



Terrence J. Irmen

From The Chairman's Desk

It seems like it was only a few years ago when the Forbeck Foundation began, although the reality is we are now in our 22nd year of operation. Many of the core group of volunteers assembled by *George and Jennifer Forbeck* in 1984 remain active with the Foundation, serving on the Board of Trustees and the Scientific Advisory Board. The magic of the Forbeck Foundation is the close working relationship between these two groups.

The Board of Trustees has been strengthened with the addition of two new members, *Bill Herbkersman*, South Carolina State Representative, and *Jeffrey Hadden*, attorney and Chairman of the Technology Company Practice of Goodwin/Proctor LLP. We look forward to the resources and talents that they each bring to the Foundation.

The Scientific Advisory Board has three members who have been with us from the beginning, *John Kemshead, PhD*, Baxter Healthcare, *Bruce Chabner, MD*, Massachusetts General Hospital, and *Arnold Freeman, MD*, Hadassah Hospital and Hebrew University. They are joined by *John Minna, MD*, University of Texas, *David Fisher, MD, PhD*, Dana Farber Cancer Institute, and *Jean Wang, PhD*, University of California. The Forbeck Foundation is so very fortunate to have this caliber of scientists to develop the scientific direction of our forums.

The original mission developed during our first year continues as our

beacon for growth, promoting advances in the field of oncology, particularly pediatric oncology. This past year's forum addressed "*Innovations in Imaging in Cancer Research*" chaired by *Harvey R. Herschmann*, University of California, and *Ralph Weissleder*, Massachusetts General Hospital. The 2006 Forum topic on "*Stem Cells*" will be chaired by *John Dick, PhD*, University of Toronto and *David Scadden, MD*, Massachusetts General Hospital. We plan to continue these forums as long as there is work to be done.

Our Junior Board, led by *Jamie Forbeck*, organized a Fall Festival Auction to raise funds that can be used by the Foundation. These funds were utilized to establish a new initiative called the Forbeck Scholar Program. The first Scholar Retreat was held last September in Lake Geneva, Wisconsin, directed by *David Fisher* (Scientific Advisory Board) and was reviewed by all attendees as an overwhelming success.

We believe that we can make a difference and that a cure for cancer is immanent, however it is important to remain grounded enough to be prepared for a long battle. We thank the many dedicated volunteers who have contributed so much to make the Forbeck Foundation the force that it is becoming in the fight against cancer.

Terrence J. Irmen
Chairman, Board of Trustees

SCIENTIFIC ADVISORY BOARD REPORT

I believe that last year was the most successful year for the Foundation to date. Three scientific conferences were organized and funded. In addition to an extremely successful Hilton Head Forum on novel imaging modalities, we funded an International meeting on Neuroblastoma staging, and a Scholar Retreat. The latter event deserves pride of place in my mind as it really takes the Foundation into a new area that builds upon our overall mission in a significant fashion.

Each year we invite the crème de la crème of scientists to our annual Forum and up to four scholars that have yet to complete their training in either science and / or medicine. The choice of these scholars gets harder each year as their caliber only seems to increase. During their time at the Foundation's main Forum the scholars have the opportunity to interact with the scientists in a fashion that would be hard to duplicate in a



John T. Kemshead, PhD

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2005 Forbeck Forum: XXIst Annual Forum

November 3–5, 2005 Hilton Head Island, South Carolina

Subject: Innovations in Imaging in Cancer Research

- I: Mouse models of Cancer
- II: Models, continued, and Clinical Applications
- III: Chemistry of Probes
- IV: Chemistry, continued and Instrumentation

Chairmen

Harvey R. Herschman, PhD	University of California	Los Angeles, CA
Ralph Weissleder, MD, PhD	Massachusetts General Hospital	Charlestown, MA

Participants

Anton Berns	The Netherlands Cancer Institute	Amsterdam, Netherlands
Remy Brossel, MD	Mauna Kea Technologies	Paris, France
Simon R. Cherry, PhD	University of California	Davis, CA
William G. Kaelin, Jr. MD	Dana-Farber Cancer Institute	Boston, MA
Steve Larson, MD	Memorial Sloan Kettering Cancer Center	New York, NY
Claude F. Meares, PhD	University of California	Davis, CA
Vasilis Ntziachristos, PhD	Massachusetts General Hospital	Charlestown, MA
Neal Rosen, MD, PhD	Memorial Sloan-Kettering Cancer Center	New York, NY
Prof. Dr. Markus Schwaiger	Technischen Universitat Munchen	Munchen, Germany
Daniel C. Sullivan, MD	National Cancer Institute	Rockville, MD
Roger Y. Tsien, PhD	University of California, San Diego	La Jolla, CA
Gregory L. Verdine	Harvard University	Cambridge, MA
Michael John Welch, PhD	Washington University School of Medicine	St. Louis, MO
Owen N. Witte, MD	University of California	Los Angeles, CA



Harvey R. Herschman, PhD



Ralph Weissleder, MD, PhD

2005 Conference Report on “Innovations in Imaging in Cancer Research”

by Harvey R. Herschman, Ph.D. & Ralph Weissleder, M.D., Ph.D.

Both diagnosis and treatment of cancer have changed dramatically in the recent past, as research in animal models and patients has identified the molecular alterations that occur in the initiation and progression of many tumors. This new level of understanding has identified a myriad of targets for potential drugs designed to inhibit specific alterations in tumor cells, provided opportunities to stratify patients according to level of risk, and suggested methods to detect cancer earlier. In parallel, our ability to image functionally the molecular and biochemical changes that occur in tumors has advanced dramatically – both in patients and in animal cancer models. Magnetic resonance imaging (MRI) can identify previously undetectable lesions, positron emission tomography (PET) can utilize changes in tumor biochemistry to locate tumors and monitor their functional characteristics and optical imaging technologies (FRI, FMT) are at the verge of being introduced into clinical care to expand the realm of what the human eye can perceive. These technologies, coupled with other imaging modalities, have altered our

ability to detect tumors, stage tumor progression, observe metastases, detect recurrences and rapidly monitor tumor responses (or lack of response) to alternative therapies. The development of small animal MRI and microPET instrumentation, and instrumentation for optical imaging of bioluminescence and fluorescence, has brought non-invasive molecular imaging into the toolbox of researchers who study cancer in small animal models in which the mice are subject to extensive genetic manipulation.

Harvey Herschman and **Ralph Weissleder** led a two day meeting of experts in new imaging technologies to discuss the current state of molecular imaging applications in clinical practice, clinical research and basic research, and to consider the directions most appropriate for future research and clinical utility of molecular imaging in the diagnosis, staging, and therapy of cancer. For structural convenience, the meeting was divided into four topical themes: 1) clinical applications of molecular imaging, 2) imaging applications to cancer research in small animal models, 3) the development of new imag-

ing probes for optical, magnetic and radionuclide imaging modalities, and 4) the next generation of imaging instruments for research and clinical applications in cancer. In practice, as is common in the Forbeck Forums, the discussions in each session – and for each presentation – were wide ranging and often extended into a number of these topics.

Animal cancer models in which tumor initiation, progression, metastasis and response to therapy can be monitored repeatedly and non-invasively permit researchers to perform experiments more easily and efficiently, and – in some cases – facilitate studies that cannot be performed by other means. **Anton Berns** described development of transgenic mice in which conditionally activated luciferase reporter genes can be induced in a temporal and tissue-specific manner, along with the targeted activation of oncogenes that lead to the tumor development. He demonstrated the utility of transgenic reporter mice to monitor the onset of tumors in “spontaneous” cancer models, to observe metastases, and to compare alter-

native combinations of therapeutic drugs and their order and timing of presentation. Comparisons of therapeutic regimens for doxorubicin and cyclacell 2000 in treating an Rb deficient pituitary tumor model illustrated the value of this approach.

Many proteins and molecular pathways are regulated by targeted protein degradation. In particular, ubiquitin ligase-mediated protein degradation by the proteasome plays a major role in pathways and cell cycle functions important in cancer. Coupling proteins to luciferase, as



described by **Bill Kaelin**, provides a method to monitor non-invasively protein degradation in murine models, in response to altered oncogenes and in response to therapeutic drugs that target ubiquitin ligase and proteasomal functions. A fusion of luciferase with the cell cycle regulatory protein p27 was used to illustrate the ability of repeated bioluminescent imaging to monitor ubiquitin-proteasome mediated degradation in vivo. A genomics/proteomics approach to studying proteasome/ubiquitin ligase biology is underway with libraries of cDNA fusion proteins to both GFP and firefly luciferase, using high-throughput cell assays to identify proteins targeted for proteasomal degradation by specific ubiquitin ligases.

Activation of the endogenous immune system and the use of activated, targeted immune cells as therapeutic agents are both under active investigation for cancer therapy. **Owen Witte** discussed the potential to monitor migration and expansion of anti-tumor lymphoid cells in animal modeling of endogenous immune responses with reporter imaging genes



and the use of both HSV1-TK (for PET) and luciferase (for bioluminescence) marked targeted T cells for immunotherapy, in a murine sarcoma model system. Remarkably, using microPET imaging of HSV1-TK with positron labeled substrate and systemic glucose metabolism with FDG, the tumor (HSV1-TK) and the adjacent lymph node could be distinguished. This observation provoked a discussion on the need to re-evaluate FDG-PET scanning data, to consider the possibility that activated immune cells as well as tumors are being detected in clinical studies.

Cyclooxygenase 2 (COX-2) is activated in a wide range of cancers, and is thought to be causal in the progression of many tumors (e.g., colon, breast). Early COX-2 expression is proposed as a “biomarker” to distinguish benign tumors that will progress to malignant forms. A “knock-in” mouse in which the firefly

luciferase coding region replaces the COX-2 coding region was reported by **Harvey Herschman**. COX-2 gene activation in the skin of heterozygous mice can be repeatedly monitored by bioluminescence in response to wounding and inflammatory stimuli. In a carcinogen-tumor promoter skin tumor induction model, COX-2 gene activation can be monitored repeatedly, non-invasively and quantitatively, suggesting the relationship between COX-2 expression and papilloma-to-carcinoma progression will now be amenable to investigation and elucidation.

Marcus Schwaiger emphasized the importance of optimizing currently available clinical imaging technologies to facilitate staging of patients and to both select and monitor alternative therapies in the clinic. He discussed the role of positron-labeled tracers such as FDG, amino acids, transporters, choline and nucleotide analogues as probes for tumor response to therapy by PET. Examples of correlations of FLT (a thymidine analogue) with Ki67 histochemistry for measurement of proliferation and a comprehensive summary of the ability of alterations in FDG uptake illustrated the current value of PET in distinguishing responder and non-responders in a variety of tumor types were presented. The importance of developing adequate infrastructures for incorporating molecular imaging into clinical trials was repeatedly emphasized during this presentation.

The Von Hippel Lindau (VHL) gene is an ubiquitin E3 ligase that marks the HIF-1 α transcription factor for proteasome degradation, as a result of prolyl hydroxylation. In hypoxic conditions, HIF1- α is not hydroxylated, and thus not subjected to VHL-dependent, proteasome-mediated degradation. **Michal Safran** fused the HIF1- α “degron” to firefly luciferase, and created a transgenic mouse in which ODD-luciferase is expressed from an ubiquitous promoter. Both tissue hypoxia and the efficacy of inhibitors of HIF1- α prolyl hydroxylation can be monitored in vivo. When crossed to VHL deficient mice, kidney luciferase expression is elevated three to five fold. Preliminary data suggest that developing tumors undergoing an “angiogenic switch” can be monitored by transient hypoxia and consequent elevated luciferase activity.



Neal Rosen emphasized the importance of imaging “to find out what is happening in patients”; to determine whether targeted therapies are – in fact – inhibiting their targets and demonstrate appropriate specificity. He illustrated his point by showing how PET imaging of proliferation (with the positron-emitting thymidine analogue FLT) can distinguish MEK 7 inhibitor responses of Raf oncogene acti-

vated tumors from lack of response to this agent in Ras oncogene activated tumors. 17-AAG, an inhibitor of HSP90 regulated protein folding, is currently in clinical trials. Dr. Rosen also demonstrated, in murine xenografts, the ability of microPET imaging with a 68Ga positron-labeled antibody to monitor the loss of Her2.

Introduction of multimodality imaging, and – in particular – CT-PET has provided substantial improvement in the use of molecular imaging for staging patients and for monitoring therapeutic responses.



Steve Larson reported on the improvements in the use of positron labeled metabolic probes (FDG), proliferation probes (FLT) and receptor targeted ligands (FDHT for androgen receptor) to image tumor responses to alternative therapies, both in cancer patients and in murine xenograft tumor models. An extensive discussion on the reasons why FDG metabolism changes in response to so many therapies, despite a relatively small effect on hexokinase activity in response to these treatments, followed Dr. Larson’s presentation.

Glioblastomas frequently have mutations leading to PTEN loss and amplification and truncation of the EGF receptor. **Ingo Mellingshoff** demonstrated that EGF receptor tyrosine kinase inhibitors, effective in only 20% of a clinical cohort of stage IV glioblastoma patients, were far more effective in patients that had both the EGFRvIII mutation and a wild-type PTEN locus; six out of seven patients with this genotype showed tumor regression. In contrast, patients with the EGFRvIII mutation, but with an accompanying PTEN mutation, were refractory to EGFR TK inhibition therapy. Additional mutations in candidate tyrosine kinases are being sought by target sequencing of tumors from several tissues.

Phage display is a powerful technique to identify new imaging ligands for specific molecular targets upregulated in cancer.

Kimberly Kelly described the use of phage display to identify peptide ligands for the VCAM-1 protein on endothelial cells, for “cancer targets” in pancreatic and colon cancer tumors, and for subpopulations of macrophages, associated with “inflammatory cancers” or macrophage recruitment during therapy induced apoptosis. Specific biological screens were illustrated by using flowing phage to identify internalizing peptides and in vivo screening to identify peptides that bind to atherosclerotic plaques. Discussions included topics that included how to choose among available phage libraries, what makes a good target, identifying appropriate “hits”, identifying the targets, and optimizing imaging agents from phage peptides.

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2005 Conference Report

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Ninety seven percent of clinical PET examinations use FDG. **Michael Welch** described the preparation of a variety of additional positron-emitting isotopes (^{60}Cu , ^{61}Cu , ^{64}Cu , ^{124}I , ^{76}Br , ^{77}Br , ^{66}Ga , ^{68}Ga and ^{86}Y), and the program established at Washington University to provide such isotopes to other laboratories. The use of Cu(ASTM) as an agent to measure tissue hypoxia, to distinguish responders and non-responders for radiation therapy, and a bromine labeled Sigma 2 receptor probe that preferentially binds to proliferating cells were described as examples of the use of positron-emitting probes, other than ^{18}F , with potential for clinical application. Dr. Welch emphasized the difficult barrier presented by FDA approval in getting new imaging agents into the clinic, both for trials and for standard-of-care use.

The development of lymphotropic magnetic nanoparticles for MRI imaging has revolutionized cancer staging in patients. Current efforts are under way to design newer, highly specific tumor targeted and multimodality agents detectable by MRI and intraoperative imaging. **Ralph Weissleder** presented novel procedures for the parallel synthesis of nanoparticle libraries decorated with multiple small molecules, and high-throughput screening to identify specific nanoparticle preparations enhanced for properties such as macrophage uptake (or escape), endothelial cell uptake and selective binding to and/or uptake into cancer cells. Several new imaging agents have been identified for pancreatic cancer, a tumor which currently lacks reliable imaging agents. Discussions centered around target choice, signal amplification, enzyme conversions, activatable agents, multivalency, pre-targeting, optimized pharmacokinetics, background reduction and enhanced affinities.

Response to radiation is critically dependent on the state of hypoxia in tumors. **Benjamin Williams** described the use of electron paramagnetic resonance (EPR) as a non-invasive method to image O_2 , NO , pH and temperature. His presentation emphasize the use of EPR oximetry to monitor the concentration of molecular oxygen in vivo continuously, over several hours without invasiveness. Dr. Williams discussed potential applications of EPR oximetry, by repeated measurements of pO_2 , for guiding and monitoring radiation therapy to optimize this therapy by application at periods of relatively high oxygenation.

Targeted delivery of a wide variety of “payloads” – imaging agents, therapeutic agents – etc is a major goal in cancer research. Arginine-rich “cell penetrating peptides” are under active investigation as ligands to facilitate delivery of such pay-



loads. **Roger Tsien** has constructed hairpin polypeptides in which such polyanionic domains are coupled by cleavable peptides to inhibitory cationic domains. Cleavage of the linker, typically by proteases, releases the targeting domain and permits “transduction” of its cargo to cells in the immediate vicinity. Several murine model systems, including a murine transgenic mammary tumor and human tumor xenografts that express matrix metalloproteinases, demonstrated the in vivo applicability of this targeting procedure. Targeting of technetium and gadolinium cargos apparently accumulates in cells in a protease-dependent fashion.

Many promising molecular targets for new therapeutics and imaging agents are not suited to bind small, cell-permeable organic molecules, and are said to be “undruggable.” The laboratory of **Greg Verdine** focuses on developing new chemistry platforms that address undruggable targets – “drugging the undruggable.” They have returned to using molecules with stereochemical centers to develop libraries with greater diversity. Dr. Verdine also described a method of “molecular stapling” to force polypeptides into alpha helix configurations for the development of polypeptide drugs and probes. He illustrated examples for targeting Myc protein and development of a stapled peptide that mimics the BID protein and inhibits apoptosis. Importantly, these stapled peptides are highly cell membrane permeable (2-3 orders of magnitude compared to parent sequence). He also reported preliminary results with small RNAs that target nonWatson-Crick base pairing, to inhibit formation of undesirable RNA molecules.

One limitation of many radiopharmaceuticals is their relatively low target-to-background ratio in vivo. Pretargeting strategies such as Neorex’s avidin-biotin system, have previously been developed to improve target-to-background ratios but have been abandoned due to other concerns. **Claude Meares** introduced an

alternative amplification strategy based on developing imaging agents with “infinite affinity” to targets of choice. The basic principle of achieving this is by promoting covalent reactions that would not otherwise be favored. This was illustrated with an engineered monoclonal antibody system. By coupling this reagent to two single chain antibodies, a multivalent, high affinity imaging agent could be created.

MicroPET, microCT, and similar instruments have brought these non-invasive imaging techniques to small animal cancer models. **Simon Cherry** discussed tradeoffs in sensitivity, spatial resolution, speed of imaging, quantification, high-throughput capability, cost and other factors that are considered in the design of next-generation imaging instruments, and asked the biologists present to consider these alternatives in their evaluation of how to proceed in instrumentation design. He also discussed the question of “Why can’t PET be better”, and clarified the theoretical and practical limits for resolution and sensitivity. Dr. Cherry pointed out the often appreciated – by biology end-point users – radiation doses received by mice in microCT or combined microPET-microCT studies, and the potential effects of these doses on the biological processes under investigation.



Vasilis Ntziachristos evaluated applications and limitations of current optical fluorescence imaging systems. He differentiated reflectance imaging (photography), postprocessed reflectance imaging and quantitative tomographic imaging methods. He presented the principles of optical tomography for in vivo fluorescence imaging, using techniques that involve laser excitation, subject rotation, time gating and reconstruction algorithms that currently provide sub millimeter resolution with murine models. Fluorochrome detection threshold in the near infrared is currently in the femtomole range. He also presented newer developments to image GFP quantitatively, demonstrating a detection threshold of about 20,000 tumor cells in the esophagus of a mouse. Discussion

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International Neuroblastoma Risk Groups (INRG)

September 17-20, 2005 - Whistler, BC, Canada

By Susan Cohn, M.D. & Andrew Pearson, M.D.



Neuroblastoma is the second most common solid cancer of childhood and is one of the major causes of death from malignancy in childhood. The behaviour of neuroblastoma is variable, with some tumours regressing spontaneously in contrast to others which are resistant to intensive treatment. As a result of this broad spectrum of behaviour, treatment for children with neuroblastoma is tailored so that children receive the appropriate amount of treatment and are not under or over-treated. There are many factors which are known to predict the behaviour of neuroblastoma and most international cooperative

organisations use a combination to these factors to classify neuroblastoma tumours into high, intermediate and low risk groups, and stratify treatment accordingly.

However, at the present time, there is no international agreement on the definition of these risk-groups and the accuracy of the grouping can be improved. As a patient classified as high-risk in North America may be considered intermediate-risk in Europe, it is not possible to directly compare the results of clinical trials in different regions of the world.

The International Neuroblastoma Risk Group meeting (INRG) was held in Whistler between 17-19 September with the objective of obtaining international consensus regarding the definition of neuroblastoma risk groups. The meeting was co-chaired by Sue Cohn (Chair of the Children's Oncology Group (COG) Neuroblastoma Disease Committee of North America) and Andy Pearson (Chair of International Society

for Paediatric Oncology Europe (ESIO) Neuroblastoma Group). Fifty two delegates attended from the six major cooperative groups ESIO, COG of North America, Japan, Germany, Australia and China). Nine months prior to the meeting in Whistler, four committees [Statistical (Chair - Wendy London); Biology (Chair - Peter Ambros); Surgical (Chair - Tom Monclair) and Detection of Metastatic Disease (Chair - Kate Matthay)] were established. These committees worked extensively prior to the meeting using email and telephone conferences to prepare reports which formed the focus of discussions at Whistler.

The meeting in Whistler was highly productive and major progress was made regarding the development of an international consensus in the following areas:

- Key steps to define an internationally agreed neuroblastoma risk grouping system were taken and further statistical work will be carried out in the

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Peter Ambros, PhD	Vienna, Austria	Michele Haber, PhD	Randwick, Australia	Hidetaka Niizuma, MD	Chiba, Japan
Klaus Beiske, MD PhD	Oslo, Norway	Dr Barbara Hero	Koeln, Germany	Jed G Nuchtern, MD	Houston, TX
Frank Berthold, MD	Koeln, Germany	Eiso Hiyama, MD, PhD	Hiroshima, Japan	Julie R Park, MD	Seattle, WA
Dr Herve Brisse	Paris, France	Dr Keith Holmes	London, UK	Andrew D J Pearson, MD	Surrey, UK
Garrett M Brodeur, MD	Philadelphia, PA	Dr Tomoko Iehara	Kyoto, Japan	Dr Michel Peuchmaur	Paris, France
Dr Sue Burchill	Leeds, UK	Dr Helen Irving	Brisbane, Australia	C Patrick Reynolds, MD PhD	Los Angeles, CA
Victoria Castel, MD	Valencia, Spain	Michio Kaneko, MD PhD	Tsukuba, Japan	Dr Gudrun Schleiermacher	Paris, France
Prof Giovanni Cecchetto	Padova, Italy	Javed Khan, MD	Bethesda, MD	Dr Roswitha Schumacher	Cologne, Germany
Dr Irene Cheung	New York, NY	Prof Dr Ruth Ladenstein	Vienna, Austria	Robert C Seeger, MD	Los Angeles, CA
Dr Nai-Kong Cheung	New York, NY	Wendy B London, PhD	Gainesville, FL	Hiroki Shimada, MD, PhD	Los Angeles, CA
Susan L Cohn, MD	Chicago, IL	Professor David Machin	Dorset, UK	Barry Shulkin, MD, MBA	Memphis, TN
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Dr Emmanuele S G d'Amore	Vicenza, Italy	Katherine K Matthay, MD	San Francisco, CA	Dr Toby Trahair	Sydney, Australia
Bruno De Bernardi, MD	Genova, Italy	Jean M Michon, MD	Paris, France	Nadine Van Roy, PhD	Gent, Belgium
Dr Andreas Faldum	Mainz, Germany	Tom Monclair, MD, PhD	Oslo, Norway	Prof Dietrich von Schweinitz	Munich, Germany
Dr Francesco Giammarile	Lyon, France	Akira Nakagawara, MD PhD	Chiba, Japan	Dr Jinhua Zhang	ShenYang, China

Foundation Junior Board



Jamie Forbeck

The Junior Board has had another amazing year. Fall Fest 2005 was again a fun event and a fruitful evening for the Foundation forums. On the same September weekend, we held the first Forbeck Scholar Retreat. This program turned out to be a challenging addition to Junior Board activities. Members of the Junior Board chipped in throughout the 3 days of events. Everyone worked on getting the fundraiser ready. Other members helped to shuttle the doctors, set up picnics during meeting breaks, gave tours to doctors or their spouses and made sure the meetings ran smoothly.

Fall Fest was a beautiful evening by the lake. The music by Wendy Yanke and her group was perfect. It was a lot of fun raffling gifts and once the auction got going it was lively and successful. *Bryant Rowean* took charge of the event set up and the big tent at Aurora George Williams looked beautiful. *Demi Sibbing* and *Glenn Pankau* made interesting M.C.s throughout the night. *Dick Payne* was a great volunteer bartender and helped out a lot. Lake Geneva Country Club bartenders George and Matt were a big hit at the Sponsor Martini bar. The result of this entertaining evening was a very successful year enabling the Junior Board to fund a 2nd Scholar Retreat in 2006.

The Scholar Retreat received great reviews from all the doctors involved. This young group of scientists is extremely talented and accomplished. Their scientific talks and interaction were educational even to the more established scientists. The Foundation was honored to have the high caliber of senior scientists who participated as mentors. The interaction amongst the Scholars and Mentors seemed to be effective and enlightening for both groups. Due to the success of the meeting there were motions at the annual board meeting to lengthen the retreat.



Junior Board members Renee Dabstrom, Jean Gallucci and Glenn Pankau plan Fallfest

This year the meetings will go through Saturday and hopefully most of the doctors will join us for Fall Fest.

It is important to the Junior Board and the Foundation that our supporters recognize the difference that their donations and attendance at Fall Fest make to these meetings and cancer research. With out the amazing support and generosity of the people of Lake Geneva, Chicago and everyone involved, the Junior Board would never have had the inspiration to create the Scholar Retreat. Many comments from the Scholars suggested this meeting could rival other forums and awards such as the PEW Scholars, and has the possibility to evolve into not only an important meeting but an honor to attend.

The most important people to thank for this meeting are the Junior Board members. Their continued participation has made this event possible. Everyone pitches in along the way and particularly the day of the event. It was especially great for the doctors and Junior Board members to have dinner together the evening before the event. Hopefully they understood the appreciation of the doctors for their hard work and also that their contributions are important in making a difference in the progress of cancer research.

Jamie Forbeck

MEMBERS OF THE JUNIOR BOARD

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Brendan Cashman	Chicago, IL
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How to contact the Junior Board:

Junior Board page on the web site

www.wgfrf.org

Email: jamie@wgfrf.org

Contact any Junior Board member

HOW YOU CAN HELP

Mark your calendars! September 16th
Donate or solicit live & silent auction items
Help find sponsors.

CONTRIBUTIONS TO JUNIOR BOARD

SPONSORS: Each year, our sponsors pledge a generous contribution, allowing the Junior Board to cover the up front expenses of the Fallfest fund raising event. We are grateful for the support from

Tricia Forbeck Real Estate
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Many people help make the Junior Board fund raising project a success, through general contributions or through donation of event supplies and auction items. Many thanks to the following:

Sarah Alioto
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Lars and April Brunk
Bruno's Liquors
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Erin Grant
Diane Greengross
Gabe Hammerstrom
David Hanley
Michael and Pat Hanley
Anna and Paul Harmon
Christopher Hart
Sandra and John Hatch

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1st Scholar Retreat

September 15-17, 2005 - Lake Geneva, WI



David Fisher

The first Junior Forbeck Cancer Research Symposium was held at Williams College, Lake Geneva, Wisconsin in September 2005. The meeting represented the remarkable organizational and fundraising accom-

plishments of the Forbeck Foundation's Junior Board, spearheaded largely by *Jamie Forbeck*. Attendees at the meeting were previous Forbeck Scholar awardees, a group of young cancer researchers in training who had been competitively selected to attend one of the Hilton Head Forbeck Symposia within the previous 4 years. In addition, 5 senior cancer researchers attended, both to participate scientifically, and to offer mentorship advice. *David Fisher*, a prior Scholar himself and member of the Forbeck Foundation scientific advisory committee, served as scientific chair of the Symposium.

By all measures, this new meeting was a resounding success. Scientific presentations represented a stunning cross-section of hot topics in cancer research. They differed from the Hilton Head Symposia in the diversity of topics, rather than the highly concentrated themes typical of the Hilton Head meetings. The quality of science presented, as well as the intensity of the discussion was virtually indistinguishable from the meetings attended by senior researchers. The presented research spanned fundamental mechanisms of cell growth and survival, to identification of novel oncogenes in human cancers. The combination of scientific as well as clinical expertise of the participants permitted an especially fertile testing ground for discussions of how to apply basic discoveries to the cancer clinic. Adding further to the value of Junior Symposium were the opportunities for mentoring and advising, including informal discussions of how to deal with prestigious journal editors, to grant-writing.

Finally, the Junior Symposium brought together an outstanding cohort of rising stars in cancer research, unified as Forbeck awardees, and representing a prestigious grouping of university Assistant Professors across broad geographical settings. Personal and scientific relationships among the Forbeck Scholars suggest that this is a remarkable "club" of gifted young cancer scientists. The decision to nurture this group has fortified the Forbeck legacy through focusing on those who represent the future of cancer research.



Participants visiting Yerkes Observatory

2005 ATTENDEES

SENIOR INVESTIGATORS

David E. Fisher, MD PhD	Dana Farber Cancer Institute	Boston, MA
Scott Lowe, PhD	Cold Spring Harbor Lab	Cold Spring Harbor, NY
Charles L. Sawyers, MD	University of California	Los Angeles, CA
Charles Sherr, MD, PhD	St Jude Children's Research Hospital	Memphis, TN
Craig Thompson, M.D.	University of Pennsylvania	Philadelphia, PA

2002 SCHOLARS

Alison A. Bertuch, MD, PhD	Baylor College of Medicine	Houston, TX
Jan Karlseder, PhD	The Salk Institute	La Jolla, CA
Masashi Narita, MD, PhD	Cold Spring Harbor Lab	Cold Spring Harbor, NY

2003 SCHOLARS

James F Amatruda, MD, PhD	Univ Texas Southwestern Medical Ctr	Dallas, TX
Christopher Bakkenist, PhD	University of Pittsburgh	Pittsburgh, PA
Elsa Flores, PhD	Univ. Texas M.D. Anderson Cancer Ctr	Houston, TX
Norman Sharpless, MD	Univ. North Carolina	Chapel Hill, NC

2004 SCHOLARS

Edward Attiyeh, MD	Children's Hospital of Philadelphia	Philadelphia, PA
Nabeel Bardeesy, PhD	Dana Farber Cancer Institute	Boston, MA
Anthony G. Letai, MD, PhD	Dana Farber Cancer Institute	Boston, MA
W. Kimryn Rathmell, MD, PhD	University of North Carolina	Chapel Hill, NC



"Overall the Junior Board achieved something that is, at least in my experience, unique. My impression is that the Scholar Retreat, even as it is now, may have a greater influence on all the scientists present than the Senior Meeting. Of course the seniors enjoy meeting and sharing ideas but there are many quorums in which they can achieve this each year. The Scholar Retreat is a quorum where new investigators can present some thoughts in a small setting and by doing so they are given a boost as they embark on

their independent careers. This would seem to be a very good investment of the Foundation's money, with the investment and therefore risk, spread over more than ten new laboratories. It has certainly had a positive impact on me.

I thank you for inviting me to participate and I hope you invite me back. It really was an excellent and rewarding meeting. I am optimistic about its future. I believe that David is correct; the reputation of Forbeck Scholars could come to rival that of Pew Scholars, which would be no mean feat."

Chris Bakkenist, PhD



"The Scholar retreat was another fantastic experience. I love these meetings! I'd just like to know how grateful we are to you and your family for making these events happen. Its a treat for us to go AND a wonderful environment for sharing ideas. I think one of the clearest tributes to your

commitment and enthusiasm is the quality of the of Mentors who came to the Scholar meeting. They were in the highest caliber of cancer researchers and so it said a lot that they offered their time to come to help guide and inspire us. David Fisher told me that virtually each person he asked happily accepted the invitation."

Nabeel Bardeesy, PhD

Junior Board Contributors

Continued from Page 6

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"FOCUS on the FUTURE" - The FORBECK SCHOLAR AWARD

The William Guy Forbeck Research Foundation is pleased to sponsor this program to further the advance of cancer research. The "Scholar Award" recognizes promising young scientists working in this field.

The Foundation looks for outstanding clinician or post-doctoral fellows with an interest in cancer research. Award recipients are invited to attend the Foundation Forum held in November in Hilton Head Island, South Carolina. Nominations are made by letter of recommendation from the applicant's director of studies, including a short synopsis of the applicant's research interest and a brief explanation of why this individual is recommended. Nominations are due in the spring of each year.

The Foundation received a number of very qualified applications for the 2005 Forbeck Scholar Award. The Scientific Advisory Board selected four outstanding young scientists to attend the 2005 Forum and receive this award. The Foundation was pleased to present this year's Scholars.

2005 SCHOLARS



Kimberly Kelly, PhD is a Postdoctoral Fellow in the lab of *Dr. Ralph Weissleder* at Massachusetts General Hospital, working on developing novel imaging agents for colon cancer through the use of combinatorial chemistry. Dr. Weissleder describes Kimberly as "a highly capable intelligent young woman who has impressed me as a clear thinker that is able to integrate information readily. Her manner is deliberate in the laboratory and she has developed and optimized many of the approaches that are used in our laboratory for the high throughput screening of imaging agents."

"The Forbeck Forum would definitely broaden her vision helping to establish herself as an independent investigator. Kim's interaction will also be beneficial for the Junior group, giving Kim the opportunity for productive collaborations."



Ingo K. Mellinboff, MD joined the laboratory of *Dr. Charles Sawyers* in 2002 "at the beginning of the research phase of his clinical hematology/oncology fellowship at UCLA. He is now an Assistant Professor in the Medical and Molecular Pharmacology Department" as well as continuing his laboratory work on the use of kinase inhibitors as therapeutic agents in oncolo-

gy. When Dr. Sawyers first met Ingo, "he had impeccable clinical skills. At that time I was somewhat surprised by his intense desire to pursue basic laboratory training in order to become a physician-scientist. During his last 2 years in my group, he has established himself as one of the gurus in the lab, always sought out for advice from very senior PhD graduate students and postdocs. I believe Ingo exemplifies precisely what we are looking for in young physician-scientists who have the potential to move back and forth from bench to bedside."



Michal Safran, PhD received her Master of Science and Ph.D. degrees from the Weizmann Institute of Science in Israel then became a Postdoctoral Fellow at the Dana Farber Cancer Institute in 1999. In his nomination letter, *Dr. William Kaelin* says "she has spearheaded the use of mouse models and pioneered the use of bioluminescent imaging in my group. Michal is a bright young investigator who has been very productive in my laboratory. She is a critical thinker, has very good hands at the bench, and has helped to pioneer the use of luciferase fusion proteins for molecular imaging studies. I think attending the Forbeck Forum would be a marvelous opportunity for Michal to see her work in the broader context of new developments in molecular imaging and cancer."



Benjamin B. Williams, PhD earned his degree in Medical Physics at the University of Chicago where his thesis addressed the use of Electron Paramagnetic Resonance (EPR) spectroscopy and imaging. He continues his interest at the Dartmouth Medical School. *Dr. Harold Swartz* said "In the relatively short time that Ben has been a member of our lab, he has made a very positive impression and impact on our research. The development of *in vivo* EPR oximetry methods requires a multi-disciplinary approach, where skills in computational modeling of biological and physical systems, electrical engineering, and statistical analysis of experimental data are combined with a solid understanding of the complex physiologic phenomena under investigation. Ben possesses this combination of physical, mathematical, and biological knowledge and has applied these strengths as a very productive and valuable member of our laboratory. Participation in this year's Forum will further Ben's development as an already suc-

continued on issues of resolution, sensitivity, etc in the context of biological questions. Optical imaging has another unique application in medicine by bringing microscopic resolution to endoscopic and intra-operative procedures.

Remy Brossel described the development of several generations of “fiber-optic confocal fluorescence microscopes”, to image at cellular resolution in inner organs and body cavities. He illustrated the potential utility of the real-time confocal microscopy technique in mice measuring GFP expression and/or autofluorescence. He also presented first clinical data showing that the fiberoptic method can indeed be combined with clinical endoscopy and reveal malignant and subtle premalignant “spots”. Dr. Brossel postulated use of the technology for detecting early cancers, follow-up of “suspicious” lesions, monitoring tumor angiogenic properties and imaging with fluorescent imaging probes currently being developed.

International Neuroblastoma Risk Groups (INRG)

Continued from Page 5

next four months to refine these groupings. The final International Neuroblastoma Risk Groups will be agreed in May 2006.

- A new staging system for neuroblastoma, the International Neuroblastoma Risk Group Staging System was developed. This staging system will allow more accurate comparison of the extent of localised tumours.
- Methods to analyze the status of the *MYCN* gene and the definition of *MYCN* amplification.
- Additional genetic features of neuroblastoma which should be determined in all patients with neuroblastoma;
- Methods to interpret or score MIBG scans, to determine the extent and spread of neuroblastoma;
- Methods to determine the extent of bone marrow involvement with neuroblastoma.

The important results of this meeting will be published in a number of leading international scientific journals in 2006.

These achievements would not have been possible without the very generous support of the William Guy Forbeck Foundation.

FORUM PLANNING

2006 Forum: Stem Cells

The 2006 Forbeck Foundation Forum in Hilton Head will be held on the topic of Stem Cells and will be chaired by *Dr. David Scadden* from Massachusetts General Hospital and *Dr. John Dick* from the University of Toronto.

There should be no misconception that this meeting has little to do with the controversial use of embryonic stem cells for tissue repair. Rather, the focus of this meeting will be on tumor stem cells; how they arise and how they differ from the progeny that originate from these stem cells.

Until 1998, stem cell biology was a field of narrow interest to developmental biologists with a single point of contact to adult human medicine: bone marrow transplantation. The first human embryonic stem cell lines were reported that year and a virtual revolution was begun. Over the same time interval, an explosion of information about adult stem cells in many tissues has emerged albeit with less of a fanfare and more realistic expectations.

At least two consequences of the rapid developments in these areas are relevant to the cancer problem. First, is a greater understanding of the normal stem cells that exist in tissues and how these cells both regenerate and differentiate into normal tissue counter-parts. If one understands how normal cells behave there is more of a chance that we will understand the malignant process. This should in turn help to define approaches to destroying cancer cells in the body.

Second, the relationship of a normal stem cell to its environment is viewed as critical for its regulated growth and its ultimate survival. Studies in this field may shed light into the problem of metastasis and again identify new approach to treatment.

Bringing together experts in the areas of stem cell biology, should enable us to hold a Forum on cancer stem cells and metastasis; topics that are highly relevant today to defining what we all seek; a cure for cancer.

2007 Forum: MicroRNA and Cancer

The 2007 Forbeck Foundation Forum will focus on the topic of microRNA. MicroRNA, as the name implies, are small RNA that have been identified in human cells. Despite their small sizes, microRNA have big roles in human biology. Recently, scientists have discovered that microRNA are involved in cancer, and that microRNA will be useful in the prediction, the diagnosis and the treatment of cancer. The Forbeck Forum on MicroRNA and Cancer will be a catalyst for expanding this forefront of cancer research.

What are microRNA and why are they important?

To answer these questions, we need to recall the central dogma of biology established in the second half of 20th century based on the double-helical DNA structure and the studies of simple organisms such as bacteria. In this central dogma, DNA is the genetic repository. DNA is transcribed into three types of RNA- messenger (mRNA), transfer (tRNA) and ribosomal (rRNA). Together, these three types of RNA assemble proteins from amino acids and the proteins then carry out the biological functions. This central dogma has spun tremendous progress in biology, leading to the identification of mutated human genes that encode defective or dangerous proteins to cause various diseases including cancer.

After the human genome sequence was completed at the beginning of this century, biologists were surprised to find that only 2% of the genome coded for proteins. Some of the genome sequences are used to build the infrastructure for gene expression and chromosome maintenance, but this infrastructure does not take up 98% of the genome. Most recently, biologists have realized that our genome encodes RNA other than mRNA, tRNA and rRNA. Among these new types of RNA are the microRNA. At the moment, computational methods have predicted that there are about 1000 microRNA genes in the human genome. The exact number will probably not be known for a while.

So far, biologists have found microRNA to function as an inhibitor of mRNA. MicroRNA bind to mRNA with two consequences, either causing mRNA to be degraded, or preventing mRNA from being translated into proteins. A microRNA can bind to several different mRNA. Conversely, more than one microRNA can target a single mRNA. In fact, two human microRNA have been found to bind an mRNA that codes for a protein, which cancer cells depend on for their survival in the body. Patients with defects in those two microRNA genes end up with too much of this protein and therefore are at a higher risk for cancer.

The Forbeck Forum will bring together leaders in the microRNA field. The organizers of this Forum will be *Dr. Carlo Croce*, who has discovered microRNA mutations in a large number of human cancers, and *Dr. Greg Hannon*, who has created microRNA to block genes that cause cancer. Because microRNA are small, scientists believe that they can be efficiently delivered into cancer cells in the body. Therefore, microRNA holds the promise for being a brand new class of medicine that can be used to treat cancers that are difficult to eradicate with the currently available therapies.

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In the early years of the Foundation, each of the Founding Sponsors made a commitment for \$5,000 per year for five years. These pledges provided a stable financial basis for the Foundation and allowed efforts to be concentrated on establishing the Foundation and organizing programs.

In grateful acknowledgement of our donors... (from January, 2005 thru mid-March, 2006)

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less intense environment. This alone is clearly a success as we know of instances where these interactions have shaped the careers of the scholars attending the meeting.

A brainstorming session with the Foundation's Junior Board developed the idea to hold an annual Retreat, bringing together the past three year's scholars to discuss their work and future plans with a small number of senior scientist mentors. These scholars represent the future of science and medicine and what could be better than establishing links with each other at an early stage in their careers. This fits precisely with the Foundation's mission of promoting interactions between scientists and clinicians to improve the survival of cancer patients.

The Scholar Retreat was organized and funded by the Foundation Junior Board and took place in Lake Geneva, Wisconsin in early fall, 2005. Although I was only there for a day and a half, the feedback from both the scientific mentors and the scholars was phenomenal. The scholars will be coming back this year and I truly hope that we can establish this meeting as an annual event in the future.

I missed the last part of the Scholar Retreat to attend the fourth Foundation sponsored International Neuroblastoma staging conference held in Whistler, Canada. This meeting preceded a major international paediatric oncology meeting in nearby Vancouver. Through the hard work of organizers Drs. Sue Cohn and Andy Pearson, a group of pediatric oncologists, surgeons, radiologists, pathologists and scientists came together to review the staging system currently in place for this disease. Major neuroblastoma groups from the US, Europe, Australasia and even China were represented. Through significant pre-planning a data-set of around 7000 patients was reviewed to come up with an updated staging system. For such a rare disease that has a major impact on the lives of children and their families this was a remarkable achievement for both the organizers and the Foundation.

One can only wonder at the technology being developed in the imaging of tumors in the body. The 2005 Forum topic, "*Innovations in Imaging*," gave new insights to the attendees in what is possible today and what may be possible for the future in identifying smaller and smaller tumors in the body. As a generalization the link between early treatment and survival is strong and if tumors can be identified and treated early then improved survival will ensue.

All in all not bad for one year's activity and we intend to keep up the good work. My thanks, as always, to all of you who support us and believe what we all know; we are making an impact and we will go from strength to strength.

John T. Kemshead, PhD
Chairman, Scientific Advisory Board

2005 FINANCIAL REPORT

The accounting firm of Cherry, Bekaert and Holland audits the Foundation's financial records annually.

The Foundation has established a very sound financial position. Steady growth in income has allowed the Foundation to expand its program in additional funded projects and now through the efforts of the Junior Board, the "Scholar Retreat." The Trustees continue to aim at a very high mark - that 90% of the total expense goes directly to support scientific programs. In 2005, 94.6% of all expenses funded scientific activities.

BASIS OF SUPPORT

The William Guy Forbeck Research Foundation desires and has a broad base of support. Of major significance to the Foundation are the contributions from many individuals and their families. Many people have chosen to use the Foundation as a fitting memorial gift. A number of corporations and other foundations have also supported the Foundation with contributions, some having very rigorous qualifications for grants.

In 2005, the newly organized Junior Board raised over \$50,000 through the Fallfest fund raising event and contributions.

EXPENSES

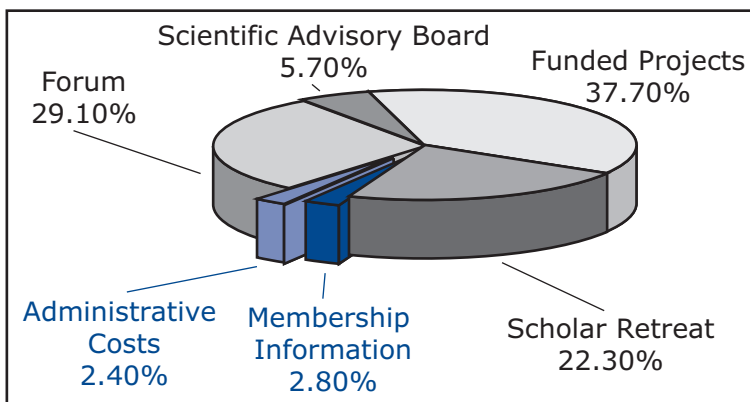
Historically, 85%-90% of the total expenses go directly to supporting the annual Forum and Foundation projects.

Membership information costs include the annual newsletter, member mailings, the video and the web page.

The Foundation has no paid employees, and the trustees participate at their own expense. Administration expenses include auditing costs, as well as printing and postage expense.

Members of the Scientific Advisory Board attend the Forum meeting in Hilton Head and hold their annual meeting at that time. The SAB provides the technical direction for the Forum and the Foundation.

Projects funded during 2005 included an International Neuroblastoma Standards meeting, four Scholar Awards and the first Scholar Retreat.



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In Appreciation



Our heartfelt thanks go to all the people who have worked to make the activities of the Foundation a success.

We are grateful to the Scientific Advisory Board and the Forum participants, the scientists and clinicians whose leadership and effort are the front line in the war against Cancer.

Our special appreciation goes to the Foundation trustees and volunteers whose thoughtfulness, time and energy have done so much for the success of the Foundation and the Forums.

Most importantly, our thanks go to the hundreds of donors, individuals, businesses and foundations, whose financial support assures our continued work in Cancer research.

Sincere Thanks,

George and Jennifer Forbeck

Mission

The mission of the William Guy Forbeck Research Foundation is to promote advances in the field of oncology, particularly pediatric oncology, by shortening the cancer research timetable.

Strategies

- While the Foundation may provide grants for pilot research studies and educational efforts, its centerpiece activity will be an annual Forum, a scientific roundtable held at Hilton Head Island, South Carolina.
- Attending the Forum each year will be twelve to fifteen physicians and scientists who will meet in a completely private "think tank" environment, where they can exchange ideas freely in the hope of building on each other's ideas, knowledge, and experience.
- The objective is not to discuss published research, but rather to provide a forum for the cross fertilization of ideas, concepts, and observations.
- Participants will be invited to the Forum based on the recommendation of the Foundation's Scientific Advisory Board, a distinguished panel of physicians and scientists.
- We fully support the activities of the William Guy Forbeck Research Foundation Junior Board, particularly the Scholar Retreat.