

DISCUSSION SESSION ON LECTURE #5: STUDY QUESTIONS

ASSIGNED PAPERS: Cherezov V et al. (2007) High-resolution crystal structure of an engineered human β_2 -adrenergic G protein-coupled receptor. *Science* **318**: 1258-1265; Rosenbaum DM et al. (2007) GPCR engineering yields high-resolution structural insights into β_2 -adrenergic receptor function. *Science* **318**: 1266-1273.

- (1) What are the endogenous ligands for the beta-adrenergic receptor? Agonist occupancy of this GPCR is important to elicit the signaling necessary for what biological processes?
- (2) What extraordinary measures were required to generate crystals of β_2 AR that were suitable for X-ray diffraction at sufficient resolution to acquire atomic-level detail and why were these tactics necessary?
- (3) What are the strengths and limitations of X-ray crystallography for deducing how ligand binding evokes G-protein activation mediated by β_2 AR? What additional information is necessary to fully understand these mechanisms?
- (4) The only other GPCR that has been viewed at atomic resolution is the visual pigment, rhodopsin, from retinal rod cells [see: Ridge KD, Palczewski K (2007) Visual rhodopsin sees the light: structure and mechanism of G protein signaling. *J. Biol. Chem.* 282: 9297-9301]. Compare and contrast the biological and structural features of β_2 AR and rhodopsin.

Quantitative Question: If a representative mammalian cell has an average diameter of 20 μm , and up to 25% of its total surface area can be occupied by receptor molecules, and the extracellular aspect of a typical receptor has a diameter of 100 \AA , calculate:

- (a) What is the maximum (total) number of receptors that can be displayed on the surface of the plasma membrane? [Assume, for the sake of this question, that the mammalian cell in question is roughly spherical in shape and the extracellular face of any type of receptor is roughly circular.]
- (b) Assuming that any given receptor type (say, β_2 AR or the EGF receptor) is present at $\sim 10^5$ per cell, what does the number you calculated in (a) suggest about the maximum number of different receptor types that can be displayed on the surface of a mammalian cell at any given time?