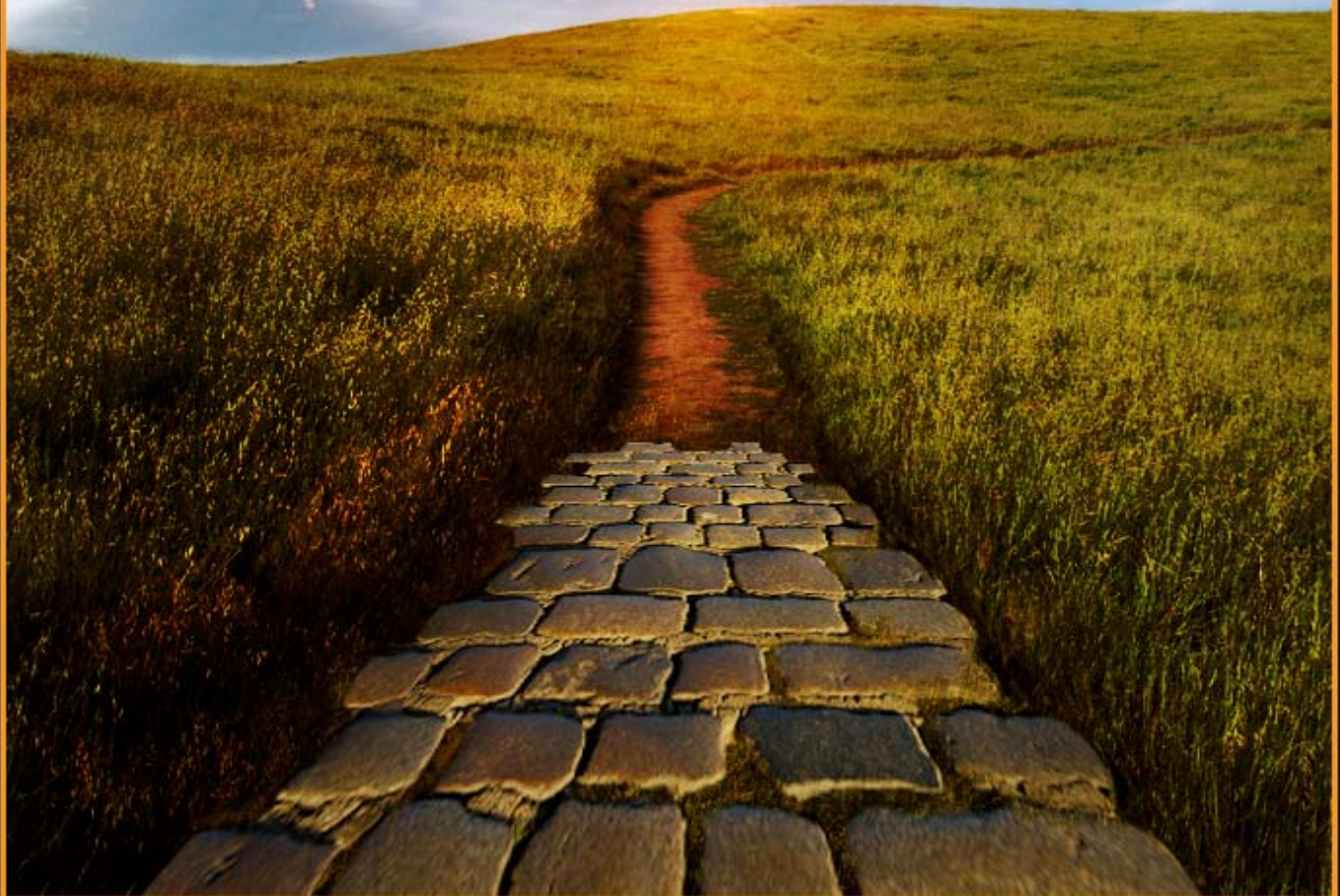


GASTRO INTESTINAL STROMAL TUMOR

PATHWAY

Cure TO A



The Life Raft Group

PATHWAY TO A CURE

Summer 2008

Pathway to a Cure began in 2005 with the planning of an initial five-year strategic plan to find ways to counteract Gleevec-resistance in Gastrointestinal Stromal Tumors (GIST). Many GIST patients who had initially benefited from Gleevec treatment started developing resistance to this single-regimen therapy within a few years. People facing resistance had limited options and time was of the essence. A cure for GIST was not on the horizon nor was there a coordinated research effort in place to find a cure anytime soon. With the traditional research and drug development process taking up to 15 years to produce new therapies, LRG decided to take action. Instead of following traditional rules and handing over money to cancer research, LRG opted to carve out a seat for itself at the research decision-making table and create a partnership with the research community. Discussions took place with key GIST researchers who readily embraced the concepts of collaboration and coordination. *Pathway to a Cure* was born.

Our goals were clear:

- **First, turn GIST from a life-threatening illness into a chronic disease.**
- **Second, find a cure.**

Fast-forward to 2008. The GIST treatment landscape is somewhat different. There is a second line drug — Sutent and a number of other drugs in clinical trials. However, no therapy has yet emerged with the clinical punch of Gleevec. As the race against the drug-resistant clock ticks louder every day, LRG remains steadfast in its commitment to fulfilling its mission of ensuring the survival of GIST patients. Our goals not only remain clear but more importantly, within reach.

LRG's *Pathway to a Cure* is making strides but we cannot reach our goal alone. We invite you to be part of this endeavor so that we can save lives today and create a legacy of hope for all those that will be affected by GIST for generations to come.

Norman J. Scherzer
Executive Director

WHY PATIENT-DRIVEN RESEARCH?

LRG’s cutting-edge research model is representative of a new direction among disease-focused organizations to find cures by becoming actively involved in the research process. LRG is part of a relatively small group of innovative organizations who share a sense of urgency to keep their members alive by identifying new treatment options and ultimately finding cures. FasterCures (<http://www.fastercures.org/programs/train/>), an organization dedicated to overcoming the barriers to finding cures, brings together organizations such as the Michael J. Fox Foundation, The Multiple Myeloma Research Foundation and the Cystic Fibrosis Foundation to help organizations realize their goals. All of these organizations have one thing in common — they are all building new research paradigms that will produce better and faster research results for those living with these illnesses. Patients, more than any other group, understand that time is of the essence. Patient-driven organizations like LRG are all motivated to shortening the time from “bench-to-patient” and in funding targeted research that has the highest probability of finding a cure.

BARRIERS TO RESEARCH

Traditionally, most cancer research decisions are made by three key players: the Pharmaceutical Industry, the Researchers and the Government. Each year, billions of dollars are contributed by government, charities and individuals to fund cancer research. In the United States alone, \$116 billion was spent on biomedical research in 2006. What has all this money done to change cancer death rates? Despite significant

sums of money being put into research, cancer death rates over the last 50 years, compared to other diseases, such as heart disease, have hardly changed. Based on 2002 data from the National Cancer Institute, death rates from heart disease between 1950 and 2002 dropped from 586.8 to 240.1 per 100,000 people. During that same time, deaths from cancer were virtually the same as they were in 1950 at 193.9 per 100,000 people. Additionally, if one looks at the success rates for new cancer treatments in 2006 (Figure 1), acclaimed treatments often only extend life by months, not even years. Cures are no where to be found.

If money is not the real reason a cure for cancer has not been discovered then what are the barriers? According to FasterCures “Fierce competition for funds, publications, and patents serves as a disincentive to institutionalized communication and data exchange between basic and clinical researchers and among research institutions (*Entrepreneurs for Cures, 2008, p6*).”

Figure 1: 2006 Cancer Drug Successes

Drug	Improvement	Actual Improvement
Avastin	Doubled Progression Free Survival	5.4 months ⇨ 10.2 months
Sorafenib	44% longer life	7.9 months ⇨ 10.7 months
Radiotherapy	53% longer life	17 weeks ⇨ 29 weeks

SOURCE: Clinical Cancer Advances 2007, A Report from the American Society of Clinical Oncology, Vol. 26, No. 2, 1/10/08

This process lacks any deliberate sense of critical accountability for how research money is actually spent and particularly for what it has accomplished. Even when an individual research grant is followed by a publication it is rarely connected to any overall strategy or to any criteria of success related to significantly improved treatments and survival of cancer patients. Often the publication of the research is the endpoint in and of itself.

LRG'S RESEARCH DESIGN:

Cooperation, Coordination and Accountability are Key Factors

To overcome traditional barriers in research LRG designed a research process with the key components needed for success (Figure 2). **Pathway to a Cure** brought together a core group of the world's best GIST scientists. We challenged them to create a strategy which consisted of specific prioritized projects with the greatest chance of having successful outcomes and to commit to a collaborative rather than a competitive philosophy. We created a grants structure designed to give maximum support to this research effort, including a 10% cap on the administrative overhead versus the traditional 75%. We also asked each of our investigators to assume a cross cutting responsibility for coordinating and reporting on key priority areas. LRG created tissue banks, both for adult and pediatric GIST and provided support to enhance the team's collaborative efforts.

To further ensure success, great pains have been taken to enable collaboration while eliminating redundant research efforts such that team achievements are emphasized. For the past two years our team has been working to find a cure for GIST and based on these results, has mapped out a direction to get us there in the next 3 years.

LRG'S RESEARCH PHILOSOPHY

Imagine

Planning replaces Disorganization
 Cooperation replaces Competition
 Urgency replaces Complacency

Imagine

A Cure for Cancer

Imagine That

View the LRG's "Imagine" Research video at
www.liferaftgroup.org/video_lrg_research.html



PATHWAY TO A CURE PROJECTS

In Phase I (March 2006-June 2008), progress was achieved in identifying novel treatment strategies for GIST by studying GIST surgical specimens, GIST cell lines, and mouse models of GIST. The urgent aims in all these studies was to identify therapies that function synergistically with Gleevec in destroying GIST cells. Each of the priority projects funded by LRG had substantial near-term potential for enabling development of novel GIST therapies. Detailed progress for each of these high-priority projects can be found on the LRG website or in the 2007 Annual Report.

WHAT'S NEW ?



Building on Phase I successes, Phase II will see an expansion into two new areas with the addition of two researchers. Dr. Anette Duensing of the University of Pittsburgh Cancer Institute and Dr. Sebastian Bauer, West German Cancer Center, University of Essen in Germany will round out LRG's GIST Research team for Phase II. Dr. Duensing will be advancing the understanding of apoptosis, or how cancer cells die. Dr. Bauer extends the team's translational



research ability and opens up the potential for testing new compounds and drugs.

PRIORITY PROJECTS

Oncogenic signaling mechanisms as novel therapeutic targets: Identify critical parts of the KIT and PDGFRA signaling pathways that will provide synergistic and/or alternate therapeutic targets in GIST.

KIT/PDGFR Wildtype GISTs: Identify the important pathways in GISTs that do not have KIT or PDGFRA mutations using methods, such as cDNA arrays and proteomics, that examine many genes at once.

Primary Resistance: Identify resistance mechanisms and evaluate effective therapies for GISTs that are resistant to initial Gleevec therapy. These include specific types of KIT or PDGFRA mutations called "activation loop mutants" and GISTs without mutations in KIT or PDGFRA.

Apoptosis: How and why cancer cells die is of critical importance to finding a cure for GIST. Critical studies will evaluate imatinib and apoptosis in stable disease and examine pathways to promote apoptosis to keep patients from progressing.

Stable disease after imatinib: Identify the mechanisms that cause some tumors to remain stable for long periods, but prevent these tumor cells from undergoing cell death, including development of therapeutic strategies for cells that are not actively dividing

(quiescent GIST cells).

Secondary resistance mechanisms & clinical

evaluation: Evaluate new therapies for GISTs that have developed resistance to Gleevec. These crucial studies will be performed using a variety of methods, such as GIST cell cultures and other cells that have been altered to have KIT or PDGFRA mutations.

Kit Degradation: To examine the role of “chaperone” proteins (such as HSP90) that normally protect KIT from being destroyed within the cell, and to evaluate GIST therapies in which these proteins are inhibited, resulting in destruction of KIT.

Mouse Imatinib Sensitive and Resistant Models:

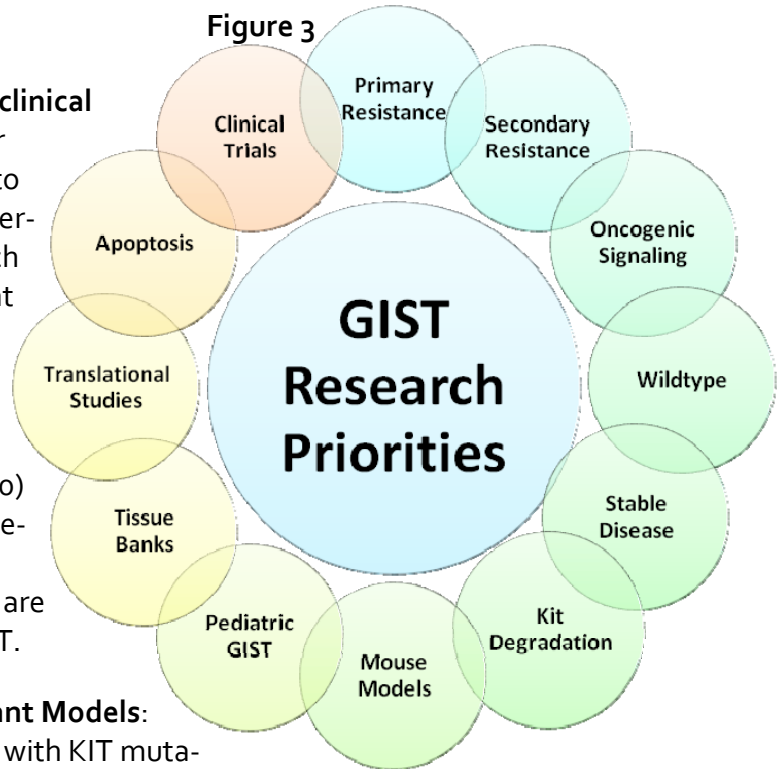
Using mice that have been engineered with KIT mutations, evaluate therapeutic strategies to maximize initial response to Gleevec, as well as the development of resistant mice for the study of therapies for secondary resistance.

Resource Development (imatinib sensitive & resistant): Develop additional GIST research resources (tools) including natural GIST cell lines (Gleevec sensitive and resistant) as well as “engineered” cell lines that have been created in the lab with a variety of KIT or PDGFRA mutations.

Pediatric GIST: Identify the molecular mechanisms and potential drug targets for Pediatric GIST.

Tissue Banks: We are funding two GIST tissue banks. An adult tissue bank is being housed at Stanford University under the supervision of Matt van de Rijn and a Pediatric tissue bank is being housed at Memorial Sloan Kettering under the direction of Cristina Antonescu. Each is responsible for being the point person for the rapid transfer of tissue and data across multiple institutions. New and existing tissue from pediatric GISTs and untreated, stable and progressing adult GISTs will be collected at each tissue bank for analysis and annotation by the various research institutions.

Translational Studies: A key part of bringing treatments to patients is testing compounds and drugs in the lab in preparation for clinical trials.



GIST PATIENT REGISTRY

On a parallel track the LRG continues to expand both the scope and the content of its GIST Patient Registry with medical updates provided by patients. We utilize the data from this registry to identify critical areas not being covered in a timely way by clinical trials or by the traditional cancer research community, including understanding the non-toxic but life altering side effects of cancer drugs and understanding how dosage levels impact survivorship. In the coming year LRG will be conducting a new study examining long-term side effects as well as Gleevec plasma levels. Results from this Patient-based research combined with the Lab-based Research will yield faster breakthroughs that have direct applications to GIST patients (Figure 4).

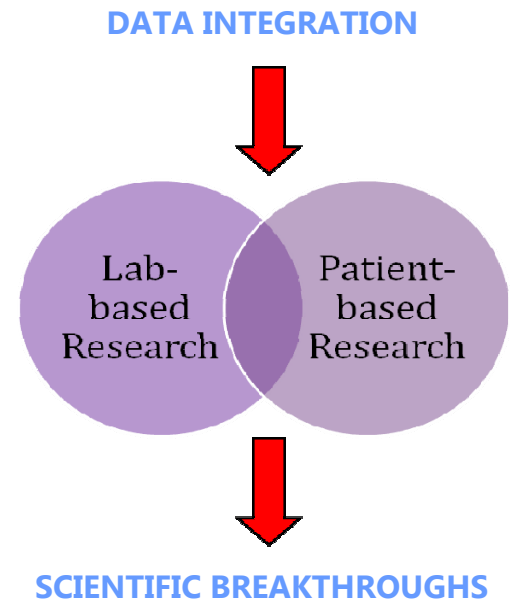


Figure 4

GRANTS INFRASTRUCTURE

To complement this strategic process the LRG has created a supportive grants infrastructure that holds each researcher accountable for specific results, redirects resources when research dead ends and supplements resources when new needs arise.

Phase I (March 2006-June 2008) was allocated two million dollars for direct grants to those researchers best suited to implement our strategic plan. This directed research funding process permits LRG to rapidly address those priority areas that have been determined to give us the best options for accomplishing our objectives.

Phase II (July 2008—June 2010) LRG has awarded another two million dollars to researchers who successfully complete Phase I projects.

Indirect Costs: Indirect costs are capped at 10% for all grants greater than \$50,000 and are completely eliminated for all grants up to \$50,000.

Two-year grants are being awarded but funding is committed for six months, with non-competitive renewals conditioned upon receipt of satisfactory progress reports.

Accelerated funding: In the event that a project completes its yearly project milestone early, the grantee will be permitted to apply for an early start for the next phase.

Supplemental funding: In situations where unexpected costs hinder the successful completion of a priority project we will consider supplemental funding, contingent upon the availability of funds.

COLLABORATION

Telecommunications & Information Sharing: By relying upon meeting by telecommunication, the team can meet on a regular basis to share results and brainstorm new approaches while reducing travel and administrative costs. LRG also maintains a secure website for the Research Team to share data and resources.

Summits: Twice annually the Research Team will gather in person for in-depth meetings to discuss and share results. GIST specialists with complementary expertise may be invited to be part of this collaborative process.

FUTURE PLANS

Data Bank: LRG is working to establish a research data bank for use by the LRG Team.

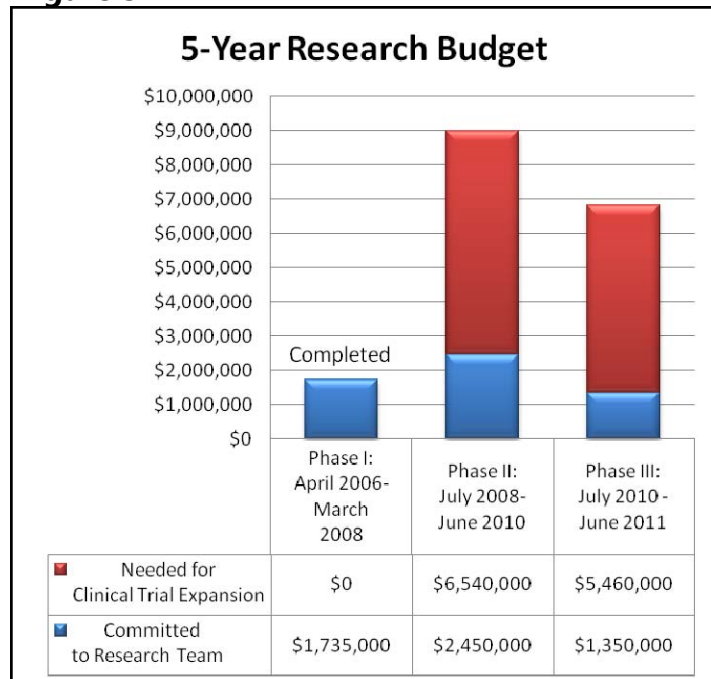
Clinical Trial Consortium: To facilitate new drugs and drug combination testing, LRG plans to coordinate its own clinical trials by 2010.

LRG Funded Clinical Trials: Phase II will include planning for LRG-directed clinical trials. Results from lab-based and patient-based research conducted by LRG will help our team identify new compounds and combinations of compounds that show the most promise in increasing GIST survivability.

FUNDING RESEARCH

LRG has raised over \$6,000,000 (Figure 5) to fund basic research through 2011. However, it has become evident that LRG must take a more proactive role in the identification, testing and marketing of new therapies if we are to accelerate the average drug development process of 15 years. To this end, LRG has initiated a planning process to create a clinical trials consortium by 2010, replicating the model used successfully by a number of other patient-driven organizations such as the Multiple Myeloma Research Foundation (www.mmrc.org) and the Cystic Fibrosis Foundation (www.cff.org).

Figure 5



To reach our goal of finding a cure for GIST we must join together to raise the capital necessary to make **Pathway to a Cure** a reality (see page 15).



Meet The LRG Research Team

Dr. Cristina Antonescu

Memorial Sloan-Kettering Cancer Center



Cristina Antonescu, M.D. is a member of the Memorial Sloan-Kettering Cancer Center's research team. She graduated from the Carol Davila Faculty of Medicine and Pharmacy in Bucharest, Romania. Dr. Antonescu's areas of clinical expertise include bone and soft tissue sarcoma pathology and electron microscopy. She has a strong interest in the field of adult and pediatric GIST research. Her recent contributions included mechanisms of imatinib resistance and pathology of pediatric GIST, as well as many other research projects. Dr. Anonescu is leading the Pediatric GIST Project which includes a tissue bank specifically for pediatric tumors.

Dr. Sebastian Bauer

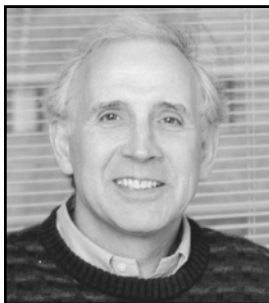
West German Cancer Center, University of Essen, Germany

.Sebastian Bauer, M.D. graduated from the University of Wuerzburg Medical School, Germany and received his medical oncology training at the West German Cancer Center in Essen, Germany. Following a post-doctoral fellowship at Jonathan Fletchers research lab (Brigham & Women's hospital in Boston, MA) he now works as a medical oncologist (sarcoma program) and scientist at the West German Cancer Center in Essen. His research in GIST has focused on evaluation and validation of therapeutically relevant signaling pathways in GIST.



Dr. Peter Besmer

Memorial Sloan-Kettering Cancer Center



Peter Besmer, Dr. sc. nat., born in Winterthur Switzerland, started his education at the Swiss Federal Institute of Technology in Zurich. He completed his studies in Cambridge at the Massachusetts Institute of Technology. Currently, Dr. Besmer is at the Sloan-Kettering Institute in New York. Recently he has focused on identification and characterization of the c-kit gene. An expert with murine models, Dr. Besmer is the group leader for the Oncogenic Signaling Mechanisms Project.

Dr. Christopher Corless

Oregon Health and Science University

After undergraduate studies at the Univ. of California, Berkeley, Dr. Corless received his MD and PhD degrees from Washington University, St. Louis. He did his residency training in Anatomic Pathology at the Brigham & Women's Hospital, Boston, where he also completed fellowship training in GI Pathology and GU Pathology. In 1994, he joined the faculty of Oregon Health & Science University, as an Assistant Professor. He has served as the residency program director in Pathology and is currently medical director of surgical pathology for OHSU Hospital. He is also director of the Cancer Pathology Shared Resource for the Oregon Cancer Institute. In addition to practicing surgical pathology, Dr. Corless has expertise in the application of molecular diagnostics to the classification and prognostication of solid tumors. An author on over 125 publications, he was promoted to Professor of Pathology in 2004. Dr. Corless is lending his expertise as leader of the Primary Resistance Project.



Dr. Maria Debiec-Rychter

Catholic University of Leuven. Belgium

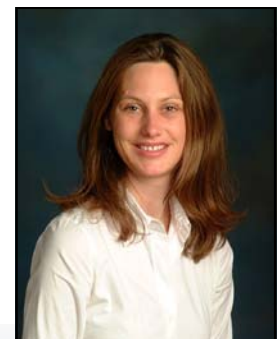
Dr. Maria Debiec-Rychter obtained a M.D. degree (1978) and Ph.D. degree in Somatic Genetics (1986) from the Medical University of Lodz, Poland. She remained at the University of Lodz as an Associate Professor until 1989, when she became a visiting scientist to the Michigan Cancer Foundation, Detroit, MI. Dr. Debiec-Rychter has worked with Wayne State University, Detroit, MI and the Armed Forces Institute of Pathology, Washington, DC. She has been appointed as an Associate Professor at Catholic University of Leuven, Belgium since 1999. Her research interests are related to the cytogenetic and molecular characterization of solid tumors, and cancer related targeted therapy. Currently, she is involved in the studies of the molecular mechanisms of resistance to imatinib in GIST patients. Dr. Debiec-Rychter is leading the Stable Disease Project.



Dr. Anette Duensing

University of Pittsburg Cancer Center

Dr. Anette Duensing studied medicine in Germany and the U.K., and received her M.D. from the University of Hannover Medical School, Germany. She wrote her dissertation on molecular genetics of liver tumors in the Department of Pathology at the University of Hannover Medical School. Dr. Duensing then completed three years of residency training in



this department, where she participated mainly in the morphological and molecular diagnosis of hematological diseases. In 1999, Dr. Duensing joined Dr. Jonathan Fletcher's laboratory at the Brigham and Women's Hospital in Boston for a post-doctoral fellowship. In the past few years, she has been leading the GIST-related studies in Dr. Fletcher's lab. During that time, most of her research was focused on activated intracellular signaling pathways in GISTs that are triggered by the mutant KIT protein. This research has led to the identification of proteins which might be targeted by new kinase inhibitors as a complement to KIT inhibition. Since 2003, Dr. Duensing is Research Assistant Professor in the Department of Pathology at the University of Pittsburgh Medical School.

Dr. Jonathan Fletcher

Brigham and Women's Hospital



Dr. Fletcher is a medical and pediatric oncologist whose clinical activities are in cancer diagnostics, with a focus on molecular and cytogenetic methods. His laboratory program is studying tyrosine kinase (such as KIT and PDGFRA) mechanisms in sarcomas. He has developed novel methods for rapid profiling of tyrosine kinase activation in frozen human tumors, and these techniques have identified effective therapeutic targets in several types of sarcoma, including GIST. His primary research aims are to identify therapeutic strategies that can synergize with KIT inhibition to cure GIST. Dr. Fletcher is head of the Life Raft Group's Research Team as well as leading the KIT Degradation and Resource Development Projects.

Dr. Michael Heinrich

Oregon Health and Science University

Michael Heinrich is currently a Professor of Medicine at Oregon Health & Science University. He earned his medical degree in 1984 from Johns Hopkins School of Medicine in Baltimore and completed both his residency training and Hematology and Medical Oncology fellowship at OHSU. His primary research interest is in the development of novel tyrosine kinase inhibitors for treatment of human cancers. Dr. Heinrich's research includes both pre-clinical identification of novel molecular targets and testing of new agents in the laboratory and the clinic. Dr. Heinrich is leading the KIT Degradation Project.



Dr. Matthew van de Rijn

Stanford University Medical Center

Matt van de Rijn received his MD and PhD degrees from the University of Amsterdam. Matt van de Rijn received his MD and PhD degrees from the University of Amsterdam in 1986. Subsequently he performed a postdoctoral fellowship in the laboratory of



Dr. Irving Weissman, which was followed by residency training in surgical pathology at Stanford University Medical Center. He next worked as an assistant professor in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania Medical Center in Philadelphia. In 1998 he returned to Stanford and is now an associate professor of pathology. Upon his return to Stanford he started collaborating with the combined laboratories of Drs. Pat Brown and David Botstein and developed an interest in gene microarray analysis as used for gene expression profiling and comparative genomic hybridization. These techniques, combined with the technique of tissue microarrays in which gene array data can be validated by immunohistochemistry and in situ hybridization studies, now form the core of his

laboratory. In his laboratory his work is mainly focused on sarcomas with specific emphasis on leiomyosarcomas and gastrointestinal stromal tumors. His research is translational in nature and is focused on the discovery of new diagnostic markers, the discovery of new tumor subsets with different prognoses and/or different response to various treatments and the identification of new therapeutic targets. Dr. van de Rijn is hosting the Adult Tissue Bank.

Dr. Brian Rubin

The Cleveland Clinic

Brian Rubin graduated from University of California, Berkeley with a BA in Cell Biology in 1983. He spent the next 3 years in the Peace Corps working for the WHO malaria control program in Thailand. He moved on to work as a research technician at Amgen from 1986-1987. He attended the MD/PhD program at Cornell University Medical College from 1987-1995. Dr. Rubin was a resident and fellow at Brigham and Women's Hospital from 1995-2000 where he did focused fellowships in soft tissue pathology with Chris Fletcher and a post-doc in the lab of Jonathan Fletcher working on genomics of sarcomas including GIST. In 2000 he moved to the University of Washington where he spent five and 1/2 years as the Director of Bone and Soft Tissue Pathology. Dr. Rubin is now the director of Soft Tissue Pathology at Cleveland Clinic. He currently shares appointments at Cleveland Clinic in the Department of Molecular Genetics at the Lerner Research Institute and in the Department of Pathology. Dr. Rubin's lab is focused on genomics and proteomics of sarcomas, targeted therapies of sarcomas and developing mouse models of sarcomas.



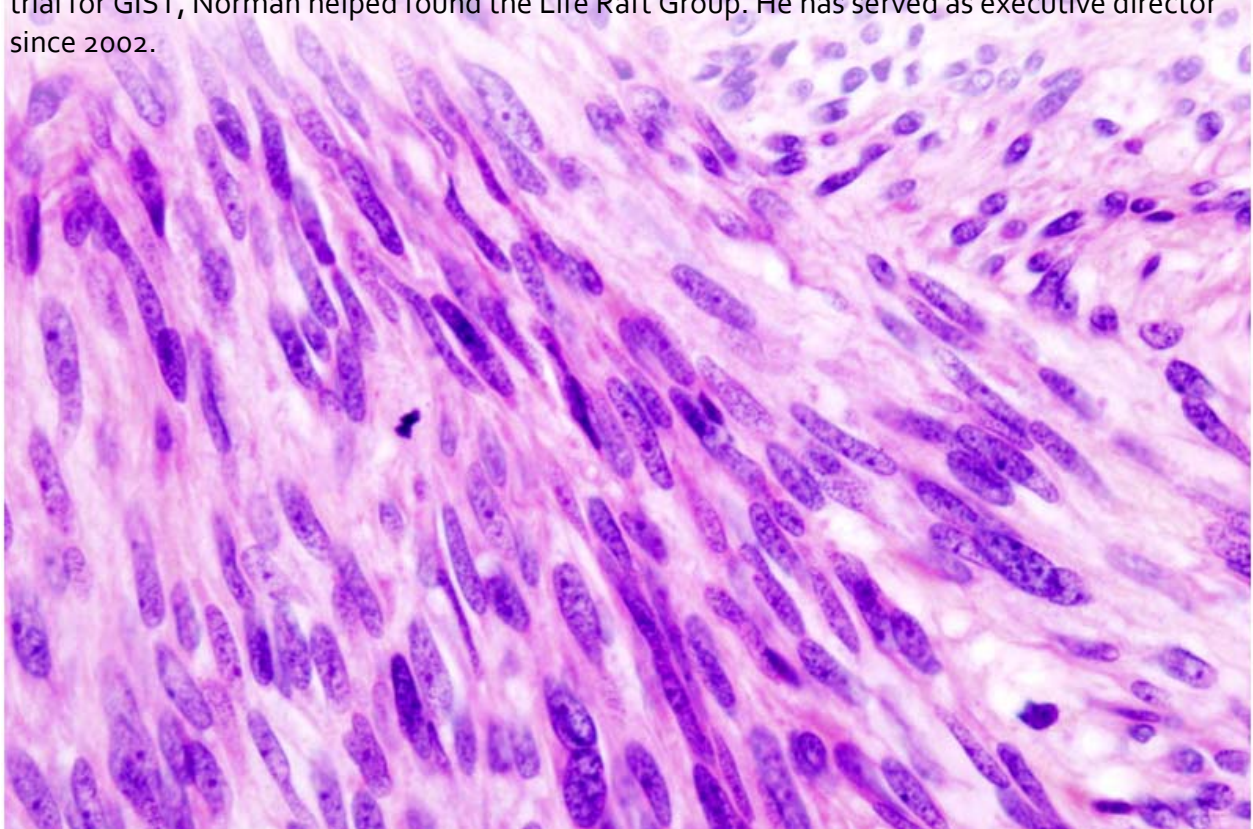
Mr. Norman Scherzer

The Life Raft Group



Norman J. Scherzer is executive director of The Life Raft Group. Norman Scherzer began a career in public health as a disease management specialist for the Centers for Disease Control. He has served as a director of the New York City Department of Health's Sexually Transmitted Disease Program and as a director of the New York City Prison Health Services Program. After serving as the New York Regional Consultant for Disease Control for the United States Public Health Service, Norman went on to become the Assistant Commissioner of Health for New York City where he helped spearhead the city's childhood immunization initiative and its response to the AIDS crisis. Following his formal retirement from public health, Norman became the Chief Executive Officer of Graham-Windham services to families and children, the

oldest non sectarian child care agency in the United States, founded in 1806. Norman then became the President and CEO of a health policy and management consulting firm called 22nd Century Health Concepts, Inc. whose clients included the Harvard University Institute for International Development. When his wife, Anita, a GIST patient entered the first clinical trial for GIST, Norman helped found the Life Raft Group. He has served as executive director since 2002.



GIST cells

INVEST IN A CURE

Donation	Category	Purpose
\$ 1,000,000	Innovator	Develop New Targeted Therapies: Help bring new treatments from the pre-clinical stage through multi-clinical trial phases.
\$ 500,000	Challenger	Adopt a Project: Fund a team of scientists in one of the LRG priority areas
\$ 100,000	Benefactor	Fund a Researcher: Support one researcher for one year
\$ 20,000	Sponsor	Support a Research Summit: Fund a scientific session for the LRG Research Team to further collaboration
\$ 10,000	Collaborator	Build LRG's Science Team website: Supporting web-based meetings and data sharing among GIST researchers
\$ 5,000	Supporter	Strengthen GIST Tissue Banks: Help future research and science by supporting GIST bio-banking projects
\$ 1,000	Sustainer	GIST Patient Registry Expansion: Accelerate analysis of patient-driven data

To make an investment in *Pathway to a Cure* call the Life Raft Group or go to:
www.liferaftgroup.org/donate.html



LIFE RAFT GROUP

Ensuring that no one has to face GIST alone!

**40 Galesi Drive
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**973-837-9092
973-837-9095 (F)**

www.liferaftgroup.org

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