KING'S College LONDON

INSTITUTE OF PSYCHIATRY,
PSYCHOLOGY & NEUROSCIENCE

Module:
Biological Foundations of Mental Health

Week 2:
Building blocks of the brain

Prof. Jack Price

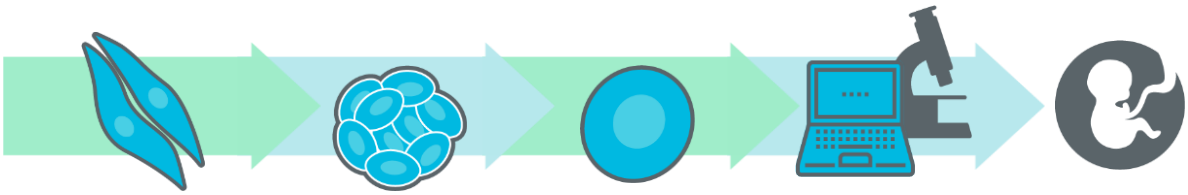
Topic 3:

Exploring mental health using stem cells

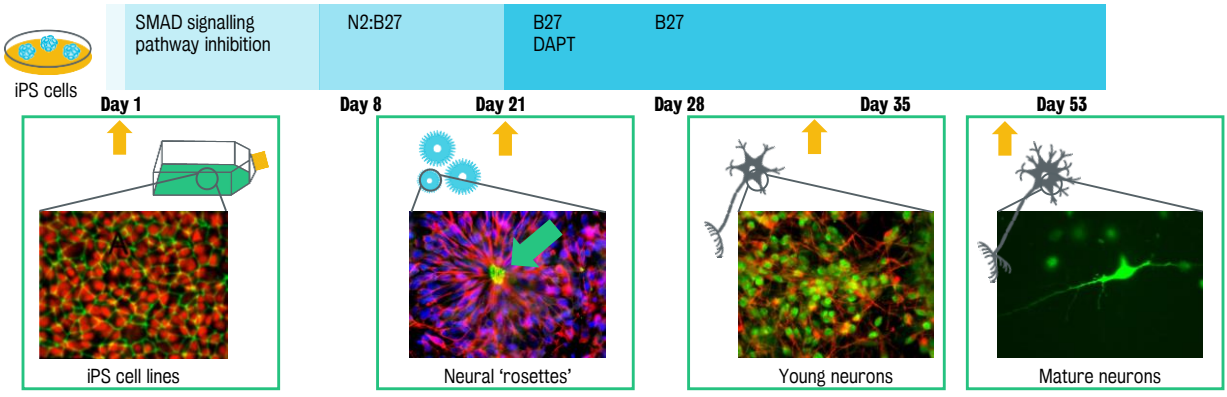
Part 3 of 3

Part 3

The aetiology of neurodevelopmental disorders



Reviewing the timeline of iPSCs' generated neurons



Cocks et al. (2014)

iPSCs and neurodevelopment disorders: Possible studies

How can we use iPS cells to address questions around the aetiology of neurodevelopmental disorders?

Possible studies

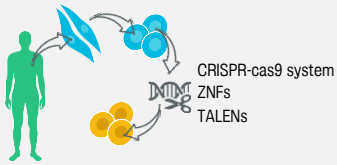
Compare lines from patients and controls

Patients: Individuals with particular disabilities or particular neurovariants

Controls: Neurotypical individuals

Induce mutations in iPSCs

There are several ways of inducing genetic variation (genome editing) into cells *in vitro*:



Study environmental risk factors

Autism risk increases if the mum suffers from influenza during her first trimester.

iPSCs and neurodevelopment disorders: Possible phenotypes

What kind of assays are we going to run on these cells to detect differences?

Possible phenotypes

Gene expression

Patients or controls

Genetic mutations or exposure to environmental risk factors

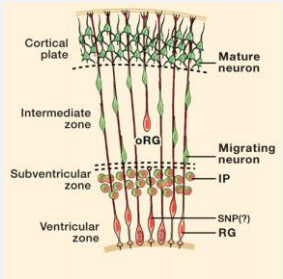
Study differences in gene expression during development

Physiological

iPS cells eventually become electrophysiologically active.

They develop the kind of channels and receptors commonly present in human neurons.

Morphogenetic

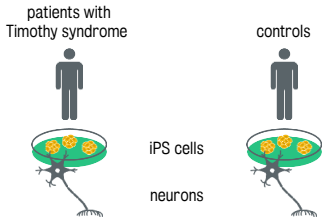


Compare the histogenesis of iPSCs derived from patient and control cells

Using iPSCs to study disease pathophysiology

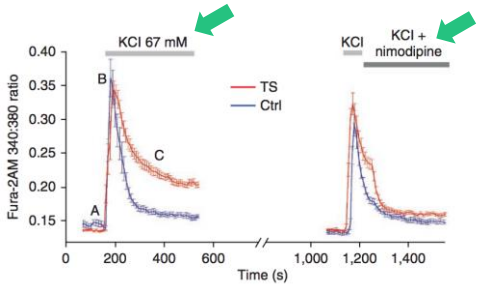
Pasca and colleagues (2011)

Study:
Use of iPS-derived neurons to study the pathophysiology of Timothy syndrome (caused by point mutation in CACNA1C and encodes the α1 subunit of $Ca_v1.2$.).



Method:
Examine the differences between patients and controls in terms of neurons and behavior of the calcium channel.

Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy Syndrome



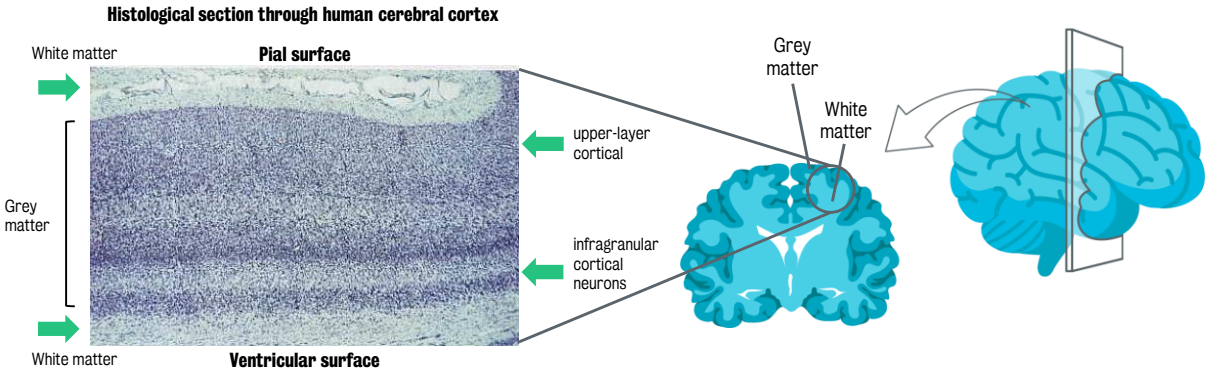
Despite the conclusive results, these were inevitably predicable.

Pasca et al. (2011)

Histogenesis and corticogenesis

Pasca and colleagues (2011)

Histological section through human cerebral cortex

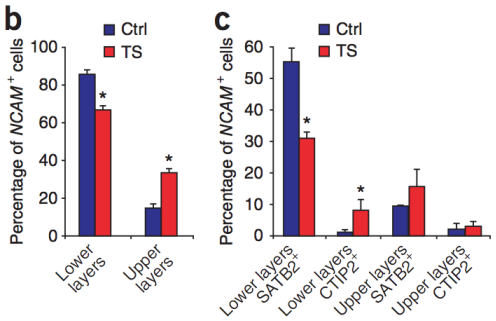


Pasca et al. (2011)

Timothy syndrome: Altered SATB2 neurons (1)

Pasca and colleagues (2011)

Altered generation of SATB2 neurons in Timothy Syndrome

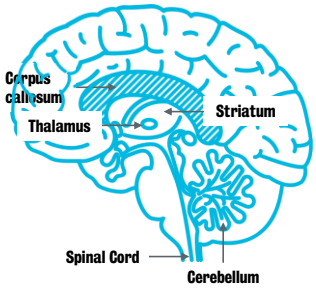


Findings:

- neurons derived from the Timothy syndrome iPSCs had a greater propensity to make upper-layer neurons, and a reduced propensity to make lower-layer neurons
- a smaller proportion of the lower-layer cells showed expression of gene SATB2

Subcortically projecting neurons: Project to subcortical regions of the brain

Callosal projecting neurons (where SATB2-positive cells belong): Project across the corpus callosum to the cerebral cortex on the other hemisphere.



Conclusion:

- neurons from the Timothy syndrome patients have a lower proportion of the SATB2-positive cells (a lower proportion of the callosal projecting neurons)

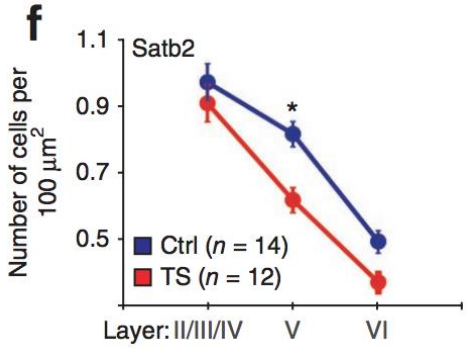
Pasca et al. (2011)

Timothy syndrome: Altered SATB2 neurons (2)

The authors were also able to look at transgenic mice engineered to carry precisely the mutation that is found in the Timothy syndrome.

TS mouse: This mouse is generated using a different technique not involving iPSCs

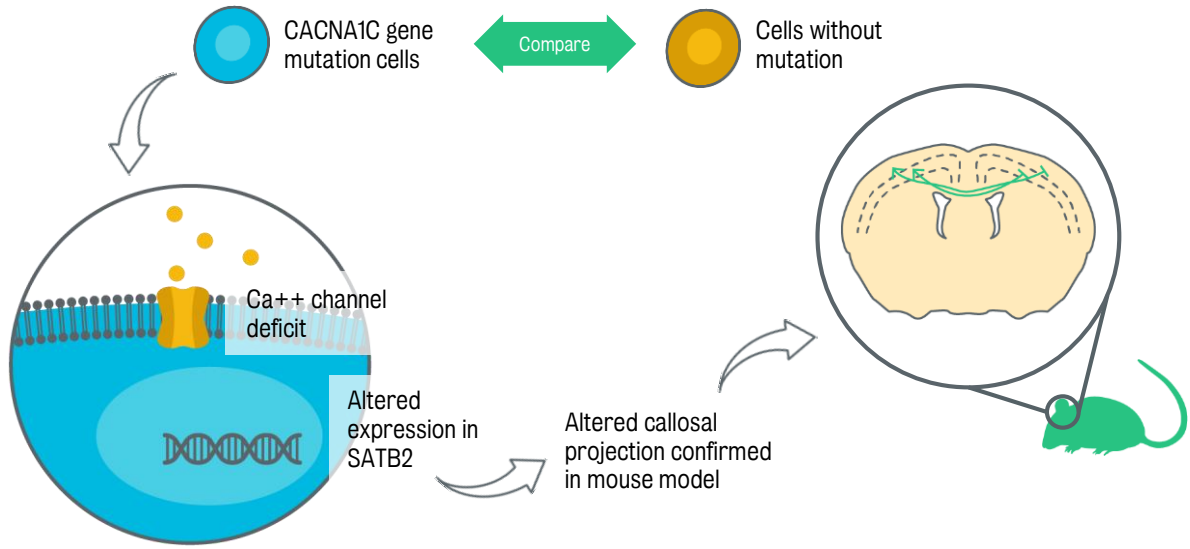
Cortical structure in the transgenic mice



Findings:
There is a lower number of SATB2 positive cells in the lower layer of the cortex of the Timothy syndrome mutated mouse in comparison to controls.

Pasca et al. (2011)

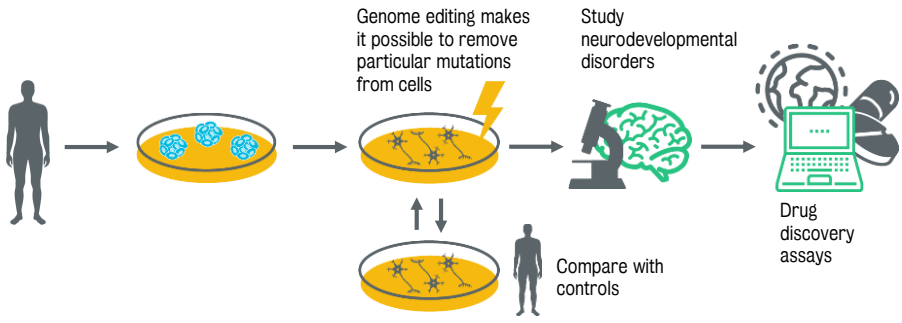
CACNA1C cells: Summary diagram



Cellular models of neurodevelopmental disorders: Advantages

Advantages:

- true human cells
- good construct validity
- good controls
- tractable system
- high through-put screening
- able to be manipulated genetically and phenotypically



Cellular models of neurodevelopmental disorders: Disadvantages

Disadvantages:

- variability
- system properties inaccessible
- slow development
- no behaviour

Genetic and epigenetic differences between individuals.

Higher variability in human cells when compared to cells derived from mice, which can be genome controlled to become genetically identical.

The long wait required for the development of iPS cells is a disadvantage in terms of practicability and logistics.

iPS cells lack the behaviour phenotypes present in several neurodevelopment disorders, such as autism.

To observe behavioural changes, animal models are still needed.

References

Cocks, G., Curran, S., Gami, P., Uwanogho, D., Jeffries, A. R., Kathuria, A., ... & Steckler, T. (2014). The utility of patient specific induced pluripotent stem cells for the modelling of Autistic Spectrum Disorders. *Psychopharmacology*, *231*(6), 1079-1088.

Lamba, D. A., McUsic, A., Hirata, R. K., Wang, P. R., Russell, D., & Reh, T. A. (2010). Generation, purification and transplantation of photoreceptors derived from human induced pluripotent stem cells. *PloS One*, *5*(1), e8763.

Lancaster, M. A., Renner, M., Martin, C. A., Wenzel, D., Bicknell, L. S., Hurles, M. E., ... & Knoblich, J. A. (2013). Cerebral organoids model human brain development and microcephaly. *Nature*, *501*(7467), 373–379.

Lui, J. H., Hansen, D. V., & Kriegstein, A. R. (2011). Development and evolution of the human neocortex. *Cell*, *146*(1), 18-36.

Paşca, S. P., Portmann, T., Voineagu, I., Yazawa, M., Shcheglovitov, A., Paşca, A. M., ... & Bernstein, J. A. (2011). Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome. *Nature Medicine*, *17*(12), 1657.

Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., & Yamanaka, S. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*, *131*(5), 861-872.

Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*, *126*(4), 663-676.

Attributions

Chan, D. (2012). *Professor Sir John Gurdon, winner of Nobel Prize for Physiology or Medicine 2012, at the annual Scholar's Dinner of Magdalene College, Cambridge, 10 October 2012* [photograph]. Retrieved from https://commons.wikimedia.org/w/index.php?curid=22009185

Garvin, W., Harms, U., Shearer, C., & Simonneaux, L. (1998). *Transgenic Animals. European Initiative for Biotechnology Education, 11, 8/10/2011*. Retrieved from https://web.wpi.edu/Pubs/E-project/Available/E-project-082511-160224/unrestricted/Rebecca_Cunningham_and_Andrew_Reed,_IQP_Final.pdf
Hoban, M. D., & Bauer, D. E. (2016). A genome editing primer for the hematologist. *Blood*, *127*(21), 2525-2535.

Hughes, H. K., Ko, E. M., Rose, D., & Ashwood, P. (2018). Immune Dysfunction and Autoimmunity as Pathological Mechanisms in Autism Spectrum Disorders. *Frontiers in Cellular Neuroscience*, *12*.

Id711, English Wikipedia. (2007). *Transferred from en.wikipedia to Commons by Sreejithk2000 using CommonsHelper* [image]. Retrieved from https://commons.wikimedia.org/w/index.php?curid=10773872

Jones, M., English Wikipedia. (2006). *The source of pluripotent stems cells from developing embryos* [image]. Retrieved from https://commons.wikimedia.org/w/index.php?curid=1351705

National Institutes of Health. (2013). *Dr. Shinya Yamanaka* [photograph]. Retrieved from https://commons.wikimedia.org/w/index.php?curid=27101450

OpenStax College - Anatomy & Physiology, Connexions Web site. (2013). *Illustration from Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013* [image]. Retrieved from https://commons.wikimedia.org/w/index.php?curid=30131300

Wu, J., Yamauchi, T., & Belmonte, J. C. I. (2016). An overview of mammalian pluripotency. *Development*, *143*(10), 1644-1648.

End of topic