Chemically Modified Nell-1 and Methods of Making and Using the Same

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SUMMARY

UCLA researchers have developed ways to chemically modify NELL-1, an osteoinductive factor, that significantly prolong the in vivo circulation time of the protein and retain its osteoblastic activity without any appreciable cytotoxicity.

BACKGROUND

Osteoporosis is a progressive bone disease due to low osteoblast activity and/or high osteoclast activity. With the aging population, the biomedical burden of osteoporosis is significantly elevating, with no novel therapeutic to address systemic bone loss. In the United States, osteoporosis is a major public health threat for 24 million Americas. Roughly 1 in 4 women more than age 50 has osteoporosis. The cost of hip fractures alone is projected to reach $62 billion in the United States by the year 2020.

NELL-1 is an osteoinductive factor recently discovered to induce bone formation and reverse osteoporotic bone loss when administrated intravenously. However, similar to other protein drugs, the bioavailability of NELL-1 is limited by its in vivo half-life and rapid clearance from body. Unmodified NELL-1 requires an impractical 48hr injection frequency and thus limits NELL-1's translation into a clinical setting. Currently, one of the most popular technologies to prolong the half-life time of protein is to use water-soluble polymers as a macromolecular carrier. PEG is a water-soluble polymer with excellent biocompatibility but without immunogenicity. As it is approved for human use by FDA, the non-toxic PEG molecule is widely used in numerous biomedical applications.

INNOVATION

UCLA researchers PEGylated NELL-1 by random conjugation using 3 different PEG sizes. The thermal stability, cytotoxicity, in vivo bioactivity and pharmacokinetic behavior of the multiple forms of PEGylated NELL-1 were evaluated and the most effective forms were selected. Specific forms of PEGylation of NELL-1 significantly increases the elimination half-life of the protein from 5.5h to 15.5h while distributing more than 2-3 times the amount of protein to bone tissue in vivo. Systemic NELL-PEG therapy administered every 4-7 days significantly increases not only percent bone volume but also new bone formation throughout the overall skeleton after 4 weeks of treatment.

APPLICATIONS

A principal application of this invention is for treatment of osteoporosis.

ADVANTAGES

- This invention allows further development of NELL-1 into an effective systemic therapeutic for the treatment of osteoporosis. NELL-1 can be administrated with a low dose and low frequency, possibly leading to lower treatment cost and higher patient compliance.
- Unlike BMP-2 which has undesirable side effects such as excessive and ectopic bone formation, bone resorption, etc., NELL-1 has less side effects occurring during application in vivo.

PATENT STATUS

Patent Pending

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Nell-1 As An Anti-Osteoinflammatory, Disease-Modifying Anti-Arthritis Agent

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OTHER INFORMATION

KEYWORDS

Nell-1, osteoporosis, PEGylation, bioavailability, circulation time

CATEGORIZED AS

- **Medical**
  - Disease: Musculoskeletal Disorders
  - New Chemical Entities, Drug Leads
  - Therapeutics

RELATED CASES

2015-573-0

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