

NEWSLETTER

Fall/Winter 2012

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A Time for Hope

Dear Friends,

The Paul Nabil Bustany Fund for Synovial Sarcoma Research is entering its sixth year of operation as a vehicle to raise funds for basic research on synovial sarcoma. As we launch our fundraising for 2013, we are delighted to bring you the wonderful news that our collective efforts are paying off.

One of our two grantees, Kevin B. Jones, MD, under the mentorship of 2007 Nobel Laureate for Physiology and Medicine Dr. Mario R. Capecchi at the Institute of Human Genetics, Utah University Medical School, has discovered "An Achilles Heel" in synovial sarcoma which responds to one of the new therapeutic drugs already on the market when tested in mice inflicted with human synovial sarcoma. This breakthrough should give hope to the many young people afflicted with this disease.

The results were published in the July 16th issue of *Oncogene*, a publication of *Nature*. In addition, Dr. Jones has received a three-year grant from The Damon Runyon Cancer Research Foundation to launch clinical trials exclusively on synovial sarcoma. He said in a letter last spring: "It is largely thanks to your support that this honor has been bestowed."

Our other research team, under the leadership of Marc Ladanyi, MD (clinical co-leader) and C. David Allis MD (basic science co-leader), and co-investigators, Ping Chi, MD, and Tatsuo Ito, MD, at Memorial Sloan-Kettering Cancer Center, continue their research on elucidating SYT-SSX-dependent histone code alterations to guide targeted epigenetic therapy for synovial sarcoma. In the July 10th issue of *Cancer Research*, Dr. Ladanyi reports where another drug combination is being suggested for synovial sarcoma and on their multifaceted research teams at MSKCC. He's seeking funds to support collaboration among several international scientists who are synovial sarcoma specialists.

Both science teams have acknowledged the PNB Fund's support in their publications and expressed their gratitude for our sustained contributions over the years. Our steadfastness builds confidence and helps them attract some of the best scientists in this field as well as financial aid from other sources.

Our goal this year is to raise \$80,000 to continue to support the excellent work of our scientists working to find a cure. Your support is needed now more than ever, and as the PNB Fund is entirely run by volunteers, you can be sure that 100% of your donations will go directly to synovial sarcoma research.

We can be proud that our "seeds" are sprouting—but they need nurturing until we have a guaranteed cure for this disease.

With hope and gratitude,

The Paul Nabil Bustany Fund for Synovial Sarcoma Research Board of Directors: Rami Badawy, Christine Bustany, Laufey Bustany, Samir Ted Bustany, Alex Kaplan, Asu Okyay, Alex Rafal, Anthony Rizzo, and Sabrina Tom

**Research Update from Kevin B. Jones, MD,
of the Capecchi Genetics Laboratory, University of Utah**

***Discovering an Achilles Heel: Promising Results of a
New Class of Drugs for Synovial Sarcoma***



The Capecchi laboratory team researching synovial sarcoma at the University of Utah, pictured here from left to right: Huifeng Jin, MS; Krystal Straessler, graduate student; Emanuele Panza, PhD; Mario R. Capecchi, PhD; Kevin B. Jones, MD.

With the support of the Paul Nabil Bustany Fund for Synovial Sarcoma Research, the sarcoma team from the Capecchi genetics laboratory at the University of Utah recently discovered an Achilles heel of synovial sarcoma.

Every cell in the human body holds itself carefully in a balance between signals that will initiate a program of cell-death in response to distress and opposing signals that promote survival of the cell. Cancer cells, because they harbor so much internal distress, often depend on very powerful cell-survival-promoting signals to keep the strong cell-death signals in check. Synovial sarcoma has a bizarre balance of these signals that makes it very resistant to many chemotherapies used to try to kill the tumor.

Experiments in the lab have recently shown that this balance of signals is uniquely susceptible to a new class of targeted chemotherapy drugs. SS18-SSX2, the fusion gene characteristic of synovial sarcoma, specifically shuts down the escape routes that many other tumors use, making synovial sarcomas especially sensitive to these new drugs. These findings were recently published in the journal *Oncogene* (1). Work is underway to develop an ideal regimen for this drug class to be administered in patients with synovial sarcoma.

We also continue to work to improve understanding of the balance of pro-death and pro-survival signals in synovial sarcoma cells and learn how to topple that balance in favor of killing tumor cells and helping patients survive. Our growing experience with now a variety of mouse models of synovial sarcoma enable us to understand the pathways by which these cancers develop and test novel ways to attack them.

(1) Kevin B. Jones et al. "SS18-SSX2 and the mitochondrial apoptosis pathway in mouse and human synovial sarcoma." *Oncogene*, July 16, 2012: 1-7. Short Communication.

**Research Update from Marc Ladanyi, MD,
of Memorial Sloan-Kettering Cancer Center**

New Therapies To Treat Synovial Sarcoma: Three Collaborative Projects

In this year's update, I would like to highlight how support by the Paul Nabil Bustany Fund for Synovial Sarcoma Research has served to enable and facilitate ongoing work on synovial sarcoma, highlighting three collaborative projects focused on potential novel therapies. First, data from our laboratory's studies on synovial sarcoma tumor samples had revealed that the growth factor receptor PDGFRA was unusually highly expressed in synovial sarcoma, suggesting that PDGFRA may be uniquely significant for the development and survival of synovial sarcoma cells. These data led to a collaboration with our MSKCC colleague Dr Gary Schwartz, whose lab showed that using the PDGFRA inhibitor imatinib in combination with an mTOR inhibitor (everolimus or rapamycin) could represent a novel treatment combination for future evaluation in a clinical trial. The work was published on July 10 in *Cancer Research* (1).

Secondly, previous work in our laboratory had revealed that another growth signaling pathway called "Hedgehog" was strongly active in a subset of synovial sarcoma cases. These data have now led to a collaboration with another MSKCC colleague, Dr Marilyn Resh whose laboratory has developed a new class of Hedgehog pathway inhibitors. Her group is now testing these novel agents on synovial sarcoma cell lines from our laboratory. Her laboratory's work on synovial sarcoma cell lines is funded as a "developmental research project" through the MSKCC Sarcoma SPORE (Specialized Programs of Research Excellence) grant from the NIH.

Another "developmental research project" supported by this same funding mechanism represents our third collaborative project focused on potential novel therapeutic strategies for synovial sarcoma. In this project, "Defining Epigenetic Vulnerabilities of Synovial Sarcoma", our MSKCC colleague and collaborator, Dr Scott Lowe, plans to use "RNA interference" technology to block genes that control gene expression by altering the proteins that cover DNA (histones) in the hope of thereby identifying an "Achille's heel" in SYT-SSX driven tumors. This collaboration with the Scott Lowe group also dovetails with our own ongoing work within the MSKCC Sarcoma SPORE grant, on Project #4, "Elucidating SYT-SSX-dependent histone code alterations to guide targeted epigenetic therapy for synovial sarcoma". Dr. Tatsuo Ito, a postdoctoral fellow in my laboratory previously supported by the PNB Fund, is continuing work on this project. Dr. Yoshiyuki Suehara, another postdoctoral fellow in my research group, published his previous work on the expression of a protein, secernin, that appears to correlate with metastasis and survival of patients with synovial sarcoma (2). He has been working to confirm these observations in samples from synovial sarcoma patients treated at our institution.

We are very grateful for the support provided by the Paul Nabil Bustany Fund which has provided seed money and support for our own ongoing work and has also allowed us to function as a focal point or catalyst for the exciting synovial sarcoma collaborations described above. We are committed to advancing and facilitating research efforts that could lead to real clinical advances for patients affected by this sarcoma.

(1) Ho AL, Deraje Vasudeva S, Lae M, Saito T, Barbashina V, Antonescu CR, Ladanyi M, Schwartz GK. "PDGF receptor alpha is an alternative mediator of rapamycin-induced Akt activation: implications for combination targeted therapy of synovial sarcoma." *Cancer Research*, July 2012.

(2) Suehara Y, et al. "Secernin-1 as a novel prognostic biomarker candidate of synovial sarcoma revealed by proteomics." *Journal of Proteomics*, May 2011.

Fundraising Updates

Special Thanks to Cynthia Singiser!

We'd like to extend a huge thank you to Cynthia Singiser, Paul's friend and long-time PNB Fund supporter, who will run a half-marathon in California to raise money for the Fund. This isn't the first time Cynthia has run to raise money for the Fund and we want her to know how much we appreciate her efforts and loyal friendship.

If any of you are planning to run/walk in a race of your own and would consider doing the same thing as Cynthia, please let us know. Your help is invaluable.

Grantmaking

In 2011 the PNB Fund granted \$45,000 to Dr. Ladanyi's team at Memorial Sloan-Kettering Cancer Center, and \$30,000 to Dr. Kevin B. Jones in Dr. Capecchi's group at Human Genetics, University of Utah; and in 2012, Dr. Jones was awarded a \$50,000 Grant from the Fund.

Upcoming Events

We are currently planning a benefit event for 2013, so please stay tuned for more details!

How to Donate

Option 1: Write a check to *The Paul Nabil Bustany Fund for Synovial Sarcoma Research*. Send your check to: 15 Footes Lane, Morristown, NJ, 07960.

Option 2: Donate online at **www.pnbustanyfund.org**.

The PNB Fund is a 501(c)(3) nonprofit organization. All donations are tax deductible.

The purpose of the Paul Nabil Bustany Fund for Synovial Sarcoma Research is to raise money for basic scientific research on synovial sarcoma. The PNB Fund is entirely run by volunteers and all donations go directly to synovial sarcoma research. Thank you for your support.