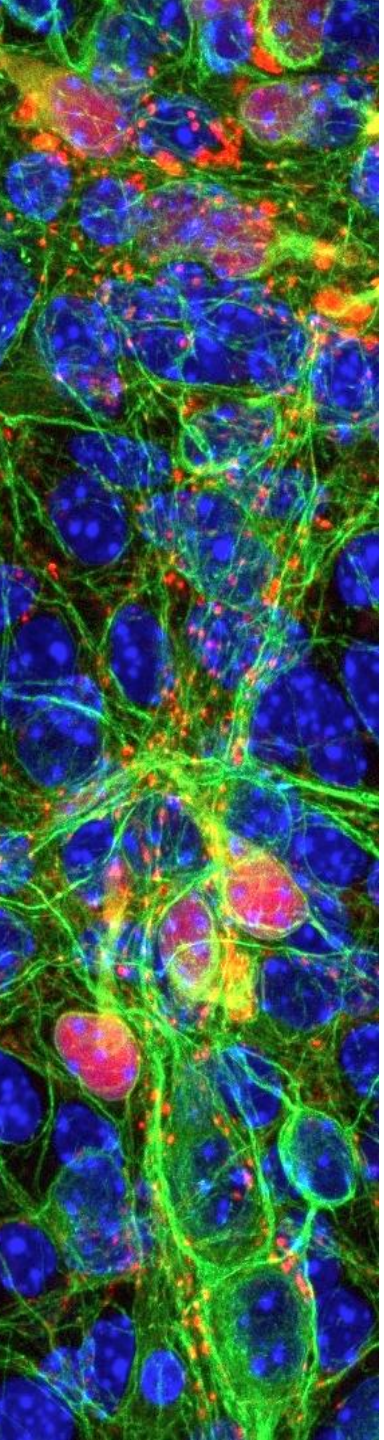


THE UNIVERSITY of EDINBURGH

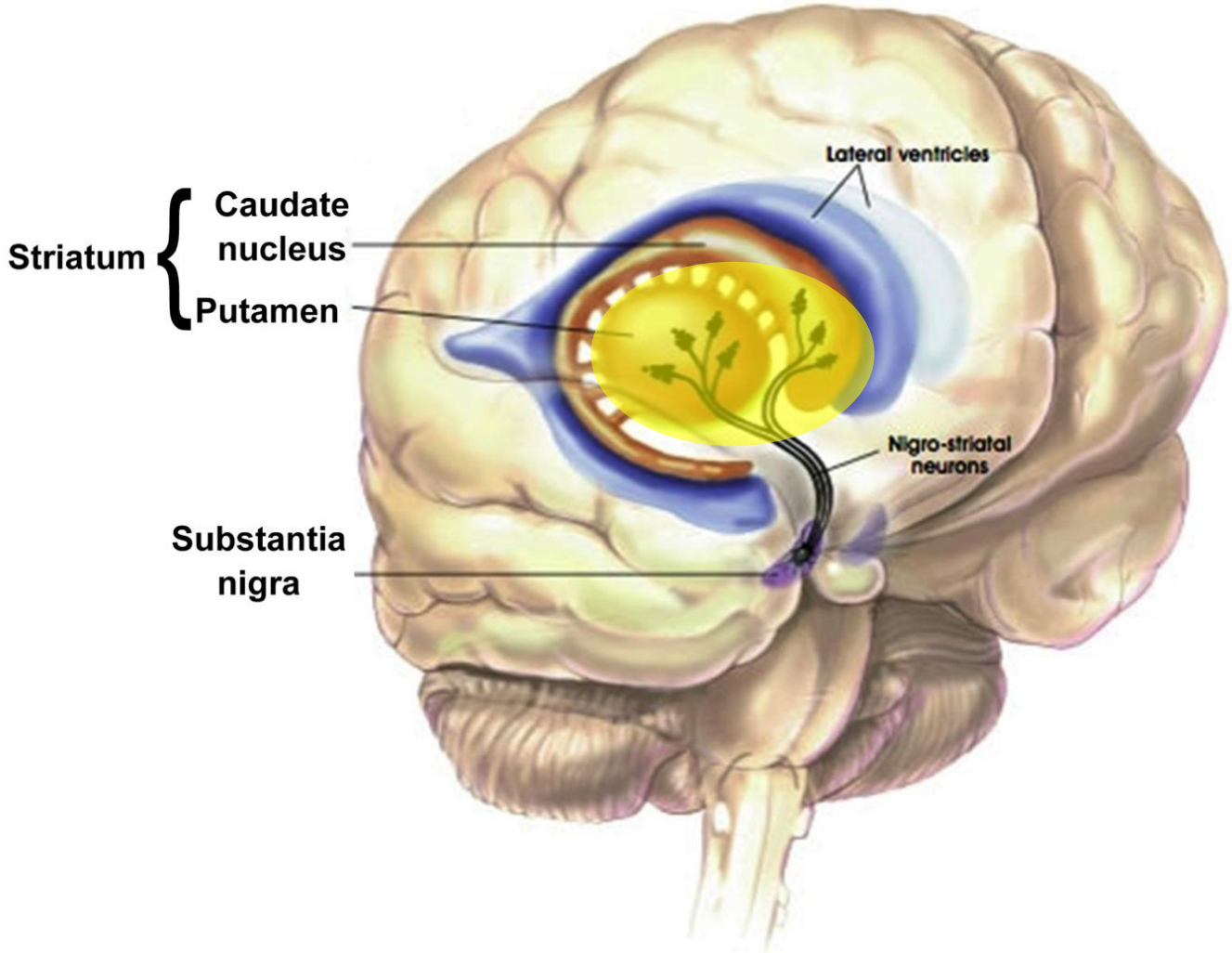
Centre for Regenerative Medicine

UK Centre for Mammalian Synthetic Biology

Update on recent progress towards cell replacement therapy for Parkinson's

Tilo Kunath

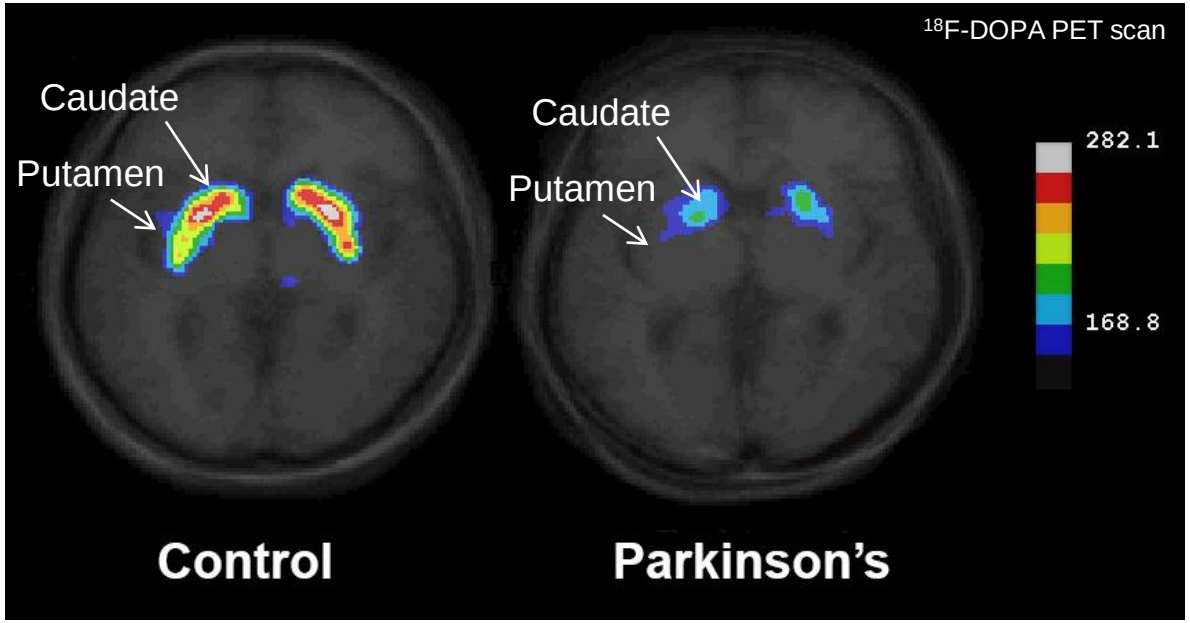
Substantia nigra “dopaminergic” neurons release dopamine in the striatum

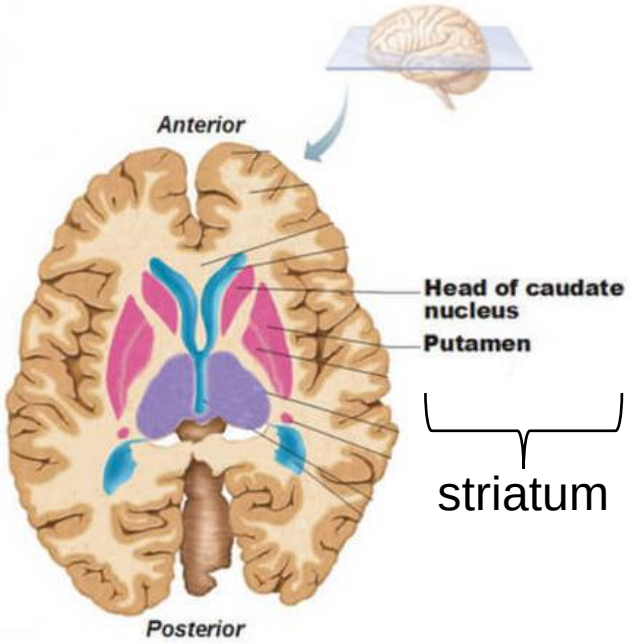


In Parkinson's *substantia nigra* nerve cells are slowly being lost

- Motor symptoms caused by loss of **dopaminergic neurons**
- The loss is very localised to the **caudate** and **putamen**

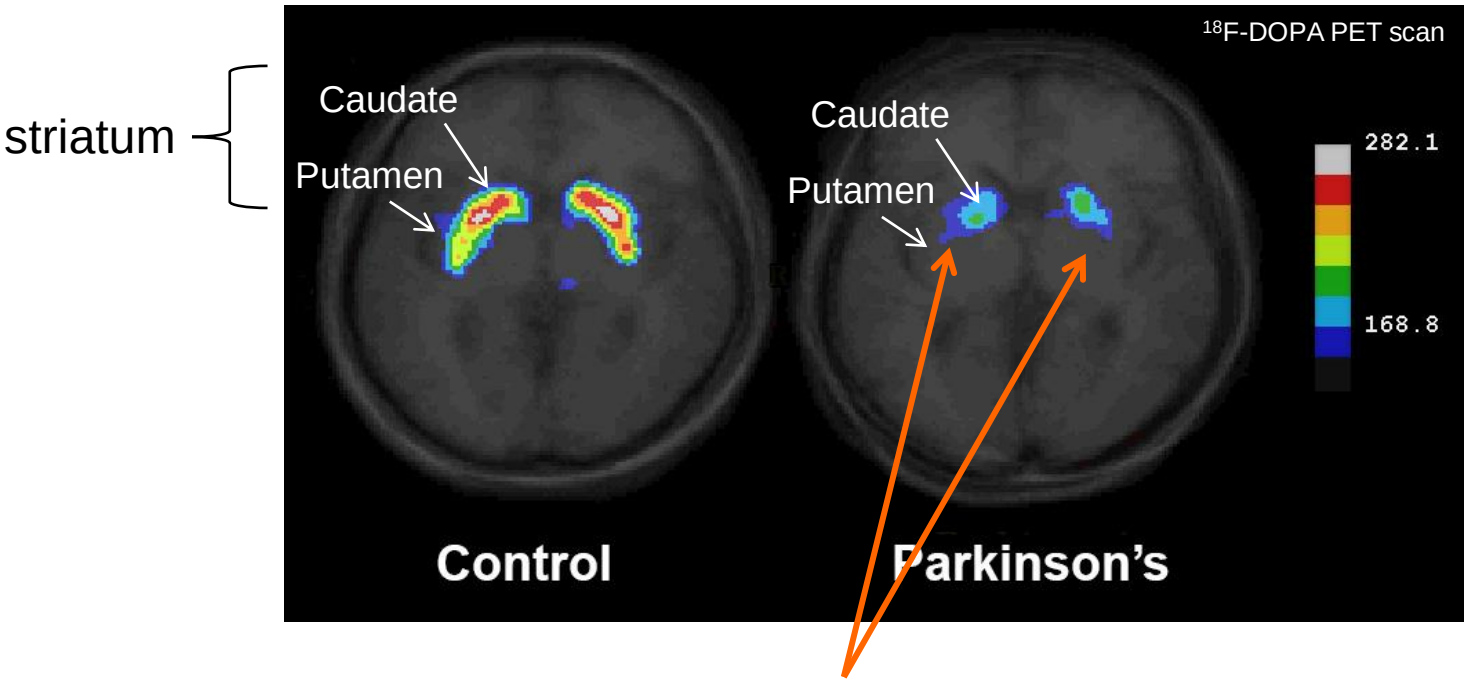
striatum

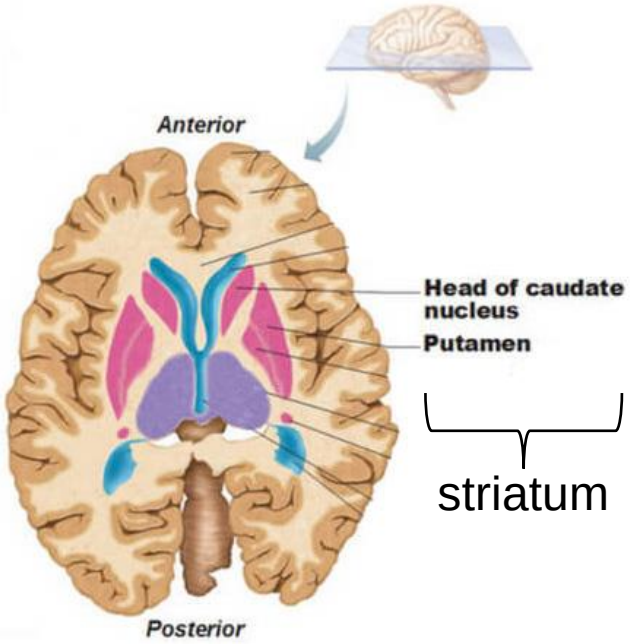




Cell replacement therapy for Parkinson's

- Motor symptoms caused by loss of **dopaminergic neurons**
- The loss is very localised to the **caudate** and **putamen**



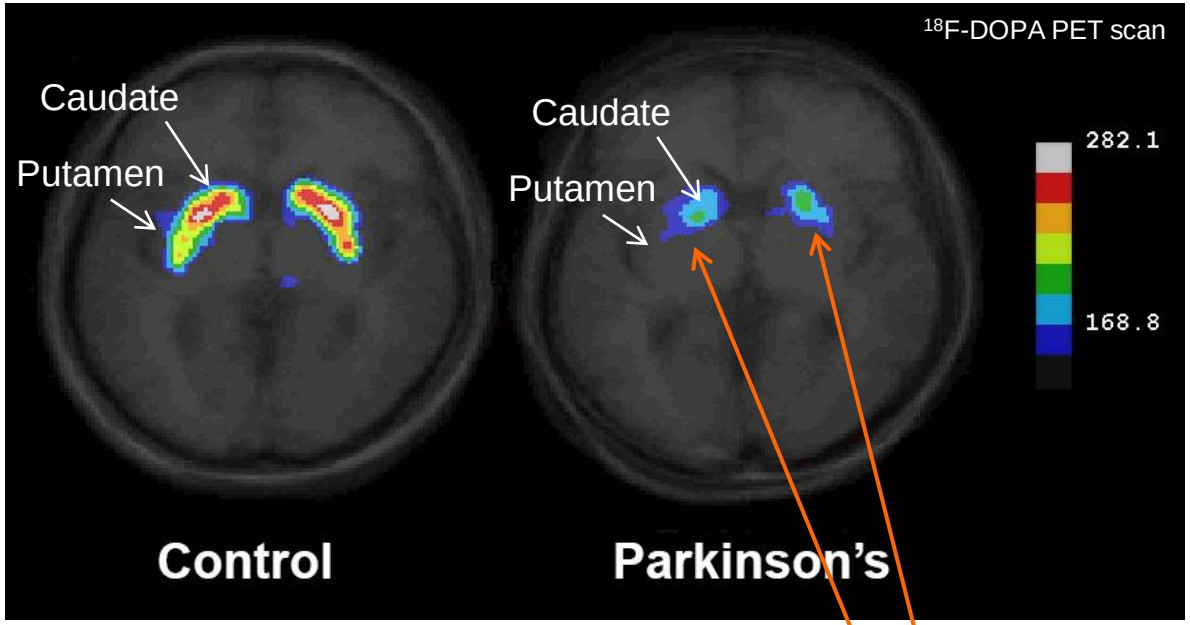


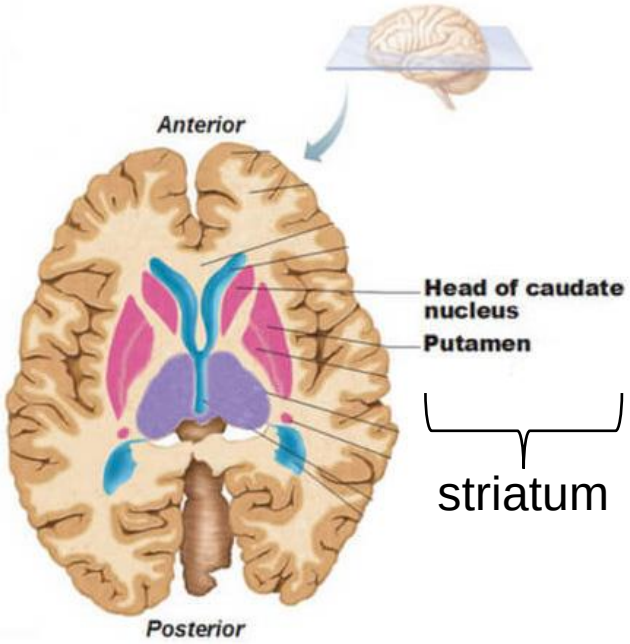
Therapy: Transplant ***new*** dopaminergic neurons into putamen

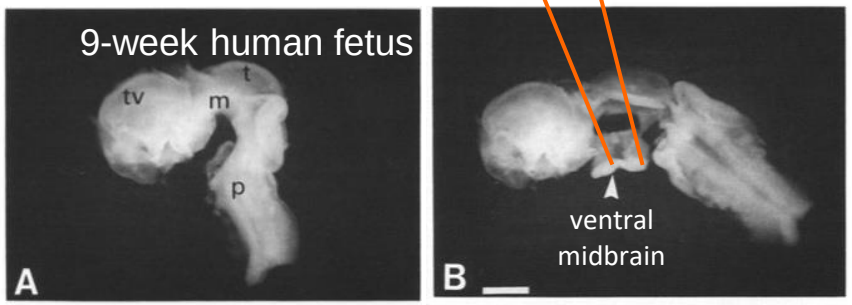
Cell replacement therapy for Parkinson's

- Motor symptoms caused by loss of **dopaminergic neurons**
- The loss is very localised to the **caudate** and **putamen**

striatum

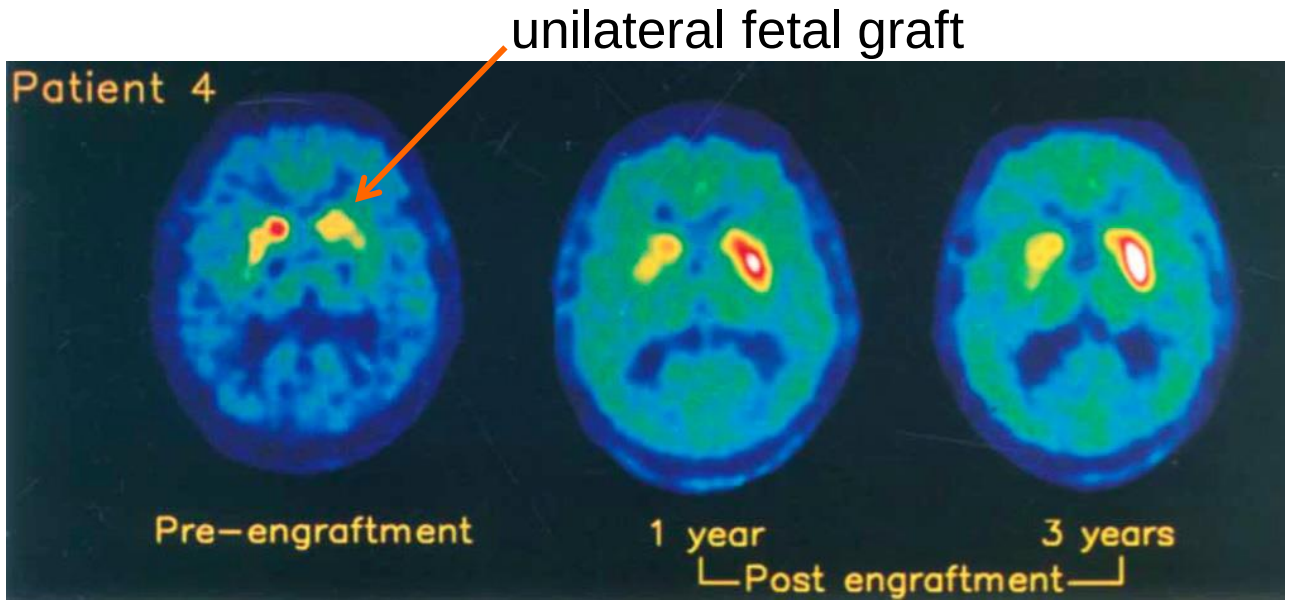






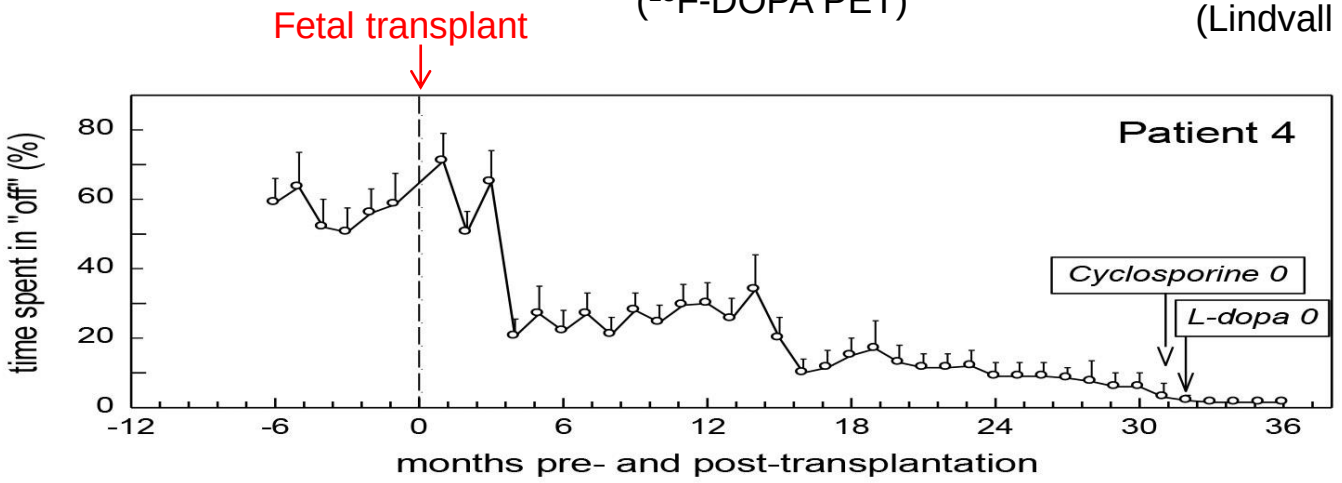
(Brundin *et al*, 1986, *Exp Brain Res*)

Human clinical trials with fetal ventral midbrain tissue



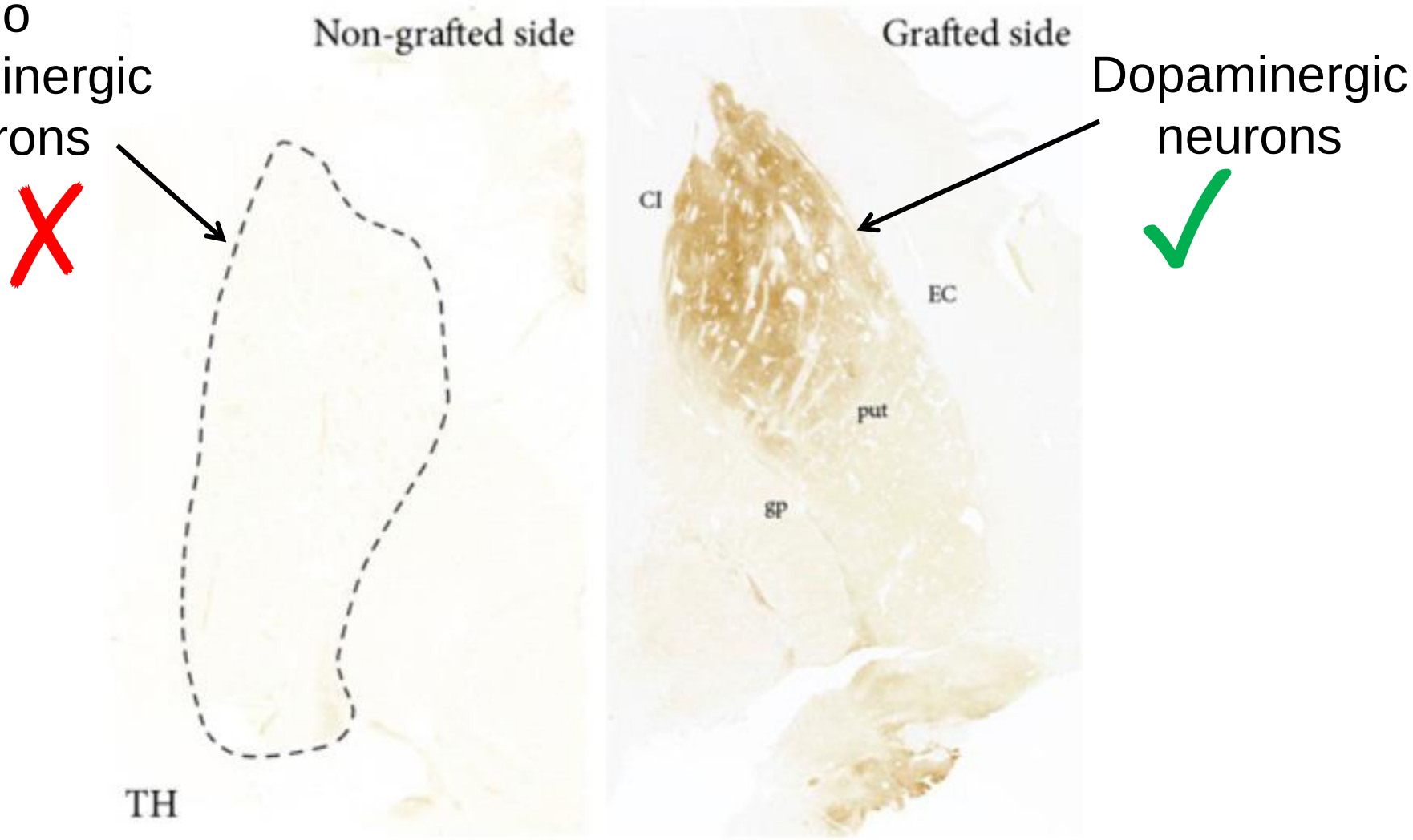
(^{18}F-DOPA PET)

(Lindvall *et al*, 1994)



24 years after fetal transplant

No dopaminergic neurons

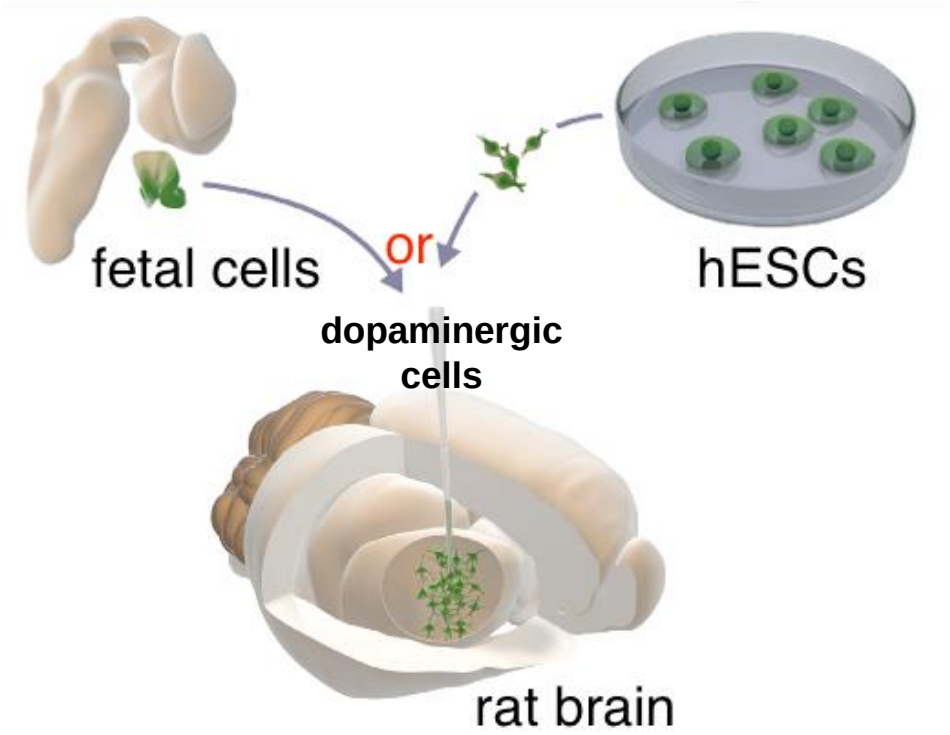


Dopaminergic neurons

TH = tyrosine hydroxylase, put = putamen

(Li *et al*, 2016, *PNAS*)

Fetal tissue replaced by hESC/iPSC-derived cells



(Grealish et al., 2014)

Two types of pluripotent stem cells

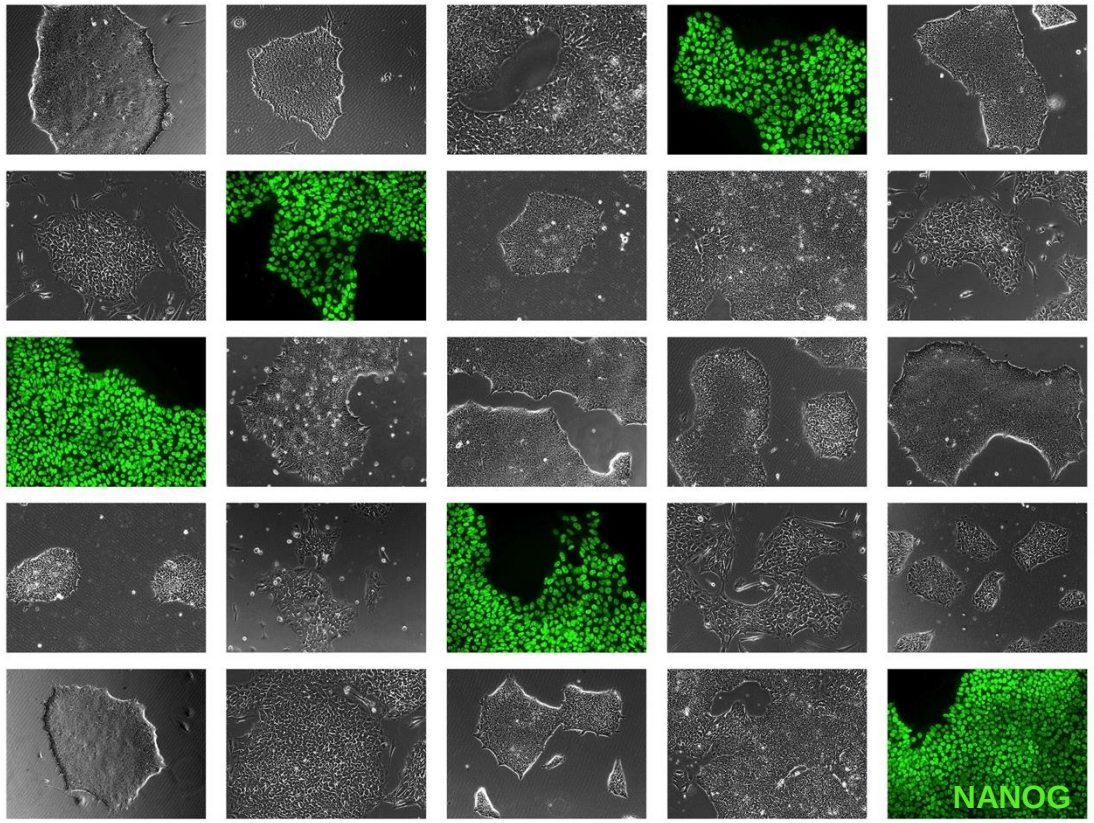
Embryonic Stem cells (ESCs)

(from embryos – IVF clinics)

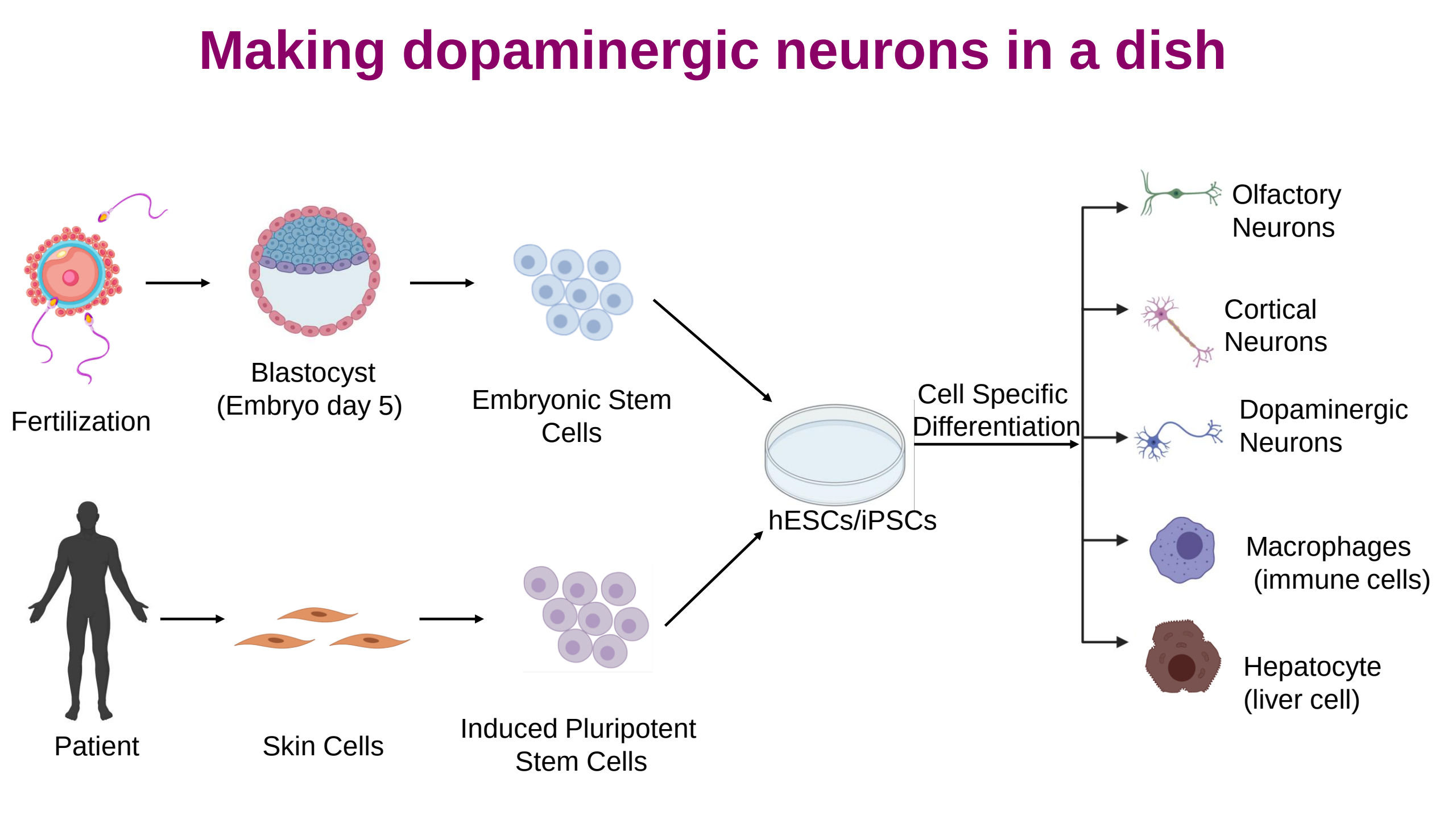
induced Pluripotent Stem cells (iPSCs)

(from adults – blood or skin cells)

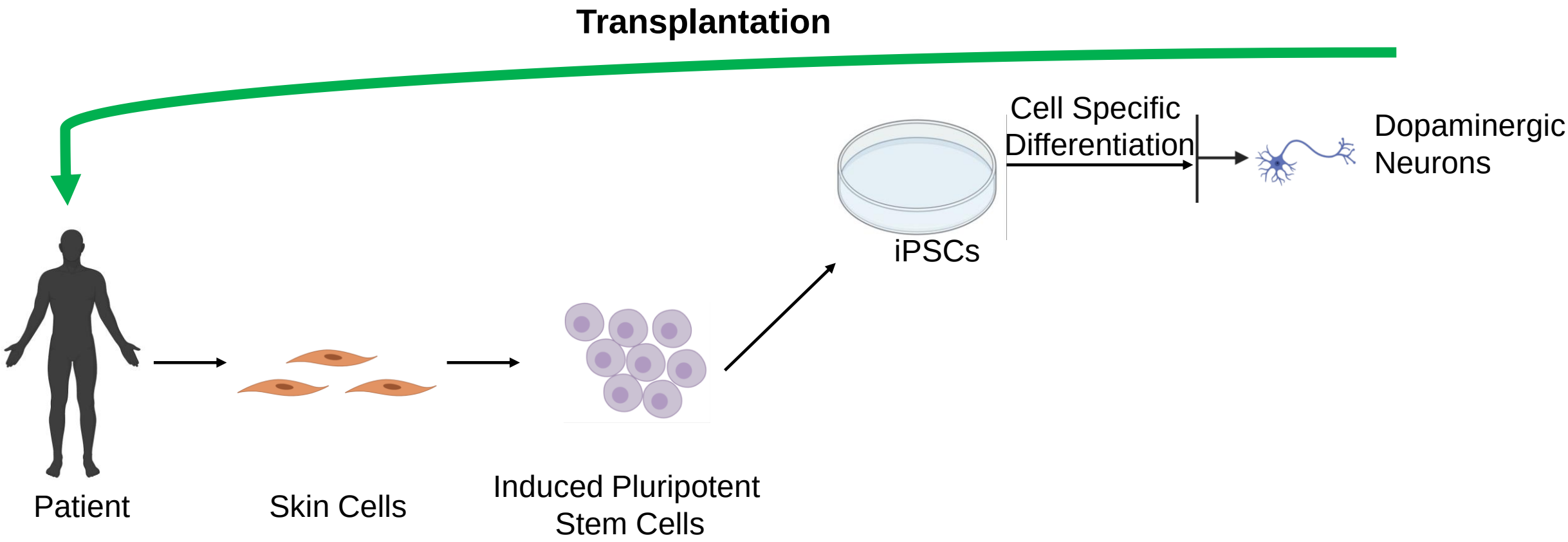
Different
hESC lines



Making dopaminergic neurons in a dish



Making dopaminergic neurons for ‘personalized’ medicine



The NEW ENGLAND JOURNAL of MEDICINE

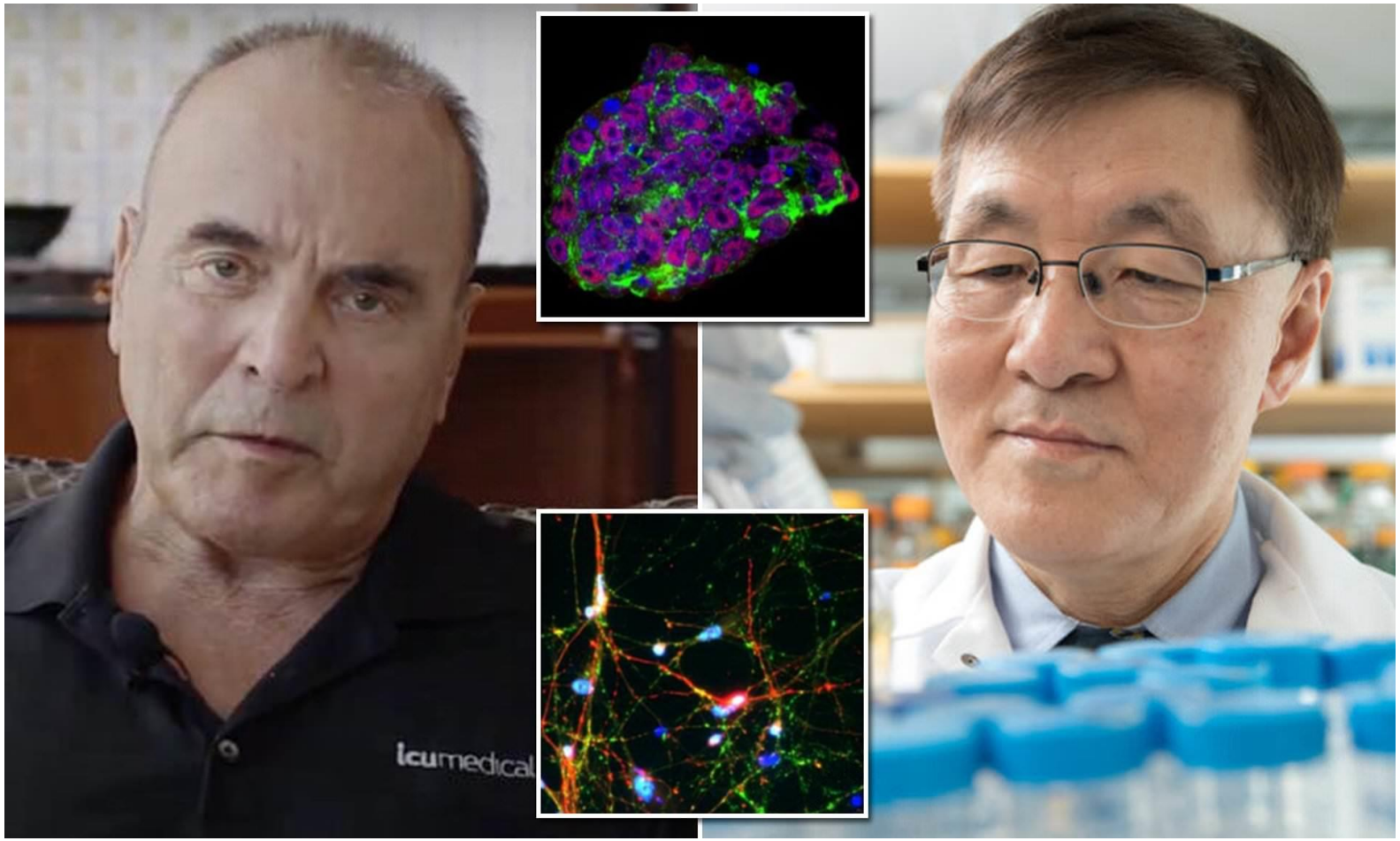
BRIEF REPORT

Personalized iPSC-Derived Dopamine Progenitor Cells for Parkinson's Disease

Jeffrey S. Schweitzer, M.D., Ph.D., Bin Song, M.D., Ph.D., Todd M. Herrington, M.D., Ph.D., Tae-Yoon Park, Ph.D., Nayeon Lee, Ph.D., Sanghyeok Ko, Ph.D., Jeha Jeon, Ph.D., Young Cha, Ph.D., Kyungsang Kim, Ph.D., Quanzheng Li, Ph.D., Claire Henchcliffe, M.D., D.Phil., Michael Kaplitt, M.D., Ph.D., Carolyn Neff, M.D., Otto Rapalino, M.D., Hyemyung Seo, Ph.D., In-Hee Lee, Ph.D., Jisun Kim, Ph.D., Taewoo Kim, Ph.D., Gregory A. Petsko, D.Phil., Jerome Ritz, M.D., Bruce M. Cohen, M.D., Ph.D., Sek-Won Kong, M.D., Pierre Leblanc, Ph.D., Bob S. Carter, M.D., Ph.D., and Kwang-Soo Kim, Ph.D.

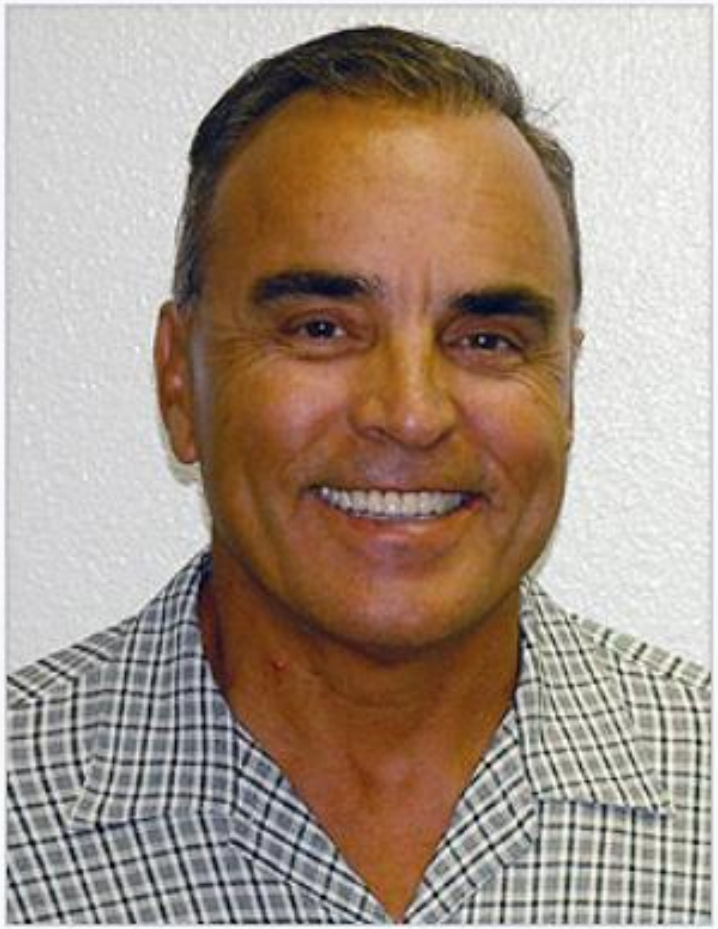
George Lopez

Kwang-Soo Kim



https://youtu.be/PjUtACvuqT8

George Lopez



ICU Medical Founder Dr. George "Doc" Lopez.

Dr. Lopez poses beside his world record blue marlin in 2004

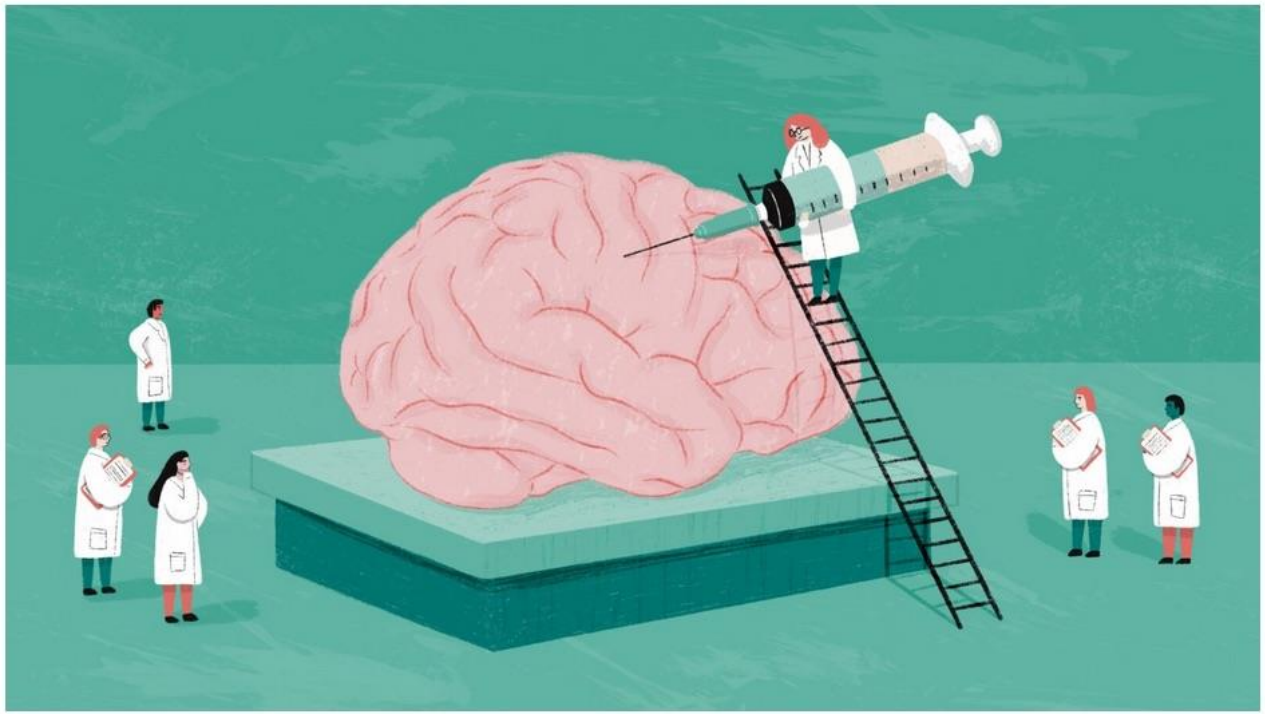
Dr. George 'Doc' Lopez after setting US National record for the Free Immersion diving in 2006.

Personalised Parkinson's *cell replacement therapy*

EXCLUSIVE

A secret experiment revealed: In a medical first, doctors treat Parkinson's with a novel brain cell transplant

By SHARON BEGLEY @sxbegle / MAY 12, 2020 Reprints



https://www.statnews.com/2020/05/12/medical-first-parkinsons-brain-cell-transplant-stem-cells/

Personalised Parkinson's *cell replacement therapy*

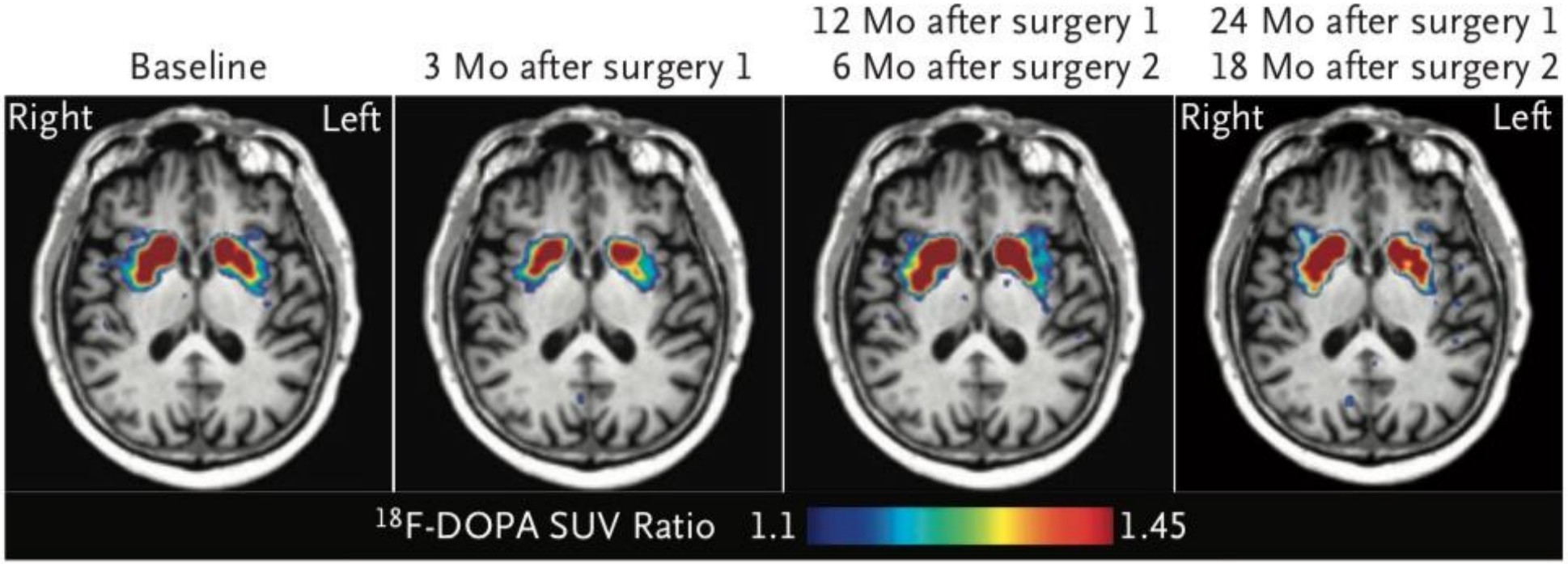
In January 2017, the FDA signed off on the 2,500-page "compassionate use" protocol they had submitted, green-lighting a **one-patient experiment**.

Transplantation surgeries – 6 months apart
Left side: 5th September, 2017
Right side: 6th March, 2018

After 2 years, patient had no infections, no tumours, and no complications.

PET imaging up to 2 years after surgery

A Positron-Emission Tomography



Change in regional putaminal uptake

		Right	Left
→	Anterior	–4.0%	–4.8%
	Posterior	5.4%	–1.6%
→	Anterior	10.7%	1.6%
	Posterior	13.5%	9.8%

Clinical measures up to 2 years after surgery

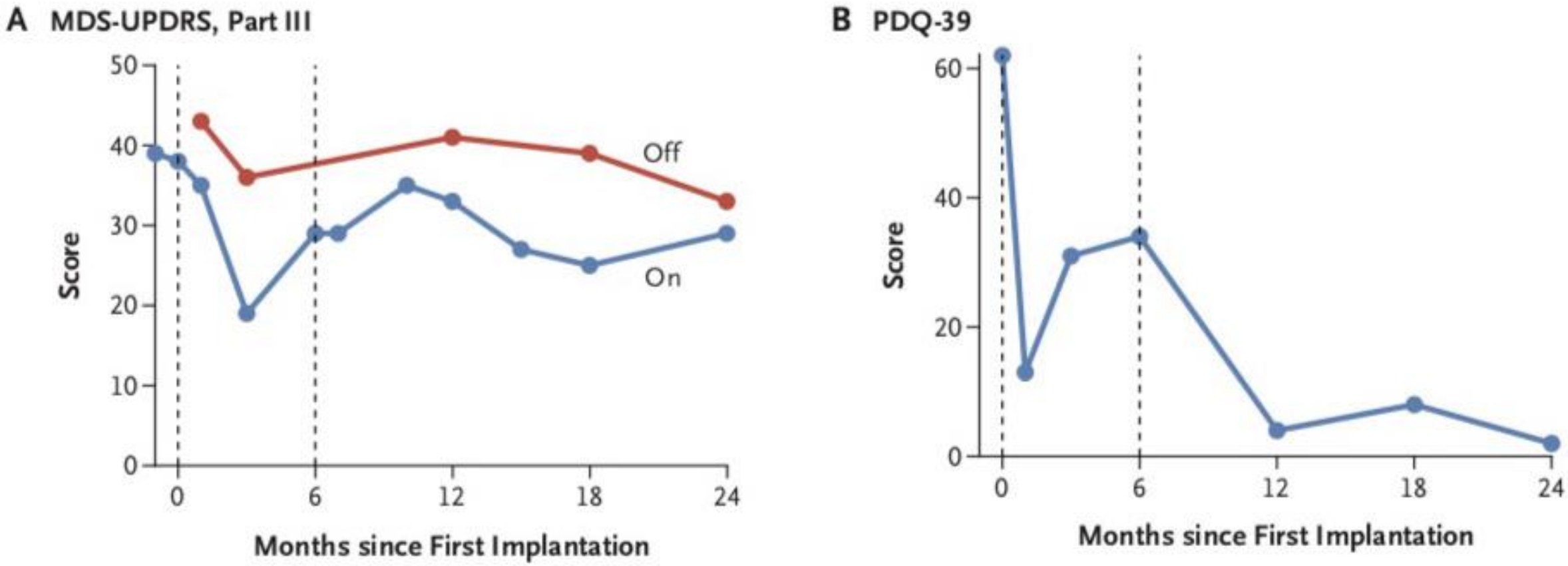
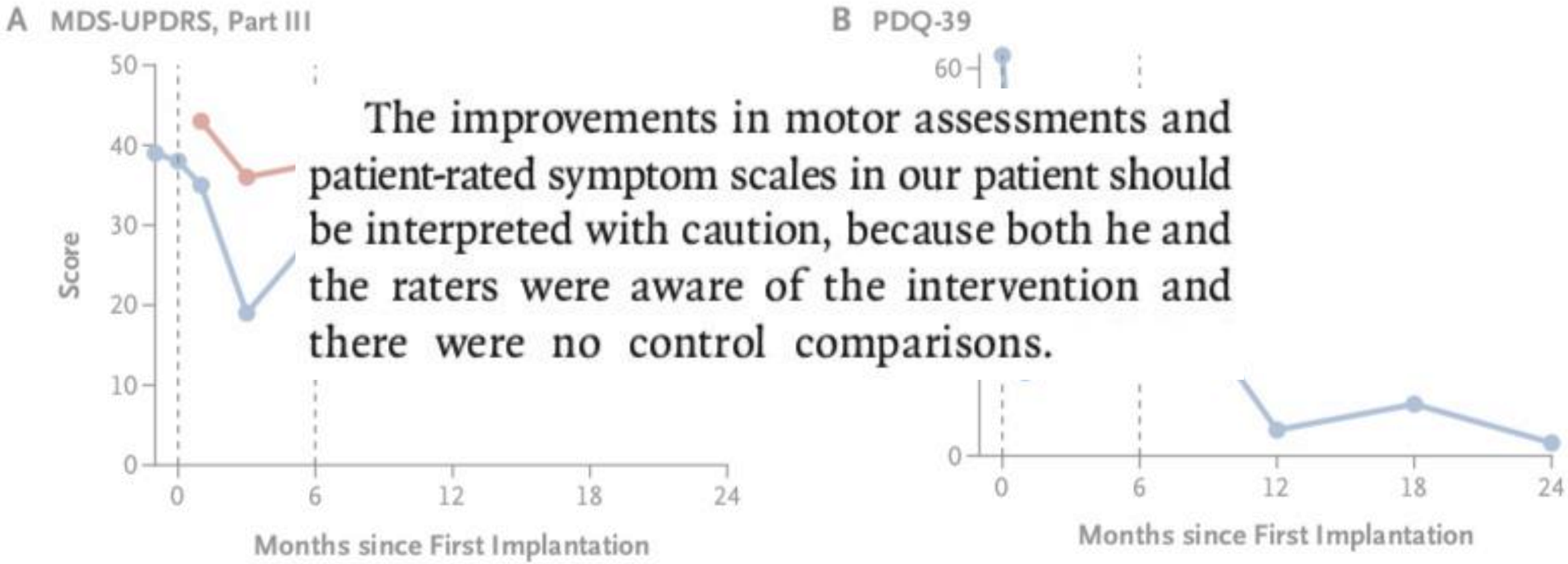


Figure 3. Longitudinal Clinical Assessments of Parkinson's Disease–Related Motor Function and Quality of Life.

Clinical measures up to 2 years after surgery



The improvements in motor assessments and patient-rated symptom scales in our patient should be interpreted with caution, because both he and the raters were aware of the intervention and there were no control comparisons.

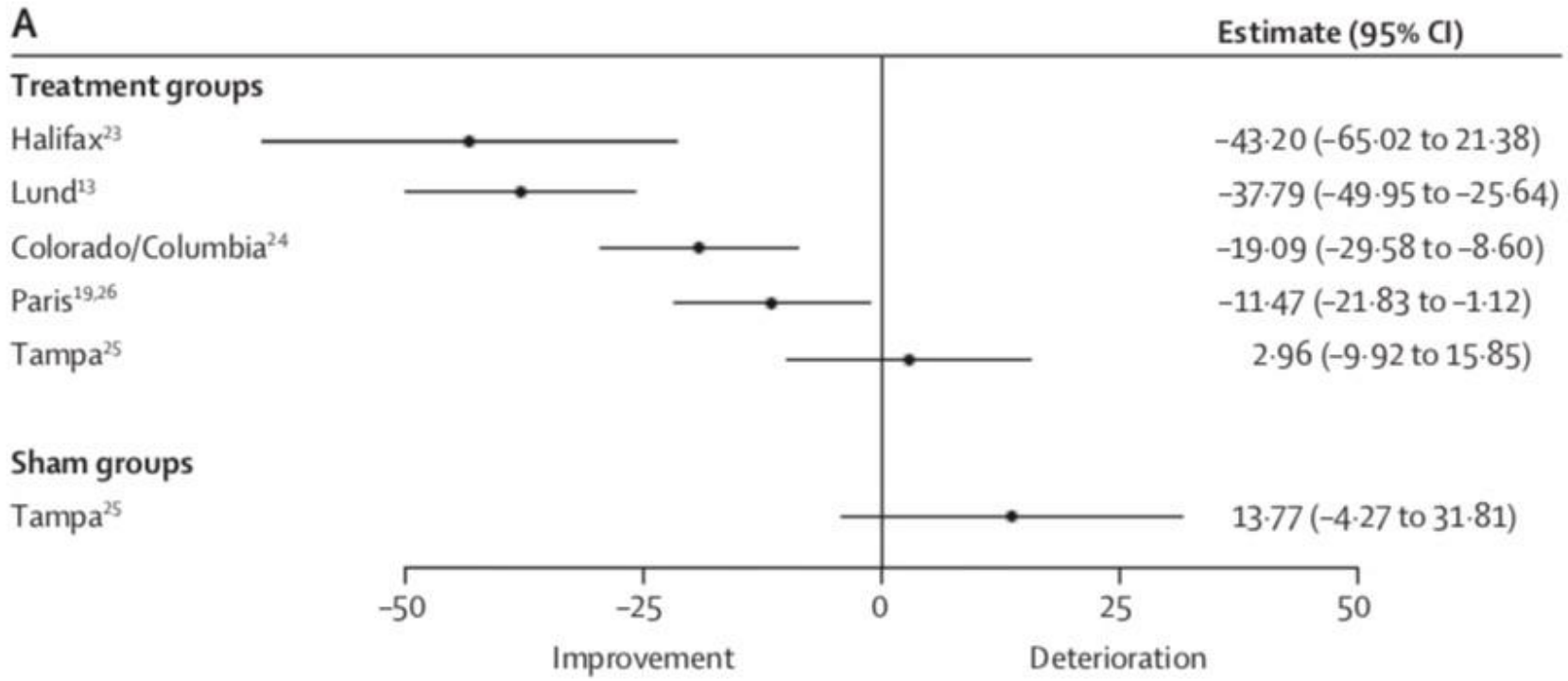
Figure 3. Longitudinal Clinical Assessments of Parkinson's Disease–Related Motor Function and Quality of Life.

Future outlook

Fetal dopaminergic transplantation trials and the future of neural grafting in Parkinson's disease

Roger A Barker, Jessica Barrett, Sarah L Mason, Anders Björklund

Lancet Neurol 2013; 12: 84–91



Future outlook

Cell Stem Cell
Forum

CellPress

Human Trials of Stem Cell-Derived Dopamine Neurons for Parkinson's Disease: Dawn of a New Era

Roger A. Barker,[1] Malin Parmar,[2,*] Lorenz Studer,[3] and Jun Takahashi[4]
[1]Department of Clinical Neuroscience and Cambridge Stem Cell Institute, Forvie Site, Cambridge CB2 0PY, UK
[2]Developmental and Regenerative Neurobiology, Wallenberg Neuroscience Center, and Lund Stem Cell Centre, Department of Experimental Medical Science, Lund University, 22184, Lund, Sweden
[3]Developmental Biology, The Center for Stem Cell Biology, Memorial Sloan Kettering Cancer Center, New York, NY 10022, USA
[4]Department of Clinical Application, Center for iPS Cell Research and Application, Kyoto University, 606-8507, Kyoto, Japan

Beyond cell transplantation…

Astrocytes rewired to replace neurons lost in Parkinson's disease

In situ cell conversion

Article

Reversing a model of Parkinson's disease with in situ converted nigral neurons

https://doi.org/10.1038/s41586-020-2388-4

Received: 12 November 2018

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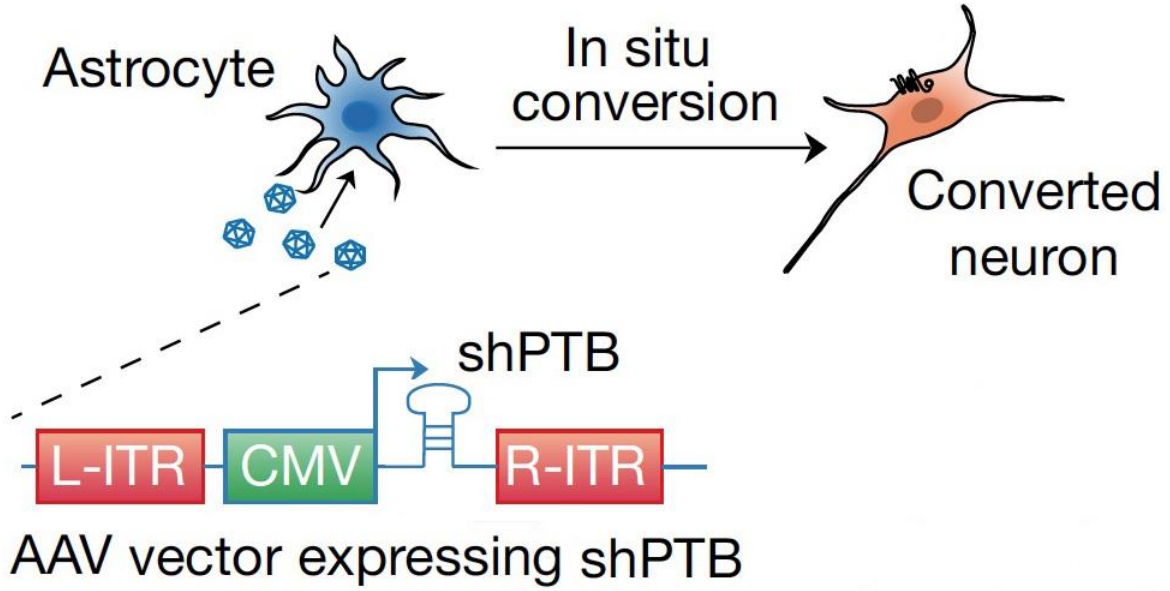
Published online: 24 June 2020

Hao Qian[1], Xinjiang Kang[2,3], Jing Hu[1,8], Dongyang Zhang[4], Zhengyu Liang[1], Fan Meng[1], Xuan Zhang[1], Yuanchao Xue[1,9], Roy Maimon[1,5], Steven F. Dowdy[1], Neal K. Devaraj[4], Zhuan Zhou[2], William C. Mobley[6], Don W. Cleveland[1,5] & Xiang-Dong Fu[1,7]✉

Use a virus to knock-down ***one gene***, *PTB*, in astrocytes



AAV = adeno-associated virus
sh = short-hairpin

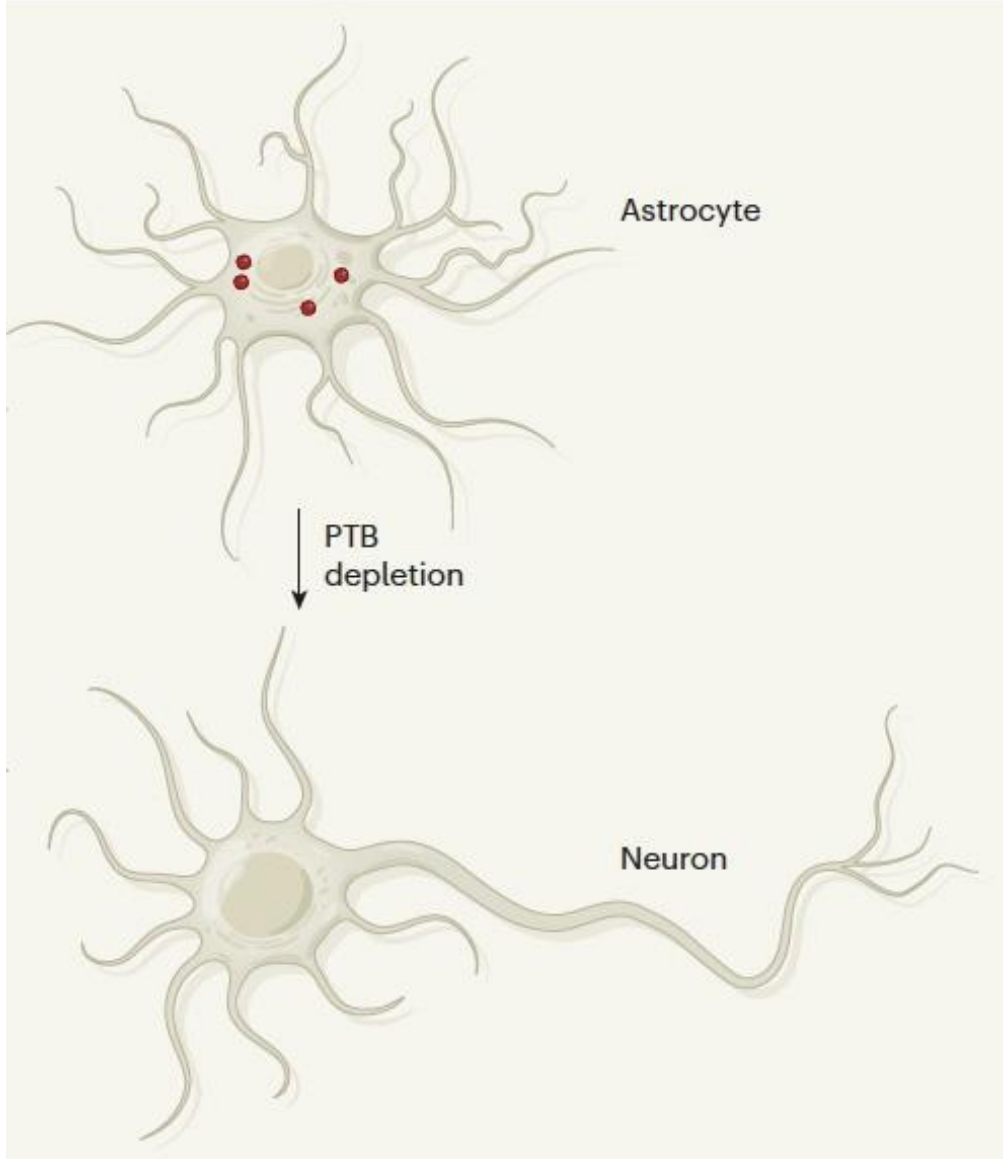
In situ cell conversion

Parkinson's disease

Unleashing the neuronal side of astrocyte cells

Ernest Arenas

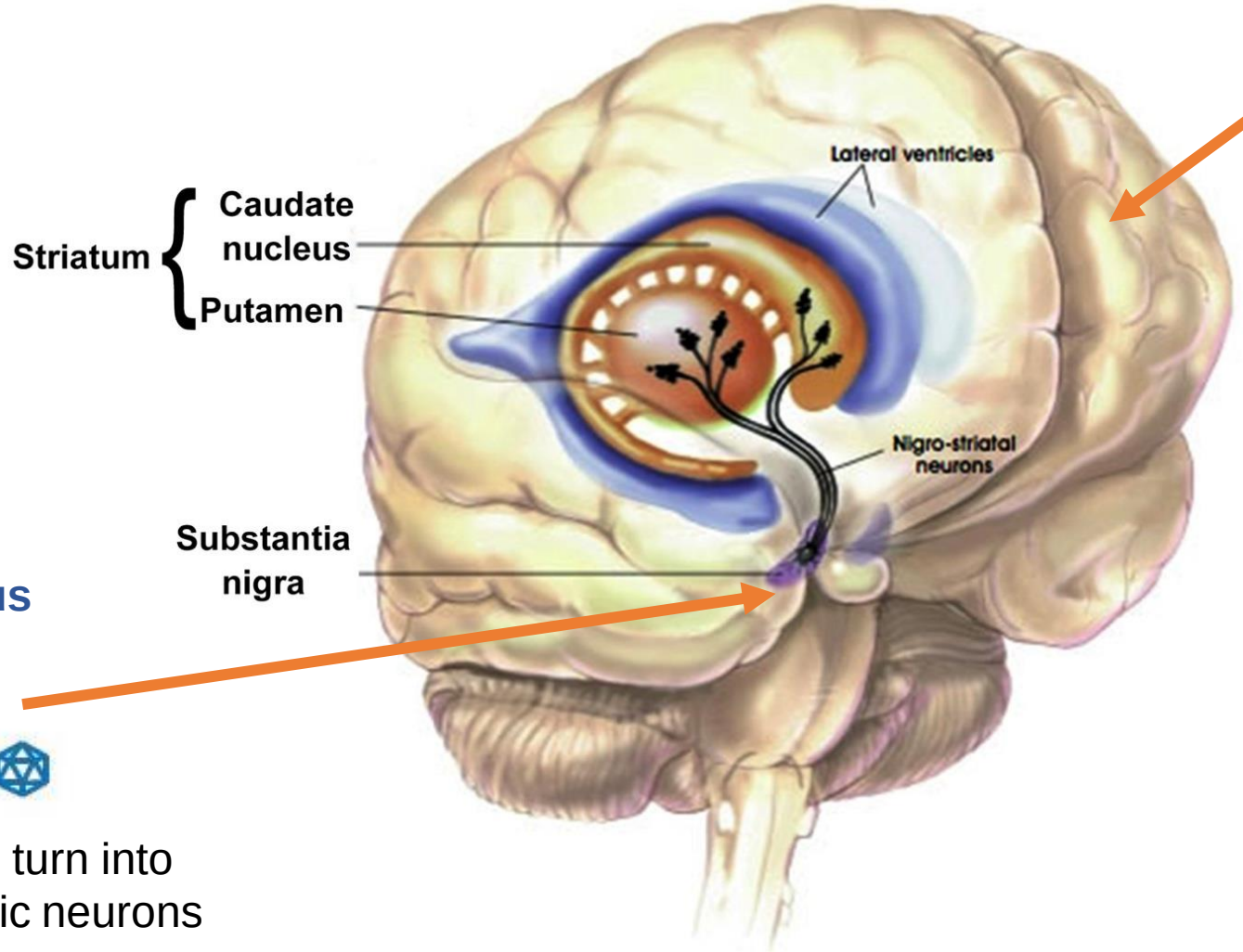
Astrocytes are non-neuronal brain cells that express a protein called PTB. It emerges that PTB depletion unlocks the potential of astrocytes to convert to neurons in a mouse model of Parkinson's disease. **See p.550**



In situ cell conversion

shPTB virus

Astrocytes turn into cortical neurons



shPTB virus

Astrocytes turn into dopaminergic neurons

Thank you

THE UNIVERSITY of EDINBURGH

Centre for Regenerative Medicine

THE LAB
Sophie Glendinning
David McNay
Craig Leighton
Nicola Drummond
Yixi Chen
Ammar Natalwala

MRC Medical Research Council

The Cure Parkinson's Trust

UK Centre for Mammalian Synthetic Biology

wellcome trust

BBSRC bioscience for the future

EPSRC Engineering and Physical Sciences Research Council

MRC Medical Research Council

PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.