November 2012

IU researchers report first effective treatment of tumors arising from common genetic disease NF1

Physician-researchers at Indiana University School of Medicine have reported the first effective therapy for a class of previously untreatable and potentially life-threatening tumors often found in children.

Announcing their findings in the online first edition of Lancet Oncology, the researchers said the drug imatinib mesylate, marketed as Gleevec as a treatment for chronic myeloid leukemia, provided relief to a significant number of patients with plexiform neurofibromas, tumors caused by neurofibromatosis type 1, or NF1.

“Although this was a small study, the results were significant, particularly given that such patients have had few treatment options for what can be a very debilitating disease,” said first author **Kent Robertson**, MD, PhD. “We believe these findings warrant larger trials of both imatinib mesylate as well as other similar compounds that would appear promising in laboratory tests.”


Robertson

Affecting about 1 in every 3,000 children born, NF1 is the most common neurological disorder caused by mutations in a single gene. Including a much rarer related type, NF2, neurofibromatosis is a genetic disorder that is more prevalent than cystic fibrosis, Duchenne muscular dystrophy and Huntington's disease combined, according to the Children's Tumor Foundation.

The mutation produces a variety of symptoms, from mild to severe. Patients can develop café au lait spots and disfiguring tumors on or just under the skin. Internally, tumors can develop along nerve tissue and cause problems if they begin to press against vital organs or the windpipe. Some patients suffer from chronic pain.

The tumors have been nearly impossible to treat effectively. Because they are relatively slow growing, they are not affected by radiation treatments or cancer chemotherapy drugs. They also are often not good candidates for surgery because they are dangerously close to vital organs.

In the study reported in Lancet Oncology, of 23 patients who received the drug for at least six months, six experienced a 20 percent or more decrease in the volume of one or more plexiform neurofibromas, and 30 percent of patients had improvements in symptoms.

Primary investigator **D. Wade Clapp**, MD, noted that even relatively small reductions in tumor size can result in significant relief of symptoms for patients, such as improved breathing and restoration of bladder control.

In earlier laboratory research, the researchers determined that Gleevec was effective in tissue culture and mouse models of NF1 tumors after discovering that a cellular

signaling mechanism that Gleevec targets in chronic myeloid leukemia also played an important role in development of NF1 tumors. Reporting that finding in the journal Cell in 2008, the research team also reported that in a compassionate use protocol, they had treated a 3-year-old girl with a life-threatening tumor compressing her airway. The girl's tumor shrank by half within three months of treatment.

Although Gleevec has been widely used as a treatment for chronic myeloid leukemia and has been prescribed in some cases for long periods without serious side effects, 13 of the initial 36 patients enrolled in the IU study dropped out before their results could be analyzed at six months of treatment. Nine of the 13 left due to problems taking the drug or side effects. The authors noted that they used the previously established maximum tolerated dose for Gleevec for this study to ensure that any drug activity against any NF1 tumors would be observed. This approach was taken among patients who had been living with slow-growing tumors for long periods of time and therefore were less likely to accept drug side effects than patients with malignant tumors, the authors suggested. Dosages have been modified in subsequent studies.

Additional authors from the IU Simon Cancer Center included **Feng-Chun Yang**, MD, **Jeffrey Travers**, MD, **David Ingram**, MD, **Gary Hutchins**, PhD, **James Croop**, MD, **Terry Vik**, MD, **Kamnesh Pradhan**, MD, and **James Fletcher**, MD.

Sources of funding for the research included the IU Simon Cancer Center, the Wells Center for Pediatric Research, a KL2 TR000163 Clinical and Translational Sciences Award from the National Institutes of Health, and NIH grants P50 NS 052606 and RO1CA74177. Novartis Pharmaceuticals provided the imatinib mesylate study drug.

--Eric Schoch

November 2012

Inhibition of enzyme could lead to improved chemotherapy and stem cell transplant results

Blocking the action of one enzyme could mean improved results for thousands of cancer patients who undergo bone marrow or cord blood transplants after chemotherapy, an IU research team has reported.

Moreover, the enzyme -- dipeptidylpeptidase 4, or DPP4 -- can be blocked by sitagliptin, marketed by Merck and Co. as Januvia, a drug already on the market and approved for use in treating Type 2 diabetes.

“By blocking the activity of this enzyme, we believe there is potential to improve the activity of a variety of important compounds that could lead to improved outcomes for these procedures,” **Hal Broxmeyer**, PhD, said.


Broxmeyer

The research was published by the journal *Nature Medicine*.

For many cancer patients, suppression of bone marrow activity is an unwelcome side effect of undergoing chemotherapy treatment. Other patients may undergo chemotherapy treatments meant to destroy the blood-producing stem cells in the bone marrow to eliminate the source of the cancerous cells. Those patients receive replacement stem cells either from bone marrow transplants or transplants using blood from umbilical cords.

The transplant procedures depend on the stem cells’ “homing” ability to find their way to the bone marrow compartments to restore the patients’ ability to produce vital blood and immune system cells. Already risky procedures, the cord blood transplants are also complicated by the relatively few number of stem cells available from the small amount of cord blood that can be used, especially when the recipients are adults.

In earlier work, Dr. Broxmeyer and his colleagues found that the DPP4 enzyme truncated an important compound -- stromal cell-derived factor-1, or SDF-1 -- that plays a role in helping the transplanted stem cells engraft into the patients’ bone marrow. In its truncated form, SDF-1 is much less effective. In the earlier work, the IU researchers determined that preventing DPP4 from truncating SDF-1 resulted in more efficient stem cell engraftment.

In the Nature Medicine paper, the researchers reported that in laboratory and animal model experiments, DPP4 also acted to truncate other compounds that are important when the transplanted stem cells reconstitute the bone marrow and begin the process of producing blood and immune system cells, called hematopoiesis.

The results suggest that blocking DPP4 could help patients' bone marrow bounce back from chemotherapy treatment and stem cell transplants.

Additional research is needed to optimize sitagliptin for this use, and to conduct clinical trials to determine its effectiveness in patients, Dr. Broxmeyer said.

In addition to the hematopoietic proteins affected, important proteins in other cell and organ systems in the body also have truncation sites that could be targeted by DPP4, suggesting more research is needed to determine whether the enzyme may play a role in other cell systems and diseases, Dr. Broxmeyer said.

In addition to Dr. Broxmeyer, the first author, other IU Simon Cancer Center members involved in the research were **Sherif Farag**, MBBS, PhD; **Louis Pelus**, PhD; and **Edward Srour**, PhD.

The research was supported by grants from the National Institutes of Health (R01 HL056416, R01 HL067284 and R01 HL112669, T32 DK07519, T32 HL07910, RR25 GM079657, a Center of Excellence in Hematology grant P01 DK090948, and HL69669 and HL96305).

--Eric Schoch

November 2012

Core spotlight

Therapeutic Validation

Physician scientists increasingly employ advanced molecular analyses to better understand the mechanisms of drug action and treatment outcomes. This approach is vital to the cancer center's mission of conducting outstanding translational research aimed to transform basic science advances into better patient care.

Nagendra Prasad, BVSc, PhD, director of the Therapeutic Validation Core, said the core was established in June 2010 to meet a growing need for a dedicated basic science laboratory that assists physicians in translating basic science discoveries to clinical care. Dr. Prasad said the core's purpose is to enable investigator-initiated hypothesis-driven clinical research by helping physician scientists to incorporate cutting-edge biological correlative assays in clinical trials.

Therapeutic Validation

The Therapeutic Validation Core is located in Walther Hall, C343.

Questions? Contact Dr. Nagendra Prasad, PhD, core director, at 278-6608 or nkprasad@iupui.edu.

You can find all of the IU Simon Cancer Center cores here.

The core's services include:

- consultation on correlative aspects
- help develop/prepare grant applications
- budget and feasibility analysis
- new assay development and optimization
- generation of preliminary data
- data analysis, help with publications, and research reports

The core is set up as a collaborative resource to assist physician scientists with subsidized fees for IU Simon Cancer Center members.

The Therapeutic Validation Core can also help physician scientists by serving as a liaison with other IU School of Medicine and Indiana Clinical and Translational Sciences Institute (ICTSI) cores. It is an ICTSI-designated core and is eligible to receive ICTSI core pilot grants. As such, faculty from ICTSI partner institutions may apply for up to $10,000 in core pilot grants to use the core's services.

To date, the core has been involved in more than 50 projects for consultation and 10 projects at bench.

November 2012

News briefs

Komen Tissue Bank at IU Simon Cancer reaches milestone: 3,002 women donate tissue

The world's only known healthy breast tissue bank has set a milestone.

During a breast tissue collection on Nov. 3, the Susan G. Komen for the Cure Tissue Bank at the IU Simon Cancer Center reached and exceeded its 3,000th donor since its establishment in 2007. The tissue bank currently has breast tissue samples from 3,002 women.

TISSUE BANK AT THE IU SIMON CANCER CENTER

"I continue to be awed and inspired by the women who willingly give a piece of themselves for breast cancer research," Anna Maria Storniolo, MD, principle investigator of the tissue bank, said. "The research community did not believe that healthy women would do so, but 3,002 women have proven them wrong. We owe a debt of gratitude to these women."

By collecting samples from women without breast cancer, researchers may be able to determine the differences between healthy and cancerous tissue, which will lead to a better understanding of the cellular changes of the disease.

In July 2013, tissue bank staff will travel to Kenya to collect samples that will enhance research into why breast cancer behaves differently in people of different ethnic backgrounds. The tissue bank will also hold collection events in Houston in September and Orange County, Calif., in November.

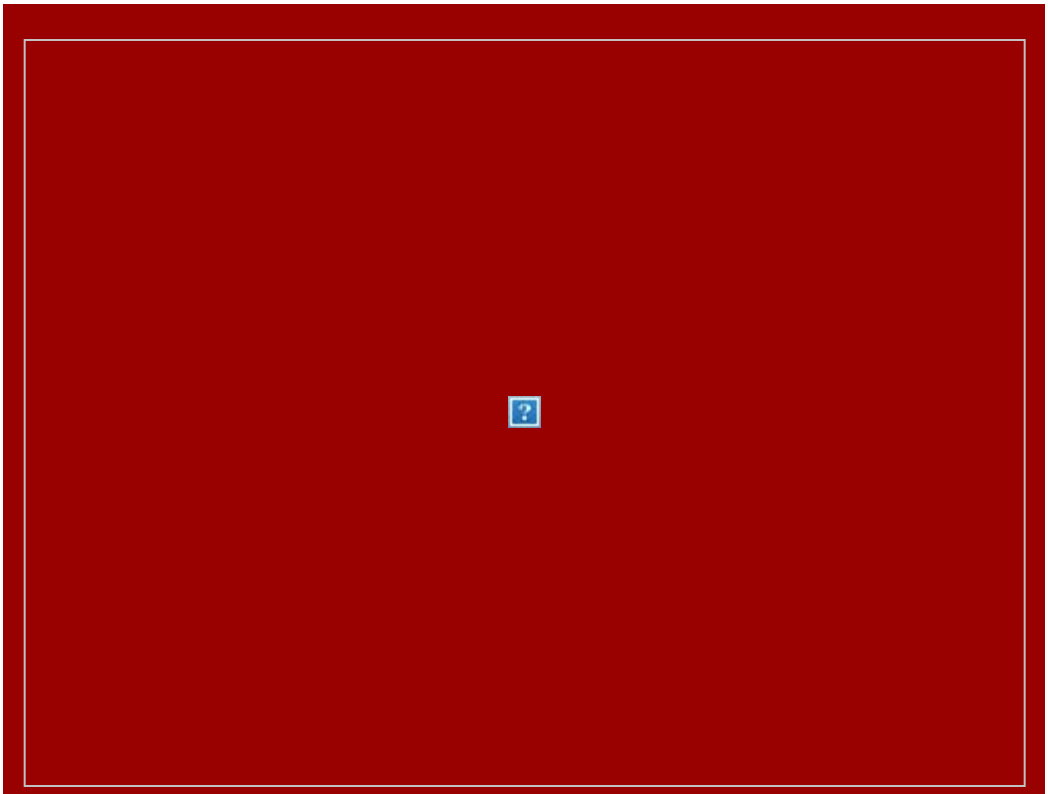
Indiana Cancer Consortium finds need in connecting patient navigators

In an effort to better connect, educate and share best practices among patient navigators in Indiana, the Indiana Cancer Consortium (ICC) is distributing a comprehensive survey, the *2012 Indiana Patient Navigation Assessment*. The assessment was developed by the ICC's Patient Navigation Committee. "The survey aims to begin building a substantial network of patient navigators and patient navigator programs in order to foster collaboration and education across the state," Rivienne Shedd-Steele, Patient Navigation Committee chair and director of the Office for Health Disparities and Outreach at the IU Simon Cancer Center, said. "The potential impact the ICC can make on connecting patient navigators in Indiana is substantial considering Indiana's cancer burden." Survey results will be published and distributed in late 2012. If you have questions or would like additional information about the ICC and the Patient Navigation Committee, contact Caleb Levell, ICC coordinator, at Caleb@indianacancer.org.

Reminder

IUSCC's Cancer Center Support Grant due in fall 2013

In September 2013, the IU Simon Cancer Center's National Cancer Institute Cancer Center Support Grant (CCSG) will be due. Consequently, the cancer center's executive committee and research program leaders are currently undertaking a critical review of the program and its membership, as well as finalizing program themes, goals, and aims. All members are encouraged to assist their program leaders as they begin working on their respective narratives. The program leaders will need assistance from their members on compiling research highlights for those narratives. Program leaders are also planning retreats and participation among members is important. The CCSG is an important source of funding for the cancer center's shared facilities. This support, along with IU Simon Cancer Center funding, assures that cancer center members have access to the highest quality technology for their research. For a current overview of the cancer center, watch the "State of the Cancer Center" presentation that Patrick Loehrer, MD, director of the IU Simon Cancer Center, delivered on Sept. 6.



Dr. Larry Cripe (far right), Coach Pagano's physician, accepts a check from the Indianapolis Colts for $219,000 that has been raised for leukemia research at the IU Simon Cancer Center through the sale of Chuck Strong T-shirts and wrist bands. The Colts made the check presentation during the Nov. 4 game.

Cancer center members in the news

- The following cancer center members will attend the 2012 San Antonio Breast Cancer Symposium Dec. 4-8: **Susan Clare**, PhD**; Linda Han**, MD; **Harikrishna Nakshatri**, PhD; **Milan Radovich**, PhD; and **George Sledge**, MD.

- **Alexander Dent**, MD, has published a paper ranked in the top 10 percent of articles in the Nov. 15 issue of the *Journal of Immunology.* "Bcl6 Controls the Th2

Inflammatory Activity of Regulatory T Cells by Repressing Gata3 Function" appears in the “In This Issue” section of the journal.

- **Patrick Loehrer**, MD, was a participant in this year’s Old Masters program at Purdue University, his alma mater. The Old Masters program invites outstanding individuals to campus to share ideas and experiences with Purdue students.


Loehrer

- **Hal Broxmeyer**, PhD, and **G. David Roodman**, MD, each have been named a fellow by the American Association for the Advancement of Science. Dr. Broxmeyer received the award for distinguished contributions to hematopoietic stem cell biology, and cytokine and chemokine actions, and particularly for initiating and advancing the field of cord blood transplantation. Dr. Roodman received the award for significant contributions to research and education in cancer and bone research, especially Paget's disease. "There are few honors in the world of science as prestigious as being named a fellow with the American Association for the Advancement of Science," D. Craig Brater, MD, dean of the IU School of Medicine and vice president for university clinical affairs at IU, said. "The two IU School of Medicine faculty elected this year are not just influential in their respective fields but are esteemed by their colleagues at IU. I am honored to call Hal Broxmeyer and David Roodman colleagues and know that the medical school and our students have benefited from the contributions to our school and our world made by these outstanding scientists."