New biologic effective against major infection in early tests

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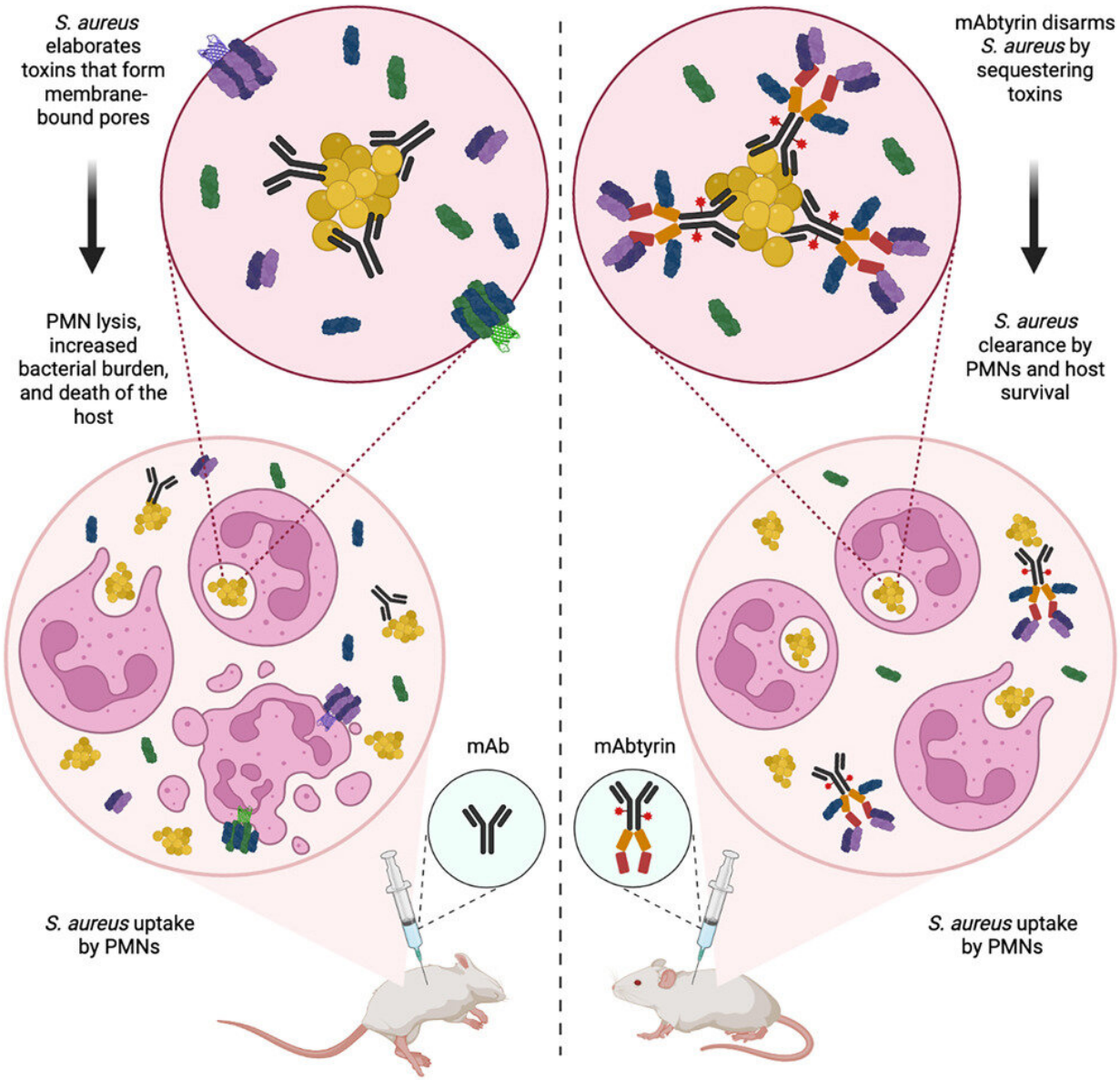

Graphical Abstract. Credit: *Cell Host & Microbe* (2023). DOI: 10.1016/j.chom.2023.04.004

Researchers at NYU Grossman School of Medicine and Janssen Biotech, Inc. have shown in early tests that a bioengineered drug candidate can counter infection with Staphylococcus aureus—a bacterial species widely resistant to antibiotics and a major cause of death in hospitalized patients.

Experiments demonstrated that SM1B74, an antibacterial biologic agent, was superior to a standard antibiotic drug at treating mice infected with S. aureus, including its treatment-resistant form known as MRSA.

Published in *Cell Host & Microbe*, the new paper describes the early testing of mAbtyrins, a combination molecule based on an engineered version of a human monoclonal antibody (mAb), a protein that clings to and marks S. aureus for uptake and destruction by immune cells. Attached to the mAb are centyrins, small proteins that prevent these bacteria from boring holes into the human immune cells in which they hide. As the invaders multiply, these cells die and burst, eliminating their threat to the bacteria.

Together, the experimental treatment targets ten disease-causing mechanisms employed by S. aureus, but without killing it, say the study authors. This approach promises to address antibiotic resistance, say the researchers, where antibiotics kill vulnerable strains first, only to make more space for others that happen to be less vulnerable until the drugs no longer work.

"To our knowledge, this is the first report showing that mAbtyrins can drastically reduce the populations of this pathogen in cell studies, and in

live mice infected with drug-resistant strains so common in hospitals," said lead study author Victor Torres, Ph.D., the C.V. Starr Professor of Microbiology and director of the NYU Langone Health Antimicrobial-Resistant Pathogen Program. "Our goal was to design a biologic that works against S. aureus inside and outside of cells, while also taking away the weapons it uses to evade the immune system."

One-third of the human population are carriers of S. aureus without symptoms, but those with weakened immune systems may develop life-threatening lung, heart, bone, or bloodstream infections, especially among hospitalized patients.

Inside out

The new study is the culmination of a five-year research partnership between scientists at NYU Grossman School of Medicine and Janssen to address the unique nature of S. aureus.

The NYU Langone team together with Janssen researchers, published in 2019 a study that found that centyrins interfere with the action of potent toxins used by S. aureus to bore into immune cells. They used a molecular biology technique to make changes in a single parental centyrin, instantly creating a trillion slightly different versions of it via automation.

Out of this "library," careful screening revealed a small set of centyrins that cling more tightly to the toxins blocking their function.

Building on this work, the team fused the centyrins to a mAb originally taken from a patient recovering from S. aureus infection. Already primed by its encounter with the bacteria, the mAb could label the bacterial cells such that they are pulled into bacteria-destroying pockets inside of roving immune cells called phagocytes. That is unless the same

toxins that enable S. aureus to drill into immune cells from the outside let it drill out of the pockets to invade from the inside.

In a "marvel of bioengineering," part of the team's mAbtyrin serves as the passport recognized by immune cells, which then engulf the entire, attached mAbtyrin, along with its centyrins, and fold it into the pockets along with bacteria. Once inside, the centyrins block the bacterial toxins there. This, say the authors, sets their effort apart from antibody combinations that target the toxins only outside of cells.

The team made several additional changes to their mAbtyrin that defeat S. aureus by, for instance, activating chain reactions that amplify the immune response, as well by preventing certain bacterial enzymes from cutting up antibodies and others from gumming up their action.

In terms of experiments, the researchers tracked the growth of S. aureus strains commonly occurring in US communities in the presence of primary human immune cells (phagocytes). Bacterial populations grew almost normally in the presence of the parental antibody, slightly less well in the presence of the team's engineered mAb, and half as fast when the mAbtyrin was used.

In another test, 98% of mice treated with a control mAb (no centyrins) developed bacteria-filled sores on their kidneys when infected with a deadly strain of S. aureus, while only 38% of mice did so when treated with the mAbtyrin. Further, when these tissues were removed and colonies of bacteria in them counted, the mice treated with the mAbtyrin had one hundred times (two logs) fewer bacterial cells than those treated with a control mAb.

Finally, the combination of small doses of the antibiotic vancomycin with the mAbtyrin in mice significantly improved the efficacy of the mAbtyrin, resulting in maximum reduction of bacterial loads in the

kidneys and greater than 70% protection from kidney lesions.

"It is incredibly important," said Torres, "that we find new ways to boost the action of vancomycin, a last line of defense against MRSA."

More information: Victor J Torres, Multivalent human antibody-centyrin fusion protein to prevent and treat Staphylococcus aureus infections, *Cell Host & Microbe* (2023). DOI: 10.1016/j.chom.2023.04.004. www.cell.com/cell-host-microbe … 1931-3128(23)00148-8

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