LUDWIG LINK

MARCH 2014

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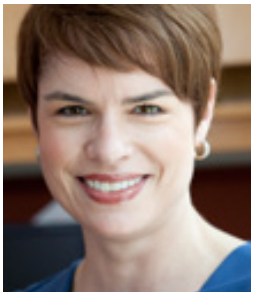
LUDWIG CANCER RESEARCH

LETTER



The Ludwig Twitter feed, under the handle @Ludwig_Cancer, has launched! It features a combination of Ludwig news and other important cancer research developments from around the world. Twitter is incredibly efficient and much less daunting than the growing list of unread articles in your Google reader. So be sure to follow us the next time you log into your Twitter account. And if you don't have an account, now's a great time to sign up.

Twitter will help connect us with people and topics the Ludwig community cares about. Tweeting is an art form of sorts, the digital answer to the haiku, even if the typical tweet is more about communication and debate than is its poetic counterpart. We get 140 characters, max, to tweet what we want to say—and that includes spaces, commas and urls. So don't expect any detailed expositions on Ludwig science. But we do hope more people will learn of it from our tweets, and you can help us achieve this goal by retweeting what we tweet.

Sincerely,

Rachel Steinhardt
Director of Communications

On the cover: Amy Fan of Ludwig's MIT Center

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DOC-IN-CHIEF

José Baselga, physician-in-chief at Memorial Sloan Kettering Cancer Center (MSK), has rejoined Ludwig's Scientific Advisory Committee. José is an internationally recognized physician-scientist with an expertise in translational research. He is particularly interested in the identification of novel targeted therapies and mechanisms of resistance to current cancer therapies. His laboratory investigations have focused primarily on breast cancer, particularly in the area of growth factor receptor targets for breast cancer therapy. On the clinical front, José has considerable experience in the development and implementation of early clinical trials for novel therapies with strong translational research endpoints.

"José has an outstanding reputation in study design and execution, and will provide me with guidance on Ludwig clinical research to accelerate cancer discovery and help bring new and more effective treatments to the clinic," said David Lane, Ludwig's scientific director. José recently led early clinical development and pivotal clinical studies that resulted in Food and Drug Administration approval of two drugs for breast cancer treatment.

They are pertuzumab (Perjeta), for the treatment of patients with HER2-positive metastatic disease, and everolimus (Afinitor), for the treatment of advanced hormone receptor-positive, HER2-negative breast cancer. His current work focuses on developing PI3K inhibitors for patients with tumors that have PI3K mutations.

As we welcome José back, we say goodbye to Craig Thompson, president of MSK and key member of the committee, who has elected to step down this year to focus his efforts on the Ludwig MSK Center and Collaborative Laboratory.

José Baselga
Ludwig Scientific Advisory Committee

A SCIENTIST'S SCIENTIST

Karen Vousden, a former Ludwig assistant member and head of the human papillomavirus group at the St. Mary's branch, thinks big in a detail-oriented world. As director of the Beatson Institute for Cancer Research in Glasgow, Scotland, she leads the tumor suppression group and is one of the world's leading researchers on the *p53* gene. She's also the newest member of Ludwig's Scientific Advisory Committee.

"I worked closely with Karen when I was the chief scientist of Cancer Research UK, as she was developing the Beatson Institute in Glasgow. She'll bring expertise in molecular and cellular biology to Ludwig along with her growing interest in animal models of invasion and metastasis," said David Lane, Ludwig's scientific director. She has also showed great leadership in developing the Beatson Institute and overseeing the design of its wonderful new building.

Karen has been studying *p53* since the early stages of her career as an independent scientist. Her team is investigating how the gene prevents cancer, and how the loss of its many functions fuels malignancy. They've made several key discoveries, such as showing how *p53* is controlled and how this control is undermined in cancer cells. They are searching for drugs to help switch *p53* back on in cancer cells. This could stop tumor cells from growing or even kill the cells.

In January 2010, Karen was appointed commander of the British Empire for services to clinical science. She has been elected to the Royal Society of London and the Royal Society of Edinburgh, and in August 2009 she was awarded the Royal Society of Edinburgh's prestigious Royal Medal for her outstanding contributions to cancer research.

Karen Vousden
Ludwig Scientific Advisory Committee

ALL THE QUEEN'S MEN

Nobel Foundation Chairman of the Board Calle Heldin of Ludwig Uppsala escorts Queen Silvia of Sweden.
© Nobel Media 2013. Photo: Helena Paulin Strömbe

"

Alfred Nobel was a broad-minded person. He realized that mankind is not only in need of progress within scientific disciplines, but also needs culture and a peaceful world. Cross-fertilization between science and culture enriches both sides.

From Calle Heldin's opening address at the Nobel Prize Award Ceremony on December 10, 2013.

Click here to read the entire speech.

"

A KNIGHT TO REMEMBER

Ludwig Oxford's Peter Ratcliffe has been recognized by Queen Elizabeth II in the 2014 New Year's Honours list. Sir Peter was knighted for his services to medicine. This is just the latest in a series of honors awarded to this outstanding clinician and scientist. Peter is a cell and molecular biologist best known for his pioneering research on how cells in the body detect how much oxygen is available to them, and especially how they respond to a lack of oxygen. This has led to a better understanding of the development of diseases such as cancer and pulmonary or cardiovascular disease, where a lack of oxygen in the cell plays an important role. He is working on how to better understand these pathways and how they might be manipulated to treat these diseases.

"We are delighted that Peter's work has been recognized by this extraordinary honor," said Xin Lu, Ludwig Oxford's director. "Not only does his outstanding research have potential for the development of new cancer treatments, but he continues to look after patients in the hospital who may in time benefit directly from his research."

Peter is also one of four winners of the 13th Annual Wiley Prize in Biomedical Sciences for his contributions to the field of oxygen-sensing systems. Cancer cells frequently co-opt the oxygen-sensing circuitry to support runaway growth. Peter's contributions to this field are sure to guide research and development of cancer treatment and prevention, and shed light on diseases caused by inadequate oxygen delivery.

This year's award of $35,000 will be presented on April 11, 2014, at the Wiley Prize luncheon at Rockefeller University. There, each recipient also will deliver an honorary lecture as part of the Rockefeller University Lecture Series. Established in 2001, the Wiley Prize in Biomedical Sciences is awarded annually to recognize contributions that have opened new fields of research or have advanced concepts in a particular biomedical discipline.

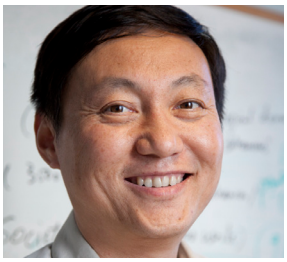
"Not only does his outstanding research have potential for the development of new cancer treatments, but he continues to look after patients in the hospital who may in time benefit directly from his research."

Peter Ratcliffe
Ludwig Oxford

STELLAR FELLOW

Ludwig scientist Bing Ren has been named a fellow of the American Association for the Advancement of Science (AAAS), the world's largest general scientific society. Election as a fellow is an honor bestowed upon AAAS members by their peers. Bing was lauded for his outstanding original contributions to the analysis of genome-wide distributions of regulatory factors, transcriptional regulatory sequences and the large-scale organization of eukaryotic genomes.

Bing's research focuses on the growing understanding of the human genome, and how to use that information to change the course of disease. His work has been at the forefront of efforts to map human DNA to elucidate the genetic drivers of disease. He has directed a project in the Roadmap Epigenomics Program to produce reference human epigenome maps since 2008, and is currently leading an ENCODE production project to annotate mammalian transcriptional regulatory sequences.



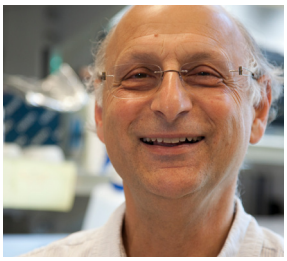
Bing Ren
Ludwig San Diego

MAKING AN IMPACT

Richard Kolodner of Ludwig San Diego has been elected to the Institute of Medicine, one of 70 people so honored last year. This is one of the highest honors in the fields of health and medicine. New members are elected by active members through a process that recognizes individuals who have made major contributions to the advancement of the medical sciences, health care and public health.

The recognition is well deserved. Richard's research has contributed enormously to our understanding of cancer genetics, and many of the techniques he has pioneered have become standard tools of the field. He was recognized for his discoveries in the field of DNA mismatch repair, which concerns the ability of cells to repair genetic errors that can disrupt the integrity of DNA, and its connection to human cancer.

Established in 1970 by the National Academy of Sciences, the Institute of Medicine asks and answers the nation's most pressing questions about health and health care. It serves as an advisory organization to Congress and policy makers on important health questions.



Richard Kolodner
Ludwig San Diego

GLIMMER OF POSSIBILITIES

Radiation therapy kills tumor cells, but it is often inadequate for tumor control because many cancers quickly develop resistance to the therapy–a phenomenon that has traditionally been attributed to stepped-up DNA repair by tumor cells. In the January 13 online issue of *Proceedings of the National Academy of Sciences*, a team of researchers led by Ludwig Chicago's Ralph Weichselbaum and Nikolai Khodarev report another mechanism by which such cells resist radiation therapy.

Recent data suggest that radiation kills tumor cells in part by inducing signaling by anti-viral proteins called interferons, and the genes they activate. Interferons are key components of radiation-induced killing in some human tumors. The study shows that LGP2 protein, which is expressed by an interferon-stimulated gene, accumulates in tumor cells exposed to radiation, shuts down a signaling pathway that boosts expression of interferon-β and blocks the cytotoxic effects of radiotherapy.

Ralph, Nikolai and their colleagues show that elevated LGP2 expression is associated with resistance to radiotherapy in a broad spectrum of cancer cell lines. It is also linked with a poor prognosis in cancer patients, especially those with malignant glioma. LGP2 is essential for producing effective antiviral responses against many viruses that are recognized by the pattern recognition receptors RIG-I and MDA5, which can also trigger antiviral responses.

Ralph Weichselbaum
Ludwig Chicago

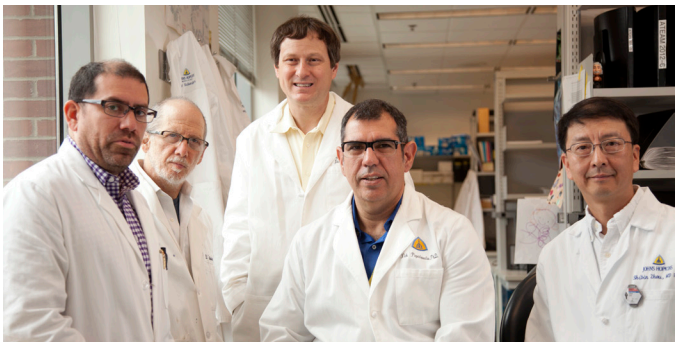
GUILTY PARTY

Scleroderma is an autoimmune disease that causes progressive thickening and tightening of the skin. It can lead to serious internal organ damage and, in some cases, death. It affects an estimated 300,000 people in the United States, and most commonly afflicts young to middle-aged women. Its cause is unknown, but Ludwig scientists at Johns Hopkins say they've found a possible trigger: cancer. The findings, published in the December 5 issue of *Science*, also suggest that a normal immune system is critical for preventing the development of common types of cancer. The results could change the way doctors evaluate and treat autoimmune diseases like scleroderma.

According to the researchers, patients with scleroderma produce antibodies to a protein called RPC1. These antibodies are responsible for the organ damage seen in scleroderma. What causes these antibodies to be produced has remained a mystery until now. When the researchers examined tumor tissue and blood samples from 16 scleroderma patients with various types of cancer, they found that the cancers in most of the

patients had a mutation in a gene called *POLR3A*, which encodes RPC1. When the mutation was present, however, a foreign form of the protein was produced, triggering a response from the patient's immune system.

"This study speaks to the power of the immune system and the emerging picture of harnessing the immune system to treat cancer, adding support to the notion that the immune system may be keeping cancers in check naturally," said Ken Kinzler, co-director of Ludwig Johns Hopkins.



Ludwig Johns Hopkins team. Left to right. Luis Diaz, Bert Vogelstein, Ken Kinzler, Nickolas Papadopoulos, Shibin Zhou

NO TWO ALIKE

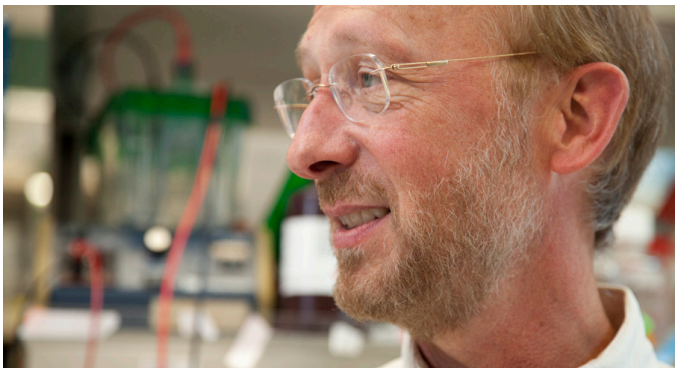
No two people are exactly alike, even if they're identical twins. Why is this? Rickard Sandberg of Ludwig Stockholm has just added to the reasons why. His recent study in *Science* helps explain why genetically identical animals are sometimes so different in biology and appearance, and why some inherited disorders caused by a shared set of aberrant genes can vary in severity in different people. The discovery was made possible by a powerful new technique developed by Rickard's lab for analyzing the global expression of genes in single cells.

"We have captured a fundamental randomness at the level of gene expression that has never before been described—one that persists throughout development and into adulthood," said Rickard. Every mammal inherits one copy of every gene from each of its parents. Each of those copies is known as an allele, which is an alternative form of a gene that can determine variations in the body such as hair color. The essential randomness of allelic expression explains in some measure why identical twins can differ in appearance and propensity for disease. The finding also has implications for our understanding of some genetic diseases, such as neurofibromatosis, a genetic disorder that disturbs cell growth in the nervous system, causing tumors to form on nerve tissue.

Ilgar Abdullayer and Rickard Sandberg
Ludwig Stockholm

YOU'RE HISTORY

We're a step closer to making two lethal neurological diseases history. Ludwig San Diego researchers Don Cleveland and Clotilde Lagier-Tourenne are part of a team that has identified a novel strategy for treating the most common genetic cause of amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. It is a fatal disease in which motor neurons in the brain and spinal cord degenerate, leading to paralysis and frontotemporal dementia, a form of dementia in which patients primarily experience deterioration in behavior, personality or language.



Don Cleveland
Ludwig San Diego

In a study published online on October 29 in *Proceedings of the National Academy of Sciences*, the researchers determined that segments of genetic material called antisense oligonucleotides could impede the buildup of toxic RNA that contributes to the most common form of ALS and frontotemporal dementia, and selectively break the RNA down. The team demonstrated that they could remove the toxic RNA without affecting the normal RNA encoding a protein called C9orf72.

The gene encoding C9orf72 is implicated in both ALS and frontotemporal dementia. Repeat expansions in the gene seem to be linked to 40% of people with familial ALS, and to 1 of 20 cases of ALS across the globe. "Treatment with antisense oligonucleotides appears to reduce levels of expanded C9orf72 RNAs. Selective silencing of a toxic RNA is the holy grail of gene silencing approaches, and we showed we had accomplished it," Clotilde said. The next step is to develop treatment strategies that destroy expanded RNAs in people with the disease.

> The team demonstrated that they could remove the toxic RNA without affecting the normal RNA encoding a protein called C9orf72.

FAMILY TIES

Personalized medicine is one step closer to becoming a reality. DNA sequencing technologies are getting faster and cheaper. Soon, a genome could be sequenced for about $1,000, and sequencing could become part of the standard of care. HaploSeq, a new technique developed by Ludwig San Diego researchers Bing Ren, Siddarth Selvaraj and Jesse Dixon can determine whether a particular genetic sequence comes from an individual's mother or father. This will enable clinicians to better assess a person's individual risk for disease, a cornerstone of personalized medicine.

"This advance has direct implications for the utility of genomics in clinical practice and will also have profound effects on genetic research and discovery," said Siddarth. Humans inherit two copies of genetic material. Although current sequencing methods can precisely catalog genetic variants, these methods are extremely limited in their ability to discern which variants are inherited together, as a single haplotype, on the same chromosome. A haplotype is a set of DNA variations that tend to be inherited together.

HaploSeq provides haplotypes of genetic content, allowing researchers to get a better handle on how genes contribute to disease. It could enable prenatal sequencing of fetal genomes, improve the process of matching donors with organs and help scientists better understand human migration patterns.

"This advance has direct implications for the utility of genomics in clinical practice and will also have profound effects on genetic research and discovery..."

PLAYING GAMES

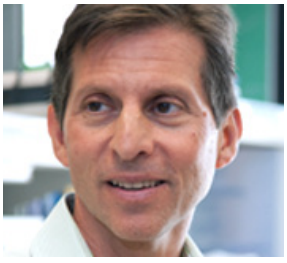
It's a deadly game of hide and seek. Brain cancer cells can evade cancer drugs while they're present in the body. What's more, once the therapy has stopped, the cancer cells can re-emerge. A team of researchers from Ludwig San Diego, including Paul Mischel, Web Cavenee, and Frank Furnari, uncovered a novel mechanism by which glioblastomas, the most common type of brain tumors, can evade targeted therapies. A new study published in the December 5 online issue of *Science* revealed that brain cancer cells discard their growth-enhancing gene, *EGFRvIII*, when the tumors are treated with an inhibitor that specifically targets it. When the treatment is removed, *EGFRvIII* reappears in the cells at normal levels, and the tumor continues its growth.

According to the researchers, this study has huge implications for the future treatment of a brain cancer for which more effective therapies are desperately needed. “The mechanism by which the DNA is sensing the drug is really not understood,” Paul said. “But the theory is that the DNA is sensing the signals that are being sent indirectly by the drug.” The study’s findings better explain why glioblastoma becomes resistant to targeted therapies. It may help doctors determine a better course of treatment for patients.

Another study, published in the October 17 online issue of *Cell Metabolism*, shows how cancer cells get energy and raw materials for growth from glucose. Paul Mischel, Web Cavenee and Kenta Matsui identified a key mechanism by which cancer cells change how they metabolize glucose to generate the energy and raw materials required to sustain their runaway growth. The researchers uncovered several possible targets for new drugs that might disrupt cancer cell metabolism to destroy tumors.

Web Cavenee
Ludwig San Diego

Frank Furnari
Ludwig San Diego



Paul Mischel
Ludwig San Diego

EXPANDING TOOLBOX

Serametrix Corporation has announced the launch of an important new blood test for cancer patients, developed at Ludwig MSK by Jedd Wolchok and Alex Lesokin. The test measures a patient’s level of circulating myeloid-derived suppressor cells, which decrease antitumor immunity and are associated with poor survival rates in cancer patients. The researchers discovered that patients with low levels of a subgroup of these cells were more likely to respond well to ipilimumab, an immunotherapy approved for the treatment of melanoma.

The test will initially be offered to drug companies engaged in clinical development of experimental immunotherapies. In the future, the test may also be used by clinicians to monitor the likelihood of recurrence in cancer patients. “This novel assay has the potential to become a valuable tool in the clinical development of immune therapy in cancer patients,” said Jedd.

Serametrix offers a variety of immunological profiling assays based on technology and know-how established at Ludwig MSK and licensed in 2009 from Ludwig, which partly owns Serametrix. The new test will be an important addition to this existing suite of assays. It characterizes the highly productive interaction between the company and Ludwig MSK.

MULTIPRONGED ATTACK

Immune checkpoint modulators, proteins that are potential targets for the development of cancer immunotherapies, are expected to become a cornerstone of cancer therapy. Ludwig, the Cancer Research Institute and MedImmune have created a program for conducting trials of optimal combinations of checkpoint inhibitors. Different cancer immunotherapies are designed to have distinct yet potentially complementary effects on the immune system. Developing treatments that use combinations of immunotherapies could enable scientists to attack a particular cancer on multiple fronts and prevent it from escaping the immune response.

The first trial designed to evaluate the safety and tolerability of a combination of two of these modulators, anti-PD-L1 (MEDI4736) and anti-CTLA-4 (tremelimumab), in subjects with advanced solid tumors has been initiated at sites within the CVC Trials Network. The trial is sponsored by Ludwig and funding is provided by the Cancer Research Institute and MedImmune. "The successful approval and implementation of this complex study of two investigational agents is a significant milestone for our program and is a result of a highly interactive engagement among the clinical trials management teams at MedImmune and Ludwig and our clinical investigators," said Jonathan Skipper, Ludwig's head of technology development.

Jonathan Skipper
Ludwig

THE RNA PEOPLE

CureVac is a pioneer in the development of a new class of immunotherapies based on RNA. The company is collaborating with Ludwig and the Cancer Research Institute to enable clinical testing of novel cancer immunotherapy treatment options involving CureVac's RNActive vaccines. Combining immunotherapy approaches holds great potential for the treatment of cancer.

"CureVac's immunotherapy platform, which is built upon several Ludwig antigens, has shown promising results in early-stage clinical trials in non-small-cell lung cancer. Our collaboration will enable us to combine this novel technology with different immunotherapeutic approaches, such as immune checkpoint modulators, to test whether this can extend the clinical impact of these agents to a larger number of cancer patients," said Jonathan Skipper.

Under the collaboration, Ludwig and the Cancer Research Institute may conduct clinical studies of cancer immunotherapy combinations through their CVC Trials Network using CureVac's investigational drug, CV9202, combined with other agents to which Ludwig and Cancer Research Institute have access via their internal portfolios or additional collaborative partnerships.

Why do we die from cancer?

The human body, composed of trillions of cells, consumes and produces energy: 4 million cells are renewed every second. Tiny genetic malfunctions can interfere, and cancer occurs when the systems repairing genetic alterations fail. Medical treatments can cure people or prolong their life expectancy. However, once cancer prevents the body from producing or consuming energy, this wonderful machinery dies.

NATHALIE DEMOTTE
Ludwig Brussels

Survival in cancer correlates with tumor genetics. For example, poor prognosis in neuroblastoma is associated with specific chromosomal abnormalities different from those in children with early-stage tumors and high survival. Identifying genes causing these prognostic differences will help us to prevent cancer deaths.

KARIN WALLIS
Ludwig Stockholm

Cancer is difficult to treat because cancer cells can switch between benign and aggressive states. Treatments targeting aggressive cancer cells may not target benign ones, enabling remaining benign cells to regenerate aggressive cells over time. Targeting aggressive cells and preventing benign ones from becoming aggressive will improve patient survival.

CHRISTINE CHAFFER
Ludwig MIT

Ludwig's secret weapon

What is the LICR Fund?

Daniel Ludwig donated substantially all of his net worth to cancer research. He gifted his international businesses to support the Ludwig Institute. The assets of those businesses over time were sold and the proceeds placed under the control of the Fund to be reinvested in a more liquid and broadly diversified spectrum of assets. The Fund's sole purpose is to support the Ludwig Institute, and it currently supplies approximately 60% of the Institute's total annual operating budget. Separately, Mr. Ludwig gave his US-based business interests to support cancer research at six US Ludwig Centers. The six Ludwig Centers and the Ludwig Institute together comprise Ludwig Cancer Research.

What are the key objectives in managing the Fund?

Bottom line, we don't chase short-term performance; we invest with a long-term view. Our team's goal is to provide sustainable spending for the Institute while maintaining the Fund's purchasing power for future generations of scientists. In order to accomplish this, we need to generate a high enough return after taking into account inflation to take care of annual Institute operating commitments while also preserving the real value of the Fund.

Xing Chen
Ludwig Fund

How has the Ludwig Fund performed over the past five years?

The Fund has delivered top quartile investment performance among our endowment and foundation peers over the past decade. This return profile has allowed us to fully support the Institute's operations while rebuilding the Fund's purchasing power after the setbacks of 2008.

Very impressive. Can you share your management secrets?

Insistence on high quality and excellence is critical. I never put things on autopilot. I'm constantly and continuously engaged with

> "Bottom line, we don't chase short-term performance; we invest with a long-term view."

what's happening with asset managers, their portfolios, the markets, politics, social trends, demographics, absolutely everything I can possibly process in order to have as broad a perspective as possible. When I go to sleep each night, I look forward to getting up in the morning and doing it all again.

What risk controls and measures do you have in place?

The world in many ways is fundamentally riskier than it was 10 or 20 years ago. There are lots of stresses and imbalances in the global economy creating an unusual level of uncertainty. So we have fairly normal return expectations but abnormally high concern about fundamental risks.
For that reason the Fund is configured with a value bias to protect our capital in market downturns.

In constructing the overall investment portfolio, we focus on risk-adjusted returns, not nominal returns. In that way we understand the volatility associated with our expected stream of returns. The Fund's portfolio incorporates a range of asset classes and strategies. Within those various asset classes and strategies, the individual asset manager portfolios are further broadly diversified with respect to exposure to issuers, industry sectors, regional markets and investment instruments.

We're overseen by a board of directors that determines investment policy and objectives and defines guidelines for the allocation of assets. As a further safeguard, Ludwig's assets have always resided with third-party custodians or administrators instead of with the individual asset managers. This precludes a Madoff-type situation from arising within the portfolio.

How do you evaluate and monitor an investment, and what decisions do you make along the way to stick with it or get out?

Predicting exactly when the market may spike or fall is virtually impossible. History

"In constructing the overall investment portfolio, we focus on risk-adjusted returns, not nominal returns. In that way we understand the volatility associated with our expected stream of returns."

has proven time and time again that very few investors are nimble enough to both "get out" and "get back in" at the right times.

Ludwig is a long-term investor with a focus on the fundamental value of investments. We're not trigger-happy traders and do not chase returns. The deployment of capital to a particular asset manager involves a rigorous due-diligence process. Our objective is to distinguish repeatable outperformance from luck. We conduct extensive investigations of a candidate firm, its investment professionals (are they an experienced and stable team?), its investment process (is it disciplined and sound?) and the whole operation (legal, accounting and so on). We speak with institutions who are already investing with the firm. Because our goal is to have the highest quality portfolio possible, we apply the highest standards in our search process. It's better to spend the time and effort up front instead of making changes later.

We're not slaves to benchmarks because otherwise we might forgo potentially huge opportunities outside those limits. We monitor investments daily and conduct portfolio reviews quarterly. During those reviews, we discuss the full range of issues related to managers and their investments with our eye on the long term.

Are there any special challenges in managing the Fund as compared with university endowments?

Like a university endowment, we have a long-term investment time horizon. University endowments, however, enjoy structural advantages over institutions such as ours, such as significant cash inflows from legacies, donations, extensive alumni networks and low and flexible spending rates.

These factors have allowed Ivy League schools to assume more risk and leverage in their portfolios than our Fund is comfortable with. As a result, they have historically delivered some of the highest returns among institutional investors. But the 2008 financial crisis exposed stress fractures in this high risk–high leverage model and, as a result, many schools suffered heavy losses. Nonetheless, the ability and willingness to take on higher risk and leverage is still a hallmark of the Ivy endowments.

Ludwig's current situation is very different from that of the Ivy League schools. We have substantially fewer resources, and we depend far more on our endowment for annual operating expenses, which are 60% of the budget versus 30% or so for the Ivies. Owing to the mission and character of the Institute, reducing

"Because our goal is to have the highest quality portfolio possible, we apply the highest standards in our search process. It's better to spend the time and effort up front instead of making changes later."

spending levels in response to any market downturn is neither desirable nor practical. This requires that we insulate the Institute and Fund as much as possible with the assumption of a string of poor returns.

What lessons did you learn from the 2008 financial crisis?

2008 was truly a shock point. I think there were a couple of important lessons that we learned from the meltdown. Focus on the big picture and identify risks early in the game. Pay attention to the valuation and liquidity of the portfolio. Have a disciplined process that avoids chasing an overvalued market and maintain ample liquidity to avoid forced, panicked selling at the bottom. This positions the portfolio to be able to take advantage of strategic opportunities that will unfold as markets recover.

The bottom line is to remain calm and never let market volatility or emotion take over.

What makes Ludwig a special place to work?

I see our role as one of the pillars in the fight against cancer. The Fund's mission is to help and support our scientists and move the fight against cancer forward. Like our researchers, we're obsessed with numbers. Worldwide, 12.7 million people learn they have cancer and 7.6 million people die from the disease. Every year. And every dollar we make helps contribute to bringing those numbers down.

We're proud to be part of an organization that constantly challenges itself to achieve Daniel Ludwig's mission. Collectively we can turn the tide. Ludwig has transformed the landscape of the disease over the past 40 years and has had a tangible effect on the fight against cancer. We like to think we're part of that equation.

DID YOU KNOW…

"Science" rivals "selfie" for top word of 2013…
It was the battle of the dictionaries. The British publishers of the Oxford Dictionaries picked "selfie" as their word of the year, but the American publishers at Merriam-Webster picked "science"!

Oxford's buzz-worthy choice of "selfie" last month was a result of the word's growing usage and digital fame. But Oxford's US counterpart picked "science" based on a whopping 176% increase in lookups of the word in its online dictionary. This could be due to a surge of interest in science-related issues, including climate change, new therapies, the brain, vaccines, education and technology.

Our prediction for 2014 word of the year – SCIENTIST…

Required Reading

Ludwig Brussels

Cancer Discovery
2013 November 21
(Epub ahead of print)
Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy
Shi H, Hugo W, Kong X, Hong A, Koya RC, Moriceau G, Chodon T, Guo R, Johnson DB, Dahlman KB, Kelley MC, Kefford RF, Chmielowski B, Glaspy JA, Sosman JA, van Baren N, Long GV, Ribas A, Lo RS.

Ludwig Chicago

Journal of Clinical Investigation
2014 January 2
(Epub ahead of print)
Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice
Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, Fu YX.

Ludwig Johns Hopkins

Science
2013 December 5
(Epub ahead of print)
Association of the autoimmune disease scleroderma with an immunologic response to cancer
Joseph CG, Darrah E, Shah AA, Skora AD, Casciola-Rosen LA, Wigley FM, Boin F, Fava A, Thoburn C, Kinde I, Jiao Y, Papadopoulos N, Kinzler KW, Vogelstein B, Rosen A.

Ludwig Melbourne

Journal of Clinical Oncology
2013 December 10
BRAF inhibitor–driven tumor proliferation in a KRAS-mutated colon carcinoma is not overcome by MEK1/2 inhibition
Andrews MC, Behren A, Chionh F, Mariadason J, Vella LJ, Do H, Dobrovic A, Tebbutt N, Cebon J.

Ludwig Oxford

Proceedings of the National Academy of Sciences USA
2013 December 3
RVX-208, an inhibitor of BET transcriptional regulators with selectivity for the second bromodomain
Picaud S, Wells C, Felletar I, Brotherton D, Martin S, Savitsky P, Diez-Dacal B, Philpott M, Bountra C, Lingard H, Fedorov O, Müller S, Brennan PE, Knapp S, Filippakopoulos P.

Ludwig San Diego

Science
2013 December 5
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