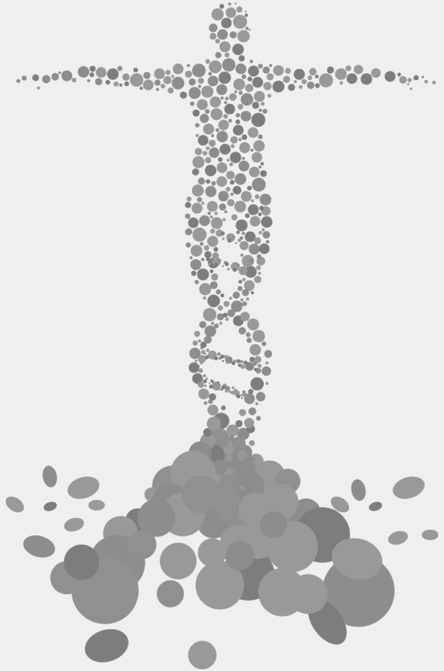
# SAMD9 and SAMD9L Syndromes

## Insights into Pathogenesis and Clinical Picture

St. Jude 2019

**Bone Marrow** Failure Expert Meeting



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## Welcome

SAMD9 and SAMD9L (SAMD9/9L) genes are paralogue genes on chromosome 7q involved in viral host defense, endosome formation, and cellular proliferation. Germline mutations in both genes are associated with diverse clinical phenotypes and a risk for myelodysplastic syndromes with non-random loss of chromosome 7. The full clinical picture is not defined, and recommendations on management and surveillance of mutation carriers are lacking. Furthermore, the physiological function of SAMD9/9L genes, as well as the mechanistic link between germline mutations and disease remain elusive.

We offer a two-day meeting that aims to bring together the international body of SAMD9/SAMD9L experts to assemble a network of investigators who are focused on the study of these genes as well as associated syndromes. During this time, we will listen to multiple presentations describing the current knowledge within the field and potential directions forward to answer the most pressing scientific questions. Additionally, we will have representatives from around the world describe the clinical presentations of their SAMD9/9L patient cohorts so to open a discussion to develop a clinical registry, and establish consensus guidelines on diagnosis, therapy and surveillance based on expert knowledge.

## Conference Hosts

### Marcin Wlodarski, MD, PhD

*Assistant Member, St. Jude Faculty*
**Hematology Department**

Marcin was trained as a pediatrician and hematologist/oncologist at the University of Freiburg in Germany where under mentorship of Charlotte Niemeyer and studying large European patient cohorts he gained expertise in knowledge in bone marrow failure and pediatric MDS. His lab focuses on characterization on genes predisposing to pediatric MDS/BMF and contributed to the understanding of GATA2 and SAMD9/9L genes as MDS germline drivers. In 2018 he joined St. Jude as faculty to establish a BMF/MDS clinical and translational research program.

### Jason R. Schwartz, MD, PhD

*Instructor, St. Jude Faculty*
**Hematology & Pathology Departments**

Jason completed his general pediatrics residency at the Children's Hospital Vanderbilt and his pediatric hematology/oncology fellowship at St. Jude. During his fellowship and under the mentorship of Dr. Klco, Jason described the genomic landscape of pediatric MDS and identified that germline SAMD9/9L mutations are common causal lesions in pediatric MDS. Currently, he aims to further understand the biological impacts of SAMD9/9L mutations while actively caring for these patients in the clinical setting.

### Jeffery M. Klco, MD, PhD

*Associate Member, St. Jude Faculty*
**Pathology Department**

Jeff obtained his MD and PhD at Washington University School of Medicine, followed by clinical training in Anatomic Pathology and Hematopathology and post-doctoral fellowship under the mentorship of Tim Ley. Since his arrival at St. Jude in 2014, he has established an independent lab focused on the genomics and molecular mechanisms of pediatric myeloid tumors. In addition to his active research program, which studies the molecular mechanisms of SAMD9 and SAMD9L mutations, Jeff is also a staff hematopathologist at St. Jude.

# Agenda

## Thursday, October 31, 2019

| Time | Event |
|---|---|
| 7:30 pm | Reception at The Peabody Hotel, Louis XVI Room |

## Friday, November 1, 2019

| Time | Event |
|---|---|
| 7:30 am | Pick-up at The Peabody Hotel, Valet area |
| **Session 1: Overview of History and Clinical Aspects** – Moderators: Inga Hoffman-Zhang, MD (Madison) and Thierry LeBlanc, MD (Paris) | |
| 7:55 am | Introduction and Welcome - Mitch Weiss, MD, PhD (Memphis) and Marcin Wlodarski, MD, PhD (Memphis) |
| 8:00 am | ***From Monosomy 7 Syndrome to SAMD9/9L Germline Mutations: Where Are We Now?*** – Kevin Shannon, MD (San Francisco) |
| 8:30 am | *Strange Bedfellows: Ataxia and Pancytopenia* – Wendy H. Raskind, MD, PhD (Seattle) |
| 9:00 am | ***Pediatric MDS and Predisposition to Myeloid Neoplasia: Time for a Universal Classification of Hypoplastic Bone Marrow Disease?*** - Charlotte Niemeyer, MD (Freiburg) |
| 9:30 am | ***MIRAGE*** – Satoshi Narumi, MD, PhD (Tokyo) |
| 9:50 am | Break |
| **Session 2: Disease Phenotypes and Genotypes** – Moderators: Lauren Jeffries, DO, FACMG (New Haven) and Lisa J. McReynolds, MD, PhD (Bethesda) | |
| 10:20 am | ***SAMD9 in Endocrine Development and Growth*** – John Achermann, MD, PhD (London) |
| 10:50 am | ***Novel mutations in SAMD9L: Mimics of the Autoinflammatory Interferonopathy*** CANDLE – Raphaela T. Goldbach-Mansky, MD, MHS (Bethesda) and Katherine Calvo, MD, PhD (Bethesda) |
| 11:10 am | ***SAMD9/9L Variant Curation and Computational Prediction*** – Sushree Sahoo, PhD (Memphis) |
| 11:30 am | Lunch |
| **Session 3: Model Systems and Mechanisms** – Moderators: Kanako Tanase-Nakao, PhD (Tokyo) and Jeff Klco, MD, PhD (Memphis) | |
| 1:30 pm | ***Establishment of Mouse Models to Elucidate Normal and Mutated SAMD9/L Function*** – Toshiya Inaba, MD, PhD (Hiroshima) |
| 2:00 pm | ***Modeling Chromosome 7q22 Segmental Deletions in Mice*** – Jasmine C.Y. Wong, PhD (San Francisco) |
| 2:20 pm | ***The Basic Research on the SAMD9 Protein: What, Where and With Whom?*** – Satoshi Narumi, MD, PhD (Tokyo) |
| 2:50 pm | ***SAMD9/9L Structural Investigation*** – Melvin Thomas, PhD (Memphis) |
| 3:10 pm | ***iPSC Modeling of SAMD9/9L Gain-of-Function Mutations*** – Jason Schwartz, MD, PhD (Memphis) |
| 3:30 pm | Break |
| **Session 4: Host Defense and Immune Dysregulation** – Moderators: Hirotaka Matsui, MD, PhD (Kumamoto) and Bonnie Lau, MD, PhD (Baltimore) | |
| 4:00 pm | ***SAMD9 and SAMD9L Form an Essential Host Barrier Against Poxvirus Infection*** – Yan Xiang, PhD (San Antonio) |
| 4:25 pm | ***Mechanism of SAMD9 inhibition by poxvirus C7 and K1*** – Junpeng Deng, PhD (Stillwater) |
| 4:50 pm | ***Studying SAMD9/9L Function with Poxviruses as a Tool*** – Jia Liu, PhD (Little Rock) |
| 5:15 pm | ***Sterile Alpha Motif Domain-Dependent Mechanisms in Cellular Signaling and Survival***-Kyle Hewitt, PhD (Boston) |
| 6:00 pm | Departure to Graceland, The Home of Elvis Presley (Tour and Dinner) |

## Saturday, November 2, 2019

| Time | Event |
|---|---|
| 7:30 am | Pick-up at The Peabody Hotel, Valet area |
| **Session 5: Clinical Practice** – Moderators: Jean Soulier, MD, PhD (Paris) and Shinsuke Hirabayashi, MD (Hokkaido) | |
| 8:00 am | ***St. Jude Experience and Proposal for a Natural History Registry*** – Catherine (Katie) Nelson, DO (Phoenix) |
| 8:20 am | ***The French Experience on SAMD9/9L Families*** – Marie Sebert, MD, PhD (Paris) |
| 8:40 am | ***Difficult Transplants*** – Rakesh K. Goyal, MD, MRCP (Kansas City) |
| 8:50 am | ***Clinical Outcomes of Patients with SAMD9/9L Mutations - EWOG MDS Experience*** – Brigitte Strahm, MD (Freiburg) |

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|---|---|
| **Session 6: Case series (Rapid Fire)** –<br>Moderators: Jessica Boklan, MD (Phoenix) and Luiz Fernando Lopes, MD (Brazil) | |
| 9:20 am | **Sarah A. Bannon, MS** (Houston) *26 Years to Diagnosis: SAMD9 mutation in a 28-Year- Old Woman with Mosaic Turner Syndrome with Isochromosome Xq*<br>**Timothy Olson, MD, PhD** (Philadelphia) *SAMD9/SAMD9L at CHOP. One Size Doesn't Fit All*<br>**Shang-Hsien Yang, MD** (Boston) *Play it Again and Again, SAM*<br>**Yigal Dror, MD, FRCP(C)** (Toronto) *Familial Monosomy 7*<br>**Bonnie Lau, MD, PhD** (Baltimore) *Diagnosed with Russell Silver Syndrome…until Age 9*<br>**Alison Bertuch, MD, PhD** (Houston) *A Family with Ataxia and a Child with Variable Pancytopenia*<br>Lisa J. McReynolds, MD (Bethesda) *8 month old male with a SAMD9L mutation presenting with pancytopenia and infections progressing to HLH* |
| 10:00 am | Break |
| **Session 7: Assembly of an Expert Opinion** –<br>Moderators: Taizo Nakano, MD (Aurora), and Marcin Wlodarski, MD, PhD (Memphis) | |
| 10:30 am | **Panel Discussion:**<br>**Diagnostic approach: Initial tests, what is a pathogenic mutation?**<br>• **Thierry LeBlanc, MD** (Paris; pediatric and adult hematology)<br>• **Satoshi Narumi, MD, PhD** (Tokyo; genetic assays)<br>• **John Achermann, MD, PhD** (London; endocrinology)<br>**Surveillance approach: Frequency of monitoring and what should be included?**<br>• **Jason Schwartz, MD, PhD** (Memphis; pediatric hematology, MDS genomics)<br>• **Sara Lewis, MS, LCGC** (Memphis; genetic counselor)<br>• **Wendy Raskind, MD, PhD** (Seattle; genetecis, neurology)<br>**Treatment approach: Thresholds for transplant, type of transplant?**<br>• **Brigitte Strahm, MD** (Freiburg; BMT specialty)<br>• **Timothy Olson, MD, PhD** (Philadelphia; BMT specialty)<br>• **Alison Bertuch, MD, PhD** (Houston, bone marrow failure expert) |
| 12:00 pm | Lunch |
| 12:30 pm | Departure to The National Civil Rights Museum |
| 6:00 pm | Dinner |

# SAMD9 and SAMD9L Syndromes
# Insights into Pathogenesis and Clinical Picture

Marlo Thomas Center for Global
Education and Collaboration

Lecture Hall/Room IA-1010

November 1-2, 2019

### Kevin Shannon, MD

American Cancer Society Research Professor
Auerback Distinguished Professor of Molecular Oncology
Department of Pediatrics
*University of California, San Francisco*
*San Francisco, California, USA*

**From Monosomy 7 Syndrome to SAMD9/9L Germline Mutations: Where Are We Now?**

I will attempt to place the remarkable discovery by Narumi and colleagues of germline gain-of-function SAMD9 and SAMD9L mutations as an initiating event in the development of MDS in the context of previous clinical and laboratory observations. My goal is to frame key questions for discussion and for subsequent exploration.

### Wendy H. Raskind, MD, PhD

Professor, Department of Medicine, Division of Medical Genetics
Professor, Department of Psychiatry and Behavioral Sciences
(Joint) Professor, Genome Science (Adjunct)
*University of Washington*
*Seattle, Washington, USA*

**Strange Bedfellows: Ataxia and Pancytopenia**

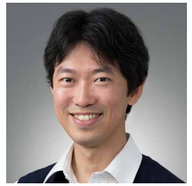
How SAMD9L is identified as the gene for Ataxia-Pancytopenia syndrome and then focus on the neurological manifestations. The course of neurologic impairment will be illustrated through neuroimages and patient videos.

### Charlotte Niemeyer, MD

Division of Hematology and Oncology
*University Children's Hospital Freiburg*
*Freiburg, Germany*

**Pediatric MDS and Predisposition to Myeloid Neoplasia - Time for a Universal Classification of Hypoplastic Bone Marrow Disease?**

I will discuss pediatric MDS with emphasis on bone marrow failure and predisposition syndromes, go into detail of the current pediatric WHO classification, and describe the different national practices to diagnose these patients resulting in the inclusion of distinct registries.



### Satoshi Narumi, MD, PhD

Department of Molecular Endocrinology
*National Research Institute for Child Health and Development*
*Tokyo, Japan*

**MIRAGE**

Investigating the molecular functions of SAMD9, using the "disease-model" HEK293 cells and patient-derived skin fibroblast cells. The preliminary results showed that SAMD9 is as mysterious as a mirage.

### John Achermann, MD, PhD

Professor of Paediatric Endocrinology
Wellcome Trust Senior Research Fellow in Clinical Science Genetics & Genomic Medicine
*University College London (UCL) Great Ormond Street (GOS) Institute of Child Health*
*London, United Kingdom*

**SAMD9 in Endocrine Development and Growth**

I will review our work leading up to the identification of SAMD9 as an important regulator of human adrenal and gonad development, as well as the identification of children with gain-of-function SAMD9 variants and MIRAGE syndrome. I will discuss some of the clinical features associated with SAMD9 variants and will highlight how mechanisms of dynamic revertant mosaicism and aneuploidy can modify phenotype and affect penetrance. I will also consider if new technologies such as iPSC generation and scRNASeq analysis can help in studying SAMD9-related events, as well as whether SAMD9 can influence other phenotypes in families or the population.

### Raphaela T. Goldbach-Mansky, MD, MHS

Section Chief, Translational Autoinflammatory Diseases Section
Laboratory of Clinical Immunology and Microbiology (LCIM)
Division of Intramural Research (DIR) *National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH)*
*Bethesda, Maryland, USA*

**Novel Mutations in SAMD9L: Mimics of the Autoinflammatory Interferonopathy CANDLE**

The focus of Dr. Goldbach-Mansky's research is the description, study of pathogenesis, and treatment of patients with autoinflammatory diseases who present with systemic and organ-specific sterile inflammation early in childhood. Many patients have monogenic defects that point to critical innate immune pathways. While screening patients with undifferentiated autoinflammatory phenotypes, we identified patients with neutrophilic panniculitis, severe viral induced interstitial lung disease and a chronic IFN signature in the blood, who harbor novel, de novo frameshift mutations in SAMD9L. Although the pathways that lead to their IFN signature are still poorly understood, I will present their clinical description, treatment and preliminary pathogenic characterization.

### Katherine Calvo, MD, PhD

Senior Research Physician
Hematology Section Department of Laboratory Medicine
*National Institutes of Health (NIH) Clinical Center*
*Bethesda, Maryland, USA*

Dr. Katherine Calvo's research is focused on the pathology and diagnosis bone marrow diseases with germline predisposition to myeloid malignancy. She will describe the bone marrow features of our SAMD9L cohort and other disease mimics.

### Sushree Sahoo, PhD

Postdoctoral Research Associate
Department of Hematology
*St. Jude Children's Research Hospital*
*Memphis, Tennessee, USA*

**SAMD9/9L Variant Curation and Computational Prediction**

Based on our experience from a large cohort of patients with SAMD9/9L variants identified in the European EWOG-MDS registries, and previously published data, we will present our first attempts to systematically curate variants identified in patients. We will discuss the role of clinical phenotyping, in vitro testing in cell lines, and computational prediction in the classification of variants found in SAMD9/9L genes.


**Toshiya Inaba, MD, PhD**

Professor
Department of Molecular Oncology and
Leukemia Program Project
*Research Institute for Radiation Biology and Medicine*
*Hiroshima University Kagamiyama, Higashihiroshima,*
*Hiroshima, Japan*


**Establishment of Mouse Models to Elucidate Normal and Mutated SAMD9/L Function**

We established two mouse lines that have illustrated the deep connection of the Samd9/L genes with human diseases. Both homo- and heterozygotes of Samd9L-deficient mice were born and grew up normally, but later developed MDS. Mice carrying a Samd9L mutation had a short life with apparently a small body and suffered from multiple organ abnormalities including anemia, neutropenia, gonadal hypoplasia, and immunological abnormalities that mimic the MIRAGE syndrome. Bone marrow cells from Samd9L-deficient mice proliferated better than those from normal littermates in lethally irradiated mice, whereas cells carrying mutated Samd9L had less potential for bone marrow reconstitution. This could be due to abnormal sensitivity to cytokines in part, because we observed the persistence of cytokine signals in cells lacking the Samd9L gene, while reduction of signals in cells expressing mutated Samd9L. Samd9/L likely affects cytokine signals by interacting with factors regulating endosomal trafficking.


**Jasmine C.Y. Wong, PhD**

Assistant Adjunct Professor
Department of Pediatric Oncology
*University of California, San Francisco*
*San Francisco, California, USA*


**Modeling Chromosome 7q22 Segmental Deletions in Mice**

My research interest is focused on genetically engineering mice to accurately model recurrent chromosome band 7q22 deletions found in human myeloid disease. We have created two mouse models, 5A3+/del and 5G2+/del, harboring deletions of 13 and 29 genes respectively, which are syntenic to the most common 7q22 chromosomal deletion identified in human patients. These mice provide an in vivo model system that allows for functional studies into the role of this chromosome loss in cancer development, including how they might cooperate with Samd9l haploinsufficiency, which would facilitate implementing new therapeutic strategies.


**Melvin Thomas, PhD**

Postdoctoral Research Associate
Department of Pathology
*St. Jude Children's Research Hospital*
*Memphis, Tennessee, USA*


**SAMD9/9L Structural Investigation**

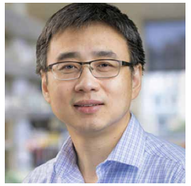
I am interested in understanding the molecular and biochemical function of SAMD9 and SAMD9L at the protein level. My presentation will be a review of the predicted three-dimensional structure of SAMD9 and SAMD9L, and the potential role of their predicted functional domains in pediatric MDS.


**Jason Schwartz, MD, PhD**

Instructor
Clinical Education and Training
*St. Jude Children's Research Hospital*
*Memphis, Tennessee, USA*


**iPSC Modeling of SAMD9/9L Gain-of-Function Mutations**

Germline SAMD9 mutations identified in familial monosomy 7 and MDS are associated with decreased growth of hematopoietic stem and progenitor cells (HSPCs) and bone marrow hypocellularity. Active investigation by Schwartz seeks to develop an iPSC model system that recapitulates this phenotype through CRSIPR/Cas9-mediated mutation of the endogenous SAMD9 locus. Development of this model system will provide a tool for further investigation into pathogenic mechanisms of SAMD9/9L mutations.

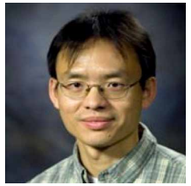


## Yan Xiang, PhD

Professor
Department of Microbiology, Immunology and Molecular Genetics
*The University of Texas Health Science Center at San Antonio*
*San Antonio, Texas, USA*

### SAMD9 and SAMD9L Form an Essential Host Barrier Against Poxvirus Infection

The primary focus of my laboratory is on innate immunity and viral mechanisms of evading the innate immunity. I will discuss our published studies demonstrating that SAMD9 and SAMD9L form a critical host barrier that poxviruses must overcome to establish infection and pathogenesis. In addition, I will present our recent studies in uncovering how viral infection activates SAMD9 and how SAMD9 inhibits viral replication.



## Junpeng Deng, PhD

Professor
Biochemistry and Molecular Biology
*Oklahoma State University*
*Stillwater, Oklahoma, USA*

### Mechanism of SAMD9 Inhibition by Poxvirus C7 and K1

In the lab, we use biochemical and biophysical approaches including x-ray crystallography to reveal the molecular mechanisms of protein-protein interactions at atomic level. The structural and functional data on SAMD9 inhibitors C7 and K1 and their specific interactions with human SAMD9 will be presented.

## Jia Liu, PhD

Assistant Professor
Department of Microbiology and Immunology
College of Medicine
*University of Arkansas for Medical Sciences (UAMS)*
*Little Rock, Arkansas, USA*

### Studying SAMD9/9L Function with Poxviruses as a Tool

Dr. Liu is using poxviruses as tools to study host intrinsic and innate immune responses; she is also interested in understanding how poxviruses evade host defense to cause pathogenesis. SAMD9 is a restriction factor of poxviruses and highly virulent mammalian poxviruses evolved to evade SAMD9 pathway. Because of the complex domain structure and its unknown mode of action, my lab uses poxvirus viral proteins that inhibit SAMD9 as a major tool to study its cellular function. We found that SAMD9 influences many aspects of cell biology. Among them, one role of SAMD9 is to regulate the inducible innate immune responses. We will present our unpublished findings on this perspective. Dr. Liu has been studying the antiviral function of SAMD9 protein family.

## Kyle Hewitt, PhD

Department of Genetics, Cell Biology and Anatomy University of Nebraska Medical Center
College of Medicine

### Sterile Alpha Motif Domain-Dependent Mechanisms in Cellular Signaling and Survival

The majority of Sterile Alpha Motif (SAM) domains throughout the human proteome have not been functionally analyzed. Our group has identified that the SAM domain of a GATA2-target gene (Samd14) - structurally-similar to the SAMD9/9L SAM domains - mediates MAPK/Akt signaling downstream of the c-Kit receptor and promotes cellular survival. Ongoing efforts are focused on elucidating the molecular determinants for SAM domain-dependent mechanisms in the contexts of normal hematopoiesis and stress.

**Catherine (Katie) Nelson, DO**

Pediatric Hematology Oncology
Second Year Fellow
*Phoenix Children's Hospital*
*Phoenix, Arizona, USA*

**St. Jude Experience and Proposal for a Natural History Registry**

I will present our experience on children with SAMD9/SAMD9L and discuss a proposal for prospective registry to monitor patients using longitudinal cytogenetics and NGS to early identify patients at risk for clonal transformation. While we will start this database at St Jude, the ultimate goal would be to register patients nationwide and help develop a standardized treatment approach for patients with these genetic mutations.

**Marie Sebert, MD, PhD**

Department of Hematology
Saint-Louis Hospital
Paris, France

**The French Experience on SAMD9/9L Families**

We have identified patients with germline heterozygous SAMD9 or SAMD9L mutations by exome sequencing of fibroblast DNA in a large cohort of patients with likely-inherited but unresolved bone marrow failure (BMF) or MDS (Bluteau, Sebert et al., Blood 2018). A salient clinical feature in these patients was a frequent pancytopenia and monosomy 7 in the bone marrow, which turned out to be transient by spontaneous reversion with clinical recovery. We have now extended our cohort to more SAMD9/SAMD9L-mutated patients and related family members, including healthy carriers, in order to better understand the natural history in these disorders.

**Rakesh K. Goyal, MD, MRCP**

Section Chief, Bone Marrow Transplantation
Associate Division Director, Hematology/Oncology/BMT
Professor of Pediatrics
*UMKC School of Medicine*
*Children's Mercy Kansas City*
*Kansas City, Missouri, USA*

**Difficult Transplants**

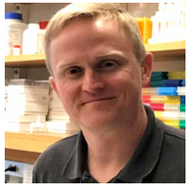
Gain-of-function heterozygous mutations in SAMD9 and SAMD9L gene lead to cellular growth restriction and hypoplasia, resulting in cytopenias, bone marrow failure, and immunodeficiency, often associated with loss of the mutated allele via full or partial deletion of chromosome 7. While donor hematopoietic cell transplantation (HCT) can be curative, a decision to proceed with transplant is not straightforward because marrow cells can undergo somatic "genetic correction" events and spontaneous blood count recovery. In this presentation, we would describe transplant details and outcomes in a series of patients with hematologic diseases associated with SAMD9/SAMD9L germline mutations. The talk will focus on the very problematic cases with MIRAGE syndrome to show what clinicians should be aware of and what acute complications can be anticipated, and ongoing issues in transplant survivors.

**Brigitte Strahm, MD**

Division of Hematology and Oncology
*University Children's Hospital Freiburg*
*Freiburg, Germany*

**Clinical Outcomes of Patients with SAMD9/9L Mutations - EWOG MDS Experience**

Brigitte Strahm chairs the HSCT board of EWOG-MDS and has a long standing experience in the field of allogeneic stem cell transplantation for aquired and inherited bone marrow failure syndromes, myeloid predisposition syndromes and myelodysplastic syndromes in children. EWOG-MDS has implemented algorithms for HSCT in pediatric patients with MDS based on MDS subtype (i.e. RCC vs MDS EB), disease severity (i.e. peripheral blood counts and/or transfusion dependence) and karytotype. Outcomes of HSCT in patients with MDS treated according to these algorithms with special attention to SAMD9/SAMD9L germline mutations will be presented.



## Timothy Olson, MD, PhD

Medical Director, Pediatric Blood and Marrow Transplant Program Cell Therapy and Transplant Section Division of Pediatric Hematology Bone Marrow Failure Center Division of Pediatric Hematology
*The Children's Hospital of Philadelphia Assistant Professor of Pediatrics University of Pennsylvania*
*Philadelphia, Pennsylvania, USA*

### SAMD9/SAMD9L at CHOP. One Size Doesn't Fit All

At CHOP, we have cared for patients that have spanned the spectrum of syndromic features and disease biology that are intrinsic to SAMD9/SAMD9L related disorders. This spectrum includes patients with bone marrow failure, MDS and acute myeloid leukemia, as well as patients with non-hematologic manifestations that have lacked hematologic abnormalities. In this presentation, we will highlight four cases that demonstrate this phenotypic spectrum.

## Sarah A. Bannon, MS

Senior Genetic Counselor
Department of Clinical Cancer Genetics
*The University of Texas MD Anderson Cancer Center*
*Houston, Texas, USA*

### 26 Years to Diagnosis: SAMD9 mutation in a 28-Year-Old Woman with Mosaic Turner Syndrome with Isochromosome Xq

The patient is a now 28-years-old Caucasian female born at 36 weeks gestation. Global developmental delay was noted in early childhood. She was diagnosed with mosaic Turner syndrome (45,X/46,X,i(Xq)). Comprehensive genetic evaluation for Rett syndrome, 22q11 deletion syndrome, karyotype, array comparative genomic hybridization (array CGH), Fragile X, and methylation for Prader Willi/Angelman syndromes was performed and negative. She has had lifelong recurrent infections, low IgG and IgA levels. She was diagnosed with thrombocytopenia (plt 90-150k) and anemia (8 g/dL). She has clinical bleeding propensity. She underwent whole exome sequencing in 2018 which identified a SAMD9 likely pathogenic variant c.2141T>C (p.L714P); parental studies confirmed this mutation as de novo. Bone marrow aspiration and biopsy in 2018 revealed cellular bone marrow, 60%, with adequate trilineage maturation, 1% blasts, 45,X (in the setting of known Turner syndrome), negative FISH for monosomy 7 or del(7q31). Flow cytometry was negative for MDS or atypical aberrant myeloid precursors. An 81-gene somatic panel was negative for mutations.

## Akiko Shimamura, MD, PhD

Professor of Pediatrics
Harvard Medical School
Samuel E. Lux IV Chair in Hematology/Oncology
Director, Bone Marrow Failure and MDS Program
*Dana-Farber/Boston Children's Cancer and Blood Disorders Center*
*Boston, Massachusetts, USA*

### Play it Again and Again, SAM

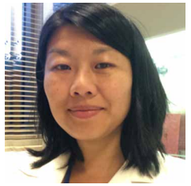
A panel of patients with SAMD9 and SAMD9L variants will be presented. Clinical phenotypes and challenges with variant analysis will be discussed.

## Yigal Dror MD, FRCP(C)

Professor of Paediatrics
Division of Hematology/Oncology
Director, Marrow Failure and Myelodysplasia Program
Senior Scientist, Program in Genetics and Genome Biology, Research Institute
*The Hospital for Sick Children*
*The University of Toronto*
*Toronto, Ontario, Canada*

### Familial Monosomy 7

In this presentation, we will describe two families with an inherited bone marrow failure syndrome and heterozygous SAMD9L variants. In the first family a variant in the AlbA domain with a predictable high damaging effect on the protein was identified in the index case. The child had severe anemia and thrombocytopenia at birth that gradually improved, short stature, failure to thrive, developmental delay and physical malformations including microcephaly, jejunal atresia and others. A second variant in the AlbA domain appeared with or without the first variant in other apparently healthy family members of this family; resembling segregation in other published cases with SAMD9L mutations. The second variant was not predicted to reduce the function of SAMD9L. A second family that was previously reported will also be discussed.



**Bonnie Lau, MD, PhD**

Assistant Professor, Pediatric Hematology
*The Johns Hopkins University School of Medicine*
*Baltimore, Maryland, USA*

**Diagnosed with Russell Silver Syndrome...until Age 9**

The patient was diagnosed with Russell Silver Syndrome when she initially presented with poor growth, dysmorphic facial features, developmental delay, and multiple gastrointestinal issues. She was managed mostly by GI physicians for most of her life. Then whole exome sequencing done at 9 years of age led to the diagnosis of MIRAGE syndrome, and thus the need to see Hematology for the increased risk of MDS/AML.

**Alison Bertuch, MD, PhD**

Director, Bone Marrow Failure Program
Associate Professor, Department of Pediatrics, Section of Hematology/Oncology Associate Professor, Molecular and Human Genetics Associate Professor, Program in Integrative Molecular and Biomedical Sciences Assistant Dean for Curriculum, Graduate School of Biomedical Sciences *Baylor College of Medicine*
*Houston, Texas, USA*

**A Family with Ataxia and a Child with Variable Pancytopenia**

Four generation family with a likely pathogenic SAMD9L missense variant, identical to one present in a family with ataxia-pancytopenia syndrome without transformation to MDS/AML (Chen et al, Blood 2016). The 5-year patient's cytopenias have varied from severe to absent and bone marrow is markedly hypocellular (10-20%), whereas none of the known or inferred carrier family members are known to have significant cytopenias.

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**Bone Marrow Failure and MDS Program**
at St. Jude Children's Research Hospital,
Department of Hematology

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