Docket #: S07-208

GPCR Fusion Proteins and Method for Crystallizing GPCRs

The invention consists of a general strategy for modifying GPCRs to enhance biochemical stability and facilitate the formation of diffraction quality crystals. As proof of principle, the method was used to successfully determine the three-dimensional chemical structure of the Beta2 Adrenergic Receptor (Beta2AR). One of the intracellular loops of the Beta2AR was replaced with a certain lysozyme, one of the most stable and crystallizable protein domains known in the biochemical literature. The site of insertion of the lysozyme was optimized to preserve receptor function and enhance receptor stability. This GPCR Lysozyme fusion retains the pharmacologic properties of the receptor, has enhanced stability relative to the unmodified GPCR, and can be crystallized for X-ray structure determination.

Applications

- The general purpose of the invention is to facilitate the formation of diffraction quality crystals of GPCRs that can be used for three-dimensional structure determination. This invention has the potential to significantly impact GPCR-directed drug discovery, an area of research which accounts for a large percentage of currently approved pharmaceuticals.

Advantages

- The elucidation of non-rhodopsin GPCR structures has proven largely intractable by standard methods of detergent-based membrane-protein crystallization. This invention will help to satisfy the largely unmet need for high-resolution structural information on these proteins, helping us to understand how GPCR-targeted drugs work and how to better design more selective and effective drugs. In addition, the implementation of crystallizable

GPCR Lysozyme fusion proteins is less costly and potentially more general than other methods for GPCR stabilization, such as formation of antibody complexes.

Patents

- Published Application: WO2009051769
- Published Application: 20090118474
- Published Application: 20110009603
- Published Application: 20110189756
- Published Application: 20110171728
- Published Application: 20120136137
- Published Application: 20110164731
- Published Application: 20150210751
- Issued: 7,790,850 (USA)
- Issued: 8,260,596 (USA)
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Innovators

- Brian Kobilka
- Daniel Rosenbaum

Licensing Contact

Cheryl Cathey

Senior Licensing and Strategic Alliance Manager

Email