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Methods to Optimise PK Properties & Binding Affinity of Peptides & Proteins to Enhance their Therapeutic Potential

Dr Goncalo Bernardes and his team from the Department of Chemistry at the University of Cambridge have developed 2 novel stapling methods to stabilise and enhance the binding affinity of peptides, proteins & antibodies.

Potential Applications

- Improvement of therapeutic potential of peptides/proteins
- Enhancement of efficacy of protein vaccines
- Generation of Antibody Drug Conjugates

The Methods

- Involve incorporation of a small water compatible group (oxetane or Staple 2) through site selective bis-alkylation of cysteine residues on peptides/proteins
- Use mild, biocompatible conditions
- May be performed as a one pot reaction with the peptide/protein in culture medium
- Can be applied to linear & cyclic peptides and proteins

Key Features

- Optimise PK properties of peptides and proteins
- Potential to enhance binding affinity of peptides/proteins
- Potential to improve other peptide/protein properties e.g. passive membrane permeability
- Antibody Drug Conjugates may be generated using the method

Dr Goncalo Bernardes

For further information please contact:

Dr Vibha Tamboli
Vibha.tamboli@enterprise.cam.ac.uk
+44 (0)1223 760339
Cambridge Enterprise Limited, University of Cambridge
Hauser Forum, 3 Charles Babbage Road, Cambridge CB3 0GT UK
www.enterprise.cam.ac.uk

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Background

The therapeutic potential of peptides and proteins is limited by their stability *in vivo*. Many stapling technologies have been developed to improve this. Cysteine crosslinking is the only stapling approach applied to large fully folded proteins e.g. thioredoxin & phage display proteins, however:

- there is no simple method which uses the necessary water compatible cross-linkers
- mild reaction conditions
- results in comparable/improved binding affinity of such proteins
- results in stabilised proteins with a better half life

Technology

Dr Goncalo Bernades and his team have developed 2 novel stapling methods to stabilise and enhance the binding affinity of peptides, proteins & antibodies.

Potential Applications:

- improvement of therapeutic potential of peptides/ proteins
- enhancement of efficacy of protein vaccines
- generation of Antibody Drug Conjugates

The Methods:

- involve incorporation of a small water compatible group (oxetane or Staple 2) through site selective bis-alkylation of cysteine residues
- uses mild, biocompatible conditions
- can be performed as a one pot reaction with the peptide/protein in culture medium
- can be applied to linear & cyclic peptides and proteins
- does not require any sequence engineering

Key Features

- potential to enhance binding affinity of peptides/ proteins, e.g. :
  - oxetane stapled somatostatin has 4 fold better binding to its receptor
- optimise PK properties of peptides and proteins, e.g:
  - no significant degradation of oxetane stapled somatostatin observed at 48hrs in human plasma
- potential to improve other peptide/protein properties e.g. passive membrane permeability

Figure 1: Structure of somatostatin & oxetane stapled somatostatin

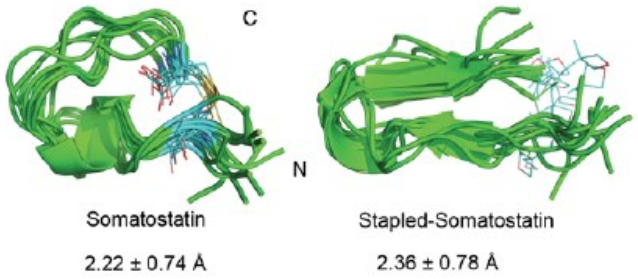
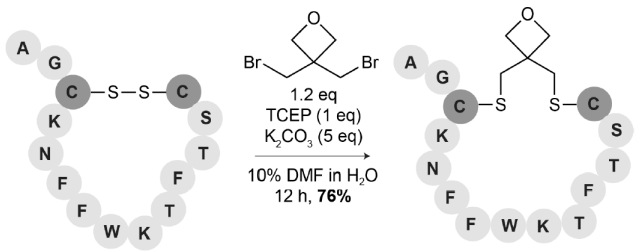
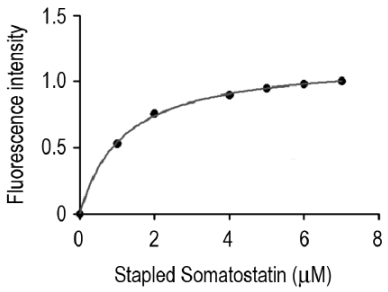


Figure 2: Oxetane stapled somatostatin has a 4 fold enhancement in binding affinity to SSTR2 than its native form

(a)



(b)



(a) stapling of somatostatin

(b) the dissociation, KD curve for the binding of stapled somatostatin to the SSTR2 (1.16uM) vs somatostatin (4.56uM)

Commercialisation

We are seeking a commercial partner for licensing, collaboration and development of this technology which is protected by patent application no. GB1704922.2 filed on 28th March 2017.