
STEM CELL-BASED MEDICINE

MIKE McCONNELL, Ph.D.

ASSISTANT PROFESSOR

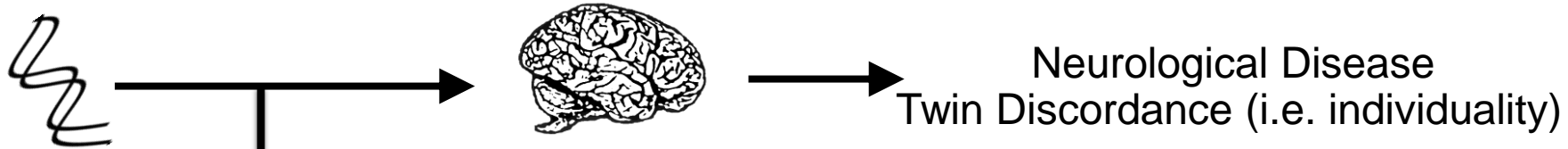
DEPARTMENT of BIOCHEMISTRY *and* MOLECULAR GENETICS

UNIVERSITY of VIRGINIA

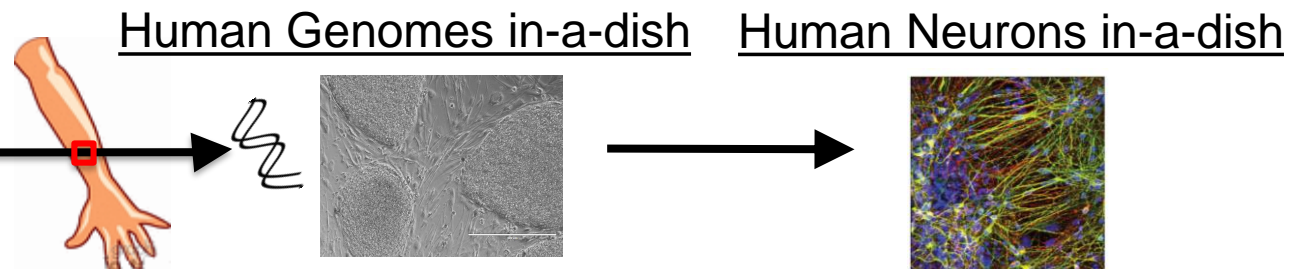
SCHOOL of MEDICINE

mikemc@virginia.edu

How do human genomes encode human brains?

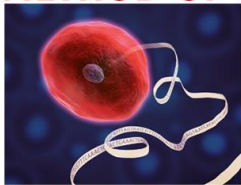


Human induced Pluripotent Stem Cells



Single Cell Genomics

METHOD OF THE YEAR

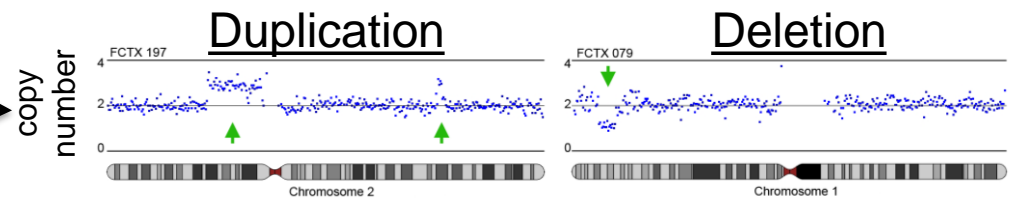


"We are just beginning to understand the molecular diversity of cells in the brain," says Thomas Insel, director of the US National Institute of Mental Health. "Single-cell methods will be critical, not only for defining the taxonomy of neurons and glia but for revealing the effects of experience or development on profiles of expression within a brain region."

© 2013, single-cell sequencing methods made their way to the mainstream.

NATURE METHODS | VOL.11 NO.1 | JANUARY 2014 | 13

Mosaic Copy Number Variation in Human Neurons

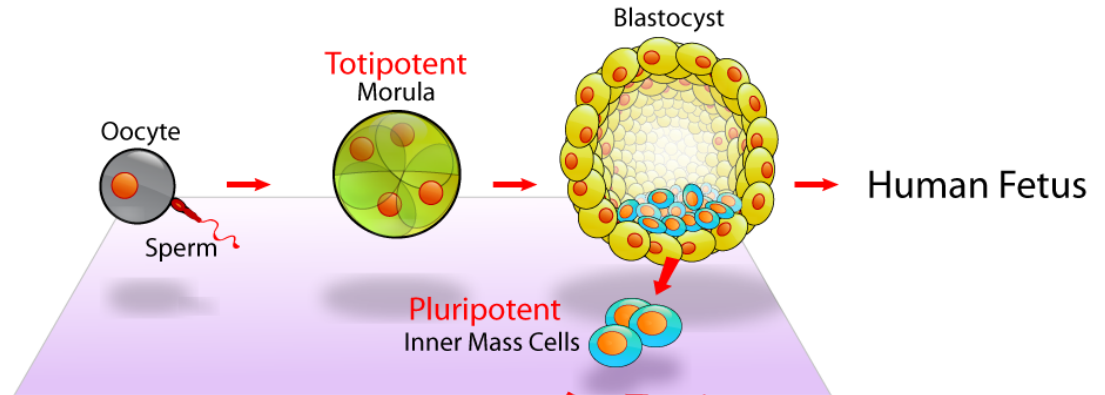


McConnell, et al. (2013) *Science*

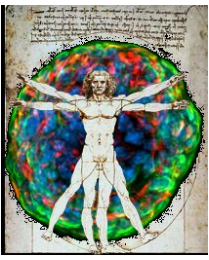
Embryonic Stem Cells (hESCs)



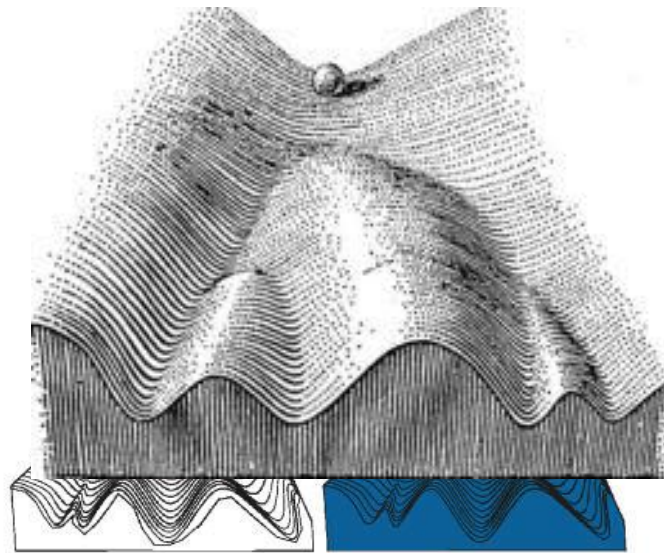
- exist only at the earliest stages of embryonic development.
- In humans, these cells no longer exist after about five days of development.
- When grown in a lab dish these hESCs can continue dividing indefinitely.
- James Thomson, a professor of Anatomy at the University of Wisconsin, isolated and first propagated hESCs in 1998.



Restricted Fate Potential during Development

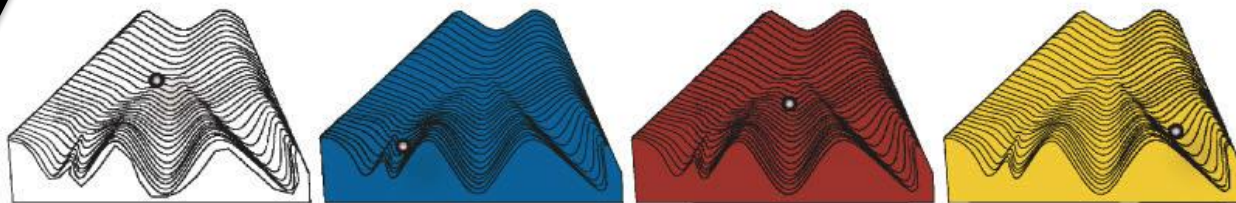


Waddington (1942)
“epigenetic landscape”



Cell

Tissue



Organ



Induced Pluripotent Stem Cells (iPSCs) *Reprogramming Adult Cells*

Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi¹ and Shinya Yamanaka^{1,2,*}

¹ Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan

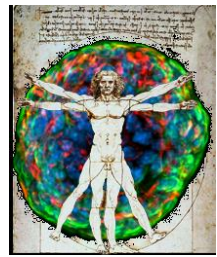
² CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan

*Contact: yamanaka@frontier.kyoto-u.ac.jp

DOI 10.1016/j.cell.2006.07.024

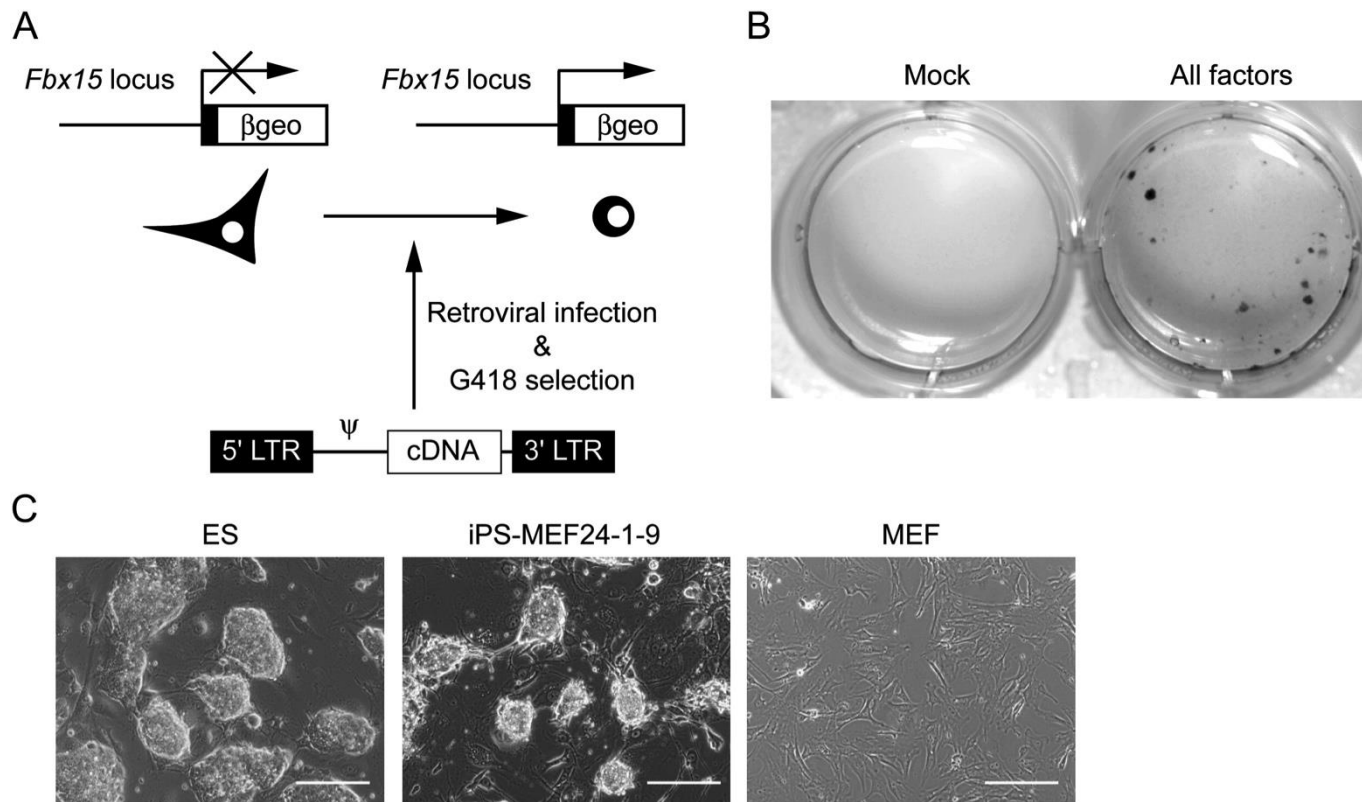
Candidate Pluripotency factors:

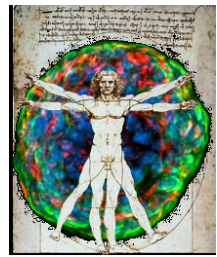
Ecat1	Sox15	Utf1
Dppa5	Dppa4	Tel1
Fbxo15	Dppa2	Dppa3
Nanog	Fthl17	Klf4
ERas	Sall4	B-catenin
Dnmt3l	Oct3/4	c-Myc
Ecat8	Sox2	Stat3
Gdf3	Rex1	Grb2



Induced Pluripotent Stem Cells (iPSCs)

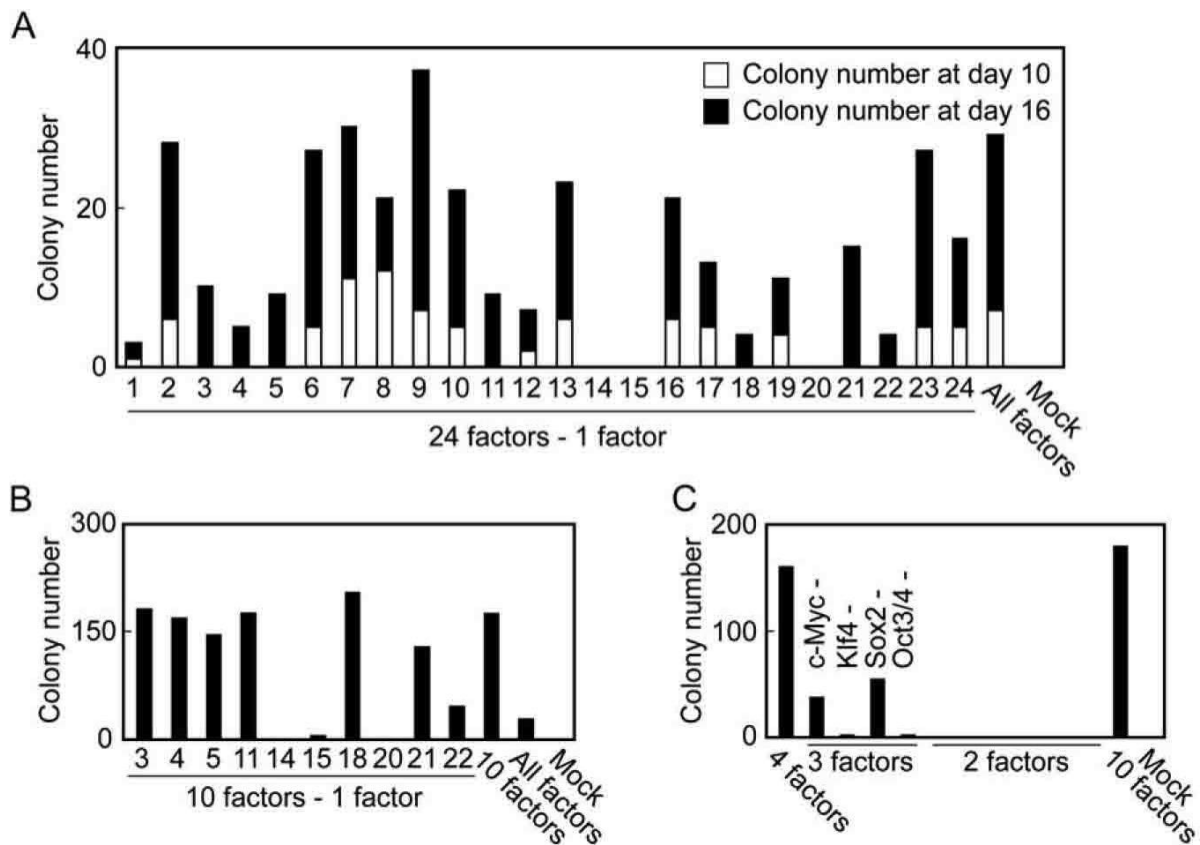
All 24 factors together can reprogram fibroblasts

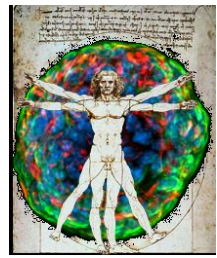




Induced Pluripotent Stem Cells (iPSCs)

Subtraction Experiments to Find Minimal Combination of Factors





Induced Pluripotent Stem Cells (iPSCs)

Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Kazutoshi Takahashi,¹ Koji Tanabe,¹ Mari Ohnuki,¹ Megumi Narita,^{1,2} Tomoko Ichisaka,^{1,2} Kiichiro Tomoda,³ and Shinya Yamanaka^{1,2,3,4,*}

¹Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan

²CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan

³Gladstone Institute of Cardiovascular Disease, San Francisco, CA 94158, USA

⁴Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8507, Japan

*Correspondence: yamanaka@frontier.kyoto-u.ac.jp

DOI 10.1016/j.cell.2007.11.019

Yamanka four factors (OKSM)

Oct4

Klf4

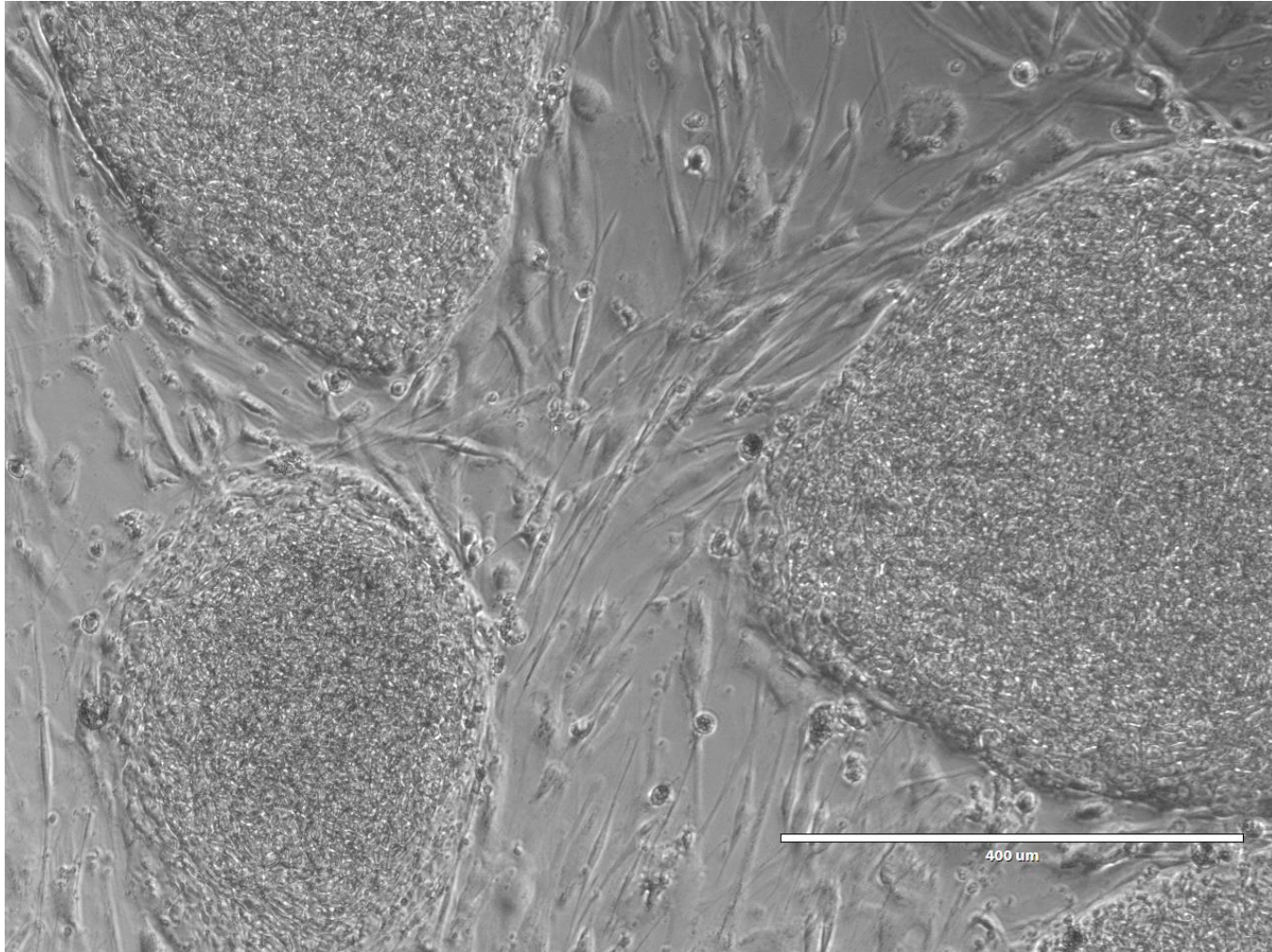
Sox2

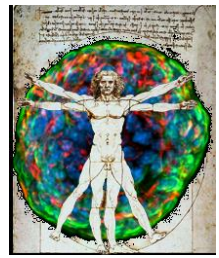
c-Myc





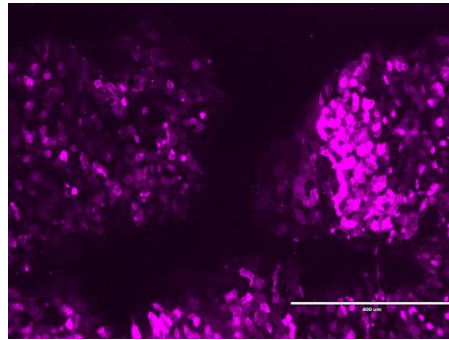
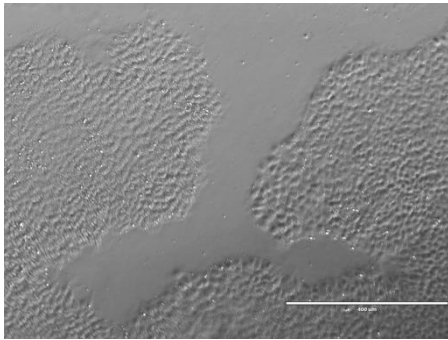
hiPSCs



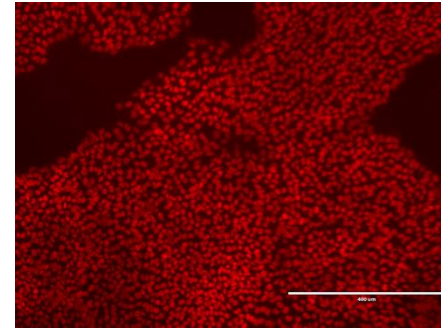
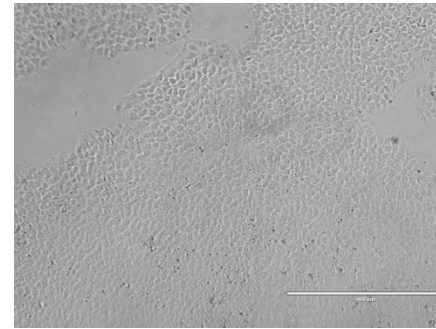


hiPSCs

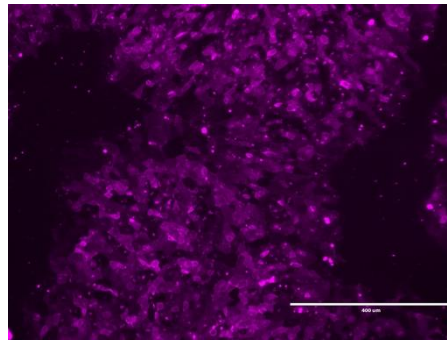
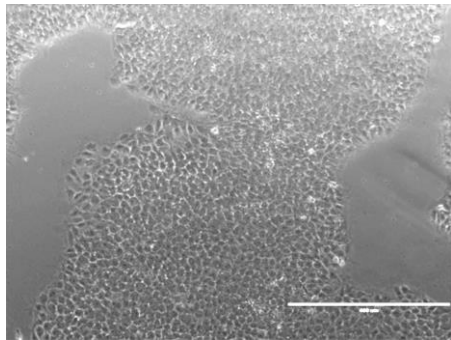
TRA-1-60



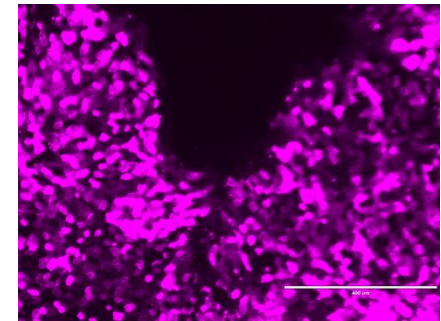
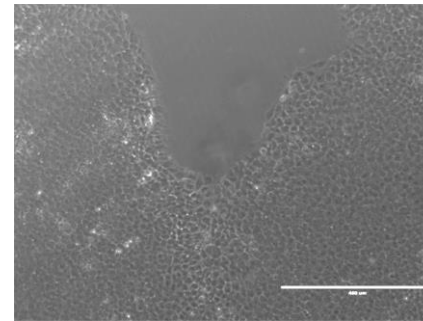
OCT4



SSEA4



TRA-1-81

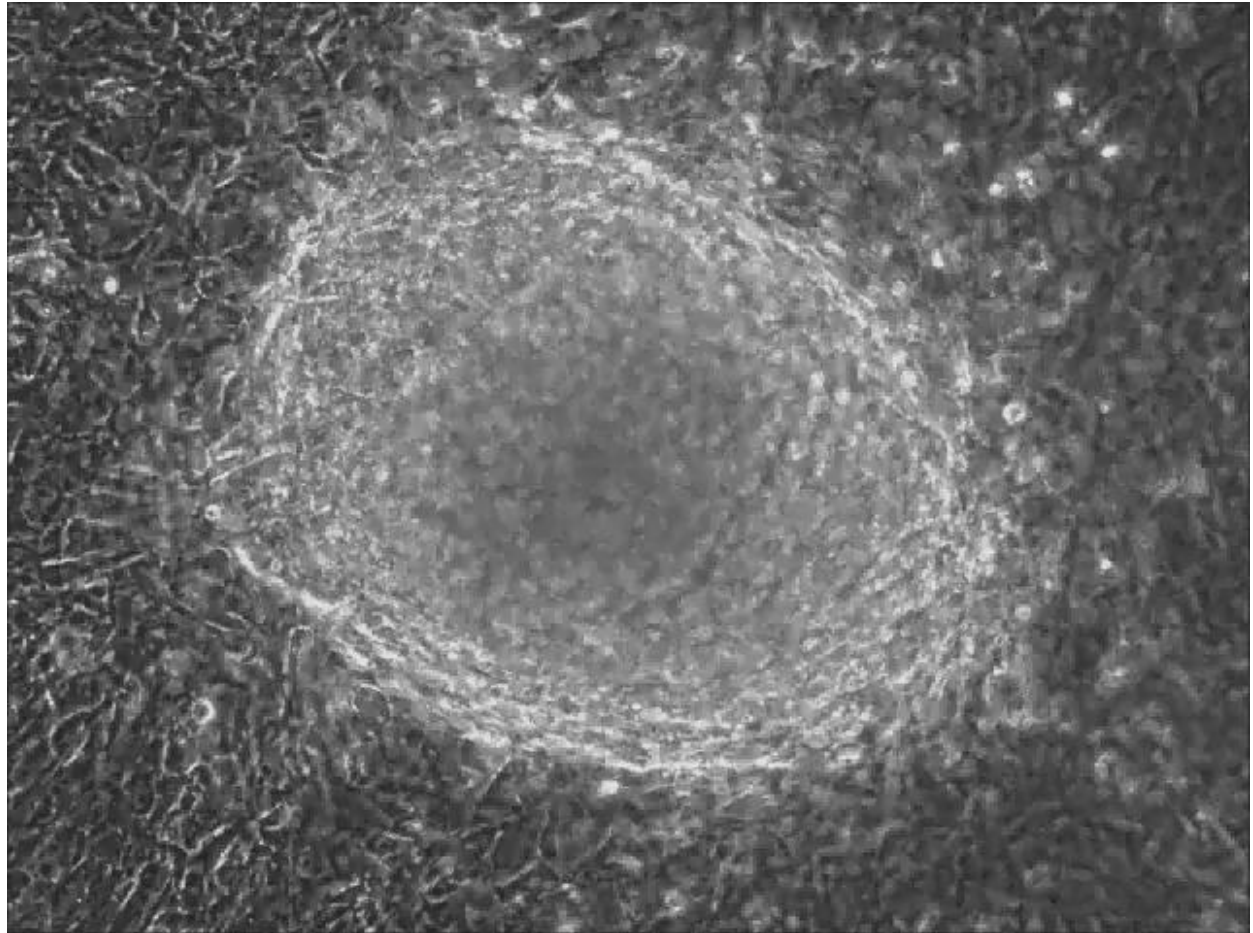


hiPSC-derived cardiomyocytes



Cardiomyocytes

In-A-Dish!



hiPSC-derived cardiomyocytes

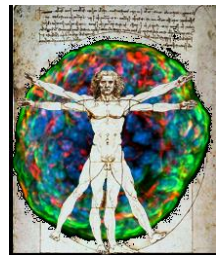


Cardiomyocytes

In-A-Dish!

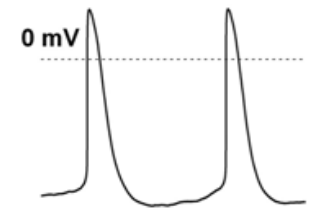
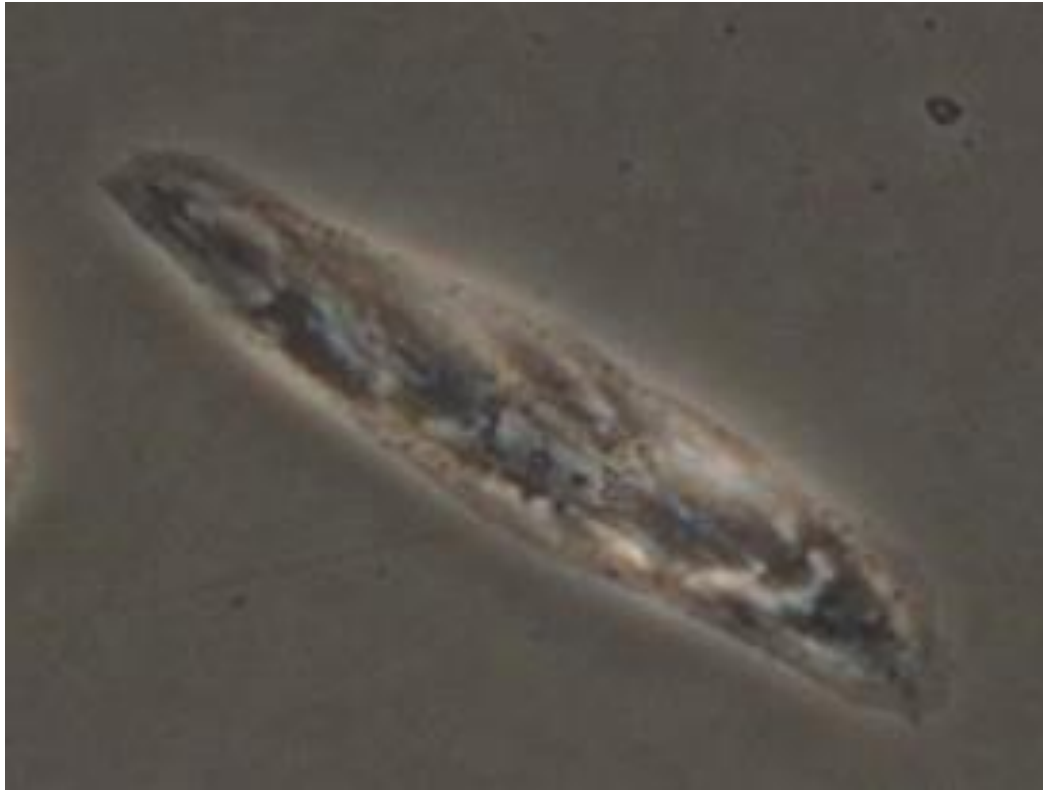


hiPSC-derived cardiomyocytes

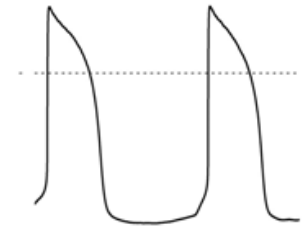


Cardiomyocytes

In-A-Dish!



Atrial-like



Ventricular-like

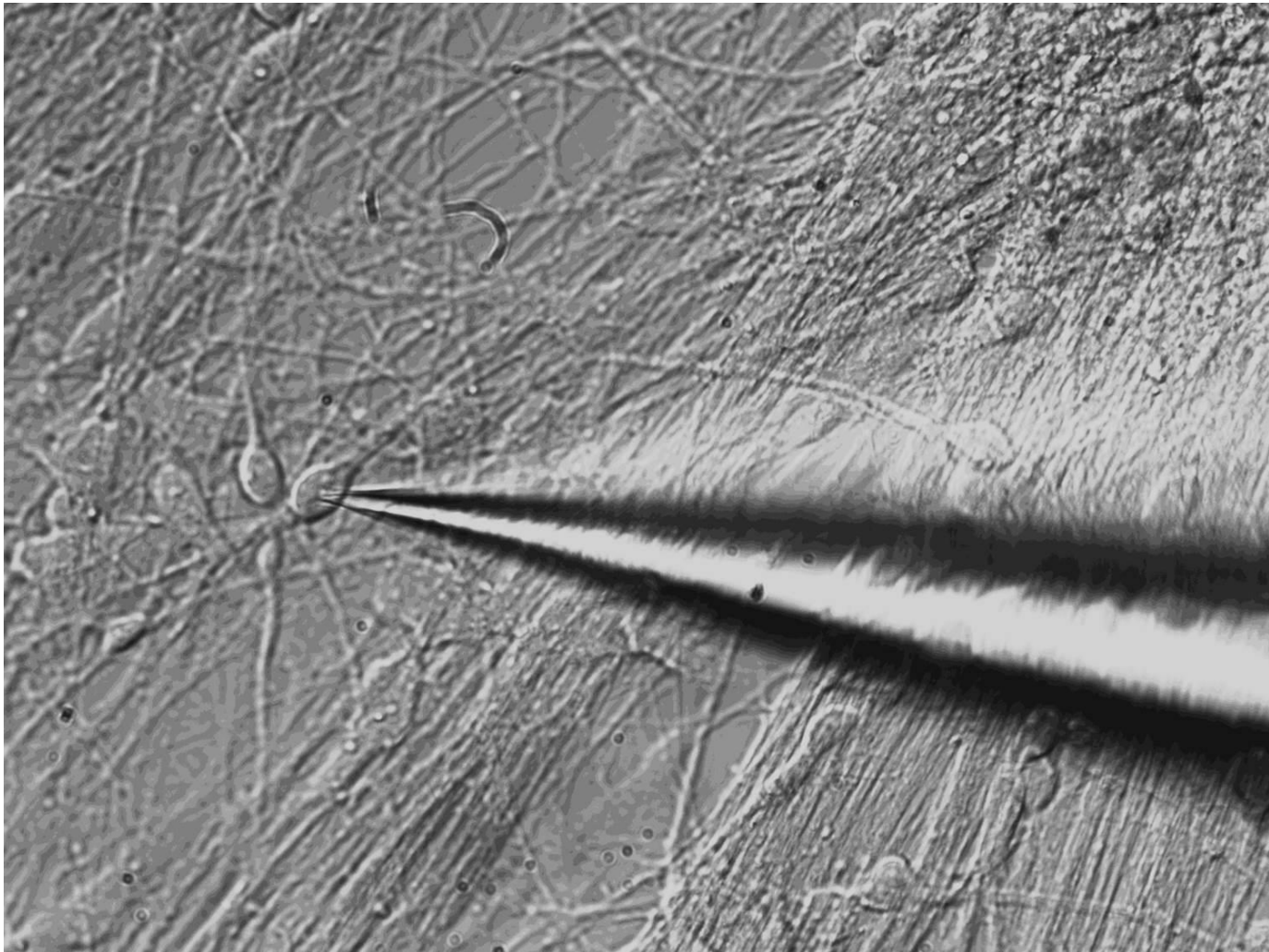
20 mV
400 msec

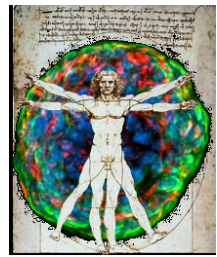
Uosaki, et al. (2011) PLoS ONE.

Ma J et al. (2011) Am J Physiol Heart Circ Physiol.

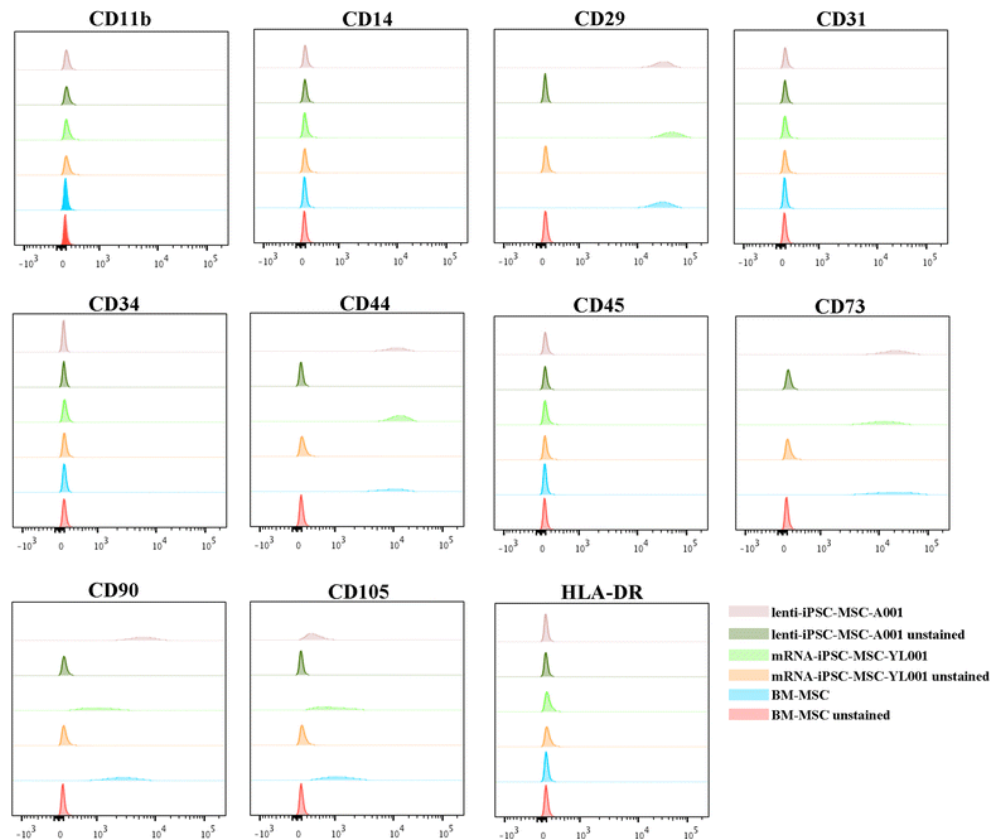


hiPSC-derived Neurons



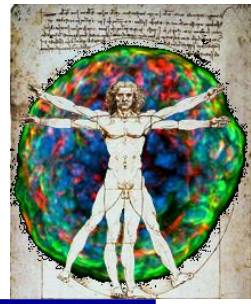


hiPSC-derived MSCs



MSC Markers	CD11b	CD14	CD29	CD31	CD34	CD44	CD45	CD73	CD90	CD105	HLA-DR
BM-MSC	-	-	+	-	-	+	-	+	+	+	-
lenti-iPSC-MSC-A001	0.08	0.18	99.79	0	0	99.12	0.34	98.77	97.88	98.22	0.75
mRNA-iPSC-MSC-YL001	0.12	0.23	99.22	0.27	0	97.34	0.28	98.72	98.15	85.64	0
mRNA-iPSC-MSC-YL001	0.42	0	95.56	0.11	1.02	96.07	0.2	94.22	89.18	87.47	0

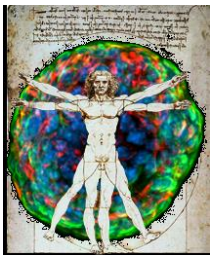
The University of Virginia Stem Cell Core Facility



- 1) Provide control hiPSCs and CRISPR-derived isogenic lines.
- 1) Provide hiPSC-derived lineages (NPCs, Neurons, Cardiomyocytes, others).
- 2) Provide hands-on training in hiPSC culture for students, post-docs, others.
- 1) Provide project-based support for generation of patient-derived hiPSC lines.
- 1) Stem Cells and Regeneration Seminar Series.

Director: Araz Toumadje
ph. 434.297.5302
at5kh@virginia.edu

hiPSC-based Medicine



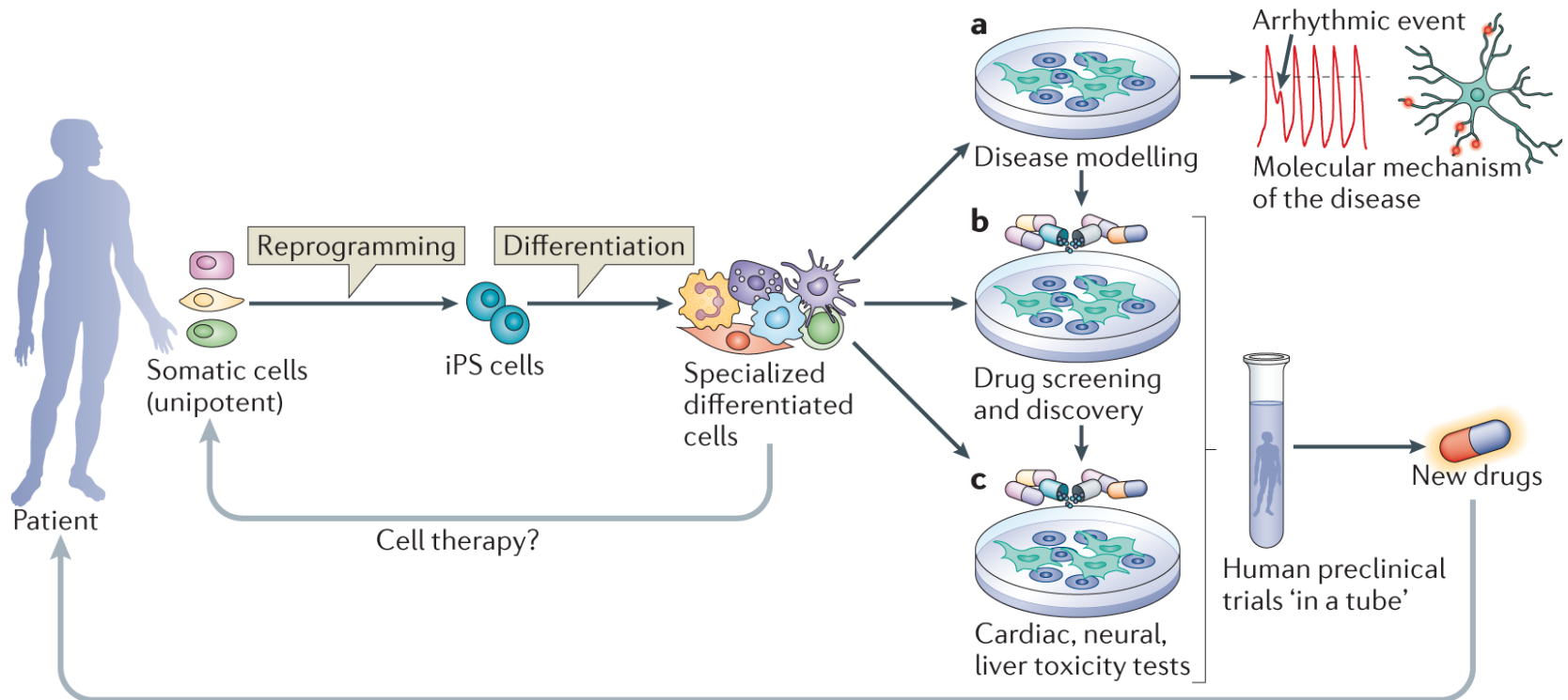
Induced pluripotent stem cells: the new patient?

Milena Bellin¹, Maria C. Marchetto², Fred H. Gage² and Christine L. Mummery¹

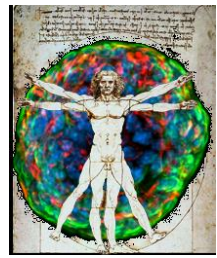
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hiPSC-derived Retina



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NATURE | NEWS



Japanese woman is first recipient of next-generation stem cells

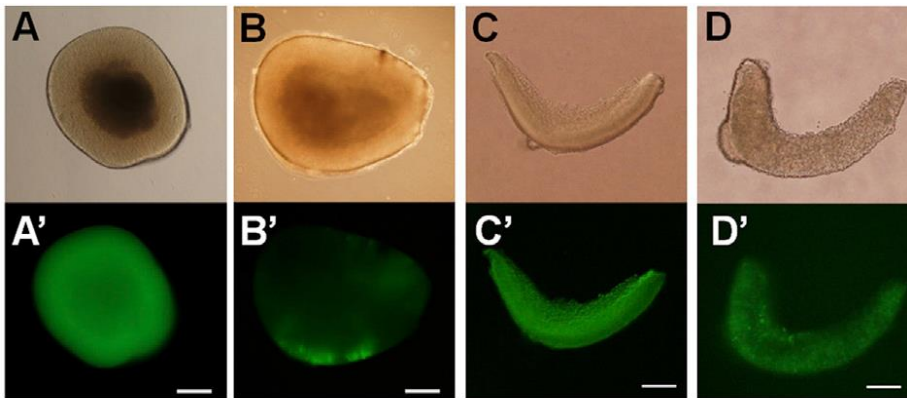
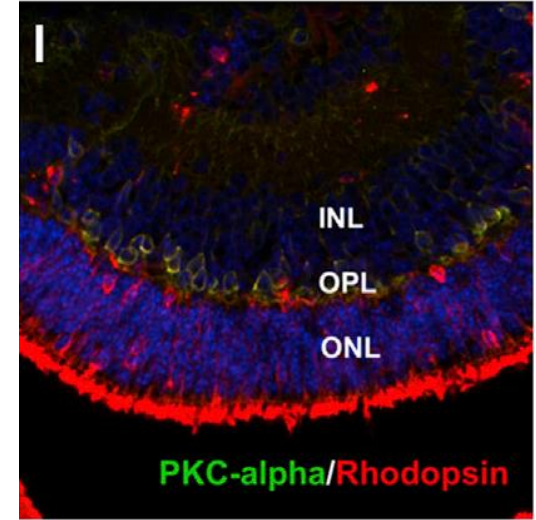
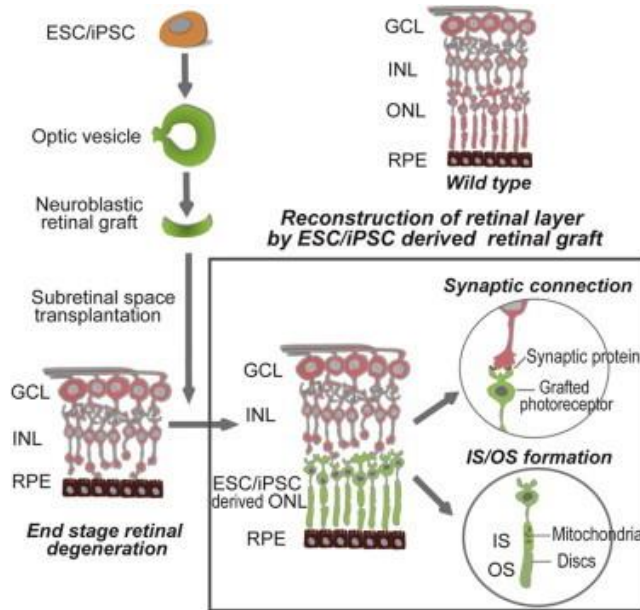
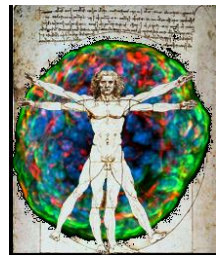
Surgeons implanted retinal tissue created after reverting the patient's own cells to 'pluripotent' state.

David Cyranoski

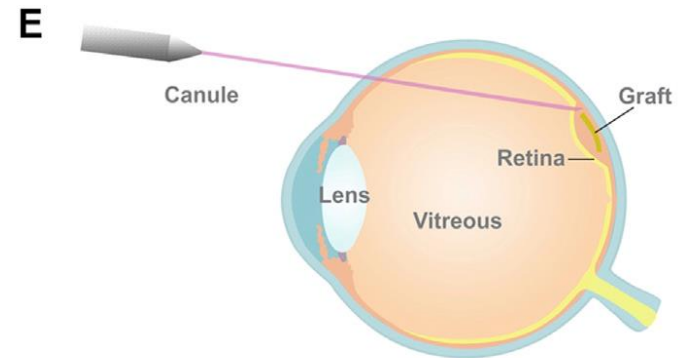
12 September 2014

In a two-hour procedure starting at 14:20 local time today, a team of three eye specialists lead by Yasuo Kurimoto of the Kobe City Medical Center General Hospital, implanted a 1.3 by 3.0 millimetre sheet of retinal pigment epithelium cells into an eye of the Hyogo prefecture resident, who suffers from age-related macular degeneration, a common eye condition that can lead to blindness.

hiPSC-derived Retina



Retina in-a-dish



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