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TITLE: **DCB001: a new precision antibiotic candidate against MRSA**

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Abstract:

Nosocomial infections are often caused by contamination of medical equipment, infections linked to prosthetic surgery and skin infections, one of the main agents of which is *Staphylococcus aureus*. Antibiotic resistance in this bacterium is a recurring subject (> 50% of strains from severe patients are multi-resistant to antibiotics) and constitutes a major problem for global public health. In addition, the imbalance of the microbiota due to broad-spectrum antibiotics and the hypersensitivity of patients to certain antibiotics increase the number of difficult-to-treat patients, which may be the cause of a future therapeutic impasse. The current scenario indicates that research and development of new classes of antibiotics is a priority.

To address this issue, we screened several hundred synthetic compounds in order to identify antibacterial molecules that are specifically active against *S. aureus*. Interestingly, a molecule harboring trichloroacetimidamide activity was identified, a family of molecules that has never been described as an antimicrobial agent.

After a first optimization phase which included the synthesis of 57 derivatives, we were able to identify DCB001 as a potential lead. The antibacterial activity of DCB001 has been demonstrated against several multidrug-resistant *S. aureus* strains (including MRSA strains) and testing in primary human cell models has shown its safety even at high concentrations. In addition to its high efficacy and low toxicity, it is important to note that DCB001 has *S. aureus* specific activity which could reduce side effects related to microbiota imbalance. Finally, single-, and multiple-step resistance/mutation rate assays have shown a low (undetectable) mutation rate, increasing the interest of this new class of antibiotic candidates.

Overall, DCB001 is a potential precision antibiotic that is part of a new chemical class. This compound showed high activity against several multidrug-resistant *S. aureus* strains (all strains were resistant to at least 4 antibiotics) and low resistance rates. The preclinical phase is underway and preliminary data in a severe bacteremia model showed the interest of our molecule as a future antibiotic.