Summary of Congress Abstracts

Session 1. Clinical Features
Discussion Leader: Kimberly Smith Whitley, MD, Children’s Hospital of Philadelphia, PA

Gastrointestinal Features of Shwachman-Diamond Syndrome
Peter R Durie, MD FRCPC, Hospital for Sick Children and University of Toronto, Canada

Most people with Shwachman Diamond syndrome (SDS) first have symptoms in infancy from pancreatic failure. This included fatty bulky bowel motions, malnutrition and growth failure. Some patients have severe feeding problems while others have a voracious appetite. With the exception of infants and children with feeding difficulties, malnutrition is rarely a long-term problem, provided appropriate treatment with enzyme and vitamin supplements is introduced. It is important to know that in about 50% of people with SDS the function of pancreas can improve with age, such that digestion of fat and protein can become normal. This usually happens in within the first 4 to 5 years of life. Therefore, it is important to monitor the pancreas closely because those individuals who show enough improvement may be able to discontinue enzymes.

Being short is part of having SDS. Newborns with SDS exhibit a moderate deficiency in both height and weight. While SDS patients are generally shorter than average, they are expected to grow at a normal rate. There is no difference in stature between patients with pancreatic insufficiency and those with pancreatic sufficiency. Therefore, poor digestions and the need for enzyme replacement therapy does not account for short stature.

Many infants with SDS have an enlarged liver but the liver size tends to normalize with advancing age. Biochemical tests of the liver also show some mild changes but these tend to improve as well.

Hematologic features of Shwachman-Diamond syndrome
Akiko Shimamura, MD, PhD, Children’s Hospital Boston, MA

Blood cell production by the bone marrow is decreased in patients with SDS. Symptoms may include infection, bleeding, and lack of energy. SDS patients may develop leukemia. Regular monitoring of the blood counts and the bone marrow is important. G-CSF may increase the neutrophil counts but potential effects on leukemia risk are currently unclear. The only cure for bone marrow failure or leukemia is a bone marrow transplant, but transplant risks must be carefully considered for each patient.

Skeletal Features of SDS
Outi Makitie, MD, PhD, Hospital for Children and Adolescents, University of Helsinki, Finland

In addition to pancreatic and bone marrow problems, patients with SDS have a variety of unique skeletal features. These include abnormal growth in height, abnormal appearance of growth plates on X-rays, and increased risk for osteoporosis.

Bone Density Monitoring and Management in Children with Chronic Disease
Ingrid A. Holm, MD, MPH, Children’s Hospital Boston, MA

Oral and dental findings in Shwachman-Diamond Syndrome (SDS)
Carol Mason, BDS(Hons), FDSRCS(Eng), ILT(M), Great Ormond Street Hospital for Children NHS Trust, UK

This group of children with SDS were found to have more tooth decay, gum inflammation and enamel defects than the national average. In addition, they had more mouth ulcers and tooth wear.

Neuropsychological Aspects of SDS
Elizabeth Kerr, BASc, MA, PhD, The Hospital for Sick Children, Canada

This study assessed the learning patterns of 32 children with SDS and compared their results to the
general population, children with Cystic Fibrosis, and siblings. While a range of capabilities was observed, as a group, weaknesses in reasoning, visual-motor integration, complex language skills, phonological processing, processing speed and flexible problem solving were documented. Parents reported heightened concerns attention difficulties, social competence and functional independence.

Molecular Genetics of Shwachman-Diamond Syndrome
Johanna Rommens, PhD*, The Hospital for Sick Children, University of Toronto, Canada
* Jason Bennette Memorial Lecturer

Specific Genetic Counseling Issues in SDS
Ellis J. Neufeld, MD, PhD, Children’s Hospital Boston, MA
This presentation will focus on what makes genetic counseling different from other types of medical encounters, and how this counseling is applied specifically to Shwachman-Diamond Syndrome. Possibilities regarding genetic diagnosis, prenatal versus preimplantation genetic testing, and making predictions about prognosis based on genetics will be discussed.

Malignancies In Shwachman-Diamond Syndrome: Data from the Literature
Blanche P Alter, MD, MPH, National Cancer Institute, MD
Patients with SDS are at increased risk of leukemia, myelodysplastic syndrome, and bone marrow cytogenetic clones without additional hematologic problems. A large prospective cohort is needed to determine the predictors and optimal management of these complications.

Session 2. Surveillance, Management, and Treatment
Discussion Leader: M. James Lopez, MD, PhD, University of Michigan, MI

Psychosocial issues for families of children with SDS
Nancy Cincotta, M.S.W., Mount Sinai School of Medicine, NY

Surveillance, Management and Treatment of Nutritional and Gastrointestinal Problems in Patients with Shwachman-Diamond syndrome
Mark E Lowe, MD, PhD, Children’s Hospital of Pittsburgh at the University of Pittsburgh Medical Center, PA

Jeffrey M. Lipton, M.D., Ph.D. , Schneider Children’s Hospital, Albert Einstein College of Medicine, NY
The etiology of leukemia in patients with Shwachman Diamond syndrome is unclear. As well the prognosis for patients with leukemia remains quite poor.

Hematopoietic Stem Cell Transplantation in Shwachman-Diamond Syndrome
Charlotte Niemeyer, MD, University Children’s Hospital Freiburg, Germany

Workshop: Shwachman Diamond Syndrome: Clinical Diagnosis and Work up
Discussion Leader: Johanna Rommens*/ Akiko Shimamura
* Jason Bennette Memorial Lecturer
Session 3. Shwachman Diamond Syndrome Registries Workshop
Discussion Leader: Peter R Durie, MD FRCPC, Hospital for Sick Children and University of Toronto, Canada

DISCUSSION PANEL:
Marco Cipolli, MD, Cystic Fibrosis Center-Verona, Italy; David C. Dale, MD, University of Washington, WA; Jean Donadieu, MD, PhD, Hopital Trousseau, France; Yigal Dror, MD, The Hospital for Sick Children, Canada; Richard E. Harris, MD, Cincinnati Children’s Hospital Medical Center, OH; Sally E. Kinsey, MD, FRCP, FRCPath, FRCPCH, The Leeds Teaching Hospital NHS Trust, UK; Elene Psiachou Leonard, MRCPCH, MRCP(I), FGPA, FGHA, Leicester University Hospitals NHS Trust, UK; Corneila Zeidler, MD, Medizinische Hochschule Hannover, Germany

Session 4. SDS Genetics
Session Chair: Taco W. Kuijpers, MD, PhD, Emma Children’s Hospital, The Netherlands

Mouse Models for Shwachman-Diamond Syndrome
Johanna Rommens, PhD*, The Hospital for Sick Children, University of Toronto, Canada
* Jason Bennette Memorial Lecturer

Phenotypic Extension of SBDS Mutations
Shiro Ikegawa, MD, PhD, SRC, RIKEN, Tokyo, Japan
We identified SBDS gene mutations in two cases with severe skeletal dysplasia. The phenotypes of the patients are compatible with spondylometaphyseal dysplasia (SMD) Sedaghatian type, a skeletal dysplasia characterized by platyspondyly, rhizomelic shortness of long bones, metaphyseal dysplasia and narrow rib cage. The phenotypic spectrum of SBDS mutations may extend further.

Session 5. SBDS Function
Session Chair: Johanna Rommens, PhD*, The Hospital for Sick Children, University of Toronto, Canada

The role of Sbds in cell survival
Yigal Dror, MD, The Hospital for Sick Children, Canada
Our lab studies why cells from patients with Shwachman-Diamond syndrome do not grow properly. In this work we found that a death protein called Fas tends to abnormally accumulate at the cell surface of Sbds-deficient cells leading to increased cell death and reduced cell growth. Further understanding of this abnormality may help developing novel strategies to improve cell growth and organ function.

Mechanisms of Cell Death with Depletion of the Shwachman-Diamond Syndrome Protein, SBDS
Johnson M. Liu, MD, Schneider Children’s Hospital, NY
Our experiments are aimed at uncovering the mechanisms that lead to cell death and cancer cell growth in Shwachman-Diamond syndrome. We hope that a detailed understanding of these mechanisms will lead to new therapeutic and cancer prevention strategies.

Cell cycle and surface marker changes in the bone marrow of patients with Shwachman Diamond syndrome and other inherited bone marrow failure syndromes: comparison with acquired disorders
M. Tarek Elghetany, MD, University of Texas Medical Branch at Galveston, TX
There are some bone marrow changes in SDS and other inherited bone marrow failure syndromes...
that may help differentiate them from non-inherited bone marrow diseases.

**Cytogenetics in Shwachman Syndrome: chromosome changes and haematological implications.**
Emanuela Maserati, MD, PhD, University of Insubria Varese, Italy

We report cytogenetic and FISH results in 18 new SS patients. So in the cohort of 33 cases collected in our laboratory, clonal bone marrow anomalies were present in 12. We discuss the mechanism of origin of the i(7)(q10), and confirm the hypothesis that SS mutations imply a mutator effect which leads to chromosome changes, responsible of MDS/AML. We postulate that a higher risk of MDS/AML evolution in SS is associated with all BM clonal chromosome changes, including those of chromosomes 7 and 20.

**SBDS and Genomic Instability**
Akiko Shimamura, MD, PhD, Children’s Hospital Boston, MA

When a cell divides, the parental cell must duplicate its chromosomes and distribute the chromosomes evenly between its two progeny cells. We identified a role for SBDS in regulating how chromosomes are distributed when cells replicate. Loss of this SBDS function may contribute to the chromosomal abnormalities that frequently arise in the bone marrows of patients with SDS.

**Shwachman-Bodian-Diamond syndrome protein mediates translational activation of ribosomes in yeast**
Alan J. Warren, PhD FRCP FRCPath, University of Cambridge, UK

Ribosomes are machines that make all the proteins in the body. Using yeast as a model organism, we have discovered that the pathway involved in making new ribosomes requires the protein that is deficient in Shwachman-Diamond syndrome (SDS). Uncovering this pathway opens up the possibility of finding new ways to treat SDS.

**Session 6. SBDS and Leukemia**
Session Chair: Alan J. Warren, PhD FRCP FRCPath, University of Cambridge, UK

**Transcription factors, myeloid development, and leukemia**
Daniel G. Tenen, MD, Harvard Institutes of Medicine, MA

**Chromosome segregation and centrosome number: potential roles in marrow failure and cancer**
David Pellman, MD Dana Farber Cancer Institute, MA

**Dissecting Cancer Pathways using the Zebrafish: Chk1 Suppresses a Novel p53-Independent Apoptotic Axis**
A. Thomas Look, MD, Dana Farber Cancer Institute, MA

**Candidate myeloid tumor suppressor gene isolation from chromosome band 7q22 and targeting a syntenic interval in the mouse**
Jasmine C. Y. Wong, PhD, University of California, San Francisco

Cancer cells from leukemia patients often demonstrate the loss of all or part of chromosome 7. We have extensively characterized the genes in a region on chromosome 7q22 that is commonly deleted in human leukemia samples, and have created a genetically engineered mouse model as an experimental system to study how the loss of this region contributes to leukemia. These studies help us understand the genetic basis of leukemia in patients with chromosome 7 deletions, and provide a foundation for developing therapeutics.
Session 7. SBDS and Hematopoiesis
Session Chair: Yigal Dror, MD, The Hospital for Sick Children, Canada

Modeling bone marrow failure syndromes using human embryonic stem cells
George Q. Daley, MD, PhD, Children’s Hospital Boston, MA

Hematological abnormalities in Shwachman Diamond syndrome: And the potential mechanisms setting the myeloid clock
Taco W. Kuijpers, MD, PhD, Emma Children’s Hospital, The Netherlands

Murine model of Shwachman-Diamond Syndrome
Daniel C. Link, M.D., Washington University, MO

Session 8. Links Between SDS and Other Bone Marrow Failure Syndromes
Discussion Leader: Jeffrey M. Lipton, M.D., Ph.D., Schneider Children’s Hospital, Albert Einstein College of Medicine, NY

An Overview of SDS and the Inherited Bone Marrow Failure Syndromes (IBMFS)
Johnson M. Liu, MD, Schneider Children’s Hospital, NY

Our experiments are aimed at uncovering the mechanisms that lead to cell death and cancer cell growth in Shwachman-Diamond syndrome. We hope that a detailed understanding of these mechanisms will lead to new therapeutic and cancer prevention strategies.

Cellular Consequences of Ribosomal Defects: A Tale of Two Diamonds
Steven R. Ellis, Ph.D., University of Louisville, KY

These studies compare and contrast the potential molecular underpinnings of Shwachman-Diamond syndrome and Diamond Blackfan anemia. We will also discuss current efforts to identify small molecules that compensate for the absence of the yeast ortholog of SBDS, which may represent potential therapeutic leads for the human disorder.

Dyskeratosis Congenita and Ribosome Biogenesis
U. Thomas Meier, Ph.D., Albert Einstein College of Medicine, NY

Dyskeratosis congenita is a rare but often-fatal inherited disease that generally impacts rapidly dividing tissues, such as the bone marrow. Its most severe form is caused by mutations in a protein, which, as part of a larger complex, serves multiple functions, e.g., protein synthesis and telomere maintenance. We are molecularly dissecting if these functions are equally or specifically affected by mutations observed in dyskeratosis congenita.

Dyskeratosis congenita: a bone marrow failure syndrome
Inderjeet Dokal, MBChB, MD, FRCP, FRCPC, FRCPath, Imperial College London, UK

Dyskeratosis congenita (DC) is a multi-system disorder characterised by abnormalities of the skin (pigmentation), nails (riding, destruction and loss of nails) and mucous membranes (such as white patches on the tongue). In approximately 80% of cases, it is associated with abnormalities of the bone marrow leading eventually to anaemia and an increased risk of bleeding and infection. A variety of other abnormalities have been reported. Three genes (DKC1, TERC and TERT) have been identified, defects in
which cause DC. The products of these genes encode an important enzyme called telomerase which is critical for maintaining the telomeres (the ends) of chromosomes. These advances now enable accurate genetic diagnosis in many patients and provide the platform for developing new treatments.

**Role of rRNA modifications in translation control and Dyskeratosis Congenita pathogenesis**
Davide Ruggero, Ph.D., Fox Chase Cancer Center, PA

Our research is focused on understanding how defects in the protein synthetic machinery may underlie a human disease known as X-linked Dyskeratosis Congenita characterized by fatal pathological features such as bone marrow failure and cancer susceptibility.

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**Session 9. Organ Development and Failure**
Session Chair: Mark E Lowe, MD, PhD, Children’s Hospital of Pittsburgh

**Fetal Development of the Acinar Pancreas**
Raymond J. MacDonald, Ph.D., UT Southwestern Medical Center, TX

The formation of the fetal pancreas with its acini, which make digestive enzymes, ducts, which make the fluid that flushes the digestive enzymes to the intestine, and islets, which make potent hormones occurs through a series of complex developmental steps. We know many of the genes that direct pancreas development, and mutations in these genes disrupt formation of the acini, ducts or islets, or all three simultaneously. One of these control genes, Ptf1a, is required during early development for all three tissues, and later specifically for the completion of proper, functional acinar cells with their complement of digestive enzymes.

**Cardiac imaging and myocardial function in Shwachman-Diamond Syndrome**
Sanna Toiviainen Salo, MD, Hospital for Children and Adolescents, University of Helsinki, Finland

Patients with SDS had normal heart anatomy and showed no signs of heart muscle damage or impairment of cardiac function in imaging studies.

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**Session 10. Novel Diagnostics and Therapeutics**
Inderjeet Dokal, MBChB, MD, FRCP, FRCPCH, FRCPath, Imperial College London, UK

**Transplantation in Shwachman-Diamond Syndrome**
Adrianna Vlachos, MD, Schneider Children’s Hospital, NY

**Transplantation in Shwachman-Diamond Syndrome: Outcomes Using Cord Blood Donors and the Role of Autologous Stem Cell Harvesting for Future Treatment**
Frederick D. Goldman, MD, University of Iowa, IA

SDS is associated with an increased likelihood of developing aplastic anemia, a condition that often can only be cured with a bone marrow transplant. There are new ways to perform bone marrow transplants, including using cord blood as a source of blood stem cells instead of bone marrow. We report data on the successful treatment using cord blood donors in SDS. In addition, one might also consider collecting stem cells from SDS patients prior to their potential development of bone marrow failure for future use.
Inherited bone marrow failure states such as Fanconi anemia and Shwachman Diamond Syndrome are due to defective stem cells. Treating these diseases will require the development of model systems to test a variety of genetic and pharmacologic approaches. We have in the laboratory been able to grow human embryonic stem cells that mimic the stem cells found in patients. Development of new approaches to correcting these cells will be discussed.

We have determined that residual SBDS protein and mRNA levels in blood leukocytes from SDS patients can be directly measured. This offers new tools to study the biological effects of the wide range of SBDS mutations.