



5th International **RASopathies** Symposium:

When Development and Cancer Intersect

July 28-30, 2017
Renaissance Orlando

RASopathiesNet

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July 28, 2017

Welcome to the 5th International RASopathies Symposium!

It's been ten years since our first symposium. Looking at syndromes with a cellular pathway lens continues to surprise us – life is complicated!

We are so pleased to see in the mainstream news about new breakthroughs in cancer therapy targeting somatic tumors' mutations. This is exactly the connection we've been hoping to see, as we work to better understand human development through the germline Rasopathies.

We hope that you find our agenda and networking opportunities useful to help you find novel ways to expedite strategies to increase the quality of life for those affected by a RASopathy, as well as for those who develop a Ras-related cancer. Our goal for this meeting is to nurture your shared interest.

Finally, many thanks to all who helped us pull this symposium together, including the Chairs Frank McCormick and Katherine A. Rauen, the RASopathies Network Scientific Advisory Board, the Advocates' Advisory Board, the speakers, and the moderators.

Cheers!

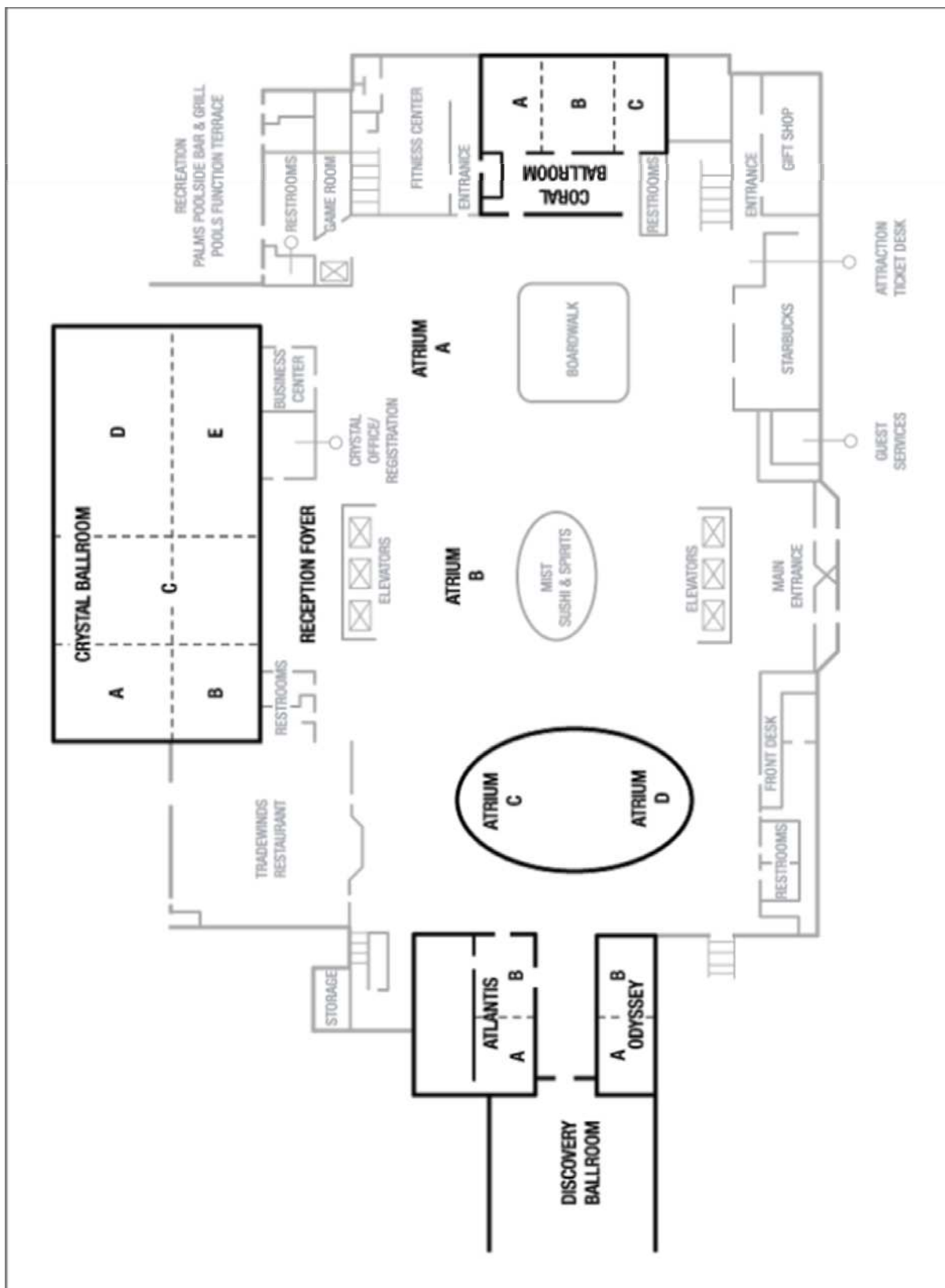
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5th International **RAS**opathies Symposium: When Development and Cancer Intersect

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5th International RASopathies Symposium: When Development and Cancer Intersect

AGENDA- **updated**

Renaissance Orlando at SeaWorld, Orlando, Florida ~ Friday, July 28 to Sunday, July 30, 2017

DAY 1 – FRIDAY 7/28/17 – *Atrium A & B*

8:00-10:00 pm	Dessert and Poster Session (Scientists and advocacy/family groups) <u>Goal:</u> Encourage collaboration between researchers and families in a nonclinical setting
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DAY 2 – SATURDAY 7/29/17 – *Crystal E*

7:00-8:00 am	Breakfast (<i>Crystal D</i>)
9:00 am-5:00 pm	Family Photo Shoot in and around meeting areas - Rick Guidotti
8:00-10:00 am	Session 1: What Defines a RASopathy? <u>Moderator:</u> Martin Zenker, MD <u>Goals:</u> Hear from patients and families about their experiences living with a RASopathy. Lay the scientific foundation for a comprehensive and accurate understanding of the current definition of a RASopathy.
8:00-8:30 am	RASopathy Individuals/Caregivers Panel: Perspectives from the Home Front-‘Aging’
8:30-9:00 am	Frank McCormick, PhD, FRS: Molecular primer on the Ras signaling pathway
9:00-9:30 am	Katherine A. Rauen, MD, PhD: The RASopathies
9:30-10:00 am	<i>Discussion</i> (Clinical Diagnosis, Phenotype-Centered vs. Molecularly Defined)
10:00-10:10 am	Break
10:10 am-12:00 pm	Session 2: Syndromic and Sporadic Cancers of the Ras Pathway <u>Moderator:</u> Karen Gripp, MD <u>Goal:</u> Examine cancer types and mechanisms in individuals with RASopathies
10:10-10:50 am	KEYNOTE: Nancy Ratner, PhD: Preclinical studies to guide NF1 clinical trials
10:50-11:10 am	Corinne Linardic, MD: Pediatric sarcomas, rhabdomyosarcoma
11:10-11:30 am	Hélène Cavé, PharmD PhD: Myoproliferative neoplasms (JMML) in RASopathies
11:30-11:50 am	Brigitte Widemann, MD: Clinical trial updates, NF1 Plexiforms and MPNSTs
11:50 am–12:00 pm	<i>Discussion</i>
12:00 – 1:00 pm	Lunch and Learn: Rick Guidotti: Positive Exposure (<i>Crystal D</i>)
1:00-4:30 pm	Session 3: Human Development: Effects on Organ Systems <u>Moderator:</u> Bruce Korf, MD, PhD Ashley Cannon, PhD, MS, CGC <u>Goal:</u> Learn how RASopathy mutations affect developing tissues, organs, and body systems
1:00-1:40 pm	KEYNOTE: Marco Tartaglia, PhD: Molecular genetics of RASopathies. Common themes and novel mechanisms in RAS signaling dysregulation. Ashley Cannon, PhD MS CGC Cutaneous neurofibromas in Neurofibromatosis Type I: quantitative natural history study and clinical trial
1:40-2:40 pm	NERVOUS SYSTEM
1:40-2:00 pm	Erika Yeh, PhD (Weiss lab): From skin cells to neurons
2:00-2:20 pm	Erik Ullian, PhD: How do astrocytes affect brain function in RASopathies?
2:20-2:40 pm	Giuseppe Zampino, MD: Penn MDBR 2015 Grantee - Pain in RASopathies: new investigative techniques and treatments

2:40-2:50 pm	<i>Discussion</i>
2:50-3:00 pm	<i>Break</i>
3:00-3:40 pm	CIRCULATORY SYSTEMS
3:00-3:20 pm	Bruce Gelb, MD: Human inducible pluripotent stem cells for the study of heart defects
3:20-3:40 pm	Max Itkin, MD: Imaging of the central lymphatic system in patients with Noonan syndrome using Dynamic Contrast Enhanced MR Lymphangiography
3:40-4:00 pm	GASTROINTESTINAL SYSTEM Cheng Sun, PhD (Kontaridis lab): Penn MDDR 2014 Grantee - Using human inducible pluripotent stem cells to delineate the cause of gastrointestinal abnormalities in RASopathy disorders
4:00-4:10 pm	<i>Discussion</i>
4:10-4:20 pm	<i>Break</i>
4:20-5:50 pm	Session 4: Developmental Perspective: Modeling RASopathies in Animals and in Silico Moderator: Suma Shankar, MD, PhD Goal: Discuss nonhuman model experimental systems and how they are used to study RASopathies
4:20-4:40 pm	Stanislav Shvartsman, PhD: Quantitative biology of RASopathies
4:40-5:00 pm	Ethan Perlstein, PhD (Perlara): Rare disease drug discovery using whole animal disease models
5:00-5:20 pm	Edward Stites, MD, PhD: Computational analysis of pathological Ras mutants
5:20-5:40 pm	Annette Schenck, PhD: Habituation learning in <i>Drosophila</i> - a high-throughput platform to identify drugs that ameliorate cognitive and behavioral problems in RASopathies
5:40-5:50 pm	<i>Discussion</i>
5:50-6:30 pm	<i>Break</i>
6:30-8:30 pm	Networking Dinner with Cash Bar (Crystal C)

DAY 3 – SUNDAY 7/30/17 – Crystal E

7:00-8:00 am	Breakfast Meeting: How Do You Define a RASopathy? (Crystal D)
8:00-9:30 am	Session 5: Ras Pathway Mechanics Moderator: Martin McMahon, PhD Goal: To discuss molecular mechanisms of Ras pathway signaling: How do crystal structures and dynamic imaging shed new light?
8:00-8:20 am	William Huang, PhD: Membrane signaling dynamics
8:20-8:40 am	John Albeck, PhD: Quantifying the cellular effects of Ras pathway mutations with live-cell imaging
8:40-9:00 am	Deborah Morrison, PhD: Divide and Conquer: Targeting Raf Regulatory Interactions
9:00-9:20 am	Marc Therrien, PhD: Allosteric control of RAF activation by dimerization
9:20-9:30 am	<i>Discussion/Break</i>
9:30-11:00 am	Session 6: Potential Therapeutics Moderator: David Stevenson, MD Goal: Discuss promises and challenges of Ras pathway therapeutic drug development
9:30-9:50 am	Brage Andresen, PhD, FRCPATH: Splice switching oligonucleotides (SSOs) for HRAS exon 2 skipping
9:50-10:10 am	Steven Fruchtmann, MD (Onconova Therapeutics): Rigosertib: A novel small molecule Ras Binding Domain antagonist. Can we target the untargetable?
10:10-10:30 am	Christopher Gibson, MD, PhD (Recursion Pharmaceuticals): Image-based high throughput screens for rare disease therapeutics

10:30-10:50 am	Philip Stork, MD: Penn MDBR 2016 Grantee - What can Ras-dependent cancers teach us about RASopathies?
10:50-11:00 am	<i>Discussion/ Break</i>
11:00-12:30 am	Session 7: Next Generation: Junior Investigator Poster Session Abstracts and Closing Keynote <u>Moderator:</u> Bronwyn Kerr, MBBS <u>Goal:</u> Attract and highlight research on RASopathies from junior investigators
11:00-11:30 am	Junior Investigator Poster Finalists: Four 10-minute presentations
11:30-12:20 pm	KEYNOTE: Frank McCormick, PhD, FRS: Targeting Ras and NF1-related malignancies
12:20-12:30 pm	<i>Discussion and Next Steps</i> Frank McCormick, PhD, FRS, Katherine A. Rauen, MD, PhD, Lisa Schoyer, MFA
12:30-1:30 pm	Breakout Sessions for RASopathy Family Groups: CFC and NS: Bruce Gelb, MD, and Katherine A. Rauen, MD, PhD (<i>Coral C</i>) CS: Karen Gripp, MD, David Stevenson, MD, and Bronwyn Kerr, MBBS (<i>Coral A</i>)
12:30-1:30 pm	NIH Q&A: William C. Timmer, PhD, NCI Program Director (<i>Labrid B</i>)
12:30-6:00 pm	NF Network's Post-Symposium Family Meeting (<i>Coral B</i>)
2:30-4:30 pm	RASopathy Advocacy Organizations' Meeting on Approaching Data Collecting and Sharing (<i>Labrid B</i>)
2:30-6:00 pm	Post-Symposium Events for CFC and NS families

5th International RASopathies Symposium**Speaker Abstracts****SESSION 1: WHAT DEFINES A RASOPATHY?****Moderator: Martin Zenker****Advocate/Caregiver Panel: Perspectives from the Home Front- 'Aging'****Les Rogers (CFC), Erin Hefner (CS), Bev Oberlander (NF1), Michelle Ellis (NS).**

In this session, individuals with a RASopathy and caregivers will discuss aging in the RASopathies. Specifically, they will address differences between childhood and adulthood; conditions that improve and conditions that worsen or develop with age; the greatest concerns individuals with a RASopathy and family members have about aging; and what adults with a RASopathy want researchers to know about their syndromes.

Introducing the RAS/MAP Kinase pathway

Frank McCormick. *UCSF Helen Diller Comprehensive Cancer Center, San Francisco, California and Ras Initiative, Frederick National Lab, Frederick, MD*

The RAS/MAP Kinase (MAPK) pathway is a highly-conserved signal transduction pathway that controls cell proliferation. The pathway is identical in flies, worms and mammals. The pathway connects growth factor receptors at the cell surface with transcription factors in the nucleus. The pathway is regulated by RAS proteins that act as simple binary ON/OFF switches. In resting cells, RAS proteins are kept in their off-state by proteins called GAPs, of which the NF1 protein neurofibromin is the most important. When growth factors bind to receptors, RAS proteins are turned ON, and activate a kinase cascade that begins with RAF kinases (A-RAF, B-RAF or C-RAF). RAS activates RAF kinases by direct binding and recruitment to the cell membrane. RAF kinase then activates MEK, which, in turn activates ERK. Active ERK moves into the nucleus to phosphorylate transcription factors that turn on production of proteins that drive cells through the cell cycle into S-phase.

In RASopathies, the pathway is hyper-active, causing uncontrolled cell proliferation. Activation can occur at almost any level in the pathway. In NF1 disease, loss of the NF1 protein neurofibromin leads to high levels of active RAS, even in the absence of growth factors. Neurofibromin acts in partnership with SPRED1, a protein which is mutated in Legius Syndrome. Loss of SPRED1 prevents neurofibromin from keeping RAS in the active state, again leading to high levels of active protein.

In Noonan syndrome, mutations activate the pathway by increasing signaling from receptors (SHP-2 or CBL), by activating RAS proteins directly, or by activating C-RAF kinase or proteins that regulate RAF kinase, such as SHOC2 and PPIC. In Costello Syndrome, mutations activate HRAS by making it resistant to neurofibromin. In CFC, mutations activate B-RAF or MEK kinases.

In sporadic cancers, the RAS/MAPK pathway is frequently hyper-activated, and plays a major, causal role. Almost all pancreatic cancers, half of all colorectal cancers and a third of all lung cancers are caused by mutations in KRAS alone. Loss of NF1 or SPRED1 accounts for about 10% of all cancers. Mutations in BRAF or NRAS cause most malignant melanomas, and many leukemias, lymphomas and myelomas are driven by activating mutations in the RAS/MAPK pathway.

While the spectrum of mutations that cause RASopathies and sporadic cancers are different, the molecular basis of these diseases are similar. Furthermore, drugs developed to treat sporadic cancers may have efficacy in RASopathies, and vice versa. A better understanding of the pathway in normal cells and during development, as well as in diseases caused by mis-regulation of the pathway, will lead to better therapies in the near future.

The RASopathies

Katherine A Rauen. *University of California, Davis, Department of Pediatrics, Division of Genomic Medicine, UC Davis MIND Institute, Sacramento, CA, USA*

Signal transduction pathways that are drivers in oncogenesis are also critical pathways in human development and cellular homeostasis. As an example, the Ras pathway plays an essential role in the regulation of growth, differentiation, cell cycle, cell senescence and apoptosis, all of which have been studied in the context of cancer. However, the Ras pathway is also critical to normal development. The RASopathies are a group of medical genetics syndromes that are caused by germ-line mutations in genes that encode components or regulators of the Ras/mitogen-activated protein kinase (MAPK) pathway. These components or regulators are the same that when mutated somatically can also lead to cancer. Because of the common underlying Ras/MAPK pathway activation and dysregulation, the RASopathies exhibit numerous overlapping phenotypic features, which may include craniofacial dysmorphology, cardiac malformations, cutaneous, musculoskeletal, and ocular abnormalities, neurocognitive impairment and an increased cancer risk. RASopathies can be caused by several pathogenetic mechanisms that ultimately impact or alter the normal function and regulation of the MAPK pathway. These diverse mechanisms can include functional alteration of GTPases, Ras GTPase-activating proteins, Ras guanine exchange factors, kinases, scaffolding or adaptor proteins, ubiquitin ligases, phosphatases and pathway inhibitors, again, the same mechanisms that can be altered in oncogenesis. The RASopathies represent an excellent model of study to explore the intersection of the effects of dysregulation and its consequence in both development and oncogenesis.

SESSION 2: SYNDROMIC AND SPORADIC CANCERS OF THE RAS PATHWAY

Moderator: Karen Gripp

Keynote: Preclinical studies to guide NF1 clinical trials

¹Wu, J., ¹Jousma, E., ¹Aschbacher-Smith ¹Rizvi, T.A., ¹Dunn, R.S., ²Jones, D.R., ³Cripe, T.P., ⁵Kim, M-O., ⁴Marcus, L., ⁴Dombi, E., ⁴Widemann, B. and ¹Ratner, N. ¹*Division of Exp. Hematol. and Cancer Biology, Cincinnati Children's Hospital, Cincinnati, OH;* ²*Div. of Clinical Pharmacol., Dept. of Medicine, Indiana University School of Med.;* ³*Center for Childhood Cancer and Blood Diseases, Nationwide Children's Hospital, Columbus, OH;* ⁴*Pediatric Oncology Branch, NCI, Bethesda, MD;* ⁵*Biostatistics Core, UCSF Helen Diller Family Comprehensive Cancer Center, Dept. of Epidemiology & Biostatistics, UCSF, San Francisco, CA*

Background: Neurofibromatosis type 1 (NF1) patients are predisposed to develop benign plexiform neurofibromas (PNs) that can cause substantial morbidity. Surgery, the only standard treatment, is not feasible for many tumors. The NF1 gene product accelerates Ras-GTP hydrolysis to Ras-GDP and thus functions as a potent negative regulator of Ras. We developed a genetically engineered mouse model of neurofibroma, *DhhCre;Nf1fl/fl*, for use in preclinical testing; response is monitored by MRI imaging and

volumetric analysis in conjunction with pharmacokinetic and pharmacodynamic readouts. The most effective neurofibroma therapy in this neurofibroma mouse model to date is drug candidates targeting inhibition of MEK1/2, in mouse and human (Jessen, W. et al., *J. Clin. Invest.*, 2013; Dombi et al., *New Engl. J. Med.*, 2016). However, as a single agent, MEK inhibition does not shrink all tumors and tumors regrow on drug cessation. Therefore, additional strategies are needed to target even these benign RASopathy manifestations.

Results: We have undertaken combination trials with allosteric MEK inhibitors and agents targeting other signaling pathways, including the JAK2/STAT3 pathway. We use gene expression analysis and genetic strategies to identify new targets for assessment. We establish a minimum effective dose (MED) for new agents, alone and in combination with MEK inhibition, in this mouse model and then carry out efficacy trials for 2 months. These preclinical studies are enabled by participation in a preclinical testing consortium funded by charitable contributions. Pharmacodynamics and pharmacokinetic measurements enable assessment of drug efficacy. For example, a therapeutic Stat3 antisense oligonucleotide, in combination with MEK inhibitors, caused cell death micro-environmental changes, and additional benefit in shrinking mouse neurofibromas.

Conclusions: A genetically engineered mouse model of neurofibromatosis is predictive of response to therapy in human NF1, supporting use of a drug testing platform that integrates mouse models and human trials. MEK inhibition downstream of Ras-GTP may be effective as a single agent, at low doses, to treat pediatric patients with neurofibroma (and perhaps other RASopathy manifestations) and warrants further study, but combination therapies are likely to be necessary to cure neurofibromas.

Supported by the National Institutes of Health (NINDS) and the Children's Tumor Foundation/NTAP Neurofibromatosis Therapeutic Consortium to NR.

Pediatric Sarcomas, Rhabdomyosarcoma

Corinne Linardic, MD PhD. *Duke University School of Medicine, Durham, NC*

Rhabdomyosarcoma (RMS) is a soft tissue cancer associated with the skeletal muscle lineage. There are two common variants, called embryonal and alveolar, based on their appearance under light microscopy. It is the embryonal variant that sometimes arises in children with RASopathies. Diagnosis and treatment of RMS is accomplished through multi-disciplinary management involving pediatric pathologists, oncologists, surgeons, and radiation therapists. These multidisciplinary groups are most often found at established Sarcoma Centers. While outcome for RMS has improved over the last several decades, children with high-risk disease still have a 5-year survival of less than 30%. Ongoing efforts from cooperative clinical trials groups and RMS biologists have identified specific mutations in RMS and their possible roles in the origin and progression of this cancer.

This presentation will first summarize the standard diagnosis and treatment strategies for RMS, and introduce some of the mutations known for many years to be associated with RMS including the Ras oncogenes. The presentation will conclude with a review of novel therapies being evaluated for RMS including small molecules and immunotherapy, and novel laboratory approaches including high-throughput screening and mouse models, to better understand how we can more successfully treat this cancer.

Myeloproliferative neoplasms (JMML) in RASopathies

Hélène Cavé, PharmD PhD^{1,2}, Aurélie Caye^{1,2}, PharmD, Marion Strullu, MD¹. ¹INSERM UMR_S1131, Institut Universitaire d'Hématologie, Université Paris Diderot, Paris-Sorbonne-Cité, Paris, France; ²Assistance Publique des Hôpitaux de Paris (AP-HP), Hôpital Robert Debré, Département de Génétique, Paris, France

RASopathies are autosomal dominant disorders caused by over activation of the RAS/MAPK signaling pathway. The importance of the RAS/MAPK pathway was first recognized in human oncogenesis since 20 to 30% of all tumors harbor an activating mutation in one of the RAS genes. Juvenile myelomonocytic leukemia (JMML) is considered a unique example of RAS-driven oncogenesis because it is thought to be initiated by germline or somatic RAS-activating mutations in RAS genes (*NRAS* or *KRAS*) or RAS pathway upstream regulators (*PTPN11*, *NF1* or *CBL*). This rare and severe myelodysplastic and myeloproliferative neoplasm of early childhood can be sporadic or develop in patients displaying RASopathies such as Noonan syndrome (NS), type-1 neurofibromatosis (NF1) and CBL syndrome (CBLS). In NS, JMML is preferentially associated with *PTPN11* mutations but was also described in patients with *NRAS*, *RIT1* or *RRAS* mutations. Whereas sporadic JMML is known to be aggressive, JMML occurring in patients with NS is often considered as benign and transitory. However, the study of a large cohort of 641 patients with a germline *PTPN11* mutation evidenced a more mixed picture. Hematological features of MPN were found in 36 (5.6%) patients and encompassed a broad phenotypic spectrum ranging from transient myeloproliferative neoplasm (MPN) to clinical courses similar to sporadic JMML in 20 patients (3%). Almost all patients with severe neonatal JMML were males, 60% had severe neonatal manifestations with a higher frequency of hemodynamic and/or respiratory failure related to chylothorax and heart defects, and half died in the first month of life. Two females who survived MPN/JMML subsequently developed another malignancy during childhood. Although the risk of developing MPN/JMML could not be fully predicted by the underlying *PTPN11* mutation, some germline *PTPN11* mutations were preferentially associated with myeloproliferation: 21% of patients with a mutation targeting p.Asp61 developed MPN/JMML in infancy. Patients with a p.Thr73Ile mutation also had more chances to develop MPN/JMML but with a milder clinical course.

Patients with NF1 or CBLS are also predisposed to developing JMML. JMML occurrence is then usually associated with the loss of the wild type allele in hematopoietic cells due to either deletion, point mutation or acquired uniparental isodisomy. Patients harboring the CBL mutation Y371H may be particularly prone to developing JMML. In patients with CBLS, JMML are usually mild and spontaneously regress. Bone marrow transplantation has shown no benefit and a 'wait-and-see' approach is now recommended. In contrast, NF1-associated JMML occur later in life and are associated with a very unfavorable outcome.

Genetic profiling and whole-exome sequencing of a large JMML cohort showed that somatic events were restricted to sporadic or NF1-associated JMML cases whereas almost no additional mutations were detected in patients with CBLS or NS. In line with phenotype-genotype correlations and with data obtained from iPS derived from the fibroblasts of NS patients, this observation supports a strong endogenous role for germline *PTPN11* and *CBL* mutations in the occurrence of MPN. It also suggests that parameters other than additional somatic gene mutations might support leukemogenesis. In this respect, the recent demonstration that a *PTPN11* mutation restricted to the hematopoietic microenvironment may be sufficient to induce myeloproliferation in mice is particularly interesting.

In conclusion, JMML represents the first cause of death in *PTPN11*-associated but NS but remains probably partly overlooked due to early death, comorbidities or lack of confirmatory tests. However, infants with NS- or CBLS-MPN should be managed conservatively unless refractory cytopenias, compromised vital organ functions, or an overt leukemia with blast crisis develops. We recommend that

all NS children be systematically evaluated for clinical signs of MPN (splenomegaly, hepatomegaly) and basic hematological parameters at least every three months during the first year of life and twice during the second year of life.

Clinical trial updates: NF1 plexiform neurofibromas and MPNST

Brigitte C. Widemann. *Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Neurofibromatosis type 1 (NF1) is a common (incidence 1:2,700) inherited disorder characterized by the development of peripheral nerve sheath tumors including plexiform neurofibromas (PN) and malignant peripheral nerve sheath tumors (MPNST). While PN are histologically benign they can result in substantial morbidity including pain, disfigurement and neurologic or functional deficits. Importantly, PN are at risk for transformation to MPNST with a lifetime incidence in NF1 of 15.8%. In a phase I trial we recently identified that MEK inhibition results in shrinkage in the majority of children with inoperable PN. Phase II trials for children and adults with inoperable PN are ongoing to confirm the response rate and evaluate the effect of MEK inhibition on quality of life, pain, and function. In addition, we are evaluating the effect of MEK inhibition on the growth of distinct nodular lesions (DNL). These lesions have distinct imaging characteristics, and some are atypical neurofibromas, which are precursor lesions to MPNST. Ongoing trials directed at PN and MPNST will be reviewed.

SESSION 3: HUMAN DEVELOPMENT - EFFECTS ON ORGAN SYSTEMS

Moderator: Bruce Korf

Keynote: Molecular genetics of RASopathies. Common themes and novel mechanisms in RAS signaling dysregulation. Not Presented

Marco Tartaglia, PhD. *Genetics and Rare Diseases, Ospedale Pediatrico Bambino Gesù, Rome, Italy.*
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RAS proteins are small monomeric GTPases that function as molecular switches controlling a major intracellular signaling network that, depending on the cellular context, guides diverse biological functions such as proliferation, migration, survival, cell fate determination, differentiation, and senescence. Within this network, signal flow through the RAF-MEK-ERK protein kinase pathway, the first described mitogen-associated protein kinase (MAPK) cascade, controls early and late developmental processes, including determination of morphology, organogenesis, synaptic plasticity, and growth. Signaling through the RAS-MAPK cascade is tightly controlled, and its enhanced activation has been known for decades to represent a major event in oncogenesis. Activating somatic RAS gene mutations occur in approximately 30% of human cancers, but the upregulation of this signaling pathway can also result from enhanced function of upstream signal transducers or RAS effectors, as well as from inefficient function of feedback mechanisms.

Unexpectedly, discoveries derived from a massive disease gene hunting effort performed in the last 17 years have established a novel scenario in which the upregulation of this signaling cascade underlies a group of clinically related developmental disorders, the RASopathies, sharing facial dysmorphism, cardiac defects, reduced postnatal growth, ectodermal and skeletal anomalies, variable cognitive deficits, and susceptibility to certain malignancies as major features. These disorders are caused by heterozygosity for mutations in genes encoding RAS proteins, regulators of RAS function, modulators of

RAS interaction with effectors, or downstream signal transducers. The majority of these disease genes have been identified by using a hypothesis-driven approach based on “gene candidacy”, and the collection of data on the molecular spectrum of mutations in each of these genes has allowed to appreciate the differential impact of RASopathy-causing and cancer-associated mutations on protein function and intracellular signaling. Remarkably, these discoveries have also permitted to identify novel molecular mechanisms driving dysregulated RAS signaling able to perturb certain developmental processes but that apparently do not contribute significantly to oncogenesis, as well as to recognize “common themes” in the dysregulation of RAS signaling underlying the RASopathies.

More recently, the “hypothesis-free” strategy based on the sequencing of the exome, the protein-coding portion of the genome, in trios with sporadic Noonan syndrome, the most common and clinically variable among RASopathies, has allowed to identify disease genes that are more remotely related to the RAS-MAPK signaling backbone, expanding the concept of “RASopathy gene”. Consistent with the data collected by dissecting the extent and branching of signaling dysregulation driven by RASopathy-causing mutations, these new findings further document the relevance of additional signaling pathways in disease pathogenesis in the RASopathies. Due to the differential perturbing impact elicited by individual mutations on intracellular signaling, and the high level of cross-talk with other signaling pathways, a more accurate and systematic characterization of the functional consequences of RASopathy mutations is required for the development of therapeutic interventions to efficiently restore proper intracellular signaling and ameliorate the major postnatal issues altered in RASopathies.

Cutaneous neurofibromas in Neurofibromatosis Type I: quantitative natural history study and clinical trial

Ashley Cannon, PhD, MS, CGC, Mei-Jan Chen, MD, Peng Li, PhD, Kevin P. Boyd, MD, Amy Theos, MD, David T. Redden, PhD, Bruce Korf, MD, PhD

Background: Neurofibromatosis type 1 (NF1) is a disorder characterized by a predisposition to develop multiple benign tumors, including localized cutaneous neurofibromas (cNFs) that affects >99% of adults with NF1. Previous reports have correlated increased burden of cNFs with age and pregnancy, but longitudinal data are not available to establish a quantitative natural history.

Objective: The purpose of this study was to quantify cutaneous neurofibroma number and size to establish a quantitative natural history of these lesions.

Methods: A prospective cohort analysis of 22 adults with NF1 was conducted over an 8-year period.

Results: The average monthly increase in volume for cutaneous neurofibromas was 0.37 mm³ in the back region (95% CI (0.23, 0.51), $p < 0.0001$), 0.28 mm³ in the abdominal region (95% CI (0.16, 0.41), $p < 0.0001$), and 0.21 mm³ in the arm/leg region (95% CI (0.08, 0.34), $p = 0.0022$). The number of cutaneous neurofibromas significantly increased in the back (slope=0.032, $p = 0.011$) and abdominal (slope=0.018, $p = 0.026$) regions, while the leg/arm regions retained a positive trend (slope=0.004, $p = 0.055$).

Conclusions: The number and volume of cutaneous neurofibromas significantly increased over an 8-year timespan; however, the rate of increase is variable by individual and body region. These findings may provide insight into cutaneous neurofibroma development and benefit researchers considering clinical trials targeting cutaneous neurofibromas.

From skin cells to neurons

Erika Yeh, PhD. *Postdoctoral Research Fellow • UCSF Weill Institute for Neurosciences*

Our research group has established the strong connection between RASopathies and autism. Because of the difficulty of getting brain samples for research, it has been difficult to establish a biological mechanism for autism. However, the development of the technique called iPSC (induced pluripotent stem cell) has made it possible to use specialized cell that are easy to obtain, such as skin cells, to transform into neurons, the cells that make up the brain. With the use of iPSC, our lab was able to generate neurons with *BRAF* mutation from the skin cells of 4 CFC patients. We could produce mature neurons that are functional and have spontaneous electrical activity. Moreover, we were able to establish differences in shape, activity and in the activity of key molecules in CFC neurons that can help explain the association of RASopathies and autism. In the future, we hope that we can extend this model to more RASopathies and use it to study possible therapeutical molecules.

How do astrocytes affect brain function in RASopathies?

Erik Ullian, PhD. *University of California, San Francisco, Dept. of Ophthalmology and Physiology, San Francisco, CA*

Astrocytes produce an assortment of signals that promote neuronal maturation according to a precise developmental timeline. Is this orchestrated timing and signaling altered in human neurodevelopmental disorders? To address this question, the astroglial lineage was investigated in two model systems of a developmental disorder with intellectual disability caused by mutant Harvey rat sarcoma viral oncogene homolog (HRAS) termed Costello syndrome: mutant HRAS human induced pluripotent stem cells (iPSCs) and transgenic mice. Human iPSCs derived from patients with Costello syndrome differentiated to astroglia more rapidly in vitro than those derived from wild-type cell lines with normal HRAS, exhibited hyperplasia, and also generated an abundance of extracellular matrix remodeling factors and proteoglycans. Acute treatment with a farnesyl transferase inhibitor and knockdown of the transcription factor SNAI2 reduced expression of several proteoglycans in Costello syndrome iPSC-derived astrocytes. Similarly, mice in which mutant HRAS was expressed selectively in astrocytes exhibited experience-independent increased accumulation of perineuronal net proteoglycans in cortex, as well as increased parvalbumin expression in interneurons, when compared to wild-type mice. Our data indicate that astrocytes expressing mutant HRAS dysregulate cortical maturation during development as shown by abnormal extracellular matrix remodeling and implicate excessive astrocyte-to-neuron signaling as a possible drug target for treating mental impairment and enhancing neuroplasticity.

Pain in RASopathies

Giuseppe Zampino, MD. *Center for Rare Diseases and Birth Defects, Department for the Health of the Woman and the Child, Università Cattolica del Sacro Cuore, Rome, Italy*

Pain in RASopathies is an underreported clinical problem that, based on our continuing observations, considerably affects the quality of life both in pediatric and adult patients. Anecdotal reports about individuals with RASopathies experiencing joint and neuropathic pain have been published; however, an objective and comprehensive evaluation of pain in RASopathies is still lacking.

To better understand the etiology, pathophysiology, distribution and characteristics of “pain” in RASopathies, we performed an observational study on a cohort of subjects with molecularly confirmed

RASopathies on regular follow up at the Center for Rare Diseases and Birth Defects, Fondazione Policlinico Universitario “A. Gemelli”, Rome, by applying the following study protocol:

- Assessment of patients’ muscle-skeletal abnormalities, brain or spine structural impairments, and gastro-intestinal abnormalities;
- Administration of standardized pain questionnaires filled in by parents/caregivers/physicians to screen the presence of and characterize acute and/or chronic pain;
- Examination of nociceptive pathways profiling by laser evoked potentials (LEPs) analysis;
- Evaluation of the influence of pain on quality of life and sleep patterns using quality of life (QoL) questionnaires and questionnaires of sleep disturbances.

Between April 2016 and March 2017, 67 patients with molecularly confirmed diagnosis of Noonan syndrome (NS), Costello syndrome (CS) and cardiofaciocutaneous syndrome (CFCS) were enrolled in the study (age range: 0.85-32 years; average age \pm SD: 12.15 \pm 7.94 years). Past medical history of each patient was reviewed. According to patients’ IQ and adaptive behavior profiles, dedicated standardized questionnaires were administered to screen the presence of acute/chronic pain, its localization (when possible), sleep disturbances and QoL. Questionnaires were filled in by patients when possible or by parents/clinicians.

The survey documented that pain in RASopathies is an underreported and relevant clinical problem. Chronic pain was documented in more than half cohort of individuals (55% of subjects in the whole cohort) with comparable high prevalence among disorders (CS 68%, CFCS 55%, NS 45%), even though it was documented more frequently in CFCS and less commonly in NS.

Of all the patients who were diagnosed with chronic pain, 58% was able to provide an accurate report of pain localization, which was represented by osteo-articular pain in most cases. Higher prevalence of muscle-skeletal anomalies, osteopenia/osteoporosis, abdominal pain, aerophagia, constipation as well as increased frequency of previous surgical interventions was also recorded.

We were able to define Pain Intensity Scores in 21 patients through a qualitative-pain-describing-questionnaire “Neuropathic Pain Symptom Inventory” (average score = 13.3 \pm 10.34, on a scale from 0 to 100) and in 17 patients through a quantitative-pain-describing-questionnaire “Brief Pain Inventory” (average score = 3.31 \pm 2.57, on a scale from 0 to 10). These findings document a relevant impact of pain in the quality of life of patients.

No statistically significant difference in respect to sleep disturbances was documented between subjects subgrouped according to the presence of chronic pain ($p = 0.16$).

The performance of the LEPs study in 19 patients excluded the possibility that their pain is a consequence of peripheral nociceptive pathways’ injury. Because of an up-going trend in the results of one of the LEPs parameters representing the central re-elaboration of a painful stimulus, we speculate that perception of pain in patients with RASopathies can be the result, in part, of an altered modulation and elaboration of the painful stimulus at a central level, and possibly related to the concept of “pain memory”.

In conclusion, pain negatively affects the quality of life of patients with RASopathies, and represents an important complication that requires an accurate characterization in order to personalize pharmacological and/or non-pharmacological (*e.g.*, psychological) programs to improve patients’ everyday life and reduce parents’ stress, as the administration of such therapies in some of our more serious patients proved.

Modeling Cardiovascular Involvement in the RASopathies

Rebecca Josowitz, Nelson Rodriguez, Sonia Mulero-Navarro, Angelika Nitzl, Céline Guichard, Jared Gatto, Tirtha Das, Rupa Mirmira, Ross Cagan, Bruce D. Gelb. *Icahn School of Medicine, New York, NY*

Cardiovascular involvement is prevalent among individuals with the RASopathies. Broadly, these comprise three types: congenital heart defects (CHD), atrial arrhythmias, and hypertrophic cardiomyopathy (HCM). While conventional therapeutic approaches are largely efficacious for CHD, effective therapy for the arrhythmias can be challenging and HCM treatment is primarily directed at symptoms. Moreover, RASopathy-associated HCM is life-threatening in a fraction of affected infants. Thus, there is a need for a better understanding of the pathogenesis of these cardiac problems and for the development of novel therapeutics to address them.

In this presentation, the ongoing research effort in the Gelb group to model RASopathy-associated cardiovascular disease using human induced pluripotent stem cells (iPSCs) and transgenic *Drosophila melanogaster*. To date, we have been able to recapitulate features of atrial arrhythmias and HCM *in vitro* using the human iPSCs. For the latter, we have identified both cell autonomous and cell non-autonomous effects. Using transgenic models of mutations associated positively and negatively with HCM, we have observed remarkably diverse phenotypic effects. Our drug discovery efforts have identified novel compounds with efficacy in rescuing early and later fly developmental abnormalities as well as for normalizing of Erk activation.

Advanced imaging and interventions of the lymphatic system

Maxim Itkin MD, FSIR. *Associate Professor of Radiology and Pediatrics, Director of CHOP/HUP Center for Lymphatic Imaging and Interventions, University of Pennsylvania Medical Center, Children's Hospital of Philadelphia*

Patients with Noonan syndrome are known to have a malformation of their central lymphatic system. However, the exact anatomy has been difficult to understand due to a lack of lymphatic imaging. Imaging of the central lymphatic system (cisterna chyli and thoracic duct) is challenging due to the difficulty of introducing imaging contrast agents. The recent development of lymphatic imaging techniques, such as dynamic contrast enhanced MR lymphangiography (DCMRL) and Intranodal Lymphangiography (IL), allowed new insight into the anatomy and pathology of the central lymphatic system. Both techniques utilize injection of contrast material into the inguinal lymph nodes using ultrasound guidance. DCMRL and IL allowed discovery of the causes of diseases such as plastic bronchitis, neonatal chylothorax, and pulmonary lymphatic dysplasia. IL also provides excellent imaging guidance for lymphatic interventions.

Over the last 4 years we were able to perform DCMRL and IL in 6 neonates (average 5 months, F/M=3/4) and one adult (M, 50yo) patient with Noonan syndrome. Six patients presented with symptoms of chylothorax and one with diffuse body edema. DCMRL was performed in 5 patients and IL in 6 patients. In all patients, lymphatic imaging demonstrated significant central lymphatic abnormalities, such as absence of the central lymphatic system, multiple thoracic ducts, pulmonary lymphatic flow from the central thoracic duct and dermal back flow. In four patients, intranodal lipiodol injection or embolization of the thoracic duct resulted in resolution of the symptoms.

In conclusion, advanced lymphatic imaging and interventions in patients with Noonan can allow a better understanding of the clinical course of patients with Noonan disease and provide guidance for the interventional treatment.

Using inducible pluripotent stem cells to delineate the molecular mechanisms that cause gastrointestinal difficulties in RASopathy patients

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RASopathies are a group of rare genetic disorders caused by mutations in the Ras-MAPK signaling cascade. While individually rare, collectively, this group of diseases is considered one of the most common types of congenital disorders worldwide. The nonreceptor tyrosine phosphatase SHP2 is a critical component of the Ras-MAPK pathway, serving as a positive regulator to induce activation of downstream signaling. Mutations in SHP2 are pathogenic, causing both Noonan Syndrome (NS, ~50%) and Noonan Syndrome with Multiple Lentigines (NSML, formerly LEOPARD, ~90%) RASopathy disorders. Intriguingly, though NS and NSML patients have similar clinical characteristics, including developmental delays, cardiac abnormalities, and gastrointestinal difficulties, individual mutations in each disorder are unique, resulting in opposing catalytic functions of SHP2; whereas NS mutations in SHP2 are gain-of-function, NSML-associated SHP2 mutations are loss-of-function and behave as dominant negatives. In mice, deletion of SHP2 specifically in the intestine and colon was recently found to affect the development of secretory lineages, disrupting goblet and paneth cell differentiation; however, SHP2 mediated molecular mechanisms that mediate these defects remained poorly understood. Here, we investigated the molecular effects of SHP2 on gastrointestinal abnormalities using human inducible pluripotent stem cells (iPSCs) derived from patients with various mutations in SHP2. Our data suggest that NS mutants have increased proliferation, but generate smaller goblet cells that produce less MUCIN, the secretory protein important for mucosal barrier protection. In contrast, NSML mutants proliferate slower, but have hyperplastic and enlarged goblet cells that express increased levels of MUCIN in both iPSC-derived intestinal organoids and in colon from NSML mutant mice. These data suggest that phosphatase activity is essential for goblet cell fate determination and mucin production. Concomitantly, we also found that expression of the paneth cell marker LYSOSYME is ectopically upregulated in both NS and NSML iPSC-derived organoids, suggesting that differentiation of these cells, in contrast to goblet cell regulation, is phosphatase-independent. Taken together, our data suggest that SHP2 is an important regulator of secretory function in the intestine, mediating both phosphatase-dependent (goblet cells) as well as –independent (paneth cells) signaling mechanisms.

SESSION 4: DEVELOPMENTAL PERSPECTIVE - MODELING RASOPATHIES IN ANIMALS AND IN SILICO

Moderator: Suma Shankar

Quantitative studies of the Ras pathway mutations from human diseases

Stanislav Y. Shvartsman, Princeton University

Mutations in the Ras/ERK signaling pathway components are associated with both developmental abnormalities and cancers. This pathway has been studied for over two decades since the cloning of individual components, but our understanding of the mechanisms of the Ras-dependent diseases is far from complete, mainly because of the lack of suitable approaches for characterizing the effects of genetic perturbations *in vivo*. We are using the terminal patterning of the *Drosophila* embryo as a

powerful model for this purpose, focusing on the activating mutations in MEK1. Terminal patterning is initiated during the second hour of development, when the Ras pathway specifies the head and tail structures of the embryo. This stage is ideal for quantifying the effects of genetic perturbations of Ras signaling. Surprisingly, our analysis of a panel of activating mutations in MEK1 revealed that they lead to strong loss of function effects, manifested by significant reductions of the ERK phosphorylation at the poles and partial loss of the terminal structures. We propose that these effects result from a negative feedback loop, which is triggered by mutation-dependent, precocious activation of the Ras pathway and desensitizes cells to future endogenous signals. We are testing this model using transcriptional profiling studies and experiments with loss of function perturbations of the candidate feedback regulators.

Rare disease drug discovery using whole animal disease models

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Most drug discovery efforts involve human cell-based phenotypic screens or *in vitro* target-based screens. While model organisms are routinely used in investigations of basic biology they remain largely absent or under-utilized in drug discovery, especially rare genetic (monogenic) disease drug discovery. We initially focused on lysosomal diseases, which are well suited to invertebrate models because causal disease genes and pathophysiological cascades are evolutionarily conserved. Here we show that a primary drug screen for novel chemical matter that rescue the delayed onset of adulthood of a nematode model of Niemann-Pick Type C (NPC) followed by hit validation studies in NPC patient fibroblasts yielded in less than a year an orally bioavailable, brain-penetrant and well-tolerated un-optimized primary screening hit called PERL101. A pilot efficacy study of PERL101 in a NPC1 KO mouse model showed improvement of liver biomarkers. Mechanism-of-action studies reveal that PERL101 increases cholesterol and ceramide bioavailability while reducing the accumulation of sphingomyelin. Target identification is currently underway using RNAseq, lipidomics and pooled CRISPR knockout library approaches. We also present assay development and drug repurposing data for nematode, fly and patient cell models of the other diseases currently in our pipeline, including NGLY1 Deficiency, Mucopolidosis IV, Niemann-Pick Type A, Gaucher, and PMM2-CDG.

Computational Analysis of RASopathy RAS Mutants

Ed Stites, MD, PhD. *Salk Institute for Biological Studies, La Jolla, CA*

Germline mutations to the *RAS* genes play important roles in several of the RASopathies. Somatic mutations to the *RAS* genes play important roles in many different types of cancer. The mutant RAS proteins found in both types of disease tend to promote increased RAS signaling, and this increased signaling is believed to underlie the pathology of these diseases. Over the past three plus decades, extensive research has characterized the mechanisms that regulate RAS signaling. Additional research has revealed that disease promoting mutations disrupt the normal regulation of RAS with the consequence of increased RAS signaling. RAS signal regulation is now known to involve multiple, nonlinear, processes, each characterized by multiple parameters, and several processes may be perturbed by a single disease promoting mutation. This complexity makes it difficult to mentally link measured biochemical changes with observed signaling changes. To address this problem, I have previously developed a mathematical model of the multiple processes that regulate RAS signaling. The model has been applied to oncogenic RAS mutants and has resulted in multiple non-obvious predictions about how RAS mutants promote pathological signaling that have been prospectively validated experimentally. Here, I discuss the extension of the model to the biochemically characterized

RASopathy RAS mutants. Analysis of the model leads to several new insights into the relationship between RAS mutations and RASopathy disease phenotypes. The model may be a valuable tool for addressing problems in RASopathy drug development and patient response, and it is now demonstrating these capabilities with anti-cancer agents. The modeling approach should be extensible to other genes in the RAS pathway associated with RASopathies; as more biochemical data on these proteins become available, it should be possible to perform similar analyses on these other mutants. At the present, the model also applies well to neurofibromin and reproduces patterns of RAS signaling seen in neurofibromatosis patients.

Habituation learning in *Drosophila* - a high-throughput platform to identify drugs that ameliorate cognitive and behavioral problems in RASopathies

Michaela Fenckova¹, L. Asztalos², P. Cizek³, E.L. Singgih¹, L.E.R. Blok¹, C. Zweier⁴, Sarah Lippé⁵, E.E. Eichler⁶, R.A. Bernier⁷, Z. Asztalos², and A. Schenck¹. ¹Dept Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center (Radboud umc), Nijmegen, NL; ²Aktogen Ltd., Dept Genetics, University of Cambridge, Cambridge, UK; ³CMBI, Radboud Institute for Molecular Life Sciences, Radboud umc, Nijmegen, NL; ⁴Inst Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; ⁵Departement de Psychologie & Research Center of the CHU Ste-Justine Mother and Child University Hospital Center, Université de Montreal, Quebec, Canada; ⁶Dept Genome Sciences, University of Washington School of Medicine & HHMI, University of Washington, Seattle, USA; ⁷Dept of Psychiatry and Behavioral Sciences, University of Washington, Seattle, USA

Habituation, the ability to suppress a reaction to repeated nonthreatening stimuli, is one of the most ancient and fundamental forms of learning. It serves as a neuronal mechanism to filter out irrelevant information and represents a prerequisite for higher-order cognitive functioning. Defects in habituation learning have been reported in a number of cognitive and behavioral disorders, including autism spectrum disorder (ASD) but the underlying genetics remain poorly understood. To determine the genetic basis of habituation and its relevance for human disease, we use genes implicated in human cognitive disorders as a window and high-throughput light-off jump habituation in the fruit fly *Drosophila*, a powerful genetic model organism, as a readout.

In our work, we identified orthologs of >100 genes implicated in intellectual disability (ID) that control habituation learning in *Drosophila*. These genes characterize ID disorders with co-morbid autism spectrum disorder (ASD), and highlight specific ASD related behavioral anomalies. They converge on increased Ras-MAPK signaling, the molecular mechanism underlying cognitive impairments in NF1 and other RASopathies. Habituation defects in RASopathy *Drosophila* models originate from loss of NF1 in inhibitory, GABAergic neurons, resembling the GABAergic origin of learning defects in the NF1 mouse model (Costa et al. 2002, Nature). In addition to Ras-MAPK signaling, also the recently identified NF1 downstream effector HCN1, a promising target for therapeutic intervention, is associated with defective habituation. Stimulating HCN1 by its agonist, lamotrigine partially corrected habituation defects in NF1 *Drosophila* models in adulthood.

Our work shows that habituation is a suitable readout to study cognitive deficits associated with RASopathies and other intellectual disability and autism spectrum disorders. The unique advantage of *Drosophila* light-off jump habituation is the high efficiency of the assay that allows us to test scientific hypotheses and drugs in high-throughput. We already found that lamotrigine, the agonist of the recently identified NF1 downstream effector HCN1 (Omrani et al. 2015, Mol Psychiatry), partially corrected habituation defects of the NF1 *Drosophila* model. We aim at unbiased drug screening and systematic testing of the identified beneficial drugs in RASopathy models.

Based on the fundamental importance of habituation and the results of our work in *Drosophila*, we propose that defective habituation is a key mechanism underlying cognitive and behavioral problems in RASopathy and many other cognitive disorders. To facilitate translation of drugs identified in *Drosophila* to the clinic, we also aim to implement highly similar, objective and quantitative habituation paradigms as outcome measures for clinical trials. Together, this work can open completely new avenues for improved translational research and treatment of cognitive and behavioral deficits in NF1 and other RASopathies.

SESSION 5: RAS PATHWAY MECHANICS

Moderator: Martin McMahon

Membrane signaling dynamics – the molecular timing of Ras activation by SOS

William Y.C. Huang, PhD, Jay Groves, PhD. *Department of Chemistry, UC Berkeley*

Many signaling proteins are autoinhibited in the cytosol and only activate upon membrane recruitment. Release of autoinhibition generally involves structural rearrangements of the protein at the membrane surfaces that introduce a time lag between initial recruitment and activation. Both the mean and distribution of the activation lag times play critical roles in enabling regulatory processes such as kinetic proofreading. We develop a single-molecule assay to temporally resolve the activation process of the Ras guanine nucleotide exchange factor SOS on membrane surfaces. Simultaneous imaging of individual SOS molecules and localized Ras activation on supported membrane microarrays maps the activation timing resulting from receptor-mediated membrane recruitment of SOS. The gamma-like shape of the activation time distribution reveals rate-limiting kinetic intermediates in the release of autoinhibition and establishes a basis for kinetic proofreading in the activation of Ras. Once activated, a single SOS molecule is highly processive, capable of activating hundreds of Ras molecules. Together, these results suggest that the timing of Ras activation on membranes can play a central role in signal transduction.

Quantifying the cellular effects of Ras pathway mutations with live-cell imaging

Michael Pargett¹, Taryn E. Gillies¹, Jillian Silva², Breanne Sparta¹, Carolyn K. Teragawa¹, Marta Minguet¹, Alexander E. Davies¹, Katherine A. Rauen³, Frank McCormick², and John G. Albeck¹.

¹*Department of Molecular and Cellular Biology, University of California, Davis;* ²*Helen Diller Comprehensive Cancer Center, University of California, San Francisco;* ³*MIND Institute and Department of Pediatrics, University of California, Davis*

The Ras/ERK pathway is the main signaling network controlling cell proliferation, migration, and differentiation. Proper function of this pathway is essential for human development and homeostasis. Hereditary mutations affecting this network result in the RASopathy syndromes, which include symptoms of cardiac malformations and increased risk of cancer. A major unanswered question is what differentiates normal from pathological Ras/ERK signaling. It is known that the dynamic patterns of ERK and Akt activity – including the strength, frequency, and duration of their activation – are essential for proper signaling. However, the standard methods for measuring these activities lack the single-cell precision needed to resolve essential details. In our research, we use live-cell imaging, which allows continuous monitoring of thousands of cells simultaneously, to collect data on mutant-driven ERK and Akt signaling that is far more accurate and detailed than was previously available. We are using this

imaging platform to compare the changes in ERK and Akt signaling resulting from disease-causing mutations at the single cell level. To quantify signaling differences induced by Ras mutations, we are using a cell culture model system in which only single isoforms of Ras are expressed, allowing for unambiguous measurement of kinetics. In parallel, we are quantifying the changes in signaling dynamics induced by different pharmacological inhibitors of the pathway, with a focus on making measurements in increasingly physiologically realistic cell systems. Finally, we are using CRISPR-based reporters of gene expression to develop quantitative models of how ERK pathway dynamics control gene expression output. We anticipate several practical outcomes from this work. First, it will reveal the quantitative limits of signal behavior that are compatible with normal cellular and tissue function, allowing us to understand how Ras pathway mutations lead to disease, and why some mutations are more severe than others. Secondly, it will allow us to make rational choices about which drugs to give to patients with different mutations, so that treatment can be personalized to best normalize each individual's specific signaling patterns. Finally, it will result in a mathematical model of the link between kinase activity and downstream gene expression programs that will allow us to better understand developmental programs and engineer desired cellular responses using existing drugs that target kinase activity.

Divide and Conquer: Targeting Raf Regulatory Interactions **Not Presented**

Deborah K. Morrison. *Laboratory of Cell and Developmental Signaling, National Cancer Institute, Frederick, MD*

Raf kinases are essential for normal Ras-Raf-MEK-ERK pathway signaling, and activating mutations in components of this pathway are associated with a variety of human cancers as well as the related developmental disorders known collectively as the RASopathies. Of the core pathway components, the mechanisms that modulate the Raf family kinases are by far the most complex, involving changes in subcellular localization, protein interactions, and phosphorylation/dephosphorylation events. In addition, like numerous other protein kinases, the Raf kinases can form dimers. Functional studies investigating the importance of Raf dimerization have revealed that Raf dimer formation is required for normal Ras-dependent Raf activation and for the biological activity of many disease-associated Raf mutants. At the meeting, I will present recent work examining the regulatory differences among Raf family members and how these differences contribute to Raf-mediated disease signaling. I will also discuss the effect that various therapeutic agents have on Raf regulatory interactions as well as new approaches to disrupt Ras-Raf-MEK-ERK pathway signaling.

Allosteric control of RAF activation by dimerization

Hugo Lavoie¹, Malha Sahmi¹, Pierre Maisonneuve², Sara Marullo¹, Ting Jin¹, Neroshan Thevakumaran^{2,3}, Frank Sicheri^{2,3,4}, and Marc Therrien^{1,5}. *¹Institute for Research in Immunology and Cancer, University of Montreal, Canada; ²Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada; ³Department of Biochemistry, University of Toronto, Canada; ⁴Department of Molecular Genetics, University of Toronto, Canada; ⁵Department of Pathology and Cell Biology, University of Montreal, Canada*

RAF family kinases are major proto-oncogenes that channel Ras signals through the ERK pathway. Their unbridled activity is closely associated to cancer onset as well as to various RASopathies. RAF enzymes are maintained autoinhibited in quiescent cells owing to an intramolecular interaction between their N-terminal regulatory region (NTR) and kinase domain. In addition to Ras-GTP binding to the Ras-binding domain (RBD) located in the NTR of RAF isoforms, dimerization of their kinase domain has emerged as a central step underlying Ras-mediated RAF activation. This event has been shown to be part of a

mechanism by which current RAF inhibitors paradoxically induce ERK signaling. We previously showed that this latter phenomenon is caused by the ability of ATP competitors to stabilize a close/active-like conformation of the kinase domain, which is conducive to dimerization and thereby allosterically activates the opposite drug-free protomer. In parallel to this work we investigated the mechanism by which the RAF-like pseudokinase KSR1 promotes BRAF catalytic activity. We discovered that MEK binding to KSR1 selectively induces BRAF-KSR1 heterodimerization. Interestingly, this event allows BRAF to phosphorylate MEK molecules not bound to KSR1. Moreover, in addition to kinase domain contacts, we found that BRAF-KSR1 complexes assemble through selective contacts between their NTRs. Unexpectedly, NTR interactions are induced not only by Ras, but also by MEK binding to the kinase domain of KSR1. Together, it appears that Ras and MEK collaborate to impinge on the conformation of BRAF and KSR proteins, which in turn drive BRAF-KSR1 dimerization and BRAF transactivation. Moreover, our findings indicate that KSR proteins are not mere scaffolding proteins as frequently portrayed, but act instead as MEK-dependent allosteric RAF activators.

SESSION 6: POTENTIAL THERAPEUTICS

Moderator: David Stevenson

Splice switching oligonucleotides (SSOs) for *HRAS* exon 2 skipping

Brage Storstein Andresen. *Department of Biochemistry and Molecular Biology and the Villum Center for Bioanalytical Sciences, University of Southern Denmark, Odense M, Denmark*

The RAS genes (*HRAS*, *NRAS* and *KRAS*) encode small GTPases, which are crucial for proliferation, growth and survival of cells. Aberrant regulation of RAS in somatic cells usually leads to cancer, whereas germline mutations lead to severe congenital syndromes. Approximately 30% of all cancers harbor activating Ras mutations which affect the codons for glycine 12 or 13 of exon 2 and result in a constitutively active Ras protein.

We have previously reported that a particular mutation, c.35_36GC>TG (p.Gly12Val) in a patient with Costello syndrome (CS) causes a milder form of CS due to exon 2 skipping. Employing our *HRAS*, *NRAS* and *KRAS* minigenes, we show that exon 2 is weakly defined in all three RAS genes. *HRAS* exon 2 has the weakest exon 2, due to an intrinsically weak 3' splice site, in particular due to the presence of a GGG triplet which functions as an intronic hnRNP/H binding splicing silencer. Therefore inclusion of *HRAS* exon 2 into the mRNA depends on a finely tuned balance between exonic splicing enhancer elements (ESE) and exonic splicing silencer (ESS) elements. Blocking the accessibility of splicing regulatory proteins to essential splicing regulatory sequences (SREs) in *HRAS* exon 2, would result in exon 2 skipping and consequently translation of little or none oncogenic mutant protein.

We have identified and characterized important SREs in *HRAS* exon 2, which could be targeted by Splice Switching Oligonucleotides (SSO) to promote exon skipping. We performed a SSO walk covering the entire exon 2 and employed *HRAS* minigenes with serial deletions. Using this approach we identified a new SRE region and confirmed the importance of the previously identified ESE located in codon 12 and 13. Using RNA-affinity purification we have investigated binding of splicing regulatory proteins to the new SRE.

Based on the localization of the essential SREs, we have designed new SSOs, which successfully mediate exon 2 skipping in T24 bladder cancer cells harboring the p.G12V mutation. The SSO induced exclusion of *HRAS* exon 2 disrupts HRAS protein function and causes a decrease in proliferation and/or cell death. To obtain more efficient exon skipping, we further improved the SSOs by attaching a nucleotide tail

containing exon splicing silencer (ESS) motifs, shown to inhibit *HRAS* exon 2 inclusion. This ESS motif recruits the splicing inhibitory factors hnRNP F/H thereby further increasing the level of exon 2 skipping. We hope that our SSO based approach can be further developed into a future potential therapy for CS and cancer.

Rigosertib: A novel small molecule Ras Binding Domain antagonist. Can we target the untargetable?

Steven M. Fruchtman, M.D., *Chief Medical Officer, Sr VP; Research and Development, Onconova Therapeutics, Newtown, PA 18940*

Design of small molecules that disrupt protein-protein interactions, including the interaction of RAS proteins and their effectors, may provide chemical probes and therapeutic agents. The majority of human cancers exhibit aberrant signaling of the small G protein Ras. This can occur through Ras point mutations, which are oncogenic drivers in 20-30% of human cancers, or through mutations in upstream or downstream signaling molecules. Somatic mutations in Ras are the most common genetic abnormalities found in human cancers. Mutations of Ras are also a common link of the RASopathies.

MDS is a neoplastic disease of the marrow associated with a multitude of genomic abnormalities, frequently including those of Ras or Ras effector proteins. MDS leads to marrow dysfunction as manifested in the peripheral blood by cytopenias; and a significant incidence of transformation to acute myeloid leukemia. For higher risk adult MDS (HR-MDS) patients the standard of care is hypomethylating agents (HMA); either azacitidine or decitabine. Azacitidine is also being investigated in patients with JMML. Clinical trials are underway with rigosertib as a single intravenous agent in adult HR-MDS and as an oral agent in combination with azacitidine with the goal of improving marrow function and overall survival. Ongoing studies in HMA refractory HR-MDS and HMA de novo HR-MDS will be presented.

Imaged-based high throughput screens for rare disease therapeutics

Christopher Gibson, MD, PhD. *Recursion Pharmaceuticals, Salt Lake City, UT*

The complex molecular biology of many rare diseases is poorly understood, making traditional target-based drug discovery approaches difficult. Target agnostic approaches, which circumvent the lack of molecular understanding, may be a useful alternative strategy. A number of target-agnostic approaches will be discussed, along with a detailed discussion of work being done at Recursion Pharmaceuticals to use complex and subtle signatures at the level of individual cells as the basis for broad drug discovery approaches.

What can Ras-dependent cancers teach us about RASopathies?

Philip J. S. Stork and Maho Takahashi. *Vollum Institute, Oregon Health & Science University, Portland OR*

RASopathies are a set of genetic disorders associated with overlapping constellations of symptoms including craniofacial, cardiac, cognitive, and other developmental abnormalities. Despite their diversity, nearly all RASopathies are caused by hyperactive signaling through the small GTPase Ras and its downstream effectors, the kinases Raf, MEK, and ERK. Our understanding of these pathological signaling pathways has been informed by the larger experience of studying Ras-mutant cancers. An emerging model in the cancer field is that Ras-mutant cancers require dimerization of the Ras effector C-Raf, either as C-Raf homodimers or C-Raf/B-Raf heterodimers, to achieve constitutive activation of the MAP

kinase cascade. Using pancreatic cancer cell lines and their oncogenic Ras mutations, we will present data that support a model that Ras-dependent dimerization of Raf is enhanced by a specific phosphorylation on C-Raf itself, on tyrosine 341 (Y341). Phosphorylation of Y341 occurs within the N-terminal acidic region (NtA or N-region) within the kinase domain of C-Raf. In contrast, a second well-characterized phosphorylation in this region (on S338) does not appear to regulate dimerization.

Y341 phosphorylation in Ras-mutant cancer cells can be triggered by the tyrosine kinase Src (and related Src family kinases) and can be blocked by Src inhibitors, such as dasatinib and PP2. These inhibitors also block the constitutive C-Raf/B-Raf dimerization, the basal levels of ERK activation, and ERK-dependent cell growth that characterize these cells. Constitutive dimerization of C-Raf will likely also be required for the elevated Ras-dependent signaling seen in many RASopathies. We will discuss the possibility that a subset of all RASopathies may require Y341 phosphorylation for C-Raf dimerization. If so, this would suggest that the kinase(s) mediating C-Raf Y341 phosphorylation may represent a potential therapeutic target in this subset.

SESSION 7: NEXT GENERATION: JUNIOR INVESTIGATORS AND CLOSING KEYNOTE

Moderator: Bronwyn Kerr

Junior Investigator Poster Abstracts Selected for Oral Presentation

See pages 23-26.

Keynote: Targeting RAS and NF1-related malignancies

Frank McCormick, *UCSF Helen Diller Comprehensive Cancer Center, San Francisco, California and Ras Initiative, Frederick National Lab, Frederick, MD*

RAS proteins play a major role in human cancer, causing about one million deaths/year. Ras-driven cancers are refractory to most therapeutic protocols and present a major unmet clinical need. RASopathies, including NF1, affect more than 300,000 in the US alone and represent a major clinical need with few effective therapeutic options.

Targeting RAS proteins themselves presents a technical challenge: these proteins do not possess deep pockets to which small molecules could bind, and are highly conserved and are essential to normal cell function. Nevertheless, progress has been made in identifying small molecules that bind, either by taking advantage of covalent binding, that off-sets the need for high-affinity non-covalent binding, or using biophysical techniques that detect low-affinity interactions. Of these, NMR-based fragment discovery has been the most widely used, but recently, we have used a new technique called Second Harmonic Generation to identify novel Ras-binders. Results of this approach will be presented.

The covalent-binding approach has been used most successfully by Shokat and colleagues, who identified compounds that bind to the cysteine residue on G12C mutant K-Ras, a major contributor to lung adenocarcinoma. We have used a similar approach to attack C185 on KRAS 4B, the site at which KRAS 4B is farnesylated. We have identified small molecules that bind to KRAS and block farnesylation by covalent reaction with this cysteine. These compounds are active in cells and may represent a new class of anti-KRAS compounds. In addition, we have identified residues specific to KRAS, not HRAS or NRAS, that could be targeted therapeutically.

While targeting RAS proteins directly has been challenging, tremendous progress has been made in developing drugs that target downstream pathways, especially the MAPK pathway. Clinical success has been achieved in NF-deficient tumors, a remarkable achievement, but this approach has not yet been successful in tumors driven by mutant RAS. I will summarize these efforts briefly. RAS proteins activate additional pathways, and turn on expression of the cytokine LIF, a stem-cell factor in the IL6 family. Targeting LIF has therapeutic potential, using antibodies that neutralize LIF or block its receptor.

Other approaches to targeting Ras-driven malignancies include unbiased synthetic lethal approaches aimed at finding genes that RAS depends on, whether they are in the direct RAS pathway or not, and immunotherapy based efforts. These will also be summarized.

5th International RASopathies Symposium

Junior Investigator Abstracts

*selected for oral presentation

*** *RASA3* as a novel candidate for RASopathy spectrum disorders**

Hauer, NN.¹, De Luca, A.², Mayer, C.¹, Uebe, S.¹, Ekici, AB.¹, Zenker, M.³, Reis, A.¹, Thiel, CT.¹ *¹Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; ²Mendel Laboratory, Casa Sollievo della Sofferenza Hospital, IRCCS, San Giovanni Rotondo, Rome, Italy; ³Institute of Human Genetics Otto-von-Guericke University Magdeburg, Magdeburg, Germany*

We set up a cohort of 565 patients with short stature and performed systematic phenotyping. Targeted diagnostic evaluation revealed a diagnostic yield of 14 %. In a representative study group of 200 yet unsolved cases, exome sequencing enabled a diagnosis in additional 17 % of the patients. In the remaining patients, by thorough candidate gene characterization we identified *RASA3* as one outstanding candidate gene. In this gene 2 of the 200 patients showed de novo pathogenic and likely pathogenic variants. One patient carried a frameshift variant p.(Asp298Ilefs*10) resulting in a preterminal stop codon (ExAC-frequency: 3.318×10^{-5}). She presented with a height of -2.2 SD, a barrel-shaped chest and café au lait spots. An additional missense variant p.(Val85Ala) (absent from ExAC; CADD = 17.57) was identified in one further patient. Her height was -3.2 SD prior to growth hormone treatment, which ameliorated to -1.1 SD after 2 years of treatment. She also presented with a barrel-shaped chest in addition to a mild syndactyly of the toes. As other Ras GTPase activating proteins were reported to cause diseases of the RASopathy spectrum, we also consider that the functional disruption of *RASA3* in our patients might cause a reduced inactivation of RAS resulting in RAS hyperactivation and consequently lead to the observed phenotype in these patients. Functional protein analysis of CRISPR-Cas9 edited cell lines to confirm this hypothesis as well as screening of further patients with suggestive phenotypes for *RASA3* mutations are ongoing.

*** Brain Morphometry in Noonan Syndrome**

Alexandra Ishak B.S.¹, Emily Madison Johnson B.A.¹, Allan L. Reiss M.D.^{1,2}, Tamar Green M.D.¹ *¹Division of Interdisciplinary Brain Sciences, Stanford University; ²Department of Radiology and Pediatrics, Stanford University*

Introduction: The Ras/MAPK pathway is central for brain development and function. In children, genetic mutations affecting the Ras/MAPK pathway lead to multiple disorders with cognitive-behavioral phenotypes, collectively termed “RASopathies” (e.g. Noonan syndrome, neurofibromatosis 1, Costello syndrome). As a collection of conditions, RASopathies are common genetic disorders (1:1000), and Noonan syndrome (NS) is the most common of these conditions (1:2000), even more so than neurofibromatosis 1 (1:3000). There is strong empirical support that NS affects cognition and behavior, particularly increasing risk for behaviors associated with ADHD, and cognitive impairments in executive function and memory. Further, data collected from animal models of NS show significant effects on brain development, brain function and behavior. Yet, no systematic investigation of early human brain development in NS has been conducted to date. Thus, major gaps exist in understanding how NS increases risk for cognitive-behavioral deficits in children.

Methods: We assessed 12 children with NS between the ages of 4.0-11.0 (8.98 ± 2.33) and 12 age- and sex- matched typically developing (TD) controls between the ages of 4.0-11.0 years (8.79 ± 2.17). We

acquired data using a fast-spoiled gradient-recalled (FSPGR) echo sequence utilizing a 3T MRI scanner. Cortical reconstruction and subcortical segmentation were performed using FreeSurfer image analysis software (version 5.3, <http://surfer.nmr.mgh.harvard.edu/>).

Results: After controlling for total brain volume (TBV), within both the left and right hemispheres, the **caudate** (left: $W=31$, $p=0.029$, effect size=-1.154; right: $W=23$, $p=0.018$, effect size=-1.311), **putamen** (left: $W=27$, $p=0.029$, effect size=-1.244; right: $W=30$, $p=0.034$, effect size=-1.148,) and **pallidum** (left: $W=29$, $p=0.029$, effect size=-1.032; right: $W=32$, $p=0.034$, effect size=-1.235) volumes were significantly smaller in NS participants when compared to TD. Overall, using effect sizes, we detected an effect of NS on the hippocampal or amygdala regional volumes, occipital and parietal regions in the medial aspect of the brain as well as on the frontal regions in the lateral aspect of the brain. NS effects were detected in the gray matter volume (GMV), surface area (SA), and cortical thickness (CT).

Conclusion: We detected an effect of NS on the human brain. Specifically, we detected an effect in the corpus striatum. Morphometric aberrations in the corpus striatum have been implicated in idiopathic ADHD and other neurodevelopmental conditions. Thus, aberrations in the corpus striatum might be associated with ADHD symptoms in NS. Effects were also detected on other subcortical structures such as the hippocampus and cortical structures. In mouse models of NS, mutations of PTPN11 are associated with abnormalities of brain development, particularly in the hippocampus and the forebrain. These abnormalities in the mouse brain are related to behavioral phenotypes that include reduced motor coordination, increased locomotor activity, aberrant spatial information acquisition, and anxiety-like behavior. Data presented provide a translation of NS associated mutation on the mouse brain into the effects of NS on the human brain.

*** Patient specific iPSC-derived cardiomyocytes reveal abnormal signaling pathways underlying hypertrophic cardiomyopathy in Noonan Syndrome**

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Noonan Syndrome (NS), an autosomal dominant RASopathy disorder, is caused by germ-line mutations that affect the canonical RAS/ERK1/2-MAPK pathway. >90% of NS patients with an S257L/+ mutation in *Raf1* exhibit severe hypertrophic cardiomyopathy (HCM). However, the molecular mechanisms that elicit HCM in these patients remain unknown. Here, we modeled NS-associated HCM by differentiating inducible pluripotent stem cells (iPSCs) generated from a patient with a *Raf1* S257L/+ mutation into cardiomyocytes (iCMs). In addition, we corrected the *Raf1* mutation using CRISPR-Cas9 double nickase technology to generate an isogenic control iPSC line. We found that, though proliferation rates were similar (72.25% Ki67⁺ iCMs \pm 4.70 vs 72.50% Ki67⁺ iCMs \pm 2.53, $n=4$, $p<0.01$), S257L/+ iCMs displayed increased cell surface area, as compared to isogenic control cells (3,742 $\mu\text{m}^2 \pm 212$ vs 2,199 $\mu\text{m}^2 \pm 178$, $n=6$, $p<0.01$). In addition, S257L/+ iCMs exhibited significant myofibrillar disarray, characteristic of cardiomyocyte HCM pathophysiology. At the molecular level, while S257L/+ iCMs had elevated RAF1 activity, as demonstrated by robust increase in phosphorylation of its downstream effector, MEK1/2 (5 fold over control level, $p<0.01$), ERK1/2 itself was only modestly enhanced (1.8 fold over control level, $p<0.01$) due to simultaneous overexpression of the specific ERK1/2 phosphatase MKP3 in mutant cells (5 fold over control level, $p<0.01$).

To test whether enhanced ERK1/2 activity was responsible for increased size of S257L/+ iCMs, we inhibited MEK1/2 activity with three different small molecules (UO126, PD98059 or Trametinib) and found that, while neither PD98059 nor Trametinib reduced mutant iCMs area, all three inhibitors rescued myofibrillar disarray, demonstrating that activation of the ERK1/2 pathway is important for regulation of myofilament organization in iCMs. Strikingly, UO126 was the only inhibitor able to drastically reduce S257L/+ iCMs surface area ($3,684 \mu\text{m}^2 \pm 211$ vs $2,363 \mu\text{m}^2 \pm 111$, $n=4-5$, $p<0.01$), suggesting that inhibition of an ERK1/2 independent pathway is likely responsible for the mutant iCM hypertrophy phenotype. In this regard, it was previously demonstrated that UO126 can also inhibit MEK5; as such, we treated S257L/+ iCMs with a specific MEK5/ERK5 inhibitor, BIX02189, and found that we could strongly reduce iCM hypertrophy in our mutant, indicating that the MEK5/ERK5 pathway triggers hypertrophy in S257L/+ iCMs. Finally, using RNA sequencing and RT-qPCR validation in isogenic iCMs, we identified genes whose expression is significantly dysregulated in the RAF1 mutant iCMs, downstream of either the MEK1/2-ERK1/2 or MEK5/ERK5 pathway. Particularly, we found that mRNA expression of several sarcomeric proteins and modulators of transcription factors were altered in the S257L/+ iCMs. Taken together, our data show that mutant cardiomyocytes phenocopy the HCM pathology in patients with the S257L/+ RAF1 mutation. Moreover, we have uncovered that activation of the MEK5/ERK5 pathway is required to mediate this aberrant phenotype. Although not involved in the regulation of mutant iCMs cell size, we also revealed that activation of ERK1/2 downstream of S257L/+ RAF1 leads to abnormal organization of the sarcomere, thereby contributing to the pathogenicity observed in mutant RAF1 iCMs.

*** Noonan syndrome mutations in components of the SHOC2-MRAS-PP1 phosphatase complex function through enhanced complex formation and positive regulation of RAF activity.**

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De-phosphorylation of the inhibitory 14-3-3 binding site on RAF (S259 on CRAF, S365 on BRAF) is one of the key steps in the process of RAF activation. Many of the CRAF mutations identified in Noonan syndrome (NS) cluster around S259 and have been shown to disrupt 14-3-3 binding, emphasizing that precise regulation of this site is critical for maintaining normal pathway dynamics. We have previously characterized the de-phosphorylation of this site, and subsequent control of downstream ERK activation, by a heterotrimeric complex consisting of the MRAS GTPase, SHOC2 and protein phosphatase PP1 (Rodriguez-Viciana *et al.*, 2006. *Mol Cell*, 22(2): 217-230).

Noonan-like syndrome with loose anagen hair is caused by an activating mutation in SHOC2 (S2G), which results in constitutive membrane targeting and enhanced ERK pathway activation. Recently, multiple mutations in PP1 and MRAS, as well as a further mutation (M173I) in SHOC2, have also been described in patients with NS features. We sought to further examine the biochemical nature of these mutations and establish whether they are gain-of-function mutations through modified SHOC2-MRAS-PP1 complex signaling.

We find that the SHOC2-S2G and M173I mutations are enhanced for PP1/MRAS interaction and both mutant proteins can rescue P-ERK levels in EGF-stimulated SHOC2-deficient cells. The location of the M173I mutation highlights a critical region involved in complex formation, when taken together with the previous finding that the close-proximity D175N mutation (a loss-of-function mutation identified in *C. elegans*) is completely defective for MRAS/PP1 binding.

Of the RAS superfamily GTPases, MRAS is the closest relative of the classical RAS proteins by sequence identity and in its active form can similarly bind and activate RAF directly. MRAS-G23V (the equivalent of RAS-G13V) has previously been described as an activating mutation, and we extend this finding to show that it increases SHOC2/PP1 binding and stimulates BRAF-S365 de-phosphorylation. We find that the NS mutation, MRAS-T68I, also increases binding to SHOC2/PP1. However, MRAS-T68I does not bind RAF, suggesting that this particular mutation, located in the Switch II region of MRAS, is selective for SHOC2/PP1.

PP1 has many known targets and substrate specificity within the cell is dictated by interaction with one of a large range of known PP1-regulatory proteins. Syndromic mutations in PP1CB do not fall within the catalytic or substrate-recognition regions of the phosphatase, suggesting that they are therefore more likely involved in regulatory protein binding. We report that the more common PP1CB-P49R mutation is enhanced for SHOC2 binding, but critically not for other PP1-regulatory proteins MYPT1 and SCRIB. Other PP1 mutations remain to be tested, but importantly they point to regions of PP1 predicted to be involved in SHOC2/MRAS binding. These studies suggest that the NS phenotype in individuals with SHOC2, MRAS or PP1CB mutations is driven at the biochemical level by enhanced complex formation and highlight the crucial role of this complex in RAF-S259 de-phosphorylation and ERK pathway dynamics.

Melanocytic lesions in RASopathies

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Dermatological abnormalities in RASopathies represent a frequent clinical findings helping clinician in the diagnosis of Noonan (NS), Costello (CS), CFC (CFCS) and NF1 syndrome. Each condition seems to have distinct “skin markers” helping clinicians in the differential diagnosis between RASopathies. Melanocytic lesion in RASopathies are a under-reported clinical findings. Few papers reported the presence of these specific lesions only in individual affecting by CFC syndrome caring *BRAF* mutation.

In the last 2 years we perform serial dermoscopy evaluations in our cohort of RASopathies (46 individual affected by NS, 19 CFCS, 16 CS, 20 NF1) demonstrating a different prevalence of melanocytic lesion in Noonan, NF1, Costello and CFC syndrome. Within the melanocytic lesions there was a peculiar distribution of atypical nevi according to the gene mutation. We found a good correlation between atypical nevi diagnosed by dermoscopy study and histological examination performed on lesions surgically removed based on dermatologist request.

These preliminary results should represent a first step study to propose future protocol of monitoring and treatment of melanocytic lesions in RASopathies.

Increased Nuchal Translucency and Noonan Spectrum Disorders – A Mount Sinai Hospital experience

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Sick Children, Toronto, Canada; ²GeneDX, Whole Exome Sequencing Program; ³Medical Informatics – Information Sciences, Mount Sinai Hospital, Joseph and Wolf Lebovic Health Complex; ⁴Prenatal Diagnosis and Medical Genetics, Department of Obstetrics and Gynecology, Mount Sinai Hospital – Joseph and Wolf Lebovic Health Complex; ⁵Division of Diagnostic Medical Genetics, Department of Pathology and Laboratory Medicine, Mount Sinai Hospital – Joseph and Wolf Lebovic Health Complex; ⁶Maternal and Fetal Medicine, Department of Obstetrics and Gynecology, Mount Sinai Hospital – Joseph and Wolf Lebovic Complex

Objective: To examine a cohort of patients seen at the Prenatal Diagnosis and Medical Genetics Program - Mount Sinai Hospital between 2013 – 2015, with fetal ultrasound findings of an increased nuchal translucency (NT \geq 3.5mm), and to:

1. Correlate between the NT measurements and a diagnosis of Noonan Spectrum Disorders (NSD)
2. Conduct a systematic literature review to determine the correlation between NT measurement and a diagnosis of NSD
3. To create a clinical protocol to guide physicians in the investigation of an increased fetal NT

Methods: A cohort of patients presenting between 2013 – 2015 with fetal ultrasound findings of increased NT. All patients were offered amniocentesis/CVS for QF-PCR as a first line test. If negative, patients proceeded to karyotype/microarray analysis and NSD panel testing. Patients were also offered fetal ultrasounds at 16 weeks and 18 – 22 weeks gestation (GA) along with fetal echocardiogram.

A systematic review was conducted in accordance to PRISMA criteria. Pubmed, Embase, Ovid MEDLINE and Web of Science were searched from January 2005 – August 2016 for articles involving NSD and increased NT. Seventeen papers were included for analysis.

Results: 226 patients with increased fetal NT were seen. In 116/226 patients, chromosomal aneuploidy was detected through QF-PCR. The remaining 110/226 patients had further testing. 8 had karyotype abnormalities, 13 had abnormal microarray findings and 5 had NSD findings through DNA analysis.

Discussion: Based on the cohort findings and literature review the following guidelines were created regarding the best approach to a fetus with an increased NT:

1. QF-PCR and microarray should be performed for NT \geq 3.5 mm
2. If QF-PCR/microarray analysis is normal, DNA analysis for NSD should be performed for NT \geq 4.0 mm
3. Early anatomic ultrasounds at 16 weeks GA
4. Fetal echocardiogram at 18 – 22 weeks GA
5. Detailed fetal ultrasound at 18 – 22 weeks GA

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Poster Abstracts

Structural Basis for GAP-insensitivity of KRAS P34R

Asim K Bera[†], Jia Lu[†], Wei Yan[†], Sudershan Gondi[†], and Kenneth D. Westover^{†*}. *[†]Departments of Biochemistry and Radiation Oncology, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75390, United States*

RAS proteins are commonly mutated in cancerous tumors, but germline RAS mutations are also found in a number of RASopathy syndromes including Noonan (NS), Legius, Costello, and Cardio-facio-cutaneous (CFC) syndromes. Although RASopathy syndromes can include mutations in genes other than RAS, such as the GTP exchange factor NF1, activation of RAS proteins or proteins regulated by RAS is a defining feature. RAS mutations fall into functional classes that lead to RAS activation through various mechanisms. Understanding the structural basis for these mechanisms may provide clues for how to manage syndromes associated with certain RAS mutations. We determined high resolution x-ray structures of an important RASopathy mutant KRAS P34R, seen in NS and CFC. KRAS P34R was previously shown to be profoundly insensitive to GTPase activating proteins (GAPs), which catalyze GTP hydrolysis within RAS to inactivate the protein. Structures were obtained in both the GDP and GTP analogue-bound forms. Interestingly P34R-GMPPNP protein crystallized in three different lattices yielding a range of protein conformations for study. In particular we noted alterations in the conformations of switch I, notably involving residues Y32, R34 and T35. Interestingly switch II does not engage the gamma phosphate of GTP as seen in previous RAS-GMPPNP structures. These results explain the GAP-insensitivity of KRAS P34R and provide insights regarding the interplay between switch I and II in determining RAS protein dynamics.

Shoc2-mediated ERK1/2 pathway signals in zebrafish development

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Activity of the extracellular-signal-regulated kinase 1/2 (ERK1/2) pathway plays a critical role in normal human development. Aberrant ERK1/2 signaling caused by germline mutations in genes of the Ras-mediated ERK1/2 pathway results in developmental disorders cumulatively called 'RASopathies'. Shoc2, the scaffold protein in the ERK1/2 pathway, accelerates ERK1/2 signals by bringing the components of the pathway, Ras and Raf-1, to close proximity. Noonan-like RASopathy causing Shoc2 mutations emphasize the significance of ERK1/2 signals transmitted through the Shoc2 scaffolding module. However, the physiological role of Shoc2 and the specificity of ERK1/2 signals transduced through the Shoc2 scaffolding complex remain largely unknown.

In our work, we took advantage of the vertebrate zebrafish model that is ideally suited for developmental genetic studies due to its optical transparency and ex vivo development. To delineate the developmental ERK1/2 signals mediated through the Shoc2 complex, two experimental strategies were utilized: the acute depletion of Shoc2 in zebrafish embryos using a translation-blocking morpholino and CRISPR/Cas9 gene editing to generate the Shoc2 zebrafish knockout. We found that both depletion and loss of Shoc2 resulted in decreased ERK1/2 activity leading to early embryonic death due to multiple developmental deficiencies. We will now utilize Shoc2 CRISPR/Cas9 zebrafish knockout model to examine quantitative changes in the ERK1/2 transcriptional programs.

Use of a new business model for RASopathies: MEK inhibitor case study

Pamela Knight, MS, Salvatore La Rosa, PhD, Marco Nievo, PhD, Patrice Pancza, and Annette Bakker, PhD. *Children's Tumor Foundation*

"RASopathies" are a class of developmental disorders caused by germline mutations in genes that encode protein components of the Ras/MAPK pathway such as MEK (mitogen-activated protein kinase). While each RASopathy syndrome exhibits different phenotypic features, there are a great number of overlapping features among them such as characteristic facial features, cardiac defects, cutaneous abnormalities, learning disabilities, and a predisposition to malignancies. In the last couple of years a few studies were published which directly connected the molecular mechanism of these diseases to each other, bringing a new opportunity to cross-validate the effect of modulating the RAS pathway at different stages and in different disorders. We use the example of the development of MEK inhibitors to demonstrate another approach that may be applicable to other RAS-related as well as other types of disease foundations.

This approach is a novel business model, in which the Children's Tumor Foundation (CTF) has repositioned itself to become more a research partner than solely a funding agency. CTF has invested in broad, sharable resources including a patient registry, biobank, open data platform, etc. CTF has also massively invested in team science consortia to connect research to patients and to all the steps of the drug discovery process. It also works with an external board of key opinion leaders in pharma to align our research efforts with proven market models. CTF's approach has already sped the development of several MEK inhibitor clinical trials, which now are yielding encouraging results showing significant tumor shrinkage in children with NF1.

Developing a translational pipeline for NF1-mutant malignancies

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Neurofibromatosis type 1 (NF1) is a prevalent familial cancer syndrome affecting one in 3500 individuals worldwide. The most commonly lethal feature associated with NF1 is malignant peripheral nerve sheath tumors (MPNST). These soft tissue sarcomas are highly aggressive and frequently metastasize. Despite radiation and chemotherapy, inoperable tumors rapidly progress and are universally lethal. Therefore, identifying effective treatments for MPNST is critical.

The *NF1* tumor suppressor gene encodes a Ras GTPase activating protein that negatively regulates Ras by accelerating GTP hydrolysis. As such, Ras and its downstream kinases become aberrantly activated in *NF1*-mutant tumors. Despite an extensive understanding of Ras signaling networks and the availability of compounds that target various Ras effectors, there are currently no effective treatments for *NF1*-deficient cancers. Moreover, selection and prioritization of agents for clinical trials is a key challenge for *NF1* as only a few agents can be tested in the clinical setting due to patient numbers, time, and cost.

We have established, through NIH Program Announcement PAR 15-287, *Opportunities for Collaborative Research at the NIH Clinical Center*, a consortium to rapidly develop and test new therapies for *NF1* patients. This *NF1* Consortium will leverage the unique resources of the NIH Clinical Center and harness the specialized expertise of clinical investigators at the NCI and Children's National Medical Center, while utilizing the extramural experts in *NF1* biology and therapeutic development at BWH. Specifically, new discoveries of mechanisms that drive *NF1*-related tumorigenesis together with recent insights into

the immunoreactivity of MPNST will be used to develop rational combination therapies and will be tested in a robust preclinical MPNST mouse model. These insights will then be used to perform clinical trials in MPNST patients at the NIH Clinical Center and Children's National Medical Center, with an emphasis on evaluating more than one combination therapy within the same trial.

Through these efforts we have found that immunotherapies enhance the effects of specific targeted agents, resulting in the dramatic regression of MPNSTs in our GEMM tumor model, which will be presented. We are also ready to initiate our first clinical trial based on the success of this pipeline. Our goal will be to continue moving our most promising combination therapies into clinical trials with an emphasis on 1) the development of a pipeline of combinations, 2) the inclusion of predictive biomarkers, 3) parallel exome sequencing and epigenetic profiling of tumor samples, and 4) trial designs which will allow for more rapid completion and for the evaluation of more than one combination therapy within the same trial. This will allow for more timely identification of active agents, and allow patients with this highly refractory disease to have more treatment options available to them.

A novel direct Ras inhibitor **Not Presented**

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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 that 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 both 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.

Phosphorylation of the C-Raf N-region promotes Raf dimerization in selected cancers and RASopathy mutants

Maho Takahashi, **Philip J.S. Stork**. *Vollum Institute, Oregon Health and Science University, Portland, OR*

Activation of the C-Raf kinase by the small GTPase Ras requires multiple phosphorylations. One of these phosphorylations (phospho-Y341) lies within the N-terminal acidic region (N-region) and is required for C-Raf dimerization. This action can be replicated by phosphomimetic mutants both *in vivo* and *in vitro*. Y341 phosphorylation in Ras-mutant cancer cells can be triggered by the tyrosine kinase Src (and related Src family kinases) and can be blocked by Src inhibitors, such as dasatinib. Dasatinib also blocks constitutive C-Raf/B-Raf dimerization, the basal levels of ERK activation, and ERK-dependent cell growth that characterize these cancer cells.

Nearly all RASopathies are caused by hyperactive signaling through the small GTPase Ras and its downstream effectors, the kinases Raf, MEK, and ERK. Constitutive dimerization of C-Raf will likely be required for the elevated Ras-dependent signaling seen in many RASopathies.

We will show data that address the requirement of Y341 phosphorylation for C-Raf dimerization in a subset of RASopathy mutants. We have also examined whether this dimerization is blocked by inhibition

of Src family kinases in this subset of RASopathy mutants. These examples may help determine whether Src family kinases might be therapeutic target in the respective Rasopathies.

Relevance of systematic phenotyping and exome sequencing for the diagnostic yield of RASopathies in patients with idiopathic short stature

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In short stature the underlying cause often remains elusive due its heterogeneity. By standard targeted diagnostic assessment following phenotypic examination, we identified a known disease-cause in only 14 % of the 565 patients. A clinical diagnosis of Noonan spectrum disorder was made in 3 of these patients (0.5%) by the identification of mutations in *SHOC2*, *PTPN11*, and *RAF1*. We then randomly selected 200 for whole exome sequencing. Using WES we identified mutations in 27 known short stature associated genes in 17% of patients with only part of the symptomatology precluding an early clinical diagnosis. 54 % of the affected proteins are involved in the main functional categories cartilage formation, chromatin modification and Ras-MAPK signaling. Within the Ras-MAPK signaling pathway we identified likely pathogenic missense mutations in *MAP2K1*, *KRAS*, *NEF* and *PTPN11* in 4 patients (2%). Phenotypic reevaluation showed that these patients were lacking some of the characteristic clinical feature. Hence, the clinical diagnosis was formerly missed.

These results demonstrated that deep phenotyping combined with targeted genetic testing and whole exome sequencing is able to increase the diagnostic yield in short stature up to 31% overall. In particular, the broad clinical spectrum of the RASopathies requires an unbiased diagnostic approach in many patients.

JOHN ALBECK, PHD (SPEAKER)



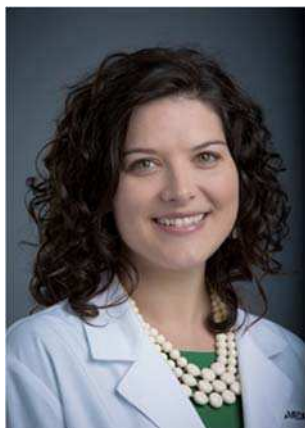
John Albeck received his training in computational and cancer cell biology at MIT and Harvard Medical School. His research group at UC Davis brings together biologists, physicians, and engineers to study how signaling pathways are integrated to control cellular metabolism, proliferation, and death. By developing technology to image biochemical signaling activities in individual living cells, they collect time-resolved data from millions of cells to build quantitative models of how cellular communication goes awry in cancer and the RASopathies.

BRAGE ANDRESEN, PHD FRCPATH (SPEAKER)



Brage Storstein Andresen is a professor of Human Molecular Genetics at the Department of Biochemistry and Molecular Biology, University of Southern Denmark. He obtained his Ph.D. in 1996 from Aarhus University, Denmark. He is a Fellow of The Royal College of Pathologists, UK and have published more than 100 papers in Scientific Journals. His laboratory has for years focused on the molecular genetics and the molecular pathology of human disease with a special emphasis on regulation of normal and aberrant alternative pre-mRNA splicing. They use splice shifting oligonucleotides (SSOs) to modulate splicing aiming at development of new therapies for inherited diseases as well as cancer.

Ashley Cannon, PhD, MS, CGC (Speaker)



Ashley Cannon, PhD, alumna of the University of Alabama Health Professions' Genetic Counseling Program, and member of the UAB Department of Genetics, serves as both a genetic counselor and neuroscientist. In 2016, she was named the recipient of the prestigious Francis S. Collins Scholars Program Award and accepted into the Francis S. Collins Scholars Program in Neurofibromatosis Clinical and Translational Research, sponsored by the neurofibromatosis therapeutic acceleration program at Johns Hopkins University.

HÉLÈNE CAVÉ, PHARMD PHD (SPEAKER)



Hélène Cavé is Professor of Biochemistry and Molecular Biology at Paris-Diderot University (France) and steers the molecular genetics unit of the Genetics department of Robert-Debré University Hospital, one of the largest pediatric hospitals in Europe. Her research activities are directly derived from her hospital activities on developmental diseases and pediatric leukemia with main research foci 1) Acute lymphoblastic leukemia, 2) Germline and somatic diseases associated with pathological RAS/MAPK activation, e.g. RASopathies and juvenile myelomonocytic leukemia, and 3) the link between development and leukemogenesis. She contributed to more than 150 peer-reviewed manuscripts and book chapters. She coordinates biological studies of the EORTC-Children Leukemia Group and of the French working group on Juvenile Myelomonocytic leukemia (JMML).

MICHELLE ELLIS (PANELIST, 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 RNUSA, 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*.

STEVEN FRUCHTMAN, MD (SPEAKER)



Dr. Fruchtmann joined Onconova in January, 2015. He has extensive experience in large and small biopharmaceutical companies and has led successful clinical development programs while serving in senior positions at Ortho Biotech Products, Novartis, Allos Therapeutics, Spectrum Pharmaceuticals and Syndax Pharmaceuticals. Earlier, Dr. Fruchtmann was on the faculty of the Mount Sinai School of Medicine and the Director of the Stem Cell Transplantation and Myeloproliferative Disorder Programs at Mount Sinai Hospital in New York City. He is an author of more than 170 lectures, presentations, books, chapters, and abstracts and serves as an external reviewer for multiple medical journals. Dr. Fruchtmann received his medical degree from New York Medical College with the distinction of membership in the Alpha Omega Alpha honorary medical fraternity.

BRUCE D. GELB, MD (SPEAKER)



Dr. Bruce Gelb is a pediatric cardiologist at the Mount Sinai School of Medicine. He trained in pediatrics at Columbia-Presbyterian Medical Center and in pediatric cardiology at Texas Children's Hospital. Dr. Gelb is pursuing molecular cardiology/genetics research on inherited cardiovascular disease, particularly congenital heart defects. His group has discovered several disease genes including those underlying Noonan syndrome and related disorders, which are RAS signaling defects.

CHRISTOPHER GIBSON, PhD (SPEAKER)



Chris Gibson, PhD, is the Co-Founder and CEO of Recursion Pharmaceuticals, a biotech company leveraging the latest in automation, artificial intelligence and biology to do drug discovery at scale. Chris developed the technology and approach underlying Recursion as part of his MD/PhD graduate work in the lab of Co-Founder Dr. Dean Li at the University of Utah. Chris left medical school to transform this technology into the rapidly growing company it is today. Chris is a graduate of Rice University with degrees in bioengineering and managerial studies, as well as a graduate of an intense entrepreneurship course at Stanford GSB. He is a Board Member of CureHHT, a patient advocacy group for Hereditary Hemorrhagic Telangiectasia, and a member of the Rare and Undiagnosed Network Advisory Board. Outside of work, Chris enjoys cycling on both the road and the trails that cut through Utah's great

wilderness, as well as spending time with family.

KAREN GRIPP, MD (MODERATOR)



Karen W. Gripp, MD is the Chief of the Division of Medical Genetics and the Medical Director of the Molecular Diagnostic Laboratory 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 and clinical molecular diagnostic genetics. Her areas of particular clinical expertise include craniofacial malformations 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 the professional advisory board. In addition to co-authoring the Handbook of Physical Measurements, Dr. Gripp has >100 peer reviewed publications. Her professional activities include membership in the ClinGen panel on RASopathies, an active role

in ACMG committees, and organizing the "D.W. Smith Meeting on Malformation and Morphogenesis" and the "Diagnostic Dilemmas" session at the annual ASHG meeting. She is on the scientific advisory board for FDNA, the parent company for Face2Gene.

RICK GUIDOTTI (SPEAKER)



Rick Guidotti, an award-winning photographer, has spent the past eighteen years collaborating internationally with advocacy organizations/NGOs, medical schools, universities and other educational institutions to effect a sea-change in societal attitudes towards individuals living with genetic, physical, behavioral or intellectual difference; his work has been published in newspapers, magazines and journals as diverse as Elle, GQ, People, the American Journal of Medical Genetics, The Lancet, Spirituality and Health, the Washington Post, Atlantic Monthly and LIFE Magazine. Rick is the founder and director of Positive Exposure, an innovative arts, education, and advocacy organization working with individuals living with genetic difference. Positive Exposure utilizes the visual arts to significantly impact the fields of genetics, mental health and human rights. Positive Exposure explores the social and psychological experiences of people living with genetic conditions of all ages and ethno-cultural heritages. This impressive and powerful collection of imagery, film and narratives celebrates the richness and beauty of human diversity and dignity. Positive Exposure provides new opportunities to see individuals living with a difference first and foremost as a human being rather than as a specific diagnosis or disease.

ERIN HEFNER (PANELIST, CS ADVOCATE)



Erin Hefner is a 31 year old female with Costello Syndrome. She was born and raised in Creve Coeur, Illinois (near Peoria). She works two half-day jobs in child care and volunteers at her church. Once a week she attends a social group of special needs peers, Heart of Morton, who have aged out of the school system. They go on outings, eat, and just hang out. Erin enjoys riding horses at Central Illinois Riding Therapy and Special Olympics bowling. Erin lives with her parents and has an older brother.

WILLIAM HUANG, PHD (SPEAKER)



William Y. C. Huang received a Ph.D. in Chemistry from University of California, Berkeley in 2016. His research interests center on the physical principles of signal transduction, from a dynamical standpoint. Under the guidance of Prof. Jay Groves, his doctoral work focused on experimentally resolving the timing mechanism, molecular organization, and catalysis of membrane signaling reactions, from single-molecule dynamics to small network responses. He is currently a postdoctoral fellow at UC Berkeley.

MAXIM ITKIN, MD FSIR (SPEAKER)



Dr. Itkin is an Associate Professor of Radiology and Pediatrics at the University of Pennsylvania and the Children's Hospital of Philadelphia where he is a director of the Center for Lymphatic Imaging and Interventions. Dr. Itkin earned his MD from Moscow State University of Medicine and Dentistry in 1989. He completed his internship and residency at the Rabin Medical Center in Israel. In 2003, after completion of a fellowship in Interventional Radiology at the University of Pennsylvania Hospital, he stayed on there as a staff member. Dr. Itkin is nationally and internationally recognized for his clinical and research expertise in treatment of the lymphatic disorders. Over the past 15 years, Dr. Itkin has been actively involved in the development of image-guided interventions of the lymphatic system. Dr. Itkin has lectured extensively nationally and internationally and has 90 peer-reviewed publications, reviews and editorials in leading journals. He is a member of many professional societies and in 2011 was inducted into the Society of the Interventional Radiology as a Fellow member as recognition of significant contributions to the field of cardiovascular and interventional radiology.

BRONWYN KERR, MBBS (MODERATOR)



Bronwyn Kerr, MD is a consultant clinical geneticist who studied medicine at the University of Sydney before qualifying in pediatrics and genetics in Australia. After completing a two-year research fellowship, she moved to the UK in 1993. She was appointed Consultant Clinical Geneticist in the Regional Genetic Service in Manchester in 1995, based largely at Royal Manchester Children's Hospital (RMCH). Clinical interests include the causes of developmental disability and congenital abnormality. Her principal research interest has been Costello syndrome, and other disorders of the RAS/MAPK pathway. She was a founder member of the Medical Advisory Boards of the International Costello syndrome support group, the Association Française des syndromes de Costello and CFC, and the Costello Family Support Network.

BRUCE KORF, MD PhD (MODERATOR)



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.

CORINNE LINARDIC, MD PHD (SPEAKER)



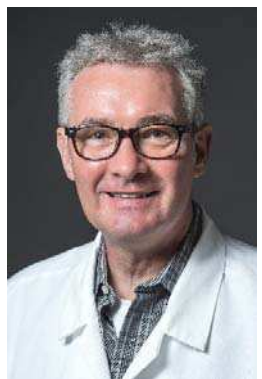
Corinne Linardic, MD, PhD is a physician-scientist in the Division of Pediatric Hematology-Oncology at Duke University School of Medicine in Durham, NC. She received her training at Duke and the Children's Hospital of Philadelphia. Her clinical and research interest is pediatric sarcomas, with an emphasis on rhabdomyosarcoma. At Duke, she cares for children in both outpatient and inpatient settings, teaches and mentors medical students, residents, and fellows, directs a basic science lab, and joins advocacy efforts for children with cancer and their families. She enjoys her collaborative work with the Children's Oncology Group and other rhabdomyosarcoma experts around the world.

FRANK MCCORMICK, PHD FRS DSc HON (SPEAKER)



Dr. McCormick is the David A. Wood Chair of Tumor Biology and Cancer Research at University of California, San Francisco (UCSF) and a professor in the UCSF Helen Diller Family Comprehensive Cancer Center. He also leads the National Cancer Institute Ras Initiative to develop therapies against Ras-driven cancers. Prior to joining the UCSF faculty, Dr. McCormick pursued cancer-related research with several Bay Area biotechnology companies. This included founding Onyx Pharmaceuticals and developing Sorafenib (Nexavar), which is used to treat advanced renal cell carcinoma and hepatocellular carcinoma. His current research interests center on developing new ways of targeting RAS pathway and NF1-related malignancies.

MARTIN MCMAHON, PHD (MODERATOR)



Martin McMahon, PhD is the Senior Director of Preclinical Translational Science and Investigator with Huntsman Cancer Institute, and a Professor with the Department of Dermatology at the University of Utah. He received his PhD from King's College, University of London for studies on the mechanism of interferon action conducted with Drs. Ian Kerr and George Stark at the Imperial Cancer Research Fund (London, UK) and Stanford University (Stanford, CA), and was a Professor with the University of California, San Francisco from 1998-2015. Dr. McMahon's research program focuses on the mechanisms underlying the development of metastatic melanoma, lung and thyroid cancer, by working with cultured human cancer-derived cells and with genetically engineered mouse models of human cancer.

DEBORAH MORRISON, PHD (SPEAKER)



Dr. Morrison investigates the signal transduction pathways regulated by the Ras family of GTPases. These pathways are required for normal growth and development, and mutations in various pathway components can function as disease drivers in human cancer and certain developmental disorders. Dr. Morrison has extensive expertise in the identification of protein phosphorylation sites and in the proteomic analysis of signaling complexes, which has been instrumental for her studies investigating the role of the Raf protein kinases and the KSR and CNK scaffolds in Ras-dependent signaling. Her work seeks to identify critical regulatory mechanisms that may prove helpful in the diagnosis and/or treatment of human disease states with aberrant Ras-pathway signaling.

BEV OBERLANDER (PANELIST, NF1 ADVOCATE)



Beverly Oberlander is the middle generation of a multi-generational family with Neurofibromatosis Type 1. Born in Chicago, she has lived in California for the past 13 years. A graduate of the University of Illinois Urbana-Champaign, with a Masters Degree in Marketing Communications from Roosevelt University in Chicago, she has been involved as a Patient Advocate Volunteer with various NF organizations for over 30 years. A past president and officer with Neurofibromatosis Midwest until her move to California, a board member with NF California and an advocate with the Neurofibromatosis Network, Mrs. Oberlander has also served as a Consumer Reviewer with the Army's Neurofibromatosis Research Program. She is extremely grateful for the support of her husband Lewis and her son Eli, as well as her mother Gertrude and her late father Martin who helped start her on her journey.

ELISABETH PARKER (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 B.S. in Liberal Studies and an emphasis in Sociology and Anthropology. She is a yoga practitioner and instructor for both kids and adults. She also spent some time studying graphic design and uses those skills marketing for the yoga studio where she teaches and for various other professional and volunteer projects. Elisabeth's favorite role is being a wife and mom of two boys. She chronicles her family's journey with Noonan syndrome on her blog and Instagram. As a RASNet board member, she is excited about continuing to educate and advocate for the RASopathies through the use of social media.

ETHAN PERLSTEIN, PHD (SPEAKER)



Dr. Ethan Perlstein is the founder and CEO of Perlara, based in South San Francisco. Ethan received his PhD from the Dept. of Molecular & Cellular Biology at Harvard in Prof. Stuart Schreiber's lab in 2006, and then was a Lewis-Sigler Fellow at Princeton from 2007-2012.

NANCY RATNER, PHD (SPEAKER)



Dr. Ratner is interested in peripheral nerve tumors that occur in the Neurofibromatoses, NF1 and NF2, and studies the brain in Neurofibromatosis type 1. She uses genomics to study neurofibroma formation and carries out neurofibroma and MPNST preclinical 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 the Marine Biological Laboratory), and was a postdoctoral fellow at Washington University in St. Louis where she studied Schwann cells in nerve development under Richard Bunge and Luis Glaser. A member of the faculty at the University of Cincinnati 1987 – 2004, she is currently a Professor in the Department of Pediatrics, Cincinnati Children's

Hospital, University of Cincinnati, where she holds the Beatrice C. Lampkin Endowed Chair in Cancer Biology. She co-leads the RASopathy Program and serves as the Program Leader for the Cancer Biology and Neural Tumors Program in the Cancer and Blood Disorders Institute. 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 a Jacob K. Javits Neuroscience Investigator Award (NIH-NINDS Merit Award) in 2014. She has been an active member of the NFTC since its inception.

KATHERINE RAUEN, MD PHD (SPEAKER)



Katherine (Kate) Rauen, MD, PhD 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 an MS in Human Physiology and a PhD in Genetics from UC Davis, then obtained her MD at UC Irvine. 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. Dr. Rauen led the research team, including the CFC International Family Support Group that discovered the genetic cause of cardio-facio-cutaneous syndrome and independently identified the genetic cause of Costello syndrome. She is the innovator of the world-renowned NF/Ras Pathway Clinic, which she initiated in 2007 and this clinic has now been 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 advisory boards for RASopathies Network USA and Global Genes. Dr. Rauen was recently awarded the Presidential Early Career Award for Scientists and Engineers (PECASE) on her work for CFC and Costello syndrome. 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. Additionally in June 2014, Dr. Rauen won an International Advocacy Award, the “Global Genes RARE Champion of Hope in Science”.

LESLIE ROGERS (PANELIST, CFC ADVOCATE)



Les lives in Roseburg, Oregon with his wife, Jennifer, and daughters Aurora and Gloria. Gloria was born in 2013 and was diagnosed at eight months old with CFC. Les is an advocate for the developmentally disabled community, and his experience growing up with a disabled adopted sister helped prepare him well for life as an advocate at the regional and state level in Oregon. Les is a Human Development Instructor and Advisor for the TRiO program at Umpqua Community College. Les has also worked as a high school teacher, and a football coach at an early college high school in California. Les is passionate about informing and supporting families affected by CFC Syndrome, Infantile Spasms/West Syndrome, and the greater developmentally disabled community. Les holds a B.A. in Economics and a Master of Public Administration Degree from California State University, Stanislaus. Les is also a credentialed teacher in both California and Oregon.

ANNETTE SCHENCK, PHD (SPEAKER)



Annette Schenck is Associate Professor and head of the Drosophila models of brain disorders group at Nijmegen’s Human Genetics Department, Radboud University Medical Centre, the Netherlands. Apart from numerous past studies into mechanisms and molecular networks in Intellectual Disability, her group conducts the first large-scale approaches to Intellectual Disability Disorders to systematically map the modular landscape of cognitive genes in health and disease. Her research aims to uncover fundamental mechanisms that underlie learning and memory, to integrate Drosophila into Next Generation Genome Diagnostics, and to exploit her model and the identified molecular networks to develop therapeutic strategies to (groups of) cognitive disorders.

LISA SCHILL (VICE PRESIDENT, RASOPATHIES NETWORK)



Lisa Schill voluntarily serves as the Vice President of the RASopathies Network USA. Lisa is also the Special Events Program Coordinator for the EveryLife Foundation for Rare Diseases. 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. Lisa graduated Magna Cum Laude from the University of North Carolina Greensboro with a dual major in Biology and Exercise and Sport Science where she was president of the Tri Beta National Biological Honor Society. When Lisa isn't busy roaring for rare, you can find her spending time with her husband and three sons, or taking on new outdoorsy challenges. Her favorite life experiences include backcountry

camping in Havasupai, jumping off the Cape May Lewis Ferry in the Escape the Cape triathlon, and bicycling the Katy trail.

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 also is a trustee of the International Costello Syndrome Support Group (ICSSG), as well as Secretary and Past President 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 Los Angeles County Department of Public Health's program for children with special needs (2003-2009), and currently for the County's Department of Mental Health in the Family and Community Partnerships/Child Prevention and Early Intervention Unit.

SUMA SHANKAR, MD PhD (MODERATOR)



Dr. Suma Shankar is an Associate Professor in the Department of Pediatrics, Division of Genomic Medicine at UC Davis Medical Center. She is the Director of Precision Genomics and will lead the effort in bringing genomics to every day clinical practice. Dr. Shankar is a clinician scientist who received her medical degree from Bangalore Medical College, Bangalore and PhD in Molecular Genetics from University of Iowa, USA. She is an ophthalmologist trained in the UK and is a Fellow of the Royal College of Surgeons (FRCS), Edinburgh and Member of the Royal College of Ophthalmologists (MRCOphth), London. She also completed a fellowship in Medical Genetics at the University of California, San Francisco and is board certified in Medical Genetics by the American Board of Medical Genetics

(FACMG). She was faculty in the Departments of Human Genetics and Ophthalmology at Emory

University, School of Medicine, where she initiated Ocular Precision Health Initiative with biobank and genetic studies for inherited eye diseases for the first time in Georgia. She served as Medical Director for Emory Genetics Laboratory and was primary investigator on a number of clinical trials investigating novel therapies for rare genetic disorders.

STAS SHVARTSMAN, PHD (SPEAKER)



Stas Shvartsman was trained in physical chemistry and chemical engineering, specializing on chemical kinetics and transport (at Moscow State University, Technion-Israel Institute of Technology, Princeton University, and MIT). His laboratory at the Princeton's Institute for Integrative Genomics focuses on dynamics of developmental signal transduction, using *Drosophila* as the main experimental model. One of the current projects explores the mechanisms by which mutations from RASopathies affect multiple aspects of developmental pattern formation and tissue morphogenesis.

DAVID STEVENSON, MD (MODERATOR)



Dr. Stevenson is a pediatrician and medical geneticist. He is currently a Professor of Pediatrics in the Division of Medical Genetics at Stanford University. He has an active medical genetics clinic including a monthly RASopathy clinic. His research interests focus on the role of the Ras/MAPK pathway on the musculoskeletal system.

EDWARD STITES, MD PHD (SPEAKER)



Ed Stites, MD, PhD, is a physician-scientist trained in clinical pathology and clinical genomics, as well as in biophysics and mathematics. Now at the Salk Institute, his research utilizes mathematical models of biochemical networks to study disease and its response to treatment. His work has been focused on the RAS signaling pathway.

PHILIP STORK, MD (SPEAKER)



Philip Stork, M.D. is a staff scientist at the Vollum Institute and a Professor at the Oregon Health & Sciences University, Portland, Oregon. His scientific interests include elucidating the mechanisms of growth factor receptor specificity and Ras-dependent functions, with a focus on regulation of the MAP kinase signaling cascade by G protein-coupled pathways. His studies have uncovered similarities and differences between two small G proteins, Ras and Rap1, in their downstream signaling pathways. Current interests include how Ras effectors B-Raf and C-Raf are differentially regulated in Ras-dependent cancers and in Ras-dependent developmental disorders.

BETH STRONACH, PHD (BOARD MEMBER, RASOPATHIES NETWORK)



Beth Stronach has been an academic research scientist for over a dozen years. After receiving a Ph.D. 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 Dept. 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'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 complex diseases. She is currently a Scientist Administrator in the Office of Research for Health Sciences at the University of Pittsburgh.

CHENG SUN, PHD (SPEAKER)



Dr. Sun obtained his Bachelor of Science degree at the China Agricultural University in Beijing, China. He then went on to receive his Ph.D. at Tulane University, New Orleans, in 2015, studying development of the cardiac conduction system under the tutelage of Dr. Yiping Chen. To continue his training in understanding the signaling pathways affected in embryogenesis, he moved to Dr. Kontaridis' Lab at Harvard Medical School, Beth Israel Deaconess Medical Center, Boston as a postdoctoral fellow in 2016. His project there is focused on using inducible pluripotent stem cell-derived gastrointestinal organoids to dissect the molecular mechanisms that cause feeding difficulties in RASopathy patients.

MARCO TARTAGLIA, PHD (SPEAKER)



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 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 focused on the identification of the disease genes implicated in these disorders, elucidation of the mechanisms underlying pathogenesis, and gathering clinically relevant information for more effective patient care. A second major focus is 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.

MARC THERRIEN, PHD (SPEAKER)



Marc Therrien is a professor in the Department of Pathology and Cell Biology at the University of Montréal, Québec, Canada. He completed his postdoctoral training in the laboratory of Gerald M. Rubin at the University of California, Berkeley, USA. He currently holds the position of Scientific Director of the Institute for Research in Immunology and Cancer (IRIC) at the University of Montréal. He is also Principal Investigator of the Intracellular Signaling Unit at IRIC. He and his team study the RAS–ERK pathway at structural, biochemical and functional levels, using *Drosophila melanogaster* and human cancer cell models.

WILLIAM TIMMER, PHD (SPEAKER)



Dr. 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 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 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. He has received numerous honor awards from both the NIH and the FDA, and is completing thirty years of federal service.

ERIK ULLIAN, PHD (SPEAKER)



Erik Ullian is a neuroscientist who studies how nerve cells connect. Dr. Ullian performed graduate studies in Neuroscience at UCSF and completed his postdoctoral fellowship at Stanford University. He then moved back to UCSF to establish his own lab in Ophthalmology and Physiology. The Ullian lab studies how glial cells impact brain function in development and disease. They have developed new tools to model human neuron-glial interactions to uncover novel aspects of human brain function.

BRIGITTE WIDEMANN, MD (SPEAKER)



Dr. Widemann received her M.D. from the University of Cologne, Cologne Germany, where she also completed her pediatric residency. She moved to the United States to train as a fellow for pediatric hematology and oncology at the NCI, Pediatric Branch in 1992, and has since stayed at the NCI. She received tenure at the NCI in 2009, and became the Head of Pharmacology and Experimental Therapeutics (PET) Section. She became Chief of the NCI Pediatric Oncology Branch in 2016, and also serves as a Clinical Deputy director of the NCI's Center for cancer Research. Her research program focuses on the clinical development of new agents for the treatment of refractory childhood cancers (leukemias and solid tumors) and genetic tumor predisposition syndromes (GTPS), in particular neurofibromatosis type 1 (plexiform neurofibromas and malignant peripheral nerve sheath tumors), but also hereditary medullary thyroid carcinoma, and neurofibromatosis type 2. Clinical trials are conducted as single and limited institution studies and in collaboration with consortia, for example, the Children's Oncology Group Phase I/Pilot Consortium, the NF Clinical Trials Consortium, and the sarcoma Consortium SARC.

ERIKA YEH, PHD (SPEAKER)



Originally from Brazil, Dr. Yeh has always been fascinated in understanding the unique molecular control behind rare monogenic disorders. She obtained her PhD in Human Genetics from University of Sao Paulo (Brazil) studying Ras/MAPK related bone malformations in Apert Syndrome. In 2011, she did her first postdoctoral research at Stanford University developing a mouse model for another skeletal disorder: Robinow Syndrome. Since late 2012, Dr. Yeh's been working on her second postdoctoral research at UCSF, where she uses stem cells obtained from patients to model and to understand brain formation in RASopathies.

GIUSEPPE ZAMPINO, MD PHD (SPEAKER)



Giuseppe Zampino is Associate Professor in Pediatrics, and serves as chief of the Rare Diseases and Birth Defects Unit, Department of Pediatrics, at the Agostino Gemelli Hospital in Rome. His unit is in charge of more than 150 patients affected by RASopathies. He has a longstanding expertise in clinical aspects of this family of disorders, particularly on Costello syndrome. He has been PI of several clinically oriented research projects focused on the natural history of these syndromes, their genetic basis, and genotype-phenotype correlations. Recent efforts have been directed to the understanding of cognitive and behavioral profiling, sleeping patterns, bone metabolism, and energetic expenditure. He is a member of the scientific board of the two Italian RASopathy supporting groups (Costello-CFC and Angeli Noonan).

MARTIN ZENKER, MD (MODERATOR)



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.

5th International RASopathies Symposium

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Life with a RASopathy



Kimberly Luntsford, 42
Kalispell, MT, USA

Hobbies

- Playing electronic keyboard
- Listening to music
- Watching movies
- Cooking in my microwave
- Finding and reading books from thrift stores
- Loving my cats, especially my Siamese



CFC Syndrome

GENE MUTATION: BRAF



When I first knew I had a RASopathy:

I was included in the 1989 paper by Reynolds and Opitz that identified CFC syndrome as distinct from Noonan syndrome. Years later after the 2006 identification of the genes causing CFC, I was tested and confirmed to have a BRAF mutation. At that point, my mom called Primary Children's Hospital in Salt Lake City and reconnected with Dr. Opitz, who was thrilled to hear about how I was doing.

How I can get help when I need it and who my supports are:

I'm not shy, I'm willing to ask. My sister and five nieces and nephews are a big help.

What bothers me about living with a RASopathy:

I have difficulty with my eyesight. It is hard to judge steps and distances. I sometimes trip or stumble when there are curbs. I also started having seizures 3 years ago. They have been controlled with medication until a few months ago when I had another one. The doctors are working on changing my medication to try to prevent more.

What I like about living with a RASopathy:

I thrived on the attention I received from school and events that took place and with family members. I love looking at pictures of children/people on the website and seeing others that I can relate to.

What I would tell younger children with a RASopathy or parents or doctors:

I have developmental issues and my curly hair, lack of eyebrows, and glasses indicate that I have CFC syndrome. But if you asked me, I would tell you I am perfectly normal and live a normal life. I am just like everyone else. When I was young I had a lot of medical and developmental issues that required lots of doctor and therapy visits. But as I have become older, my health has become more stable – other than the seizures.

What I want in life and what my dreams are for my life:

I love my life as it is. I want to live at home in my little apartment in my family's home. I don't ever want to move out into a group home. I love my family and my sister and nieces and nephews. I love to socialize with my friends and I love to talk!

Medications

- Trileptal (oxycarbazepine)
- Daily vitamin
- Calcium (over-the-counter)

Medical Consultants

- General Practitioner
- Neurologist
- Optometrist

Medical Issues

- Had feeding issues until 5 years old, when a very bright teacher remained with me throughout my gag reflexes and would continually keep feeding me orally day after day and my vomiting over and over. Within a month, I reached for a piece of turkey on Thanksgiving Day and put it in my mouth. We worked over the course of another few months to get me to chew and I did as good as I have ever done. I still have to be reminded to take smaller bites.
- Health is more stable, except for the seizures
- Had first seizure 3 years ago, medication controlled, but had a second seizure ~1 month ago
- Hearing loss in the last two years – we will going to talk about hearing aids soon. For now, everyone talks louder!

Life with a RASopathy

CFC Syndrome

GENE MUTATION: MEK1/MAP2K1 Y130c:
c.389 A>G; Variant= p.Tyr130Cys (Y130C);
Heterozygous



41 months

Gloria Ann Rogers, 3
Roseburg, Oregon, USA

Education/Profession: Preschool

Hobbies

- Being read to
- Children's puzzles
- Listening to music, especially Bruno Mars
- Riding in my Radio Flyer wagon
- Watching Super Why



One hour after birth



4 months, during
infant spasms
(West syndrome)



8 months, infant
spasms stopped



12 months



18 months



20 months



24 months, blowing kisses



30 months



36 months



38 months

When I first knew I had a RASopathy:

I was informed at 9 months old following a test that was conducted when I was 4.5 months old.

How I can get help when I need it and who my supports are:

I can use sign language for help, or ask for it verbally now with phrases with a few words.

What bothers me about living with a RASopathy:

I don't sleep well, itch constantly, and I vomit mucous several times a day on average and cannot clear it which makes me suction dependent (my suction machine and I never part).

What I like about living with a RASopathy:

I am very flexible due to hypotonia.

What I would tell younger children with a RASopathy or parents or doctors:

Focus on how you can be included, and don't listen to those that say you can't attend preschool, or you can't play a sport because you can't walk etc. Get in your gait trainer and do it.

How others can include me better:

Give me time to process information and respond. Be open to having me in your child's traditional class some so that I can make friends and gather the support network I am going to need in my community for the rest of my life.

What I want in life and what my dreams are for my life:

I want to learn to eat, stand, walk, and run. I want to be included in my neighborhood general education school and not be bused across the city and placed into a classroom that doesn't meet my needs. I want to be able to live independently with proper supports.

Doctors and Specialists:

- Allergist
- Cardiologist at Doernbecher
- Cardiologist at local hospital
- Dentist
- Dermatologist
- Dietician
- Endocrinologist at Doernbecher
- Endocrinologist at local hospital
- Gastroenterologist
- Genetics Counselor
- Geneticist
- Occupational Therapist
- Ophthalmologist
- Neurologist at local hospital
- Neurologist and Epileptologist at Doernbecher
- Pediatrician
- Physical therapist
- Pulmonologist
- Social Worker
- Speech Therapist
- Orthopedist

Medications

- Benadryl
- Zyrtec
- Xopenex
- Cetaphil Cream
- Compounded diaper cream (petroleum jelly, zinc oxide, baking soda)
- Grew out of infantile spasms/West syndrome – took Vigabatrin/Sabril after trying Prednisone and ACTH
- Peritactin and omeprazole didn't affect vomiting when removed, so just going on without them

Mental Health/Behavioral Health

- Behavior Therapy, Evaluation and Plan

School Services

- Early Childhood Special Education
- Early Intervention
- Individualized Education Plan (IEP)
- Occupational Therapist
- Physical Therapist
- Speech Language Pathologist

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Life with a RASopathy



Helaina Stone, 23
Manchester, England

Education/Profession:

I am currently doing a one-year course at a local college, studying Maths, English and Citizenship.

I am also doing a work placement at a primary school for children with special needs.

Hobbies

- Dancing
- Shopping
- Craft

Costello Syndrome

GENE MUTATION: G12S



When I first knew I had a RASopathy:

My mum and dad told me as soon as thought I could understand. Bronwyn my geneticist would talk to me about Costello syndrome.

How I can get help when I need it and who my supports are:

I ask for help when I can't do things. I need help with lots of things. My Personal Assistants help me, teachers at college help me, as well as my mum and dad. At hospital the nurses and doctors help me as well.

What bothers me about living with a RASopathy:

I wish I could ride a bike.

I wish I could do more by myself and be independent.

I wish I did not have to take lots of medications.

What I like about living with a RASopathy:

Going to college and seeing my friends

Dancing competitions, doing the Duke of Edinburgh award. People are nice and kind there.

I like being a young leader at cub scouts.

Going out shopping.

What I would tell younger children with a RASopathy or parents or doctors:

Go to the CostelloKids website, see happy faces and watch the videos.

Ask your doctor how to get more information.

Read our leaflets and booklet.

Go onto the internet and ask my dad to help.

Visit the Facebook pages.

Don't be worried about having Costello syndrome.

Talk to the doctors, nurses, other parents or brothers and sisters, if you have them.

Tell the doctors to read up on the CostelloKids website and read the papers. Be happy to be alive.

How others can include me better:

Talk to me.

Ask me to join in.

Some people forget about me and forget I am there, come over and talk to me and ask me what I want to do.

What I want in life and what my dreams are for my life:

Stay at college for another year.

I want to work part time at Rodney House (a special needs school)

Go out with my Personal Assistants (PAs) and get a break from my parents.

Live at home.

Make sure I look after my health and go for check-ups.

Meet new friends.

Continue my dancing and do more competitions.

Keep in touch with my PA Fay and see her baby.

Keep in touch with friends from college.

Going to new places in America.

Medications

- Ciprofloxacin – antibiotic prophylaxis for bladder/kidneys
- Desmopressin – reduces nighttime urine production
- Ethinylestradiol – estrogen
- Gabapentin – nerve pain
- Hux – high dose vitamin D
- Magnesium glycerophosphate – magnesium supplement
- MST continus suspension – morphine
- Mucodyne – thins mucus
- Norditropin SimpleXx – growth hormone for GHD
- Sando-K effervescent tablets – potassium supplement
- Fexofenadine – hay fever

Medical Consultants

- Prof Bronwyn Kerr – Geneticist
- Prof Peter Clayton – Endocrinologist
- Tim Clayton – Dermatologist
- Jane Ashworth – Ophthalmologist
- Stefan Meyer – Oncology
- Petra Jenkins – Cardiology
- Mike Rothera – Ear, Nose, Throat
- Peter Selby – Orthotics
- John Thorn – Neurology
- David Johnson – Orthopedist

Others

- Julie Bishop – Podiatrist
- Kellie Armstrong – Special Needs Dentist
- Holly – Physio
- Anne – Speech and Language Therapist



07-2017

Life with a RASopathy

Costello Syndrome

GENE MUTATION: G12S



Jalisa Sullivan, 21
Rockland, Massachusetts, USA

Education/Profession:

I go to school. I'm learning about jobs, writing my resume, and working in the school store. I volunteer at the Soup Kitchen, deliver Meals on Wheels, and help people in wheelchairs to go bowling. I still do 'programs' – learning about science, writing, reading, math, geography and history. I also get OT, PT, and Speech Therapy.

Hobbies

- YouTube
- Music
- Facebook
- Talking to my friends and family on FaceTime
- Shopping at the mall (one of my favorite things to do!)
- Piercings, tattoos, and coloring my hair



When I first knew I had a RASopathy:

I've always known I have Costello Syndrome, but I just started learning that it is a RASopathy.

How I can get help when I need it and who my supports are:

I ask for help from my mom or my family. My staff at my house helps me, too. My doctors always help me when I feel like something is wrong.

What bothers me about living with a RASopathy:

I can't live by myself in my own place and I can't drive. I have to go to the doctor a lot.

What I like about living with a RASopathy:

Not much!

What I would tell younger children with a RASopathy or parents or doctors:

It will be okay even if it's different from your brothers and sisters.

How others can include me better:

Listen when I talk and tell me if you don't understand me. Help me to know what you're talking about. Sometimes it's hard to understand you, too.

What I want in life and what my dreams are for my life:

I want to get a job and move into my adult house. I want to learn languages, keep being part of my church, go out with my friends, and maybe take karate.

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Medications

- Abilify
- Prozac
- Trazadone
- Acitretin
- Omeprazole
- Calcium
- Vitamin D
- Multivitamin
- Inhaler

Health Providers

- Primary care
- Occupational Therapist
- Physical Therapist
- Speech Therapist
- Dermatologist
- Gastroenterologist
- Chiropractor
- Dentist
- Neurosurgeon
- Orthopedist
- Geneticist
- Endocrinologist
- Optometrist
- and sometimes ENT

Mental Health Services

- Psychiatrist to prescribe medications
- Counseling at school

School Services

I'm transitioning from school services in December 2017, but I still have an IEP that helps my staff know how to help me learn, and a behavior team to help me with my behavior.

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Life with a RASopathy



Zachery Cru Leach, 4
Orlando, Florida, USA

Education: Pre Kindergarten

- a special needs class from 8am – 2pm
- a private day care from 2pm – 6pm

Hobbies

- Dinosaurs (I love dinosaurs)
- Cars
- Planes & trains
- Playing outside
- Playing on tablet
- Watching TV



When I first knew I had a RASopathy:

Mom knew when Zac was two months old. Café au lait spots began to appear, and she sought out genetic testing to see if Zac was positive for NF1. Zac, however, still does not know why he is different and has only recently begun noticing his spots.

How I can get help when I need it and who my supports are:

Ask as best I can, also lots of pointing and hand-over-hand; also use communication assistance apps & boards.

What bothers me about living with a RASopathy:

Lots of doctor appointments & tests. Treated differently by peers because of speech difficulties and spots.

What I like about living with a RASopathy:

Unique, get to share my story.

What I would tell younger children with a RASopathy or parents or doctors:

Educate yourself (family and friends too) about the condition, you are your best advocate, stay on top of therapies and medical records.

How others can include me better:

Don't judge because of speech delay or individual characteristics, but give a chance to get to know me and help me learn.

What I want in life and what my dreams are for my life:

Have a healthy and productive life. Share my story to help others. Advocate for NF to bring awareness.

Medical Professionals

- Pediatrician
- Ophthalmologist
- NF Clinic
- ENT
- Endocrinologist
- Urologist

Interventions

- ABA therapy (1:1) at private day care with other neurotypical kids

School Services

- IEP and in a special needs class through the local public school
- Speech therapy
- Occupational therapy

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Life with a RASopathy

NF1 Neurofibromatosis type 1



Beverly Oberlander, 63
Murietta, USA

Profession:

I don't work outside the home anymore although I have a Master's Degree in Marketing Communications. I do a lot of Volunteer work. When my son was younger, I volunteered at his school. For the past 30 years, I have volunteered with various Neurofibromatosis organizations.

Hobbies

- Reading (voracious)
- Theater
- Playing Mah Jongg
- Spending a lot of time with friends, my mother
- Traveling



When I first knew I had a RASopathy:

I was diagnosed with NF 35 years ago, despite the fact my dad and brother had NF and I had all the signs. We had been told it only went from father to son. At the time, not enough was known about NF to call it a RASopathy.

How I can get help when I need it and who my supports are:

Luckily I am tied into a strong support system with the Neurofibromatosis Network and a strong group of friends and family from my 30+ years of working with NF organizations, and can rely on this group for help. Also, as the middle generation of a multi-generational NF family, I am well aware of what needs to be done and have acquired a firm knowledge base. I also am fortunate to have knowledgeable doctors, go to the NF clinic at the University of Chicago and have local physicians who are not afraid to ask others if they have a question about my treatment.

What bothers me about living with a RASopathy:

I hate the unpredictability of this disorder, not knowing what to expect down the road. It is not so much for me, but the worry I have for my 31 year old son who has had more than his share of problems with this disorder and my 38 year old niece who has already had an MPNST.

What I like about living with a RASopathy:

I would prefer not to have an unpredictable disease and to have passed it down to my child, nor to have watched my father suffer. The positive aspect is that I have met an incredible group of people through my work with the various NF organizations who have become much more than dear friends, but family. I also feel that through my work, as a consumer reviewer on the Army's Neurofibromatosis Research Program and as a patient advocate, and a spokesperson for NF I may have made a small difference in the lives of others.

What I would tell younger children with a RASopathy or parents or doctors:

I would tell both children and parents to not let the disease or disorders stop them from doing whatever they want to do. My son has had many surgeries and is in constant pain but has the attitude that "I am me, I am not my disease." They cannot let the disease define who they are, deal with issues as they come up, but try to live as normal a life as possible. As for doctors, listen to parents. They know their child best. If they sense or see something wrong, they are most likely right. They see their child everyday – they can see things that might not be obvious on a yearly or semi-annual visit.

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How others can include me better:

As an adult, this isn't a problem I have had. No one has shunned me because of my NF, in fact my friends have been highly supportive. As a kid, try to find just a few good friends who might share similar interests. Being a good listener is always helpful as both a child and an adult.

What I want in life and what my dreams are for my life:

I am looking forward to my husband Lew's retirement in another year and to travel more. Our son is secure in his job and has a house – I would love to see him settled down with a wife and family. He is happy now but I would like him to have that last piece. I have seen tremendous progress in NF research in my lifetime and would love to see more progress and treatments for some of the more devastating problems of this disorder.

Medications

- Omeprazole
- Topiramate
- Lovastatin
- Amitriptyline
- Ranitidine (daily)
- Calcium
- Vitamin D
- Fioricet as needed for migraine
- Norco as needed for pain
- Metaxalone as needed

Medical Consultants

- Family Medicine
- Neurologist/NF Specialist (in Chicago)
- Plastic Surgeon/Cranio-facial Reconstruction
- Gynecologist
- Breast Surgeon
- Oncology
- Gastroenterology

Medical Success Story

Last December I completed 10 years of anti-estrogen drugs for my Stage III breast cancer. YAY!!!

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Life with a RASopathy



Owain Wilks, 8
Milton Keynes, United Kingdom

Education:

Year 3 in mainstream school
with full-time teaching assistant support

Hobbies

- Vaulting
- Horse riding
- Reading
- Cub scouts
- Singing

Noonan Syndrome

GENE MUTATION: PTPN11



When I first knew I had a RASopathy:

Owain was born with a heart murmur and at three weeks bloods were taken to check for genetic conditions. We got the results at his 4 month-old cardiology review. The doctor knew very little of Noonan syndrome and we were handed information printed from online.

How I can get help when I need it and who my supports are:

With Owain diagnosis came an understanding that we would need to research the condition ourselves so we could go to professionals with confidence.

What bothers me about living with a RASopathy:

Owain has never had anything other than knowing he has Noonan syndrome so he carries on smiling no matter how many operations blood test and exams examinations he has to put up with.

What I like about living with a RASopathy:

Owain likes being special and unique and a superhero.

What I would tell younger children with a RASopathy or parents or doctors:

We have always tried to never let a diagnosis stop Owain from succeeding. We always said the the diagnosis is a map to follow but he will make his own route on that journey. Doctors need to understand that parents know their children best and just want the best for their child.

How others can include me better:

Awareness of Noonan syndrome and its effects on the person will help people to be more understanding of our children which means they can feel more included in activities and school.

What I want in life and what my dreams are for my life:

Owain's dreams and ambitions change regularly but all we ask is he is able to grow as a person and the superhero he is.

Medical Consultants

- Cardiologist
- Community Pediatrician
- Pediatrician
- Ear, Nose and Throat
- Gastroenterologist
- Ophthalmologist
- Spinal surgeon
- Physiotherapist

Medications

- Melatonin
- Regular paracetamol (acetaminophen)

School

Mainstream school with a full education and health plan with 30hrs teaching assistant support.

Surgeries (16 to date)

- Nissen fundoplication
- PEG placement
- Orchiopexies (several)
- Tonsillectomy
- Adenoidectomy
- Grommets/tubes (several)
- Tooth extractions (several)
- Gastrostomy stoma replacement
- Gastrostomy stoma closure
- Tooth extractions due to medical formula

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Life with a RASopathy

Noonan Syndrome

GENE MUTATION: RAF1

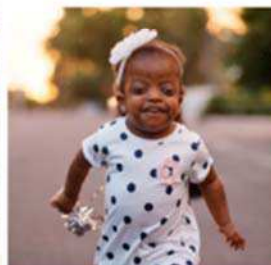


London Jeanell Channer, 4
Ft Lauderdale, Florida, USA

Education: In Pre-kindergarten

Hobbies:

- Dancing
- Singing
- Playing on IPAD
- Spending time with family
- Have books read to me
- Playing outside



When I first knew I had a RASopathy:

The geneticist visually diagnosed London with Noonan syndrome when she was 4 days old while in the PICU. Genetic testing confirmed the diagnosis six weeks later.

How I can get help when I need it and who my supports are:

London has immense support from our local children's hospital, Joe DiMaggio Children's, where all of her vast amount of medical physicians, and favorite nurse she's known since birth take great care of her. Also Facebook Noonan Syndrome support group, and family and friends who support her any way possible.

What bothers me about living with a RASopathy:

All the doctors and hospital appointments and testing. London knows the exit from the highway for the hospital, so when she realizes where she is going, it becomes hard to keep her calm during the very long appointment days.

What I like about living with a RASopathy:

- Proving the doctors wrong
- Showing how GOD is still in control
- Spreading awareness

What I would tell younger children with a RASopathy or parents or doctors:

- Take one day at a time/minute, hour if needed
- Take breaks from doctors medical life. Give them/yourself a break
- Let them be kids
- Take lots of pictures on good and bad days
- Its ok to say enough/NO sometimes is the best answer
- Accept the help/ask for help
- Don't be ashamed of your child

What I want in life and what my dreams are for my life:

- Live a happy and healthy full life. No future surgeries, New Heart remains healthy, grow up and have friends, be loved, and full of hope
- Continue to prove doctors wrong
- Show what God can do (Jeremiah 29:11) (Proverbs 3:5)

Medications

Medication	Dose	Frequency	Start Date	End Date	Status
Aspirin	100mg	Once daily	1/1/17	12/31/17	Active
Acetaminophen	100mg	As needed	1/1/17	12/31/17	Active
Amoxicillin	250mg	Twice daily	1/1/17	12/31/17	Active
Clonidine	0.1mg	Twice daily	1/1/17	12/31/17	Active
Hydrocortisone	10mg	Twice daily	1/1/17	12/31/17	Active
Insulin	10 units	Twice daily	1/1/17	12/31/17	Active
Levothyroxine	50mcg	Once daily	1/1/17	12/31/17	Active
Lisinopril	10mg	Once daily	1/1/17	12/31/17	Active
Metoprolol	25mg	Twice daily	1/1/17	12/31/17	Active
Phenylephrine	10mg	Twice daily	1/1/17	12/31/17	Active
Simvastatin	20mg	Once daily	1/1/17	12/31/17	Active
Sildenafil	20mg	Twice daily	1/1/17	12/31/17	Active
Tamoxifen	20mg	Twice daily	1/1/17	12/31/17	Active
Torsemide	10mg	Once daily	1/1/17	12/31/17	Active
Warfarin	5mg	Once daily	1/1/17	12/31/17	Active

Medical Consultants

- Pediatrician
- Cardiologist
- ENT
- Geneticist
- Joe DiMaggio Children's Hospital

School

- IEP for developmental delay
- Pre-K Program
- Physical Therapy
- Occupational Therapy

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Life with a RASopathy

Noonan Syndrome

GENE MUTATION: SOS1



Kimberly Reid, 37
Kansas City, Missouri, USA

Profession: At-Home Mom

Hobbies

- Crafts
- Card-making
- Organizing



Newborn



10 years old



18 years old



29 years old

When I first knew I had a RASopathy:

I found out when I was 27 years old. After my son was tested.

How I can get help when I need it and who my supports are:

I speak with the GP and she helps anyway that I need. She really listens and learns from me.

What bothers me about living with a RASopathy:

That people do not understand it.

What I like about living with a RASopathy:

It has taught me how to be a stronger person and to teach about my syndrome.

What I would tell younger children with a RASopathy or parents or doctors:

That it will be ok. Just be honest, understanding, and loving. We all need someone to lean on.

How others can include me better:

I think understanding is a major factor. Once they understand they will come around to include.

What I want in life and what my dreams are for my life:

My dreams is to help all Noonan Syndrome individuals not have struggles when it comes to the medical world. To get the help they need, when it is needed.

Medications

- Acetylcarnitine
- Alpha Hydroxy Acids
- Alpha Lipoic Acid
- Citalopram Hydrobromide
- CoQ10
- Cyclobenzaprine
- Dasyee (levonorgestrel and ethinyl estradiol)
- Diclofenac
- Erogcalciferol (Vitamin D₂)
- Fluticasone
- Horizant (gabapentin encarbil extended release)
- Ketoconazole
- Levothyroxine
- Loratadine
- Meloxicam
- Prilosec
- Symbicort (budesonide – formoterol fumarate dihydrate)
- ProAir (albuterol sulfate)
- Valtrex (valacyclovir hydrochloride)
- Vitamin B12
- Vitamin D

Medical Consultants

- Primary Care Physician
- Cardiologist
- Dermatologist
- ENT
- Endocrinologist
- Neurologist
- Ocularist
- Ophthalmologist

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Lisa Schill, Co-Investigator
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- Annette Bakker, President and Chief Scientific Officer, Children's Tumor Foundation (CTF)
- Traceann Rose, Director of Parent Engagement, Children's Tumor Foundation (CTF)

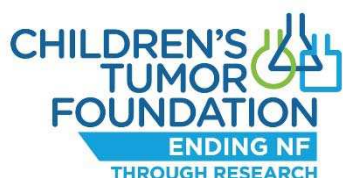
Noonan syndrome:

- Michelle Ellis, Director, Noonan UK
- Rebekah Busbee, President, Noonan Syndrome Foundation (NSF)
- Ian Legg, Chair of the Trustees, Noonan Syndrome Association

Notes

RASopathiesNet

Thank You to Our Partnering Organizations



Noonan UK



ICSSG
International Costello
syndrome Support group



SAVE THE DATE!

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