Cellular Drug Delivery from the Inside Out

BY KERRY GIBSON

IN THE 1966 SCIENCE-FICTION blockbuster, "Fantastic Voyage," a small submarine and its medical crew are miniaturized to microscopic size and injected into the body of a dying scientist. They journey through the man's body to remove a blood clot in his brain.

Fast forward 40 years. In a somewhat similar plot line, Ames Lab chemist Victor Lin has found a way to use nanoscale "capsules" to deliver a dose of chemotherapy drugs to specific cancer cells without the risk of side affects to healthy cells.

Using tiny silica particles called mesoporous nanospheres to carry drugs inside living cells, Lin is studying different methods to control whether the particle delivers its pharmaceutical payload.

"First, the nanospheres are only about 200 nanometers in diameter, roughly the size of a virus, so they won't trigger an immune response in the body," Lin says. "They're also biocompatible so they can be readily absorbed by the cells."

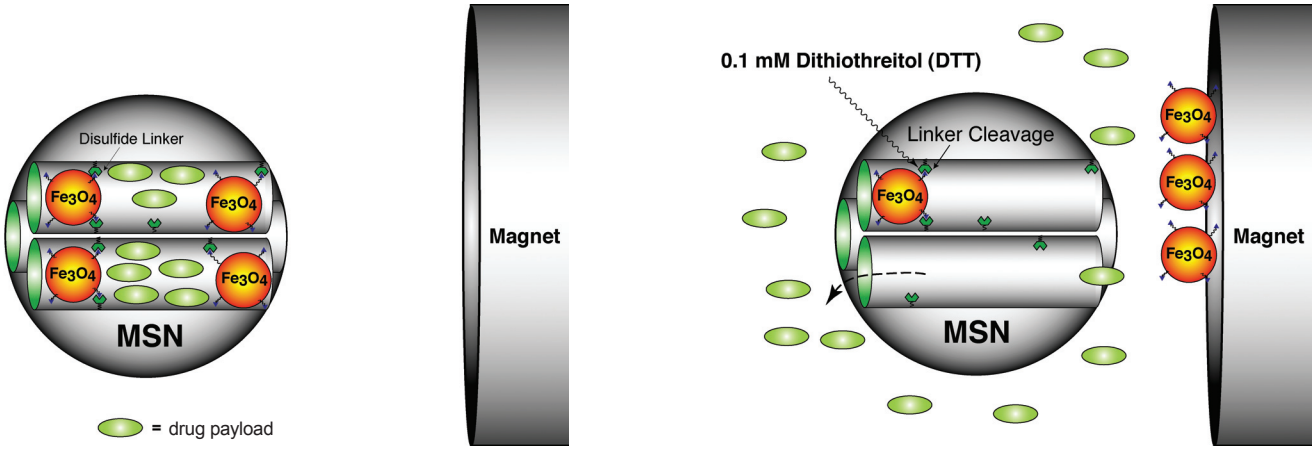
But it's the structure of the nanospheres that makes drug delivery possible. The spheres have thousands of parallel channels running completely through them. Through capillary action, the spheres can soak up molecules of the drug to be delivered. When the channels are filled, the ends of the channels are "capped" to safely seal the drug inside. Once the caps are in place, the nanospheres are "washed" to remove the drug from the outer surface.

Controllable caps

The type of material used for the end caps, how they're held in place and how they're released is the focus of Lin's work. The caps can be dendrimers, biodegradable polymers, genes, proteins, metallic nanoparticles or semiconductor nanocrystals – also known as quantum dots – and are held in place by chemical bonds.

Mesoporous silica nanospheres are the focus of Victor Lin's research

(left) Living human cervical cancer cells containing mesoporous silica nanospheres capped with iron-oxide nanoparticles are drawn through solution toward a small rare-earth magnet placed beside the vial.



This diagram shows how the iron-oxide caps hold the drugs within the channels in the nanospheres.

By manipulating the magnetic field, the caps "pop" free, releasing the drug.

Once the nanospheres are inside the target cells, a trigger is used to pop the caps off and release the drug.

"We're looking at two levels of control," Lin says of the trigger mechanism. "One level is to have the cell control the release and the other would be to control the release externally." Lin explains that the chemical-bond holding the cap in place can be engineered to be unphased by chemicals present in normal cells. However, in cancer cells these chemicals, such as antioxidants, appear in much higher concentrations and would break the bonds on the caps and release the drugs. In this way, only cancer cells could be targeted with powerful chemotherapy drugs, such as Taxol or doxorubicin, while the nanospheres inside the normal cells would remain capped and not cause unwanted side affects by damaging healthy cells.

To achieve external control, Lin is using iron-oxide nanoparticle caps that can be manipulated by a magnetic field. In a simple demonstration of the principle, Lin holds a small rare-earth magnet up to a liquid-filled glass vial containing human cervical cancer cells grown *in vitro* that contain nanospheres capped with iron-oxide particles. The cells slowly migrate and cluster to the side of the vial next to the magnet.

"By using a powerful magnet, we can first concentrate the nanospheres at a particular point, such as a tumor site, and then use the magnetic field to remove the caps and release the drug," Lin says. "The advantage of using a magnetic trigger as opposed to an ultraviolet light trigger is that there's no limit to the depth of tissue we are able to probe — think of an MRI."

Other possibilities

Beyond the possibilities for intercellular drug delivery, the nanospheres may provide the key to studying what takes place within a cell. Currently, scientists have difficulty introducing chemicals or genes into cells without either damaging the cell or causing a chain reaction of events that can't be tracked.

Victor Lin

"With current gene therapy, it's possible to switch genes on and off, but you don't really know if you are affecting other parts and processes of the cell as well," Lin says. "You may be able to get a plant cell to produce a certain desired product, but the yield may drop significantly." By using externally controlled nanospheres, Lin explains that it may be possible to sequentially release genes, chemical markers and other materials within cells in order to track what happens and what specific changes take place. This phase of Lin's research ties into a larger plant metabolomics project at Ames Laboratory being undertaken by senior chemist and Chemical and Biological Sciences Program Director, Ed Yeung.

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For more information:
Victor Lin, (515) 294-3135
vsylin@iastate.edu

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