Novel Method of Packaging Peptides to Ensure Bioactivity, Proteolytic Resistance, and Cellular Uptake

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OTHER INFORMATION

CATEGORIZED AS

- **Materials & Chemicals**
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2015-036-0

BACKGROUND

As of 2012, the pharmaceutical market share of peptide/protein therapeutics was >$40 billion annually. However, due to their instability *in vivo*, most peptide therapeutics must be directly injected at the site of action. This has a negative impact on patient compliance and, as such, many peptide therapies are only used clinically as salvage treatments.

Several existing approaches for producing peptides protected from proteolysis involve chemical modification of the amino acid sequence. This generally necessitates multiple rounds of structure-function studies to verify that the activity of the peptide is not altered. Other approaches not using chemical modification of the amino acid sequence may involve conjugation of the peptide to a pre-formed higher molecular weight structure, such as a polymer or nanomaterial. The downside of these approaches is that they require multiple conjugation and purification steps and the generation of the high molecular weight carrier.

Inefficiencies in cellular uptake and rapid digestion by proteases are two key problems that have limited the clinical efficacy of peptide-based therapeutics.

TECHNOLOGY DESCRIPTION

Chemists at UC San Diego have developed a novel method of packaging peptides, which renders them resistant to proteolysis in a tunable fashion but does not alter their amino acid sequence and therefore preserves their biological activities. This patent-pending technology can be employed broadly to render therapeutic peptides or peptide-based sensors resistant to proteolysis, thus improving their bioavailability and clinical efficacy.

This technology leverages a direct (graft-through) polymerization of peptide-containing norbornene monomers via ring-opening metathesis polymerisation (ROMP). This obviates the need for the purification steps common with more traditional synthetic routes to peptide-containing polymers, which involve chemical conjugation of the peptide to a pre-formed polymer. This technology offers an attractive alternative to existing methods of protecting peptides from proteolysis because it is simple, does not alter the amino acid sequence of the peptide, and enables easy functionalization with other useful moieties or cargo. It is applicable to any peptide based therapeutic agent or biosensor that requires maintained fidelity after exposure to a harsh proteolytic milieu.

ADVANTAGES

Peptides are directly incorporated into high density brushes without modifying the actual amino acid sequence of the peptide, which dictates its function. As such, the peptide maintain their inherent bioactivity.

STATE OF DEVELOPMENT

As a proof-of-concept, the inventors polymerized well-known cell penetrating peptides into brush polymers using ring opening metathesis polymerization. These brush polymers were resistant to proteolysis and maintained their ability to penetrate cells. The inventors have also established that several other peptide substrates are resistant to proteolysis when prepared as brush polymers. Moreover, the proteolytic susceptibility of the peptide brushes can be tuned by adjusting the density of the brush as confirmed by both experimental and computational studies. The inventors have also shown that peptides that do not enter cells on their own can permeate cells when polymerized, if a single positively charged residue, Lys or Arg, is present in the peptide sequence or if one is added.

RELATED MATERIALS

- AP Blum, JK Kammeyer, J Yin, Dustin T. Crystal, AM Rush, MK Gilson, NC Gianneschi. Peptides Displayed as High Density Brush Polymers Resist Proteolysis and Retain Bioactivity. J. Am. Chem. Soc. 2014, 136, 15422-15437 - 10/14/2014

PATENT STATUS

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United States Of America	Published Application	20180042843	02/15/2018	2015-036

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