Docket #: S23-011

Functionally biased ligands for the Complement 5a Receptor

Stanford scientists have discovered multiple functionally biased ligands that can selectively activate distinct subsets of signaling pathways downstream of the complement 5a receptor. These ligands will be useful for the scientific study of complement 5a receptor signaling and, more importantly, can potentially be used as therapeutics.

The complement 5a receptor (C5aR) is an important cellular receptor that exerts many critical physiological functions, including regulating the immune response and promoting cancer resistance to treatments. It has been shown that C5aR can simultaneously activate many downstream signaling pathways; however, the biological consequences of individual pathways are unclear. The biggest obstacle in the understanding of C5aR signaling is the lack of pharmacological tools to selectively modulate subsets of the signaling pathways and allow the analysis of their biological functions in isolation.

There are two major signaling pathways downstream of C5aR: cAMP and beta-arrestin. Various mutants have been discovered: 1) those that completely abolish beta-arrestin signaling, 2) those that partially inhibit the cAMP pathway 3) those that inhibit both beta-arrestin and cAMP pathways. The short-term application of these ligands would be their use as research tools to dissect the signaling pathways downstream of C5aR. In the long term, with a better understanding of the physiological functions of the ligands, they could be used as therapeutics to treat diseases that require the selective activation of the related signaling pathways.

Stage of Development:
Preclinical – in-vitro data
Continued research – elucidation of the exact biological function of the ligands

Applications

- Use as research tools to dissect C5aR signaling
- Therapeutics for diseases that benefit from the selective activation of C5aR

Advantages

- Selectively activate a subset of C5aR signaling pathways as opposed to complete blockage
- Use of peptides leads to much stronger binding affinity

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