PROFILE

Within CNB, the Research Group uses the pathogen methicillin-resistant Staphylococus aureus (MRSA) to investigate the contribution of bacterial cell organization to the development of infections. This Research Group is a pioneer in the discovery of functional membrane microdomains in bacteria, similar to eukaryotic lipid rafts, where protein complexes related to infections and resistance to antibiotics are organized. The group has developed techniques and protocols that are used globally by laboratories interested in exploring the complexity of the microbial world.

SPEAKER

Dr Daniel López started his laboratory at the University of Würzburg (Germany 2010-2015) and he is currently at CNB (Spain 2015-present). Previously, he was a postdoc at Harvard University (USA) and completed his PhD at the University of Murcia (Spain). His work is published in the most prestigious journals. Daniel Lopez is elected member of the European Academy of Microbiology (since 2018). He obtained the Banco Sabadell Foundation Award for Biomedicine (2018) and the Caja Granada Foundation Health Award (2018).

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PRODUCT

Anti-raft therapies to fight multi-drug resistant infections

MECHANISM OF ACTION

Anti-raft molecules perturb the architecture of bacterial lipid rafts by inhibiting the production of the membrane lipids that constitute the rafts. Bacterial lipid rafts are membrane lipids of isoprenoid nature; their biosynthetic pathway resembles that of cholesterol synthesis in humans. Anti-rafts molecules inhibit key enzymes of raft lipids production. In the absence of these lipids, many raft-associated proteins lose their functionality causing a severe perturbation of bacterial survival. As several antibiotic-resistant proteins, such as PBP2a, are raft-associated proteins, the inhibition of raft lipids synthesis also compromises bacterial antibiotic resistance.

The protein PBP2a responsible for penicillin resistance in MDR Staphylococcus aureus (MRSA), serves as case study. These "anti-raft" compounds are non-toxic to humans; some of them are commercially available as cholesterol-lowering drugs. Nanomolar concentrations of these compounds inhibited raft-associated proteins, including PBP2a, resulting in inhibition of antibiotic resistance thus rendering MRSA infections susceptible to penicillin. Anti-rafts molecules combined with conventional penicillins eliminate MRSA infections and open up the possibility of recycling penicillins in disuse due to multi-drug resistance.

TARGET INDICATIONS

The alarming increase of multi-drug resistant (MDR) pathogens represents an unprecedented global health problem. MDR pathogens threaten our ability to treat common infections, causing severe complications for medical or surgical procedures. Our anti-raft technology can be implemented in healthcare systems to fight MDR

infections that cannot be treated otherwise. This technology will reduce risks of medical procedures as well as the cost of hospital stays and intensive care. Anti-raft technology opens up the possibility of reusing antibiotics currently discarded due to the rising of MDR pathogens.

CURRENT STATUS

- We demonstrated that perturbation of bacterial rafts assembly using anti-rafts compounds results in MRSA infections susceptible to penicillin treatment.
- To test the versatility of our anti-raft therapy, we developed a mouse pneumonia infection model to recapitulate distinct infection scenarios common in ICU.
- The main outcomes are: 1) Anti-raft therapy prevents the progress of already ongoing MRSA infections, to recapitulate patients with complicated pneumonia. 2) Anti-raft pre-treatment prevents the development of MRSA infections, to protect patients that will require risk procedures (e.g., surgery). 3) Anti-raft therapy is active against all MRSA clinical isolates tested. We tested isolates from pandemic, multi-resistant, chronic and acute infections). 4) Anti-raft therapy works against other pathogens such as Listeria monocytogenes or Pseudomonas aeruginosa (in vitro). 5) In collaboration with several Spanish hospitals (e.g., Hospital Virgen de Rocio, Seville) we correlated our laboratory results with prospective clinical studies in patients

INNOVATIVE ASPECTS

- We target bacterial lipid rafts to fight bacterial infections by simultaneously inhibiting many raft-associated proteins related to infection and antibiotic resistance.
- The current antibiotic crisis teaches us that new antibiotics become ineffective soon after they are introduced into the clinic due to rapidly evolving resistance in pathogenic bacteria.
- In the current scenario, our anti-raft therapy provides benefits that cannot be achieved with the available antibiotics: to eliminate MDR infections that show resistance to clinically available antibiotics, our therapy can be used to treat infections that cannot be treated otherwise.
- In addition, this therapy is able to recover currently discarded antibiotics. This can alleviate the antibiotic crisis, to circumvent large investments in cost and time for the discovery and development of new antibiotics.

IPR

Patented in 2017. Patent of applicability extended to Europe and USA.

PARTNERING OPPORTUNITIES

We look for the impulse of the industrial sector to implement this product in hospital environments.