



Weill Cornell Medicine

Circuit-Guided Approach for Identifying Synergistic Drug Combinations for Treatment-Resistant Depression

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Background & Unmet Need

- Depression is a leading cause of global disability with a lifetime prevalence of ~17%
- Selective serotonin reuptake inhibitors (SSRIs) and monoamine-targeting drugs only achieve full remission in one-third of depression patients, leaving two-thirds with partial or no response
- Ketamine provides rapid antidepressant effects within hours of treatment, unlike traditional antidepressants that take weeks to work
- Despite ketamine's effectiveness, its unclear mechanism of action contributes to significant limitations, including transient benefits and side effects that require controlled administration settings
- **Unmet Need:** Development of mechanistically-driven antidepressant treatments that can provide rapid and effective relief for treatment-resistant depression with reduced side effects

Technology Overview

- **The Technology:** A therapeutic strategy targeting multiple GPCRs to achieve synergistic antidepressant effects
- **The Discovery:** Ketamine's antidepressant effects are initiated through Gi/o signaling via mu-opioid receptors within somatostatin (Sst) interneurons
- RNA-seq identified several GPCRs enriched in Sst+ interneurons after chronic unpredictable stress (CUS)
- The inventors developed a drug cocktail that synergistically targets three Sst+ interneuron-enriched GPCRs
- **PoC Data:** The drug cocktail produced rapid antidepressant effects within 60 minutes that persisted for at least 24 hours in stress-treated mice
- The drug cocktail demonstrated superior safety compared to ketamine, showing no impairment in motor coordination, normal locomotion, and anxiolytic effects

Inventors:

Conor Liston
Joshua Levitz
Hermany Munguba

Patents:

PCT Application Filed

Publications:

[Munguba et al. Cell. 2026.](#)

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Cornell Reference:

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Technology Applications

- Development of synergistic drug cocktails for depression
- Combination with low-dose ketamine to maximize benefits and minimize side effects
- Screening platform for identifying GPCR targets in specific cell types, applicable to depression, anxiety, PTSD, and OCD treatment

Technology Advantages

- Superior therapeutic effects through strategic targeting of multiple complementary pathways at lower doses
- Faster clinical translation through repurposing existing FDA-approved GPCR-targeting compounds
- Enables precision medicine approach by matching specific drug combinations to individual symptom profiles

Supporting Data / Figures

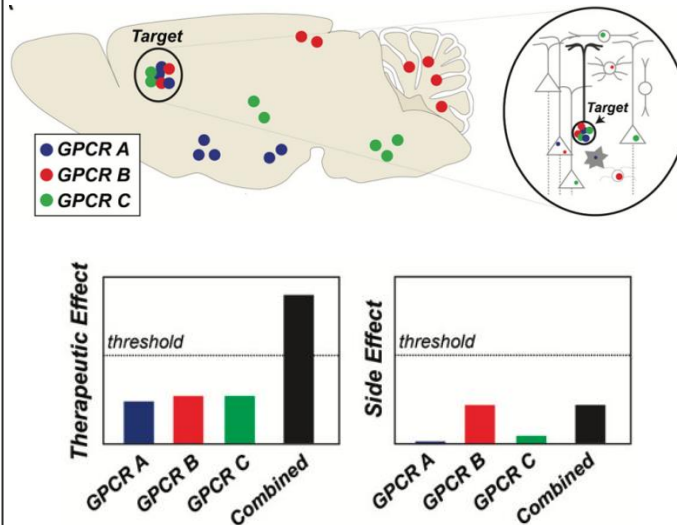


Figure 1: Screening tool is based on distinct patterns of brain connectivity associated with depression symptoms: anhedonia¹ (A) and anxiety (B)

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