Modeling ASD using human pluripotent stem cells

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Autism spectrum disorders represent a high unmet medical need with no current therapy available.
Autism spectrum disorders is genetically complex - limited pathophysiological understanding

ASD genetically complex:
• Caused by genetic and environmental factors (hereditability estimated at 70%)
• Dozen of genes have been implicated. None account for >1%

Unresolved:
• Is there Convergence? If so what and where?
  ➢ Need for human relevant predictive models

Experimental tools needed to understand and treat ASD
Dysfunction at the synapse is central to ASD

**Transcriptional regulation**
- **Gene**
  - MECP2
  - MEF2C
  - CBP
- **Disorder**
  - Rett syndrome
  - Autism spectrum disorder
  - Rubinstein-Taybi syndrome

**Synaptic scaffolding/structures**
- **Gene**
  - SHANK3
  - NRXNs
  - NLGNs
- **Disorder**
  - Phelan-McDermid syndrome
  - Autism spectrum disorder

**Translation-dependent synaptic signaling**
- **Gene**
  - TSC1/2
  - FMR1
  - PTEN
  - NF1
- **Disorder**
  - Tuberous sclerosis
  - Fragile X syndrome
  - Cowden syndrome
  - Neurofibromatosis type 1

*red : models generated in EU-AIMS*
Modelling ASD using human pluripotent stem cells

ASD Patient → Hair cells → iPS cell lines → Neuronal differentiation → Molecular/cellular phenotyping

Drug therapy

Drug screening: High content Screening, network oscillations, ...

IMI Stakeholder Forum – 21 May 2014 - Brussels
EU-AIMS achievements so far modelling ASD using human pluripotent stem cells

Generated several ASD models in a dish...
- ASD hiPSC lines
- Highly reproducible differentiation to functional neurons
- Identified molecular, synaptic and network deficits mimicking those in patients
- Promising tools for drug screening
Open questions:

- Can we identify using iPS cells from genetically different groups of ASD individuals the same deficits in the neurons and networks?
- Can we use this to guide the discovery of drug targets for specific groups of patients?
- How can we extend these results to a more general patient population?
  - Sampling from observational clinical trial
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