Cancer Research & Treatment Fund, Inc.
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NEWS

Visit From John Crispino, PhD, MBA

This July, Dr. John Crispino, was a visiting lecturer at the Weill Cornell Division of Hematology/Medical Oncology. He spoke on the development of blood cells in normal and abnormal states. He met with several members of the staff and exchanged productive ideas for research. This visit was partially supported by CR&T as part of its education mission.

Dr. Crispino, is the Robert I Lurie, MD and Lora S Lurie Professor of Medicine at Northwestern University and the Associate Director of Education and Training for the Robert H. Lurie Comprehensive Cancer Center. Dr. Crispino received his PhD from the Massachusetts Institute of Technology for research on the mechanisms of RNA splicing performed in the laboratory of Dr. Phillip Sharp, Nobel Laureate in Physiology or Medicine. He then performed post-doctoral hematology research at Harvard Medical School before moving to Chicago in 2000. In 2011, Dr. Crispino received an MBA from the Kellogg School of Management at Northwestern University.

Over the past decade, Dr. Crispino and members of his laboratory have made many important contributions to improve our understanding of the mechanisms of normal and malignant blood development. He was the first to identify specific genetic mutations that are associated with leukemia in children with Down syndrome. Currently, his research is focused on understanding the role of transcription factors in the specification and maturation of blood cells, characterizing genetic defects that lead to myeloproliferative neoplasms and acute myeloid leukemia, and developing novel, targeted therapies for patients with these malignancies. He has authored over 90 manuscripts and was named the 2011 Illinois Leukemia Researcher of the year by the Pamela B. Katten Memorial Leukemia Research Foundation.

He is currently the Scientific Advisor to the Myeloproliferative Neoplasm Research Foundation where he worked closely with our President, David Boule and Medical Advisory Board member Andrew Schafer, M.D., and on the medical advisory boards for the Rally Foundation for Childhood Cancer Research and the Leukemia Research Foundation.

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LEADING RESEARCH

Why CR&T. The need for private funding in cancer research

Richard T. Silver, MD, Vice President & Medical Director, CR&T

More than 1.6 million Americans will be diagnosed with cancer this year. Unfortunately, the incidence of cancer will increase even more as our population ages, and will account for the 1 out of every 4 deaths in the United States. The American Society of Clinical Oncology (ASCO) highlighted many research breakthroughs improving the lives of people suffering from cancer at its annual meeting in June 2014 which I attended. There was considerable cause for increasing optimism, but also pessimism regarding our future ability to advance cancer care which depends upon continuing clinical, translation and basic research. In a recent article in the American Society of Clinical Oncology Daily News, Dr. Richard Shilsky pointed out that patients with cancer are living longer and better than even before and more are being cured. Cancer deaths have declined by 1.5% per year over the past decade. Scientific breakthroughs are occurring at a rapid pace and are translated into new drugs and devices that benefit patients more quickly and more frequently than ever before. Nevertheless, the budget of the National Institute of Health adjusted for inflation has decreased by more than 36.4 billion dollars (23%) since fiscal year 2001.

Because of this, Dr. Shilsky noted that more than 600 research projects that were scientifically sound were not funded in 2012 by NIH. Many researchers have reduced the size of their research programs and enrollment in National Cancer Institute supported clinical trials is approaching a very low level. This means that clinical investigators are turning more to pharmaceutical companies for clinical trial support and this has obvious dangers.

It is depressing to many of us that not too long ago the United States was the leading center for clinical trials but this has now shifted overseas to Europe; even China and Russia are becoming quite active in clinical (and basic) research. It is for this reason that the companion article by Professor Selina Chen-Kiang is so important to our supporters of CR&T. It is a very good example of our mission. It illustrates how properly selected and funded research projects can make such a meaningful impact in cancer biology and treatment. We are grateful to all our donors for helping us to continue our mission!

Researchers Supported by Cancer Research & Treatment Fund Have Identified Mechanism for Resistance to Ibrutinib in Lymphoma

Selina Chen-Kiang, PhD

Researchers supported by CR&T have recently identified both the molecular mechanism that causes some mantle cell lymphoma (MCL) patients to be resistant to ibrutinib (Imbruvica), and ways to overcome that resistance. Selina Chen-Kiang, PhD, Professor of Pathology and Professor of Immunology and Microbial Pathogenesis at Weill Cornell Medical College, and her colleagues published the results of their research at Cancer Discovery on September 1 of 2014. Dr. David Chiron, the first author of this paper, has been supported by a postdoctoral fellowship from CR&T.

Ibrutinib received approval from the U.S. Food and Drug Administration (FDA) for treatment of MCL in November 2013, and has shown promise in treating many MCL patients. Unfortunately, about one-third of patients are resistant to ibrutinib and many patients become resistant after the initial response. "Relapse is a challenge because it is frequent in MCL, the tumors grow faster than before and there are no effective therapeutic options," Dr. Chen-Kiang says. She and her colleagues, including CR&T Board member John Leonard, MD, used longitudinal genomic and RNA sequencing analysis of both MCL tumors and healthy tissue to identify a relapse-specific genetic mutation, C481S in Burton's Tyrosine Kinase (BTK), which ibrutinib specifically targets. This is the first identified mutation specific to MCL patients who relapse from ibrutinib after a durable response. However, this BTK mutation is not found in MCL patients who do not respond to ibrutinib or become resistance after transient response, suggesting two patterns of ibrutnib resistance in MCL.

Ibrutinib resistance appears to correlate to an increased activation of a number of other molecular mechanisms known to contribute to MCL growth, among them the protein CDK4, and signaling along the PI3K-AKT pathway. The researchers then discovered that targeting CDK4 with palbociclib (PD 0332991), a selective CDK4-inhibitor, made the MCL tumor cells sensitive to ibrutinib when BTK is not mutated, and to inhibitors of PI3K regardless of

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Patient's Corner

A Story From Cancer Survivor Karla Lyden

Maybe It Was a Chicken

By Karla Layden

No one is ever sure which came first, the chicken or the egg. Well, for me, it appeared to be the egg…or shall we say, something the size of an egg? Nothing painful, but suddenly appearing over my left collarbone. A pulled muscle? It would go away. Of course it would go away. I only got sick with things that went away.

The egg didn't go away. Thanksgiving holiday was coming. I made an appointment with my hometown doctor. He pushed and pressed and poked the "egg," did a little hmmming and said he thought it was a muscle bunch, and that he would like to biopsy it. I could feel the color drain from my face. He could see the color drain from my face. Abandoning that tack for the moment he asked me to take a medication that would bring down the swelling and we'd see if that worked.

It did…but…there was that little blip in there, the size of a pea. It wasn't quite gone at Christmas. A bit more hmmming from Dr. Becker and then he went the way of Solomon the Wise, "Karla, you are about to return to a university with a medical school and a medical center for the students. Why don't you go see someone at the med center and have the doctors give us a second opinion?"

Being the obedient little Catholic school girl that I am, I did go to the Med Center, only after I had registered for that semester's courses. Eventually, a doctor saw me. He examined me and looked at the egg. It was unswollen, but the blip was still there. He excused himself for a few minutes and came back with another white-coated figure who looked, pressed, pushed and poked and left the room with doctor #1. A few minutes later, doctor #3 came in and did the same thing. Dr. #4 was a woman. Dr. #5 was the head of the Medical Center. Big guy, asked a few questions, had me puff up my neck

by holding my nose and blowing out. Cute little trick. He didn't leave. "I'd like to have you see a surgeon and get this biopsied."

Doctor's Hospital was located on the edge of the campus of the University of Miami in Coral Gables. Mom and I went over from my campus apartment with my little go bag (in those days it was a ditty bag, we didn't go anywhere in a hurry then). I had to go to the lab for bloods. Seems like the easiest thing in the world. Don't you believe it! Multiple sticks later, the phlebotomist on duty gave up the ghost and asked for an IV nurse to see me in my hospital room and draw the blood. By then, I was tense and upset and wishing I'd never gone to the Med Center. The IV nurse came in and looked carefully at my arms. Calmly and slowly she got a baby-gauge needle, wiped alcohol on the spot (if only she had poured it down my throat), and stuck me. Done. I remember my mother thanking her and looking at me and saying, "Honey, you have your smile back."

For a while…

The next morning I went to surgery, sacrificed three lymph nodes. A nerve was cut to get at them that left me numb in that spot for twenty-five years. The wait for the pathology verdict began. Three days and three pathologists later, my mother was told that I had Hodgkin's Lymphoma. That information was never actually passed on to me. One day months later I was left alone in an examining room with my chart. After a few moments of worrying about not being supposed to read it, I looked. In time I found a reasonable definition that told me what I hadn't known, but had intuited. I had a form of cancer.

Thirty-five years later, I developed Non-Hodgkin's Lymphoma. For nearly forty-five years, I have survived. I do pretty much all that I want to do and when my memoirs come out, they will need to be "boxed" like Proust, because I have a lot to say!

That egg crossed the road and is on its way, racing to a broken down coop somewhere. I get to be a living reminder that cancer is not a death sentence, it is simply a unique lifestyle.

The only chickens in this story were the two lymphomas; I didn't back down, neither did the many doctors who rescued me from that no man's land of illness to another life through the leadership and efforts of Dr. Richard Silver, researchers and donors to CR&T whose heroic sacrifice and generosity made available to me the treatment that makes it possible for me to be writing here.

OTHER NEWS

Resistance to Ibrutinib in Lymphoma

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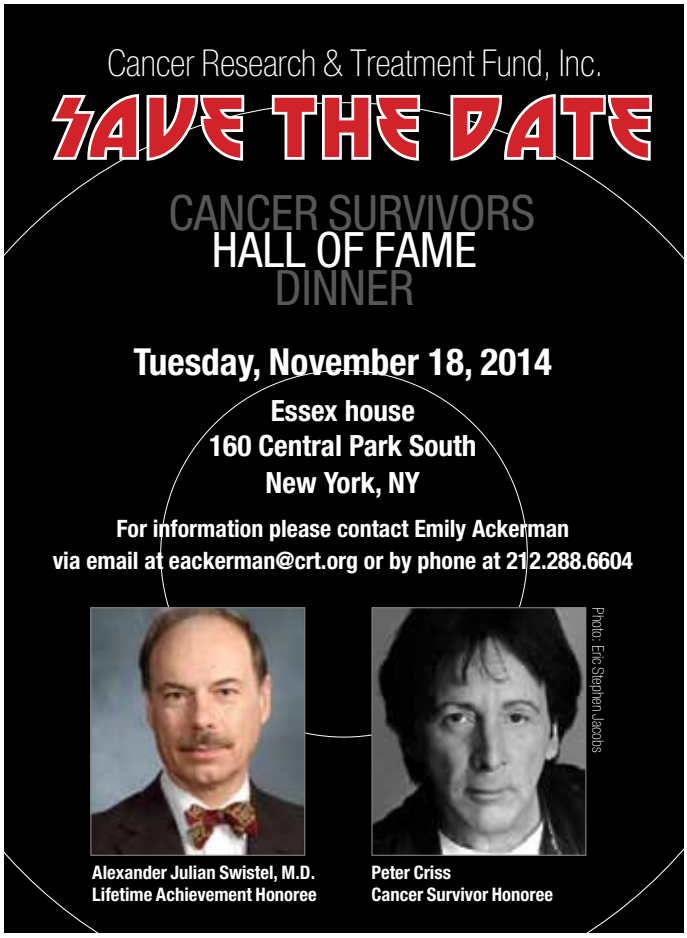
BTK mutation. These findings suggest that a combination therapy of palbociclib and ibrutinib or a PI3K inhibitor may be an effective strategy in overcoming ibrutinib resistance.

The timely and critical support from CR&T made it possible for Dr. Chiron to complete his postdoctoral research with Drs. Chen-Kiang and Leonard, which was instrumental for these ground-breaking discoveries and for developing genome-based, hypothesis driven therapies that overcome drug resistance. This, in turn, has helped Dr. Chen-Kiang and her colleagues receive funding from the National Cancer Institute (NCI) to open a clinical trial to test palbociclib and ibrutinib as a combination therapy. "We are happy to have contributed to the understanding of ibrutinib resistance and offered alternative therapies that have a potential to benefit MCL and other patients who are treated with ibrutinib," Dr. Chen-Kiang says. "It is also exciting because CDK4 is a new kind of drug target; it controls the cell cycle, which is a central cancer pathway. As such, targeting CDK4 is not just important for mantle cell lymphoma but for many forms of cancer. For example, when combined with letrozole, palbociclib more than doubled the progression free survival of metastatic breast cancer patients."



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Cancer Research and Treatment Fund, Inc,
is a non-profit group of physicians, nurses, and other medical professionals dedicated to funding research for the treatment of cancer and other blood diseases.
Richard T. Silver, MD FACP founded CR&T in 1968.

Dr. Silver is Professor of Medicine and Director Emeritus, Richard T. Silver, M.D. Myeloproliferative Neoplasm Center at Weill Cornell. He is also Attending Physician at New York Presbyterian Hospital/Weill Cornell Medical Center

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