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FROM DYNAMIC STRUCTURES TO FUNCTIONAL MATERIALS

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 viability[1]. 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 regulation [2]. 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.

References

1. S. Chagri *et al.* *Nature Chemical Biology.* Under Revision.
2. J. Xing, X. Zheng *et al*. *Nature Chemical Biology.* (2026).