A four-year partnership has yielded potential new antibiotics to fight bacteria that cause infectious diseases. Read More.

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Microbial DNA speeds clues to cancer drug discovery

Yi-Qiang “Eric” Cheng, an assistant professor of biological sciences at UWM, discovered two chemical compounds derived from the bacterium Burkholderia thailandensis that were tested recently by the National Cancer Institute (NCI) and found to be effective against about 20 different kinds of cancer.

It is the first time an anti-cancer compound from a UWM lab has been tested by the NCI with such encouraging results.

Sifting through bacterial DNA sequences is not the usual first step for scientists involved in drug discovery, but chemogenomics is a fairly new field – and one that is already showing promise.

“Endless experimental approaches have failed in finding anti-cancer compounds. We started our anti-cancer drug discovery research from FK228, a compound discovered in the 1990s by the Japanese pharmaceutical company Fujisawa,” says Cheng. FK228 (and spiruchostatins later found by the same company) inhibits the function of a class of enzymes (called histone deacetylases) that are often hyperactive in cancer cells. FK228, under the commercial name of Istodax, was approved by the FDA in November for the treatment of cutaneous T-cell lymphoma.

But with gazillions (the actual number is 5 x 10^30) of bacteria on Earth, how did Cheng find a matching compound in another microbe so quickly?

He first cloned the complex gene cluster involved in the formation of FK228 and then searched the sequence database GenBank for other gene clusters that contain a similar stretch of genes. The hunt eventually led him to discovering two new compounds that he named thailandepsins. These also inhibit the functioning of histone deacetylases, but are structurally different from the Fujisawa compounds.

The gold standard

Cheng submitted thailandepsins to the National Cancer Institute’s Developmental Therapeutics Program, which offers free testing of promising compounds against 60 different cancer cell lines.

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- Eric Cheng

Results showed the thailandepsins were significantly potent against 17 to 20 kinds of cancer. The compounds also proved to be selective in targeting the cancer cells, indicating that they might not be toxic to healthy cells.

Lastly, Cheng’s compounds were active against a different portfolio of cancers than those of FK228, giving them distinctive features.
“I’m very pleased,” he says. “It has enhanced my confidence that what we’ve found will be as useful as, if not better than, those compounds already available.”

In addition to a wide spectrum of cancers, Cheng speculates thailandepsins may also be useful in the treatment of neurodegenerative diseases, inflammatory disorders and diabetes, other diseases in which the histone deacetylases play a role.

**Closer to the market**

With biosynthetic pathways from three microbes now dissected, Cheng’s lab is in a good position to start combinatorial biosynthesis to create a library of lead compounds for the drug discovery process.

He already holds two patents from his postdoctoral research and was the first UWM faculty member to file a patent application with the newly formed UWM Research Foundation in 2006. Currently he has two patent applications with the UWMRF on this work, says president Brian Thompson.

After the patents are approved, pharmaceutical companies can license them to develop commercial products.

Bringing new drugs to the marketplace is a long process, says Thompson, but Cheng has overcome an early but important hurdle.

“To realize the significant commercial potential of this work, we’ll need to find the right partners who will work closely with Dr. Cheng so that they see the data at each step of the process,” he says.