**Unconventional GPCR-kinase signaling in primary cilia**

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**Introduction.** Primary cilia are specialized organelles that control key signaling pathways essential for human development, tissue homeostasis, and disease. Despite their importance, the molecular mechanisms by which cilia mediate signal transduction remain poorly understood, limiting our ability to explain their roles in physiology or target cilia-based pathways therapeutically. The Hedgehog (Hh) pathway is a major cilia-dependent signaling system, where activation of the atypical GPCR Smoothened (SMO) regulates diverse developmental and pathological processes. Yet, how SMO is activated and signals within the ciliary membrane has remained a longstanding mystery, as it bypasses conventional GPCR signaling mechanisms.

**Aims**. We set out to understand how SMO is activated and signals within the primary cilium.

**Methods**. We combined in vitro reconstitution and structural methods to develop a mechanistic biochemical model SMO activation along with cell biological approaches to evaluate that model in primary cilia.

**Results.** We uncovered how SMO directly controls protein kinase A (PKA) activity through unexpected, G protein-independent mechanisms – one involving a direct binding interaction between SMO and the PKA catalytic subunit that physically blocks PKA enzymatic activity, and another involving regulation of the trafficking of the ciliary Gs-coupled GPCR GPR161.

**Discussion.** These findings clarify fundamental aspects of ciliary signaling, resolve key questions in developmental and cancer biology, and suggest new opportunities for targeting cilia-based pathways in disease.