Duke chemists synthesize promising anti-cancer product

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Duke University chemists have patented an efficient technique for synthesizing a marine algae extract in sufficient quantities to now test its ability to inhibit the growth of cancerous cells while leaving normal cells unaffected.

The researchers also deduced that this molecule -- called largazole -- acts on cells through the same chemical mechanism as other anti-cancer compounds on the market or in clinical trials. "It's a very exciting molecule," said Jiyong Hong, a Duke assistant chemistry professor.

Hong's graduate student, Yongcheng Ying, will describe the work in an Aug. 20 talk in Philadelphia during the 236th national meeting of the American Chemical Society. It has also been described in a May 29 report in the *Journal of the American Chemical Society* (JACS).

Hendrik Luesch, a natural product chemist at the University of Florida who led the group that discovered largazole, was a corresponding author of the May JACS report along with Hong. Luesch's team first extracted and identified largazole from a marine blue-green algae collected at Key Largo, Fla.

Guided by evidence of therapeutic benefits from extracts of a related algae, the Florida group demonstrated that largazole could impede breast cancer cell growth better than the anti-tumor drug Taxol without causing Taxol-like side effects on normal breast tissue.

But Luesch's group "isolated just one milligram, a very tiny amount, from natural sources that were very difficult to grow," Hong said. "We needed to develop a concise and efficient synthetic route to make enough largazole for animal studies."

Winning a race with several other groups, the Duke team devised a method to produce gram-sized quantities -- about 1,000 times more -- by identifying three key building blocks in largazole's ring-shaped molecular architecture.

The scientists were then able to use commercially available chemicals to make largazole in eight steps, netting what Hong called a "very, very efficient" 20 percent yield.

"My lab's next task was finding the origin of lagarzole's biological activity," Hong said. The molecule appeared to initiate some signaling cascades that could affect inappropriately proliferating cells but not normal ones.

In the process of sleuthing this question, Hong said his group accidentally discovered that largazole was structurally similar to another molecule called FK228. FK228 is known to inhibit histone deacytelases (HDACs), enzymes regulating genetic activity that can foment cancerous cell growth.

The Duke team confirmed that, like FK228, largazole also suppressed HDACs. Another HDAC suppressor, marketed as Zolinza, has now been approved for the treatment of T-cell lymphoma, Hong said. Others, including FK228, are undergoing clinical trials as anti-cancer drugs.

Hong's group is now doing follow-up research aimed at changing largazole's structure to increase its effects on cell growth. "It could be a very good drug candidate for the treatment of various cancers," he said.

Source: Duke University