

6th International **RASopathies** Symposium:

Precision Medicine - From Promise to Practice

UPDATED

August 2-4, 2019
Baltimore Hunt Valley

RASopathiesNet

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WELCOME!

August 2, 2019

Thank you for joining us at the 6th International RASopathies Symposium:
Precision Medicine - from Promise to Practice!

Looking at these syndromes with a cellular pathway lens continues to amaze us. This year, we consider new mutations, including how they help reframe our understanding of the RASopathies, share lessons learned from clinical trial strategies, and discuss patient-reported outcomes (PROs), among other important topics to bring together researchers and affected families.

We hope that this year's agenda, approach to encourage discussion, and networking opportunities help you find effective ways to better the lives of those affected by a RASopathy, as well as for those who develop a Ras-related cancer. Our goal for this meeting is to buoy your shared interest.

With continued breakthroughs in cancer therapy targeting somatic tumors' mutations and expanding understanding of RASopathies mutations on affected individuals, opportunities to collaborate are increasing. To paraphrase Louis Pasteur, we are on the verge of mysteries and the veil is getting thinner and thinner.

Finally, we would like to all who helped us pull this symposium together, including the Chairs Karen Gripp and Nancy Ratner, the Advocates' Advisory Board, the speakers, and the moderators.

In Friendship,

The RASopathies Network Board

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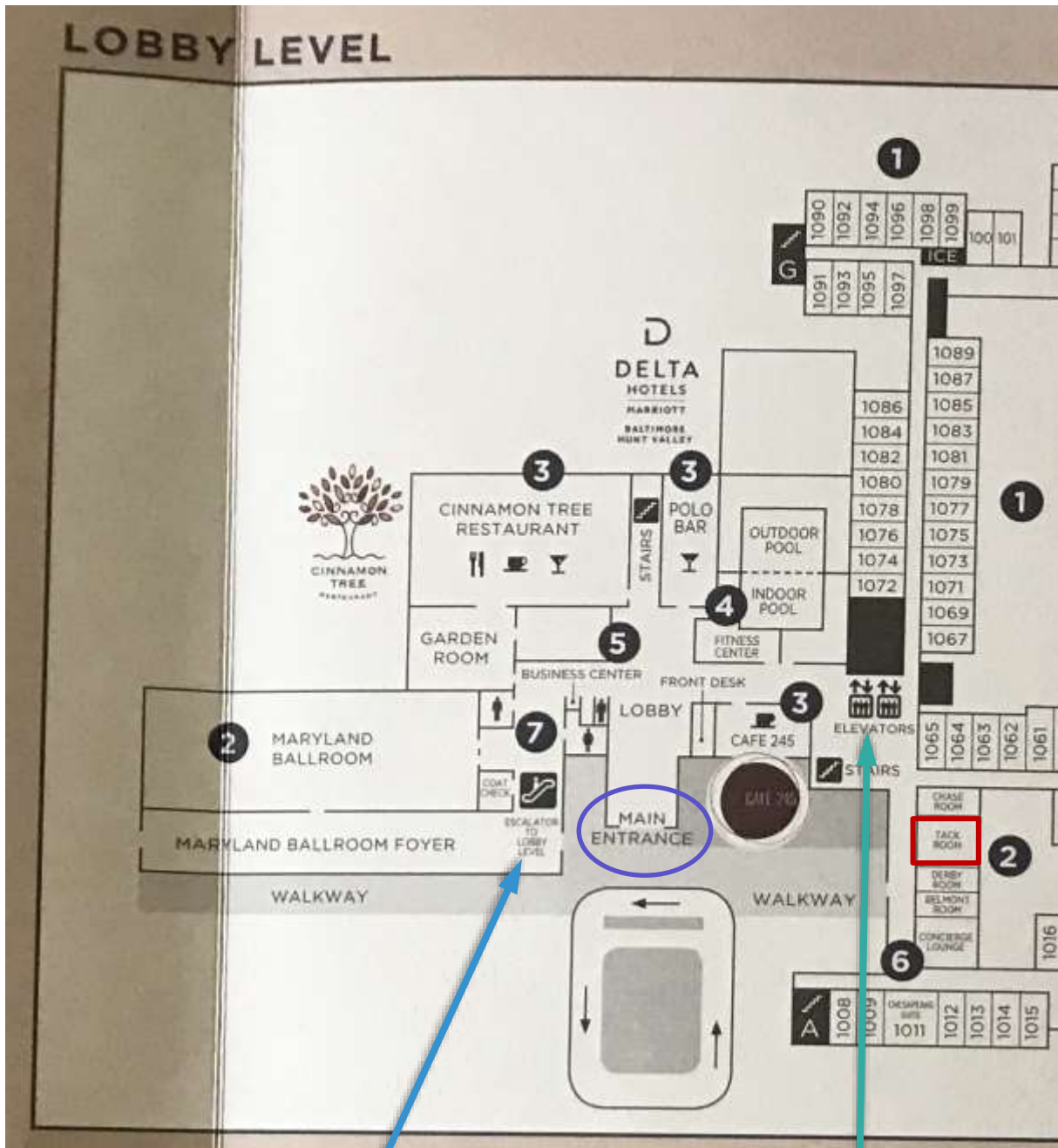
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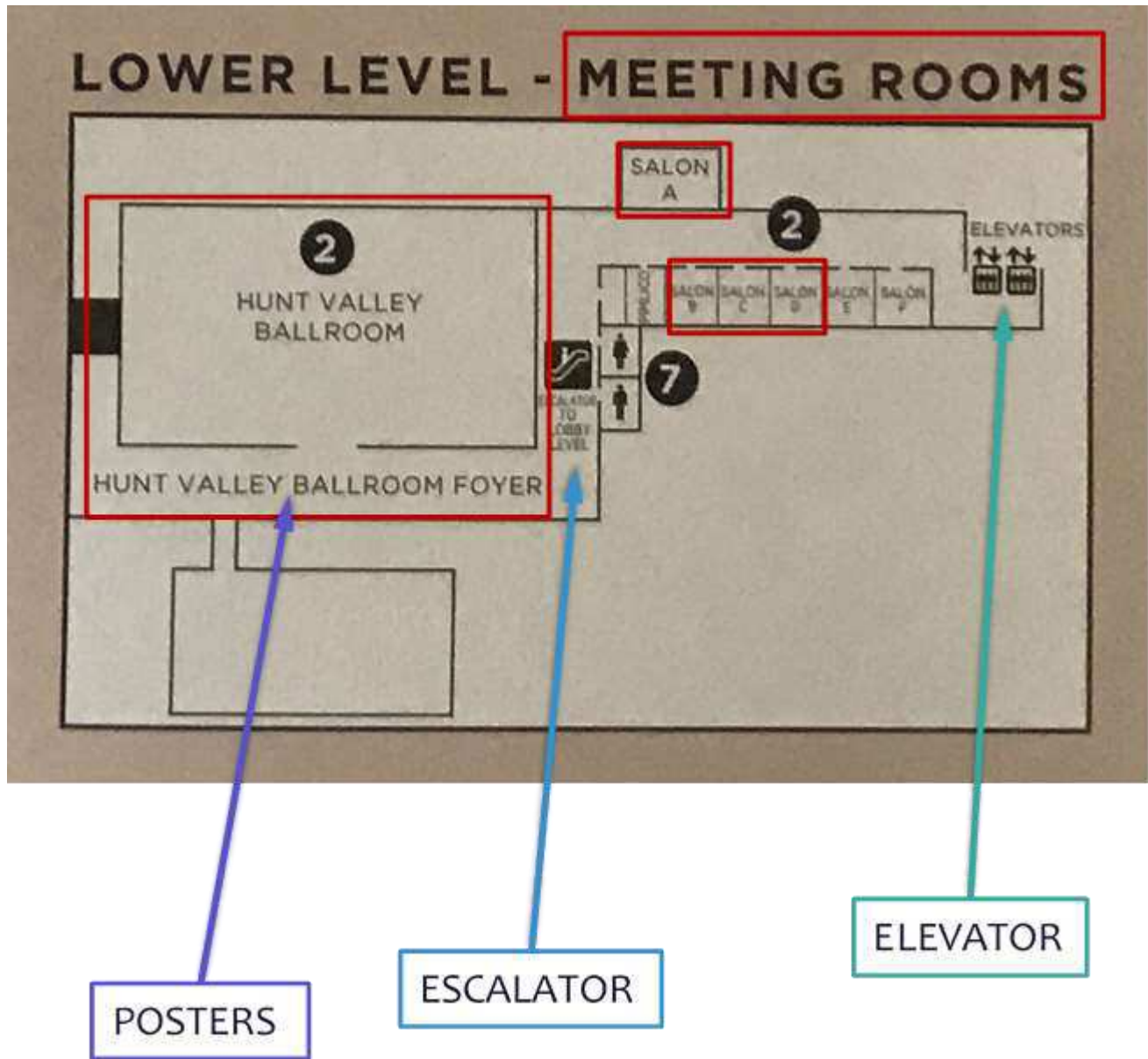
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ESCALATOR

ELEVATOR



AGENDA-UPDATED

Family-friendly Sessions

DAY 1 – FRIDAY 8/2/19 – Hunt Valley Foyer

8:00-10:00 pm	WELCOME REMARKS Dessert Reception and Poster Session (Scientists and advocacy/family groups) <i>Sponsored by IGIA Pharmaceuticals</i>
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DAY 2 – SATURDAY 8/3/19 – Hunt Valley Ballroom

7:00-8:00 am	Breakfast (Hunt Ballroom)
8:00-8:20 am	Introductory Remarks: Katherine A. Rauen, MD PhD - The RASopathies Umbrella (Valley Ballroom)
8:20-10:05 am	Session 1: Novel Mutations/Genes in the Field (Valley Ballroom) Moderator: Marco Tartaglia, PhD
8:20-8:35 am	Martin Zenker, MD: LZTR1-Phenotypic overlap with RASopathies
8:35-8:50 am	Anna Sablina, PhD: Mutations in LZTR1 Drive Human Disease by Dysregulating RAS Ubiquitination and Signaling
8:50-9:05 am	Pablo Rodriguez-Viciano, PhD: The SHOC2-MRAS-PP1 complex: Molecular Details and Pathway Function
9:05-9:20 am	Karen Gripp, MD: PPP1CB - Phenotypic Overlap with RASopathies
9:20-9:35 am	Gavin Rumbaugh, PhD: Biology of SYNGAP1-related Neurodevelopmental Disorders: Should They Be Considered RASopathies?
9:35-9:50 am	Jimmy Holder, MD PhD: SYNGAP1 – Phenotypic and Molecular Overlap with RASopathies
9:50-10:05 am	<i>Discussion over Coffee</i>
10:05-11:25 pm	Session 2: New Functions of RASopathy Genes (Valley Ballroom) Moderator: Emma Burkitt-Wright, MD PhD
10:05-10:20 am	Shin-ichi Inoue, PhD: Metabolic Effects in Mouse Model of Costello Syndrome
10:20-10:45 am	Ben Neel, MD PhD: Targeting SHP2 for Neurofibromatosis and Other Malignancies
10:45-11:10 am	Frank McCormick, PhD FRS DSc: Structural and Functional Analysis of Neurofibromin and SPRED1
11:10-11:25 am	<i>Discussion</i>
11:25 am-12:15 pm	KEYNOTE: Neal Rosen, MD PhD: The inhibitor Landscape and RAS signaling Feedback Loops
12:20-1:20 pm	Lunch Presentation: Steph Nimmo, Author “Was This in the Plan?” (Hunt Ballroom) <i>Sponsored by IGIA Pharmaceuticals</i>
1:30-3:05 pm	Session 3: Therapeutic Inhibitors (Valley Ballroom) Moderator: William Timmer, PhD
1:30-1:50 pm	Alan Ho, MD PhD: Cancer driven by HRAS: Tipifarnib Clinical Trial Results
1:50-2:10 pm	Andrea Gross, MD: Functional Endpoints on the SPRINT Study
2:10-2:25 pm	Anton Bennett, PhD: Low-Dose Dasatinib for Cardiomyopathy in Noonan Syndrome
2:25-2:45 pm	Darryl McConnell, PhD (Boehringer Ingelheim): Drugging RAS from Multiple Angles
2:45-3:05 pm	<i>Discussion over Coffee</i>
3:10-5:15 pm	Session 4: Potential Endpoints for Clinical Trials in RASopathies (Valley Ballroom) Moderator: Nancy Ratner, PhD
3:10-3:25 pm	Alcino Silva, PhD: Temporal Dynamics of Contextual Memory linking in PTPN11 ^{D61G} Mutant Mice Did not present Manuel Lopez Aranda, PhD: Post-Natal Immune Activation and Its Role In Adult Phenotypes in a RASopathy Model
3:25-3:40 pm	Carlos Prada, MD: Antioxidant Testing in Preclinical Models and RASopathy Patients
3:40-3:55 pm	Tamar Green, MD: Bridging the Gaps in our Knowledge: Brain Development in Children with Noonan Syndrome
3:55-4:10 pm	Susan Blaser, MD FRCP: Neuroimaging of RASopathies in the Newborn and Young Child

4:10-4:25 pm	Maria Kontaridis, PhD: iPSC-derived Cardiomyocytes Reveal Aberrant ERK5 and MEK1/2 Signaling Concomitantly Promote Hypertrophic Cardiomyopathy in RAF1-associated Noonan Syndrome
4:25-4:40 pm	Rebecca Burdine, PhD: Unraveling the Cause of Developmental Disease Using Zebrafish: MAP4K4 Truncations as a Potential Cause of RASopathies
4:40-5:10 pm	<i>Discussion</i>
	Break
6:00-8:00 pm	Networking Dinner & Cash Bar (Hunt Ballroom) / CSFN Tailgate Party (Maryland Ballroom)

DAY 3 – SUNDAY 8/4/19 – Hunt Valley Ballroom

7:00-8:00 am	Breakfast (Hunt Ballroom)
8:00-8:50 am	Session 5: Prenatal Findings, Manifestations, Diagnosis and Management (Valley Ballroom) Moderator: Pilar Magoulas, MS CGC
8:00-8:40 am	Panelists: Sandra Darilek, MS CGC and Angie Jelin, MD
8:40-8:50 am	<i>Discussion</i>
8:50-10:40 am	Session 6: Clinical Trial Endpoints Roundtable (Valley Ballroom) Moderator: Richard Klein
8:50-9:05 am	Annie Kennedy: PPMD-On the Forefront of PRO
9:05-9:20 am	Pam Wolters, PhD: Benefits, Challenges, and Strategies for Incorporating Patient-Reported Outcomes in Pediatric Trials for RASopathies
9:20-9:35 am	Karin Walsh, PsyD: A Prospective Study of the Impact of MEK1/2 Inhibition on Neurocognitive Functioning in Children and Adults with NF1
9:40-10:10 am	Advocacy Organizations Panel Moderator: Michelle Ellis, Noonan UK Participants: CFC International- Tuesdi Dyer; CSFN- Angel Thomas; CTF- Alwyn Dias; NF Network- Gregg Erikson; NSF- Amanda Brown
10:10-10:40 am	<i>Discussion</i>
10:45-12:15 am	Session 7: Junior Investigators, MDBR Grantees, and Closing Comments (Valley Ballroom) Moderator: Amy Roberts, MD
10:45-11:00 am	Jr Investigator Finalist 1, Pau Castel, PhD: Modeling LZTR1 Loss-of-Function in Vivo: A Novel Noonan Syndrome Mouse Model
11:00-11:15 am	Jr Investigator Finalist 2, Maja Solman, PhD: Hematopoietic Defects in a Zebrafish Knock-in Model of Noonan Syndrome
11:15-11:30 am	Jr Investigator Finalist 3, Jae-Sung Yi, PhD: SHP2/PTPN11 Interactions with Protein Zero Related (PZR) Promotes Hypertrophic Cardiomyopathy in Noonan Syndrome with Multiple Lentiginosis (NSML)
11:30-11:45 am	Million Dollar Bike Ride 2018 Grantee, Kartik Venkatachalam, PhD: Using a Clinically Approved Antiemetic, Meclizine, to Attenuate Hyperactive RAS–MAPK Signaling
11:45 am-12:00 pm	Million Dollar Bike Ride 2019 Grantee, Bruce Gelb, MD: Advancing a Novel Therapeutic Lead for the RASopathies
12:00-12:15 pm	<i>Discussion and Closing Remarks</i>

12:30-1:30 pm	Breakout Sessions for RASopathy Family Groups: CFC Families - Pilar Magoulas, MS CGC, Dave Stevenson, MD (<i>Salon B</i>) Sponsored by KURA Oncology CS Families - Hosted by CSFN - Karen Gripp, MD, Emma Burkitt-Wright, MD PhD (<i>Tack Room</i>) Sponsored by KURA Oncology NS, NSML Families - Bruce Gelb, MD, Amy Roberts, MD (<i>Salon A</i>) NF1 Families - Hosted by NF Network - Bruce Korf MD PhD, Karin Walsh PsyD, Pam Wolters PhD (NF1 only 12:30–3:30 pm) (<i>Salon C/D</i>) Sponsored by Boehringer Ingelheim and UAB Medical Genomics Laboratory
2:30-4:00 pm	RASopathies Network Open Board Meeting (Salon B)

SPEAKER ABSTRACTS

Introductory Remarks:

The RASopathies

Katherine (Kate) Rauen MD PhD, *UC Davis MIND Institute, California, USA*

The RASopathies are a group of clinically related developmental disorders which are caused by germline mutations in genes that encode components, or regulators of the Ras/mitogen activated protein kinase (MAPK) pathway. As a group, the RASopathies are one of the largest groups of malformation syndromes known, affecting approximately 1:1,000 individuals. The Ras/MAPK pathway plays an essential role in the regulation of the cell cycle, differentiation, growth and cell senescence, all of which are critical to normal development. As a result, Ras/MAPK pathway dysregulation has been shown to have profound deleterious effects on both embryonic and later stages of development. Because the underlying molecular mechanism for these syndromes is dysregulation of the Ras/MAPK pathway, the RASopathies exhibit numerous overlapping phenotypic features, including reduced growth, characteristic facial features, cardiac defects, cutaneous abnormalities, neurocognitive delay and a predisposition to neoplasia, both benign and malignant.

Session 1: Novel Mutations/Genes in the Field

Moderator: Marco Tartaglia PhD

LZTR1 – Phenotypic Overlap with RASopathies

Martin Zenker MD* on behalf of the NSEuroNet consortium, **Institute of Human Genetics, University Hospital Magdeburg, Leipziger Str. 44, 39104 Magdeburg, Germany*

LZTR1 encodes the leucine zipper-like transcriptional regulator 1 protein, which functions as an adaptor for the Cullin 3 (CUL3) ubiquitin ligase complex. The association of LZTR1 variants with Noonan syndrome (NS) was first reported by Yamamoto et al. (*J Med Genet* 2015). Inactivating variants in this gene have also been reported as somatic events in cancer and as germline mutations in schwannomatosis. Recently published research from several groups has established LZTR1 as a specific negative regulator of RAS-MAPK signaling acting through the ubiquitylation of proteins of the RAS family (Steklov et al., *Science* 2018; Bigenzahn et al., *Science* 2018; Castel et al. *Science* 2019; Motta et al., *Hum Mol Genet* 2019; Umeki et al., *Hum Genet* 2019). While LZTR1-related Noonan syndrome was first described with an autosomal dominant (AD) mode of inheritance and a considerable rate of *de novo* mutations, an autosomal recessive (AR) type has more recently been reported (Johnston et al., *Genet Med* 2018).

We present genotype and phenotype data on a large cohort of patients with LZTR1-related NS from the NSEuroNet consortium and collaborating partners. The majority of cases carry heterozygous (presumably AD) mutations, while about 20% of families are AR, and in a few cases the mode of inheritance remained uncertain. The mutation spectrum is distinct with only little overlap: Specific recurrent missense mutations mostly affecting the Kelch domains in the more N-terminal part of the protein prevail in AD LZTR1-related NS, while AR LZTR1-related NS has a more variable mutation

spectrum with distribution over the entire gene, including also several truncating and splice site mutations. Individual genotypes suggest that in AR LZTR1-related NS at least one allele carries a probable hypomorphic mutation. The phenotype of LZTR1-related NS comprises virtually all features seen also in NS of other genetic etiologies. However, variable expression and even apparent incomplete penetrance may be observed in AD families. Regarding cardiology, the observed spectrum of cardiac anomalies is typical for RASopathies, with a relatively high frequency of hypertrophic cardiomyopathy especially in AR LZTR1-related NS. There is also an increased frequency of hydrops fetalis and fetal loss in AR LZTR1-related NS. More details will be presented at the meeting. Overall, LZTR1 mutations accounted for a considerable number of previously unsolved cases of NS in our joint cohort, and LZTR1 thus seems to belong to the five most commonly mutated genes in NS (after PTPN11, SOS1, RAF1, and RIT1).

Mutations in LZTR1 Drive Human Disease by Dysregulating RAS Ubiquitination and Signaling

Anna Sablina PhD, *VIB-KU Leuven Center for Cancer Biology, Leuven, Belgium*

Genetic evidence explicitly points out a role for LZTR1, an adaptor for Cullin 3 (CUL3) ubiquitin ligase complex, in human disease, yet its mechanism of action remains unknown. We found that Lztr1 haploinsufficiency in mice recapitulates Noonan Syndrome phenotypes including growth delay, craniofacial dysmorphism, and congenital heart defects; whereas loss of LZTR1 in Schwann cells drives their dedifferentiation into proliferating, pro-myelinating cells. By trapping LZTR1 complexes from intact mammalian cells, we identified RAS as a substrate for the LZTR1/CUL3 ubiquitin ligase complex. Unbiased proteomic analysis of the ubiquitin landscape demonstrated that Lztr1 knockout abrogates RAS ubiquitination. LZTR1-mediated ubiquitination inhibits the RAS signaling pathway by attenuating its association with the membrane. Disease-associated LZTR1 mutations disrupt either the LZTR1/CUL3 complex formation, or the interaction with RAS proteins. The discovered molecular mechanism of RAS regulation by LZTR1-mediated ubiquitination provides a fundamental explanation for the role of LZTR1 in human disease.

The SHOC2-MRAS-PP1 complex: Molecular Details and Pathway Function

Pablo Rodriguez-Viciano PhD, *UCL Cancer Institute, London, UK*

Despite the crucial role of the RAS-RAF-MEK-ERK pathway in cell signaling and disease, we still lack a complete understanding of its regulation. The MRAS GTPase, a close relative of RAS oncoproteins, interacts with the leucine-rich repeat protein SHOC2 and protein phosphatase 1 (PP1) to form a ternary phosphatase complex (the SHOC2-MRAS-PP1 complex) that specifically dephosphorylates a conserved 'S259' inhibitory site on RAF kinases that is critically required for RAF dimerization and activation.

Noonan-like syndrome with Loose Anagen Hair is caused by an activating mutation in SHOC2 (S2G), which results in constitutive membrane targeting and enhanced complex formation with MRAS and PP1. Mutations in PPP1CB and MRAS as well as an additional mutation in SHOC2 (M173I), have also been described in patients with Noonan Syndrome features. We have shown that syndromic mutations specifically promote ternary complex formation with each other highlighting the crucial role of the SHOC2-MRAS-PP1 holophosphatase complex in RAF-S259 dephosphorylation and ERK pathway dynamics.

However, SHOC2-MRAS-PP1 complex independent mechanisms of RAF activation also exist that rely instead on N-region phosphorylation of CRAF and can be differentially engaged in a context and spatio-temporal dependent manner. Redundant SHOC2-MRAS-PP1 complex dependent and independent mechanisms of RAF-ERK activation likely accounts for the observation that systemic genetic ablation of SHOC2 in adult mice is relatively well tolerated. On the other hand, KRAS oncogenic signaling preferentially depends on SHOC2 dependent-mechanisms for ERK pathway activation, which thus presents a therapeutic opportunity. Our studies suggest the SHOC2-MRAS-PP1 complex provides a regulatory node of the ERK pathway with ideal properties for therapeutic intervention in the context of deregulated RAS-ERK signaling, both in cancer and in RASopathies.

PPP1CB Associated Noonan Syndrome with Loose Anagen Hair - Phenotypic Overlap with RASopathies

Karen W. Gripp MD, *Nemours/A.I. DuPont Hospital for Children, Wilmington, DE*

RASopathies are heterogeneous disorders sharing characteristic physical and neurodevelopmental findings, first recognized as Noonan syndrome with cardiac and extracardiac manifestations. Subsequently, cardio-facio-cutaneous syndrome, Costello syndrome, Noonan syndrome with multiple lentigines and Noonan syndrome with loose anagen hair were clinically delineated. As the disease-causing genes and mutations were discovered their shared biological effect of disrupting regulation of the RAS/mitogen activated protein kinase (MAPK) pathway was uncovered and the term RASopathies was coined. Gene discovery for RASopathies continues and genotype/phenotype correlation is debated in regard to the syndrome name and disease-causing genes, as well as each specific missense variant's effect on the RAS/MAPK pathway and its pathogenicity.

Novel de novo missense variants in protein phosphatase-1 catalytic subunit beta (*PPP1CB*) were reported in individuals with a RASopathy phenotype (Gripp et al., 2016; Ma et al., 2016), most closely resembling Noonan syndrome with loose anagen hair due to a recurrent missense mutation in *SHOC2*. Functional data had previously shown that PP1C and SHOC2 form a complex which, following stimulation by MRAS, activates the RAS/MAPK pathway through RAF dephosphorylation. LZTR1, originally phenotypically linked to Noonan syndrome without known direct effect on the RAS/MAPK pathway, interacts with this RAF1/SHOC2/PPP1CB complex (Umeki et al., 2018), providing functional evidence for an LZTR1 related RASopathy.

The close functional relationship between RASopathy related proteins is reflected in the shared phenotype. Typically, RASopathies encompass short stature with relative macrocephaly, distinctive facial features, congenital heart disease including pulmonic valve stenosis and atrial septal defect, hypertrophic cardiomyopathy, pigmentary abnormalities, learning differences and an increased malignancy risk. In addition to facial and growth features typical for RASopathies, several individuals with a *PPP1CB* mutation had slow growing hair with an unruly texture resembling Noonan syndrome with loose anagen hair (NSLH) due to *SHOC2* mutation. Thus, the phenotype associated with *PPP1CB* is considered NSLH2 (OMIM# 617506). As in the *SHOC2* associated NSLH, neurologic manifestations and skin pigmentary anomalies appear relatively common. No malignancy has been reported in an individual with *PPP1CB* mutation. It remains to be seen if the presentation associated with the recurrent p.Pro49Arg variant can be distinguished clinically from other *PPP1CB* missense mutations. While at least 16 individuals with *PPP1CB* mutation have been reported, the delineation of the associated phenotypic spectrum is ongoing.

Biology of SYNGAP1-related Neurodevelopmental Disorders: Should They Be Considered RASopathies?

Gavin Rumbaugh PhD, *Scripps Research Institute, FL*

SYNGAP1 haploinsufficiency is a relatively frequent cause of sporadic neurodevelopmental disorders. Humans expressing pathogenic SYNGAP1 variants have high rates of generalized epilepsy, cognitive impairment, autistic features, and behavioral abnormalities. This gene encodes the SynGAPs, a collection of brain-enriched protein isoforms that contain an active RasGAP domain. SynGAP proteins are known to suppress Ras-signaling in developing neurons. However, SynGAP has been shown to regulate the activity of other GTPases, including Rap1/2 and Rab5. Thus, it is unclear to what extent elevated Ras function contributes to disease-relevant phenotypes in patients and animal models for SYNGAP1 haploinsufficiency. In this talk, I will discuss our current understanding of how altered Ras signaling contributes to aspects of SYNGAP1-related neurodevelopmental disorders.

SYNGAP1 – Phenotypic and Molecular Overlap with RASopathies

Jimmy Holder MD PhD, *Baylor College of Medicine, Houston, TX*

Loss of function mutations in SYNGAP1 causes SYNGAP1-related intellectual disability. This clinical disorder presents with developmental delay and seizures then evolves into intellectual disability and autism. Children with SYNGAP1 mutations often have moderate to severe intellectual disability. The spectrum of seizures can range from atypical absence with eyelid myoclonia to atonic to generalized tonic-clonic. Evaluation of electroencephalographic studies from these patients has revealed characteristic posterior-dominant electrographic discharges.

The SynGAP protein is a GTPase activating protein (GAP) which induces GTPase activity of RAS and Rab proteins. Haploinsufficiency of SYNGAP1 leads to reduced GTPase activity of these small G-proteins and their increased activation. One consequence of this sustained activation is increased transport of AMPA receptors to the surface of neurons leading to their hyperexcitability thought to underlie many of the clinical phenotypes due SYNGAP1 mutations.

We have further evaluated the utility of electrographic abnormalities as a biomarker of developmental progression. Children with SYNGAP1 mutations have slowing of their posterior dominant rhythm (PDR) compared with neurotypical children. The degree of slowing of the PDR correlates with their degree of developmental delay serving as a possible predictive biomarker.

In order to further investigate the neurophysiologic consequences of patient mutations, we have developed induced pluripotent stem cells (iPSCs) from patients. These stem cells have been induced to form cortical neurons in culture. We have determined that these neurons precociously and exuberantly fire compared with wild-type neurons. Induced neurons from our patients will serve as an experimental platform for validating our protein boosting screen for genetic modifiers of SynGAP protein stability.

Session 2: New Functions of RASopathy Genes

Moderator: Emma Burkitt-Wright MBChB PhD MRCP

Metabolic Effects in Mouse Model of Costello Syndrome

Shin-ichi Inoue PhD¹, Daiju Oba², Sachiko Miyagawa-Tomita^{3,4}, Yasumi Nakashima⁵, Tetsuya Niihori¹, Seiji Yamaguchi⁶, Yoichi Matsubara^{1,7}, Yoko Aoki¹

¹Department of Medical Genetics, Tohoku University School of Medicine, Sendai, Japan, ²Division of Medical Genetics, Saitama Children's Medical Center, Saitama, Japan, ³Department of Animal Nursing Science, Yamazaki University of Animal Health Technology, Tokyo, Japan, ⁴Department of Physiological Chemistry and Metabolism, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, ⁵Department of Pediatrics, Seirei Hamamatsu General Hospital, Hamamatsu, Japan, ⁶Department of Pediatrics, Shimane University, Faculty of Medicine, Shimane, Japan, ⁷National Center for Child Health and Development, Tokyo, Japan

Costello syndrome is one of the “RASopathies” that is characterized by growth retardation, distinctive facial features, hypertrophic cardiomyopathy, intellectual disabilities and tumor predisposition. More than 80% of patients with Costello syndrome harbor a heterozygous germline G12S mutation in *HRAS*. Altered metabolic regulation has been suspected because patients with Costello syndrome exhibit hypoketotic hypoglycemia, growth hormone deficiency and increased resting energy expenditure, and their growth is severely retarded. To examine the mechanisms of energy reprogramming by *HRAS* activation *in vivo*, we generated knock-in mice expressing a heterozygous *Hras* G12S mutation (*Hras*^{G12S/+} mice) as a mouse model of Costello syndrome. These *Hras*^{G12S/+} mice exhibited dysmorphic facial appearance, cardiomegaly with cardiomyocyte hypertrophy and kidney fibrosis. On a high-fat diet, *Hras*^{G12S/+} mice developed a lean phenotype with microvesicular hepatic steatosis, resulting in early death compared with wild-type mice. Under starvation conditions, hypoketosis and elevated blood levels of long-chain fatty acylcarnitines were observed, suggesting impaired mitochondrial fatty acid oxidation. In an intraperitoneal glucose tolerance test, *Hras*^{G12S/+} mice showed lower blood glucose levels than *Hras*^{+/+} mice. Furthermore, *Hras*^{G12S/+} mice fed a control diet displayed significantly lower blood glucose levels after 30 min of fasting. Our findings suggest that the oncogenic *Hras* mutation modulates energy homeostasis *in vivo*.

Targeting SHP2 for Neurofibromatosis and Other Malignancies

Benjamin Neel MD PhD, NYU Langone Medical Center, NY

Neurofibromatosis type 1 (NF1)-associated malignant peripheral nerve sheath tumors (MPNSTs) are malignant sarcomas occurring in approximately 15% of NF1 patients. The mortality caused by these tumors is high, approaching 100% in patients with unresectable, metastatic or recurrent disease (1). Targeted inhibition of the MAP kinase (MAPK) pathway has been attempted in clinical trials using MEK inhibitors (MEKi). While emerging data are exciting, MEKi block MPNST progression only to a limited extent. Combination strategies targeting both the MAPK and PI3K/AKT pathways (horizontal inhibition) have had limited clinical success due to excessive toxicities which precludes delivery of optimal therapeutic concentrations. Thus, novel approaches and complementary treatment strategies that are tolerable and prevent adaptive resistance mechanisms in NF1 MPNST are urgently needed.

We have succeeded in establishing orthotopic *in vivo* models (patient-derived human xenografts-PDXs and genetically engineered mouse models- GEMMs) via implantation of tumor cells into the sciatic nerve, an approach that is critical, because it preserves the tumor microenvironment. Furthermore, we have optimized MPNST culture conditions, allowing us to establish robust primary cultures of MPNSTs while retaining key biological features of the original tumors. Using this preclinical testing platform, we demonstrate that –

1. A feedback loop mediated by induction of receptor tyrosine kinase (RTK) signaling becomes hyperactivated upon MEK inhibition (MEKi). This subsequently activates the MAPK pathway to

such an extent that MEKi alone is unable to completely block signaling to ERK, thereby maintaining tumor proliferation.

2. SHP2 is a protein tyrosine phosphatase (PTP) that functions as a positive signal transducer, acting between RTKs and RAS and thus, functions as physiological mediator for RAS activation. A treatment paradigm where MEKi is combined with SHP099, an allosteric SHP2 inhibitor to counteract the rebound increase in RTK mediated signaling to RAS-MEK-ERK results in effective attenuation of MEK-ERK signaling. In vivo studies demonstrate that the drug combination exhibits synergistic effects on tumor growth inhibition and significantly prolongs survival.
3. SHP099 disrupts a functional complex (SOS1/GRB2) which is essential to RAS-GTP loading and inhibits RAS-mediated downstream MAP kinase signaling in NF1 MPNST.

Our results provide a mechanistic context for SHP2's precise role in the regulation of RAS-GTP and demonstrate that SHP2i can prevent adaptive resistance to MEKi. Given that SHP2i are currently in clinical trials (NCT03114319), our studies can be rapidly translated into a clinical trial to evaluate a combination of SHP2i and MEKi as a novel treatment approach in NF1-MPNSTs.

Structural and Functional Analysis of Neurofibromin and SPRED1

Frank McCormick, PhD, Professor, HDF Comprehensive Cancer Center, University of California San Francisco; Scientific Director, NCI Ras Initiative, Frederick National Laboratory for Cancer Research/Leidos Biomedical Research, Inc.

SPRED1 and neurofibromin form a high affinity complex that is essential for neurofibromin to act on RAS. Complex formation involves the EVH1 domain of SPRED1 and the sequences that flank the GAP-related domain in neurofibromin. Binding of SPRED1 does not affect GAP activity directly, but, most likely, positions neurofibromin in the plasma membrane to interact with RAS. SPRED1 binding to the plasma membrane could involve palmitoylation of the SPROUTY domain and/or direct binding to receptors such as c-KIT. The structural details of this interaction, solved by Drs Yan, Simanshu and colleagues at Frederick National Labs, will be presented. Binding of SPRED1 to neurofibromin can be regulated by phosphorylation of SPRED1 on Ser-107: this allows RAS to accumulate in the active state persistently.

Neurofibromin itself is an obligate dimer. Structures of the full-length dimer, solved by Dr. Esposito and colleagues in collaboration with Dr. Han at UCSF will also be presented. Dimerization could have clinical consequences: unstable mutant proteins could potentially be stabilized by binding to wild-type neurofibromin, or, alternatively, mutant proteins could de-stabilize wild-type neurofibromin. In both cases, the phenotype associated with the heterozygous state would be impacted.

Mutations in codon 848 of neurofibromin have a severe phenotype. We have investigated the mechanism involved and discovered that these mutations de-stabilize the protein, and increase its association with chaperone proteins. These discoveries suggest strategies for stabilizing the mutant protein that could have therapeutic benefit.

Keynote Address: The Inhibitor Landscape and RAS Signaling Feedback

Neal Rosen MD PhD, Memorial Sloan Kettering Cancer Center, NY

ABSTRACT

Session 3: Therapeutic Inhibitors

Moderator: William Timmer PhD

Cancer Driven by HRAS: Tipifarnib Clinical Trial Results

Alan Ho MD PhD, *Memorial Sloan Kettering Cancer Center, NY*

HRAS is a proto-oncogene mutated in salivary gland tumors, urothelial cancer, squamous head and neck cancer (HNSCC), and rhabdomyosarcoma, among other malignancies. Tipifarnib is a potent and highly selective inhibitor of farnesyltransferase, a critical enzyme for proper HRAS function. A multi-institutional, open-label trial was conducted to determine the efficacy and safety of tipifarnib in patients with locally advanced/unresectable and/or metastatic solid tumors with HRAS mutations and RECIST v1.1 measurable disease (NCT02383927). This study met recently its primary objective with significant activity in patients with HNSCC, including durable responses. Based on these data, a pivotal study (AIM-HN and SEQ-HN Study, NCT03719690) evaluating the efficacy of tipifarnib in HRAS^m HNSCC (AIM-HN) and the impact of HRAS^m on first line HNSCC therapies for (SEQ-HN) have been initiated. Additional studies in other HRAS mutant indications are ongoing or under consideration.

Functional Endpoints on the Neurofibromatosis Type 1 Plexiform Neurofibroma Phase II Selumetinib Study (SPRINT)

Andrea Gross MD, *NCI Center for Cancer Research, Bethesda, MD*

Plexiform neurofibromas (PN), histologically benign peripheral nerve sheath tumors, are one of the most common causes of morbidity in patients with neurofibromatosis type 1 (NF1). The types and severity of symptoms caused by these tumors are extremely heterogeneous, depending on their size and location. As new treatment strategies, such as MEK inhibitors, have been able to consistently shrink PN for the first time, the ability to measure changes in PN-related symptoms and functional impairments will be crucial to establish clinical benefit and the risk-benefit ratio for these medications. In our phase 2 study of selumetinib for pediatric patients with NF1 and inoperable PN (SPRINT), we utilized a variety of standardized functional and patient reported outcome measures, including assessments of pain, quality of life as well as objective measurements of motor, airway, vision and bowel/bladder function over time. This presentation will provide an overview of our experience of the utility and pitfalls of functional endpoints when utilized in the clinical trial setting.

Low-Dose Dasatinib for Cardiomyopathy in Noonan Syndrome

Anton Bennett PhD, *Yale University, New Haven, CT*

Protein zero-related (PZR) is a transmembrane glycoprotein that binds SHP2 and represents one of the most aberrantly hyper-tyrosyl phosphorylated proteins in the heart of mouse models of Noonan syndrome (NS) and NS with multiple lentiginos (NSML). These observations suggest that PZR, and the tyrosine kinase that catalyzes its phosphorylation, represent common targets for NS and NSML. Previously, we showed that the anti-cancer tyrosine kinase inhibitor, dasatinib, at doses orders of magnitude lower than that used for its anti-cancer activities inhibits PZR hyper tyrosyl phosphorylation and rescues the cardiac functionality of NS mice. Given that PZR is hyper tyrosyl phosphorylated in NSML and that NSML manifests in hypertrophic cardiomyopathy (HCM), we tested whether low dose

dasatinib has an effect on HCM progression in NSML mice. We show that NSML mice treated with low dose dasatinib exhibited reduced PZR tyrosyl phosphorylation and the development of HCM was significantly inhibited. Low dose dasatinib treatment of NSML mice reduced Akt activity in NSML mouse hearts. Given that PZR is a major hyper tyrosyl phosphorylated SHP2 binding target in the hearts of NSML mice we sought to test the contribution of PZR tyrosyl phosphorylation, and hence SHP2 binding, in the progression of NSML-mediated HCM. We generated a tyrosyl phosphorylation-defective PZR knock-in mutant mouse (Mpz11 Y242F/Y242F ; PZR Y242F mice) which was intercrossed into NSML mice to generate NSML mice expressing PZR Y242F (PZR Y242F :NSML). NSML mice expressed the tyrosyl phosphorylation defective mutant of PZR at equivalent levels as compared with controls but failed to undergo hypertyrosyl phosphorylation in NSML mice. Remarkably, the development of HCM was completely prevented in PZR Y242F :NSML mice and analysis of downstream signaling targets in the hearts of these mice revealed that Akt, but not ERK1/2, was inhibited. These results demonstrate that PZR tyrosyl phosphorylation, and thus PZR/SHP2 complex formation, is a major contributing pathway in the development of NSML-mediated HCM. Further, these data support the strategy of targeting the tyrosine kinase that phosphorylates PZR as a potential therapeutic for the treatment of HCM in NSML.

Drugging RAS from Multiple Angles

Darryl B. McConnell PhD, *Boehringer Ingelheim Regional Centre Vienna, Austria*

The RAS/MAPK pathway is dysregulated through somatic mutations in both cancer and RASopathies. RAS itself is the most common oncogenic driver in human cancers while Noonan Syndrome is characterized by mutations in PTPN11, SOS1, RAF1, KRAS and NRAS for example. No therapeutic agents directly targeting these mutated proteins have been clinically approved. This is because these proteins are controlled and signal primarily through protein-protein interactions (PPIs) which are perceived by many to be “undruggable”. Drugging PPIs with small molecules has been difficult due to the large flat interaction interfaces between protein partners, which lack deep, lipophilic pockets amenable to binding small molecules. The talk will outline the multiple approaches that Boehringer-Ingelheim is taking to drug the RAS/MAPK pathway with the goal to bring benefit to patients with cancer and RASopathies.

Session 4: Potential Endpoints for Clinical Trials in RASopathies

Moderator: Nancy Ratner PhD

Temporal Dynamics of Contextual Memory Linking in PTPN11^{D61G} Mutant Mice – **Did Not Present**

Ying Cai, Ashlee Macalino, LeWen Chiu, Cecili Riviere-Cazaux, Yang Shen, Ayal Lavi, Daniel Almeida Filho, Megha Sehgal & **Alcino J Silva PhD**, *Departments of Neurobiology, Psychology, Psychiatry, Integrative Center for Learning and Memory and Brain Research Institute, University of California, Los Angeles, Los Angeles, USA*

Previous results in our laboratory showed that the PTPN11^{D61G} mutation associated with Noonan Syndrome, disrupted ERK signaling, long term potentiation (LTP) in the hippocampal CA1 region as

well as spatial learning and memory in mice. We recently tested the dynamics of CA1 neuronal ensembles with *in vivo* recordings of GCAMP6f calcium signals with head-mounted fluorescent miniscopes developed in our laboratory (miniscope.org). *PTPN11^{D61G}* mice were imaged while exploring either the same context 4 different times separated by 7 days, 5 h and 24h, or 4 different contexts separated by the time intervals just described. The miniscope data were analyzed as described in our recent paper (Cai et al, Nature 2016). Remarkably, analyses of the results of the same context experiments did not reveal any significant differences between mutants and control littermates, demonstrating that CA1 LTP, which is absent in the *Ptpn11^{D61G}* mice, is not required for the stability of CA1 ensembles activated by contextual exploration. Importantly, studies of the information content (how well each neuron codes for spatial location) of CA1 neurons in *Ptpn11^{D61G}* mice did show that they have lower information content than their WT littermate controls. Similarly, the 4 different contexts experiment showed that *Ptpn11^{D61G}* mice have robust deficits in the degree of neuronal ensemble overlap, a critical mechanism for memory linking. Memories are dynamic in nature and a cohesive representation of the world requires memories to be linked with other related memories. Our laboratory has recently demonstrated that the overlap between the hippocampal CA1 ensembles encoding two contextual memories acquired close in time mediates memory linking, whereby the recall of one memory can lead to the recall of another memory (Cai et al. 2016). Our neuronal CA1 ensemble analyses showed that the mechanisms underlying this process are impaired in *Ptpn11^{D61G}* mice. All together our analyses of neuronal ensemble function in *Ptpn11^{D61G}* mice showed that despite their profound molecular and cellular deficits, and related abnormalities in circuit function, there were unexpectedly intact aspects of neuronal ensemble function critical for memory processing, a result that bodes well for efforts designed to reverse cognitive deficits in Noonan syndrome.

Antioxidant Testing in Preclinical Models and RASopathy Patients

Carlos Prada MD, Cincinnati Children's Hospital, Cincinnati, OH

Neurofibromatosis (NF1) is an autosomal dominant condition affecting many organs, resulting from mutations in the neurofibromin 1 gene. Characteristically, individuals with this condition have cutaneous manifestations, most prominently hyperpigmented macules termed “café-au-lait” spots. The neurofibromin gene functions in part as a tumor suppressor, and persons with NF1 are susceptible to malignant and benign tumors in multiple organs. What is less well studied is that individuals with NF1 commonly suffer from difficulties with behavioral and emotional regulation including attention-deficit/hyperactivity disorder (ADHD) symptoms, learning disabilities, and developmental delays in motor function. These cause substantial morbidity in childhood and throughout life. There are no effective treatments for motor behavior and/or learning difficulties for NF1 and other RASopathies. Lack of sensitive objective biomarkers that can evaluate motor system or behavioral symptoms causes difficulties in evaluating the efficacy of pharmacological interventions in NF1.

Clinically, 50% of children with NF1 are underperforming or failing in school. This frequently leads to decreased educational attainment and fewer opportunities as adults. The high prevalence of behavioral, emotional, and/or cognitive problems in persons with NF1 suggests that neurofibromin may play a role in maintaining the structure and/or healthy, efficient function of the brain. Clarifying this is challenging. Most likely, behavioral cognitive, and motor impairments in NF1 result, as in other genetic conditions, from multiple complex factors including environmental factors and genetic modifiers in addition to from the major effect of neurofibromin function. Moreover, cognitive and behavioral symptoms are difficult to quantify. Rating scales capture impressions of parents and teachers in the important domains of home and school, but they are subjective ratings, not brain-based measures. Also, if treatments during

a clinical trial are beneficial, there may be biological changes that precede clinical ones. Measuring biological and clinical changes may be important for validating treatment mechanisms and effects.

Inducible *Nf1* loss, *inducible proteolipid protein (iPlp)-Cre;Nf1fl/+* or *fl/fl*) in oligodendrocytes causes elevated oligodendrocyte nitric oxide (NO). The mice also show defects in oligodendrocyte myelin compaction and enlarged white matter tracts, and secondary defects develop in astrocytes and endothelial cells, cells that comprise the blood brain barrier. Mice with elevated RAS-GTP have the same phenotypes. Changes in myelin have recently been correlated with changes in behavior, and NF1 and Costello syndrome patients are known to display frequent behavioral deficits.

NO can disrupt tight junctions and gap junctions, altering blood vessels. *Nf1* loss or Ras hyperactivation in oligodendrocytes upregulates NO and NOS in white matter, correlating with disrupted tight junctions and gap junctions, and altered blood vessel permeability. Treating mice with *Nf1* loss or Ras hyperactivation with the antioxidant N-acetyl cysteine corrects cellular phenotypes and behavioral abnormalities.

This data from animal models of NF1 along with uncontrolled clinical observations in children with NF1 suggest that the antioxidant compound, NAC, may reduce these impairments.

Bridging the Gaps in our Knowledge: Brain Development of Children with Noonan Syndrome

Tamar Green MD, *Stanford University, CA*

This talk will cover the essential neuroscience and cognitive-behavioral aspects of Noonan syndrome, particularly as related to neuropsychiatric issues. Recent findings from the careful study of genotype-phenotype associations in Noonan syndrome will be covered. Specifically, as related to brain structure and connectivity. These data will be used to propose and examine new approaches for diagnosis and treatment of human neuropsychiatric disorders such as ADHD and autism.

Neuroimaging of RASopathies in the Newborn and Young Child

Susan Blaser MD, *Hospital for Sick Children, Toronto Ontario, Canada*

RASopathies are a family of multisystemic disorders with overlapping phenotypic features caused by germline mutations in genes coding for proteins that are part of the RAS/MAPK pathway. This pathway is essential for cell proliferation, differentiation and senescence. Characteristic neuroimaging findings have been extensively reported in NF1 and in the oculocutaneous mosaic RASopathies, such as oculoectodermal syndrome (OES), encephalocutaneous lipomatosis (ECCL) and Schimmelpenning-Feuerstein-Mims (SFMS) syndromes, amongst others.

Neuroimaging features in the non-NF1 RASopathies have been less well described. The most common of the non-NF1 RASopathies are Noonan, Noonan-like disorder with loose anagen hair (NSLAH), Costello (CS), cardio-facio-cutaneous (CFC), NS with multiple lentigines (formerly known as LEOPARD) and Legius syndromes. Prenatal manifestations are nonspecific and include cardiac and renal abnormalities and lymphatic dysplasia. Craniofacial dysmorphisms, respiratory distress and hypotonia may present after birth, while developmental delays become apparent during infancy. Until recently, neuroimaging has not been routinely performed in the neonatal period. In a comparison study of 16 newborns with confirmed RASopathies and 32 control newborns, we found both acquired abnormalities and structural anomalies of the CNS. An increased incidence of cerebral white matter

lesions and of peripheral cerebellar hemorrhage, extra-cerebral space enlargement and isolated ventriculomegaly were more common in the RASopathy cohort. Structural abnormalities included simplification of cortical gyrification for age, vertical or underdeveloped splenium, vermis hypoplasia, steep tentorial configuration, persistence of fetal durovenous sinus drainage patterns and depressed cranial base angles.

iPSC-Derived Cardiomyocytes Reveal Aberrant ERK5 and MEK1/2 Signaling Concomitantly Promote Hypertrophic Cardiomyopathy in RAF1-Associated Noonan Syndrome

Fabrice Jaffré^{1,2}, Clint L. Miller³, Anne Schänzer⁴, Todd Evans², Amy E. Roberts⁵, Andreas Hahn⁶, and **Maria I. Kontaridis PhD^{1,7,8,9}**

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Background: More than 90% of Noonan syndrome (NS) individuals with mutations clustered in the CR2 domain of RAF1 present with severe and often lethal hypertrophic cardiomyopathy (HCM). The signaling pathways by which NS RAF1 mutations promote HCM remain elusive, and so far, there is no known treatment for NS-associated-HCM.

Methods: We used patient-derived RAF1S257L/+ 37 and CRISPR-Cas9-generated isogenic control iPSC-derived cardiomyocytes (iCMs) to model NS RAF1-associated HCM and to further delineate the molecular mechanisms underlying the disease.

Results: We show that mutant iCMs phenocopy the pathology seen in patient NS hearts by exhibiting hypertrophy and structural defects. Through pharmacological and genetic targeting, we identify two perturbed concomitant pathways that, together, mediate HCM in RAF1 mutant iCMs; hyper-activation of MEK1/2, but not ERK1/2, causes myofibrillar disarray, whereas the enlarged cardiomyocyte phenotype is a direct consequence of increased ERK5 signaling, a pathway not previously known to be involved in NS. RNA-sequencing reveals genes with abnormal expression in RAF1 mutant iCMs and identifies subsets of genes dysregulated by aberrant MEK1/2 or ERK5 pathways that could contribute to the NS-associated HCM.

Conclusions: Taken together, our study identifies the molecular mechanisms by which NS RAF1 mutations cause HCM and reveals downstream effectors that could serve as therapeutic targets for treatment of NS, and perhaps other, more common, congenital HCM disorders as well.

Unraveling the Cause of Developmental Disease Using Zebrafish: MAP4K4 Truncations as a Potential Cause of RASopathies

Victoria L. Patterson PhD, Dong Li PhD, Elizabeth J. Bhoj MD PhD, **Rebecca D. Burdine PhD**, Princeton University, NJ

Congenital malformations can arise in isolation or within complex syndromes, and are the leading cause of infant mortality in the USA. One group of complex developmental syndromes is the RASopathies, caused by inappropriate activation of RAS signaling.

RASopathy patients typically carry mutations in components of the core signaling pathway. However, there are patients with “RASopathy-like” features that lack specific molecular diagnoses. Identifying new disease associated variants can potentially improve patient care, while extending our understanding of normal development. To detect novel variants, we performed whole exome sequencing on a cohort of patients presenting with RASopathy features, namely congenital heart defects, neurological dysfunction and craniofacial anomalies. We identified seven individuals from four families with variants in *Mitogen-Activated Protein Kinase Kinase Kinase 4* (*MAP4K4*). *MAP4K4* is known to function in a range of signaling pathways that control many vital cellular processes, including proliferation, embryonic development, and apoptosis. To determine if these variants are pathogenic, we are utilizing rapid assays and CRISPR/Cas9 mutagenesis to assess *MAP4K4* function in zebrafish. Overexpressing *MAP4K4*^{WT} in zebrafish embryos causes multiple developmental abnormalities. However, overexpressing *MAP4K4*^{L864X} has little effect, suggesting the L864X mutation is hypomorphic. Pharmacological inhibition of *MAP4K4* impacts the same structures as affected in patients, causing cardiac defects and craniofacial anomalies. Introducing truncating mutations in the zebrafish locus with CRISPR/Cas9 produced similar phenotypes as pharmacological inhibition. Furthermore, increasing *MAP4K4* levels in embryos rescued phenotypes induced by hyperactive RAS signaling. Together, our data suggest *MAP4K4* may act as a negative regulator of RAS signaling, and that loss of *MAP4K4* function underlies patient pathophysiology. This brings *MAP4K4* into the cohort of genes underlying RASopathies in humans for the first time.

Session 5: Prenatal Findings, Manifestations, Diagnosis, and Management

Panel Moderator: Pilar Magoulas MS CGC

Panelists: Sandra Darilek, MS CGC, Angie Jelin, MD-MFM

Session 6: Clinical Trial Endpoints Roundtable

Moderator: Richard Klein

Parent Project Muscular Dystrophy at the Forefront of Patient-Reported Outcomes

Annie Kennedy BS, Senior Vice President– Legislation & Policy, PPMD, Hackensack, NJ

Since inception, Parent Project Muscular Dystrophy (PPMD) has been working to inform the development and collection of patient-reported outcomes by convening key stakeholders around innovative efforts aimed to move Duchenne therapy discovery forward. These efforts include The Duchenne Registry, planning for the Duchenne Platform Trial, and a recent Duchenne Outcomes Meeting.

Annie will reflect on how these efforts have supported researchers and sponsors as they work to advance care and treatments for individuals with Duchenne. And how – most as Duchenne products have moved into the approval environment – PPMD's initiatives have expanded to incorporate payer and health technology assessors in informing outcome collection. Annie will also describe the recent launch of PPMD's Duchenne Outcomes Research Interchange, a bringing together of the PPMD patient reported data registry, with electronic health records from Certified Duchenne Care Centers, and post-market surveillance data.

Benefits, Challenges, and Strategies for Incorporating Patient-Reported Outcomes in Pediatric Trials for RASopathies

Pam Wolters PhD, *NCI Center for Cancer Research, Bethesda, MD*

Patient-reported outcomes (PROs) can be used to assess psychosocial functioning in natural history studies and perceived clinical changes in treatment trials. This talk will review the benefits and challenges to using PRO measures in children, adolescents, and young adults with RASopathies as well as the strategies for incorporating them into clinical trials. The process for developing new measures as part of the FDA Clinical Outcome Assessment program also will be presented.

A Prospective Study of the Impact of MEK1/2 Inhibition on Neurocognitive Functioning in Children and Adults with NF1

Karin S. Walsh PsyD, *Children's National Health System, Washington DC*

Background: In NF1, Ras is overactive and associated with cognitive deficits. Manipulation of the Ras/ERK pathway has rescued cognitive impairments in the *Nf1* mouse. In trials directed at NF1 tumors, MEK inhibitors have shown activity. A NF1 mouse study suggested that inhibition of MEK1/2 may improve cognitive function. This prospective, multi-center, single-arm, ancillary study aimed to examine the potential benefit of MEK inhibitors on cognition in children and young adults with NF1.

Methods: Sixty-three patients with NF1, 5-33 years (median = 12), enrolled on MEK inhibitor trials for NF1 tumor completed computerized cognitive assessment and parent-reported executive functioning at baseline (T₀), 3, 6 (T₂), and 12 months. The primary outcome is change in metacognition (Cogstate ONB+OCL Composite, BRIEF Metacognitive Index [MCI]) from T₀ to T₂. One-sample t-tests analyzed group mean differences from T₀ to T₂, and reliable change analysis evaluated individual clinically significant change.

Results: At T₀, 21.5% of patients were rated to have clinically elevated deficits in metacognition (BRIEF, MCI), which was significantly higher than at T₂ (15.7%, $p=.002$). Behavior regulation impairments were reported in 11.5% at T₀, also significantly higher than at T₂ (7.7%, $p=.01$). Mean scores on the Cogstate composite were significantly lower at T₀ ($M=-0.24$, $SD=1.08$) than T₂ ($M=0.10$, $SD=0.87$; $p=0.02$, $d=0.32$). Reliable change analyses indicated that more patients receiving selumetinib showed clinically significant improvement in metacognition (BRIEF MCI) at T₂ compared to that expected by chance (25.5% improved v. 10% expected at 80% CI; $p=.04$, $OR=3.1$). Despite a similar trend for behavioral regulation (21.2% improved v. 10% expected) significance was not achieved ($p=.09$). The number of participants improved in executive function efficiency on Cogstate was not significantly greater than chance (16.4% improved, 10% expected) but working memory accuracy approached significance (18.9% improved, 10% expected, $p=0.07$).

Conclusions: Our study demonstrates stable cognitive performance over 12 months of treatment with MEKi (no neurotoxicity). Informant (parent) reports of daily functional working memory and executive functions indicate significant positive change from pre-tx to 6 months and additional benefit by 12 months. Findings are limited without a comparison group but support further research on the potential therapeutic effect of MEK inhibition on cognitive morbidities in NF1.

Advocacy Organizations Panel

Moderator: **Michelle Ellis**, Noonan UK

Panelists: **Tuesdi Dyer**, CFC International; **Angel Thomas**, Costello Syndrome Family Network; **Alwyn Dias**, Children's Tumor Foundation; **Gregg Erikson**, NF Network; **Amanda Brown**, Noonan Syndrome Foundation

Session 7: Junior Investigators, MDBR Grantees, Closing Comments

Moderator: Amy Roberts MD

Finalist 1: Modelling LZTR1 loss-of-function *in vivo*: a Novel Noonan Syndrome Mouse Model

Pau Castel¹, Alice Cheng¹, Joaquim Grego-Bessa², Katherine Rauen³, Frank McCormick¹

¹Helen Diller Family Comprehensive Cancer Center, University of California San Francisco; ²Spanish National Center for Cardiovascular Research (CNIC); ³MIND Institute, University of California Davis

Pathogenic germline variants in LZTR1 have been recently identified in Noonan syndrome. Such variants are loss-of-function and are often inherited following an autosomal recessive pattern. However, in the context of RASopathies, the association of LZTR1 has been controversial because the molecular mechanism by which this protein regulates the canonical MAPK pathway has been largely unknown.

We and others have recently demonstrated that LZTR1 belongs to the family of Kelch/BTB/BACK proteins that interact with the E3 ubiquitin ligase Cullin 3 to form a complex that promotes ubiquitination and degradation of specific substrates. We have established that, in physiological conditions, RIT1 is the main functional substrate of the LZTR1/Cullin3 degradation complex (Castel, *et al*, 2019 Science, **363**, 1226). RIT1 is a Ras-related small GTPase able to activate the canonical MAPK pathway and activating mutations in this protein have also been identified in 5-9% of Noonan syndrome patients. We have showed that pathogenic variants affecting LZTR1 impair RIT1 ubiquitination and proteasomal degradation, resulting in its accumulation and subsequent dysregulation and activation of the MAPK pathway.

To further analyze the effect of LZTR1 loss-of-function at the organismal level, we have generated mice that are knockout for this gene. Heterozygous mice were born at the expected Mendelian ratios and failed to exhibit the classic phenotype of NS, including reduced growth, craniofacial dysmorphia, cardiomegaly, and splenomegaly. In contrast, homozygous mice were determined to be embryonically lethal, since we were unable to recover viable pups. Upon closer examination, we found extensive hemorrhages in knockout embryos between embryonic days (E)15.5 to 18.5. Histological analysis of

E18.5 hearts showed a prominent cardiovascular phenotype in *Lztr1* knockout embryos, that was characterized by hypertrophic cardiac valves and sporadic septum defects. The valve phenotype was the result of increased proliferation, as determined by Ki67 staining, and likely the cause of embryonic lethality. Similar observations have been described in mice carrying Noonan syndrome alleles in *Ptpn11* and *Kras* when bred in the C57BL/6 mouse strain, because this genetic background results in more severe cardiovascular phenotypes. To overcome this limitation, we decided to use the 129Sv mouse strain, which is more permissive to such phenotype. Through a series of backcrossings, we demonstrated that *Lztr1* knockout mice in the 129Sv background are in fact viable and exhibit features of NS: : knockout mice were smaller than wild type littermates, displayed a significant craniofacial dysmorphia, and presented with both cardiomegaly and splenomegaly. Furthermore, tissues isolated from these mice exhibited an increased expression of RIT1 when compared to *wild type* and heterozygous littermates.

In summary, until recently, LZTR1 and its association with RASopathies has been unclear. We demonstrate that LZTR1 loss-of-function in the mouse germline recapitulates the phenotype of Noonan syndrome patients and highlights the importance of genetic modifiers in driving the severity of the cardiovascular manifestations. Importantly, we describe the first LZTR1 mutant mouse model of Noonan syndrome, which will be used to further study the pathogenesis of this disorder *in vivo* and test novel pharmacological approaches for the treatment of Noonan syndrome-associated symptoms.

Finalist 2: Hematopoietic Defects in a Zebrafish Knock-in Model of Noonan Syndrome

Maja Solman PhD¹, Sasja Blokzijl-Franke¹ and Jeroen den Hertog^{1,2}; *1. Hubrecht Institute-KNAW and University Medical Center Utrecht, the Netherlands; 2. Institute Biology Leiden, Leiden University, the Netherlands*

Shp2 has an important role in hematopoiesis, which is underlined by Shp2 often being mutated in leukemias, such as juvenile myelomonocytic leukemia (JMML). Noonan syndrome patients, in particular the ones carrying Shp2 mutations, display increased predisposition to develop JMML. The pathogenesis of JMML is poorly understood and the only therapy available is blood stem cell transplantation. Zebrafish is established as an exciting model to study the effect of Rasopathies-associated mutant proteins on embryonic development. However, there are no genetic zebrafish Rasopathy models and so far, these analyses were limited to embryos transiently and ubiquitously overexpressing mutant proteins.

We generated a genetic zebrafish Noonan syndrome model, using CRISPR/ Cas9 based knock-in of the patient-associated D61G mutation in zebrafish *Shp2a* (*ptpn11a* gene). The generated mutant closely resembles the Noonan syndrome features, such as growth and craniofacial defects, and is viable into adulthood. We used this mutant zebrafish model to study hematopoiesis during early embryonic development in detail. Distinct blood lineages were monitored in whole embryos, either by in-situ hybridization using lineage-specific markers, or in transgenic zebrafish lines. While primitive hematopoiesis appeared normal, definitive hematopoiesis was defective. We observed an expansion of hematopoietic stem cells (HSCs) and myeloid lineages, such as macrophages and neutrophils, in mutant embryos. On the other hand, there was a decrease in the number of erythrocytes and thrombocytes, while the lymphoid lineage seemed not to be affected. The expansion of HSCs and myeloid lineage was attenuated upon treatment with MEK inhibitor CI1040 or PI3K inhibitor LY294002, indicating that the observed defects were dependent on both MAPK and PI3K pathway.

Next, we explored whether transcriptional reprogramming of hematopoietic stem and progenitor cells (HSPCs) was involved in the observed blood defects. Single cell RNA sequencing was performed on HSPCs, isolated from mutant and wild-type sibling zebrafish embryos. We observed expression of genes leading to early differentiation bias towards myeloid lineage, at the expense of erythro- and thrombopoiesis. Expression of selected genes was validated in zebrafish embryos by in-situ hybridization. Furthermore, single cell RNA sequencing revealed an expansion of monocyte progenitors among mutant HSPCs, which seems to have a specific inflammatory gene expression signature. Currently we are investigating the role of these early monocyte progenitors in the development of the observed blood defects and whether they could be an effective future therapy target. Taken together, we have generated a knock-in zebrafish model for Noonan syndrome, which displayed hematopoietic defects and revealed an inflammatory transcriptional signature in differentiating monocytes.

Finalist 3: SHP2/PTPN11 Interactions with Protein Zero Related (PZR) Promotes Hypertrophic Cardiomyopathy in Noonan Syndrome with Multiple Lentigines (NSML).

Jae Sung Yi PhD, Yale School of Medicine, New Haven, CT

Noonan syndrome with multiple lentigines (NSML) is a rare autosomal dominant disorder that presents with craniofacial anomalies, developmental retardation and cardiac defects, such as hypertrophic cardiomyopathy (HCM). Approximately 90% of NSML cases are caused by catalytically inactive mutations in the *PTPN11* gene that encodes the Src homology 2 (SH2) domain-containing protein phosphatase 2 (SHP2). Protein zero-related (PZR), a transmembrane ITIM-containing glycoprotein, has been identified as an interacting partner and scaffolding protein for SHP2. Our previous work demonstrated that NSML-SHP2 mutations bind c-Src causing PZR hyper tyrosylphosphorylation resulting in increased PZR/NSML-SHP2 complexes and subsequently aberrant downstream signaling. Postnatal administration of a low-dose of dasatinib (Abl and Src kinase inhibitor) blocked PZR hypertyrosyl phosphorylation, PZR/SHP2 complex formation and rescued HCM in a mouse model of NSML (*Ptpn11*^{Y279C/+}). In order to understand the role of PZR tyrosyl phosphorylation, and hence its interaction with SHP2, in the causality of HCM in NSML, we generated a tyrosyl phosphorylation-defective PZR knock-in mutant mouse (*Mpz1*^{Y242F/Y242F}; PZR^{Y242F} mice). PZR^{Y242F} mice were intercrossed with NSML mice to generate NSML mice expressing PZR^{Y242F} (PZR^{Y242F}:NSML). Mice expressing PZR^{Y242F} alone exhibited a normal cardiac phenotype. However, PZR^{Y242F}:NSML mice were completely protected from the development of HCM. Molecular markers of HCM, such as *Anf*, *Bnp* and the ratio of *Myh7/Myh6* although expectedly elevated in NSML mice hearts, were comparable in PZR^{Y242F}:NSML mice with wild type controls. The phosphorylation of Akt as shown previously was elevated in the hearts of NSML mice but was rescued in the hearts of PZR^{Y242F}:NSML mice to wild type control levels. We identified that interleukin-6 (IL6), a pro-inflammatory cytokine implicated in HCM, was significantly upregulated in the heart of NSML mice and inhibiting PZR tyrosyl phosphorylation in the PZR^{Y242F}:NSML mice reduced IL6 expression to levels comparable to that of wild type mice. Thus, we link the PZR/SHP2 complex to HCM-driving signaling pathways, Akt and IL-6, in the pathogenesis of NSML-mediated HCM. Given that PZR is a major hyper tyrosyl phosphorylated SHP2-interacting protein in NSML hearts, these results support the targeting of this adapter protein for the treatment of NSML cardiomyopathies.

Using a Clinically-Approved Antiemetic, Meclizine, to Attenuate Hyperactive RAS–MAPK Signaling

Kartik Venkatachalam PhD, *McGovern Medical School at University of Texas Health Science Center, Houston, TX*

By operating at the nexus of growth factor receptors and mitogen-activated protein kinases (MAPKs), RAS GTPases mediate faithful transmission of signals between the two. In helping fulfill this role in signal transduction, subcellular locations of RAS proteins are of incontrovertible importance. All three RAS isoforms, HRAS, NRAS, and KRAS, bear structural motifs and post-translational modifications that direct attachment to specific domains in the plasma membrane (PM). For instance, localization and clustering of HRAS and NRAS occur in cholesterol-enriched domains. Perturbations that disrupt RAS localization decisively attenuate MAPK signaling.

We recently found that lysosomal exocytosis is necessary for recycling of cholesterol moieties that get collaterally internalized during endocytosis. Inhibition of lysosomal trafficking reduces PM cholesterol, and thus attenuates MAPK signaling in cells with activated HRAS. In fact, any perturbation that lowers PM cholesterol attenuates MAPK signaling in cells that express activated HRAS. Neither HRAS surface localization nor MAPK signaling are altered by blocking lysosomal exocytosis in cells with wild type HRAS. In other words, PM cholesterol appears to set the gain of MAPK signaling by selectively filtering out the strong signals while allowing the passage of weaker ones. Given that hyperactive MAPK signaling is responsible congenital RASopathies, selective mitigation of RAS hyperactivation is of tremendous clinical significance.

During this presentation, I will describe a signaling axis that functions orthogonally to lysosomes in regulating PM cholesterol and RAS–MAPK signaling. Our findings demonstrate that the antiemetic, **Meclizine**, attenuates MAPK signaling and cell proliferation by inhibiting phosphate cytidylyltransferase 2 (PCYT2) — an enzyme that participates in the synthesis of phosphatidylethanolamine (PE). Meclizine and PCYT2 knockdown exerted their influence on MAPK signaling via an unexpected increase in sphingomyelin, which sequesters, and thereby, lowers free cholesterol. Mechanistically, the upregulation of sphingomyelin arises from the influence of PCYT2 on mitochondria. Our data support the model that loss of PCYT2 results in mitochondrial dysfunction associated with a dramatic increase in mitochondrial iron. Suggesting the involvement of iron dyshomeostasis in elevated sphingomyelin levels, we identified increased expression of genes encoding enzymes of the sphingomyelin biosynthesis pathway, whose sequences contained iron response elements (IREs). In summary, PCYT2 is required for maintenance of iron homeostasis, preventing the translation of sphingolipid biosynthesis enzymes, and thus, regulating the gain of MAPK signaling. Application of Meclizine attenuates MAPK signaling via diminished stability of chaperones in the Fe-S cluster biosynthesis pathway, inform the use of this drug in treating diseases that stem from hyperactive RAS–MAPK signaling.

Advancing a Novel Therapeutic Lead for RASopathies

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The RASopathies are a collection of inherited disorders that are characterized by mutations that elevate activity of the RAS/ERK signaling network. Patients present with a broad range of developmental defects as well as those that emerge postnatally. In addition to reducing quality of life, most patients with these traits encounter some RASopathy-associated morbidities such as hypertrophic cardiomyopathy (HCM), which can be life-threatening.

Currently, only symptomatic care is available for affected individuals. Since the biology of the RAS signal transduction pathway is well understood, there is a significant opportunity for developing mechanistic therapies for the RASopathies. For example, several anti-cancer drugs that reduce RAS/ERK pathway activity have been assessed in clinical trials with additional trials ongoing, but to date none has been FDA approved for RASopathies. To address this continuing unmet need, the Gelb and Cagan laboratories have been working together to identify new lead therapeutics through a novel approach: using a *Drosophila* RASopathy model as a whole-animal screening platform.

Screening a large chemical library, we identified a set of four especially promising novel hits. Here, we are now pursuing these hits with the intention of advancing at least one hit to lead compound status. To achieve this, we are using a standard medicinal chemistry approach to improve druggability of our four hits by generating 15-20 analogs for each, a total of 60-80 new candidate compounds. We will then test our 60-80 candidate compounds in an expanded set of *Drosophila* RASopathy lines, with the intent of identifying the most promising lead compound.

Using a *Drosophila* *RAF*^{S257L} RASopathy model as a whole animal screening platform, we screened a Maybridge Hitfinder library of 14,400 compounds. Four compounds showed consistent rescue of *RAFS257L*-induced lethality as well as reduced RAS/ERK activity *in vivo*. These compounds, M1-M4, represent novel chemical inhibitors of RAS/ERK activity. Although each showed whole animal activity, based on their relatively simple chemical structures, compounds M1-M4 require further chemical elaboration to be considered as lead compounds. Due to its superior chemical structure, M1 was selected as the lead to advance first. We worked with a medicinal chemistry team at Mount Sinai to develop 17 chemical analogs for M1, which have been screened in our RASopathy fly model. Having refined the relevant chemical space, we are now iterating on the M1 analog with the best rescue activity to further improve drug-like properties.

We have recently generated 14 *Drosophila* RASopathy models by expressing human RASopathy isoforms of *RAF1*, *BRAF*, *KRAS*, *HRAS*, and *SHP-2*. Our fly models show striking phenotypic differences, mirroring differences in RASopathy patients. We are beginning to test our novel M1 chemical derivatives in additional *Drosophila* RASopathy models. Ultimately, we will assess overall animal viability, phenotypes in the eye and wing, and RAS pathway signaling based on western blot analysis. These data will help us prioritize our best M1 leads based on their ability to address multiple disease subtypes.

Closing Remarks

POSTER ABSTRACTS

[** indicates submission for Junior Investigator competition]

ClinGen Partners with Advocacy Groups to Inform RASopathy Gene and Variant Curation

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The Clinical Genome Resource, ClinGen, is an NIH-funded effort focused on defining the clinical relevance of genes and variants for use in precision medicine and research. ClinGen facilitates genomic and health data sharing with NCBI's ClinVar database from laboratories, clinicians, researchers and patients. Evidence frameworks have been developed to enable evaluation of gene-disease associations and variant pathogenicity. Clinicians, researchers and laboratory representatives in specific clinical areas form Gene Curation and Variant Curation Expert Panels (GCEPs and VCEPs) to drive this work. Here, we describe the ClinGen RASopathy GCEP and VCEP efforts and collaboration with advocacy groups to enrich available genomic and phenotypic information.

In 2014, the RASopathy GCEP and VCEP were established and began improving variant classification for the RASopathies by providing specifications to the ACMG/AMP guidelines for the interpretation of sequence variants in BRAF, HRAS, KRAS, MAP2K1, MAP2K2, PTPN11, RAF1, SHOC2, and SOS1. To date, 234 variant classifications have been assessed by these guidelines and submitted to ClinVar by the RASopathy VCEP. The GCEP has assessed 104 gene-disease associations by ClinGen's evidence-based framework, results of which are available at clinicalgenome.org. Assessment and periodic reassessment of gene and variant curations is ongoing.

To engage individuals who have had genetic testing in data sharing, ClinGen launched a patient registry, GenomeConnect, in 2014. Participants consent to broad data sharing, upload genetic test results, and complete health surveys. This genetic and clinical data from participants is then de-identified and submitted to ClinVar. To broaden the goal of supporting patient-centered data sharing, GenomeConnect began partnering with external patient registries in 2018. To date, two RASopathy-related registries have enrolled – CFC International and the Costello Syndrome Family Network. CFC International has recruited 33 participants and 19 have uploaded a copy of their genetic testing report with variants that can be shared with ClinVar. The Costello Syndrome Family Network, which recently launched their registry, is actively recruiting.

To enhance the health data that participants are sharing through these registries, we led the development of a RASopathy phenotype survey. The survey content was reviewed by the RASopathy GCEP/VCEP and is now under review by representatives from CFC International and the Costello Syndrome Family Network. Survey responses will be mapped to corresponding Human Phenotype Ontology (HPO) terms. The survey will be offered to participants of GenomeConnect who have indicated a diagnosis of a RASopathy and any external registries that would like to implement it. The additional phenotypic data derived from a participant's response can then be paired with their shared genetic testing results.

The ClinGen RASopathy Expert Panel has worked for five years to standardize and generate variant and gene curation. In the current phase of our work, we are harnessing the expertise of individuals and families affected by RASopathies to enhance collection of genetic and phenotypic data available for curation.

****Epigenetic suppression of Sox10 induces apoptosis in proliferative cells from large/giant congenital nevi with oncogenic NRAS**

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Background: Pediatric large/giant congenital nevus (CMN) is a congenital neoplasm of rare occurrence predominantly associated with a post-zygotic somatic mutation in NRAS. CMN is considered to be in the pathogenetic category of "mosaic RASopathies". The disease is characterized by large or giant (>40 cm) pigmented benign lesions of nevo-melanocytes covering 60-70% of the skin. These lesions pose increased risk of malignant transformation. Currently there is no specific chemotherapy available for CMN patients. In previously reported studies, genetic suppression of Sox10 showed induction of apoptosis in nevo-melanocytes in a mouse model, which led to the hypothesis that Sox10, a regulator of MITF gene expression could be a therapeutic target in this disease. In this study, we tested Histone deacetylase inhibitor drugs (iHDACs) *Vorinostat*, *Belinostat* and *Romidepsin* as pharmacological agents to suppress Sox10 gene expression in proliferative cells isolated from large/giant CMN lesions.

Method: Proliferative cells were cultured from patients' lesions carrying NRAS codon 61 mutation. Cells were treated with iHDACs and cell viability was assessed by MTT assay. Acetylation by iHDACs was verified by western blot using anti-acetyl histone antibody and by immunocytochemistry using anti-acetyl tubulin antibody. Sox 10 gene expression was analyzed from extracted total RNA from patient's cells using quantitative real time PCR. The nature of cell death was determined by apoptosis assay.

Results: iHDAC drugs treatment reduced viability of nevocytes in culture in a dose dependent manner. iHDACs induced acetylation of histone and tubulin. Sox10 and MITF gene expression levels decreased in drug treated cells compared to control. The number of cells undergoing apoptosis increased significantly upon drug treatment.

Conclusion: Our results indicate that Sox10 and MITF gene expression could be suppressed in nevocytes by HDAC inhibition. Resulting apoptosis in the drug treated cells suggest that HDAC inhibitors could be considered

a therapeutic agent for NRAS mutated large/giant congenital nevi as a potential alternative to morbid surgical interventions.

A novel direct Ras inhibitor

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RASopathies are caused by mutations in Ras or its regulators that result in an over-active Ras protein. The most obvious treatment would be a drug which binds and inhibits Ras so that the over-activity could be suppressed. We have developed a novel Ras binding molecule that blocks the ability of Ras to interact with its downstream effector components and thus down-regulates Ras signaling. The compound suppresses the transforming activity of mutant forms of Ras as well as the wild type protein when it is over-active due to defects in the NF1 protein. The compound has no detectable toxicity in animals and readily crosses the blood-brain barrier. It is potently active in animal models of Ras mediated transformation and can eradicate the ability of Ras addicted tumor cells to form tumors in animals. We propose the compound may serve as the basis for the development of new treatments for many RASopathy symptoms.

**Phenotypic Landscape of RASopathies in Mexico: The Experience in Genetic Clinics

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The RASopathies are a group of genetic syndromes caused by germline pathogenic variants in genes of the Ras-Mitogen-Activated Protein kinase (RAS-MAPK) pathway. RASopathies include Neurofibromatosis Type 1 (NF1), Noonan Syndrome (NS), Noonan syndrome with multiple lentigines (NSML/LEOPARD), Costello syndrome (CS), Cardio-facio-cutaneous syndrome (CFC), capillary malformation-arteriovenous malformation syndrome (CM-AVM), and Legius Syndrome (LS). RASopathies affect approximately 1 in 1,000 individuals. Although each of the RASopathies is a distinct syndrome, these syndromes share many overlapping characteristics: postnatal growth failure, craniofacial and dental dysmorphisms, cardiac, cutaneous, musculoskeletal, gastrointestinal, genitourinary, neurological and ocular abnormalities, neurocognitive impairment, hypotonia, and cancer predisposition. A literature search about RASopathies in Mexico showed few efforts describing specific abnormalities of some cases, but no general information about the epidemiological and phenotypic features of these diseases. We proposed some questions: What is the distribution of the different types of RASopathies in Mexico? What are the epidemiological and phenotypic features in those patients?

Objective: To describe the distribution and phenotype of RASopathies in Mexican patients.

Methods: We sent a data collection sheet to different Genetic Clinics in Mexico to evaluate the information about epidemiological and phenotypic features of patients with clinical diagnosis of RASopathies. We determined the frequencies of each type of RASopathy, the current age and at the time of diagnosis, the reason for sending to the Genetic Clinic, familiar history of RASopathy and the presence of cancer. For the statistical analysis we used Microsoft Excel and STATA; p-values < 0.5 were significant.

Results: We received information of 86 patients from 14 different clinical genetics centers across the country. The female percentage was 55.8% overall ($p=0.7$). The distribution of the RASopathies was: 11.6% unclassifiable RASopathy (UR), 41.9% NF1, 37.2% NS, 9.3% CS, and no patients with clinical diagnosis of CFC, NSML/LEOPARD, LS, or CM-AVM. The median of current age was 6 years old overall; 3, 8, 4, and 4.5 years old for UR, NF1, NS and CS, respectively ($p>0.05$). The median of age at diagnosis in the whole group was 12 months; 11, 42, 7, and 9 months for UR, NF1, NS, and CS, respectively ($p=0.04$ for NF1 compared with the rest of patients together [non-NF1 patients]). The reasons for sending to the genetics consultation were malformations and dysplasias, facial dysmorphisms, short stature, and cancer; some patients with a combination of these reasons. The percentages of reason(s) for sending varied depend on the clinical diagnosis. Regarding café au lait macules only patients with NF1 were referred due to this abnormality (83%); 60, 63, and 50% of patients with UR, NS, and CS, respectively, were sent to the consultation because of heart anomalies; 20, 19 and 25% of UR, NS, and CS, respectively, were referred due to short stature; in 40, 19, and 50% of patients with UR, NS, and CS, respectively, the reason for sending was facial dysmorphisms; and finally, 11% of patients with NF1 were evaluated due to cancer. Half of the cases were sent to the genetic clinics as a RASopathy suspicion, either NF1 or NS. A third of the patients had a familiar history of RASopathies, 70% of them had NF1. Four patients with NF1 developed cancer, 2 cases of optic nerve glioma (3 years old in both cases) and 2 cases of breast cancer (51 and 49 years old).

Conclusions: This is the first effort that describes and analyzes the epidemiological and phenotypic features of patients with RASopathies in Mexico. Overall, there was no difference in the sex ratio. In more than 10% of cases, the assignment to specific type of RASopathy was not possible based on the clinical evaluation. The most frequent diagnoses were NF1 (41.9%) and NS (37.2%), and only 9.3% with CS; no patient was assigned as CFC, NSML/LEOPARD, LS or CM-AVM. The age at diagnosis was significant higher for patients with NF1 compared with other diagnosis. The reasons for sending patients with NF1 were café au lait macules and cancer and the patients with NS and CS were referred due to heart disease, short stature and facial dysmorphisms. Both family cases and those sent to the clinic with suspicion of RASopathy were from patients with NF1 and CS. The only diagnosis with a history of cancer was NF1.

Predictors of social functioning outcomes in children and adolescents with RASopathies

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Objective: This review sought to provide a better understanding of the factors that contribute to social functioning outcomes in children, adolescents and adults with RASopathies (i.e., genetic syndromes caused by disruption to the RAS-MAPK cellular signaling pathway).

Data Selection: A systematic literature search in the Medline, EMBASE, PsycINFO electronic databases yielded 462 articles on social functioning in individuals with RASopathies. An additional five articles were identified through hand searches. Two researchers independently reviewed each article abstract, resulting in 58 full-text articles to be assessed for eligibility. Thirty-one articles met full criteria for inclusion in the review. Studies were required to include at least three participants with a single RASopathy and had to examine the relationship between an aspect of social functioning and a factor that might influence social functioning.

Data Synthesis: The 31 articles meeting inclusion criteria were classified based on the predictors studied. Components examined during full review included: the syndrome(s) studied, participants, the aspect of social functioning assessed, the factor(s) studied in relation to social functioning, study measures, and key findings and limitations. Predictor variables were classified into the following categories: cognitive, affective, communicative, medical, and environmental.

Conclusions: Individuals with RASopathies are at higher risk of social functioning deficits. The vast majority of studies examined social functioning in neurofibromatosis type 1 (NF1). However, Noonan syndrome (NS), cardio-

facio-cutaneous (CFC) syndrome, and Costello syndrome (CS) also appeared in the literature. Though a number of neuropsychological, medical, and environmental risk factors have been found to correlate with social deficits in this population, the majority of the research has focused on cognitive and affective predictors. Symptoms of attention deficit-hyperactivity disorder and social processing difficulties had the most evidence as predictors of social outcomes for these individuals.

****Biallelic Germline Mutation in *RGL2* as Putative Cause of a Novel Rasopathy Syndrome with Primary MDS/MPD Presentation**

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Individuals with RASopathies are at risk for myeloproliferative disorders (MPDs), in particular, juvenile myelomonocytic leukemia (JMML). JMML is a unique form of pediatric MPD characterized by hyperactivation of the Ras signal transduction pathway. Approximately 90% of patients with JMML harbor molecular alteration in either *NRAS*, *KRAS*, *PTPN11*, *CBL*, or *NF1*, while the molecular status of the remaining 10% remains unknown. Although hyperactivation of the canonical Ras-MAPK pathway is the hallmark of JMML, multiple studies suggest that alteration of genes in the non-canonical Ras pathway is sufficient to produce similar Ras-transforming capability. With the recognition of Ral (Ras-like) guanine nucleotide exchange factors (RalGEFs) as direct Ras effectors and Ral G-protein activation as a direct consequence of Ras activation there have been increased efforts to establish the roles of the Ras-RalGEF-Ral pathway in human hematopoiesis. Recently, we identified and characterized a homozygous splicing variant (c.1020+4T>A) in *RGL2*, one of the RalGEFs, in a 16-month-old female patient with a familial MPD syndrome manifesting with pancytopenia, hypercellular marrow, hepatosplenomegaly, liver fibrosis and cardiomyopathy.

We verified by qPCR that this splicing variant resulted in decreased *RGL2* expression levels by 70% in patient's white blood cells and 96% in CD71+ reticulocytes pointing to a deleterious variant effect. While the mutation was not predicted to disrupt known splicing elements, we hypothesized that it may impair splicing of this gene. To directly interrogate this, we introduced this homozygous splicing variant to K562 cell line (K562 SV) using CRISPR/Cas9-mediated gene editing. As demonstrated by semiquantitative RT-PCR and cDNA sequencing, this splicing variant reduced normal splicing of this region of by removing 442 nucleotides of exon 5 and 6 resulting in a truncated transcript that would undergo non-sense mediated decay. We confirmed by qPCR that *RGL2* expression in K562 SV decreased by 98% compared to K562 control.

To gain further insight into the mechanism by which the *RGL2* intronic variant disrupts human hematopoiesis, we transduced human CD34+ cells with lentivirus encoding shRNA targeting *RGL2* mRNA and then cultured them in a previously validated 3-phase culture system that recapitulates erythropoiesis ex vivo. A scrambled shRNA sequence was used as control. The efficiency of the shRNAs used to knock-down *RGL2* expression was initially validated by qPCR after transduction of K562 cells. Our study demonstrated that knockdown of *RGL2* expression resulted in decreased erythroid cell growth in ex vivo erythropoiesis. We further showed that knockdown of *RGL2* expression also led to delayed terminal erythroid differentiation by flow cytometric analysis using glycophorin A (GPA), band 3, and $\alpha 4$ -integrin as markers of maturing erythroblasts. Our studies indicate an essential role for *RGL2* in human erythropoiesis by affecting cell proliferation and terminal erythroid differentiation. Our findings not only provide insights into regulation of hematopoiesis but also indicate that *RGL2* may be a novel candidate gene associated with RASopathies.

Dissection of The Impact Of Dominant And Recessive Noonan Syndrome-Causing *Lztr1* Mutations On Ras-Mapk Signaling

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Noonan syndrome (NS) is caused by mutations upregulating signaling through RAS and the MAPK cascade. The use of hypothesis-free approaches based on exome sequencing has recently allowed the discovery of novel NS genes encoding signal transducers or modulators not belonging to the “classical” RAS-MAPK signaling backbone, suggesting the existence of unrecognized circuits contributing to signal modulation in this pathway. Among these genes, *LZTR1* encodes a functionally poorly characterized member of the BTB/POZ protein superfamily. *LZTR1* binds to Cullin 3 (*CUL3*) and has been suggested to serve as substrate receptor for the *CUL3*-RING ubiquitin ligase (*CRL3*) complex, a multi-subunit RING-class E3 ligase implicated in protein mono- and poly-ubiquitination. Two classes of germline *LZTR1* mutations underlie dominant and recessive forms of NS, while constitutional monoallelic, mostly inactivating, mutations in the same gene cause schwannomatosis, a cancer-prone disorder supposed to be clinically distinct from NS.

Here, we characterize functionally a relatively large and representative panel of missense *LZTR1* mutations to explore their impact on intracellular signaling. Differently from what is observed for recessive NS-associated *LZTR1* mutations, we show that the dominantly acting ones causing NS do not affect substantially *LZTR1* stability and subcellular localization. We provide the first evidence that these mutations, but not the missense changes associated with recessive NS, enhance stimulus-dependent RAS-MAPK signaling, which is triggered, at least in part, by an increased RAS protein pool. At the same time, we report that *LZTR1* negatively modulates RAS activation through a novel circuit that uses ubiquitination and proteasomal degradation to control RAS abundance and signaling. Finally, we document that dominant NS-causing mutations do not perturb binding of *LZTR1* to *CUL3*, the scaffold coordinating the assembly of the multimeric *CRL3* complex, and specifically affect the surface of the Kelch domain mediating substrate binding to the complex.

Collectively, our data suggest a model in which *LZTR1* contributes to the ubiquitination of proteins functioning as positive modulators of the RAS-MAPK signaling pathway. In this model, dominant NS-causing *LZTR1* mutations impair binding of these substrates to the *CRL3* complex, while the recessive NS-causing ones behave as loss-of-function mutations, affecting *LZTR1* synthesis, stability, and/or binding to *CUL3*. These qualitatively different effects on the *CRL3* complex converge in dominant and recessive NS promoting MAPK signaling upregulation.

**Trametinib Treatment in Noonan Syndrome: An Update on Two Cases and Report of a Third Case with *RIT1* Mutations

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Background: Germline mutations in the RAS/MAPK signaling pathway cause developmental syndromes known as the RASopathies. Mutations of *RIT1* are responsible for Noonan syndrome (NS) and can lead to a lethal form of hypertrophic cardiomyopathy (HCM).

Patients: We here report an additional patient with *RIT1*-associated NS/HCM (A94T) as well as further follow up on the two previously reported patients with HCM and *RIT1* mutations (S35T, F82L).

Results: Patient 1 (previously not reported) showed polyhydramnios in the fetal period, with normal echocardiography. Postnatal follow-up showed mild hypertrophy initially, with rapid evolution towards severe HCM (indexed LV mass, from 91 mg/ m^{2.7} to 137 mg/ m^{2.7}) and bilateral outflow tract obstruction at the age of 3½ months. Despite maximal propranolol treatment, cardiac hypertrophy progressed further (peak 177g/m^{2.7} at 5 months), and due to chylothorax, the patient required octreotide treatment as well as two pleural drainages (at 3½ and 4½ months). Trametinib treatment was started at 4½ months at previously reported doses. Chylothorax ceased after 11 days of trametinib treatment, and left ventricular mass decreased after 6 weeks of treatment to 116 g/ m^{2.7}.

For patients 2 and 3 with *RIT1*-associated HCM (previously reported), we now have 27 months of follow-up each. Evaluation of left ventricular mass by magnetic resonance imaging showed sustained improvement in both of these patients in serial exams at 0, 4 and 24 months of therapy: patient 2, 75 g/m², 59 g/m², 52 g/m²; patient 3, 119 g/m², 78 g/m², 68.6 g/m².

Discussion: Our observations replicate a positive response to MEK-inhibition in a third patient with *RIT1*-associated early onset, severe HCM. In addition, further follow-up of the two previously reported patients now show a sustained response after more than two years of treatment. A parallel improvement in clinical status was documented. An important challenge remains in determining the total duration of therapy, given that no long-term studies on potential trametinib toxicity are available in children.

****LZTR1 Variants Identified by Genetic Test of RASopathies Using a Targeted NGS Panel**

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RASopathies are a group of developmental disorders caused by mutations in genes that regulate the RAS/MAPK pathway and include Noonan syndrome, Costello syndrome, cardio-facio-cutaneous syndrome and other related disorders. To date, more than 20 genes have been reported as causative genes of RASopathies. *LZTR1* is a tumor suppressor gene that encodes a protein belonging to the BTB-Kelch superfamily. *LZTR1* has been reported as a causative gene of autosomal-dominant or autosomal-recessive Noonan syndrome. However, the pathogenicity of identified variants and the genotype-phenotype relationship have not been fully elucidated. We have reported eight *LZTR1* variants in 7 patients with Noonan syndrome and demonstrated that *LZTR1* is associated with the RAF1-PPP1CB complex as a component of the RAS/MAPK pathway (Umeki et al. 2018). In this study, we analyzed samples from another cohort of patients with Noonan syndrome and related disorders using a custom-designed NGS panel on 41 causative or candidate genes for RASopathies. *LZTR1* variants were identified in eight patients who are suspected to have Noonan syndrome. One mutation was found to be *de novo*. Two *LZTR1* variants were identified in a patient. One patient has a *LZTR1* variant as well as a pathogenic variant in *PTPN11*. Another patient had a *LZTR1* variant together with a variant with unknown significance in *MAP2K1*. Further delineation of clinical manifestations in patients with *LZTR1* variants will be important to determine the pathogenicity of variants and the genotype-phenotype relationship of the patients.

Germline-Activating RRAS2 Mutations Cause Noonan Syndrome

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Noonan syndrome (NS) is characterized by distinctive craniofacial appearance, short stature, and congenital heart disease. Approximately 80% of individuals with NS harbor mutations in genes whose products are involved in the RAS/mitogen-activating protein kinase (MAPK) pathway. However, the underlying genetic causes in nearly 20% of individuals with NS phenotype remain unexplained. We identified four de novo RRAS2 variants in three individuals with NS. RRAS2 is a member of the RAS subfamily, and is ubiquitously expressed. Three variants, c.70_78dup; p. Gly24_Gly26dup, c.216A>T; p. Gln72His, and c.215A>T; p. Gln72Leu have been found in cancers; our functional analyses showed that these three changes induced elevated association of RAF1 and that they activated ERK1/2 and ELK1. Notably, prominent activation of ERK1/2 and ELK1 by p. Gln72Leu associates with the severe phenotype of the individual harboring this change. To examine variant pathogenicity *in vivo*, we generated zebrafish models. Larvae overexpressing c.70_78dup; p. Gly24_Gly26dup or c.216A>T; p. Gln72His variants, but not wild-type RRAS2 RNAs, showed craniofacial defects and macrocephaly. The same dose injection of mRNA encoding c.215A>T; p. Gln72Leu caused severe developmental impairments and low dose overexpression of this variant induced craniofacial defects. In contrast, the RRAS2 c.224T>G; p. Phe75Cys change, located on the same allele with p. Gln72His in an individual with NS, resulted in no aberrant *in vitro* or *in vivo* phenotypes by itself. Together, our findings suggest that activating RRAS2 mutations can cause NS and expand the involvement of RRAS2 proto-oncogene to rare germline disorders.

**A Novel Model to Uncover the Function of Scaffold Shoc2 Mediated ERK1/2 Signaling in Early Zebrafish Development

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The highly conserved extracellular signal-regulated kinase 1 and 2 (ERK1/2) pathway is critical for numerous cellular processes including embryonic development. Scaffolding proteins create temporal and spatial microenvironments to guide signal transduction. The non-enzymatic scaffold protein Shoc2 accelerates ERK1/2 signaling by facilitating the binding of Ras and RAF-1. Germline mutations in *shoc2* dysregulate the Ras/MAPK pathway resulting in the genetic developmental disease Noonan-like Rasopathy. However, the nature of the signals transduced through the Shoc2 scaffold complex remain largely unknown. Our studies are unraveling the underlying molecular mechanisms through which Shoc2 provides regulation and signaling specificity to the ERK1/2 pathway.

To delineate the Shoc2 complex-mediated ERK1/2 signals we take advantage of the vertebrate zebrafish model. In our studies we utilize zebrafish Shoc2 knockout lines generated by either CRISPR/Cas9 methodology or N-ethyl-N-nitrosourea (ENU) random mutagenesis. The loss of Shoc2 in homozygous *shoc2* mutants, confirmed by western blot and RT-PCR, is embryonically lethal. Further investigation concluded that Shoc2 null embryos have decreased ERK1/2 phosphorylation. Shoc2 null embryos exhibited severe developmental defects including anemia, severe body and eye edemas, abnormal melanocyte development, and underdeveloped cartilage and bone structures. In addition, quantitative transcription analysis determined that Shoc2 null larvae have altered

expression of genes regulating hematopoiesis and neural crest. Together, these findings suggest that *Shoc2* is critical for embryonic development.

In conclusion, our studies demonstrate that *Shoc2* null larvae recapitulate phenotypes observed in Noonan-like Rasopathy patients. As such, this novel, clinically relevant, vertebrate model provides us with a unique opportunity to investigate the biological activities of *Shoc2*-mediated ERK1/2 signaling. Future studies using *shoc2* mutant zebrafish will determine the molecular mechanisms by which *Shoc2* regulates the neural crest during early embryonic development.

****Germline Rasopathy Mutations Provide Functional Insights into the Raf Cysteine-Rich Domain (CRD)**

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Mutations in the pro-proliferative Ras-Raf-MEK-ERK pathway are prevalent in human cancer and RASopathy developmental syndromes. However, unlike the somatic driver mutations found in many cancers, which are often embryonic lethal, germline RASopathy mutations subtly increase pathway output within the tolerance of the developing embryo. Central to this pathway is the three-member Raf kinase family (A-, B- and C-Raf), of which C-Raf and B-Raf mutations are causative of Noonan syndrome and Cardiofaciocutaneous (CFC) syndrome, respectively. Here we examine B-Raf mutations, which are present in ~67% of CFC cases, specifically those which cluster around the cysteine-rich domain (CRD). Although B-Raf CRD is not well characterized, the CRD of C-Raf has been shown to bind phosphatidylserine (PS) but unlike many of the PKC CRDs, it does not bind DAG or phorbol esters. Our studies show that these B-Raf CRD mutants act to increase its biological activity via two distinct mechanisms. Class I CRD mutants add positively charged residues within the membrane binding interface, thus increasing its interaction with negatively charged PS at the plasma membrane, this in turn increases B-Raf interaction with Ras. Interestingly, the most common CRD mutant, Q257R, is capable of enhancing B-Raf biological activity and cell proliferation independently of Ras. The unparalleled ability of Q257R to increase B-Raf plasma membrane localization combined with the relatively high basal activity of B-Raf likely explains this unique mechanism of activation. Indeed, this class of CRD mutation is not found in C-Raf, which has a markedly lower basal activity than B-Raf. In contrast to mutants in Class I, Class II CRD mutations do not significantly increase PS binding, PM localization or Ras interaction. Rather they promote the open, active state of B-Raf by reducing the association of the regulatory domain with the kinase domain. This finding suggests a key role for the CRD in stabilizing the closed autoinhibited state of Raf. Finally, through surface plasmon resonance binding assays, we find that B-Raf CRD has ~5-fold higher affinity for PS than C-Raf CRD, which correlates with greatly enhanced plasma membrane localization. Further analysis reveals that 4 CRD residues can determine these binding affinities and that the exchange of these residues between B-Raf CRD and C-Raf CRD results in a complete reversal of this phenotype in terms of PS binding and plasma membrane localization. Of note all of these residues are in the vicinity of the Class I CRD mutations, further demonstrating the critical nature of this region for plasma membrane binding.

****Noonan Syndrome Model Mice With *RIT1* A57G Mutation Exhibit Cardiac Hypertrophy and Susceptibility to β -Adrenergic Stimulation-Induced Cardiac Fibrosis**

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Noonan syndrome (NS) is the most common type of RASopathies, featured by short stature, a distinctive facial appearance and heart defects. In 2013, we discovered *RIT1*, which is a member of the RAS subfamily of small GTPases, as a novel causative gene of NS. Genotype-phenotype analysis revealed that NS patients with *RIT1* mutations have a high incidence of hypertrophic cardiomyopathy and edematous phenotype; however, the specific role of *RIT1* remains unclear. In this study, we generated knock-in mice that carried a NS-associated *Rit1* A57G mutation (*Rit1*^{A57G/+}), which is one of the most common mutation sites and yielding the higher contribution to hypertrophic cardiomyopathy.

Rit1^{A57G/+} embryos exhibited decreased viability, edema, subcutaneous hemorrhage and increased AKT phosphorylation in whole lysates. Surviving *Rit1*^{A57G/+} mice had a short stature, craniofacial abnormalities and splenomegaly, which are characteristics of NS. Furthermore, they had significant cardiac hypertrophy without deterioration of cardiac function compared to wild type littermates. Histological examination revealed that *Rit1*^{A57G/+} mice had cardiac fibrosis with increased expression of S100A4, vimentin and periostin, but not cardiomyocyte hypertrophy. Furthermore, upon β -adrenergic stimulation with isoproterenol, cardiac hypertrophy and fibrosis was remarkably increased in *Rit1*^{A57G/+} mice. Phosphorylated AKT at T308 levels were also elevated in cardiomyocytes lysates from isoproterenol-treated *Rit1*^{A57G/+} mice.

In conclusion, we have successfully generated *RIT1* A57G mutation knock-in mice recapitulating NS features including short stature, craniofacial abnormalities, edema, cardiac hypertrophy and cardiac fibrosis. Our data indicated that the AKT signaling pathway might be related to downstream signaling in the *RIT1* A57G mutant at a developmental stage and under β -adrenergic stimulation in the heart. We are currently investigating the effects of mTOR/AKT and MEK inhibitors on cardiac hypertrophy and fibrosis in *Rit1*^{A57G/+} mice and will present preliminary data on treatment and plans for the future.

****Role of Capicua in Adult Neural Stem Cells and Microglia – Implications for CIC Haploinsufficiency Syndrome**

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Capicua (CIC), a transcriptional repressor, has emerged to be a key downstream effector of the Ras/ERK signaling. Activation of the Ras/ERK pathway leads to phosphorylation of capicua, causing it to degrade or to be translocated from the nucleus to the cytoplasm. This results in de-repression of capicua target genes and the onset of a Ras/ERK-dependent transcriptional program. Accordingly, loss of capicua mimics hyperactivation of the Ras/ERK signaling.

Recent studies demonstrate that capicua plays an important role in brain and hematopoietic cell development and function, and that *CIC* haploinsufficiency causes a neurodevelopmental syndrome with predisposition to hematological cancer (Lu*, Tan* et al. *Nat. Genet.*, 2017; Tan et al, *PNAS*, 2018; Tan and Zoghbi, **Neurobiol. Learn. Mem.**, in press). Specifically, people haploinsufficient for *CIC* have prominent neurobehavioral phenotypes, including developmental delay/intellectual disability (DD/ID), autism, and attention deficit/hyperactivity disorder (ADHD). These phenotypes were recapitulated in brain region-specific capicua knockout mice. Additionally, studies from animal models show that capicua is critical for the postnatal maturation/maintenance of upper layer neurons in the cortex; loss of capicua leads to a reduction of upper layer neurons during early postnatal development. One individual with *CIC* haploinsufficiency has a history of leukemia and this aspect of the disease is recapitulated in hematopoietic cell-specific capicua knockout mice. Given the well-established role

of capicua in Ras/ERK signaling and similarities in disease phenotypes between CIC haploinsufficiency and RASopathies, it is possible that CIC haploinsufficiency syndrome might be in fact a RASopathy syndrome.

Our current work builds on these recent discoveries and aim to address two unanswered questions of the pathobiology of CIC haploinsufficiency syndrome: (1) what molecular and cellular mechanism contributes to intellectual disability, and (2) do nonneuronal-lineage cells such as microglia play a role in disease pathogenesis or modifying disease phenotypes? To address the first question, we examined the function of capicua in the maintenance of dentate gyrus of the hippocampus, as mice lacking capicua in the hippocampus have learning/memory defects and decreased dentate gyrus granule neurons in adulthood. Our initial data show that loss of capicua impairs the proliferation of adult neural stem cells. To address the second question, we investigated capicua's function in microglia using cell type-specific knockout mice. Our initial results suggest that capicua regulates microglia activation under neuroinflammatory conditions. We speculate that anomalies in adult neurogenesis and microglia activation—during development and/or in response to neuroinflammation—contribute to neurobehavioral deficits in individuals haploinsufficient for CIC. Our studies of the molecular and cellular functions of capicua will further our understanding of the pathomechanisms of diseases due to hyperactivation of Ras/ERK signaling.

Gain-Of-Function Mutations in *RRAS2* Cause Noonan Syndrome

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Noonan syndrome (NS), the most common RASopathy, is caused by mutations affecting signaling through the RAS-MAPK pathway. Despite the relatively large number of genes that have been implicated in this disorder, about 10%–20% of affected individuals with clinical diagnosis of NS do not have mutations in known RASopathy genes, indicating that other unidentified genes contribute to this disorder. By using a mixed strategy of functional candidacy and exome sequencing, we identify *RRAS2* as a novel gene implicated in NS in six unrelated

subjects/families. We show that *RRAS2* mutations alter highly conserved amino acid residues localized around the nucleotide-binding pocket of the GTPase and are predicted to variably affect diverse aspects of *RRAS2* biochemical behavior, including nucleotide binding, GTP hydrolysis, and interaction with effectors. We also demonstrate that the pathogenic variants variably increase activation of the MAPK cascade and promote cytoskeletal rearrangement. The phenotypes associated with *RRAS2* mutations fit well within the clinical spectrum of NS even though they appear variable in terms of severity. While the small size of the studied cohort does not allow to outline specific genotype-phenotype correlations, such variable expressivity likely reflects the differential strength of individual variants to perturb *RRAS2* function and intracellular signaling.

RASopathy Advocate
 2019 International RASopathies Symposium
 August 2-4, 2019



**CFC
 Syndrome
 MAP2K1**

Cora Knight
 3 years old
 Dallas, Texas, USA

Information provided by Lauren Knight (mother)



Profession:
 Preschooler

- Hobbies:**
- Singing songs (particularly ones containing animal sounds)
 - Eating
 - Playing in water

How Others Can Include Cora Better:
 Cora loves having people's attention. Saying hello and allowing her to touch your arm or face and showing warmth to her really makes her light up. And if there's a fun children's song you know, she would love to hear it!

The Most Challenging Neurocognitive Issue Cora faces:
 At almost 4, Cora is still not walking. She is capable, and can walk holding one hand but she is not confident or secure doing so.

The Most Challenging Cardio Issue:
 Cora has a very mild ASD and pulmonary valve stenosis, both almost undetectable at this point.

The Most Challenging GI/Feeding/Swallowing/Speech Issues:
 Communication is our biggest challenge in this department. As she is getting older, she has so much desire to communicate and really tries hard but still only has a handful of words and very rarely can put two words together.

The Most Challenging Gross Motor/Rehab Issues:
 At almost 4, Cora is still not walking. She is capable, and can walk holding one hand but she is not confident or secure doing so.

The Most Challenging Sleep Issue:
 Cora may actually sleep TOO MUCH. She sleeps about 12 hours at night and takes a 3- to 4-hour nap during the day. She loves her bed and naps.

- Medications:**
- Omnitrope
 - Levothyroxine

- Medical Consultants:**
- Endocrinology – for Growth
 - Endocrinology – for high cholesterol
 - Cardiology
 - Neurosurgery
 - Ophthalmologist
 - Nutritionist

Medical Success Story:
 Our current biggest success is Cora's feeding. Cora was 6 months old when she was first described as having Failure to Thrive. Along with a myriad of other unique characteristics, Cora would only nurse (no bottle) and eat for ~30 minutes total. We eventually started with outpatient therapy and when that didn't seem to help, we were admitted to a 30-day intensive inpatient feeding program when Cora was 8 months old. Every day we fought to gain even the slightest amount of weight and avoid the NG tube. Cora made what appeared to be little progress, but enough that we could be released on our last day. With talk of a G-tube still looming over us we didn't know if we had actually won that battle. Cora ate every 2 hours around the clock until 12 months old. What she could manage from a bottle, and with enough persistence she was able to have major victory in this area. Since then, with the help of some wonderful therapists, Cora now eats independently and is a bottomless pit! She can eat anything that is bite-size, and is working to take bites.

Strengths Gained by a Previous Failure:
 Our whole family has learned to have patience and be better in-tune with Cora and each other. It was very difficult at first trying to communicate and take the time that Cora needs in order to make communication happen. This has also helped us in the way we parent our other children. And our other children have also learned so much about what it means to set a good example and treat people with love and kindness - even if they don't want to.

Most Unique Challenge:
 We are dealing with high cholesterol that is baffling even some of the researchers that discovered LDL. She does have familial hypercholesterolemia, but the way her body is responding to diet and how quickly that response happens is not what is typical for that mutation, so I am told. We want to avoid statins if we can, but her energy needs are so high that we can't take out those higher fat foods without impacting her ability to function daily.

We would like the researchers to further study:
 The Relationship between CFC and metabolic abnormalities

RASopathy Advocate
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**CFC
Syndrome
MEK2**

**Alexander "Alex" James
Tindle**
24 years old
Denham Springs, Louisiana, USA

Information provided by James Tindle (mother)



Profession:
Alex works 3 days per week as a Service Clerk at Rouse's Supermarket near our home and has been employed there for the past 4 years.

- Hobbies:**
- Spending time with family & friends
 - Going to the movie theater
 - Watching movies at home with family and friends
 - Telling jokes & laughing
 - Attending and volunteering at his church
 - Volunteering and serving in the community with a local non-profit that serves individuals with disabilities
 - Attending and co-presenting with his mom at various speaking engagements
 - Going to the local fitness center and getting exercise 2-3 days per week

How Others Can Include Alex Better:
We live a very inclusive lifestyle. I work for a non-profit family resource center for individuals with disabilities and their families. Their mission promotes inclusion so much of the way we live, work and recreate is in inclusive environments. But when Alex was younger in the late 90's and early 2000 inclusion was not as common and many people would act very insensitive or Alex would be excluded from his typical peers at school. Today inclusion is improving and hopefully will continue to do so. I would like for others to presume that no matter what our outward appearance may be, we can understand and appreciate kindness and respect just like everyone else.

The Most Challenging Neurocognitive Issue Alex faces:
Alex cannot read although he has always wanted to. His inability to read is directly related to a lack in processing through vision and so Alex has been an audible learner most of his life. Through his life I feel the most challenging issue is the independence Alex would like to have through reading. I also see Alex's lack of expressing his emotions is a struggle for him along with a struggle in problem solving.

The Most Challenging Cardio Issue:
Alex has been cleared by his cardiologist from any heart defects. However, as a toddler and in adolescent years Alex did have a couple of serious bouts of fluid around his heart. We continue to have cardiologist check up every two years.

The Most Challenging GI/Feeding/Swallowing/Speech Issues:
As an adult Alex remains 100% g tube fed which first began when he was 7 months old. Although we've tried every feeding therapy possible for Alex, we've decided that g tube feeding is a part of our life for now and no longer pursue therapy for feeding. The MOST challenging issues are with speech. Alex often will not speak to those he is not familiar with as he thinks they will not understand him. However, when he is with friends and family, he has an endless vocabulary and loves to be funny, tell jokes and laugh.

The Most Challenging Gross Motor/Rehab Issues:
Alex uses a power wheelchair for independent mobility. He can also walk short distances with his posterior walker. All gross motor skills are a challenge for Alex due to overall muscle weakness. Not being able to walk independently is by far Alex's biggest challenge.

The Most Challenging Sleep Issue:
Alex did have sleep apnea with 14 episodes of stopping to breathe each hour. He was very restless at night. At age 21, because of his very small airway/esophagus, his ENT had surgery to scrape his larynx and remove his tonsils. Alex now only has 1 episode per hour while sleeping. He also takes 50mg Trazodone for sleep.

Alex's Typical and Medication Schedule
7:25: 200mg Risperidone (Risperidone) 200mg
8:00: 100mg Sertraline (Zoloft) 100mg
8:30: 100mg Sertraline (Zoloft) 100mg
9:00: 100mg Sertraline (Zoloft) 100mg
9:30: 100mg Sertraline (Zoloft) 100mg
10:00: 100mg Sertraline (Zoloft) 100mg
10:30: 100mg Sertraline (Zoloft) 100mg
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RA SOPATHY Advocate
 2019 International RASopathies Symposium
 August 2-4, 2019



Costello Syndrome

Ali Kazakoff
 9 years old
 Edson, Alberta, Canada

Information provided by Ali Kazakoff (mother)



Profession:
 Student

Hobbies:

- Dance (ballet and tap)
- Books
- Playing outside (trampoline)
- Crafts

How Others Can Include You Better:
 By treating me the way they like to be treated, by keeping my low vision in mind and by asking me to repeat myself when they don't understand me. I am very social and want to be included but sometimes I need a little extra help.

The Most Challenging Neurocognitive Issue I face:
 Motor dyspraxia. I have trouble with processing thoughts, following or remembering instructions, difficulties with concentration and I struggle to be organized. I learn much better in one on one situations and sometimes get frustrated so I act silly to avoid my task.

The Most Challenging Cardio Issue:
 My heart is stable. I have mild hypertrophic cardiomyopathy and some minor structural defects. I was born with supraventricular tachycardia but now that I'm older, it rarely occurs.

The Most Challenging GI/Feeding/Swallowing/Speech Issues:
 Making myself understood. I have complex oral motor issues including apraxia, open bite and a large tongue and I often have to repeat myself many times or try different words to get my message across.

The Most Challenging Gross Motor/Rehab Issues:
 Motor planning. I have to repeat the same movements many times before I can do them reliably. I have trouble figuring out how much force to use, I do things very slowly and I often appear awkward or clumsy. I fall more than my peers.

The Most Challenging Sleep Issue:
 I don't seem to need much sleep. I have trouble settling, wake up early and get up many times to use the washroom or look around at night but I have come a long, long way on my sleep journey!

- Medications:**
- Actikeral (topical)
 - Growth hormone (Hematrope)
 - Proac
 - Multivitamins
 - Vitamin D
 - Neuromega (Omega 3)
 - Fluorouracil (topical)
 - Nasaline
 - Melatonin

- Medical Consultants:**
- Pediatrician
 - Orthopedic Surgeon
 - Psychiatrist
 - Endocrinologist
 - Cardiologist
 - Neuro-ophthalmologist
 - Neurosurgeon
 - Dermatologist
 - Pediatric Dentist
 - Occupational Therapist
 - Speech Therapist
 - Vision Consultant
 - Quarterly u/s screening for abdominal and pelvic tumors

Medical Success Story:
 During a growth spurt, my foot rapidly became deformed (high arch with severe eversion/rotation of the hind foot) and I experienced incontinence. Despite a negative MRI, after much consultation, I had exploratory surgery to confirm and release an occult tethered cord. I became continent again and a year later my foot was reconstructed.

Strengths Gained by a Previous Failure:
 As an infant my parents tried to feed me orally. I screamed and vomited. It was too hard for me so they asked for a G-tube. They thought they'd failed. But life got calmer and less stressful, my development improved, and when I was ready, I learned to feed orally and loved it!

Most Unique Challenge:
 My vision. I have cortical vision impairment, nystagmus, optic motor apraxia and I am nearsighted. Each one of my diagnoses has a substantial impact. Most of them are not correctable. Although in a familiar environment I can function well, I have low vision and need many modifications.

I would like the researchers to further study:
 Better ways to help me learn. I love learning new things, particularly learning to read but I have to work very hard and I wish there was more research available to help my school team and my parents.

RASopathy Advocate
2019 International RASopathies Symposium
August 2-4, 2019



Costello Syndrome
HRAS G13D

Pete Scampavia
31 years old
Arlington, Virginia, USA

Information provided with assistance from Charis Williams (mother)



Profession:
Self Advocate, Courtesy Clerk

- Hobbies:**
- Playing with my dog, Cali
 - Talking with my girlfriend, Krysten
 - Maggipolis
 - Hang out with friends

Bio:
Pete Scampavia, a 31 year-old with Costello syndrome, revels in exceeding expectations. As a medically-fragile two-year old, he defied the medical community's efforts to diagnose his condition. An exasperated geneticist caustically noted that "We don't know what Pete has, but we know that he won't go to college". Pete learned to walk, talk, read, write, and text. Pete wasn't diagnosed with Costello syndrome until he was 18. He received the Presidential Youth Voluntary Service Award from President George W. Bush for starting a social club for students with and without disabilities. He graduated from high school, attended the George Mason University LIFE program for people with disabilities and now lives in his own apartment. His Eagle Scout project, "Don't Bully Be a Friend" won the National Capital Area Boy Scouts of America project of the year and is available on YouTube. Pete performs in the Arlington theatre arts program and his most recent role was "Billy-Bob", one of Medusa's snakes. He continues to advocate for people with disabilities and has worked at Safeway store he was 16.

How Others Can Include You Better:
Invite me to hang out.

The Most Challenging Neurocognitive Issue I face:
My nausea that is caused by anxiety.

The Most Challenging Cardio Issue:
I have a heart murmur.

The Most Challenging GI/Feeding/Swallowing/Speech Issues:
I always wake up feeling nauseous.

The Most Challenging Gross Motor/Rehab Issues:
It is hard for me to balance and I can't walk on slippery surfaces because I can't catch myself if I fall

The Most Challenging Sleep Issue:
I didn't sleep through the night until I was six years old, but I no longer have sleep issues.

- Medications:**
- Zyrtec (allergic)
 - lasartin (heart murmur)
 - Clozapine
 - Sertraline

Medical Success Story:
Had severe scoliosis that was corrected with a full spinal fusion.

Strengths Gained by a Previous Failure:
I had trouble meeting the hiking requirements for my Eagle Scout project so I liked the same number of required miles, one hike at a time. Someone tried to stuff me into a locker, I found out that my friends would stick up for me. I wanted to live on my own, so now I'm able to live on my own.

Most Unique Challenge:
I feel nauseous all the time.

I would like the researchers to further study:
Ways so I don't have to feel like I have to throw up so much

- Medical Consultants:**
- Allergist
 - Cardiologist
 - Dentist
 - ENT
 - Endocrinologist
 - Gastroenterologist
 - Geneticist
 - Ophthalmologist
 - Physical Therapist
 - Psychiatrist
 - Speech/Language Pathologist

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**Neurofibromatosis
Type 1**

Gus Erickson
7 years old
Rochester, Minnesota, USA

Information provided by Gregg Erickson (Father)



Profession:
Student

- Hobbies:**
- Baseball
 - Soccer
 - Swimming
 - Slip-n-slide
 - Tormenting his big sisters

How Others Can Include You Better:
As a recent 1st grade graduate with no outwardly-manifesting symptoms of NF at this time other than my cafe-au-lait spots, I feel included!

The Most Challenging Neurocognitive Issue I face:
Working on my diction with my speech therapist.

The Most Challenging Cardio Issue:
(no cardiac issues)

The Most Challenging GI/Feeding/Swallowing/Speech Issues:
Improving my diction through speech therapy. I'm working on my "R"s!

The Most Challenging Gross Motor/Rehab Issues:
I am finding it harder than most kids my age to ride my bicycle without training wheels. Mom says it's because I like to do things well the first time and if I can't, I get discouraged.

The Most Challenging Sleep Issue:
Not a problem anymore. For 2 full years after having my brain tumor surgery, I would wake up at about 3am every night, thinking it was time to wake up for the day and didn't want to go back to sleep. Mom told my doctors that my circadian rhythm was all out of whack. Luckily, I sleep through the night now and my parents like that much better.

- Medications:**
- Ketotifen
 - Pediatric Lupron Depot
 - Albuterol as needed for asthma
 - Lotion for itchy skin

- Medical Consultants:**
- Dermatologist
 - Endocrinologist
 - Geneticist/NF Specialist
 - Oncologist
 - Ophthalmologist
 - Neurologist

Medical Success Story:
When Gus was 3 years old, we received the nightmarish news that our little boy had a brain tumor. A racquetball-sized mass pressing down on his pituitary stalk, growing into his hypothalamus, stretching his optic nerves apart & choking off the supply of cerebral spinal fluid in his brain. Hydrocephaly had begun & Gus' doctors told us that if we had waited much longer, he'd be coming to them in a coma. Terrified, we handed our little boy over to the neurosurgery team at Mayo Clinic Hospital. It was the hardest thing we've ever done. It was the longest day we've ever lived. We didn't know what kind of brain damage Gus might be left with or if we'd even get our baby back at all. Although his recovery involved some scary complications, he came through and sustained no known cognitive impairments.

Strengths Gained by a Previous Failure:
Gus is a very empathetic child. He, like many other rare disease patients I've met, is always thinking of others first. I'm not sure where these children/adults draw that strength from, but I suspect it is a gift to help them deal with whatever obstacles may come their way.

Most Unique Challenge:
The course of my disease is unpredictable. I had two big complications before my 8th birthday: a life-threatening brain tumor when I was in preschool and the diagnosis of precocious puberty when I was in Kindergarten. My metabolism completely changed after my surgery and I try to eat more protein and fewer carbs now to maintain a healthy weight. I have optic glioma tumors behind both of my eyes, but my doctor says that those are probably done growing since I'm a big kid now. Because my condition is progressive, my future tumor burden is unknown. I don't think about that because I'm 7 and don't understand what NF is capable of yet. But my parents do and the not knowing is the hardest part for them.

I would like the researchers to further study:
I would like researchers to study the psychosocial impact of neurofibromatosis so I can live a happy, productive life. Right now I'm participating in a study that looks at what causes hypothalamic obesity and other unexplained metabolic changes in kids who have had brain tumors.
I would also REALLY like researchers to study how gene therapy can help me and other people living with rare diseases!

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Neurofibromatosis Type 1

Alwyn J. Dias, MSW
 43 years old
 Morristown, New Jersey, USA



Profession:
 Executive Coach, HR Consultant, and Professor at Rutgers University's Graduate School of Healthcare Administration

Hobbies:
 • Passion for music
 • Studying meditation
 • Traveling

Diagnosis:
 I was diagnosed at 4yrs old, when my parents found a marble size tumor on my back. At that time with NF being so rare or unheard of, the only intervention was surgery. Being new to the country, we didn't have solid access to specialists in this arena. However, we were blessed with great neurosurgeons that were focused on children.

How Others Can Include You Better:
 Just be asked to assist in an individual's journey.

The Most Challenging Neurocognitive Psychological Issue I face:
 As a child NFI caused much anxiety as a child for many reasons, which then resulted in depression. During summers I was always fearing taking my shirt off, as I had tumors across my chest and back. This would occur during summers by the pool, sleepovers and gym class. The fear of being ridiculed for having so abnormal body was very painful. Surgery was the only option to remove tumors at that time and for the most part even now. This only added to the general anxiety, as there was just more things to worry about.

The Most Challenging Cardio Issue:
 I have 45% lung capacity and constantly feel a shortness of breath. I also just was diagnosed with sleep apnea and have started to use a CPAP machine.

The Most Challenging GI/Feeding/Swallowing/Speech Issues: (Nothing unusual to report)

The Most Challenging Gross Motor/Rehab Issues:
 After having my most recent surgery - where I learned how to walk again - I needed a cane for some time to stabilize myself. I don't use one anymore. However, there are times that I feel off balance after I've been very active.

The Most Challenging Sleep Issue:
 My sleep apnea is physiological issue. This is exacerbated by the large tumors obstructing my lungs.

Medications:
 • Anti-anxiety medications
 • Depression medications

Medical Consults:
 • NYU Langone's Center for Neurofibromatosis
 • Dr. Jeffrey Allen & Carol Mitchell, MD

Medical Success Story:
 Growing up I never felt that "this is happening because I have NF." I remember my parents taking me to hospitals and doctors every other waking minute. Although hard to grasp as an adult, for me as a child - it was my reality. I never realized that my life was any different than anyone else's. As an adult, I took little interest in my condition and just powered through life. It really only hit me recently at the age of 39 - I slipped on a patch of ice, causing me to feel numbness from my chest down, which later led to me being paralyzed. I learned that by neglecting myself of the care I needed and resources like the Children's Tumor Foundation and NYU Langone NF Center, I was not loving and investing in myself enough. I was not paying attention to my life. It's great that I was not limited by NF, but it wasn't smart that I avoided caring for myself. Actually, in a surreal way, my condition has taught me the importance of self-love and this fortunate opportunity we have to live life...sounds cheesy, I know.

Having NF did lead to a lot of anxiety as a child. Interestingly, it was not necessarily about a pending doctor's visit (like getting a shot), it was more about school work or something small that I would make huge. I wish I knew then that you never realize how strong you can be and the unpredictability of where life leads you. The one critical component is to have hope and faith that you will be better off, as long as you don't limit yourself to your circumstances.

Strengths Gained by a Previous Failure:
 With my recent restrictions I'm more aware of my limitations, I've learned to think smarter not harder.

Most Unique Challenge:
 The most unique challenge I face is more of a nuisance than anything. Due to the location of my tumors, it is difficult to find shirts that fit me. My tumors are mostly on my chest and back, making it difficult to button them up. As tumors grow, I can go through multiple shirt sizes every couple of years.

I would like the researchers to further study:
 I would be so grateful if researchers could further study minimizing the risks during surgery. My tumors are large and within my chest cavity - I have been told that surgery would be very extensive and could cause much bleeding. This would require a long time for recovery and at the worst - could be fatal. Having information on how to reduce this risk, so that I could have surgery would be great.
 Pain - Pain is always an issue for me. I wonder what my life would be like without so much of it. I know there is already research in this area, but continued work is still needed.

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**Noonan
 Syndrome
 PTPN11**

Rainier “Rainey” Davies
 2-1/2 years old
 York, Pennsylvania, USA

Information provided by Maia Higa (mother)



Profession:
 Early Start student

Hobbies:
 • Playing with toy cars, trucks, airplanes, and emergency vehicles
 • Dancing
 • Wrestling with his big brother and Daddy

How Others Can Include You Better:
 Rainey has a lot of doctors' appointments with sometimes uncomfortable procedures. Finding ways to combine these appointments (and having timely access to necessary specialists) would make things easier for his parents.

The Most Challenging Neurocognitive Issue I face:
 We won't know the extent of this until he gets a little older.

The Most Challenging Cardio Issue:
 Rainey has moderate pulmonary valve stenosis; it's not severe enough to operate so we're just watching to make sure he's growing and functioning ok

The Most Challenging GI/Feeding/Swallowing/Speech Issues:
 Rainey had a delayed expressive speech delay diagnosed at 1 year. He's been receiving early intervention and speech therapy weekly to improve communication. We're excited that his most recent evaluation showed a significant improvement to within 1.5 SD of average!

The Most Challenging Gross Motor/Rehab Issues:
 Rainey is slightly behind his peers, but has just started running. We're working on jumping and walking down (small) stairs independently.

The Most Challenging Sleep Issue:
 Rainey takes a good nap during the day but likes to wake up EARLY in the morning. We are working on getting him to put himself back to sleep and waking his parents up at a more acceptable morning hour.

Medications:
 • Humatrope (somatropin)
 • Multivitamin with fluoride

Medical Consultants:
 • Pediatrics
 • Cardiology
 • Endocrinology
 • Genetics
 • Hematology-Oncology (predisposition program)
 • Developmental Pediatrics
 • Pediatric Ophthalmology
 • Otolaryngology

Medical Success Story:
 Rainey was diagnosed less than a year ago; we're just happy that (thus far) he has relatively mild symptoms that are largely treatable.

Strengths Gained by a Previous Failure:
 N/A

Most Unique Challenge:
 I doubt this is unique, but being small for his age comes with challenges that don't affect his peers. He can't reach most handrails on the stairs yet and things designed for toddlers are too big for him (potty chairs, kid tables and chairs). This makes it difficult for him to be as independent as he would like.

I would like the researchers to further study:
 Symptoms and behaviors associated with specific genes and mutations. There is such a wide spectrum when it comes to Noonan syndrome that it's difficult to determine what might apply to my child. Also, I've heard conflicting opinions on the safety of taking growth hormone and the affect it might have increasing the possibility of cancer. A more definitive answer to this would help many parents make informed decisions about what would be best for their child.

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Noonan Syndrome

Martha Ann Goodwin
 54 years old
 St. Marys, Georgia, USA



- Professions Before Retirement:**
- Pre-law degree
 - Heart monitor technician on a telemetry floor in a hospital
 - Ultrasound tech

- Hobbies:**
- Crafting
 - Beaching
 - Reading

How Others Can Include You Better:
 Accept me for who I am. Especially the way I look. Most people tend to judge me before they even get to know me. It has happened more than it hasn't happened. They look at my short stature, my unusual looking facial features (my facial features bother me the most), and other features they pick up on and immediately judge me. After a lifetime of encounters with people you know when someone dismisses you or is repelled by you. If there was anything about Noonan's I could change would be my facial features. I feel this is the hardest thing to live with and overcome. If people would just take the time to get to know me, but people don't take time these days.

The Most Challenging Neurocognitive Issue I face:
 I have struggled with severe depression at times. I've been on medication, but no longer. I've learned to know the signs of when I'm about to go down the rabbit hole of depression and I've learned techniques to stop the spiral. That being said if I ever needed to go back on medication I would. I've also had to deal with memory and spatial-temporal awareness. These were particularly hard to overcome when I was in school.

The Most Challenging Cardio Issue:
 Currently I am having some cardiac issues which is involving huge changes in my cardiac and pulmonary function. This is affecting my life daily in my physical abilities and energy levels.

The Most Challenging GI/feeding/swallowing/speech issues:
 Thankfully I don't have any of these issues.

The Most Challenging Gross Motor/Rehab Issues:
 My balance and lack of ROM in my cervical column due to the Chiari malformation and because they had to perform cervical fusion during both surgeries due to cervical instability. This is challenging and very frustrating as my activity and life desires do not meet up to my physical abilities.

The Most Challenging Sleep Issue:
 Waking up 4 times a night for no reason. Probably not due to Noonan, instead it's Marvelous Menopause (not so marvelous)! In my childhood, I had leg cramps. My dad gave me tonic water with quinine.

- Medications:**
- Alvan
 - Gabapentin
 - Vrayvaf ER
- Medical Consultants:**
- Adult Congenital Cardiologist
 - Primary Care
 - Pulmonologist

Medical Success Story:
 When I was 7 years old, I had open heart surgery to repair my quarter size ASD and PS. This was prior to valveuloplasty. Post-surgery, I got pneumonia and almost died. I wore a horrible brace (Milwaukee brace) 23 hours a day for 7 years to then have Harrington rods put in and wore a full body cast for 6 months. When I was 40 years old, I had brain surgery for Chiari malformation. 11 months later, I had to have another brain surgery for ACM. After this surgery I was told I could no longer work. I've also had a cardiac ablation (probably looking at another in the near future), a cholecystectomy, 3 ptosis surgeries on each eye, and 2 strabismus surgeries. I feel ALL of these surgeries make up my medical success story. Some of these were easier than others. Some were complication-free and some were not. But they and the scars (physical and emotional) ARE ALL MINE. Because I'm here and alive they are a SUCCESS!

Strengths Gained by a Previous Failure:
 I have had many failures in my life. Most times I feel like I had more failures than successes. The failures have forced me to never give up. Adjectives like stick-to-it-iveness, relentless, courageous, resilient, adventurous, and limitless have made me who I am today. Not always easy! But I always try 100% and that is due to the many many failures.

Most Unique Challenge:
 Just knowing without a doubt that my sons see me as a success and the best loving mom. But years of criticism and not meeting up to others' successes and accomplishments have taken a huge toll on my self-esteem and self-worth. That being said, I've worked very hard on this and have come a long way.

I would like the researchers to further study:
 Adults with Noonan syndrome. I know children are the priority, but they will also grow up to be adults. Research adults. We are the forgotten in the Noonan syndrome family. What is happening to us as we age. The gene mutation never stops working so what does that mean for us as adults. Especially those over 45 going into their 50's and on.

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Noonan Syndrome

LZTR1

Brent Anderson
 36 years old
Ivan Anderson
 3 years old
 Tipton, Iowa, USA

Brent Anderson



Ivan Anderson – information provided by Sandra Anderson



How Others Can Include You Better:

Brent: Be more accepting of my social anxiety.
Ivan: By learning that as each individual without a genetic condition is different and unique, so are people with genetic conditions. Learning about each person is crucial for a comfortable living and learning environment.

The Most Challenging Neurocognitive Issue I face:

Brent: Sensory issues, social anxiety, genetic ASD diagnosis pending at the moment.
Ivan: ASD, arachnoid cyst in cranium, and Noonan Syndrome LZTR1.

The Most Challenging Cardio Issue:

Brent: I have a dilated Aorta, and bi-cuspid valve.
Ivan: Recent diagnosis of cardiac hypertrophy. Also undiagnosed connective tissue disorder, due to some of his heart condition.

The Most Challenging GI/Feeding/Swallowing/Speech Issues:

Brent: I'm on a high calorie, low phosphate diet. I also have to drink a lot water due to my kidney cysts.
Ivan: High palate, low muscle tone, loose joints and oral aversions, lip tie (has been surgically fixed), severe speech deficiencies

The Most Challenging Gross Motor/Rehab Issues:

Brent: I recently been put on restrictions due to dilated Aorta, I also have low muscle tone and loose joints.
Ivan: Flat footed. There are more, he is due for an assessment

The Most Challenging Sleep Issue:

Brent: Some nights I have trouble falling asleep.
Ivan: Falling asleep, mostly at night

Profession:

Brent: Service Technician, Music Producer
Ivan: Preschool Student

Medications:

- Brent:**
 - Omeprazole
- Ivan:**
 - Omeprazole
 - Meetas
 - Vitamins
 - Melatonin

Hobbies:

- Brent:**
 - Music (multi-instrumentalist)
 - Rocketry
 - Fishing
 - Gardening
- Ivan:**
 - Listen to music
 - Dance
 - Finger paint
 - Be outside
 - Play with cars
 - Pop bubbles

Medical Consultants:

- Brent:**
 - Cardiology
 - Genetics
 - Nephrology
- Ivan:**
 - Cardiology
 - Child Psychology
 - ENT
 - Endocrinology
 - Genetics
 - Hematology
 - Neurology
 - Ophthalmology
 - Speech/Language Pathologist
 - Wait list:
 - Physical Therapy
 - Occupational Therapy

Medical Success Story:

Brent: I've had low muscle tone as long as I remember. I've also had physical delays growing up. I was diagnosed with LZTR1 NS at the age of 34. Since my diagnosis and new dietary requirements it explains a lot about my delays. I'm learning to live with my limitations and learning to live life to it's fullest potential.

Strengths Gained by a Previous Failure:

Brent: With my recent restrictions I'm more aware of my limitations, I've learned to think smarter not harder.
Ivan: Literal strength! He was almost unable to grow and thrive until after his diaphragm surgery. That along with his g-tube has helped him survive and grow into the sweet little boy we know.

Most Unique Challenge:

Brent: Learning about parts of myself I never knew since my diagnosis.
Ivan: Self expression and social skills, drinking liquids and handling food textures and other sensory stimuli.

I would like the researchers to further study:

Brent: Why are heart conditions so common with Noonan Syndrome
Sandra for Ivan: The LZTR1 mutation and the most common anomalies and the missing link to prevent them or predict the symptoms as they correlate with the specific gene.

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Noonan Syndrome with Loose Anagen Hair

PPP1CB

Chloé Burgess
 17 years old
 Alpharetta, Georgia, USA

Information provided by Dawn Burgess (mother)



Profession:
 Student
 Employee at Publix Supermarkets

Hobbies/Activities:

- Color Guard
- Unified Cross-Country
- Special Olympics
- Animal Lover

Medications:

- Latuda (mood dysregulation)
- Fluvoxamine (anxiety)
- Estradiol (estrogen)
- Unisom (sleep aid)

Medical Consultants Since Birth:

- Frequent pediatrician visits for consult on colic, feeding issues and failure to thrive
- Physical Therapy & Occupational Therapy to assist with gross motor & fine motor delay
- Pediatric Cardiologist for evaluation and atrial septal defect repair
- Psychiatrist & Psychologist for mood and anxiety management
- Pediatric ophthalmologist for consult & eye muscle surgery
- Pediatric Neurologist (Consult)
- Geneticist Emory University
- Geneticist & Genetic Counseling Team WellStar, Marietta, GA for Whole Exome Sequencing through GeneDx
- Pediatric Endocrinologist (Consult)
- General surgeon for repair of double inguinal hernias
- Orthopedic specialist for foot/wrist break and toe walking management
- Dermatologist for consult on extremely slow hair growth

Medical Success Story:
 We waited 15 years for a diagnosis. And if it hadn't been for a strange sequence of events, which includes my taking a job with GeneDx, we may not have one today. Her diagnosis is a testament to the incredible evolution of genetic testing. PPP1CB is a gene that was only documented to be associated with RASopathies within the year prior to Chloé's testing, so if she had had testing even six months earlier, it would have been inconclusive.

Clinicians may say, "What difference does having a diagnosis make in this instance because there is no treatment for the disease?" For the patient and the patient's family, it makes a huge difference to have a biological explanation for everything that we've been through. Understanding the origin of the disease is such a relief. Whole exome sequencing and the scientists at GeneDx (who analyze both the patient cases and the exome test results) are amazing.

Strengths Gained by a Previous Failure:
 Tenacity. Also sensitivity to others socially and being incredibly inclusive. The desire to help others and be an advocate to others.

Most Unique Challenge:
 Being in the middle developmentally & intellectually. Higher functioning than classmates but unable to keep up with "gen-ed" academically. Also social skills are a challenge.

Chloé's family would like the researchers to further study:
 The impact of this genetic mutation on neurological function and impact on focus & mood specifically. Is there a way to intervene and compensate for the outcome of this molecular dysfunction?

How Others Can Include Chloé Better:
 Not sure how to answer this as social skill improvement should help with this but Chloé stays busy and is involved in lots of stuff. Maybe that's her strength. She is her own greatest advocate.

The Most Challenging Neurocognitive Issue Chloé faces:
 The ability to focus/learn new things and take direction without becoming frustrated and angry

The Most Challenging Cardio Issue:
 Currently none. ASD is repaired and no current cardiac restrictions exist

The Most Challenging GI/Feeding/Swallowing/Speech Issues:
 Difficult to feed as an infant because of chronic colic. Failure to thrive and very slow weight gain. From 80th percentile at birth to 10th percentile at 12 months. Some language issues as far as pronunciation and articulation go but very conversational, inquisitive and intuitive. Lack of sensory awareness when eating.

The Most Challenging Gross Motor/Rehab Issues:
 Coordination issues putting at high risk for falls/breaks

The Most Challenging Sleep Issue:
 Some trouble falling asleep hence a very low dose of Unisom.

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SYNGAP1 Syndrome

Jack Emerson Mishkin

10 years old
Potomac, Maryland, USA

Information provided by Julie Mishkin (mother)



Profession:
Student

- Hobbies:**
- Playing with puzzles and talking books
 - Watching music cartoons on YouTube Kids
 - Playing kids' apps on the iPad
 - Spending time at playgrounds, particularly the slides
 - Water parks and amusement parks
 - In general, all things Jack can ride in or on are motivating
 - Escalators
 - Elevators
 - Car rides
 - Being read and sung to

How Others Can Include Jack Better:

The community needs to consistently make settings sensory-friendly to allow Jack more comfort in busy settings. Joining Jack in what he enjoys and can physically do is often a way to "woo" him into wanting to be a part of a group, but he is much better 1:1 or with an adult facilitator. Outside of family, he has the strongest connection with two young adult women that befriended him through Friendship Circle and the inclusion program at our local Jewish Community Center.

The Most Challenging Neurocognitive Issue Jack faces:

Jack struggles with social cognition which results in him having significant difficulty reading social situations and social cues. I think, in part, this is why he is uninterested in people unless he already has a connection with them. With people he is connected to, he loves being physically close (hugs, tickles, cuddling, holding hands) and loves reading, singing and being silly with them. He is non-verbal but will point to what he wants read and will indicate what song he wants sung. Jack can read (decode), though I'm unsure of his comprehension. He struggles academically with math as he knows all his numbers, but the value they represent needed for equations is hard. Somehow, he has memorized things like all of the states and capitals, but generalizing this ability to curriculum has not been easy.

The Most Challenging Cardio Issue:

Luckily, Jack does not have any heart issues.

The Most Challenging GI/Feeding/Swallowing/Speech Issues:

Jack sometimes struggles with diarrhea but he poops everyday (somewhat effortful at times) so maybe it would be considered mild constipation. Probiotics and a diet rich in fruit seems to help.

The Most Challenging Gross Motor/Rehab Issues:

Jack is very ataxic and wears AFO's. Gross motor skills are not solid to three years old as he cannot jump or catch a ball, and his running is not well-coordinated. His fine motor skills are equally impaired. He cannot write and has to work hard to use feeding utensils. He needs help with many aspects of dressing.

The Most Challenging Sleep Issue:

Jack is consistently inconsistent with sleep. He is unable to get from awake to drowsy without medicine. Once drowsy, he will fall asleep, but he is often up for hours a night. He will wake anywhere between 2 and 5, often for a few hours and may or may not go back to sleep. On average, he sleeps through the night (falling asleep around 8:30/9 and waking between 6 and 7 three nights a week and of the other 4 nights, he may go back to sleep only 2 times at best.

Medications:

- To control early onset absence seizures and help with behavior:
 - Lamictal
 - A Cannabis Tincture
- To support sleep:
 - Clonidine
 - A Different Cannabis Tincture
- Allergy medications as needed
- Vitamins

Medical Consultants:

- Pediatrician
- Dentist
- Neurologist
- Geneticist
- Allergist
- Physiatrist
- ENT/Audiologist
- Less frequently: ophthalmology

Medical Success Story:

We began our diagnostic odyssey when he around 2 years old when he started having seizures. I pushed to have genetic testing because I knew there was something going on, but because he does not have any dysmorphic features, I was told he just needed time to catch up and epilepsy and autism often happen together. A few weeks before his 9th birthday, he was enrolled in the NIH's Undiagnosed Diseases Program (UDP). The results of the genome 6 months later finally gave us a diagnosis. SYNGAP1 mutation. The other "medical success" was being able to get significant seizure control with a combination of pharmaceutical drugs and trial and error with cannabis tinctures. This was a long process as we moved to California the summer of 2014 to try CBD before it was available in Maryland.

Strengths Gained by a Previous Failure:

Jack has a strong "can do" attitude and perseveres when he wants to master something (ex. putting on his socks, challenging playground equipment). As his parents, we have learned that Jack is incredibly sensitive to over the counter and prescription meds even when they are dosed below what is considered a therapeutic level. He has had huge behavioral shifts on antihistamines and has been so nauseous from certain anticonvulsants that he starved himself or was so sedated he could not function. We have learned to go low and slow-titrate up any and all medications, and to advocate for particular manufacturers of his medications as we see big differences in behavior and efficacy between manufacturers of generics.

Most Unique Challenge:

Before Jack's diagnosis, I had a hunch that his brain wasn't wired right and I knew there were aspects of sensory processing that were vastly different from others, including low awareness/registration of tactile and proprioceptive inputs needed for body in space awareness, lip and tongue position needed to accurately form speech sounds, ability to drink from an open cup and eat neatly, a high pain threshold, and sensitivity to some forms of auditory and visual inputs. Jack cannot discern interoceptive input so if he has a tummy ache, headache, is hungry, tired, etc. he disintegrates and can't quite communicate what is wrong or what he needs - he just falls apart. He doesn't have many self-regulation skills and is non-verbal, an inefficient signer (can't feel how his fingers are moving) and is still learning how to use his voice output device, so communication is very challenging.

Jack's family would like the researchers to further study:

Ways to "fix" Jack's defective gene to hopefully help him gain more skills to maximize his potential to develop his motor and cognitive skills. His twin brother's development is a constant reminder of how pervasive Jack's disability is. As a family, we try our best to have a sense of normalcy, but we live paycheck to paycheck as Jack's needs are quite expensive. When you are middle class and have a kid that has significant medical complications as part of their disability, Medicaid financial eligibility or needs-based eligibility is not available. Middle class squeeze means a lot of unexpected expenses (example: \$380 out-of-pocket for orthotics). Therapies, school supports, etc. - it all adds up!

PARTICIPANT BIOGRAPHIES



Anton Bennett, PhD (SPEAKER)

Dr. Bennett is the Dorys McConnell Duberg Professor of Pharmacology and Professor of Comparative Medicine; Co-Director, Program in Integrative Cell Signaling and Neurobiology of Metabolism; and Director, BBS Minority Affairs at Yale University. The broad interest of the laboratory is in the area of signal transduction by protein tyrosine phosphatases (PTPs). Our research provides insight into the signaling pathways regulated by protein tyrosine phosphorylation, which serves as a fundamental mechanism for the control of virtually all biological processes. When the regulation of phosphate group removal by PTPs on proteins is disrupted, this can cause disease in humans. As such, PTPs have been directly linked to a variety of human diseases such as cancer, diabetes, and cardiovascular disease. This lab

investigates how PTPs are involved in various human diseases and whether, once identified, if these PTPs can be targeted for therapeutic purposes. Currently, we are actively pursuing targeting PTPs for therapeutic intervention of rare diseases for Noonan syndrome and dystrophic muscle disease.

Susan Blaser, MD FRCP (SPEAKER)

Dr. Blaser completed a pediatric internship and radiology residency training at the Cleveland Clinic. A neuroradiology fellowship at the University Hospitals of Case Western Reserve ensued and was followed by further fellowship training in pediatric neuroradiology at SickKids in Toronto and University of Toronto, where she is now a staff Neuroradiologist and Professor of Neuroradiology. She has a special interest in the fields of neurometabolics, fetal imaging, and skull base and labyrinthine imaging. She is the recipient of the 2013 American Society of Pediatric Neuroradiology Gold Medal.



Amanda Brown, RN BSN (PANELIST, NS ADVOCATE)

I graduated with my Bachelors of Nursing and a minor in Leadership in 2004. I have worked in the Critical Care areas for 15 years. I have been the President of the Noonan Syndrome Foundation since 2017. I have been blessed to live in several areas of our country. I have lived in Birmingham, Alabama Meridian, Mississippi and now I am settled in the Kansas City, Missouri area. I have been married to my husband Jon for 14 years. We have twins who are 10 (Morgan and Alia) along with Colton (PTPN11) who is 7. Along with the volunteer role for the NSF I am also the co-leader for Alia's Girl Scout troop, the treasurer for the Boy Scout troop pack that our boys participate in and I enjoy volunteering biweekly at the school.



Rebecca Burdine, PhD (SPEAKER)

Dr. Rebecca Burdine is an Associate Professor in the Department of Molecular Biology at Princeton University, where she uses zebrafish to model human disease including those involved in motile Ciliopathies, idiopathic scoliosis, and RASopathies. Dr. Burdine serves on the board of the Genetics Society of America and the International Zebrafish Society, and on several scientific advisory board for rare neurological disorders. Dr. Burdine was elected as AAAS Fellow in 2018.



Emma Burkitt-Wright, MBChB PhD MRCP (MODERATOR, CS BREAKOUT SESSION)



I was awarded my PhD on germline disorders of the Ras-MAPK pathway, funded by a Wellcome Trust clinical research training fellowship at the University of Manchester, in 2014. I finished my higher specialist training in clinical genetics and started as a consultant clinical geneticist in the Manchester Centre for Genomic Medicine later that year. The majority of my clinical commitments revolve around Ras-MAPK pathway disorders, both within the multidisciplinary NHS nationally commissioned highly specialised service for patients with complex neurofibromatosis type I and also our clinic for patients with Noonan, Costello and cardiofaciocutaneous syndromes.

Pau Castel, PhD (SPEAKER - JR. INVESTIGATOR)

Dr. Pau Castel is currently a postdoctoral fellow of the Jane Coffin Childs Fund at the laboratory of Dr. Frank McCormick at the University of California, San Francisco. During his PhD at Memorial Sloan Kettering Cancer Center (New York, NY), he studied therapies targeting the enzyme PI3K in breast cancer. As a postdoctoral fellow, Dr. Castel has gained interest in RASopathies and has described mouse models of Noonan syndrome driven by RIT1 and LZTR1 mutations.



Sandra Darilek, MS CGC (PANELIST)



Sandra Darilek is a Genetic Counselor and Assistant Professor in the Department of Molecular and Human Genetics at Baylor College of Medicine. She has a Master of Science degree in Genetic Counseling from The University of Texas-Houston Health Science Center Graduate School of Biomedical Sciences and received her board certification from the American Board of Genetic Counseling in 2005. Sandra is Co-manager of the Prenatal Genetic Counseling Service at Baylor College of Medicine and Texas Children's Hospital, and is chief of the Baylor College of Medicine Consultagene Clinic. She specializes in providing genetic counseling for preconception, prenatal, infertility, and preimplantation genetic testing (PGT) patients.

Alwyn Dias, MSW (PANELIST, NF1 ADVOCATE)

Alwyn Dias has a strong passion for supporting individuals reach their highest potential and personal goals. He was raised internationally and was diagnosed with NF1 at 4 years old. Alwyn Dias is a professor at Rutgers University's Graduate School of Healthcare Administration and has his own practice as an Executive Coach and HR Consultant.



Tuesdi Dyer, BA (PANELIST, CFC ADVOCATE)

Tuesdi Dyer is a Certified Fundraising Executive and the Executive Director of CFC International, a global medical research and treatment foundation dedicated to the support of patients impacted by CFC syndrome. This is also the rare disease her 5-year-old son was diagnosed with at just 4 months old. As a result, she is a Leadership Council Member of the Global Genes Foundation Alliance. She has been a member of the Johns Hopkins All Children's Hospital Advisory Board, where she worked with clinicians in the Department of Medicine to improve quality of care for all children. Tuesdi has worked as a Director in nonprofits for 20 years, has served on multiple community boards, which includes serving as President of the Junior League of St. Petersburg. Through the Nonprofit Leadership Center, she has consulted with and coached nonprofits; training them on fundraising, board governance, volunteer management, and business planning for social enterprise. She's been recognized by the Chamber of Commerce as Young Professional of the Year and the *Tampa Bay Times* as Rising Star. Tuesdi recently moved from St. Petersburg, Florida to Phoenix, AZ with her husband and two children. She holds a BA in Political Science from Texas A&M University.

Michelle Ellis (MODERATOR, NS ADVOCATE)

Michelle Ellis is an adult with NS who first heard of NS when she was diagnosed in Belgium at the age of 17. She was active supporting the Noonan Syndrome Support Group, assisting with their family conferences, working with the researchers and setting up the UK chapter, Noonan UK. She has worked with the Genetic Alliance UK, and is a founding member of the RASopathies Network UK. After merging with RASopathies Network USA, Michelle has been an enthusiastic advocate advisor. Michelle has presented in the USA, the UK, and the Netherlands. Her message to parents, people with NS, doctors and researchers continues to be "Although NS can and does present challenges, if you are determined and positive, there is very little that you can't do. It is part of who we are but it shouldn't define us." Michelle firmly believes *Knowledge IS Power*.





Gregg Erikson (PANELIST, NF1 ADVOCATE)

Gregg Erickson is the Executive Director of Neurofibromatosis North Central (NFNC), a member organization of the NF Network, which serves the NF communities in MN, WI, ND, SD, MT and WY. The father of three, Gregg lives in Rochester, MN where he coaches his kids' sports teams and aspires, one day, to fully understand what motivates his tween daughters. Gregg serves on the NF Network Board of Directors & its Leadership Council, the REiNS International Collaboration Council of Directors, and is a Patient Advocacy Representative for two REiNS working groups. He has also served as a Consumer Reviewer for the U.S. Army's NF Research Program Peer Review Panel under the Congressionally-Directed Medical Research Program.

Bruce D. Gelb, MD (SPEAKER, NS/NSML BREAKOUT SESSION)

Bruce D. Gelb, MD, is the Director and Gogel Family Professor of the Mindich Child Health and Development Institute at the Icahn School of Medicine at Mount Sinai. He is Professor of Pediatrics and of Genetics and Genomic Sciences. Dr. Gelb completed a pediatric residency and pediatric cardiology fellowship at Babies Hospital of Columbia-Presbyterian Medical Center and Texas Children's Hospital at the Baylor College of Medicine, respectively. He joined the faculty at Mount Sinai in 1991 after fellowship and has remained there since. He developed and now oversees an extensive program in genomics/gene discovery for congenital heart disease. Dr. Gelb has received the E. Mead Johnson Award from the Society for Pediatric Research and the Norman J. Siegel New Member Outstanding Science Award from the American Pediatric Society. He was elected to the American Society of Clinical Investigation and the National Academy of Medicine (formerly, the Institute of Medicine). Dr. Gelb is the Past President for the American Pediatric Society and Treasurer for the American Society of Human Genetics. In addition to his research, he co-directs the Cardiovascular Genetics Program at Mount Sinai. Dr. Gelb is also a member of the RASopathies Network Scientific Advisory Board.



Tamar Green, MD (SPEAKER)

Dr. Green is a physician-scientist and a child psychiatrist who works primarily with children with neurodevelopmental disorders such as ADHD and autism, as well as children with known genetic conditions ("neurogenetic syndromes" such as Noonan syndrome and other RASopathies, Turner syndrome, 22q11.2 deletion syndrome). She trained as a child psychiatrist at Tel Aviv University in Israel, completed a postdoctoral research fellowship in neuroscience at the Center for Interdisciplinary Brain Sciences Research at the Department of Psychiatry and Behavioral Sciences at Stanford University, and is currently an instructor in the department. Dr. Green's research focus is the RASopathies, a collection of syndromes associated with genetic mutations affecting the Ras/MAPK pathway.

Among the RASopathies, she is specifically interested in Noonan syndrome. These studies are directed at uncovering neural correlates associated with deficits in attention, memory and social skills in this syndrome. Results of ongoing research also have the potential to yield valuable new insights into the role of the Ras/MAPK pathway in brain development in general. Dr. Green is also a member of the RASopathies Network Scientific Advisory Board.

Karen Gripp, MD (CHAIR, SPEAKER, CS BREAKOUT SESSION)

Karen W. Gripp, MD, is the Chief of the Division of Medical Genetics at the A.I. du Pont Hospital for Children/Nemours in Wilmington, DE. She is a Professor of Pediatrics at the S. Kimmel Medical College at T. Jefferson University. She is board certified in pediatrics and clinical molecular diagnostic genetics. Dr. Gripp serves as medical director for the Genetic Testing Stewardship Program and the Molecular Diagnostic Laboratory at Nemours. Her areas of particular clinical expertise include dysmorphism and RASopathies. Costello syndrome is the focus of her research and she is closely involved with the Costello Syndrome Family Support network as the co-director of their professional advisory board. In addition to co-authoring the Handbook of Physical Measurements, Dr. Gripp has >150 peer reviewed publications. Her professional activities include membership in the ClinGen panels on RASopathies and on inherited cancer predisposition, membership on the board of directors for the American College of Medical Genetics and Genomics, and organizing the “D.W. Smith Workshop on Malformation and Morphogenesis”. Dr. Gripp is the chief medical officer for FDNA, parent company for Face2Gene. Dr. Gripp is on the RASopathies Network Scientific Advisory Board.



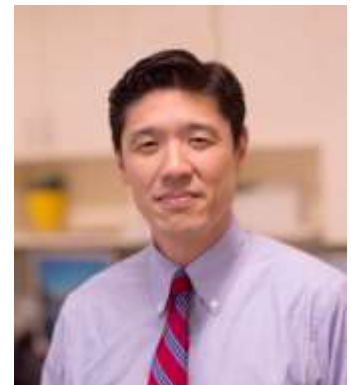
Andrea Gross, MD (SPEAKER)



Dr. Andrea Gross is a board-certified pediatrician who earned her medical degree at the University of Connecticut and completed pediatric residency and a chief resident year at Cincinnati Children’s Hospital Medical Center. She completed a pediatric hematology/oncology fellowship at Children’s National Medical Center and is currently an Assistant Research Physician working in the Pediatric Oncology Branch at the National Cancer Institute under the mentorship of Dr. Brigitte Widemann. Her research focuses on developing new therapeutics through clinical trials for tumor predisposition syndromes, such as NF1. Other areas of interest include developing and utilizing functional outcome measures for tumor predisposition syndromes, working with rare disease patient advocates to increase patient engagement in clinical trial design, and dealing with the challenge of medication adherence in the NF1 population.

Alan Ho, MD PhD (SPEAKER)

Dr. Ho is a translational clinical researcher at Memorial Sloan Kettering Cancer Center focused on developing novel therapeutics for malignancies of the head and neck. He has served as the national and international chair for targeted therapy trials focused on rare disease subsets. He now serves as a board member for the International Thyroid Oncology Group, chair of the head and neck subsection of the International Clinical Trials in Rare Cancers Initiative, and is a member of the Experimental Therapeutics Committee of the Alliance cooperative group, National Comprehensive Cancer Network Investigator Steering Committee, and NCI Head and Neck Steering Committee.



Jimmy L. Holder Jr., MD PhD (SPEAKER)



Dr. Jimmy Holder is an Investigator in the Jan and Dan Duncan Neurological Research Institute at Texas Children’s Hospital, and Assistant Professor of Pediatrics in the Division of Neurology and Developmental Neuroscience at Baylor College of Medicine. He received his undergraduate education at Johns Hopkins University followed by MD and PhD in Human Genetics at the University of Texas Southwestern Medical Center in Dallas, Texas. He then completed his clinical training in Pediatrics and Child Neurology at Baylor College of Medicine. Dr. Holder has established a synaptopathy clinic at Texas Children’s Hospital to care for children with neurological disorders due to mutations in genes critical for synapse function. In his laboratory, he studies how mutations in these same genes result in molecular, neuronal and circuit abnormalities. He is further investigating genetic modifiers of these genes as potential therapeutic entry points for neurodevelopmental disorders.

Shin-ichi Inoue, PhD (SPEAKER)

Dr. Inoue is an assistant professor in the Department of Medical Genetics at Tohoku University School of Medicine. His research focuses on the molecular mechanisms and treatment of Noonan syndrome, Costello syndrome and cardio-facio-cutaneous syndrome using mouse models. His current research aims at understanding the energy metabolism and cardiac diseases in RASopathies.



Angie Jelin, MD (PANELIST)



Angie Jelin is an Assistant Professor in Maternal-Fetal Medicine at Johns Hopkins Hospital and Director of Perinatal Ultrasound. She is board certified in both Maternal-Fetal Medicine and Genetics with a clinical focus on prenatal diagnosis, fetal imaging, and diagnostic procedures including chorionic villus sampling and amniocentesis. She is engaged in research evaluating whole exome and whole genome sequencing for pathologic single nucleotide variants.

Annie Kennedy, BS (SPEAKER)

Focused on improving health outcomes for people living with Duchenne muscular dystrophy, Annie’s work includes building strong partnerships with policy makers, federal agencies, Industry, and alliances that can serve as force multipliers in moving Duchenne community priorities forward. Current areas of emphasis include implementation of key provisions within PDUFA VI and the 21st Century Cures Act, MD-CARE Act implementation, engagement with the FDA and Industry around regulatory policy and therapeutic pipelines, launching a national newborn screening pilot program, developing resources for adults with Duchenne, optimizing clinical trial infrastructure, and innovating around therapy valuation and access issues. Annie currently serves on the Board of Directors of Cure SMA, on the steering committee of ‘Transition to Care’ coalition, as Co-Chair of the National Health Council’s Medical Innovation Action Team, and recently served as a Design Team member of the NCATS/ORDR Tool Kit Project and on the FasterCures Patients Count Leadership Council.





Richard Klein (MODERATOR)

Richard Klein recently left the FDA after more than 41 years with the agency. He served as the director of the FDA's Patient Liaison Program in the agency's Office of Health and Constituent Affairs, the primary agency interface with patients and patient communities.

Maria I. Kontaridis, PhD (SPEAKER)

Dr. Maria Irene Kontaridis is currently the Gordon K. Moe Professor and Chair of Biomedical Research and Translational Medicine, and the Director of Research at the Masonic Medical Research Institute in Utica, NY. She also holds a part-time faculty appointment as an Associate Professor of Medicine at Harvard Medical School and Beth Israel Deaconess Medical Center, Department of Medicine/Division of Cardiology in Boston, MA. Dr. Kontaridis received her undergraduate degrees (BA and BS) from the University of Florida in Classics and Chemistry, and subsequently obtained her master's degrees both in Pharmacology and in Biomedical and Biological Sciences from Yale University in 1999 and 2001, respectively. In 2002, she was awarded a PhD from Yale University for work with Dr. Anton Bennett on the role of protein tyrosine phosphatases, particularly SHP2, in cell growth and skeletal muscle differentiation. Dr. Kontaridis' independent research program focuses on the fundamental mechanisms underlying both congenital heart disease and end-stage heart failure, and the processes that lead to abnormal development, aberrant signaling and disease onset. She has made several seminal observations about SHP2 and its role in cardiac pathophysiology and disease, and in autoimmunity. Her work has been awarded grants from the Milton Foundation, the Children's Cardiomyopathy Foundation, the Saving Tiny Hearts Foundation, the Harvard Stem Cell Institute, the Alliance of Lupus Research and the National Institutes of Health (NHLBI-R01s and NCATS-TRND) as well as has garnered support from industry and pharmaceutical companies (Novartis, GSK, Arqule).



Bruce R. Korf, MD PhD (NF1 BREAKOUT SESSION)



Dr. Korf is Wayne H. and Sara Crews Finley Chair in Medical Genetics, Professor and Chair of the Department of Genetics, Director of the Heflin Center for Genomic Sciences at UAB, and Co-Director of the UAB-HudsonAlpha Center for Genomic Medicine. He is a medical geneticist, pediatrician, and child neurologist, certified by the American Board of Medical Genetics (clinical genetics, clinical cytogenetics, clinical molecular genetics), American Board of Pediatrics, and American Board of Psychiatry and Neurology (child neurology). Dr. Korf is past president of the Association of Professors of Human and Medical Genetics, past president of the American College of Medical Genetics and Genomics, and current president of the ACMG Foundation for Genetic and Genomic Medicine. He has served on the Board

of Scientific Counselors of the National Cancer Institute and the National Human Genome Research Institute at the NIH. His major research interests are molecular diagnosis of genetic disorders and the natural history, genetics, and treatment of neurofibromatosis. He serves as principal investigator of the Department of Defense funded Neurofibromatosis Clinical Trials Consortium. He is co-author of *Human Genetics and Genomics* (medical student textbook, now in fourth edition), *Medical Genetics at a Glance* (medical student textbook, now in third edition), *Emery and Rimoin's Principles and Practice of Medical Genetics* (now in 6th edition), and *Current Protocols in Human Genetics*. Dr. Korf is also on the RASopathies Network Scientific Advisory Board.

Pilar L. Magoulas, MS CGC
(MODERATOR, CFC BREAKOUT SESSION)

Pilar Magoulas is a certified genetic counselor and Assistant Professor in the Department of Molecular and Human Genetics at Texas Children’s Hospital and Baylor College of Medicine. She received her Bachelor of Science degree in Psychology from the University of Florida in 2001 and a Master of Science degree in Genetic Counseling from Northwestern University in 2003. She currently works as a pediatric genetic counselor at Texas Children’s Hospital where she serves as the Manager of the Pediatric Genetics clinic, and Chief of the Division of Genetic Counseling. Pilar is a member of the National Society of Genetic Counselors and American College of Medical Genetics. She serves on the Board of directors for CFC International, support group for individuals with Cardio-facio-cutaneous syndrome, on the Scientific Advisory Council for the National Foundation for Ectodermal Dysplasias, and the RASopathies Network USA, and serves on the Program Committee for the American College of Medical Genetics and Genomics.



Darryl McConnell, PhD (SPEAKER)



Darryl McConnell is currently Senior Vice President and Research Site Head at Boehringer-Ingelheim Regional Centre Vienna, Austria. His goal is to discover new chemical therapeutics for cancer’s so-called undruggable targets together with the team at BI. Darryl’s interests lie in drugging protein-protein interactions, kinases and pushing the frontiers of PROTAC for cancer patients. Fragment screening, protein crystallography, protein NMR, drug resistance, agile methods in drug discovery and natural product inspired medicinal chemistry are some of his areas of scientific interest. Darryl commenced his career with Boehringer-Ingelheim in 2002 as a Research Laboratory Head and is in his current role since 2015. Prior to this Darryl has worked for Intervet in Vienna from 2001, for Biota Holdings Ltd in Melbourne, Australia from 1999 in the area of respiratory viruses and Chiron Technologies in Melbourne from 1997. Darryl McConnell received his Bachelor of Science with First Class Honours in 1991 with Professor John Elix at the Australian National University in Canberra. He performed his PhD at the University of New South Wales in Sydney with Professor David Black for which he was awarded the Cornforth Medal for the best chemistry PhD thesis in Australia for that year. Following this he performed a 2-yr Postdoctoral study at the University of Sydney with Professor Leslie Field in organometallic chemistry.

Frank McCormick, PhD FRS DSc (Hon) (SPEAKER)

Dr. McCormick is a Professor and former Director of the UCSF Helen Diller Family Comprehensive Cancer Center; he holds the David A. Wood Chair of Tumor Biology and Cancer Research at UCSF. Prior to joining the UCSF faculty, Dr. McCormick pursued cancer-related work with several biotechnology firms, including Cetus Corporation as Director of Molecular Biology from 1981 to 1990 and Vice President of Research from 1990 to 1991, and Chiron Corporation as Vice President of Research from 1991 to 1992. In 1992, Dr. McCormick founded Onyx Pharmaceuticals and served as its Chief Scientific Officer until 1996. At Onyx Pharmaceuticals, he initiated drug discovery efforts that led to the approval of Sorafenib in 2005 for treatment of renal cell cancer, and for liver cancer in 2007, and the approval of



ONYX-015 in 2006 in China for treatment of nasopharyngeal cancer. In addition, Dr. McCormick's group led to the identification of the CDK4 kinase inhibitor, Palbociclib, approved for treating advanced breast cancer. Dr. McCormick's current research interests center on ways of targeting Ras proteins and their regulators, including the NF1 protein neurofibromin. Since 2013, Dr. McCormick has led the National Cancer Institute's Ras Initiative at the Frederick National Laboratories for Cancer Research overseeing the national effort to develop therapies against Ras-driven cancers. These cancers include most pancreatic cancers, and many colorectal and lung cancers, and are amongst the most difficult cancers to treat. Dr. McCormick is a Fellow of the Royal Society, a member of the National Academy of Sciences since 2014 and has served as President, 2012-2013, for the American Association for Cancer Research.



Benjamin G. Neel, MD PhD (SPEAKER)

Dr. Neel is the Director of the Laura and Isaac Perlmutter Cancer Center and Professor of Medicine at NYU Langone Health in New York City. Dr. Neel's research focuses on cellular signaling, with a particular interest in the biology and regulation of protein-tyrosine kinases and -phosphatases, the role of RAS/ERK pathway mutations in developmental disease and malignancy, and the biology of breast and ovarian cancer. Dr. Neel earned his PhD in viral oncology from The Rockefeller University in 1982 and his MD from Cornell University Medical School the following year. His graduate work on oncogene activation by slowly transforming RNA tumor viruses had major impact on the field. He has authored >230 primary papers and 33 reviews, many in leading journals including *Cell*, *Molecular Cell*, *Developmental Cell*, *Science*, *Nature*, *Nature Medicine* and *Nature Genetics*. He is an elected member of the AAP, a former Program Chair of the Annual Meeting and Member of Board of Directors of AACR, recipient of the Gertrude Elion Award of AACR and the Premier of Ontario Summit Award and the co-founder of Northern Biologics, a company focusing on antibody therapeutics for cancer and Navire Pharmaceuticals, which is developing SHP2 inhibitors for cancer.

Steph Nimmo, MS (SPEAKER)

Stephanie Nimmo is a writer and freelance journalist. She has been writing the award-winning blog www.wasthisintheplan.com for nearly 12 years sharing the realities of life caring for her daughter, Daisy, who had Costello syndrome. Daisy died in January 2017 and Steph has subsequently written two best-selling books, *Was this in the plan?* and *Goodbye Daisy*, both of which tackle the difficult conversations around death and dying. With a background in both Anthropology and Marketing, Steph is passionate about improving communication between medical professionals and parent caregivers and has been an advisor on several independent think tanks on the subject. She is a visiting speaker on several medical training programs at Great Ormond Street Hospital. She has written for the *BMJ* and writes and speaks regularly in the UK media.





Elisabeth Parker, BS
(BOARD MEMBER, RASOPATHIES NETWORK)

Elisabeth Parker is the mother of Ezra, who has Noonan syndrome (PTPN11). She graduated Magna Cum Laude from Oregon State University with a BS in Liberal Studies and an emphasis in Sociology and Anthropology. Elisabeth and her family love living in the Pacific Northwest where she works part time as a Baptiste yoga instructor and full time as a mom and rare disease advocate. She is passionate about encouraging other parents by sharing her family's (extra)ordinary journey with Noonan syndrome through yoga and stories and photos of their everyday life. As a RASNet board member, she is excited to educate and advocate for the RASopathies

through social media.

Carlos E. Prada, MD (SPEAKER)

Carlos E. Prada, MD, is an Associate Professor of Clinical Genetics at Cincinnati Children's Hospital Medical Center within the UC Department of Pediatrics and Co-director for the RASopathies program, a multidisciplinary program across the institution to provide comprehensive care to our patients. Dr. Prada completed a combined pediatrics and human genetics residency at Cincinnati Children's Hospital Medical Center, followed by a fellowship in clinical biochemical genetics. Dr. Prada's clinical and research efforts are to develop a comprehensive program for the diagnosis, management, and treatment of patients with RASopathies. As an Associate Professor of Human Genetics at Cincinnati Children's within the UC Department of Pediatrics, Dr. Prada spends the majority of his time caring for patients with RASopathies, lysosomal storage diseases, and metabolic disorders. He participates in natural history studies of genetic diseases, biomarker discovery, and clinical trials for novel therapies including gene therapy. He is also actively involved in the education of health care providers regarding the application of genetics for patient care, including newborn screening, and gene therapy. Dr. Prada has expertise in telehealth and he is the director for a Telegenetics program in the Caribbean. He has developed a partnership with the Centro de Ginecología y Obstetricia to follow children with complex rare diseases in Santo Domingo, Dominican Republic. In the Fundación Cardiovascular de Colombia, Dr. Prada is the director of the Center for Genomics and Metabolism.



Nancy Ratner, PhD (CHAIR, MODERATOR)



Dr. Ratner is interested in the brain in Neurofibromatosis type 1 and RASopathies, and in peripheral nerve tumors that occur in the Neurofibromatoses, NF1 and NF2. She uses genomics, animal, and cell culture models to study neurofibroma formation and neurofibroma therapeutics. Ratner received her bachelor's degree from Brown University, her doctorate from Indiana University, Bloomington (during which time she was a student in the Neurobiology Course at MBL), and was a postdoctoral fellow at Washington University in St. Louis. A member of the faculty at the University of Cincinnati from 1987 – 2004, she is currently a Professor in the Department of Pediatrics, Cincinnati Children's Hospital, University of Cincinnati, and the Program Leader for Cancer Biology and Neural Tumors Program in the Cancer and Blood

Disorders Institute where she also co-Leads the RASopathy Program and holds the Beatrice C. Lampkin Endowed Chair in Cancer Biology. She has served on numerous national and international review panels and authored over 100 peer-reviewed manuscripts and 30 reviews. She was awarded the von Recklinghausen Award in 2010, and received a Jacob K. Javits NIH Neuroscience Investigator Award in 2014.

Katherine A. Rauen, MD PhD (SPEAKER)

Dr. Rauen is a Professor in the Department of Pediatrics, Division of Genomic Medicine at the UC Davis where she currently serves as the Chief of Genomic Medicine and holds the Albert Holmes Rowe Endowed Chair in Human Genetics. She received a MS in Human Physiology and a PhD in Genetics from UC Davis doing research on gene dosage compensation and genetic evolution. She obtained her MD at UC Irvine where she also did research in cancer genetics. Dr. Rauen did her residency training in Pediatrics and fellowship in Medical Genetics at UC San Francisco. Dr. Rauen is internationally known for her pioneering work in the early application of microarray technology in clinical genetics and as a leader and major contributor to the understanding of the “RASopathies,” the Ras/MAPK pathway genetics syndromes. Her research program involves the clinical and basic science study of cancer syndromes with effort to identify underlying genetic abnormalities affecting common developmental and cancer pathways. Her current laboratory research includes the study of skeletal myogenesis in both Costello syndrome and cardio-facio-cutaneous (CFC) syndrome. Dr. Rauen led the research team, which included CFC International, the CFC family support group, that discovered the genetic cause of CFC and independently identified the genetic cause of Costello syndrome. Dr. Rauen is committed to academic medicine, medical education, and advancing best practices for patients with RASopathies. She is the innovator of the world-renowned NF/Ras Pathway Clinic in 2007, now emulated around the globe. She serves on the medical advisory board of CFC International, is a Co-Director for the Costello Syndrome Family Network, and serves on the Global Genes advocacy advisory board and the RASopathies Network USA Scientific Advisory Board. Dr. Rauen was awarded the Presidential Early Career Award for Scientists and Engineers (PECASE) on her work for CFC and Costello syndromes. This Award is the highest honor bestowed by the United States Government on science and engineering professionals in the early stages of their independent research careers.



Amy Roberts, MD

(MODERATOR, NS/NSML BREAKOUT SESSION)

Amy Roberts is Associate Professor of Medicine at Harvard Medical School and Director of Clinical Cardiovascular Genetics at Boston Children’s Hospital. She has a long-standing research interest in the RASopathies including gene discovery, genotype phenotype correlation, natural history, and treatment. She has been involved with the scientific symposiums since their inception, and is on the RASopathies Network Scientific Advisory Board.

Pablo Rodriguez-Viciana, PhD (SPEAKER)

Pablo Rodriguez-Viciana, PhD, is an Associate Professor at University College London Cancer Institute, UK. His area of expertise is signalling by RAS family GTPases. He has been involved in the identification and characterization of both effectors and modulators of the RAS protein function and is particularly interested in identifying nodes within the RAS pathway that can be used as therapeutic targets.





Neal Rosen, MD PhD (KEYNOTE SPEAKER)

Dr. Neal Rosen is a Member of both the Program in Molecular Pharmacology and the Department of Medicine at Memorial Sloan Kettering Cancer Center and the co-director of the Center for Mechanism Based Therapeutics. Dr. Rosen's major interests are the identification and study of the key molecular events and growth signaling pathways responsible for the development of human cancers, and the use of this information for the development of mechanism-based therapeutic strategies. Dr. Rosen has played a leading role in the development of inhibitors of tyrosine kinase-mediated signaling and has pioneered the concept that feedback reactivation of parallel signaling pathways is a common cause of adaptive resistance to selective pathway inhibitors. Dr. Rosen received his undergraduate degree in chemistry from Columbia College and an MD PhD in Molecular Biology from the Albert Einstein College of Medicine. He completed a residency in Internal Medicine at the Brigham and Women's Hospital, and postdoctoral training and a fellowship in Medical Oncology at the National Cancer Institute. He was on the senior staff of the Medicine Branch at the NCI prior to joining the faculty of Memorial Sloan Kettering Cancer Center.

Gavin Rumbaugh, PhD (SPEAKER)

Gavin is a Professor of Neuroscience at The Scripps Research Institute, in Jupiter, Florida. Gavin's lab has identified several genes that are critical regulators of synapse biology, excitatory balance, and cognitive function. These genes also increase the risk for developing neurodevelopmental disorders. Current studies in the lab are aimed at understanding how risk genes disrupt synaptic and circuit properties during developmentally sensitive periods and how this process triggers behavioral impairment and seizure. The lab's overarching goal is to apply knowledge gained from biological studies of genetic risk factors to accelerate the development of therapeutic agents to treat impaired brain excitability and behavioral dysfunction.



Anna Sablina, PhD (SPEAKER)

Anna Sablina is a group leader at the VIB Center for Cancer Biology and an associate professor at the University of Leuven, Belgium. She received her PhD from the Cancer Research Center in Moscow. Dr. Sablina pursued postdoctoral training at the Cleveland Clinic Foundation and in the laboratory of Dr. William Hahn at the Dana Farber Cancer Institute. The major focus of Anna Sablina's laboratory is elucidating the role of ubiquitin system in human disease.



Lisa Schill (VICE PRESIDENT, RASOPATHIES NETWORK)

Lisa Schill voluntarily serves as the Vice President of the RASopathies Network. She is a parent advocate that specializes in connecting caregivers, researchers, support organizations, and families to help support patients in the pursuit of advancing treatment options and patient outcomes. She helped work to pass the 21st Century Cures Act to bring new innovations and advances to patients more efficiently.



Lisa Schoyer, MFA (PRESIDENT, RASOPATHIES NETWORK)



Lisa Schoyer is the mom of Quin Johnson, who had Costello syndrome (G12S) and died in 2002 at 6-1/5 years old, of embryonal rhabdomyosarcoma (eRMS) related to the syndrome. She is founder and President of the RASopathies Network USA. Lisa is also a trustee of the International Costello Syndrome Support Group (ICSSG), as well as past President and past Secretary for the American Costello Syndrome Family Network (CSFN). Though trained as a professor of studio art, after Quin died, she was hired by the County of Los Angeles first as Chief of Family Support at the Department of Public Health's program for children with special healthcare needs (2003-2009), and, since then, for the County's Department of Mental Health in the Family and Community Partnerships unit - where she is working to sustain/develop

Subject Matter Mavens on providing mental health interventions for individuals with co-occurring developmental disabilities.

Alcino J. Silva, PhD (SPEAKER)

Alcino J. Silva pioneered the field of Molecular and Cellular Cognition, and in 2002 founded and became the first President of the Molecular and Cellular Cognition Society. In 2006/2007 Dr. Silva served as Scientific Director of the Intramural Program of the National Institute of Mental Health. He currently serves as the Director of the UCLA Integrative Center for Learning and Memory and is a Distinguished Professor in the Departments of Neurobiology, Psychiatry & Biobehavioral Sciences and Psychology at UCLA. His laboratory is searching for the molecular, cellular and circuit processes that underlie the allocation, encoding, storage and linking of information in the brain. Insights into mechanisms of memory are being used to unravel the causes and develop treatments for cognitive deficits associated with aging, intellectual disabilities, and autism. His work has been recognized by numerous prizes and awards, including the National Institute of Aging Merit award in 2006, in 2008 the Order of Prince Henry (Portuguese Knighthood), and Senior Roche Award for Translational Neuroscience in 2009. He was elected to the American Association for the Advancement of Science in 2013.





Maja Solman, PhD (SPEAKER - JR. INVESTIGATOR)

Maja Solman received her PhD from Abo Akademi University in Turku, Finland in 2016, for her work on nanoscale molecular mechanisms of Ras in cancer. Currently she holds a Postdoctoral fellow position in the laboratory of Prof. Jeroen den Hertog at the Hubrecht Institute in the Netherlands. Here, she utilizes the zebrafish model to study developmental defects in RASopathies.

David A. Stevenson, MD (CFC BREAKOUT SESSION)

David A. Stevenson, MD - Pediatrician and Medical Geneticist, Stanford University. Dr. Stevenson completed his residency in Pediatrics at the University of New Mexico and a 3-year fellowship in medical genetics at the University of Utah. He was on faculty at the University of Utah for 10 years before joining the faculty in the Division of Medical Genetics at Stanford University. His initial research focused on neurofibromatosis type 1 (NF1), and since that time he has expanded his research to RASopathies focusing on the musculoskeletal problems and genotype-phenotype correlations. He has received grant funding from the NIH, Doris Duke Charitable Foundation, Thrasher Research Fund, and Department of Defense to investigate the musculoskeletal system in syndromes of the Ras/MAPK pathway. He currently serves as a member of the CFC Medical Advisory Board, Costello Syndrome Family Support Network Professional Advisory Committee, and RASopathies Network Scientific Advisory Board, is the co-chair of the Children's Tumor Foundation International NF1 Bone Abnormalities Consortium, and is a member of the National Prader-Willi Syndrome Association (PWSA) USA Scientific Advisory Board. He has published over 120 scientific articles, and 2 GeneReviews focused on Ras/MAPK syndromes.



Beth Stronach, PhD (BOARD MEMBER, RASOPATHIES NETWORK)

Beth Stronach has been an academic research scientist for over a dozen years. After receiving a PhD in Biology from the University of Utah in 1997 and pursuing postdoctoral work in Genetics at Harvard Medical School, she moved to Pittsburgh in 2002. Since then, she has been a faculty member at the University of Pittsburgh, first in the Dept. of Biological Sciences, then in the Microbiology and Molecular Genetics department at the School of Medicine. Her research focused on understanding how cells organize into complex tissues during organism development. Ironically, the subject of Dr. Stronach's research was a signaling pathway closely related to the RAS pathway, so it was quite a shock to learn of her son Sam's diagnosis of Noonan syndrome (PTPN11) in 2007. Yet, his diagnosis validated for her the importance of basic research science to understand the molecular underpinnings of health and disease. She is currently a Scientist Administrator in the Office of Research for Health Sciences at the University of Pittsburgh and Secretary for RASopathiesNet.

Marco Tartaglia, PhD (MODERATOR)

Dr. Tartaglia is senior scientist, and Head of the *Genetics and Rare Diseases* Research Division at the Ospedale Pediatrico Bambino Gesù, Rome, Italy. For 10 years, he served as Section Director at the Istituto Superiore di Sanità, the Italian National Health Institute. His research has been focused on understanding the molecular bases of diseases affecting development and growth, and exploring disease pathogenesis. A major longstanding interest deals with Noonan syndrome and other RASopathies, with efforts that have mainly been directed to the identification of the disease genes implicated in these disorders, elucidation of the mechanisms underlying pathogenesis, and on clinically oriented research focused on the delineation of genotype-phenotype correlations and natural history of these diseases. A second major focus has linked to the use of genomics to gain insights into the molecular causes of rare and “orphan” diseases, and understanding the molecular and cellular processes altered in these disorders. He serves as a member of the scientific boards of the Italian RASopathy supporting groups *Costello*, *CFC*, and *Associazione Nazionale Sindrome di Noonan*.



Angel Thomas, BS (PANELIST, CS ADVOCATE)



Angel Thomas is the Vice President of the Costello Syndrome Family Network. Her son Westin is 8 years old and has Costello syndrome. He attended his first of five Costello syndrome family conferences in Chicago in 2011, when he was 5 months old. In her role as Vice President of CSFN, Angel reaches out to newly diagnosed families to welcome them and help answer their questions about Costello syndrome. Angel is also a Yield Enhancement Engineer with NXP Semiconductors in Austin, Texas. She holds a Bachelor of Science Degree in Chemical Engineering from the University of Iowa. In her free time, she enjoys traveling and has visited over 35 countries. Her son Westin has been on over 100 flights and her 5-year old daughter has been on 75 flights!

William Timmer, PhD (MODERATOR)

Dr. William Timmer joined the National Cancer Institute (NCI) in September 2007 as a Program Director (Health Science Administrator) in the Cancer Therapy Evaluation Program (CTEP). His principal effort is scientific and administrative management of a portfolio of clinical oncology research grants (principally involving brain, head and neck, lung, liver, colorectal, pancreatic, sarcoma and neuroblastoma). He is also the NCI Program Director for both the Adult Brain Tumor Consortium and the Childhood Cancer Survivor Study. Dr. Timmer received his PhD in Chemistry from the University of Wisconsin, and he immediately began his federal career at the NIH. He studied the immunoregulatory effects of cytokines on HIV replication with Dr. Anthony Fauci in the Laboratory of Immunoregulation of at the National Institute of Allergy and Infectious Diseases (NIAID). He subsequently joined the Food and Drug Administration (FDA) where, over a fifteen-year period, he held a variety of scientific and regulatory positions of increasing influence in three different FDA Centers: Foods, Drugs, and Biologics. At the Centers for Drugs and Biologics, Dr. Timmer evaluated regulatory submissions in the areas of HIV detection kits, cellular and gene therapies, medical devices, and served as a review team member for several currently-marketed oncology drugs. Dr. Timmer has over 100 publications and presentations to his credit. He has received numerous honor awards from both the NIH and the FDA, and is completing thirty years of federal service.





Kartik Venkatachalam, PhD (SPEAKER)

Dr. Kartik Venkatachalam is an Associate Professor in the Department of Integrative Biology and Pharmacology at the McGovern School of Medicine at the University of Texas Health Sciences Center, Houston. His laboratory uses a variety of animal and cell models to examine alterations in biochemical signaling pathways in human diseases. An area of exceptional interest to his lab relates to how lipid and protein trafficking within cells affect MAPK signaling driven by activating mutations in RAS genes.

Karin Walsh, PsyD (SPEAKER, NF1 BREAKOUT SESSION)

Karin S. Walsh, PsyD, is a pediatric neuropsychologist in the Division of Neuropsychology at Children’s National Health System and an Associate Professor of Pediatrics and Psychiatry at the George Washington University School of Medicine in Washington DC, USA. She has 15 years’ experience as a clinical neuropsychologist and scientist caring for and studying children with NF1 and other RASopathies. Her primary areas of interest are the understanding of cognitive dysfunction in children with RASopathies and developing treatments to reduce the burden of these diseases on young children and their families.



Pam Wolters, PhD (SPEAKER, NF1 BREAKOUT SESSION)



Pam Wolters, PhD is a licensed psychologist who leads the Health Psychology and Neurobehavioral Research Program and co-directs the Behavioral Health Core of the Pediatric Oncology Branch, National Cancer Institute at the National Institutes of Health, Bethesda, MD. As a senior associate scientist, Dr. Wolters leads a clinical research program that characterizes the longitudinal effects of disease and treatment on neuropsychological functioning and quality of life (QOL) in children and adults with chronic illness, including cancer and neurofibromatosis type-1 (NF1). She and her team develop and evaluate novel interventions to ameliorate the detrimental effects of illness and treatments.

More specifically, Dr. Wolters is pioneering the use of physical activity to improve the cognitive late effects of radiation-induced cognitive impairments in children with brain tumors. She also is developing patient-reported outcomes to assess QOL, pain, and neurotoxicity in children with medical conditions enrolled in clinical trials.

Jae-Sung Yi, PhD (SPEAKER – JR. INVESTIGATOR)

Dr. Jae-Sung Yi received his undergraduate and graduate degrees at Korea University in Seoul, South Korea, where he conducted research on the mechanisms of ubiquitin E3 ligase in skeletal muscle development and insulin signaling. Dr. Yi is currently an Associate Research Scientist in the Pharmacology Department at Yale School of Medicine. Dr. Yi's research interests are to understand key developmental signaling pathways in cardiac and skeletal muscles and how these pathways contribute to human disease. He pursued postdoctoral studies with Dr. Anton Bennett to characterize Shp2 signaling in cardiac failures using mouse models, resulting in the identification of Protein Zero Related (PZR) and its role along with Shp2 in NS and NSML RASopathy syndromes.



Martin Zenker, MD (SPEAKER)



Martin Zenker, MD, is Professor of Human Genetics and Head of the Department of Human Genetics of the University Hospital of Magdeburg, Germany. He is board certified in pediatrics and human genetics. His area of clinical expertise and research is regarding human developmental disorders with a particular focus on RASopathies. He has been involved in the discovery of several genes underlying Noonan syndrome and is particularly interested in studying genotype-phenotype correlations for RASopathies. Dr. Zenker is closely involved with the German Noonan and CFC syndrome family support groups and a member of the ClinGen expert panel on RASopathies. He is a co-organizer of the biannual European Meeting on Rare Disorders of the RAS-MAPK Pathway.

Tip-in

Manuel Lopez Aranda, PhD (SPEAKER, SILVA LAB)



I received my PhD in Dr. Zafar U. Khan's laboratory at University of Malaga (Spain) in 2010. During my PhD, the goal of my research was to explore the physiological functions of sGai2 and RGS-14 proteins in brain. In 2010, I became a Postdoctoral Scholar in Dr. Alcino J Silva's laboratory. Although during my thesis I used lentivirus to modify certain areas of the brain to study memory, when I started working in Dr. Silva's laboratory I was impressed by the huge potential of transgenic mice to study the relationship between neuropsychiatric disorders and environmental factors. Currently, I am an Assistant Project Scientist in Dr. Alcino J Silva's laboratory. Using a mouse model of TSC, we found that an early post-natal immune activation induces long lasting social memory deficits in adult *Tsc2^{+/-}* mice as well as alterations in the ultrasonic vocalization patterns in pups. Moreover, we found that the prevalence of hospitalizations due to infections is associated with future development of autism spectrum disorders (ASD).

Post-Natal Immune Activation and Its Role In Adult Phenotypes in a RASopathy Model

Manuel Lopez Aranda PhD, Alcino J Silva, *Integrative Center for Learning and Memory and Brain Research Institute, University of California, Los Angeles, USA*

There is growing evidence that environmental factors, such as immune activation, contribute to the severity and range of cognitive phenotypes in neuropsychiatric disorders. However, the cell types and the molecular mechanism(s) responsible for these cognitive phenotypes remain unclear. We have multiple lines of evidence that in male mice with a tuberous sclerosis mutation ($Tsc2^{+/-}$), immune activation during a critical phase of post-natal development triggers an mTOR-dependent, self-perpetuating cycle of IFN production in microglia. This disrupts hippocampal plasticity and causes behavioral phenotypes, including social memory deficits as well as alterations in ultrasonic vocalization patterns (USV), under conditions that do not affect either wild type or female mice. Importantly, our human epidemiological studies show a strong correlation between the prevalence of infections during childhood, and a future diagnosis of ASD, suggesting that our results in mice are mirrored by human findings. Altogether, our results illustrate the importance of synergistic interactions between strong early post-natal immune activation and mutations associated with RASopathies as well as reinforce the critical necessity for vaccination early postnatally.

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