Highlights from 50 Years of IDD Research

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President Kennedy’s Plan to Promote Research
Core Grants and Leveraging

**Infrastructure:**
Fund scientific cores (NICHD)

**Leveraging:**
Faculty Research Affiliates involved in relevant research (NIH grants)

**Task:**
Develop a coherent university-based interdisciplinary center
Highlights from the 50th Year Anniversary Article
The Translational Research Cycle

- Characterization and Etiology
- Clinical Trials
- Model System Development
- Target Identification
- Target Validation/Preclinical Trials
- IDDRCs

- IDDRCs
- Characterization and Etiology
- Clinical Trials
- Model System Development
- Target Identification
- Target Validation/Preclinical Trials
Vulnerable Groups

- Environmental Risk
- Biological Risk
- Intellectual Disability
- Autism Spectrum Disorder

Directions
- Specificity
- Overlap
- Translational Research Cycle
The Translational Research Cycle

- Characterization and Etiology
- Model System Development
- Clinical Trials
- Target Identification
- Target Validation/Preclinical Trials
- IDDRCs

The cycle is iterative, allowing for feedback and refinement.
The Translational Research Cycle

**Characterization and Etiology**

**IDDRCs**

**Highlights**
- Baylor
- Boston
- CHOP
- CNMS
- KKI
- UC Davis
- UCLA
- UW

**Genetic Etiology**
- Fragile X syndrome (Centers of Excellence)
- Rett syndrome (MECP2)
- Duchenne muscular dystrophy
- 22Q deletion syndrome
- Urea Cycle Disease Consortium
- X-Linked adrenoleukodystrophy
- CHD8 mutations
- CNTNAP2 mutations
The Translational Research Cycle

**Characterization and Etiology**

**Etiology**

**Genetic Screening**
- Prenatal screening
  - Tay-Sachs disease
  - Fetal trisomy detection and other chromosomal abnormalities
- Newborn screening
  - Premutation carriers (Fragile X)
  - Lysosomal storage diseases
  - Arginase deficiency

**Highlights**
- Einstein
- UCLA
- UW
The Translational Research Cycle

**Characterization and Etiology**

**Etiology**
- Pre- and Post-natal toxins
- Lead
- Alcohol (FASD)

**Highlights**
- Boston
- UW

**IDDRCs**
The Translational Research Cycle

**Characterization and Etiology**

**Highlights**
- Boston
- UNC
- UW
- WUSTL

**Biological Risk**
- Preterm birth
- ASD (genetic risk – siblings)
The Translational Research Cycle

**Highlights**
- Boston
- Kansas
- UCLA
- UNC
- UW
- WUSTL

**Characterization and Etiology**

**Environmental Risk**
- Adverse environments
- Cumulative risk

**Gene-Environment Interactions**
The Translational Research Cycle

**Highlights**
- Kansas
- UC Davis
- Vanderbilt
- WUSTL

**Characterization and Etiology**

**Clinical Trials**

**IDDRCs**

**Etiologic Specificity (Longitudinal Studies)**

**Behavioral Phenotype**

**Developmental Resources**
- Cognition
- Language
- Motor
- Social-emotional
- Sensory-perceptual

**Organizational Processes**
- Executive function
- Metacognition
- Social cognition
- Motivation
- Emotion regulation

**Social and Cognitive Competence**

**Measurement (Human Studies)**
- Language
- Imitation
- Social orienting
- Social responsiveness

**Social and Cognitive Competence**
The Translational Research Cycle

- Characterization and Etiology
- Clinical Trials
- Target Validation/Preclinical Trials
- Target Identification
- Model System Development

IDDRCs
Model Systems

- Fragile X syndrome (mouse, rat, fly)
- MECP2 mouse – replicates many features in humans
- Canavan disease (mouse)
- Epilepsy in immature rodents including West syndrome
- Neural tube defects (mouse)
- ASD – CNTNAP2 (mouse)
- Down syndrome – mouse models, homologue with Trisomy 21
- Neonatal hypoxia (rodents, piglets)
- Arginase deficiency (mouse)
- Neonatal brain injury (non-human primates, rodents)
- ASD and maternal antibodies (mouse)

Behavioral Assays –
- 3-chambered social approach test (ASD)
  - CHD8
  - MECP2
  - FMR1
  - Maternal antibodies

Highlights

- Baylor
- CNMS
- Einstein
- KKI
- UC Davis
- UCLA
- UNC
Target Identification

Decreases and increases in MECP2
Intracellular pathways to promote regrowth of injured CNS axons
Nature of brain injury associated with preterm birth
Fetal inflammatory response (preterm birth)
Genetic imprinting for Prader Willi and Angelman syndromes
Niemann-Pick type C – over-synthesis of gangliosides
X-Linked adrenoleukodystrophy – long chain fatty acids
Down syndrome – signaling pathway cerebellum
Neural generators of epileptic activity
Maternal anti-brain autoantibodies (ASD)
Down syndrome, Fragile X syndrome, Rett syndrome: embryonic stem cells
Neurogenesis subventricular zone (congenital heart disease)

Research Cycle

Highlights

- Baylor
- Boston
- CNMS
- Einstein
- KKI
- UC Davis
- UCLA
- UNC
- Wisconsin
The Translational Research Cycle

Preclinical
- Reverse symptoms in mouse model of MECP2 duplication syndrome
- Deep brain stimulation of fornix - Rett syndrome mouse model
- Niemann-Pick type C – inhibitor ganglioside synthesis
- GABA_A and early life seizures
- Cortical injury reorganization through retraining (motor learning)
- Neonatal brain injury – Epidermal growth factor
- Down syndrome – agonist to Sonic Hedgehog growth factor
- Neural tube defects – Iron and folate supplementation
- Unsilenced paternal UBE3A allele – Angelman syndrome (mouse)
- Preterm birth – erythropoietin (Epo) (rodents, non-human primates)

Highlights
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- Einstein
- Kansas
- KKI
- UNC
- UW

Target Validation/Preclinical Trials

IDDRCs
The Translational Research Cycle

**Clinical Trials: Biological**
- Nitrous oxide supplementation – urea cycle disorders
- Fetal surgery for Spina Bifida (myelomeningocele in utero repair)
- X-Linked adrenoleukodystrophy – Lorenzo’s oil
- Niemann-Pick type C – drugs to inhibit ganglioside synthesis (in process)
- Preterm birth and hypoxic-ischemic encephalopathy (Epo)

**Highlights**
- Baylor
- CHOP
- CNMS
- Einstein
- KKI
- UW

**IDDRCs**

**Clinical Trials**
The Translational Research Cycle

- Characterization and Etiology
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IDDRCs
The Translational Research Cycle
(Human Studies)

- Characterization and Etiology
- Model System Development
- Target Identification
- Clinical Trials
- Target Validation/Preclinical Trials
- Efficacy and Effectiveness Trials
- Focused and Comprehensive
- Single Subject Designs
  - Small-scale trials

- Observational Studies (Interactions)
  - Parent-Child Interactions
    - Discourse framework
    - Instructional partnership
    - Socioemotional connectedness

- IDDRCs
The Translational Research Cycle (Human Studies)

- Characterization and Etiology
- Target Identification
- Target Validation/Preclinical Trials
- Clinical Trials
- Model System Development
- IDDRCs

Linguistic input for environmentally at-risk children
- Kansas

Observational Studies (Interactions)

Maternal responsivity, contingencies, elaboration
- Kansas, Vanderbilt, Wisconsin, UCLA

Discourse Framework
- Instructional Partnership
- Socioemotional connectedness

Efficacy and Effectiveness Trials
- Focused and Comprehensive

Single Subject Designs
- Small-scale trials
The Translational Research Cycle (Human Studies)

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- Vanderbilt
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**Clinical Trials**
- **Intellectual disability**: Language interactions; prelinguistic and minimally verbal children
- **ASD**: (Early Start Denver Model – Toddlers)
- **Environmental risk**: Abecedarian project
- **Biological risk**: Preterm birth (IHDP)
The Translational Research Cycle (Human Studies)

Highlights
- CNMS
- UC Davis
- UNC
- UW
- WUSTL

Clinical Trials

IDDRCs

Biomarkers (Influence or predict clinical outcome)
- Toddlers (event related potential, spectral power)
- Presymptomatic (hyper-expansion cortical surface)
- Functional MRI; resting state functional connectivity – individual brain maturity
- Neuroimaging – Urea Cycle Disorder
National Network:
Research, Interdisciplinary Training, Clinical Services, Outreach, and Advocacy

- IDDRCs (1 of 14)
- UCEDDs (1 of 67)
- LENDs (1 of 52)

American Samoa
Guam
Puerto Rico
US Virgin Islands