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TECHNOLOGY TRANSFER OFFICE

Advanced Peptide Synthesis: Method for Peptide Macrocyclization

UNIVERSITY OF COLORADO

TECHNOLOGY TRANSFER OFFICE

Boulder + Colo. Springs
4740 Walnut Street
Suite 100
Campus Box 589
Boulder, CO 80309

(303) 492-5647

Denver + Anschutz
Medical Campus
12635 E. Montview Blvd
Suite 350
Campus Stop F411
Aurora, CO 80045

303-724-0221

www.cu.edu/techtransfer

IP Status:

Patent pending, available for exclusive or non-exclusive licensing.

Case Manager:

MaryBeth Vellequette

Email

Ref # CU2452B

Background

Over the past decade, therapeutic peptides have become an important part of the pharmaceutical landscape, due in large part to their ability to selectively bind to both intra-and extra-cellular targets. Typically, these protein fragments exhibit higher binding affinity and thus greater potency than similar small molecule therapies. However, peptides often lack the clinical efficacy of the native proteins from which they are derived. Peptides lack defined conformation which decreases their bioavailability and makes them particularly susceptible to proteases.

A variety of peptide macrocyclization methods have been developed to address these drawbacks. Cyclization stabilizes the peptide molecule by constraining its conformation, thus increasing potency and decreasing proteolysis (thus increasing *in vivo* half-life). However, cyclic peptide synthesis is slow process, sometimes requiring days to complete the process.

Multivalent peptides are characterized by multiple antigenic regions that are capable of simultaneous ligand interactions that increase binding affinity and specificity. Multivalent interactions play an important role in a variety of biological systems and are of particular clinical interest, especially for vaccine development. Existing synthesis and purification methods for multivalent peptides have proven problematic.

Technology

Researchers at the University of Colorado led by Dr. Kristi Anseth have developed a highly specific method for synthesizing cyclic, multivalent peptides using sequential thiol -mediated reactions. By leveraging thiol-ene/-yne "click chemistry", CU researchers have created a high yield method for the macrocyclization of peptides and their subsequent attachment to a peptide core backbone. The reaction is capable of clustering two peptides at each alkyne functional group on the peptide core; multiple alkyne groups on a given core results in multiple peptide clusters on that core (see graphic, next page).

This method is quite fast compared to existing multivalent peptide synthesis technologies. Furthermore, the multimerized cyclic peptides exhibit enhanced bioactivity. Efficacy studies for the model RGD peptide indicate that intermediate cyclized peptides show improved potency compared with a corresponding linear precursor. In addition, multimerized cyclic peptides exhibited 1.5 to 2 orders of magnitude greater bioactivity than the monomeric cyclized species. Rapid, high-yield synthesis of complex cyclic multivalent peptides will be essential to vaccine development and drug delivery.

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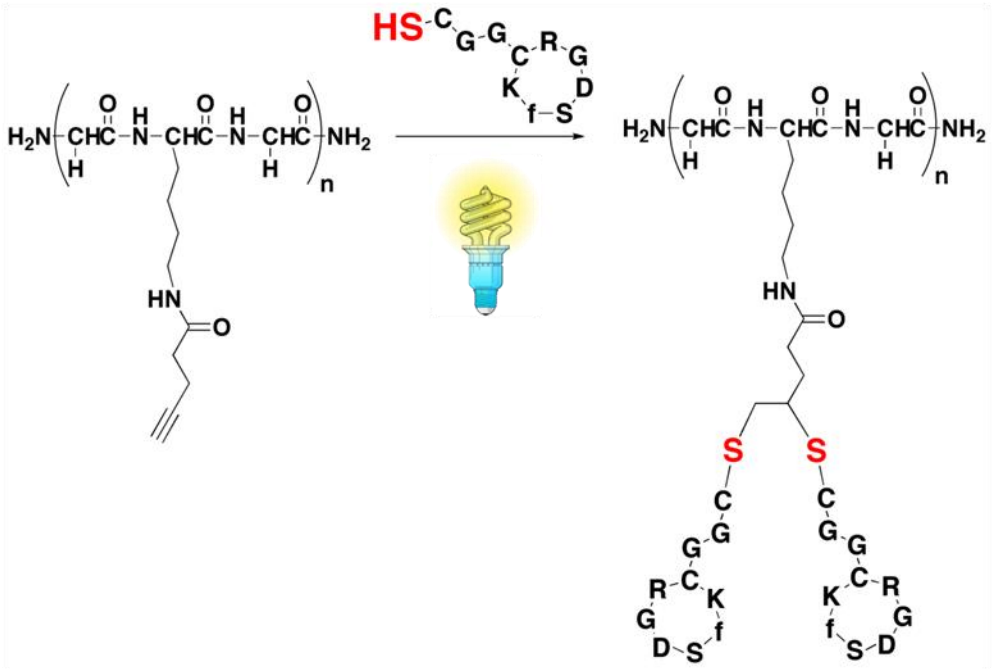

A graphical representation of on-resin peptide cyclization using a photoinitiated thiol–ene click reaction and subsequent clustering using thiol–yne photochemistry.

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Key Documents

Method For Synthesizing A Cyclic Multivalent Peptide Using A Thiol-Mediated Reaction. PCT application filed June 10, 2011.

On-resin peptide macrocyclization using thiol-ene click chemistry. Chem Commun (Camb). 2010 Jun 21;46(23):4061-3. *PDF available upon request.*

Synthesis of cyclic, multivalent Arg-Gly-Asp using sequential thiol–ene/thiol–yne photoreactions. Chem Commun (Camb). 2010 Aug 21;46(31):5781-3. *PDF available upon request*