Expanding platinum's potential

By Kai-Jye Lou, Staff Writer

Researchers at **Northern Illinois University** and **Ohio University** have identified a new class of platinum complexes that exhibit anticancer activity without binding to DNA.¹ Although platinum-based cancer therapeutics are generally believed to work by binding DNA, this paper shows that these drugs may exert at least part of their effects through other mechanisms.

According to the researchers, the findings may lead to next-generation platinum-based cancer therapeutics with fewer side effects and less potential for drug resistance than marketed platinum drugs.

In a paper in the *Proceedings of the National Academy of Sciences*, the research group, led by Rathindra Bose, professor in the Department of Biomedical Sciences and the Department of Chemistry and Biochemistry at Ohio University, identified a class of platinum-phosphato complexes that did not form covalent bonds with DNA. Moreover, one of the complexes, dubbed pyrodach-2, showed superior cytotoxicity compared with cisplatin and carboplatin in platinum-resistant ovarian cancer cells.

A gene expression assay showed that pyrodach-2 upregulated the expression of proapoptotic genes, including those that code for transmembrane proteins. The combined results suggest that some of pyrodach-2's therapeutic effects may result from interactions with transmembrane proteins.¹

"I wanted to show that there are mechanisms other than DNA binding that contribute to the therapeutic effects of platinum-based drugs," Bose told *SciBX*.

To show that cisplatin may be exerting its effects by both DNA-binding and non-DNA-binding mechanisms, his group removed the DNA-binding effects from a platinum complex and showed that it still had anticancer activity.

"The finding from our group suggests the existence of new criteria for the synthesis and screening of platinum-based anticancer agents," Bose said.

Excising excision

According to Bose, platinum-phosphato complexes could have two main advantages over conventional platinum drugs: less potential for resistance and improved safety.

Platinum-based chemotherapeutics such as cisplatin bind to DNA and cause cross-links that block DNA replication and transcription. These cross-links, however, are recognized and repaired by nucleotide excision repair enzymes.

"Resistance to conventional platinum-based therapeutics is likely to occur when cells become able to effectively repair the DNA damage caused by these compounds," Bose said. "Nucleotide excision repair

Box 1. Paradigm shift.

A group at **Wake Forest University** has developed platinum-acridine complexes that bind to and damage DNA without forming cross-linking structures.² Such chemotherapeutics may be able to evade the host excision repair enzymes that can cause resistance to conventional platinum drugs.

In their paper in the *Journal of Medicinal Chemistry*, the researchers show that in mice with aggressive human non-small cell lung cancer (NSCLC), a 0.5 mg/kg dose of a platinum-acridine complex derivative lowered tumor volume by 40% compared with what was seen in vehicle-treated controls ($p < 0.01$).

NMR studies showed that the compounds bind to DNA, but enzyme inhibition assays revealed that the platinum-acridine complex does not form DNA cross-linking structures and dam-

ages DNA at sites distinct from those seen with cisplatin treatment.

"This work is breaking the paradigm that cross-linking is the key mechanism for platinum-based therapeutics," said Ulrich Bierbach, an associate professor in the Department of Chemistry at Wake Forest and principal investigator on the *JMC* paper. "Our drug not only targets DNA more efficiently than cisplatin, but also forms adducts that, unlike the cross-links formed by the clinical agent, do not bend and destabilize DNA."

Bierbach thinks that the more subtle structural changes induced by the compound are not recognized by DNA repair enzymes, but he noted that this hypothesis needs to be tested.

Going forward, Bierbach said his group will evaluate additional analogs of the parent platinum-acridine complex

in mice. He said his team still needs to optimize the therapeutic index of the compounds by making them more potent while decreasing their toxicity.

He also wants to conclusively demonstrate that these platinum complexes circumvent the activity of nucleotide excision repair enzymes. Bierbach said this can be demonstrated by constructing DNA fragments containing a single adduct formed by a platinum-acridine complex or cisplatin, exposing them to cell-free extracts containing nuclear excision repair enzymes and comparing the level of repair activity between the fragments.

The platinum-acridine complexes are available for licensing from the Wake Forest University Health Sciences Center Office of Technology Asset Management.

—KJL

can efficiently remove platinum from DNA, but since our compound is not binding to DNA, this resistance mechanism would not factor into reducing the efficacy of our compound.”

“Right now, resistance is the main problem with platinum drugs,” said James Dabrowiak, a professor in the Department of Chemistry at **Syracuse University**. “Maybe Bose’s compounds will provide some new leads outside the normal structure-activity relationships for platinum that can better overcome resistance.”

Not all approaches try to circumvent DNA binding altogether. For example, alternative approaches include the development of chemotherapeutics that may be able to evade the host excision repair enzymes (see **Box 1**, “**Paradigm shift**”).

Regarding safety, Bose noted that most of the toxic effects of a platinum-based drug stem from its entering the cell and the nucleus, where it can inhibit the function of several key enzymes. He noted that in the aqueous intracellular environment, cisplatin readily forms into highly reactive species that can disrupt the activity of a large number of molecules, including DNA. Not only is this important for efficacy, but it also contributes to the well-known nephrotoxic, renal and neurotoxic side effects of cisplatin.

Bose noted that cellular accumulation assays in the *PNAS* paper showed that much less pyrodach-2 entered ovarian cancer cells than did cisplatin, which suggests that the complex is exerting its anticancer effects via a non-intracellular mechanism.

Moreover, pyrodach-2 showed no evidence of decomposition into highly reactive species when placed in an aqueous environment for seven days at neutral pH, which also suggests the potential for fewer side effects.

Moving into the living

Nicholas Farrell, a professor in the Department of Chemistry at **Virginia Commonwealth University**, wants to see additional studies of the non-DNA-binding mechanism. “The novel mechanisms not

involving DNA binding demonstrated in the *in vitro* assays would need to be verified in the *in vivo* setting,” he said.

Farrell added that cell fractionation studies would help show whether the platinum complexes are associating with intracellular proteins.

Similarly, Dabrowiak said he would like to see the compounds evaluated in additional cell lines and animal models.

Going forward, Bose said his group is evaluating the platinum-phosphato complexes in various mouse models to verify that it is a protein-binding compound and not a DNA-binding compound.

His group is also doing dose tolerance studies that compare the platinum-phosphato complexes with other platinum compounds. Preliminary results, he said, suggest the complexes are effective in drug-resistant ovarian, head and neck, and testicular cancers.

Bose said patent cooperation treaty (PCT) and U.S. patents have been filed covering the use of the compounds in cancer. The compounds are available for licensing from the Ohio University Technology Transfer Office.

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REFERENCES

1. Bose, R.N. *et al. Proc. Natl. Acad. Sci. USA*; published online Nov. 17, 2008; doi:10.1073/pnas.0803094105
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2. Ma, Z. *et al. J. Med. Chem.*; published online Nov. 14, 2008; doi:10.1021/jm800900g
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