

The battle to beat Parkinson's disease: the end of the beginning

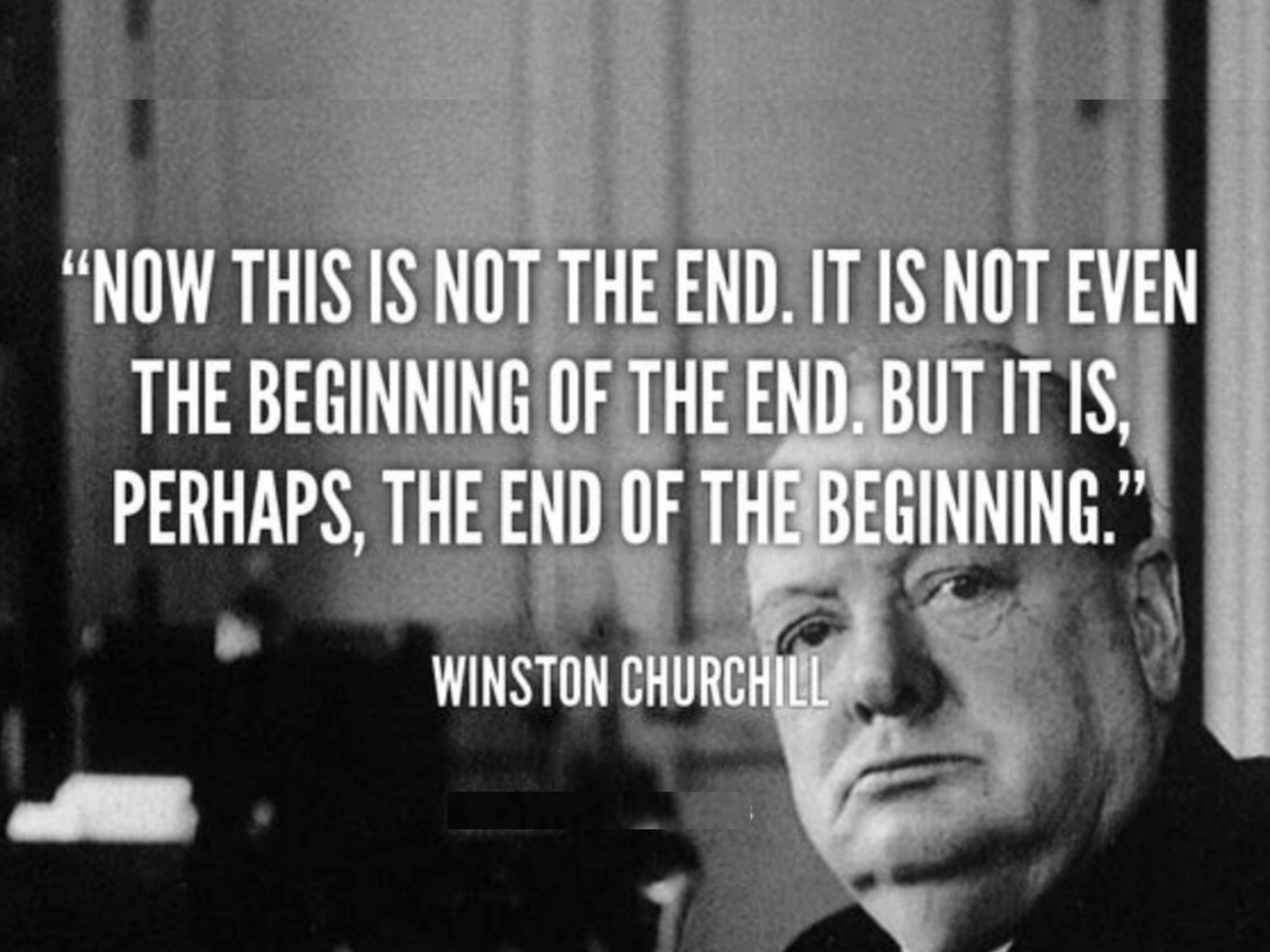
Patrik Brundin

Jay van Andel Endowed Chair for Parkinson's
Research

Center for Neurodegenerative Science
Van Andel Research Institute
Grand Rapids, MI
USA

Edinburgh Parkinson Lecture
Edinburgh, Scotland, UK
April 22nd, 2015



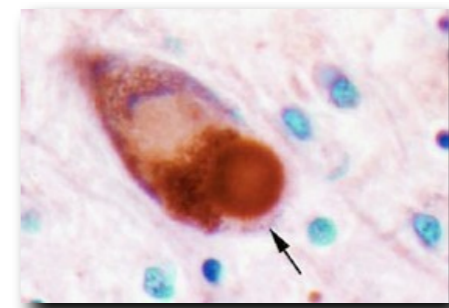
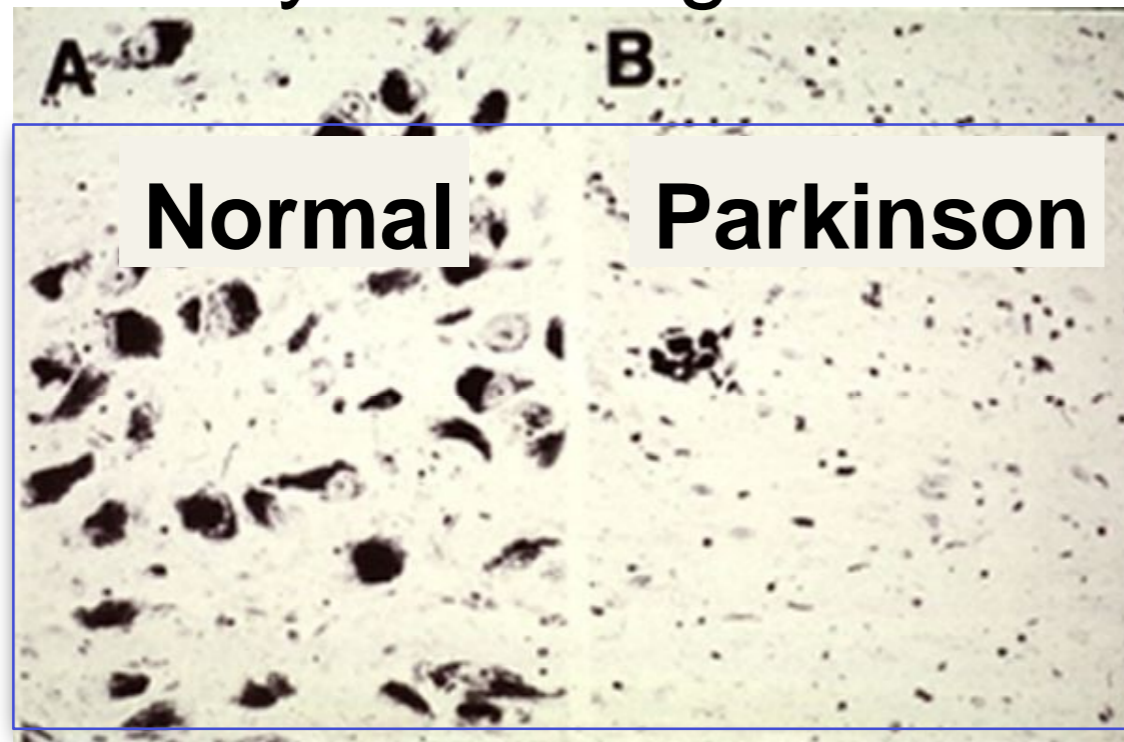
A black and white portrait of Winston Churchill, looking slightly to the right with a serious expression. The background is dark and out of focus.

**“NOW THIS IS NOT THE END. IT IS NOT EVEN
THE BEGINNING OF THE END. BUT IT IS,
PERHAPS, THE END OF THE BEGINNING.”**

WINSTON CHURCHILL

Parkinson's pathology in 30 sec

- Death of midbrain dopamine neurons is key to motor symptoms
- Lewy bodies (α -synuclein) indicate protein "clumping"
- Many brain regions are eventually affected



Today's talk

- Understanding unmet needs in Parkinson's
- Repairing the brain with cells and genes
- Using the right experimental models
- Drug repurposing: cheaper, faster, maybe better?
- Rallying to the challenge!

Understanding unmet medical needs



The “Parkinson’s journey” broken down into 7 psychological zones

<https://www.youtube.com/watch?v=IVrALMrnriU>

Unmet medical needs

- Dopaminergic therapies treat motor symptoms well for several years
 - Dyskinesia still an issue
- Non-motor symptoms lack effective therapies
- No therapies effectively slow PD progression

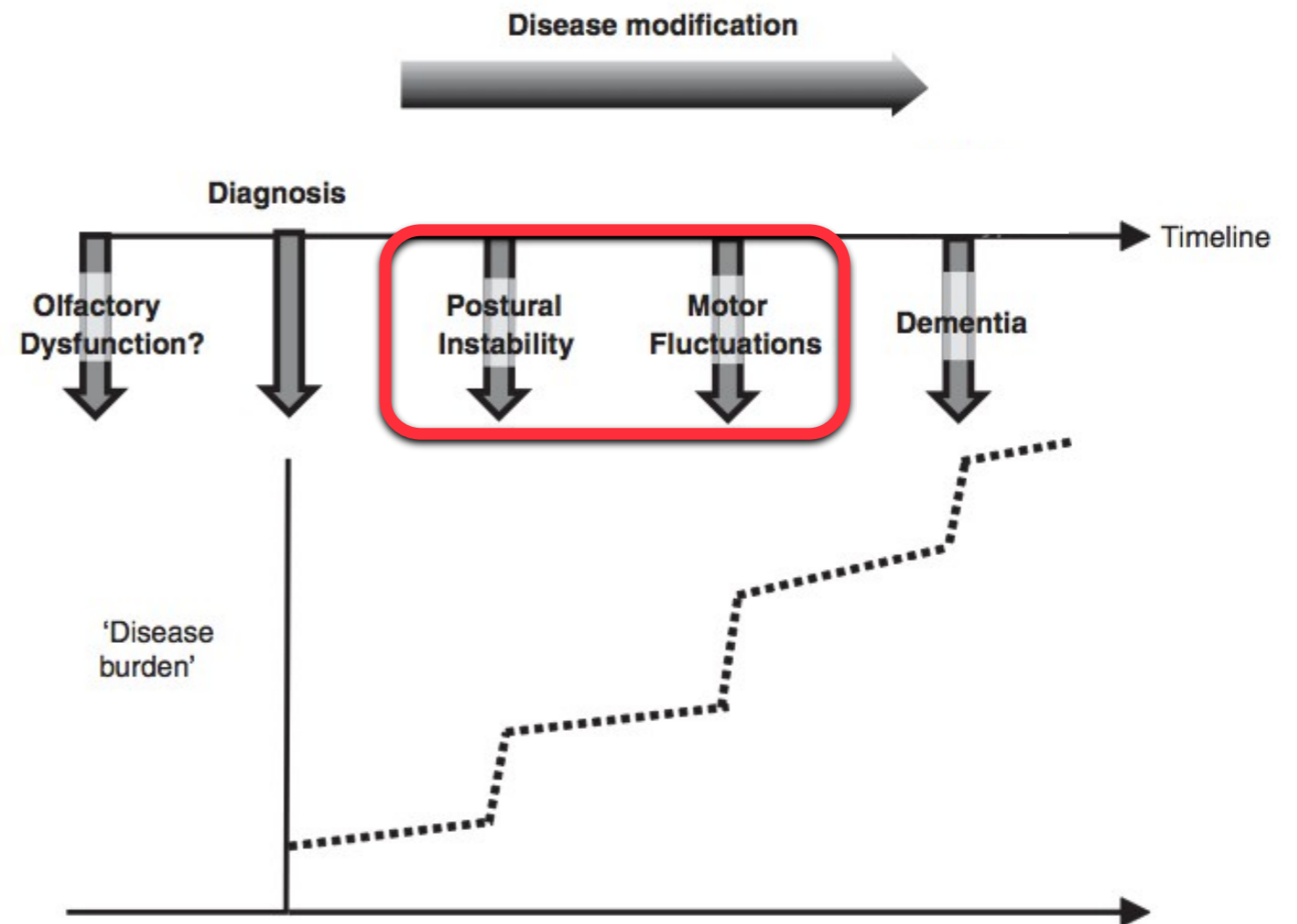


What features need targeting?

Defining meaningful outcome measures in trials of disease-modifying therapies in Parkinson's disease

Jonathan R Evans[†] & Roger A Barker

[†]University of Cambridge, Cambridge Centre for Brain Repair, Forvie Site, Cambridge, UK



Repairing the brain

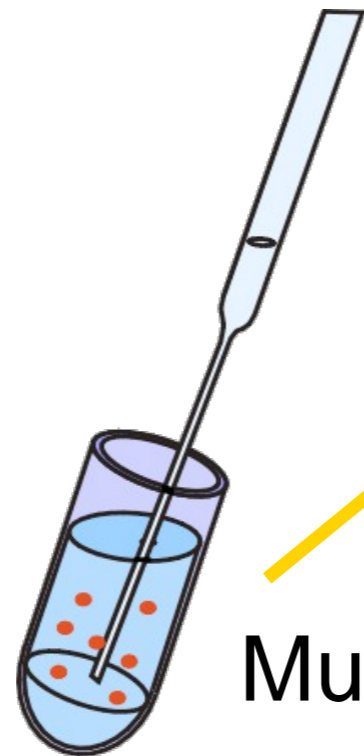
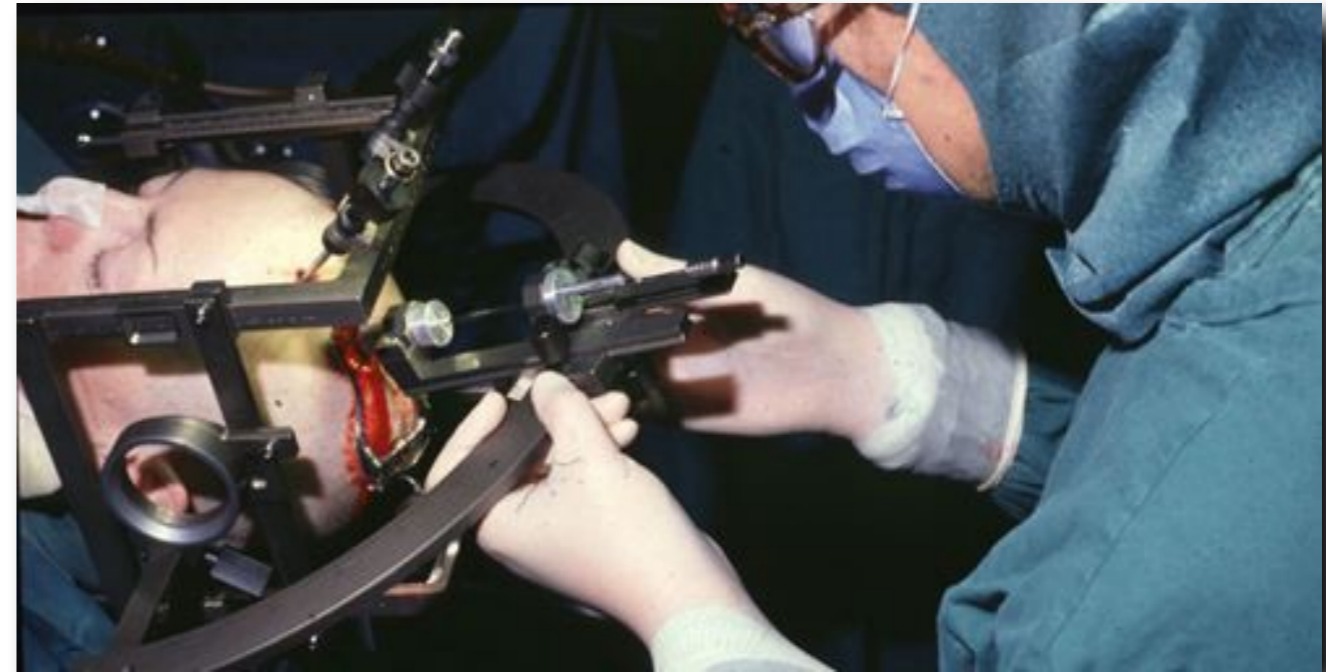
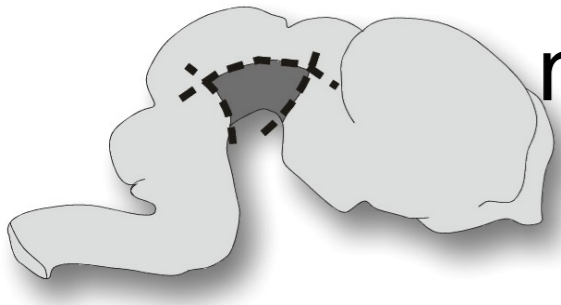
New cells



18 patients grafted in 1987-1999

Immunosuppressed
patients

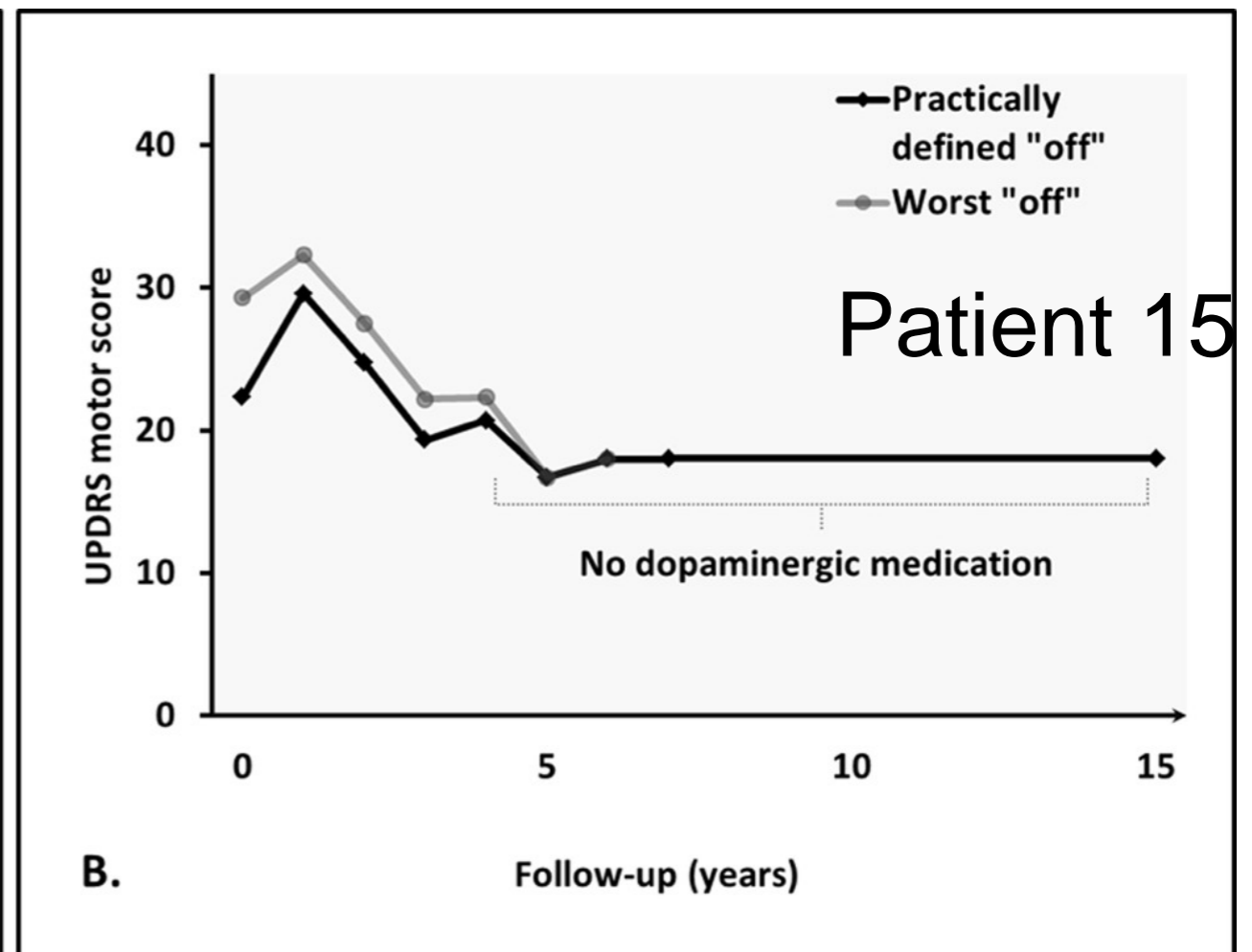
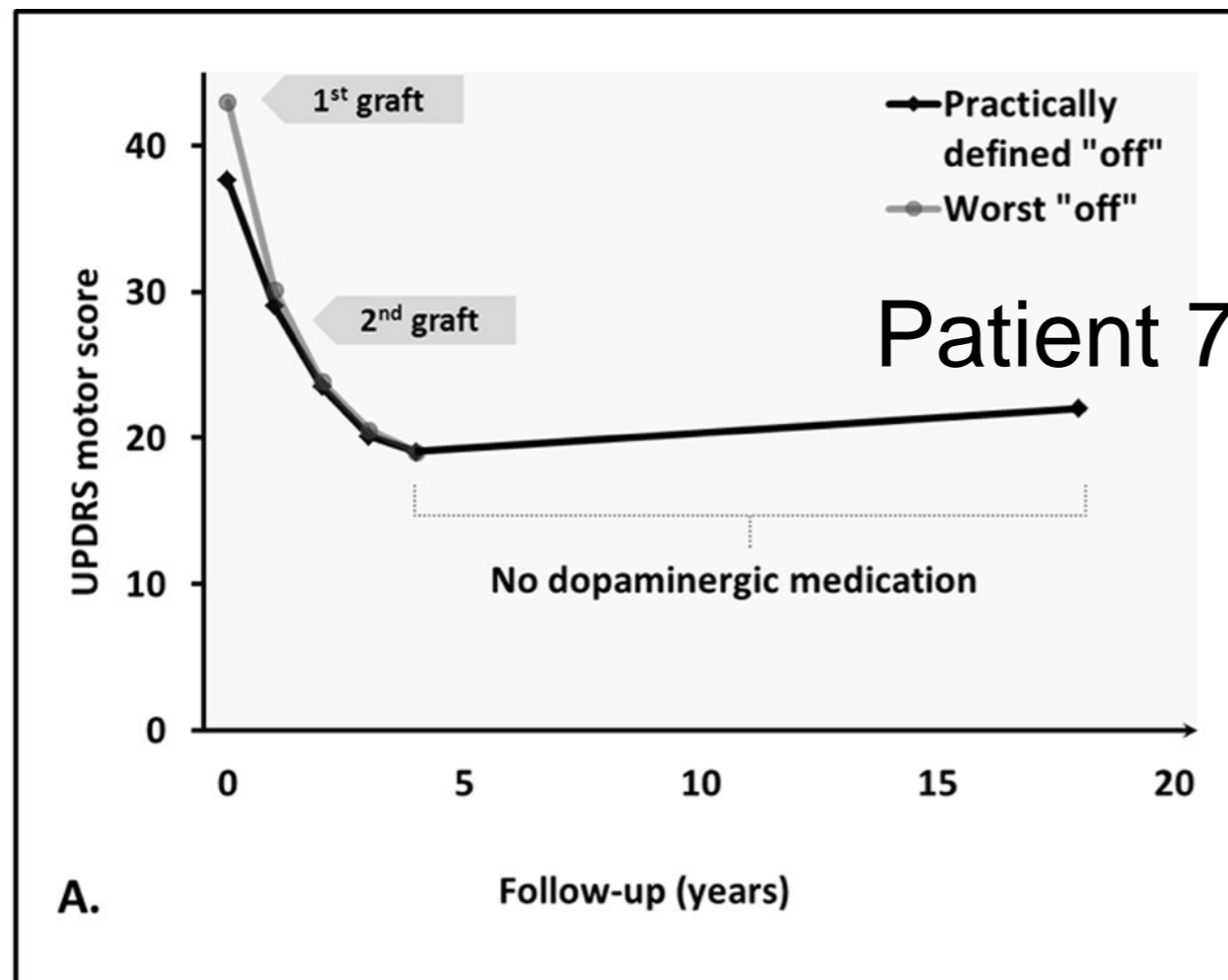
Fetal dopamine
neurons



Multiple donors for
each brain

Very long term outcome

Patients 7 and 15, operated in Lund, Sweden



Why use stem cells instead?

- Logistics simpler
- Reproducible source
- Ethics are less complicated
- Avoid immune rejection (autografts)?

“Foreign” cells

Cell

replacement
therapy

ES cells

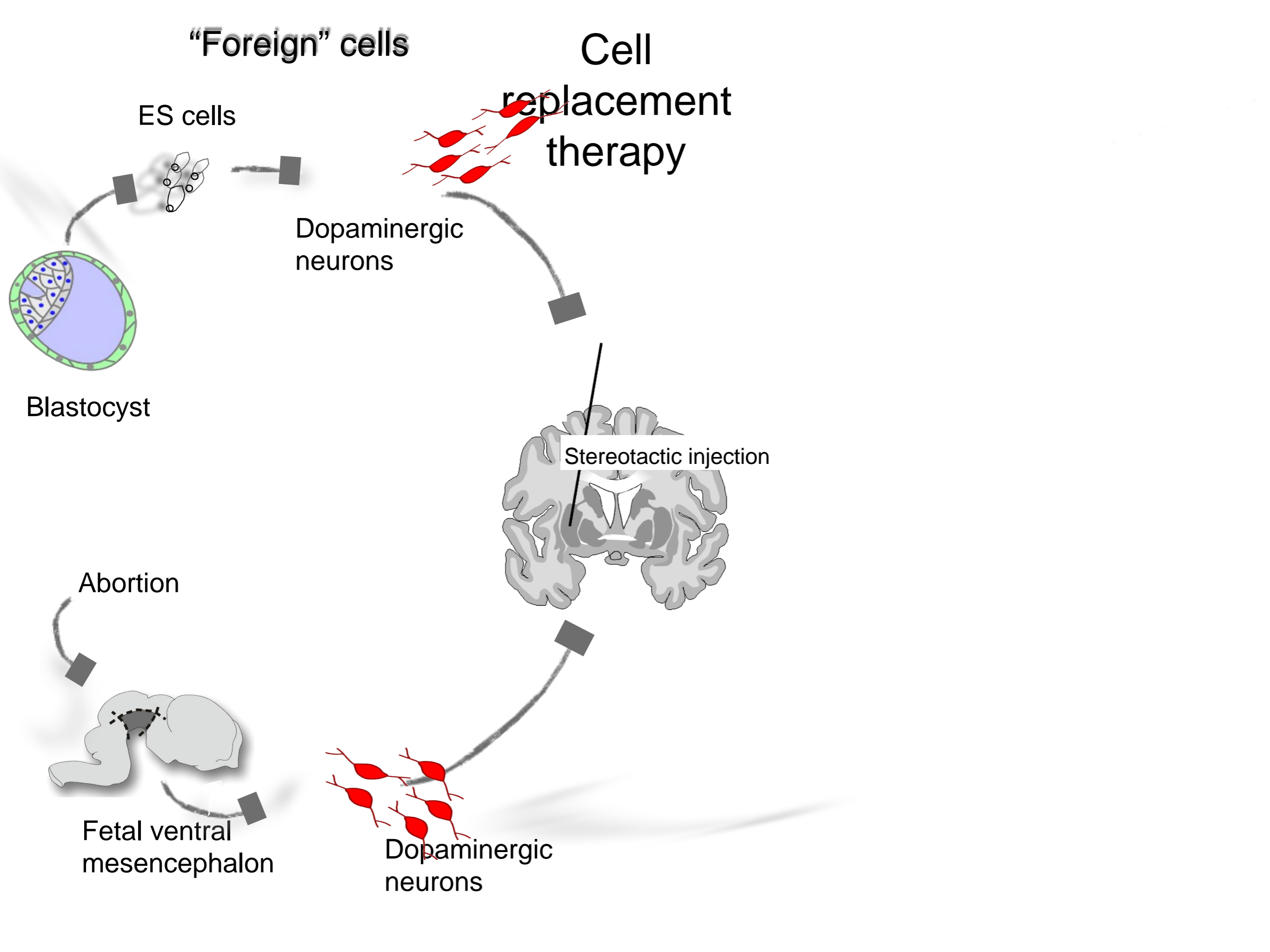
Dopaminergic
neurons

Stereotactic injection

Abortion

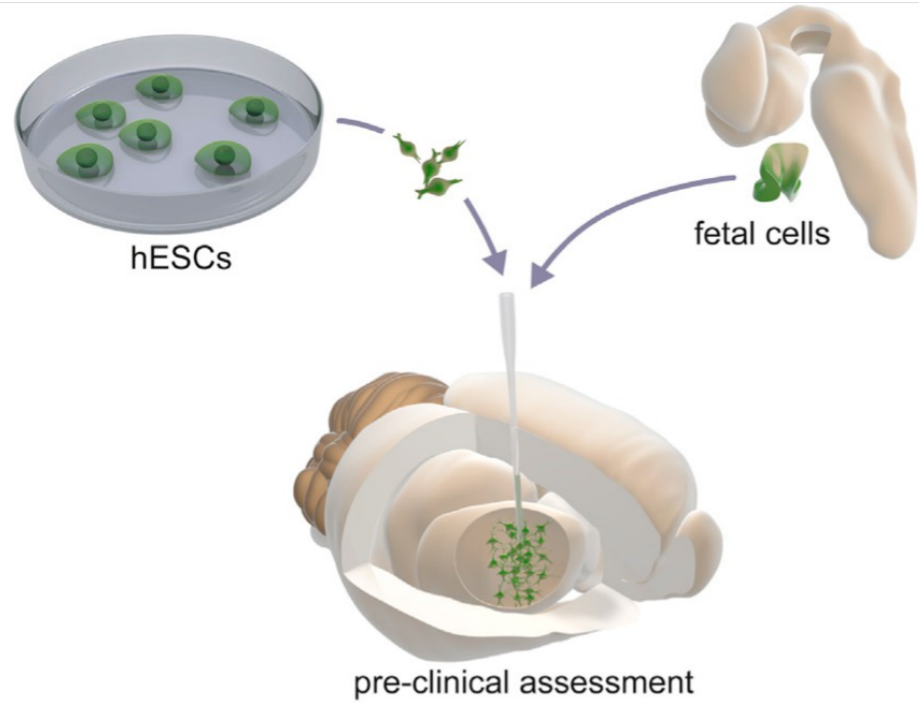
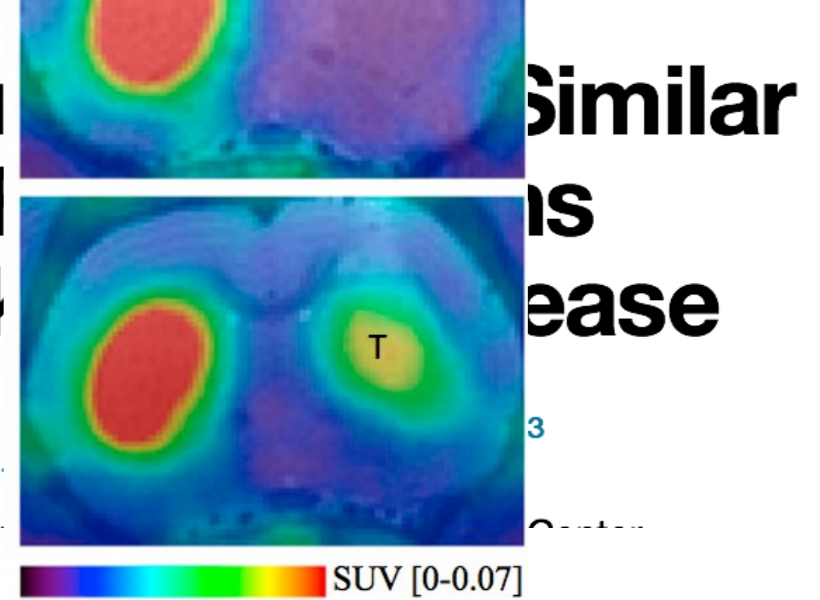
Fetal ventral
mesencephalon

Dopaminergic
neurons

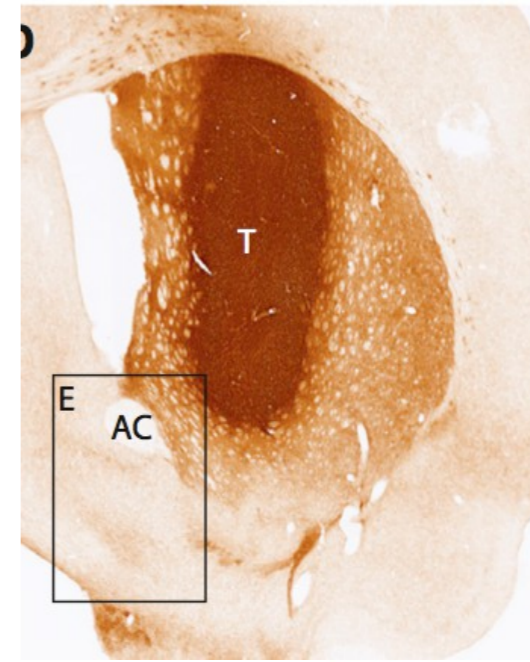
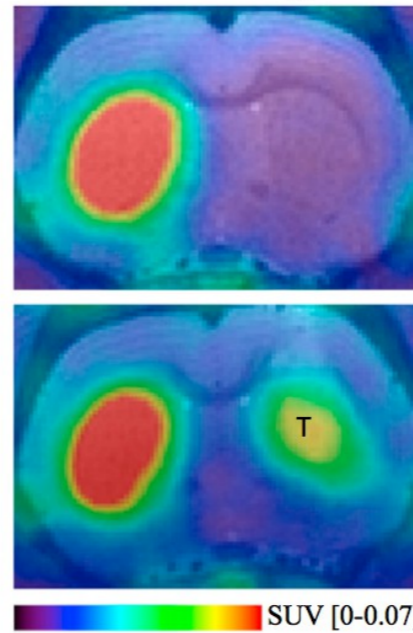


Human ESC-Derived Dopamine Neurons Preclinical Efficacy and Potency to Improve when Grafted in a Rat Model of Parkinson's Disease

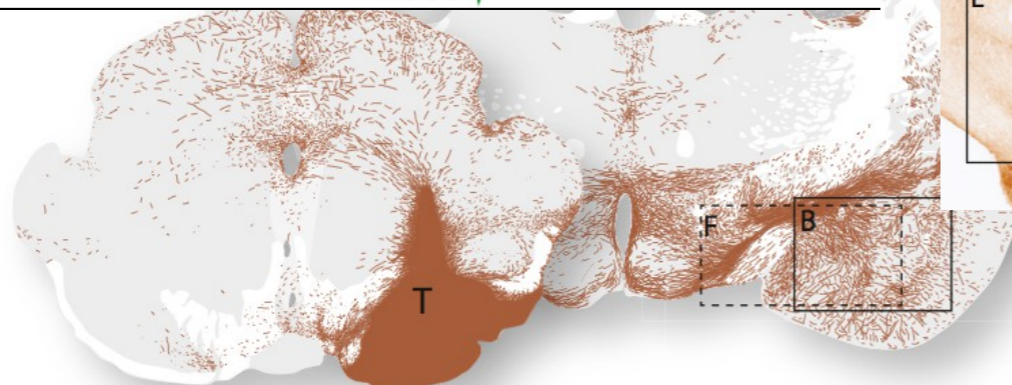
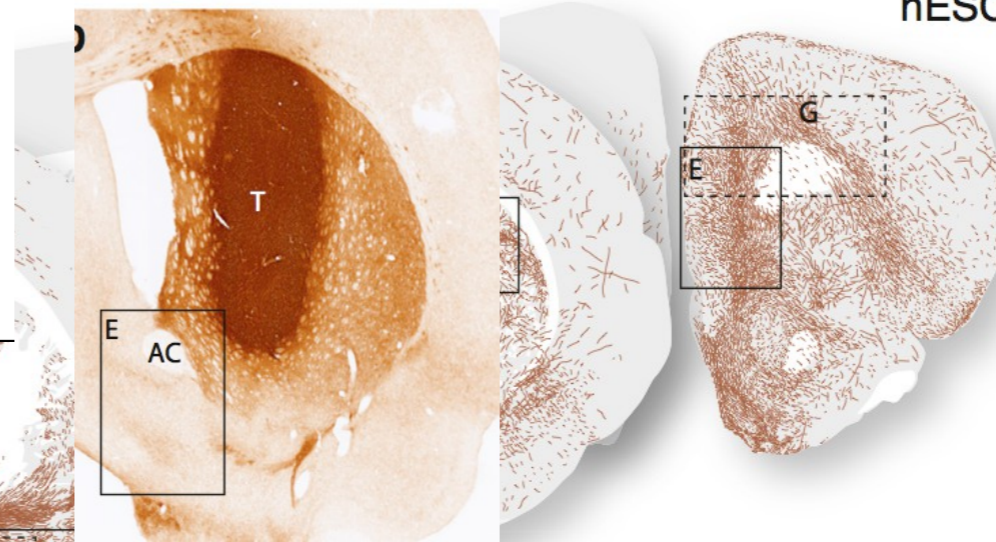
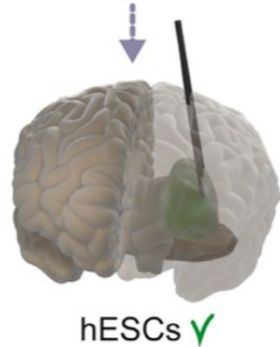
Shane Grealish,^{1,2,*} Elsa Diguët,³ Agnete Kirkeby,^{1,2} Bengt Mattsson,¹ Andreas Nadja Van Camp,³ Anselme L. Perrier,^{4,5} Philippe Hantraye,³ Anders Björklund,^{1,2}



¹⁸F-LBT999 PET
DAT binding



pre-clinical assessment



Dr Yamanaka - father of the iPS cell



“Foreign” cells

Cell

“Own” cells

replacement
therapy

ES cells

Dopaminergic
neurons

Somatic cells
(e.g. fibroblasts)

Reprogramming

Blastocyst

Patient
(skin)
biopsy

iPS cells

Stereotactic injection

Direct
reprogramming
(iN cells)

Abortion

Direct
reprogramming
(iN cells)

In vitro
differentiation

Fetal ventral
mesencephalon

Dopaminergic
neurons

Dopaminergic
neurons

