POND family Day 2018

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Associate Professor, Department of Pediatrics, University of Toronto
<table>
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<tr>
<th>Time</th>
<th>Session</th>
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<tr>
<td>8:30am-9:30am</td>
<td>Registration and Continental Breakfast</td>
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<tr>
<td>9:30am-9:45am</td>
<td>Opening Remarks: Introductions to the day</td>
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<tr>
<td>9:45am-10:15am</td>
<td>Dr. Evdokia Anagnostou: Alternative Therapies</td>
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<td>10:15am-10:45am</td>
<td>Dr. Yona Lunsky: Transitions into Adulthood</td>
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<td>10:45am-11:00am</td>
<td>Break</td>
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<td>11:00am-11:30pm</td>
<td>Dr. Jason Lerch: Sex differences in Neurodevelopmental Disorders</td>
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<td>11:30pm-12:00pm</td>
<td>Dr. Michelle Siu: Epigenetics and Neurodevelopmental Disorders</td>
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<td>12:00pm-1:10pm</td>
<td>Lunch</td>
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<td>1:10pm-1:40pm</td>
<td>Dr. Melanie Penner: Puberty and Neurodevelopmental Disorders</td>
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<td>1:40pm-2:10pm</td>
<td>Panel: PAC</td>
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<td>2:10pm-2:40 pm</td>
<td>Dr. Stephanie Ameis: Mental Health/Anxiety and Neurodevelopmental Disorders</td>
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<td>2:40 pm-3:10 pm</td>
<td>Dr. Evdokia Anagnostou: Research Updates and Closing Remarks</td>
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• Renewed for another 5 years!!!!, $13million
• >2500 children with NDDs in our consortium
• Completed 2 clinical trials in ASD
• Currently we are about to start one more trial in ASD and one in Rett syndrome
• Planning phases for an across-diagnostic labels trial of probiotics
The Factor Structure of Combined Autistic and ADHD Symptoms in a POND Research Sample
Normalized Factor Scores in Profile Analysis

Profile Plot: Diagnosis (ADHD, ASD) by Gender (Female, Male)

* p < .01 Diagnosis effect
° p < .01 Gender effect
Imaging across disorders

A Diffusion Tensor Imaging Study in Children With ADHD, Autism Spectrum Disorder, OCD, and Matched Controls: Distinct and Non-Distinct White Matter Disruption and Dimensional Brain-Behavior Relationships


AJP in Advance (doi: 10.1176/appi.ajp.2016.15111435)
Shared functional network in children with neurodevelopmental disorders (ND: ASD, ADHD, and OCD)

EunJung Choi, MD
• Degree: the number of connections or edges

• Clustering coefficient: probability that the neighbors of this vertex are also connected to each other

• Local efficiency: inverse of the average shortest path connecting all neighbors of that vertex
Each ND vs TD

- **Group difference in degree**
  - Across all comparisons, each ND showed decreased DMN degree and increased SC network degree.
Clinical Trials

- Development of POND-OCTN
Current Approaches

POND network: HB, UfT; McMaster; Lawson (Western)
ATN: HB; OSU; Pittsburgh; Vanderbilt
Other: Minnesota, Rush U, Mount Sinai NY

• Target emerging genomic variation
  - Riluzole
  - Memantine
  - Tideglusib

• Target neuropathology targets
  - Omega 3 fatty acids
  - Pioglitazone

• Target neurocircuitry of interest
  - Oxytocin
Riluzole vs placebo in ASD
(co-Pis: Rob Nicolson, Terry Bennet)
RILISE STUDY

- Randomized 60 children and adolescents
  - 1:1 fashion
  - Stratified for age
    - Mean age: 11.5 years +/- 3.0
    - Mean IQ: 74 +/- 28
Rilise – Social Withdrawal

ABC Lethargy Score Across Study Time

- **Treatment**
  - Placebo
  - Riluzole

- **Study Week**
  - Week 0
  - Week 4
  - Week 8
  - Week 12
  - Week 16
Externalizing behaviors

**ABC Irritability Across Study Time**

- Treatment comparison:
  - Placebo
  - Riluzole

**ABC Hyperactivity Across Study Time**

- Treatment comparison:
  - Placebo
  - Riluzole

- *p = 0.02; d = 0.45*
- Coeff estimate for riluzole: -4.56

- *P = 0.02; d = 0.4*
- Coeff estimate for riluzole: -5.24
Pharmacological agents that can deplete GSK-3β such as Tideglusib have been shown to rescue the phenotype of the Fragile X – FMR1 knockout transgenic mouse. Rescued or improved domains included learning and memory, hyperactivity, anxiety and fear conditioning, as well as repetitive behaviors (Franklin et al., 2013, Figure 2).
TIDE study

- Regulates circadian clock
- Regulates inflammatory response (reduces pro-inflammatory cytokines, increases anti-inflammatory cytokines)
- Regulates neurogenesis/cell differentiation
- Phosphorylates histone deacetylase 3
- Key role in synaptic plasticity (via NMDA mediated LTD).
  - 100% recruitment
Primary outcome measure: social withdrawal

Average ABC Lethargy Over Time By Treatment Group With 95% (Bootstrap) Confidence Intervals

% Change ABC Social Withdrawal Score

Cohen’s D effect size = 0.44

p = 0.055

p < 0.01

Placebo AMO-02

Cohen’s D effect size = 0.66

p = 0.055

p < 0.01

Holland Bloorview
Kids Rehabilitation Hospital
Secondary outcome: repetitive behaviors

Average RBS-R Over Time By Treatment Group With 95% (Bootstrap) Confidence Intervals

Cohen's D effect size = 0.66

p < 0.01

Cohen's D effect size = 0.66
Adaptive function and Biomarkers

![Graph showing changes in clinical outcomes and percent inhibition pAkt between Placebo and AMO-02.](image)

*Note: The graph illustrates the comparison of clinical outcomes and percent inhibition pAkt between Placebo and AMO-02 treatment groups. The data points indicate a significant difference in clinical improvement and pAkt inhibition between the two groups.*

**Kids Rehabilitation Hospital**
Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder
A Randomized Clinical Trial

Figure 2. Metformin Effect on Body Mass Index (BMI) z Score and Weight Change

A  BMI z score

B  Raw weight

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<tr>
<th>Study Week</th>
<th>Metformin</th>
<th>Placebo</th>
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<td>0</td>
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<td>16</td>
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No. at risk
Metformin 28 28 26 27 25 24
Placebo 32 31 31 30 30 30
JLA initiative

• Updates:
  • Launched in December
    – >175 respondents
      – 80% urban, 20% rural
      – 20% Eastern, 21% Central, 24% Toronto, 21% Western, 12% Northern Ontario
    – >700 questions
    – Mostly parent / self advocates

  – http://www.braininstitute.ca/NDDpriorities
The Top 10

The Top 10 research priorities from the neurodevelopmental disorder community are:

1. What are the most effective treatment options/plans (e.g., timing, frequency, duration, type, intensity or dosage) for individuals with neurodevelopmental disorders for both short and long-term benefits?

2. How can system navigation be organized in a manner that enables coordinated services and supports across the lifespan for individuals with neurodevelopmental disorders and their families?

3. Which biological treatments (including medications, gene therapy, stem cell therapy, etc.) are effective for neurodevelopmental disorders and associated symptoms?

4. Which child and family-centered interventions or approaches promote optimal individual and family functioning?

5. Which interventions best help individuals with neurodevelopmental disorders develop emotional and behavioral regulation (including increasing impulse control and reducing compulsive behaviour)?

6. Which resources are needed to more effectively address the health, social and emotional needs of families or caregivers of individuals with neurodevelopmental disorders?

7. How can treatment decisions for individuals with neurodevelopmental disorders be more precise (i.e., based on the diagnosis, age, functional need of the individual)?

8. Which are the most effective pharmacological and non-pharmacological treatments for aggressive and self-injurious behaviour in individuals with neurodevelopmental disorders?

9. Which are the most effective pharmacological and non-pharmacological intervention(s) to reduce anxiety in individuals with neurodevelopmental disorders?

10. Which interventions are most effective to help individuals with neurodevelopmental disorders improve their social skills and develop and maintain social relationships?
From disability to possibility

Thank you
Targeting networks of relevance: the example of oxytocin

OT-KO Mice: Deficit In Social Recognition

Ferguson et al. Nature Genetics 2000
Research Report

**Intranasal oxytocin in the treatment of autism spectrum disorders: A review of literature and early safety and efficacy data in youth**

Evdokia Anagnostou\(^a\),\(^*\), Latha Soorya\(^b\), Jessica Brian\(^a\), Annie Dupuis\(^c\), Deepali Mankad\(^a\), Sharon Smile\(^a\), Suma Jacob\(^d\)

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*CrossMark*
RCT of oxytocin vs placebo in youth with ASD

- 60 youth randomized, 1:1
  - Holland Bloorview, University of Toronto
  - University of Minnesota – Dr Jacob

- 12 weeks exposure
- Follow-up at 24 weeks

- Dose: 0.4IU/kg/ dose, 2 doses a day, 8 +/- 2 hours apart
Intranasal oxytocin vs placebo in adolescents with ASD

Let's Face It: Faces

Let's Face It: Houses

Holland Bloorview
Kids Rehabilitation Hospital
Intranasal oxytocin vs placebo in adolescents with ASD