IDDRC FOCUS AREAS AND THEMES

MISSION OF BCH IDDRC:

IDDRCs' funding comes from the Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD), our nation's first and foremost sustained effort to prevent and treat disabilities through biomedical and behavioral research. IDDRCs also contribute to the development and implementation of evidence-based practices by evaluating the effectiveness of biological, biochemical, and behavioral interventions; developing assistive technologies; and advancing prenatal diagnosis and newborn screening.

Reflecting the capacities of our unique research community, IDDRC Boston focuses its efforts in the areas of Genetics, Genomics and Neuroscience (basic and clinical/translational).

FOUR MAJOR THEMES OF RESEARCH CONDUCTED BY BCH IDDRC INVESTIGATORS:

I. Discovery of **genetic and non-genetic causes** of IDD.

II. Determination of the **cellular bases** of IDDs.

III. Identification of **translational phenotypes in animal models** of IDD to validate therapeutics.

IV. Accelerated **translation** of research discoveries into new prevention and treatment strategies for IDDs

FOCUS AREAS FOR ALL IDDRCS (DEFINED BY NICHD)

Applications must include at least one specific Research Project that has not been previously funded and addresses one or more of the focus themes identified as an area of research need. These are recognized as potentially exploratory, discovery-based, and/or high-risk projects, with the goal of yielding interpretable results that will either prove or disprove the proposed hypothesis.

Each Research Project must utilize at least two cores of the IDDRC, which may include the Administrative Core and/or the Clinical Translational Core. Primary funding must be through this P50 mechanism, but other sources of funding are allowed (federal grant, philanthropic, or foundational support). The project can address a broad array of intellectual disorders, including new, recently characterized, or under-researched areas such as comorbid mental health conditions in IDD. The focus areas are as follows, in no order of priority:

Comprehensive –omics Approaches

Comprehensive -omics approaches (e.g., genomic, transcriptomic, epigenomic, proteomic, metabolomic) that will markedly increase our understanding of IDD conditions to improve diagnosis, management, and potentially, treatment. Examples include, but are not limited to:

- Whole exome or whole genome sequencing of a well-defined cohort of subjects with IDD to identify genetic or genomic variants likely to cause the phenotype;

- Methylation, chromatin immunoprecipitation (ChIP), histone modification, or other epigenetic studies on individuals with a shared or related IDD diagnosis but variable manifestations (such as range of cognitive or behavioral function) to identify potential epigenetic contributors;
- Tandem mass spectrometry on biological samples such as saliva, blood or urine from a group of individuals with metabolic or other disorders associated with intellectual disability that might define distinctive biomarkers or metabolic signatures that would allow monitoring of outcomes or response to treatment;
- Single-cell transcriptomics on samples of differentiated human induced pluripotential stem cells (iPSC), brain organoids, or central nervous system tissue.

Development of Biomarkers or Assessment Measures in More than one IDD Condition

Development of a biomarker, assessment measure, or clinical intervention for more than one IDD condition or a group of related IDD conditions that share a common feature or metabolic or molecular pathway. Examples include, but are not limited to:

- Use of a human iPSC or brain organoid model to develop a biomarker or measure for a group of related conditions that demonstrates sensitivity to biologically-relevant perturbations to the system;
- Development of an assessment paradigm for an allelic series in an animal model for an IDD condition that exhibits a range of phenotypes;
- Development of an electrophysiological paradigm for two or more IDD conditions that share a common metabolic or molecular pathway;
- Creation of a clinical trial for a plausible target in two or more IDD conditions that reflects a shared etiology or molecular pathway.

Outcome Measures or Biomarkers for Interventions or Treatments

Development of preclinical or clinical outcome measures or biomarkers for the cognitive and/or behavioral phenotypes of IDD that have the potential to demonstrate a change in response to intervention or treatment. Examples include, but are not limited to:

- Development of a measure or biomarker for an animal model (e.g., mouse, rat, nonhuman primate) of an IDD disorder that reliably detects changes in cognitive function or behavioral response to a drug treatment;
- Development of a measure of cognitive or behavioral function (e.g., depression, psychotic ideation) in individuals with an IDD condition that is sensitive to an intervention;
- Development of a measure or biomarker that can be applied to more than one IDD conditions that share a common feature or metabolic or molecular pathway;
- Demonstration of changes in an existing measure or biomarker in individuals with an IDD condition in response to therapy.

Multi-modal Treatment Approaches

Development of bi- or multi-modal treatment approaches for a single IDD condition or a group of IDD conditions or spectrum disorders to demonstrate combinatorial effects to ameliorate a cognitive or behavioral symptom(s)

of the condition(s). The interventions may or may not be disease-specific, and the potential to broaden to multiple IDD disorders is encouraged. A medication can be repurposed from its original indication, but any clinical trial must adhere to NIH Clinical Trial guidelines (https://grants.nih.gov/policy/clinical-trials.htm), with defined milestones and go/no-go decision points. Examples include, but are not limited to:

- Use of a drug and a training paradigm in an animal model of an IDD to demonstrate improvement in a cognitive or behavioral measure;
- Use of a medication and behavioral treatment in combination for individuals with an IDD condition to demonstrate improved or synergistic efficacy;
- Use of one well-established intervention plus 1-2 medications to improve general symptoms of a mood disorder in individuals with different IDD conditions who share that mood disorder.

Preventing and Mitigating the Impact of Exposures that Can Cause IDD

Exposures of many types – medications, substances of abuse, infectious agents, environmental exposures, toxins – increase the risk of developing IDD. Therefore, therapeutic agents that can prevent or mitigate the risk of IDD following such exposures have the potential for broad clinical and public health impact. Exposures of interest may occur in the pre-conceptional, prenatal, postnatal or childhood period, and may involve the broader family or community. Examples include, but are not limited to:

- A project that develops a therapy or treatment for an animal model subjected to an exposure associated with an IDD-related cognitive or behavioral phenotype;
- A project that proposes an intervention to reduce the risk of developing an IDD due to preterm birth;
- A project looking at factors that may mitigate the impact of a prenatal exposure, such as alcohol, opioid or other medication, other substance of abuse, cytomegalovirus, Zika virus, etc. on a child's risk of IDD;
- Studies of a therapeutic intervention that may mitigate the impact of an environmental toxin (such as lead) that can lead to IDD.

Interventions and Management of Co-morbid Mental Health Conditions

Individuals with IDD experience behavioral symptoms and mental health conditions at considerably higher rates than the general population, including behavioral symptoms such as depression, aggression, or suicidal ideation or mental health conditions such as attention deficit hyperactivity disorder (ADHD), bipolar disorder, or psychotic disorders. These can be extremely challenging to manage in individuals with IDD due to the language, cognitive, and sensory impairments that often impede traditional strategies for evaluation and treatment. Many children and adults with IDD are diagnosed with behavioral or mental health conditions in the absence of assessment tools appropriate to IDD populations, and psychotropic medications are often administered to individuals with IDD, without an adequate understanding of their potential interactions and associated safety risks. Studies are encouraged that include individuals with IDD who are on multiple psychotropic medications in the study design. Priority will be given to novel interventions that go beyond traditional behavioral management of symptoms. Examples include, but are not limited to:

- Development of new tools or adaptation of existing tools that can be used in the management of behavioral symptoms or mental health conditions that identify and account for level of cognitive functioning in individuals with IDD;

- Studies of the safety and efficacy of commonly-used psychotropic medications in treating specific behavioral symptoms or mental health conditions in individuals with IDD;
- Studies to delineate variability in pharmacokinetics and pharmacodynamics of psychotropic medications in individuals with IDD;
- Studies that use pharmacogenomic strategies to select the safest and most efficacious psychotropic medications for use in individuals with IDD, which can then be clinically validated.

Innovative Technologies to Improve Assessments, Interventions, and Outcomes for Those with IDD

There has been an explosion of new technologies aimed at assessing and improving health, including wearable devices, communication aids, robotics and e-textiles. There have also been enormous advances in technologies that were not created for health-related purposes, but that have potential applicability to health assessments and interventions, including mobile device applications ("apps") and social media platforms. Most of these technologies were originally developed for use in adults, particularly those with typical development, so there is a need for valid and reliable technological tools and adaptive devices for those with IDD. Examples include, but are not limited to:

- Development of validated eye tracking technologies to identify and monitor social gaze preferences in children with autism receiving interventions targeting their social interactions;
- Use of actimetry sensors to identify and monitor sleep behaviors or activity levels to measure biological indicators and response to interventions;
- Development of devices that monitor physiologic parameters (such as heart rate monitors, multi-channel EEGs, or instruments that measure metabolite levels) for digital phenotyping or to serve as a proxy measure for other outcomes of interest, such as anxiety;
- Validation of apps, devices, and social media platforms to aid communication in individuals with IDD and language impairments;
- Application of mobile technologies to deliver video- or computer-based interventions to individuals unable to travel to academic centers to participate in research or clinical programs.

For questions or more information please contact:
Sylvia Lewinstein, Program Administrative Manager II
Intellectual and Developmental Disabilities Research Center
Dept. of Neurology, Boston Children's Hospital

sylvia.lewinstein@childrens.harvard.edu
www.iddrc.org