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BOOK OF ABSTRACTS



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Oral Talks



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Liquid-Liquid Phase Separation in Polyelectrolyte Mixtures Proceeds via an Oligomerization Process

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A predictive model of liquid-liquid phase separation (LLPS) in polyelectrolyte mixtures is proposed and tested against experimental data. It is based on the Flory-Huggins theory with the addition of a new physical idea, namely, that even with highly monodisperse polyions, there will be association among oppositely charged polyions, leading to a polydisperse, multimeric state, even in the homogeneous solution or at very low polymer concentration. Relying on recently published analytical solutions to the Flory-Huggins theory, including for polydisperse systems, and reasonable empirical fits for association and interaction parameters, we compare the model to the measured phase diagrams for monodisperse mixtures of polylysine-polyglutamate polypeptides. This comparison demonstrates that LLPS in polyelectrolyte mixtures is markedly influenced by the association-induced polydispersity. Previously unrecognized physical behavior results in the form of an open miscibility gap and cloud points that depend on the concentration of polymer in solution. These are clear signatures of polydispersity in the phase separating components and the fact that LLPS in polyelectrolyte mixtures proceeds *via* an oligomerization process. Processes in which LLPS occurs the presence of complex mixtures of charged macromolecules, such as the formation of biological condensates, could be strongly influenced by this association-induced polydispersity. This presentation is based on an on-going collaboration with Matthias BallauM and Vincent Ohls-Czepan of the Freie Universität Berlin, who have developed the model, and experimental data from our lab, which have been previously published.

L. Lu, *et al.*, *Macromolecules*. **51**, 2988-2995 (2018).



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From Liquid Coacervates to Structure-Defined Fibers: Sequence Control over Peptide Self-Assembly

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Peptide self-assembly spans a continuum, from liquid coacervates formed by liquid–liquid phase separation to structurally ordered cross- β fibers. Both states are governed by the same weak, multivalent interactions (π – π , cation– π , and hydrogen bonding), which is why the metastable coacervate is often a precursor to the thermodynamically stable fiber. In this talk, I show how we deliberately target both ends of this transition, and I present two complementary strategies from our work: arresting minimal peptides as functional coacervates, and driving designed peptides through to fibers of defined structure.

Biomolecular condensates are central to intracellular organization, enabling spatial and temporal regulation of a wide range of cellular processes. Inspired by these membraneless compartments, peptide-based coacervates have recently attracted attention as simplified model systems for artificial organelles. Owing to their biomimetic architecture and their ability to create highly crowded microenvironments, they offer a promising platform for cell-like functional compartments, yet their broader implementation has been limited by poor colloidal stability, restricted control over internal microenvironments, and the absence of inherent chemical functionality. In the first part of this talk, we report a minimalist strategy for the formation of dipeptide coacervates incorporating photocatalytic peptide monomers capable of mediating bio-organic reactions within cellular environments. These dynamically self-assembled coacervates exhibit enhanced stability, improved catalytic activity, and a pronounced hydrophobic interior. This hydrophobic microenvironment promotes efficient sequestration of nonpolar molecules and enables the incorporation of diverse substrates for compartmentalized organic reactions in aqueous media. Importantly, integration of photocatalytic units within the coacervate matrix allows redox transformations to proceed without the need for external catalysts such as enzymes or added small molecules. Loading of hydrophobic cargo increases droplet size, which reversibly returns to its original state upon light-triggered chemical conversion. We further demonstrate the utility of these coacervates for intracellular prodrug delivery, where controlled release is achieved through photochemical activation, establishing intrinsically functional, photocatalytic peptide coacervates as a versatile platform for catalysis and molecular delivery.

In the second part, we design amphiphilic nonapeptides that complete the transition to fibers of defined structure, where our central contribution is structural elucidation. Using cryo-EM, we resolve a sequence-encoded hexagonal cross- β architecture with continuous, hydrated ~ 5 nm nanochannels at near-atomic resolution. A modular sequence logic of cross- β dimer, inversion point, and trimeric junction (DILT) programs symmetry, lateral growth, and channel topology, and systematic mutations yield experimentally validated sequence–structure rules that link residue position to supramolecular symmetry, lattice propagation, and channel topology.

Together, these approaches define design rules across the coacervate-to-fiber continuum and open a route to programmable, functional peptide materials, with implications for synthetic biology, organic chemistry, catalysis, and molecular delivery.

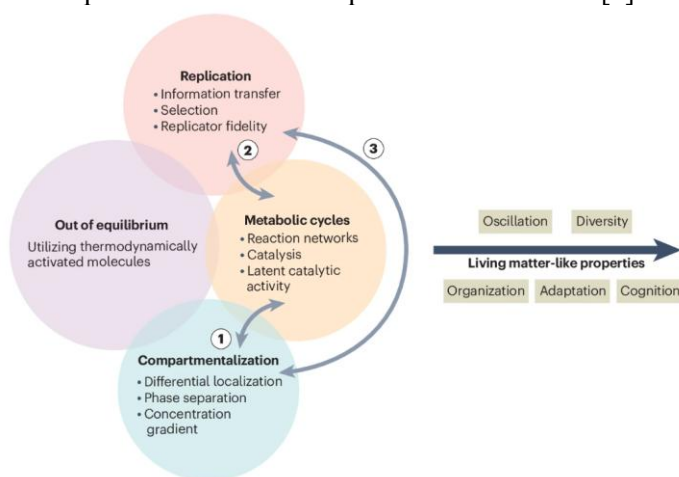


Non-equilibrium self-assembly for living matter-like properties

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Life's soft and wet machinery arose from spatially confined assemblies of biomolecules capable of replication, integrated with metabolic reaction cycles that function far from equilibrium.[1] By methodically synthesizing and integrating these key elements, i.e. replication, metabolism, and confinement under non-equilibrium conditions, we can begin to explore how chemically constructed systems might acquire life-like, evolving properties.[2-5] This ambitious goal lies at the heart of systems chemistry. In this talk, I will outline recent insights into how reaction networks, self-reproduction, and compartmentalization can be brought together under non-equilibrium settings.[1] I will also delve into the interplay between reaction networks and transient compartmentalization, and explore the development of self-replicating systems capable of sustained operation in far-from-equilibrium conditions.[1]



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Chemically fueled peptide assembly—from dynamic structure towards de novo life

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In our laboratory, we use fuel reaction cycles to drive peptides away from thermodynamic equilibrium, creating molecular assemblies that exist only as long as energy is continuously supplied. In this lecture, I will focus on our work on peptide phase separation, which unveiled new dissipative structures. I will also describe our work using these droplets as a model for synthetic life, as our fuel-dependent coacervate protocells can undergo cycles of emergence, growth, decay, and even self-division, and we are working to integrate molecular replication to establish genotype–phenotype relationships.



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Steps in Building a Peptide-Based Minimal Form of Life

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How chemistry can yield life is one of the most intriguing questions in contemporary science. We have explored experimentally how the key properties of life can emerge from complex molecular networks of fully synthetic molecules. The interplay between bond formation, bond breakage and assembly and disassembly processes gave rise to all of the key features of life: self-replication, metabolism, compartmentalization and even evolution.



Specifically, self-replicators have been developed¹ that, in addition to their own formation, are able to catalyse reactions. These reactions can yield products that are utilized by the system, representing a minimal metabolism.^{2,3} Replicators can produce molecules that assemble into compartments (coacervate droplets), into which the replicator partitions spontaneously. Rudimentary Darwinian evolution has also been achieved, showing survival of the fittest, coexistence through niche partitioning, minimal eco-evolutionary dynamics, and selection for photocatalytic activity.⁴⁻⁶ With the integration of all of these characteristics, the prospect of synthesizing life de novo is becoming increasingly realistic.^{7,8}

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⁹ Otto, S. *Acc. Chem. Res.* **2022**, 55, 145-155.



ATP-Driven Control of Disordered Protein Condensation by Enzymatic Phosphorylation

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Cellular processes are organized by the phase separation of protein condensates. These condensates are shaped by post-translational modifications, in particular phosphorylation. Phosphorylation of proteins by kinase enzymes consumes the chemical fuel ATP. We resolve how kinases interact with proteins and their condensates using coarse-grained molecular dynamics simulations. Importantly, our simulations capture ATP-driven dynamics and are thermodynamically consistent, which we verify with a generally applicable Markov-state modeling approach. Our simulations show how the neurodegeneration-linked protein TDP-43 interacts with the kinase CK1 δ . CK1 δ binds not only to TDP-43 in dilute solution but also to TDP-43 condensates. Phosphorylation modulates the interaction between the substrate and kinase. Enzymatic phosphorylation eventually triggers the dissolution of TDP-43 condensates in our simulations. At lower levels, phosphorylation can also control the partial de-mixing of some proteins, which may be an important mechanism by which enzymatic phosphorylation contributes to biological regulation.



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Data-driven Understanding of the Multifunctional Property Space of Peptide Amphiphiles

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Nature leverages proteins and peptides as highly modular, programmable building blocks to execute an extraordinary array of chemical and materials functions from a restricted pool of canonical amino acids. This functional diversity is entirely encoded within the primary sequence, dictating the hierarchical self-assembly, conformational landscape, and emergent macroscopic properties of the biomaterial. However, the material properties are typically driven by complex, sequence-specific interactions that act across time and length scales.[2] To disentangle this complexity, and enable targeted design of novel peptide materials, experimental high-throughput investigations are essential.

We have recently established a pipeline for high-throughput synthesis and analysis of peptides. We will discuss how this high-throughput approach has enabled us to uncover counterintuitive, but general, design rules for amphiphilic peptide surfactants. Surface activity is a central property that determines interfacial properties of peptides, such as cell penetration,[3] emulsification,[4] and likely is also a driver for antimicrobial activity.[5] We are cross-correlating these fundamental interfacial properties with functional properties, including foaming, antibacterial activity, and organocatalysis. These experiments show that correlations between functional properties of peptide materials are valid when certain sequence characteristics are specified. We will explain these characteristics for several properties, and show how this data-driven approach enables targeted design of functional peptide materials with tailored responsiveness.

In summary, we have implemented a high-throughput synthesis and analysis platform for peptide materials that enables us to learn general sequence-property relationships, while simultaneously leading to serendipitous material discovery.

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PEPTIDE SELF ASSEMBLY CONFERENCE 2026



Mimicking collagen's mechanochemical function in self-assembled peptides

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Mechanical forces generate radicals by rupturing covalent bonds in synthetic polymers, and we recently discovered that the same mechanochemical process occurs in collagen and elastin, the principal structural proteins of the extracellular matrix, even under physiological loads. We find that collagen is not merely a source of mechanoradicals, but specifically funnels ruptures into sacrificial crosslinks bonds, where they can be efficiently scavenged by adjacent built-in catechol motifs. We recapitulate the radical scavenging capacity of collagen in self-assembling collagen-mimetic peptides that form stable triple helices. Currently, using deep learning-based do novo design, we exploit these principles to design proteins harboring collagen-mimetic crosslinks with sacrificial bonds for programmable mechanochemical and redox properties, establishing a foundation for mechanochemically responsive biomaterials and new strategies to investigate tissue ageing and disease.

¹Zapp et al, Nat Comm, 2020

²Rennekamp et al, Nat Comm, 2023

³Keil et al, in preparation



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Emergence of Function in Living Systems by Supramolecular Design

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Biological macromolecules rely on supramolecular chemistry to generate emergent functions, enabling the remarkable diversity of life to arise from a relatively limited set of biogenic building blocks. Their organization into hierarchical assemblies coordinates biochemical reactions, amplifies and translates molecular signals into cell-wide responses, and integrates function across scales from molecules to entire organisms. At each level, new functions often emerge from the structural organization and three-dimensional conformations of these ensembles rather than from their chemical composition alone, as exemplified by ion channels, the cytoskeleton, and the nuclear pore complex. Inspired by these principles, our group seeks to engineer supramolecular materials that acquire biological, catalytic, and other functions simply through controlling molecular order and the state of assembly.

We develop minimalistic peptide systems that integrate self-assembly, spatiotemporal control, and imaging capabilities within a single molecular framework. Our studies demonstrate that distinct structural organizations arising from the same molecular identity can profoundly alter function, highlighting the rich structure–activity relationships that exist at the ensemble level. In living cells, we employ both endogenous cues (e.g., pH, ROS, GSH, and lactate) and exogenous stimuli (e.g., light) to induce the emergence of novel biological functions from otherwise inactive small molecules through the activation of distinct protein expression pathways. Through this work, we aim to advance this additional dimension of supramolecular engineering and inspire the development of artificial hierarchical functions across chemical biology, therapeutics, and life-like materials.

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Unravelling how biointerfacial structures and interactions underpin the antimicrobial efficacy of antimicrobial peptides using neutron reflection and SANS

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Abstract:

Short, designed antimicrobial peptides (AMPs) offer considerable promise for optimising antimicrobial efficacy while minimising cytotoxicity through rational structural design. A key challenge, however, is to elucidate how AMPs interact with the membranes of pathogens and host cells, and how their structural features relate to antimicrobial potency and biocompatibility. Neutron reflection (NR) and small-angle neutron scattering (SANS) are becoming increasingly important tools for resolving interfacial structures and are highly complementary to X-ray reflection and related techniques. Their rapid uptake across research communities is largely due to their high structural sensitivity, typically providing depth resolution of a few Å when combined with H/D isotopic substitution. In this talk, I will present selected examples of interfacial interactions in model systems that mimic the binding of biocides and AMPs to bacterial membranes, illustrating how these interactions correlate with antimicrobial efficacy as assessed by minimum inhibitory concentration, minimum bactericidal concentration and 50% loss of host-cell bioactivity. Together with antimicrobial and biophysical assays that probe AMP binding and membrane disruption, NR and SANS provide a comprehensive assessment of AMP performance and generate valuable data for simulations and model development.

About Professor Jian R. Lu: Professor Lu heads the Biological Physics Group in the Department of Physics and Astronomy at the University of Manchester. His research focuses on wet interfacial phenomena, with particular emphasis on linking molecular processes at interfaces to cellular behaviour. His group makes extensive use of neutron reflection, SANS, and imaging techniques including AFM and cryo-TEM to provide mechanistic insights into areas such as selective membrane binding and in-membrane aggregation of antimicrobial peptides, and to relate these processes to antimicrobial efficacy and cytotoxicity. Beyond antimicrobial research, his work also addresses the self-assembly of short peptide amphiphiles, establishing correlations between peptide sequence and the nanostructures formed, with particular attention to sequences containing chiral amino acids.



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Bridging the Scales: Multiscale Modeling of Supramolecular Peptide Scaffolds

Ayşenur İşcen Akatay

Boğaziçi University, Istanbul, Türkiye

Through tunable hydrogen-bonding networks, peptides self-assemble into highly ordered, amyloid-like supramolecular peptide nanofibrils (PNFs). These functional scaffolds exhibit remarkable bioactivity, such as mimicking the extracellular matrix, mediating host-pathogen interactions, and transducing signals. While experimental methods, such as TEM and FTIR, give information about static structure of the PNFs, predicting their macroscopic functions from underlying structural dynamics remains a significant challenge. In this talk, I will present a multiscale simulation approach to investigate self-assembled PNFs at the microscopic level for a large library of synthetic peptides used in retroviral gene transfer. I will demonstrate how a peptide's primary amino acid sequence dictates its secondary structure and dynamic ensemble within the fibril architecture. Our computational framework successfully correlates broad biological activity with single-residue mutations, providing a mechanistic link between the micro- and macro-scales. To expand this predictive capability, we integrate machine learning models to decode complex structure-property relationships, enabling us to anticipate supramolecular architecture and biological endpoints directly from the sequence. Additionally, I will discuss how integrating varied peptide sequences through coassembly enables programmable control over the resulting supramolecular properties. Mastering these structure-property relationships establishes a predictive foundation for future materials discovery, accelerating the in silico design of advanced biomaterials.



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Sequence, Structure, Assembly, Function: Towards Predictive Peptide Materials

Tell Tuttle

University of Strathclyde, Glasgow, Scotland

Peptide self-assembly provides a versatile route to functional molecular materials, but predicting how a given sequence will assemble, and what properties will emerge from that assembly, remains a significant challenge. In this talk, I will discuss our efforts to connect peptide sequence, molecular structure, supramolecular organisation and materials function using a combination of molecular simulation, computational modelling, machine learning and experiment. The focus will be on how relatively small changes in sequence and environment can alter assembly behaviour, and how computational approaches can help identify useful patterns across peptide design space. Examples will be drawn from our work on short self-assembling peptides and peptide-based functional materials, with an emphasis on understanding rather than simply classifying assembly outcomes. The broader aim is to show how predictive tools can support, rather than replace, experimental discovery in the design of peptide materials.



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Programming peptide phase separation and function through molecular design

Ayala Lampel

Tel Aviv University, Israel

Biomolecular condensates formed through liquid–liquid phase separation have emerged as dynamic soft materials that regulate biochemical processes through molecular compartmentalization. Inspired by these biological assemblies, we develop synthetic condensates from minimalistic peptides and nucleic acid polymers to uncover how molecular interactions govern emergent material properties and function.

In our recent work, we establish how peptide backbone flexibility and ion identity dictate phase behavior and material properties. We further show that condensates formed by phase separation of minimalistic histidine-containing peptides catalyze ester hydrolysis through two distinct mechanisms. In Zn^{2+} -dependent condensates, Zn^{2+} –histidine coordination activates a coordinated water molecule for nucleophilic attack, while dense-phase basicity, internal molecular mobility, and Zn^{2+} accumulation collectively regulate catalytic efficiency.

In heterotypic peptide–DNA condensates, we demonstrate that DNA folding can be programmed, providing a model system to investigate how nanoscale structural order governs coacervation. The level of DNA folding regulates DNA/peptide multivalent interactions, and in turn, phase separation propensity, condensate diffusivity and viscosity. More broadly, I will highlight how nanotechnology-inspired design principles enable the engineering of synthetic peptide condensates and their properties.



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Why Nature Chose Acyl Phosphates: From Biology to Systems Chemistry

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Acyl phosphates occupy a unique position at the interface of energy transduction, molecular activation, and chemical organization in biology.¹ As high-energy intermediates, they participate in central biochemical processes ranging from metabolic regulation to peptide bond formation and phosphoryl transfer. Despite their reactivity, acyl phosphates operate efficiently under aqueous conditions, enabling selective chemical transformations central to life (Figure). Herein, we explore how aminoacyl phosphates can be repurposed as programmable activation motifs in systems chemistry. By tailoring the structure of the phosphate ester and the amino acid side chain, we show how acyl transfer reactions shape supramolecular organization and pathway-selective oligomerization.² The interplay between activation and supramolecular organization enables control over dynamic structure formation, peptide coupling, and assembly processes in water. Our studies reveal that subtle molecular variations influence both reactivity and material state, allowing activation pathways to encode distinct supramolecular and covalent outcomes.³ These findings establish a conceptual bridge between biological phosphates and abiotic reaction networks, highlighting acyl phosphates as versatile molecular motifs for constructing dynamic chemical systems. More broadly, our work suggests that nature may have selected acyl phosphates not merely for their favorable balance between stability and reactivity, but because they provide a unique means of coupling molecular activation to self-organization within complex chemical networks.

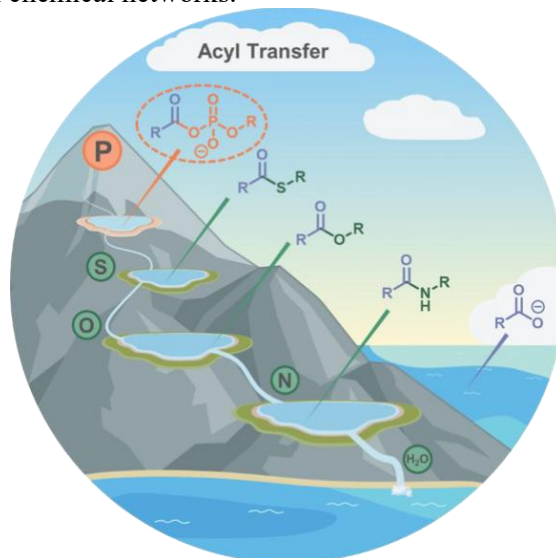


Figure: Acyl phosphates as high-energy intermediates in biological acyl transfer.

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Cysteinyldopa Connectivity: Key for Synthesizing Artificial Mussel-Glue Proteins and Blueprint for Electrochemically Debondable Adhesives

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Bio-inspired design has reshaped adhesive engineering, with marine mussels serving as source of inspiration for strong and versatile wet adhesion.

Here we exploit an underutilized chemical motif: The cysteinyldopa connectivities form via thiol–quinone Michael addition, which generate robust thiol–catechol connectivities (TCCs). The chemistry and the biogenic linkage were developed to a generic polymerization route, giving a scalable and versatile adhesive platform.¹

Originally applied to oligopeptides to create artificial mussel-glue proteins by tyrosinase activation of tyrosine/cysteine-bearing peptides,¹ the approach scales in capability as oxidized L-dihydroxyphenyl alanine (L-Dopa-quinone) can be generated not only enzymatically, but also chemically, or electrochemically on demand.^{1–3} Enzymatically activatable adhesive domains can be selected by combinatorial strategies to target specific surfaces,⁴ while the binding secrets of these mussel-glue-mimetic peptides were revealed in divergent-convergent analysis efforts.⁵ The platform polymerizes both minimal peptide motifs³ and function-integrated sequences, including activatable β -sheet domains.⁶ This enables coupling TCC-based interfacial adhesion with triggerable cohesion mechanisms e.g. by change of pH or increase of Zn^{2+} ion levels.⁶ Moreover, triggered debonding of peptide-based pressure-sensitive adhesives demonstrated release-on-demand functionality.⁷ The biogenic connectivity was mimicked by both commodity monomers for industrial feasibility⁸ and green renewable feedstocks from amino acids or bio phenol biorefinery streams.^{2, 7}

The result is a generic route to high-performance structural adhesives, where clean electrochemical oxidation of TCCs enables on-demand debonding at a push of a button.⁹ Collectively, this chemistry establishes a pathway toward a sustainable, scalable, and functionally tuneable adhesive platform.^{7, 9, 10}

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Biomolecules For Non-Biological Things: Peptide ‘Bundlemers’ Design For Model Nanoparticle Creation And Hierarchical Solution Assembly

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A solution-assembled system comprised of computationally designed coiled coil bundle motifs, also known as ‘bundlemers’, will be discussed as model colloidal nanoparticle systems for the formation of hierarchical materials. The molecules and nanostructures are non-natural amino acid sequences and provide opportunities for controlled solution behavior and arbitrary nanostructure creation with peptides. With control of the display of the amino acid side chains (both natural and non-natural) throughout the peptide bundles, desired physical and covalent (through appropriate ‘click’ chemistry) interactions are designed to control interparticle interactions in solution, which involve both individual bundlermer particles as well as polymers of connected bundlemers. With proper design of individual bundlermer particles, target nanomaterials are being created. First, interbundlermer end-to-end stacking is observed between particles through physical interactions to form lyotropic liquid crystal phases. Important for liquid crystal formation is the design of single charge bundlermer particles (e.g., with only positive/basic amino acids) that lack of opposite charges on the particle surfaces so that there are no attractive electrostatic patches to disrupt the LC alignment. The liquid crystal phases span nematic to hexagonal columnar to smectic depending on peptide concentration as well as on specific peptide design (e.g., number of negative or positive charges, spatial display of charge, amino acid type to create charge). Particles with charge patches also have been designed so that liquid crystal formation is observed at extreme pHs from 1 to 14 with the bundlermer particles still folded and stable. Second, nanoporous lattices can be formed through simply solution mixing. The lattices display crystalline-like structure but with regular pores on the nanoscale. The lattice structures are formed through two different assembly mechanisms; the functionalization of bundlermer particles with hydrophobic side chains on their exterior for lattice formation through interparticle hydrophobic interactions or through the mixing of oppositely charged, single charged bundlemers through electrostatic complexation. Included in the discussion will be new, single charge peptide molecule design, hierarchical assembly pathway design, control of nanostructure, and characterization with cryotransmission electron microscopy, transmission electron microscopy, small-angle x-ray scattering, and molecular dynamics simulations.





Genetically encoded supercharged polypeptides: From self-assembly to function

Andreas Herrmann

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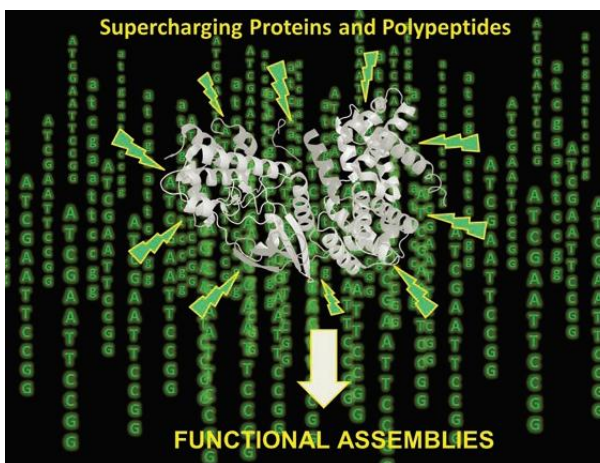
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Protein engineering and directed evolution have led to impressive designer enzymes with remarkable catalytic activities and functions.[1,2] The molecular biology tools that have been exploited to generate these enzymes can be applied to design and fabricate polypeptide sequences with perfect sequence control leading to exciting protein-based materials. Thereby, Nature is a great inspiration for translating precise amino acid sequences into hierarchically assembled architectures enabling versatile opportunities for the de novo design of functional biomaterials.[3] Our group developed supercharged polypeptides (SUPs) that are based on the elastin motif

(VPGXG)_n with X being glutamic acid or lysine resulting in unfolded protein polyanions and polycations with high charge density, respectively.[4] The high number of net charges can be exploited to evolve molecular functions and superstructures by electrostatic interactions. Negatively charged SUPs act as proton conducting materials and form free-standing membranes when combined with spider silk motifs.[5] The combination of SUPs with oppositely charged aromatic surfactants leads to liquid-liquid phase separation. The resulting coacervates form ultra-strong bioglues with homeostatic and accelerated wound healing characteristics.[6] By fusion of neutral LCST fragments to SUPs, thermo-switchable adhesives were generated.[7] Another trigger to control protein function is ultrasound. Thereby, SUP chains fused to functional proteins act as biophysical transducers of shear forces from solution onto the enzyme scaffold.[8] Finally, dissipative self-dividing fibrils were realized by coacervates consisting of GFP-SUP fusions and RNA that were embedded within out-of-equilibrium self-assembly proteins, i.e. a bacterial homologue of tubulin.[9]



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Cationic Lipopeptide Self-Assembly and Bioactivity

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Cationic lipopeptides have a range of interesting self-assembly properties and bioactivities. We will present recent work from our group¹⁻³ on model lipopeptides bearing lysine-based tripeptide sequences which show sequence- and pH- dependent self-assembly into micellar and fibrillar/nanotape nanostructures and which also exhibit antimicrobial activity against Gram- positive and -negative bacteria (Fig.1). The effect of lysine stereochemistry was also explored by comparing D-Lys and L-Lys variants.

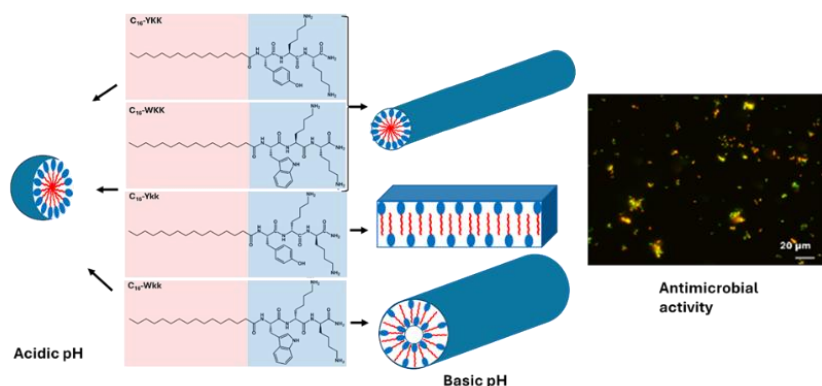


Figure 1. Self-assembly and bioactivity of model lysine-rich lipopeptides.

The highly charged lipopeptide micelles serve as model colloidal systems and the inter-particle potential was obtained from SAXS data, and the structure and conformation of the micelles was analysed using atomistic molecular dynamics simulations.³ The influence of sequence was investigated by both MD and a numerical molecular theory.⁴

We will also discuss our recent findings on the self-assembly of the anti-diabetes and obesity therapeutic lipopeptide semaglutide. We find pH-dependent self-assembly, with micelle formation at pH 8 and twisted fibrils at pH 2.4.⁵⁻⁶ A model for the twisted fibril structure is derived from atomistic molecular dynamics simulations.

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Chiral Glass Formation by Dipeptide Salts

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A simple dipeptide WR (tryptophan–arginine) in the form of salts with organic acids tartaric acid or crotonic acid is shown to form glasses through a benign preparation route by evaporation of aqueous solution.¹ Investigation of glass precursor dipeptide salt solutions shows that the glasses form from an initial unordered solution containing chiral peptide molecules. The glasses show self-healing and adhesive properties, and have accessible glass transition temperatures. The glasses are shown to be amorphous via small-angle and wide-angle X-ray scattering and scanning electron microscopy.

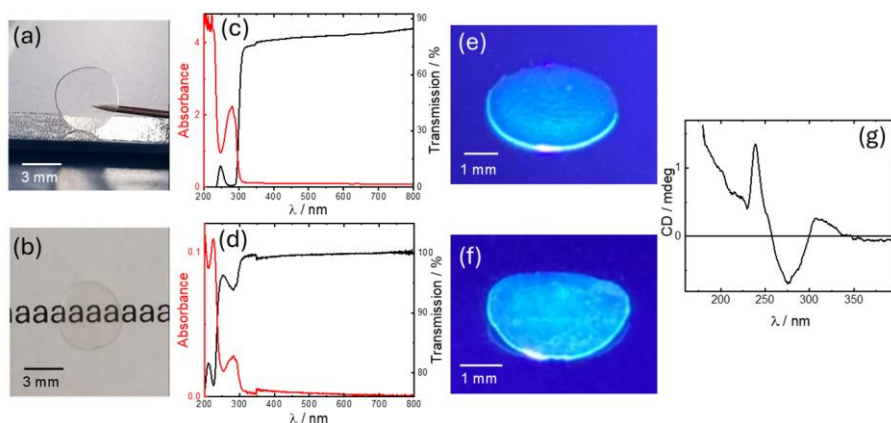


Fig.1. Optical properties. (a,b) Images of WR crotonate glass showing transparency. Measured UV/vis transmission/absorbance spectra for (c) WR tartrate and (d) WR crotonate glasses. Images of fluorescent glasses upon illumination with 395 nm light (e) WR tartrate, (f) WR crotonate, (g) CD spectrum of WR crotonate glass.

The glasses have a remarkable range of properties including moldability (Fig. 1a), high transparency across a broad range of wavelengths (Figs 1b-d), and fluorescence (Figs. 1e-f). Remarkably, the glasses are found to have a chiral structure, as shown by circular dichroism spectroscopy (Fig.1g).

The diverse properties of the dipeptide glass materials points to a wide range of potential future applications.

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Peptides Self-Assembling Piezoelectricity

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With growing interest in bioinspired alternatives for existing technologies, bio-piezoelectricity is attracting increasing attention in biomaterials, bioelectronics, bio-machine interface and biomedical engineering fields^{1,2}. However, the development of bio-piezoelectric systems still faces significant bottlenecks in performance optimization and mechanistic understanding. Therefore, our study focuses on the self-assembling peptides, tracing the structural origin of piezoelectric activity in peptide assemblies and systematically elucidating the molecular mechanisms of polarization generation underlying secondary structures (Figure 1). On this basis, the amphiphilic peptides were designed whose morphologies and piezoelectric properties were finely controlled by leveraging hydrogen bonding and π - π stacking, enhancing the electromechanical coupling efficiency at the molecular level (Figure 2). Furthermore, the crosslinking strategy was employed to extend the piezoelectric peptide nanofibers to macroscopic piezogels whose potential application in precision biomedicine was also demonstrated. Our work provides a systematic perspective from molecules to devices covering the chemical mechanism of peptides self-assembly-based bio-piezoelectricity and its application in life and health³.

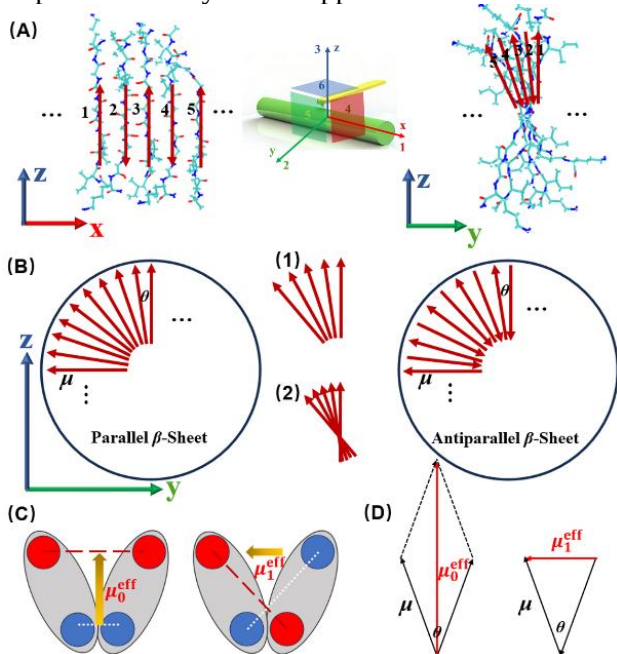


Figure 1. Molecular mechanisms underlying polarization generation in parallel and antiparallel β -sheets

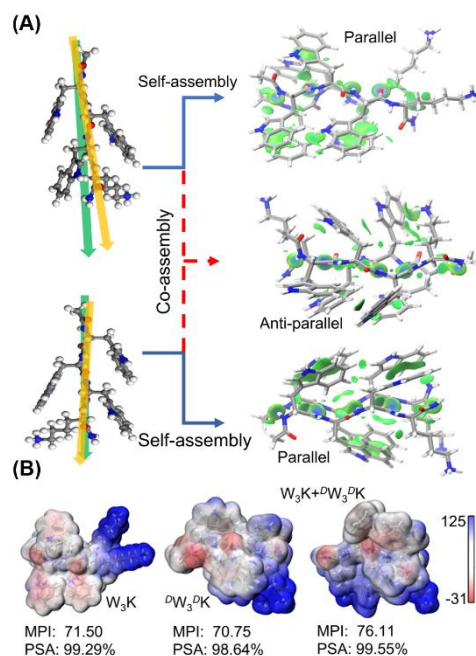


Figure 2. Synergistic effects of hydrogen bonding and π - π stacking enhance piezoelectric performance

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Peptide-Based Functional Nanomaterials: Tailoring Piezoelectric Properties through Nanostructural and Chiroptical Modulation

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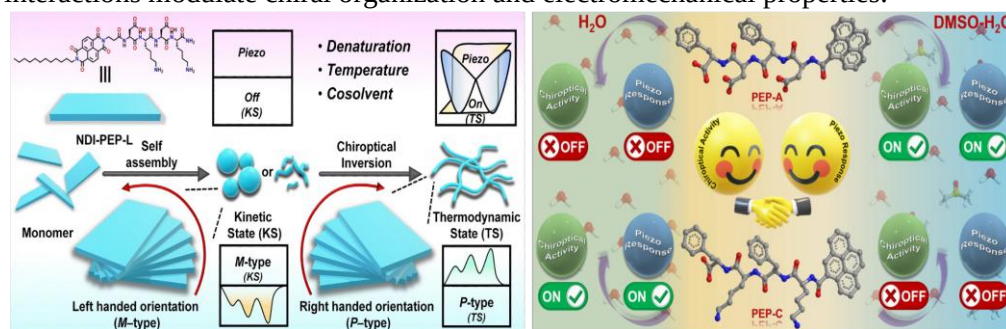
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Peptide self-assembly has emerged as a powerful strategy for constructing functional soft nanomaterials owing to its inherent biocompatibility, biodegradability, structural programmability, and ability to generate diverse hierarchical architectures through non-covalent interactions. Among the emerging functionalities of peptide-based materials, piezoelectricity has attracted increasing attention due to its potential applications in self-powered bioelectronics, wearable devices, sensors, actuators, and energy-harvesting systems. However, the fundamental structure–property relationships governing piezoelectric responses in peptide assemblies remain poorly understood.

In this presentation, we demonstrate how nanostructural organization and supramolecular chirality can be exploited to tailor the piezoelectric properties of peptide-based nanomaterials (Scheme 1, *left*).¹ In the first study, pathway-controlled self-assembly enabled the generation of distinct nanostructures with different dimensionalities. While kinetically trapped nanorods and spherical nanoparticles exhibited negligible piezoelectric responses, their thermodynamically stable entangled nanofibrous counterparts displayed pronounced piezoelectric activity, revealing the critical role of supramolecular organization and hierarchical morphology in governing electromechanical functionality.

In a second study, we established a direct correlation between supramolecular chirality and piezoelectric behavior (Scheme 1, *right*).² Peptide assemblies formed in pure water produced non-helical, chiroptically silent nanofibers that showed no measurable piezoresponse. Remarkably, the introduction of a small amount of cosolvent induced helical supramolecular organization and strong chiroptical activity, accompanied by the emergence of significant piezoelectric responses. Experimental investigations combined with molecular simulations revealed how subtle changes in molecular packing and intermolecular interactions modulate chiral organization and electromechanical properties.



Scheme 1. Influence of nanostructures on piezo-response (*left*) and effect of chiroptical activity on piezo-response.

Collectively, these studies demonstrate that piezoelectricity in peptide-based materials is not solely an intrinsic molecular property but an emergent phenomenon governed by hierarchical self-assembly, supramolecular chirality, and pathway-dependent organization. The findings establish new molecular design principles for engineering adaptive, biodegradable, and biocompatible electromechanical materials and open exciting opportunities for integrating peptide-based functional nanomaterials into next-generation bioelectronic and energy-harvesting technologies.

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PEPTIDE SELF ASSEMBLY CONFERENCE 2026



The many lives of antimicrobial and virulence peptide amyloids

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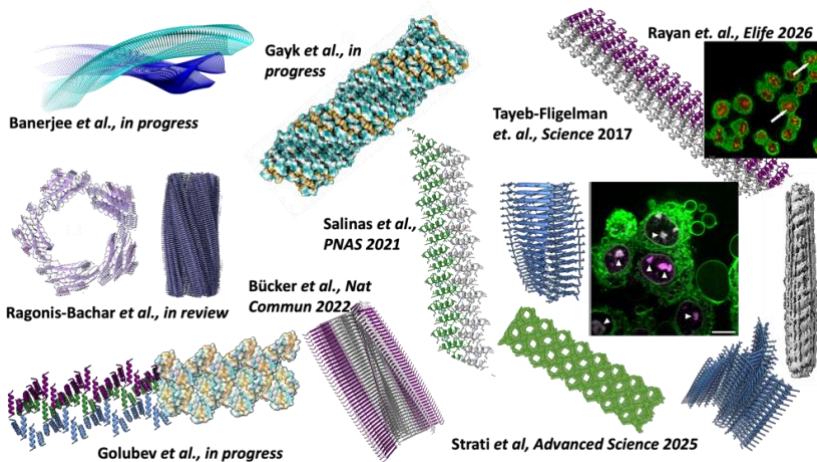
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Peptide self-assembly into amyloid fibrils underlies some of the most consequential processes in biology, from the ordered fibrils of the extracellular matrix to the pathological aggregates of neurodegenerative disease. Microbial systems exploit this same principle: bacteria and fungi deploy amyloid-forming peptides as structural and virulence-associated assemblies, while antimicrobial peptides (AMPs) from across the kingdoms of life harness self-assembly into fibrils to kill pathogens. Using X-ray crystallography and cryo-electron microscopy (cryo-EM), we have resolved the atomic architectures of a broad range of these naturally occurring peptide assemblies and uncovered a remarkable structural landscape. Beyond the canonical cross- β spine of classical amyloids, we identify non-canonical cross- α architectures, in which amphipathic α -helices stack perpendicular to the fibril axis, as well as highly polymorphic states in which a single peptide sequence populates structurally distinct fibril forms with fundamentally different functional outputs.

A central question in the field is what governs the selection between competing assembly states. Our work demonstrates that amyloid formation is not an irreversible endpoint but a dynamic, stimulus-responsive process subject to environmental control. Membranes and, strikingly, RNA emerge as key modulators that reshape peptide assembly free-energy landscapes, driving reversible structural transitions and triggering phase separation into condensates with distinct cytotoxic or antimicrobial properties. These findings reveal nucleic acid–peptide co-assembly as a previously underappreciated regulatory mechanism, one with broad implications for understanding how assembly state is controlled in cellular environments and how it can be exploited in the design of stimuli-responsive peptide materials.

Together, our results reframe amyloid peptides as a versatile self-assembly toolkit a set of tunable, environmentally switchable nanostructures whose form and function are governed by sequence, context, and molecular co-factors. This perspective opens new avenues for the design of stimuli-responsive biomaterials and sequence-programmable fibril architectures, and provides a structural foundation for next-generation antivirulence and antimicrobial strategies.



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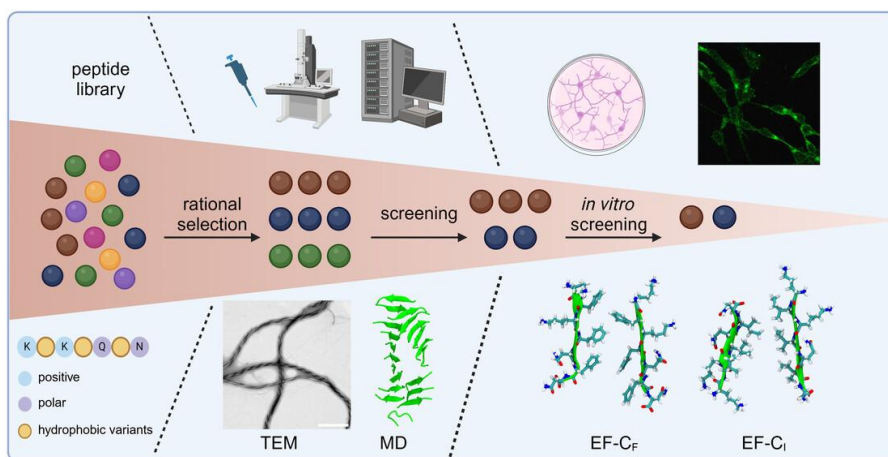
Peptide Self-Assembly at Interfaces: From Molecular Mechanisms to Functional Nanomaterials

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Establishing links between peptide sequence, physicochemical environment, and emergent nanostructure is a central challenge in peptide materials science. Our group pursues this goal through integrated workflows combining molecular dynamics (MD) simulations with biophysical experiments, including quartz crystal microbalance with dissipation monitoring (QCM-D), targeting both mechanistic understanding and rational design of peptide-based nanofibrils. A central focus is the role of lipid membranes as active modulators of peptide self-assembly. Using model membranes of varied lipid composition, including oxidized lipids, we demonstrate that electrostatic interactions, peptide surface adsorption, and interface-induced secondary structure stabilization collectively determine whether membranes accelerate or suppress aggregation in a peptide-specific manner.¹ MD simulations resolve the molecular detail of these processes, while QCM-D measurements quantify adsorption kinetics and viscoelastic changes at the peptide-membrane interface, enabling direct mechanistic comparison between simulation and experiment. Together, these approaches reveal how membrane chemistry actively reshapes aggregation pathways rather than acting as a passive scaffold. Beyond lipid membranes, nanoparticle surfaces present a related class of interfaces where curvature, charge, and surface chemistry govern peptide adsorption, corona formation, and fibril nucleation.² These studies reveal shared mechanistic principles, supporting a unified framework for interface-controlled self-assembly. Building on these insights, we apply sequence-guided design strategies to engineer functional peptide fibrils with controlled morphology and bioactivity, informed by the interfacial environments in which they assemble.³ Together, this work positions interface chemistry as a central and designable parameter in the development of peptide-based nanomaterials.

The presented studies build on collaborations with the co-authors of the cited publications.



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From atomic-precision pi-driven peptide nanofibers to photoresponsive hydrogels

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Self-assembly is emerging as a superior method to prepare responsive and adaptive nanomaterials. The structure and function of these materials is entirely determined by the dynamic and weak interactions of the constituent molecular “building blocks” of the material. Since the inherent interactions are weak, these versatile materials readily respond to even small changes and stimuli in their environment.

In this contribution I will show that a π -extended aromatic unit can be integrated into a terminally uncapped peptide to create a class of supramolecular hydrogels with high structural order. A pyrene-modified dipeptide hierarchically assembles into monodisperse helical nanofibers and self-healing hydrogels. Cryo-electron microscopy resolves the nanofibers at near-atomic precision (1.7 Å), revealing tightly packed protofilaments, continuous ordered water channels, and a unidirectional dipole extending along the fiber. These results demonstrate how reinforced aromatic stacking, polar interactions, and cooperative water organization can be orchestrated to generate emergent electrostatics and mechanical resilience, bridging conjugated materials and biomolecular matter, enabling functional soft materials inaccessible to either domain alone.

In our latest work, we focus on the design of photoresponsive peptide hydrogels based on enhanced π -interactions and arylazopyrazole photoswitches. These hydrogels feature unprecedented supramolecular structural precision and highly reversible macroscopic properties.



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Molecular conformation as a determinant of tripeptide self-assembly

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In this work we evaluate whether computed tripeptide conformational ensembles are informative of self-assembly propensity. To do this we focused on previously reported tripeptides (the six C-terminal amidated D/Y/F¹ sequence isomers and FFD²) and analyzed their conformational ensembles using all-atom molecular dynamics (AA-MD) simulations and intramolecular sidechain dihedral angles as a collective variable³. Using a novel method to numerically characterize the conformational free energy landscapes (FELs) generated from these ensembles, we find a correlation between FEL steepness and a sequence's tendency to self-assemble or remain in solution (Figure 1). This observation is in agreement with our earlier work for the PXX tripeptides (where X = F or W) where it was found that the C-terminal amino acid identity either promotes (PXW) or suppresses crystallization (PXF); this differential behavior can be explained in terms of the relative steepness of these conformational FELs, which we find share this same sequence dependence⁴. The presented methodology implicitly accounts for amino acid sequence context, which is a major determinant of divergent properties for sequence isomers⁵. It also has a low associated computational cost, making use of single molecule simulations to predict supramolecular assembly outcomes. These features make it an important advancement in the generation of theory-informed rules for the design of self-assembling peptides.

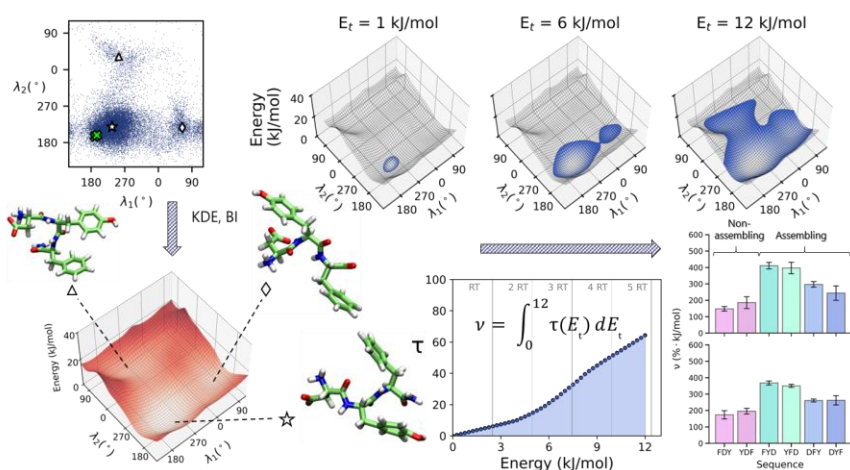


Figure 1. Summary of conformational free energy landscape (FEL) analysis technique where curvature is evaluated numerically and shows correlation with self-assembly behavior.

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⁵ K. Kaygisiz, *et al.* *Nat Rev Mater* **10**, 449 (2025)





Heterochiral Tripeptide Self-Assembly for Biomedical Applications

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Short-peptide assemblies based on non-covalent interactions have emerged as a versatile class of soft biomaterials capable of forming functional nanostructures, including hydrogels, with promising biomedical applications. Specifically, tripeptides are appealing due to their straightforward synthesis and potential for cost-effective upscaling. In this context, the heterochiral tripeptide ^DLeu–Phe–Phe (IFF) has been identified as a minimalistic self-assembling motif able to gel at physiologically-compatible conditions.¹ Its assembly features parallel stacking, thanks to H-bonding between amides, and hydrophobic interactions between Phe residues, which promote ordered amphipathic architectures, with one hydrophobic side featuring zipper-like motifs, and an opposite, hydrophilic side featuring the peptide backbone and the charged termini at neutral pH, as recently revealed by single-crystal X-ray diffraction. Such supramolecular structure was exploited to investigate a range of potential biological applications.

Due to the hydrophobic zippers, these materials can serve as reservoirs for small hydrophobic and poorly soluble drugs, enabling controlled release profiles. The capability of IFF-based hydrogels to host hydrophobic aromatic drugs had been explored through co-assembly studies with naproxen, ketoprofen² and, recently, ibuprofen. These structurally related anti-inflammatory agents enabled evaluation of how aromaticity, stereochemical features, and subtle differences in molecular geometry influence drug incorporation within the peptide network. All compounds were successfully incorporated at concentrations relevant to commercial pharmaceutical formulations, confirming the suitability of ultrashort peptide matrices for drug loading. The results further indicate that the fused aromatic system of naproxen may engage more effectively in non-covalent interactions with the peptide scaffold compared with the non-fused aromatic rings of ketoprofen and ibuprofen, resulting in different drug release profiles. Furthermore, enantioselective retention propensity was assessed in the case of racemic ibuprofen.

In parallel, a covalent drug delivery strategy was developed using a chemotherapeutic drug 5-fluorouracil (5-FU) as a model.³ The drug was conjugated to the ^DLeu–Phe–Phe sequence via a disulfide-based linker to generate a redox-sensitive prodrug hydrogelator. This 5-FU–SS–IFF conjugate retained its ability to self-assemble into mechanically robust hydrogels with viscoelastic properties similar to the parent peptide system. Under reducing conditions, cleavage of the disulfide bond triggered controlled release of 5-FU, and the system demonstrated antitumor activity in hepatocellular carcinoma spheroid models.

Lastly, the fact that the hydrophilic backbone is polycationic under physiological conditions, makes ^DLeu–Phe–Phe a lead candidate to develop smart antimicrobials that can be switched on/off with assembly/disassembly cycles. Several sequences have been derived and are currently studied to derive structure-activity relationships, while monitoring cytocompatibility on fibroblasts.

Overall, this work shows how even a simple heterochiral tripeptide can act as a versatile building block for supramolecular hydrogels, for drug delivery, and as antimicrobial materials.

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³ M. Mihajlovic, *et al.*, *ACS Bioconj Chem*, submitted (2026)





Macroscopic membranes of Carrageenan and self-assembling peptides

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²Avram and Stella Goldstein-Goren, Department of Biotechnology Engineering, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

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Three-dimensional (3D) scaffolds for cell culture aim to mimic the natural extracellular matrix (ECM) by providing structural and biochemical cues that support cell growth, organization, and function.¹ However, reproducing the complexity and hierarchical organization of native tissues remains a major challenge. Macroscopic membranes formed by self-assembly at the interface of oppositely charged biopolymer and peptide aqueous solutions (MMBPs) represent a promising approach for generating biomimetic structures. These systems can form as either planar membranes or enclosed spherical sacs with hierarchical fibrous organization.²

Building upon this concept, our lab previously developed alginate-based MMBPs using the amphiphilic β -sheet-forming peptide Pro-Lys-(Phe-Lys)₅-Pro (PFK), which self-assembles into elongated fibrillar structures.³ Depending on the assembly conditions, these membranes exhibited either fully developed hierarchical structures characterized by fibers oriented perpendicular to the membrane interface or non-fully developed porous morphologies lacking this organization. However, the limited mechanical robustness and structural stability of alginate-based sacs motivated the exploration of alternative polysaccharides.

Here, we aim to utilize λ - and κ -carrageenan as alternative building blocks for membrane formation with PFK. These are negatively charged, sulfated polysaccharides with distinct charge densities and gelation behaviors, and are used extensively in the food industry. To that end, we established a fabrication process of carrageenan/PFK spherical sacs with tunable size, morphology, and mechanical properties. These Membranes' structural evolution were studied using Small-Angle X-ray Scattering (SAXS), scanning electron microscopy (SEM), and confocal microscopy. Particular emphasis was placed on understanding how the carrageenan type (i.e., charge density and gelation kinetics) influences the membranes' stability and fibrillar organization.

This work establishes carrageenan/PFK sacs as a versatile platform for the design of stable and reproducible biomimetic materials and provides new insights into the role of polymer properties in directing interfacial self-assembly processes relevant to tissue engineering and regenerative medicine.

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Simulating Ice–Water Interfaces: Foundations for Antifreeze Peptide Design

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Anti-freeze materials are of great interest for their ability to protect biological and industrial systems from the damaging effects of ice formation, with applications spanning cryopreservation, anti-icing coatings, and the protection of infrastructure in sub-zero environments.^{1,2} Anti-freeze peptides (AFPs) represent a particularly promising class of such materials.³ Found in organisms that survive freezing temperatures, including fish, insects, and plants, AFPs act by adsorbing irreversibly to specific faces of ice crystals and inhibiting further growth. This causes a local depression of the freezing point without affecting the melting point, a phenomenon termed thermal hysteresis, and their structural diversity makes AFPs attractive candidates for engineering bespoke anti-freeze materials with tailored properties.

One such AFP has been engineered from the protein 4DT5, extracted from the haemolymph of the Longhorn beetle *Rhagium inquisitor*, a species capable of surviving prolonged sub-zero temperatures.^{4,5} This beetle AFP exhibits thermal hysteresis activity significantly greater than that of fish AFPs, and is understood to bind to the basal plane of ice. Understanding how this peptide interacts with the ice surface at a molecular level is essential to informing the rational design of AFP-based materials.

Molecular dynamics (MD) simulation offers a powerful computational approach to probe such interactions at atomic resolution, enabling the study of AFP adsorption, interface dynamics, and the thermodynamic conditions governing ice growth. Here we explore the development, validation and deployment of an MD methodology for simulating the ice-water interface and how AFPs can change it.

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Activating physical crosslinking in synthetic extracellular matrices by switch peptides

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The native extracellular matrix (ECM) comprises a network of polysaccharides and proteins, which integrates diverse dynamic chemical and physical signals to regulate cellular processes. Among these signals are cryptic sites, short signaling peptides buried within ECM proteins that remain inaccessible to cells until activation for rearrangement exposes them to the cells.

The dynamic mechanical properties of ECM, also known as viscoelasticity or time-dependent stress response, have recently been shown to play a significant role in shaping cellular behavior and function. However, understanding how cells respond to changes in tissue viscoelasticity within the ECM remains a major unresolved challenge in cell biology, tissue engineering, and regenerative medicine. While static synthetic ECMs, such as hydrogels, have provided valuable insight into cellular responses to biophysical cues, they fail to capture the dynamic, cell-modulated nature of native ECM. Developing dynamic synthetic ECM that responds directly to cellular activity is, therefore, essential for advancing our understanding of how viscoelasticity guides cell behavior.

Within this framework, we aim to develop a synthetic material capable of mimicking the process by which cryptic sites are exposed and influence viscoelasticity. To that end, we seek to construct a dual crosslinked network hydrogel composed of a primary network of chemically crosslinked polymer chains decorated with switch peptides, that upon enzymatic action, will rearrange to form sequences that tend to self-assemble to form fibers; thus, creating secondary physical crosslinks that change the viscoelasticity of the hydrogel.

The hydrogel network is constructed from oxidized alginate chains crosslinked through dynamic hydrazone bonds and functionalized with switch peptides via carbodiimide coupling.

We systematically investigate how peptide sequence, peptide-to-polymer ratio, and crosslinking density influence the emergence of supramolecular assembly and the resulting elastic and viscous properties before and after enzymatic activation.

Structural evolution and supramolecular assembly are characterized using cryoEM and SAXS, while oscillatory rheology is used to correlate assembly formation with viscoelastic behavior.





Towards the Design of Targeted Therapeutics based on Antimicrobial Amyloids

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Antimicrobial peptides (AMPs) are key components of innate immunity and attractive alternatives to conventional antibiotics due to their broad-spectrum activity and lower tendency to induce resistance. A subset of AMPs can self-assemble into fibrils, including amyloid-like structures, which may enhance peptide stability, bioavailability, and functional regulation. While classical amyloids adopt cross- β architectures, recent studies identified cross- α fibrils composed of amphipathic α -helices. Notably, some fibril-forming AMPs (ff-AMPs) can switch between distinct secondary structures depending on environmental conditions, with their antimicrobial activity tightly linked to their conformational state. These secondary-structure-switching (SSW) ff-AMPs therefore represent promising candidates for stable and controllable antimicrobial agents.

To identify novel cross- α and SSW ff-AMPs, I developed a sequence-based computational framework integrating secondary-structure prediction with biochemical and biophysical analyses. Existing bioinformatic tools are often limited in addressing the complexity of non-canonical amyloid systems, particularly cross- α and SSW fibrils. The new framework addresses this gap by combining and refining existing approaches to predict ff-AMPs with these unique structural properties. Experimental validation confirmed the predictions and led to the discovery of dozens of new ff-AMPs and toxic peptides, including at least 15 previously undescribed amyloid morphologies. These findings highlight the widespread ability of AMPs to self-assemble into functional fibrils.

Amyloids are highly polymorphic in sequence, structure, and function, yet share a common ability to self-assemble into ordered fibrils. The discovery of ff-AMPs further expands the amyloid landscape and raises fundamental questions about the determinants of amyloid assembly and function. To explore these properties, an extensive structural analysis using AlphaFold2 (AF2) was performed. Surprisingly, AF2 frequently predicted cross- α rather than canonical cross- β conformations, particularly in toxic and antimicrobial amyloids, supporting the hypothesis that cross- α architectures are linked to functional amyloid states. Furthermore, analysis of Protein Data Bank (PDB) entries revealed that among the few proteins experimentally documented in multiple secondary structures, most are amyloids, emphasizing their exceptional structural plasticity.

To systematically characterize different amyloid types, I developed a computational pipeline that incorporates the ESM protein language model, along with supervised and unsupervised machine-learning approaches. This framework enabled classification and feature extraction of fibril- and amyloid-forming proteins, revealing that amino acid composition is strongly associated with amyloid type and function. Most importantly, our PLM-based analysis demonstrates for the first time that ff-AMPs constitute a distinct class of self-assembling peptides, clearly separated from other amyloid and peptide groups. These findings provide new insights into the principles governing functional amyloid formation and establish a foundation for the rational design of self-assembling bioactive peptides.





Self-Assembly of Fatty Acid–Diphenylalanine Amphiphiles into 2D-Sheets

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Peptide amphiphiles typically self-assemble into one-dimensional nanostructures, while the formation of two-dimensional sheets are less common.^{1–5} Here, we show that a minimal fatty acid–diphenylalanine amphiphile,^{6, 7} $C_nH_{2n+1}CO-FF-OH$, can access micelles to 2D nanosheets simply by tuning solvent composition. Using acetonitrile/water mixtures, $C_9H_{19}CO-FF-OH$ undergoes a solvent-driven transition from micelles in acetonitrile to wormlike micelles, helical ribbons, and sheets at higher water contents. Tail length strongly influences the final assembly stability: $C_7H_{15}CO-FF-OH$ forms exceptionally large, stable nanosheets, while longer homologues favor precipitation or crystallization. C-terminal capping alters the assembly pathway. These results show the importance of solvent composition and hydrophobic tail length as key parameters for programming peptide amphiphile self-assembly.

Keywords: Peptide amphiphiles, Self-assembly, 2D materials, Diphenylalanine, Nanosheets

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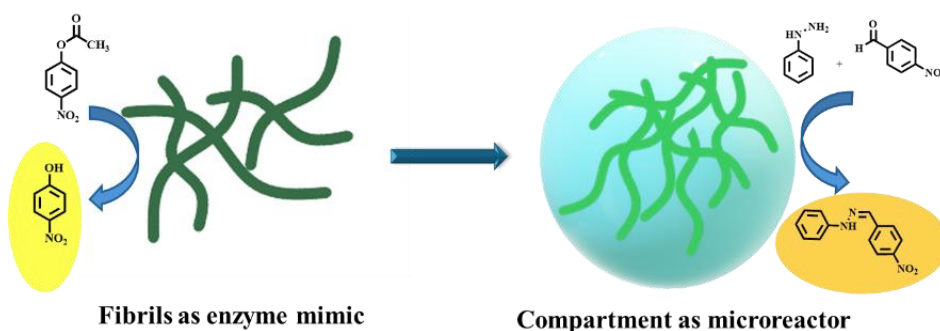


Development of Dipeptide-Based Liquid Droplets and Fibrils as Enzyme-Mimics

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The emergence of functional complexity from simple molecular building blocks remains a central challenge in prebiotic chemistry and synthetic biology. While coacervates, liquid droplets formed by liquid-liquid phase separation (LLPS) have attracted considerable attention as protocell models, their design has largely relied on macromolecular polyelectrolytes or multi-component systems. Similarly, peptide-based enzyme mimics have typically demanded longer sequences or metal cofactors to achieve meaningful catalysis. Here, we break both barriers with a single minimalistic dipeptide. We present a rationally designed dipeptide (Boc-Phe-His-OMe, **1a**) comprising one hydrophobic phenylalanine and one polar histidine residue that undergoes a remarkable, concentration-dependent morphological switch between two functionally distinct supramolecular architectures. At low concentrations (0.3 mg mL^{-1}), **1a** self-assembles into well-defined nanofibrils driven by π - π stacking and hydrophobic interactions. At higher concentrations ($\geq 3 \text{ mg mL}^{-1}$), the same peptide undergoes spontaneous self-coacervation into micrometre-sized liquid droplets across a pH range of 6.0–11.0. This single-component, single-sequence morphological programmability from fibrils to coacervates in a sub-0.5 kDa molecule represents a significant departure from existing paradigms. The coacervate droplets exhibit a hydrophobic microenvironment that functions as an efficient microreactor, accelerating hydrazone bond formation by up to 3.5-fold at pH 8.0 through proximity-based catalysis. Crucially, the fibrillar morphology presents an ordered display of catalytic histidine imidazole groups, enabling robust esterase-like hydrolysis of 4-nitrophenyl acetate. Michaelis-Menten kinetic analysis yields a $k_{\text{cat}}/K_{\text{M}}$ of $0.123 \text{ M}^{-1}\text{s}^{-1}$, comparable to previously reported His-containing fibrillar catalysts. Both assemblies exhibit intrinsic autofluorescence, attributed to supramolecular chromophore formation through carbonyl clustering, enabling direct confocal characterization without external labels. Systematic structure-activity studies across a series of dipeptides (varying hydrophobic residue: Trp, Ala, Gly) confirm that the precise hydrophobic-hydrophilic balance of phenylalanine and histidine is essential. This work establishes a minimal design grammar for programmable peptide self-assembly and opens new avenues for compartmentalized catalysis, synthetic protocells, and biomimetic systems chemistry.



A Unifying Thermodynamic Model for Phase Separation and Aging of Biopolymers

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Phase separation of, in particular, intrinsically disordered proteins into condensates is a ubiquitous process by which cells regulate a plethora of biological processes. In aberrant cases, such as encountered in neurodegeneration, these initially liquid condensates ‘age’ to become more solid-like. Understanding the interplay between phase separation and aging seems essential in the development of new therapeutic strategies. Our approach to generating such insight is by applying minimal models that aim to capture the essence of biological transitions in terms of driving forces and thermodynamics. Minimal models capable of discriminating between mono- and multivalent directed association on the one hand and non-specific, non-saturating interactions on the other appear to be surprisingly versatile in reproducing and predicting biopolymer phase behaviour (Figure 1A), while at the same time providing essential mechanistic insight. We will give an overview of our work in this field, combining theory with experiments and demonstrating how relatively simple descriptions can (re)produce complex multi-component phase behaviour.^{1,2} We will present a dynamic model,³ which provides for a thermodynamically unifying description of phase separation and aging of IDP condensates. Our calculations explain, for instance, why the ‘stickiness’ of the proteins due to beta-folding can change spontaneously with time and concentration (Figure 1B), how the coupling between association and solvation determines viscoelasticity (Figure 1C) and how aging proceeds in a spatially anisotropic way across the condensate.

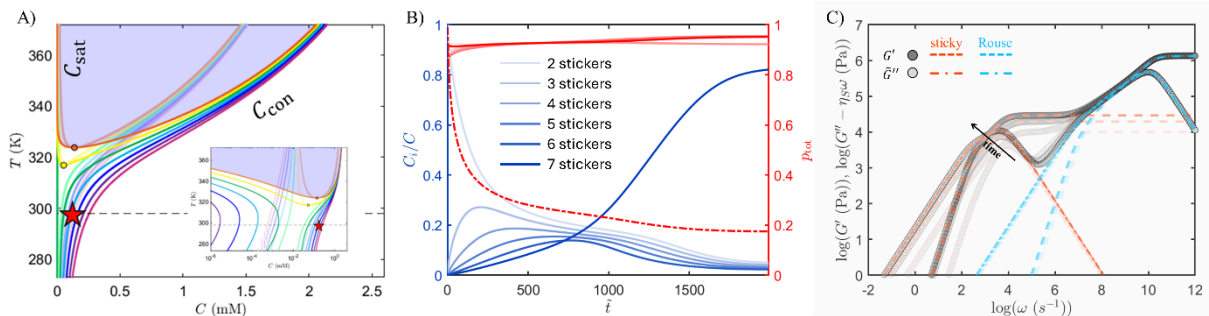


Figure 1. A) Hourglass phase diagrams of intrinsically disordered proteins, predicted by mean-field sticker-spacer theory. B) Predicted spontaneous increase in sticker valency of an aging IDP condensate. C) Increase in viscoelasticity of a condensate during aging, predicted by a time-dependent sticky-Rouse model.

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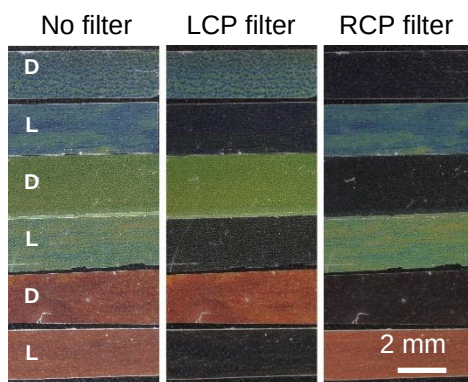


Cholesteric polypeptide self-assembly and application in structural coloured materials

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Cholesteric liquid crystals (CLCs), characterized by their helical periodic organization, have emerged as an important class of structural colouration materials because their pitch can be precisely tuned to selectively reflect specific wavelengths of light through Bragg reflection.¹ In nature, a variety of polymeric biomaterials, including DNA, cellulose, chitin, and proteins, spontaneously form cholesteric phases whose handedness originates from the intrinsic chirality of their molecular building blocks. Among these systems, cellulose and its derivatives have been extensively investigated for sustainable photonic materials owing to their abundance, renewability, and ability to generate vivid structural colours.^{2,3} However, the optical response of cellulose-based cholesteric systems is typically limited to a single handedness, restricting opportunities for manipulating circularly polarized light. In contrast, polypeptides and proteins offer unique advantages, including molecular programmability, structural diversity, biodegradability, and precise control over chirality, yet their potential as sustainable photonic materials remain largely unexplored.⁴ Here, we present a synthetic polypeptide-based cholesteric liquid crystal platform that enables programmable control over the handedness of reflected circularly polarized light through molecular chirality engineering. By tailoring the chirality of the constituent polypeptide blocks, the supramolecular helicity of the cholesteric phase can be switched between opposite handedness, resulting in selective reflection of either left- or right-circularly polarized light (LCP/RCP). These findings establish synthetic polypeptides as a versatile and sustainable platform for structural colouration and provide new opportunities for the design of bioinspired photonic materials with tunable chiroptical properties.



Polypeptide-based structural colourations and selective reflection of RCP and LCP light

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Programmable structural plasticity in peptide nanofibrils via interfacial energy balance

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Self-assembly of peptides into synthetic amyloids offers a powerful route to develop novel functional nanomaterials. However, rational design remains challenging due to unpredictable architecture formation. We report hexagonally ordered nanofibrils easily yielded by a class of amphiphilic self-assembly peptides, representing a significant advance in structural predictability and tunability.

Using single-particle CryoEM, we resolve at near atomic-level the architecture of these fibrils, revealing that their exceptional order arises from sequence-encoded, “LEGO-like”, interaction between two peptide motifs. The assembly is driven by a combination of dimeric cross- β and trimeric junction motif, forming a hexagonal lattice with 5 nm pores that extend over micrometer lengths via backbone hydrogen bonding¹. We systematically investigate the limits of this design principle via targeted point mutations that disrupt these interactions, leading to three distinct fibril architectures: hexagonal fibril, cross- β fibrils, and β -tape. Our analysis uncovers the atomic-level forces governing structural diversity and investigates the nucleation pathways that determine final assembly: by tuning initial conditions, we explore the energy landscape that leads to different structural states. We reveal that the structural plasticity is encoded in balanced interfacial energies derived by the dual amphiphilic pattern of these peptides. Furthermore, the atomic analysis uncovers the principles necessary for trimeric junction stabilization and subsequent hexagonal formation. Lastly, we characterize macroscopic behavior and correlate this to the nanomaterial architecture visualized at sub-nanometer level.

This work establishes a general framework for the rational design of peptide nanomaterials and highlights the power of single-particle CryoEM in bridging atomic-level insights in functional material and achieving structure-function studies.

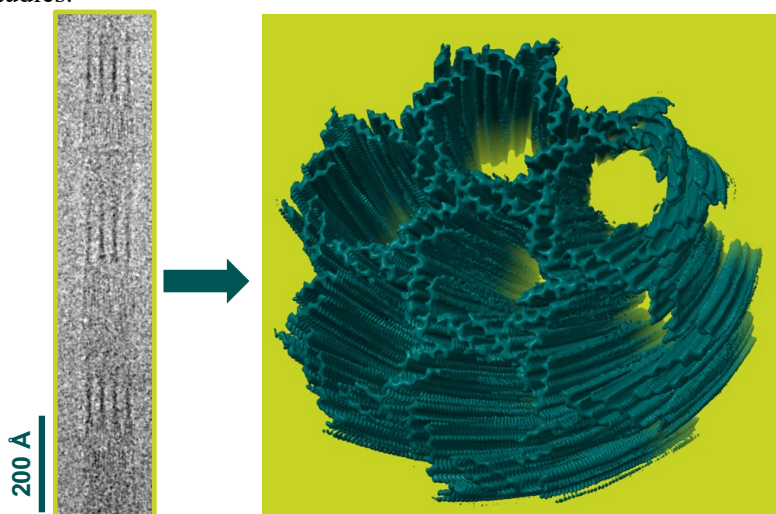


Figure 1. From CryoEM morphology to a 2.9 Å resolution volume of hexagonally ordered nanofibrils.

¹ PDB DOI: <https://doi.org/10.2210/pdb9H7U/pdb>



When Chirality Collides: Pathway Complexity to Emergent Supramolecular Asymmetry in Peptide Assemblies

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Controlling supramolecular chirality during the non-covalent synthesis of peptide assemblies is critical for designing biomaterials with programmable mechanical and bioactive properties. However, most helical peptide assemblies formed via supramolecular polymerization rely solely on amino acid point chirality, precluding emergent phenomena such as the majority-rules effect, where modest enantiomeric excess (ee) drives nonlinear asymmetric amplification. While this effect is well established in non-peptidic systems, it remains largely absent in peptides. Here, we introduce a non-covalent synthesis strategy in which peptide point chirality interacts with the dynamic helical chirality of tetraphenylethylene (TPE) during supramolecular polymerization in water.¹ Combined spectroscopic, scattering, microscopy, and computational analyses reveal two distinct regimes. In pH-induced homopolymerization, geometric incompatibility between chiral TPE propeller stacking and the twisted β -sheet hydrogen-bonding network produces a frustrated energy landscape with two polymorphs: kinetically trapped helical nanofibers and thermodynamically favored helical nano-springs, each with distinct helicity. Replacing protons with sodium or calcium ions modulates electrostatic interactions, steering polymorph selection toward nanofibers. In copolymerization with different ratios of enantiomers, the same chirality interplay perturbs β -sheet organization of L/D peptides and reduces the mismatch penalty of opposite enantiomers to $\sim 1\text{--}2\text{ kJ mol}^{-1}$. This enables heterochiral copolymerization and generates a pronounced majority-rules effect, where $\sim 50\%$ ee dictates global helicity, a phenomenon previously absent in peptide systems.

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Computational Tools For Peptide Engineering and Their Potential For Peptide Self-Assembly Applications

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Protein–protein interactions (PPIs) are involved in most biological processes. However, the efficient and reliable prediction and engineering of PPIs remains a challenge given the vast search space involved. To address this challenge, we combine machine learning (ML) tools with physics-based approaches. We developed PPI-Detect1 as a sequence-based ML model for the prediction of the likelihood of protein–protein interactions2 and PPI-Affinity3 for the prediction of the binding affinity (BA) of protein–protein and protein–peptide complexes as well as for protein engineering applications.4-5 The Central Limit Free Energy Perturbation approach (CL-FEP)6 is a method based on molecular, full-atomistic simulations that allows evaluating Gibbs energy changes directly from the energy samples of the end states of a system transformation, without fitted parameters or stratification. The CL-FEP approach delivered excellent accuracy estimating the binding Gibbs energy of a large set of benchmark systems and found real-life applications.7-9 In this talk, I will briefly introduce these tools and discuss selected applications for peptide engineering and their potential for the regulation of peptide self-assembly.

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Cryo-electron microscopy of fibrillar biotechnological protein assemblies

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Amyloid fibrils are fibrillar polypeptide aggregates with a cross- β structure. They can occur inside the body and are commonly associated with debilitating conditions such as neurodegenerative diseases or systemic amyloidosis. They can also be found in nature with functional properties, for example in plants seeds as protein storage or in bacteria in biofilm to survive in harsh natural environments. There is also increasing interest to use the structural scaffold of amyloid fibrils for different biotechnological purposes like conductive nanowires, materials for the selective capture of carbon dioxide, aerogels for water purification, catalytic agents or enhancers of retroviral transduction. To understand how molecular information are encoding three-dimensional structure and organisation structural information is crucial. One important technique to investigate these structures and their mechanism is cryo-electron microscopy (cryo-EM). Cryo-EM allows to investigate protein structures in their native form frozen in vitreous ice at a high resolution (below 3 Å), that were not accessible with other techniques. I want present some examples of cryo-EM structures of biotechnological amyloid fibrils. Peptide PNF-18¹ is a 7-mer peptide that was artificially designed as retroviral transduction enhancer and increases HIV-1 infection rates of TZM-bl cells by a factor of more than a hundred-fold. Cryo-EM reconstructions at 2.9 Å of the structure showed that each protofilament is built by two paired cross- β sheets that interact by the hydrophobic side of the amphipathic peptide, while polar residues are pointing outwards creating a positive surface. These structural features provide insights into the molecular basis of the amyloid polymorphism and virus binding. Another recently studied examples are synthetic nanochannel-forming amyloid fibrils that are highly ordered with a hexagonal protofilament structure with a nanochannel inside. These peptides can form amyloid fibrils with different numbers and arrangements of these protofilament. Here the obtained structural data at resolutions of 1.78 Å and 1.9 Å and showed the stability of the designed sequence against arginine mutations at different positions and provides a basis for the rational sequence design of other sequence variants of these synthetic nanochannel-forming self-assembling peptides.

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A structural chameleon in cryo-EM: cross- α /cross- β amyloids & nanotubes

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Amyloids, typically recognised as hallmarks of pathogenicity, have been increasingly linked to antimicrobial activity, which points towards physiological roles of amyloidogenic peptides and proteins. To explore underlying mechanisms of amyloid structure-activity-relationships, we previously developed a computational platform to screen for fibril-forming AMPs (ffAMPs)^{1,2}. Here, we examine an amphibian ffAMP candidate of the Temporin family and report a condition-dependent structural chameleonism between cross- α /cross- β amyloids and α -helical nanotubes. A similar secondary structure switch was previously observed for the ffAMP Uperin-3.5², but with selective detection of either crystallographic cross- α or cryo-EM cross- β species. Now, we observed both cross- α / β amyloid forms of this Temporin in cryo-EM and present high-resolution details of its cross- α topology. We demonstrate that the amino acid composition of Temporin allows robust secondary structure switching and filament nucleation in response to peptide concentration and solvent composition. In addition, we link its antimicrobial behaviour to membrane-disruption in solution and lipid-induced fibril dissolution for potential amplification of antimicrobial functions. Altogether, this study underscores the complexity of amyloidogenic (antimicrobial) peptides, emphasises the *in vitro* condition-sensitivity of these, and offers valuable insights into sequence–structure–function relationships.

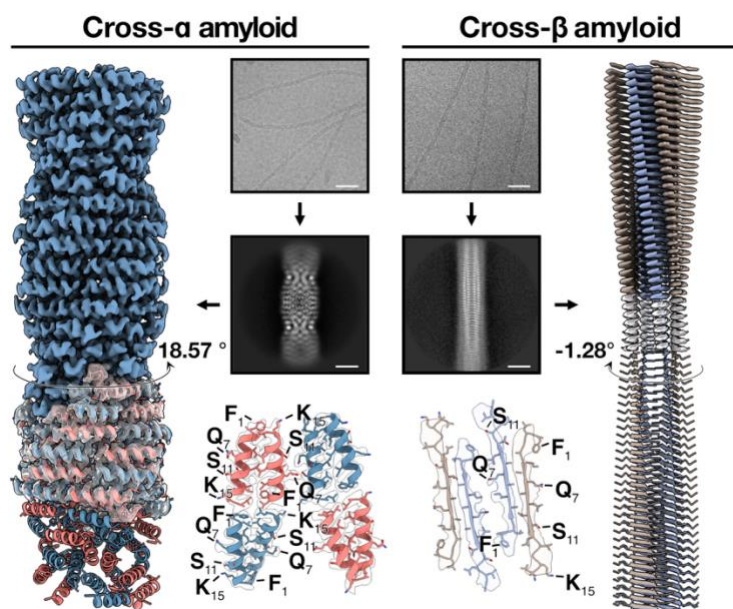


Figure 1. Cryo-EM reconstructions of Temporin cross- α and cross- β amyloid forms. Shown in the centre are sections of representative raw cryo-EM micrographs from the Temporin cross- α (100 μ M HFIP-treated peptide in 10 mM HEPES, pH 7.0, 150 mM NaCl, 4 days at 37 °C) and cross- β (500 μ M non-HFIP-treated peptide in 10 mM HEPES, pH 7.0, 15 mM NaCl, 4 days at 37 °C) data sets; scale bar 30 nm. Below are 2D classification previews of filaments used for 3D helical reconstructions; scale bar 5 nm. Cryo-EM density maps are continued with atomic models towards the bottom. At the bottom centre are single fibril layer map-model overlays with milestone amino acid labelling in one-letter codes. The reconstruction resolution of the Temporin cross- β map only allowed a rough overlay of β -sheets for all residues of outer strands (brown) and residues 1–14 of inner strands (purple).

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Chirality Transfer in 3_{10} -Poly(Aib) Helices for Light-Responsive CISS Switching

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α -Aminoisobutyric acid (Aib) is an achiral, α,α -disubstituted amino acid with a pronounced tendency to promote well-defined 3_{10} -helical secondary structures in peptides and peptide-like oligomers. Since the early work of Toniolo and Benedetti on the polypeptide 3_{10} -helix, Aib-rich systems have become important model structures for understanding helix formation, conformational stability, and secondary-structure control in peptides [1]. More recently, Clayden and co-workers have demonstrated how screw-sense induction and conformational communication in Aib foldamers can transmit stereochemical information over several residues, making these systems attractive platforms for studying chiral transfer through achiral backbones [2]. We extend the concept of screw-sense induction and long-range chirality transfer in Aib 3_{10} -helices towards Chiral-Induced Spin Selectivity (CISS), where chiral molecular structures preferentially transport electrons of one spin orientation without an external magnetic field. Oligomers of the general structure $A^*-(Aib)_n-S$ ($n = 7-15$) were prepared by ring-opening polymerisation via a single centrochiral initiator (A^*), to induce either P- or M-helicity according to the sergeant and soldier principle [3]. By further end-group modification (S), a sulfur terminus was introduced *via* heterogeneous peptide coupling with lipoic acid, enabling adsorption onto gold surfaces and the formation of self-assembled monolayers approximately 6 nm in height [4]. Spin-selective electron transport through these systems was investigated using conductive atomic force microscopy (c-AFM) and scanning tunnelling microscopy (STM). We found that the current-voltage response strongly depends on both the oligomer's helicity and the magnetisation direction of the substrate. High spin-polarisation values and selectivities were observed, reaching up to 99% in C-AFM and 90% in STM [5]. Based on this concept, poly(Aib) oligomers incorporating a Feringa-type molecular photoswitch [6] as the head group were synthesised, providing a platform for investigating dynamic, light-induced modulation of polymer helicity and its influence on spin-selective electron transport.

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Building membranes from elastin-like polypeptides

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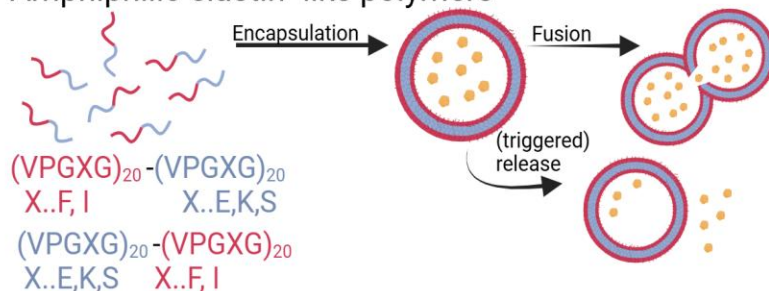
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Elastin-like polypeptides (ELPs) are genetically engineered biopolymers characterized by the repetitive pentapeptide motif VPGXG. They can be responsive to temperature, ionic strength, and pH. Due to their sequence-defined structure and options for modifications and conjugations, ELPs are highly attractive biomaterials for biomedical and biophysical applications, particularly in drug delivery and biomimetic membrane systems. Amphiphilic ELPs can self-assemble into supramolecular structures, such as nanoparticles, micelles, and vesicles, which act as protein-based analogues of liposomes with added advantages including genetic tunability and responsiveness to stimuli¹. However, the mechanisms of ELP self-assembly and membrane analog processes remain incompletely understood. The recombinant production of ELPs and the optimization of expression and purification protocols represent key prerequisites for any systematic biophysical study. We investigate the ELP assemblies using monolayer methods and fluorescence-based techniques.

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Amphiphilic elastin-like polymers





Molecular Determinants of Self-Assembly in the Immunodominant 33-mer Gliadin Peptide

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Gluten-related disorders (GRDs), which are multiorgan diseases affecting around 5% of the general population, include the autoimmune disease celiac disease (CeD) (1), wheat allergy (WA), and other less well-understood conditions such as non-celiac gluten sensitivity (NCGS) and gluten ataxia (2). In wheat gluten, gliadins are the most investigated as a CeD trigger. The main problem with these proteins is that they are resistant to proteolytic digestion by human proteases, and large undigested gliadin peptides reach the small intestinal epithelium, where, in predisposed people, they trigger gluten-related disorders (3).

Importantly, these proteolysis-resistant gliadin peptides (PRGP) can self-assemble into various nanostructures, including oligomers, thin plates, and amyloid-like fibrils (4). In the last decade, we have been working to understand the self-assembly process of the immunodominant 33-mer peptide, 57LQLQPF (PQPQLPY)₃ PQPQPF₈₉, which has a PPII secondary structure, a low critical aggregation concentration of 75 nM, and forms oligomers above 50 μ M. Above this concentration, there is a shift in the secondary structure towards higher β -structure, forming large thin plates that activate inflammatory pathways such as NF κ B in macrophages (5). Due to 33-mer repetitive sequences, the molecular understanding of the self-assembly process remains unclear.

Here, we present our latest efforts to elucidate the 33-mer self-assembly process by synthesizing a library of hexapeptides comprising different 33-mer domains and investigating their folding and self-assembly propensities using NMR, Circular dichroism, and advanced microscopy in combination with cellular models.

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From Nanofibers to Nanotoroids: Visible-Light-Regulated Pathway Selection in Fluoroazobenzene–Peptide Self-Assembly

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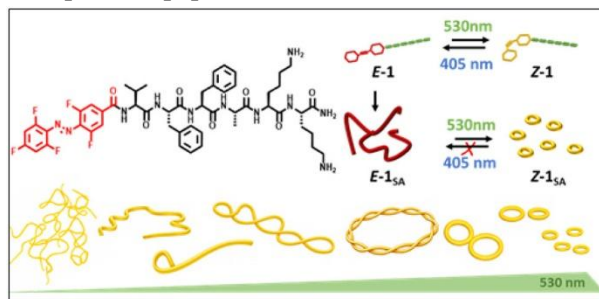
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Controlling supramolecular pathway selection is crucial for understanding and designing adaptive peptide-based materials. Here, we report a visible-light-responsive fluoroazobenzene-peptide conjugate that exhibits topology-dependent self-assembly, providing insights into pathway complexity and structural memory in peptide systems. The molecular design consists of a pentafluorinated azobenzene photoswitch conjugated to the amyloidogenic peptide sequence VFFAKK. In aqueous media, the linear E-isomer self-assembles into β -sheet-rich nanofibers through a cooperative nucleation–elongation mechanism. Upon irradiation with visible light, photoisomerization introduces a conformational change that redirects the assembly pathway toward discrete nanotoroidal architectures. Microscopic and spectroscopic investigations reveal a remarkable nanofiber-to-nanotoroid transformation accompanied by reorganization of the supramolecular packing. Unlike the fibrillar state, the nanotoroidal assemblies are kinetically trapped and exhibit persistent structural memory, highlighting the role of molecular geometry in governing access to distinct regions of the supramolecular energy landscape. Computational studies suggest that the bent geometry of the Z-isomer, together with fluorine-mediated interactions, promotes curvature and stabilizes the toroidal topology. More broadly, this work establishes a strategy for navigating complex self-assembly landscapes and accessing nonequilibrium states through external stimuli, offering new opportunities for the development of adaptive and responsive peptide-based materials.



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Mutational Tolerance of Synthetic Nanochannel-forming Amyloid Fibrils analyzed *via* Cryogenic Electron Microscopy

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Amyloid fibrils are self-assembling protein aggregates with a highly ordered cross- β structure, often associated with diseases. Recently it has been shown that dimer inversion lock trimer (DILT) nonapeptides assemble into multi-channel amyloid fibrils with a honeycomb-like three-dimensional (3D) structure. The design rationale provides a dimerization (KVKV) and a junction interface (SQINM) to selectively produce, highly ordered multi-channel amyloid fibrils. To probe the tolerance of this honeycomb structure against mutations, sequence variants were synthesised and fibrils assembled. Sequences “DILT2” and “DILT3” which carry an arginine substitution instead of a lysine, at the first and third positions respectively, were chosen for further analysis.

Comprehensive structural characterisation of these mutated multi-channel amyloid fibrils (DILT2 & DILT 3) was performed via cryo-EM and subsequent helical reconstruction.

The resulting 3D electron density maps of the most common morphologies present in the sample were resolved at 1.9 Å for DILT2 and 1.78 Å for DILT3. At these resolutions, side-chain conformations within both the dimer interface and the trimeric junction interfaces are identifiable. The structures demonstrate that the peptides primarily form a morphology based on a hexagonal basic unit that extend into a regularly ordered lattice .

The hexagonal basic structure is formed by dipeptides connected by a trimeric junction interface. The structural data show that the trimeric junction, the global hexagonal lattice, and the ~5 nm continuous nanochannel pore diameter are invariant across the analysed mutants. The morphological difference between the variants is in the arrangement of the hexagonal basic units, which for DILT2 predominantly adopt a six-fold rotational symmetry, while in the case of DILT3 they primarily adopt a three-fold rotational symmetry around the fibril axis.

The obtained structural data show the robustness of the designed sequence against arginine mutations at the first and third positions and provide a basis for the rational sequence design of further sequence variants of honeycomb forming amyloidogenic peptides. Approaches could include, tuning of pore size and pore shape.





Photoinduced Morphological Transformation in the Azobenzene-Cored Hybrid Peptides

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The discovery of template-directed peptide self-replication has opened a new perspective on the origin of life research. It has opened up the innumerable avenues for the design of peptide-based molecules as potential progenitors of the present DNA-based world. Herein, we present stimuli-responsive pseudopeptides that undergo reversible morphological transition upon photoirradiation. We designed and synthesized simple photo-responsive designer azobenzene-cored pseudopeptides that self-assemble to vesicles and fibers. The tryptophan (Trp)-appended azobenzene-cored pseudopeptide assembles to vesicles in its *trans* form, while irradiation with light causes isomerization to *cis* form, leading to a larger number of vesicles. This apparent increase in the number of vesicles has a striking similarity to biological self-replication. In addition, we also report the light-induced transformation of right-handed helical fibers into vesicles in a Phenylalanine (Phe)-appended pseudopeptide and spherical aggregates into vesicles in a Leucine (Leu)-appended pseudopeptide. Detailed high resolution microscopic imaging (scanning electron, transmission electron, atomic force and confocal microscopies), and spectroscopic studies are utilized for probing the self-assembly. Confocal imaging without any external probe, utilizing the autofluorescence of the self-assembled state, stemming from the aggregation of chromophores, enabled us to probe the morphological transformation. SEM and Confocal microscopic imaging of vesicles illustrated the fission and fusion of vesicles in case of the Trp-appended pseudopeptide. The self-assembly of azobenzene-cored pseudopeptides to vesicles and fibers arises from its intrinsic property to associate. The hydrogen-bond-directed self-assembly is evident from the single crystal X-ray structure analysis of leu-appended azobenzene-cored pseudopeptides.





D4 peptide nanofibrils as efficient transduction enhancers for ex vivo gene transfer in CAR-T and NK cell generation

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Chimeric antigen receptor (CAR)-T and natural killer (NK) cell therapies are promising treatments for hematologic malignancies and are increasingly explored for solid tumors and autoimmune diseases^{1, 2}. However, their manufacturing remains labor-intensive and costly. A key limitation is the inefficient viral transduction due to electrostatic repulsion between negatively charged viral and cellular membranes. Transduction enhancers, such as peptide nanofibrils (PNFs), can overcome this limitation, thereby reducing manufacturing costs and improving cell yields. However, established enhancers like Vectofusin-1 show variable performance depending on the viral vector system³.

We identified a novel PNF, D4, through in silico screening followed by experimental optimization. Its transduction efficiency was evaluated across different viral vectors and cell types and compared to Vectofusin-1. Mechanistic studies were done including imaging of virus–PNF–cell interactions as well as a simulation of a CAR-T cell production process to assess stability and degradation.

D4 PNFs demonstrated comparable or superior transduction efficiency relative to Vectofusin-1. Notably, D4 enhanced transduction independently of the viral vector type (lentiviral (LV) or retroviral (RV)) and glycoprotein used for pseudotyping, including VSV-G–pseudotyped LV, which are poorly enhanced by Vectofusin-1. In NK cells, D4 increased transduction efficiency without the need for spinfection, improving infection rates from 0.4% to ~23% for RD114-LV and from 15% to 65% for baboon endogenous virus envelope pseudotypes (BaEV-LV)³.

Mechanistically, D4 PNFs exhibited a high density of viral binding sites, facilitating the formation of virus–PNF complexes that are actively captured by filopodia and transported to the cell body. This promotes efficient membrane fusion or endocytic uptake. Following internalization, PNFs are degraded in lysosomes. Approximately 98% of D4 aggregates were degraded within three days in a CAR-T production simulation. Importantly, D4 did not negatively affect cell viability or proliferation. In cell-free conditions, D4 aggregates gradually disassembled, suggesting a favorable safety profile due to reduced persistence and lower risk of immune activation or vascular occlusion⁴.

These findings highlight the potential benefits of using the transduction enhancer D4 in ex vivo gene transfer processes, such as CAR-T cell production.¹

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Engineering Supramolecular Biomaterials through Self-Assembly of Minimalist Peptides for Tissue Regeneration and Drug Delivery

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Supramolecular assembly is a ubiquitous phenomenon in nature for the synthesis of various functional materials required for the sustainability of life. From DNA condensation in the nucleus to the actin filaments that support cytoskeletal dynamics, most processes are predominantly governed by non-covalent interactions of their biomolecular assemblies. Peptides form self-assemblies, which are stable, biocompatible, and highly tunable and can be used to develop biomaterials, sensors, piezoelectric materials, and energy storage devices. The self-assembling peptides were first reported by Zhang *et al.*, who used a 16-amino acid beta-sheet-forming peptide to form nanofibers.¹ Later, Gazit *et al.* adopted a minimalist approach, using the Phe-Phe sequence to form supramolecular assemblies.² In recent years, many dynamic and adaptive systems have been designed through peptide self-assembly, addressing fundamental to advanced questions in science.³ In the current work, we have designed a minimalist peptide, Fmoc-Phe-Lys-Ser-OH, which self-assembles in aqueous medium at 1.5% w/v to form a supramolecular gel. This gel exhibited a nanofibrous morphology, as evidenced by AFM imaging, and its rheological characterization revealed its viscoelastic nature. We further used it as a supramolecular template and conjugated a functional DGEA peptide sequence to its carboxyl terminus. The Fmoc-FKSDGEA sequence so formed self-assembled into a rigid gel with an ECM-like nanostructure. The gel was found to be cytocompatible towards murine fibroblasts (L929 cells) and macrophages (RAW 264.7 cells). The nanofibrous network-coated plates effectively modulated LPS-induced proinflammatory macrophages, promoting their transition to an anti-inflammatory phenotype, hence, showing potential in immunomodulatory tissue engineering. We have further used the Fmoc-FKS tripeptide template to develop a supramolecular drug depot. The serine side-chain hydroxyl group was functionalized with the NSAID, naproxen, via an ester linkage, and we are currently assessing its esterase-responsive drug-release behavior for application in inflammatory disease conditions.

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Novel Peptide Targeting CXCR4: Rational Design and characterization through Computational Modeling

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Given its role in immune cell trafficking and cancer metastasis, CXCR4 represents a promising target for the development of peptide-based antagonists. Recent evidence showed a connection between the G Protein-Coupled Receptor 15 Ligand (GPR15LG) and CXCR4 signalling, prompting us to design GPR15LG-derived peptides to target CXCR4. Starting from the full-length GPR15LG, we performed Gaussian accelerated molecular dynamics (GaMD) simulations as enhanced sampling technique to explore its binding to CXCR4 receptor. These results guided the design of an N-terminal peptide derivative, GPR15LG-N, which exhibited conserved binding to CXCR4. Using energy-reweighted potential of mean force (PMF) maps we identified the main binding mode of GPR15LG-N, which is characterized by cooperative ion-pair contacts between the peptide ³⁵RRTR³⁸ motif and acidic pocket residues D187, D262, and E277 (Figure 1). Alanine mutations at the N-terminal latch (D20/D22) increased pose heterogeneity and promoted off-site binding. Additionally, we ranked the peptide variants using PPI-Affinity, our machine-learning tool, and identified key residues for the interaction interface. Ultimately, this integrated *in silico* framework combines GaMD simulations with machine-learning predictions to streamline the identification and engineering of therapeutic peptide derivatives.

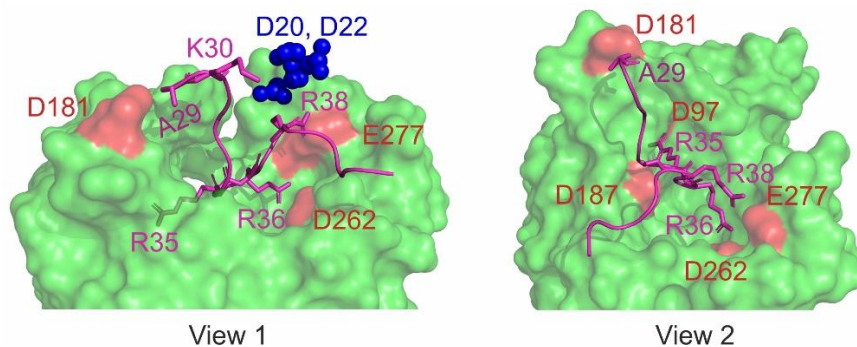


Figure 1. Main binding mode of GPR15LG-N peptide (purple cartoon) with the CXCR4 receptor (green surface) obtained from enhanced sampling simulations.

Coupled amyloid self-assembly and guanine crystallization generate hybrid protein–crystal architectures

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Background. Biogenic guanine crystals are widespread across the animal kingdom, from fish to insects, crustaceans and mollusks.¹ Owing to their exceptionally high refractive index, these crystals perform diverse optical functions, including structural coloration and vision enhancement, particularly in aquatic environments.^{2,3} Despite their biological importance, little is known about the molecular machinery that orchestrates crystal formation and maintains crystal morphology and organization.⁴ Recent evidence suggests that protein matrices seed and spatially organize guanine crystals.⁵ In particular, fibrous protein assemblies with amyloid-like structural signatures have been proposed to act as scaffolds for crystal growth and polymorphism, enabling the coherent tissue-level optical properties observed *in vivo*.⁶

Objectives. Here, we investigate the molecular basis of protein–crystal interactions (PCIs) using a reductionist, bottom-up approach. First, we tested lysozyme, a well-characterized amyloidogenic protein, for its ability to form protein–crystal complexes. We then designed a screening strategy to systematically dissect the molecular forces governing protein–crystal crosstalk using peptides as minimal models.

Results. Time-course turbidimetry and Thioflavin T fluorescence revealed a dose-dependent inhibition of guanine crystallization during lysozyme amyloid self-assembly. Confocal microscopy confirmed that lysozyme forms the core of spherulitic guanine crystals, indicating that crystallization and protein self-assembly are mechanistically intertwined. Prompted by these findings, we designed a panel of 12 peptides comprising hexapeptide steric zippers that assemble into rigid amyloid structures and peptide stretches that remain conformationally flexible. Because hydrogen bonding and π – π interactions govern crystalline architecture,⁷ we probed aromatically enriched hydrophilic sequences in two structural contexts: (i) steric zippers from Sup35, prion, transthyretin and GPNMB to test the effect of periodic aromatic patterning at the fibril interface;^{8–10} and (ii) flexible, non-fibrillar hexapeptides derived from amyloidogenic and chaperone proteins to determine whether less ordered aromatic interactions can likewise direct crystal morphogenesis. Using SEM, XRD and Raman spectroscopy to assess crystal morphology, structure and composition, we aim to reduce the protein determinants of guanine crystallization to the peptide scale.

Conclusions. Beyond providing a mechanistic framework for protein-guided crystallization, this work aims to decipher the sequence determinants underlying PCIs, enabling the systematic discovery of crystal-interacting proteins across natural proteomes. In addition, it will guide the rational design of peptide-based morphogens for engineering hybrid crystalline biomaterials with programmable structural and optical properties.

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Aryl Azo Pyrazole-Driven Photoswitching of Supramolecular Peptide Self-Assembly

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Peptides are versatile molecules which modulate numerous biological phenomena. Chemists utilise the self-assembling behaviour of the peptides to design functional materials, finding various applications in smart drug delivery, bioelectronics, self-healing hydrogels and catalysis. Imparting responsiveness into the peptide assembly to external stimuli, allows smart control of functions in peptide materials.¹ In particular, light can be an extremely non-invasive and inexpensive trigger to control the structure of the peptide and thus control its supramolecular aggregation and function. Till date, azobenzene has been the most widely used moiety which can provide photocontrol over the peptide folding or assembly. When attached to peptides, it often suffers from either low E to Z conversion efficiency or short half-life of the Z isomer.² Herein, we have utilized the aryl azo pyrazole photowitch to design a photo switchable peptide which shows superior conversion to the Z isomer at the photo stationary state upon irradiation with 365nm light. Also, the half life time of this peptide is higher compared to the azobenzene analogues.

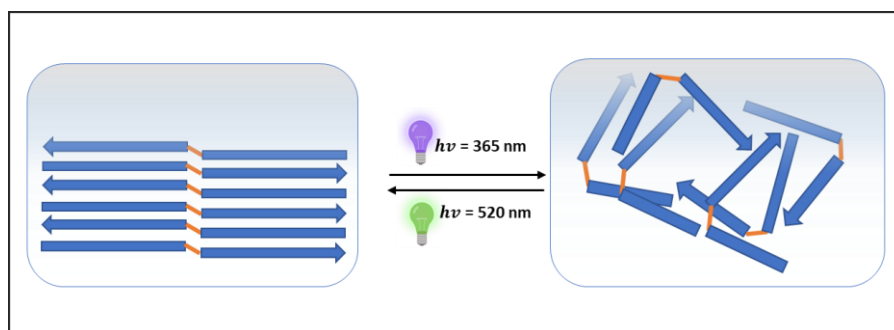


Figure 1. The reversible photo switching from ordered to disordered assembly of the peptides using UV and green light.

Circular dichroism spectral data indicates that the pristine peptide self-assembles into β -sheet in phosphate buffer of pH 7.5 and this ordered arrangement is destroyed when the peptide assumes the folded Z conformation. This supramolecular assembly can be obtained back by turning the conformation of the peptide to the E isomer using green light and reversible switching can be achieved at least in five cycles without hysteresis. This reversible self-assembly has potential to act as a photo-activable catalyst.

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Resolving the Hierarchy of Non-Covalent Interactions in Squaramide Bola-Amphiphile Self-Assembly, with an Odd Preference for Hydrophobicity

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Supramolecular self-assembly in aqueous media is fundamental to the formation of functional biomaterials; however, it remains difficult to predict because multiple non-covalent interactions act simultaneously, and hydrophobic effects often dominate, masking the contributions of other forces. Using a series of squaramide-based bola-amphiphiles with a systematically increasing number of squaramide units and a fixed internal alkyl spacer, we used water-miscible organic solvents as reference points to isolate the roles of hydrogen bonding and π - π stacking before returning to water as the system of interest. Isopropanol, a polar protic solvent, favours extended intermolecular hydrogen bonding, driving all analogues alike toward large, ordered, head-to-tail assemblies with a characteristic absorption feature at 330 nm. Acetonitrile, a polar aprotic solvent, does not solvate via hydrogen bonding to the same extent, and instead favours π - π stacking over hydrogen bonding. The series here first shows a deviation from linearity along the parity line of squaramide units. Even-numbered analogues continue to form head-to-tail assemblies, while for odd-numbered analogues, π -stacking completely overpowers extended hydrogen bonding, resulting in the loss of the 330 nm band. In water, both packing modes remain accessible, but which one will dominate depends on hydrophobicity, which strongly adds a further driving force on top of hydrogen bonding and π - π stacking, and it favours π -stacked, turn-stack-turn-like packing over the extended head-to-tail arrangement. But this hydrophobic effect does not vary evenly across the series: it is most pronounced for the odd-numbered analogues, and especially for the three-squaramide analogue, which predominantly forms short, turn-stack-turn-like fibers; at higher concentration, it can also access the head-to-tail state, but the turn-stack-turn packing remains dominant. This effect does not simply scale up with squaramide number; for the four-squaramide analogue, the trend loses its edge, as the increasing number of hydrogen-bonding units and the increasing hydrophobicity that come with each added squaramide unit in the molecular design counterbalance one another, leaving its behaviour intermediate and probably having a mixture of aggregates using both the two packing modes. The three-squaramide analogue thus stands out as the clearest case where hydrophobicity, rather than hydrogen bonding, dictates the assembly outcome, establishing squaramide unit parity as a key design parameter for directing self-assembled architecture in water.

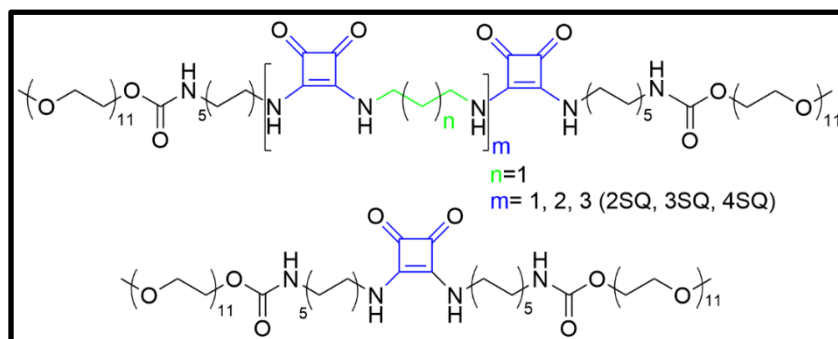


Figure1: Structures of the multi-SQ series (Top) and control molecule, 1SQ (bottom)



An Assembly-Driven Acyl Hydrazone Self-Replicator

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Life at its' simplest form only has a few characteristics. Great effort has been put in creating life-like molecule that can initiate some of these behaviors¹. Our system of disulfide self-replicators and other has demonstrated emergent properties such as forming proto-cells, metabolism, and evolution. However, combining them has limitation that lead to potential lost of function². This work aims to introduce complementary architectures based on acyl hydrazones, which are known to be orthogonal to disulfides³. Our objective is integrate multiple systems, using each specialization to achieve new behavior toward De-novo Life

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Beyond Acyl Adenylates: Tailored Phosphate Esters Drive Pathway-Dependent Peptide Assembly

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Phosphate esters and anhydrides are central to life, known for their unique combination of reactivity and stability, powering key biological processes. Acyl and phosphoryl transfer reactions in particular, underpin essential functions in metabolism, signaling and molecular construction. However, outside of biology, coupling of acyl phosphates with selective processes such as acyl and phosphoryl transfer remain challenging. Here, we explore the potential of amino acyl phosphate esters as structural intermediates in abiotic peptide assembly. By systematically varying the phosphate leaving group ethyl, phenyl, naphthyl, or dodecyl, while keeping the amino acid residue constant, we demonstrate how subtle structural differences dictate divergent supramolecular outcomes and guide distinct reaction pathways. Ethyl and phenyl substitution resulted in soluble phosphate esters while naphthyl and dodecyl formed compartments. Each amino acyl phosphate reacts with amino acid nucleophiles to yield an identical covalent product, yet their assemblies differ profoundly. The self-assemblies of the formed dipeptides depend on the followed pathway (Figure 1). This approach also enables selective acyl transfer reactions for peptide coupling tailored to the reactivity profiles of specific phosphate esters in competitive experiments. We also harnessed these amino acyl phosphate esters for phosphoryl transfer reactions using different phosphoryl agents such as adenosine monophosphate, orthophosphoric acid, and pyrophosphoric acid to investigate their influence on peptide oligomerization, owing to variations in reactivity.^{1,2}

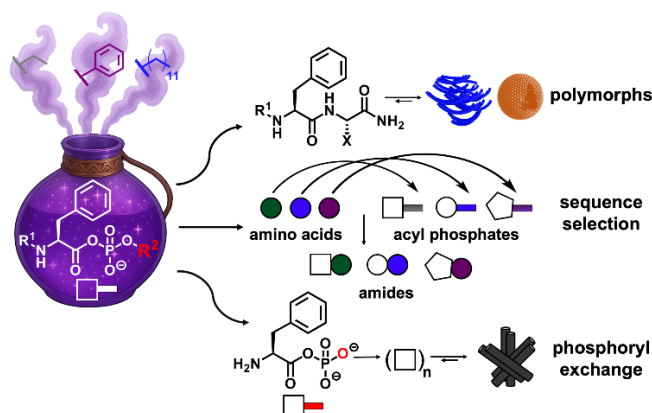


Figure 1. Tailored Phosphate Leaving Groups Direct Pathway-Dependent Self-Assembly.

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Light-Controlled Intracellular Peptide Assembly

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The ability to control supramolecular peptide assembly with high spatial and temporal precision offers exciting opportunities for engineering adaptive biomaterials and studying dynamic cellular processes. Light is a particularly attractive stimulus owing to its non-invasive nature and excellent spatiotemporal resolution, enabling precise regulation of molecular interactions in complex biological environments. Here, we present complementary strategies for light-controlled intracellular peptide assembly that combine molecular design with programmable supramolecular organization.

At the molecular level, light-responsive peptide building blocks were engineered to regulate peptide conformation and intermolecular interactions through photoactivation.^{1,2} By incorporating photoresponsive motifs into self-assembling peptides, light serves as an external trigger to initiate or modulate supramolecular organization, providing dynamic control over structural order and assembly pathways. This molecular toolbox enables reversible access² to distinct supramolecular states and highlights how subtle changes in peptide conformation can dictate the architecture of higher-order assemblies.

Building on these design principles, light-triggered peptide assembly was translated into living cells, where visible-light activation initiates the formation of intracellular nanostructures with high spatial and temporal precision.¹ The controlled emergence of peptide assemblies within the cellular environment demonstrates how external optical stimuli can direct the formation of functional supramolecular materials while minimizing off-target effects. Combining molecular-level control with intracellular assembly further enables investigation of the relationship between supramolecular structure, assembly kinetics, and cellular responses.

Together, these studies establish a versatile platform for programming peptide self-assembly through light-responsive molecular design. By integrating precise optical control with intracellular supramolecular engineering, this work provides new opportunities to investigate dynamic biological processes and develop responsive peptide-based materials. Beyond fundamental studies of self-assembly, light-controlled peptide systems hold considerable promise for applications in chemical biology, synthetic biomaterials, intracellular engineering, and targeted therapeutic strategies, where precise regulation of material formation in space and time is essential.

This poster will be presented together with Yong Ren.

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²J. Link, *et al.*, *Angewandte Chemie. International Edition*. **65**, e14781 (2026).





Intracellular Peptide Assemblies as Synthetic Regulators of T Cell Function

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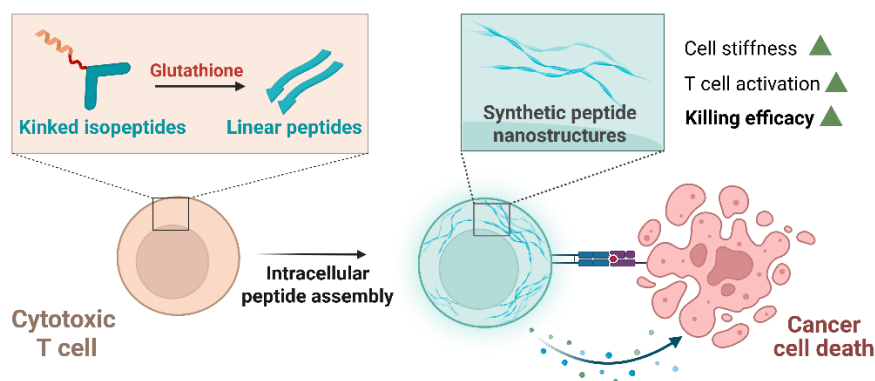
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Intracellular peptide assembly enables the bottom-up construction of synthetic architectures within living cells. To date, however, most intracellular assembly systems have been designed to disrupt cellular homeostasis and induce cell death. Here, we demonstrate that intracellular peptide assembly can instead be harnessed to enhance the function of therapeutically relevant immune cells.

We designed glutathione-responsive isopeptides that undergo reductive cleavage and rearrangement into linear self-assembling peptides within activated human cytotoxic T cells. The resulting peptide monomers assemble into synthetic intracellular nanostructures with dimensions comparable to natural cytoskeletal filaments. Correlative light and electron microscopy revealed extensive intracellular assemblies throughout the cytosol and perinuclear regions. Importantly, assembly formation occurred without compromising cell viability or subcellular integrity of the treated T cells.

Intracellular peptide assembly altered the mechanical phenotype of cytotoxic T cells, increasing cellular stiffness and reducing deformability. In parallel, we observed enhanced activation of MAPK and PI3K/Akt/mTOR signalling pathways together with transcriptional changes associated with metabolic fitness. These assembly-driven effects translated into biological function: T cells containing synthetic peptide nanostructures exhibited a ten-fold increase in cytotoxic potency against HER2-positive breast cancer cells in a co-culture model.

This work establishes a new role for intracellular peptide assembly. Rather than acting directly as disruptive synthetic assemblies, intracellular peptide nanostructures can function as active regulators of cellular behaviour, providing a supramolecular strategy for enhancing beneficial cell functions and opening new opportunities for peptide-based cell engineering.



Molecular architecture of bottlebrush polymers governs phase behaviour

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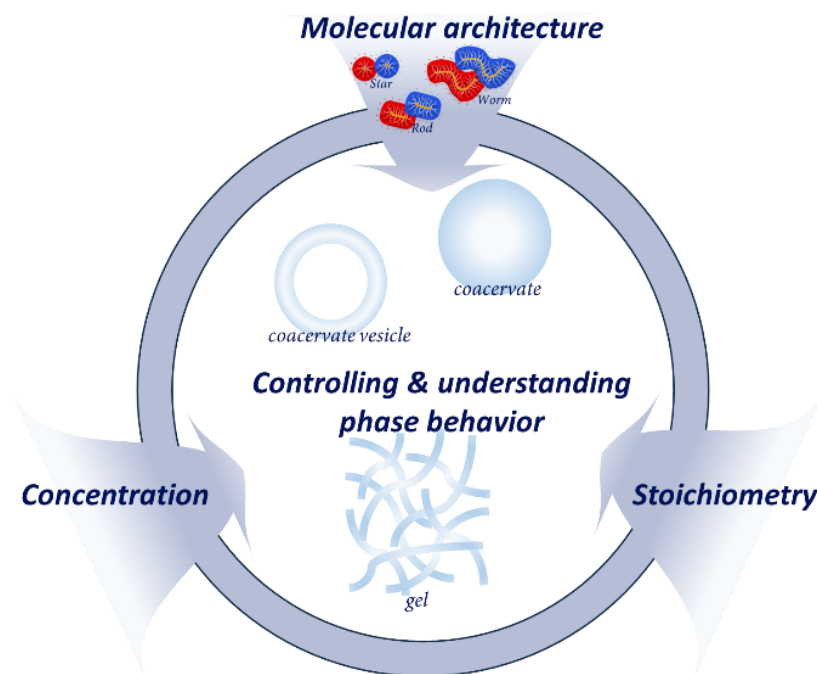
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Cells are extremely crowded, yet maintain precise spatial organization through compartments with distinct material states, including liquid condensates, viscoelastic networks, and membrane-bound organelles. This complex organization is essential for cellular functioning, and its disruption is linked to diseases, such as neurodegeneration, cancer and viral infection.¹ The variety in material states arises from chemically similar biomolecules, suggesting an important role of molecular geometry on its mesoscale assembly and subsequent material state.

To address this question, we have synthesized oppositely charged bottlebrush polymers (BBPs) with high grafting density, forming stretched and stiff macromolecules. By varying the backbone length, while keeping the side chains constant, BBPs are created with distinct molecular geometries (spherical, rod-like or worm-like). Using this versatile platform, we systematically investigate the effect of BBP architecture on its phase separation and material properties.

Remarkably, the BBP architecture determines the formation of coacervates, coacervate vesicles or gel-like networks. Not only morphology is tuned in this way, but also the dynamics of these assemblies are drastically changed. Notably, anisotropic rod-like BBPs form liquid vesicles, likely driven by directional stacking interactions and slow relaxation. These findings demonstrate that the geometry of the molecular building block can encode several biologically relevant material states, providing mechanistic insights into the role of biomolecular architecture in cellular organization.



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Dynamic Supramolecular Biofabrication Platform

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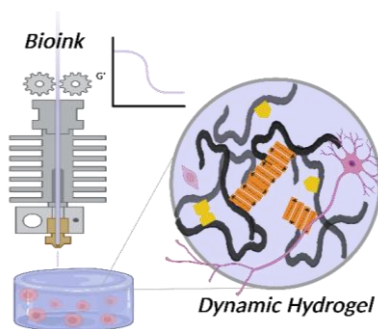
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Dynamic hydrogels represent a promising class of biomaterials for engineering extracellular matrix-mimetic environments with tunable mechanical and biological properties. Here, we present a bioinspired dynamic hydrogel that combines dynamic supramolecular interactions with a modified polysaccharide network to achieve enhanced self-healing, structural resilience, and printability. Short self-assembling peptides (SAPs) were engineered as stimuli-responsive (pH-responsive depsipeptide) variants and grafted onto modified polysaccharide backbones to create dynamic supramolecular biohybrid hydrogels with extracellular matrix-mimetic properties. By integrating peptide nanofibril (PNF)-forming SAPs as supramolecular gelators within biopolymer networks, we developed biomimetic hydrogels with rationally tunable mechanical, structural, and biological characteristics. The biohybrids were analysed regarding their chemical composition (e.g., nuclear magnetic resonance spectroscopy), mechanical (gelation, rheology), different printing method and biological properties (cytocompatibility, bioactivity, multiple cell types), and evaluated for different applications.

The resulting hydrogels exhibit rapid gelation, shear-thinning behavior, autonomous self-healing, and mechanical properties comparable to soft tissues, enabling excellent performance in both extrusion-based and drop-on-demand bioprinting while maintaining high construct fidelity. Comprehensive characterization, including nuclear magnetic resonance spectroscopy, rheological analysis, and biological evaluation, confirmed the successful incorporation of SAPs and the formation of dynamic supramolecular networks. In vitro studies demonstrated excellent cytocompatibility, sustained cell viability, and favorable cell-matrix interactions across multiple cell types, supporting cellular elongation and neuronal differentiation in 3D culture.

The combination of biopolymer-derived backbones with PNF-forming SAPs introduces the self-assembling and dynamic nature of peptide supramolecular interactions into biohybrid materials. These findings highlight the potential of SAP-based dynamic hydrogels as next-generation biofabrication platforms for tissue engineering and regenerative medicine.



Overview of the dynamic hydrogel biofabrication platform.



Acyl Transfer Drives Dynamic Reaction Droplets

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How chemical reactions become spatially organized and feed back to regulate chemistry is a central question in the design of life-like chemical systems. Dynamic phase-separated compartments^{1,2} offer a powerful route to address this challenge by concentrating molecules, creating distinct microenvironments, and coupling chemical turnover to material formation and dissolution. However, a key challenge remains: how can synthetic non-equilibrium compartments participate in feedback loops that regulate chemical reactions, rather than merely representing passive outputs of a reaction cycle?

Here, we demonstrate a “structured-fuel” strategy^{3,4} in which aminoacyl phosphate-driven acyl transfer generates transient peptide coacervates that actively shape their formation, composition, and lifetime. By selectively recruiting fuels, precursors, and transient products, these coacervates establish reciprocal feedback between chemical activation and phase separation. This reaction-phase separation coupling gives rise to collective behaviours inaccessible from the individual components alone: cross-activation of otherwise inefficient peptide precursors within a shared condensed phase, synchronization of apparent reaction kinetics across chemically distinct peptide systems, and dynamic reprogramming of molecular recruitment through reaction-driven changes in condensate composition. We further extend this concept to oil droplets that form a feedback loop with an acyl phosphate reaction network. Here, the droplet environment promotes ester hydrolysis, while the hydrolysis products reinforce droplet formation, creating an autocatalytic feedback loop. By controlling the assembly state in situ, the system can be switched over time between reaction-ON droplet states and reaction-OFF aggregation states.

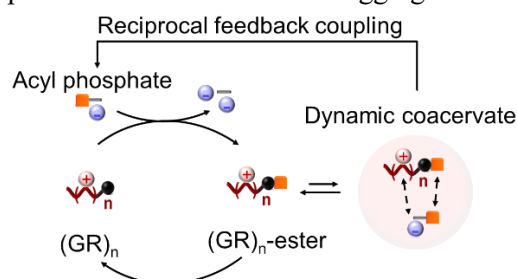


Fig.1 Acyl transfer drives transient peptide coacervates with reciprocal reaction–phase feedback

Together, these two systems demonstrate that non-equilibrium droplets can actively feed back into reaction networks, reshape reaction pathways, coordinate multicomponent chemistry, and encode temporal control through evolving phase states. This work provides a framework for designing reaction-active condensates and programmable life-like materials (Fig. 1).

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Molecular-Level Insights into Multi-Component Peptide Assembly by NMR

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Natural supramolecular systems are rarely composed of a single molecular component. Biological structures and functions instead emerge from the coordinated interactions of multiple molecules with different chemical identities, interaction motifs, and assembly preferences. Understanding how such components recognize one another, associate, and select specific assembly pathways is therefore essential for deciphering complex biological organization and for designing synthetic multicomponent materials.

Multi-component peptide systems provide a particularly versatile platform for addressing these questions. Depending on sequence compatibility, solvent environment, and preparation pathway, different peptide components may cooperatively co-assemble, self-sort, or interfere with each other's assembly.¹ However, it remains unclear what determines which of these outcomes is selected.

To address this question, nuclear magnetic resonance (NMR) spectroscopy is used as a central analytical platform to follow two peptides with distinct assembly preferences from soluble and pre-associated states to supramolecular assemblies. Because peptide interactions are encoded by amino-acid sequence, identifying which residues and functional groups respond during association is essential for understanding how sequence directs assembly.² Through residue-specific analyses, the molecular sites that participate in or respond to peptide-peptide interactions can be pinpointed, while complementary analytical methods provide additional structural and thermodynamic information.

The results show that weak, residue-specific peptide interactions can occur before aqueous assembly. Through-space NMR correlations revealed close contacts between specific side-chain regions, while selected residues near charged groups showed pronounced sensitivity to the local environment. Upon transfer to aqueous conditions, the presence of a second peptide caused stronger line broadening and signal intensity loss, indicating reduced molecular mobility and a larger fraction of peptide entering NMR-invisible assembled states. Importantly, premixing the peptides before assembly and adding one peptide to pre-assembled structures produced distinct signal intensities and temperature-dependent responses, showing that the timing of the first molecular encounter influences the resulting assembly state.

Together, these findings show that multi-component peptide assembly cannot be explained solely by the final structures formed. Instead, early molecular recognition, solvent-sensitive pre-association, and pathway dependence all contribute to the resulting assembly state. More broadly, this work demonstrates how NMR can identify the molecular sites involved in peptide association and connect early interactions with subsequent supramolecular assembly.

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² K. Kaygisiz *et al.*, *Nature Reviews Materials* **10**, 449 (2025)



Reaction-encoded structural plasticity in peptide nanofibrils for adaptive supramolecular catalysis

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Peptide-based supramolecular assemblies offer a versatile platform for mimicking enzyme-like catalysis, yet their structures are typically static and lack the adaptive behavior found in natural enzymes. Here, we introduce a native chemical ligation-inspired transthioesterification strategy that imparts structural plasticity to catalytic peptide assemblies. Naphthyl thioester donors transfer hydrophobic groups to cysteine-containing, Lys- or His-rich acceptor peptides, generating mono- and di-substituted products with distinct self-assembly behavior and nanostructures.

By varying the donor-to-acceptor ratio, the ligation reaction produces nanofiber ensembles with tunable retro-aldolase- and hydrolase-like activities. Cryogenic electron microscopy reveals that dynamic ligation governs fiber morphology and internal order while enabling access to structural states that cannot be achieved through direct assembly of pre-synthesized ligation products. Comparison of in situ ligation, direct assembly, and iterative addition protocols further demonstrates that gradual, reaction-driven formation of ligation products is essential for generating highly ordered assemblies with enhanced catalytic performance. These findings establish reaction-driven structural plasticity as a powerful strategy for programming the structure and function of supramolecular peptide catalysts, bringing synthetic catalytic assemblies closer to the adaptive behavior of natural enzymes.

This poster will be presented together with Maximilian Schuler.

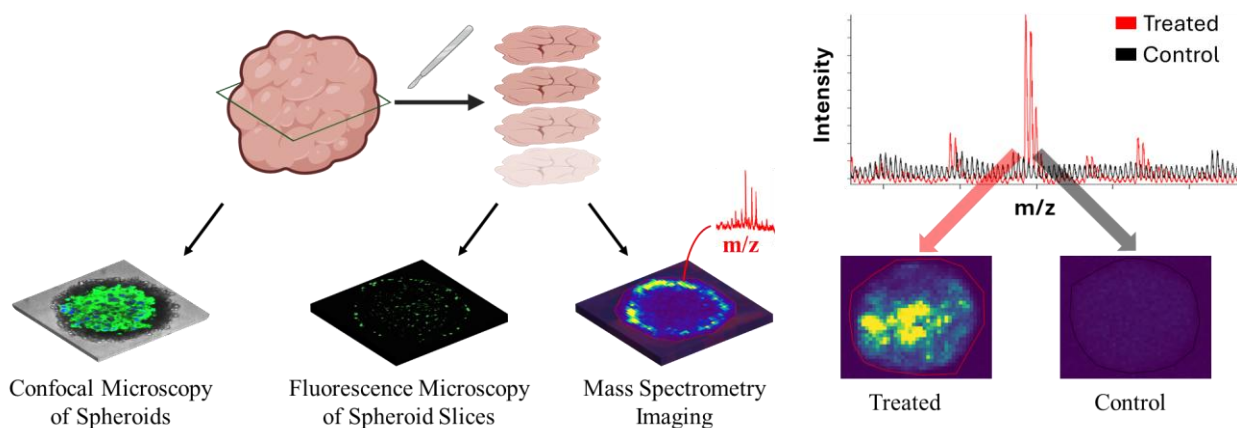


Mass Spectrometry for Characterizing Bioresponsive Molecules in Biological Environments

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The rational design of bioresponsive molecules enables the spatiotemporal control over the molecular activation, which can be utilized for therapeutic applications as well as for biomaterials or biosensors. These molecules react to specific biological conditions, such as changes in pH, enzymes or the redox environment, thereby triggering the conversion from an inactive precursor into its active form.^{1,2} Understanding the activation process in a complex biological environment or biologically relevant model systems is essential for the rational design of next-generation bioresponsive molecules. Current methods to study these processes often rely on labelling the bioresponsive precursors with fluorophores, allowing for high spatiotemporal resolution. However, incorporation of a fluorophore increases synthetic complexity and may alter the physicochemical properties, biodistribution, or activation behavior of the bioresponsive molecule. Mass spectrometry (MS) provides a label-free approach for characterizing homogenized cell lysates by detecting bioresponsive precursor molecules, their active forms, as well as intermediates and potential side products. While conventional MS methods lack spatial information, mass spectrometry imaging (MSI) combines molecular specificity and spatial resolution, thereby enabling the visualization of activation pathways and the detection of drugs, metabolites, biomolecules, and degradation products directly from 3D tumor spheroids.^{3,4} Thus, MSI complements conventional methods, providing spatially resolved insights into the activation, distribution and stability of bioresponsive molecules in complex biological environments.⁵



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Multicomponent Supramolecular Polymers for the Design of Fully Synthetic Antitumor Vaccines

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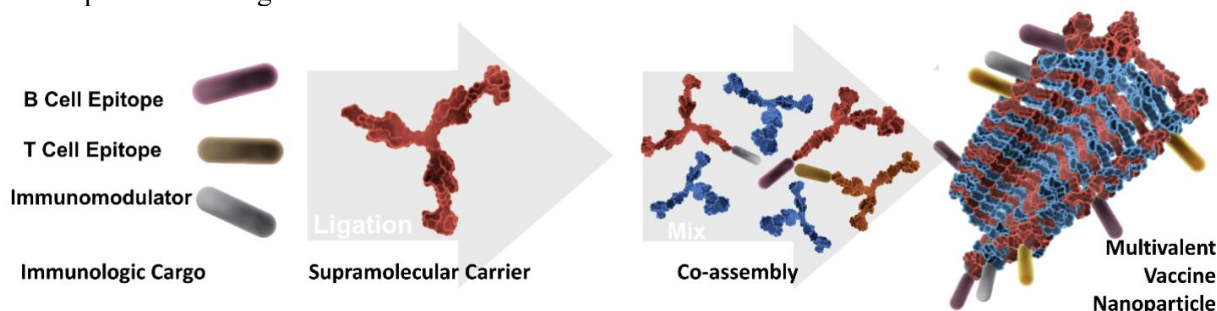
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Synthetic vaccines commonly rely on the conjugation of antigens to immunogenic carrier proteins of biological origin to enhance immunogenicity. Although these bioconjugate vaccines have proven highly effective, their biological complexity introduces challenges related to batch-to-batch variability, limited structural characterization, and inconsistent antigen loading. Such heterogeneity can compromise manufacturing reproducibility and ultimately affect vaccine efficacy, underscoring the need for alternative platforms that enable precise molecular control while maintaining robust immune activation.

Supramolecular polymers have emerged as a versatile class of materials that combine structural order with dynamic, reversible intermolecular interactions. Their modular design enables the construction of adaptive assemblies that mimic key features of biological systems, including responsiveness to external stimuli and environmental adaptability. Among these, peptide-based supramolecular materials are particularly attractive for biomedical applications owing to their intrinsic biocompatibility, synthetic accessibility, and the broad range of physicochemical properties afforded by amino acid building blocks. These characteristics provide unique opportunities to engineer well-defined, multifunctional nanostructures with precisely controlled composition.

The modularity of supramolecular polymers makes them especially well suited for vaccine design, where the controlled presentation of multiple functional components—including antigens, targeting ligands, and immunostimulatory molecules—is essential for eliciting effective immune responses. A universal supramolecular polymer platform capable of incorporating these functionalities through simple co-assembly combines the immunological advantages of protein conjugate vaccines with the synthetic precision, compositional control, and stability of small-molecule-based systems. This approach provides a versatile strategy for the multivalent presentation of tumor-associated antigens and facilitate the development of next-generation antitumor vaccines.





Supramolecular polymer scaffolds for reversible bioconjugation using curcubit[8]uril based dynamic host-guest-chemistry

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Biological systems often rely on switch-like all-or-none responses which are mostly either feedback loops or based on molecular cooperativity. Understanding the underlying mechanisms of RNA splicing events through RNA binding proteins (RBPs) would support the prevention of diseases and enable the design of new switches for numerous biological applications. Our aim is to investigate the supramolecular (bio)conjugation of synthetic host-guest systems in aqueous environment to modulate RNA-protein complexation. Guest components are represented by polymer-peptide conjugates functionalized with phenylalanine-glycine-glycine (FGG) and pentafluorophenylalanine-glycine-glycine (F₅FGG) recognition motifs linked to a polyethylene glycol backbone, whereas curcubit[8]uril serves as host species.¹ The resulting systems show tunable thermodynamic and kinetic properties.² This presentation focuses on investigating the impact of F₅FGG-binding in homo- and hetero-complementary complexes as well as the resulting network formation. Elucidating the underlying exchange dynamics is essential for assessing the impact of multivalent host-guest complexation and RNA-protein binding. To probe the formation of supramolecular complexes, the fluorescent protein mCitrine (mCFP) is incorporated into the host-guest network. Thereby a framework for further studies on reversible and suitable RNA binding motifs is established. Our approach to investigate supramolecular assemblies and quantify diffusion kinetics involves a combination of complementary methodologies such as shear rheology and fluorescence correlation spectroscopy (FCS).

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Biomimetic Peptide Coacervates: Towards Functional Artificial Organelles

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The **Biocondensates Group** investigates the design and function of **short peptide-based coacervates** as minimalistic yet powerful models for biomolecular condensation and intracellular organization. Our research focuses on understanding and harnessing **liquid–liquid phase separation (LLPS)** to create dynamic, tunable systems with programmable properties. We study how sequence-defined short peptides spontaneously assemble into **coacervate droplets**, how these assemblies undergo **stimuli-responsive phase transitions**—for example, switching between soluble, coacervate, and fibrous states in response to pH—and how these transitions can be controlled at the molecular level.

A key aspect of our work is the **covalent integration of functional chemical groups** (e.g., photocatalytic or redox-active moieties) to impart **intrinsic reactivity and responsiveness** to peptide condensates. Furthermore, we explore strategies for **organelle-specific targeting** using functionalized peptide coacervates as **drug-delivery vehicles** capable of selective localization and controlled release. Together, these efforts aim to advance the fundamental understanding and technological potential of peptide-based biomolecular condensates.





Chirality Directs the Formation, Structure, and Function of Peptide Coacervates

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Chirality governs molecular recognition and assembly, yet its influence on condensed soft phases remains unknown. We show that stereochemical configuration directly regulates phase separation and internal organization in small-molecule coacervates formed by diphenylalanine derivatives. Homochiral peptides undergo coacervation at lower concentrations to form compact, ordered droplets stabilized by hydrogen bonding and π - π stacking, whereas heterochiral combinations yield more dynamic, permeable condensates. These differences extend to tripeptide systems, revealing a stereochemical control axis that defines droplet order, stability, and molecular selectivity. Thus, these results establish stereochemistry as a regulator of packing geometry and mesoscale organization in condensed phases, providing a general physical principle by which chirality programs order, fluidity, and molecular selectivity in soft matter.

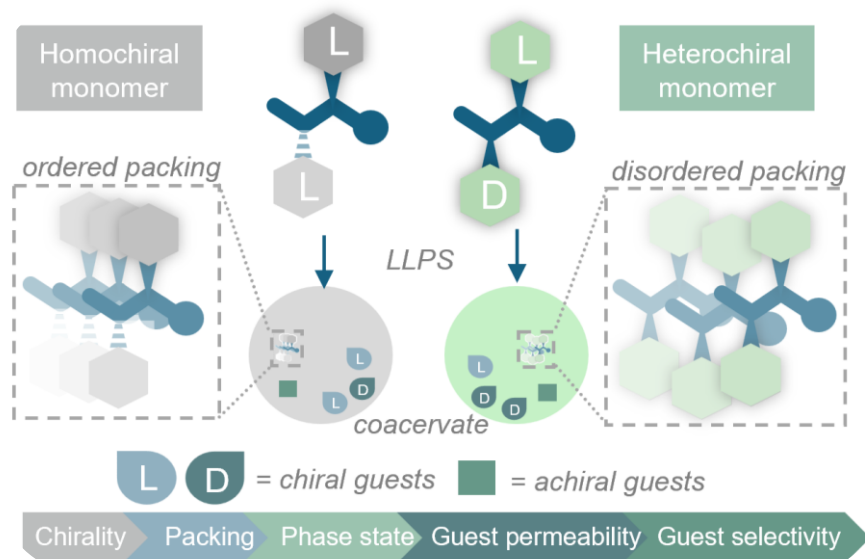


Figure 1. Chirality directs peptide coacervate formation by regulating molecular packing. Homochiral assemblies exhibit ordered packing, while heterochiral assemblies display disordered packing, leading to differences in condensate properties, guest permeability, and molecular selectivity.

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Pathway Complexity in Supramolecular Polymerisation of Multidomain Peptide Amphiphiles

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Precise control over the special and temporal aspects of peptide self-assembly is fundamental to developing adaptive supramolecular materials that emulate the dynamic behavior of biological systems. Although peptide-based assemblies show great potential for applications ranging from biomaterials to synthetic protocells, achieving programmable control over formation and growth under non-equilibrium conditions remains a significant challenge. Here, we present a light-responsive strategy that couples enzymatic reaction networks with peptide self-assembly to direct supramolecular structure formation with spatiotemporal precision.

Our approach uses light-induced glucose release as an external trigger to initiate an enzymatic cascade that generates localized proton release. The resulting dynamic pH change activates the self-assembly of pH-responsive peptide building blocks, enabling temporal regulation of supramolecular organization without direct chemical intervention. By integrating a lipid bilayer interface into the system, nucleation is spatially confined to membrane surfaces, allowing peptide assembly to be selectively initiated at biologically relevant interfaces. This interfacial control provides a means to decouple nucleation from bulk assembly, resulting in localized growth of supramolecular peptide structures.

The combination of photochemical activation, enzyme-mediated proton generation, and membrane-directed nucleation establishes a versatile platform for regulating peptide self-assembly in dynamic environments.





Characterisation of Supramolecular Copolymers across Multiple Length-scales

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Multicomponent supramolecular copolymers have emerged as a versatile class of biomaterials for applications ranging from vaccine delivery to regenerative medicine. Their modular architecture enables the incorporation of multiple functional building blocks into a single assembly, providing a highly adaptable platform for engineering materials with tailored biological and physicochemical properties. In particular, peptide amphiphiles have attracted considerable interest because they spontaneously self-assemble into well-defined one-dimensional nanostructures under physiological conditions while offering excellent biocompatibility and synthetic flexibility.

A defining characteristic of supramolecular peptide assemblies is their dynamic nature, arising from the reversible, non-covalent interactions that govern their formation. The continuous exchange of monomeric building blocks enables these materials to adapt to their environment, heal structural defects, and respond to external stimuli. Understanding the molecular exchange dynamics within these assemblies is therefore essential for establishing structure–property relationships and for the rational design of supramolecular biomaterials with predictable functions.

A comprehensive characterization of supramolecular dynamics requires analytical approaches that probe molecular exchange across multiple length scales. Fluorescence-based methods, such as Förster resonance energy transfer (FRET), enable direct visualization of monomer exchange, while label-free techniques including hydrogen/deuterium exchange mass spectrometry (HDX-MS) provide complementary insights into molecular dynamics. In parallel, advanced imaging methods offer detailed information on nanostructure morphology and co-assembly, whereas rheological characterization links molecular organization to the macroscopic mechanical properties of the resulting hydrogels. Together, these complementary techniques provide a powerful framework for understanding the dynamic behavior of supramolecular peptide amphiphile assemblies and guiding the development of functional biomaterials for biomedical applications.





Gelation in Biomedical Applications – The Functional Roles of Self-Assembling Peptides in Re-programming Biopolymers

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The development of advanced biomaterials was followed by a growing demand for hydrogels that mimic the properties of soft tissues to promote regeneration and allow minimally invasive treatment. Existing supramolecular systems are often limited by poor mechanical robustness, while covalent systems feature permanently cross-linked networks that hinder their ability to replicate the dynamic cell-matrix interactions in native tissues. Therefore, these materials are often unable to support important biological processes including cell migration, matrix remodelling and adaptive tissue regeneration.

Nanofibril-forming self-assembling peptides (SAPs) show great potential as extracellular-matrix-like scaffolds, providing dynamic cell environments mimicking those found in native tissues. Their ability to spontaneously organize into well-defined architectures through non-covalent interactions enables the formation of dynamic materials with tunable mechanical properties. Furthermore, conceptualizing a sequence enables precise control over morphology and functionality.

The integration of SAPs with otherwise bioinert biopolymers, such as agarose, alginate, and hyaluronic acid, provides functionalization with bioactive motifs as well as structural stability to the system, resulting in 3D scaffold hydrogels with optimized mechanical, tunable physicochemical and advanced biochemical characteristics. As a result, tailorable and broadly tunable 3D soft materials with excellent mechanical properties, such as shear-thinning and autonomous recovery of supramolecular crosslinks, were obtained, offering sustainable alternatives to traditional, synthetic polymer-based hydrogels and presenting significant potential for tissue engineering, regenerative medicine, and other advanced biomedical applications.





Cucurbit[8]uril Couples Enzymatic and Supramolecular Reaction Networks for Peptide Isomerization and Recognition in Gain-of-Function Hydrogels

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Adaptive biological systems regulate molecular recognition by enzymatically converting inactive precursors into functional states. Replicating such gain-of-function behavior in synthetic supramolecular systems remains challenging because productive activation is frequently outcompeted by undesired deactivation pathways. Here, we present an enzyme-responsive depsipeptide switch^{1, 2} in which cucurbit[8]uril (CB[8]) functions as a supramolecular chaperone, transiently stabilizing a latent peptide precursor and promoting its productive enzymatic transformation. The branched depsipeptide initially forms a weak binary complex with CB[8], suppressing hydrolysis and intramolecular cyclization while increasing the likelihood of trypsin-mediated cleavage. Proteolytic cleavage, followed by spontaneous rearrangement, converts the precursor into a linear peptide that binds CB[8] with high affinity to form a homoternary complex, thereby driving a transition from binary to ternary supramolecular assembly.³ Time-resolved LC–MS, NMR spectroscopy, and isothermal titration calorimetry reveal the interplay between competing complexation and deactivation pathways and identify a tyrosine-containing depsipeptide that provides the optimal balance between hydrolytic stability and enzymatic responsiveness. Extending this strategy to hyaluronic acid conjugates enables enzyme-triggered supramolecular hydrogel reconfiguration through CB[8]-mediated intermolecular crosslinking, affording adaptive hydrogels with enhanced viscoelasticity and shear-thinning properties. This work establishes a chaperone-assisted approach for integrating enzymatic regulation with supramolecular molecular recognition, providing a versatile platform for programmable adaptive soft materials.

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Excretory-guided supramolecular assembly of a synthetic extracellular matrix

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The cellular interface is a critical nexus for therapeutic intervention, yet direct engineering of the pericellular space remains challenging due to the fragility of the plasma membrane and the dynamic complexity of the native extracellular matrix (ECM). Intracellular peptide self-assembly has emerged as a promising strategy to engineer both the extracellular microenvironment and cell behavior. However, the intracellular self-assembly pathways of peptides in living cells remain poorly understood, limiting the rational control of their biological functions.

Here, we combine sequence-programmed bio-responsive peptides with phasor fluorescence lifetime imaging (Phasor-FLIM), which has been well practiced in our group, to track intracellular dynamic self-assembly processes and investigate how distinct intracellular assembly pathways influence different biological outcomes.^{1,2}

A glutathione-sensitive peptide bearing slow self-assembly kinetics is delivered intracellularly via TAT-mediated endocytosis and activated by reductive cleavage. This delayed assembly promotes trafficking into secretory vesicles, enabling vesicle-mediated excretion and extracellular fibril formation. The resulting synthetic extracellular matrix (syn-ECM) integrates seamlessly with the native ECM and presents orthogonal handles for chemical modification via click chemistry. High-density syn-ECM formation inhibits angiogenic signaling and suppresses cancer cell proliferation.

To further explore how intracellular assembly pathways influence biological functions, sequence-programmed bio-responsive peptides with distinct molecular architectures were designed to generate different intracellular assembly dynamics. These programmed assembly pathways finally lead to diverse biological outcomes.

Together, these studies demonstrate that programming intracellular peptide self-assembly provides a versatile strategy for engineering both extracellular matrices and cell behaviors, offering new opportunities for biomaterials, therapeutic intervention, and mechanistic studies of cell–material interactions.

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Abstract: Expanding the Functional Scope of NVOC Photocages for Light-Controlled Peptide Self-Assembly

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Stimulus responsive peptide materials are an interesting class of materials due to their capability to undergo chemical transformation upon exposure to an external stimulus. Photocages are especially interesting as light yields spatial and temporal control for chemical transformations with the potential of releasing proassembling peptides¹ and manipulating supramolecular structures². Building on the findings of the photolytic redox activity of the Nvoc photocage³ the photolytic oxidative conversion of hydroxylamine containing peptide assemblies to nitroxide containing peptide assemblies has been realized. Furthermore, the Nvoc scaffold was engineered into a bifunctional photocage platform that enables the incorporation of an additional stimulus-responsive trigger, providing a strategy for sequential control over peptide self-assembly.⁴

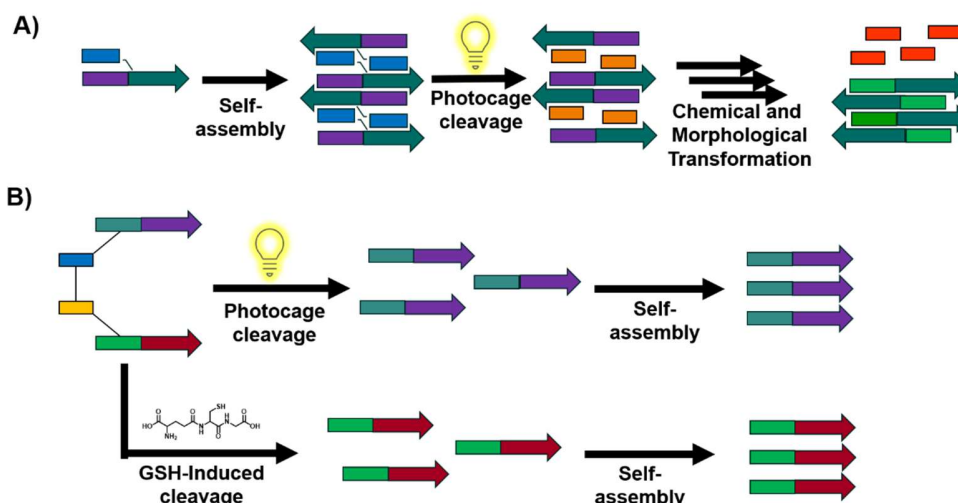


Figure 1: A) Schematic representation of the UV-light-induced oxidation of peptide assemblies. Photolysis of the NVOC photocage generates a nitroso species that converts hydroxylamine into nitroxide, accompanied by formation of the amine cage by-product. **B)** Schematic representation of a bifunctional NVOC photocage enabling orthogonal control over peptide self-assembly. Light-induced photocleavage and glutathione-mediated disulfide reduction independently release two pro-assembling isopeptides, triggering self-assembly of the respective peptide building blocks.

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Poster will be presented together with Patrick Kral.



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Programming Cellular Function through Dynamic Supramolecular Assemblies

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Cell-based immunotherapies have transformed cancer treatment, yet their clinical efficacy depends not only on the cytotoxic activity of immune cells but also on their long-term metabolic fitness and homeostatic regulation. Supramolecular peptide assemblies offer a promising strategy to engineer cellular functions; however, existing intracellular assembly systems often disrupt cellular homeostasis and induce cytotoxicity, limiting their therapeutic potential.

Here, we first developed glutathione-responsive isopeptides that selectively generate self-assembling peptides in activated human cytotoxic T cells without compromising cell viability¹. Following glutathione-triggered cleavage and molecular rearrangement, the peptides assemble into intracellular nanofibrils with dimensions comparable to endogenous cytoskeletal filaments. Correlative light and electron microscopy revealed increased cellular stiffness and enhanced phosphorylation of key signalling proteins, while transcriptomic analysis demonstrated upregulation of metabolic and stress-response pathways associated with improved cellular fitness. Consequently, engineered T cells exhibited enhanced cytotoxicity in a bispecific engager-based breast cancer model.

While these findings establish intracellular peptide self-assembly as a strategy to potentiate T-cell function, durable cellular immunotherapy also requires adaptive mechanisms to maintain homeostasis and prevent dysfunction. To this end, we further engineered a genetic circuit that enables living bacterial cells to dynamically respond to synthetic nanoassemblies through bidirectional coupling between supramolecular transformations and genetic regulation². A photosensitizer–peptide conjugate undergoes reversible redox cycling between methionine and methionine sulfoxide, driving interconversion between nanofibers and nanoparticles. Upon photo-oxidation, nanoparticles are internalized by engineered bacteria, where oxidative stress activates methionine sulfoxide reductase expression. Intracellular enzymatic reduction converts the nanoparticles back into nanofibers, which are subsequently expelled, establishing programmable influx–efflux cycles that restore redox and energy homeostasis.

Together, these studies demonstrate that integrating dynamic supramolecular assemblies with cellular regulatory networks enables both functional enhancement and adaptive homeostatic control. This work establishes a foundation for autonomous, self-regulating cellular immunotherapies with improved efficacy, persistence, and long-term safety.

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Deposition of neuro-supportive self-assembling peptides by zone casting for bio-electronic applications

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The self-assembly of peptides, although an ancient and naturally occurring process in biological systems, has only been explored by materials science over the past few decades. Peptides typically undergo self-assembly into stable β -sheet secondary structures, forming amyloid-like architectures that are observed microscopically and macroscopically as fibrillar networks. The combination of the inherent biocompatibility and low toxicity of peptides¹, arising from their chemical structure, with their ability to form fibrous assemblies upon self-assembly provides a promising platform for the fabrication of novel biomaterials. Such materials are particularly attractive for biological applications, including cell culture, where electrically responsive cells, such as neurons, could be cultured in an organized manner with properties desirable for bioelectronic devices.

Several factors promote fibril formation and stabilize the peptide secondary structure, including pH, temperature, peptide concentration, ionic strength, and amino acid sequence. These parameters influence intermolecular interactions such as hydrogen bonding, electrostatic interactions, and π - π stacking². From a materials science perspective, many of these parameters can be precisely controlled during thin-film fabrication. For example, temperature can be readily adjusted in zone-casting, a meniscus-guided coating (MGC) technique capable of producing highly homogeneous polycrystalline thin films. Likewise, peptide concentration, pH, and chemical structure can be systematically tailored to complement the processing conditions during zone casting, thereby recreating the physicochemical environment required to induce peptide self-assembly.

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Multicomponent Supramolecular Hydrogels for Drug Delivery and Cell Culture

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Introduction: Low molecular weight gelators (LMWGs) can self-assemble through non-covalent interactions to form supramolecular hydrogels with potential applications in drug delivery and cell culture¹. However, single-component systems are often limited by poor mechanical strength, low stability, and sensitivity to environmental conditions, restricting their use in biologically relevant media². This study explores the development of multicomponent hydrogels by combining LMWGs with high molecular weight gelators (HMWGs), including alginate, hydroxypropyl methylcellulose (HPMC), and Pluronic F127. The aim is to enhance structural integrity, tunability, and functionality.

Materials and method: A series of sugar-based and Fmoc-functionalised LMWGs were synthesised and characterised using NMR, mass spectrometry, XRD, SEM, and FT-IR. Hydrogel formation was systematically screened across a wide range of compositions, generating over 170 formulations. Gelation was assessed based on self-supporting behaviour, optical clarity, and reproducibility. Thermal stability was evaluated using $T_{\text{gel-sol}}$ analysis, and selected hydrogels were tested for long-term stability in biologically relevant media, including DMEM, RPMI, and PBS.

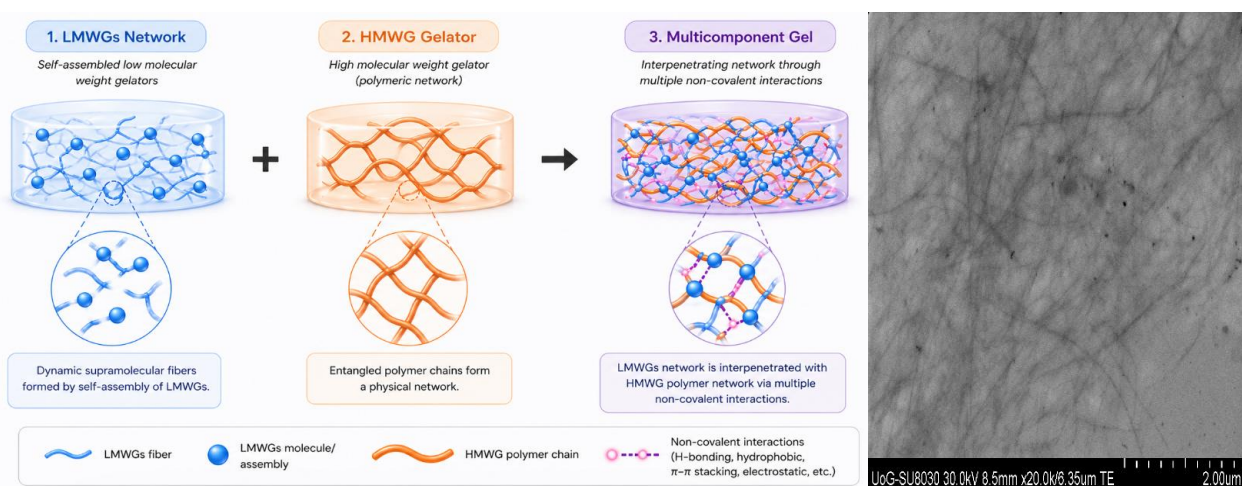


Figure 1. Schematic illustration of multicomponent hydrogel formation and a representative TEM image (right) for Indomethacin in F127 pluronics showing the interconnected fibrous architecture of the resulting multicomponent hydrogel.

Results: Fifteen multicomponent hydrogels were identified as optimal candidates, demonstrating consistent gelation and enhanced stability under physiological conditions. Transmission electron microscopy (TEM) confirmed the formation of interconnected fibrous networks, supporting the successful integration of LMWG self-assembly with HMWG polymer matrices.

Conclusion: These results demonstrate that multicomponent design effectively overcomes the limitations of single-component supramolecular gels, producing robust and functional materials suitable for biomedical applications such as controlled drug delivery and three-dimensional cell culture systems.

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Single Amino Acid and Minimalistic Peptide Self-Assembly as a Platform for Functional Soft Materials

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Abstract: Nature employs molecular self-assembly to create complex functional systems from simple building blocks.¹ Inspired by this principle, we explore how amino acid and minimalistic peptide derivatives can be engineered into multifunctional supramolecular materials. The strategic introduction of two Fmoc groups into the α - and ϵ -amino positions of lysine in the dipeptide Fmoc-Lys(Fmoc)-Phe significantly enhances aromatic interactions and hydrophobicity, yielding a supragelator with a critical gelation concentration (0.05% w/v).² The resulting hydrogel exhibits remarkable self-sustaining and self-healing behavior, driven by dynamic supramolecular interactions within its nanofibrous networks. Nanoengineering these assemblies with edge-functionalized graphene oxide yields conductive soft matter with enhanced mechanical stability and efficient charge-transport properties, expanding their potential for sensing and bioelectronic applications.² In parallel, the single amino acid derivative (Fmoc-Trp) provides a minimalistic platform for investigating the emergence of catalytic function through molecular self-assembly.³ The confined, highly organized microenvironment of the nanofibrous matrix promotes enzyme-like catalytic activity, and the integration of graphene-based nanomaterials further augments catalytic performance.³ Fmoc-Trp gel also serves as a versatile nanoreactor for the in-situ generation and stabilization of metallic nanoparticles without external reducing or capping agents, yielding hybrid materials with diverse catalytic functions, including peroxidase-like activity, catalytic degradation of pollutants. To enhance processability and practical utility, the supramolecular hydrogels were engineered into reusable core-shell bead architectures that integrate synthetic and biomimetic catalysis within a single platform. The nanoparticle-loaded bead systems facilitate efficient C-C bond-forming transformations under mild conditions, including challenging reactions involving sulfur-containing substrates, while exhibiting remarkable resistance to deactivation by Lewis basic amines and excellent recyclability over multiple cycles. Collectively, these findings underscore the ability of amino acid and minimalistic peptide self-assembly to translate molecular design into emergent material functions.

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The Cross-scale Potential of Self-Assembling Peptides – Programming Molecular Information for Assembly to Nanofibril Architectures and Soft Matter Functions

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Molecular information gives rise to functional supramolecular assemblies across length scales in nature. Inspired by this programmability of cross-scale structural complexity of biological soft materials, self-assembling peptides (SAPs) were molecularly programmed in their supramolecular organisation via establishment of discrete interaction motifs. This anchors the hierarchically orchestrated assembly into peptide nanofibrils (PNFs) with complex precision architectures such as multichannel nanofibrils in the molecular identity and can even transcend from the molecular level into the macroscopic regime, where SAPs can introduce reversible cross-links as PNF gelators to create soft materials and extracellular-matrix-like scaffolds. This strategy offers a promising approach to dynamic cell environments similar to those found in nature and creates functional soft materials that overcome limitations that current systems frequently exhibit the material scale, such as non-balanced level of physical crosslinking yielding materials with insufficient mechanical profiles or static crosslinking, that is opposed to native dynamic cell-matrix interactions, enabling cross-scale innovation in biofabrication and -medicine. Furthermore, the combination of biopolymer-derived backbones with such SAP gelators combines their programmability of supramolecular dynamic interactions and multifaceted structure formation with mechanical stability offered by the backbone to enable new functions in rationally tailorable and broadly tunable 3D soft materials as sustainable alternatives to classical, synthetic polymer-based hydrogels. In the presented systems, the bio-inspired interactions give rise to excellent mechanical and biochemical properties, such as shear-thinning and autonomous recovery of supramolecular crosslinks as well as cytocompatibility with multiple cell-types. As important prerequisite, these features enable the development of biopolymer conjugates, so-called biohybrids, as bioinks for next-generation 3D bioprinting for different printing approaches. The necessity for functional 3D soft materials that combine scalable molecular precision, reproducibility, biocompatibility, and advanced and tailorable mechanical properties has grown steadily. Overall, the presented SAPs and PNF systems give rise to functional soft materials and act as platforms opening various application scenarios based on the cross-scale potential of self-assembling peptides as precision molecules.

Peptide-Inspired Modular Self-Assembly of Carbonic Anhydrase on Cellulose Interfaces for Direct Air Capture of CO₂

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The continuous rise in atmospheric CO₂ levels is a key contributor to global climate change, driving the need for advanced functional materials capable of efficient carbon capture. Peptide self-assembly principles offer a framework for constructing hierarchical, functional biomaterials through modular, non-covalent organization. Therefore, we worked on a hybrid self-assembling biocatalytic system for direct air capture (DAC) of CO₂ using engineered enzyme–cellulose interfaces. Carbonic anhydrase (CA), a highly efficient zinc metalloenzyme, catalyzes rapid CO₂ hydration, however, its practical deployment depends on stable immobilization within structured and recyclable material platforms. To achieve this, we designed a recombinant fusion protein composed of the cellulose-binding module CBM3a (from *Clostridium thermocellum* CipA), green fluorescent protein (GFP) as a structural tracer and thermostable carbonic anhydrase from *Sulfurihydrogenibium azorense* (SazCA). This modular architecture enables spontaneous organization on cellulose substrates, mimicking peptide-driven supramolecular assembly through affinity-guided molecular recognition.

The fusion protein was expressed recombinantly and confirmed by SDS-PAGE (~75 kDa). Upon incubation with cellulose cheesecloth, the construct self-assembled into a stable functional layer via CBM-mediated binding. GFP fluorescence confirmed uniform surface distribution and successful nanoscale organization of the fusion proteins on the cellulose matrix.

The immobilized enzyme retained high catalytic efficiency, maintaining >80% activity after 10 days, while free enzyme lost over 50% activity. Reusability tests showed ~50% residual activity after 10 catalytic cycles, demonstrating strong operational stability.

This study highlighted how peptide-inspired modular assembly concepts can be extended to enzyme–biomaterial engineering, enabling the formation of self-organized, functional cellulose-based catalytic interfaces for sustainable CO₂ capture applications.



Metabolite-Driven Engineering of Dynamic Tumor Microenvironments Across Multiple Length Scales

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The extracellular matrix (ECM) and the pericellular interface provide essential biochemical and mechanical cues that regulate cellular behavior and integrate adhesion, migration, and metabolic signaling pathways.¹ In tumor microenvironments (TMEs), altered cancer cell metabolism strongly influences these reciprocal interactions, offering opportunities to develop dynamic biomaterials that respond directly to endogenous cellular signals.² Here, we present two complementary strategies that exploit tumor-derived lactate as a metabolic trigger for engineering functional extracellular environments.

A chemically defined, self-assembling peptide (SAP) platform was developed to generate modular extracellular nanofiber scaffolds directly on living cancer cell surfaces without genetic modification. Screening pyrene-capped amphiphilic peptides differing by a single N-terminal amino acid identified Py-IH as the unique variant capable of forming stable fibrillar structures on A549 lung cancer cells while maintaining 94% cell viability. The Py-IH scaffold enabled non-covalent recruitment of structural and enzymatically active proteins, including lactate oxidase (LOx), achieving up to 40% immobilization efficiency while preserving catalytic activity. Localized lactate oxidation by scaffold-bound LOx generated hydrogen peroxide at the cell surface, inducing hallmarks of regulated cell death, including nuclear condensation, mitochondrial fragmentation, and membrane disruption. Substitution of isoleucine by valine or phenylalanine abolished cell-surface assembly despite comparable fiber formation in solution, demonstrating that subtle changes in interfacial hydrophobicity regulate membrane anchoring.^{3,4} Furthermore, co-assembly with an azide-functionalized Py-IH analogue enabled bioorthogonal conjugation of small-molecule cargo without affecting nanofiber morphology.

In parallel, a metabolite-responsive hydrogel system based on tyramine-functionalized alginate (Alg-TA) was developed to enable cell-instructed extracellular matrix formation. Alg-TA remains soluble until tumor-derived lactate is converted by LOx into hydrogen peroxide, which drives horseradish peroxidase-mediated covalent crosslinking of phenol groups. This mechanism enables rapid hydrogel formation within minutes with tunable mechanical properties ranging from 10 Pa to 5 kPa. In tumor spheroid models, including patient-derived glioblastoma spheroids, endogenous lactate production generated spatially confined gelation zones extending up to 1 mm from the tumor surface. Nanoindentation and fluorescence correlation spectroscopy revealed radial gradients in matrix stiffness and polymer density, while proteomic profiling indicated altered signaling pathways associated with proliferation, migration, and matrix remodeling.

Together, these approaches demonstrate how endogenous tumor metabolism can be harnessed as an instructive signal to drive extracellular material assembly across different length scales. By translating cellular metabolic activity into engineered biochemical and mechanical cues, these platforms provide versatile tools for investigating cell–matrix reciprocity and designing adaptive biomaterials for tumor microenvironment engineering.

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