Institute of Psychiatry

at The Maudsley

CCBB at the IoP

KING'S College LONDON

Brain Reconstruction: the next biomedical breakthrough, or a biological impossibility?

Jack Price

Centre for the Cellular Basis of Behaviour

Institute of Psychiatry, KCL.

1.

Brain Repair with stem cells

2.

The Impossibility of Brain Reconstruction?

3.

A way forward?

Brain Repair:
the unmet medical need

- Stroke
- Traumatic Brain Injury
- Alzheimer’s disease
- Parkinson’s disease
- Batten’s disease
- Cerebral palsy

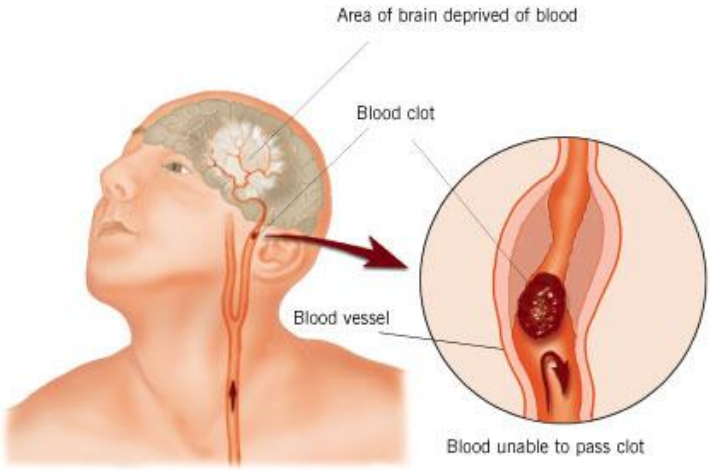
Stroke

-**150,000** Britons per year

- Third most common cause of death in the USA & Europe

-Most common cause of severe disability

-A major area of unmet medical need.



Brain Reconstruction:

the fantasy?

When Will We Be Able to Build Brains Like Ours?: Scientific American 18/04/2012 14:43

SCIENTIFIC AMERICAN™

Permanent Address: **http://www.scientificamerican.com/article.cfm?id=when-build-brains-like-ours**

When Will We Be Able to Build Brains Like Ours?

Sooner than you think -- and the race has lately caused a 'catfight'

By Terry Sejnowski | Tuesday, April 27, 2010 | 47 comments

Blue Brain Project

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

"It is not impossible to build a human brain and we can do it in 10 years."

Henry Markham

Human Enhancement

- Positive

> “These same powers that can repair and replace diseased or damaged tissue may, in a healthy individual, augment normal functioning. That is why regenerative medicine may never be simply or merely therapeutic, but is likely always to have an enhancing dimension.”

Harris (2007)

Human Enhancement

- Negative

> "…there is at least a theoretical prospect that these cells will alter the recipients' cognition, mood, and behaviour—brain functions that are central to our concept of the self (especially to our personality, character, and agency)."

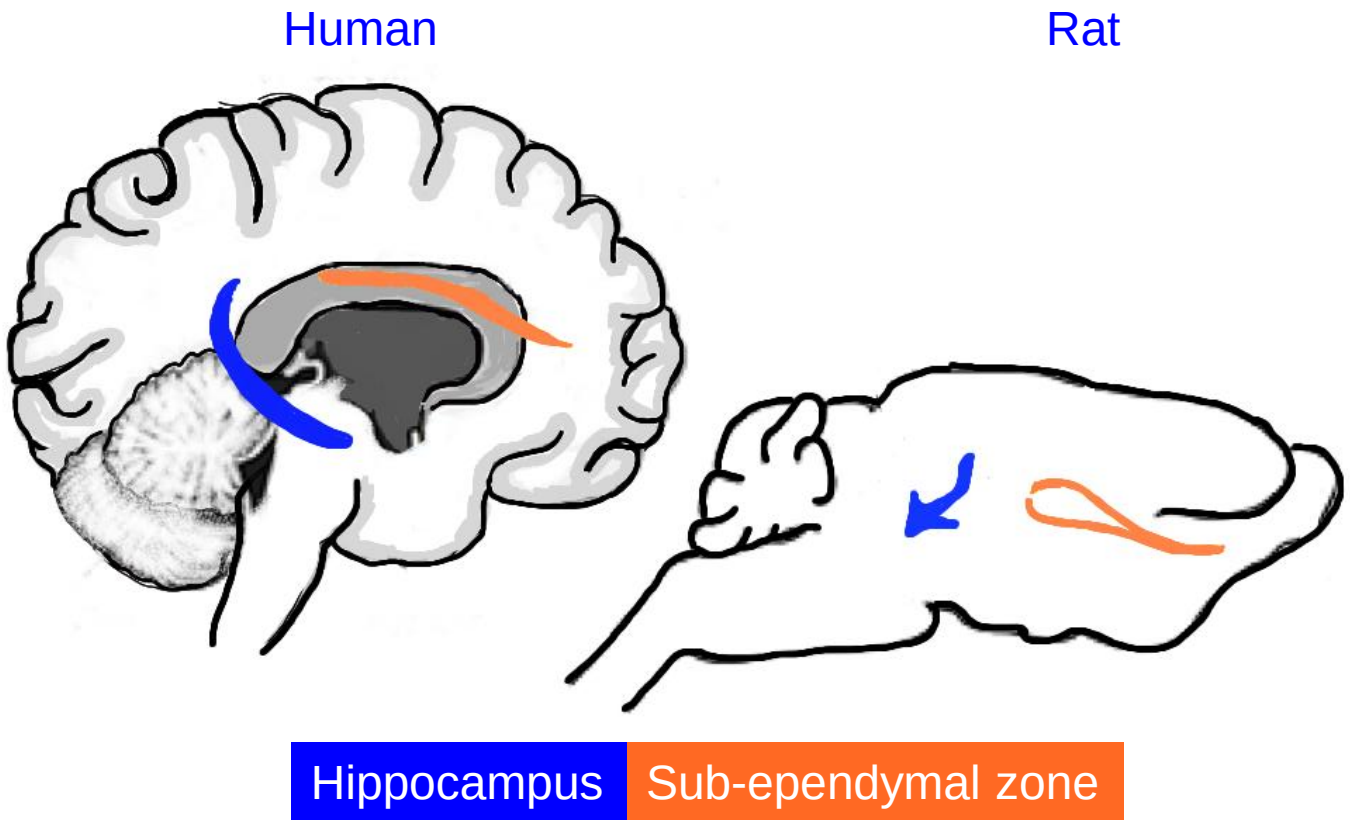
> "That early human trials of CBIs for neurological conditions must monitor subjects for changes in cognition, mood, and behaviour."

Duggan et al (2009) AM J BIOETHICS

Approaches to Brain Reconstruction

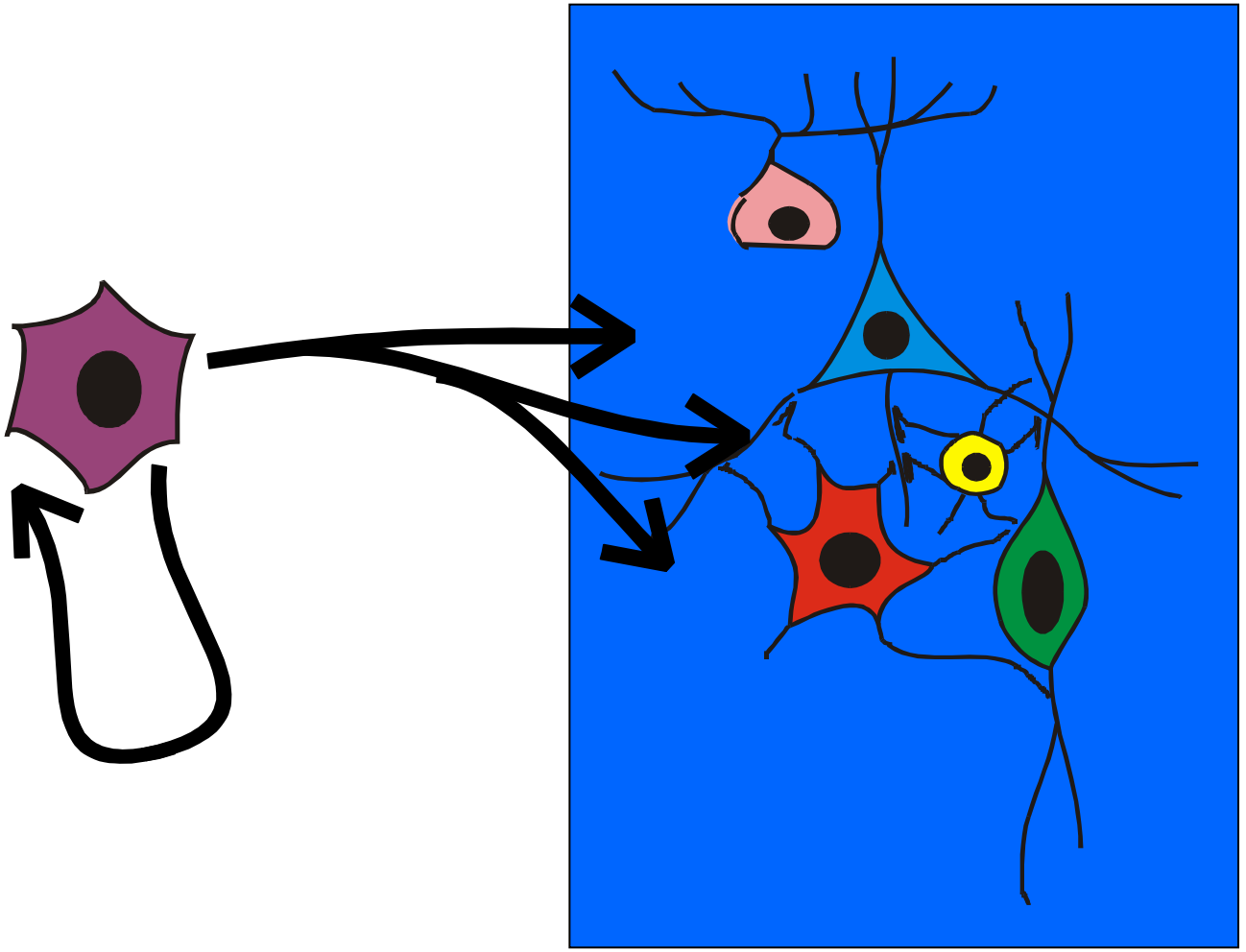
- Endogenous neurogenesis
- Stem cell transplantation
- Stem cells ‘plus’

Sites of adult neurogenesis

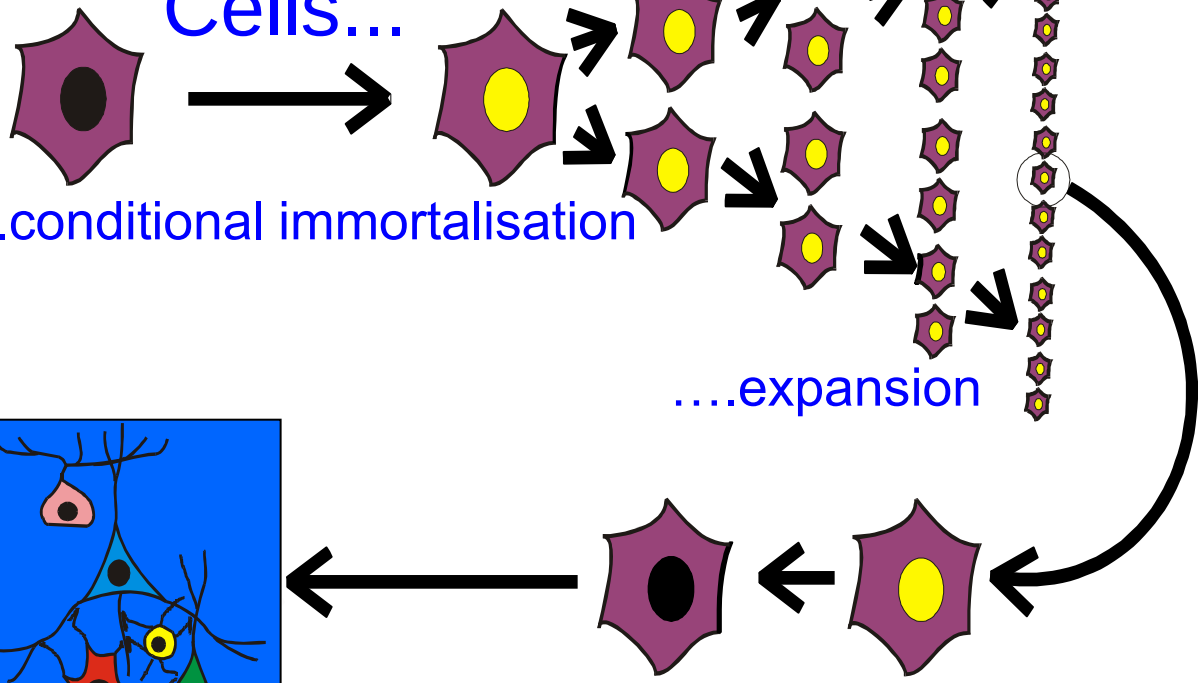


A stem cell transplantation strategy

Neural Stem Cells….



Neural Stem Cells...

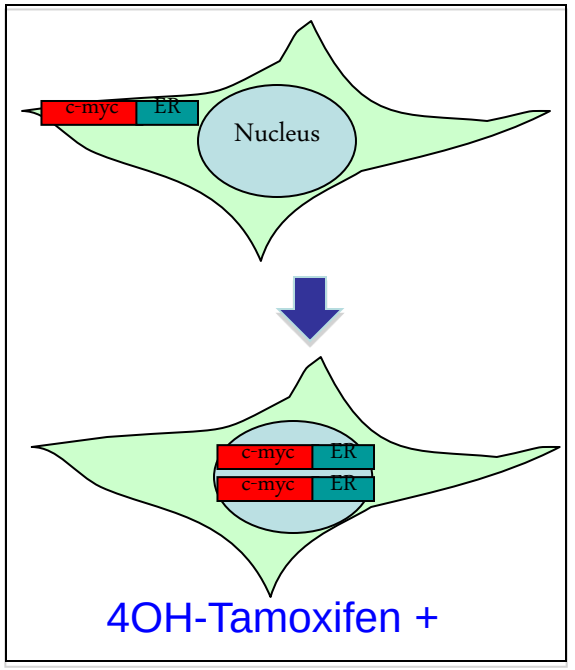


….conditional immortalisation

….expansion

….and retention of multipotentiality

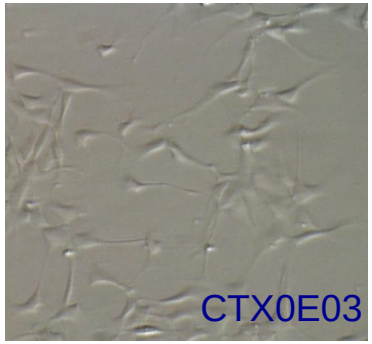
...and differentiation

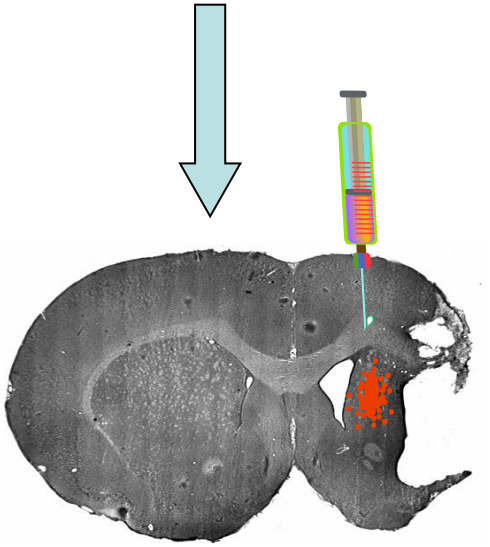


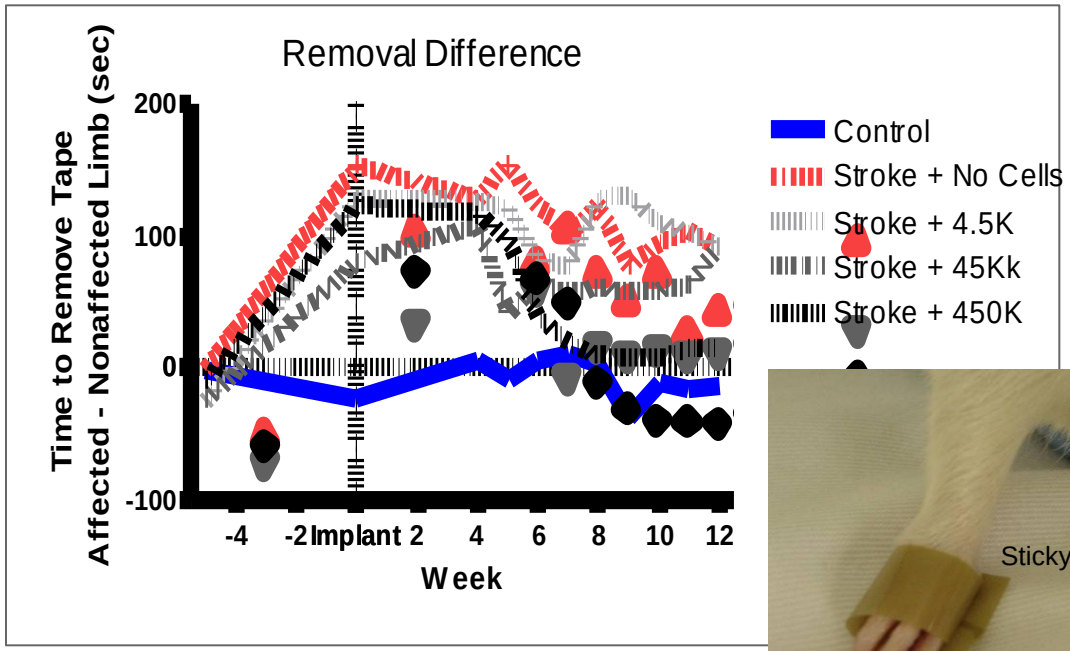
4OH-Tamoxifen +

Pollock et al (2006) *Exp. Neurol.*

Stroke







Mike Modo
Paul Stroemer.

Monday 22 November 2010 — Log in | Register

The Telegraph

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Health News

World's first stem cell trial for stroke patients

Doctors have injected stem cells into the brain of a British stroke patient in the world's first trial of its kind.

By Stephen Adams, Medical Correspondent 2:23PM GMT 16 Nov 2010

Comments

The elderly man was injected with roughly two million neural stem cells at Southern General Hospital in Glasgow. They hope the stem cells will help the man recover from his stroke, by transforming themselves into mature neurons and also stimulating the brain to harness its own recuperative powers.

His progress will be monitored over the next two years.

The method controversially uses neural stem cells, those taken from the nascent brain of a discarded foetus.

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PharmaTimes ONLINE

Tapping into the patient pathway

First patient treated in ReNeuron's UK stem cell trial

BBC NEWS HEALTH

11 October 2010 Last updated at 16:34

First trial of embryonic stem cells in humans

By Michelle Roberts, Health reporter, BBC News

US doctors have begun the first official trial of using human embryonic stem cells in patients after getting the green light from regulators.

The Food and Drug Administration has given a licence to Geron to use the controversial cells to treat people with spinal injuries.

The cells have the potential to become many of the different cell types found in the body, including nerve cells.

The trials at a hospital in Atlanta will check if the treatment is safe.

Pivotal research

Geron, a biotech company based in "silicon valley" south of San Francisco, has spent $170m on developing a stem cell treatment for spinal cord injury.

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News › Science › Embryos and stem cells

Stem cells injected into the brain of a stroke patient in world first

Researchers hope the brain stem cells will stimulate the growth of new neurons and reduce inflammation caused by the stroke

Tweet 133 Share 994

Comments (60)

Ian Sample, science correspondent
guardian.co.uk, Tuesday 16 November 2010 13.03 GMT
Article history

A larger | smaller

The stem cells will release chemicals that may help heal brain damage resulting from the stroke. Photograph: Bbs United/Getty Images

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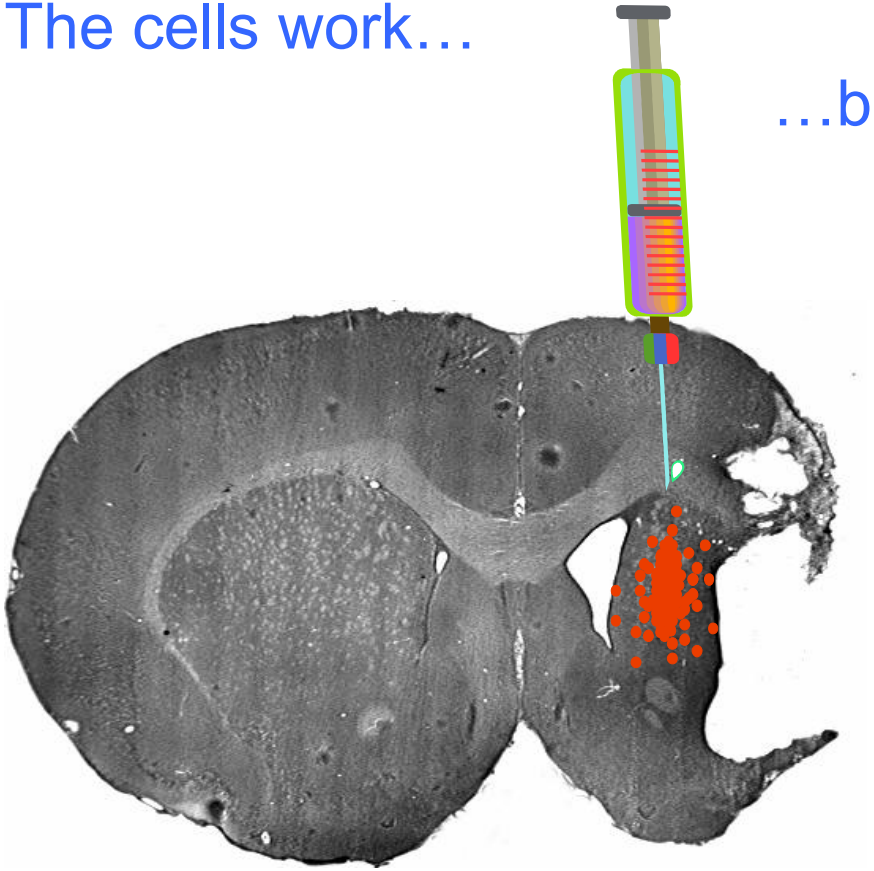
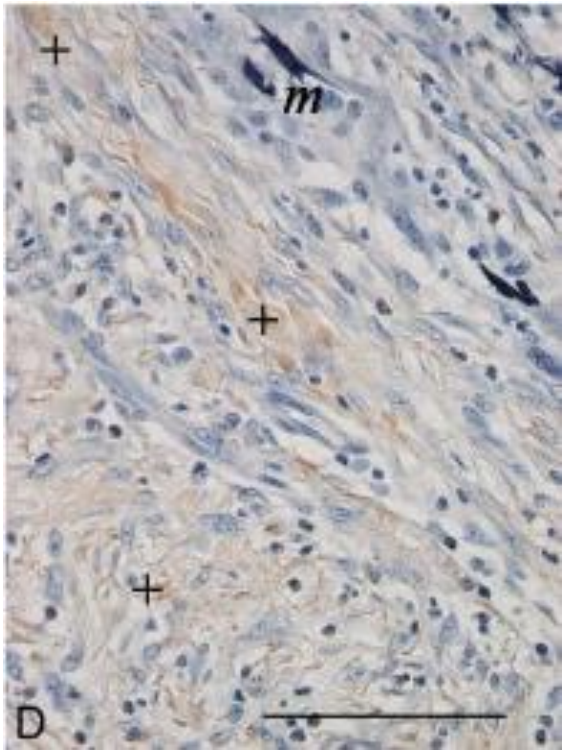
Problem:

The cells work…



…but not the way we anticipated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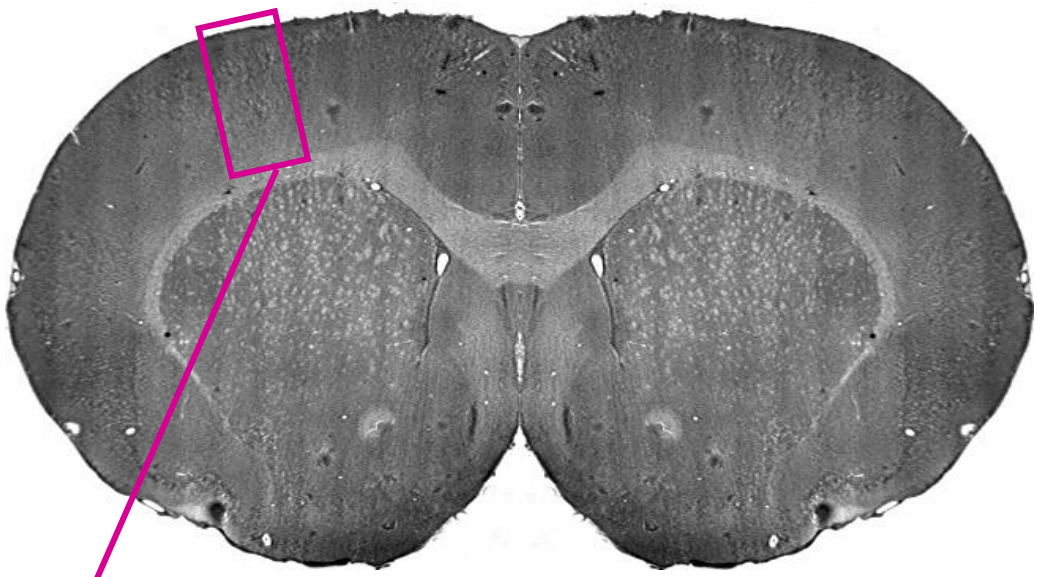

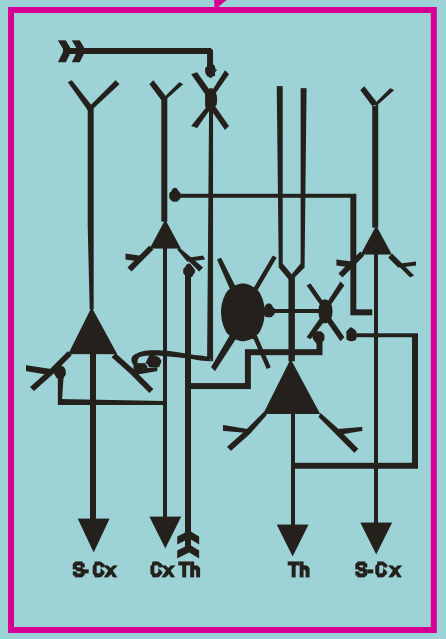
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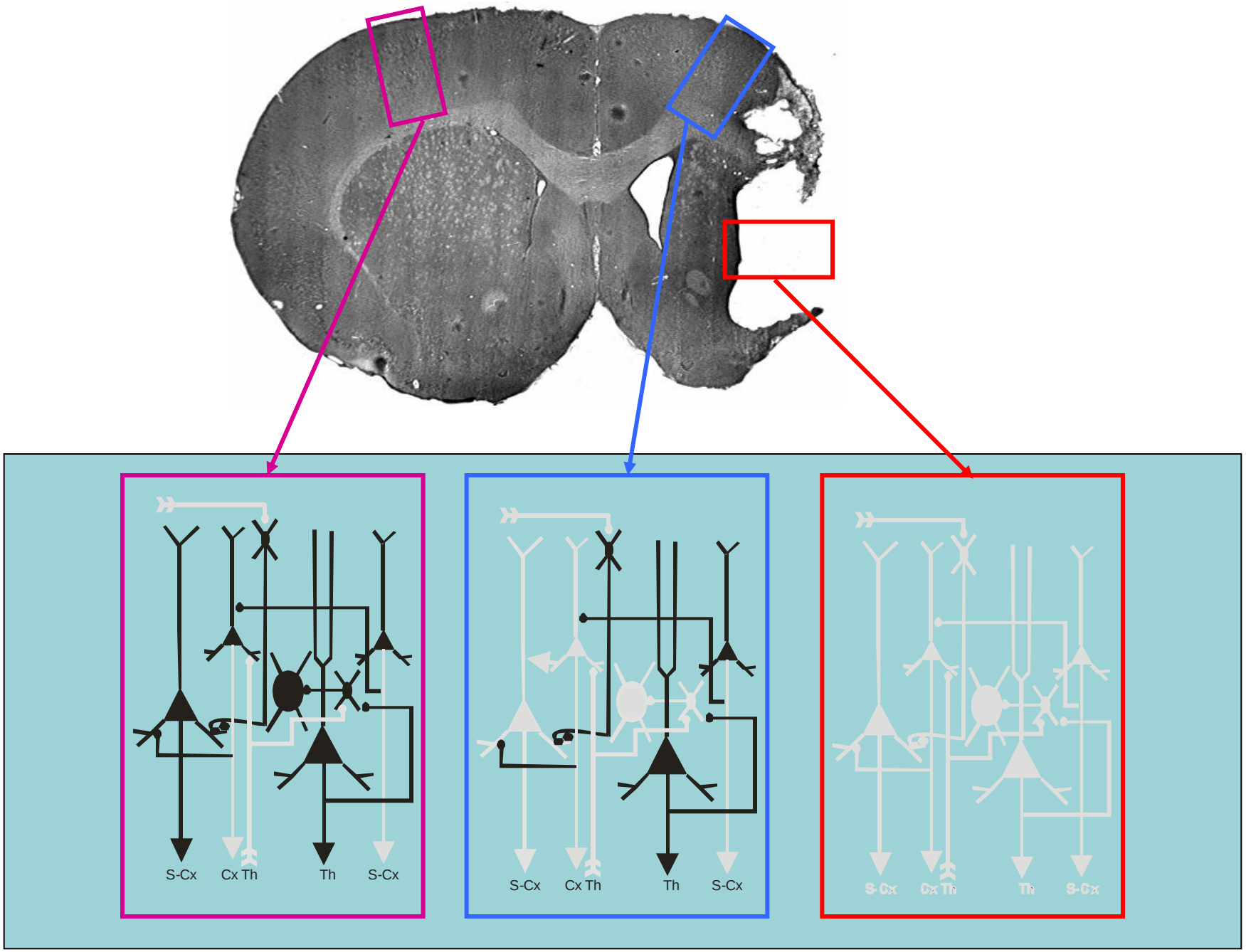
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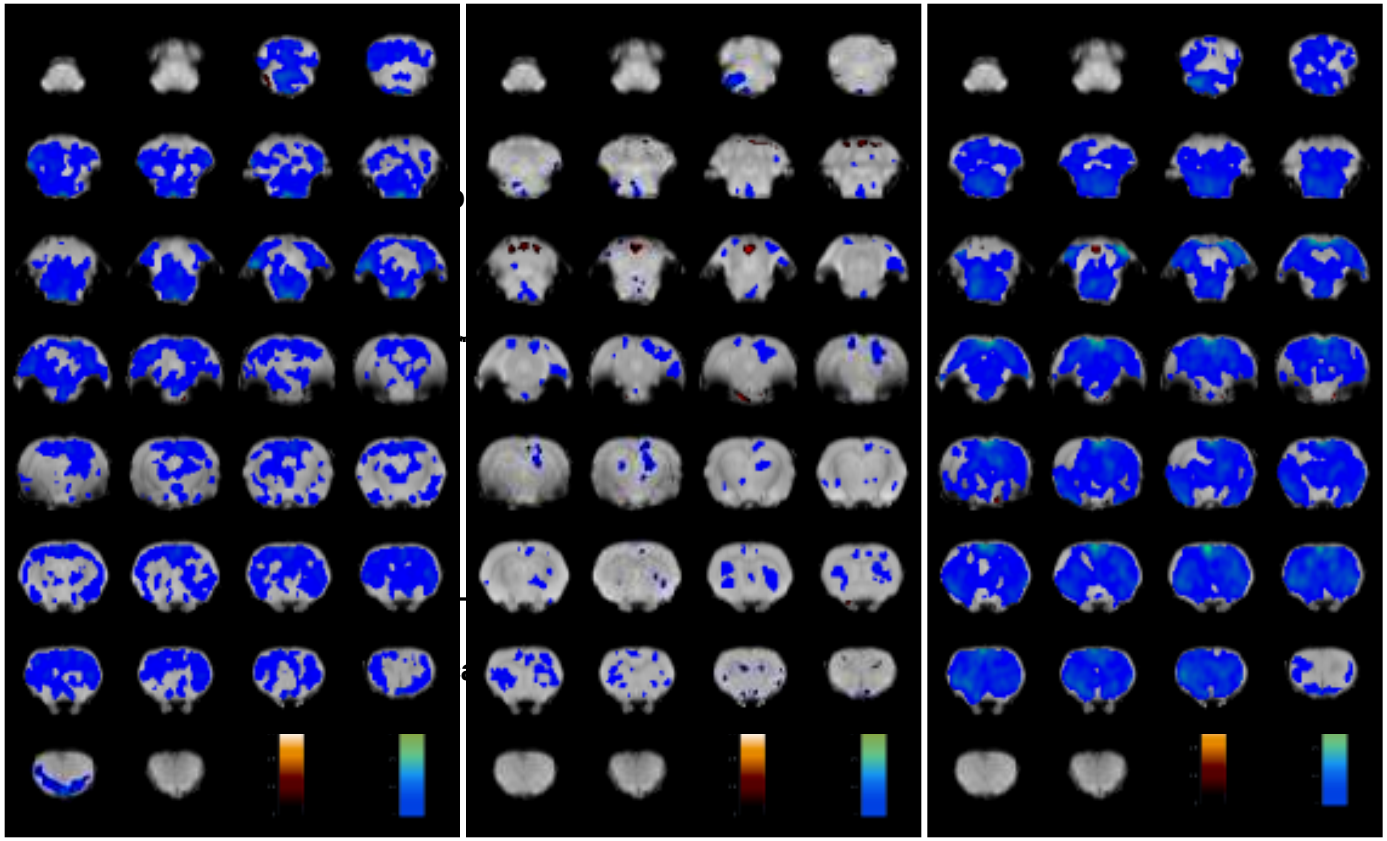
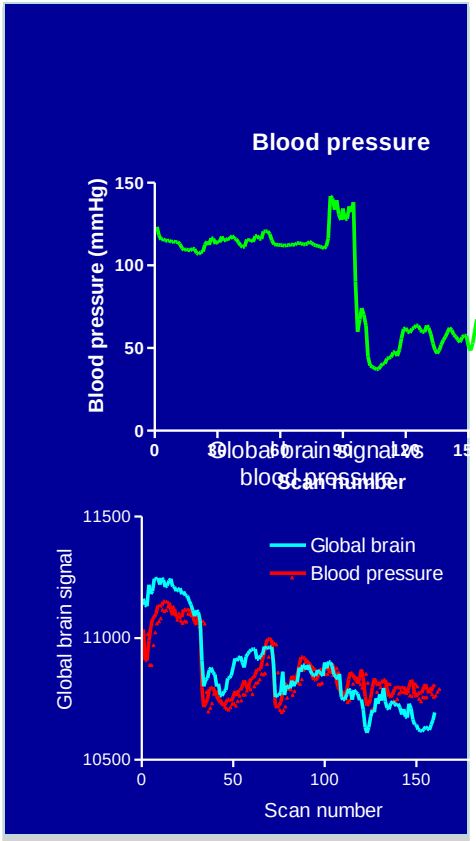
phMRI of D2-agonist bromocriptine

Control Lesion Transplant

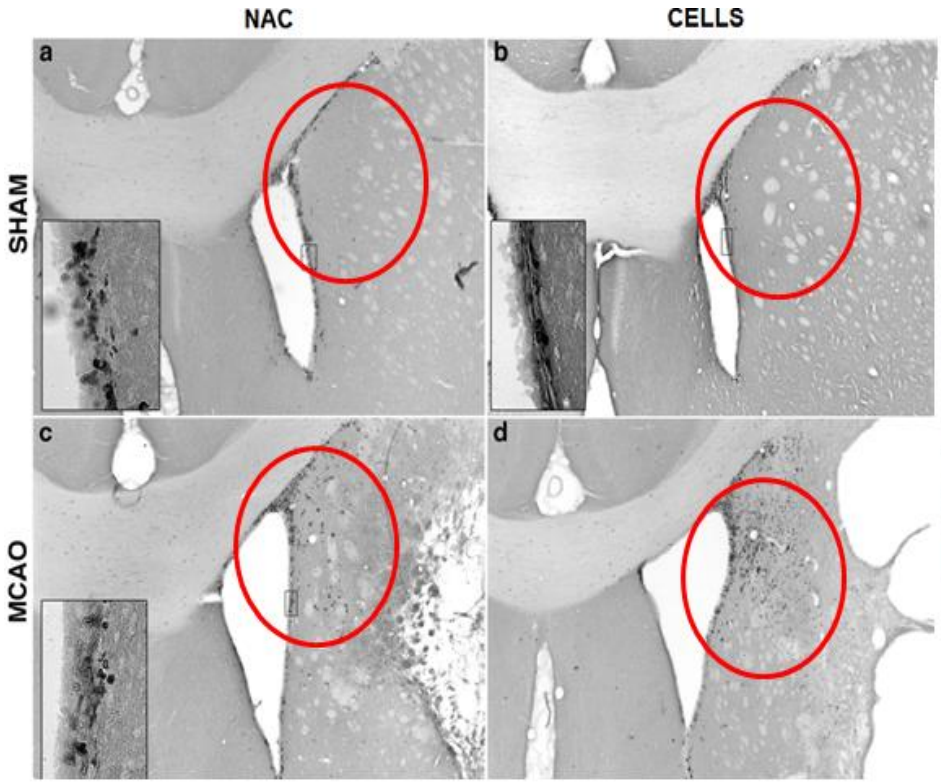


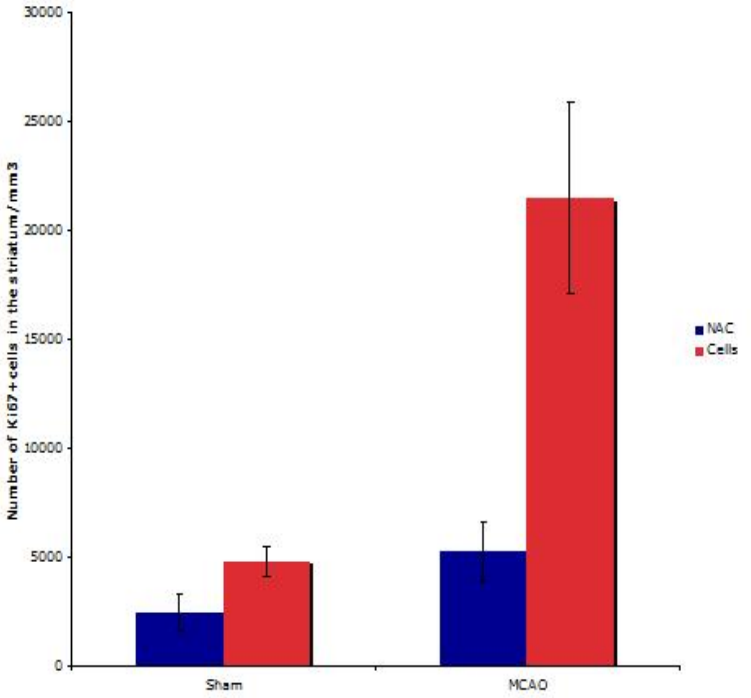


BOLD—blood oxygen level dependant phMRI

Toby Roberts
Mike Modo
Steve Williams

More young neurons in following a stroke and graft.





Zahra Hassani
Sandrine Thuret
Paul Stroemer

The Good News

…we have a novel potential therapy…

The Bad News

…it is NOT brain reconstruction

(except in a narrow sense)

How close are we to true Brain Reconstruction?

…not very.

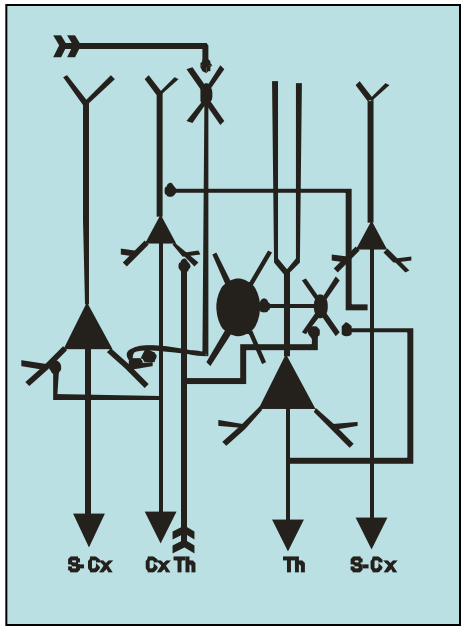
Problems:

- Conceptual: how to build brain tissue?
- Regulatory: how to generate a therapeutic?

Technical/Conceptual issues

1. We don’t know how to build brain tissue

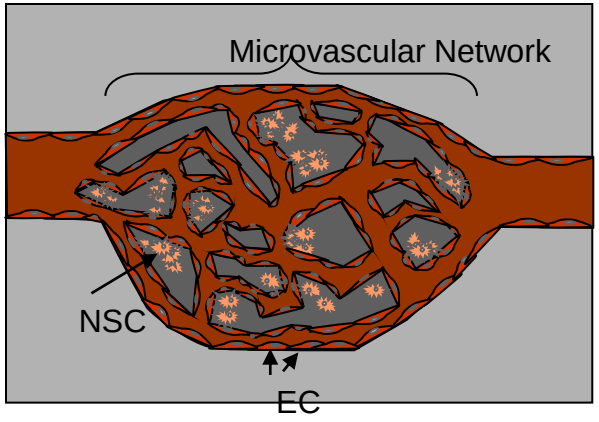
This is not development, and the brain has no blastema

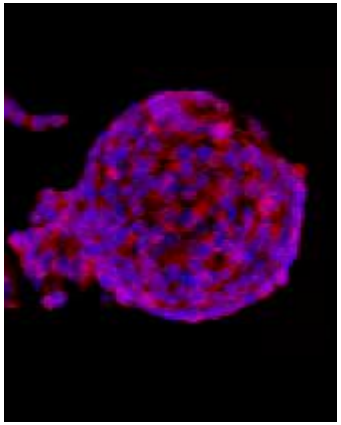


- Cell fate
- Building circuits
- Embryonic parameters
- Ephemeral factors
- Emergent properties

Technical/Conceptual issues

2. How to build a brain reconstruction device?





- A fully constructed device?
- A self-assembly system?

Regulatory Issues

How would you test safety and efficacy of such a device?

- The device would have to integrate into intact brain without causing neuropathic pain, seizures, dystonia, or tissue rejection
- The device would mimic and enhance human brain function, yet deliver efficacy in an animal model

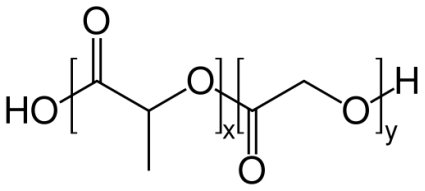
Consider

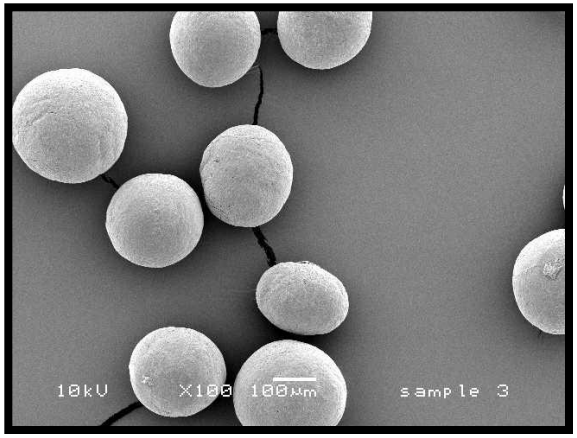
• The Stanfield experiment

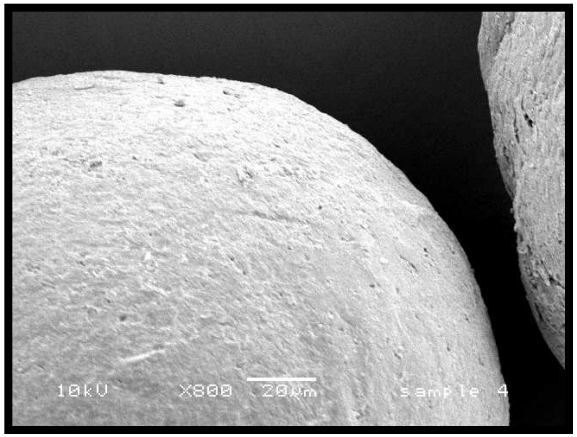
• Human cortical connectivity

The ‘Stem Cell Plus’ strategy

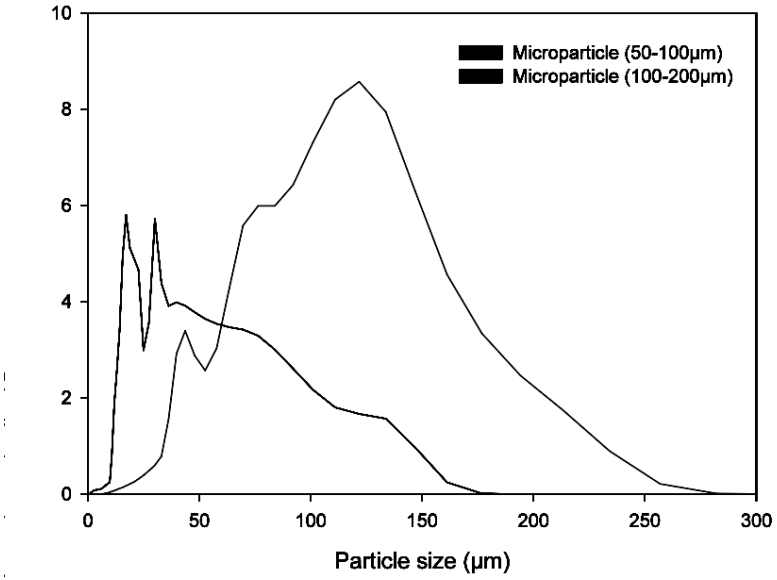
Poly(lactic-*co*-glycolic acid)







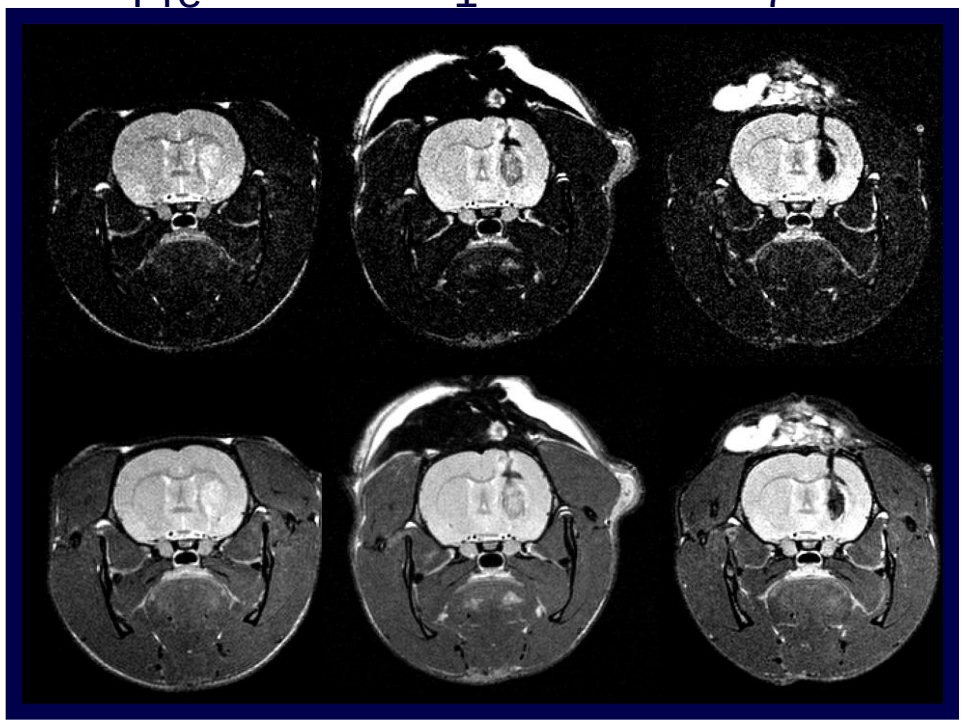
Engineering Scaffold Particles

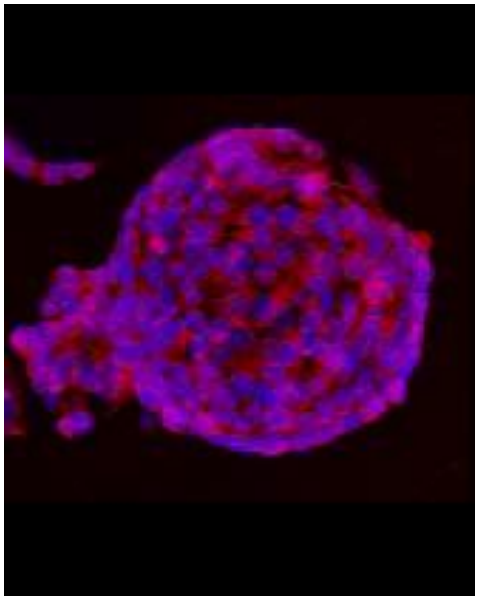


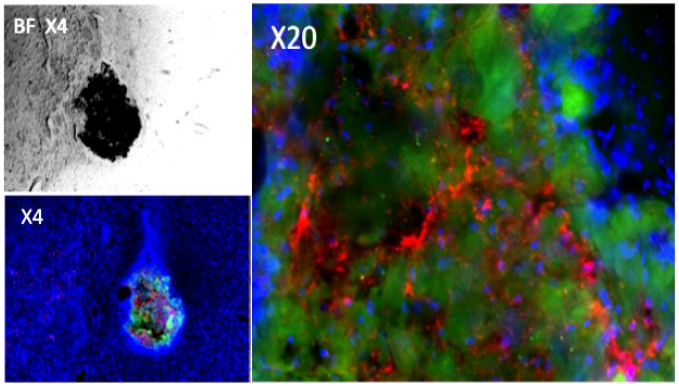
Bible et al (2009) Biomaterials

Bible et al (2009) Nature Protocols

The ‘stem cell plus’ strategy

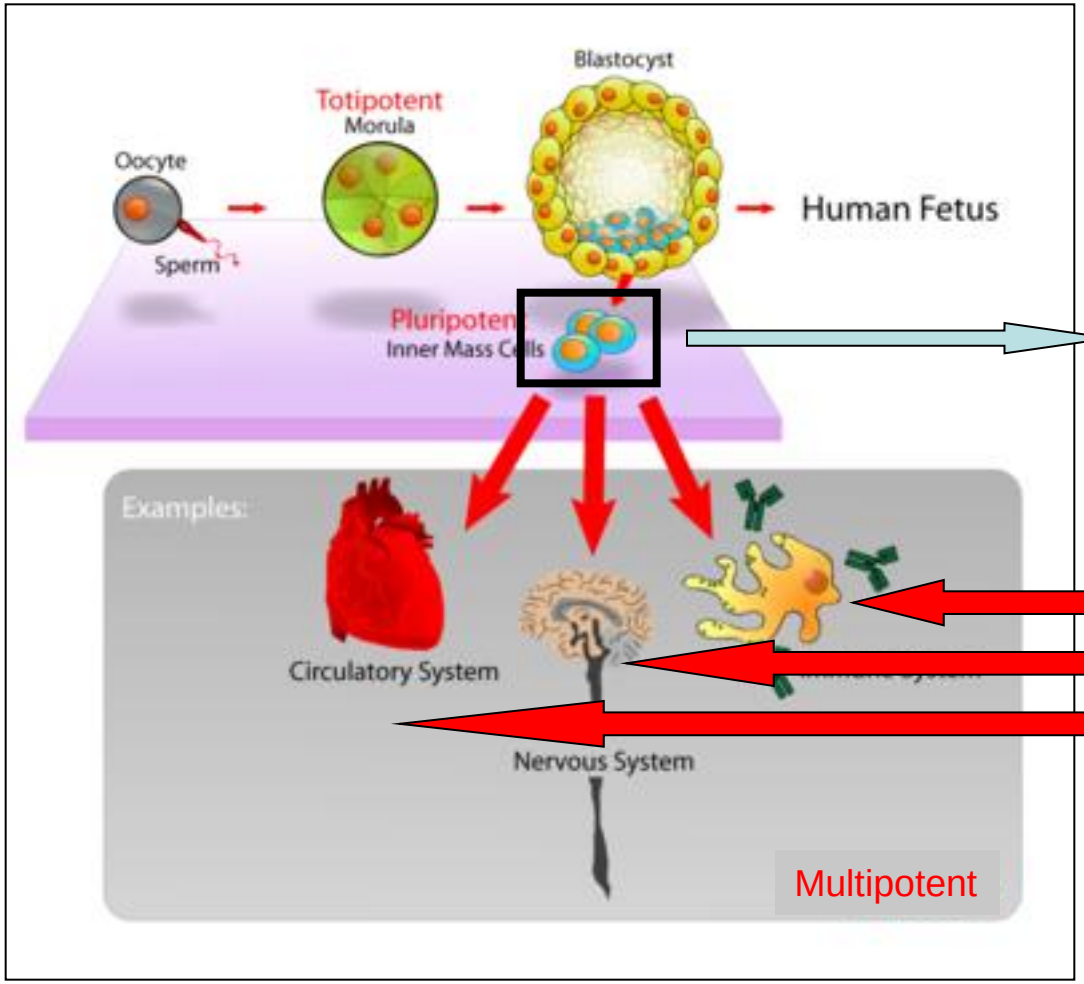


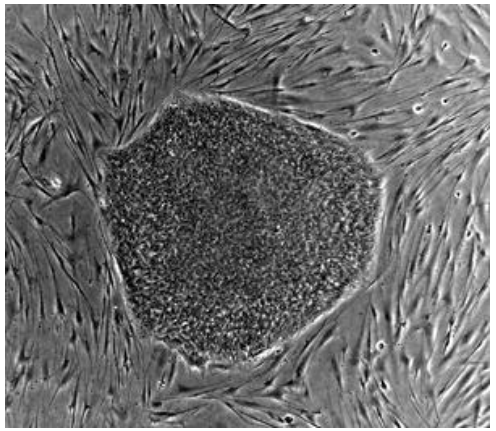




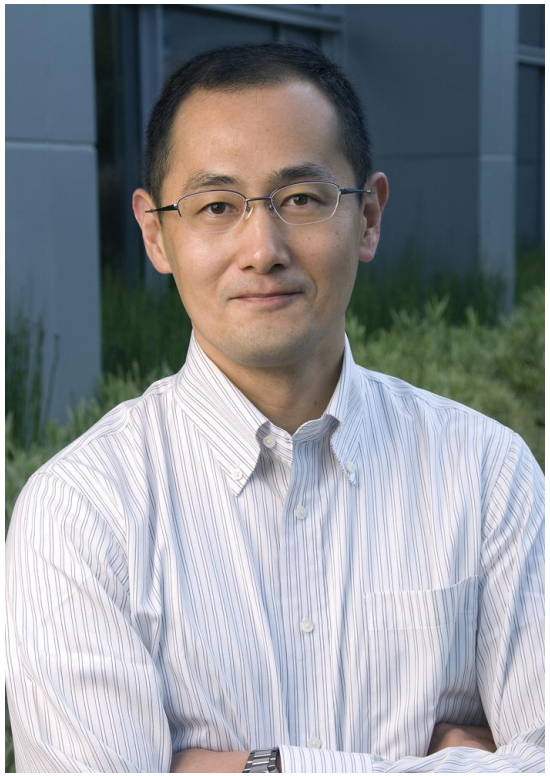
Mike Modo
Ellen Bible
David Chao
Kevin Shakesheff
Jack Price

A way forward?
pluripotent stem cells





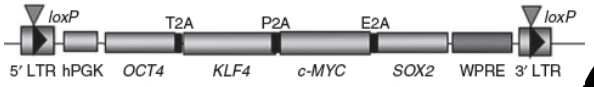
ES cells



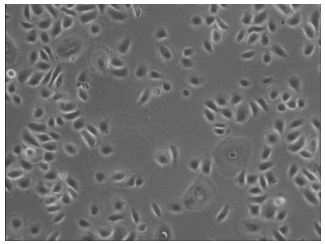
Shinya Yamanaka

Induced pluripotent cells (iPSCs) from human hair

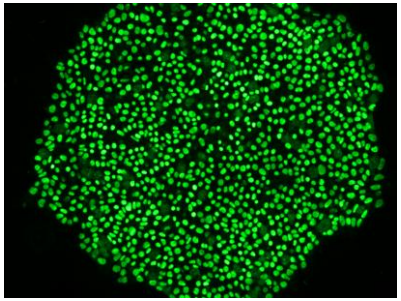
The four 'Yamanaka Factors'



Keratinocytes

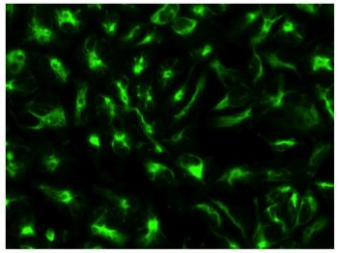


Hair sample

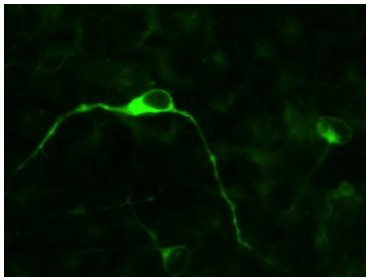


iPS Colonies

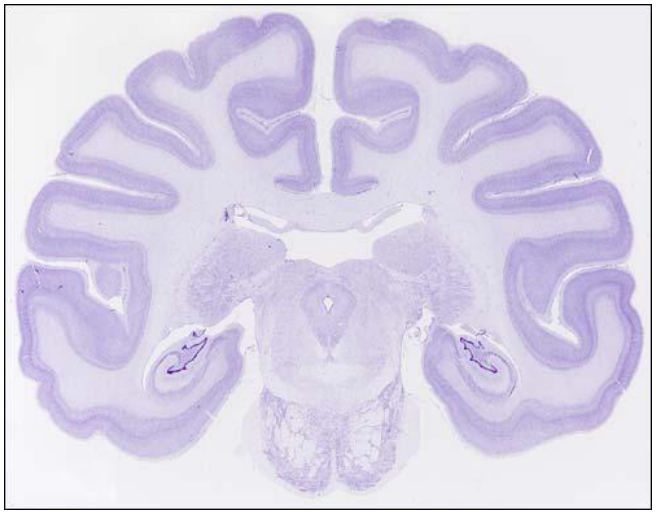
Neural stem cells

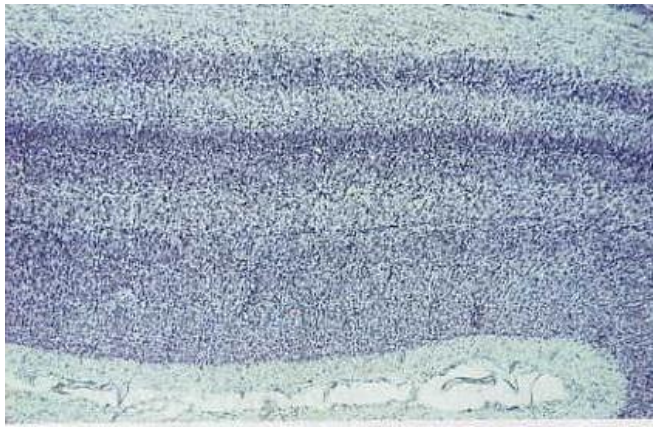


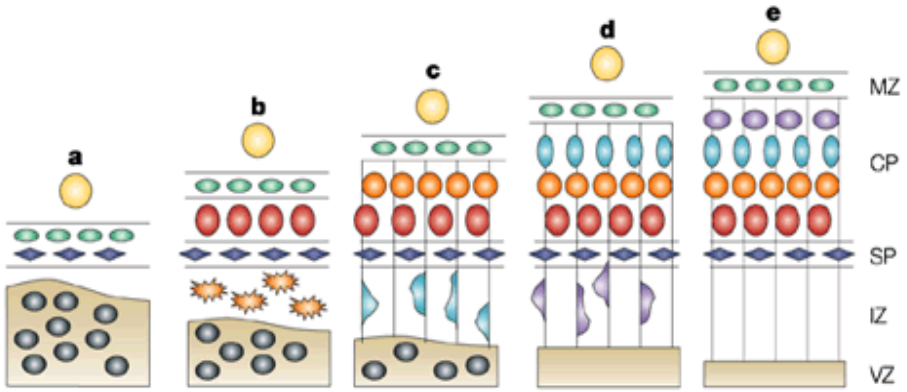
Neurons



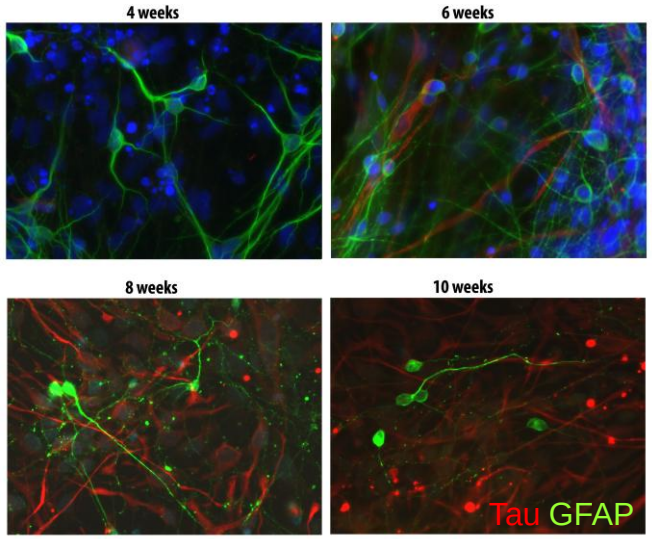
Corticogenesis

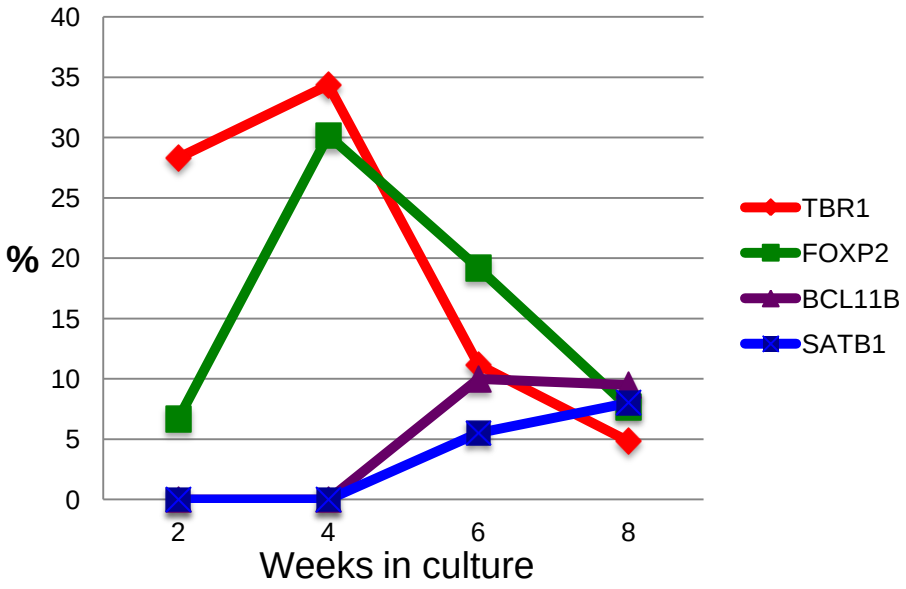


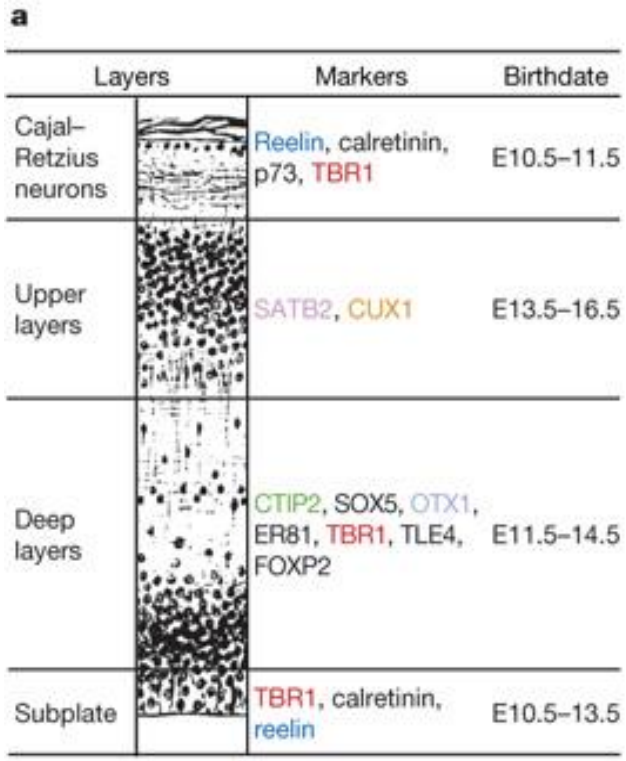




Corticogenesis







N Gaspard *et al. Nature* **455**, 351-357 (2008)

…or more like