Brain-on-a-chip models for Kleefstra syndrome



Nael Nadif Kasri, Radboudumc Nijmegen, the Netherlands June 30th 2018





Strategy in disease modeling



Disease modeling







ORGAN-ON-CHIP TECHNOLOGY



Micro-Electrode Arrays





ORGAN-ON-CHIP TECHNOLOGY



Micro-Electrode Arrays



Synchronous events on MEA



ORGAN-ON-CHIP TECHNOLOGY



Micro-Electrode Arrays





Research Update

• Approach

Measuring neuronal communication on "smart dishes" Micro-Electrode Arrays



Kleefstra patient hiPSCs lines:





Neuronal network activity







Communication between neurons is:

- More active
- Less regular

K.I.D.S. IQ Project - Nijmegen



-Phase 1a: identify "hit" compounds that can revert neuronal network phenotype

-Phase 1b: validate hit compounds

-Phase 2: Pre-clinical validation: test validated compound in mouse model

Radboud Research Update: Phase 1a

- Tested focused group of compounds (less than 100)
 - Those that "modify" the **epigenome** in some manner
 - Limited testing around dosing and number of patient lines



Dynamic methylation of histones HMT: histone methyltransferases; HDM: histone demethylases



Radboud Research Update: Phase 1b

- Further investigation to validate results and move from "hit" to "lead"
 - Dosage analysis:

1b

Phase

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Phase

- Exposure time to drug:
- Expanding patient cohort (i.e. number of lines tested):

Non-specific effect of drug

Preclinical validation in mouse model for Kleefstra syndrome: X

Radboud Research Update: What is next

- Back to basic research and compound screening
 - Basic research: what causes 'hyperactivity"?
 - Testing of dosing and number of patient lines



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Radboud Nijmegen

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