

- **The person's current involvement in research in intellectual disabilities**

Dr. Giorgio Albertini, Chief of the Department of the “Child, Adult, Aging Developmental Center” of San Raffaele Scientific and Research Institute in Rome and Scientific Director of San Raffaele Cassino, follows a multi-disciplinary approach to patient care that involves the expertise of physicians and nurses, as well as other health professionals such as, dietitians, child developmental evaluation specialists like psychologists, physical, speech and occupational therapists, educators who work as a team together with scientific researchers to ensure the best treatment for children and adults with developmental disabilities.

### 1) Neurological studies

With this aim the scientific group of Prof. Albertini is devoted to investigate brain intellectual disabilities, such as Down syndrome, cerebral palsy and autistic spectrum disorders, in young people, aging from infancy to late adolescence in a life span perspective.

Brain anatomy aberrations are highlighted by means of MRI voxel-based morphometry (VBM), that is able to afford a rapid and global survey of grey matter, white matter and cerebral spinal fluid abnormalities related to these disabilities. While functional brain features are studied using quantitative electroencefalography (qEEG) measurements, reflecting cortical activity, transcranial magnetic stimulation, a modern approach to stimulate the brain non invasively and painlessly that nowadays is also applied to a wide range of research and therapeutic areas.

Another important field of interest is represented by studies in children with Cerebral Palsy (CP) (one out of 500 newborn in Italy). CP affects movement and posture and is caused by brain damage before, during, or after birth. Treatment of CP varies with the age of patients, and many options are now available.

Prof. Giorgio Albertini is building up a cooperative team (together with the Università Cattolica del Sacro Cuore and Dr. Paolo Onorati, Università di Roma, La Sapienza) composed by neurosurgeons, pediatric neurologist, neurophysiologists and bioengineers with the aim to apply in Italy the Selective Dorsal Rhizotomy, an innovative surgical treatment of spasticity, performed by Dr T.S. Park, Neurosurgeon-in-chief at St. Louis Children’s Hospital, Washington University School of Medicine, USA.

### 2) Movement analysis :

One of the most important research field is the quantitative study of movement, in particular with the direction of the Gait Analysis Labs in IRCCS San Raffaele in Rome, San Raffaele Cassino and the new Gait Analysis Lab installed by Tosinvest in 2007 at the IBR, Staten Island, New York.

These studies are conducted in a strict scientific collaboration with the Bioengineer Department of Polytechnic Institute of Milan (Eng. Manuela Galli)

The main research fields in movement analysis are:

- Children and adults with cerebral palsy before and after treatments (Botulinum toxin, orthosis, baclofen pump, orthopaedic surgery,...)
- Children and adults with Down syndrome
- Patients with Parkinson disease

- Movement evaluation of animal model with Down syndrome.

Dr. Albertini and the IRCCS San Raffaele are actually involved in the EC program TRAMA project with Bioengineer Dept of Polytechnical Institute of Milan (which is the coordinator of the project).

### 3) Basic research

Our basic research activity in neuroscience started in 2001 as a collaborative effort between the Child Development Center, IRCCS San Raffaele Pisana Roma, the Department of Developmental Neurobiology at NYS Institute for Basic Research in Developmental Disabilities, New York, USA and the Department of Neuroscience, Mount Sinai School of Medicine NY

The main projects are:

- Proteomic approach to mouse model of Down Syndrome

Proteomic is the large-scale study of proteins, particularly their structures and functions. Proteins are vital parts of living organisms, as they are the main components of the physiological metabolic pathways of cells. The word "proteome" is a portmanteau of "protein" and "genome". The proteome of an organism is the set of proteins produced by it during its life, and its genome is its set of genes.

Proteomics is often considered the next step in the study of biological systems, after genomics. It is much more complicated than genomics, mostly because while an organism's genome is rather constant, a proteome differs from cell to cell and constantly changes through its biochemical interactions with the genome and the environment. One organism has radically different protein expression in different parts of its body, different stages of its life cycle and different environmental conditions. Another major difficulty is the complexity of proteins relative to nucleic acids. E.g., in human there are about 25 000 identified genes but an estimated >500 000 proteins that are derived from these genes. This increased complexity derives from mechanisms such as alternative splicing, protein modification (glycosylation, phosphorylation) and protein degradation.

Scientists are very interested in proteomics because it gives a much better understanding of an organism than genomics. First, the level of transcription of a gene gives only a rough estimate of its level of expression into a protein. An mRNA produced in abundance may be degraded rapidly or translated inefficiently, resulting in a small amount of protein. Second, many proteins experience post-translational modifications that profoundly affect their activities; for example some proteins are not active until they become phosphorylated. Methods such as phosphoproteomics and glycoproteomics are used to study post-translational modifications. Third, many transcripts give rise to more than one protein, through alternative splicing or alternative post-translational modifications. Finally, many proteins form complexes with other proteins or RNA molecules, and only function in the presence of these other molecules. Since proteins play a central role in the life of an organism, proteomics is instrumental in discovery of biomarkers, such as markers that indicate a particular disease.

Down Syndrome (DS) is the most common birth defect associated with mental retardation. However, it remains unclear how the extra copy of chromosome 21 leads to characteristic brain abnormalities (decreased number of neurons, abnormal cortical lamination, delayed myelination, synaptic changes and early Alzheimer pathology) causing cognitive and motor dysfunction. It appears that the DS phenotype can be regarded as an outcome of altered gene and protein homeostasis resulting from abnormal gene-gene and protein-protein interactions. Genome-wide analyses of DS transcriptome in humans and mouse models of DS revealed changes in expression of hundred of genes, also those located on diploid chromosome. As proteins are ultimate executors of biological functions, proteome of DS brain also was investigated. Among mouse model of DS that have been created to facilitate research into the pathogenesis of DS, Ts65Dn have been most studied. These mice have segmental trisomy for the 16Mb region of mouse chromosome 16 that extends from the Mrpl39 to the Znf 295 gene and encompassed a predicted 132 genes that are homologous to those located in 21q11 - 21q22.13 of HSA21.

Ts65Dn mice demonstrate several phenotypic features of DS such as craniofacial abnormalities, reduced neuronal density in the cerebellar cortex and dentate gyrus, age-related degeneration of basal forebrain cholinergic neurons, reduction in excitatory synapses in the temporal cortex, astrogliosis, and

learning and behavioural deficits. In addition Ts65Dn mice manifest several behavioural changes observed in individuals with DS: hyperactivity, deficits in spatial learning, and working and long-term memory. Hence, Ts65Dn mice appear to be useful to study the molecular mechanisms underlying DS brain phenotype and potential therapeutic interventions.

We hypothesized that by using a proteomic approach in the Ts65Dn mice model, we will be able to identify proteins differentially expressed in DS, which could allow us to unravel the pathomechanism of DS-specific brain dysfunction and damage. Our own proteomic approach to study pathogenesis of DS brain is based on a two-steps strategy. Our target was first, to isolate proteins differentially expressed in the brain of Ts65Dn mice in comparison with disomic littermates by using two-dimensional (2-D) electrophoresis followed by identification of protein spots by mass spectrometry (MS), and then to verify the proteomic data in mouse and human brain tissue by using Western blotting and immunocytochemistry. We believed that identification and assessment of protein expression using a proteomic approach was an important first step in understanding the molecular mechanisms leading to altered development and progressive neurodegeneration of DS brain.

#### - Relationship between learning/memory deficits and developmental neuronal plasticity in a model of Down Syndrome Ts65Dn mouse

Numerous studies showed that in rodents, housing of animals in enriched environment, thus exposing them to sensory, cognitive, motor and social stimulation or even a simple physical activity in a running wheel alone can cause behavioral, biochemical and structural cerebral changes throughout the life span. Enriched environment significantly improves learning and memory, enhances neurogenesis and/or survival of newly born neurons in the dentate gyrus (depending on the model of enrichment used) also in adult brain, increases synaptogenesis, development of dendritic spines and dendritic branches, gliogenesis and vasculogenesis. Molecular bases of these phenomena are not yet clear, but contribution of many genes/proteins implicated in brain development and plasticity emerges from studies performed to date. Enriched environment also significantly improves behavioral and motor deficits in animal models of several human disorders such as Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy, stroke, traumatic brain injury, and fragile X syndrome. In some of these animal models, also the disease progress was alleviated, and structural changes were less prominent and the levels of some factors associated with brain plasticity increased. Enriched environment also improves behavioural deficits in Ts65Dn female mice pointing to the preservation of the brain plasticity potential in these genetically compromised animals. Molecular factors that might contribute to this behavioural improvement in Ts65Dn mice have not yet been studied. We reasoned that if DS phenotype is associated with overexpression of genes located in triplicated chromosome as it is proposed by "gene dose effect" theory, then behavioural improvement should be paralleled with normalization/reduction of the increased levels of those proteins located in Down syndrome critical region (DSCR) that are engaged in learning/memory processes. Such a candidate protein is DYRK1

#### - Abnormal Expression of Synaptic Proteins in Down Syndrome mouse model

Down Syndrome (DS) subjects show deficits in learning and memory and cognitive functions in general. Morphological studies have revealed that over development, the brain of DS subjects show dendritic and spine structural alterations and cell loss. These defects concern many brain regions including the hippocampus, which is known to play a critical role in memory and cognition. Most of these defects are reproduced in the mouse model Ts65Dn, which is partially trisomic for the mouse chromosome 16. Thus, Ts65Dn is widely utilized to study DS abnormalities. In fact, this mouse shows several histological defects of DS, including alterations in synapse structure and cell number in the hippocampus and cortex, reduced volume and neuronal density in the cerebellum. In line with these alterations, it also shows impaired cognitive functions, including deficits in hippocampal learning and memory as well as deficits in hippocampal long-term synaptic plasticity. To better understand the molecular defects underlying the cognitive impairments of DS, we determined whether the expression of molecules known to play critical roles in long-term synaptic plasticity and long-term memory in a variety of species is dysregulated in neonatal brain and adult hippocampus of Ts65Dn mice. We found abnormal expressions of the synaptic proteins synaptophysin, MAP2 and CDK5 and the neurotrophin

NT-3. While some alteration was restricted to either age, others were maintained throughout development. These results suggest that a dysregulation in the expression of proteins involved in synaptic development and plasticity functions and neurotrophins seem to be a hallmark of the DS mouse model Ts65Dn, suggesting a potential role for these abnormalities in the neural pathology of DS in humans.

- **The person's experience within IASSID:**

Dr. Albertini is member of IASSID ever since many years, also as a council member, and he contributed to the creation of the “Journal of Policy and Practice in Intellectual Disabilities”

He has international relationship in different fields related to developmental disabilities, not only biomedical issues but also psychological and educational aspects.

- **The person's experience relevant to the role for which the nomination is submitted:**

Actual roles of Dr. Albertini that can be cited as part of the personal experience relevant for the nomination for IASSID President:

Chief of the Department of the “Child, Adult, Aging Developmental Center” of San Raffaele Scientific and Research Institute in Rome

Scientific Director of San Raffaele Cassino, a clinical and research institute that in going to be recognized as a new Scientific and Research Institute

Senior research associate at Institute for Basic Researches in Developmental Disabilities (IBR), Staten Island, New York

Previous vice president of Mental Health in Mental Retardation

Professor of Child Neuropsychiatry at University Rome 3, Faculty of Education

Author of scientific papers, has very often been invited as speaker for magisterial lesson in various topics of developmental disabilities.

- **The person's capacity to undertake the role between 2008 and 2012:**

Able and capable

- **The person's capacity to undertake the role between 2012 and 2016 should he or she be elected to another term (or the person's capacity to undertake the role of President-Elect between 2012 and 2016 should the person be nominated as President**

Able and capable

- **The person's goals for IASSID and the contributions to he or she could make :**

According to Dr. Albertini, IASSID is living now an expansive phase: it is being recognized as an important institution not only in Europe and North America, but also in South America and Asia and it will be recognized also in Africa with the next IASSID Congress.

Dr Albertini has always believed in the internationalisation of relationships and in his program he would continue in this direction, with the objective to integrate the biomedical aspects of people with intellectual disabilities with the other related disciplines (psychological, educational, social issues) and looking at basic and translational research (see CV)

A brief CV listing key scientific and professional achievements.

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