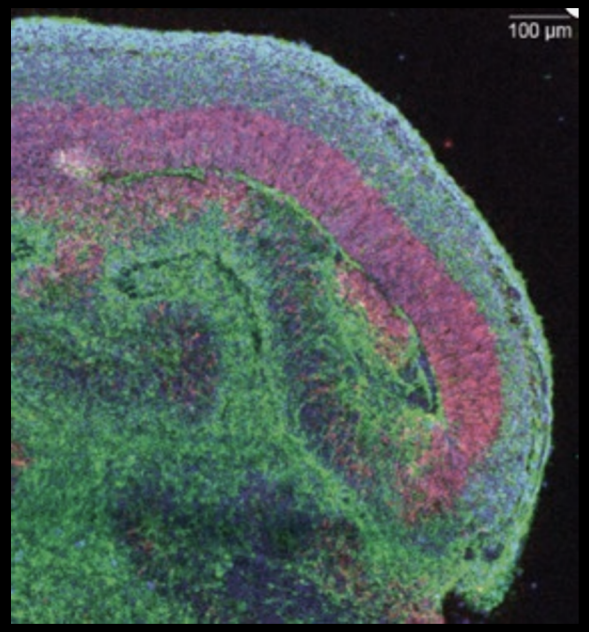


A brain organoid created from my cells?

Ethical challenges in human brain organoid research

Kate MacDuffie, PhD MA

Oregon Bioethics and Humanities Colloquium • Nov 8, 2021

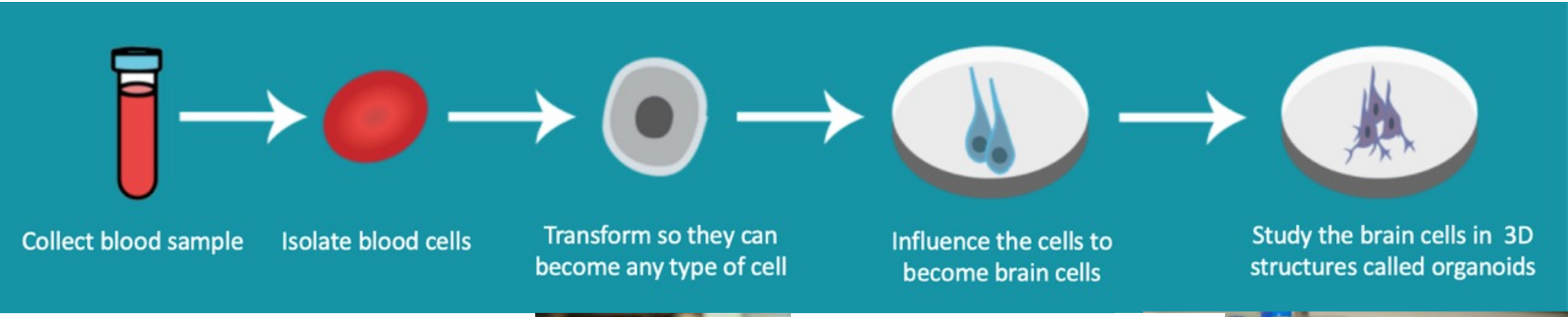
Post-doctoral research associate
University of Washington Autism Center
Seattle Children's Treuman Katz Center for Pediatric Bioethics

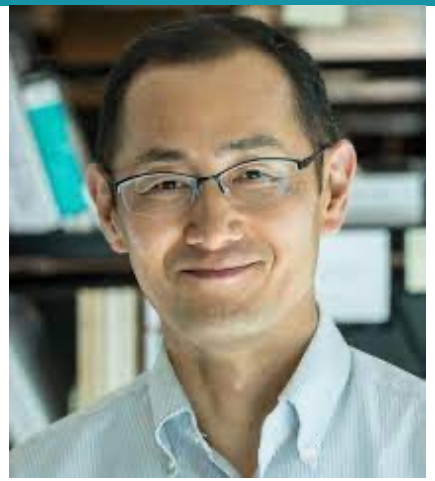
Agenda

1. Intro to human brain organoids
2. Anticipated ethical challenges
3. Informed consent of donors
4. Preview: donor attitude data

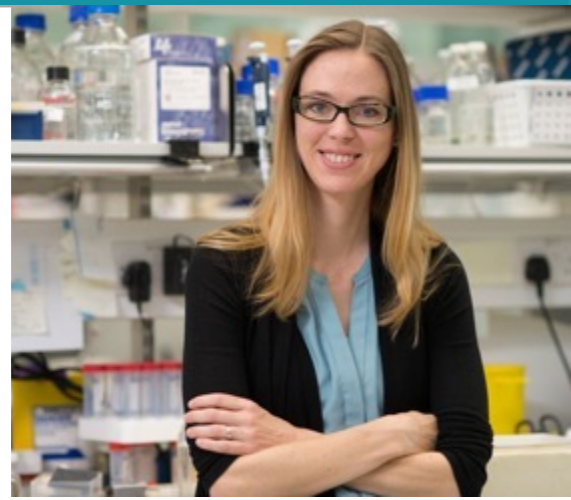
Quanta Magazine
Title slide photos: Lancaster Lab, BBC

Building a human brain organoid



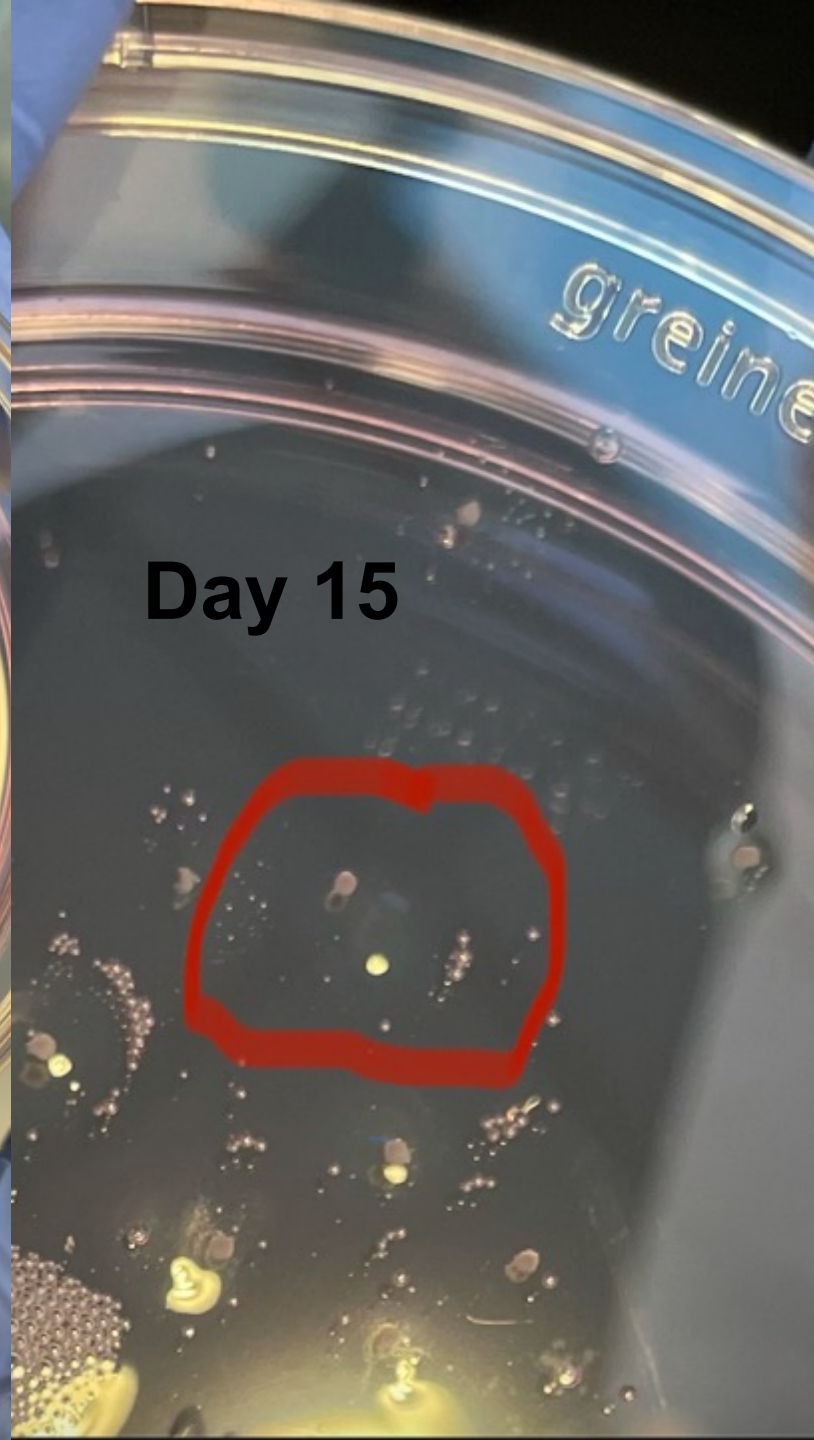


Shinya Yamanaka
2006: induced pluripotent stem cells (iPSCs)
2007: human iPSCs



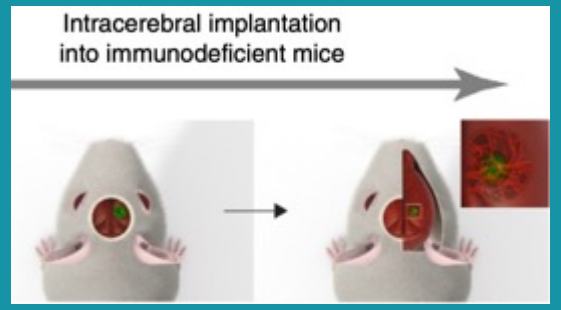
Madeline Lancaster
2013: human brain organoids

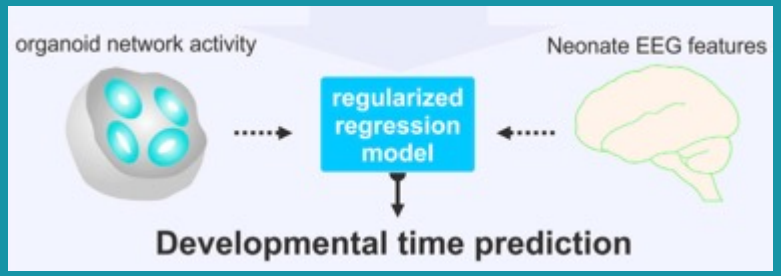
Many thanks to Kira Evitts and the Young lab at the University of Washington!



and to Rose Glass and the Stein lab at the University of North Carolina, Chapel Hill!

Ethically-relevant advances in organoid science





Abed AlFatah Mansour
2018: Demonstrated vascularization and functional synaptic activity between transplanted human brain organoid and adult mouse host

Cleber Trujillo
2019: Organoid oscillatory activity mimics patterns seen in premature infant brain

Alysson Muotri
2019: Brain organoids in space

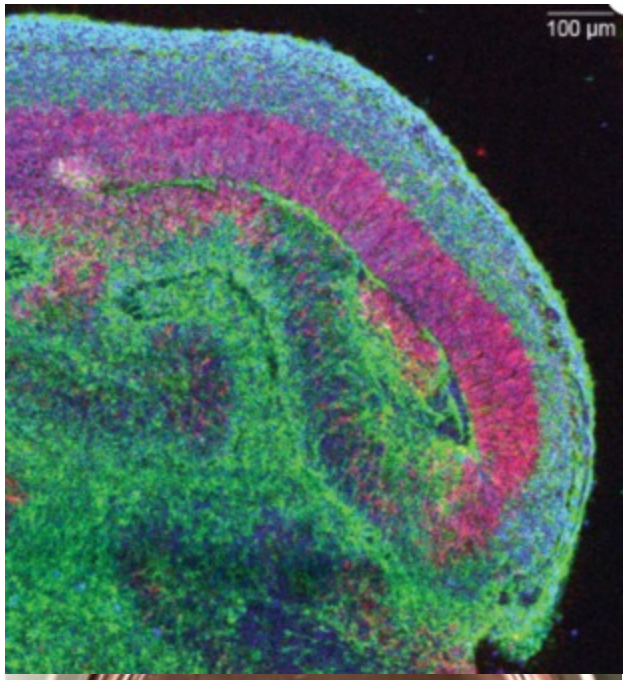
Why organoids?

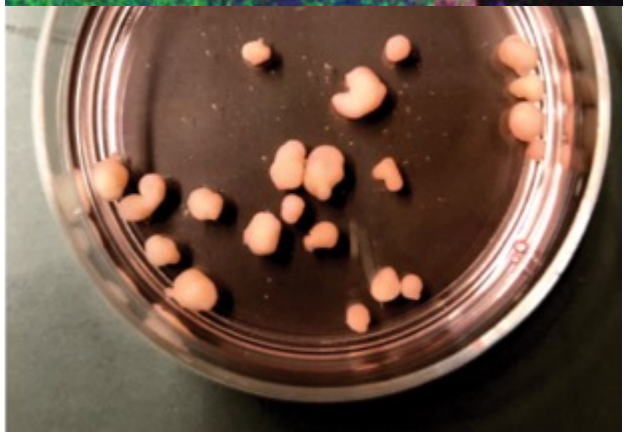
Advantages

- Self organize to recapitulate aspects of human cortical development
- Advance knowledge of human developmental processes that are difficult or impossible to model in animals
- Provide a platform for testing treatments (gene editing or pharmacologic)
- Have potential to advance precision medicine

Disadvantages

- Not perfectly reproducible; protocols differ across labs
- Limits on growth without vascularization (~4mm)
- Limits on cell types represented (lack endothelial cells, microglia)
- (So far) have not created organized structural nodes with white matter connections between them.





Brain organoids in the ethical spotlight

Simplified 3D brain organoids can be grown in a dish using human stem cells as the starting material.

The ethics of experimenting with human brain tissue

Difficult questions will be raised as models of the human brain get closer to replicating its functions, explain **Nita A. Farahany**, **Henry T. Greely** and 15 colleagues.

26 APRIL 2018 | VOL 556 | NATURE | 431

RESEARCH *Science* **355**, 260 (2017) 20 January 2017

REVIEW SUMMARY

ORGANOIDS

Human tissues in a dish: The research and ethical implications of organoid technology

Annelien L. Bredenoord, Hans Clevers, Juergen A. Knoblich*

THE AMERICAN JOURNAL OF BIOETHICS
2020, VOL. 21, NO. 1, 34–45
https://doi.org/10.1080/15265161.2020.1845853

TARGET ARTICLE

Human Brain Surrogates Research: The Onrushing Ethical Dilemma

Henry T. Greely

Stanford Law School

The role of ethics in brain organoid research

Ethicists can:

- ❑ Identify and raise awareness of ethical challenges
- ❑ Alert scientists to relevant guidelines or scholarship
- ❑ Provide normative judgements and deliberate about appropriate courses of action
- ❑ Anticipate societal impacts
- ❑ Conduct empirical bioethics research to inform an anticipatory and constructively guiding approach

Identifying ethical challenges

Capacity for consciousness

Humanization of animal models

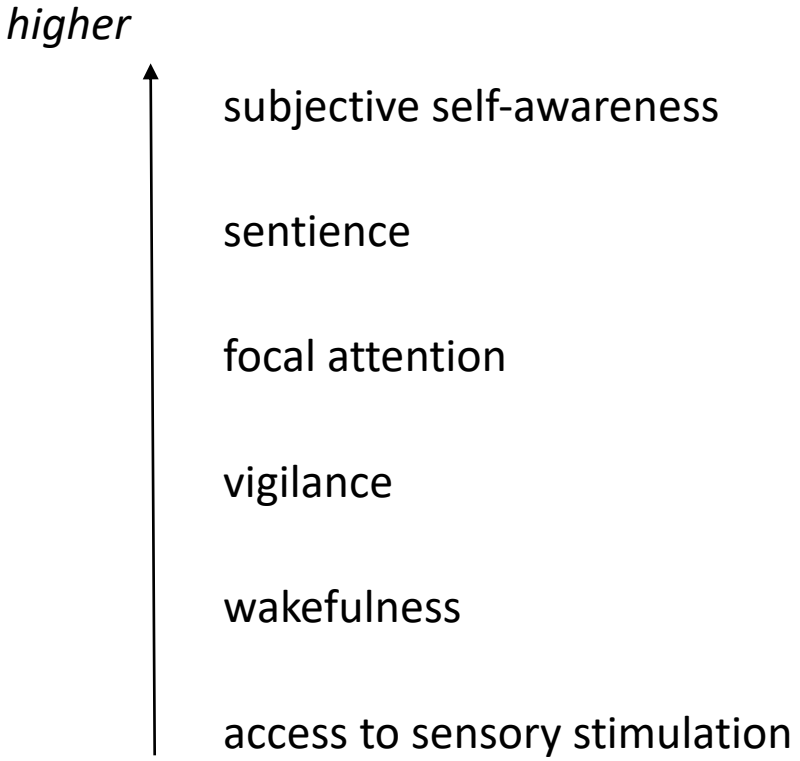
Procurement of biospecimens

Identifying ethical challenges

Capacity for consciousness

Humanization of animal models

Procurement of biospecimens



"Brain organoids lack the complex network structure, the full complement of cell types, and the sensory inputs necessary to give rise to any discernable subjective experiences."

Hyun et al, *Brain Research,* 2020

Identifying ethical challenges

Capacity for consciousness

Humanization of animal models

Procurement of biospecimens

"We can treat brain organoids according to existing regulatory frameworks for stem cell research until the point at which organoids develop consciousness, but we should restrict the kinds of research that can take place beyond this point."

Table 1

Proposed research limits

Equivalent stage of human *in vivo* brain development	Research restrictions
Non-conscious brain organoids (e.g., equivalent to fewer than 20 weeks' *in vivo* brain development)	Research should be regulated according to existing frameworks for stem cell and human biospecimen research
Conscious or potentially conscious brain organoids (e.g., equivalent to 20 weeks' *in vivo* brain development or more)	In addition to the above constraints, research should be subject to the following restrictions: 1. The expected benefits of the research must be sufficiently great to justify the moral costs, including potential harms to brain organoids. 2. Conscious brain organoids should be used only if the goals of the research cannot be met using non-sentient material. 3. The minimum possible number of brain organoids should be used, compatible with achieving the goals of the research. 4. Conscious brain organoids should not have greater potential for suffering than is necessary to achieve the goals of the research. 5. Conscious brain organoids must not experience greater harm than is necessary to achieve the goals of the research. 6. Brain organoids should not be made to experience severe long-term harm unless necessary to achieve some critically important purpose.

Koplin & Savulescu, *Journal of Law, Medicine and Ethics,* 2019

Identifying ethical challenges

Capacity for consciousness

Chimera: introduction of human cells into other animal species

Humanization of animal models

Moral status

- Does the presence of any human element automatically confer moral status?
- Do only entities capable of making rational, conscious choice possess moral value?

Brain enhancement potential

- No evidence of enhancement yet exists
- Could require greater welfare protections (minimize pain and suffering, enriched environment)

Procurement of biospecimens

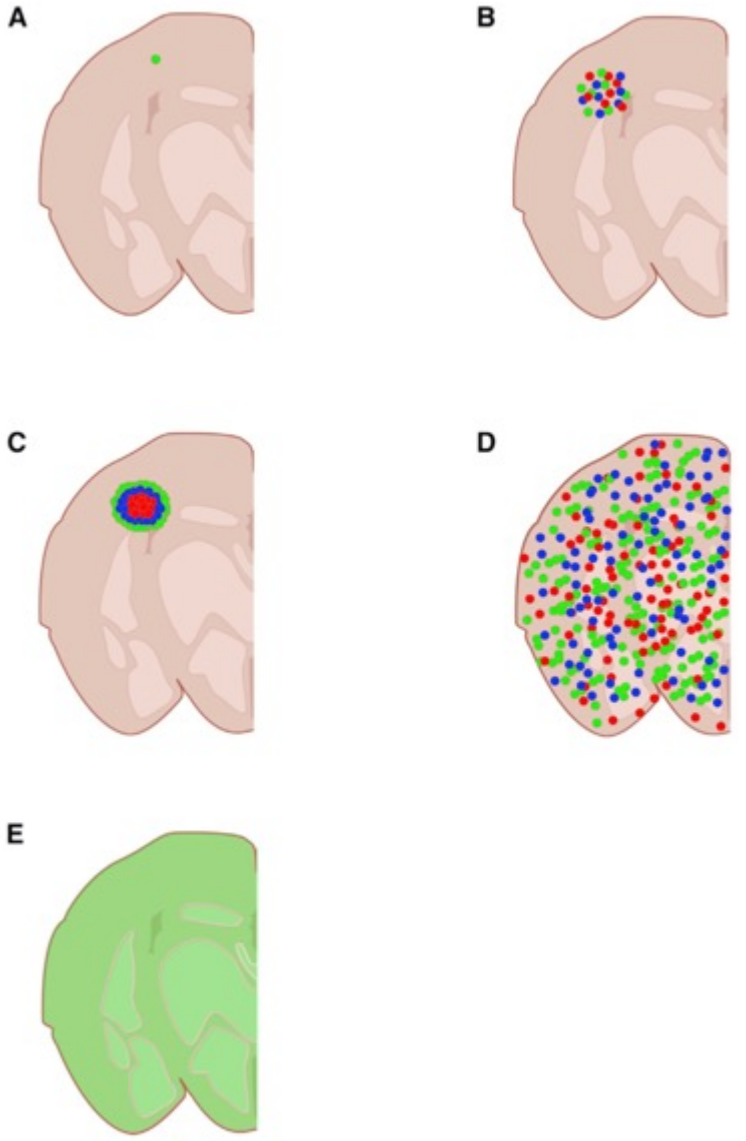


Figure 1. Spectrum of Human-Animal Brain Chimeras

Chen et al. *Cell Stem Cell*, 2020

Identifying ethical challenges

Capacity for consciousness

Humanization of animal models

Procurement of biospecimens

- What are the risks and benefits to biospecimen donors?
- What should informed consent look like for brain organoid research?

Broad consent for biospecimen donation

Less burden, less control	Type of consent	Description
	No consent	Do not obtain donor consent
	Blanket	Consent to future research with no limitations
	Broad*	Consent to future research with specified limitations
	Checklist	Donors choose which types of future studies allowed
More burden, more control	Study specific	Consent for each specific future study

Grady et al., 2015

Future Use Statement
All personal identifiers will be removed from cells collected, and after such removal, the cells may be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative. The data you contribute may continue to benefit the scientific community in the future.

Is broad consent sufficient?

	Explain iPSCs	Explain organoids	Return of results	Future studies	Storage described	Shared with others	End of study
Form 1	Yes	No	No	Yes, not specified	Yes	Yes	Not described
Form 2	Yes	No	Optional	Yes, not specified	No	Yes	Not described
Form 3	No	No	Optional	Yes, not specified	Yes	Yes	Not described
Form 4	Yes	No	Optional	Yes, not specified	No	Yes	Not described

Purpose of informed consent for iPSC research (Lowenthal et al., 2012)
"to provide sufficient baseline information that enables potential participants to decide whether to give permission for iPSC research to proceed with their specimens."

Functions of informed consent (Dickert et al., *AJOB*, 2017)

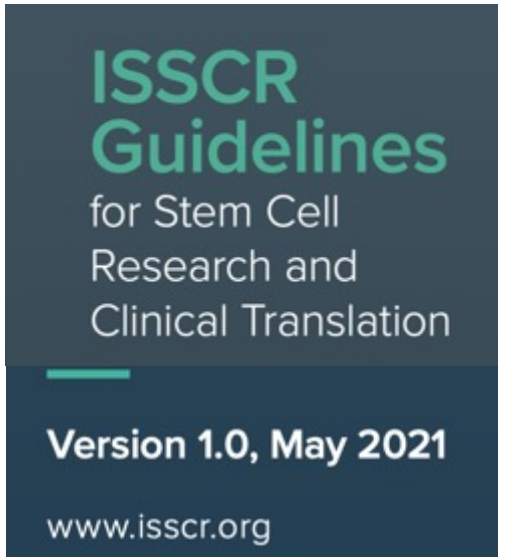
1. Providing transparency
2. Allowing control and authorization
3. Promoting concordance with participant's values

Gaps in current informed consent policy

- **Clinical samples:** In many healthcare settings, leftover (de-id)clinical samples can be used for research without consent (Munsie et al., 2017)
- **Existing samples:** Prior donors to biobanks/tissue banks did not consent to use of samples for brain organoid research (Hyun et al., 2020)
- **Regulatory vacuum:** De-id tissues and cell lines are not considered human subjects research (Common Rule, ISSCR, NAS consensus report, 2021)

TABLE 4-1 Oversight of Research Based on the Use of Human Stem Cells

Type of Research	Common Rule (federal regulations for research funded by U.S. government)	National Institutes of Health (NIH) Guidelines for Human Stem Cell Research (funding requirement)	Nonbinding Guidance
Research using human induced pluripotent stem cells (iPSCs) from deidentified donor cells (e.g., from a biobank)	Exempt from institutional review boards (IRB) review if cells are appropriately deidentified	N/A	Exempt from Embryonic Stem Cell Research Oversight (ESCRO) committee review (NRC and IOM, 2010) Exempt from Embryonic Research Oversight (EMRO) review (ISSCR, 2016)
Research using human iPSCs from identifiable donor cells	IRB oversight to determine appropriate informed consent (including broad consent or waiver of consent), confidentiality, etc.	N/A	IRB review should determine that informed consent includes the possibility of use in animals (NRC and IOM, 2010, ISSCR, 2016)



CATEGORY 1

1A

Exempt from review by a specialized oversight process

- Most *in vitro* pluripotent stem cell research
- Most *in vitro* organoid research
- Transfer of human stem cells into postnatal animal hosts

Proposed solutions

Consent for governance

Donors should consent to contributing to an infrastructure that is subject to certain governance conditions (Boers & Bredenoord, 2018)

- management of data and samples
- property rights and commercial interests
- ongoing communication with donors
- ethical oversight of future research uses

Henrietta Lacks biospecimen consent policy

"A genuine culture of respect for research participants demands that they be asked to agree to the use of their biospecimens, regardless of identifiability." (Wolinetz & Collins, *JAMA*, 2020)

Sustained interaction with participants

- Reconsent for future research, disclosing individual results, soliciting updated health information, ensuring continued consent from pediatric patients (Lowenthal, 2012)
- Allows for withdrawal of samples (Grady et al., 2015)
- Fulfills social contract with participants; increases trust (Purvis et al, 2017)

The role of ethics in brain organoid research

Science & Society

OPEN ACCESS

EMBO reports

Real-time ethics engagement in biomedical research

Ethics from bench to bedside

Jeremy Sugarman[1] & Annelien L Bredenoord[2]

DOI 10.15252/embr.201949919 | EMBO Reports (2020) 21: e49919 | Published online 15 January 2020

Ethicists can:

- ☑ Identify and raise awareness of ethical challenges
- ☑ Alert scientists to relevant guidelines or scholarship
- ☑ Provide normative judgements and deliberate about appropriate courses of action
- ☑ Anticipate societal impacts
- ☐ Conduct empirical bioethics research to inform an anticipatory and constructively guiding approach

Perspectives of prospective and current donors

Aim 1: Semi-structured qualitative interviews

Aim 2: Quantitative survey

NEURODEGENERATIVE DISEASE

NEURODEVELOPMENTAL DISORDERS

NIH National Institute of Mental Health

NIH The BRAIN Initiative®

Interviews with prospective and current donors

NEURODEGENERATIVE DISEASE

Potential Donors

Familial AD risk and MCI

Eran Klein, MD, PhD
OHSU & UW

Donors

Genetic dementia risk

Suman Jayadev, MD
UW

NEURODEVELOPMENTAL DISORDERS

Potential Donors

Autistic adults

TBD

Donors

Joubert syndrome (parents)

Dan Doherty, MD, PhD
UW

Autism (parents)

Jason Stein, PhD
& IBIS network

IBIS

Interview guide

- Reasons for participating in research
- [brain organoid intro]

- Initial impressions
- Out of scope uses: different diseases, chimeras
- Discretion of donor/surrogate
- Recontact if change in scope
- Child's role when turns 18 *or* Continued use after death

- Commercial use
- Ownership
- Relationship/feelings towards brain organoid
- Brain vs. other organoid types

- Return of results (general and individual)
- Privacy/de-identification

Teaser quote

“I think that, especially when we were first diagnosed, and you're desperate for information, and just feel super helpless, you know, communication, like any shred of hope you can get are really, really important.

So I think, especially for newly diagnosed families who are participating in the research, like, it's really important to have communication, and just any type of, you know, feedback and things like that really help families

…these new families are important for the research.”

- Joubert parent

Acknowledgements

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Research assistant (UW)
Katie Emmons

Research assistant (OHSU)
Emily Lehman

Layton Aging and Alzheimer's Disease Research Center

National Institute of Mental Health

The BRAIN Initiative®