Esculentin 1a derivatives and uses thereof / Esculentin 1a derivatives thereof for treatment of microbial keratitis.

KEYWORDS

- KERATITIS
- OCULAR SURFACE INFECTIONS
- NEW OPHTHALMIC AGENTS
- ANTI-INFECTIVE AGENTS
- ANTIMICROBIAL PEPTIDES
- SELF-STERILIZING CONTACT LENSES

AREA

- PHARMACEUTICAL

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Priority Number
Provisional USA n. 61/890521 _ 14.10.2013.
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Patent Type
Patent for invention.

Co-Ownership
Sapienza University of Rome 50%, University of Houston 50%.

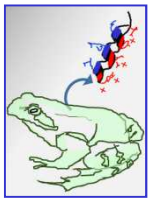
Inventors
Alison M. McDermott, Maria Luisa Mangoni.

Industrial & Commercial Reference
Medicine:ophthalmology; Pharmaceutical: development of new antibiotics and their delivery. Nanotechnologies: medical devices (e.g. antimicrobial contact lens).

Time to Market
Preclinical phase: experiments with animal models of keratitis and contact lens wear.

Availability
Licensing, Research, Development and Experimentation.

Fig. 1
Schematic representation of the AMP esculentin 1a produced by frog skin secretion.



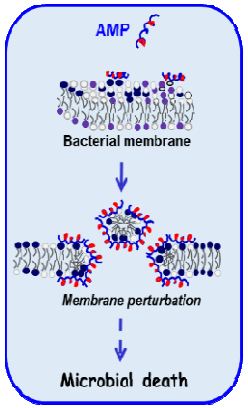


Fig. 2
Schematic representation of the mechanism of microbial membrane perturbation by the patented AMPs

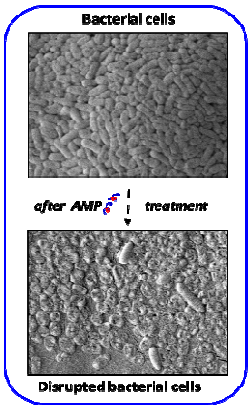
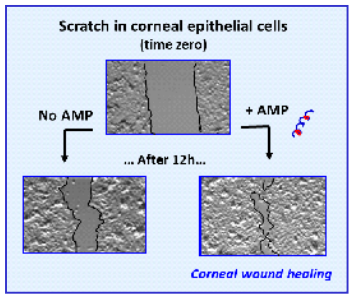


Fig. 3
Effect of AMP on bacterial cells.

Fig. 4
Effect of "wound healing" of AMPs on human corneal epithelial cells.



Abstract
The present invention provides for synthetic antimicrobial peptides (AMPs) derived from the frog-skin AMP esculentin 1a, especially against ocular surface infections.
More specifically, it is directed to their topical formulation for treatment and prevention of microbial keratitis, a serious infection of the cornea, especially in contact lens wearers.
It also provides methods of delivery of these peptides, either in free form or after encapsulation in a pharmaceutically acceptable carrier (for treatment of keratitis) or after covalent conjugation to contact lenses (for prevention of ocular surface infection).

Publications

- Esculentin-1a(1-21)NH2: a frog skin-derived peptide for microbial keratitis. Cell Mol Life Sci, 2015, 72:617-27.
- Promising Approaches to Optimize the Biological Properties of the Antimicrobial Peptide Esculentin-1a(1-21)NH2: Amino Acids Substitution and Conjugation to Nanoparticles. Front Chem, 2017, 5:26.
- Esculentin-1a derived peptides kill Pseudomonas aeruginosa biofilm on soft contact lenses and retain antibacterial activity upon immobilization to the lens surface. Biopolymers, 2017 (in press), doi: 10.1002/bip.23074.

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Technical Description

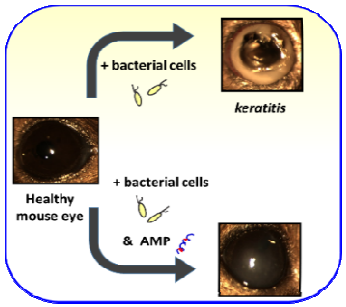
The AMP esculentin 1a and derivatives thereof are a novel treatment/preventative for microbial keratitis.

Due to their mechanism of action, these peptides have a low risk of inducing microbial resistance. In contrast with traditional antibiotics, they are active against bacteria, fungi, protozoa and have immunomodulatory functions.

A representative example for treatment of keratitis includes a topical peptide-based formulation applied drop-wise to the eye in a suitable solution or delivered via nanoparticles or via specialized therapeutic contact lens to provide sustained peptide release to the surface of the eye over time.

Another advantage is that these peptides can be used to coat a contact lens to prevent microbial pathogens from adhering to the lens surface. This would prevent their transfer to the eye so stopping infection from occuring in the first place.

Fig. 5 Effect of peptide treatment in mouse models of bacterial keratitis.



Technologies & Advantages

Microbial keratitis is a vision threatening infection potentially leading to blindness, if untreated. In particular, millions of individuals who wear contact lenses are at increased risk for microbial keratitis.

In contrast with classical antibiotics, esculentin 1a derivatives have the advantage to rapidly kill a broad spectrum of microorganisms (bacteria, fungi, protozoa) by a membrane-perturbing mechanism which does not induce resistance.

They have the ability to stimulate corneal epithelial cell migration accelerating wound healing and to preserve antimicrobial activity upon covalent conjugation to biomaterials.

Together, these findings make the selected frog-skin derived AMPs attractive molecules for the development of novel anti-infective agents to overcome the worldwide health concern related to microbial resistance to currently used antibiotics. In addition, compared to mammalian AMPs or de-novo designed AMPs, they retain antimicrobial activity in the presence of tears and significantly reduce severity of infection in animal models of bacterial keratitis upon drop-wise ocular administration.

Furthermore, they have short amino acid sequences, which reduce the production cost.

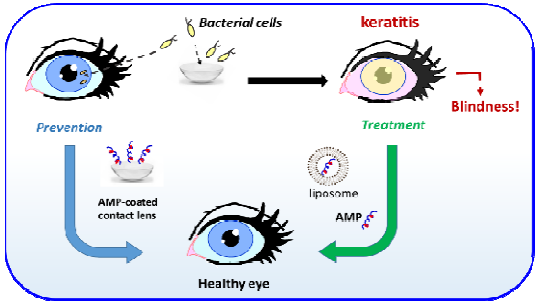
Applications

The selected peptides have high potential to be developed for future medical preparations to treat microbial keratitis and to favour healing of the cornea, when administered drop-wise to the ocular surface in the free or encapsulated form (e.g. inside liposomes).

Furthermore, they have high potential to prevent keratitis upon covalent conjugation to contact lenses.

Overall, they are promising candidates for the development of new therapeutic agents (e.g. ophthalmic agents) to prevent/treat ocular surface microbial infections, with a low risk to induce resistance.

Fig. 6 Schematic representation of the prevention and treatment of keratitis by selected AMPs.



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