Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

July 2008 | In memory of Joe Trinca | Vol. 9, No. 7

NIH clinic a success: Pediatric GISTers show up en masse!

The Life Raft Group visited the National Institutes for Health (NIH) on June 18 for it's first-ever Pediatric GIST clinic. Care and consultation was provided gratis for each of the 14 patients who attended.

The clinic's program included a roundtable discussion on the future of Pediatric GIST research and an intense review of patients' medical histories and current state of health by experts flown in from all over the country.

The NIH also addressed patient care issues such as pain management, coping and alternative therapies.

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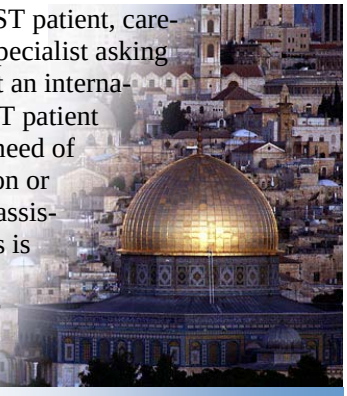
LRG's Israeli efforts win big

By Sara Rothschild
LRG Program Coordinator

The Life Raft Group performs a number of functions to carry out its mission of ensuring that no one has to face GIST alone, but the public might not be aware of the extent to which we assist our international GIST community.

At least once a week, the Life Raft Group receives a phone call or an e-mail from a GIST patient, caregiver, or specialist asking us to assist an international GIST patient who is in need of consultation or treatment assistance. This is the largest part of our advocacy program.



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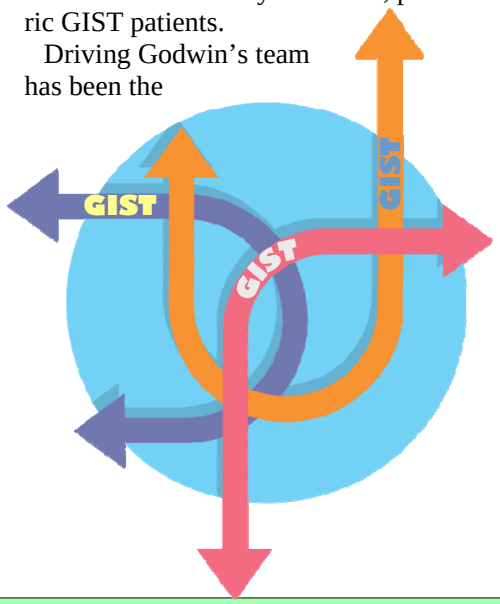
Potential new signal pathway in GIST

By Jim Hughes
LRG Clinical Trials Coordinator

Dr. Andrew Godwin, a researcher at Fox Chase Cancer Center in Philadelphia, Penn., presented data at the 2008 American Society of Clinical Oncology conference (ASCO) indicating that the Insulin-like Growth Factor 1 Receptor (IGF-1R) may have a role in GIST oncogenesis. Up to now, most research has focused on the mutant c-KIT or PDGFRα proteins that have been identified as the initiating pathogenic event in over 80 percent of GIST tumors. However there has always been five to ten percent of GIST that have no mutation and are called "Wild-type". While some of these GISTs have responded to c-KIT inhibitors, it is clear that another mechanism has been involved in their growth. Godwin's research focused on these wild-type tumors, which occur in adults but also mainly in female, pediatric GIST patients.

Driving Godwin's team has been the awareness that wild-type GIST patients have historically had poorer prognosis in GIST trials measuring progression-free survival and overall survival. This observation raised the question of what alternative mechanisms were at work. Since 2003, several research papers have pointed to IGF-1R as a potential research target. It has also been observed that infrequently, GIST patients have experienced disruptions in their glucose metabolism, exhibited by low glucose symptoms, possibly due to insulin-like factors produced in the tumors. Recent publications discussing GIST metabolism, gene profiling and DNA copy analysis have preceded this latest research on IGF-1R in GIST.



IGF-1R is a tyrosine kinase similar to c-KIT but with important differences. Unlike c-KIT, IGF-1R is made up of two

See IGF1R, Page 6

New details for Life Fest 2008 inside! Check out page 9.

New BOD president announced!

By Erin Kristoff
LRG Newsletter Editor

This past month, Stan Bunn, the President of the Life Raft Group Board of Directors stepped down from his position. Secretary-Treasurer for the Board, Jerry Cudzil was voted in as its new president. Bunn will continue to serve on the board as a director.

In his nearly six-year tenure, Stan Bunn solidified himself as one of the board's top fundraisers year after year. He has traveled across the United States and Mexico on behalf of the LRG and the hundreds of patients it represents. Perhaps the largest evidence of the strength of Bunn's character is his commitment to the Life Raft Group after his wife, Ana Maria, lost her struggle with GIST in April 2002. LRG Executive Director, Norman Scherzer says, "For over five years, he has provided time, energy, leadership and inspiration."


BUNN

While the LRG will deeply miss Stan Bunn as president, we are looking forward to Cudzil's term. Like Bunn, Cudzil has also shown to be a top fundraiser. Since joining in 2003, he has hosted a New York City Poker Tournament every year in honor of his father-in-law and GIST patient, Bill Roth. This tournament has proven to be the most successful "single-event" fundraiser in Life Raft Group history.

Also like Bunn, Cudzil has a demanding career and family life and still commits his time to help GIST patients.

The following open letter was written by Jerry Cudzil in response to his appointment.

It is with humility, hope and optimism with which I accept the role of President of the Board of Directors of the Life Raft Group. Over the past six years, the Life Raft Group has accomplished significantly more than most thought possible. We have helped educate the world about a rare form of cancer called Gastrointestinal Stromal Tumor. We have provided patient support, in a myriad of ways, to thousands of patients and caregivers. Among many other things, we more recently helped structure a research effort which is second to none and one that has further enhanced our credibility as an organization worldwide. And most importantly, we remain focused on the main goal of ***survival****. We now have the privilege, ability and responsibility to both enhance our past efforts and forge ahead to the ultimate goal of one day soon finding a cure.*


CUDZIL

I would like to recognize Stan Bunn's efforts as president of the board for the last five years. Stan's tireless efforts— whether mental, emotional or financial— have helped make the organization what it is today. We are fortunate that Stan will play a key role in the organization and the board on a go-forward basis. I am grateful for Stan's efforts thus far and appreciative of his assistance during this time of transition.

I would also like to recognize the indefatigable efforts of the staff and volunteers. I am impressed and encouraged by the team's consistent work ethic. I know if we all put forth that same focus and determination our success will be limited only by our imaginations.

My goal as president will not be to change the Life Raft Group. My goal will be to hopefully positively influence the group even if only in a small way. We lose friends and loved ones too often. With the collaborative efforts of the Board, along with the staff and researchers, I am optimistic about our ability to accomplish all which we set out to accomplish.

The Life Raft Group

Who are we, what do we do?

The Life Raft Group is an international, Internet-based, non-profit organization offering support through education and research to patients with a rare cancer called GIST (gastrointestinal stromal tumor). The Association of Cancer Online Resources provides the group with several listservs that permit members to communicate via secure e-mail. Many members are being successfully treated with an oral cancer drug Gleevec (Glivec outside the U.S.A.). This molecularly targeted therapy represents a new category of drugs known as signal transduction inhibitors and has been described by the scientific community as the medical model for the treatment of cancer. Several new drugs are now in clinical trials.

How to join

GIST patients and their caregivers may apply for membership free of charge at the Life Raft Group's Web site, www.liferaftgroup.org or by contacting our office directly.

Privacy

Privacy is of paramount concern, and we try to err on the side of privacy. We do not send information that might be considered private to anyone outside the group, including medical professionals. However, this newsletter serves as an outreach and is widely distributed. Hence, all articles are edited to maintain the anonymity of members unless they have granted publication of more information.

How to help

Donations to The Life Raft Group, incorporated in New Jersey, U.S.A., as a 501(c)(3) nonprofit organization, are tax deductible in the United States.

Donations, payable to The Life Raft Group, should be mailed to:

The Life Raft Group
40 Galesi Dr., Suite 19
Wayne, NJ 07470

Disclaimer

We are patients and caregivers, not doctors. Information shared is not a substitute for discussion with your doctor. As for the newsletter, every effort to achieve accuracy is made but we are human and errors occur. Please advise the newsletter editor of any errors.

July 2008 international clinical trials

By Jim Hughes
LRG Science Team member

Internationally:

Dasatinib Phase I and LBH589 Phase I: These trials in Japan are no longer recruiting patients.

Imatinib or Sutent Phase III: This trial has expanded to new sites in Hong Kong, Italy, Korea and Spain

In the US:

Imatinib + Bevacizumab Phase III: This is a large phase III trial accruing over 570 GIST patients who have not received any TKI therapy in the US and Canada. Patients are randomized to either daily imatinib alone or daily imatinib plus Bevacizumab administered by IV on day one of a 21 day cycle. Patients enrolled must have histologically confirmed GIST (must be c-KIT positive) and must be metastatic or unresectable. Biopsy is not required. Patients must not have taken imatinib or other agents targeting KIT, PDGFRA or VEGF. The only exception to this rule is prior adjuvant therapy longer than 12 months before trial entry.

Since April this trial has started recruiting at 24 sites in six states. Study chairs are listed as Charles Blanke (now at University of British Colombia in Vancouver), George Demetri at Dana-Farber and Vivien Bramwell at Tom Baker Cancer Center in Calgary, Alberta. Margaret von Mehren at Fox Chase is listed as an investigator. Sponsors include the NCI, The Canadian NCIC, the Southwest Oncology Group and the Cancel and Leukemia Group B.

Imatinib (Glivec) or Sunitinib (Sutent)

Safety and effectiveness of daily dosing with sunitinib or imatinib in patients with GIST

Phase: III
Conditions: GIST
Strategy: Inhibit KIT and/or impede tumor vascularization
NCT#: NCT00372567
Telephone: 1-877-369-9753
Sites: Milano, Italy, 20133
Bologna, Italy
Lai Chi Kok, Kowloon, Hong Kong
Tuen Mun, New Territories, Hong Kong
Seoul, Republic of Korea
Barcelona, Spain

Dasatinib (BMS-354825)

Dasatinib as first-line therapy in treating GIST patients

Phase: II
Conditions: GIST
Strategy: Inhibit KIT
NCT#: NCT00568750
Telephone: 41-21-314-0150
Sites: **Hospitalier Universitaire Vaudois,** Lausanne, Switzerland CH-1011
Michael Montemurro, MD

Imatinib + RAD001 (everolimus)

Treatment with everolimus + imatinib in progressive GIST and imatinib-resistance

Phase: II
Conditions: GIST
Strategy: Inhibit target KIT downstream signaling (mToR)
NCT#: NCT00510354
Telephone: 41-6-1324-1111
Sites: Clinicaltrials.gov lists 9 sites as open in Germany. Use the Novartis number above for specific site information or go to the German Novartis site at www.novartis.de.

LBH589

LBH589 in patients with advanced solid tumors or cutaneous T-Cell lymphoma

Phase: I
Conditions: Tumors
Strategy: Destroy KIT + Inhibit cell cycle + Induce apoptosis (HDAC)
NCT#: NCT00412997
Telephone: +81-3-3797-8748
Sites: Tokyo, Japan

Radiation Therapy as Palliative Treatment of GIST (GIST RT)

Phase: I/1l
Conditions: GIST
Strategy: Kill GIST cells (Radiation)
NCT#: NCT00515931
Telephone: 947173208 Ext. 358
Sites: **Helsinki University Central Hospital**, Helsinki, Finland
heikki.joensuu@hus.fi

Dasatinib (BMS-354825)

Study of dasatinib(BMS-354825) in patients with solid tumors

Phase: I
Conditions: Tumors
Strategy: Inhibit KIT
NCT#: NCT00339144
Contact: **This site is no longer recruiting.**

Glivec + Interleukin 2 (IL2)

Phase I trial in solid tumor and GIST resistant to imatinib and/or sunitinib (IMAIL-2)

Phase: I
Conditions: Solid tumors and GIST
Strategy: Kill GIST cells (Immunotherapy)
Contact: Dr. Nathalie Chaput
nathalie.chaput@igr.fr
Telephone: +33(0)1 42 11 50 05
Sites: **Institute Gustave Roussy,** Villejuif, France

Multi-Bacteria Vaccine

A Phase 1 study of mixed bacteria vaccine in patients with tumors expressing NY-ESO-1 Antigen

Phase: I
Conditions: GIST
Strategy: Immune response attacks tumor
NCT#: NCT00623831
Contact: Antje Neumann,
069 7601 4161
neumann.antje@khnw.de
Sites: **Krankenhaus Nordwest,** Frankfurt, Germany

OSI-930

Dose escalation study of daily oral OSI-930 in patients with advanced solid tumors

Phase: I
Conditions: Solid Tumors/Sarcoma
Strategy: Multiple Targets
NCT#: NCT00513851
Contact: ContactUs@emergingmed.com
Telephone: (877) 601-8601
Sites: **Dept. of Cancer Therapeutics Institute of Cancer Research,** Sutton, Surrey, United Kingdom

XL147

Study of safety and pharmacokinetics of XL147 in adults with solid tumors

Phase: I
Conditions: Cancer
Strategy: Target KIT downstream signaling (PI3-K)
NCT#: NCT00486135
Contact: Gemma Sala
Telephone: +34 93 489 4158
Sites: **Hospital Universitario Vall d'Hebron**, Barcelona, Spain, 08035
Jose Baselga, MD, PhD

Have a technical question about a drug or protocol? Email LRG Science Coordinator, Jerry Call at jcall@liferaftgroup.org

Second phase of LRG "Pathway to a Cure" research program launched

By Marisa Bolognese
LRG Director of Planning & Development

On July 1, 2008, the Life Raft Group will be launching Phase II of its "Pathway to a Cure" research program. Building upon the success of its first two years, LRG's innovative research initiative will be expanding both its scope and its goals.

Pathway to a Cure began in 2006 with the creation of a five-year strategic plan to identify priority projects needed to overcome GIST treatment resistance. The goal was to find a cure for GIST within five years. The LRG brought together a core group of the world's best GIST researchers (Figure 1) and introduced cooperation, coordination and accountability as key building blocks of this historic effort. Additionally, the LRG created a grants structure designed to give maximum support to this research effort, including a ten percent cap on the administrative overhead. We also asked each of our investigators to assume a cross-cutting responsibility for coordinating and reporting on key priority areas. We created tissue banks, both for adult and pediatric GIST to support this research process. Most significantly, after two successful years our plan is beginning to work.

Figure 1

From left to right: Dr. Christopher Corless, Dr. Peter Besmer, Dr. Brian Rubin, Dr. Matt van de Rijn, Dr. Maria Debiec-Rychter, Dr. Michael Heinrich, Dr. Jonathan Fletcher, Dr. Cristina Antonescu

The 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. The LRG is part of a select group of innovative organizations, collectively known as The Redstone Acceleration and Innovative Network (TRAIN), all of whom share a sense of urgency to keep their members alive by identifying new treatment options and ultimately finding cures. The Life Raft Group is working together with FasterCures and other TRAIN organizations such as the Michael J. Fox Foundation, the Multiple Myeloma Research Foundation and the Cystic Fibrosis Foundation to support each other's efforts to produce better and faster research results. The collective goal is to shorten the time from "bench-to-bedside" by funding targeted research that has the highest probability of finding a cure. For in the end it is the patients to whom curing disease is the primary focus and the patient's will needed to see that this goal is achieved.

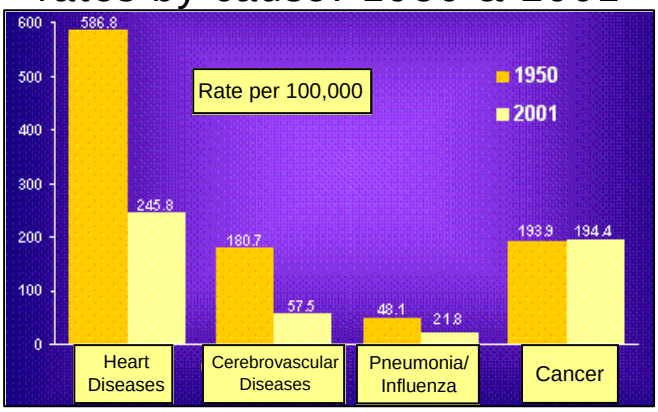
Why the need for innovative research models?

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 dollars was spent on biomedical research in 2006. What has all this money done to change cancer death rates? If you look at cancer death rates compared to other diseases, such as heart disease, over the last 50 years (Figure 2), you can see that there has not been a significant change in cancer deaths.

Why is this?

High on the list of obstacles to finding cancer cures and new treatments is the nature of biomedical research itself. There are three phases in the therapeutic drug discovery pipeline (Figure 3 (Pg. 8)). *First is basic research or discovery*. This is the research carried out by researchers in labs with minimal direct application to treatment in humans. *The second phase is "translational research", which applies the basic biological discoveries to the treatment and prevention of human disease.* It includes steps like the identification of biomarkers, target and pathway validation and testing in animal models. *The third and final phase is clinical research in humans and approval of drugs.* Despite scientific advancements in the discovery phase, the amount of time it takes to

Figure 2: Change in US death rates by cause: 1950 & 2001



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Infinity's IPI-504 completes phase I

By Jim Hughes
LRG Clinical Trials Coordinator

HSP90 inhibitor IPI-504 from Infinity has completed phase I testing at five sites in the United States and Canada.

HSP-90 is a protein that acts as a chaperone for other proteins during cell stress conditions— a condition often found within inflamed and necrotic tumors. IPI-504 acts by maintaining client protein conformation thereby protecting the client protein from the cell's natural housekeeping functions. One of the client proteins protected by HSP-90 is mutant c-KIT in GIST. By inhibiting HSP-90, IPI-504 allows the cell to identify and destroy mutant c-KIT. According to Infinity, the more mutant the client the more effective the HSP-90 inhibition and the greater the opportunity for the cell's self-cleaning process to work. In theory, IPI-504's effect is also mutation-independent.

The phase I trial results reported at the 2008 American Society of Clinical Oncology conference involved 45 heavily pre-treated GIST patients. Over 90 percent had failed both Imatinib and Sutent, while 38 percent had three or more GIST treatments and 20 percent had failed nilotinib. A maximum tolerable dose (MTD) was reached at 400 mg/m2 administered as two IV infusions per week for two weeks with one week off-drug in a three week cycle. The top five most common side effects were fatigue, headache, nausea, diarrhea and muscle pain. In a subset of 22 GIST patients who had FDG/PET to measure initial metabolic response at day 11 of the first cycle there were five partial responses and 15 with stable disease for a 90 percent beneficial metabolic response rate. In another subset of 36 GIST patients with CT scans at six weeks, 70 percent had beneficial response by RECIST criteria (3% partial response 67% stable disease). In the RECIST GIST patient subset, progression-free survival was 12 weeks. The partial response was a 70 percent reduction in a patient pretreated with imatinib and sunitinib, both for one year each. In both response subsets GIST patient dosages varied below and up to the MTD. Overall, approximately 58 percent of the 45 GIST patients were at MTD.

RECIST criteria- uses tumor size to quantitatively define shrinkage or growth of a tumor. These are used in clinical trials to define complete response, partial response, stable disease, and progression of disease.

There are several notable aspects of this trial. These were heavily pre-treated GIST patients with progressive disease— a difficult test. The most common RECIST response was stability with only one partial response. Progression-free survival was lower than historic norms, three months versus 24 months for Gleevec and six months for Sutent. In this regard, dosage ranged below the MTD for over 40 percent of GIST patients. So, eventual response rates and survival numbers may improve. Lastly, this class of drugs may work best when paired with other GIST drugs.

Plans are now underway for a Phase III trial accruing 195 patients at 50 sites in the United States and internationally. We shall be reporting on this trial in our next newsletter.

Joseph Trinca, 58, passes away with family at his side

Joseph Mark Trinca, 58, passed away peacefully in his home with his wife and two daughters at his bedside on Monday, June 16, 2008.

Joe was born on September 26, 1949 in Fulton, Kentucky to Peter Joseph Trinca, M.D. and Mary Jean Stahr Trinca. He grew up in El Dorado, Arkansas and graduated from Cascia Hall in Tulsa, Oklahoma.


TRINCA

Joe attended Hendrix College in Conway, Arkansas, entered the U.S. Army and served in the 101st Airborne Division as a medic during the Vietnam War. After being discharged, he moved to Houston, met his wife, Paula Taliaferro, and married on August 17, 1974.

For many years, Joe worked for Southwestern Bell and AT&T and went on to form his own company, Progressive Communications. He was a member of St. Cecilia Catholic Community and participated in Parish retreats. He was very giving of his time and often volunteered in the community. He enjoyed golfing, hunting, fishing, and travelling. He was devoted to his family and was a loving husband, father, grandfather, and brother.

Joe is survived by his wife of 33 years, Paula Taliaferro Trinca; daughters, Kara Trinca Crumpler and boyfriend, B.J. Edwards, Kimberly Trinca, M.D. and husband, Nicholas Golde; granddaughter, Baileigh Jean Crumpler. He is also survived by his sister, Diane Pieroni and husband, August, brother, Samuel Trinca, D.D.S. and wife, Linda, and many nieces and nephews.

In lieu of usual remembrances, donations in Joe's memory may be made to M.D. Anderson Cancer Center, P.O. Box 4486 Houston, TX 77210. Please designate your gift to the Sarcoma Center.

Reprinted from the El Dorado News-Times

IGF1R

From Page 1

parts: an α part outside the cell and a β part inside the cell. Like c-KIT, two similar configurations must join together to become active (in this case one α+β joins with another α+β). There are two ligands, or proteins, that join the extracellular part of the paired receptors to activate the intra-cellular kinase portion of the pair. The ligands are IGF-1 and IGF-2.

As c-KIT is similar to PDGFRA, IGF-1R is very similar to the insulin receptor (Believe it or not, the insulin receptor does not have an acronym; it is called the "insulin receptor"). A challenge for inhibitor designers is to design a drug that inhibits IGF-1R, but not the insulin receptor. Inhibiting either receptor can disrupt glucose metabolism, so IGF-1R inhibitor clinical trials may have precautions for metabolic side-effects.

Like c-KIT, IGF-1R is involved in cell growth and tumor formation and has been identified as a potential target in a number of cancers. Unlike c-KIT, there is presently no known mutation driving IGF-1R.

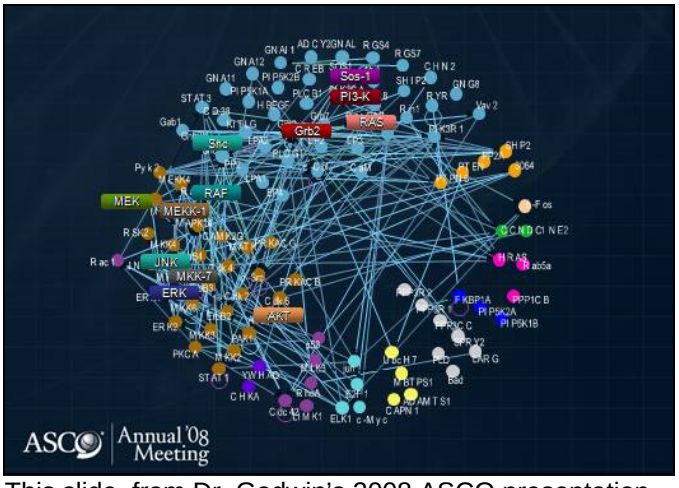
It is important to note that key to the Godwin study was the availability of frozen tumor samples from collaborating researchers and from patients and families.

By comparing "normal" mutant GIST tumors with Wild-type, Dr. Godwin was able to establish significant increased IGF-1R expression in Wild-type GIST by multiple methods:

- Using western blotting whereby tumor cell contents were filtered through a matrix and separated by molecular weight, Wild-type had higher expression of IGF-1R than mutant GIST (10 fold)
- Using immunohistochemical analysis (IHC), in which tumor samples are stained and interpreted by microscopic analysis, Godwin's team found that wild-type GIST scored significantly higher IGF-1R levels among a team of analysts blinded to the mutation status. Blinding removed subjective bias in a test that can be highly subjective.
- Further tumor specimen analysis using mRNA based assays indicated an even higher (80 fold) difference in IGF-1R expression with wild-type GIST— much higher than mutant.
- Using Fluorescent In Situ Hybridization (FISH), whereby snips of DNA designed to match a target sequence are given a fluorescent tag and allowed to mix with tumor sample DNA, Godwin's team found that Wild-type cells had multiple copies of the region that produces IGF-1R, more so than mutant tumor samples. This was further confirmed using Quantitative Polymerase Chain Reaction (qPCR) analysis, whereby regions of test DNA are replicated and compared to determine relative copy number differences. Interestingly, while IGF-1R copy numbers were higher in Wild-type, Godwin also found a high number of copies in mutant GIST indicating a possible area of investigation.

Godwin's team then tested an IGF-1R inhibitor against mutant GIST cell lines. They used a compound from Novartis called NVP-AEW541 (NVP), which is highly specific for IGF-1R. They found that:

- NVP can shut down common GIST signaling pathways downstream from IGF-1R.
- Inhibiting IGF-1R reduces cell growth and causes apoptosis in exon 11 and exon 13 mutant GIST cell lines similar to high concentrations of imatinib.
- There was no synergy observed in combining NVP and imatinib (Synergy has been reported in another more recent paper).
- NVP probably also inhibits other off-target GIST pathways. In his presentation, Godwin pointed out that IGF-1R is involved in a complex of pathways ("a lot more complicated than you actually can imagine"), with major interactions at multiple levels varying between proteins and even cell types.



This slide, from Dr. Godwin's 2008 ASCO presentation, demonstrates the complexity of signaling pathways.

Glossary

Wild-type GIST: refers to the absence of c-KIT and PDGFRα mutations in GIST. The test performed is called genotyping and involves looking at the DNA sequence from paraffin embedded GIST tumor samples. The test looks for changes, deletions, insertions and duplications in the normal sequence of the c-KIT and PDGFRα genes. If the sample shows both wild-type c-KIT and wild-type PDGFR α it is classified as wild-type GIST.

c-KIT positive or negative: Refers to the result of an antibody test performed on paraffin embedded GIST tumor samples that results in a stain or color infused into the sample. The darker and more profuse the stain under the microscope, the more c-KIT protein-present and the more positive the test result will be.

Wild-type GIST tumors can test c-KIT positive due to the over expression of normal c-KIT protein. c-KIT negative GIST tumors can have a mutation in either the c-KIT or the PDGFRα gene and still not express c-KIT. It is recommended that all GIST patients have primary tumors genotyped and especially c-KIT negative patients.

Conclusions:

- IGF-1R is activated in both mutant and wild-type GIST.
- IGF-1R is over expressed in a subset of adult and pediatric wild-type GIST (not in 100%, but in a significant fraction).

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ISRAEL

From Page 1

Since its establishment in 2002, the Life Raft Group has helped patients in over 35 countries—most of them in developing countries in Eastern Europe and the Middle East. Patients approach us primarily because of political and financial barriers that prevent them from obtaining the treatment they need in their country. Until now, the majority of these cases have involved Gleevec. Novartis Pharmaceuticals has helped tremendously in this area by establishing the GIPAP program to assist most of these patients. This program is one of the most comprehensive and far-reaching treatment-access programs ever developed on a global scale. It provides Gleevec free-of-charge to patients in developing countries who meet specific medical and socioeconomic guidelines.

With the growing threat of disease resistance, patients are now approaching us about alternative therapies after failing Gleevec. Unfortunately, since this is a relatively new phenomenon, no other assistance programs have been established to help international GIST patients. In fact, Pfizer pharmaceuticals is currently working on establishing an international Sutent assistance program this year, in conjunction with Axios International.

More information will be available on our website once Sutent's assistance site is officially launched.

A Patient Case in Israel

For the past several years the Life Raft Group has been working with a growing LRG chapter in Israel. One member has frequently been in contact with us due to a number of recurrences resulting in jumps from drug to drug. Last year, his physician prescribed Nexavar, but unfortunately, it was not approved in Israel and was very difficult to access. He was forced to pay $6,000 out of pocket for a month supply.

He reached out to Bayer pharmaceuticals in his country to see if they had an assistance program. Bayer responded that they could supply him with a pack free of charge if he paid for a few packs on his own. Over the course of the year, this man paid approximately $73,000 for nine months supply with a few packs given to him free of charge.

This is not the first time that the Life Raft Group has heard of a case of rationing life-saving drugs to GIST patients. While rationing might seem like a suitable solution for financial reasons, it is our opinion that it is unethical to ration medicines that help sustain someone's life. In the case of this Israeli patient, the LRG appealed to Bayer to change their policy. After six months of exhaustive miscommunication, LRG staff finally reached the right person at Bayer to push this issue to top of their agenda. On June 2, Bayer contacted the Life Raft Group to inform us that the patient is now receiving Nexavar on a compassionate-use basis, which the company has never done before. Because of this case, they are now considering the creation of an international patient assistance program to help patients in need of drugs they cannot afford.

We are happy to report that because of our efforts, we were able to extend the life of a GIST patient as well as pave the way for future GIST patients.

The Life Raft Group would like to thank Bayer pharmaceuticals for their assistance in helping patients access Nexavar.

Global GIST Network

In 2005, as part of our international assistance program, the LRG established the Global GIST Network in collaboration with Gilles Frydman, President of Association of Online Cancer Resources (ACOR) and Markus Wartenburg, Spokesperson for Das Lebenshaus (House of Life). The Global GIST Network was formed to serve as a directory of resources available to GIST patients and their families in their own countries and languages. The focus was to identify the support available in a given country or for a given language ranging from a liaison, e-mail community, organization or website. With the help of this Network, we are able to help save many more patients' lives. If you would like to view the Global GIST Network, visit: www.globalgist.org/.

LRG represents at ASCO 2008!

Life Raft Group staff did more at this year's American Society of Clinical Oncology conference than attend presentations (Special thanks to Jim Hughes and Paula Vettel for taking on that responsibility); they also manned a booth at the Patient Advocacy lounge. The lounge exists to raise awareness and allow groups to disseminate information to the thousands of doctors and pharmaceutical representatives attending.

Those who helped run the booth are Leigh Borland, Doris Dallow (Pictured left to the right of LRG Director of Operations, Tricia McAleer) Sherri Janousky, Pat Johnson, Dick Kinzig and Pam Lewkovich.

Clinical trials webcast: an interactive demo on searching for the latest trials

By Sara Rothschild
LRG Program Coordinator

In 2000, a very effective new drug, STI571 (now known as Gleevec), became available to GIST patients in clinical trials. With no other effective therapy for metastatic disease, nearly two thousand GIST patients entered clinical trials within the next two years. This introduced GIST patients to the world of clinical trials in an unprecedented manner.

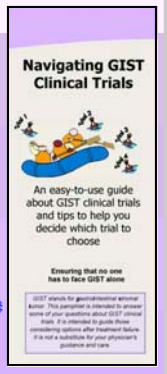
On June 12th, Jim Hughes, the Clinical Trials Coordinator for The Life Raft Group, elucidated our understanding of the different types of clinical trials available for GIST patients. He explored the various characteristics of trials and discussed the decision making process.

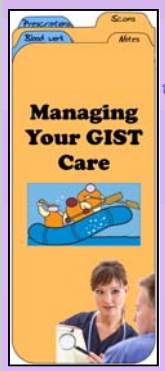
A remarkable interactive demonstration was a part of the webcast, where Jim went into the Clinicaltrials.gov, Cancer.gov, and Life Raft Group websites and showed the various tools available to help patients search trial information more easily. For a patient who may be overwhelmed searching for treatment options, this presentation can help the patient visually learn how to navigate this process at ease.

The latest clinical trial news from ASCO was also covered.

To view the recording, please visit: www.liferaftgroup.org/library_videos.html

Make sure you check out the "Navigating GIST Clinical Trials" pamphlet for tips on how to choose and understand clinical trials.





...And make sure to order or download our new pamphlet, "Managing Your GIST Care", coming out this month.

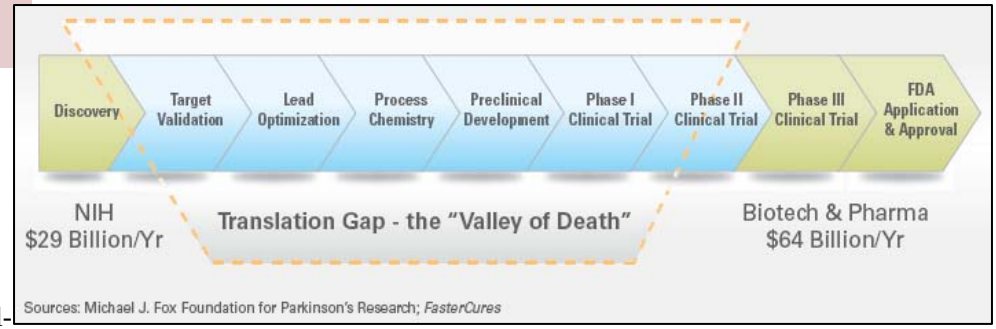
RESEARCH

From Page 2

bring new treatments to market is still ten to 15 years.

Besides the gap in the pipeline process, there are also significant barriers to accelerating patient-relevant outcomes (Figure 3). "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."[1] This process lacks any deliberate sense of critical accountability for how research money was 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. Unfortunately, the publication of the research is often the endpoint in and of itself. As to any sense of urgency in finding and sharing information about more effective cancer treatments, it simply is not consistent with the culture of the cancer research community.

Figure 3: Therapeutic Drug Discovery Pipeline



Based on an analysis of the barriers to finding a cure and because GIST patients are dying faster than new treatments can be developed, the Life Raft Group decided not to follow traditional rules and simply hand over money to cancer centers for GIST research. The LRG decided to carve out a seat for itself at the cancer research decision-making table and create a partnership with the research community. Out of this collaborative process came the LRG's "Pathway to a Cure" and a five-year plan committed to finding ways to counteract Gleevec-resistance in GIST, prevent Gleevec resistance altogether and identify and validate new targeted therapies. Despite remarkable clinical responses to Gleevec, we are increasingly seeing relapses of GIST, even in patients with initial response to Gleevec. Many GIST patients currently benefiting from Gleevec treatment will eventually develop resistance on the single-regimen therapy. We are indeed in a race to find a cure before patients develop resistance.

To accomplish our goal, "priority"

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CLINIC

From Page 1

In the next newsletter issue, we will have more in-depth coverage of the NIH clinic, from two perspectives: that of patient and that of medical professional. Until then, enjoy these snapshots of the event.

(Right) Pediatric GIST patients Nora Winstead and Stefanie Peyk are two of the Life Raft Group members to at-

Around the table from top: Dr. Alberto Pappo, Becky Bensenhaver, Phyllis Gay, Dr. Katherine Janeway, Dr. Constantine Stratakis, Su Young Kim, Dr. George Demetri, Dr. Michael LaQuaglia, Norman J. Scherzer, Dr. Lee Helman and Dr. Cristina Antonescu.

Drs.George Demetri and Michael LaQuaglia discuss Pediatric GIST care.

A sneak peek at the "Managing Your GIST Care" pamphlet, out this month...

Why Manage Your Own Care?

There are a number of reasons why a patient should take an active and managing role in their own care. Medical care is quite complex and mistakes do happen. Furthermore, oncology is a broad field and GIST is a rare disease. You must realize that it is your body and ultimately your decisions to make.

Record Keeping is Essential

It is important that you keep a record of pathology reports and information that you may not be able to remember, such as prior treatment side-effects or trials. This not only helps you keep track of your medical history, but it also helps the various doctors on your healthcare team.

LIFE FEST 2008 UPDATE

We are honored to announce that Jonathan Trent, GIST specialist at MD Anderson Cancer Center in Houston, Texas has accepted the LRG's invitation to speak at Life Fest 2008.

Dr. Trent will give an overview on the basics of GIST and the latest treatment options.

Life Fest will be held at the Hyatt Regency O'Hare in Chicago on **September 12-14**.

Hyatt Regency O'Hare
9300 Bryn Mawr Ave.
Rosemont, IL 60018

- Check out the LRG website at www.liferaftgroup.org/members_ lifefest.html to register online for Life Fest and to view a slideshow of highlights of Life Fest 2006 and pictures from the Hyatt.
- If you want to make hotel reservations, please call the Hyatt at (847) 696-1234 (Website: www.ohare.hyatt.com). Make sure to indicate that you are with the Life Raft Group. The LRG rate is $109 (+tax) per night for single and double occupancy rooms.
- There is still time left to make your opinions for the Life Fest agenda heard on our site. Visit www.liferaftgroup.org/members_lifefest.html and click "Help Us Plan the Agenda" to vote on what you think would be valuable workshops to include.

RESEARCH

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projects were highlighted for immediate funding (Figure 4).

We also decided not to send out a call for research proposals from individual investigators. Instead , the LRG identified a core group of the world's leading GIST cancer researchers whose complementary expertise and combined personalities would permit them to work together synergistically.

We challenged them to create a strategy which consisted of specific prioritized projects with the greatest chance of success to guide GIST cancer research and to commit to a collaborative, rather than a competitive philosophy. Great pains have been taken to enable collaboration while eliminating redundant research efforts, such that team achievements are emphasized. In return, the LRG committed to allocate our research funds to implement that strategy and to support and enhance the team's collaborative efforts.

Phase I results

In Phase I (March 2006-June 2008), LRG research funding has seen progress in identifying novel treatment strategies for GIST by studying new treatment methods in GIST surgical specimens, GIST cell lines, and mouse models of GIST. The urgent aims in all these studies are to identify therapies that function synergistically with Gleevec in destroying GIST cells.

Each of the funded scientists performs GIST research that is coordinated with the efforts of the other scientists in this LRG program in an effort to identify treatment approaches that synergize with Gleevec and other KIT kinase inhibitors in enabling a higher cure rate for patients with GIST.

BAUER

Gleevec-resistance studies are essential to therapeutic progress in GIST. These studies will likely reveal that combinations of GIST therapies are needed to consolidate initial remissions,

Figure 4

forestall the emergence of clinical resistance, and lead to increased cure rates. Each of the priority projects funded by LRG in Phase I have substantial, near-term potential for enabling development of novel GIST therapies. Detailed progress for each of these high-priority projects may be found at www.liferaftgroup.org or in the 2007 Annual Report.

What's new for Phase II

Building on Phase I successes, Phase II will see an expansion into two new areas and the addition of two new 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 the Life Raft Group'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.

DUENSING

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. The Life Raft Group utilizes 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, the LRG will be conducting a new study examining long-term side effects as well as the cutting-edge area of Gleevec plasma levels.

GIST cancer research provides a perfect model for demonstrating how to cure other cancers. GIST is a relatively simple cancer and has an increasingly understood mechanism of cancer mutations. Further, there is a growing list of targeted drugs to address these mutations.

We are approaching a critical intersection on the road to finding a cure for GIST. We have the right scientific tools and the right researchers at the perfect time and place. We have achieved a historic understanding of the fundamental genetics driving GIST and the know-how to identify and overcome the remaining downstream pathways of resistance. We have two approved targeted drugs, Gleevec and Sutent, and a number of other promising ones in the pipelines. This opportunity to complete the "Pathway to a Cure" is unprecedented and well within our grasp. For if we don't find a cure, who will?

References

[1] Entrepreneurs for a Cure: The Critical Need for Innovative Approaches to Disease Research. FasterCures, 2008, p.6

LRG Holiday campaign raises over $180,000!!

The 2007 LRG Holiday campaign raised an unprecedented 180,000 dollars this year for GIST research. Many thanks must go to each and every person who helped us complete the "Pathway to a Cure". A complete list of donors for 2007 can be found in the 2007 Annual Report (Coming to a mailbox near you!) and www.liferaftgroup.org/donations_2007.html.

IGF1R

From Page 6

- Gene amplification or ligand overexpression may be the contributing oncogenic effect.
- Targeting IGF-1R can induce cytotoxicity in mutant GIST cell lines.

Next Steps:

- Godwin's group has developed wild-type cell lines and they are now testing IGF-1R inhibitors currently in clinical trials against these lines.
- Plans are ongoing to develop clinical trials of IGF-1R inhibitors in GIST.
- Godwin's presentation referenced two recent papers on the subject of IGF-1R in GIST.

Dr. Chi Tarn, a member of the Godwin team was lead author on a paper providing details on much of the material in the oral presentation at ASCO (Tarn et al. 8387-92).

A paper by an Italian research team identified the IGF-1 and IGF-2 ligand expression as associated with GIST relapse in a series of 94 tumors. Sample expression levels were rated as "Absent", "Moderate" and "Strong". They found that 80 percent of tumors express one or the other ligand. There was significant correlation with high mitotic index, larger size, higher risk, metastatic disease and relapse. There was also significance between the increasing levels worsening disease-free survival. GIST genotype (exon) did not matter. This study also used blinded assays due to the subjectivity of the test results. One caution is that the level of IGF-1 and IGF-2 staining is often low and hard to measure. Using the same IHC methodology, Godwin's team found no difference in the levels of these ligands between mutant and wild-type GIST tumor and noted the difficulty in measurement as a possible reason. These results, and Godwin's in vitro analysis, both point to the possibility of a role for IGF-1R inhibition in mutant GIST. They also may open the door to screening patients for markers (IGF-1 and IGF2), potentially indicating treatment options (Braconi et al.).

A recent paper by researchers at Memorial Sloan-Kettering in New York, has also identified IGF-1R as overexpressed in pediatric GIST (Agaram et al. 3204-15).

For GIST patients, IGF-1R inhibition will continue to be an area of interest, especially for those without c-KIT or PDGFRa mutations. Also, while other signal pathways have not yet produced another Gleevec, it is encouraging to see new possibilities emerge and move forward from the lab. While pending success in the clinic, these results also point to the growing importance of genotyping.

Reference List

Agaram, N. P., et al. "Molecular characterization of pediatric gastrointestinal stromal tumors." Clin Cancer Res 14.10 (2008): 3204-15.

Braconi, C., et al. "Insulin-like growth factor (IGF) 1 and 2 help to predict disease outcome in GIST patients." Ann.Oncol (2008).

Tarn, C., et al. "Insulin-like growth factor 1 receptor is a potential therapeutic target for gastrointestinal stromal tumors." Proc Natl.Acad.Sci.U.S.A 105.24 (2008): 8387-92.

HAPPY CANCER-VERSARY TO LIZ SKREE!

On June 24, 2008, Pediatric GIST patient, Liz Skree celebrated her 5-year cancerversary. "Some days I let everyone and everything know that yes, I have cancer - But look at how confident, healthy, and fun I am!! Other days, I want nothing to do with it, yet I feel permanently branded, like I have "cancer" across my forehead and I can't hide from it. And then I feel ashamed for hiding a part of me that is SO much a part of me. In short, I know it all :)"

Mark your calendars!

- Pennsylvania-area GIST patients will be meeting on Saturday, **July 12** at 11:30am at the Three Loaves Café in Elizabethtown. Contact Kimberly Trout at musikwithkim@yahoo.com for more details.
- "Reeling and Healing Midwest" will hold a fly-fishing retreat for cancer survivors **July 13-15** in Grayling, Mich. Call 866-237-5725 or visit www.reelingandhealing.org for more details.

- "The Asian and Pacific Islander National Cancer Survivors Network" will hold a Cancer Survivorship Conference in Burlingame, Calif. **July 22-24**. For more information, visit www. apiahf.org/programs/cdp/ncsn.htm.
- **This Just In.** The annual GIST Cancer Research Fund "Walk for a Cure" will be held **October 19**. Visit www.gistinfo.org for more details.

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