Engineered Lactococcus Lactis for the controlled production of KGF.

KEYWORDS

- ❑ MENOPAUSE
- ❑ VAGINAL ATROPHY
- ❑ ENGINEREED LACTOBACILLUS
- ❑ KGF
- ❑ THERAPY

AREA

- ❑ PHARMACEUTICAL

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Priority Number
n. 102019000003115_04.03.2019.

Patent Type
Patent for invention.

Ownership
Sapienza Università di Roma 100%.

Inventors
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Industrial & Commercial Reference
The invention is addressed to the business of menopausal products .

Time to Market
The engineered Lactobacillus has been validated in vitro by testing KGF production upon induction and its efficacy on vaginal mucosa cells (TRL4).

Availability
Cession, Licensing, Research, Development, Experimentation and Collaboration.

Fig. 1 Visual representation of the key-words related to our patent, that give greater prominence to words that appear more frequently.

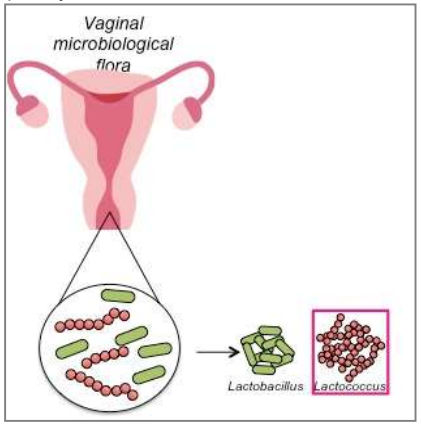

Fig. 2 The strain to be engineered was chosen among the normal hosts of the vaginal mucosa. We have selected L. lactis, an organism recognized as safe and already tested to convey other therapeutic agents

Abstract
The present invention relates to a genetically modified probiotic microorganism expressing the human keratinocyte growth factor (KGF / FGF7). Vaginal atrophy, caused by the reduction of circulating estrogens, can be treated with KGF which, administered locally, restores vaginal trophism without systemic effects. The engineered lactobacillus object of the present invention is able to directly colonize the vaginal mucosa, and to produce KGF locally in a controlled manner by means of an inducible system, allowing to improve the effectiveness of the KGF-based therapy for vaginal atrophy and the patients' compliance.

Pubblicazioni

❖ Ceccarelli S, D'Amici S, Vescarelli E, et al. Topical KGF treatment as a therapeutic strategy for vaginal atrophy in a model of ovariectomized mice. J Cell Mol Med. 2014 Sep;18(9):1895-907. doi: 10.1111/jcmm.12334.

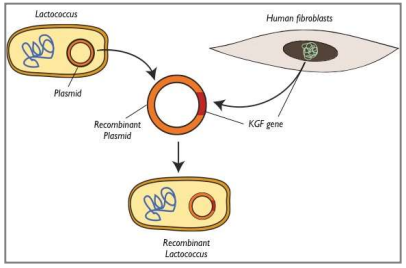

Fig. 3 The gene of interest (KGF) was isolated from human fibroblasts and inserted into a bacterial plasmid, then transferred to the selected strain (L. lactis).

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Technical Description

The present invention is based on the engineering of a lactobacillus compatible with the vaginal microenvironment, in order to produce KGF in a controlled manner. Our procedure involved the amplification of KGF gene from human fibroblasts. Then, to obtain KGF release from Lactobacillus cells, a construct containing a signal sequence for secretion was generated. This construct was subsequently transferred to the bacterial strain under an inducible expression system, to allow control of KGF protein production. Finally, the efficacy of KGF produced by the engineered microorganism was tested in human vaginal cells.

Fig. 4 To allow accurate control of the locally released KGF dose, we used an expression vector under the control of an inducible promoter, so that KGF was produced only after administration of an inducer.

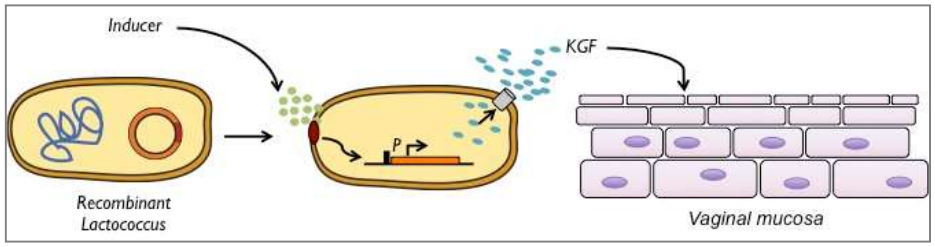
Technologies & Advantages

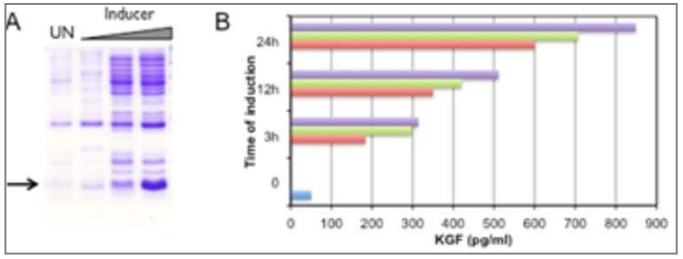
Starting from previous evidence on the effectiveness of local administration of KGF in the treatment of vaginal atrophy, our patent proposal is based on the use of a genetically modified probiotic microorganism to induce KGF production, in order to convey this therapeutic agent directly into the vaginal mucosa. KGF safety is known, as it is already used as a drug (Kepivance trade name) and as it is released in a controlled manner by the exogenous administration of a food supplement. The Lactobacillus object of the patent is a GRAS (a generally recognized as safe organism), already used in food production, and is a normal host of human vaginal mucosa devoid of known pathogenicity. Furthermore, Lactobacillus is designed to release KGF directly into the affected tissues, avoiding the risks of systemic exposure and allowing greater treatment efficacy and tolerability.

Applications

Object of the invention are Lactobacillus strains engineered for the production of keratinocyte growth factor (KGF / FGF7), for use in the treatment of vaginal atrophy, dysuria, vaginal pain and / or vaginal dryness induced by a post-menopausal state, from surgery, from a pathology and / or from chemotherapy or radiotherapy treatments. The use of microorganisms that directly colonize the vaginal mucosa, allowing the local and controlled release of KGF, can improve its therapeutic efficacy and therefore replace the local therapies already in use.

Fig. 5 SDS-PAGE (A) and ELISA assay (B) show that induction determines the production of the KGF protein, and its controlled secretion..





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