### EPIGENETICS, STEM CELL-DERIVED NEURONS AND PD

Implications for disease modelling

### Searching for the cause of iPD



### Maybe epigenetics?



#### Sayyed K. Zaidi et al. Mol. Cell. Biol. 2010;30:4758-4766

### Epigenetic drift

#### **Epigenetic Drift** Normal aging: **Biological** Premature aging decline in stem cell function, Age immunosenescence Genetic + 60 environmental risk factors (smoking, High disease obesity,...) risk 40 Deregulation of Healthy aging DNA methylome 20 Lifestyle Low disease Longevity genes? risk **Reprogramming?** 20 60 40 Chronological Age

Teschendorff et al., Human Molecular Genetics, 2013, Vol. 22, Review Issue 1

#### Methylation Regulates Alpha-Synuclein Expression and Is Decreased in Parkinson's Disease Patients' Brains



Jowaed et al. The Journal of Neuroscience, May 5, 2010 30(18):6355-6359

# What about iPSC-derived patient-specific neurons?



### iPSC models of PD



#### Jacobs, Journal of Parkinson's Disease 4 (2014) 15-27

## Aberrant epigenome in iPSC-derived dopaminergic neurons from Parkinson's disease patients



c; 7(12): 1529–1546.

## Aberrant epigenome in iPSC-derived dopaminergic neurons from Parkinson's disease patients



Fernández-Santiago et al. EMBO Mol Med. 2015 Dec; 7(12): 1529–1546.

## Variability of DNA methylation patterns in iPSC- and ESC-derived neurons



ESC iPSC

### Caveats

(1) Reprogrammingassociated epigenetic differences

(2) Rejuvenation of iPSCderived cells

(3) In vitro vs. native neurons



## Reprogramming does not lead to an aberrant gene expression pattern





Choi, Jiho et al. Nature biotechnology 33.11 (2015): 1173–1181.

## Reprogramming does not lead to an aberrant epigenome



#### Reprogramming does not lead to an aberrant epigenome

genome-wide DNA methylation (450K, Illumina) hES-NSC hES-NSC 0.96 0.97 0.99 0.96 0.96 0.97 0.98 0.97 0.97 0.91 0.90 0.86 0.87 0.97 iPS-NSC clone 1 iPS-NSC clone 1 0.98 0.98 0.96 0.99 0.98 0.98 0.98 0.97 0.91 0.92 0.87 0.88 iPS-NSC clone 2 iPS-NSC clone 2 0.99 0.95 0.96 0.99 0.98 0.97 0.90 0.90 0.86 0.87 iPS-NSC clone 3 iPS-NSC clone 3 0.96 0.97 0.98 0.99 0.90 0.90 0.86 0.88 hES-Neuron hES-Neuron 0.97 0.96 0.97 0.97 0.96 0.97 iPS-Neuron clone 1 iPS-Neuron clone 1 0.97 0.98 0.96 0.97 iPS-Neuron clone 2 iPS-Neuron clone 2 0.99 0.98 iPS-Neuron iPS-Neuron clone 3 clone 3

genome-wide expression levels (HT-12 v4, Illumina)

### Caveats



### iPSC-derived Neurons vs. iN







Mertens et al., Cell Stem Cell, Volume 17, Issue 6, 3 December 2015, Pages 705-718

### Generating aged iPSC-derived neurons





Miller et al. Cell Stem Cell. 2013 Dec 5; 13(6): 691-705

### Generating aged iPSC-derived neurons





### Generating aged iPSC-derived neurons



### Caveats



### In vitro vs. native neurons



### In vitro vs. native neurons



Xia et al., Scientific Reports volume 6, Article number: 20270 (2016) doi:10.1038/srep20270

### Caveats



# The way is the goal – but where are we going?

