Antibody-Based Inhibitors of the Staphylococcus aureus Multidrug Efflux Pump NorA

Innovative and efficacious therapeutics to treat drug-resistant S. aureus infections.

Technology

NorA is a well-characterized S. aureus multidrug efflux pump that confers resistance against members of the fluoroquinolone class of antibiotics; most notably, ciprofloxacin and norfloxacin. Using a synthetic antigen-binding fragment (Fab) library, the inventors engineered Fabs that bind NorA from the extracellular side of the membrane with high affinity and specificity. Based on the NorA-Fab structures, peptide derivatives were synthesized that mimic a key loop in these Fabs observed to insert and occlude the NorA drug-binding pocket. In proof-of-concept (PoC) studies using a clinically relevant methicillin-resistant S. aureus (MRSA) strain resistant to norfloxacin, exogenous addition of an anti-NorA peptide was demonstrated to potentiate the anti-bacterial activity of norfloxacin. This anti-NorA peptide, therefore, represents a promising efflux pumps inhibitor (EPI) lead for the treatment of fluoroquinolone-resistant MRSA infections stemming from NorA-mediated fluoroquinolone efflux.

Background

Drug-resistant strains of Staphylococcus aureus, such as MRSA, are a major threat to public health. In 2017, the Centers for Disease Control and Prevention (CDC) reported over 119,000 bloodstream infections caused by S. aureus resulting in greater than 20,000 deaths. Like other bacteria, S. aureus possesses multiple resistance mechanisms to survive treatments with antibiotics and disinfectants (biocides). One such resistance mechanism is drug efflux mediated by membrane-embedded transporters (termed “efflux pumps”). Efflux pumps function to extrude a diverse array of structurally dissimilar drugs out of the cell, which thereby acts to lower the intracellular drug concentration and render such antibiotics/biocides ineffective in antagonizing their respective intracellular targets. Therefore, pharmacological inhibition of efflux pumps is a critical yet underexplored therapeutic avenue to help treat drug-resistant S. aureus infections, such as MRSA, where the drug-resistant phenotype stems from efflux pump activity. EPIs would be used in combination with antibiotics/biocides rendered ineffective by drug efflux to potentiate their anti-bacterial activity. While several small molecule bacterial EPIs have been identified and optimized, there are currently no FDA approved bacterial EPIs in the clinic.

Applications

For use as a combination treatment with a fluoroquinolone to treat fluoroquinolone-resistant MRSA infections stemming from NorA-mediated fluoroquinolone efflux.

- Applicable to such MRSA infections in humans, domesticated pets, and livestock

Technology ID

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Category

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For use as a clinical diagnostic tool to detect and/or quantify NorA expression levels in patient or animal-derived MRSA isolates

For use as a laboratory reagent tool to detect and/or quantify NorA expression in MRSA cell lines for academic or industrial research purposes

Advantages

- Achieves functional inhibition of NorA from the extracellular side of the membrane: No need to traverse the cellular membrane
- Large protein-protein interaction interface: This results in higher specificity, lower off-target effects, and greater tractability for optimization
- Low likelihood for the acquisition of resistance mutations given the peptide EPI binds to several NorA residues critical for function

IP Status

Provisional patent application pending

References

1. Brawley, D.N., Sauer, D.B., Li, J. et al. , Structural basis for inhibition of the drug efflux pump NorA from Staphylococcus aureus