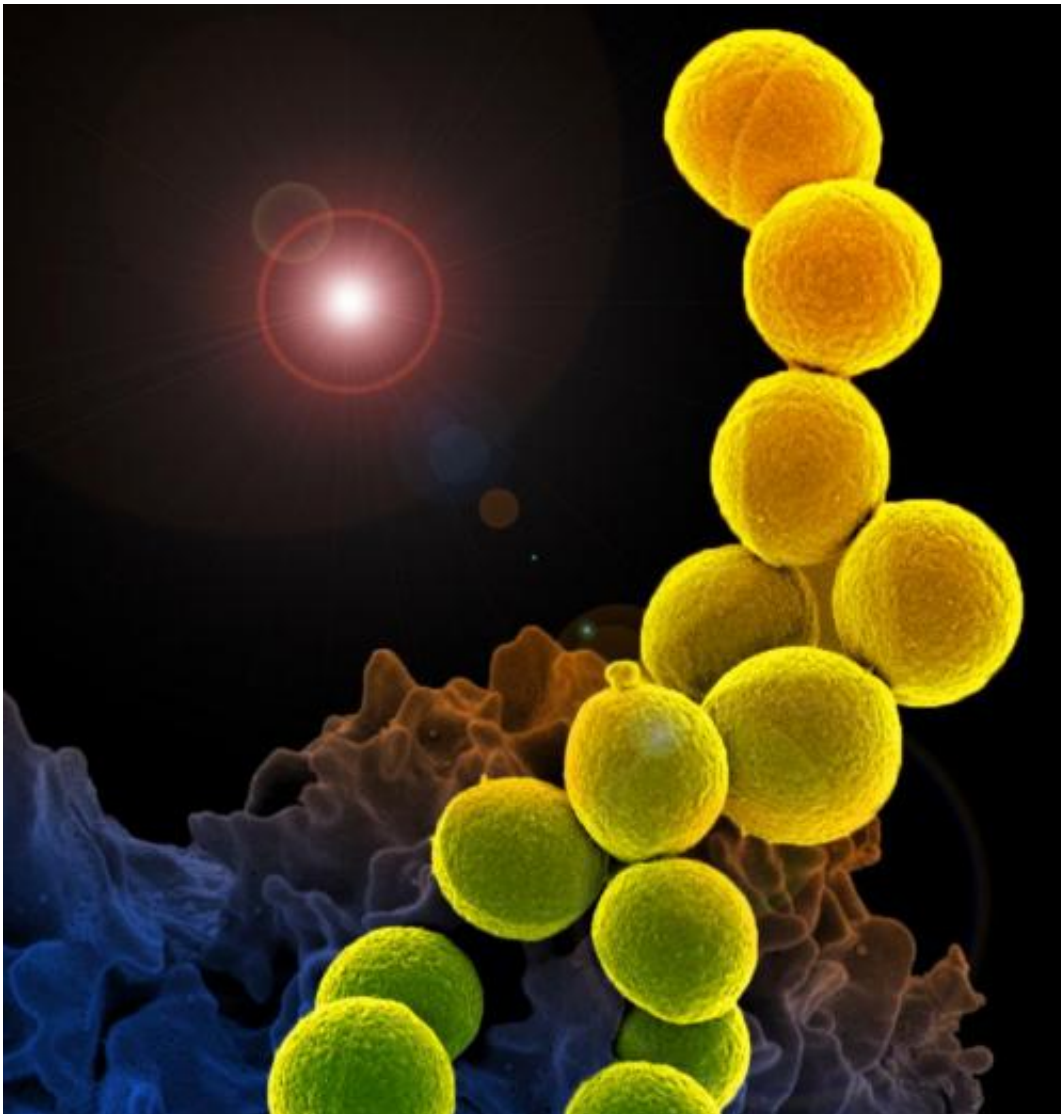


Identification of much-needed drug target against MRSA, gram-positive infections

February 2 2015



In this electron micrograph, a white blood cell eats an antibiotic resistant bacteria called methicillin-resistant *Staphylococcus aureus*, or MRSA. Credit: National Institute of Allergy and Infectious Diseases

The increasing prevalence of antibiotic resistance, when infectious bacteria evolve to evade drugs designed to control them, is a pressing public health concern. Each year two million Americans acquire antibiotic-resistant infections, leading to 23,000 deaths. In light of these unsettling statistics, there has been a call to develop new weapons to combat bacterial threats to human health.

Scientists at the University of Utah and the University of Georgia have uncovered a pharmacological target that could enable development of novel drugs against antibiotic-resistant pathogens, including Methicillin-resistant *Staphylococcus aureus* (MRSA) and other infectious Gram-positive organisms such as *Listeria* and *Mycobacterium tuberculosis*. The target was revealed upon discovery of a Gram-positive bacteria-specific pathway for making heme, an essential iron-carrying molecule. The findings were reported in the journal, *Proceedings of the National Academy of Sciences (PNAS)*.

"The therapeutic target could be used to create a completely new class of drugs for fighting Gram-positive bacteria including those that cause antibiotic-resistant infections," says John Phillips, Ph.D., senior author of the paper and research professor in hematology at the University of Utah School of Medicine.

The fortuitous discovery was an outcome of a quest to solve a case of mistaken identity. For the past 100 years, the prevailing notion was that every organism - from bacteria to man - used the same eight-step recipe to make the essential, snowflake-shaped iron transporter, heme. That's why Harry Dailey, Ph.D., first author and biochemistry professor at the University of Georgia, was puzzled when he noticed that proteins that were given the name HemN, a key component of the historically-defined heme pathway, looked very different in Gram-positive bacteria than in

other classes of bacteria. The code of amino acids - building blocks of proteins - that were recorded as Gram-positive "HemN" didn't match up with the rest.

"It made me wonder, 'What do we know, as opposed to what do we think we know?'" recalled Harry Dailey, Ph.D., first author and professor of biochemistry at the University of Georgia.

In the lab, he found that the so-called Gram-positive bacteria "Heme N" was, in fact, incapable of making heme. Determined to figure out what substitutes for HemN, Dailey collaborated with Phillips to purify components of the heme pathway in Gram-positive bacteria. Like figuring out how to make a cake by seeing how it looks after each step of the recipe is completed, they collected the intermediates of the heme pathway, and determined that the last three were completely different than expected. Biochemical experiments further showed that a Gram-positive specific enzyme called HemQ is required for the final step. A survey of heme pathway components in over 350 other organisms support the idea that only Gram-positive bacteria use the alternate, HemQ-dependent recipe for making heme.

The implications were immediately obvious to Dailey and Phillips. "A drug that disables HemQ, will knock out heme biosynthesis only in Gram-positive [bacteria](#), sparing this important pathway in our own cells," explains Dailey. He has already demonstrated that genetically eliminating HemQ severely disables the troublesome germs, suggesting a drug that targets the protein will do the same. If screens against existing compounds identify one that is capable of blocking HemQ, a drug could be available in as quickly as two years; development of a new antibiotic could take ten years.

"The original goal of this work was to sort out the naming of different bacterial genes, but the result was identifying a completely new

metabolic pathway that can be exploited to improve healthcare," says Phillips. "It's a reminder that, to paraphrase Louis Pasteur, chance favors the prepared mind."

More information: Noncanonical coproporphyrin-dependent bacterial heme biosynthesis pathway that does not use protoporphyrin. *PNAS Early Edition*, Feb. 2, 2015

www.pnas.org/cgi/doi/10.1073/pnas.1416285112

Provided by University of Utah Health Sciences

Citation: Identification of much-needed drug target against MRSA, gram-positive infections (2015, February 2) retrieved 12 May 2024 from <https://phys.org/news/2015-02-identification-much-needed-drug-mrsa-gram-positive.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.