ALPINE BIOSCIENCES TECHNOLOGY FACT SHEET: THE PROTOCELL

Realizing the Promise of Nanomedicine

- Protocell technology can fuel the development of new product candidates in oncology, immunotherapy, and rare diseases, with the potential to improve the lives and outcomes of patients worldwide.
- The modular nature of protocell synthesis allows for manufacturing, scale-up, and lower costs relative to alternative approaches.
- *"The properties engineered into this system elegantly synergize to approach the goal of an ideal targeted-delivery agent."*[1]

Protocells are a nanoconstruct designed to address previously intractable therapeutic challenges

Fluid-phase lipid membranes surround a drug-loaded nanoporous silica core to provide:

Increased Stability and Loading:

- Past efforts in nanoparticle delivery technologies resulted in poor stability, with cargo leakage and off-target toxicities.
- The nanoporous silica core of the protocell stabilizes the payload, while carrying 1000x the cargo of liposomes.
- Pore sizes within the silica core can be varied to fine-tune release rates, affording payload delivery times that can range from hours to weeks.
- Colloidal stability minimizes interactions with the immune system, reduces non-specific binding, and allows for a long serum half-life.

Enhanced Targeting:

- Previous therapeutic constructs, such as liposomal delivery systems, relied primarily on enhanced permeability and retention (EPR) characteristics.
- A fluid lipid bilayer with targeting ligands creates conditions favorable for multivalent and cooperative binding to target cells, leading to a 100x improvement over similarly-targeted liposomes.
- Superior targeting due to the fluid lipid bilayer improves retention, allowing for the delivery of active payloads to the organ or cell of interest while minimizing off-target binding.

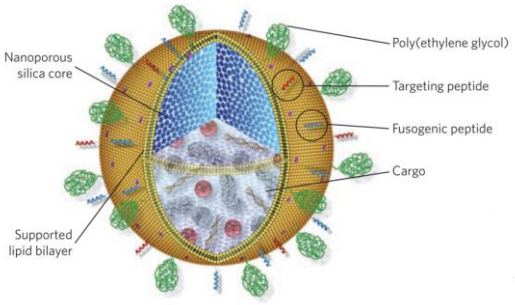
Greater Safety with Less Immunogenicity:

- Earlier nanotechnologies sought to achieve enhanced target specificity through increases in the target ligand density, but this led to greater immunogenicity.
- In protocells, targeting is achieved with a minimal number of ligands, thereby reducing unintended interactions and reducing the immune profile.
- In an oncology setting, protocells carrying combination therapy payloads may enable higher tumor concentrations with diminished systemic toxicities.

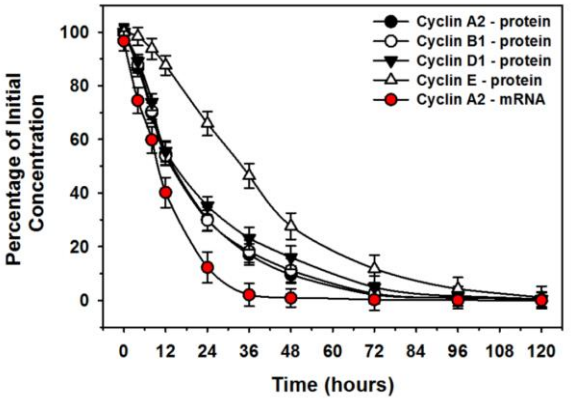
Unrivaled Therapeutic Applicability:

- Protocells are capable of delivering large payloads of chemically disparate cargo to precisely targeted destinations.
- Unprecedented payload capabilities include not only small molecules, but all forms of nucleic acids (DNA, siRNA, mRNA) for non-integrating gene therapies or gene silencing, or full proteins for protein replacement.

ARCHITECTURE OF THE PROTOCELL[1,2]



PRECLINICAL DATA[3]



Protocells loaded with therapeutic small-interfering RNA (siRNA) targeting hepatocellular carcinoma cells have been shown to repress expression of a variety of cyclin family members at the protein level. By protecting siRNA cargos from degradation, protocells provide a unique delivery platform for therapeutic oligonucleotides.[3]

COMPANY CONTACT

Jay Venkatesan, MD

Direct.....617.548.7547

1. Irvine DJ. Drug delivery: One nanoparticle, one kill. *Nat Mater.* 2011:10:342-3.
2. Ashley CE, et al. The targeted delivery of multicomponent cargos to cancer cells by nanoporous particle-supported lipid bilayers. *Nat Mater.* 2011:10:389-97.
3. Ashley CE, et al. Delivery of small interfering RNA by peptide-targeted mesoporous silica nanoparticle-supported lipid bilayers. *ACS Nano.* 2012;6:2174-88.

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