Neurodevelopmental Influences on outcomes
Themes apply to generic and specific

Understanding phenotype
- Angelmans
- VCFS
- Prader Willi
- Retts
- Non syndromic ID
- Autism

Genetic & Biological
- Array
- Gene Sequencing
- Bio informatics
- RNA Expression
- Epigenetic studies
- KO Mouse

Therapies & Outcome Evaluation
- Clinical Trials
- Mouse models
- Behavioural Programs
- Outcome measures

Translation to Community
- Education Programs
- CMAP
- Presentation & Publication
- Policy

Mater
Children’s Hospital
Scope of research

• Specific disorders
• Non Syndromic Intellectual Disability
• Autism 1/100-25 x in last 30 years
  – CRC $31 million-12 essential partners
  – UQ lead
    • Program 1- Early Identification/biological understanding/phenotypic description
    • Program 2- Early Intervention models/targeted therapies
    • Program 3- Adult outcomes
Origins and effects on outcomes:

Cost implications:
Autism: Early Intervention programs
Modelled scenarios- 86,000/ child cost BCRs 11 and 4.1 (Synergies)
Even if less than 5% change in severe end of spectrum requiring intensive support

Epidemiology
• Cohort studies
  – MUSP
  – British cohorts – BCS70, AVON

Predictions of later outcomes developmental, learning and mental health have origins in infancy (certainly pre childhood)
Sleep

• Sleep cohorts
• Typically developing cohort
• PWS- Growth hormone and respiratory compromise in Prader-Willi Syndrome.
• Large national study underway of the neurocognitive effects of adenotonsillectomy on children with mild, moderate sleep apnoea- a surgical RCT
Understanding phenotype specifics

• Human models
  – Fragile X
  – PWS/ Angelman
  – Tuberous sclerosis
  – SLOS- SHH
  – 22q11del/ VCFS/ Di George

• Individuals with these phenotypes may have ASD traits
Neuronal imaging techniques

- Adds to phenotypic description
- Neuroscience and neuronal development
Making connections

- Fragile X
- TSC
- NF1
- Angelmans
- 22q11del
- Autism
- Intellectual Disability
- Schizophrenia
Genetic and biological studies

Wayman et al Calmodulin Kinases: Modulators of Neuronal Development and plasticity Neuron 59(6) 2008
Therapies and outcomes

• Early Intervention-
  - Early intervention evaluation programs-AEIOU

• Sleep
  - Melatonin program (PK, Dosing studies, Efficacy)

• Behaviour

• Environmental

• Targeted biological/ pharmaco-therapeutic interventions
  - Clinical trials- Fragile X, Angelmans, Down syndrome, Risperidone
Targeting interventions

- Shared pathophysiology with other disorders
- Oxytocin- sociability in PWS/ Autism
- MGLUR (metabotropic glutamate receptors) - synaptic plasticity – targeted therapies have demonstrated improvements particularly in anxiety (FRAX) - adults (just approved for trials in children)
Multiple sites of intervention in FXS

Ganaxolone, allopregnanolone

Levenga et al 2010
**Targeted interventions**

- TSC – SEGA response
- Trials now underway with Rapamycin and epilepsy and neurocognitive deficits
- Animal models show improved memory and cognitive function
- Adults also show improved cognitive function
- Trials underway for children
- International Collaboration - NIH (TOSCA)
The minocyclin story

• Tetracycline antibiotic- inhibition of MMP
• Promotes Dendritic spine maturation in culture and in vivo in
  – Fragile X KO mouse  Bilousova TV et al J Med Genetics 46(2) 2009
  – Children with Fragile X  Leigh MJ, J Dev Behav Pediatr. 2013 Apr;34(3)
  – Angelman KO mouse  E Weeber
  – Open label trial in children 4-12  (Weeber et al manuscript in prep)
Translation to practice

• Rare disorders:
  – RCTS: difficult- International collaborations/ n=1 aggregated trials
  – Empowerment of individuals and families
  – QCIDD studies- Health assessments- GP education/ facilitation

• Education:
  – Lecture program (Sleep) psychologist, GPs
  – Lecture program schools