An alternative to chemotherapy: Nanoparticles tackle pediatric brain tumors

July 14 2008

An interdisciplinary team of researchers at Washington University in St. Louis, led by Karen L. Wooley, Ph.D., James S. McDonnell Distinguished University Professor in Arts & Sciences, is a step closer to delivering cancer-killing drugs to pediatric brain tumors, similar to the tumor that Senator Ted Kennedy is suffering from.

Such tumors are often difficult to completely remove surgically; frequently, cancerous cells remain following surgery and the tumor returns. Chemotherapy, while effective at treating tumors, often harms healthy cells as well, leading to severe side effects especially in young children that are still developing their brain functions.

In an effort to solve this problem, the Wooley lab has developed polymeric nanoparticles that can entrap doxorubicin, a drug commonly used in chemotherapy, and slowly release the drug over an extended time period. By tuning the polymer composition, they were able to tailor the release rate of the drug and improve its solubility.

The work was published in *Chemical Communications* and supported by The Children's Discovery Institute of St. Louis Children's Hospital and by the National Heart, Lung and Blood Institute of the National Institutes of Health as a Program of Excellence in Nanotechnology.

With their approach, the Wooley lab was able to load more doxorubicin into the cores of the nanoparticles, compared with similar constructs.

" Typically, a polymeric micelle has three to four percent [drug] loading per nanoparticle mass. In our case, we achieved 18 to 19 percent for our nanoparticles," said Andreas Nystrom, Ph.D., a post-doctoral associate, supported by the Knut and Alice Wallenberg Foundation, who worked on the project.

However, the nanoparticles carrying the doxorubicin were not as effective at killing cancer cells compared to the neat drug, because in these initial nanoparticles, no targeting groups were included and also the entire drug payload of the nanoparticle is not released. The identification and attachment of targeting ligands onto the nanoparticles and the rate and extent of drug release are now what the researchers will concentrate on and seek to improve. Ligands in this application are comprised of peptides and antibodies that bind to specific cell receptors over-expressed in cancer cells.

The cell studies were performed in vitro by Zhiqiang (Jack) Xu, Ph.D., a post-doctoral associate, together with Professor Jeff Leonard, M.D., in the Department of Neurological Surgery and Professor Sheila Stewart, Ph.D., in the Department of Cell Biology and Physiology, each in the School of Medicine at Washington University. Ultimately, in vivo, the nanoparticles are expected to target the tumors through the use of active targeting ligands and also through passive diffusion, as particles are well known to be taken up selectively into tumors by a process called the enhanced permeability and retention effect. The amount of drug released from the nanoparticles "might be enough for the intended therapy, if side effects are limited by selective tumor targeting," Nystrom said.

For these drug-filled nanoparticles to be effective for treating brain tumors, one challenge remains—decorating the nanoparticles with signatures that direct them to the tumors and away from healthy cells, a process known as tissue specific targeting. Once attached to the tumor, the nanoparticles can release their deadly contents, killing the cancer

cells and leaving the healthy cells unharmed.

"Everything depends on getting the nanoparticle to the tissue (tumor) of choice," said Nystrom.

Wooley agrees. "We have been studying these nanoparticles for some time now as a platform technology, achieving high radiolabeling efficiencies and demonstrating variable bio-distributions through a collaboration with the laboratory of Professor Mike Welch, in the Department of Radiology," she said. " Now, we are poised to take advantage of the progress made to develop the particles for diagnosis and treatment of several diseases.

"In this latest work, the nanoparticles were designed with thermally tunable core properties to serve as a host system that retains drug molecules at room temperature and then releases the cargo at physiological temperature, with a controlled drug release profile. The results are highly promising and are allowing us to move forward to a fully functional, tumor-targeted drug delivery device. The key to making this happen is the interdisciplinary team of investigators, each of whom brings a different chemical, biological or medical expertise."

Source: Washington University in St. Louis