Roscoff (France), 7-11 octobre 2010

Le retard mental : des gènes aux synapses, fonctions et disfonctions

Mental retardation: from genes to synapses, functions and dysfunctions

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Rapport sur la Conférence

Conference Report

RESUME DU RAPPORT

Conférence Jacques Monod intitulée : Le retard mental : des gènes aux synapses, fonctions et dysfonctions

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Le retard mental (RM) est parmi les causes les plus communes de handicap d'origine génétique et, avec une prévalence de 1-3%, représente un des problèmes médicaux et sociaux majeurs. Les bases moléculaires et cellulaires du RM sont assez hétérogènes, comme suggéré par le grand nombre de gènes différentes, impliqués dans le RM, qui ont été identifies jusqu'à présent. Un des principaux défis du domaine est donné par l'étude fonctionnelle des gènes du RM qui devraient aboutir à l'identification de possibles thérapies, comme les travaux conduits jusqu'à présent sur les syndromes de l'X fragile et de Down l'ont démontré. De plus, plusieurs évidences suggèrent que les protéines qui causent RM puissent former des réseaux moléculaires. Donc, la recherche sur le RM pourrait amener à l'identification de molécules clé des voies de régulations qui contrôlent le développement du cerveau et de l'apprentissage. En partant de ces considérations nous avons organisé la conférence "Le retard mental : des gènes aux synapses, fonctions et dysfonctions" dans le but de faciliter la rencontre et l'échange d'informations entre les généticiens, qui sont surtout impliqués dans le clonage des gènes du RM, et les neurobiologistes, qui étudient la structure et la fonction des synapses et d'autres aspects qui peuvent être importants pour la compréhension du RM.

Cette conférence a eu lieu à Roscoff du 7 au 11 octobre 2010. Elle a réuni 99 scientifiques, dont 27 conférenciers invités et 72 participants (45 chercheurs ou professeurs ayant un poste statutaire, 16 post-docs et 11 étudiants) de 19 pays différents (Europe, Australie, Brésil, Canada, États-Unis).

La conférence a été structurée en 10 sessions, qui ont compris les présentations de 27 conférenciers invités (25 minutes plus 5-10 minutes de discussion) et 18 présentations plus courtes (10 minutes plus 5 de discussion) qui ont été sélectionnées parmi les abstracts. Deux sessions de posters ont eu lieu et 25 posters ont été présentés pendant chaque session. Toutes les sessions ont été remarquables avec des présentations de très haut niveau scientifique. Plusieurs travaux présentés oralement ou pendant les sessions poster n' étaient pas encore publiés au moment de la conférence ou, pour certains, présentés pour la première fois pendant une conférence.

Les organisateurs ont eu la nette impression que la conférence a été très appréciée par tous les participants. De plus, le fait que la plupart des participants soient des chercheurs confirmés montre le grand intérêt que cette approche nouvelle a suscité dans la communauté scientifique travaillant sur ce sujet. Le but initial a sûrement été atteint, et la discussion entre scientifiques ayant des formations/parcours scientifiques différents a permis d'identifier certains points clé pour développer la recherche dans le futur :

- Stratégies pour identifier de nouveaux gènes impliqués dans le RM.

- Identification de voies de régulations communes à plusieurs formes de RM. En particulier, plusieurs participants ont souligné la nécessité d'intensifier les études fonctionnelles sur les gènes qui causent le RM. D'ailleurs, le nombre des gènes du RM a augmenté sensiblement pendant les dernières années grâce aux techniques de séquençage de nouvelle génération.

- Rôle des interneurones dans l'apprentissage et le RM.

- Rôle du micro ARNs dans le RM.

- Identification des différents types d'épines dendritiques qui participent à la transmission synaptique.

- Rôle des altérations des réseaux dendritiques et axonales dans la physiopathologie du RM

- Définition de l'espace temporel idéale pour un traitement précoce du RM.

- Altérations des interactions protéine/protéine dans des complexes qui sont importantes dans la fonction synaptique et qui pourraient être à la base du RM.

CONFERENCE REPORT

Final report from the Jacques-Monod Conference entitled: Mental retardation: from genes to synapses, functions and disfunctions

Roscoff, October 7-11, 2010

1 – General description of the meeting

The Jacques Monod Conference « Mental Retardation: from genes to synapses, functions and dysfunctions » took place in Roscoff from Oct. 7 to Oct. 11, 2010.

Participants were 99 in total, among them:

-27 invited speakers (26 scientists with tenure position and one post-doc) were selected on the basis of their scientific excellence and proved experience in human genetics (cloning and characterization of genes involved in intellectual disabilities) or in aspects of neuroscience, such as structure and function of synapses or brain development, that are particularly important to unravel the neurobiology of ID. The female representation among the invited speakers was 29%.

-72 applicants selected upon abstract submission (45 tenure positions, 16 post-docs and 11 students). Females represented 55% of participants.

Considering all the participants, 19 countries were represented, as illustrated in the following table :

Country	Invited Speakers	Scientists (application)	Students (application)
France	10	33	3
Italy	2	6	1
USA	5	2	
Germany	2	3	1
Netherlands	2	1	3
Spain	1	3	1
Switzerland	2	1	
UK		2	1
Canada	1	1	
Poland		1	1
Portugal		2	
Australia	1		

Austria	1		
Belgium		1	
Brazil		1	
Bulgaria		1	
Estonia		1	
Finland		1	
Norway		1	
Total	**27**	**61**	**11**

The meeting was organized in 10 sessions of oral presentations (listed below) and two poster sessions:

- Introduction to the meeting and Identification of genes causing intellectual disabilities
- Synaptic function, receptors and neurodevelopment pathologies (part I)
- Fragile X syndrome: from genetics to treatment
- Mental retardation: from genetics to treatment
- Early neuronal development and intellectual disabilities
- Synaptic function: presynaptic aspects
- Structure and synaptic function (part I)
- RNA metabolism and intellectual disabilities
- Structure and synaptic function (part II)
- Identification and characterization of genes causing intellectual disabilities
- Synaptic function, receptors and neurodevelopmental pathologies (part II)

Each session was a mix of talks given by an invited speaker (25 minutes + 5-10 minutes of discussion) and short talks (10 minutes + 5 of discussion) given by participants whose presentation was selected on the basis of their submitted abstract. A total of 18 short oral presentations were selected based on the scientific interest of the subject and the consistence with the specific session of the meeting. The female representation among the selected speakers was 44%.

The chairperson of each session was selected as a scientist having a strong insight in the subject of the session and able to enhance the discussion on the topics.

The scientific quality of all talks was very high. Most of the data presented were not yet published at the time of the meeting and in some cases were presented for the first time at this meeting.

A total of 50 posters were presented during two sessions of 2 hours each; half of the number of posters was presented in each session. The scientific quality of the poster sessions was also very high and also in this case most of the presented studies were unpublished.

Mrs Dominique Lidoreau took perfectly care of the practical organization of the meeting and her support to the organizers was absolutely essential for the success of the meeting. The

technical support and the logistic offered by the Biological Station in Roscoff were strongly appreciated, as well as the accommodations in several hotels in Roscoff and the quality and variety of food served at the Gulf Stream Hotel.

We organized an excursion to the island of Batz on Saturday Oct.9 afternoon. This break during the meeting was also appreciated as an occasion for informal discussions.

CNRS provided the main funding to support the conference. Furthermore, the organizers received a substantial financial support by the **Jérôme Lejeune Foundation** and by the **Italian National Research Council** (CNR). We were also supported by several commercial sponsors: **Hybrigenics, Sutter Instuments, Chroma, Abcam and Eppendorf**.

During the conclusion of the meeting on Oct. 11 morning, Maria Vincenza Catania was confirmed chairman for the next conference. The election of the vice-president was not finalized at the meeting because some participants were potentially interested in being involved in the future organization of the meeting but at least one of them did not attend the last session of the meeting.

Considering that the large amount of non-invited participants were senior scientists (45 tenure positions), the organizers believe that the novel and original subject of the conference was appreciated and considered exciting by experienced scientists in the field. Moreover, the feedbacks received during and after the meeting confirmed the organizers' impression that the meeting had been a great success. Indeed, during the meeting many participants expressed their positive comments concerning both the scientific quality and the practical organization of this Jacques Monod Conference. Furthermore, after the meeting, some participants wrote or called to thank the organizers for the great opportunity that the meeting represented to improve the research on the field. In some cases they even described this Monod conference as the best meeting they attended.

2 - Report on scientific aspects.

Intellectual disability (ID) / mental retardation (MR) is among the most common form of genetic handicaps with a prevalence of 1 to 3 % and constitutes a major medical and social problem. The causes of MR are extremely heterogeneous, as it is suggested by the 440 ID genes that have been identified to date. A main challenge in the field is represented by functional studies that could eventually result in the identification of therapeutic strategies, as, for instance, shown by studies on Fragile X and Down syndromes. Furthermore there is accumulating evidence that MR genes/proteins form molecular networks. Thus, a consistent advancement in the identification of key molecular pathways that control brain development and cognition might result from research on ID.

Starting from these considerations we proposed a Jacques Monod Conference entitled "Mental Retardation: from genes to synapses, functions and dysfunction" during which geneticists involved in the search for MR genes, and neuroscientists involved in understanding structure and mechanisms of function of synapses as well as other aspects of neuronal functions potentially relevant for MR, might exchange information and propose alternative research strategies.

The meeting started with the an introduction to the cloning of genes involved in mental retardation, given by **Hans Hilger Ropers** (Berlin, Germany), who analyzed in a critical manner the different approaches leading to the identification of more than 90 ID genes only

on the X chromosome. In particular Dr. Ropers emphasized the results obtained by the introduction of next generation sequencing obtained by two different consortia.

The first session of the meeting "**Identification of genes causing intellectual disabilities"** was chaired by **Jozef Gecz** (Adelaide, Australia) and started with **Laurence Colleaux** (Paris, France) who explained the involvement of her laboratory in the cloning of genes causing autosomal recessive non syndromic ID, which was obtained by autozygosity mapping of the multiplex consanguineous families, and the functional characterization of these genes using cellular and animal models to define their impact on neuronal development. She illustrated in detail the cloning and characterization of the *neurotrypsin*, *N33*, *MED23* and *TRAPPC9* genes. All these genes emphasized the role of different cellular pathways in ID, showing the variety of processes that underpin these diseases. **Lucy Raymond** (Cambridge, UK) discussed a new approach to find mutations in X-linked intellectual disability (XLID) by analyzing the copy number variants in 251 families (with evidence of XLID) by array comparative genomic hybridization on a high-density oligonucleotide X chromosome array platform. This study resulted in the identification of four genes, *PTCHD1*, *WDR13*, *FAAH2* and *GSPT2* as candidates for XLID. **Annette Schenck** (Nijmegen, The Netherlands) talked about the approach of her lab that systematically investigates MR gene function using the fruit fly *Drosophila melanogaster* as a model organism. In particularly she detailed her work on the fly model of Kleefstra syndrome due to mutations on *Euchromatin histone methyltransferase 1* (*EHMT1*) gene. Interestingly, this study resulted in the identification by Chip-to-Chip analysis of genes that are putative targets of EHMT1 protein. **Guy Froyen** (Leuven, Belgium) found putative XLID genes by identification of pathological micro duplications. Two candidates, *HUWE1* and *GDI1,* were studied using primary rat hippocampal neurons as a cell model and fly as animal model. To close this section, an interesting approach was presented by **Ferdinando Di Cunto** (Torino, Italy) who presented the TS-CoExp, a user-friendly web resource that allows investigating conserved co-expression at multi-tissue, tissue-specific or condition-specific levels, for the purpose of functional annotation and XLID gene prioritization.

In the second session **"Synaptic function, receptors and neurodevelopment pathologies (part I) ",** chaired by **Yzekiel Ben-Ari** (Marseille, France), the first speaker, **Roberto Malinow** (Los Angeles, USA), discussed the role of APP in dendritic synaptogenesis and in synaptic activity, supporting the idea that this protein has a pivotal role in development of neurons and a putative impact on different synaptopathies and not only in Alzheimer disease. Next, **Pierre Billuart** (Paris, France) presented his studies on Interleukin-1-Receptor Accessory Protein Like 1 (*IL1RAPL1*), whose mutations cause syndromic and non syndromic ID. In particular, he showed that IL1RAPL1 regulates the synaptic localization of PSD-95 by controlling JNK (c-Jun terminal Kinase) activity and PSD-95 phosphorylation.

Daniel Choquet (Bordeaux, France) introduced the concept of single molecule high resolution imaging to monitor AMPA glutamate receptor (AMPAR) trafficking. Single molecule imaging techniques allow for the direct and unperturbed monitoring of single molecule dynamics. He presented data on the imaging of the fast diffusion of AMPARs in live neurons. Repetitive synaptic stimulation is known to reduce synaptic transmission. He demonstrated that fast lateral diffusion of AMPARs could replenish desensitized receptors with functional AMPAR in tens of millisecond time range.

The Session **"Fragile X syndrome: from genetics to treatment"**, chaired by **Jamel Chelly** (Paris, France) was introduced by **Jean-Louis Mandel** (Paris/Illkirch, France) who presented the main results obtained in the field of Fragile X since the identification of the mutation, from the cloning of the gene until the recent discovery of promising treatment by drugs,

particularly antagonists of mGlu5 receptor. Next, **David Nelson** (Houston, USA) introduced the concept of "acute requirement of FMRP". He presented 2 new models of *Fmr1*KO mouse. One model allows the *Fmr1* gene to be expressed until it is turned off at a specific time point. The second model allows the *Fmr1* gene to be turned on at a defined time after growth and development. The phenotype of these animals was studied at the behavioural, cellular (neuron morphology) and molecular levels. The authors could demonstrate that the abnormal *Fmr1* KO phenotypes are dependent on the presence or absence of FMRP, but not on the state of expression of the protein during development. The last speaker of this session, **Ben Oostra** (Rotterdam, The Netherlands) studied the effect of two mGlu5 receptor antagonists (Fenobam and AFQ056) on the behaviour of *Fmr1* null mice and on the morphology of *Fmr1* null primary cultured neurons. He showed that AFQ056 might be a useful molecule in the treatment of Fragile X phenotype.

The following session "**Mental Retardation syndromes: from genetics to treatment"**, chaired by **Jean-Louis Mandel** (Illkirch/Paris, France) was started by **David Picketts** (Ottawa, Canada) who presented his results on the inactivation of *alpha-thalassemia mental retardation (ATR-X)* gene in a mouse and cell line models. This latter one enabled him to suggest a novel role of ATR-X in maintaining genomic integrity that could result on cell-specific expression pattern and then in neuronal function. **Catharina Van der Zee** (Nijmegen, The Netherlands) presented a characterization of *Euchromatin histone methyltransferase 1* (*EHMT1*) null mice, as a model for Kleefstra syndrome. She showed alteration of dendritic morphology in CA1 neurons of these mice that for their altered behaviour represent a clear model of ID. The last 3 speakers of the day focused their presentations on Down syndrome (DS). The first, **Jean Maurice Delabar** (Paris, France) presented the rescue of some phenotypes in two mouse models for DS with an inhibitor of Dyrk1a, a polyphenol from green tea (PGT), epigallocatechin gallate (EGCG). On the same track, the next speaker, **Mara Dierssen** (Barcelona, Spain) introduced the possibility to improve some cognitive alterations of a mouse model for DS by environmental enrichment. Furthermore, she presented evidence that Dyrk1A over-expression affects axonal and dendritic growth and also synaptogenesis. She also suggested that Dyrk1a carries out this role via the regulation of cytoskeleton dynamics. **Franck Sturtz** (Limoges, France) studied the effect of leucovorin (or folinic acid) treatment on cognitive functions in DS patients with and without thyroid dysfunction. The conclusions of this analysis indicated that leucovorin could improve psychomotor development in children with DS needing thyroxin treatment.

The second day of the Conference started with the first part of the session «**Early neuronal development and intellectual disabilities»** that was chaired by **Maria Vincenza Catania** (Catania, Italy). This session was introduced by **Yezekiel Ben-Ari** (Marseille, France) who presented an overview of the developmental sequences leading to brain maturation, which are essential for the establishment of neuronal networks. Based on results obtained using siRNA *in utero* and electrophysiological recording from neurons of developing and adult normal and pathological brains he proposed the hypothesis that neurons misplaced, misconnected or misassembled maintain their immature signature and that several disorders including developmental or even neurodegenerative disorders might have their origin in an early blockade of developmental maturation. **Hannah Monyer** (Heidelberg, Germany) highlighted the role of parvalbumin-positive hippocampal interneurons in network synchronization and presented recent results obtained in her laboratory indicating that mice with a selective ablation of NMDA receptors in parvalbumin-positive interneurons mice exhibit both network and behavioural deficits. Last speaker of this session, **Alice Davy** (Toulouse, France), presented results obtained in ephrin-B1 mutant mice, which show both disorganization of cortical lamina as well as deficits in non-spatial memory. The second part of the session

«Early neuronal development and intellectual Disabilities» was chaired by **David Nelson** (Houston, USA) and started with the talk of **Fiona Francis** (Paris, France), who presented new data concerning the identification of a new microtubule-associated protein, possibly involved in the mechanisms of heterotopic band formation in the cortex, by using linkage and transcriptome analysis in the HeCo mouse, a model for subcortical band heterotopia in humans. **Barbara Bardoni** (Valbonne, France) started her talk with an overview of her past work on the characterization of both RNA and protein partners of FMRP and then focused on more recent results obtained by using proteomics, genomics and metabolomics from different brain regions and embryonic stem cells of *Fmr1* KO mice. The next two presentations were both focused on a early-onset seizure variant of Rett syndrome due to mutations of the *CDKL5* gene. **Ilaria Meloni** (Siena, Italy) described the methods which she used to obtain Induced Pluripotent Stem (IPS) cells from patients with *CDKL5* mutations and **Charlotte Kilstrup-Nielsen** (Busto Arsizio, Italy) presented her recent data on the possible role of a new identified protein interacting with CDKL5 in the early phase of neuronal maturation.

The session **«Synaptic function: presynaptic aspects»** was chaired by **Hannah Monyer** (Heidelberg, Germany) and started with the presentation of **Olivier Manzoni** (Marseille, France) who presented new data obtained in the nucleus accumbens of Fmr1 KO mice, where he found that mGlu5-dependent long term depression is reduced through a mechanism which involve the subcellular organization of the post-synaptic machinery and subsequent cross-talk between the post- and pre-synaptic compartments. **Yann Humeau** (Bordeaux, France) showed that mice deficient for the X-linked MR gene *Oligophrenin1* exhibit a selective deficit in pre-synaptic long-term potentiation through a mechanism that involves the uncoupling between the evoked synaptic neurotransmitter release and cAMP/PKA signalling. **Thierry Galli** (Paris, France) concluded the session with an extensive overview on the role of vesicular SNAREs in neuronal development and particularly in both axonal and dendritic outgrowth. The session **«Structure and synaptic function (part I) »** which was chaired by **Francesco Ferraguti** (Innsbruck, Austria), started with the presentation of **Laurent Fagni** (Montpellier, France), who highlighted the role of *Shank3* as a biological substrate for mental retardation. Shank3 plays an important role in spine formation and several *Shank3* mutation have been identified in patients affected by autism spectrum disorder and learning deficit. He focused his presentation on the role of a new protein, identified by using a proteomic approach, which links Shank3 to signalling pathways implicated in spine morphogenesis. The talk of the second speaker, **Dominique Muller** (Geneva, Switzerland) was focused on the ability that synaptic activity has to modulate spine shape, formation and stability during development. In particular, he presented recent data on the role of the mental retardation gene *PAK3* in affecting spine dynamics by using a biolistic transfection approach in organotypic slice cultures. **Isabelle Caillé** (Paris, France) presented recent data regarding the role of FMRP in the differentiation of progenitor cells in the SVZ and their integration in the mouse olfactory bulb. By using RNA interference in WT mice, she showed that the ability of FMRP in stabilizing spine morphology is cell-autonomous and that this effect is also particularly evident upon olfactory enrichment.

The session **"RNA metabolism and intellectual disabilities",** chaired by **Barbara Bardoni** (Valbonne, France), was introduced by **Henri Tiedge** (New York, USA) who compared behavioural and physiological /pathological aspects (epilepsy and other synaptic plasticity) of two animal models: the *BC1* knock-out mouse, *Fmr1* KO and the double KO. The results presented not only explored some new aspects of alteration of the synaptic plasticity linked to alteration of the RNA metabolism but also definitively excluded a direct interaction of FMRP and BC1, as previously reported in the literature. Next speaker, **Hervé Moine** (Illkirch, France), presented new aspects of the transport of mRNA in dendrites. He showed that two

target mRNAs of FMRP, harbouring a G-quadruplex RNA forming structure, are addressed to synapses through this structure. Similarly, a reporter RNA engineered with a G-quadruplex RNA is transported along dendrites and axons and the G-quartet behaves like a dendritic target element (DTE), the cis-acting RNA element that determine the dendritic localization of RNA. These results open new perspectives on the function of FMRP as a *trans*-acting factors (TAFs) recognizing and binding a DTE. **Marius Sudol** (New York, USA) presented another ID, Golabi-Ito-Hall or Repenning syndrome, that is due to mutations in a protein regulating pre-mRNA splicing and transcription, Poly glutamine tract-binding protein 1 (PQBP1). In particular he showed the critical role of WW domain in the function of PQBP1 and in the molecular mechanism underpinning the intellectual disability characterizing this syndrome. **Kenneth Kosik** (Santa Barbara, USA) presentation was focused on the role of microRNA – mediated control of dendritic protein synthesis in the regulation of synaptic plasticity. Indeed, he defined the mechanism of function of the MOV10 protein, a component of the RISC complex, through the identification of its target mRNAs. One of these, the Lypla1 mRNA, is associated with the brain-enriched microRNA miR-138. Using a photo convertible translation reporter (Kaede) they analyzed activity-dependent protein synthesis driven by Lypla1 and alpha-CaMKII 3'UTRs. They established this protein synthesis to be MOV10-and proteasome-dependent. These results suggest a unifying picture of a local translational regulatory mechanism during synaptic plasticity.

The session **«Structure and synaptic function» (Part II)**, was chaired by **Laurent Fagni** (Montpellier, France) and started with the talk of **Thomas Oertner** (Basel, Switzerland) who introduced the concept of functional diversity of spines by illustrating differences between endolasmic reticulum containing and not containing spines. He also presented new results on the role of AMPA receptors in determining the temporal window for spike-timing-dependent potentiation. **Marie-Christine Simmler** (Paris, France) presentation was focused on vezatin, a novel cytoskeletal protein of the cell-cell adhesion complex, which is involved in synaptic transmission and in cognition as evidenced by her studies on genetically modified mice. The last speaker of the session, **Laurie Doering** (Hamilton, Canada) presented data which support a role for astrocytic factors in determining the altered morphology and possibly synapse formation in the absence of FMRP, based on data obtained in neuronal/astrocytic co-cultures from WT and *Fmr1* KO mice.

The session **"Identification and characterization of genes causing intellectual disabilities"** was chaired by **Ben Oostra** (Rotterdam, The Netherlands) and started with the presentation of **Jamel Chelly** (Paris, France) describing mutations in the *TUBA1A*, *TUBB2B* and *TUBB3* genes in patients affected by lissencephaly and bilateral polymicrogyria. Interestingly, in contrast with what published before, new findings demonstrate that the spectrum of TUBB3-related phenotype is broader than previously described and includes malformations of cortical development (MCD) associated with neuronal migration and differentiation defects, axonal guidance and tract organization impairment. *TUBB3B* mutants lost the ability to homodimerize and this abnormality is responsible for the abnormal microtubules dynamics that is likely to be the cause of the phenotype. **Patrizia D'Adamo** (Milan, Italy) presented her functional characterization of *RAB39B,* whose mutations cause a form of non-syndromic XLID. In particular the interaction of RAB39 with GDI, another gene involved in XLID, at the membrane, could be the mechanism underlying the mental handicap.

Michelle Pirruccello (New Haven, USA), a post-doc in the laboratory of Pietro De Camilli introduced their studies on the inositol 5-phosphatase OCRL, whose mutations cause the X-linked Oculo-cerebral Renal syndrome of Lowe and Dent disease. They identified 2 new interacting proteins of OCRL whose binding to OCRL is mutually exclusive and is disrupted by the same missense mutations in the ASH-RhoGAP-like domain. Both these OCRL

partners are localized on endosomes but reside on different endosomal subpopulations. These findings define a consensus motif for OCRL binding and suggest that Lowe syndrome and Dent disease result from perturbations at multiple sites within the endocytic pathway.

Jozef Gecz (Adelaide, Australia) focused on the nonsense mediated RNA surveillance pathway (NMD), which was recently identified to be involved in syndromic and non-syndromic XLID. Comparing the expression profile in cells of patients carrying mutations in *UPF3B* versus normal people they identified 597 genes significantly deregulated. Among them *ARGGAP24* –a highly up-regulated gene in these patients -blocks the differentiation of PC12 cells in neurons when over-expressed. This finding suggests that overexpression of this gene is likely to contribute to the phenotypes seen in UPF3B patients.

The last session of the meeting **«Synaptic function, receptors and neurodevelopmental pathologies» Part II**, was chaired by **Thierry Galli** (Paris, France) and started with the talk of **Francesco Ferraguti** (Innsbruck, Austria) who introduced the principles and applications of the novel freeze-fracture replica immunolabelling technique (SDS-FRL), which allows the measurements of synaptic and extrasynaptic content of receptors as well as the full synaptic area. He described recently obtained results showing that fear learning produces a reversible enlargement of GABAergic synapses in the basal nucleus of amygdala. The presentation of **Jean-Vianney Barnier** (Gif-sur Yvette, France) was focused on the mechanisms by which p21-activated kinase 3 (PAK3), a protein involved in mental retardation, might regulate AMPA receptor-dependent synaptic transmission. He presented data showing that PAK3 is able to reduce AMPA receptor miniature EPSCs and that the interaction between PAK3 and Nck2 is necessary for this effect. Next speaker, **Julie Perroy** (Montpellier, France) proposed a model by which the physical interaction between NMDA and mGlu5 receptors, which down-regulates NMDA receptor function, is promoted by the disruption of mGlu5-Homer3 interaction. This mechanism might occur during synaptic plasticity and may also play a role in the pathophysiology of Fragile X syndrome, where a physical disruption of mGlu5-Homer interaction has been reported. **Maria Vincenza Catania** (Catania, Italy) presented an overview of results supporting a role of group-I mGlu receptors in different steps of neural development and in the pathophysiology of Fragile X syndrome and then showed recent results concerning the expression of mGlu5 receptors in *Fmr1* null mouse and the modulation of the interaction of FMRP with its interactors FXR1P and FXR2P by the activation of group-I metabotropic glutamate receptors.

3. Conclusions & Discussion.

We believe that the idea to bring together geneticists and neuroscientists resulted in a quite special meeting in which scientists having different backgrounds and using different methodologies had the opportunity to discuss and compare their views for a successful strategy aimed at understanding and curing intellectual disabilities. The approach was innovative and appeared to be appreciated by the vast majority of attendants. Several of them expressed their appreciation for a meeting in which the variety of topics gave the participants the opportunity to learn in fields other than their own.

Several questions and concepts emerged during the discussion of each session which need to be further addressed to improve the advance of the research in the field. The most noteworthy are here summarized:

- New strategies to identify genes for ID.

- Identification of the right pathways to be targeted given the enormous amount of information gained by the most advanced new technologies. In particular, several scientists

underlined that the field needs a big effort to study the functional properties of gene products causing ID, whose number increased during last years due to next generation sequencing techniques.

- The role of interneurons in ID.
- The role of micro-RNA in ID.
- The Identification of different types of spines participating to synaptic transmission
- The role of dendritic architecture and axonal connection in the pathogenesis of ID
- The importance of defining the temporal window for an early treatment in neurodevelopmental disorders, considering that neurons during development have a different behaviour than mature neurons.
- The disruption of protein-protein interaction occurring at synapses may underlie the pathogenesis of ID.

We believe that we fulfilled our initial purpose of fostering interesting discussions and that for the success of the formula proposed and for the importance of the topics treated this type of meeting may get a high chance to have a great success in the future as well.