LUDWIG INSTITUTE FOR CANCER RESEARCH

LudwigLink

April 2012

DRIVEN BY DISCOVERY

What makes scientists tick? Scientists love discovery. Their discoveries have given us the Human Genome Project, satellite navigation, stem cell research, LASIK surgery ... inventions and concepts that changed our lives forever. Putting together pieces of a complex puzzle and solving mysteries are the chief rewards of the scientific life. The puzzles Ludwig scientists pursue involve the transition from scientific discovery to clinical application.

Cancer is not a single disease but many different diseases that have hundreds to thousands of variations. Because of this, the search for cures is complex and ongoing, and obstacles remain to be addressed. Surgery can be curative when tumors are locally confined, although this is seldom the case. Chemotherapy and radiation are still the most widely available treatment options for later-stage cancers, but unfortunately their efficacy is limited. Regrettably, more advanced tumors are seldom cured by any of these treatment modalities. Immunotherapy is a more experimental treatment method, aimed at mobilizing the body's immune cells to attack tumor cells. The ultimate goal of cancer immunotherapy is the eradication of tumor cells by the immune system.

In the News Roundup section of this issue, we've highlighted several promising developments in immunotherapy, which underscore the immune system's ability to find and eliminate cancer cells. These advances could ultimately be applicable to many cancer types. The Institute continues to be a leader in discovering and developing new immunotherapies and bringing them into the clinic to improve patient outcomes.

Sincerely,

Edward A. McDermott, Jr.
President and CEO

Andrew J. G. Simpson
Scientific Director

Q&A WITH FRANK FURNARI

Senior Investigator, Professor of Pathology, San Diego Branch

Who is Frank Furnari? Scientist, researcher, teacher, mentor, team leader and dad. These are some of the monikers that describe the Senior Investigator and UCSD Professor of Pathology at the Ludwig San Diego Branch. Frank leads the Section of Human Carcinogenesis in the Tumor Biology Laboratory, headed by Web Cavenee. For him, science is a team sport. Frank adheres to several key principles in monitoring and maintaining the success of the team.

Tell us a little bit about your history with LICR. How did you first come to hear of the Ludwig Institute for Cancer Research?

In 1991-92, while I was in graduate school at the University of North Carolina-Chapel Hill and thinking about where I'd like to do my postdoctoral work, one of my committee members, Buddy Weissman, Professor of Pathology and Laboratory Medicine at UNC, suggested I talk to Web Cavenee who had just moved the Ludwig Branch from Montreal to San Diego.

Web was doing pioneering work on the mechanisms of cancer predisposition and progression. I wanted to take my career in that direction and get involved in what was a relatively new field. Tumor suppressor genes were just starting to be studied and understood, the first one being retinoblastoma, an area that Web was spearheading.

What makes the Ludwig Institute unique?

The Ludwig Institute is a formidable global research entity. Over the past 18 years, I've come to realize there's no scientific

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"The Institute is synonymous with research and excellence filled with dedicated, mission-oriented people."

Frank Furnari
Senior Investigator, Professor of Pathology
San Diego Branch

INSIDE

NEWS ROUNDUP

A practical partnership

Sometimes, the sum of the parts can be greater than the whole. This applies to cancer therapies as well. There is a growing recognition that cancer can exert a profound suppressive effect on the immune response. Combining chemotherapy and immunotherapy in cancer treatment can enhance the immune system's ability to find and eliminate cancer cells, even when the cancer-associated proteins targeted by the immune system are hidden behind the cancer cell membrane.

An international team of scientists in Japan, Switzerland, and the United States including several Ludwig scientists in New York, has shown that antibodies, which have been successful in treating certain types of cancers, can effectively reach elusive intracellular targets, delaying tumor growth and prolonging survival when combined with chemotherapy. Certain "cell-killing," therapies such as chemotherapy and radiation, used in strategic ways, can synergize with immunotherapies to strengthen or expand the anti-tumor immune response.

The majority of markers that can distinguish cancer cells from normal cells are found exclusively inside cancer cells, where antibodies typically cannot access them. "Antibody-based therapies that can successfully target cancer antigens found within cancer cells may be able to fight cancer without causing unwanted side effects due to collateral damage to healthy cells," said study co-lead author Gerd Ritter, Associate Director of the New York Branch and a leading member of the CRI/LICR Cancer Vaccine Collaborative.

Based on the success of their preclinical investigations, the study researchers are eager to take the approach into clinical testing. Such a trial would bridge what immunologists refer to as passive immunotherapy and active immunotherapy.

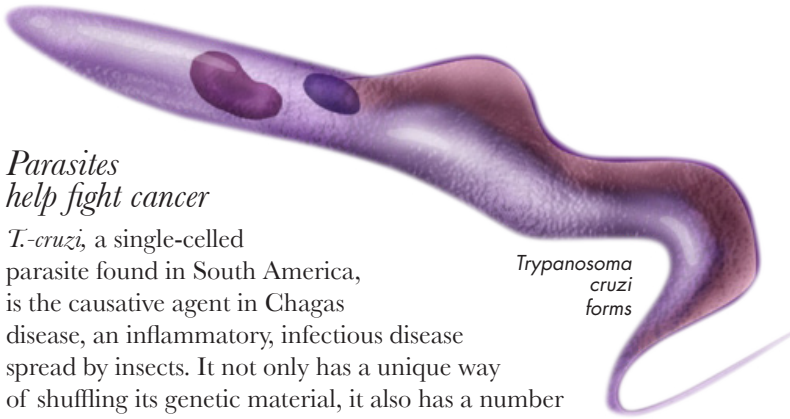
The study was published in the February 13 issue of *Cancer Research* and can be found **here**.

Ipilimumab (ip-ih-lim-yoo-mab)

It might be tough to pronounce, but ipilimumab is the first agent proven to improve survival in advanced melanoma. It works by basically removing the brakes from the body's immune system and activating it to fight melanoma by inhibiting CTLA-4, a type of white blood cell that plays a critical role in regulating natural immune responses. The presence of CTLA-4 suppresses the immune system's response to disease, so blocking its activity stimulates the immune system to fight the melanoma.

Melanoma, the most serious type of skin cancer, develops in the cells that produce melanin – the pigment that gives skin its color. Jedd Wolchok, Assistant Member at the Ludwig New York Branch, and his team studied one person's response to the combination of ipilimumab and radiation.

The patient's dramatic systemic response has spurred interest in pursuing clinical trials to further validate this approach for prostate and melanoma cancers. The size of both the tumor that was treated with radiation and distant tumors in the patient were reduced. "The radiation decreased the level of a population of suppressive cells, allowing the immune system to function more robustly leading to better recognition and control of the disease," said Jedd. The results of the study were published in the March 8 issue of the *New England Journal of Medicine* and can be found **here**.

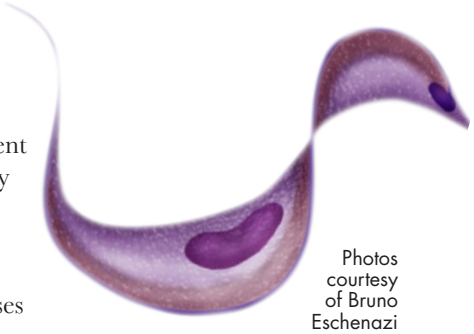


Trypanosoma cruzi forms

Parasites help fight cancer

T.-cruzi, a single-celled parasite found in South America, is the causative agent in Chagas disease, an inflammatory, infectious disease spread by insects. It not only has a unique way of shuffling its genetic material, it also has a number of features that make it stand out as a potential cancer immunotherapy. The parasites contain their own adjuvant, enhancing the immune response to an antigen and eliminating the need for additional compounds to activate the immune system.

One of the Institute's collaborators, Ricardo Gazzinelli, together with his research team and Ludwig scientists in New York, has taken advantage of the stealth yet stimulatory property of parasites to target cancer. They expressed a cancer antigen in a strongly attenuated strain of *T.-cruzi,* also known as *Trypanosoma cruzi*. This live vaccine showed great protection against tumors in both prophylactic and therapeutic preclinical models.



Photos courtesy of Bruno Eschenazi

T. cruzi was chosen as the carrier for several reasons. It's able to survive in host tissue and support a sustained immune response; it delivers antigen in a way that induces a strong CD8+ T cell response; and it naturally expresses activating ligands of toll-like receptors (TLRs), which could make the use of additional adjuvants unnecessary.

A study about the findings was published on December 6, 2011, in the *Proceedings of the National Academy of Sciences* and can be found **here**; an article was published in the January 12 issue of ***SciBX*: *Science-Business eXchange*** (pdf).

Tricking the immune system

TDO is an enzyme that can be co-opted by tumors and used to trick the immune system to prevent it from recognizing and destroying certain types of tumors. The enzyme works by depriving immune cells of tryptophan, an amino acid essential to their activity. And we know this thanks to Ludwig researchers at the Brussels Branch who recently published a **study** in the *Proceedings of the National Academy of Sciences.*

Led by Benoît Van den Eynde, a team of researchers then developed a TDO inhibitor, which prevented the production of TDO and subsequently restored the ability of mice to reject TDO-expressing experimental tumors. The ability of the TDO inhibitor to reverse tumor immune resistance suggests it could become a promising cancer immunotherapy.

A successful experiment was performed in mice whereby a small molecule TDO inhibitor promoted the immune rejection of tumors without signs of toxicity.

"Our study showed quite beautifully that the TDO inhibitor restored the ability of mice to reject tumors despite the presence of TDO in tumor cells," said Benoît. The team plans to screen for an even more effective version of the inhibitor that could be advanced into the clinic.

Body armor

Antibodies are proteins that detect and destroy invaders. They act as the body's army. Unlike current comparable therapies, monoclonal antibody ABT-806, a Ludwig discovery, may prove to have significant benefit to patients with a broad array of cancer types, including brain, lung, head and neck, skin and colorectal cancers with minimal side effects.

The first-in-patient trial with ABT-806i is underway at Austin Health in Melbourne. The **study** is sponsored by Abbott Laboratories through a licensing arrangement with a Ludwig spin-off company, Life Sciences Pharmaceuticals, Inc.

The study will evaluate the uptake of the ABT-806i antibody in tumor and normal tissues using state-of-the-art imaging technology and expertise from the Ludwig Melbourne-Austin Branch. Preclinical studies with the antibody have shown its ability to bind to cancer cells, but not to cells of normal tissue.

ABT-806i was created from the monoclonal antibody mAb806, a seminal discovery by Ludwig scientists that resulted from a long-term collaboration between the Melbourne-Austin, Melbourne-Parkville, New York and San Diego Branches. "Data from the trial will help define dosing strategies for ABT-806, and may also enable us to predict who might be more likely to respond to treatment," said Andrew Scott, Ludwig Melbourne-Branch Director.

PEOPLE ON THE MOVE

ULF HELLMAN

Still going full throttle

After spending 25 years at the Uppsala Branch, Ulf downplays the 'r' word, instead calling his retirement as Member and Group Leader of the Protein Structure Group, a role change. "These years have been the happiest and most productive of my life thanks to Calle's leadership and the unflagging support of the Ludwig Institute."

Ulf's research interest is the development of microtechniques—various methods of handling and preparing material for analyses by mass spectrometry (microscopic observation and study). His collaborations spanned the globe. He lectured frequently in Buenos Aires and, in 2011, received the Dr. Luis Federico Leloir Medal for international scientific cooperation with Argentina from Prof. Dr. R.F. Matera, the Argentinean minister for science and technology.

The infusion of new researchers into the Branch kept the work stimulating and every day brought a new challenge. Ulf's work and contribution were significant. "You are widely and deeply appreciated both within and outside the Institute and will be greatly missed. Your willingness to apply your expertise with such generosity to so many collaborators has been notable," said Andy Simpson.

An exciting life awaits Ulf outside the Institute's walls. "I'm not really retiring, just planning on going 'full throttle'—indulging grandchildren, spending time at our summer house and pursuing my passion, vintage bicycles and motorcycles."

IAN DAVIS

Ties that bind

Great colleague. Great collaborator. Ian Davis, Head of the Ludwig Uro-Oncology Laboratory at the Melbourne-Austin Branch, has accepted a new position as Professor of Medicine, Monash University and Eastern Health, and Head of Eastern Health Clinical School. While it's a change in career direction, Ian will continue his oncology clinical work and basic and translational research while building research, clinical and teaching programs across a range of disciplines. He will maintain links with the Ludwig Melbourne-Austin Branch, and continue his involvement with the Olivia Newton-John Cancer & Wellness Centre. Ian will assume his new role mid-June and transition his lab over the next 12 months.

"What I enjoyed most were the wonderful people I worked with, their generosity of time, wisdom and support as well as the opportunity to work in a unique organization where basic and translational research is closely linked to our clinical service," Ian said. "I don't know anywhere else that does this the way Ludwig does, and it is something to be treasured."

Q&A WITH FRANK FURNARI *(continued from page 1)*

question too big or complex that can't be addressed by the talent that makes up the Institute.

The Institute is synonymous with research excellence and filled with dedicated, mission-oriented people. I think of it as an organization that looks 'over the horizon.' Eliminating cancer has always been an institute-wide pursuit, and being able to work toward helping to decrease the suffering and the toll cancer takes is very important to me.

If you could make one change at the Institute, what would it be?

More cowbell! Seriously—more of the programmatic-type meetings like the one held at the end of September in Oxford. These meetings are instrumental in forging partnerships and exchanging ideas. They can often yield impressive results and be the genesis of solutions. I returned to San Diego with new collaborations and new insights into my work as well as the work of other participants.

Coming out of the recent meeting, we're going to be looking at CT antigens with individuals in New York and undertaking some collaborative work with colleagues in São Paulo and Brussels. In fact, we just hosted a post doc from São Paulo in the lab for the past eight weeks. These experiences remind us that being part of a global institute has extraordinary advantages in fostering collaborations that allow us to tackle the tough problems and work towards solutions.

Congratulations on your Award for Excellence in Translational Research from the Society of Neuro-oncology. Was it awarded for a specific piece of your research? Tell us more about the award and the research.

I received the award for an abstract entitled *PTEN phosphorylation by fibroblast growth factor receptors and SRC mediates resistance to epidermal growth factor receptor inhibitors in glioblastoma.* Our lab has focused mainly on the mechanisms of why brain tumors are so difficult to treat even though we have great targets such as the epidermal growth factor receptor (EGFR). But invariably, even with small molecules that target mutations such as EGFR or pathways of this receptor, these tumors find ways to become resistant.

A postdoc in the lab, Timothy Fenton, discovered that one such mechanism of resistance was a specific posttranslational modification on the PTEN tumor suppressor gene, which could mimic genetic inactivation of this gene, thus rendering tumor cells insensitive to therapeutics targeting EGFR.

Can you describe in layman's terms your particular area of research?

Our lab works on glioblastomas (GBM), which are among the most common and devastating primary brain tumors that affect adults. These tumors grow rapidly, invade nearby tissue and contain cells that are very malignant. We've been investigating mutations that increase the malignancy of these types of tumors and right now the lab is working on how we can improve the therapeutics for those patients who suffer from these tumors.

GBM tumors kill patients within 12 to 15 months and current therapeutics extend survival by only a couple of weeks or months. It has been a harsh reality in this field to measure advances in glioblastoma patient survival in weeks, not in months or years as in other types of cancers.

Despite progress being slow, I'm convinced we'll know a lot more about the targets we should be pursuing in GBM in the coming decade, which will translate into more effective therapeutics.

What role does technology play in your research?

A great deal. The Institute is constantly keeping up with the newest technologies. We use various imaging techniques to monitor tumors before, during, and after treatment to assess therapeutic response. The Branch has just acquired a new piece of equipment that will allow us to do *in vivo* imaging of brain tumors in animals.

Now we have an instrument that allows us to follow tumor growth in real time. We can image the tumors as often as we want, see them growing and create a three-dimensional snapshot at what's happening.

We can also treat these mice with therapeutics and look at the consequences on tumor growth. This type of technology really opens the door for us to be able to better assess how well the therapeutics are doing without having to surgically open the skull of the mouse and look at the tumor site.

What advances do you see in the coming decade as a result of the work you're doing?

Approximately 13,000 Americans die of malignant brain tumors every year, about 2% of all U.S. cancer deaths. Every patient's tumor is unique. In order to develop effective treatments, we must first figure out the initial genetic errors that lead a cell to become cancerous. We have the technology to completely sequence and understand the compendium of mutations in an individual's tumor, and in the future, we'll be able to tailor therapeutics specific to a patient's tumor profile.

You were born in Queens, attended Hofstra and received your Ph.D. from the University of North Carolina and subsequently became a postdoc in Web Cavenee's laboratory. Do you miss New York?

I do miss New York and don't visit as often as I used to. My first job out of college was as a research technician at the Memorial Sloan-Kettering Cancer Center working with John Mendelsohn. It was a wonderful experience for a 21-year-old kid fresh out of college experiencing the city and one of its premier research environments. One major advantage was that the hospital was right there and offered a lot of interaction with the patients.

What are the biggest misconceptions about scientists?

That we wear white socks and our pants are too short. The truth is that sometimes we wear black socks. People do have a lot of misconceptions about scientists and I think part of this is due to the fact that scientists are rarely celebrated in the mainstream media, and there's a perceived lack of fame, fortune or excitement associated with a scientific career.

We don't talk much about science and mathematics in this country and people don't understand what scientists do. Even when I tell friends or family members that I'm a scientist and work in cancer biology, the first question they always ask is not what do I do, but how close we are to curing cancer.

What qualities do you think distinguish scientists from other professions?

Cancer doesn't take a day off. Scientists rarely take a day off; it's a profession that never stops. You're constantly monitoring experiments, answering emails, and writing grants and papers.

"Cancer doesn't take a day off.
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Frank Furnari
Senior Investigator, Professor of Pathology, San Diego Branch

When not working in the lab, what do you do?

I'm a family man and love spending time with my raisons d'être, my wife and daughter. My daughter is almost 16 and the teenage years are going by very quickly. The time is rapidly approaching when she'll be in college and I cherish the time we spend together.

Is there anything else you think is important, or that you would like to share with the readers?

I'd like to pay tribute to my family and heritage. I'm a second-generation Italian American and the first one in my family to graduate from college. My grandparents came to this country from Italy in the early 1900's with less than $50. Theirs was a quintessentially American narrative of faith, family, and hard work. I admire their passion for this country and the opportunities it provided them. Their drive and perseverance taught me valuable lessons about life and the entrepreneurial spirit. That drive and perseverance has translated into my work and have been mainstays in the way I approach the rigors of science.

REQUIRED READING

San Diego
Cell 2012 Feb 17;148(4):816-31

Base-Resolution Analyses of Sequence and Parent-of-Origin Dependent DNA Methylation in the Mouse Genome

Xie W, Barr CL, Kim A, Yue F, Lee AY, Eubanks J, Dempster EL, Ren B.

New York
New England Journal of Medicine 2012 Mar 8;366(10):925-31.

Immunologic correlates of the abscopal effect in a patient with melanoma

Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, Mu Z, Rasalan T, Adamow M, Ritter E, Sedrak C, Jungbluth AA, Chua R, Yang AS, Roman RA, Rosner S, Benson B, Allison JP, Lesokhin AM, Gnjatic S, Wolchok JD.

Cancer Research 2012 Feb 8. [Epub ahead of print]

Intracellular tumor-associated antigens represent effective targets for passive immunotherapy

Noguchi T, Kato T, Wang L, Maeda Y, Ikeda H, Sato E, Knuth A, Gnjatic S, Ritter G, Sakaguchi S, Old LJ, Shiku H, Nishikawa H.

Did you know...

Few things compare to the adrenalin rush and exhilaration of being up close and personal with a Great White.

Mary Temple, Ludwig Director of Taxes, came within kissing distance on her last dive off the coast of South Africa. "They're huge, graceful, and simply breathtaking to watch," she said.

Mary (a.k.a. Scuba Mary) is a skilled and a passionate diver with three diving certifications—basic, advanced and nitrox (enriched air)—and has done cave diving with a guide.

If it's something you want to tick off your bucket list, **click here** to watch Mary's video.

Brussels
Proceedings of the National Academy of Sciences USA 2012 Feb 14;109(7):2497-502.

Reversal of tumoral immune resistance by inhibition of tryptophan 2,3-dioxygenase

Pilotte L, Larrieu P, Stroobant V, Colau D, Dolusic E, Frédérick R, De Plaen E, Uyttenhove C, Wouters J, Masereel B, Van den Eynde BJ.

FINALLY…

In January, we announced a contest to help us rename NewsLink. We're excited to announce that we have a new name …

... Drum roll, please!

The grand prize winner is Pece Kocovski, from the Melbourne-Austin Branch who submitted the winning name: *Ludwig Link.*

The second place winner is a tie between Qi Zhao, from the Ludwig Collaborative Group at Johns Hopkins University and Peter Andrew, from the New York Office who both submitted *LICR Connect.*

The third place winner is Mary Temple, who submitted *The Decoder.*

A big thanks to everyone from around the world who entered January's contest. We were blown away by all the creative names you came up with. Needless to say, choosing a winner was not an easy task.

Congratulations to all of our winners! We'll be in touch to send you your prizes.

And stay tuned for the next issue of *Ludwig Link!*

LUDWIG INSTITUTE FOR CANCER RESEARCH **LudwigLink**