# Pathway-resolved profiling identifies non-canonical 5-HT7A/Gα15 signaling by MSD-001 (5-MeO-MiPT)

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## Question and Assay

We evaluated whether 5-MeO-MiPT activates recombinant human 5-HT7A primarily through canonical Gαs signaling or through non-canonical pathways detected using a 16-output BRET biosensor panel. Readouts were measured after 10-15 min and 60 min and normalized to serotonin.

## Main Results

Gα15 potency was closer to the reported 5-HT7 binding-affinity range (Ki approximately 20–120 nM) than canonical Gαs potency.[1,2] Interpretation remains provisional for native physiology and requires follow-up in HTR7+/GNA15+ cellular contexts

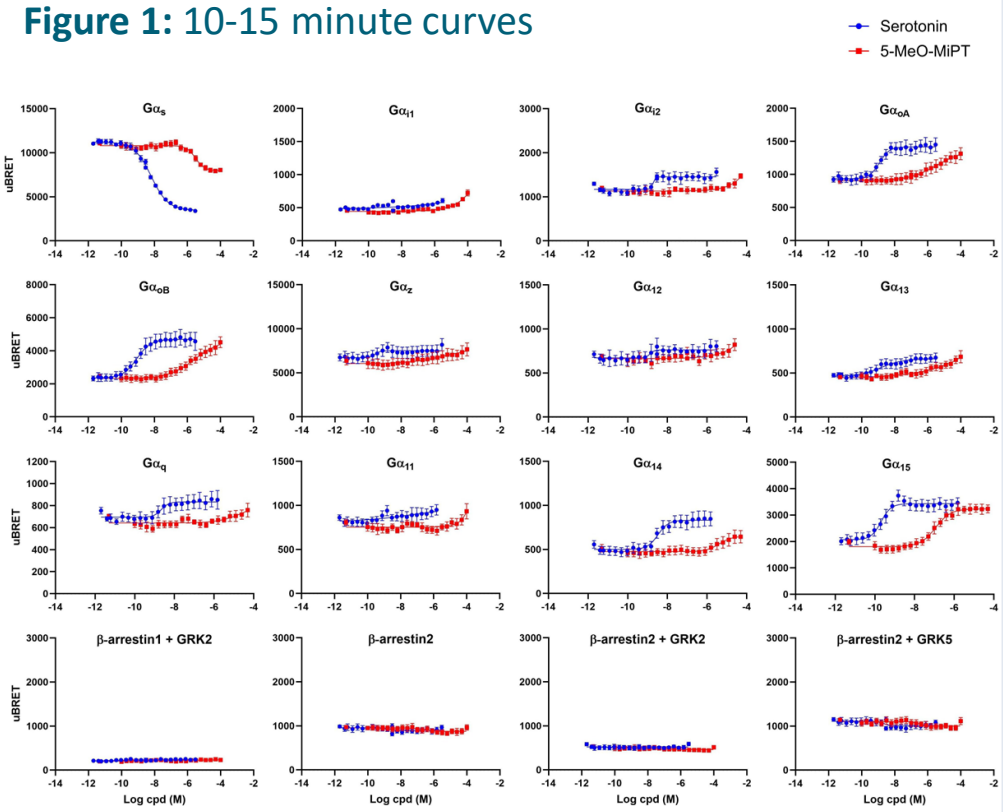
## Quantified pathway separation

| | |
|---|---|
| Gα15 EC50, 10-15 min | 114.6 ± 28.6 nM |
| Gα15 Emax, 10-15 min | 88.19 ± 4.27% |
| Gαs EC50, 10-15 min | 3139 ± 638 nM |
| Gαs Emax, 10-15 min | 42.00 ± 2.41% |

## Assay principle underlying BRET-based biosensors


Activated Gα recruits RlucII-tagged effectors to membrane GFP, increasing BRET; Gαs activation instead causes dissociation and decreases BRET.

## Figure 1: 10-15 minute curves




**Pathway-resolved 5-HT7A responses after 10-15 minutes**

Serotonin and 5-MeO-MiPT responses were measured across 12 G-protein and four β-arrestin biosensors. Gα15 produced the strongest quantified 5-MeO-MiPT response; β-arrestin responses remained below reliable quantitation. Gαs activation decreases uBRET, whereas most other pathways increased it.

## Table 1: Gα15 preference maintained at 60 minutes

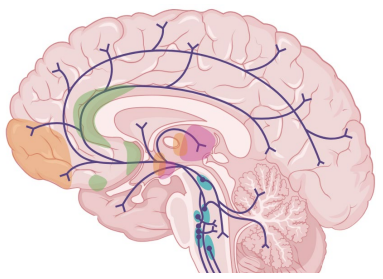
| Pathway | Parameter | 10-15 Minutes | 60 Minutes |
|---|---|---|---|
| Gα15 | EC50 | 114.6 ± 28.6 nM | 145.0 ± 49.2 nM |
| | Emax | 88.19 ± 4.27% | 89.56 ± 6.07% |
| Gαs | EC50 | 3139 ± 638 nM | 3160 ± 2041 nM |
| | Emax | 42.00 ± 2.41% | 50.33 ± 8.89% |

**Quantitative comparison of pathway-resolved 5-HT7A responses**

The relative separation between Gα15 and Gαs was maintained at 60 minutes. Gα15 potency and maximal response were similar across time points, whereas Gαs remained substantially less potent. Data are mean ± SEM from 3-4 independent experiments and were fitted using four-parameter nonlinear regression; Emax values were normalized to plate-matched serotonin.

## Figure 2: Native-cell context for 5HT7/Gα15

**A.**




**B.**

| Allen WHB L5ET_117 | Broad L2/3-6 IT | HTR7/GNAS canonical |
|---|---|---|
| 516/2,655 (19.4%) | 326/79,631 (0.4%) | 1,523/1,581 (96.3%) |

**Figure 2. Native-cell context for the 5-HT7/Gα15 hypothesis**

**A:** Schematic showing anatomical regions represented in the transcriptomic analysis. **B:** HTR7/GNA15 co-expression was enriched in a restricted L5ET-like brain signal relative to the cortical comparator populations shown. This signal mapped to PS7N-enriched regions including FI, ACC, A25, AON and MTG, identifying candidate contexts for functional testing. Transcript co-detection does not establish protein expression, native receptor–transducer coupling or circuit engagement.

## DISCOVERY TAKAWAY:

**A 16-output 5-HT7A transducer panel revealed prominent non-canonical Gα15 signaling that could be underrepresented by Gαs-only assays.**

**NEXT STEPS:** Test functional 5-HT7/Gα15 coupling in HTR7+/GNA15+ neuronal models

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