Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

March 2007 | In memory of Mark Thomas, Gerard Hetterscheid, & Stephen Gratz | Vol. 8, No. 3

Immunotherapy: a new hope for GIST treatment

LeCointe interviews Professor Laurence Zitvogel about a new therapy for GIST

By Estelle LeCointe
Director of Association Française des Patients du GIST

A French phase I clinical trial, combining Gleevec + interleukin 2 (IL-2) should open in April 2007 at the Institute Gustave Roussy in Villejuif, France. The aim of this study, organized by a team of Professor Laurence Zitvogel's, is to evaluate the efficacy as well as the toxicity of this medicinal combination in the treatment of various cancers, including GIST, but also to identify the presence and the action of Interferon Killer

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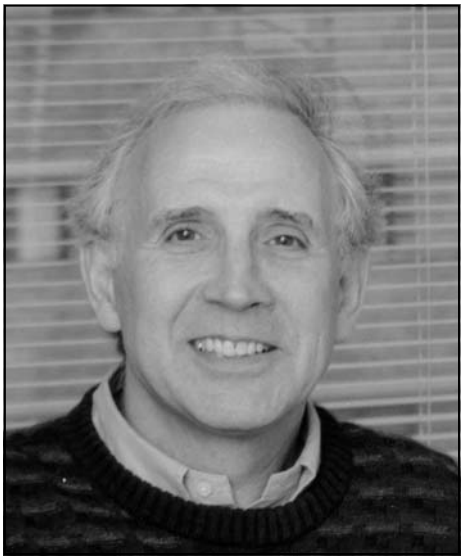
LECOINTE

The use of mouse models to help investigate GIST

By Dr. Peter Besmer
Memorial Sloan-Kettering Cancer Center

Dr. Peter Besmer is a member of the LRG Research Team working to understand and overcome GIST treatment resistance. This is the third article in a series to be written by each of the key research team members.

In this newsletter I would like to highlight the importance and usefulness of mice or mouse models in biological and cancer research by using the Kit receptor tyrosine kinase as an example. Receptor tyrosine kinases are molecules which reside in the membrane of cells. They consist of an extracellular domain, a single transmembrane domain and a cytoplasmic domain which includes a tyrosine kinase. Tyrosine kinases are proteins which phosphorylate proteins, or attach phosphate residues, specifically on tyrosine moieties of target proteins. Binding of a ligand to a respective receptor activates the kinase, and this sets in motion distinct signalling events in the receptor expressing cell. Whereas the receptor tyrosine kinase may be expressed in only



BESMER

a few distinct cell populations in the organism/animal, the available signalling machinery available to transmit receptor initiated signals in these different cell types may differ. Thus a receptor initiated signal in different cell types may differ and result in different outcomes.

In our studies of the Kit receptor, a most important observation we had made in collaboration with Alan Bernstein's group in Toronto was the demon-

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Note from the Executive Director Norman J. Scherzer: Although we strive for a balance between scientific and more general interest articles, we are not always successful. This newsletter tilts somewhat toward our scientific audience with important information that may help find a cure for GIST.

Gleevec: revolutionizing GIST cancer treatment

Is there a role in cancer immunotherapy as well?

By Jerry Call

In this month's March 2007 newsletter, Estelle LeCointe, the director of Association Française des Patients du GIST: Ensemble contre le GIST, has shared the story of the work of Professor Laurence Zitvogel. Professor Zitvogel and her colleagues are engaged in a project combining Gleevec and immunotherapy. It has been very interesting to watch this work evolve over the last few years. This research has culminated in the discovery of a new type of immune cell (in mice) and is poised to enter clinical trials in 2007.

Unexpected responses in GIST

A 2004 paper in the *Journal of Clinical Investigation*, "Novel mode of action of c-kit tyrosine kinase inhibitors leading to NK cell-dependent anti-tumor effects" by Dr. Christophe Borg, Dr. Laurence Zitvogel and colleagues was the first in a series of papers describing the work of Professor Zitvogel's team.

They reported that 6 cases (3 in a phase I/II French study and 3 in a phase II U.S. study) of GISTs that did not have KIT or PDGFRA mutations (wild-type GISTs) still exhibited objective tumor responses. Two of these patients that had liver, stomach or lung metastases had complete responses to Gleevec with 26 months of disease-free survival. Because patients with wild-type GISTs are not expected to respond as well to Gleevec, the finding prompted a search for an alternate mode of action of Gleevec.

Inhibiting KIT signaling in dendritic cells stimulates NK cells

Zitvogel and colleagues tested Gleevec against the B16F10 melanoma cell line, and found no inhibition in the test tube (in vitro), but found that Gleevec significantly hampered the formation of lung metastases in mice (melanoma). Gleevec also induced significant anti-tumor effects against the AK7 mesothelioma and the MCA102 fibrosarcoma models. They found that these effects could be potentiated by the addition of FL, a blood growth factor (the ligand for FLT-3). A short administration of Gleevec (4 days) combined with FL (Gleevec + FL) promoted synergistic anti-tumor effects against AK7 mesothelioma with up to 45

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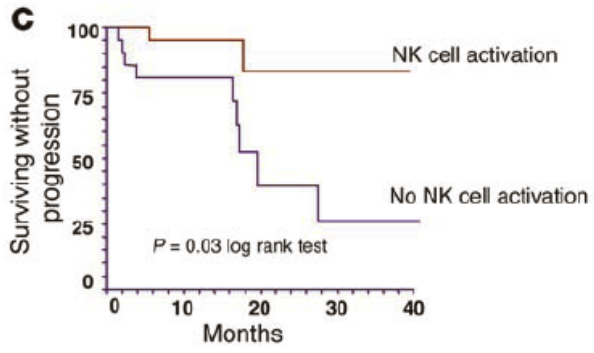
Figure 1. Effect of Natural Killer (NK) cell activation on Progression-free Survival in GIST patients



Novel mode of action of c-kit tyrosine kinase inhibitors leading to NK cell-dependent anti-tumor effects. *The Journal of Clinical Investigation*, Borg et al.

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.

March 2007 clinical trial update

By Jim Hughes
Member of LRG Science Team

In this month's newsletter, you will find a new format for reporting clinical trials. We hope that this method is easier for the reader to track clinical trials.

Two New Tables:

1. Drug Names Table (See Page 12):

This reference is intended to track the different names of GIST drugs.

When first introduced a new drug or Investigational New Drug (IND) is given an alphanumeric designation that is often a combination of an abbreviation of the manufacturers name and a number representing a compound of interest. In the case of Gleevec, the original name was STI-571. STI for "Signal Transduction Inhibitor" and "571" for the compound number being tested.

The International Non-proprietary Name (INN) is assigned by the World Health Organization (WHO) when a manufacturer applies for a generic name for a new compound. The WHO has a scheme whereby the active part of the drug is classified and given a "stem" as part of the name. Stems used in the GIST world include:

- "tinib" refer to a tyrosine kinase inhibitor.
- "anib" refers to an angiogenesis inhibitor.
- "mycins" are antibiotics.
- "imus' refers to immunosuppressants.

INN's are also referred to as "generic" drug names.

The Proprietary Name is the trademarked name chosen by the drug company for marketing the drug. Different drug companies will have different names for the same INN compound.

The strategy is a broad category intended to group drugs that have a similar target. It is important to note that while drugs target some component of GIST viability, they often can have effects beyond GIST. The rash that can accompany Gleevec usage may be a result of Gleevec's effect on normal mast cells. It is also worth noting that cell signalling is a highly complex and interactive environment. They say there is a lot of "cross-talk." The effect of a single drug sometimes may come from a mechanism not originally targeted. As an example, it has recently been reported that Gleevec can positively affect the immune system response to GIST!

HUGHES

It has been suggested that GIST therapy may eventually involve a combination of targeted drugs. Newer GIST drugs and trials use a combination of strategies. Drugs like Sutent incorporate multiple strategies. Some new drug trials may also incorporate a combination of multi-acting drugs. The table on page 12 lists some of the specific targets included in each strategy.

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Life Rafters raise $30,000 with third annual holiday campaign

Life Rafters have brought in a total amount of $30,000 through the Magic Leaves Campaign this past year. The top three star fundraisers for the 2006 campaign are:

- **Doris Dallow, raising a total of $3,150**
- **Pat Lemeshka, raising a total of $1,525**
- **Rachel Tate, raising a total of $1,035**

Congratulations ladies, you have inspired your friends and family to support you in your fight against GIST!

Each year, the money raised from the annual holiday campaign goes to these program areas: Research and Treatment Surveillance, Information and Support, Patient Outreach and Assistance, and Advocacy. Please visit www.liferaftgroup.org for more details.

We're incredibly grateful for all your past and ongoing support. It's because of you — the Life Raft Group community — that we can continue working towards our mission. To see a list of the people and organizations who have generously contributed their support to the LRG, please keep your eye out for the annual report in March 2007.

If you have any questions, contact ekristoff@liferaftgroup.org.

MOUSE MODELS

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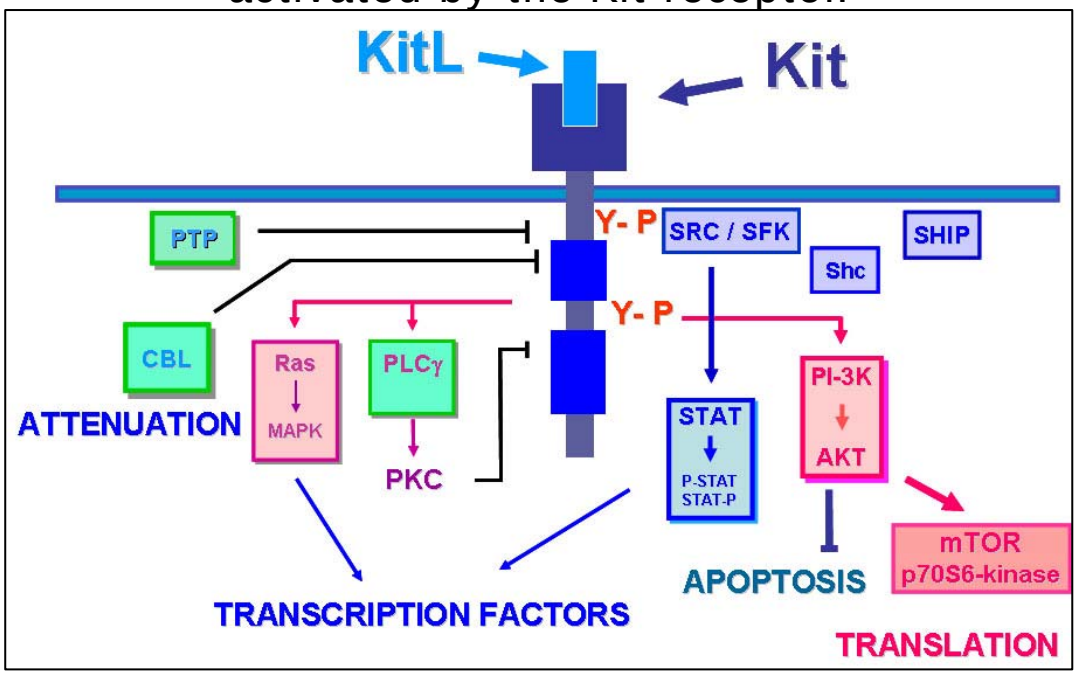
stration that the Kit receptor gene was encoded at the White spotting locus in the mouse (2, 4). Mutations in the White spotting/Kit gene had been reported quite some time ago due to the effect of the mutation on pigment formation and the consequent lack of pigmentation in these mice – hence the designation white spotting mutation. Previous work had shown that the wild-kit gene had important roles in melanogenesis (the formation of pigment cells), in germ cell development and in hematopoiesis. Mice which lack Kit receptor function lacked coat pigment, they were sterile, and the formation of red blood cells and mast cells were affected. Therefore, the mutant animals died perinatally as a result of the red blood cell deficiency. At the time, the demonstration that Kit was encoded at the white spotting locus was a breakthrough. Subsequent work in the 1990s in great part focused on the role of Kit in hematopoiesis. Today we know that Kit has a role in hematopoietic stem cells, in the progenitors/precursors of all of the hematopoietic cell lineages, including lymphocytes. In the early 1990s, using a monoclonal antibody which blocks Kit receptor function, Nishikawa's group in Japan observed that treatment of mice with this monoclonal antibody would cause dysfunctional gastrointestinal motility (9). This then led to the identification and characterization of the interstitial cells of Cajal, which we know today are the cells which may give rise to GIST. Based on phenotypes of Kit mutant mice, the cellular responses which Kit may mediate appear to be quite diverse and include cell proliferation, cell survival (suppression of apoptosis/cell death), cell adhesion, migration, secretory responses and differentiation.

How does the Kit receptor mediate these diverse outcomes? The Kit receptor is known to activate several distinct signalling cascades including phosphatidyl inositol-3 kinase (PI 3-kinase) and Src family kinases (SFK) (See Figure 1). Both signalling cascades have critical roles in receptor tyrosine kinase signalling and oncogenic transformation. To investigate this question we modified the Kit gene in the mouse genome by substituting critical tyrosine residues in the Kit protein with phenylalanine (1, 5, 8). These substitution mutations in the Kit receptor block either PI 3-kinase or SFK activation (15). The analysis of the phenotypes of the mice carrying these mutations brought to light that PI 3-kinase is critical in male germ cell development, but had no other discernible phenotypes, whereas the SFK mutant mice had defects in hematopoietic cell lineages, but not in germ cell development. These results highlight the critical importance of the cellular environment in which the Kit receptor functions and demonstrates that animal models are critical for elucidating the role and mechanisms of receptor tyrosine kinase signalling in different cell types.

Figure 1: Signalling pathways which may be activated by the Kit receptor.



In the 1980s Kit was identified as an oncogene of a feline sarcoma virus (3), but it was only in the 1990s that a role for Kit in human cancer became evident (6, 7, 10). The cancers which are associated with oncogenic activation of Kit include most importantly GIST, but oncogenic activation of Kit is also observed in mastocytosis, seminomas, a small subset of AMLs and a small subset of melanomas. In most cancers, mutation or oncogenic activation of the cancer genes occur in somatic cells and thus are only found in one tissue. However, in rare occasions oncogenic mutations are acquired in germ cells and may be transmitted in the germ line (i.e. the oncogenic activation mutation is inherited). Interestingly, some cases of familial GIST have been reported where a Kit gene carrying an oncogenic mutation is inherited (11). We have engineered a mutation found in a familial GIST case into the mouse genome by using homologous recombination approaches. A mouse strain which carries this mutation

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Illustrating gives Greenwood comfort through his GIST battle

By Erin Kristoff

This article is part of the "Artists of the Life Raft Group" series. The series focuses on the various talents of our members and how it helps them cope with their cancer.

For Peter Greenwood, a successful freelance illustrator, GIST is a burden and a tool. Like most GIST patients he feels the pressure of scans and occasional hopelessness. But despite all of this, Peter has found ways to use GIST to his advantage, to use it for inspiration by using his illustrations as tools to fight GIST. "[My illustrations] helped me come to terms with [GIST] and give me hope; I think that's what I've found. One of the images I did recently is the idea of kind of being looked after, that I was in the right hands and it's all going to be okay. It's an image I'm really pleased with, I feel like someone's looking after me. It gives me solace."

Peter, who lives in Brighton on the south coast of the United Kingdom, uses a computer to transform his sketches into works of art. His sketch is scanned into the computer, which he then uses to color the drawing. "The possibilities for manipulating and working on images are quite vast [with computers]. You can produce images that you never could with paint."

Peter spends his time working on commercial illustrations as well as his own. "I do illustrations that I am commissioned to do, and also I create my own work, which keeps me sane." Peter works for book and magazine publishers and advertising agencies. "It can be a little soulless doing that and it can be quite restrictive, that's when I do my own work."

Peter has illustrated numerous book covers in the United Kingdom under the names of Peter Greenwood and Peter Mac and recently illustrated a mural for the entrance for the head office of Greater Manchester Transport; it measured an impressive 40 feet by eight feet. He got his inspiration from experts such as Ralph Steadman, illustrator of *Fear and Loathing in Las Vegas* and W. Heath Robinson, who illustrated many

GREENWOOD

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The Life Raft Group Facebook

The Life Raft Group Facebook is designed to put "faces to names". Haven't we all wondered at one point what the person behind the touching words looks like? Here is your chance. This is your yearbook. The LRG community is like a school in that everyone is learning and leaning on each other. And sometimes it is nice to look back in that book and see the faces of those who have gone through the experience with you. We offer this to you as a reminder that you are not alone.

We will be selling the Facebooks at the end of April for a small fee to cover costs. Sending your picture does not mean you must buy the book.

Pictures are due by **March 15, 2007**. Please email your completed questionnaire and your photo (preferably a head shot) to ekristoff@liferaftgroup.org. We will also accept photos through the mail. Please send them to the LRG office: The Life Raft Group, Attn: FACEBOOK, 40 Galesi Drive, Suite 19, Wayne, NJ 07470.

ZITVOGEL

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Dendritic Cells (IKDCs) in humans.

IKDC: Killer cells

Interferon Killer Dendritic Cells are cells of the immune system which are naturally produced by mice bodies and are located in the bone marrow, liver, spleen and ganglions. Their peculiarity lies in their capacity to kill cancer cells.

Several studies conducted on mice allowed Professor Zitvogel's team to highlight that when IKDCs are numerous and stimulated, they spontaneously move to tumor cells and reduce them to nothingness in a few hours, thanks to the large amount of interferon gamma (IFN-γ) and complex lyse systems (perforine/granzyme, TRAIL) they naturally secrete or secrete after stimulation.

Indeed, the studies conducted on animals have tended to demonstrate that this natural secretion of IFN-γ plays a key role in the efficacy of IKDCs. It helps other cells of the immune system called "T lymphocytes" to identify and reach tumor cells. IFN-γ also has an effect on tumor angiogenesis and therefore facilitates killing cancer cells.

A necessary stimulation

Unfortunately, IKDCs are very rare and therefore have an extremely limited natural effect on tumors. From this, Professor Zitvogel's work involves stimulating the production of IKDCs in order to increase the secretion of IFN-γ and to boost the efficacy of the immune system.

Why combine Gleevec and IL-2?

Experiments on animals led to the hypothesis that the Gleevec + IL-2 combination would not only contribute fourfold to the production of IKDCs but would also boost their activity in the body. IL-2, which is a growth factor commonly used in immunotherapy, would facilitate the migration of IKDCs to the tumor sites, while Gleevec would stimulate the communication between dendritic cells and some lymphocytes called "NK cells" or "Natural Killer cells," making them capable of killing cancer cells.

NK cells are naturally triggered by dendritic cells which stimulate the immune system. The activation of NK entails the secretion of IFN-γ and therefore facilitates the decline of the tumor.

In 2004, scientists observed in GIST patients that NK cell activation during Gleevec treatment was a predictive factor for an objective tumor response to Gleevec and was often correlated to a longer time to progression. About 60 percent of the Gleevec-treated GIST patients, with various exon mutation profiles, had an enhanced activation of NK cells.

ZITVOGEL

In vitro studies allowed Professor Zitvogel's team to prove that Gleevec was acting on murine (mouse) or human dendritic cells and facilitated their capacity to activate NK lymphocytes. Thus:

· Without Gleevec: 1 dendritic cell does not activate any NK cells.

· With Gleevec: 1 dendritic cell activates 10 NK cells.

Regulating the production of Treg cells

Forty percent of the Gleevec-treated GIST patients do not have NK cell activation. This could be assigned to an unexplained overproduction of "Treg" lymphocytes (regulatory T cells) which significantly inhibits NK cell functions and therefore facilitates the progression of the disease.

Treg cells are CD4+CD25+FoxP3+ lymphocytes naturally produced to fight against healthy tissue self-destruction phenomenon (autoimmune diseases). Treg cells represent less than 5 percent of the T CD4+ circulating lymphocytes but can dramatically increase in the tumor site and its draining ganglions during tumor growth.

Apparently, there is no particular link between the overproduction of Treg cells and the *KIT* and/or PDGFRa mutational status.

Even though Gleevec can promote the capacity of dendritic cells to stimulate NK cells, it has absolutely no effect on Treg lymphocytes. Therefore, it's necessary to decrease the number of Treg cells to try and contain tumors. The neutralization of Treg lymphocytes is possible with a low dose pre-treatment of "cyclophosphamide." The action of cyclophosphamide on angiogenesis and tumor progression has been demonstrated during a non-GIST study in 2006 (Ghiringheili et al. CII, 2007).

The upcoming French "Gleevec+IL-2" clinical trial represents a real hope for many patients. If the existence of IKDCs in humans is confirmed, this would probably lead to a new approach of cancer treatment for thousands of hopeless patients whose diseases could not be controlled for a long time. Immunotherapy may be a step towards a cure.

Gratz, 64, fought a courageous battle

Stephen K. "Steve" Gratz, age 64, of Savage, Minn., passed away peacefully at his home surrounded by his family after losing a courageous battle with GIST cancer on Feb. 1, 2007. He was the original owner, along with his wife, Karolyn, of the Children´s Store in Boise. Steve will always be remembered for his love and devotion to his family and friends. He is survived by his loving wife, Karolyn "Boots"; sons, Kris and Peter; daughter, Miranda; grandchildren, Chelsea and Hailey; brother, Robert "Doc" and many other relatives and friends.

Contributed by IdahoStatesman.com.

CALL

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percent tumor-free mice using FL+ Gleevec versus 14 percent using FL only and zero percent using Gleevec alone. They concluded that even in cancers where Gleevec had no direct anti-tumor effect, Gleevec somehow caused an indirect anti-tumor effect (later shown to be due to Gleevec's effect on the immune system).

Through observations, Zitvogel et al. noticed that the Gleevec + FL combination was unable to protect mice against some tumors. Because these tumors did not express proteins needed to activate a type of immune cell, called natural killer (NK) cells, they hypothesized that NK cells might be the critical cells activated. In experiments where NK cells were neutralized with anti-NK1.1 monoclonal antibodies, the anti-tumor effects of the combination were significantly hampered.

The team noted that treatment with Gleevec + FL did not increase the number of NK cells and could not directly boost the secretion of interferon gamma (IFN-γ). Gleevec did not seem to directly affect the NK cells. They noticed, however, that IFN-γ was produced when the NK cells were cultured together with another type of immune cell, dendritic cells. Dendritic cells help target the immune system by presenting antigens to other immune cells, effectively helping to identify targets for the immune system. Apparently Gleevec was acting on the dendritic cells which then affected the NK cells. One untreated dendritic cell was unable to "activate" NK cells, but when treated with Gleevec, one dendritic cell was able to activate 10 NK cells.

The combination of Gleevec and FL was able to increase the number of dendritic cells compared to FL alone. In addition, the team showed that KIT (c-kit) signaling in dendritic cells inhibited NK cell activation. Therefore, treatment with Gleevec helped stimulate NK cell activation by disrupting KIT signaling in the dendritic cells.

GIST patients with NK cell activation appear to do better than those without NK cell activation

The team was intrigued by their findings. They wondered whether NK cells might be responsible for some of the therapeutic effects in GIST patients. They assessed NK cell function in 49 GIST patients. Using IFN-γ as a marker of NK cell activation, they found that NK cells were "activated" in 24 of 49 GIST patients treated with Gleevec. In contrast, only 21 percent of untreated GISTs or 11 percent of normal volunteers had signs of NK cell activation. They noted that NK cell activation was

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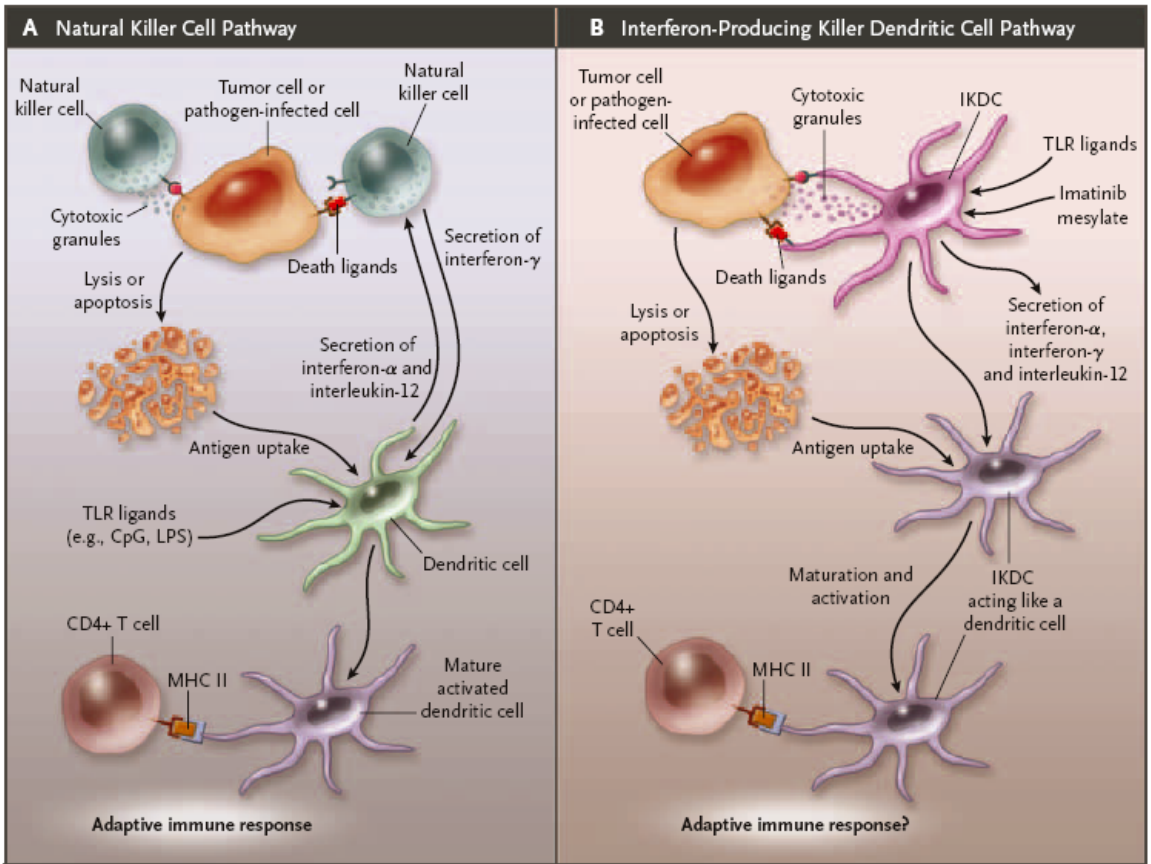
Figure 2: A New Type of Immune Cell



Two recent studies[2,3] have identified a new type of immune cell: the interferon-producing killer dendritic cell (IKDC). It may carry out several functions in immune surveillance and serve as a link between innate and adaptive immunity. Interactions between dendritic cells and natural killer cells occur during various stages of the immune response to pathogens or tumors (Panel A). Natural killer cells can kill target cells after recognizing them. Dendritic cells then respond to the cell death in part by recognizing dead-cell detritus through pattern-recognition receptors, including toll-like receptors (TLRs), and then activating an adaptive immune response including CD4+ cells. The new studies[2,3] indicate an alternative pathway to adaptive immunity, in which just one type of cell, the IKDC, both kills the infected cell and subsequently activates CD4+ T cells (Panel B). One of the studies[2] showed that imatinib mesylate activates the IKDC in a mouse model of cancer, perhaps explaining the therapeutic effect of the drug in some gastrointestinal stromal tumors that are resistant to its antiproliferative effect. CpG denotes a motif of bacterial DNA, LPS lipopolysaccharide, and MHC II major-histocompatibility-complex class II molecule.

MOUSE MODELS

From Page 4

in the germline has also been obtained (13, 14). Remarkably, these mice recapitulate human familial GIST quite faithfully.

These findings first of all demonstrate that the Kit mutation is the initiating event in the development of familial and presumably non-familial GIST. Secondly, they highlight the unique specificity of the mutant Kit receptor to produce GIST and not other cancers and this implies that the cellular machinery in GIST cells and their microenvironment is quite unique in supporting tumor formation and tumor maintenance. These GIST mice provide a unique opportunity to investigate the mechanism of oncogenic Kit receptor signalling and they provide a superior opportunity to evaluate second generation drugs which might be useful in the treatment of imatinib resistant GIST. In this regard we have been able to identify Kit specific signalling cascades that are inhibited by treatment of these mice with imatinib and begin investigating efficacy of second generation drugs that might be useful to treat imatinib resistant GIST (12). Furthermore, encouraged by our success to recapitulate familial GIST in mice, efforts are now under way to produce a model for imatinib resistant GIST.

Definitions:

Moieties – A specific segment of a molecule.

Chemotaxis – A kind of movement in which bodily cells, bacteria, and other single-cell or multicellular organisms direct their movements according to certain chemicals in their environment. In multicellular organisms, chemotaxis is critical to development as well as normal function.

Perinatally – The period of time occurring around the time of birth.

Hematopoietic – Pertaining to or related to the formation of blood cells.

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LRG Science Team meets in Chicago

Life Raft Group members Rick Ware, Jim Hughes, Jerry Call and Norman Scherzer met in Chicago in early February to discuss many topics, such as the science content of the Life Raft Group Web site and how to make it more user-friendly

Rick and Jim in particular generously donate much of their time to the LRG on a number of projects. It is important for the LRG to make productive use of its volunteers and their talents. Rick's wife, Kathy, and Jim's wife, Margi, were extremely supportive and joined the group for part of the meeting, and Richard Kinzig, Chicago area coordinator, also joined the group for dinner.

GREENWOOD

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of Hans Christian Andersen's works including *The Arabian Nights* and *Tales From Shakespeare.*

Peter feels that his illustrations are a meditative act, "I get a break from having to worry about cancer." He also ensures that he does not spend too much time on his commercial work. "I'm continually writing down ideas, and in the last few months I seem to be getting more direction in my personal work."

The reason for Peter's sudden creative burst could be the state of his health recently. "I've been great. I'm nine months on Glivec and it has been helping me. The last scan showed that my tumors are still shrinking and one has disappeared. It makes me feel like I can concentrate on my own work."

Pictured above: One of Greenwood's favorite illustrations. To view more illustrations, visit his two websites: http://www.petermac.com and http://www.peter-greenwood.com.

When Peter is not using his art to support him through GIST, he has plenty of places to turn. He is able to get a great deal of support from groups like The Life Raft Group, GSI and GIST Support UK, as well as his family (Peter has two kids, a "fantastic, supportive" wife, Clare, two rabbits, one "mad pup" named Midgley and three chickens). Although he enjoys watching live music and tinkering with his old Citroën DS, Peter really loves spending time with his family. "My greatest realization from having GIST has been that my family is so important to me. We have become a tight unit and are very loving to each other, and this is precious!"

Peter is someone who insists on living life to the fullest and never lets GIST hold him down. His favorite quote is by filmmaker Marcel Pagnol, "Everyone knew it was impossible, except for one idiot who went ahead and did it." This quote truly describes Peter's outlook on life and GIST as well. "I have learned not to worry about the future too much and I know it's an old cliché, but I have moments of living in the present. That is a very important lesson to learn.

He is also confident in the abilities of the medical community. "Through the LRG I can keep an overview on all that is going on medically, my hopes are that they are really going to crack it."

Peter recently read a book that he believes is useful to anyone living with cancer, *Man's Search for Meaning* by Viktor Frankl. "He was a Jewish prisoner in Auschwitz. What he talks about is whatever awful situation humans are involved in, they can always manage to find a way of having hope and creatively making the situation ok for them. The ideas spoke volumes to me and other patients as well. It really speaks to the cancer patient; you replace concentration camp with cancer. Those prisoners didn't know when or if their time would come, the comparisons are all there. They were still able to have dignity."

CALL

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increased in 9 of 11 patients after treatment with Gleevec compared to before treatment with Gleevec. More importantly, they noted that patients with NK cell activation seemed to do much better than patients without NK cell activation (See Figure 1). This effect was statistically significant. None of 10 patients with progressive disease had enhanced NK cell function.

According to Zitvogel and colleagues, GIST tumors have molecular features of NK cell sensitivity: TAP-1 deficiency, loss of MHC class I molecules, high expression on NKG2D ligands and GIST recognition by NK cells comparable to that of K562 cells.

The 2004 paper was extremely interesting. The experiments seemed to be well thought out. The only caveat with this paper is that there was no attempt to relate NK cell activation to response by exon status. An intriguing question is whether Gleevec sensitive tumors become more susceptible to the immune system while taking Gleevec as compared to non-responding tumors; in other words, does Gleevec downregulate signals/proteins on the tumor cell that are involved in immune system evasion?

Too many Treg cells reduce NK cell activity

Regulatory T cells (Treg cells) discriminate between self and non-self. A tilt towards over-recognition of self results in autoimmune diseases, but with perhaps more activity against some cancer cells. A tilt in the other direction results in less autoimmune disease, but with perhaps less anti-tumor activity.

In 2005 at the American Society of Clinical Oncology (ASCO) conference, Zitvogel submitted Abstract 2516 that identifies the reason why half of the GIST patients did not have NK cell activation. Patients with high numbers of $CD4^{+}CD25^{high}$ regulatory T cells (Treg) in the blood at entry were shown to have less NK cell function. In GIST patients with good NK cell function/activation, the percentage of Treg cells were not elevated compared to normal volunteers (1.1% vs. 1.2%). In the group with no NK cell activation, Treg cell levels were three times higher (3.2% vs. 0.8%).

Reducing Treg cells has therapeutic implications

In the 2005 ASCO abstract, Zitvogel suggests a possible way to reduce the number of Treg cells with a low-dose type of cytotoxic chemotherapy, cyclophosphamide. She noted that a combination of Gleevec + cyclophosphamide was synergistic in a mouse model of lung melanoma metastases. She notes that NK cell activation is a novel surrogate marker of efficacy of Gleevec which is critical for time to progression and could be enhanced by pre-treatment of GIST patients with Treg inhibitors.

Cyclophosphamide is also given in a low-dose regiment to kill endothelial cells, thereby having an antiangiogenic effect. This type treatment, known as metronomic dosing, is under investigation as an antiangiogenic treatment. At ASCO 2006, Ghiringhelli (with Zitvogel as one of the co-authors) submitted Abstract 2561, "Metronomic cyclophosphamide regimen electively depletes CD4+ CD25+ regulatory T cells in patients with advanced solid tumors." In 6 patients (not GIST), they found that the percentage of Treg cells was reduced by half (from 7.7% before versus 3.3% after) after treatment with cyclophosphamide. They concluded "metronomic cyclophosphamide has not only effect on tumor angiogenesis, but also strongly curtail immunosuppressive Treg, which could favor a better control of tumor progression." A paper on this subject was published on September 6, 2006 in *Cancer Immunology Immunotherapy*.

By this time, Zitvogel and colleagues have found two possible ways to stimulate the immune system to work better with Gleevec: adding the growth factor FL and pre-treatment with cyclophosphamide (an approved chemotherapy).

The discovery of a new type of immune cell

By early 2006, Zitvogel and her team (with Dr. Julien Taieb as the lead author) had published a new paper in *Nature Medicine*, "A novel dendritic dell subset involved in tumor immunosurveillance." At virtually the same time, another team (C.W. Chan et al.) from Johns Hopkins University published another article in

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Definitions:

Regulatory T cells – (Treg cell) Regulatory T cells (also known as suppressor T cells) are a specialized subpopulation of T cells that act to suppress activation of the immune system and thereby maintain immune system homeostasis and tolerance to self.

Dendritic Cells – Immune cells that process antigen material and present it on their surface to other cells of the immune system. Once activated, they interact with other immune cells to shape the immune response.

Natural Killer Cells – A type of immune cell that is involved in the early stages of an immune response. They form a major component of the innate immune system.

Interferon-producing Killer Dendritic Cells – immune cells that seem to provide a link between the innate and adaptive immune systems. This cell was reported in mice by two groups in 2006. It has yet to be reported in humans.

T Cells – One of the main types of cells that form the adaptive immune system.

Adaptive immune system - provides the ability to recognize and remember specific pathogens (to generate immunity) and to mount stronger attacks each time the pathogen is encountered.

Innate immune system – cells and mechanisms that defend the host from infection by other organisms in a non-specific manner. This system provides immediate defense against infection.

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Nature Medicine, "Interferon-producing killer dendritic cells provide a link between innate and adaptive immunity." Both groups discovered in mice a new type of immune cell that appeared to be a cross between a dendritic cell and a NK cell. This cell plays the role of both assassin *and* messenger. When stimulated, the new cells produce large amounts of IFN-γ. They named the new cells "interferon-producing killer dendritic cells" (or IKDC).

IKDCs begin their lives behaving like a NK cell. After the cell encounters a pathogen, the cell switches roles from killer to dendritic-like messenger and, according to the researchers at Johns Hopkins, the swap occurs only once. Then, the cell dies and is replenished by the bone marrow.

"When an IKDC cell switches to its messenger function, the transformation is quite astonishing," says Drew Pardoll, M.D., Ph.D., of Johns Hopkins Kimmel Cancer Center. The cell sprouts long, hairy tentacles called dendrites. It uses its "arms" to increase the amount of surface area it reaches to communicate and interact with other immune cells.

Professor Zitvogel and her French colleagues found that they could expand the number of IKDC in mice by fourfold during treatment with Gleevec + Interleukin-2 (IL-2). IL-2 is a type of growth factor that stimulates the production of some types of immune cells (it is especially noted for stimulating the production of T cells). IL-2 is one of the more common treatments used in immunotherapy today.

Although the discovery of IKDC still has not been confirmed in humans, Zitvogel appears to have found a third potential way (IL-2) to stimulate the immune system to synergize with Gleevec. Now, armed with a better understanding of how Gleevec affects the immune system and how to augment the immune response, it is time for the ultimate test—clinical trials in humans.

CLINICAL TRIAL

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The drug names table is sorted first by strategy and then by IND name within a strategy.

2. Clinical Trial Table (See Pages 13-15):

The new clinical trial table is designed to make it easier to find and compare GIST clinical trials.

The "Therapy" column takes the name of the trial drug being tested directly from the published trial description (sometimes it is the older IND name).

The "Title" column contains the short description of the trial found at the clinicaltrials.gov website.

The "Trial #" column contains the published numeric designation for a trial. Usually this is the NCT number assigned when the trial is listed on the clinicaltrials.gov website. When contacting a clinical trial site patients are asked to refer to this number to identify the trial. In practice, most trial sites will know the trial by the title.

The Phase column identifies the phase of the trial. Some trials are listed as combined phase I and phase II trials. The phase is taken from the published trial description.

The "For" column contains the indication or condition published in the trial description. This will be the conditions in the clinicaltrials.gov listing or the condition described in the trial title for trials not in the clinicaltrials.gov website.

U.S. Locations and Contacts: For trials in the United States, this is the most up-to-date information we have on who to contact. Most often it comes from the clinicaltrials.gov website. In some cases we have called the manufacturer or the firm managing the trial to establish the best contact.

The International Clinical Trials Table has the same information with the addition of the contact and location information for international patients.

The Clinical Trials table is sorted first by "Phase" with higher phases first and then by "Therapy" within each phase.

We are publishing versions of these tables on our website with hot links to the trial descriptions. Go to "Treatments" on www.liferaftgroup.org and follow the "Clinical Trials" menu item to "Clinical Trial Datasheets."

We are interested in your feedback on the new table design. Please send comments to Sara Rothschild at: srothschild@liferaftgroup.org.

Below are the updates that have been changed in the clinical trial update since the February 2007 newsletter:

A second site for the IPI-504 phase I trial has opened at University of Michigan, Ann Arbor, Mich. The contact is Rashmi Chugh, M.D., 734-936-0453, rashmim@umich.edu.

The Perifosine + Sunitinib phase I trial listing now shows sites recruiting in Pomona and Santa Monica, Calif., as well as Kalamazoo, Mich. and Huntsville, Ala. The Park Ridge, Ill. site is no longer listed.

The RAD001 trial is closed and is no longer listed in our report as we wait for Novartis on future plans. We continue to get reports of patients prescribed "Rapamune" off-label.

The BMS-354825 phase I trial is now listed as "no longer recruiting" at all sites in the United States and the United Kingdom. A separate phase I trial for BMS-354825 continues to remain open in Japan and is reflected for the first time in our report.

The BAY 43-9006 phase II trial is now also open at City of Hope in Duarte, Calif. in addition to the University of Chicago and Memorial Sloan-Kettering Cancer Center.

The OSI-930 phase I trial contact at the University of Colorado Cancer Center trial site in Aurora, Colo. is Dr. Ross Camidge.

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Drug Names Table

Pharmaceutical Company	IND	INN	Proprietary Name	Approved For	Strategy
Novartis	AMN107	nilotinib	Tasigna		Inhibit KIT (PDGFRA signaling)
Bristol-Myers Squibb	BMS354825	dasatinib	Sprycel	CML/ALL	
SuperGen	MP371				
Novartis	STI-571	imatinib	Gleevec/Glivec	GIST	
Genentech	rhuMAb VEGF	bevacizumab	Avastin	NSCLC/Colorectal	Impede Tumor Vascularization (Antiangiogenesis) (PDGFRb, VEGF, VEGFR)
(multiple)	17DMAG	geldanamycin			Destroy KIT (HSP90)
Biogen-Idec	CNF2024				
Infinity	IPI-504				
Kosan Biosciences, Inc.	KOS-1022	alvespimycin			
Aventis	HMR1275	alvocidib	Flavopiridol		Inhibit the Production of KIT
Ariad	AP23573				Target KIT Downstream Signaling (i.e. AKT, mTOR, BCL-2, SRC, RAF-1, etc.)
Wyeth	AY 22989	sirolimus/rapamycin	Rapamune	Renal Transplant	
Wyeth	CCI-779	temsirolimus	Torisel		
Genta	G3139	oblimersen	Genasense		
Keryx	KRX-0401	perifosine			
Novartis	RAD001	everolimus	Certican		
Gloucester	FR901228	romidepsin			Destroy KIT plus Inhibit the cell cycle plus Induce apoptosis (HDAC)
Novartis	LBH589				
Merck	SAHA	vorinostat	Zolinza	CTCL	
Amgen	AMG706				Multiple Targets
Astra Zeneca	AZD2171		Recentin		
Bayer	BAY439006	sorafenib	Nexavar	RCC	
OSI	OSI-930				
Novartis	PKC412				
Novartis	PTK787	vatalanib			
Pfizer	SU11248	sunitinib	Sutent	GIST	
Novartis	TKI-258				
Exelixis	XL820				

Definitions: IND - Investigational New Drug name, **INN** - also known as rINN, for recommended International Nonproprietary Name. Same as generic name, **Proprietary Name** - Same as Brand Name

CLINICAL TRIAL

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United States Clinical Trial Table

Therapy	Title	Trial #	Phase	For
AMN-107 *Nilotinib Tasigna*			III	GIST
	U.S. Locations & Contacts: Phase I/II Closed. Phase III is pending introduction in April, 2007.			
FR901228 *Romidepsin*	FR901228 in Treating Patients With Metastatic or Unresectable Soft Tissue Sarcoma	NCT00112463	II	GIST/Sarcoma/ Ewings
	U.S. Locations & Contacts: Wake Forest University Comprehensive Cancer Center, Winston-Salem, N.C., 336-713-6771, Paul D. Savage, M.D., Study Chair. Open sites include Columbus, OH; Phoenix, Ariz.; Oakland, Calif.; Decatur, Ill. plus multiple sites in southern and south-eatern United States. For more information, look-up NCT00112463 in the clinicaltrials.gov database for detailed site contact information.			
Perifosine (*KRX-0401*) **+ Imatinib** (*STI-571, Gleevec/Glivec*)	Phase II Study of Perifosine plus Imatinib Mesylate for Patients With Resistant Gastrointestinal Stromal Tumor (GIST)	MDACC 2004-0968	II	GIST
	U.S. Locations & Contacts: M.D. Anderson Cancer Center, Houston, TX, 800-392-1611; Oncology Specialists, Park Ridge, Ill.; Cancer Center at Century City, Los Angeles, Calif., Dr. Sant Chawla; From outside the United States, call M.D. Anderson at 713-792-6161.			
Sorafenib *BAY439006 Nexavar*	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
	U.S. Locations & Contacts: University of Chicago Cancer Research Center, Chicago, Ill., 773-834-7424; Memorial Sloan-Kettering New York, N.Y., Dr. David D'Adamo, M.D., Ph.D., at 212-639-7573; City of Hope, Duarte, Calif. 1-877-482-4673.			
BMS-354825 *Dasatinib Sprycel*	A Phase I Dose-Escalation Study of BMS-354825 in Patients With Refractory Solid Tumors	NCT00099606	I	Neoplasms
	U.S. Locations & Contacts: BMS Call Center, 1-866-892-1BMS, Ext. 131; Dana Farber, Boston, Mass.; Karmanos Cancer Center, Detroit, Mich. THIS TRIAL IS NOW LISTED AS NO LONGER RECRUITING.			
CNF2024	Study of Oral CNF2024 in Advanced Solid Tumors or Lymphomas	NCT00345189	I	Tumors/Lymphoma
	U.S. Locations & Contacts: Biogen Idec, oncologyclinicaltrials@biogenidec.com; Scottsdale, Ariz.; New Haven, Conn.; San Antonio, TX.			
Doxorubicin + Flavopiridol *(HMR1275, alvocidib)*	Doxorubicin and Flavopiridol in Treating Patients With Metastatic or Recurrent Sarcoma That Cannot Be Removed By Surgery	NCT00098579	I	GIST/Sarcoma
	U.S. Locations & Contacts: Memorial Sloan-Kettering Cancer Center, New York, N.Y., David R. D'Adamo, M.D., Ph.D., 212-639-7573.			

CLINICAL TRIAL

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United States Clinical Trial Table (continued)

Therapy	Title	Trial #	Phase	For
IPI-504	Safety Study of IPI-504 for GASTROINTESTINAL Stromal Tumors (GIST)	NCT00276302	I	GIST
	U.S. Locations & Contacts: Dana Farber, Boston, Mass., Michael T Quigley, RN, 617-632-5117, Michael_Quigley@dfci.harvard.edu; Univ. Of Mich., Ann Arbor, Mich., Rashmi Chugh, M.D., 734-936-0453, rashmim@umich.edu.			
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
	U.S. Locations & Contacts: Nevada Cancer Institute, Las Vegas, Nev., Donna Adkins, 702-822-5173.			
Oblimersen *(G3139, Genasense)* **+ Imatinib** *(STI-571, Gleevec/Glivec)*	Oblimersen and Imatinib Mesylate in Treating Patients With Advanced GASTROINTESTINAL Stromal Tumors That Cannot Be Removed By Surgery	NCT00091078	I	GIST
	U.S. Locations & Contacts: Dana-Farber Cancer Institute, Boston, Mass., 617-582-8480; University of Michigan Ann Arbor, Mich., 800-865-1125; Mayo Clinic Cancer Center, Rochester, Minn., 507-538-7623, cancerclinicaltrials@mayo.edu; Memorial Sloan-Kettering Cancer Center, New York, N.Y., Robert Maki, M.D., Ph.D., 212-639-5720; M.D. Anderson Cancer Center, Houston, TX, 713-792-3245.			
OSI-930	Dose Escalation Study of Daily Oral OSI-930 in Patients with Advanced Solid Tumors - Sarcoma	EmergingMed	I	Advanced Solid Tumors - Sarcoma
	U.S. Locations & Contacts: Dana-Farber, Boston, Mass., Michael T Quigley, RN, 617-632-5117, Michael_Quigley@dfci.harvard.edu; Colorado University, Denver, Colo., Dr. Ross Camidge.			
Perifosine (*KRX-0401*) **+ Sunitinib** *(SU11248, Sutent)*	Perifosine + Sunitinib Malate for Patients With Advanced Cancers	NCT00399152	I	GIST/RCC
	U.S. Locations & Contacts: Online Collaborative Oncology Group, 415-946-2410, ocogtrials@ocog.net; Huntsville, Ala.; Tower Hematology and Oncology, Beverly Hills, Calif.; Pomona, Calif.; Santa Monica, Calif.; Kalamazoo, Mich.			
XL820	Study of XL820 Given Orally Daily to Subjects With Solid Tumors	NCT00350831	I	Cancer/Solid Tumor
	U.S. Locations & Contacts: The Cancer Institute of New Jersey, New Brunswick, N.J., Pamela Scott, 732-235-7459, scottpd@umdnj.edu, Mark Stein, M.D., Principal Investigator; Cancer Therapy and Research Center, San Antonio, TX, Pat O'Rourke, 210-616-5976, porourke@idd.org, Kyriakos P. Papadopoulos, M.D., Principal Investigator.			

CLINICAL TRIAL

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International Clinical Trial Table

Therapy	Title	Trial #	Phase	For
Sutent *SU11248* *Sunitnib*	A Treatment Protocol for Patients With Gastrointestinal Stromal Tumor (GIST) Who May Derive Benefit From Treatment With SU011248	NCT00094029	III	GIST
	International Contact: EmergingMed 1-877-416-6248, sutent@emergingmed.com Locations: Chile, Colombia, India, Turkey, Spain, Finland, Taiwan, Singapore, Rep. of Korea, Hong Kong			
AZD2171 *Recentin*	The Biological Activity of AZD2171 in GIST	NCT00385203	II	GIST
	International Contact: information.center@astrazeneca.com Locations: The Royal Marsden NHS Foundation Trust in London and Christie Hospital NHS Trust in Manchester U.S. Contact: AstraZeneca Cancer Support Network: 1-866-992-9276,			
PTK787 *Vatalanib*	PTK787/ZK222584 in the Treatment of Metastatic Gastrointestinal Stromal Tumors Resistant to Imatinib	NCT00117299	II	GIST
	International Contact: Heikki Joensuu, M.D., +358-9-471 73208, heikki.joensuu@hus.fi; Mia Viskari, +358-9-4711, mia.viskari@hus.fi Locations: Helsinki University Central Hospital, Helsinki, FIN-00029, Finland			
BMS-354825 *Dasatinib* *Sprycel*	A Phase I Dose-Escalation Study of BMS-354825 in Patients With Refractory Solid Tumors	NCT00099606	I	Neoplasms
	International Contact: THIS TRIAL IS NOW LISTED AS NO LONGER RECRUITING. BMS Call Center Outside the United States & Canada, 941-906-4711, Ext. 131 Locations: Glasgow, Strathclyd, United Kingdom US Contact: BMS Call Center, 1-866-892-1BMS Ext. 131; Boston, Mass.; Detroit, Mich.			
BMS-354825 *Dasatinib* *Sprycel*	A Phase I Study of BMS-354825 in Patients With Solid Tumors	NCT00339144	I	Tumors
	International Contact: BMS Call Center Outside the United States & Canada, 941-906-4711, Ext. 376 Locations: Toshima-Ku, Tokyo, Japan US Contact: BMS Call Center, 1-866-892-1BMS Ext. 376			
LBH589	LBH589 in Adult Patients With Advanced Solid Tumors or Cutaneous T-Cell Lymphoma	NCT00412997	I	Advanced Solid Tumors
	International Contact: Novartis +81-3-3797-8748 Locations: Tokyo, Japan			
OSI-930	A Phase I Dose Escalation Study of Daily Oral OSI-930 in Patients with Advanced Solid Tumors	EmergingMed	I	Advanced Solid Tumors
	International Contact: Dr. Michelle Scurr, Principal Investigator, Royal Marsden NHS, Sutton, United Kingdom Locations: Royal Marsden NHS, Sutton, United Kingdom			

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