SCRO Application Form

I. Investigator Information

Study Title:	Engineering and Transplantation of Human Serotonergic Neuron Organoids for Functional Integration and Neuromodulation in Animal Models	**SCRO record # *(office use only)*:**	
	Name	**Email**	**Phone**
Principal Investigator:	**C. Mera**	**merac@university.edu**	**(xxx) abc-1234**
Faculty position:	**Assistant Professor**		
Department:	**Biology**		
	Name	**Email:**	**Phone**
Contact Person if different from PI:			
Staff position:			
Department:			
***Mailing Address:**	**Mailing address TBD**		

*This address is the location where you would like signed materials delivered.

Please note: Your proposal may require other institutional compliance reviews. The SCRO office will work with applicable Compliance Offices (e.g., EH&S, IACUC, IRB) to facilitate concurrent reviews and will notify these Offices promptly of SCRO approval. Please note that the Principal Investigator is responsible for obtaining the required compliance approvals.

II. Proposed Study

Abstract - Describe the following in lay terms (250-word limit):

- *goals of the research,*
- *brief description of the approach,*
- *rationale for using human embryos, hESC or hiPSCs, complex embryo models, or brain or gonadal organoids.*
- *significance of the research for human health.*

Note: If the research has ended, please indicate closure of the study and provide a brief description of study results.

This study aims to develop a human stem cell-based platform for generating serotonergic neurons and evaluating their capacity to integrate into host brain circuits following transplantation. Using human induced pluripotent stem cells (hiPSCs), we will generate hindbrain-patterned organoids enriched for serotonergic neurons through controlled differentiation protocols. These cells will be transplanted into defined brain regions of rodent models relevant to mood and neuropsychiatric disorders.

Following differentiation into serotonergic neuron-enriched organoids, the grafts will be transplanted and allowed to mature in vivo for an extended period, typically on the order of several weeks to a few months (e.g., ~8–16 weeks), to enable neuronal maturation, projection development, and functional integration.

We will assess survival, maturation, and circuit integration using electrophysiology, imaging, and anatomical tracing. Functional output will be evaluated using activity-dependent reporters and pharmacological modulation, including inducible systems such as tamoxifen-dependent genetic switches to regulate neuronal activity.

We estimate using 60 animals in total for this initial study. Appropriate control groups will be included. These would consist of (i) sham-operated animals, and (ii) animals transplanted with control (e.g., non-serotonergic or undifferentiated) cell populations, to distinguish specific effects of the serotonergic grafts.

Behavioral assays will be used to determine whether grafted cells influence host behavior. The rationale for using human stem cell-derived neurons is that serotonergic systems exhibit species-specific developmental and functional properties that are not fully recapitulated in rodent models. Organoid based approaches enable controlled generation of defined neuronal populations and allow investigation of human-specific circuit properties in vivo.

This work has potential significance for developing cell-based therapies for neuropsychiatric disorders, including depression and anxiety, by establishing proof-of concept for generating, integrating, and functionally controlling human serotonergic neurons in living brain circuits.

Empty field.

III. Intended Research

Check all that apply and provide additional information where requested.

☐ Studies involving *in vitro* passage or differentiation of hESC lines. **Complete Appendix A**

☐ Studies that involve the destruction of human embryos in your lab or in another lab that is sharing cells or embryos with your lab for analysis. **Complete Appendix B**

☒ Transplantation of hESCs, hiPSCs, or cells derived from either, into non-human research animals. **Complete Appendix C**

☒ Generation of embryos, complex embryo models (e.g., blastoids, gastruloids, assembloids), brain organoids, or gametes from either hESCs or hiPSCs. **Complete Appendix D**

**Check with SCRO if your intended research is not captured in the above categories.*

IV. Additional Oversight

Complete the information for all other Oversight that may apply to the research described in this application.

Other Committees/Offices	**Oversight Office** *if known*	**Approval date** *(office use only)*
Environmental Health & Safety (EH&S)	BUA # TBD	
Institutional Animal Care and Use Committee (IACUC)	IACUC # TBD	
Institutional Review Board (IRB)	IRB # TBD	
Office of Technology Transfer	MTA # TBD	
Financial Conflict of Interest (FCOI) disclosure	# No COI	

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V. Conflict of Interest

Does the Principal Investigator, any co-investigator, or research coordinator involved with this study (or in aggregate with his/her spouse, dependents, or member of his/her household) have a financial relationship with the source of funding that requires filing out a Significant Financial Interest Disclosure (SFID) Form?

☐ ***Yes** ☒ **No**

** If **Yes**, SCRO will not approve the protocol until the relevant conflict-of-interest approvals have occurred.*

VI. Investigator Certification

I, the Principal Investigator:

a. am responsible for assuring that **all** personnel (researchers and staff) involved with this proposal understand and comply with the University's policies.
b. will participate in an annual update describing any significant changes in specific aims for this research.
c. will adhere to all University Oversight Office requirements that are applicable to this proposal.
d. certify that I have answered all questions on this document and its attachments truthfully.

VII. Principal Investigator Signature

Date:	Print Name: C. Mera _____
Signature:	C. Mera _____ **I am responsible for ensuring this research complies with the policies listed in the Investigator Certification and any other relevant guidelines from the University and Federal and State**

SCRO Office Use Only

SCRO record #: _____

SCRO review/approval type: New: ☒ Renewal # ☐ Closure: ☐
SCRO review/approval type: Full ☒ Administrative: ☐
SCRO agenda date

_____ _____
SCRO Committee Chair signature or designee SCRO Chair release date

SCRO approval from date: approval to date:

Copy sent to:
☒ IACUC ☒ EH&S ☒ IRB ☒ OTT ☒ FCOI ☐ School or College (write in name) _____

Date sent:
SCRO staff initials:

Appendix A
Studies involving in vitro passage or differentiation of hESC lines

Please provide the name(s) of the cell line(s) and source information (name of investigator and institution from which you received the cell lines). If you have derived the cell line(s) directly from specimens donated by a human donor, please write "donor" and the IRB protocol number.*

Name of cell line(s)	**Source**	**NIH hESC Registry # (if applicable)**

***For hESC research that is not currently eligible for federal funding:**

a) Append the approved consent-of-origin form if using hESCs not listed on the NIH Human Embryonic Stem Cell Registry. If the consent form is not available, please explain.

b) Explain your funding source.

Appendix B
Studies involving destruction of human embryos

Please provide the following information:

1. Describe:

   - Source and number of embryos that will be used.
   - Significant aspects of the methods, including how cells will be derived (if applicable).
   - Process for disposal of human tissues.

2. Scientific justification, including:

   - Reason for destroying embryos.
   - Where applicable, rationale for using particular genotypes.

Applicants must:

Append the approved original donor consent-of-origin form and consent for use of embryos for research.

Please note: IRB approval is required.

Appendix C

Transplantation of hESCs, hiPSCs, or cells derived from either, into non-human research animals

Please provide the following information:

1. Name(s) of the cell line(s) and source information (name of investigator and institution from which you received the cell lines). If you have derived the cell line(s) directly from specimens donated by a human donor, please write "donor" and the IRB protocol number.*

Name of cell line(s)	Source	NIH hESC Registry # (if applicable)
Human induced pluripotent stem cell (hiPSC) lines derived from 4 healthy donors	**Institutional stem cell core; IRB-approved protocols TBD**	**NA**

2. Species of research animal(s) used as recipient. *

   Immunodeficient rat models (nude rats).

3. Specific aims of research, brief description of methods, and endpoints of transplant studies.*

   The primary aim is to evaluate survival, maturation, and functional integration of human serotonergic neurons following transplantation. hiPSCs will be differentiated into serotonergic neuron-enriched organoids using hindbrain patterning factors, including SHH and FGF4/8 modulation. Cells will be transplanted into target regions such as the dorsal raphe or forebrain projection areas. Integration will be assessed using patch-clamp electrophysiology, calcium imaging, axonal projection tracing, and

immunohistochemistry for serotonergic markers including TPH2 and SERT. Functional modulation will be achieved using inducible genetic systems, including tamoxifen-activated Cre systems or chemogenetics. Behavioral endpoints may include assays relevant to mood regulation, such as open field and forced swim testing.

4. Scientific justification for transplanting hESCs or hiPSCs into research animals.

   Human serotonergic neurons exhibit developmental and functional properties that are not fully captured in rodent systems. Transplantation allows assessment of human-specific circuit integration and neuromodulatory function in vivo.

5. Address any ethical issues that these experiments might raise.

   All procedures will minimize animal suffering and follow IACUC guidelines. Human cells will be used under approved consent protocols. No germline transmission is expected or permitted.

***For hESC research that is not currently eligible for federal funding and if applicable, for hIPSCs you are proposing to use:**

a) Append the approved consent-of-origin form if using hESCs not listed on the NIH Human Embryonic Stem Cell Registry as well as for hIPSCs you are proposing to use. If the consent form is not available, please explain.

hiPSC lines will be obtained through IRB-approved institutional protocols. Consent-of-origin documentation and protocol identifiers will be provided when finalized; current protocol information is TBD.

b) Explain your funding source.

NIH – National Institute of Mental Health

Please note: IACUC approval is required.

Pending

Appendix D

Generation of embryos, complex embryo models (e.g., blastoids, gastruloids, assembloids), brain organoids, or gametes from either hESCs or hiPSCs.

Please describe:

1. Overall research goals.

   To generate human serotonergic neuron-enriched organoids for transplantation and circuit analysis.

2. Source of hESCs or hiPSCs that will be used.*

   hiPSC lines from institutional repositories under IRB-approved protocols.

3. Specific aims and brief description of methods.

   Directed differentiation toward hindbrain fate will be performed using defined morphogens, including SHH and WNT pathway modulation. Organoids will be cultured to promote serotonergic neuron specification and maturation prior to transplantation.

4. Scientific justification (for example, if generating an organoid model, briefly state what will be learned from an organoid model compared to a standard two-dimensional cell culture model). Explain any ways you will control or limit culture of embryos or gametes (i.e., prevention of allowing development to extend past legal or ethical limits; prevention of fertilization occurring between sperm and eggs).

   Organoids enable generation of human neuronal populations with developmental fidelity that is not achievable in standard two-dimensional culture. This approach supports analysis of human-specific serotonergic development and circuit integration. No embryos or gametes will be generated, and cultures will be limited in accordance with SCRO guidance and applicable ethical boundaries.

5. Address any ethical issues that these experiments might raise.
   Organoids will not be cultured beyond stages associated with sensory processing. No reproductive structures will be generated. All work will comply with SCRO guidelines.

*For hESC research that is not currently eligible for federal funding and if applicable, for hIPSCs you are proposing to use:

a) Append the approved consent-of-origin form if using hESCs not listed on the NIH Human Embryonic Stem Cell Registry as well as for hIPSCs you are proposing to use. If the consent form is not available, please explain.

b) Explain your funding source.

Please note: Other Oversight Office approval, such as IRB, IACUC, may be required.