WGFRF.org
William Guy Forbeck Research Foundation

23 Peninsula Drive
Hilton Head Island, South Carolina 29926

WGFRF NEWSLETTER // VOLUME 28 // SPRING 2013

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William Guy Forbeck Research Foundation

FROM THE CHAIRMAN'S DESK

The mission of the William Guy Forbeck Foundation is to promote advances in the field of oncology, particularly pediatric oncology, by shortening the cancer research timetable. This year we need to recognize and express our tremendous gratitude to two individuals who have helped advance this mission, Ed Frick and Terry Irmen.

Ed Frick served as our Chairman from 1989 to 2004. During his tenure, Ed was instrumental in the formation and maturing of this organization as a major player in the global search for the cure. In 2004, Terry took the helm from Ed and continued to strengthen the organization by expanding the focus to include young scientists via the Scholar Retreat, providing funding for pilot research and other educational efforts. While Ed and Terry have decided to focus their attentions on other parts of their lives, we will be forever grateful for their contributions. Their imprints on this organization will be everlasting!

Now, we open a new chapter in our organizational maturity. As your new Chairman, I will continue the work that Ed and Terry began by maintaining the focus on our centerpiece event, the annual forum in Hilton Head, South Carolina. This think tank brings together the brightest scientific minds from across the globe to share and collaborate in a non-competitive, non-threatening, roundtable environment. At the same time, we will continue to look for opportunities that will increase our relevance and secure our position as a major contributor in the world of cancer research.

We have enjoyed a successful history during the past 26 years. It is with much joy and humbleness that I accept the responsibility to lead the Foundation in making significant contributions to find a cure as quickly as possible.

Respectfully,
Luis E. Taveras, PhD
Chairman, Board of Trustees

2012 FINANCIAL REPORT

The accounting firm of Cherry, Bekaert and Holland audits the Foundation's financial records annually. The Foundation has established a sound financial position. Steady income has allowed the Foundation to expand its programs. The Foundation strives to secure its financial future and maintain a platform for strategic growth.

BASIS OF SUPPORT The William Guy Forbeck Research Foundation has a broad base of support. Of major significance to the Foundation are the contributions from individuals, families, and their memorial gifts. A number of corporations and other foundations have also supported the Foundation with contributions, some having very rigorous qualifications for grants. Contributions are tax deductible for federal IRS purposes. The IRS file number is 580063499.

EXPENSES Historically, over 80% of Direct public support or donations goes to scientific activities. Membership information costs include the annual newsletter, member mailings, and the website. Administration expenses have been increasing with expanding programs. The Foundation is currently in a growth phase but will strive to maintain strict funding guidelines.

MISSION

The mission of the William Guy Forbeck Research Foundation is to promote advances in the field of oncology, particularly pediatric oncology, by shortening the cancer research timetable. It is through your generous support that continuing research in the field of childhood cancer can be ensured.

Save the Dates

THE 5TH ANNUAL WGFRF GOLF OUTING

GOLF OUTING
FRIDAY, SEPTEMBER 13TH, 2013

11:00 am Shotgun Start
Lakewood Golf Club
Lake Geneva, Wisconsin
Contact Galen Eckland to register: galen@culture22.com

Denim & Martinis
11th Annual Blue Jean Ball

BLUE JEAN BALL
SATURDAY, SEPTEMBER 14TH, 2013

6:00–10:00 pm
Lake Geneva Country Club
Lake Geneva, Wisconsin
Purchase tickets under About Us/Blue Jean Ball at wgfrf.org

IN THIS ISSUE

IN APPRECIATION

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

My family is 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.

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

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

Sincere Thanks,
Jennifer Forbeck

SCIENTIFIC ADVISORY BOARD

John T. Kemshead, PhD
Chairman, Scientific Advisory Board

This year's meeting in Hilton Head focuses on drug resistance with particular reference to targeted therapies. The need for this meeting suggests that we are not as clever as we think. To explain a little more, conventional therapy for the treatment of cancer usually relies on a combination of surgery, drugs and radiation therapy. Many of the drugs have their origins in history, having been around for decades. One of the clear lessons we have learnt around the use of these drugs is that they need to be used in cocktails that have been refined over the years for different types of tumors. Using these approaches, we have been able to improve the survival rates in many different diseases. However, two main problems remain, there is still a cohort of tumors that do not respond well to the drugs we have available and resistance to the drugs build up over time, making them ineffective. Both of these issues give rise to the search for more specific and more effective drugs for the treatment of cancer.

The previous generation of drugs used in the clinic are considered not specific for the elimination of tumor cells from the body. In essence they kill all dividing cells. The fact that tumor cells tend to divide faster than other cell types makes them effective but as most people know the side effects of these types of drugs are significant.

Over the last sixty years our knowledge of how cells function has increased exponentially. We are able to map out pathways that show how cells control both their metabolism and how we think they divide. The control of cell division and the cells ability to form the different tissues making up our bodies is one of the most intensive areas of study in molecular biology. This has led to us being able to draw up an atlas of cell functionality that is extremely sophisticated. It is like having a road atlas in front of you with main routes (pathways) and alternative pathways (side-roads) being identified at an ever-increasing rate. These complex maps enable scientists to see how tumor cells function in comparison to their normal cellular counterparts. Armed with this information drug companies can develop a road-block to close off the pathways in the cancer cells and therefore eliminate them. This tailored approach to cancer therapy is in its infancy but it is true to say that it has led to a hope that these treatments will be both more effective and less toxic.

So far the results of this approach have been mixed. Some drugs have proved to be highly effective hitting their targets as expected, while others have proven to not work at all. Surprisingly some drugs developed for the treatment of one type of cancer work better on another tumor. However, the same problem seen with the earlier generation of drugs appears to have surfaced, the issue of resistance. Think of the road-block analogy presented above. Our road system is designed so that if one road is blocked it is possible to go around the obstacle and get to your destination. The same thing seems to be possible in cells; there is not just one control pathway for any particular event in the cell but a multitude. If you block one, the cells will find a way around to still carry out their desired function. Perhaps this is not surprising knowing the level of control cells must have to function properly in the body.

How to deal with the issue of drug resistance with the new generation of drugs is the theme of the 2013 meeting. It is an ideal topic for discussion as it brings together scientists working on the cellular pathways and clinicians trying to exploit this information in ever increasingly complex ways. With our ability to sequence the genome becoming less and less costly the ultimate answer may be to sequence the tumor before and during treatment to see how resistance to drugs arises in the cancer cells. This is becoming a reality and will add to our knowledge in ways that a few years ago seemed to be pure science fiction.

IN MEMORIAM

James Barrett
Louis A Boni
Rose Brown
Lindsay Noble Buchanan
Michael E Daly
Dale Dellinger
Harry Strouse Eklof
Robert Evans
Paulina Feit
A George Forbeck
William Guy Forbeck
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William H Frackelton
Joan Gelderman
Pearl Geschke
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Liz Hannon
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Cynthia McKee Hinman
Jack Kammerer
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Richard A Kinzer
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The INRGdb

The Interactive International Neuroblastoma Risk Group (INRG) Database (db)

Excerpt from Progress Report. See website for complete article.

The Forbeck Foundation has been supporting the International Neuroblastoma Research Group (INRG) since the first Forum in 1985 where the Staging System was created. The Foundation has continued to support the INRG through the years updating the classification system and is currently funding the INRG database. Check our website for the complete progress report.

The overall goal of this project is to develop a web-based, Interactive International Neuroblastoma Risk Group database (iINRGdb) that will facilitate international, multi-institutional, interdisciplinary research in childhood neuroblastoma, advance our understanding of the pathogenesis of this neoplasm, and ultimately lead to the development of more effective treatment strategies for children with neuroblastoma. We also foresee that technologies developed and implemented as part of this initiative will be applicable across a wide variety of pediatric and adult malignancies.

2nd Year Progress Report
The database has completely transformed the original, flat-field data structure of the INRG data and has developed a web-based system with technology that enables linkage with other databases. Thirty-four clinical and biologic metrics on over 11,000 patients diagnosed between 1974 and 2002 are included in the iINRGdb. We instantiated the dataset into a PostgreSQL database, and using the Django web framework, created a data model for rapid development of tools and views and built a front-end interface for generating complex queries.

The current status of the iINRGdb is summarized below:

- The database infrastructure has been successfully developed at the University of Chicago.
- The database contains information on the original ~11,000 INRG cohort and an additional 1,705 patients from COG (Children's Oncology Group) diagnosed after 2002.
- We have updated follow-up data on the COG patients included in the original INRG data set and are negotiating with our European and Japanese colleagues regarding updating follow-up data on additional patients included in the iINRGdb.
- Legal concerns regarding privacy laws in the European Union are close to resolution.
- The front-end of the website has been built and is designed to accommodate complex queries.
- We have created a paradigm for statisticians to securely update and add data.
- We have developed a verification system that checks for internal validity and will be able to provide a report of the transaction.
- Our system can initiate queries and accept results in a variety of standards-compliant formats.
- Once the query is performed, the end-user is presented with the number and geographic region of patients who match their search terms and for whom specimens are available.
- The user is finally offered the option of populating a specimen request form to be sent to the INRG.
- A link between iINRGdb and COG Biobank databases has been successfully established.

In summary, we believe we have made significant progress in the development of the iINRGdb and the goals outlined in the original grant. We are now poised to focus on aim 3. With the computational team at the University of Chicago and our partnership with the NCI and other investigators throughout Europe and Japan, we are confident that will be able to successfully link the neuroblastoma phenotype collected by the INRG Task Force with the genomic data generated in laboratories around the world. The iINRGdb resource will be made available to investigators focused on neuroblastoma research. As demonstrated by the references listed above, we already have a strong track record of successful collaboration. Each reference acknowledges the support of the Forbeck Foundation. With the addition of the linked genomic data in the iINRGdb, more complex analyses will be possible. These studies will lead to new knowledge regarding biology of this tumor, and hopefully, will ultimately result in the identification of new therapeutic targets.

This work would not have been possible without the support of the Forbeck Foundation, and we thank you for your dedication.

Sincerely,
Susan L. Cohn, MD
Professor and Director
Clinical Sciences
Department of Pediatrics
Section of Pediatric Hematology/Oncology
University of Chicago

2012 CONFERENCE REPORT ON "TUMOR METABOLISM"

By Drs. Eileen White and Lewis C. Cantley

The focus of the 2012 Fobeck Foundation Forum was on the role of tumor metabolism on oncogenesis. While it has been known for over 50 years that the metabolism of cancer cells is distinct from that of normal cells, the reasons for this have only been emerging recently. Now that we are beginning to understand how and why metabolic pathways are altered in cancer, there is the potential to make use of this knowledge to improve cancer treatment. This is a very exciting and timely topic for the think tank-like meeting as the Forbeck Forum provides.

The revelation provided by Otto Warburg 50 years ago that unlike normal cells cancer cells undergo glycolysis in the presence of oxygen we can now begin to explain. We also now know that the activation of oncogenes and the loss of tumor suppressor genes changes metabolism; that is an important property for converting a normal cell into a cancer cells. Furthermore, mutations in some key metabolic genes predispose to certain types of cancers. These oncogenic metabolic changes are important for providing the building blocks for new cancer cells, meeting energy demands and managing stress. This meeting was to discuss the mechanisms by which this is accomplished and how it can be targeted to improve cancer therapy. Specifically the attendees were asked to discuss: How are transcription factors, chromatin modifications, nucleosome remodeling and DNA methylation involved in control of gene expression? How do chromatin and DNA modifications maintain expression/repression during development? Why does loss of a widespread modification lead to relatively few gene expression changes? Are newly defined mutations in epigenetic machinery responsible for initiation and/or maintenance of cancer? How will we test/incorporate potential new "epigenetic" therapies that take many days or weeks to induce a biological change? What new small molecules/therapies are on the horizon for clinical assessment?

SESSION I was chaired by Lew Cantley and focused on metabolism and tumor growth control.

DR. LEWIS CANTLEY

Beth Israel Deaconess Medical Center

Dr. Lewis Cantley discussed the importance of altered tumor metaoblism in the control of redox balance. Cancer cells have a greater demand for NADPH than most non-cancerous cells because of an increased demand of this reducing potential to combat ROS and to synthesize fatty acids and nucleic acids. A failure to meet this demand can result in cell stasis or cell death. This greater demand for NADPH can be achieved by altering pathways for glucose and glutamine metabolism to increase NADPH production, at the expense of decreased ATP synthesis. The particular way that a cancer cell solves this metabolic problem is dictated by the mutational and epigenic changes that occur during tumor development. He reported how Got1, an enzyme that promotes NADPH production in the cytoplasm, is important for cancer cell growth.

DR. DAVID SABATINI

Whitehead Institute

Dr. David Sabatini discussed mechanisms of growth control by mTOR. mTOR is the target of the immunosuppressive drug rapamycin and the central component of a nutrient- and hormone-sensitive signaling pathway that regulates cell growth and proliferation. This pathway becomes deregulated in many human cancers and has an important role in the control of metabolism and aging. Two distinct mTOR-containing proteins complexes, mTORC1 and mTORC2, that regulate growth through S6K and cell survival through Akt have been identified. How mTOR contributes to tumor growth at the level or organismal metabolism is not understood. Feeding (AL) activates mTOR, and caloric restriction (CR) that inhibits mTOR can have anti-tumor effects. In the intestine, it was found that CR promoted tumor stem cell production whereas CR followed by AL promoted tumor growth.

DR. JOHN BLENIS

Harvard Medical School

Dr. John Blenis discussed how deregulation of the master regulator of cell growth, mTOR, contributes to cancer. Mutations in the TSC1 or TSC2 genes are responsible for causing Tuberous Sclerosis Complex (TSC) and Lymphangioleiomyomatosis (LAM). These mutations lead to the uncontrolled activation mTORC1. Cells with TSC1/2 mutations require increased energy and carbon sources to meet their high metabolic needs for cell growth. To meet this demand, it has been found that activated mTORC1 uses distinct mechanisms to increase glutamine consumption (glutaminolysis) by elevating the expression of glutaminase and the activity of glutamate dehydrogenase. Furthermore, TSC mutant cells sense the increased energy production, and in a positive feedback loop, promote more mTORC1 assembly via an AMP kinase (AMPK)-dependent, and a novel AMPK-independent mechanism. This acquired addiction to glutamine provides a novel therapeutic strategy for treating patients with activated mTORC1. Indeed, by acutely blocking the ability of TSC-mutant cells to use glutamine, cells can be selectively killed with mutations in TSC1 or TSC2 without damaging normal cells. Dr. Blenis anticipates that these studies will lead to the development of "synthetic-lethal" drugs useful in the treatment of cancers with inappropriate regulation of mTORC1. It has been identified that the TTT-RUVBL1/2 complex regulates mTORC1 lysosomal localization and dimerization.

SCHOLAR DR. MOHIT JAIN

Harvard Medical School

Dr. Mohit Jain discussed integrative profiling of cancer cell metabolism. He examined the NCI 60 panel of human cancer cell lines for metabolite consumption and release as a measure of altered nutrient uptake and utilization. Using global LC-MS/MS based profiling of 219 metabolites in spent media, his team quantitatively measured the consumption of nutrients and release of metabolite byproducts across the 60 diverse cancer cell lines. They found that uptake of major nutrients, including glucose

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2012 SCHOLAR AWARD

The Foundation received a number of very qualified applications for the 2012 Forbeck Scholar Award. The Scientific Advisory Board selected four outstanding young scientists to attend the 2012 Forum in Hilton Head to receive this award. The Foundation was pleased to present this year's Scholar Award to Mohit Jain, Kathryn E. Wellen, Julie-Aurore Losman, and Hao Zhu. Visit www.wgfrf.org to learn how to sponsor a scholar.

2012 SCHOLAR AWARDEES

DR. MOHIT JAIN, MD/PhD

Dr. Mohit Jain, MD/PhD, was nominated by Dr. Vamsi K. Mootha, MD, a professor at Harvard Medical School. Mohit completed his MD/PhD at Boston University, during which time he defined a novel role for metabolic enzymes in mediating cellular redox homeostasis. After his prolific graduate career, he pursued residency and fellowship training at Brigham and Women's Hospital. He subsequently joined the Broad Institute-based portion of Dr. Mootha's laboratory, where he has been leading many of the lab's newest efforts in systems metabolism. Mohit has developed a deep interest in the metabolic basis of human disease, and his current work is distinguished by a highly integrative approach. Mohit recently completed his first such study, which is exceptionally innovative. The data from this study is in press now at *Science*. In this paper, Mohit performed an integrated analysis of metabolome flux and gene expression of the NCI60 cell collection. He then sought to identify pathways that are strongly correlated to reported measures of cell proliferation. He discovered an unexpected reliance on mitochondrial glycine metabolism in rapidly proliferating cancer cells, a phenotype that was not observed in rapidly proliferating nontransformed cells. These findings point to glycine consumption and metabolism as a potentially cancer-specific vulnerability. The methodology, the global observations of cancer metabolism, and the specific insights into the role of glycine in proliferation are all novel and of broad interest.

DR. KATHRYN E. WELLEN, PhD

Dr. Kathryn E. Wellen, PhD, was nominated by Dr. M. Celeste Simon, PhD, Scientific Director of the Abramson Family Cancer Research Institute at Howard Hughes Medical Institute. Kathryn recently completed her postdoctoral fellowship in the laboratory of Craig B. Thompson, MD. Kathryn is a new Assistant Investigator in the Abramson Family Cancer Research Institute (AFCRI) and Assistant Professor in the Department of Cancer Biology at the University of Pennsylvania. Her current work focuses on the interaction between cancer cell metabolism and epigenetics. Kathryn's postdoctoral work in the Thompson lab showed that histone acetylation levels can be modulated by nutrient availability through the enzyme ATP-citrate lyase, which produces acetyl-CoA from citrate. She is currently exploring the hypothesis that total histone acetylation might be regulated within tumor cells as consequences of metabolic reprogramming and /or metabolic stress associated with a heterogeneous tumor microenvironment. Changes in nutrient-sensitive histone acetylation could potentially impact a range of chromatin-dependent activities, including gene expression, DNA replication, and DNA damage repair, thus influencing cancer cell survival and proliferation. However, how histone acetylation is regulated in tumors remains poorly understood. Kathryn's work promises to elucidate the links between cancer cell metabolism and epigenetics and the implications of such regulation for tumorigenesis.

DR. JULIE-AURORE LOSMAN, MD/PhD

Dr. Julie-Aurore Losman, MD/PhD, was nominated by Dr. William G. Kaelin, Jr., MD, professor of medicine at Harvard Medical School and associate director of Dana-Farber/Harvard Cancer Center. Julie-Aurore conducted her doctoral studies with Paul Rothman, focusing on Pim kinases and cytokine signaling. After completing her clinical studies, she joined the laboratory of Dr. Gary Gilliland, an expert in the molecular pathogenesis of leukemia. The work of Dr. Kaelin's laboratory involves elucidating the link between oxygen, metabolism, and the control of gene expression. The enzymes induced by low oxygen include enzymes involved in histone methylation and DNA methylation. Dr. Kaelin's laboratory and others showed that the stability of the HIF transcription factor is linked to oxygen availability because the alpha subunit of the HIF heterodimer becomes prolyl hydroxylated when oxygen is present. Julie-Aurore has developed the first robust cell-based assays for monitoring the ability of mutant IDH1, which has recently been discovered in leukemias and brain tumors, as well as 2-HG itself, to transform leukemic cells in vitro. With these assays in hand, she is doing clever, unbiased, genetic screens to identify the enzymes that, when modulated by 2-HG, contribute to IDH mutant leukemias. She contributed to a recent paper of Dr. Karlin's laboratory in *Nature* (Koivunen et al 2011) and her own work is currently being assembled into what should be another high profile manuscript.

DR. HAO ZHU, MD

Dr. Hao Zhu, MD, was nominated by Dr. George Q. Daley, MD/PhD, professor of biological chemistry, molecular pharmacology and pediatrics at Harvard Medical School, and Director of the Stem Cell Transplantation Program at HHMI/Children's Hospital in Boston. Hao is a clinically trained oncologist with a research interest in microRNA regulation of normal and cancer metabolism. In Dr. Daley's lab, Hao has been investigation the function of Lin28, a protein originally described in worms as a regulator of developmental timing, which they have showed is an oncogene by virtue of its ability to inhibit the let-7 family of tumor suppressor microRNA's. While Hao was setting up transgenic mice to investigate Lin28's role in cancer, several genome wide association studies (GWAS) were published linking human height and puberty phenotypes to genetic variants around the LIN28B paralogue. Based on the human genetics, Hao looked for effects on body size and puberty timing in the transgenic mice, and remarkably found that the mice indeed reflected the human phenotypes. These fascination data, published in *Nature Genetics* (Zhu et al, 2010), demonstrate the conservation of Lin28 protein from worms to humans. Hao's work was identified fascination and novel phenomena linking Lin28 to mouse developmental timing and metabolism, and his work is now poised to have a major impact in cancer biology.

and glutamine, were closely mirrored by the release of byproduct metabolites, lactate and glutamate, respectively. Moreover, they found that uptake of the nonessential amino acid glycine as well as expression of the mitochondrial glycine biosynthesis pathway were both strongly correlated with rates of cancer cell proliferation across diverse tumor types. Limiting extracellular glycine availability or silencing of the endogenous mitochondrial glycine biosynthesis pathway selectively impaired rapidly proliferating cancer cells. Stable isotope labeling of substrates and tracer analysis revealed that consumed glycine contributes to de novo nucleotide biosynthesis through direct incorporation into the purine ring in rapidly proliferating cells. Finally, expression of the mitochondrial glycine biosynthesis pathway is associated with increased mortality in multiple cohorts of patients with breast cancer. Increased reliance on glycine metabolism may represent a metabolic vulnerability and allow for selective targeting of rapid cancer cell proliferation.

DR. MATHEW VANDER HEIDEN

MIT

Dr. Mathew Vander Heiden presented the means by which altered metabolism can support cell proliferation. His lab has found that cancer cells can use a variety of carbon sources to support anabolic processes and this is determined by both the cellular environmental context. They determined that glucose and glutamine are the major contributors of biomass. Interestingly, cancer cells can acquire glutamine from mircropinocytosis and catabolism of extracellular protein. Furthermore, how nutrients are metabolized can also impact whether cells can proliferate. The M2 isoform of pyruvate kinase (PK-M2) is selected in cancer cells, at least in part because lower pyruvate kinase activity promotes anabolic metabolism.

SESSION II, Oncogenic Rewiring of Metabolism, was chaired by William G. Kaelin, Jr.

WILLIAM G. KAELIN, JR.

Dana-Farber Cancer Institute

William G. Kaelin, Jr. presented how the 2-oxoglutarate-dependent dioxygenases regulate cell growth. The EglNs belong to a large superfamily of 2-oxoglutarate-dependent dioxygenases, which also includes the JmjC histone demethylases and TET DNA hydroxylases. Inactivating mutations affecting Succinate Dehydrogenase and Fumarate have been identified in certain cancers and cause the accumulation of succinate and fumarate, respectively, which can inhibit 2-oxoglutarate-dependent enzymes in vitro and in vivo. Isocitrate dehydrogenase (IDH) 1 and 2 mutations have recently been identified in brain tumors and leukemias. The corresponding mutants acquire the ability to produce the R enantiomer of 2-hydroxyglutarate, which can also inhibit 2-oxoglutarate-dependent enzymes. His team found, unexpectedly, that an exception to this rule relates to the EglN family. The R-enantiomer, but not the S-enantiomer, activates EglN function leading to decreased HIF activity. Moreover, down-regulation of HIF promotes the transformation of astrocytes and is permissive for transformation of leukemic cells. Data was presented suggesting that R-2HG, but not S-2HG, is sufficient to transform cells and that its effects are reversible.

SCHOLAR JULIE-AURORE LOSMAN

Dana-Farber Cancer Institute

Scholar Julie-Aurore Losman discussed the role of the R-enantiomer of 2-hydroxyglutarate produced by IDH mutant cancers in growth regulation. IDH1 and IDH2 mutants are common in several cancers and cause overproduction of the (R)-enantiomer of 2-hydroxyglutarate [(R)-2-HG]. (R)-2-HG is hypothesized to function as an oncometabolite by inhibiting the activity of diverse α-ketoglutarate-dependent enzymes that regulate the epigenetic landscape of cells, including the TET family of 5-methylcytosine hydroxylases and the jumonji-domain-containing family of histone demethylases. However, it has not been formally proven that (R)-2-HG is sufficient to transform cells or that the putative transforming activity of (R)-2-HG is reversible. To investigate the role of (R)-2-HG in leukemogenesis, her team developed a transformation assay using TF-1 cells, a growth factor-dependent human myeloid leukemia cell line. They found that a canonical IDH1 mutant, IDH1 R132H, is able to promote cytokine-independence and block differentiation of TF-1 cells. Interesting, these effects could be recapitulated by a cell membrane-permeable form of (R)-2-HG, TFMB-(R)-2- HG, but not by TFMB-(S)-2-HG. This is noteworthy as (S)-2-HG is a more potent inhibitor than (R)-2-HG of TET2, an enzyme that has been previously linked to the pathogenesis of IDH mutant leukemias. They found that this paradox relates to the ability of (S)-2-HG, but not (R)-2-HG, to inhibit the EglN prolyl hydroxylases, and found that inhibition of EglN1 is antithetical to transformation by mutant IDH. Furthermore, they found that transformation by TFMB-(R)-2-HG and by IDH1 R132H is reversible upon removal of (R)-2-HG. This suggests that inhibitors that target (R)-2-HG and inhibitors that target EglN1 prolyl-4-hydroxylase activity may have therapeutic efficacy in the treatment of myeloid leukemias that harbor IDH mutations.

DR. CHI VAN DANG

Abramson Cancer Center

Dr. Chi Van Dang discussed how to target Myc-regulated cancer metabolism. The Myc oncogene is involved in many human cancers and encodes a master transcription factor that amplifies the expression of many genes, particularly those involved in ribosome biogenesis and metabolism. Deregulated Myc expression triggers constitutive biosynthesis and biomass accumulation, seemingly rendering cancer cells addicted to nutrients such as glucose and glutamine. Withdrawal of nutrients from Myc overexpressing cells triggers apoptosis, while control cells undergo quiescence. Furthermore, inhibition of glutamine or glucose metabolic enzymes with drug-like molecules could curb tumor progression in vivo. In this regard, targeting cancer metabolism is feasible, but the therapeutic window remains unclear with respect to inhibition of specific metabolic enzymes. Combination therapy with metabolic inhibitors will be necessary to have a clinical impact. Additional therapeutic window opportunity may reside in circadian fluctuation of normal metabolism

versus Myc-mediated disruption of the cellular clock in transformed cells.

SCHOLAR DR. HAO ZHU

Children's Hospital of Boston

Dr. Hao Zhu presented how the Lin28/let-7 pathway regulates growth, metabolism, and carcinogenesis. The let-7 microRNAs (miRNAs) negatively regulate the translation of oncogenes and cell cycle regulators in cancer. The RNA-binding proteins Lin28a and Lin28b (collectively referred to as Lin28s) block the processing of all let-7 members to promote tumor progression and stem cell pluripotency. His team found that activation of either Lin28a or Lin28b promoted an insulin-sensitized state that resisted diet-induced diabetes in inducible transgenic mice, whereas loss of Lin28a or gain of let-7 expression resulted in insulin resistance and impaired glucose uptake. These phenomena occurred in part through let-7-mediated repression of multiple components of the insulin-PI3K-mTOR pathway, including IGF1R, INSR, and IRS2. mTOR inhibition abrogated these Lin28 phenotypes in mice, indicating strong connections between these pathways. let-7 targets were also enriched for genes identified in human diabetes and fasting glucose GWAS. This work establishes the Lin28/let-7 pathway as a regulator of mammalian glucose metabolism and growth and suggests that cancer may utilize Lin28's potent ability to block all let-7s in order to shift the metabolic program toward one that promotes growth in cancer. Future efforts will be focused on exploiting these mechanisms to inhibit tumorigenesis and to enhance tissue repair.

SESSION III, Mechanisms to Control Cancer Metabolism, was chaired by Carol Prives.

DR. CAROL PRIVES

Columbia University

Dr. Carol Prives discussed regulation of mevalonate pathway and other pro-oncogenic genes by mutant and wild-type forms of p53. Whereas wild-type p53 plays many roles in tumor suppression, the common missense mutant forms of p53 that occur frequently in human cancer can promote neoplasia. Her lab is interested in the modes by which such tumor-derived mutant forms of p53 contribute to the malignant phenotype. They reported that some breast cancer cell lines harboring mutant forms of p53 grown in 3D cultures appear less invasive and disordered when their resident p53 is ablated by shRNA. In this setting mutant p53 regulates expression of myriad genes in the mevalonate pathway that results in cholesterol biosynthesis, and this pathway contributes to the malignant appearance of these cells. In breast cancer datasets mutant p53 expression is correlated with increased mevalonate pathway gene expression, and both are correlated with poorer patient survival. Wild-type p53 can actually repress expression of mevalonate pathway genes, in particular HMGCR that encodes the rate-limiting enzyme in cholesterol biosynthesis, and mutant p53 up-regulates the VEGFR and integrin beta 4 genes that play roles in invasion and angiogenesis.

DR. EILEEN WHITE

The Cancer Institute of New Jersey
Rutgers University

Dr. Eileen White discussed the role of catabolism by autophagy in promoting the survival of tumors. Macroautophagy (autophagy hereafter), or cellular self-digestion, degrades and recycles proteins and organelles and is an adaptive stress response that supports cellular metabolism and survival. Oncogenic Ras upregulates basal autophagy, and Ras-transformed cell lines require autophagy to maintain mitochondrial function, survive stress, and efficiently form engrafted tumors. To explore the role of autophagy in initiation and progression of spontaneously occurring Ras-driven tumors, the essential autophagy gene, autophagy-related-7, atg7, was deleted concurrently with K-rasG12D activation in mouse lung in a model of non-small-cell lung cancer (NSCLC). Her team found that deficiency in atg7 did not alter early tumor growth, but it led to accumulation of autophagy substrates and dysfunctional mitochondria and growth arrest with eventual tumor atrophy. Atg7 loss altered tumor fate from adenoma and adenocarcinoma to oncocytoma, a rare, predominantly benign tumor characterized by the dramatic accumulation of defective mitochondria. Thus, lung tumors require autophagy for functional mitochondria, efficient progression to carcinoma, and for tumor maintenance. This suggests that autophagy inhibition may be an approach to lung cancer treatment and that autophagy defects may be a molecular basis for oncocytoma.

DR. JAMES L. MANLEY

Columbia University

Dr. James L. Manley presented how HnRNP proteins contribute to cancer cell metabolism and glioblastoma. HnRNP proteins are overexpressed in many cancers. His lab defined a pathway whereby expression of three of these, hnRNPA1, A2 and PTB, is upregulated by the cMyc, which leads to a switch in splicing of the pyruvate kinase M (PKM) pre-mRNA such that a form of PKM necessary for tumor cell proliferation is made. They defined the complex mechanism by which these hnRNPs bind the PKM pre-mRNA to modulate its mutually exclusive splicing pattern, identified other pathways that can contribute to overexpression of the hnRNPs, and begun to elucidate the role that these proteins play in glioblastoma (GBM). For example, in human GBM patients, expression of these proteins inversely correlates with survival. These hnRNP proteins are significantly overexpressed in GBM, and reducing their expression inhibits GBM cell proliferation and tumor formation. Comparing RNA-seq data they obtained following knockdown of these proteins in U87 GBM cells with known changes in alternative splicing in GBM brain samples, they identified five transcripts, which include PKM, that are direct targets of the hnRNP proteins and relevant to GBM.

DR. HEATHER CHRISTOFK

UCLA

Dr. Heather Christofk discussed how oncogenic viruses alter metabolism. The study of DNA viruses has had enormous impact on identifying cellular networks that are deregulated in cancer. Some well-established cellular hallmarks of DNA virus infection that are also hallmarks of cancer include self-sufficiency in proliferative signaling,

Thanks for everything, especially for the retreats! It was truly useful and rewarding each time. You all worked hard to get us great mentors and make our time together super productive. Each project I presented at the retreat resulted in a grant—so that was literally rewarding, but the other, more intangible rewards included the connections and re-connections with folks like Peggy Goodell and Mike Caligiuiri who continue to mentor from afar—the generosity and thoughtfulness of mentors like Inder Verma who recommended I connect with my now local mentor, Al Baldwin unwittingly made a huge difference for me. No other venue allows for the critical, vital interactions made at Forbeck retreats—I am forever grateful, knowing that my work was truly jumpstarted on Lake Geneva!

Thank you to you, your family (your amazing parents) and your extended family/friends who made that possible for me and who continue to help so many like me.

Stefanie Sarantopoulos
University of North Carolina
Chapel Hill, NC

BLUE JEAN BALL TURNS 10! SEPTEMBER 14, 2013

Trustee: Galen Eckland

The Blue Jean Ball continues to grow and again funded the entire Scholar Retreat weekend! Thank you to our loyal supporters for your commitment and to the Retreat scientists for your participation.

The Blue Jean Ball is a unique opportunity for supporters and scientists to directly interact, and we get so many positive comments of mutual admiration as each understands the important role the other plays.

We look forward to seeing you in 2013 at Lake Geneva Country Club on the beautiful shore of Geneva Lake. The Blue Jean Ball goes Rat Pack style with "Denim & Martinis." Enjoy a 3-piece ensemble laying down the music of "Ole Blue Eyes," "Deano," "Sammy," Mel, Tony and more.

Save the Date: September 14 at Lake Geneva Country Club. Event registration and tickets available at the About Us/Blue Jean Ball page at www.wgfrf.org.

SCHOLAR RETREAT GOLF OUTING SEPTEMBER 13, 2013

Trustee: Galen Eckland

How better to start off the weekend than a golf outing at the beautiful Lakewood Golf Club. Mr. Dan McLean continued his dedicated and gracious support of WGFRF by again donating the use of Lakewood Golf Club, allowing WGFRF to maximize its support of cancer research. Thank you, Mr. McLean!

If you have never played Lakewood, you should join fellow WGFRF supporters from Chicago, Milwaukee and Madison for this truly unique experience. Lakewood's staff is terrific, and the view over the lake after the round is just awesome.

Save the Date: September 13th at Lakewood Golf Club in Lake Geneva, Wisconsin. Interested participants can contact Galen at galen@culture22.com.

FORBECK SCHOLAR AWARD

The William Guy Forbeck Research Foundation is pleased to sponsor the "Scholar Award," recognizing promising young scientists working in this field. The Foundation selects outstanding clinicial 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, SC. After receiving this award, scholars are invited to participate in the Scholar Retreat held in Lake Geneva, Wisconsin.

Scholar 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.

FORBECK FOUNDATION SCHOLAR RETREAT

SEPTEMBER 13-15, 2012

Lake Geneva, WI
Chair Report

The 8th annual Scholar Retreat featured presentations by Scholars and Mentors in each of the topics of the four most recent annual forums: the Biology and Treatment of Primary Brain Tumors, Immunotherapy and Breaking Tolerance, Cancer Genomics, and Epigenetics. One extremely heartening theme that was common to all of these sessions was that it was clear that our ability to study human tumors directly has increased vastly. No longer is it necessary to study only models and cells that are remote approximations of patients' own tumors. Now the trip between patient tumor, hypothesis generation and testing in the laboratory, and back to the patient is occurring nearly continuously, a vast improvement in recent years.

This Retreat was fortunate to benefit from the experience of Forbeck stalwart Chuck Sherr (St. Jude's, Memphis) who kicked off the Retreat with a fascinating discussion of why if one particular type of mutation is selected in a cancer cell, another is not, and how this can teach you about the cancer's cell of origin. The Brain Tumor session that followed, chaired by Martine Roussel (St. Jude's, Memphis), was characterized by the type of bedside-to-bench investigation that is providing information so much more rapidly today, even in the challenging disease of glioma.

The Dinner was accompanied by an exciting keynote address by Tom Gajewski (University of Chicago), who shared recent advances in manipulating the immune system to recognize and destroy cancers. He particularly described how a certain type of immune cell, the T cell, can be directed against cancer cells. Most interestingly, his talk was not merely describing immunology theory, but also presented results of testing in patients, some of which showed strikingly encouraging responses. The lesson that came across was that the immune system can be recruited as a powerful ally in the search for durable remissions in even very challenging cancers.

The final day was a combination of Genomics and Epigenetics. Cancer Genomics is the study of the changes in the genetic code of cancer cells. This type of study has been tremendously advanced by the speed and economy of genome sequencing, so that now it is possible to sequence all the DNA in a tumor so efficiently that one can compare sequences among many tumors simultaneously. It is a challenge to manage the huge amount of information produced, but we learned that the payoff is that one can potentially use this information to identify new targets for cancer therapy and perhaps also to individualize cancer therapy based on the tumor's individual genome.

However, the genome does not tell the whole story. For example, the cells of your eyeball, your skin, and your heart have the identical genome but look and function very differently. It is Epigenetics that creates these critical differences. Epigenetics is the study of all the extra chemical marks on the genome that influence how the genetic code is read. If the genome contains the genetic letters, the epigenome provides the punctuation. We heard about modern techniques to read how a cancer cell's entire epigenome differs from that of normal cells and about how these differences might arise. Particularly excitingly, Jay Bradner (Dana-Farber, Boston) told us about how drugs can be developed to alter the epigenome of cancer cells, perhaps forcing them to misread their altered DNA and forget they are cancer cells, with some stunning examples of the effects on tumors. It was made clear that manipulation of the epigenome by drugs is laden with ample, unexploited potential in cancer.

A summary of the content of the presentations does not do justice to the amount of interaction that takes place during a Retreat. The format of the meeting is more conducive to rapid learning and immediate response than the vast majority of cancer meetings elsewhere, and it permits dissemination of ideas in a way not possible at larger meetings. While some of this interaction takes place in the meeting rooms, it continues at the relaxed social events made possible by the organizers, and even after the meeting in collaboration via email. As always, the setting was most conducive to discussing science and the setting most congenial to the scientists themselves, all one could want from a retreat.

Tony Letai, Chair
Dana-Farber, Boston

insensitivity to growth suppressive signaling, and evasion of apoptosis. DNA virus proteins and tumor cell mutations converge upon many of the same molecular networks to mediate these cellular alterations and their mutual goal of limitless propagation. Although less studied, an additional feature shared by both virus-infected cells and cancer cells is altered metabolism. Impressively, the high replication and mutation rate of DNA viruses with minimal genomes has enabled rapid protein evolution and optimization of small viral proteins that hijack critical cellular networks. Adenovirus is a DNA tumor virus that expresses 11 "early" proteins responsible for reprogramming the host cell to propagate the viral genome and proteins. Her group investigated the mechanism by which one small adenoviral early protein hijacks host cell metabolism to enable anabolic processes required for virus replication. Since mechanistic elucidation of adenoviral protein function has proven to be a powerful biochemical strategy for understanding multiple aspects of cancer biology, they have applied this same approach to identify molecular networks relevant to cancer metabolism.

DR. JEFF RATHMELL

Duke University

Dr. Jeff Rathmell discussed how lymphocyte

metabolism is important in immunity and leukemia. Lymphocyte activation leads to a rapid transition from a quiescent state to rapid proliferation and differentiation that is necessary for proper immune function. To support this proliferation and effector function, both T and B cells upregulate glycolytic metabolism and activate a metabolic program strikingly reminiscent of the Warburg metabolism of cancer cells. Ultimately, stimulated CD4 T cells differentiate into functional subsets to promote or suppress inflammatory effector function. His team examined this metabolic reprogramming and found that each subset is metabolically distinct. The effector T cell fates, such as Th1, Th2, Th17, each activate a highly glycolytic program that resembles that of cancer cells. Regulatory T cells (Treg), in contrast, utilize a more oxidative metabolism and utilize lipids as a major fuel. These metabolic distinctions may allow new understanding and approaches to manipulate immunity and cancer cell survival. To directly target T cell metabolic pathways and test how direct metabolic targeting impacts T cell fate in vitro and in vivo, they examined Glut1 regulation and Glut1 conditional knockout animals. Glut1 is a member of the glucose transporter family, of which lymphocytes express several members. Effector and leukemic T cells rely on Glut1, and Glut1 deletion in these cells inhibits cell growth and survival. In contrast, resting T cells and Treg do not appear dependent on Glut1 in vitro or in vivo. These data show that effector and leukemic T cells are highly glucose-dependent and provide a means to begin to understand how cells respond to metabolic stress to initiate apoptosis. Targeting glucose uptake and metabolism may, therefore, provide a means to target both inflammatory T cells and cancer cells.

SCHOLAR DR. KATHRYN E. WELLEN

University of Pennsylania

Dr. Kathryn E. Wellen discussed how acetylation is a key link between cellular metabolism and the epigenome. Cancer cells are characterized by major alterations in both cellular metabolism and epigenetic profiles. Current understanding of links between metabolism and chromatin in the context of cancer is currently very limited. Her group demonstrated that acetylation of histones is sensitive to glucose availability through the enzyme ATP-citrate lyase (ACL), which produces acetyl-CoA from citrate. While this is likely to impact chromatin-dependent process such as transcription, the molecular mechanisms and functional significance of metabolic regulation of histone acetylation are poorly understood. Histone acetylation levels are frequently altered in tumors, and strategies targeting acetylation show promise in cancer therapy. Hence, if histone modifications are altered in response to metabolic changes, this is likely to impact tumorigenesis.

The hurricane affected many of the 2012 Forum participants travel to the meeting and more importantly their labs. We greatly appreciate everyone's efforts to participate and wish them the best.

WGFRF is committed to expanding its existing cancer-focused initiatives, as well as building on these accomplishments to implement new programs that are specifically focused on advancing neuroblastoma research. This will be spearheaded by creating a Consortium of Neuroblastoma Foundations to facilitate collaboration between these groups around their common goals and will extend to developing strategies for supporting further collaborations between neuroblastoma researchers, strategically funding neuroblastoma research where it is most needed, and engaging industry and federal funding agencies in the search for effective treatments for neuroblastoma.

2013: RESISTANCE MECHANISMS NOVEMBER 7–10

Joan Brugge
Harvard Medical School
Boston, MA

Jeffrey Engelman
Massachusetts General Hospital
Boston, MA

Cancer therapies that specifically target the genetic alterations associated with subsets of advanced cancers have shown impressive success in the clinic. Examples include ABL inhibitors for chronic myelogenous leukemia, RAF inhibitors for BRAF mutant melanomas, EGFR inhibitors for EGFR mutant lung cancers, and HER2 inhibitors for HER2 amplified breast cancers. In each of these cancer paradigms, the treatments are often highly effective, leading to remarkable remissions that have a profound beneficial impact on patients. These successes have changed the landscape of the diagnosis and treatment of cancer for the foreseeable future.

Despite such remarkable successes, initially sensitive cancers ultimately become resistant to targeted therapies, usually within one year. This type of resistance, often termed acquired resistance, has been the major obstacle preventing initially effective targeted therapies from providing a more lasting and transformative impact on patients. Over the past several years, the scientific community has intensely investigated how cancers develop resistance to targeted therapies. These studies have identified several mechanisms and conceptual frameworks underlying the acquisition of resistance. Many cancers become resistant via secondary mutations in the drug target that abrogate the capacity of the drug to inhibit the target. For example, about half of the EGFR mutant lung cancers that become resistant to EGFR inhibitors develop a specific mutation, T790M, that renders the EGFR inhibitor ineffective. In addition to mutations in the drug target, other mechanisms of resistance have been identified. These include the development of new signaling pathways that bypass the need for continued output from original drug target. Resistance can also emerge when inhibition of the drug target leads to the de-repression of negative feedback signaling loops, leading to activation of survival signals. Less well-established mechanisms of resistance include acquired defects in cellular growth arrest and apoptosis as well as alterations in drug pharmacokinetics.

In addition to the challenges of overcoming a specific mechanism of resistance, there are additional obstacles in overcoming resistance in a patient. For example, accumulating data indicate that different mechanisms of resistance can develop in distinct populations of cancer cells in a single patient. To have a profound effect on overcoming resistance to cancer, there will be an increasing need to monitor and mathematically model the emergence of different populations of cancer cells with distinct resistance mechanisms and to utilize multi-drug cocktails to eliminate the emergence of resistance.

The 2013 Forum to be led by Dr. Joan Brugge of Harvard Medical School and Dr. Jeffrey Engelman of Massachusetts General Hospital and Harvard Medical School will provide an opportunity to discuss the current state of the biology of resistance and how we can apply this knowledge to develop new therapeutic approaches for cancer patients.

WGFRF Spearheads a Groundbreaking Initiative:

The Consortium of Neuroblastoma Foundations

Since its founding in 1985, WGFRF has supported initiatives to stimulate communication between cancer scientists and clinicians, in the recognition that nurturing these partnerships accelerates research progress. Though many foundations do this today, WGFRF was a pioneer in adopting this approach in the 1980's, and its success is evident from the annual Forbeck Forum and Scholar Retreat.

While these programs focus broadly on cancer, WGFRF also maintains a specific commitment to neuroblastoma, the pediatric cancer that claimed the life of Billy Guy Forbeck for whom the foundation was named. In the mid-1980's, WGFRF convened the neuroblastoma medical community to create the first International Neuroblastoma Staging System (INSS), which then evolved into the International Neuroblastoma Risk Group (INRG), the measures used to diagnose and evaluate neuroblastoma. Today, WGFRF funds the INRG Database, a neuroblastoma patient registry at the University of Chicago. These resources are vital drivers of neuroblastoma research and clinical care around the world.

In 2012, WGFRF applied these two areas of interest—neuroblastoma and nurturing collaboration—to the neuroblastoma foundation world, by spearheading the Consortium of Neuroblastoma Foundations. WGFRF took this step after its global analysis of neuroblastoma research to identify "gaps" in need of attention that may be slowing research progress. One of the outcomes of the resulting Neuroblastoma Research Landscape* was the finding that collectively, foundations are major funders of neuroblastoma research. During the period 2008 to 2012, foundations committed around $35 million to neuroblastoma research—about 50% of the amount committed by the National Institutes of Health in the same period. Therefore, although each foundation may support only a little research, together they are potentially powerful players in the neuroblastoma arena.

The Neuroblastoma Research Landscape identified over 50 foundations of various sizes whose mission is fully or partly focused on neuroblastoma. There are past and current examples of neuroblastoma collaborations between two or more foundations, but no effort has connected neuroblastoma foundations globally. WGFRF surveyed the 50+ foundations identified to ask if there would be interest in such an initiative. A number of positive responses were received, and the Consortium of Neuroblastoma Foundations was born. The Consortium has met by phone every 3 months since September 2012, has drafted an Operations Plan and commenced development of a website (www.neuroblastomaconsortium.org).

The Consortium aims to serve three populations—families, foundations, and medical researchers—by providing an online platform for sharing neuroblastoma resources that have been created by member organizations. By centralizing existing information from different foundations, rather than "reinventing the wheel", the Consortium hopes to create a streamlined resource in a near term timeframe. Consortium subcommittees currently guide the growth of each area. As the Consortium evolves a Scientific & Medical Advisory Board will be created.

Current Consortium participants include Bear Necessities Pediatric Cancer Foundation, Children's Neuroblastoma Cancer Foundation, Just-In-Time Neuroblastoma Foundation, St. Baldrick's Foundation, Soupy for Loopy Foundation, TeamConnor Childhood Cancer Foundation (United States); The James Fund for Neuroblastoma Research (Canada); Neuroblastoma Society (United Kingdom); and Villa Joep (The Netherlands). A number of other foundations have expressed interest, and we expect the number to grow as the Consortium takes shape.

As the Consortium is evolving, the membership process has not yet been formalized but will include member dues to support Consortium management services, though grant support will also be sought to defray these costs. For the time being, WGFRF is playing the critical role of serving as the fiscal sponsor of the Consortium as it develops and becomes established.

The Consortium should not in any way detract from the individual programs or initiatives of member foundations; indeed, the goal is to promote these and increase their success. However, it is anticipated that as the Consortium evolves, "gaps" will be identified that could be filled by collaborative ventures set up between member foundations. It is hoped the Consortium will be an exciting opportunity for all members to grow, learn and benefit from each other and, most importantly, to better serve those affected by neuroblastoma.

Perhaps the most significant accomplishment to date is that the Consortium has been recognized by the Advances in Neuroblastoma Research Association (ANRA), the leading professional neuroblastoma association. The Consortium has been approved by ANRA to participate in the next ANR International Meeting in May 2014 in Cologne, Germany. The Consortium will hold a one-day meeting prior to the main ANR conference, and it is anticipated to be an exciting opportunity to share the Consortium's goals and—by then—accomplishments with the international neuroblastoma community.

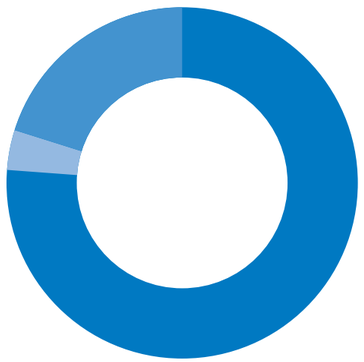
** The Neuroblastoma Research Landscape is available in full at www.wgfrf.org.*

despite its pediatric clinical significance, there is almost no neuroblastoma activity in the pharmaceutical and biotechnology sector. This is likely due in part to the small number of patients affected and the challenges of conducting clinical trials in children. Although 50% of cancers diagnosed in infants are neuroblastoma, only 11% (6/53) of children's cancer medicines in development today are for neuroblastoma.

Who Funds Neuroblastoma Research?

The Neuroblastoma Research Landscape collated information on neuroblastoma research funding from 2002 to 2011. A total of **$161,403,038** in research funded was identified from government agencies and foundations.

NEUROBLASTOMA RESEARCH FUNDING



The National Institutes of Health (NIH) has funded $123 Million in neuroblastoma research since 2002. The NIH has no proactive "master plan" for neuroblastoma; this funding is issued in response to grant applications. The NIH is the leading source of medical research funding in the United States and largest funder of medical research in the United States, and it has an annual budget of over $30 billion. NIH is responsible for funding many diseases; however, considering neuroblastoma is responsible for 50% of pediatric cancers, $12 million year is a modest sum.

The Department of Defense has funded $6 million in neuroblastoma research since 2002. Many rare diseases have benefited from Department of Defense research support through Congressionally-Directed Medical Research Programs (CDMRPs), which develop through lobbying efforts driven by affected families. Neuroblastoma does not have a dedicated CDMRP but has been the beneficiary of grants through other CDMRPs.

Medical research foundations fund $32 million in neuroblastoma research since 2007. Over 50 foundations were identified whose mission is solely or partly neuroblastoma, ranging from small, family foundations to large entities. The majority of this funding comes from six foundations, with some infrastructure, committing $1.5 million to $7 million. The remainder came from over 30 groups: small and family-run with no real infrastructure. As much information on funding as possible was collected, but data could only be located as far back as 2007 (5 years). Some private foundations do not make their funding information readily accessible. It is likely this amount is much higher. A significant amount of foundation funding is directed to clinical trials or high risk research targeted at finding treatments in the near term.

Recommendations to Accelerate the Identification of Effective Treatments for Neuroblastoma

These five actions were identified from the Neuroblastoma Research Landscape and have the potential to accelerate neuroblastoma research. They also leverage WGFRF's strengths of driving collaboration and communication.

1. Establish a Neuroblastoma Consortium of Foundations. There have been past efforts for neuroblastoma-focused foundations to collaborate on funding research. However, there has been no overarching effort to provide a platform where these foundations could share working models and best practices, learn from each other and cooperate with their collective financial and social heft to accelerate neuroblastoma research. WGFRF is creating such a Consortium and inviting all other foundations with an interest in neuroblastoma to participate.

2. Facilitate Communication Between Neuroblastoma Clinicians and Researchers. This would build on the momentum created by the biennial Advances in Neuroblastoma Research workshop and can include a series of workshops focused on specific areas of neuroblastoma. It is particularly important to stimulate discussion and collaboration between preclinical researchers and clinical trials groups.

3. Engage the Biotechnology and Pharmaceutical Sectors in Neuroblastoma. Past efforts to engage industry in neuroblastoma have not been very successful. However, with the formation of the Consortium of Neuroblastoma Foundations, there is an opportunity to use the collective patient representation, trusted relationships to researchers and fundraising ability to educate and engage industry in advancing the path to effective treatments for neuroblastoma.

4. Funding Neuroblastoma Research in Areas of Need. The Consortium of Neuroblastoma Foundations will provide an opportunity for foundations to co-fund strategic areas of research that might significantly advance neuroblastoma research. This may include pilot funding of preclinical drug testing; funding research grants for young scientists in neuroblastoma; funding studies to utilize the INRG database; or funding "grand challenges" to stimulate new thinking in neuroblastoma research.

5. Engage the National Institutes of Health and advocate for federal funding of neuroblastoma research. The NIH is the largest funder of medical research in the United States but has not heavily engaged in neuroblastoma research. It is important to strategically engage NIH institutes in our goals by educating them on the state of neuroblastoma research and our efforts to establish a Consortium of Neuroblastoma Foundations. NIH should be apprised of the areas of neuroblastoma research in greatest need of greatest support so that neuroblastoma researchers can be alerted to appropriate funding opportunities and research resources.

2014: INVASION AND METASTASIS NOVEMBER 6–9

Ann Chambers, PhD
University of Western Ontario
London, ON Canada

Zena Werb, PhD
University of California
San Francisco, CA

Most cancer deaths are due to metastasis—the spread of cancer from its site of origin to distant, vital organs and the physiological damage caused by tumor growth in those organs. While the broad outlines of the process of metastatic spread are known, much of the details of the process remain poorly understood. To continue to improve cancer survival rates, we must face and tackle the problems inherent to metastatic disease. Cancers that are detected early, before they are believed to have spread to other organs, are generally treated with more success than cancers that are metastatic at diagnosis. However, even cancers that are detected early will recur in some patients, but our ability to predict which individuals will have recurrences is limited. Thus, adjuvant therapy is often given to patients with early stage disease who are believed as a group to be at risk for recurrence, leading to over-treatment of some patients to benefit a subset of them. Some recurrences can occur years or even decades after apparently successful primary treatment, and research on tumor dormancy is providing insights into these delayed recurrences.

Progress has been made in the basic biology of tumor invasion and metastasis and in understanding some of the complexities of interactions of tumor cells with host cells in their microenvironment. Great advances have been made for many cancers in terms of molecular markers/subtypes that are associated with favorable vs. poor outcome, as well as prediction of response to a growing list of molecularly targeted agents. However, we also recognize that tumors are not static entities but instead evolve and change over time, and information from a primary tumor specimen may poorly characterize individual metastases that occur years later. Bioinformatic analyses of tumors and their metastases, over time, are providing a wealth of data to be interpreted. New models are being developed to address problems in metastasis.

The challenge is to learn how to harness this growing body of information to help patients with cancer. Can we prevent metastasis? Can we delay appearance of metastases following primary treatment, either through information inherent to the primary tumor or through life style or anti-metastatic chemoprevention strategies? Can we learn how to better treat metastases once they have developed?

The 2014 Forum on Invasion and Metastasis will be chaired by Dr. Ann Chambers of the University of Western Ontario in Canada and Dr. Zena Werb from the University of California San Francisco. The goal is to bring together leaders from multiple disciplines to help understand current progress and discuss ways forward to translate this information for the clinic to prevent deaths from metastasis.

A Legacy of Collaboration, a Future of Partnership:

Strategies to Advance Neuroblastoma Research

About the William Guy Forbeck Research Foundation

The William Guy Forbeck Research Foundation (WGFRF) was established by in 1985 by George and Jennifer Forbeck in honor of their young son, Billy Guy, who had succumbed to neuroblastoma, a childhood cancer for which there is no effective treatment. During Billy Guy's clinical treatments, the Forbecks were deeply impressed by the collaboration they saw between their son's doctors, sharing ideas as they sought new treatments for this devastating cancer. WGFRF was founded with an overarching goal to facilitate the collaborations between cancer researchers that are so important in advancing progress toward finding cancer treatments.

The cornerstone program of WGFRF is the annual Forbeck Forum, a high-level "think tank" that brings together 10–15 top-level scientists and physicians. Each year since 1985, the Forum has addressed an emerging area of cancer research such as stem cells, gene therapy and genomics. The impact of the Forbeck Forum has been far reaching.

Since 1985, WGFRF has played a central role in creating international guidelines for neuroblastoma diagnosis and clinical monitoring through its support of the International Neuroblastoma Staging System and International Neuroblastoma Risk Group (INSS/INRG), a collaboration of physicians and scientists from around the world.

In 2011, WGFRF commenced its support of the INRG Database at the University of Chicago. This is the world's first international neuroblastoma Database. This growing Database is collecting information on neuroblastoma patients from around the world. As neuroblastoma is a rare disease, this Database provides a unique and vital resource for researchers around the world and should hasten the development of effective treatments.

Each year the Forbeck Scholar Awards recognize four promising early-career cancer researchers. Forbeck Scholars convene annually to present their research to fellow Scholars and a mentor team of leading cancer investigators. Scholars are also invited to the Forbeck Forum, an invaluable career networking opportunity. Scholars may also apply for a Forbeck Focus Meeting Award which may be used to fund small workshops focused on key topics in cancer research.

The William Guy Forbeck Foundation: Building On a Legacy of Collaboration

The William Guy Forbeck Research Foundation (WGFRF) has its roots in the founding belief that facilitating collaboration will advance cancer research progress. Since 1985, WGFRF has convened leading cancer researchers at its annual forum, bringing together selected international experts and sparking the connections that stimulate the emergence of new ideas. WGFRF also nurtures the "next generation" by honoring and bringing together the best and brightest young cancer-focused physicians and scientists through its annual Scholar Awards and Scholar Retreat programs.

Since its outset, WGFRF has had a special focus on neuroblastoma, the childhood cancer that took the life of Billy Guy Forbeck. The first annual Research Forum in 1985 led to the creation of the International Neuroblastoma Staging System, the first consensus guidelines for neuroblastoma diagnosis. WGFRF has supported the INSS and its successor, the International Neuroblastoma Response Group (INRG), a collaborative in which doctors can compare the efficacy of neuroblastoma treatments among clinics. In 2011, WGFRF funded the INRG Database, the world's first international registry of neuroblastoma patients. Already populated by over 10,000 patient records accessible online by researchers around the world, this database will revolutionize neuroblastoma research.

To better understand the priorities that need to be addressed in neuroblastoma research today, WGFRF developed a "Neuroblastoma Research Landscape". This document reviewed the status of neuroblastoma research, clinical care and clinical trials and identified areas that need to be addressed in neuroblastoma research to accelerate the identification of effective treatments.

WGFRF is now creating a "Consortium of Neuroblastoma Foundations" to harness the strength and maximize the impact of these organizations. A central finding of the Neuroblastoma Research Landscape was that medical research foundations are funding a significant portion of neuroblastoma research. Over 50 medical foundations support neuroblastoma research in the United States. Building on this, WGFRF is creating a "Consortium of Neuroblastoma Foundations" for foundations to share strategies, collaborate, address unmet needs in neuroblastoma research, and ultimately accelerate the identification of effective treatments for neuroblastoma and offer hope to those affected by this cancer.

About Neuroblastoma

Neuroblastoma accounts for 50% of all cases of childhood cancer. A nerve-based cancer, neuroblastoma primarily affects children under age 6; half of all children diagnosed are under age 2; and only 2% of cases are in adults. There are about 650 new cases of neuroblastoma per year in the United States, where it is estimated that a child dies from neuroblastoma every 16 hours.

The majority of cases are not inherited, meaning that neuroblastoma can affect any family.

As a rare disease with many symptoms, it can take a long time for parents to get a firm diagnosis of neuroblastoma for their child. The symptoms are common to other childhood ailments: fever, joint or bone pain, abdominal complaints, weakness or paralysis, and bruises or change in skin color. To add to this, many pediatricians may not have seen a case of neuroblastoma before. Typically the child with neuroblastoma will be also tested first to rule out leukemia, Ewing's Sarcoma, Wilm's Tumor, and rhabdomyosarcoma.

By the time of diagnosis, more than half of children with neuroblastoma will already have a tumor metastasis. This may be in the bone or bone marrow, lymph nodes and liver, lung, brain or skin.

Neuroblastoma can be a very aggressive malignancy. Half of all neuroblastoma diagnoses are classified as high risk. Standard therapy will include chemotherapy, surgery, radiation and a stem cell transplant.

At least 20% will not respond to standard therapy. One third who respond to therapy will then relapse. Today, for these children, there are no guaranteed, effective treatments.

How Can a Discovery Lead to Drug Development, Clinical Trials and Effective Treatments for Neuroblastoma?

The progression of medical research from an initial discovery all the way to the availability of an effective new drug is known as the "bench-to-bedside" pathway. The map below lays out, for neuroblastoma, a simplified version of this pathway.

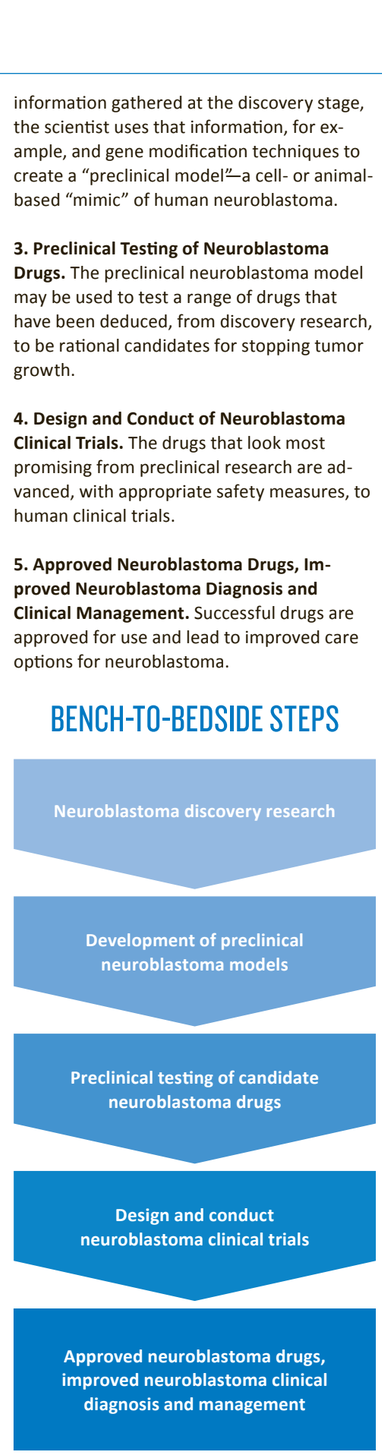
1. Neuroblastoma Discovery Research. A scientist makes a discovery about the biology of neuroblastoma, such as identifying a gene or a molecule that is helping to promote the formation and growth of tumors. These studies can also provide early clues as to what types of drugs might help stop tumor growth.

2. Development of Preclinical Neuroblastoma Models. Using the genetic or molecular information gathered at the discovery stage, the scientist uses that information, for example, and gene modification techniques to create a "preclinical model"—a cell- or animal-based "mimic" of human neuroblastoma.

3. Preclinical Testing of Neuroblastoma Drugs. The preclinical neuroblastoma model may be used to test a range of drugs that have been deduced, from discovery research, to be rational candidates for stopping tumor growth.

4. Design and Conduct of Neuroblastoma Clinical Trials. The drugs that look most promising from preclinical research are advanced, with appropriate safety measures, to human clinical trials.

5. Approved Neuroblastoma Drugs, Improved Neuroblastoma Diagnosis and Clinical Management. Successful drugs are approved for use and lead to improved care options for neuroblastoma.



What Is the Status of Drug Development and Clinical Trials for Neuroblastoma?

There is a well-organized community of neuroblastoma clinical care professionals. Through the support of WGFRF and others, the INSS/INRG has resulted in well-established diagnostic and clinical monitoring guidelines for neuroblastoma. This has also provided a launch platform for improving upon the standard of care therapy and, most recently, for implementing clinical trials of new drugs. An important venue for collaboration is the Advances in Neuroblastoma Research Meeting, a biennial gathering of international neuroblastoma research and clinical leadership.

There are a number of established multi-site clinical trials networks. In North America, these include the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC), the New Approaches to Neuroblastoma Therapies Consortium (NANT), and the Children's Oncology Group (COG); and in Europe, the International Society of Paediatric Oncology European Neuroblastoma Research Network. There is communication between these groups regarding ongoing trials; in fact small NANT trials are a feeder pipeline for larger COG trials.

A number of neuroblastoma clinical trials are underway. In 2012, www.clinicaltrials.gov listed around 60 clinical trials specifically for neuroblastoma. Trial regimes included new combinations of chemotherapy and/or radiation, as well as next-generation molecularly-targeted biologic drugs, such as Avastin (bevacizumab) and Xikori (Crizotinib) that have showed success in treating adult cancers and may also offer promise in neuroblastoma.

There is no pipeline of new drugs specifically for neuroblastoma. Neuroblastoma clinical trials largely use drugs repurposed from adult cancers and other diseases. In addition to this, neuroblastoma preclinical models that are currently used are not optimal; however, others are being developed. This limits the flow of new drug treatment options for clinical trials.

Finding effective treamtents for neuroblastoma is not a priority for industry. One of the greatest challenges in finding effective treatments for neuroblastoma is that,