4TH INTERNATIONAL ANGELMAN SYNDROME SCIENTIFIC CONFERENCE

1915 - 1965 - 2015

LIVERPOOL

CONFERENCE PROGRAMME

Hosted by Assert

ASA ANGELMAN SYNDROME ALLIANCE

LOTTERY FUNDED

The Angelman Syndrome Support Education and Research Trust (ASSERT) is proud to host
The Fourth European Angelman Syndrome Scientific Conference
2nd-3rd October 2015 Liverpool, UK

A very warm welcome to Liverpool in this momentous year for the Angelman Syndrome (AS) community. It is 50 years since Dr Harry Angelman first described AS, and 2015 would have also been his 100th birthday.

We hope this conference will provide an opportunity to continue his work, to share ideas and gain new knowledge, to form new collaborations and further awareness and research into Angelman Syndrome. The trustee's are delighted that so many from both the international community and from closer to home have been able to join us for the 4th Angelman Syndrome Alliance Scientific Conference and the first Scientific Conference hosted by ASSERT.

In this programme you will find details of all that is taking place over the weekend. Please take some time to familiarise yourself with the agenda for both Friday and Saturday.

If you have any questions or complaints during the weekend please do not hesitate to find one of the ASSERT trustees. Alternatively, if the matter is regarding your accommodation please speak to the hotel staff who will be able to assist you. In emergencies please contact Lisa Court 07870234947 or Rachel Martin 07460357418.

ASSERT Trustees

A MESSAGE FROM ASSERTS PATRON

The award winning British director, who has a niece with Angelman Syndrome. Gareth's most notable success to date is the hugely successful Godzilla (2014). Gareth is currently working on 'Star Wars: Rogue One' for Disney/Lucas film. This is due for release in December 2016.

I am thrilled to be invited to attend the Celebration Gala as part of the 4th Angelman Syndrome Alliance conference. I know that 2015 is a special year for the Angelman Syndrome world and it will be great to come along and join the celebration. These are exciting times and I know there is lots going on with regards to research to try and understand more about the syndrome and how this can be best utilised for future research. I know first hand how hard it can be to have a child with Angelman Syndrome, my niece Ella certainly keeps my sister busy! I hope everyone who attends this weekend comes away with a little bit more understanding of the science and research work, aswell as enjoying the Gala in the evening.

Gareth Edwards

A MESSAGE FROM OUR GUEST OF HONOUR

Liz Huglin, niece of Dr Harry Angelman.

I am very honoured to be invited here this weekend to meet you all. I have many happy childhood memories of Uncle Harry, and they are mostly of somebody quite exotic, coming home during the war from India and showing us home movies of the hospital, the doctors and the children, bringing me a silver filigree bracelet, which for a 4 year old was beyond dreaming!
All his family are very proud of him and his achievements and we all wish you an interesting and wonderful weekend in Liverpool.
I am looking forward to meeting everybody.

Liz Huglin

Thursday to Sunday at a glance

Thursday

8.00pm – late	Evening meal – The Marriott Hotel. Menu enclosed

Friday

6.30am onwards	Breakfast
7.45am	Meet in the hotel foyer to board the coach
8.30am – 5.30pm	4th International Angelman Syndrome Scientific Conference – Alder Hey Education Centre. (see page 4 for more detail)
5.30pm – 6.00pm	Return coach to The Marriott hotel
8.00pm – late	Evening meal – The Marriott Hotel. Menu enclosed

Saturday

7.30am onwards	Breakfast
9.00am – 5.30pm	Family Scientific Symposium – Merchant Suite, The Marriott Hotel (see page 5 for more detail)
7.30pm	Welcome Drinks
8.00pm – 9.30pm	Celebration Gala Meal
9.30pm – 1.30pm	Live Entertainment

The Celebration Gala is being held in the Merchant Suite. Please arrive at 7.30pm for a welcome drink and to be seated for dinner by 8pm. The Celebration Gala bar will close at 1am. The hotel bar (located by the foyer) will remain open for residents.

Sunday

7.30am – 11am	Breakfast
12pm	Final check-out

Please note: The Angelman Syndrome Alliance Closed Meeting will be held on Saturday from 2pm to 4pm in the Lever Room in The Marriott Hotel.

Friday 2nd October
Alder Hey Education Centre, Liverpool

8.30	-	9.00	Registration and Tea / coffee on arrival
9.00	-	9.15	Welcome – ASSERT & The Angelman Syndrome Alliance
9.15	-	9.45	Ben Distel (Academic Medical Center (AMC), Netherlands) Structural and functional analysis of Ube3a/E6AP.
9.45	-	10.15	Ype Elgersma (Neuroscience Institute, Erasmus University, Netherlands) Dissociation of locomotor and cerebellar deficits in Ube3a mice
10.15	-	10.45	Ugo Mayor (Ikerbasque, Basque, Spain) UBE3A substrate identification: past, present and future.
10.45	-	11.10	Tea / coffee & biscuits
11.10	-	11.40	Noelle Germain (University of Connecticut health Center, USA) Human Induced Pluripotent Stem Cell Models of Angelman Syndrome.
11.40	-	12.10	Ilaria Tonazzini (NEST, Istituto Nanoscienze-CNR, Italy) Impaired neurite contact guidance in Ubiquitin ligase E3a-deficient neurons.
12.10	-	12.40	Qing-Jun Meng (Manchester University, UK) UBE3A, a E3 ubiquitin ligase that regulates the circadian clock in mammalian cells and flies.
12.40	-	1.15	Buffet Lunch
1.15	-	1.45	Matthew During (Ovid Therapeutics, USA) OV101: enhancing tonic inhibition as a therapeutic approach to Angelman Syndrome.
1.45	-	2.15	David Clayton (Queen Mary University of London, UK) Birdsong communication and learning.
2.15	-	2.45	Jill Clayton-Smith (Manchester University, UK) Using Newer Genetic Technologies to Diagnose Angelman-Like Disorders.
2.45	-	3.15	Rosie Conroy (Manchester University, UK) Medical problems and provision of care for patients with Angelman Syndrome
3.15	-	4.00	Afternoon tea
4.00	-	4.30	Karen Bindels-de Heus, Marie-Claire de Wit (ENCORE Expertise Centre for Angelman Syndrome, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands) A multidisciplinary expertise center for Angelman syndrome: Clinical features and genotype-phenotype correlation in a large cohort of children with Angelman Syndrome.
4.30	-	5.00	Elles van der Louw (ENCORE Expertise Centre for Angelman Syndrome, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands) Dietary therapy of children with Angelman Syndrome and refractory epilepsy; design of a randomized controlled trial.
5.00	-	5.30	Art Beaudet (Baylor College of Medicine, USA) & Frank Rigo (ISIS Pharmaceuticals) Towards a therapy for Angelman syndrome by targeting a long non-coding RNA. Note: This is a remote video conference call.

Saturday 3rd October
The Merchant Suite, The Marriott Hotel, Liverpool

9.00	-	9.30	Registration and Tea / coffee on arrival
9.30	-	9.35	Welcome – ASSERT
9.35	-	9.50	Becky Burdine (Princeton University, USA) Overview of recent scientific advances in Angelman Syndrome research.
9.50	-	10.05	Matthew During (Ovid Therapeutics, USA) Ovid Therapeutics: A partner committed to making a meaningful difference in the lives of those with Angelman Syndrome and their families.
10.05	-	10.20	Elles van der Louw (ENCORE Expertise Centre for Angelman Syndrome, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands) Dietary therapy of children with Angelman Syndrome and refractory epilepsy; design of a randomized controlled trial.
10.20	-	10.35	Noelle Germain (University of Connecticut health Center, USA) Human Induced Pluripotent Stem Cell Models of Angelman Syndrome.
10.35	-	10.50	Ugo Mayor (Ikerbasque, Basque, Spain) What can model animal systems tell us about Angelman Syndrome?
10.50	-	11.10	Tea / coffee & biscuits
11.10	-	11.25	Rossella Avagliano Trezza (Academic Medical Center (AMC), Netherlands) Characterization of a newly identified E6AP interacting protein.
11.25	-	11.55	Karen Bindels-de Heus, Marie-Claire de Wit (ENCORE Expertise Centre for Angelman Syndrome, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands) Multidisciplinary expertise center for Angelman syndrome: Presentation of the center, results of the first 5 years and goals for the next 5 years.
11.55	-	12.10	Jill Clayton-Smith (Manchester University, UK) Using Newer Genetic Technologies to Diagnose Angelman-Like Disorders.
12.10	-	12.25	Helen Cross (UCL Institute of Child Health, Great Ormond Street Hospital, London) Childhood Epilepsy
12.25	-	12.40	Chris Oliver/Mary Heald (University of Birmingham) Difficult behaviour in Angelman syndrome: From description to syndrome sensitive intervention.
12.40	-	12.55	Jeanne Wolstencroft, Imagine ID (UCL, University of London, UK) A study of intellectual disability, mental health and genetics.
12.55	-	1.10	David Clayton (Queen Mary University of London, UK) Birdsong communication and learning.
1.10	-	2.00	Buffet Lunch
2.00	-	4.00	Erin Sheldon & Mary-Louise Bertram Getting Started with AAC: Supporting our sons & daughters to access language
4.00	-	4.30	Tea / Coffee & Biscuits
4.30	-	5.30	All speakers, ASSERT & ASA Questions and answers to the scientific panel.

Saturday Schedule for those not attending the ASSERT conference.

11.00	-	1.00	Optional Coach tour of Liverpool (meet in hotel foyer 10.45am)
1.10	-	2.00	Buffet Lunch
2.00	-	4.00	Angelman Syndrome Alliance meeting (Lever room)
4.00	-	4.30	Tea / Coffee & biscuits
4.30	-	5.30	Return to The Merchant Suite for final Q&A session.

Rossella Avagliano Trezza (Academic Medical Centre (AMC), Netherlands)

Title: Characterization of a newly identified E6AP interacting protein.

Abstract:
Angelman syndrome (AS) is caused by deletion or mutations of the UBE3A gene. The UBE3A gene encodes an E3 ubiquitin ligase called E6AP that marks proteins with an ubiquitin tag. Ubiquitination of a protein usually results in its degradation by a large protease complex, the proteasome. The inability of mutated E6AP to ubiquitinate its target(s), and hence inadequately mark them for degradation, is believed to cause AS. Several potential substrates of E6AP have been reported, however, most of these potential substrates are not brain-specific and their contribution to the severe neurological phenotype in AS patients remains unclear. Therefore, identification of the critical E6AP target(s) and understanding their mechanistic contribution to the disorder is a first step in developing a therapy for AS. By employing a protein-protein interaction screen we have recently identified several proteins that interact with E6AP. Here, I will describe the techniques applied for their identification and the tools we have to understand the molecular basis of such interactions.

Art Beaudet (Baylor College of Medicine, USA) & Frank Rigo (ISIS Pharmaceuticals)

Title: Towards a therapy for Angelman syndrome by targeting a long non-coding RNA.

Abstract:
Angelman syndrome is a single-gene disorder characterized by intellectual disability, developmental delay, behavioural uniqueness, speech impairment, seizures and ataxia1,2. It is caused bymaternal deficiency of the imprinted geneUBE3A, encoding an E3ubiquitin ligase3–5.All patients carry at least one copy of paternal UBE3A, which is intact but silenced by a nuclear-localized long non-coding RNA, UBE3A antisense transcript (UBE3A-ATS)6–8.MurineUbe3a-ATS reduction by either transcription termination or topoisomerase I inhibition has been shownto increase paternalUbe3a expression9,10. Despite a clear understanding of the disease-causing event in Angelman syndrome and the potential to harness the intact paternal allele to correct the disease, no gene-specific treatment exists for patients. Here we developed a potential therapeutic intervention forAngelman syndrome by reducingUbe3a-ATS with antisense oligonucleotides (ASOs). ASO treatment achieved specific reduction of Ube3a-ATS and sustained unsilencing of paternal Ube3a in neurons in vitro and in vivo. Partial restoration of UBE3Aprotein in an Angelman syndrome mouse model ameliorated some cognitive deficits associated with the disease.

Although additional studies of phenotypic correction are needed, we have developed a sequence-specific and clinically feasible method to activate expression of the paternal Ube3a allele.

Friday: Karen Bindels-de Heus, Marie-Claire de Wit (ENCORE Expertise Centre for Angelman Syndrome, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands)

Title: A multidisciplinary expertise centre for Angelman syndrome: Clinical features and genotype-phenotype correlation in a large cohort of children with Angelman Syndrome.

Abstract:
G.C.B. Bindels-de Heus, MD1, C.C. Moor1, A. van den Elzen, MD PhD1, A.B. Rietman, BSc2, L.W. ten Hoopen, MD3, P.F.A. de Nijs, MD PhD3, C. Navis4, H. Diermen-van Gastel5, E.J.T.M. van der Louw6, L.P.C.M. Mocking2, A.S. Brooks, MD PhD7, Y. Elgersma, Prof8, M.C.Y. de Wit, MD PhD2

1. Dept. of Pediatrics
2. Dept. of Neurology
3. Dept. of Child and Adolescent Psychiatry and Psychology
4. Dept. of Speech and Language Therapy
5. Dept. of Physical Therapy
6. Dept. of Dietetics
7. Dept. of Clinical Genetics
8. Dept. of Neuroscience

ENCORE Expertise Centre for Angelman Syndrome, Erasmus MC, Sophia Children's
Hospital, Rotterdam, the Netherlands
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Background
In 2009 the ENCORE Expertise center for rare neurocognitive developmental disorders started a clinic for children with Angelman Syndrome. Patients are seen yearly by a multidisciplinary team. We have seen 90 children at least once by now.

Objective
To present our multidisciplinary team, our first results and our goals for (future) research, to improve insight into the clinical variation of symptoms, complications and prognosis, and to correlate clinical features and genotype.

Methods
A cohort of 90 children will be analyzed for the conference. For statistics, uniparental disomy (UPD) and imprinting defect (ID) are grouped, as they are clinically similar and these numbers are small.

Results
In a pilot study of the first 70 patients, 44 (69%) children had a microdeletion (MD), 13 (18%) UPD/ID and 13 (18%) UBE3A mutation. Mean age at diagnosis was 28 months with a lower age in patients with MD than UPD/ID ($p= 0.001$) or UBE3A mutation ($p<0.001$). The head circumference of MD children was smaller than of children with UPD/ID ($p=0.039$). Weight-for-height increased with age ($p<0.001$) and with hyperphagia

(p<0.001). More children with UPD/ID were able to walk than children with MD (12/13 vs 21/40, p=0.019). Children with MD had a higher incidence of epilepsy (88% vs 69%, p= 0.013) and a lower age of onset of epilepsy than in children with UPD/ID (p<0.001). Over 85% of parents reported sleep problems.26/70 children had language testing. Children with an UPD or mutation scored higher on a non-speech test for communication.

We will present an updated analysis with 20 additional children seen at the clinic by now including their developmental and behavioral profile and first prospective follow-up findings. An update on the communication skills evaluation will be given separately by our speech therapist.

Research goals are prioritized by our clinical findings and the preferences of the parent organizations to include natural history both in child- and adulthood, developmental and behavioral profile, dietary treatment of epilepsy, behavioral treatment of sleep problems, evaluation of communication skills and use of assisted communication methods and motor problems in puberty. We aim to perform translational medication trials of promising treatments in the future.

Conclusion
There is phenotypic variability between and within subgroups. Future prospective follow-up analysis will produce more reliable conclusions.

Saturday: Karen Bindels-de Heus, Marie-Claire de Wit (ENCORE Expertise Centre for Angelman Syndrome, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands)

Title: A multidisciplinary expertise center for Angelman syndrome: Presentation of the center, results of the first 5 years and goals for the next 5 years.

Abstract:
G.C.B. Bindels-de Heus, MD1, A.B. Rietman, BSc2, L.W. ten Hoopen, MD3, P.F.A. de Nijs, MD PhD3, C. Navis4, H. Diermen-van Gastel5, E.J.T.M. van der Louw6, L.P.C.M. Mocking2, L. Bastiaanse, MD PhD7, M. Valstar, MD PhD7, A.S. Brooks, MD PhD8, Y. Elgersma, Prof9, M.C.Y. de Wit, MD PhD2

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Background
In 2009 the ENCORE Expertise center for rare neurocognitive developmental disorders started a clinic for children and in 2014 also for adults with Angelman Syndrome. Patients are seen yearly by a multidisciplinary team. We have seen 90 children and 13 adults at least once by now.
Aim
To present our multidisciplinary team, first results and our goals for future care and research.

Summary
We will present the Angelman team, follow-up schedule, cooperation with the parent organizations and possibility for patients outside the Netherlands to visit.
We will give an overview of the clinical features and genotype-phenotype correlation of 90 children with Angelman syndrome. Research goals are prioritized by our clinical findings and the preferences of the parent organizations to include natural history both in child- and adulthood, developmental and behavioral profile, dietary treatment of epilepsy, behavioral treatment of sleep problems, evaluation of communication skills and use of assisted communication methods and motor problems in puberty. We aim to perform translational medication trials of promising treatments in the future.

Becky Burdine

Title: Overview of recent scientific advances in Angelman Syndrome research.

Abstract:
Becky Burdine will give a brief genetics 101 on the causes of AS, followed by an overview of the strategies scientists are currently using to look for therapeutics in AS. Becky will also provide a summary of updates about the science presented the day before - followed by any questions and answers.

David Clayton
(Queen Mary University of London, UK)

Title: Birdsong communication and learning.

Abstract:
Songbirds communicate through vocalizations they learn. Here I will review the many parallels between birdsong learning and human speech and language learning. These include the progression of learning during juvenile life, and similarities in the underlying neural control circuits. The major songbird species used in laboratory research is the zebra finch. Experiments in the zebra finch have already shown that genes implicated in human learning and language development also play roles in song learning. A focus for the future is to determine whether song learning ability can be promoted or reactivated in adult zebra finches, after the end of the normal juvenile learning period. Thus the zebra finch may serve as a uniquely relevant model for Angelman syndrome research.

Jill Clayton-Smith (Manchester University, UK)

Title: Using Newer Genetic Technologies to Diagnose Angelman-Like Disorders.

Abstract:

Jill Clayton-Smith, Beverley Anderson, Jill Urquhart
Manchester Centre for Genomic Medicine. St Mary's Hospital, Manchester, M13 9WL. Jill.Clayton-Smith@cmft.nhs.uk

Angelman syndrome (AS) , first described by Harry Angelman in 1965 is a neurodevelopmental disorder characterised by intellectual disability, ataxia, seizures with abnormal EEG, absent or very limited speech, sociable disposition and subtle, but characteristic facial features. The condition is caused by a number of genetic mechanisms which all interfere with the expression of the maternally expressed UBE3A gene at chromosome 15q11-13. Within the cohort of children clinically diagnosed as having Angelman syndrome, researchers have always traditionally included a group of individuals with typical clinical presentations, but where no genetic abnormality affecting the AS locus can be found. In some studies these are referred to as the "quadruple none" group as they lack deletions, uniparental disomy, imprinting defects and UBE3A mutations. Explanations put forward for this group include the existence of a second AS gene, lack of sensitivity of the available tests, mosaisicm and the presence of AS phenocopies. We recruited a cohort of 120 patients with a clinical diagnosis of AS but no genetic diagnosis and reviewed clinical features, performed array CGH studies and sequenced a panel of 60 genes for AS-like disorders. In some, where these results were negative we also carried out whole exome sequencing. We present the genetic findings in this cohort which reveal that the main explanation for the "quadruple none" cases is that these individuals have alternative diagnoses, and we discuss the clinical clues to diagnosis of these disorders.

Rosie Conroy

Title: Medical problems and provision of care for patients with Angelman Syndrome

Abstract:

In 2010, the Dyscerne Angelman Syndrome guidelines were created to provide clear and evidenced-based recommendations for the management of patents with AS. Since its publication, there has been no formal review of the guidelines. As such this study aimed to verify the content of the information in the Dyscerne guidelines and audit current compliance with recommendations. Distributed via the UK's Angelman charity, ASSERT, parents and carers of patients with AS completed an anonymous online questionnaire. Respondents were recruited on an 'opt-in' basis via ASSERT's newsletter and online resources. All 12 sections of the Dyscerne guidelines were audited in accordance with 53 standards. Compliance was recorded as 'poor' (<50%), 'satisfactory' (50-80%) or 'good' (>80%.) 27/53 (50.9%) had 'poor' compliance, 9/53(17.0%) 'satisfactory' compliance and 17/53(32.1%) 'good' compliance. This study provides an insight into the day-to-day management issues for families of AS patients and highlights many areas of good practice. Despite this, currently the provision of care for AS patients remains suboptimal in some areas.

Helen Cross (UCL Institute of Child Health, Great Ormond Street Hospital, London)

Title: Childhood Epilepsy

Abstract:

Professor Helen Cross is The Prince of Wales's Chair of Childhood Epilepsy and Honorary Consultant in Paediatric Neurology at UCL Institute of Child Health, Great Ormond Street Hospital for Children NHS Trust, London, and Young Epilepsy, Lingfield.

She is currently Clinical Advisor to the Children's Epilepsy Surgery Services (CESS) (2012-present), is Chair of the Medicines for Children Research Network Neurosciences Clinical Study Group (2012-present), Chair of the Evidence Update of the NICE Guidelines for Epilepsy (2013) and was recently elected Secretary General of the ILAE to serve 2013-2017.

She is on the Editorial Board of Epileptic Disorders, Epilepsy Research, Developmental Medicine Child Neurology and European Journal of Paediatric Neurology.

Ben Distel (Academic Medical Centre (AMC), Netherlands)

Title: Structural and functional analysis of Ube3a/E6AP.

Abstract:

The UBE3A gene encodes the ubiquitin protein ligase E6AP, for which impairment in E6AP-mediated ubiquitination of its target(s) is believed to cause Angelman syndrome. However, the critical neuronal targets of E6AP are still unknown. We have employed yeast two-hybrid screens and comparative ubiquitin-proteomics (Ube3a knock-out versus wild type) to identify novel targets of E6AP. In addition, we have established the tools to validate these targets at the biochemical level. I will present the initial characterization of a newly identified E6AP target, and discuss the role of a structural domain of E6AP in binding of the target. Finally, I will discuss the development of innovative approaches aimed at identifying novel neuronal substrates and regulators of E6AP.

Matthew During (Ovid Therapeutics, USA)

Friday Title: OV101: enhancing tonic inhibition as a therapeutic approach to Angelman Syndrome.

Saturday Title: Ovid Therapeutics: A partner committed to making a meaningful difference in the lives of those with Angelman Syndrome and their families.

Ype Elgersma (Neuroscience Institute, Erasmus University, Netherlands)

Title: Dissociation of locomotor and cerebellar deficits in Ube3a mice

Abstract:
Angelman syndrome (AS) is associated with prominent movement and balance impairments, which are widely considered to be of cerebellar origin. Using the cerebellar-specific vestibulo-ocular reflex (VOR) paradigm, we determined that cerebellar function is only mildly impaired in AS (Ube3am–/p+) model mice. These deficits are likely due to reduced tonic inhibition between Golgi cells and granule cells. Purkinje cell physiology, in contrast, was normal in AS mice as shown by synaptic plasticity and spontaneous firing properties that resembled controls. Accordingly, neither VOR phase reversal learning nor locomotion were impaired following selective deletion of Ube3a in Purkinje cells. However, genetic normalization of alpha-CaMKII inhibitory phosphorylation fully rescued locomotor deficits despite failing to improve cerebellar learning in AS mice, suggesting extra-cerebellar circuit involvement in locomotor learning. We confirmed this through cerebellum-specific reinstatement of Ube3a, which prevented cerebellar learning deficits but did not rescue locomotor deficits. This double dissociation of locomotion and cerebellar phenotypes strongly suggests that the locomotor deficits of AS mice do not arise from impaired cerebellar cortex function. Our results provide novel insights into the etiology of motor deficits associated with AS and are important for future trial design in which motor function is an outcome parameter.

Noelle Germain (University of Connecticut health Centre, USA)

Title: Human Induced Pluripotent Stem Cell Models of Angelman Syndrome.

Abstract:
Animal models of Angelman syndrome (AS) have been extremely informative to the research community and have helped us begin to understand the cellular processes involved in AS phenotypes. However, the ideal model for use in understanding how AS is manifested in cells of the human brain and for the development and testing of drug therapies is the human AS neuron itself. Induced pluripotent stem cell (iPSC) technology allows us to transform AS patient samples into pluripotent cell lines that maintain the underlying genetic variants of those individuals. These cells can then be differentiated into functionally mature neurons, which are amenable to genetic and pharmacological manipulations in vitro. We have established human iPSC models of AS both by cellular reprogramming of patient samples as well as by using genome editing technology. I will discuss ongoing work in the Chamberlain lab in which we are utilizing these iPSCs and their neural derivatives to investigate both the process of UBE3A imprinting in human neurons and the contribution of different UBE3A isoforms to a neuronal phenotype. This work allows us to further establish a human in vitro model system for testing candidate therapies.

Friday: Ugo Mayor (Ikerbasque, Basque, Spain)

Title: UBE3A substrate identification: past, present and future.

Abstract:
Angelman Syndrome (AS) was first described in 1965, but its cause being a missing or mutated maternal contribution of the UBE3A gene, located on chromosome 15q, only discovered in 1997. The molecular basis for this pathology was however not any clearer after the discovery, since the product of the UBE3A gene is an ubiquitin E3 ligase responsible of the attachment of ubiquitin molecules onto its target proteins. E3 ligases can have multiple substrates, and therefore the manifestations of AS could be caused by the misregulation of any of the neuronal substrates of UBE3A. Despite its involvement in many physiological and disease-related processes, ubiquitination usually targets just a small fraction of any given protein, and it is still very challenging to identify this post-translational modification from human samples. The lack of a mammalian model system for both in vivo identification and validation of ubiquitination targets, has meant that several candidate UBE3A substrates reported during the last decade were only validated in vitro, with later in vivo studies contradicting the earlier conclusions. A review of the current state of the field will be presented, including advances by our lab.

Saturday: Ugo Mayor

Title: What can model animal systems tell us about Angelman Syndrome?

Abstract:
Angelman Syndrome (AS) is a neurological disorder without cure and whose symptoms receive a limited treatment. The cause of AS was identified in 1997 to be the mutation in the gene UBE3A, which codes for a ubiquitin E3 ligase responsible of the attachment of ubiquitin molecules onto its target proteins. As of today, we still do not know which proteins are directly regulated by UBE3A. Despite its involvement in many physiological and disease-related processes, ubiquitination usually targets just a small fraction of any given protein, and it is still very challenging to identify this modification from human samples. Since the cell biology of humans is not that different from that of mice and flies, we can use those animal model systems to advance in our biochemical studies. A review of the current state of the field will be presented, including advances by our lab.

Qing-Jun Meng (Manchester University, UK)

Title: UBE3A, a E3 ubiquitin ligase that regulates the circadian clock in mammalian cells and flies.

Abstract:
Nicole C Gossan1, Feng Zhang1, Baoqiang Guo1, Ding Jin1, Hikari Yoshitane2, Aiyu Yao3, Nick Glossop1, Yong Q Zhang3, Yoshitaka Fukada2, Qing-Jun Meng1*
1Faculty of Life Sciences, University of Manchester, Oxford Road, Manchester, M13 9PT, UK. 2Department of Biophysics and Biochemistry, University of Tokyo, Tokyo 113-0033, Japan. 3Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing 100101, China. *Correspondence to: Qing-Jun.Meng@manchester.ac.uk

Post-translational modifications (such as ubiquitination) of the clock proteins are critical in maintaining the precision and robustness of the evolutionarily conserved circadian clock. Ubiquitination of the core clock transcription factor BMAL1 (Brain and Muscle Arnt-Like 1) has recently been reported. However, it remains unknown whether BMAL1 ubiquitination affects circadian pacemaking, and what ubiquitin ligase(s) is involved. Here, we show that activating UBE3A (by expressing viral oncogenes E6/E7) disrupts circadian oscillations in mouse embryonic fibroblasts, measured using PER2::Luc dynamics, and rhythms in endogenous mRNA and protein levels of BMAL1. Over-expression of E6/E7 reduced the level of BMAL1, increasing its ubiquitination and proteasomal degradation. UBE3A could bind to and degrade BMAL1 in a ubiquitin ligase-dependent manner. This occurred both in the presence and absence of E6/E7. We provide in vitro (knockdown/overexpression in mammalian cells) and in vivo (genetic manipulation in Drosophila) evidence for an endogenous role of UBE3A in regulating circadian dynamics and rhythmic locomotor behaviour. Together, our data reveal an essential and conserved role of UBE3A in the regulation of the circadian system in mammals and flies, and identify a novel mechanistic link (UBE3A) between oncogene E6/E7-mediated cell transformation and circadian (BMAL1) disruption.

Chris Oliver/Mary Heald (University of Birmingham)

Title: Difficult behaviour in Angelman syndrome: From description to syndrome sensitive intervention.

Abstract:
In this presentation we describe a series of research studies in which we have: 1) identified specific behavioural difficulties that are more common in Angelman syndrome than others with intellectual disability, 2) developed and trialled successful proof of principle interventions for some of these specific problems and 3) started to develop a broad intervention strategy that is Angelman syndrome sensitive. We will also describe new research into sleep problems and communication that is underway at the Cerebra Centre for Neurodevelopmental Disorders.

Erin Sheldon & Mary-Louise Bertram

Title: Getting started with AAC: supporting our sons and daughters to access language.

Abstract:
Supporting our sons and daughters to access a communication system requires a long-term commitment. The international Angelman parent community has been making this commitment because we so badly want to know the thoughts, dreams, and frustrations our children are experiencing. Mary-Louise and Erin will describe a long-term plan for how every family can join the Angelman family communication revolution! This revolution is grounded in the research into language acquisition and symbol learning through aided modeling. It sounds complicated but it's really not: at its heart, our job is to provide our children with a language they can access when speech is not an option. Come hear firsthand how families are creating this access!

Ilaria Tonazzini (NEST, Istituto Nanoscienze-CNR, Italy)

Title: Impaired neurite contact guidance in Ubiquitin ligase E3a-Knock Out (Ube3a-KO) neurons.

Abtract:
Tonazzini I 1,2, Meucci S 2, Van Woerden GM 3, Elgersma Y 3, Beltram F 2 and Cecchini M 2
1 Fondazione Umberto Veronesi (Milano, Italy)
2 NEST, Istituto Nanoscienze-CNR and Scuola Normale Superiore (Pisa, Italy)
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In the central nervous system, the contact sensing combines with complex signaling patterns that are integrated by cells leading to cytoskeleton remodeling to establish neuronal adhesion, migration, growth-cone path-finding and the final neuronal architecture and plasticity. Focal adhesions (FAs) act as sensors by integrating signals from both the extracellular matrix environment and chemo-attractive/repulsive factors, orchestrating cytoskeleton dynamical shaping.

In order to study cell contact sensing, one promising approach exploits nano/micro-structured substrates. These systems allow to finely controlling the properties of the extracellular environment in vitro. Nano-engineered substrates are in fact able to induce specific topographical stimuli to cells, resembling in vitro several features of the physiological extracellular matrix cues.

Although the dynamics of neuronal contact sensing are emerging as crucial for neuronal functionality, little is known about these processes in pathological conditions. Nowadays E3 ubiquitin ligases are increasingly recognized as key regulators of neuronal morphogenesis and connectivity. Among these, Ubiquitin E3a ligase (Ube3a) has a key role in brain functioning. Recent data suggest that the loss of Ube3a is associated with defects in neuronal structure in several brain areas; however how its loss of function results in neurocognitive impairment, the Angelman Syndrome (AS; OMIN 105830), is still unclear.

Here, the role of Ube3a was investigated in neurite contact guidance during neuronal development in vitro. We studied the contact sensing of Wild-Type (WT) and Ube3a-KO neurons by exploiting nano-grooved substrates with different topographical characteristics with the aim to compare the capability of neurons to read and follow physical directional stimuli. As expected, WT neurons could polarize along the NGs, showing efficient neurite alignment. Conversely, in Ube3a-KO neurons mechanotransduction was less efficient, as highlighted by an initial loss of cell polarization and neurite alignment. In order to evaluate if this behavior was due to altered adhesion mechanisms in Ube3a-KO neurons, the activation of FA pathway was investigated, at level of focal adhesion kinase (FAK) and paxillin (PAX). We found that this behavior is linked to an impaired activation of FA pathway.

Overall, our results indicate that neuronal topography sensing machinery might be affected in Angelman Syndrome.

Elles van der Louw (ENCORE Expertise Centre for Angelman Syndrome, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands)

Title: Dietary therapy of children with Angelman Syndrome and refractory epilepsy; design of a randomized controlled trial.

Abstract:

Elles J.T.M. van der Louw, RD[1], Karen C.B. Bindels- de Heus MD[2], Sabine.E. Mous, Msc PhD[3], Joanne F Olieman, RD, PhD[1], Sylvia Walet, RD[1], Marit Verhagen, RD[1], Andre B. Rietman, PhD[3], Marie Claire. Y. de Wit, MD,PhD[4]

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Background

The majority of children with Angelman Syndrome (AS) have intractable epilepsy. Additional (non-pharmacological) treatment options are needed, like dietary regimes. Studies show low glycemic index diet (LGID) to be successful and ketosis should have no beneficial effect. Due to typical feeding difficulties, behavioral and medical problems strict dietary regimes like classical ketogenic diet (KD), which induces ketogenisis, is believed not to be feasible in AS. Our daily practice shows increased seizure reduction when reaching ketosis or medium chain triglycerides (MCT fat) use and unexpected feasibility reported by parents.

Methods/design

A group of 20 patients will be randomized after one month optimal anti-epileptic drugs (AED) use into a ketogenic diet (KD) group (n=10) and control group (n=10). The KD consists of 90 energy% of fat of which 15 energy% of MCT fat and 5 energy% of carbohydrates. The control group (n=10) maintains AED use. After 3 months patients with success on KD switch to Modified Atkins Diet (MAD) which consist of 30 grams of carbohydrates per day, fat and protein intake at libitum, while continuing 15 energy% of MCT fat use. The control group starts KD treatment for 3 months. Epilepsy dairies, questionnaires of Qol, feeding difficulties and parental stress are used baseline, 4 and 7 months.

Aim

Determine effectiveness (50% or more seizure reduction) of dietary treatment based on reaching adequate ketosis (3-4+ mmol/l in blood) with respect to Qol, feasibility, parental cooping and stress. Determine maintenance of seizure reduction on moderate diet MAD.

Jeanne Wolstencroft, Imagine ID (UCL, University of London, UK)

Title: A study of intellectual disability, mental health and genetics.

Abstract:

When a child is diagnosed with a rare genetic change there is often limited knowledge available for doctors to answer parents' next question: "So what does this mean for my child?" The IMAGINE ID study aims to answer this question by investigating the relationship between genetic changes, development and behaviour in children with intellectual disability.

One of the highlights of the weekend has to be our Celebration Gala. We hope that everyone will have a wonderful evening enjoying good food and great conversation. This is a very special evening to celebrate everything that has been achieved so far, and to look forward to what we can achieve in the coming years. 2015 is a double celebration – 50 years since the discovery of Angelman Syndrome and also what would have been Dr Harry Angelman's 100th birthday. We are thrilled to have a brilliant live band who will be performing during the evening and what makes this even more special is the fact that one of the band members is one of our very own AS parents – Charles Villiers.

'Sunshine Soul Revue'

are a Brighton based soul band. The players are cherry-picked from the most exciting and creative bands on the scene and have been providing the soundtrack for their home town throughout the noughties. Musically, they place a strong emphasis on an authentic sound and vide, as they try to evoke the incredible spirit of the golden age of soul. Their shows are inclusive, joyful and downright funky!

A NOTE FROM CHARLES....

My name's Charles and I am father to Dexter, who is 4 and was diagnosed with AS at 2 and a half. Ever since, we have been part of the ASSERT community and have got a lot of useful information and support from the Facebook groups and website.

Now, however, we are going up a gear and coming to the 2015 conference in Liverpool which is extremely exciting in itself but I have to confess that I am doubly excited because ASSERT have chosen our soul band to be your entertainment for the night!

I have always played in local bands, for better or for worse, and somehow never given up and now, aged a million and one with two young kids (Blanche is aged 7), I'm so glad I didn't. The soul band is made up of friends who I've been playing with for years and we pride ourselves on knowing loads about the music we perform. We read the books, we get the old gear, we copy the originals to the letter and yet preserve the rock and roll spirit in which they were originally performed. Pond-wise, it's Motown, Stax, Philly, Atlantic over there, Celtic Soul, British Invasion and of course Mersey Beat this side.

I think we're a fine band, especially when the audience is up for a bit of a knees up, so we'll be giving 110% for the Gala show. I'm really looking forward to it and to being involved in such a special event.

Charles Villiers

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www.angelmanuk.org
Rachel Martin
Rich Williams
Lisa Court
Katie Cunnea
Andrea Baines
Catrina Fraser
Mairi Leith-McGaw
Sue Williams
Jonathan Allen
Sian Cartwright
Diane Fox-Jones
Linda Holmes

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Angelman Syndroom Nederland (formerly PWAV)
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Johan Klein
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Switzerland

Angelman Verein Schweiz
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Karen Jones

France

Association Francaise du Syndrome D'Angelman (AFSA)
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Denise Laporte
Nicolas Viens
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The ASSERT trustees would like to say a special thank you to all our speakers who have very kindly given up their weekend to attend our Scientific Conference. Without you this would not have been possible. We appreciate your support and dedication to Angelman Syndrome and we look forward to see what the future holds in the coming years.

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Thank you!








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