

'Wrapping' Gleevec fights drug-resistant cancer

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A new study highlighted on the cover of this week's issue of *Cancer Research* finds that the anti-cancer drug Gleevec® is far more effective against a drug-resistant strain of cancer when the drug wraps the target with a molecular bandage that seals out water from a critical area. The research appears as a priority report in the journal's May 1 issue.

The wrapping version of the drug – known as WBZ-7 – was created, produced and tested by three research teams, one headed by Ariel Fernandez from Rice University and the other two headed respectively by William Bornmann and Dr. Gabriel Lopez-Berestein from the University of Texas M. D. Anderson Cancer Center in Houston. The work sprang from a new collaborative partnership between the two institutions. In laboratory studies, WBZ-7 was found to be effective against a form of gastrointestinal cancer that has developed a resistance to imatinib, the drug sold under the brand name Gleevec®.

Imatinib is one of the most effective of a new generation of cancer drugs that are designed to attack cancer cells and leave healthy cells unharmed. Imatinib targets a protein called KIT that plays a role in cell reproduction. In healthy cells, KIT is active only on rare occasions, but in some cancers the protein is always "on," acting as a biochemical catalyst that spurs cancer cells to constantly reproduce.

"The re-engineered version of imatinib accomplishes three things," said Rice bioengineering professor Ariel Fernandez, who designed the modified drug. "It binds with KIT. It binds with the most effective

imatinib-resistant version of KIT. And finally, it binds in a way that ensures that any further version of KIT that becomes resistant to WBZ-7 will no longer be effective as a catalyst for cell reproduction."

Fernandez and his Rice colleagues – postdoctoral researcher Alejandro Crespo and graduate student Xi Zhang – developed the wrapping Gleevec® variant WBZ-7. The wrapping prototype is a kind of molecular bandage that's designed to keep water molecules from getting near the "active site" of KIT – the part of the protein that imatinib targets.

"Like virtually all proteins, KIT has packing defects that leave some hydrogen bonds poorly shielded from water attack," Fernandez said. "These bonds, which are called dehydrons, are in the twilight zone between order and disorder."

In KIT, there is a dehydron near the active site that plays a key role in drug resistance. WBZ-7 seals off this dehydron.

Fernandez said WBZ-7 is identical to imatinib, save for the addition of four atoms – a carbon and three hydrogens – at a key point. Though the change appears to be minimal at first glance, finding a method to synthesize the compound was complex and challenging, Fernandez said. The task fell on Bornmann, a director of the Center for Targeted Therapy's Translational Chemistry Service, and his colleagues Shimei Wang and Zhenghong Peng – who dubbed the compound WBZ-7 based on their initials and the fact that it was the seventh compound they'd made together.

Following the drug's synthesis, a second team of M. D. Anderson researchers, led by Lopez-Berestein, a professor in the Department of Experimental Therapeutics, and including Angela Sanguino and Eylem Ozturk, embarked on a comprehensive testing program. In the first stage

of testing, WBZ-7's effects were tested against more than 250 catalytic proteins called kinases, which are in the same class of proteins as KIT, to make sure the drug would not have unintended consequences. Finally, a range of in vitro tests were conducted. The tests confirmed that WBZ-7 was just as effective against both non-resistant and drug-resistant strains of gastrointestinal cancer cells.

WBZ-7 is not yet available for human testing, and a date for human trials has not been set. Fernandez said the research team is preparing for the next phase of testing in laboratory animals.

Source: M. D. Anderson Cancer Center

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