THE PATH WAY

December, 2014

Volume 5, Issue 4

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

DEPARTMENT of PATHOLOGY & LABORATORY MEDICINE

Steven L. Carroll, M.D., Ph.D.

Inside this issue:

Dr. Makio Ogawa, Professor Emeritus
Pathology and Laboratory Medicine

Dr. Makio Ogawa, Professor Emeritus of Pathology and Laboratory Medicine, dedicated thirty-eight years of his career to the Medical University of South Carolina. During that time, he was a pioneer in the field of experimental hematology, leading the way to understand the contribution of the hematopoietic stem cell (HSC) in physiological and pathological conditions.

Dr. Ogawa obtained his MD from the Osaka University School of Medicine and underwent his clinical training at the Naval Hospital in Yokosuka, Japan. After completing a residency and two fellowships at Dartmouth Medical School, Dr. Ogawa joined the University of Toronto where he earned his PhD under the mentorship of Drs. Till and McCulloch, hailed as the grandfathers of stem cell research. In 1973, he became a faculty member and staff physician at the Medical University of South Carolina and the Ralph H. Johnson VAMC, respectively. Dr. Ogawa served as a member of the VA Research and Development Committee for nearly thirty years and as Chair for four.

Dr. Ogawa enjoying a game of Mahjong in his man cave with visiting former fellows.

In addition, Dr. Ogawa served as the Associate Chief of Staff for Research and Development at the Ralph H. Johnson VAMC from 1993 through 1998, during which time he established the center as one of the top training centers in the county.

This newsletter is made possible from the generous contributions of MUSC's Pathology and Laboratory Medicine Faculty and Staff. The success of this publication is dependent upon this support. Thank you for your interest, time and information. For inquiries, suggestions or submission information please contact Lori Roten (roten@musc.edu).

Dr. Ogawa's studies have led to major contributions to the fields of hematopoiesis and hematopoietic stem cell biology, including demonstration of the stochastic nature of stem cell differentiation, elucidation of the role of IL-6 and IL-11 in stem cell cycling, and clarification of the controversy concerning the mechanisms controlling CD34 expression on HSCs. Most recently, his research revealed hitherto unknown roles for the HSC in the generation of mesenchymal cells and tissues. He has published well over two hundred manuscripts in the field and maintained a sustained and distinguished track record of federal funding for his research program, including two Medical Investigator Scholarships from the Department of Veteran's Affairs. During his career, he was inducted into the American Society for Clinical Investigation, the Association for American Physicians, and the American Society of Hematology. Dr. Ogawa's scientific contributions to the field have been recognized by numerous awards including the VA William S. Middleton Award of the Department of Veterans Affairs, the South Carolina Governor's Award for Excellence in Science, and the William Dameshek Prize for Research from the American Society of Hematology. His position as a leader in the field is further highlighted by copious invited lectures, appointments as a reviewer for NIH study sections and the VA Medical Research Advisory Group (Hematology/Oncology), and membership in prestigious academic societies.

While Dr. Ogawa remains one of the most influential scientists in the field of stem cell biology, among his most significant contribution to the field of hematology has been his willingness to share his knowledge, experience, and laboratory with young scientists. Having both MD and PhD training, Dr. Ogawa instilled the importance of not only providing the best care for patients, but also the need to question current therapies and explore research alternatives. His most valuable lesson was, and still is, the significance of critical thinking. Many of his trainees consider time spent in Dr. Ogawa's laboratory to be of the most formative periods in their careers. The greatest testament to his impact as a mentor has been the eagerness of his former fellows to have their trainees spend time in Dr. Ogawa's laboratory. To his former fellows and those familiar with his works, a pedigree that includes an "Ogawa Fellowship" is considered priceless. Dr. Ogawa trained over thirty students and postdoctoral fellows in his laboratory, nearly all of whom have gone on to careers in academics or industry. Indeed, eight of his former trainees are currently department chairs or vice chairs, and many are full professors at prominent academic institutions. For many of his trainees, he has served as a career-long mentor and advisor. This is highlighted by his annual participation in the American Society of Hematology Meeting where he and his former fellows reunite, as well as his frequent invitations to present at scientific meetings in Japan.

Upon his retirement in 2011, Dr. Ogawa and his wife, Mary-Jane Ogawa, relocated to West Lebanon, New Hampshire. Since that time, Dr. Ogawa has continued to contribute to scientific manuscripts, publishing an invited review in Blood Cells, Molecules and Diseases, and to present his work at national and international meetings, most recently having been invited to present at the "Acute Leukemia Forum 2015." In addition to his continued contributions to science, Dr. Ogawa has been active in the local kendo club and he and his wife spend their time gardening, entertaining many visitors, and traveling. In the winter months, they enjoy skiing, cross-country skiing, snow shoeing, and enjoying the picturesque views from their home.

HAPPY HOLIDAY EMAIL FROM DR. MAKIO OGAWA

I hope things are going well with you and the Department. I continue to enjoy retirement life without major health problems. We already had two snow storms and the ground is covered by a foot of snow. All ski resorts around here are open. I am attaching a photo of our backyard showing turkeys having difficult time in walking on fresh snow.

I will be an invited speaker (as an Emeritus Professor of the Department) at Acute Leukemia Forum 2015 on March 27, 2015 in San Francisco. It will be more than 4 years after I gave the last presentation. I'll have to brush up some terminology in stem cell research.

I wish you a Happy Holiday Season.

Makio

CONGRATULATIONS!!

Jack Yang, M.D.
was granted Tenure
Effective January 1, 2015

Yusheng Zhu, Ph.D
was granted Tenure
Effective January 1, 2015

2014 GOLDEN APPLE AWARDS

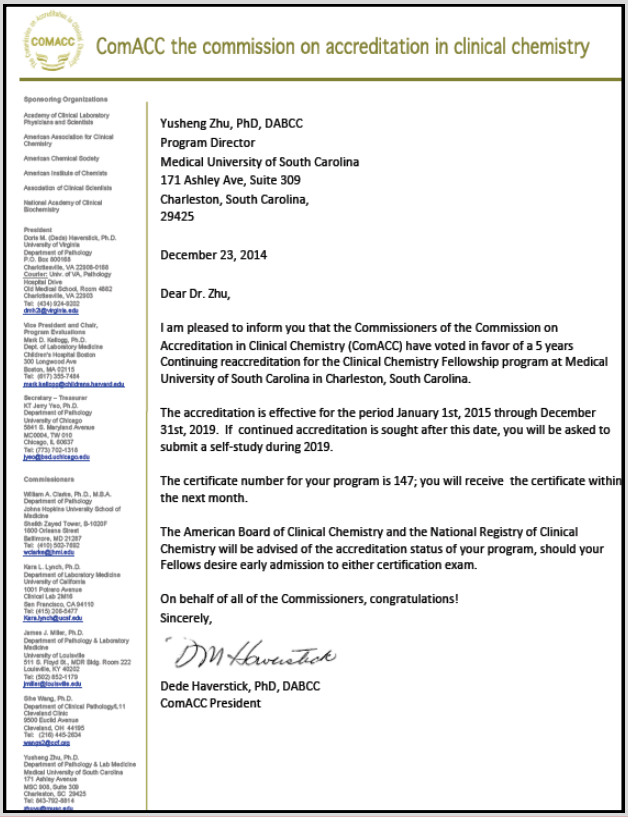
First Year Class Faculty Award
Michael Caplan, M.D. — Nominee

Second Year Class Faculty Award
Jerry Squires, M.D., Ph.D. — Nominee

Third and Fourth Year Class Faculty Awards
Nick Batalis, M.D. — Nominee

House Staff Award
Tripp Tracy, M.D. — Nominee

With your support, the Commission on Accreditation in Clinical Chemistry (ComACC) has accredited the Clinical Chemistry Fellowship Program at MUSC for a further 5 years. Thank you again for your help.
Yusheng Zhu, PhD, DABCC, FACB



COMACC ComACC the commission on accreditation in clinical chemistry

Sponsoring Organizations

Academy of Clinical Laboratory Physicians and Scientists
American Association for Clinical Chemistry
American Chemical Society
American Institute of Chemists
Association of Clinical Scientists
National Academy of Clinical Biochemistry

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December 23, 2014

Dear Dr. Zhu,

I am pleased to inform you that the Commissioners of the Commission on Accreditation in Clinical Chemistry (ComACC) have voted in favor of a 5 years Continuing reaccreditation for the Clinical Chemistry Fellowship program at Medical University of South Carolina in Charleston, South Carolina.

The accreditation is effective for the period January 1st, 2015 through December 31st, 2019. If continued accreditation is sought after this date, you will be asked to submit a self-study during 2019.

The certificate number for your program is 147; you will receive the certificate within the next month.

The American Board of Clinical Chemistry and the National Registry of Clinical Chemistry will be advised of the accreditation status of your program, should your Fellows desire early admission to either certification exam.

On behalf of all of the Commissioners, congratulations!
Sincerely,

DM Haverstick

Dede Haverstick, PhD, DABCC
ComACC President

ARRIVALS:

- **Ashley Wooldridge arrived on 11/3/14 as a Technical Medical Associate II in Forensic Pathology**
- **Benjamine Van Peel joined Dr. Bart Smits lab as a Research Specialist II on 10/6/2014**

PATHOLOGY AND LABORATORY MEDICINE "WINS"

On Monday, Dec. 1, 2014, Dr. Christine Papadea began another exciting project of historical importance related to the Pathology Department. This one involves archived autopsy reports from the department that are bound in dozens of volumes dating back to the mid-1950's going forward to 2014. These volumes are stored in the archives section of the main library. Most of the reports are from the years when Dr. Kenneth Lynch was the first -- for a while, the only-- pathologist at this institution, then called the Medical College of South Carolina.

Dr. Papadea's work will be done in the main library and will include: digitizing all the reports, recording the data into spreadsheets, and editing the digitized formats to redact all PHI before the reports can be made available electronically to the public. She will be working with and under the supervision of Tabitha Samuel, library archivist, and Susan Hoffius, curator of the Waring Historical Library.

Dr. Papadea will continue coming to the Pathology museum a few hours/week to keep an eye on the restored specimens/containers and their upkeep. Also, she is very interested in seeing visitors in the museum and will be glad to help with pre-scheduled tours when requests come my way.

CONGRATUATIONS!

Jessica Sugianto, M.D.

2013-2014 Dermatopathology Fellow passed her Dermatopathology Boards

Great Job Demetri Spyropoulos, Ph.D.!

Click the link below to view the

MUSC Public Relations Office: News Story on Gulf Oil spill Project

http://academicdepartments.musc.edu/pr/newscenter/2014/HMLoverview.html#.VHUJjShUG24

RESEARCH DIVISION UPDATE

Statistics for the Division of Research from October through December.
Twelve grant proposals were submitted requesting $2,915,033
in total first year costs.
Also, during this period four grants were awarded totaling $466,952.

Bradley Schulte, Ph.D., Vice Chair of Research

SUBMITTED 10/1/2014 – 12/31/2014:

Steve Ethier, Ph.D.
Title: Breast Cancer Oncogenes on the 8p11 Amplicon
$371,522 – Proposed Start Date 7/01/15

Victoria Findlay Ph.D.
Title: MicroRNA510 as a Biomarker of Response Platinum-Based chemotherapy $196,361 – Proposed Start Date 7/01/15

Victoria Findlay Ph.D.
Title: miR-204 Regulation of Cav-1 as a Mechanism Driving Breast Cancer Disparity $224,250 – Proposed Start Date 7/01/15

Amanda LaRue, Ph.D.
Title: Hematopoietic Stem Cell-Derived Carcinoma Associated Fibroblasts in Tumor $261,460 – Proposed Start Date 2/01/15

Chandrakala Puligilla Ph.D.
Title: Molecular Regulation of Sensory Epithelial Cell Patterning $373,750 – Proposed Start Date 7/01/15

Bart Smits, Ph.D.
Title: A Novel Genetic Rat Model to Study Non-Protein Coding Mechanisms Underlying Racial Disparities in Breast Cancer $224,250 – Proposed Start Date 7/01/15

Demetri Spyropoulos, Ph.D.
Title: Patient-Derived Xenografts with "Thawed Live" Tissue Technology and 3-D Human ex vivo Models for Metestasis $411,125 – Proposed Start Date 7/01/15

Jerry Squires, M.D., Ph.D. & Lee Marie Tormos, M.D.
Title: The Use of Smartphone and Tablet Technology to Deliver "Just-in-Time" Education in Transfusion Medicine
$2,605 – Proposed Start Date 1/01/15

Yong Wang, Ph.D.
Title: Therapy-Induced Cancer Cell Enrichment
$373,750 – Proposed Start Date 7/01/15

Yong Wang, Ph.D.
Title: Targeting Cancer Stem Cells in Breast Cancer
$158,859 – Proposed Start Date 7/01/15

Yong Wang, Ph.D.
Title: Novel Strategies to Enhance the Efficacy of Lung Cancer Radiotherapy $186,875 – Proposed Start Date 7/01/15

Ying Xiong, Ph.D.
Title: The Role of Hemotopoietic Stem Cell-Derived Adopocytes in High Fat Diet-Induced Obesity and Inflammation $130,226 – Proposed Start Date 7/01/15

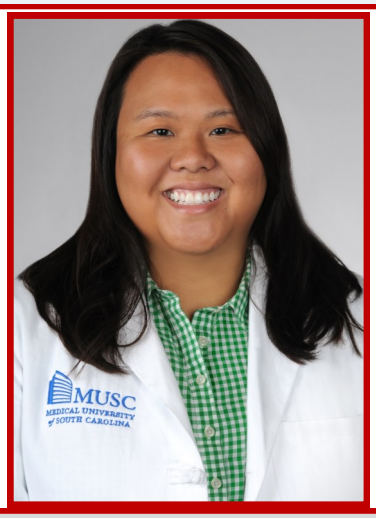
AWARDED 10/1/2014 – 12/31/2014:

Lisa Steed, Ph.D.
Title: Invasive Aspergillosis and Rare Molds Virtual Advisory Network $3,250 – Start Date 10/23/14

Suhua Sha, M.D.
Title: A Rapid Assay for RNA Targeted Drugs
$64,285 – Start Date 12/1/14

Demetri Spyropoulos, Ph.D.
Title: Using Embryonic Stem Cell Fate to Determine Potential Adverse Effects of Petroleum/Dispersant Exposure $380,157 – Start Date 12/1/14

David Turner, Ph.D.
Title: Vitamin D3 Supplementation for Low-Risk Prostate Cancer: A Randomized Trial $19,260 – Start Date 10/1/14

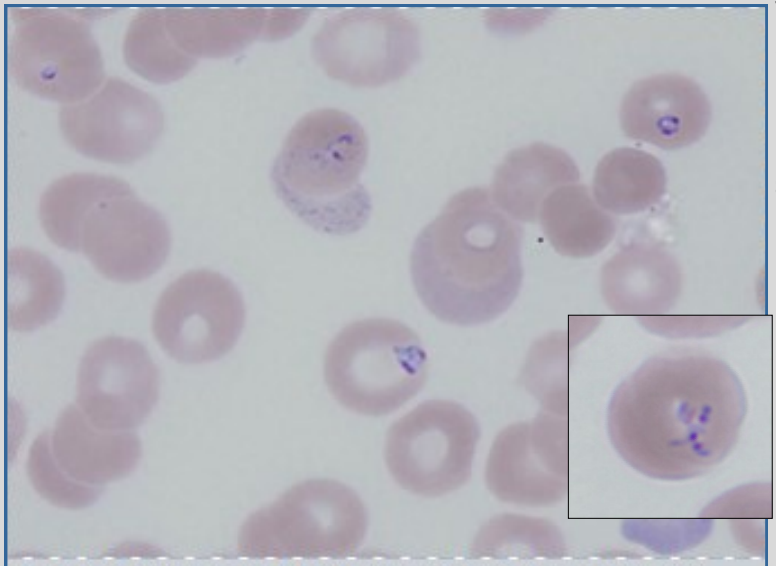


MUSC's First Experience with Transfusion-Associated *Babesia microti* in a NICU Patient

By: Angie Duong, M.D.

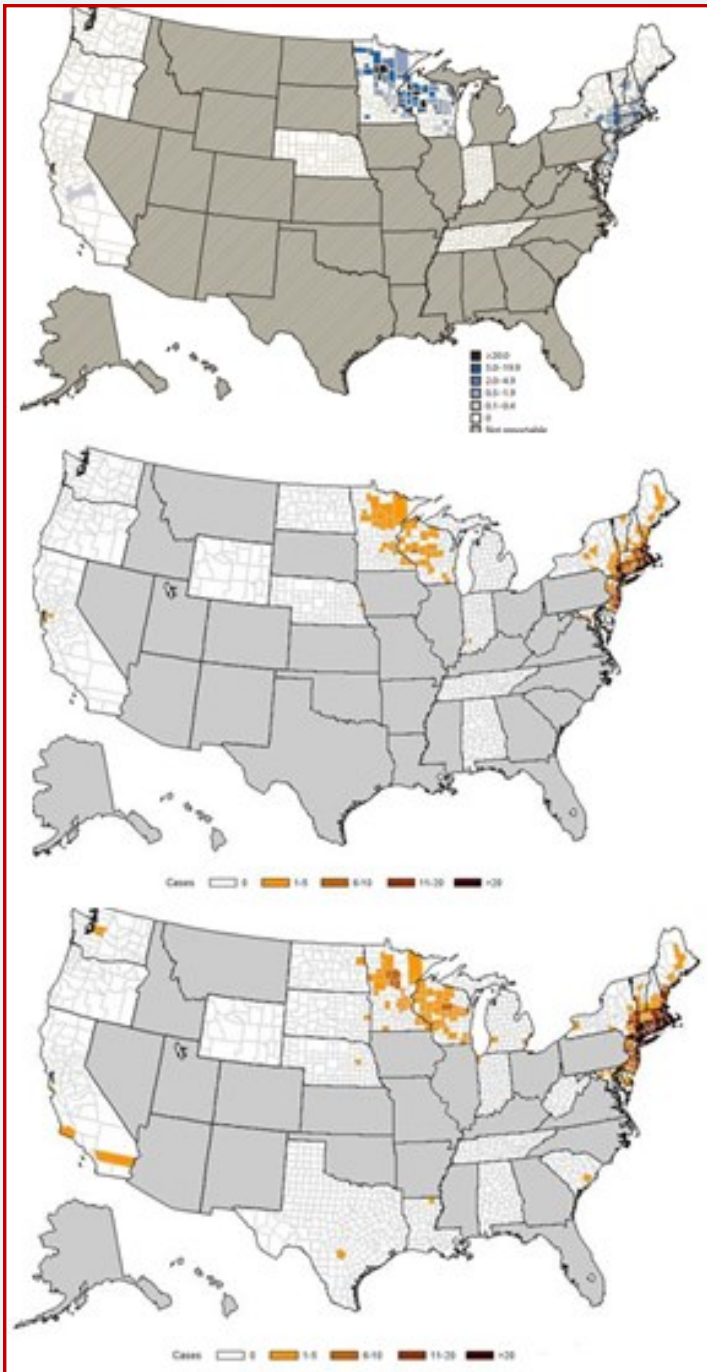
A 5 month-old (born prematurely at 27 weeks) is in the Neonatal Intensive Care Unit (NICU) with multiple respiratory problems associated with prematurity. He had moved directly from Labor and Delivery to the NICU, never leaving the hospital. More recently, he has also developed a hemolytic anemia, thrombocytopenia with a platelet count around 30-50 k/mm^3, hepatosplenomegaly, and intermittent fevers. A peripheral smear was sent to the hematology lab, where intraerythroid parasites were identified in 10-15% of red blood cells, consistent with *Malaria* or *Babesia* species.

Multiple pictures of these organisms were sent to the Centers for Disease Control (CDC) for species identification. Additionally, a current blood sample was taken to the microbiology laboratory where a Malaria antigen-detection test was performed and found to be negative. At this time, the diagnosis of *Babesia* was favored and another blood sample was sent to the Mayo Clinic Laboratory for *Babesia* speciation. Given the patient's low risk of a tick bite and clinical history of an asymptomatic mother, it was assumed that this is most likely a case of transfusion-transmitted *Babesia*. The patient's neonatologist was contacted early in the day regarding this finding. By the late afternoon/early evening, with the recommendations of pediatric infectious disease, the patient was started on double exchange transfusion. Following the double exchange, he received 14-day courses of atovaquone and azithromycin. The parasitemia rapidly declined following initiation of therapy. The day following the exchange transfusion, the parasitemia level was 2%. By day 3 status post-exchange transfusion, parasitemia was <1% and by day 7 no intraerythroid organisms were seen.



Peripheral Smear, Wright-Giemsa stain, 100x: Numerous *Babesia microti* organisms can be seen within the red blood cells. A *Babesia* tetrad, the "maltese cross" can be is pictured in the inset.

A thorough blood bank look back showed that during his hospital course, the patient had received multiple bullets of packed red blood cells from 5 different donors. The units that were still present in the blood bank were immediately sequestered. Additionally, segments from the completely transfused units were identified. Other hospital patients that received blood from the suspicious units were identified and peripheral smears were made. No additional Babesia infections were detected. Concurrently, slides of the previous peripheral blood samples from the patient were made and evaluated for parasites. Previously, these samples were run on the automated counter, which does not have the ability to identify the intracellular organisms. A slide from 16 days prior to initial diagnosis was found and it showed rare parasites, less than 1%. This finding along with the blood transfusion records eliminated two of the five donors. The remaining three donors were identified and contacted by the Red Cross. The Red Cross reported that one of the three donors is from a *Babesia*-endemic states.



Incidence of reported cases of Babesiosis, 2011-2013.
In 2011, *Babesia* became a CDC reportable infection. Over a period of 3 years, *Babesia* has been found not only more frequently but also more commonly in non-endemic states.
Source: CDC Babesia Data and Statistics

Babesia is an intraerythroid protozoan that is most commonly transmitted to humans via a deer tick (*Ixodes scapularis*) bite in endemic areas that includes the Northeast and Upper Midwest United States; however, this parasite can also be transmitted in blood transfusions as well as vertically transmitted from mother to fetus. The three species affecting humans are *Babesia microti, Babesia duncani, and Babesia* divergens with *B. microti* being the most common by far. Symptoms vary greatly in *Babesia* infection, ranging from asymptomatic to severe, with a mortality rate of up to 5%. Symptoms, when present, occur 1 to 6 weeks following inoculation and includes fever, chills, myalgias, fatigue, hepatosplenomegaly, and hemolytic anemia.

Patients with asplenia/splenic dysfunction are prone to higher parasitemia and therefore signs and symptoms.

The peripheral blood smear in infected individuals will show small, delicate, intraerythroid ring trophozoites that are 2-3 microns in size with one to two chromatin dots. At high parasitemia, it is not uncommon to see multiple organisms within a single red blood cell. Unique from *Malaria* species, *Babesia* can form tetrads in the merozoite stage, known as "maltese crosses" as well as being found in the extracellular space. The tetrads and extracellular forms can be quite rare.

Babesia has historically been of major concern in endemic areas (Massachusetts, New York, Connecticut, Minnesota, Rhode Island, New Jersey, and Wisconsin); however, over time, *Babesia* has been identified in non-endemic areas. This is most likely related to not only the mobility of humans, but also the presence and usage of a national blood donor pool.

Babesiosis is the most common reported cause of transfusion-transmitted infection in the United States with greater than 150 cases if transfusion-transmitted Babesiosis reported. In endemic states, donor seroprevalance has been reported as high as 2%, with incidence ranging from 1 in 604 to 1 in 100,000 cases per RBC units transfused. The current method of identifying *Babesia* in the donor pool is using the "Uniform Donor Health History Questionnaire," which is an imperfect method seeing that up to 50% of *Babesia* infected people are asymptomatic. Numerous publications regarding the cost versus benefit of donor testing by donor antibody and polymerase chain reaction (PCR) screening have reported the costliness of this method, with reports of universal donor testing in endemic regions costing up to $8.8 million per quality-adjusted life years. At this cost, 3-4 cases of transfusion-transmitted *Babesia* would be avoided. Many of these articles leave off with the question of whether society is willing to pay the cost for a safer blood pool, a difficult problem with little consensus.

As mentioned in Simonsen et al.'s paper, neonatologists should have a high index of suspicion for *Babesia* in premature infants exposed to blood transfusion. Since MUSC uses the Red Cross and accesses a national blood pool, neonatologists in non-endemic areas should also be aware that *Babesia* infection can occur in their patient population. This case not only adds support for improved *Babesia* screening in blood products, but also demonstrates how rapid reporting and cooperation between many laboratory pathology areas (microbiology, hematology, and blood bank) led to prompt patient management and patient safety actions.

References

Simon MS, Leff JA, Pandya A, et al. Cost-effectiveness of blood donor screening for *Babesia microti* in endemic regions of the United States. Transfusion 2014;54:889-899.

Johnson ST, Cable RG, and Leiby DA. Lookback investigations of *Babesia-microti*-seropositive blood donors: seven-year experience in a *Babesia*-endemica area. Transfusion 2012;52:1509-1516.

Simonsen KA, Harwell JI, and Lainwala S. Clinical presentation and treatment of transfusion-associated *Babesiosis* in Premature Infants. Pediatrics 2011;128:e1019-e1024.

Goodell AJ, Bloch EM, Krause PJ, and Custer B. Costs, consequences, and cost-effectiveness of strategies for *Babesia microti* donor screening of the US blood supply. Transfusion 2014;54:2245-2257.

Herwaldt BL, Linden JV, Bosserman E, et al. Transfusion-associated Babesiosis in the United States: a decription of cases. Annals of Internal Medicine 2011;155(8):509-519.

http://www.cdc.gov/parasites/babesiosis/

HOLIDAY PARTY

2014

Thank you to **Sergeant Demos**, **Lance Corporal Profit, Lance Corporal Foster, Lance Corporal Cramer** and **Lance Corporal Kapicka** from the **United States Marine Corps** for their help with the Toy for Tots!!

FACULTY FOCUS

M. Timothy Smith, M.D.

My life has not been exceptionally exciting. If it were this would be like a spy novel rather than common prose. The great lesson I was taught was to work hard and be happy. These lessons are important.

I was born in San Angelo, Texas. That's halfway between San Antonio and El Paso. Millions of people have driven right past it. John Wayne, Roy Rogers and Gene Autry were / are my heroes. My dad was an Air Force officer and my mother was a housewife and mother. Even back in the 40s Daddy was involved in the early stages of electronic warfare. Life as an Air Force brat was secure and focused with an intense awareness of the world stage. Our parents made certain that I and my sister performed well in school. In San Antonio I worked in the grade school cafeteria for free lunches which was a really good deal. My job was to clean the plates and place them in the racks to go in the mechanical dish washers. The little kids never finished their deserts so I often ate their left over lemon meringue pie. If I wasn't working in that cafeteria my favorite lunch was 3 tamales and rice for a quarter. In that city back to the stone ages and at that time the worst tamales you could find were fantastic; still are. Daddy was transferred to the Pentagon and I went to high school in northern Virginia's Fairfax County. Cs were unacceptable school grades. I always liked science and the extra books I read turned out to be good preparation for pathology reading. A biology teacher encouraged me to apply to West Virginia University and I loved it. The weather was horrible but the education and classical college atmosphere were exceptional. Studying was fun. The fraternity house was fun; just like the movie "Animal House." There are many stories of fraternity life but ……. College is where I found Carol who was and is the greatest joy and foundation of my life. She came to a party with someone else and was incredibly impressed with how well I could dance on top of a '53 Chevy. She married me after graduation. The USAF could have been impressed with my car dancing too, and sent me to medical school. For a kid from a non-medical family medical school was the most exciting and fascinating experience ever. Not even a single day seemed like work. Pathology actually came to me the summer before medical school when I worked for a pathologist doing odd jobs in the lab. Pathology was to provide enough fascination for a lifetime.

After internship at Wilford Hall USAF Medical Center I found residency and fellowship at University of Texas San Antonio where Carol was faculty in pharmacology. The 21 year Air Force career took me to non-tourist places and provided exceptional experiences. I never had to worry about having a job; only the location was indefinite. The combination of seven years at the AFIP and

Faculty Focus, cont'd

membership in the Association of Directors of Anatomic and Surgical Pathology privileged me with knowing many pathology greats. Ramon Font, Lorenz Zimmerman, Franz Enzinger, Kash Mostofi, Charlie Davis, Lionel Rabin, Elson Helwig, Kamal Ishak, Vince Hyams, Juan Rosai, Kenneth Earle, Paul Yakovlev, Sharon Weiss, Lent Johnson, Don Sweet are legends from the AFIP whom I knew. A similar but longer list could be quoted from the ADASP but I spare you. I was certainly fortunate to land an assignment at the old AFIP. Simultaneous with assignments in pathology the department of defense IG tapped me for "special" duty on inspection teams that originated the term "quality assurance." In my last military assignment I was back at good old Wilford Hall where I interned, but this time as pathology chair. My residents from that time are still practicing pathology, one in South Carolina.

Pathology at MUSC has been intellectually exciting and fulfilling from day one. The cases are world class challenging daily. The staff and faculty are a close knit team that works great together. It is a privilege to work with colleagues like Drs. Bruner, Carroll, Chajewski, Duong, Lazarchick, Lewin, Metcalf, Ralston, Richardson, Self, Spruill, Sun, Welsh and Yang. The residents work hard for patients and earn their places in the department. I have never been in a place where I can truly subspecialize so I split most of my time doing GU pathology, neuropathology and soft tissue pathology. These provide plenty of challenges, excitement, anxiety and neural stimulation. So this job has been a delight along with my other great loves; family and my garden. I work almost every weekend making the garden around the house colorful and pleasing for the family and me too! Recently ten sasanqua camellias were added in carefully selected locations where they will receive part sun throughout the year. The whole garden just keeps expanding as parts of the 22 acre jungle is pushed back for decorative shrubs. It's a thrill watching the grandchildren picking flowers and running through the grass.

UPCOMING MEETINGS

PATHOLOGY SPRING SYMPOSIA, FEBRUARY 24 – 28, 2015
AT THE CHARLESTON PLACE HOTEL

MUSC Department *of* Pathology & Laboratory Medicine Mission Statement:

To serve patients, health care providers, research scientists, scholars, and society by providing excellence and innovation in diagnostic services and educational resources in a respectful, professional and culturally diverse atmosphere.

Vision:
To become a preeminent leader in academic anatomic and clinical pathology while translating basic science discovery to improved clinical care.

www.musc.edu/pathology