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Genetic behavioral screen identifies an orphan anti-opioid system

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Invertebrate genetic model organisms are tremendous tools for studying major questions in neuroscience. One example is the nematode *C. elegans*, which has a rich history of forward genetic discoveries that have driven the field forward. Recently, we embarked upon efforts aimed at using an engineered *C. elegans* platform, drug-inducible behavioral readouts, and unbiased forward genetics to address pressing questions in GPCR biology.
Our first foray on this front was developing an engineered *C. elegans* GPCR signaling platform using the mammalian μ-opioid receptor (MOR), the principle GPCR mediating analgesia and addiction to opioid drugs. To do so, we transgenically engineered mammalian MOR into the *C. elegans* nervous system endowing the resulting animal model (tgMOR) with opioid sensitivity. The tgMOR platform was validated by showing conservation of pharmacological properties and MOR signaling regulators. Unbiased, forward genetics isolated numerous tgMOR mutants with altered opioid responses. A combination of whole genome sequencing, CRISPR/Cas9 editing and transgenic rescue identified one opioid hypersensitive mutant that affects FRPR-13, a poorly understood orphan GPCR. Phylogenetic and functional analysis revealed that the mammalian ortholog of FRPR-13 is the orphan GPCR GPR139. Outcomes from mice indicated that knocking out GPR139 results in hypersensitivity to morphine-induced analgesia and reward, and reduced withdrawal from chronic opioid exposure. Collectively, these findings indicate that GPR139 functions as a conserved anti-opioid system. Moreover, our studies reveal the tremendous potential of engineered *C. elegans* behavioral models in biomedical research.