Treatment of degenerative neuromuscular diseases

KEYWORDS

- ❑ NEURO-DEGENERATIVE DISEASES
- ❑ AGGREGATION DISEASES
- ❑ ALS TREATMENT
- ❑ RNA MODIFICATIONS
- ❑ CATALYTIC INHIBITOR

AREA

- ❑ BIOMEDICAL

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Patent Type
Patent for invention.

Co-Ownership
Sapienza University of Rome 75%, Italian Institute of Technology 25%.

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Industrial & Commercial Reference
The invention can be applied both in the medical field such as in the neuro-degenerative or aggregation diseases treatment, and in the pharmaceutical field, for instance, development of drugs based on RNA modification enzyme inhibitors.

Time to Market
Preclinical phase: experiments conducted on cellular models of Amyotrophic Lateral Sclerosis (TRL4).

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

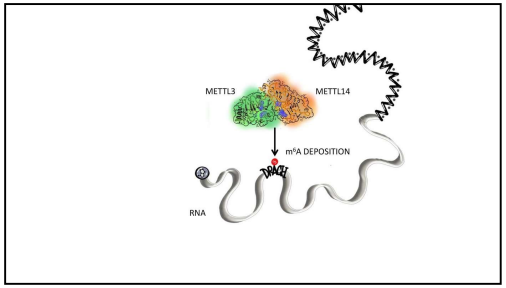

Fig.1 METTL3-METTL14 complex. RNA methylation mechanism

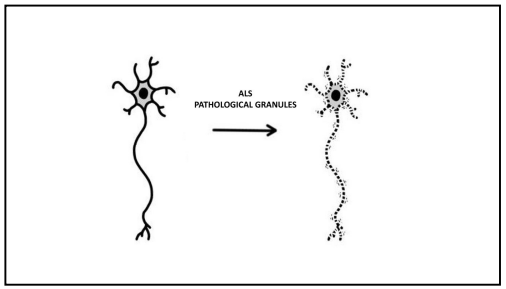

Fig.2 Motor neurons of patients affected by ALS undergo progressive neurodegeneration

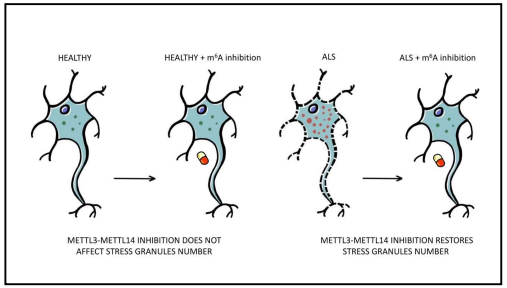

Fig.3 METTL3 inhibition restores the number of granules to physiological levels

Abstract
The present invention relates to the treatment of neuromuscular degenerative disorders, in particular to the treatment of disorders characterized by the formation and the persistence in the cells of protein aggregates, for example aberrant stress granules.
More specifically, it relates to the treatment of Amyotrophic lateral sclerosis through the use of inhibitors of the METTL3-METTL14 inhibitors.
It is also object of the present invention a composition comprising an inhibitor of the METTL3-METTL14 complex for use in the treatment of said degenerative pathologies.

Treatment of degenerative neuromuscular diseases

Technical Description

The treatment of neuromuscular degenerative diseases, particularly those predisposing to the formation of pathogenic cytoplasmic aggregates represents a crucial challenge in the medical field. The presence of these aggregates is promoted by the activity of the METTL3-METTL14 protein complex. The object of the invention involves the use of inhibitors of the METTL3-METTL14 complex thus resulting in, a modification of RNA, called methylation, at position 6 of adenosine (m6A). The inventors' findings highlight that in the presence of mutations associated with neuromuscular degenerative diseases such as, for example, Amyotrophic Lateral Sclerosis (ALS). An inhibition of the activity of METTL3-METTL14 protein complex results in a decrease in the number of pathogenic cytoplasmic aggregates improving the disease outcome.

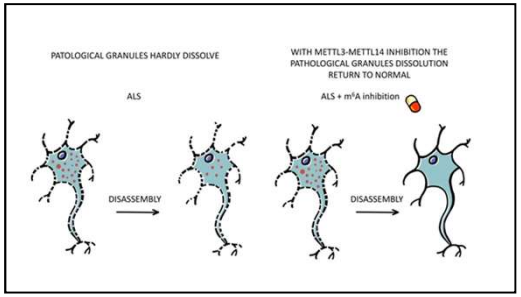

Fig.4 The inhibition of METTL3 reestablish their properties and confers them a physiologic disassembly dynamic

Technologies & Advantages

Among progressive neuromuscular diseases ALS, due to a gradual degeneration of motor neurons resulting in atrophy of innervated muscles, is among those with the most ominous prognosis. At present, there is no resolving drug therapy for the disease. Its etiology involves the formation of stress granules or aggregates due to mutated proteins, leading to liquid-solid phase transition and protein aggregation.

The unique selling proposition (USP) of the invention is the possibility of the use of synthetic small molecules with low manufacturing cost and easy route administration that inhibit the METTL3-METTL14 complex.

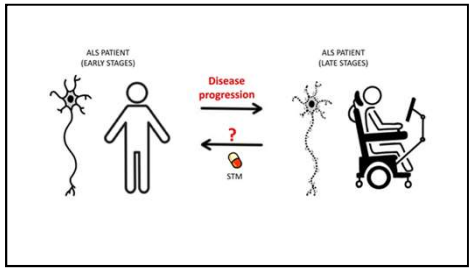

Fig.5 The inhibition of the activity of METTL3-METTL14 could represent a new therapeutical approach for the treatment of degenerative neuromuscular diseases.

Applications

The METTL3-METTL14 complex inhibition is a promising tool for the drugs development in the treatment of neuromuscular degenerative diseases characterized by the accumulation of pathological protein aggregates or aberrant stress granules, such as ALS. Specifically, these molecules have the ability to delay neurodegenerative pathways and to regulate cytoplasmic aggregate formation at physiological levels. Inhibitors of the METTL3-METTL14 complex have already been used in clinical trials for the treatment of other diseases such as cancer. These features make them promising therapeutic agents for the treatment of neuromuscular degenerative diseases both when, used alone and, in synergy with other drugs. Moreover, in the future, they may represent the starting point for the development of new therapeutic approaches.

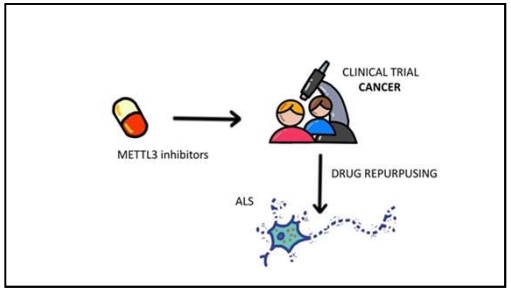

Fig.6 Extensive clinical studies have already been conducted with chemical inhibitors of METTL3 in the context of cancer

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