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## Scientists Develop High-Capacity Nanoparticles for Targeted Delivery of Drug Cocktails

Liposome-wrapped porous silica nanoparticles were found to be more selective and stable than liposomes.

Researchers report on the development of a new class of high-capacity drug carrier they claim combines the best features of both porous silica nanoparticles and liposomes. The University of New Mexico, Albuquerque-led team claims their porous nanoparticle-supported lipid bilayers, termed protocells, display high capacity, selectivity, affinity, and stability for the targeted delivery and internalization of a range or cocktail of drugs or diagnostic agents directly into the cytosol of cancer cells.

Carlee E. Ashley, Ph.D., at the University's Center for Micro-Engineered Materials, and colleagues, describe the construction and initial testing of protocells in *Nature Materials* in a paper titled, "The targeted delivery of multicomponent cargos to cancer cells by nanoporous particle-supported lipid bilayers."

Targeted delivery of drugs encapsulated within nanocarriers can overcome the drawbacks of conventional unencapsulated drugs, such as poor solubility, limited stability, rapid clearance, and the lack of selectivity that causes toxicity to normal cells, the university team writes. However, targeting and carrier approaches developed to date have their own problems. Passive targeting schemes that rely on the enhanced permeability of tumor vasculature lack the cell-specific interactions needed to induce nanocarrier internalization, while selective targeting strategies using ligands that specifically interact with target cell-specific surface receptors require the presence of differentially expressed or highly overexpressed targets relative to normal cells.

Conjugating multiple copies of a targeting ligand to a nanocarrier surface to promote multivalent binding can boost affinity and drug delivery and help prevent multidrug resistance efflux mechanisms, the researchers assert. However, high ligand densities can also cause nonspecific interactions with noncancerous cells and increased immunogenicity, which leads to accelerated clearance of the nanoparticles. Modifying the nanocarrier surface with hydrophilic polymers such as polyethylene glycol (PEG) increases circulation times and mitigates uptake by phagocytic cells, but in turn reduces targeting specificity. "The main challenge for targeted nanocarriers is to simultaneously achieve high targeting specificity and delivery efficiency, while avoiding nonspecific binding and entrapment by the body's defenses," Dr. Ashley and colleagues conclude.

Building on the best features of technologies that are available, the University of New Mexico researchers constructed their protocells by fusing liposomes to a spherical, high-surface-area nanoporous silica core, and then modifying the resulting supported lipid bilayer (SLB) with multiple copies of a targeting peptide, a fusogenic peptide, and PEG. The PEG enhances carrier stability, whereas the peptides impart high binding affinity to malignant cells and induce the uptake of protocells by cancer cells and release of their cargo in the cytosol.

Importantly, the researchers claim, the high surface area of the nanoporous silica core means protocells possess a higher capacity for therapeutic and diagnostic agents than similarly sized liposomes. As a result, the protocells have a 1,000 times higher capacity for doxorubicin than liposomes, and in addition release nearly 90% of their encapsulated doxorubicin in a bioactive form on endocytosis by hepatocellular carcinoma (HCC). Moreover, studies using protocells modified with a targeting peptide that binds to human HCC suggest the carriers exhibit a 10,000-fold greater affinity for HCC cells than for hepatocytes, endothelial cells, or immune cells, the authors add.

DOPC (1,2-dioleoyl-*sn*-glycero-3-phosphocholine)-formulated protocells were found to release about 50% of encapsulated doxorubicin within four hours and exhibited long-term stability when maintained in a simulated body fluid. In contrast, the researchers point out, DOPC liposomes leaked 90% of their encapsulated doxorubicin within 72 hours and demonstrated a release profile comparable to that of the nanoporous core with no SLB.

The team believes one of the most striking features of protocells is their ability to deliver high concentrations of diverse cargos and cocktails of chemically disparate components. “The enormous capacity of the high-surface-area nanoporous core combined with the enhanced targeting efficacy enabled by the fluid-supported lipid bilayer enable a single protocell loaded with a drug cocktail to kill a drug-resistant human hepatocellular carcinoma cell, representing a 106-fold improvement over comparable liposomes,” they claim.

The Albuquerque team maintains that drug-loaded DOPC protocells modified with a minimal number of targeting peptides can effectively solve the conundrum of simultaneously achieving high targeting specificity, high cytotoxicity to the target cell, and low collateral damage to noncancerous cells. Modifying the protocell SLB with ligands that bind to cell-specific or overexpressed surface receptors, together with a ligand that promotes internalization, will also enable both selective targeting and intracellular delivery for cancers where cell-specific receptors are not normally endocytosed.

“We have demonstrated that targeted protocells possess the high specificity, enhanced cargo capacity, and long-term stability necessary to deliver a variety of chemically disparate therapeutic and diagnostic agents to cancer cells with minimal nonspecific binding and toxicity to normal cells,” the authors write. “We have, furthermore, shown that the nanoporous core can be adapted to release encapsulated cargo within 24 hours or over the course of several weeks, and that the SLB can be modified with a variety of ligands including peptides, antibodies, and glycoproteins to promote specific affinity for a target cell. So far, no other nanoparticle-based delivery vehicle has been reported that possesses all of these attributes, making protocells the first example of a nanocarrier that simultaneously addresses the complex requirements of targeted, multicomponent delivery.”