K-State scientists change the channel on cancer drug delivery

By Marcia Locke

The common chemotherapy drug cisplatin was FDA-approved for use in testicular and ovarian cancers in 1978. Yet, after all these years, scientists still do not know exactly how it and similar drugs work. Such drugs enter cancerous cells and cause them to kill themselves, but it is not clear how they enter the cell to begin with.

Two Kansas State University researchers with different, but complementary, skill sets have teamed up to figure out, in molecular detail, how substances penetrate cell membranes in both normal circumstances and diseased states.

Peying Fong, associate professor of anatomy and physiology, is an expert in cell membrane physiology. Jeffrey Comer, assistant professor of anatomy and physiology, is an expert in computer simulation of molecules. Together, they are working to better understand cell membrane proteins that mediate the movement of substances into and out of cells called transport proteins.

Currently, Fong and Comer are focusing on LRRC8 proteins, which assemble themselves into channels, like pores, in the cell membrane. There are five types of LRRC8 proteins — A through E — and their channel-forming configurations can vary.

Channels containing LRRC8D allow cisplatin to permeate the cell. Interestingly, ovarian cancers with poor prognosis have fewer of these channels. It is not yet known whether other LRRC8 proteins can carry cisplatin or other drugs.

With an Innovative Research Award from the Johnson Cancer Research Center, Fong and Comer are unraveling the complexities of LRRC8 channels, hoping to uncover information that could help create new cancer therapeutics.

One approach they're taking is to build on past work done by K-State researchers Annelise Nguyen, associate professor of diagnostic medicine and pathobiology; Dee Takemoto, professor emeritus of biochemistry; and Duy Hua, university distinguished professor of chemistry. This team discovered compounds that alter channels similar to LRRC8s, raising the possibility that these drugs also affect LRRC8s.

Substances don't just enter cells; they also travel from cell to cell. This is how cells communicate with each other — and how drugs spread throughout a tumor. However, cancer cells do not communicate well because some of their channels, called gap junction hemi-channels, close. This suppresses drug distribution.

Nguyen's team identified compounds, called PQs, which open the gap junction hemi-channels and restore communication between cancer cells. This could allow drugs to spread more easily, meaning smaller quantities could be used. This is good because cancer drugs can be toxic to healthy cells.

Fong and Comer want to know if PQs work similarly with LRRC8 channels.

"Since LRRC8s organize across plasma membranes in a pattern much like that of gap junction hemi-channels, it is important to determine whether PQs similarly enhance function of different LRRC8 channels," said Fong.

Discovering how drugs permeate different LRRC8 channels could help ascertain whether PQs could have other applications in cancer therapeutics, according to Fong.

"If PQs can both open LRRC8 channels and restore gap junction communication, then co-administering PQs with cancer therapeutic agents could promote not only entry but drug distribution throughout the tumor," Fong said.

This is where Comer's expertise comes in. He is creating computer simulations of the LRRC8 proteins and their different assemblies. The models can then be screened for PQ binding and permeation, as well as permeation of chemotherapeutic agents.

"Proteins are tiny machines that make our bodies work," Comer said. "Being able to visualize them by using the same technologies that go into video games helps us understand how they work."

"We anticipate that these computer models will significantly advance our research," Fong said.

Fong is grateful for the Johnson Cancer Research Center's support of her and her students' research over the years. This most recent support helped her initiate this collaboration with Comer and they were able to present preliminary data in a promising grant application to the National Institutes of Health.

$3,579,956 has been invested in promising cancer studies since 2003. But $5,566,762 has been requested.