

Paving the Way for Therapy

2nd International Conference of the Trisomy 21 Research Society June 7-11, 2017 Feinberg Conference Center, Northwestern Memorial Hospital Chicago, IL USA

Founding Sponsors of T21RS













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2nd International Conference of the Trisomy 21 Research Society June 7-11, 2017 Feinberg Conference Center, Northwestern Memorial Hospital Chicago, IL USA

Conference Organizers

Roger Reeves, PhD Johns Hopkins University School of Medicine Mara Dierssen, MD, PhD CRG – Center for Genomic Regulation

Jean Delabar, PhD CNRS-ICM John O'Bryan, PhD University of Illinois Chicago

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Annette Karmiloff-Smith Thesis Award Program COMPETITION FOR OUTSTANDING PH.D. THESIS

Application Deadline: June 30, 2018

Prizes will be awarded for up to 2 outstanding doctoral dissertations. Each recipient will receive an honorarium of 1,000 Euros. The topic of the dissertation must be in the field of Down syndrome

Eligibility

Participation in the 2017 competition is limited to candidates who obtained the Ph.D. title during the period January 1, 2016-December 31, 2017. Applicants must be members of T21RS (www.t21rs.org/register).

Required Documentation

Documentation accompanying the application must be submitted exclusively in an email to education@T21RS.org in PDF format and must be written in English. The candidates must state their current title and provide full mailing address, email and telephone numbers.

Candidates must also include:

1. Dissertation Summary Page.

2. A short description of the dissertation research and its conclusions, written by the nominee. Format requirements: Up to 2 double-spaced pages with 12-point font, each page bearing the nominee's name and page number. Minimal appendices containing non-textual material, such as charts or tables, may be included in addition to the 2 pages.

3. Brief (3-page) curriculum vitae highlighting:

- a. education history,
- b. honors and publications.

4. Documentation from the Registrar of the awarding University attesting completion of all requirements for a Ph.D.

5. A letter of recommendation from the dissertation advisor. The dissertation advisor must be member of T21RS at the time of submission (www.t21rs.org/register). The letter should comment on:

- a. the originality and importance of the research,
- b. the potential for significant contribution to the field of Down syndrome research.

6. A letter of recommendation from another member of T21RS who must be member of T21RS at the time of submission (www.t21rs.org/register).

7. A copy of the full dissertation (PDF format).

Selection and Announcement of Awards

The Fellowships, Education and Training Committee will be responsible for the selection procedure and will identify the winners of the competition. Selection will be based on the originality and importance of the research, and the potential for the student to make an unusually significant contribution to the discipline. In assessing candidates, the Committee will also take into account their letters of reference and academic curriculum. The decision of the Committee shall be final, no correspondence relating thereto shall be allowed, and the decision shall not be subject to appeal. The Committee can assign a number of prizes lower than the number foreseen, or none if the theses were to be considered not particularly outstanding in any particular year. Authors of awarded dissertations will be notified by November 30, 2018. Registration will be waived for the next T21RS meeting following the award and the winners will be asked to present their main findings at that meeting.

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CONGRESS SPONSORING ORGANIZATIONS

Global Down Syndrome Foundation Denver, CO USA

Jerome Lejeune Foundation Paris, France

LuMind Research Down Syndrome Foundation Marlborough, MA USA

National Institutes of Health National Institute on Aging Nation Institute of Neurological Disorders and Stroke Bethesda, MD USA

> National Down Syndrome Society New York, NY USA

> > Alzheimer's Association Chicago, IL USA

Down Syndrome Association UK United Kingdom

Down Syndrome International United Kingdom

> ProBio Drug Germany













Learn about the new groundbreaking research at the Crnic Institute for Down Syndrome

Thursday, June 8th - 3:00PM

Understanding Down syndrome as an Interferonopathy: implications for the understanding of leukemia and other co-morbidities driven by trisomy 21.

Joaquin M. Espinosa, PhD Associate Director for Science Linda Crnic Institute for Down Syndrome

Saturday, June 10th - 5:45PM

T21RS Committee for Science & Society Panel Medical care for adults with Down syndrome – Lifting Barriers

Michelle Whitten, President & CEO Global Down Syndrome Foundation

Poster Sessions Speakers From Linda Crnic Institute for Down Syndrome

Donnie Evans, PhD, Research Associate Tristan McClure-Begley, Senior Research Assistant Rani Powers, PhD Angela Rachubinski, PhD, Instructor Keith Smith, Senior Research Assistant Kelly Sullivan, PhD, Instructor Kate Waugh, PhD, Instructor

GlobalDownSyndrome.org

Dedicated to significantly improving the lives of people with Down syndrome through RESEARCH, MEDICAL CARE, EDUCATION and ADVOCACY

JEROME LEJEUNE FOUNDATION



Professor Jérôme Lejeune (1926-1994)

Doctor and Researcher, discovered the *cause* of **Down syndrome** (Lejeune/Gautier/Turpin) in 1959.

The Jérôme Lejeune Foundation (public interest status in 1996) works for individuals affected by genetic intelligence disorders (Down syndrome, Williams-Beuren, Fragile X, "Cri du chat" and other unexplained intellectual disability). At the service of affected individuals and their families, the Jérôme Lejeune Foundation is driven by three objectives: Research, Care and Advocacy.

It implements and supports research programs to develop treatments under the supervision of the Scientific Board (**25 international experts in Fundamental, Translational and Clinical Research)** in France and abroad thanks to a **3,5 to 4 M€ private funds per year Research Funds allocation**. Among them, projects on protein to protein interactions, animal models -new Rat models- (Bettencourt-Schueller Foundation), genes located on Chromosome 21 (Dyrk1a and CBS), Clinical trials (Tesdad) and allocates Prizes (Young Searcher Awards and Sisley d'Ornano-J. Lejeune Postdoctoral Award). It recently focuses also its Research Strategy on cross pathologies (DS-Autism, -Alzheimer and -Oncology)

The Jérôme Lejeune Foundation is highly vigilant about Bioethical issues. In a context in which ever-accelerating scientific progress and ideological pressure pose fundamental questions for society, the Foundation provides its scientific expertise **together with its Ethical Values**.

www.fondationlejeune.org

JEROME LEJEUNE INSTITUTE "With them, all throughout life..."

Created in 1997 and funded mainly by the Jérôme Lejeune Foundation, the Jérôme Lejeune Institute is a clinical center for specialized medical and paramedical consultations located in Paris. With 34 Care professionals, 8400 patients in the cohort, 35 to 40 new patients per month, 10 Research Programs and Clinical Trials (Acthyf, Perseus, Respire21...) **the Institute** has three goals: **Care, Research, Training.**

The Institute is dedicated to patients with Down syndrome and other intellectual disabilities from genetic origin, and their families.

www.institutlejeune.org



The **CRB BioJeL** Free Biobank is a resource open to all scientists following approval by a Scientific Board (5500 biosamples with clinical data)

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The National Down Syndrome Society (NDSS), founded in 1979, is the leading human rights organization for all individuals with Down syndrome. NDSS envisions a world in which all people with Down syndrome

have the opportunity to enhance their quality of life, realize their life aspirations and become valued members of welcoming communities.

NDSS' four areas of programing increase public awareness, acceptance and inclusion of individuals with Down syndrome.

 The National Advocacy and Public Policy Center creates systematic change through legislative advocacy. NDSS, one



of the leading forces behind the passing of the ABLE Act, works with Members of



- Congress to enhance the lives of individuals with Down syndrome through policy changes.
 The National Buddy Walk® Program honors and celebrates individuals in their
- communities. Over 250 Buddy Walk® events take place each year to promote the understanding and acceptance of individuals with Down syndrome.

NDSS brings new and positive presentations of Down syndrome to the public through

Public Awareness initiatives such as the #DSWORKS® Employment Campaign. Launched in 2016, the #DSWORKS® Employment initiative encourages companies and businesses to invest in hiring individuals with Down syndrome. NDSS shares Employment Success Stories of individuals who have meaningful jobs as a means of increasing opportunities for those with Down syndrome.



• NDSS' community outreach programs provide comprehensive and accurate information and resources encompassing the lifespan of individuals with Down syndrome.

For more information, please visit www.ndss.org

*Support for this conference was also provided by the National Institute on Aging and the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health





*Down Syndrome International



(*More information about these sponsors is located after the Alphabetical List of Presenters)



Scientific Program, 2nd International Conference of the T21RS Chicago, June 7-11, 2017

June 7 17:00 – 18:00 Registration 18:45 Cocktail party Sponsored by Lumind RDS

June 8

9:00 - 18:00 Registration

09:00 – 09:30 Welcome to T21RS Chicago! Roger Reeves, president T21RS

09:30 – 11:00 SESSION 1. From transcriptome to structure to metabolism: novel insights into the genotype-to-phenotype relationship in Down syndrome – Chair: Jorge Busciglio

Understanding what is the relationship between abnormal gene expression and the various clinical symptoms afflicting people with Down syndrome is critical to develop targeted therapies. This session will provide an overview of recent progress towards understanding the gene expression anomalies that sculpt the structural and metabolic alterations that define Down syndrome in both humans and animal models.

9:30 Dysmyelination in Down syndrome: the molecular and cellular causes and what we might be able to do about it. *Tarik Haydar*, Boston University, USA

10:00 Functional genomics studies of human brain development and neurodevelopment disorders.

Nenad Sestan, Yale University, USA

10:30 A mitochondrial rubicon in autosomal trisomies. *Pablo Helguera,* Instituto de Investigaciones Medicas Mercedes y Martin Ferreyra, Cordoba, Argentina

11:00 – 11:30 Coffee break

11:30 – 13:00 SESSION 2. Molecular pathways involved in the physiopathology of Down syndrome, Fragile X syndrome and other cognitive disorders: towards common therapies? – Chair: Barbara Bardoni

Recent advances in genetics and animal models associated with biochemical/cell biology/molecular biology studies for many costive disorders have led to the definition of targeted treatments that can reverse neurobiological abnormalities in animal models. There are remarkable commonalities in the dysfunction of key pathways and the molecular mechanisms involved in synaptic plasticity across cognitive disorders.

11:30 Physiopathological role of altered cAMP pathway in Fragile X syndrome, Down syndrome and other neurodevelopmental disorders.

Barbara Bardoni, Institute of Molecular and Cellular Pharmacology, CNRS, Valbonne, France

12:00 The APP theory for Fragile X syndrome and Down syndrome. *Cara Westmark*, Waisman Center Madison, USA

12:30 The endocannabinoid system as a novel therapeutic target for developmental disorders.

Viviana Trezza, Roma Tre University, Rome, Italy

13:00 – 14:30 Lunch break

14:30 – 16:00 SESSION 3. Cancer in Down syndrome – Chair: John Crispino/Daniel Satgé.

Sponsored by the Global Down Syndrome Foundation

Down syndrome shows a unique distribution of cancers with an increased incidence of leukemia, and decreased frequency of solid tumors. Irene Roberts (Oxford UK) will describe the link between altered hematopoiesis in fetal life and leukemia. Joachim Espinosa (Aurora, USA) will present data on the impact of the interferon pathway on hematopoiesis and discuss the implications in oncogenesis in general. The importance of a precise evaluation of the frequency and histology of tumors will be underlined by Daniel Satgé (Montpellier, France).

14:30 Impact of trisomy 21 on hematopoiesis and leukemia in early life.

Irene Roberts, Weatherall Institute of Molecular Medicine, University of Oxford, UK

15:00 Understanding Down syndrome as an Interferonopathy: implications for the understanding of leukemia and other co-morbidities driven by trisomy 21.

Joaquin M. Espinosa, Linda Crnic Institute for Down Syndrome, Aurora, CO, USA

15:30 A tissue-related distribution of solid tumors in Down syndrome. **Daniel Satgé**, Oncodefi and University Institute for Clinical Research (IURC), Montpellier, France

16:00 – 16:30 Coffee break

16:30 – 18:00 SESSION 4. Breakthrough/oral communication session (talks to be selected from the abstracts) – Chair Marie Claude Potier

16:30 Can "trisomy silencing" correct known cell pathologies of Down syndrome? **Jen-Chieh Chiang**

16:45 Spatio-temporal up-regulation of sonic hedgehog signaling to ameliorate cognitive impairment in mouse models of Down syndrome. **Feng J. Gao**

17:00 Intracellular chloride accumulation impairs GABAAR-mediated inhibition and memory in Down syndrome. **Andrea Contestabile**

17:15 Suprachiasmatic lesions improve learning in Ts65Dn mice. H. Craig Heller

17:30 Urinary biomarkers and obstructive sleep apnea in patients with Down syndrome. **Brian G. Skotko**

17:45 Metabolomic patterns in second-trimester amniotic fluid and maternal serum associated with fetal trisomy 21. **Stephanie L. Sherman**

18:00 – 20:00 Speakers corner flash poster presenters and Poster Session I with hors d'oeuvres (Posters are exposed during the whole day)

Flash Poster presentations (5-minute)

1. Applying the CANTAB based visual discrimination test to evaluate hippocampal learning in mouse models of Down syndrome. **Faycal Guedj**

2. Skeletal structure exhibits sexual dimorphism and age differences in the Dp1Tyb mouse model of Down syndrome. Jonathan M LaCombe

3. Modeling the non-linear influence of Dyrk1A on actin polymerization **María Martínez** de Lagrán

4. Double edge sword of the Down syndrome critical region (DSCR)-1 function in endothelium. **Takashi Minami**

5. Is targeting trisomic Dyrk1A with EGCG sufficient to improve Down syndrome cognitive and skeletal phenotypes? **Randall J. Roper**

6. Cross-sectional ageing and cognitive decline in adults with Down syndrome. **Carla Startin**

7. Quantitative MRI analyses of regional brain growth and cerebral sulcal development in living fetuses with Down syndrome. **Tomo Tarui**

8. Erythromyeloid cell derived TREM-2: a major determinant of innate immunity in early onset Alzheimer's disease and Down syndrome. **Ruma Raha-Chowdhury**

June 9

8:30-9:30 PLENARY LECTURE A disrupted mechanism of memory and potential biomarker in Down syndrome

Paul Worley, Johns Hopkins University School of Medicine, USA.

The Worley laboratory examines mechanisms of protein-synthesis dependent memory that are mediated by cellular immediate early genes (IEGs) acting directly at excitatory synapses. In parallel studies examining the contribution of these mechanisms to the pathophysiology of Alzheimer's disease and Down syndrome, we found a shared mechanism of reduced IEG expression in brain of Down syndrome (mean age 28) and Alzheimer's disease (mean age 83) individuals. CSF levels distinguish Alzheimer's disease from controls and correlate with measures of hippocampal volume and cognitive status. Implications for understanding disease and ongoing efforts to establish bioassays will be described.

09:30 – 11:00 SESSION 5: Distinct Memory Phenotypes in Down syndrome: implication for cognitive treatment. Chair: Deny Menghini

In this Symposium, we will focus the discussion on recent studies examining memory abilities in individuals with Down syndrome, with the purpose to identify therapeutic approach that can be helpful in improving learning strategies. With this aim, we present different memory components, such as observational learning, procedural learning and explicit memory, and will discuss potential moderating factors that may influence the cognitive development of individuals with Down syndrome, in order to provide data-driven suggestions for intervention programs.

9:30 Dissociable systems of memory in Down syndrome.

Stefano Vicari, Child Neuropsychiatric Unit, Children Hospital Bambino Gesù, Rome, Italy

10:00 Deciphering distinct "hippocampus-dependent" spatial memory processes in Down syndrome.

Pamela Banta Lavenex, Institute of Psychology and Laboratory of Brain and Cognitive Development Quartier UNIL- Lausanne

10:30 Examining Recall Memory and the Flexible Application of Learned Information by Children with Down syndrome

Angela Lukowski, Department of Psychology and Social Behavior, University of California, Irvine

11:00 – 11:30 Coffee break

11:30 – 13:00 SESSION 6. Novel mechanisms In Down syndrome pathophysiology. Possible new therapeutic targets – Chair: Pablo Caviedes

Down syndrome poses a situation of gene overdose that underlie specific impairments in various cellular functions, such as electrical membrane properties, neurotransmitter mediated function, and inflammation. Understanding the pathophysiological mechanisms underlying the aforementioned impairments can identify new targets that can be approached from a therapeutic point of view. This symposium will present various novel cellular mechanisms that are impaired in several Down syndrome models, and will discuss their application in the design of potential treatments that may overcome the anomalies noted.

11:30 Chronic suppression of monoacylglycerol lipase improves adult neurogenesis in the dentate gyrus of aged Ts65Dn mice.

Alexander Kleschevnikov, University of California San Diego, USA

12:00 Lipid metabolism is restrained in a cellular model of Down syndrome: the role of oleic acid as therapeutic target.

Ana Velasco, Institute of Neurosciences (INCYL) University of Salamanca, Spain

12:30 Designer receptors reveal an important role for noradrenergic systems in Down syndrome pathology.

Lotta Gramholm, Knoebel Institute for Healthy Aging (KIHA), University of Denver, Denver, CO, USA.

13:00 – 14:30 Lunch break

14:30 – 16:00 SESSION 7. Clinical trials – Chair: Jean Delabar

In the past ten years there have been several breakthroughs in understanding the neurochemistry in Down syndrome. This improved knowledge base has led to a series of discoveries with therapeutic promise paving the way to clinical trials that have been or are being performed.

14:30 Development of a selective GABAα5 negative allosteric modulator (basmisanil) for intellectual disability associated with Down syndrome: results, challenges and lessons learnt from the Roche clinical trials

Xavier Liogier d'Ardhuy, F. Hoffmann-La Roche Ltd, Roche Innovation Center Basel, Switzerland

15:00 Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down syndrome (TESDAD): a double blind, randomized, placebo-controlled, phase 2 trial.

Rafael de la Torre, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain

15:30 PERSEUS: a future clinical study of safety and efficacy of Epigallocatechin-3-gallate in children with Down syndrome.

Cécile Cieuta-Walti, Lejeune Medical Institute, Paris, France

15:40 Transcranial direct current stimulation in healthy adults and children with Down syndrome.

Chrysanthy Ikonomidou, University of Wisconsin, Madison, USA

15:50 Pharmacological interventions to improve cognition and adaptive functioning in Down syndrome: strides to date

Sarah J. Hart, Duke University Medical Center, Durham, NC

16:00 – 18:30 Speakers corner flash poster presentations and posters session II with coffee (posters are exposed during the whole day).

Flash Poster presentations (5-minute)

1. The UPR is a major participant in the development of Alzheimer disease-like neuropathology in a mouse model of Down syndrome. **Fabio Di Domenico**

2. The uneven development of memory in Down syndrome in childhood. Kate M. O. Hughes

3. Extensive perturbations of the immune system among individuals with trisomy 21 **Katherine A. Waugh**

4. Targeted metabolomic analysis in adults with Down syndrome: purines, pyrimidines, amino acids and nitrosative stress biomarkers. **Angelo Carfi**

5. Highly restricted Down syndrome critical region identified on human chromosome 21. **Maria Chiara Pelleri**

6. A role for thrombospondin-1 in learning and memory and neuroplasticity. Maria Torres

7. Depression in mild cognitive impairment and dementia in adults with Down syndrome. Sharon J. Krinsky-McHale

8. Towards genetic dissection of pathologies in trisomy 21 using human cellular models. Aoife Murray

20:00 – GALA DINER

June 10

8:30 - 9:30 PLENARY LECTURE Modeling human neurodevelopment and neural developmental disorders using human induced pluripotent stem cells

Guo-li Ming, Institute for Cell Engineering at Johns Hopkins University School of Medicine, USA.

Cerebral organoids, three-dimensional cultures that model organogenesis of the brain, provide a new platform to investigate human brain development as well as diseases. Using engineered miniature bioreactors to better mimic the growth environment and enhance the nutrient supply, we have developed protocols to generate brain region-specific organoids from human iPSCs. Our forebrain-specific organoids recapitulate key features of human cortical development, and provide a platform to further understand molecular events and mechanisms underlying early brain development. I will also discuss how we can use this system to model brain disorders with a developmental origin.

09:30 – 11:00 SESSION 8. Probing neural development and function in Down syndrome with induced pluripotent stem cell (iPSC) technology – Chairs: Anita Bhattacharyya and Dean Nizetic

Human induced pluripotent stem cells (iPSCs) generated from somatic cells of individuals with specific diseases and disorders offer an important model system to reveal cellular and molecular events underlying pathogenesis as well as provide a means for initial assessments of potential therapeutic interventions. Studies using iPSCs are especially valuable for enhancing our understanding of complex conditions, such as Down syndrome. This symposium will provide insight into the advantages and challenges associated with using human Ts21 iPSCs to study neurodevelopment and neurodegeneration in Down syndrome. Recent technological advances will be presented that are being used in the effort to better understand consequences of Ts21 on the human brain.

9:30 Ts21 iPSCs to model neurodevelopmental and neurodegeneration Down syndrome *Anita Bhattacharyya*, Waisman Center, University of Wisconsin-Madison, USA

10:00 Cerebral organoids in the study of central nervous system development in Down syndrome

Tristan D. McClure-Begley, Department of Molecular, Cellular and Developmental Biology, University of Colorado, Boulder, USA

10:30 Illuminating neural circuitry in patient-iPSC derived brain model with Down syndrome. *Lin Tian*, Department of Biochemistry and Molecular Medicine, University of California, Davis, USA

11:00 – 11:30 Coffee break

11:30 - 13:00 SESSION 9. Cross-species correspondence: dialogue between mouse and human phenotyping – Chair: Victor Tybulewicz

This session will focus on cognition in Down syndrome. Since direct studies of mechanism and pathology of cognitive defects are difficult in humans, mouse models offer an important route to approach such questions. However, it remains unclear how well mouse models recapitulate the human condition.

11:30 The challenges of aligning mouse and human infant cognitive studies. *Hana D'Souza*, Centre for Brain & Cognitive Development, Birkbeck University of London, London UK and The London Down Syndrome Consortium

12:00 Memory processes in mouse models of Down syndrome. *Mark Good,* School of Psychology, Cardiff University, Cardiff, UK

12:30 Decoding the genotype-phenotype relationships in Down syndrome by studying new models in mouse and rat.

Yann Herault, Institut de Génétique et de Biologie Moléculaire et Cellulaire, Illkirch, France

13:00 – 13:30 Lunch break – members collect box lunch and return to the Main Meeting Room

13:30 – 14:30 T21RS General Assembly – (ALL members please attend as important business must be transacted)

14:30 15:30 PLENARY LECTURE

Diana Bianchi, Tufts University School of Medicine and Tufts Medical Center, Boston, USA

15:30 – 17:00 SESSION 10. Breakthrough/Oral Communication sessions – Chair: Mara Dierssen

15:30 Trisomy 21 Research Society: moving forward research on Down syndrome. **Roger Reeves**, President T21RS, Johns Hopkins University School of Medicine, USA.

15:45 A specialized pro-resolution mediator approach to chronic inflammation in the Ts65Dn mouse model of Down syndrome. **Eric Hamlett**

16:00 Mapping congenital heart defects in Down syndrome to a minimum of 2 loci within a 26-gene region. **Eva Lana-Elola**

16:15 A pair of maternal chromosomes derived from meiotic nondisjunction in trisomy 21 affects nuclear architecture and transcriptional regulation. **Yasuji Kitabatake**

16:30 Early endosome clustering in Down syndrome revealed by high-resolution microscopy. Alexandra Botté

16:45 Trans-acting Epigenetic Effects of Chromosomal Aneuploidies: Lessons from Human Trisomy 21 and mouse models. **Benjamin Tycko and Eugene Yu**

T21RS Science & Society Symposium - Session chair: Peter De Deyn

Sponsored by the National Down Syndrome Society (NDSS)

Session coordination: **T21RS Committee for Science & Society (panel)** Peter Paul De Deyn (Belgium, chairman), Alain Dekker (NL), Juan Fortea (SP), Sebastian Videla (SP), Lotta Granholm (US, SW), Cindy Lemere (USA), Diana Bianchi (USA)

17:00 Welcome and Introduction

Peter De Deyn (chairman T21RS Committee for Science & Society) Sara Weir (president, NDSS)

17:05 T21RS Committee for Science & Society: aims & achievements *Peter De Deyn*

17:15 The pros and cons of having my relative with Down syndrome participate in clinical research Sub-session chair: Diana Bianchi

Two families are invited for a debate: one family in favor of, and one family against participating in scientific research + discussion with panel and plenary audience

17:45 Medical policies for people with Down syndrome Sub-session chairs: Juan Fortea and Cindy Lemere

Four initiatives to integrate care and research with social aspects for patients/clients and family members + discussion with panel and plenary audience Sebastian Videla (Catalan DS Foundation) Melissa Parisi (NIH/NICHD) Michelle Whitten (Global Down Syndrome) *Medical care for adults with Down syndrome - lifting barriers* Sara Weir (NDSS) *ABLE Act – Progress Report*

18:40 Break

18:55 Association introduction round: DS associations as research partners

Each DS association will briefly introduce themselves (3 minutes) by focusing on how they contribute to research, with the aim to get acquainted, share ideas and facilitate discussion.

- 1. National Down Syndrome Society (USA), Sara Weir
- 2. Global Down Syndrome (USA), *Michelle Whitten*
- 3. Fondation Jérôme Lejeune (France), Catherine Lemmonier
- 4. LumindRDS (USA), Hampus Hillerstrom
- 5. The Matthew Foundation (USA), John Blascovich
- 6. Trisomie 21 France (France), *Renaud Touraine*
- 7. Down's Syndrome Association UK (UK), Gillian Bird
- 8. Band of Angels (USA), Brian Skotko
- 9. Alana (Brazil), Claudia Moreira
- 10. Catalan Down Syndrome Foundation (Spain), Katy Trias
- 11. Down Syndrome International (UK/international), Helen Powell
- 12. Association Française pour la Recherche sur la Trisomie 21 (France), Jean Marc Richard
- 13. Down Syndrome Hungary (Hungary), Agnes Toth
- 14. AMIPI-Bernard Vendre (France), Marie-Laure Blandin
- 15. Down Syndrome OPTIONs (USA), Alexandria Durkin
- 20:05 Summary Peter De Deyn
- 20:10 End

June 11

9:00 – 9:30 PLENARY LECTURE Biomarkers for dementia in Down syndrome *Ira T. Lott*, University of California, Irvine and CHOC Children's Hospital

09:30 – 11:00 SESSION 11. Horizon21 and DS1000 – European collaborations for studies of Alzheimer's disease in Down syndrome – Chair: Andre Strydom.

There are several groups in Europe currently following cohorts of older individuals with Down syndrome. We will describe these existing studies, which are contributing data to a genomics consortium, and provide an update on the ongoing efforts to harmonize data and establish a platform for multi-center studies.

9:30 Clinical assessments in studies of ageing in Down syndrome: core data and harmonization.

Tonnie Coppus, Radboud University, Netherlands

10:00 Neuroimaging of Alzheimer's disease in Down syndrome. *Shahid Zaman*, University of Cambridge, UK

10:30 Cerebrospinal fluid biomarker studies in Down syndrome. *Juan Fortea,* Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

11:15 – 11:30 Coffee break

11:30 – 13:00 SESSION 12. Breakthroughs/Oral communication session – Chair: Cynthia Lemere

11:30 Annette Karmiloff-Smith Thesis Award. Neurogenesis and memory enhancement following treatment with an agonist of the BDNF-Trkb receptor in a model of Down syndrome. Fiorenza Stagni

11:45 Trisomy 21 causes a deficit in lysosomal cathepsins and alters APP/Aβ processing, independently of an extra copy of APP. **Frances K. Wiseman**

12:00 The early onset of brain insulin resistance in Down syndrome: a bridge towards the development of Alzheimer-like neuropathology. **Eugenio Barone**

12:15 Premorbid IQ as a predictor of performance in assessments of clinical dementia status. Wayne Silverman

12:30 NPTX2 and cognitive dysfunction in Alzheimer's disease and Down syndrome. **Mei-Fang Xiao**

12:45 Behavioral and psychological symptoms of dementia in Down syndrome. Alain D. Dekker

13:00 – 14:30 Lunch

14:30 – 16:00 SESSION 13. Brain Imaging Biomarkers of dementia in Down syndrome – Chair: Ben Handen

Sponsored by the Global Down Syndrome Foundation

Aging adults with Down syndrome are vulnerable to the development of dementia and most, if not all, have Alzheimer's disease neuropathology by 40 years of age. However, there is a wide range in age at onset and not all people with Down syndrome develop clinical signs of dementia; if they do, it is typically almost a decade after brain pathology is present.

14:30 Brain Imaging Measures of Amyloid Deposition in Adults with Down syndrome *Brad Christian*, Waisman Brain Imaging Laboratory, University of Wisconsin-Madison, USA

15:00 Magnetic Resonance Spectroscopy and Dementia in Down syndrome *Ai-Ling Lin,* Sanders-Brown Center on Aging, University of Kentucky, Lexington, USA

15:30 Correlating Imaging to Plasma Biomarkers in Down syndrome

Mike Raffi, Alzheimer's Therapeutic Research Institute, University of Southern California, Department of Neuroscience, University of California, San Diego, USA

16:00 – 17:30 SESSION 14. Biomarkers of Alzheimer's disease in Down syndrome – Chair: Elisabeth Head

Sponsored by the Lumind RDS Foundation

It is critical to understand when risk of dementia in people with Down syndrome increases and what the early signs of dementia are so that appropriate treatments/interventions can be implemented. Studies of plasma or cerebrospinal fluid biomarkers for early dementia changes will yield critical data documenting the transition from normal aging to mild cognitive impairment to clinical dementia in individuals with Down syndrome.

16:00 Study of cerebrospinal fluid biomarkers in a cohort of Down syndrome patients.

Bessy Benejam, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau, Barcelona, Spain

16:30 Down syndrome individuals with Alzheimer's disease have a distinct neuroinflammatory phenotype compared to sporadic Alzheimer's disease.

Donna Wilcock, University of Kentucky, Sanders-Brown Center on Aging, Department of Physiology, Lexington, USA

17:00 Analysis of DYRK1A and markers associated with DYRK1A level in plasma and lymphoblastoid cell lines from Alzheimer disease and Down syndrome patients. *Nathalie Janel,* University Paris Diderot, Sorbonne Paris Cité, France

17:30 Closing remarks (Roger Reeves)

Departure



SESSION 1. FROM TRANSCRIPTOME TO STRUCTURE TO METABOLISM: NOVEL INSIGHTS INTO THE GENOTYPE-TO-PHENOTYPE RELATIONSHIP IN DOWN SYNDROME

DYSMYELINATION IN DOWN SYNDROME: THE MOLECULAR AND CELLULAR CAUSES AND WHAT WE MIGHT BE ABLE TO DO ABOUT IT

Tarik F. Haydar

Boston University School of Medicine, Boston, Massachusetts, United States

Recent gene expression studies in the brains of people with Down syndrome (DS) have identified changes in approximately 60 gene networks. Many of these networks are altered regionally or during specific times in development. However, we have found that genes expressed in the oligodendroglial lineage are dysregulated throughout life in DS. In particular, genes expressed in oligodendrocyte progenitor cells are upregulated while genes expressed in mature myelinating oligodendrocytes (mOL) are downregulated. Our data in the Ts65Dn mouse model shows a corresponding defect in myelin protein expression and mOL differentiation in the white matter of the forebrain, cerebellum and spinal cord. The electrophysiological and behavioral consequences of the resulting dysmyelination will be discussed, as will our current strategy for treating this new cellular deficit in the trisomic brain.

FROM FUNCTIONAL NEUROGENOMICS TO SPECIFIC CELLULAR PHENOTYPES IN DOWN SYNDROME

Nenad Sestan

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Down syndrome (DS), the most common genetic cause of developmental delay and intellectual disability, results from the presence of a full or partial extra copy of chromosome 21. This extra genetic material may lead to altered regulation and expression of numerous genes throughout the genome, some of which might serve as therapeutic targets potentially ameliorating the causes or symptoms of DS. We therefore conducted a multi-regional transcriptome analysis of DS and euploid control brains spanning mid-fetal development through adulthood. Among the genes and biological processes we found to be dysregulated were several associated with oligodendrocyte differentiation and myelination. Diminished expression of myelin-associated mRNA and protein was confirmed by ddPCR and western blot. Moreover, myelinated fibers in human fetal and adult cerebral cortex displayed atypical organization and were diminished in number. These discoveries were validated through a cross-species comparison to Ts65Dn mice, a rodent model for DS. We determined that hypomyelination present in these mice was correlated with impairments in oligodendrocyte maturation and resulted in slower neocortical action potential transmission. Studies in purified olidodendrocytes revealed that defects in maturation and myelination of Ts65Dn were cell autonomous. These results suggest defects in oligodendrocyte development and function may be a core feature of DS neuropathogenesis and novel therapeutic targets.

A MITOCHONDRIAL RUBICON IN AUTOSOMAL TRISOMIES

Pablo Helguera

Instituto de Investigación Médica Mercedes y Martín Ferreyra, INIMEC-CONICET-Universidad Nacional de Córdoba, Argentina Down syndrome (DS) cells are characterized by a complex phenotype including early senescence, increased levels of reactive oxygen species (ROS) and mitochondrial structural and metabolic dysfunction, conditions that trigger activation of the Nrf2 antioxidant pathway. Cells from patients bearing autosomal trisomies 13 and 18 also share chronic oxidative stress; therefore, we compared their mitochondrial function, metabolism and structural organization and recycling. RNAseq analysis rendered particular transcriptional profiles that contextualize commonalities and differences in these convergent phenotypes. Expression of antioxidant enzyme catalase targeted to mitochondria (mCAT) reverted both metabolic and functional defects in DS cells, reducing oxidative stress, restored mitochondrial structure and function, normalized replicative and wound healing capacity, and rendered the Nrf2 mediated antioxidant response dispensable. These results underscore mitochondrial specific interventions as a key aspect of metabolic restoration therapies.

SESSION 2. MOLECULAR PATHWAYS INVOLVED IN THE PHYSIOPATHOLOGY OF DOWN SYNDROME, FRAGILE X SYNDROME AND OTHER COGNITIVE DISORDERS: TOWARDS COMMON THERAPIES?

PHYSIOPATHOLOGICAL ROLE OF cAMP/cGMP SIGNALLING IN FRAGILE X AND DOWN SYNDROME

Barbara Bardoni, Thomas Maurin

CNRS UMR7275 Institute of Molecular and Cellular Pharmacology, Valbonne, FRANCE Background: Fragile X syndrome (FXS) is the most common form of inherited intellectual disability and a leading cause of autism. It is due to the silencing of the FMR1 gene coding for an RNA-binding protein, FMRP, which modulates translation of a subset of synaptic proteins. To date no specific treatment is available for this disorder. Objective: The identification of an effective therapy for FXS is intimately linked to the deciphering of FMRP functions. Since remarkable commonalities exist in the dysfunction of key pathways involved in synaptic plasticity across neurodevelopmental disorders, unraveling the molecular bases of FXS will help in understanding also other forms of intellectual disability and/or autism. Methods: We performed a CLIP (Cross-Link UV Immunoprecipitation) analysis in brain cortex and hippocampus of 13-day-old mice (when FMRP reaches its highest expression and there is a peak in synaptogenesis) using highly specific new antibodies directed against FMRP. Results: This analysis allowed us to: 1) Define a consensus motif for RNAs that are targeted by FMRP in brain; 2) Develop a new therapy for FXS by modulating the intracellular levels of both cAMP and cGMP. By using this new therapeutic approach to treat Fmr1-null mice - the mouse model of FXS - we observed the rescue of in vitro/ex-vivo and the deficits in communication, social discrimination and interaction of *Fmr1*-KO mice. Conclusions: In this context it is interesting to underline that both cAMP and cGMP are essential in various cellular functions and exert their effect both pre- and post-synaptically. Thus, we will compare the role of these molecules in physiopathology of FXS, Down syndrome and other forms of neurodevelopmental disorders

THE APP THEORY FOR FRAGILE X

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Fragile X syndrome is a debilitating genetic disorder with no cure and few therapeutic options. Excessive signaling through metabotropic glutamate receptor 5 in Fragile X leads to increased translation of numerous synaptic proteins and exaggerated long-term depression. Two of the overexpressed proteins are amyloid-beta protein precursor (APP) and its metabolite amyloid-beta, which have been well studied in Alzheimer's disease. Accumulating evidence suggests that dysregulated levels of APP and its catabolites contribute to the impaired synaptic plasticity and seizure incidence observed in several neurodevelopmental disorders including fragile X and Down syndrome. We hypothesize that pharmaceuticals under study for the modulation of APP and amyloid-beta in Alzheimer's disease might be viable therapeutic strategies for fragile X and Down syndrome. Specifically, we are studying the efficacy of BACE1 inhibitors in reducing amyloid-beta levels and the corresponding effects on seizure, learning & memory, and sleep phenotypes in Fmr1KO mice. In addition, APP and its proteolytic fragments are emerging as biomarkers for neurological health. Multiple recent fragile X clinical trials have failed on their primary endpoints indicating that there is a compelling need for validated biomarkers and outcome measures in the field. Thus, we further hypothesize that APP and amyloid-beta may be viable blood-based biomarkers that are responsive to drug treatment in fragile X. Studies to understand the role of APP metabolites in developmental conditions such as fragile X are a quantum leap for the neuroscience field, which has traditionally restricted any role of APP to Alzheimer's disease and aging.

THE ENDOCANNABINOID SYSTEM AS A NOVEL THERAPEUTIC TARGET FOR DEVELOPMENTAL DISORDERS

Viviana Trezza

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Background: The endocannabinoid system is a unique neuromodulatory system that consists of cannabinoid receptors, their endogenous ligands (endocannabinoids, mainly anandamide and 2-arachidonoylglycerol) and the enzymes for endocannabinoid synthesis and degradation. Cannabinoid receptors are highly expressed in brain areas that modulate cognitive processes and emotional states, where endocannabinoids regulate ion channel activity and neurotransmitter release. Endocannabinoid ability to modulate synaptic activity has a wide range of functional consequences and provides unique therapeutic possibilities. Objective: I will discuss data showing that the endocannabinoid system may be a novel therapeutic target to treat the social and cognitive deficits observed in autism spectrum disorders (ASD). Furthermore, I will discuss the results of preliminary studies that are evaluating the role of the endocannabinoid system in the social and cognitive dysfunctions observed in an animal model of Fragile X Syndrome (FXS). Methods: We tested the effects of drugs that target the endocannabinoid system in animal models mimicking the main features of ASD and FXS, with special focus on the social and cognitive domains. As animal model of ASD, we used rats prenatally exposed to the anticonvulsant and mood stabilizer drug valproic acid (VPA), which is known to induce autistic-like features both in laboratory

animals and humans. FMRP-deficient (fmr1 KO) mice were used as animal model of FXS. Results: VPA-exposed rats displayed altered phosphorylation of CB1 cannabinoid receptors in different brain areas, associated with changes in anandamide metabolism. Interestingly, enhancing anandamide signalling through inhibition of its degradation rescued the social and cognitive deficits displayed by VPA-exposed rats. We are currently evaluating the ability of drugs that interfere with endocannabinoid deactivation to rescue the social and cognitive dysfunctions observed in fmr1 KO mice. Conclusions: This study shows that the endocannabinoid system may represent a novel therapeutic target for the social and cognitive dysfunctions observed in developmental psychiatric disorders.

SESSION 3. CANCER IN DOWN SYNDROME

IMPACT OF TRISOMY 21 (T21) ON HEMATOPOIESIS AND LEUKEMIA IN EARLY LIFE Irene Roberts,

Department of Paediatrics and MRC Molecular Haematology Unit, Weatherall Institute of Molecular Medicine, University of Oxford, UK

The high frequency of myeloid and lymphoid leukemias in young children with DS is intriguing given their reduced susceptibility to non-hematopoietic cancers. The unique characteristics of DS-associated leukemias hint at how T21 alters hematopoietic stem and progenitor cell (HSPC) behavior in early life. Myeloid Leukemia of DS (ML-DS) originates in fetal HSPC and presents as a neonatal preleukemic syndrome, Transient Abnormal Myelopoiesis (TAM), which evolves to full-blown ML-DS before age 5 in 10-20% of cases. ML-DS and TAM leukemic cells have acquired N-terminal truncating mutations in the transcription factor gene GATA1 which result in exclusive production of a short GATA1 protein (Gata1s) with altered functional properties. Since such mutations are not leukemogenic in the absence of T21, this suggests T21 provides a permissive cellular context for GATA1-mediated transformation. Consistent with this, T21 itself perturbs fetal liver HSPC function, increasing megakaryocyte-erythroid cell proliferation at stem/progenitor level and impairing B-cell and granulocyte-monocyte development in the absence of GATA1 mutations. We recently identified GATA1 mutations at an unexpectedly high frequency (25-30%) in neonates with DS. However, GATA1 mutations are not acquired after birth supporting the importance of the fetal cell context. Mutations in additional genes, e.g. cohesin and PRC2-complex genes, are necessary for development of ML-DS. Although TAM and ML-DS provide a natural human model to interrogate the impact of T21 on HSPC and leukemogenesis, mechanistic experiments to identify the role of specific genes are difficult in human cells. As a complementary approach, mouse models of DS have identified several potential genes and pathways, which may contribute to perturbation of HSPC development by T21, including the Hsa21, genes ERG, DYRK1A, HMGN1, USP16 and miR125b. Integration of data from these models with emerging data from studies in human cells will continue to provide important insights into the unique role of T21 in human leukemogenesis.

UNDERSTANDING DOWN SYNDROME AS AN INTERFERONOPATHY

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Although it is clear that trisomy 21 causes Down syndrome, the molecular events acting downstream of the trisomy remain ill defined. Using complementary genomics analyses generated from our ongoing cohort study of the population with trisomy 21, the Crnic Institute's Human Trisome ProjectTM (www.trisome.org), we identified the interferon pathway (IFN) as the major signaling cascade consistently activated by trisomy 21. Transcriptome analyses revealed that trisomy 21 activates the IFN transcriptional response in diverse cell types, including circulating T cells and monocytes. Trisomy 21 cells show increased induction of IFN-stimulated genes and decreased expression of ribosomal proteins and translation factors. A large plasma proteomics study involving 298 participants revealed consistent dysregulation of dozens of factors involved in immune control, with clear upregulation of many potent pro-inflammatory cytokines (e.g. IL-6, TNF-D). Plasma metabolomics studies from 100+ participants demonstrated that trisomy 21 produces a metabolic signature consistent with chronic autoinflammation, including dysregulation of succinate and tryptophan metabolism leading to production of neurotoxic metabolites. Single cell mass-spectometry (CYTOF) analysis of 150+ immune cell types demonstrated profound alterations in the immune cell repertoire in people with Down syndrome, including increased numbers of immune cell types with potent cytotoxic activities. Therefore, we propose that IFN hyperactivation, likely via increased gene dosage of the four IFN receptors encoded on chromosome 21, drives many of the clinical manifestations of trisomy 21, including the decreased rates of solid tumors and increased risk of leukemias, and that IFN antagonists could have therapeutic benefits. We will discuss the ongoing efforts to test the central hypothesis that Down syndrome can be classified as an Interferonopathy, including the recent generation of a mouse model of trisomy 21 without triplication of the IFN receptors.

A TISSUE-RELATED DISTRIBUTION OF SOLID TUMORS IN DOWN SYNDROME Daniel SATGE

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Adults and children with Down syndrome (DS) have a particular tumor profile with an increased incidence of leukemia and a reduced incidence of solid tumors. An extensive review of the literature allowed comparing the frequency of solid malignancies with those found in the people with intellectual disability (PWIDs). This approach documents more precisely modifications linked to the supernumerary 21 chromosome. According to the current data, in DS malignant solid tumors are two times less frequent (50%) than in the general population (GP), and two times less frequent than in PWIDs. However, in DS, some cancers are nonetheless more frequent than in the GP, particularly gonadal and extragonadal germ cell tumors, and probably cancers of liver, gallbladder, pancreas and bone in childhood. Some cancers are possibly as frequent as in GP: ovarian cancer, lymphoma.

Others, breast, neural, cutaneous, uterine-cervix, prostate and brain cancers are less frequently reported. From a histological point of view, hematopoietic tissue and germ cells seem to be at an increased cancer risk while epithelial tissue and neural tissue seem less vulnerable. Hypotheses to explain the modified frequency of cancer in DS have been proposed: DNA repair defects, oxidative stress, decreased angiogenesis, the protective role of the stroma, and the impact of triplicated HSA2I genes DSCRI, DYRKIA, ETS2, SIM1, ERG, BTG3, S 100B and others. The complexity of the DS tumor profile suggests that more than a single mechanism is responsible for the variations. Animal and in vitro studies should explore specific and clear modifications: the excess of germ cell tumors and less frequent cancers breast carcinoma and neural tumors of childhood neuroblastoma, medulloblastoma. *A grant of the Fondation Jérôme Lejeune supports the study of cancer in people with Down syndrome and intellectual disability*.

SESSION 4. Breakthrough/Oral Communication

CAN "TRISOMY SILENCING" CORRECT KNOWN CELL PATHOLOGIES OF DOWN SYNDROME?

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Previously, our lab demonstrated that RNA from an XIST gene inserted into one chromosome 21 could silence that autosome in cis, reducing Chr21 transcriptional output in Down syndrome (DS) patient-derived iPS cells to near disomic levels. Our lab is working to extend this approach for translational research and potential therapeutic strategies for DS, in human cells in vitro and in a DS mouse model. A critical question is whether "trisomy silencing" is sufficiently effective to correct known cellular pathologies of DS in trisomic cells. We tested the phenotypic effects of "trisomy silencing" in the hematopoietic system, for which the underlying DS cell pathologies are best established. We investigated overproduction of hematopoietic cells in fetal liver, which predisposes patients to myeloproliferative disorder and acute megakaryocytic leukemia, in an isogenic panel of DS iPS clones carrying an inducible XIST gene, compared to isogenic disomic and trisomic cells. In multiple transgenic clones, comparing parallel cultures undergoing hematopoiesis with and without induced XIST, over-production of megakaryocytes and erythrocytes was clearly corrected by XIST-mediated chromosome 21 silencing. Consistent with clinical features of DS, XIST expression had the opposite effect on production of neural stem cells. Additional analyses of early stages of hematopoietic differentiation indicate that trisomy 21 enhances formation of hematopoietic progenitors from hemogenic endothelium, not before. Results also indicate that expression of non-Chr21 genes involved in IGF signaling is impacted by trisomy 21, supporting and extending an earlier finding in AMKL. This provides proof-of-principle that chromosome silencing can normalize DS cell pathologies in vitro, and our lab also has work in progress to test in vivo correction of the Ts65Dn mouse model by targeted Xist expression from the extra marker chromosome 16.

SPATIOTEMPORAL UP-REGULATION OF SONIC HEDGEHOG SIGNALING TO AMELIORATE COGNITIVE IMPAIRMENT IN MOUSE MODELS OF DOWN SYNDROME

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Down syndrome (DS) is the most common genetic cause of intellectual disabilities, which is caused by trisomy for human chromosome 21 (Hsa21). Structural abnormalities in the cerebellum and hippocampus are seen in people with DS and are likely to be related to learning deficits. Finding treatments that ameliorating abnormal development in these specialized brain areas could enhance learning and memory and improve life quality for individuals with DS. Previous studies suggested that the deficiency in sonic hedgehog (Shh) signaling, which controls stem and progenitor cell proliferation and differentiation throughout brain development, is a likely contributor to of hypoplasia in hippocampus and cerebellum in DS. We recently discovered that a single injection of Shh agonist (SAG 1.1) into P0 Ts65Dn mice, a mouse model of DS, permanently normalizes the size and gross anatomy of the cerebellum, leads to better adult spatial problem solving, and restores electrophysiological correlates of learning in the CA1-hippocampal subfield. Before translating the finding into clinical application, we need to dissect the mechanistic underpinnings of SAG-dependent improvement of cognitive in animal models of DS. We now report a new tetracyclineinducible Shh transgenic mouse model (Zsgreen1-biTRE-hShh), which is designed to achieve spatiotemporal up-regulation of human Shh (hShh) ligand. We crossed this Shh mouse with Camk2a-tTA transgenic mouse to achieve Shh overexpression in hippocampus, and crossed the Shh mouse with PCP2-tTA transgenic mice to allow us to have cerebellar Purkinje cell-specific Shh expression. We confirmed that the resulting bi-transgenic mice reversibly express correctly processed hShh ligand and enhanced Shh signaling in a tissuespecific manner, and that Zsgreen1 is a robust reporter to track hShh locations. We are investigating electrophysiological and behavioral outcomes from DS mouse models in which these transgenes are expressed to determine whether/how genetically enhanced Shh signaling ameliorates cognitive impairment in DS mouse models.

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INTRACELLULAR CHLORIDE ACCUMULATION IMPAIRS GABAAR-MEDIATED INHIBITION AND MEMORY IN DOWN SYNDROME

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Trisomic mouse models of Down syndrome (DS) reproduce the main cognitive disabilities of the human syndrome. In particular, DS mice show learning and memory deficits, largely determined by altered GABAergic transmission through chloride-permeable GABA_A receptors (GABA_ARs). Specifically, we have recently found that intracellular chloride accumulation renders GABA_AR-mediated currents depolarizing in the adult brain of the Ts65Dn mouse model of DS. Accordingly, intracellular chloride accumulation is paralleled by increased expression of the chloride importer NKCC1 in the brains of both trisomic mice and DS patients. Importantly, pharmacological inhibition of NKCC1 with the FDA-approved drug Bumetanide restores learning and memory in Ts65Dn mice. However, our findings on NKCC1 as a pivotal molecular target for the rescue of cognitive deficits in DS have raised many new questions regarding the role of chloride dysregulation in neuronal communication and memory impairment in DS. By calcium-imaging, patch-clamp and multi-electrode array (MEA) experiments, we show here that neural response to GABAergic drugs are profoundly altered at the network level during development and in mature neurons in culture, and are consistent with depolarizing actions of GABA. In agreement with depolarizing GABA actions, the positive allosteric modulator of GABAAR Diazepam demonstrates a paradoxical anxiogenic effect in trisomic mice, which is reverted by Bumetanide. Moreover, knockdown of NKCC1 expression by RNA interference rescues intracellular chloride accumulation and GABA_AR-mediated inhibition in trisomic neurons. Most importantly, AAV-mediated neuronspecific NKCC1 knockdown in vivo in the hippocampus of adult Ts65Dn animals rescues behavioral performance on different learning and memory tests at levels undistinguishable from those of WT mice. Our findings demonstrate that NKCC1 overexpression drives depolarizing GABA_ARs signaling in trisomic cells, leading to altered neuronal network activity and behavioral impairments in DS mice. Moreover, our study identifies a new molecular target for treatments aimed at rescuing cognitive disabilities in individuals with DS.

SUPRACHIASMATIC LESIONS IMPROVE LEARNING IN TS65DN MICE

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Background: Our previous work demonstrated that chronic low doses of the GABAAR antagonist pentylenetetrazole over two weeks resulted in long-term rescue of the ability of Ts65Dn mice to perform in the novel object recognition (NOR) test. However, the drug was only efficacious when administered during the daily light or rest phase, the circadian phase when suprachiasmatic nucleus (SCN) activity is highest (Colas et al 2013). Objective: Test the hypothesis that the SCN, directly or indirectly, inhibits neuroplasticity of Ts65Dn mice. Method: Evaluate performance of Ts65Dn mice and 2N littermates in the Novel Object Recognition (NOR) Test. Lesion or sham-lesion their SCNs. Record patterns of activity under constant conditions to reveal completeness of lesions. Re-evaluate NOR performance. Evaluate lesions histologically. Results: Before lesion surgery, 2N mice had significant learning index (LI) scores and Ts65Dn mice did not. Following lesion surgery, the 2N mice had significant LI scores whether they were rhythmic (shams, n=11) or arrhythmic (complete, n=20). Ts65Dn mice receiving sham or incomplete lesions (n=6) did not have significant LIs, but those that were rendered arrhythmic by virtue of complete SCN lesions (n=9) had significant LI scores. Conclusions: Lesions of the SCN improve the ability of Ts65Dn mice to learn and remember. This finding leads to the hypothesis that the circadian system modulates neuroplasticity suppressing it during the light or rest phase. A possible function of this suppression of neuroplasticity during the sleep phase is to stabilize memory transcripts during the process of consolidation, in the Ts65Dn mouse consolidation is impaired by excessive inhibition, which might be reflected in the greater power of circadian rhythms in these mice (Ruby et al. 2010).

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References: Colas, D. et. al (2013 British Journal of Pharmacology. 169:763-773. Ruby, N. F. et al. (2010) J. Biol. Rhythms 25:63-66.

URINARY BIOMARKERS AND OBSTRUCTIVE SLEEP APNEA IN PATIENTS WITH DOWN SYNDROME

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Background/Problem Statement: Obstructive sleep apnea (OSA) is particularly prevalent in individuals with Down syndrome, and polysomnography poses a greater challenge in these individuals. Urinary biomarkers have not previously been specifically studied in this population. Study Objectives: The study aim was to compare urinary biomarkers in individuals with Down syndrome (DS) with and without OSA to those of age- and sexmatched neurotypically developing healthy controls (HC). We further investigated whether we could predict OSA in individuals with DS using these biomarkers. Methods: Urine samples were collected from 58 individuals with DS the night before or the morning after their scheduled overnight polysomnogram or both, of who 47 could be age- and sexmatched to a sample of 43 HC. Concentrations of 12 neurotransmitters were determined by enzyme-linked immunosorbent assay. Log-transformed creatinine-corrected assay levels were normalized. Normalized z-scores were compared between individuals with DS vs. HC, between individuals with DS with vs. without OSA, and to derive composite models to predict OSA. Results: Most night-sampled urinary biomarkers were elevated among individuals with DS relative to matched HC. No urinary biomarker levels differed between individuals with DS with vs. without OSA. A combination of four urinary biomarkers predicted apnea-hypopnea index AHI > 1 (the standardized measure of apnea on polysomnograms) with a positive predictive value of 90% and a negative predictive value of 68%. Conclusions: Having DS, even in the absence of concurrent OSA, is associated with a different urinary biomarker profile when compared to HC. Therefore, while urinary biomarkers may be predictive of OSA in the general pediatric population, a different approach is needed in interpreting urinary biomarker assays in individuals with DS. Certain biomarkers also seem promising to be predictive of OSA in individuals with DS.

METABOLOMIC PATTERNS IN SECOND-TRIMESTER AMNIOTIC FLUID AND MATERNAL SERUM ASSOCIATED WITH FETAL TRISOMY 21

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Trisomy 21 is associated with a vast array of medical conditions and birth defects including cognitive impairment and congenital heart defects, yet the biological mechanisms driving the variable presentation of associated phenotypes remain largely unknown. Metabolomic analysis of a large set of paired second-trimester maternal serum and amniotic fluid samples was performed with the objective to 1) further elucidate the fetal metabolic fingerprint associated with trisomy 21 at mid-pregnancy and 2) investigate whether metabolic pathways dysregulated in trisomy 21 fetuses offer potential mechanisms of associated disorders. We used untargeted high-resolution metabolomic analysis based on a dual liquid chromatography setup. Data were obtained from 39 pairs of maternal serum and amniotic fluid samples from trisomy 21 pregnancies and from 80 karyotypically normal pregnancy control sample pairs. Discriminatory features were identified in both biofluids using partial least squares discriminant analysis and variable importance in projection scores after adjusting for significant covariates. These features were then used as input for metabolic pathway enrichment analysis using the program Mummichog. Feature selection based on results from the amniotic fluid samples and subsequent pathway analysis showed a complex and extensive set of perturbations associated with trisomy 21. Results indicated dysregulation of multiple pathways. The top ranked among these (p<0.001) were related to steroid metabolism, lipid metabolism, nucleotide metabolism, and amino acid metabolism. Parallel analyses are currently being conducted on the maternal serum samples to detect possible environmental exposures associated with trisomy 21 pregnancies. Overall, results revealed a broad array of metabolic perturbations in second-trimester trisomy 21 amniotic fluid. These offer novel insight into possible fetal origins of the cognitive impairment, agerelated neurodegeneration, and associated birth defects. This untargeted analytical platform will lay a foundation for follow-up targeted studies to confirm metabolic associations of interest and their role in phenotypic outcome pathogenesis.

PLENARY LECTURE

A disrupted mechanism of memory and potential biomarker in Down syndrome Paul Worley

Johns Hopkins University School of Medicine, USA

The Worley laboratory examines mechanisms of protein-synthesis dependent memory that are mediated by cellular immediate early genes (IEGs) acting directly at excitatory synapses. In parallel studies examining the contribution of these mechanisms to the pathophysiology of Alzheimer's disease (AD) and Down syndrome (DS), we find a shared mechanism of reduced IEG expression in brain of DS (mean age 28) and AD (mean age 83) individuals. CSF levels distinguish AD from controls and correlate with measures of hippocampal volume and cognitive status. Implications for understanding disease and ongoing efforts to establish bioassays will be described.

SESSION 5 Distinct memory phenotypes in Down syndrome: Implication for cognitive treatment

DISSOCIABLE SYSTEMS OF MEMORY IN DOWN SYNDROME Stefano Vicari¹ ¹Head of Child Neuropsychiatric Unit Department of Neuroscience, Research Institute Children's Hospital Bambino Gesù Piazza Sant'Onofrio 4, I-00165, Rome (Italy)

Memory is one of the most important aspects of cognition affected in individuals with Down Syndrome (DS), which seriously interferes with their possibility of learning and modifying behavior on the basis of experience. Based on this assumption, a large body of studies aimed at clarifying whether the impairment in DS affects all components of the memory architecture or whether some components are more disorganized than others. Several reviews have established children with DS are poor in tasks measuring immediate memory for verbal material, while their immediate memory for visuospatial material is relatively better. However, generalized problems on working memory tasks, requiring simultaneous processing and storage are reported. As concerns long-term memory, our earlier studies reported a widespread deficit in the explicit domain compared to the implicit domain, with a relatively proficient priming effect and procedural learning. Within the explicit domain, verbal semantic and episodic memory are particularly poor, while episodic learning of visual-spatial sequences is superior to visual-object patterns. Recently, in a study on observational learning, we found that children and adolescents with DS do not take advantage of observing another person performing a task (requiring more explicit abilities) but are efficient as controls in detecting a sequence by trial and error (requiring more implicit and procedural learning abilities). Even if memory impairment in DS seems large and widespread, there are some relatively spared domains, as implicit and procedural memory. This evidence has important implications for rehabilitative purposes and may help in improving learning strategies of individuals with DS.

DECIPHERING DISTINCT "HIPPOCAMPUS-DEPENDENT' SPATIAL MEMORY PROCESSES IN DOWN SYNDROME

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We have shown that individuals with Down syndrome (DS) are generally impaired at using a "hippocampus-dependent" allocentric representation to solve a spatial memory task requiring participants to locate three goals among 12 locations distributed in an open-field environment. Nevertheless, we found significant individual variation: 40% of DS individuals were unable to solve aspects of the task requiring low spatial resolution abilities; 40% of DS individuals were able to solve aspects of the task requiring low spatial resolution abilities but failed to solve aspects of the task requiring high resolution abilities; 20% of DS individuals were able to solve aspects the task requiring high resolution abilities. However, the design of our task, including three goals among 12 locations, may not have enabled all participants to demonstrate their low-resolution spatial abilities. We therefore tested DS individuals in two "hippocampus-dependent" allocentric tasks requiring low-resolution abilities. The first required participants to locate one goal among four locations distributed in an open-field environment. The second required blindfolded participants to find the locations of four different objects after an experimenter-guided exploration of these objects in absence of visual information. Preliminary findings suggest that DS individuals are able to solve lowresolution "hippocampus-dependent" spatial tasks with or without vision. Together with our previous findings, these results suggest that DS individuals may exhibit relatively preserved

performance in low-resolution tasks dependent on the function of the CA1 region of the hippocampus, and be more greatly impaired at solving high-resolution tasks dependent on the function of the dentate gyrus.

EXAMINING RECALL MEMORY AND THE FLEXIBLE APPLICATION OF LEARNED INFORMATION BY CHILDREN WITH DOWN SYNDROME Angela F. Lukowski¹

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The ability to recall the past is undeniably important: recall memory allows us to report on the episodes of our lives, from the mundane ("I had a chicken salad sandwich for lunch yesterday") to the significant ("the first time I held my newborn daughter was best moment of my life"). A cognitive function that is arguably even more important, however, is the ability to flexibly apply learned information across contexts and cues. This basic cognitive capacity ensures that individuals do not have to learn anew about every item in the environment when it is encountered in new contexts or in different variants. Understanding the emergence and development of recall memory and generalization abilities in children with Down syndrome (DS) is of critical importance to maximize to effectiveness of the intervention programs in which they participate. Such research is necessary because these basic cognitive abilities are recruited each and every time children participate in invention programs: children must encode what is presented to them, remember learned information over the long term, and apply their knowledge in various contexts and across different exemplars. Despite the importance of this work, relatively little basic science research has been conducted to date with the goal of informing the effectiveness of the intervention programs in which children with DS participate. As such, existing interventions may not be well-suited to promoting long-term retention of learned information and the flexible application of knowledge across contexts and/or cues. The proposed talk will (1) examine basic cognitive processes associated with recall memory and generalization across cues and/or contexts in children with DS and neurotypical controls matched on developmental age and (2) discuss potential moderating variables that may be of therapeutic or clinical relevance to children with DS, with the long-term goal of providing data-driven recommendations as to the conditions under which young children with DS obtain the most benefit from the intervention programs in which they participate.

SESSION 6. Novel mechanisms in Down syndrome pathophysiology. Possible new therapeutic targets

CHRONIC SUPPRESSION OF MONOACYLGLYCEROL LIPASE IMPROVES ADULT NEUROGENESIS IN THE DENTATE GYRUS OF AGED TS65DN MICE

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Chronic treatment with the selective monoacylglycerol lipase (MAGL) inhibitor JZL184 restored hippocampal long-term potentiation and improved cognition of aged Ts65Dn mice, the most studied genetic model of Down syndrome (DS) (Lysenko et al, 2014). To assess

possible mechanisms responsible for these improvements, here we examined the effects of JZL184 treatment on adult neurogenesis in the Ts65Dn dentate gyrus (DG). JZL184 (8 µg/kg, i.p.) or vehicle were injected in 9 months old trisomic and control euploid (2N) mice once a day during 20 days. BrdU was injected on days 11-14 of the JZL184 treatment. Total number and density of BrdU-positive cells were significantly reduced in the vehicle-treated Ts65Dn mice indicating reduced adult neurogenesis. JZL184 treatment increased the rate of adult neurogenesis in Ts65Dn but not in 2N mice. Reduced neurogenesis in Ts65Dn DG was accompanied by profound changes in morphological parameters: total volume of the granule cell layer (GCL) was reduced, and the lengths of both the superior and the inferior DG blades were diminished. JZL184 treatment fully restored these morphological parameters in Ts65Dn mice, but had no effect in 2N mice. Finally, rate of apoptosis was assessed by measuring density of the activated caspase 3 (AC3) – immunopositive cells. The AC3 cell density was not different in Ts65Dn vs. 2N mice, and it was not affected by the JZL184 treatment. Thus, chronic treatment of aged Ts65Dn mice with the selective MAGL inhibitor JZL184 improved the rate of DG adult neurogenesis and restored morphological parameters of the GCL in DG. Together with our previous data, these results show that JZL184 treatment have multiple beneficial effects in the Ts65Dn model of DS and can be regarded as a prospective approach for pharmacotherapy of cognitive impairment in DS. Supported by The Jerome Lejeune Foundation (Grant FJL #1483).

LIPID METABOLISM IS RESTRAINED IN A CELLULAR MODEL OF DOWN'S SYNDROME. ROLE OF OLEIC ACID AS THERAPEUTICAL TARGET

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Aberrant formation of the cerebral cortex could be attributed to the lack of suitable substrates that direct the migration of neurons. Oleic acid is a neurotrophic factor that promotes neuronal differentiation and increases the level of proteins implicated in their differentiation as MAP (dendritic growth marker protein) or GAP-43 (growth axonal marker protein). Furthermore, it has recently been shown that it induces migration and formation of new synapses in euploid cells. Down's syndrome is a genetic disease characterized by the intellectual disability. It is primarily a consequence of alterations in neurogenesis, neuronal differentiation, myelination, dendritogenesis and synaptogenesis during embryonic and development. We propose that oleic acid effect, as neurotrophic factor is dependent of membrane lipid composition. As many of the signal transduction pathways involved in synaptic plasticity depend on the lipid environment which carries the signal to the nucleus, the difference in the composition of the membrane may be essential to understand why oleic acid promotes higher cell plasticity in euploid than in trisomic cells. In addition, we also hypothesize that DYRK1A overexpression may be modulating the composition of the plasma membrane either directly by phosphorylation of synaptic vesicles or by altering the activity of the cytoskeleton.

DESIGNER RECEPTORS REVEAL AN IMPORTANT ROLE FOR NORADRENERGIC SYSTEMS IN DOWN SYNDROME PATHOLOGY.

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Knoebel Institute for Healthy Aging (KIHA), University of Denver. Denver, CO, USA.

Down syndrome (DS) is the most common cause of genetically determined intellectual disability in the United States, affecting approximately 1 in 700 live births and an estimated 350.000 Americans. A close association between DS and Alzheimer's disease (AD) has been established, and this has become a paramount concern since improved medical care has led to increased life expectancy, with an average life span of close to 60 years of age. Individuals with DS exhibit AD neuropathological hallmarks including amyloid plagues and neurofibrillary tangles as early as in their 30s. AD pathology may develop early in life, and therefore could be the target for neuroprotection therapies. However, little is known about mechanisms for the development of memory impairment and AD pathology in those with DS. We have utilized a mouse model of Down syndrome, Ts65Dn mice, as well as a novel chemogenetic tool, Designer Receptors (DREADDs), to examine the role of locus coeruleus (LC) noradrenergic (NE) neurons for AD pathology in DS. These mice have many similarities with DS in humans, showing AD-like pathology in the brain, and progressive memory loss with aging. LC-NE neurons degenerate early in AD, and enhancement of the NE transmitter system may lead to novel treatment options for dementia in DS with AD. The NE neurons are highly involved in regulating attention and executive dysfunction and are known to regulate the expression of brain-derived neurotrophic factor (BDNF), a protein involved in memory and learning processes. Our studies demonstrated that administration of stimulatory DREADDs (hM3Dg) via AAV stereotaxic injection under a promoter specific for LC-NE neurons gave rise to increased performance in a novel object and a water radial arm maze, coupled with decreased hyperactivity and reduced expression of B1-adrenoreceptors in the hippocampus of middle-aged Ts65Dn mice. Further, administration of the inhibitory DREADD hM4Di gave rise to the opposite effects in younger Ts65Dn mice, as well as in age-matched normosomic control mice. These findings strongly point to a significant contribution of the degenerating LC-NE neurons to memory loss in this DS model, and holds promise for development of NE enhancing therapy in humans with DS as they age. Supported by a grant from Alzheimer Association (DSADIIP-13-284845).

SESSION 7 Clinical Trials

DEVELOPMENT OF BASMISANIL FOR INTELLECTUAL DISABILITY ASSOCIATED WITH DOWN SYNDROME: RESULTS, CHALLENGES AND LESSONS LEARNT FROM THE ROCHE CLINICAL TRIALS

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Increased GABA-mediated inhibition has been proposed as a mechanism underlying deficient cognition in Down syndrome (DS). Basmisanil is a novel selective GABA_Aa5 NAM that is hypothesized to improve learning and memory deficits associated with DS. The primary objective of the phase 2 trial was to evaluate the safety and efficacy of basmisanil in young adults with DS after 6 months of treatment. In this multicenter, randomized, doubleblind, placebo-controlled study, young adults with DS were randomized to receive either placebo, 120mg or 240mg basmisanil BID for 26 weeks. EEG recordings were conducted as a safety and pharmacodynamic tool. Responders were defined as showing improvement in both, cognition (RBANS word list tasks) and functioning (CGI-I or VABS composite scores). 156 participants completed the study (drop-out rate of 7%). Overall, the incidence of AE associated with basmisanil was similar to placebo. There were no relevant changes in any safety parameters. The gEEG analysis revealed treatment-related increases ~4 Hz, p=0.022 and decreases in ~20 Hz, p=0.001. After 6 months of treatment, 29%, 20% and 25% met the responder criteria, for the placebo, 120 and 240mg group respectively. There was no statistically significant change from baseline in favor of basmisanil for the VABS composite or domain scores and no difference between the treatment groups in CGI-I (range: 3.1 -3.5). No consistent trends of improvement with basmisanil were observed across the word list tasks or secondary measures. No age differences in changes from baseline were noticed in any scale. Basmisanil was overall well-tolerated, and target engagement was demonstrated. However, no evidence of clinical efficacy based on measures used was observed. Key highlights, challenges and lessons learned will be discussed. Despite these results, our study is invaluable in paving way for trials in neurodevelopmental disorders and may serve as a model for future trials.

SAFETY AND EFFICACY OF COGNITIVE TRAINING PLUS EPIGALLOCATECHIN-3-GALLATE IN YOUNG ADULTS WITH DOWN SYNDROME (TESDAD STUDY)

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Preclinical studies suggest that modulating DYRk1A activity with a green tea extract containing epigallocatechin-3-gallate (EGCG) would improve cognitive performance in young adults with Down's syndrome. We enrolled adults (aged 16-34 years) with Down syndrome from outpatient settings in a double blind, placebo-controlled, phase 2, single center trial (the TESDAD study). Participants were randomly assigned to receive EGCG (9 mg/kg per day) or placebo and cognitive training for 12 months. We followed-up participants for 6 months after treatment discontinuation. Participants, families, and researchers assessing the participants were masked to treatment allocation. The primary endpoint was cognitive improvement assessed with a battery of cognitive tests for episodic memory, executive function, and functional measurements. This trial is registered with ClinicalTrials.gov, number NCT01699711. EGCG and cognitive training for 12 months was significantly more effective than placebo and cognitive behavior. No differences were noted in adverse effects between the two treatment groups. Phase 3 trials with a larger population of individuals with Down's syndrome will be needed to assess and confirm the long-term

efficacy of EGCG and cognitive training. The TESDAD approach was proven to be effective also in improving cognitive performance and adaptive functionality in adults with Fragile X syndrome (the TESFX study). We are currently carrying out a multicenter study in Down syndrome pediatric population (6-12 years) administering EGCG, primarily designed at evaluating safety and secondarily efficacy (the PERSEUS study).

Funding from Jérôme Lejeune Foundation, Instituto de Salud Carlos III FEDER, MINECO, Generalitat de Catalunya.

PERSEUS: A FUTURE EXPLORATORY CLINICAL STUDY OF SAFETY AND EFFICACY OF EPIGALLOCATECHIN-3-GALLATE IN CHILDREN WITH DOWN SYNDROME

Cecile Cieuta-Walti MD¹; Rafael de la Torre, PharmD²; Silvia Sacco, PhD¹; Aida Maria Cuenca, PhD², Julien Dairou, PhD³, Nathalie Janel⁴, PhD. Mara Dierssen, MD, PhD².

(1) Institut Lejeune, Paris. (2) IMIM (Hospital del Mar Medical Research Institute) Integrative Pharmacology and systems Neuroscience research group, Barcelona. (3) Laboratoire de Chimie et Biochimie Pharmacologique et Toxicologiques, Université Paris Descartes, CNRS UMR8601 (4) Unité de Biologie Fonctionnelle & Adaptative, Université Paris Diderot-Paris 7, CNRS UMR 8251, Equipe processus dégénératifs, stress et vieillissement.

Background: The serine/threonine kinase DYRK1A is a gene overexpressed in Down Syndrome (DS) and considered to be a major contributor of cognitive dysfunctions. Epigallocatechin-3-gallate (EGCG) is a DYRK1A inhibitor and was associated with slight benefits in cognition and good tolerance in two clinical studies (TESDAD) realized in young adults with DS. Objectives: We hypothesized that because cerebral plasticity is maximal during childhood, we will have a better improvement of cognitive functions when EGCG is administered earlier in children with DS. Methods: Prof Janel and Dr. Dairou have realized a preclinical Study of Safety and efficacy Biomarkers of EGCG at three different doses in wildtype and transgenic DYRK1A mice. This preclinical study have shown that EGCG seems to be safe for hepatic and cardiac functions in mice and identified as the best dose (10 mg/kg/d) as the dose to give. With the TESDAD study group, we proposed to conduct together, a randomized, double bind, placebo-controlled, parallel groups, study in children (6-12 years) with DS (n=60). Patients will be randomized in two treatment conditions, dose 1 (10mg/kg/d) and placebo for 6 months. First we will evaluate safety and tolerability of EGCG in children with DS. The secondary objectives are to evaluate if EGCG improves cognitive performance and adaptive functionality in pediatric population with DS after 6 months of treatment.

TRANSCRANIAL DIRECT CURRENT STIMULATION IN HEALTHY ADULTS AND CHILDREN WITH DOWN SYNDROME

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High definition tDCS (HD-tDCS) enables noninvasive electrical stimulation of the brain. It has been shown to improve some cognitive functions in humans. The purpose of our research is to explore cognitive enhancing properties of HD-tDCS in children with Down

syndrome. Phase I was designed to study feasibility, tolerability, and safety of HD-tDCS applied over 2-4 different brain regions and administered daily for a total of 20 sessions in healthy adults. The purpose of Phase II is to study these parameters in 5-10 year old children with Down syndrome. Phase I has been completed and IRB approval has been obtained for Phase II. Five healthy adults were recruited (2 females, 3 males, mean age 23.4y). Subjects underwent physical and neurological examination, electrocardiogram, electroencephalogram and IMPACT test before study initiation, during the study and at completion of the study. Four networks were stimulated using HD-tDCS, left and right temporooccipital and left and right frontal. Sessions 1-10 included stimulation of both temporooccipital networks (1mA in week 1, 1.5 mA in week 2 over 20 min/network). Sessions 11-15 included 20 min long stimulations of all 4 networks at 1.5 mA/network. Sessions 16-20 included 2 stimulation cycles/day of all 4 networks at 1.5 mA/network. Only one network was stimulated at a given time point. All subjects completed the trial. Adverse events were tingling, transient redness, feeling of being stimulated for 2 hrs. after one session and one incident of headache. There were no abnormalities detected on EKG, EEG, physical and neurologic exam. The scores in the IMPACT test were similar before and after the 20 stimulation sessions. This pilot trial demonstrates that prolonged daily stimulation of multiple brain regions over 4 consecutive weeks using HD-tDCS is feasible and well tolerated in healthy adults.

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PHARMACOLOGICAL INTERVENTIONS TO IMPROVE COGNITION AND ADAPTIVE FUNCTIONING IN DOWN SYNDROME: STRIDES TO DATE

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Background: Significant advances have been made in the understanding of the unique cognitive and adaptive profiles in individuals with Down syndrome. While an increasing number of clinical trials have been developed for cognition in Down syndrome, there has been limited success to date in identifying effective interventions. Methods: We performed a literature review of the progression from pre-clinical studies with mouse models to human clinical trials research using pharmacological interventions to improve cognition and adaptive functioning in Down syndrome. Based on our group's collective experience in the field of Down syndrome research since the late 1990s, we also developed considerations for investigators when conducting human clinical trials and described strategies for the pharmaceutical industry to advance the field in drug discovery for Down syndrome. Results:

Our review indicated that despite the increased knowledge about cognition in DS, the body of research to date has significant limitations, including a focus on older study participants, limited information about reliability or suitability of study measures, and heterogeneity among individuals in study populations. Conclusions: Future research focusing on pharmaceutical interventions with younger study participants, development of outcome measures with increased sensitivity, and greater collaboration between industry, academia, advocacy, and regulatory groups will be important for addressing limitations from prior studies and developing potential effective interventions for cognition in Down syndrome.

PLENARY LECTURE. Modeling human neurodevelopment and neural developmental disorders using human induced pluripotent stem cells Guo-li Ming,

Johns Hopkins University School of Medicine USA

Cerebral organoids, three-dimensional cultures that model organogenesis of the brain, provide a new platform to investigate human brain development as well as diseases. Using engineered miniature bioreactors to better mimic the growth environment and enhance the nutrient supply, we have developed protocols to generate brain region-specific organoids from human iPSCs. Our forebrain-specific organoids recapitulate key features of human cortical development, and provide a platform to further understand molecular events and mechanisms underlying early brain development. I will also discuss how we can use this system to model brain disorders with a developmental origin

SESSION 8. Probing neural development and function in Down syndrome with induced pluripotent stem cell (iPSC) technology

TS21 IPSCS TO MODEL NEURODEVELOPMENT AND NEURODEGENERATION IN DS Anita Bhattacharyya, PhD

Senior Scientist, Waisman Center, University of Wisconsin-Madison, Madison WI USA With the advent of iPSC technology, we can now study early development of human neurons and their function. Skin or blood cells from individuals with DS can be reprogrammed into iPSCs and retain disease features. The basic steps of neuronal development can be analyzed through the differentiation of these iPSCs to neurons and glia, thus identifying steps that go awry in cells that harbor Ts21. Specific neuronal subtypes (e.g. excitatory or inhibitory cortical neurons) can be differentiated to study neuronal function and dysfunction caused by Ts21. The analyses of Ts21 iPSC-derived neurons allows us to better understand the neurobiological basis of human DS brain deficits, a critical step to intelligently design therapeutics to increase cognitive function in DS individuals. Pure populations of specific Ts21 neural cell types derived enable screening of pharmaceutical compounds on human cells, potentially accelerating drug discovery and advancing treatments.

CEREBRAL ORGANOIDS IN THE STUDY OF CENTRAL NERVOUS SYSTEM DEVELOPMENT IN DOWN SYNDROME

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To better understand the cellular and molecular processes associated with Down syndrome (DS) in the human central nervous system (CNS), we generated a model of early neuronal development using human induced pluripotent stem cells (IPSc) as a starting template. We obtained IPSc from an individual with DS and a line from an unrelated euploid individual. With some modifications to the method first described by Lancaster et al (Nature, 2013), we successfully generated human cerebral organoids from both cell lines and used them for imaging experiments examining markers of stem cell populations, mitotic features, and neuronal differentiation over a 45 day period spanning the cells in 2D culture as IPSCs, through induction into 3D embryoid bodies and neurospheres, and finally as expanding neuronal populations in organoids. We performed deep proteome profiling with label-free quantitation of samples taken at each stage in organoid production: a) IPSc growing in 2dimensional standard maintenance culture, b) embryoid bodies grown in suspension, c) neurospheres with fate-restricted neural progenitor populations and radial neuroectoderm, and d) organoids grown following embedding in extracellular matrix, cultured in suspension for 21 days. We quantified over 8,500 proteins in each sample and our proteomics analysis shows many proteins changing in significant abundance due to Trisomy 21, with alterations in members of Wnt and Notch signaling pathways, neurotransmitter metabolism, axon guidance, cell adhesion and extracellular matrix interactions. We also examined the effects of pharmacological inhibition of the protein kinase DYRK1A, located on the Down Syndrome Critical Region (DSCR), and observed changes in the proteome with drug treatment consistent with significant normalization effects on expression levels of several key signaling pathway members involved in neuronal differentiation and axon guidance. These data demonstrate the utility of IPSC-derived neuronal tissues and analysis of their in vitro developmental trajectories to study complex regulatory processes in neurodevelopment.

ILLUMINATING ASTROCYTE CALCIUM DYNAMICS IN A STEM CELL MODEL OF DOWN SYNDROME.

Lin Tian, PhD

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Down syndrome (DS) is a neurodevelopmental disorder caused by trisomy of chromosome 21 (Ts21). DS brains show various pathophysiological changes associated with the specific profile of intellectual disability, including changes in brain size and alterations in the number and/or the morphology of both neurons and astrocytes, and in local and long-range neuronal connectivity patterns. Research on DS using rodent models has been mostly neuron-centric and focused on the gene-dosage hypothesis by exploring the expression patterns and function of candidate genes. However, the mechanism by which the overdosed genes give rise to altered brain function is largely unknown. Though the neuronal networks form the "wiring" of the brain, glial cells guide the brain's development and support and modulate neurons. Precise communication between neurons and glial cells, especially, astrocytes, has been proposed to play critical roles in orchestrating higher brain functions. Advances in

induced pluripotent stem cell (iPSC) technology have facilitated new and promising approaches to studying diseases such as DS in the context of human cell biology. Recent studies using human iPSC-based models suggest both trophic and supporting roles of astrocytes in DS pathogenesis. However, key questions regarding human astrocyte function, such as the importance of intracellular calcium to healthy and diseased cellular and circuit phenotypes remain largely unexplored. Furthermore, direct investigation of the function of DS astroglia and their effect on neuronal global excitability has not been previously reported. Here, we used human iPSCs to generate neurons and astroglia, and combined this with the use of genetically encoded Ca²⁺ indicators to monitor cellular function. Compared to isogenic astroglia, DS astroglia exhibited more frequent spontaneous calcium fluctuations, which reduced the excitability of co-cultured neurons and promoted hyperactive synapse formation. These calcium fluctuations are regulated by S100B, a chromosome 21 protein, and associated molecular components. The suppressed neuronal activity was rescued by blocking either astrocytic calcium or adenosine-mediated astrocyteneuron communication. Our results suggest a novel mechanism by which DS cause altered neural circuitry and provide potential targets for therapeutics. Additionally, our study establishes an optical neurophysiological platform for studying human astrocyte function in developing neural circuits, beyond molecular analysis of trophic and supporting roles of astrocytes.

SESSION 9. Cross-species correspondence: dialogue between mouse and human phenotyping

THE CHALLENGES OF ALIGNING MOUSE MODELS OF DOWN SYNDROME AND HUMAN INFANT COGNITIVE STUDIES

Hana D'Souza^{1,2}, Dan Brady^{1,2}, Esha Massand^{1,2}, Denis Mareschal^{1,2}, Michael S. C. Thomas^{1,2}, Annette Karmiloff-Smith^{1,2}

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Down syndrome (DS) is the most prevalent neurodevelopmental disorder of known genetic origin associated with intellectual disability. Yet, the mechanisms that give rise to the cognitive phenotype associated with DS remain largely unknown. Several mouse models hold great promise for advancing our understanding of the etiology of cognitive profiles in humans with DS and may pave the way for more targeted interventions. However, the validity of each mouse model critically depends on how well the tasks used with the mice map onto cognitive processes of interest in humans. Yet, mouse modeling and human phenotyping are often done independently with little crosstalk between the two. We are aiming to bridge this gap by moving the designs of the memory tasks we are using to test human infants/toddlers with DS towards designs with mice. We tested object and object-in-place memory in 85 human infants/toddlers with DS (6-63 months) and 60 typically developing controls (4-52 months). To test object memory, children were familiarized with objects on screen and then tested on an array, which contained a novel object amongst these. To test object-in-place memory, children were familiarized with objects on screen and

then tested on an array in which two of the familiarized objects swapped their location. Although children with DS showed eye gaze patterns consistent with the ability to detect the change in both tasks, during the initial stages of learning in the object memory task their pattern was less pronounced than typically developing controls'. This is consistent with an interpretation that children with DS benefit from prolonged exposure of stimuli. We will discuss how an overlap between designs in tasks for humans and mice may deepen our understanding of the cognitive profiles associated with DS. We will also highlight the challenges of aligning tasks across species.

MEMORY PROCESSES IN MOUSE MODELS OF DOWN SYNDROME Mark Good

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Trisomy 21 is associated with cognitive deficits and changes in key brain regions linked to memory function. Considerable focus has been placed on trisomy 21 influences medial temporal lobe structures, such as the hippocampus. I shall discuss recent work from my laboratory that has examined the profile of cognitive changes in the Tc1 mouse model of Trisomy 21 and how learning-related neural network activity in the hippocampus and cortex (using immediate early gene expression) is affected by the mutation. In addition, I shall describe the behavioral effects of a putative cognitive enhancer, an AMPA receptor positive allosteric modulator (AMPA-R PAMs), on memory processes in Tc1 mice.

DECODING THE GENOTYPE-PHENOTYPE RELATIONSHIPS IN DOWN SYNDROME BY STUDYING NEW MODELS IN MOUSE AND RAT

Yann Herault^{1,2}, Claire Chevalier¹, Damien Maréchal², Marie-Christine Birling², Guillaume Pavlovic², Valérie Nalesso¹, Maria del Mar Muniz Moreno¹, Guillaume Pani¹, Thu Lan Nguyen^{1, 3}, Aline Dubos¹, Michel Roux¹, Véronique Brault¹, Arnaud Duchon¹,

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Introduction: According to the literature we hypothesized that the phenotypes observed in Down Syndrome (DS) patient results from the complex genetic interactions of several regions located on Hsa21 with key candidate genes such as DYRK1A. Methods: In order to test this hypothesis, we continue our effort to generate new DS models and we developed the CRISMERE strategy that can be used in mouse and rat (Birling et al., 2017). We also performed a standardized behavioral analysis of DS mouse models carrying duplications of different Hsa21 homologous regions in order to fill the gap in the phenotype–genotype relationship and start the comparison between mouse and rat models. To complete the study we carried out a transcriptome analysis of the hippocampus, a region of the brain involved in various learning and memory processes. Results: The CRISMERE method allows us to generate new mouse models and also rat DS. In addition we succeed in engineering the Ts65Dn mini-chromosome in order to remove the part non homologous to the Hsa21. The behavioral analysis using single, or combination of, trisomic mouse models unraveled the complexity of the genetic interactions involved in some phenotypes detected by the object recognition or the Y maze tests. The expression analysis confirms the

complexity of the mis-regulated pathways in the DS hippocampi, with different pathways altered depending on the trisomic region.Conclusion: The data generated here are challenging our current knowledge on DS and its impact on brain and cognitive functions. Such studies will lead to a better understanding of mechanisms controlling cognition and behavior in model organisms and in human and certainly how to define new preclinical multi-target treatments.

PLENARY LECTURE

Diana Bianchi

Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health USA

SESSION 10 Breakthrough/Oral Communication

A SPECIALIZED PRO-RESOLUTION MEDIATOR APPROACH TO CHRONIC INFLAMMATION IN THE TS65DN MOUSE MODEL OF DOWN SYNDROME

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Background: Alzheimer's disease (AD) occurs early in individuals with Down syndrome (DS) and progresses to near uniformity by the age of sixty. Chronic inflammation, including microglial activation and elevated proinflammatory cytokines, is a key hallmark of DS-AD and a primary therapeutic target. Inflammation is normally counter-regulated by specialized pro-resolving mediators (SPMs), which bind a special class of conserved G-protein coupled receptors that promote resolution processes. In vivo SPM therapy is in Phase II clinical trials but the therapeutic potential to augment chronic brain inflammation remains unexplored. Resolution factors in the DS brain are uncharacterized. Objective: To reveal recent studies of the therapeutic potential of Resolvin E1, a potent SPM, in the well-characterized DS mouse model, Ts65Dn. To evaluate resolution components in post mortem brains from individuals with DS-AD. Methods: At 8 months of age, Resolvin E1 (RvE1) or vehicle was delivered by subcutaneous mini-osmotic pumps for a 30 days period. At 9 months of age, behavioral tasks were employed to assess locomotion, short-term vs. long-term object discrimination and cue-based memory performance. Important resolution receptors, SPMrelated enzymes and microglia markers were quantified by immunostain. Proinflammatory cytokines (TNF- α , IL-1 β , IL-6, IL-12) were quantified with multiplex ELISA in serum or by classical western blot technique of brain region extracts. Results: Resolution receptors are more highly expressed in pathology-positive post mortem DS-AD brain sections. Chronic RvE1 treatment significantly enhances memory behavior tasks while normalizing open-field hyperactivity. Chronic RvE1 treatment also reduces peripheral inflammatory cytokines and brain microglial activation in Ts65Dn mice. Conclusions: Resolution receptors perturbations are correlated with pathological events in post mortem DS-AD brains. This suggests a potential involvement of resolution processes with chronic inflammation. The positive results

from our chronic RvE1 treatment in Ts65Dn mice suggest a safe clinically relevant therapy that could target chronic brain inflammation

MAPPING CONGENITAL HEART DEFECTS IN DOWN SYNDROME TO A MINIMUM OF 2 LOCI WITHIN A 26 GENE REGION

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Down syndrome is the most common genetic cause of congenital heart defects (CHD), particularly atrio-ventricular septal defects (AVSD). However, the precise genetic or mechanistic causes of these defects remain unclear. Using high-resolution episcopic microscopy (HREM) in embryonic hearts, which provides precise three-dimensional morphology of the developing hearts, we have established that a large duplication containing around 148 genes orthologous to Hsa21, results in CHDs whose typology closely resembles those observed in individuals with DS. In order to identify dosage-sensitive genes that when present in three copies cause CHD in DS, we have generated a high-resolution mapping panel of 14 new mouse strains with partial duplications or deletions for regions of mouse chromosome 16, orthologous to Hsa21. We used this mouse-mapping panel to investigate the cardiac defects in DS. We narrowed down the critical region for CHD in DS to a region containing 26 protein-coding genes (from *Dyrk1a* to *Zbtb21*) and we show that this region contains at least two dosage-sensitive loci required in three copies to cause CHD

A PAIR OF MATERNAL CHROMOSOMES DERIVED FROM MEIOTIC NONDISJUNCTION IN TRISOMY 21 AFFECTS NUCLEAR ARCHITECTURE AND TRANSCRIPTIONAL REGULATION

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Eukaryotic genomes are organized into complex higher-order structures within the nucleus, and the three-dimensional arrangement of chromosomes is functionally important for global gene regulation. The existence of supernumerary chromosome 21 in Down syndrome may perturb the nuclear architecture at different levels, which is normally optimized to maintain the physiological balance of gene expression. However, it has not been clearly elucidated whether and how aberrant configuration of chromosomes affects gene activities. To investigate the parental-origin-specific effects on chromosome organization and transcriptional regulation in trisomy 21, we performed three-dimensional fluorescent imaging analysis of chromosome-edited human induced pluripotent stem cells (iPSCs). We successfully distinguished the one paternal chromosome from the two copies of the maternal chromosome and identified their localization patterns in the nucleus, using an artificially generated partial trisomy iPSC line. We further introduced targeted chromosome elimination using chromosome-editing technologies and established three corrected disomy 21 iPSC lines in which each one of the three copies of chromosome 21 was selectively eliminated from the trisomy 21 iPSCs. We found that two copies of maternal chromosomes resulting from meiotic nondisjunction had a higher tendency to form an adjacent pair and were located relatively distant from the nuclear membrane, suggesting the conserved interaction between these homologous chromosomes. Intriguingly, gene expression profiling of these iPSC lines demonstrated that there were several genes whose expression levels were significantly upregulated only in the maternal alleles, despite the almost equal amounts of transcripts among each allele for other genes. These results suggest the unique effects of a pair of maternal chromosomes in trisomy 21, which may contribute to the pathological phenotype.

Reference: Omori S et al. Scientific Rep 2017; in press

EARLY ENDOSOME CLUSTERING IN DOWN SYNDROME REVEALED BY HIGH-RESOLUTION MICROSCOPY

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Early morphological alterations of subcellular organelles from the endo-lysosomal pathway in Alzheimer's disease (AD) and Down Syndrome (DS) were widely observed, notably an increase in size of early endosomes (EE). Neurons bearing enlarged EE have been described before amyloid pathology and clinical symptoms. Endosomal enlargement was also detected in peripheral cells from individuals with DS and AD patients, in the brain of mouse models of familial AD with mutations in the gene encoding APP and in the brain of Ts65Dn mice modeling DS. Despite the nanometric size range of EE, this phenotype was mainly investigated with conventional light microscopy. Here, we used super-resolution microscopy and ultrastructural imaging to further characterize the endosomal compartment in cellular and mouse models of DS, as well as in post-mortem brains from individuals with DS. We immunolabelled EE in cells from individuals with DS (lymphoblastoid cell lines, fibroblasts and isogenic neurons derived from induced pluripotent stem cell clones from an individual with a mosaic trisomy 21) and in basal forebrain cholinergic neurons (BFCNs) from Ts65Dn brains. In all models, confocal microscopy confirmed EE enlargement in DS when compared to controls, but electron microscopy revealed clusters of normal-sized EE, suggesting that enlarged EE are rather clustered EE. We next performed optical superresolution imaging of EE in human isogenic neurons derived from induced pluripotent stem cells and in post-mortem brains from individuals with DS. Super-resolution structured illumination microscopy observations revealed that apparently enlarged EE corresponded to clusters of normal-sized EE in the DS condition. Thus, we confirm the significance of EE dysfunction in DS. Using high resolution microscopies, we unveil the presence of aggregates of normal-sized EE rather than enlarged EE. This new result implies to redirect the effort made on the understanding of EE abnormalities and their implication in DS and AD pathogenesis.

TRANS-ACTING EPIGENETIC EFFECTS OF CHROMOSOMAL ANEUPLOIDIES: LESSONS FROM HUMAN TRISOMY 21

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Background/problem statement: An important line of post-genomic research seeks to understand how chromosomal aneuploidies can act in trans to alter epigenetic patterning across the genome. Objectives: We are studying the epigenetic consequences of trisomy 21 (Ts21) in Down syndrome (DS), asking whether these data can provide mechanistic insights, and whether altered patterns of DNA methylation play a biological role in DS. Methods: To identify changes in DNA methylation patterns (DS-DM) in blood and brain cells from DS compared to age-matched controls, we generated array-based and bisulfite sequencing data. We assessed correlations with gene expression by RNA-seq, and we are investigating phenotypic correlates of DS-DM, including mortality risk, in adults with DS. The findings are being further dissected using chromosomally engineered mouse models generated in the Yu laboratory (see linked Abstract). Results: We find recurrent, tissuespecific, DS-DM in regulatory sequences of specific sets of downstream target genes throughout the genome, some of which are differentially expressed. Bioinformatic enrichment analyses suggest a role for over-expressed chromosome 21-encoded transcription factors (TFs), including RUNX1 and ETS-family TFs, in shaping the patterns of DS-DM. Findings in a well characterized adult cohort suggest that DS-DM affecting RUNX1 may act in a compensatory manner to influence lifespan/mortality in DS.Conclusions: Our data point to a role for altered TF binding site occupancies in producing altered DNA methylation patterns in cells with Ts21. Phenotypic correlations in a cohort of individuals with DS suggest that DS-DM can act, at least in part, as a biologically compensatory mechanism. These findings may have broad relevance for trans-acting genetic-epigenetic interactions in situations ranging from human developmental syndromes to neoplasia.

Kerkel K, Schupf N, et al. (2010) PLoS Genet 6:e1001212. Mendioroz M, Do C, et al. (2015) Genome Biology, 16:263. Do C, Xing Z, et al. (2017) Epigenomics, 9(2):189-207.

DOWN SYNDROME-SPECIFIC EPIGENETIC PATTERNING IN MOUSE MODELS

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Background: The Tycko laboratory has found changes of DNA methylation patterns (DS-DM) in specific sets of downstream target genes in tissues and cells from individuals with Down syndrome (DS), compared to euploid individuals (reviewed in 1; see linked Abstract). The DS-DM genes are reproducible across independent human studies, but the mechanisms remain to be determined. Objectives: Our laboratory has generated chromosomally engineered mouse models of DS (reviewed in 2). We are using these models to ask (i) are the sets of DS-DM target loci similar in matched tissues from human DS and the mouse models?; (ii) can data from the mice reveal the identities of the transacting effector genes that produce DS-DM? Experimental Methods: We prepared samples from the cerebrum, and cerebral cortical grey matter, from three mouse models of DS, Dp(16)1Yey, Ts65Dn, and Dp(10)1Yey, which carry triplication of different Hsa21 syntenic regions, and wild-type controls. Genomic DNAs were analyzed by whole-genome bisulfite sequencing (WGBS) in the Tycko lab, and the results were compared with data from human DS and control brain tissues. Results: The human DS-DM signature is partly but significantly recapitulated in the mice, and enrichment analyses support a role for TF binding site occupancies in shaping the patterns of DS-DM. In addition, greater levels of hypermethylation are seen in Dp(10) than in Dp(16), which suggests a role for overexpression of methylation pathway genes, including Dnmt3I, which are located on the distal q-arm of Hsa21. Conclusions: The mouse can serve as a useful genetic model for dissecting the molecular mechanisms of DS-DM. The resulting mechanistic insights may turn out to be broadly relevant in biological situations with chromosomal or sub-chromosomal aneuploidies, ranging from developmental syndromes to cancers.

Do C, Xing Z, et al. (2017) Epigenomics 9:189-207.

Xing Z, Li Y, et al. (2016) Br Med Bull 120:111-122.

SCIENCE AND SOCIETY SYMPOSIUM

T21RS SCIENCE & SOCIETY SYMPOSIUM

Peter P. De Deyn^{1,2,*} (chairman), Diana Bianchi^{1,3}, Juan Fortea^{1,4}, Lotta Granholm^{1,5}, Cindy Lemere^{1,6}, Sebastian Videla^{1,4} and Alain D. Dekker^{1,2}

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Besides being the scientific network for the Down syndrome community, T21RS aims to be a source of scientifically-founded information. The T21RS Committee for Science & Society has been established to stimulate the interaction between researchers and Down syndrome societies. Chaired by prof. dr. Peter Paul De Deyn (Belgium/The Netherlands), the committee cooperates with local and (inter)national Down syndrome associations, provides updates on recent scientific discoveries via the T21RS Science & Society Bulletin, and

organizes the Science & Society Symposium. This Symposium aims to bring together scientists and Down syndrome associations from all over the world to get acquainted with each other, share thoughts and ideas, and discuss about research and future directions. First, Diana Bianchi will chair a debate between one family in favor of, and one family against participating in scientific research, focusing on the pros and cons of having a relative with Down syndrome participate in clinical research. Next, a sub-session will take place on medical policies, including four inspiring initiatives integrating care and research with social aspects for clients and their family members. Resembling the successful first edition of the Science & Society Symposium (2015, Paris), the lively Association Introduction Round is on the program again. In this round, Down syndrome associations from around the globe get a 3-minute platform to introduce themselves and give a taste of their great contributions to research and care. The committee is pleased to welcome the National Down Syndrome Society (USA), Global Down Syndrome (USA), Fondation Jérôme Lejeune (France), The Matthew Foundation (UK), Trisomie 21 France, Down's Syndrome Association UK, Band of Angels (USA), Alana (Brazil), Catalan Down Syndrome Foundation (Spain), Down Syndrome International (UK), Association Française pour la Recherche sur la Trisomie 21 (France), Down Syndrome Hungary, AMIPI-Bernard Vendre, (France) and Down Syndrome OPTIONs (USA).

PLENARY LECTURE

Biomarkers for dementia in Down syndrome Ira Lott University of California, Irvine CHOC Children's Hospital

SESSION 11 Horizon21 and DS1000 – European collaborations for studies of Alzheimer's disease in Down syndrome

CLINICAL DATA IN MULTI-CENTER STUDIES

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There is evidence of considerable variability in age of onset, presentation, and progression of Alzheimer's Disease (AD) in Down Syndrome (DS), which is far from understood. The high variability in clinical expression of AD in DS suggests that factors other than the amyloid precursor protein gene (genetic and environmental) may play a role. There may be several mechanisms that may explain the high variation in individuals with DS. Although necessary, very few longitudinal studies have been reported in DS, and no longitudinal multi-center studies. It is challenging combining clinical data, which have been collected using different protocols from available single-center cohorts in different countries. There is therefore a need for multi-center cohort studies, with cross-center harmonization of the procedures. Barriers to such research include the challenges in funding, and recruiting cohorts of people with DS and lack of reliable test-instruments. This presentation will cover these issues, as well as progress with harmonization between ongoing projects, and protocol recommendations for future multi-site studies. The overall aims are for better prevention, diagnosis, management, and ultimately, treatment of AD in people with DS.

NEUROIMAGING OF ALZHEIMER'S DISEASE IN DOWN SYNDROME

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OBJECTIVES: To characterise the neuropathological effects of fibrillar amyloid-beta (fA) in Alzheimer's disease (AD) in adults with Down syndrome (DS) and evaluate brain structural effects and clinical phenotype correlations. METHODS: Neuropsychological and clinical measures were obtained in conjunction with the quantitation and distribution of the deposition of brain fA using [11-C]-Pittsburgh Compound-B (PiB)-positron imaging tomography (PET) and magnetic resonance imaging (MRI) from a cross-section of 49 with DS aged 30 or over. Structural MRI was used to evaluate the effect of fA on brain morphology (volumetry and vertex-wise cortical thickness) and on "brain-predicted age" (using machine learning) when compared to healthy non-DS controls. RESULTS: With respect to age, fA deposition emerged at approximately 35 years (initially in striatum) and it then rapidly increased to appear in most parts of the brain and reach a plateau by the age of around 50 years. There was significant PiB-binding prior to cognitive or functional decline, but also a positive correlation with AD. Relative increases in cortical thickness and in the sizes of specific deep grey matter regions in the "fA -negative" group versus healthy controls was observed; reductions in cortical thickness in the "fAD-positive" group corresponding to areas associated with sporadic AD pathology were evident. The brainpredicted age of DS showed evidence of earlier ageing and fA -associated ageing. CONCLUSIONS: DS brain is susceptible to early onset of fA deposition, which supports the notion of early onset of AD pathology that correlates with dementia. Lifelong excess $A \square$ causes specific developmental cortical dysmorphology at sites that later develop AD pathology and early brain ageing.

Annus T., et al. 2017. *Neurobiol Aging* [IN PRESS]

Annus T., et al., 2017. *Neurobiol Aging.* 53:11-19.

Annus, T., et al., 2016. *Alzheimer's & Dementia*. 12(5):538-45

MULTIMODAL CSF AND IMAGING STUDIES DOWN SYNDROME Juan Fortea

Fundació Catalana Síndrome de Down / Hospital of Sant Pau, Barcelona, Spain Background: Down syndrome (DS) has been proposed as a genetic form of Alzheimer's Disease (AD). However, no studies have assessed the cerebrospinal fluid (CSF) and imaging correlates of AD and aging in DS. Our objective was to evaluate CSF and imaging biomarkers related to AD in DS and determine biomarker cut-offs. Methods: Subjects were recruited from the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI), a longitudinal cohort to study AD in DS. 68 subjects underwent a 3 Tesla structural MRI and a lumbar puncture (mean age: 41.32, 34.1% female), 22 subjects underwent a Florbetapir-PET. DS subjects were classified into a cognitive stable group (cs-DS, N=52) and an AD group (N=16). CSF core AD biomarkers (A β 42, Tau, pTau) levels were measured by ELISA. Cortical thickness (CTh) and normalized hippocampal volume (HV) were obtained using Freesurfer v5.1. We computed the mean CTh in a well-known AD signature map (Dickerson 2009). Mean florbetapir uptake was computed using Landau regions and normalized by the mean cerebellar uptake. We performed correlations and ROC analysis. Results: Age correlated with structural AD signature (r=-0.461, p<0.001), mean Florbetapir uptake (r=0.684, p<0.001), normalized HV (r=-0.598, p<0.001), CSF-Aβ42 (r=-0.614, p<0.001), CSF-Tau (r=0.625, p<0.001), and CSF-pTau (r=0.557, p<0.001). The resulting cut-off were 2.68 mm for structural AD signature (AUC=0.823, p<0.001, Se=0.75, Sp=0.75), 1.11 for mean florbetapir uptake (AUC=0.952, p=0.001, Se=0.86, Sp=0.93), 0.0043 for HV (AUC=0.932, p<0.001, Se=0.92 Sp=0.86), 4543pg/mL for CSF- Aβ42 (AUC=0.963, p<0.001, Se=0.92, Sp= 0.94), 2713pg/mL for CSF-Tau (AUC=0.811, p=0.001, Se= 0.75, Sp=0.75), and 53.3pg/mL CSF-pTau (AUC= 0.779, p=0.004, Se=0.75, Sp=0.70).

Conclusions: Neuroimaging and CSF biomarkers correlate with age. Cut-off of CSF and neuroimaging biomarkers differs from those in sporadic AD. Our data suggest that the pathophysiological process of AD can be detected in DS, however cut-offs should be adapted to this population.

SESSION 12 Breakthrough/Oral Communications

NEUROGENESIS AND MEMORY ENHANCEMENT FOLLOWING TREATMENT WITH AN AGONIST OF THE BDNF-TRKB RECEPTOR IN A MODEL OF DOWN SYNDROME

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Neurogenesis impairment starting from fetal life stages and dendritic hypotrophy are considered major determinants of cognitive disability in Down syndrome (DS). No therapies currently exist for intellectual disability in DS. Previous studies from our group have shown that perinatal treatment with fluoxetine, a selective serotonin reuptake inhibitor, fully restores brain development and cognitive performance in the Ts65Dn mouse model of DS. These beneficial effects were accompanied by an increase in the levels of brain-derived neurotrophic factor (BDNF), a neurotrophin that by binding to the TrkB receptor (TrkB-R), fosters neurogenesis and neuronal maturation. This suggests that BDNF may be an important determinant of the proneurogenic effect of fluoxetine. After this promising discovery we deem it important to find a therapeutic strategy that is as effective as fluoxetine but may pose fewer caveats for clinical application in children and pregnant women. A therapy based on BDNF systemic administration is impracticable due its poor blood-brain barrier penetration. Using small molecules that binds to its TrkB-R could circumvent this

problem. Based on these premises, the goal of our study was to establish whether early treatment with a naturally-occurring flavone that specifically binds to the TrkB-R (7,8-DHF) rescues the trisomy-linked neurodevelopmental defects. We found that neonatal treatment with 7,8-DHF from P3-P15 was able to increase neural precursor cells proliferation in the dentate gyrus of Ts65Dn mice. This effect was accompanied by an increase in dendritic spine density. Importantly, Ts65Dn mice, treated with 7,8-DHF from birth to adolescence (P3-P45) exhibited a large improvement in learning and restoration of hippocampus-dependent memory, as assessed with the Morris Water Maze. This study, in a mouse model of DS, provides novel evidence that treatment with 7,8-DHF positively impacts the neurodevelopmental defects characterizing DS and cognitive performance, thereby providing new prospects for the rescue of intellectual disability in DS.

TRISOMY 21 CAUSES A DEFICIT IN LYSOSOMAL CATHEPSINS AND ALTERS APP/AB PROCESSING, INDEPENDENTLY OF AN EXTRA COPY OF *APP*

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Background: Down syndrome (DS) increases the risk of Alzheimer disease (AD). Three copies of the chromosome 21 (Hsa21) gene *APP* are sufficient to cause early-onset AD but how trisomy of other Hsa21 genes influences disease development is unclear. Methods: To understand how Hsa21 genes other than *APP* affect APP and A β processing, we crossed the Tc1 model of Hsa21 trisomy, which is not functionally trisomic for *APP*, with the J20 *APP* transgenic model. We analyzed the progeny of this cross, using a combination of pulse-chase analysis, western blotting, immunohistochemistry, ELISA, mass-spectrometry, enzymatic assays and *in vivo* A β clearance study. Additionally we undertook behavioral phenotyping and an aging study to understand how trisomy of Hsa21-associated APP/A β processing changes effect learning and aging. We then went on to validate our proposed mechanism in patient fibroblasts and post-mortem brain material from people who have DS and AD pathology. Results: Here we show that trisomy of Hsa21 sequences in the Tc1

mouse model, other than *APP*, alter the metabolism of APP/A β . These changes decrease the soluble A β 38/42 ratio and are associated with an increase in A β aggregation and deposition, and this result in exacerbation of APP/A β -associated hyper-activity and specific deficits in two tests of short-term memory. These trisomy-associated changes in APP/A β metabolism occur independently of alterations in α -, β - or γ -secretase activity in the brain, or changes in the rate of extracellular A β -clearance from hippocampal interstitial fluid, but are associated with cysteine cathepsin deficits that occur independently of gross-enlargement of the endo-lysosomes. We also observe cysteine cathepsin deficits in DS patient fibroblasts and also in post-mortem brain material from people who have DS and AD pathology. Conclusions: We propose that trisomy Hsa21-associated cathepsin deficits are a novel AD-DS pathomechanism that alters APP/A β processing and may contribute to the development of AD in people who have DS.

THE EARLY ONSET OF BRAIN INSULIN RESISTANCE IN DOWN SYNDROME: A BRIDGE TOWARDS THE DEVELOPMENT OF ALZHEIMER-LIKE NEUROPATHOLOGY Eugenio, Barone¹, Antonella, Tramutola¹, Fabio, Di Domenico¹, Elizabeth, Head² and Marzia, Perluigi¹

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Background: A dysregulation of the insulin signaling with reduced downstream neuronal survival and plasticity mechanisms are fundamental abnormalities observed in Alzheimer Disease (AD) brain. This phenomenon, known as brain insulin resistance (BIR), is associated with poor cognitive performance and is driven by the uncoupling of insulin receptor (IR) from its direct substrate (IRS1). Objectives: Considering that Down syndrome (DS) and AD neuropathology shares many common features we were interested in understanding the metabolic side of neurodegeneration, i.e. BIR, in DS and how it might accelerate the progression to AD. Methods: We analyzed expression levels and activation of IR and IRS1 together with downstream targets including (i) MAPK (involved in the regulation of genes controlling synapses growth, neuronal maintenance and repair processes) and (ii) Akt (involved in the maintenance of synaptic plasticity, stress response and neuronal metabolism). In parallel specific regulators of the insulin signaling cascade including BVR-A, PTEN and Sirt1 have been also evaluated. Age-associated changes of APP processing/A production were investigated to understand any possible correlation with changes of insulin signaling. All these analyses were performed in the pre-frontal cortex of wild type and Ts65Dn mice at 1, 3, 9 and 18 months of age and in the pre-frontal cortex of human DS and DS/AD brain samples compared with their age-matched controls.Results: We observed increased IR activation together with IRS1 inhibition along with the aberrant activation of either Akt or MAPK in the presence of reduced activity of PTEN and Sirt1 in Ts65Dn mice compared with wild type mice at 1 month, thus suggesting that an uncoupling of the proteins belonging to the insulin signaling cascade occurs very early in DS. This picture persists with aging and it seems to be independent of $A \square$ levels. Intriguingly, similar observations have been made in both DS and DS/AD human brain confirming mice data. Conclusions: Based on these evidence, we suggest that markers of BIR rise earlier in DS compared with the

general population and may contribute to the cognitive impairment that ultimately results in AD. Therefore, therapeutic strategies aimed to restore insulin signaling may prove to be beneficial also in DS

PREMORBID IQ AS A PREDICTOR OF PERFORMANCE IN ASSESSMENTS OF CLINICAL DEMENTIA STATUS

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Background. Adults with Down syndrome (DS) are at high risk for Alzheimer's disease (AD). While diagnosis of early AD-related decline, referred to as "mild cognitive impairment (MCI)", is complicated by pre-existing impairments that vary substantially in severity among individuals with DS, two strategies have promise for informing diagnosis: (a) objective quantification of decline, requiring an established premorbid baseline, and (b) a single assessment at the time of concern (or risk defined by chronological age) that takes into account the severity of prior lifelong impairment. The objective of the present analyses is to evaluate the validity of these strategies, with pre-morbid IQ serving as the indicator of lifelong impairment. Methods. Adults with DS (Age \geq 40 years; IQ \geq 25) were assessed with a combination of direct cognitive testing and informant interviews at intervals of approximately 18 months. Following each assessment, dementia status (Aging "normally", MCI-DS, Dementia, Uncertain) was determined during consensus conferences that considered all available data. The present analyses focused on two consecutive assessments cycles for two subgroups: (a) one continuing to age "normally" (N = 137), and (b) a second transitioning from normal aging to incident MCI-DS (N = 141). Findings from seven measures identified a priori as most likely to be sensitive to incident MCI-DS were related to consensus classifications. Results. Clear group differences were present for both change and IQ-referenced dementia scores (Group X Time interaction Fs > 20, ps < .001, and ts > 5.0, ps < .0001, respectively), with one-time assessments performing as well as direct quantification of change. Conclusions. Results underscore the practical value of adult IQ assessment. While many factors have contributed to a decline in "routine" IQ testing during recent decades, it may be time to re-evaluate the benefits of having a valid premorbid IQ available.

NPTX2 AND COGNITIVE DYSFUNCTION IN ALZHEIMER'S DISEASE AND DOWN SYNDROME

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Synaptic dysfunction and cognitive failure are shared common features of Alzheimer's disease (AD) and Down syndrome (DS), yet the cause of cognitive dysfunction in AD and DS remains unknown. Neuronal pentraxin 2 (NPTX2), an immediate early gene expressed and secreted by excitatory neurons, can strengthen inhibitory circuits in a homeostatic response to increased neuronal activity by interacting with AMPA receptor subunit GluA4 at excitatory synapses on parvalbumin interneuron (PV-IN). In DS mouse model, we observed NPTX2 protein level is significantly reduced in Ts65Dn mice. In a mouse model of AD amyloidosis, Nptx2^{-/-} results in reduced GluA4 expression, disrupted rhythmicity, and increased pyramidal neuron excitability. We used carefully archived human brain and cerebrospinal fluid (CSF) samples, and found postmortem human AD cortex shows profound reductions of NPTX2 and coordinate reductions of GluA4, whereas NPTX2 was not reduced in brain of subjects who were cognitively normal at death but whose brains exhibit pathology typical of AD [asymptomatic AD (ASYMAD)]. Nptx2 protein and mRNA were also reduced in middle frontal gyrus of individuals with DS aged 19 y/o to 40 y/o. Older DS individuals with AD showed similar reduction of Nptx2 protein and mRNA in brains. Consistent with NPTX2 reduction, miRNAs that regulate Nptx2 mRNA were increased in AD and DS postmortem brains. NPTX2 is detected in human CSF by WB and ELISA. NPTX2 levels in human CSF are significantly reduced in patients with clinically diagnosed AD and shows robust correlations with cognitive performance and hippocampal volume. These findings implicate failure of adaptive control of pyramidal neuron-PV circuits as a pathophysiological mechanism contributing to cognitive failure in AD and DS.

BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA IN DOWN SYNDROME

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Background: People with Down syndrome (DS) face an extremely high risk to develop Alzheimer's disease (AD). Although Behavioural and Psychological Symptoms of Dementia (BPSD) are core features of dementia, they have been largely neglected in DS due to a lack of adapted assessment tools. Objective: To develop and validate the novel BPSD-DS evaluation scale for the comprehensive assessment of BPSD in DS, i.e. to disentangle behavioral changes from characteristic behavior that has always been present in an individual. Methods: In a multidisciplinary collaboration of major academic research centers and intellectual disability institutions in the Netherlands and Europe we developed the BPSD-DS scale, taking the pre-existing ID and behavior into account. After multiple

optimization rounds, the scale has been cross-sectionally validated in 2016 including a total of 281 DS individuals (with AD, with questionable AD, and without AD). We adopted an informant interview approach: trained clinicians/psychologists interviewed the key informant(s) of the DS individual to score frequency, severity and caregiver burden of each behavioral item. Results: Twelve main behavioral clusters were evaluated between the three groups: 1) anxiety & nervousness, 2) sleep disturbances, 3) irritability, 4) obstinacy, 5) agitation & stereotypical behavior, 6) aggression, 7) apathy & spontaneity, 8) depressive symptoms, 9) delusions, 10) hallucinations, 11) disinhibition & sexual behavior, and 12) eating and drinking behavior. Primary outcome measures are behavioral changes over time (last six months vs. characteristic behavior in the past). The first promising results of this large cross-sectional cohort study of behaviorally characterized DS individuals will be presented, including, amongst others, a significant dementia-related increase in anxious behavior. Conclusions: Administration of the novel BPSD-DS scale is promising and strongly contributes to the comprehensive assessment of BPSD in DS, which is of utmost importance for understanding of changes by caregivers, and enabling adaptive caregiving and therapeutic interventions.

SESSION 13 Brain imaging biomarkers of dementia in Down syndrome

BRAIN IMAGING MEASURES OF AMYLOID DEPOSITION IN ADULTS WITH DOWN SYNDROME

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Individuals with Down syndrome (DS) are at high risk for developing Alzheimer's Disease (AD) due to the presence of an extra copy of chromosome 21, which codes for the A-beta precursor protein (APP) gene. Positron emission tomography (PET) is a powerful neuroimaging method that can be used to measure the level of A-beta burden in the brain. These A-beta levels can then be related to MRI measured structural changes in the brain and measures of cognition and behavior to further our understanding of AD neuropathology and symptomatology. In this presentation, we will discuss the findings of a collaborative project between the Universities of Pittsburgh and Wisconsin-Madison to measure and document amyloid deposition in adults with DS without symptoms of dementia (age > 30 yrs.) and follow these individuals at 3-year intervals to understand the course of amyloid deposition and its effect on functioning over time. These data provided the foundation for a newly launched larger multi-center trial to gather biofluid and neuroimaging measures as biomarkers for AD in the DS population. These biomarkers will provide valuable information to deepen our understanding of the pathophysiology of AD in Down syndrome and may have additional implications for the general population.

MAGNETIC RESONANCE SPECTROSCOPY AND DEMENTIA IN DOWN SYNDROME Ai-Ling Lin¹

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People with Down syndrome (DS) develop Alzheimer disease (AD) neuropathology by the time they reach 40 years of age. However, dementia may not be observable until people are in their 50's and some people with DS do not develop dementia at all. To determine if proton magnetic resonance spectroscopy (1H-MRS) detects differences in dementia status in adults with DS, we used 1H-MRS. Neuronal and glial metabolites were measured in the posterior cingulate cortex in 22 adults with DS and in 15 age- and gender-matched healthy controls (CTL). We evaluated associations between 1H-MRS metabolites and cognition among DS participants. Neuronal biomarkers, including N-acetylaspartate (NAA) and glutamate-glutamine complex (Glx), were significantly lower in people with DS and AD (DSAD) when compared to non-demented DS and CTL. Neuronal biomarkers may reflect dementia status in DS. In contrast, all DS participants had significantly higher myo-inositol (MI), a putative glial biomarker, compared to CTL. Our data indicate that there may be an overall higher glial inflammatory component in DS compared to CTL prior to and possibly independent of developing dementia. When computing the NAA to MI ratio, we found that presence or absence of dementia could be distinguished in DS. In addition, NAA, GIx, and NAA/MI in all DS participants were correlated with scores from the Brief Praxis Test and the Severe Impairment Battery. 1H-MRS may be a useful diagnostic tool in future longitudinal studies to measure AD progression in persons with DS. In particular, NAA and the NAA/MI ratio are sensitive to the functional status of adults with DS, including prior to dementia.

CORRELATING IMAGING TO PLASMA BIOMARKERS IN DOWN SYNDROME Michael Raffi¹

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Background: Individuals with Down syndrome (DS) represent a population at high risk for Alzheimer's disease (AD). Tau pathology, in addition to amyloid plaque deposition is a hallmark of AD. Using the tau PET agent 18F-AV-1451, we examined retention patterns in adults with DS as part of the Down Syndrome Biomarker Initiative (DSBI) in order to better understand the relationship between tau pathology and age, amyloid deposition, neurodegeneration (as assessed by structural MRI and FDG PET) and cognitive performance in adults with DS. We also sought to differentiate, using image analysis, ADspecific changes from DS-specific brain changes. Methods: Tau PET (AV1451) scans were acquired for 9 of the DSBI participants (ages 30-60) at year 2, and T1 MRI scans were acquired at year 1 and year 2 for 11 of the participants, adding to FDG PET, T1 MRI, and amyloid PET (AV45) scans previously acquired at baseline. All scans were spatially transformed to a common template, which also produced modulated gray MRI segments for analysis. Tau scans were intensity normalized to gray cerebellum, and regions of interest (ROIs) corresponding to Braak staging were measured. Tau scans were also evaluated using a multivariate tau classifier that determines a single numeric score corresponding to a subject's expression of an overall tau deposition pattern typical of AD. ROI values and numeric scores corresponding to each subject's expression of patterns differentiating groups, were examined in relationship to one another and to age, amyloid status, and cognitive and functional scores. Results: Of three Am- or threshold subjects who had tau

scans, all were negative for tau. Of the six Am+ subjects who had tau scans available, three had tau deposition in regions associated with Braak stages I-VI, two with stages I-V (one hippocampal sparing), and one with stages I-II. Amyloid and tau both correlated with age. The MRI analysis produced two distinct patterns. The first pattern differentiated DS from both NL and AD, did not correlate with age or amyloid status, and was longitudinally stable, while the second pattern differentiated NL- from AD+. Tau PET scores correlated with several cognitive and functional measures including Observer Memory Questionnaire – Parent Form (OMQ-PF), Total Memory, and Daily Living (R = -0.72, -0.64, -0.47, respectively), as did the MRI and FDG PET findings. Conclusions: Despite a limited sample size, results suggest that in DS adults, tau accumulation is associated with amyloid positivity and age, and with progressive neurodegeneration as measured using FDG (hypometabolism) and MRI (atrophy). Tau accumulation correlates with clinical decline in these subjects, as do AD-specific aspects of hypometabolism and atrophy that can be dissociated from DS effects using optimized multivariate image classifiers.

Disclosure: Dr. Rafii has received research grant support from AC Immune, Accera, Avid, Baxter, Bristol Myers Squibb, Dana Foundation, Elan, Genentech, Janssen, Eli Lilly, Lumind Foundation, Merck, Roche and the National Institutes of Health.

SESSION 14. Biomarkers of Alzheimer's disease in Down syndrome

STUDY OF CEREBROSPINAL FLUID BIOMARKERS IN A COHORT OF DOWN SYNDROME PATIENTS

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Background: Down syndrome (DS) is a genetically determined form of Alzheimer disease (AD). The AD pathophysiological process can be studied using cerebrospinal fluid (CSF) biomarkers however there might be differences between DS and sporadic AD. Methods. Core AD (A β 42, total-tau, and phospho-tau), other amyloid- β protein precursor (APP) processing (A β 40, sAPP β , β -secretase activity), and inflammatory (YKL-40) biomarkers were determined in CSF from a cohort of subjects with DS with (dDS) and without cognitive decline (ndDS). Results were compared with data from sporadic AD patients and healthy controls (HC). The correlation between age and biomarkers in the DS cohort was analyzed. Results: We studied 83 subjects with DS: 34 dDS (mean age 52.4) and 49 ndDS (mean age 36.6); 48 patients with sporadic AD (mean age 71.4); and 67 HC (mean age 59.1). In the DS cohort, we found a correlation between age and core AD biomarkers and YKL-40. ndDS subjects had lower β -secretase activity and YKL-40 than HC, but no differences on other biomarkers were detected. dDS patients had lower A β 42 and higher tau, p-tau and YKL-40 levels than ndDS patients. In dDS, a lower β -secretase activity than in AD was the only difference detected. Conclusions: An age-associated AD pathophysiological process can be

detected in ndDS, supporting the conceptualization of DS as a form of genetically determined AD. The CSF AD core biomarkers are similar in dDS subjects and sporadic AD, but other markers like β -secretase activity or YKL-40 might reflect differences in APP processing and in the neuroinflammatory profile in DS.

DOWN SYNDROME INDIVIDUALS WITH ALZHEIMER'S DISEASE HAVE A DISTINCT NEUROINFLAMMATORY PHENOTPE COMPARED TO SPORADIC ALZHEIMER'S DISEASE

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Down syndrome (DS) is the most common genetic cause of intellectual disability and is primarily caused by the triplication of chromosome 21. The overexpression of APP may be sufficient to drive Alzheimer's disease (AD) neuropathology that is observed in virtually all individuals with DS by the age of 40 years. There is relatively little information about inflammation in the DS brain and how the genetics of DS may alter inflammatory responses and modify the course of AD pathogenesis in this disorder. Using the macrophage classification system of M1, M2a, M2b and M2c inflammatory phenotypes we have shown that the early stages of AD are associated with a bias toward an M1 or M2a phenotype. In later stages of AD, markers of M1, M2a and M2c are elevated. We now report the inflammatory phenotype in a DS autopsy series to compare this with the progression in sporadic AD. Tissue from young DS cases (under 40 years of age, pre-AD) show a bias toward M1 and M2b states with little M2a or M2c observed. Older DS cases (over 40 with AD pathology) show a distinct bias toward an M2b phenotype. Importantly, this is distinct from sporadic AD. Biomarkers are essential to distinguish these distinct phenotypes in individuals, and track them as disease progresses. Also, biomarkers will serve as key indicators for change in clinical trials and could be early predictors of adverse events. We are measuring inflammatory markers in longitudinal serum samples from aging DS individuals to track changes in these markers over time. Stimulated by immune complex activation of microglial cells and toll-like receptor activation, the M2b phenotype represents a unique neuroinflammatory state in diseased brain and may have significant implications for therapeutic intervention for persons with DS.

Disclosure: Donna M Wilcock is a paid consultant of AC Immune and Alector Inc

ANALYSIS OF DYRK1A AND MARKERS ASSOCIATED WITH DYRK1A LEVEL IN PLASMA AND LYMPHOBLASTOID CELL LINES FROM ALZHEIMER DISEASE AND DOWN SYNDROME PATIENTS

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The sequence of events leading to Alzheimer's disease (AD) and the exact pathways involved continue to be a source of debate, since beyond the prominent role of amyloid and tau pathology, further factors (e.g. vascular disease, cognitive reserve) modify the impact of neuropathological alterations on clinical symptoms. Identification and validation of cost-

effective, non-invasive methods to identify early AD and to monitor treatment effects in mildmoderate AD patients could revolutionize current clinical diagnostic workup and research approaches especially within the framework of developing causal therapies. Dementia, associated with AB plaques and neurofibrillary tangles, is very prevalent in people with Down's syndrome (DS). It is a common form of dementia in individuals with DS younger than 50 years. Almost 40% of people with DS who are 60 years or older suffer from dementia. The serine/threonine kinase DYRK1A could be a link between amyloid beta and tau driven hypotheses. We measured plasma DYRK1A levels in individuals with AD that present either mild cognitive impairment or dementia compared from control subjects. In human plasma from two independent cohorts, we have shown that decreased levels of plasma DYRK1A are associated with established markers of AD, such as the presence of cognitive deficits and positive amyloid imaging, and plasma levels of other markers previously demonstrated to be related to DYRK1A levels. ROC curves and logistic regression analyses were used to analyse the combined assessment of DYRK1A and markers related to DYRK1A levels. Moreover, we also found that DYRK1A levels were significantly lower in lymphoblastoid cell lines (LCLs) from AD patients as compared to agematched controls. We therefore analysed DYRK1A levels in LCLs from patients with DS and found a decreased level of DYRK1A in patients with DS and dementia compared to DS patients without dementia. This decreased level was also correlated with markers related to DYRK1A levels. Taken together, the blood level of DYRK1A and markers related to DYRK1A levels could offer risk assessment utility to predict cognitive decline in the general population and in DS patients.

POSTER SESSION I

#1

APPLYING THE CANTAB BASED VISUAL DISCRIMINATION TEST TO EVALUATE HIPPOCAMPAL LEARNING IN MOUSE MODELS OF DOWN SYNDROME

Faycal Guedj¹ (Primary Presenter), Ashley Siegel¹, Diana Bianchi¹

¹Medical Genetics Branch, National Human Genome Research Institute-NIH, Bethesda, USA People with DS have hypoplasia of the frontal cortex, hippocampus and cerebellum. The computer-based Cambridge Neuropsychological Test Automated Battery (CANTAB) has shown that cognitive tasks associated with these regions are impaired in individuals with DS. Here we translated the CANTAB visual discrimination (VD) task to analyze hippocampal learning in the Dp16, Ts65Dn and Ts1Cje mouse models of DS. During pre-training (stages 1-5), three-month old mice (Dp16/B6=14, Ts65Dn/F1=12, Ts1Cje/B6=12, and Euploid [Eup] controls) were trained to press a "Flower" image on a touchscreen in exchange for a milkshake reward. To advance to VD the mice had to discriminate between two novel images ("Airplane," associated with a reward and "Spider," with no reward). No food or water deprivation was used prior to testing. The number of days to reach 70% correct answers and percent of correct responses was analyzed. All Ts1Cje, Dp16 and Eup mice reached Stage 5 in less than 50 days of training. No differences between genotypes were found in % of correct responses. Five Ts65Dn and 1 Eup animals reached Stage 5 after 63 days of training. Ts1Cje mice took longer time (17.86±3.19 days) to move to VD vs. Eup (11.44±1.96 days, p=0.09). There were no differences between Dp16 and Eup mice. At the end of pre-training, 58% Dp16 vs. 73% Eup, and 58% Ts1Cie vs. 64% of Eup moved to VD. At VD, the average percent of correct answers was significantly lower in both Dp16 (23.53±3.39%) and Ts1Cje (22.70±1.93%) compared to Eup (35.51±2.45% and 32.18±1.49%, respectively, p<0.05). Only one Ts65Dn mouse reached VD. In conclusion, we were able to apply human cognitive tests to evaluate hippocampal learning in mouse models. These studies demonstrate significant cognitive differences between strains. Future experiments will evaluate whether deprivation and/or pre- and postnatal therapy decreases the time intervals to achieve training milestones.

Supported by funding from Illumina and the Sie Foundation.

#2

BEHAVIOR AND DIFFERENTIAL GENE EXPRESSION IN ADULT DP16, TS65DN AND TS1CJE MOUSE MODELS OF DOWN SYNDROME

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We compared adult behavior and brain gene expression in the Dp16, Ts65Dn and Ts1Cje mouse models of Down syndrome (DS). We wished to determine the best model(s) for therapeutic trials and identify treatment endpoints. Three-month old Dp16, Ts65Dn, Ts1Cje males and euploid littermates were assessed using open field (OF), fear conditioning (FC), Morris water maze (MWM) and rotarod tests. In 6-7 month old mice RNA was isolated from cerebral cortex, hippocampus and cerebellum and hybridized to gene expression arrays.

Differentially expressed genes (DEX) and dysregulated pathways were analyzed using normalized values. In the OF, distance traveled by Ts65Dn and Ts1Cje was significantly higher than eup (p<0.05) or Dp16 mice. In the FC test, all 3 strains showed lower freezing versus eup; Dp16 were more severely affected. In MWM, Ts65Dn showed significant delays in the hidden platform, probe and reversal trials (p < 0.05). Dp16 mice showed milder deficits in the hidden platform trial but severe deficits in reversal learning. In contrast, Ts1Cje mice had no spatial memory deficits. In rotarod, Dp16 performed poorly in fixed and accelerating speed trials (p<0.001), while Ts1Cje was only abnormal at high speeds (p<0.05). Ts65Dn rotarod performance was unaffected. Compared to euploid, Ts65Dn had a higher number of DEX genes in cortex and cerebellum, while Ts1Cie had more DEX genes in hippocampus and cerebellum. Dp16 had the lowest number of DEX genes in all regions analyzed. Pathway analyses highlighted commonly dysregulated pathways, including Gprotein signaling, oxidative stress, interferon signaling, glycosylation and disulfide bonds. Adult Dp16, Ts65Dn and Ts1Cje mice demonstrate surprisingly few similarities in dysregulated genes or behavior despite having shared trisomic *Mmu*16 regions. Together with our embryonic data, these data suggest that factors other than genotype affect phenotypes of these mouse models. These data will inform choice of models for future preclinical studies.

Supported by funding from Illumina and the Sie Foundation.

#3

SKELETAL STRUCTURE EXHIBITS SEXUAL DIMORPHISM AND AGE DIFFERENCES IN THE DP1TYB MOUSE MODEL OF DOWN SYNDROME

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Background: All individuals with Down syndrome (DS) have skeletal abnormalities and increased risk of osteoporosis. Individuals with DS generally display lower bone mineral density (BMD) and this phenotype is more pronounced in females with DS. It has been hypothesized that young females with DS acquire bone mass at a reduced rate compared to males. Bone abnormalities including lower BMD, percent bone volume (BV/TV) and strength have been identified in male Ts65Dn DS mice, but female mice have not been extensively examined due to their importance in colony maintenance. Objective: Dp1Tyb mice have 148 Mmu16 genes that are orthologous to Hsa21 in three copies. We hypothesized that Dp1Tyb mice would exhibit sexual dimorphism and longitudinal age differences in DS-related skeletal properties. Methods: Microcomputed tomography and mechanical bone breakage were used to analyze male and female Dp1Tyb and euploid femurs at 6 and 16 weeks of age. Age specific and longitudinal differences were identified by ANOVA.Results: BV/TV was significantly reduced at 6 weeks in male Dp1Tyb mice but equal to euploid mice by 16 weeks, largely due to an increase in trabecular number at 16 weeks in male Dp1Tyb mice. Female euploid and Dp1Tyb mice had similar BV/TV at 6 and 16 weeks. Male and female Dp1Tyb had significant deficiencies in cortical geometry and mechanical properties at 6 weeks compared to euploid mice; female mice had reduced cortical and strength properties compared to males. More cortical differences were observed between male and female mice at 16 as compared to 6 weeks. Conclusions: Significant skeletal sexual dimorphisms were found in BMD, trabecular, cortical, and strength measures between Dp1Tyb male and female mice, and female Dp1Tyb mice exhibit deficient bone accrual over time. Dp1Tyb mice can be used to understand the genetic, molecular and sex-related differences in DS skeletal measures.

#4

MODELING THE NON-LINEAR INFLUENCE OF DYRK1A ON ACTIN POLYMERIZATION Maria Martínez de Lagrán1,2,3, German Patterson1,2,3, Mara Dierssen1,2,3

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Background: Dyrk1A, a Down syndrome candidate gene, encodes a serine-threonine kinase which plays a significant role in signaling pathways regulating cell proliferation and brain development. Subtle changes in Dyrk1A expression lead to dendritic alterations affecting neurite outgrowth and complexity regardless the direction of this change (over- or underexpression). Probably, dendritic alterations could arise from regulation of cytoskeleton rearrangements by Dyrk1A since it can phosphorylates several microtubule- and actinassociated proteins. Among others, Dyrk1A acts as negative regulator on N-WASP activity, a key protein in the regulation of actin polymerization and dynamics. Phosphorylation of N-WASP affects its stability and intramolecular regulation with the consequent reduction of Arp2/3-mediated actin filament assembly, essential for neurite formation. Objective: To explore the influence of Dyrk1A dosage in regulation of N-WASP activity. Methods: We have mathematically modeled the dosage dependent interaction of Dyrk1A with N-WASP to predict to what extent over or under Dyrk1A expression could affect actin polimerization. We have validated the model using primary cortical cultures submitted to controlled changes in Dyrk1A expression. Results: Considering that Dyrk1A promotes N-WASP phosphorylation while an unidentified phosphatase produces the molecule desphophorylation to restore the equilibrium, our model predict that for a given phosphatase level, there is a nonmonotonic relationship between active N-WASP and Dyrk1A. Conclusions: The optimum Dyrk1A level found may explain why the neuronal development is dosage sensitive regardless the direction of change.

#5

DOUBLE EDGE SWORD OF THE DOWN SYNDROME CRITICAL REGION (DSCR)-1 FUNCTION IN ENDOTHELIUM

Takashi Minami¹, Masashi Muramatsu¹, Tohru Takeo¹, Keri Schadler², Sandra Ryeom³, Akiyoshi Uemura⁴

¹Div. of Molecular and Vascular Biology, IRDA, Kumamoto University, Kumamoto 860-0811, Japan ²Dept. of Pediatrics Research, MD Anderson Cancer Center, Houston ³Dept. of Cancer Biology, University of Pennsylvania School of Medicine, Philadelphia, USA ⁴Dept of Ophthalmology, Nagoya City Medical School, Nagoya, Japan Epidemiological studies suggest that although individuals with Down syndrome (DS) have an increased risk of leukemia, early aging and neuronal regression, they have reduced incidence of most solid tumors, advanced atherosclerosis and hypertension. Such data indicate that one or more of the trisomy genes on HSA21 or Mmu16 is responsible for protecting these individuals against vascular disease such as pathological angiogenesis and chronic inflammation. We previously reported the Down



syndrome critical region (DSCR)-1 gene lies on HSA21/Mmu16 and encodes an adaptive regulator for VEGF-calcineurin-NFAT signaling in endothelial cells (ECs). DSCR-1 plays critical functions in the prevention of septic mortality, tumor growth and metastasis (Minami, et.al. J.Biol.Chem. 2004, Nature 2009, J.Clin.Invest. 2009, Cell Rep. 2013). Here, to elucidate the connection between DSCR-1 mediated vessel regulation and DS etiology, we performed phenotypic analysis of newly generated EC-specific conditional DSCR-1 transgenic mice with constitutively high EC expression of DSCR-1 (EC-DSCR-1 Tg) and knockout (Dscr-1^{-/-}) mice, and DS trisomy model mice; Ts65Dn and Ts1Cje. EC-DSCR-1 Tg mice exhibited embryonic lethality before day E9.5, while doxycycline mediated-conditionally reduced DSCR-1 expressed mice survived postnatally. The embryo sizes of EC-DSCR-1 Tg were smaller than the wild-type littermate control. EC-DSCR-1 Tg mice embryos had dysfunctional branch formations, neural layer detachment and bleeds in subsets of vasculature in various organs, typically in brain and retina. VEGF levels in peripheral blood was significantly decreased in EC-DSCR-1 Tg and Ts65Dn, but markedly increased in Dscr- $1^{-/-}$. Similar to DS patients, severe and mild spermatogenesis dysfunction was detected in Ts65Dn and Ts1Cje or EC-DSCR-1 Tg, respectively. Collectively, our studies provide new insights into the threshold theory of NFAT/DSCR-1 signaling in ECs, which are at least partially reflected the DS pathology in patients.

#6

IS TARGETING TRISOMIC DYRK1A WITH EGCG SUFFICIENT TO IMPROVE DOWN SYNDROME COGNITIVE AND SKELETAL PHENOTYPES?

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Background: Cognitive and skeletal phenotypes occur in all individuals with Down syndrome (DS) and there is increasing interest to improve Trisomy 21 (Ts21) phenotypes by reducing the product or activity of a specific trisomic gene linked to one or more DS traits. One of the most frequent targets is trisomic *Dyrk1a*, an important candidate contributor to DS-associated cognitive and skeletal phenotypes. Epigallocatechin-3-gallate (EGCG) inhibits Dyrk1a kinase activity *in vitro* and has been hypothesized to reduce Dyrk1a activity and improve Ts21 traits *in vivo*. Data from mouse model experiments using pure EGCG or EGCG-containing supplements have provided mixed results. Methods: Four different

dosages of pure EGCG were given to adolescent Ts65Dn mice for 3-7 weeks. Behavioral tests, bone analyses, Western blot, and an HPLC-based kinase activity assay were performed to determine effects on cognition, appendicular skeletal phenotypes, Dyrk1a protein levels, and kinase activity, respectively. Results: Pure EGCG given at low concentrations improved skeletal trabecular deficits but treatment at higher concentrations or with EGCG-containing supplements weakened bone strength. Only minimal improvements in cognitive phenotypes were documented after pure EGCG treatment at any dosage. Adult trisomic kinase activity and Dyrk1a protein levels were not correlated with cognitive phenotypes, nor were-they specifically targeted or reduced by EGCG treatment in brain. Conclusions: In DS mouse models, the efficacy of EGCG appears to vary based on 1) the timing of EGCG administration, 2) the dosage of EGCG, 3) whether EGCG is given alone or in combination with other additives. A major obstacle is that the mechanisms by which EGCG may provide any therapeutic effects have not been conclusively established. Although trisomic Dyrk1a remains a potential therapeutic target, EGCG itself appears to have only limited benefits and may target other mechanisms that are only peripherally related to Dyrk1a overexpression.

#7

CROSS-SECTIONAL AGEING AND COGNITIVE DECLINE IN ADULTS WITH DOWN SYNDROME

Carla Startin¹, Sarah Hamburg¹, Rosalyn Hithersay¹, Tamara al Janabi¹, Andre Strydom¹ ¹ Division of Psychiatry, University College London, London, UK; LonDownS Consortium Background: Individuals with Down syndrome (DS) are at an ultra-high risk of developing Alzheimer's disease, with the lifetime incidence of dementia estimated to be around 90%. However, there is large variability in the age of onset of dementia; some adults are diagnosed in their late 30s while others show no decline into their 60s. Detailed knowledge of changes in cognitive abilities related to ageing and the development of dementia at a population level are required to fully understand the time course of dementia development in people with DS. This will aid us in identifying the optimal age for interventions to delay the onset of dementia. Objective: We determined cross-sectional changes in cognitive ability at the population level for adults with DS from the LonDownS cohort and cognitive test battery. Methods: We have recruited approximately 300 adults with DS aged 16-60, and performed detailed cognitive assessments to assess memory, executive functioning, attention, and motor co-ordination abilities. We compared performance in a young adult group prior to the onset of cognitive decline (age 16-30) to older 5-year age groups to assess cognitive changes related to ageing and cognitive decline in our battery. Results: Performance declined with increasing age in outcomes across our battery. The earliest and largest ageing-related changes in abilities were seen for tasks assessing short-term memory and attention, with changes in the early 40s. Verbal, orientation and adaptive abilities showed the latest age-related changes, in the early 50s. Conclusions: We have investigated changes in cognitive abilities related to ageing in adults with DS in a large cohort recruited for the LonDownS study. Our results suggest that within our cohort and our test battery, the very earliest cognitive changes associated with cognitive decline in adults with DS are found in tasks assessing short-term memory and attention abilities.

#8

QUANTITATIVE MRI ANALYSES OF REGIONAL BRAIN GROWTH AND CEREBRAL SULCAL DEVELOPMENT IN LIVING FETUSES WITH DOWN SYNDROME

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Background: Neurodevelopmental pathology of Down syndrome (DS) originates in fetal life. Currently, we lack safe and validated methods to evaluate brain development and anatomical changes in living fetuses with DS. Objectives: To establish baseline guantitative fetal brain developmental data by implementing post-acquisition novel quantitative fetal magnetic resonance imaging (MRI) analyses to precisely evaluate regional brain growth and cerebral sulcal development in living fetuses with DS. Methods: Pregnant women with positive cell-free DNA screens for trisomy 21 (T21) or whose fetuses were diagnosed with T21 by karyotype or microarrays were prospectively recruited for a fetal MRI. Healthy pregnant women with fetuses without apparent medical conditions were recruited as controls. We used post-acquisition quantitative fetal MRI regional volumetric analysis and novel Similarity Index based sulcal pattern matching/similarity analysis, to compare growth trajectories of brain structures and sulcal development pattern differences between 7 fetuses with DS (29.9+/-3.9 week of gestation, mean+/-SD) and 10 controls (25.5+/-5.3). Statistical analysis was performed using non-linear regression model and two-sample t-test, with significance set at 0.05. Results: Growth trajectories of cerebellar hemispheres were significantly smaller in fetuses with DS compared to the controls (p-value = 0.001). Whole cerebellum volume appeared to be smaller in DS but the difference was not statistically significant (p-value = 0.103). In the sulcal pattern analysis, the absolute position (left and right hemispheres, respectively in following data, p-value=0.002 and 0.002, t-test,) and relative inter-sulcal positional relationships (p-value=0.015 and 0.005, t-test) of overall evolving sulci were different in fetuses with DS compared to the controls. Conclusions: Quantitative fetal MRI analyses identified decreased cerebellar development and altered positional cerebral sulcal patterns in living fetuses with DS that may be the structural correlate of neurodevelopmental impairment in affected children. This technology may enable evaluation of brain development in individual fetuses, allowing assessment of the effects of prenatal therapies.

#9

ERYTHROMYELOID CELL DERIVED TREM-2: A MAJOR DETERMINANT OF INNATE IMMUNITY IN EARLY ONSET ALZHEIMER'S DISEASE AND DOWN SYNDROME

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Neuroinflammation and activation of innate immunity are early events in Alzheimer's disease (AD) and Down syndrome (DS). Rare mutations in TREM2 (e.g. R47H) which is an immunerelated gene have been associated with substantial increases in the risk of developing late onset AD. We aimed to understand the role of TREM2 in innate immunity in AD and in DS. TREM2 genotype and protein expression was investigated in serum, blood smears and brain sections of individuals with AD, DS and age-matched controls. A human myeloid cell line was analyzed to investigate role of TREM2 in phagocytosis and gene silencing. Western blotting revealed that protein levels (in serum) decline with age and disease progression in both DS and AD. In normal brains TREM2 was detected in the neurogenic niche (such as the dentate gyrus) and in the pyramidal neurons in the cortex. TREM2 protein was highly expressed in peripheral and choroid plexus macrophages, in bone marrow myeloid precursor cells, in mesenchymal stem cells and participates in erythrophagocytosis. Two DS subjects with the R47H mutation revealed abnormal erythromegakaryocyte morphology and impaired TREM2 trafficking to the erythroid plasma membrane. Silencing the TREM2 gene with anti-sense oligo-RNA we observed resulted in an increase in cell death. Our findings suggest that TREM2 not only plays a critical role in the inflammation but is also involved in neuronal cell survival and neurogenesis. Analysis of blood and serum showed that soluble TREM2 protein was carried by platelets and erythrocytes through the blood and entered the brain parenchyma through a subset of phagocytotic macrophages. Therefore, during the later stages of life, the lack of TREM2 protein may accelerate the ageing processes, via a mechanism involving neuronal cell death and reduced microglial activity, ultimately leading to neuroinflammation. TREM2 could thus be a missing link between immunomodulation and neuroprotection.

#10

MANIPULATION OF THE DOPAMINERGIC SIGNALLING MAKES SOCIAL RECOGNITION MEMORY RESISTANT AGAINST INTERFERENCE IN MICE

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Retroactive interference is the phenomenon that occurs when newly learned information interferes with the ability to recall previously acquired information. Social recognition memory, which refers to the ability to discriminate between familiar and non-familiar conspecifics, is sensitive to this type of interference and is, thus, a suitable tool for studies

aimed at testing cognitive enhancers. Modafinil has already been used as a cognitive enhancer in patients with mental disorders, as the inhibition of dopamine re-uptake via dopamine transporters explains the increase of dopamine levels and, thus, its beneficial effects on learning and memory. However, Modafinil has a low micromolar affinity to the dopamine transporters, so new components with an increased affinity would be expected to exert greater effects. Here we investigated the potential memory enhancing effects of distinct dopamine re-uptake inhibitors that have higher micromolar affinities, by testing their ability to make social memory resistant against interference. R-Modafinil (R-enantiomer), CE-123 (racemate of both R- and S-enantiomers), and R-CE-123 were subcutaneously injected in mice before the learning session, with social recognition memory tesed 24 hours later. During the 24 hour interval, interference was induced at two time points, either three or six hours after learning. Our data demonstrate that R-Modafinil is able to block the interference on social recognition memory at both time points tested. CE-123 blocked retroactive interference that was induced at three hours, but not at six hours after learning, while R-CE-123 blocked interference induced at six hours after learning only. Thus, the results obtained in the present study provide cognitive enhancing effects of dopamine reuptake inhibitors by making social memory resistant to interference. Of particular interest are the distinct temporal effects for the defined substances tested. Our findings encourage the use of these new dopamine transporter inhibitors as pharmacotherapy for correcting the cognitive impairment reported for mouse models of Down syndrome.

#11

GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR RESCUES MEMORY DEFICITS IN THE Dp16 MOUSE MODEL OF DOWN SYNDROME

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Granulocyte-macrophage colonv stimulating factor (GM-CSF) exhibits neuroprotective/restorative activity in several mouse models of CNS disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and stroke. Currently, recombinant human GM-CSF (FDA-approved Leukine[®]) is in Phase 2 clinical trials of AD patients at the Anschutz Medical Campus and the Rocky Mountain Alzheimer's Disease Center, University of Colorado, Denver, and a successful Phase 1 pilot trial in PD patients was completed recently at the University of Nebraska Medical Center. Every individual with Down syndrome (DS) develops AD brain neuropathology by the age of 40, and DS is associated with several neuronal abnormalities that lead to intellectual disability (ID). To evaluate the potential efficacy of GM-CSF for ID in DS, we tested 12-14 month old male and female Dp(16)1Yev (abbreviated Dp16) mice and their age- and sex-matched littermate controls for performance in several behavioral assays before and after treatment with GM-CSF. Without GM-CSF, both male and female Dp16 mice showed elevated locomotor activity compared with controls in the open field assay. Female, but not male, Dp16 mice were impaired in the

alternating Y-maze; neither sex displayed deficits in either novel object recognition or placement. Male Dp16 mice were impaired in the radial arm water maze (RAWM) (females could not be tested because of poor swimming ability). RAWM deficits in male Dp16 mice were rescued by a daily subcutaneous injection of 5 g GM-CSF administered for 24 days. Although further assessments are in progress, based on these preliminary findings, we conclude that older Dp16 mice show gender-specific behavioral deficits, and that at least some of them can be reversed by chronic administration of GM-CSF. Ongoing experiments are investigating the effect(s) of GM-CSF on DS relevant neuronal cellular/morphological abnormalities in Dp16 mice. These results will determine the potential for GM-CSF/Leukine[®] as a therapeutic for individuals with DS.

#12

EFFECTS OF GABA α 5 INVERSE AGONIST AND IGF-1 ON NEUROGENESIS IN THE DOWN SYNDROME MODEL Ts65Dn.

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Down syndrome is characterized by a reduction of progenitor proliferation and neuronal differentiation appearing during brain development. Ts65Dn mice modeling DS, show embryonic, postnatal and adult neurogenesis deficits. In this study, we tested two drugs susceptible of restoring neurogenesis in Ts65Dn: an inverse agonist of a5GABAAbenzodiazepine receptors (α 5IA) able to restore cognitive deficits and immediate early genes expression in Ts65Dn mice, and the neurotrophin IGF-1 able to ameliorate breathing and behavioral abnormalities in Rett syndrome. Ts65Dn and WT mice received daily injections of α 5IA(5mg/kg), IGF-1(0.25mg/kg) or vehicle from post-natal day 3 (P3) to P15. BrdU(150mg/kg) was injected at P15 2 hours before sacrifice. Effects of α5IA on neurogenesis, the number of GABAergic neurons and behavior were analyzed in adult Ts65Dn, Ts65Dn*GAD67GFP and WT. BrdU-labeled cells were counted in the dentate gyrus, the number of GAD67 positive cells was measured in the CA1 of the hippocampus and behavioral effects were analyzed on a Morris Water Maze (MWM) paradigm.We showed reduced number of BrdU-labeled cells at P15 in Ts65Dn mice as compared to WT (p= 0.0141) which was not rescued by α 5IA. We could not evidence any significant increase of GAD67 positive cells in the CA1 of adult Ts65Dn as compared to WT. α5IA had no significant effect on the number of GAD67 positive cells in Ts65Dn and WT mice when injected one week before sacrifice. In the MWM, α 5IA injected before the learning phase could not restore learning deficits of Ts65Dn mice. Effects of postnatal IGF-1 treatment on neurogenesis will be presented. Our study shows that α 5IA, at a dose showing procognitive effects in adult Ts65Dn and WT mice, could not improve neurogenesis when administered during postnatal period or in the adult, suggesting that GABAergic neurons might have different maturation in Ts65Dn mice as compared to WT.

#13

TRANSCRIPTIONAL ANALYSIS OF THE DP1TYB MOUSE MODEL OF DOWN SYNDROME

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¹The Francis Crick Institute, London, ²Great Ormond Street Hospital, ³Department of Mathematics, University College London, Gower Street, London, ⁴Department of Neurodegenerative Disease, University College London, Institute of Neurology, London. Down Syndrome (DS) is hypothesized to be a gene dosage disorder where an additional copy of ~230 coding genes on human chromosome 21 (Hsa21) results in a broad range of phenotypes. This hypothesis requires that expression of the trisomic genes is increased. In addition, it is possible that increased expression of Hsa21 genes could in turn affect expression of genes on other chromosomes. It has been proposed that one such effect is the coordinated up- or down-regulation of groups of neighbouring genes in so-called gene expression dysregulation domains (GEDDs). We have investigated both of these questions using a series of mouse models of DS that carry duplications of regions of mouse chromosomes that are orthologous to Hsa21. Specifically, we used RNAseq to analyse expression of genes in mouse embryonic fibroblasts (MEFs) from the Dp1Tyb mouse strain, which carries a duplication from *Lipi* to *Zbtb21* encompassing 148 genes orthologous to Hsa21, and four further strains with segmental duplications spanning different segments of the region duplicated in Dp1Tyb. RNAseq confirmed increased expression of genes found within the duplicated regions of Mmu16. However, to our surprise, very few non-duplicated genes were significantly differentially expressed, with a maximum of 50 differentially-expressed genes (DEGs) detected. To examine whether increased expression of Hsa21-orthologous genes leads to changes in expression in GEDDs, we devised a rigorous statistical approach to investigate if genes whose expression is altered in the Dp1Tyb strain are clustered into domains. Our results suggest that there is no such clustering that is dependent on the genotype of the MEFs, and hence we conclude that we cannot detect GEDDs in this model of DS.

#14

CROSS-COMPARISON OF EMBRYONIC BRAIN DEVELOPMENT, GENE EXPRESSION, AND PERINATAL BEHAVIOR IN THE TS1CJE, TS65DN, AND DP16 MOUSE MODELS OF DOWN SYNDROME

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Down syndrome (DS), a genetic condition leading to intellectual disability, is characterized by triplication of human chromosome 21. Neuropathological hallmarks of DS include atypical central nervous system development that manifests antenatally and extends throughout life.
As a result, newborns with DS exhibit cognitive and motor deficits and have delays in achieving developmental milestones. A critical question is how human prenatal and postnatal phenotypes are recapitulated in different mouse models of DS. To begin answering this question, we directly compared differences in embryonic brain development, gene expression, perinatal behavior, and early postnatal changes in neuronal and oligodendroglial populations in three cytogenetically distinct mouse models of DS—Ts1Cje, Ts65Dn and Dp16/1Yey (Dp16). At embryonic day 15.5, data indicate that Ts65Dn mice are the most profoundly and consistently affected with respect to somatic growth, brain morphogenesis, and neurogenesis compared to Ts1Cje and Dp16 embryos. However, gene expression results show that Ts65Dn and Ts1Cje embryonic forebrains have a relatively high number of differentially expressed genes compared to Dp16, with little overlap in gene identities and chromosomal distribution observed among these models. Additionally, postnatal histological analyses show varying degrees of cell population and brain histogenesis abnormalities among the three strains. Behavioral testing also highlights differences among the models in their ability to meet various developmental milestones. Altogether, our data show widespread and unexpected fundamental differences in behavioral, gene expression, and brain development phenotypes between these mice. Our findings illustrate unique potential applications for each model when studying aspects of brain development and function in DS. Moreover, this work helps to inform model selection in studies aimed at elucidating how observed neurodevelopmental abnormalities arise and how they contribute to cognitive impairment. Additionally, these results will also aid in model selection for future preclinical studies of neurocognitive therapeutics aimed at ameliorating the intellectual disability associated with DS

#15

SEGMENTAL TRISOMIES OF MMU16, 10 AND 17 REVEAL DISRUPTION OF DISTINCT MEMORY PROCESSES IN MICE

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Background/Objective: Impaired memory function is a common trait of individuals with Trisomy 21. Genes on chromosome 21 are conserved on 3 mouse chromosomes (Mmu16, Mmu10, Mmu17) but the contribution of these distinct gene subsets to memory function is unclear. Here, we assessed recognition memory in 3 mouse segmental trisomy models (Dp1Tyb for Mmu16, Dp2Yey for Mmu10 and Dp3Yey for Mmu17). Methods: Adult mice were tested on a battery of behavioural tasks assessing recognition memory for object identity, places and object-in-place associations. Performance on these tests relies on integrated activity within a neural circuit involving the perirhinal cortex, hippocampus and medial prefrontal cortex. Animals were placed in an arena and allowed to explore novel/familiar objects in familiar locations and familiar objects in novel/familiar locations. Contact times with the objects were recorded and preference for exploration of novelty provided an index of memory. Results: Dp1Tyb showed intact memory for objects at all retention intervals. However, Dp1Tyb mice showed impaired short-term (but not long-term) memory for object-in-place associations. Dp2Yey mice were impaired at all retention

intervals in the object identity and object-in-place tests. Nevertheless, Dp1Tyb and Dp2Yey mice showed normal memory for places. Finally, Dp3Yey mice were not impaired on any of the memory tests. Conclusion: The Mmu16 and Mmu10 trisomies selectively disrupted distinct recognition memory processes. The most severe disruption was associated with trisomy of genes encoded on Mmu10, which impaired object memory but preserved spatial novelty detection. Trisomy of Mmu16 was associated with a relatively selective deficit in short-term associative recognition memory. Further work will establish how these mutations influence the expression of synaptic receptors and activation of plasticity signalling cascades in the recognition network.

#16

CAUSES OF MORTALITY IN ADULTS WITH DOWN SYNDROME: A RETROSPECTIVE STUDY OF A COHORT OF ADULTS WITH DOWN SYNDROME

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People with Down syndrome (DS) have a lower life expectancy compared to the general population. However, the life expectancy of people with DS has increased dramatically in recent decades. Considering the changing life expectancy in people with DS, there is a need for updated study to assess the causes of death in adults with DS. A retrospective chart review was performed of the records of individuals served at the Adult Down Syndrome Center who died from September 2003 to January 2016. Inclusion criteria included deceased who were diagnosed with DS during their life. Data collected included, age at death, source of information (death certificate, records review, combination of those sources), cause(s) of death, and contributing cause(s). The records of 292 individuals diagnosed with DS who were now deceased were reviewed. Of those individuals, the age of death was available for 196 individuals: females: 92 (47%), males: 94 (53%). The average age of death was 53.2 years (SD 9.5 years); for females: 53.4 (SD 8.7 years) and males: 53.0 (SD 9.5 years). The cause of death was available for 149 (51%) individuals. Alzheimer disease (AD) was the leading cause of death overall and in individuals greater than 40. Congenital heart disease was the leading cause of death in younger individuals (less than age 40) and second in patients who died in their 40s. Infectious disease is a leading cause or contributing cause of death, particularly when associated with AD. 37 of the 47 individuals for whom pneumonia was a cause of death also had AD as a cause of or contributing cause of death. As the population of people with DS is living longer, in our cohort of adults with DS, AD is the leading cause of death in older individuals.

#17

NEURONAL CELL AUTONOMOUS DEFECTS IN A MOUSE MODEL OF DOWN SYNDROME: CONTRIBUTION OF TTC3 GENE

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Down Syndrome (DS) is the most common genetic disorder associated with intellectual disability (ID). It is characterized by several brain alterations, including a simplified dendritic structure and spine maturation impairment. In this work we explored the contribution of cell autonomous alterations to abnormal cortical phenotype of DS brains. Therefore, we cultured cortical neurons from newborn Ts65Dn mice (referred as "Ts") and evaluated their ability to differentiate in *ex vivo* conditions. Our data indicate that neuronal polarity and dendritogenesis are unaffected, while dendritic spines are both reduced and immature, evidencing an intrinsic cell phenotype. Furthermore, we studied TTC3, a negative regulator of neuritogenesis (Berto et al. 2007, 2014), that is located on HSA21 and overexpressed in DS and Ts brains. Preliminary results obtained modulating TTC3 levels in Ts primary cortical neurons *in vitro* indicated a role of the gene in Ts abnormal dendritic spine development. Together, these data suggest that defective Ts brain functionality can be attributable not only to circuitry or to unbalanced cellular composition alterations, but also to specific defects within neurons caused by abnormal expression of genes, such as TTC3.

#18

SYNDROME SPECIFICITY: A COMPARISON BETWEEN DOWN SYNDROME AND FRAGILE X SCHOOL-AGED CHILDREEN

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Despite the shared presence of cognitive impairments, there are important phenotypic differences between Down syndrome (DS) and fragile X syndrome (FXS). For example, behavioral problems are more common in FXS, whereas language deficits are greater in DS. These conclusions, however, are based on a synthesis across studies, each of which typically includes only measures of a few neuropsychological domains. Moreover, the age range and IQ level of participants often differs dramatically across studies. Firmer conclusions regarding phenotypic features specific to DS and FXS requires a single comprehensive multi-domain assessment of participants with the syndrome groups well matched on age and IQ. The current study was designed to fill this gap by assessing several neuropsychological domains in 28 individuals with DS and 29 with FXS (10 to16 years) matched on age and IQ. Because FXS is X-linked, FXS females were excluded. Neuropsychological outcomes involved direct assessment or parent report of the participants' receptive and expressive language, false belief (understanding that an individual's belief about the world may contrast with reality) plus pragmatics and behavioral difficulties in everyday settings. Results show that more than 73% (d>0.6) of DS participants scored below the mean performance of the FXS group on false belief understanding and receptive grammar and more than 80% (d>0.8) on receptive and expressive vocabulary. expressive grammar and fluency skills. Regarding pragmatics, individuals with DS demonstrated better nonverbal communication skills and less stereotyped language than males with FXS. Finally, individuals with DS were less likely to demonstrate internalizing

behaviors than FXS. Non-significant differences were observed for the remaining cognitive outcomes (|d| -0.3 to0.3 and/or CIs including 0). Our results are consistent with previous reports indicating more severe structural language impairments in DS but greater pragmatic and behavioral difficulties in FXS. Clinical implications of these findings will be discussed.

#19

BLOOD PROTEOMICS OF CHILDREN WITH DOWN SYNDROME

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While it has been known since 1959 that Down syndrome results from trisomy of human chromosome 21 (T21), how T21 results in the conditions that commonly accompany this syndrome is not known. Recent transcriptomic experiments have demonstrated that T21 results in many changes in gene expression at the RNA level, including for some HSA21 genes, but most of the resultant changes are spread throughout the rest of the genome. However, for most of the genes studied, it wasn't known if these expression changes were also present at the protein level. This information is very important given that many drugs target proteins, not RNAs or DNA. In order to address this question, we took advantage of a new proteomics technology, the SOMAscan, to look at the relative protein levels of over 3,500 proteins in the blood of children with Down syndrome compared to typically developing controls. Nearly 300 proteins were differentially expressed between the two cohorts. Similar to previous transcriptomic findings, the majority of these proteins are encoded by genes that are located throughout the genome and are not restricted to HSA21. These proteins are known to be involved in many of the phenotypes that have previously been observed in Down syndrome experimental systems (mitochondrial dysfunction and oxidative stress [APOE], apoptosis [Diablo], protein folding [ATF6], brain development [NOG], etc.). Many of these proteins are known to be involved in the immune response, which is particularly interesting in light of the recent results demonstrating the consistent activation of interferon signaling in Down syndrome. These results offer many new potential therapeutic targets for improving the lives of individuals with DS by ameliorating the ill effects that can accompany the syndrome.

#20

THE CONTINUUM OF THE NEUROINFLAMMATORY PROCESS IN ALZHEIMER'S DISEASE IN DOWN SYNDROME

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Background: Little is known about the evolution of the neuroinflammatory process in preclinical stages of Alzheimer's disease (AD). We have reported in transgenic rodent models of AD, the occurrence of an early disease-aggravating pro-inflammatory process associated to the intraneuronal accumulation of soluble Aβ-oligomers (Ferretti 2012, Hanzel 2014). While anti-inflammatory medications administered for symptomatic-AD have failed to show efficacy, long-term anti-inflammatory treatment in cognitively normal individuals reduces the risk of developing AD. Such results suggest that the AD-related neuroinflammation differs at various stages of the AD pathology. Down syndrome (DS) fetuses display intraneuronal-A β accumulation (Busciglio 2002). DS individuals further develop progressive AD neuropathology, and in most cases AD dementia by the age of 55-60 years (Busciglio 2002, Mori 2002). We have reported an upregulation of inflammatory molecules in the plasma of DS-AD-asymptomatic individuals (Julita 2016). In accordance with this, we hypothesize that an A β -driven early neuroinflammatory process will occur in preclinical stages of AD in DS; such inflammatory profile should differ from the one present at clinical AD stages in DS. Furthermore, recent investigations suggest that inflammasome activation contributes to the neuroinflammatory process in AD. We hypothesize that its activation will occur at the preclinical stages of AD in DS. Objective(s): To characterize the neuroinflammatory process across the lifespan of DS individuals. Methods: Inflammatory gene expression in postmortem frozen frontal cortical tissue of DS individuals (infants and DS-AD adults) and healthy controls was analyzed by qPCR. Results: Pro-inflammatory qPCR array analysis shows an upregulation of IL-1B, IL-6, IL-12a, IL12b, MCP-1, TNFSF11, TNFSF14, pro-inflammatory caspases-1 and 5 and inflammasome receptors NLRP3, NLRP4, NLRP6 in DS infants. Some of these genes were also upregulated in DS-AD adults; however, this upregulation is more substantial in DS-infants than in DS-AD-adults. Conclusions: DS individuals exhibit a differential neuroinflammatory process at the preclinical and clinical stages of AD.

#21

NEUROANATOMICAL AND FUNCTIONAL ALTERATIONS IN THE PERIRHINAL CORTEX OF THE Ts65Dn MODEL OF DOWN SYNDROME

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Individuals with Down syndrome (DS) are impaired in several cognitive domains including hippocampus-dependent declarative memory. Accordingly, long-term potentiation (LTP), a cellular correlate of memory, is disrupted in the dentate gyrus and hippocampus of the Ts65Dn mouse model of DS. The perirhinal cortex (PRC) is a region fundamental for visual

recognition memory, a function that is impaired in individual with DS and Ts65Dn mice (as assessed with the Novel Object Recognition test). Since no study has explored the organization of the PRC in Ts65Dn mice so far, our goal was to establish whether the PRC of this model exhibits neuroanatomical and functional defects that may contribute to visual recognition memory impairment. To this purpose we examined cellularity, spine density, connectivity and LTP in the PRC of adult (1.5-3.5 month-old) Ts65Dn and euploid mice. We found that Ts65Dn mice exhibited reduced cellularity, reduced spine density but no differences in synaptic protein levels in comparison with euploid mice. In horizontal brain slices, we used theta burst stimulation to elicit LTP in the superficial layers of the PRC. We found that LTP had a similar time-course but a reduced magnitude in trisomic in comparison with euploid slices. While exposure to the $GABA_A$ receptor antagonist picrotoxin had no effect on LTP magnitude in trisomic slices, exposure to the GABA_B receptor antagonist CGP caused an increase in LTP magnitude that became even larger than in euploid slices. Western blot analysis showed increased levels of GIRK2 (G-protein-activated-inwardlyrectifying potassium channel 2) in the PRC of Ts65Dn mice, consistent with triplication of the gene coding for GIRK2. This suggests that GIRK2-dependent excessive GABA_B receptormediated inhibition may underlie LTP impairment. Results show anatomical and functional defects in the PRC of Ts65Dn mice. These defects may contribute to trisomy-due impairment in visual recognition memory.

#22

TREATMENT WITH TIDEGLUSIB DOES NOT IMPROVE COGNITIVE PERFORMANCE IN THE Ts65Dn MOUSE MODEL OF DS

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Disruption of hippocampal neurogenesis is a key determinant of declarative memory alterations in Down syndrome (DS). Thus, it is conceivable that treatments that increase hippocampal neurogenesis may translate into a benefit in the memory domain. Based on evidence that tideglusib (NP031112), a non-ATP competitive GSK3-beta inhibitor, increases neurogenesis in rats, the goal of the current study was to establish whether tideglusib increases neurogenesis in the hippocampal dentate gyrus (DG) of the Ts65Dn model of DS, thereby improving hippocampus-dependent memory. Four- month-old Ts65Dn and euploid mice were treated with saline (controls), vehicle (corn oil; VEH mice), or tideglusib dissolved in the vehicle (TIDE mice) for 30 days and behaviorally tested with the Morris Water Maze. Results showed that TIDE Ts65Dn mice did not undergo any learning and memory improvement. These results are consistent with the finding that TIDE Ts65Dn mice did not show any neurogenesis increase in the DG. In contrast, VEH Ts65Dn mice underwent some improvement in both learning and memory. Evaluation of neurogenesis in Ts65Dn pups showed no neurogenesis increase in TIDE Ts65Dn mice but increase in VEH Ts65Dn mice. This evidence indicates that the lack of effects of Tideglusib on neurogenesis is not-age-

dependent. These findings suggest that corn oil (the vehicle) has pro-neurogenic effects that are offset by co-administration of tideglusib. The Ts65Dn model of DS is bound to develop Alzheimer's disease (AD) after 5-6 months of age. Tideglusib has been used in clinical trials in individuals with AD but with no clinical benefits. The current finding that tideglusib does not improve neurogenesis and behavior suggests that it may not represent a suitable treatment for DS and for AD prevention in DS.

#23

STUDY OF CRANIAL MUSCLE PLASTICITY IN MOUSE MODELS OF DOWN SYNDROME

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Down syndrome (DS) is associated with developmental oromotor differences. The present study uses two mouse models of DS: Ts65Dn and Dp(16)1Yey, in the same genetic background, to study oromotor and postnatal cranial muscle differences associated with DS. The objectives are: 1) To validate a soft food consistency paradigm for the study of postnatal cranial muscle plasticity in mice, and 2) To test the hypothesis that cranial muscles of mouse models of DS differ from those of controls in that they fail to upregulate fast Myosin Heavy Chain Isoforms (MyHC) in response to altered functional demands imposed by post-natal feeding transitions. *Methods:* At weaning on postnatal day 21, Ts65Dn, Dp(16)1Yey, and sibling control mice are assigned to receive either a hard pellet diet, or a nutritionally equivalent soft consistency diet. Mice are also provided ad libitum access to a water spout. Mouse weight and water consumption volume are recorded daily. After two weeks of diet conditions, mastication rates and licking rates are assessed by high-speed video, after which cranial muscles and limb muscles are isolated for MyHC analysis through SDS-PAGE. Results: Mice in soft food consistency groups consistently lick significantly less water than mice in hard food consistency groups. In WT/euploid mice, soft food consistency does not affect MyHC 2b content in soleus or extensor digitorum longus muscles of the limbs, but does coincide with significant reductions in MyHC 2b levels in the posterior digastric muscle (n=5-6/group). While all genotypes show steady weight gain on both diet consistencies, in both diet conditions Ts65Dn show lower weights relative to euploid controls (n=8-9/group). Analysis of other groups and measures are pending and results will be reported. Conclusions: Current findings demonstrate the feasibility of applying this investigational paradigm of postnatal cranial muscle plasticity to studies of oromotor impairment in mouse models of DS.

#24

NEUROANATOMICAL ALTERATIONS IN THE TEMPORAL CORTEX OF HUMAN FETUSES WITH DOWN SYNDROME

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Cognitive impairment in subjects with Down syndrome (DS) has been attributed to the hypoplasia that characterizes the DS brain. Previous evidence from our group showed a

notable reduction in cell proliferation and cellularity in the hippocampal region of DS fetuses. which may account for the alterations of declarative memory that characterize DS. The inferior temporal gyrus (ITG) plays a key role in visual recognition memory, a function that is also impaired in DS. The goal of the current study was to establish whether fetuses with DS exhibit neuroanatomical alterations in the ITG that may underlie recognition memory impairment. Fetal brains (18-21 weeks of gestation) were obtained according to procedures approved by the Ethical Committee of the St. Orsola-Malpighi Hospital, Bologna, Italy. In Nissl-stained coronal brain sections, we evaluated with the optical disector method the number of cells per unit area both in the superficial and deep layers of the ITG. We found that fetuses with DS had fewer cells both in the superficial (-15%) and deep (-17%) layers in comparison with control fetuses. Furthermore, while the cortex of normal fetuses exhibited a columnar cellular structure, the cortex of DS fetuses of similar gestational age had a disorganized architecture. In sections subjected to immunohistochemistry for Calretinin, a marker of inhibitory GABAergic interneurons, we evaluated the number of Calretinin-positive cells in the ITG. While DS fetuses had a similar number of Calretinin-positive cells as control fetuses, they had a ratio of Calretinin-positive cells over total cell number greater (+11%) than control fetuses, suggesting a greater inhibitory weight in their ITG. Results indicate that the ITG of Down fetuses is notably underdeveloped and disorganized. The cellularity reduction in conjunction with an increased inhibitory weight may underlie the functional alterations in visual recognition memory in children with DS.

#25

DYRK1A INHIBITORS INHIBIT THE FUNCTIONS OF FOXP3+ T-REGULATORY CELLS

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Background: The Dyrk1a gene encoding dual specificity tyrosine-phosphorylation-regulated kinase-1a is localized in the Down syndrome (DS) critical region of chromosome 21, and is a strong candidate gene for learning defects associated with DS. Overexpression of Dyrk1a is also linked with the markedly increased incidence of Alzheimer disease seen in DS patients. Use of Dyrk1a inhibitors may decrease the extent of amyloid-beta deposition and tau pathology in the brains of DS patients. However, on the principle of first, do no harm, we investigated the immunological effects of Dyrk1a inhibitors that are of potential therapeutic value in DS patients. Objective: To test effects of Dyrk1a inhibitors on immune functions. Methods: Using C57BL/6 mice, we treated conventional T cells and Foxp3+ T-regulatory (Treg) cells with 3 different Dyrk1a inhibitory compounds, Epigallocatechin gallate (EGCG), Harmine, and INDY. Results: Using 1-10 µM concentrations, Dyrk1a inhibitors did not inhibit T cell proliferation in vitro. However, in contrast to vehicle-treated controls, all 3 Dyrk1a inhibitors impaired Treg suppressive function in a dose-dependent manner, and were associated with decreased Foxp3 expression and increased GITR and IL-2 production. When administered in vivo, Dyrk1a inhibitors promoted anti-tumor immunity, with decreased intratumoral infiltration by Foxp3+ Treg cells and increased production of IFN- by tumorinfiltrating CD8+ conventional T cells. Conclusions: EGCG, extracted from green tea, has multiple effects beyond inhibiting Dyrk1a, whereas Harmine and INDY are considerably more specific and potent snall molecule Dyrk1a inhibitors. Our data show that use of Dyrk1a inhibitors in mice can impair Foxp3+ Treg function and promote conventional T cell responses. Studies of the effects of conditional deletion of Dyrk1a will allow further dissection of its immune effects. However, our studies suggest that therapy with Dyrk1a inhibitors in DS patients may require careful consideration and monitoring, given an already increased risk of autoimmune diseases in DS patients.

#26

DIFFERENT MODIFICATIONS OF MONOAMINES PATHWAYS IN VARIOUS BRAIN AREAS FROM FEMALE AND MALE TRANSGENIC MICE FOR THE *DYRK1A* GENE

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Background: Neural transmission is altered in persons with trisomy 21 (T21) and deficits in monoamines have been documented in platelets and post mortem brain from these persons. DYRK1A is one of the key genes to understand this complex pathology.Objective(s): Evaluation of the consequences of DYRK1A overexpression on the monoamines contents in various areas of transgenic mice for this gene. Methods, High performance liquid Chromatography with electrochemical detection (HPLC-ED) I was used for measurements of the monoamines contents in four murine brain areas. Results: Female and male express different monoamines contents either in control or in transgenic mice for the DYRK1A gene (mBactgDyrk1a mice). Overexpression of DYRK1A gene induces dramatic decrease of serotonin in the four brain areas tested (hypothalamus, thalamus, hippocampus and striatum) and for both female and male mice. In the dopamine pathway, le DA contents were decreased in the hypothalamus for both genders. In the noradrenergic pathway decreases were measured mainly for male tissues. Conclusions: The main modifications induced by DYRK1A overexpression were dramatic serotonin decreases in the four areas for both genders. Serotonin is involved in brain development, dendrites and spines morphogenesis, synaptic plasticity leading to appropriate learning and cognition and these deficits are present in the *mBactgDyrk1a* mice. Thus serotonin deficit induced by gene dosage of DYRK1A might be a key marker and could be used to follow some of the pharmacological trials, which are ongoing for person with T21. Moreover as DYRK1A gene dosage and mutations have been recently demonstrated in persons with autism spectrum disorder, intellectual disabilities without T21 and also Alzheimer disease, it might be valuable to focused more on monoamines pathways for these persons.

#27

SYSTEMATIC CELLULAR DISEASE MODELS REVEAL SYNERGISTIC INTERACTION OF TRISOMY 21 AND GATA1 MUTATIONS IN HEMATOPOIETIC ABNORMALITIES Yasuji Kitabatake¹, Kimihiko Banno¹, Savaka Omori¹, Keiichi Ozono¹ ¹Department of Pediatrics, Graduate School of Medicine, Osaka University, Suita, Japan

DS patients have an increased risk of certain hematopoietic abnormalities, including transient myeloproliferative disorder (TMD) and leukemia (myeloid leukemia associated with Down syndrome; ML-DS). Both DS-TMD and ML-DS cells harbor somatic mutations in GATA1, which result in loss of the full-length protein product and the exclusive production of a short GATA1 variant (GATA1s).



Somatically acquired GATA1s-producing mutations and constitutive trisomy 21 are now considered necessary and sufficient to cause TMD. To better understand functional interplay between these two factors in hematopoiesis, we established systematic and strategically designed cellular disease models by combining patient-derived human induced pluripotent stem cells (hiPSCs), genome-editing technologies, and chromosome engineering techniques. Twenty types (and more than 40 clones) of hiPSC were generated and subjected to hematopoietic differentiation to explore the synergistic interaction between *GATA1* mutation and gene dosage effects of trisomy 21 in hematopoiesis. Constitutive trisomy 21 not only accelerates the production of early hematopoietic progenitors, which leads to enhanced multilineage differentiation, but also upregulates GATA1s expression, giving rise to the excessive generation of abnormal megakaryoblasts. We succeeded in isolating a 4-Mb region critical for hematopoietic defects in DS and identified three genes, *RUNX1*, *ETS2*, and *ERG*, as key molecules involved in an interconnected regulatory network. The results demonstrate synergistic effects of aneuploidy and a specific gene mutation on the leukemogenesis.

(Banno K et al. *Cell Rep* 2016; 15: 1228–1241)

#28

NEURONAL EXOSOMES REVEAL ALZHEIMER'S DISEASE BIOMARKERS IN DOWN SYNDROME

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Individuals with Down syndrome (DS) develop Alzheimer's disease (AD) pathology and dementia early in life. Postmortem studies have shown elevated levels of neuropathogenic proteins such as amyloid-beta 42 (A β 42) and phosphorylated Tau (p-Tau) in cerebrospinal fluid and brain tissue of individuals with Down syndrome, but there is a need for the development of reliable blood-based biomarkers for AD in this population. The objective of this collaborative study was to analyze neuronal exosomes isolated from blood in DS to examine the levels of neuropathogenic biomarkers amyloid-beta 42 (AB42) and phosphorylated Tau (p-Tau). Neuron-derived exosomes were purified from blood, and Aβ42, phosphorylated Tau (p-Tau T181 and S396) were measured using enzyme-linked immunosorbent assays. Neuron-derived exosomes revealed significantly elevated levels of Aβ42, p-Tau T181 and p-Tau S396 in individuals with Down syndrome compared with agematched controls, as early as 8 years of age. This study suggests that neuron-derived exosomes isolated from blood offers a comprehensive way for interrogating early events in AD pathogenesis, and thus could represent a valuable diagnostic tool for individuals from Down syndrome. Continued work in our lab now includes validating exosome cargo and comparing findings with BDNF levels and other biomarkers for brain health.

#29

DOWN SYNDROME: A NEW GROUP AT RISK FOR PREMATURITY?

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Background: Preterms are at higher risk for morbimortality and various risk factors for prematurity have been described. Down syndrome (DS), however, has not been associated to a higher risk of preterm labour. Our team described a rate of 26% of prematurity in our general cohort, however, factors associated to prematurity were not studied. Objectives: To evaluate factors associated with prematurity in a group of neonates with DS. Methods: Birth charts of babies with DS born at Hospital Clínico UC between 2007 and 2017 were revised. Obstetric, perinatal and neonatal information was extracted. Univariate analysis was performed with Fisher exact test for categorical data and Mann-Whitney for continuous variables with SPSS. Results: 120 registries were reviewed. 44.9% were male, mean GA was 37 w (± 2.7 SD; 27-41 w) and 38.6% were preterm. Mean birth weight (BW) was 2.730 gr (±719 gr) and 30.5% were small for gestational age. The only associations with prematurity in univariate analysis were pregestational comorbidity (p 0.04), and previous preterm birth (p 0.004). All twins were preterm. There was no association between prematurity and the following maternal factors: maternal age (p 0.802), lower socioeconomic status (p 0.133), excess malnutrition (p 0.597), parity (p 0.589), mode of delivery (p 0.07), gestational comorbidity (p 0.074), group B streptococcus (p 1.000), smoking (p 1.000) and alcohol consumption (p 0.384). No association was found with the following neonatal factors: gender (p 0.446), congenital heart defect (p 0.568), gastrointestinal malformation (p 0.409), and neonatal sepsis (p 0.220). Conclusions: A high rate of prematurity in DS

neonates is reported, much superior to general population. The majority of obstetric and perinatal factors of mothers and babies with DS did not explain the increased risk of prematurity, suggesting that DS itself might play a role in increasing the chances of preterm birth.

#30

THYROID STATUS IN CHILEAN CHILDREN WITH DOWN SYNDROME

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Background: Children with Down syndrome (DS) can present thyroid diseases with more frequency. We present the results of a historical cohort of 871 Chilean patients. Objectives: To describe the thyroid status of Chilean children and adolescents with DS. Methods: Descriptive study of the most recent medical record of patients in control at the DS Clinic Follow-Up Program, between 2007 and 2017. Results: Records of 871 patients were revised. The median age was 4.6ys (0-23ys), and 50,5% was male. Median follow-up was 1.3ys (0-10ys). Regarding thyroid status: 51.3% were euthyroid, 4.6% had subclinical hypothyroidism in investigation state, 40.2% had hypothyroidism being treated (clinical and subclinical), 0.4% had hyperthyroidism and 3.5% were unknown. Age at diagnosis of hypothyroidism was at follow: 36.2% (60/165) congenital, 42.4% (70/165) between 1 month and 2 yrs, 12.7% (21/165) between 2 and 6 yrs, 5.5% (9/165) between 6 and 10 yrs, and 3.6% (6/165) were older than 10 yrs. Of the patients with hypothyroidism, 103 had antibodies available and 58.5% were positive. 101 patients had ultrasonography available, and 83% were normal. Ultrasonographic findings were as follows: 4 patients had difuse goiter, 8 thyroiditis, 3 nodules, 1 colloid cyst and 1 lobule asymmetry. Comparing hypothyroidism vs. patients without thyroid disease, there was no difference according to gender and nutritional status. With regards to the neonatal period; 8.2% (60/731) had transient neonatal hyperthyrotropinemia, of which 25% (15/60) evolved to overt hypothyroidism before 6 yrs. Conclusions: Children with DS have a high frequency of thyroid disease in Chile. In children younger than 6 yrs, those that had transient neonatal hyperthyrotropinemia had a higher prevalence of overt hypothyroidism, supporting the importance of follow-up in these patients. Also, a high frequency of autoimmune thyroid disease is noted, suggesting the importance of completing workup with both ultrasonography and antibodies.

#31

DELAYED DEVELOPMENTAL SPECIALIZATION OF THE MOTOR SYSTEM IN INFANTS AND TODDLERS WITH DOWN SYNDROME

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A growing body of evidence indicates that the infant brain starts out "broadly tuned". producing more widespread activation in response to stimuli than later in development. Such an account has hitherto been applied to socio-cognitive development. We investigated whether purposeful action is also initially "broadly tuned" and widespread across limbs. In a series of experiments, we found that extraneous movements (movements in the other limbs that accompany the movement of a limb engaged in goal-directed action) decreased between 9- and 12-months of age in typically developing (TD) infants. Thus, we concluded that infant motor activity starts out broadly tuned and becomes progressively specialized over development. We subsequently extended our investigation to include children with Down syndrome (DS), because this population is known to have motor difficulties. Fourteen infants and toddlers with DS (20.6 - 35.5 months) and 24 TD controls (11.8 - 34.1 months) were presented with small objects and encouraged to reach for them. Mental age was measured using the Mullen Scales of Early Learning (Mullen, 1995). Extraneous movements accompanying unimanual reaches were analyzed using cross-sectional developmental trajectories (Thomas et al., 2009). This analysis indicated delayed motor specialization in DS. This was the case for trajectories based on chronological age as well as mental age, suggesting that the developmental decrease of extraneous movements in DS is delayed beyond what would be expected for children at that developmental level. Taken together with growing evidence that motor difficulties often appear before the onset of other behavioral symptomatology in disorders of unknown etiology, this opens up an important line of research in the possibility of using extraneous movements as an early marker of neurodevelopmental difficulties and relatively easily measurable outcome of interventions.

#32

OBJECT EXPLORATION DURING INTERACTION BETWEEN INFANTS/TODDLERS WITH DOWN SYNDROME AND THEIR PARENTS

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Variation in object exploration constrains learning and is related to numerous domains including problem solving, 3D perception, social attention, and language development in typically developing (TD) children. Exploratory behavior in young children with Down syndrome (DS) has been reported to be less frequent and shorter in duration than in TD controls. In this study, we focused on the handling of objects by children and their parents during free play. Ten infants/toddlers with DS between 18 and 30 months of age were matched on mental age to nine TD infants/toddlers, using the Mullen Scales of Early Learning (Mullen, 1995). Although children with DS spent significantly less time handling objects than TD children, the number of objects they handled was not significantly different. This is consistent with an interpretation that curiosity seeking in both groups of children may be similar, but perseverance and sustained attention is something that children with DS

struggle with. Interestingly, the behavior of the parents did not generally differ between the dyads in the TD and DS groups. When we compared the children with their parents within each dyad, there was no significant difference between how long the children with DS handled the objects compared to their parents. A different pattern emerged in the TD group. The TD children manipulated objects for significantly longer than their parents. The differences in objects handling we observed in infants and toddlers with DS in this study may contribute to the emerging phenotype in this neurodevelopmental disorder. Understanding parent-child interactions can inform the scope for parent-based interventions.

POSTER SESSION II

#1

THE UPR IS A MAJOR PARTICIPANT IN THE DEVELOPMENT OF ALZHEIMER DISEASE-LIKE NEUROPATHOLOGY IN A MOUSE MODEL OF DOWN SYNDROME

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Background: The accumulation of misfolded proteins in the endoplasmic reticulum (ER) triggers a cellular stress response called the Unfolded Protein Response (UPR). Long-term activation of the UPR mediates neuronal dysfunction in Alzheimer disease (AD). The common pathological and symptomatic features between AD and Down Syndrome (DS), led us to hypothesize that the UPR is also altered in DS. Objectives: The main goal of this project is to identify potential links between UPR activation and AD-related neurodegeneration in a DS mouse model. Methods: We performed a gene card array analysis of cDNA obtained from the hippocampus of the Ts65Dn mouse model of DS at different time points (3, 9 and 18 months old) compared to the euploid controls. In addition, we analyzed by western blot and immunofluorescent (IF) staining the expression levels and brain localization of the main protein component of UPR. Results: We observed sustained ER stress response in Ts65Dn at 3 months of age when compared to control as evidenced by robust gene over-expression of the UPR gatekeepers PERK, eIF2 α , ATF6 and IRE1. Gene expression is paralleled by protein levels data that support the main involvement of PERK pathway in the early UPR activation. However, such over-activation decreases with age demonstrating a significant suppression of the ER stress response in 18 months-old Ts65Dn mice. Conclusions: Our data suggest that UPR activation in Ts65Dn mice occurs before consistent brain pathology and might contribute to both early tau hypephosphorylation and failure of proteostasis. Long-term ER stress induces apoptotic cell death, which may lead to the accelerated aging of UPR, confirmed by gene expression reduction in old Ts65Dn mice. Together, these data suggest that UPR alterations are involved in DS neuropathology and might contributes to the development of AD-like cognitive decline in DS subjects.

#2

THE UNEVEN DEVELOPMENT OF MEMORY IN DOWN SYNDROME IN CHILDHOOD

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Although memory in Down syndrome (DS) has been extensively explored in late childhood, adolescence and adulthood, development of these abilities in early childhood has not been characterised. This study utilised a mixture of original and pre-existing tasks to characterise a wide range of memory abilities at varying levels of cognitive demand in participants with DS (N=43) and chronological age (CA) matched controls (N=32). The abilities were both compared between early (3 to 9 years) and late (10 to 15 years) childhood, and across all participants. Standardised tasks were used to produce mental-age (MA) equivalents for verbal and non-verbal memory abilities (BPVS, BAS II pattern construction sub-test)

development that is impaired for CA, but MA-appropriate, demonstrates synchrony within domains that are delayed for CA. Verbal working memory was the only measure that was developmentally delayed over both CA and MA. At low levels of cognitive demand betweendomain associative short and long-term memory appeared typically developing across the CA range, suggesting a relative strength of the DS population. Within visuospatial memory, working memory, despite being impaired at the youngest CA, developed faster than longterm memory abilities. Indeed, visuospatial long-term memory did not appear to develop over CA, as did digit span and verbal fluency. However, this could be a side-effect of crosssectional analyses. Verbal fluency and digit span developed at MA-appropriate rates, whereas visuospatial long-term memory appeared to develop faster than controls across pattern construction abilities. Associative long-term and visual short-term memory abilities both improve to typical level abilities in late childhood, representing relative strengths in the DS population. Overall, although the development of visuospatial abilities is more typical, verbal domain abilities appear more in-sychrony with other cognitive abilities. Results of the study showed the uneven development of abilities at different levels of cognitive demand over both CA and domain-relevant MA.

#3

A NOVEL COMPUTERIZED ASSESSMENT FOR EXAMINING MEMORY IN CHILDREN WITH INTELLECTUAL DISABILITY

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Basic science has informed several potential treatments for cognitive dysfunction in Down syndrome (DS). In order to move these therapies into clinical trials, reliable and valid outcome assessments are needed, especially for young children with ID. To minimize the likelihood that these interventions will fail due to inappropriate cognitive assessments, there is a requirement for novel assessments. Hippocampal function is a major target of interventions in ID, therefore memory assessments for atypical development are required to accurately characterize the ability levels of individuals across the intervention. The aim of this study is to develop a battery that can assess a range of memory abilities at multiple time-points, called the Arizona Memory Assessment for Preschoolers and Special Populations (A-MAP). The A-MAP is completely computerized iPAD assessment with 25 measures of memory and executive control with 3 alternate forms under development. The A-MAP will be applied at three sites, the University of Arizona, Drexel University and University of California, Davis. This poster reports the results of pilot studies. This 45-minute screen-based assessment of verbal and non-verbal abilities, processing speed and executive control was applied to participants with Down syndrome (DS, N=28, age 6-25 years) and typical controls (N=28, age 2-6 years). This pilot study confirmed the validity of the assessment and that the DS group displayed deficits in temporal or spatial pattern processing. The battery will now be applied to groups of individuals with DS and Fragile-X syndrome (FXS), as well as controls, both cross-sectionally and longitudinally. Our intention in presenting the task at the T21 meeting is to receive critical feedback from potential future

users, as the task is still in the development phase and would benefit from the collaborative input from conference attendees.

#4

EXTENSIVE PERTURBATIONS OF THE IMMUNE SYSTEM AMONG INDIVIDUALS WITH TRISOMY 21

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Individuals born with trisomy of HSA21 (T21) experience intellectual disabilities and a unique disease spectrum. Interestingly, while T21 predisposes individuals to respiratory tract infections, autoimmune disorders, and leukemia, this genetic condition also protects them from solid tumors. Previous studies of the T21 immune system are contradictory. We therefore simultaneously characterized approximately 150 immune cell subsets from the whole blood of individuals with T21 by mass cytometry. We identified a T21 immune signature that is quantitatively, phenotypically, and functionally distinct from age- and sexmatched controls. This global immune dysregulation encompassed some published, hypothesized, controversial, and completely novel results. For instance, individuals with T21 have an increased amount of age-associated B cells (ABCs). ABCs are a B cell subset that accumulates with age and are strongly associated with viral infections as well as autoimmunity. They are induced by concurrent stimulation through the B cell receptor (BCR), a virus recognition receptor (TLR7), and an anti-virus/cancer cytokine (IFN-y). To our knowledge, ABCs have not been previously investigated in T21. Additionally, distinct immune cell subsets, such as ABCs, had increased surface protein expression of an IFN receptor that is located on HSA21. We hypothesize that aberrant IFN signaling contributes to the global immune dysregulation in T21, and that variable aspects of the immune signature correlate with various manifestations of T21. We are testing this hypothesis using clinical surveys and expanded mass cytometry characterization of leukocytes for single-cellresolution examination of cytokines, including IFNs, and additional signaling proteins both up- and downstream of IFNs after brief stimulations with IFNs and agents that cause cytokine production, such as TLR7. Collectively, these analyses of immune dysregulation in T21 could identify possible nodes of intervention facilitated through precision medicine.

#5

TARGETED METABOLOMIC ANALYSIS IN ADULTS WITH DOWN SYNDROME: PURINES, PYRIMIDINES, AMINO ACIDS AND NITROSATIVE STRESS BIOMARKERS

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#6

AUDIOLOGIC ASSESSMENT IN ADULTS WITH DOWN SYNDROME

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BACKGROUND: Increased life expectancy in persons with Down Syndrome (DS) is associated with premature age-related changes. AIM. To assess auditory function in adults with DS and to evaluate the prevalence of hearing loss in this population.METHODS: Audiometric tests were performed in 72 adults with DS (mean age 37.3 ± 10.1 years, 51.4% females). Air conduction pure tone average (PTA) thresholds at frequencies 0.5-1-2-4 kHz were calculated to assess hearing function. Hearing loss was present if the PTA threshold was > 20 dB hearing level. Higher frequencies of 4 and 8 kHz were also assessed.

RESULTS: Hearing loss was shown in 47(65.3%) participants. The prevalence of hearing loss increased with age, ranging from 42.86% in the 20-29 years group to 90.91% in the 50-59 years group. High frequencies (4 and 8 kHz) were more often impaired than other frequencies used to measure PTA. CONCLUSIONS: Hearing loss is common in adults with DS and shows a pattern compatible with precocious aging of the hearing system. Auditory evaluation is strongly recommended in adults with DS.

#7

BONE MINERAL DENSITY IN ADULTS WITH DOWN SYNDROME

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INTRODUCTION. Down syndrome (DS) in adulthood presents with a high prevalence of osteoporosis. However, in DS, bone mineral density (BMD) can be underestimated due to short stature. Furthermore, the rate of age-related decline in BMD and its association with gender in DS has been rarely evaluated or compared with the general population. AIM. To assess the variation of BMD with age and gender in a sample of adults with DS and to compare these data with those of the general population, after adjusting for anthropometric differences. METHODS. Adults with DS, aged 18 or older, were assessed dual-energy-Xray-absorptiometry (DXA) at the femoral neck and at the lumbar spine. They were compared with the general population enrolled in the National Health and Nutrition Examination Survey (NHANES) 2009-2010 dataset. In order to correct for anthropometric differences between the two groups, volumetric BMD was estimated for each individual through bone mineral apparent density (BMAD) calculation. RESULTS. DXA was evaluated in 234 subjects with DS (mean age 36.93±11.83 years, ranging from 20 to 69 years; 50.4% females). In the lumbar spine mean BMD (DS:0.886±0.008 vs. NHANES:1.061±0.004, p<0.001) and BMAD(DS:0.138±0.001 vs. NHANES:0.152±0.001, p<0.001) were significantly lower in the DS sample than in the NAHNES cohort, as was femoral neck BMD (DS:0.682±0.008 vs. NHANES:0.832±0.003, p<0.001). On the contrary, femoral neck BMAD (DS:0.157±0.002 vs. NHANES:0.158±0.000, p=0.586) didn't show differences overall but only when performing the analyses for age groups: older subjects in DS showed decreased bone density. Furthermore, BMAD in the femoral neck decreased with age more rapidly in the DS group, while in the lumbar spine region no significant linear correlation between BMAD and age could be observed. CONCLUSIONS. Adults with DS show lower bone mineral density compared to the general population, and faster decline of bone density with age, leading to a potentially higher fracture risk.

#8

MULTIDIMENSIONAL EVALUATION OF ADULTS WITH DOWN SYNDROME USING THE INTERRAI ID INSTRUMENT

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BACKGROUND. Individuals with Down syndrome (DS) are now living into adulthood and old age. They present with early aging and multiple morbidities, including cognitive and functional decline, behavioral disturbances, sensory impairment, as well as heart, breathing, thyroid, gastrointestinal and bone disorders. As such, multidimensional evaluation (MDE) is needed to provide appropriate care. MDE in adults with DS are to date scarce, promoted by few research centers and obtained with unstandardized, fragmented and obsolete instruments. Often, the focus is on neuropsychological evaluation, while functional domains remain unaddressed. AIM. To use MDE to get a full picture of the status and needs of adults with DS, and to show the characteristics of this population. METHODS. This cross-sectional study of MDE was carried out using the interRAI-ID instrument in 3 countries: Italy, US, and Canada, in different care settings such as community, day hospital, and institution.RESULTS. Data were available on over 300 adults with DS. interRAI ID items will inform on: age, sex, level of cognitive and functional impairment, physical and mental health problems, behavioral and social issues, and status of informal caregivers. CONCLUSIONS. Adults with DS experience complex and multiple health and social issues, which can be reliably evaluated by the interRAI-ID instrument. This instrument can thus be used to provide a MDE that could inform care planning decisions. Furthermore, given the availability of a compatible interRAI instrument for young persons with intellectual and developmental disabilities (i.e., interRAI Child and Youth Mental Health-Developmental Disabilities, or ChYMH-DD), consideration of implementation of both the ChYMH-DD and interRAI ID presents a unique opportunity to employ a lifespan approach to data collection, which would assist in the transition from pediatric to adult care. While important for DS, this approach and instrumentation could also be useful for adults with rare diseases and other special needs.

#9

HIGHLY RESTRICTED DOWN SYNDROME CRITICAL REGION IDENTIFIED ON HUMAN CHROMOSOME 21

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Partial trisomy 21 (PT21), the duplication of only a delimited segment of human chromosome 21 (Hsa21) associated or not to Down syndrome (DS), is an invaluable condition in providing strong evidence that not all Hsa21 loci are required for the manifestation of DS. A "Down Syndrome critical region" (DSCR) sufficient to induce the

most constant phenotypes of DS had been identified by studying PT21 as an interval of 0.6-8.3 Mb within Hsa21, although its existence was later questioned. We propose an innovative, systematic reanalysis of all described PT21 cases (from 1973 to 2015): we build an integrated, comparative map from 125 cases with or without DS fulfilling stringent cytogenetic and clinical criteria. The map allowed to define or exclude as candidates for DS fine Hsa21 sequence intervals, also integrating duplication copy number variants (CNVs) data. A highly restricted DSCR (HR-DSCR) of 34 kb on 21g22.13 has been identified as the minimal region whose duplication is shared by all DS subjects and is absent in all non-DS subjects. Also, being spared by any duplication CNV in healthy subjects, HR-DSCR is proposed as a candidate for the typical DS features, the intellectual disability (ID) and some facial phenotypes. HR-DSCR contains no known gene and has relevant homology only to the chimpanzee genome. Our results suggest that a single region associated with the manifestation of core DS features lies on 21q22.13; it appears much smaller than previously suspected and possibly contains currently undescribed genes. Bioinformatic analysis of the HR-DSCR shows RNA-Seg data annotated on UCSC Genome browser database; moreover, closed to some of these transcripts, regions of open chromatin and transcription start sites have been annotated in FANTOM5. In vitro experimental validation is in progress. Further studies are needed to characterize the region likely containing relevant targets for a cure of DS ID

#10

A ROLE FOR THROMBOSPONDIN-1 IN LEARNING AND MEMORY AND NEUROPLASTICITY

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Thrombospondin-1 (TSP-1) is an extracellular glycoprotein involved in cell-cell and cellmatrix communication. It is highly expressed during development by neurons and astrocytes in the CNS. We previously identified TSP-1 as a potent modulator of dendritic spine and synaptic formation, which is altered in Down syndrome (DS). In this study, we further analyzed the role of TSP-1 in learning and memory and neuroplasticity. We generated TSP1^{+/+}, TSP1^{-/-}, and TSP1^{+/-} mice expressing green fluorescent protein driven by the Thy-1 promoter to facilitate structural analysis of dendritic spines. We assessed cognition and dendritic spine number at 2 and 4 months of age. A coculture system was established for functional assays to study the role of TSP-1 molecular domains in spine formation.TSP-1-/mice exhibit dramatic defects in long-term memory correlating with changes in dendritic spine morphology in the hippocampus. Impaired long-term memory and alterations in dendritic spine structure are more significant at 2 months than at 4 months of age, suggesting a temporal window for TSP-1 activity. We also found that the ability of TSP-1 to mediate spine formation resides in the EGF-like repeat. Finally, we identified DS-associated interferon y (IFN y) hypersensitivity as a primary factor involved in TSP-1 deregulation in DS. The results suggest a critical role for TSP-1 in structural plasticity, learning and memory, and in the modulation of dendritic spines in vivo. Moreover, TSP-1 and associated

signaling pathways represent potential therapeutic targets to preserve neuronal connectivity in DS and other neurological disorders.

#11

DEPRESSION IN MILD COGNITIVE IMPAIRMENT AND DEMENTIA IN ADULTS WITH DOWN SYNDROME

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Introduction. In adults with Down syndrome relatively little is known about the characteristics of depressive symptomatology including changes associated with clinical progression of Alzheimer's disease. This study expands on our previous research into neuropsychiatric concerns associated with dementia status by examining these symptoms in incident versus prevalent cases of mild cognitive impairment (MCI-DS) and dementia. Objective(s). We examined the association of having significant depression (≥ 3 symptoms) across the continuum of declining cognition. We also determined if these symptoms are predictive of dementia risk. Methods. Adults with Down syndrome (age \geq 40 years; N= 368) received comprehensive evaluations at approximately 18-month intervals. The assessment battery included the Reiss Screen for Maladaptive Behavior (RSMB), which examined indications of depression and other neuropsychiatric conditions. Following the completion of data collection, the dementia status of each participant was rated at a consensus conference taking into account all the available information but excluding the RSMB. We examined dementia status and depressive symptoms at baseline (cross-sectional analyses) and at a follow-up test cycle (longitudinal analyses). Results. We found that participants with prevalent MCI were significantly more likely to show symptoms of depression (41%) than participants who were cognitively intact (25%), $\chi^2(1, 342)=5.90$, p=.015. Likewise, participants with prevalent dementia were significantly more likely to have depression (65%) compared to cognitively intact participants $\chi^2(1, 312)=18.90$, p<.001 and those with MCI-DS, $\chi^{2}(1, 82) = 4.20$, p=.040. Depressive symptomatology was also predictive of increased risk of incident dementia but not of incident MCI. Conclusions. For adults with Down syndrome, depression may become more common and severe with disease progression. Its occurrence may serve as a risk biomarker and should alert caregivers and clinicians to an increased likelihood that cognitive decline may occur in the future. However, it is not diagnostic and differential diagnosis and appropriate treatment is essential in all cases.

#12

TOWARDS GENETIC DISSECTION OF PATHOLOGIES IN TRISOMY 21 USING HUMAN CELLULAR MODELS

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Background and Objectives: Trisomy of APP seems obviously responsible for extremely high incidence and early onset of AD pathology in Down syndrome (DS) brains. However, other genes on human chr21 likely modulate the age of onset, severity and modality of the clinical picture, as DS individuals have later or absent onset of clinical AD, and less intracerebral haemorrhage pathology, than euploid individuals with dupAPP. Our aim is to identify such modulator genes on chr21 using cellular models Methods: Neurons derived from isogenic hiPSCs generated from a mosaic DS individual, unpublished iPSCs from segmental trisomy 21 DS and non-DS individuals, as well as from DS individuals with extremely early or late dementia onset are used in 2D, 3D and cerebral organoid paradigms. Optogenetic stimulation of Channelrhodopsin-2 engineered hiPSCs is used to determine the neuronal activity-dependent cellular phenotype modulation. Results: We have generated a panel of human iPSC lines with the aim of genetically dissecting DS pathologies. New iPSCs were generated from a segmental trisomy 21 patient with DS, containing a duplication of 4 Mbp DS Critical Region Only (CRO-1), and another partial trisomy 21 case (iPSCs in progress) lacking APP and all of the proximal portion of the chromosome. Selected genes, (APP, SOD1, DYRK1A and BACE2) are targeted using CRISPR/Cas9, with the aim of reducing the 3 copies back to normal 2 for one-gene-at-a-time, keeping the rest of the chromosome in trisomy, in our isogenic DS iPSC system. Conclusions: Cellular phenotypes relevant for AD pathology caused by trisomy21 can be reproduced in iPSCderived and primary NSC-derived neurons and differences sharpened by the use of cerebral organoid technology. Isogenic iPSCs allow detection of subtle changes in phenotypes and evaluation of single gene's trisomy contribution using CRISPR/Cas9 editing. Effective gRNAs were identified for all 4 genes of interest: APP, SOD1, DYRK1A and BACE2.

#13

A REPOSITORY FOR MOUSE MODELS OF CYTOGENETIC DISORDERS: VALUE OF THE RESOURCE AND A CALL FOR FEEDBACK

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Background: The National Institutes of Health (NIH)/NICHD funded repository for mouse models of cytogenetic disorders at The Jackson Laboratory (JAX) archives, distributes, and maintains live stocks of aneuploid mice with an emphasis on mouse models of Down syndrome (DS). Objective: The objective of the resources is to supply DS investigators with relevant mouse models to facilitate research and enable evaluation of potential therapeutic interventions. Mice are available to NIH and federally-funded investigators at a subsidized cost.Methods: Here we present an overview of the resource and its associated research projects. The repository includes many commonly used mouse models, including: the Ts65Dn strains developed by Muriel Davisson, the chromosome 16 duplication mice Dp(16) from Eugene Yu, as well as the translocation created by Charles Epstein, Rb(12.Ts17¹⁶65Dn)2Cje. These strains model genetic and clinical features of DS, and breeding pairs are readily available. All mice are maintained in a high barrier production facility with routine pathogen testing, fertility assessment, and genetic and phenotypic quality control. Moreover, JAX is a certified NIH vendor, which at most institutions, ensures that animals will be exempt from guarantine or re-derivation procedures. Results: The repository maximizes accessibility to critical research models and ensures reproducibility. The repository also conducts research to improve and optimize mouse model performance, explore the impact of genetic background and trisomy parent-of-origin on molecular and physiological phenotypes, and provide second-site validation of clinical phenotypes across models. The resource will be creating a "field guide" with comparative phenotypic information on several of the DS model strains, with a request for input regarding the neurobehavioral assays of greatest value. Conclusions: We invite feedback from the scientific community on the value of existing strains, suggestions for new strains of mice to include, and a call for provision of strains to the resource to benefit the DS community.

#14

RESPIRE 21 STUDY: EARLY DETECTION AND TREATMENT OF RESPIRATORY SLEEP DISORDERS IN CHILDREN WITH DOWN SYNDROME

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Based on the observation that OSA (obstructive sleep apnea) is common in Down Syndrome (DS) and that the OSA has effects on cognition, language development and behavior, we are interested to study OSA in children (between 6 month and 3 years of age) with DS. Our hypothesis is that a systematic screening and an optimal correction of OSA within the first 3 years of life of DS children are associated with an improved neurocognitive development and behavior at the age of 3 years. We want to demonstrate that an early

(from 6 months of age) and systematic (every 6 months) screening of OSA by polysomnography (PSG) in infants with DS during the first 3 years of life is associated with an improved neurocognitive development and an improved behavior at the age of 3. We will compare two groups: a test group with systematic screening of OSA from 6 months of age and the other one, a non-screened control group. We want to enroll 40 patients in each group. Cognitive outcomes were assessed by Griffith Mental Development Scale (GMDS) at the age of 3 for both groups. We also want to try to identify simple objective tools which could be used as a screening tool (and as a surrogate for PSG) for OSA in infants with DS. Respire 21 is a non-randomized prospective study that will start in June 2017 at Jérôme Lejeune Institut in France in collaboration with Pr Fauroux at Necker Hospital lasting 5 years in total 2 years for enrollment and 3 years of follow up.

#15

OVEREXPRESSION OF CHROMOSOME 21 MICRORNA HSA-LET-7C IMPAIRS SYNAPTIC FUNCTION IN HUMAN NEURONS.

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Trisomy 21 (T21) is characterized by a number of clinical hallmarks, including cognitive impairment and mild to moderate intellectual disability. Animal models and human induced pluripotent stem (iPS) cell models have demonstrated synaptic aberrations, including altered synaptic density and reduced synaptic connectivity. The formation and maintenance of synaptic connections is highly regulated. Emerging evidence implicates non-coding RNAs, including microRNAs (miRNAs), in regulating synaptic function. Several miRNAs have been implicated in spinogenesis, dendritic arborization, and synaptogenesis. Thus, over- or under-expression of miRNAs may contribute to synaptic dysfunction in neurodevelopmental disorders. T21 results in increased gene dosage of several miRNAs encoded by human chromosome 21 (HSA21), including hsa-let-7c. In the developing brain, the let-7 family of miRNAs are involved in myriad functions, including neuronal differentiation, subtype specification, and synapse formation. A definitive synaptic role for hsa-let-7 in human neurons, however, has yet to be explored, largely due to the lack of accessible live human brain tissue. Utilizing the innovative induced neuronal (iN) cell technology we are studying the effects of let-7 miRNAs on synaptogenesis in human neurons by overexpressing hsa-let-7c in control (i.e. euploid) iPS cell-derived iN cells. Morphological analysis by IHC has revealed a reduction in soma size, dendritic complexity, and density of synapsin-positive puncta in iN cells that overexpress let-7c. Likewise, electrophysiological analysis has revealed synaptic deficits, as well as an overall reduction in neuronal excitability. RNA sequencing confirms that gene networks involved in synaptic transmission, as well as neurite extension are perturbed in neurons that overexpress let-7c. By combining interdisciplinary analytical methodologies with the iN cell and iPS cell technologies to examine the functions of has-let-7c in the nervous system, we wish not only to broaden our overall knowledge of its biological functions, but also to provide important insight into potential synaptic consequences of HSA21-miRNA overexpression in T21 neurons.

#16

CELL-TYPE SPECIFIC TRANSCRIPTIONAL AND EPIGENETIC ABERRATIONS INDUCED BY TRISOMY 21

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Down Syndrome (DS) patients exhibit a spectrum of pathologies which include heart disease, cancer, craniofacial abnormalities and most predominantly ~99% of DS patients have deficits in memory and learning. However, the molecular mechanism of how triplication of Chromosome 21 elicits cognitive deficits remains unclear. Here we utilize patient derived iPSCs as well as an isogenic control to generate specific cell types of the brain to capture the epigenetic and transcriptomic signatures unique to DS. We observe genome-wide transcriptional and epigenetic alterations spanning beyond chromosome 21 and these alterations recapitulate the observed phenotypes in human patients as well as DS mouse model.

#17

IDENTIFICATION OF HSA21 GENES UNDERLYING DEFICIENT SONIC HEDGEHOG SIGNALING IN DOWN SYNDROME

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An abnormal mitogenic response to Sonic hedgehog (SHH) causes cerebellar hypoplasia and neural crest abnormalities in the Ts65Dn mouse model of Down syndrome (DS). Because SHH signaling is involved in many distinct developmental processes, dampened signal transduction could provoke pleiotropic phenotypes in the heart, brain, craniofacial skeleton, and enteric nervous system. While treatment with a Sonic agonist rescues cerebellar morphology and performance in learning and memory tasks, it is unknown which human chromosome 21 (HSA21) genes are responsible for corresponding phenotypes in individuals with DS. Additionally, the central role of SHH in development suggests that multiple trisomic genes could contribute to inappropriate integration of SHH signals. To identify HSA21 genes that alter SHH signaling, we constructed a library of HSA21 cDNAs with high homology to mouse genes and designed a multilevel screen with both in vitro and in vivo readouts of SHH signaling. Surveying this library in luciferase assays and in zebrafish established a set of 40 candidate genes, which will be filtered using cell-based assays prior to validation in mouse models. Establishing which genes and related pathways are responsible for diminished response to SHH may suggest new therapeutic avenues for ameliorating a range of phenotypes in Down syndrome. Moreover, the HSA21 cDNA library is publicly available and offers a valuable tool for examining other aspects of trisomy 21.

#18

MODULATION OF THE ENDOCANNABINOID SYSTEM AS A NOVEL APPROACH TO TREAT COGNITIVE IMPAIRMENT IN DOWN SYNDROME MOUSE MODELS

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Down syndrome (DS) is caused by an extra copy of the human chromosome 21 and it is the most common genetic cause of intellectual disability. Nowadays, efforts are focused on reducing such disability with different combinations of cognitive training and pharmacological interventions. Mouse models of DS have allowed characterization of a number of phenotypes in the disorder as well as assessment of novel therapies and even speculation on their mechanism of action. Among the preclinical models, the segmentally trisomic Ts65Dn mouse line and the transgenic overexpressing DYRK1A (TgDyrk1A), a kinase relevant for the cognitive and neuronal alterations on DS patients, allow obtaining complementary clues of the physiopathological and the therapeutic potential of the pharmacological approaches. The endocannabinoid system, a retrograde neuromodulatory system that controls neurotransmitter release, plays a major role in learning and memory. The content of endocannabinoids has been found enhanced in whole brain homogenates from old Ts65Dn mice, and the inhibition of endocannabinoid degradation improved the performance in Ts65Dn old mice. We explored whether the modulation of the endocannabinoid system could affect the cognitive phenotype in young adult individuals of both preclinical models of DS. Both models displayed a significant impairment in the novel object recognition and novel place recognition memory tasks, accompanied by well characterized alterations in the proliferative niches in the subgranular zone of the dentate gyrus. The modulation of the endocannabinoid system activity through pharmacological tools improved the performance in both memory tests. In addition, proliferative alterations were modified in both models after these pharmacological treatments. In conclusion, our results suggest that the modulation of the endocannabinoid system activity may have beneficial effects in the treatment of intellectual disability in DS.

#19

CEREBRAL ORGANOIDS IN THE STUDY OF CENTRAL NERVOUS SYSTEM DEVELOPMENT IN DOWN SYNDROME

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To better understand the cellular and molecular processes associated with Down syndrome (DS) in the human central nervous system (CNS), we generated a model of early neuronal development using human induced pluripotent stem cells (IPSc) as a starting template. We obtained IPSc from an individual with Down syndrome and a line from an unrelated euploid individual. With some modifications to the method first described by Lancaster et al (Nature,

2013), we successfully generated human cerebral organoids from both cell lines and used them for imaging experiments examining markers of stem cell populations, mitotic features, and neuronal differentiation over a 45 day period spanning the cells in 2D culture as IPSCs. through induction into 3D embryoid bodies and neurospheres, and finally as expanding neuronal populations in organoids. We performed deep proteome profiling with label-free quantitation of samples taken at each stage in organoid production: a.) IPSc growing in 2dimensional standard maintenance culture, b.) embryoid bodies grown in suspension, 3.) neurospheres with fate-restricted neural progenitor populations and radial neuroectoderm, and 4.) organoids grown following embedding in extracellular matrix, cultured in suspension for 21 days. We quantified over 8,500 proteins in each sample and our proteomics analysis shows many proteins changing in significant abundance due to Trisomy 21, with alterations in members of Wnt and Notch signaling pathways, neurotransmitter metabolism, axon guidance, cell adhesion and extracellular matrix interactions. We also examined the effects of pharmacological inhibition of the protein kinase DYRK1A, located on the Down Syndrome Critical Region (DSCR), and observed changes in the proteome with drug treatment consistent with significant normalization effects on expression levels of several key signaling pathway members involved in neuronal differentiation and axon guidance. These data demonstrate the utility of IPSC-derived neuronal tissues and analysis of their in vitro developmental trajectories to study complex regulatory processes in neurodevelopment.

#20

THE DS-CONNECT[®] REGISTRY PROFESSIONAL PORTAL: SUMMARY OF SUPPORTED DOWN SYNDROME RESEARCH PROJECTS

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Background: The National Institutes of Health (NIH) supports Down syndrome (DS) research to better understand the condition and develop treatments and interventions. launched DS-Connect[®]: The Down NICHD/NIH Syndrome Reaistrv (http://DSConnect.nih.gov) in 2013 to facilitate information sharing among persons with DS, families, and researchers. In 2014, the professional portal was launched to allow investigators to access the de-identified data for research purposes. In addition, NIH has published updated research objectives for DS in Down Syndrome Directions: The NIH Research Plan Down Svndrome on (https://www.nichd.nih.gov/publications/pages/pubs_details.aspx?pubs_id=5865). Objective: The goal of DS-Connect[®] is to facilitate information sharing among persons with DS, families, and researchers. The registry also enables researchers to use de-identified data to develop studies on the etiology, natural history, and treatments for DS and associated conditions. Methods: Participants enter demographic and health information into the online, secure, confidential DS-Connect® database. They can answer surveys, see graphs of their child's growth parameters, look up health care providers provided by other families, and

view aggregate de-identified data from all participants. Opportunities for clinicians and researchers to access the DS-Connect[®] professional portal include three levels of access depending on their needs. A summary of research projects and resulting publications that have used DS-Connect[®] will be presented. Results: As of April 2017, the registry had over 3500 participants. Over 253 individuals have signed up for a professional account, and 18 have requested level 2 or 3 access to use the data for assistance with presentations or completing studies. The registry has been successful in helping researchers meet their recruitment goals, especially in survey-based studies, but also for NIH-funded projects. Conclusions: Feedback from families indicates the value of being active participants in research that impacts them. DS-Connect[®] is a resource that both disseminates information to families and facilitates access to study participants by the DS research community.

#21

DEVELOPMENTAL EXPRESSION AND DYSREGULATION OF MIR-146A AND MIR-155 IN DOWN SYNDROME HUMAN BRAIN AND MOUSE MODEL

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Background: The role of the inflammation in Down Syndrome (DS) neuropathology is poorly understood. Increasing evidences support the involvement of miRNAs in the inflammatory response during neurodegeneration, including Alzheimer disease. Objectives: We hypothesized that dysregulation of specific miRNAs, such as miR-146a and miR-155, may be involved both in neurodevelopment and neurodegeneration in DS. Methods: The expression patterns and cellular distribution of miR-146a and miR-155 were investigated by in situ hybridization in control and DS hippocampus during the pre- and early postnatal development and quantitative real-time PCR was employed to evaluate the miRNA levels, the expression of putative targets (i.e TRAF6, IRAK1, IRAK2, CFH and SHIP1), as well as the levels of interleukin-1 β in hippocampus and cortex from DS, with and without AD neuropathology, and from Ts65Dn mice from 4-5 weeks to 18 months compared to agematched euploid mice. Results: Both miRNAs show a similar temporal and spatial neuronal pattern of expression in human DS and control hippocampus. However, in human DS hippocampus we observed increased miR-146a expression in reactive astrocytes. We detected in adult (18 months of age) Ts65Dn mice an upregulation of IL-1ß and a reduction of miR-146a (hippocampus and cortex) and miR-155 (hippocampus) compared to young animals (4-5 weeks). In the cortex, the expression of miR-146 was negatively correlated with the its target Traf6, suggesting a modulation of the IL-1 β pathway. The mechanisms underlying the age and region specific changes of miR-146a and miR-155 in Ts65Dn mice are still unclear and deserve further investigation. Conclusions: This study provides the first description of the expression pattern and cellular localization of two inflammation-related miRNAs, associated with the activation of the IL-1 β pathway in control and DS hippocampus that suggests a possible involvement of miR-146a and miR-155 both in brain development and neurodegeneration.

#22

PROGRESSIVE ASSEMBLY OF MICROGLIA-ASTROCYTE REACTIVE GLIAL NETS IN THE ADULT AND AGED DOWN SYNDROME BRAIN.

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Major advances in the management of symptoms associated with Down Syndrome (DS) have led to a dramatic increase in life expectancy. However prolonged life expectancy comes with challenges including the development of Alzheimer's disease (AD) neuropathology in a high proportion of DS adults. Like in AD, DS brain pathology includes synaptic loss, neurodegeneration, beta amyloid (1-42) (AB) deposition, tauopathy, neurofibrillary tangles, glial reactivity, and neuroinflammation. To better understand brain pathology in DS and AD we pioneered a labeling and imaging method, which enables multichannel 3D light microscopic analysis of neuronal and glial pathology in long-term fixed DS and AD tissue samples. Using this method we investigated the reorganization of activated microglia and reactive astrocytes near sites of neuropathology such as A β plagues and neurofibrillary tangles in DS. Detailed quantifications show extensive glial remodeling in DS and the assembly of specialized structures that we term Reactive Glial Nets (RGNs) around distinct A β plaque types. Interestingly, we also show progressive changes in the interactions of microglia and astrocytes with A β plaques with age in both the frontal cortex and in the hippocampus. These changes suggest that microglia migrate to A^β plaques first and are later followed by the reorganization of astrocytes to form the RGN. To study molecular mechanisms involved in glial-mediated pathology in DS, we have developed an in vitro model using Induced pluripotent stem cells (iPSCs) reprogrammed from fibroblasts of DS and control individuals. We have developed protocols to differentiate these cells into astrocytes and neurons and are now investigating the contributions astrocytes to neuronal pathology. In the future, this IPSC model will provide a platform for modifying both glial and neuronal pathways that contribute to cellular dysfunction related to DS.

#23

PLASMA METABOLOMICS REVEALS A DISTINCT SIGNATURE OF METABOLIC CHANGES ASSOCIATED WITH TRISOMY 21

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Down syndrome (DS) is caused by a triplication of chromosome 21 (trisomy 21) and is characterized by a complex phenotype including both developmental and chronic health complications. For example, individuals with DS have an increased risk of developing comorbidities such as Alzheimer's disease and autoimmune disorders. The clinical manifestation of DS comorbidities is highly variable, however, and our understanding of the systemic, cellular and physiological mechanisms modulating the effects of trisomy 21 in individuals with DS is limited. Metabolomics has increasingly been used to investigate the systems biology underlying complex phenotypes. A major strength of this approach is its potential to provide a global overview of multiple biochemical pathways, reflecting the cumulative effects of environmental and genetic regulation. Prior studies have observed changes in plasma metabolite concentration in adults with DS that may indicate abnormalities in the immune system. However, these studies were limited in cohort size and the number of metabolites measured. Therefore, to characterize the global profile of metabolic changes associated with trisomy 21, we performed untargeted mass spectrometry metabolomics on plasma collected from 49 individuals with DS and 49 controls. Our analysis revealed consistent changes in tryptophan pathway metabolites: individuals with DS had lower tryptophan levels and significantly increased levels of the downstream products kynurenine and guinolinic acid. Kynurenine is produced in response to immune activation and increased levels have been associated with cognitive deficits and Alzheimer's disease. Quinolinic acid is a potent neurotoxin produced by microglia and macrophages in response to stimulation by inflammatory cytokines. We hypothesize that altered flux through the kynurenine arm of tryptophan metabolism could contribute to ill effects of trisomy 21, including neurodevelopmental abnormalities and an increased risk of Alzheimer's disease. This work represents a critical first step towards characterizing metabolic alterations in DS and understanding their potential physiological implications.

#24

DOWN SYNDROME: IT'S NOT ALWAYS ALZHEIMER'S

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Alzheimer's disease (AD) is the major comorbidity of Down syndrome (DS) with aging with more than 75% of DS patients have AD after 65 years. AD in DS is genetically determined because chromosome 21 carries the *APP* gene. Due to trisomy 21, the presence of an extra copy of the *APP* gene leads to the overproduction of amyloid peptide in the brain and to AD pathogenesis. The fact that the association between AD and DS is now well-identified leads patients' caregivers to interpret any behavioral changes or any cognitive or functional alteration as a symptom of dementia. Most of the time, patients come to our geriatric consultation service with questions concerning dementia. Here we report cases of differential diagnosis of AD in elderly DS patients to emphasize that "for Down syndrome patients: it's not always Alzheimer's". Many comorbidities can affect cognition such as

obstructive sleep apnea (OSA) which is also very common in DS. Patients with a cognitive decline should be systematically tested for OSA, as for vision and hearing. In a case of pheochromocytoma, systemic inflammation caused sickness behavior, which was interpreted like cognitive decline. Abdominal pain was responsible of gait disorders and hypotension of falls, also interpreted like functional decline. Finally, dementia can have other causes than AD, e.g. Huntington's disease. Alzheimer's diagnosis in DS is a difficult diagnosis. It requires a complete evaluation of the patient by a multidisciplinary team, made up of expert health care professionals who have specialized knowledge and training in complex conditions associated with intellectual disability and aging.

#25

PHARMACOLOGICAL INTERVENTION TO PROMOTE MYELINATION IN DOWN SYNDROME

Patricia Rein¹, Nadine Aziz¹, Chelsea Leblang¹, Cristina Pineda Delgado¹, Tarik Haydar¹ ¹Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston Insufficient myelination can reduce neuronal communication speed and result in widespread complications implicated in Down syndrome (DS), such as loss of motor skills and cognitive impairment. Our prior work, investigating changes in gene expression due to triplication of human chromosome 21, demonstrated disruption in genes related to oligodendrocyte precursor cells and the maturation of oligodendrocytes. This finding is modeled in Ts65Dn mice, where it was shown that compared to euploid littermates, Ts65Dn animals have a significantly thinner myelin sheath surrounding cortical axons, and a significant increase in the number of immature oligodendrocytes at the expense of mature oligodendrocytes. These cellular changes are correlated with functional changes; measurements of compound action potentials across the corpus callosum show a reduced velocity in myelinated fibers in Ts65Dn animals, compared to euploid littermates. Together, these findings suggest that in DS there is a deficit in the ability of OPCs to differentiate into mature oligodendrocytes, leading to disruptions in myelin structure and integrity. Three compounds have been shown to promote OPC differentiation in vitro and our preliminary in vivo studies illustrate that these compounds increase the number of mature oligodendrocytes in both euploid and Ts65Dn corpus callosum. Treating animals during the postnatal period of active myelination increased the ratio of mature to immature oligodendrocytes. Future studies will examine the functional changes that result from these treatments and develop novel pharmacological therapies that facilitate the healthy development of OPCs to maturation. Finding novel target sites and developing compounds to promote OPC differentiation could serve as a potential therapy for the cognitive and motor deficits found in DS.

#26

A DRUG REPOSITIONING STRATEGY FOR IDENTIFICATION OF DRUGS WHICH MAY CORRECT PROLIFERATION DEFICITS IN TRISOMIC NEURAL PROGENITORS

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Down syndrome (DS) is a neurodevelopmental disorder caused by the triplication of human chromosome 21 and the most common genetic cause of intellectual disability. Up to now no pharmacotherapies are available. A well characterized preclinical model for DS is the Ts65Dn mouse line. This model shows reduced proliferation of neural progenitor cells (NPC), reduced neurogenesis, with, in parallel, increased gliogenesis and, importantly, cognitive impairment. In vivo mouse data show that trisomy-linked brain abnormalities can be corrected with treatments in the early stages of life or during pregnancy. Our goal is to develop an in vitro phenotypic assay to screen drugs for their potential to correct proliferative deficits in trisomic neonatal NPC. To do that we decided to apply a drug repositiong strategy that consists in finding new therapeutic indications for clinicallyapproved drugs. To this aim we established a proliferation assay using primary cultures of NPC obtained from the subventricular zone (SVZ) of Ts65Dn (Trisomic, TS) and euploid (EU) pups (1-2 day postnatal). The assay development workflow included an initial optimization phase of materials, reagents, cell conditions and all the parameters to obtain a miniaturized, reproducible, time-resolved, and sensitive assay. We are currently screening 1895 FDA approved drugs from two different commercial libraries. The assay can not only identify drugs that promote proliferation, but also previously unrecognized drugs which can be toxic to NPC. After completion and identification of hits we plan to confirm data in a secondary assay, based on BrdU incorporation, and potentially select promising candidate drugs to be tested in vivo in Ts65Dn mice. We believe that such an effort can potentially increase our current knowledge on mechanisms underlying NPC proliferation deficits in DS as well as suggest new potential therapies for this neurodevelopmental disorder

#27

UTILITY OF EMR-INTEGRATION FOR SELECT AMERICAN ACADEMY OF PEDIATRICS GUIDELINES FOR DOWN SYNDROME

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Introduction: Established guidelines for the care of children with Down syndrome from the American Academy of Pediatrics (AAP) are not always followed. A previous physician survey resulted in repeated suggestions to integrate the AAP guidelines directly into the electronic medical record (EMR). Aims: Integrate components of the AAP guidelines into the EMR and track adherence to components of the AAP guidelines over time to evaluate the impact of EMR-integration. Design: Two methods of EMR-integration were created: 1) a best practice advisory (BPA) prompting an order for referral to genetics and 2) a Health Maintenance record which tracked CBC/hemoglobin, TSH, Echo and sleep study. These quidelines were chosen because they are universal guidelines for all children with Down syndrome within a given age range and do not require that specific symptoms are present. Additionally, they are guidelines which are frequently completed at our institution allowing us to track completion. Age-associated logic in EMR-integrations allowed us to only prompt guidelines which are recommended for the patient's age. The BPA also included a link to the current AAP recommendations. The Health Maintenance record tracked if guidelines were completed and the due date for the next guideline. EMR-integration was implemented in June 2016 at select locations: primary care centers, neonatal intensive care units and genetics clinic. Methods. EMR guery by ICD-10 code identified patients with Down syndrome and any visit to Nationwide Children's Hospital (NCH). Targeted chart review for components of AAP guidelines and basic demographic information was completed. Agerelated adherence and total monthly adherence rates were calculated and tracked longitudinally in a p-chart. Results: 272 visits to the locations with EMR-integration corresponded to 155 patients of ages 0-29 years. Baseline age-related adherence was 65.3%; monthly baseline adherence ranged from 60.5% to 72.4%. Baseline net adherence prior to EMR-integration for each of these five measures ranged from 54% to 79%. EMRintegration was associated with a shift in age-related adherence to 72.5% with monthly postintervention values ranging from 33.3% to 87.8%. Tracking this data on a p-chart showed trends in improvement and a shift in data corresponding to timing of EMR-integration. Comparing baseline to post-intervention adherence for all age-associated guidelines using Fisher's exact test yields p= 0.058; further data is needed to reach statistical significance. Focusing on BPA guideline (Genetics referral) yielded small numbers with high variability due to limited number of patients in the age at which this guideline applies. Focusing on Health Maintenance guidelines showed trends similar to that for all guidelines with a shift in June and improvement in adherence from baseline of 65.0% to 69.6%, p=0.155. Conclusion: EMR-integration is a useful tool in improving adherence to the health supervision guidelines for Down syndrome. However, EMR-integration in isolation does not result in 100% adherence suggesting need for continued improvement.

#28

RESTORING GENE DOSAGE IN DOWN SYNDROME VIA CRISPR/CAS9-MEDIATED GENOME EDITING

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¹Istituto Italiano di Tecnologia (IIT), Department of Neuroscience and Brain Technologies, Genova Italy.² Università degli Studi di Genova, Genova; Italy.³ Dulbecco Telethon Institute Down syndrome (DS), is a genetic disorder caused by the presence of a third copy of chromosome 21 and it is considered the most common genetic cause of intellectual disability. Among the 500 genes and putative genes overexpressed, NKCC1, APP and Dyrk1A have been object of recent studies demonstrating their possible involvement in hippocampus dependent-cognitive dysfunctions in adult DS mice. Nevertheless, DS is diagnosed in utero and NKCC1, APP and Dyrk1A exert a crucial role during early brain development. Here, we propose to take advantage of the CRISP-Cas9 tool coupled to tripolar in utero electroporation (IUE) to restore un-harmful levels in the expression of NKCC1 APP and Dyrk1A in neuronal progenitors of the hippocampus, starting from embryonal stages in the Ts65Dn mouse model of DS. To this aim, we designed specific RNA guides (sgRNA) against our genes and we tested them in vitro in N2a neuroblastoma cells. First, we analyzed the guides' ability to edit DNA by the Surveyor Mutation detection kit, demonstrating that at least one guide edited the selected genes. Accordingly, we found that the tested guides reduced the expression levels of the protein encoded by their respective target genes. We are currently studying our guides' ability to rescue impaired proliferation and differentiation in DS neural progenitors. In parallel, we validated the Cas9 cutting efficiency in hippocampal neural progenitors in vivo IUE. Indeed, we are currently

injecting the guide targeting APP in the hippocampal progenitors of DS embryos and evaluating its ability to determine a possible rescue in the hippocampal-dependent cognitive deficits. Altogether, our in vitro and in vivo preliminary results suggest that the downregulation of APP, NKCC1 and Dyrk1A by CRISP-Cas9 technology at early stages of development may represent a possible therapy.

#29

FACTORS ASSOCIATED WITH COGNITION AND BEHAVIOR AMONG INDIVIDUALS WITH DOWN SYNDROME: A REPORT FROM THE DOWN SYNDROME COGNITION PROJECT

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The cause of the high degree of variability in cognition and behavior among individuals with Down syndrome (DS) is unknown. We hypothesize that a combination of genetic and environmental factors affect an individual's level of function and that identifying contributions of specific factors will illuminate the mechanisms underlying cognitive impairment. This report is a description of the first 234 individuals (age 6-25 years) enrolled in the DS Cognition Project. Information from medical records, parent interviews, and a modified version of the Arizona Cognitive Test Battery (ACTB) was obtained. We focused on birth defects requiring surgery in the first years of life (congenital heart defects (CHD) and gastrointestinal (GI) defects) as well as gender, race/ethnicity, and social economic status as possible factors that increase the risk for poorer cognitive and behavioral outcomes. We found that certain tests of the ACTB were influenced not only by the age of the participant, but by other factors such as sex, age of entry into services, and household income. These factors need to be considered when testing for associations of performance among those with DS. Also, these results underscore the importance of early intervention and support to increase the potential of individuals with DS. We then examined the effect of CHD and GI defects on test outcomes. Our results suggest that having such defects does not predict significantly worse cognitive or behavioral outcomes in these school-age children with DS. We are now poised to conduct genetic studies to identify altered pathways that may contribute to an individual's level of function. Our goal is to increase our sample size and obtain genotype information through DS360, a proposed DS Research Consortium.

#30

THE CRNIC INSTITUTE HUMAN TRISOME PROJECT BIOBANK

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Espinosa, PhD^{1,3}

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People with trisomy of HSA21 (T21) have a different disease spectrum, as they are protected from some conditions while predisposed to others. T21 is the most common chromosomal abnormality, occurring in approximately 1 in 700 live births, and it is estimated that >300,000 individuals in the U.S.A. are affected by this condition. To elucidate how T21 causes a different disease spectrum, we established the Human Trisome Project (HTP) in July 2016. The HTP aims to be the largest and most comprehensive study of individuals with Down syndrome, including extensive characterization at the clinical, physiological, cellular and molecular levels. The Biobank that supports the HTP provides de-identified samples to approved projects to significantly increase the speed of Down syndrome research and the understanding of associated medical conditions. Enrollment began in October 2016 with primary emphasis on adults with Down syndrome, their family members, and unrelated controls from the community. The project biobanks numerous specimen types for multi-omics data generation from 1500 participants over 5 years including, but not limited to, whole blood, plasma, red blood cell lysates, peripheral blood mononuclear cells, fluorescence activated sorted immune cells, oral and fecal samples, and induced pluripotent stem cells (iPSCs) generated from renal cells in urine. In addition to comprehensive specimen acquisition, extensive clinical data is collected from each participant, with both a self-reported questionnaire, medical records review, and cognitive and behavioral assessments. The HTP currently engages 38 investigative labs and over 100 scientists with 15 collaborations that rely on the HTP Biobank for human specimens. The HTP facilitates a multidisciplinary approach to studying Down syndrome and the HTP Biobank is providing qualified researchers with specimens and clinical information needed to significantly improve the lives of people with Down syndrome.

#31

BIOLOGICAL RESOURCES CENTER BIOJEL (CRB-BIOJEL): AN ASSET FOR RESEARCH ON THE GENETIC INTELLECTUAL DISABILITIES.

Stora Samantha¹, David Mikaël¹, Labidi Anis², Du Boispean Céline¹, Gillart Anne-Céline¹, Gambarini Alicia¹, Megarbane André¹¹*Institut Jérôme Lejeune, CRB-BioJeL, Paris, France* In spite of the significant scientific results with the animal testing, the access to human samples is essential both for basic research and diagnostic or therapeutic issues with a human application. In 2001, to meet the needs, the OCDE has launched the concept of Biological Resources Centers (CRB). Founded in 1995, the 'Fondation Jérôme Lejeune' focusses its activities around the genetic intellectual disabilities research and supports the 'Institut Jérôme Lejeune', referent center in the intellectual disabilities. The Institute associates consultation with research and, since December 2008, to develop research activities and offer a tool to the scientist community, a biobank was created in the associated lab to collect phenotypic data and collect-transform-store validated biological samples, for their provision. CRB-BioJeL has been certified since 2011 (NF S96-900). To date, 1747 resources has been implicated in scientific collaborations. Thus, CRB-BioJel developed 4 collections: Down Syndrome, Mental Retardation (non-diagnosed) Others mental retardation (diagnosed), Control

Collection Down Syndrome: 1134 blood collections (160 are longitudinal)		
Resources	DNA	1039
	PBMCs	862
	Lymphoblastoid lines	626
	Plasmas	815
Sub-collections	T21 free	569
(number of blood collect)	T21 whitout karyotype	418
	T21 translocation	28
	T21 mosaic	10
	Parents	109
Age	0-7 years	149
(number of blood collect)	8-15 years	244
	16-35 years	354
	≥36 years	387

Down Syndrome collection contains :

#32

TRISOMY 21 CONSISTENTLY ACTIVATES THE INTERFERON RESPONSE

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Down syndrome (DS) is the most common chromosomal abnormality in the human population and is the result of trisomy of Hsa21 (T21). The population with DS presents with a completely different disease spectrum than the typical population. Individuals with DS have a greatly reduced risk of solid tumors, coronary artery disease, and heart attacks, while at the same time they have increased risk of disorders affecting many major organ systems. Individuals with DS experience much higher rates of Alzheimer's disease, immune disorders, and pediatric leukemias. Using a panel of 12 fibroblast cell lines, half of them with T21, we identified a gene expression signature caused by T21 that withstands variations in age, sex, genetic background, and site of biopsy. Interestingly, this signature is dominated by marked overexpression of Interferon Stimulated Genes (ISGs) downstream of Type I, II, and III IFN signaling. Using pathway enrichment analysis, we found that the global gene expression signature could be explained in large measure by activation of multiple

components of the IFN signaling pathway. Using recombinant IFN ligands, we found that T21 fibroblasts are hypersensitive to IFN stimulation, as revealed by super-induction of canonical ISGs. Furthermore, we found that the ISG expression signature could be reversed by pharmacological inhibition of JAK1/2 kinases, which in turn were identified in a kinome shRNA screening as differential negative regulators of T21 cell survival and proliferation. Consistent activation of the IFN response by T21 was observed in three other cell types: B cell-derived lymphoblastoids, and fresh isolates of monocytes and T cells. Therefore, we propose that interferon activation, likely via increased gene dosage of the four interferon receptors encoded on chromosome 21, contributes to many of the clinical impacts of trisomy 21, and that interferon signaling antagonists could have therapeutic benefits in DS.

#33

ACTIVITY-DEPENDENT PLASTICITY AND REFINEMENT DEFECTS IN VISUAL AND OLFACTORY SENSORY SYSTEMS IN MOUSE MODELS OF DOWN SYNDROME

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Activity-dependent refinement of circuitry plays an essential role in the development of functional connectivity in the brain during early postnatal life. Disruption of this process may contribute to developmental delay and subsequent cognitive impairment in Down syndrome (DS) patients and defects in the refinement of sensory systems may further contribute to impairment in the maturation and function of higher order circuitry. To test the hypothesis that developmental plasticity in sensory systems is impaired in DS, activity-dependent plasticity and refinement were assessed in the visual and olfactory systems in the Ts65Dn and Ts1Rhr DS mouse models. We find that Ts65Dn mice demonstrate a defect in ocular dominance (OD) plasticity, the visual cortical plastic response to monocular deprivation. This phenotype is similar to a plasticity defect we previously demonstrated in transgenic mice overexpressing a mutant allele of Amyloid precursor protein (APP); however, restoring the number of copies of APP to 2N fails to rescue plasticity, suggesting that trisomy of APP is not required for this phenotype. The Ts1Rhr DS mouse model, harboring a smaller duplication, demonstrates the same OD plasticity defect, suggesting a gene or genes sufficient to drive the phenotype are located in that smaller duplication. In addition, we find that Ts65Dn mice demonstrate an abnormality in olfactory system connectivity, a defect in the refinement of connections to second-order neurons in the olfactory bulb. Ts1Rhr mice do not demonstrate a defect in glomerular refinement, suggesting either that distinct genes or sets of genes underlie visual and olfactory system phenotypes. These data suggest that developmental plasticity and connectivity are impaired in sensory systems in DS model mice, that such defects may contribute to functional impairment in DS patients, and that these phenotypes provide novel means by which to examine the genetic and molecular bases for neurodevelopmental impairment in model mice in vivo.

#34

AFRT, THE FIRST EUROPEAN ASSOCIATION DEDICATED TO RESEARCH ON TRISOMY 21

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AFRT, the French Association for Research on Trisomy 21, was created in 1990. In the early 90's, the idea was that Down syndrome was almost impossible to understand, as due to a whole chromosome. AFRT was among the ones trying to reverse that idea and to give some hope to the families. Even if trisomy 21 (T21) is very complex and affects differently each person, it is only through research that one can make progress in studying this syndrome and find some basic and pharmacological pathways to interfere with the deficits. This point of view is nowadays more widely accepted, and the recent results are, rather encouraging. Since 1995, AFRT informs its members about recent and ongoing research through a publication: "News from Chromosome 21". In January 2005, AFRT initiated the choice of March 21st, as an emblematic day for T21 (3 chromosomes 21), and decided to hold a workshop every March 21st. The meeting of March 2005 took place in Paris, with the participation of FAIT21 and Fondation Jérôme Lejeune. In June 2005, at an international meeting held in Palma de Majorca and attended by some board members of DSI and EDSA. the president of AFRT proposed March 21st as the World Down Syndrome Day, and that is how this date was settled and later approved by WHO in 2007 and UN in 2011. Since 2005, AFRT organizes every year a meeting in France around March 21st. The 2016 meeting was in Marseilles and the 2017 one in Grenoble, each gathering about 200 participants. Our web site afrt.fr displays the program and the slides of the last meetings, showing the amount of new information on medical, scientific and societal topics which is now available for persons with T21, their families, and the people involved in a better life for them. Besides collecting and spreading information about trisomy 21, AFRT also promotes research through some fellowships for students and grants for research teams. In recent years, support was mainly focused on the detection of sleep apnea, the aging aspects of ocular problems and nervous and mental breakdown.

#35

AUTOSOMAL TRISOMIES 21, 18, 13 AND MALIGNANCIES Daniel Satge

Oncodéfi and University Institute for Clinical Research EA2415 (IURC) Montpellier, France Aim: comparison of cancer risk and cancer distribution in children with trisomy 21 (T21, Down syndrome, DS) trisomy 18 (T18, Edwards syndrome, ES) and trisomy 13 (T13, Patau syndrome, PS), to allow an adapted cancer surveillance and to understand the impact of a supernumerary chromosome on oncogenesis. Method: extensive review of the literature and comparison with cancer distribution in euploid children up to 14 years. Results: T21 (1/1,000 births) globally increases cancer risk with hundreds of reported malignancies, while only 47 malignancies have been reported in T18 (1/7,000 births) and only 15 malignancies in T13 (1/15,000 births). Additionally, there is a particular distribution. T21 is associated with a high risk of leukemia, occurring early. T18 favors hepatoblastoma and nephroblastoma. T13 is associated with all types of cancer including carcinoma. In T21 embryonic tumors are rare (neuroblastoma, nephroblastoma, hepatoblastoma, medulloblastoma), in T18 brain tumors and hematopoietic tumors are very rare. In T13 the distribution is on the contrary widened to epithelial cancers (two neonatal carcinomas). Discussion: correlation with congenital malformations, body weight, organ weight is not obvious. Correlation with known cancer genes on chromosomes 21, 18 and 13 is not clear. Conclusion: Down syndrome, Edwards syndrome and Patau syndrome have a particular tumor profile. ES and PS do not seem to increase cancer risk. These oncological phenotypes are not clearly related to known oncogenes and suppressor genes which map to chromosomes 21, 18 and 13. In these conditions malignancies could be the indirect result of complex interactions of genes on tissues.

A grant from the Fondation Jérôme Lejeune supports the study on cancer in Down syndrome

#36

DIFFERENTIAL EXPRESSION PROFILE STUDY AND GENE FUNCTION ANALYSIS OF MATERNAL FETAL-DERIVED CIRCRNA FOR DOWN'S SYNDROME

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Aims: Screening of differentially expressed circRNAs and mRNAs related to Down's syndrome, and analysis of the difference of the expression of circRNA and mRNA, to investigate the expression of circRNA in Down's syndrome and its mechanism. Methods: In this study, we collected 12 umbilical cord blood samples from pregnant females; use the gene chip technology to screen out the differentially expressed circRNAs and mRNAs from the cord blood, and then identified by PT-PCR technology. Results: 735 differentially expressed circons (414 up-regulated and 321 down-regulated) were detected in the two groups of umbilical cord blood samples. Through the GO analysis and pathway analysis, we found that the differential gene was significantly enriched 73 pathways, of which, 23 pathways were up-regulated, 50 pathways were down-regulated. By associating the 2-fold difference of the circRNA with the corresponding differential gene expression profile information, we found that 254 differentially expressed circRNAs could regulate the expression of target mRNA by adsorbing specific miRNAs. Hsa circRNA 103112 not only showed significant difference in the cord blood of DS fetus, but also showed significant difference in the peripheral blood. Hsa circRNA 103112 may have been over-expressed in DS patients. Conclusion: circRNAs are differentially expressed in DS samples based on a small sample size. Differential expression of the circRNA with its corresponding miRNA binding site, may act as miRNA sponges to bind miRNAs so as to regulate the expression of the target gene. The gene expression disorder caused by abnormal copies of chromosome 21, may be associated with DS fetal immune system developmental defects, and the emergence of low immunity, mental development abnormalities, physical retardation and other clinical symptoms. Hsa_circRNA_103112 in peripheral blood of pregnant woman may be one of the potentially important markers of fetal DS noninvasive prenatal screening.

#37

HEALTHCARE QUALITY FOR PEOPLE WITH DOWN SYNDROME: THE PATIENT PERSPECTIVE

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In the past decades, many DS-specialized healthcare initiatives have been introduced. However, little is known about their quality, which hampers monitoring and improvement, and reduces transparency for people with DS and their parents. Quality indicators (QIs) can provide insight into healthcare quality, unhide opportunities for improvement, and increase transparency. QIs for DS still need to be developed. Development of QIs should involve both care receivers (people with DS) and providers, in order to create indicators that are relevant for both groups. This study explores the patient perspective on healthcare quality for people with DS, by involving people with DS, their parents/family members and their professional carers (in case of residential care). The study aims to identify starting points for QIs by exploring how qualitative good healthcare contributes to a good life quality of people with DS. The study has a qualitative design including individual interviews with people with DS and focus group discussions with parents/family members and professional carers. Topics discussed during the interviews and focus groups are similar, including experiences with received healthcare, influence on life quality and healthcare improvement. Here we present results of the focus groups with parents. At the conference, results from interviews with people with DS will also be available and presented. According to parents, relevant issues regarding healthcare guality are: Patient-centered care in which optimal functioning of the person with DS is central; Respectful doctor-patient communication; Multidisciplinary care including actors outside healthcare (e.g. school, work) and good coordination; Information about available care. These issues will be used as starting point for the development of QIs measuring healthcare quality for people with DS. By focusing on the patient perspective we expect to develop QIs which enable healthcare improvements that are truly relevant to people with DS, add value to their lives, and enhance healthcare efficiency.

Other Sponsor Information



National Institute of Neurological Disorders and Stroke



The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. To support this mission, NINDS:

- Supports and performs basic, translational, and clinical neuroscience research.
- Funds and conducts research training and career development programs to increase basic, translational, and clinical neuroscience expertise and to ensure a vibrant, talented, and diverse work force.
- Promotes the timely dissemination of scientific discoveries and their implications for neurological health to the public, health professionals, researchers, and policy-makers.
- Supports research relevant to over 600 disease and disorder-related topics.
- Promotes neuroscience research related to Down Syndrome.

Basic neuroscience research

- Basic research is a crucial engine of discovery.
- Gaps in understanding the normal development and function of the nervous system and mechanisms of disease can form roadblocks to advances in diagnosis, treatment, and prevention. Basic research to fill those gaps is a critical piece of the NINDS mission – and an area unlikely to find sustained investment from the private sector.



 Investigator-initiated, peer-reviewed research is the foundation of the NINDS basic research program.

Translational neuroscience research

- Translational research brings new therapeutic and diagnostic strategies through preclinical testing in cells and animals to readiness for clinical testing in people.
- NINDS administers a range of funding opportunities and programs for different types of therapies at different stages of research.

Clinical trials in neuroscience and neurology

- Clinical research includes clinical trials to test the safety and effectiveness of new therapies.
- Rare diseases with small markets, therapeutic strategies that carry a high risk of failure or require long time horizons, new uses for existing drugs, and comparison of the effectiveness of available prevention strategies and treatments are among the many clinical opportunities that NINDS, rather than industry, is most likely to move forward.

Down Syndrome International (DSi)

Connecting the global Down syndrome community

- DSi is a GLOBAL NETWORK of member organisations and individuals from 136 countries across the world.
- We are committed to IMPROVING QUALITY OF LIFE for people with Down syndrome and promoting their right to be accepted and included as valued and equal members of their communities, wherever they are.
- DSi is a UK based international charity.

What we do

- We work with the international community to provide support and accurate, up-to-date INFORMATION and resources to our members and those who need it, with specific focus on developing countries.
- We REPRESENT people with Down syndrome at a global level and encourage international communication and cooperation.
- We raise AWARENESS about Down syndrome and the potential of people with Down syndrome to be valued members of their communities.

How we do it

- Through our outreach training programmes 'REACH OUT' in developing countries;
- Via our MEMBERSHIP NETWORK: sharing information and representing people with Down syndrome worldwide;
- By organising the WORLD DOWN SYNDROME CONGRESS (WDSC), a biennial meeting place for the global Down syndrome community.
- By promoting WORLD DOWN SYNDROME DAY (WDSD) on 21 March, a day recognised by the United Nations, dedicated to people with Down syndrome.

Research interests

- DISSEMINATION OF HIGH QUALITY RESEARCH to the international community in a clear, factual, understandable, sensitive and unbiased way.
- PUBLICATION of selected research abstracts on our website quarterly.
- Development of INTERNATIONAL CONSENSUS GUIDELINES in healthcare and in other areas that affect the lives of people with Down syndrome, with input from expert advisors and stakeholders.
- PROMOTION OF T21RS by having a permanent link on the homepage of our website and featuring their bulletins in our newsletter.

Contact Down Syndrome International (DSi)

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Visit DSi website: <u>https://ds-int.org/</u>

Visit World Down Syndrome Day (WDSD) website: https://worlddownsyndromeday.org/



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