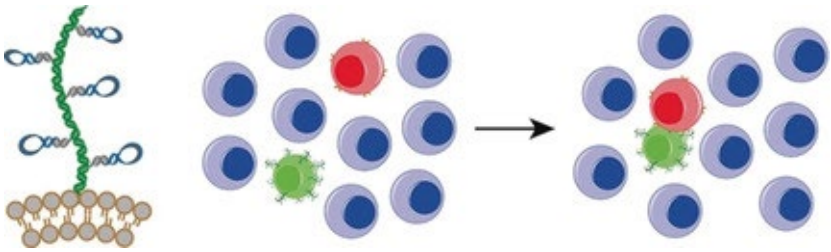
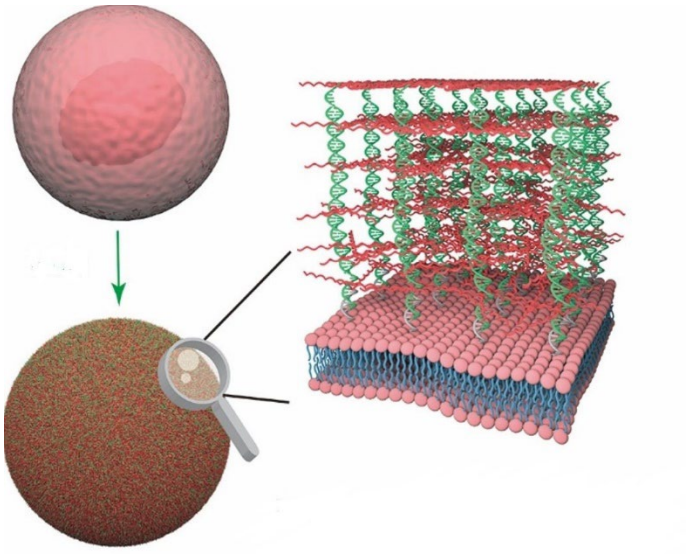
TR&D 3: Bioinspired Equipment-Free Stress-Free Cell Surface Engineering

Goal: Transplanted cells face a survival challenge due to numerous stress factors such as the immune attack. Our lab has utilized DNA as a building block for cell surface engineering. The goal of this TR&D project is to finely tune this fundamental construction concept to meet the diverse requirements of cell-based applications across molecular, nanoscale, and microscale levels.

Published and preliminary data

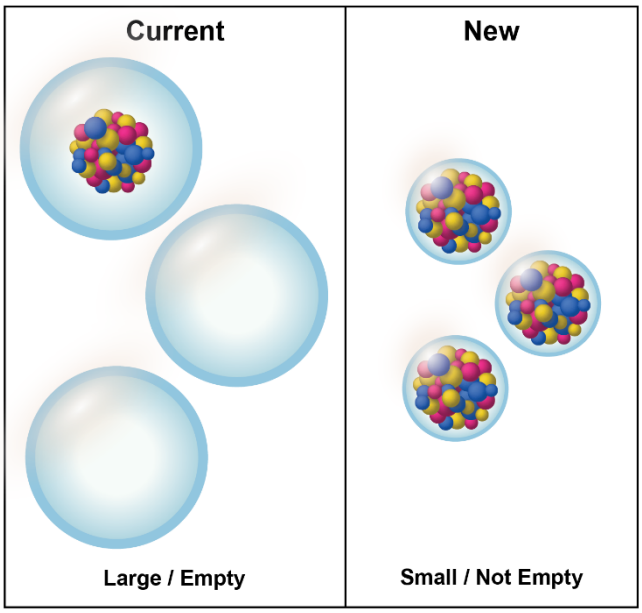


Biomolecular surface engineering of living cells. The cell membrane, beyond acting as a physical barrier, serves as a dynamic interface that governs communication between the cell and its environment. Our lab specializes in biomolecular surface engineering of living cells, using DNA aptamers and DNA-based nanostructures to precisely modulate cell–cell and cell–environment interactions. By functionalizing the cell membrane with these synthetic components, we can extend cellular functions beyond their natural roles. Our work employs both chemical conjugation and physical binding strategies for monovalent and polyvalent surface modifications, enabling applications such as enhancing cell recognition, regulating intracellular signaling pathways, protecting therapeutic cells, and sensing microenvironments. While technologies like aptamer-based platforms for immune cell targeting highlight the potential of our methods, our broader focus lies in developing versatile tools to control cellular behavior across various biological and therapeutic settings. (Angewandte Chemie International Edition 2020, 59 (29): 11892-11897. *J. Am. Chem. Soc.* 2024, 146 (1): 868–877. Nature Biotechnology 2024, 42:1224–1231.)



Nanocoating of living cells. Our lab also works on advanced cell nanocoating technologies to protect and regulate mammalian cells in various applications. Unlike plant and microbial cells, mammalian cells lack a protective exterior cell wall, making them vulnerable to environmental assaults. To address this question, we have engineered biomimetic cell walls (BCWs) that act as protective shields on the plasma membranes of live mammalian cells. These BCWs are synthesized using a supramolecular DNA structure as a framing template and a polyelectrolyte complex as the crosslinked matrix. The entire process is conducted under physiological conditions, ensuring that the coated cells maintain high bioactivity while gaining resistance to both physical and biological stresses. In addition to protection, our research explores techniques that enable not only safeguarding but also regulating cellular functions by using nanoparticles (NPs). By decorating the

nanocoatings with functional NPs, we can dynamically control intracellular responses. (Nature Communications 2019, 10: 2223. Angewandte Chemie International Edition 2023, 135(31), e202306583)



Microcoating of living cells. Lantidra, approved by the FDA in 2023, is the first-ever cell therapy for the treatment of type 1 diabetes. However, this therapy requires lifelong immunosuppression, posing significant risks such as increased susceptibility to infections, cancer development, nephrotoxicity, and neutropenia. While cell nanocoating technologies provide some protection against immune attacks, they are more suited for in vivo regenerative medicine applications and are unsuitable for long-term cell transplantation, as nanocoated cells typically lose viability within a few weeks. In contrast, cells embedded in microcapsules—ranging from a few hundred microns to over one millimeter in diameter—have demonstrated prolonged protection, eliminating the need for continuous immunosuppression. Unfortunately, the large size of these capsules and the inevitable production of empty microcapsules increase transplantation volumes, limiting the number of cells that can be housed within an organ. Additionally, the size of the capsules impairs molecular transport, which is critical for maintaining cell viability. Notably, cells are often exposed to harmful conditions, such as low pH, free radicals, or shear stress, during many existing nanocoating and microencapsulation processes. These conditions can cause both immediate and long-term cell damage. To address these challenges, we are developing an unprecedented microcoating method with a coating thickness of approximately 20 μm. This novel approach avoids harsh conditions and does not require complex instrumentation, while achieving 100% microcoating efficiency. In an ongoing pilot study, immunocompetent diabetic mice receiving microcoated allogeneic or xenogeneic islets have maintained normal blood glucose levels without immunosuppression. This observation highlights the potential of our method for safer, long-term cell transplantation in diabetes treatment.