Laser Imaging Studies Shed Light On Brain Blood Flow Abnormalities In Myeloproliferative Neoplasms

By Chris Schaffer, Ph.D and Puifai Sakultarm

Myeloproliferative neoplasms are disorders of the blood that present themselves in four main forms: polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myelogenous leukemia. In these diseases, malignancies in the bone marrow lead to abnormal quantities of red blood cells, white blood cells, and platelets. For polycythemia vera and essential thrombocythemia, which share an acquired mutation in the JAK2 gene in most patients, quality of life is significantly reduced due to excessive production of red blood cells and platelets. Those affected by the diseases often experience fatigue, chronic headache, and thrombosis as a result of blood flow and coagulation problems. They require frequent doctor visits to monitor and adjust the blood condition by means of medication as well as phlebotomy. The abnormal circulation can lead to a number of secondary clinical manifestations including neurological problems, which are poorly studied even sixty years after the discovery of myeloproliferative neoplasms.

In 2007, Dr. Richard Silver, Weill Cornell Medical College, and Prof. Chris Schaffer, Department of Biomedical Engineering at Cornell University, set out to explore the impacts of polycythemia vera and essential thrombocythemia on microcirculation of the brain, combining their expertise in hematology and advanced optical imaging.

continued on page 2

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Cancer Research & Treatment Fund has proudly entered the world of social media by starting our own Facebook page! Our profile page is a work in progress and we will be updating it regularly with our latest news and events. We hope to reach out to a broader audience through this medium so please help us spread the work of CR&T by following us on Facebook and sharing us with your friends.

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This collaborative effort was launched by Ms. Puifai Santisakultarm, then a first-year Ph.D. candidate in Biomedical Engineering, who spent two months working with Dr. Silver in New York to learn the genetic and physiological basis of myeloproliferative neoplasms. She then returned to Cornell University in Ithaca, NY with a background in the clinical side of these diseases and the tools and drive to try to uncover potential mechanisms of microcirculation problems during her Ph.D. research in Prof. Schaffer’s lab. With continuous collaboration from Dr. Silver and generous financial support of the Cancer Research and Treatment Fund, Ms. Santisakultarm has made a few very important discoveries in the last four years that may shed new light on how myeloproliferative neoplasms affect brain function.

In her graduate study, Ms. Santisakultarm uncovered a significant amount of brain capillaries with blockages in mouse models of polycythemia vera and essential thrombocythemia. Although there is some clinical evidence which suggests possible cognitive decline in these diseases, no direct observation has pinpointed a potential mechanism for injury to the brain until this detailed study of brain microcirculation using in vivo two-photon excited fluorescent microscopy. Severe reductions in brain blood flow, such as those Ms. Santisakultarm has shown to occur in mice with myeloproliferative neoplasms, are known to be associated with neurological decline in many disorders such as Alzheimer’s and dementia. In addition, the research team found white blood cells and platelets to be the leading reason for these capillary occlusions. The flow disruption is temporary in the case of white blood cells, while permanent in a subpopulation of platelet clots. The results underline alterations in blood composition as an important factor in the health and functions of organs with numerous small blood vessels as well as the roles that various blood cells play in potentially disrupting blood flow.

The knowledge gained from this study has many implications. It demonstrates the significance of physical properties of the blood, which is sensitive to alteration of blood composition, and the attention that physicians must pay to this issue when treating patients. It also generates new ideas for therapeutic strategies for those who suffer from myeloproliferative neoplasms as well as disorders where microcirculation problems play a crucial role. Dr. Silver, Prof. Schaffer, and Ms. Santisakultarm are currently working to test strategies to interfere with white blood cells and platelets aggregation in hope of eliminating the capillary stalls and restoring brain blood flow. This ongoing work has received continued financial support from the Cancer Research and Treatment Fund.
6th International Patient Symposium on Myeloproliferative Diseases

November 2, 2011

Richard T. Silver, MD
Program Chair

David Boule
Patient Committee Chair

Schedule

7:45 AM  REGISTRATION
8:45 AM  David Boule
          Welcome
8:55 AM  Dr. Richard T. Silver
          Introductions
9:00 AM  Dr. Babette Weksler
          Thrombosis
9:30 AM  Dr. Ross Levine
          Genome Sequencing to find Mutations that cause MPD's
10:00 AM Dr. Richard T. Silver
          Interferon in the Treatment of MPD's
10:30 AM BREAK
11:00 AM Dr. Jerry Spivak
          MPD Disease Progression
11:30 AM Dr. Srdan Verstovsek
          JAK2 Inhibitors and New Drugs and Therapies
12:00 PM Dr. Shahin Rafii
          Stem Cell Transplantation
12:30 PM LUNCH
1:45 AM  Dr. Ronald Hoffman
          MPD Research Consortium
2:15 PM  Dr. Richard T. Silver
          Moderated Q & A
3:15 PM  David Boule & Robert Rosen
          A Word From Our Sponsors
3:30 PM  BREAK
4:00 PM  Breakout Sessions
          Polycythemia Vera: Dr. Jerry Spivak, Lecturer
          Panel: Spivak (Chair), Silver, Levine
          Essential Thrombocythemia:
          Dr. Tiziano Barbui, Lecturer
          Panel: Barbui (Chair), Weksler
          Myelofibrosis: Dr. Ruben Mesa, Lecturer
          Panel: Mesa (Chair), Verstovsek
4:45 PM  BREAK
5:30 PM  ADJOURNMENT

Please remember to register for the symposium as space is limited. For information, contact CR&T at 212-288-6604.
Jennifer Friel, a long-time friend of CR&T, organized a group of bikers to join Pelotonia and raised $8,000 for a cancer research center at Ohio State University. The team of six proudly wore our logo in honor of Jennifer’s father, David L. Johns, who was Dr. Silver’s patient.

In June, we received a wonderful letter from our youngest contributor, 10 year old Miss Nicole Schwartz. She set up a fundraiser in her school and collected $71 dollars! We are so proud and grateful to have her support. Nicole exemplifies the spirit of CR&T. Please join in this spirit by making your contribution today.
1. How did you get involved with CR&T?
   Dr. Silver was an inspiration to go into this area and has been a mentor for a long time.

2. What are your main areas of expertise?
   Lung cancer, breast cancer, hematologic malignancies

3. What is on the horizon for cancer research?
   Sadly, government cutbacks are occurring because we are trying to balance the budget. With budget spending going down, this will negatively impact our leadership position in making advances in research. This is when private philanthropy becomes even more important.

4. Who would you like to see play in the Super Bowl this year?
   Giants

5. Which scientists do you most admire and why?
   Dr. Gerald Fink of the Whitehead Institute at MIT and Dr. Harold Varmus, Director of NCI, for their work in molecular biology.

6. Mac or PC?
   PC

7. In your opinion, what technological advancement has helped improve patient care?
   The advancement of screening, especially for colon, lung, and breast cancers.

Anti-cancer agents grant: A Progress report from David Scheinberg, MD, PH.D

Inhibition of a Mitochondrial Enzyme (peptide deformylase) Disrupts Mitochondrial Function and Kills Cancer Cells Selectively

David A. Scheinberg, MD, Ph.D; Sindy Escobar-Alvarez, Ph.D; Hakim Djaballah, Ph.D; Aneesh Sheth, student

Mitochondria are organelles in all human cells that are responsible for production of energy from glucose and oxygen. The mitochondria are also master controllers of cell death. The human mitochondrial protein, peptide deformylase, (PDF) is an enzyme that removes the ends of key proteins that are involved in the energy production process. We have shown that inhibition of PDF decreases human cancer cell growth in a variety of human cancers in model systems. Similarly, pharmacologic inhibition of PDF with the antibiotic inhibitor actinonin results in mitochondrial dysfunction and promotes cell death or growth arrest in a wide variety of cancer cell lines.

The mechanism for how blocking PDF kills cancer cells more than normal cells is not known, but the understanding of this process would allow development of better anti-cancer drugs. We show that inhibition of PDF function in mitochondria of human cancer cell lines reduces accumulation of the key proteins that are involved in making energy for the cell; energy production by the mitochondria drops. We are in the process of trying to develop more potent inhibitors that might be used as drugs for human cancers.
Cancer Survivors Hall of Fame Dinner
Tuesday, November 15, 2011
Essex House
160 Central Park South, New York, NY

Please join us for a very special evening honoring courageous cancer survivors, outstanding medical professionals, and compassionate humanitarians for their dedication and accomplishments this year. Cancer Research & Treatment Fund is proud to have Maria Brisbane and Amanda Johns Perez as our Co-Chairs for this wonderful event. All proceeds will go directly to CR&T so that we may continue to do our part in finding a cure for cancer. For more information, please contact CR&T at 212-288-6604 or www.crt.org.

Judy O. Higgins will be presented with the 2011 Humanitarian Award at our Hall of Fame Dinner. Judy is an invaluable supporter of Cancer Research & Treatment Fund, helping to fund research that will move us closer to a cure for cancer. Her involvement with CR&T first began when her husband, Bill, became a patient of Dr. Silver’s 25 years ago. She has chosen to remain involved with CR&T, as has her family, through the years because she believes that Dr. Silver and his colleagues are making significant progress in finding a cure for a number of blood diseases. She graciously accepts this award on behalf of her entire family. Mrs. Higgins is an active member of her community, serving on the board of the Greenwich Emergency Medical Service, the Boys and Girls Club of Greenwich, and St. Mary Church. She is a graduate of Smith College and was an educator for over 18 years. Please join us on November 15th at the Essex House, to honor our friend, Judy O. Higgins.

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Cancer Research and Treatment Fund, Inc., is a non-profit group of physicians, nurses, and other medical professionals dedicated to research for the treatment of cancer and other blood diseases. Richard T. Silver, MD FACP founded CR&T in 1968.

Dr. Silver is Professor of Medicine and Director of the Leukemia and Myeloproliferative Center at Weill Medical College at Cornell University. He is Attending Physician at New York Presbyterian Hospital/Weill-Cornell Medical Center.

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