Medical Xpress

Novel approach to detoxifying cancer drugs

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Anticancer drugs are often highly toxic when delivered straight, but "wrapping" them inside larger molecules can lessen the side effects as well as make them more effective, according to a new study by researchers at the University of California, Berkeley, and UC San Francisco.

In recent experiments, a powerful cancer drug, doxorubicin, enveloped in a large polymer produced a 100 percent cure in mice with induced colon cancer, while all mice treated with the drug doxorubicin only died. The doxorubicin-polymer combination proved as effective as a liposomal therapy - doxorubicin encapsulated in fat bubbles called liposomes - now used to treat several types of cancer in humans.

"There's nothing better than comparing a drug against what works in people, and in our tests in mice, the new technique cured 100 percent of the mice, performing at least as well as the liposomal drug," said Jean Fréchet, professor of chemistry and chemical engineering at UC Berkeley and a researcher at Lawrence Berkeley National Laboratory. "We think the new technique has many advantages over liposome delivery."

Fréchet's colleague Frank Szoka, professor of pharmaceutical chemistry at UCSF and developer of the liposome-encapsulated doxorubicin, agreed.

"The dendrimer is as good as Doxil. Doxil is a lot less toxic than doxorubicin, and I think the dendrimer will be a lot less toxic for many

of the same reasons," Szoka said, referring to the trade name of the doxorubicin-filled liposomes, which are made by a subsidiary of Ortho Biotech Products, L.P. and approved for treatment of ovarian cancer and Kaposi's sarcoma. Szoka is the scientific founder of Sequus Pharmaceuticals Inc., the Menlo Park company that invented the Doxil product.

Fréchet, Szoka and their colleagues reported their success in a paper appearing last week in the Online Early Edition of the *Proceedings of the National Academy of Sciences*.

The idea of attaching bulky molecules to smallish drugs has fueled a lot of polymer research in the past 30 years, based on expectations that the larger molecules will remain in the blood for longer periods, allowing more time for them to infiltrate tumors to deliver a lethal dose. Theoretically, the larger molecules also would be less likely to slip through tightly knit blood vessel walls into healthy tissue, though still able to seep into cancerous tissue through their poorly built and leaky blood vessels.

"This way, you can target fast-growing tumors, like colon cancer, that have lots of leaky vasculature," Fréchet said. "As a result, the tumors accumulate the drug, but very little is taken up by other tissues."

Most chemists have focused, however, on attaching long-chain polymers to drugs, which requires costly synthetic chemistry. In addition, the polymer-drug combinations haven't behaved as predicted, and the chemical upon which most of these polymers are based - methacrylate - does not degrade in the body, which means it accumulates until eliminated by the kidney.

Fréchet, however, saw an advantage with branching polymers instead of linear polymers. Called dendrimers because of their tree-like structure,

they don't pass through filtration pores in the kidney for the same reason that it's hard to force a tree branch though a hole. Tests show a half life in the body - the time it takes for half the drug to be eliminated or degraded - of up to 30 hours, versus a few minutes for pure doxorubicin. A linear polymer with the same half life would be impractical, Fréchet said.

In addition, Fréchet based the dendrimer polymers on a chemical structure, a polyester, that is degraded naturally inside the body, which prevents its accumulation.

"Our contribution to this field was to recognize that polymer architecture makes a difference, and Jean's contribution was to recognize that polyester is a great backbone for doing this," Szoka said.

Fréchet and his UC Berkeley graduate students synthesized a branching polyester polymer they refer to as a "bowtie" dendrimer because it has two halves that branch out from a center where they're tied together. The team chemically attached up to 32 doxorubicin molecules to one side of the bowtie, and a smaller number of linear chains to the other half, which wrapped around the package like a hairball protecting the drug.

The mice were injected with colon cancer cells, and several days later with doxorubicin, doxorubicin-dendrimer or Doxil. Though the latter two cured the mice, the group did not address long term toxicity, which would require tests in larger animals. Doxorubicin is known to be toxic to the heart after repeated use, though liposome encapsulation seems to prevent this.

"Much less drug goes to the heart with the dendrimer and the liposome, so I would predict there would be much less cardial toxicity with the dendrimer also," Szoka said.

One advantage of the dendrimer over liposomes is that the therapy can be delivered via one injection, while liposome treatment is by intravenous infusion. Both deliver a higher dose of drug - three to four times as much - than can be achieved with doxorubicin alone, since the drug is so toxic. Thus, attachment to the dendrimer considerably reduces its side-effects.

One big disadvantage of the dendrimer is that it requires laborious synthesis, but Fréchet already is at work on a new chemical process that could solve that problem, making synthesis relatively inexpensive. Another advantage of the dendrimer is its stability, which allows the doxorubicin polymer be dried and stored for long periods of time, then rehydrated. Liposomes have the disadvantage that they are fragile and have an 18-month shelf-life if frozen.

"Liposomes also can break in the bloodstream, increasing the chance of side effects," Fréchet said. "The doxorubicin dendrimer has little or no impact until it penetrates a cell, which eliminates the chance of drug side effects."

While Fréchet and Szoka pursue research on the new dendrimer-doxorubicin compound, they are looking at other drugs that could be delivered via dendrimers. It may even be possible to attach a cocktail of drugs to a single dendrimer so the drugs can be delivered together.

Source: University of California, Berkeley