Death carrot' could hold the key to new cancer drugs

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A pretty yellow flower could hold the key to the next generation of cancer drugs, and is about to head into human clinical trials.

The flowering *Thapsia garganica* plant looks innocent enough, but the common Mediterranean weed is highly toxic to sheep and cattle, earning it the moniker "death carrot" in ancient Greek literature.

But this lethal plant could find a new use: targeting and killing cancer cells. The challenge lies in harnessing the power of this toxic substance, goading it into killing just the cancer cells while leaving healthy cells alone.

The task has been taken on by Samuel Denmeade, an oncologist at Johns Hopkins University in Baltimore. He and his team spent 15 years engineering an analogue of thapsigargin, the active ingredient in the plant, to fight cancer cells exclusively.

Thapsigargin typically works by passing through cell membranes and shutting down calcium pumps – essential for cell survival – on the inside of cells. Denmeade's team modified the thapsigargin molecule by adding an extra peptide chain which prevents the toxin from entering cells. That is, until it encounters PSMA – an enzyme commonly found on the surface of many prostate cancer cells. PSMA cleaves the extra chain off the toxin, setting it free to do its devastating business.

Precision killer

While traditional chemotherapy drugs only target cells undergoing rapid growth, this new toxin is a generalist, destroying not just the cancer cells currently growing, but also those lying dormant as well as non-cancer cells recruited to help the tumour grow.

"You can envision it as a grenade," Denmeade says. "One guy pulls the pin, but it kills all the guys standing around." Fortunately for the mouse test subjects, though, the effects of the toxin stay local, causing minimal collateral damage to healthy tissues nearby.

PSMA is an oft-targeted site for prostate cancer researchers, but creating a drug that goes beyond seeking out the PSMA enzyme and actually takes advantage of its ability to cleave proteins is a major innovation, says David Nanus at Weill Cornell Medical College in New York City.

The results of extensive animal studies are promising enough for the drug to now be moving into phase 1 clinical trials, focusing first on prostate cancer. Recent studies have shown that PSMA is also found in tumours outside the prostate, so trials on other cancers may not be far away.

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