An old drug finds a new use

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Dr. Anglea Wandinger-Ness and Dr. Laurie Hudson were awarded a Provocative Questions grant to investigate the use of R-ketorolac against ovarian cancer. Ketorolac is an NSAID that the FDA approved for human use in 1991. They are investigating their hypothesis that R-ketorolac, and not S-ketorolac, acts on GTPases in the cell to control cell adhesion and growth in ovarian cancer cells.

Most drugs take ten years—and frequently, more—to go from concept to FDA approval. One way to reduce this time investment is to look for already-approved drugs that could be put to new uses. And that's just what Angela Wandinger-Ness, PhD, UNM Professor of Pathology, and Laurie Hudson, PhD, UNM Professor of Pharmaceutical Sciences, have done. Drs. Wandinger-Ness and Hudson, both at the University of New Mexico Cancer Center, were recently awarded a two-year exploratory National Cancer Institute (NCI) grant to investigate the use of R-ketorolac against ovarian cancer cells.

Ketorolac is an NSAID, or non-steroidal anti-inflammatory drug. The FDA approved its use for pain relief in humans in 1991. "Inflammation is an important process in cancer," says Dr. Hudson. Dr. Wandinger-Ness adds, "So the provocative question is: why? Why are some NSAIDs protective in cancer, while others are not? What are the protective mechanisms, anti-inflammatory or other basis? We know that NSAIDs work, but lack a complete understanding of the basis of anti-cancer efficacy."

In fact, several areas in cancer research are not well understood. So to

consider some of these areas now that new technologies can be used to explore them, the NCI created a list of 24 Provocative Questions and awarded grants in these areas. Dr. Wandinger-Ness and Dr. Hudson are two of only 57 Provocative Questions grant recipients. Their work centers on demonstrating one path by which anti-inflammatory drugs can protect against cancer.

Dr. Wandinger-Ness's work with GTPases—the chemical switches inside a cell which regulate processes ranging from cell growth to how cells adhere to each other—dovetailed nicely with Dr. Hudson's work on how ovarian cancer spreads. They have been collaborating now for over 5 years. Their collaboration also synergizes with the work of other researchers—"Team Science," as Dr. Wandinger-Ness calls it.

Capitalizing on the flow cytometry expertise of Larry Sklar, PhD, UNM Professor of Pathology, and the drug conformation computer modeling expertise of Tudor Oprea, MD, PhD, UNM Professor of Biochemistry and Molecular Biology (both at UNM Cancer Center), Dr. Wandinger-Ness and Dr. Hudson identified drugs they thought would control GTPases in a cell. The process was similar to finding the proverbial needle in the haystack. "Technologies like flow cytometry and advanced computer modeling allow this kind of discovery to be made," says Dr. Hudson.

The first drug the team found, R-naproxen, was FDA approved but not available for human use so they found a second candidate, R-ketorolac. Now, working with Jennifer Golden, PhD, Assistant Director at the Kansas University Specialized Chemistry Center, they are precisely targeting particular types of GTPases in a cell to modulate cancer cell behaviors that affect tumor growth and spread. Their many experiments and initial animal studies using R-ketorolac against ovarian cancer look very promising in keeping tumor growth in check.

R-naproxen and R-ketorolac are not anti-inflammatory agents, though. While their mirror images, S-naproxen and S-ketorolac, target a specific class of proteins called cyclooxygenases that strongly inhibit inflammation—making them potent NSAIDs—R-naproxen and R-ketorolac do not have these properties. It's a provocative twist to Provocative Question number 5 on the NCI's list.

Ketorolac is marketed as Toradol for post-operative pain and consists of an R-ketorolac and S-ketorolac mixture allowing both forms of the drug to be administered in a single dose. Although both forms have exactly the same chemical formula, they are not the same molecule in three dimensions just as your left hand and your right hand are not the same. Thus, they behave differently inside a cell because the drugs interact with different proteins just as "the right hand only fits a right hand glove, but doesn't fit into the left hand glove," as Dr. Hudson explains.

Dr. Wandinger-Ness and Dr. Hudson are now proposing that R-ketorolac has a possible new activity inside the cell. "We think R-ketorolac interacts with the GTPases," says Dr. Wandinger-Ness. GTPases control cell growth and cell adherence, two important characteristics of ovarian cancer cells. "We have good of evidence that R-naproxen interacts with this GTPase pathway," Dr. Hudson says. So now, through their NCI grant, they're working to demonstrate that R-ketorolac can inhibit the specific GTPase cascades that enable ovarian cancer cell behaviors contributing to tumor growth and spread.

Dr. Wandinger-Ness and Dr. Hudson along with Carolyn Muller, MD, UNM Professor of Obstetrics and Gynecologic Oncology, want to expand these studies to benefit people. That's why, through several other grants, they intend to begin Phase I clinical trials of R-ketorolac for ovarian cancer. "Building something like this requires a long time and it requires seed money," says Dr. Wandinger-Ness. "We want to acknowledge cancer donors and the UNM Cancer Center grant."

Through this complex network of scientific teamwork and funding, they'll be able to bring this research to the clinic far faster than any new drug to the marketplace.

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