KARIN GRUNEBAUM
cancer research foundation

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Founded in 1958

From the Chair

Dear Friends of the Karin Grunebaum Cancer Research Foundation:

Thank you, thank you, thank you! We called out for help and you responded. When we told you that after 54 years we needed to increase our donations or risk losing our tax-exempt status and ability to fund further cancer research you answered the call. Both the amount of received donations and the number of new donors hit an all-time high. Special kudos go to Trustee Shawna Wallach who introduced the highest number of new donors to the Foundation.

Now, if each person who donated last year continues to donate at least the same amount each year, the Foundation will be on track to regain its "Public Charity" status in 4 more years (the IRS uses a sliding 5-year period for designation). Please, please continue to show your support so that we can eliminate the wasted additional cost of accounting and taxes required to be paid as a "Private Foundation." **Rest assured, we are still a 501 (c) (3) charity, and your entire donation is tax-deductible to the extent allowed by law.**

Now for the fun stuff: the extra funds raised allowed the Foundation to continue to expand its activities. In addition to our primary mission of on-going support for junior faculty members engaged in cancer research at Boston University School of Medicine and Harvard Medical School, we were able to sponsor an expanded program in the Cancer Biology area of Harvard Medical School's Biological and Biomedical Science Graduate Program – exposing 65 to 75 budding medical researchers to the opportunities and challenges available in pursuing a career in cancer research. Take a look at the enclosed article showing how the funds received from the Foundation have bolstered Harvard's program.

At Boston University, the Foundation was also able to expand its funding of undergraduate students engaged in cancer research programs over the summer. Without this funding (which includes required lab fees) many of these students would never be exposed to the possibilities of entering the cancer research field simply because their schools do not have adequate research facilities.

If you really want to see some potent results from the funds donated over the years, I suggest you take a look at the Foundation's website: www.grunebaumfoundation.org and open the tab under *"Focus on Research"* which highlights some of our past Fellows who have made their marks in the fields of academic medicine and medical research. It's a most gratifying experience to see such an illustrious list and realize how much this Foundation has achieved in the war on cancer.

On behalf of the Board of Trustees, I again thank you for such a successful year, and urge each of you to please continue to support the Foundation to the best of your ability so that we can continue to push back the scourge of cancer through our efforts.

Thank you.
Steven Wallach
Chairperson

From the Fellows

Boston University School of Medicine

Valentina Perissi

B-cell Chronic Lymphocytic Leukemia (B-CLL) is the most common type of leukemia in the Western world. The clinical features of this pathology are heterogeneous, with some patients showing an indolent course with mild symptoms while others develop a more aggressive disease that can greatly reduce their life expectancy. While the treatment outcome of CLL has improved considerably since the introduction of monoclonal antibody therapies, importantly there are patients that are refractory to these treatments or relapse after treatment. Thus, we believe it is important to explore new avenues of research to identify novel molecules that could be promising targets for therapeutic treatment.

Genetic analyses have indicated that a strong prognostic power resides in few molecular markers, including the mutational status of the IgV_H gene and the type of chromosomal aberrations. Recurrent loss or gain of genomic material is indeed a major feature of CLL and a variety of chromosomal aberrations have been described, including 13q14, 11q and 17p13 deletions. In particular, deletion of chromosome 17p is associated with a rapid disease progression and 17p- patients exhibit very poor prognosis due to their refractoriness to conventional therapies. Interestingly, gene expression profilings of B-CLL have identified few genes are consistently misregulated and maybe relevant in the pathogenesis of B-CLL. The GPS2 (G-protein pathway suppressor 2) gene, encoding for a multifunctional protein with both nuclear and cytoplasmic functions, is localized within the 17p13 chromosomal region and is differentially regulated in 17p- B-CLL patients.

B-CLL is characterized by a clonal expansion of CD5+ mature B-cells, which is caused by an increased survival rather than a hyper-proliferative phenotype. Intriguingly, these cells exhibit a significant increase in cytokine production, including TNFá? and constitutively activated signaling pathways. Our lab has been interested in GPS2 for a long time, since its initial characterization as a component of the NCoR/SMRT corepressor complex. Interestingly, we have recently identified a non-transcriptional role for GPS2 as a guardian against hyper-activation of the pro-inflammatory response upon TNFá stimulation in the adipose tissue (Cardamone et al., *Molecular Cell*, 2012). Based on these results, we believe that GPS2 presence in B cells may be similarly required to avoid the hyper-activation of pro-survival signaling pathways, and we are now investigating the hypothesis that GPS2 functions as a novel tumor suppressor gene whose loss or downregulation in B-CLL patients results in a particularly aggressive form of leukemia.

Boston University School of Medicine Summer Research Fellowships

The original goal of the Karin Grunebaum Foundation was to support the training of medical and graduate students in cancer research. More recently, the focus has shifted somewhat, to providing support to outstanding new clinical and translational investigators during their critical early independent research years. However, it is clear that we also need to provide cancer research opportunities to encourage the next generation of scientists to take up the goal of curing cancer. Boston University School of Medicine has therefore established the Karin Grunebaum Summer Research Fellowships to provide promising medical and college students with the opportunity to spend a summer working in the laboratory of a leading cancer scientist. These Fellowships provide a stipend to the students to assist with living expenses, and a small amount to pay for laboratory supplies. Now completing its second year, these Fellowships have provided a unique research experience to three outstanding students. Their projects have ranged widely. One student, working in Cancer Center laboratories, carried out studies to determine the role of epigenetic regulation in breast and prostate cancer recurrence, in order to identify new epigenetic factors that would predict breast and prostate cancer recurrence, and may lead to the development of new treatment strategies for recurrences of these cancers. Another student, working in the Department of Dermatology, investigated the possibility of developing a blood test to detect occult malignant melanoma at its earliest and curable stage. A third young scientist, working in Cancer Center laboratories, has focused her efforts on developing new treatment approaches for triple-negative breast cancers (TNBC). These cancers are very prevalent in our patient population, and carry a poor prognosis. She has investigated the use of epigenetic modifying drugs (histone deacetylase inhibitors) to sensitize these TNBC cells to more conventional chemotherapeutic agents. This novel approach appears to show great promise, and she hopes, in the future, that it will move towards clinical application. The students agree that these experiences have fostered in them an enthusiasm and passion for cancer research. They each can see how their work could eventually be direct benefit to patients. We are extremely grateful that the KGCRF has provided our students with the opportunity to carry out cancer research, and consider it as a career.

Harvard Medical School

Elisabeth M. Battinelli M.D., Ph.D., Brigham and Women's Hospital

The importance of platelets controlling bleeding is well known. Recently however, it emerged that platelets are multifaceted and have many important responsibilities in a variety of biological functions. One such role is in establishing cancer metastasis. It has been shown that platelets and tumor cells "communicate" with each other aiding in tumor growth and metastasis formation. A plethora of studies have indicated an essential role for platelets in aiding tumor cells in their journey through the blood stream. Tumor cells traversing the vasculature are cloaked in a protective layer of platelets that allow them to evade immune surveillance. When the tumor cells reach their desired destination, the platelets are instrumental in enabling them to adhere to the endothelium.

In order for tumors to grow beyond 1-2mm, they must establish their own blood supply through angiogenesis, and there is evidence that angiogenesis is regulated by platelets. Upon activation, platelets release over 300 proteins many of which regulate angiogenesis. In breast cancer, platelets are the major serum source of many potent pro-angiogenic proteins, including over 80% of circulating vascular endothelial growth factor (VEGF). Recently, work in our laboratory has implicated platelets in aiding the new blood vessel formation (angiogenesis) that is essential for feeding tumor growth and metastasis formation. When platelets come into contact with breast cancer cells, the platelet releases factors into the blood that promote angiogenesis. We have found that release of these factors can be blocked by treating the platelets with antiplatelet medications, such as aspirin, prior to exposing them to breast cancer cells.

Clinical studies evaluating the role of these medications revealed that those patients who received anticoagulation medication not only had a decreased risk of developing a repeat clotting event but also had a prolonged survival and less metastatic disease formation.

The link between platelets and malignancy has been appreciated for years. The association between hemostasis and malignancy was first recognized by Armand Trousseau in 1865 when he described a series of cases of primary thrombophlebitis occurring in patients with occult malignancy. Since these original findings, clinical data have confirmed the association of thrombosis and malignancy with evidence that hemostasis is essential for tumorigenesis. Patients with cancer have increased risk for developing blood clots termed thrombosis, this risk is especially high in breast cancer patients. These patients are treated with heparin, a anticoagulation medication aimed at blocking clotting pathways. Clinical studies evaluating the role of these medications revealed that those patients who received anticoagulation medication not only had a decreased risk of developing a repeat clotting event but also had a prolonged survival and less metastatic disease formation. The mechanism underlying the anti-cancer effects of heparins is yet to be determined. In most preclinical studies the anticancer effects of anticoagulants did not affect the primary tumor directly, but rather reflected interference in the metastatic pathway.

Our preliminary studies have revealed that anticoagulants can attenuate the angiogenic potential of platelets through disruption of the platelet-tumor cell interplay. We hypothesize that anticoagulants' ability to modulate platelet function may be key to understanding its ability to regulate metastasis formation, thereby setting the stage for improved survival in patients with breast cancer. It is our goal to better understand how anticoagulation medications disrupt the interplay between breast cancer cells and platelets. Our goal is to explore the mechanisms by which anticoagulants disrupt the communication between platelets and breast cancer cells and how this disruption impacts the angiogenic potential of platelets. We will use this knowledge to explore the platelet's role in patients with breast cancer. Ultimately, this work will lead to the use of targeted platelet therapies that can hijack the platelets' role as a mediator of angiogenesis leading to decreased tumor growth and inhibition of metastatic disease formation in breast cancer.

Since most cancer therapies currently in use focus on the malignant tumor itself, arrest of metastatic spread is a potential novel area of therapeutic intervention. As more clinical studies demonstrate the utility of anticoagulation in interfering with breast cancer progression, understanding the role of platelets, which influence both coagulation and malignancy, becomes of utmost importance. Existing research provides compelling evidence for disrupting platelet-tumor cross-talk to down-regulate tumor spread leading to a new avenue for breast cancer therapy. Understanding platelet and breast cancer cell communication, as well as its modulation by anticoagulation, may lead to targeted drug design regulating platelet-mediated angiogenesis as a means of limiting metastatic disease progression in breast cancer.

Harvard Medical School Biological and Biomedical Sciences Cancer Biology Area of Concentration, *May 2012*

Overview

Cancer Biology is an area of concentration within the Biological and Biomedical Sciences Graduate Program at Harvard Medical School. This educational initiative seekd to provide advanced training and an integrated community for students interested in pursuing cancer-related research. The directors of the Cancer Biology program are Professors Chuck Stiles (Dana-Farber Cancer Institute), Karen Cichowski (BWH), Andrea McClatchey (MGH), and Narveen Jandu (HMS).

The Cancer Biology curriculum emphasizes cell signaling, cell biology, pathology, and translational research related to cancer. The program provides both courses and training opportunities for graduate students. Graduate students can self-select to become members of the Cancer Biology Area of Concentration. The program currently has 66 student members, including a student steering committee of 5 students. Additional information can be found on the program's website: www.hms.harvard.edu/dms/bbs/cancerbio.

Several important cancer biology educational and training initiatives include the Fall Welcome Event, the Student Data Club, and the Seminar Speaker Lunch series

Several important cancer biology educational and training initiatives include the Fall Welcome Event, the Student Data Club, and the Seminar Speaker Lunch series. The Fall Welcome Event is held in September at the start of the academic year. One of the main goals of the Welcome Event is to provide incoming graduate students with an opportunity to meet and network with faculty members conducting cancer biology research at HMS and HMS-affiliated institutions. At this early stage in their graduate careers, these students are looking for potential labs through which to rotate and ultimately to join. The faculty members in attendance discuss their research and potential student projects with these students in a casual, non-intimidating setting.

Our Fall Welcome event also serves as an orientation for the graduate students to the Cancer Biology area of concentration. Here we introduce and disseminate information about the courses and other training activities. Students are also introduced to faculty members who are conducting cancer biology research and the labs that they could join.

Funds from the Karin Grunebaum Cancer Research Foundation will allow us to host a Fall Welcome event large enough to accommodate the entire incoming class of BBS students (65-75 students). By inviting the entire class, we will have the opportunity to capture as many students as possible into the area of cancer biology research. Foundation funds will also allow us to offer faculty the opportunity to showcase their research on posters during the Fall Welcome event.

The Cancer Biology Student Data Club is a monthly series that provides an opportunity for students, at all stages of their graduate work, to present their research to their peers. This is a student-only training opportunity, which allows the students to experience both peer review and peer critique. In this forum, the junior students gain practice giving a presentation, brainstorm their research ideas, and get candid advice from the senior students. The junior students also have the opportunity to meet students with similar research interests. Participation in the data club allows senior students to practice their presentations for a meeting or conference; they can also practice presentations of their dissertation research. The data club is also a forum for senior students to give advice on searching for potential post-doctorial labs. Funds from the Karin Grunebaum Cancer Research Foundation will allow us to continue holding the Cancer Biology Student Data Club, and may allow us to expand this series with a complementary Student Journal Club.

Cancer Biology students also regularly attend the weekly Seminars in Oncology at the Dana-Farber Cancer Institute. The seminar speakers for this series are invited, nationally recognized cancer biology researchers. This series allows students to hear and learn about cancer biology research at other institutions and labs. Students also begin to think about potential post-doctoral labs and research projects as they hear about the latest research in cancer biology.

In conjunction with the DFCI Seminars in Oncology, the Cancer Biology Area of Concentration has introduced a Seminar Speaker Lunch series. Each of these educational events allows 8-10 students the opportunity to have lunch with the DCFI Seminar speaker. This casual forum allows our students to get external feedback and advice on various aspects of their graduate careers, from their current research projects to new results, an upcoming conference, how to build collaborations, next career steps, and how to find a post-doctoral lab.

In the future, Cancer Biology hopes to be able to invite more students to attend these lunches, as they are a rare opportunity for all students and vital for our senior students who are searching for post-doctoral labs. Funds from the Karin Grunebaum Cancer Research Foundation would allow us to increase the number of participants at our lunches, allowing more students to attend and meet the seminar speakers.