Radboud's path forward on Kleefstra Syndrome drug development

Hans van Bokhoven, Molecular Neurogenetics
2018 Kleefstra Syndrome Conference

Donders Institute
for Brain, Cognition and Behaviour
Radboudumc
university medical center

Nijmegen the Netherlands

Nijmegen:
Oldest city in the Netherlands
(city rights AD 98)

Radboud University

Radboudumc
university medical center

Radboud university medical center

Human Genetics

Human Genetics Nijmegen

~400 employees

- Clinical Genetics
- Genome Diagnostics
- Genome Reserarch

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REPORT

Loss-of-Function Mutations in *Euchromatin Histone Methyl Transferase 1* (*EHMT1*) Cause the 9q34 Subtelomeric Deletion Syndrome

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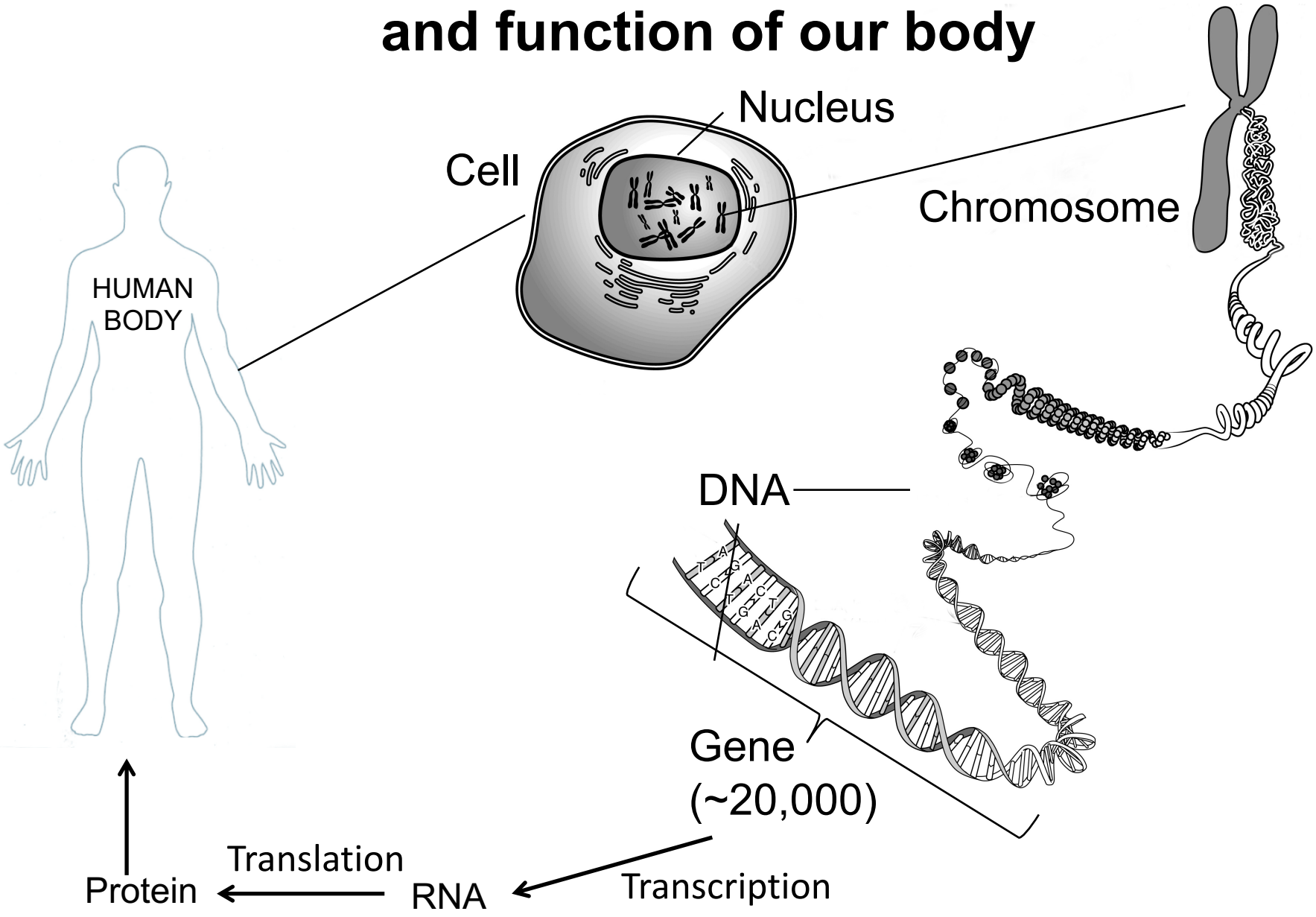
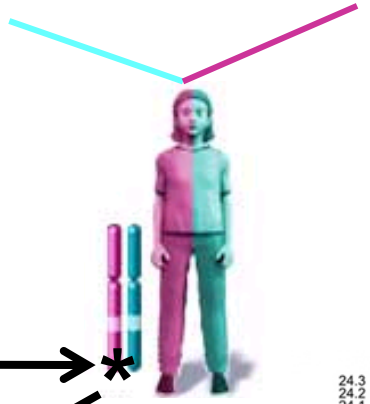
Genes contain the instructions for development and function of our body

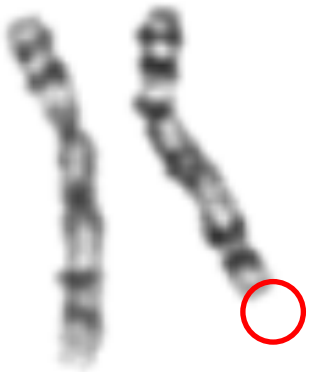




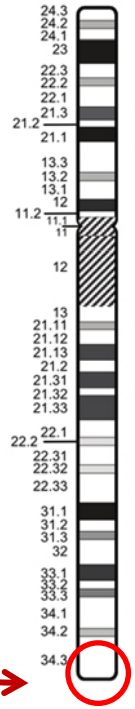
Child with Kleefstra syndrome

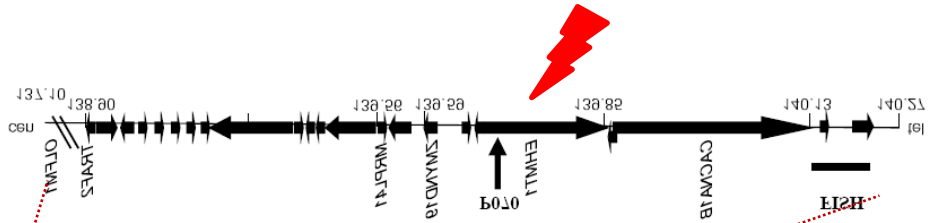
Kleefstra syndrome: Lack of 1 of 2 functional copies of the gene EHMT1

euchromatin histone methyltransferase 1

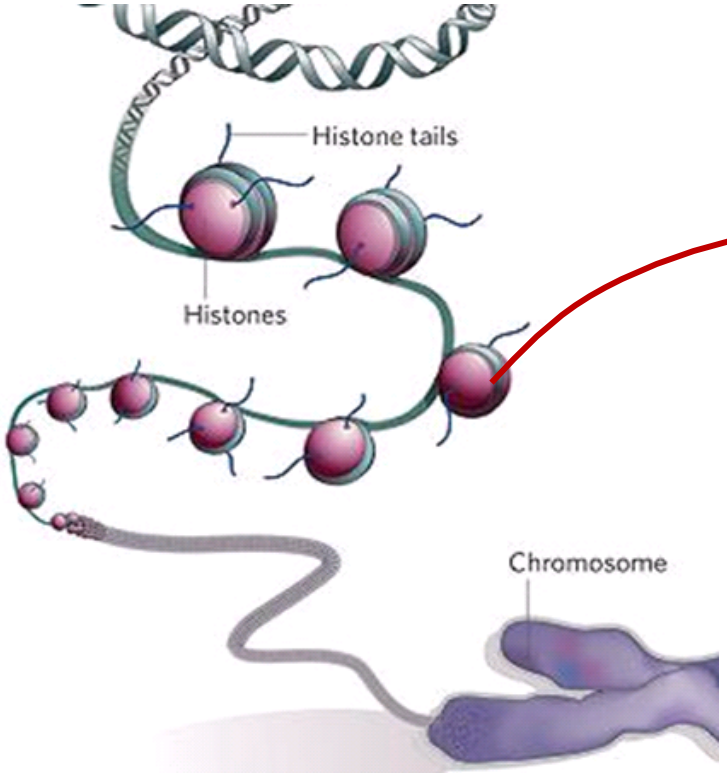


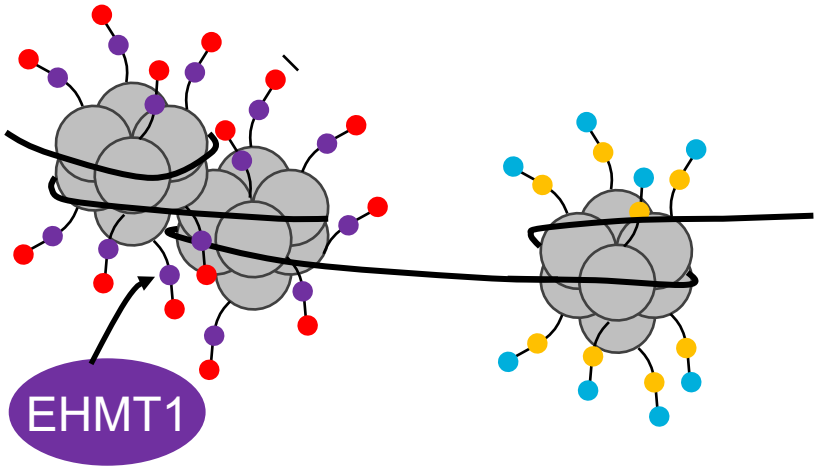
Deletion 9q34.3





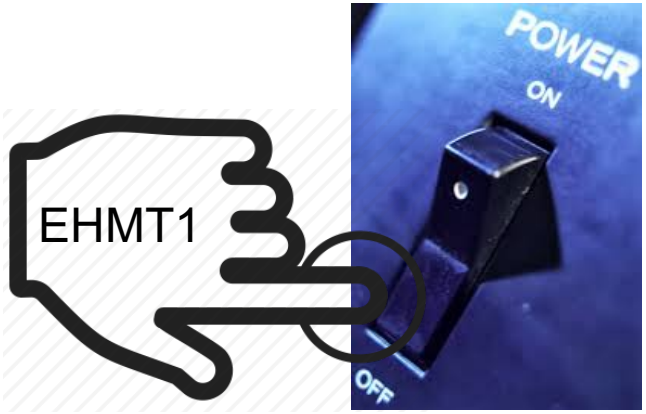
EHMT1 is a regulator of the accessibility of DNA





Inactive marks
- H3K9me
- H3K27me

Active marks
- H3K4me
- H3K27Ac

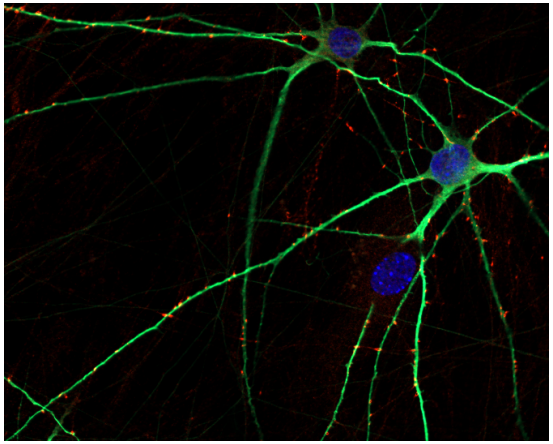


Main Research questions at Radboudumc

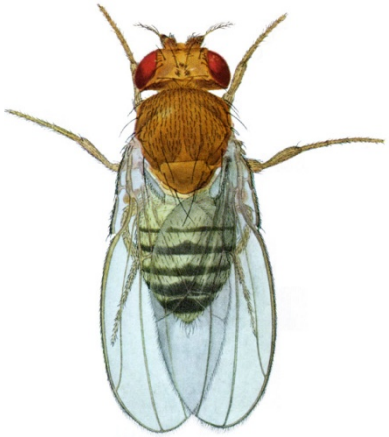
- What is the role of EHMT1 in the nervous system?
- What is the role in early development?
- How do mutations cause the syndrome?
- Can we rescue the effects of EHMT1 mutations?

Modeling Kleefstra in cell and animal models

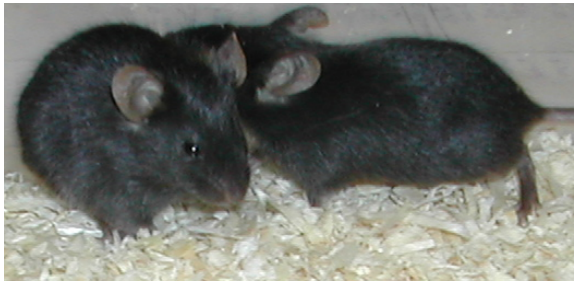
Clinical, molecular and functional characterization of *EHMT1* mutations in model organisms



Cells



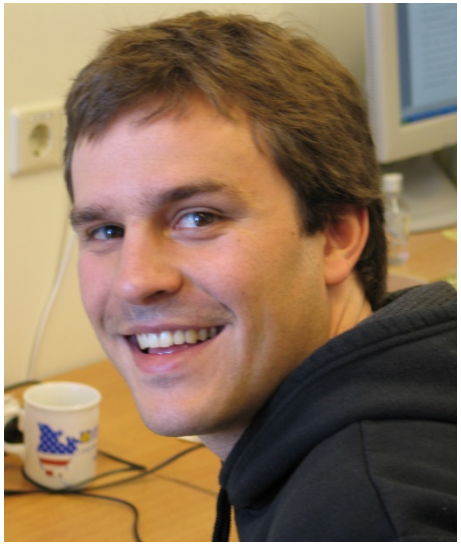
Fruit fly



Mouse

Fruit flies (*Drosophila*) are a simple and efficient model for studying genetic disorders

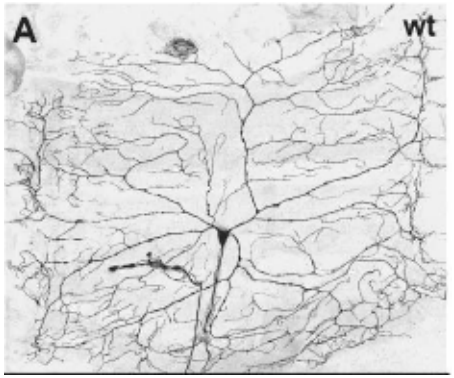
Annette Schenck

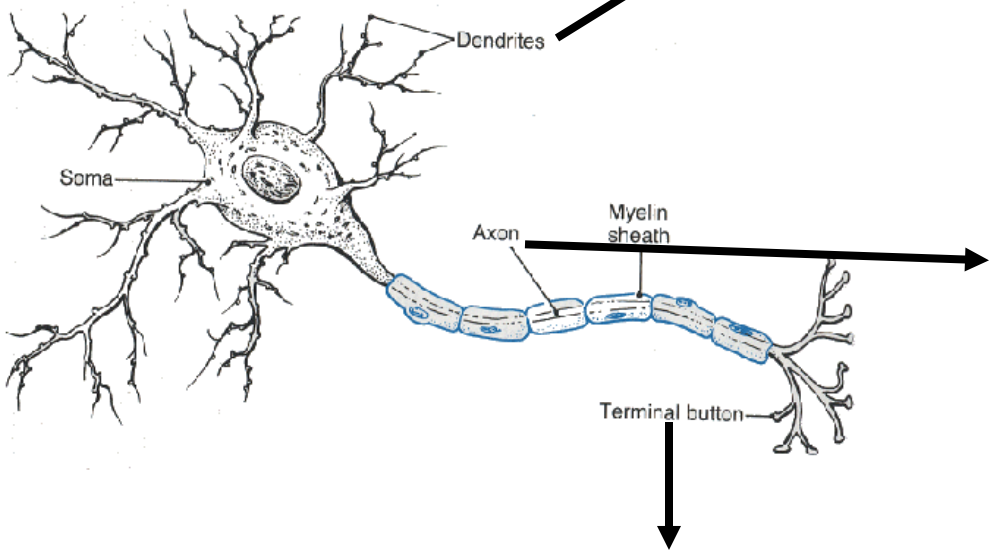


Jamie Kramer

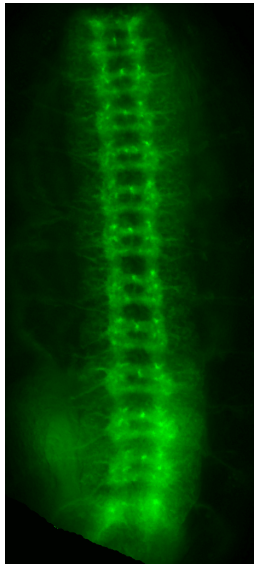
Analysis of Neuronal Development in Flies

Larval multidendrite neurons

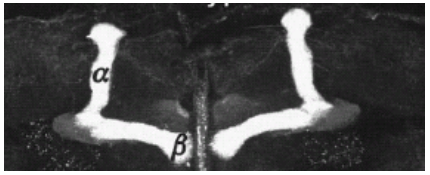




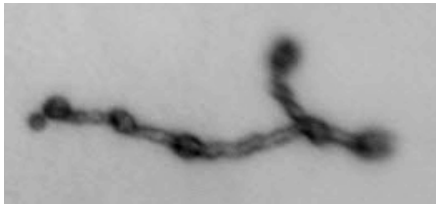
Embryonic CNS



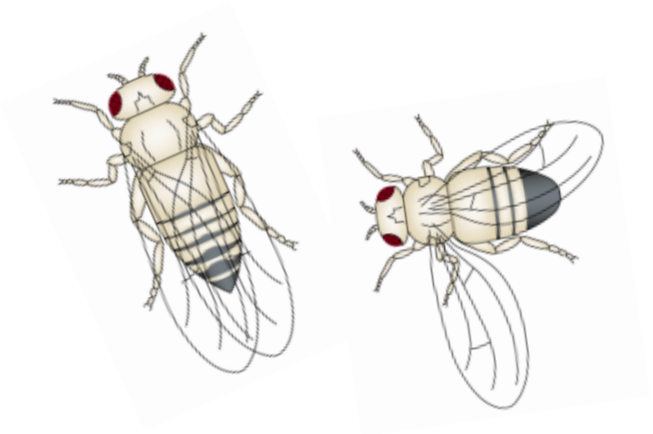
Mushroom bodies



Larval Neuromuscular Junction



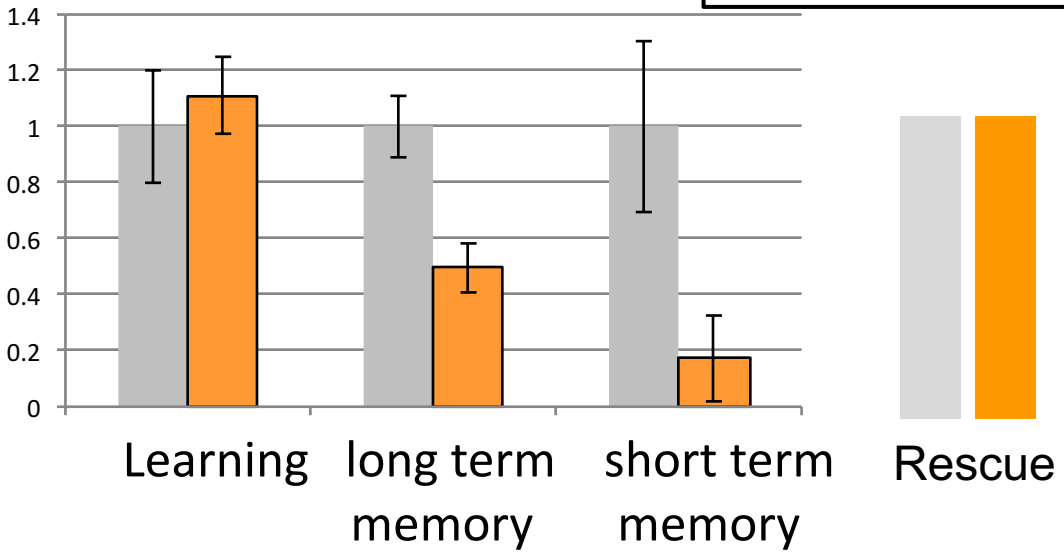
Mutant flies have memory deficits in several tests (courtship conditioning)



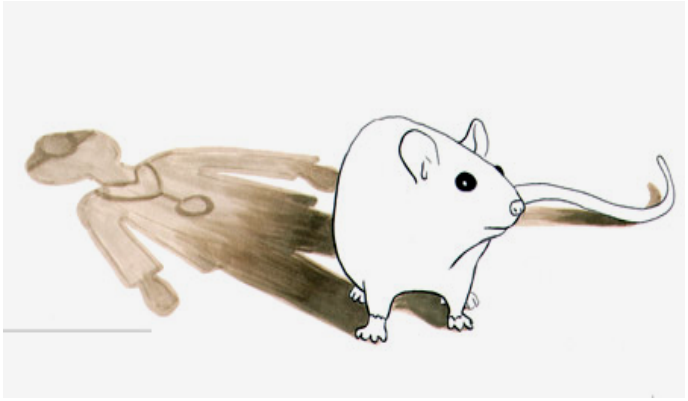
Memory deficit can be rescued
By restoring EHMT expression
in adult flies

Control flies

EHMT mutant



Ehmt1$^{+/-}$ mice phenotype



Balemans et al. Behav Brain Res 2010
Kleefstra et al. Am J Hum Genet 2012
Balemans et al. Hum Mol Genet 2013
Balemans et al. Dev Biol 2014
Benevento et al., Neuron 2016
Benevento et al., Sci rep 2017
Martens et al., 2016 Sci rep

Human phenotype:

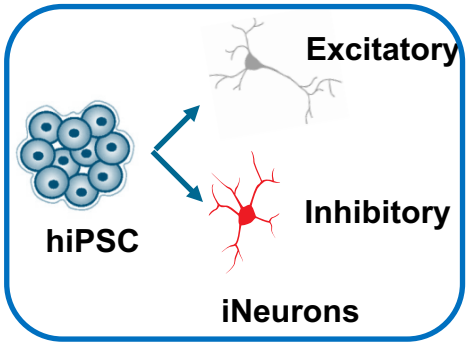
- ✓ Moderate-Severe ID
- ✓ Hypotonia
- ✓ Autistic behavior
- ✓ Facial/skull abnormalities
- ✓ Developmental delay

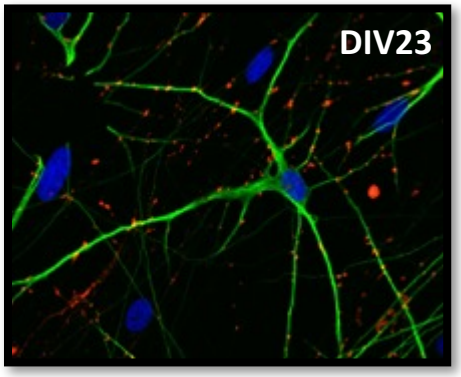
Ehmt1$^{+/-}$

- Learning and memory deficit (fear extinction, novel & spatial object)
- Hypotonia
- Anxiety, social interaction
- Facial/skull abnormalities
- Developmental delay
- Dendrite/synapse morphology
- Synaptic activity defects

Ehmt1$^{+/-}$ mice recapitulate the core features of Kleefstra syndrome

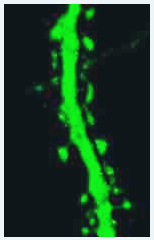
iNeurons: Human Neurons derived from Induced Pluripotent Stem Cells of Kleefstra syndrome patients



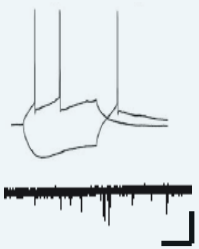


Neurons with the genetic background of the patient

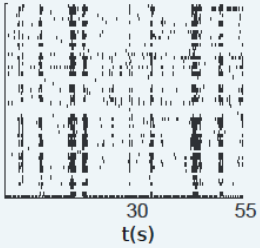
Molecular
expression
Epigenome



Cellular
Neuronal morphology



Synaptic
synaptic structure, function & Plasticity



Neuronal Network
MEA

Therapy
Drug screens
Genetic editing

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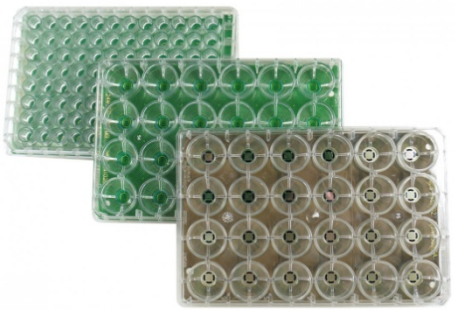
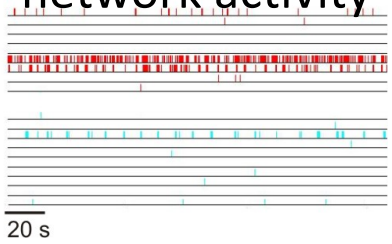
Strategy for identifying potential therapeutics

iNeurons on MEAs

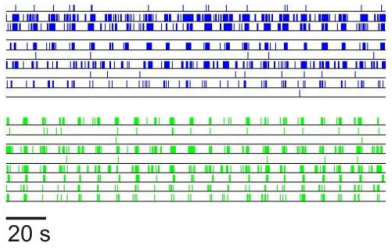


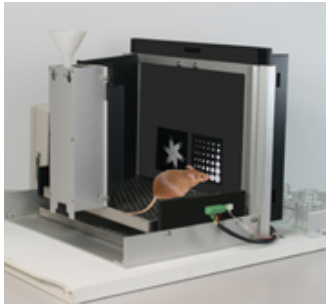
Abnormal network activity



Screen (epigenetic) compound libraries

Corrected network activity





Use most effective compounds for in vivo testing

genespark.org

Thanks

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Jamie Kramer
Annette Schenck

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Giovanni Iacono
Henk Stunnenberg

SEVENTH FRAMEWORK PROGRAMME

Genetic and Epigenetic Networks in Cognitive Dysfunction
ENCODYS

NWO

ZonMw

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