A UNIVERSITY OF PENNSYLVANIA VENTURE COMPANY

***Implantable Brain Pathways*: Biofabricated Neural Tissue Replacement for Axon Tract Reconstruction and Biologically-Based Deep Brain Stimulation**

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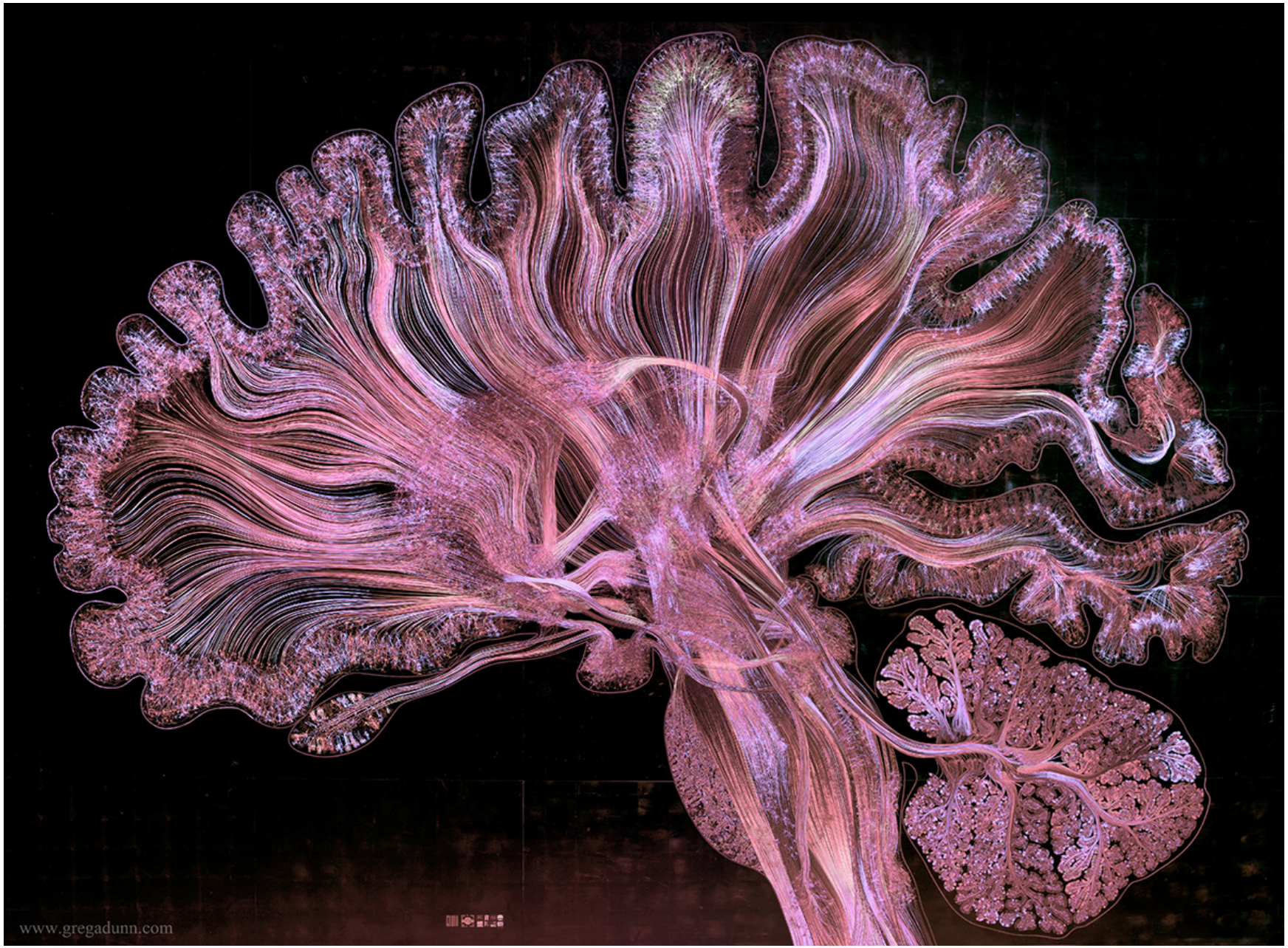
Penn
University of Pennsylvania

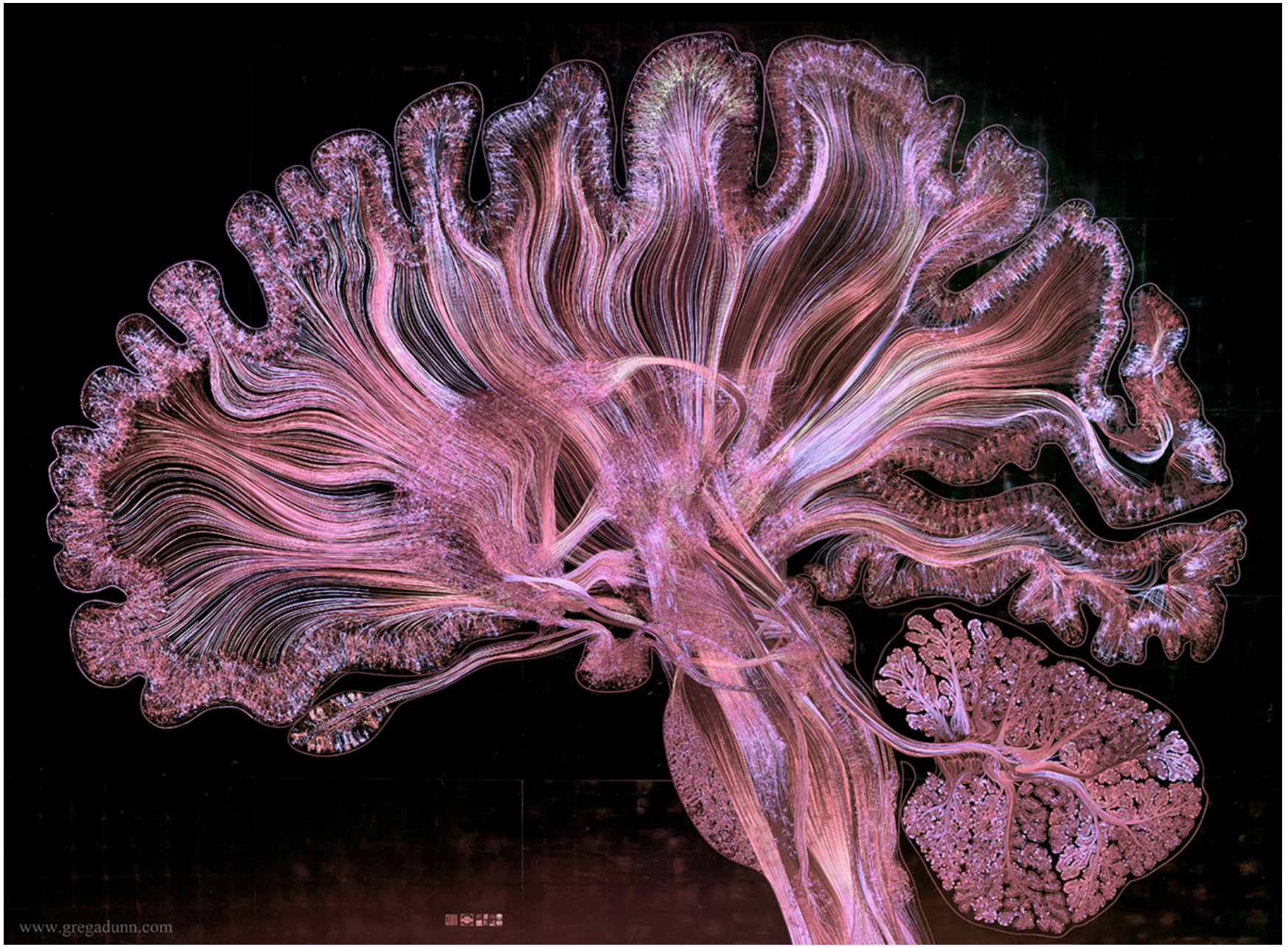
June 2, 2019

The Unmet Need – There is No Current Strategy Capable of Rebuilding Brain Circuitry



The Unmet Need – There is No Current Strategy Capable of Rebuilding Brain Circuitry

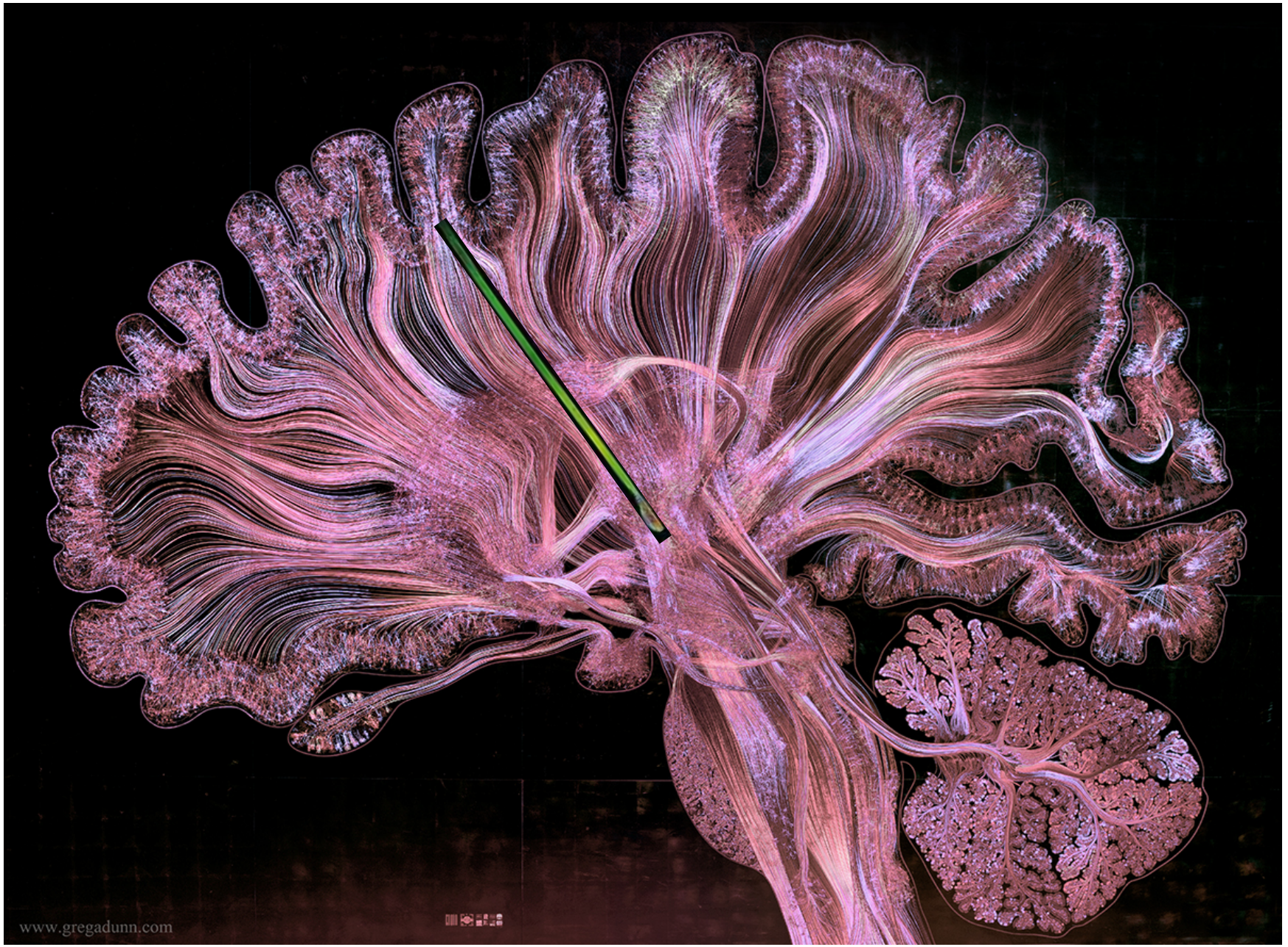
*<u>Brain circuitry disruption</u> underlies the neurological deficits caused by a host of nervous system disorders and diseases, including **TBI**, **stroke** and **Parkinson's disease***



The Unmet Need – There is No Current Strategy Capable of Rebuilding Brain Circuitry

*<u>Brain circuitry disruption</u> underlies the neurological deficits caused by a host of nervous system disorders and diseases, including **TBI**, **stroke** and **Parkinson's disease***

<u>Our solution</u>: ***Implantable, tissue engineered brain pathways*** *can physically reconstruct lost brain circuitry on a per-patient basis*



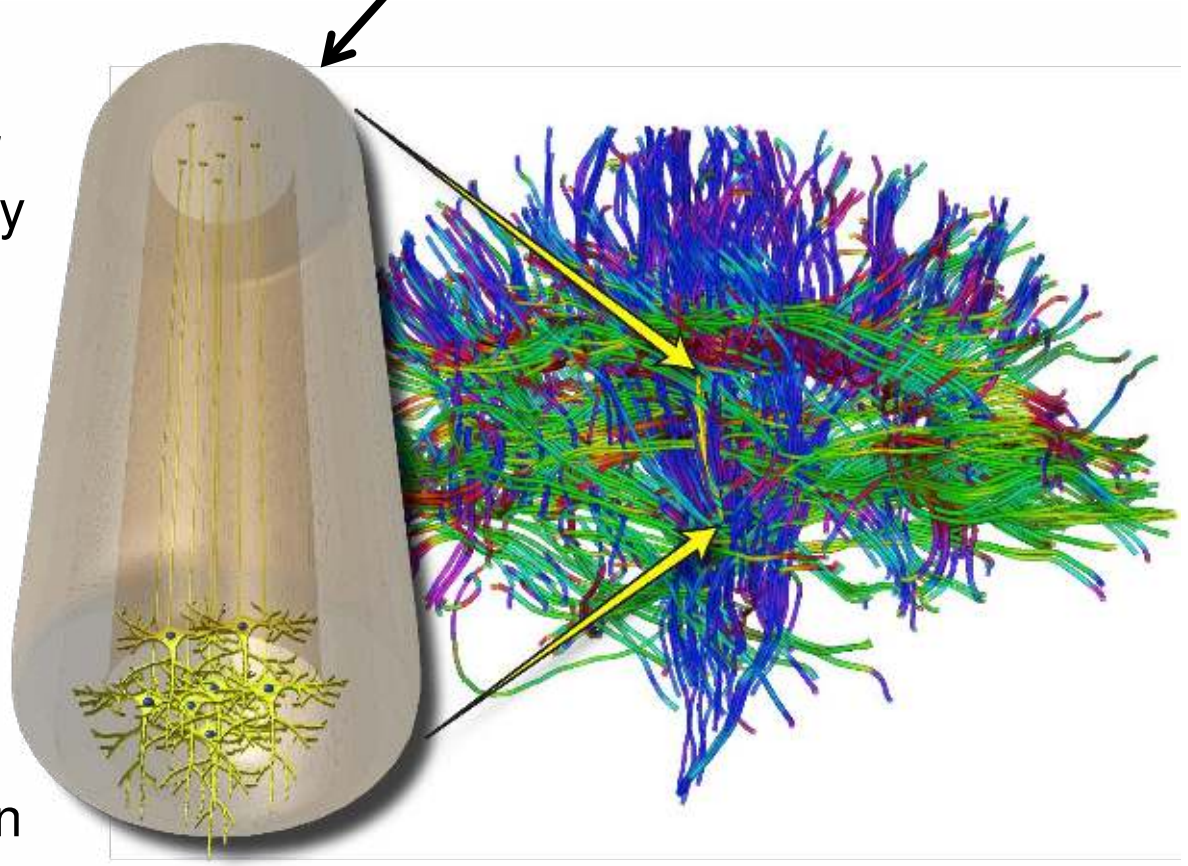
Company Overview

INNERVACE is a University of Pennsylvania spin-out company co-founded by **D. Kacy Cullen**, Ph.D. (Neurosurgery & Bioengineering) and **Douglas H. Smith**, M.D. (Neurosurgery).

Core Technology: **Implantable Tissue Engineered Brain Pathways**

- We are only the group in the world capable of fabricating *entire brain pathways* for transplant.
- These ***Biomanufactured Brain Pathways*** are *living tissues* to *directly replace* the exquisite neuroanatomy lost by an *individual patient*, and thus "wire-in" to physically reconnect distinct regions.
- *Preclinical data in animal models suggest we can repair what is currently irreparable*. No other technology or approach can replicate our products and their unique mechanism of action.
- Our products will transform care and treatment of patients suffering from a debilitating neurological injury or disease, including Parkinson's disease, brain injury, and stroke.

Implantable Tissue Engineered Brain Pathway for Parkinson's Disease Reconstruction



Team

D. Kacy Cullen, PhD
Founder

Leading Expert in Neural Tissue Engineering

INNERVACE Technology Developed by Dr. Cullen's Laboratory

Associate Professor of Neurosurgery & Bioengineering Perelman School of Medicine, University of Pennsylvania

Director, Center for Neurotrauma, Neurodegeneration & Restoration, Corporal Michael J. Crescenz VA Medical Center

James Harris, PhD
Consultant

10 Years of Experience in Translational Neuroengineering (including manufacturing & regulatory)

PhD in Biomedical Engineering, Case Western Reserve

Former Senior Project Manager at Inscopix

Former DARPA Neurotechnology Consultant in Brain Machine Interface & Nerve Modulation

Douglas Smith, MD
Co-Founder

Robert A. Groff Professor of Teaching And Research In Neurosurgery, University of Pennsylvania

Director, Center for Brain Injury & Repair, Perelman School of Medicine, University of Pennsylvania

Mijail "Misha" Serruya, MD, PhD
Consultant

Assistant Professor of Neurology, Jefferson University

20 Years of Experience in Neural Engineering & Neurophysiology (including studies in non-human primates and clinical trials)

Previously Co-Founder, Program Manager, and Clinical Scientist at Cyberkinetics

Lead Product: Tissue Engineered Brain Pathways

Why is our solution unique?

Most experimental regenerative medicine therapies for nervous system repair involve the implantation of stem or differentiated neural cells (i.e. neurons). *These strategies fail to replace long-distance connections between brain regions, and therefore have limited utility*.

What can our technology treat?

Tissue Engineered Brain Pathways will treat a range of neurological disorders and diseases – such as Parkinson's disease (PD) – described as "disconnection" syndromes, where *connections* between different parts of the brain are lost resulting in cognitive and/or motor deficits.

What is the business model and market size?

Tissue Engineered Brain Pathways will be first-in-class/best-in-class as a transformative solution for PD treatment. Tissue biomanufacturing will utilize either an allogeneic or autologous cell source and released products will be shipped for surgical implantation.

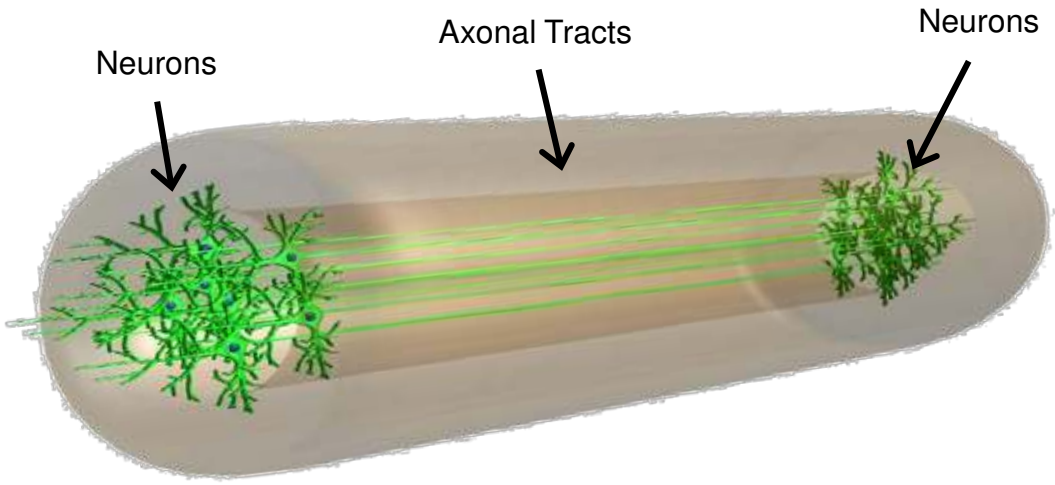
A restorative therapy for PD alone is a multi-billion dollar market.

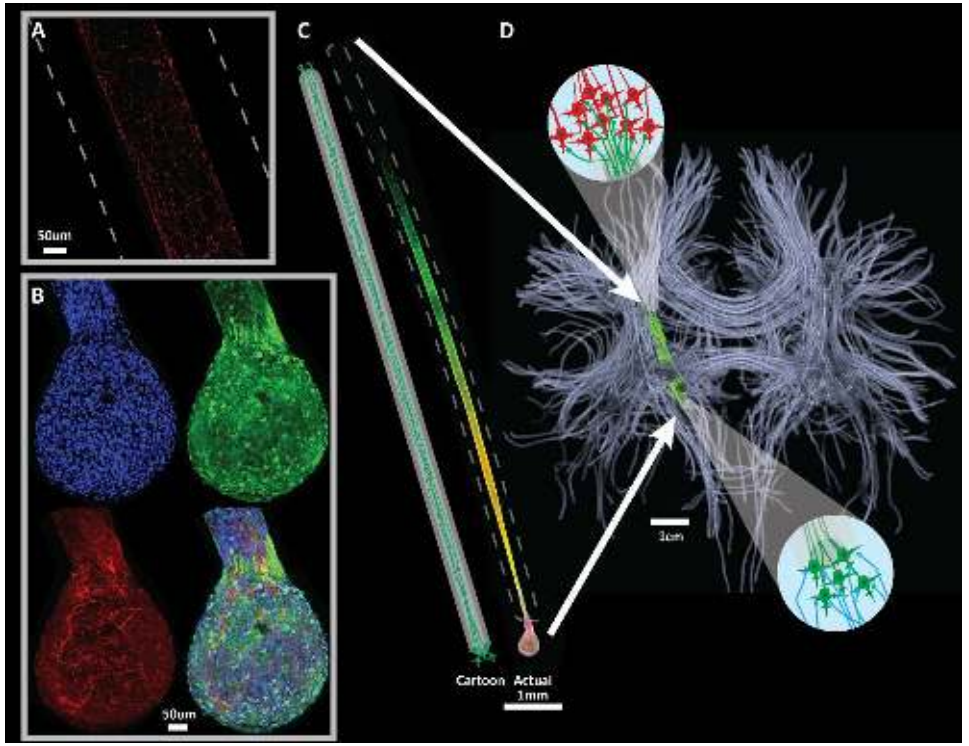
What stage is the company at?

INNERVACE is currently fundraising and looking for strategic partner(s) to guide product development and accelerate the path to clinic.

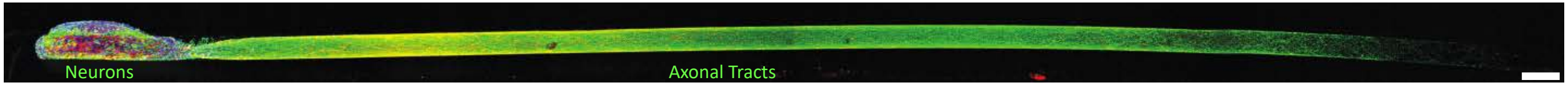
Our Solution: Tissue Engineered Brain Pathways

We are the only group in the world that can biofabricate *living neural networks* with *preformed axon pathways* suitable for transplantation





- *Anatomically inspired: architecture replicates the anatomy of long-distance brain pathways (spanning centimeters)*
- *Miniaturized cross-section permits minimally invasive delivery into brain*
- *Can be unidirectional or bidirectional axonal constructs*
- *Implantable brain pathways are the only approach capable of replacing brain circuits – which implanted neurons alone cannot do – and therefore ensure proper connectivity, "close the loop" to allow for endogenous feedback/regulation, and restore lost function*



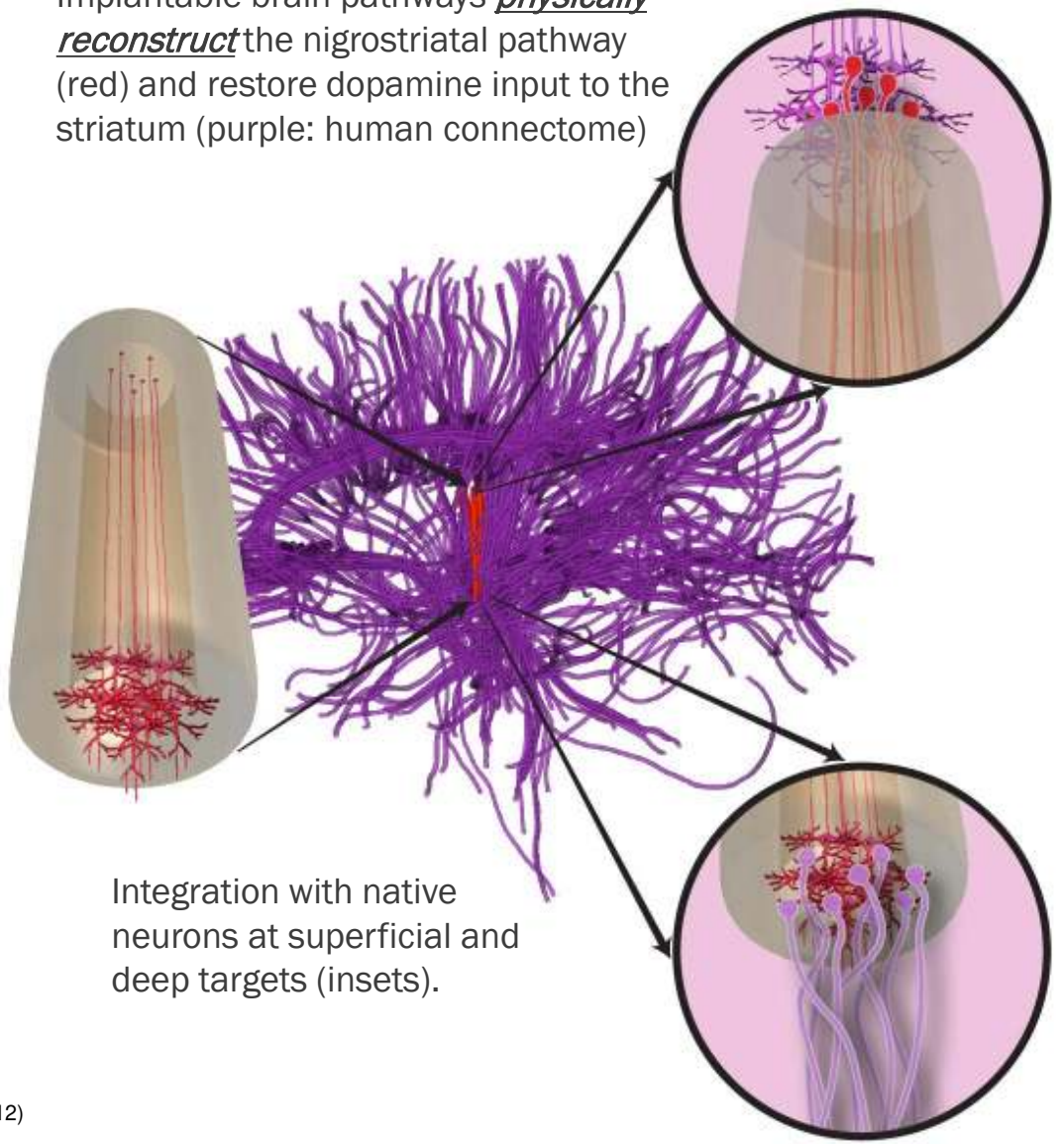
This living neural microtissue reconstitutes the anatomy of white matter pathways in the brain: discrete neuron populations spanned by long axon tracts

Cullen DK et al., *Tissue Engineering*, "Microtissue Engineered Constructs with Living Axons for Targeted Nervous System Reconstruction" (2012)

Our Solution: Tissue Engineered Brain Pathways to Directly Restore the Nigrostriatal Pathway[1,2,3]

- **Biofabricated brain pathways mimic the general cytoarchitecture of the nigrostriatal pathway**
  - Discrete population of dopaminergic neurons with long-projecting, unidirectional, axonal tracts
- **Dopaminergic axonal tracts can be grown to clinically relevant lengths to reconstruct the nigrostriatal pathway**
  - Readily generated from dopaminergic neurons derived from differentiated sources as well as human stem cells
- **Human cell-derived brain pathways will, at a minimum, meet specifications believed to be of clinical benefit**
  - Dopaminergic neurons (80,000) and *in vitro* production of dopamine (7ng/mg tissue) for fetal tissue grafts[4,5]
- **Can be deployed clinically following conventional stereotaxic implantation methods used for cell implants and tissue grafts**

Implantable brain pathways ***physically reconstruct*** the nigrostriatal pathway (red) and restore dopamine input to the striatum (purple: human connectome)



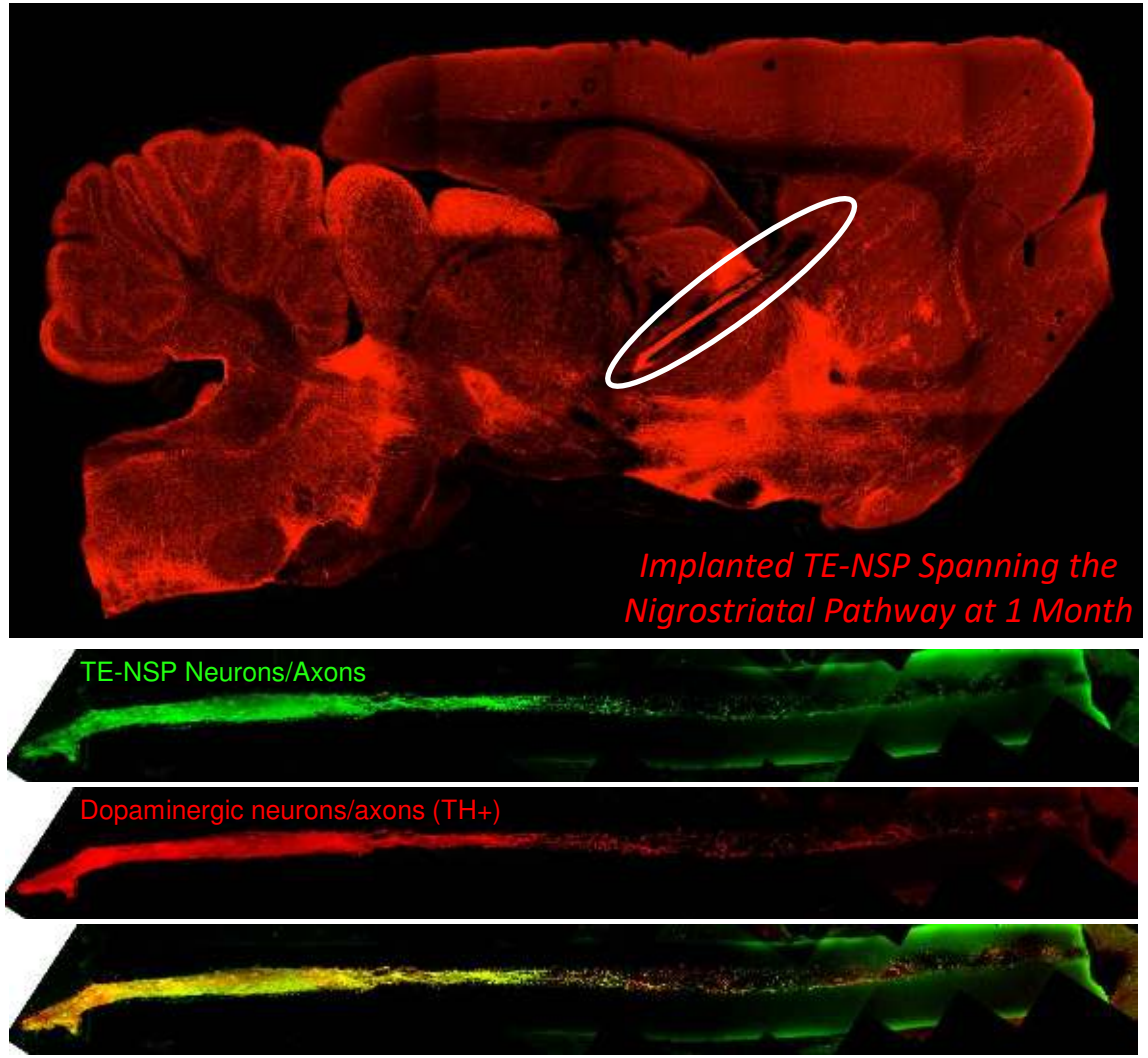
Integration with native neurons at superficial and deep targets (insets).

1. Cullen DK et al., *Tissue Engineering*, "Micro-Tissue Engineered Constructs with Living Axons for Targeted Nervous System Reconstruction" (2012)
2. Struzyna LA et al., *Tissue Engineering,* "Restoring Brain Circuitry with Living Micro-Tissue Engineering Neural Networks" (2015)
3. Harris JP et al., *J Neural Engin*, "Advanced Biomaterial Strategies to Transplant Preformed Micro-Tissue Engineered Neural Networks into the Brain" (2016)
4. Björklund, Anders, and Olle Lindvall, "Cell replacement therapies for central nervous system disorders." Nature neuroscience 3.6 (2000): 537
5. Kish, Stephen J., et al., "Striatal dopaminergic and serotonergic markers in human heroin users." Neuropsychopharmacology 24.5 (2001): 561-567.

Tissue Engineered Nigrostriatal Pathway: Stable Integration Following Transplantation

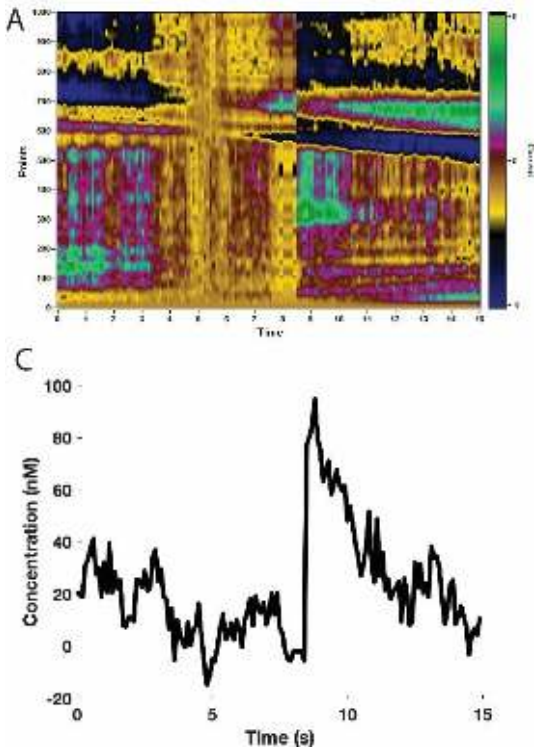
Tissue Engineered Nigrostriatal Pathways (TE-NSPs) Structurally Replaced the Lost Pathway and Elicited Functional Benefits After Transplantation into Rat 6-OHDA Model of PD

Immunohistochemistry & Confocal Microscopy Show TE-NSP Survival

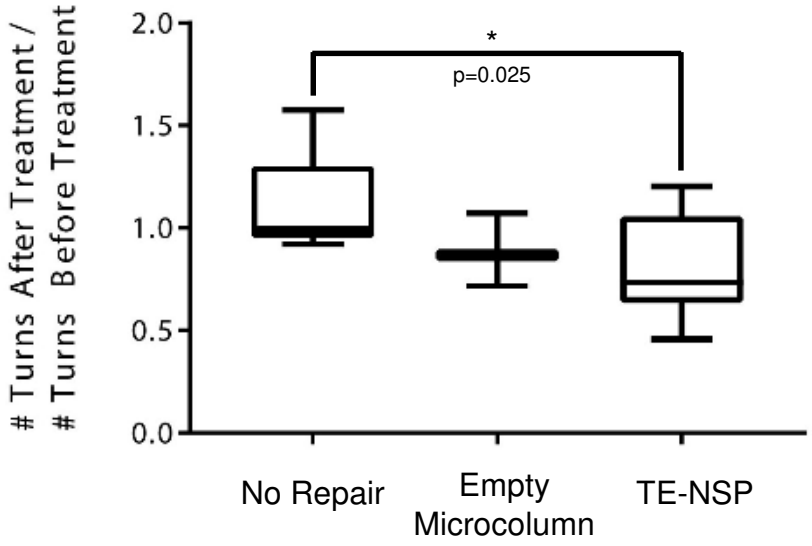


Functional Measures Show Recovery

FSCV Revealed Restoration of Striatal Dopamine Levels *In Vivo*



Change in Apomorphine Challenge

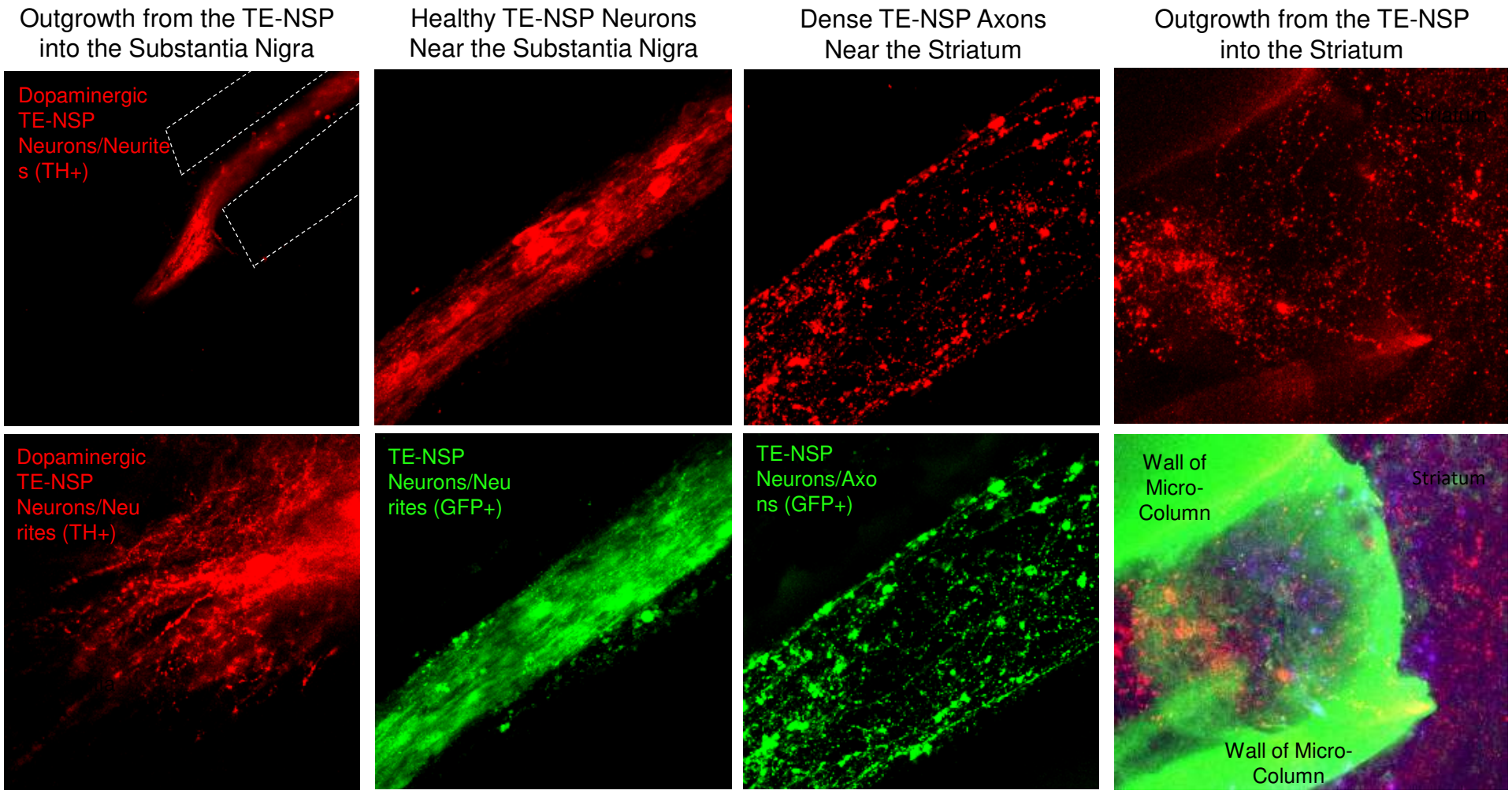


There was dopamine release in the striatum and a reduction in the turning behavior (upon apomorphine challenge) following implantation of TE-NSPs

These findings show that TE-NSPs span the nigrostriatal pathway and restore striatal dopamine at 1 month post-implant

Tissue Engineered Nigrostriatal Pathway: Stable Integration Following Transplantation

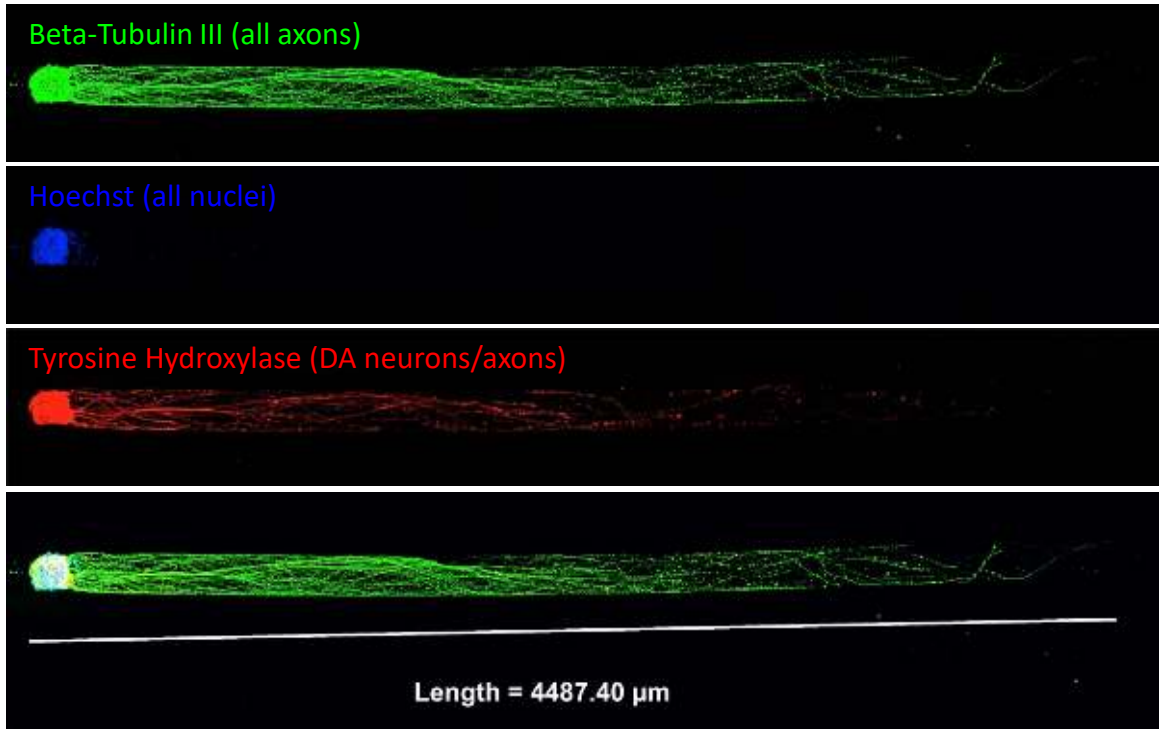
Tissue Engineered Nigrostriatal Pathways (TE-NSPs) Survived, Maintained Axonal Architecture, and Integrated with Host After Transplantation into Rat 6-OHDA Model of PD



TE-NSP neurons remain healthy and projected neurites to integrate with the substantia nigra. Similarly, axonal tracts were maintained within the micro-column lumen and dopaminergic axonal extension was observed into the striatal at 1 month post-implant

Human Stem Cell Derived Tissue Engineered Brain Pathways

Human Dopaminergic Tissue Engineered Brain Pathways

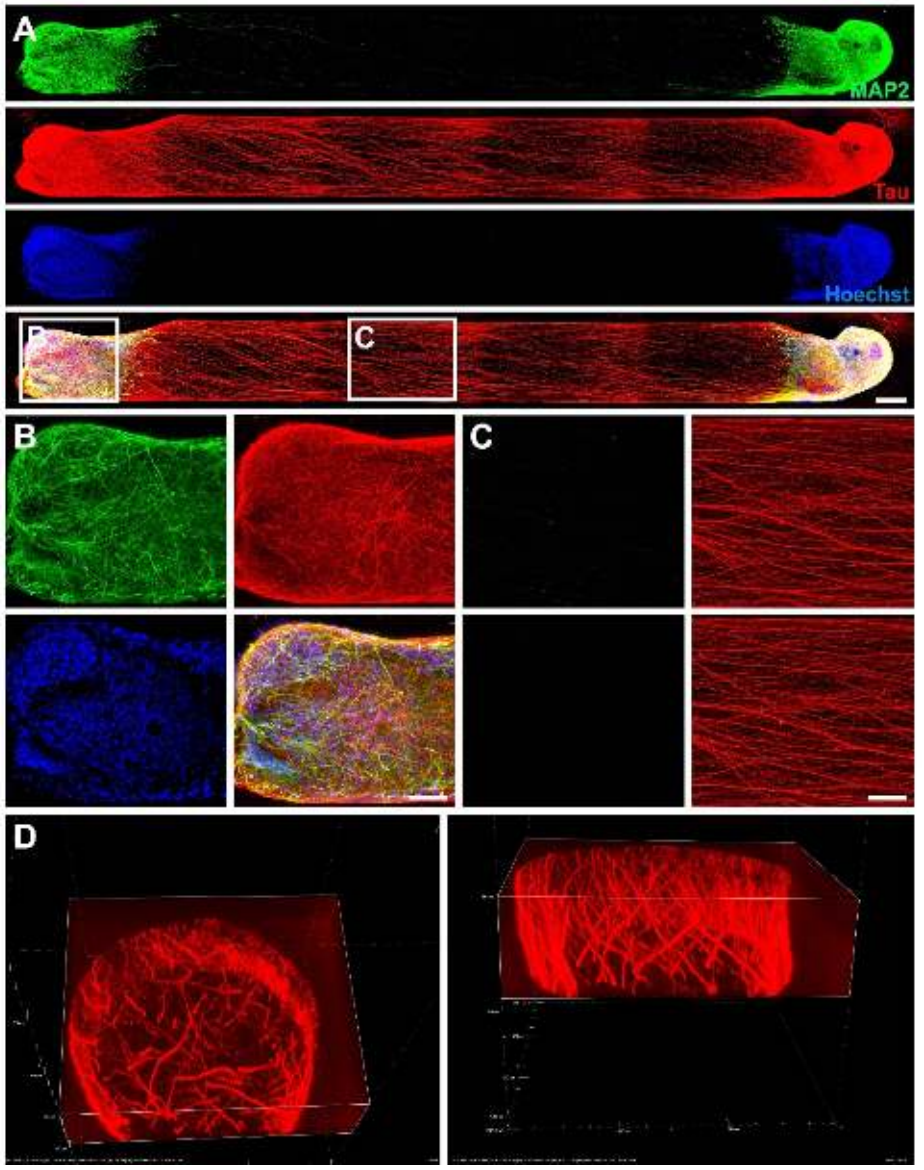


Human Cortical Organoid Tissue Engineered Brain Pathways

MAP-2 (neuron cell bodies)

Tau (all axons)

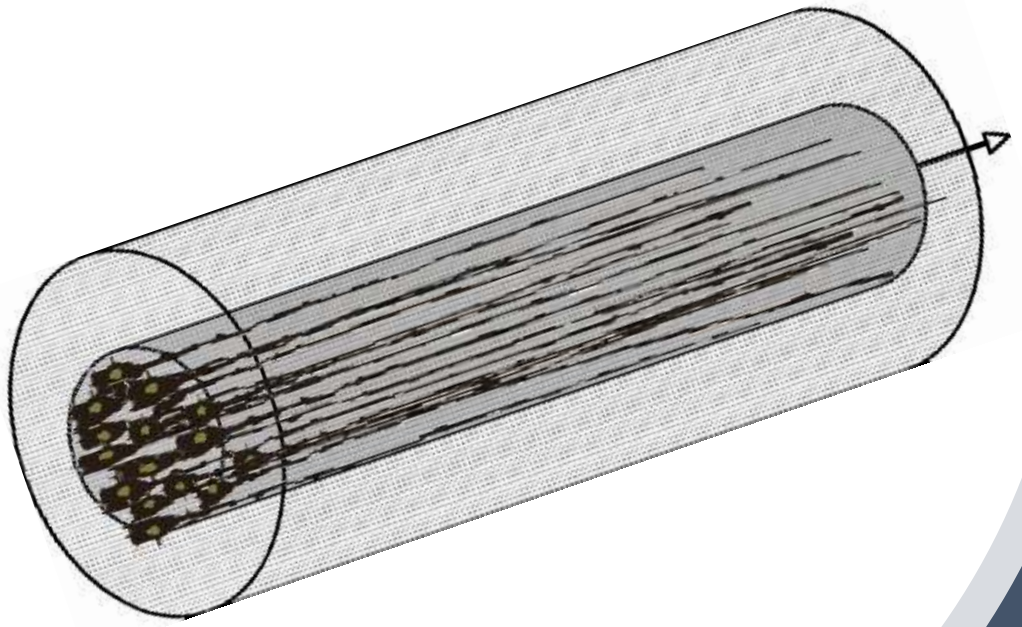
Hoechst (all nuclei)



Demonstration of our ability to create tissue engineered brain pathways from a human-derived starting biomass is important for the ultimate translation of this technology into the clinic

Struzyna LS et al., *J Tissue Engineering & Regenerative Medicine*, "Tissue Engineered Nigrostriatal Pathway for Treatment of Parkinson's Disease" (2018)
Cullen DK et al., *Cell Reports*, Three-Dimensional Human Axon Tracts Derived from Cerebral Organoids (in review)

PD Product



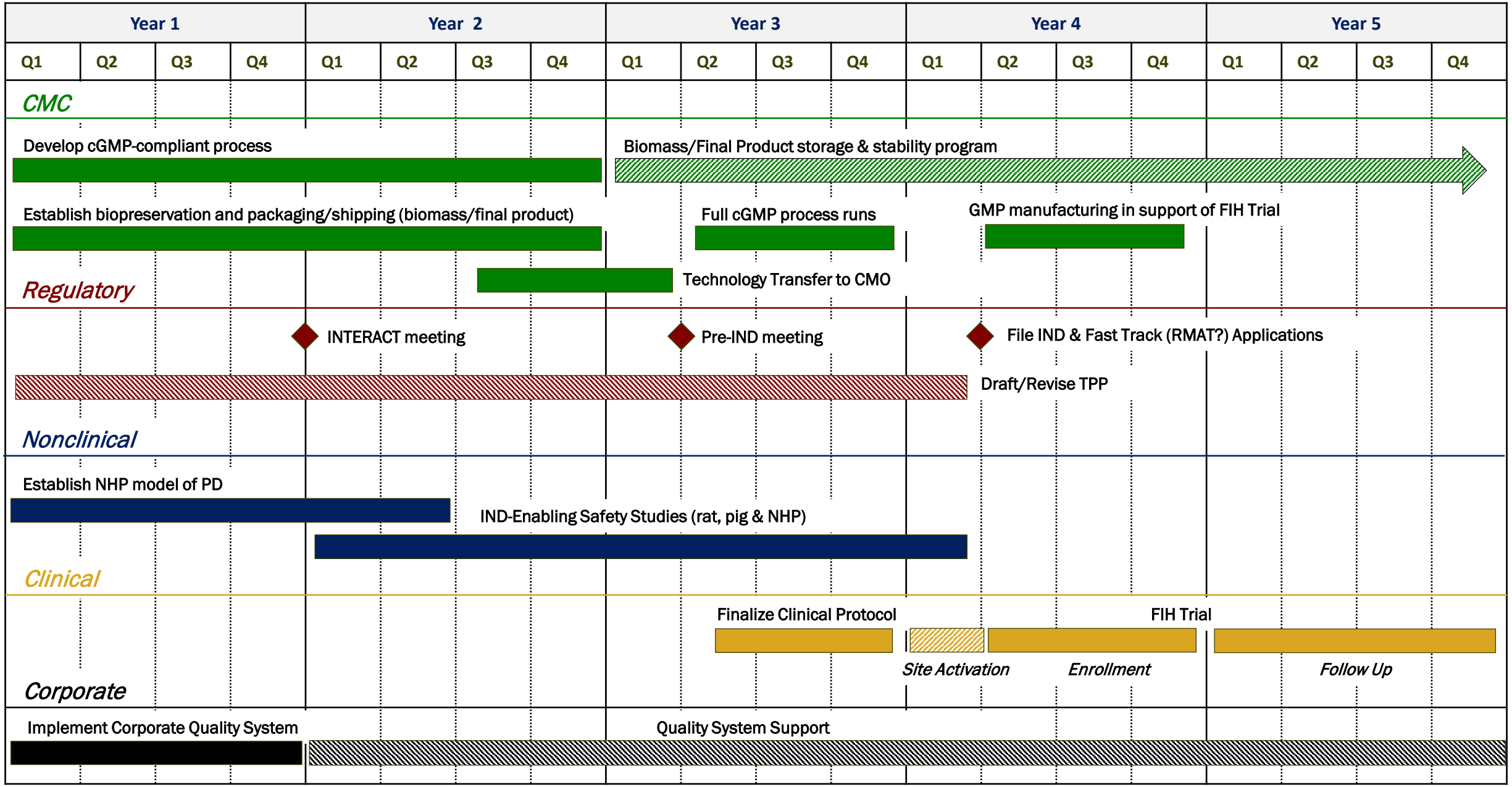
Product Description

- Biologic (Neurons + Axon Tracts) + Hydrogel Encasement
- Allogeneic (off the shelf) or Autologous (personalized) product
- Regulated under BLA
- Indication: PD patients (current DBS candidates)
- Fits with current precision neurosurgical practices

Ready to initiate IND-enabling activities

- Completed initial preclinical efficacy and MoA studies alongside preliminary safety
- Collaboration with multinational 3D Bioprinting company for manufacture and encasement
- Ready to initiate cGMP scale-up and process development
- Defined GLP safety program
- Scaling for large animal IND-enabling safety and efficacy studies
- Drafted clinical development and regulatory strategies

Proposed timeline to completion of FIH Trial



Tissue Engineered Brain Pathways: Platforms, Opportunities & Mechanism of Action

Pathway Reconstruction

Parkinson's Disease (PD)*

Brain Injury
Replace cortical-thalamic pathways after TBI, Stroke, Tumor Removal

Biofabricated Organs
Organogenesis Scaffold

Biofidelic *In Vitro* Test-Beds

Direct reestablishment of neural circuitry

Neuromodulation

Parkinson's Disease*

Brain-Machine Interface
Sensory feedback from advanced prosthetic limbs

Electroceuticals
PNS: organ/immune modulation
CNS: OCD, Depression, Pain

Epilepsy*

Biologically-based modulation of dysfunctional neural circuits

** Lead Programs*

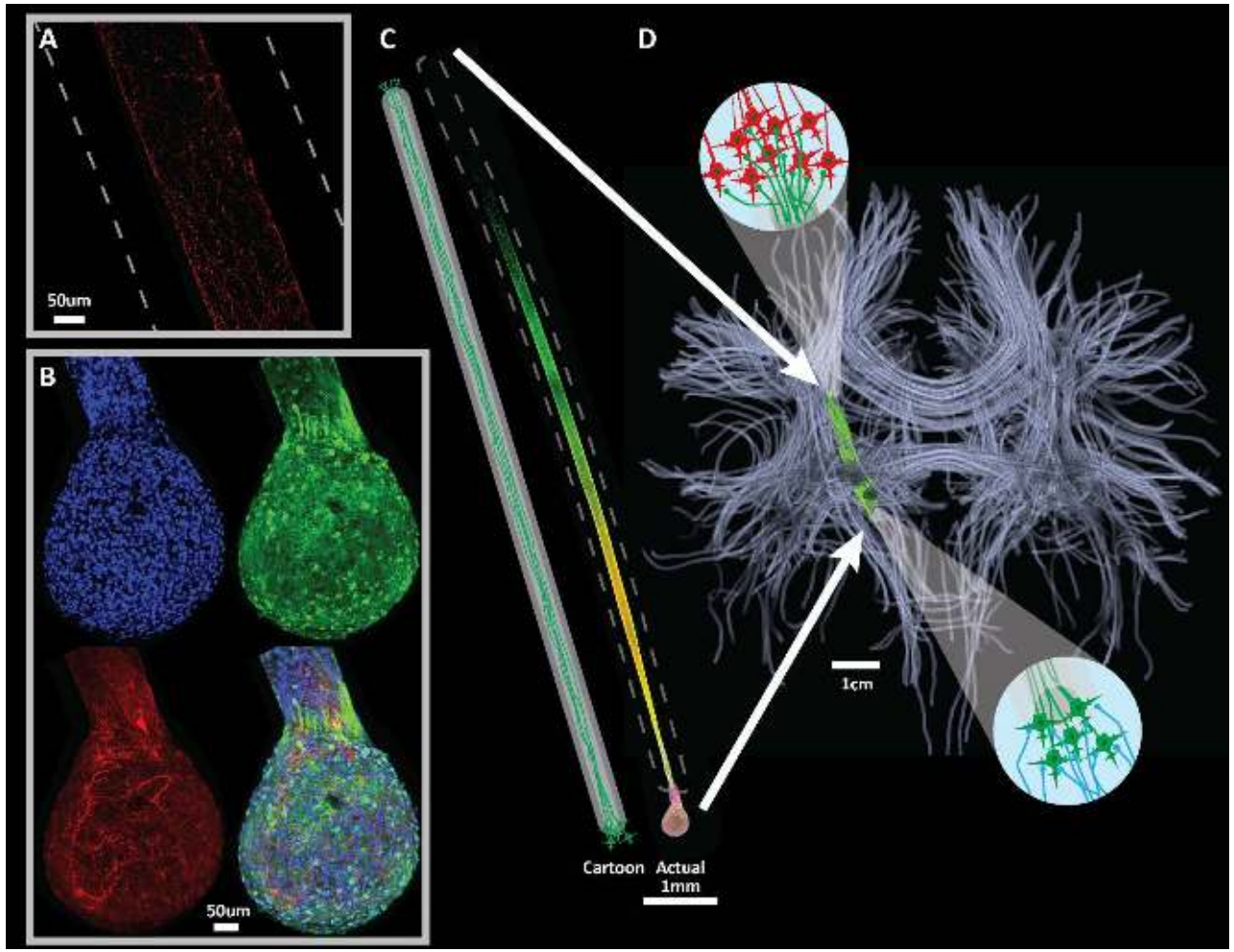
Tissue Engineered Brain Pathways: Platforms, Opportunities & Mechanism of Action

Pathway Reconstruction

- **Parkinson's Disease (PD)***
- **Brain Injury**
  Replace cortical-thalamic pathways after TBI, Stroke, Tumor Removal
- **Biofabricated Organs**
  Organogenesis Scaffold
- **Biofidelic *In Vitro* Test-Beds**

Direct reestablishment of neural circuitry

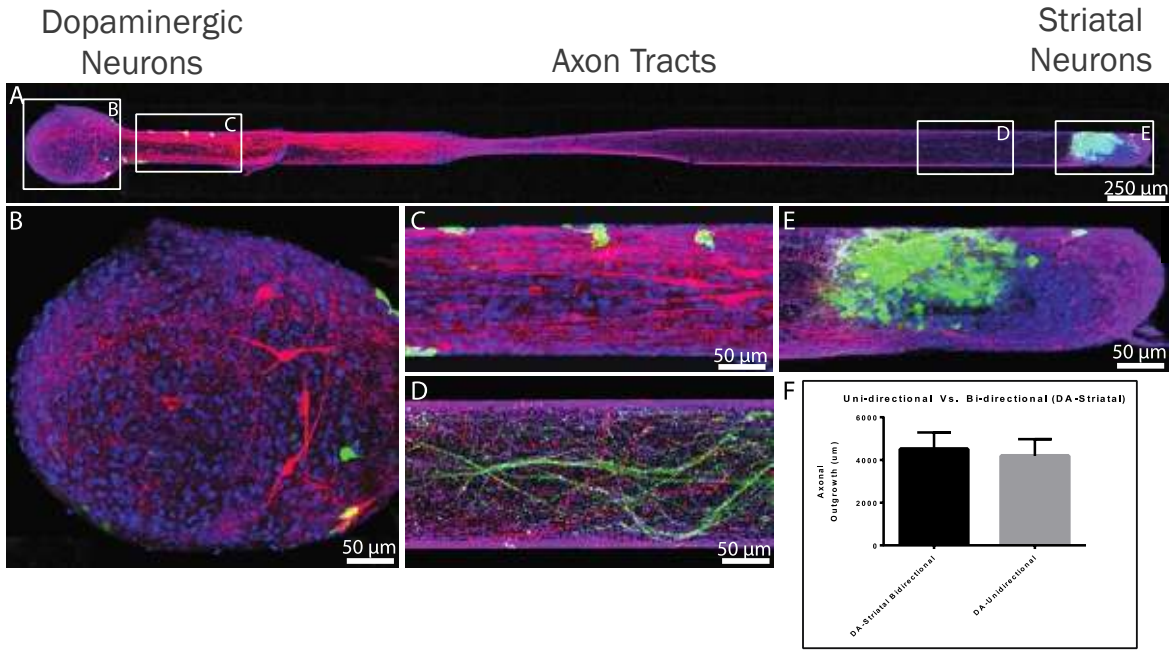
Tissue Engineered Nigrostriatal Pathway for PD Reconstruction



** Lead Program*

Anatomically-Inspired Testbeds to Study Diseases Featuring Axonopathy and Rapidly Triage Treatments

Integration with a Striatal End Target *In Vitro*

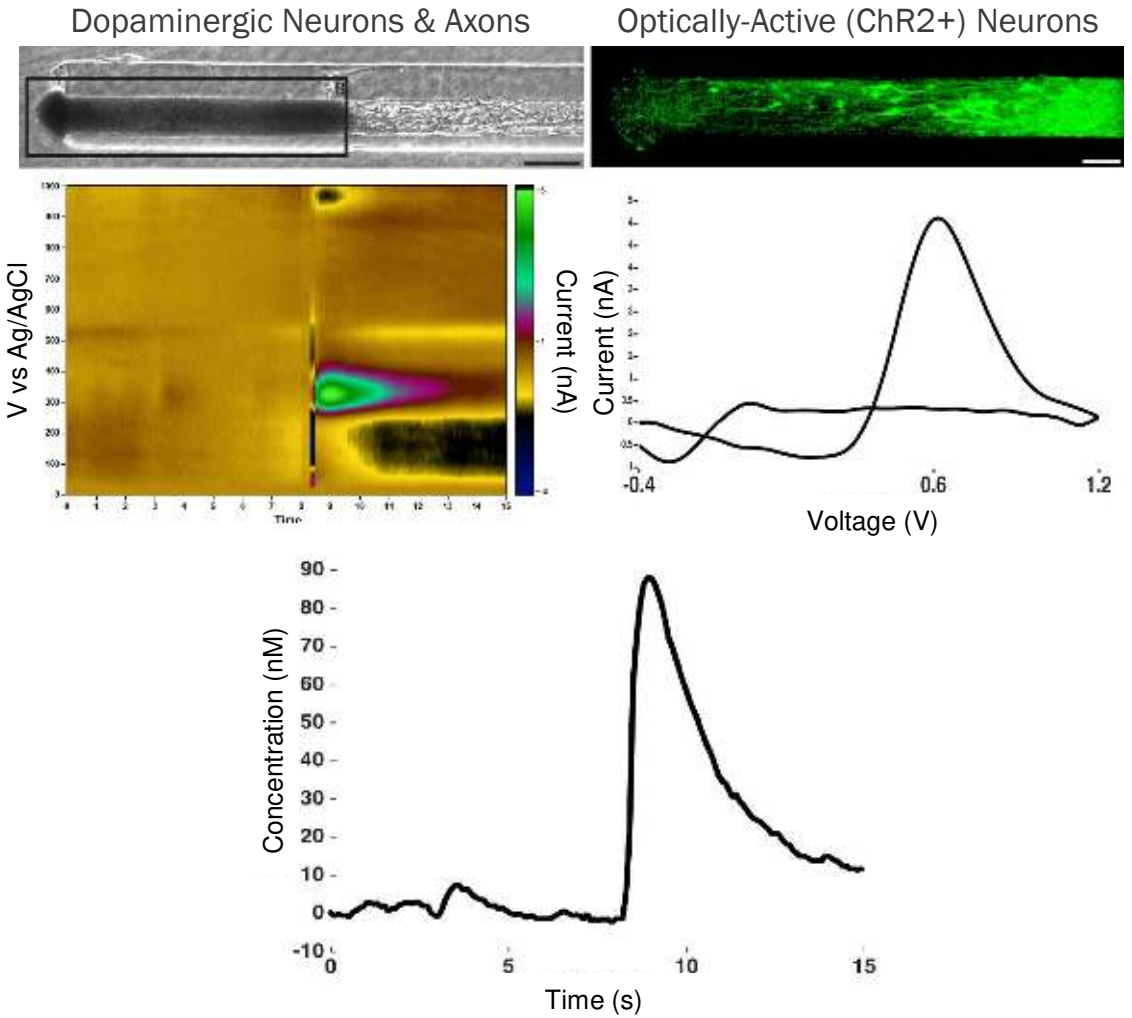


Dopaminergic tissue engineered brain pathways form synapses with striatal neurons

This may serve as a anatomically- and physiologically-relevant test-bed to study patient-specific disease mechanisms and pharmacological strategies based on a constructs built using a *patients own cells*

Struzyna LS et al.. *J Tissue Engineering & Regenerative Medicine*, "Tissue Engineered Nigrostriatal Pathway for Treatment of Parkinson's Disease" (2018

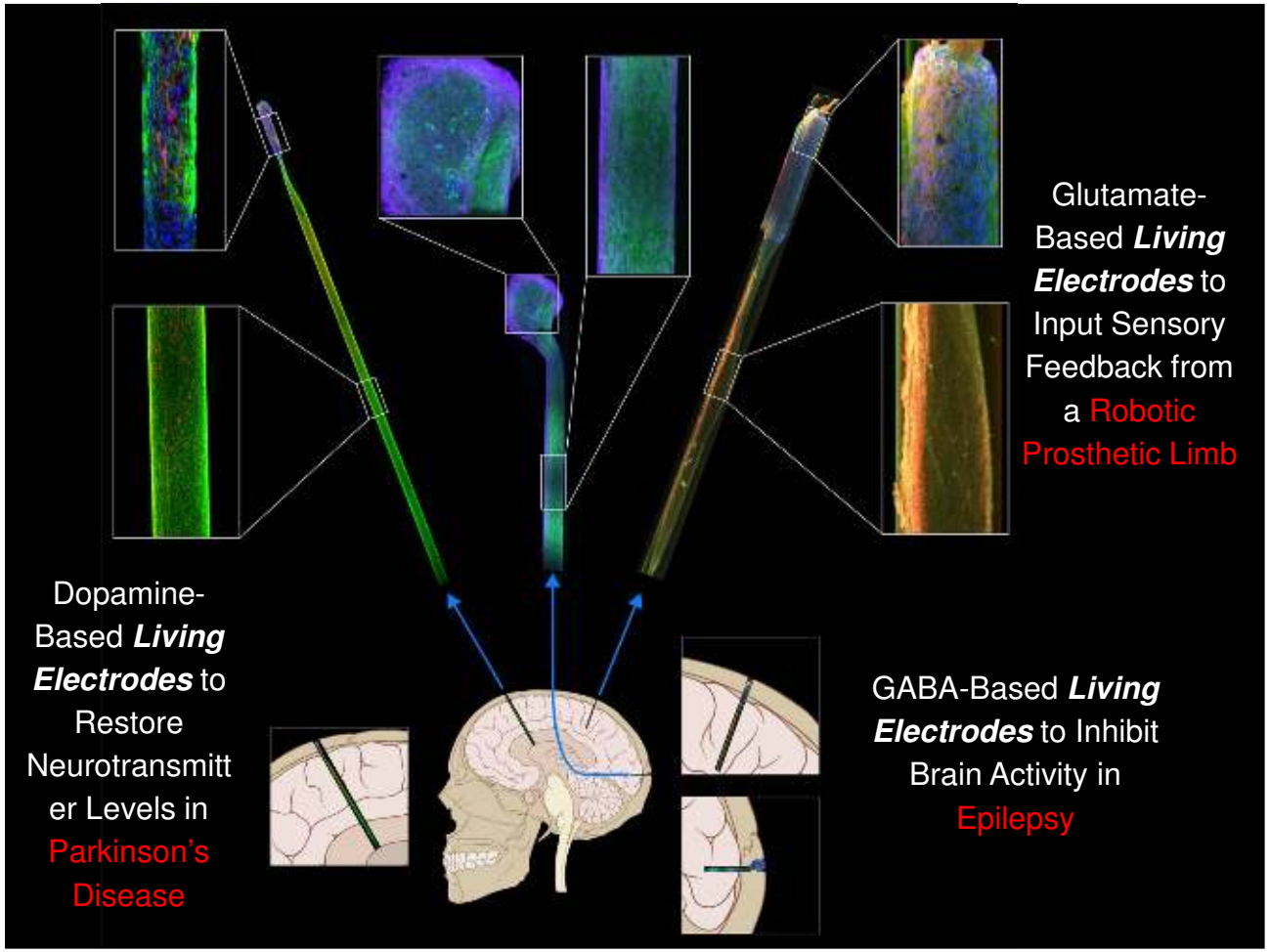
Electrically and Optically-Evoked Dopamine Release *In Vitro*

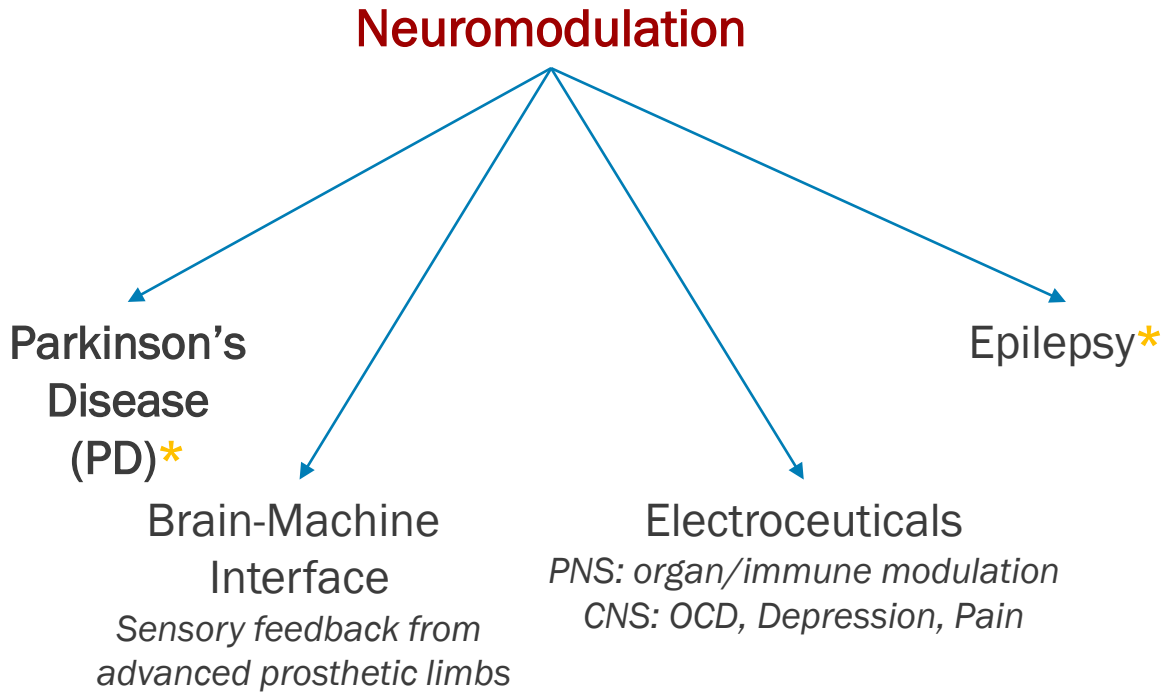


Tissue engineered brain pathways can be electrically or optically (if expressing ChR2) stimulated to measure evoked dopamine release – useful validation prior to implantation

Tissue Engineered Brain Pathways: Platforms, Opportunities & Mechanism of Action

Living Deep Brain Stimulation for Biologically-Mediated Neuromodulation





Biologically-based modulation of dysfunctional neural circuits

** Lead Programs*

Intellectual Property

All intellectual property (IP) is owned by the University of Pennsylvania

IP consists of patent applications (Dr. Cullen is lead inventor on all applications)

Applications

1. Engineering of Innervated Tissue and Modulation of Peripheral Organ Activity (**Cullen DK**, Das S, Gordian-Velez WJ), U.S. Provisional Patent App. 62/758,203 filed 11/9/2018
2. Implantable Living Electrodes and Methods for Use Thereof (**Cullen DK**, Harris JP, Wolf JA, Chen HI, Smith DH, Serruya M), U.S Provisional Patent App. 62/322,434; PCT Patent App. PCT/US2017/027705 (WO 2017/181068)
3. Methods of Promoting Nervous System Regeneration (**Cullen DK**), U.S. Patent App. 15/534,934; U.S Provisional Patent App. 62/091,245; PCT International Patent App. PCT/US2015/065353
4. Neuronal Replacement and Reestablishment of Axonal Connections (**Cullen DK**, Smith DH), U.S. Patent App. 15/032,677 (US 2016-0250385-A1); U.S Provisional Patent App. 61/899,517; PCT International Patent App. PCT/US2014/63720

Future Filings

1. Bio-Manufacturing of Tissue Engineered Brain Pathways, in preparation
2. Future Filings: we anticipate that investment will generate new IP, e.g., Hu DA pathway biofabrication methods, composition of matter, biomaterial containment, delivery tools & techniques, assessment methodology

Series A Financing: $ 12-15 MM will allow us to complete the following within 3 years (2021-2023)

Complete cGMP Process Development and Nonclinical Safety & Tolerability Studies

1. Establish cGMP process for manufacture of human brain pathways (24 months)
   - Have PreIND meeting with FDA
   - Secure supply chain for human tissue and biomaterial encasement
     - Several sources/partnerships for human tissue are available (partnership structure will have budget implications)
     - We have demonstrated the ability to create human tissue engineered brain pathways
   - Validate first generation cGMP process in Penn's facility suitable for Phase I/II Clinical Trials
2. Finalize nonclinical efficacy studies (36 months)
   - Complete short-term safety, tolerability & efficacy study in porcine model of PD using cGMP product
   - Complete study establishing surgical protocols, safety, tolerability, and efficacy of cGMP product in nonhuman primate model of PD
3. Draft Target Product Profile (TPP) and Clinical Development Plan (CDP) for PD (18 months)
   - TPP – Defines the minimal/ideal profile of the final marketed product and outlines the ultimate goals of the proposed development effort
   - CDP – Detailed plan, timeline and budget for clinical development and registration of product
     - ***Clear pathway through Phase 1 in PD***

This plan will allow for Series B Financing in 2023 followed by commencement of Phase I or I/II Clinical Trial

Why Invest in INNERVACE?

The company's lead product addresses a significant unmet medical need in PD

- Market estimated to be multi-billion in the US alone
- Our strong IP position and the product's novel mechanism of action enable us to be a dominant player

Provides investors with a platform technology and opportunity for significant returns

- Our paradigm shifting strategy to treat neurological injury and disease will translate into multiple high value product opportunities
- Our platform technology will be disruptive in the neurological device market, which was >$6.3 billion in 2016 alone and is growing at 5.2% per year (2009-2016)

There is opportunity, optimism, and funding in the Neuro space

- Due to a confluence of factors, there is significant interest in neuro-related treatments & technologies
- Opportunities for strategic partnerships and/or co-investments in human stem cells, biologics, devices, etc.

INNERVACE

The Company

University of Pennsylvania spinout

Initiated operations in May 2018

Program supported by NIH, VA, and MJFF (totaling over $3.7 million)

Core team of Cullen, Smith, Serruya, and Harris have been collaborating for 5+ years on technology and PD products

Getting to the Clinic

Execute on financing strategy

- Secure additional funding from the VA, NIH and MJFF
- Leverage non-dilutive funding toward Seed/Series A funding

Expand and build

- Recruit CMC, Quality, Clinical and Regulatory teams
- Expand IP portfolio
- Secure laboratory & office space in region
- Leverage Univ. of Pennsylvania capabilities and rich scientific infrastructure in Philadelphia (e.g., cGMP manufacturing space, clinical trial networks)

INNERVACE

Reconnecting the Nervous System

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Penn
University of Pennsylvania