Modeling ASD using human pluripotent stem cells

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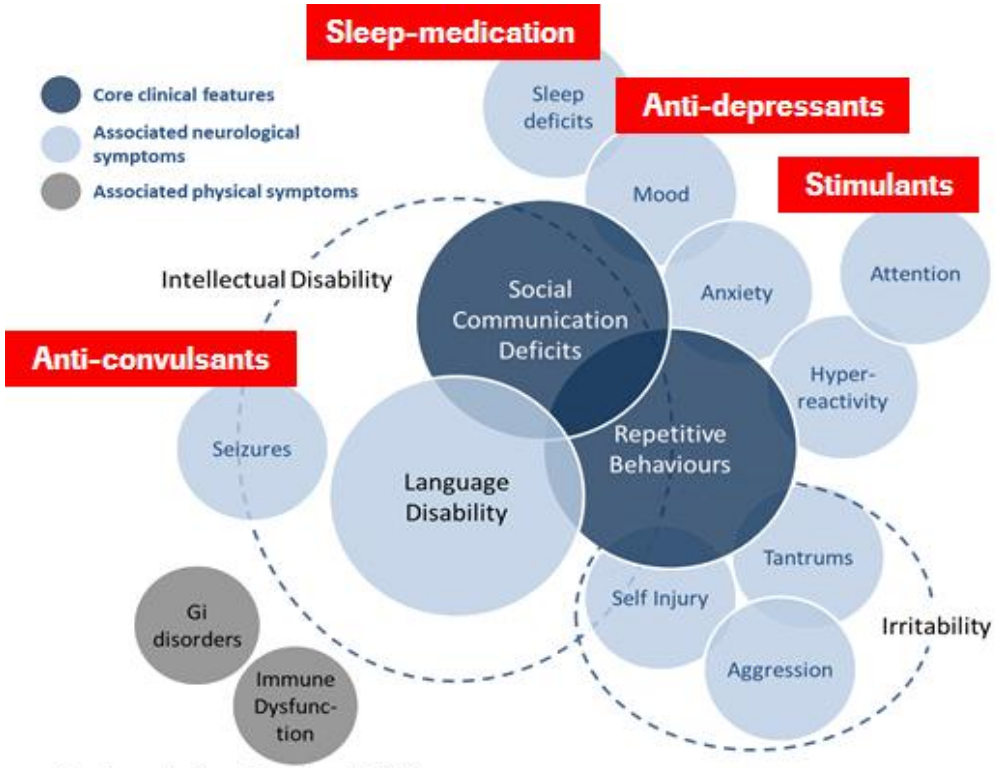
Autism spectrum disorders represent a high unmet medical need with no current therapy available



Courtesy: Autism Speaks – Rob Ring

Autism spectrum disorders is geneticaly complex - limited pathophysiological understanding

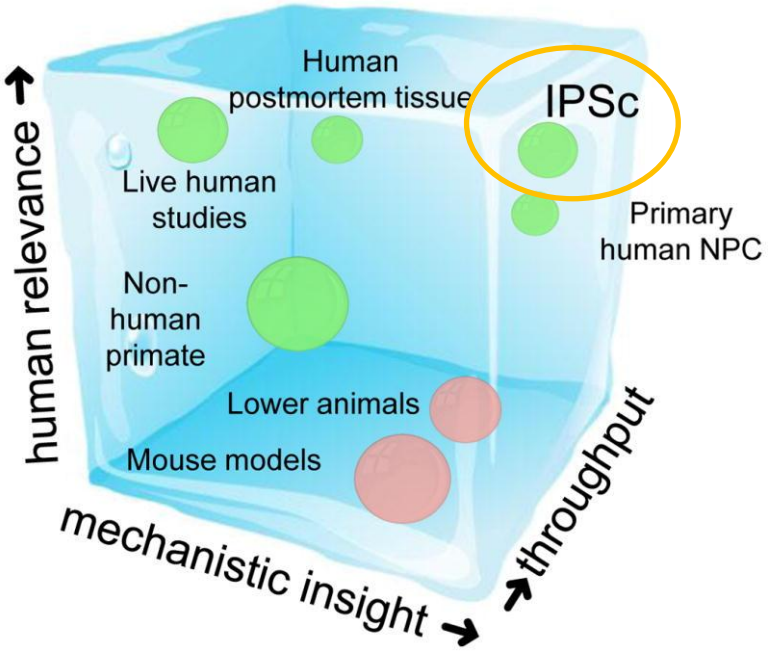
ASD genetically complex:

- 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

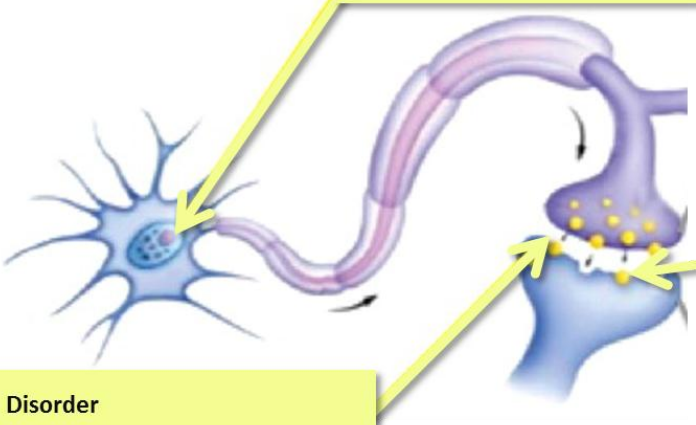
Experimental tools needed to understand and treat ASD



Dysfunction at the synapse is central to ASD

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

Transcriptional regulation



Gene	Disorder
SHANK3	Phelan-McDermid syndrome
NRXNs	Autism spectrum disorder
NLGNs	Autism spectrum disorder

Synaptic scaffolding/structures

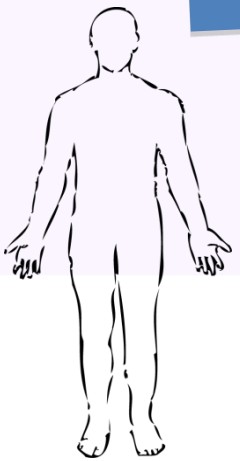
Gene	Disorder
TSC1/2	Tuberous sclerosis
FMR1	Fragile X syndrome
PTEN	Cowden syndrome
NF1	Neurofibromatosis type 1

Translation-dependent synaptic signaling

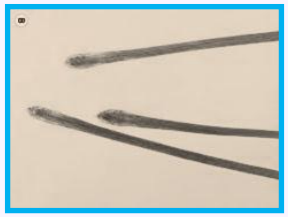
red : models generated in EU-AIMS

Modelling ASD using human pluripotent stem cells

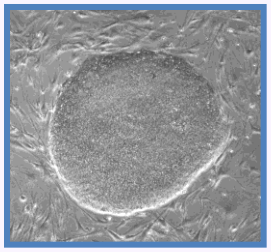
ASD Patient



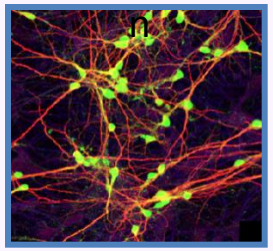
Hair cells



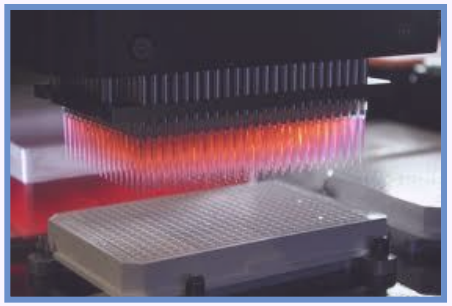
iPS cell lines



Neuronal differentiatio



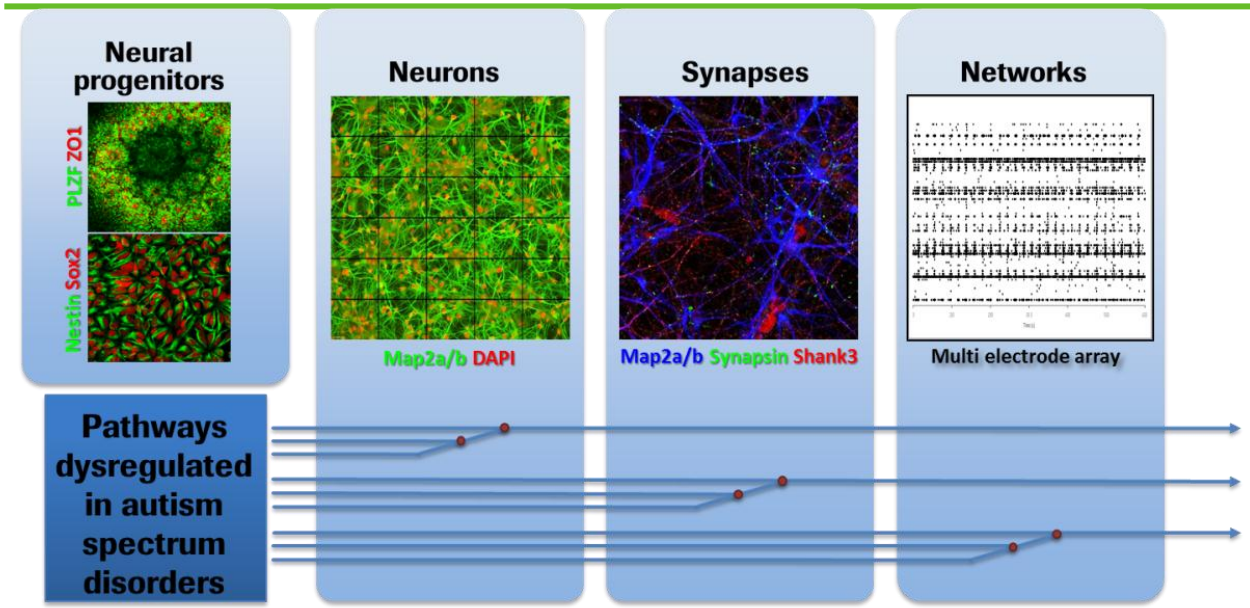
Molecular/ cellular phenotyping



Drug screening: High content Screening, network oscillations, …

Drug therapy

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

Summary and outlook – Opportunies and challenges

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

Acknowledgments

EU-AIMS Autism Research in Europe

WP1

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