Single-Dose Drug-Loaded Dendrimer Cures Mice of Colon Cancer

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In a dramatic demonstration of the power of nanotechnology, a team of investigators has designed a nanoscale, polymeric drug delivery vehicle that when loaded with a widely used anticancer agent cures colon cancer in mice with a single dose.

The researchers, led by Francis Szoka, Ph.D., of the University of California, San Francisco, and Jean Fréchet, Ph.D., of the University of California, Berkeley, published the results of these experiments in the *Proceedings of the National Academy of Sciences USA*. This current work represents a milestone in a concerted effort to design nearly every aspect of a nanoscale drug delivery vehicle in order to maximize the anticancer activity of the drug payload.

To create their drug delivery vehicle, the investigators used a highly branched polymer, known as a dendrimer, that naturally forms nanoparticles with myriad sites for drug loading. In this particular case, the researchers created what they call a bow-tie polyester dendrimer, whose molecular structure somewhat resembles a bow-tie with two discrete halves. Previous work by these investigators had already shown that the body readily degrades this dendrimer and that the dendrimer does not accumulate in the body. Earlier work had also shown that this dendrimer has superior pharmacokinetic properties if it has a mass larger than 40 kiloDaltons.

On one half of the dendrimer, the researchers attached a second polymer, poly(ethylene glycol) (PEG), in order to make the dendrimer

water soluble. Again, earlier work had provided details on the optimal number of PEG molecules to attach to the dendrimer in order to maximize its lifetime in the body. Next, the investigators attached the anticancer drug doxorubicin to the other half of the dendrimer using a chemical linkage designed to break when exposed to acidic conditions. Not coincidentally, the inside of tumor cells is acidic, while the bloodstream has a neutral pH. Results presented in this paper show that the resulting drug-dendrimer formulation releases virtually all of its drug within 48 hours in acidic conditions but less than 10 percent of its payload at neutral pH.

When tested in cultured colon tumor cells, the researchers found that the drug-dendrimer construct was considerably less toxic than free doxorubicin when they dosed the cells with equivalent amounts of doxorubicin. The researchers note that this somewhat surprising finding likely results from slower uptake by the tumor cells of the dendrimer, compared to free drug, and because once taken up by cells the drug is released slowly from the dendrimer.

However, when the researchers treated tumor-bearing mice with either free doxorubicin or the doxorubicin-dendrimer formulation, the dendrimer performed far better than free drug. After a single intravenous injection, every mouse treated with the dendrimer-drug construct survived until the end of the 60-day experiment and every mouse showed complete tumor regression. In contrast, none of the mice treated with only doxorubicin survived, which an average survival time of only 24 days. The researchers also noted that the mice treated with the dendrimer formulation experienced fewer adverse side-effects than did those treated with either free drug or a clinically approved liposomal formulation of doxorubicin that the researchers also tested for the sake of comparison. The liposomal formulation produced a 90 percent cure rate over the 60-day experiment.

This work is detailed in a paper titled, “A single dose of doxorubicin-functionalized bow-tie dendrimer cures mice bearing C-26 colon carcinomas.” An abstract of this paper is available through PubMed.

Source: National Cancer Institute