



Edward A. Frick

## From The Chairman's Desk

**The most productive use of cancer research dollars** is the

reaction that you get when the William

Guy Forbeck Cancer Research Foundation is discussed by leading scientific researchers. This has been the emphasis of the Foundation since it was founded in 1984. With over 1,000,000 people in the United States diagnosed with cancer each year, making cancer dollars more efficient is vital. We are beginning to understand the causes of cancer and to initiate new methods of prevention, diagnosis, and treatment. The "war on cancer" is far from being won, but some of the battles are beginning to turn our way.

**This past year's forum** addressed a key topic, "Cellular Senescence and Cancer", and was chaired by *Dr. Ronald DePinho* from Dana Farber Cancer Institute in Boston and *Dr. Charles Sherr* from St. Jude Children's Research Hospital in Memphis. It was one of the best sessions ever. **The 2003 Forum** topic will focus on "DNA Damage and Cancer Susceptibility Syndromes" and will be chaired by *Dr. Alan D'Andrea* from Dana Farber Cancer Institute in Boston and *Prof. Dr. Jan Hoeijmakers* from the Erasmus University of Rotterdam (Netherlands).

In 1999 the foundation established the "Focus on the Future" program where grants are awarded to allow the recipients to hold meetings similar in content and format to the very successful annual Hilton Head Forums. The **2003 Focus grant** was been awarded to *Dr.*

*Moritz Ziegler* to address the topic of "The New Biology of Enigmatic Neuroblastoma and Relevant Treatment Strategies."

An Appreciation Meeting was held in June to thank our many loyal Lake Geneva supporters. It was held at the Lake Geneva CC with over 250 people in attendance. *Dr. John Kemshead* from Baxter Labs, *Dr. Bruce Chabner* from Harvard and *Dr. James Stewart* from the University of Wisconsin participated in a stimulating and informative round table discussion. At the meeting *Bobby Smyth* was presented with a Trustee Emeritus Award for his many years of outstanding service to the Foundation.

There is a very special place in our heart for *Jim and Jennifer Buchanan*, and their daughter *Lindsay*. Jim and Jennifer started the Homefront Bike Tour and raised over \$345,000 for the Foundation. Lindsay had neuroblastoma and in spite of this, was a tremendously positive young girl. Everything possible was done worldwide to stop this terrible disease but Lindsay passed away on May 25<sup>th</sup>. Her courageous spirit will always inspire the Foundation and not a day goes by that I don't say a prayer for her.

This is the time of the year when we ask for your renewed support to maintain the momentum that has been established. It is through your generous help that continuing progress will be made.

Thank you for your continuing assistance to the Foundation.

**Edward R. Frick**  
Chairman, Board of Trustees

## SCIENTIFIC ADVISORY BOARD REPORT

### Cell Death and Cancer - an Intimate Link.

Several of our meetings in Hilton Head have focused on cell death. This may seem rather strange



John T. Kemshead, PhD

as cancer is the antithesis of this; it primarily being thought of as resulting from uncontrolled cell growth. However, there are two reasons for our considered focus on this topic. The first is the hope that if we understand more about cell control processes then we will understand more about cancer. The second reason is that another way in which a malignancy may arise is through cells not understanding when to die. This results in a mass or tumour as cells are not being eliminated from the body at the right time.

The reasons why we do not suffer from more cancers than we do, is in my view down to control processes. Cells

...Continued on page 9

In This Issue...	From the Chairman's Desk.....	1
	Scientific Advisory Board .....	1
	Forum 2002:	
	<i>Cellular Senescence and Cancer</i> .....	2
	Awards and Grants.....	6
	Forums 2003 and 2004 .....	8
	Financial Report.....	9
	Benefactor List .....	10
	Objectives .....	12
	Board of Trustees &	
	Scientific Advisory Board .....	12

# 2002 Forbeck Forum: XVIII<sup>th</sup> Annual Forum

November 7–9, 2002 Hilton Head Island, South Carolina

## Subject: Cellular Senescence and Cancer

- I: Telomere Biology in Human Cell Systems
- II: Tumor Suppressors / Senescence Pathways
- III: Modeling Cancer & Cancer Genomes
- IV: Models / Methods to Probe Senescence

## Chairmen

Ronald DePinho, MD	Harvard Medical School	Boston, MA
Charles Sherr, MD, PhD	St Jude Children's Research Hospital	Memphis, TN

## Participants

Judith Campisi, PhD	Lawrence Berkeley National Laboratory	Berkeley, CA
Titia de Lange, PhD	Rockefeller University	New York, NY
Steven Elledge, PhD	Baylor College of Medicine	Houston, TX
Gerard Evan, PhD	University of California	San Francisco, CA
William Hahn, MD	Harvard Medical School	Boston, MA
Gregory Hannon	Cold Spring Harbor Laboratory	Cold Spring Harbor, NY
Jacqueline A. Lees	MIT Center for Cancer Research	Cambridge, MA
Scott Lowe, PhD	Cold Spring Harbor Laboratory	Cold Spring Harbor, NY
Jerry W. Shay, PhD	UT Southwestern Medical Center	Dallas, TX
Maarten van Lohuizen	the Netherlands Cancer Institute	Amsterdam, Netherlands
Karen H. Vousden, PhD	National Cancer Institute	Frederick, MD



Ron DePinho, MD

*"Each day, I encounter patients and their families whose lives are touched by cancer. It is heartening to see such dedication on your part to eliminate this modern black plague."*

Ron DePinho, MD

*"I thought that the meeting was a great success. I enjoyed everything — the science and the venue and the socializing."*

Charles Sherr, MD, PhD



Charles Sherr, MD, PhD

## 2002 Conference Report

by Ronald A. DePinho, M.D. & Charles J. Sherr, M.D. Ph.D.

This exciting and highly productive Forum focused on cellular senescence – a biological response governed by known cancer-relevant pathways and thought to be integral to the suppression of cancer and the response to anti-cancer agents. Investigators from diverse areas discussed the cellular senescence mechanism from the molecular, cellular and organismal perspectives. Numerous outstanding questions were discussed including: Does senescence represent an effective mammalian tumor suppressor mechanism on one hand yet drives the age-related pathologies on the other? Are there species-specific differences in mice and humans or does this relate to experimental design? What role do telomeres play in suppressing or fueling chromosomal instability and how does this influence the initiation and progress of cancer in the organism? What are the nature of the signals emanating from the telomere and how is this signal mediated by damage signaling pathways in normal and neoplastic cells? How is telomerase regulated? How do cellular senescence

pathways influence the biological impact of oncogenic lesions such as Myc and can we forge a link to the core cell cycle machinery? A discussion of these issues generated more questions than answers and the level of discussion was so robust that most speakers found it challenging to get past the first few slides of their talk.

**Dr. Judith Campisi** of Lawrence Berkeley National Laboratory focused on the issue of the cellular senescence is an example of evolutionary antagonistic pleiotropy and presented evidence that cellular senescence in cultured cells is driven by a process linked to accumulated oxidative stress. She also reviewed the evidence that strongly suggests that senescent cells accumulate in normal tissues, and that these cells may provide

*"This was one of the most stimulating and enjoyable meetings I've ever attended. Many good ideas (and some collaborations) have already come out of it, and more will percolate through in the future, I am sure."*

Judith Campisi, PhD

a permissive microenvironment for epithelial carcinogenesis. Such senescent microenvironment cells secrete proteases among other factors that have been linked to tumor progression.

**Dr. Titia de Lange** of the Rockefeller University discussed how abnormal telomere structure activates a senescent response in mouse and human cells. She emphasized that, although there is general agreement on the involvement of p53 in the senescence signaling pathway, the data are less clear on the role of p16. Furthermore, the telomere damage signaling pathway appears to be different in human and mouse cells as reflected in the response of these cultured cells to alterations in telomere structure brought about by the expression of aberrant telomere binding proteins.

**Dr. Ron DePinho** of the Dana-Farber Cancer Institute and Harvard Medical School presented his work on engineered mice harboring defective tumor suppressor pathways and critically shortened telomeres and how such alterations impact on processing of aging and

cancer. He presented data showing that advancing age, telomere attrition, and accompanying genomic instability cooperate to compromise the overall health and well-being of mammals on the level of tissue stem cells. The telomerase knockout mouse has provided a model to dissect the complex role of telomeres in cancer pathogenesis. Cancer, particularly epithelial carcinomas, is among the most common aspects of aging in humans and telomere erosion has been cited as a risk factor in the genesis of certain human tumor types. In line with this view, late generation mTERC null mice exhibit an age- and generation-dependent increase in cytogenetic abnormalities and a significant increase in the incidence of spontaneous cancers. To examine the genetic interactions between telomere dysfunction and key checkpoint pathways in relation to tumor formation, the cellular response to telomere dysfunction was examined against the backdrop of various tumor suppressor mutations. In p53<sup>-/-</sup> (but not Ink4a/Arf or Atm<sup>-/-</sup>) mice, carcinomas emerged as the largest class of clinically apparent tumors, greatly exceeding sarcomas and lymphomas. These epithelial cancers emerged with complex cytogenetic profiles similar to that seen in human carcinomas, pointing to telomere dysfunction as a mechanism driving chromosomal instability. Acquisition of fully malignant phenotype including metastases may require telomerase-mediated telomere maintenance as a late event in the evolution of these cancers.



**Dr. Steve Elledge** of Baylor College of Medicine provided an overview of the cellular response to double strand breaks in DNA. He discussed the relationship of this

response to the process of telomere erosion that occurs when cells have undergone extensive proliferation, such as during the early stages of tumorigenesis. He then discussed how cells can overcome the defects in telomere erosion by inducing the catalytic subunit of human telomerase and described a number of

genes he recently identified in genetic screens that repress telomerase expression in normal cells. Many of these were linked to tumor suppressor pathways, furthering the link between telomerase and cancer.

**Dr. Gerard Evan** of University of California presented his elegant mouse models of cancer designed to understand the immense complexity of the tumor phenotype and the underlying genotype. In particular, he delineated the issues surrounding the concept of tumor establishment and maintenance. He focused on the possibility that cancers require only a very restricted complement of interlocking mutations but which can only be acquired by a circuitous and protracted evolutionary process. A case in point is the Myc oncoprotein. Deregulation of expression of the c-Myc protein represents an archetypical proliferation-deregulating oncogenic lesion found in most human cancers. However, the potent pro-apoptotic activity of c-Myc means that its deregulation can only be accommodated in cells in which cell death is being potently suppressed. They have explored the mechanisms by which c-Myc induces apoptosis and identified a novel p53-independent pathway by which c-Myc directly influences mitochondrial integrity. To explore the role of c-Myc-induced apoptosis in limiting c-Myc oncogenesis *in vivo*, they constructed mice that harbor a switchable c-Myc protein targeted to specific tissues. These animals allow the direct examination *in vivo* of both the immediate and the delayed consequences of acute activation of the *c-myc* oncogene in different somatic settings. Activation of c-Myc targeted to pancreatic  $\beta$  cells using the insulin promoter rapidly (16 hours) induces ~100% sustained  $\beta$  cell proliferation in all islets, in the absence of any other growth-promoting lesion. However, such  $\beta$  cell proliferation is accompanied by overwhelming apoptosis that rapidly leads to islet involution and concomitant acute diabetes. The clear implication is that  $\beta$  cell neoplasia cannot arise without early suppression of apoptosis. To confirm the predicted oncogenic synergy between *c-myc* and suppression of apoptosis in  $\beta$  cells, we co-expressed the anti-apoptotic Bcl-x<sub>L</sub>

protein in  $\beta$  cells together with switchable c-Myc. In this case, activation of c-Myc triggers rapid, progressive and inexorable  $\beta$  cell neoplasia that is immediately accompanied by profound angiogenesis and local invasion. Similar oncogenic results are obtained upon activation of c-Myc in  $\beta$  cells lacking the tumor suppressors p19<sup>ARF</sup> or p53, although each type of anti-apoptotic lesion has its own distinct suite of attendant characteristics. Thus, inhibition of c-Myc induced apoptosis, either through the mitochondrial or ARF/p53 pathway, is sufficient to enable Myc to induce a state resembling full malignancy. Subsequent deactivation of the switchable Myc oncoprotein triggers rapid and complete regression of all  $\beta$  cell adenomas, indicating that Myc is required both to induce and to maintain the neoplastic state. He concluded with an outline of the implications of these data both for our understanding of the evolution of tumors and for identification of useful therapeutic targets.

**Dr. William Hahn** of the Dana Farber Cancer Institute presented a provocative series of results showing that the rate limiting, telomerase catalytic subunit, hTERT, is expressed in primary, pre-senescent human fibroblasts, previously believed to lack hTERT and telomerase expression, during transit through the cell cycle. Disruption of this expression of telomerase inhibits cell proliferation, induces early entry into replicative senescence and alters the maintenance of the 3' single-stranded telomeric overhang. These observations support the view that telomerase and telomere structure is dynamically regulated in normal human cells and that telomere length alone is unlikely to trigger entry into replicative senescence.



**Dr. Gregory Hannon** of Cold Spring Harbor Laboratory provided exciting new insights on RNAi in mammalian cells that build on the use of biochemical systems from *Drosophila* and genetic studies in plants and invertebrates.

...Continued on page 4

Together, these efforts have begun to reveal a mechanistic basis for RNA interference and related phenomena. The canonical model involves a two-step mechanism that includes an RNaseIII family nuclease, Dicer, which initiates RNAi by processing dsRNA silencing triggers into small RNAs of ~22 nt in length. These enter an effector complex RISC, which seeks out and degrades homologous substrates. Genetic studies of Dicer-null animals (i.e., *C. elegans*) have suggested roles for the RNAi machinery in the regulation of endogenous genes. Specifically, Dicer and components of the RISC complex have been implicated in processing of and in gene regulation by endogenously encoded small hairpin RNAs, known collectively as microRNAs (miRNAs). The Hannon group exploited these observations to test the possibility that miRNAs might be remodeled to regulate genes of interest. They demonstrated that expression of shRNAs from RNA polymerase III or RNA polymerase II promoters results in silencing of homologous genes and have recently extended these findings to living animals. They continue to pursue parallel paths toward a deeper understanding of the underlying mechanism of RNAi and toward expanding the applications of RNAi as a tool for investigating gene function in mammals.

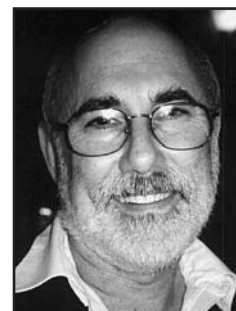
**Dr. Jacqueline Lees** of MIT Center for Cancer Research reviewed the complexity of the RB-E2F signaling network in normal and cancer cells. Through the analysis of various *E2f* mutant mouse strains and the resultant E2F-deficient mouse embryonic fibroblasts (MEFs) has demonstrated that E2F3 as a key inducer of cellular proliferation. E2F3 acts in a dose-dependent manner to induce the cell cycle dependent expression of almost all known E2F-responsive genes. The reduced expression of one or more of these E2F3-regulated genes delays passage through the G<sub>1</sub>/S transition and significantly reduces the rate of DNA synthesis. As a result, E2F3-deficient MEFs have a major defect in their ability to re-enter the cell cycle in response to mitogen stimulation and proliferate at a markedly reduced rate relative to wild-type con-

trols. They have identified additional changes in the E2F3-deficient cells that are typically associated with cellular stresses such as senescence and oncogenic challenge. These include increased expression of p16<sup>INK4A</sup>, p21<sup>CIP1</sup> and p19<sup>ARF</sup>. The increased expression of p19<sup>ARF</sup> is particularly surprising given the prevailing view that *p19<sup>ARF</sup>* is an E2F-responsive gene. In addition, p53 appears to be activated in the E2F3-deficient cells, revealing significant cross-talk between the E2F and the p53 pathways. We have generated *E2f3:p19<sup>ARF</sup>*, *E2f3:p16<sup>INK4A</sup>* and *E2f3:p53* compound mutant mice to investigate how this interplay is mediated and how it contributes to both cell cycle control and tumorigenesis. She presented considerable progress in establishing the properties of the double mutant MEFs (DKOs). The homozygous mutation of either *p19<sup>ARF</sup>* or *p16<sup>INK4A</sup>* does not affect either the up-regulation of p21<sup>CIP1</sup> or the proliferation defect of the E2F3-deficient cells. In contrast, the inactivation of p53 specifically suppresses the inappropriate expression of p21<sup>CIP1</sup>, but not p16<sup>INK4A</sup> or p19<sup>ARF</sup>, indicating that the changes in p21 expression are predominantly p53-dependent. Surprisingly, the inactivation of p53 and resulting reduction in p21 levels did not suppress the proliferation defect of the E2F3-deficient cells. Moreover, *E2f3:p19<sup>ARF</sup>*, *E2f3:p16<sup>INK4A</sup>* and *E2f3:p53* DKOs that have been transformed with rasV12 show similar impaired proliferation when tested in either focus formation or soft agar colony assays. Importantly, however, E2F3-loss did not affect the well-documented, immortalized phenotypes of the *p19<sup>ARF</sup>*, *p16<sup>INK4A</sup>* and *p53* mutant MEFs. She therefore concluded that *p19<sup>ARF</sup>*, *p16<sup>INK4A</sup>* or *p53* act upstream of E2F3 in the control of cellular proliferation but downstream of E2F3 in the control of cellular senescence. Her program continues to investigate how E2F3-loss results in the activation of p53 and the induced expression of p16<sup>INK4A</sup> and p19<sup>ARF</sup>.



**Dr. Scott Lowe** of the Cold

Spring Harbor Laboratory presented the idea that the process of cellular senescence can be conceptualized much like apoptosis, in that both processes involve defined programs that can eliminate damaged cells following stress. With this analogy in mind, Dr. Lowe discussed several issues, including: (1) factors that influence the decision to apoptose or senesce; (2) how different stress signals are integrated into a common arrest program; and (3) the molecular mechanisms that drive senescent cells into an apparently irreversible cell cycle arrest. He also discussed how disruption of specific nodes in tumor suppressor networks can influence cellular responses to cancer chemotherapy. In particular, Lowe and colleagues have shown that a senescence program controlled by p53 and p16<sup>INK4A</sup> contributes to treatment outcome in vivo, and that these proteins act in a cooperative manner to engage the cell-cycle arrest program. In parallel, they have also identified an important role for the Rb tumor suppressor in the



process by which senescent cells are maintained in a state that is non-responsive to mitogens.

**Dr. Jerry Shay** of the UT Southwestern Medical Center

used the example of neuroblastoma (IVS) to discuss the relationship between telomeres, senescence and telomerase. Two important concepts emerged, first telomerase is not needed for the initiation of cancer but a mechanism to maintain telomeres is required for the long term progression of all human cancers. Other topics covered by Dr. Shay included: 1. Is progressive telomere shortening in human cells a mechanism to prevent cancer or a cancer-initiating mechanism leading to increased genomic instability? 2. What is the evidence that telomere shortening is important in chronic human diseases leading to increased susceptibility to cancer? 3. What are the most promising approaches for inhibiting telomerase for use in cancer therapeutics? 4. What is the evidence for alternatives to telomerase for telomere-maintenance and

how can we investigate these mechanisms? In particular, he reviewed evidence that cell grown in typical culture conditions are exposed to a continuous state of oxidative stress that may not be representative of cells *in vivo*. This oxidative stress leads to increased ROS that may be sensed by p16 leading to a growth arrest state that mimics replicative senescence. Many “stressors” including oligonucleotide-based cancer therapies, ectopic over-expression of genes, irradiation, as well as inadequate culture conditions can induced this premature senescence (stasis, culture shock) state. He emphasized that these effects have largely been misinterpreted as fundamental biological mechanisms involved in regulating cellular senescence that are telomere length independent. He articulated the view that the analysis of the mechanisms of signal transduction, regulation of gene expression, proliferation, senescence and death may be compromised by the failure to consider the environment in which the cells are propagated.

**Dr. Charles Sherr** of St Jude Children’s Research Hospital discussed the family of INK4 protein in cell cycle regulation and cancer suppression. He reported that, among the family of four INK4 proteins, only one (p16INK4a) has been frequently linked to cellular senescence and tumor suppression. In mice, the four proteins are expressed in different patterns, with p18INK4c and p19INK4d being detected during development in utero, and with p16INK4a and p15INK4b being induced in cultured cells in response to stress, and in mice in haphazard patterns as they age. The so-called “Rb pathway” (p16 — cyclin D/Cdks — Rb family) is not linear, because p27 and p21 are normally sequestered into cyclin D/Cdk complexes and these Cdk inhibitors are “mobilized” by INK4 proteins to block cyclin E/Cdk2 and cyclin A/Cdk2 activity. Finally, both INK4a and ARF are actively suppressed during embryonic development. Although ARF is an E2F-responsive gene, it is not periodically expressed during the cell cycle, implying that its promoter is insulated from responding to transient signals. Although some have suggested that Myc and E2F1 regulate apoptosis by inducing ARF (and even that Myc may depend upon E2F1 for

this activity), our unpublished results reveal that Myc-induced apoptosis does not require E2F1 activity.

**Dr. Maarten van Lohuizen** of the Netherlands Cancer Institute presented his studies on the regulation of INK4a/ARF tumor suppressor locus in normal and neoplastic cells. The INK4a/ARF tumor suppressors are now well established as an important cancer-prevention mechanism by halting cell cycle progression upon different kinds of stress signals, such as activation of oncogenes. The INK4a/ARF locus is under stringent control (strongly repressed in normal cells) and there is evidence for different ‘threshold levels’ for Arf in mediating ‘stasis/senescence’ arrest and suppression of oncogenic transformation. Therefore, important questions to be answered further are how is the INK4a/ARF locus regulated and do we know all the downstream effectors of INK4a/ARF signaling? He and his colleagues approached these issues by generating INK4a/Arf reporter constructs and by developing genetic screens in primary cells to bypass stasis/senescence. Another relatively unexplored issue of interest is a possible role for the INK4a/ARF fail-safe during development. Such connections are suggested by the transcriptional regulation of INK4a/ARF by developmental regulators such as Polycomb repressors and TBX2/3. These connections are of special interest to cancer in light of the emerging role for Polycomb repressors in controlling the balance between differentiation and proliferation (self renewal) of precursor cells/stem cells.

**Dr. Karen H. Vousden** reviewed the p53 response indicating that cell cycle arrest and apoptosis reflect separable functions of p53 that can be controlled independently. Several mechanisms that contribute to the choice of response induced by p53 have been identified, including differential expression of cell cycle arrest and apoptotic target genes, and selective inhibition of expression of cell cycle arrest targets. p53-mediated induction of proteins with anti-apoptotic activity may also contribute to the overall choice of response. The apoptotic



activity of p53 is key for tumor suppression, and is likely to be an effective activity to target for restoration by new therapies. It is therefore of interest to

understand the mechanisms that determine the outcome to p53 activation. A therapeutic approach in tumors that retain wild type p53 is to inhibit HDM2 - the ubiquitin ligase for p53 - and so stabilize p53. It remains unclear, however, how tumor cells will respond to such treatment. Small molecules with this activity would, to some extent, mimic the function of HMD2-binding proteins like ARF and L11. Interestingly, their preliminary work has suggested that p53 responses induced by ARF and L11 are not the same, and understanding the basis for these differences will contribute to the development of new therapeutics.

In closing, the Forum resulted in an extremely robust exchange among the participants. Several attendees remarked on how effective the Forum was in communicating new unpublished information and ‘out-of-the-box’ thinking that will no doubt stimulate new lines of basic research and new opportunities for cancer intervention. The regulation of telomeres and telomerase play a critical role in determining genomic stability and replicative lifespan. The work discussed at the forum will the participants to re-investigate some of the paradigms that describe how telomere maintenance regulates replicative senescence. Further studies promise to incorporate observations not easily explained by prior models of telomere function and to help define how this knowledge can be exploited to better understand and treat cancer.

*Ronald DePinho*  
*Charles J. Sherr*

2002 Forum Chairmen:  
Ronald DePinho, MD  
Charles Sherr, MD, PhD

*“I go to a lot of scientific meetings and really this was one of the most useful and productive ones that I have attended. I think you are making a fabulous contribution to cancer.”*

Karen H. Vousden, PhD

## 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. A \$1,000 contribution is made to each award recipient’s institution. 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 which 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.



2002 Scholars: Alison Bertuch, Jan Karlseder, Masashi Narita

### 2002 SCHOLAR AWARD

The Foundation received a number of very qualified applications for the 2002 Forbeck Scholar Award. The Scientific Advisory Board selected three outstanding young scientists to attend the 2002 Forum and receive this award.

We were pleased to present this year’s Scholar Award to three candidates.

**Alison Bertuch, MD, PhD** is an assistant professor in Pediatrics at Baylor College of Medicine in Houston, Texas. She obtained her B.S. from MIT and her M.D. and Ph.D. from the University of Rochester. Alison was nominated for the Foundation Scholar Award by *David Poplack, MD*, who said “Dr. Bertuch is an intelligent, highly motivated and driven individual. She has demonstrated the ability to approach medical problems with scientific inquiry and has a strong inclination to pursue problems that ultimately relate to patient care. She has keen analytical abilities, and a single-minded interest in molecular aspects of oncology.” Alison’s research interest focuses on Ku, a protein shown previously to be critical for DNA repair which, paradoxically, also functions at telomeres. Using yeast as a model system, she has performed a detailed mutagenesis of Ku, which has enabled her to dissect its roles at the telomere versus at DNA breaks.

*“Attending the 2002 Forum was an extremely valuable experience. Having the opportunity to meet such a distinguished group of scientists and discuss my work and future goals with them was very special. I left with an even stronger determination than ever to extract from all of this great science its specific application to pediatric oncology with the hope that it will make the difference in the lives of children in the future.”*

*Alison Bertuch*

**Jan Karlseder, PhD** is an assistant professor at the Salk Institute in La Jolla,

California. Jan was the first to show that it is p53 that responds to telomere dysfunction and also identified ATM as the upstream kinase responsible for p53 activation, and more recently, discovered that replicative senescence is induced by a change in telomere status, not complete loss of telomeric DNA as was previously thought. Jan was nominated by *Titia de Lange, PhD* from the Rockefeller University. Dr. de Lange said Jan “has a strong interest in pursuing similar problems for the future as an independent investigator. He is a very interactive and outgoing contributor at meetings and always initiates interesting discussion by asking probing questions.”

*“Interaction between the participants was impressive and constructive, and the surroundings were wonderful. I was deeply moved by the way you converted something tragic into something so positive.”*

*Jan Karlseder*

**Masashi Narita, MD, PhD** is a post doctoral fellow at Cold Spring Harbor Laboratory in New York. He received his M.D., and Ph.D. from Osaka University School of Medicine in Japan. Masashi was nominated by Scott Lowe, Ph.D. and currently works in Dr. Lowe’s laboratory. His interest is in cellular senescence and he hypothesized that, as during apoptosis, different stress-inducing stimuli might induce senescence through a common mechanism, leading to activation of a ‘senescence machinery.’ In a series of cell biology experiments, Masashi showed that changes in heterochromatin accompany senescence, including a redistribution of HP1 proteins and K9methyl histone H3. Regarding certain studies in his lab, Dr. Lowe says “Masashi has been the single driving force behind generating these results, and has worked tirelessly for two years to get to this stage.”

Forum participants have agreed these scholars add to the dynamic interaction of the Forum.

*“It was scary experience, and so it was extremely precious experience for me. I am learning and learning everyday (of course learning English too), and this forum was so inspiring, encouraging, and big step for me. I really feel like I have changed a little after the forum.”*

*Masashi Narita*

## 2003 FOCUS on the FUTURE GRANT AWARD

In the 5<sup>th</sup> year of the Focus program, the Foundation Scientific Advisory Board reviewed grant applications and awarded the grant to *Moritz M. Zeigler, MD*, Children's Hospital, Boston.

### *The New Biology of Enigmatic Neuroblastoma And Relevant Treatment Strategies*

March, 2003

Neuroblastoma remains the most frequent solid abdominal and thoracic malignancy of childhood, a tumor characterized by an aggressive behavior and a dismal outcome. Therapeutic strategies have historically emphasized aggressive multimodal therapy, and the marginal improved prognosis seen in the last several years has depended on the acceleration and further intensification of such treatment. Such a strategy is contradictory to the observation that the diagnosis of low stage neuroblastoma is possible by mass population screening, and low stage patients have a worse outcome in the face of more aggressive therapy. Furthermore, despite its poor prognosis, neuroblastoma is that tumor characterized by two uniquely enigmatic, yet favorable, behaviors. First, it can spontaneously or by exogenous manipulation be stimulated to change its phenotype from an aggressive and metas-

tasizing malignancy to a mature and benign ganglioneuroma. Second, it has the potential to undergo spontaneous regression, and even frank disappearance, despite an original large and even disseminated tumor burden.

As investigators have sought to understand this biological behavior, a series of specific areas of investigation have evolved that will serve as the focus for this meeting. They include a delineation of the immunobiology of neuroblastoma, a definition of signaling mediators, receptors, and their mechanisms, the study of angiogenesis, angiogenic inhibitors, and their potential linkage to signaling as well as the immune response, and the investigation of the genetic analysis of neuroblastoma as well as the putative application of gene therapy as an effector for these various treatment strategies.

## 2002 FOCUS SUMMARY REPORT

### *Tumor specific immunological memory as a tool in cancer treatment*

#### **Chairmen:**

Prof. Volker Schirmmacher and Dr. Philipp Beckhove  
German Cancer Research Ctr, Heidelberg, Germany  
*April 24-27, 2002 - Deidesheim, Germany*

The meeting intended to introduce a new field of cancer immunology to an interdisciplinary group of outstanding experts, both basic scientists and clinicians who cover all major aspects of the topic from basic immunology to problems related to the clinical application of new immunotherapeutic approaches. The meeting was focused on the interdisciplinary exchange of expertise in order to accelerate scientific progress and to draw up future clinical applications.

In the past, a number of tumor-associated-antigens (TAAs) have been characterised to be capable of initiating autologous and allogeneic T-lymphocyte responses against the respective tumors. Thus, TAA-reactive T cells may be potent agents for cancer treatment. It has been recently demonstrated that cancer patients are able to generate high frequencies of tumor-reactive T cells. Isolated and re-activated in vitro, these cells exert potent anti-tumor functions in vitro and in vivo. Thus, clinical application of memory lymphocytes may become potent a potent tool in cancer treatment. Throughout

the workshop, issues such as differentiation, homeostasis and functional characteristics, migration, homing to tumors and lymphoid tissues and redistribution of such memory T cells, as well as their interactions with B cells and dendritic cells were discussed lively and controversy. The underlying expert presentations provided the basis for these discussions and the consecutive lectures on issues related with clinical applications of such cells. The meeting enlarged profoundly the experts knowledge and understanding of the subject and led to a variety of scientific and clinical cooperations.

#### **Summary**

- I. Memory T lymphocytes, dendritic cells, chemokines and T cell trafficking
- II. Lymphocyte recirculation and homing in lymphoid and peripheral tissues
- III. Systemic role of homeostatic chemokines in adaptive immunity
- IV. TCR-Repertoire-analysis of tumor-reactive T cells in cancer patients
- V. Autologous B-lymphocyte responses to solid tumors; Serex-method
- VI. Tumor-associated antigens of solid tumors; autologous T cell immunity
- VII. T cell monitoring in infectious and malignant diseases
- VIII. Adoptive T cell therapies
- IX. Clinical application and monitoring of specific cellular immunotherapies

*For additional information, contact  
the meeting chairmen or the Foundation.*

## FORUM PLANNING

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### 2003 Forum: DNA Damage and Cancer Susceptibility Syndromes

The Forbeck Foundation Forum in 2003 will be chaired by Dr. Alan D'Andrea of the Dana Farber Cancer Institute in Boston and Dr. Jan Hoeijmakers of the Erasmus University in Rotterdam. The topic for the forum will be "DNA Damage and Cancer Susceptibility Syndromes". The important role that DNA damage plays in cancer development is illustrated by the clear connections between exposures to certain types of DNA damaging agents in the environment and the development of cancer, such as the links between cigarette smoking and lung cancer or sunlight exposure and skin cancer. In addition, the majority of inherited syndromes characterized to date that lead to increased cancer development in families result from inherited mutations in genes that are important for DNA damage responses. For example, inherited mutations in either the Brca1 or p53 genes results in a very high risk of developing breast cancer and both of these gene products are important for helping cells respond to various types of DNA damage. The genes mutated in certain rare diseases that affect children, such as Fanconi's Anemia, Ataxia-telangiectasia, and Xeroderma Pigmentosum, all play roles in cellular responses to DNA damage and children with these diseases have very high incidences of certain cancers. Studies of the genes mutated in these diseases have led to a much better understanding of how all cells respond to DNA damage and even more importantly to insights about how cancers develop. In addition, since radiation therapy and most chemotherapies used to treat cancer cause DNA damage, understanding how these gene products operate provides new ways to approach the treatment of cancer. The discussions at the forum will focus on how these gene products function, how they contribute to cancer development, and how they can be manipulated to improve cancer therapies. ☐

#### FOUNDATION VIDEO (DVD) AVAILABLE

A video presentation "showing" the history, purpose and activity of the Foundation is available by contacting the Foundation. Please specify VHS video or DVD format.

### 2004 Forum: Targeted Therapies in Pediatric Malignancies

The Forbeck Foundation Forum in the year 2004 will be co-chaired by Drs. Charles Sawyer from University of California at Los Angeles, and Gary Gilliland, Howard Hughes Medical Institute and Brigham & Women's Hospital, Harvard Medical School. The theme for the forum will be "Targeted therapies in Pediatric Malignancies." This topic pertains to the new quest of utilizing molecular and genetic information about cancer to specifically design treatments which target functionally important molecular lesions. In the past several decades enormous quantities of information have accumulated regarding the precise mutations which either activate or disrupt genes in many human cancers. In some cases this information has permitted new classification of cancers, and the molecular abnormalities have become central to the diagnosis of specific tumors. While large strides have been made in the identification of gene abnormalities in cancer, therapeutic advances have not been as forthcoming. This stems largely from the fact that traditional cancer therapies have been employed prior to a complete understanding of the mechanisms through which they work or the cellular targets which they attack. The "Targeted Therapy" concept stems from the goal of developing cancer treatments which specifically focus on disrupting molecules within cancer cells which are known to be central to the malignant behavior of the cell. Such targets have included activated oncogenes such as Abl, a factor whose inhibition by the drug Gleevec has produced dramatic remissions in certain forms of leukemia. The discussion at this Forum will focus both on the identification of targets as well as in strategies to design drugs capable of inhibiting them in order to convert the information learned about cancer into therapeutic advances. ☐

#### WEB SITE - [www.wgfrf.org](http://www.wgfrf.org)

The Foundation web site contains general information, a summary article on each of the Forums organized by the Foundation, information about "Focus on the Future" awards and grants, and several web site "pointers" for more information on cancer.

## Scientific Advisory Board Report

...Continued from Page 1

must have multiple ways of controlling their growth and function and there must be a great deal of redundancy built into the overall control process. When these control processes fail then a tumour may arise.

The above reasoning is why so many of our Foundation meetings have focussed on cell division and cell death. In the past we have held a meeting on programmed cell death or apoptosis. This is a particular cell process leading to cell's death, and it often occurs as a result of cellular damage. However, this topic is not necessarily relevant to cells dying of old age. Cells, like our bodies, age and then die. Each cell type within us appears to have a finite life and this differs from cell to cell. For example red blood cells have a half-life of about 120 days, the cells lining of our intestines turn over very quickly whereas our nerve cells live for many years. Understanding, natural cell senescence or cell aging, the topic of our 2002 meeting, can hopefully give important clues as to what goes wrong when cells do not die at the right time in the right way.

Over the last two decades we have made phenomenal progress in understanding the process of cell death. We know that there are mechanisms that protect our chromosomes from damage throughout the life of the cell. In addition, year by year we are learning about the complexities of the pathways that function to tell our cells to either divide, remain active and functional or die. These topics were reviewed in depth, during the 2002 meeting along with discussions as to how one might interfere with these pathways. For those of you who want a little more detail a report of the meeting is included in this newsletter.

It is hard to imagine the complexity surrounding our bodies. These are made up of not just millions but trillions of cells. Each of these cells appears to understand that it has a function and it normally undertakes this until the time comes when it is eliminated. When one considers that cancers are thought to arise from errors in just one cell it is remarkable that the disease is not more prevalent.

The pharmaceutical companies are ploughing ahead, trying to identify targets for drugs within the cell that can control cancer. One good example of this is Glevac, a drug that has been developed that works in chronic myeloid leukaemia. This recognises a particular target within the cancer cells and blocks their ability to divide. The incredible thing about Glevac is that it appears to have little effect on normal cells within our bodies. Clearly, now that proof of principle has been demonstrated, a massive effort is being made, by the drug companies, to identify other molecules that can block the division of different cancer types. However, as indicated above the complexity of the machinery of the cell is immense. This is the prime reason for continuing to encourage research by academics, clinicians, biotechnology companies and the pharmaceutical industry. Bringing individuals from these disciplines together is just as important as it was when the Foundation was formed nearly two decades ago. So much progress is being made but more remains before we can say we have cancer under control.

**John T. Kemshead, PhD**  
Chairman, Scientific Advisory Board

## 2002 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. 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.

A significant increase in income 1997-2001 was due to the 5-year pledge of support of the Homefront Bike Tour.

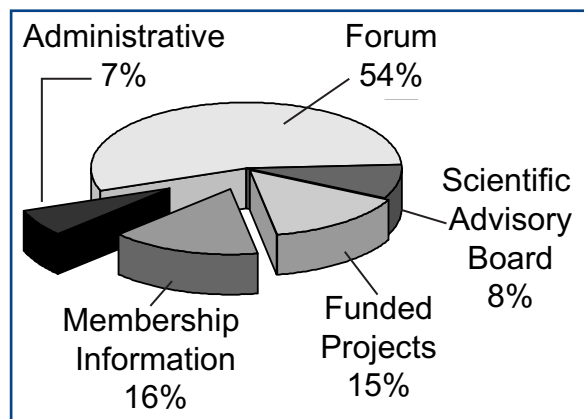
### EXPENSES 2002

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 2002 include the Scholar Award and funding one Focus meeting grant.



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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, 2002 thru February, 2003)*

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Several people, very close to the Foundation, passed away in 2002.

**Lindsay Noble Buchanan** died May 25<sup>th</sup> at the age of 10. For seven years, Lindsay battled neuroblastoma, one of the most virulent of childhood cancers. She was a little girl, bravely fighting a very large disease.



Lindsay taught her friends and family many things, in particular, that it is not necessary to be an adult to be a warrior. Over the seven years of her treatment for cancer, she participated in six experimental clinical trials at four cancer centers around the globe, including Dana Farber in Boston, Memorial Sloan-Kettering in New York, City of Hope in California and the Children's Hospital in the Netherlands. Lindsay knew that her treatment might help her. She also knew that it could help pave the way for thousands of adults and children living with this terrible disease and navigating through its treatment. She worked very hard to make a difference.

In their efforts to fight her disease, Lindsay's parents, Jennifer and Jim Buchanan, became involved with the Foundation in 1996. They organized the "Homefront Tour - A Ride for a Cure," and set a goal of raising \$250,000 over five years with the proceeds going to the Foundation to help find a cure for cancer. Every August for five years, the Buchanans and others biked 140 miles from Manchester, Massachusetts to Harrison, Maine. Their determination resulted in the significant support, involvement and awareness of the many people who supported Jim and Jennifer, and \$350,000 in contributions over the five-years.

Jim and Jennifer continue to work with the Foundation in their fight against cancer. Jim continues to participate as a member of the Foundation's Board of Trustees. Recently, Jennifer represented the Foundation at a Focus meeting which addressed the subject of Neuroblastoma.

*"The 4<sup>th</sup> annual Home Front Tour was more difficult than we could have imagined. A week prior to the ride and almost five years to thre day, our daughter Lindsay relapsed. We were stunned. Words can't describe the feeling. We thought about canceling but felt it was necessary to stay with our commitment to help battle cancer, cancer that attacks kids. After all, a commitment is what changes a promise to reality."*

*Jim Buchanan, Aug-2001*

The Buchanan family, Lindsay and her parents, personify Jim Buchanan's words "**a committment is what changes a promise to reality.**"



**Dr. William H Frackelton** died in Hilton Head on December 4<sup>th</sup> at the age of 91. "Dr. Bill" was one of the original trustees of the William Guy Forbeck Research Foundation, involved in the creation of the Foundation in 1984, and was actively involved for many years, contributing his sincere interest, wisdom, insight into the medical world, and his own brand of humor.

Dr. Frackelton was predeceased by his wife, **Jane McMillan Frackelton**, who died on November 3<sup>rd</sup>. She was the grandmother of William Guy Forbeck. Before retiring to Hilton Head Island, the Frackeltons lived in Milwaukee, Wisconsin, where Dr. Frackelton practised reconstructive surgery.

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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

## 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 write: William Guy Forbeck Research Foundation, 23 Peninsula Drive, Hilton Head Island, South Carolina 29926 or fax: (843) 837-3088 or visit our web site <[www.wgfrf.org](http://www.wgfrf.org)>*