Novel Stapled Peptides as Therapeutic Agents Against Integrin-Related Diseases

(FCCC Ref. 541-JW)

Background

Integrin hyperactivation and the overexpression of talin, a major cytoplasmic activator of integrins, have been linked to thrombotic disorders, impaired immune function, cardiovascular diseases, and cancer. Current anti-integrin therapeutic reagents, targeting the extracellular ligand-binding sites of integrins, have not been successful in treating integrin-related tumor metastasis, and may lead to severe adverse effects associated with either unwanted complete loss or unexpected elevation of integrin activity. Recent data suggest that suppressing integrin functions by blocking talin-mediated integrin activation may achieve optimal potency and greater selectivity, and may inhibit the ligand-independent integrin activity.

Summary of the Invention

Researcher from Fox Chase Cancer Center designed stapled peptide that has the potential to effectively inhibit integrin activity by blocking the translocation of talin, the integrin activator molecule and the subsequent talin:integrin association simultaneously. The crystal structure of a prototype stapled peptide bound to talin was determined. Data show that the stapled peptide affords a much-stabilized helical configuration, possesses outstanding membrane permeability, and is able to inhibit integrin activation. Thus, the peptide and its optimized derivatives are projected highly effective therapeutic agents against integrin-related diseases such as thrombotic disorders, auto-immune diseases, CVD, and cancers.

Reference: Gao T. et al., Inhibition of Talin-induced Integrin Activation by a Double-hit Stapled Peptide, BioRxiv August 12, 2022. https://www.biorxiv.org/content/10.1101/2022.08.12.503760v1

Advantages

- Novel peptide-based therapeutics to treat talin-related diseases such as thrombotic disorders, auto-immune diseases, CVD, and cancers.
- Greater effectiveness than the current anti-integrin therapeutic reagents: (1) first peptide-mimetic agent that targets integrin function by interacting with the cytoplasmic activator talin; (2) is able to hit the target protein at multiple sites simultaneously, resulting in enhanced effect; and (3) possesses high cell permeability, strong binding affinity, and significant biological effect.
- Existing crystal structure facilitates further development.

IP Status

International Patent Application has been published WO2022/165127 A3 . Patent pending.

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