



The University of Edinburgh
Edinburgh Neuroscience



Simons
Initiative for the
Developing
Brain



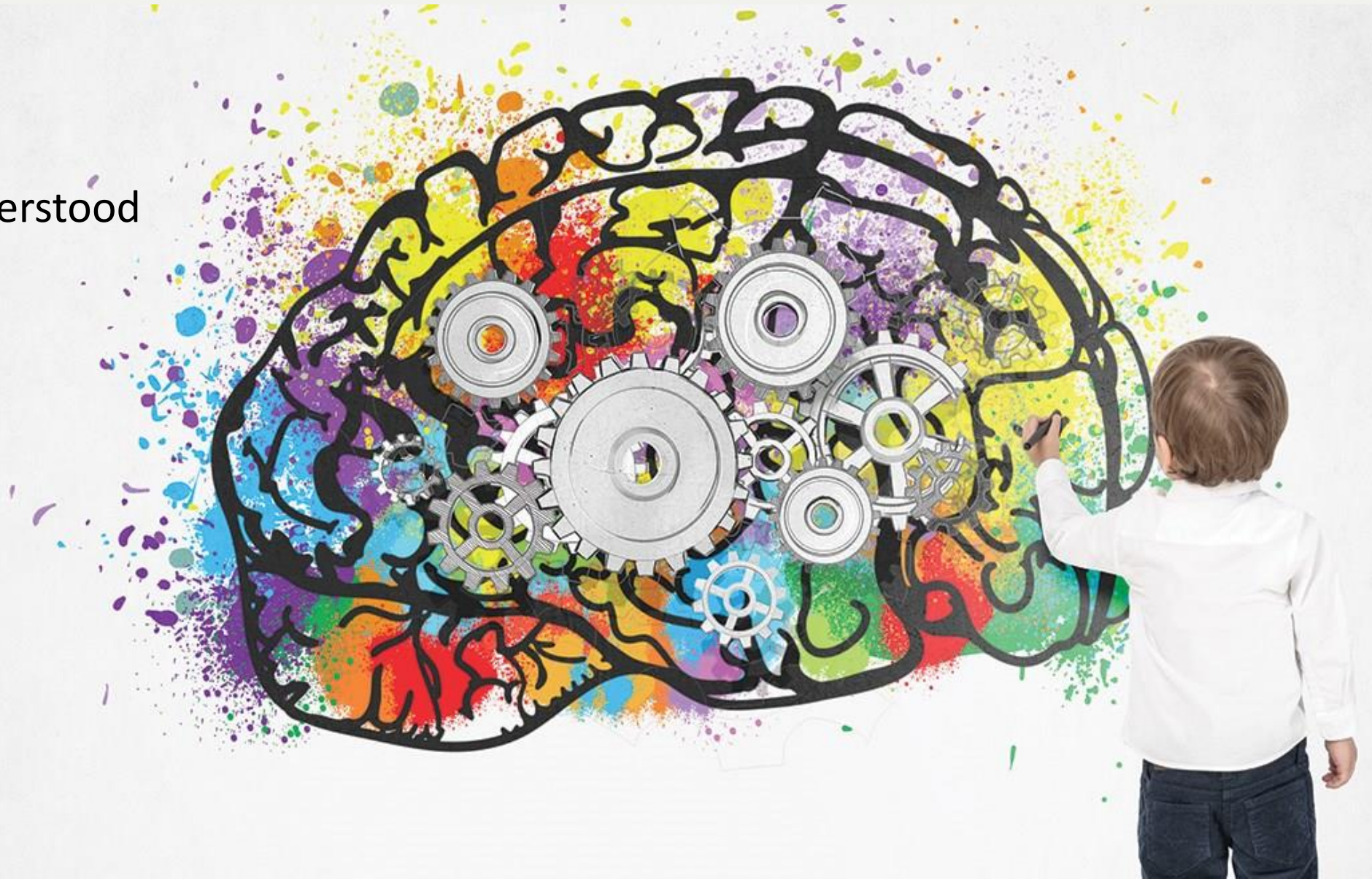
How Basic Neuroscience is Informing the Development of New Treatments

Stuart Cobb



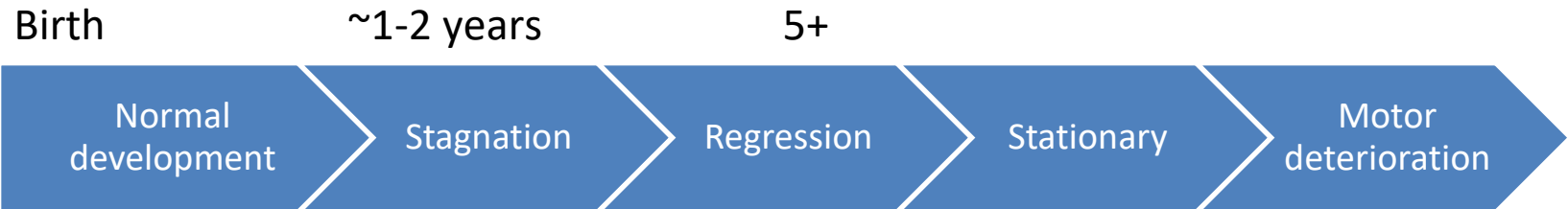
Neurodevelopmental Disorders

- Common
- Often genetic
- Often poorly understood
- Varied in severity



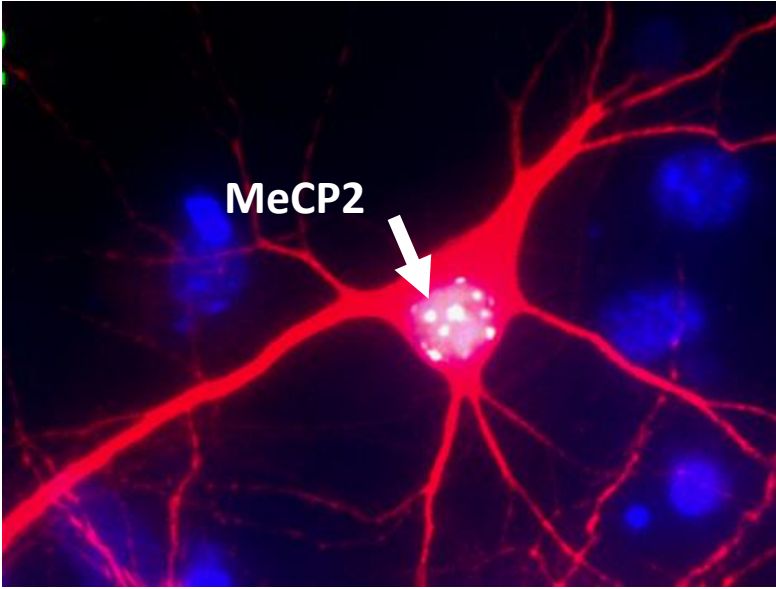
What is Rett Syndrome?

- Severe disability mainly affecting females

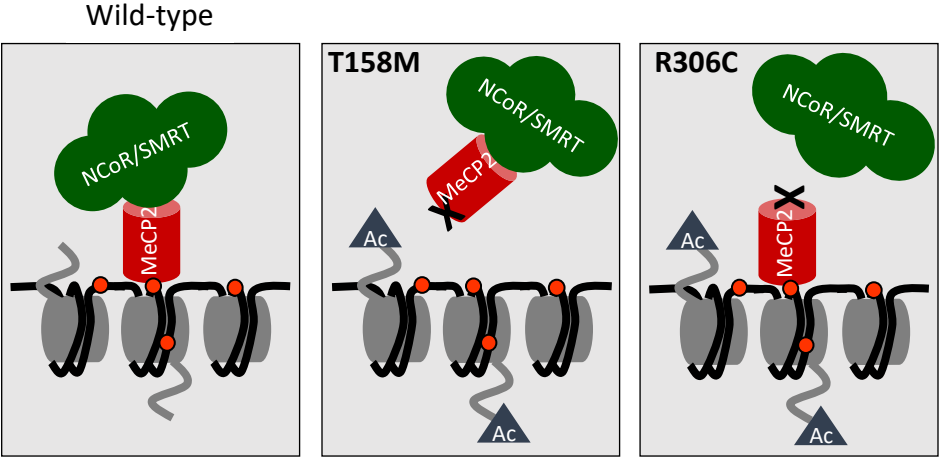


- Loss of hand skills
- Loss of speech
- Social interaction
- Intellectual impairment
- Seizures
- Abnormal breathing

- Loss of mobility
- Parkinsonism



- Lifelong disability, epilepsy, breathing dysfunction
- Caused by mutations in **MECP2** gene



Rett Syndrome Can be Accurately Modeled in Experimental Systems (cells & animals)

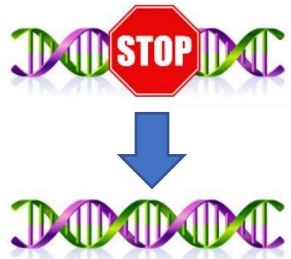
Mouse model created by KO of *Mecp2* gene

- Normal early development ✓
- Cognitive impairment ✓
- Gait disturbances ✓
- Breathing dysfunction ✓
- Seizures / aberrant EEG ✓
- Limb clasping ✓
- More severe in males ✓

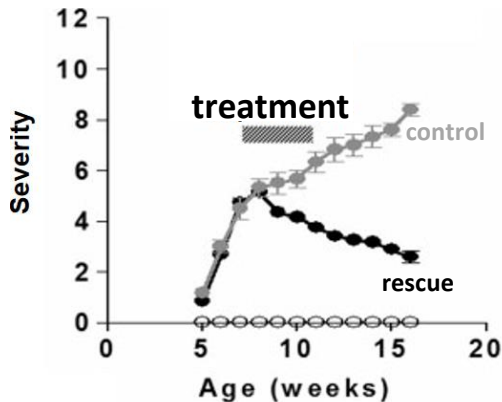


What have we learned from basic neuroscience studies?

Reversibility



Mecp2

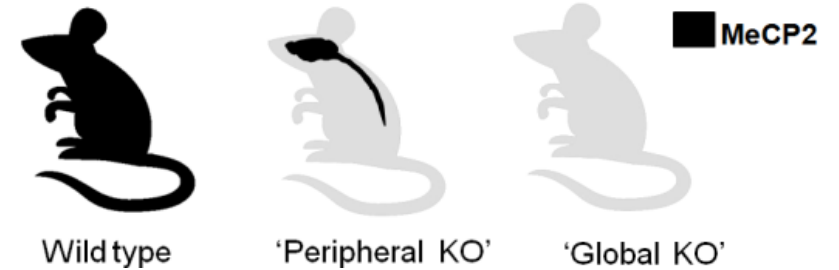


- | | <u>Improvement?</u> |
|-----------------------|---------------------|
| Tremor | ✓ |
| Locomotion | ✓ |
| Exploratory activity | ✓ |
| Balance beam | ✓ |
| Grip strength | ✓ |
| Rotarod | ✓ |
| Gait | ✓ |
| Breathing | ✓ |
| Cognition | ? |
| Abnormal EEG | ✓ |
| Epileptiform activity | ✓ |
| Behaviour (anxiety) | ✓ |
| Thermoregulation | ✓ |
| Neuronal morphology | ✓ |
| Synaptic plasticity | ✓ |

Guy et al., 2007 *Science*
 Robinson et al., 2012 *Brain*
 Lang et al., 2013 *Hum. Mol. Genet.*
 Tillotson et al., 2017 *Nature*



Importance of cell types / brain areas

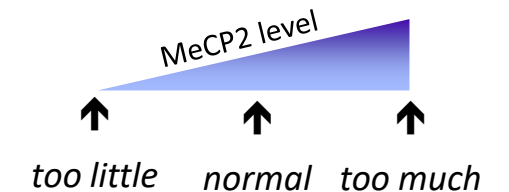


Importance of MeCP2 levels

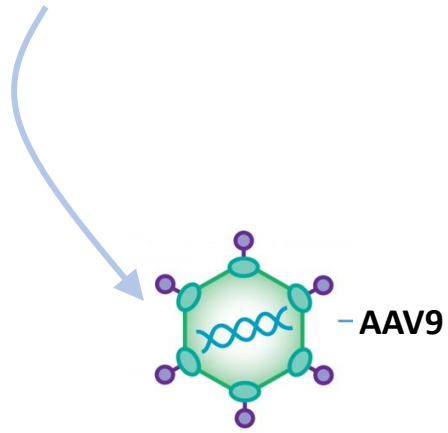
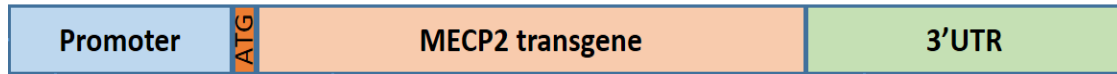
Rett syndrome



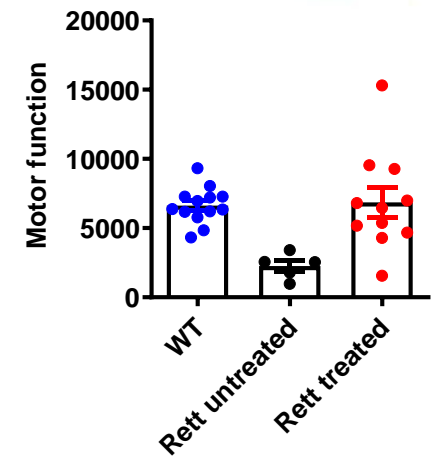
MECP2 duplication syn.



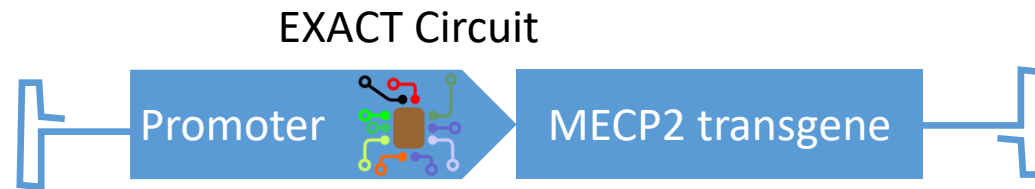
Concept of Gene Therapy in Rett Syndrome



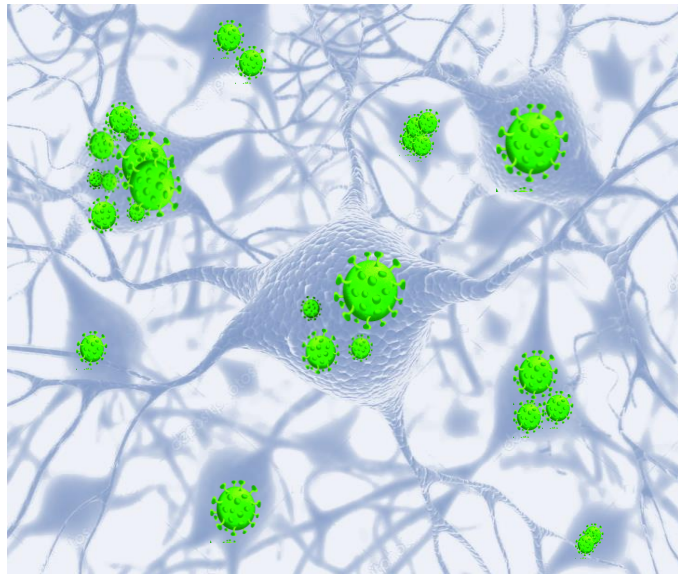
Deliver MECP2 as a therapeutic transgene



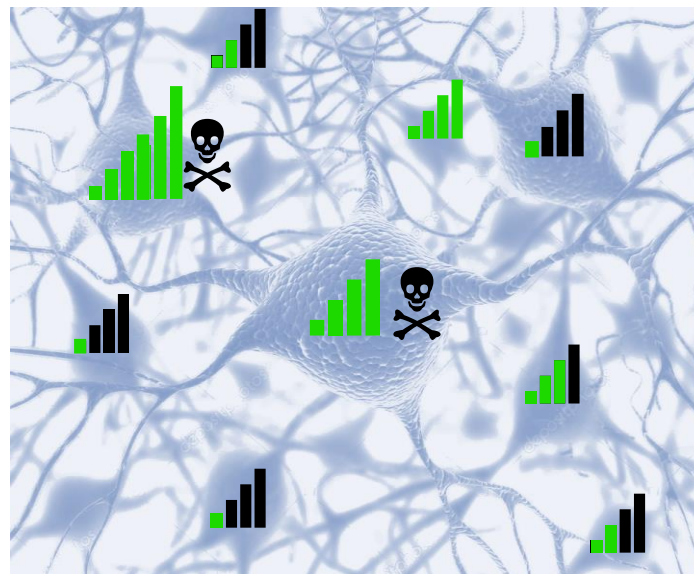
Development of Thermostat-like Control Circuit



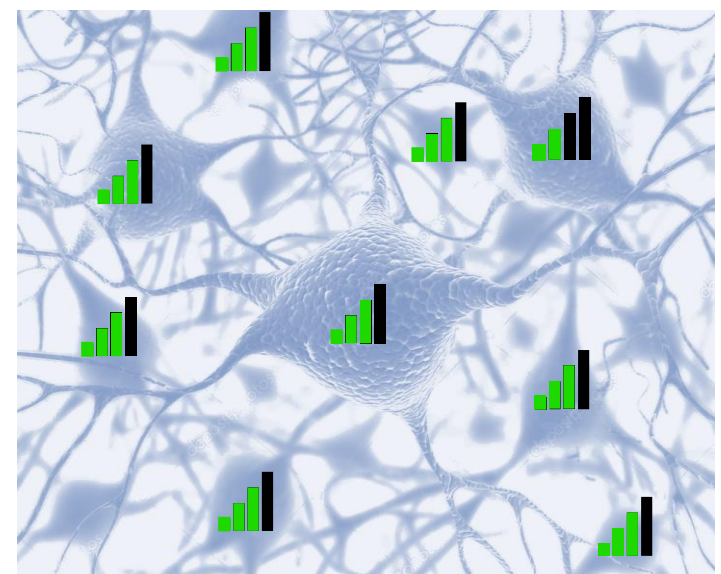
Vector



MeCP2 Protein



MeCP2 Protein



From Basic Neuroscience to New Treatments...

- Basic neuroscience studies predict Rett syndrome to be a treatable disorder
- Rett syndrome is a gene dosage-sensitive disorder and gene therapy requires appropriate regulation in order to be safe and effective
- EXACT technology embedded in NGN-401 enables:
 - Autoregulation of MeCP2 protein expression
 - Superior efficacy and safety relative to conventional gene therapy
- In January 2023, the FDA cleared the IND for a first-in-human clinical trial for NGN-401
- Phase 1/2 gene therapy trial in females (4-10yrs) with typical Rett syndrome

Key Milestones in Rett Syndrome

Neurology

Blue sky research

Neurogenetics

Basic & translational neuroscience

TAYSHA
GENE THERAPIES

Clinical description

Discovery of
MeCP2

Link between
MECP2 & Rett

Reversibility of Rett
syndrome

1st proof-of-concept for
gene therapy



Andreas Rett
(Vienna)

Adrian Bird
(Vienna/Edinburgh)

Huda Zoghbi
(Houston)

Adrian Bird

1966

1992

1999

2007

2013

2017

Academic research intensity

Industry research
(genetic therapy)



+ others