Targeting Tumor Antigens using Bispecific Chemically Self-Assembled Nanorings (CSANs)

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Cell therapy has become an invaluable tool for guiding interactions between cells. The ability to direct intercellular interactions has the potential for utility across different areas such as tissue engineering, cell-based immunotherapy, enhanced-cell delivery, and regenerative medicine. In recent years, cell engineering has emerged as an efficacious approach to modifying cells. Despite genetic engineering's effectiveness, modifications to cells are permanent and can be expensive and inefficient to produce. To circumvent the limitations associated with genetic modifications, efforts have been made to develop non-genetic strategies to engineer cell surfaces with targeting elements capable of directing specific cell-cell interactions.[1] Accordingly, we sought to build upon this prior work and conceived an approach that does not require genetic modification.

The Wagner lab has developed a multivalent bispecific scaffold called chemically self-assembled nanorings (CSANs). CSANs are formed by oligomerizing bivalent dihydrofolate reductase (DHFR2) fusion proteins using the chemical dimerizer bis-methotrexate.[1,2] With targeting proteins fused onto DHFR2 monomers, CSANs can target specific cellular antigens. In recent work, CSANs have acted as prosthetic antigen receptors (PARs) to non-genetically modify T cells by binding to the T cell receptor and redirecting them to specific tumor antigens.[3,4] Currently, we are developing a novel fusion protein that contains two targeting elements coupled to DHFR2 instead of one. Characterization of the dual-targeting fusion protein is underway.

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