

Scherzer Editorial: companies need patent protection to help with future drug development

By Norman J. Scherzer

A recent *New York Times* article, titled “Battle Pits Patent Rights Against Low-Cost Generic Drugs”, stated that patient rights organizations opposed a Novartis legal challenge to India’s patent law which had denied Novartis patent protection for Gleevec. A similar article in the *Wall Street Journal* presented the same point of view.



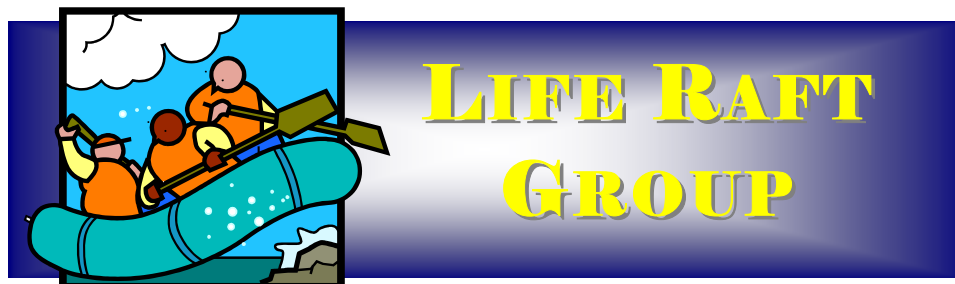
SCHERZER

The organizations cited, Doctors Without Borders and Oxfam, seemed to suggest that millions of people would be without access to Gleevec, a Novartis drug patented around the world, should this company prevail in its Indian court challenge. Though the primary focus of these organizations’ concerns seems to be the worldwide AIDS programs, the drug in question, Gleevec, is targeted to certain rare cancers, including Gastrointestinal Stromal Tumors (GIST).

As the Executive Director of the Life Raft Group, I have had the opportunity to monitor the stories of hundreds of such patients who needed access to Gleevec and, on dozens of occasions, to request the assistance of Novartis in providing this drug to patients unable to afford it, both within the United States and in remote corners of the world. We have never been turned down by Novartis and while there may well be some exceptions, I am not aware of any GIST patient who needed help from Novartis to access Gleevec that did not receive it. It would be easy, and probably popular, to join our well meaning colleagues in their vilification of Novartis, but it just would neither be correct nor right.

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Battling gastrointestinal stromal tumor



April 2007

In memory of Gregory Boitnott, Maria Adela Ruiz Diaz, Leslie Millers & Carlos Ramos

Vol. 8, No. 4

Gene microarray technology yields interesting results in the laboratory

By Dr. Matt van de Rijn
Stanford University

Dr. Matt van de Rijn is a member of the LRG Research Team working to understand and overcome GIST treatment resistance. This is the fourth article in a series to be written by each of the key research team members.

In this issue of the newsletter I would like to describe the type of experiments we perform in my laboratory. Less than ten years ago, Pat Brown of Stanford University and others developed the “gene microarray technology.” I was fortunate enough to start collaborating with Dr. Brown on a number of projects at about the same time. Gene microarray technology allows researchers to look at the expression levels for essentially all human

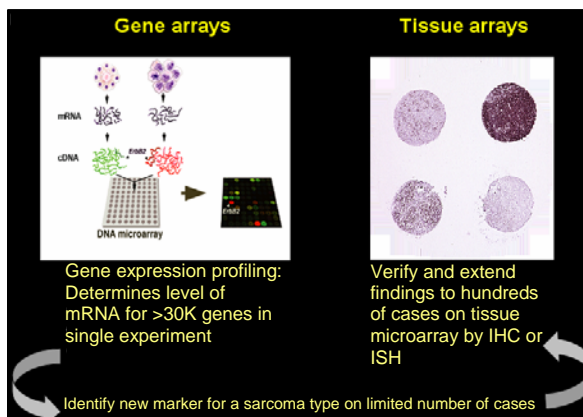
genes in a single specimen using an overnight test. This approach represents an immense advantage over prior techniques in which each gene had to be investigated one at a time, making a “genome-wide” analysis of gene expression levels practically impossible.

Using gene microarray technology, one can therefore (Figure 1) determine the level of message or messenger RNA for each of the approximately 30,000 human genes in a single experiment. In this way one creates extremely large datasets. For example if one would analyze 30 samples of GISTs, one would generate a dataset of 900,000 datapoints. Clearly analysis of such large datasets requires an entirely new set of tools for the researchers.

At Stanford, we are extremely fortunate that the Stanford Microarray Database (SMD, <http://genome-www5.stanford.edu/>) has developed

software that allows researchers such as myself, who do not have an in-depth knowledge of statistical methods, to nevertheless interrogate these enormous datasets and discover interesting gene expression profiles. An example of this is the DOG1 marker (stands for “discovered on GIST 1”). We found high levels of messenger RNA for this protein in all GIST specimens that we analyzed on gene microarrays but in none of the other samples of

Figure 1: Representation of workflow in lab



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'Treatments, trials and trails, oh my' but life must go on: Part 1

By Mark Becker

This is the first part of Mark's story regarding his experiences with GIST. The article will finish in the next issue.

Occasionally I have read that some survivors say that getting cancer was the best thing that ever happened to him. I think, "That person is insane."

We all have a story to tell. The story may help explain how we live our lives and why we are who we are. It may not; but I have not yet met a person who has lived with cancer and has not been changed by the experience. This story is about my experience living with cancer and participating in a recent clinical trial.

My experience living with GIST began in February, 1997 with a case of constipation so acute I had to leave work. My

family doctor examined me and found a mass in my rectum. Unsure of what it was, he called a local surgeon to schedule a consult for me that afternoon.

The surgeon examined inside my rectum with a pencil-thin video camera and determined that my rectum was ninety percent obstructed by the mass. By that afternoon I was a patient at the local hospital, where I was diagnosed with leiomyosarcoma.

My wife and I were stunned and pretty much left on our own to decide what to do next. The surgeon generously offered to remove the tumor but I thought there were probably better options out there somewhere. I asked for suggestions for a



Mark and little Cole.

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ternative to the pharmaceutical industry for the development of the new drugs that we, and other cancer patients, need to stay alive. Until this happens it does not make any sense to me to create any disincentives, such as a lack of patent protection, to the only current hope we have for accomplishing such a task.

I have to acknowledge a personal bias in that my wife was one of the first GIST cancer patients in the world to benefit from Gleevec, responding dramatically only days from certain death. Further, the Life Raft Group has been the beneficiary of no-strings grants from Novartis to support our educational, outreach and research programs, which we have used to reach patients and doctors around the world and to initiate a novel strategic plan to find a cure for this disease. I would invite our colleagues at Doctors Without Borders, Oxfam, and other such prestigious patient organizations, to join with cancer support groups such as the Life Raft to identify additional ways to discover the new drugs that are desperately needed to treat different cancers.

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.

PATENTS

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The photo in the article shows a demonstrator with a sign that says *Patent Kills Patient*. That is a powerful slogan but the reality for most cancer patients, including those with GIST, is that we do not yet have drugs that will cure cancers. Although Gleevec is a breakthrough treatment for GIST patients, with initial responses of about 85 percent, most patients develop resistance over time, as is usually the case, with single-agent cancer therapies. These patients continue to die in great numbers, not because of a lack of access to Gleevec but primarily because the new drugs we need to overcome treatment resistance have not yet been developed by the pharmaceutical industry. I have neither the luxury of time nor the legal expertise to debate the ownership of yesterday's drugs and instead must focus upon the urgent need to find those for tomorrow. Perhaps someone much smarter than I can find an al-

April 2007 clinical trial update

By **Jim Hughes**
LRG Science Team Member

BMS-354825



HUGHES

The BMS-354825 trial has closed and is removed from the list. Dr. Demetri indicated that trial patients still continue to receive the

drug. He also expects the results of the phase I trial to be published. BMS-354825 has been approved for use in CML (as Sprycel) and will likely be tested in other cancers.

Genasense

According to Dr. Demetri's staff, the Genasense phase I trial is not available at Dana-Farber. This information in the clinicaltrials.gov database is not correct.

IPI-504

All new patients are getting the drug on a continuous schedule instead of the 2 weeks on, one week off schedule. Responses are being seen in GIST patient PET scans.

XL-820

The principal investigator at Cancer Therapy and Research Center in San

Antonio, TX has changed from Dr. Papadopoulos to Dr. Catalin Mita. The contact is: Epp Goodwin, Clinical Trials Referral Coordinator, CTCRC-Grossman Bldg, 7979 Wurzbach Road, San Antonio, TX 78229, Phone: 210-450-5798, E-mail: egoodwin@idd.org.

CNF2024

The contact at the Cancer Therapy and Research Center in San Antonio, TX is: Epp Goodwin, Clinical Trials Referral Coordinator, CTCRC-Grossman Bldg, 7979 Wurzbach Road, San Antonio, TX 78229, Phone: 210-450-5798, E-mail: egoodwin@idd.org.

AZD-2171

The contact number outside the United States is: 001-866-992-9276.

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Fourth annual spring meeting of Swiss GIST patient group

By **Ulrich Schnorf**
Swiss GIST Patient Group Leader

Ulrich Schnorf, leader of the Swiss GIST patient group, organized their fourth spring meeting. Members, caregivers, Swiss GIST experts, representatives of pharmaceutical companies and others were invited to the February 16, 2007 meeting in Zurich.



SCHNORF

Sixty GIST patients and caregivers, twelve GIST experts and five Swiss representatives of pharmaceutical companies researching on GIST (Bristol-Myers Squibb, Novartis, Pfizer) were in attendance. Guests from France, Germany (amongst them Markus Wartenberg, director of Das Lebenshaus), Italy (Anna Costato, founder and leader of the Italian GIST patient group) and others were also present.

The meeting began with four presentations by Swiss GIST experts; one quarter

of that time was reserved for questions and answers.

Everything was simultaneously translated from German to French to German (earphones and microphones were provided) because a quarter of the participants and speakers were French-speaking.

Dr. Urs Metzger, chief surgeon of a prominent hospital in Zurich, spoke on GIST surgery and its limits, adjuvant and neo-adjuvant GIST treatment as well as the newest possibilities. He accentuated the importance of cooperation in a team of experts (surgeons, oncologists, pathologists, radiologists) with GIST experience for competent diagnosis and treatment of GIST.

Dr. Roger von Moos, medical director of oncology at the state hospital of the Grisons in Chur, presented the actual and most modern treatment of GIST from the view of the oncologist. He is also clinically researching new medicines for Gleevec-resistant patients.

Dr. Serge Leyvraz, medical director of the multidisciplinary center of oncology in the CHUV state hospital or the University of Vaud in Lausanne (for the french-speaking part of Switzerland), presented the coming clinical trials with dasatinib and nilotinib, experiences with sunitinib and strategies for patients who became resistant to Gleevec. He pointed out in which cases PET scans are important and much more favorable than a CT scan for fast information on the efficacy of a treatment with targeted GIST medicines. Finally, he spoke about the increasing importance of exon determinations for finding the best therapeutic strategy in GIST.

Dr. Michael Montemurro, Swiss member of the medical-



Dr. Metzger speaking at meeting.

board of Das Lebenshaus as representative for Prof. Leyvraz (who is not German-speaking), gave a very informative,

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BECKER

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second opinion and decided on Fox Chase Cancer Center in Philadelphia after talking on the phone with the surgeon there, Dr. John Hoffman. It was only a half hour away and had an excellent reputation, as did Hoffman.

At our first meeting at Fox Chase, my wife, Janet and I met with Dr. Hoffman, who continues now as my surgeon and attending physician. We also met Dr. Margaret Von Mehren, my current oncologist, who has since become a widely recognized GIST specialist and Dr. Richard Greenberg, oncology urologist and surgeon. All are wonderful people, medical professionals, researchers, and physician teachers.

For nine months, this exceptional team treated me. Under the care of Dr. Von Mehren, I had three months of chemotherapy during late winter and required three to four days a month of in-patient IV chemo via an implanted port. I became weak. My appetite waned and my weight dropped quickly. My hair fell out which was a bizarre experience although I have to admit, I did enjoy not having to shave. I could have done without the public stares; no hair, eyebrows or eyelashes and the pale skin and gaunt appearance made for a different fashion statement. People frequently did not recognize me. Tall, thin, hairless and apparently menacing-looking in my black leather trench coat with dark glasses, people parted to either side as I walked along the downtown Philadelphia city sidewalk. I frequently caught people staring at me. I felt freakish, but I knew my appearance was temporary so I put the experience aside emotionally. Eventually, I had to give myself daily injections of Neupogen for my blood count and to ward off the risk of infection which kept me home, away from those crowds of people.

When chemo was over, I began radiation therapy. I drove to Fox Chase first thing in the morning, every weekday for six weeks for my dose of radiation (rads). Soon after beginning, my bowels seemed to cook with a burning sensation

as the daily radiation dose drilled into the tumor. Although not as physically taxing as the chemo, the pain in my guts was a constant reminder of my situation. I smeared lidocaine ointment regularly on my burning anus. At the end of six weeks, I got a month off from treatment to recuperate and prepare for surgery to remove the tumor. I also can no longer have radiation treatment in my pelvis area as I have had the maximum amount of rads a person can have in a lifetime.

In June of 1997, Dr. Hoffman operated, removing my rectum as well as my bladder and prostate as the cancer had also spread to those organs. Over the course of eleven hours of surgery, both Dr. Hoffman and Dr. Greenberg removed all afflicted tissue and created an internal urinary diversion called an Indiana pouch created from the right side of my colon to which my urethras were attached and a stoma created in my lower abdomen so that I could catheterize myself to urinate. My colon was connected directly to the rectal stump allowing me to eliminate feces as before since my sphincter muscle was fully functional. I also had a temporary colostomy to allow my bowels to heal.

The recovery was long, physically difficult and emotionally and psychologically painful. I remember little from the Intensive Care Unit after surgery other than snippets of visits from family and friends through a fog of medication. However, the nursing staff was wonderful and made the time bearable with excellent attention to my recovery. After over a week, my wife brought me home to continue to heal and deal with my new anatomy.

After six weeks, my body was healed and I elected to return to Fox Chase to have my colostomy reversed. I returned home after that surgery to heal again. After about a week, I developed severe abdominal pain which early one morning reached a point where I was vomiting feces and experiencing unbearable

pain. At the local hospital, an x-ray showed a complete bowel obstruction. I was transferred to Fox Chase by ambulance. Dr. Hoffman quickly appeared and determined that immediate surgery was required to save me. He discovered that scar tissue and adhesions had caused

my bowels to clog shut. He fixed me and eventually I went home to live my life with frequent visits to Fox Chase to follow-up with the members of my medical team over the following years.

I went back for a regularly scheduled follow-up with Dr. Hoffman coincidentally at five years, expecting to get a clear bill of health and walk out an official cancer

survivor. Instead, Dr. Hoffman told me that the cancer was back and he would have to remove my entire bowel. Also, the required clear margins would result in damage to the sciatic nerves leaving me with limited use of my legs and a permanent colostomy. I was devastated. As an alternative, he set up a consult with a radiologist to discuss the possibility of implanted radiation seeding in my pelvis to reduce the size of the tumor and the surgically required clear margins and spare some damage.

In the course of that consult, the radiologist suggested I speak with Dr. Von Mehren regarding a new drug called Gleevec. It was proving very successful in treating my disease, now identified as GIST (not leiomyosarcoma).

Dr. Von Mehren put me on 600mg daily and in a couple of months, I had a “complete response”—I was clear of GIST. Everybody—my doctors, I and my family were amazed and happy, to say the least. I continued on with the daily dose of Gleevec and took additional medications to deal with the gastric side effects, pervasive fatigue, uncontrollable muscle cramps and spasms, and other unpleasantities. So what? I was disease-free after all.



Mark and Jake the schnauzer at a New Jersey local meeting.

DOG 1

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other tumors that we were examining, such as synovial sarcoma or leiomyosarcoma.

We therefore realized that this DOG1 marker could be a potential novel diagnostic marker for GIST and could be helpful in the diagnosis of these tumors. The identification of this new marker was then verified by using “tissue microarrays,” using immunohistochemistry or in situ hybridization to detect the DOG1 protein and DOG1 messenger RNA respectively. This has been a repeating theme in our work. We use gene arrays to examine one sample at a time but for many markers (30,000 genes) and then, through biostatistical analysis, pick out one or two interesting genes to further study by immunohistochemistry or in situ hybridization on tissue microarrays.

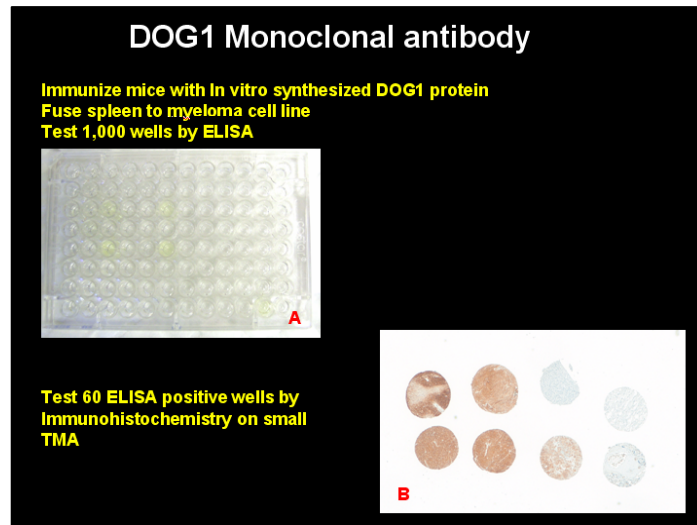
In the principle of tissue microarray (TMA), as developed by Dr. Olli Kallioniemi and his colleagues, a simple instrument removes a core of a paraffin

block containing a tumor sample and positions this core in a pre-drilled hole in an empty paraffin block. By repeating

tory of Mike Cleary of Stanford University. In this technique, mice are immunized with a DOG1 protein fragment

that was generated in a test tube. The immunized mice are sacrificed and their spleen cells or B-lymphocytes are fused to a myeloma cell line. The myeloma cell line provides the B-lymphocytes with the ability to be cultured in vitro. Next, we tested approximately one thousand “supernatants” (the culture medium of a single clone from the myeloma/lymphocyte fusion experiment) for re-

Figure 2: Tests used to generate a monoclonal antibody for DOG1



this process one can position up to 500 cores taken from 500 different tumor samples in a single TMA.

Essentially, what you would see are cross-sections of the cylinders of tumor tissue that have been placed in neat rows and columns. We keep track of which tumor is represented by which core. A section of such a tissue microarray brings a collection of tumor specimens together on a single microscopic glass slide. This can then be stained for protein expression by an antibody or can be used for the detection of messenger RNA for a particular gene by in situ hybridization.

Using such a TMA, we were able to show that a conventional antiserum, raised by injecting a peptide derived from the DOG1 DNA sequence into rabbits, was able to recognize many GISTs that failed to stain for the KIT marker. Approximately 10 to 15 percent of GISTs do not react for KIT using immunohistochemistry and many of those GISTs that failed to stain with KIT antibodies reacted for DOG1 antiserum.

Unfortunately, the rabbit only yielded a small amount of antiserum before it died. We therefore decided to make a monoclonal antibody against the DOG1 protein, in collaboration with a labora-

activity with the same DOG1 peptide that was used for immunization. Of the one thousand wells that we tested, by a technique we call ELISA, sixty showed reactivity. In Figure 2, panel A shows the appearance of such an ELISA test. The faint yellow color represents the presence of an antibody that binds to the DOG1 peptide. Sixty of such wells were identified and the supernatants from those wells were then used by immunohistochemistry on a small tissue microarray shown in panel B. The five cores that stained brown were samples of five different GIST specimens, while the two cores at the right top-hand corner were taken from leiomyosarcoma samples. The lower right hand core is a background control core taken from normal human placenta. Of the sixty antibodies thus screened, two showed promising staining patterns and were further subcloned and retested. Ultimately, we ended up with a monoclonal antibody that we called DOG1.1.

In subsequent studies, we have now further characterized this monoclonal antibody on a number of TMAs. One of these TMAs was made by Drs. Chris Corless and Mike Heinrich and contains a large number of GIST cases for which

Definitions:



Dataset: Collection of data, usually presented in tabular form.

RNA (Ribonucleic acid): Nucleic acid that acts as a messenger to convert information stored in genes (in DNA) into proteins.

Peptides: The family of short molecules formed from the linking, in defined order, of various α -amino acids.

Monoclonal antibody: An antibody is a protein used by the immune system which recognizes and binds to specific molecules, such as other proteins. Antibodies to specific proteins are often used to help identify cell types.

Immunohistochemistry: Method for staining cells; antibodies to specific proteins are used as probes to analyze specimens and identify specific types of cells.

In situ hybridization: Lab test that uses a complementary DNA/RNA strand to localize a specific DNA/RNA sequence in a portion of tissue.

CLINICAL TRIALS

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Each color in the table describes a different drug strategy.	Strategy
	Inhibit KIT (PDGFRA signaling)
	Inhibit KIT (PDGFRA signaling) plus Impede tumor vascularization (Antiangiogenesis)
	Impede tumor vascularization (Antiangiogenesis)
	Destroy KIT
	Inhibit the production of KIT
	Target KIT downstream signaling
Destroy KIT plus Inhibit the cell cycle plus Induce apoptosis	

Therapy	Title	Trial #	Phase	For
AMN-107		NCT00135005	III	GIST
FR901228	FR901228 in treating patients with metastatic or unresectable soft tissue sarcoma	NCT00112463	II	GIST/Sarcoma/Ewings
Perifosine + Imatinib	Phase II Study of Perifosine plus imatinib mesylate for patients with resistant Gastrointestinal Stromal Tumor	MDACC 2004-0968	II	GIST
Sorafenib	Sorafenib in treating patients with malignant Gastrointestinal Stromal Tumor that progressed during or after previous treatment With imatinib mesylate and sunitinib malate	NCT00265798	II	GIST
CNF2024	Study of oral CNF2024 in advanced solid tumors or lymphomas	NCT00345189	I	Tumors/Lymphoma
Doxorubicin + Flavopiridol	Doxorubicin and flavopiridol in treating patients with metastatic or recurrent sarcoma that cannot be removed by surgery	NCT00098579	I	GIST/Sarcoma
IPI-504	Safety study of IPI-504 for Gastrointestinal Stromal Tumors	NCT00276302	I	GIST
LBH589	A phase IA, two-arm, multi-center, dose escalating study of LBH589 administered intravenously on two dose schedules in adult patients with advanced solid tumors & non-Hodgkin's lymphoma.	NVCI	I	Advanced Solid Tumors
Oblimersen + Imatinib	Oblimersen and imatinib mesylate in treating patients with advanced Gastrointestinal Stromal Tumors that cannot be removed by surgery	NCT00091078	I	GIST
OSI-930	Dose escalation study of daily oral OSI-930 in patients with advanced solid tumors - sarcoma	EmergingMed	I	Advanced Solid Tumors - Sarcoma
Perifosine + Sunitinib	Perifosine + sunitinib malate for patients with advanced cancers	NCT00399152	I	GIST/RCC
XL820	Study of XL820 given orally daily to subjects with solid tumors	NCT00350831	I	Cancer/Solid Tumor

Novel KIT inhibitor also targets a new suspect; clinical trials to begin this year

By Jerry Call

Researchers, led by Daruka Mahadevan M.D., Ph.D., at the University of Arizona in Tucson, have characterized a novel mechanism of resistance to Gleevec that may be present in some GIST patients. Clinical trials that test this discovery are expected to start in the first half of 2007.

Dr. Mahadevan and his colleagues have found that some GISTs may switch from being dependent on the KIT signaling pathway to being dependent on another tyrosine kinase receptor called AXL. Mahadevan and colleagues took an existing GIST cell line, GIST882, developed in the labs of Dr. Jonathan Fletcher and subjected it to sub-therapeutic levels of Gleevec and then slowly increased the levels of Gleevec. This resulted in Gleevec-resistant cells called GIST-R.

The GIST-R cells had lost expression of KIT and were no longer responsive to Gleevec. They had also changed in appearance, changing from spindle-shaped cells (longer, more tubular looking) to epithelioid shaped (more rounded). With the loss of KIT expression, they no longer stained positive for KIT and had become KIT-negative GISTs. Mahadevan and his team also found this same mechanism of resistance in two of their Gleevec-resistant patients.

Mutations in KIT are the primary cause of GIST and being able to inhibit the signal of the mutated KIT protein is what makes Gleevec so effective in GIST. In both the GIST-R cells and the two Gleevec-resistant patients, KIT expression was more than 100-fold down-regulated, whereas AXL was overexpressed by 49-fold in GIST-R, 11-fold for the two GIST patients; c-Met, another receptor tyrosine kinase, was overexpressed by 19-fold in GIST-R. In the GIST-R cells, AXL was phosphorylated, implying an activated receptor, thus

maintaining a proliferative signal despite Gleevec. Furthermore, the growth factor that normally stimulates AXL (GAS-6) was overexpressed by 6-fold. In addition, the growth factor for c-Met (HGF) was 14-fold overexpressed suggesting a dual mechanism for cell proliferation.



CALL

AXL and perhaps to c-Met as well.

The Mahadevan team, which also included David Bearss, Ph.D., tested the GIST-R cells against a new compound that had been developed at the University of Arizona and found that the Gleevec-resistant cells were sensitive to this new compound, which they called MP-470.

In 2003, Bearss and Dallin Anderson founded Montigen Pharmaceuticals to further develop and commercialize the research conducted by Bearss in collaboration with Daniel Von Hoff M.D., including the development of MP-470. In 2006, Montigen was acquired by SuperGen Pharmaceuticals.

MP-470 is a new tyrosine kinase inhibitor that inhibits several kinases, including KIT, PDGFR, AXL, c-Met and c-Ret. Interestingly, MP-470 appears to also potently inhibit some of the secondary mutations that cause resistance to Gleevec. In fact, it inhibits all of the ten or so secondary mutations that it has been tested against.

There are several things that poten-

tially make MP-470 different from other kinase inhibitors. First, the drug inhibits AXL and c-Met in addition to KIT and PDGFRA. This has the potential to make it effective in the Gleevec-resistant GISTs that have lost KIT expression, if the AXL hypothesis is correct (estimates based on small numbers suggest that 10 to 20 percent of GISTs become resistant by losing KIT expression). The activity profile also suggests it could be effective against secondary KIT mutations as well.

The cells had undergone what Mahadevan called a “novel tyrosine kinase switch.” They had lost dependence on KIT and appeared to be dependent on

the second thing that potentially separates MP-470 from other kinase inhibitors is that it indirectly inhibits another protein, known as RAD51. This protein is involved in the repair of DNA breaks. In-vitro studies with MP-470 have shown that it often has synergistic effects with other, more traditional therapies including radiation, cisplatin, topo I inhibitors and doxorubicin. In the GIST-R cells, it was synergistic with docetaxel, a common microtubule-targeting chemotherapy.

MP-470 has been well-tolerated in animal studies and appears to have a wide therapeutic dosage range. Phase I, first-in-human trials are expected to start soon at two locations: Johns Hopkins University under Manual Hidalgo and Wells Messersmith and the University of Arizona in Scottsdale under Dan Von Hoff. While the preliminary work by the Arizona team is interesting, it is based on small sample sizes (one cell line and two patients).

The phase I trial is open to patients with advanced solid tumors but like other phase I solid tumors trials with KIT inhibitors, it is hoped that some GIST patients will enroll. Clinical trials should help to further define whether or not AXL activation is important in some patients, whether or not MP-470 is effective at inhibiting AXL and mutant KIT signaling and most importantly, whether or not MP-470 is effective in Gleevec/Sutent-resistant GIST patients.

SWISS

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visual model for GIST patients and caregivers about GIST, including exon mutations, constant signalling and consecutive cancer growth as well as the mechanism of the action of signal-blockers / inhibitors like Gleevec and the differences between the newer inhibitors (sutent, nilotinib, dasatinib etc.) and Gleevec.

After lunch and the possibility of informal discussions between all the participants and speakers, the afternoon program started.

Four workshops were held (1 in French, 3 in German or Swiss dialect) for GIST patients and caregivers on the topic “Living with GIST”, which lasted ninety minutes. Because the groups were small (15 persons each), a very open and spontaneous discussion took place. The participants were very satisfied and discussed future spring meetings.

The experts from four GIST competent clinics in Basel, Chur, Lausanne and Zurich and the specialized GIST pathologists from Basel and Lausanne (see the website www.gastrointestinale-stromatumoren.com, Kliniken mit

GIST-Kompetenz, in German and French) met for medical discussion on the following topics:

- Getting acquainted with each other
- Informing about the newest update of the international consensus for diagnosis and treatment of GIST which was elaborated in Boston (November 2006) and in Germany (February 2007).
- Informing about and coordinating the foreseen clinical trials with dasatinib and nilotinib among the four clinics.
- Discussing cooperation and consulting among the four clinics in general and especially for difficult cases of GIST.

The chief oncologists and surgeons in the clinics as well as two pathologists specializing in exon mutation determination were all present and after a two-hour discussion were satisfied with the result. It was a small miracle that I could get all of them for this important meeting!

Note: The Swiss GIST patient group is

the Switzerland organization of Das Lebenshaus under the leadership of Ulrich Schnorf (one of 14 founding members of Das Lebenshaus in June of 2003), who is also member of the Life Raft Group



Swiss group listening to Schnorf. (this is in addition to two already existing:

since January 2002 and is its Swiss country representative. The group was founded November 2003 and has just launched two new regional groups this year: Bern-Basle and Chur-Zurich-Schaffhausen

the French speaking group and the members of central Switzerland). These groups have regional meetings for informal discussion. Swiss members who can read and write English can also reach the link to the Life Raft Group and some are also members.

The meeting can be summarized with a written statement by Dr. von Moos:

“The GIST patients who are members of the Swiss GIST-patients group come enormously well informed into my medical consultation. This is a challenge for me, but very valuable for the respective patients: it leads in the shortest time to a good treatment.”

LRG works with medical institutions on Familial GIST study

By Erin Kristoff

GIST is generally not an inherited disease; yet there is a small subset where this is not the case. People with familial GIST inherit a mutated gene from one of their parents. It is a very rare type of GIST that affects very few families in the world (this is subject to change as we learn more about GIST). These people usually have KIT mutations in every cell in their body.

It has been mentioned that the Life Raft Group has a number of GIST registries that track patient information. We have a small number of reports within the registry of familial GIST and have been tracking one large family in particular for quite a while. This family has undergone medical treatment at various

medical facilities across the country, with different investigators encountering parts of the family.

The Life Raft Group is trying to coor-



minate information across institutional boundaries, but the main issue is trying to figure out a way to match and unduplicate information between institutions. The problem is working around the Health Insurance Portability and Ac-

countability Act (HIPAA) and confidentiality requirements of each institution.

These are a few main objectives:

- What to do with patients who carry the mutation but do not yet have the disease.
- Identify surrogate markers that can act as preliminary indicators that a person is at high risk for carrying the mutation.
- A long term goal of this study is to identify why some persons with the same mutation develop cancer and some do not.

The Life Raft Group is working with professionals at Dana Farber Cancer Institute, who recently received a grant to study familial GIST, and MD Anderson Cancer Center to try and answer these questions.

DOG 1

From Page 5

they determined the mutation status for the KIT and PDGFRa genes. We have found that the mouse monoclonal antibody DOG1.1 is superior to the original DOG1 rabbit antiserum in that it shows a very high specific reactivity for GIST. It also fails to react with the vast majority of other sarcomas and also carcinomas, melanomas and seminomas. The latter is an important point because KIT antibodies can react with a small number of carcinomas and at a greater frequency with melanomas and seminomas. Thus, the DOG1 monoclonal antibody is an example of how we can use global or full genome screening to identify a single gene that may be clinically relevant. We hope that this antibody will show its usefulness in the clinic in the future (Iñigo Espinosa et al. – manuscript submitted).

One frustrating aspect of performing gene microarray analysis is that, until recently, we were obligated to use fresh-frozen tumor tissue. While in theory it appears simple to save a small fragment of a tumor that is surgically resected from a patient and store it in a freezer, this often does not happen for a variety of reasons. As a result, fresh-frozen tissue always has been and probably will remain difficult to obtain.

In the last year we have become familiar with a new type of gene microarray that is different from the prior type based on cDNA spot fragments spotted on glass. The new type, called “HEEBO” arrays (<http://www.microarray.org/sfgf/heebo.do>) uses small, seventy nucleotide-long fragments of DNA as probes for each gene. In contrast to the

older cDNA arrays, this array type lends itself to using messenger RNA that is derived from formalin-fixed paraffin-embedded material (FFPE). In Figure 3,

an example of such an array is seen and the well-formed red, green and yellow dots each represent a different gene that is sampled in this test. A red signal indicates the presence of a large amount of messenger RNA for a particular gene whereas a green signal represents a very low level of messenger RNA.

To date, we have had good results with this type of analysis although formal proof of the efficacy of this method is still some months away. Figure 4 shows an example of the analysis that we performed. In the columns labeled “Benchmark 18”, we have shown the top genes that distinguish six samples of each of the three tumors tested in this experiment. The samples are located in the columns while the rows represent the genes. A red color indicates that a gene is relatively highly expressed in a sample. The three tumors used for this test were: DTF (desmoid-type fibromatosis), SFT (solitary fibrous tumor), and GIST. For

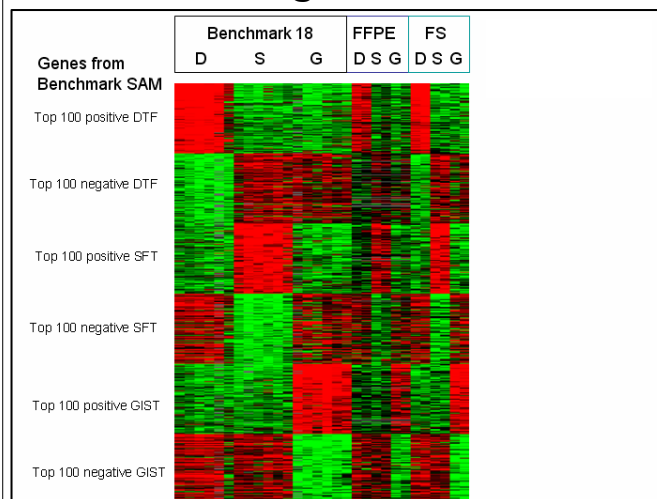
each tumor, we asked the microarray database to yield one hundred genes that were exclusively expressed at high levels in each tumor and an additional one hundred genes that were expressed at very low levels in the tumor. Compare for example the top one hundred positive GISTs versus the top one hundred negative GIST

genes in column labeled G under Benchmark 18.

We then performed two separate analyses on six tumors (two each of DTF, SFT and GIST) that were different tumors from the ones that were analyzed in the Benchmark 18 group. For each of these six tumors, analysis was performed on messenger RNA isolated from formalin-fixed, paraffin-embedded tissue (FFPE) and from frozen tissue (FS). The signals for each of the six one hundred positive or one hundred negative gene-sets are quite similar in the FFPE and FS columns and are quite similar to the genes expression levels seen in the “benchmark” set of tumors. Future experiments that are currently being performed, will show the degree with which this technique can yield new results.

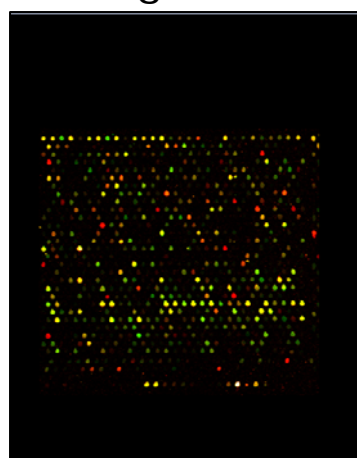
In collaboration with Dr. Chris Corless, we are currently studying a set of “wild type GISTs.” These are GISTs without a known mutation in the KIT or the PDGFRa gene. These wild type GISTs are extremely rare and very few have available fresh-frozen tissue. We therefore hope that these studies using paraffin-embedded tissues will yield data that are otherwise unobtainable.

Figure 4



A comparison of gene expression profiles derived from 18 tumor samples using fresh frozen material with profiles obtained from mRNA isolated from FFPE material.

Figure 3



High magnification images of the new HEEO arrays using mRNA isolated from FFPE material.

Simple two-gene test sorts out similar gastrointestinal cancers

The following is an excerpt from an M.D. Anderson news release entitled “Simple Two-Gene Test Sorts Out Similar Gastrointestinal Cancers; Top Scoring Pair Analysis Applicable to Other Cancers, Personalized Care”.

Houston, February 12, 2007—“A powerful two-gene test distinguishes between a pair of nearly identical gastrointestinal cancers that require radically different courses of treatment, researchers report this week in the online Early Edition of the Proceedings of the National Academy of Sciences.

“This simple and accurate test has the potential to be relatively quickly implemented in the clinic to benefit patients by guiding appropriate treatment,” says senior author Wei Zhang, Ph.D., professor in the Department of Pathology at

The University of Texas M. D. Anderson Cancer Center.

The analytical technique employed to tell gastrointestinal stromal tumor (GIST) from leiomyosarcoma (LMS) with near perfect accuracy will have



wider application in more individualized diagnosis and treatment of other types of cancer, study co-authors from M.D. Anderson and the Institute for Systems Biology in Seattle conclude.

GIST was once thought to be a type of leiomyosarcoma because both originate in the smooth muscle cells of the gastrointestinal tract. However, GIST is treat-

able with the targeted medication known as Gleevec and is relatively unresponsive to chemotherapy. The opposite is true of LMS.

An existing test distinguishes among the two cancers with about 87% accuracy, but intensive and time-consuming additional analyses are required for uncertain cases, Zhang says....”

Jonathan Trent, M.D., Ph.D., also stated in an interview with Medscape, “We hope that the test will be commercially available in about 6 to 12 months, in the meantime, clinicians can send samples to us for testing.”

M.D. Anderson is also working on a similar approach to differentiate sarcoma responders from non-responders, according to Dr. Trent.

Dutch LRG changes name and plans 2007 GIST meeting

By Anja Long

Contact Group GIST/Life Raft Group

The 2007 National Contact Day for the Dutch/Belgian Life Raft Group will be held on Saturday, September 29th, 2007. The venue is planned for a central location in the Netherlands.

One speaker has already been confirmed, Stefan Sleijfer, M.D., Ph.D., internist/oncologist at the Erasmus MC-Daniel-den Hoed Cancer Center in Rotterdam. The organizing committee suggested a second speaker from the discipline of oncological nursing.

Other news from the Netherlands

The Dutch Life Raft Group also decided at the last committee meeting to change the official name to Contact Group GIST/Life Raft Group. The committee felt the name will be more recognizable to GIST patients and their caregivers in the Netherlands and Belgium.

The committee has also been increased by one member from Belgium, Kris Heyman, who will have the task of promoting the group to Belgian (Flemish-speaking) patients.

Another committee member, Carolien Verhoogt, was appointed to a paid position at twenty hours a week. This was possible via a grant from Novartis in the Netherlands.

The youngest member of the group, a 16-year-old teenager named Jasper Smit has been interviewed on Dutch television. Jasper is an avid soccer-fan but the demanding treatment for GIST has meant that he has not been able to play for his local team as he would like. He has now completed training to become a soccer referee and as such is one of the youngest in the game!

On March 10, a big event took place in Utrecht, called the Cancer Genomics Market Plaza, subtitled: “A new approach to cancer”. It was a manifestation for cancer patients, professionals and anybody else interested or involved in any way with cancer. The event was organized by the

Cancer Genomics Center, the NFK (Dutch Federation of Cancer Patient Societies, of which the Dutch LRG is a member) and the KWF Kankerbestrijding (Dutch Cancer Fund). There were presentations by specialists as well as “Ask the experts” workshops on various aspects of cancer, including one on bowel and stomach cancer and GIST, two of the speakers are well-known GIST experts, Winette de Graaf, M.D., Ph.D., and Jaap Verweij, M.D., Ph.D. The “Market Plaza” was available all day, with information stalls (including one for the Life Raft Group), book signings, a traveling DNA lab where you could have your DNA determined, informal meetings with young researchers and films about cancer. The event attracted nearly one thousand attendees and the whole event was publicized on Dutch television, March 6. Interviews were shown with three cancer patients, one of whom has GIST. He described his experiences taking Gleevec.

GIST is on the agenda in the Netherlands!

John Leary, a wonderful father, husband, friend and student

With help from wife, Janice Leary & sister, Kristen Lofstrom

John Leary was a man committed to living his life. No matter what he chose to do, he did it his own way. Because of this, he had the respect of everyone around him.

On January 25, John died in his home, after a long and courageous battle with GIST, surrounded by a family that was as devoted to him as he was to them. "John created a world of love and happiness that he enveloped his friends and family within. That world orbited around his irresistible charisma, his sense of adventure, and his witty insightfulness," said his wife, Janice.

This "sense of adventure" brought John to places others might only dream of, "from the summit of a 12,000-foot mountain, to cliff diving into the Caribbean Sea." His passions included hiking with his wife, gardening, dancing to live music, kayaking, boating, fishing with his dad, and setting out on a new adventure every day. For John, life was about what you could do with it. He "believed we are all here to enjoy life and all it has to offer, while honoring our responsibility to care and give back to the beautiful earth we call home."

And give back he did. John was adamant about protecting the environment and infused it into everything he did.

Besides inspiring his family to keep environmentally-friendly homes, John managed to change an entire school. The Massachusetts Maritime Academy (from which John graduated in 2006) didn't recycle until John went to school there. Through sheer determination and passion, John managed to make recycling at the academy a permanent rule.

It was this passion that led him through his life. He entered Massachusetts Maritime right out of high school and spent time going to school, traveling around the country and working carpentry and landscaping jobs. Twelve years later he received an honorary degree from the school. Because of GIST, he was unable to fulfill the degree requirement of shipping out to sea but the President of Academy knew how important this was to John and granted him his degree anyway. Also, this spring Maritime Academy will be making a presentation and dedicating their newest shell (boat for the sport of crew) to John's memory. John made an impact on that school and it on him. It was not just a

sense of accomplishment that fueled John's need for a degree, it was his son Christopher John, who turned one in September 2006.



John on swing with son, Christopher John.

He wanted to show his son how important an education is in life. According to his sister, Kristen, "He was why John hung out as long as he did. His passion was taking care of that baby.

He liked to stay at home and take care

of his child."

"He was the strongest, bravest person I ever met; I'm proud to be his sister and I love him."

John is survived and loved by many family and friends including his wife Janice and their son Christopher John of Buzzards Bay; his parents, John and Judy Leary; his sister, Kristen Lofstrom and her husband, Ray; his nieces, Olivia and Anna; nephew, Raymond Lofstrom of Bridgewater; his paternal grandmother, Marjorie B. Leary of Bridgewater; his in-laws, Rick and Helen Duffy; and his brother-in-law, R.J. Duffy, all of South Plymouth.

Donations can be made in his memory to the Christopher John Leary Scholarship Fund, c/o TD Banknorth, 121 Main St., Buzzards Bay, MA 02532.



Pediatric GIST is discussed at San Diego meeting

Jerry Call, LRG science coordinator (second from right) and Norman Scherzer, LRG executive director (right), to discuss progress in Pediatric GIST research. A major focus

was the need to increase the number of tissue specimens sent to the Pediatric GIST Tissue Bank housed at Memorial Sloan-Kettering, including the handling of frozen tissue samples.

Following the March 24 meeting of the LRG Research Team in San Diego, Calif., Drs. Cristina Antonescu (far left) and Jonathan Fletcher (second from left) met with

Israeli group holds its fifth monthly meeting

The Israeli group, led by Ben Shtang, held their fifth monthly meeting this past February.

The subject of the lecture was "Nutrition during Cancer" and was given by Dr. Niba Shapira.

Previous lectures have been given by Professor Merimsky on GIST, Professor Kreitler on the importance of support to cancer patients and others.

Ben is working diligently to raise funds in order to reach more patients.

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Learn more about the Global GIST Network: www.globalgist.org