



t21
RESEARCH
SOCIETY

1st International Conference of the Trisomy 21 Research Society

Changing paradigms in Down Syndrome

www.T21rs-international-conference2015.com

June 4-7, 2015, Paris

Hôpital Pitié Salpêtrière



Institut du Cerveau et de la Moelle épinière

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Dear Colleagues,

For years the rather small international community of researchers committed to understand the effects of trisomy 21 and to use this knowledge to expand opportunities for people with Down syndrome has struggled to obtain resources to support research, to recruit new generations of investigators to this area, and to enable investigators to communicate with each other to reach common goals.

A core group of those investigators have established the Trisomy 21 Research Society, an international professional organization for those engaged in Down syndrome research. The Society will provide a nexus for organizing communication between researchers and with organizations that have the means to disseminate this news to families; to assure that young researchers see the excitement and potential of a career in a rapidly advancing area of research that is making contributions to the quality of life for people with Down syndrome every day; and to coordinate a biannual international meeting of investigators.

This first meeting will be held in Paris in the Hospital Pitié Salpêtrière famous in history of neurosciences in the Brain and Spine Institute new building.

This three and half day event will discuss many aspects of Down syndrome from development to aging and clinical trials in an informal academic setting. Topics for discussion include molecular mechanisms, animal modelling, drug discovery and care. With plenty of opportunity for networking and debating, this informal international meeting will bring you up to date with current research and thinking regarding Down syndrome.

D. Jean-Maurice Delabar, President of T21RS



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COMMITTEE

Jorge Busciglio, Neurobiology and Behavior, UCI, Irvine

M-C Potier, Brain and Spine Institute, Paris

E Head, Sanders-Brown Center on aging, Kentucky

F Wiseman, University College, London

K Gardiner, Department of Pediatrics ,University of Colorado, Denver

M Dierssen, Centre for Biomedical Research on Rare Diseases-CIBERER, Barcelona

J O'Bryan, Department of Pharmacology, University of Illinois, Chicago

R Bartesaghi, Department of Biomedical and Neuromotor Sciences, University of Bologna

LOCAL ORGANISING COMMITTEE

MC Potier, Brain and Spine Institute, Paris

Jean Delabar, University of Paris Diderot and Brain and Spine Institute, Paris

Bernadette Allinquant, Centre de Psychiatrie and neurosciences

Nathalie Janel, University of Paris Diderot, Paris



PROGRAM

Day 1. June 4, 2015

7:30 – 8:00 Registration

8:00 – 8:30 Welcome/Introduction of T21RS/J Delabar

8:30 – 10:00. SESSION 1. – “State of the field: Defining DS”

Session coordinator K Gardiner

- **Genes and gender in Down syndrome** : K Gardiner, University of Colorado School of Medicine, USA
- **DS Research and the Trisomy 21 Research Society** : R Reeves, Johns Hopkins Univ. School of Medicine, USA
- **Down syndrome and Alzheimer disease. A genetic description** : J Hardy, UCL Institute of Neurology, UK

10:00 – 10:15. COFFEE BREAK

10:15 - 12:15. SESSION 2. “From molecules to systems: neuropathology in the adult with DS”

Session coordinator M Dierssen

- **Down syndrome (DS)-related proteins interaction mapping** : V Hindie, Hybrigenics services SAS, France
- **Alternative approaches in brain morphometry** : S Durrleman, ICM, France
- **Remodelling the neuronal forest in intellectual disability** : M Dierssen, Centre for Genomic Regulation, Spain
- **Redox signature in Down Syndrome brain: clues for transition to Alzheimer disease** : M Perluigi, Sapienza University of Rome, Italy
- **Early Amyloid--- β Pathogenesis in Down Syndrome** : C Lemere, Center for Neurologic Diseases, USA

- **White matter integrity, cerebrovascular pathology, aging and Alzheimer's disease in Down syndrome** : L Head, Sanders-Brown Center on Aging, USA

12:30 – 1:45. LUNCH

1:45 - 2:45. “Breakthrough Research Symposium 1”

Chair N Créau

- **Behavior and synaptic plasticity in the Ts65Dn:Kcnj6^{+/+} mouse model of Down syndrome** : A Kleschevnikov, University of California San Diego, USA
- **Impacts of duplications of human chromosome 21 orthologous regions on the mouse hematopoietic system with or without the co-presence of the Gata1s mutation** : E Yu, Roswell Park Cancer Institute, USA
- **Rescue of the abnormal skeletal phenotype in Ts65Dn Down syndrome mice using genetic and therapeutic modulation of trisomic Dyrk1a** : R Roper, Indiana University, USA
- **Reversing excitatory GABA signaling restores synaptic plasticity and memory in a mouse model of Down syndrome** : A Contestabile, Fondazione Istituto Italiano di Tecnologia, Italy

2:45 - 3:00. Coffee break

3:00 – 5:00. SESSION 3. “DS: Beyond Neuropathology and Cognition”

Session coordinator J O'Bryan

- **Dysregulation of signaling in Down syndrome: Role of Intersectin 1 (ITSN1) and Ras.** : J O'Bryan, University of Illinois at Chicago, USA
- **The Chromosome 21 Kinase DYRK1A in normal and malignant hematopoiesis** : J Crispino, Northwestern University, USA
- **Landscape of gene mutations in Down syndrome related myeloid disorders** : S Ogawa, University of Kyoto, Japan
- **Thyroid dysfunction in Down Syndrome: clinical aspects and study of the transgenic Dyrk1A mice as a model of thyroid dysgenesis in Down Syndrome** : M Polak, Hôpital Universitaire Necker, France
- **DYRK1A control of pancreatic beta cell fate and mass.** : L Rachdi, Institut Cochin, France
- **A Down syndrome screening model identifies that RCAN1 is overexpressed in Type 2 diabetic islets and causes β -cell mitochondrial dysfunction** : D Keating, Flinders University, Australia

5:15 – 7:15. POSTER SESSION 1.

5:15 to 5:45 6 selected platform presentations of posters

Chair: F Guedj

- **The Down syndrome critical region (DSCR) gene 1 is critical for the regulation of proper vessel formation and vascular inflammation** : T. Minami, The University of Tokyo, Japan
- **A Specialized Pro-Resolution Mediator Approach to Cognitive Performance in the Ts65Dn Mouse model of Down Syndrome** : E Hamlett, Medical University of South Carolina, USA
- **Effects of Prenatal Treatment With Apigenin in the Ts1Cje Mouse Model of Down Syndrome** : F Guedj, Tufts Medical Center, USA
- **The role of chromosome 21-encoded miRNAs in synaptic dysfunction in Down syndrome.** : H McGowan, Rutgers Robert Wood Johnson Medical School, USA
- **Alzheimer disease in Down syndrome: Development of an assay to quantify synaptic loss in response to A β ; oligomers in a mouse model of DS** : J Tosh, UCL Institute of Neurology, UK
- **Endo-lysosomal dysfunctions in cholinergic neurons of mice modeling Down syndrome and Alzheimer's disease.** : A Botté, Institut du Cerveau et de la Moelle, Paris, France

6:45 – 7:45. COCKTAIL

Day 2. June 5, 2015

8:00 – 10:00. SESSION 4. “Biomarkers of Pathology Progression in DS”

Session coordinator M-C Potier

- **Lessons from the mouse aneuploid zoo and new opportunities for therapeutic interventions** : Y Hérault, Institut de Génétique Biologie Moléculaire et Cellulaire, Strasbourg, France
- **Cholinertrophic Basal Forebrain Pathology in DS and AD** : EJ Mufson, Barrow Neurological Institute, USA
- **Circadian Biomarkers of Pathology Progression in Down syndrome** : F Fernandez, University of Arizona, USA
- **Genetic risk factors for dementia in adults with Down syndrome** : J Lee, Columbia University, USA
- **Validating DYRK1A as a biomarker in plasma and lymphoblastoid cell lines from Alzheimer disease and Down syndrome patients** : N Janel, University Paris Diderot, France

- **Biogenic amines underlying behavioural and psychological symptoms of dementia (BPSD) in AD and DS-AD** : P de Deyn, University of Groningen, Netherlands

10:00 – 10:15. Coffee break

10:15 – 12:15. SESSION 5. “DS: Prenatal diagnosis and treatment”

Symposium proposed by D Bianchi and sponsored by Transition Therapeutics USA.

Session coordinator D Bianchi

- **Developmental abnormalities in mouse models of Down syndrome identify early alterations of CNS formation and function.** : T Haydar, Laboratory of Neural Development and Intellectual Disorders, USA
- **Brain development in fetuses with Down syndrome** : T Tarui, Tufts Medical Center, USA
- **Genomic and bioinformatics approaches to prenatal screening for and treatment of Down syndrome** : D Bianchi, Tufts Medical Center, USA
- **Prenatal pharmacotherapy can rescue brain development and cognitive performance in the Ts65Dn mouse model of Down syndrome** : R Bartesaghi, University of Bologna, Italy
- **Prenatal corrective strategies targeting DYRK1A** : JM Delabar, ICM & Université Paris Diderot, France
- **Maternal choline supplementation: A prenatal intervention strategy for Down Syndrome** : J Ash, University of Oxford, UK

12:30 – 1:45 LUNCH

1:45 - 2:45. “Breakthrough Research Symposium 2”

Chair: B Allinquant

- **Down syndrome beyond non-disjunction.** : D Goldgaber, Stony Brook University, USA
- **Magnetic Resonance Imaging Study of the Developing Fetal Brain in Trisomy 21** : P.A Patkee, King's College London, UK
- **A regulatory crosstalk in Down syndrome: competing mRNA-miRNA network** : M Scarpato, National Research Council, Italy
- **A marked brain NGF metabolic dysfunction in Down Syndrome** : C Cuello, McGill University, Canada

2:45 - 3:00. Coffee break

3:00 – 5:00. SESSION 6. “Defining Translational Pathways for DS”

Session coordinator F Wiseman

- **A novel role for the DYRK1A protein kinase as a gene-specific RNA polymerase II CTD kinase** : S de la Luna, Centre for Genomic Regulation (CRG), Spain
- **Synaptic dysfunction and growth inhibition by APP mutation and overexpression** : W Song, The University of British Columbia, Canada
- **Alzheimer’s disease in Down syndrome: understanding the mechanism** : F Wiseman, University College London, UK
- **Biomarkers in down syndrome-related Alzheimer’s disease** : C Granholm, Medical University of South Carolina, USA
- **Endo-lysosomal alterations in Down syndrome and Alzheimer’s disease.** : M-C Potier, Brain & Spine Institute, Salpetriere Hospital, France
- **Preventing Alzheimer Disease in Down Syndrome: Challenges and Opportunities** : W Mobley, University of California, San Diego, USA

5:15 – 7:15. POSTER SESSION 2.

5:15 to 5:45: 5 selected platform presentations of posters.

Chair: A Dekker

- **Regulation of feeding behavior and glucose homeostasis in a Down syndrome mouse model** : M Fructuoso, Center for Genomic Regulation (CRG), Spain
- **Response time during dual motor task among children with Intellectual Disabilities** : P Rao, School of Allied Health Sciences, India
- **Behavioural and psychological symptoms of dementia in Down syndrome: Early indicators of clinical Alzheimer’s disease?** : A Dekker, University Medical Center Groningen, Netherlands
- **Characterization of pharmacological Dyrk1A kinase inhibitors for therapeutic use in Down Syndrome models**: TL Nguyen, IGBMC, FR
- **Searching for a molecular signature of Alzheimer’s disease in Down syndrome plasma** : F Iulita, McGill University, Canada

8:00 – 1:00 GALA DINNER (casual dress)

Day 3. June 6, 2015

8:00 – 10:00 SESSION 7. “Cognition in DS”

Session coordinator J Edgin

- **Studying cognitive development in babies with Down syndrome :** A Karmiloff Smith, University of London, UK
- **Allocentric spatial learning and memory deficits in Down syndrome :** P Banta Lavenex, University of Lausanne, Switzerland
- **Measuring Language Change in Individuals with Down Syndrome: Expressive Language Sampling :** L Abedutto, University of California, USA
- **Memory, Language, and Sleep in Down syndrome :** J Edgin, University of Arizona, USA
- **Dissociations in cortical thickness and surface area in the developing brain in Down syndrome: A pediatric structural neuroimaging investigation :** N Lee, NIMH, USA
- **Executive Function and Developmental Status in children with Down Syndrome :** D Fidler, Colorado State University, USA

10:00 – 10:15. Coffee break

10:15 – 12:15 SESSION 8. “Impact and strategies for aneuploidy in gene expression and metabolism”

Session coordinator J Busciglio

- **Transcriptome dysregulation and single cell analysis in Trisomy 21 :** S Antonarakis, University of Geneva, Switzerland
- **Epigenetics: the neglected key to minimize learning and memory deficits in Down syndrome :** M Rots, University Medical Center Groningen, Netherlands
- **Gene dosage imbalance: genomic, transcriptomic and proteomic impact. :** R Veitia, Paris Diderot University and Institut Jacques Monod, France
- **Energy Metabolism and Cellular Function in Down Syndrome :** J Busciglio, University of California-Irvine, USA
- **Multigenic origin of autophagy and mitophagy deficits in Down syndrome:** R Nixon, Nathan Kline Institute - New York University Langone Medical Center, USA
- **Cellular phenotypes caused by trisomy 21 in 2D-neuronal and brain-organoid cultures :** D Nizetic, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

12:30 – 1:30 LUNCH

1:30 – 2:45 SESSION 9 “Clinical evaluation and caring in Down syndrome”

Chair: T Blumenthal

- **Predicting Obstructive Sleep Apnea in Patients with Down Syndrome: B Skotko,** Massachusetts General Hospital, USA
- **Exploring risk factors for dementia in Down syndrome: C Startin,** UCL, UK
- **Factors Associated with Inclusion for Children with Down syndrome: D Stein,** Boston Children's Hospital/Harvard Medical School, USA
- **New tools to develop autonomy in people with Down syndrome: C Dupas,** TRISOMIE 21 FRANCE, France
- **French validation of the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID) in a cohort of Down Syndrome patients aged 40 and over:**
AS Rebillat, Jérôme Lejeune Institute, FR

2:45 – 3:15 SESSION 10. NIH agenda; DS Connect

Chair: T Blumenthal

- **DS Connect-The Down Syndrome Registry: R Riddle,** NIH/NINDS, USA

3:15 – 3:30 Coffee break

3:30 – 5:30 SESSION 11. “Tools for assessment of therapeutic approaches. Clinical trials for DS”

Sponsored by Hoffman La Roche; Session coordinator: JM Delabar

- **Regulation of self-renewal and senescence in Down's syndrome Stem Cells. :**
M Adorno, Institute for Stem Cells and Regenerative Medicine, USA
- **Dementia symptoms and diagnostic criteria in Down syndrome : A Strydom,** UCL, UK
- **Multimodal Assessment of AD Biomarkers in Down Syndrome : M Raffi,** University of California, USA
- **Efficacy assessment of folonic acid and thyroid hormone systematic treatment on the psychomotor development of young down syndrome children : C Mircher,** Jérôme Lejeune Institute, France
- **Targeted Treatment for Down syndrome: Clinical Development of RG1662 :**
J Visootsak, Hoffman-La Roche, USA
- **Tools for assessment of therapeutic approaches. Clinical trials for DS. :**
R de la Torre, Human Pharmacology and Clinical Neurosciences Research Group, Spain

5:30 – 6:00 CLOSING REMARKS by MC Potier

Day 4. June 7, 2015

8:00 – 10:00 T21RS General Assembly Meeting 1st year report

2014 budget

2016-2017 Committees

Votes

2017 Meeting

10:00 – 13:00 T21RS Science & Society Symposium

Session coordination: T21RS Committee for Science & Society, chairman:

P De Deyn

10:00 **Welcome: P De Deyn (chairman T21RS Committee for Science & Society)**

10:05 **Introduction to Trisomy 21 Research Society : A D Dekker**

Formation of the society, main aims, structure, methods, introduction to the different committees.

Time for a few general questions regarding T21RS. Specific discussion topics are intended for the general discussion at 12:00

10:30 **Introduction to attending DS associations/foundations**

11:10 Coffee break

11:30 **Introduction to Committee for Science & Society : P P De Deyn**

Current aims, established collaborations and achievements, future directions.

11:50 **Committee for Science & Society: The Dementia Table Initiative: sharing & improving knowledge about ageing and dementia in people with intellectual disabilities – How to involve relatives and caregivers? (S Overbeek, C Thoolen)**

12:00 **General discussion about Science & Society (P P De Deyn)**

1) The gap between science & society – main issues

2) How can T21RS help to close the gap?

3) New initiatives, collaborations with T21RS Committee for Science & Society

Participants:

Catalan Down Syndrome Foundation: Katy Trias

Down syndrome international:

Andrew Boys

Fondation AMIPI-Bernard Vendre : Rémi Cornubert, L Blandin

Fondation Jérôme Lejeune

Global Down Syndrome Foundation

Lumind : Michael Harpold

Matthew Foundation :

John Blascovich, Jessamy Tang

Trisomie 21 France :

Cécile Dupas

T21RS Committee for Science & Society:

Peter Paul De Deyn (Belgium)

Alain Dekker (The Netherlands)

Sebastian Videla (Spain)

Hannah Wishnek (USA – TBC)

1:00 – 2:00pm Lunch

2:00 Visit of La Salpêtrière

ABSTRACTS

SESSION 1

STATE OF THE FIELD / DEFINING DS

Genes and gender in Down syndrome

Gardiner, Katheleen

University of Colorado School of Medicine
Linda Crnic Institute for Down syndrome, Departments of Pediatrics,
and Biochemistry and
Molecular Genetics

Clinical trials for cognition in Down syndrome have been conducted, are in progress or are planned for a number of drugs with a diverse array of targets and mechanisms of action. Decisions to proceed to clinical trials are based largely on demonstrations of efficacy in one partial trisomy mouse model of DS, using only male mice, and without knowledge of the molecular links between drug action and the functions of Hsa21 genes, the molecular responses to effective drugs, or how these may differ in full trisomy Hsa21 and in females. The following issues will be discussed: (i) the genes that are encoded by Hsa21 and their similarities and differences from those that are trisomic in major mouse models of DS; (ii) gender differences in protein profiles in control mice and how these are altered in trisomy; and (iii) the complexity of protein responses to drug treatments and how computational approaches may aid in interpretation of these complexities. Comprehensive experimental exploration of these issues would improve the possibility of effective clinical trials for cognition in DS.

DS Research and the Trisomy 21 Research Society

Reeves, Roger

Johns Hopkins Univ. School of Medicine, Baltimore

Strengthening the intersection of basic research, preclinical development and clinical application has been a priority for investigators in all three areas (and their funders) for some time. The area of Down syndrome research can boast a rich variety of basic findings with a patient-oriented perspective, some of which are influencing Pharma and clinical practice and many in response to the needs of these groups. A fundamental reason for the creation of T21RS is to enrich this interface and add the critical dimension of the input from self-advocates and care-givers for persons with trisomy 21. In this presentation, I will give a perspective on a number of promising areas of interaction and of the role the Society might play in reaching the common goal of improving opportunities for people with trisomy 21.

Down syndrome and Alzheimer disease. A genetic description

Hardy, John

UCL Institute of Neurology, London

The relationship between DS and AD has long been recognised and was key to our understanding of the pathogenesis of AD. The APP gene dosage is clearly the main reason for the association however it is not the only determinant.

In my talk I will discuss how we are finding other determinants. I will suggest that all DS cases with APP trisomy will get AD dementia and the importance of carrying out Ab clinical trials in this population.

SESSION 2
FROM MOLECULES TO SYSTEMS:
NEUROPATHOLOGY IN THE ADULT
WITH DS

Down syndrome (DS)-related proteins interaction mapping

HINDIE, Valérie

Hybrigenics services SAS,

Nicole CREAU (1)

Marie-Claude POTIER (2)

Jean DELABAR (1)

Lydie LANE (3)

Anne-Sixtine LEKIEFFRE (4)

Henri BLEHAUT (4)

Jean-Christophe RAIN (5)

Protein interaction mapping has proven instrumental for the delineation and understanding of signaling pathways involved in disorders of the nervous system. We now report the construction of a DS-related protein interaction map using our high-throughput, domain-based yeast two-hybrid (Y2H) technology. 52 human proteins, selected for their putative role in DS and most importantly the associated intellectual deficiency, were used as entry points to screen a highly complex random-primed adult brain cDNA library comprising 10 million independent fragments in yeast. To ensure reproducible and exhaustive results, the library was screened to saturation thanks to an optimized mating procedure that allowed for testing on average 96 million interactions per screen, corresponding to a 9-fold coverage of the library. Moreover, multiple, independent fragments of the same interactant could be isolated, enabling the delineation of a minimal interacting domain and the computation of a confidence score. A database containing over eight thousand cDNA screens realized with this technique permits a rigorous calculation of relative prey connectivity and understanding of true/false positives and sticky proteins.

More than 1200 protein-protein interactions were identified. This experimental data has been integrated in the PIMRider software which has allowed for the dynamic exploration of the interaction network and extensive analysis of functional domains and sequences of bait and prey proteins. Finally, the experimental protein interaction map was extended by including protein interaction data from the literature.

We believe that this protein interaction map centered on DS proteins will be a valuable resource for researchers in the field. General features of the network will be described and specific interactions will be studied in details.

The InterPP program is funded by the Jérôme Lejeune Foundation.

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(3) SIB, CALIPHO, 1211, Geneva, Switzerland

(4) TRT 2.1, 75015, Paris, France

(5) Hybrigenics services SAS, 75014, Paris, France

Alternative approaches in brain morphometry

Durrleman, Stanley

ICM, ARAMIS lab (1)

Group studies in neuroimaging are dominated by “voxel-based” approaches, which compare image intensity at each voxel across all subjects. These approaches have important limitations though, such as the difficulty (and even the impossibility) to find correspondences at each location within the brain, the difficulty to account for correlations among different anatomical regions, the problem of statistical corrections due comparisons of millions of variables, or the difficulty to interpret findings.

In this talk, we will present an alternative approach for the analysis of the variations of the anatomical phenotype within a group of subjects. This approach relies on the estimation of one or several reference anatomical configuration(s), which are specific to a group of subjects. The anatomical configuration of each subject is compared to the reference(s) via spatial deformations. The parameters of the deformations are used in multivariate statistical analyses. This method allows to interpret differences between subjects or between populations as typical deformations of their brain structures.

We will present applications of this approach to address several neuro-anatomical questions, including the specificity of the shape of deep brain structures in Down syndrome patients.

(1) INRIA/CNRS/INSERM/UPMC/ICM, ARAMIS lab, 75014, Paris, France

Remodelling the neuronal forest in intellectual disability

Dierssen, Mara

Centre for Genomic Regulation, Barcelona

Networks of living neurons exhibit diverse patterns of activity, including oscillations, synchrony, and waves that originate from their wiring properties and give rise to neuropsychological qualities such as memory, exploratory behavior and spatial orientation, among others. Intellectual disability pathologies present characteristic alterations in neuronal structure and connectivity that induce relative changes of the neuronal network dynamics and, eventually, in their function. Understanding both the role and importance of the connectivity patterns that can be observed at different scales in the central nervous system are of crucial interest for advancing our knowledge on neuroscience in health and disease. I will present some examples in Down syndrome mouse models (Ts65Dn and TgDyrk1A) that recapitulate both cognitive impairments and neuromorphological alterations observed in the human chromosome 21 trisomy to systematically analyze short and long-range connectivity patterns both in homogeneous neuronal cultures and intact fixed brains.

Funded by the Jérôme Lejeune Foundation and the Spanish Ministry of Economy and Innovation (SAF2013-49129-C2-1-R)

Redox signature in Down Syndrome brain: clues for transition to Alzheimer disease

Perluigi, Marzia

Sapienza University of Rome, Department of Biochemical Sciences

The role of oxidative stress (OS) in neurodegeneration is well recognised, but in the case of Down Syndrome (DS) and Alzheimer (AD) neuropathology, genetic similarities, due to the fact that some of the genes responsible for familial form of AD are encoded by Chr21, provide the basis to better understand disturbance of redox-regulated intracellular pathways. Results obtained by the analysis of human brain samples from DS, with and without AD pathology, support the evidence of a molecular link between protein oxidation/aggregation, the integrity of protein quality control system (proteasome, UPS and autophagy), dysfunction of energy metabolism and neurodegeneration. Many common pathological hallmarks have been proposed for DS and AD including deposition of amyloid plaques, NFTs, increased oxidative damage, impaired mitochondrial function and aging effects. Results obtained by our group suggest that all these processes seem to be joined by a “leitmotif” - OS - since they are all the cause and/or the consequence of increased free radical burden. If from one side low amount of ROS can activate the protective cellular apparatus such as the antioxidant and heat shock responses, cell cycle regulation, DNA repair, UPR and autophagy, chronic exposure to ROS cause irreversible damage to all intracellular macromolecules. Among these, protein oxidation impairs multiple cellular functions by an irreversible process that results in altered, mostly reduced, protein activity. It is likely that stressed neurons have to challenge the increasing load of oxidatively damaged proteins, which overwhelm the ability of protein quality control. This in turn promotes further accumulation of damaged proteins, increasingly prone to aggregation, ultimately resulting in neuronal death.

Collectively, our findings suggest that redox alteration of protein homeostasis coupled with increasing demand for protein degradation, and reduced ATP production may promote a vicious cycle that may push the neurodegenerative process.

Early Amyloid--- β Pathogenesis in Down Syndrome

Lemere, Cynthia

Neurologic Diseases, Brigham and Women's Hospital and Harvard Medical School

Amyloid--- β ($A\beta$) plaques and neurofibrillary tangles (NFTs) are the major histopathological hallmarks of Alzheimer's disease (AD). People with Down syndrome (DS) invariably develop AD pathology by 40 years of age, although the onset of clinical dementia is quite variable and less predictable. Over the past two decades, we have examined the temporal progression of $A\beta$ and Apo E deposition and inflammation in relation to neuritic changes and the appearance of NFTs in cortex from a large number of DS brains from individuals from 3 to 73 years of age. We observed early intraneuronal $A\beta_{42}$ labeling in very young DS brain (3 yr) that preceded the presence of extracellular $A\beta_{42}$ ---positive plaque deposition as early as 12 years of age. Intraneuronal $A\beta_{42}$ was not associated with gliosis but was inversely correlated with plaque deposition.

Although $A\beta_{42}$ ---positive plaques were observed in only 7 of 16 DS individuals under 30 years, they were abundant, mostly diffuse, were $A\beta_{40}$ ---negative, and the level of $A\beta_{42}$ plaques remained stable across older DS brains. Apo E co---deposited in a subset of plaques as early as 12 yr. $A\beta_{40}$ ---positive and fibrillar (Thio S) deposits, plaque---associated dystrophic neurites and NFTs were mainly observed in brains of DS individuals over 30 years of age and increased with age. However, some of these more mature AD pathologies were detected in cortex from a 15 yo (with a few neuritic plaques) and a 29 yo (neuritic plaques and NFTs). In addition, gliosis and complement immunoreactivity were evident in and around mature, neuritic plaques and some NFTs when present in DS brain. An N---terminally truncated and modified form of $A\beta$, pyroglutamate---3 $A\beta$, was detected in most, if not all plaques in briefly---fixed DS brain tissue (cases over 30 yr of age). Vascular amyloid containing $A\beta_{40}$ starting at Asp1 and pyroglutamate---3 was observed in parenchymal arterioles and leptomeningeal blood vessels in middle---aged and older DS brains, and often colocalized with Apo E immunoreactivity. We conclude that although the onset of AD pathogenesis varies in DS brain, it appears that intracellular $A\beta_{42}$ precedes deposition of extracellular diffuse $A\beta_{42}$ plaque deposition, which is followed by plaque maturation, neuritic dystrophy, inflammation, vascular amyloid and the formation of NFTs in neocortex. It is unclear which factors determine the timing of the onset of AD pathology in DS or the tipping point for clinical dementia. However, closer examination of biomarkers and cognitive testing during life, and further AD pathological staging in autopsied brain tissue and correlation with dementia status should help in understanding AD in DS brain and may provide insight into when and what to provide for therapy.

White matter integrity, cerebrovascular pathology, aging and Alzheimer's disease in Down syndrome

Head, Elizabeth

University of Kentucky, Sanders-Brown Center on Aging

Elizabeth HEAD (1)

David POWELL (1)

James FITCH (1)

Brian GOLD (1)

Gregory JICHA (1)

William ROBERTSON (1)

Donna WILCOCK (1)

Allison CABAN-HOLT (1)

Roberta DAVIS (1)

Frederick SCHMITT (1)

Research has shown that adults with Down syndrome (DS) develop significant levels of Alzheimer's disease (AD) neuropathology around the age of 40 years, well in advance of clinical dementia symptoms that are often seen over a decade later. As part of a longitudinal study that is evaluating brain white matter (WM) changes and their association to dementia evolution in DS, fractional anisotropy (FA) from diffusion tensor imaging (DTI) was evaluated in association with the degree of impairment reported on several neuropsychological outcome measures. WM integrity is lower in the frontal cortex of DS compared with age-matched controls and further lowered in DS with AD. Further, WM integrity in different cortical regions was correlated with scores on the Brief Praxis Test and the Severe Impairment Battery. An interesting outcome of the study was the pattern of WM integrity changes suggesting a cerebrovascular component to losses in WM. Cerebral amyloid angiopathy is a consistent feature of the aging DS brain and may lead to cerebrovascular dysfunction, and thus, microhemorrhages. To address the possible role of cerebrovascular pathology as a function of age and AD in DS, we stained sections using Prussian blue to visualize microhemorrhages (MH). Counts of the number of MH showed that compared to controls and to sporadic AD cases, MH counts were the highest in DS with AD. In our ongoing longitudinal study of aging in DS we will be including imaging approaches that will detect MH in vivo to detect longitudinal aging changes, and links to cognitive decline and dementia.

SESSION 3

DS: BEYOND NEUROPATHOLOGY AND COGNITION

Dysregulation of signaling in Down Syndrome: Role of Intersectin 1 (ITSN1) and Ras.

O'Bryan, John P.

University of Illinois College of Medicine,
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Trisomy 21 or Down Syndrome (DS) results in triplication of numerous genes on human chromosome 21. One such locus, ITSN1, encodes a multidomain scaffold protein involved in numerous biochemical processes including endocytosis, exocytosis, ubiquitylation and cell signaling [reviewed in(1, 2)]. ITSN1 is overexpressed in Down Syndrome patients both at the RNA and protein levels (3, 4) and we have postulated that this overexpression may contribute to the sequelae of DS, including the emergence of malignancies. While children with DS have a lower incidence of solid tumors, there is a 10-50-fold higher incidence of leukemias in DS patients. A recent study identified mutations in Ras family GTPases (KRas and NRas) in DS leukemias highlighting the involvement of Ras in DS cancers. Our previous work demonstrated a novel role for ITSN1 in Ras activation (5) as well as oncogenesis (6-8). We have recently described a novel pathway by which ITSN1 regulates Ras activation on intracellular vesicles (9). This pathway involves phosphatidylinositol 3-kinase ClassII β (PI3KC2 β) binding to nucleotide-free Ras (nf-Ras) on vesicles. Subsequent recruitment of ITSN1 to this complex results in dissociation of Ras from PI3KC2 β resulting in immediate GTP binding and activation of Ras (9). To characterize this pathway further, we have developed novel affinity reagents to Ras termed monobodies. We have isolated highly specific Ras monobodies with nM affinity to nf-Ras (R15 and R18) as well as monobodies which recognize Ras regardless of the presence or absence of bound nucleotide (NS1). Interestingly, NS1 functions as a highly specific inhibitor of Ras function. We will present data demonstrating that NS specifically inhibits Ras-dependent signaling and transformation of cells. These reagents may prove useful in targeting Ras in human tumors, particularly in DS-associated leukemias that possess mutant Ras alleles.

The Chromosome 21 Kinase DYRK1A in normal and malignant hematopoiesis

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The dual specificity tyrosine-regulated kinase 1A (DYRK1A) phosphorylates a growing number of proteins to influence various aspects of cell biology, including survival, apoptosis, proliferation, and neuronal development and function. Encoded on human chromosome 21, the DYRK1A locus resides in the Down syndrome critical region (DSCR) and has been implicated in the pathogenesis of neurocognitive deficits that result from trisomy 21. We recently demonstrated a prominent tumor-promoting role for DYRK1A in acute megakaryoblastic leukemia in children with DS (DS-AMKL). This discovery prompted us to ask whether DYRK1A is important for normal hematopoiesis, and if additional types of leukemia result from enhanced DYRK1A activity.

Apart from our study in DS-AMKL, the involvement of DYRK1A in normal and malignant hematopoiesis has not been described. *Dyrk1a* germline knockout mice die mid-gestation; therefore, we generated conditional knockout (CKO) mice to allow inducible deletion of the kinase in hematopoietic cells with Mx1-Cre. In the bone marrow, CKO mice exhibit significant reductions of the hematopoietic stem cell-enriched LSK and common lymphoid progenitor populations. In B cell lineage, CKO mice have 2-fold reductions of small pre-B and immature B cells, and a 5-fold reduction of mature recirculating B cells. In the thymus, CKO mice show dramatic loss of CD4⁺/CD8⁺ double positive cells. Furthermore, DYRK1A-deficient cells fail to reconstitute lymphoid cells in competitive bone marrow transplantation experiments and give rise to virtually no pre-B cell colonies in ex vivo assays. In contrast to these lymphoid defects, myeloid development is largely normal, with slightly increased numbers of erythroid precursors, granulocytes, and monocytes.

Both B- and T-lineage ALL express high levels of DYRK1A relative to other tumor types. Having observed that DYRK1A is essential for lymphoid cells, we next asked whether targeting DYRK1A with small molecule inhibitors would be an effective therapy for ALL.

We found that EHT 1610, a highly selective DYRK1 inhibitor dose-dependently induced apoptosis in B- and T-ALL cell lines and primary human pediatric ALL samples. Thus far, all cell lines and all primary samples tested are exquisitely sensitive to EHT 1610. Moreover, EHT 1610 induced apoptosis of primary ALL cells that were resistant to cytarabine, suggesting that DYRK1A inhibitors may be used in combination with standard ALL therapies for refractory or relapsed cases. Together, our data establish novel essential roles for DYRK1A in both normal and malignant lymphoid development and provide rationale for the design of DYRK1A-targeted ALL therapies.

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Landscape of gene mutations in Down syndrome related myeloid disorders

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Transient abnormal myelopoiesis (TAM) is a myeloid proliferation resembling acute megakaryoblastic leukemia (AMKL), exclusively affecting perinatal infants with Down syndrome (DS-AMKL). Although self-limiting, TAM may recur as non-self-limited AMKL after spontaneous remission. Pathogenesis of these DS-related myeloid disorders is poorly understood, except for GATA1 mutations found in most cases. To obtain a full registry of gene mutations in TAM/AMKL, we performed whole exome sequencing of 15 TAM and 14 AMKL samples. Whole genome sequencing was also performed in 4 paired TAM/AMKL samples. Recurrent mutations in the discovery cohort were screened in an extended cohort of TAM (n = 41), DS-AMKL (n = 49), and non-DS-AMKL (n = 19). Relapsed AMKL evolved from one of the multiple pre-existing subclones in the TAM phase with newly acquired mutations. DS-AMKL (5.8/sample) had significantly higher somatic mutations than TAM (1.7/sample) ($p = 0.0002$). While GATA1 was the only recurrent mutational target in TAM, several genes, including NRAS, DCAF7, KANSL1, EZH2, TP53, CTCF, and the cohesin complex, were recurrently mutated in AMKL. Conspicuously, multiple cohesin components, including STAG2, RAD21, NIPBL, SMC1A, and SMC3, were mutated/deleted in 26/49 DS-AMKL samples. EZH2 and CTCF were also commonly mutated/deleted, affecting 33% and 20% of DS-AMKL, but none of the TAM, cases. TAM is most probably caused by a single GATA1 mutation in combination with constitutive trisomy 21. Subsequent AMKL evolves from a TAM clone acquiring additional mutations, where deregulated cohesin/CTCF functions and other epigenetic machineries and signaling pathways play a major role.

Thyroid dysfunction in Down Syndrome: clinical aspects and study of the transgenic Dyrk1A mice as a model of thyroid dysgenesis in Down Syndrome

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Down syndrome (DS) is characterized by a high prevalence of thyroid dysfunction during childhood. In this study, we review the different kinds of thyroid dysfunction that occur excluding those of autoimmune origin: congenital hypothyroidism (elevated plasma TSH with low plasma T4 occurring at birth usually detected by neonatal screening), subclinical hypothyroidism (elevated plasma TSH with plasma T4 in the normal range, which can be congenital or acquired) and acquired primary hypothyroidism (elevated plasma TSH and low plasma T4 occurring after birth). These dysfunctions, while not due to autoimmunity, are of thyroidal origin. However, the mechanisms leading to these different thyroidal abnormalities have not been clearly defined.

In order to understand, we used as a DS murine model the transgenic Dyrk1A mice, containing 3 copies of the Dyrk1A gene. We demonstrated that these mice were a model for the study of thyroid dysgenesis in DS. Their thyroids have functional impairments (lower plasma T4 secretion and heavier disorganised thyroids) probably due to thyroidal development impairments and a dysregulation of transcription factor involved in thyroidal development.

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DYRK1A control of pancreatic beta cell fate and mass.

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Regulation of pancreatic beta cell mass and function is a major determinant for the development of diabetes. Growth factors and nutrients are important regulators of beta cell mass and function. The signalling pathways by which these growth signals modulate these processes have not been completely elucidated. DYRK1A (also named MNB/minibrain) is a member of the dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) family that has been implicating in brain growth and adult brain function, as well as in neurodegeneration and Down syndrome.

We have shown that DYRK1A is an attractive candidate to modulate beta cell mass growth. To study the role of Dyrk1A in beta-cells growth, we used mice deficient or overexpressing Dyrk1A.

We provide evidence that changes in Dyrk1A gene dosage in the mouse strongly modulate insulin blood levels. Experiments in Dyrk1A haploinsufficient mice showed severe glucose intolerance and reduced beta-cell mass by decreased proliferation. In contrast, mice overexpressing Dyrk1A exhibited decreased glucose levels, hyperinsulinemia associated with an expansion of beta cell mass by increased proliferation and cell size.

I will present evidence suggesting that Dyrk1A gene-dosage is a critical kinase for beta cell proliferation as Dyrk1A haploinsufficient mice show diabetic profile. The mechanism involved in development and in adult beta cell will be discussed and correlated with Down syndrome.

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A Down syndrome screening model identifies that RCAN1 is overexpressed in Type 2 diabetic islets and causes β -cell mitochondrial dysfunction

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Mitochondrial dysfunction is observed in human Type 2 diabetes (T2D) β -cells and is central to β -cell dysfunction in this disease. Down syndrome (DS, Trisomy 21) also presents with β -cell mitochondrial dysfunction. By profiling the glycaemic status of different DS mouse lines, a shortlist of candidate genes contributing to hyperglycemia in some DS lines was generated. We then identified which of these have increased expression in a large cohort of control and T2D human islets. This approach identified a single candidate, RCAN1. Gene expression is increased in human ($p < 0.01$) T2D islets and RCAN1 protein levels increase 3-fold in db/db mouse islets ($p < 0.01$). Glucose-stimulated insulin secretion (GSIS) is reduced in mice overexpressing RCAN1. Mouse β -cells overexpressing RCAN1 display mitochondrial dysfunction exemplified by reduced mitochondrial respiration and low islet ATP. Insulin secretion in response to methyl succinate is lower when RCAN1 is overexpressed ($p < 0.01$), indicating a defect downstream of complex II in the electron transport chain. In vitro GSIS is reduced by inhibition of the mitochondrial ATP translocator in WT islets, but inhibition has no effect when RCAN1 expression is increased. Thus, increased RCAN1 inhibits ATP translocation from the mitochondria. This lack of cytosolic ATP negatively affects multiple steps of the insulin secretion pathway by reducing glucose-stimulated membrane depolarisation ($p < 0.01$) and lowering insulin exocytosis in response to a series of depolarising pulses ($p < 0.05$). Thus, amongst the ~5,000 gene expression changes identified in T2D β -cells, our novel screening approach identifies increased RCAN1 expression as a functionally relevant gene expression change that causes mitochondrial dysfunction in β -cells.

SESSION 4

BIOMARKERS OF PATHOLOGY

PROGRESSION IN DS

Lessons from the mouse aneuploid zoo and new opportunities for therapeutic interventions

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Down syndrome (DS) is induced by the human trisomy 21 and represents the major cause of intellectual disabilities in association with a large panel of features. In order to better understand the physiopathology of the DS and to identify the genes involved in the various phenotypes, we created a DS zoo with new partial monosomies and trisomies in the mouse for homologous regions, and models of candidate genes. Here we will report the standardized characterization of the trisomic mouse models for various regions of interest and the analysis of candidate genes involved in DS using standardized tests to highlight behavioral, cognitive and morphological traits similar to the human features. Based on the new series of models and further studies, additional information has been captured on the genotype to phenotype relationship and on the pathophysiology of the DS. We will focus our attention to certain candidates which were identified and we will characterize their specific contribution to DS features. The data generated are challenging our current knowledge on the role of unique genes in the DS physiopathology, suggesting interactions of several loci and certainly cross-talks in pathways. Such studies offer perspectives for treating neuronal impairment and for facilitating the life of people with DS and their family.

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Cholinergic basal forebrain systems in Down Syndrome and Alzheimer's disease: Neuroplasticity and biomarkers

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Down's syndrome (DS) individuals develop neuropathological features similar to Alzheimer's disease (AD), including degeneration of cholinergic basal forebrain (CBF) neurons, which require nerve growth factor (NGF) and its cognate receptors, trkA and p75NTR for survival. A reduction in CBF neurons is associated with a novel neural plasticity response consisting of an overexpression of fibers containing the inhibitory neuropeptide galanin upon remaining cholinergic basal forebrain neurons in AD. The present study examined the interrelationship between reductions in CBF/trkA-containing neurons and the over-expression of galaninergic fibers within the nucleus basalis in DS. Within the nucleus basalis complex stereology revealed a 46% reduction in the number of trkA immunopositive neurons, whereas optical density measurements displayed a non-significant 18% reduction in neuronal trkA immunoreactivity in DS patients compared to age matched controls. Western blot analysis also showed a significant reduction in cortical trkA protein levels in DS similar to AD. However, a semiquantitative examination of galaninergic fiber innervation did not reveal hypertrophy of galaninergic fibers upon CBF/trkA positive neurons within the nucleus basalis in DS compared to AD. The present findings indicate a significant reduction in trkA nucleus basalis neurons and protein levels in cortex without galaninergic fiber hypertrophy upon cholinergic neurons in DS. These observations suggest that DS may not be an exact genetic model for investigation of changes in the AD basal forebrain. Recently, we found that proNGF, the precursor molecule for NGF, is upregulated in the cortex early in the onset of AD suggesting that it may be a novel biomarker for disease progression. Initial western blot studies indicate that cerebrospinal fluid (CSF) proNGF levels are significantly elevated from patients who died with a clinical diagnosis of mild cognitive impaired, a prodromal stage of AD. Increased proNGF CSF levels were associated with poorer cognitive impairment test scores suggesting its use as a biomarker for the onset of AD. Since Iulita et al. (2014) reported increased levels of proNGF in the DS brain; it will be of interest to determine whether proNGF marks the progression of cognitive decline in DS.

Circadian Biomarkers of Pathology Progression in Down syndrome

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Circadian function deteriorates to varying degrees in typically developing people as they age. Despite the presence of some interindividual differences in the sixth and seventh decade of life, many older adults show evidence of fragmentation of behavioral activity patterns across the 24h day, dampened, less robust cycles of hormone secretion and glucose utilization, and, overall, loss of circadian flexibility (e.g., poor entrainment to the light/dark schedule, slower adaptation to transmeridian travel, and milder responses to time-shifting cues). These observations persist in elder individuals without complications of frailty owing to muscle weakness or decreased energy.

While natural aging or senescence unquestionably takes a toll on the performance of the circadian system, seniors who will eventually meet diagnostic criteria for Alzheimer related dementia experience more severe circadian problems than can be accounted for by chronological age during the period when they are otherwise asymptomatic. These departures, which include relative and absolute flattening of the circadian activity rhythm (CAR) amplitude and high CAR fragmentation, have been correlated to a higher probability of onset of mild-cognitive-impairment/dementia within 5 years of actigraphy assessment. Breakdowns in CAR presage deficits in verbal fluency—a readout of semantic memory—and executive function.

Due to APP gene dosage, people with Down syndrome (DS) will develop some of the neurohistopathological hallmarks of Alzheimer disease by their mid twenties, with the majority proceeding to a clinical diagnosis of dementia within the ensuing 3 decades. The progression of these events tends to be quite variable from one person with DS to the next, limiting the potential that a uniform standard of care could be devised for when preemptive treatments might be started to ward off loss of cognitive & adaptive skills individuals with DS struggle over a lifetime to build.

Given the relationships that have been established between circadian function, aging, and dementia onset, we have started a long-term program of study to chart the CAR profiles of people with DS across the lifespan starting from 6 months after birth. We hypothesize that several elements of the CAR profile might be strong prospective indicators for those with DS at increased risk for early AD-related cognitive decline. The current talk will review actigraphy data collected from the first 40 toddlers with DS from our study. Preliminary findings on what the DS circadian system looks like at this stage of childhood will be discussed.

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Genetic risk factors for dementia in adults with Down syndrome

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Introduction: Adults with Down Syndrome (DS) carry 3 copies of the gene for β amyloid precursor protein (APP), and they have an increased risk of Alzheimer disease (AD); yet, age at onset of AD varies widely among adults with DS. Previous genetic studies in the general population have identified over 20 genes that contribute to the risk for AD. We and others have examined the role of genetic factors on risk of AD in adults with DS. Here we present the results from the candidate gene and the exome sequencing study to identify genetic variants that may contribute to the risk of AD.

Methods: We first performed a candidate gene study using 357 adults with DS with ages ranging from 30 to 78 years at study entry. Participants were ascertained through the developmental disability service systems of New York and neighboring states and were followed at 14-18 month intervals (mean=4.7 years). Cognitive assessments, caregiver interviews, medical record reviews and neurological examinations were used to classify AD. Genotyping was performed using the Illumina GoldenGate custom array to allow genotyping of trisomy. The candidate gene study identified APP, CST3 and MARK4 after multiple test correction. To further evaluate these positive signals, we performed exome sequencing using the Illumina HiSeq platform. We sequenced the exome of 46 adults with DS from a total of 357 who had been previously genotyped. Among 46 sequenced adults, 23 had AD, and none had a copy of APOE ϵ_4 allele.

Results: The candidate gene study identified SNPs in 3 candidate genes, namely APP, CST3, and MARK4. The CST3 gene may influence formation of amyloid fibril and the MARK4 gene may be involved in microtubule regulation. Our exome sequencing identified 206,197 autosomal SNPs after screening through quality control filters. In the APP gene, we identified 3 rare nonsynonymous variants that were present in either affected or unaffected individuals only. For the CST3 gene on 20p11.21 and the MARK4 gene on 19q13.32, a SNP with the strongest effect size was observed in MARK4 (OR=5.18); however, the strength of association did not reach statistical significance. For the remaining exome, we are currently performing gene-wise and variant-specific analysis.

Conclusions: The candidate gene study identified SNPs in APP, CST3, and MARK4 that were associated with AD, and the exome sequencing study identified rare coding variants that may contribute to an elevated risk of AD. These findings further demonstrate that multiple variants from genes on chromosome 21 and other chromosomes influence variation in AD risk. Because these genetic variants are rare, the present study serves as a discovery study that will need to be validated in a larger set of adults with DS and the general population.

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Validating DYRK1A as a biomarker in plasma and lymphoblastoid cell lines from Alzheimer disease and Down syndrome patients

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Extensive brain amyloidosis, typically associated with dementia, has been noted at autopsy of older individuals who exhibited few or no cognitive complaints prior to death. Amyloid accumulates years before symptoms become apparent, and current tests depend on detection of either amyloid accumulation in brain or tau proteins in cerebrospinal fluid. Biomarkers that may help predict disease before onset or progression of symptoms are critically needed. A two-hybrid screen for human DYRK1A suggested the presence of DYRK1A extracellular interactants in plasma. DYRK1A was subsequently detected by immunoblot in plasma from transgenic mouse models having different gene dosage of Dyrk1a and, consequently, different relative protein expression. We next measured plasma DYRK1A levels in individuals with Alzheimer's disease (AD) that present either mild cognitive impairment (MCI-AD) or dementia relative to plasma from control subjects. 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 shown to be related to DYRK1A levels. These results have been confirmed in a second independent cohort. Moreover, DYRK1A levels were also significantly lower in lymphoblastoid cell lines (LCLs) from AD patients as compared to age-matched controls. AD-like dementia is also common in older individuals with Down syndrome (DS) though with a much earlier onset. We analysed DYRK1A levels in LCLs from patients with DS and found a decreased level of DYRK1A in patients with DS and dementia. Taken together, these findings suggest that a decrease of DYRK1A in plasma might be a novel risk factor for AD and a useful biomarker predicting of AD in the general population and in DS patients.

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Biogenic amines underlying behavioural and psychological symptoms of dementia (BPSD) in AD and DS-AD

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Behavioural and psychological symptoms of dementia (BPSD), or neuropsychiatric symptoms, are found in all types of dementia and are among the core symptoms, in addition to cognitive decline and impaired activities of daily living. BPSD are defined as 'signs and symptoms of disturbed perception, thought content, mood, or behaviour that frequently occur in patients with dementia' 1, such as psychosis, aggression, anxiety disorders and mood disturbances, and are associated with increased suffering, accelerated cognitive decline, earlier institutionalization, severe burden on family and caregivers, and increased financial costs.

Importantly, nearly all dementia patients suffer from BPSD at some point during their disease course, i.e. 80-97% of AD patients in the general population, causing BPSD to be extensively studied. Contrarily, despite the high risk to develop AD, BPSD have not been comprehensively studied in DS. Accurate clinical recognition, and subsequent neurobiological studies are of great importance to unravel the underlying neurobiological mechanisms of BPSD in AD and DS-AD, and may contribute to the development of targeted therapeutic, and possibly preventive, interventions.

The monoamine hypothesis in AD mostly relies upon a disease- and regional-specific degeneration of subcortical neuronal populations, particularly cholinergic and monoaminergic (MA-ergic) systems, in addition to the deposition of plaques and neurofibrillary tangles. More specifically, the main MA-ergic nuclei, such as the locus coeruleus (LC; noradrenalin (NA)), substantia nigra (dopamine) and raphe nuclei (serotonin), with extensive axonal projections throughout the entire brain, become affected, thereby depriving (sub)cortical and hippocampal neurons from their critical modulatory input, which leads to severe cognitive and behavioral deficits.

Previous (pre)clinical research thus concluded that neuronal loss and associated monoaminergic neurotransmitter alterations may serve as main etiology underlying both cognitive and non-cognitive symptoms, not only in AD, but also DS and DS-AD. Very recently, our team found that the serum level of 3-methoxy-4-hydroxyphenylglycol (MHPG), NA's main metabolite, strongly predicted conversion to AD in DS individuals and was associated with various BPSD. Marked loss of neurons in the LC has been reported in DS, as well as AD, and further degeneration in DS with AD would consequently lead to lower NA levels and, since MHPG diffuses freely over the blood-brain barrier, also reduced serum MHPG.

Furthermore, several preclinical studies showed that pharmacotherapeutics targeting altered dopaminergic, serotonergic and/or (nor)adrenergic neurotransmitter systems might restore cognitive dysfunction and even reduce AD-related pathology. Such therapeutic interventions are most effective when BPSD are recognized in an early stage, thus pointing at the necessity to carefully assess BPSD in DS and further study the neurobiological underpinnings.

1 Finkel et al. (1996). *Int. Psychogeriatr.* 8 Suppl 3, 497–500.

SESSION 5

DS: PRENATAL DIAGNOSIS AND TREATMENT

Developmental abnormalities in mouse models of Down syndrome identify early alterations of CNS formation and function

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For the past three decades, mouse models of Down syndrome (DS) have provided an essential window into the mechanisms that are altered in the CNS during prenatal and postnatal development. While human brain studies have indicated that microcephaly appears before birth, most of our information of how this paucity of brain cells arises and how this impacts cognitive and behavioral growth has come largely from several murine models. These studies have highlighted and quantified clear defects in neural stem and progenitor cell proliferation in several developing brain areas that alters the balance of cell types participating in the neuronal circuitry. Changes in the development and function of multiple glial cell types has also been observed. In particular, our recent studies have uncovered clear defects in oligodendrocyte differentiation, resulting in dysmyelination which reduces the speed of neuronal transmission in the trisomy brain. Altogether, alterations in neuron and glial cell production occur in DS brain at several early stages of development and all of these are likely to impact cognition later in life. These recognized changes in formative, elemental processes are important targets of early treatment strategies for humans with DS.

Brain development in fetuses with Down syndrome

Tarui, Tomo

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People with Down syndrome (DS) have altered brain development and maturation that originates in fetal life. Although much knowledge has been accumulated in the ongoing processes of brain development during adulthood and childhood, there is a significant gap with regard to how the fetal brain develops in DS. Here I will present an overview of alterations in brain development in a longitudinal view from fetal life to adulthood, with a special focus on fetal brain development in DS. Preliminary data from a non-invasive, quantitative fetal MRI study to evaluate brain development in fetuses with DS compared to euploid fetuses will be introduced. Anticipating that prenatal treatment clinical trials may start in the next few years, such knowledge will help us to better understand anatomical landmarks in the developing brains of fetuses with DS. Such information will help to evaluate the effects of fetal therapy.

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Genomic and bioinformatics approaches to prenatal screening for and treatment of Down syndrome

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Noninvasive prenatal testing [NIPT] for Down syndrome [DS], using massively parallel sequencing of maternal plasma DNA, facilitates early detection of affected fetuses. If NIPT is performed at ~ 12 weeks of gestation there is a potential 28-week window of opportunity in which to treat the fetus by orally administering small molecules to the mother. Our laboratory is using a four phase translational approach that involves human biomaterials (amniocytes and amniotic fluid), a mouse model of DS, and living human fetuses. In phase 1 we compared gene expression in fetuses with and without DS by analysis of cell-free RNA in amniotic fluid. We showed that oxidative stress was a significant difference in the affected fetuses. In phase 2 we uploaded differentially-regulated genes into the Connectivity Map to identify candidate FDA-approved therapeutic molecules. In phase 3 drugs that had high efficacy in negating oxidative stress and showed low toxicity were selected for further studies in a mouse model. We use the Ts1Cje mouse model of DS because affected males are fertile, yet cognition is significantly impaired. We can therefore use wild type females for the treatment experiments, ensuring both a normal intrauterine environment and normal postnatal nurturing behavior. Treated and untreated affected pups and littermate controls are then evaluated using a variety of brain studies that include analyses of gene expression, histology, cellular proliferation and migration, and neurobehavior. In parallel, in phase 4 we are preparing for a human clinical trial by analyzing fetal brain growth using quantitative fetal magnetic resonance imaging (MRIs). To date, we have identified significant phenotypic differences in Ts1Cje embryos, neonates, and adults as endpoints to evaluate the effects of therapy. We have also shown encouraging, statistically-significant improvement in some neurobehavioral tests in adult mice. Our results suggest that (1) there is genome-wide dysregulation in DS, (2) there are significant abnormalities in DS embryos, and (3) that treating affected mice prenatally may have maximal therapeutic effects.

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Prenatal pharmacotherapy can rescue brain development and cognitive performance in the Ts65Dn mouse model of Down syndrome

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Intellectual disability is the unavoidable hallmark of Down syndrome (DS), and has a heavy impact on families and society. Accumulating evidence suggests that a severe reduction in neurogenesis during the prenatal period, a critical time window for brain development, may be a major determinant of intellectual disability. DS is characterized by early alterations in the serotonergic system, which plays a fundamental role in neurogenesis. In our study we exploited the Ts65Dn mouse model of DS in order to establish whether prenatal therapy targeted to the serotonergic system can rescue neurogenesis and behavior. We treated pregnant Ts65Dn females from E10 to delivery with either fluoxetine, a selective serotonin reuptake inhibitor, or vehicle and examined the effects of treatment on the progeny. We found that untreated Ts65Dn pups exhibited a severe neurogenesis reduction and hypocellularity throughout the forebrain, midbrain and hindbrain. In Ts65Dn mice that had been embryonically-treated with fluoxetine, precursor proliferation and cellularity were fully restored in all these regions. To verify whether the effect of embryonic treatment extended beyond the neonatal life stages, we examined the 1.5 month-old offspring of treated and untreated mothers. We found that neural precursor proliferation was still restored in the two major postnatal brain neurogenic niches (subventricular zone of the lateral ventricle and subgranular zone of the dentate gyrus). In addition, in the dentate gyrus the typical reduction in the acquisition of a neuronal phenotype and the relative increase in astrogliogenesis were fully corrected, indicating a long-term effect on the differentiation program. The total number of granule neurons was also restored. Furthermore, in embryonically-treated Ts65Dn mice dendritic development of postnatally-born granule neurons was normalized, with full correction of the severe dendritic hypotrophy that characterizes the trisomic condition. The counterpart of this effect was restoration of pre- and postsynaptic terminals. Finally, embryonically-treated Ts65Dn mice aged 1.5 months exhibited restoration of cognitive performance, indicating that the positive impact of embryonic treatment on brain architecture was functionally effective in adulthood. These results show that it is possible to fully restore brain development and behavior in DS, provided that treatment is administered prenatally, and that the effects of early treatment persist after treatment discontinuation. The discovery that trisomy-linked brain abnormalities can be prevented with early interventions in a mouse model of DS gives us reason to believe that treatments during pregnancy may be used to rescue brain development in fetuses with DS.

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Prenatal corrective strategies targeting DYRK1A

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Cognitive deficits in Down syndrome (DS) have been linked to increased synaptic inhibition, leading to an imbalance of excitation/inhibition (E/I). Various mouse models and studies from human brains have implicated an HSA21 gene, the serine/threonine kinase DYRK1A, as a candidate for inducing cognitive dysfunction. Here, consequences of alterations in Dyrk1a dosage were assessed in mouse models with varying copy numbers of Dyrk1a: mBACtgDyrk1a, Ts65Dn and Dp(16)1Yey (with 3 gene copies) and Dyrk1a(+/-2;) (one functional copy). Molecular (i.e. immunoblotting/immunohistochemistry) and behavioral analyses (e.g., rotarod, Morris water maze, Y-maze) were performed in mBACtgDyrk1a mice. Increased expression of DYRK1A in mBACtgDyrk1a induced molecular alterations in synaptic plasticity pathways, particularly expression changes in GABAergic and glutaminergic related proteins. Similar alterations were observed in models with partial trisomy of MMU16, Ts65Dn and Dp(16)1Yey, and were reversed in the Dyrk1a(+/-2;)model. Dyrk1a overexpression produced an increased number and signal intensity of GAD67 positive neurons, indicating enhanced inhibition pathways in three different models: mBACtgDyrk1a, hYACtgDyrk1a and Dp(16)1Yey. Functionally, Dyrk1a overexpression protected mice from PTZ-induced seizures related to GABAergic neuron plasticity. Our study shows that DYRK1A overexpression affects pathways involved in synaptogenesis and synaptic plasticity and influences E/I balance toward inhibition. EGCG, a catechin found in green tea, is a non-competitive inhibitor of DYRK1A. EGCG-based treatments of mice overexpressing DYRK1A rescue brain markers of synaptic plasticity together with cognitive phenotypes providing a basis for the treatment of Down syndrome patients. The action of EGCG is dose dependent and developmental stage dependent; a stronger rescue is obtained when treatment is initiated prenatally.

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Maternal choline supplementation: A prenatal intervention strategy for Down Syndrome

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Despite tremendous progress in our understanding of Down Syndrome (DS), there are still no effective treatments for this disorder. However, there is reason for optimism; compelling evidence suggests that there may be a window of opportunity for therapeutic interventions during fetal development that can provide lasting cognitive and behavioral benefits for DS offspring throughout the lifespan. Studies from our lab using the Ts65Dn mouse model of DS have demonstrated that supplementing the maternal diet with additional choline may be one prenatal intervention strategy to improve the intellectual disability that is a key hallmark of this disorder as well as offer some degree of neuroprotection to the degenerative changes seen with the onset of Alzheimer's Disease. We have demonstrated that maternal choline supplementation (MCS) significantly improves spatial learning/memory, attentional function, and emotion regulation in the trisomic offspring. This early intervention also normalizes adult hippocampal neurogenesis and offers neuroprotection to basal forebrain cholinergic neurons (BFCNs) during aging, both of which correlate with the improved spatial cognition seen in the same animals, suggesting functional links. In addition, we found that MCS exerts lasting beneficial effects on choline metabolism for Ts65Dn offspring mice with increased endogenous synthesis of a choline metabolite enriched in omega-3 fatty acids and its preferential partitioning towards the brain, which may also contribute to their improved cognitive functions. Taken together, these findings suggest that supplementing the maternal diet with additional choline may serve as an effective and safe prenatal strategy for improving cognitive functioning in DS. In light of growing evidence that all pregnancies would benefit from increased maternal choline intake, this type of recommendation could be given to all pregnant women, thereby providing a very early intervention for DS fetuses, and include babies born to mothers unaware that they are carrying a DS fetus.

SESSION 6

DEFINING TRANSLATIONAL PATHWAYS FOR DS

A novel role for the DYRK1A protein kinase as a gene-specific RNA polymerase II CTD kinase

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DYRK1A (dual-specificity tyrosine-regulated kinase 1A) belongs to a highly conserved family of kinases represented in all eukaryotes and it is known to fulfil key roles during brain development. Analysis of mouse models of loss and gain of function, as well as experiments with induced pluripotent stem cells derived from individuals with trisomy 21 point to DYRK1A as one of the chromosome 21 genes important for the proliferation and differentiation defects associated with Down syndrome. Moreover, the extreme dosage dependence of this kinase is highlighted by the fact that truncating mutations in humans cause general developmental delay and primary microcephaly. DYRK1A substrates are both nuclear and cytosolic proteins reflecting the presence of DYRK1A in these two cellular compartments. While cytosolic proteins represent the most abundant DYRK1A targets, the role of DYRK1A within the nuclear compartment remains largely unexplored. We have found that nuclear DYRK1A is an active kinase that participates in high molecular weight complexes, interacting with several components of the basal transcriptional machinery, including RNA polymerase II. We mapped the genome-wide profile of DYRK1A interactions with chromatin and found that the kinase is recruited to proximal promoter regions of a subset of genes that are functionally associated with translation, RNA processing, and cell cycle. We found that DYRK1A binds promoter regions displaying a highly conserved palindromic sequence, which is necessary for DYRK1A-mediated transcriptional activation. Our molecular analysis shows that DYRK1A interacts and phosphorylates the C-terminal domain (CTD) of RNA polymerase II at Ser2 and Ser5. Depletion of DYRK1A results in reduced association of RNA polymerase II at the target promoters as well as hypophosphorylation of the RNA polymerase II CTD along the target gene bodies. These results are consistent with DYRK1A being a transcriptional regulator by acting as a CTD kinase. Therefore, our data widen the context of DYRK1A activity by acting as a direct transcriptional regulator of specific gene expression programs.

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Synaptic dysfunction and growth inhibition by APP mutation and overexpression

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Down syndrome (DS), one of the most common genetic disorders, is caused by trisomy of chromosome 21. Most DS patients inevitably develop the neuropathological hallmarks of Alzheimer's disease (AD) after middle age, including amyloid plaques, neurofibrillary tangles and neuronal loss. AD is the most common neurodegenerative disease. A number of amyloid β ; precursor protein (APP) mutations were found in AD patients and studies of APP and its mutations profoundly improved our understanding of AD pathogenesis in DS. We found that APP A713T mutation impaired APP protein's ER to Golgi transportation, its maturation, turnover and suppressed APP proteolytic processing by the secretases. Although the A β ; generation was reduced by A713T mutation, the A β ; harboring this mutation exacerbated the neuronal toxicity compared with the wildtype A β ;. More importantly, the A713T mutation significantly impaired the synaptogenesis. Furthermore, we performed transcriptional profiling in APP overexpressed cells. We found that 3004 genes were dysregulated in APP overexpression cells, including 1763 down-regulated genes and 1261 up-regulated genes. The dysregulated genes are involved in the negative regulation of cell metabolism and cell cycle progression, and positive regulation of stress response. APP overexpression dramatically inhibits cell proliferation. Taken together, we demonstrate that dysregulation of APP contributes to the growth inhibition through multiple pathways and impairs synaptogenesis. Our data suggests that an extra copy of APP in DS not only promotes AD pathogenesis but also contributes to the growth and development impairment at early age.

Alzheimer's disease in Down syndrome: understanding the mechanism

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People who have Down syndrome, which is caused by trisomy of chromosome 21, are at significantly increased risk of developing Alzheimer's disease (AD). An additional copy of the chromosome 21 encoded gene, APP, is known to promote the development of AD. However, the effect of trisomy of the other ~300 chromosome 21 genes on disease is unclear. Using mouse models we have shown that trisomy of chromosome 21 (in the absence of APP duplication) makes a significant contribution to the development of AD. Trisomy of chromosome 21 significantly enhances A β deposition and associated synaptic transmission and cognitive deficits, and reduces survival. Our data show that trisomy of chromosome 21 alters the development of A β pathology by modulating the production and resultant aggregation of A β . Thus people who have Down syndrome may have an increased risk of developing Alzheimer's disease not only because they have an additional copy of APP but because trisomy of a further chromosome 21 encoded gene, or genes, modulates disease. We now aim to identify this gene or genes, to provide further novel mechanistic insight into the development of Alzheimer's disease.

Biomarkers in down syndrome-related alzheimer's disease

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Down syndrome (DS) is the most prevalent intellectual disability with an incidence of approximately one in 700 live births. Individuals with DS exhibit high comorbidity with Alzheimer's disease (AD), and AD neuropathology including neurofibrillary tangles, beta amyloid plaques, and neuroinflammation. We are quantifying levels of Abeta1-42 and P-tau isomers in blood neuronally-derived exosome cargo from subjects with DS of all ages, to predict trajectory and age of onset for AD pathology in DS. We are correlating AD neuropathology markers with BDNF levels in serum, to determine whether BDNF is an early biomarker for conversion to dementia in adults with DS. Further, we are utilizing matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI-IMS) for global analysis of N-glycosylation products in paraffin embedded postmortem tissue from DS vs. non-DS brains. We have found significant alterations in protein glycosylation in the hippocampus of subjects with DS and dementia, which might signal early manifestations of neuroinflammation and/or other pathological processes in the brain. Our findings demonstrate inflammatory changes in brain from DS subjects, as well as coupling of blood biomarkers with altered pathology in DS brains that may reflect neuroinflammatory onset prior to classical dementia or AD pathology. Our collaborative work is aimed at exploring early biomarkers in blood or brain tissue that may predict onset and progression of dementia and AD neuropathology in those with DS in order to design meaningful prevention or treatment paradigms. Supported by a grant from Alzheimer Association (DSADIIP-13-284845).

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Endo-lysosomal alterations in Down syndrome and Alzheimer's disease.

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Modifications of the endo-lysosomal compartment have been observed in neurons from postmortem brains of individuals with Alzheimer's disease (AD) and Down syndrome (DS) before the formation of amyloid deposits (Cataldo et al. 2000). We characterized the endosomal and lysosomal compartments of cholinergic neurons from the medial superior temporal area of mouse models of DS and AD. In peripheral cells from individuals with DS (blood cells, lymphoblastoid cell lines (LCL) and fibroblasts) we and others have shown the presence of these enlarged endosomes (Cataldo et al. 2008; Cossec et al. 2012). We found that in trisomic cells, enlarged endosomes observed by confocal microscopy appeared as clusters of endosomes by transmission electron microscopy. We then analyzed LCLs from individuals with DS with or without AD and observed a significant increase of the percentage of aggregated endosomes in DS with AD as compared to DS without AD. These morphological alterations could be related to changes in the dynamic rate of internalization of membrane proteins.

Since the amyloid precursor protein (APP) is mainly produced through the endo-lysosomal pathway after internalization, increase of amyloid- β 1538; peptides secretion could result from these endo-lysosomal alterations. We showed that LCLs from familial AD cases carrying APP microduplications did not contain enlarged endosomes and that LCLs from partial trisomies 21 overexpressing the chromosome 21 gene synaptotagmin1 (SYNJ1) could induce endosomal enlargement. SYNJ1 is the major phosphoinositide(4,5)biphosphate phosphatase in the brain and its haploinsufficiency has been shown to improve AD-associated behavioral and synaptic deficits in AD transgenic mice (McIntire et al. 2012). We found that endosomes remained unchanged in cells overexpressing mutants of the 5-phosphatase domain and of the endophilin binding domain of SYNJ1 while endosomes were increased in size with the SAC1-like phosphatase mutant.

In conclusion morphological alterations of the endo-lysosomal compartment are detected in neuronal as well as in peripheral cells in DS and are functionally linked to the overexpression of SYNJ1 with both the endophilin binding domain and the 5-phosphatase domain of SYNJ1 being involved. In peripheral cells of DS individuals, the "enlarged endosomes" appear at high resolution as aggregates of endosomes suggesting modifications in the traffic of endosomes along the endo-lysosomal pathway.

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Preventing Alzheimer Disease in Down Syndrome: Challenges and Opportunities

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The presence of the characteristic features of Alzheimer disease in all adults with Down syndrome (trisomy 21) by age 40, and emergence of dementia at the median age of 55, suggests shared pathogenetic mechanisms and possible approaches to treatment. The opportunity to define the evolution of pathogenesis and to elucidate early diagnostic markers and initiate preventive treatments is an exciting possibility for patients with DS as well as those with other genetic and sporadic forms of Alzheimer disease.

The past ten years have seen considerable advances in the neurobiology of Down syndrome. Important contributions have come from studies in mouse models. Work in many laboratories has documented relevant phenotypes, including changes in synaptic structure and function affecting cognitive circuits. Chromosomal engineering has provided ideal models to define phenotypes and to explore underlying genetic and molecular mechanisms. In particular, studies of Alzheimer-related changes have revealed similar neurodegenerative events that selectively affect neuronal populations shown to be vulnerable in Alzheimer disease and Down syndrome. While mouse models of DS fail to show neuritic plaque and neurofibrillary tangles, they have faithfully recapitulated dysfunction and loss of these populations. Drawing an important parallel in studies on humans, with DS, mouse model studies have demonstrated the necessity of increased APP gene dose for degeneration of cholinergic neurons of the basal forebrain and noradrenergic neurons of the locus coeruleus. In recent studies we have elucidated a mechanism by which increased APP gene dose acts to compromise the structure and function of the endocytic pathway and its ability to transmit the signals of neurotrophic factors. Building on these findings, we are investigating new diagnostic modalities and therapeutic targets for preventing and possibly reversing neurodegeneration in DS. We will discuss ongoing studies and their potential for understanding and treating the biology of Alzheimer disease in Down syndrome.

SESSION 7

COGNITION IN DS

Studying cognitive development in babies with Down syndrome

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In this talk I will first argue that it is critical to trace developmental trajectories of cognitive outcomes back to their origins in infancy, and that this is particularly true of individuals with neurodevelopmental disorders such as Down syndrome. Second, I will argue that cross-syndrome studies often reveal more subtle differences in development than comparisons with typically-developing controls. These arguments will be illustrated from studies using three methodologies with babies: behavioural, electrophysiology and eye tracking. Two studies focus on precursors to language in the form of sensitivity to auditory discrimination and the influence of socio-economic status, both using electrophysiology. Two further studies examine early visual attention as well as paired associate memory, using eye tracking. Finally, we briefly examine the relationship of sleep to early cognition as well as parent-child interaction comparing twin babies discordant for Down syndrome, using behavioural measures. The talk will conclude by pointing to some of the challenges that arise when testing babies with neurodevelopmental disorders.

Allocentric spatial learning and memory deficits in Down syndrome

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Studies have shown that persons with Down Syndrome (DS) exhibit impaired verbal and visuo-perceptual memory, whereas their visuospatial memory capacities appear comparatively spared. For example, individuals with DS recall better where an object was previously seen than what object was previously seen. However, most of the evidence concerning preserved visuospatial memory comes from tabletop or computerized experiments which are biased towards testing egocentric (viewpoint-dependent) spatial representations. Accordingly, allocentric (viewpoint-independent) spatial learning and memory capacities may not be necessary to perform these tasks. Thus, in order to more fully characterize the spatial capacities of individuals with DS, allocentric processes underlying real-world navigation must also be investigated. We tested 20 participants with DS and 16 mental age-matched, typically developing (TD) children in a real-world, allocentric spatial memory task. During local cue (LC) trials, participants had to locate three rewards marked by local color cues, among 12 locations distributed in a 4 m X 4 m arena. During allocentric spatial (AS) trials, participants had to locate the same three rewards, in absence of local cues, based on their relations to distal environmental cues. All TD participants chose rewarded locations in LC and AS trials at above chance level. In contrast, although all but one of the participants with DS exhibited a preference for the rewarded locations in LC trials, only 50% of participants with DS chose the rewarded locations at above chance level in AS trials. As a group, participants with DS performed worse than TD children on all measures of task performance. These findings demonstrate that individuals with DS are impaired at using an allocentric spatial representation to learn and remember discrete locations in a controlled environment, suggesting persistent and pervasive deficits in hippocampus-dependent memory in DS.

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Measuring Language Change in Individuals with Down Syndrome: Expressive Language Sampling

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Numerous clinical trials of targeted pharmaceutical agents are now being evaluated for individuals with Down syndrome. Behavioral interventions targeting core features of the Down syndrome phenotype are also being developed. Evaluation of the efficacy of both pharmaceutical and behavioral interventions, however, is being hampered by the lack of cognitive and behavioral outcome measures that capture the positive effects of these interventions. We will present data regarding the utility of Expressive Language Sampling (ELS) as a source of outcome measures for treatment studies involving Down syndrome and other conditions associated with intellectual disability. In ELS, samples of an individual's spoken language are taken under scripted, yet naturalistic, conditions that allow robust inferences about his or her skill in numerous domains of speech and language, including articulation, vocabulary, and grammar.

In this presentation, we present the ELS methods we have developed and summarize data from our decade-long program of research documenting the utility of these methods for characterizing the language phenotype of people with Down syndrome. We also present preliminary data from an ongoing project regarding the psychometric properties of these methods and their promise as outcome measures. The preliminary data to be presented address feasibility, test-retest reliability, short-term practice effects, and construct validity. We also will compare findings for Down syndrome to those from fragile X syndrome to understand the generalizability of the ELS methods across disorders. The participants for the psychometric studies range in age from 6 to 23 years.

ELS methods have several advantages compared to standardized language tests. ELS methods yield data that are more reflective of performance in functional and meaningful real-world contexts for individuals with Down syndrome. Numerous dependent measures, each reflecting a different aspect of spoken language, can be computed from a single language sample. ELS methods also have limited floor effects for individuals producing at least some multiword utterances. ELS methods are also relatively brief and require minimal training to administer. The data we will present suggest that ELS yields outcome measures ideal for studies of treatment efficacy in individuals with Down syndrome.

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Memory, Language, and Sleep in Down syndrome

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Sleep disruption may be an important factor relating to individual differences in cognitive development and decline in Down syndrome (DS). In Breslin et al. (2014) we describe the correlation between Obstructive Sleep Apnea Syndrome (OSAS) and cognitive outcomes on the Arizona Cognitive Test Battery for Down syndrome (Edgin et al., 2010), finding that children with DS with OSAS had impaired executive function and a verbal IQ nine points lower than those without apnea. These results are unique because we compared children of the same age and background factors who differed only on OSAS status, defined by polysomnography, the gold standard of sleep assessment. In a study conducted in toddlers, Edgin et al. (in press, *Child Development*) examined language, behavioral development, and actigraphy-derived sleep patterns in young children with DS (ages 2-5 years), finding that children with sleep disruption had impaired expressive language in comparison to peers that were sleeping well. Based on these findings, I discuss the candidate mechanisms underlying these associations, including the potential for sleep disruption to disturb periods of deep sleep (i.e., slow wave sleep) that are necessary for memory consolidation and word-learning. As such, even when individuals with DS can overcome encoding difficulties to learn new information (i.e., through more repetitions), they may be unable to consolidate information across sleep periods. I expand to discuss new avenues for understanding links between cognition and sleep in DS, including preliminary data from a longitudinal sleep study in infants, a study of sleep-dependent learning in toddlers, and results from the implementation of new techniques to teach children words based on their sleep profile. While previous research has often suggested instability in knowledge acquisition (Wishart et al., 1993) in this population, more work is needed to define the specific mechanisms underlying delayed loss of learned materials. Defining these mechanisms could guide novel treatment approaches for cognitive and language dysfunction in DS.

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Dissociations in cortical thickness and surface area in the developing brain in Down syndrome: A pediatric structural neuroimaging investigation

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Background: Despite the fact that Down syndrome (DS) is the most common genetic cause of intellectual disability, surprisingly little is known about the developing cortex in youth with the syndrome studied in vivo using magnetic resonance imaging (MRI). Thus, the current pediatric neuroimaging study sought to provide fine-grained descriptions of deviations in cortical thickness (CT) and surface area (CSA) in DS quantified at ~81,000 vertices across the cerebral cortex.

Methods: Participants included 31 youth with DS and 45 typically developing (TD) age- and sex-matched peers (M Age=15; Range=5-24 years; 40 females). All MRI scans were obtained on the same GE 3T scanner and processed with Montreal Neurological Institute's CIVET pipeline.

Results: A dissociation between CSA and CT was found. Namely, CSA was largely reduced while CT was largely increased. These findings were observed at the whole cortex- and vertex-level. Pronounced areas of CSA reduction were identified in the superior temporal and frontal lobes; in contrast, CT was largely increased, particularly in more anterior and posterior brain regions (with peak deviations corresponding to several nodes in the default mode network). **Conclusions:** These results suggest that cortical volume reductions in DS are driven by reduced CSA, particularly in the frontal and temporal lobes, consistent with the executive function and language weaknesses associated with the syndrome. On average, the cortex is thicker in DS, with the greatest deviations found in regions overlapping with the default mode network. Given the link between default mode network function and Alzheimer's disease symptoms in the chromosomally-typical population, future DS research may benefit from focusing on the developing cortex in default mode network regions, as these studies may provide important clues to the early onset of Alzheimer's disease in DS.

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Executive Function and Developmental Status in children with Down Syndrome

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Individuals with Down syndrome (DS) are predisposed to areas of relative strengths and challenges in many domains of development. One area of potential relevance for adaptation in home, school, and community environment relates to the cognitive underpinnings of goal-directed behavior, or executive functions (EF). In this study, we examined EF in school-aged children with DS to explore whether aspects of EF are yoked to overall nonverbal developmental status in similar patterns to typically developing children.

Participants were 65 students with DS (mean CA = 88.53 mos; SD = 18.48) and 35 nonverbal mental-age matched typically developing children who were chronologically younger (mean CA = 40.57 mos; SD = 5.47). Groups were matched for nonverbal mental age using the Leiter-R (Roid & Miller, 1997; DS mean age equivalent = 48.83 mos, SD = 12.96; TD = 50.60, SD = 6.31). Child participants completed a laboratory based battery of EF that included assessments of working memory (modified Bear/Dragon; Carlson, 2005; Flynn, 2007; Garon, Bryson, & Smith, 2008; Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996; Murray & Kochanska, 2002), planning (generativity; Fidler et al., 2014; Rutherford & Rogers, 2003), shifting (DCCS; Zelazo, & Jacques, 1996; Zelazo, Frye, & Rapus, 1996; Zelazo, 2006), and inhibition (snack delay; Carlson 2005; Carlson, Mandell, & Williams, 2004; Kochanska, Murray, & Harlan, 2000).

Results from a one-way MANOVA showed that children with DS performed more poorly on EF battery tasks than their MA-matched TD counterparts, $F(4, 77) = 7.92$, $p = .0001$. Differing patterns of association were observed between nonverbal mental age on the Leiter-R and performance on the EF battery tasks in the two groups. A comprehensive descriptive account of performance by NVMA will be presented. Notable between-group differences include the following: At the overall NVMA of 60 or higher, 79% of the TD children had correct post-switch performances on the DCCS, while only 44.4% of the children with DS did so. At the overall NVMA of 52 months or higher, the TD children were only showing an average of 1.5 dysregulated behaviors on the snack delay task, while their DS counterparts still showed an average of 3.5 dysregulated behaviors. Similarly, TD children with an overall NVMA of 52 months or greater gave an average of 6.88 correct responses on the working memory task, while children with DS at the same overall NVMA gave an average of 3.85 correct responses. Children with DS across all NVMAs gave poorer performances on the generativity planning task.

These findings offer an initial investigation in the atypical trajectory of EF skill acquisition in childhood in DS, and suggest that EF skills are not acquired in accordance with overall nonverbal developmental status in ways that are similar to TD children. Implications for education and intervention will be discussed.

SESSION 8
IMPACT AND STRATEGIES FOR
ANEUPLOIDY IN GENE EXPRESSION
AND METABOLISM

Transcriptome dysregulation and single cell analysis in Trisomy 21

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Trisomy 21 is the most frequent genetic cause of cognitive impairment. To assess the perturbations of gene expression in trisomy 21, and to eliminate the noise of genomic variability, we studied the transcriptome of fetal fibroblasts from a pair of monozygotic twins discordant for trisomy 21. We have shown that the differential expression between the twins is organized in domains along all chromosomes that are either upregulated or downregulated. These gene expression dysregulation domains (GEDDs) can be defined by the expression level of their gene content, and are well conserved in induced pluripotent stem cells derived from the twins' fibroblasts. Comparison of the transcriptome of the Ts65Dn mouse model of Down's syndrome and normal littermate mouse fibroblasts also showed GEDDs along the mouse chromosomes that were syntenic in human. The GEDDs correlate with the lamina-associated (LADs) and replication domains of mammalian cells. The overall position of LADs was not altered in trisomic cells; however, the H3K4me3 profile of the trisomic fibroblasts was modified and accurately followed the GEDD pattern. These results indicate that the nuclear compartments of trisomic cells undergo modifications of the chromatin environment influencing the overall transcriptome, and that GEDDs may therefore contribute to some trisomy 21 phenotypes.

The study of gene expression in mammalian single cells via genomic technologies now provides the possibility to investigate the patterns of allelic gene expression. We used single-cell RNA sequencing to detect the allele-specific mRNA level in 203 single human primary fibroblasts over 133,633 unique heterozygous single-nucleotide variants (hetSNVs). We observed that at the snapshot of analyses, each cell contained mostly transcripts from one allele from the majority of genes; indeed, 76.4% of the hetSNVs displayed stochastic monoallelic expression in single cells. Remarkably, adjacent hetSNVs exhibited a haplotype-consistent allelic ratio; in contrast, distant sites located in two different genes were independent of the haplotype structure. Moreover, the allele-specific expression in single cells correlated with the abundance of the cellular transcript. We observed that genes expressing both alleles in the majority of the single cells at a given time point were rare and enriched with highly expressed. Overall, these results have direct implications in cellular phenotypic variability. Single cell transcriptome analysis in trisomy 21 will be discussed.

Epigenetics: the neglected key to minimize learning and memory deficits in Down syndrome

Rots, Marianne

Univ Med Center Groningen, Medical Biology

Alain Dekker (1)

Peter De Deyn (2)

Marianne Rots (3)

The triplication of the human chromosome 21 (HSA21) in Down syndrome (DS) theoretically leads to a 1.5 fold increase in gene transcription. Interestingly, transcript levels of many genes significantly deviate from this 1.5-fold. So far, the underlying cause of this gene expression variation has been largely neglected. Epigenetic mechanisms, including DNA methylation and post-translational histone modifications, regulate gene expression in a stable, yet reversible manner. As such, epigenetics might play a crucial role in the development of the cognitive deficits in DS. Various overexpressed HSA21 proteins affect epigenetic mechanisms and DS individuals are thus likely to present epigenetic aberrations. Importantly, as epigenetic marks are reversible, insights in abnormal epigenetic landscapes offer novel therapeutic potentials to alleviate or even cure certain genetic deficits. Current epigenetic therapies are already used for cancer and epilepsy, and might provide possibilities for cognition-enhancing treatment in DS as well.

A major disadvantage of current epigenetic therapies includes their genome-wide effects. To modulate the expression of a particular gene, Artificial Transcription Factors (ATF) can be engineered to either repress or induce the expression. However, ATFs have no catalytic activity themselves and the approach is presumed to result in transient effects. Therefore, we aimed to induce sustained gene expression modulation by rewriting epigenetic marks at any genomic locus of interest¹. To specifically, and sustainably, re-express or silence dysregulated genes, we developed a novel technique called Epigenetic Editing.¹ To target promoter areas, we engineer DNA binding zinc finger proteins (ZFPs) or employ CRISPR/dCas9. These agents are subsequently fused to epigenetic enzymes (writers/erasers) to locally rewrite the epigenetic signature. Data from my laboratory, as well as from others, have demonstrated that rewritten epigenetic marks do result in gene expression changes. For example, adding H3K9Me3 to an overexpressed oncogene Her2neu reduced its expression,² whereas removal of DNA methylation induced gene re-expression.³ To investigate sustainability of the effects, we engineer stable cell lines, to transiently induce the expression of the Epigenetic Editor. Such systems allow to determine the effects of native chromatin microenvironments in permitting or preventing sustained epigenetic reprogramming. Our data show that targeting epigenetic effector domains to a gene of interest is a promising new strategy to modulate gene expression. Dependent on the chromatin microenvironment, prolonged gene expression changes can be induced. Therefore, Epigenetic Editing could partially repress overexpressed HSA21-encoded genes, yielding physiological expression levels that might alleviate the cognitive deficits in DS.⁴

1.de Groote et al, NAR 2012 2.Chen et al, NAR 2014 3.Falahi et al, MCR 2013 4.Dekker et al, Neurosc Biobeh Rev. 201

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Gene dosage imbalance: genomic, transcriptomic and proteomic impact.

Veitia, Reiner

Paris Diderot University and Institut Jacques Monod.,
Reiner VEITIA

Total or partial aneuploidy, gene copy number variants or regulatory alterations often lead to stoichiometric imbalances in macromolecular complexes and in signaling/transcriptional networks. This is the source of dosage-dependent phenotypes. In some cases, the phenotypic perturbations induced by such alterations can be subtle or be lacking because nonlinearities in the process of protein complex assembly or cell signaling can provide some degree of buffering. In other cases the dosage effects can be exacerbated. Here, I will outline the cellular effects of dosage imbalances and the mechanisms underlying buffering at the transcriptional, post-transcriptional and translational levels.

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Energy Metabolism and Cellular Function in Down Syndrome

Busciglio, Jorge

University of California-Irvine, Neurobiology and Behavior

Jorge Busciglio (1)

Several lines of evidence indicate the presence of chronic energy deficits and oxidative stress in Down's syndrome (DS) leading to a number of clinical conditions including Alzheimer's disease (AD). We are currently conducting studies directed to: 1) determine the mechanisms that lead to chronic mitochondrial dysfunction and oxidative damage in DS; 2) develop targeted and combined therapeutic strategies to preserve energy metabolism and cellular homeostasis in DS, and 3) characterize novel peripheral biomarkers of disease progression in DS individuals. Our results suggest that aneuploid states in general (e.g. trisomies 21, 13 and polyploidy) disrupt cellular metabolism by converging mechanisms and increase susceptibility to oxidative damage and energy deficits. Mitochondrial-targeted expression of the antioxidant enzyme catalase reduced chronic energy deficits and oxidative stress in DS neurons and astrocytes and re-established the balance of fission and fusion in the mitochondrial network. Finally, metabolic assays in lymphoblastic cell lines (LCLs) derived from I- subjects with DS with AD dementia (DSAD), II- without AD dementia (DS), III- subjects with sporadic AD (sAD), and IV- age-matched controls indicate significant mitochondrial functional changes in DS, DSAD and sAD LCLs. Metabolic parameters analyzed under regular or minimal feeding regimes with galactose or glucose to assess energy metabolism under glycolysis and oxidative phosphorylation respectively were consistently different between DS, DSAD, and sAD lines suggesting that differential/transitional metabolic states between LCL groups may be utilized as biomarkers of disease progression and/or treatment outcome. In summary, our results point to mitochondria as a source as well as a target of chronic free radicals in DS, leading to structural damage and activation of signaling pathways associated with ageing and age-related neurodegeneration, underscoring the need of therapies directed to manage energy metabolism in DS individuals.

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Multigenic origin of autophagy and mitophagy deficits in Down syndrome (DS)

Nixon, Ralph

Nathan Kline Institute - New York University Langone Medical Center

Autophagy is a lysosomal pathway for turnover of cellular constituents that may be upregulated under conditions of cellular stress. Macroautophagy, the major autophagy pathway, is solely responsible for eliminating damaged or obsolete membranous organelles. In Alzheimer's Disease (AD) and AD/DS, marked autophagy impairment is a significant pathogenic factor contributing to diverse features of the disease phenotype, including neurodegeneration. We find that macroautophagy in DS is negatively influenced at different stages of this process by multiple genes on Chromosome 21 (Chr21). The net effect is a substantially reduced rate of turnover of autophagic substrates and an impaired mitophagic response to mitochondrial injury, associated with a greater burden of abnormal mitochondria and cellular oxidative stress. In fibroblasts from individuals with DS and DS mouse models, the extra copy of App in DS acts through its BACE1-cleaved C-terminal fragment not only to promote cholinergic neurodegeneration via pathologically activated rab5 but to markedly accelerate endocytosis and overburden lysosomes with substrates, thereby impairing lysosomal proteolysis of both autophagic and endocytic substrates. Contributing to these deficits are additional Chr21 genes further aggravating the β CTF pathway or suppressing lysosomal function independently of App identified through siRNA screens in DS fibroblasts. Autophagy in DS is also down-regulated by App-independent genetic factors that cause abnormally high activation of mTOR and thereby suppress autophagy induction and autophagosome formation. We also find that the Parkin-PINK1-mediated mitophagy response to mitochondrial injury is delayed in DS fibroblasts leading to a greater number of damaged mitochondria. This mitophagy deficit is at least partly a consequence of the mTOR hyperactivation in DS because autophagosome formation and mitophagy are rescued by AZD, a specific inhibitor of TORC1 and TORC2. The broad range of autophagy impairments in DS - greater than even that known to exist in sporadic AD - may contribute to the accelerated onset of AD in DS individuals as well as to neural dysfunction arising during brain development.

Cellular phenotypes caused by trisomy 21 in 2D-neuronal and brain-organoid cultures

Nizetic, Dean

Lee Kong Chian School of Medicine,
Nanyang Technological University, Mechanisms of Ageing and Diseases via
Studying Down Syndrome Laboratory

People with DS have a paradoxical epidemiological relationship with Alzheimer's Disease (AD): obligatory development of pathological hallmarks of AD in the brain tissue is extremely early in DS (in the 30-s), but despite this, up to 50% of people with DS seem protected from developing clinical picture of AD, and/or have a much delayed AD onset, despite the triplication of the amyloid precursor protein gene, a genetic abnormality that leads to 100%-penetrant early onset familial AD in non-DS people. DS individuals have risk factors that can accelerate clinical onset of dementia, as well as factors that can protect from AD. This is why studying the mechanisms of AD in DS has the potential to uncover early biomarkers, understanding of the developmental trajectory of AD pathogenesis, and lead to novel protective mechanisms that could be exploited in aiding the battle against dementia in general population.

Modelling Down Syndrome (DS) is beginning to yield first pharmaceutical interventions for amelioration of intellectual disability, and study of the relation between DS and cancer yields important new insights that could be exploited as cancer treatment strategies. Primary cells from DS individuals show a number of phenotypes, reproducible in embryonic stem cell (ESC) and fibroblast mouse model cells, that have direct correlates to the pathogenic processes of DS. New drugs could be identified through cellular phenotype correction, but well-controlled cell model systems are required.

We have developed a first non-integration-reprogrammed isogenic human induced-pluripotent-stem-cells (iPSC) model of DS by reprogramming the skin fibroblasts from an adult individual with constitutional mosaicism for DS, and separately cloned multiple isogenic T21 and euploid (D21) iPSC lines. Our model shows a very low number of reprogramming rearrangements as assessed by a high-resolution whole genome CGH-array hybridisation and it reproduces several pathologies seen in primary human DS cells, as assessed by automated high-content microscopic analysis. Early differentiation shows an imbalance of the lineage-specific stem/progenitor cell compartments: T21 causes slower proliferation of neural and faster expansion of hematopoietic lineage. T21 iPSC-derived neurons show increased production of amyloid peptide-containing material, a decrease in mitochondrial membrane potential, and an increased number and abnormal appearance of mitochondria. T21-derived neurons show significantly higher number of DNA double-strand breaks than isogenic D21 controls. Our fully isogenic system therefore opens possibilities for modelling mechanisms of developmental, accelerated ageing, and neurodegenerative pathologies caused by T21 (Murray A et al. Stem Cells, Feb 2015). We obtained further (unpublished) data showing T21-caused abnormalities using 3-D neuronal cultures and cerebral organoid cultures, derived from both hiPSCs and primary T21 and normal neurospheres, that will be discussed.

SESSION 9

CLINICAL EVALUATION AND CARING IN DOWN SYNDROME

Predicting Obstructive Sleep Apnea in Patients with Down Syndrome

Skotko, Brian

Massachusetts General Hospital, Medical Genetics

Obstructive sleep apnea (OSA) in individuals with Down syndrome is associated with multiple morbidities: systemic and pulmonary hypertension, glucose intolerance, cardiovascular and cerebrovascular disease, and behavioral problems. The prevalence of OSA in this population is very high, with estimates ranging between 55-97%. Currently, an overnight polysomnogram (sleep study) is the gold-standard diagnostic test for patients with Down syndrome. Yet, this testing is cumbersome, poorly tolerated by these children, costly, and not widely available around the country. Our team sought to identify predictive factors for OSA in persons with Down syndrome—that is, we aimed to establish an effective, reliable, and user-friendly tool to screen for OSA in individuals with Down syndrome without needing a polysomnogram. We enrolled 100 subjects, ages 3-35 years, from the Down Syndrome Program at Children’s Hospital Boston. For each patient, we collected subjective and objective measurements using validated parental survey instruments, standardized physical exams, lateral cephalograms, 3D-digital photogrammetry, and urine samples. All participants then completed standardized polysomnography at the Children’s Hospital Boston Sleep Laboratory where objective measurements will be collected on OSA. We analyzed which combination of our assessment methods could best predict OSA as ultimately determined by polysomnography. During this talk, we will present our preliminary data for the first time.

Exploring risk factors for dementia in Down syndrome

Startin, Carla

UCL, Division of Psychiatry

The London Down Syndrome Consortium (LonDownS) is exploring individual differences in people with Down syndrome (DS), including differences related to the age of onset of dementia. Individuals with DS are at an increased risk of developing Alzheimer's disease, and although the neuropathological signs are present in the brains of adults aged over 35 there is considerable variation in the age at which people present with signs of dementia and receive a diagnosis. Some people are diagnosed with dementia in their late 30s, whereas others in their 60s do not show any signs of dementia. LonDownS is investigating factors that increase risk for and protect against dementia. We are currently comparing individuals at the extremes for the dementia phenotype, i.e. those who receive a dementia diagnosis before the age of 50 ($n=15$) and those who are aged 55 and over who do not have a diagnosis of dementia ($n=13$). Factors compared between the groups include demographic information, the presence or absence of specific medical conditions over the lifetime, and physical measurements.

Factors associated with a diagnosis of dementia before the age of 50 are lifetime recurrent infections, lifetime immunological conditions, a lifetime history of epilepsy (diagnosed before the age of 30), and a smaller head circumference.

These results point to several risk factors that may increase risk of developing dementia in people with DS. Firstly, they suggest an important role of the immune system in increasing risk for an earlier diagnosis of dementia. Supporting these results, a role for the immune system in the development of Alzheimer's disease in the general population has also been proposed. Secondly, a diagnosis of epilepsy before the age of 30 may also increase risk for an earlier diagnosis dementia, possibly due to increasing the vulnerability of the brain to neurodegeneration. Finally, a smaller head circumference may also increase risk for dementia. This may indicate a smaller brain volume, and so may be consistent with the cognitive reserve hypothesis.

Factors Associated with Inclusion for Children with Down syndrome

Stein, David

Boston Children's Hospital/Harvard Medical School, Developmental Medicine Center

Inclusion of children with intellectual disability (ID) including Down syndrome (DS) in general education (GE) settings is increasingly prevalent and is shown to improve developmental outcomes. However, national US data indicate that children with ID continue to spend far more time outside of the GE classroom than other children with disabilities. US federal law dictates that children be served in the least restrictive environment, but what factors predict placement for those with ID? The purpose of this study was to investigate several factors associated with classroom placement for children with ID.

Participants were children with Down syndrome (N= 60; mean age= 8.9 years) who received psychological evaluations, including testing of cognitive, language, social, and adaptive skills, at a major academic medical center. Family income data were used as a proxy for SES. A logistic regression model was employed to evaluate the ability of the independent variables to properly predict placement in inclusive or substantially separate settings (using US Dept. of Education criteria for educational setting).

Results indicated that in a multivariate model, only SES ($p= 0.032$), and to a lesser extent IQ ($p= 0.038$), were significant predictors of classroom placement (inclusion vs. sub-separate) for participants. For a one unit upward change in SES, the likelihood that an individual was placed in a G.E. setting increased by 56 times. Language, social, and adaptive skills had no effect on educational placement.

This finding suggests that SES is far more influential than virtually all measured child factors, aside from IQ, in educational placement determinations for study participants. This highlights a challenge within the movement toward increased inclusion programming for those with ID/DS. Children with ID/DS seem to benefit developmentally from increased inclusion, but the factors determining inclusive placement may not be based on the individual child's neurodevelopmental profile and needs. Future research should continue to investigate this issue with larger samples. Should the trend continue, such findings may influence policy, leading to increased inclusion and consequently, improved developmental outcomes for those with ID/DS.

New tools to develop autonomy in people with Down syndrome
Dupas, Cécile
TRISOMIE 21 FRANCE,

The Act of February 2005 for the Promotion of Equal Rights and Opportunities, for the Participation and Citizenship of People with Disabilities, questions the way these principles are being implemented in society at large.

Since 2005, people with Down Syndrome and Intellectual Disabilities, supported by their families and their care-givers, have stated that their needs in the fields of education, health and citizenship are not properly identified and sufficiently taken into account. In 2008, a mixed commission, composed of various actors in the field of disabilities, recommended the creation and the use of tools that would facilitate the autonomy and self-determination of people with Intellectual Disabilities.

In 2015, what has been done in terms of accessibility for people with Intellectual Disabilities?

By way of an answer, some professionals and administrators of the associations' Trisomy 21, with the help of university research laboratories and communication professionals, have conceived a series of accessible and inventive tools. They are meant to support people with ID in the organisation of their daily lives and to reinforce their autonomy.

☐ A website www.santetresfacile.fr (from April 2015). It is a personalized interface, in easy-to-read language. It can be used on several digital appliances and it is meant to make it easier for people with DS or ID to get medical knowledge and to be responsible of their own medical follow-up.

☐ A digital device to facilitate the formulation of their own life plans.

☐ An accessible information system enabling the persons with DS or ID to be the actors of their own life plans, thus strengthening their empowerment.

T21 France believes that acting on their own lives enhances the quality of life of people with ID and increases their abilities.

The tools have been developed by people with ID for people with ID. Thus people with ID are the main actors, the creators, and the users of these tools. These tools have been or will be tested by the users.

The projects that T21 France has pushed forward for 42 years now show that it is possible to make the mainstream public services accessible. "Nothing for us without us": it is thanks to this ambition that the image of people with DS or with ID will change eventually.

Consequently, it is of the utmost importance to promote applied research along with fundamental and clinical research; it has a direct and complementary impact on people's quality of life.

We propose to present these innovative solutions to help people care about their own health and make effective and informed choices, in order to support their autonomy and self-determination.

French validation of the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID) in a cohort of Down Syndrome patients aged 40 and over

Rebillat, Anne-Sophie

Institut Jérôme Lejeune, Paris

Individuals with Down Syndrome (DS) have an increased risk of developing dementia with aging.

Studies found that almost all adults with DS have Alzheimer's disease (AD) neuropathology by age 40 years, because trisomy 21 leads to deregulation of APP and other genes. Although 80 % of patients present symptoms of AD dementia at the age of 65, cognitive and behavioral profiles are highly variable depending on the level of intellectual disability and clinical diagnosis remains difficult.

The Jérôme Lejeune Institute provides a medical follow-up to a cohort of about 500 DS patients aged 40 to 70 and over. 150 patients had dementia screening test during the geriatric consultation using a french translation of the DSQIID (Deb and coll., 2007). All patients had clinical examination with comorbidities assessment and treatment (obstructive sleep apnea, vision and hearing disorders, epilepsy, depression, thyroid disorders etc).

To validate sensitivity and specificity of DSQIID in its french translation, a third of this population received neuropsychological assessment including verbal and non-verbal reasoning, naming, fluency, visuo-motor and cancellation tasks, as well as episodic memory evaluation. Dementia Questionnaire for Persons with Mental retardation (DMR) and Sovener questionnaires were also proposed for AD dementia and depression diagnosis. Intellectual disability level was obtained from verbal and non-verbal reasoning tasks. For those that had not neuropsychological assessment, intellectual disability level was obtained referring to speech ability and autonomy degree in daily living.

As described by Deb, DSQIID is a user-friendly observer-rated dementia screening questionnaire with strong psychometric properties for adults with intellectual disabilities. Used as a routine clinical assessment, it could allow early detection of cognitive decline and thus improve the care of DS patients with advancing age.

SESSION 10

NIH AGENDA, DS CONNECT

SESSION 11
TOOLS FOR ASSESSMENT OF
THERAPEUTIC APPROACHES. CLINICAL
TRIALS FOR DS

Regulation of self-renewal and senescence in Down's Syndrome Stem Cells

Adorno, Maddalena

Stanford University, Institute for Stem Cells and Regenerative Medicine

Maddalena Adorno (1)

Michael Clarke (1)

Craig Garner (2)

Craig Heller (2)

Somatic stem cells are important to maintain normal tissue homeostasis and defects in stem cells are linked to aging and inherited disorders. We recently demonstrated that mice models of Down Syndrome (DS), such as Ts65Dn mice, present a generalized defect in stem cells in several tissue compartments, including bone marrow, fibroblasts, mammary gland and brain. We reported that Usp16, one of the genes located in HSA21, is a key determinant in this process, since it acts as an epigenetic regulator of self-renewal and aging. Usp16 is associated with decreased ubiquitination of Cdkn2a and accelerated senescence in Ts65Dn fibroblasts. Usp16 can remove ubiquitin from histone H2A on lysine 119, a critical mark for the maintenance of multiple somatic tissues. Downregulation of Usp16, either by mutation of a single normal Usp16 allele or by short interfering RNAs, largely rescues all of these defects. Furthermore, in human tissues overexpression of USP16 reduces the expansion of normal fibroblasts and postnatal neural progenitors, whereas downregulation of USP16 partially rescues the proliferation defects of Down's syndrome fibroblasts. Taken together, these results suggest that USP16 has an important role in antagonizing the self-renewal and/or senescence pathways in Down's syndrome and could serve as an attractive target to ameliorate some of the associated pathologies.

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Dementia symptoms and diagnostic criteria in Down syndrome

Strydom, André

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The presentation of dementia in Down syndrome (DS) differs from typical Alzheimer's disease (AD), which affects how clinicians diagnose dementia in this population. The presentation of dementia in Down syndrome (DS) differs from typical Alzheimer's disease (AD), which affects how clinicians diagnose dementia in this population. This should be considered when selecting or designing outcome measures for clinical trials to treat AD in DS. Diagnostic issues in DS will be reviewed as well as results from studies that have compared clinical diagnoses of dementia against manualised criteria, including International Classification of Diseases (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) dementia criteria as well as the new DSM-5 criteria for neurocognitive disorder. Implications for diagnostic and outcome measures in clinical studies will be discussed.

Multimodal Assessment of AD Biomarkers in Down Syndrome

Rafii, Michael

University of California, San Diego, Neurosciences

Michael Rafii (1)

Robert Rissman (1)

James Brewer (1)

Paul Aisen (1)

William Mobley (1)

We enrolled 12 non-demented participants with DS between the ages of 30-60 years old. Participants underwent extensive cognitive testing, volumetric MRI, amyloid PET 18F-florbetapir, 18F-fluorodeoxyglucose (18F-FDG) PET, and retinal amyloid imaging. In addition, plasma beta-amyloid species were measured and ApoE genotyping was performed. Consistent with previous autopsy studies, most subjects demonstrated amyloid PET positivity reflecting fibrillar amyloid plaque deposition. Results from our multimodal analysis also suggest greater hippocampal atrophy with amyloid load. Additionally, we identified an inverse relationship between amyloid load and regional glucose metabolism. Cognitive and functional measures did not correlate with amyloid load in DS but did correlate with regional FDG PET measures. Biomarkers of AD can be readily studied in adults with DS as in other preclinical AD populations. Importantly, all subjects in this feasibility study were able to complete all measures. Larger studies of adults with DS are in the planning stages to better inform possible outcome measures for AD clinical trials in this population.

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Efficacy assesment of folinic acid and thyroid hormone systematic treatment on the psychomotor development of young down syndrome children

Mircher, Clotilde

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MIRCHER Clotilde

SACCO Silvia

NONNOTTE Emilie

RAVEL Aimé

CIEUTA-WALTI Cécile

LE GALLOUDEC Eric

BOUIS Charles

STORA Samantha

STURTZ Franck

Thyroid metabolism is crucial for the CNS child development, and frequently affected in DS children. It is shown to be constantly affected in newborns and young children with Down syndrome (DS), with low limit FT4 associated with TSH high level trend, and that from birth to 2 years at least (van Trotsenburg et al, 2003). Folate deficiency is known to cause neurological and cognitive disorders. 7 genes involved in folate metabolism pathway are located on chromosome 21, and DS probably involves defective folate use.

ENTRAIN study investigated the effect of folinic acid supplementation in young DS children (PlosOne, 2010); the Intent to treat analysis did not show a positive effect; however a peer protocol analysis revealed a positive effect on developmental age, particularly strong in patient receiving concomitant thyroxin treatment. This finding led us to investigate the connections between the metabolism of folates and that of thyroid hormones (TH) with a new clinical trial, ACTHYF.

ACTHYF study is a monocentric, random, comparative Phase III study, in four arms (Folinic acid, TH, both, neither one). Patients age at inclusion ranges from 6 to 18 months. A total number of 256 patients are planned to be analyzed in this trial. The main endpoint will be the evolution of the general development quotient measured by the Griffiths scale (GMDS).

To understand the finding of the study, additional analysis will be conducted in collaboration with external university team for (i) Redox status and (ii) Folate metabolism; DNA extracts and cell line are also stored in our BioBank BioJel (under embargo until the end of the study).

Inclusion rate is slower than expected, but steady: 115 children have been included at the moment. No adverse effect related to the treatment was observed. Interim analysis will be conducted once 50% of patients have been completed the protocol.

Results of this trial are expected within 3 years. This target can also reinforce close collaborations between clinicians and basic scientists.

Targeted Treatment for Down syndrome: Clinical Development of RG1662

Visootsak, Jeannie

Hoffman-La Roche, Roche Innovation Center New York
Jeannie VISOOTSAK (1)

Dr. Jeannie Visootsak will discuss the development of new molecular entities for treatment of intellectual disability associated with Down syndrome from the perspective of the biopharmaceutical industry. She will draw on Roche's experience to date in developing RG1662, a novel GABA-A α 5 negative allosteric modulator. The presentation will include clinical trial design including selection and validation of endpoints and outcome measures as well as broader clinical development considerations for new molecules. This will cover pre-clinical efficacy and safety, first-in-human studies, assessment of target engagement as well as regulatory, operational and ethical considerations in drug development in adults and children with Down syndrome.

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Tools for assessment of therapeutic approaches. Clinical trials for DS.

De la Torre, Raphael

Human Pharmacology and Clinical Neurosciences Research Group, Neurosciences Research Programme, Barcelona

Human Pharmacology and Clinical Neurosciences Research Group, Neurosciences Research Programme

Background: Several tools are available for the assessment of efficacy in the context of clinical trials in DS populations. Some of them have been applied in the context of the TESAD clinical study: neuroimaging, neurophysiology and biomarkers (biochemical, genetic). Baseline values of these techniques in DS are missing and needed to be determined/validated preliminarily before evaluating their value for assessing therapeutic effects.

Objective: This study aims to understand how different tools as: resting-state whole-brain connectivity degree maps (fcMRI), paired pulse transcranial magnetic stimulation (TMS), amyloidosis plasma biomarkers concentrations and the evaluation of dopamine polymorphisms interact in DS young adult population with the cognitive phenotype assessment.

Methods: Biological markers of amyloidosis (A β 40, A β 42 and A β 42/40 plasma conc.; n=59) and genetic polymorphisms defining dopamine brain availability (VNTR-DAT 1 and COMT Val158Met; n=72) were assessed in DS subjects. A subsequent statistical analysis assessed their interaction with cognitive performance and daily life functionality of subjects. Resting-state whole-brain connectivity degree maps (fcMRI) were generated in 20 DS and 20 control age matched (24 y) subjects. A subsequent region-of-interest mapping served to assess the cognitive and functional contribution by using a seed-based approach. TMS variables, for 26 DS and 26 age-matched controls, included resting motor threshold (RMT) and motor evoked potentials (MEP) inhibited (at 5 and 3 ms) and facilitated (at 10 and 15 ms) by paired pulse stimuli averages. A subsequent correlation between this values and a full neuropsychological battery was analysed in order to assess the contribution of cortical DS pattern in cognition.

Results: Our results have shown that A β 42 plasma concentrations are related with verbal fluency, communication skills and preclinical signs of dementia (DMR). In addition, other genetic variables further than trisomy 21, as genetic polymorphisms defining striatal and prefrontal dopamine availability (VNTR-DAT 1 and COMT Val158Met genotypes) contribute to attention, mental flexibility and social skills. Regarding to DS functional brain status we found a distinctive brain functional organization with an opposite effect on frontal and anterior temporal structures and relative sparing of posterior brain areas which accounted for communication skill deficiencies. Regarding to neurophysiology measures; anomalous DS overactivation in SIC1 and ICIF is reported. SIC1 overactivation correlates with higher IQ, vocabulary, verbal and working memory and ICIF with better visual memory.

Conclusions: We conclude that several tools are useful to assess brain activity (fcMRI, TMS). Plasma concentrations of given parameters or genetic polymorphisms can be used either as surrogate biomarkers or as covariates in the evaluation of efficacy. All of them display strong correlations with the cognitive phenotype in DS young adult population. These results support their use in clinical trials to evaluate efficacy (cognitive and functional daily living outcomes) in cognitive enhancement treatments.

BREAKTHROUGH RESEARCH SYMPOSIUM 1

Behavior and synaptic plasticity in the Ts65Dn:Kcnj6⁺ mouse model of Down syndrome

Kleschevnikov, Alexander

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Down syndrome (DS) is caused by the triplication of chromosome 21. Which genes contribute to DS phenotypes is largely undefined. One of the genes present in three copies in DS is Kcnj6. This gene encodes Kir3.2 (Girk2) subunits of G-protein-coupled inwardly-rectifying potassium channels, which serve as effectors for several postsynaptic metabotropic receptors. Kir3.2 protein levels are increased in proportion to the gene dose in the Ts65Dn hippocampus, and this change correlates with increased signaling through the metabotropic receptors linked to these channels. Since activation of Kir3.2 subunit-containing potassium channels results in neuronal hyperpolarization, we hypothesized that increased signaling through these channels may contribute to reduced hippocampal synaptic plasticity and deficient cognition in DS. To test this hypothesis, we produced Ts65Dn mice with either 2 or 3 copies of the Kcnj6 gene (i.e., Ts65Dn:Kcnj6⁺⁺⁺ and Ts65Dn:Kcnj6⁺⁺). Here we report results of biochemical, behavioral, and electrophysiological studies of these mice. We confirmed that the expression levels of Kir3.2 protein are ~50% greater in Ts65Dn:Kcnj6⁺⁺⁺ vs. the normosomic 2N:Kcnj6⁺⁺ mice. Importantly, we observed that the levels of Kir3.2 were not different in the Ts65Dn:Kcnj6⁺⁺ vs. 2N:Kcnj6⁺⁺ mice. Locomotor activity was increased in Ts65Dn:Kcnj6⁺⁺⁺ vs. 2N:Kcnj6⁺⁺ mice but was not different in the Ts65Dn:Kcnj6⁺⁺ vs. 2N:Kcnj6⁺⁺ mice. Working memory, tested in the Y-maze, was similarly deficient in both Ts65Dn:Kcnj6⁺⁺⁺ and Ts65Dn:Kcnj6⁺⁺ mice. Long-term object recognition memory was deficient in the Ts65Dn:Kcnj6⁺⁺⁺ vs. 2N:Kcnj6⁺⁺ but was normal in the Ts65Dn:Kcnj6⁺⁺ mice. Synaptic plasticity was examined using hippocampal slices. Long-term potentiation (LTP) in the middle molecular layer of the dentate gyrus was reduced in Ts65Dn:Kcnj6⁺⁺⁺ vs. 2N:Kcnj6⁺⁺, but was not different in Ts65Dn:Kcnj6⁺⁺ vs. 2N:Kcnj6⁺⁺ mice, providing evidence that increased activity of Kir3.2 channels contributes to the suppression of LTP in Ts65Dn mice. To explore this, we examined the effects of fluoxetine, an effective, albeit nonspecific, blocker of Kir3.2 channels. Fluoxetine (10 μ M) improved LTP in Ts65Dn to the levels observed in 2N slices. We conclude that the presence of one extra copy of Kcnj6 contributes significantly to reduced synaptic plasticity and deficient cognition in the Ts65Dn model of DS. (Supported by grants from the Jérôme Lejeune Foundation, LuMind Foundation, L.L. Hillblom Foundation, and NIH R01NS066072).

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Impacts of duplications of human chromosome 21 orthologous regions on the mouse hematopoietic system with or without the co-presence of the Gata1s mutation

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Human trisomy 21, the chromosomal basis of Down syndrome (DS), is the most common aneuploidy compatible with postnatal survival. Children with DS frequently have hematopoietic abnormalities, including transit myeloproliferative disorder (TMD) and acute megakaryoblastic leukemia (AMKL), which are associated with acquired GATA1 mutations that produce a truncated protein, GATA1s. The mouse has been used for modeling DS based on the syntenic conservation between human chromosome 21 (Hsa21) and the three regions in the mouse genome located on mouse chromosome 10 (Mmu10), Mmu16 and Mmu17. To assess the impact of the dosage increase of Hsa21 gene orthologs on the hematopoietic system, we characterized the related phenotype in the Dp(10)1Yey/+;Dp(16)1Yey/+;Dp(17)1Yey/+ mouse model, which carry the duplications spanning the entire Hsa21 orthologous regions on Mmu10, Mmu16 and Mmu17. We found that the Dp(10)1Yey/+;Dp(16)1Yey/+;Dp(17)1Yey/+ mice exhibited anemia, macrocytosis, myeloproliferative disorder and increase of megakaryocyte-erythrocyte progenitor cells. To better mimic DS, we engineered a Gata1s mutation in mice. Compounding the Gata1s mutation with Dp(10)1Yey/+;Dp(16)1Yey/+;Dp(17)1Yey/+ led to increased mean platelet volume and more severe macrocytic anemia. The megakaryocyte-erythrocyte progenitors were significantly increased in both models. These results indicate that triplications of all Hsa21 syntenic regions with or without a Gata1s mutation significantly affect hematopoietic development, leading to a pre-leukemic state. Our results shared some similarities to what have been observed in the Ts65Dn mouse model of Down syndrome, suggesting the same triplicated Mmu16 region among these models underlie certain hematopoietic phenotype regardless the region is present as a segmental duplication or trisomy.

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Rescue of the abnormal skeletal phenotype in Ts65Dn Down syndrome mice using genetic and therapeutic modulation of trisomic Dyrk1a

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Trisomy 21 causes skeletal alterations in individuals with Down syndrome (DS) but the causative trisomic gene and a therapeutic approach to rescue these abnormalities are unknown. Individuals with DS display skeletal alterations including reduced bone mineral density, modified bone structure and distinctive facial features. Due to peripheral skeletal anomalies and extended longevity, individuals with DS are increasingly more susceptible to bone fractures. Understanding the genetic and developmental origins of DS skeletal abnormalities would facilitate the development of therapies to rescue these and other deficiencies associated with DS. DYRK1A is found in three copies in individuals with DS and Ts65Dn DS mice and has been hypothesized to be involved in many Trisomy 21 phenotypes including skeletal abnormalities. Return of Dyrk1a copy number to normal levels in Ts65Dn mice rescued the appendicular bone abnormalities, suggesting that appropriate levels of DYRK1A expression are critical for the development and maintenance of the DS appendicular skeleton. Therapy using the DYRK1A inhibitor EGCG improved Ts65Dn skeletal phenotypes. These outcomes suggest that the osteopenic phenotype associated with DS may be rescued postnatally by targeting trisomic Dyrk1a.

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Reversing excitatory GABA signaling restores synaptic plasticity and memory in a mouse model of Down syndrome

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Trisomic mouse models of Down syndrome (DS) reproduce the main cognitive disabilities of the human syndrome. In particular, Ts65Dn mice show impaired synaptic plasticity as well as learning and memory deficits. Increased GABAergic transmission through chloride-permeable GABA-A receptors (GABAAR) has been shown to largely determine these deficits in DS mice. However, the efficacy of GABAergic transmission has never been directly assessed in DS. Here, we show that GABAAR signaling is excitatory rather than inhibitory, and the reversal potential for GABAAR-driven chloride currents (E_{Cl}) is shifted toward more positive potentials in the hippocampi of adult DS mice. Accordingly, hippocampal expression of the cation chloride cotransporter NKCC1 was increased in both trisomic mice and individuals with DS. Notably, NKCC1 inhibition by the FDA-approved drug bumetanide restored E_{Cl}, synaptic plasticity and hippocampus-dependent memory in adult DS mice. Our findings demonstrate that GABAAR signaling is excitatory in adult DS mice and identify a new therapeutic approach for the potential rescue of cognitive disabilities in individuals with DS.

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BREAKTHROUGH RESEARCH SYMPOSIUM 2

Down syndrome beyond non-disjunction.

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Major efforts by geneticists who study Down syndrome (DS) have been focused on understanding the determinants of non-disjunction of chromosome 21. Less attention has been paid to other factors that may contribute to the birth of a child with DS. It is recognized that non-disjunction and other genetic events leading to aneuploidy are very common in oogenesis. Up to 25% of human oocytes had aneuploidy often resulting from non-disjunction of at least one chromosome. Studies in human abortuses have found that a substantial percentage were trisomic or monosomic. In fact, aneuploidy was called “astonishingly common in our species”. It has been estimated that no fewer than 5% of all clinically recognized pregnancies are trisomic or monosomic. With few exceptions most aneuploid embryos are spontaneously aborted. Trisomy 21 embryos represent a rare exception from the rule. While 75% of trisomy 21 embryos are spontaneously aborted, 25% develop and are born. This high rate of spontaneous abortion may simply reflect a primary non-viability of the fetus due to the trisomic state. We present an alternative explanation. We postulate the existence of a maternal surveillance and embryo rejection system that includes a mechanism of communication between the embryo and maternal tissues that recognizes genetic abnormalities. Failure of this system to recognize such abnormalities to reject genetically abnormal embryo would result in a live birth of a child with trisomy 21. Our preliminary studies suggested that pericentrin (PCNT) may be involved in communication between the embryo and the maternal tissues and play a role in this surveillance system. Impairment of PCNT functions might result in errors of communication and subsequently in non-recognition of the genetic abnormality of the embryo. The PCNT gene is located near the telomere of chromosome 21. The multifunctional pericentrin protein is present at a microtubule organizing center in a pericentriolar region of the centrosome. It is crucially involved in meiosis, mitosis, and ciliogenesis. Mutations in the PCNT gene are associated with a range of diseases including primordial dwarfism and ciliopathies. While the importance of pericentrin in meiosis could suggest that it might be involved in non-disjunction, our data forced us to look at the events that occurred beyond non-disjunction. PCNT is involved in ciliogenesis of primary cilium that is critical for embryonic development. PCNT has been detected multiple embryonic tissues and in sections of human full term placenta, amniochorion, amnion epithelium, trophoblast layer and in the first trimester chorionic villus trophoblast. Our alternative explanation posits the existence of a pro-active maternal system for recognition and rejection of embryos with an abnormal number of chromosomes. The birth of a child with DS would represent a failure of such a system. PCNT gene variants may play a role of parental risk factors for having a child with DS.

Magnetic Resonance Imaging Study of the Developing Fetal Brain in Trisomy 21

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INTRODUCTION: Down syndrome (DS) (Trisomy 21), is the most frequent genetic cause of intellectual disability – approximately 750 babies are born with the condition, each year in the UK. The neurodevelopmental phenotype is associated with cognitive deficits and shows variable impairments in speech, motor and language functions. DS is also commonly associated with congenital heart defects which can adversely impact neurodevelopment. Currently, the relationship between structural brain morphology and the spectrum of cognitive phenotypes in DS, is not understood.

METHODS: Fetuses were recruited with parental consent and ethical approval from London hospitals. Fetal magnetic resonance imaging (MRI) was performed on 20 DS fetuses, with and without cardiac lesions, (gestational age (GA) range of 21-36 weeks). 3D reconstructions were produced and structural volumetric data across various neuroanatomical structures was compared with 60 normal controls. Infants will be scanned postnatally to obtain further structural and functional information, and will undergo neurodevelopmental assessments from 6 months of age, to correlate longitudinal MRI findings with specific developmental delays.

RESULTS: Preliminary MRI results demonstrate smaller whole brain, cortical and cerebellar volumes in DS fetuses from 25 weeks GA, compared to control brains. DS fetuses also exhibit significant enlargement of the fourth ventricle.

CONCLUSION: DS fetuses show deviation in development and altered gross and regional brain growth from 25 weeks GA. Future work, based on a larger cohort, will aim to map the developing DS brain to identify and characterise abnormal intrauterine development. Furthermore, genetic analysis of patient saliva samples will examine the overexpression of specific T21 genes and will be compared to imaging and neurodevelopmental data to establish early biomarkers of poorer neurodevelopmental outcome. In cases where termination is performed, the post mortem fetal brain tissue will be used for histological analysis, which will focus on characterising the neuronal and glial phenotype in DS.

A regulatory crosstalk in Down syndrome: competing mRNA-miRNA network

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Down syndrome (DS) - also known as Trisomy 21 - is a genetic disorder caused by an extra copy of all or part of human chromosome 21 (HSA21). DS is a complex genetic condition characterized by over 80 clinically different phenotypes of variable penetrance and expressivity. Alterations - both structural and functional - affecting different organs and systems suggest that a perturbation of embryogenesis occurs in individuals with Down syndrome, due to Trisomy 21. Large-scale gene expression studies have revealed a complex scenario, highlighting a global transcriptional deregulation, extended to euploid genes. In this context, direct and/or indirect interactions between gene products of HSA21 and those from the other chromosomes can better explain the complexity of the clinical manifestations of the disorder. Recent studies have pointed out a previously unexpected role of non-coding RNAs (ncRNAs) on gene expression regulation. In particular, a new crosstalk mediated by the competition for the binding to specific miRNAs has been demonstrated among transcripts. Such a regulatory crosstalk represents a new and interesting "RNA language" through which different mRNAs regulate each other by competing for miRNAs' availability. Given these recent findings and considering that Trisomy 21-induced gene imbalance perturbs the entire transcriptome and occurs throughout the embryogenesis, we hypothesize the above-described regulatory crosstalk may be altered by the pathological overexpression of HSA21 genes in DS fetuses. In turn, it would cause typical multisystem clinical manifestations of Down syndrome. Thus, we explored the global gene deregulation in DS, and the potential role of microRNAs' "sponges" played by HSA21 genes that are overexpressed during embryonic development of DS fetuses. Taking advantage of publicly available mRNA and miRNA expression datasets, a regulatory miRNA/mRNA network was established. Afterwards, HSA21 genes overexpressed in DS embryos that belong to this network were identified using RNA-Seq datasets from DS and euploid matched chorionic villi. HUNK gene was computationally selected as the best candidate to be an HSA21-derived miRNA sponge. Experimental studies confirmed that the overexpression of its 3'UTR induces an increased expression of genes involved in embryonic development, including BCL2, CLIC5, EPHA5, ERBB4, HIPK2, MECP2, ONECUT2, and WNT5A. Accordingly a reduced expression of correlated miRNAs, including miR-17, miR-20a, miR-20b, miR-128 and miR-200c, was observed. The results of both the computational and the experimental studies strongly suggest that the overexpression of HSA21 genes may perturb the physiologic regulatory miRNA/mRNA network during DS embryos' development. This would explain, at least partially, the multisystemic nature of the alterations that typically occur in individuals with the syndrome.

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A marked brain NGF metabolic dysfunction in Down Syndrome

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It is well established that there is an atrophy of basal forebrain cholinergic neurons (BFCN) in Down Syndrome (DS). These neurons play an important role in cognitive functions. The phenotypic maintenance of this neuronal system is closely dependent on the supply of endogenous nerve growth factor (NGF). Its atrophy in DS should contribute to late cognitive decline and dementia, coincidental with the establishment of Alzheimer's-like pathology. In Alzheimer's disease (AD) AD brains, the synthesis of NGF remains normal with high levels of the NGF precursor molecule (proNGF). We have resolved this apparent paradox by demonstrating in AD brains that atrophy of BFCN is caused by a deficit in NGF's extracellular metabolism. We have recently demonstrated a similar imbalance is present in DS brains and even in cultures of DS fetal cortical cells. We have found a significant increase in proNGF in human DS brain samples, with a reduction in the levels of plasminogen and tPA, molecules which are responsible for the extracellular proNGF maturation into mature and biologically active NGF (mNGF). Furthermore, our studies revealed that the resulting mNGF in DS brains would have a short life-span as these brains also revealed an elevated MMP-9 activity. MMP-9 being the major NGF-degrading protease. Thus our investigations reveal a failure in proNGF maturation in DS brains along with a likely enhanced proteolytic degradation of mNGF. In sum, these neurochemical changes revealing a significant compromise the trophic support of BFCN which would explain the apparent paradox of a normal NGF system along with atrophy of BFCN in both AD and DS. What is also remarkable is the finding of analogous alterations in proNGF and MMP-9 in DS fetal cultures which would indicate that the failure in the NGF trophic support might have a very early start in DS, well before frank dementia onset. Our study thus provides a novel paradigm to consider an early cholinergic neuroprotection strategies.

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POSTERS

PLATFORM PRESENTATION 1

1 - The Down syndrome critical region (DSCR) gene 1 is critical for the regulation of proper vessel formation and vascular inflammation

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Epidemiological studies suggest that although individuals with Down syndrome have an increased risk of leukemia and neuronal diseases, they have a considerably reduced incidence of most solid tumors and advanced atherosclerosis. Such data indicate that one or more of the 231 trisomic genes on chromosome 21 are responsible for protecting these individuals against vasculopathic disease such as tumor angiogenesis, diabetic retinopathy and chronic inflammation. We previously reported the Down syndrome critical region (DSCR)-1, also known as regulator of calcineurin (RCAN) 1, gene lies on chromosome 21 and encodes a negative feedback regulator of vascular endothelial growth factor (VEGF)-nuclear factor of activated T cells (NFAT)-calcineurin signaling in endothelium. Null mutation of *Dscr-1* demonstrated increased septic mortality, angiogenic balance, and susceptibility of preferential tumor metastasize to the lung. In contrast, overexpression of *Dscr-1* prevents pathological angiogenesis, inflammations, and tumor lung metastasis in our mouse models.

In this time, to survey the effects of constitutive *Dscr-1* overexpression and atherosclerotic plaque burden, we generated endothelial specific conditional *DSCR-1* transgenic (Tg) mice and crossed with ApoE-null mice. Stable *DSCR-1* expression in vascular endothelium resulted in the partial lethal during the embryonic stages. Embryo sizes with *DSCR-1* Tg were smaller than the wild-type littermate control. After birth, these mice were developed normally. However these *DSCR-1* Tg mice revealed dysfunctional branch formations in subsets of vascular in any organs, and typically in brain, total blood vessel density was markedly reduced. Combined null mutations of *Dscr-1* and ApoE resulted in the hyper blood cholesteromia but reduced atherosclerotic plaque level in aorta compared to the single ApoE null mice. Furthermore, *Dscr-1*^{-/-} and ApoE^{-/-} mice caused peripheral advanced impaired angiogenesis and corneal opacity with age. Taken together, our studies provide new insights into mechanisms underlying angiogenesis, inflammation and atherosclerosis in vascular biology with both Down syndrome model mice and patients in future.

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2 - A Specialized Pro-Resolution Mediator Approach to Cognitive Performance in the Ts65Dn Mouse model of Down Syndrome

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Individuals with Down Syndrome (DS) develop Alzheimer's disease (AD) neuropathology with high incidence. The central theories that try to explain DS-AD pathology are intricately tied to immunological stress. Previous studies in blood samples from subjects with DS have revealed that serum levels of IL-1 β , IL-6, IL-12 and TNF- α ; cytokines are elevated while anti-inflammatory cytokines are lowered. Further, chronic inflammation has been observed in rampant activation of microglia leading to aggregation, senescence and, finally to microglial loss. Pro-inflammation signaling is not self-limiting, but rather is coordinated by the pro-resolution signaling process, the final stage of an inflammatory response. Failure of resolution signaling is postulated to lead to chronic inflammation, which may contribute to neuropathology in the brain of individuals suffering from AD or DS-AD.

We provide early evidence of perturbations in one resolution signaling pathway in post mortem human DS-AD brain samples. Our preliminary results show that the distribution of resolution receptors is perturbed and warrant further investigation of resolution signaling. The Ts65Dn mouse model of DS recapitulates the immune stress seen in humans with DS-AD, mimics accelerated brain pathology and cognitive decline, and provides an invaluable mouse model to study resolution processes. In this poster, we introduce pharmacological tools intended to enhance resolution signaling. Finally, we present our most recent data regarding Ts65Dn cognitive/memory performance after long-term treatment with a pro-resolution mediator. Our preliminary results show that pro-resolution mediators may be effective in dealing with chronic immunological stress and that they may promote better brain aging in the Ts65Dn mouse. Specialized proresolving mediators may be useful in modulating inflammation and decrease accelerated-neuropathology seen in DS.

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3 - Effects of Prenatal Treatment With Apigenin in the Ts1Cje Mouse Model of Down Syndrome

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Background: Human fetuses with Down syndrome (DS) demonstrate abnormal brain growth and neurogenesis. We identified oxidative stress as the major functional abnormality in RNA from amniotic fluid supernatant in fetuses with DS vs. euploid controls. We hypothesized that apigenin, an FDA-approved antioxidant identified by the Connectivity Map database (CMAP) could suppress oxidative stress in DS and improve cognition.

Methods: Ts1Cje mice and WT littermate controls were randomized to receive 200-250 mg/kg/day of apigenin in chow (Api) or only chow (Pow), starting with mating and continuing until 8-10 weeks of postnatal age. RNA from embryonic day (E) 15.5 telencephalon of Ts1CjePow (n=5), WTPow (n=5), Ts1CjeApi (n=5) and WTApi (n=5) embryos was processed and hybridized on gene expression arrays. For neonatal behavior, Ts1CjePow (n=19), WTPow (n=31), Ts1CjeApi (n=25) and WTApi (n=28) pups were assessed using the Fox scale from P3-21. Exploratory behavior and motor coordination were tested in 8-10 week old Ts1CjePow (n=19), WTPow (n=31), Ts1CjeApi (n=25) and WTApi (n=28) mice using the open field and rotarod tests.

Results: Microarrays studies identified 76 differentially regulated genes in the Ts1CjePow telencephalon versus WTPow littermates, including 40 trisomic, 4 monosomic and 35 disomic genes. Prenatal treatment resulted in down-regulation of 24 disomic genes and normalization of 16 trisomic genes, including Dscam, Kcnj6 and Pcp4. Apigenin up-regulated 24 trisomic and 11 disomic genes. Ts1CjePow E15.5 brain displayed dysregulation of cell cycle, Jak-Stat pathway, synaptogenesis and amino-acid transport. Treatment improved amino-acid transport, synaptogenesis, response to oxidative stress and Jak-stat signaling, however, cell cycle, G-protein signaling and apoptosis were unaffected.

Neonatal behavioral studies in Ts1CjePow mice revealed significant deficits in surface righting, cliff aversion, negative geotaxis, and forelimb grasp (Mann-Whitney test, $p<0.05$). Prenatal apigenin treatment significantly improved surface righting and the cliff aversion test (Kruskal-Wallis test, $p<0.05$), but did not affect performance in the negative geotaxis and forelimb grasp tests.

Adult behavioral studies in Ts1CjePow mice demonstrated significant differences in the open field, showing hyperactive behavior with higher average distance traveled by Ts1CjePow versus WTPow mice ($p<0.01$). Ts1CjeApi mice had significantly reduced hyperactivity ($p=0.01$). Ts1CjePow mice demonstrated significant deficits in the rotarod test versus WTPow mice ($p<0.05$). Apigenin treatment did not improve motor coordination in Ts1CjeApi mice.

Conclusions: Our results demonstrate that prenatal treatment with apigenin improves some aspects of embryonic pathway perturbations, neonatal and adult behaviors in the Ts1Cje mouse model of DS. These data provide proof of principle for using a translational approach involving human fetal RNA and the CMAP to identify novel treatments.

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4 - The role of chromosome 21-encoded miRNAs in synaptic dysfunction in Down syndrome.

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Down syndrome (DS) is characterized almost universally by cognitive impairment and mild to moderate intellectual disability. Animal models of DS have demonstrated synaptic aberrations, including altered synaptic density, impaired endocytosis with the accumulation of large endosomes, and excessive inhibitory signaling. Additionally, human induced pluripotent stem (iPS) cell models of DS have demonstrated reduced synaptic connectivity. The formation and maintenance of appropriate and functional synaptic connections is central to all central nervous system function, and is a highly regulated process, with misregulation resulting in disordered cognition. Given the emerging information about gene expression regulation by non-coding RNAs, synaptic functions are likely to be regulated at least in part by non-coding RNAs, including microRNAs (miRNAs). Several miRNAs have been implicated in spinogenesis, dendritic arborization, and synaptogenesis. Thus, over- or under-expression of miRNAs in the brain could conceivably contribute to synaptic dysfunction resulting in neurological or neuropsychiatric disorders. Human chromosome 21 (HSA21) codes for 5 known miRNAs, which if overexpressed in accordance with the gene dosage seen in DS, could contribute to dysfunctional synaptic transmission and the resultant cognitive impairment. Furthermore, our preliminary evidence suggests that HSA21 miRNAs target methyl CpG binding protein 2 (MeCP2), which is known to play a role in neuronal maturation and synapse formation.

Utilizing the innovative induced pluripotent stem (iPS) cell and induced neuronal (iN) cell technologies, we are studying the effects of HSA21 miRNAs on the synapses of human neurons. We have confirmed MeCP2 as a target of these miRNAs by dual luciferase assay. We have also overexpressed HSA21 miRNAs in control iNs and demonstrated reduced MeCP2 expression by immunocytochemistry (ICC). We have confirmed the overexpression of HSA21 miRNAs in DS iNs, and our preliminary data suggests reduced MeCP2 expression in these neurons, as well. Synaptic function in DS iNs will be assessed by morphological and functional analyses, including electrophysiology and Calcium imaging, and indeed our preliminary electrophysiological data suggest that DS iNs are less synaptically active. After we have fully morphologically and functionally characterized these DS iNs at the synapse, we will then establish a cause-effect relationship between HSA21 miRNA overexpression and synaptic defects using Tough Decoys to antagonize the miRNAs and “rescue” the synaptic function of DS-iN cells, as well as the expression level of MeCP2. Therefore, by combining interdisciplinary methodologies with the iN and iPS cell technologies to examine the functions of HSA21 miRNAs, we will broaden our knowledge of the biological functions of these important regulatory molecules and provide important insight into the mechanistic and molecular bases for the synaptic dysfunction seen in DS.

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5 - Alzheimer disease in Down syndrome: Development of an assay to quantify synaptic loss in response to A β ; oligomers in a mouse model of DS

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Down syndrome (DS) occurs due to inheritance of an complete or partial extra copy of Human chromosome 21 (Hsa21) leading to abnormal gene dosage which causes intellectual disability, heart defects and a greatly increased risk of developing Alzheimer Disease (AD). The presence of the Amyloid Precursor Protein gene (APP) on Hsa21 has been confirmed as a major contributor of AD pathology in people with DS, however there is considerable evidence pointing to other genes on Hsa21 which may modulate APP/A β ; related pathology in DS. The Ts1Tyb mouse model (currently unpublished) is trisomic for the Hsa21 syntenic region on Mouse chromosome 16 (Mmu16) which spans 22.9 Mb and contains around 115 Hsa21 gene orthologues including murine App. Synaptic loss has been shown to be associated with the cognitive deficits found in AD in the general population. To study this in the context of trisomy we have developed an assay to quantify the effects of soluble oligomeric A β ; – a proposed mediator of synaptic dysfunction in AD - on trisomic neurons in primary culture conditions. Primary hippocampal cultures were prepared from P0 Ts1Tyb pups and cultured for 14 days in vitro. Synaptic response to oligomeric Amyloid β ; was assayed using immunofluorescence staining with confocal imaging for pre and post-synaptic markers following treatment with soluble A β ; oligomers. The response of the trisomic neurons was measured by quantification of synaptic marker co-localisation puncta in the Ts1Tyb cells and compared with the wildtype response.

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6 - Endo-lysosomal dysfunctions in cholinergic neurons of mice modeling Down syndrome and Alzheimer's disease.

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The endo-lysosomal compartment is central in Alzheimer's disease (AD) and Down syndrome (DS) since the amyloid precursor protein (APP) is processed along this route. Enlarged-endosomes-bearing neurons were described as the earliest morphological change observed in post-mortem brains from patients with DS, sporadic AD and familial forms of AD with APP mutations. We showed previously by immunocytochemistry that peripheral blood mononuclear cells, lymphoblastoids and fibroblasts from individuals with DS contained enlarged endosomes.

Interestingly, electron microscopy in DS cellular models identified aggregates of apparently normal-sized endosomes rather than enlarged endosomes, suggesting local clustering of endosomes. Endosomes aggregation in neurons could lead to amyloid peptide overproduction and increased amyloid pathology.

Currently, our studies aim at characterizing morphological alterations of endosomes and lysosomes in the brain of mice modeling DS and AD. We performed immunohistochemistry experiments on Ts65Dn and euploid mice from 3 to 5 months of age and compared to 6 month-old TgAPP(sw/Ind), APP/PS1 KI and control mice, using markers of the endo-lysosomal pathway (EEA1 for early endosomes and Cathepsin-B for lysosomes). We focused our analysis on the basal forebrain cholinergic neurons (BFCNs) of the medial septum nucleus, for these neurons degenerate in Ts65Dn at 6 months, likely inducing cognitive impairments.

By immunofluorescence staining and confocal microscopy, we showed a significant enlargement of early endosomes with an increase in the number of BFCNs containing bigger endosomes in Ts65Dn mice. Using electron microscopy, we observed both endosomal enlargement and clustering in BFCNs. We noticed a strong increase in the number of lysosomes in BFCNs in Ts65Dn and control mice as compared to non-cholinergic neurons. In addition, the number of lysosomes was higher in BFCNs of Ts65Dn mice as compared to euploid littermates.

We thus show alterations of the endo-lysosomal compartment of BFCNs in DS mouse model before degeneration: increase in the size and aggregation of early endosomes and increase in the number of lysosomes. We will now analyze the endo-lysosomal compartment in AD mouse models: the TgAPP(sw/Ind) and the APP/PS1 KI. Super-resolution live microscopy experiments will be necessary to decipher the mechanisms underlying these endo-lysosomal dysfunctions.

DISPLAYED POSTERS – DAY 1

7 - Evaluation of a novel DYRK1A inhibitor in two mouse model of Down syndrome: Ts65Dn and mBACtgDYRK1A

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Down syndrome (DS), induced by trisomy of human chromosome 21 (Hsa21) is the most common genetic cause of mental retardation. Ts65Dn mice carrying a segmental trisomy of mouse chromosome 16, orthologous to Hsa21, is the most widely used and best characterized model of DS. In addition several transgenic mouse models have been developed, including the mBACtgDYRK1A overexpressing the Dual-specificity-tyrosine-phosphorylation-regulated kinase 1A. Ts65Dn and mBACtgDYRK1A mice have a reduced performance in the Morris water maze (MWM), indicating impairment in spatial learning and long-term spatial memory. We recently synthesized new DYRK1A inhibitors (DANDYs) with high affinity and specificity for DYRK1A. Here we tested the pharmacological effects of one of these novel DANDYs, the NF016, on cognitive performances of Ts65Dn and mBACtgDYRK1A mice after 2 weeks pre-treatment.

Male mice received daily injections of NF016 at 20mg/kg i.p. during two weeks. During the 7 days of the acquisition phase of the MWM (4 trials per day), mice were put in a 150cm diameter pool filled with opacified water where they had 90 sec. to locate a hidden platform using spatial clues around the room. After the 7th day of training, the platform was removed from the pool and swimming patterns were measured.

Two weeks pre-treatment of Ts65Dn euploid mice did not increase their learning performances (% of platform hits: Bonferroni test: WT-placebo vs. WT-NF016: $p > 0.9999$). On the other hand, the NF016 was able to correct the deficit in Ts65Dn mice (Bonferroni test: WT-Placebo vs. Ts65Dn-Placebo: $p = 0.0001^{***}$; WT-Placebo vs. Ts65Dn-NF016: $p = 0.1583$). Thigmotaxis behavior, significantly increased in Ts65Dn, (Bonferroni test: WT-Placebo vs. Ts65Dn-Placebo: $p = 0.0002^{****}$) was reduced by NF016 (WT-Placebo vs. Ts65Dn-NF016: $p = 0.0312^{*}$). NF016 showed a slight effect in mBACtgDYRK1a (Bonferroni test: WT-Placebo vs. mBACtgDYRK1a-Placebo: $p = 0.0070^{**}$; WT-Placebo vs. mBACtgDYRK1a- NF016: $p = 0.2414$, ns) but no effect in the control mice (% platform hits: Bonferroni test: WT-Placebo vs. WT-NF016: $p > 0.9999$). Whereas NF016 reduced thigmotaxis in Ts65Dn mice, it did not produce any effect in mBACtgDYRK1A (% thigmotaxis: Bonferroni test: WT-Placebo vs. mBAC-Placebo: $p = 0.0120^{*}$; WT-Placebo vs. mBAC-NF016: $p = 0.0082^{**}$). However, NF016 had a positive effect on spatial memory in mBACtgDYRK1A mice, as it improved their performances in the Probe test (mean distance from platform: Bonferroni test: WT-Placebo vs. mBAC-Placebo: $p = 0.0003^{***}$; WT-Placebo vs. mBAC-NF016: $p = 0.0548$).

We thus showed that 2 weeks treatment with the new DYRK1A inhibitor NF016 was sufficient to improve the performances of Ts65Dn mice in the MWM. However, when administrated to the mBACtgDYRK1A mice NF016 failed to correct the learning deficits of these mice. It will be interesting to test the NF016 in other behavioral tests in adult and younger mice.

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8 - SET translocation in Down syndrome patients and Ts65Dn mice may accelerate the progression of the disease through tau hyperphosphorylation

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Tau hyperphosphorylation in the brain of individuals with Down syndrome may result from the overexpression of Dyrk1 kinase and/or decreased phosphatase 2A (PP2A) activity modulating tau phosphorylation. We recently observed in the hippocampus of 3 individuals with Down syndrome an increase of SET, a multifunctional protein localized in the nucleus which can act as an inhibitor of PP2A when translocated in the cytoplasm. SET translocation was present in the whole hippocampus of Down syndrome cases probably as the result of an increase of SET in the nucleus. In 6 Ts65Dn mice we observed an increase of SET in CA1 comparatively to 5 wild type littermates. SET was also found translocated to the end of neurites as in Down syndrome brains. In addition, translocated SET correlated with an increase of tau hyperphosphorylated at Ser 202. In mouse brain slices we demonstrated that the presence of SET in the neuronal cytoplasm internalized through a cell permeable peptide leads to an increase of tau phosphorylation at different sites including Ser 202. In this model, the increase of tau phosphorylation results from the interaction of SET with PP2A thus decreasing PP2A methylation required for its phosphatase activity. Taken together, these data suggest that the translocation of SET in the cytoplasm is an event which could accelerate the progression of the disease and may be related to the high increase of SET expression. Mechanisms responsible for SET overexpression remain to be determined and may be related to the overexpression of chromosome 21 genes or their metabolites. Blocking their signaling pathway would suppress the increase of SET and consequently SET translocation and tau hyperphosphorylation. These data can open a field of investigations to new therapeutic and preventive strategies.

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9 - Triplication of DYRK1A regulates the cell cycle length and neurogenic potential of radial glial progenitors causing early cortical defects in Down syndrome

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The many types of projection neurons in the brain cerebral cortex derived from pluripotent radial glial progenitors of the dorsal telencephalon. Different evidences indicate that the neurogenic potential of these progenitors is influenced by the duration of the cell cycle G1 phase. Alterations in cerebral cortex connectivity lead to intellectual disability and in Down syndrome, this is associated with a deficit in cortical neurons that arises during prenatal development. In the trisomic Ts65Dn mouse model of Down syndrome the growth of the neocortical wall is delayed due to the impaired production of neurons early in neurogenesis that is concomitant with a lengthening of the cell cycle in the ventricular germinal layer. This and studies in Down syndrome fetuses suggest that cell cycle defects underpin the deficit of cortical neurons in Down syndrome. However, the gene/s on chromosome 21 involved in this deficit and the underlying pathogenic mechanisms have not yet been defined.

In this study we have assessed the possibility that triplication of the chromosome 21 gene DYRK1A (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A) contributes to the hypocellularity of the cerebral cortex associated with Down syndrome. We show that during the early phase of cortical neurogenesis DYRK1A tightly regulates the nuclear levels of Cyclin D1 in embryonic radial glia progenitors, and that a modest increase in DYRK1A protein in transgenic embryos bearing three copies of the mouse *Dyrk1a* gene (mBACtgDyrk1a) lengthens the G1 phase in these progenitors. These alterations promote asymmetric proliferative divisions at the expense of neurogenic divisions, producing a deficit in cortical projection neurons that persists in postnatal stages. Moreover, we show that radial glial progenitors in the Ts65Dn model have less Cyclin D1, and that *Dyrk1a* is the triplicated gene that causes both early cortical neurogenic defects and decreased nuclear Cyclin D1 levels in this model. These data provide insights into the mechanisms that couple cell cycle regulation and neuron production in cortical neural stem cells, emphasizing that the deleterious effect of DYRK1A triplication in the formation of the cerebral cortex begins at the onset of neurogenesis, which is relevant to the search for early therapeutic interventions in Down syndrome.

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10 - The role of p53 in down syndrome brain

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Gene dosage imbalance associated with DS may introduce multiple subtle differences in the expression of many genes, which will eventually converge on complex phenotypes. A broad spectrum of abnormalities related to oxidative stress, including mental retardation, early onset Alzheimer's disease (AD) and premature ageing, has been associated with DS neuropathology. Apoptosis is physiologically involved in development and aging, as well as in numerous pathological processes. Altered apoptosis has been proposed as a putative mechanism underlying many DS phenotypes. Though human and animal studies indicate that apoptosis does not have a prominent role in brain development in trisomy 21, it is likely to be involved in AD-like neurodegenerative process. Considering the recent interest on the role of p53 in aging and neurodegeneration, we analysed the p53-dependent pathways in DS human brain, with (DS/AD) and without Alzheimer neuropathology, and in an animal model of the disease (Ts65Dn mice). A number of post translational modifications can occur in p53 that have critical effects on its stability and function, including phosphorylation, acetylation, oxidation and others. Among these, the balance between acetylation and ubiquitination seems to be crucial to regulate p53 transcriptional activity of antiapoptotic genes. In the present study we found an increased acetylation and phosphorylation of p53, as well alteration of its expression levels, that might be responsible of activating an apoptotic response. As a consequence, members of the apoptotic cascade were found to be elevated in DS and DS/AD and in Ts65Dn mice vs. their age-matched controls. However, some apoptotic marker did not show a significant change, suggesting that activation of p53 cascade may not necessarily leads to neuronal death but most likely drive a senescent phenotype.

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11 - Overexpression of the amyloid precursor protein triggers altered APP c-terminal cleavage in murine trisomy 16 neuronal cell lines, an animal model of Down syndrome.

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Down syndrome, or trisomy of autosome 21, is the chromosomal hyperdiploidy that most frequently survives pregnancy, and it is the most common cause of mental retardation of genetic origin. Among the genes overexpressed from chromosome 21, several can potentially affect neural development and function. One particular gene is that encoding for the amyloid precursor protein (APP). APP can bind to p21-activated kinases (PAKs) and affect their activities. Hence, APP overexpression can deregulate PAK activity and in turn disrupt several developmental and neural physiological processes. Although it has been described that APP binds PAKs through the APP C-terminal domain, it is not known if the complete membrane-bound APP or if its C-31 fragment are sufficient to activate PAK. C-31 is released by the action of caspases, which cleave APP at Asp664 in the C-terminus of APP. The increased activity of PAKs may alter actin dynamics and cofilin via phosphorylation of LIMK. This in turn can affect the stability of actin filaments and reduce the number of dendritic spines, as well as axon growth, all of which constitute morphological features underlying cognitive impairment. Therefore, it is important to determine the interaction of APP with PAKs and its relation with C-terminal cleavage in a cellular model of Down syndrome, where APP is overexpressed. In the present study, we utilized a neuronal cell line -named CTb - derived from the cerebral cortex of a trisomy 16 mouse (Ts16), an animal model of human Down syndrome, and a control cell line - named CNh- derived from the cortex of a normal littermate. Firstly we evaluate APP C-terminal cleavage and generation of C-31 peptides to then evaluate the relation will have with the interaction and activation of PAK. APP overexpression was confirmed with immunoblotting and FACS techniques. Our results indicate that in CNh cells APP is susceptible to caspase cleavage. However, trisomic CTb cells appear to be resistant to caspases. This work could help identify potential therapeutic targets to address Down syndrome pathology.

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12 - In vivo functional characterization of TTC3: a Down Syndrome Critical gene

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Down syndrome (DS) is a multi-genic disorder produced by trisomy of Chromosome (Chr.) 21 and principally characterized by intellectual disability (ID), which also represents the most invalidating manifestation of the disease (Rachidi et al., 2000). A number of studies performed on patients and on animal models demonstrated that the brain structures more heavily affected are the hippocampus, the cerebellum and the cerebral neocortex (Rueda et al., 2012; Dierssen et al., 2009). However, MRI studies revealed that neuroanatomic abnormalities in the cerebral cortex are particularly well correlated with the cognitive profile of DS patients (Pinter et al., 2001), thus leading to the idea that DS cognitive dysfunction is mainly neocortical. Many specific alterations in neuronal circuits of the cerebral neocortex including reduced neuron density, decreased dendrite extension and abnormal dendritic spines, are believed to contribute to the ID of DS. However, the causative events that alter neuronal circuitry within the cortex remain unknown. Thus, it is fundamental to better characterize them both at the phenotypical and molecular levels. As a possible factor contributing to producing these abnormalities, we will focus our attention on TTC3, a Down Syndrome Critical Region gene upregulated in patients and in DS mouse models (Delabar et al., 1993; Korenberg et al., 1994). We have previously demonstrated that this protein negatively regulates neuritegenesis, triggering RhoA activation and subsequent actin polymerization (Berto et al., 2007, 2014). Here, we want to investigate TTC3 role in neuronal migration and connectivity in DS mouse model.

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13 - DNA-methylation and Down Syndrome

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Down syndrome (DS) is world wide the most frequent genetic cause of intellectual disability. Although DS has been studied extensively, it remains unclear how the presence of an extra chromosome 21 causes the characteristic DS features. In this study we evaluate the role of DNA-methylation in the establishment of the DS-phenotype. Since DNA-methylation plays an important role regarding gene transcription regulation, differentially methylated loci of specific genes can either cause increased or decreased transcription. This altered transcription may play a major role in causing several of the specific features of the DS-phenotype.

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14 - Early brain amyloid clearance ameliorates brain pathology and behaviour in a transgenic mouse model of Down syndrome

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Down syndrome (DS) is characterized by an age-dependent brain amyloid pathology, which often results Alzheimer's like dementia. We tested the effect of preventive treatment with a nonsteroidal anti-inflammatory (NSAID) derivative [1-(3',4'-dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropanecarboxylic acid or CSP-1103 (previously CHF5074) on Ts65Dn, a widely used mouse model for DS. CSP-1103 has modest effects on Ab production, but uniquely binds to a distinct location that is down stream of the gamma secretase cleavage site in APP profoundly affecting the activity of the intracellular domain (AICD). We treated Ts65Dn mouse from 5 to 19 months of age. Twenty animals were included in each group. We measured molecular parameters related to APP and Ab peptides, synaptology and behavior. We founded no changes in APP mRNA expression level in the basal ganglia and hippocampus. Intraneuronal accumulation of APP and amyloid-peptides is higher in Ts65Dn standard compared to 2N Standard, such as the percentage of cells displaying nuclear AICD staining. The long-term treatment with CSP-1103 has a normalizing effect on both. We founded that the level of Ab40 and Ab42 peptides in the cerebral cortex and plasma was significantly higher in Ts65Dn than 2N mice. While CSP-1103 long-term treatment did not affect either Ab40 and Ab42 content in brain tissue, we observed a significant increase in Ab42 plasma levels in Ts65Dn mice treated with CSP-1103. We then analyzed tissue expression of GFAP and Iba1, as markers for microglia and astrocyte, respectively. Although no differences were observed in GFAP and Iba1 immunoreactivity in Ts65Dn compared to 2N animals, CSP-1103 reduced both markers in Ts65Dn, but not 2N animals. We finally investigated synaptic contacts and behavior. We observed a reduction of VGLUT1 and an increase of VGAT mean intensity in Ts65Dn fed with standard diet compared to 2N standard. While CSP-1103 treatment did not affect VGLUT1, it reduced VGAT expression, thus rebalancing toward 2N the excitatory/inhibitory inputs in the hippocampus. The impairment in Y maze learning and memory test and in gait parameters observed in Ts65Dn old mice, were partially preserved in CSP-1103-treated mice. In the light of the fact that the drug has demonstrated safety and potential efficacy in patients with Mild Cognitive Impairment, we suggest that CSP-1103 could be explored as a clinical candidate for individuals with DS before they develop dementia with the aim of preventing deterioration

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15 - Environmental and pharmacological intervention restores cognitive impairment and prevents neurodegeneration in Ts65Dn

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Neuroplasticity occupies a central role in generating neural function and substantiating learning and memory and is altered in Down syndrome (DS). Effective neuroplasticity-targeted therapy may thus improve learning and memory and prevent neurodegeneration later in life.

Here we aimed at boosting the effect of physiological learning by pharmacologically targeting core neuroplasticity molecules that are constitutively dysregulated in DS. The dual specificity tyrosine-phosphorylation-regulated kinase 1A (Dyrk1A) has been postulated as a primary cause of DS phenotypes. It encodes a serine-threonine kinase that phosphorylates critical substrates involved in neuroplasticity, cognitive function and neurodegeneration. Our lab has previously demonstrated that Dyrk1A is modulated by environmental enrichment, thus suggesting its role in activity-dependent neuroplasticity. We tested if normalization of Dyrk1A activity using Epigallocatechin-3-Gallate (EGCG), the main polyphenolic constituent of green tea and a potent Dyrk1A inhibitor, potentiates the learning-enhancing effects of an enriched environment (EE) in the Ts65Dn mouse model. To this end we analyzed the effect of a combined EGCG-EE intervention on the cognitive performance of Ts65Dn mice. Our results show that the combined use of EGCG-EE improves morris water maze and passive avoidance performance in young and middle-age Ts65Dn mice. This suggests that EE-EGCG restores hippocampal neuroplasticity potential and prevents cholinergic neurodegeneration-related cognitive decline. We will also present ongoing experiments on the neurochemical, structural and functional correlates of these cognitive effects. In summary, EGCG-EE intervention leads to beneficial effects in trisomic mice along lifetime.

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16 - Immortalized neuronal cell lines from animal models of human trisomy 21. Exploring Down syndrome and Alzheimer's like pathology in vitro

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Down syndrome (DS) in humans is caused by the trisomy of autosome 21, and it represents the hyperdiploidy that most frequently survives birth. The condition determines multisystemic anomalies, in particular in the central nervous system (CNS), resulting in mental retardation and early onset of Alzheimer's disease neuropathology. The trisomy entails a situation of gene overdose, and several studies, including our own, using in vitro neuronal preparations have determined specific impairments in electrical membrane properties (shorter action potential, altered ionic current kinetics), and severe cholinergic dysfunction in this condition, all of which may greatly contribute to abnormal CNS cognitive functions in DS.

The use of human neuronal tissue presents practical and ethical problems. Fortunately, murine animal models of the human condition do exist, where the first to be identified was the trisomy of chromosome 16 (Ts16), a chromosome which shares great homology with human autosome 21. Ts16 mice neurons exhibit similar electrophysiological impairments as their human counterparts, along with comparable cholinergic dysfunction. However, Ts16 animals do not survive gestation, hence experiments in this model are limited to whole tissue and primary culture studies taken from aborted fetuses. To overcome this limitation, we have established immortal cell lines from normal and Ts16 mice using a proprietary method, termed UCHT1 protocol, to establish cell lines from both normal and Ts16 mouse nerve tissue. Cell lines so established reproduce the anomalies described in primary cultures.

We present these cell lines as models to study the specific effects of overexpressed DS-related genes. Our approach entails individual knockdown of such genes with antisense RNA or siRNA transfection to normalize their expression. In this fashion, we have explored the effect of knocking down App, Sod1, Slc5a3, Dscan. as well as two DS-related genes involved in both development and neuronal function: Dyrk1a (Human homolog of minibrain) and the regulator of calcineurin Rcan1. Once expression of a target gene is normalized, the effect on various cell functions is studied. This approach contributes to assess DS gene-related pathophysiological mechanisms, and to identify potential therapeutic targets.

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17 - Cell-autonomous vs non cell-autonomous cortical defects in a mouse model of Down syndrome

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Down syndrome (DS) is a multigenic disease, caused by a total or a partial trisomy of Human Chromosome 21 (HSA21); patients affected by DS show a complex combination of dysmorphic features and symptoms, however an invariable hallmark of the pathology is intellectual disability (ID) (Rachidi et al, 2000), a condition in which children display delay in oral language acquisition, memory skills, social rules and adaptive behavior deficits. It has been shown that DS brains are characterized by impaired dendritic structure and spines morphology (Dierssen and Remakers, 2006). However, no studies have been performed to define whether these cortical phenotypes are cell autonomous (i.e. inability to differentiate properly) or if they derive from an altered cortical structure that does not allow neurons to connect correctly. In order to investigate this, we took advantage of primary cortical neurons, derived from a well established DS mouse model that is Ts65Dn (Davisson et al, 1993), and we looked at their ability to differentiate in vitro. Moreover, although DS is a multigenic syndrome, it is of paramount importance to elucidate which are the candidate genes that give rise to the above alterations. We focused on the tetratricopeptide repeat domain 3 protein (TTC3), whose gene is located in a genetic locus found triplicated in DS patients (Delabar et al 1993, Korenberg et al 1994) and whose protein we found upregulated in Ts65Dn mouse. We have previously demonstrated that this protein negatively regulates neurogenesis, triggering small Rho GTPase RhoA activation and subsequent actin polymerization (Berto et al, 2007, 2014). Thus, we are investigating TTC3 functional role in DS cortical defects, especially in the development of dendritic spines.

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18 - Brain localisation of the PCD and chromosome 21 gene, RSPH1, and its partners.

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RSPH1 (Radial Spoke Head 1 homolog) is a chromosome 21 gene encoding an axonemal protein containing several MORN (Membrane Occupation and Recognition Nexus) motifs which has been recently shown to be altered in cases of primary ciliary dyskinesia (PCD) inducing defects of the radial spokes and of the axonemal central pair of microtubules of the cilia (CILD24). This gene known also as Tsga2 (Testis specific gene A2) was previously shown to be present in the acrosomal crescent, and the midpiece and proximal principal piece of the sperm flagellum and localized on MMU17 in the mouse genome. In motile cilia of epithelial cells, RSPH1 is associated to the radial spoke head through interactions not yet identified. In Down syndrome (DS), previous studies have also shown that this gene is differentially expressed in lymphoblastoid cell lines of DS with heart defects vs those of DS without heart defects (Ripoll et al., 2012). All these data suggested that RSPH1 might be expressed in different tissues and play a role in some phenotypes of DS. To evaluate its potential role in DS brain alterations, we searched for its localization in brain using immunohistochemistry. Moreover, its partners were searched, through the InterPP program, using yeast-two-hybrid system. The proteins found to interact with RSPH1 belong to different classes, including “cytoskeleton and cilia”, “transport”, and “secretion”. Validation of these interactions and co-localizations of these partners in the brain are currently analyzed. In particular, the identification of the localization of RSPH1 in ependymocytes and in the circumventricular organs, namely the subcommissural organ (SCO) which participates to the production of the cerebrospinal fluid (CSF), suggests that this protein might have unexplored roles in brain function.

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19 - Dysregulation of neuronal protein synthesis and mTOR by the amyloid peptide

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Alzheimer's disease (AD) is the most common senile dementia. Cognitive deficits are widely believed to result from progressive synaptic dysfunction and neurodegeneration, most likely caused by soluble oligomers of the amyloid peptide (A β O). Synaptic plasticity (for instance long term potentiation (LTP)) that underlies memory, involves changes in synapse efficacy associated with a variation in number, size and morphology of dendritic spines. A β O induce dendritic spine abnormalities and inhibit synaptic plasticity. These effects are likely to account for the cognitive defects associated with AD, and maybe also for the defects associated with trisomy 21, but the mechanisms remain obscure.

LTP depends on de novo protein synthesis. Using a technique based on the detection of puromycin incorporated into nascent peptide chains, we observed an increase in de novo protein synthesis in dendrites of cultured hippocampal neurons upon induction of chemical LTP with Forskolin, BDNF, or dopamine. This activity-dependent mRNA translation was severely blocked by A β O (500 nM, 3h). In contrast, in unstimulated neurons, lower doses of A β O (100 nM, 3h) increase de novo protein synthesis. Similar results have been obtained using cultures of neurons from Tg2576 mice expressing a pathogenic mutant of APP.

These effects of A β O on mRNA translation are due changes in the activity of mTOR. We observed that A β O at 100 nM increased mTOR activity by activating the BDNF/PI3-kinase/Akt pathway. Higher doses of A β O impair mRNA translation in neurons by activating NMDA receptors, Calcium/Calmodulin kinase kinase and AMP-kinase. The latter phosphorylates Raptor, a component of mTORC1, leading to mTOR inhibition at least in part by preventing the recruitment of mTOR on late endosomes and lysosomes.

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20 - Ubiquitin-bound protein profile in human brain from Down syndrome individuals prior and after the development of Alzheimer-like dementia

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Down syndrome (DS) is the most frequent chromosomal abnormality that causes intellectual disability. The neuropathology of DS is complex and includes development of Alzheimer disease (AD). The accumulation of amyloid beta (A β)-peptide in DS brain can be observed as early as 8–12 years of age. Interestingly, the incidence of dementia typically does not increase until adults with DS are over the age 50 years. Within this context, it has been suggested that DS may serve as a model for the study the early molecular events in the pathogenesis and progression of AD neuropathology.

Recent studies suggest that accumulation of insoluble protein aggregates, such as those formed by A β , is mediated by impairment of degradative systems: lysosomal (autophagy) and the ubiquitin-proteasome systems (UPS). We focused our study on the UPS system, a multifaceted enzymatic pathway that ligates ubiquitin to other cellular proteins leading these to degradation by proteasome complex. Previous studies by our group showed the impairment, as result of increased oxidative damage, of several components of the proteasome demonstrating a decrease of trypsin-, chymotrypsin- and caspase-like activity in DS individuals. The aim of this study is to elucidate the pathological role of dysfunctional UPS in the pathogenesis of progression of Alzheimer-like dementia in post-mortem brain samples from DS and DS with AD pathology in comparison with their age-matched controls. Ubiquitin-bound proteins have been analyzed by proteomics approach in order to identify specific proteins that show an altered pattern of ubiquitination in the different groups of comparison. Proteins were isolated by using an ubiquitin enrichment kit, separated by two-dimensional electrophoresis, examined by image analysis software and identified by ESI-MS/MS technology.

Our results displayed that all the proteins identified with aberrant ubiquitination profile in DS and DS/AD individuals are involved in important biological functions including intracellular quality control systems, cytoskeleton network and energy metabolism. In addition, we demonstrated that accumulation of ubiquitinated proteins is an early event in DS, as well as dysfunction of protein-degradation systems.

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21 - Morphological alterations of early endosomes in individuals with Down syndrome, with or without Alzheimer's disease.

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Down syndrome (DS) is the most common genetic cause of intellectual disability. It is caused by an extra copy of human chromosome 21. About 40% of people with DS have Alzheimer's disease (AD)-type dementia at 57 years. Postmortem analysis of their brains showed the presence of neuropathological features similar to AD, including deposition of amyloid- β ; peptides (A β), the presence of hyperphosphorylated tau-containing neurofibrillary tangles (NFTs) and morphological alterations of the endosomal compartment. Particularly, an enlargement of early endosomes was observed in neurons, fibroblasts, peripheral blood mononuclear cells and lymphoblastoid cell lines (LCL) from young and pre-AD subjects with DS. Notably this change in the morphology of early endosomes is one of the earliest hallmarks of AD pathology.

Here, our aim was to analyze the endosomal compartment of LCLs from 14 individuals with DS with (7) or without (7) dementia using immunocytochemistry and fluorescence confocal microscopy. In addition, the level of endocytosis of Alexa 488-transferrin was measured using flow cytometry. Because the size of early endosomes is just at the resolution of confocal microscopes we also analyzed the endosomal compartment of LCLs from individuals with or without DS using electron microscopy.

Increase in endosome size in LCLs was significantly more pronounced in individuals with DS and AD type dementia as compared to individuals with DS without dementia. In addition we found a significant increase in the percentage of cells containing larger endosomes in individuals with DS and AD. Finally in trisomic cells, enlarged endosomes detected by fluorescent confocal microscopy appeared as clusters of endosomes by transmission electron microscopy.

Altogether these results suggest that endosomal alterations in cells from individuals with DS are worsened with AD type dementia.

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22 - The Tc1 mouse model of Down Syndrome dissociates components of recognition memory.

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The Tc1 mouse is a model of trisomy 21, which manifests as Down syndrome (DS) in humans. Previous work has suggested a specific deficit in short-term (STM) but not long-term (LTM) recognition memory in Tc1 mice (Morice et al., 2008). O'Doherty and colleagues (2005) presented evidence that object recognition even after a consolidation period was also disrupted by the Tc1 mutation. The present study was designed to characterise the effect of the Tc1 mutation on recognition memory and examine the effects of the mutation on processing reactivated object memories using a context priming procedure. The results confirm and extend the observation that Tc1 mice displayed impaired short-term (10 min) but intact long-term (24 hr) recognition memory. Further, the results indicate that the effect of context priming on recognition memory was similarly disrupted in Tc1 mice following a 10 min delay. An analysis of regional c-Fos expression indicated a suppression of activity in the perirhinal cortex following context priming in wild type animals that was aberrant in Tc1 mice. The results indicate that synaptic processes initiated in the perirhinal cortex over a brief retention interval are impaired in Tc1 mice.

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23 - Reversal of oxidative damage in DS cells by expression of mitochondrial targeted catalase

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Individuals with Down syndrome (DS) experience an early onset of clinical conditions associated with aging. Accordingly, DS cells display reduced replicative capacity or cellular senescence concomitant with chronic high levels of reactive oxygen species (ROS), stress-related fragmentation of the mitochondrial network and diminished mitochondrial function. It has been proposed that aging is the consequence of the progressive accumulation of oxidative damage during life caused by ROS generated mainly in mitochondria. We and others have shown that antioxidants improve viability and mitochondrial function in DS cells. Consequently, long-term interventions directed to preserve mitochondrial function and reduce the generation of free radicals in DS cells represent an attractive therapeutic target. To this end, we evaluated the effect of the antioxidant enzyme catalase, a peroxisomal protein that mediates the conversion of hydrogen peroxide to oxygen and water, which has been genetically targeted to the mitochondrial matrix (mCAT). We designed a lentiviral mCAT vector to drive expression of functional catalase to mitochondria. Antioxidant capacity was assayed in mouse embryonic fibroblasts (MEF) and human fibroblasts (HF) exposed to chronic pro-oxidant treatments with hydrogen peroxide and paraquat, and finally tested in DS primary cells. The results indicate that mCAT expression significantly improved cell viability, rescued the cellular mitochondrial network and reduced oxidative damage. When tested in DS cells, mCAT successfully enhanced cell survival, reverted the fragmentation of the mitochondrial network and lowered ROS production. Ongoing experiments are focused on the alterations in mitochondrial dynamics observed in DS cells and how they can be corrected by modulating mitochondrial membrane potential and mitochondrial functionality. These results indicate that strategies aimed to reduce oxidative damage and protect mitochondrial function and dynamics may prove useful to maintain and prolong cellular homeostasis and delay the appearance of age-related phenotypes commonly associated with DS

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24 - Characterization of abnormalities in the brain of Ts1Cje, a mouse model of Down syndrome, by multiple “-omics” techniques

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The Ts1Cje mouse, a model of Down syndrome, carries a subset of triplicated human chromosome 21 gene orthologs, and exhibits a number of abnormal phenotypes such as impaired spatial learning. To identify molecular candidates involved in brain disabilities of Ts1Cje mice, we here conducted three comparative -omics analyses, proteomics, lipidomics, and metallomics. Two-dimensional gel-based proteomics analyses with prenatal (embryonic day 14.5 (E14.5)) and postnatal brains (3-month-old) of wild-type (WT) and Ts1Cje mice revealed that five proteins were differentially expressed in the brains of Ts1Cje mice at E14.5, but not at 3 months of age. The differentially expressed five proteins were identified as calcyclin-binding protein (CACYPB), nucleoside diphosphate kinase-B (NDPK-B), transketolase (TK), pyruvate kinase (PK), and 60S acidic ribosomal protein P0 (RPLP0) by peptide mass fingerprinting. CACYPB and NDPK-B were involved in cell proliferation, whereas TK and PK were associated with energy metabolism. Experiments focusing on cell proliferation demonstrated that the number of M-phase cells, which were detected immunohistochemically with anti-phosphohistone H3 antibodies, was significantly increased in the ganglionic eminence (GE) of E14.5 Ts1Cje brain. Furthermore, *in vivo* BrdU labeling experiment revealed that cell proliferation in the GE was significantly increased in Ts1Cje mice compared with WT mice. Our findings suggest that the dysregulated expression of proteins could participate in increased cell proliferation in GE, and may associate with abnormalities in the DS brain during embryonic life. In addition, we performed comprehensive analyses for quantification of other components, lipids and metals in the brains of WT and Ts1Cje mice at the adulthood. Membrane phospholipids isolated from the hippocampus were quantified by GC-MS. Although 12 fatty acid peaks were appeared, no peak with altered amount of fatty acids between the genotypes was detected in this platform. Comprehensive quantification for elements in the periodic table including the biogenic metals by inductively coupled plasma-mass spectrometry showed that some of them were upregulated in the hippocampus, cerebral cortex, and cerebellum of Ts1Cje mice compared with WT mice. In conclusion, we identified differential accumulation of cellular components in embryonic and adult brains of Ts1Cje mice compared with WT mice by multiple “-omics” platforms. These components may be potent therapeutic targets of DS symptoms.

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25 - Perturbations of Heart Development and Function in Cardiomyocytes from hESC with Trisomy 21

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Congenital heart defects (CHD) occur in approximately 50% of patients with Down syndrome (DS); the mechanisms for this occurrence however remain unknown. In order to understand how these defects evolve in early development in Down Syndrome, we focused on the earliest stages of cardiogenesis to ascertain perturbations in development leading to CHD. Using a trisomy 21 (T21) sibling human embryonic stem cell (hESC) model of DS, we show that T21-hESC display many significant differences in expression of genes and cell populations associated with mesodermal, and more notably, secondary heart field (SHF) development, in particular a reduced number of Isl1+ progenitor cells. Furthermore, we provide evidence for two candidate genes located on chromosome 21, Ets2 and Erg, whose overexpression during cardiac commitment likely accounts for the disruption of SHF development, as revealed by down regulation or overexpression experiments. Additionally, we uncover an abnormal electrophysiological phenotype in functional T21-cardiomyocytes, a result further supported by mRNA expression data acquired using RNA-Seq. These data, in combination, revealed a cardiomyocyte-specific phenotype in T21-cardiomyocytes, likely due to the overexpression of genes such as RyR2, NCX and L-type Ca²⁺ channel. These results contribute to the understanding of the mechanisms involved in the development of CHD.

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26 - Cystatin C overexpression ameliorates trisomic phenotypes in a mouse model of Down syndrome

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Down syndrome (DS) is caused by the overexpression of genes on triplicated regions of human chromosome 21. Individuals with DS have variable but significant levels of cognitive and behavioral impairments. An established treatment modality that could confer improvement in cognition and alleviate major DS impairments with no long-term side effects is not available. Several mouse models of DS were generated in order to study DS-associated abnormalities and to test pharmacological interventions for restoring some of the characteristic DS phenotypes. The Ts[Rb(12.1716)]2Cje (Ts2 mouse), a segmental trisomy mouse model of DS, bears a partial trisomic chromosomal rearrangement translocated to mouse chromosome 12 (MMU 12) containing approximately half the genes of chromosome 16 which are homologous to genes on human chromosome 21. We have previously reported that these mice recapitulate well documented behavioral and physiological features of DS. In the mouse, these include object recognition and spontaneous alternation tasks, and hippocampal glutamatergic neurotransmission aberrations.

We have been investigating the effect of cystatin C (CysC) on trisomic phenotypes observed in 8 months old Ts2 mice. Our earlier in vitro studies have shown that CysC protects neuronal cells from various types of toxicity. Furthermore, CysC is neuroprotective in vivo, in mouse models of neurodegenerative diseases such as progressive myoclonic epilepsy type 1 (EPM1). Here we demonstrate that low level of CysC overexpression reduces pathological changes in the Ts2 segmental trisomy model of DS. Crossbreeding of Ts2 mice with CysC-overexpressing transgenic mice showed that neuropathologies, including early endosomal enlargements in the fronto-parietal cortical neurons, cholinergic cell population loss in the basal forebrain, hippocampal gliosis, and behavior dysfunctions, such as abnormal nesting behavior and spatial memory deficits, are rescued by CysC overexpression. Thus, CysC effectively prevents the pathophysiological changes and behavioral anomalies induced by trisomy. We suggest that CysC, a ubiquitously expressed protein secreted into all body fluids, can be safely implemented as a novel therapeutic intervention to reverse DS phenotypes and potentially improve cognition in DS individuals.

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27 - New mouse models for Down syndrome show atrio-ventricular septal defects with and intact vestibular spine and reveal congenital heart defects map to two different loci

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Down syndrome (DS) is caused by trisomy of human chromosome 21 (Hsa21) and 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 we have established that a large duplication, containing around 135 genes orthologous to Hsa21, results in CHDs whose typology closely resembles those observed in individuals with DS. Interestingly, these mice present a specific subtype of incomplete AVSD with exclusive ventricular shunting. In order to unravel the mechanisms behind these defects we combined genetic lineage markers and HREM to model in 3D the development of the vestibular spine or dorsal mesenchymal protrusion (DMP), a tissue derived from the second heart field that has been shown to be involved in the etiology of AVSDs. The development of the DMP appears to be unaffected in the DS mouse models and we propose that this specific subtype of AVSD is not caused by a failure in the formation of the DMP. Moreover, 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 16 new mouse strains with partial duplications and deletions for regions of mouse chromosome 16, orthologous to Hsa21. Analysis of embryonic hearts from a number of strains with shorter duplications has allowed us to narrow down the critical genomic region for DS-CHD and demonstrate that DS-associated AVSDs are caused by an additional copy of at least 2 different loci/genes.

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28 - Triplication of the chr.21q22 gene Hmgn1 drives epigenetic alterations, global transcriptional de-repression, and lymphoid leukemia in Down syndrome models

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Down syndrome (DS) confers an increased risk of B cell acute lymphoblastic leukemia (B-ALL). However, the gene(s) that drive lymphoid transformation in DS have not been elucidated. We found that triplication of 31 genes orthologous to human chr.21q22 in the Ts1Rhr mouse model increased B cell self-renewal, caused B cell maturation defects, and cooperated with B-ALL oncogenes to induce leukemia. We next studied histone modifications and the transcriptome of Ts1Rhr cells. This revealed hypomethylation of histone H3 lysine 27 (H3K27) at gene promoters, and expression signatures enriched for genes regulated by polycomb repressor complex 2 (PRC2). PRC2 trimethylates H3K27 and is known to control developmental genes. Thus, chr.21q22 triplication may affect B cell development by depleting the H3K27me3 repressive mark from genes critical for lymphoid maturation. In support of this hypothesis, pharmacologic inhibition of PRC2 function was sufficient to confer self-renewal in wild-type B cells, while inhibition of H3K27 demethylases blocked self-renewal induced by chr.21q22 triplication. In B-ALL patients PRC2/H3K27 gene signatures distinguished leukemias with +21 from those without, suggesting similar biology in Down syndrome. One of the 31 Ts1Rhr genes, Hmgn1, encodes a nucleosome binding protein known to modulate chromatin structure. In an RNA interference screen, Hmgn1 was the gene most necessary to maintain the Ts1Rhr phenotype. When overexpressed in B cells, HMGN1 reduced H3K27 methylation. In vivo, transgenic mice (HMGN1_OE) that overexpress only human HMGN1 (~2-fold above endogenous) had a defect in B cell maturation, increased colony forming capacity, and a transcriptional signature overlapping with that of Ts1Rhr. HMGN1_OE animals developed BCR-ABL-driven leukemia with decreased latency and increased penetrance compared to wild-type. To reconcile global chromatin alterations with transcriptional consequences we repeated RNAseq, normalizing to "spike-in" exogenous RNA rather than to the sample medians. Spike-in normalization revealed a striking de-repression of transcription (~1.3-fold) of thousands of genes in Ts1Rhr or HMGN1_OE cells compared to wild-type. Integrated analysis of RNA-seq and ChIP-seq datasets showed HMGN1-associated transcriptional amplification primarily affects "bivalent" genes (those with co-localized activating and repressive histone marks), which enriches for developmentally important genes known to be epigenetically controlled during differentiation. This chromatin-based transcriptional amplification offers an alternative interpretation of the recent reports of global epigenetic changes in multiple DS tissues, and implicates HMGN1 as a driver of that process. In sum, these data indicate that HMGN1 is a B-ALL oncogene, and targeting HMGN1 or its impact on the epigenome may be effective in DS leukemia. Further study of the contribution of HMGN1 and epigenetic dysregulation to other DS phenotypes is warranted.

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29 - High level of protein Dyrk1a is associated to a greater stability of NFκB inhibitor (IκBα) due to a decreased calpain activity, and to a higher TGBβ1 synthesis, in brain of mice.

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Background

Dyrk1a (dual specificity tyrosine phosphorylation-regulated kinase 1A), a chromosome 21 gene, has become an attractive drug target because increasing evidence suggests that its overexpression may induce Down-Syndrome (DS)-like neurobiological alterations such as neuronal deficit, precocious Alzheimer's-like neurodegeneration and cognitive deficits. Dyrk1a would play a role in many pathways, such as NFκB-dependent signaling pathway. The transcription factor NFκB participates in the regulation of various target genes controlling inflammatory responses and cellular survival. It is now accepted that inflammation plays a primary role in cognitive disorders. A recent study showed that this NFκB pro-inflammatory pathway is deregulated in immortalized lymphoblastoid cell lines of DS patients (Granese and al, 2013).

Objective

Our objective is to determine the molecular and cellular mechanisms linking Dyrk1a and the NFκB pathway, in brain of adult transgenic mice overexpressing Dyrk1a.

Procedure

Cytoplasmic NFκB sequestration was evaluated by quantifying IκBα level by slot blotting and RT-PCR of target genes. Two possible ways of IκBα degradation were investigated: the balance of IKKβ/PP2A which regulates IκBα degradation by proteasome and the balance of calpain/calpastatine. IKKβ, phosphorylated IκBα, and calpastatine were quantified by slot blotting. PP2A and calpain activity were measured spectrophotometrically. mRNA expression of cIAP2 and HO-1, two target genes of NFκB, and TGBβ1 were quantified by RT-PCR. These parameters were compared between mice overexpressing Dyrk1a (BACTgDyrk1a) and control mice. No difference was found between males and females.

Results

We found a 20% increase of IκBα protein level in brain of mice overexpressing Dyrk1a, compared to control ($p < 0,05$ $n=15$; n number of mice per group) but no difference was found in mRNA expression, suggesting greater protein stability. This could be explained in part by a decreased calpain activity ($P < 0,01$ $n=11-12$). Moreover, expression of genes targeted by NFκB pathway is decreased (-5% for cIAP2 mRNA, $P < 0,05$ and -30% for HO-1 mRNA, $P = 0,05$; $n=9-11$), but TGBβ1 mRNA expression is increased by 20% ($P < 0,05$ $n=8-11$).

Conclusion

Taken together, these results suggest that a high brain level of Dyrk1a may have anti-inflammatory properties in adult mice.

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30 - Role of Intersectin-1 in metal ion homeostasis, cognition and hyperactivity in Down syndrome

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All individuals with Down syndrome (DS) have partial or whole extra chromosome 21. Intersectin-1 (ITSN1) is located on chromosome 21 and up-regulated in DS. It has two isoforms; long (predominantly expressed in neurons) and short (expressed in all tissues). This study characterizes genetically modified mice to provide a better understanding of the biological changes due to absence or overexpression of ITSN1. Mice where the long isoform of ITSN1 is knocked out (LKO) and mice where both short and long isoforms are over-expressed (Tg) are used for this study. We investigated behaviour (the Morris water maze), brain activity (long term potentiation-LTP), motor function (rotarod and locomotor tests), cell signalling (western blotting), metals in the brain (mass spectrometry) and brain weight. For $n \geq 6$ per genotype in each case: for LKO, we found significant decreases in brain weight, long term and spatial memory, LTP, cell signalling activity (Mitogen-activated protein kinase (MAP kinase) and AKT), and a significant increase in the cortical levels of iron, zinc and copper. The Tg mice showed no difference in long term and spatial memory, LTP or cell signalling activity but motor function was affected as evidenced by a significant increase in the total distance moved and number of rearings in the open field test. Consistent with altered motor activity, cerebellar iron, zinc and copper levels were significantly decreased. These data show that over-expression of ITSN1 disrupts metal ion homeostasis in the cerebellum which may explain the hyperactivity observed, and that the ITSN1 long isoform may have an important role in cognition and metal ion homeostasis in the cortex.

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31 - Rapamycin reverses plasticity and memory deficits of Ts1Cje mice

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Our lab has previously shown that hippocampal local translation - a crucial process for synaptic plasticity - is deregulated in the trisomic mouse model Ts1Cje due to mTOR hyperactivation (Troca-Marin et al., J Neurosci, 2011). Interestingly, two other labs have recently reported mTOR hyperactivation in postmortem brains from Down syndrome (DS) patients (Perluigi et al., Biochim Biophys Acta, 2014; Iyer et al., J Neuropathol Exp Neurol, 2014).

We have now found that Ts1Cje mice exhibit deficits in BDNF-long term potentiation, a type of plasticity that depends on mTOR-driven local translation. In addition, these mice also show impaired persistence of spatial long-term memory. Remarkably, both plasticity and memory defaults are reversed by rapamycin, a Food and Drug Administration-approved specific mTOR inhibitor, suggesting a novel pharmacotherapy to improve cognition in DS.

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32 - Altered synaptic plasticity and network function in a mouse model of Alzheimer's Disease in Down Syndrome

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Down syndrome (DS) results from trisomy of human chromosome 21 (Hsa21) and is the most common genetic cause of intellectual disability. Individuals with DS are at an elevated risk of early onset Alzheimer's Disease (AD), and AD onset in DS is associated with a dramatic increase in seizure susceptibility. Up to 84% of AD-DS patients develop seizures, and this has been linked to accelerated cognitive decline. Triplication of APP gene on Hsa21 is sufficient to cause familial AD, however Hsa21 contains approximately 300 other genes, and trisomy 21 results in widespread transcriptional dysregulation. Other factors in addition to APP triplication are therefore likely to modify the risk of both Alzheimer's Disease and seizures, in the context of DS.

To model this interaction, the Tc1 mouse model of DS - which contains a freely segregating copy of Hsa21 and is therefore functionally trisomic for approximately 75% of the genes, but critically not for APP, has been crossed with the J20 model of AD, which overexpresses mutant human APP (APP^{Swe}/Ind). In this model, Hsa21 has been shown to exacerbate amyloid pathology and behavioural deficits, reflecting the changes seen in DS patients. This phenotype suggests synaptic plasticity and network function may also be impaired. To characterize this, we used extracellular field recordings from acute hippocampal slices to investigate synaptic plasticity in medial perforant pathway of the hippocampus. This is one of the first pathways to be affected in AD and plays a key role in spatial memory. Additionally, 24h intracranial EEG was recorded from awake and freely moving mice to assess spontaneous seizures and aberrant activity.

Long term potentiation (LTP) is considered to be a cellular correlate of memory. Our data indicate that Hsa21 causes a deficit in LTP at 6 months of age, and this deficit is enhanced by APP overexpression. No deficit was observed as a result of APP overexpression alone at this time point. Blocking GABAA receptors does not rescue LTP in this model, indicating that it is not mediated by excessive inhibition. No genotype differences were observed in basal synaptic transmission or paired pulse ratio. Abnormal EEG activity was observed in both trisomic and mutant APP models. This suggests that mutant-APP interacts with other Hsa21 genes to exacerbate deficits in synaptic plasticity and network function in the Tc1-J20 model, and that these genes may therefore be significant in modulating AD pathology in the DS population.

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33 - Physical exercise rescues adult neurogenesis, synaptic plasticity and memory in Down syndrome mice

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Down syndrome (DS), caused by the triplication of human chromosome 21, is the most frequent genetic cause of mental retardation. The Ts65Dn mouse model of DS shows many neurological similarities to the human syndrome, including decreased hippocampal neurogenesis and cognitive impairment. In this study, we have investigated the effect of aerobic physical exercise on adult neurogenesis, synaptic plasticity and memory in Ts65Dn mice. Exposure of adult Ts65Dn mice to running wheels for one month increased the proliferation of neuronal precursor cell and stimulated adult neurogenesis in the hippocampal dentate gyrus. Moreover, physical exercise promoted the recovery of hippocampal synaptic plasticity and, most importantly, fully restored learning and memory in different behavioral tasks in trisomic mice. These findings demonstrate that Ts65Dn mice benefit from voluntary wheel running and provide evidence that physical exercise could represent a valuable complementary therapy for pharmacological interventions aimed at rescuing cognitive disabilities in DS patients.

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34 - Astrocytes and Microglia Form Specialized Reactive Glial Nets Around β -amyloid Plaques in Down Syndrome.

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Astrocytes and Microglia Form Specialized Reactive Glial Nets Around β -Amyloid Plaques in Down Syndrome.

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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 additional challenges including the development of Alzheimer's disease (AD) pathology in a high proportion of DS adults. Like in AD, DS brain pathology includes synaptic loss, neurodegeneration, beta amyloid (1-42) (A β) deposition, tauopathy, neurofibrillary tangles, glial reactivity, and neuroinflammation. To better understand brain pathology in DS and AD, we pioneered a labeling and imaging method that enables multi-channel 3D light microscopic analysis of neurons and glial cells in long-term fixed DS and AD tissue samples. This approach enables high resolution imaging of large areas of hippocampus and cortex and allows detailed analysis of neuronal and glial pathology. Using this method we investigated the reorganization of activated microglia and reactive astrocytes near sites of neuropathology such as A β plaques 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 types. Interestingly, we also show progressive changes in the interactions of microglia and astrocytes with A β plaques with age in both in the frontal cortex and hippocampus. Thus, glial cells actively participate in brain pathology in DS.

To study molecular mechanisms involved in glial-mediated pathology in DS, we are developing an in vitro model using induced Pluripotent Stem Cells (iPSCs) reprogrammed from fibroblasts of DS individuals. Differentiating these cells into both neurons and astrocytes will enable us to investigate the contributions of DS 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.

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35 - Is Trisomy 21 Mosaicism a Biomarker or a Cause of Alzheimer's and Other Neurodegenerative Diseases, or Both?

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Genetic and biochemical studies have indicated that the formation and oligo/polymerization of the A β peptide is a key step in the pathogenic pathway to Alzheimer's disease. Mutations in the APP gene that generate more or a modified form of A β , duplication of the APP gene on one chromosome 21, or duplication of the entire chromosome (trisomy 21 in Down syndrome) leads to Alzheimer's disease pathology with 100% penetrance. Based on our hypothesis that trisomy 21 might underlie the development of AD, as it does in DS, we searched for and found trisomy 21 mosaicism in fibroblasts from both familial and sporadic AD patients. Trisomy 21 and other aneuploidy was also found in buccal cells, peripheral blood lymphocytes, and brain cells, both neurons and glia by different investigators. For example in the brain some 30% of neurons are aneuploid, including 10% trisomic for chromosome 21. More recently, we and others have found trisomy 21 mosaicism in fibroblasts, lymphocytes, and/or brain cells, both neurons and glia, in patients with Niemann Pick C1, either sporadic and familial Fronto-temporal Lobar Degeneration, and, preliminarily, Huntington's disease. These data indicate that a common characteristic of a wide variety of neurodegenerative diseases caused by different mechanisms is the presence of mosaicism for trisomy 21 and other aneuploidies—a biomarker for a disease-associated cell cycle defect. The key question remaining is whether mosaic aneuploidy including trisomy 21 is also a contributing cause of neurodegeneration. Several lines of evidence support this conclusion. For example transgenic and knock-in mouse models of AD carrying either APP or presenilin mutations lead to mosaic aneuploidy, including trisomy 16, in spleen cells, neurons, and glia. Furthermore exposure of karyotypically normal cells to A β peptide leads to chromosome missegregation and 20% total aneuploidy within 48 hours, including trisomy 16, through A β ; inhibition of specific kinesin-related motors required in mitosis. Furthermore transgenic mouse models of familial FTLD and Niemann pick C1 also exhibit mosaic aneuploidy. Introduction of an FTLD-causing MAPT mutation into cells also leads to abnormal mitotic spindles, chromosome segregation, mosaic aneuploidy, and apoptosis. The finding of Arendt and colleagues that aneuploid cells develop in the early stages of Alzheimer's disease and then preferentially degenerate allows a calculation that 90% of the neurodegeneration in AD is the specific loss of aneuploid cells. Thus chromosome segregation and the specific formation of trisomy 21 mosaicism is characteristic of a number of neurodegenerative diseases and leads to apoptosis. In sum, mosaic trisomy 21 and other aneuploidy may not only be a potentially useful biomarker of neurodegeneration, as revealed systemically, but may also be an important step in the pathogenic pathway and thus a target for preventative therapies.

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36 - Alzheimer's disease in Down Syndrome: mapping the genetic contributors

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Down syndrome (DS), caused by trisomy of human chromosome 21 (Hsa21), leads to a greatly elevated risk of developing early-onset Alzheimer's disease (AD). Whilst virtually all individuals with DS exhibit the classic AD plaques and tangles, not all go on to develop dementia and the age of onset varies. A major factor contributing to the onset of AD pathology is the presence of an extra copy of the amyloid precursor protein gene (APP) on Hsa21. APP is processed to produce A-beta, which is thought to be the causative agent of AD. Evidence from mouse models of DS, however, suggests that other genes may contribute to, or even protect against APP/A-beta-related pathology.

The Tc1 mouse model of DS contains a freely segregating copy of Hsa21, but is not functionally trisomic for APP, due to a genomic rearrangement. When crossed with the J20 (APPSwInd) mouse model of APP/A-beta pathology, presence of the Tc1 trisomy causes reduced survival, increased A-beta accumulation and an exacerbation of behavioural deficits. Partial trisomy models of DS allow mapping of these phenotypes to specific regions of the chromosome. To look at the contribution of 40 Hsa21 genes present on mouse chromosome 10 (Mmu10), the Ts2Yey mouse was crossed to the J20 model of APP/A-beta pathology.

Trisomy of the Hsa21 orthologous region on Mmu10 rescues the sudden death phenotype observed in J20 mice and may result in an improvement in short-term spatial memory. Thus far this phenotypic improvement has not been associated with an alleviation of A-beta pathology: no change in soluble or insoluble A-beta levels, A-beta plaque load or full length APP protein expression has been observed as a result of the trisomy. A reduction in astrocyte activation in Ts2Yey mice was observed and may contribute to this protection.

Trisomy of the Ts2Yey region of Hsa21 may alleviate cognitive deficits caused by AD pathology. This highlights the genetic complexity of DS and helps explain the heterogeneity of AD/DS cases. Analysis of further DS models will aid in elucidating the mechanisms driving AD pathogenesis in DS.

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37 - Jerome Lejeune Institute: a multidisciplinary team dedicated to intellectually disabled patients

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Since September 1997 the Jérôme Lejeune Institute gives specialized consultations in diagnosis and follow-up for patients with genetic intellectual disability from birth to death. Adults come once a year, babies twice a year. Our reference medical consultations last 1 hour; possibly followed by other medical consultation (neurologist, orthopedist, and psychiatrist), speech or neuropsychological assessment, social evaluation or nurses care.

We follow about 7 500 patients: 80 % have trisomy 21 (Down syndrome); others have fragile X syndrome, Smith-Magenis syndrome, Angelman syndrome, etc.

Our practitioners have a good knowledge of these patients and of their medical conditions. At Lejeune Institute, we take time for clinical examination. It is precious because our patients are anxious, delicate and sometimes move with difficulty. An attentive interview establishes current problems, situation of parents and sibs, medical, family and social history, caregivers situation. We propose a longitudinal medical follow-up what allows the best possible prevention of comorbidities occurring in adulthood or during ageing.

Our institute is also involved in research on genetic intellectual disability diseases. We lead transversal and longitudinal epidemiological studies as well as clinical trials. We provide biological samples collections for the scientific community thanks to our biobank, BioJel.

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38 - Investigating the genetic architecture of Down syndrome-associated atrioventricular septal defects

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Congenital heart defects (CHD) are the most common birth defect seen in infants with Down syndrome (DS). They occur in ~50% of individuals with DS, the majority being septal defects. The most severe form of DS-associated CHD is an atrioventricular septal defect (AVSD). While the incidence of non-syndromic AVSD in the general population is low (~1 in 10 000 live births), about 20% of individuals with DS have complete AVSD, corresponding to a 2000-fold increased risk. This severe condition requires surgery in the first year of life, influences the cognitive trajectory during childhood, and causes health complications later in life. Thus, the costs and burdens of CHD are clearly high among those with DS and their families.

The goal of our research is to identify genetic factors the influence this 2000-fold increased risk. We have conducted genome-wide association and copy number variant (CNV) analyses among individuals with DS and complete AVSD (DS+AVSD, 210 cases) compared with those with DS and structurally normal hearts (DS-CHD, 242 controls). Our findings suggest that large increased risk in DS-associated AVSD cannot be explained by common variants of large effect size. In addition, we found no evidence for the involvement of chromosome 21-associated CNVs in a follow-up study using array CGH. Instead, we found a significant burden of large, rare deletions among DS+AVSD cases, with a suggestive enrichment for deletions intersecting ciliome genes. Whole exome sequencing performed on a subset of this cohort (137 cases, 138 controls) provides further evidence for the involvement of the ciliome: we found a significant enrichment ($p < 0.01$) of rare genetic variants in DS+AVSD cases compared with DS-CHD controls in genes known to be expressed in heart and predicted to be in the ciliome. Our previous targeted sequencing studies also revealed an excess of rare predicted deleterious variants in the CRELD1/VEGFA pathway, occurring in ~10% of DS+AVSD cases. Whole genome sequencing of a novel cohort (172 cases, 41 controls) will be used to replicate these findings. Collectively, our data suggest that rare potentially deleterious variants in ciliome genes play a substantial role in the etiology of AVSD.

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39 - Neonatal treatment with epigallocatechin-3-gallate reinstates hippocampal development in the Ts65Dn mouse model of Down syndrome

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The major causes of intellectual disability in DS are neurogenesis defects that can be traced back to fetal life stages. Recent evidence shows that epigallocatechin-3-gallate (EGCG), an inhibitor of DYRK1A, improves behavior in adult Dyrk1A transgenic and Ts65Dn mice. Since brain alterations start very early during ontogenesis, therapies at early life stages are expected to have an impact on the trisomic brain larger than at later times, being potentially able to radically correct brain alterations. Unlike in the rest of the brain, the bulk of hippocampal neurogenesis takes place in the first postnatal period. Thus, the goal of the current study was to establish whether neonatal treatment with EGCG restores hippocampal development in the Ts65Dn mouse model of DS.

We first examined the effect of EGCG in cultures of neural precursor cells (NPCs) derived from the subventricular zone (SVZ) of euploid (EU) and Ts65Dn (TS) mice. NPCs were treated with EGCG 20 μ M and exposed to BrdU in order to label proliferating cells. While untreated TS cultures exhibited a reduced number of proliferating cells, in treated cultures the number of proliferating cells became similar to that of EU cultures, indicating that treatment had restored the proliferation defect that characterizes trisomic NPCs. Trisomic NPCs, in addition to proliferation impairment, exhibit defective development of neuritic processes. Evaluation of the neuritic length of TS NPCs treated with EGCG during differentiation showed that treatment rescued defective neurite development so that total neurite length became similar to that of untreated EU NPCs. We then examined the effect of EGCG in vivo. EU and TS mice received a daily injection of EGCG (25 mg/kg) or saline during the postnatal period P3-P15 and were killed at P15. We found that treatment had no adverse effects on body weight and pups' viability. Evaluation of the pool of cycling cells in the SVZ and DG with Ki-67 immunohistochemistry showed that treatment fully restored the reduced number of cycling cells in the SVZ and DG of TS mice, that became similar to that of EU mice. The increase in the number of cycling cells in the DG was accompanied by full restoration of total number of granule neurons in the granule cell layer. Evaluation of the effect of treatment on connectivity showed that in untreated TS mice there were reduced levels of both pre- and postsynaptic proteins in the DG, hippocampus and neocortex and that this defect was fully rescued by treatment.

This study shows that EGCG restores the neurogenesis defects that characterize the trisomic brain and that treatment during the neonatal period rescues hippocampal cellularity and connectivity. In view of the key role of hippocampus in learning and memory, these effects are expected to lead to restoration of hippocampus-dependent memory functions.

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40 - Prefrontal synaptopathies linked to the Down syndrome candidate gene Dyrk1a overexpression

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Down syndrome, the most common genetic source of mental retardation, is caused by the presence of an extra copy of human chromosome 21. Genotype/phenotype correlations have defined candidate regions involved. The smallest contains 13 genes including Dyrk1a gene. It encodes a pleiotropic serine-threonine kinase, DYRK1A, which chiefly plays a role in the control of gene expression and synaptic transmission. Mouse models of partial trisomy containing Dyrk1a gene present a number of Down syndrome-relevant central nervous system phenotypes including changes in neuronal morphology and functional deficits such as cognitive impairments in cortical-dependent learning tasks. These establish DYRK1A as a potential target to modify synaptic activity. Our investigations, as part of my PhD, aimed to characterize the synaptic transmission and plasticity at prefrontal cortex excitatory synapses in a newly constructed Down syndrome mouse model with an extra copy of the complete murine Dyrk1a gene (BACtgDyrk1a). By using ex-vivo techniques, we showed that these mice displayed dendritic alterations of deep layer prefrontal cortex pyramidal neurons associated with anomalous synaptic plasticity. We also revealed that administration of green tea extracts containing epigallocatechin 3-gallate, a potent DYRK1A inhibitor, to adult mBACtgDyrk1a mice normalized several synaptic impairments. These results shed light on previously undisclosed participation of Dyrk1a gene in adult prefrontal cortex synaptic function, and identified green tea extracts as a viable therapeutic strategy for certain phenotypes of Down syndrome.

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41 - Impairment of mitochondrial oxidative phosphorylation in neural progenitor cells of Ts65Dn mouse model of Down syndrome

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Neurons critically depend on mitochondrial energy metabolism and oxygen supply to execute the complex processes of neurogenesis, neurotransmission and synaptic plasticity; thus, mitochondrial dysfunctions critically impair nervous system development and are potentially involved in the pathogenesis of various neurodevelopmental syndromes, including Down syndrome (DS) (for refs see 1).

We recently provided new evidence for a critical role of mitochondrial dysfunction in the pathogenesis of DS; we showed a decreased efficiency of the mitochondrial energy production apparatus in human peripheral (fibroblasts and lymphoblastoids) DS cells, selectively involving specific signaling pathways, which regulate oxidative phosphorylation (OXPHOS) (2, 3).

It is reported that adult hippocampal neurogenesis is impaired in the Ts65Dn mouse model of DS (4), however the causative mechanism leading to this impairment is not completely clarified. Since it is known that OXPHOS inhibition selectively impairs proliferation of neural progenitor cells (NPCs) and neurogenesis in mouse (5), in this study we analyzed whether and how mitochondrial bioenergetics is affected in hippocampal NPCs of Ts65Dn.

We found several mitochondrial alterations in DS NPCs involving i) bioenergetics: reduced respiration capacity and mitochondrial ATP production via OXPHOS due to a selective deficit of mitochondrial respiratory chain complex I and ATP synthase activities ascribed to post-translational alterations of cAMP/PKA-mediated pathways and increase of protein degradation; ii) mitochondrial biogenesis: decrease of mitochondrial mass associated with reduced PGC-1 α , NRF-1 and T-FAM protein levels; iii) mitochondrial dynamics: increased mitochondrial fragmentation and reduced mitochondrial fusion.

This study establishes a potential rationale into devising therapeutic strategies promoting mitochondrial bioenergetics for managing some of the clinical manifestations commonly associated with DS.

References and acknowledgements

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1. Valenti D, de Bari L, De Filippis B, Henrion-Caude A, Vacca RA, *Neurosci. Biobehav. Rev.* 2014, 46:202-217.

2. Valenti D, Tullo A, Caratozzolo MF, Merafina RS, Scartezzini P, Marra E, Vacca RA, *Biochem. J.* 2010, 431:299-310.

3. Valenti D, Manente GA, Moro L, Marra E, Vacca RA, *Biochem. J.* 2011, 435:679-688.

4. Contestabile A, Greco B, Ghezzi D, Tucci V, Benfenati F, Gasparini L, *J. Clin. Invest.* 2013, 123:348-61.

5. Lee Y, Oh SB, Park HR, Kim HS, Kim MS, Lee J, *Neurosci. Lett.* 2013, 535:134-139.

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42 - Genetic dissection of motor coordination defects in mouse models of Down Syndrome.

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Down Syndrome (DS) is caused by trisomy of chromosome 21 (Hsa21). This increased gene dosage leads to a number of disorders in individuals with DS including motor problems. Children with DS have a delayed development of gross motor skills and adults with DS exhibit poor coordination and exhibit gait differences.

There are a number of mouse models of DS including the Tc1 mouse, which carries a freely segregating human chromosome 21 (Hsa21) and the Ts1Yey, which contains a duplication of the portion of mouse chromosome 16 (Mmu16) orthologous to Hsa21. These mice recapitulate many of the phenotypes seen in individuals with DS including a motor defect as shown by a RotaRod assay.

To begin dissecting dosage-sensitive genes responsible for this phenotype, mice containing small chromosomal deletions in regions orthologous to Hsa21 have been crossed to the Tc1 mouse. This returns the genes within the deletion from 3 copies to 2. If a cross results in the amelioration of the phenotype, a dosage-sensitive gene must lie in that interval. Furthermore, we have analysed mice bearing small duplications of portions of the orthologous mouse chromosomes to Hsa21. The presence of the phenotype indicates a dosage sensitive gene sufficient to cause the phenotype. Using this strategy we have mapped a single dosage sensitive gene necessary, which when present in 3 copies, for the RotaRod phenotype. We are now extending this study to identify the neurological causes, which may underlie this phenotype. Examination of granule cells, Purkinje cells and interneurons in the cerebellum indicates no significant differences in the numbers of these cells in these mouse models at both postnatal and adult ages, making it unlikely that defects in neuronal number in the cerebellum account for the motor defects.

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POSTERS

PLATFORM PRESENTATION 2

1 - Regulation of feeding behavior and glucose homeostasis in a Down syndrome mouse model

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Down syndrome (DS) is associated with anomalies of both nervous and endocrine systems, with high obesity prevalence. To understand how genetic imbalance affects feeding behavior leading to overweight, we used a trisomic DS mouse model (Ts(1716)65Dn; abbreviated Ts65Dn) that carries a small chromosome derived primarily from mouse chromosome 16, causing dosage imbalance for approximately half of human chromosome 21 orthologs. Ts65Dn mice fed with standard chow (SC) diet showed lower eating rate and less number of SC meals than 2N mice. However, the average SC intake and the duration of the meals were higher. Exposition to a high-fat diet (HFD) regime induced obesity and feeding behavior changes in Ts65Dn young adult mice. Interestingly, in the oral glucose tolerance test Ts65Dn mice showed a more rapid recovery of basal glycemic profiles after administration of a glucose load in basal conditions (fed with standard chow; (SC). This indicates a better glycemic control that was previously reported in DS patients. We will present the glucose homeostasis and the endocrine pancreatic function in Ts65Dn mice after HFD regime, since HFD is often associated with the installation of insulin resistance state as a compensatory mechanism through the up-regulation of pancreatic β ; cell mass and insulin secretion. We will also show pancreatic β ; cell mass in Ts65Dn mice under SC and HFD. Taken together, the results will help to better understand the complexity of the obesity phenotype in Down syndrome and ultimately improve future therapeutic solutions.

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2 - Response time during dual motor task among children with Intellectual Disabilities

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Background: Children with disabilities have greater difficulty in responding quickly to a stimulus. Activities of daily living require children to perform these actions in dual task conditions. It is therefore necessary to understand how dual task influences the response time (RT) in children with Down Syndrome (DS), children with Intellectual Disabilities without DS (ID) and typically developing children (TDC). **Purpose:** Does dual task affect the response time among children with DS, ID and TDC?

Methods: Fifteen children with DS (16 males and 10 females, mean age = 12.8 years), twenty two children with ID (21 males and 16 females, mean age = 13.1 years) and forty TDC (23 males and 17 females, mean age = 12.3 years), participated in this cross-sectional study. RT of these children were assessed using an indigenously developed response time analyzer within their school settings. RT of children was assessed for the right and left hand, first for a simple task, followed by dual task, on two separate days. The child was instructed to press the response switch with the index finger as soon as the visual stimulus (light) appeared. After a period of familiarization, best of the three responses were recorded for time for the right and the left hand separately. The first task involved performing the simple RT task and the second task involved performing the simple RT task, while simultaneously performing a motor task (pedaling with lower extremities using a stationary pedal). The primary outcome measure was RT in milliseconds.

Results: A mixed effects ANOVA was performed to understand the interaction between the task, i.e. the active and the passive task with the subjects. There was a statistically significant difference ($p < 0.001$), when the interactions between the different tasks and the groups was taken into consideration. Among the groups, the time taken to perform the task was longest and the force with which the tasks were performed were least among children with DS. There was no significant difference when the interactions between the right and left extremities were assessed.

Conclusion: Dual task activities increases the time required for children to perform a given task, irrespective of whether the child has any underlying pathology. Among the three groups children with DS were the slowest to perform across the tasks. Future studies can evaluate the effects of different types or intensities of secondary motor tasks, on RT in children with DS and ID.

Implications: Assessment of RT should form a part of the physical therapy evaluation for children with DS and ID. The lower RT among children with DS and ID, observed in this study suggests future implications for developing specific rehabilitation interventions.

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3 - Behavioural and psychological symptoms of dementia in Down syndrome: Early indicators of clinical Alzheimer's disease?

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Behavioural and Psychological Symptoms of Dementia (BPSD) are a core symptom of dementia in addition to cognitive decline and impaired activities of daily living, and are extensively studied in patients with Alzheimer's disease (AD) in the general population. BPSD, or neuropsychiatric symptoms, are associated with suffering, earlier institutionalization and accelerated cognitive decline for patients, increased caregiver burden, and higher financial costs. Despite the high risk for Down syndrome (DS) individuals to develop dementia, BPSD have not been comprehensively assessed in the DS population. Due to the great variety of DS cohorts, diagnostic methodologies, sub-optimal scales, covariates and outcome measures, it is questionable whether BPSD have always been accurately assessed. However, accurate recognition of BPSD may increase awareness and understanding of these behavioural aberrations, thus enabling adaptive caregiving and, importantly, allowing for therapeutic interventions. Particular BPSD can be observed (long) before clinical dementia diagnosis and could therefore serve as early indicators of those at risk, and provide a new, non-invasive way to monitor, or at least give an indication of, the complex progression to dementia in DS. Strikingly, not a single behavioural assessment scale has been adapted and validated for AD in DS, thus not taking the DS-specific circumstances into account, such as pre-existing behaviour and limitations associated with intellectual disability. Therefore, we aim to develop a novel scale for BPSD in DS. The first phase of scale development will be presented, including an extensive evaluation of the rather limited knowledge on BPSD in DS, identification of key behavioural items and diagnostic issues, and the importance and potential of accurate recognition of BPSD in DS for daily clinical practice.

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4 - Characterization of pharmacological Dyrk1A kinase inhibitors for therapeutic use in Down Syndrome models abstract

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The Down Syndrome or Trisomy 21 (DS), is due to an extra copy of the chromosome 21, and is the most frequent mental retardation which affects about 1 new born per 700 births.

Among the candidates implicated in DS intellectual disabilities, the Dual Specificity Tyrosine Phosphorylation regulated Kinase, Dyrk1a, found in the DS critical region of chromosome 21, is one of the most relevant. Indeed, several studies have shown a correlation between an increase of its kinase activity and the intellectual defects observed in DS models.

In order to go further understand the mechanisms underlying the impact of Dyrk1a dosage on the cognitive alterations, we used different trisomic mice models expressed Dyrk1a alone or with additional Hsa21 homologous genes and specific Dyrk1A inhibitors from ManRos Therapeutics.

We will present here the consequence of the treatment using Leucettine 41, a synthetic Dyrk1A inhibitor, when administered to several DS mouse models on the behaviour and cognition and on several activities of Dyrk1a. Further analysis of the phosphoproteome of DS mouse models treated or not with L41 unravels a few targets and pathways which are involved in the restoration of cognitive capacities of DS models. These results supported the potential of Dyrk1A inhibitor in therapeutic approach to ameliorate cognitive function in DS patients.

5 - Searching for a molecular signature of Alzheimer's disease in Down syndrome plasma

Iulita, M. Florencia

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Individuals with Down syndrome (DS) are at increased risk of developing Alzheimer's disease (AD) compared to the rest of the population. The development of Alzheimer's pathology in DS occurs in a temporal, gradual manner since early life. Notably, diagnosing AD in DS is challenging due to the underlying intellectual disability and cognitive decline associated with aging. Therefore, the overarching goal of this study was to identify biomarker candidates of an evolving amyloid pathology in plasma samples from DS individuals and to correlate this with cognitive decline as measured by the Test for Severe Impairment before and after 12-15 months follow-up. Amyloid-beta (Ab) peptides ending at amino acids 38, 40 and 42 were quantified using a Multi-Spot quantitative V-PLEX array (MesoScale Discovery, USA). Ab38 was detectable only in 11 cases out of 62 plasma samples, with no apparent differences between control and DS subjects. In contrast, Ab40 peptides were significantly elevated in asymptomatic, non-demented individuals with DS ($p < 0.01$), compared to age-matched controls, and remained higher in individuals with clinical signs of AD ($p < 0.001$). Levels of Ab42 in plasma were higher in DS compared to controls but significantly elevated only in DS cases with established dementia ($p < 0.05$). We observed a negative correlation between cognitive decline and baseline plasma levels of Ab40 ($r = -0.7887$ $P < 0.0001$) and Ab42 ($r = -0.7393$ $P < 0.001$) peptides, in asymptomatic DS subjects. Ab peptides will be further evaluated following 12-15 months from baseline measurements in order to establish possible associations between changes in plasma Ab, decline in cognition and dementia development. Classical pro-inflammatory mediators are also being investigated in plasma with the goal to establish possible associations between an inflammatory profile, amyloid biomarkers and cognition.

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DISPLAYED POSTERS – DAY 2

6 - Learning by observation and learning by doing in the presence of intellectual disabilities: a comparison between Down and Williams syndromes

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Background: New competencies may be learned through active experience (learning by trial and error) or observation of others' experiences (learning by observation). Observing another person performing a complex action accelerates the observer's acquisition of the same action and limits the time consuming process of learning by trial and error. The aim of this study was to analyze the ability to learn by observation and by trial and error in Down syndrome (DS) and Williams syndrome (WS), in order to facilitate interventions that develop the acquisition of new cognitive and motor abilities in the presence of intellectual disabilities.

Method: The performance of twenty-four DS individuals (mean mental age 5.08 ± 0.03) and twenty-four WS individuals (mean mental age 5.09 ± 0.02) was compared with that of twenty-four typically developing (TD) children matched for mental age and gender on tasks of learning of a visuo-motor sequence by observation or by trial and error. The participants learned the sequence either by performing the task after in an observational training (observing an actor detecting the sequence) or by actually performing the task by trial and error.

Results: The syndromic groups showed specular learning profiles. Indeed, DS individuals were impaired in learning the sequence by observation and they were as efficient as TD children in detecting the sequence by trial and error. In contrast, WS individuals were able in learning the sequence by observation and they were impaired to learn the sequence by trial and error in comparison to TD children.

Conclusion: The present results have important implications for developing specific programs to facilitate the acquisition of new cognitive and motor competencies allowing better social integration and development of self-efficacy and self-confidence in individuals with intellectual disabilities.

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7 - DSM-5 and diagnosing neurocognitive disorders in people with Down syndrome

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Sarah WHITWHAM

The clinical manifestation of dementia in the Down syndrome (DS) population often precedes its appearance among individuals with non-DS intellectual disability or the general population by more than two decades. The disorder also appears to be more rapidly progressive among individuals with DS than among those with non-DS intellectual disability or within the general population, though data on progression is limited.

Given that cognitive and functional decline occur as overlays upon pre-existing deficits associated with developmental disability, it is important to rule out all factors that may complicate both the presentation and course of the condition including depression, sensory loss and other co-morbid psychiatric or medical illness. It is thus important to consider the applicability of standard dementia diagnostic criteria to the DS population

The Diagnostic and Statistical Manual (DSM) is widely used for dementia diagnosis and the latest version (DSM-5) was published in 2013, superseding DSM-IV. The new edition re-characterised dementia as neurocognitive disorder and modified some of the diagnostic criteria. We propose modified DSM-5 criteria for use in the DS and non-DS intellectual disability population taking the above considerations into account.

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8 - Discrimination of Area and Number in Children with Down Syndrome

Arias-Trejo, Natalia

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Individuals with Down syndrome (DS) have a great difficulty at learning mathematics (Brigstocke, Hulme, & Nye, 2008). In current years, research has focused on investigating if precursors of later mathematics, such as estimating and comparing numerosities, are preserved in DS (Camos, 2009; Lanfranchi, Berteletti, Torrisi, Vianello, & Zorzi, 2015; Paterson, Girelli, Butterworth, & Karmiloff-Smith, 2006; Sella, Lanfranchi, & Zorzi, 2013). Albeit the suggestion of a strong relationship between the ability to compare continuous quantities (e.g., area of an object) and to compare numerosities (Brannon, Lutz, & Cordes, 2006), it is still unknown whether this ability is preserved in DS. The present study investigated the abilities of individuals with DS to compare area and number, and contrasted them with those of two other control groups of typically developing individuals. Participants were sixteen individuals with DS [Mean Mental Age (MA) = 4.27 years, range 2.3 to 7.4 years; mean Chronological Age (CA) = 12.29 years, range 3.83 to 22.42 years], sixteen typically developing individuals matched by mental age (MA group), and sixteen typically developing individuals matched by chronological age (CA group). All participants performed two eye-tracking tasks: an area comparison task (ACT) and a number comparison task (NCT). Stimuli of the two tasks differed in the same ratios (1:3, 1:2, 2:3, 3:4) in order to compare individuals' performance across both tasks. We performed a 3x2x4 mixed-design repeated measures ANOVA with Group (SD, MA, and CA groups) as between-subjects factor, and Task (ACT and NCT) and Ratio (1:3, 1:2, 2:3, and 3:4) as within-subjects factors with LLK difference as the dependent measure, which revealed a significant effect of Group ($F(2,45) = 29.19$, $p < .001$), Task ($F(1,45) = 27.41$, $p < .001$), and Ratio ($F(3,43) = 6.08$, $p < .01$). Post hoc comparisons indicated that the ratio effect was driven by a better performance in easier ratios than harder ones (1:3, 1:2 > 2:3, 3:4), while the Task effect by a better performance in the ACT than in the NCT. More importantly, the Group effect was driven by a better performance of the CA in comparison to the other two groups (CA group > SD group = MA group). These results indicate that performance of individuals with DS, in both tasks, is aligned with that of individuals with their same MA. The current study also shows that the ability to compare area is preserved in DS, and that those individuals with this syndrome show similar abilities to typically developing individuals, that is, a better performance at comparing area than number. The advantage that individuals with DS have at discriminating area could be used in interventions seeking to improve number comparison abilities in DS.

Brannon, E., Lutz, D., & Cordes, S. (2006). The development of area discrimination and its implications of number representation in infancy. *Developmental Science*, 9(6), F59-F64.

Brigstocke, S., Hulme, C., & Nye, J. (2008). Number and arithmetic skills in children with Down syndrome. *Down Syndrome Research and Practice*, 74-78.

Camos, V. (2009). Numerosity Discrimination in Children With Down Syndrome. *Developmental Neuropsychology*, 34, 435-447.

Lanfranchi, S., Berteletti, I., Torrisi, E., Vianello, R., & Zorzi, M. (2015). Numerical estimation in individuals with Down syndrome. *Research in Developmental Disabilities*, 36, 222-229.

Paterson, S. J., Girelli, L., Butterworth, B., & Karmiloff-Smith, A. (2006). Are numerical impairments syndrome specific? Evidence from Williams syndrome and Down's syndrome. *Journal of Child Psychology and Psychiatry*, 47, 190-204.

Sella, F., Lanfranchi, S., & Zorzi, M. (2013). Enumeration skills in Down syndrome. *Research in Developmental Disabilities*, 34, 3798-3806.

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9 - Comprehension of morphological markers in people with Down syndrome

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Children need to learn grammatical rules such as those corresponding to gender and number. In Spanish the understanding of the information related to gender (words ending in 'a' tend to be feminine and words ending in 'o' masculine) and number ('s' or 'es' ending for plural) results in a more efficient and rapid language processing. Recent investigations have established that young children with typical development are sensitive to grammatical gender agreement between articles and nouns. The speech of people with Down syndrome (DS) usually lacks the inclusion of morphological markers; however, it is unknown whether they are able to process and use them to support their understanding.

Therefore, the main goal of the current research was to explore whether DS children could use singular indefinite articles (un-una in Spanish) to find a target before it was labelled.

Sixteen DS children (mean chronological age = 6.8 years, SD = 2.11; mean mental age = 34.6 months, SD= 6.7) participated in a preferential looking task. In each trial, children saw during 2000 ms two pictures (target-distracter), during this period the carrier phrase 'mira' was heard. At 2000 ms children heard a masculine ('un') or a feminine ('una') article; finally, at 4000 ms the target name was heard. In half of the trials, the nouns had a regular ending matching its gender (e.g., 'o' for masculine and 'a' for feminine). The other half of the trials introduced nouns with an irregular ending (e.g., 'e' for masculine or feminine). The results indicated that DS children with a 34-month-old mental age anticipated the target referent by using the information contained in the indefinite article (un-una). Importantly, children were able to correctly anticipate the target when facing regular (ending in 'a' or 'o') or irregular nouns (other ending).

The results of this research demonstrate that DS children can use gender information embedded in an article to anticipate a referent. This ability enhances a more rapid and accurate online language processing by allowing disambiguation of familiar items irrespectively of hearing their names. Participants with Down syndrome were able to understand the information of grammatical gender of their mother tongue, which shows an early ability to understand formal rules. The outcome could be employed to design intervention programs to improve other lexical abilities in DS children.

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10 - Evaluation of functional, social and emotional skills in children with intellectual disability

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By referring to the definition and diagnostic criteria internationally recognized of the intellectual deficiency (American Association Intellectual and Developmental Disabilities, AAIDD, 2011), we note in children with intellectual disability a combination of limitations of the intellectual functioning and the adaptive functioning (integrating deficits in conceptual, social, relational and adaptive capacities). Furthermore, in the light of the increasing interest for functional and socio-emotional skills by professionals and parents, eager to improve the autonomy, the quality of life and the social-emotional adaptation to the everyday life of their children, it seemed crucial to carry out a research able to meet these concerns.

Therefore, a research is organized within the Cliniques Universitaires Saint Luc aiming to analyze the trajectories of the functional skills evolution [by means of an innovative instrument, curriculum-based and ecological approaches : the EIS program - evaluation, intervention and follow-up - French version, Dionne, Rivest & Tavares, 2006], and to put them in connection with the social and emotional skills in children with intellectual disability (with Down syndrome) and typically developing [Matson Evaluation Social Skills for Youngsters - II - (French version, Nader-Grosbois, 2013, MESSY) and the Emotion Regulation Checklist (ERC, Shields & Cicchetti, 1995) (French version, Nader-Grosbois, 2013)]. Comparisons will be made between both groups of children.

For this purpose, the poster of this research will present the objectives and the methodology of the search. It will present the first results of this research and recommendations in order to adapt intervention to such children with intellectual disability (with Down syndrome).

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11 - Neuropsychiatric Symptoms in Patients with Down Syndrome and Alzheimer Disease Dementia.

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Background: Neuropsychiatric symptoms (NPS) are frequently present in Alzheimer's disease (AD), but are also present in subjects with intellectual disability. NPS in Down syndrome (DS) patients are more difficult to assess and often rely on clinically observable behavior and information from informants. We aimed to assess NPS through the Neuropsychiatric Inventory Questionnaire (NPI-Q) in DS subjects with (AD-DS) and without AD dementia (healthy-DS).

Method: single-center, cross-sectional study. We prospectively used the NPI-Q to examine behavioral and psychological signs and symptoms of dementia through a structured interview with a caregiver. Dementia of the Alzheimer type was diagnosed based on DSM-IV criteria.

Results: NPI was administered to 28 AD-DS and 77 healthy-DS. AD-DS patients were significantly older than healthy-DS [mean age (SD): healthy-DS, 36,7 (10,7); AD-DS, 55 (5,4); $p < 0.000$]. There were no differences in gender. Overall 53,2% of the healthy-DS and 28,6% of the AD-DS patients were free of NPS as assessed by the NPI-Q. AD-DS presented significantly higher scores on the total NPI-Q score (9,39 vs 4,21; $p=0,008$) and on the following subscores: agitation (0,64 vs 0,14; $p=0,04$), apathy (2,18 vs 0,87; $p=0,001$) and irritability (1,04 vs 0,40; $p=0,03$).

Conclusion: NPS are common in DS patients who develop AD. The NPI-Q profile is qualitatively similar to that described in sporadic AD. However, caregivers may have incomplete perception of patient NPS possibly due to misinterpretation of symptoms as part of the intellectual disability.

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12 - Cerebrospinal fluid biomarkers in a cohort of down syndrome patients

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Background

Most patients with Down syndrome (DS) develop presenile onset Alzheimer disease (AD). However, AD diagnosis represents a diagnostic challenge due to the intellectual disability associated with DS. The AD pathophysiological process can be studied using cerebrospinal fluid (CSF) biomarkers.

Methods

We measured markers of amyloid- β protein precursor (APP) processing, (A β 42, sAPP β , β -secretase activity), neuronal damage (total tau, p-tau), and inflammation (YKL-40) in CSF from a cohort of DS subjects with and without dementia. Results were compared with data from AD patients and healthy controls (HC) and the correlation between age and biomarkers in the DS cohort was analyzed.

Results

We included 30 DS subjects, 13 demented (median age 54.7) and 17 non-demented (median age 41.9); 48 AD patients (median age 72); and 67 HC (median age 57.3). In the DS cohort, we found a correlation between age and A β 42, tau, p-tau and YKL-40. Non-demented DS subjects had lower A β 42 and YKL-40 than HC, but no differences on other APP processing biomarkers was detected. Demented DS patients had lower A β 42 and higher tau, p-tau and YKL-40 levels than non-demented DS patients. There were no differences between Demented DS and AD patients in A β 42, sAPP β , injury or inflammatory markers, but demented DS patients had lower β -secretase activity than AD patients.

Conclusions

The CSF profile is similar in demented DS subjects and sporadic AD, but an age-associated AD pathophysiological process can be detected in DS without dementia. This finding is compatible with the conceptualization of DS as a form of preclinical AD.

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13 - The immune deficiency of Down Syndrome patients is due to a severe reduction of memory B cells.

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Notwithstanding normal serum antibody levels, DS children suffer from recurrent infections of the respiratory tract and have an increased risk of severe sepsis, suggesting a B-cell dysfunction. We show that trisomy 21 affects the differentiation of B cells at several developmental stages and checkpoints. In DS children the bone marrow produces 50% of the normal number of B cells and mature-naïve B cells in the periphery are reduced to half. The most severe defect is observed in the switched memory pool. This population is generated in the germinal centers in response to infections or vaccinations and is indispensable for the generation of recall responses to previously encountered pathogens and the prevention of re-infections. In DS children switched memory B cells are reduced to 10-15% of normal and show an increased ability of differentiating into plasma cells *in vitro*. In order to ask the question of whether the low number of switched memory B cells is due to a reduced production or to their rapid usage and differentiation into antibody secreting cells, we immunized DS children against influenza and measured antigen-specific switched memory B cells and serum antibodies. We compared 15 DS children to their age-closest siblings in order to avoid the variables due to the environment and the genetic background (other than trisomy 21). We found that in response to a primary single-dose immunization DS children produce 10 fold less specific memory B cells and a slightly reduced level of neutralizing antibodies. We also measured the ability of previously generated memory B cells to respond to a recall immunization with Prevenar 13. DS children had significantly less memory B cells than their siblings 3-4 years after a complete vaccination cycle, but the response to the booster was comparable in DS and siblings increasing the level of both specific antibodies and memory B cells.

The relative inefficacy of a single-dose immunization associated to the loss of memory B cells years after a complete cycle strongly suggest the need of tailored immunization schedules for an effective vaccine-induced protection of DS children against infection.

We do not know which sequences on chromosome 21 influence the immune response. High steady state levels of certain microRNAs have been recently demonstrated in the peripheral blood cells of DS children, including microRNA 125b and 155. Both microRNA play a role in the germinal center reaction. Further studies are in progress to investigate this novel genetic aspect of DS and their importance not only in the alteration of the immune response but also in the genesis of transient altered haematopoiesis and leukemia of patients with trisomy 21.

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14 - Neuropeptides, neurotrophins and cytokines in the peripheral blood of children with Down syndrome. A case-control study.

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Background:

In spite of being such a notorious syndrome, the mechanisms underlying the neuropathology of Down syndrome (DS) are not well understood. Neuropeptides (VIP, ADNP and ADNP2), neurotrophins (NGF and BDNF), cytokines (IL-6 and IL-8) and IGF-1 are known for their fundamental and pleiotropic activity in neurodevelopment and neuroprotection. Their roles have been previously investigated in mouse models of DS but few studies have been carried out on children affected by DS. Thus, we performed a case-control study to clarify the role of neuropeptides, neurotrophins and cytokines in DS children and to establish if there is any connection between their levels in peripheral circulation and age, gender, ethnicity and comorbidities.

Materials and Methods:

187 DS children were recruited for this study with 90 typically developing disomic controls matched for age and gender (proportion 2:1). Children were assigned to 6 age categories: Class 1: 12-35 months; Class 2: 3-4 years; Class 3: 5-6 years; Class 4: 7-9 years; Class 5: 10-12 years; Class 6: 13-15 years

Strict exclusion criteria were adopted, for both groups, to avoid fluctuations of peptides levels due to inflammatory processes or infections. Patients underwent a detailed anamnestic pediatric evaluation; all comorbidities were registered.

- Premature birth (gestational age at birth \leq 34 weeks);
- Allergic bronchial asthma;
- Celiac disease with positive markers in the last 6 months;
- Acute enteritis in the last 2 weeks;
- Hyperpyrexia in the last 2 weeks;
- Flu or respiratory syndrome in the last 2 weeks.

A peripheral blood sample of about 10 mL was drawn from each child and immediately processed for the isolation of plasma and of peripheral blood mononuclear cells (PBMCs).

Plasmatic levels of NGF, BDNF, IL-6, IL-8 and IGF-1 were measured using a double-antibody immunoaffinity assay (Luminex), while mRNA levels of the neuropeptides (VIP, ADNP, ADNP2) was assayed in PBMCs by quantitative Real Time-PCR.

We compared the levels of the biomarkers between DS and controls overall and adjusting for age and gender. Moreover, we evaluated the correlation between biomarkers and age and the correlation among the biomarkers in DS and controls.

Results:

VIP mRNA level was found higher in DS children compared with controls ($p < 0.001$).

Plasmatic IL-6 and IL-8 levels were significantly higher in DS children compared with controls (both $p < 0.001$). ADNP/ADNP2 correlation was significantly weaker in DS compared with controls. Only in DS children, VIP significantly increased with age, whereas IL-6 and IL-8 decreased with age (statistical significance $p < 0.001$). Finally, some comorbidities, such as hearing impairment, significantly affected mRNAs or peptides levels within DS cohort.

Discussion:

Alterations of VIP, IL-6 and IL-8 levels may be involved in molecular basis of impaired neurodevelopment of children with DS, although their precise roles and interactions still need to be clarified.

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15 - Infantile spasms in Down Syndrome-Factors associated with evolution with autistic features.

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Purpose: To investigate the factors associated with autistic features in infants with Down Syndrome with infantile spasms.

Methods: We studied retrospectively thirty three patients followed at Lejeune Institute during a median of 10.9 years (1 m-34y).

Results: Sixteen patients presented autistic features (48%) (groupe A), versus seventeen patients without (52%) (groupe B). The sex ratio was similar in the two groups, nine male and seven girl in groupe A and ten male and seven girl in group B. Infantile spasms appeared at the same age in the two groups, respectively at a median of 7.59 months (5-15 m) in group A and 7.47 months (4-12 m). The two groups were treated by vigabatrin and corticotherapy (hydrocortisone or synacthene) in a similar proportion in 56%(9/16) in group A versus 43.7%(7/16) in group B. However, when the information was available, the treatment lag ≥ 2 months was more often found in the group A in 54.5% (6/11) versus the group B in 22% (2/9). In the two groups, infantile spasms disappeared but another seizures appeared in 43.75% (7/16) in the group A versus 0.058% in group B (1/17).

Conclusions: This study shows that a treatment lag ≥ 2 months and the occurrence of a later epilepsy are associated with a bad outcome with autistic features and that age, sex and antiepileptic treatment usually used for the treatment of infantile spasms didn't change the evolution. Another factors are probably involved and must be searched with genetic analyses.

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16 - DigiDown, A nationwide Down syndrome patient registry

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Introduction: Down syndrome (DS) is associated with an increased incidence of congenital and acquired diseases, auto-immunity and hematological malignancies. Conditions as obesity, mobility restrictions, visual and hearing impairment, depression, hypothyroidism, epilepsy and Alzheimer's disease are known to become increasingly prevalent in later life. The overall day-to-day treatment of DS individuals is commonly based on data obtained from non-DS subjects, although diseases reveal themselves differently in individuals with DS. Data are needed to study all these aspects. For this, a nationwide patient registry will be a solid basis. The DigiDown project team will build such a registry, based upon the network of the Dutch multidisciplinary Downteam Research Consortium (DOC), of which the active Dutch Down Syndrome Patient Organization SDS is an integral partner.

Objective: 1) To develop a nationwide patient registration database for Down syndrome. 2) To develop a platform for research purposes.

Method: Patients and/or caregivers will be asked (by their pediatrician or medical doctor) to give informed consent for the registration in DigiDown. If informed consent is given, a digital link for the registration will be sent by email. The patient receives a personal identification number (PIN). Only the responsible health care providers themselves can link the Personal Identification Number (PIN) used in the registry to the actual identity of the patient. After registration, the parents and/or caregivers will regularly receive questionnaires. The registry will contain data on overall day-to-day health care, data on the social background, data from quality of life questionnaires, data concerning economic aspects, and detailed results of laboratory, radiological and other tests, if performed in routine patient care. Research projects regarding e.g. development, behavior or (para)medical treatments can be added to the database (with additional informed consent procedures if needed). Parents and/or caregivers will enter many data themselves; if this is not feasible because (para)medical details are needed, trained research nurses will enter the data under supervision of the responsible health care providers. The data will be stored on secured computers via the Research Manager® software program.

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17 - Genetic polymorphisms in monoamine neurotransmitter systems (COMT val/met and 5-HTTLPR) contribute on Down syndrome's (DS) cognitive and behavioural phenotype.

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DS trisomy leads to a cognitive phenotype characterized by deficits in psychomotoricity, learning/memory, executive functions, and language. Anxiety and depression are also common, increasing maladaptive behaviours. Reduced levels of serotonin and dopamine in frontal cortex in DS brain lead to vulnerability to depression and anxiety. Previous studies on the influence of monoamine neurotransmitters in cognition and mood showed that prefrontal DA is central to working memory while serotonin to learning and mood. The purpose of this study is to evaluate whether COMT and 5-HTT polymorphisms contribute to cognition and/or adaptive behaviour in DS. Procedures: A subpopulation of 73 DS subjects treated previously for 12 months in an intervention study with green tea was evaluated 6 months after discontinuing treatment. This evaluation was selected to analyse cognitive performance vs. genetic polymorphisms (COMT val158met, 5HTTLPR) interaction. The TESAD BATTERY was used to explore the following cognitive domains: psychomotor speed (MOT), attention (digits-F, SSP-F, Choice Reaction Test), memory (PAL, PRM, CRT), executive function (SSP-B, digits-B, Word Fluency, Cats & dogs, TOLDX, WCST) and language (BNT, Token Test). Everyday life functionality was evaluated using: adaptive behaviour (ABAS-II), quality of sleep (PSQI) and dementia symptoms (DMR). Genomic DNA was extracted using Flexi Gene DNA kit, genotyping was performed using polymerase chain reaction (RT-PCR). One way- ANOVA was fitted for all neurocognitive measures, first using polymorphism grouping and second treatment as factors. Univariate GLM was also carried with COMT, 5HTTLPR and treatment as fixed factors. Results: Regarding to COMTval158met, val/ val carriers had better planning abilities ($p=0.003$) and better functionality reported in both ABAS-II($p=0.029$) and DMR total and social score ($p=0.049$ and $p=0.023$). Otherwise the met* carriers had a better psychomotor speed ($p=0.009$) and a shorter latency in working memory ($p=0.001$) and in delayed visual memory ($p=0.019$). Regarding to 5-HTTLPR the s/s had a worse performance in immediate visuospatial memory ($p=0.018$), comprehensive language ($p=0.033$) and reported more alterations of sleep ($p=0.014$). We find an interaction between COMT val158met, 5HTTLPR in planning executive function and ABAS-II in s/s and val/val genotype's carriers. Conclusion: Our data suggests that val/val have higher latency of response in memory and working memory and lower psychomotor speed while perform better in prefrontal planning executive tasks and had better everyday life functionality. Regarding to 5-HTTLPR the l/l performs better in visuospatial memory and high order comprehensive language and reports lower sleep alterations. Results suggest that other genetic variables further than trisomy 21 have an influence on the cognitive/behavioural DS phenotype.

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18 - Cytokines plasma levels in Down's syndrome patients from childhood to old age

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Background: Down's syndrome (DS) is the most frequent chromosomal disorder: its incidence is about 1 for 800. It is accompanied by an intellectual deficiency and by characteristic morphological changes, but also by a deregulation of the immune system, that induces a higher sensibility to infections and autoimmune diseases. Moreover, DS patients are prone to autistic spectrum disorders (ASD), ADHD, epilepsy and have a high risk of developing Alzheimer's disease. Cytokines may have a part of responsibility in the DS immune deficiency, as they play a major role in the immune system. Also, pro-inflammatory cytokines may have a role in inducing the mental retardation in DS and in the afore mentioned pathologies, as they are involved in neuro-inflammation.

There are reports showing that pro-inflammatory cytokines are deregulated in DS patients. However, none of these reports followed their evolution throughout the life of DS patients. We will analyze cytokine levels in serum samples in patients of various ages, and compared them with samples from healthy and non DS intellectually disabled patients. This will help us establish the links between cytokines and aging and cytokines and mental retardation.

Material and methods: the study includes 60 patients: 30 with DS and 30 control subjects, aged 1-2 years old, 5-7 years old, 12-14 years old, 20-30 years old, 45-55 years old and over 60 years old. Patients suffering from autism spectrum disorder, dementia, autoimmune and infectious diseases are excluded. All patients are followed at the Institut Jérôme Lejeune and have blood samples collected for the biobank CRB Biojel. The concentrations of the cytokines, TNF-alpha, INF-gamma, IL-1beta, IL-6, IL-10, GM-CSF, MCP-1 and SDF-1 are determined by quantitative Elisa. These cytokines were selected for their inflammatory role, their brain function and because they have already been related to DS. We will further correlate cytokines plasma levels to oxidative stress by measuring SOD (RT-PCR).

Results: We describe whether there is an increase of the cytokine plasma concentrations in DS patients accordingly to age and if this evolution is faster than in the controls. These results will serve as referential material for future researches on DS and ASD and on DS and aging. They will also give some leads on the impact of cytokines on mental retardation.

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19 - Down syndrome: interest of an integrated multidisciplinary medical and developmental approach.

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Health supervision in Down syndrome includes internationally recognized and specific recommendations in different fields of medical care. These recommendations represent an impressive number of specialized consultations, mainly during early childhood and childhood.

Many families reported their difficulties to follow exactly these recommendations.

On request of parents of children with Down syndrome and congenital heart diseases, a multidisciplinary clinic for these children was created in 2001 in the cardiopédiatric department of Cliniques universitaires St Luc in Brussels (Belgium). Later, we also included any children with Down syndrome, but without any cardiac diseases.

We propose in 1 or 2 sessions diverse medical consultations: general pediatrics, orthopedics, ophthalmology, medical follow-up of ENT (ear-nose and throat), dental and others depending on age and needs (cardiology, digestive, endocrinology, dermatology...).

Furthermore, we propose in another session a neurodevelopmental assessment with a pediatric neurologist, physiotherapist, speech therapist and a neurodevelopmental psychologist.

The psychologist analyse the trajectories of the functional skills evolution [by means of an instrument: the EIS program - evaluation, intervention and follow-up - French version, Dionne, Rivest & Tavares, 2006]. The EIS program evaluates the emerging skills of the child, proposes practical activities to stimulate the apparition of these skills and follows the progress realized in the different fields of the development.

We are no more in an "IQ-obsessed culture" but in a positive perspective (more interested in the skills than in the deficiencies).

Different principles are present in this multidisciplinary approach:

- no psychological well-being without physical well-being first
- preventive medicine has to be global (including all fields of medicine) but also individualized to give optimal physical well-being
- meeting of the paramedical and medical team is an important point: we share the opinions about the children; medical, developmental, behavioural issues are explored before general conclusions and propositions.

We report benefits from this approach:

- the preventive medical program is better followed than 15 years ago. Parents appreciate this multidisciplinary assessment (time-sparing for them); other hospitals in Belgium are adopting this approach.
- the developmental program EIS gives a positive qualitative perspective, an important point for families.
- The 2 teams (medical and neurodevelopmental ones) mix their observations for a better prevention/treatment of behavioural problems, and in long term, for a better autonomy and quality of life.

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20 - Cognitive flexibility and receptive vocabulary in children with Down syndrome

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Down syndrome (DS) is the most common genetic cause of intellectual disability. People with DS have deficits on measures of cognitive flexibility (CF). Nonetheless, their receptive vocabulary (RV) skills are better developed. A significant relationship between CF and RV has been reported, however little is known regarding the factors involved in such relationship. The present study aimed to investigate the association between the CF and the RV in Spanish-speaking children with DS compared to typically developing (TD) children of the same RV level. A group of 14 children with DS (9 males; mean chronological age=11.14 years; SD=2.41) and a control group of 14 TD children (9 males; mean chronological age=3.09 years; SD=0.67) were evaluated with the Card Sorting Task (CST) extracted of the Frontal Lobes and Executive Functions Battery BANFE, as well as the Peabody Picture Vocabulary Test (PPVT-III). Furthermore, the parents of the TD children were asked to complete the MacArthur-Bates Communicative Development Inventories (CDI), and the parents of the children with DS an adaptation of the CDI to the developmental profile of children with DS (CDI-DS). The results revealed that in children with DS, neither the RV from the PPVT-III ($r=0.152$, $p=0.605$) nor the RV from the CDI-DS ($r=0.458$, $p=0.183$) correlated with the perseverations of the CST. In contrast, in TD children the correlation between the RV from the PPVT-III and the perseverations of the CST approached significance ($r=0.464$, $p=0.095$), but not the RV from the CDI ($r=0.316$, $p=0.293$). Moreover, the RV from the PPVT-III correlated significantly with the normal errors of the CST ($r=-0.574$, $p<0.05$). No significant differences between groups were found in the perseverations ($t(26)=0$, $p=1$), the correct responses ($t(26)=1.227$, $p=0.231$) or the normal errors of the CST ($t(26)=-0.856$, $p=0.400$). In conclusion, our results showed that in children with DS the RV and the CF are not linked. In contrast, in TD children our results suggest a relationship between the RV and the CF. Also, the developmental level of CF is the same for the children with DS and TD children when the RV corresponds to 2-4 years old. Intervention strategies centered in executive functions improvements such CF are deem prudent.

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21 - Cognitive function and Thrombospondin-1 (TSP-1) levels in Down syndrome

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Down syndrome (DS) is the main cause of mental disability. Deficits in processes of attention, verbal memory, expressive language and executive functioning (EF) have been described in people with DS. Thrombospondin-1 (TSP-1) is the major component of blood platelets and it is highly expressed during development of the central nervous system. DS brains show a reduction in TSP-1 levels affecting the morphology and density of dendritic spines. These changes could be affecting neural circuits involved in cognition. However it is unknown whether TSP-1 levels in blood correlate with cognitive deficits in DS. Twenty-two 7-28 year-old participants (13 males and 9 females) with DS were evaluated with the neuropsychological test NEUROPSI Attention and Memory. Blood samples of participants were obtained to assess TSP-1 levels by ELISA immunoassay (R & D System). The relationship between TSP-1 levels and NEUROPSI Attention and Memory scores was evaluated performing Spearman correlations. Our results show an inverse correlation between the levels of TSP-1 and performance on Fluency Nonverbal subtest, $r = -.894$ ($p = .041$), and Verbal Recognition Memory subtest. We also encountered an inverse relationship between the levels of TSP-1 and Categories $r = -.538$ ($p = 0.071$), Semantic Verbal Fluency $r = -.754$ ($p = 0.084$), and Phonological Verbal Fluency (FVF) $r = -.736$ ($p = 0.096$) scores. Our results suggest that higher levels of TSP-1 in plasma are associated with lower cognitive performance, while lower levels of TSP-1 are associated with a better cognitive performance in people with DS.

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22 - Exploring EEG resting-state brain activity in young adults with Down syndrome: How alpha band activity relates to cognitive abilities

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Brain activity in the alpha band is associated with IQ performance as well as specific learning and memory processes in the general population. It has been suggested that impaired cognitive abilities in individuals with Down syndrome (DS) may be related to atypical alpha band activity (including power, frequency and topographical properties); however conflicting results have been reported, particularly in relation to younger adults with DS. We aimed to explore individual differences in alpha band properties (e.g. individual alpha peak frequency) and their relationship with cognitive abilities in younger adults with DS using resting-state electroencephalography (EEG), and will report cross-sectional data from 35 adults aged 16-35. Exploring alpha band properties may be important for understanding brain development, brain maturation and cognitive decline in DS, as well as for identifying potential EEG characteristics indicative of decline (biomarkers). Future work will involve exploring the effect of ageing, cognitive decline, brain connectivity and network architecture in adults with DS.

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23 - Initial findings from The London Down Syndrome Consortium (LonDownS): an integrated study of cognition and risk for Alzheimer's Disease in Down Syndrome

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London Down Syndrome Consortium (LonDownS) is a large, multi-disciplinary project investigating cognition and risk for Alzheimer's disease in Down syndrome. Our aim is to examine cognitive and behavioural phenotypes (including dementia status) in relation to genetic and cellular data. We will additionally have access to detailed medical histories and socio-demographic information. Here we will present initial phenotypic data from our first 110 older (36 years and over) and 70 younger (35 years and younger) adults, including the psychometric properties of our cognitive assessment battery based on the Arizona Cognitive Test battery (ACTB).

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24 - Response to Hepatitis B vaccination is less well sustained in Down syndrome children

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Background: Several studies describe lower responses to vaccination in Down syndrome (DS). Post-vaccination titers after routine hepatitis B (HBV-)vaccination are adequate but lower in DS; long-term follow-up data on anti-HBs-titer in DS are lacking.

Objective: To compare long-term anti-HBs-titers and prevalence of long-term post-vaccination adequate HBV-protection (anti-HBs-titer ≥ 10 IU/l) in DS versus non-DS children.

Methods: Retrospective study in the Jeroen Bosch Hospital (JBH) 's-Hertogenbosch, Máxima Medical Centre Veldhoven, the Netherlands, and University Hospital Antwerp, Belgium. Parents (n=398) were contacted by mail; 120 parents gave informed consent. Of these stored serum of 100 DS-children was available; 81 of these DS-children were HBV-vaccinated (parental information). The anti-HBs-titer was determined by chemiluminescence-immunoassay (UniCel-Dxl-600; JBH). Results were compared to literature data of non-DS children [Zanetti et al. 2005].

Results: All 0-2-year-old vaccinated DS-children had an anti-HBs-titer of ≥ 10 IU/l (geometric mean (GM) 254.5 IU/l; 95%-CI: 117.1-552.8). Over time, titers rapidly decrease to a GM of 5.9 IU/l (95%-CI: 2.9-11.9) in DS-children aged ≥ 7 yrs. In non-DS children 2 in 3 had adequate protection for >10 yrs with a GM of 32.1 IU/l; 95%-CI: 28.6-36.0. In children with DS ≥ 7 yrs, only 1 in 3 had maintained a long term protective anti-HBs-titer.

Discussion and conclusion: Recently, impaired adaptive immunity is described in DS; this might be causally related to the fast decrease in HBV-titer we found in this DS cohort. Follow-up studies are needed to determine the maintenance in anti-HBs-titer after booster vaccination and to decide whether decreased levels found in this study are clinically relevant enough to advise routine follow-up titer(s) with booster vaccination(s), in DS.

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25 - Allergy and asthma less common in Down syndrome

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Background: The recurrence of wheezing and airway infections in – especially younger – children with Down syndrome (DS) regularly leads to the presumption of atopy and/or asthma/bronchial hyperreactivity (BHR). In general – in non-DS – the absence of allergic sensitization has a high negative predictive value for clinically relevant allergy.

Objective: Determine whether the prevalence of allergic sensitization, defined as ≥ 1 allergen-specific IgE-titer $\geq 0,35 \text{ kU/l}$, is lower in children with DS compared to children without DS.

Methods: Retrospective study in the Jeroen Bosch Hospital (JBH) 's-Hertogenbosch, Máxima Medical Centre Veldhoven, the Netherlands, and University Hospital Antwerp, Belgium. Parents ($n=398$) were contacted by mail; 120 parents gave informed consent, of these stored serum of 96 DS-children was available. Allergy-related complaints were evaluated using medical files and a short questionnaire. Sensitization was determined using inhalation- and food mixes with determination of specific IgE's on positive mix results (Immulite-2000 XPi; JBH). Results were compared to literature data of non-DS children [Schmitz et al. 2013].

Results: Allergic sensitization (≥ 1 allergen-specific IgE-titer $\geq 0,35 \text{ kU/l}$) was present in 6,3% (95%-CI: 1,3-11,2) children with DS; often with low specific IgE-titers. In control children without DS 40,2% (95%-CI: 39,0-41,4) are sensitized. Inhalation medicine was prescribed to 40,9% (95%-CI: 31,7-50,0) of DS-children as maintenance treatment; in 80,9% (95%-CI: 69,2-92,5) this treatment was already ceased. More than 35% of DS-children >2 years had received diagnostic tests for specific IgE.

Conclusion: Allergic sensitization is uncommon in DS; the seldom long-term use of inhalation medicine makes the diagnosis of asthma in DS unlikely. When allergy/asthma is presumed in DS, it is recommended to consider other causes before initiating diagnostic tests or treatment.

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26 - Defining quality in chronic care: the case of Down syndrome

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Background: Down syndrome (DS), or (partial) trisomy 21, is associated with a broad variety of medical problems. The care chain around DS is challenging and complex, involving numerous professionals. This requires planning, coordination of care and adequate age- and service-related transitions. The current quality is unknown. Quality indicators have the potential to improve clinical decisions at individual and organizational levels. **Objective:** Review of the literature on indicators that assess clinical and organisational quality of medical DS-care and/or Intellectual Disability (ID) care in general.

Methods: In November 2014 we systematically searched six databases (PubMed, EMBASE, Web of Science, CINAHL, PsycINFO, Google Scholar), using predefined inclusion and exclusion criteria. Studies concerning the development, implementation and/or evaluation of quality indicators in ID-care were included.

Results and discussion: Fourteen out of the 915 initially retrieved studies could be included, with data originating from questionnaires (patient/family/staff), medical files and/or national databases. Most studies developed and/or measured indicators in a multidisciplinary manner with relevant stakeholders, some of which used focus groups to include people with ID. Quality indicators specific for DS-care have not been published to date; 22 indicators of ID-care were identified which have potential relevance towards DS-care. Existing indicators in ID-care predominantly focus on support services instead of medical care. In addition, they solely seem to focus on structure and processes that do not necessarily lead to desired, qualitative health outcomes at individual levels. They measure inputs more than results. Furthermore, they tend to evaluate single organizations rather than integrated total care cycles.

Conclusion: Though the DS-care supply chain is continuously evolving with new organizational strategies, questions on quality of care remain. Therefore, an indicator set specific for DS is needed. Future indicators should preferably be patient-centered and outcome-oriented, including user-perspectives, while developed in a multidisciplinary way to achieve successful implementation. We intend to develop a compact set of indicators to evaluate and monitor the quality of the DS-care cycle as a whole. This set can also provide an example for other chronic care settings.

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27 - Studying risk and protective factors that might link Down syndrome in children aged 4 to 16 years to subsequent Alzheimer's disease

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Introduction: Down syndrome (DS) is caused by the presence of an extra chromosome 21, where the amyloid precursor protein gene lies. This gene produces amyloid protein, the main component of β -amyloid plaques that, along with hyperphosphorylated neurofibrillary tau tangles, make up the pathological brain characteristics of Alzheimer's disease (AD). Almost 100% of people with DS will develop this brain pathology but, although there is higher rate of AD than the typically developing population, (around 50% age 50 display symptoms), it never reaches full penetrance (Lai & Williams, 1989). This study investigates the presence of individual differences that increase or decrease the likelihood of individuals with DS developing AD.

What makes this project different from so many investigating neurodegeneration is that fact that we are studying children. Although this may seem counter-intuitive for an adult onset condition, the genetic nature of DS ensures that the changes leading to potential AD are present from conception; indeed, β -amyloid deposition has been observed in children with DS from aged 8 onwards (Lemere et al, 1996; Leverenz & Raskind, 1998). Additionally, individual differences in DS are observed as early as infancy (Crawley & Spiker, 1983), demonstrating the potential for childhood to contain information about the changes occurring in the human brain prior to symptom onset.

Materials and Methods: Seventy children with and seventy without DS have been recruited, between the ages of 4 and 16 years. These individuals were assessed for genetic, neural, cognitive, behavioural, and environmental factors, in order to create rich individual profiles and to compare these to identify genetic links to altered behaviour or phenotypic alterations linked to atypical neural pathways.

Results: I present the preliminary results of our analysis of the first 16 months of research, such as the reversal of target looking time over age in DS compared to TD, significant memory task individual differences, and interesting trends found in data so far.

References:

- Crawley, S. B., & Spiker, D. (1983). Mother-Child Interactions Involving Two-Year-Olds with Down Syndrome: A Look at Individual Differences. *Child Development*, 54(5), 1312–1323. doi:10.2307/1129684
- Lai, F., & Williams, R. S. (1989). A prospective study of Alzheimer disease in Down syndrome. *Archives of Neurology*, 46(8), 849–853.
- Lemere, C. A., Blusztajn, J. K., Yamaguchi, H., Wisniewski, T., Saido, T. C., & Selkoe, D. J. (1996). Sequence of deposition of heterogeneous amyloid β -peptides and APO E in Down syndrome: implications for initial events in amyloid plaque formation. *Neurobiology of Disease*, 3(1), 16–32.
- Leverenz, J. B., & Raskind, M. A. (1998). Early Amyloid Deposition in the Medial Temporal Lobe of Young Down Syndrome Patients: A Regional Quantitative Analysis. *Experimental Neurology*, 150(2), 296–304. doi:<http://dx.doi.org/10.1006/exnr.1997.6777>

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28 - Association between levels of neuroproteins, neurotrophins and cytokines and adaptive and cognitive development in children with Down Syndrome.

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We previously performed a case-control study to clarify the role of neuroproteins, neurotrophins and cytokines in a large cohort of Down syndrome (DS) children (n=187) compared to normally developing children (n=90) and we established a statistically significant increased levels of VIP, IL-6 and IL-8 in DS children that may be involved in molecular basis of impaired neurodevelopment, although their precise roles and interactions still need to be clarified. Thus, we decided to investigate the association between altered levels of neuroproteins, neurotrophins and cytokines and adaptive and cognitive development in DS children. A subgroup of children with DS (n=120) was considered to quantify their adaptive and cognitive development using the Vineland Adaptive Behavior Scales (VABS), Griffiths Mental Developmental Scales (GMDS) and the Wechsler Intelligence Children Scale IV (WISC-IV).

The subjects of this study were 120 children between 12 months and 15 years of age. Strict exclusion criteria were adopted to avoid fluctuations of peptides levels due to inflammatory processes or infections. Patients underwent a detailed anamnestic pediatric evaluation; so all comorbidities were registered. A peripheral blood sample of about 10 mL was drawn from each child and immediately processed for the isolation of plasma and of peripheral blood mononuclear cells (PBMCs). Plasmatic levels of NGF, BDNF, IL-6, IL-8 and IGF-1 were measured using a double-antibody immunoaffinity assay (Luminex), while mRNA levels of the neuropeptides (VIP, ADNP, ADNP2) was assayed in PBMCs by quantitative Real Time-PCR. Concerning cognitive development, 18 children (12-23 months) were evaluated with the GMDS 0-2 and 44 children (2-6 years) with the GMDS 2-8. WISC-IV was used to test 58 children between 10 and 15 years of age. For children older than 18 months, adaptive functions were evaluated by administering the VABS to a parent.

IGF1 plasmatic level was found to be correlated with cognitive Z scores (Spearman rho= -0.62, p value< 0.0001), cognitive communication Z scores (Spearman rho= -0.7, p value< 0.0001) and adaptive ratio IQ (Spearman rho= 0.37, p value= 0.0086), only in young children (12 months-6 years). Also BDNF plasmatic level was shown to be weakly related with adaptive communication ratio IQ both overall (Spearman rho= 0.25, p value= 0.0154), in young children (12 months-6 years) (Spearman rho= 0.33, p value= 0.0254). Other biomarkers were not significantly related with any score. Firstly in literature, we investigated the association between these biomarkers and development in DS and the only correlations were found in young children between IGF-1 and BDNF with cognitive and adaptive abilities. Thus, the observed relation between IGF1 and BDNF plasmatic levels and cognitive and adaptive skills in young children could be due to a real effect of the biomarkers or to a variety of indirect effects such as age.

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29 - In vivo Test of a Novel Agent for Treating Interferon Related Cognitive Difficulties

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We have recently reported (J Interferon Cytokine Res. 34:510 2014) using a mouse model, systemic treatment with B18R, a potent vaccinia virus interferon-alpha (IFN-alpha) inhibitor, can reduce the aberrant brain mononuclear phagocyte activity and diminish dendritic abnormalities associated with HIV brain infection. These studies demonstrated that B18R is a stable, non-toxic agent that can pass through the blood brain barrier and down-regulate the interferon system in the brain.

IFN-alpha activity in the brain was assessed using rtPCR of IFN-alpha-induced signature gene mRNA. Brain IFN α 4, IFN α 15, and ISG15 mRNA levels were all significantly increased in HIV treated animals ($p < 0.05$) and significantly returned to near control levels by B18R treatment ($p < 0.05$). Mononuclear phagocytes were measured using CD45 staining and densitometry. Densitometry of mononuclear phagocyte staining that was elevated by HIV was significantly returned to control levels by B18R treatment ($p < 0.05$). Dendritic loss was measured using MAP2 staining and densitometry. Significant return to control arborization levels was observed in the B18R treated animals ($p < 0.05$). Aberrant mononuclear phagocyte increases and dendritic simplification are similarly seen in the Down syndrome brain suggesting that HIV associated cognitive difficulties may share aspects of its etiology with Down syndrome. To treat either of these conditions a new agent is needed since all previous related studies have used polyclonal anti-IFN-alpha antibodies or anti-receptor antibodies that are not practical for use as human therapeutics.

Evidence continues to accumulate implicating IFN-alpha in the etiology of cognitive difficulties. In addition to the presence of the receptor genes, there are a number of brain related genes on chromosome 21 that have interferon response elements. These could contribute to the interferon hypersensitivity of trisomy 21 cells. Transgenic mice that over express IFN-alpha in the brain show neurodegenerative pathology. Patients treated with IFN-alpha can have cognitive difficulties. IFN-alpha levels correlate with AIDS dementia severity and a recent report suggests that reducing interferon action can reduce symptoms in a mouse model of Aging Related Cognitive Decline (Science 346:89 2014). Taken together, these observations suggest that a systemically available IFN-alpha inhibitor may be of value for the treatment of the cognitive difficulties associated with Down syndrome.

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30 - Detecting psychopathological profile in genetic syndromes: a comparison of Williams syndrome and Down syndrome

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The high psychopathological vulnerability in people with intellectual disability (ID) has received few attentions in research and it is still to clarify whether the psychopathological phenotype varies greatly despite a common diagnosis of ID. The study have addressed the issue of psychopathological profile of individuals with Down syndrome (DS) and Williams Syndrome (WS). We adopted a semi-structured interview and a psychiatric examination to assess Anxiety disorders, Behaviour disorders, Mood disorders and Psychosis. A wide sample of individuals with DS (112) and with WS (85), matched for chronological and mental age, were compared on the prevalence of psychopathological disorders. The interaction between psychiatric symptom clusters and the effect of age were also investigated. Results showed that rate of psychopathological disorders in the group with DS was lower than in the group with WS. Anxiety was the most prevalent disorder in each group. However, when comparing the two groups, the rate of Anxiety disorder in participant with DS was significantly lower than in participants with WS. In addition, the rate of Psychosis was lower in participants with DS than with WS. The data suggest that Anxiety disorder in individuals with DS is less common than in other population with ID and that the effect of unknown resilience factors associated with DS may protect against the development of Psychosis.

The psychiatric profile, however, changed by age since Anxiety disorder was lower in individuals with DS compared to WS in young age, while Psychosis in old age. Moreover, distinct Behavior and Anxiety disorder subtypes emerged between groups. In the group with DS, Anxiety disorders subtypes were more equally distributed, while in the group with WS there was the highest prevalence of Simple Phobia and Generalized Anxiety disorder. Behavioral problems in individuals with DS have been mainly related to Oppositional Defiant disorder while an opposite profile emerged in the group with WS, exclusively characterized by ADHD.

Results indicate that the genetic etiology of ID differently affects the psychiatric characteristics of the groups. The differences in prevalence of psychiatric disorders between individuals with DS and WS justify a targeted care for psychiatric disease in these populations and healthcare professionals need to tailor focused psychopharmacological treatment and psychological support.

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31 - Cognitive development and adaptive functions in children with Down syndrome aged 12 months to 15 years

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Background. Few studies have focused on the adaptive behavior of children with Down Syndrome (DS) and its relationship with cognitive delay and they have reported controversial results: some authors have found that adaptive skills gradually and steadily increase until 30 years of age and that they follow cognitive abilities closely, only to surpass them in adolescence; whereas others have observed age-related gains in adaptive behavior in children aged 1 to 7 and no association between chronological age and adaptive behavior in older subjects (7 to 11.5 years).

Aim. To analyze the relationship between cognitive development and adaptive functions, and to assess their patterns of change with age in children with DS.

Materials and methods. 120 children with DS (from the outpatient Child and Adolescent Mental Health Clinic, San Gerardo Hospital, Monza, Italy), aged 12 months to 15 years. Cognitive development was evaluated using the Griffiths Mental Development Scales, GMDS 0-2 for 18 children between 12 and 23 months and GMDS 2-8 for 44 children between 2 and 6 years, and the Wechsler Intelligence Children Scale IV (WISC-IV) for 58 subjects aged 10 to 15 years. For the first group we calculated the ratio IQ ((mental age/chronological age) x 100), whereas for children older than 23 months we converted raw scores into z scores (raw score-mean) / standard deviation). Adaptive functions were evaluated by administering the Vineland Adaptive Behavior Scales (VABS) to one of the two parents. Besides age equivalents, ratio IQs (mental age/chronological age) both for the composite score and the communication domain were computed.

Results. A strong correlation between cognitive and adaptive mental ages for children up to 6 years (Pearson Rho 0.89, $p < 0.001$) and a moderate one between cognitive z scores and adaptive ratio IQ (Spearman Rho 0.51, $p < 0.001$) were observed. Moreover, both for cognitive and adaptive scores we found a strong correlation between composite scores and communication sub-scores (0.83 and 0.8 respectively, $p < 0.001$). Adaptive mental age increased across the years, along with variability of the scores, whereas the adaptive ratio IQ did not show any change across ages, except for children up to 35 months, for whom it showed to be significantly higher than in older children. Adaptive mental age was higher than the cognitive one, even though this could be assessed only for children up to 6 years.

Discussion. Adaptive functions of children with DS were correlated with their cognitive skills, although adaptive abilities were significantly higher than cognitive functions. In younger children, aged 12 to 35 months the gap with subjects with typical development was reduced compared with older children, for whom the ratio IQ resulted lower and stable across age classes.

Communication skills showed to play an essential role in adaptive functions, confirming the importance of the language domain in treatment plans.

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32- Calcineurin: A point of convergence or divergence in Alzheimer's disease and Down Syndrome?

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Hyperactivation of the Ca²⁺ dependent protein phosphatase calcineurin (CN) has been widely implicated as a causative factor in neuroinflammation, synapse dysfunction, amyloidosis, and neuronal death associated with Alzheimer's disease (AD). Many of these features are also found in Down Syndrome (DS), suggesting that elevated CN signaling is a common pathological mechanism in both disorders. This idea is seemingly bolstered by the fact that CN is a primary target of RCAN1 (Regulator of CALciNeurin 1), the gene of which is located on human chromosome 21, and consequently overexpressed in DS. However, numerous studies have shown that the forced overexpression of RCAN1 results in the inhibition of CN, suggesting that the status of CN signaling represents a key difference, rather than a common mechanism, between AD and DS (i.e. CN activity is increased in AD, but reduced in DS). Presently, the relative contribution of CN to AD and DS is complicated by putative positive feedback interactions between CN and RCAN1. For instance, induction of RCAN1 is robustly stimulated by CN-dependent transcription factors (e.g. NFATs), while the role of RCAN1 as CN inhibitor may flip to enable or facilitate CN activity under unique conditions, depending on the presence of other accessory proteins. Ongoing work from our research group is using human postmortem autopsy samples collected from individuals at different ages with DS (3 months-68 years) and contrasting those with and without AD neuropathology to establish the lifespan changes in CN signaling and its relationship to other major DS biomarkers including beta-amyloid plaques, neurofibrillary tangles, synapse protein losses and neuroinflammation. By comparing DS with AD to sporadic AD cases, this work will establish whether CN signaling is a major point of convergence or divergence in AD and DS and may lead to new approaches for interventions that may prevent or reduce AD in DS.

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33 - Metabolic aging in Down syndrome: a potential trigger for several diseases

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Background: alterations in one carbon metabolism in Down syndrome (DS) can be a result of additional copy of cystathionine beta synthase. Alterations in phospholipids (PLs) can be triggered by choline or S-adenosylmethionine and can trigger accelerated aging and amyloid beta 42 accumulation. Methods: We investigated plasma concentrations of metabolites of the methionine pathway, the main PLs classes, and choline metabolites in relation to plasma amyloid beta 42 in blood samples from 35 people with DS and 46 controls of similar age. PLs were also tested in platelet extracts from a subgroup of 24 DS and 14 controls. Results: Plasma concentrations of homocysteine were lower and choline and amyloid beta 42 were higher in individuals with DS compared to the controls. Compared to the controls, people with DS had higher plasma concentrations of several PL species (PCs, LPCs, PEs, SMs). Also extracts of blood platelets showed significantly higher concentrations of several PC, PE and SM species in DS compared to non-DS individuals. The ratio of SM16:1/PC38:4, SM18:1/PC38:4, and that of SM18:0/PC38:5 were significantly higher in plasma of DS compared to non-DS participants. Plasma concentrations of amyloid beta 42 correlated to levels of different SM species in individuals with DS. A higher S-adenosylmethionine/s-adenosylhomocysteine ratio (more methyl groups available) was associated with higher PL concentrations (probably via inducing PEMT pathway). Discussion: individuals with DS showed a dysbalance in the methionine cycle, distinct lipidom profile in plasma and in cell extracts. The results suggest a role for nutritional factors in modifying the methylation and PLs profile in DS. The relevance to diseases like dementia, immune dysfunction and diabetes is discussed.

34 - Thyroid Hormone Metabolism in Children with Down Syndrome

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Peirson Erica (1)

Nearly every child with Down syndrome struggles with thyroid hormone function to some degree. Many studies exist seeking the connection between the very similar symptoms for Down syndrome and hypothyroidism. It is imperative for their health and development that proper assessment of thyroid hormone function be a part of the healthcare management of every child with Down syndrome.

Particularly noteworthy is an elevated reverse T3 that is often seen by this author. It has been stated that "high serum rT3 concentration in the newborn becomes comparable to that in the normal adult by 9-11 days of neonatal life." However, this author often sees reverse T3 that is elevated, sometimes drastically, in infants with Down syndrome who are 3 months old and older. The major causes of an elevated reverse T3 include:

1. Elevated oxidative stress
2. Inflammation
3. Aberrant cortisol levels
4. Anemia
5. Nutrient deficiencies

Children with Down syndrome, unfortunately, can experience all of these, especially elevated oxidative stress. In addition, the similarities of the symptoms of congenital hypothyroidism and Down syndrome cannot be ignored. The consequences of hypothyroidism in a child whose biochemistry is already contributing to impaired cell function are devastating.

There is a great need for more research in the area of complete thyroid hormone function in children with Down syndrome, autism and other neurodevelopmental disorders. Given that thyroid hormone function is much more complicated than the function of thyroid stimulating hormone (TSH) alone, studies looking at reverse T3 levels, thyroid antibody levels, thyroid receptors and subtle variations in T4 and T3 levels need to all be conducted.

This presentation will include the highlights of what we know at this point about thyroid hormone function in children with Down syndrome, how we can optimize thyroid hormone function and how to use exogenous thyroid hormone to ameliorate the phenotype of Trisomy 21. It will also include some amazing case reports of children and infants with Ds who have been helped by the use of thyroid hormone optimization in ways that many never thought was possible.

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35 - Identification of candidate serum protein bio-markers in Down's syndrome for detection of pre-clinical dementia

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Background:

Down syndrome (DS) individuals with trisomy 21 have an increased risk of developing early-onset Alzheimer's disease (AD). Amyloid plaques are a pathologically defining feature of AD neuropathology and are well established before a clinical diagnosis of AD can be made. The detection of pre-symptomatic AD when potential disease-modifying therapeutic interventions are most likely to yield benefit can be achieved by developing biological markers that can serve as supportive early screening detection of AD before it is clinically evident.

Methods and results:

Blood samples from well characterised DS subjects (n=50, age 39 ± 26 years) who have had brain positron emission tomography (PET) to detect fibrillar amyloid-beta using [^{11}C]-Pittsburgh Compound-B-PET scanning and from age matched controls (n=50) were analysed. A centrifugation method was developed to isolate fibril binding proteins from serum. Gel electrophoresis, mass spectrometry peptide fingerprinting identified eighty-five proteins represented by multiple tryptic peptides, twenty of which showed significant differences between DS and controls. Western analysis revealed twelve proteins that differentially expressed in the DS group compared to controls: transthyretin, cystatin-C, ceruloplasmin, afamin, alpha-1-microglobulin, apolipoprotein C-II, apolipoprotein E, serum amyloid-P, hemopexin, neuronal pentraxin receptor, hepcidin and defensin were significantly up-regulated and clusterin and retinol binding protein 4 were significantly down-regulated. Many other proteins identified were involved in immune regulation, epigenomics and mitochondrial stress.

Conclusion:

All differentially expressed proteins are candidate biomarkers for DS, providing opportunities for the development of early and non-invasive diagnosis. Understanding their known function can help in understanding the pathogenesis of AD in DS. Thus, hepcidin regulates iron homeostasis, apolipoprotein C-II regulates lipid metabolism, afamin carries the fat-soluble vitamins E, while transthyretin transports both thyroxine and retinol binding protein and seem to play an important role in the fibril formation in AD. As these are preliminary findings, follow-up experiments are needed for their evaluation.

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36 - Developing a new cognitive informant questionnaire for people with Down syndrome

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The London Down Syndrome Consortium (LonDownS) is investigating individual differences, including cognitive abilities, in people with Down syndrome. In particular, we are assessing memory and executive function abilities, both through informant questionnaires and cognitive assessments. Two of the informant questionnaires currently being used to assess cognitive abilities are the Observer Memory Quotient (OMQ) and the Behavior Rating Inventory of Executive Function (BRIEF). These questionnaires were designed for the typically developing population and some of the questions are therefore not suitable for people with learning disabilities. To overcome this issue, we have developed a new questionnaire that uses more applicable questions. The new questions were based on a range of different domains of memory, executive functioning (e.g. working memory and attention) and language abilities, using questions from the BRIEF, OMQ, Dementia for Learning Disabilities (DLD) and the Vineland Adaptive Behavior Scale as a starting point. Half of the questions were reverse phrased to reduce likelihood of response bias. Parents or carers of adults aged 16-45 were asked to complete the questionnaire. Any adults who had shown cognitive decline, as assessed using the CAMDEX-DS, were excluded. In total, we collected questionnaire ratings for 89 individuals. A second rater gave ratings for 31 participants. During the analysis, questions with poor discriminatory results or poor inter-rater reliability were removed. We then performed factor analysis, and were left with a set of questions that related to people's abilities. We also looked for correlations between questionnaire scores, IQ scores (assessed using the K-bit 2) and adaptive abilities (using the short Adaptive Behavior Scale). In the future, the questionnaire may have possible benefits for detecting improvements in clinical trials and cognitive decline.

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37 - Down syndrome and associated congenital anomalies

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Down syndrome is a common type of congenital anomaly plentifully studied since at least 150 years. However, the type and the frequency of congenital anomalies associated with Down syndrome are still controversial. The objectives of this study were to examine the major congenital anomalies present in infants and fetuses with Down syndrome. The material for this study came from 402,532 consecutive births of known outcome registered in our registry of congenital anomalies between 1979 and 2008. Of the 703 patients with Down syndrome, 659 (93.9%) had a regular trisomy 21, 24 (3.4%) were carrier of a translocation, and 19 (2.7%) were mosaic. Four hundred thirty five (62%) of the cases had major congenital anomalies. The most common congenital anomaly in Down syndrome is a cardiac defect. In the present material 323 (46%) of the cases had a cardiac anomaly. The most common cardiac anomaly was atrioventricular septal defect (43%) followed by ventricular septal defect (32%), patent ductus arteriosus (5%), coarctation of aorta (5%), and tetralogy of Fallot (3%). Forty two (6%) of the cases had a gastrointestinal anomaly recorded, duodenal atresia (76%), Hirschsprung disease (14%), and tracheo-esophageal atresia (9%) being the most common. Twenty seven (4%) of the Down syndrome patients had an obstructive anomaly of the renal pelvis, including hydronephrosis. The other most common associated anomalies were hypospadias, polydactyly, syndactyly, club foot, cataract, cleft palate, and omphalocele.

In conclusion, we observed a striking prevalence of total congenital anomalies and specific patterns of malformations associated with Down syndrome which emphasizes the need to evaluate all patients with Down syndrome for possible associated major congenital anomalies.

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38 - Biological Resources Center-BioJeL (CRB-BioJeL): an asset for the Down Syndrome Research.

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Jérôme Lejeune Foundation's activities are concentrated around genetic intellectual disabilities research. It also supports the Jérôme Lejeune Institute.

The Institute's major objectives are focused on medical consultation, biomedical research and formation.

On December 2008, the biobank BioJeL and its dedicated lab were created to develop research activities and to offer a specific tool to the scientific community.

The CRB-BioJeL project acts for collecting phenotypic data and collecting-transforming-storing validated biological samples.

80% of patients followed in Institute have Down syndrome.

Multidisciplinary skills of the medical staff allow the following up of these patients throughout their life.

Thus, the collected biological resources are attached with very rich phenotypic data.

Moreover, CRB BioJeL puts in a lot of effort around consents: all resources proposed to the scientific community are associated with a signed informed consent with respect to French law and guidelines.

A website presents CRB-BioJeL activities and the biological resources collections.

Around 4500 resources are available. There are 4 collections: 64% for Down syndrome, 22% for Non-Diagnosed Mental Retardation, 10% for Other Mental Retardations and 4% for Controls, with 32% of DNA, 25% of PBL, 20% of lymphoblastoid lines and 23% of plasmas.

Website address: www.crb-institutlejeune.com

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49 - Clinical trials for individuals with intellectual disabilities: methodological and ethical issues

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Clinical trials tremendously improved survival rate and life quality of patients with cancer or cardiovascular diseases. In children with prematurity, leukemia, and cystic fibrosis, these trials have led to unprecedented survival and improved health and developmental outcomes. Thus clinical trials are an urgent need for patients with cognitive impairment of genetic origin to improve their lives. However, for individuals with intellectual disability previously classified as mental deficiency or mental retardation (Down Syndrome for instance), clinical trials exhibit several specific problems: ethical issues, objective issues, and feasibility issues. Based on our experiences, in developing indicators of health, development, and functioning for multicenter trials, we will describe the challenges and opportunities required for addressing these issues.

Ethical issues are important for persons with intellectual disability who will not be able to give an informed consent. Thus, as already requested by laws in different countries, clear and understandable information must be patiently delivered to the parents (or to caretakers) who will have to give their consent for their child and when patients are smart enough to understand their condition even though they are affected, it seems mandatory (as requested in the French law) to ask for their signed consent too. Furthermore, as unexpected side effects may occur in such patients, it seems important to particularly weigh the risks of the studied molecule(s).

Objectives of such trials are important but also difficult to define. Which, if not all, of the cognitive functions needs to be improved the most ? Memory (short term, long term, working memory) ? Executive functions (strategies, concepts, attention, decision making) ? Language issues (oral, reading and written) ? Mathematical issues (counting, main operations, complex operations) ? Praxia (clothing, eating) ? Gnosia (recognition of faces, locations, melodies) ? Psychomotor behavior (limb and body coordination, visuospatial adjustment, reactivity) ? Psychosocial behavior (relationships, mood adjustment, empathy, autistic behaviors) ?

Once objectives have been defined, feasibility of the trial has to be addressed. Neuropsychometric scales do not measure all of the cognitive functions equally and are not available for all functions. Furthermore, many are defined for specific age ranges. This makes trials sometimes very difficult to organize and to set up. Issues pertaining to the drug and the placebo production may also hinder the trial. Finally, recruitment and inclusion, because of exclusion criteria, may be more difficult than expected. These issues are even more acute when multisite trials involving multiple countries, cultures, or languages are foreseen. Thus, an international collaboration of experts to determine robust judgment criteria and to validate them should be rapidly organized.

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40 - Contributions of a Specialty Center for Down Syndrome's patients

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We investigated what added value a Down Syndrome (DS) specialty clinic brings to the healthcare needs of children and adolescents with Down Syndrome. Such a clinic didn't exist in Italy, for that reason in December 2013 has born a new Down Syndrome Center, that is positioned within the Bambino Gesù Children's Hospital in Rome. During one day, children undergo a multidisciplinary evaluation by a general pediatrician, a nutritionist, an audiologist, an orthopedic, a cardiologist, an oculist, a dentist, an endocrinologist, and, when needed, other specialists. The healthcare process and supervision require a careful planning and organization given the complexity of procedures, their heterogeneity and the involvement of different stakeholders. We implemented a hospital project to optimize all processes in the clinical path of children with Down syndrome, and to support them at home. We developed a customer relationship management (CRM) platform to manage visits, diagnostic tests and specialist consultations. The platform allows to set specific time slots for each procedure which is planned according to internationally recognized clinical guidelines. The platform also allows to manage different professional profiles as pediatricians, specialists, and nurses. Together with this platform, families of children with Down syndrome have been enrolled in a pilot study to test usability and function of a smartphone app. The functions of the app include personal diaries to monitor growth, blood pressure, oxygen saturation, or other clinical parameters, personalized reminders for immunizations, visits and drug assumptions, a GPS locator for monitoring return from school, and a video communication client for televisits. Data collected through the app are stored in a personal health record and are accessible by the hospital staff. We performed a retrospective chart review of 379 new patients with DS, on average 7.3 years old, seen during the inaugural year. We analyzed how many patients were up to date on the recommended DS healthcare screenings, the top concerns of their parents when coming to our center and the new diagnoses of comorbidities in patients with DS. Only 10,7% of our patients were current on all the recommended Down Syndrome healthcare screenings. Parents and caregivers wanted to discuss about to sleeping issues (85%), recurrent respiratory infections (83%), weight (79%), diet issues (62%), irregular bowel (55%). We made new diagnosis of hypodontia and delayed dental eruption (26%), refractive errors (20%), expressive language disorders (19,3%), overweight (16,8%), hearing loss (10%), obesity (10%), thyroid disease (2%), obstructive sleep apnea (2,5%), cryptorchidism (2,1%), celiac disease (2%), atlanto-axial instability (0,5%). A DS Center can identify and address many healthcare needs of children and adolescents with DS beyond that which is provided in primary care settings.

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41 - Sleep-disordered breathing in children with Down Syndrome: importance of the screening

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Introduction: In Italy there are about 48,000 people with Down Syndrome (DS); individuals with DS are predisposed to numerous comorbid diseases, many of which are preventable and treatable. The prevalence of sleep-disordered breathing (DRS) in DS patients is very high, estimated between 55% and 97%, moreover, complications of DRS are important and include cardiovascular, metabolic and neurocognitive diseases. For this reason, the latest guidelines from the American Academy of Pediatrics (AAP) recommend performing a sleep study in patients over the age of 4 years.

As part of the Down Syndrome Center at Bambino Gesù Children's Hospital in Rome, we screened all children with DS through "Obstructive Sleep Apnea-questionnaire" (OSA-18) and Night-time Pulse-Oximetry (PO).

Aims:The aim of the study is evaluate the epidemiology of DRS in order to refer patients to the appropriate treatment earlier.

Methods: We enrolled 53 patients (male: 34, mean age 8.42 ± 4.98 years, Body Mass Index (BMI): 19.73 ± 4.24). All patients completed the OSA-18 questionnaire and underwent PO and clinical examination and history, with particular attention to nocturnal sleep and anatomical cranio-facial characteristics.

Results: Patients with DS have mean SaO₂% of 92.72 ± 18.85 , ODI-10 2.37 ± 2.08 and ODI-0 of 2.85 ± 2.30 . 13 out of 53 patient, were positive at PO screening (mean SaO₂: $93.55 \pm 5.10\%$, ODI-10: 7.88 ± 6.24 , ODI-0: 7.17 ± 5.73) and underwent Polysomnography (PSG) to confirm and assess the entity of DRS. These patients had also a greater BMI (22.55 ± 6.36), compared with the group with negative PO (mean BMI 18.62 ± 3.69) ($p < 0.05$) and this confirms the importance of weight in the pathogenesis of DRS, also in DS. PSG showed moderate (Apnea Hypopnea Index >5 events/h of sleep) (61.44 %) and severe (Apnea Hypopnea Index >10 events/h of sleep)(38.46 %) Obstructive Sleep Apnea.

Conclusion: A careful evaluation of DRS in DS is necessary with at least one study of respiratory function of sleep in order to prevent and treat cardiovascular, metabolic and neurocognitive complications in this population at increased risk.

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42 - Non-invasive Prenatal Testing for Trisomy 21 and Trisomy 18 Based on Analysis of Cell-Free Fetal DNA Circulating in the Maternal Plasma

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OBJECTIVE: The aim of this study was to report the clinical performance of massively parallel sequencing-based noninvasive prenatal testing (NIPT) in detecting Trisomy 21 and Trisomy 18 in 2375 clinical samples. NIPT performance in low-risk pregnancies and high-risk pregnancies was also compared.

METHODS: From May 1, 2012 to April 31, 2013, 2375 pregnancies were offered with NIPT using low-coverage whole-genome sequencing of plasma cell free DNA. NIPT results were validated by karyotyping confirmation or follow-up of clinical outcomes.

RESULTS: In 2375 cases, NIPT results were obtained in 2358 cases; 13 cases were classified as positive, including 8 cases of trisomy 21, 5 cases of trisomy 18, and all the cases were confirmed by karyotyping. Sensitivity and specificity for detection of trisomies 21 and 18 and 13 were 100%. Additionally, NIPT revealed one case with "Extra genetic material derived from chromosome 9", and cytogenetic analysis of amniotic fluid confirmed it a mosaic tetrasomy 9p.

CONCLUSION: Noninvasive prenatal testing allows a more suitable and efficient workflow for our patients' needs, together with invasive procedures allows a higher prenatal detection of chromosomal aneuploidies.

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43 - Medical and Parental Attempt to Bring Science to Everyday Life of a Person with Trisomy 21 - a Preliminary Strategy

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There is an abundance of scientific data pointing both to a complexity and diversity in dysfunctions associated with trisomy 21 and consequently proposing numerous potential targets for supplements, drugs and dietary (life-style) intervention.

Based on data available in literature, the results of preclinical and clinical studies, as well as parental observations, we set up a working strategy (to be discussed) of a pharmaceutical and life-style approach to persons with trisomy 21. The pharmaceutical approach comprises the application of EGCG, curcumin, Gingko Biloba, fluoxetine, L-thyroxine (if needed), Q10-ubiquinol, vitamin D3, vitamin E, melatonin, Se, Zn, Mg, B vitamins (also in a methylated form if needed) and synbiotics.

Known and suggested contraindications to medicines and supplements used will be discussed along with dosages for various ages.

The life-style approach focuses on providing the patient with a diet characterized by appropriate amounts of macro- and micronutrients with special emphasis on omega3 fatty acids, folic acid, vitamin B12, betaine, choline, antioxidants including polyphenols, fiber and probiotics. Also, a reduction in the amount of pro-inflammatory and allergen-containing foodstuffs is implemented. The life-style approach also includes physical activity and adequate BMI, both of which also reduce pro-inflammatory condition and affect the patient's mental state.

The individualization of the approach being proposed is based on a number of laboratory tests. These include complete blood count, plasma: glucose, lipid profile, transferrin, methylation pathway profile, Se, Zn, Mg, folic acid, B12, 25(OH)D3, liver and thyroid function, celiac disease and food intolerance tests along with gut bacterial flora, candida infection, and methylation pathway SNPs profile.

The proposed "treatment" makes it possible to address both functional and morphological abnormalities and therefore reduce both the mental and physical consequences of the overexpression of chromosome 21 located genes and epigenetic abnormalities (DNA methylation), neurotransmitters dysregulation, mitochondrial dysfunctions, oxidative stress, pro-inflammatory conditions, and leaky gut syndrome. Hence, the discussed multi-target intervention can increase intellectual, physical and social activity and also reduce the incidence of comorbidities common in people with trisomy 21.

The aim of this presentation is to provoke a fruitful discussion among scientists and specialists that could result in the formulation of clinical advice directed to parents and medical practitioners dealing with trisomy 21 patients. This could help overcome the common misconception by both parents and healthcare providers who believe that nothing can be done to improve the quality of life of people with trisomy 21.

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