

Innovating Therapies for Down Syndrome: An International Virtual Conference of the T21 Research Society

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Keywords

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Abstract

Research focused on Down syndrome continued to gain momentum in the last several years and is advancing our understanding of how trisomy 21 (T21) modifies molecular and cellular processes. The Trisomy 21 Research Society (T21RS) is the premier scientific organization for researchers and clinicians studying Down syndrome. During the COVID pandemic, T21RS held its first virtual conference program, sponsored by the University of California at Irvine, on June 8–10, 2021 and brought together 342 scientists, families, and in-

dustry representatives from over 25 countries to share the latest discoveries on underlying cellular and molecular mechanisms of T21, cognitive and behavioral changes, and comorbidities associated with Down syndrome, including Alzheimer's disease and Regression Disorder. Presentations of 91 cutting-edge abstracts reflecting neuroscience, neurology, model systems, psychology, biomarkers, and molecular and pharmacological therapeutic approaches demonstrate the compelling interest and continuing advancement toward innovating biomarkers and therapies aimed at ameliorating health conditions associated with T21.

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Introduction

Down syndrome (DS), or trisomy 21 (T21), is the most common genetic cause of intellectual disability [Hendrix et al., 2021]. The prevalence of DS in the United States is approximately 250,000 individuals [Presson et al., 2013], with estimates between 1 in 1,000 to 1 in 1,100 live births. Improved medical care and lifestyle enrichment have significantly improved the quality of life and expanded the life expectancy of individuals with DS, from 12 years of age in 1949 to over 60 years of age currently [Penrose, 1949; de Graaf et al., 2017]. The vision for the T21 Research Society (T21RS; <https://www.t21rs.org/>) is to promote basic and applied research on DS, stimulate translational research, and apply new scientific knowledge to develop innovative therapies that improve the quality of life for individuals with DS. To achieve this mission, the T21RS has the following goals: (1) to facilitate interactions between researchers studying DS using our website, scientific meetings, publications in journals, and the 2-yearly T21RS International Conference; (2) to establish standard protocols both for basic research (animal model studies, stem cells studies) and translational research (biomarkers, clinical trials, cognitive assessment paradigms, etc.); (3) to support the education and training of

young researchers interested in DS in all stages of their careers, by providing training programs and grants to young scientists; (4) to explain (recent) findings in DS studies to the general public and to inform legislators and other policymakers about new scientific knowledge and recent developments and their implications for public policy and society; and (5) to promote the interaction between scientists and patient associations/foundations.

In implementing these 5 goals, T21RS holds an international conference to innovate novel therapies to improve health and life expectancy for all individuals with DS. The 4th International Conference was planned to be held in Long Beach, California in 2021, but was postponed due to the COVID-19 pandemic. In its place, we quickly assembled a smaller virtual program held on June 8–10, 2021 that was attended by 324 people from 25 different countries (see Fig. 1). Our program included a data blitz session for junior investigators, and we received 54 abstracts and were able to have 30 investigators give a pre-taped 2-min talk. These young investigators represent the next generation of DS researchers and it is critical to encourage more people to join the field and promote collaboration with current DS researchers to increase progress in DS research. We anticipate that the 2022 meeting will attract over 300 attendees with a similar demograph-

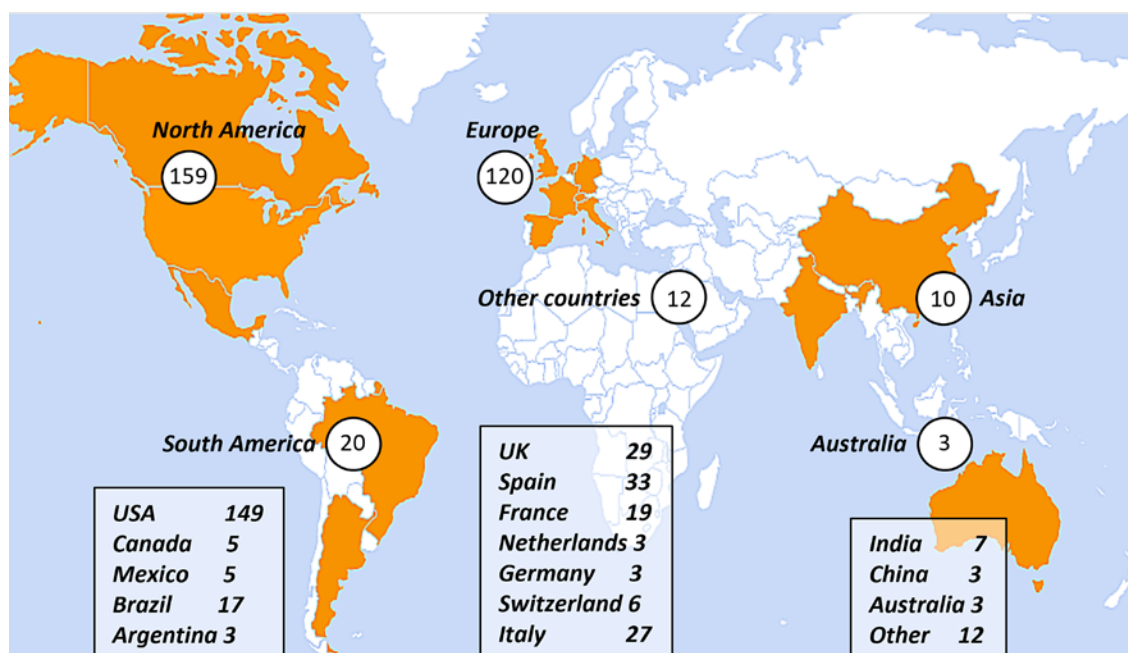


Fig. 1. Distribution of attendees for the virtual T21RS conference in 2021 by country highlighted (in orange). Note that a proportion of attendees represent countries with a low income designation. T21RS also hosted many junior investigators from these regions thanks to specific financial support from sponsors.

ic distribution. By building on the success of the last three T21RS meetings and our interim virtual meeting using a hybrid format, we aim to engage new researchers to the field of DS and promote collaboration with current DS researchers in the 4th T21RS International Conference to be held on June 8–12, 2022 in Long Beach, CA. This conference will focus on building upon recent innovative research, current technological advances, and rigorous research on the varied impacts of DS. At the 2022 T21RS meeting, we anticipate receiving many abstracts from junior researchers, of whom a large percentage will request financial aid to attend the meeting.

Biomarkers and Neuropathology in DS

Increased lifespan for individuals with DS in the last 4 decades has elevated the need to address Alzheimer's disease (AD), which affects up to 80% of individuals with DS, often at very early onset (by age 40) [Wiseman et al., 2015]. Identifying biomarkers of AD progression in DS can provide valuable insights into pathogenesis, can suggest targets for disease-modifying treatments, and provide prognostic indicators for novel therapies in clinical trials. T21RS hosted several virtual lectures to discuss the latest advances in magnetic resonance imaging (MRI), positron emission tomography (PET) blood and cerebrospinal fluid (CSF) biomarkers, to highlight how DS alters cellular transport mechanisms and to explore the latest evidence in DS neuropathology.

Translational Biomarkers of AD in DS

Significant progress has been recently made in evaluating novel biomarkers of AD in DS. Benjamin Handen (USA) gave a plenary lecture detailing the Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS), which is a multi-center, longitudinal study of AD biomarkers in adults with DS [Handen et al., 2020]. The ABC-DS has over 400 participants with DS, along with a group of sibling controls, involved in up to 3 cycles of data collection. Measured biomarkers include an extensive battery of neuropsychological assessments, MRI scans, PET scans of beta-amyloid and tau, FDG-PET scans, metabolomics, and proteomics; CSF; and genetics. Dr. Handen argued that tau PET radioligand uptake was more predictive of episodic memory decline in participants with DS when they had amyloid-beta accumulation measured with a similar PET imaging approach. Even though amyloid accumulation happens earlier during the pathogenesis of AD, tau was also associated with in-

creased amyloid-beta accumulation in individuals with DS [Petersen et al., 2021]. Dr. Handen's current research will be extended well into 2025. It will include the following projects: (1) a focus on biomarkers of DS-AD progression, (2) expanding upon the AT(N) national, NIA/AA neuropathology criteria, (3) determining if select non-genetic factors modify AD progression, and (4) examination of genetic factors that modify DS-AD risk. Collectively, the ABC-DS consortium seeks to harmonize all findings to develop precision medicine-ready biomarkers that can be used in AD in DS clinical trials.

Cellular Endolysosome Dysfunction in DS

Modifications of the endolysosomal compartment are found in neuronal and peripheral cells of individuals with DS or with AD [Colacurcio et al., 2018]. Marie-Claude Potier (France) gave a plenary lecture about her recent studies of endolysosomal morphology in DS and AD and described some of the molecular causes of such alterations in DS [Botte and Potier, 2020]. The study involved super-resolution microscopies, including cryoelectron microscopy with immunofluorescence techniques to study fibroblasts, iPSC-derived neurons, lymphocytes, and lymphoblastoid cell models with diploid and T21 genetic backgrounds. Additionally, RNAseq was done to characterize the gene expression profile from fibroblasts. T21 cells exhibited enlarged positive early endosomal protein 1 (EEA1) puncta. RNAseq analyses revealed 1,084 deregulated genes, of which 44 belonged to the endosomal pathway, 28 genes were associated with the cargo-sorting route towards the degradation pathway. Potier's results suggest the occurrence of a traffic jam in the endolysosomal compartment with an increased number of endosomes, cargo sorting dysfunction along the endolysosomal pathway and decreased degradation in the lysosomal compartment. Such impairments may be related to phosphoinositide signaling dysfunction [Botte et al., 2020]. Potier also showed that in AD familial cases, APP microduplication is sufficient to modify the endosomes of cortical neurons in postmortem DS brain samples. Potier also investigated endosome pathology in neurons from the locus coeruleus, a noradrenergic nucleus that degenerates early in the continuum of AD. Endosomal EEA1-positive puncta from noradrenergic neurons were larger in AD cases, while in DS they remained unchanged.

Postmortem Neuropathology Biomarkers in DS

Most individuals with DS develop AD neuropathology by age 40 [Snyder et al., 2020]. The examination of postmortem brain tissue leads to an accurate diagnosis of

brain pathology, including the pathology that occurs with age or AD in individuals with DS. Neuropathological studies can also point to new biomarkers that have yet to be explored in clinical studies and reveal as of yet unknown biological mechanisms. Ann-Charlotte Granholm (USA) chaired the first symposium session, which was focused on molecular and cellular pathologies observed in brain tissue from individuals with DS, AD, and age-matched controls. Significant findings regarding novel biomarkers and gene profiling were revealed.

Tau Profiling in Demented and Non-Demented Individuals with DS

A primary question in the research field is when, during AD disease progression, does tau neuropathology occur. Elliot Mufson (USA) explored the molecular signatures in tau-bearing neurons by studying several pathogenic post-translational modifications of the tau protein and by gene profiling of single cells using laser capture microdissection techniques. Mufson and his collaborators discovered that individuals with DS-AD exhibited more neurofibrillary tangles with advanced pathological tau biomarkers than those without dementia, suggesting that progression of tangle pathology is an important biomarker for dementia in DS [Perez et al., 2019]. Further, gene signatures of individual neurons in the frontal cortex with tau pathology differed between individuals with DS versus DS-AD. From a proteomics perspective, the most significant differences were in synaptic and post-synaptic membrane pathways and neurotransmitter receptor activity networks. These single-cell assays suggest specific networks that can be further validated and may lay the groundwork for the further development of novel pharmacological targets that can combat the onset and progression of dementia in those with DS and AD.

Inflammation and Iron-Homeostasis in DS

Ruma Raha-Chowdhury (UK) next presented research focused on Hepcidin, a protein that regulates iron flux [Raha et al., 2021]. This type of iron regulation is favored during inflammation, and high levels of the inflammatory cytokine interleukin (IL)-6 can promote Hepcidin expression leading to an abnormal iron accumulation in the brain [Wessling-Resnick, 2010]. Using immunohistochemistry on postmortem brain tissue as well as immunoassays on CSF and blood specimens, Dr. Raha-Chowdhury discovered that individuals with DS had higher accumulations of Hepcidin in brain parenchyma than brain tissue samples from persons without DS. Raha-Chowdhury reported significant elevations in both

Hepcidin and IL-6 in blood samples from individuals with DS, suggesting that iron management may be systemically imbalanced in individuals with this condition. Raha-Chowdhury also provided evidence that Hepcidin in peripheral blood entered the CSF through the choroid plexus and localized to brain parenchyma within trans-migrating macrophage cells [Raha et al., 2022], therefore contributing to the elevated inflammatory state observed in postmortem brain samples from donors with DS.

Lewy Body Pathology in the DS Brain

Amyloid and tau are the most frequent protein-related brain pathologies investigated in DS-AD and AD. However, some evidence has associated Lewy body pathology with AD [Armstrong and Cairns, 2009] as well as with DS-AD [Raghavan et al., 1993]. Isabel Barroeta (Spain) and the Barcelona DS research team (IDIBAPS) studied whether Lewy body pathology was widespread in the brain of older patients with DS. Barroeta's investigations revealed that alpha-synuclein accumulated in over half of the postmortem DS brains investigated and often appeared in very young individuals as well, suggesting that this finding could represent an early biomarker for DS-related dementia. Using immunohistochemistry and high-resolution array tomography, Barroeta showed that abnormal alpha-synuclein accumulation could be observed in globular intracellular structures (Lewy bodies) and dystrophic neurites. Alpha-synuclein-rich Lewy bodies were particularly abundant in the amygdala in DS-AD and occurred more frequently than in sporadic AD cases.

Behavioral and Clinical Studies in DS

Individuals with DS have unique cognitive abilities that require innovative approaches to study in clinical and behavioral settings. Identifying neurological correlates in DS can provide valuable insights into mental health and prognostic indicators for the efficacy of novel therapies being tested in clinical trials. T21RS hosted several virtual lectures to discuss the latest collaborative COVID-19 initiative, new neurological studies that employ various methods such as EEG and multimodal MRI data, and to communicate the latest understandings of a regression disorder that affects some individuals with DS.

Trisomy 21 Research Society COVID-19 Initiative

The DS population has been disproportionately affected by Coronavirus 2019 (COVID-19) in terms of experiencing severe illness and death [Huls et al., 2020]. In ad-

dition to health effects, efforts to curb the spread of CoV-2 infection through social distancing may have significant detrimental effects on the daily lives of individuals with DS. The T21RS COVID-19 Initiative was launched as an international survey for clinicians or caregivers to systematically quantify and characterize individuals with DS that were infected with SARS-CoV-2, giving rise to COVID-19. This cross-sectional study collected data from different countries, and nearly 1,050 cases were enrolled between April and October 2020. Data were analyzed and compared with a UK survey (ISARIC4C0) of hospitalized COVID-19 patients with and without DS.

Stephanie Sherman (USA) gave a plenary lecture describing the initiative's investigations to characterize COVID-19 symptoms, rates of hospitalization and mortality, along with associated risk factors in people with DS [Huls et al., 2021]. Overall, presenting signs and symptoms of COVID-19 in people with DS were similar to those in the general population, the most frequent being fever, cough, and shortness of breath. Joint and muscle pain, vomiting, or nausea were less frequent, whereas altered consciousness and confusion were more frequent. Medical complications occurred among 60% of people with DS, as reported by clinicians. Complications included an increased frequency of viral and bacterial pneumonia and acute respiratory syndrome. Most importantly, mortality rates showed a rapid increase from age 40 for patients with DS compared with after age 65 for those without DS. Risk factors for hospitalization were similar to the general population (increasing age, male, diabetes, and obesity), with the addition of congenital heart defects. Risk factors for mortality were also similar to the general population and included increasing age, being male and having dementia. Even after accounting for known risk factors, individuals with DS were still 2.5 times more likely to die after being hospitalized due to COVID-19.

The initiative also conducted a study that focused on pediatric COVID-19 cases (<18 years of age) with DS, drawing data from the same international survey and using a US comparison group [Emes et al., 2021]. Overall, children with DS were at increased risk for more severe presentations of COVID-19. Hospitalized pediatric cases with DS ($n = 127$) had a higher frequency of presenting signs and symptoms than those without DS ($n = 224$), although the profile of presentation was similar. Medical complications were associated with a higher frequency of respiratory symptoms compared with controls. Older age, obesity, and epilepsy were risk factors for hospitalization, while age and thyroid disorders were significant risk factors for acute respiratory

distress syndrome. Mortality rates were low in all pediatric COVID-19 patients (with and without DS), in contrast to adults with DS.

These results emphasize the importance of vaccinating children and adults with DS as soon as they are eligible. Increased shielding/masking and monitoring for symptoms, especially among those with known risk factors, should be considered. The T21RS COVID-19 Initiative is continuing its work, with a focus on vaccine response and the psychological impact of the pandemic on individuals with DS.

Neural Correlates of Intellectual Disability

Adequate treatments for intellectual disability and AD-associated cognitive decline are urgent and unmet medical needs for many individuals with DS. Neural activity signals and detailed brain structure images, measured non-invasively by electroencephalogram (EEG) and MRI, respectively, are increasingly used to identify neural correlates of multiple issues associated with brain disorders and may provide suitable targets for improving cognitive difficulties in individuals with DS. In the second symposium session chaired by Dr. Victoria Puig (Spain), the investigators reported their recent findings regarding the neural substrates associated with intellectual disability and cognitive decline in mouse models of DS and adults with DS. In these studies, neuronal connections appear to be systemically altered in individuals with DS and mouse models of DS, with differences in neuronal communication, information processing, brain function, and behavior.

Prefrontal-Hippocampal Neural Dynamics as Predictors of Cognitive Impairment and Rescue in DS

The Ts65Dn mouse model of DS has impaired performance in tasks involving prefrontal cortical and hippocampal brain regions. When measuring neural activity in these two regions with intracerebral electroencephalograms (iEEG), neural network activity occurring in wave patterns with different frequencies can be detected and circuit connectivity quantified. Victoria Puig (Spain) studied iEEG patterns in the Ts65Dn mouse model of DS during rest, sleep, and memory performance. Her team discovered that trisomic mice showed increased theta and gamma oscillations in the prefrontal cortex and the hippocampus and abnormal circuit connectivity [Alemany-Gonzalez et al., 2020]. Memory performances correlated strongly with functional connectivity measures and were rescued by epigallocatechin-3-gallate, a flavonoid found

in green tea. Puig pointed out that iEEG and behavioral assessments can be combined to test new drug candidates to improve memory performance.

Electrocortical Correlates of Auditory Processing in DS

Mismatch negativity is an auditory-related neuronal event that occurs when a sequence of repetitive sounds is interrupted by an occasional “oddball” sound that differs in frequency or duration [de Souza and Biaggio, 2021]. The inferior frontal gyrus and superior temporal gyrus are the neural generators of the mismatch negativity. Fedal Saini (UK) investigated mismatch negativity in 53 adult individuals with DS and compared the results to each participant’s language ability to investigate possible associations. EEG was used to measure mismatch negativity-induced neuronal activation during an “auditory oddball” task, and a battery of verbal fluency and IQ tasks were utilized to measure verbal and non-verbal abilities. Saini discovered that adults with DS could discriminate tone deviations but have trouble with pitch deviations. There was no association between the neuronal activation due to mismatch negativity and language ability. However, having a high non-verbal IQ and a higher score in language ability was associated with higher chances of producing mismatch negativity.

Multimodal MRI and Cognitive Biomarkers for AD in DS

One of the earliest areas of the brain that develops pathological tau deposits in AD is the entorhinal cortex [McCann et al., 2021]. Since tau is associated with neuronal loss and dementia, Michael Yassa (USA) sought to determine if MRI methods might help predict the early transition to the cognitive dysfunction associated with AD. At least 775 MRI scans from non-DS with no cognitive impairments or at various stages of AD-related dementia were analyzed. Yassa discovered that an MRI-based measure of entorhinal cortical thickness was a superior predictive measure to other biomarkers such as those measured in CSF. Yassa then studied MRI scans from individuals with DS with normal baseline cognitive abilities or at various stages of AD-related dementia and observed similar findings in this population. Yassa described that entorhinal cortex thinning is a salient feature of the early transition to AD and is associated with elevated levels of a novel protein biomarker, called neurofilament light chain, that is measured in biofluids. Future studies will determine if these released neurofilaments spread neurotoxicity in the brain.

Down Syndrome Regression Disorder: Clinical Characteristics and Differential Diagnosis

Some adolescents and young adults with DS appear to show a sudden onset of cognitive deterioration characterized by acute cognitive decline, catatonia, insomnia, autistic features, loss of autonomy, loss of speech, and loss of previously acquired skills [Rosso et al., 2020]. This condition is now called Down Syndrome Regression Disorder (DSRD) or Regression and has an unknown etiology. While the disorder is recognized across the medical community, there remains debate on the terminology and criteria used to describe this condition, and several etiological hypotheses are proposed. In the third symposium session, which Jonathan Santoro (USA) chaired, clinical investigators explained what DSRD entails as clinical features and discussed the importance of seeking increased medical attention at these ages to improve diagnosis, care, and possibly treatment.

Are We Underestimating the Presence and Treatment of Mental Illness in People with DS?

The predisposing factors for developing mental illness in DS include increased risk of adverse experiences (such as changes in the home environment or school-related issues), poor self-concept, and low expectancies for success. However, little is known about the relationship between these conditions and DSRD. Maria Ortega (Spain) detailed the primary psychiatric disorders in DS and compared these disorders to DSRD. The factors driving DSRD may have biopsychosocial causes that are likely linked to biochemical or neurological abnormalities. A highlight of Ortega’s discussion was that primary management of the DSRD condition with psychotropic medications is effective in a subset of individuals and that treatment may occur simultaneously with other therapies, such as immune treatment, where some physicians have employed steroidal drugs.

DSRD: Multi-Center Data on Clinical Phenotypes

Stephanie Santoro (USA) described clinical experiences in 35 cases of DSRD from 8 academic institutions that were pharmacologically treated. She presented a multi-case study and found no concurrent medical conditions that were common to all cases. Santoro presented a checklist of phenotypic symptoms that could be used in the identification of patients, although she acknowledged that each patient with DSRD could present differently, and symptoms may emerge at any time point. She further detailed that individuals suffering from DSRD experienced 4 times as many mental health concerns compared

to the general population of individuals with DS. Santoro detailed the main psychosocial changes associated with DSRD and her programmatic management plan's success factors, including 159 patient visits.

DSRD: Neuroimmunologic Phenomenon and Responses to Immunomodulatory Therapy

Jonathan D. Santoro (USA) reported on a cohort of 48 individuals with DSRD. Although DSRD has been reported in the literature for some time, work-ups and treatments for this condition have been highly heterogeneous and primarily focused on the disease being psychiatric in nature. In the analyzed cohort, 26% of individuals had abnormalities on electroencephalography, 21% had neuroimaging abnormalities, and 19% had abnormalities on lumbar puncture wherein CSF was noted to have multiple inflammatory biomarkers. In those with neurodiagnostic abnormalities, Santoro reported a 4 times higher responsiveness to immunotherapy such as intravenous immunoglobulin (IVIg), indicating that a neuroimmunologic or neuroinflammatory etiology may be present in a subset of individuals with DSRD [Cardinale et al., 2019]. Santoro pushed for the development of uniform diagnostic criteria, neurodiagnostic work-ups, and investigations into immunotherapy as a mechanism for treating DSRD.

Inflammation in DS

Characteristic features/biomarkers of innate immune system activation and inflammation are associated with DS across lifetime. Inflammation in peripheral organs or as blood cytokine signals may interact with and modify neuroinflammation in the central nervous system. These emergent understandings have led to the additional postulate that developing methods to dampen inflammation would be an effective therapeutic approach. Given the complexity of innate immune system biology with DS, T21RS hosted a special focus session to address the latest understanding of how inflammation manifests in individuals with DS. Speakers addressed children and adults with DS and also focused on systemic inflammation versus brain-specific neuroinflammation contexts.

Brain and Systemic Inflammation in Individuals with DS

Individuals with DS display chronic immune dysregulation and inflammation. Moreover, AD has been associated with the development of chronic neuroinflammation. The investigators in this fourth symposium, chaired

by Lisi Flores-Aguilar (Canada), discussed recent findings regarding brain inflammatory protein expression and microglial morphological changes across the Alzheimer's continuum in individuals with DS. Moreover, the speakers discussed peripheral immune dysregulation in children and adults with DS. Clinical trials targeting the immune dysregulation observed in DS were presented.

Neuroinflammation across the Lifespan of Individuals with DS

A primary interest in the field is understanding how brain inflammation in DS affects AD. Lisi Flores-Aguilar (Canada) conducted a comprehensive analysis of the brain inflammatory profile and microglial morphological changes across the lifespan of individuals with DS [Flores-Aguilar et al., 2020]. Flores-Aguilar found that before the appearance of AD neuropathology (amyloid-beta and tau accumulation), there was already an increase in brain inflammatory proteins and microglial reactivity in children and young adults with DS. Some inflammatory proteins were diminished after the development of full-blown AD pathology. Moreover, microglial cells were dystrophic in adults with DS. Flores Aguilar's investigations revealed that the brain inflammatory process in DS is highly dynamic across the lifespan of individuals with DS.

Systemic Inflammation in Children with DS

Children with DS are more susceptible to infections, and more research is needed to understand perinatal and early neonatal inflammatory responses in health and disease. Eleanor Molloy (Ireland) discussed that children with DS commonly display immune dysregulation, including differences in immune cell counts, antibody responses to immunizations, immune cell chemotaxis, and inflammatory protein dysregulation [Huggard et al., 2020]. Dr. Molloy reported an increase in inflammatory and anti-inflammatory proteins in the blood of children with DS. Moreover, this increase was more marked in children with DS that had recent cardiac surgery. Molloy observed that in vitro administration of melatonin lessened the levels of specific proteins associated with the inflammatory response [Huggard et al., 2021]. In the future, Dr. Molloy will study the impact of immune dysregulation and immunomodulation on neurodevelopmental and multi-organ outcomes in children with DS.

Interferon Hyperactivity in DS: Causes, Consequences, and Therapeutic Opportunities

Joaquin Espinosa (USA) and his team have proposed that DS could be understood in part as an Interferonopa-

thy [Sullivan et al., 2016]. Espinosa's team found that interferon signaling is hyperactivated in multiple cell types with trisomy 21 [Araya et al., 2019; Waugh et al., 2019]. Furthermore, they documented proteomics and metabolomic signatures indicative of chronic autoinflammation [Sullivan et al., 2017; Powers et al., 2019]. Espinosa's team is also investigating the use of immunotherapies to decrease interferon signaling in individuals with DS. These therapies have ameliorated alopecia and psoriasis in individuals with DS [Rachubinski et al., 2019; Pham et al., 2021]. Clinical trials testing attenuation of interferon signaling to treat autoimmune conditions in individuals with DS are ongoing.

Clinical Trials to Prevent AD in DS: State-of-the-Art Clinical Outcome Measures

Studies have shown that individuals with DS develop AD brain pathology by age 40 and that the majority will develop dementia by age 65 years. Since cognitive abilities can be highly variable for individuals with DS, sensitive measures of brain abilities must be set. In the fifth symposium session, which André Strydom (UK) chaired, investigators presented recent advances in new cognitive tests being developed as outcome measures in clinical trials.

CAMCOG-DS-II: A Clinical and Research Tool for Diagnosis and Neuropsychological Assessment in People with DS with Suspected Dementia

The CAMCOG-DS is a set of tests used to assess the level of cognitive ability of adults with DS. The CAMCOG-DS tests cognition in several areas, including remembering verbally or visually presented items, the person's orientation, focus (attention), and language, among others. These areas of cognition can be affected by dementia to varying degrees. The CAMCOG-DS battery test helps support the diagnosis of dementia and quantify the degree of cognitive change [Benejam et al., 2020]. Shahid Zaman (UK) and his research team developed an updated and improved version of the CAMCOG-DS-II, which will be tested to determine its performance compared with the older version [Fortea et al., 2020].

The H21/Life-DSR Cognitive Test Battery: Identification of a Trial Outcome Measure for Early Intervention in DS and AD

There is no consensus on what cognitive tests should be included in a neuropsychological test battery to use as

an endpoint in clinical trials of AD in DS. Andrew Aschenbrenner (USA) analyzed data from 5 longitudinal cohorts to identify specific cognitive domains that are most sensitive to rates of change in healthy adults with DS. A panel of experts was convened to agree on which particular measures to include in the final cognitive test battery [Aschenbrenner et al., 2021]. Criteria considered included ease of administration and scoring in a global clinical trial (i.e., the test must not be culturally specific). The final selected battery measures a variety of cognitive domains, including memory, attention, language, and executive function, and may have utility as an outcome measure in clinical trials.

Novel Endpoints in DS-AD: Using Goal Attainment Scaling to Measure Patient-Centered Outcomes

When choosing clinical trial outcome measures, it is difficult to choose the best measure to track meaningful changes in individuals with DS. Much of the challenge arises from their diverse capabilities and needs. One person's most highly desired goal could present deterioration from the baseline for someone else. One approach that may work well is to track how a given treatment could help individuals attain their goals. Kenneth Rockwood (Canada) shared results pertaining the Goal Attainment Scaling, which follows change from each individual's baseline [Knox et al., 2021]. In this way, varying degrees of success, or lack of success, can be described and tracked. Rockwood successfully assessed meaningful changes in each DS patient in the presented study with this tool.

Fostering a New Generation of Researchers

Nearly 16% of attendees were students and post-doctoral fellows representing the next generation of DS researchers. To fulfill the mission of T21RS to stimulate young members to carry out high-level research, the society awarded 2 competitive dissertation awards, 3 research blitz awards, and hosted interactive poster sessions online.

Dissertation Awards

T21RS recognized 2 young recently graduated doctorates' merit and high-level research quality with the Annette Karmiloff-Smith and Michael Harpold Thesis Awards. The Annette Karmiloff-Smith Dissertation Award was presented to Rosalyn Hithersay (UK), whose Ph.D. thesis was "*Exploring executive functioning and*

frontal cortical activity using functional near-infrared spectroscopy." Hithersay investigated the feasibility of using fNIRS to measure frontal cortical activity in adults with DS during executive function tasks, comparing age and cognitive decline [Hithersay et al., 2021]. Andrea Giacomini (Italy) received the Michael Harpold Dissertation Award for his Ph.D. thesis entitled "*Pharmacotherapies targeted to neurogenesis in order to rescue cognitive performance in Down syndrome.*" Giacomini analyzed the effects of neonatal treatment with several pharmacotherapies (ELND006, EGCG, 7,8-DHF) to improve cognition in the Ts65Dn mouse model of DS [Stagni et al., 2016, 2017; Giacomini et al., 2019].

Trainees "Blitz" Elevator Pitch and Poster Session

Thirty young T21RS investigators presented in a data blitz session to the conference attendees, and three were chosen for the excellent delivery of their findings. Nathanael Shing's (UK) pitch was entitled "*Investigation of hippocampal ripples and parvalbumin-positive interneurons in a segmental D. syndrome model, the Dp1Tyb mouse;*" Sarah Pape's (UK) pitch was entitled "*The association between physical activity and dementia-related symptoms in Down syndrome,*" and Javier Zorilla De San Martin's (France) pitch was entitled "*Excessive dendritic inhibition in the prefrontal cortex of Ts65Dn Mice – Persist throughout development into adulthood.*" All winners received a laptop to enhance their studies. The poster session included 18 unique entries that spanned a broad range of topics relevant to DS health. The unique virtual venue allowed all conference participants to view posters online during breaks or after the conference. The virtual forum allowed great flexibility and more time to evaluate all posters carefully.

Science and Society Program

The T21RS committee for Science & Society aims to approach science to people and promote access to research for individuals with DS. Maria Carmona-Iragui (Spain) and Anne-Sophie Rebillat (France) opened and closed the session, accompanied by Arianna and Florence, two young women with DS. They highlighted that by working together, people with DS and researchers are essential to conducting research projects to benefit individuals with DS. Carmona encouraged everyone to get the CoV-2 vaccine, especially individuals with DS who are more vulnerable and all caregivers who have close contact with those with DS. The program was accessible

to anyone who wanted to join and was shared online via the conference website and several social media channels.

The DS Community Informing Research

James Hendrix (USA), Chief Science Officer of the LuMind IDSC Foundation (USA), emphasized that there are increased numbers of research projects regarding DS and increased funding, especially from the NIH [Hendrix et al., 2021]. However, research activities need more participants (5 to 10 times more) in clinical trials investigating AD, especially adults with DS. Hendrix emphasized that successful recruitment strategies must start with community engagement. Hendrix introduced the Down Syndrome Community web portal (myDSC), a free, digital library of evidence-based resources and tools for parents of children with a wide range of disabilities. Evidence-based resources may be essential for community engagement as the field seeks methods to measure successful recruitment and engagement strategies to meet the pressing demands of future clinical trials. myDSC is hosted by LuMind IDSC and can be found online here: LuMind IDSC Foundation - Login (imodules.com).

Community-Engaged Research: Centering Self-Advocates

Priya Chandan (USA) spoke about how community engagement is used as a method of teaching and research to promote health equity, while also providing a benefit or service to the community. Community-engaged scholarship ensures that research is relevant to the community and involves the community in the research process. Chandan pointed out that it is important to partner with people with DS in research efforts, even when studies are focused on the perspective of caregivers [Santoro et al., 2022]. When guiding adolescents with DS who are transitioning to adult services and when caring for individuals with DS across the lifespan, Chandan stressed that we must prevent marginalization, which is more likely to happen when health professionals serve patients with conditions that they do not experience themselves, such as DS.

Research and the Voice of Caregivers: Results of Surveys and Focus Groups

Successful clinical trial recruitment starts with strong community engagement. Hampus Hillerstrom (USA), President and CEO of the LuMind Foundation (USA), presented several recent findings from surveys and focus groups: The LuMind caregiver survey on sleep apnea diagnosis and treatment had 724 participants (mean age 12;

0–67). Treatment was described as challenging because only 17% of participants with severe obstructive sleep apnea use therapeutic strategies, like continuous positive airway pressure (CPAP), more than 4 hours per night. Engagement techniques must therefore be improved. A caregiver survey on independence had 400 participants, 92% of the persons with DS aged 0–35, 80% of their caregivers aged 35–64 [White et al., 2022]. Independence concerns for the child were mainly sexual abuse, healthy eating, and living alone. Independence concern for the caregiver is essentially the question, “*What will happen after I am gone?*” A caregiver survey on topics of interest had 337 participants who all answered that the priority was research on AD, regardless of the individual’s age. This indicated more awareness in the community about neurodegenerative conditions affecting individuals with DS. The key non-medical topics of interest were independence and behavior. Focus groups on clinical trial recruitment with Eli Lilly, LuMind IDSC Foundation, and the National DS society (NDSS) had 52 participants. These focus groups revealed that individuals with DS and their caregivers need to understand expectations for clinical trial recruitment clearly. Furthermore, Lilly, LuMind IDSC, and NDSS compared the caregiver role between late-onset AD and DS-related AD caregivers. In the case of late-onset AD, being a caregiver was regarded as a new role, whereas in DS, caregiving and advocacy were seen as a life identity.

Longitudinal Data Outcomes on Adults with DS and Dementia Supported in Group Homes

Matthew Janicki (USA), co-chair of the US National Task Group on Intellectual Disabilities and Dementia Practices, reported on data collected over 10 years on individuals with DS and other intellectual disabilities diagnosed with dementia and living in 3 group homes ($N = 22$ residents, a third of them with DS) [Jokinen et al., 2018; Santos et al., 2018]. Data collected included resident function demographics, health, and other related information that provided insight into the impact of dementia long-term care in specialty group homes. The majority of early admitted adults were individuals with DS. The mean years for entry to death was 5.4 years. Adults with DS did survive longer, however, perhaps because they had been admitted earlier in the course of the disease. Residents with DS showed fewer comorbidities (heartburn, foot pain, and thyroid disorder) than residents with other intellectual disabilities. Behavioral symptoms of dementia were slightly different in people with DS and included less alertness to surroundings, tearfulness, and being nonco-

operative. Knowing about the probabilities of occurrence of co-conditions can help with medical management and planning home admissions. Janicki invited everyone to learn more at the National Task Group website (<https://www.the-ntg.org/wichita-project>).

Cultural Program, Entitled “Love”

Sujay Ghosh (India), the T21RS Indian Chapter, and other T21 members organized a powerful cultural program. The program’s theme was “Love” and was based on the concept and ideology of Tagore, the great Indian Nobel Laureate poet, composer, and philosopher. Three children with DS performed a traditional Indian dance with Tagore’s composed music and songs that describe different forms of love for nature. The performers were Nilanjana, Meghna, and Shreya. The rhythmic congo drums were played by Sayak, an 18-year-old who also has DS. All songs and music were chosen to promote a focus on nature to maintain people’s health. The program ended with a message of hope as we all strive to overcome the recent stressors of the pandemic crisis.

Finale

The T21RS virtual meeting was a great success and continued the legacy of sharing outstanding research worldwide with a focus on improving the quality of life for people with DS. As per the goals of our T21RS, the meeting platform allowed the exchange of information across the lifespan of people with DS, and spanned genetic, molecular, preclinical, and clinical research fields. We were able to actively engage junior investigators, families, self-advocates, and advocacy groups. Overall, as highlighted in this review of the proceedings, our T21RS meeting continues to grow and attract more investigators to the field.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors wrote relevant sections of the manuscript. Eric D. Hamlett and Lisi Flores-Aguilar compiled a majority of the manuscript. Benjamin Handen, Marie-Claude Potier, Ann-Charlotte Granholm, Stephanie Sherman, Victoria Puig, Jonathan D. Santoro, María Carmona-Iragui, André Strydom, and Anne-Sophie Rebillat made significant revisions, edits, and grammar contributions. Elizabeth Head and Jorge Busciglio wrote the introduction and finale and also made significant revisions, and editing contributions.

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