NIMH Autism Research Program

Discovering the Causes & Cures of Autism and Conducting Meaningful “Until Then” Research

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NIH Intramural Research Program
Finding the Causes & Cures for Autism

Environmental Trigger → Genetically Susceptible Host

Abnormal Brain Development, Structure &/or Function → Developmentally Sensitive Period

Symptoms of Autism
NIMH Autism Research Program

• Multi-disciplinary Clinical Research Team
  – M.D.’s – Pediatrics, child psychiatry, neurology
  – Ph.D.’s – Developmental & clinical psychologists
  – Other professionals – Social work, biostatistics

• Support staff and Trainees
  – Administrative and support staff
  – Clinical and research fellows – Physicians, psychologists, speech and language pathologist
  – Post-baccalaureate IRTAs who plan to attend medical school or graduate school in 1 – 2 years
Collaborative Relationships

• Within NIMH
  – CBDB: Emotional processing
  – CHP: DTI and Structural MRI scans
  – LBC: Social cognition; executive functions; fMRI (resting state)
  – LBN: Animal models
  – LNT: Proteomics/metabolomics
  – MAP: Co-morbid disorders; treatment trials; biostatistics
  – MIB: Magnetic resonance spectroscopy

• Within NIH
  – NCI: Neuroinflammatory markers
  – NHGRI: Specific genetic syndromes (e.g. SMS)
  – NIAID: Lymphocyte phenotyping and viral titers
  – NICHD: Clinical genetics (WAGR, SLO); CTDB; stem cell models (from skin fibroblasts)
  – NIDCR: Dysmorphology
  – NINDS: Electroencephalography & polysomnography
  – CIT: Database development
  – Clinical Center: Sedation safety; pharmaceutical development
• With Extramural Investigators
  – FL State Univ: OCD in autism; speech/language abnormalities; early identification screening tool
  – Johns Hopkins: CSF/blood immune markers; cytokines response to minocycline; cholesterol study (also NICHD & OSU)
  – Mass General: MRI Clinical Findings; polysomnography studies
  – M.I.N.D: Phenome project; behavioral phenotyping
  – N.Y.U. Child Study Center: Sleep disorders in autism
  – UCLA: Genetics (expression profiling; SNPs)
  – UC Davis: Immunology; environmental factors
  – Univ Michigan: Diagnosis in toddlers
  – Vanderbilt: MET gene (Levitt); sleep and EEG abnormalities

• Others
  – Autism Treatment Network (Autism Speaks)
  – Clinical Trials Network (Autism Speaks)
  – Children’s National Hospital: CSF collection
  – DSM-V Neurodevelopmental Disorders workgroup
  – Emory & Baylor: Genetic microarrays and MECP-2 testing
  – Medical Neurogenetics: Neurotransmitter metabolites
  – NIMH Autism Genetics Repository
  – IVIG Treatment Trial (Industry/Yale/Okla.)
Screening Study is Entry Point

- Comprehensive Diagnostic and Behavioral Evaluation
  - ADOS & ADI-R
  - IQ and Adaptive Functioning
  - Additional testing as needed

Cedar Lane clinic opened in Fall 2006
Since then, the Behavioral Evaluation Team have conducted more than 400 in-person screenings with more than 200 subjects eligible for PDN studies
Types of Investigations

• Phenomenologic (Phenotyping) Investigations
  – “Subtypes” study of 1 – 4 yr old children
  – Individuals with Remitted Autism
  – Specific neurodevelopmental disorders (e.g. SMS)

• Therapeutic Trials
  – Hypothesis-driven/generating studies
    • Minocycline for anti-inflammatory effects
  – Symptom-specific therapies
    • Riluzole for repetitive behaviors
    • Donepezil for REM sleep deficits

• Hypothesis-testing Experiments
  – fMRI study of oxytocin vs. vasopressin vs. placebo
  – MRS evaluation of treatment effects and response
The Autism Phenotyping Study

CLINICAL OR PHENOTYPIC VARIABILITY

There are many ways to trigger disruption of development AND there are many different outcomes of that disruption, but all are products of the brain … the proverbial “black box”

ETIOLOGIC VARIABILITY

Common pathways leading to autistic outcomes – number and type is unknown
The Autism Phenotyping Study

• Also called the Subtypes Study
• Comprehensive baseline evaluation with extensive behavioral and medical work-up
• Longitudinal follow-up for 3+ years
• Young children (ages 12-60 months)
  – 50 with AUTISM (no regression)
  – 50 with REGRESSIVE AUTISM
  – 50 Typically Developing CONTROLS
  – 25 with non-ASD DEVELOPMENTAL DELAY
## The Regression Subtype

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<tr>
<td><strong>No early signs</strong></td>
<td>Typical child</td>
<td>Regressive Autism</td>
</tr>
<tr>
<td><strong>Early signs</strong></td>
<td>Autism</td>
<td>Autism with Regression</td>
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The Regression Subtype

- However, it’s not actually that simple
- Continuum, not dichotomy
- Does pattern of onset provide clues to etiology and pathophysiology?

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<th>No regression</th>
<th>Some Regression</th>
<th>Significant Regression</th>
</tr>
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<td></td>
<td>Regressive Autism</td>
</tr>
<tr>
<td>Some early Signs</td>
<td>Seen frequently</td>
<td></td>
<td>Seen occasionally</td>
</tr>
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<td>Seen frequently</td>
<td>Autism with regression</td>
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</table>
Subtypes Study: Preliminary Findings
Electroencephalography (EEG)

- EEGs in first 50 autistic pts without epilepsy
  - Routine EEGs abnormal in 10 studies (20%)
    - Nonepileptiform 3
    - Epileptiform 9
  - Overnight EEGs abnormal in 30 studies (60%)
    - Nonepileptiform 5
    - Epileptiform 25
      - 15 frequent and 9 infrequent
      - 11 diffuse, 4 multifocal, and 11 focal (mostly left temporal)

- Epileptiform discharges may provide new therapeutic target
Modified Polysomnography (PSG) can measure sleep parameters in real-time.

Preliminary Findings (n = 50):
- Decreased sleep efficiency
- Prolonged latency to REM sleep
- Decreased total time spent in REM sleep

NOTE: Most of these children did NOT have reported sleep difficulties.
Comparison of Mean REM Percentages for Regressive and Non-Regressive Autism, Dev. Delay and Typically Developing Groups
Trial of Donepezil to Treat Sleep Abnormalities in Autism

• Clinical trial to determine whether donepezil (Aricept) has an effect on REM sleep.
• Among elderly adults, donepezil increases REM.
• Open label trial with 3 doses of donepezil and repeated overnight sleep studies (polysomnography)
• Titrate dose to maximize response and ensure sustained effects
Donepezil Dose-Response Curves
Minocycline Treatment Trial

- Has shown benefits in neurodegenerative conditions (Huntington’s, ALS, MS)
- Mechanism may be its anti-inflammatory properties (blockade of NF-kappa B)
- OPEN LABEL trial in 15(10) children with regressive autism
- Measures include:
  - Changes in CSF & serum cytokine and chemokine analyses before and after therapy (Analyses by Dr. Carlos Pardo at Johns Hopkins Univ)
  - Effect on behavioral change
- Placebo-controlled trial will enroll children with “responders” pre-treatment CSF profile
Riluzole Treatment Trial

- Riluzole is a glutamate "antagonist" -- glutamate is the primary excitatory neurotransmitter in the fronto-cortical-striatal circuit (involved in OCD and tic disorders).
- Placebo-controlled trial
  - 30 subjects w/ OCD
  - 30 subjects w/ OCD + ASD
- 12 weeks double-blind
- 9 months open-label
- Recruitment is ongoing

Open Label Trial in 6 pts w/ OCD
REMITTED AUTISM STUDY

- Purpose is to identify effective treatment regimens and predictors of remission as first step in developing new, more effective therapies.

- Comprehensive evaluation of:
  - 40 children whose symptoms have remitted
  - 40 children (similar at baseline) who retain symptoms of autism.
REMITTED AUTISM STUDY

- NIH review of medical and developmental records
- Comprehensive medical and behavioral evaluation
- MRI, EEG, and Neuropsychological testing during 2 days inpatient stay
NIMH Contact Information

• Remitted Autism Study
  – Phone: 301-435-6205
  – AutismOutcomeStudy@mail.nih.gov

• Other Studies
  – Phone: 301-435-7962
  – NIMH-ASD@mail.nih.gov