Integrated Computational Modeling and Experimental Design of Functional Protein Biomaterials

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PROJECT SUMMARY

❑ There is a critical need to understand how tissue culture stimulation affects tissue construct development and function, with the ultimate goal of eliminating resource-intensive trial-and-error screening.

❑ Our goal is to develop predictive assessments of the in vivo performance of biomaterials so that a more rational approach based on a **bottom-up modeling toolkit** is used to guide the preparation of the required biomaterials.

❑ An important feature of our approach is the **direct integration of modeling and experimentation** at multiple length scales, and the use of **hierarchical material architectures** across length scales, to reach enhanced material function (**Fig. 1**).

❑ Two well studied degradable polymer systems, **silks** and **collagen**, will be used for the experimental studies and model building, as they are directly amendable to highly controlled preparations and processing and cover a range of mechanical properties and degradation rates.
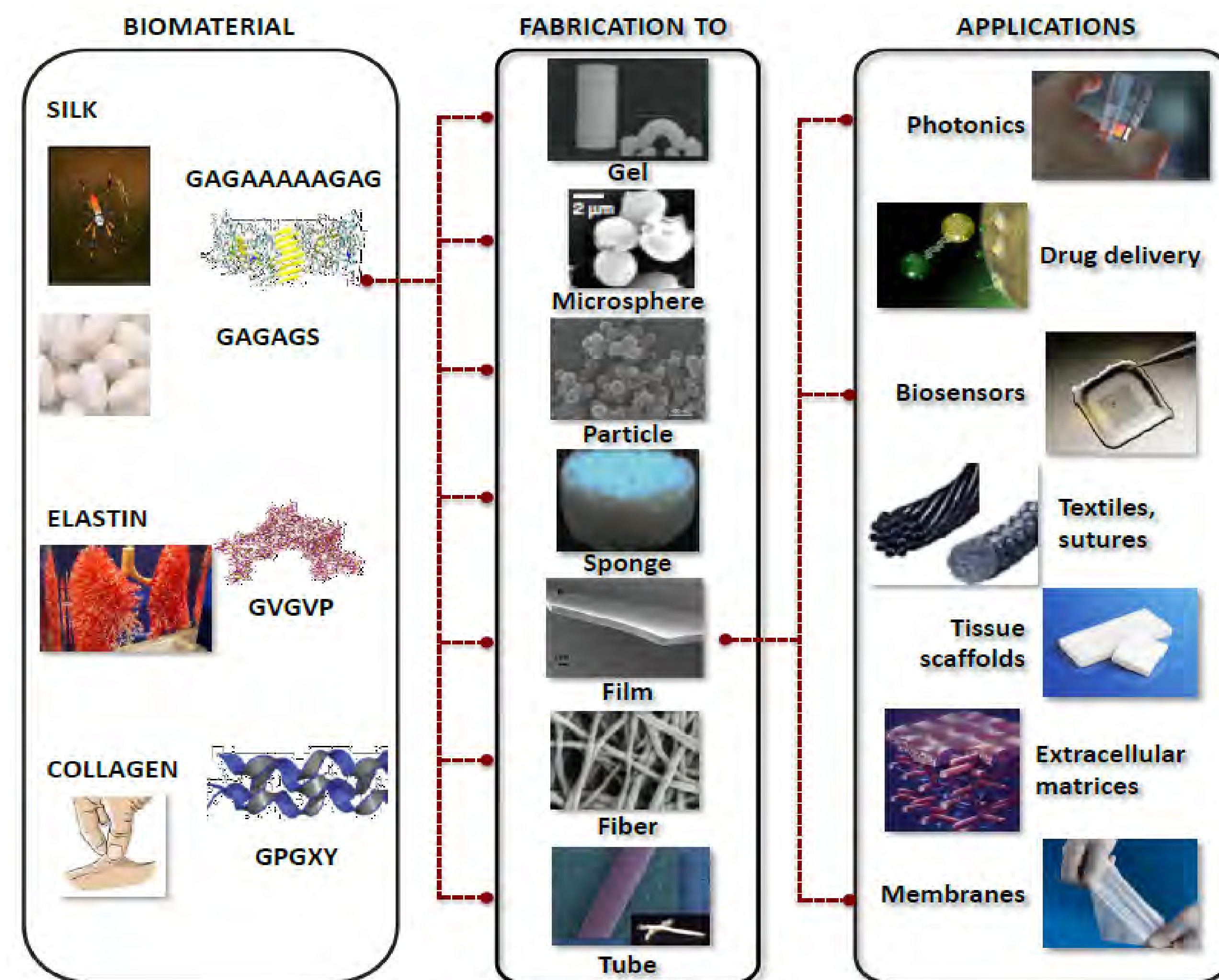

Figure 1. Potential applications of functional biomaterials (silk and collagen) made from simple molecular building blocks (amino acids) and the resulting versatile self-assembled structures.[1]

AIM 1: in vitro preparation and characterization of fiber-based biomaterials.
AIM 2: in silico multiscale modeling and design of fiber-based biomaterials.
AIM 3: in vivo characterization of fiber-based biomaterials.

❑ The proposed study would allow novel designs of biomaterial matrix for tissue replacement and regeneration materials by establishing a predictive modeling toolkit.

❑ Inputs such as the amino acid sequence, molecular weight, and processing conditions can be used to predict new outcomes: hierarchical structure from the molecular level upwards and mechanical properties at all relevant scales.

❑ The same "universal" library of elements (amino acids) can be extended to many biomaterials as diverse as spider silk, tendon, cornea, blood vessels, or cells, each of which displays greatly variegated functional properties.

❑ We anticipate that our insights from the planned study would have broad impact and utility in a range of biomaterial and regenerative medicine needs.

INTEGRATED METHODS

❑ To fully harness the advantage in natural silk spinning processes to generate defined material features, our integrated research group combines multi-scale computational modeling and experimental processes to produce artificial silk-based fibers using regenerated silkworm and recombinant spider silks (**Fig. 2**).

❑ We also address the synthetic limitations by unifying the knowledge about the interplay between structure, processing, and properties.
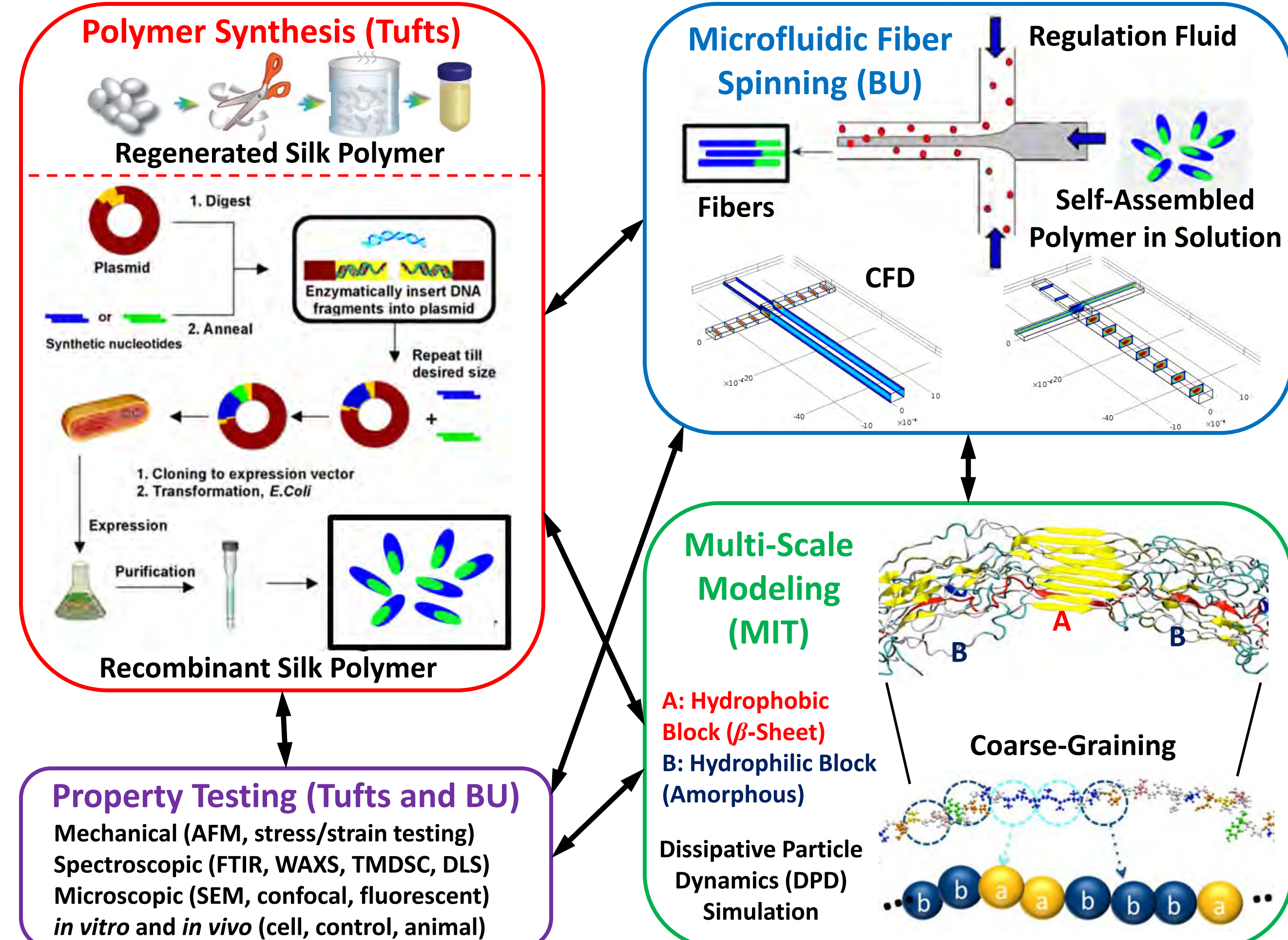

Figure 2. Synergetic integrations of multi-scale modeling, silk polymer synthesis, and microfluidic fiber spinning to study the hierarchical structure of silk polymers and their self-assembly process.[2]

YEAR ONE PROGRESS AND MILESTONE

❑ First microfluidic spinning of the mixture of regenerated silkworm fibroin (RSF) and recombinant silk protein was achieved (**Fig. 3a**).

❑ Different selections of the sequence for the recombinant silk protein (HAB_3 and HBA_3) leads to very different self-assembled structures and spinning results (**Fig. 3b**).

❑ Computational modeling reveals that HAB_3 forms smaller aggregates centered around A blocks and form more bridges with B blocks, compared to HBA_3 (**Fig. 3c**).

❑ Experimental morphological studies using SEM and DLS both confirmed the predicted qualitative trend from simulations (**Fig. 4**).
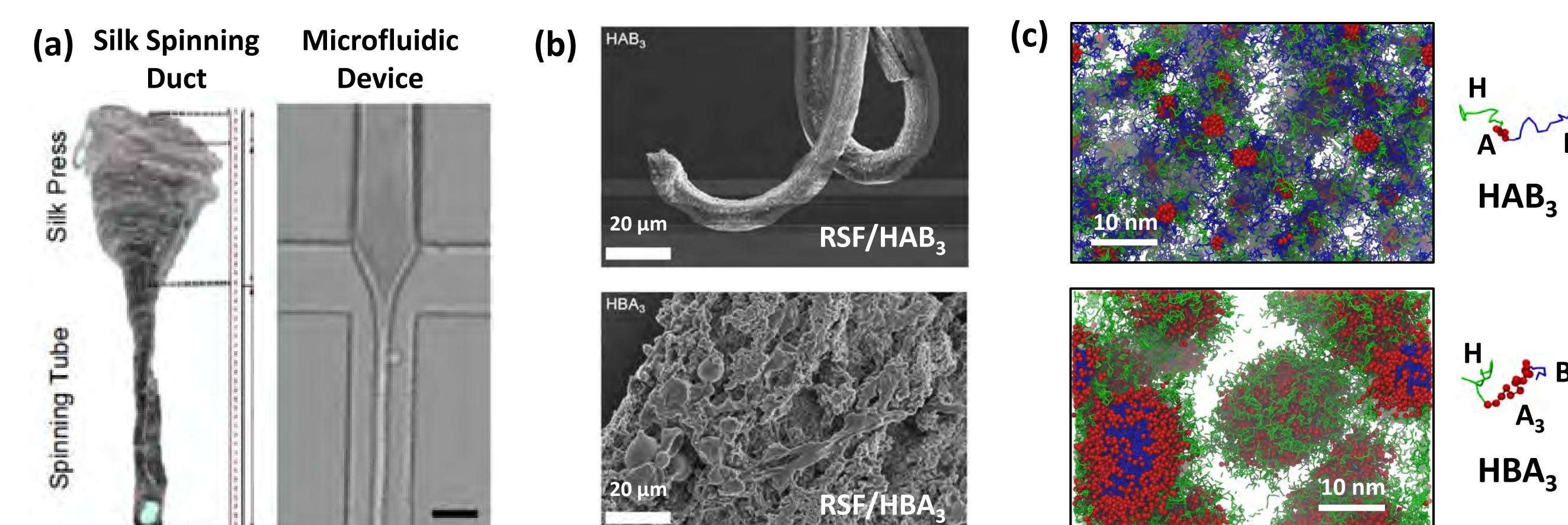

Figure 3. (a) Microfluidic device that mimics the natural silk spinning duct in spiders or silkworms. **(b)** Post-processed silk protein fibers (up) and films (bottom) using different recombinant silk protein sequences.[3,4] **(c)** Computational modeling results of the aggregate morphology of two recombinant silk protein sequences after applying the Couette shear flow in silico.
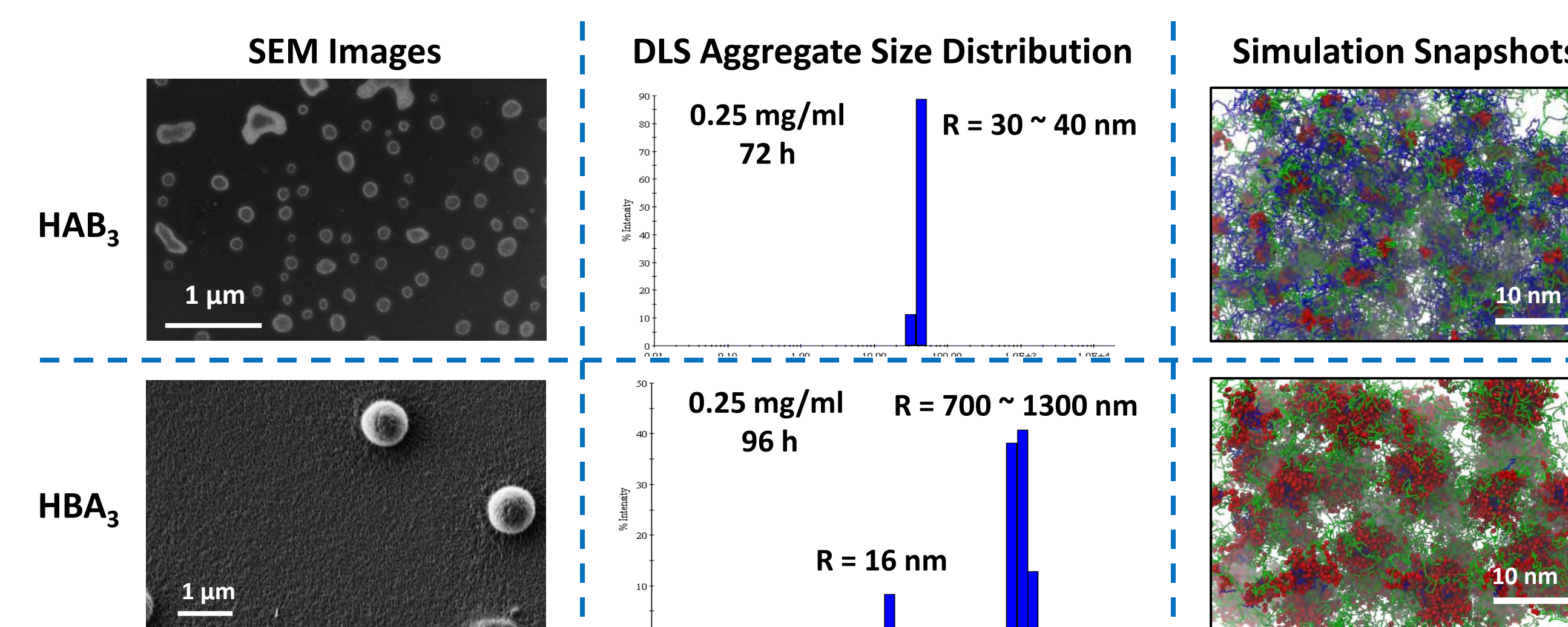

Figure 4. Comparison among SEM, DLS, and simulation results on aggregate morphologies of two different recombinant silk protein sequences.

❑ New designs of optimal fiber materials were proposed computationally (**Fig. 5**). We found that longer polymers under higher concentrations and larger shear rates lead to better fiber network connections and mechanical properties.

❑ Experimental AFM scratching test in dilute polymer solution directly demonstrates the polymer length effect on fiber formation propensity (**Fig. 6**).
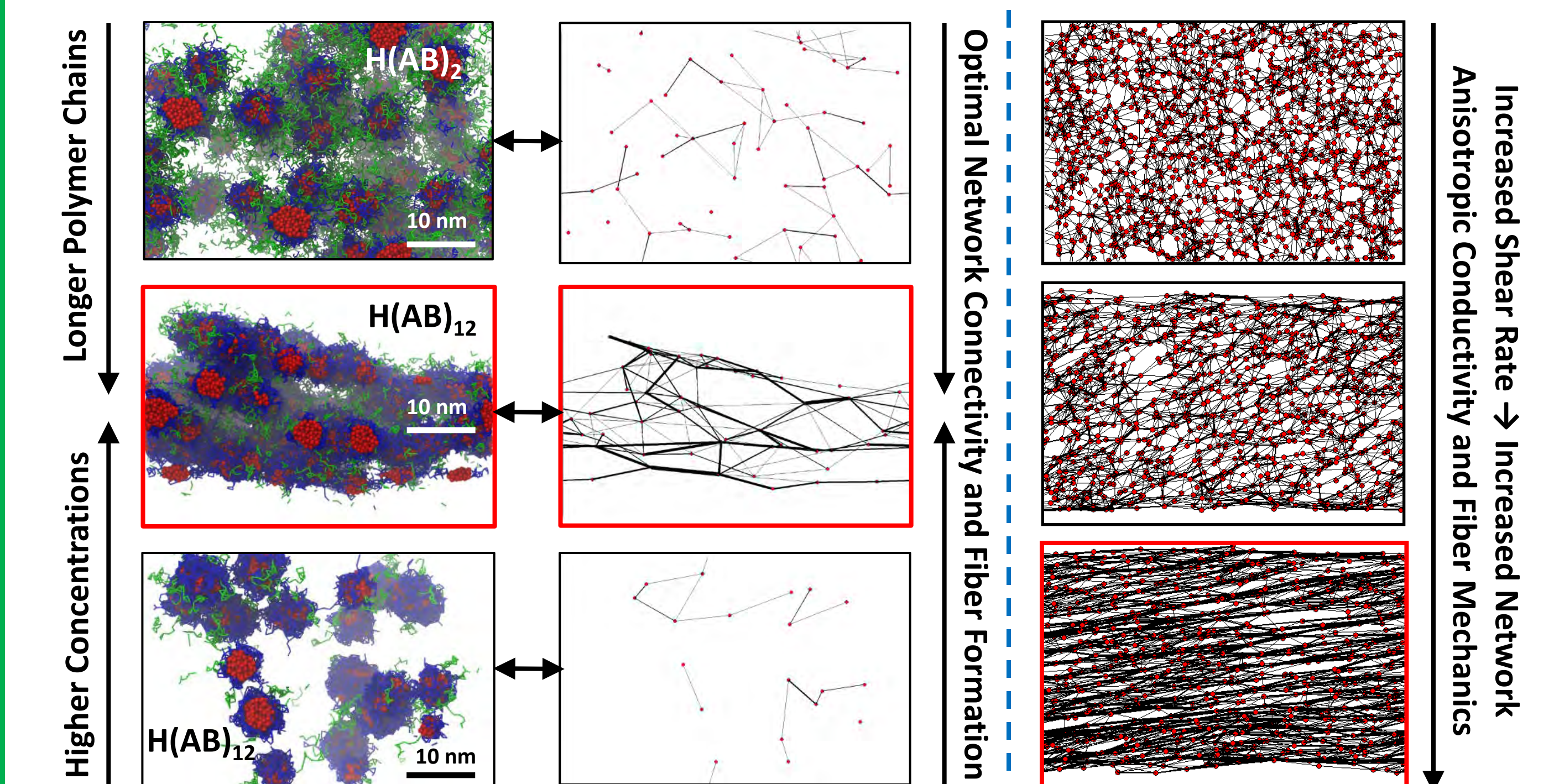

Figure 5. Computational modeling results on optimal fiber formation using recombinant silk proteins with different lengths and under different polymer solution concentrations and shear flow rates.
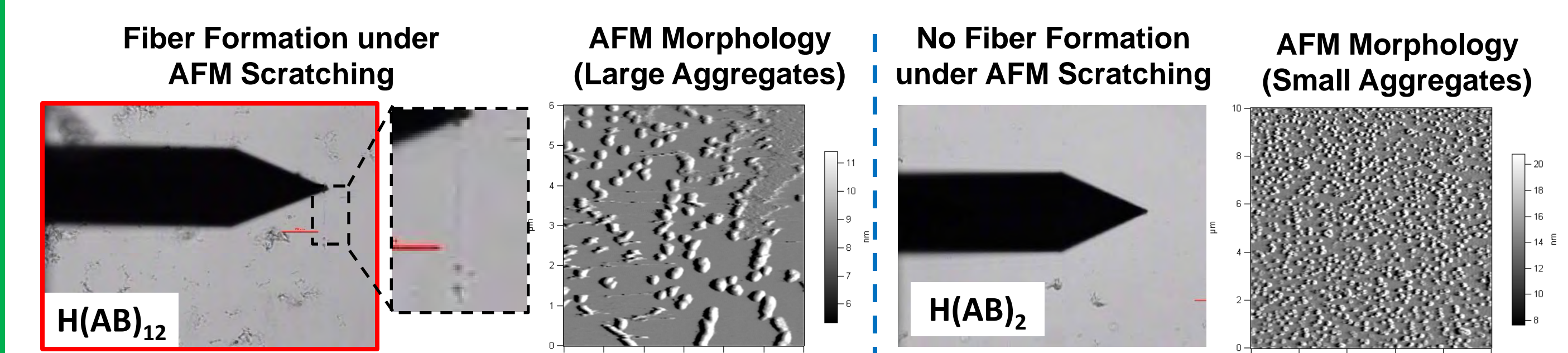

Figure 6. Experimental AFM scratching test on two silk protein (with different lengths) solutions.

PROPOSED WORK FOR YEAR TWO

❑ Synthesize new sets of protein variants with special methods used to increase protein solubility and yield of purified protein from bioreactors.

❑ Improve the multi-scale modeling framework to incorporate the effects from solution pH, solvent type, and ionic strength (integration with CFD calculations).

❑ Redesign microfluidic process to reduce fouling of protein on the interior wall and clogging of the device, as well as to enhance concentrated shear flow conditions.

❑ Investigate collagen mimicking fibers using different protein variants and models.

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