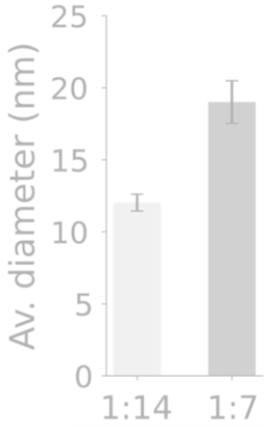


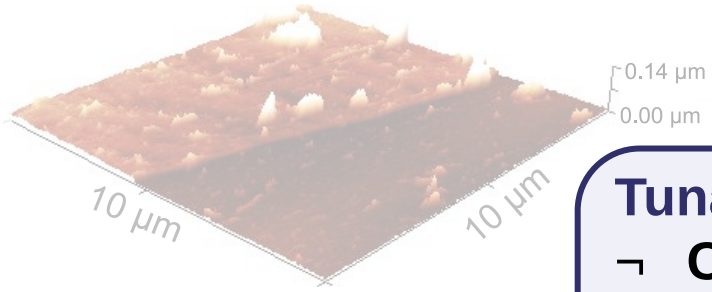


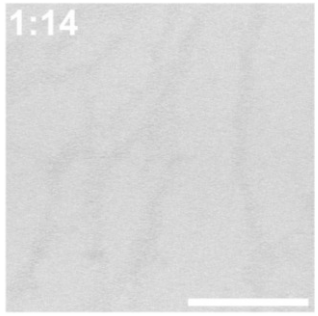


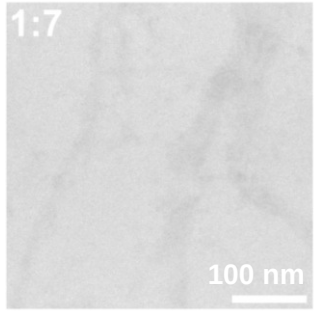
protein:peptide ratio



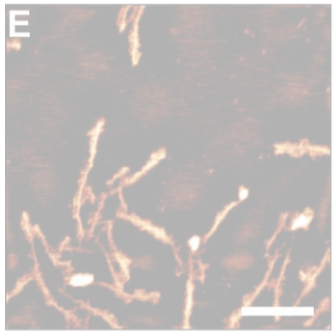






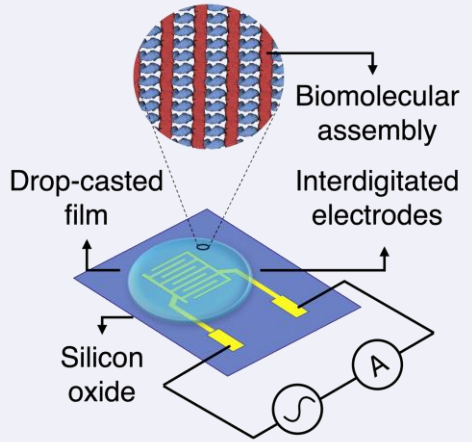


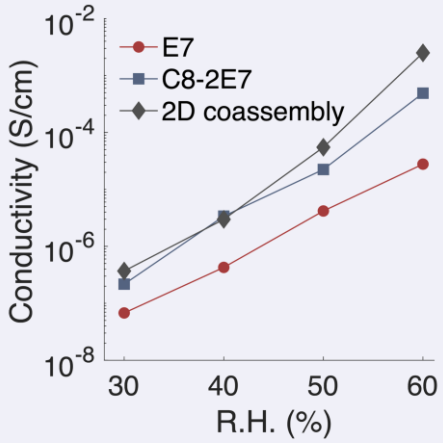
Disassembled control



Tunable 2D materials

¬ **Controlled thickness & morphology**

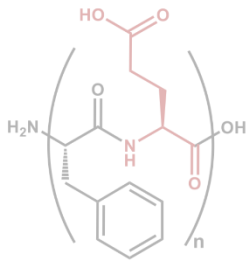




Self-assembling Peptide Design

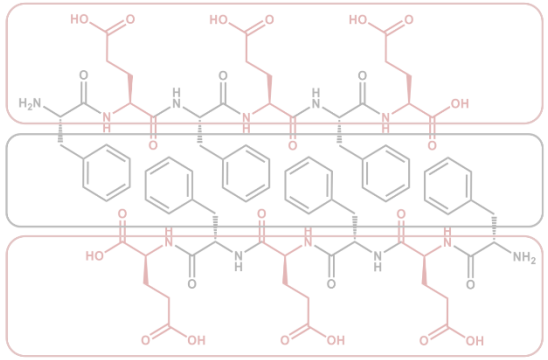


Glutamic acid



Phenylalanine

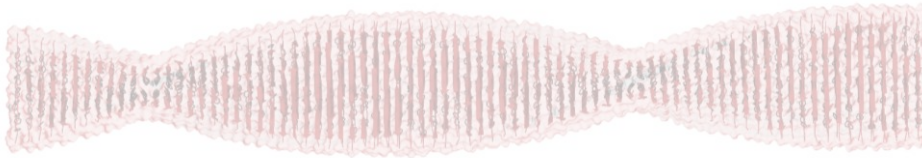
n repetitions

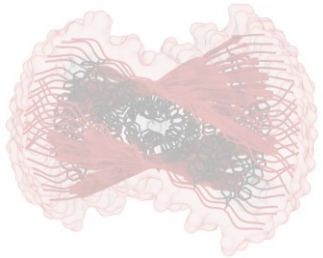


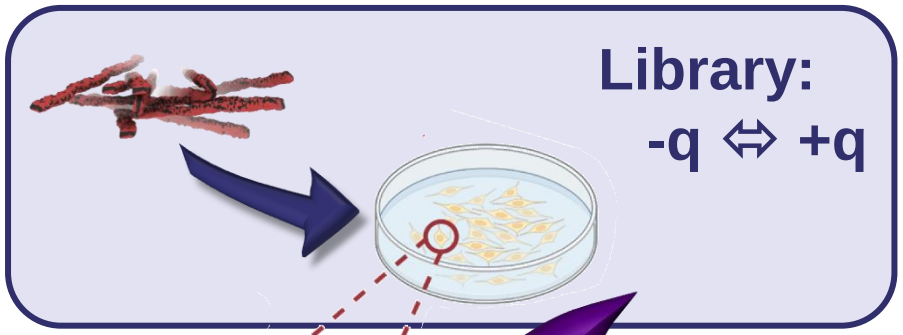
Hydrophilic surface

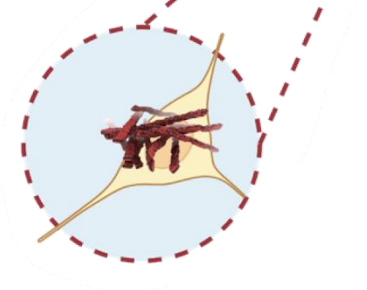
Hydrophobic core

Hydrophilic surface



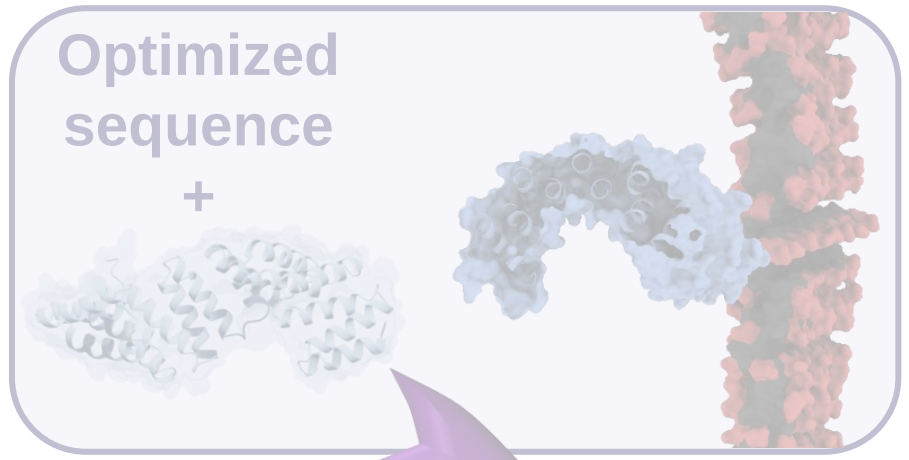






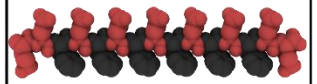
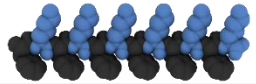
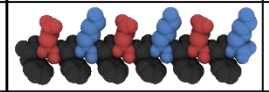
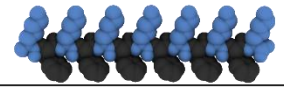
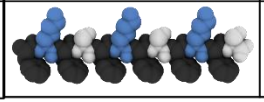
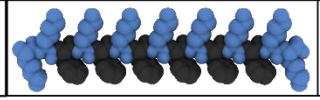
Bioactivity=f(q)

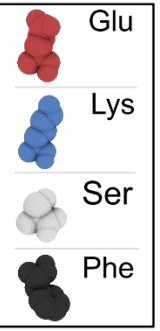
q	n
-9	1
-7	2
-6	3
-3	4
0	5
+3	6
+6	7
+7	8
+9	



Co-assembly

SPA Library with Charges: -9 – +9

Peptide	Charge	Name	Peptide	Charge	Name	Peptide	Charge	Name
	- 9	E9		- 3	E3		+ 6	K6
	- 7	E7		0	EK		+ 7	K7
	- 6	E6		+ 3	K3		+ 9	K9



Negative

Positive

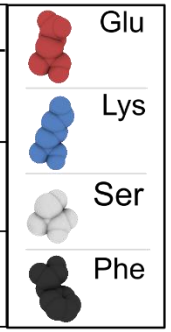
Polar

Hydrophobic

Sasselli, Alvarez, Cortajarena, *et al. Adv. Sci.* **2026**, *13*, e07946

SPA Library Screening using CG-MD

Peptide	Charge	Name	Peptide	Charge	Name	Peptide	Charge	Name
	- 9	E9		- 3	E3		+ 6	K6
	- 7	E7		0	EK		+ 7	K7
	- 6	E6		+ 3	K3		+ 9	K9

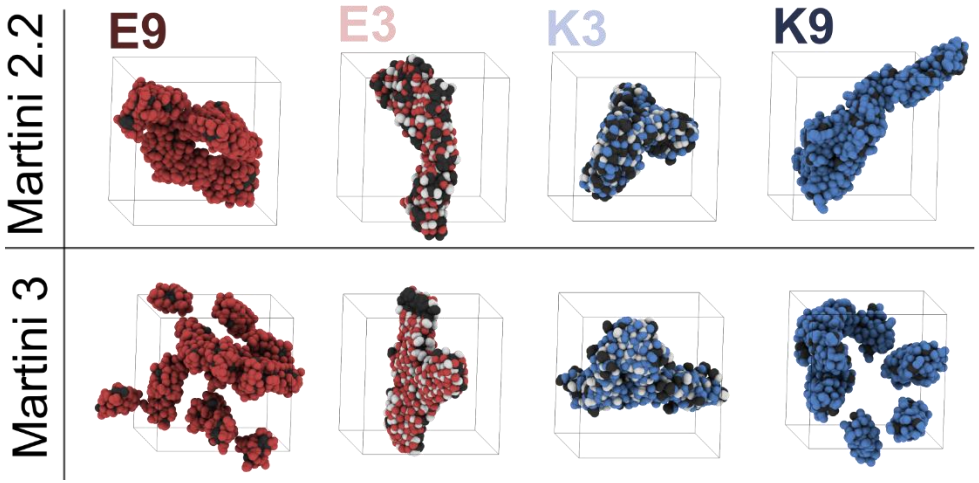


Negative

Positive

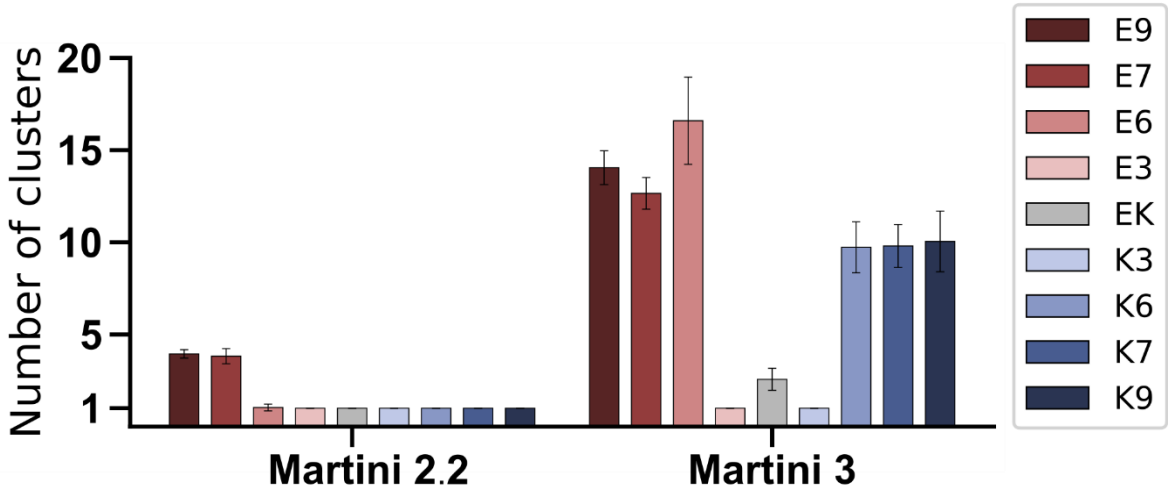
Polar

Hydrophobic



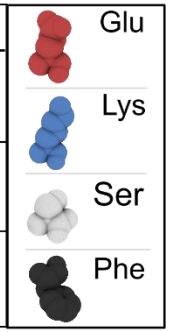
MARTINI 2.2 vs MARTINI 3 screening

- MARTINI 2.2: all SPAs self-assemble
- MARTINI 3: discrepancies at q ↑ (±6-9)



SPA Library Screening using CG-MD

Peptide	Charge	Name	Peptide	Charge	Name	Peptide	Charge	Name
	- 9	E9		- 3	E3		+ 6	K6
	- 7	E7		0	EK		+ 7	K7
	- 6	E6		+ 3	K3		+ 9	K9

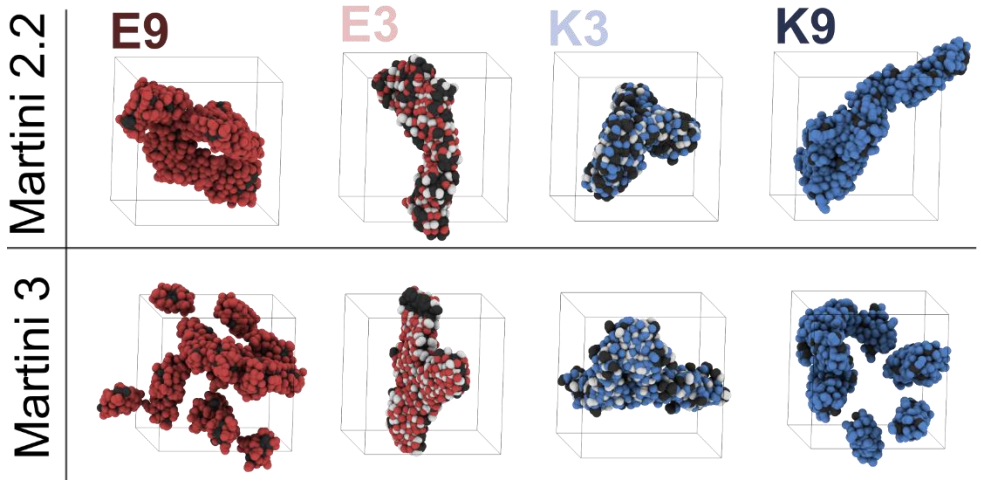


Negative

Positive

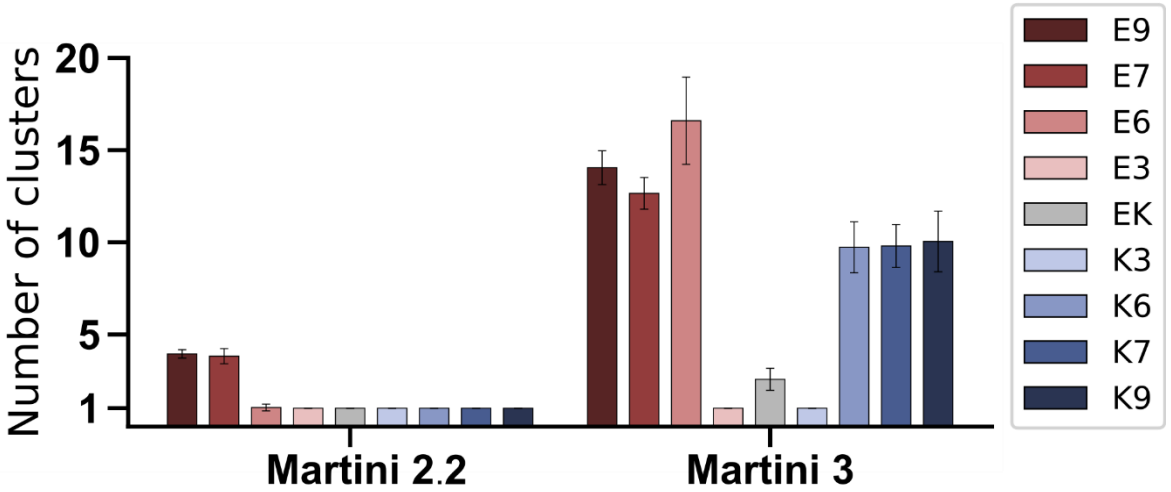
Polar

Hydrophobic



MARTINI 2.2 vs MARTINI 3 screening

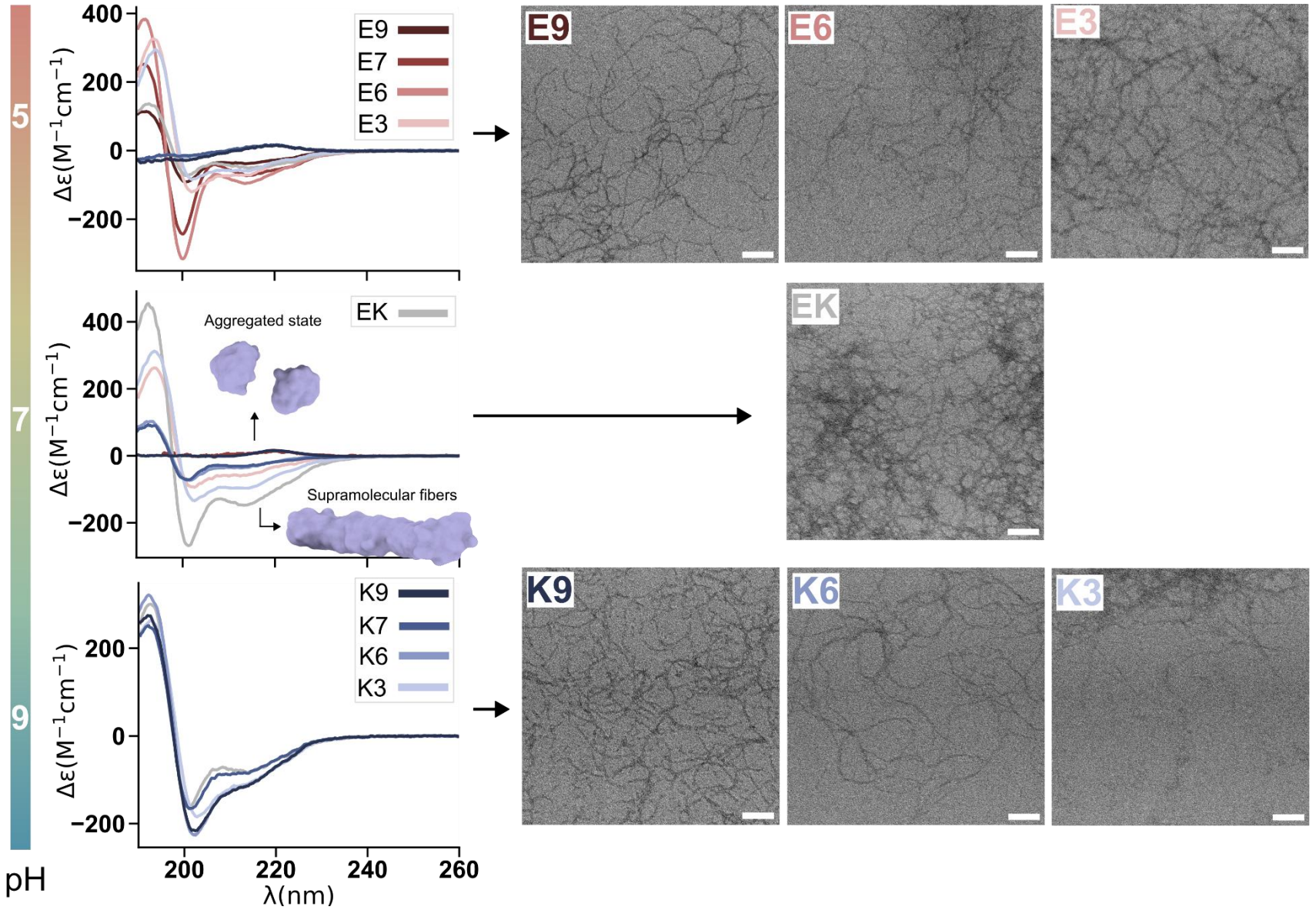
- MARTINI 2.2: all SPAs self-assemble
- MARTINI 3: discrepancies at q ↑ (±6-9)



***q* = ±6-9 → electrostatic repulsion @ pH 7**

- K (pk_a=10.53) → pH 9
- E (pk_a=4.25) → pH 5

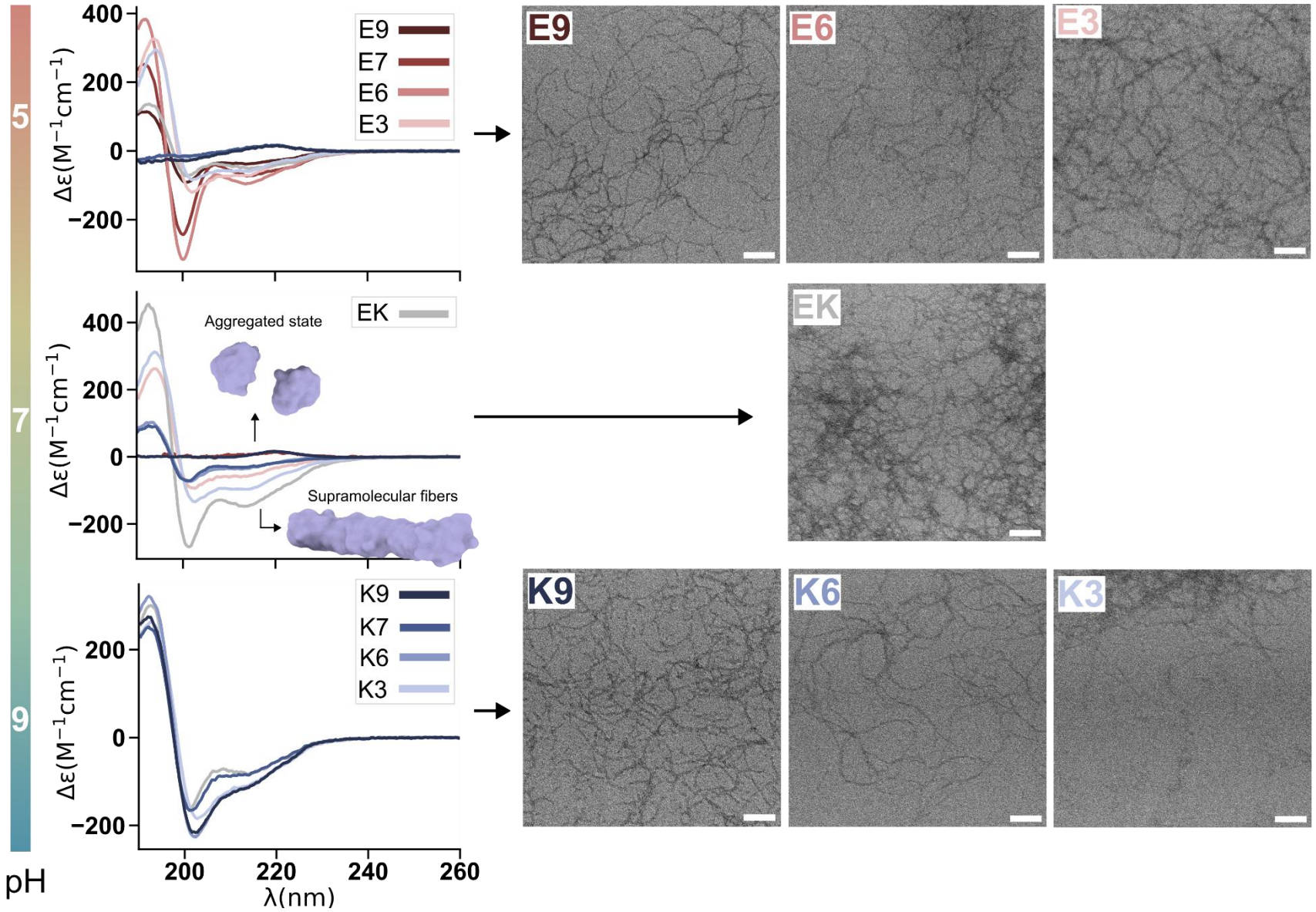
SPA Library – Experimental Characterization



All peptides form fibers:

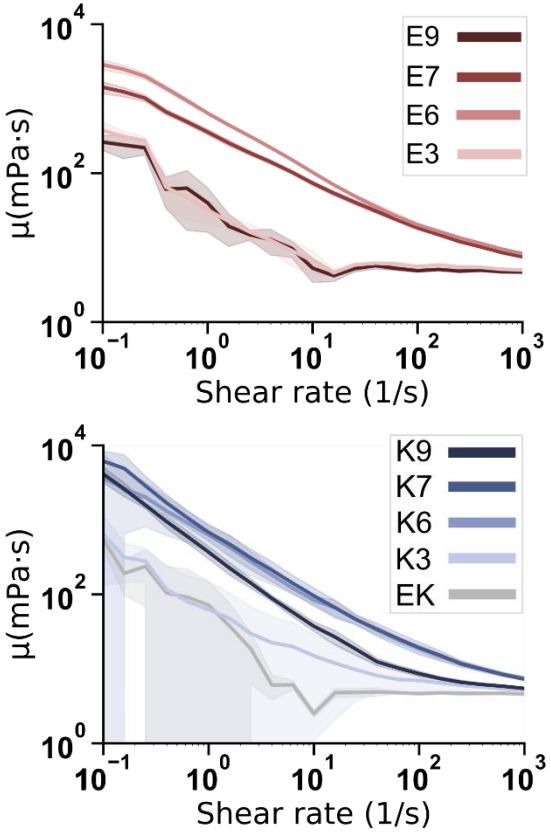
- ≈ size
- ≈ morphology
- ≈ intermolecular order

SPA Library – Experimental Characterization

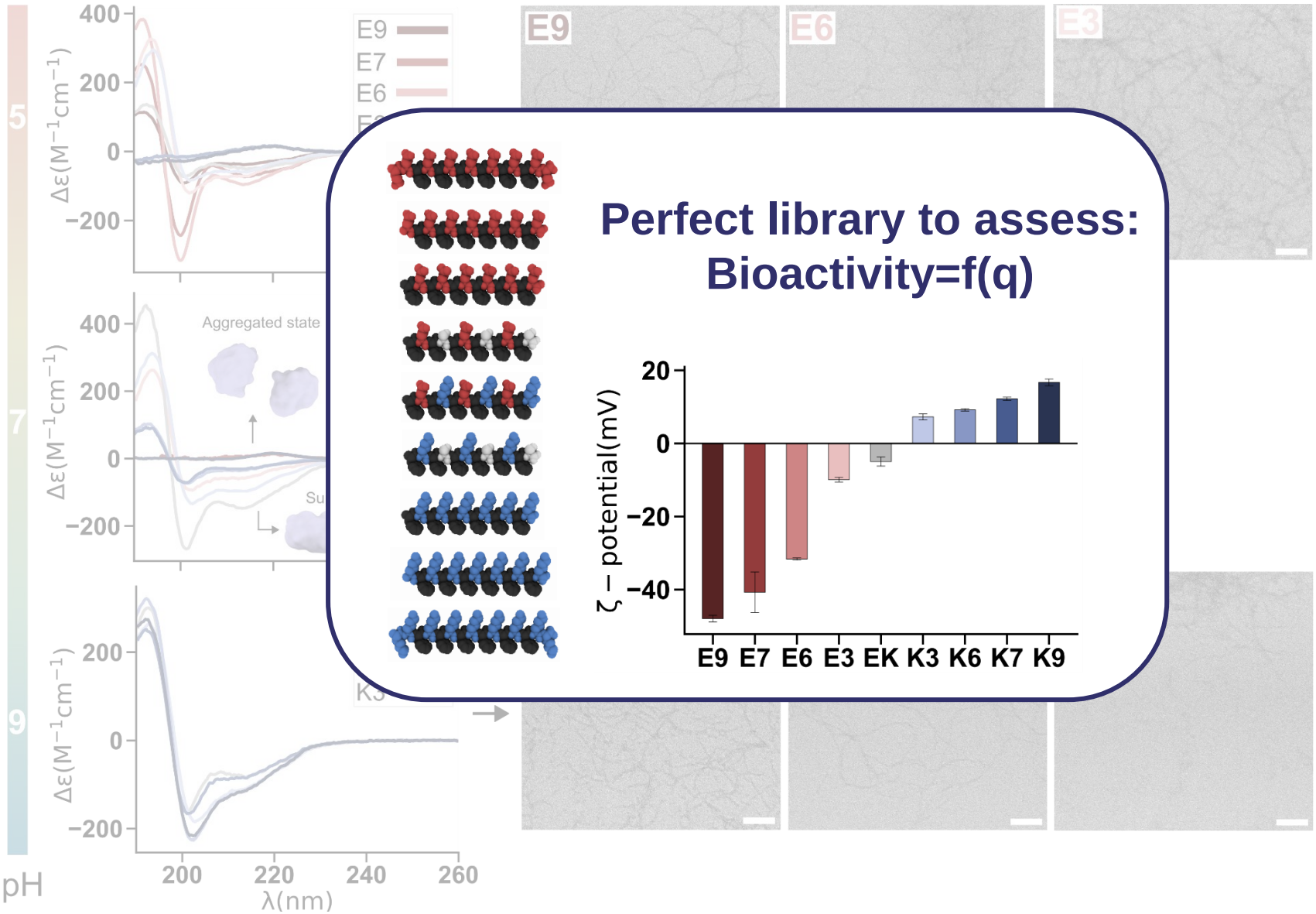


All peptides form fibers:

- ≈ size
- ≈ morphology
- ≈ intermolecular order
- ≈ mechanical properties



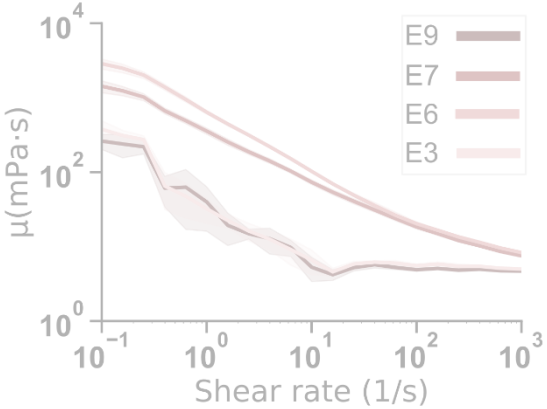
SPA Library – Experimental Characterization

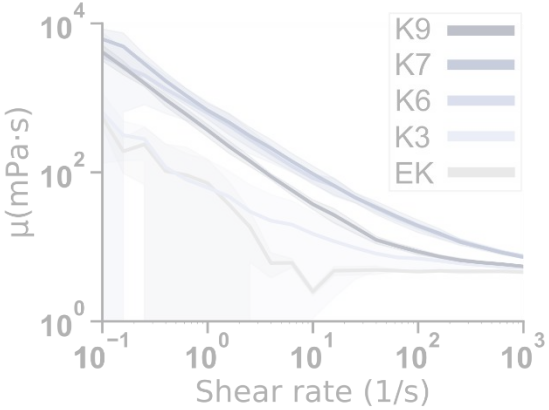


Perfect library to assess:
Bioactivity=f(q)

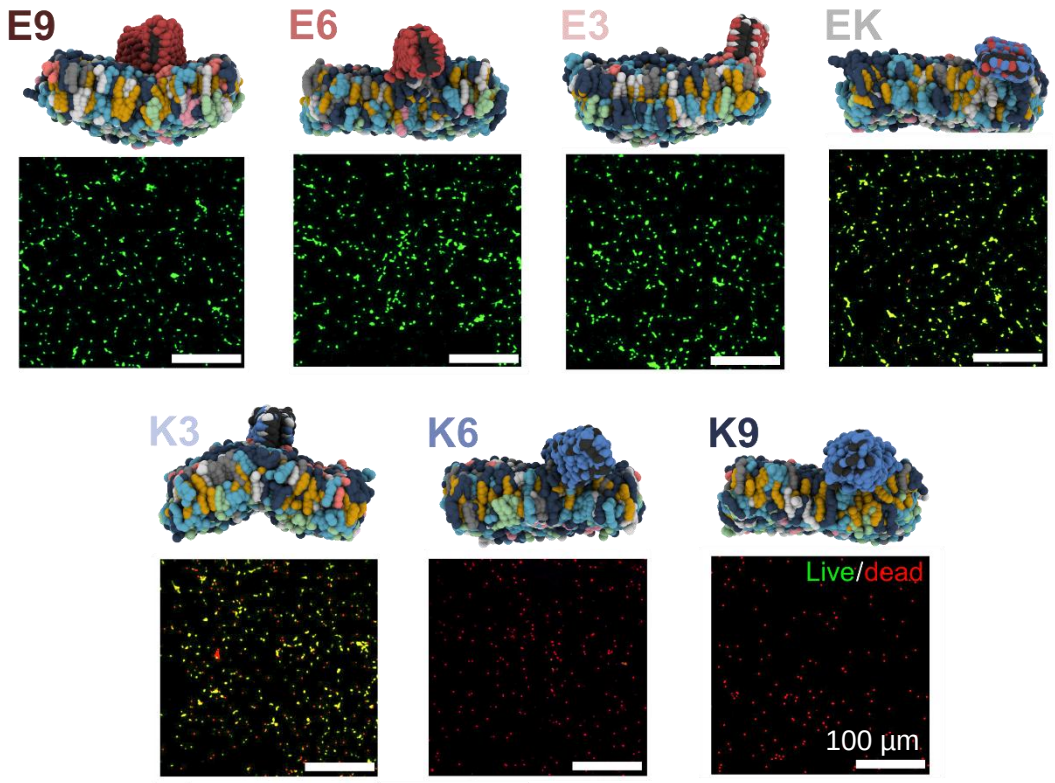
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- ≈ size
- ≈ morphology
- ≈ intermolecular order
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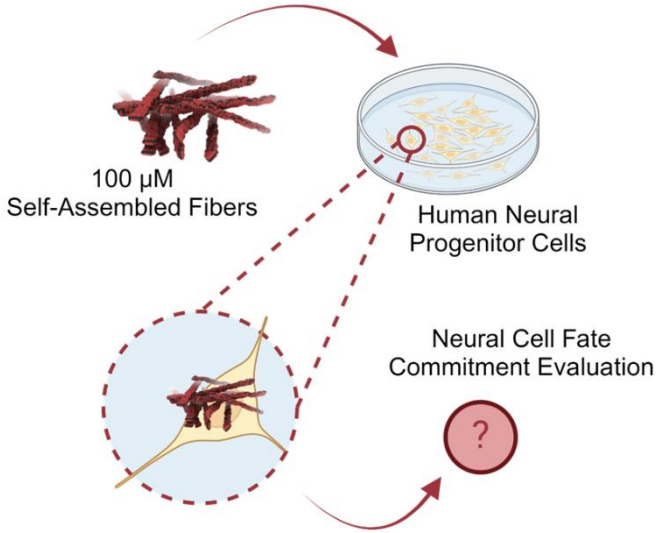


Electrostatics Modulates Cytotoxicity



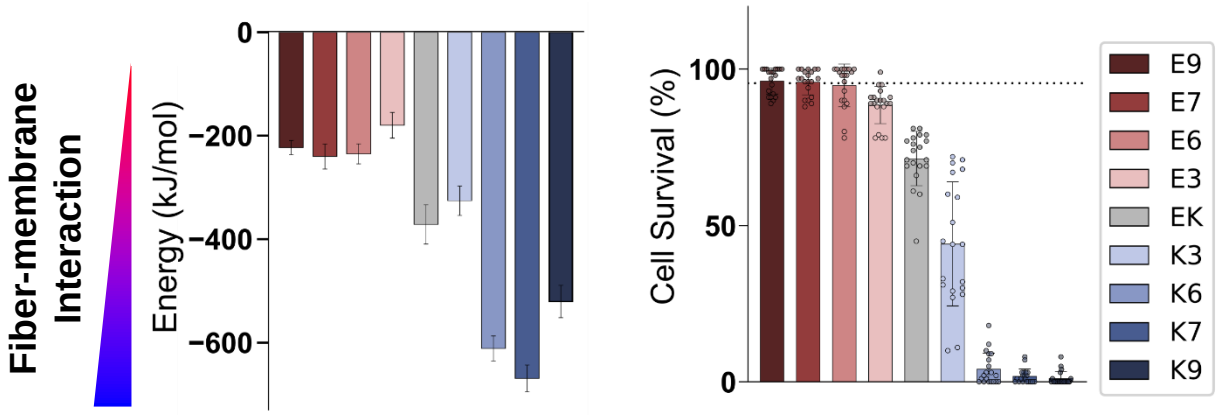


Zaida Alvarez



Charge affects survival:

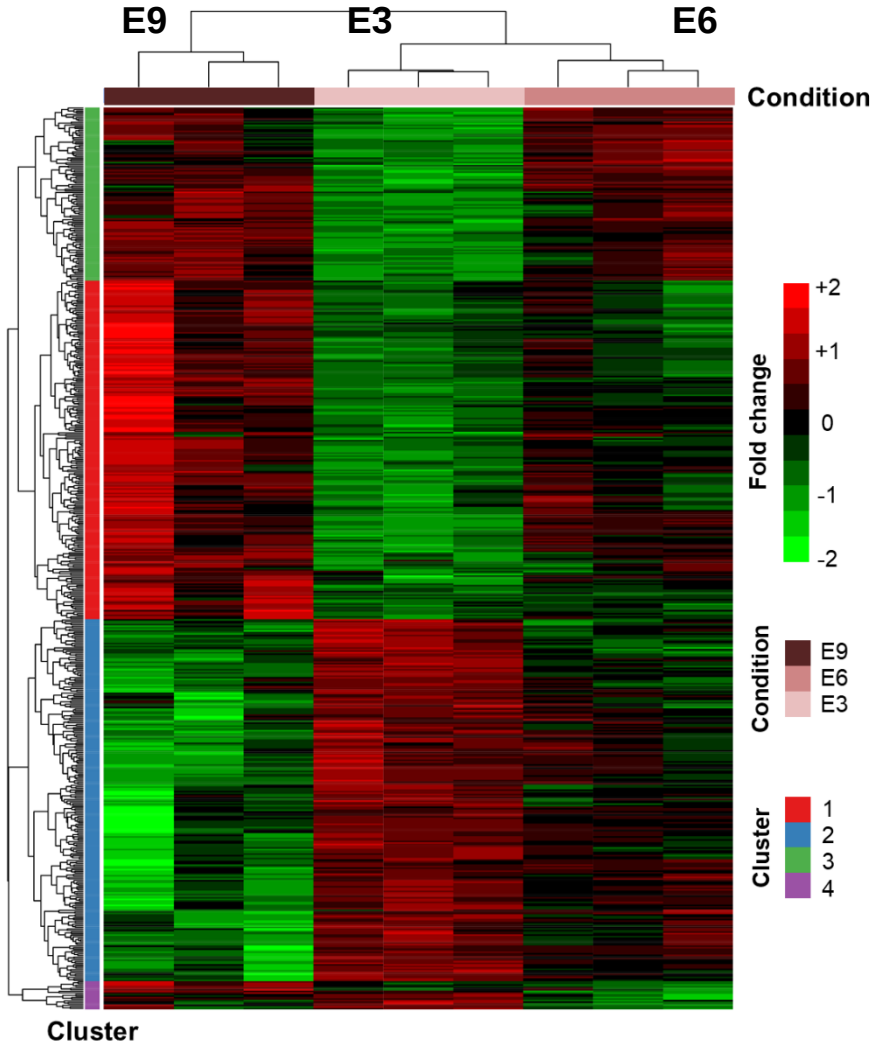
- Negative charges:
  - ↑ survival
- Positive charges:
  - ↑ interaction with membrane
  - ↑ cytotoxicity



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Electrostatics Modulates Bioactivity

Hierarchical clustering heatmap of differentially abundant proteins:

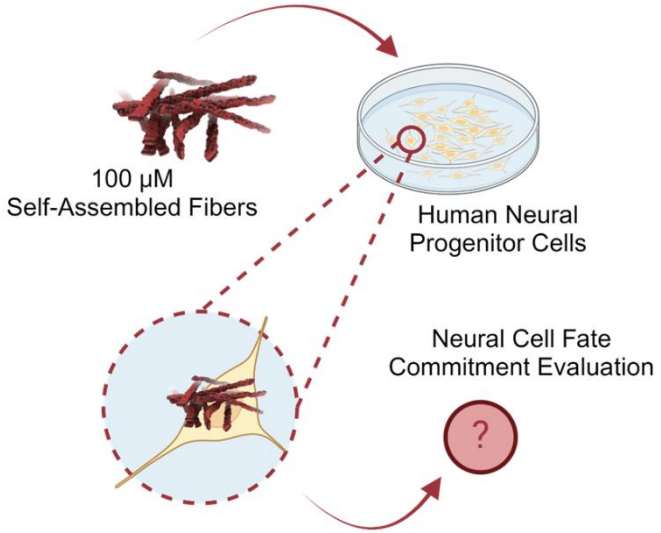


E3:

- ↑ metabolic adaptations
- ↑ stress responses

E9:

- ↑ cell-cell adhesion
- ↑ cell-substrate adhesion
- ↑ neuron projection development
- ↑ positive regulation of the MAPK cascade



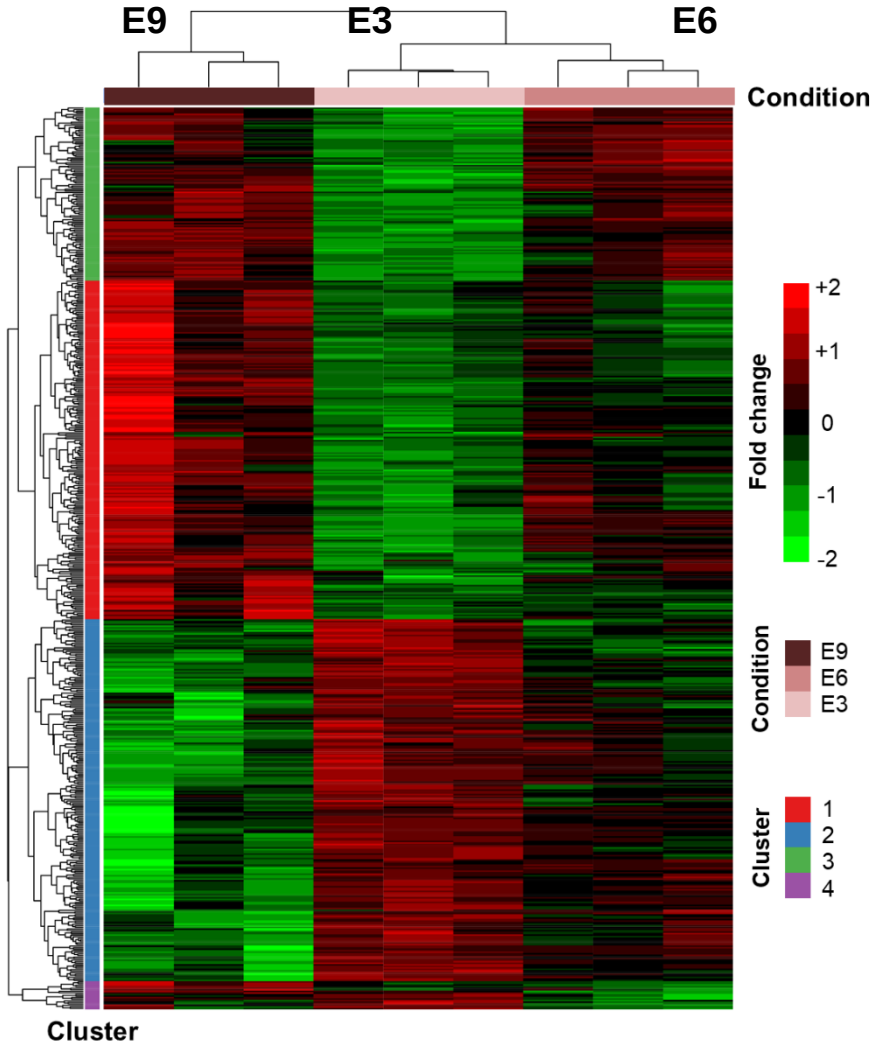


Zaida Alvarez

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Electrostatics Modulates Bioactivity

Hierarchical clustering heatmap of differentially abundant proteins:

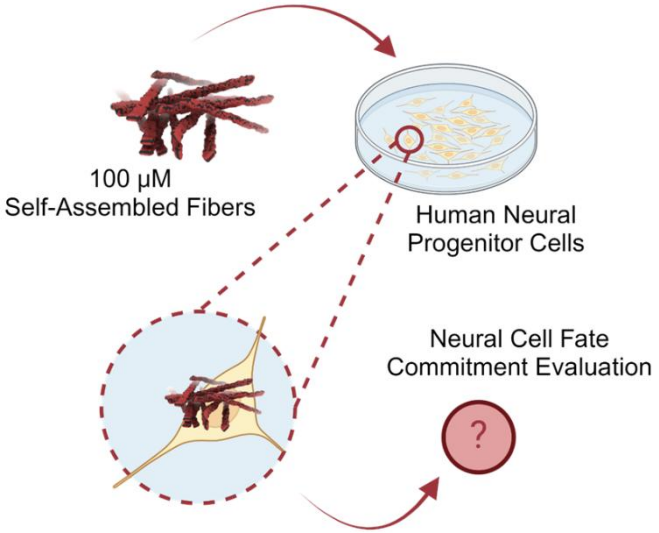


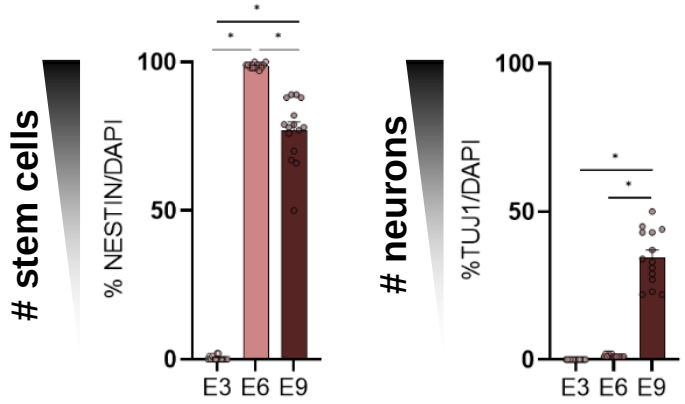
E3:

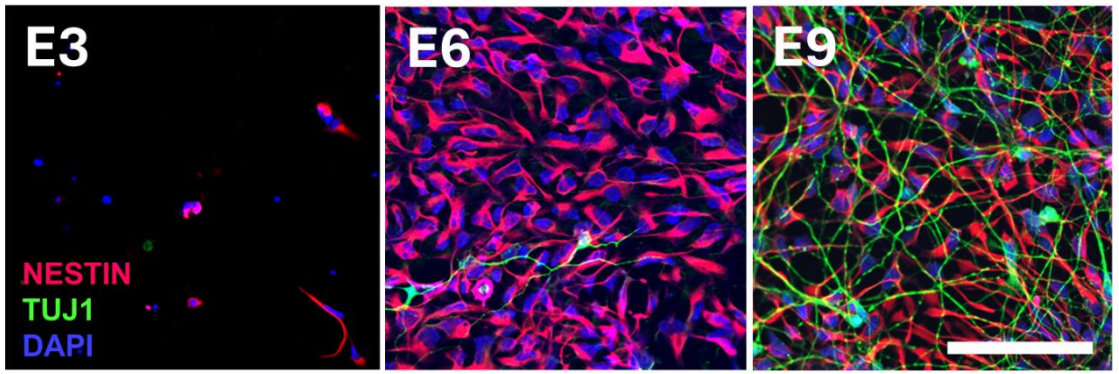
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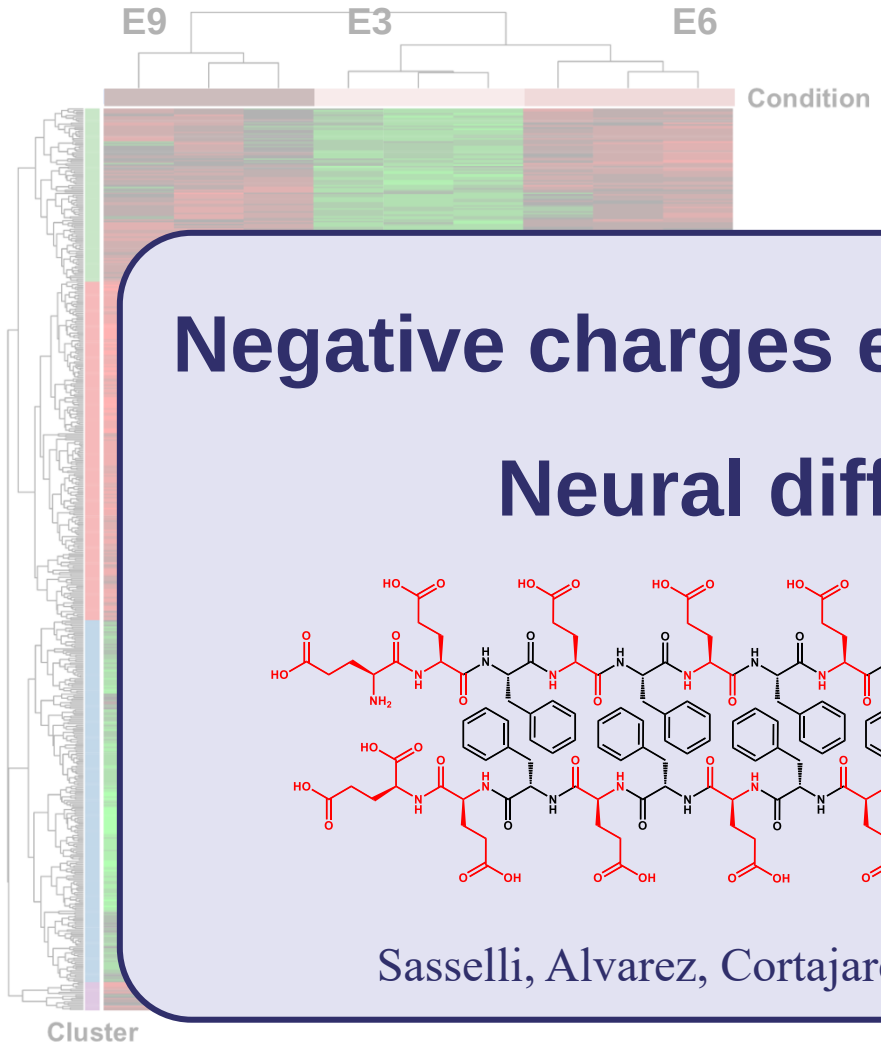






Electrostatics Modulates Bioactivity

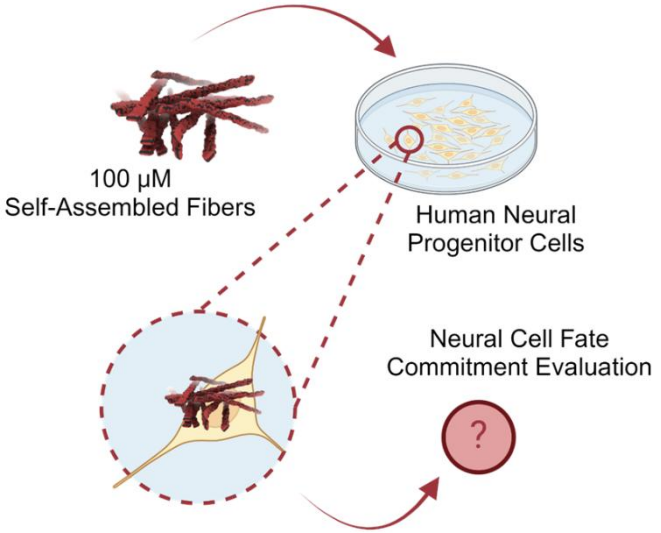
Hierarchical clustering heatmap of differentially abundant proteins:



E3:

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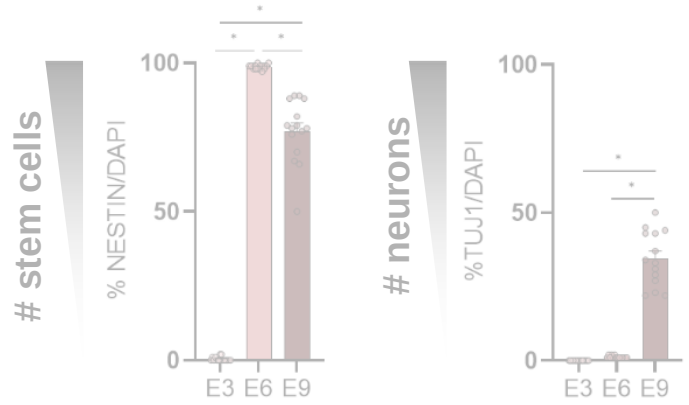
E9:

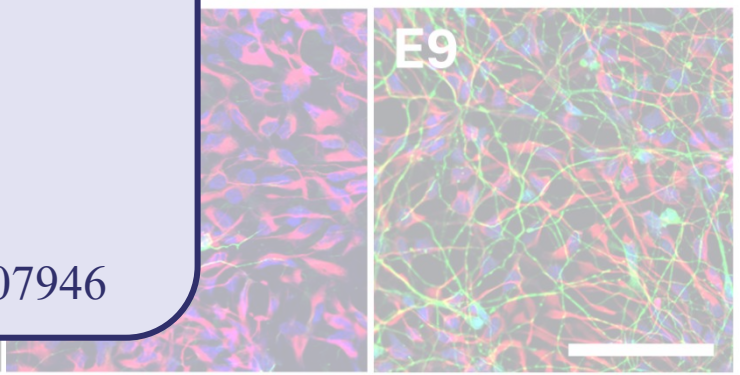


Negative charges enhance bioactivity:

Neural differentiation

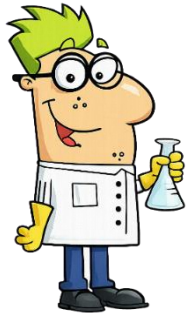
Sasselli, Alvarez, Cortajarena, *et al. Adv. Sci.* **2026**, *13*, e07946



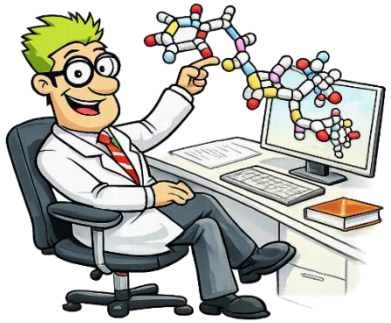


Take Home Messages

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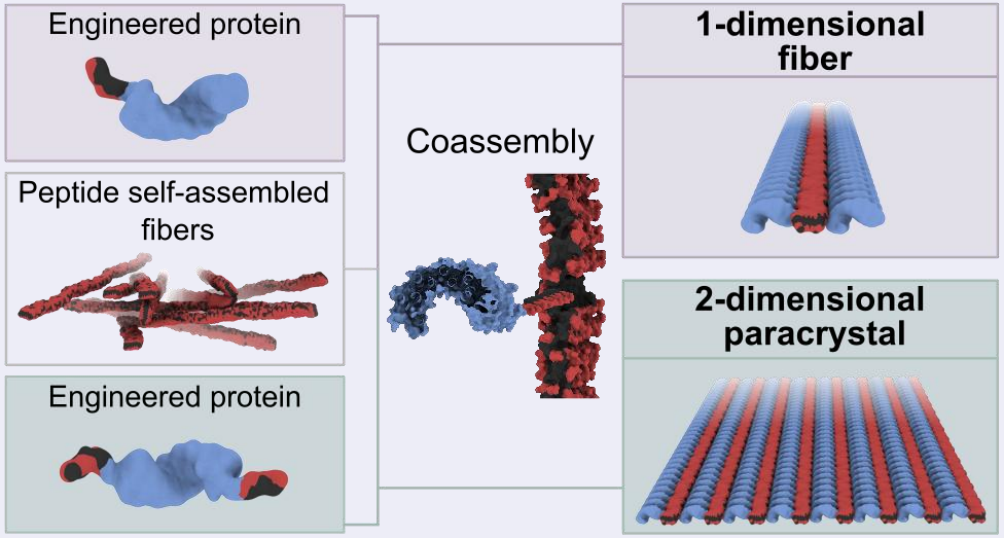


Computational/Experimental Symbiosis:



Design of Complex Architectures

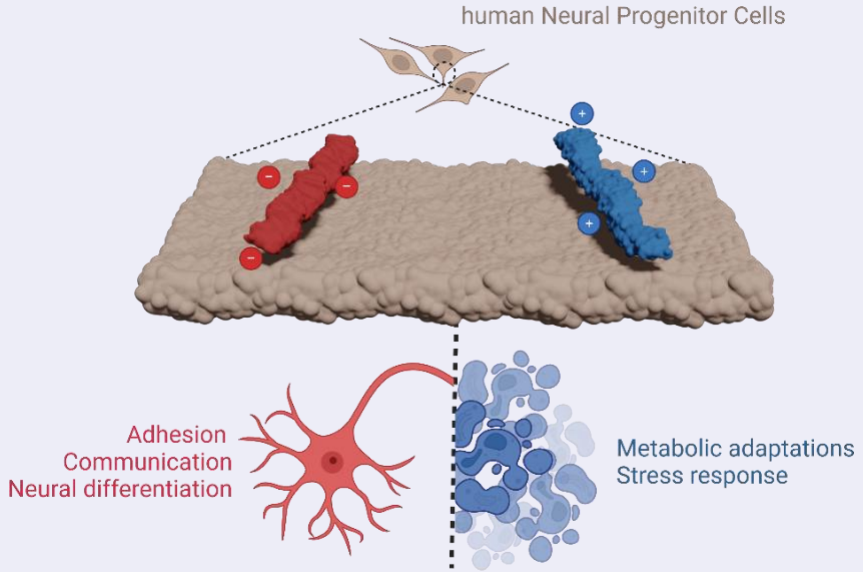
→ 2D Protein-Peptide Co-assemblies



Cortajarena, Sasselli, *et al.*
ACS Nano **2025**, *19*, 16500.

Library of peptides (q= -9 – +9):

→ Electrostatics Effect in Bioactivity



Sasselli, Alvarez, Cortajarena,
et al. Adv. Sci. **2026**, *13*, e07946



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- **Irene Carbajo de la Guerra**
- **Irene Toledo Alday**

Alumni:

- **Laura Perez-Chirinos Lallana**

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Centro de Física de Materiales

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