Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

September 2007

In memory of Herb Flom, Marilyn Bohan, Lauralee Bucholtz, Dick Singleton, Wokie David, Chrystine Slokan, Pete Richetti & Peter van der Meer

Vol. 8, No. 8

# Rigg: The healthiest woman, despite GIST

**By Darlene Rigg**

*In 2003, Darlene Rigg wrote a humorous and poignant reflection on her first experience with GIST on the LRG listserv. This month we are reprinting that letter. Next month Darlene will once again tell her story, four years later.*

My name is Darlene, and I come from the northwest corner of Indiana, just a 20-minute drive from the scenic Lake Michigan Dunes to the north, or 25 minutes west to Gary, murder/crime capital of the country. Actually, we live in a rural area, surrounded by corn and soybean fields and the occasional pig farm when hog prices go up, which hasn't been lately. My children's public school includes K-12, and my daughter's senior class boasted 33 graduates.

This is my story:

I am the healthiest person in Indiana, if not in the entire country. I am so seldom sick that I actually surpassed the quota of sixty sick days that you're allowed to accumulate, and I ended up not getting anymore because I never used them.

Then last fall something happened: I got hives. This was a month-long, soles-of-the-feet-to-top-of-the-scalp, 24-hours-a-day-for-a-month type of hives. At first I was reluctant to see my doctor; when you raise silkworms, grow 400+ species

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# Pediatric GIST: an evolving concept

**By Dr. Cristina Antonescu**
Memorial Sloan-Kettering Cancer Center

*Dr. Antonescu is a member of the LRG Research Team. This article is part of a series written by each of the key team members.*

Although GISTs occurring in the pediatric age group are extremely rare, comprising no more than two to three percent of cases, they constitute a distinct clinical and molecular subset from the adult tumors. We and others have previously described the characteristic features of this rare type of sarcoma in children, with strong predominance for females and wild-type genotype for *KIT* and *PDGFRA* (*1*). Pediatric GISTs are preferentially located in the stomach as multiple nodules and histologically have either an epithelioid or mixed spindle and epithelioid morphology (*1, 2*). Of interest is that unlike in adults, the majority of GISTs in pediatric patients follow an indolent course, in spite of the high rate of metastasis to the peritoneal cavity and liver. Furthermore, metastasis to loco-regional lymph nodes is common in pediatric GIST patients and rare in adults (*1*). Since our initial report comprising five female patients with wild-type gastric GIST, we have expanded our analysis to 17 children. This includes five male patients, one of whom had a solitary small bowel tumor. In this larger cohort, we confirm that pediatric GIST is more prevalent in females, who develop multiple tumors within the stomach, without associated interstitial cell of Cajal hyperplasia. Microscopically, these tumors often show an epithelioid morphology, with a vari-

ANTONESCU

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# One year research team milestone reached

**By Norman Scherzer**
*LRG Executive Director*

At the one year milestone our research team reported substantial progress in implementing nine of their ten priority research projects. The cover of our July 2007 newsletter featured a progress report by Dr. Jonathan Fletcher, our lead researcher. In addition, you can go to our website (www.liferaftgroup.org) and listen to Dr. Fletcher's web cast where he discusses this research and responds to questions.

We are approaching a critical intersection on the pathway to finding a cure for a cancer. We have the right scientific tools and the right researchers at the perfect time and place to demonstrate how to treat and cure cancer. 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, imatinib (Gleevec) and sunitinib (Sutent) and a number of other promising ones in the pipelines.

SCHERZER

The initial funding for this research program covered the first two years of a

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# GIST–legal headlines

## Medicare eases proposed restrictions on anemia drugs used by cancer patients

A *New York Times* article recently reported on July 31 that Medicare has eased up on some of its proposed restrictions for anemia drugs, Aranesp and Procrit, made by Amgen and Johnson & Johnson, respectively. The drugs are used to treat chronic anemia and also anemia caused by cancer treatments.

The Centers for Medicare and Medicaid services had announced in May that they would severely limit coverage for the drugs.


However, "the agency received more than 2,600 comments, many of them from doctors, medical societies and patient groups who said the proposed restrictions went too far, were not based on scientific evidence and would possibly harm patients," according to the article. This led to the pullback on July 30 for those patients whose anemia was caused by cancer treatment. There has been no such statement made about patients using Procrit and Aranesp to treat chronic anemia so limited coverage is still expected for that indication.

Below is a communication made by LRG Executive Director Norman Scherzer to the Centers for Medicare and Medicaid as part of the patient advocacy response.

*The Life Raft Group represents patients with a rare cancer called GIST, or GI Stromal Tumor.*

*GIST patients have had great success with an oral targeted drug called Gleevec. A number of GIST patients are now entering their seventh year on Gleevec. The prognosis for those that do not develop resistance is to remain on Gleevec indefinitely. One of the side effects of Gleevec is anemia. The proposed regulation changes could force significant numbers of GIST-Gleevec patients to have to resort to fairly routine blood transfusions should ESA drugs like Procrit not be available. These drugs have been quite effective in helping GIST patients manage their anemia without relying upon transfusion. We hope that a clear exception will be made to allow this to continue.*

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## Court rejects right to use drugs being tested

On February 7, a federal court ruled that terminal patients did not have a right to use medicines that have not yet won regulatory approval, said a recent *Times* article.

The Court of Appeals ruled 8-to-2 against the Abigail Alliance for Better Access to Developmental Drugs, who filed the suit against the Food and Drug Administration (FDA). The Alliance was founded by a man after his daughter, Abigail, died from cancer while waiting to receive experimental drugs. These drugs were later approved.

The group felt that, "the process of clinical trials deprived dying patients of their right to self-defense and violated the Fifth Amendment clause stating that people cannot be deprived of life, liberty or property without due process of law," as reported in the article.

On the other side of the battle, the FDA and supporters feel that early availability with only preliminary testing could mean that drug companies would neglect conducting full clinical trials. "Robert Erwin, of the Marti Nelson Cancer Foundation, stated in the article that it would allow the companies to "profit from offering empty hope".

A district court had originally ruled against the Abigail Alliance in this matter. That decision was reversed by an appellate court panel before the full ap-

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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.). 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.

# NCCN task force takes strong stand in genotyping debate

**By Jerry Call**

The National Comprehensive Cancer Network (NCCN) GIST task force, including GIST experts in oncology, surgery, pathology and research from around the world, met in December of 2006. In July, The *Journal of the National Comprehensive Cancer Network* published the updated treatment recommendations of the task force.


CALL

The report, "NCCN Task Force Report: Management of Patients with Gastrointestinal Stromal Tumor (GIST)—Update of the NCCN Clinical Practice Guidelines", is available on the NCCN website (www.nccn.org). Physicians and medical professionals can apply for continuing medical education (CME) credits upon completion of the course. Dr. Margaret von Mehren, director of sarcoma oncology at Fox Chase Cancer Center, also gave an online presentation covering this topic on the Medscape website (also approved for CME).

The task force took the strongest stance to date supporting the use of genotyping in GIST. The task force ". . . strongly encourages that mutational analysis be performed if imatinib therapy is begun for unresectable or metastatic disease." They also noted, "Mutational analysis can be considered for patients with primary disease, particularly those with high-risk tumors." Mutational testing can be done from any available paraffin-embedded tumor sample: primary, recurrent, or metastatic.

A new risk assessment table was included in the report. This table was adapted from work done by Dr. Marku Miettinen and Dr. Jersey Lasota at the Armed Forces Institute of Pathology (AFIP). The data in this table was developed based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GISTs. The updated table adds primary tumor location to the existing parameters of primary tumor size and mitotic index to assess the risk of a recurrence after the removal of a primary tumor.

The report includes recommendations for the management of side effects caused by both Gleevec and Sutent. Also included are tables listing potential drug interactions for both Gleevec and Sutent. For the first time, a specific recommendation was made to limit Tylenol (acetaminophen) for patients taking Gleevec. The report noted that "For most patients, this means taking 1300 mg acetaminophen per day or less".

A detailed discussion of the principles of surgery for GIST and need for multidisciplinary management was presented. Noteworthy in this discussion were:

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# September 2007 clinical trial update

**By Jim Hughes**
*LRG Science Team Member*

This month we have made the format easier to read. Also, United States trials and international trials will now be reported on alternating months to save space. This issue we are highlighting US trials, please refer to next month's newsletter for international trials. The following are recent developents:

**AMN107 Phase III:** Three new sites opened; Washington Cancer Institute, Washington, D.C.; Karmanos Cancer Center, Detroit, MI; UCLA Los Angeles, CA.

**Perifosine Plus Imatinib Phase II:** Sites have been updated.

**IPI504 Phase I:** Added Scottsdale, AZ site.

**OSI-903 Phase I:** Now has an NCT number and an entry in the clinicaltrials.gov database.

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## Community Beat


Life Raft Group member Bob Spiegel recently took this photo when driving through Ocala, Florida near his home. "I thought it interesting that we have our very own RV dealer in Florida!"
Thanks, Bob!

## Sara had a baby!

LRG staffer, Sara Rothschild gave birth to a healthy baby boy on June 16, 2007. Little Benjamin is now 11 weeks old and full of smiles!

## Stay tuned...

Markus Wartenburg's wife is pregnant too! The Das Lebenshaus director is expecting his first child soon.

Do you have your copy of the LRG Facebook yet? Pick one up at www.liferaftgroup.org today.

## NCCN

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• Recommendation for all GISTs two cm in size or greater to be resected.
• The expanding role for laparoscopy was noted. Two studies that demonstrated a low recurrence rate were cited. The report noted that "Generally, gastric GISTs five cm in size or less may be removed by a laparoscopic wedge resection.
• The indications for surgery in recurrent or metastatic GIST.
• Surgery is now recommended in addition to tyrosine kinase inhibitors for *selected* patients with metastatic GIST
• A discussion of "subclinical GISTs". In a study that examined whole stomachs removed from 100 gastric cancer patients (not GIST patients), 35 patients had very small GISTs (less than 5mm in size) in their stomach. Apparently many people have very small "GISTs" that never develop enough to become noticeable.

Multidisciplinary management of GIST was emphasized.

"Thus, patients with GIST need to be managed with combined pathology, medical oncology, surgical oncology, and imaging expertise in both initial evaluation and management as well as in continued follow-up. Reducing recurrent disease, optimizing timing of surgery and organ preservation, prolonging survival, increasing the number of resectable cases by pharmacologic debulking, and possibly enhancing response to imatinib by surgical cytoreduction are all potential benefits of multidisciplinary management."

The report also noted that "In general, patients should be managed by a multidisciplinary team with expertise in sarcoma or tumors of the GI tract". In addition, they noted, "Any GIST patient with complicated or unusual features or those patients with advanced refractory disease should be appropriately referred to a center with specialty expertise and experience in the management of GIST."

An excellent discussion on imaging was also presented in the report. Included was a discussion of the "Choi" criteria for CT scans and when and how to use PET scans.

One caveat that should be mentioned is that the task force met prior to two potentially important studies that were presented at the annual American Society of Clinical Oncology (ASCO) meeting in June. These were the report of the meta-GIST analysis. In this study, data from the two large phase III trials were combined. Of particular note in this study is that the combined data on exon 9 tumors showed a statistically significant progression-free survival (PFS) time for high-dose Gleevec whereas the data from the U.S./Canadian trial did not. The other study of particular interest at ASCO was the report by Dr. Ronald DeMatteo that showed that adjuvant Gleevec significantly increases recurrence-free survival time.

## Member Suggestions

Brought to us from Life Rafter Richard Palmer: "I took my first Gleevec capsules in January 2001. As I swallowed my four orange capsules, Judy Orem said she and her fellow CML patients had found eating some chocolate with the Gleevec helped minimize nausea. My bride, Linda, immediately bought some Hershey's Kisses. It's great to have a medical excuse for eating chocolate!"

## Mark your calendars!


Florida GISTers will be once again meeting on **November 10.** More details will follow.

There will be two events hosted on October 14. The annual GIST Cancer Research Fund "Walk-For-A-Cure" will be held in two locations: Rockland Lake State Park in Congers, New York and San Buenaventura State Beach in Ventura, California. Go to www.gistinfo.org for details.


In Long Beach, California, Paul Montuori and team will be running in for member, Carolina Williams (As reported in our August 2007 newsletter). Please go to www.runlongbeach.com for further information.

# Peter Richetti, 47, beloved son, cherished brother and dedicated uncle

Peter J. Richetti, 47, passed away on Monday, August 27, 2007 at the Hope Hospice in Fort Myers, Florida, surrounded by many beloved family members.

Born in Plainfield, New Jersey, Peter was raised in South Plainfield and lived in Virginia Beach for 22 years before settling in Estero, Florida 18 months ago.

Peter worked as a Sales Engineer for Ingersol-Rand in Virginia for many years before recently retiring.

An avid golfer, Mr. Richetti loved the N.Y. Yankees as well as the N.Y. Giants.

A loving uncle to his 2 nephews Justin C. and Nicholas T. Miller, Peter was also fond of being godfather to several of his close friends children.

In addition to his 2 nephews, Mr. Richetti is survived by his loving parents; Thomas P. Sr. and Rose T. (Rabone) Richetti of South Plainfield, his sister and her husband Robyn T. Miller and Jeffrey of Bridgewater and by his brother Thomas P. Jr. of San Diego.

Funeral Services will be held on Saturday, September 1, 2007 beginning at 8:30 AM in the McCriskin - Gustafson Home For Funerals, 2425 Plainfield Ave., South Plainfield followed by a 10:00 AM funeral mass at Sacred Heart RC Church, South Plainfield.

In lieu of flowers, donations can be made in Peter's name to the Life Raft Group.

## NEWS

From Page 2

peals court upheld the original decision on the seventh.

Alliance founder, Frank Burroughs, promised to appeal to the supreme court.

## Setback for Novartis in India over drug patent

On August 6, a court rejected a challenge to Indian patent law made by Novartis regarding GIST drug, Gleevec.

The *Times* article stated, "Novartis asked the High Court in Madras to clarify a key element of India's 2005 patent legislation, arguing that it violated trade rules and breached the Indian Constitution. Indian law says a drug qualifies for a patent when it is a new invention or a significant improvement to an existing one. The law denies patent protection to new versions of drugs invented before 1995."

Indian patent law had allowed an Indian company to distribute its generic version of Gleevec. The court denied Novartis's challenge on the grounds that because the molecular structure of Gleevec is not unique, it was not protected by Indian patent law.

## RIGG

From Page 1

of hot house plants, and keep pet giant Madagascar hissing roaches and snakes for pets, it's easier to go out of town for the weekend just in case it's only an allergy. But the hives got worse.

My doctor, when I finally saw him, nodded sagely and told me it was an allergic reaction. "Try Allegra," he said. Thankfully, the hives went away within 24 hours. But the very next day, a bee stung me, and my legs swelled with water, and my ankles slopped over the tops of my shoes.

The good doctor thought maybe I should see an allergist, who had an opening a week later. Meanwhile I had to stop the Allegra, so now I was a humanoid hive factory with tree-trunk ankles sprouting from my shoes. In a way it was rather comical— until the allergist told me, almost immediately, that it was no allergic reaction (the bee had stung me in the hand, not the legs), and, after he touched my abdomen, that I had some sort of massive growth that merited immediate investigation.

The next day I got a CT scan, and the day after that I was given an appointment to talk with a surgeon. I was supposed to pick up my scans on the way to his office, but he had an emergency surgery, so I picked up the scans and went home. That was when I saw the "STOMACH CANCER" label on the film envelope. How on earth, I wondered, could anyone think I had stomach cancer when I hadn't even had a biopsy? Surely this was a mistake, because it is common knowledge that most growths, masses, tumors are benign.

**"He was about as proud of retrieving it as my cat is when she drops a dead mouse on the front porch."**

Still, I couldn't resist a peek at the pictures. I know very little about medicine in general and x-ray pictures in specific, and the little I do know could easily fit on the head of a pin with enough room left over for the Lord's Prayer, which about that time I was thinking I might need. Even I could see that the very biggest thing on the films didn't belong there.

The next day, when I finally saw the surgeon, he confirmed it, and the wild rumpus began. As it happened, it was my vacation week, so I still hadn't used any sick days. According to the doctor, surgery was pretty uneventful, except for the size of the tumor: 30x21x14 cm., or as he put it "the size of your head." (Hopefully, my head isn't as ugly, though.) He was about as proud of retrieving it as my cat is when she drops a dead mouse on the front porch. He even had Polaroid photos of his hands and his partner's lifting it out of my abdomen, which he showed my husband immediately afterwards.

All right, I can hear at least half of you wondering if I wasn't an "obese beast" if I hadn't noticed a growth of that size, so let me tell you right now that while I'm not exactly anorexic, I thought I was fairly normal looking, though waist-less. As anyone who occasionally watches the diet/exercise gurus on Oprah's show knows, middle-aged women tend to either gain weight in their hips, develop-

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## New York GISTers meet

Good times were had at a recent gathering of GIST patients in the NYC area on August 11. Amongst those present, which included LRG Executive Director Norman Scherzer with wife, Anita, was LRG member Anita Getler, who said, "It was good to have the camaraderie of the group."

# MILESTONE

From Page 1

five-year plan and will run out in 2008. The team's ultimate success in finding a cure for GIST will depend upon our raising additional funds for the remaining three years and, as importantly, in continuing to leverage this money to effectively implement the world's first strategic plan to find a cure for this particular cancer. This opportunity to complete the pathway to a cure is unprecedented and well within our grasp.

In addition to raising additional funds, we are concerned that one of our ten priority projects, KIT/PDGFRA Wild-type GISTs, has had to be tabled because of a lack of Wild-type frozen tumor tissue. This project was created to identify alternative oncogenic mechanisms in GISTs that lack either KIT or PDGFRA mutations. This is particularly important because patients with such a genetic profile generally do not respond well to Gleevec (imatinib).

The collection of frozen tissue is a long standing problem, particularly when trying to obtain subsets of a rare cancer like GIST. The opportunity for such tissue collection is generally surgery but we rarely know in advance what mutational subtype a GIST patient has— unless the surgery has been preceded by mutational analysis performed during a needle biopsy or a prior surgery. Very few patients have such a mutational analysis going into surgery.

The situation is further complicated by the lack of experience many hospitals, particularly community-based hospitals, have in collecting, managing and shipping frozen tumor tissue. This is made even more difficult if the few patients from whom such tissue is collected send them to different medical researchers. Although the Life Raft Group research team is committed to sharing and coordinating such frozen tissue, this in not always the case in the broader research community.

Patients who are anticipating surgery and who know that their mutational status is Wild-type (i.e, they have had a mutational test done on their tissue and no mutations can be found) are urged to contact the Life Raft Group office prior to such surgery so that we can work together to get this vitally needed tumor tissue to our researchers.

**GIST is the perfect model for demonstrating how to cure cancers**

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. Finally, we have created an innovative research strategy, including prioritized project areas and the means to achieve them.

The history of this disease is summarized below. It has brought us to the point where we have the right scientific tools and the right researchers at the perfect time and place to demonstrate how to treat and cure cancer.

## 1900-2000

Biology: Poor understanding; most GIST cases are misdiagnosed.

Treatment: Almost all cases resistant to traditional chemotherapy; what few responses are of short duration.

Remarks: Surgery is the only effective treatment; After surgery is no longer feasible, death is usually the inevitable outcome.

## 2001-2006

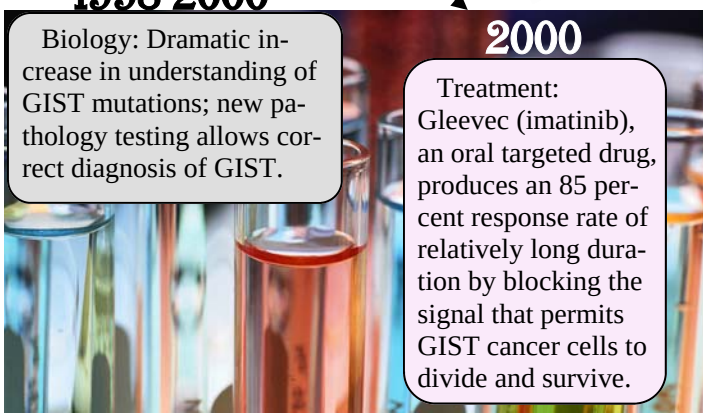
Biology: More breakthroughs in understanding the mutational explanations for Gleevec resistance.

Treatment: New targeted drugs like Sutent (sunitinib) begin to address Gleevec treatment resistance.

Remarks: Relatively long period of response provides a window of opportunity for destroying residual cancer cells


## 1998-2000

Biology: Dramatic increase in understanding of GIST mutations; new pathology testing allows correct diagnosis of GIST.



## 2000

Treatment: Gleevec (imatinib), an oral targeted drug, produces an 85 percent response rate of relatively long duration by blocking the signal that permits GIST cancer cells to divide and survive.

## 2007-2011: Pathway to a cure

Biology: We will identify the remaining key reasons for GIST resistance and we will figure out how to target and destroy the residual cancer cells that have not yet responded to treatment.

Treatment: We will bring together a combination of drugs that target the key pathways that permit GIST cancer cells to divide and survive and we will come up with a treatment regimen that will kill all the cancer cells, including the residual ones.

Remarks: GIST will become a chronic disease that can be managed by a cocktail mix of drugs. The final step is the cure of GIST which will eliminate the need for a lifetime of very expensive drugs, some with significant side effects.

# PEDIATRIC

From Page 1

able proliferation index. All female patients and about two-thirds of male patients lack activating mutations in *KIT/PDGFRA*. Our experience is in concordance with Miettinen et al. (*2*), who identified a wild-type *KIT/PDGFRA* genotype in all 13 pediatric GISTs analyzed, although sequencing analysis was not performed in the only pediatric male patient. Activating mutations were found, however, in two of our five male patients, one in the juxtamembrane domain of KIT receptor and the other in the kinase domain of PDGFRA. In the study by Price et al., two of their five pediatric patients were males, and one of them harbored a novel point mutation in codon 456 of *KIT* exon 9, while the other was wild-type (*3*). In spite of the overwhelming prevalence of wild-type genotype, pediatric GIST tumors consistently overexpress KIT protein, as evidenced by the strong immunostaining for CD117 (*1*,*4*) and KIT phosphorylation on biochemical assays. This finding is further supported by the high KIT mRNA expression on transcriptional profiling. The mechanism of constitutive activation of the KIT protein in these cases remains unclear. The transcriptional signature of pediatric GIST is distinct from adult wild-type or gastric GISTs (Figure 1). The top ranked genes overexpressed in the pediatric subset include: *BAALC, FGF4, PLAG1, IGF1R, NELL1,* and *CRLF1*.

The association of multifocal gastric GIST with paragangliomas and pulmonary chondromas affecting mostly females is diagnostic of Carney's triad (*5*). Although mostly sporadic, a few familial cases were included in the original cohort of Carney's triad (*6*). More recently it was recognized that the autosomal dominant inheritance of the dyad "paraganglioma and gastric GIST", or the "Carney-Stratakis syndrome" (CSS), represents a separate condition which affects both males and females and lacks the association with pulmonary chondromas (*7*). Mutations of the genes coding for succinate dehydrogenase (SDH) subunits, typically associated with familial paragangliomas, are most likely implicated in the pathogenesis of CSS (*8*). Once cases of CSS are eliminated, there are no inherited cases of the Carney's triad. The significant overlap between clinicopathologic features of pediatric GIST and Carney's triad, such as female predisposition, multifocal gastric location requiring multiple gastric operations and relatively long survival (even in the presence of lymph node or peritoneal/liver metastatic disease) suggests a pathogenetic link. Thus, at least a subset of the pediatric GIST patients may represent a *form fruste* of Carney's triad. Indeed, longer follow-up in some patients reveals the development of a second neoplasm, diagnostic of this syndrome. Furthermore, in a recent comprehensive genetic analysis of 41 tumors from 37 patients with Carney's triad, sequencing analysis for the entire coding region of *KIT, PDGFRA, SDHA, SDHB, SDHC,* and *SDHD* failed to identify any activating mutations (*9*). This result parallels the findings of a wild-type genotype in the majority of pediatric GIST patients.

There are a few controversial points regarding the prediction of outcome in pediatric GIST. The conventional criteria for assessing risk of malignancy, such as tumor size, mitotic activity and anatomic location are not reliable in pediatric GIST. These patients frequently present with multiple nodules within the stomach, thus the largest tumor dimension cannot be easily defined. Furthermore, we noted a wide range of variability in proliferation index between patients and even among multiple tumors from the same patient. Our experience is similar with that of Miettinen (*2*), who noted that some pediatric patients with GIST developed metastasis despite being classified as low risk by criteria established in adult GIST. Similarly, most of our patients with a low proliferation index (<5MF/50HPFs) eventually progressed with recurrent disease within the peri-gastric lymph nodes, peritoneal cavity or liver. These findings suggest that GISTs in children are unpredictable, being more prone to metastasis than comparable gastric tumors in adults. Secondly, the biology of pediatric GIST appears to be more indolent than the adult counterpart, with long-term survival even in the presence of metastatic disease and without kinase inhibition therapy.

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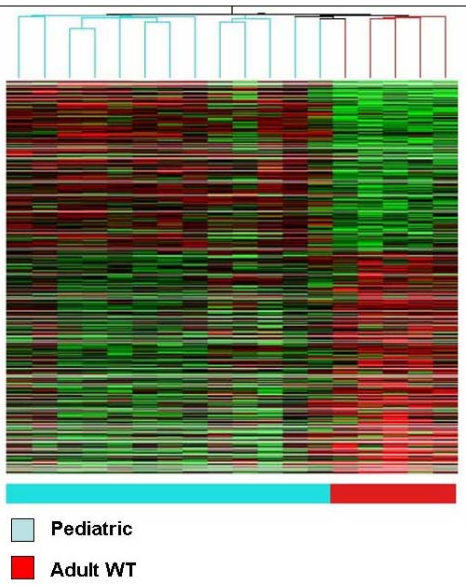
## Figure 1




Unsupervised hierarchical clustering of 13 pediatric GISTs and 5 adult wild-type GISTs showing distinct clustering of the two groups.

## Definitions:

**Indolent**- Relatively benign or inactive
**Loco-regional**- Limited to a local region
**Hyperplasia**- Abnormal increase in cells in a tissue, excluding tumor formation
**Proliferation index**- How quickly cells are dividing, how quickly a tumor is growing.
**Phosphorylation**- The addition of phosphate to a protein molecule. In most cases, synonymous with the activation of a protein.
**Paragangliomas**- Rare tumor that can be found in the abdomen, chest and head/neck region.
**Pulmonary chondromas**- Appear in lung. Because they usually do not cause symptoms and do not affect lung function, they do not usually need to be removed.
**Autosomal**- Referring to a chromosome that is not a sex chromosome.
**Succinate dehydrogenase**- A key enzyme in the citric acid cycle; it oxidizes succinate to fumarate.
***Form fruste***– An incomplete, abortive or unusual form of a disease.
**Heterogeneous**- Complex; consists of a diverse range of items or characteristics.

# TRIALS

From Page 3

## AMN107 (nilotinib, Tasigna)

*Efficacy and safety of AMN107 compared to current treatment options in patients who have failed imatinib and sunitinib*

Phase: III
Conditions: GIST
Strategy: Inhibit KIT (PDGFRA signaling)
NCT#: NCT00471328
US Contact: Novartis 800-340-6843
Trial# CAMN107A2201
Telephone: 862-778-8300
US Sites: **Dana Farber**, Boston, MA
Michael Quigley, 617-632-5117
**Washington Univ.,** St. Louis, MO
Nick Fisher 314-454-5102
**Karmanos Cancer Center**, Detroit, MI
Anne Marie Ferris, 313-576-9373
**UCLA**, Los Angeles, CA
Suzana Cobb, 310-206-1446
**Fox Chase**, Philadelphia, PA
1-800-Fox-Chase
**Washington Cancer Inst.**, Washington, DC
Jake Paterson, 202-877-5371

## Sunitinib (Sutent) or Imatinib (Gleevec)

*Safety and effectiveness of daily dosing with sunitinib*

Phase: III
Conditions: GIST
Strategy: Multiple Targets
NCT#: NCT00372567
US Contact: Pfizer Clinical Trial Information Service
PfizerCancerTrials@emergingmed.com
Telephone: 877-369-9753
US Sites: Contact Pfizer

## Perifosine + Gleevec

*Phase II study of Perifosine plus Gleevec for GIST patients*

Phase: II
Conditions: GIST
Strategy: Multiple Targets
NCT#: MDACC 2004-0968, NCT00455559
US Contact: Online Collaborative Oncology Group
ocogtrials@ocog.net
Telephone: 415-946-2410
US Sites: **MD Anderson Cancer Center**,
Houston, TX
800-392-1611
**Oncology Specialists**, Park Ridge, IL
Kathy Tolzein, RN, 847-268-8200
**Cancer Center at Century City**,
Los Angeles, CA
Dr. Sant Chawla
Coeur D'Alene, ID
Grand Rapids, MI
Sayre, PA

## Sorafenib (BAY 43-9006, Nexavar)

*Sorafenib in treating patients with malignant GIST that progressed during or after previous treatment with imatinib and sunitinib*

Phase: II
Conditions: GIST
Strategy: Multiple Targets
NCT#: NCT00265798
US Sites: **Univ. of Chicago Cancer Research Center**, Chicago, IL
773-834-7424
**Memorial Sloan-Kettering Cancer Center**, New York, NY
Dr. David D'Adamo, 212-639-7573
**City of Hope,** Duarte, CA
Warren Chow, MD, (866) 434-4673 x 64215
**Cancer Care Specialists**, Decatur, IL
James Wade III, MD, 217-876-6617
**Oncology/Hematology Assoc. of Cent. Illinois**, Peoria, IL
John Kugler, MD, (309) 243-3605.

## FR 901228

*FR901228 in treating patients with metastatic or unresectable soft tissue sarcoma*

Phase: II
Conditions: GIST/Sarcoma/Ewings
Strategy: Destroy kit+inhibit cell cycle+induce apoptosis (HDAC)
NCT#: NCT00112463
US Contact: Wake Forest University Comprehensive Cancer Center, Winston-Salem
Paul D. Savage, MD, Study Chair
Telephone: 336-713-6771
US Sites: Colombus, OH
Phoenix, AZ
Oakland, CA
Decatur, IL, plus multiple sites in the S and SE US
For more information go to clinicaltrials.gov

## IPI-504

*Safety Study of IPI-504 for GIST*

Phase: I
Conditions: GIST
Strategy: Destroy KIT (HSP90)
NCT#: NCT00276302
US Sites: **Dana Farber Cancer Institute**, Boston, MA
Michael T Quigley, RN, 617-632-5117
**Univ. Of Michigan,** Ann Arbor, MI
Rashmi Chugh, MD, 734-936-0453
**Premiere Oncology,** Santa Monica, CA
Courtney Carmichael, RN, 310-633-8400
**Premiere Oncology,** Scottsdale, AZ
Michael S. Gordon, MD, 480-860-5000

## Oblimersen + Imatinib

*Oblimersen and imatinib in treating patients with advanced GIST that cannot be removed by surgery*

Phase: I
Conditions: GIST
Strategy: Target KIT downstream signaling (AKT)
NCT#: NCT00091078
US Contact: Closed as of Mid July 2007

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# TRIALS

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## MP470

*MP470 in treating patients with unresectable or metastatic solid tumor or lymphoma*

Phase: I
Conditions: GIST
Strategy: Multiple Targets
NCT#: NCT00504205
US Contact: **South Texas Accelerated Research Therapeutics (START)**, San Antonio, TX
Telephone: Anthony Tolcher, MD, (210) 593-5250
US Sites: **Virginia Piper Cancer Center**, Scottsdale, AZ
Raoul Tibes, MD, 480-323-1350

## Perifosine + Sunitinib

*Perifosine + sunitinib for patients with advanced cancers*

Phase: I
Conditions: GIST/RCC
Strategy: Multiple Targets
NCT#: NCT00399152
US Contact: Online Collaborative Oncology Group
Telephone: 415-946-2410
US Sites: Huntsville, AL
**Tower Hematology and Oncology**, Beverly Hills, CA
Pomona, CA
Santa Monica, CA
Kalamazoo, MI
**Oncology Specialists**, Park Ridge, IL
Kathy Tolzien, RN, 847-268-8200.

## Doxorubicin + Flavopiridol

*Doxorubicin and Flavopiridol in treating patients with metastatic or recurrent sarcoma that cannot be removed by surgery*

Phase: I
Conditions: GIST/Sarcoma
Strategy: Inhibits production of KIT
NCT#: NCT00098579
US Contact: **Memorial Sloan-Kettering Cancer Center**, New York, NY
David R. D'Adamo, MD, PhD
Telephone: 212-639-7573

## CNF2024

*Study of oral CNF2024 in advanced solid tumors or lymphomas*

Phase: I
Conditions: Tumors/Lymphoma
Strategy: Destroy KIT (HSP90)
NCT#: NCT00345189
US Contact: **Biogen Idec**
oncologyclinicaltrials@biogenidec.com
US Sites: Scottsdale, AZ
New Haven, CT
**Cancer Therapy and Research Center**, San Antonio, TX
Pat O'Rourke, 210-616-5976

## KOS1022

*Study of oral KOS-1022 in patients with advanced solid tumors*

Phase: I
Conditions: Advanced solid tumors
Strategy: Destroy KIT (HSP90)
NCT#: Univ. of Colorado COMIRB 05-0627
US Contact: Anschutz Cancer Pavilion, Aurora, CO
Telephone: Sarah Eppers, 720-848-0052

## LBH589

*Phase IA, two-arm, multi-center, dose escalating study and administered by IV on 2 dose schedules in adult patients*

Phase: I
Conditions: Advances solid tumors
Strategy: Destroy kit+inhibit cell cycle+induce apoptosis (HDAC)
US Contact: **Nevada Cancer Institute**, Las Vegas, NV
Telephone: Donna Adkins, (702) 822-5173

## XL820

*Study of XL820 given orally daily to subjects with solid tumors*

Phase: 1
Conditions: Cancer/Solid tumor
Strategy: Multiple Targets
NCT#: NCT00350831
US Sites: **The Cancer Institute of New Jersey**, New Brunswick, NJ
Pamela Scott, 732-235-7459
PI: Mark Stein, MD
**Cancer Therapy and Research Center**, San Antonio, TX
Pat O'Rourke, 210-616-5976
PI: Alain C. Mita, MD

# PEDIATRIC

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GIST in young adults is a heterogeneous entity, with some cases resembling the clinicopathologic features of pediatric disease, while most are more in keeping with the adult counterpart. Although there is still a female sex and gastric location predominance, up to one-third of cases occur in male patients and in an extra-gastric location. About two-thirds of GISTs from young adults show the presence of *KIT/PDGFRA* mutation, with a similar distribution as in adult tumors, most in *KIT* exon 11, few in *KIT* exon 9, and rare in *PDGFRA* exon 12. The remaining one-third of GIST in young adults lack *KIT/PDGFRA* mutations, being mostly located in the stomach and occurring in female patients. It is this subset of young adult GIST patients that shares clinicopathologic fea-

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# PEDIATRIC

From Page 7

tures indistinguishable from pediatric GIST. By gene expression analysis also, these tumors cluster together with the pediatric GIST group, distinct from other adult wild-type GIST samples. The same distinctive set of genes found to be up-regulated in pediatric GIST are also found to be overexpressed in the GISTs from young adults. These findings suggest that a subset of GISTs occurring in patients younger than thirty years old may be biologically related to pediatric GIST. However, the majority of cases recapitulate closely the adult GIST phenotype.

Extrapolating from the adult experience, in which the wild-type genomic subset is the least sensitive to imatinib inhibition, the question still remains if pediatric GISTs, which typically lack *KIT/PDGFRA* mutations, will respond to imatinib. This question remains unresolved due to the rarity of pediatric GIST and its indolent natural history, both of which preclude large clinical trials. Anecdotal evidence based mainly on case reports shows poor clinical responses to imatinib (*10*). Preliminary data on a few patients suggest that sunitinib may have a better activity on pediatric wild-type GIST. Effective agents for pediatric GIST are needed. Also of interest is that the pattern of excruciating somatic soft tissue and bone pain seen in some children treated with imatinib and/or sunitinib, has not been previously described in imatinib-treated children with other diseases, such as pediatric CML and ALL (*11*). Our *in vitro* data suggest that second generation kinase inhibitors are more effective than imatinib against wild-type KIT transfected cells.

In summary, although pediatric GIST was initially regarded as a homogenous clinical and genetic subset with a predilection for females, gastric location and wild-type genotype, the analysis of additional cases expanded this view. Up to one third of cases may occur in males and these can harbor activating *KIT/PDGFRA* mutations and occur in the small bowel. With longer follow-up it is now becoming clear that some pediatric patients eventually develop secondary neoplasms diagnostic for Carney's triad, obscuring the distinction from the more common form of pediatric GIST. However, the gene expression profiles of pediatric tumors is distinct from the wild-type adult GIST and includes overexpression of *BAALC, IGF1R, FGF4, PLAG1* and *NELL1*. A subset of GISTs occurring in young adults share clinicopathologic features as well as a similar gene expression profile with the pediatric counterpart. Our *in vitro* data suggest that second generation kinase inhibitors are superior to imatinib therapy against wild-typeT KIT transfected cells. It remains to be determined, if these newer generation, broad-based inhibitors will prove efficacious in pediatric GIST patients as well.

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## Global GIST Network adds new GIST representative

Global GIST-Network

**Uruguay**
**Fabrizio Martilotta**
fabrizio.martilotta@gamil.com

# RIGG

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ing a pear shape, or they gain around their middle and have an apple shape. In my fifties, I just thought I was one of the apples.

Now, here comes the good news. That was the only tumor, and as big as it was, it didn't involve much of my innards that were terribly important, just a very small portion of stomach and my left diaphragm. So after a 16-day hospital stay, (True love means your husband will feed your snakes if you're in the hospital.) I was home, feeling reasonably well physically, but pretty shaky emotionally— until I linked up with the Life Raft Group, that is.

Darlene Rigg striking a pose with husband, Steve.

Using hindsight I ask myself if there were any signs I'd missed that should have given the doctor or me an earlier clue. There was the time 3 years previous that I had mentioned to him I felt a fist-sized lump in my left side, but he said there was nothing amiss, so I never mentioned it again. And there was the fact that I was anemic, but he said to get some over-the-counter iron pills, and that was the last either of us thought about it, although we never did another blood test to see if the iron pills helped (Don't worry, I've finally figured out that this particular doctor is a tad "slow", and I have not seen him since he sent me to the allergist.).

Then there was the fact that over the last couple of years I'd gone from my normal 5-6 hours of sleep to eight, but I just thought that now that I'm middle-aged, I was slowing down to normal. Let's face it, I am the healthiest person in Indiana, if not the USA, and I am never sick.

After a couple of stupefying weeks home from the hospital, I was appalled at myself when I realized I had just spent an hour watching Dr. Phil toilet train babies on TV! (My youngest "babies" are both 20 years old!) So in just under 5 weeks from surgery, I went back to work full time, where I am the head of a small town library reference department and known to the locals as "the woman in charge of useless information." My spirits took a definite change for the better as soon as I was being asked to settle the daily bet at the local body shop— what was the name of Poncho's horse on the 1950's TV show "The Cisco Kid"? (Answer: Loco)

And things have gotten better every day since. I was fortunate enough to meet some of you at January's Chicago Life Raft members' meeting, which gave a real boost to my morale. And last week, my 6-month CT scan showed no tumors yet, so I'm not even on Gleevec (but I take daily comfort and courage from the postings and advice the rest of you so generously offer).

Actually, I can honestly say that I'm better than ever. I haven't had a migraine since surgery (I used to have 3-4 a month). I walk at least 3 miles a day, uphill no less, and have done twice that without tiring. I only need 5-6 hours of sleep, although I sometimes lie in bed and read for another hour. And (this is the very best part) I'm a perfect size 12 again. I never told anyone at work what exactly was wrong with me; when I came back, the common consensus was that it must have been lyposuction and a tummy tuck, and I didn't tell them differently.

So here I am, looking forward to putting in our annual half-acre garden in a few weeks and going to the big city (Indianapolis) for the state's annual librarians' convention, where I'm planning to walk downtown and gape at tall buildings.

Life is good.

*Bye for now from the healthiest feeling person in Indiana, maybe in the USA,*

*Darlene*

## Did you Know?

Recently, someone on the listserv asked the question, "Is Sutent covered by Medicare?"

The answer? It depends on where you live.

•First go to **http://formularyfinder.medicare.gov/formularyfinder/selectstate.asp**.
•Select your **state**.
•Enter drug **name**.
•Click **"Continue with Selected Drugs"**

The Formulary finder will then list all plans that have Sutent in their formulary.

By clicking on a specific plan, you can see the limitations that may or may not be for the particular drug.

It's that simple.

# The Life Raft Group

## Life Raft staff

| | | |
|---|---|---|
| Executive Director | **Norman Scherzer** | nscherzer@liferaftgroup.org |
| Director of Operations | **Tricia McAleer** | tmcaleer@liferaftgroup.org |
| Assistant Program Coordinator | **Erin Kristoff** | ekristoff@liferaftgroup.org |
| Program Coordinator | **Sara Rothschild** | srothschild@liferaftgroup.org |
| Research Projects Coordinator | **Elizabeth Braun** | ebraun@liferaftgroup.org |
| Research Assistant | **Pamela Barckett** | pbarckett@liferaftgroup.org |
| Science Coordinator | **Jerry Call** | Jerry.Call@comcast.net |
| Office Assistant | **Gale Kenny** | gkenny@liferaftgroup.org |
| Administrative Assistant | **Matthew Mattioli** | mmattioli@liferaftgroup.org |
| Summer Database Assistant | **Marko Filipovic** | mfilipovic@liferaftgroup.org |

### Contact the Life Raft Group

40 Galesi Drive
Wayne, NJ 07470
Phone: 973-837-9092
Fax: 973-837-9095
Internet: www.liferaftgroup.org
E-mail: liferaft@liferaftgroup.org

## Life Raft volunteers

| | | |
|---|---|---|
| General Counsel | **Thomas Overley** | guitarman335@msn.com |
| Accountant | **Kristi Rosenberg** | kristi@mackeycpas.com |
| Accounting Firm | **Mackey & Mackey** | calvin@mackeycpas.com |
| Database Consultant | | |
| | **Steven Rigg** | StevenRigg@aol.com |
| List Manager | **Mia Byrne** | mebmcb@wowway.com |
| Newsletter Editor Emeritus | | |
| | **Richard Palmer** | richardpalmer@hawaii.rr.com |
| Web Designer | **Tami Margolis** | tami@comcast.net |
| Fund-raising co-chairs | | |
| | **John Poss** | John@PossHaus.com |
| | & **Gerald Knapp** | gsknapp@winfirst.com |
| Science Team | **Jim Hughes** | tjhughes43@comcast.net |
| | **David Josephy** | djosephy@uoguelph.ca |
| | **Michael Josephy** | mjosephy@gmail.com |
| | **Rick Ware** | rwkathie1@aol.com |
| | **Glenn Wishon** | gwishon@earthlink.net |

## Board of Directors

### Executive Committee

| | |
|---|---|
| **Stan Bunn**, President | SBunn@BSTGlobal.com |
| **Jerry Cudzil**, Secretary-Treasurer | Jerry.Cudzil@DACFunds.com |
| **John Poss**, Fund-raising | John@PossHaus.com |

### Directors

| | |
|---|---|
| **Robert Book** | RMBook2@aol.com |
| **Mia Byrne** | mebmcb@wowway.com |
| **Chris Carley** | ccarley@fordhamco.com |
| **Jim Hughes** | tjhughes43@comcast.net |
| **Jerry Knapp** | gsknapp@winfirst.com |
| **Dr. Arnold Kwart** | amkbmp@aol.com |
| **Ray Montague** | rmontague@avalonexhibits.com |
| **Rodrigo Salas** | rsalas@maprex.com.mx |
| **Silvia Steinhilber** | nswplas@mts.net |

## Life Raft regional chapters

| | | |
|---|---|---|
| Alabama | **Pat George** | patgeorge@bham.rr.com |
| Arizona | **Linda Martinez** | linda.martinez1@cox.net |
| Colorado | **Jerry Call** | Jerry.Call@comcast.net |
| Connecticut | **Anita Getler** | aquarius2550@comcast.net |
| California | **Floyd Pothoven** | floyd@fastsemi.com |
| | **Martha Zielinski** | john.martha@sbcglobal.net |
| Florida | **Skip Ryan** | skipryan@tampabay.rr.com |
| Georgia | **Pat Lemeshka** | riyank@bellsouth.net |
| Idaho | **Janet Conley** | jkconley73@cableone.net |
| Illinois | **Richard Kinzig** | rjkinz@aol.com |
| Indiana | **Robert Book** | RMBook2@aol.com |
| Kansas | **Jim Toyne** | jimtoto@aol.com |
| Maryland | **Bonnie Emerson** | bteensey1@hotmail.com |
| Massachusetts | **Janice Leary** | jleary@orr.mec.edu |
| Michigan | **Ellen Rosenthal** | ebrosenthal@comcast.net |
| Nevada | **Erik Krauch** | erik.krauch@cox.net |
| New Jersey | **Amy Spires** | amylspires@hotmail.com |
| New York | **Dan Cunningham** | Daniel.Cunningham2@pseg.com |
| North Carolina | **Chuck Korte** | pckorte@earthlink.net |
| Ohio | **Kaye Thompson** | tnt.1@sbcglobal.net |
| Oregon | **Gail Mansfield** | timothy.mansfield@GTE.NET |
| Pennsylvania | **Tina Smith** | jt3smith@ptd.net |
| South Carolina | **Al Boyle** | captboo@alltel.net |
| Tennessee | **Alice Sulkowski** | abigs@charter.net |
| Texas | **Kerry Hammett** | hammett@uthscsa.edu |
| Washington | **Deanne Snodgrass** | g-d-snodgrass@comcast.NET |
| Wisconsin | **Rick Ware** | rkwelmwood@yahoo.com |

## Life Raft country liaisons: **Learn more about the Global GIST Network: www.globalgist.org**

| | | |
|---|---|---|
| Australia | **Katharine Kimball** | katharine_kimball@hotmail.com |
| Belgium | **Kris Heyman** | kh@contactgroepgist.be |
| Bolivia | **Virginia Ossio** | vossiop@acelerate.com |
| Brazil | **Vanessa Passos** | vanessa@endo.med.br |
| Canada | **David Josephy** | djosephy@uoguelph.ca |
| China | **Ruijia Mu** | mu_ruijia@yahoo.com |
| Colombia | **Jaime Peralta** | peraltas@cable.net.co |
| Costa Rica | **Michael Josephy** | mjosephy@gmail.com |
| France | **Estelle LeCointe** | gist.estelle@laposte.net |
| Germany | **Markus Wartenberg** | wartenberg@lebenshauspost.org |
| Iran | **Negar Amirfarhad** | negaraf@sympatico.ca |
| Ireland | **Carol Jones** | roycal-re-gist@hotmail.com |
| Israel | **Ben Shtang** | ehuds@merkavim.co.il |
| Italy | **Anna Costato** | anna.costato@virgilio.it |
| Kenya | **Francis Kariuki** | bridgestone@coopkenya.com |
| Lithuania | **Virginija Zukauskiene** | virginija.starkute@gmail.com |
| Malaysia | **Yong Choo Sian** | ycspj2005@yahoo.com |
| Mexico | **Rodrigo Salas** | rsalas@maprex.com.mx |
| Netherlands | **Ton de Keijser** | tdk@liferaftgroup.nl |
| Norway | **Jan Einar Moe** | lrgnor@online.no |
| Poland | **Stan Kulisz** | listy@gist.pl |
| Romania | **Simona Ene** | si_mi_ene@yahoo.com |
| Russia | **Tanya Soldak** | tsoldak@citihope.org |
| Singapore | **Yong Choo Sian** | ycspj2005@yahoo.com |
| Switzerland | **Ulrich Schnorf** | ulrich.schnorf@bluewin.ch |
| Turkey | **Haver Tanbay** | tanbay@tanbay.net |
| U.K. | **David Cook** | D.Cook@sheffield.ac.uk |
| Uruguay | **Fabrizio Martilotta** | fabrizio.martilotta@gmail.com |