



# **Third International Meeting on Genetic Syndromes of the Ras/MAPK Pathway: Towards a Therapeutic Approach**

**Renaissance Orlando at SeaWorld  
August 2-4, 2013**

**Hosted by:  
The University of Alabama at Birmingham  
Department of Genetics**

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# ACKNOWLEDGEMENTS

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# PROGRAM AGENDA

## Third International Meeting on Genetic Syndromes of the RAS/MAPK Pathway: Towards a Therapeutic Approach

August 2-4, 2013  
Renaissance Orlando at SeaWorld

### Friday ~ August 2, 2013

8:00 – 10:00 pm      *Dessert and Poster Session for Symposium Attendees and  
Advocacy/Family Support Groups*  
\*ATRIUM C/D

### Saturday ~ August 3, 2013

7:00 – 8:15 am      *Breakfast \*OCEANS 5*

8:15 – 8:30 am      *Meeting \*OCEANS 6*  
*Welcoming Comments and Introduction*  
*Bruce Korf, University of Alabama at Birmingham,*  
*Alcino Silva, University of California, Los Angeles*

8:30 – 9:00 am      *Keynote Presentation: TRND*  
*Program at NIH and possibilities for drug discovery in the Ras/MAPK disorder*  
*Sittampalam Gurusingham, NCATS*

9:00 – 9:30 am      *Advocates' Panel*  
*Advocates Representing CFC, Costello, Neurofibromatosis type 1 and Noonan syndromes*

9:30 – 10:50 am      *Ras/MAPK Pathway Phenotypes and Therapeutic Goals*  
*Moderators: Karen Gripp, DuPont Hospital for Children and*  
*Judith Allanson, Children's Hospital, Eastern Ontario*

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*Therapeutic endpoints in NF1*

*Scott Plotkin*  
*Massachusetts General Hospital*

*Cardio-facio-cutaneous syndrome*

*Emma Burkitt Wright*  
*University of Manchester*

*Costello syndrome*

*Browyn Kerr*  
*University of Manchester*

*Noonan syndrome*

*Amy Roberts*  
*Children's Hospital, Boston*

10:50 – 11:10 am      *Break*

<b>11:10 – 12:30 pm</b>	<b>Genomic Approaches</b>	
	<b>Moderator: Ludwine Messiaen, University of Alabama at Birmingham</b>	
	<b>Molecular analysis of NF1</b>	<b>Ludwine Messiaen, University of Alabama at Birmingham</b>
	<b>Structural and functional characterization of RAS mutants</b>	<b>Reza Ahmadian, Heinrich-Heine University</b>
	<b>Use of antisense morpholino oligomers as a gene-therapeutic approach to restore normal splicing</b>	<b>Conxi Lázaro, IMPPC Barcelona</b>
	<b>Ras pathway gene mutations in human genetic disorders</b>	<b>Yoko Aoki, Tohoku University</b>
<b>12:30 – 1:35 pm</b>	<b>Lunch *OCEANS 5</b>	
<b>1:35 – 2:20 pm</b>	<b>Presentation of Submitted Abstracts by Young Investigators</b>	
	<b>Moderators: Bruce Korf, University of Alabama at Birmingham and Alcino Silva, University of California, Los Angeles</b>	
<b>2:20 – 3:40 pm</b>	<b>Ras Pathway Biology and Identification of Therapeutic Targets</b>	
	<b>Moderators: Ype Elgersma, Erasmus University and Benjamin Neel, Ontario Cancer Institute</b>	
	<b>Mechanism and treatment for the cognitive deficits associated with animal models of Noonan syndrome</b>	<b>Alcino Silva, UCLA</b>
	<b>Modeling RASopathies with hiPSC</b>	<b>Sonia Mulero-Navarro, Mt. Sinai School of Medicine</b>
	<b>Learning difficulties in the RASopathies: Pathogenesis and treatment</b>	<b>Ype Elgersma, Erasmus University</b>
<b>3:40 – 4:00 pm</b>	<b>Break</b>	
<b>4:00 – 5:20 pm</b>	<b>Preclinical Drug Development and Testing</b>	
	<b>Moderator: Bruce Gelb, Mt. Sinai School of Medicine</b>	
	<b>Therapeutic approach to HCM in Noonan syndrome with multiple lentiginos</b>	<b>Maria Kontaridis, Harvard Medical School</b>
	<b>Mouse models of Noonan syndrome and other RASopathies</b>	<b>Benjamin Neel, Ontario Inst. Can. Res.</b>
	<b>Drug screening for Noonan syndrome with Drosophila</b>	<b>Bruce Gelb, Mt. Sinai School of Medicine</b>
<b>6:00 pm</b>	<b>Dinner: for Registrants who signed up for:</b>	
	<ul style="list-style-type: none"> <li>• CFC International family forum dinner *CRYSTAL BALLROOM D, E</li> <li>• Noonan Syndrome Foundation family forum dinner *CRYSTAL BALLROOM A, B, C</li> </ul>	

**6:30 pm**                    **Dinner: for Registrants who signed up for Costello syndrome family forum dinner**  
**\*DISCOVERY BALLROOM**

**Sunday ~ August 4, 2013**

**7:00 – 8:00 am**            **Breakfast \*CRYSTAL B**

**8:00 – 9:20 am**            **Meeting \*DISCOVERY BALLROOM**

**Clinical Trials**

**Moderator: Katherine Rauen, University of California, San Francisco**

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**NF Clinical Trials Consortium**                    **Bruce Korf, University of Alabama at Birmingham**

**Clinical trials for Fragile X syndrome**                    **Reymundo Lozano, University of California, Davis**

**Use of Raf inhibitors for treatment of melanoma**                    **Chao Zhang, Plexxicon**

**The NS clinical trial**                    **Calum MacRae  
Brigham and Women's Hospital**

**9:20 – 10:20 am**            **Infrastructure to Support Therapeutic Development**

**Moderator: Amy Roberts, Children's Hospital, Boston**

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**The CTF therapeutic development pipeline**                    **Annette Bakker, Children's Tumor Foundation**

**Tissue banking in pediatric oncology**                    **Corrine Linardic, Duke University School of Medicine**

**Patient-driven disease registries**                    **Pat Furlong, Parent Project Muscular Dystrophy**

**10:20 – 10:35 am**            **Break**

**10:35 – 12:15 pm**            **Break-out Sessions with RASopathies Families**

**CFC syndrome families**

**ATLANTIS A  
Rebecca Joswitz  
Mt. Sinai School of Medicine**

**Katherine Rauen  
University of California, San Francisco**

**Costello syndrome families**

**ATLANTIS B  
Karen Gripp  
DuPont Hospital for Children**

**Bronwyn Kerr  
University of Manchester**

**Angie Lin  
Harvard Medical School**

***Neurofibromatosis type I families***

***ODYSSEY A***  
***Bruce Korf***  
***University of Alabama at Birmingham***

***David Viskochil***  
***University of Utah***

***Noonan syndrome families***

***ODYSSEY B***  
***Judith Allanson***  
***Children's Hospital, Eastern Ontario***

***Bruce Gelb***  
***Mt. Sinai School of Medicine***

***Amy Roberts***  
***Children's Hospital, Boston***

***Alcino Silva***  
***University of California, Los Angeles***

***Md. Abdur Razaque***  
***Cincinnati Children's Hospital***

***12:15 – 12:30 pm***      ***Final Comments and Discussion***

***Bruce Korf, University of Alabama, at Birmingham***

***Alcino Silva, University of California, Los Angeles***

***Lisa Schoyer, RASopathies Network USA***

***1:15 – 4:00 pm***      ***NF Network Break-out***

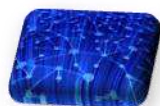
***ODYSSEY A***

***Ludwine Messiaen***  
***University of Alabama at Birmingham***

***Alcino Silva, University of California, Los Angeles***

***David Viskochil***  
***University of Utah***





# ABSTRACTS

## **THERAPEUTICS FOR RARE & NEGLECTED DISEASES (TRND) PROGRAM AT NIH AND POSSIBILITIES FOR DRUG DISCOVERY IN THE RAS/MAPK DISORDERS**

**G. Sitta Sittampalam, Ph.D.**

*Therapeutics for Rare & Neglected Diseases, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, 9800 Medical Center Drive, Rockville, MD, USA.*

The TRND program at the National Center for Advancing Translational Sciences (NCATS/NIH) was established in 2009 to stimulate and speed the discovery & development of new drugs for rare and neglected diseases. It is a unique collaborative model between the NIH and academic scientists, non-profit organizations and pharmaceutical and biotechnology companies. These collaborations involve early drug discovery through high Throughput Screening (HTS) and repurposing known drugs to the clinic via access to development capabilities, such as lead optimization, ADME, PK/PD, toxicology, formulation development, scale up API and clinical & regulatory activities.

The involvement of RAS pathways in many rare diseases (RASopathies) is well recognized, and the current symposium provides an excellent venue to discuss potential collaboration and non-traditional funding models available at NCATS to rapidly advance therapeutic innovations directly to the patients with RASopathies. The current TRND portfolio and case studies on rare disease drug development will be highlighted to exemplify potential opportunities for collaboration.

## **GETTING TO YES: THE RESPONSE EVALUATION IN NEUROFIBROMATOSIS AND SCHWANNOMATOSIS (REINS) INTERNATIONAL COLLABORATION**

**Scott R. Plotkin**

*Massachusetts General Hospital; Boston, MA*

Neurofibromatosis 1 (NF1) is a complex neurogenetic disorder with features of a tumor-suppressor syndrome and a rasopathy. The condition is characterized by a predisposition to multiple tumor types, learning disability, bony lesions, and other disease manifestations, which often result in functional disability, reduced quality of life, pain, and in some cases malignancy. With increasing knowledge of the biology and pathogenesis of NF1, clinical trials with targeted agents directed at NF1-related complications have become available. Most clinical trials for patients with NF have used designs and endpoints similar to oncology trials. However, differences in the disease manifestations and natural history of NF1 (compared to cancers) require the development of new designs and endpoints to perform meaningful clinical trials. The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration was established in 2011 at the Children's Tumor Foundation meeting to achieve consensus within the NF community about the design of future clinical trials with a specific emphasis on endpoints. The REiNS Collaboration includes seven working groups that focus on imaging of tumor response; functional, visual, patient-reported, and neurocognitive outcomes; whole-body MRI; and disease biomarkers. The working groups have made the first series of recommendations on behalf of the REiNS collaboration. The hope is that these recommendations will be adopted by the broader research community to standardize the measurement of outcomes and thus improve clinical trials for patients with NF1. Ultimately, the REiNS collaboration plans to engage industry partners and national regulatory agencies in this process to facilitate the approval of drugs for NF1 patients.

## **CARDIO-FACIO-CUTANEOUS SYNDROME**

**Emma M. M. Burkitt Wright** <sup>1,2</sup>

*Wellcome Trust Clinical Research Training Fellow, Manchester Centre for Genomic Medicine* <sup>1,2</sup>, <sup>1</sup>*Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester;* <sup>2</sup>*St. Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester M13 9WL, UK.*

Cardio-facio-cutaneous syndrome (CFC) is a multisystem disorder due to germline mutations that cause dysregulation of the Ras-MAPK pathway, and frequently has severe manifestations. Patients demonstrate a wide variety of clinical problems, including neurological features such as learning disability and epilepsy, congenital heart disease and cardiomyopathy, and a wide variety of cutaneous manifestations. Genetic and phenotypic similarities to Noonan syndrome (NS) are present, and as in NS, extensive genetic heterogeneity is demonstrated, and a proportion of patients remain without a molecular diagnosis. These barriers to comprehensive molecular confirmation, combined with the wide variety and variability of clinical manifestations, make it challenging to characterise this disorder fully. The UK's national genetic testing service for CFC and Costello syndrome is based in Manchester, and has also diagnosed many patients from elsewhere in the world. Knowledge of this large cohort, now numbering over 200 patients with molecularly proven diagnoses, provides opportunities for better understanding of CFC, and the identification of common and novel features and genotype-phenotype correlations. These findings will allow for better anticipatory management for patients, and can provide critical information when determining future therapeutic goals.

## **COSTELLO SYNDROME PHENOTYPES AND THERAPEUTIC GOALS**

**Bronwyn Kerr, MBBS**

*Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre (MAHSC), Manchester M13 9WL, UK.*

Costello syndrome was first described in the 1970s by Jack Costello, a New Zealand Paediatrician, who recognised the key characteristics in 2 patients. There were no further publications until 1991, when der Kaloustian published a third case, suggested the name "Costello syndrome" and noted the resemblance to Noonan and Cardio-facio-cutaneous syndromes. Over the next decade, a number of reports expanded the clinical features, and a high risk of malignancy, particularly embryonal rhabdomyosarcoma, emerged.

The discovery by Aoki and colleagues of activating mutations in HRAS in 2005 as the cause of Costello syndrome has allowed precise definition of the core adult and childhood phenotypes, the recognition of prenatal and severe neonatal phenotypes, and also mild and atypical phenotypes. It has also supported the long-term study of Professor Karen Gripp and more accurate delineation of natural history. These studies are a prerequisite for considering treatment trials, and accurate outcome measures. The views of affected patients and their families are however of at least equal importance in evaluating endpoints.

## **NOONAN SYNDROME: PHENOTYPES AND THERAPEUTIC GOALS**

**Amy E. Roberts, MD**

*Boston Children's Hospital  
Harvard Medical School*

Given the prevalence of Ras mutations (20% of malignancies) and ERK hyperactivation due to activating mutations in Ras or BRAF (30% of human cancers), the development of inhibitors of the Ras/mitogen-activated protein kinase (MAPK) pathway has been of profound interest to cancer researchers. Noonan syndrome mutations are also activating and the question has been raised if these drugs might also be useful as systemic therapies after birth. Choosing phenotypic targets requires detailed knowledge of the natural history (what is the expected disease progression so it can be determined if treatment has

actually changed anything). Genotype phenotype correlations for a given feature help in selection of appropriate populations to treat. There must also be reliable end points to measure to determine the efficacy of the treatment. Finally, it is imperative that efficacious doses avoid severe toxicities for a treatment that will likely be needed long term if not lifelong. Treatment of short stature is the only extensively used and evaluated therapy for NS to date and our experience thus far will be discussed. Pharmacogenomically informed treatment of learning issues and cardiomyopathy, reported in animal models, will also be reviewed.

## **MOLECULAR ANALYSIS OF NF1 AND SPRED1**

**Ludwine Messiaen, Ph.D.**

*Department of Genetics, University of Alabama at Birmingham.*

The *NF1* gene is a large and complex gene spread over 280Kb of genomic DNA on chromosome 17q11.2, comprising 57 constitutive exons and at minimum 3 alternatively spliced exons. Mutations in the *NF1* gene affect worldwide ~1/3000 individuals and are associated with Neurofibromatosis type 1. Molecular analysis can help with the clinical diagnosis, especially when atypical forms of NF1 are present (such as spinal NF, NF-Noonan, Watson syndrome, segmental NF, ...).

Legius syndrome, a recently ras-o-pathy identified, is caused by mutations in the *SPRED1* gene on chromosome 15q13.2. Individuals with Legius syndrome present mainly with CAL-macules (CALM) and skinfold freckling, indistinguishable in size, shape and number from NF1, however, other typical NF1-associated features, such as Lisch nodules, neurofibromas, specific bone lesions, optic pathway gliomas and malignant peripheral nerve sheath tumors, are absent.

CALMs are the most common first sign of NF1, and are present in up to 95% of NF1 patients by age of 1 year. Multiple CALMs with or without skinfold freckling are usually the only findings in the small child, suspected of having NF1 and it may take up to 5 more years before additional clinical features appear and the diagnosis of NF1 can be made confidently based solely on clinical grounds. As ~50% of patients with Legius syndrome fulfill NIH diagnostic criteria for NF1, but the tumor complications typically reported in NF1 are however absent, a molecular confirmation of NF1 versus Legius syndrome is important for counseling and management. In all scenarios considered, *SPRED1* mutations are rare compared to *NF1* mutations. Several factors may affect sensitivity and specificity of the *NF1/SPRED1* mutational analyses and our experiences with a large cohort of patients will be discussed.

## **STRUCTURAL AND FUNCTIONAL CHARACTERIZATION OF RAS MUTANTS**

**Reza Ahmadian, PhD**

*Institute of Biochemistry & Molecular Biology II, Heinrich-Heine University Düsseldorf, Germany.*

The RAS-MAPK (mitogen-activated protein kinase) pathway is a kinase cascade leading to cell proliferation and differentiation. This signaling pathway has been intensively studied due to its importance in cancer development. In the past decade a new group of genetic developmental diseases determined by germline mutations related to RAS/MAPK pathway components were identified and intensively studied. These so called RAS-MAPK-related disorders include Noonan syndrome (NS), Costello syndrome (CS), and cardiofacio-cutaneous syndrome (CFCS). Recently, we described in detail the functional properties of a spectrum of KRAS-B and NRAS mutations related to NS. Overall, our studies revealed several new mechanisms by which germline *KRAS* mutations contribute to human disease and lead to disturbed embryonic development. Two aspects are of high importance for the understanding of RAS function(s): (i) we showed that the mild gain-of-function in the case of *KRAS* mutations at positions 34 and 60 is due to a mechanism counterbalancing GAP resistance by a reduced RAF1 interaction; and (ii) *NRAS* at position 50 most likely leads to an impaired interaction between RAS and the plasma membrane. The identification of a direct interaction of RAS protein with both membrane lipids, in addition to its posttranslational lipid modifications, has provided insights into the critical roles

of accessory proteins in modulating and integrating RAS in various signaling networks at biological membranes. However, the nature of these additional RAS interacting proteins as novel modulators of RAS signaling remains to be investigated. We consider that these control elements safeguard the strength, efficiency, and specificity of RAS-dependent signal transduction and provide an attractive *new generation* of highly selective drug *targets* that attenuate rather than inhibit RAS signaling.

## **USE OF ANTISENSE MORPHOLINO OLIGOMERS AS A GENE-THERAPEUTIC APPROACH TO RESTORE NORMAL SPLICING**

**Conxi Lázaro, Ph.D.**

*Hereditary Cancer Program, Genetic Diagnostics Unit, Hereditary Cancer Program, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain.*

A significant proportion of germline mutations causing Neurofibromatosis type 1 affect the correct splicing of the *NF1* gene. Splicing is a complex mechanism by which introns from a pre-mRNA are removed. This process is finely regulated at the cellular level, and it has been shown that it can be modulated by using antisense oligonucleotides (AONs). Multiple studies have demonstrated the power of AONs in modulating abnormal splicing caused by constitutive DNA mutations, first in cultured cells, later in preclinical animal models and currently in several promising clinical trials. A subset of splicing mutations, known as deep intronic mutations, creates or strengthens acceptor or donor splice sites that, using a wild-type counterpart sequence, lead to the inclusion of a cryptic exon in the mRNA that will eventually produce an aberrant protein. In *NF1*, deep intronic mutations account for approximately 2% of all *NF1* germline mutations identified to date. I will review different examples in which Phosphorodiamidate Morpholino Oligomers (PMOs, a class of AONs) have been used to efficiently correct the abnormal splicing produced by *NF1* deep intronic mutations. Reestablishment of normal splicing after PMO treatment has been analyzed at the mRNA level in different patient-derived primary cell cultures. Furthermore, indirect evidence of neurofibromin function restoration has been assessed by quantifying the levels of active Ras before and after PMO treatment. *In vitro* results collected so far have demonstrated the considerable potential of this type of antisense therapy for deep intronic *NF1*-causing mutations, although further experimental studies, particularly in preclinical animal models, will be required in order to safely translate these results into clinical trials and eventually to the clinic. The success of clinical trials using AON technology for other mis-splicing mutations causing Duchenne muscular dystrophy (DMD) is an encouraging result and outlines a possible path from bench to bedside for these types of mutations causing Neurofibromatosis type 1.

## **GENETIC SYNDROMES ASSOCIATED WITH THE RAS/MAPK PATHWAY AND THE IDENTIFICATION OF MUTATIONS IN A NEW GENE, *RIT1*, FOR NOONAN SYNDROME**

**Yoko Aoki, Tetsuya Niihori, Shin-Ichi Inoue, Yoichi Matsubara**

*Department of Medical Genetics, Tohoku University School of Medicine, Sendai, Japan.*

Recent studies have shown that a group of genetic disorders results from dysregulation of the Ras/MAPK cascade. These disorders include: 1) Noonan syndrome caused by mutations in *PTPN11*, *SOS1*, *RAF1*, *KRAS*, *BRAF*, and *NRAS*; 2) LEOPARD (multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth and sensorineural deafness) syndrome caused by mutations in *PTPN11* and *RAF1*; 3) Costello syndrome caused by activating mutations in *HRAS*; 4) cardio-facio-cutaneous (CFC) syndrome caused by mutations in *BRAF*, *MAP2K1/2* and *KRAS*; 5) Noonan-like syndrome caused by mutations in *SHOC2* or *CBL*; 6) neurofibromatosis type I caused by haploinsufficiency of neurofibromin; 7) NF-1 like syndrome caused by haploinsufficiency of *SPRED1*; 7) hereditary gingival fibromatosis caused by a mutation in *SOS1*; 8) capillary malformation-arteriovenous malformation caused by haploinsufficiency of *RASA1* (p120 GAP).

It has been suggested that these syndromes be comprehensively termed Ras/MAPK pathway syndromes or RASopathies.

Using whole exome sequencing, we have identified a total of nine missense, nonsynonymous mutations in *RIT1* GTPase in 17 of 180 individuals (9%) with Noonan syndrome and related conditions, who had no detectable mutations in known Noonan-related genes. *RIT1* shows the highest homology with *RIT2/RIN*, which is another member of GTPase without the CAAX prenylation motif. The downstream effectors of RIT1 have not been fully elucidated. Luciferase assays in NIH3T3 cells showed that five *RIT1* mutations identified in children with Noonan syndrome enhanced ELK1 transactivation. The introduction of mRNAs of mutant *RIT1* into one cell-stage zebrafish embryos was found to result in a significant increase of embryos with craniofacial abnormalities, heart defects and an elongated yolk sac. These results demonstrated that gain-of-function mutations in *RIT1* cause Noonan syndrome, showing a similar biological effect to mutations in other RASopathy genes.

## **MECHANISM AND TREATMENT FOR THE LEARNING AND MEMORY DEFICITS ASSOCIATED WITH MOUSE MODELS OF NOONAN SYNDROME**

**Yong-Seok Lee<sup>1</sup>, Dan Ehninger<sup>1+</sup>, Miou Zhou<sup>1</sup>, Delana Butz<sup>3</sup>, Toshiyuki Araki<sup>2</sup>, Christine I. Nam<sup>1</sup>, J. Balaji<sup>1#</sup>, Aida Amin<sup>1</sup>, Corinna Burger<sup>3</sup>, Benjamin G. Neel<sup>2</sup>, and Alcino J. Silva<sup>1,\*</sup>**

<sup>1</sup>*Departments of Neurobiology, Psychiatry and Biobehavioral Sciences, Psychology and Brain Research Institute, Integrative Center for Learning and Memory, University of California Los Angeles, Los Angeles, CA 90095, USA.*

<sup>2</sup>*Campbell Family Cancer Research Institute, Ontario Cancer Institute, Princess Margaret Hospital, University Health Network, Toronto, ON, Canada M5G1L7.*

<sup>3</sup>*Department of Neurology, University of Wisconsin-Madison, Madison, WI 53706, USA*

<sup>+</sup>*Current address: DZNE, German Center for Neurodegenerative Diseases, Ludwig-Erhard-Allee 2, 53175 Bonn, Germany.*

<sup>#</sup>*Current address: Center for Neuroscience, Indian Institute of Science, Bangalore, 560012, India.*

Noonan syndrome (NS) is an autosomal dominant genetic disorder with an incidence of ~1 in 2,500 live births characterized by facial abnormalities, short stature, motor delay and cardiac defects. Importantly, 30% to 50% of NS patients show cognitive deficits. Mutations in the *PTPN11* gene, which up-regulate Ras-ERK signaling, account for ~50% of NS. We will report that heterozygous knock-in mice expressing common NS-associated gain-of-function *Ptpn11* mutations (*Ptpn11*<sup>D61G/+</sup> and *Ptpn11*<sup>N308D/+</sup>) show hippocampal-dependent spatial learning impairments caused by deficits in hippocampal long-term potentiation (LTP). First, we show that the learning and the LTP phenotypes associated with the more severe *Ptpn11*<sup>D61G/+</sup> mutation in mice are more profound than the LTP and learning phenotypes associated with milder *Ptpn11*<sup>N308D/+</sup> mutation. Second, viral overexpression of the *PTPN11*<sup>D61G</sup> gene, specifically in adult CA fields of the hippocampus, results in increased basal ERK signaling, deficits in hippocampal CA1 LTP and consequently in spatial learning impairments, demonstrating that altered *Ptpn11* function and associated LTP deficits specifically in adult CA fields are sufficient to cause spatial learning deficits. Third, a MEK inhibitor (SL327), that targets the hyperactive ERK signaling pathway, can reverse the LTP and learning deficits caused by the *PTPN11*<sup>D61G</sup> mutation. More importantly, we show that a brief treatment with an FDA approved drug (lovastatin), which reduces Ras-ERK activation in the brain, rescues both the LTP and learning deficits in adult *Ptpn11*<sup>D61G/+</sup> mice, whereas the same lovastatin treatment does not affect wild type controls. Our results demonstrate that increased basal ERK signaling and corresponding impairments in LTP are responsible for the learning deficits in mouse models of NS. Interestingly, the cellular mechanism underlying the deficit in NS is different from that of Neurofibromatosis type I (NF1), a closely related disorder also characterized by learning and memory impairments. Previous studies in our laboratory showed that the deficits in NF1 were due to increased GABBA-mediated inhibition.

## MODELING RASOPATHIES WITH HIPSC

Sonia Mulero-Navarro

*The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai. New York. USA.*

Induced pluripotent stem technology gives us the opportunity to study genetic congenital disorders such as the RASopathies, characterized by a limited cellular source. Noonan syndrome (NS) patients harboring *PTPN11* mutations have a higher risk to develop juvenile myelomonocytic leukemia (JMML), and hypertrophic cardiomyopathy is observed in 90% of patients with LEOPARD syndrome (LS). To further elucidate the molecular mechanisms of hematological and cardiovascular manifestations, we generated human induced pluripotent stem cell (hiPSC)-derived myeloid and cardiomyocytes to model both syndromes. Hematopoietic cells differentiated from hiPSCs harboring NS/JMML-causing *PTPN11* mutations recapitulated JMML clinical features including excessive number of monocytic/granulocytic cells, granulocyte macrophage colony-stimulating factor hypersensitivity and increased fetal hemoglobin. As a new insight of this leukemia, we discovered significant up-regulation of two hematopoiesis-related micro-RNAs in hiPSC-derived NS/JMML myeloid cells and also observed reduced mRNA levels for several predicted target genes of these micro-RNAs in JMML cells from patients. For LS, we have previously demonstrated that hiPSC-derived cardiomyocytes with LS-associated *PTPN11* mutation exhibit altered RAS/MAPK signaling and display a molecular phenotype consistent with the cardiac hypertrophy observed clinically. Here, we report the partial recovering of cardiac phenotype in those hiPSC-derived cardiomyocytes treated with rapamycin. In summary, hiPSC-derived NS/JMML myeloid cells provide a *bona fide* model of JMML and the findings confirm the utility of studying inherited human cancer syndromes with hiPSCs to understand early oncogenesis prior to the accumulation of secondary genomic alterations, providing opportunities for therapeutic target discovery and small molecule testing. In addition, the rescue of the cardiac hypertrophy in hiPSC-derived cardiomyocytes with rapamycin confirms the animal model data, providing further impetus for a clinical trial in LS patients.

## MECHANISMS UNDERLYING COGNITIVE DEFICITS IN THE RASOPATHIES: A FAMILY WITH DISTINCT PERSONALITIES

Ype Elgersma, Ph.D.

*Erasmus University, Netherlands.*

RASopathies are caused by mutations in the Ras/ERK signaling pathway, resulting in over-activation of this pathway. These disorders typically present with varying degrees of cognitive disability. Although the Ras/ERK pathway is ubiquitously expressed in most neurons, studies on Neurofibromatosis type 1 (NF1), which is one of the best-studied RASopathies, showed that the neuronal deficits are specific to inhibitory neurons. Here, I will present new data in which we investigated whether a gain-of function mutation in the H-Ras protein, which is negatively regulated by NF1, recapitulates this cell-specific phenotype of NF1.

We made use of a mouse mouse model of Costello syndrome (CS), which is caused by activating mutation (H-Ras<sup>G12V</sup>) in the H-RAS gene. We confirm that the H-Ras<sup>G12V</sup> mouse is a suitable model to study CS by showing that these mice have hyperactive Ras/ERK pathway and a profound learning deficit as assessed in the Morris water maze (MWM). Furthermore, we found that mice expressing the H-Ras<sup>G12V</sup> mutation only in excitatory neurons show similar learning deficits in the MWM and a hyperactive Ras/ERK pathway, and that the plasticity deficits were not the same as the deficits observed in Nf1 mice. These results indicate that the mechanism underlying the CS phenotype is different from NF1.

To investigate the molecular basis of the cell-type specific pathophysiology of Nf1 we made use of a novel mouse mutant lacking a neuron-specific isoform of neurofibromin (*Nf1*<sup>9a-/9a-</sup> mice), we identify the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel 1 as a neurofibromin interacting

protein, and demonstrate that a selective attenuation of HCN current in parvalbumin-expressing interneurons is a cause of increased inhibition in *Nf1* mutants. We further show that the HCN channel agonist lamotrigine rescues the synaptic plasticity and learning deficits in both *Nf1*<sup>9a-/9a-</sup> mice and *Nf1*<sup>+/-</sup> mice. Together, our results highlight a critical role for HCN channels in the pathophysiology of NF1-associated cognitive deficit, and identify a novel target for clinical drug development.

In summary, our data suggest that although both CS and NF1 affect the same pathway and have a similar biochemical and behavioral outcome, the neuronal mechanisms underlying the cognitive deficits are only partially overlapping. Costello syndrome (CS) is a rare RASopathy characterised by moderate to severe mental retardation, morphological brain abnormalities, craniofacial anomalies, increased birth weight, failure to thrive, short stature, cardiovascular dysfunction and a predisposition to develop tumors. CS is caused by germline point mutations (Gly12Val) in the H-Ras gene that render the protein constitutively active, which leads to increased activation of the Ras/ERK pathway. Mice with a homozygous G12V knock-in mutation in the H-Ras gene are suitable as a model to study the mechanism underlying learning deficits observed in Costello patients because these mice show 1) an increased phosphorylation of H-Ras' main downstream target ERK, 2) spatial learning problems in the Morris water maze (MWM) and 3) deficits in long-term depression (LTD). To further investigate the mechanism underlying LTD deficit in CS mice we can use extracellular field potential recordings in hippocampal slices. Using pharmacological approach we can distinguish between different mGluR-LTD mechanisms by measuring impact of different drugs on mGluR LTD induction and expression in WT and H-RasG12V mice e.g. by application of protein synthesis blockers (anisomycin or cycloheximide), protein tyrosine phosphatase (PTP) inhibitors (orthovanadate and phenylarsine oxide), proteolysis inhibitors (calpain inhibitor III). In addition, the role of presynaptic component of mGluR-LTD involving the retrograde signaling of e.g. endocannabinoids and/or dopamine, would be of particular interest for us, since H-Ras is strongly expressed at the presynaptic nerve terminals. By means of pharmacological modulation of e.g. endocannabinoid (CB) receptors by AM281 (antagonist) and WIN55, 212-2 (agonist) we could extrapolate modulatory effect of CBs on mGluR-LTD and their possible dysfunction in H-RasG12V mice. Furthermore, synaptic vesicle depletion protocols in field recordings would help to gain more insight in presynaptic mechanisms and their possible involvement in H-Ras G12V phenotype.

Furthermore expression and posttranslational modifications of proteins involved in mGluR-LTD (e.g. Arc, ETEP) mechanisms would be of our interest. In particular, it would be interesting to access the expression level of a scaffolding protein caveolin-1, which is required for mGluR5 mediated LTD as well as for the membrane targeting of H-Ras. In addition, it has been reported that oncogenic H-Ras G12V can influence caveolin-1 expression suggesting that this protein might downregulated in H-RasG12V mice and thus important for the observed LTD phenotype \*

## **THERAPEUTIC APPROACHES TO HCM IN NOONAN SYNDROME WITH MULTIPLE LENTIGENES (LEOPARD SYNDROME)**

**Maria I. Kontaridis, Ph.D.1, 2 and Amy Roberts, M.D.3**

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Essentially all cases of Noonan syndrome with multiple lentigenes (NS-ML ; formally termed LEOPARD Syndrome), a rare autosomal dominant, multi-systemic disease, are caused by mutations in the SH2 domain-containing protein tyrosine phosphatase SHP2, encoded by *PTPN11*. NS-ML presents with phenotypic characteristics similar to those observed in other RASopathy disorders, including multiple lentigenes, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness. However, the most common cardiac manifestation in NS-ML is hypertrophic cardiomyopathy (HCM), with an estimated prevalence of

70-80%. Currently, there is no existing treatment for LS patients with HCM, and many die early of end-stage heart failure.

To determine the biological and functional mechanisms in LS, we generated inducible knock-in mice harboring one of the two most common mutations in human LS, the Y279C *PTPN11* mutation. Our mice recapitulated nearly all major aspects of the LS phenotype. Furthermore, biochemical analyses of hearts and primary cardiomyocytes from these mice identified the molecular basis for HCM as a hyperactivation of the Akt/mTor (mammalian target of rapamycin) signaling pathway. As a result, we identified a pharmacological intervention for HCM in LS using rapamycin, which both prevented and reversed the LS mouse cardiac defects *in vivo*.

Together, our data identify the first possible medical treatment for LS. In collaboration with the TRND platform, we hope to now establish a multi-site clinical trial for use of rapamycin/rapamycin analogs in the treatment of HCM in LS patients. These studies also highlight the importance of using individualized therapies in the treatment of RASopathy disorders, which as a group may affect as many as one in 1000-2,000 people. Finally, understanding the mechanisms of rare diseases such as LS may have even broader implications, i.e., use of a similar therapeutic strategy in the treatment of other, more common types of congenital cardiomyopathy.

## MODELING RASOPATHIES IN MOUSE AND HUMAN

**Benjamin G. Neel**

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We showed previously that *Raf1*<sup>L613V/+</sup> mice fully recapitulate the cardiac features of *RAF1* mutant Noonan Syndrome, including cardiac hypertrophy, enhanced contractility and chamber dilatation. Postnatal MEK inhibitor treatment normalizes all NS phenotypes in these mice, yet it remains unclear whether genetic ablation of *Erk* would have the same effect. It also is not known whether the cardiac phenotypes derive from distinct cell(s)-of-origin and human models for NS cardiac phenotypes remain elusive. To address these issues, we used tissue-specific Cre-expressing mice to promote inducible expression of *Raf1*<sup>L613V/+</sup> in various cells in the mouse heart. Mice with cardiomyocyte-specific expression of *Raf1*<sup>L613V</sup> (*Mlc2v*-LV) showed enhanced contractility, but not cardiac hypertrophy. By contrast, endocardial-specific *Raf1*<sup>L613V</sup> expression (*Nfatc1*-LV) caused eccentric cardiac hypertrophy without hypercontractility. Our results suggest that distinct cell types regulate different aspects of the NS cardiac phenotype and collaborate to cause NS-associated HCM. Furthermore, genetic ablation of *Erk1* in *Raf1*<sup>L613V/+</sup> mice normalizes contractility, but not cardiac hypertrophy. Finally, we also generated engineered heart tissue (EHT) from hiPSC- and hESC-derived cells, and found that these preparations showed hypertrophy that could be reversed by MEK-inhibitor treatment.

## DRUG SCREENING FOR NOONAN SYNDROME WITH *DROSOPHILA*

**Bruce D. Gelb**

*Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, NY.*

Noonan syndrome (NS) has pleomorphic features of varying severity, which can not currently be prevented or addressed at their root cause. The elucidation of the genetic abnormalities underlying NS and subsequent mechanistic studies, particularly animal modeling, have provided the potential to develop therapies directly addressing the altered signal transduction. Currently, the two leading clinical aspects to target are hypertrophic cardiomyopathy (HCM) and intellectual and developmental delays. While strategies relying on small molecules directly inhibiting the canonical RAS-MAPK signaling, which might leverage current efforts primarily targeting cancer, might prove efficacious, there is risk that the safety profile of such therapies will not be acceptable for more aspects of NS.

To look for small molecules that might push the complex RAS-MAPK signaling network towards normality without powerfully inhibiting it, we undertook the development of a non-traditional approach



to drug screening. Previously, we generated transgenic fruitfly (*Drosophila melanogaster*) models of NS and other RASopathies. Given HCM as a possible target, we are using a *RAF1* mutant fly (*S259G* allele). After establishing conditions that gave pupal lethality (*ms1096-Gal4*, 25 °C), we screened a small number of compounds likely related to RAS/MAPK signaling, finding that the multiple kinase inhibitors sorafaneib and sunitinib showed the strongest rescue. We are currently completing the screen with a library of 640 FDA-approved medicines (Enzo) at two concentrations. We have also initiated secondary screening to confirm the most promising hits. For the presentation, the status of this drug screen will be discussed.

## **NEUROFIBROMATOSIS CLINICAL TRIALS CONSORTIUM**

**Bruce R. Korf, MD, Ph.D.**

*Department of Genetics, University of Alabama at Birmingham.*

The neurofibromatoses, including NF1, NF2, and schwannomatosis, are a set of related genetic disorders characterized by the development of benign tumors of the nerve sheath. NF1 is the most common of these disorders, affecting about 1 in 3,000 individuals. Aside from neurofibromas, patients may develop optic glioma, skeletal dysplasia, learning disabilities, and many other problems. Neurofibromas, though benign, can be disfiguring, and are at risk of transformation to malignant peripheral nerve sheath tumor. The *NF1* gene is a tumor suppressor that includes a GTPase activating protein domain that regulates conversion of Ras-GTP to Ras-GDP. This mechanism opens the possibility of development of specific treatments that target the Ras signaling pathway, but clinical trials are hampered by challenges in measuring outcomes and recruiting a sufficiently large number of patients to achieve a statistically valid study. In 2006 the Department of Defense initiated funding of the Neurofibromatosis Clinical Trials Consortium with the goal of supporting clinical trials using biologically-based therapies. For the first five years the focus was on NF1, but when the Consortium was refunded in 2012 the mission was expanded to other forms of neurofibromatosis. The Consortium consists of an Operations Center at UAB and clinical trial recruitment sites (initially 9 and currently 17). Protocols are developed by committees that focus on particular disease manifestations. Four trials were launched in the first five years targeting plexiform neurofibromas (rapamycin), neurocognitive problems (lovastatin), low-grade glioma (everolimus), and malignant peripheral nerve sheath tumors (everolimus and bevacizumab). There are currently three additional trials soon to be launched, targeting vestibular schwannomas in NF2 (bevacizumab), and two trials aimed at treatment of plexiform neurofibromas. Additional trials for skeletal features and neurocognitive problems are in development.

## **CLINICAL TRIALS FOR FRAGILE X SYNDROME**

**Reymundo Lozano MD.**

*Department of Pediatrics, UC California, Davis, Health System.*

*Fragile X Research and Treatment Center, UC Davis, MIND Institute, Sacramento, CA.*

Fragile X syndrome (FXS) is the most prevalent and well-understood monogenetic cause of intellectual disability (ID) and autism spectrum disorder (ASD); its high penetrance and the seminal importance of FMRP in synaptic plasticity make FXS an ideal model for the study of neurodevelopmental disorders in general. In fact recent studies suggest that there is functional convergence of a number of genes that are implicated in ID and ASD, indicating that an understanding of the cellular and biochemical dysfunction that occurs in monogenic forms of ID are likely to reveal common targeted treatments. Recent progress in understanding the biological mechanisms of FXS has provided information about how the loss of function of FMRP results in biochemical, anatomical and physiological dysfunction and how these abnormalities can be rescued in animal models with targeted treatments that reverse these neurobiological changes. Most promising are the targeted treatments of mGluR5 antagonists and GABAa agonists that are now in clinical trials in patients with FXS. The challenges faced in evaluating

improvements and efficacy of targeted treatments will be reviewed. FXS has led to a new era in which targeted molecular treatments for a variety of neurodevelopmental disorders, including the RASopathies is becoming a reality.

## **USE OF RAF INHIBITORS FOR TREATMENT OF MELANOMA**

**Chao Zhang, Gideon Bollag (on behalf of the Plexikon team)**

*Plexikon Inc., Berkeley, CA.*

The identification of activating BRAF mutations (primarily missense substitutions for Valine-600 or BRAF<sup>V600</sup>) in melanoma and other tumors supports a functionally important role for BRAF in the pathogenesis of these malignancies. Specific BRAF inhibitors including vemurafenib have demonstrated both objective tumor response and overall survival benefit in mutant BRAF driven melanoma. The clinical effectiveness of BRAF inhibitor-based therapy depends on complete abolition of the MAPK pathway output in tumors harboring BRAF mutations. However the first generation BRAF inhibitors paradoxically activate the MAPK pathway in cells bearing oncogenic RAS or elevated upstream receptor signaling. This activation can lead to cellular proliferation and has been associated clinically with appearance of cutaneous squamous cell carcinomas (cuSCC) and keratoacanthomas (KAs). In order to improve the durability and tolerability of therapy, Plexikon has been pursuing multiple strategies. We have designed a series of next generation BRAF inhibitors that exhibit potent anti-BRAF efficacy without causing paradoxical pathway activation in RAS mutant cells. These compounds, dubbed 'Paradox Breakers,' are also active against certain BRAF isoforms that are resistant to inhibition by first-generation compounds. Furthermore, we have pursued studies to identify agents that synergize with BRAF inhibition by blocking cell-autonomous mechanisms and also by targeting cells of the tumor microenvironment. Plans to develop these approaches into clinical projects will be discussed.

## **A CLINICAL TRIAL OF MEK INHIBITION IN NOONAN SYNDROME WITH HYPERTROPHIC CARDIOMYOPATHY**

**Calum A. MacRae<sup>1</sup>, William J. McKenna<sup>2</sup>, Craig T. Basson<sup>3</sup>, Eric Svensson<sup>3</sup>, Denise Yates<sup>3</sup>, Jessie Gu<sup>3</sup>. 1, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; 2, The Heart Hospital and University College London, UK; 3 Novartis Institute of Biomedical Research, Cambridge, MA**

The purpose of the study is to provide proof-of-concept to determine whether the ability of MEK162 to antagonize MEK activation in Noonan Syndrome HCM patients, who usually have upstream mutations in the Ras-Raf-Mek-Erk pathway that lead to MEK activation, would be beneficial over a 6 month treatment period in hypertrophy regression. The study is designed as an open label study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of MEK162 in Noonan Syndrome Hypertrophic Cardiomyopathy. Primary endpoint will be the change from baseline in Left ventricular mass (LVM) after 6 months of treatment evaluated by cardiac magnetic resonance imaging (MRI). Such regression may result in cardiovascular clinical benefits with longer term treatment. Secondary endpoints include safety, tolerability and the change from baseline in cardiac energetics at 3 months and 6 months assessed by magnetic resonance spectroscopy (MRS). This study will enroll adult NS patients between the age of 18-65, with confirmed hypertrophic cardiomyopathy.

## **CTF THERAPEUTIC DEVELOPMENT PIPELINE**

**Annette Bakker, Salvatore La Rosa, Marco Nievo**

*Children's Tumor Foundation.*

The Children's Tumor Foundation is the world's leading non-government funder of NF research to find effective treatments for neurofibromatosis. Foundation-funded research was critical in isolating the genes that cause NF and is now focused on finding treatments to improve the lives of those living with the disorder. This includes the foundation's active participation in drug discovery research and clinical trials. We sponsor a network of 44 NF Clinics throughout the country to improve access to quality care for those with NF, and ensure best practices in treating the disorder.

The key research goals for the Foundation are to attract pharmaceutical industry and biotech to the NF field via a collaborative business model, actively bridging academic science to industry to patients. We offer an industry-level testing platform and the necessary tools to allow preclinical proof-of-concept testing of both existing molecules (that are in development or on the market for other disease indications) as well as innovative still undisclosed molecular mechanisms. The Children's Tumor Foundation continues its active scouting for compounds that may benefit NF patients, and expands the necessary services that allow clinical trials, such as the NF Patient Registry, a biobank, and the development of consented efficacy outcome measures (REINS).

This new business model, allowing CTF to be a partner/collaborator with academia and industry, rather than only a funder, will be presented. Multiple pilots along these lines are currently ongoing.

## **TISSUE BANKING IN PEDIATRIC ONCOLOGY**

**Corinne Linardic MD, Ph.D.**

*Duke University School of Medicine, Departments of Pediatrics and Pharmacology & Cancer Biology, Member of the Children's Oncology Group.*

The last several decades have witnessed remarkable advances in identifying the genetic causes of many childhood syndromes, both oncologic and non-oncologic. Subsequent team efforts by clinicians, patients, their families and advocates have supported clinical trials to evaluate new therapies for those affected. In the background and often unnoticed, there are parallel team efforts by pathologists and their staff to obtain and "bank" tissue samples from children with these diseases. It is hoped that by analyzing the original tissue from the affected individuals, additional insight will be gained into disease origin and treatment possibilities. The Children's Oncology Group (COG) represents the largest consortium in North America that is banking tissue from children with cancer. Working in collaboration with the NIH-funded Cooperative Human Tissue Network, the COG receives, evaluates, annotates, and stores human tissue samples submitted through IRB-approved protocols from all over the world. Investigators then apply in a regulated fashion for access to these tissues, using them to translate biology from the bench to the bedside. A recent example of the success of this program is the detection of *RAS* mutations in 14% of rhabdomyosarcoma samples using genomic analysis of submitted cases. This session will review the "nuts and bolts" of tissue banking in pediatric oncology, so that it is an approachable and practical topic for clinicians, researchers, patients, and their families.

## **Genetic Syndromes of the Ras/MAPK Pathway: Towards a Therapeutic Approach**

August 2-4, 2013  
Orlando, FL

The University of Alabama School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Alabama School of Medicine designates this live activity for a maximum of 11.75 *AMA PRA Category 1 Credits*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

### **DISCLOSURES AND ACKNOWLEDGEMENTS**

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### **THEREFORE THE FOLLOWING DISCLOSURES ARE MADE**

The following persons have disclosed that, related to their participation in this activity, neither they nor their families have any relevant financial relationships with any commercial interests:

*Reza Ahmadian, PhD*

*Judith Allanson, MD*

*Yoko Aoki, MD, PhD*

*Annette Bakker, PhD*

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*David Viskochil, MD, PhD*

The following persons have disclosed these relationships with commercial interests related to their participation in this activity:

<i>Bruce Gelb, MD</i>	<i>Grants/research support / grants pending and Honoraria – Shire; Support for travel to meetings or other purposes – Novartis; Royalties – GeneDX, Correlegan</i>
<i>Maria Kontavidis, PhD</i>	<i>Consulting fee and Support for travel to meetings or other purposes – Novartis</i>
<i>Calum MacRae, MD, PhD</i>	<i>Grants/research support / grants pending and Consulting fee – Novartis</i>
<i>Benjamin Neel, MD, PhD</i>	<i>Consulting fee and Board Membership – Kolltan Pharmaceuticals</i>
<i>Emma Burkitt Wright, MBChB, MPhil</i>	<i>Grants/research support / grants pending and Employment – Wellcome Trust</i>
<i>Chao Zhang, PhD</i>	<i>Employment, Patents (planned, pending, or issued) and Royalties – Plexxikon, Inc.</i>

*This activity was supported in part by unrestricted educational grants from:*

*The Children’s Tumor Foundation  
The March of Dimes  
The National Institutes of Health (NIH)  
Novo Nordisk, Inc.  
Novartis*

# NOTES

# Third International Meeting on the Genetic Syndromes of the Ras/MAPK Pathway: Towards a Therapeutic Approach



International Costello Syndrome  
Support Group

