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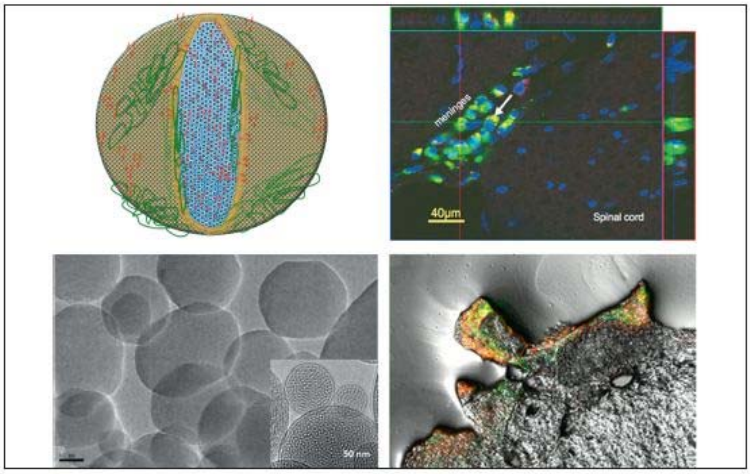

COVER STORY
Protocells for DNA cargo delivery to the spinal cord

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Cover story

Protocells for DNA cargo delivery to the spinal cord

Gene therapy has a great potential in treating various diseases and many *in vitro* studies have shown that the approach is indeed feasible. The real challenge for clinical applications, however, is the development of suitable vectors that can deliver therapeutic genes to target cells. Viral vectors have shown efficacy in gene therapy but they are considered to be dangerous with unforeseen side effects, which are sometimes detrimental. Naturally, efficient non-viral vectors have been actively pursued. Gene delivery systems, whether viral or non-viral, have to meet two critical requirements: delivery to the specific target tissue and cells (i.e., systemic targeting); and subsequent crossing through the cell membrane and releasing the gene cargo at the right place inside the cell (i.e., intracelluar targeting). One of the emerging non-viral vectors for gene and drug delivery is an inorganic nanoparticle vector [1].

Inorganic nanoparticles such as silica have advantages over other nanoparticles made of cationic polymers, liposomes, or recombinant proteins. Inorganic nanoparticles are known to be easy to manufacture, straightforward for surface modification, biocompatible, and stable during long-term storage [2]. While silicas are present in crystalline and non-crystalline (amorphous) forms, only amorphous silicas are thought to be devoid of toxic biological effects. Mesoporous silica particles are solid with a 'honey-comb-like' porous structure with numerous empty channels (mesopores) that can be exploited to absorb bioactive molecules [3]. Mesoporous silica nanoparticles are particularly attractive because of their precisely defined mesoporosity that allows for gene/drug loading with adjustable release profiles through modifications in the pore size and surface chemistry [1,4]. Positively charged liposome can be fused onto the surface of negatively charged mesoporous silica particles creating a synergistic system that loads and seals cargo into the silica core. This "protocell" construct was shown to enhance delivery of bioactive molecules, including DNA, across a cell membrane [5,6].

In this issue the article by Professor Erin Milligan and her team describes for the first time, long-duration *in vivo* characterization of protocells, i.e., mesoporous silica nanoparticle supported lipid bilayers, as non-viral gene therapy carriers for their biocompatibility and functional transgene expression [7]. In particular, the pain-suppressive therapeutic application of protocells was examined following their application within the intrathecal peri-spinal cord region (subarachnoid) of experimental rats. There were no adverse effects for at least 8 weeks. One of the advantages of direct intrathecal injection of protocells carrying a therapeutic transgene is that it bypasses the blood–brain barrier (or blood–spinal barrier) that could not otherwise be achievable by intravascular injection. While this is only one *in vivo* example and clearly more studies need to be done, the Milligan team has shown that protocells are highly promising as a gene/drug delivery vehicle to achieve region-specific targeted delivery. This first successful step by the protocell approach is expected to accelerate its development for ultimate clinical applications of treating various pathological conditions of the central nervous system.

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