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 administrated 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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