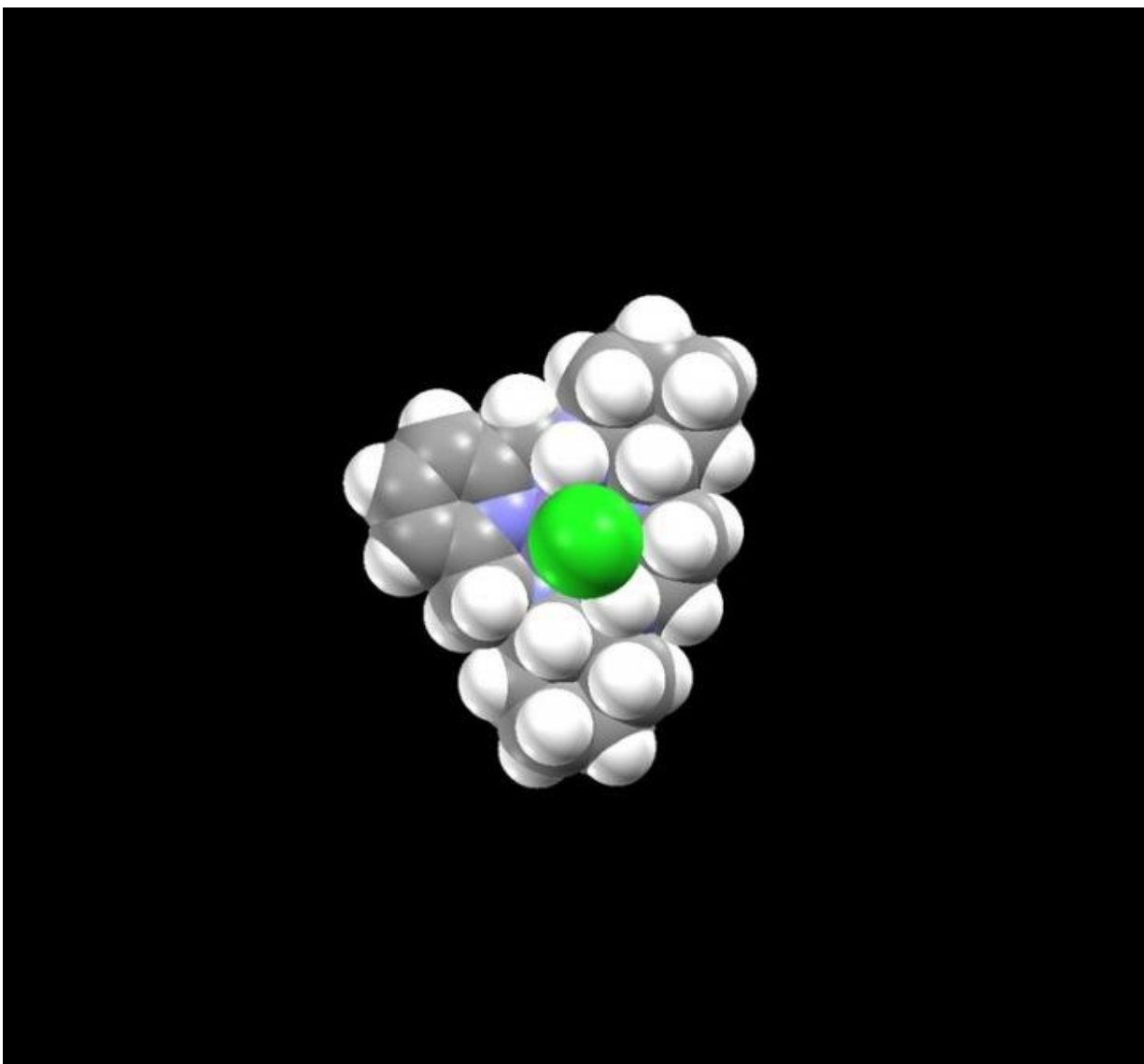


New drug could prevent debilitating side effect of cancer treatment

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Space-filling structure depiction of GC4419 based on X-ray crystal structure

determination. Credit: Dennis Riley

About 50,000 people in the U.S. are diagnosed annually with head, neck, nasal and oral cancers. Most are treated with radiation, and of those, 70-80 percent develop a painful and debilitating side effect called severe oral mucositis (SOM). While some drugs are available to treat SOM once it develops, none can prevent it. But today, researchers are reporting on a new drug, called GC4419, that appears to do just that. Although still in clinical trials, it has already been designated by the U.S. Food and Drug Administration as a "breakthrough therapy."

The researchers will present their results today at the 256th National Meeting & Exposition of the American Chemical Society (ACS).

"It is exciting to publicly report on the structure and synthesis of GC4419 for the first time," says Dennis P. Riley, Ph.D., leader of the study. "We believe GC4419 has the potential to address an important unmet medical need in the treatment of cancer patients undergoing [radiation therapy](#), and we look forward to commencing a Phase 3 trial with GC4419 in head and neck cancer patients this year."

Oral mucositis (OM) is a painful and problematic complication during cancer treatment, especially radiation therapy, which breaks down the epithelial cells lining the mouth. Patients suffering from OM experience severe pain, inflammation, ulceration and bleeding. Most patients receiving chemoradiotherapy develop SOM, as defined by the World Health Organization as grade 3 or 4 of OM. In the most severe cases, patients can't swallow or consume liquids or solid food, often leading to the use of feeding tubes and narcotic analgesics. Patients are also susceptible to infections that can lead to hospitalization.

Radiation therapy creates elevated superoxide radical levels, which are believed to be responsible for most of the side effects associated with this treatment, including OM. "The synthetic enzyme we designed and made mimics the function of the naturally occurring superoxide dismutase, an enzyme that converts superoxide to molecular oxygen and [hydrogen peroxide](#)," says Riley, who is with Galera Therapeutics. "Hydrogen peroxide is very toxic to cancer cells but not to normal cells. Thus, we create two opportunities to improve radiation therapy: reducing toxicity for normal cells while increasing the toxicity to the cancerous ones."

Designing and creating the synthetic superoxide dismutase was complex, and Riley's team tried many variations of synthetic enzyme mimics before settling on GC4419. The research began decades ago when Riley worked at Monsanto/Searle. The molecules his team were working with had four chiral carbon centers, which meant there were a very large number of potential mimics.

"We had to figure out which isomer would work best and be the most 'druggable,'" he reports. "Our current synthesis involves using a template to make the 15-membered macrocyclic ring complex in a single GMP [Good Manufacturing Practice] step. It uses pyridine-2,6-dicarboxyaldehyde, manganese(II) chloride and a linear tetramine synthesized from S,S-1,2 diaminocyclohexane. It is an elegantly simple 'one-pot' synthesis that yields the desired molecule with more than 99.5 percent chemical purity."

GC4419 successfully completed Phase 1 and 2 [clinical trials](#), showing safety and efficacy in preventing SOM in head and neck cancer patients undergoing radiation therapy. If further clinical trials are successful and GC4419 gets FDA approval, Riley says, "there's no reason it could not be used to prevent side effects from radiation treatment of other cancers. You can think of [pancreatic cancer](#), for example, in which you might

want to use high-dose radiation for locally advanced disease, but the pancreas is too close to other organs that cannot handle the side effects of radiation. We are currently studying GC4419's anti-tumor effect in a Phase 1/2 clinical trial in pancreatic [cancer](#) at MD Anderson Cancer Center. If successful, this drug has the potential to change the management of radiation therapy since 70 percent of all solid tumors are treated with [radiation](#)."

A press conference on this topic will be held Monday, August 20, at 1:30 p.m. Eastern time in the Boston Convention & Exhibition Center. Reporters may check-in at the press center, Room 102 A, or watch live on YouTube http://bit.ly/ACSLive_Boston2018. To ask questions online, sign in with a Google account.

More information: Design and development of a synthetic enzyme for use as a pharmaceutical agent to reduce the undesired side effects of radiation treatment in cancer therapy, 256th National Meeting & Exposition of the American Chemical Society (ACS).

Provided by American Chemical Society

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