GOING FOR

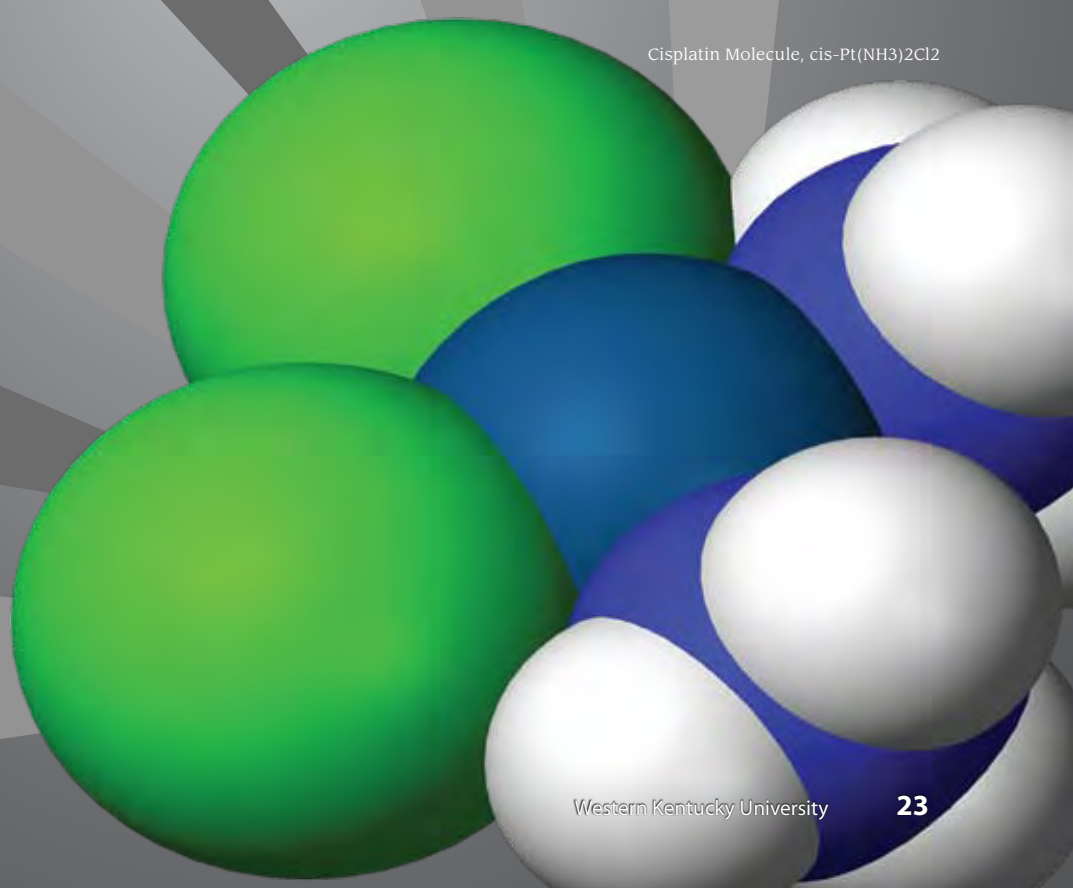
PLATINUM

BY BOB SKIPPER

AS WITH MANY CANCER DRUGS, THE PLATINUM COMPOUND CISPLATIN IS TOXIC. IT ALSO HAS A TENDENCY TO REACT TO PROTEINS INSTEAD OF THE TARGETED DNA, AND CELLS ARE PRONE TO DEVELOPING RESISTANCE. KEVIN WILLIAMS, ASSISTANT PROFESSOR OF CHEMISTRY AT WESTERN KENTUCKY UNIVERSITY, IS LOOKING AT HOW THE SIZE AND SHAPE OF THE PLATINUM MOLECULES MIGHT IMPROVE CISPLATIN'S EFFECTIVENESS.

Cisplatin, cis-Pt(NH3)2Cl2, has been around since the nineteenth century. Its use as an anti-cancer drug began in the 1970s. "It's really successful against testicular cancer and pretty successful against ovarian cancer," Dr. Williams said. However, since cells tend to develop resistance, the first dose is more effective than subsequent doses, he explained. "In general, we want to get the dosage down so that it doesn't take as much of the platinum compound to be effective."

Cisplatin's effectiveness comes in its reaction with the cancer's DNA. "It tends to interfere with the DNA replication processes and since cancer cells grow faster than



Cisplatin Molecule, cis-Pt(NH3)2Cl2

Kevin Williams and undergraduate assistant Michael Starling examine data obtained from the NMR spectrometer. The NMR spectrometer characterizes products formed with the platinum compounds.

other cells, it tends to target cancer cells," Dr. Williams said. The platinum compound also reacts with proteins. Some studies have shown that even on the first day, the majority of the cisplatin begins reacting with proteins instead of DNA.

"There has been a lot of speculation as to what the protein reaction does," Williams related. "It could be that some of the side effects are caused by the protein reactions. The resistance may be a consequence of the protein reactions. In general you're going to need a higher dosage if you want to target DNA." In simple terms, the reaction with proteins is the unwanted outcome and the reaction with DNA is the wanted outcome.

"What we've been doing is looking more at the reaction to proteins and trying to find ways to prevent protein binding relative to DNA binding," he said. "We figure if we can decrease the unwanted adduct and not eliminate the reaction with DNA, it would be helpful."

Working with up to fifteen students, Dr. Williams has been looking at the structure of cisplatin molecules, specifically their size and shape. "Cisplatin is about as small of a molecule that you can make to have the properties that it has, so just about anything that you make is going to be bigger," he said. "We're looking at what happens if you take a molecule that's pretty close to the size of cisplatin and compare it to something bigger to see if that affects things differently."

In simple terms, the reaction with proteins (methionine) is the unwanted outcome and the reaction with DNA (guanine) is the wanted outcome.

Since the main DNA target, guanine, is less bulky than the main protein target, methionine, Dr. Williams theorizes that changing the size and shape could cause the platinum molecules to react with one over the other. "Fortunately for us, the protein target is a little bigger target to hit. By making the platinum molecules bigger, we're hoping to see selective reaction with DNA and not with proteins," he said. The researchers attach carbon and hydrogen atoms to cisplatin to add bulk.

"We have developed parameters that will allow us to use molecular mechanics calculations to generate computer models of complexes between platinum and methionine residues, and we are using parameters developed previously for platinum and guanine," he said. "These calculations are being used to predict the effect of the size and shape of the platinum complex on the stability of guanine and methionine complexes."

Dr. Williams has synthesized selected cisplatin analogs and reacted these analogs with methionine and guanine derivatives. He and his students have used nuclear magnetic resonance spectroscopy to characterize the products. They have also studied the effects of carrier ligand size on the rate of protein adduct formation and will use instrumentation from WKU's Materials Characterization Center to determine the amount of platinum bound to the protein. They are also using liquid chromatography/mass spectrometry and gel electrophoresis to study the cleavage of proteins by selected platinum complexes.

While changing the size and shape of the platinum molecules has affected their reactions, Dr. Williams said the rate of those reactions is also important. "Just because you can get the products to form doesn't mean they are going to form in a timeframe that is reasonable biologically," he said. "We found that regardless of which target you are looking at, the bulkier compound is going to react slower. What is a little more interesting is that both of the platinum compounds that we tested reacted faster with our guanine target. What that's suggesting is that if you have a little bulk on the platinum compound you might get fewer protein adducts and fewer protein adducts might make it work better."

But that particular compound is too slow to react to be effective as a cancer drug, he said. "There has to be a balance and that's where we are headed in the future, to see how much bulk it takes in order to get the reaction with protein slowed down and not interfere too much with the reaction with DNA. We don't know if we're going to find something that will work really well or if we're going to have to keep being creative."

Dr. Williams is using a $197,000 grant from the National Institutes of Health to continue this part of the research. "With this grant, we are looking at several different platinum compounds to see if any of them might be the magic compound," he said. "Our goal is not necessarily to produce the next generation of anti-cancer drug out of our lab. It is more to find the trend."

Dr. Williams began working with platinum compounds while in graduate school at Emory University. It was there that he studied how shape affected reactions with DNA. When he came to WKU to teach in 2002, he developed the idea that proteins would be affected differently and received funding from Kentucky Experimental Program to Stimulate Cooperative Research (EPSCoR) for a one- to two-year project.

"By the end of the first summer we had figured out what was happening and that led to our first paper," Dr. Williams said. "That's when he realized the dramatic effect the bulk of the platinum molecule was having and that the rates of reaction were going to be important."

When he started, Williams said he did not envision continuing to where the research is now. The research has led to one honors thesis and two articles in which five students have been co-authors. "I really have had some good students who have worked with me and I consider their success more a testimony to their talent than to the project," he said.

Williams also asserted that many of the ideas during this research evolved from conversations with students. "Whether the idea was mine or theirs, it came up during the conversation so they contributed to it." ■

Kevin Williams loads a sample into the departmental NMR spectrometer for analysis.