

LifeFest 2010: Celebrating a decade of life

By Marisa Bolognese
LRG Director Planning &
Development

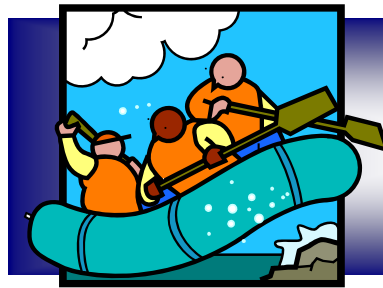
It has been a remarkable decade for the GIST community as scientific discovery, medical treatment and drug development have put GIST at the cutting edge of cancer treatment and care. Between 2000 and 2010, GIST has gone from being a misdiagnosed rare cancer, with only a five percent response to treatment, to one of the best understood cancers, where patients can now expect an 85 percent initial response to



The Hyatt Regency Hotel on the Hudson River in New Jersey will be the location for Life Fest 2010.

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Battling gastrointestinal stromal tumor



LIFE RAFT GROUP

October 2009

In memory of Kenneth Rowan, Nurit Mantz, Jessica Macneil and Linda Chuyko

Vol 10, No. 8

Defining molecular mechanisms of imatinib in the treatment of GIST

By Dr. Anette Duensing
University of Pittsburgh Cancer
Institute & LRG Research Team

Gastrointestinal stromal tumors (GISTs) are caused by mutations in the KIT or PDGFRA (platelet-derive growth factor receptor alpha) receptor tyrosine kinase genes and can successfully be treated with imatinib mesylate (Gleevec®). However, despite dramatic response rates and more than 85 percent of the patients initially benefitting from therapy, imatinib treatment is not a cure.

A major problem of imatinib therapy is that a considerable proportion of patients develop resistance to the drug over the

course of treatment.

A second, interrelated problem of imatinib therapy is the fact that although many patients do achieve tumor stability, complete remissions are rare. In other words, oftentimes even bulky tumor remains under therapy and tumors relapse once imatinib therapy is terminated. These observations are corroborated by scan results during therapy that can show detectable



DUENSING

See DUENSING, Page 7

Jerry Call: the man behind the scene

By Erin Kristoff
LRG Newsletter Editor

You sit alone in a dreary doctor's office; evidence of his medical expertise and importance adorn the walls. Maybe you sit there with a loved one, equally as scared and unprepared as you. The doctor hands you a verdict that says your time is up. Well now what do you do?

At times like this, people feel a range of emotions: defeat, clarity, redemption, remorse, to name but a few. In



Jerry & Stephanie in Nederland, Colorado, just 3 weeks prior to Stephanie's diagnosis.

the GIST community we have also heard and experienced stories of triumph and miracles, rising from rock bottom and greeting the world anew. A world where David can and does beat Goliath.

Ten years ago, Jerry Call was introduced to this world as he sat next to his wife of 15 years, Stephanie, and learned of her leiomyosarcoma (LMS) diagnosis. Amidst the shock and disbelief, her oncologist's voice rang out, "This is probably going to take you away from us."

After two rounds of a harsh chemo-

See JERRY, Page 4

GIST Research: LRG Articles on the Science of GIST

It's time to consider mutational status for resistant GIST patients: PDGFRA Mutations

By Jerry Call
LRG Science Coordinator

This is the second article in a series discussing mutational status and resistant GIST. In the last article we began with a brief overview and wild-type GIST. In this article we focus on PDGFRA mutations with an emphasis on the imatinib-resistant D842V mutation.

Mutations in the KIT and PDGFRA gene are the most frequent genetic event that drives the biology of GIST tumors. Targeting these defects remains the primary drug therapy for GIST. While KIT mutations are much more common, PDGFRA mutations still represent a significant percentage of GISTs. Approximately two-thirds of PDGFRA mutations are insensitive to

Editor's Note:

There are several differences between GISTs with PDGFRA mutations and those with KIT mutations. The cells of PDGFRA-mutant GIST tumors are often an epithelioid type (round shape) and more often stain weakly or negative for KIT (Corless et al.). In addition, PDGFRA mutations occur predominantly in the stomach, but can also occur in the mesentery and omentum. It has been noted (Lasota et al) that PDGFRA-mutant GISTs tend to have a lower risk of recurrence than KIT-mutant GIST.

Gleevec. This makes the management of patients with PDGFRA mutations more complex than those with KIT mutations.

In 2005, Drs. Christopher Corless, Michael Heinrich and colleagues reported on the PDGFRA mutational status of 1,105 GIST tumors. In this group, 80 tumors (7.2%) were found to have a PDGFRA mutation. The most common PDGFRA mutation was one that occurs in exon 18, a D842V mutation. D842V mutations are insensitive to Gleevec and Sutent, the two currently approved drugs for GIST.

Patients that are resistant to both Gleevec and Sutent may elect to participate in clinical trials. Many patients (at least in the United States) will try off-label treatment with drugs that are approved for other cancers but not for GIST. The two approved KIT inhibitors (other than Gleevec and Sutent) that are the most advanced in trials for GIST are nilotinib (Tasigna) and sorafenib (Nexavar) and patients will often try one of these two drugs after failing Gleevec and Sutent. Both nilotinib and sorafenib, however, have shown limited effectiveness against the D842V mutation in the laboratory.

In 2008, Dr. Maria Debiec-Rychter of the Catholic University of Leuven, Belgium and her colleagues identified two drugs that inhibit the PDGFRA D842V mutation and represent possible treatments for patients with this mutation. Barbara Dewaele was the first author of the paper which was published in Clinical Cancer Research.

The Leuven team found that dasatinib and IPI-504 were both effective inhibitors of PDGFRA^{D842V} mutations in laboratory experiments. These experiments included tests against Ba/F3 cells (cells

The Life Raft Group

Who are we, what do we do?

The Life Raft Group (LRG) directs research to find a cure for a rare cancer and help those affected through support and advocacy until we do.

The LRG provides support, information and assistance to patients and families with a rare cancer called Gastrointestinal Stromal Tumor (GIST). The LRG achieves this by providing an online community for patients and caregivers, supporting local in-person meetings, patient education through monthly newsletters and webcasts, one-on-one patient consultations, and most importantly, managing a major research project to find the cure for GIST.

How to help

Donations to The Life Raft Group, a 501(c)(3) nonprofit organization, are tax deductible in the United States.

You can donate by **credit card** at www.liferaftgroup.org/donate.htm or by sending a **check** to:

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Please advise Erin Kristoff, the Newsletter Editor, at ekristoff@liferaftgroup.org of any errors.

engineered to test specific mutations) and actual tumor cells taken from a patient with the PDGFRA^{D842V} mutation.

Dasatinib has been extremely effective for Gleevec-resistant chronic myelogenous leukemia (CML) and it is approved for that purpose in the United States and some other countries. Dasatinib is manufactured by Bristol-Myers Squibb and the trade name in America is Sprycel; while in trials, it is/was called BMS-354825.

After a slow start in phase I trials that included 18 GIST patients, there is some renewed interest in dasatinib for GIST, at least in some unexplored populations, such as the open phase II trial in Switzerland for GIST patients that have

GIST Research: LRG Articles on the Science of GIST

REGISTER Study Open in Australia, New Zealand and South Korea

By Jim Hughes

Clinical Trials Coordinator

An interesting Phase 2 REGISTER study is ongoing and actively recruiting at 15 sites in Australia. Two sites in New Zealand and two sites in South Korea are also planned.

Upon entry advanced GIST patients are classified as high or low risk based on mutation type. Exon 9 and wildtype mutations are classified as high risk; exon 11 patients are classified as low risk.

All patients receive imatinib at 400 mg for up to six weeks as initial therapy. High risk patients are then escalated to imatinib 800 mg. Low risk patients can be escalated to 800 mg imatinib under two scenarios:

1. Incomplete response on PET scans at six weeks.

2. Complete response on PET scans at six weeks but experiencing progressive disease (RECIST) on a regular three month follow-up CT scan

Editor's Note: While risk is categorized in this study by mutation, in metastatic GIST, risk is characterized not just by mutation type, but also tumor size and mitotic rate.

After escalation to 800 mg imatinib, patients receive early PET scans to check for progression. Progressing or partially responding patients are then treated with Nilotinib 800 mg. Sunitinib is not offered as a drug treatment in this trial.

There are multiple notable features in this trial design:

- Patients for the first time are classified

and treated by risk (genotype)

- Higher risk genotypes are automatically escalated to higher imatinib doses
- Progression is monitored early by PET scans.

- Escalation of imatinib dose is based on PET scan results for exon 11 patients.

- Escalation of imatinib dose occurs in steps from 400 to 600 to 800 mg

- Imatinib blood levels are tested at multiple points in the protocol

- Sunitinib is not offered even though it is the standard of treatment for second line.

- A second line tyrosine-kinase inhibitor, nilotinib, is offered in tandem with first line imatinib.

The trial's primary end point is progression-free survival and its targeted accrual is 100 adult patients.

The AGITG website has more protocol detail at: <http://www.gicancer.org.au/trials/open/REGISTER.html>

October 2009 clinical trials update

By Jim Hughes

Clinical Trials Coordinator

Two important new trials are highlighted in separate articles in this month's newsletter:

- The REGISTER trial in Australia, New Zealand and South Korea for newly diagnosed advanced GIST.

- The new five year adjuvant imatinib study recently opened in the United States for newly resected patients. (NCT00867113)

Other GIST clinical trial news in-

cludes:

- The Phase 3 imatinib with or without Bevacizumab trial has closed to accrual in the US and Canada. No reason was given. Accrual had not been as high as expected. (NCT00324987)

- A Nilotinib Pharmacokinetic (PK) study has been started in Japan. Researchers will look at the effect of surgery on Nilotinib PK. They are investigating how prior surgery might affect nilotinib absorption. (NCT00976612)

- Radboud University Hospital in the Netherlands has an ongoing palliative study (newly listed) that is investigating the link between angiogenesis inhibitors

sunitinib and sorafenib and fatigue and depression in several cancers including GIST. (NCT00979329)

- Pfizer has added detailed study results to two major sunitinib trials including the phase 3 registration trial.

- The Pfizer treatment-use protocol for Sutent access for GIST patients remains open in India in Mumbai and New Delhi. (NCT00094029)

Please visit the Clinical Trials database at www.liferaftgroup.org/treat_trials.html for a complete listing of clinical trials. There you can view a table, search recruiting trials and much more.

JERRY

From Page 1

therapy called MAID, her doctor announced that it was not working and there were no further options for Stephanie. Having never done anything halfway in his life, Jerry refused to accept this as the end. Because one doctor said there was nothing left to be done, should they just quit? He immediately went home and came up with a plan to save Stephanie's life.

"I was always a very independent person. When I was diagnosed, I just lost it," recalls Stephanie, "We knew the only way to get control of the situation was to get online and do research. So Jerry self taught himself. He actually had to tell numerous oncologists what was out there for treatment and they were not ready for that."

At home, Jerry outlined a plan of attack. First they would arrange a consultation with Dr. George Demetri of Dana Farber Cancer Institute in Boston. He also set up an appointment with a liver surgeon at the University of Colorado and began investigations into an experimental treatment available only in Ireland.

"All of a sudden we went from no options—no hope—to having three different paths that we were going to pursue," recalls Jerry. A former marine, Jerry started issuing orders; his mother would arrange travel and his brother researched passport requirements, in case he would need to travel to Ireland.

In Dr. George Demetri, the Calls found a compassionate expert who was the most knowledgeable person they had ever met. He suspected Stephanie actually had GIST and had been misdiagnosed (this was later confirmed by a c-kit test), but there were still no effective treatments for GIST. As Demetri read off options, Jerry could tell that he had little faith in them.

After another strikeout with the liver surgeon, Jerry found himself on a plane to Ireland with 2,700 dollars for a three month supply of an experimental drug.

The Call's first year with GIST was a rough one. After the MAID chemo,

Stephanie began a rollercoaster of treatment beginning with the Irish drug; she then had a painful biopsy test, followed by seven rounds of an additional chemo called Taxotere, and then began taking Interferon which caused an allergic reaction.

"I lost hope a few times, but Jerry kept going," says Stephanie.

Finally, after reading thousands of emails he came across one very important piece of information: a new trial for a drug called STI-571 (Gleevec).

The Gleevec trial proved to be a turning point for Stephanie and truthfully, for Jerry as well. While Stephanie experienced benefit from Gleevec for more than four years, Jerry was introduced to more and more GIST patients, dozens of "Stephanies", who needed guidance.

When the LRG first formed, Jerry began working for the organization on a part-time basis. He retained his position as a home inspector in his hometown of Boulder, Colorado and was also able to stay home most of the time with Stephanie.

Using what he had learned during his wife's rocky first year; Jerry targeted his efforts on the GIST patient community as a whole, researching all he could on molecularly targeted therapies, signal pathways and GIST biology. He had truly found his calling.

When Executive Director, Norman

Scherzer introduced him at meetings, it would be as the third smartest man in the world.

"I say that because I assume there are two people in the world who are smarter than him... but I haven't met them."

Eventually, in 2004, Jerry became the full-time Science Coordinator of the Life Raft Group.

Says Stephanie, "We get calls from patients 24 hours a day, seven days a week on every phone we have. He is always giving pep talks and positive thinking to people and different ideas."



Jerry discusses GIST care with LRG members at Life Fest 2006.

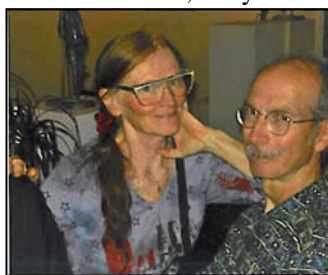
One such person is Judi Lifton, whose partner, Lee, experienced great difficulties in his GIST journey. Over the course of years, Jerry offered whatever help he could: analytical and supportive.

"Jerry Call is a cross between Johnny Appleseed and Albert Einstein," laughs Judi, "Appleseed was creative and Einstein was calculating. Jerry really was a wonderful sounding board; he was an innovator."

Lee passed away in January 2007, but Judi and Jerry still speak regularly, "He became a friend and I can't say enough about him. He is really a special guy."

This kind of story is not uncommon in the GIST community; to many, Jerry is the man in the machine, climbing out of the ether and empowering patients to manage their own care. He works every day to level the playing field between patients and medical professionals.

This has not gone unappreciated in the GIST medical community. At a 2006



Judi Lifton & Lee Emerson.

Donor appreciation never gets old

When compiling the list of donors for the year 2008, the LRG inadvertently left out a number of donors who should have been included.

At the LRG, we are grateful for each and every donation and are sincerely moved by the continued generosity of our supporters.

We would like to apologize for this mistake and have included that list of donors below with our deep appreciation:

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JERRY

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Life Fest meeting in Dallas, Texas, Dr. Jonathan Fletcher, LRG Research Team leader, stood before a crowd of over one hundred to accept an LRG award of “Researcher of the Year”; during his speech he took a few moments to thank Jerry for his contribution to GIST research.

“I speak for all of my research colleagues in GIST in assuring you that if there is some angle out there which is relevant, a new drug that is being used for some other tumor, that smacks of a promise in GIST, then Jerry is going to in his genteel, quiet way let us know about it, and he doesn’t do so in a knee-

jerk way. He thinks about it, he considers the possible payoff and when we get an email from Jerry or a call from Jerry, we always know it’s something good,” announced Fletcher, “We really value his oversight and judgment when it comes to scientific matters.”

The LRG Research Team has grown in size and

scale since that speech, but the team continues to rely extensively upon Jerry for his suggestions about important areas of research focus in GIST, insists Fletcher.

Indeed, Jerry has grown to become something of an icon in the GIST community. Some see him as that mysterious benefactor in the computer, some as the friend they’ve been searching for, even more as the man who gave them the strength to get back in the driver’s seat of their own medical care. But to one woman—Stephanie Call—he’s still just her soul mate, the man who saved her life.

“He’s been through so much with me,” says Stephanie, “I’ve been close to death like three times. He is a very strong person, a very dedicated person, and loyal.”

Despite numerous oncologists and specialists proclamations to the contrary, Jerry never accepted that it was Stephanie’s time to go. In August, Jerry and Stephanie celebrated their 25th wedding anniversary; this month, they will celebrate her 10-year “cancer”versary.

“He truly does love me, he doesn’t want to lose me and he doesn’t want a life without me.”

A note from Jerry Call:

Stephanie would not be alive today without the help of many wonderful doctors and nurses. Special thanks goes to Dr. Keith Skubitz, University of Minnesota, who allowed Stephanie in to the Sutent treatment-use trial. He could easily have said she was too sick to qualify. Thanks to Dr. Dwight McKee for his compassion and thinking outside the box. The ICU of Boulder Community Hospital did a fantastic job in a crisis in 2003. Thanks to Dr. Charles Blanke who took care of Stephanie in the Gleevec phase II trial. Thanks to Dr. George Demetri for his compassion, wisdom and support through the years. The nurses at RMCC and BCH have done a wonderful job of taking care of Stephanie over the last 10 years. And last, but not least, thanks to Dr. Jenny Fox, 'Stephanie's oncologist, for taking care of Stephanie for the last 7 years and for putting up with me for all that time.

Chicago-area GISTers meet!



Last month’s Chicago-area meeting, was a reunion of sorts for many attendees. Dr. Margaret Shoup, surgical oncologist at Loyola University Health System, was the group’s very first speaker in 2003 and returned for this meeting to talk about surgery in GIST. There were many questions and answers and, as always, a good time was had by all.

DUENSING

From Page 1

tumor mass in the CT scan although the tumor is responding to imatinib according to a “cold” PET scan. These findings can be interpreted in a way that not all cells have undergone apoptosis in response to imatinib therapy, but instead have significantly reduced their metabolism (which is measured by the PET scan). These remaining cells pose a significant risk to the patient as it is conceivable that they may already contain imatinib resistance mutations that can ultimately contribute to disease progression.

It is therefore imperative to define the exact molecular mechanisms of action of imatinib with the two major questions being (a) how does imatinib lead to

been known as mere structural scaffold proteins that help to package the cell’s

we can now look for alternative ways to target H2AX upregulation as a possible means to circumvent imatinib resistance. (For more detailed information on histones, histone H2AX and its role in imatinib-induced apoptosis please see the December 2007 issue of the LRG newsletter.)

Addressing the second question, the problem of incomplete remissions during imatinib treatment, leads us to a fundamental topic in tumor biology and therapy: tumor cell quiescence (3). Quiescent cells are not only unlikely to undergo apoptosis, but they also do not respond to conventional anticancer treatments that target dividing cells. Therefore, tumor cell quiescence is an important problem for cancer therapy in general.

The definition of cellular quiescence is quite simple. Quiescent cells are cells that lack growth/proliferation and that have exited the cell division cycle. Quiescence is a reversible mechanism, which is in contrast to another cellular state called senescence that is irreversible. One of the main molecular regulators of quiescence is the cyclin dependent kinase (CDK) inhibitor p27^{Kip1}, whose levels are high in cells that have entered quiescence (4). P27^{Kip1} levels on the other hand are regulated by a protein called SKP2. Since the function of SKP2 is to prepare p27^{Kip1} for degradation, SKP2 levels need to be kept low in quiescent cells. In contrast, dividing cells have high levels of SKP2, which results in low levels of p27^{Kip1} (5). The complex molecular

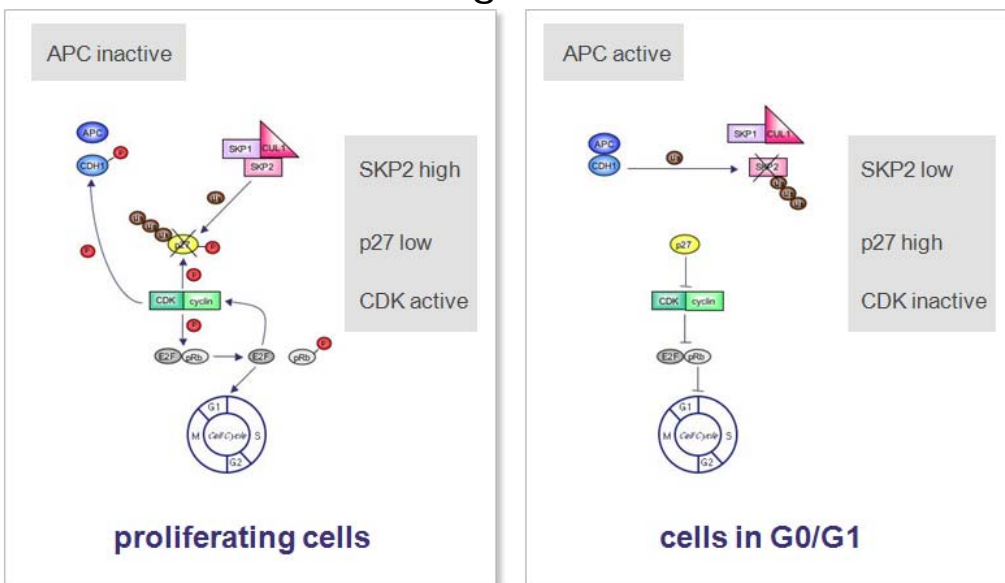
events of cell cycle regulation in proliferating and quiescent cells are also depicted in Figure 1.

In an attempt to explain the fact of incomplete remissions, we asked whether imatinib is not only capable of inducing GIST cell apoptosis, but could potentially also lead to tumor cell quiescence in GIST cells. To address this question, we treated a GIST cell line model (GIST882) with imatinib and looked for changes in the levels of several known

“These results indicate that imatinib treatment provokes an either-or decision with respect to apoptosis or quiescence.”

DNA into its nucleus. They form the so-called nucleosomes, around which the DNA is wrapped. More recently, a plethora of novel functions of histones have been discovered. One major finding was the identification of histone H2AX as a key player in the signaling cascades that are activated after the cellular DNA is damaged (for example, by gamma-irradiation such as X-rays). We have now discovered yet another function of histone H2AX, which is separate from its role in DNA damage response. Histone H2AX is causatively involved in

Figure 1



GIST cell death (apoptosis) and (b) how can we explain or potentially circumvent incomplete remissions? Answering these questions will not only identify the molecular players that are involved, but also lead to the definition of novel therapeutic targets. Ultimately, our goal is to overcome resistance with an aim towards cure.

Addressing the question of imatinib-induced apoptosis, we have recently identified one of the molecular players: histone H2AX (1). Histones have long

the induction of GIST cell death after imatinib treatment and can also lead to apoptosis in other cell types that are not treated with imatinib (2). We found that levels of H2AX are massively upregulated in GIST after imatinib, and that most of the H2AX molecules in this context are not part of the nucleosomes, but are free in the cytoplasm or nucleus of the cell. We have shown that the mechanism by which H2AX leads to GIST cell apoptosis involves the inhibition of gene transcription. Importantly,

PDGFRA

From Page 2

never had Gleevec (first-line treatment or “Gleevec-naïve”). Gleevec-resistant GIST patients are also eligible for a phase II trial of dasatinib in advanced sarcomas in the United States.

IPI-504 also effectively inhibited the PDGFRA^{D842V} mutation in the lab by a different mechanism than dasatinib. While dasatinib blocks the PDGFRA signal without damaging the PDGFRA protein, IPI-504 treatment results in the destruction of the PDGFRA protein. IPI-504 is an HSP90 inhibitor that was in phase III trials for GIST. This trial was terminated in April of 2009 because of a higher than anticipated mortality rate for patients receiving IPI-504. It remains to be seen whether other HSP90 inhibitors in trials will be effective in GIST in general or the D842V mutation in particular.

Several other drugs have also shown some activity in the lab against the D842V mutation or the closely related D816V mutation in KIT. Given the similarity between these two mutations one could speculate that a drug that inhibits one mutation would have a good chance of inhibiting the other. In fact, this has been demonstrated with dasatinib which was shown to inhibit the KIT D816V

mutation in 2006 (Shah et al) and PDGFRA D842V in 2008 (Dewaele et al).

Some other drugs that have shown in-vitro activity against the D842V or the KIT D816V mutation and are still in clinical trials are:

- MP470 (in phase I trials) – active against D842V
- PKC412 (in phase II trials) – active against D842V
- MLN518 (in phase II trials) – has shown activity against D816V mutation.

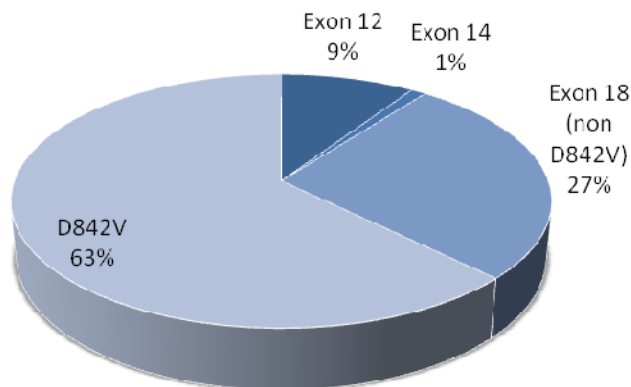
Drugs that have shown in-vitro activity against the D816V or D842V mutation but appear to have been withdrawn from development include:

- AP23464
- AP23848
- XL820 (Trials terminated in GIST)

The last few paragraphs illustrate both the promise and the perils of in-vitro

testing. It is important to note that only twenty percent of drugs that enter into clinical trials will be approved. They may have unacceptable toxicity, limited effectiveness, or they may be directed against a target that turns out to be less important than it was thought to be. However, for patients with a D842V mutation entering a clinical trial, in-vitro testing may prove to be the best available determining factor in choosing a drug treatment.

Summary of published PDGFRA mutations in GIST (Corless et al- 2005)



The D842V mutation that occurs in 63% of PDGFRA mutations is resistant to Gleevec and Sutent.

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LIFEFEEST

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treatment. The year 2010 marks the tenth anniversary of a breakthrough in GIST treatment as the first group of patients to receive a drug to treat metastatic GIST will reach their ten-year survival benchmark.

The Life Raft Group will be celebrating this amazing decade of achievement over the course of the next year through a number of events and initiatives, all culminating with Life Fest 2010 on June 25-27, 2010 at the Hyatt Regency in Jersey City, NJ.

On Friday night, June 25, Life Fest 2010 will open with a gala event: **GIST 2010—A Decade of Difference**. The evening will feature a look back at the key scientific and medical milestones over the last ten years and a look forward to the most promising treatments

and discoveries on the horizon. Special recognition will be given to the *10 Who Made A Difference*, honorees from the GIST patient, medical and scientific communities who have not only made significant contributions to the understanding and treatment of GIST, but whose accomplishments have made a difference to the survival of GIST patients. The celebration will continue throughout the course of the weekend with other key awards including *Humanitarian of the Year*, *Clinician of the Year* and *Volunteer of the Year*. With Life Fest 2010's emphasis on achievement and survival, a new annually-awarded honor will be unveiled; *The Beacon of Hope Award* for the most promising scientific or pharmaceutical breakthrough.

A retrospective of GIST scientific discoveries and medical advances as well as profiles of the Life Fest 2010 honorees will be featured in the LRG Newslet-

ters and communications in the months leading up to Life Fest 2010. The complete GIST historical retrospective and honoree profiles will then be compiled for a special commemorative program that every Life Fest 2010 attendee will receive.

Finally, in the next ten months, the Life Raft Group will be gathering stories from all those who've been involved on the front lines of GIST—patients, family members as well as the scientists, doctors and nurses who fight alongside them. These stories of courage, perseverance and determination will be featured throughout Life Fest 2010, and in a multi-media production to be premiered at Friday night's gala.

Most important of all, Life Fest 2010 is a celebration of survival and hope and a time to recognize the enormous courage of every patient and family member who has battled and continues to battle GIST. Life Fest 2010 will offer the entire GIST community—GIST patients, their friends and family members, GIST medical professionals, researchers and scientists—an opportunity to come together to honor and celebrate the past and to forge a path forward to find a cure.

For more information or to volunteer to help plan Life Fest 2010, please contact the Life Raft Group office at 973-837-9092. If you'd like to share your story or that of a loved one, please send us an email at liferaft@liferaftgroup.org.



The view from the Hyatt Regency Hotel of New York City, just a short trip across the river.

DUENSING

From Page 7

regulators of quiescence, including SKP2 and p27^{Kip1}. We indeed found that levels of SKP2 decreased in a time-dependent manner after imatinib treatment as would be expected for cells exiting the cell division cycle. Consequently, because low levels of SKP2 are not sufficient to earmark p27^{Kip1} for destruction, levels of p27^{Kip1} increased over this period of time indicating that the cells were entering quiescence as a direct result of imatinib treatment (6).

We next asked which pathways downstream of KIT are important for entering quiescence after imatinib treatment. It has been shown previously that the so-called PI3K/AKT/mTOR pathway is crucial for GIST cell survival and that a parallel pathway, the MAPK pathway, is less important in this context. Interestingly, we now found that the same is true for the induction of quiescence after imatinib treatment (7).

The next question that we addressed was whether undergoing apoptosis or exiting the cell cycle after imatinib therapy are events that are mutually exclusive. In fact, our experiments showed that nearly all cells that did not die in response to imatinib treatment indeed entered quiescence as indicated by positivity for p27^{Kip1}. These results indicate that imatinib treatment provokes an either-or decision with respect to apoptosis or quiescence. However, it is not clear at this point how this decision is triggered within a cell. We then went one step further and engineered GIST cells to express high amounts of the SKP2 protein. When these cells were treated with imatinib, they were protected from cell cycle exit and kept proliferating. This indicates that the SKP2/p27^{Kip1} axis is actively involved in regulating the entry into quiescence during imatinib.

Finally, we wondered whether it would be possible to make use of our findings and translate them into a clinical application. We decided to look at levels of the SKP2 protein in a number of GIST resection specimens and to correlate the

results with clinical parameters. We designed a small tissue microarray containing samples from about thirty primary GISTs. When we stained the array for expression of the SKP2 protein, we found that the level of SKP2 positively correlated with the mitotic index, indicating that these two parameters are related to each other. More importantly, we found that the level of SKP2 expression also correlated with an increased risk for recurrence making high SKP2 expression a potential prognostic parameter.

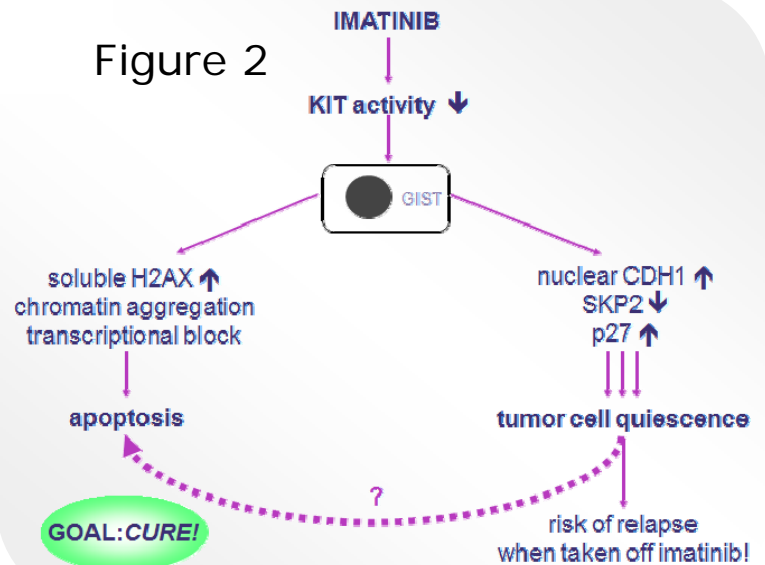
In closing, I would like to introduce you to our current model of the molecular mechanism of imatinib in GIST (Figure 2). Our findings provide evidence that imatinib has several modes of action in GIST. It is not only able to induce apoptosis, but also to directly induce tumor cell quiescence. Therefore, imatinib itself seems to set the stage for future resistance by leading to a pool of cells that are not actively dividing, but that are not dead and may already contain resistance mutations. These cells could ultimately give rise to an imatinib-resistant clone. Our findings could also be the explanation for the fact that even patients that do respond to therapy still have bulky disease, which bears the risk of relapse when taken off imatinib. We do not know which of these two pathways prevails in an individual setting. This could be different from patient to patient and from tumor to tumor and could possibly depend on many factors, such as the mutation type as well as others that still need to be defined. Never-

theless, our results indicate that in pursuing our goal to find a cure for GIST we may need to look for pathways that can manipulate quiescent tumor cells to undergo apoptosis.

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Figure 2



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Rowan passes with family by his side

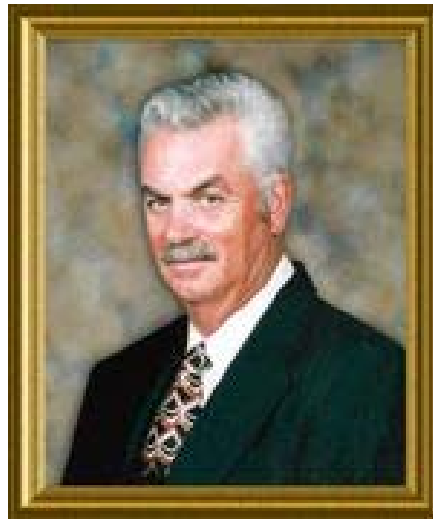
Mr. Kenneth Ray Rowan, of Muse, Oklahoma, passed away peacefully at his residence September 30, 2009 while in the presence of family and close friends. He is now in his new home, serving the Lord as he did here on earth, with love and joy.

Kenneth was born in Muse, Oklahoma on September 23, 1941, the son of the late Earl and Katheryn (Carmack) Rowan.

He was a member of Muse Assembly of God Church and Walnut Ridge Masonic Lodge #390 of Hot Springs, Arkansas. He was also Past Master of Sumpter Masonic Lodge in Hot Springs, Arkansas.

He was the husband of Jane (Bellinghausen) Rowan. They were married December 12, 1996 in Reno, Nevada.

Kenneth is survived by his wife, Jane of the home, two daughters, Billie Ray Combs and Danny Robichaux of Midwest City, Oklahoma, Tammie Mae



Richard Earl Rowan, and a sister, Barbara Jean Barrett-Hart.

Bisineeru-McDaniel and husband Randy of Moore, Oklahoma, a son, Thomas Edward Rowan and wife Cheryl of McCloud, Oklahoma, a step son, Sean Travis Hillyer of Redding, CA.

He is also survived by 19 Grandchildren & seven Great Grandchildren, numerous nieces & nephews as well as many wonderful heartfelt friends

Kenneth is preceded in death by his parents, a son, Gary Rowan, a brother,

Mark your calendars!

GIST Support International is sponsoring an event for GISTers at MD Anderson Cancer Center in Houston on **October 10**. Go to www.gistsupport.org/gsi-community/gists.php for more.

• GISTers in the New England area will be meeting on **October 17** for a luncheon at the home of Susan Farmer. Contact Susan at sfarmer10@cox.net for details.

• GCRF still has 2 more walks to go this year: **October 17** in Washington and **October 25** in San Jose. Please visit www.gistinfo.org for information on how to participate.

• St Louis GISTers will be meeting on **October 24**. Please email giststlouis@hotmail.com for more information.

• The LRG will be holding its 4th Annual NYC Poker Tournament on **November 19**, so email us at liferaft@liferaftgroup.org if you want the details.

Nurit Mantz, wonderful wife and mother, passes away at 46

Nurit Mantz, 46, of Reagan Street, passed away on Wednesday, Sept. 2, 2009, at Geisinger Medical Center, Danville.

She was born Oct. 28, 1962, in Israel, a daughter of Uri and Jemina Finkelstein, of Israel. On July 9, 1988, she married Richard Mantz, who survives. She was a 1981 graduate of North Hollywood High School in Florida and attended Broward Area Community College, Florida.

Nurit was employed by County Hearthside Inn, Selingsgrove, and formerly was employed at Weis Food Service, Northumberland. She enjoyed gardening, beach vacations and trips to New

York City. She was dedicated to her family, especially to her two sons and their basketball and baseball interests. She attended all their games and kept large scrapbooks of their achievements. In addition to her husband, she is survived by her sons, Andrew, 19, and Taylor, 15; two sisters, Vered Reese and Daganit Finkelstein; her father and mother-in-law, Richard and Drena Mantz, of Sunbury; sister-in-law, Melissa Whitmer; and one niece, Jennifer Whitmer.

In lieu of flowers, donations may be made in Nurit's memory to the Shikellamy basketball team's fund for its trip to Ireland, in care of Tim

Foor, 12 Calvin Drive, Selingsgrove, PA 17870.



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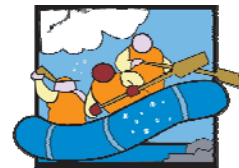
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