Editing genes to tackle neurological conditions

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II. Lvs. undivided or irregularly lobed, ovate or elliptic.
1. Wings of the samara acutely angled; lvs. pubescent along the nerves beneath.
M. If margins irregularly sharply and doubly serrate, 2-10cm, the long dull green.
   A. ginnala
MM. H. margins entire or irregularly lobed, 3-6cm. A. Oliverianum.
   Long, glossy above, often glaucous beneath. A. bryophorum.
LL. Wings of the samara obtusely angled or nearly horizontal; lvs. ovate to oblong, subcordate at base, abruptly pointed at tip, 3-5cm. Long margins remotely serrate near and below apex or nearly entire. A. cardamum

DO. Lvs. 3-7 lobed; segments sharply serrate; wings of the samara obtusely angle.
   P. Petioles and peduncles glabrous or nearly so:
   N. Petioles and peduncles glabrous or nearly so:

A. truncatum
Plant biology and taxonomy

Classification by their form, or their function?
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B.Sc. Chemistry, 2010
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From genomic variations to human diseases

Classify brain cell functions, one cell at a time.
Cells are our basic units

Diverse cells are classified by their location, morphologies, function, molecules.
Disease risks and resilience in our genome

Cell type-specific actions of risk genes

Risk variants:

Neuropsychiatric conditions, neurodevelopmental disorders, neurodegeneration, aging, etc
Many risk genes

Many cell types

We build *in vivo* Perturb-seq: systematically and scalably dissect genome functions, *one cell at a time*. 
Long lists of genetic variants in neuropsychiatric illnesses

2012
<10 genes

2020
101 genes
FDR<0.2

2022
255 genes
FDR<0.1
71 genes
FDR<0.001

25,000+ autism/neurodevelopmental delay: whole exome sequencing
Stephan Sanders, Mike Talkowski, Joseph Buxbaum, Kathryn Roeder, Bernie Devlin, Mark Daly and teams
Reproducible genetic variants
Common mechanism(s)?
General strategy to other diseases?

25,000+ autism/neurodevelopmental delay: whole exome sequencing
Stephan Sanders, Mike Talkowski, Joseph Buxbaum, Kathryn Roeder, Bernie Devlin, Mark Daly and teams
Perturb-seq: a systems genetic approach towards disease gene functions

CRISPR gene editing

Jin et al Science 2020
Perturb-seq: a systems genetic approach towards disease gene functions

2020: in vivo Perturb-seq
Reveals convergent cell type networks impacted by autism risk genes

Jin et al Science 2020
Major cell types from cortex

- Excitatory neurons
- Oligodendrocytes
- Inhibitory neurons
- Microglia
- Astrocytes

High-resolution phenotypic readout of cell subtype and cell state

Analysed 35 risk gene perturbation function with 46,770 cells
High-resolution phenotypic readout of cell subtype and cell state

Major cell types from cortex

- Excitatory neurons
- Inhibitory neurons
- Astrocytes
- Microgglia
- Oligodendrocytes

Excitatory projection neurons

Inhibitory neurons

- Astrocytes
- Microglia
- Oligodendrocytes

Jin et al, Science 2020

Analyzed 46,770 cells with 35 risk gene perturbation
A systems genetic approach to map gene functions in human disease

2020: *in vivo* Perturb-seq
Reveals convergent cell type networks impacted by autism risk genes

2023: massively parallel Perturb-seq
Analyzing over 30,000 individual cells within a single experiment

Jin et al Science 2020
Zheng et al BioRxiv 2023, in revision
Identification of optimal vectors to expand the scale and expression

Adeno Associated Viral (AAV) vectors

Testing 86 AAV vectors including:
AAV1, AAV2, AAV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12 & AAV13

Collaboration with Joshua Levin (Broad), Xiangmin Xu (UCI)
An accelerated platform to achieve massively parallel Perturb-seq

48 hours after AAV injection

Analysis of > 30,000 cells in one experiment

Collaboration with Joshua Levin (Broad), Xiangmin Xu (UCI)

Xinhe Zheng
Frank J. Dixon Graduate Scholar
FOXG1 perturbation leads to hybrid states in distinct cell types

Perturbation of an autism risk gene Foxg1

Collaboration with Joshua Levin (Broad), Xiangmin Xu (UCI)

Xinhe Zheng
Frank J. Dixon Graduate Scholar
Functional genomics: scalable, *in vivo* screen with high-resolution readout

The tissue we study

Bulk analysis

Single-cell analysis

Tissue clearing and whole brain imaging

From Bo Xia and DALL-E
Perturb-map: cytoarchitecture changes in an intact brain

Tissue clearing

Collaboration with Zhuhao Wu (Weill Cornell)
Perturb-map: cytoarchitecture changes in an intact brain

Tissue clearing

Sparsely labeled cells with different genetic perturbations
Light sheet imaging of an intact, whole mouse brain

Collaboration with Zhuhao Wu (Weill Cornell)
Perturb-map: cytoarchitecture changes resulting from disease risk genes
Towards genomics-inspired therapeutics

Vector engineering & Massively parallel Perturb-seq

FOXG1: context-specific role in cell fate determination

Versatile readouts with Perturb-map

Human genetics

CRISPR gene editing

Molecular engineering

In vivo genetic analysis

Cell type-specific, risk gene-associated effects
Towards genomics-inspired therapeutics

From diverse risk genes

To actionable drug targets
Collaborators

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