Inhibition of the Aggregation of Transthyretin by Specific Binding of Peptides to Aggregation-Driving Segments

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SUMMARY

UCLA researchers from the Department of Chemistry and Biochemistry have developed a novel process to inhibit amyloid aggregation of Transthyretin, which is associated with three debilitating disorders including senile systemic amyloidosis (SSA), Familial Amyloidotic Polyneuropathies (FAP), and Familial Amyloidotic Cardiomyopathies (FAC).

BACKGROUND

Transthyretin (TTR) is a transport protein that is present in blood and cerebrospinal fluid. TTR is normally present as a tetramer and facilitates the important transport of retinol binding protein as well as thyroxine. Pathological disassociation of the TTR tetramer into monomers results in the self-association of TTR monomers into amyloid aggregates. These amyloids can then deposit into many organ systems, including peripheral nerves, heart, eye, skin, kidneys, and the gastrointestinal tract, causing several diseases including senile systemic amyloidosis (SSA), Familial Amyloidotic Polyneuropathies (FAP), and Familial Amyloidotic Cardiomyopathies (FAC). There is currently no cure for TTR-related amyloidosis and it is hypothesized that there exists segments on TTR itself that drives protein self-association into amyloid aggregates.

INNOVATION

UCLA researchers have developed a novel method to inhibit TTR monomers from forming amyloids. Two segments of TTR have been identified and validated to be drivers of amyloid formation. Correspondingly, two optimized peptide inhibitors have been developed which target these TTR segments. These two peptides have been shown to disrupt amyloid formation and show a synergistic effect in a dose-dependent manner. These peptides were verified to not affect TTR stability or binding with its normal targets such as thyroxine.

APPLICATIONS

- Prevention of Transthyretin (TTR)-related amyloidosis
- Slowing progression of TTR-amyloidotic diseases

ADVANTAGES

- Targets the formation process of TTR-amyloids
- Synergistic effect between the two peptides
- Does not affect TTR stability
- Does not affect TTR normal function

RELATED MATERIALS

- Jiang, L., Liu, C., Leibly, D., Landau, M., Zhao, M., Hughes, M. P., and Eisenberg, D. S. Structure-based discovery of fiber-binding compounds that reduce the cytotoxicity of amyloid beta, Elife, 2013.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	11,028,128	06/08/2021	2016-694

CONTACT

UCLA Technology Development Group
ncd@tdg.ucla.edu
tel: 310.794.0558.

INVENTORS

- Eisenberg, David S.

OTHER INFORMATION

KEYWORDS

Transthyretin, TTR, amyloid, amyloidosis, protein folding, self-association, neuropathy, cardiomyopathy, senile systemic amyloidosis, familial amyloidosis, peptide inhibitor, thyroxine, retinol binding protein

CATEGORIZED AS

- **Medical**
  - Disease: Blood and Lymphatic System
  - Disease: Cardiovascular and Circulatory System
  - Disease: Central Nervous System
  - Disease: Genetic Diseases and Dysmorphic Syndromes
  - Therapeutics

RELATED CASES

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UCLA Technology Development Group

10889 Wilshire Blvd., Suite 920,Los Angeles,CA 90095

tdg.ucla.edu

Tel: 310.794.0558 | Fax: 310.794.0638 | ncd@tdg.ucla.edu