DOMAIN THERAPEUTICS

TECHNOLOGY OVERVIEW

bioSensAll™ — A Unique Platform for GPCR Drug Discovery Collaborations

bioSensAll™ is a patented live-cell BRET-based biosensor platform, that allows the assessment of **proximal** signal transduction pathways engaged on activation of **unmodified cell surface receptors,** including **G Protein-Coupled Receptors (GPCRs).**

Current challenges: GPCRs represent one of the most important druggable target, yet **their full potential remains underexploited due to incomplete data.**

Current methodologies used for GPCR ligand profiling involve the measurement of second messenger production (i.e., calcium, inositol trisphosphate, cAMP). Such readouts are relatively distal to the GPCR and rely on biological responses that can be modulated by various (often cross-talking) receptor downstream signaling pathways.

Consequently, **second messenger levels alone are not directly indicative of a ligand's activity or efficacy** and their use for ligand profiling may thus lead to erroneous conclusions [1].

The **downstream signaling pathway assessment** of GPCR ligands aims to provide new insights into the therapeutic efficacy of pharmacologically active compounds. Characterizing such proximal signaling signatures should **better inform the pharmaceutical industry in their lead selection process** and ultimately reduce attrition risks.

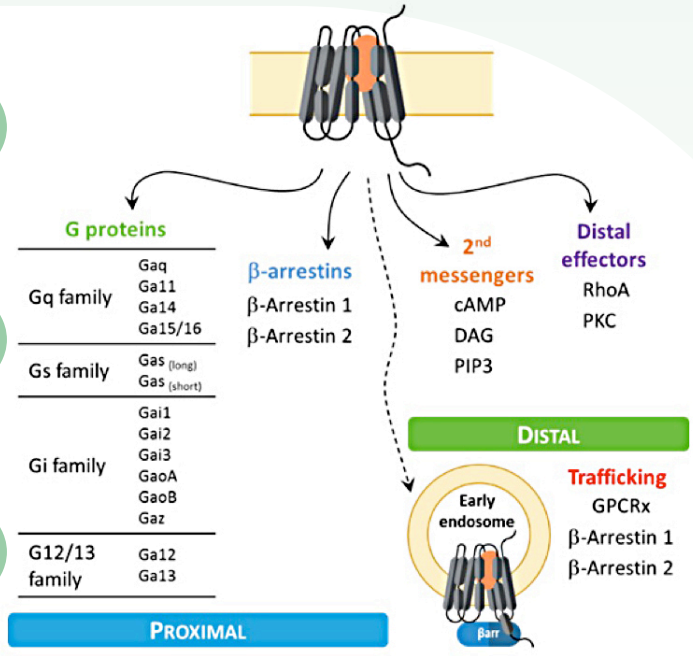
Technology: bioSensAll™ is a proprietary technology revolving around the **spatiotemporal monitoring of receptor proximal events directly linked to GPCR activation.**

Unique to this approach to ligand and receptor profiling, is its ability to directly quantify receptor coupling to specific heterotrimeric G-protein subtypes and ß-arrestin isoforms.

To date, the **bioSensAll™** platform includes biosensors for the activation of **13 distinct heterotrimeric G-proteins**, as well as sensors for the engagement of **ß-arrestin 1 and 2** (See figure below).

Conclusion: The **bioSensAll™** platform includes a unique set of biosensors spanning different effectors and offers a **pluridimensional vision of GPCR signaling signature.** Its unique combination of **adaptability, HTS compatibility** and **real-time kinetics** capabilities help generate the quality of data required to **enhance drug discovery in the field of GPCRs.**

bioSensAll™ GPCR biosensors panel



COMPETITIVE ADVANTAGES

	Other HTS Technologies	bioSensAll™
Real time kinetics on distal indicators (Ca2+, cAMP, ...)	±	✓
Unmodified GPCRs	✗	✓
Proximal biosensors detection	✗	✓
Real time kinetics on proximal biosensors	✗	✓
Proximal biosensors localization	✗	✓
G proteins discrimination	✗	✓
G12/G13 detection	✗	✓
Constitutive activity measurement	✗	✓

References:
[1] Mancini, A., Frauli, M., Breton, B. (2015). Exploring the Technology Landscape of 7TMR Drug Signaling Profiling. Curr Top Med Chem. 2015;15(24):2528-42.

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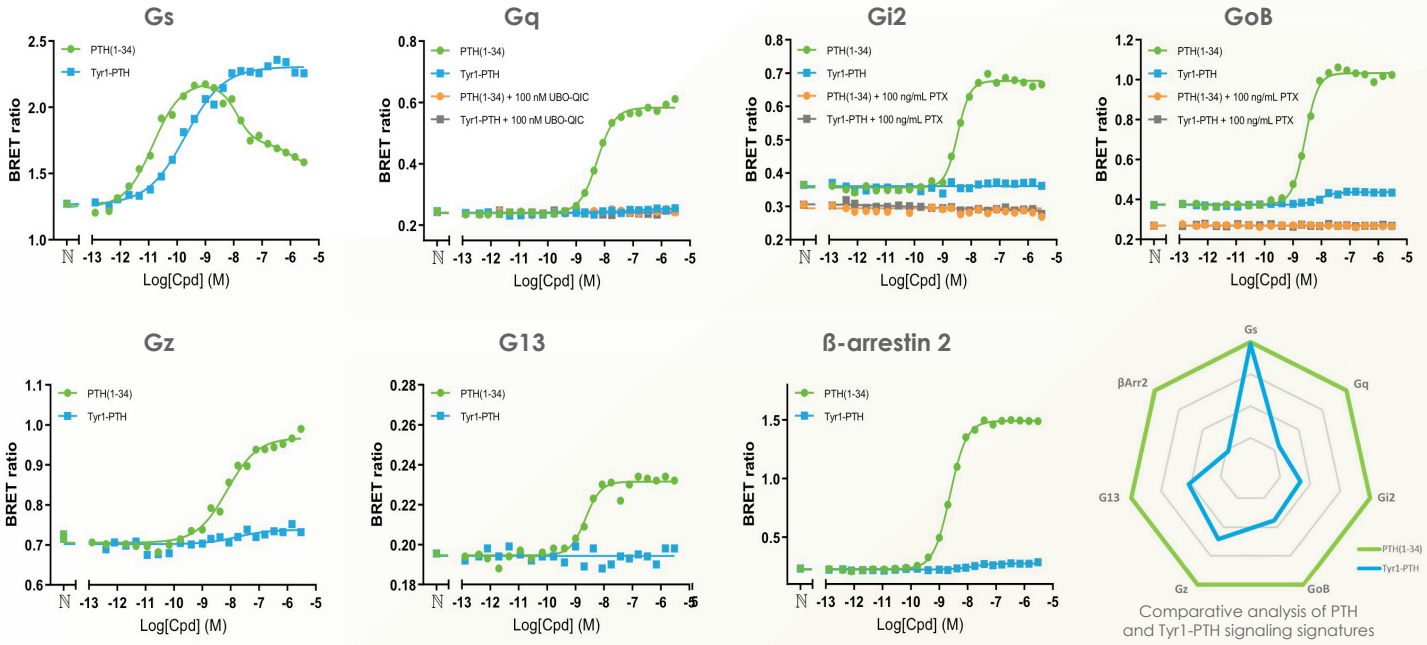
CASE STUDY: Characterization of hPTH1R signaling signature



Comparative analysis of PTH and Tyr1-PTH signaling signatures

RESULTS AND CONCLUSION

In response to its endogenous ligand PTH, hPTH1R engaged Gαs, Gαq, Gi-family G-proteins (i.e., Gαi2, GαoB, Gαz), Gα13 and ß-arrestin 2. Interestingly, the synthetic ligand Tyr1-PTH only activated Gas (full agonist) while remaining relatively ineffective at stimulating the other pathways engaged by PTH. Gαi/o and Gαq responses were reversed by PTX and UBO-QIC respectively.

The bioSensAll™ platform provides a pluridimensional assessment of a receptor's complete signaling repertoire and allows for the identification of biased ligands. Defining a ligand's proximal signaling signature is particularly useful in forecasting its therapeutic efficacy and safety.

TECHNOLOGY HIGHLIGHTS

- Wide range of receptor proximal biosensors applied to **non-modified GPCRs** (distal biosensors also developed)
- Compatible with **High Throughput Screening** (HTS)
- Applicable for **small molecules, peptides and biologics**

RESEARCH COLLABORATION WITH DOMAIN THERAPEUTICS

- Offers a **strong track record** of drug discovery partnerships with major pharmaceutical companies
- **De-risk the early-stage drug discovery** process
- Brings a unique combination of **novel drug discovery technologies** combined with extensive experience in transmembrane receptors

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