

August blessings for April: a baby born in the LRG!

By Erin Kristoff

On August 19 at 6:52 AM, LRG member and pediatric GIST patient, April Calloway Stephens gave birth to a healthy baby girl named Mary Catherine Stephens (nine pounds, one ounce, 21 inches in case anyone is wondering). This is the first time a pediatric member of the LRG has had a child.

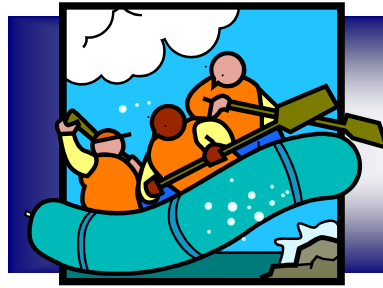
April always hoped to be able to start a family with her husband, Heath. "We had discussed this with my doctor and he was comfortable with our plans."

Her doctor advised her to go five years on Gleevec before stopping treatment and remained in touch with Dr. George Demetri of Dana Farber to get his recommendations and review other cases. "But there weren't any other cases to guide us, so we had to trust everything would be okay and this was the right



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Battling gastrointestinal stromal tumor



LIFE RAFT GROUP

October 2007

In memory of Lee Kavaloski, Bruce Staffin, Candace Frank & Joe Marlatt

Vol. 8, No. 10

Building blocks of tumor progression

By Dr. Brian Rubin
Cleveland Clinic

This is the eighth article in a series written by each of the key members of the LRG Resistance Research Team.

Several articles in the LRG newsletter from our GIST Resistance Research Team have been written over the last year, focusing mainly on the role of *KIT* and *PDGFRA* mutation in the genesis and treatment of GIST. We know that *KIT* and likely *PDGFRA* are very important for the interstitial cells of Cajal (ICC), a cell that resides along the entire length of the intestinal tract and has the important function of coordinating peristalsis, the

movement that propels food along the digestive tract. ICC strongly express *KIT* protein and loss of *KIT* results in loss of ICC. Much like the pacemaker cells of the heart, which coordinate contraction, ICC coordinate peristalsis through an inherent pacemaker function. After receiving a signal from the brain that food has been consumed, rhythmic contractions are set up with the help of the ICC that propel food along the gastrointestinal tract. Thus, the ICC serve a critical function in normal gastrointestinal function. As you



RUBIN

might imagine, ICC are known or thought to be involved in many diseases of the gastrointestinal tract. There are many lines of evidence that have shown

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GIST in the UK: realities bite hard

By Roger Wilson
Director, Sarcoma UK

The fact that there is a battle to get GIST patients in the UK the treatment which their doctors (observing normal international clinical practice) want them to have may seem strange to those who know that



WILSON

the UK is a member of G8, the group of the eight wealthiest nations in the world. Some background will help.

Healthcare in the UK is funded and run through the National Health Service, the NHS. It has a near 60 year record of treating people in the UK free at the point of need. It is committed to evidence-based medicine. The NHS is a top down structure funded through the taxation system. Indi-

vidual hospitals are financially managed autonomously, even though owned by the NHS, and they bill their services to Primary Care Trusts (or PCTs) (in England) and local Health Boards (in Scotland and Wales). The work of the PCTs is co-ordinated through regional Strategic Health Authorities; the Health Boards report directly to the national governments in Wales and Scotland. (I shall refer to them all as PCTs).

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Check out the second half of Darlene Rigg's story on page 2

Questions no one wants to face: Five years later, Rigg's still got it

By Darlene Rigg

This is the second part of a two-part series by Rigg. Last month, we published her listserv post from 2003, this month Darlene gives an update on what has changed in the last five years.

This October is a bit of a milestone for me – it's been five years since surgery that removed a 10+ pound GIST, quite easily the most shocking surprise of my life. I remember pressing the chief oncologist at our local hospital as to my life expectancy and hearing her say with a smile, as though she were being generous, "I think I can promise you two years." As soon as she left the room, I burst into tears; I wasn't quite sure if the doctor's "two years" meant two years before recurrence or two years before a miserable death, but in either case, it was at least thirty years too short for this 52-year-old woman.

As soon as I got home from my 16-day hospitalization, I threw out all the plastic cups in the kitchen cupboards. Then I replaced them with the pretty drinking glasses I'd always reserved for company. In the past I could never bring myself to risk them on an everyday basis (not with four kids in the house!) lest they all break. Now I was kicking myself for not treating my family and myself at least as well as we treated our guests.

My newfound pleasure with the drinking glasses, however, did not inspire me in other facets of my life. Never having been much of a shopper, now I was even more reluctant to buy anything new. Why buy a new pair of shoes, for instance, when the ones I had in the closet might make it another two years? I felt exactly the same way about my sewing supplies, even though I am an avid crafter. With a dozen unfinished projects in the works and a mountain of sewing supplies, I wasn't about to buy more just

to have it all go to my sister-in-law Charlotte after my demise. It wasn't that I had anything against Char, who enjoys sewing as much as I do, but I just wasn't in the mood to "share my toys" if I had to die to do it. I'd rather have no toys at all.

Finding the Life Raft Group on the Internet soon after my diagnosis helped to ease my sour attitude a bit. Being able to speak with fellow Gisters face-to-face at a Chicago meeting was an even bigger blessing. Here I found living examples of how to temper fear and suffering with courage, sympathy, grace. Shamefully, I grasped at every hopeful story and took everyone's experiences to heart, but my negativity was slow to disappear. In a blatant fit of self pity I splurged on a hundred candles, and envisioned my husband Steven using the leftovers to send me out in a blaze of glory.

Fourteen short months after my GIST surgery, another health problem led to a D&C and a cone biopsy. The gynecological oncologist informed Steven and me, "I won't know for sure until next week when the results are in, but it looks like you may have another type of cancer." That next week of fear and uncertainty, was one of defiance, too: cancer might snatch me bald-headed, but I wouldn't be wasting my time fiddling around with wigs! Meanwhile, I girded myself up to such a high level to hear bad news that I wasn't prepared for the good news – although I needed an operation, I didn't have cancer. And that's how a hysterectomy became my favorite Christmas present that year.

So here I am five years later. In many ways I feel like a fraud when I read everyone's posts. I don't feel like I can contribute much; I'm still GIST free and have never been on Gleevec, so I don't have any useful advice or experience to offer anyone. Only hope.

Once, I asked the doctor whether my original diagnosis could have been

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.

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International clinical trial update

By Jerry Call

LRG Science Coordinator

This month we will be reporting on international trials outside of the United States. Please refer to last month's or next month's newsletters for U.S. trials.

AMN107 (Nilotinib, Tasigna)

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

Phase: III
Conditions: GIST
Strategy: Inhibit KIT
NCT#: NCT00471328
Contact: Novartis maintains a central contact number for this trial.
Telephone: 800-340-6843
Sites: We have reports of as many as 30 sites being open. We were unable to confirm this at the time of this publication. Use the central contact number for the latest information.

Imatinib + RAD001 (everolimus)

Treatment of patients with everolimus and imatinib mesylate who have progressive GIST and are resistant to imatinib mesylate

Phase: II
Conditions: GIST
Strategy: Inhibit/target KIT downstream signaling
NCT#: NCT00510354
Telephone: 41 61 324 1111
Sites: The clinicaltrials.gov website lists 10 sites as open in Germany. We were unable to independently verify this at the time this newsletter was published. Please use the listed contact number for specific trial site information.

Imatinib + RAD001 Phase II

Clinicaltrials.gov now lists a phase II trial combining Gleevec (imatinib) + RAD001 (everolimus) as recruiting. Ten sites are listed in Germany, but we were unable to verify if all of these sites (or any of them) were open.

Masatinib, (AB1010)

Evaluation de l'efficacité et de la tolérance de l'AB1010 en traitement de première ligne pour les tumeurs GIST localement avancées et/ou métastatiques, inopérables

Phase: II
Conditions: GIST
Strategy: Inhibit KIT
NCT#: Masatinib
Contact: lecesne@igr.fr
Telephone: +33 142114211
Sites: Institute Gustave-Roussy Villejuif Cedex, France

Radiation Therapy as Palliative Treatment of GIST (GIST-RT)

Phase: I/II
Conditions: GIST
Strategy: Radiation
NCT#: NCT00515931
Telephone: 947173208 Ext. 358
Sites: Helsinki Univ. Central Hospital Helsinki, Finland

AZD2171

The Biological Activity of AZD2171 in GIST

Phase: II
Conditions: GIST, Sarcoma
Strategy: Multiple targets
NCT#: NCT00385203
Telephone: 1-866-992-9276
Sites: Christie Hospital NHS Trust Manchester, United Kingdom
Dept. of Cancer Therapeutics
Institute of Cancer Research
Sutton, Surrey, United Kingdom

AMN107 Phase III

We have reports of as many as 30 sites being open. We were unable to confirm this at the time of this publication.

Palliative Radiation Phase I/II

A new trial using radiation for palliative treatment opened in Helsinki.

PTK787, ZK222584

PTK787/ZK222584 in the treatment of metastatic GIST resistant to imatinib

Phase: II
Conditions: Sarcoma
Strategy: Multiple targets
NCT#: NCT00117299
Telephone: +358-9-471-73208
Sites: Helsinki Univ. Central Hospital Helsinki, Finland
Istituto Nazionale Dei Tumori Milan, Italy

OSI-930

Dose Escalation Study of Daily Oral OSI-930 in Patients with Advanced Solid Tumors -Sarcoma

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

Global GIST Network adds new GIST representative



Global GIST-Network



Thailand
Kittikhun Pornpakakul
kittikun_p@yahoo.com

PROGRESSION

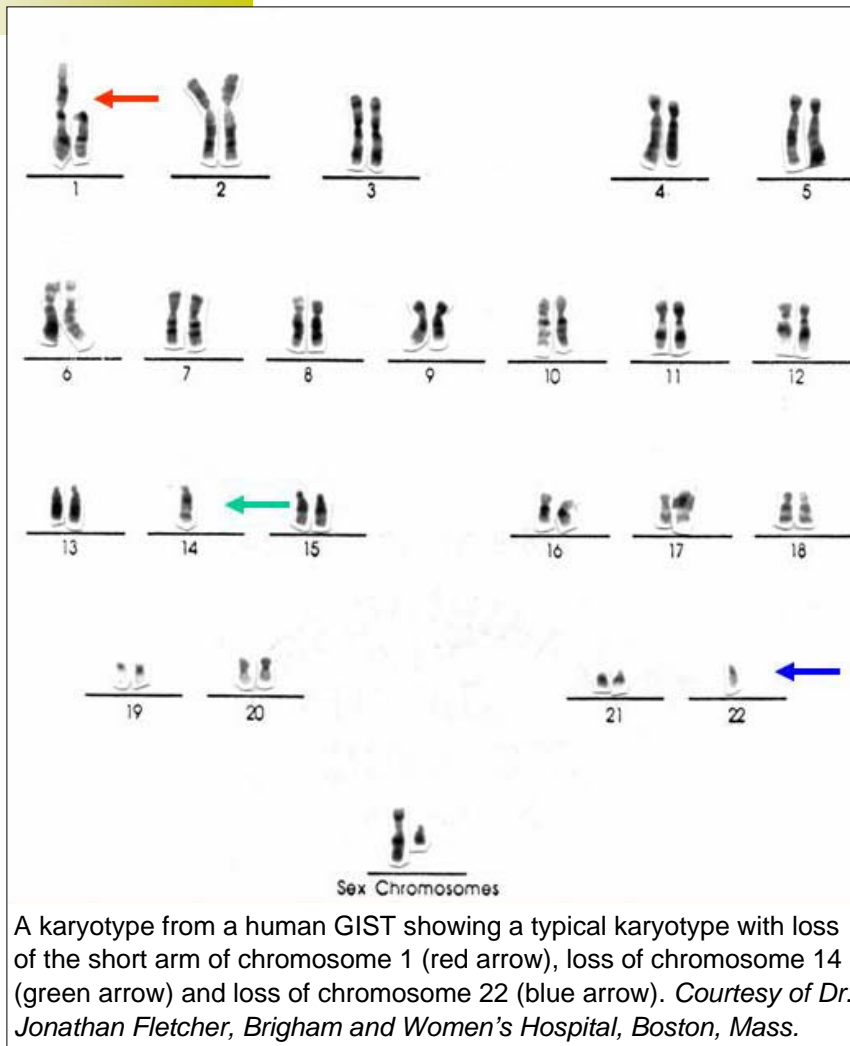
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that an activating mutation in *KIT* or *PDGFRA* within ICC or a related pre-ICC-type cell, causes the cell to proliferate in an uncontrolled fashion, resulting in a GIST. *KIT* or *PDGFRA* mutation is said to be the initiating event (tumor initiation) that gives rise to GIST. We know that *KIT* or *PDGFRA* mutation is important because when we target them with a drug (eg. Gleevec/ Imatinib mesylate or Sutent/ Sunitinib maleate), GISTs stop growing. However, *KIT* or *PDGFRA* mutation is “the tip of the iceberg” in

terms of important genetic changes that are found in GIST. Several more of these changes take place in GISTs after initiation by *KIT* or *PDGFRA* mutation. In aggregate these changes are involved in what is known generically as tumor progression.

While I don’t want to belittle tumor initiation – after all, understanding tumor initiation has led to some amazing therapeutic options for the treatment of GIST – tumor progression is what takes a rather innocuous tumor that is not very likely to do much harm to anyone and turns it into a nasty cancer capable of moving within the body (metastasis) to sites like the liver and in the end, is what enables a cancer to kill the patient. Therefore, it is likely that to truly cure GIST we will need to understand tumor

Figure 1.



progression. While much is known about tumor progression in other systems, very little is known in GIST.

Genes/proteins involved in tumor progression can be grouped into tumor suppressors and oncogenes. The normal function of tumor suppressors is to stop cells from dividing/proliferating inappropriately while the normal function of oncogenes is to facilitate cellular division/proliferation, cell migration, etc.. Generally, inactivating mutations arise in tumor suppressors, resulting in increased/inappropriate cell division/proliferation while oncogenes generally have activating mutations and/or are amplified genetically so there is a lot more protein around than is normal.

TP53 (known as P53) is a well-known tumor suppressor involved in many

types of cancer. Its job is to prevent cells from dividing inappropriately, as in the case of a cell with extensive DNA damage. RAS is a well known oncogene. RAS seems to control growth through positive actions.

Much of what we know about tumor progression in GIST comes from cytogenetic/ chromosomal analysis of GISTs. Jonathan Fletcher and Maria Debiec-Rychter from the GIST Resistance Research Team are expert cytogeneticists and have both contributed many karyotypes/cytogenetic profiles of GISTs. Cytogeneticists examine the chromosome number and structure of cells to identify regions that are abnormal. Humans have twenty three pairs of chromosomes, twenty-two pairs of autosomes (numbered 1-22) and one pair of sex chromosomes (designated X or Y). Men have an X and a Y chromosome while women have two X chromosomes. Each chromosome has a short arm (designated “p”) and a long arm (designated “q”). Other techniques have also been used to identify chromosomal regions that are consistently abnormal in GIST including

Fluorescence in-situ Hybridization, *Loss of Heterozygosity Studies* and *Comparative Genomic Hybridization*. A description of these techniques is beyond the scope of this article but essentially, they allow a more fine structure analysis of chromosomes than cytogenetic analysis. All of these studies are complementary.

KIT and *PDGFRA* both reside next to each other on the long arm of chromosome 4 but this region of chromosome 4 looks normal in GIST. This is because GISTs are highly dependent on full-length *KIT* or *PDGFRA* in most cases and the genetic changes we find in *KIT* and *PDGFRA* are too small to be seen by these types of studies, which require

Two reports of good Nexavar response

By Jerry Call
LRG Science Coordinator

The Life Raft Group has received two recent reports of patients that had failed multiple therapies and then apparently responded to Nexavar (also known as sorafenib or BAY 43-9006). In both cases, the patients had failed Gleevec, Sutent and AMN107.

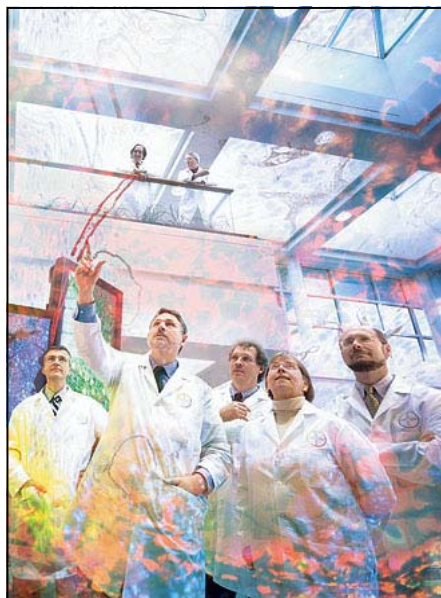
Anecdotal reports like this should be viewed with considerable caution. Carefully designed clinical trials are ultimately the only way to prove drug efficacy. We do, however, occasionally report on interesting or unusual cases.

In the most striking case, an Israeli patient had failed six therapies, including Gleevec, Sutent and AMN107. After failing all of these, he managed to obtain Nexavar. After 70 days on Nexavar, a CT scan showed shrinkage in everyone of his 15 metastases ranging from 15 percent to 50 percent. Shrinkage of GIST after initial treatment with Gleevec is a rare event. This patient was known to have a primary exon 11 mutation with at least one secondary exon 17 mutation (resistant patients often have many undetectable secondary mutations).

In the second case, the patient was able to leave hospice and had dramatic symptomatic improvement. A CT scan is

needed to verify his response. In both cases patients reported that unwanted weight loss was a problem.

Nexavar was approved in December



Courtesy of Bayer 2005 Annual Report

2005 for kidney cancer and is in phase II trials for GIST. Patients wishing to try Nexavar or other new agents are encouraged to enter clinical trials if they are eligible. Some patients, however, may not be eligible for or may not be physically able to get to the clinical trials. For these patients, off-label prescription of Nexavar may represent another option after failure of Gleevec and Sutent. Off-

label treatments such as this have many challenges, including unproven efficacy, unknown toxicity (for combinations) and possibly denial of coverage by insurance but they may represent a last hope for some patients.

Nexavar is in some ways similar to Sutent. It inhibits KIT and the VEGF receptors (like Sutent) and also adds RAF inhibition. KIT inhibitors have different activity profiles however. Mutations occur at many different places in KIT and almost all KIT inhibitors inhibit some mutations but not others. Both Nexavar and Sutent have recently been shown to inhibit the KIT “gatekeeper” mutation in exon 14 (T670I). This is a common secondary mutation in GIST and is not inhibited by Gleevec. Nexavar also inhibits several other kinases including VEGFR-2, VEGFR-3, PDGFR-β, FLT3, and RET.

The phase II trial for BAY 43-9006 is open and recruiting patients. The University of Chicago maintains a central contact point for this trial at the University of Chicago Clinical Trials Office, 773-834-7424. The trial sites are:

- University of Chicago- Chicago, Ill.
- Decatur Memorial Hospital- Decatur, Ill.
- Oncology/Hematology Associates of Central Illinois- Peoria, Ill.
- Memorial Sloan-Kettering Cancer Center-New York, N.Y.
- City of Hope – Duarte, Calif.

Long Beach Marathon team have surpassed the half-way mark to their \$10,000 goal!

Last week, Paul Montuori reported that he and his team had reached \$5,000.

Paul has asked his volunteers, “C'mon, everyone needs to reach down deep and encourage everyone we know to make a donation!”

Donations, which will be used to support LRG GIST research, can be made online by credit card at:



www.active.com/donate/3montys4cure

Or a check can be mailed to:
Life Raft Group
Attn: Long Beach Marathon
40 Galesi Dr, Suite 19
Wayne, NJ 07470

If you have any questions, please email Paul at moose239@hotmail.com.

PCTs

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PCTs (there are 135 of them in England alone) have a high degree of autonomy and a financial limit to their annual budget. This is funded in a way that an overspend in one year has to be clawed back during the next year, although the deficit accumulates on its balance sheet as well. This double whammy of accounting mystery is an important influence in their decision making. PCTs have contracts with their local hospitals to treat common illnesses and all of them are required to have a process in place to handle funding decisions about treatment in 'exceptional' situations, those not covered by those contracts or by national guidance.

National guidance within the NHS comes from the National Institute for Health and Clinical Excellence, known as NICE. It is mandatory for PCTs to fund treatment which meets NICE recommendations.

So how does all this affect GIST patients ?

In 2003/4 NICE undertook a technology appraisal of imatinib (Glivec) and concluded that treatment for metastatic or unresectable GIST at 400mg/d was cost effective and should be funded. It did not approve an escalated dose (600mg/d or 800mg/d), saying that the evidence did not exist for efficacy. Its cut off point for evidence was one month before the first publication in September 2004 of the first data on 800mg/d from the two large scale trials. Nor did it approve 400mg/d for patients who had evidence of tumour growth on CT. This decision was immediately in conflict with the growing data on the clinical effect imatinib has on GIST tumours.

The resulting guidance was mandatory on PCTs from November 2004. With the weight of evidence building up almost monthly in peer-reviewed publications, let alone what clinicians themselves were learning about imatinib from using it with their patients, it was out of date before it was in force.

The last three years have presented

patients, doctors and advocates with a sterling challenge. As patients have failed imatinib at 400mg/d there have been battles to gain funding for an escalated dose. Some PCTs (usually those without budget problems) accept the doctor's recommendation and there are no problems. Others, usually with financial problems, are likely to lean on the (out of date) NICE recommendation and refuse funding. Some will recant on appeal, others will be quite adamant. I will return to the story of one of these shortly.

The result is what is known in the UK as a "postcode lottery". It is quite possible for two patients with identical problems, living in the same neighborhood, being treated by the same doctor, to have different treatments because one lives in the area of a PCT which will fund, and one lives in the area of another who won't.

The arrival of sunitinib (Sutent) complicated things further. Through the worldwide trial and compassionate use both before and after the trial was terminated in early 2006, a number of patients moved to sunitinib rather than a higher dose of imatinib on relapse. When these patients fail sunitinib an escalated dose of imatinib may be appropriate and, if isn't or if the patient fails again, at the very least a maintenance dose of 400mg/d imatinib should be available. Each of these situations becomes a fight as well.

Here I have to pay tribute to our specialist oncologists up and down the country. Their advocacy has been by far the most important factor in moving us to the current position where it is now becoming accepted that 800mg/d of imatinib is the 'norm' on failure at 400mg/d, although we are still a long way from getting escalation to the 800mg/d dose agreed as the first-line treatment for specific GIST patients based on their tumour mutation.

Our main problems at present lie with funding for sunitinib – usually as third-line treatment. In a recent battle with one PCT the advocate (the patient's inspiringly determined wife) was able to draw on information from the GIST Support UK community, from the experience of Kidney Cancer UK in gaining funding for sunitinib for renal cancer patients, and from Sarcoma UK which has had access to legal papers about PCT decision-making. The case was won on appeal by establishing the exceptional nature of the situation, after a lot of stress and hard work.

It is that word 'exceptional' which we are learning to use more and more. GIST is a rare disease and the understanding of it in PCTs is at best limited and in most cases nil. They are reliant on expert advice and on their own understanding of the legal requirements to have a proper policy, a carefully managed process, to conduct their decision-making with probity and to have full regard for the individual patient's human rights.

On this last issue alone this prevents them creating a blanket rule for refusing funding, every exceptional circumstance must be reviewed individually. Only NICE can issue guidance with the effect of law.

In one case, which has still not been resolved, Bromley PCT in south-east London refused funding for 800mg/d of imatinib in summer 2006 relying on the opinion of a public health doctor to contradict the opinion of Professor Ian Judson. The opinion was obtained verbally and the doctor did not see the papers he was commenting on, saw no scan reports, and did not examine the scans himself. Professor Judson's opinion that the patient had an "unequivocal response" to a trial dose of 800mg/d imatinib was thus ignored and no second opinion was sought. I am sure most readers will know that Prof Judson is one of the world's leading GIST experts (and this year's chair of CTOS). You might choose not to agree with me that



Carney-Stratakis syndrome explained

By Jerry Call

LRG Science Coordinator

A diverse group of researchers has found the genetic defects that cause a rare type of familial GIST called “Carney-Stratakis syndrome”. This syndrome has some similarities to Carney’s Triad but it is a distinct entity. This discovery may one day lead to better treatments for the affected patients and may give researchers new insights into Carney’s Triad and possibly into pediatric GIST in general.

Researchers from the Carney Triad and Carney-Stratakis Dyad Consortium have discovered that patients with Carney-Stratakis syndrome have an inherited mutation in one of three (of the four) genes that code of the succinate dehydrogenase protein complex.

Succinate dehydrogenase (also known as succinate-coenzyme Q reductase) is an important enzyme complex that is bound to the inner membrane of the mitochondria. Mitochondria are “organelles” (separate cellular structure having a specialized function and enclosed in its own membrane) within the cell. Mitochondria are known as “cellular power plants” because they generate most of the cell’s supply of ATP, an important source of energy.

Succinate dehydrogenase (SDH) converts succinate into fumarate in the citric acid cycle (also known as the tricarboxylic acid cycle or the Krebs cycle). It also participates in the electron transport chain (Complex II).

SDH acts as a tumor suppressor gene. Defects in SDH result in a reduction in enzymatic activity. One effect of this is that succinate levels increase. This causes an increase in the levels of HIF1- α (by blocking HIF1- α degradation), an important protein which stimulates the

formation of new blood vessels (angiogenesis) and induces other tumor promoting genes. Another effect can be an increase in Reactive Oxygen Species (ROS) such as superoxide.

Background

In 1977, Dr. P. Aidan Carney, a pathologist at the Mayo Clinic, first described Carney’s Triad. Carney’s Triad occurs mostly in younger females. Patients with Carney’s triad may have several different types of tumors including GIST, pulmonary chondroma, and paragangliomas. If any two of these tumors are present, a diagnosis of the “triad” is usually made.



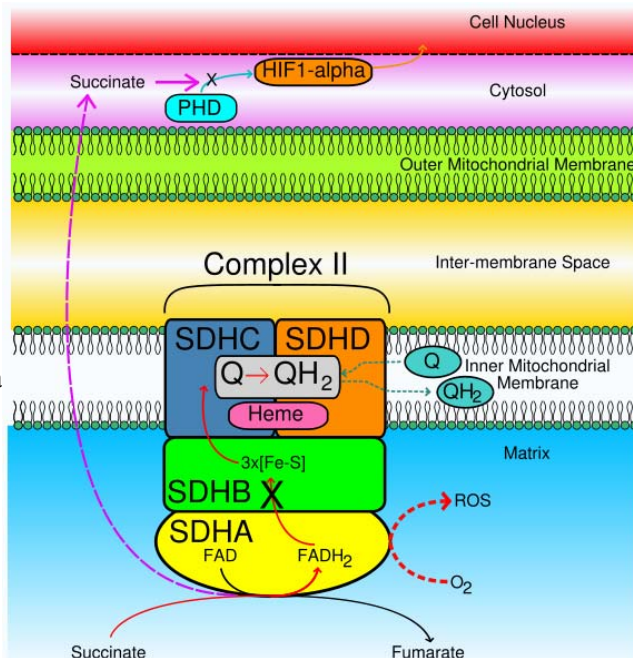
STRATAKIS

tant differences compared to the rest of the Triad cases. First, the patients in the familial group never had pulmonary chondromas. The second thing that they found was that the familial group had many more males (almost half were males) than the rest of the patients with Carney’s Triad, which had many more females than males. In 2002, Carney and Stratakis published their findings and medicine had a new syndrome. They called this syndrome “Familial Paraganglioma and Gastric Stromal Sarcoma.”

Carney and Stratakis began collaborating with other researchers from France, Italy and the U.S. and together they formed the Carney Triad and Carney-Stratakis Dyad Consortium. Focusing on the familial group, the researchers homed-in on succinate dehydrogenase, an enzyme known to have mutations in familial forms of paraganglioma. They found what they were looking for. The affected families had germline mutations in either SDHB, SDHC or SDHD; three of the four genes that code for succinate dehydrogenase. These results were recently published in the European Journal of Human Genetics and the New England Journal of Medicine.

The consortium also searched for mutations in the remaining Carney’s Triad patients, but did not find mutations in any of the succinate dehydrogenase genes or in the KIT or PDGFRA genes (frequently mutated in adult GISTs). They did find however, that there were some “secondary” changes in this group; the most frequent change was that tumors had lost 1 of the 2 SDHC genes (had lost one of the two alleles). The importance of this finding has yet to be determined. These findings were published in the Journal of Clinical Endocrinology & Metabolism in 2007.

These findings may lead to new treatment options for the affected families. Some potential candidates include HIF1- α inhibitors (in trials) and derivatives of α -ketoglutarate or dichloroacetate (DCA). The benefits of these type drugs for other pediatric GIST patients, including Carney’s Triad, is less clear.



Disease pathways for SDHB mutations. (Courtesy of Wikipedia)

In about 2001, Dr. Carney began working with Dr. Constantine Stratakis, a Pediatric Endocrinologist at the National Institute of Health. An important clue was that a few of the “Triad” cases appeared to be familial (run in families). When Carney and Stratakis focused on the familial cases they noted two impor-

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very high resolution studies such as DNA sequence analysis. However, other chromosomal changes are relatively common in GIST. Several chromosomes and chromosomal regions have been implicated in tumor progression. The most common regions of chromosomal loss are the long arms of chromosomes 14 and 22 and the short arms of chromosome 1 and 9 and the most common region of chromosomal gain is the long arm of chromosome 8 (see Figure 1). Interestingly, loss of material from the short arm of chromosome 9 is associated with aggressive/malignant behavior.

The area on chromosome 9 that is of particular interest has been narrowed down to two well-known genes known as *CDKN2A* and *CDKN2B*. These two genes encode three important cell regu-

latory proteins known as p16(INK4A), p14(ARF), and p15(INK4b). The accumulated evidence so far suggests that loss of both p16(INK4A) and p14(ARF), which are both encoded by the *CDKN2A* gene, is very important in tumor progression in GIST. p16(INK4A) and p14(ARF) control important checkpoints in the cell division cycle. Checkpoints are points within the cell division cycle where a cell decides whether to divide or not. It is not hard to imagine that loss of proteins responsible for telling the cell to stop dividing would be advantageous for a cancer. If one were to think of a GIST as a car, I might suggest that *KIT* or *PDGFRA* activating mutations are the equivalent of pushing the gas pedal to the floor (pedal to the metal) while inactivation of *CDKN2A* is like removing the brakes. This results in a car (or tumor) that is accelerating out of control without the ability to stop. A major challenge is how we might exploit loss of

CDKN2A therapeutically. As far as I know, therapeutics have not been designed that enable one to re-establish p16(INK4A) and/or p14(ARF) function. Of course, the other chromosomal regions with consistent losses and gains are being studied by several groups so hopefully, one or more of those areas will present a good opportunity for a targeted therapy that could be used independently or in conjunction with Gleevec or Sutent. Through this work and others, we are all hoping that some day soon we will be able to cure GISTs.

References

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2. Perrone F, Tamborini E, Dagrada GP, Colombo F et al. 9p21 locus analysis in high-risk gastrointestinal stromal tumors characterized for c-kit and platelet-derived growth factor receptor α gene alterations. *Cancer* 2005;104:159.

BABY

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thing to do.”

In March of 2006, April stopped taking her Gleevec. In the July & November following she had scans that would let her know what had happened without treatment.

“[They] showed no changes, so my doctor was okay with us trying to get pregnant.”

April was always comfortable with her decision to start a family but she understood the gravity of her actions and what that might mean to other patients. “I think stopping Gleevec to start a family is something that each patient would have to consider closely with their doctor. I was fortunate enough to be “No Evidence of Disease” since my surgery in 2000, so my



April and Mary Catherine pose for the LRG.

family, doctor and I were comfortable stopping it. There are many factors to consider and there is also still so much being discovered

about Gleevec and GIST that might help patients like myself make decisions about stopping Gleevec.”

April will get her first scan since delivering the baby in October. “I am a bit nervous about the scan since it has been almost a year since my last one, but I just pray that there will have been no changes since last November.”

Despite the anxiety and waiting, April is excited to be a mommy. “Being a mother is great! The excitement of having

a new baby makes it easy to forget sometimes that I am a cancer patient and I’m about to go back for another scan. She is changing almost daily. She makes the cutest faces and we both love to watch her. We feel so blessed to have such a healthy baby girl!



And baby makes three...or is it four? The Stephens family takes a moment with the stork.

Fourth annual poker tournament in NYC will be held on October 17

This year the annual New York City Poker Tournament will be held on October 17 at SLATE at 54 West 21st Street. Registration will begin at 6:30 PM and cards and games are scheduled to begin at 7:00 PM.

Anyone interested in attending should contact the Life Raft Group at (973)837-9092 or liferaft@liferaftgroup.org.

As always, second and third place winners will receive different-sized flat screen TVs and the first place winner will get a

chance to play in the World Series of Poker in Las Vegas, Nevada.

Last year's winner, Richard Joyce graciously gave his ticket to a friend, Zach Boisi, who had the honor of attending the WSOP in July. He reported his experiences to us.

"Unfortunately, I got knocked out on Day two. I did not catch ANY good cards and when I finally made my move with A-6 suited and a small chip stack, the other small chip stack called with a pair of pocket sixes. It was not my day! I believe I finished in the top 800 of the original 6000.



First place in the NYC Poker Tournament gets you an entry into the World Series of Poker, held in Las Vegas.

Not a horrible showing.

I have to say a great big THANK YOU for giving me the opportunity to play. It was a life-long dream that hopefully I can fulfill again in the near future."

Medical mistakes happen: stay in control

By Erin Kristoff

Floyd Pothoven hasn't had a lot of luck with diagnoses. When his GIST tumor symptoms began, doctors

thought he had a urinary infection. Fortunately a conscientious primary care physician sent out for a CT scan. In July 2001, surgeons scheduled an operation for Floyd's tumor removal; they sewed him back up and told him there was nothing they could do.

However rumors of Gleevec prompted Floyd and his doctors to check into the new drug. Thanks to supreme efforts by his doctors at UCLA, Floyd was the last patient to join the phase III Gleevec trial on August 31, 2001. He has been on 800 mg of Gleevec ever since.

Floyd enjoyed initial shrinkage and then stability for the first few years and then, two years ago, a metastasis on his mesentery appeared to be growing.



Floyd was about to drop out of the phase III trials. Once again, a smart doctor realized that "things were just moving around", according to Floyd. So, another crisis was averted.

Three months ago, a radiologist let Floyd know that his primary tumor looked as if it were growing. This may have sent someone else into a blind panic, not Floyd. Because of years of "bad luck", Floyd remained calm and insisted another CT scan be done before he was kicked off the trial. LRG Executive Director, Norman Scherzer and Science Coordinator, Jerry Call, agreed with Floyd.

The next CT scan showed that things were normal and the fake crisis was averted yet again.

Floyd has some advice for anyone who finds themselves in a similar situation. "It may be a misinterpretation. One has to be real careful and get a track record and not jump off the deep end for one

scan. Try and get the same person reading the films, I think you get much, much better results."

Ohio local group meets

On September 15, the Ohio GIS-Ters met, local group leader, Kaye Thompson had a few things to say about the gathering.

"Our Saturday meeting was great! We all had an enjoyable time.

Those in attendance: Bob & Helen Hall (Bob is the patient) from Parkersburg, West Virginia; Mary Netting & Clark (Mary is the patient) from Rockbridge, Ohio; Susan Arnoczky from Grove City, Ohio; Carol Webb (her daughter is the patient) from Wheeling West Virginia and of course me & my husband. Everyone is doing pretty good at this time and hope and pray it continues that way.

We discussed our individual circumstances and which treatment methods we are pursuing.

We are planning our next meeting in January after the holidays."

PCTs

From Page 6

this was scandalous, though I doubt it.

As well as the obvious failings of process, examining meeting minutes and letters from the PCT gave us many concerns about the probity of the decision-making committee. It appeared to us that the decision not to fund was predetermined and that the chair of the committee bullied that decision out of a group who, to be frank, had no suitable qualifications to understand the sophisticated situation they were being asked to consider and did not have the courage to argue. They were all staff of the PCT so the possibility of ‘corporate bullying’ is very real.

We were able to petition the Secretary of State for Health (the responsible government minister) (not an easy thing to do against a protective civil service) and she instructed NHS London, the relevant strategic health authority, to conduct an investigation. This started in January 2007 and continues to reverberate as I write.

Sarcoma UK has had to use the Freedom of Information Act to gain access to reports and correspondence relevant to

the investigation and we still have not got the story of what happened out into the open. Both Bromley PCT and NHS London are being obstructive, clearly trying to cover up the failings and to protect people against completely justifiable allegations of professional failure.

Those allegations are not made by us alone. The investigation engaged three independent reviewers who considered the paperwork trail of the decision. One (a clinician) used the word ‘appalling’ so many times it almost began to lose its effect. Another (a lawyer) identified at least five breaches of the law. The third (a pharmacist) was clearly very uncomfortable with the language and the tone of the committee’s meetings as evidenced by minutes and papers.

NHS London has, so far, failed to address the detail of these reviews with the PCT. Bromley PCT itself has finally acknowledged in writing that it failed, though the words used could be described as a tortured avoidance of key issues. It is reconvening a special exceptional treatment decision committee, over a year after the original one sat, to

once again review the evidence for treatment, the patient’s personal and medical circumstances and to consider the full legal framework necessary to make a fair and proper decision. Crucially it has commissioned a second ‘normative’ opinion, which we have no doubt will support Professor Judson’s recommendations.

Thankfully our patient is still with us. Support from family, friends, doctors and the wider cancer community have ensured that treatment has continued appropriately. It has happened despite the NHS, an organisation which our new Prime Minister proudly asserts treats patients free at the point of need, according to the best clinical advice. You might think there are double standards; how could I possibly comment on that?

In part two (for a future issue) we will follow what has been done to try and change things. The cancer advocacy community is deeply concerned about the “postcode lottery” issue which affects all cancers in a similar way. If action is not taken in the near future (December is the anticipated timing) the broad agreements that exist between the NHS, Parliament, oncology doctors and cancer patients, and which carry change forward in the NHS, may break down.

RIGG

From Page 2

wrong, but she assured me that it wasn’t, even though GIST had never recurred. What can I say? If GIST returns, it certainly will be no surprise, just a disappointment. For now, however, hope has found a crevice in my spirit and has taken root.

Meanwhile, the world keeps spinning. Sadly, my candle supply has had to be replenished, and it breaks my heart that so many friends (both the ones I’ve met in person or through e-mail and the ones I’ve come to love just from reading their

posts) are gone. Our family has changed, too. With both sons married and our youngest daughter in her own apartment, we are empty nesters now. My reluctance to go shopping gave way as the most colorful floss and yarns and the brightest pieces of materials dwindled from my stockpile. The house is once again filled with crafts and sewing projects in every stage of development – and enough baby afghans already finished for each daughter-in-law to produce a set of quintuplets.

These days I find myself working just a little harder than I used to and playing a little bit more, too. Last week I finished canning the tomatoes (100 jars of

the best pizza sauce on earth) in anticipation of plenty of company this winter, while Steven bought season tickets to shows put on by our community theater guild (because we love musicals and my husband knows I refuse to kick the bucket and let his sister use the rest of my ticket).

One more thing – I’ve also bought more drinking glasses. The ones I had five years ago, formerly used just for company, keep breaking, dammit! I guess I didn’t have a lifetime supply after all.

Life is good.

Darlene in Indiana



A first person look at European Cancer Conference

By Estelle Lecointe
Association Française de Patients du
GIST: Ensemble Contre Le GIST

I'm just back from the ECCO14 (European Cancer Conference) meeting in Barcelona. It was very exhausting but very interesting as usual.

There was a great interactive GIST symposium on Sunday chaired by George Demetri (Dana Farber Cancer Institute, Mass., US). Heikki Joensuu (University of Helsinki, Finland), Peter Reichardt (Robert-Rossle-Klinik-Charite Campus Buch, Germany), Jean-Yves Blay (Centre Leon Bernard Frances, France) and Axel Le Cesne (Institut Gustave-Roussy, France) also made presentations during this session.

The topics were the following :

- **MetaGIST** : A combined analysis of the US and European co-operative group trials (George Demetri)
- **The risk of progression with imatinib discontinuation in metastatic GIST- Clinical trial of the French Sar-**

coma Group (BFR14) - (Axel Le Cesne)

- **New options in imatinib intolerant and resistant GIST** (Jean-Yves Blay)
- **Practical management of GIST - Clinical dilemmas** (Heikki Joensuu)
- **Early GIST : improved recurrence free survival with adjuvant imatinib** (Peter Reichardt)

On Tuesday, I participated in an international press conference, aimed at celebrating the sixth anniversary of Gleevec, beside Jean-Yves Blay, Peter Reichardt and Philippe Drouet (Novartis). The aim of my participation was to explain what imatinib changed in the patient's life and to tell about GIST PAG's (Patient Advocacy Groups) involvement in research.

I made a brief summary of the LRG Resistance Research Plan during my presentation

to show that patient-initiated research will have a great impact in the future and that PAGs are now becoming fundamental partners to impulse scientific research.

I also made a speech about the Global GIST Network to illustrate that the GIST community was a very well structured and organized one and that mutual support was one of our key principles.



(From left) Dr. George Demetri, Dr. Florence Duffaud (Hôpital de la Timone, Marseille), Dr. Alex LeCesne, Estelle Lecointe & Dr. Jean-Yves Blay at the ECCO Conference, that ran September 23-27 in Barcelona.

MARKUS'S WIFE HAD HER BABY!



Baby Philine at three hours old.

Well, there must be something in the air. Just after April Calloway

Stephens had her little girl (See front page), Das Lebenshaus director, Markus Wartenburg got his own little "gift" from the stork.



"After her mummy Brigitte fought a whole weekend enormously, 'Philine Sarah' came (15 days after the calculated date) on September 3, 2007." She joins older sister, Julia.

The name Philine comes from the Greek: philai, philéon and means love, to fondle, kiss.

Other meanings are also: "the fine one", "sensitive one", "friend", "loving" and "horse friend"

Mark your calendars!

Reminders:

- Florida GISTers will be meeting at 1:00 PM on November 10 at Crab House on International Drive in Orlando.
- The GIST Cancer Research Fund's "Walk-for-a-Cure" will take place on October 14 in Congers, NY and October 21 in Ventura, Calif.
- The Long Beach Marathon will be held October 14 in Long Beach, Calif.
- The NYC Poker Tournament will be held on October 17 (See page 9)



Also, the first Texas Poker Tournament will be held on November 7, look in the next issue for more details on that event.

This year's Thanksgiving fundraiser will kick off at the beginning of November; 100% of donations will go toward GIST resistance research.

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