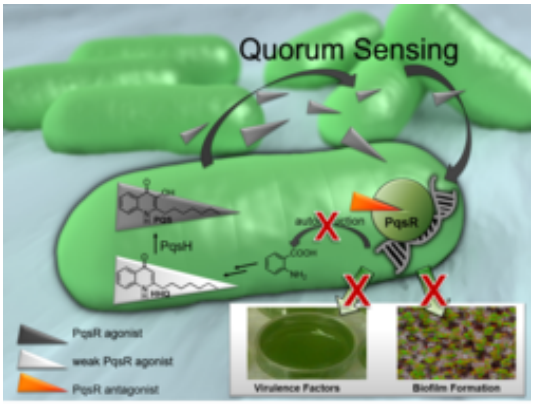
Technology Offer

Innovative Inhibitors of Pseudomonas Pathogenicity

Reference Number 02-00316

Challenge

Pseudomonas aeruginosa causes chronic infections of the lung, bloodstream, skin and other tissue of immune-pompromised hosts including chronic lower respiratory tract infections in patients suffering from cystic fibrosis or bronchiectasis. This opportunistic, ubiquitous gram-negative bacterium is able to switch to the biofilm mode of life, which serves as a physical barrier to survive antibiotic treatment and host immune defense. In addition *P. aeruginosa* develops high resistance towards antibiotics resulting in maintenance of chronic infections and high mortality of infected patients. The *Pseudomonas* quorum sensing (PQS) system is essential for bacterial virulence and biofilm formation. Importantly, the PQS signalling system is in an on-state in chronic lung infections making it a suitable target for inhibiting drugs acting as blockers of *P. aeruginosa*`s pathogenicity.



Concept of PqsR antagonists as QS inhibitors

Technology

The present invention relates to antagonists of the PqsR (MvfR) quorum sensing receptor which is required for full *P. aeruginosa* virulence. The function of multiple quorum sensing-regulated virulence factors and the synthesis of 4-hydroxy-2-alkylquinolines (HAQs), including the *Pseudomonas* quinolone signal, make PqsR a key regulator of *Pseudomonas* pathogenicity. A first compound series inspired by the natural PQS auto-inducer molecule HHQ showed activities *in vivo* in the nanomolar range. Currently, new structure-divergent lead series of PqsR antagonists derived from a fragment-based approach and the receptor-ligand-complex-structure of a derivative are being developed through means of structure-guided medicinal chemistry. First hot spots were identified and the results indicate even more favourable properties compared with the first compound series. The resulting antagonists will preferably be administered by inhalation and will be developed as preemptive or adjunctive treatment in *Pseudomonas* eradication and suppression therapy for cystic fibrosis and bronchiectasis.

Commercial Opportunity

The invention is offered for co-development and licensing.

Development Status

Data from *in vitro* and *in cellulo* assays and a *Galleria mellonella in vivo* infection model are available. First very promising *in vivo* efficacy data were obtained in mice.

Patent Situation

An international priority application was filed in April 2014 (WO2015149821). A European patent has been granted, a US patent application is pending. A new European priority application has been filed in June 2018 covering the current lead series.

Further Reading

Lu C, Maurer CK, Kirsch B, Steinbach A, Hartmann RW. Overcoming the unexpected functional inversion of a PqsR antagonist in Pseudomonas aeruginosa: an in vivo potent antivirulence agent targeting pqs quorum sensing. Angew Chem Int Ed Engl. 2014 Jan 20;53(4):1109-12.
Lu C, Kirsch B, Maurer CK, de Jong JC, Braunshausen A, Steinbach A, Hartmann RW. Optimization of anti-virulence PqsR antagonists regarding aqueous solubility and biological properties resulting in new insights in structure-activity relationships. Eur J Med Chem. 2014 May 22;79:173-83. doi: 10.1016/j.ejmech.2014.04.016.

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