Scientists report first 3-D view of anti-cancer agent

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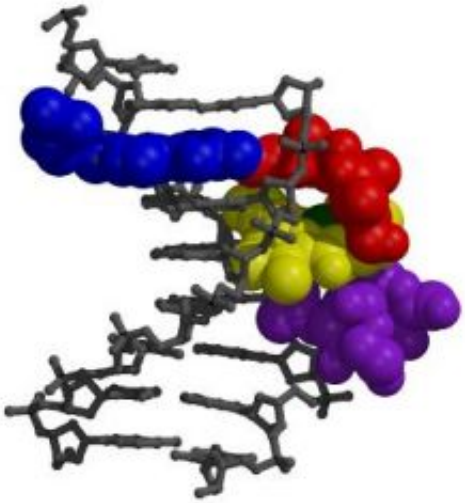

The image shows bleomycin represented in a space-filling rendering bound to DNA, in a gray ball-and-stick rendering. The color scheme highlights the different moieties that make up bleomycin: blue, bithiazole; red, linker; yellow, metal-binding domain; purple, dissacharide; and green, Co (III). Credit: Kristie Goodwin, Ph.D., Indiana University School of Medicine

Researchers from the Indiana University School of Medicine and the Purdue School of Science at Indiana University-Purdue University Indianapolis have created the first three-dimensional image of how a well-established chemotherapy agent targets and binds to DNA. The study, which publishes online the week of March 17 in the *Early Edition*

of the Proceedings of the National Academy of Sciences, may help scientists develop better chemotherapy drugs to treat a wide range of cancers.

Using X-ray crystallography, the scientists produced the first 3-D molecular level images of bleomycin bound to DNA. X-ray crystallography is a widely used analytical technique in which X-rays are directed through crystals and results are deduced from the pattern of diffraction of the X-rays.

“Although bleomycin has been studied for 40 years and much is known about the mechanism of action of bleomycin, without an accurate 3-D picture you can’t fully understand how the drug targets and sits on the DNA. If you want to improve on the properties of the drug, to make it a better chemo agent, you need to understand in great detail how it works,” said Millie M. Georgiadis, Ph.D., associate professor of biochemistry and molecular biology at the IU School of Medicine and at the Purdue School of Science. She and Eric C. Long, Ph.D., professor of chemistry & chemical biology at the Purdue School of Science, are senior authors of the study.

A combination chemotherapy regimen including bleomycin was successfully pioneered at the IU School of Medicine by oncologist Lawrence H. Einhorn, M.D., distinguished professor of medicine. This multi-agent therapy, which mutes the toxicity of bleomycin, is now the standard of care for testicular cancer. Because it causes lung damage, bleomycin is not typically used to treat other cancers.

“Our 3-D picture of the structure of bleomycin gives us a much better understanding of exactly how the drug interacts with the DNA so we can begin thinking about engineering a better drug, with less toxicity. Since it’s a DNA targeting agent, there’s no limit to what type of cancers we could target with bleomycin if we can decrease the toxicity,” said Dr.

Georgiadis, a structural biologist.

Many successful chemotherapeutics are DNA targeting agents.

Source: Indiana University