Down Syndrome Research:
The Intersection of Basic Science and Clinical Cohort Development

November 9-10, 2020

NIH-Sponsored Virtual Meeting[1]

EXECUTIVE SUMMARY

On November 9-10, 2020, the National Institutes of Health (NIH) in Bethesda, MD, sponsored a virtual workshop of the INCLUDE Project (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) titled "Down Syndrome Research: The Intersection of Basic Science and Clinical Cohort Development." Representatives from NIH, basic and clinical research fields,

Keynote Presentations : Perspectives from Research Study Participants

Day 1 of the meeting included keynote presentations by young people with DS and their families who have participated in clinical studies of DS. The presenters offered their personal views on the importance of engaging with participants throughout the course of the clinical trial, making the experience personal and relevant, and sharing the outcomes of the study. In addition, they said their research experience gave them a familiarity with hospitals and health providers, which made going to see the doctor a more positive experience. They asked that investigators try to schedule invasive research procedures such as blood draws to coincide with the participants' routine health care visits. The advocates emphasized the need to keep study participants informed about research updates using social media and understandable language and educate and engage potential candidates about clinical trials. They suggested that more information about the transition from adolescence to young adulthood is needed.

Day 1 Reports from Working Groups and Breakout Sessions

Presentations on co-morbidities associated with DS followed the keynote presentations, with discussions on neurodevelopment, behavior, cardiovascular disease and pulmonary hypertension, and respiratory and airway conditions. Additional presentations were given on cancer, autoimmunity and infections, endocrine, metabolic, and skeletal conditions, and aging and Alzheimer's disease (AD). The meeting then divided into Breakout Groups 1 (Development and Behavior), 2 (Heart and Lung), 3 (Cancer and Immunity), and 4 (Aging and Metabolic Conditions). The breakout groups identified some common themes, including the need for longitudinal cohort studies with well-validated endpoints, better animal and cellular models for preclinical data, more cohort diversity, integration of adult and pediatric cohorts into a single cohort across the lifespan, collection of "samples of convenience" from routine surgical procedures, and better harmonization and linkage of databases. On the basic science side, the breakout groups discussed the need to bring together information on phenotypes of various mouse models, provide more funding opportunities for model development, and develop induced stem cells to generate lines from people with DS. It was announced during Day 1 of the meeting that whole genome sequencing data on 2,600 people with DS would soon be available to be shared with the community.

Day 2 Session on Basic Science: Model Systems and Tools to Advance Down Syndrome Basic and Preclinical Science

This session focused on the current state of DS mouse models. An overarching issue was the importance of knowing the background of the mouse model used in research studies because many factors can affect the mouse phenotype, such as the strain of the mouse and how the model was derived. One promising model is the TcMAC21 mouse, which has an artificial chromosome containing the long arm of human chromosome 21, retains 93% of the human chromosome protein coding genes, and is not mosaic. Work has also begun to put the human chromosome 21 in rats, which tolerate the human centromere better than mice and, unlike mice, are rarely mosaic. Research using human induced pluripotent stem cells (iPSCs) is moving forward. Investigators can now use patient-derived iPSCs to study conditions common in people with DS, such as congenital heart defects, intellectual disability, and AD. More researchers are now using three-dimensional cell cultures that allow cells to self-organize into organoids. This method supports greater numbers of cell types and cell interactions than two-dimensional cell cultures. Another presentation described research generating neuronal cell lines containing the presenilin mutation from patients with familial AD to use in three-dimensional cultures. This presentation also described studies of the role of extracellular vesicles in AD pathogenesis.

Day 2 Session on Cohort Development: INCLUDE Data Coordinating Center and Existing and Future Cohorts

NIH has funded multiple projects in support of development of DS cohort studies. One such effort is to involve creation of a data coordinating center (DCC) and a data portal to standardize, harmonize, and aggregate DS data into a virtual biorepository, with a goal of providing data access and analysis tools for transformative DS research. The findings of a survey of 57 existing cohorts and databases related to DS research will serve as a starting point for the DCC. Another presentation described a variety of options for linking data, including Global

Unique Identifiers (GUIDs), PCORnet, Datavant, and a federated model that is being used in the eDS