The fellowship begins with a year of intensive clinical training in hematopathology, general hematology, hematologic genetics, hemoglobinopathies, diagnostic DNA assays (hereditary diseases, malignancy, etc.) and hemostasis and thrombosis. Service responsibilities include: 1) work-up of hematopathology material including interpretation of morphology, immunohistochemistry, flow cytometry, and molecular studies for B and T cell clonality and translocation detection, 2) work-up of hemoglobinopathy and thalassemia cases, 3) evaluation of unusual general hematology results, and 4) interpretation of specialized hemostasis and thrombosis testing. Teaching responsibilities include: 1) small group sessions at the microscope with students, housestaff and clinicians, 2) lectures to larger groups in our hematopathology course, and 3) teaching clinical pathology residents during their hematology rotation.

The remainder of the fellowship is spent primarily doing research with less emphasis on clinical responsibilities. The fellow will select a faculty advisor with whom to work on a research project. Past projects have included clinical assessment of new DNA probes and flow cytometric analysis of malignancies. Fellows present their research on a regular basis at a weekly departmental research conference.

A brief description of the various laboratory areas and current research projects are listed below.

**General Hematology Laboratories**: These laboratories carry out the studies which are required for work-up of the general patient population. Studies include such tests as blood smear review and the various cell measurements which are performed on large automated hematology instruments. The laboratory at the University of Washington Medical Center is directed by Drs. Sabath, Wood, Greisman, Fromm and Cherian, and Harborview Medical Center by Dr. Chandler.

**Hematopathology Laboratories**: Under the direction of Drs. Sabath, Wood, Greisman, Fromm and Cherian, this laboratory is responsible for the evaluation and diagnosis of leukemias and lymphomas. A wide range of technologies are brought to bear on these problems. These technologies involve the assessment of peripheral blood, lymph node, bone marrow, and other tissues by immunocytochemical studies on solid tissue, multicolor flow cytometric analysis of cell surface and intracellular antigens, and molecular diagnostic studies. Cell culture facilities are used to study both malignant and normal cell lines in vitro. Active research projects include the clinical application of high-level multicolor flow cytometry and new molecular methods.

**Red Cell Disorders Laboratory**: Under the direction of Dr. Sabath, this laboratory is involved primarily in the study of patients with thalassemia, hemoglobinopathies and red cell enzyme deficiencies. Research relates to the use of clinical data in the diagnosis of conditions identified by this testing.

**Hemostasis and Thrombosis Laboratory**: Under the direction of Drs. Chandler and La Spada, this laboratory performs all standard diagnostic coagulation tests and special testing including factor assays, von Willebrand's disease work-ups, and platelet aggregation studies. In addition, this laboratory evaluates patients with inherited or acquired thrombophilia using a range of assays for: antithrombin III, protein C, protein S, tissue plasminogen activator, plasminogen activator inhibitor, lupus anticoagulant, and plasminogen. Active research areas include the regulation and pathophysiology of the fibrinolytic system.

**ALLIED DIVISION INTERACTIONS**

**Genetics Division**: Under the direction of Dr. Tait, Dr. Sabath, and Dr. Karen Stephens, this laboratory provides diagnostic testing for hereditary diseases using DNA probes.

**Management**: A unique course in laboratory management is given in the spring of odd numbered years under the direction of Dr. Chandler. This course provides instruction in the application of leadership and management principles in the laboratory setting.

**DEPARTMENTAL FACULTY** (Laboratory responsibilities and areas of interest)

James S. Fine, M.D., M.S. (Chair, medical computer applications and management)

Daniel E. Sabath, M.D., Ph.D. (Head, Hematology Division and Director, Red Cell Disorders and Molecular Diagnosis Sections and Assistant Director, Genetics Division, Director, Hematology Fellowship Program; laboratory diagnosis of genetic red cell disorders, laboratory instrumentation, molecular hematology, regulation of gene expression)

Brent L. Wood, M.D., Ph.D. (Director, Hematopathology Section and University of Washington General Hematology Section; laboratory diagnosis of hematopoietic disorders using high-level multicolor flow cytometry, molecular hematopathology)

Harvey Greisman, M.D, Ph.D. (Associate Director, Hematopathology Section; molecular pathology of hematopoietic disorders)
Sindhu Cherian, M.D. (Associate Director, Hematopathology Section; flow cytometric characterization of myelodysplastic disorders)
Jonathan R. Fromm, M.D., Ph.D. (Associate Director, Hematopathology Section; development of new flow cytometry methods)
Jonathan F. Tait, M.D., Ph.D. (Head, Genetics Division; biochemistry of annexins, clinical molecular genetics)
Wayne L. Chandler, M.D. (Head, Coagulation Division, Director, Harborview Medical Center, General Section; fibrinolysis, clinical hematology and coagulation)
Albert La Spada, M.D., Ph.D. (Associate Director, Coagulation Division, molecular genetics, biology of tri-nucleotide repeat disorders)
Lisa McDonnel, M.S. (MT) ASCP (Co-director, University of Washington Medical Center General Hematology Section; clinical hematology and coagulation methodologies)

Applications for fellowship to begin July 1 should be received by the preceding August 1st.
Additional information about our fellowship can be obtained from our web site:
http://www.labmed.washington.edu (follow Education link)

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Coordination of the compliance efforts of the University of Washington with respect to all of these laws & regulations is under the direction of the Assistant Provost for Equal Opportunity, Equal Opportunity Office, 4045 Brooklyn Ave. NE, Room 234, Box 354560, University of Washington, Seattle, WA 98195, telephone (206) 543-2624.
Wayne L. Chandler, MD
Professor, Laboratory Medicine
University of Washington
Research program:

My primary interest is research on hemostasis and thrombosis. Hemostasis is a balance between factors that promote thrombus formation (the coagulation system, platelets), those that block thrombus formation (inhibitors such as antithrombin III or protein C/S) and those that promote removal of thrombi (fibrinolysis). Current projects include:

1. Regulation of hemostasis: To understand quantitatively how hemostasis is regulated in vivo we developed a computer model of the human vascular and hemostatic systems. Using measured blood volumes, blood flow rates, and levels of hemostatic factors and activation markers, the computer model is used to simulate selected aspects of individual subject’s hemostatic and vascular systems. The model takes into account hemodynamic processes that affect factor levels including clearance, blood loss and transfusion. This model has been used to analyze the effects of exercise, adrenergic agonist infusion, plasminogen activator infusion, and liver transplantation on the regulation of fibrinolysis and the effect of cardiopulmonary bypass on overall hemostatic regulation. For more information on modeling hemostasis visit our website:

Hemostasis Simulation Project
http://depts.washington.edu/labweb/dept/staff/bios/hemostas/index.html

Recent publications on hemostatic regulation and modeling:


Chandler WL, Velan T. Estimating the rate of thrombin and fibrin generation in vivo during


2. Hemostatic abnormalities in childhood hemolytic uremic syndrome: HUS in children is most often the result of intestinal infection with *E. coli* O157:H7 which releases Shiga-like toxins that damage renal vascular endothelial cells. We have determined that endothelial damage stimulates thrombin generation, fibrin formation and in some cases classic HUS with fibrin occlusion of renal microvasculature, renal failure, thrombocytopenia and hemolytic anemia. We have determined that the hemostatic activation occurs at least 4-5 days prior to onset of HUS, and the HUS occurs more commonly in the patients with the most intense activation of hemostasis. We are currently studying the relationship between hemostatic regulation, thrombin generation and total and soluble fibrin formation in the pathophysiology of *E. coli* O157:H7 associated HUS.

Recent publications on hemolytic uremic syndrome:


Dr. Sindhu Cherian

Dr. Cherian is a faculty member in the Division of Hematology in the Department of Laboratory Medicine at the University of Washington. Her clinical interests are broad within hematopathology with a focus on test development and myelodysplastic syndromes (MDS). In particular, she is interested in the application of flow cytometric analysis to diagnose and follow patients with MDS.

Although flow cytometry has long proven an invaluable tool in the diagnosis of numerous hematologic disorders such as lymphomas and leukemias, only more recently has the value of this diagnostic tool in MDS been recognized. In the past decade, several groups have described various immunophenotypic abnormalities present in different cell lineages in patients with MDS. Dr. Cherian’s current research interests include the development and validation of a peripheral blood based flow cytometric scoring system for the evaluation of patients with MDS.

Selected References:


In my laboratory, we apply the tools of molecular genetics and functional genomics to understand the mechanisms of neurological disease. In 1991, a novel type of genetic mutation known as a trinucleotide repeat expansion was discovered. At this time, it appears that 9 trinucleotide repeat diseases are caused by the expansion of a tract of glutamine residues within proteins that are unrelated to one another. We have focused our research efforts on two of these polyglutamine repeat diseases – spinocerebellar ataxia type 7 (SCA7) and spinal & bulbar muscular atrophy (SBMA). An important question that we seek to answer is why do specific neurons die in each of these diseases, although the patterns of expression of the different disease genes are widespread and overlapping throughout the neuraxis. Recent emphasis has been placed upon modeling the retinal and brainstem degeneration in SCA7, understanding its mechanism, and trying to develop therapies to reverse it. In the case of SBMA, a lower motor neuron disease caused by polyglutamine repeat expansions in the androgen receptor (AR), we are trying to understand why motor neurons are exquisitely sensitive to glutamine tract expansions in AR by developing a variety of in vitro and in vivo models. Transcription dysregulation and the role of apoptotic activation are among the hypotheses that we are investigating.

Another interest in my laboratory is the molecular basis of Parkinson's disease (PD). Our work on PD has focused upon the role of the synuclein proteins in causing neurodegeneration. Our interest in PD stems from the fact that like the polyglutamine repeat diseases, PD is characterized by the process of protein aggregation. The generation of peptide or protein aggregates in a variety of neurodegenerative diseases is a common theme in the study of neurological disorders. Our work on the polyglutamine repeat diseases and on PD is intended to address why neurons share a propensity for aggregate formation and what the protein misfolding process can tell us about neuronal dysfunction and neuron cell death. We also wish to use the mechanistic knowledge that we acquire to develop therapies to treat these disorders, so a recent area of interest is the identification of compounds and gene products that may prove beneficial in stemming the progression of disease in the models that we have developed.

Finally, our recent discovery of the gene responsible for the Purkinje cell degeneration (pcd) mouse mutant has led to an exciting study aimed at understanding how loss of a widely expressed putative protease results in the selective degeneration of certain neuronal populations. This work is a nice complement to our studies of cerebellar and retinal biology and degenerative pathways in the human polyglutamine diseases.

Selected References


La Spada AR, Roling DB, Harding AE, Warner CL, Spiegel R, Hausmanowa-Petrusewicz I, Yee WC, Fischbeck KH. Meiotic stability and genotype-phenotype correlation of the


[^ = co-first authors]


Clinical Interests

Dr. Sabath is Head of the Hematology Division in the Department of Laboratory Medicine at the University of Washington Medical Center. The division is responsible for operating the general hematology, hematopathology, red cell disorders, and molecular diagnosis laboratories. Dr. Sabath’s primary clinical role is as director of the red cell disorders and molecular diagnosis laboratories.

Dr. Sabath’s main clinical research interest is the use of molecular techniques for the diagnosis of hematologic malignancies. Currently, the polymerase chain reaction is being used to detect small numbers of lymphoma cells in peripheral blood or bone marrow specimens. PCR is used to detect clonal B or T cell populations by amplifying immunoglobulin heavy chain or T cell receptor γ chain gene rearrangements. Sensitive PCR methods are being used to detect cells with the 14;18 or 11;14 translocations seen in follicular and mantle cell lymphomas, respectively. RT-PCR is being used to detect the 9;22 translocation of chronic myelogenous leukemia. We are currently working on several new molecular assays.

Dr. Sabath’s other primary clinical interest is in red cell and hemoglobin disorders. The red cell disorders laboratory uses a combination of HPLC, isoelectric focusing, other electrophoretic techniques, and special studies to diagnose hemoglobinopathies, thalassemias, and other intrinsic red cell disorders. In unusual cases, DNA sequencing is used to identify unusual hemoglobin variants and thalassemias. The clinical genetics laboratory (under the direction of Dr. Tait and Dr. Karen Stephens) performs α globin DNA studies to diagnose α thalassemia.

Research Program and Scholarly Interests

Dr. Sabath’s main research interests include regulation of gene expression in hematopoietic cells and development of new molecular diagnostic assays. The major research activities are:

1) Development of a gene expression array-based diagnostic device for lymphomas. We have used genomic-scale gene expression profiling to identify genes that distinguish among follicular lymphomas, small lymphocytic lymphomas, mantle cell lymphomas, and reactive lymph nodes. We are currently working on developing a custom microarray that will quantify expression of these genes that can be used to diagnose lymphomas. The main thrust of this effort involves designing oligonucleotide probes that reliably quantify gene expression and choosing a microarray platform that can be used in a clinical setting. As a result of this work, we are also beginning to characterize several of these genes whose function is not known to determine what role, if any, they might have in the pathogenesis of lymphoma.

2) Structure-function studies of Mpl. Mpl, the thrombopoietin receptor, is present in an oncogenic form (v-Mpl) in the murine myeloproliferative disorder retrovirus. In previous work,
we showed that truncation of the distal extracellular domain of Mpl can cause the IL3-dependent cell line Ba/F3 to become growth factor independent. We are now trying to determine what structural features of this domain of Mpl are responsible for this phenomenon using various mutagenesis strategies. It also turns out that the deleted form of Mpl is not able to transform other IL3-dependent cell lines or primary mouse bone marrow cells. We are using gene expression profiling to determine what makes Ba/F3 cells different such that they are transformed by the deleted form of Mpl.

3) Quantitative RT-PCR to detect circulating breast cancer cells. We have developed a quantitative RT-PCR assay to measure keratin 19 mRNA in peripheral blood. We plan to use this assay to detect circulating breast cancer cells in patients at initial presentation and then at intervals during their treatment.

For Further Information

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Selected References


Jonathan F. Tait, M.D., Ph.D.

Research Program:

Dr. Tait's laboratory works on the annexin family of calcium-dependent phospholipid binding proteins. The long-range goal of this research is to understand how annexins interact with cell membranes, and to develop better means to diagnose and treat disorders related to thrombosis and apoptosis. The interaction of annexin V with phospholipids, platelets, leukocytes, and erythrocytes has been characterized quantitatively. These results show that annexin V is an excellent probe for detection and functional inhibition of cellular procoagulant phospholipid (primarily phosphatidylserine). Currently, the structural requirements for membrane binding are being investigated, and annexin V is being developed as a means to image apoptotic cells in vivo in clinical areas such as organ transplant rejection, cancer chemotherapy, myocardial infarction, and stroke.

Investigator:

Dr. Tait is Professor of Laboratory Medicine and Adjunct Professor of Pathology and Medicine/Medical Genetics. He also directs the clinical molecular genetics laboratory in Laboratory Medicine at the University of Washington Medical Center, which provides DNA-based clinical testing for genetic diseases.

Representative publications:


Brent  Lee Wood MD, PhD  
Associate Professor of Laboratory Medicine  

Clinical Interests  

Dr. Wood is Associate Director of the Hematology Laboratory and Director of the Hematopathology laboratory at the University of Washington Medical Center. In these laboratories, a wide variety of techniques are used for the diagnosis of hematologic and immunologic disorders including: morphologic examination of blood, bone marrow, and lymph node, automated cell counting, traditional cytochemical staining, immunocytochemistry, multiparametric flow cytometry, and molecular diagnostic tests such as Southern blotting and PCR.

Dr. Wood has a predominant interest in the laboratory diagnosis and monitoring of hematologic diseases including neoplastic disorders, and as a result spends a large portion of his time on the clinical service. New diagnostic tests are continually being evaluated for their clinical utility and are added to the laboratory's list of orderable tests when appropriate.

Research interests  

Dr. Wood's research interests are primarily clinical in nature, focusing on transitional projects implementing new technologies in a clinical laboratory environment. Projects include:

1. Developing and defining the clinical utility of high-level multicolor flow cytometry in the clinical laboratory. Over the past two years, we have developed instrumentation and reagents to allow the performance of 10 color flow cytometry, and have recently implemented this technology as our routine methodology in the clinical laboratory for the diagnosis of leukemia and lymphoma. The technology allows for the efficient and rapid evaluation of clinical material while using a minimum of specimen and reagents. Optimization of this technique is on-going in an effort to define a minimal set of reagents that will allow for the consistent diagnosis of the wide range of hematopoietic neoplasms. Part of this effort involves the development of new software approaches for the analysis of multiparameter flow cytometric data.

2. Detection of minimal residual disease by multicolor flow cytometery. The Hematopathology Laboratory is the second national reference laboratory for the Children’s Oncology Group (COG) for the identification of minimal residual disease in acute lymphoblastic leukemia by flow cytometry. In this role, the laboratory performs testing to support a range of clinical treatment protocols utilizing minimal residual disease detection for the stratification of patients. The intent of these protocols is to evaluate the efficacies of new therapies for the treatment of this disorder. In addition, the laboratory is involved in a Southwest Oncology Group (SWOG) clinical trialevaluating the utility of adding Myelotarg (anti-CD33) to induction chemotherapy for acute myeloid leukemia. The role of the laboratory is to assess minimal residual disease following therapy in this patient population with the long-term goal of using method as a surrogate for therapeutic response.

3. Diagnosis of myelodysplasia and myeloproliferative disorders by flow cytometry. Recent studies, including our own, have documented the utility of flow cytometry for the diagnosis of
myelodysplasia and myeloproliferative disorders. Despite this progress, new methods are still needed to diagnose certain low-grade stem cell disorders such as refractory anemia, polycythemia vera, etc. In conjunction with the Myelodysplasia Clinic at the University of Washington/Seattle Cancer Care Alliance, we have begun to attempt identification of abnormalities in erythroid antigenic expression, pro-apoptotic markers and signal transduction proteins in myelodysplasia. This work will hopefully lead to more objective diagnostic tests for these disorders.

References


