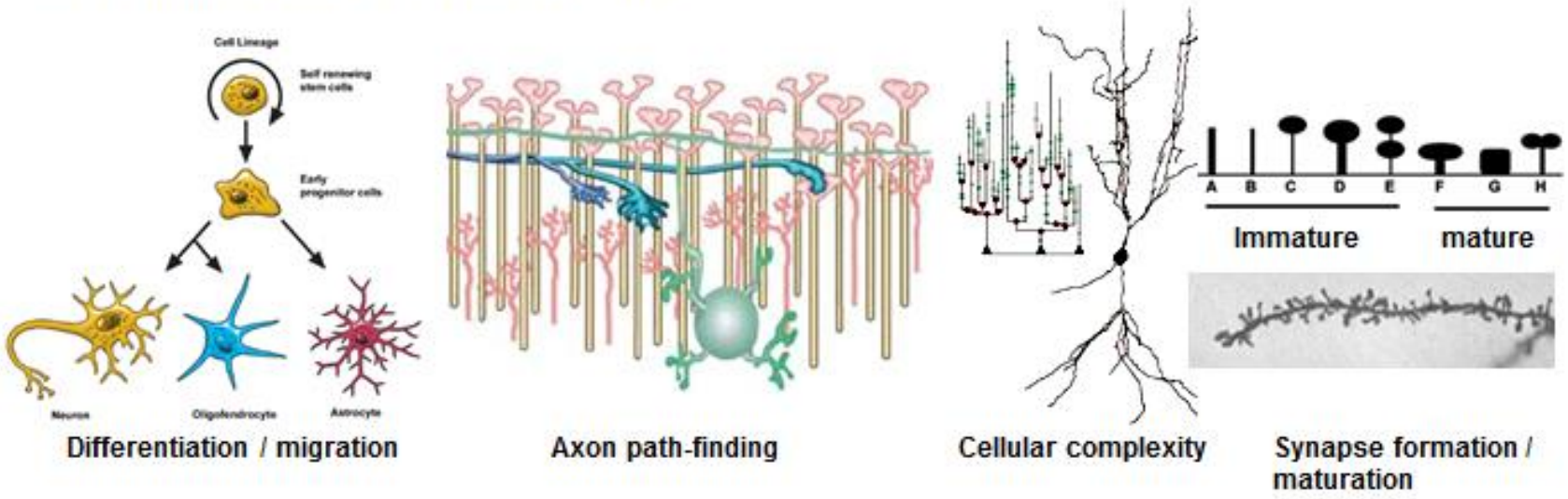
Developing genetic therapies for neurological disorders

Cobb lab

Institute of Neuroscience and Psychology

Centre for Neuroscience

Abnormalities in brain development:



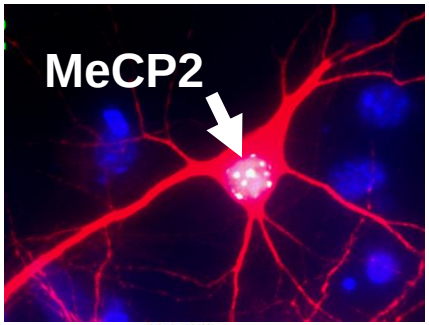
Rett Syndrome & X-linked ID

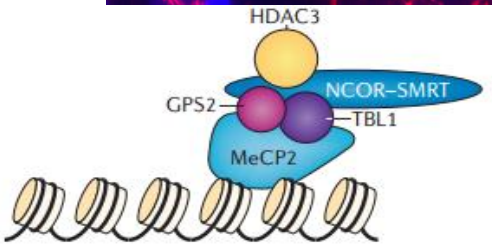
Birth ~1-2 years 5+

Normal development → Stagnation → Regression → Stationary → Motor deterioration

- Lifelong intellectual & motor disability, epilepsy, breathing dysfunction
- x-linked genes:

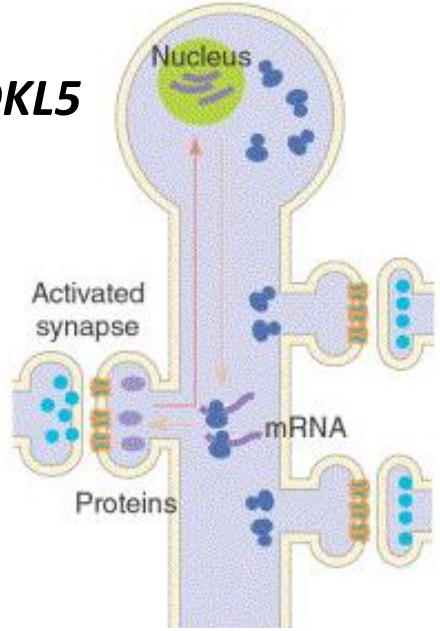
MECP2





Reader of epigenetic marks / regulates gene expression

CDKL5



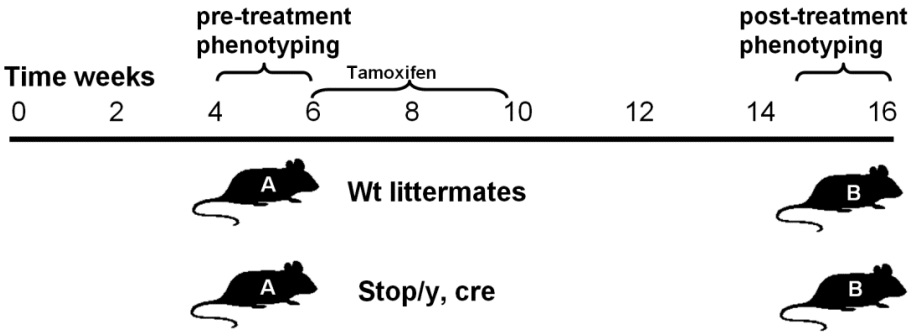
Role in gene regulation / synaptic plasticity

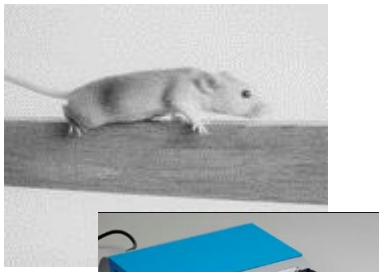
Rett syndrome can be accurately modeled in mice

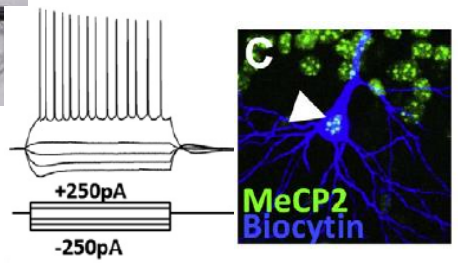
- Mouse model created by KO of *Mecp2* gene

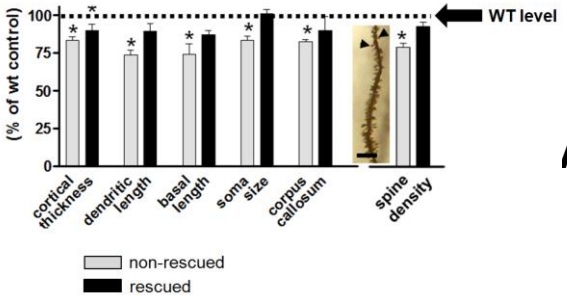
Normal early development	✓
Cognitive impairment	✓
Gait disturbances	✓
Breathing dysfunction	✓
Seizures / aberrant EEG	✓
Limb clasping	✓
Early male death	✓

Reversal in a range of behavioural / motor tasks





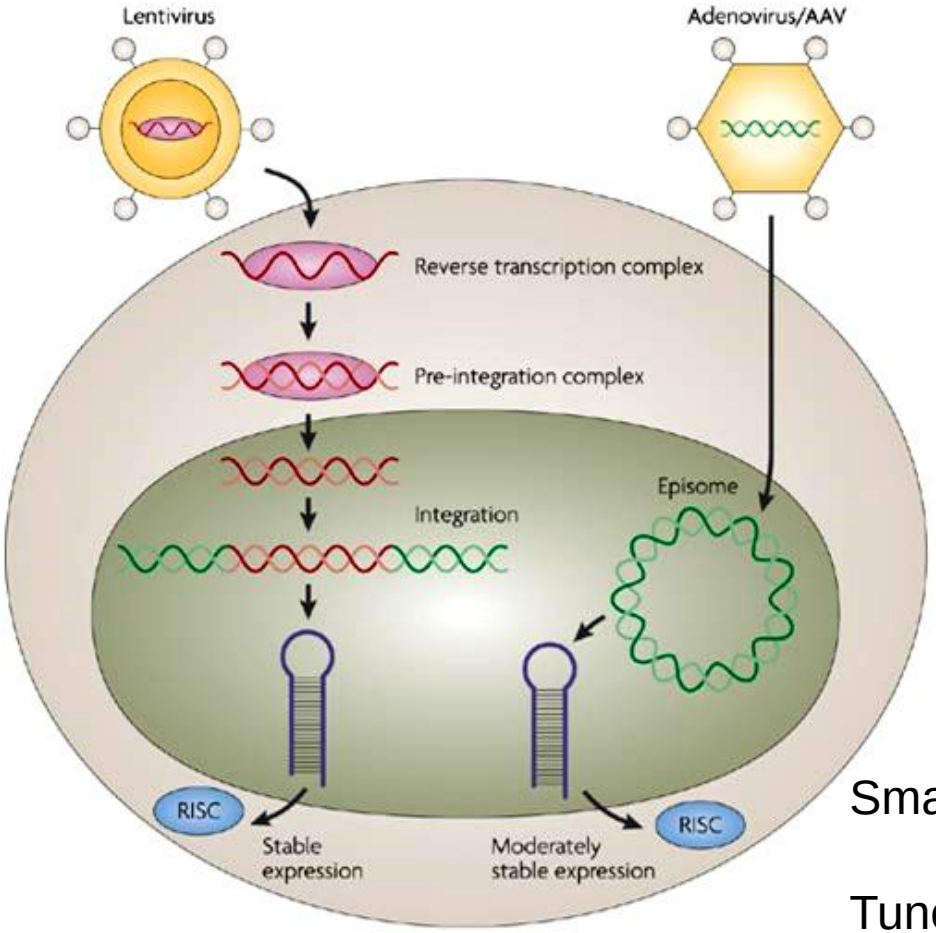




	Improvement
Tremor	✓
Locomotion	✓
Exploratory activity	✓
Balance beam	✓
Grip strength	✓
Rotarod	✓
Gait	×
Breathing	✓
Cognition	?
Structural remodelling	✓
Behaviour (anxiety)	✓
Epileptiform activity	✓
Thermoregulation	✓
Abnormal EEG	✓

Robinson *et al.* 2012 Brain.
PMID: 22525157.

Gene therapy
- conventional gene augmentation therapy

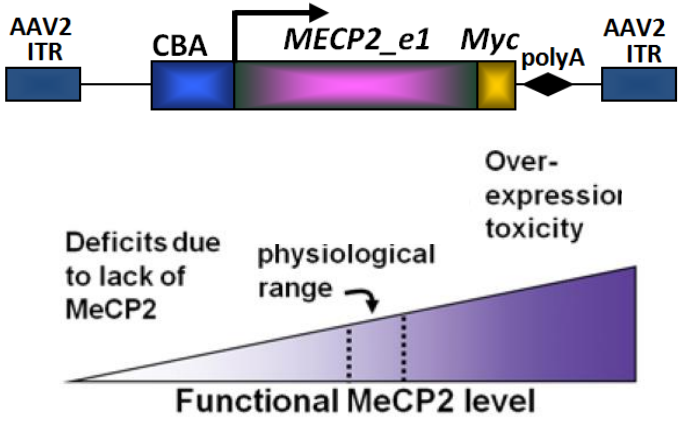


2013

original article

Improved Survival and Reduced Phenotypic Severity Following AAV9/*MECP2* Gene Transfer to Neonatal and Juvenile Male *Mecp2* Knockout Mice

Kamal KE Gadalla[1–3], Mark ES Bailey[2], Rosemary C Spike[1], Paul D Ross[1], Kenton T Woodard[4], Sahana Nagabhushan Kalburgi[4], Lavanya Bachaboina[4], Jie V Deng[5], Anne E West[5], R Jude Samulski[4], Steven J Gray[4] and Stuart R Cobb[1]



Smarter cassettes with regulatory elements

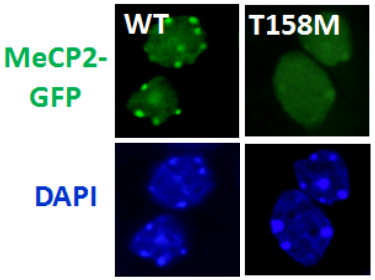
Tuneable (pharmacologically regulated) expression systems

Capsids that target / de-target particular cells

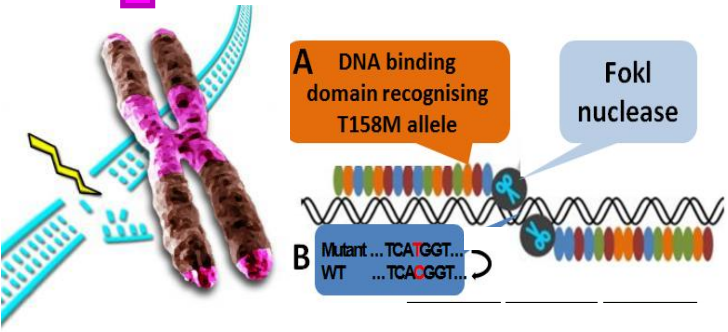
Looking to the future: mutation repair in the brain -
editing, skipping, inclusion, read-through, trans splicing…

MeCP2

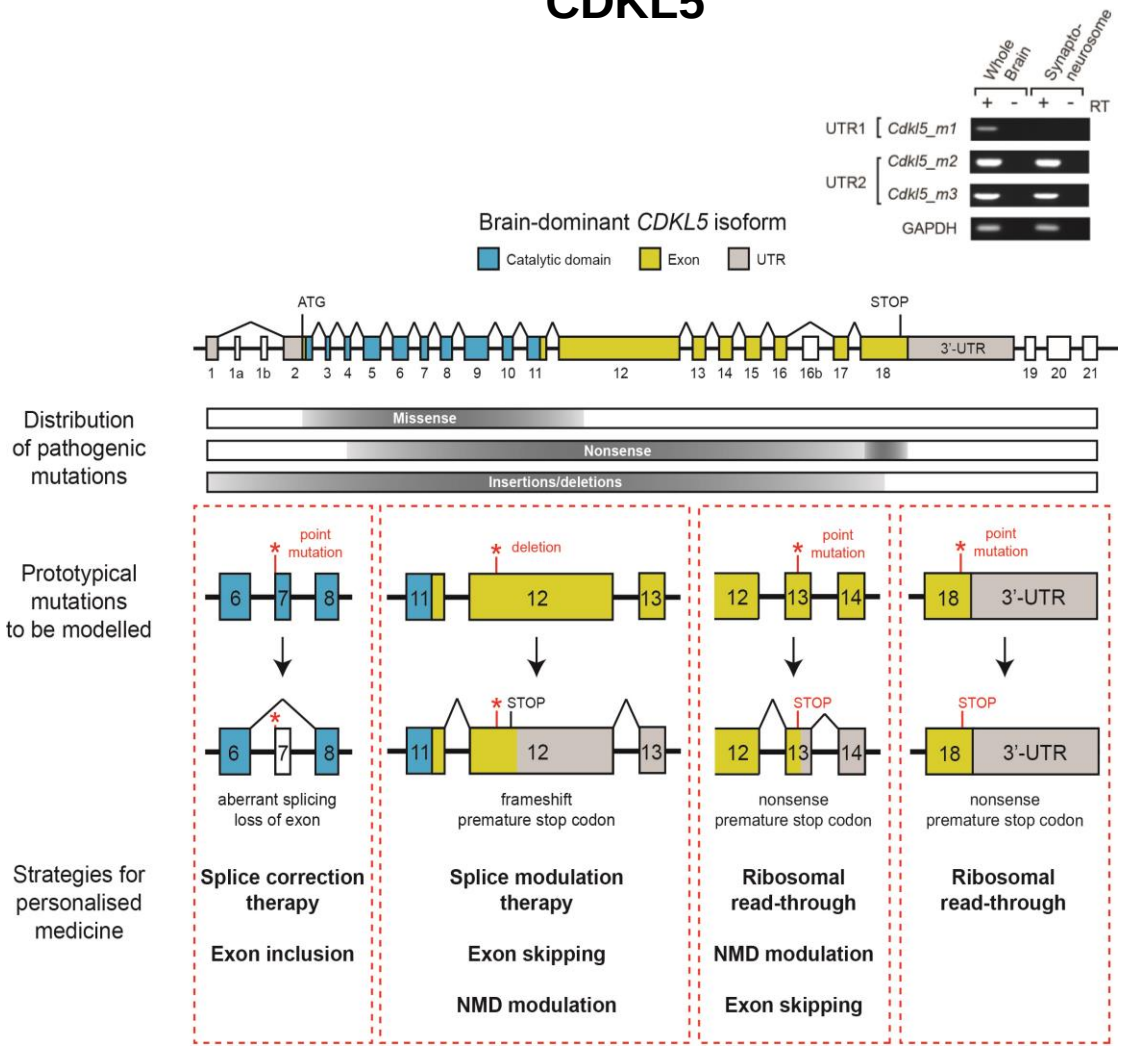
Human mutation
Knock-in



Mutation repair



CDKL5



What we need now…

Expertise in cell biology generally / primary neuronal culture / neuronal stem cells

Expertise in patient derived cells (fibroblasts, iPS etc)

Expertise in rodent EEG / telemetry

Better animal facilities for behavioural testing / cognitive studies

Mitochondrial imaging

Collaborations

Cobb Lab
Kamal Gadalla
Ralph Hector
Elaine Hunter
Paul Ross
Thishnapha Vudhironarit
Daniela Minchelia
John Craig
Noha Bahey

Glasgow
Mark Bailey (Life Sciences)
Adam/Katherine West (Cancer)
Liz Tanner (Engineering)
John Riddell (INP)
Julia Edgar (III)

Strathclyde
Trevor Bushell (SIBS)
Michele Zagnoni (Engineering)

Edinburgh
Adrian Bird / Jacky Guy / Jim Selfridge
Peter Kind

Aberdeen
Gernot Riedel

Trinity College Dublin
Kumlesh Dev

North Carolina
Steve Gray

Vollum Institute & HHMI
Gail Mandel

University of Milan
Nicoletta Landsberger
Charlotte Kipstrup-Nielsen

Stirling
Bruce Graham

rett syndrome research trust
www.ReverseRett.org

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CHIEF SCIENTIST OFFICE

Rett Syndrome
Association Scotland

Daphne Jackson Trust