Karin Grunebaum
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Karin Grunebaum Cancer Research Foundation

Founded in 1958

Dear Friends of the Karin Grunebaum Cancer Research Foundation:

My name is Steven Wallach and I am Karin Grunebaum's oldest child. On October 15, 2004 I will be honored to assume the leadership of the Foundation when the torch is passed from our current Chairperson, Andrew Culbert, to me.

This will be the first time that a family member has led the KGCRF since the Foundation's founder, Fritz Grunebaum, passed away in 1992, ironically of cancer. In the interim, the Foundation was very ably led by Dean Daniel Federman of Harvard Medical School and then by attorney Andrew Culbert. Theirs will be big shoes to fill, and I thank both of them for their tireless work for the Foundation.

Since its founding in 1958 (the year of my mother's death by cancer at age 39), the Foundation has attempted to help eradicate cancer in various ways – initially by establishing a manual cancer registry at Salem Hospital in the pre-computer days, so that doctors and staff could have relevant medical information on other patients with similar cancers who had passed through that facility.

After that, we decided to "invest in people" instead of technology. Under Fritz's guidance, and with the help of Harvard Medical School, in 1966 we started to fund cancer related research by graduate MD's at Harvard Medical School. At first we were only able to fund one researcher annually, but by 1979, we were able to fund two researchers a year.

The Foundation later also established an annual Distinguished Speaker in Cancer Research Series, which was discontinued when we started annually funding two M.D./Ph.D. cancer researchers at Boston University's School of Medicine in addition to those at Harvard.

In 2002, we established the Karin Grunebaum Chair in Cancer Research at Boston University's School of Medicine.

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Without a doubt, the work accomplished by my predecessors and their fellow Trustees represents a series of major accomplishments for a relatively small, private charitable foundation. I hope to emulate their achievements and move the Foundation onto an even higher plane in the future.

The ultimate and overriding goal of the Foundation is to help eradicate all types of cancer. In order to work toward that goal, my immediate personal objectives fall into three categories:

1. Insure that the cancer research projects undertaken by the Karin Grunebaum Fellows are brought to a final conclusion, unhampered by individual researcher's time constraints. This may involve new Fellows taking over on-going research projects from former Fellows and bringing the project to a logical conclusion to see if (and how) the results can actually be applied to solve the cancer problem.
2. Make the Karin Grunebaum Fellowship program an on-going personal and professional experience for the current and former Fellows by fostering social and professional interaction between them.
3. Increasing the funding for the Fellowships so that additional research opportunities are made available.

These are all new and exciting avenues for our Foundation to travel. We have never solicited funds directly nor had any social occasions for current and past Fellows in over 20 years. We have also never asked the researchers and their schools and laboratories to try to channel their sponsored research effort into a series of on-going, interrelated projects.

In the following weeks and months I will be asking you for some help in accomplishing these goals. First, please participate in the Foundation's upcoming social and professional programs. I think they will be very worthwhile for you and fun for all of us. Please, also let me know your thoughts on how to improve the Fellowship program. I am not a doctor or a researcher, and I value your ideas. And, yes, please give generously to our Foundation so that we can move this program forward to a new level. They say, "Paybacks are hell," but we'll at least try to make this one fun. I look forward to hearing from you.

Steven Wallach

A Note of Appreciation

The foundation would like to thank Andrew Culbert, Esq. of Masterman, Culbert and Tully LLP, for his years of service as Chair of the Karin Grunebaum Cancer Research Foundation. Andy's loyal friendship to Fritz Grunebaum, the Grunebaum Family and the Foundation has been admirable and most appreciated by the Grunebaum Family and the Trustees of the Board.

FROM HARVARD MEDICAL SCHOOL

Last week I contacted several former Grunebaum Fellows to ask them about their experiences and the impact of this fellowship on their careers. Without exception, recipients reported that without the benefit of the Grunebaum Foundation, they would not have had the luxury of taking a year to pursue research and validate their decisions to pursue careers related to the treatment of cancer. Additionally, academic medicine remains high on their list of priorities. Christina Boulton, a Grunebaum Foundation Fellow in 2001, noted that: ".....Due to the time constraints of the clerkship schedules I have had very little dedicated research time this year, however I have continued to work towards several publications. It has also given me much pleasure to serve as a resource for members of the Gilliland Lab (with whom she spent the year as a Grunebaum Fellow) now continuing to work on drug therapy testing in mouse models of hematological diseases. ..... My clinical experiences to date have reinforced my desire to pursue a career path that embraces the pursuit of both clinical medicine and basic science research. As I evaluated possible specialty choices I found myself pulled towards those with what I view to be the most exciting avenues for further advance through research."

Christina Boulton
2001Grunebaum Foundation Fellow

Dr. Stella Kim, a Grunebaum Fellow in 1992, sent the following note:

Stella Kim, M.D.
1992 Grunebaum Foundation Fellow

After graduating in 1996 from Harvard Medical School, I remained at HMS for my internship and ophthalmology residency at the Massachusetts Eye and Ear Infirmary, followed by a cornea and refractive surgical fellowship at the University of Utah. In August 2001, I joined the faculty of University of Texas, MD Anderson Cancer Center as an assistant professor of ophthalmology and radiation oncology. My clinical and research interests include anterior segment ocular tumors, ocular graft-vs-host disease in bone marrow transplantation patients,

(continued on back page)

Karin Grunebaum Foundation Fellowship Report – October, 2004

Harvard Medical School is pleased to highlight six recipients of the Karin Grunebaum Fellowship: Ms. Christine Boulton, Drs. Jason Efstathiou, Christine Chung, Linda Chan, Stella Kim and Mr. David Rosow.

Dr. Jason Efstathiou, a graduate of the Class of 2003, was selected as a Grunebaum Fellow following his second year at Harvard Medical School. He was an ideal choice for the Grunebaum Foundation Fellowship. Prior to coming to HMS, he studied at Trinity College in Oxford as a Rhodes Finalist and McKeown Scholarship recipient. The focus of his study there was "The Role of Adhesion Molecules in Colorectal Carcinogenesis." During his year as a Grunebaum Fellow, he studied with Dr. Judah Folkman and Dr. Maria Rupnick at Children's Hospital, investigating the "Angiogenesis Inhibitors that Suppress Endometriosis in a Murine Model." Dr. Efstathiou's research culminated in a senior thesis for Honors in a Special Field entitled "Novel Approaches for the Treatment of Endometriosis in a Murine Model". He was graduated cum laude and is pursuing a career in Radiation Oncology at Harvard's Combined Programs.

Dr. Christine Chung graduated in June of 2003. Following her third year, Christine was awarded the Grunebaum Fellowship and spent a year at the Dana Farber Cancer Institute and the Whitehead Institute investigating coupling of laser capture micro dissection with PCR amplification technology for microanalysis with Drs. Todd Golub and Sridhar Ramaswamy. When Christine Chung returned to her fourth year after completing her Fellowship, she was recognized as an outstanding student in her Radiation Oncology rotation. She applied the same level of excellence to her rotation as she did in her fellowship year. She consistently demonstrated a high level of commitment and the intellectual rigor required to critically evaluate research, literature, and clinical trials.

Dr. Linda Chan graduated in June of 2004 and began her residency in Radiation Oncology at UCSF. While at Harvard Medical School, Dr. Chan was awarded the Karin Grunebaum and National Cancer Institute Research Fellowships at the end of her third year. She worked under the direction of Dr. C. Norman Coleman and Dr. Kevin Camphausen in the Radiation Oncology Division of the National Cancer Institute. The focus of her research was the "Urinary Vegf Amd Mmp Levels As Predictive Markers Of One-Year Progression Free Survival In Cancer Patients Treated With Radiation Therapy: A Longitudinal Study Of Protein Kinetics Throughout Tumor Progression And Therapy". Her research was submitted for publication in the Journal of Clinical Oncology. Additionally, Dr. Chan worked with Dr. James E. Mitchell, Chair of Radiation Biology, National Cancer Institute. There, she examined the influence of tumor oxygenation status on deoxyglucose tumor uptake using position emission tomography. Dr. Chan presented her findings at the American Society of Therapeutic Radiation and Oncology.

David Rosow will graduate with the Class of 2005. Currently, he is finishing 18 months of research into the molecular causes of pancreatic cancer. He reports that the Grunebaum Foundation Fellowship has been a tremendous help – it allowed him the freedom to spend an extra year conducting the type of cancer research he plans to continue for the rest of his medical career. He has had the opportunity to present his work at numerous international conferences, and is in the midst of submitting several journal articles for publication. He plans to apply for residency positions in the field of otolaryngology-head and neck surgery, with the hope that he can apply the techniques he has learned to head and neck cancer research as a result of the Grunebaum Fellowship. David plans to submit a thesis, "Chemically Induced Pancreatic Ductal Adenocarcinomas in Mice Misespress the Sonic Hedgehog Pathway" for Honors in a Special Field.

David Rosow and his research mentors, Dr. Carlos Fernández-del Castillo, presenting a poster of his work at the meeting of the International Association of Pancreatology and Japan Pancreas Society, in Sendai, Japan (July 2004).

FROM THE BOSTON UNIVERSITY SCHOOL OF MEDICINE

Grace Monis, Grunebaum Fellow 2004, MD/PhD Pathology candidate

Primary amyloidosis is a disease of protein misfolding in which immunoglobulin light chains (AL-LCs), produced from a plasma cell dyscrasia, have a propensity to aggregate, form fibrils and deposit in various tissues. The deposits and soluble light chains disrupt the function of the organs they are found in, such as heart, kidney, spleen and lung. Symptomatic cardiac involvement occurs in 25% to 50% of amyloid patients and accounts for death in almost 50% of AL patients[1].

Our lab is studying the effects of AL-LCs on cardiac fibroblasts and the remodeling of the extracellular matrix. Using live cell confocal microscopy and fluorescently labeled AL-LCs, we have observed that cardiac fibroblasts internalize LCs within 4 hours (Trinkaus-Randall et al. 2004 in press). Experiments are being done to better understand what AL-LCs co-localize with and what cellular pathways are being disrupted or stimulated to cause the resultant pathology.

Amyloidogenic light chains have been found to cause an increase of cellular reactive oxygen species which is associated to a disruption of cardiac myocyte function[2]. We hypothesize that AL-LCs cause an overloading of chaperone / degradative pathways which normally control misfolded proteins. This puts a drain on ATP energy stores and places overwhelming stress on the cell resulting in an accumulation of reactive oxygen species. We anticipate that there is an increase in growth factors such as FGF-2 as a protective response to the oxidative stress. We predict that AL-LCs mediate the FGF-2 which in turn causes an increase in sulfation of secreted glycosaminoglycans and suppresses the production of ROS.

I would like to thank the Grunebaum Cancer Research Foundation for supporting my research.

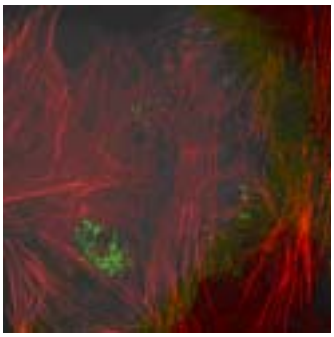

Figure 1. Confocal microscope image. Amyloidogenic LCs (green) is found to localize in a perinuclear punctate pattern in cardiac fibroblasts by 4 hours. A phalloidin dye (red) labels actin cytoarchitecture.

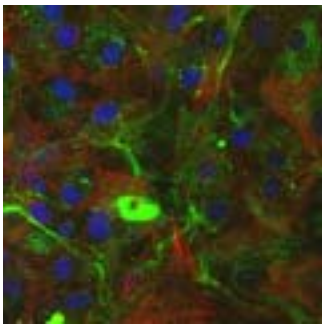

Figure 2. Confocal microscope image. Amyloidogenic LC (green) is found to form filamentous structures and aggregates on cardiac fibroblasts at longer incubation times (3 days). A phalloidin dye (red) labels actin cytoarchitecture and ToPro-3 (blue) labels nuclei.

ENDNOTES

1 Pascali E: Diagnosis and treatment of primary amyloidosis. Crit Rev Oncol Hematol 1995, 19:149-181

2 Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, Apstein CS, Liao R: Human Amyloidogenic Light Chains Directly Impair Cardiomyocyte Function Through an Increase in Cellular Oxidant Stress. Circ Res 2004

THE TROPHIC EFFECTS OF GASTRIN ARE MEDIATED BY ATTENUATION OF PPARgð SUPPRESSION OF CELL GROWTH

Albert Chang

Gastrin is a gastrointestinal peptide hormone secreted principally by the G-cells in the gastric antrum. Gastrin was discovered to be a potent gastric acid secretagogue, but now gastrin has been shown to have significant trophic properties in the gastrointestinal (GI) tract. In addition to stimulating the growth of normal GI epithelial cells, the trophic effect of gastrin on neoplastic cells, and in particular colorectal cancer (CRC) cells, has been well documented *in vivo* and *in vitro*.

In a recent large epidemiologic study of >100,000 individuals, Thorburn *et al*. found that prolonged hypergastrinemia comprised a risk factor for the development of CRC. Previous studies have shown that CRC cells also aberrantly produce gastrin peptides and exhibit increased expression of both wild-type and spliced gastrin receptors (CCK-2R), thus resulting in increased endocrine and autocrine (or paracrine) stimulation of cell growth. Furthermore, studies with transgenic mice overexpressing gastrin have demonstrated increased proliferation of the gastric and colonic epithelium after eight months. When these mice were followed for longer periods (~20 months), an increased tendency to develop neoplasia was observed. These studies strongly suggest a role for gastrin in GI cell proliferation and carcinogenesis.

(continued on back page)

The History of the Grunebaum Foundation at Boston University School of Medicine

Douglas V. Faller, Ph.D., M.D.
Grunebaum Professor in Cancer Research
Director, Cancer Center
Vice-Chair, Division of Medicine
Professor of Medicine, Biochemistry, Microbiology, Pediatrics, Pathology and Laboratory Medicine
Boston University School of Medicine

The support of the Grunebaum Foundation has played a major role in the training of physician-scientists at Boston University School of Medicine for over two decades. The foresight of the Foundation in choosing to support the training of physician-scientists occurred at a time in the history of medical education in the United States when fewer and fewer physicians were selecting a career in basic or clinical research. This was due, in large part, to decreasing opportunities for physicians to receive training in basic and translational research during their medical school experience. Both the competition with basic Ph.D.-trained investigators for fellowship opportunities, and the significant financial constraints on extending their time in medical school, served to discourage both medical students and postgraduate physicians from a career in research.

Against this concerning trend, the Grunebaum Foundation specifically targeted medical students, or in the case of Boston University School of Medicine M.D./Ph.D. students, for support. The fellowships provided by the Grunebaum Foundation therefore allowed physicians-in-training who were interested in a career in medical research the opportunity to compete for fellowship support and alleviate in part at least some of the obstacles facing physicians as they contemplate a career in medical research.

At Boston University School of Medicine, two M.D./ Ph.D. students per year have been selected as recipients of the Grunebaum Fellowship. The Fellowship Committee felt that M.D./Ph.D. students would be the most likely to pursue careers in medical research. Candidates for the Fellowship, usually students at the midpoint of their doctoral dissertation research, apply to a Committee established exclusively for the purpose of ranking the applicants and choosing the Fellows each year. The two Fellows are selected on the basis of their academic accomplishments, the cancer focus of their research project, the laboratory in which they work, and their potential for a career in cancer research. Competition for these Fellowships is fierce, with four times as many qualified student applying as eventual awardees. As a testimony to the excellence of the students eventually selected for the Grunebaum Fellowships, we have found

(continued on back page)

The History of the Grunebaum Foundation at BU

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that the recipients of the Cooperband Award and the Wein Award in the graduating medical student class each year are almost invariable past Grunebaum Fellows.

Recently, the Board of the Grunebaum Foundation chose to amplify even further their impact on cancer research and the training of future cancer researchers at Boston University School of Medicine by establishing and endowing the Grunebaum Chair and Professorship of Cancer Research. This unique endowed chair was established to support a renowned physician/scientist actively engaged in cancer research and in the education of medical and graduate students in cancer research. I have the extraordinary honor of having been selected as the first recipient of this Professorship, and am deeply indebted to the Foundation. In recognition of the seminal importance of the Grunebaum Fellowship Program to the education of a generation of physician-scientists in cancer research, Boston University School of Medicine has chosen to continue the Grunebaum Fellowship Program by supporting two new Grunebaum Fellows each year from institutional funds. The Grunebaum Professor of Cancer Research will be expected to take an active role in the development of their careers, regardless of the laboratory in which they are carrying out their research.

The foresight and commitment of the Grunebaum Foundation has thus clearly had an enormous impact on the training of physician-scientists in cancer biology and cancer medicine at Boston University School of Medicine. The establishment of the Grunebaum Chair and Professorship of Cancer Research will extend that impact into active translational cancer research programs as well as deepening the relationship to the Fellowship Program. Boston University School of Medicine, and a generation of its graduates, are perpetually grateful for the generosity of the Grunebaum Foundation and Family.

From Harvard

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management of cancer treatment-related ocular toxicities, and complicated cataract and ocular surface reconstructive surgery for cancer patients. I head the ocular protocol development for the Proton Therapy Center at MD Anderson Cancer Center that is scheduled to open in 2006. I also have an adjunct position at the Baylor College of Medicine in Ophthalmology, where I am engaged in active research and teaching collaborations.

Past Recipients of the Grunebaum Fellowship were able to explore the fields of basic, translational and/or clinical cancer research at pivotal points in their medical careers. As a direct result, each of them have resolved to make research and academic medicine a part of their lives. Harvard Medical School is grateful for the generosity of the Karin Grunebaum Foundation and for the part they play in the development of our students.

Malcolm Cox, M.D., Dean
Harvard Medical School
Elaine Field Glebus, MPA/HA
Director of Funded Opportunities

FROM THE TRUSTEES

The trustees of the Foundation want to remind everyone that the support given to the students is possible only through private donations and the generous contributions from those who have benefited from the foundation and those who are dedicated to the hope for a cancer-free world. We ask that you send your tax- free donations to: KGCRF 85 Sherman Street #8, Cambridge, MA 01940. Tax ID # given upon request.

The Trophic Effects of Gastrin..... Dr. Chang

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Although the trophic effects of gastrin have been well documented, the molecular and intracellular mechanisms by which gastrin regulates the growth of cells in the GI tract have not been fully elucidated. Many studies have previously reported that stimulation of the CCK-2R by gastrin activates various signal transduction pathways implicated in cell proliferation, including phospholipase C, *c-src* like tyrosine kinases, p125 FAK, phosphatidylinositol 3-kinase (PI3K), and the mitogen activated protein kinases (MAPK), which include ERK, JNK, and p38 kinase. However, studies downstream of these signal transduction pathways involving gastrin have, to date, been limited. For example, the peroxisome proliferator activated receptor gamma (PPARgð) is a downstream target of ERK and JNK, and gastrin has been shown to activate ERK and JNK. However, the relationship between gastrin and PPARgð has not been evaluated. Understanding the mechanisms by which gastrin promotes growth in the gastrointestinal tract through its downstream mediators is beneficial for the development of future therapies treating GI malignancies.PPARgð, a member of the nuclear hormone receptor family, functions as a transcription factor to regulate several biological processes, including growth and differentiation. PPARgð has been shown to modulate the growth of cells in various organs. Normal human colonic mucosa, colon adenocarcinoma, and cultured CRC cells express high levels of PPARgð. Activation of PPARgð in cultured colon cells induces growth inhibition and differentiation, reverses the malignant phenotype, and promotes apoptosis. For example, PPARg activation in CRC cells results in both an increase in the cyclin dependent kinase inhibitors, p21 and p27, which repress cell cycle progression, leading to a decrease in cell growth and an increase in the differentiation of cancer cells, and upregulation of caspase activity, resulting in DNA fragmentation and apoptosis. Moreover, a recent study demonstrated that 8% of primary colorectal tumors harbor a functional mutation in one allele of the PPARgð gene, further supporting the role of PPARgð as a tumor suppressor in humans.

Despite these observations, the anti-neoplastic effects of PPARgð remain controversial. For example, in the APC knockout mouse, a model of human hereditary familial adenomatous polyposis due to a mutation in the adenomatous polyposis coli tumor suppressor gene, the activation of PPARgð leads to an increase in tumorigenesis. Therefore, more studies are needed to determine the role of PPARgð in cell growth and proliferation. The purpose of our study is to investigate the relationship between gastrin and PPARgð in colorectal cancer. We believe that gastrin may promote growth through regulation of PPARgð.

Preliminary studies show that DLD-1, a human CRC cell line, expresses high levels of functional CCK-2R receptors. To assess if these cells express functional PPARgð receptors, ciglitazone and rosiglitazone, which are drugs in the thiazolidinedione class and known PPARgð agonists, were used. Ciglitazone and rosiglitazone does dependently inhibited DLD-1 cell growth after 24 h. When cells were cultured in the presence of amidated gastrin-17 (G-17) for 24 h, a significant increase in growth was detected. Furthermore, when DLD-1 cells were cultured in G-17 for 24 h, the suppression in cell growth seen with rosiglitazone and ciglitazone treatment was attenuated. To gain more insight into the mechanisms by which gastrin attenuates PPARg suppression of cell growth, we will determine if gastrin decreases the expression of PPARgð mRNA levels through quantitative polymerase chain reaction. We will also determine if gastrin promotes the degradation of PPARgð protein by western analysis. In addition, we will investigate the signal transduction pathways by which gastrin decreases PPARgð levels. Knowledge of the mechanisms by which gastrin attenuates PPARg growth suppression will provide valuable insight in future therapies for colorectal cancer.