Name: Garcia-Sanchez **First name**: Juan Antonio

Institution : Université Côte d'Azur – C3M U1065

Address: 151, Route de Saint-Antoine de Ginestière. Bâtiment Universitaire Archimed

Postal Code, City, Country: 06204, Nice (France).....

Email: juan.garcia@dimicare-biotech.com .....

TITLE: **Trichloroacetimidamides: a novel class of specific antibiotics**

Authors: **Garcia-Sanchez, J.A.**[1, 2, $]; Meola, P.[1, 2]; Pires-Gonçalves, L.[3]; Munro, P.[1, 2]; Michel G.[1, 2] ; Ruimy,R.[1,2,4] ; Ronco,C.[1,3, $] ; Boyer,L.[1,2, $]

Institutions: [1] Projet DimiCare Biotech ; [2] Laboratoire VIRINFLAM. Centre Méditerranéen de Médecine Moléculaire (C3M – INSERM U1065 – UniCA) ; [3] Laboratoire Chimie Médicinale. Institut de Chimie de Nice (ICN – CNRS UMR7272 – UniCA) ; [4] Laboratoire de Bactériologie - Centre Hospitalo-Universitaire de Nice (CHU – UniCA).

[$]These authors have co-managed the project.

Abstract:

Nosocomial infections, often linked to contaminated medical equipment, prosthetic surgery, or skin infections, represent a significant public health challenge, and *Staphylococcus aureus* is among the leading pathogens causing these infections. *S. aureus* bacteremia (SAB) affects over 750,000 hospitalized patients annually, with a mortality rate of 20–30%. Compounding the issue, 30–50% of *S. aureus* strains exhibit multidrug resistance, limiting treatment options and increasing therapeutic failures. The broad-spectrum antibiotics currently used contribute to microbiota imbalance and hypersensitivity, underscoring the urgent need for targeted new antibiotic classes.

To address this, we screened hundreds of synthetic compounds and identified a molecule with trichloroacetimidamide activity—a previously unreported family of antimicrobial compounds. Through optimization, including the synthesis of 57 derivatives, we identified DCB001 as a lead compound. DCB001 demonstrated potent antibacterial activity against multidrug-resistant *S. aureus* strains, including MRSA and PVL-positive strains (MIC/MBC = 2-4 µg/mL). Both, Safety and efficacy testing in an acute bacteremia model have demonstrated its interest as a potential treatment by oral and intra-venous administration (optimal effective dose 8-16 mg/kg depending on the model). Finally, its specificity for *S. aureus* also reduces the likelihood of microbiota-related side effects and resistance assays revealed a low mutation rate for DCB001, further highlighting its potential as a first-in-class antibiotic. Ongoing studies are investigating its novel mechanism of action, which could lead to more targeted and resistance-resistant therapies.

In summary, DCB001 is a promising precision antibiotic with high activity against multidrug-resistant *S. aureus* strains (all resistant to at least four antibiotic families) and low resistance rates. Preclinical studies, including a severe bacteremia model, support its potential as an innovative treatment for challenging bacterial infections.