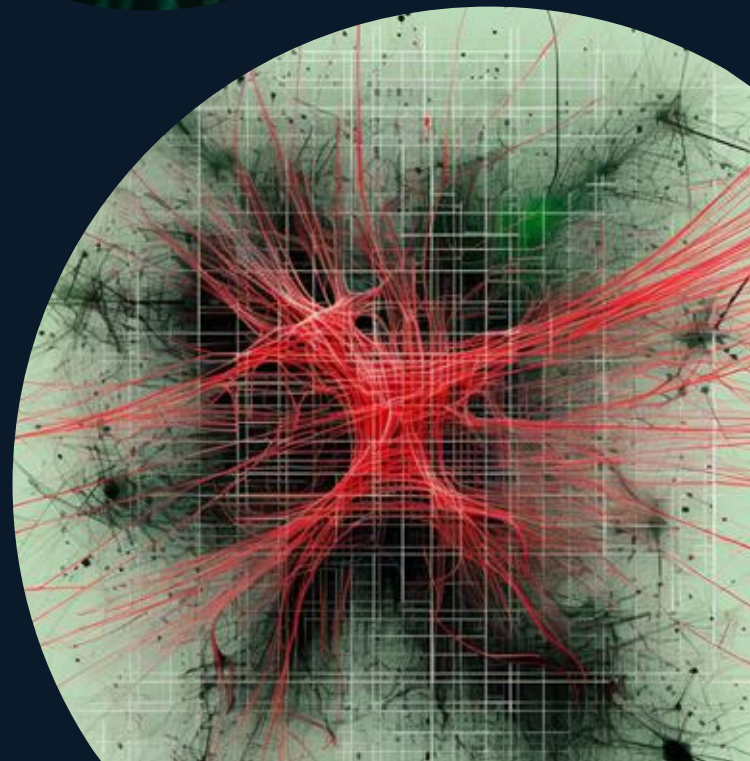
YALE · BLAVATNIK FUND ACCELERATOR

Rationally designed dual-target psychedelics



A first-in-class α_2-adrenergic / 5-HT_2A drug to reduce depression without hallucinations

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Non-hallucinogenic psychedelics are about to remake psychiatry

Massive unmet need for depression

21M U.S. adults with treatment-resistant depression. Current SSRIs fail 30–50%.

Single-dose, durable effect

Psychedelics produce rapid antidepressant action lasting weeks — but the 6-hour trip blocks scale.

Hallucinations gate access

Clinic supervision adds $2–5K per dose. Removing the trip unlocks home use and 100× scale.

THE PROBLEM

Everyone is tuning the same knob

Current non-hallucinogenic programs all engineer the 5-HT₂A receptor itself: biased agonists, partial agonists, allosteric tweaks. But psychedelics aren't single-receptor drugs.

THE EVIDENCE — JAIN ET AL., NEURON 2025

41 psychedelics profiled across chemical classes

318 human GPCRs screened in parallel

Result: classical psychedelics potently activate nearly every serotonin, dopamine, AND adrenergic receptor — not just 5-HT₂A.

So the field's bet is wrong.

If psychedelics work through a constellation of receptors, the right move isn't to perfect 5-HT₂A — it's to use polypharmacology as a feature, not a bug.

✗ **Field:** Re-engineer 5-HT₂A in isolation. Same target, marginal gains.

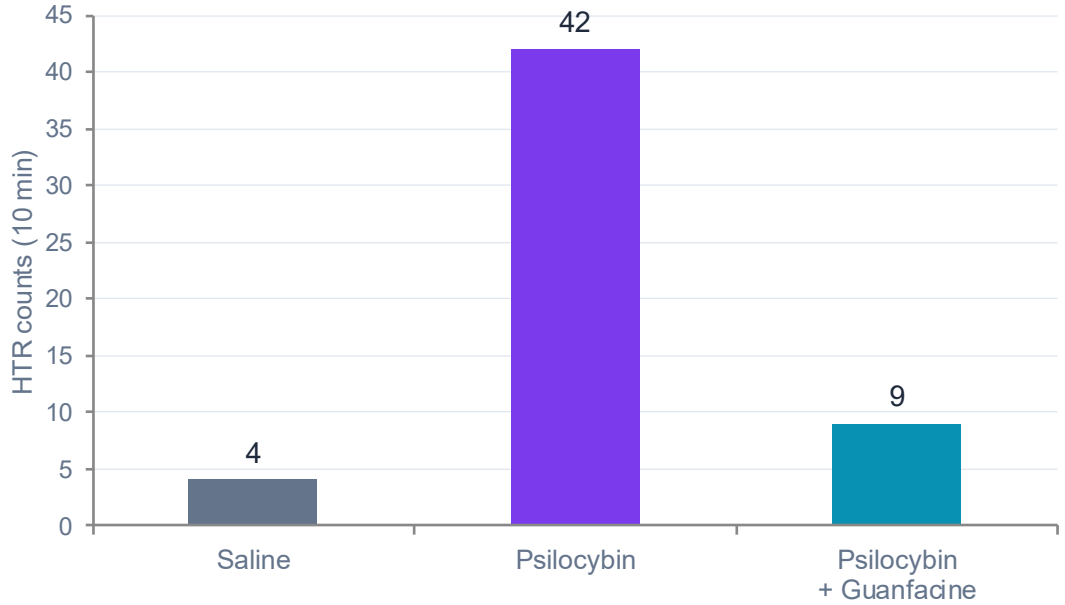
✓ **Our insight:** Recruit a second receptor that gates the trip, leaves therapy intact.

α2 activation suppresses the trip — and spares the cure

Rosado, Yu* et al., Molecular Psychiatry (accepted 2026) — Yale patent application filed.*

Hallucination proxy (HTR) in mice

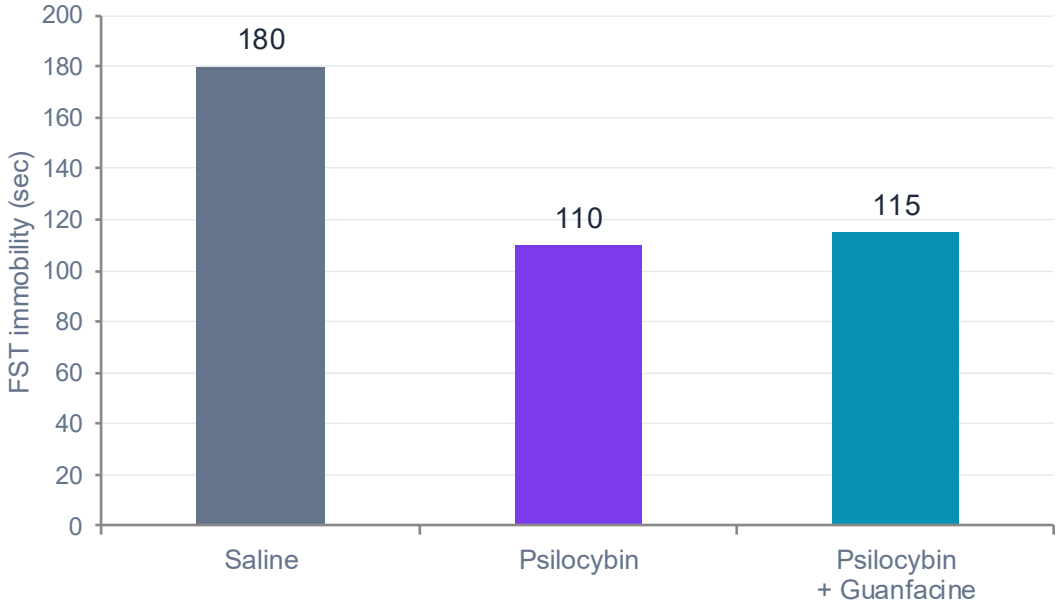
α_2 agonist guanfacine collapses head-twitch response



≈80% reduction

Antidepressant proxy (FST immobility)

Psilocybin's antidepressant effect is preserved



Antidepressant effect intact

Composition-of-matter: a single molecule, optimized α2:5-HT2A ratio

Combination therapy is a starting position, not the moat. The moat is a new chemical entity.

Our chemistry insight

1. We mined the 41-compound × 318-GPCR Jain dataset for ligands with native α_2 activity among 5-HT_2A agonists.
2. Identified a candidate scaffold and the structural locus that gates α_2 engagement.
3. Defined the chemical move that maximizes α_2 activity while preserving 5-HT_2A potency.

What we own

FILED

Yale patent application: α_2 + 5-HT_2A combination therapy

TARGET

Composition-of-matter: single molecule, engineered ratio

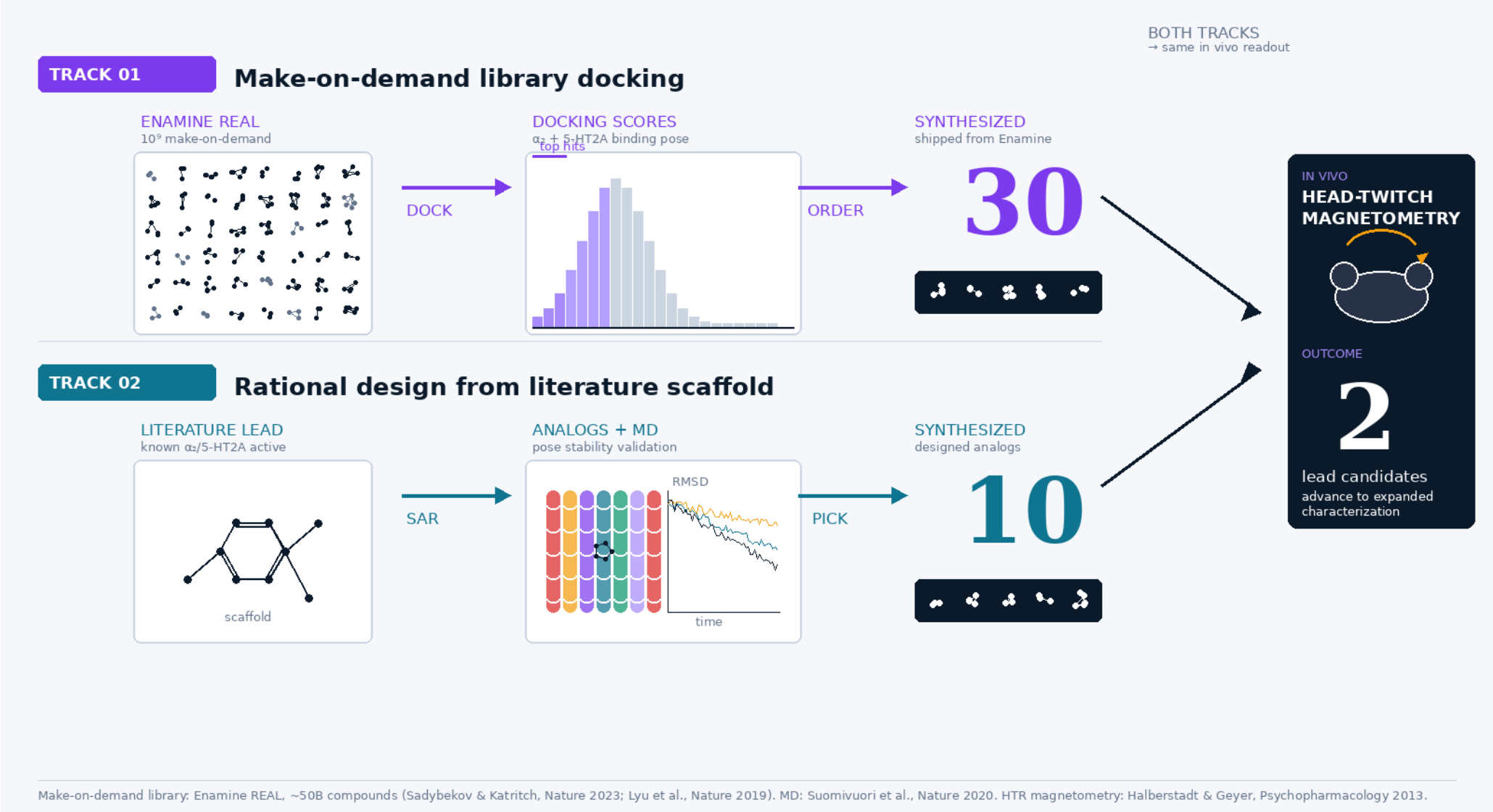
PLATFORM

In vivo readouts: HTR, fiber photometry, behavior, circuit recordings

CLINICAL

Phase 1 trial planned for combination: de-risks the novel compound

Two parallel tracks, one in vivo readout



Make-on-demand library: Enamine REAL, ~50B compounds (Sadybekov & Katritch, Nature 2023; Lyu et al., Nature 2019). MD: Suomivuori et al., Nature 2020. HTR magnetometry: Halberstadt & Geyer, Psychopharmacology 2013.

The Team

Yale SCHOOL OF MEDICINE | Yale PSYCHIATRY

Alfred Kaye, MD, Ph.D.

Assistant Professor of Psychiatry, Yale University

- Principle Investigator, expertise in studying the neurocircuitry underlying stress-related disorders and psychedelic treatment

Christopher Pittenger, MD, Ph.D.

Director, Yale Program for Psychedelics Science

- Elizabeth Mears and House Jameson Professor of Psychiatry, Yale University
- Translational research on psychedelics

John Krystal, MD

Co-Founder & Chief Scientific Advisor, Freedom Biosciences

- Department of Psychiatry Chair, Yale University
- Groundbreaking discovery of ketamine's rapid antidepressant effects in clinical populations

Carl-Mikael Suomivuori, Ph.D.

Assistant Professor of Pharmacology, Yale University

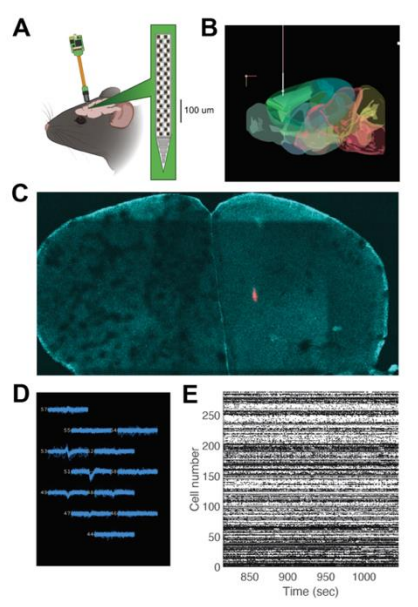
- Computational pharmacology and GPCR drug discovery
- Expert in docking and molecular dynamics

From hundreds of neurons to single dendritic spines

Neuropixels recording and 2-photon spine imaging : plasticity at different levels

NEUROPIXELS RECORDING

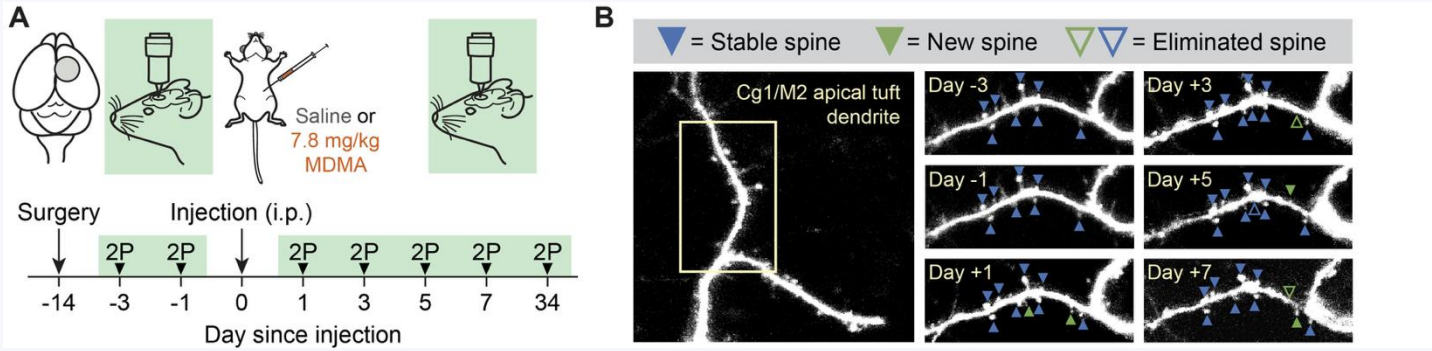
~300 neurons / session



384-channel probe across cortical & subcortical regions

2-PHOTON DENDRITIC SPINE IMAGING

Single-spine resolution, longitudinal



Same lab, same window for our COM molecule.

A single MDMA dose drove a +20% rise in apical-tuft spine density at +1 day, sustained through +7 days — new spines tagged green, eliminated spines hollow. Tracks plastogen efficacy **without** a hallucinogenic dose — the readout that separates a real plastogen from a placebo.

THE ASK

$30K accelerator → $300K follow-on → Phase 1

A staged plan with a clear molecule out of phase one and de-risked enabling data out of phase two.

BLAVATNIK ACCELERATOR

$30K

0–6 months

- Molecular docking simulations across a designed family of α_2/5-HT_2A scaffolds
- Synthesize lead candidate (NCE)
- Preliminary in vivo: HTR + behavior

FOLLOW-ON STUDY

$300K

6–18 months

- Lead optimization + medchem iteration
- ADMET / PK + safety pharmacology
- Generate IND-enabling package

FIRST-IN-HUMAN

Phase 1

18+ months

- Combination protocol validates mechanism in humans
- Lead molecule advances on parallel track
- Partnering / licensing inflection

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