Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

December 2008 In memory of Severo Lopez & Dr. Arnold Kwart Vol. 9, No. 12

On the road with the LRG

By Marisa Bolognese
LRG Director of Planning & Development

In the span of a few weeks, representatives from the LRG traveled all over the country to attend events and gatherings relevant to the GIST community, from LRG research to the research community at large and patient gatherings on opposite ends of the country. In this article, LRG Director of Planning & Development, Marisa Bolognese, details these meetings.

GIST Research Team Meeting

The LRG Researchers meet at OHSU.

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Take action to find a cure

By Tricia McAleer
LRG Director of Operations

As most Life Rafters and our friends know, we do a yearly fundraising campaign to support our research project – Pathway to a Cure.

Last year, thanks to you, this campaign raised over $180,000 for GIST research!

Many people reading this may not know that this fundraising effort is the work of GIST survivors and their loved ones sending out note cards, letters and emails asking their friends and their family for their support.

This year, we're asking everyone to get involved. Why? Cancer affects all of us. We want to invite the world to join the GIST community. For more information on how to get involved please go to **www.ACureIsInOurReach.org.**

Why is this campaign unique?

The proceeds of this campaign coupled with our Board and corporate fundraising have enabled the LRG to contribute over $4 million to propel the LRG's research project, *Pathway to a Cure,* founded in 2006. Although this is a great start, much more remains to be done.

It's no small achievement for a relatively small patient-driven organization to take on research in such a way. We are uniquely poised to champion this cause. Why is it important to do this? Simply put - We won't just wait for a cure. We have to make it happen.

Help us. Be part of the cure.

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The challenge of imatinib resistance in GIST

By Jonathan A. Fletcher, M.D. & Sebastian Bauer, M.D.
LRG Research Team

Within the past decade, GISTs have emerged from being poorly defined, treatment-resistant tumors to a well recognized, well understood, and treatable tumor entity. Rapid advances in the understanding of GIST biology have made this tumor a paradigm for molecularly targeted therapy.

Approximately 85 percent of GIST harbor activating mutations in KIT or in the closely-related receptor tyrosine kinase *PDGFRA* gene[1]. These mutations are an early event in GIST development, and create constitutively activated oncoproteins that can be therapeutically inhibited by the small-molecule tyrosine kinase inhibitors imatinib and sunitinib, among other drugs.

FLETCHER

The challenge for the LRG Research Team in the coming years is to ensure that increasing numbers of individuals will be alleviated of suffering from GIST, and that GIST will therefore remain a paradigm of success in cancer therapeutics. In particular, we must maximize the dramatic clinical successes of imatinib and like drugs by identifying additional therapeutic regimens that can synergize with these KIT/PDGFRA kinase inhibitors in lengthening clinical remissions, and in eventually curing persons afflicted with GIST. Such clinical

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Due to conflicting priorities, there will be no clinical trials update this month, check back next month for the latest news

Sorg sails through stormy GIST journey

By Rick Sorg
LRG Member

My journey with GIST began in 2000 at the age of 57 when a five centimeter stromal tumor was removed from my stomach. The pathology report on the tumor said it was benign. In August 2005, I had a series of three episodes of shakes & chills, two weeks apart.


SORG

The first one was the day after my annual physical. I wrapped myself in an electric blanket for forty minutes to get warm and called my Blue Cross doctor, who the day before had declared me very fit. A new blood test and exam showed nothing of interest. Two days after the third episode I was at the VA clinic to renew my Lipitor prescription and shared with him what had been happening. After an exam and x-ray, a mass was found on my liver. The next day I had a CT scan and two days later the doctor called me to come in. Ninety percent of my liver was filled with three major tumors and what they called "satellite" tumors. His nurse walked me over to the emergency room at the VA Hospital in Long Beach, Calif. where I spent two weeks getting every conceivable test, including a liver biopsy. They drained a gallon of fluid from one tumor over six days, but finally released me as an outpatient to come back for further tests. I immediately went to my Blue Cross doctor with a two inch stack of reports and copies of the CT scan from the VA. I started over again with a new CT scan. No one ever looked at the VA reports and only the folks doing the CT scan looked at the VA scan and then, only at my insistence.

Three days later I was admitted to Hoag Hospital in Newport Beach, Calif. where new tests were performed, including another liver biopsy. Three days after that, two doctors came into my room in the morning and told me I had cancer. They refused to answer any of my questions, stating my oncologist would be in shortly to answer any questions. She showed up at 1:00 am to tell me she was going on vacation that day and set up an appointment in four days to see her associate and also refused to answer my questions.

I was left alone with no one to answer even one question. It turns out that she and her associate knew nothing about GIST, except that you take Gleevec (which I did) and her answers to the same questions I had asked her associate a week earlier were completely different.

As a result of this, being scared, confused and not knowing how long I would live, I saw a gastroenterologist who, although admittedly had never heard of GIST, sent me back to the hospital for yet another liver biopsy from the same tumor as the previous biopsy and this time it showed a benign hemaginoma (dead tumor). He stated I did not have cancer.

You can imagine the joy I experienced. I immediately shared this good news with the Life Raft Group email community in a very detailed posting of the facts and medical terms used describing the three liver biopsies. Well, the consensus of the dozen who responded to my posting was "Sorry to bust your bubble, but we think you still have GIST and you need to see a GIST specialist".

By this time I was reading and learning everything I could about GIST and cancer. Because of this, I asked my VA oncologist to help me get an appointment with Dr. Mike Heinrich who treats GIST patients at the Portland, Ore. VA Hospital across the street from his shared lab with Dr. Chris Corless at Oregon Health and Science University. He refused, so I emailed Dr. Heinrich directly and got an appointment in June 2006. I had sent him slides from Hoag Hospital prior to my visit and he determined I indeed had GIST with an exon 11 mutation.

I am now a full time member of the LRG. I get the emails in digest form and

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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.).

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.
To donate by credit card, go to www.liferaftgroup.org/donate.htm
Donations by check can be made to The Life Raft Group and 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.

CURE

From Page 1

What Does a Cure Mean For You?

a cure for cancer is in our reach

www.acureisinourreach.org

This year, the Life Raft Group (LRG) launched www.ACureIsInOurReach.org to ask the world "What does a cure mean for you?"

We want to know what a cure actually means to those people who are dealing with cancer every day. Cancer has touched us all in some way - whether you're just concerned about it, you or someone you love has it, or you have lost someone to cancer. To increase GIST awareness, we are not only reaching out to the GIST community but to everyone affected by cancer.

We want to give a voice to the cure. We also want to show the scientific world that their work REALLY means something. We want to remind them that we are here, we are counting on them and we are real people.

Pathway to a Cure

Pathway to a Cure began in 2006 with a five-year strategic plan to find ways to help those who are failing current GIST therapies. With the traditional research and drug development process taking as long as 15 years to produce new therapies, LRG decided to take action.

We have built a research project that will produce better and faster research results for those living with GIST. Instead of handing over money to cancer research and just waiting for answers, the LRG opted to direct a more focused approach on areas that are crucial to fast track a cure. With this approach, we have entered into a successful partnership with the research community because they see the value that patients bring to the decision-making table. We have funded the top GIST scientists in the world, the "LRG Dream Team," to accelerate their research, coordinate their efforts and bring us to a cure.

Our goals are clear:
First, turn GIST from a life-threatening illness into a chronic disease.
Second, find a cure.

As the race against the clock ticks louder every day, the 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, are within reach.

LRG's Pathway to a Cure is making strides but we cannot reach our goal alone. We invite you and your loved ones to be part of this endeavor to create a legacy of hope.

Please help us by reaching out to at least five friends or family members and asking them to support the Pathway to a Cure by making a donation and telling us what a cure means to them.

We won't just wait for a cure
We are taking action
You can too

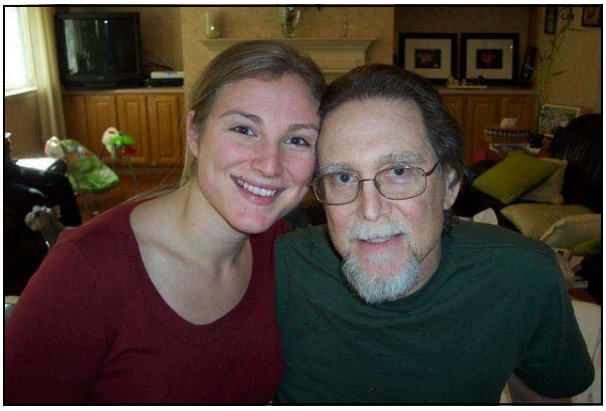
No longer content to sit on the sidelines

By Julie Cramer
Child of LRG member,
Mark Becker

It's hard for me to believe that I have not read the piece that my dad, Mark Becker, wrote for the LRG newsletter (www.liferaftgroup.org/member_stories/memberstories_becker.html) until just now. I've known of it for a long time, but for some reason I just couldn't bring myself to read it. I am a seasoned writer. I am an English teacher and I have a M.Ed., so I have done my share of writing and reading papers, but this task has been especially difficult for me. I think the reason that I've had a difficult time writing my "story" is the same as the reason I couldn't bring myself to read my dad's story until this moment. Living through it once has been hard enough.

I understand that might be selfish. I know that I am not the one who has endured chemotherapy and then discovered that the anguish associated with treatment was meaningless since chemo can't truly treat his illness. I am not the one who has had more surgeries than I care to count, more days in the hospital than on vacation and more hours that I just try to survive than days that I am truly living. As much as I can, I do understand that I have no idea how hard it must be to be my dad.

But it is also hard to sit on the sidelines and watch the man that is your hero in so many ways fight so hard for what too many take advantage of—life. Since I was 16, I have been watching. I watched the night the EMTs carried him down the stairs on the stretcher and my mom asked me, "Are you staying or coming?" The police officer said, "Everything will be okay," and the door closed and I was alone. I watched when he woke up in ICU and wasn't quite sure who I was. I have watched countless more painful events. Most of them, I have watched alone, from the sidelines. Right now, after about 12 years of this, I'm sick of watching. I want to **do**.


Julie with her Dad, Mark Becker.

The GIST Benefit Ball that I am planning really began as therapy for me. I thought I would throw myself into something positive and try to make something good come out of this struggle. I thought it would be a great way to spread awareness of this rare cancer and get people with the disease together for some fun. My hope is to raise $10,000 for cancer research this year, maybe even more next year. I will be donating this year's funds to Fox Chase Cancer Center. In the future, I will be donating to other hospitals.

If you would like more information please visit www.gistbenefitball.org or e-mail Julie Cramer at juliepc@gistbenefitball.org.

Just passed your own GIST milestone? Email us at liferaft@liferaftgroup.org and you might see *your* name in print.

HAPPY CANCER-VERSARY TO JIM MILLS!

In October 2004, LRG member, Jim Mills had a 17 cm tumor removed from his stomach and gall bladder. He has never been on Gleevec. Jim has been NED for the past four years. "I'm extremely fortunate in my good health and doubly appreciate that when I attend the local support group meetings."
Jim takes advantage of his good health whenever he can, "I'm extremely healthy and continue to exercise, lift weights, hike and backpack."
The picture to the left shows Jim in the middle of a 14-mile nature walk along Lake Superior in August.
"I was on this same 42-mile trail in about the same location in May 2004 when I began to experience abdominal pain that turned out to be GIST. Either I love the scenery or have a deep seated need to visit the scene of the crime once a year."

Congratulations Jim!

Campaign 2008

With the 2008 United States Presidential campaign behind us, it is important for the cancer community to be informed of our President-Elect's plans to combat cancer. We have compiled some of the highlights from the "Obama-Biden Cancer Agenda", which can be found in full at www.barackobama.com/issues/healthcare.

Cancer Research Funding

Cancer funding has stagnated in recent federal budgets[1]. Barack Obama and Joe Biden are committed to reversing this trend. The Obama-Biden plan will

- Double federal funding for cancer research within five years
- Work with Congress to increase funding for the Food and Drug Administration (FDA), an agency that plays a critical role in advances in cancer research
- Provide additional funding for research on rare cancers and those without effective treatment options

Access to Clinical Trials

Today, less than five percent of patients with cancer participate in clinical-trials[2], Barack Obama and Joe Biden will seek to increase participation in clinical trials to ten percent of adult cancer patients by:

- Requiring coverage of patient clinical trial costs in the new plans offered through the National Health Insurance Exchange (a proposed voluntary national pool, comprised of a range of private plans and a new public plan)
- Increasing NCI reimbursement for patient participation in clinical research requesting the NCI Director to identify regulatory barriers that prevent the timely implementation and completion of successful clinical trial

Federal Coordination of Cancer Programs

The Obama-Biden plan will maximize federal cancer funding by improving coordination both within the government and across government/private/non-profit partnerships for research, treatment and awareness efforts.

The plan calls for agency officials, academic researchers, cancer survivors and advocates for people with cancer, and state public health officials, to comprehensively examine the various cancer-related efforts of federal agencies, and provide recommendations to eliminate barriers to effective coordination across federal agencies and between the federal government and other stakeholders.

Cancer Survivor Support

The plan will:

- Direct the Centers for Disease Control to develop and carry out an epidemiologic study on cancer survivors to understand their long-term health needs.
- Foster efforts to expand psychosocial supports to cancer survivors, including directing the CDC to identify and replicate successful support group programs for cancer survivors.
- Provide the CDC $50 million in new funding to determine the most effective approaches that assist not only navigation of cancer patients through diagnosis and treatment processes, but also provide easy-to-understand information on the necessary follow-up steps to ensure continued lifelong health.

References

1. Wall Street Journal, 05/31/08
2. Leukemia and Lymphoma Society, 10/09/07, http://www.lls.org/all_news_detail.adp?cat_id=140&item_id=492805

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go through it daily. I have participated in all three GCRF California-Walks for a Cure in Ventura, San Diego, and San Jose to raise funds for GIST research and take part in Southern California GIST gatherings.

I have had two oncologists at the VA (where I get Gleevec) and am on my third and hopefully final private practice oncologist in three years.

Due to the many faults in my GIST journey, I am very cautious of who treats me and I ask tons of questions and occasionally tape record doctor visits.

Fortunately I have had great success with 400 mg of Gleevec, with only minor side-effects, and lead a very active life. One tumor has disappeared and the other two have shrunk in half and are now seven and five centimeters.

I retired in 2007 from a maintenance job of twenty years at a local church and sail three times a week on a 27-foot Catalina out of Dana Pt. Harbor. I also crew on other privately owned sailboats having sailed the equivalent of three-fourths of the way around the world since 1970. The latest sail was in April from San Diego to Puerto Vallarta, Mexico aboard a 64-foot Alden sloop, my tenth sail to Mexico. The most adventuresome trip was a four-month sail to Tahiti in 1998 on a 54-foot Schooner.

I continue to learn all I can about cancer and GIST and my interest is now focused on frequency waves to zap cancerous tumors like the Kanzius machine being studied at MD Anderson in Houston. This technology offers another approach to finding a cure.

I wear my purple GIST bracelet proudly and use it as a means to spread the word about GIST. It has been a remarkable journey and I accept the challenges it presents.

ROAD

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The LRG Research Team is presented a 2 million dollar check from the LRG. Pictured from left: Drs. Sebastian Bauer, Maria Debiec-Rychter, Brian Rubin, Anette Duensing, Mike Heinrich, Chris Corless, LRG Executive Director Norman Scherzer, Drs. Matt van de Rijn, Jonathan Fletcher, Cristina Antonescu, Science Coordinator Jerry Call and Dr. Peter Besmer

Oregon Health & Science University in beautiful Portland, Oregon was the location for LRG's Research Team meeting on October 27 and 28. This was the first meeting of the expanded ten-person expert team of GIST experts which includes: Drs. Cristina Antonescu and Peter Besmer of Memorial Sloan-Kettering Cancer Center; Sebastian Bauer of the West German Cancer Center, University of Essen, Germany; Chris Corless and Michael Heinrich of Portland VA Medical Center & Oregon Health & Science University; Anette Duensing of the University of Pittsburgh Cancer Institute; Jonathan Fletcher of Brigham & Women's Hospital; Maria Debiec-Rychter of the Catholic University of Leuven in Belgium; Matt van de Rijn of Stanford University Medical Center and Brian Rubin of The Cleveland Clinic. Also attending the Research Team meeting were LRG Executive Director, Norman Scherzer, LRG Science Coordinator, Jerry Call, and LRG Planning & Development Director, Marisa Bolognese.

The LRG marked the occasion by presenting the team a two million dollar check, which represents the next two years of funds, the LRG has committed so far to its "Pathway to a Cure" research program. Combining the two-year grants awarded in 2006 with the new two-year grants, the LRG has now raised and awarded four million dollars to find a cure for GIST. At the awards ceremony, Drs. Chris Corless and Michael Heinrich also presented a plaque to Norman Scherzer in appreciation of the LRG's ongoing support of their research.

The team gathered to share the latest findings from each of their labs and to discuss the progress of current Research Team projects. This in-person meeting provided a great opportunity for the team to brainstorm and to identify new areas of collaboration and exploration (See Dr. Fletcher's article on page 1).

The team left Portland with renewed commitment to priority areas from the first grant period, including understanding mechanisms of resistance and stable disease, investigating wildtype and Pediatric GIST and some new areas of emphasis such as apoptosis (cell death) and translational studies where lab discoveries can become treatments. Another exciting development is a plan to support lab-based research conducted by the LRG Research Team with data from the LRG's patient registry in order to accelerate scientific discoveries about GIST.

GISTers in California meet and share.

This project is in development and will be pilot tested early next year.

Bio Investor Forum, San Francisco, California

The LRG attended the Seventh Annual Bio Investor Forum on October 29 to 31 in San Francisco. The event featured over 500 Bio Tech companies and 200 investors as well as a small but growing contingent of research-focused non-profit organizations. LRG was joined by the Muscular Dystrophy Association, The Leukemia & Lymphoma Society, Juvenile Diabetes Research Foundation, The Epilepsy Project, The Prostate Cancer Foundation, The Myelin Repair Foundation and FasterCures in making presentations about their research efforts to investors and biotech companies. The event offered LRG an opportunity to talk to innovative biotech companies that may have drugs in development that could have potential application for GIST. Norman Scherzer was taped for a podcast at Bio Investor Forum that you can access at www.liferaftgroup.org.

LA Local GIST meeting

On November 11, Norman and I met with LRG members and their families in Santa Monica, California. Over lunch, people shared their stories and got an opportunity to learn about the latest scientific advancements from the LRG Research Team. Above all, it was a time to get to meet other people who are conquering GIST and make local connections with those who share the same journey. It was especially nice to meet

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successes, particularly for those with metastatic or otherwise inoperable GIST, will doubtless require treatment with combinations of drugs, because medical history tells us that cancer cells, in most people, will eventually develop resistance to a single drug, no matter how effective that drug is initially.

In this sense, we are transitioning to a new era in GIST research and therapeutics, where the recent clinical focus on single drugs, such as imatinib and sunitinib, will increasingly be enhanced by studies in which cocktails of effective drugs are administered, either concurrently or sequentially (Figure 1). The downside of treating with drug cocktails, rather than single drugs, is the likelihood of increased side-effects, since each drug can have additive toxicities against normal cells. However, the crucial benefits of drug combinations include not only the opportunity to maximize initial clinical response by killing more GIST cells, but also the possibility that fewer cells will develop resistance against multiple drugs, compared to a even a highly-effective single drug, particularly if the drugs have different mechanisms of action.

Most individuals with unresectable or metastatic GIST respond to imatinib, with the GIST tumors remaining stable for a time under treatment, after undergoing initial clinical response[2]. Although imatinib thus succeeds in blocking GIST cell growth (the residual surviving GIST cells are referred to as "quiescent"), it is imperative to identify new therapies that can kill the surviving GIST cells. **One of the priority aims of the LRG Research Team is to identify drugs that more effectively induce GIST cell death (apoptosis)** and that can be safely administered together with a KIT kinase inhibitor drug such as imatinib. Such methods may be particularly useful in consolidating the initial clinical response, for those whose GIST has responded and stabilized on imatinib, sunitinib or some other KIT kinase inhibitor.

One such option, as highlighted in previous LRG newsletters, might involve the addition of PI3-K inhibitors to imatinib, in order to maximize inhibition of GIST cell survival pathways. However, like many evolving fields in cancer research, this is complex, with many possibilities to consider. Preliminary studies (unpublished) show that various PI3-K inhibitors differ widely in their effects on GIST cells, with some having primarily cytostatic (growth-inhibiting) properties, whereas others can induce a dramatic apoptotic response, resulting in GIST cell death. These observations emphasize a general rule, which is that different drugs against a particular GIST biological "target" do not necessarily have equivalent effects on the tumor cells. Such varying drug efficacy, even within a particular class of drugs and among drugs with similar pharmacological effectiveness, can result from differential success in inhibiting the various forms of the target proteins that regulate GIST growth and survival, and can also result from so-called "off target" effects, in which a particular drug might inhibit other proteins (above and beyond those the drug is known to inhibit) which can, in unanticipated manner, contribute to GIST growth inhibition and GIST cell

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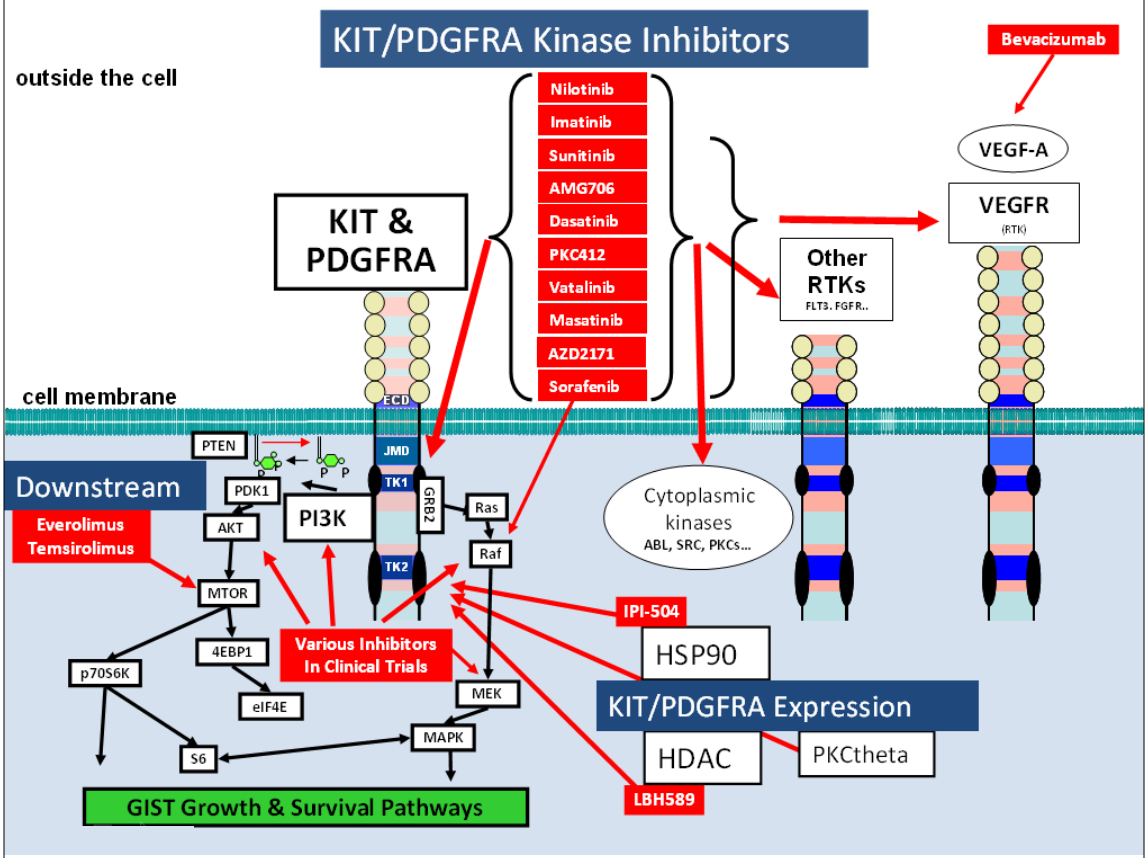
Figure 1



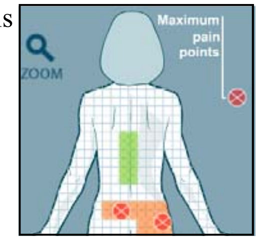
GIST therapeutic approaches can inactivate KIT and PDGFRA, reduce the amount of KIT and PDGFRA in the cells (reduce "expression"), inactivate KIT/PDGFRA-downstream signaling pathways that regulate growth and survival, and inactivate other kinases which function independently of KIT and PDGFRA but nonetheless contribute to GIST growth.

WEBSITE OF WORTH

Most cancer patients experience some sort of pain as a result of their disease or their treatment. Treating this pain is nearly as important to the patient as treating the cancer itself. ReliefInsite.com helps you track and report key aspects of your pain to share with your doctor and others involved in your care through online journaling.

The online journal offers a variety of different options depending on whether the user has a free or paid account. Some of these features include:

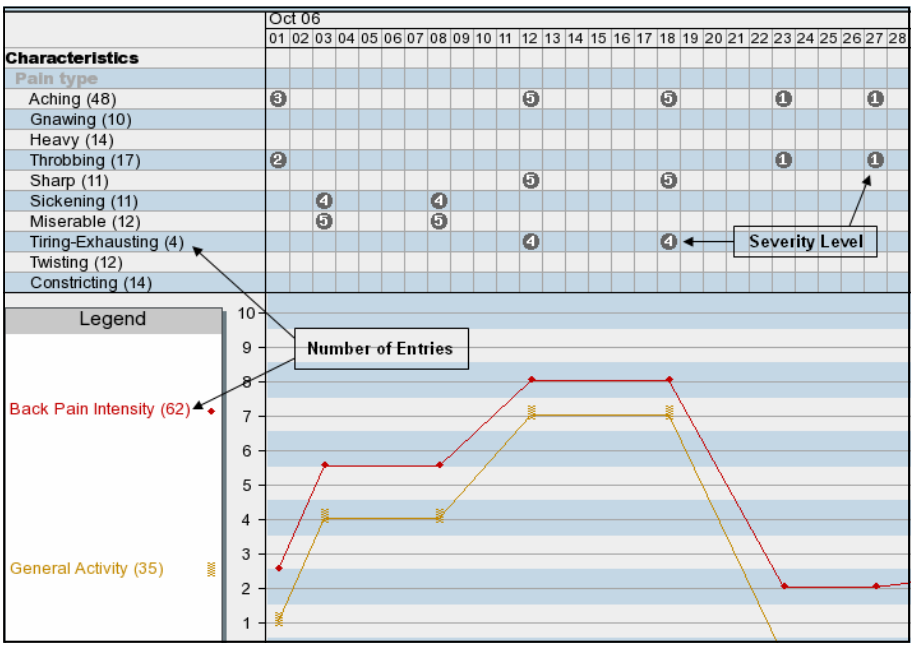
- A **calendar** which tracks past entries and daily pain levels
- A **body map** to record the location and intensity of your pain
- A **characteristics** page to describe and grade the severity of your pain
- A **medication** page to track drug treatments and treatment compliance
- The ability to create **reminders** about medications or diary entries



With this information you can print custom reports that you can print, save or e-mail to your doctor, nurse or other healthcare providers. One way to securely share this information with a medical professional is to list them as a "Sharing Partner" to your journal.

While the paid journals obviously have a great deal more detail than non-paid accounts, the user can still use body map and notes sections, as well as print basic reports.

Visit www.reliefinsite.com/users for more information.



This is one example of a report you can create at ReliefInsite.com

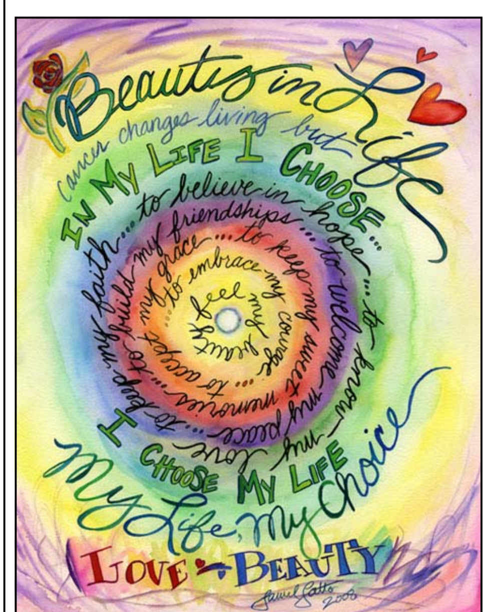
GET 'EM WHILE THEY'RE HOT!

The LRG is now selling 2009 Entertainment Coupon books for a limited time. These books offer discounts and coupons in areas like dining, travel and shopping and cost between $20 to $40. Check out our website for more information on how to get one for yourself!

Did you Know...

The Association of Online Cancer Resources (ASCO) has finished its 2009 Expressions of Hope calendar.

Go to www.cancer.net/patient/Survivorship/Survivorship+Artwork to view some of the entries and find out how you can be considered for the 2010 calendar.



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death. Therefore, it is imperative to test as many drugs as possible against GIST laboratory models, even when the drugs are expected to have similar clinical properties, so as to identify those with the greatest clinical promise, which should then be prioritized for evaluation in new clinical trials.

Recently, the LRG Research Team demonstrated substantial inter- and intralesional heterogeneity in drug resistance mutations in patients treated with imatinib alone or imatinib and sunitinib: 83 percent of patients in this study had secondary drug -resistant KIT mutations, including 67 percent with two to five different secondary mutations in separate metastases, and 34 percent with two secondary KIT mutations in the same metastasis[3]. This substantial heterogeneity of resistance mutations highlights the therapeutic challenges involved in substantially extending survival, especially after clinical progression on KIT/PDGFRA kinase-inhibitor monotherapies. This clinical reality suggests that although newer generations of broad-spectrum, increasingly potent, KIT/PDGFRA kinase inhibitors may benefit those progressing on imatinib therapy, such drugs – on their own – are unlikely to cure many patients with imatinib (or sunitinib) resistant disease. Therefore, it seems clear that multiagent treatment modalities are needed in the future, incorporating classes of drugs that inhibit the KIT/PDGFRA oncoproteins in novel ways. These are not "handcuffed" by the molecular heterogeneity of KIT/PDGFRA kinase-domain resistance mutations selected for during imatinib and sunitinib therapies. Combination therapies with various such inhibitors will prolong GIST remissions, in a manner analogous to treatment approaches used against HIV in patients with AIDS, i.e. by suppressing a broader spectrum of GIST clones from the outset of therapy. Similarly, therapeutic options less dependent on specific molecular mechanisms of KIT or PDGFRA activation are needed to overcome the substantial heterogeneity of secondary KIT/PDGFRA kinase mutations ultimately responsible for treatment failure in many persons.

To overcome the limitations of direct KIT-inhibitors we need to identify the Achilles' heels of oncogenic KIT. KIT mutations allow GIST cells to evade natural self-inhibitory mechanisms, and in that sense are like a master-switch stuck in the "on" mode, resulting in so-called "constitutive activation" of KIT-dependent growth and survival signaling pathways. Nonetheless, there are undoubtedly ways to halt these constitutive activation signals. For example, even the "switched-on", mutant KIT proteins are strongly dependent on various "helper" proteins, which are not mutant, but which bind to KIT and assist in its functions. Some of these helper proteins might represent ideal therapeutic targets in GIST.

Novel GIST therapeutic strategies, increasingly, will also focus on blocking production of the mutant KIT or PDGFRA proteins. Production of KIT/PDGFRA proteins requires transcription and translation ("reading and writing") from the KIT gene within the GIST cell DNA. Initiation of this production process is directly regulated by various transcription factors, and indirectly regulated by proteins that activate or inhibit such transcription factors.

Kinases are proteins, which – like KIT and PDGFRA – regulate the activities of cell growth and survival by transferring energy in the form of phosphorylation. We and others have shown that the kinase protein, PKCtheta, is uniquely and strongly expressed in GIST[4]. Indeed, in GIST cells, PKCtheta binds to KIT, and can likely phosphorylate KIT, whereas KIT regulates phosphorylation of PKCtheta[5]. Therefore, it seems that certain aspects of KIT and PKCtheta function are interdependent in GIST. Notably, expression of KIT itself depends on the presence of PKCtheta in the GIST cells. In laboratory experiments we reduced the amount of PKCtheta in GIST cells, which resulted in a decrease in KIT gene transcription, and also decreased the amount of mutant KIT proteins in the cells[6]. PKCtheta seems to be a potentially useful, and highly specific therapeutic target, since few normal cells in the body contain large amounts of PKCtheta. Drugs against PKCtheta would therefore be expected to have very limited toxicity, and would not likely be constrained by the presence of imatinib-resistance KIT mutations. A near-term goal is to identify and validate potent clinically-useful inhibitors of PKCtheta, particularly those which might lead to decreased amounts of KIT oncoproteins.

Transcription and translation of the KIT mutant oncogene results in a string of amino acids (the starting point for a functional protein) that, left to it's own devices, would assemble into a more or less random configuration, like an unkempt ball of wool, and which would be identified as useless and promptly diverted into the cell's trash shredder: the "proteasome". However, GIST cells contain *chaperone proteins* which en-

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Glossary

Apoptosis – Controlled cell death, a type of cellular suicide where the cell issues its own death warrant.

Cytostatic – Inhibiting cell division without causing the cell to die.

Inter/intralesional homogeneity – How similar/different is tumor tissue compared to other tumor tissue in different lesions (inter) or within the same lesion (intra).

Oncogenic – A process that tends to promote tumor formation or progression. For example, KIT mutations are oncogenic in GIST.

Oncoprotein- A defective protein that is involved in causing a cell to grow/divide abnormally, giving rise to a cancer.

Phosphorylate – Addition of a phosphate group; this is a common chemical modification of proteins and often alters the activity of an enzyme. More specifically, it often is synonymous with activation of a protein such as KIT, e.g. KIT phosphorylation equals KIT activation.

PI3-K inhibitors - PI3Ks have recently been identified as active downstream signal points in the c-KIT pathway in GIST. Inhibition of PI3K is a potential therapeutic strategy in GIST.

ROAD

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spouses, moms, and kids and see how well everyone is doing. For us, it felt like coming home and being with family. Thanks to everyone who traveled to join us and for helping to make the gathering such a success.

FasterCures

On November 12, in Los Angeles, Calif., the LRG attended a meeting sponsored by FasterCures, the action tank working to help accelerate the process of finding cures. FasterCures convenes meetings which bring together non-profits groups who are research innovators in their search for cures. These groups represent a wide range of diseases, such as ALS, heart disease, cancer, diabetes, autism and epilepsy. The LRG's participation has made a wider range of resources and information sharing possible. The November 12 meeting topic was "From Social Entrepreneurship to Cure Entrepreneurship." More than 30 senior leaders from organizations that fund medical research and from the broader sphere of social entrepreneurship met for a day of brainstorming and discussion. One key topic was how to apply lessons learned by social entrepreneurs to those pursuing what FasterCures calls "cure entrepreneurship," or novel approaches to accelerating the process of treating and curing disease. As noted in FasterCures blog (http://fastercures.blogspot.com/2008/11/from-social-entrepreneurship-to-cure.html):

"Much of the discussion during the day centered on the need for better information flows about what work is being done, by whom, and its quality; the need for better communication about why new approaches are needed and the promise they hold; and the need for nonprofits to find creative ways to leverage their relatively small funds into larger investments into new therapies. There was also a common focus on the centrality of patients and the transformative nature of empowering them to play a greater role in research.

"The social entrepreneurs and cure entrepreneurs in the room found a lot of common ground. In part because both distinct sectors function in a similar space where success is often the result of effectively leveraging the assets that it creates. It was noted however that the social business model is difficult to achieve in medical research because of its cost implications. Throughout the day, participants alluded to the need for unconventional solutions, unusual channels to reach nontraditional audiences, outcomes-focused collaborative efforts, and ideas that could be acted on in real-time by the right people".

All smiles at a Rhode Island GISTer meeting in Providence.

Attendees listen to a speaker at the FasterCures meeting in LA.

New England GIST Meeting

On November 22, in Providence, Rhode Island, the newest local GIST support group was born. Susan Farmer hosted the group in her home which proved to be a day filled with laughter, good cheer and great food (especially the desserts). The opportunity to share personal GIST journeys, information and news was a winning combination. The group was energized by each other's high spirits and positive attitudes.

The first meeting was a huge success and clearly just the beginning of what will prove to be a thriving community of friendship and support. The Life Raft Group sends a great big thank you to Susan and her family for their generous hospitality. Thanks to all those who came together on a cold but sunny November day and who left feeling uplifted by each other's support and open arms of friendship.

Global GIST Network adds new GIST representative

Global GIST-Network

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Did you Hear...

- The National Cancer Institute has just launched a new Pediatric GIST site at www.pediatricgist.cancer.gov.
- And don't forget about the next Pediatric & Wildtype GIST clinic on January 22-23 at the NIH in Washington DC!

FLETCHER

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sure that nascent KIT oncoproteins are properly folded and localized within the cell, and are protected from premature destruction. We recently showed that inhibition of the chaperone HSP90 can result in KIT oncoprotein destruction, irrespective of the imatinib-resistance mutations present[7]. And initial clinical trials of HSP90 inhibition (IPI-504) have served as a crucial proof-of-concept for HSP90 as a master-regulator of KIT in the GIST cell. Several HSP90 inhibitors are being developed by pharmaceutical companies and apparently the ability to inhibit KIT varies among them. Future studies will need to identify the most potent and clinically useful HSP90 inhibitors for GIST. An urgent priority, in future clinical trials, will be to determine the extent to which HSP90 can be truly shut down by HSP90 inhibitor drugs, and to determine what clinical efficacy (and what toxicities) result when that pharmacologic aim is achieved.

Similarly to HSP90 inhibitors, the histone deacetylase (HDAC) inhibitors – as shown by Drs. Debiec-Rychter and Bauer of the LRG Research Team (unpublished) – can also destroy the crucial KIT oncoproteins in GIST cells. While the exact mechanism for this remains to be elucidated, HDAC inhibitors not only inhibit HSP90 but may also inhibit transcription of KIT oncogenes. Other drugs that block KIT gene transcription, hence impairing KIT synthesis in the GIST, include flavopiridol[8], where the therapeutic efficacy, as for HSP90 and HDAC inhibitors, is not expected to be derailed by imatinib-resistance mutations in the KIT coding sequence.

BAUER

Another therapeutic approach to potentially circumvent imatinib-resistance mutations might involve immunotherapies, using antibodies against the part of the KIT protein that extends outside the GIST cell. Such immunotherapies might be successful even in GISTs that have developed resistance to drugs like imatinib, that bind the KIT kinase domain within the cell.

As mentioned above, recent studies from our group and others show that the PI3-kinase pathway is strongly activated in most GISTs, and is indeed dependent on KIT/PDGFRA activation[5,9,10]. In a simplified model, KIT activates PI3-K, which then activates the AKT-kinase, which then activates the mTOR kinase as a linear pathway (like dominos falling) promoting GIST cell growth and survival. In reality, these so-called "signaling pathways" are not linear, but have intricate cross-connections, and the details of the cross-connections can differ between the GIST growing in a person versus the GIST laboratory model, such as an immortal GIST cell line, used for drug-testing. Therefore, the clinical efficacy of a given GIST signaling pathway inhibitor drug cannot be definitively predicted from its efficacy (or lack thereof) in laboratory tests. Nonetheless, such studies are crucial, because KIT or PDGFRA mutant oncoproteins are the major drivers of growth and survival in most GISTs, and an improved understanding of the mechanisms of KIT/PDGFRA oncogenic signaling will undoubtedly enable more effective therapeutic strategies.

Targeting of KIT/PDGFRA signaling pathways, particularly when coupled with KIT/PDGFRA kinase inhibitors, will likely be useful clinically in maximizing initial clinical responses, prolonging remissions, and treating GISTs that have progressed on imatinib or sunitinib therapy. These more complex combination-drug therapies will require highly-coordinated efforts between laboratory and clinical researchers, to more efficiently identify therapeutically relevant drugs, and to determine the optimal dose schedules and treatment sequences for these drugs.

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Mark your calendars!

- The "LRG Research: Taking Action to Find a Cure" webcast will be on **December 10.** More information to come!
- The second annual Evidence-based Complimentary and Alternative Cancer Therapies conference will be held in West Palm Beach, FL. from **January 8-January 10**. Go to www.liferaft group.org/calendar for more information.

Watch out for the new LRG Pediatric GIST site and GISTnews.org. Both will be launching this month!

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