Roscoff (France), 3-7 octobre 2012

Déficit intellectuel : des gènes au traitement

Mechanisms of Intellectual Disability: from genes to treatment

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Rapport sur la Conférence

Conference Report

RESUME DU RAPPORT

Conférence Jacques Monod intitulée : Déficit intellectuel : des gènes au traitement

Roscoff, 3-7 octobre 2012

Les déficiences intellectuelles (DI) constituent un groupe de pathologies extrêmement hétérogènes définit comme un fonctionnement intellectuel significativement inférieur à la moyenne et associé à des difficultés d'adaptation et de socialisation. C'est le handicap le plus fréquent chez l'enfant et le jeune adulte puisqu'il concerne près de 3 % de la population générale. Les progrès de la génétique ont permis des avancées considérables dans l'explication des causes de ces maladies puisque plus de 400 gènes, dont 97 liés au chromosome X, ont déjà été identifiés. Cependant, la grande majorité des cas reste encore inexpliquée. L'identification des déterminants génétiques responsables de ces affections constitue donc l'un des grands défis scientifique et médical.

Les progrès spectaculaires de ces trois dernières années dans le domaine de la biologie moléculaire et de la bio-informatique avec l'évolution des performances et la baisse des coûts de séquençage ont eu pour conséquences une fantastique accélération des découvertes en génétique médicale en particulier dans le contexte des déficiences intellectuelles. Au-delà de la caractérisation de nouveaux gènes responsables de DI, les défis de demain sont désormais de mieux comprendre l'ensemble des mécanismes physiopathologiques sous-jacents et d'identifier des processus cellulaires communs dans lesquels interviennent les produits de ces gènes et qui pourraient donc représenter de potentielles cibles thérapeutiques. Cette conférence visait donc à stimuler les échanges entre généticiens impliqués dans la recherche de gènes de DI et neurobiologistes spécialistes du développement et de la fonction des synapses.

Cette conférence a eu lieu à Roscoff du 7 au 11 octobre 2010. Elle a réuni 86 scientifiques, dont 26 conférenciers invités et 60 participants (34 chercheurs ou professeurs ayant un poste statutaire, 11 post-docs et 15 étudiants) de 15 pays différents (Europe, Australie, Canada, États-Unis).

La conférence a été structurée en 13 sessions, qui ont compris les présentations de 26 conférenciers invités (20 minutes plus 5 minutes de discussion) et 27 présentations plus courtes (10 minutes plus 5 minutes de discussion) qui ont été sélectionnées parmi les abstracts. Deux sessions de posters ont eu lieu et 33 posters ont été présentés pendant deux sessions de deux heures. 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 et, pour certains, étaient présentés pour la première fois pendant une conférence.

Les différents sessions ont portées sur :

- Génétique et épigénétique de la cognition
- Identification et caractérisation de gènes de déficience intellectuelle
- Métabolisme de l'ARN et déficit intellectuel
- Neurogenèse et synaptogenèse
- Structure et plasticité des synapses en condition normale et pathologique
- Migration neuronale, interneurones et déficit intellectuel
- Développement des circuits neuronaux et déficit intellectuel
- De la génétique au traitement: leçons des systèmes modèles animaux

Les organisateurs ont eu la nette impression que la conférence avait été très appréciée de l'ensemble des participants. De plus, le fait que la plupart soient des chercheurs confirmés montre le grand intérêt que cette approche a suscité dans la communauté scientifique travaillant sur ce sujet. Les nombreuses discussions entre scientifiques ayant des formations/parcours scientifiques différents ont permis d'identifier certains points clé pour développer la recherche dans le futur.

CONFERENCE REPORT

Final report from the Jacques-Monod Conference entitled: Mechanisms of Intellectual Disability: from genes to treatment

Roscoff, October 3-9 2012

1 – General description of the meeting

The Jacques Monod Conference «Mechanisms of Intellectual Disability: from genes to treatment» took place in Roscoff from October 3 to October 7, 2012.

Participants were 86:

- 26 invited speakers 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 involved in the neurobiology of ID. The female representation among the invited speakers was 34 %.

- 60 applicants, selected upon abstract submission (34 tenure positions, 11 post-docs and 15 students). Females represented 62% of participants.

15 countries were represented, as illustrated in the following table

Country	invited speakers	permanent	post doc	student
France	11	13	3	4
Italy	3	5	5	7
USA	3	3		
Germany	1	3	1	1
Spain	1	3		
Belgium		1	1	2
UK	2	1		
Netherlands	2			
Switzerland	1			1
Portugal		1	1	
Australia	1	1		
Canada	1			
Poland		1		
Romania		1		
Finland		1		
Total	26	34	11	15

The meeting was organized in 13 sessions of oral presentations (listed below) and two poster sessions:

- Genetics and epigenetics of cognition and intellectual disorders I, II and III
- Gene characterization and molecular pathways I and II
- Synaptic dysfunction and Intellectual disorders I, II, III and IV
- Brain Development and intellectual disorders
- RNA metabolism in intellectual disorders
- From genes to treatment
- Neurogenesis

Each session was a mix of talks given by invited speaker (20 minutes + 5 minutes of discussion) and short talks (10 minutes + 5 minutes of discussion) given by participants whose presentation was selected on the basis of their submitted abstract. A total of 27 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 48 %. Given the number of participants and the overall high quality of the contributions we decided to shorten the length of talks given by the invited speakers to give the opportunity to applicants, especially young principal investigators to present their data to the whole audience. 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 33 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. We find that this equal distribution between posters and oral presentations provide enough time to all contributions presented to be discussed both during the oral and poster sessions.

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 organizers can affirm on their personal experience that for her professionalism, personal disposition and efficiency she has been the best collaborator they have ever had for this type of events. The technical support and the logistic offered by the Biological Station in Roscoff were also very good, 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 Friday, October 5 afternoon.

CNRS provided the main funding to support the conference. This conference was also organized with the support of the **INSERM**. Furthermore, the organizers received substantial financial supports from the **Jérôme Lejeune Foundation, Paris** and the **Italian National Research Council** (**CNR).** We were also supported by **Active Motif**, which provided bags and writing materials for all participants, **IRCCS "Associazione Oasi Maria SS", Troina, Italy**, a Institute devoted to the research, cure and assistance of Intellectual Disability in Sicily and **Techniplast, Italy.**

During the conclusion of the meeting on October 7 morning, Laurence Colleaux was confirmed chairman for the next conference, while Josef Gezc was proposed and approved as vice-president.

The choice of the subject and the original combination of genetists and neuroscientist was greatly appreciated by all participants, both experienced scientists and young investigators. Indeed, during and after the meeting many participants expressed enthusiastic comments concerning the formula of the meeting and the scientific quality of this Jacques Monod Conference, most of them wishing the organization of a next conference with similar topics and format.

2 - Report on scientific aspects.

The present conference represents the renewal of the 2010 Monod Conference "Mental retardation: from genes to synapses, functions and dysfunctions". We maintained the highly successful formula of this previous conference, which was based on the original combination of geneticists involved in the search for ID genes and neuroscientists experts of structure and mechanisms of function of synapses as well as other neuronal functions potentially relevant for ID/MR. While the present conference was based on the same consideration than the previous one (i.e. that exchanging information between geneticists and neuroscientists is useful for the advancement in the pathophysiology of ID/MR), this second edition was more focused on the perspective that a cure might follow the neurobiological understanding of ID. In addition, topics such as epigenetic, neurogenesis and circuit formation were extensively discussed in the context of the pathogenesis of Intellectual Disorders

The meeting started with the session **Genetics and Epigenetics of cognition and intellectual disorders I,** which was chaired by **Hans Van Bokhoven (Nijmegen, The Netherland)**. An introduction to the genetic basis of ID was given by **Lucy Raymond (Cambridge, England)**, who analyzed different approaches leading to the identification of critical functional proteins in developmental disorders. She emphasised the importance of selecting familial cases on the basis of stringent clinical features in order to identify gene mutations notwithstanding the advancement of high throughput approaches. **Laurence Colleaux (Paris, France)** illustrated two examples of how deciphering molecular bases of ID can gain insight into common mechanisms leading to cognitive disorders. The first one is the identification of *MED23* Mammalian mediator (MED), an evolutionary conserved multiproteincomplex that plays a role in transcriptional regulation and the second example is NF-kB. An impaired response in MED-dependent immediate early gene response and in NFKB signalling was found in cells derived from several patients with apparently unrelated cognitive deficit. **Vera Kalsheuer (Berlin, Germany**) reported results obtained from >400 unrelated XLID families, recruited by the European MRX consortium and associated group, by using hybrid capture and massive parallel sequencing of X-chromosome exome in probands. She reported changes in >17 novel genes, which can be tentatively grouped into three functional classes: a) synaptic pathways, b) transcriptional and translational regulation and c) proteasome-mediated protein degradation. **André Reis (Erlangen, Germany)** presented results obtained from exome sequencing in parent-child trios of 51 individuals with sporadic non-syndromic intellectual disability. This study demonstrate that *de novo* point mutations and small indels are a major cause of severe, sporadic non-syndromic ID with high locus heterogeneity. **Guy Froyen (Leuven, Belgium)** presented latest results from his lab demonstrating that over-expression of *HUWE1* is

responsible for the non-syndromic ID phenotype observed in patients carrying non-recurrent overlapping Xp11.22 duplications. Moreover, he provided convincing data that overexpression of the *HUWE1* Drosophila ortholog is responsible for increased axonal branching, possibly due to inhibition of Wnt pathway.

In the second session entitled **gene characterization and molecular pathways I)** and chaired by **Josef Gecz (Adelaide Australia)**, **Jamel Chelly (Paris, France)** presented new data supporting an impairment of microtubule stability in fibroblasts of patients with Rett Syndrome. **Barbara Bardoni (Valbonne, France)** illustrated recent results obtained in her lab using different approaches to unravel molecular pathways altered in Fragile X syndrome in developing brain, namely metabolomics in post-natal brain and transcriptomal analysis in embryonic stem cells. **Charles Schwartz (Greenwood, USA)** showed that mutations of the *MED12* gene, coding for one subunit of the Mediator complex and that are responsible for FG and Lujan syndromes, impaired recruitment of CDK8 onto promoters of GLI3 target gene causing disruption of the Mediator-imposed constrain on GLI3-dependent Sonic Hedgehog signalling. **Nicoletta Landsberger (Busto Arsizio, Italy)** described a novel and unexpected function for MeCP2, as a component of centrosome involved in microtubule nucleation, suggesting for a role in neuronal maturation and differentiation. These data may have important implication for understanding the pathogenesis of RETT syndrome. **Frederic Laumonnier (Tours, France)** presented results regarding the characterization of a point mutation of PTCHD1 gene leading to a truncated form of encoded PTCHD1 protein, a transmembrane protein possibly involved in Sonic Hedgehog signalling. PATCHD1 mutations are associated to autism and/or non syndromic ID and Laumonnier data reveal that PTCHD1 protein is present in dendritic spines and its targeting to membrane is dependent on the COOH terminal. The session was concluded by **Carlos Bessa (Braga, Portugal)** who illustrated a novel approach for the functional validation of genetic findings in neurodevelopmental disorders by using the nematode C-elegans.

The session **Synaptic dysfunction and intellectual disorders I** was chaired by **Laurent Fagni (Montpellier, France)** and started with the presentation of **Nael Nadif Kasri (Nijmegen, The Netherland)** which was focused on the role of oligophrenin (OPHN1) in synaptic plasticity. He showed that OPHN1 mediates AMPA receptor endocytosis triggered by activation of mGlu1 receptors through the interaction with endophylin, while it regulates basal synaptic transmission thorugh a different mechanism which require OPHNB1's Rho-GAP activity and interaction with Homer1b/c. **Antoine Triller (Paris, France)** gave an overview of single molecule high resolution imaging to monitor mobility of neurotransmitter receptors in and out of synapses, emphasising the concept that receptors interaction with scaffolding proteins and lipid composition of membrane may differently influence lateral diffusion of receptors. Following the Poster session I, the session **Synaptic dysfunction and intellectual disorders II** , chaired by **Laurent Fagni (Montpellier, France),** started with **Christophe Mulle (Bordeaux, France),** who presented functional and anatomical data obtained in his lab on the grik2 KO mouse model of ID, suggesting that a transient impairment of synaptic strength during postnatal development may have an impact on proper formation of neural circuit linked to memory. Next, **Yann Humeau (Bordeaux, France)**, presented results obtained in another model of ID, the il1rap11 deficient mouse, showing that while mutation affects both cued and contextual fear memory, it selectively affect excitatory afferent input on principal, but not inhibitory cells, suggesting that a selective target specific alteration of excitatory synapses is sufficient to generate alteration in neuronal circuit such to determine permanent cognitive deficits. The session ended with the presentation of **Ana Luisa Carvaho (Coimbra, Portugal)** who presented new data disclosing a new function for

protein acetylation at synapse focusing on the role of acetylated cortactin in the regulation of PSD95 dendritic clustering.

The second session dedicated to **Genetics and Epigenetics of cognition and intellectual disorders** was chaired by **Lucy Raymond (Cambridge, United Kingdon)** and started with the talk of **Jacques Michaud (Montreal, Canada)**. He presented a study conducted in French Canadian families leading to the identification of two novel genes, involved in the control of cilia formation and function, which are associated with Joubert syndrome. **Hans Van Bokhoven (Nijmegen, The Netherland)** introduced the concept that dysregulation of chromatin structure and chromatin-mediated transcription may affect cognition and showed genetic and functional data suggesting the involvement of a group of genes which cooperates with *EHMT1*, euchromatin histone methyltransferase, in the pathogenesis of Kleefstra syndrome. **Isabelle Mansuy (Zurich, Switzerland)** presented an experimental model of early traumatic stress in mice and provided evidences for the contribution of epigenetic mechanisms to the impact of negative factors on behaviour across generation. **Paul Tchénio (Paris, France**) described new in-vivo functional brain imaging approaches in the Drosophila model aimed at analyzing the functional role of genes and associated signalling pathways involved in ID. He focused on cAMP signalling associated with learning in mushroom bodies and RhoGTPase Rac activity during consolidation of long term memory. **Romain Peanne (Leuven, Belgium)** described a new congenital disorder of glycosylation (CDG) caused by an ER-localized a(1,2) mannosidase , MAN1B1 and characterized by mental retardation, autism and behavioural problem. This study represents the first report on MAN1B1-CDG and support a role for ER- associated degradation in ID.

The following session entitled **Brain developmental anomalies and intellectual disorders** was chaired by **Maria Vincenza Catania (Catania, Italy)** and started with the talk of **Ingrid Bureau (Marseille, France),** who discussed the role of FMRP, the protein lacking in Fragile X syndrome, in the mechanisms underlying cortical column formation and connectivity. Next, **Oscar Marin (Alicante, Spain)** presented results indicating a role for Neuregulin1 and its receptor ERBB4 in the wiring of specific classes of interneurons. **Laura Cancedda (Genoa, Italy)** showed that activation of GABAB receptors during development regulates neuronal migration and morphological maturation by cAMP/LKB1 – dependent axon/dendritic specification. **Fiona Francis (Paris, France)** presented a study leading to the identification and characterization of Eml (Echinoderm microtubule associated protein like) as a new gene involved in corticogenesis. The session ended with the talk of **Yehezekel Ben-Ari (Marseille**), who reported a significant improvement of the severity of symptoms in a group of autistic patients treated with bumetanide, a diuretic specific antagonist of the chloride importer NKCC1. The treatment with bumetanide is based on the observation that GABA produces paradoxical responses due to elevated intracellular levels of chloride during development and that this responses might be altered in autism.

The session dedicated to **RNA metabolism** was chaired by **Barbara Bardoni (Valbonne, France)** and included the presentation of **Josef Gecz (Adelaide, Australia)**, who introduced the topic by explaining the genetic basis supporting the involvement of nonsense-mediated mRNA decay (NMD) in ID and autism and presented result of an extensive study on patients suggestive of an important role for several genes codifying various NMD factors in ID. Then, **Gerhard Schratt (Marburg, Germany)** presented an in vitro characterization of activity-dependent clusters of miRNA and their validated target genes in neurons supporting the role of microRNAs (miRNAs) in the control of synaptic homeostasis.

The third session dedicated to **Synaptic dysfunction and intellectual disorders** was chaired by Christophe Mülle and started with the presentation of **Seth Grant (Edinburgh, United Kingdom)** who introduced the concept that mental illness might be the price for evolution

based on the evidence that increasing genome complexity occurring during evolution is accompanied by expansion of behaviour. **Thomas Südhof (Stanford, USA)** gave an overview on the function and dysfunction of neurexins and neuroligins, pre- and post-synaptic cell adhesion molecules involved in the assembly and function of neural circuits and described how they shape synaptic properties. In the same session, **Laurent Fagni (Montpellier, France)** presented a study which identifies the Rho-GAP interacting CIP4 homologue (Rich2) as a new partner of Shank3, a protein encoded by a gene which is mutated in ID and autism spectrum disorder. Rich2 interacts with Rac1 and controls spine density and AMPA receptor exocytosis in hippocampal neurons suggesting a role for Shank-Rich2 complex in synaptic plasticity. **Anna Francesconi (New York, USA)** ended this session by showing data from her lab indicating that recruitment of metabotropic glutamate receptor subtype 1 (mGlu1) to lipid rafts is stimulated by agonist binding and promotes mGlu1 activated ERK/MAPK receptor signalling.

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The session **Synaptic dysfunction and intellectual disorders IV** was chaired by **Ingrid Bureau (Marseille, France)** and started with **Maria Vincenza Catania (Catania, Italy)** who showed that the absence of FMRP leads to a mGlu5 receptor altered expression and signal transduction coupling, with more effective consequences during development than in adult life. **Vania Broccoli (Milan, Italy)** presented results suggesting that CDKL5, which mutations cause a severe form of RETT syndrome, ensures excitatory synapse stability by reinforcing NGL-1-PSD95 interaction in the postsynaptic compartment and is impaired in patient iPSC-derived neurons . Then, **Stephane Martin (Valbonne, France),** presented data demonstrating that there is an activity-dependent redistribution of endogenous sumoylation enzymes in hippocampal neurons and proposed that alteration of post-translational protein modification, namely sumoylation may be involved in pathogenesis of ID. **Nael Nadif Kasri (Nijmegen, The Netherland)** presented a characterization of the properties of the glutamatergic CA3–CA1 synapses in a mouse model of Kleefstra syndrome, which is caused by haploinsufficiency of euchromatin histome methyltransferase (EHMT1). Electrophysiological recording is suggestive of a reduction in pre-synaptic glutamate release and further support the growing notion that epigenetic modifications have a crucial role in cognitive functions. **Thierry Galli (Paris, France)** presented a functional and behavioural characterization of a TI-VAMP knockout mice; a striking feature appeared to be an increased anxiety level suggesting an unexpected role of Ti-VAMP mediated vesicular trafficking in anxiety. The session was concluded by the presentation of **Andreas Frick (Bordeaux,**

France), who showed that dysfunction of h-channels and BK_{Ca} channels is an underlying mechanism of the increased sensory excitability in the *Fmr1* knockout mouse model of Fragile X syndrome.

The session **Genetics and Epigenetics of cognition and intellectual disorders III** included the presentation of **Kristen Martins-Taylor (Farmigton, USA**), who described studies conducted in iPSCs and derived neurons from patients with Prader-Willi, Angelman and 15q11-q13 duplication syndrome aimed at establishing reliable in vitro models of 15q11-q13 imprinting neurodevelopmental disorders which could be eventually used to develop therapeutic strategies. Then, **Magali Naville (Paris, France)** proposed a bioinformatic method that identifies cases of evolutionary co-segregation between putative enhancers and specific genes, using the information on a large range of genomes. This method is currently developed on the human X chromosome as a part of the European NeuroXsys project, which aims at deciphering regulatory networks involved in human X-linked neurological diseases.

The session **Gene characterization and molecular pathways II** was chaired by **Jamel Chelly (Paris, France)** and started with the presentation of **Alcino Silva (Los Angeles, USA)** who presented data from animal models of different diseases associated with ID showing that reversal of symptoms can be achieved even when the treatment is started in adult. **Katheleen Gardiner (Aurora, USA)** described a system neuroscience pathways-based approach used in her lab, which combines bioinformatics and experimental methods, to understand pathways perturbation in Down syndrome and evaluate them after drug treatment, such as the NMDA receptor antagonist memantine. **Gaia Berto (Turin, Italy)** showed that the Down critical region-encoded protein TTC3 regulates early neuronal differentiation possibly repressing the main phenomena underlying neurite outgrowth, namely the availability of actin monomers and their incorporation into new actin filaments. **Anna Fassio (Genoa, Italy)** presented data revealing a role of TBC1D24, a Rab GAP protein involved in recessive forms of early-onset epilepsies associated with ID, in cerebral cortex formation.

The session **From genes to treatment** was chaired by **Alcino Silva (Los Angeles, USA) and was started by Yann Herault (Illkirch, France)** who illustrated results obtained from different mouse models of Down syndrome and a conditional cystathionine beta-synthase (*Cbs*) overexpressing transgenic mouse and pointing to the conclusion that Cbs gain of function is sufficient to induce learning and memory phenotypes of Down syndrome. **Patrizia D'Adamo (Milan, Italy)** presented recent results obtained in *Gdi*-Knock out mouse which support the notion that this model of ID can also be used as a pre-clinical model for autism. She presented encouraging data regarding the use of a mGlu2/3 negative allosteric modulator as cognitive enhancer in this mouse model. **Bianca De Filippis (Rome, Italy)** reported a significant improvement in hippocampus-dependent cognitive tests obtained with the bacterial protein Cytotoxic Necrotizing Factor 1 in a mouse model of Rett syndrome. **Maria Luz Montesinos (Sevilla, Spain)** presented data showing that in the Ts1Cje mouse model of Down syndrome the Akt-mTOR signalling cascade is hyperactive and consequently the basal protein synthesis is increased. Based on the reversal of Akt-mTOR deregulation and protein synthesis by rapamycin, she proposed that targeting this cascade might be envisioned as a novel therapeutic strategy in Down syndrome. **Yolanda De Diego Otero (Malaga, Spain)** presented a significant improvement in learning measured with WISC-R subscales obtained in Fragile X patients in a double-blind pilot clinical trial with the combination of ascorbic and alpha-tocopherol. This treatment is based on the finding that an excess of oxidative stress is present in the fmr1 knock out model of Fragile X and that a treatment with antioxidants reverses hallmarks of mouse phenotype. The session was concluded by **Franck Sturtz (Paris, France)** who explained the rational for setting up and the design of the ACTHYF clinical trial

in T21-Down syndrome patients, which would used thyroid hormones and folate supplementation.

The last session **Neurogenesis** was chaired by **Laura Cancedda (Genoa, Italy)** and started with **Antoine Nissant (Paris, France)** who focused his presentation on the role of proteins implicated in developmental brain diseases, such as doublecortin and FMRP, in the process of newborn cell development and integration, focusing on the olfactory bulb. He showed that preventing the expression of these protein in newly generated neurons influences strongly their development and synaptic integration. On the same track **Isabelle Caillé (Paris, France)** studied the possible role of FMRP in adult stem cells of the sub ventricular zone (SVZ) and concluded that, differently from what suggested in the hippocampal neurogenic niche, the absence of FMRP does not lead to altered neuronal production or altered proliferation in the SVZ. The session was concluded by **Giovanna Lalli (London, United Kingdon)** who presented new data concerning the involvement of Ral1, a Ras-like GTPase important for neuronal morphology and polarity, in the cannabinoid receptor (CB1/CB2)- mediated regulation of neuroblast migration in postnatal mammalian brain.

3 - Conclusions and future directions

This conference repeated the success of the first JMC in ID for liveliness of discussions, enthusiasm of participation and manifestation of interest by all the participants. Most participants expressed their appreciation and were favourable to the organization of a third conference on the topic of ID. The format of this conference, which brings together genetists and neuroscientists, is quite unique since other meetings dedicated to ID are devoted to diagnostic and clinical aspects, that have not been addressed here, or to the genetics and neurobiology of specific syndromes.

This conference has clearly emphasized that the rapid advancing in genetics and the use of new system biology and bio-informatic technologies will more and more lead to the identification of pathways commonly disrupted in different forms of ID. Unravelling these pathways might be extremely important for the future cure of ID. Indeed, most conditions are singularly rare and thus poorly attractive for pharmaceutical research. A possible way to overcome these limitations is thus to demonstrate that a single drug might be useful for different forms of ID linked to the same disrupted pathway. Another important and emerging concepts is that, despite the fact that most of these conditions are caused by developmental defects, delivering therapies later in adult life can have significant effect on the handicap by targeting ongoing dysfunctional biochemical mechanisms.

In conclusions, this conference provided convincing examples that the recent progresses in the field of intellectual disability make now possible thinking about therapeutics alternative. We believe that because of the importance of the topics a future Jacques Monod conferences based on the same formula might strongly contribute to the advancement toward a better comprehension of the mechanisms underlying ID and consequently toward a possible treatment.