Turning green gunk to gold, anti-cancer gold

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Combining synthetic chemistry techniques with a knowledge of the properties and actions of enzymes, scientists have been able to produce an exciting class of anti-cancer drugs originally isolated from blue-green algae.

This accomplishment is expected to make it possible to produce enough of the promising drugs for use in clinical trials.

In a study featured on the cover of the January issue of the journal *ACS Chemical Biology*, a scientific team lead by University of Michigan Life Sciences Institute Research Professor David H. Sherman and researcher Zachary Q. Beck found the trick to turning the green gunk into gold---cancer fighting gold.

"It was simply too difficult to use the native blue-green algae for high-level production using traditional fermentation approaches," said Sherman. But the compound, called cryptophycin 1, held so much promise as an anti-cancer drug that organic chemists got busy trying to find ways to make a synthetic form of the compound in large enough quantities for clinical trials.

Developing an efficient synthetic route to natural product compounds and their analogs is often an essential step in drug development. With drugs such as penicillin and tetracycline, it can easily be done, but cryptophycins present more of a challenge. Sherman's team realized that with all cryptophycins, the most difficult step came very late in the synthesis, at the point at which a key part called an epoxide---a highly

strained, three-membered ring oxygen-containing group, crucial for the drug's anti-cancer activity---becomes attached to the molecule.

The epoxide group can be attached in two configurations, designated as alpha and beta. Scientists have known for several years that the beta configuration was absolutely required for the anti-cancer properties of the drug, but were unable to devise efficient synthetic strategies that favored that configuration.

Sherman's team accomplished this by isolating the entire set of biosynthetic genes and key enzymes and developing a new, efficient method to manufacture the broad class of cryptophycin natural products, including important analogs with clinical potential. This included characterization of an enzyme, cytochrome P450, that always introduces the epoxide in the desired beta configuration.

Sherman, who is also the John G. Searle Professor of Medicinal Chemistry in the College of Pharmacy, believes that this approach will allow effective new cryptophycin analogs with low levels of side effects to be created for clinical trials.

"This issue represented an exciting target that offered not only an interesting scientific problem, but the potential to do something of practical importance in creating a promising anti-cancer drug," he said.

Source: University of Michigan