Peptide-mimetic therapeutics for disorders due to point mutations in mitochondrial tRNAs

KEYWORDS

- ❑ MITOCHONDRIAL DISEASE
- ❑ MELAS
- ❑ MIDD
- ❑ MERRF
- ❑ PEPTIDE-MIMETIC THERAPEUTIC

AREA

- ❑ PHARMACEUTI-CAL

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Patent Type
Patent for invention

Co-Ownership
Sapienza University of Rome 46%, , CNR 24%, French Muscular Dystrophy Association - AFM-Telethon 30%

Inventors
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Industrial & Commercial Reference
Pharmaceutical industry

Time to Market
TRL 4: The PMT has been tested in human cell models. Pre-clinical and clinical studies should require 2-3 years each.

Availability
Cession, Licensing, Research, Development, Experimentation, Collaboration, Start-up and Spin-off.

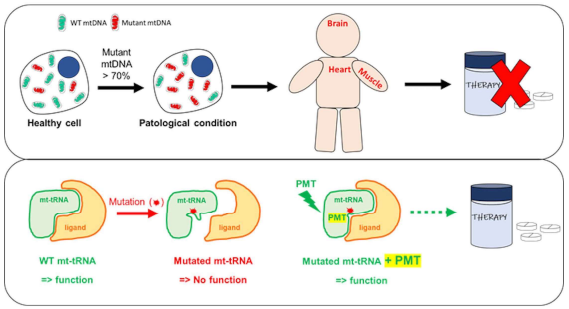

Fig. 1 Mitochondrial diseases due to point mutations in mt-tRNAs and therapeutic activity of PMTs.

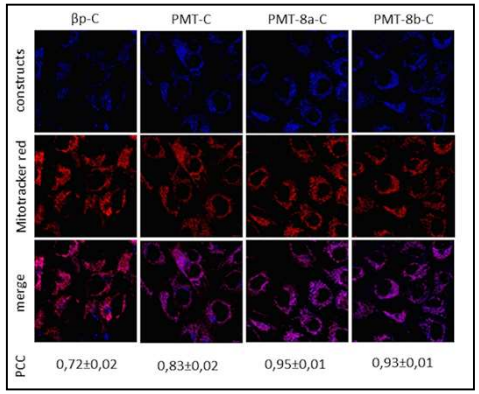

Fig. 2 Upon exogenous administration to mutant cells, all constructs are able to penetrate cell membranes and colocalize with mitochondria.

Publications

❖ Perli E, Pisano A, Pignataro MG, Campese AF, Pelullo M, Genovese I, de Turris V, Ghelli AM, Cerbelli B, Giordano C, Colotti G, Morea V, d'Amati G, 2020, Exogenous peptides are able to penetrate human cell and mitochondrial membranes, stabilize mitochondrial tRNA structures, and rescue severe mitochondrial defects, FASEB J, 34(6):7675-7686.

Abstract

We developed peptide-mimetic therapeutic (PMT) compounds able to penetrate cell and mitochondrial (mt) membranes upon exogenous administration and rescue the defective phenotype of cell models carrying pathogenic mt-tRNA mutations. These include m.3243A>G in mt-tRNALeu$^{(UUR)}$, which causes MELAS/MIDD (Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes/ Maternally Inherited Diabetes and Deafness) syndromes, and m.8344A>G in mt-tRNALys, which causes MERRF (Myoclonic Epilepsy with Ragged Red Fibers) syndrome, for which no cure is available at present. The PMTs were rationally developed based on current knowledge on the pathogenic mechanism of mt-tRNA-related disease, are endowed with significant rescuing activity in cell models and are stable in plasma. Therefore, they are ready for preclinical studies to test their therapeutic potential.

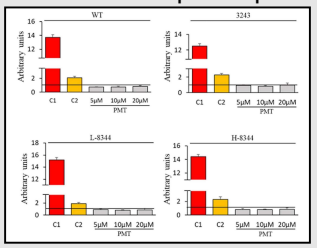

Fig. 3 Exogenously administered PMT is neither cyto- or mito-toxic up to 20 μM in wild-type or mutant cells.

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Peptide-mimetic therapeutics for disorders due to point mutations in mitochondrial tRNAs

Technical Description

PMTs are peptide-mimetic compounds, i.e., molecules which have different chemical nature from, but similar biological properties to, natural peptides, with molecular weight of 1936.5 Da (PMT), 961.3 Da (PMT-8a) and 869.2 (PMT-8b). Following incubation with cellular models of the most common mt diseases due to mutations in mt-tRNAs, i.e., MELAS and MERRF, PMTs are able to penetrate cell and mt membranes and interact with mutated mt-tRNAs, enabling them to acquire a native conformation (chaperonic activity) and, thereby, their essential functions. Due to PMT activity, vitality and mt respiration of MELAS and MERRF cells, which are significantly lower than control cells, increase to values comparable to wild-type.

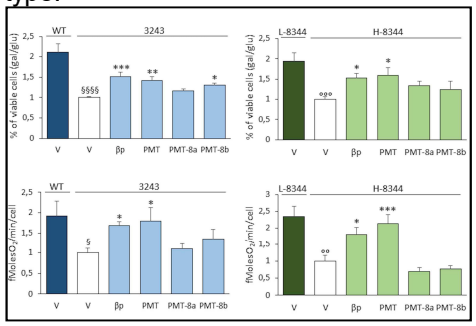

Fig. 4 Following exogenous administration, PMTs significantly improve cell viability (top panels) and mitochondrial respiration (botton panels) of mutant cells.

Technologies & Advantages

The main advantage of the invention is that it might be the first cure for diseases due to point mutations in mt-tRNAs. The PMTs are able to cure the defective phenotypes caused by two different mt-tRNA mutations in human cell models:

- m.3243A>G mutation in mt-tRNA$^{Leu(UUR)}$, which iis responsible for both the severe MELAS syndrome and MIDD, is the commonest pathogenic mtDNA point mutation and has a minimum prevalence of affected individuals of 3.5 in 100,000;
- m.8344A>G mutation is associated with the MERRF syndrome, it has a prevalence of 0.9 in 100 000 in Europe and is more common in the USA.

Additionally, PMTs of adequate quality for pre-clinical and clinical studies can be manufactured in large amounts by specialized companies.

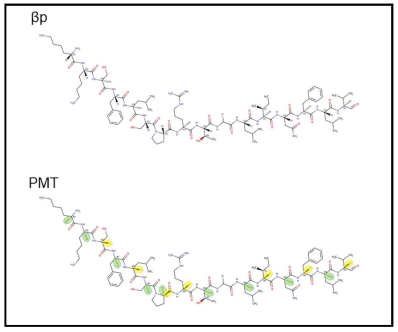

Fig. 5 Comparison between the structures of β32_33 peptide (βp) and PMT.

Applications

The main potential application of the invention is the therapeutic treatment of diseases due to point mutations in mt-tRNAs, for which no cure is currently available. In particular, the PMTs are aimed at curing the syndromes most commonly associated with mutations m.3243A>G within MT-TL1, which encodes mt-tRNA$^{Leu(UUR)}$, and m.8344A>G within MTTK, which encodes mt-tRNA^{Lys}. These are the commonest pathogenic mtDNA point mutations, and together account for about 85% of all mt-tRNA-related diseases. The syndromes most commonly associated with these mutations include the severe MELAS, MIDD, and MERRF. Importantly, PMTs may also be used as therapeutics to treat other myopathies or syndromes caused by the m.3243A>G and m.8344A>G mutations in addition MELAS, MIDD and MERRF and that occur less frequently.

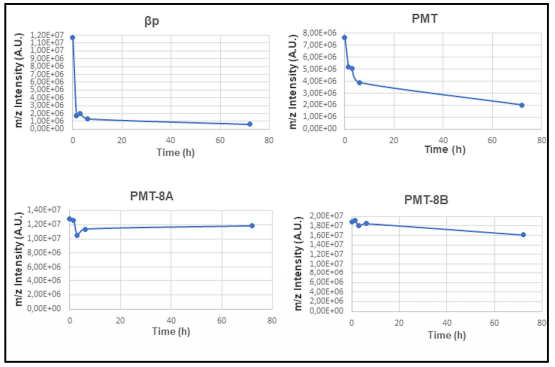

Fig. 6 The PMT, PMT-8a and PMT-8b have higher stability than the β32_33 peptide (βp) in human plasma.

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