For a WEB EXTRA with a video Q&A about the development and function of triterpenoids, see dartmed.dartmouth.edu/spring08/html/disc_trials_we.php.

Chemopreventatives show promise in trials

The discovery of a drug that could arrest cancer—or even prevent it—without nasty side effects would be big news. So findings by Dartmouth pharmacologist Michael Sporn, M.D., and his colleagues will indeed be big news, if they can make the leap from mice to humans.

In more than a dozen papers in the past two years, Sporn and Karen Liby, Ph.D., have demonstrated the potent anticancer effects of a new class of drugs called synthetic triterpenoids. Created 10 years ago by Dartmouth chemists Tadashi Honda, Ph.D., and Gordon Gribble, Ph.D., these compounds have been shown to shrink and prevent cancerous tumors in lab animals, with no toxic side effects. (For more on triterpenoids, see dartmed.dartmouth.edu/winter06/html/compound_interest.php.)

Most drugs target one molecule, or at most a few, but triterpenoids have multiple targets, some of which Sporn and his team are still discovering. This broad range of action helps give the compounds their powerful anti-inflammatory, anti-angiogenic, and cytoprotective properties. But it's also slowed down their development. Big pharmaceutical companies shy away from drugs that "do too much," says Sporn. The broader a drug's range of action, the more difficult—and expensive—it is to prove it's safe, and the more room there is for liability.

Safe: Nevertheless, Sporn was able to get a small, Texas-based company, Reata Pharmaceuticals, interested in testing triterpenoids in humans. Reata recently completed Phase I trials of the triterpenoid RTA 402, a.k.a. CDDO-Me, in patients with late-stage solid tumors and lymphoid malignancies. (Phase I trials include only 20 to 30 patients and look mostly at safety.) RTA 402 was shown to be quite safe. Furthermore, in several patients who had a high tumor burden and whose cancer was progressing, the drug halted disease progression for six months or more. RTA 402 also reduced several immunoregulatory proteins that are markers for a poor prognosis.

"It's important to remember that these patients have advanced cancers and have failed multiple other treatment options," says Melissa Krauth, a vice president at Reata. "Six months without disease progression represents a meaningful benefit. We are also excited to begin testing this drug in patients in an earlier stage of disease, where we would expect to see an even greater effect."

Effect: Reata is now conducting Phase II trials of RTA 402 in patients with pancreatic cancer, one of the deadliest and least-treatable cancers, and metastatic melanoma. "We [think] . . . RTA 402 will produce an even more profound effect when it is used in combination with standard cancer therapies," Krauth adds. "We plan to start testing it in various combinations later this year." The company expects to test RTA 402 in patients with hepatitis, rheumatoid arthritis, multiple sclerosis, and psoriasis, too. Depending on the success of these trials, and FDA timing, the drug could be available by 2010.

Meanwhile, Sporn and Liby are studying several even more potent triterpenoids that Honda has synthesized, as well as a class of drugs called rexinoids. Like triterpenoids, rexinoids—not to be confused with their cousins, retinoids, which can have toxic side effects—are also multifunctional. Sporn and researchers at other institutions have shown that rexinoids affect cell growth and differentiation, energy metabolism, and inflammation. In *Clinical Cancer Research*, Liby and Sporn reported that a rexinoid named NRX194204 prevents and treats cancer in mice. The compound reduced total lung tumor volumes by 64% to 81% and caused ER-negative breast tumors—the hardest kind to treat—to either stop growing or regress. Back in 2006, they demonstrated that another rexinoid, LG100268, can prevent ER-negative breast tumors and lung tumors in mice engineered to develop those cancers. However, Ligand Pharmaceuticals, which developed LG100268 for a purpose other than cancer treatment, has abandoned work on it and declined to comment on that decision.

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"These drugs are outcasts in the pharmaceutical community," says Sporn, "because as the conventional wisdom goes, they do too much." But there is hope that NRX194204 may reach patients. A California-based company, NuRx Pharmaceuticals (formerly Quest International, Inc.), is now conducting Phase I trials with that compound.

Cells: Neither triterpenoids nor rexinoids "fit the paradigm of being monofunctional magic bullets," says Sporn. Instead, they "have multiple actions in several different cell types, particularly in the tumor microenvironment." In other words, they affect not just cancer cells but also surrounding tissues. And this is the key to their success, Sporn points out, because cancer "is the end result of dysfunctional communication between epithelial cells and their microenvironment." As he is fond of saying, there is no such thing as *a* cancer cell.

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Sporn, rear, is shedding light on chemoprevention.