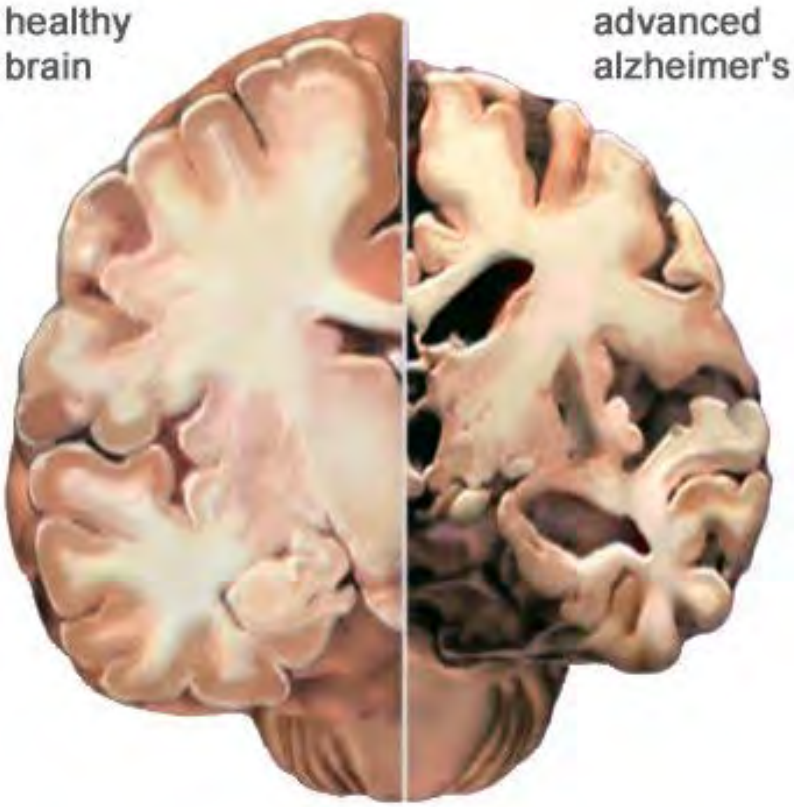
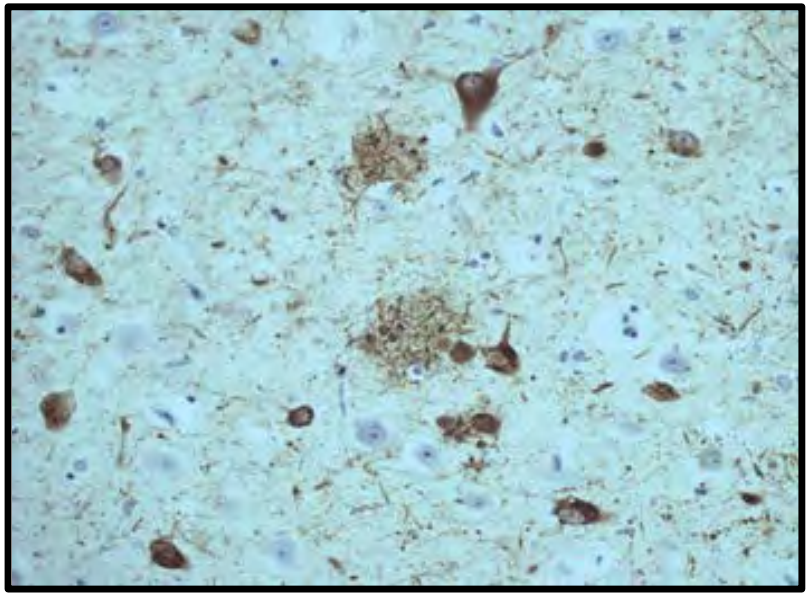
Stem cell models of dementia

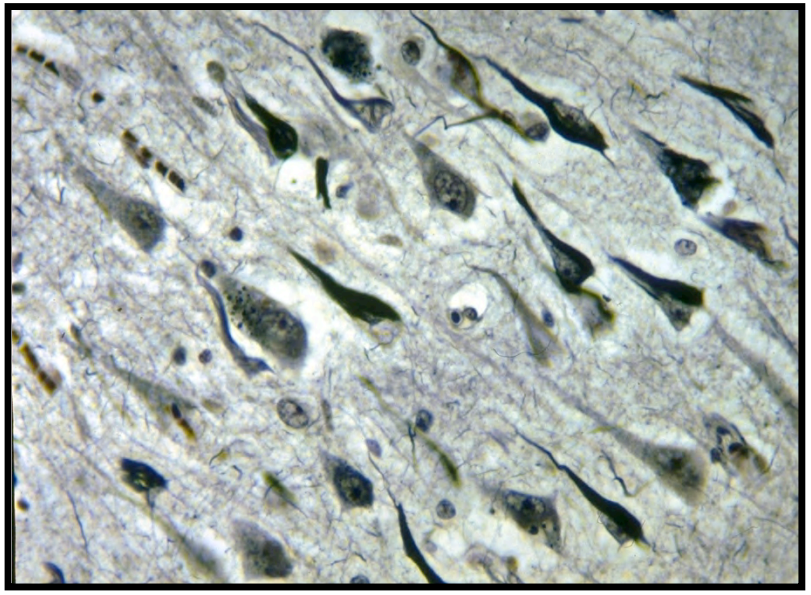
Selina Wray, PhD
Department of Molecular Neuroscience
UCL Institute of Neurology
selina.wray@ucl.ac.uk
@selinawray, @DMN_ION

The Alzheimer brain

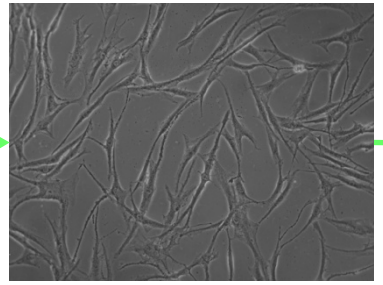




Plaques
(Aβ)

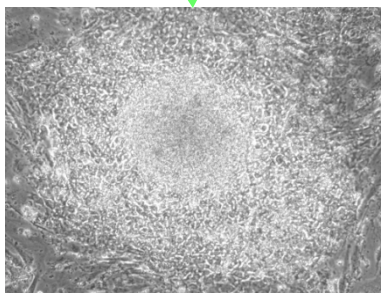


Neurofibrillary
Tangles
(Tau)



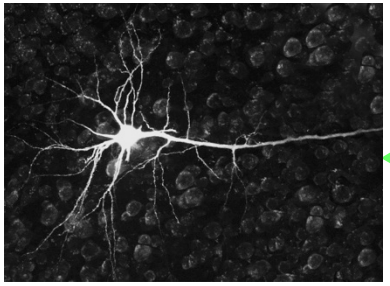
Fibroblasts

"Reprogramming factors"



iPS cells

"Neuralising factors"



Patient-derived neuron

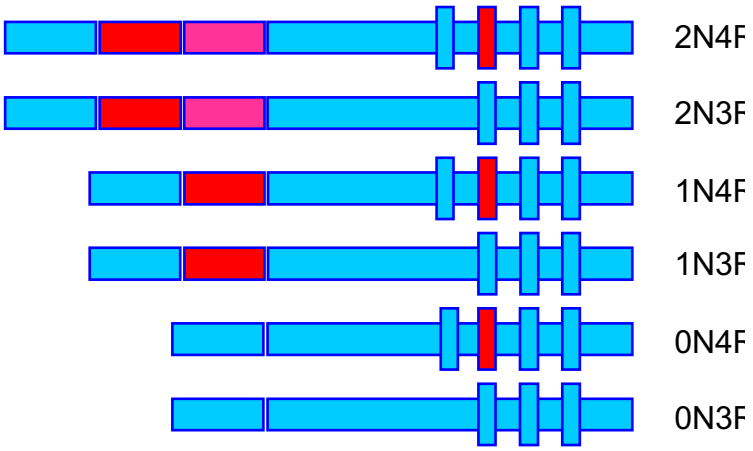
Patient
(Neurological Disease)

For the first time, we can create models of neurological disorders, containing the patients precise genome, in the cell type that selectively degenerates

- Findings from animal models have not translated into success in the clinic
- AD mouse models typically rely on overexpression of up to 3 transgenes to recapitulate AD pathology
- The AD field has been plagued by artifacts caused by overexpression
- Even in the context of overexpression, neuronal death does not occur
- iPSC offer an alternative model to overcome these issues

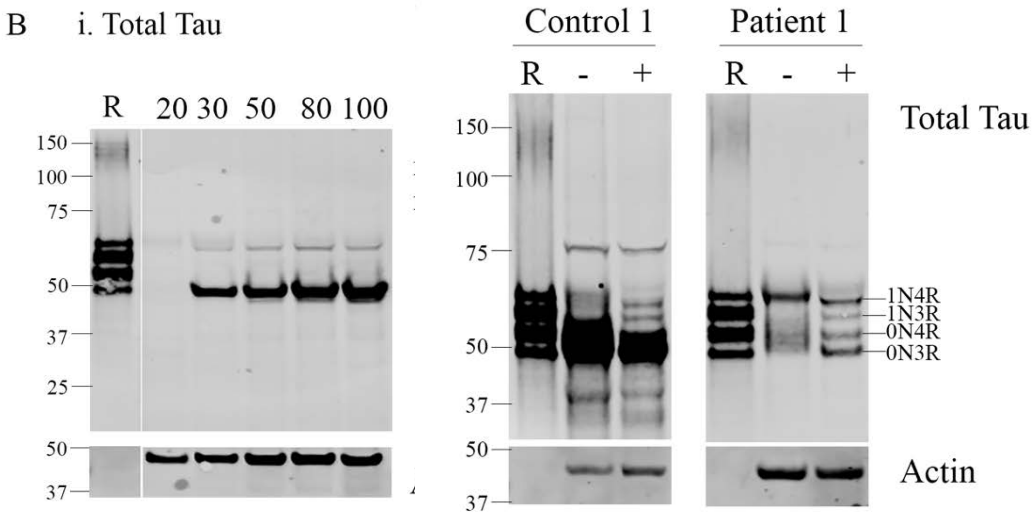
Questions and challenges (1)

iPSC-neurons are predominantly fetal: implications for disease modelling?



Fetal: Only 0N3R

Post natal: 6 isoforms, 3R=4R



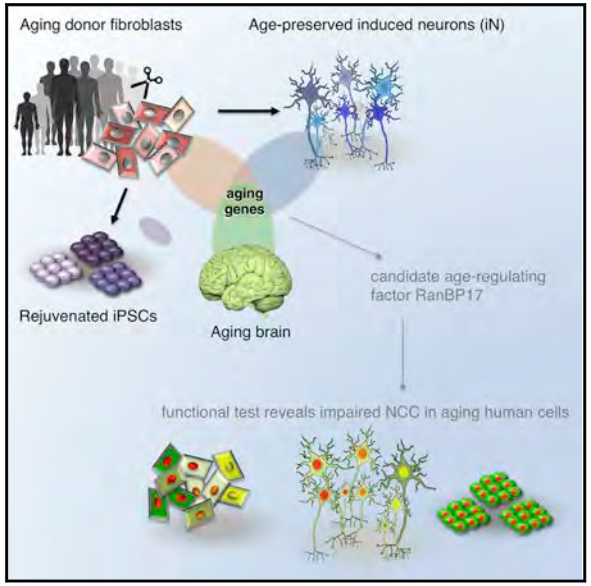
Questions and challenges (2)
Modelling aging in iPSC-neurons

Article

Cell Stem Cell

Directly Reprogrammed Human Neurons Retain Aging-Associated Transcriptomic Signatures and Reveal Age-Related Nucleocytoplasmic Defects

Graphical Abstract



Authors

Jerome Mertens, Apuã C.M. Paquola, Manching Ku, ..., Jun Yao, Martin W. Hetzer, Fred H. Gage

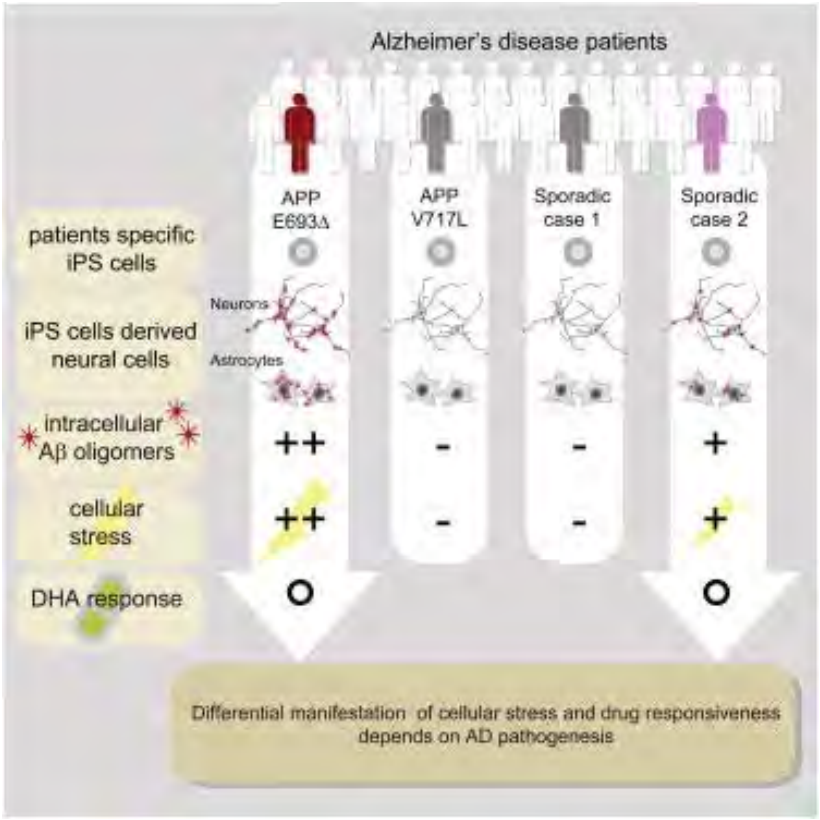
Correspondence

gage@salk.edu

In Brief

Mertens and colleagues compare transcriptomes of human fibroblasts, induced neurons (iNs), iPSCs, iPSC-derived neurons, and brain samples from a broad range of aged donors, finding that iNs retain donor aging signatures, while iPSCs are rejuvenated. RanBP17 was consistently decreased during aging, leading to compromised nucleocytoplasmic compartmentalization in aged human cells.

Questions and challenges (3)
Intra patient variability in iPSC-neurons

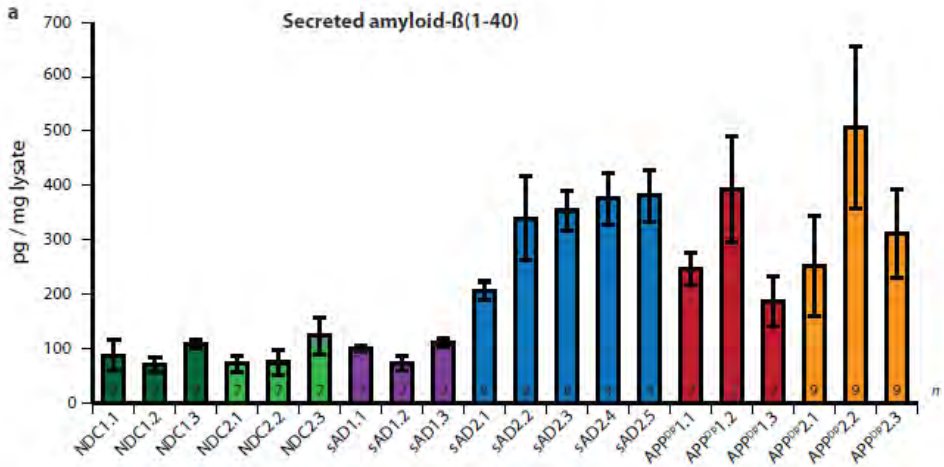


LETTER

doi:10.1038/nature10821

Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells

Mason A. Israel[1,2], Shauna H. Yuan[1,3], Cedric Bardy[4], Sol M. Reyna[1,2], Yangling Mu[4], Cheryl Herrera[1], Michael P. Hefferan[5], Sebastiaan Van Gorp[6], Kristopher L. Nazor[7], Francesca S. Boscolo[8], Christian T. Carson[9], Louise C. Laurent[8], Martin Marsala[5,10], Fred H. Gage[4], Anne M. Remes[11], Edward H. Koo[3] & Lawrence S. B. Goldstein[1,3]



Kondo et al, Cell Stem Cell, 2013

Israel et al, Nature, 2012

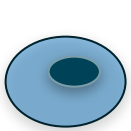
Questions and challenges: Capturing the diversity of cell types involved in the disease process

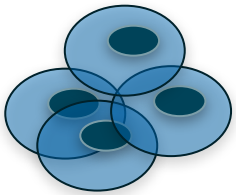
nature neuroscience

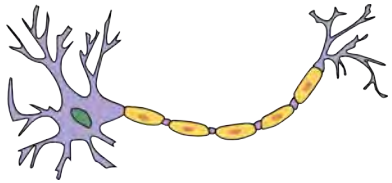
Human cerebral cortex development from pluripotent stem cells to functional excitatory synapses

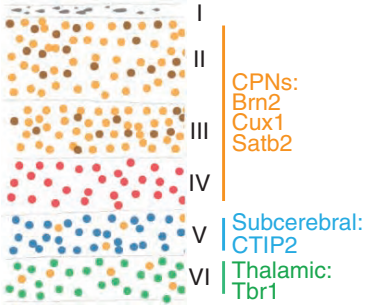
Yichen Shi[1,2], Peter Kirwan[1,2], James Smith[1,2], Hugh P C Robinson[3] & Frederick J Livesey[1,2]

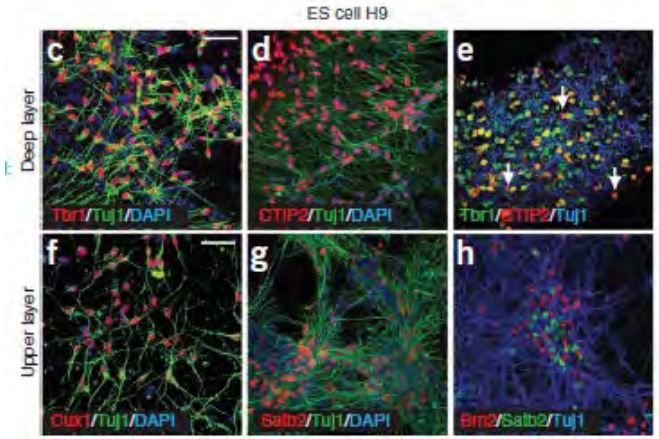
Pluripotent cell → Dual SMAD inhibition Retinoids → *Cortical progenitors* → *In vitro* corticogenesis → *Cortical neurons*

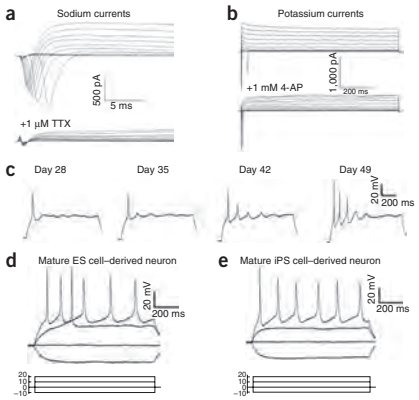




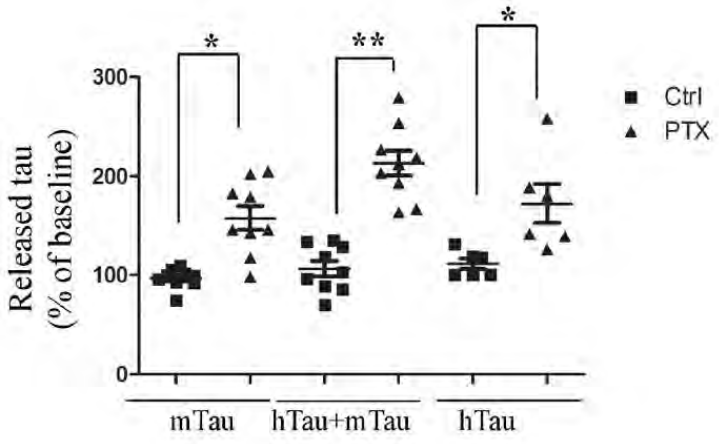


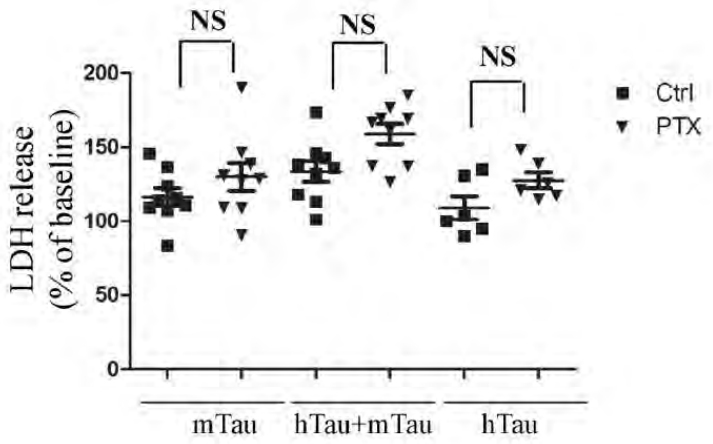






Benefits and contributions: complements and contributes to the 3Rs

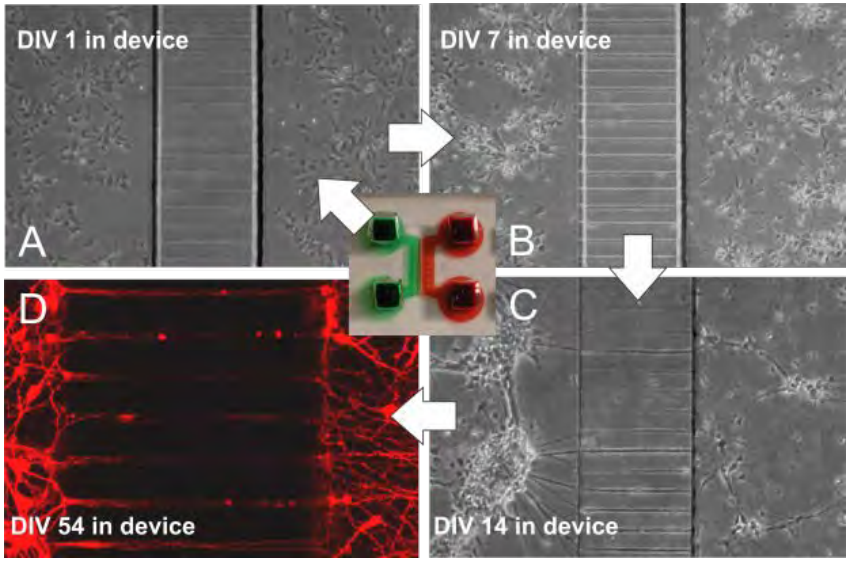




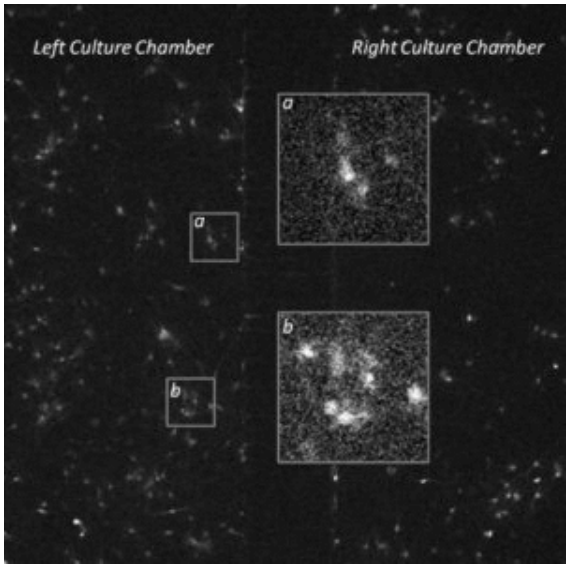
(Wu et al, Nat Neuro, 2016)

Benefits and contributions: miniaturised assays

1. iPSC-neurons culture in devices

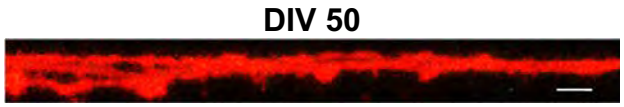


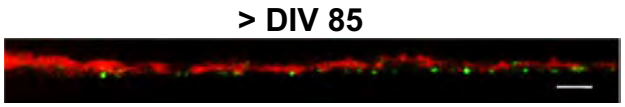
2. Calcium imaging of iPSC-neurons in microfluidics

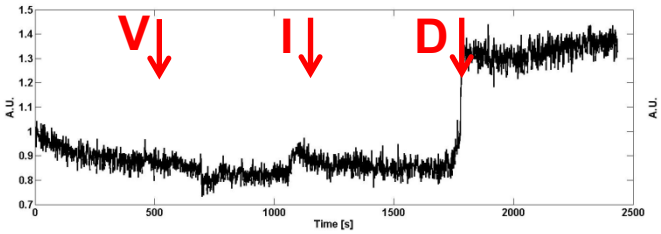


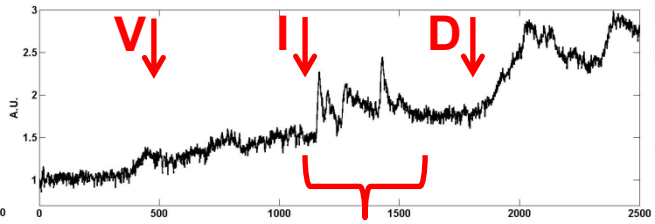
Robertson et al., Integr. Biol., 2014, 6, 636

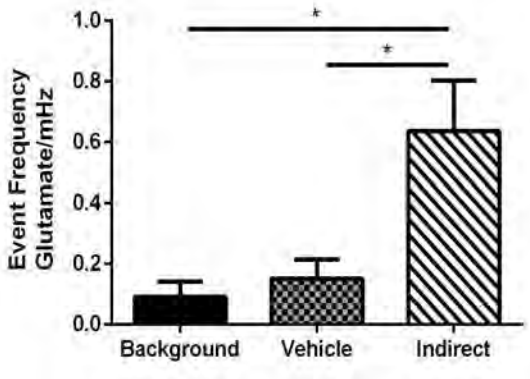
3. iPSC-neurons form functional networks after ~85 DIV in devices











(Michele Zagnoni, Trevor Bushell)