Sporn and Liby study triterpenoids—whose versatility makes them a veritable Swiss Army knife of the drug world.

For a WEB EXTRA with a list of research papers about synthetic triterpenoids, see dartmed.dartmouth.edu/sp10/we01.

Versatile drugs make use of body's own defenses

A family of drugs discovered at Dartmouth is proving more versatile than originally thought, as evidenced by more than a dozen recent papers by scientists at DMS and elsewhere. These drugs—called synthetic triterpenoids—were created to prevent and treat cancer. But due to their potent anti-inflammatory and antioxidant properties, they appear to be useful in treating not just cancer but diabetes, Parkinson's, and other diseases. And the latest findings show that triterpenoids may even help prevent age-related macular degeneration and emphysema.

Triterpenoids are not antioxidants themselves, says Michael Sporn, M.D., one of the lead scientists at Dartmouth who helped develop the drugs. Instead, "they turn on the body's own antioxidant defenses." His DMS collaborator Karen Liby, Ph.D., has shown that triterpenoids are potent inducers of Nrf2, a molecule that regulates several detoxification genes and antioxidative enzymes.

Levels: A Texas company, Reata Pharmaceuticals, has licensed some of the triterpenoids from Dartmouth. In June 2009, Reata reported that one of them, bardoxolone methyl, improved kidney function by more than 20% after 28 days of use by patients with chronic kidney disease and type 2 diabetes. The drug, which is taken orally, also lowered patients' blood sugar levels.

Rare: The company had previously tested bardoxolone in patients with advanced pancreatic cancer. Those trials resulted in the Food and Drug Administration granting Reata an orphan drug designation for bardoxolone. This provides companies with incentives, such as reductions in regulatory fees, to produce drugs for rare diseases. The company has since turned its efforts toward testing bardoxolone for the treatment of chronic kidney disease and type 2 diabetes, in hopes of bringing the drug to market sooner.

Triterpenoids "turn on the body's own antioxidant defenses."

Most of the preclinical work on bardoxolone and other synthetic triterpenoids was conducted at Dartmouth. Synthetic triterpenoids were conceived in the 1990s by Dartmouth chemists Gordon Gribble, Ph.D., and Tadashi Honda, Ph.D., and tested for bioactivity by Sporn and members of his lab. The goal was to magnify the mild anti-inflammatory and anticancer properties of triterpenoids that occur naturally in plants. In 1998, Honda synthesized a compound named CDDO, which was close to half a million times more potent than natural triterpenoids. CDDO became the backbone upon which Honda created several more compounds that are currently being tested by Reata, Sporn's lab, and scientists at Johns Hopkins and Cornell.

Lung: Sporn and Liby have shown in several studies that bardoxolone, or CDDO-methyl ester, as it is known scientifically, prevents and successfully treats lung cancer and breast cancer in mice. For example, in the December 2009 issue of *Cancer Prevention Research*, they reported that bardoxolone reduced by 92% the average number and size of tumors in mice with lung cancer. And in the July 2008 issue of *Clinical Cancer Research*, they reported that the drug arrested the growth of 86% of tumors in mice with estrogen receptor-negative breast cancer.

Now, they and their collaborators are looking at applications of synthetic triterpenoids to diseases other than cancer. Sporn and researchers at Johns Hopkins and Northwestern coauthored a review article in *Vision Research* in which they describe how Nrf2 can protect against oxidative stress in the eye and potentially prevent age-related macular degeneration, a leading cause of vision loss in the elderly. And Ian Pitha-Rowe, M.D., Ph.D., a researcher in Sporn's lab, showed that CDDO derivatives protect retinal cells from oxidative stress. Other papers in the past year reported that triterpenoids may be useful in preventing pulmonary diseases such as emphysema and in treating neurodegenerative diseases such as Parkinson's.

Market: With so many promising publications, it might seem almost a certainty that synthetic triterpenoids will make it to market. Sporn, who has been trying to develop chemopreventive drugs for more than 30 years, is optimistic about the future of triterpenoids, but cautious, too. He knows there are still several hurdles that must be cleared before the drugs make it to the bedside. The key, he says, is not to stumble in "the very last lap of this marathon." JENNIFER DURGIN