



Medical and Diagnostic Imaging Technology Alert

UNIQUE FULLERENE-BASED CONTRAST AGENTS FOR MRI SCANS

There are more than 25 million patients in the United States that undergo magnetic resonance imaging (MRI) annually, and doctors use contrast agents in almost one-fourth of those procedures to increase the sensitivity of the scans. The most effective and commonly used contrast agent for these procedures is toxic metal gadolinium. Lanthanide ion Gd^{3+} is usually chosen as an MRI contrast agent (CA) and to reduce its toxicity the Gd^{3+} aqua ion is chelated to a ligand. These agents are intravenously administered to patients and by reducing the relaxation time of water protons in the affected tissues, these agents help in producing a higher contrast diagnostic image.

MRI usually provides a good spatial resolution, but sensitivity still remains a problematic issue, especially in novel applications such as the targeting of specific cells or tissues. Since the number of Gd^{3+} complexes that can be delivered or attached to a specific cell is largely limited by biological constraints, the efficacy of each Gd^{3+} center must be improved in order to induce sufficient amount of signal intensity to image individual cells. This is the reason that makes search for more efficient, higher-relaxivity MRI agents a key objective in current MRI CA development.

Rice University's doctoral student Balaji Sitharaman has addressed this challenge of creating new forms of CAs by encasing gadolinium inside fullerenes--single molecules of carbon atoms arranged in spherical or tube-shaped structures. By enclosing the gadolinium inside the carbon molecules, he has simultaneously been able to reduce the toxicity of the metal to near zero at the same time boosting its effectiveness as a CA.

One of the key creations of Sitharaman includes a buckyball encasing a single atom of gadolinium. He has also discovered a method of encasing as many as 100 atoms of the metal inside a short length of carbon nanotubes. The resulting "gadonanotubes" are found to be 100 times more effective as CAs than the best forms in the clinical use.

Most of the contrast agents used in the clinic do not stay in the body long enough for detailed studies. The contrast agents that have higher retention and ability to get into cells such as metallofullerenes really fit this profile. Sitharaman and his colleagues have reported that two gadolinium-based metallofullerene compounds aggregated at a pH of 9 to form spherical and irregular clusters measuring 30 nm to 90 nm, with little concentration or temperature dependency. Below a pH of 9, the aggregate sizes increased steadily and dramatically to reach hydrodynamic diameters of 600 nm to 1,000 nm by a pH of 5. The researchers concluded that the tendency of these metallofullerene species to self-assemble into nanoscale aggregates in aqueous solution likely produces their unusually large, outer-sphere, pH-sensitive proton relaxivities. These results suggest that gadofullerenes can serve as pH-sensitive MRI CAs for diagnosing abnormal tissues such as tumors and arterial plaques

that are known to possess lower pH values than healthy tissue. The researchers have reported relaxivities as a function of magnetic field for water-soluble gadofullerenes noting that the pH dependency of the proton relaxivities makes these gadofullerenes derivatives prime candidates for pH responsive MRI CA applications.

This research has attracted funding from National Institutes of Health that awarded a Small Business Innovation Research grant to a joint collaboration between Rice and TDA Research Inc. in Houston, and by the Swiss National Science Foundation and the Office of Education and Science. Sitharaman expects metallofullerenes to move into the clinic in five to ten years.

For the future, Sitharaman plans to use existing methods of attaching antibodies and peptides to fullerenes to try to create a contrast agent that will only bind with diseased cells like that of cancer, and is hopeful that these tissue-specific imaging agents might allow for the first intracellular, individual cell MRIs.

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