Proposal Overview

PsyDAO

PDP-17: [Funding] Regulation of Endogenous DMT Biosynthesis

Applicants: Dr. Andrew R. Gallimore, Prof. Carl H. Smith, Dr. Chris McCurdy
Deal Shepherds: Tyler Quigley & Warren Winter

[Full Community Proposal Packet Here]

A message from Dr. Andrew Gallimore: **PsyDAO_Vid_Pitch.mp4**

1. Overview

DMT is one of the most potent psychedelic compounds known. It is endogenously produced in mammals, including humans. DMT activates multiple receptor subtypes, notably $5HT_{2A}$ and sigma-1, which are thought to contribute to its pronounced neuroplastogenic effects. Through these mechanisms, DMT has been proposed as a treatment candidate for conditions such as ischemic stroke, neurodegeneration, depression, and chronic pain, as well as a potential tool to support psychotherapeutic and cognitive enhancement applications.

This project aims to uncover how endogenous dimethyltryptamine (DMT) is regulated in the mammalian brain. The applicants suspect that an uncharacterized enzymatic “off switch” regulates DMT production by inhibiting the enzyme indole N-methyltransferase (INMT). Though first described decades ago, such an enzyme has never been fully identified.

By isolating and sequencing these enzymes, this study lays critical groundwork for understanding how the body modulates DMT levels, and whether it might one day be possible to safely activate endogenous DMT production for extended periods of time (i.e.,“endo-DMTx”) without external DMT dosing.

Clarifying how DMT is regulated endogenously may:

- Reveal new pathways to understand if/why DMT levels fluctuate in normal waking life and during certain activities.
- Establish the scientific basis for protocols to induce sustained DMT states via internal pathways (endogenous, extended state DMT).
- Enable new therapeutic levers targeting neuroprotection, learning, and mood.

This project is the **first systematic effort** to characterize the endogenous inhibitors believed to control DMT biosynthesis in the brain.

2. Experimental Plan

This project will isolate and characterize endogenous peptide inhibitors of INMT, the enzyme responsible for DMT biosynthesis.

1. *Sample Preparation*
    a. Prepare homogenates from rabbit brain and lung tissues; obtain human CSF samples.
2. *Inhibitory Activity Confirmation*
    a. Replicate prior dialysis experiments demonstrating increased INMT activity after removal of endogenous inhibitors.
3. *Fractionation and Purification*
    a. Use size-exclusion chromatography to isolate active inhibitory fractions.
4. *Enzyme Assays*
    a. Assess INMT activity in vitro via non-radiometric methods and fluorometric methyltransferase assays.
5. *Molecular Characterization*
    a. Estimate inhibitor molecular weight using calibrated columns; evaluate protease sensitivity to confirm peptide nature.
6. *Sequencing*
    a. Perform MALDI-TOF MS, de novo sequencing, and Edman degradation to identify amino acid sequences.

🔶 **To review the full proposal, see Research Proposal.**

3. Budget

This proposal requests an initial tranche of funding to launch the first milestone of the study.

- **Total project budget:** $429,506
- **Project sponsor:** Noonautics, on behalf of the principal investigators.
- **Research institution:** University of Florida, Dr. McCurdy's laboratory.

4. Financing and PsyDAO Terms

Funding requested from PsyDAO: **$107,000**

Upon successful completion of this milestone, additional funding may be derived from proceeds from tokenization to progress the remaining project aims.

In return for PsyDAO's support, Noonautics will:

- Enter into a Memorandum of Understanding (MoU) granting PsyDAO the right to tokenize this project as an IPT.
- Provide PsyDAO the right of first refusal to partner on any future intellectual property-producing research arising from this work.
- Share regular progress updates and milestone reports with the PsyDAO community.

🔶 **To review the full budget, see Budget.**

5. Expert Review Summary

Significance & Mission Alignment

- **Reviewer 1:** 5/5
  Meaningful project with broad interest inside and outside psychedelic science.
- **Reviewer 2:** 4/5
  High-risk but potentially significant; unclear how findings specifically advance applied drug development compared to exogenous DMT.

Innovation & Differentiation

- **Reviewer 1:** 4/5
  Novel approach, but builds on older, abandoned work. Potential IP questions.
- **Reviewer 2:** 3/5
  Clearly distinct and conceptually novel, but primarily based on a single 1977 study; practical applications remain unspecified.

Scientific Feasibility & Rigor

- **Reviewer 1:** 2/5
  Methods grounded in precedent but lack sufficient detail on risks, limitations, timeline, and contingency plans.
- **Reviewer 2:** 4/5
  Methods appropriate and clearly defined, but risk mitigation (Plan B) is vague.

Team Capability & Execution Plan

- **Reviewer 1:** 3/5
  Qualified team but imbalance between advisors and experimental staff; unclear workflow and resource access.
- **Reviewer 2:** 4/5
  McCurdy's expertise well aligned; roles of Gallimore and Smith and backgrounds of co-investigators need clarification.

Common Goods

- **Reviewer 1:** 4/5
  Potential for valuable datasets and protocols; specifics of data sharing and public outputs need definition.
- **Reviewer 2:** 3/5
  Generic data sharing plan; unclear how outputs will be disseminated or leveraged by the community.

Budget

- **Reviewer 1:** 3/5
  High budget weighted toward personnel and indirect costs; limited justification and unclear timeline.
- **Reviewer 2:** 3/5
  Staffing costs are mostly appropriate; no breakdown of materials budget and no mention of additional funding.

Both reviewers recommended: Revise & Resubmit

The applicants have reviewed these comments in detail and have addressed them in the final version of the proposal included in this packet. - Tyler Quigley & Warren Winter, Deal Shepherds

🔶 **To review the full reviews, see Expert Reviews.**

6. Token Strategy

Here, we introduce and propose utilizing the Commons IPT, a new IPT model developed by PsyDAO members to address the complexities of eDMT research enterprise, and to address issues we've noted in previous IPT launches in the DeSci space.

Commons IPT

Most BioDAO's fund projects with **single-project IPNFTs/IPTs**, where one token backs one research effort. While effective for focused work, this model often creates early speculative buying, rapid sell-offs, and long-term price decline disconnected from real progress.

Endogenous DMT research is different: it involves multiple teams, diverse methods, and long timelines. A single-project token is poorly suited to this complexity.

By minting $eDMT as a **Commons IPT**, we can enable the grouping of multiple eDMT projects under one token. Fundamentally, this token supports a **shared research consortium**, and benefits to holding the token may be derived from any project that is funded by and/or has joined the consortium in some capacity.

Some key benefits to this model:

- **Diversified Risk:** Success in any project benefits all holders.
- **Better Alignment:** Token value tracks the field's cumulative progress rather than binary outcomes.
- **Shared Governance:** Holders help allocate funding and set IP policies.
- **Ethical Stewardship:** Discoveries stay accessible under clear commons rules.

Fair Launch & LP Seeding

To maximize transparency and broad participation, we propose a **fair launch** for the $eDMT Commons IPT, ensuring that all participants have equal access from the start, with no preferential pricing or insider advantages.

PsyDAO will seed the initial liquidity pool with treasury funds. Trading fees generated by this liquidity will be captured and recycled into funding additional eDMT research tranches, creating a self-sustaining feedback loop between token activity and scientific progress.

PsyDAO is a hotbed for innovative approaches to BioDAO governance and action. Fair launching the first Commons IPT in the DeSci space further positions PsyDAO as a leader in community-driven, decentralized science funding.

🔶 **For a more detailed breakdown of the proposed $eDMT token launch strategy, see Project & Token Implementation Plan.**

🔶 **To read the full Commons IPT Whitepaper, see Endogenous DMT IP Commons & Tokenomics Whitepaper.**

Research Proposal

Regulation of Endogenous DMT Biosynthesis via an Inhibitory Peptide in Mammalian Brain

Dr. Andrew R. Gallimore, Prof. Carl H. Smith, Dr. Chris McCurdy

I. Project Summary

Indolamine N-methyltransferase has been detected in several vertebrate tissues. It is classified as a class 1 transmethylation enzyme, responsible for producing dimethyltryptamine (DMT) from tryptamine when a methyl donor is present. DMT is known for its hallucinogenic properties and its interaction with multiple receptors. Previous research has indicated the existence of endogenous inhibitors for INMT in rabbit brains and human cerebrospinal fluid (CSF). The specific nature and the identity of these inhibitors are still unknown. This proposal aims to detail the step- by-step procedures for isolating and identifying these endogenous inhibitors of INMT in rabbit brains and human CSF. These efforts will clarify the existence and identity of endogenous INMT inhibitors, laying the foundation for future work into their physiological function and relevance to endogenous DMT regulation.

II. Psychedelic Science Impact

Extended-state DMTx technology has the potential to revolutionise how we explore the highly unusual and exotic altered state of consciousness induced by N,N-dimethyltryptamine (DMT). But what if we could dispense with exogenous drugs and the needle entirely and use our own endogenous DMT production machinery to access the strange realms to which DMT gates access, avoiding the costs associated with the infusion of large quantities of the drug, bypassing legal issues with the administration of a scheduled molecule, and potentially allowing for smoother and more sustained access to the DMT space? DMT has been detected in the blood and cerebrospinal fluid of humans since the 1950s and a recent study measured DMT levels in a mammalian brain comparable to serotonin and dopamine, strongly suggesting a functional role in human neurochemistry. However, we still know next to nothing about how DMT production in the human brain is regulated.

If we hope to one day “hack” our endogenous DMT system to control levels of DMT in the human brain and to enter the DMT state for extended periods without the need for intravenous infusion systems – DMTx becomes endo-DMTx – understanding these regulatory mechanisms is of primary importance. Our proposed study aims to take that first step towards endo-DMTx by isolating and characterising an endogenous peptide regulator of DMT biosynthesis that was first detected in mammalian brain half a century ago but has remained buried in the literature and largely forgotten about ever

since – an endogenous “switch” that regulates and controls DMT production in the brain. All of us carry the machinery to access and explore the remarkable realms to which DMT grants access and, by supporting this PsyDAO project, all of us can play a role in making those realms accessible to all.

III. Specific Aims

1. **Detect and quantify INMT inhibitory activity in rabbit brain.** We will replicate findings from 1977 demonstrating that rabbit brain contains a heat-stable, dialyzable inhibitor of INMT activity, validating the foundational observation that endogenous regulation of DMT biosynthesis exists.
2. **Isolate and characterize peptide-like INMT inhibitor(s).** We will purify active inhibitory fractions from neonatal rabbit brain and confirm their peptide nature and molecular properties, generating enriched samples suitable for sequence analysis.
3. **Sequence and identify the inhibitory peptides.** We will determine the amino acid sequences of the inhibitory peptides and assess their novelty, establishing their identity and potential as endogenous regulators of INMT activity.

IV. Research Strategy

A. Background

Whilst DMT has been detected in the blood and urine of humans since the 1950s and in the brain of mammals more recently, neither its function in human physiology nor its regulation have been elucidated (Barker et al., 2018). Considering the remarkable effects of DMT on human consciousness, this appears as a glaring lacuna in the biochemical and neuroscientific literature. However, there is now accumulating evidence for a role in protecting neurons from hypoxic stress via activation of the sigma-1 receptor (Szabo et al., 2016; Nardai et al., 2020; Szabó et al., 2021) . Studies have also shown DMT to be a substrate for vesicular transporter proteins, suggesting a potential role as an endogenous neurotransmitter (Cozzi et al., 2009). Indeed, a very recent study demonstrated DMT levels in mammalian brain comparable to serotonin and dopamine, which strongly suggests a functional role in human neurochemistry, although we know next to nothing about how DMT levels in the brain might be regulated (Dean et al. 2024; Glynos et al., 2024).

The key enzyme for synthesis of endogenous DMT in humans is indole N-methyltransferase (INMT), a class 1 transmethylation enzyme which converts tryptamine (from tryptophan) to DMT. Many studies have detected INMT activity in several tissues of vertebrate species, including the human brain (Bhikharidas et al.,

1975; Mandell & Morgan, 1971). It is found in intermediate levels in the placenta, skeletal muscle, heart, small intestine, stomach, retina, pancreas, and lymph nodes. It is densely located in the anterior horn of the spinal cord. It was described as an alkaline enzyme catalyzing the N- methylation of several substrates using a methyl donor (S-adenosyl methionine (SAM)), such as TA and 5-HT, to create psychomimetic metabolites (Saavedra & Axelrod, 1972).

INMT is known for its production of DMT, a hallucinogen with affinity for various serotonergic, adrenergic, histaminergic, dopaminergic, and sigma-1 receptors (Chen et al., 2014). INMT is also involved in bufotenin synthesis from serotonin and its relation to psychotic illness (Axelrod, 1962; Mandell & Morgan, 1971). INMT methylates other aromatic amines (tyramine, phenylethyl amine, mescaline, and dopamine) with much lower affinity and activity rates under 50% relative to indoleamines. INMT is specific for indoleamine methylation, especially for TA and NMT. Small molecular weight INMT inhibitors within rat, rabbit, and human tissues have been detected and could be removed by dialysis.

It has been reported that DMT is an INMT inhibitor (as a self-regulatory mechanism) at rabbit recombinant INMT with IC50 of 67 μM and the DMT at high concentrations (100 μM) yields a 90% inhibition of rabbit lung INMT (Thomas & Weinshilboum, 1998). Based on INMT crystal structure, it proposed that DMT-dependent inhibition occurs through a mixed competitive and allosteric mechanism involving the formation of a hydrogen bond in INMT's allosteric pocket (Wu et al., 2005; Chu et al., 2014). Some selective inhibitors were synthesized but the endogenous inhibitors that regulate the enzyme activity are still questionable.

In 1973, it was found that, whilst INMT levels in most tissues was relatively high, its activity in converting tryptamine to DMT was very low (Wyatt et al., 1973). However INMT activity could be dramatically increased upon separation from blood samples by dialysis, suggesting the existence of an endogenous constitutive inhibitor of INMT. Four years later, this endogenous inhibitor of INMT was identified in mammalian (rabbit) brain as three forms of a fairly small peptide and their molecular weight determined in the range of 1200-1500 (suggesting a 10-15 amino acid sequence). However, a full characterisation of the peptides and their amino acid sequence was not performed, and the results have been buried and left languishing in the literature for almost half a century, with the original 1977 paper being cited a mere four times (Marzullo et al., 1977).

With modern peptide isolation, purification, and characterisation technologies, this early research presents ostensibly low-hanging fruit for studying the regulation of endogenous DMT in the mammalian brain. The identification and full sequence characterisation of a constitutive regulator of endogenous DMT biosynthesis would present a landmark result in this niche but rapidly growing field of neuroscience.

B. Question

Does a peptide-like inhibitor of INMT exist in mammalian brain tissue, and if so, what are its molecular identity, physical characteristics, and inhibitory properties?

C. Hypotheses

1. *A peptide-like INMT inhibitor exists in mammalian brain tissue and can be isolated from rabbit brain extracts.*

    a) **Rationale**: Prior work (Marzullo et al., 1977) showed that INMT activity increases after dialysis, suggesting the presence of a small, heat-stable inhibitory molecule—likely a peptide.

2. *The inhibitory molecule(s) are peptides with defined molecular weights in the 1,200–1,500 Da range and are susceptible to proteolytic digestion.*

    a) **Rationale:** Preliminary fractionation and protease assays from Marzullo et al., 1977 indicate the inhibitors are peptide-like and degrade with trypsin, consistent with short peptides.

3. *The peptide inhibitor(s) exhibit measurable, reproducible inhibition of INMT activity in vitro, and may act through non-competitive or allosteric mechanisms.*

    a) **Rationale:** Functional assays in prior studies suggested reversible, non-competitive inhibition of INMT; the modern assays will characterize the strength and mode of this inhibition.

D. Approach

1. Indolamine N-methyltransferase (INMT) Sources

a. Recombinant human INMT GST-tagged and recombinant rabbit INMT His-tagged.
b. Preparation of Rab-INMT from brain and lung tissues

The lung tissue of a young adult rabbit is homogenized in 0.1 M potassium phosphate buffer (pH 7.6) and centrifuged at 100,000 × g for 30 min. Ammonium sulfate is added to the supernatant to reach 40% saturation, followed by centrifugation at 10,000 × g for 10 min. The precipitate is discarded, and the supernatant is brought to 60% saturation with ammonium sulfate. After centrifugation, the final precipitate is dissolved into 0.1 M potassium phosphate buffer (pH 7.6). This fraction is further purified using a Sephadex G-200 column (2 × 100 cm). The active fractions are pooled,

concentrated, and used as the source of INMT. Protein content is determined by Bradford's assay.

2. **Human CSF Sources**
    a. Commercial:
        i. Lyophilized CSF
        ii. Pooled human CSF

3. **Preparation of Different Organ Tissue Homogenates for Enzyme Inhibition Screening**

Brain and lung tissues from female adult rabbits and 1–4-day-old neonates are homogenized in cold saline. High-speed supernatants are assayed before and after dialysis for 17 hours against 1,000 volumes of 0.005 M phosphate buffer (pH 7.9).

4. **Fractionation of Neonatal Rabbit Brain Homogenate**

Brains from newborn rabbits are homogenized in three volumes of water and centrifuged at 100,000 × g. The supernatant is boiled for three minutes and chromatographed on a Sephadex G-25 (medium) column.

5. **Enzyme Activity Monitoring Assays for Collected Fractions**
    a. *Non-radiometric assays – TLC and UPLC-QTOF/MS:*
        i. Tryptamine (1 mM) and 33 µM SAM in a final reaction volume of 150 µL with sodium phosphate buffer. Assay components are combined and incubated at 37°C for 60 min. Tubes with substrate omitted serve as background controls. Reaction products are extracted by adding 1 mL toluene:isoamyl alcohol and vortexed. 950 µL of the organic phase is transferred, evaporated, and resuspended in 1 mL of 30% methanol. Products are analyzed via UPLC-QTOF/MS.
    b. *Methyltransferase Fluorometric Assay Kit:*
        i. Cayman's Methyltransferase Colorimetric Assay Kit, a continuous enzyme-coupled assay that monitors SAM-dependent methyltransferases.

All active fractions are combined, lyophilized, and re-chromatographed on fine-grade Sephadex G-25.

6. **Molecular Size Estimation of the INMT Inhibitors**

Molecular size of inhibitors in active fractions is estimated using calibrated Sephadex G-25 (fine) columns with known markers: bacitracin, vasopressin, and oxytocin.

7. **Inhibitor Identification**
    a. Sequencing (based on residue count) via MALDI-TOF MS, De Novo sequencing, and Edman degradation.
    b. Identification through database comparison.

8. **Enzyme Activity Monitoring Assays**
    a. *Non-radiometric assays – TLC and UPLC-MS/MS:*
    Assay mixture: 100 µL INMT, 840 pM N-methyltryptamine (NMT), 78 µM SAM, and 68 mM potassium phosphate buffer (pH 7.9). Add 100 µL CSF concentrate and adjust to 290 µL total volume. Include blanks without enzyme and without NMT. Incubate at 37°C for 1 hour. Terminate with 120 µL of 1 M borate buffer (pH 11.0). Extract into toluene:isoamyl alcohol, dry, and redissolve in ethanol.
    b. *Methyltransferase Fluorometric Assay Kit:*
    Cayman's Methyltransferase Colorimetric Assay Kit, as above.

9. **Inhibitor Identification**
    a. Sequencing using MALDI-TOF MS, De Novo methods, and Edman degradation.
    b. Identification through database comparison.

E. Personnel

Dr. Andrew Gallimore is a chemical pharmacologist and neurobiologist and one of the leading experts on the neuroscience and chemical pharmacology of DMT. He is the author of numerous both academic and popular articles on psychedelics and has written three books devoted to psychedelic neuroscience and pharmacology with a focus on DMT. In collaboration with Dr. Rick Strassman, Andrew first proposed the DMTx protocol for extended journeys in the DMT space. Andrew originally conceived this project and his role will be as a consultant and advisor throughout the research, but will receive no compensation from the funding provided by the PsyDAO community.

Prof. Carl Hayden Smith is an Associate Professor of Media at the University of East London and the founder of the Museum of Consciousness at Oxford University. His research concentrates on the relationship between technology and the human condition. Carl has been a participant of the DMT research at Imperial College London for the last six years and was the first person in the world to sustain the full five doses of DMTx. Carl has raised over £10 million in research funding, has given over 300 invited public lectures, conference presentations and keynotes in 40 countries, and has published more than 50 academic papers. Together with Andrew, Carl will act as a consultant and advisor throughout the research, but will receive no compensation from

the funding provided by the PsyDAO community.

Dr. Christopher R. McCurdy, Ph.D., FAAPS, is a medicinal chemist, behavioral pharmacologist and pharmacist who has authored over 300 articles on the chemistry and pharmacology of psychoactive drugs. His work focuses on the isolation and chemical, pharmacological, and biochemical characterisation of psychoactive drugs from various classes, including kratom alkaloids, endocannabinoids, kavalactones, cocaine, opioids, salvinorin, and tryptamines. Dr. McCurdy's team will conduct the experimental work in its entirety in his laboratory at the University of Florida and the entirety of the funding will be used by his team.

F. Funding Request

Note: This project will be performed in the lab of Dr. McCurdy under an SRA between Noonautics (representing Andrew Gallimore and Carl Hayden Smith) as Sponsor and the University of Florida (UF).

The total cost of this project is $429,506. We are requesting a portion of this funding need from PsyDAO to fulfill our obligation to the University of Florida under the aforementioned SRA to initiate the described research project. In return, Noonautics will sign a Memorandum of Understanding (MoU) with PsyDAO granting PsyDAO the right to tokenize this project as an IPT, and the right of first refusal for future IP expansion, if such opportunities arise in the future as a result of this work. The MoU and IPT tokenization plan can be found in the Community Proposal Packet.

In this proposal, we are requesting an initial tranche of $107K to fund one of four milestones defined in the SRA between Noonautics and UF. Upon tokenization, any proceeds and/or fees generated above the initial $107K will be put towards additional milestones. The PsyDAO community should understand that, as with all experimental research, there is no guarantee that the attempt to isolate and characterise the INMT inhibitory peptide will be successful, although the previously published data gives us confidence in this regard. Should the attempt fail, any unspent funds will be returned to the PsyDAO community. All PsyDAO community members will receive regular updates on the progress of the project, which will include periodic community meetings to discuss findings as the research progresses.

G. Data Management and Sharing Plan

All experimental data will be securely stored in an cloud-based database (e.g., Google Drive) with access restricted to the project team, designated collaborators, and designated members of PsyDAO.

In alignment with the principles of DeSci, the team commits to transparency and community engagement wherever possible. Key datasets, protocols, and insights will be made available to the PsyDAO and IPT communities via periodic updates, open-access summaries, and de-identified result sets. From an intellectual property standpoint, access to information that could be considered a “public disclosure” for prior art purposes will be token-gated and accessible only to designated members of PsyDAO. Data sharing with third-party researchers or potential commercial partners will be governed by appropriate intellectual property protections and collaboration agreements. Upon publication or project completion, non-sensitive datasets will be deposited in publicly accessible repositories as appropriate.

H. Future Directions

If this project successfully identifies and characterizes peptide inhibitors of INMT, the next phase will focus on validating their regulatory function in human-relevant systems. Synthetic versions of the peptides—or molecules designed to block their inhibitory effect—could be tested in human-derived systems such as organoid lysates or cerebrospinal fluid (CSF). This would establish translational relevance and open the door to therapeutic or enhancement applications.

In parallel, if the peptide hypothesis is not supported, the research could pivot to investigate alternative regulatory molecules, such as small-molecule INMT inhibitors (<800 Da), using untargeted metabolomics. This “Plan B” pathway would preserve the broader goal of elucidating endogenous DMT regulation.

Should these studies reveal novel compounds or mechanisms with translational potential, we anticipate the opportunity to pursue intellectual property, including composition-of-matter and method-of-use patents. We are eager to explore this pathway in collaboration with PsyDAO, using tokenization strategies to align community ownership with scientific discovery. By working with PsyDAO to steward any resulting IP, we hope to help define new models for decentralized biomedicine that balance open science with meaningful public benefit.

I. References

Axelrod J. The enzymatic N-methylation of serotonin and other amines. J Pharmacol Exp Ther. 1962 Oct;138:28-33.

Barker SA. N, N-Dimethyltryptamine (DMT), an Endogenous Hallucinogen: Past, Present, and Future Research to Determine Its Role and Function. Front Neurosci. 2018 Aug 6;12:536

Bhikharidas B, Mann LR, McLeod WR. Indolamine N-methyltransferase activity in human tissues. J Neurochem. 1975 Jan;24(1):203-5.

Chu UB, Vorperian SK, Satyshur K, Eickstaedt K, Cozzi NV, Mavlyutov T, Hajipour AR, Ruoho AE. Noncompetitive inhibition of indolethylamine-N-methyltransferase by N,N-dimethyltryptamine and N,N-dimethylaminopropyltryptamine. Biochemistry. 2014 May 13;53(18):2956-65.

Cozzi NV, Gopalakrishnan A, Anderson LL, Feih JT, Shulgin AT, Daley PF, Ruoho AE. Dimethyltryptamine and other hallucinogenic tryptamines exhibit substrate behavior at the serotonin uptake transporter and the vesicle monoamine transporter. J Neural Transm (Vienna). 2009 Dec;116(12):1591-9.

Dean JG, Liu T, Huff S, Sheler B, Barker SA, Strassman RJ, Wang MM, Borjigin J. Biosynthesis and Extracellular Concentrations of N,N-dimethyltryptamine (DMT) in Mammalian Brain. Sci Rep. 2019 Jun 27;9(1):9333.

Glynos NG, Huels ER, Nelson A, Kim Y, Kennedy RT, Mashour GA, Pal D. Neurochemical and Neurophysiological Effects of Intravenous Administration of N,N-Dimethyltryptamine in Rats. bioRxiv [Preprint]. 2025 Feb 15:2024.04.19.589047.

Marzullo, G., Rosengarten, H., Friedhoff, A.J. (1977). A peptide-like inhibitor of N-methyltransferase in rabbit brain. Life sciences, 20(5), 775–783.

Nardai S, László M, Szabó A, Alpár A, Hanics J, Zahola P, Merkely B, Frecska E, Nagy Z. N,N-dimethyltryptamine reduces infarct size and improves functional recovery following transient focal brain ischemia in rats. Exp Neurol. 2020 May;327:113245.

Saavedra JM, Axelrod J. Psychotomimetic N-methylated tryptamines: formation in brain in vivo and in vitro. Science. 1972 Mar 24;175(4028):1365-6.

Szabo A, Kovacs A, Riba J, Djurovic S, Rajnavolgyi E, Frecska E. The Endogenous Hallucinogen and Trace Amine N,N-Dimethyltryptamine (DMT) Displays Potent Protective Effects against Hypoxia via Sigma-1 Receptor Activation in Human Primary iPSC-Derived Cortical Neurons and Microglia-Like Immune Cells. Front Neurosci. 2016 Sep 14;10:423.

Szabó Í, Varga VÉ, Dvorácskó S, Farkas AE, Körmöczi T, Berkecz R, Kecskés S, Menyhárt Á, Frank R, Hantosi D, Cozzi NV, Frecska E, Tömböly C, Krizbai IA, Bari F, Farkas E. N,N-Dimethyltryptamine attenuates spreading depolarization and restrains neurodegeneration by sigma-1 receptor activation in the ischemic rat brain. Neuropharmacology. 2021 Jul 1;192:108612.

Thompson MA, Weinshilboum RM. Rabbit lung indolethylamine N-methyltransferase. cDNA and gene cloning and characterization. J Biol Chem. 1998 Dec 18;273(51):34502-10.

Wu H, Dong A, Zeng H, et al. (2005) The crystal structure of human indolethylamine N-methyltransferase in complex with SAH. Protein Data Bank Entry 2A14.

Wyatt, R.J., Saavedra, J.M., Axelrod, J. (1973). A dimethyltryptamine-forming enzyme in human blood. The American journal of psychiatry, 130(7), 754–760.

Budget

Budget

The following budget justification is for the entire research project - the amount requested, $107K, comprises one milestone payment of this larger project.

Detailed research & salary breakdowns upon request from Deal Shepherds

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BUDGET JUSTIFICATION (Total direct costs $280,401)

Personnel salaries ($205,998)
Christopher R. McCurdy, PhD, MPI, Contact PI, will spend 1.8 calendar months and assume responsibility for coordinating the work of key personnel (Sharma, Seabra, Awad, Kanumuri). Dr. McCurdy will work closely with Drs. Awad, Sharma, and Seabra to design and ensure proper conduct of all experiments, including careful inspection of data collection, summary, and analyses. Dr. McCurdy will supervise one graduate student (Abouheif); this student will conduct the extensive purification and isolation studies proposed. Dr. McCurdy has over 25 years of experience with medicinal and natural products chemistry and quantitative analysis of drug action and interaction. He, along with MPI Dr. Sharma, will be responsible for ensuring that study results are disseminated to Noonautics and in publications and proceedings at research conferences.

Abhisheak Sharma, Ph.D., MPI, will spend 1.2 calendar months designing and overseeing the analytical mass spectrometry experiments, and will play a key role in data summary, analysis, and presentation. He will help supervise one Research Assistant (Kanumuri); this Research Assistant will conduct the extensive UPLC/MS studies proposed. Dr. Sharma will participate in preparing and submitting reports generated from the analytical aspects of the project.

Ahmed Awad, Ph.D., Co-I, will spend 12 calendar months on the design, and conduction of experiments. Dr. Awad is an expert natural products chemist and biochemist who will develop the necessary assays and extraction/purification procedures. He will work closely with Dr. Seabra on assay development and will have direct oversight in the lab of the graduate student. He will also be responsible to compiling data, interpretation, and reporting of the results to the MPIs (McCurdy and Sharma).

Maria Seabra, Ph.D., Co-I, will spend 1.2 calendar months assisting Dr. Awad in the establishment of assays that will be utilized to determine INMT activity. Dr. Seabra is an expert in cell biology and assay development. She will also be responsible for reporting data to the team and training the graduate student on the proper use of the assays.

Raju Kanumuri, Ph.D., Co-I, will spend 1.2 calendar months on the physical execution of the UPLC/MS/MS and UPLC QTOF analyses and will work closely with Dr. Awad to perform sequencing and other identification analyses coupled with NMR. Dr. Kanumuri is an expert in analytical chemistry and will be responsible for development of the analytical methods utilized as well as reporting and working with the MPIs to interpretate data.

A graduate student (Seif Abouheif), will spend 6 calendar months on the establishment of assays and isolation of endogenous peptides from ex vivo tissues to prepare for analysis. He

will assist Drs. McCurdy, Awad, and Seabra with data collection, summary, analyses, and presentation.

Equipment ($6,200)

This consists of automated pipettes and a Mini-PROTEAN tetra cell w/power supply.

Materials and Supplies costs ($50,000)

Materials and supplies budget breakdown per experimental category
Frozen rabbit brain/INMT/Enzymes: recombinant human and rat INMT GST-Tagged or Hist-Tagged, frozen newborn rabbit brain (whole), frozen rabbit lung (mature), carboxypeptidase A from bovine pancreas, trypsin/HBSS/EDTA, methyltransferase fluorometric assay kit, pooled human cerebrospinal fluid (CSF).

Chromatography: Sephadex G25 medium, G25 fine grade, G-200, certified. Bio-Rex 70 cation exchange resin

Standards: Bacitracin, Vasopressin, Oxytocin acetate salt hydrate, tryptamine, N-methyl tryptamine, S-(5'-Adenosyl)-L-methionine chloride
Radioligand and scintillation cocktail: SAM C-14, liquid scintillation cocktails (ultima gold)

Buffers, Solvents, glassware, gel electrophoresis gels and dyes, and disposable consumables

Sequencing: De NOVO, LC-MS, N-terminal sequencing

Tuition ($18,213)

Indirect costs ($134,394)
The University of Florida has a DHHS negotiated agreement authorizes indirect cost rate of 52.5%. Total direct costs are defined as excluding capital expenditures, tuition, and equipment.

Community Pitch

PsyDAO

Community Pitch

Date: 6/6/25
Presenter: Andrew Gallimore

- Recording Link
- Transcript

LLM Summary:

Purpose and Objectives

The meeting served as a community pitch from Dr. Andrew Gallimore regarding the eDMTx project—a proposal to study and manipulate endogenous DMT (eDMT) pathways. The aim was to:

- Explain the project's scientific foundation and experimental roadmap.
- Clarify how eDMT could be harnessed via known enzymatic and metabolic pathways.
- Address technical, philosophical, and translational implications.
- Answer community questions and foster informed decision-making ahead of a $PSY governance vote.

Key Discussion Points

- **Background and Motivation:**
  - Gallimore has long hypothesized that endogenous DMT might play a role in naturally occurring altered states of consciousness.
  - The project is designed to move beyond speculation and test whether the body contains the machinery to synthesize, regulate, and release DMT in meaningful quantities.

- **Scientific Plan:**
  - The team intends to replicate and expand upon a 1970s rabbit study suggesting DMT could be upregulated in vivo using precursors like tryptophan, co-factors like SAMe, and enzyme inducers.
  - Methods will include both in vitro enzyme assays and in vivo neurochemical monitoring (e.g., microdialysis in rodents).
  - Gallimore stressed that this is not about confirming DMT as a "consciousness molecule" but about establishing metabolic feasibility.

- **Technical Considerations:**

    - The study design accounts for detection challenges (e.g., DMT's short half-life).
    - The goal is to monitor flux through the biosynthetic pathway by manipulating rate-limiting steps.

- **Philosophical/Translational Layer:**
    - Gallimore emphasized the potential to "work with the brain" rather than externally imposing altered states (e.g., via IV DMT).
    - Long-term applications might include slow, precise modulation of DMT synthesis for therapeutic purposes.

Deadlines / Timelines

- Proposal to be posted for expert and community review by **mid-June**.

- Community governance vote likely to occur shortly after Psychedelic Science conference (late June).

Conclusion

The eDMTx project proposes a bold, high-risk/high-reward investigation into the body's capacity to produce and modulate DMT internally. The community pitch clarified the experimental design, scientific rationale, and broader significance, and helped establish trust and transparency. The next step is formal proposal review and community vote.

Expert Reviews

PsyDAO

Expert Reviews

The applicants have reviewed the comments below in detail and have addressed them in the final version of the proposal included in this packet.

- Tyler Quigley & Warren Winter, Deal Shepherds

Reviewer #1

Category	Score	Score Justification
Significance • Does the project address a meaningful, understudied, or high-impact problem in psychedelic science?	5	Yes, this project is meaningful and would be of broad interest within and outside psychedelic science.
Innovation & Differentiation • Does the project propose a novel idea, methodology, mechanism, or application? • Is it clearly distinct from prior work? • Does it open new conceptual, therapeutic, or IP territory?	4	The idea is novel, but follows in the footsteps of previously (abandoned) work in the field. There is potential for new IP should the outcome of the experiment be favourable. There is a question about whether a previously unidentified 'inhibitor' may be identified and about the realities of treating an endogenous compound as IP.
Scientific Feasibility & Rigor • Are hypotheses clearly defined? • Are the methods appropriate, replicable, and grounded in precedent? • Does the plan identify risks, limitations, and reasonable timelines?	2	The hypotheses are stated, and the method for testing the hypotheses are provided; these have not been previously applied in the same way, but are grounded in established practices. The proposal does not discuss risks or limitations in sufficient details, nor does it provide sufficient detail in regards to the 'plan B' the authors propose. A project timeline is also absent.

Team Capability & Execution Plan • Lead & team should have a background relevant for the proposal • Team has access to proper resources for completing project	3	The credentials of the proposed team are well-aligned with the project goal; yet there is an imbalance in the number of individuals in advisory role relative to those who are directly carrying out the experimental work. The work-flow of the team is unclear. It is unclear (besides university affiliation) to what resources the team has access to independently of those to be acquired via PsyDAO funding.
Common Goods • Will the project produce outputs—such as data, methods, protocols, publications, media, or tools—that would be suitable for inclusion in a shared psychedelic research commons? • Would those outputs be valuable for others to use, build on, or govern collectively? • Does the applicant expressed interest in contributing to a commons or collaborating on open dissemination?	4	There is potential for data that would be of interest to the broader psychedelic community to be generated; and there is potential for a significant number of additional projects and protocols to be built atop of the potential findings. The applicant expressed interest in contributing 'key datasets, protocols and insights' and 'access to informaiton that could be considered public disclosure', yet specific detail as to what these represent would be important.
Budget • Is the proposed budget reasonable and aligned with the project's scope, risks, and deliverables? • Are cost drivers (e.g. personnel, materials, travel, services) justified in detail? • If additional funds are anticipated (e.g. matching, co-funding, downstream investment), is the leverage strategy credible and likely to succeed?	3	The budget is high, with an imbalance towards funding personnel cost (in advisory/managerial/coordination capacity) (200k+), and indirect costs (52k+), relative to direct research expenses (36k+). It is also unclear over which timeline the funds are to be administrated, and whether the tuition fees represent the totality of a PhD tuition based at the University of Florida entirely revolving around this project, or whether they are only applicable for the year the project ought to run. There is very little justification for the budget aside from a brief justification of personnel. In file 'Budget-peptide-like inhibitor of indolamine N-methyltransferase (INMT) from Rabbit brain BASIC 2024 .xlsx' the budget is ~36k, yet in a different file it is 50k for materials. Direct research expenses ~36k and the breakdown of reagents appear

• Does the budget reflect lean, milestone-based thinking rather than institutional padding?		well justified. Additional funds are not indicated. It is unclear what period of time the indirect costs would cover and what would happen if the project milestones (timeline not provided!) are not reached in time and whether the university will demand additional funds for hosting the project. It is also unclear why the exemption to indirect costs is not applicable in this case. A letter of support from the university has not been provided.

The project presents an interesting idea of broad interest within the psychedelic research community and beyond. There is significant potential to generate IP and datasets of interest. The team is qualified to undertake it, though there is an imbalance between individuals in active experimental roles and individuals in advisory/coordination/management roles who are proposed to carry out the projects. The biggest lacunae is represented by the proposal lacking a detailed explanation of the timelines and involvement of each member at distinct timepoints and milestones. The proposal also does not address potential risks, or the 'plan B' in detail either, leaving uncertainty surrounding a specific plan of action. It is also unclear to what extent this will constitute a PhD project, and how this will overlap with 1) the much longer timelines of a PhD and 2) the university IP licensing. It is also unclear what project outputs specifically will constitute common goods in line with PsyDAO requirements. A Gantt chart illustrating the project timeline, involvement of each individual proposed, and the specific outputs resulting from those that may be part of the common goods would be useful to assess the project's further. Since the scientific potential is significant and the methodology is appropriately curated, I recommend revising and resubmitting with additional detail and precision addressing the aspects named above.

Reviewer #2

Category	Score	Score Justification
Significance • Does the project address a meaningful, understudied, or high-impact problem in psychedelic science?	4	**This basic science project seeks to uncover a hypothesized mechanism underlying the regulation of endogenous DMT. This is a high-risk project that if it is found to be accurate can be a significant development on the future development of a drug that can elevate endogenous DMT. However, the project does not outline the specific benefits of uncovering such mechanisms. For example, how will these findings specifically advance the science of endogenous DMT, or how could this be used for drug development in a way that is favorable compared to the administration of exogenous DMT.**
Innovation & Differentiation • Does the project propose a novel idea, methodology, mechanism, or application? • Is it clearly distinct from prior work? • Does it open new conceptual, therapeutic, or IP territory?	3	**The hypothesis is well founded upon a single 1977 previous study. The project is clearly distinct from prior work and is novel and attractive to uncover the mechanisms underlying endogenous DMT regulation, however it builds upon a single previous study. The project indeed does open new conceptual territory, whereas its applications and IP elements remain unspecified.**
Scientific Feasibility & Rigor • Are hypotheses clearly defined?	4	**The hypothesis and methods are clearly defined and specific to the aims of the study. The methods seem appropriate although there are no specifications based on previous work. The plan**

• Are the methods appropriate, replicable, and grounded in precedent? • Does the plan identify risks, limitations, and reasonable timelines?		**does not outline risks along the specific parts of the methods which may fail. There is a mention of a plan B but it is fairly broad.**
Team Capability & Execution Plan • Lead & team should have a background relevant for the proposal • Team has access to proper resources for completing project	**4**	**Whereas the expertise of Dr. Gallimore and Prof. Smith do not fall within the methodological realm of the project, they do fall within the realm of expertise of Dr. McCurdy. The expertise of McCurdy in natural product isolation and enzyme activity modulation fit well with the methodology and technical expertise of the project. The project does not outline the roles of Gallimore and Smith throughout the project and their inputs in project conception relative to those of Dr. McCurdy and does not outline the background and expertise of McCurdy's team named as Co-I's in the proposal. Nonetheless, McCurdy's team seem capable upon inspection of Budget Justification.**
Common Goods • Will the project produce outputs—such as data, methods, protocols, publications, media, or tools—that would be suitable for inclusion in a shared psychedelic research commons? • Would those outputs be valuable for others to use, build on, or govern collectively? • Does the applicant expressed interest in contributing to a commons or collaborating on open dissemination?	**3**	**The project has a very generic outline of data sharing, and no specifics are mentioned regarding specific outcomes and how they will be shared and how they will provide value to the community. Nonetheless, the investigators do manifest an interest in contributing to the dissemination of outcomes to key members of PsyDAO.**
Budget	**3**	**The costs of the project seem to be mostly devoted for staffing to reach the project's end goals and mostly seem appropriate. There is however, no specification in the proposal for the cost of**

• Is the proposed budget reasonable and aligned with the project's scope, risks, and deliverables? • Are cost drivers (e.g. personnel, materials, travel, services) justified in detail? • If additional funds are anticipated (e.g. matching, co-funding, downstream investment), is the leverage strategy credible and likely to succeed? • Does the budget reflect lean, milestone-based thinking rather than institutional padding?		**each of the elements of the Materials and Supplies outlined in the justification (budgeted at a total of $50k). There is no mention of additional possible funding.**

Revise and Resubmit

This is a relevant proposal aimed to characterize the mechanisms of endogenous DMT regulation. Furthermore, the methos seem adequate and specific and fall within the expertise of Dr. McCurdy's expertise and capabilities – however please note that it is important to obtain the expert review from a scientist with specific expertise with the methods outlined here as well to corroborate this and ensure that the single study from 1977 upon which this study is based on is sound to fund this study. My main concern is that the hypothesis of the project appears to come from Dr. Gallimore rather than Dr. McCurdy. Gallimore has an expertise based on Computational Neuroscience and conceptual work regarding DMT, and not the specific methods outlined in the project. Furthermore, the project seems to be high-risk (it is plausible that the hypothesised mechanism of endogenous DMT regulation proposed is incorrect) and the de-risking element of the proposal (the Plan B) is not sufficiently characterized in the methods. If the proposal is checked by an expert in the methods outlined, and de-risking of the project follows further specification, and the specific elements of Common Goods are better specified then it could be appropriate to fund this study.

Project & Token Implementation Plan

1. Funds Disbursement

a. **Recipient**: Noonautics, Inc., as the named Sponsor of Record on the University of Florida Sponsored Research Agreement (SRA).
b. **Amount**: $107,000 USD (or equivalent in ETH at the time of transfer).
c. **Payment Process**: Funds will be transferred from the PsyDAO Science Fund treasury to the designated Noonautics wallet.
d. **Documentation:** Prior to transfer, Noonautics will countersign the Memorandum of Understanding (MoU) with PsyDAO, formalizing:
    i. The Right of First Refusal (ROFR) to partner on any future projects which may produce IP related to this proposal.
    ii. The obligation to provide milestone updates and deliverables.
    iii. Transaction records will be posted in the PsyDAO governance forum for transparency.
e. **Reporting**:
    i. Noonautics will provide confirmation of funds receipt and documentation of payment to the University of Florida.
    ii. Milestone progress updates and any associated data will be shared with PsyDAO as defined in the project plan.

2. Minting of IP-NFT

a. An IP-NFT will be minted by PsyDAO to represent the Endogenous DMT Research Consortium ($eDMT).
b. The eDMTx project will be the flagship project of the Consortium.
c. The eDMTx documents tied to the IP-NFT will include the MoU and any related contractual rights established via the MoU.
d. The IP-NFT may serve as a wrapper for any future patent filings, data packages, or know-how developed from this and future projects tied to the Consortium.

3. eDMTx Legal Framework & IP Rights

a. Sponsor of Record for eDMTx: Noonautics is the named sponsor on the Sponsored Research Agreement (SRA) with the University of Florida.
b. IP Rights Agreement: Upon proposal approval, PsyDAO will execute a Memorandum of Understanding (MoU) with Noonautics. This MoU will grant PsyDAO a Right of First Refusal (ROFR) to any IP resulting from this project or from future research conducted by Noonautics related to endogenous DMT.

c. The MoU will form the legal basis for minting the IP-NFT and will be signed prior to any token issuance.

4. Minting of $eDMTx IPTs

a. A fixed supply of $eDMT IP Tokens (IPTs) will be minted and held in a Consortium multisig wallet.
b. Tokens represent participation in **Commons-based IP governance system**.
c. Holders access data, vote on funding allocation, and can shape IP morals.
d. Enables cross-project funding and utility without requiring claims on individual lab's IP.

5. $eDMT IPT Fair Launch

a. The $eDMT IPT will be launched as a fair launch, with no private sales, pre-mining, or preferential allocations.
b. All tokens will be made available to the public on equal terms through an open presale and subsequent trading on decentralized exchanges.
c. This approach avoids insider advantages and ensures aligned incentives among all participants from the start.
d. Combined with PsyDAO-seeded liquidity, the fair launch aims to:
    i. Establish a stable, credible market for the token.
    ii. Incentivize early community engagement and long-term participation.
    iii. Set a precedent for transparent, community-driven funding of psychedelic science.

6. Liquidity Pool (LP) Deployment

a. PsyDAO will seed an eDMT/ETH liquidity pool on a decentralized exchange (e.g., Uniswap) with 10 ETH and a matching amount of $eDMT
b. LP tokens will be held by the project multisig.

7. Trading Fees & Treasury Recovery

a. The first $107,000 in trading fees (~42 Eth as of 7/3/25) generated by the LP will be routed to the PsyDAO Science Fund to recoup the initial investment.
b. After initial investment is recouped:
    i. 80% of fees generated will be retained by the eDMT Consortium multisig wallet to support future eDMT projects.

ii. 20% of fees generated will be routed to the PsyDAO Science Fund to support additional psychedelic science