



Terence J. Irmen

From The Chairman's Desk

The best way to describe 2004 for the William Guy Forbeck Research Foundation is a year of change. One of the more significant changes was **Edward Frick** stepped aside as Chairman of the Board of Trustees. Ed has been with the Foundation since the beginning, serving as chairman for the past 16 years. The success of this Foundation is directly due to Ed's leadership and vision. We are delighted that Ed will remain as an active member of the Board of Trustees now serving as Vice Chairman.

We also want to recognize **Joseph Laver, MD**, Chairman of the Department of Pediatrics, Medical College of Virginia Hospital who retired from the Board. Joe provided valuable insight to help connect the Foundation to the Academic Community. The second generation of board members continues to grow with the addition of **Michael Leason** as it's newest member. Michael is the son of **Hayden Leason**, who has been a member of the Foundation since it began. Welcome Michael!

The Foundation is riding the wave of fresh energy generated by our Junior Board led by **Jamie Forbeck**. The Junior Board organizes a Fall Festival Auction in Lake Geneva to raise funds that can be used by the Foundation. The funds have been utilized to establish a new initiative called the Forbeck Scholar Program (See Jr. Board article). In addition to their fundraising efforts, various members of the Junior Board are being called upon to shore up some of the Foundation committees. **Aaron Jesser** is a member of the Junior Board and the Foundations' Public Relations committee. Aaron has completely redesigned the Forbeck Foundation web site utilizing streaming technology. This allows

viewing of the Foundation video while the video is being downloaded, lowering the cost for the Foundation to stay connected with the world.

This past summer, the Forbeck Foundation received an award from the International Neuroblastoma Staging Systems meeting in Genoa, Italy. This very prestigious award recognized the unique manner in which the Foundation works in fighting childhood cancers. We are very honored to receive this award which helps validate that we are doing something truly valuable with our time.

Amongst all the change, the mission of the Forbeck Foundation remains constant, promoting advances in the field of oncology, particularly pediatric oncology. This past year's forum addressed "**Targeted Therapies in Pediatric Malignancies**" chaired by **Charles Sawyer**, University of California at Los Angeles, and **D. Gary Gilliland, PhD, MD**, Howard Hughes Medical Institute, Brigham & Women's Hospital, Harvard Medical School. The 2005 Forum topic is "**Innovations in Imaging in Cancer Research**" and will be chaired by **Harvey R. Herschmann**, University of California, and **Ralph Weissleder**, Massachusetts General Hospital. These forums provide the catalyst for expediting the process of finding a cure for cancer.

There have been many positive changes within the Forbeck Foundation over the last 12 months, but there is still much work to be done. We thank the many dedicated people who have contributed so much to make the Foundation the force that it is becoming in the fight against cancer.

Terence J. Irmen
Chairman, Board of Trustees

SCIENTIFIC ADVISORY BOARD REPORT

Insights into the Workings of the Scientific Advisory Board (SAB)

The SAB has the responsibility for the scientific credibility of the Foundation. To this end we have to perform two critical tasks to ensure the success of our major meeting that is organized each year in Hilton Head. Taken in order our first task is to ensure that the planning for the following years meeting is optimal. We insist on meeting with the Chairperson(s) for the following years meeting and we review with them the details of the topics to be discussed and potential attendees. This guarantees that the meeting sessions will really focus on achieving the goals of the meeting and that an appropriate geographic spread of scientists and clinicians is chosen. We ensure that we truly stick to our major aim of bringing together individuals who would not normally have the opportunity to discuss their work in depth with scientists



John T. Kemshead, PhD

Continued on page 7

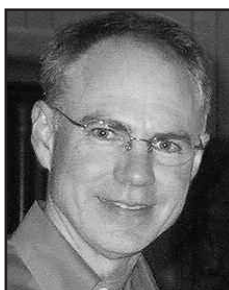
In This Issue...	From the Chairman's Desk	1
	Scientific Advisory Board	1
	Forum 2004: <i>Targeted Therapies in Pediatric Malignancies</i> ...	2
	Awards and Grants	4
	International Neuroblastoma Staging System	6
	Forums 2005 and 2006	7
	Junior Board / Scholar Retreat ...	8
	Financial Report	11
	Benefactor List	10
	Objectives.....	12
	Board of Trustees &	12
	Scientific Advisory Board	

2003 Forbeck Forum: XXth Annual Forum

November 4–6, 2004 Hilton Head Island, South Carolina



Gary Gilliland, PhD, MD



Charles L. Sawyers, MD

Subject: Targeted Therapies in Pediatric Malignancies

- I: TK and STK as targets in Therapy in Cancer
- II: Novel Approaches to Drug Development
- III: From Kinases to Oxygen Sensing: Novel Targets for Cancer Therapy
- IV: Novel Approaches to Pediatric Malignancies

Chairmen

Gary Gilliland, PhD, MD	Howard Hughes Medical Institute	Boston, MA
Charles L. Sawyers, MD	University of California	Los Angeles, CA

Participants

Dr. Sara A. Courtneidge	Van Andel Research Institute	Grand Rapids, MI
David E. Fisher, MD, PhD	Dana Farber Cancer Institute	Boston, MA
Todd R. Golub, MD	Dana Farber Cancer Institute	Boston, MA
Andrei V. Gudkov, PhD, DSci	The Cleveland Clinic Foundation	Cleveland, OH
Dr. Patrick Harran	Univ of Texas - Southwestern Medical Center	Dallas, TX
William Kaelin, MD	Dana-Farber Cancer Institute	Boston, MA
John M. Maris, MD	Children's Hospital of Philadelphia	Philadelphia, PA
William R. Sellers, MD	Dana Farber Cancer Inst	Boston, MA
Kevin Shannon, MD	University of California	San Francisco, CA
Gregory L. Verdine	Harvard University	Cambridge, MA
Marc Vidal	Dana Farber Cancer Institute	Boston, MA

2004 Overview

Prepared by: Gary Gilliland

Several themes were developed during the course of the symposium. These included the concept of “oncogene addiction” in which a cancer cell becomes “addicted” to its mutant oncogene, rendering it susceptible to induction of cell death by oncogene inhibitors. The role of the microenvironment in supporting tumor cell growth, and as a target for therapy was discussed. In addition to targeting of kinases in cancer, such as BCR-ABL, the potential for targeting the apoptotic machinery of cancer cells was presented by several investigators.

Novel approaches to drug development were reviewed by experts in organic and medicinal chemistry, as were novel approaches to understanding pathogenesis of cancer and development of new targets for treatment based on current genomic technologies and the use of network analysis.

It was noted that our data sets for

understanding cancer biology at the genomic, biochemical, cellular and organismal level are incomplete, but that there is potential in the coming years to develop such data sets using sophisticated technological approaches.

The heterogeneity of tumors was discussed in the context of drug development, including the concept of “cancer stem cells” as rare but critical targets among the larger tumor burden in cancer patients.

Finally, sociopolitical issues that related to cancer therapy were overviewed, including a discussion of the role that academic institutions are best able to play. These include mandates to discover new targets and to break paradigms in drug development currently held in industry. The development of selective small molecule kinase inhibitors such as imatinib in collaboration between industry and academics serves as a proof-of-principle for this latter approach, and promising approaches to develop small molecules that interfere

with protein-protein interaction interfaces may serve as a next frontier.

In addition, strategies for ensuring development of pediatric as well as adult drug trials were considered, as well as the most efficient approaches for the academic-industry interface in cancer drug development.

Individual Investigators

Dr. David Fisher provided an update on the role of B-RAF in cancer,

“I was just at an NCI Thinktank this past week (where they pick scientists’ brains about directions to push research initiatives in). You’ll be happy to hear that in the course of the conversation the unique format of the Forbeck

meetings was specifically raised as an example of a particularly great meeting.”



David Fisher

noting that the V600E allele has been identified in 70% of cases of melanoma, 10% of colon cancer, and 33% of papillary thyroid cancer. The remaining cases of melanoma have activating mutation in N-RAS, and thus these signal transduction pathways may serve as useful targets for therapeutic intervention. Dr. Fisher also presented data on development of a zebrafish model of melanoma induced by expression of B-RAF as a reagent to better understand modifiers of phenotype.

The role of SRC in a spectrum of cancers was discussed by **Dr. Sara Courtneidge**, who noted that SRC is often overexpressed, but only rarely mutated in cancer. There are several good SRC inhibitors currently available, begging the question of the best clinical context for application/clinical trials.



Dr. Sara Courtneidge

She also discussed the role of the microenvironment in tumorigenesis, including the characterization of the locally invasive properties of cancer cells mediated by podosomes. Proteins that are responsible for podosome formation, including a novel protein named "FISH" for five SH3 domains were discussed.

Dr. Nabeel Bardeesy provided an overview of the molecular pathogenesis of the Peutz-Jeghers cancer syndrome associated with pancreatic adenocarcinoma and colonic polyposis that is curiously caused by loss, rather than gain of function, in the serine threonine kinase LKB1. The notion that such mutations confer an inability of cells to manage energy stress response was discussed, and the paradox of how such a mutation confers a proliferative/survival advantage to cancer cells.

Imatinib resistance has emerged as an important problem in treatment of BCR-ABL positive CML, and as first described by **Dr. Charles Sawyers**, is most often attributable to point mutations in the ABL kinase itself. Dr. Sawyers presented exciting new data demonstrating preclinical and clinical efficacy of a novel ABL and SRC inhibitor, BMS354825, that overcomes resistance to imatinib for all BCR-ABL

mutations except the T315I. This compound was reported to show promising results in clinical trials, and provides a paradigm for developing drugs that can overcome resistance to small molecule kinase inhibitors as single agent.

The challenges of developing drugs for targets that are discovered in cancer was reviewed by **Dr. Greg Verdine**, who



Dr. Greg Verdine

annotated the "Lipinsky rules" for drug development that mandate that compounds be below a threshold molecular weight, have certain solubility characteristics, etc. Dr. Verdine suggested that such constraints needed to be re-evaluated, and noted a gap in what he referred to as "macrosynthetic land" in drug development. For example, alpha-helical peptide structures present major barriers in drug development due to size and predilection for proteolytic cleavage, but Dr. Verdine and his collaborators have developed strategies using "hydrocarbon staples" to stabilize such structures. These may have value in targeting the apoptotic machinery of cancer cells. Such advances provide a superb example of how academic investigators can challenge dogma in drug development, and potentially move the field toward developing novel agents.

In a similar vein, **Dr. Patrick Harran** described the development of a dimeric small molecule with the ability to impair the normal function of the IAP family of proteins through disruption of the SMAC/IAP protein-protein interface. This discovery provides proof-of-principle that small molecules can indeed disrupt protein protein interactions mediated by large surface interfaces. Such "SMAC" mimetic compounds may also be of value in targeting apoptotic machinery in cancer cells.

Another strategy for targeting the apoptotic machinery was presented by **Dr. Tony Letai**. Dr. Letai has developed a peptide "BAD BH3 sensitizer" that induces apoptosis through cytochrome C release in cancer cells but not normal cells. Such compounds have the potential to induce death in cancer cells by targeting any of a number of proapop-

totic BH3 containing proteins like BAD.

The discussion then moved from chemistry and a focus on targeting the apoptotic machinery in cancer cells to the use of genome wide strategies for characterizing cancer, for target gene discovery, and drug development. **Dr. Marc Vidal** presented sophisticated new technology for developing complex networks as probes for differences between normal and cancer cells, using frameworks referred to as "interactomes, phenomes, transcriptomes and localazomes". He likened this approach as similar to the development of supercomputing 50 years ago, as a tool that is computationally based, but should eventually allow us to understand the very complex networks at a cellular level that will enable distinctions between cancer cells and normal cells.



Dr. Bill Sellers

Dr. Bill Sellers discussed the heterogeneity of cancer, and the need to break down cancers that may be similar phenotypically into subgroups that are homogeneous genetically. As an example he noted that IGF-1 is a marker in prostate cancer that is associated with a lethal outcome, and thus serves as a tool for targeting that subset of prostate cancer with novel therapeutics, as well as allowing for stratification of response to conventional therapies. He noted that with modern genomic technologies, it should be possible to generate a complete genetic subclassification of cancer that can interface with therapeutic efficacy using response to drugs as a probe for additional subclassification.

Examples of the remarkable power of cancer genomics were provided by **Dr. Todd Golub**, who discussed the use of chemical genetic screens for compounds that can induce differentiation in acute leukemia; in determining that the metastatic potential of a tumor resides in all cells in the primary tumor; and in assessing cell autonomous and cell non-autonomous contributions to cancer pathogenesis. He noted a lack of complete data sets in understanding cancer-drug interac-

Continued on page 9

GRANTS and AWARDS: “FOCUS on the FUTURE” PROGRAMS:

The William Guy Forbeck Research Foundation is pleased to sponsor two programs to further the advance of cancer research. The “Scholar Award” recognizes promising young scientists working in this field. “Focus meeting” grants are designed to give other researchers an opportunity to conduct their own meeting along the lines of the Foundation’s annual Forum. More information can be found on our web site at wgfrf.org.

The FORBECK SCHOLAR AWARD

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.

FOCUS MEETING GRANTS

The activities of the Foundation have been expanded by offering grants to support small “Focus Meetings” to be modeled on the annual Forum held in Hilton Head. The significant variation is that this forum is proposed and organized outside the Foundation and is based on a competitive application process. The Foundation is interested in sponsoring small interactive meetings that focus on developing strategies which will improve our understanding of cancer and cancer therapeutics, and where there is a clear interchange of ideas between scientists and clinicians. Applicants identify a topic, venue, date, and take responsibility for organizing the meeting.

2004 SCHOLAR AWARD

The Foundation received a number of very qualified applications for the 2004 Forbeck Scholar Award. The Scientific Advisory Board selected three outstanding young scientists to attend the 2004 Forum and receive this award. The Foundation was pleased to present this year’s Scholar Award to four candidates.



Edward Attiyeh, MD, is a postdoctoral fellow in the lab of **Dr. John Maris** at the Children’s Hospital of Philadelphia, where he has been working on elucidating genetic determinant of the high-risk neuroblastoma phenotype. Dr. Marris said “Eddie is committed to academic medicine and to a career as a physician scientist. He has been remarkably productive in a short time. It is clear to us that Eddie is a rising star and has the potential to become a future leader in our field.”

“I had a wonderful experience at the recent Symposium and I am looking forward very much to the future retreat. I deeply appreciate and admire what the Foundation has accomplished and I very happy to be associated with your organization.”

Nabeel Bardeesy

Nabeel Bardeesy, PhD was nominated by **Ronald DePinho, MD** from the Harvard Medical School, “Nabeel possesses all of the inner qualities that predict great success in science - intense passion and courage to pursue fundamental questions...a strong sense of confidence... superior intellectual abilities...meticulous in his work and rigorous in his interpretation of data.” Nabeel’s studies focus on using engineered animal models to investigate the role of tumor suppressor gene mutations in pancreatic cancer progression.



Anthony G. Letai, MD, PhD received his MD and PhD degrees from the University of Chicago then was selected for the medical oncology fellowship

program at Dana Farber in Boston. His research work includes identifying and characterizing the molecular interaction of a series of proteins that bind to BCL-2 and thereby regulate cell death. He has shown that several of these proteins potentially activate apoptoses and their activity can be mimicked by peptide analogues. **Bruce A. Chabner, MD** said the Forum “would present an opportunity to introduce this very talented young scientist to the best established investigators in his field.”

W. Kimryn Rathmell, MD, PhD received her MD/PhD from Stanford University. During her post-doctoral



fellowship at the University of North Carolina at Chapel Hill, she has developed an independent program studying the mutational spectrum of VHL and its potential to produce renal cell carcinoma and pheochromocytomas with different levels of penetrance. **H. Shelton Earp III, MD** said “Her intelligence, laboratory background, clinical acumen, and desire to translate findings from her own laboratory to her own clinical program serve as a terrific example for all junior faculty.”

“The quality of the interactions at that meeting definitely surpasses anything I’ve ever been to, and conversations that took place there keep coming to mind in scientific discussions I have had later. Yesterday I was in a meeting with Terry Van Dyke and discussing a review article we were putting together when I mentioned some of the ideas that were mentioned at the meeting, and she also commented how useful the Forbeck meeting was that she attended now several years ago. It’s really a legacy that you have established.”

W. Kimryn Rathmell, PhD

2004 FOCUS MEETING SUMMARY REPORT:

Fertility and Reproductive Issues in Survivors of Childhood Cancer

The 2004 Focus meeting was organized by **Charles Sklar, M.D.**, from Memorial Sloan-Kettering Cancer Center. It was held September 30th in Chatham, Cape Cod, Massachusetts.



"Our conference this past weekend was (in the words of one of the attendees) "a resounding success." There was an amazing amount of dialogue and interchange. Several of the investigators actually began collaborations during the conference, while many others expressed a desire to pursue mutual areas of interest in the future. The setting was ideal and even the weather was nearly perfect!"

Chuck Sklar

Dr. Dolores Lamb from the Baylor College of Medicine presented on normal testicular development and recent advances in our understanding of the complex anatomy of the human testis. She reviewed information on the process of normal spermatogenesis, the blood testis barrier, normal germinal and supportive cell interactions and the normal hormonal milieu within the testis. There was much discussion on the implications of the blood-testis barrier in protecting germ cells from the toxic effects of systemic chemotherapy.

Dr. Alan Schmeyer from the Massachusetts General Hospital and Harvard Medical School presented on the inhibins and activins. He emphasized the importance of activins in the regulation of normal germ cell development and its role in the local communication systems that regulate gonadal function. The clinical value of inhibin B measurement as a maker of male germ cell failure were discussed and the need for additional work in this area were emphasized.

Dr. Richard Kolesnick from the Memorial Sloan-Kettering Cancer Center presented on strategies to protect germ cells from apoptosis. Data were presented on the sphingomyelin pathway and its role in oocyte apoptosis. New studies in *C elegans* demonstrate that ABL-1 distinguishes proapoptotic signals triggered by two different DNA-

damaging agents. There was much discussion on the potential clinical implications of interfering in the normal process of cell death, particularly when mutagenic damage may have occurred.

Dr. Marvin Meistrich from the M.D. Anderson Cancer Center addressed the topic of enhancement of recovery of spermatogenesis after cytotoxic therapy by suppressing endogenous testosterone production. He reviewed data from several animal models that demonstrate that reducing intratesticular testosterone has the ability to enhance differentiation of surviving stem cells. Additionally, this strategy enhances the ability of transplanted stem spermatogonia to colonize and differentiate in busulfan-treated testes. The discussion included the lack of efficacy of this approach in the human and non-human primate and the need for further data to allow further elucidation of the mechanism of this enhancement in the animal.

Dr. Kuluk Oktay from the Weil Medical College of Cornell University spoke on the options for fertility preservation in the prepubertal female. Areas discussed included protection by means of gonadotropin suppression, oocyte freezing, and ovarian cryopreservation and transplantation. The world's experience with these various techniques were reviewed. Recent advances in ovarian tissue cryopreservation were the main focus of the discussion. Differences between the European and North American approaches and the lack of good clinical guidelines were emphasized. All participants agreed that there is a need for closer collaboration between Reproductive Medicine units and Pediatric Oncologists.

Dr. Stefan Schlatt from the University of Pittsburgh discussed techniques for germ cell preservation in the prepubertal male. The focus of his presentation were on autologous germ cell transplantation and autologous/xenologous testicular grafting. In animals, investigators have recently shown that xenografting of neonatal testicular tissue from a variety of species has resulted in differentiation to the level of complete spermatogenesis. It was emphasized that these techniques remain highly investigational as the overall safety and efficacy is unknown when applied to the human.

Dr. Roger Gosden, from the Weill Medical College of Cornell University, presented on the topic of assisted repro-

duction for the infertile female. He outlined the options available for fertility preservation including embryo/oocyte banking, ovary banking, in vivo protection, and donor eggs/embryos adoption. In addition, he discussed the issues and considerations relating to unanswered questions in the area of assisted reproduction, current and future research, and the decision-making process for physicians and patients/families.

Dr. Peter Schlegel of the Department of Urology at Cornell University discussed topics related to the assisted reproduction for the infertile male. A focus of his presentation was on approaches for retrieval of sperm from patients with limited spermatogenesis, which included surgical strategies to optimize the identification of sperm-producing tubules and sperm retrieval. He described current technics for microdissection of the testicular parenchyma and the success rates achieved among a series of men with cancer therapy-induced gonadal dysfunction.

Dr. Andre van Steirteghem of the Centre for Productive Medicine at the University of Brussels addressed the topic of outcomes of assisted reproduction. He provided a brief historical perspective to assisted reproduction and then discussed the level of information that is currently available. Dr. van Steirteghem emphasized the limited number of well-designed outcome-based studies and the importance of ongoing research. Issues including methodological limitations of prospective studies of offspring to assess congenital abnormalities/health-outcomes, genetic counseling and the impact of multiple pregnancies were all discussed.

Dr. Les Robison, from the Department of Pediatrics and the Cancer Center at the University of Minnesota, provided an overview of childhood cancer survivors, emphasizing the marked and relatively rapid improvements in survival rates over the past three decades. He outlined the spectrum of issues faced by adult survivors of childhood and adolescent cancers, including fertility and health of offspring. A primary conclusion was that there must be ongoing research to better define those survivors who are at highest risk for decreased fertility.



Continued on page 6

Dr. Charles Sklar, from the Department of Pediatrics at Memorial Sloan Kettering Cancer Center, presented recent unpublished results of his research on premature menopause among adult survivors of childhood cancer. His data, from the Childhood Cancer Survivor Study cohort included more 2800 long-term survivors, demonstrates that survivors have a 13-fold increased incidence of non-surgical premature menopause compared to a cohort of sibling controls and the identification of independent risk factors. Further discussion focused on the implications of an increased risk of premature menopause for cancer survivors.

Dr. Stephen Shalet, Professor of Endocrinology at the Christie Hospital, University of Manchester, summarized the data regarding the impact of chemotherapy and radiation on fertility among male pediatric and adolescent cancer patients. He detailed the specific chemotherapeutic agents associated with gonadal toxicity emphasizing the drug- and dose-dependent nature of the long-term effects. Importantly, he detailed the potential for late recovery following chemotherapy-induced damage to the germinal epithelium. Professor Shalet also described the issues related to radiation-induced damage to the male testis, again detailing the time-dependent nature of spermatogenesis following radiation exposure.

Dr. Leslie Schover, from the Department of Behavioral Science at MD Anderson Cancer Center, discussed the psychosocial aspects of infertility after pediatric cancer, including knowledge gaps and communication issues that represent barriers to implementing possible preventive measures. She detailed the emotional, clinical and technologic components of fertility-related decision making among patients and parents. Dr. Schover presented examples of web-based resources that are being developed to aid cancer patients and families with fertility issues.

Dr. Jeff Kahn, Director of the Center for Bioethics at the University of Minnesota, discussed the ethical issues associated with assisted reproduction and germ cell preservation among children diagnosed and treated for cancer. Within the context of donation and preservation of germ cells, he described and discussed the risk-benefit considerations, issues of informed consent and control of stored tissues. The discussion of ethical considerations relating to assisted reproductive technologies (ART) focused not only on the risk-benefit issues, but also topics associated with life expectancy of the survivors, disposition of gametes/embryos and access to unused tissues. Lastly, Dr. Kahn raised points regarding defining ART-related procedures as research versus innovative therapy, as well as the role of federal funding of research and involvement of third party payers.

The participants were all in agreement that there was a great deal of additional research needed both to better understand the underlying pathophysiology of cancer treatment-induced germ cell death but also to improve the safe options available to cancer patients about to embark on treatments associated with a high-risk of infertility. It was quite clear that this Forbeck conference generated a tremendous amount of enthusiasm and thought. For many participants it helped crystallize areas that need further exploration and clarification. For all involved, the meeting was viewed as a tremendous success and a model for future meetings and collaborations.

International Neuroblastoma Staging System (INSS)

Being able to communicate across continents is very important in all spheres of life; no more so in medicine where understanding the results of clinical trial results undertaken in different countries is paramount. Take, for example, neuroblastoma a rare cancer of childhood but one that is very difficult to treat when the disease has spread. If a study of a new combination of drugs undertaken in one country shows very promising results it encourages others to follow this strategy. However, if the study involves patients who are staged differently than in other geographies the clinical trial may involve children with less aggressive forms of the disease, leading to what erroneously appears to be a better outcome.

The issue of common criteria for staging neuroblastoma came to the fore in the first Forbeck Foundation Forum held twenty years ago. Out of this meeting was born the "Forbeck Neuroblastoma Staging System" or INSS staging system. Under the auspices of the Foundation, experts on the disease from all over the world met to define a universally acceptable staging system for Neuroblastoma. Two further meetings were held in the UK in the late 1980s and early 1990s to refine the system and try to incorporate biological risk factors into the system.

Despite the fact that the staging system has been taken up universally, the role of biological risk factors in staging the disease has never been fully addressed. For experts, the question of whether biological markers add anything to conventional risk factors such as stage and age remains unknown.

Last summer the Foundation was honored at a



Jennifer Forbeck receives award in Genoa, Italy - recognizing the Foundation for "its remarkable contribution to establish an effective, long-lasting International link among clinicians and scientists involved with neuroblastoma."

Neuroblastoma meeting in Italy for providing the platform to enable clinicians to develop the INSS staging system. At the same time the Foundation was approached to fund another meeting to update the system.

It was felt that the issue of age in the staging of the disease needed further review. The need for a common definition for undertaking and interpreting mIBG scans was raised as was the question of the usefulness of

biological markers. Dr. S. Cohn in Chicago and Prof. A. Pearson in Newcastle, UK agreed to lead the team and the Foundation has agreed to fund this in the fall of 2005. Work to make the meeting a success has already begun with the working groups identified and their tasks outlined. It is planned to have all of the data required in place by July in preparation for the meeting in September.

The staging meeting will be held in Whistler, British Columbia immediately before the International Society for Paediatric Oncology, to be held in Vancouver. In keeping with the Foundation's "focus on the future," four or five junior faculty members will be invited to attend the meeting as an educational experience. We hope for a successful meeting and an outcome that enhances the International Neuroblastoma Staging System.

FORUM PLANNING

2005 Forum: Innovations in Imaging in Cancer Research

The diagnosis and treatment of cancer has changed dramatically in the past two decades as advances in medical science have revealed the causes of cancer at the molecular level. This understanding has provided new targets for drug discovery, new approaches to evaluation of high-risk patients, and methods for early detection of cancer. In parallel, and at times as a result of these basic advances, the ability to image cancer in the living organism has also undergone a revolutionary change. Magnetic resonance imaging is able to disclose detailed pictures of small tumor deposits, and in the experimental setting, can even reveal important aspects of the composition and biochemical activity of tissues. PET (Positron Emission Tomography) has likewise become a standard tool for detecting minute tumor deposits and revealing their active metabolism. While these two techniques have had great impact, there is already evidence that more sophisticated and novel uses of both will be possible, allowing the clinical researcher to extract from pictures the kind of information that was only obtainable by removal of tissue and examination in the laboratory.

The Forbeck Conference planned for 2005, will be led by *Ralph Weissleder* and *Harvey Herschman*, two international leaders in this field. The conference will convene a group of experts in the new imaging technologies, including methods that image receptors, biochemical reactions, and drug effects in the living subject, literally the equivalent of Jules Verne's trip 20,000 Leagues into the human body. Fluorescence imaging, radio labeled drug trafficking, ferro-magnetic particle localization, infra red spectroscopy and other technologies used to find and destroy cancer will be included in this outstanding program, as well.

2006 Forum: Stem Cells.

Mentioning research into stem cells can be highly controversial yet this is one of the most ill understood and exciting fields in development today. The Scientific Advisory Board was unanimous in their suggestion as this for a topic for the 2006 forum.

Stem cell research does not necessarily involve the use of embryonic cells with all of the controversy that underlies their collection. There is another field that involves the use of adult stem cells that is emerging with extremely exciting results. Although data is preliminary it appears that the stem cells that live in your bone marrow that are responsible for the generation of all of the normal blood cells can, under certain circumstances differentiate into other tissues, such as the cells that form blood vessels, liver cells, kidney cells, and even neurons. This fact in itself is highly controversial as, not all scientist believe the data and the differentiation of these stem cells into other cell types may occur selectively in different animal species.

What cannot be denied is the early clinical data on the use of these blood stem cells. There are now lots of reports that these cells, when injected near to areas of necrosis in the heart can help repair the tissue. In addition, they can be made to differentiate into bone repairing areas of damage.

This is extremely exciting but is this topic relevant to cancer medicine. The answer is obviously yes as perhaps one day these cells can be used to repair tissues that have had to be removed because they are malignant. This sound science fiction but a recently I read about a patient who now has a new lower jaw grown from adult stem cells. A mold of his jaw was made of titanium. This was seeded with chemical and his stem cells from the bone marrow and placed under his skin. Some weeks later the cells had populated the metal skeleton and made a new lower jaw bone, used to replace the jaw he had lost due to cancer.

Perhaps we are on the edge of a new form of medicine. Let us hope the promise develops into a reality!

Scientific Advisory Board Report

Continued from Page 1

and clinicians who work in related by not identical fields.

Our second task is to pick a topic for discussion in two years time. This requires considerable thought as science is moving so rapidly at the moment. We have to be cognizant of not what is happening today but what could be even more relevant in two years time. We also have to remain focused on the goals of the Foundation, namely to promote research into finding a cure for specific cancers and to have a preference for work that could help children with the disease. The different backgrounds of the SAB members is key to both promoting topics for discussion and for suggesting appropriate chairpersons for the meeting. Another consideration is the mix of topics to ensure that we get an appropriate balance of basic science and more clinically related topics. For example the focus of our meetings for the last few years has been highly scientific and directed to identifying new approaches to specifically targeting therapy to cancer cells. This has been approached by looking at complex signally pathways in the cell that control cell division and also thinking about how new drugs could be developed to target these evolving pathways. This year we change tack again and focus on a more clinical topic; namely new approaches to imaging small tumor deposits in the body.

The scientific advisory board has limited time to meet during the Foundation's Forum and so it is important that everyone comes prepared with ideas for future meetings. Usually there is a great deal of consensus but occasionally we have to agree to differ and vote on specific topics.

Although the Foundation is branching out into new areas, with our desire to promote and maintain communicating with our scholars, the annual meeting remains our premier event for the year. The reputation of the meeting amongst investigators is second to none as we have no problem is getting the very best scientists to come to the Forum. Furthermore, we can pick the very best investigators to join the board and this year I am pleased to announce that *Professor Jean Wang* from the University of California has agreed to join us. It is a credit to all of my colleagues that the Foundation has the reputation it has today and I also would like to thank the Trustees for their faith in us and for their support of our approach.



John T. Kemshead, PhD
Chairman, Scientific Advisory Board

FOUNDATION JUNIOR BOARD

Another successful year! The Junior Board of the foundation, founded in 2003, has once again surpassed all goals and continues to set new challenges. The Junior Board is comprised of a group of young professionals from Chicago and Wisconsin that continue to show their dedication and enthusiasm for the foundation.

New members of the Junior Board helped to make this year even better than the year before! Thank you to: *Chrissie and Aaron Taylor, Galen Eckland, Brie Torborst, Bridgid Kyle, Nicole Vaughan, and Bryant Rowean*

Fall Fest 2004 was a great success. Due to everyone's hard work the venue was beautiful, filled with pumpkins, fall leaves, corn stalks, candles and other wonderful fall decorations. Everyone did an unbelievable job of soliciting donations for the Silent and Live Auction which included: vacation packages, artwork, jewelry, tickets to sporting events, autographed sporting paraphernalia and the list went on and on. In the end we raised over \$45,000 for the Foundation.

Plans are under way for the **2005 Fall Fest**. It will be held at the Lake Geneva Campus of Aurora University on September 17th, 2005. The outdoor pavilion overlooking Geneva Lake will make a beautiful location for the event.



Jean Gallucci and Galen Eckland check out successful auction bidders.

How you can help:

- Mark your calendars! September 17th
- Join the Junior Board
- Donate or solicit live & silent auction items.

Contact the Junior Board:

Junior Board page on the web site
www.wgfrf.org

Email: jamie@wgfrf.org

Contact any Junior Board member

Adjusting our Goals

The original concept of younger generation of fundraisers supporting the younger generation of scientists has generated a lot of enthusiasm and support. The Junior Board has now organized two events in Lake Geneva, Wisconsin. Each year we have blown past our goals and set the bar higher for the next year. Our first fundraising goal was directed towards sponsoring the Foundation's Scholar Program, where outstanding young scientists are chosen from an impressive group of applicants. These scholars receive an award and are invited to participate in the annual forum in Hilton Head, South Carolina. In 2003 we handed over a check to the Foundation that was more than 6 times our goal.

2005 will be much more than the Junior Board had imagined when friends sat around a dinner table two years ago trying to figure out how to contribute. The results from Fall Fest 2004 surprised everyone again so it was time to adjust our goals. At this year's annual Foundation Forum, several Junior Board members met with Scientific Advisory Board members, current year scholars, and Forum Chairmen to discuss ideas for expanding the Scholar Program.



"I had the special honor of attending the Foundation's Annual Forum this past year. The enthusiasm of everyone involved, particularly the Doctors, kept a lasting impression about how special and important the Forbeck Foundation is to cancer research." Chandler Dimberg

Trustee Enthusiasm and Support

The Foundation Board of Trustees has been overwhelmingly supportive of the work the Junior Board has done over the past two years. Every step of the way trustees have been there to lend a helping hand, donate items to the auction and send words of encouragement.

Several Junior Board members have been invited to participate on Board of Trustee committees. *Chandler Dimberg* will be assisting on the Finance and Investment committee and *Nicole Mazzei* will join the Public Relations Committee. The Junior Board is excited to have this relationship with the Board of Trustees.

SCHOLAR RETREAT

In thinking about our goals we decided that we would stick with our main purpose of supporting the scholars. Past scholar and current Scientific Advisory board member, *David Fisher* was the perfect person to ask what else can the Junior Board do to assist the scholars with their research, careers and efforts in the battle against cancer? The annual Forum of the Foundation seemed like the perfect model to build from considering the twenty years of success and enthusiasm for the meetings. The recommendation was to sponsor a retreat for past scholars in Lake Geneva, WI to coincide with Fall Fest.

The participants in the Retreat will be comprised of scholars from the last three years, mentors and a key note speaker. Like the Forum, the meeting will be a 3 day event filled with meetings and social events. The purpose will be to develop the current research of the participants, break down the social barriers that can be created in such a competitive field and build stepping stones for the scientists of the future and strength in unity in the fight against cancer.

Our excitement for this coming venture has been matched by that of the scholars who will participate in the first year. Twelve scholars and two mentors have already accepted invitations to the Retreat. Many commented on how excited they were about this new opportunity and original concept.



"It will be very useful to meet with David Fisher and a group of young people who all have new laboratories. I suspect we will be able to help each other a lot. Getting a laboratory going and making a significant impact is quite a challenge."

"I think about Billy a lot and I suspect that he would approve of this new initiative. This new conference series actually could make far more of an impact than the senior's conference since we can actually use help! While you may be able to bend the senior scientists a little you may be able to propel us forward a great deal. These new meetings could be fantastic."

Chris Bakkenist (2003)

Junior Board Mission

- To increase awareness of the Foundation, its purpose, goals and progress
- To involve a younger generation that will bring fresh energy to the Foundation and ensure its future
- To develop a young group whose goal will be to support the younger generation of scientists
- Fundraising will go towards the inclusion of scholars in the annual Foundation Forums and support of the Scholar Retreat Program.



I am constantly impressed by and truly appreciate the time and effort my friends have put into the event and the foundation. I am touched by their creativity and willingness to do whatever it takes to make everything successful. So thank you to the greatest group of friends any person or foundation could ask for.

Jamie Forbeck

PAIGE'S HOTDOG STAND

Ten year old Paige Buchanan lost her older sister Lindsay, to neuroblastoma almost three years ago. Last summer she decided to do something to raise money to fight cancer. She follows the example of her parents - for five years, Jennifer and Jim Buchanan organized a bike tour from Massachusetts to Maine to benefit the Foundation. Jim has served as a trustee of the Foundation since 1997.

Paige enclosed the following description along with a drawing of the occasion.

"Last weekend my dad and I dislocated our dock and floated it out in the middle of our lake to become a hotdog stand. The hotdogs cost \$1.50 each, a hamburger cost \$2.50, lemonade cost \$0.50, and water was free. I kept telling my dad that it was getting dangerous because there were huge white caps. White caps are rough waves. From the hotdog stand we earned \$236.00. The money went to the Forbeck Foundation. The Forbeck Foundation is a fund for cancer research."

2004 Forum

Continued from Page 3

tions, and presented a strategy for testing panels of molecularly targeted therapies in a broad spectrum of cancer cell lines as an approach to understand pathophysiology of cancer, as well as for developing novel therapeutic approaches.

Dr. Kim Rathmell presented data on the interesting relationship between oxygen sensing and cancer derived from study of the Von-Hippel Landau (VHL) gene that is mutant in VHL syndrome that is associated with hemangioblastoma, pheochromocytoma and renal cell carcinomas. Dr. Rathmell characterized the effect various VHL mutations observed in humans with expression of the hypoxia inducible factors HIF1 and HIF2, and suggested that molecularly targeted therapies for this pathway, directed to e.g. HIF, VEGF or COX2 could be tested using ES cells expressing various VHL mutants.

The concept of cancer stem cells, with a focus on leukemia stem cells, was presented by *Dr. Gary Gilliland*. He noted only a small fraction of leukemia cells (~1 in 100,000) has the capacity for limitless self-renewal, and that it is thought to be these cells that are required for continued growth and propagation of leukemia and other tumor types such as breast cancer and CNS tumors. He noted that tumor relapse after initial response to therapy may be due to failure to adequately target these rare populations of cells with unlimited self-renewal capacity. He also suggested that targeting self-renewal pathways in this critical population of cells might be of therapeutic value.

Problems with current approaches to drug development, including a discussion on the value of murine models of disease in preclinical platforms, was



Dr. Bill Kaelin

overviewed by *Dr. Bill Kaelin*. Dr. Kaelin noted that although tumors may be quite complex phenotypically and genetically, and harbor a broad spectrum of mutations, they may nonetheless be exquisitely sensitive to inhibition of a single mutant allele. As

an example, he noted the remarkable responses of genetically complex gastrointestinal stromal cell (GIST) tumors with activating mutations in the tyrosine kinase KIT to imatinib. Dr. Kaelin also noted the importance of diligent and comprehensive searches for good drug targets in academic contexts. He emphasized the importance of thoughtful clinical trial design for newer molecularly targeted therapies, especially as regards rapid progress toward FDA approval.

Dr. John Maris focused attention on pediatric cancers, in particular on recent developments in our understanding of the molecular pathogenesis of neuroblastoma. He noted that a new heritable predisposition gene/locus has been identified that may shed new light on pathogenesis of neuroblastoma, and discussed recent data from animal models of disease using a novel drug METAP2. He noted that an important problem in pediatric cancer was not the lack of patients for treatment on clinical trials, but rather the lack of good targets identified thus far. Dr. Maris also noted potential for use of TRK kinase inhibitors for treatment of neuroblastoma that express these proteins, including the TRK inhibitor CEP-701 that is currently being tested in clinical trials in AML based on its ability to also inhibit FLT3.



Dr. Andrei Gudkov

Dr. Andrei Gudkov discussed p53 induced arrest and irradiation, and the role of p53 as a negative regulator of mitotic catastrophe.

In summary, a broad spectrum of topics related to cancer genetics and cancer therapeutics were overviewed. Hope and optimism was expressed for the opportunities to develop novel drugs to target cancers based on state-of-the art screening and cancer genomics strategies, both in pediatric and adult tumors. These was an overall consensus that proof-of-principle had been demonstrated for development of molecularly targeted therapies, and that it was likely that major progress would be made in cancer therapeutics in the coming years.

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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, 2004 thru mid-March, 2005)*

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2004 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, primarily through the funding of "Focus" grants 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.

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 2004, the newly organized Junior Board raised over \$45,000 through fund raising event and contributions. In addition, a significant contribution was received from the estate of Robert and Margaret Hennessy.

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, and the video.

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.

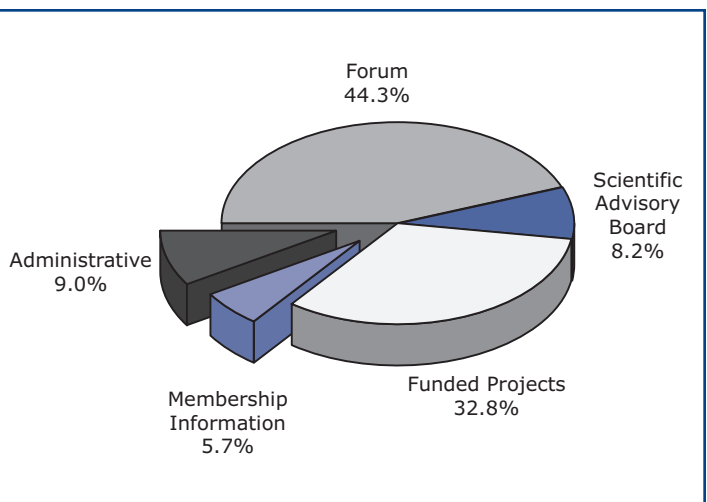
Projects funded during 2004 include four Scholar Awards and one Focus meeting grant.



Jean Marie Frick

September 21, 1930 - October, 2004
The Forbeck Foundation suffered a heart felt loss with the passing of Jean Frick, wife of our past chairman, Ed Frick. We knew when Ed moved into that role that we were getting a package that included Jean. She supported Ed and the Foundation in every way.

In doing so she became a dear friend of everyone she met, so kind, so loving and what a great sense of humor. Her funeral ceremony, designed by her family, was truly a celebration of the wonderful life she led. Jean, we will miss you. To us you will always be Our First Lady.



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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

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Objectives

- The objective of the William Guy Forbeck Research Foundation is to promote advances in the field of oncology, particularly pediatric oncology.
- While the foundation may provide grants for pilot research studies and educational efforts, its centerpiece activity will be an annual scientific roundtable held at Hilton Head Island, South Carolina.
- Attending each year will be up to twelve 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. The hope is to shorten the cancer research timetable.
- Participants will be invited on the recommendation of the Foundation's Scientific Advisory Board, a distinguished panel of medical scientists.

It is through your generous support that continuing research in the field of childhood cancer can be ensured. Contributions are tax deductible for federal IRS purposes. The IRS file number is 580063499. For additional information please fax: (843) 837-3088, visit our web site www.wgfrf.org or write: William Guy Forbeck Research Foundation, 23 Peninsula Drive, Hilton Head Island, South Carolina 29926