

Synthetic Virus-Like Particles: The Future of Targeted Drug Delivery

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Cell-selective drug delivery can overcome the downfalls of non-specific cancer therapies, such as systemic toxicity and low effectiveness. Previous research has revealed that properly modified peptides derived from the second transmembrane domain of the CXCR4 chemokine receptor inhibit receptor function and have the remarkable capability to self-assemble into homogeneous virus-like particles that fuse with cells spontaneously. Particle modification with receptor ligands would allow for receptor-mediated cell fusion and selective cell delivery. The goal of this project is to determine structural mechanisms of particle formation and generate highly selective delivery systems with multiple therapeutic applications. Studies have shown that synthetic analogs of three chemokine receptors, CCR4, CCR3, and CCR8 self-assemble into stable particles with the radii ranging from 5.7 to 9.7 nanometers. Dynamic light scattering has shown the particles to be highly homogeneous, and spherical particles were further confirmed by electron microscopy studies. Microscale Thermophoresis and Fluorescence Polarization determined critical assembly concentration to be within the nanomolar range indicating high efficacy of the assembly. Melting temperature for all particles determined by Differential Scanning Fluorimetry was around 70 degrees Celsius further confirming high stability. The data strongly suggest that self-assembly is a general property of analogs of the second transmembrane domain of chemokine receptors. Synthetic self-assembling antagonists are promising drug leads and delivery systems for targeting receptors critical to disease signaling pathways. They represent a novel concept in drug development: a multifunctional therapeutic that delivers itself to a specific target.

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