DRUG "HIT" IDENTIFIED IN KS SCREENING USING iPSC

-RESEARCH UPDATE-

August 8, 2017 (12:00pm EST)

K.I.D.S. IQ PROJECT

Advancing drug development for
Kids with Intellectual Disability Syndromes

Today's Webinar Panelists

Braden Root-McCaig (Moderator)

- Executive Director, K.I.D.S. IQ Project

Hira Verma

- Chair, Co-Founder of K.I.D.S. IQ Project

Dr. Nael Nadif Kasri

- Group Leader, Department of Human Genetics, Radboud UMC, Nijmegen, The Netherlands

Submit Your Questions

To send in questions, please use WebEx's Q&A feature (located on the right-hand side of your screen, or at the top of your screen if you're in full view mode)

Please feel free to submit questions throughout the presentation (we will address questions both throughout the presentation and at the end during our Q&A portion)

What We'll Cover Today

- KIDS IQ Project Mission
- Kleefstra Syndrome overview and drug development strategies
- iPSC technology and its useful in drug development
- An update on our Radboud research project
- What is the path forward for drug development?
- Q&A session

Our Mission

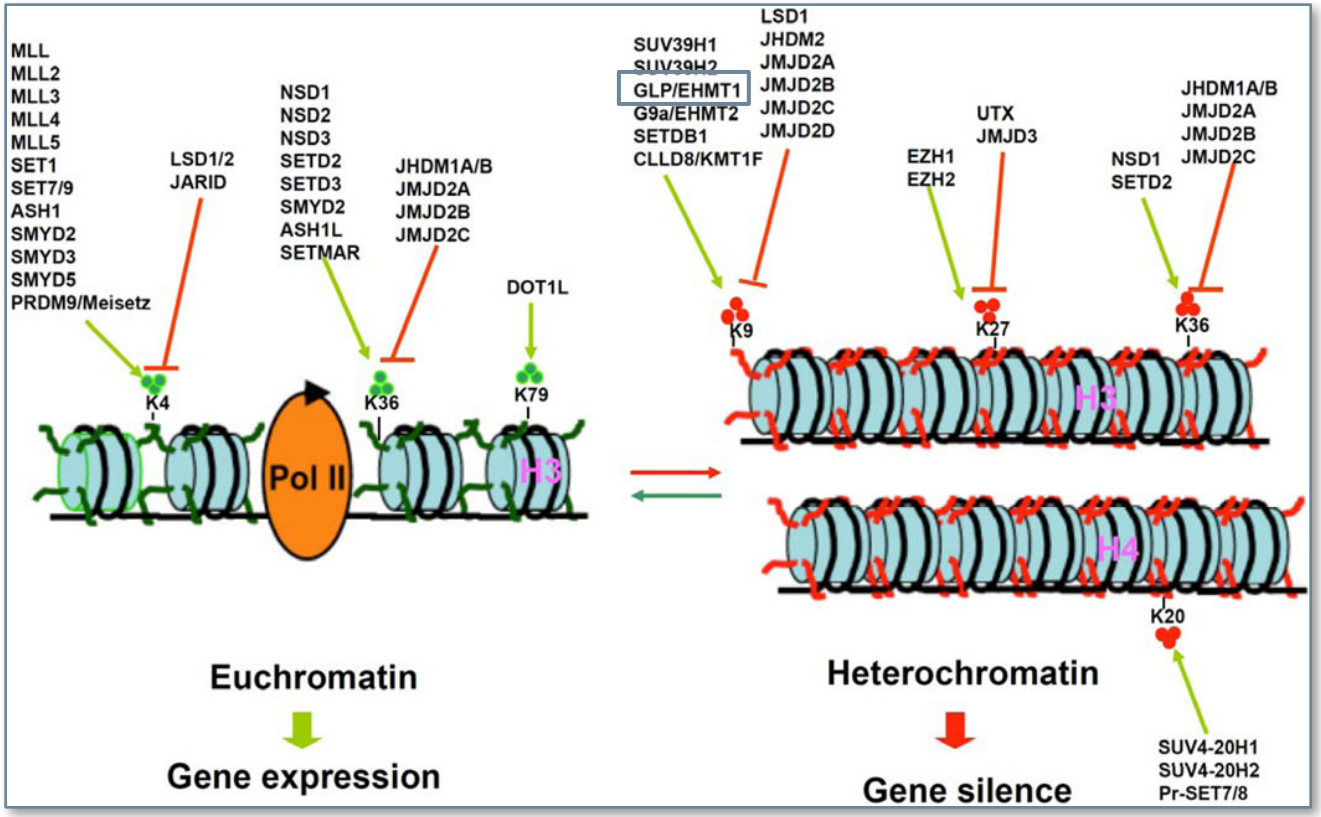
We are an international non-profit foundation focused on the advancement of drug treatments for reversible Intellectual Disability (ID) disorders, specifically those arising from a gene mutation. Our initial focus is on Kleefstra syndrome (KS) and related ID disorders.

We also aims to enhance the quality of life for those living with such ID disorders and their associated health issues by providing important educational information, programs and services.

Kleefstra Syndrome ("KS")

- Caused by a de novo mutation or deletion of a very important gene: EHMT1
- Human phenotype includes:
  - Generally, moderate to severe intellectual disability
  - Speech problems
  - Seizures (for some)
  - Hypotonia
  - Numerous other biological and medical issues
- We are not aware of any KS adults who are living independently
- Testing in its infancy in Western world; no testing in Asia and many other densely populated regions
  - Patient population growing as diagnostics improving

Why Does EHMT1 Matter?



Source: NIH/NLM – "Histone Lysine-Specific Methyltransferases and Demethylases in Carcinogenesis: New Targets for Cancer Therapy and Prevention"; authors – Xuejiao Tian, Saiyang Zhang, Hong-Min Liu, Yan-Bing Zhang, Christopher A Blair, Dan Mercola, Paolo Sassone-Corsi, and Xiaolin Zi (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3703250/)

Mutations

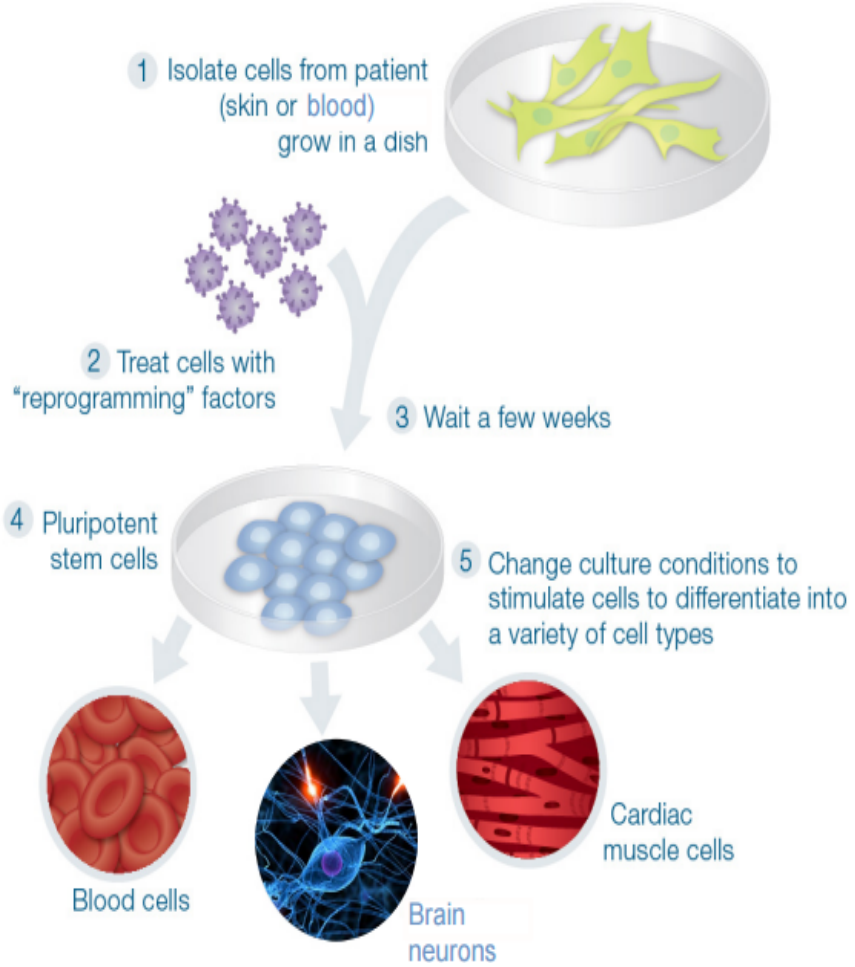
- Deletions (~75%)
- Nonsense
- Frameshift

Drug Development Strategies

Small Molecule (Compounds)	• Historically used a lot and has had success • Typically inhibitors, thought can be used to "excite" (up-regulate) genes as well
RNA-Based Approaches	• RNA interference • Long non-coding RNA
Gene Editing	• CRISPR/Cas9 – currently mostly used for developing animal models • Curing disease may be on the horizon; one to watch

Induced Pluripotent Stem Cells (iPSC)

- New technology that enables neurons (brain cells) to be derived from disease patients and control subjects (patients submit skin sample)
- Allows in vitro analysis (lab dishes) for discovering human neuron phenotypes and screening drugs
- ALS (Lou Gehrig's Disease) involves death of neurons
  - iPSC identified an anti-epilepsy drug to modify phenotype (neuronal hyperexcitability)



Source: Graphic from learn.genetics.utah.edu; text source stemcells.nih.gov

Compound Screening

- Once neurons have been developed, they can be tested with different potential drugs
  - Look for an improvement in neuronal function
- Can also look to fast-track with FDA-approved (re-purposed) or re-positioned drugs

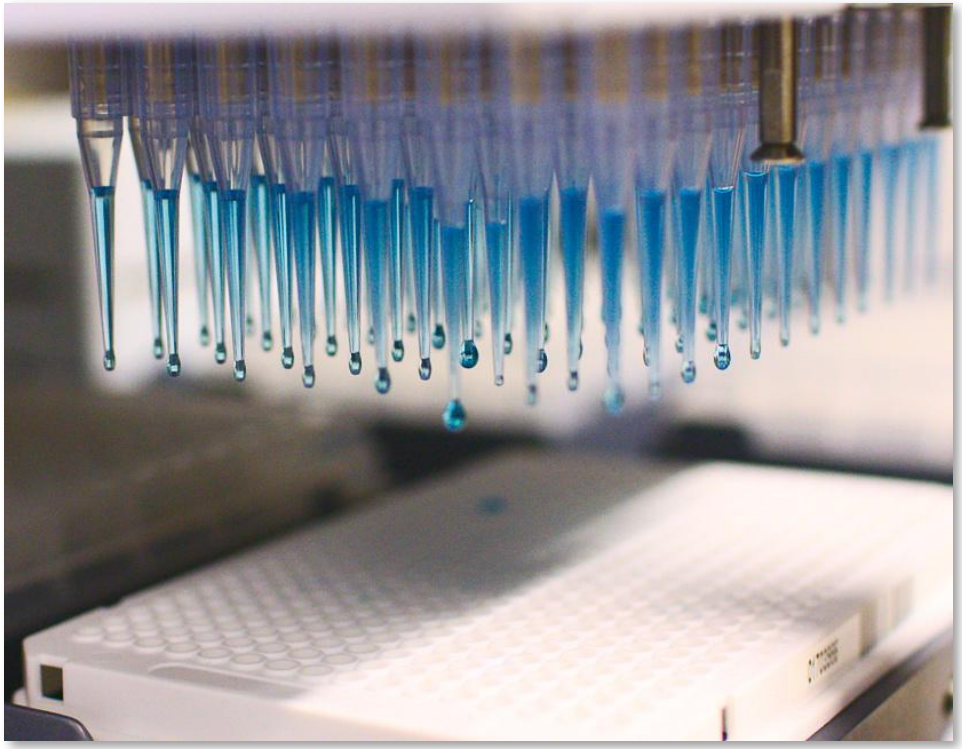
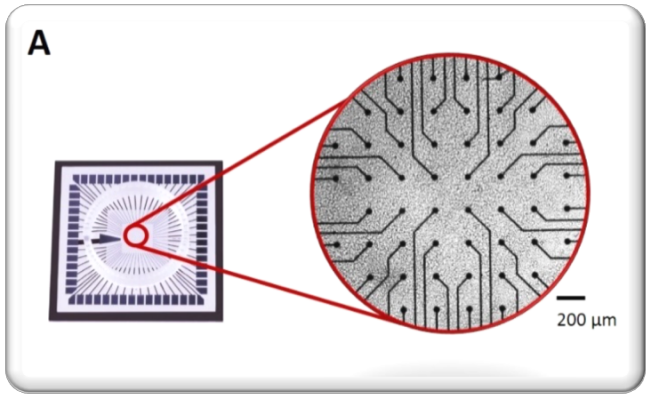


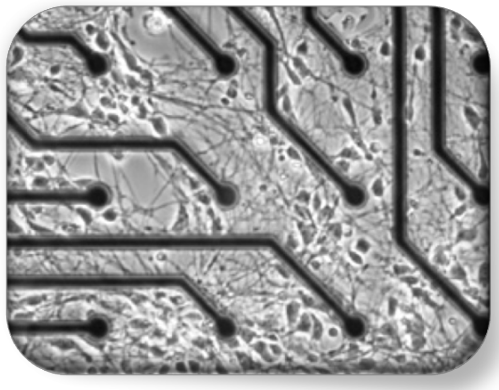
Image source: http://www.uib.no/en/rg/biorec/67592/high-throughput-screening

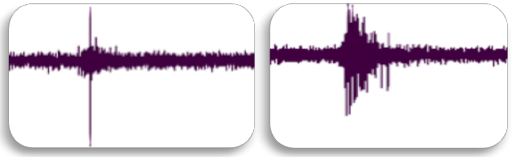
Radboud Research Update: Approach

- Measuring neuronal communication on “smart dishes”

Neurons-in-a-dish





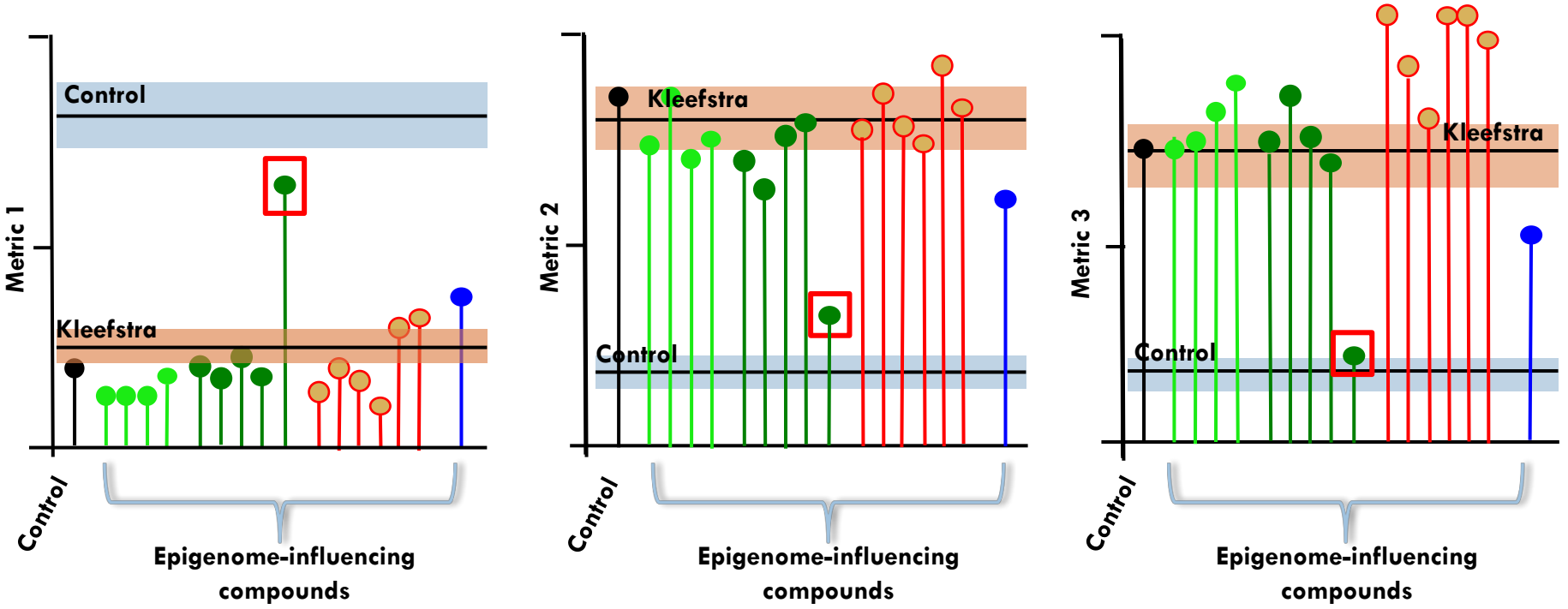


Neuronal activity

- When?
- How often?
- With who?
- How loud?

Radboud Research Update: Findings

- 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

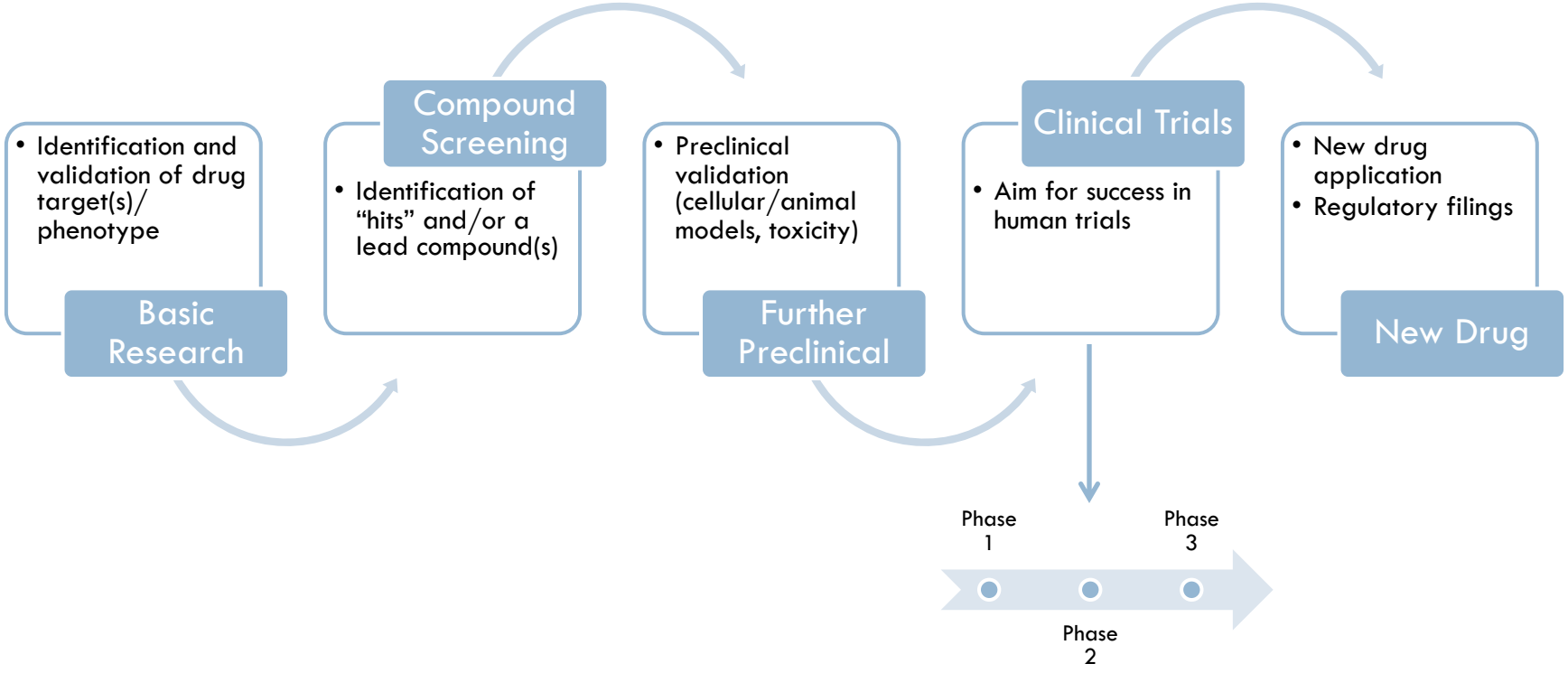


Identified one promising compound

Radboud Research Update: Next Steps

- Further investigation to validate results and move from “hit” to “lead”
  - Dosage analysis
  - Expanding patient cohort (i.e. number of lines tested)
  - Analyzing chemical structure for effective delivery to the brain
- Mouse studies
  - Preclinical validation in mouse model for Kleefstra syndrome

Timeline Review



Accelerated timelines are achievable with rare disorders and drugs that are re-purposed/re-positioned

Source: NIH

Next Steps for Families

Stay Connected	• Newsletter signup (www.kidsIQproject.org), ongoing webinar signups, Facebook Group
Submit Patient Data	• Patient database (www.kidsIQproject.org)
Volunteer	• Wide variety of volunteer skills appreciated (postings coming soon)
Donate	• Visit www.kidsIQProject.org
Fundraise	• 2017 Annual Virtual Walk-and-Roll in October (create a family fundraising page)

QUESTION & ANSWERS

Type your questions into the Q&A text box.

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