Technology Offer

Increased Availability and Efficacy of Aminoglycosides

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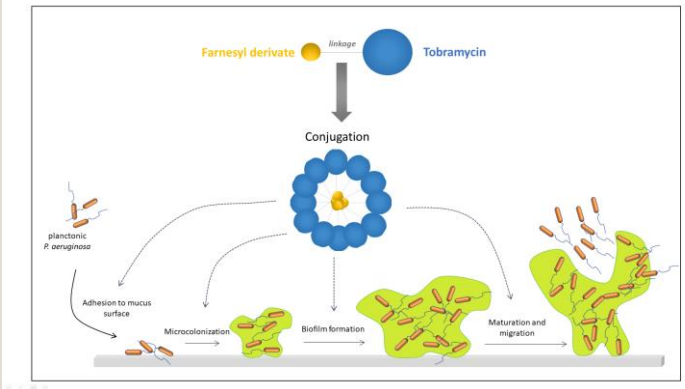
A Company of the
Life-Science Foundation
for the Promotion of
Science and Research

Challenge

Aminoglycosides such as tobramycin are clinically approved antibiotics used mainly to combat gram-negative bacteria such as *Pseudomonas aeruginosa*. They are highly positively charged and hydrophilic, resulting in low penetration through bacterial cell walls and biofilms. Consequently, relatively high doses are required to maintain clinical efficacy, which can lead to severe side effects due to toxicity. In order to extend the availability and improve the efficacy of aminoglycosides, intelligent, excipient-free assemblies with a controlled release profile would be advantageous.



Excipient-free assemblies of Tombramycin and Farnesyl derivatives which prolong the availability of Tombramycin and enhance its efficiency in all stages of infection.

Technology

The new conjugates result from covalent linking of aminoglycosides with farnesyl fractions. They show reduced hydrophilic properties, improved antibacterial properties and self-assembly properties.

The conjugates were synthesized in a one-step technique with 95% yield using imine/enamine linkage between the amine groups of the aminoglycoside and aldehyde groups of the farnesyl unit. The linkage is stable at pH > 6.0, but reacts sensitively to decreasing pH values. Aminoglycosides are therefore released in acidic environments such as biofilms, resulting in a controlled release profile in the targeted side.

Notably, farnesyl-moieties itself acts as a quorum sensing inhibitor (QSI) and antibacterial/antifungal agent. Through the formation of conjugates from two active substances, which further undergo self-assembly, excipient-free assemblies with up to 100% drug loading capacity can be achieved.

The conjugates spontaneously form uniform assemblies in aqueous media. Their diameter could be tuned in the range from 85 to 900 nm depending on preparation conditions, having the polydispersity index < 0.3.

The antimicrobial activity of the tobramycin-farnesyl conjugate and its superiority over free tobramycin was demonstrated by minimal inhibitory concentration (MIC) assay against *E. coli* and *P. aeruginosa* as well as by pyocyanin assay. The MBEC (Minimal Biofilm Eradicating Concentration) assay against *P. aeruginosa* showed a significant improvement by a factor of 16 of the conjugate compared to free tobramycin.

Developmental Status

The antimicrobial activity was shown in standard *in vitro* assays. Studies on kinetics and mechanisms are ongoing. Synthesis of conjugates can be scaled up easily. Synthesis technique is applicable for other active ingredients.

Commercial Opportunity

The invention is offered for licensing and co-development.

Patent Situation

European patent application was filed in June 2017. PCT patent application was filed in June 2018.

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