

Interfering with *Pseudomonas aeruginosa* communication (quorum sensing) using small molecules (BGN)

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Cell-to-cell communication is employed by single-cell organisms to coordinate their behavior and enable them to thrive even in the presence of competitors. Such chemical communication between bacteria, termed 'quorum sensing (QS)', leads to biofilm formation and increased virulence. Strategies that interfere with QS are considered a viable approach for the development of anti-microbial agents and may provide the newest weapon in the therapeutic arsenal against infections involving drug-resistant bacteria. *Pseudomonas aeruginosa* is a Gram-negative bacterium that causes mortality in people with weakened immune responses, such as cystic fibrosis patients or burn victims. The overall prevalence of *P. aeruginosa* infections in US hospitals is approximately 0.4%. *P. aeruginosa* is also the fourth most commonly isolated nosocomial pathogen, accounting for 10% of all hospital-acquired infections. The strain is naturally resistant to many antibiotics due to the permeability barrier afforded by its outer membrane. Also, its tendency to colonize surfaces in a biofilm form makes these cells even more resistant to antibiotics.

The Technology

Using rational drug design, several covalent molecules have been designed, synthesized and tested in vitro

in terms of binding to their target, the LasR receptor. Potent hits were shown to inhibit biofilm formation in

P. aeruginosa. A lead compound was identified that binds to the LasR receptor effectively and inhibits its activation with low micromolar IC₅₀ values. As such, we have discovered novel QS inhibitors that might serve as a novel therapeutics against resistant bacteria.

Applications

A novel approach to treat *Pseudomonas aeruginosa* infections and resistant species of the bacteria.

Advantages:

We have designed and validated new compounds targeting bacteria by a new mechanism

The novel lead compound is a low MW compound and can be orally administered

The compound targets quorum sensing communication between bacteria

The compound could be administered together with a broad range antibiotics, such as gentamicin, to afford synergistic therapeutic effects

Status of Development:

In silico design using computational chemistry towards increasing affinity to the target receptor and optimization of drug-like properties have led to structures of dozens of putative candidates designed to inhibit QS via binding to the LasR receptor

Several novel inhibitors of QS were synthesized

Lead compounds bind to the LasR receptor in the low micromolar range.

Lead compounds inhibit biofilm formation and pyocyanin production in wild type *P. aeruginosa*


Lead compounds were analyzed for stability in mouse plasma and in plasma protein-binding assays.

We are currently performing mouse model studies against *Pseudomonas* lung infection with first generation covalent inhibitors that were successful in inhibiting QS in *P. aeruginosa*

Patent Status

Pending

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