Use of a peptide derived from the human protein NTIMP3 in the therapy of diabetic nephropathy.

KEYWORDS

- ❑ DIABETES
- ❑ INFLAMMATION
- ❑ DIABETIC NEPHROPATHY
- ❑ TREATMENT
- ❑ BIOLOGIC DRUG
- ❑ CARRIER PEPTIDE
- ❑ FUSION PEPTIDE

AREA

- ❑ PHARMACEUTICS

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Patent Type
Patent for invention.

Co-Ownership
Sapienza University of Rome 10%, Tor Vergata University 90%.

Inventors
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Industrial & Commercial Reference
Health (user) and pharmaceutical (producer) market in industrialized countries.

Time to Market
The use of the fusion peptide as a drug for diabetic nephropathy is currently in preclinical phase on animal models.

Availability
Cession.

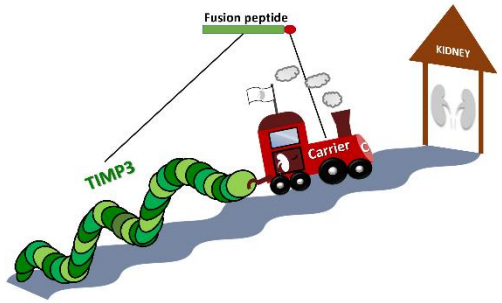

Fig. 1 **The fusion peptide.** The invention consists of a fusion peptide between a derivative of the human protein TIMP3 and a peptide carrier highly selective and efficient for transport to the kidney.

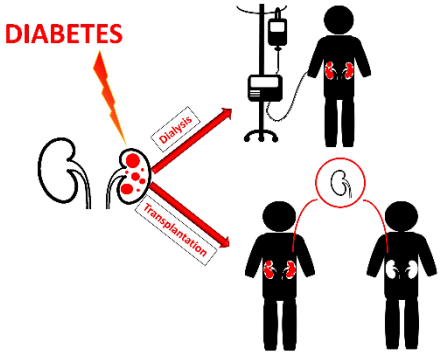

Fig. 2 **Diabetes kidney disease.** Diabetes is the leading cause of chronic kidney disease, a progressive condition that leads to renal failure. When kidneys can no longer work well enough to support their vital life functions, patients need chronic dialysis or kidney transplant.

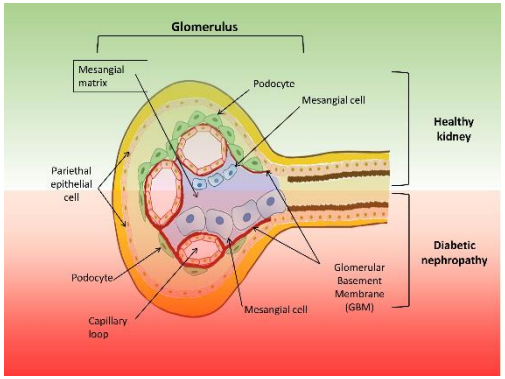

Fig. 3 **Morphological changes in diabetic nephropathy**. A glomerulus is the network of capillaries that functions as a filtration unit of kidney. Diabetic glomerulopathy is characterized by mesangial expansion, podocyte loss, restriction of glomerular capillary filtration surface and luminal volume, resulting in decline of glomerular filtration and urine production.

Abstract
The invention consists of a fusion peptide between a derivative of the human protein TIMP3 (tissue inhibitor of metallo-proteases-3) and the end N-terminal of a peptide carrier highly selective and efficient for transport to the kidney.
Such an approach allows to restore high TIMP3 activity in the kidney under conditions, such as diabetic nephropathy, in which its reduction is directly related to the disease. In detail, the peptide drug is composed of a portion of the human TIMP3 protein, mutated in such a way as to uphold the inhibitory activity of ADAM17, whose activation is involved in the renal damage associated with diabetes, and suppress that of metalloproteases.

Publications

- ❖ Wischnjow A, Sarko D, Janzer M, Kaufman C, Beijer B, Brings S, Haberkorn U, Larbig G, Kübelbeck A, Mier W. Renal Targeting: Peptide-Based Drug Delivery to Proximal Tubule Cells. Bioconjug Chem. 2016;27:1050-7.
- ❖ Janzer M, Larbig G, Kübelbeck A, Wischnjow A, Haberkorn U, Mier W. Drug Conjugation Affects Pharmacokinetics and Specificity of Kidney-Targeted Peptide Carriers. Bioconjug Chem. 2016;27:2441-9.
- ❖ Fiorentino L, Cavalera M, Menini S, Marchetti V, Mavilio M, Fabrizi M, Conserva F, Casagrande V, Menghini R, Pontrelli P, Arisi I, D'Onofrio M, Lauro D, Khokha R, Accili D, Pugliese G, Gesualdo L, Lauro R, Federici M. Loss of TIMP3 underlies diabetic nephropathy via FoxO1/STAT1 interplay. EMBO Mol Med. 2013 Mar;5(3):441-55.

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Use of a peptide derived from the human protein NTIMP3 in the therapy of diabetic nephropathy.

Technical Description

A new peptide, derived from the human TIMP3 protein modified in order to selectively and efficiently reach the renal district (patent pending N. 102017000150761) showed, in *in vivo* models of long-term renal pathology, anti-inflammatory, anti-fibrotic and anti-oxidative effects through a mechanism independent from glycemic control.

This observation indicates that this biological drug is able to exert its preventative and therapeutic effect directly, independently and in synergy with the protective effects of hypoglycaemic therapy, contributing to a significant improvement in the effectiveness of the treatment aimed at preventing and/or reducing the progression of diabetic nephropathy.

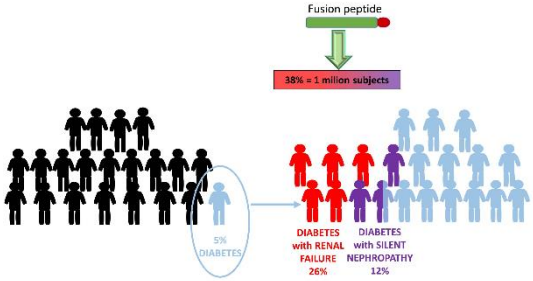

Fig. 4 **Number of subjects eligible for treatment with this type of therapy in Italy.** Diabetic nephropathy is among the top three causes of terminal kidney disease in the Western world. In Italy, the prevalence of diabetes is 5% (light blue) of the general population (black) and about 26% of this fraction has signs of renal failure (red). Including diabetic patients with silent nephropathy (purple), the number of subjects eligible for treatment extends to 38% of diabetic patients, which corresponds to about 1,000,000 subjects.

Technologies & Advantages

Nephropathy occurs in 35% of patients with type 2 diabetes and as many as 44% of patients undergoing dialysis are diabetic.

There is currently no specific therapy for diabetic nephropathy. Subjects with diabetic nephropathy are given therapies aimed at improving the metabolic profile and hypertension control, but do not take any "biological" drug aimed at a specific molecular mechanism of the pathology. The specific delivery of a drug, including proteins and peptides, to the kidney is an attractive method to increase the efficacy of the drug itself, improving the therapeutic index and the pharmacokinetic profile.The targeted delivery of an ADAM17 inhibitor allows to obtain a greater concentration of the drug at the renal level, ensuring an optimal enzymatic inhibition in this organ and the best therapeutic efficacy. The tissue-specific inhibition of ADAM17 also prevents the protease from being inhibited in other body districts, limiting possible systemic adverse effects.

Preventing or otherwise delaying kidney injury and dialysis would have a significant economic impact in terms of savings for the National Health Service.

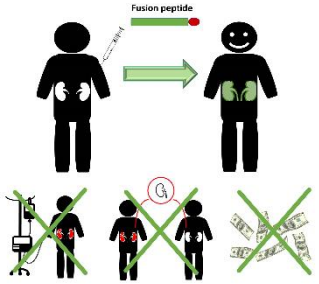

Fig. 5 **Therapeutic benefit of treatment with the fusion peptide.** The specific delivery of the TIMP3 peptide (green) allows to restore high TIMP3 activity in the kidney, ensuring the best therapeutic effect. In the long term, the decrease in the provision of dialysis and renal transplantation results in a significant saving for health expenditure.

Applications

This invention has a possible industrial application consisting in the development of a drug for the prevention and treatment of diabetic nephropathy, which is among the top 3 causes of terminal kidney disease in the Western world.

In Italy the prevalence of diabetes is 4.8% of the general population and about 26% of this fraction has signs of renal insufficiency.

It is estimated that about 720,000 people present the clinical criteria (incipient nephropathy, stage II) to use this type of therapy.

However, if we also consider diabetic patients with silent kidney disease (stage I), the number of subjects eligible for treatment extends to 38% of diabetic patients, which corresponds to about 1,000,000 subjects.

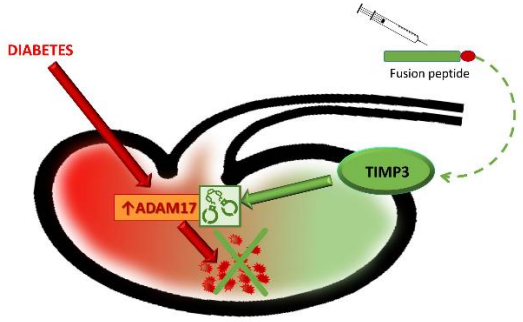

Fig. 6 **Mechanism for the protective effect of the fusion peptide.** Peptide drug is composed of a portion of the human TIMP3 protein, mutated in such a way as to uphold the inhibitory activity of ADAM17, whose activation is involved in the renal damage associated with diabetes.

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