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KARIN GRUNEBAUM
cancer research foundation

November 2024 - Volume 21

From the Chair

Dear Friends of the Karin Grunebaum Cancer Research Foundation:

As many of you know (since I keep repeating it to everyone I meet), we are thrilled that one of our KGCRF Fellows (Drew Weismann, (1984-86) won the 2023 Noble Prize in Medicine. Since we have been awarding cancer research Fellowships for 58 years (Trustee Michael Droller, 1966 was the first), that got me thinking about the state of current cancer research work being done by our prior Fellows.

One of our most renowned recent Fellows is Trustee Genevieve Boland, (2016). I asked her and Fellow Russell Jenkins (2019) to tell me about their current research, and they kindly filled me in….

Over the past ten years immunotherapy has transformed metastatic melanoma into a potentially curable disease. However, more than half of patients do not respond to existing treatments, leaving their outlook poor. We have now entered a new era of "cellular immunotherapy" offering new hope for these patients. These treatments use a patient's own immune cells, known as tumor infiltrating lymphocytes (TIL), as a tailor-made "living drug" to attack and destroy melanoma. This process involves surgically removing a tumor, isolating the immune cells within it, and multiplying those cells to large numbers. The cells are then infused back into the patient, along with medicines that stimulate the cells to multiply and seek out and destroy tumors. The result is prolonged remissions for some patients who have exhausted other options. Cellular therapy is logistically complex, requiring a large, multidisciplinary team to care for patients, and few academic cancer centers can provide this level of care. Behind the scenes, some of the world's leading immunologists are conducting pioneering research to elucidate how TIL cells destroy tumors, how tumors can sometimes evade their effects and how to design next-generation, "smarter" TIL. We have only scratched the surface. The potential of TIL therapy to treat melanoma and other cancers extends far beyond where we are today. Importantly, at present, only 1 in 3 patients benefit from TIL treatment, and the precise reasons why TIL therapy works for some patients and not others remain unknown. Currently, our research team is focused on improving the effectiveness of TIL therapy for patients with treatment-refractory melanoma and to leverage these insights to the treatment of other cancers.

Last year I also told you about Fellow Neil Ganem, (2014-2016) and his current work on the cancer-killing protein Kif18A, which is in continuing Phase 1 trials.

These trials are initially targeting breast or ovarian cancer, but some trials also include patients with other cancer types as well (esophageal, gastric, uterine, colon, bladder, head and neck). There are hundreds of patients already involved in these promising tests.

If you look at the Foundation's website: www.KGCRF.org, under the heading, "Focus on Research," you will find a list of former Fellows who are directly involved in either academic or commercial research on all modalities of cancer.

I like to think that we provided the "seed" which allowed this type of wide-ranging significant research to grow and prosper over the past half century. I'm sure that many of our other Fellows have also achieved successes in combatting this dreaded disease, and I would be most interested in hearing about those successes (and even about the failures). Please let me know at: stevenwallach561@gmail.com.

Thank you for the success we have enjoyed over the years; I am looking forward to more stories to share with you in the future.

Sincerely,

Steven Wallach

Chairperson

From Boston University Medical School

Julie Palmer, M.P.H., ScD
Karin Grunebaum Professor in Cancer Research, Boston University Chobanian and Avedisian School of Medicine, Director Slone Epidemiology Center; Co-Director, Boston University-Boston Medical Cancer Center

Dr. Julie Palmer, the Karin Grunebaum Professor in Cancer Research at Boston University Chobanian & Avedisian School of Medicine, recently had her work published in Environmental Research journal.

Summary
Large Study of Hair Relaxers Among Black Women Finds Increased Risk of Uterine Cancer

Chemical hair relaxers for straightening curly or tightly coiled hair are heavily marketed to and commonly used by Black women. These products may contain potentially harmful ingredients, including chemicals known as endocrine disruptors, which can be absorbed via inhalation or through the skin. Prior studies have linked these chemicals to a range of women's reproductive health outcomes. The Boston University Black Women's Health Study was started in 1995 to address reasons for the disproportionately high rates of many diseases among Black women. 59,000 self-identified Black women from across the U.S. enrolled in the study in 1995 and have completed health questionnaires every two years since that time. The 1997 questionnaire included detailed questions on use of hair relaxers, including frequency of use, age at first use, and number of years using relaxers. Study investigators, including senior author Dr. Julie Palmer, conducted an analysis to examine whether use of hair relaxers was related to subsequent risk of developing endometrial (uterine) cancer. Among over 45,000 participants who answered those questions and had an intact uterus, there were 347 cases of uterine cancer during the following 22 years. Women who reported using hair relaxers at least two times a years for five or more years had 1.5 times the risk of uterine cancer compared to those who never or rarely used hair relaxers, a 50% increase. This association was primarily seen in postmenopausal women. These results confirm earlier results from a smaller study conducted by researchers at the National Institute of Environmental Health Sciences. Given these findings, identification of safer alternatives to straightening hair, stricter regulation of cosmetic products, and policies to prohibit discrimination against natural hair such as the CROWN Act could represent important steps toward prevention of uterine cancer.

The published paper can be found at https://www.sciencedirect.com/science/article/abs/pii/S0013935123020327

Full citation:
Bertrand KA, Delp L, Coogan PF, Cozier YC, Lenzy YM, Rosenberg L, Palmer JR. Hair relaxer use and risk of uterine cancer in the Black Women's Health Study. Environ Res. 2023 Dec 15;239(Pt 1):117228. doi: 10.1016/j.envres.2023.117228. Epub 2023 Oct 10. PMID: 37821068; PMCID: PMC10842360.

Incoming Fellow

Thomas L. Clarke, Ph.D.
Assistant Professor, Pathology and Laboratory Medicine, Chobanian and Avedisian School of Medicine, Boston University

Synthetic killer mRNAs as novel innate immune inspired cancer immunotherapies

Background:
My lab studies the fundamental mechanisms of innate immune signaling, focusing on how and why cells die during homeostasis and disease. We investigate cell-intrinsic defenses and intercellular communication that are broadly relevant in vaccination, infectious disease, and cancer. My unique educational background in physics, chemistry, microbiology, cell biology, immunology, and genomics allows me to apply quantitative analyses to single-cell studies. I have also built a team with complementary skills and diverse perspectives that enables us to examine cell death at multiple levels from single cells to whole organisms.

Our research combines candidate-driven hypotheses and cutting-edge technologies for unbiased, high-throughput screening to tackle important questions about the causes and consequences of cell death. One technology we developed in the lab we term "precision screening" that combines synthetic biology sufficiency modeling of signal transduction, including different forms of cell death, with genome-wide CRISPR/Cas perturbations to determine unexpected and novel regulation of distinct steps within a signaling cascade. Using this established technology combined with newer forms of synthetic biology utilizing optimized modified mRNA and lipid nanoparticle reagents, we are mapping resistance and susceptibility to specific cell death mechanisms focusing on cell lysis by recently discovered gasdermin family1-4. We have focused our initial projects on unexpected and novel metabolic axis of cell death control5,6.

Tumors represent a dysregulation in cell death and proliferation7. Transformed cells develop resistance to intrinsic checkpoints that control homeostatic cell death7. Moreover, cancer cells evade immune recognition needed for extrinsically induced cell death8. Besides cancer cells, stromal and immune cell types exist within a developing tumor and are programmed by the tumor microenvironment. At homeostasis, tissue-resident myeloid cells, particularly macrophages, serve tolerogenic roles by degrading

dying cells before they are able to induce inflammation. However, the immunosuppressive function of these macrophages limits the release of damage-associated molecular patterns (DAMPs) that stimulate inflammation. Moreover, macrophage degradation of protein antigens prevents effective presentation of cancer cell peptides by dendritic cells (DCs) as targets of the adaptive immune system9. Our overall goal is to reprogram cancer-myeloid communication via cell death and stress responses to induce anti-tumor immunity. Using new technological approaches, our planned studies will elucidate and leverage innate immune mechanisms to control tumor growth.

Proposed Studies:
Tumor resident myeloid cells and cancer cells are strong candidates for manipulation by cell death pathways and inflammatory modules. By achieving the following goals, we will uncover both intrinsic and extrinsic mechanisms by which cell death pathways influence tumor progression and anti-tumor immunity. Our work will enable development of new strategies to target resistance mechanisms or susceptibility targets within immunosuppressive macrophages and cancer cells while also promoting productive antigen presenting activities of DCs to improve cancer therapies through principles of innate immunity and synthetic biology.

Goal 1: Define regulation of innate immune and cell death pathways in myeloid and cancer cells. The scientific objective of this aim is to characterize innate immune and stress responses that occur in response to delivery of engineered cell death executioners and traditional cancer therapies. Based on our prior expertise and the implication that certain forms of cell death induce inflammation, we will first focus on newly discovered regulators of lytic cell death pathways10-12. We hypothesize that heterogeneity in metabolic parameters and stress responses impact cell death pathways based on cell type and cell state. To test this hypothesis, we have developed synthetic and inducible models of cell death execution using retroviral-mediated transduction (Figure 1). We further have developed analogous mRNA reagents to create a new modality of proof-of-concept cell death immunotherapy.

Goal 2: Determine antigen presentation and adaptive immune consequences of cell death pathways. The scientific objective of this aim is to define how cell death programs in neighboring cells impact antigen presentation in DCs. DCs represent a necessary bridge between cancer cell death and stimulation of adaptive immune responses against cancer. How different forms of cancer cell death affect the ability of DCs to engulf, process, migrate, and present antigens is largely unknown. We hypothesize that different forms of cell death in neighboring cells will affect dendritic cell viability and efficacy of antigen presentation. Cell death, especially during cell lysis, releases endogenous inflammatory ligands known as damage-associated molecular patterns (DAMPs) that activate DCs. Dying cancer cells also provide corpses full of protein antigens for DC-mediated antigen presentation on major histocompatibility molecules I and II (MHCI/II) that stimulate CD8 and CD4 T cells respectively. A head-to-head comparison of cell death executioners in cancer cells is required to benchmark the ability of different forms of cell death to affect professional antigen presentation and stimulation of adaptive immunity. We will use mechanistic co-culture studies with primary DCs and primary antigen specific T cells to investigate how different pathways of cell death induced in cancer cells affect dendritic cell viability and activation of adaptive immunity.

Significance and Impact:
Upon completion of these studies, we will have defined susceptibility and resistance to cell death effectors and inflammatory circuits in important tumor resident cells including cancer cells, tumor-associated macrophages, and dendritic cells that will inform innate immune-based cancer therapies. These studies will inform next-generation immunotherapies that are inspired by innate immune signal transduction and cell death pathways. We will understand better how the metabolic landscape of tumor associated cells influences cell death fate decisions.

References:

1. Shi, J. et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature* (2015).
2. Kayagaki, N. et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. *Nature* (2015).
3. Ding, J. et al. Pore-forming activity and structural autoinhibition of the gasdermin family. *Nature* (2016).
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Incoming Fellow

Charlie Evavold, PhD
Ragon Fellow
Mass General, MIT, and Harvard

Synthetic killer mRNAs as novel innate immune inspired cancer immunotherapies

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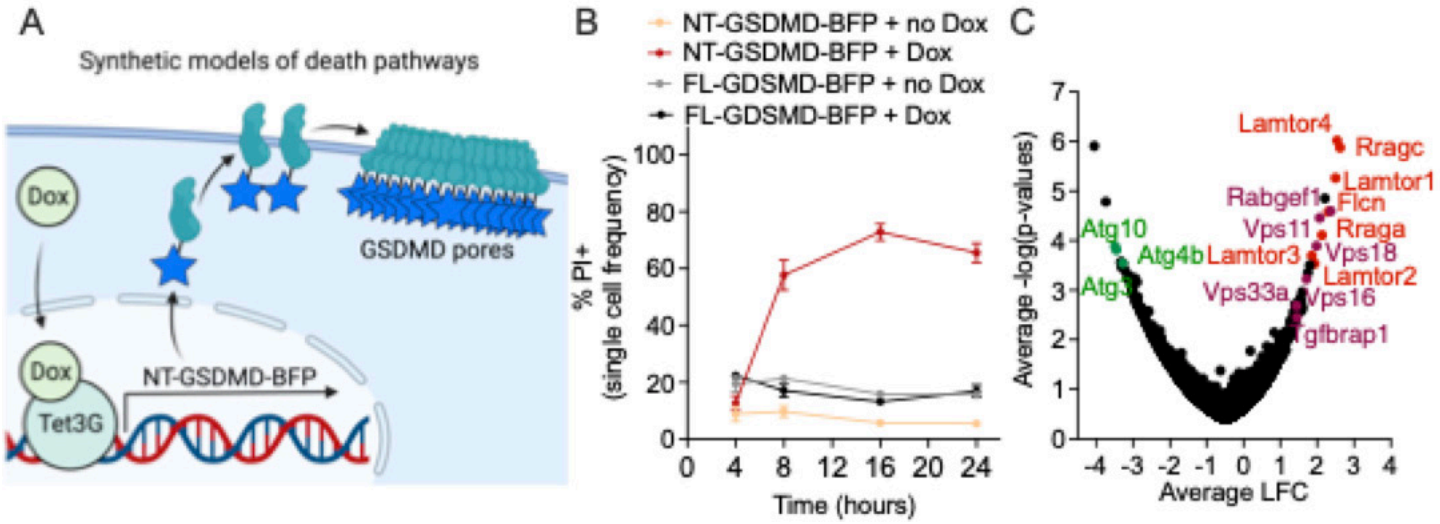

Figure 1: *Synthetic cell death induction as tools and therapies in innate immunity and cancer biology. A) Cartoon schematic of engineerable synthetic models of pyroptosis lytic cell death programs through induction of active fragments of gasdermin family of proteins. B) Propidium iodide (PI) staining as a single cell frequency metric of induced pore formation and cell death mediated by synthetic pyroptosis in macrophages. C) Survivor enrichment analysis after sorting for PI negative, tagBFP positive (expression control for NT-GSDMD fragment induction) cells after Doxycycline (Dox) induction of NT-GSDMD pore forming fragment to identify unexpected metabolic positive and negative regulators of inflammatory cell death.*

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Outgoing Fellow

Christopher Garris, PhD
Assistant Professor of Pathology
Harvard Medical School

Progress Report – Karin Grunebaum Cancer Research Foundation

Over the past year, I have established platforms for using messenger RNA (mRNA) as therapeutics in mouse cancer models. I have had a longstanding interest in activating dendritic cells (DC), an essential type of immune cell that can initiate long-term adaptive immune Responses from T cells. These studies have resulted in one published manuscript where I am serving as senior corresponding author. I was also part of a high-profile review published in Immunity in Fall 2023, where we advocate for DCs as critical "shepherds" of anti-tumor immunity.

We have identified conserved expression of critical components of the non-canonical NFkB pathway (nc-NFkB) in myeloid cells from mouse and human tumors. Specifically, we found that activated Dendritic Cells (DC), essential antigen-presenting cells that shepherd adaptive immune T lymphocyte responses, could be activated using the nc-NFkB pathway, critical in controlling T cell anti-tumor immunity. **We therefore hypothesized that agonistic targeting of DCs is the preferred method to turn T cell non-inflamed "cold" tumors into "hot" tumors.** DCs can also be used as adoptive cellular therapies, where transferred DC can direct T-cell immunity.

During this funding course, we have used DCs, programmed with mRNA, as experimental therapeutics in cancer. When complexed into a lipid nanoparticle (LNP), we show that minute quantities of mRNA can activate DCs and confer protective immunity in a mouse melanoma model. This is explained graphically in Figure 1.

We then verified that DCs could be activated by LNP-mRNA by examining the expression of DC-produced IL-12, a critical cytokine with anti-tumor functions (Figure 2). These mRNA-programmed DCs also stimulated T-cell proliferation in vitro (Figure 2). Collectively, these data show that LNP-mRNA-educated DCs can drive T-cell responses.

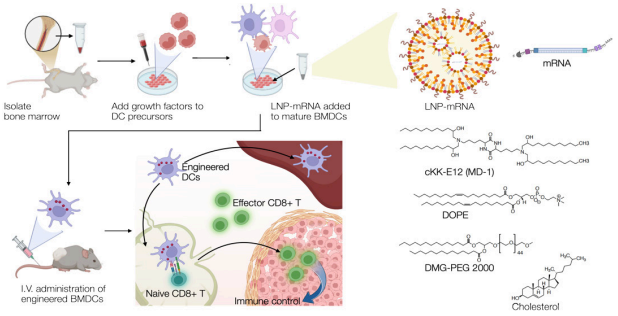

Figure 1. *Diagram of Experimental Approach. Bone marrow is isolated from mice and DCs are grown ex vivo in tissue culture. After DC differentiation, LNP-mRNA (encoding the model antigen Ovalbumin) is added to DC cultures, and DCs are then delivered to recipient mice. Mice receiving DCs are then challenged with B16-OVA melanomas.*

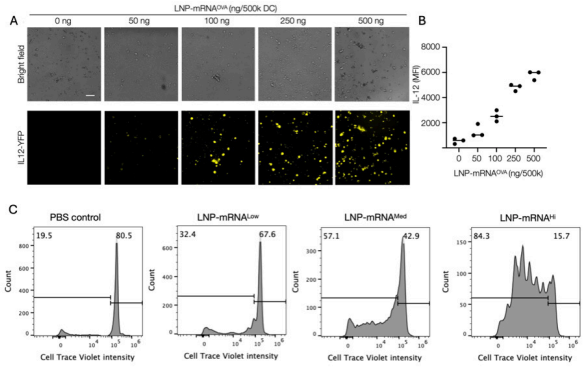

Figure 2. *Stimulatory activity of mRNA-educated DCs. (A) DCs from IL-12-eYFP reporter mice were treated with a dose titration of LNP-mRNA. Yellow reporter signal indicates IL-12 expression within DCs. (B) Quantification of data shown in A. (C) LNP-mRNA treated DCs were co-cultured with OT-I CD8 T cells, which are specific for ovalbumin antigen, which is encoded by the mRNA. T cells were labeled with Cell Trace Violet, and this cell marker dye dilutes with successive cell proliferation.*

We next tested whether these DCs could stimulate immune responses in vivo. We started by educating DCs ex vivo with LNP-mRNA and then transferring activated DCs to recipient mice, as outlined in (Figure 3). Using minute quantities of mRNA (0.5 ug), we could potently protect vaccinated mice from challenge with B16-OVA melanoma (Figure 3). These data show that we can feasibly use mRNA encoding antigen to generate DC-based adoptive cell therapy that confers protection against tumor growth.

Knowing that DCs could confer protective immunity, we next set out to examine the biodistribution of intravenously dosed DCs. Treating DCs ex vivo with firefly luciferase encoding mRNA enabled us to track DC distribution in vivo (Figure 4). This system allows for an understanding of DC tropism. We found that administered DCs could be tracked in living mice (left panel) and that DCs collected primarily within the lung and spleen, altogether avoiding the liver. We found this interesting as most directly administered nanoparticles have high liver accumulation, which can contribute to treatment toxicity. Furthermore, since the expression of luciferase signal largely depends on viable, membrane-intact cells, we demonstrate that the DCs we transfer to mice are living and biologically active.

We had previously shown that in tumor-activated DCs, the non-canonical NF-kB pathway was enriched. Genetic loss of the key activating kinase in the nc-NF-kB pathway, NF-kB-inducing kinase (NIK), eliminated anti-tumor CD8 T cell responses and response to anti-PD-1 immunotherapy. To both show the necessity of the nc-NF-kB pathway and the ability to genetically edit adoptively transferred DCs for in vivo vaccination, we

treated bone marrow-derived DCs from NIKflox mice with cre recombinase encoding mRNA, which selectively deletes NIK functionality in DCs. We delivered ovalbumin antigen encoding mRNA as outlined in Figure 5. Assessing vaccination response in recipient mice by measuring blood-derived OVA antigen-specific CD8 T cells, we found that depletion of NIK in DCs eliminated the OVA-specific CD8 T cell response. This was consistent with our prior results, showing that a DC-specific NIK defect could impair anti-tumor immunity. These data further emphasize the importance of NIK, and possibly the nc-NF-kB pathway, in DC-associated cancer therapies. Likewise, we found that tumor growth was significantly higher in NIK-depleted DC vaccination conditions, suggesting that NIK-expressing DCs elicited CD8 T cell responses.

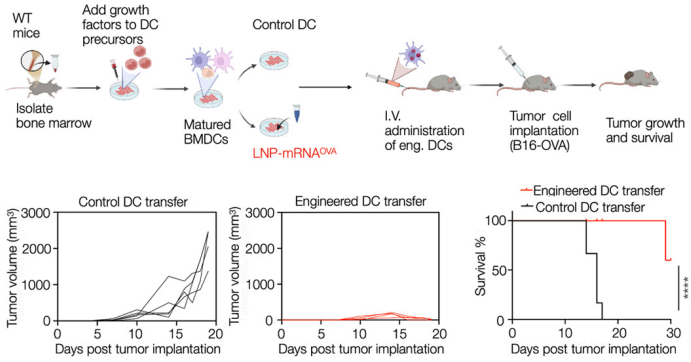

Figure 3. *In vivo protection against tumor challenge. DCs educated with LNP-mRNA were given to naïve recipient mice. Antigen loaded versus unloaded control DCs were then challenged with B16-OVA melanoma and monitored for tumor growth and survival. Engineered DCs conferred substantial protection against tumor growth, and led to a significant enhancement of survival. **** $p < 0.0001$, Log-Rank Test.*

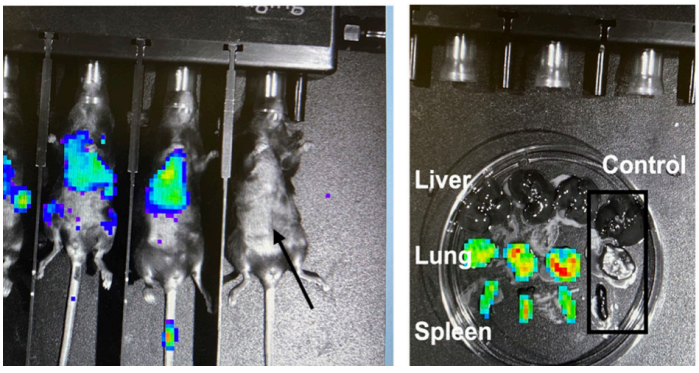

Figure 4. *In vivo biodistribution of DCs. DCs educated with luciferase mRNA were administered intravenously to mice. Intact, living mice (left) could have substantial signal resolved by IVIS imaging. Dissection of these mice (right) revealed that transferred DC located mostly within the lung and spleen, yet completely avoided the liver.*

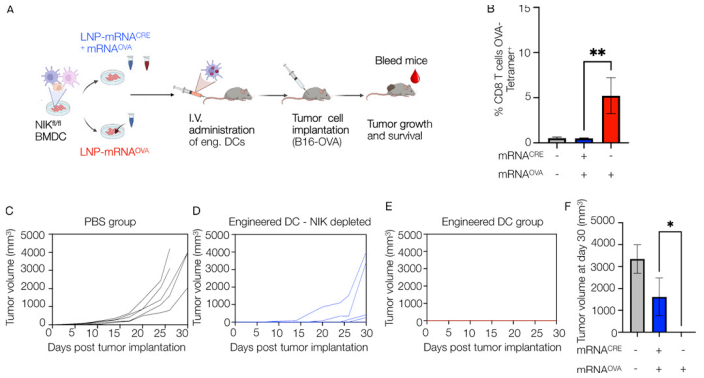

Figure 5. *Depletion of NIK in DCs impairs vaccination response. (A) Diagram of experimental approach. (B) DC vaccinated mice were bled 10 days after DC dosing and stained using OVA-specific T cell tetramers. OVA-reactive CD8 T cells were measured in each condition by flow cytometry. (C-F) Tumor growth of B16-OVA tumors from mice treated with DC vaccination. NIK depleted DCs had significantly diminished vaccination capacity compared to control DCs. * $p < 0.05$; One-way ANOVA with multiple comparisons.*

Conclusions

Over the past year, we have established mRNA and therapeutic delivery platforms targeting DCs. These initial proof of concept studies show the feasibility and benefits of using mRNA-educated DCs for adoptive cellular therapies. We have further shown using a model of genetic NIK deficiency that DC-specific loss of function of NIK impairs the generation of T cell responses in vivo and can also impair anti-tumor immunity, with significantly more tumor growth in NIK-depleted settings.

Publications Associated with the Funding Period

1. Pittet, M.J., Di Pilato, M., Garris, C., and Mempel, T.R. (2023) Dendritic cells as shepherds of T cell immunity in cancer. *Immunity*, 56, 2218–2230.

2. Das, R., Ge, X., Fan, F., Weissleder, R., Garris, C. (2024) LNP-mRNA engineered DC Adoptive Cell Therapy Enhances Cancer Immune Response. *Small Methods*, 2400633.

Outgoing Fellow

Daniel Dempsey, Ph.D.
Assistant Professor of Dermatology and Pharmacology, Physiology & Biophysics
Boston University Chobanian and Avedisian School of Medicine

I would first like to thank the trustees of the Foundation for your generous contribution to my research program by supporting me as the 2023-2024 Karin Grunebaum Faculty Research Fellow at the Boston University Chobanian & Avedisian School of Medicine. The fellowship has been vital to establishing our research team and program and has directly contributed to the success of several projects. These projects include 1) generating chemical probes to discover the cellular machinery that stabilizes proteins in cancer (detailed below) and 2) assess the molecular mechanisms of how RNA-modifying enzymes are regulated. Thanks to the foundation's support, the latter research is now being funded by the National Institutes of Health. The fellowship has helped set the trajectory for our team's future success in discovering novel molecular mechanisms of cancer that can be targeted with therapeutics.

Background

The American Cancer Society projects that there will be over two million new cases and over 600,000 cancer-related deaths in the United States in 2024, making cancer the second leading cause of death. Therefore, understanding the molecular devices that cancer uses to promote its carcinogenesis and protect its key drivers is vital for discovering new therapeutic targets. The mission of my laboratory is to use chemical, biophysical, and cellular approaches to understand the basic biological mechanisms of proteins essential to human health and cancer biology. We also aim to advance new chemical approaches to investigate protein function and regulation and cancer biology. One aspect of our work is to understand how ubiquitin influences the cellular functions of proteins and to characterize the molecular machinery that is responsible for its presence. Ubiquitin is an important modification that regulates the cellular function of proteins, including directing them to be destroyed. Our long-term goal is to use this information to exploit the natural function of the ubiquitin-proteasome system (UPS) to help clear proteins that drive cancer; however, the molecular machinery that stabilizes oncoproteins is not well defined. Deubiquitinases (DUBs) are the class of enzymes responsible for removing ubiquitin from proteins and serve a crucial role in promoting protein stability. Discovering DUBs that directly target ubiquitinated proteins has been challenging, mainly due to the lack of chemical tools to interrogate this system. In my lab, we are generating protein chemical probes that will reveal DUBs that target key oncoproteins in cancer.

Current Work

We hypothesize that deubiquitinases may serve as key molecular devices that promote the stability of proteins that drive disease. Thus, one of our goals is to generate new protein chemical probes that will reveal the DUBs responsible for this action. The funds through the fellowship were used to optimize the chemistry to generate the chemical probe. We are happy to report that we have successfully generated our first probe (Fig. 1a-c) and are currently testing it in colorectal, lung, pancreatic, and skin cancer cells. The probes are engineered to include a full-length protein that causes cancer with ubiquitin installed at its biologically relevant site, where the linkage between the ubiquitin and protein is modified to selectively trap DUBs. We are using this probe to selectively trap, enrich, and discover DUBs by mass spectrometry. We will validate DUBs discovered by our probe using recombinantly expressed proteins and cell-based assays. We will also assess the targetability of the DUBs in cancer and screen for compounds that inhibit their enzymatic function. Overall, our goal is to identify new targetable vulnerabilities within the UPS while also providing a comprehensive understanding of ubiquitin's impact on the function of these proteins on which cancer vitally depends for its proliferation and survival.

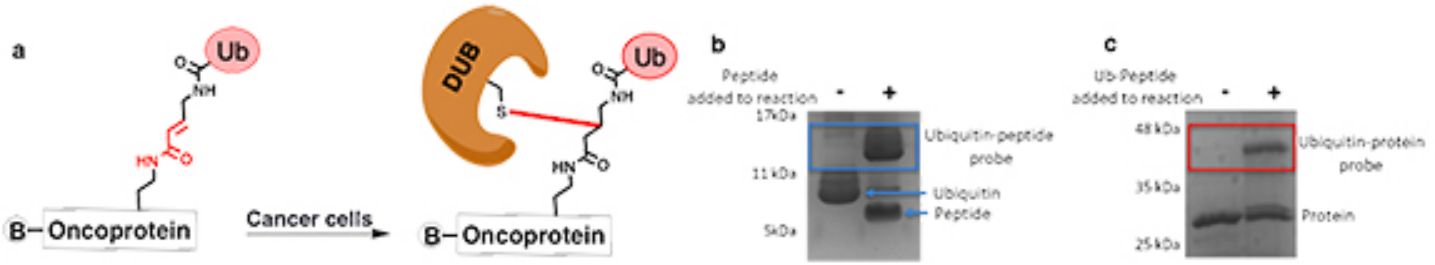

Figure 1. *Ubiquityl-protein activity-based probe. a. Scheme depicting strategy to trap deubiquitinases by covalency. B represents biotin and Ub is ubiquitin. b. Gel showing successful generation of a ubiquitinated peptide probe of an oncoprotein that was used to generate the full-length protein probe. Blue box is the Ub-peptide product. c. Gel showing successful generation of a ubiquityl-protein probe of an oncoprotein that is being used to identify DUBs in cancer cell lines. Red box is the Ub-protein product.*

Professional Development Curriculum, Cancer Biology Program at Harvard

The Cancer Biology Program at Harvard provides curricular and extracurricular activities both to teach graduate students about cutting-edge research and to hone professional skills. As a result, the Program fosters a collaborative community of researchers that is both stimulating innovation and paving the way for future discoveries. Diverse programming enriches students' educational experience – from designing and executing courses highlighting the forefront of cancer research, to organizing seminars and symposia that bring together the brightest scientific minds, to creating opportunities for mentoring and networking where students interact with faculty, industry leaders, and professionals from other cancer-related fields.

Professional development activities and resources available to the students include the Karin Grunebaum Cancer Research Foundation poster competition, attendance at national and international meetings, conferences, courses and workshops in cancer biology and related topics, society memberships, computer supplies, and books. As future leaders, the graduate students share their knowledge by teaching, mentoring, and inspiring undergraduate students. Their commitment to research is pushing the boundaries of what is known about cancer, and their discoveries are disseminated in publications and conferences around the world.

The Foundation's generous gift to the graduate training at Harvard directly supports professional development of our students. The funds are used for KGCRF Poster Competition and Professional Development Awards and the KGCRF Career Catalyst Awards.

Karin Grunebaum Cancer Research Foundation Professional Development Awards

These are monetary prizes in the amount of $1,000 each that go towards professional development and are awarded for best posters during the Annual Spring Symposium and KGCRF Poster Competition. In 2024, we awarded:

Two KGCRF Rising Young Scientist Awards
(up to and including G3s)

- Cameron Fraser, G1, Biological Sciences in Public Health, Jessalyn Ubellacker Lab
  Poster title: *Sublethal lipid peroxidation in cancer cells in lymph nodes triggers systemic anti-cancer immunity*

- Alan Wong, G3, Biological and Biomedical Sciences, Naama Kanarek Lab
  Poster title: *In vivo CRISPR screen identifies copper metabolism as a vulnerability in ALL*

Two KGCRF Early Career Investigator Award (G4s and up)

- Monica Cassandras, G4, Biological and Biomedical Sciences, Judith Agudo Lab
  Poster title: *Chronic stress promotes immune evasion in breast cancer metastasis*

- Peter Georgiev, G4, Immunology, Arlene Sharpe & Marcia Haigis Labs
  Poster title: *Age-associated contraction of tumor-specific T cells impairs anti-tumor immunity*

KGCRF Rising Young Scientist Awards

(graduate years – G1, G2, and G3)

CAMERON FRASER | G1
Biological Sciences in Public Health
Jessalyn Ubellacker Lab

Sublethal lipid peroxidation in cancer cells in lymph nodes triggers systemic anti-cancer immunity

Cancer progression requires evading immune system responses, and T cell activation plays a critical role in initiating an adaptive immune response for widespread anti-tumor clearance. While there is existing evidence that inhibition of the crucial reducing enzyme glutathione peroxidase 4 (Gpx4) in cancer cells can lead to the secretion of damage-associated molecular patterns (DAMPs), there is limited understanding of the extent to which lipid peroxidation in cancer cells can mediate an adaptive immune response. The abundance of antigen-presenting cells and immune cell populations in the lymph node comprise an ideal microenvironment for dendritic cell/T cell cross-presentation and activation in the context of anti-cancer immunogenicity. Here, we demonstrate that inducing lipid peroxidation in lymph node cancer cells enhances systemic anti-cancer immunity by promoting antigen cross-presentation and T cell activation. Using murine breast and melanoma models with Gpx4 deletion, Gpx4-/- tumors grow comparably when engrafted into lymph nodes. We establish an ex vivo system to assess immune activity and show that CD8+ T cells from Gpx4-/- lymph node tumors exhibit enhanced cytotoxicity ex vivo compared to WT. Co-culturing CD8+ T cells with CD11c+ dendritic cells further enhances cytotoxicity. These findings suggest a novel mechanism for provoking systemic anti-cancer adaptive immunity—by inhibiting Gpx4 locally in melanoma and breast cancer cells within lymph nodes, thus triggering DAMP and cytokine production to initiate immune-mediated tumor clearance both locally in the lymph nodes, and systemically at distant metastatic sites.

ALAN WONG | G3
Biological and Biomedical Sciences
Naama Kanarek Lab

In vivo CRISPR screen identifies copper metabolism as a vulnerability in ALL

Acute Lymphoblastic Leukemia (ALL) is one of the most common childhood cancers and remains a significant cause of pediatric cancer mortality in the USA. Prophylactic chemotherapy delivered to the central nervous system (CNS) is a critical part of treatment because leukemia that spreads to the CNS is often fatal. However, CNS-directed chemotherapy is associated with serious side effects including long-term cognitive disability. Our goal is to identify cancer-specific vulnerabilities of leukemia cells in the CNS that can serve as therapeutic targets.

A unique but understudied aspect of leukemia in the CNS is that cancer cells are moving from the blood to a new and quite distinct metabolic environment: the cerebrospinal fluid. We hypothesize that adapting to this new metabolic environment creates unique and targetable weaknesses in spreading leukemia cells. To address this hypothesis, we conducted a targeted 172-gene in vivo metabolic CRISPR knockout screen in a xenograft murine model of acute lymphoblastic leukemia. Our screen revealed genes involved in copper metabolism and oxidative phosphorylation as in vivo dependencies in ALL. Knockout of the cell-surface copper importer SLC31A1 significantly reduces ALL growth in vivo in the periphery as well as in the cerebrospinal fluid. In vitro, perturbation of copper metabolism by SLC31A1 knockout leads to an isolated complex IV deficiency and reduced oxygen consumption, ultimately slowing cell proliferation. Cell proliferation in knockout cells is rescued by genetic restoration of the electron transport chain (ETC), or by providing exogenous nucleotide precursors, functionally linking copper import, ETC activity and nucleotide synthesis. Our ongoing work seeks to validate the efficacy of copper chelation in cell-line based and patient-derived xenograft models of ALL, as well as to evaluate the copper status of leukemia cells in vivo.

KGCRF Early Career Scientist Awards

(graduate years – G4 and up)

MONICA CASSANDRAS | G4
Biological and Biomedical Sciences
Judith Agudo Lab

Chronic stress promotes immune evasion in breast cancer metastasis

Metastasis occurs when disseminated tumor cells (DTCs) escape killing by surveilling cytotoxic immune cells. The mechanisms of DTC immune evasion are currently not well understood, and this represents a crucial barrier to developing effective therapies. We investigate this by utilizing our novel JEDI mouse, in which cytotoxic T cells target tumor cells for killing. By profiling the DTCs that successfully survive JEDI immune attack, we unexpectedly discovered that chronic stress hormone (glucocorticoid) signaling is a top driver of immune evasion in lung metastasis. This suggests that activation of the glucocorticoid receptor (GR) promotes an immune evasive state in DTCs. Indeed, patients with advanced breast cancer have higher levels of glucocorticoids, and elevated GR activity correlates with worse survival. Consistently, we found that mice with metastasis have significantly higher levels of circulating glucocorticoids. We determined that GR signaling in DTCs directly blocks cytotoxic lymphocyte killing to increase metastatic survival. Mechanistically, DTCs harness stress hormones to repress the death receptor FAS and acquire an overall anti-apoptotic phenotype. Exploiting the mechanisms by which tumor-intrinsic GR signaling prevents killing by cytotoxic immune cells represents promising new avenues for preventing metastasis and opens the door for new combinatorial treatments with current immunotherapy regimens.

PETER GEORGIEV | G4
Immunology
Arlene Sharpe & Marcia Haigis Labs

Age-associated contraction of tumor-specific T cells impairs anti-tumor immunity

Progressive decline of the adaptive immune system with increasing age coincides with a sharp increase in cancer incidence. In this study, we set out to understand whether deficits in anti-tumor immunity with advanced age promote tumor progression and/or drive resistance to immunotherapy. We find that multiple syngeneic cancers grow more rapidly in aged versus young adult mice, driven by dysfunctional CD8+ T cell responses. By systematically mapping immune cell profiles within tumors, we identify loss of tumor antigen-specific CD8+ T cells as a primary feature accelerating the growth of tumors in aged mice and driving resistance to immunotherapy. Administration of young antigen-specific T cells to aged mice delays tumor outgrowth and is sufficient to sensitize aged animals to PD-1 blockade. These studies reveal how age-associated CD8+ T cell dysfunction may license tumorigenesis in elderly patients and have important implications for the use of aged mice as pre-clinical models of aging and cancer.

Shout Outs

- **Dr. Genevieve Boland and Dr. Russell Jenkins** were both selected as one of the first recipients for the Breakthrough Krantz Award for projects that accelerate the most promising scientific concepts in cancer research
- **Dr. Filipe Carvalho** is the recipient of BCAN's 2023 Career Development Award. His project will stud overcoming resistance to chemo and IO in patients with MIBC
- **Dr. Filipe Carvalho** received the NCI Early-Stage Surgeon Scientist Program Award
- **Dr. Genevieve Boland** – Read more about the Boland Lb where researchers use the latest technology to analyze patient-derived materials, including tumors and blook samples to better understand interactions between tumors and the immune system. How Real Time Cancer Samples Are Leading to New Discoveries (mgriblog.org)
- **Dr. Russell Jenkins** explains how Cancer cells are Difference from Normal Cells How Are Cancer Cells Different? | Mass General Brigham

Congratulations to all our past Karin Grunebaum Cancer Research Fellows!

KGCRF Career Catalyst Awards for Fall 2023

Awardee: Collins Cheruiyot
Graduate Program: Immunology
Lab: Rob Manguso

KGCRF CCA Award: To support attendance & presentation at the SITC Metabolism at the Hub of Cancer and Immunity Conference

Awardee: Maggie Dreishpoon
Graduate Program: Biological and Biomedical Sciences
Lab: Alex Toker

KGCRF CCA Award: To support attendance at the annual AACR 2024.

Awardee: Breanna Titchen
Graduate Program: Biological and Biomedical Sciences
Lab: Eli Van Allen

KGCRF CCA Award: To support attendance & presentation at Single-Cell Cancer Biology Gordon Research Conference (GRC): Deciphering Tumor Ecosystems in Space and Time

Awardee: Tevis Vitale
Graduate Program: Biological and Biomedical Sciences
Lab: Pere Puigserver

KGCRF CCA Award: To support attendance at the CD1-MR1 conference in Tasmania, Australia.

Awardee: Jackson Weir
Graduate Program: Biological and Biomedical Sciences
Lab: Fei Chen

KGCRF CCA Award: To attendance at the Single-Cell Cancer Biology Gordon Research Conference (GRC): Deciphering Tumor Ecosystems in Space and Time.

Awardee: Collins Cheruiyot
"I am seeking support from the Karin Grunebaum Cancer Research Foundation Career Catalyst Awards (KGCRF CCA) to enhance my research efforts in exploiting tumor metabolism for ***the identification of novel immunotherapy targets****. My research to date has involved extensive in vitro genome-wide screenings to unearth novel dependencies in several cancer types, including melanoma, renal, lung and pancreatic cancers.*

A significant discovery from my research is the identification of the lipid metabolism enzyme FITM2 as an essential dependency in cancers exposed to inflammatory cytokines. The suppression of FITM2 leads to an accumulation of unsaturated lipids, resulting in mitochondrial dysfunction and cell death. More importantly, loss of the FITM2 enzyme dramatically improves the efficacy of cancer immunotherapy. ***My findings suggest that cancer cells exhibit metabolic plasticity, enabling adaptation to the environmental stresses within the tumor microenvironment (TME).***

The SITC Metabolism at the Hub of Cancer and Immunity conference to be held in Miami from March 10-12, 2024, presents ***a unique opportunity to further my research in cancer metabolism and immunotherapy. I aim to present my findings, partake in workshops, and engage in discussions with both peers and mentors****, including esteemed figures such as the host Dr. Hongbo Chi. The feedback received will be instrumental in refining my metabolism research and potentially forge new collaborations.*

Funding my participation at the SITC conference through the KGCRF CCA will not only support my professional development but also contribute to the broader goal of combating cancer through innovative immunotherapeutic strategies.*"*

Awardee: Maggie Dreishpoon
"I study cellular signaling and metabolism of cancer cells in the laboratory of Dr. Alex Toker. We focus on discovering new targetable vulnerabilities within the PI3K/AKT pathway, the most frequently altered pathway across all human cancers.

With a Karin Grunebaum Cancer Research Foundation Career Catalyst Award (KGCRF CCA) for graduate students, I would ***plan to attend the annual American Association for Cancer Research (AACR) conference****. The AACR Annual Meeting is the focal point of the cancer research community, where scientists, clinicians, health care professionals, survivors, patients, and advocates gather to share the latest advances in cancer science and medicine. From population science and prevention; to cancer biology, translational, and clinical studies; to survivorship and advocacy; the AACR Annual Meeting highlights the work of the best minds in cancer research from institutions all over the world.*

This opportunity would be an ***absolutely invaluable experience for me as a graduate student and early career scientist****. To be able to attend keynote lectures given by leading scientists and clinicians in the field from around the globe would teach me many valuable skills.*

I would learn optimal presentation skills and also ***be exposed to project design from the perspectives of scientists from different countries and across the United States*** *through lectures and poster sessions. I could* ***acquire skills in new experimental techniques from the educational sessions and methods workshops****. My current research would benefit from a more comprehensive understanding of project design and execution that I would learn through my experiences at the AACR conference. I will also have the opportunity to learn of other laboratories working on topics related to my research of interest and gain their insight when it comes to proposed models and*

mechanistic insights. I can also observe the distinct approaches that are being used to address cancer signaling and metabolism-related questions.

Attending the AACR conference would allow me to network outside of my own institution and potentially form collaborations by interacting with scientists who are interested in my field of research. My career would also benefit from my involvement in this conference. I would ***gain mentorship from different scientists and clinicians at all levels of their career trajectories and learn how to best plan my own trajectory to reach my goals****. I could also learn of new funding or career development opportunities from the cancer and biomedical research career fair sessions. For these and many more reasons than I can describe, my attendance at AACR as an early-career scientist would be invaluable. Thank you for considering my application for KGCRF CCA."*

Awardee: Breanna Titchen

"I am writing to apply for the Karin Grunebaum Cancer Research Foundation Career Catalyst Award (KGCRF CCA) for the professional development training opportunity of ***attending and presenting my dissertation research at the 2024 Single-Cell Cancer Biology Gordon Research Conference (GRC): Deciphering Tumor Ecosystems in Space and Time in June 2024*** *at Southern New Hampshire University in Manchester, NH. I am a PhD student in the Harvard GSAS Division of Medical Sciences Biological and Biomedical Sciences program, and my PhD dissertation projects are grounded in cancer biology and mechanisms of treatment resistance in cancer patients. As I have not attended or presented my research at a major research conference previously, and* ***this conference melds my scientific interests in cancer biology, and in particular characterizing tumor microenvironments and metastatic ecosystems with single-cell methods, as well as features expertise in areas I am hoping to gain exposure to****, I am eager to apply for this professional development training opportunity with the generous gift of the KGCRF CCA.*

My dissertation project is ***focused on deciphering mechanisms of treatment resistance in metastatic bladder cancer (mBC)****. To probe these mechanisms, I have developed novel computational methods to disentangle and decode the microenvironment of treatment-resistant mBC tumors derived from patients at DFCI. Employing these methods, I dissected the microenvironmental immune milieu, and interacting components therein, that have emerged from a multimodal single-cell profiling applied to the dissociated mBC biopsies.*

As I am finalizing the first part of my project, and am amid the second part of my project, it would ***enhance my professional development and presentation skills to present my findings to date at a major conference for the first time, as well as network and collaborate with experts in the field of cancer biology and single-cell methods to directly complement and advance my dissertation projects****.*

Many of the discussion leaders and speakers presenting are experts in the field (and many are faculty whose research I have followed and admired) and ***attending the conference would enable me to interact with these faculty, as well as potentially form collaborations provided the intersection of our research****. In addition, the conference would enable exposure to interdisciplinary research that is a bit outside of my field, such as the sessions focused on genetic evolution and pre-malignancies, which may act as an adjuvant for new approaches and research ideas. Altogether, having the training opportunity to attend and present my research at the 2024 Single-Cell Cancer GRC would be* ***profoundly helpful for my dissertation project to elucidate treatment resistance in mBC and pinpoint actionable targets to impede metastasis from pBC that is desperately needed for this patient population, as well as paramount to my professional and career development****. Attending and presenting at the conference would also enable me to bring back what I experienced to the Landry Cancer Biology community at Harvard, a community that has been absolutely enriching to my graduate student experience as a member and a part of the student steering committee during my PhD, and I would be excited to present my research and findings at the Annual Spring Symposium as well.*

Provided the alignment of my dissertation project with the 2024 Single-Cell Cancer Biology GRC, attending and presenting my research at ***this major conference will positively enhance my professional development, as well as advance my project, which holds promise to broaden the benefit of existing cancer therapies, as well as accelerate the development of novel cancer therapies to eradicate human tumors—in accord with the KGCRF mission****. As a PhD student trained in both experimental and computational cancer biology, the KGCRF CCA would provide the exceptionally unique opportunity to grow my career in these domains by presenting my dissertation research at a major conference and support my goal of becoming an independent academic researcher in the field of cancer biology."*

Awardee: Tevis Vitale

"I am requesting $2,000 from the KGCRF CCA to go to the 2024 CD1-MR1 conference in Tasmania Australia in February of 2024. This is a smaller conference that focuses on the biology of two rare and little studied immune cells, NKT cells and MAIT cells. Our lab has recently found new ways to manipulate cancer cells to induce an immune response against them. Specifically, my project focuses on NKT cells, the subject of the conference. However, our lab has previously never studied the immune system and didn't have any background in the subject. Therefore, as one of the people leading the efforts on these projects, I have had to learn much of what I know about immunology and NKT cells on my own. While I have reached out and established collaborations with people here at Harvard, there are only two people in Boston who study NKT

cells. Therefore, my interaction with others in the field has been limited. This conference will provide me the opportunity to ***1) expand my professional network, 2) meet with collaborators***

KGCRF Career Catalyst Awards for Fall 2023 (continued)

***whose input will be critical to the success of my project 3) receive feedback on my own research from the NKT cell field and 4) learn what is up and coming in the field**. Additionally, since this conference is only held every other year, this will likely be my only opportunity during my time at Harvard to attend this conference.*

*As previously stated, very few people in Boston (and the world) study the immune cell types that I study. While I have a collaborator in the Boston area, most of the people that he collaborates with are elsewhere in the world. This conference would be a time in which I can be introduced to his connections as well as make my own. Because the conference is quite small, I will have the **opportunity to network both with other trainees and faculty**. These interactions and connections are often what produce the best science and connections for future career opportunities; therefore, **this experience will be invaluable to my future career**.*

*While there are other immune conferences that take place closer to home, no other conference focuses on the immune cells I study, and no other conference will have the concentration of NKT cell experts that will be present here. Therefore, **the feedback that I will be able to get from people who have been in the field for decades will be instrumental to help me shape the future experiments of my thesis** and better understand how reviewers might respond to my eventual submitted paper.*

In summary, going to this conference will allow me to meet other scientists in my field who I don't know as well as scientists who will be helping me in my experiments over the next year. This will also be the first time we will be able to get feedback on this project from many other experts in the field. Additionally, this conference will allow me to learn more about the field and where it is going, which will be invaluable to the rest of my graduate career at Harvard."

Awardee: Jackson Weir

*"**The beauty of science, for me, is the collaborative pursuit of curiosity at the frontiers of human understanding. I am drawn to fields of research where innovation stems from multidisciplinary approaches to solving the biggest problems. Given the complexity of cancer, therapeutic advancements are deeply reliant on collaboration.** Innovations in single-cell and spatial sequencing technology have granted cancer researchers new tools to study tumors with unprecedented resolution. As I begin my career as a research scientist, I am captivated by the intersection between spatial genomics technology, immunology, and cancer biology towards a more personalized future in cancer medicine. I am currently pursuing this end as a third-year PhD candidate in Fei Chen's lab. The Karin Grunebaum Cancer Research Foundation Career Catalyst Award would enable me to attend the 2024 Gordon Research Conference titled "Deciphering Tumor Ecosystems in Space and Time". **This conference would directly complement my thesis research by facilitating collaborations with experts applying genomics technologies to study cancer microenvironments and by expanding my knowledge on tumor evolution.***

I recently co-developed Slide-tags**, a single-nucleus barcoding method for high-resolution multimodal spatial omics (in press at Nature). Slide-tags enables spatial mapping of whole transcriptome, chromatin accessibility, and immune repertoire sequencing data simultaneously from the same cell. With Slide-tags, we stand on the cusp of uncovering novel insights into the spatial organization and metastatic behavior of tumors. **The next phase of my thesis research involves applying Slide-tags to paired primary and metastatic colorectal cancer samples, aiming to unravel the drivers behind metastatic spread within the tumor microenvironment.** While the Chen Lab provides a rich foundation in spatial genomics, our scope extends less into the realms of clinical and molecular oncology. Attending the Gordon Research Conference will fill this gap, b**ringing me into contact with leading experts in tumor biology and metastasis. These interactions will be crucial for my thesis, as it will supplement our technological expertise with a deeper understanding of cancer biology, specifically in the context of tumor microenvironments. and metastasis.

In the past year, I have had the opportunity to give several oral talks and poster presentations at various conferences and seminars, including a selected talk at a Keystone Single Cell Biology conference and an invited talk at Single Cell Genomics Day. These experiences have been invaluable for fostering collaborations within the single-cell genomics field. However, my thesis research is now at a juncture where exposure to experts in tumor biology is essential. The Gordon

*Research Conference, with sessions like "Tumour Ecosystems and Microenvironments," "Invasion and Metastasis," and "Advances in Spatial Technology," offers an unparalleled platform for this purpose. **Engaging with leading researchers like** Mario Suva, Nicholas Navin, and Ashley Laughney **will not only enhance my knowledge in the field but also catalyze collaborations that could be transformative for my research**.*

Receiving the Karin Grunebaum Cancer Research Foundation Career Catalyst Award would be a significant milestone, enabling me to leverage the expertise of leading cancer biologists in conjunction with our lab's technological advancements. This synergy is essential for maximizing the potential of Slide-tags and contributing to a deeper understanding of tumor progression and metastasis."

Boston University Chobanian and Avedisian School of Medicine
Karin Grunebaum Cancer Research Foundation Student Summer Research Fund

The stipends provided to 4 students this summer enabled them to work full-time with our faculty on cancer research projects. Our medical student research advisory committee selected the following outstanding students to engage in cancer research training with our faculty.

- Carly Batt trained with Dr. Gerald Denis on a project that investigated the intersection of metabolic dysfunction and breast cancer.
- Kaina Chen investigated the mechanisms of telomere shortening in pediatric osteosarcomas with Dr. Rachel Flynn.
- Christopher Lietz trained with Dr. Hui Feng and sought to identify novel drugs to enhance cisplatin efficacy in patients with HPV-negative head and neck squamous cell carcinoma using bioinformatic approaches.
- Sienna Wang also trained with Dr. Hui Feng and worked to develop a zebrafish model of HPV+ head and neck squamous cell carcinoma.

To note, Drs. Flynn and Feng are previous Grunebaum fellows, and it is terrific to see how your foundation supports the training of multiple generation of scientists. Our students are continuing in their research projects into the fall, and we look forward to learning more about their discoveries at our January 2025 Research Symposium.

It is the generosity of our supporters that allows the Karin Grunebaum Cancer Research Foundation to continue funding researchers who are working to eradicate all forms of cancer.

Please donate using the QR code

KGCRF Student Summer Research Fund

Summer 2024 Impact Report

August 22, 2024
Steven Wallach
Karin Grunebaum Cancer Research Foundation
Dear Steven and Trustees of the Karin Grunebaum Cancer Research Foundation,

On behalf of the Medical Student Research Program at Boston University Chobanian & Avedisian School of Medicine, I wanted to thank you for your generous support of our medical student cancer researchers. The stipends provided to 4 students this summer enabled them to work full-time with our faculty on cancer research projects. Our medical student research advisory committee selected the following outstanding students to engage in cancer research training with our faculty.

- Carly Batt trained with Dr. Gerald Denis on a project that investigated the intersection of metabolic dysfunction and breast cancer.
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To note, Drs. Flynn and Feng are previous Grunebaum fellows, and it is terrific to see how your foundation supports the training of multiple generation of scientists. Our students are continuing in their research projects into the fall, and I look forward to learning more about their discoveries at our January 2025 Research Symposium.

I also wanted to thank you and the trustees for inviting our students and me to the advisory board meeting over the summer. It was gratifying to see how the students were able to incorporate other researchers' findings into their own studies. It is these connections that enables new ideas to blossom. I have chatted with our newest Grunebaum faculty fellow Dr. Thomas Clarke, and I am optimistic that we will be able to match medical students to train in his lab for next summer, further perpetuating the impact of these training experiences. Our medical student research program continues to grow. Earlier this week 108 students in our first-year class attended our "Introduction to Research" meeting where we discussed strategies on how to find mentors. Given the numerous outstanding cancer researchers at our medical school (many of which are prior Grunebaum Fellows) and the support of the foundation, I am confident that our students will grow into future leaders and make discoveries that will have a significant impact on our understanding of the causes of cancer which will lead to new cancer therapies.

On behalf of the Boston University Chobanian & Avedisian Medical School Research Program, thank you for your continued support and would be delighted to discuss our programs further.

Best wishes, Matt

Matthew D. Layne, PhD
Assistant Dean of Research
Associate Professor of Biochemistry & Cell Biology mlayne@bu.edu; 617.358.4409

KGCRF Student Summer Research Fund

Summer 2024 Impact Report

Note of Thanks from Carly Batt (MED'23'27)

Dear Generous Donor,

Thank you so much for your generous contribution that allowed me to conduct research over this past summer. My name is Carly Batt. I am now a second-year medical student from New York. I actually will be a triple terrier when I complete Medical School, as prior to starting school I got a Master of Public Health and a Master of Medical Science from BU as well. I have always known I wanted to be a doctor and work for an underserved population, and BU offers me exactly that. The research I did this summer was in the Denis lab. We were exploring the role that Type 2 (T2D) Exosomes had on Endometrial cancer cells. This pattern was first observed in the clinics at BMC, where patients with breast or prostate cancer and comorbid T2D were having higher incidence and mortality rates. The fact that we could see our research effecting the community we work directly with is the reason I wanted to work in this lab.

Working in cancer research is my dream in medicine. The summer before I started college, I worked at a camp for children with cancer and their siblings called Sunrise Day Camp. This camp brought so much joy to the campers, and myself, and I was able to form such amazing relationships I returned to the camp the next summer. In that second summer one of my campers unfortunately passed away at 9 years old. I was devastated, but motivated. I went back to college at NYU and joined a pediatric cancer lab studying the exact cancer that killed him. After working there, I knew this was what I wanted to do for my whole life. I came to school wanting to expand to other cancer types to see everything, and I cannot thank you enough for providing me with that opportunity.

I have submitted an abstract to an AMA abstract contest where hopefully I will be able to present a poster on this, as well as keeping an eye out for future opportunities to submit. I will also be participating in the BU poster presentation later this year. I think we need more information to get to the level of a full manuscript, but hopefully we can continue the research and eventually get there.

Without your contribution I never would have been able to do this research this summer to discover more about cancer and about myself. I wish I could give you a hug to thank you. I cannot put into words what it meant to me. One day in the future, when you see my name on some headline about a revelation in cancer treatment I discovered, just know that I would have never gotten there without you.

Thank you again, Carly Batt

Note of Thanks from Kaina Chen (MED'27)

Dear Karin Grunebaum Foundation,

the opportunity to work full-time in Dr. Rachel Flynn's lab and has been formative for my interest in pursuing research after medical school. Having the funding to be a full-time student in the lab allowed me to fully participate in research activities, build a set of technical skills, and become more independent. It was an incredibly positive experience, and I'm continuing my work in the lab part-time now that I am back in classes for medical school.

After medical school, I hope to pursue residency training in either adult or pediatric general medicine and specialize in oncology. Clinically, I'm drawn to oncology because it will allow me to develop close, long-term relationships with patients and their families and to ensure that the ever evolving and complex field of cancer diagnostics and therapies are appropriately tailored to a patient's individual goals. It is incredibly exciting to be able to work towards a career where I can work with patients and their families through life-altering diagnoses, but also actively work towards finding the solutions to unmet needs in their care.

Research has challenged me to think differently, and encouraged me to be thorough, resilient and diligent. I am confident that the ways research has pushed me to grow will make me a better physician, and I am thankful to the Karin Grunebaum Foundation for making my experience possible.

Sincerely, Kaina Chen

Note of Thanks from Christopher Lietz (MED'23'27)

Dear Members of the Karin Grunebaum Cancer Research Foundation,

I am writing to express my gratitude for your generous support of my summer research scholarship, which allowed me to conduct head and neck cancer research in the lab of Dr. Hui Feng at Boston University Chobanian and Avedisian School of Medicine. This opportunity was an enriching and productive experience, and I am honored to have been selected as a recipient of your foundation's support. I am continuing to work on the summer research projects during this academic year.

I have been involved in the cancer research field since 2018, when I took a job across town at the Massachusetts General Hospital working to disentangle the genomic landscape of connective tissue tumors. This work allowed me to synergize the biological chemistry and mathematics skills I had developed through my undergraduate education towards purposeful work. These early experiences pushed me further towards the field of medicine. While completing a graduate program here at Boston University and applying to medical school, I had the opportunity to work in the Department of Otolaryngology at Boston Medical Center. Now as a medical student, your support has granted me the ability to continue the cancer research I am passionate about, in the field of otolaryngology, which I am considering pursuing as a career.

With Dr. Feng's lab, we have applied some of the bioinformatics approaches I developed through my prior experiences in novel ways to address challenges in the treatment of head and neck squamous cell carcinoma.

Through the lens of embryology, we have identified specific molecular networks which are targetable by small molecular therapeutics to reverse the drug resistance phenotype associated with these tumors. Over this summer, I was also able to contribute to two other head and neck cancer projects being carried out in the lab, relating to targeted treatment based on tumor location, and developing models to understand the immune microenvironment of head and neck tumors.

Looking ahead, I believe the experiences afforded by your generosity will help support my application to the types of residency programs which will help me further my goal of becoming a physician scientist. Once again, thank you for your generosity and support. Your investment in my education and research has had a profound impact on my academic journey, and I am deeply appreciative of the opportunities it has provided. I look forward to continuing my work in cancer research and, hopefully, making meaningful contributions to the field that align with the mission of your foundation.

Sincerely, Christopher Lietz

Note of Thanks from Sienna Wang (MED'24)

To the Karin Grunebaum Cancer Research Foundation:
I would like to start off with a thank you. I greatly appreciate your gracious support of my research project. As a medical student, I am very lucky to be able to pursue a high level of research with your assistance. I am currently working on a project to develop a novel transgenic zebrafish model of HPV+ head and neck squamous cell cancer. I first became interested in head and neck cancer after meeting patients who were undergoing aggressive treatment. After attending a talk discussing the treatment modalities further, I knew that I wanted to conduct research in this field, in order to bring more understanding to the exact tumor-immune system interactions that still remain unknown. On a more personal note, I chose to pursue my education at the Boston University Chobanian & Avedisian School of Medicine for the opportunity to serve my community. I truly believe in ultimately applying my learning to the populations that are often ignored or forgotten by our medical system. Although there are systems in place, particularly in Boston, that help individuals with food security, housing, substance use disorders, and medical insurance, there will always be people who fall through the cracks.

My interests are more specifically in improving care for individuals experiencing homelessness. While speaking to patients at Barbara McInnis House, I have learned (and am still learning) so much about what it means to provide support and care. It is so much more than prescribing medications; it is also about empowering patients and providing them with the resources to help them succeed.

In addition, I have also promoted harm reduction at the medical school and in the broader community, including access to naloxone, use of syringe exchange sites, and overall safer use. As a student leader for Medical Students for Harm Reduction, we have met with the medical education leadership to change the curriculum to promote more effective overdose response training for first-year medical students.

Ultimately, I understand that the opportunity to speak with a patient will always be an immense privilege, and I want to be a physician who will always listen with compassion and empathy to the stories and voices of those I serve. I also hope to remain curious and inquisitive about medicine, particularly with improving treatments and outcomes for patients through research.

I would like to end with a warm thank you to the Karin Grunebaum Research Foundation for their support. I hope to cross paths again and extend my gratitude in person.

Best regards, Sienna Wang

Your Support is Vital to our Mission

The KGCRF relies soley on private donations. In order to continue the fight, we ask for your support and hope that you will give what you can.

Your tax-deductible contribution will directly help fund the cancer research effort, since all our Officers and Trustees are unpaid volunteers, and the Foundation has no paid employees.
You can make your contribution via check or please use our website to donate via PayPal at https://www.grunebaumfoundation.org/html/SupportContributions.asp

I enclose my gift of:

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Beverly, MA 01915

You may also donate online at:
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The Foundation's Mission and its chosen path to Mission Accomplishment.....

Because Karin Grunebaum died at age 39 from an unknown primary site malignancy, the overriding objective of the Karin Grunebaum Cancer Research Foundation is the eradication of all types of cancer. The Foundation's original Declaration of Trust, written in 1958, mandates that the Foundation's funds be exclusively used for "...aiding research in and study of the cause, treatment and cure of cancer."

The Foundation's Trustees firmly believe that the eradication of cancer will only occur through successful research accomplishments which are followed by successful practical/commercial application. Thus, the Foundation has chosen to invest its funds directly in dedicated cancer researchers in hope of helping them achieve significant accomplishments to eliminate all types of carcinomas and thereby eradicate each and every type of cancer.

KARIN GRUNEBAUM
cancer research foundation