GPCR Efficacy and Biased Agonism

**A** Different GPCR conformations

- Ligand 1
- Ligand 2

**B** Different scaffolding protein conformations

- Agonist
- Inactive

**C** Different rate of GTP–GDP exchange

- Fast Rate
- Slow Rate

### Multiple Mechanisms Elicit Biased Agonism

1. **Different ligands induce different conformations within G protein-coupled receptors (GPCRs), promoting binding conditions for particular transducer proteins such as G proteins and arrestins.**
2. **Specific ligand-induced receptor conformations induce different conformational changes within scaffolding proteins such as arrestins, causing activation of distinct downstream signaling pathways.**

### Identifying Biased Agonism at the Adenosine A1 GPCR (A1R) Using the Operational Model

The six concentration-response curves (pictured) show activation of different signaling events for three A1R agonists, NECA (green line), R-PIA (orange line) and VCP746 (purple line). Operant behavioral testing was used to derive the transduction ratio (log(β/α), linking agonist occupied receptors to pharmacological effects) and this was plotted in a "Web of Bias".

- The "Web of Bias" chart shows each drug profile relative to the reference agonist, NECA and reference pathway 1 (as 1:1:1:1:1:1). Using this visual representation, the biased agonism of VCP746 for pathway 2 (reduced relative response to NECA and pathway 1), is easily observed. In contrast, R-PIA displays a similar signaling profile to the reference agonist, NECA.

### Spatial and Kinetic Factors

- Biased agonism is regulated by the temporal stability of transmembrane interactions between ligand, receptor and transducers or regulatory proteins. Through biased agonism, different ligands can alter the location, type and strength of signaling through the receptor subtype.

### G Protein-Coupled Receptors (GPCRs)

- GPCRs are transmembrane domain receptors, which can move between inactive-like (R, R′ and R′′) and active-like (R″ and R‴) states. This may occur in the absence of ligand or transducer (the apo state), however the energy barrier to achieving and maintaining an active-like conformation means that it’s unlikely to occur or has a lower probability in the absence of an agonist and G protein (or other transducer).

### G Protein Coupling

- The presence of an agonist and G protein (or other transducer) stabilizes the active conformation of both an agonist and transducer (e.g. G protein) stabilizes the active GPCR conformation and gives the highest probability that a signaling event will occur. The rates of transducer engagement and turnover are altered in an agonist-dependent manner that determines observed efficacy.

### Pharmacological Signaling

- Through biased agonism, different ligands can alter the location, type and strength of signaling through the receptor subtype.

### Therapeutic Application of Biased Agonism

- Studying the pharmacology of GPCR biased agonists can help improve the efficacy and safety profiles of drugs. Identification of compounds with a therapeutically beneficial activation profile that have reduced side effects can enhance patient outcomes and translation of drugs to the clinic.