AWARD NUMBER: W81XWH-21-1-0107

TITLE: Therapeutic Targeting of Nuclear Hormone Receptors in Neurofibromin/NF1-Depleted Breast Cancer

PRINCIPAL INVESTIGATOR: Dr. Bora Lim

CONTRACTING ORGANIZATION: Baylor College of Medicine, Houston, TX

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Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This project centers on the NF1/neurofibromin tumor suppressor, which was best known as a GTPase Activating Protein (GAP) that represses Ras activity. We have recently shown that NF1 has a GAP-independent activity by functioning also as a transcriptional co-repressor for estrogen receptor α (ER) in ER^+ breast cancer. ER is structurally closely related to the androgen receptor (AR). In this multi-PI grant, we will investigate the hypothesis that We **hypothesized** that NF1, analogous to its role in ER regulation, is also an AR co-repressor. Our **objective** is to assess this hypothesis to explore and exploit the broader consequences of NF1 loss in breast cancer therapeutics. The first specific aim is to define the interactions between neurofibromin and AR by studying neurofibromin's role as an AR co-repressor. Our results showed that AR and NF1 can physically interact in a ligand-dependent manner. While NF1-silencing enhanced AR-dependent transcriptional activities, NF1 overexpression inhibited it. As a result, NF1-depleted AR^+ cancer cells can grow at suboptimal levels of AR agonists. The second specific aim is to assess how hyperactivated AR due to *NF1* loss impacts the treatment of breast cancer by pre-clinically modeling the effects of AR antagonists or SARMs (selective AR modulators). The results from this project period showed that NF1-depletion can affect the choices of anti-AR agents. Enzalutimde which does not have known agonist activity is a better drug to treat these tumors than bicalutamide. Further NF1 loss actives not only AR but also Ras. In support of this, adding a MEK inhibitor can enhance the efficacy of enzalutamide.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	38	19b. TELEPHONE NUMBER *(include area code)*

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INTRODUCTION

This project centers on the NF1/neurofibromin tumor suppressor, which was best known as a GTPase Activating Protein (GAP) that represses Ras activity. We have recently shown that NF1 has a GAP-independent activity by functioning also as a transcriptional co-repressor for estrogen receptor α (ER) in ER^+ breast cancer. ER is structurally closely related to the androgen receptor (AR). In this multi-PI grant, we will investigate the hypothesis that We **hypothesized** that NF1, analogous to its role in ER regulation, is also an AR co-repressor. Our **objective** is to assess this hypothesis to explore and exploit the broader consequences of NF1 loss in breast cancer therapeutics. The specific aims are:

AIM 1: To define the interactions between neurofibromin and AR by studying neurofibromin's role as an AR co-repressor (primary responsibility of the initiating PI Eric Chang). We will measure:

(A) Ligand-dependent direct binding between neurofibromin and AR, using purified components.

(B) AR-dependent gene expression and AR recruitment to the chromatin as mediated by neurofibromin, using RNA-seq and ChIP-seq.

(C) AR ligand-mediated recruitment of neurofibrom to the chromatin by ChIP-seq.

AIM 2: To assess how hyperactivated AR due to *NF1* loss impacts the treatment of breast cancer by pre-clinically modeling the effects of AR antagonists or SARMs (primary responsibility of the partnering PI Matthew Ellis/Bora Lim).

(A) Measure *in vitro* cell growth/apoptosis upon neurofibromin-depletion in the presence of a SARM (ER^+ models) or an AR antagonist (ER^- models); if successful, these compounds will be tested in combination with a MEKi (binimetinib).
(B) Measure treatment efficacies using xenograft models, leveraging our collection of several $NF1^-$ and AR^+ PDX models as a prelude to potential clinical trials.

KEYWORDS

AI, Aromatase inhibitor
AR, Androgen receptor.
ARE, AR responsive element.
ChIP, Chromatin immunoprecipitation
Co-IP, co-immunoprecipitattion.
DHT, Dihydrotestosterone
DOX, doxycycline.
E2, estrogen/estradiol
EMT, epithelial to mesenchymal transition
ER, estrogen receptor-α
EREs, Estrogen Response Elements
FS, frameshift
GAP, GTPase Activating Protein
HR, hazard ratio HR
IHC, immunohistochemistry
IIA, Intra-iliac artery
KI, knock-in
KM, Kaplan-Meier
KO, knock-out
MEKi, MEK inhibitor.
NF1, Neurofibromatosis type 1

NS, nonsense
PDX, patient-derived xenograft
SARM, Selective AR modulator
SERM, Selective ER modulator
TCGA, The Cancer Genome Atlas

ACCOMPLISHMENTS

AIM 1: To define the interactions between neurofibromin and AR by studying neurofibromin's role as an AR co-repressor.

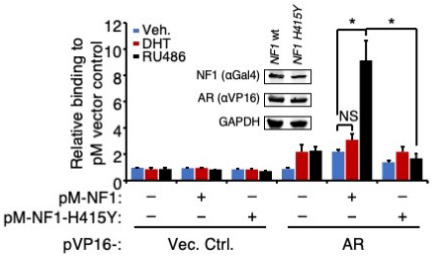

Figure 1. NF1 binds AR in a ligand dependent manner as determined by the mammalian two-hybrid assay. Wild type NF1 or NF1-H415Y mutant fused to the Gal4 activation domain was expressed by the PM vector, while the AR fused to the VP16 transcription activator domain was expressed by the pVP16 vector. These vectors were transduced into 293 cells. The inset is a representative western blot to show all fusion proteins were expressed at comparable levels. AR-NF1 binding turned on the expression of luciferase, which can be measured by bio-illuminance. The 293 cells were treated by either the AR agonist DHT or the AR antagonist RU486. The latter as expected stimulated NF1-AR interaction.

<u>NF1 binds AR in a ligand-dependent manner (Aim 1A)</u>. This project was partially inspired by the finding that a mutation in NF1's nuclear receptor binding domain, HY, was found in prostate cancer. Thus, we investigated in this sub-aim whether NF1 can form a complex with AR and whether this interaction can be weakened by the H415Y mutation. The interactions between a nuclear receptor and co-repressor are induced by an antagonist such as RU486, but not by an agonist such DHT (Dihydrotestosterone). We performed the mammalian two-hybrid assay to examine these interactions and the data agree with our model (Figure 1). That is, while the wild-type NF1 can interact with AR in the presence of RU486, this interaction was greatly reduced with the NF1-H415Y mutant.

Next, we ascertained whether the AR-NF1 interaction can be detected in AR-expressing (AR^+) prostate (LNCaP) and breast cancer cells (MDA-MB-435) by performing co-immunoprecipitation (co-IP). AR co-immunoprecipitated with NF1 in the presence of the RU486 antagonist, but not DHT (Figure 2). MDA-MB-453 breast cancer cells showed similar results (data not shown).

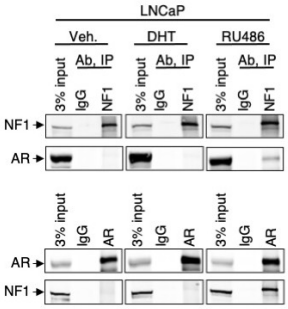

Figure 2. Ligand-dependent co-IP between NF1 and AR in LNCaP cells. LNCaP cells were pre-treated by different AR ligands before IP was performed using antibodies against either AR or NF1, while IgG was used as the antibody control. IP-ed samples were examined by western blot using AR or NF1 antibody to reveal that AR and NF1 can co-IP efficiently in the presence of the AR antagonist RU486. Similar results were obtained after examining MDA-MB-453 cells

Future studies will focus on examining whether the interaction between AR and NF1 is direct using purified components.

<u>NF1-depletion enhances AR transcriptional activities (Aim 1B)</u>. Given our model depicting NF1 as an AR co-repressor, we expect NF1 depletion can increase AR transcriptional activity. Conversely, NF1 overexpression is expected to inhibit AR transcriptional activity. We first investigated this using a luciferase reporter whose activity is under the control of an AR responsive element (ARE). When we silenced *NF1* expression (+DOX) in both LNCaP and MDA-MB-453 cells, ARE-Luc reporter activities increased (Figure 3A). In contrast, when wild type NF1 was overexpressed, ARE-Luc activity decreased (Figure 3B). As a control, we also tested the NF1-H417Y mutant, which as shown above has greatly reduced AR-binding ability, and found that it did not substantially inhibit ARE-Luc activity. To determine whether NF1 levels are also important for affecting expression of endogenous AR-responsive gene, we silenced NF1 expression in LNCaP cells and confirmed that the expression of two well-known AR-dependent genes increased (Figure 3C).

Future studies will examine genome-wide gene expression changes in an unbiased fashion by RNA-seq to further determine AR related pathway changes, and to analyze AR and NF1 recruitment to the chromatin by ChIP.

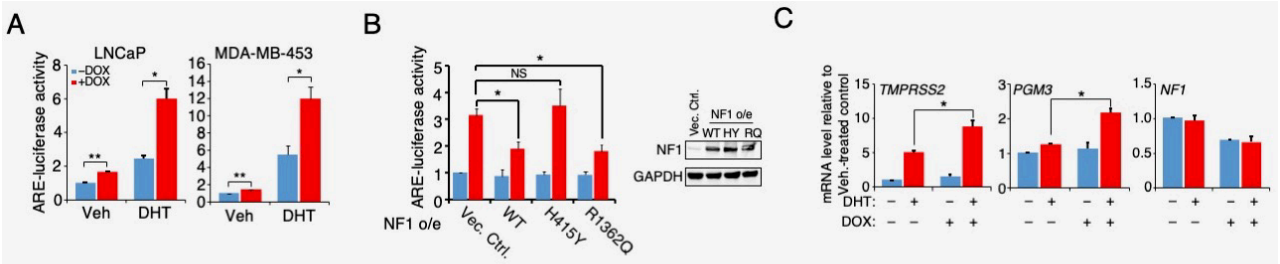

Figure 3. NF1 depletion enhanced while NF1 overexpression repress transcriptional activity of an ARE-luc reporter. A. Prostate cancer LNCaP cells and breast cancer MDA-MB-453 cells carrying the ARE-Luc reporter was transduced by a DOX-inducible shRNA vector to repress *NF1* expression. In both cell lines, *NF1* silencing (+DOX) enhanced the Luc activity, indicating enhancing transcriptional activity at the ARE. **B.** MDA-MB-453 cells carrying the ARE-luc reporter was transduced to express either wild type NF1, the AR-interfering NF1-H415Y mutant, or the GAP-inactivating mutant NF1-R1362Q. Wild type NF1 as expected inhibited ARE activity, while the NF1-H415Y mutant did not. This repression is GAP-independent because the NF1-R1362Q mutant behaved the as as cell lines expressing the wild type NF1. The western blot on the right demonstrated that all tested NF1 proteins were expressed at comparable levels. **C.** NF1 was silenced as in panel-A in LNCaP cells, and mRNA levels of two known AR-dependent genes were measured by qPCR to show that NF1 silencing (right) enhanced the expression of these genes (left).

<u>NF1-depletion induces hypersensitivity to the AR agonist (Aim 1)</u>. Since NF1 loss appears to enhance AR-dependent transcriptional activity, we asked whether NF1-silencing can cause AR^+ cells to be more sensitive to an AR agonist such as DHT. Indeed, the data demonstrated that when NF1 expression was silenced (+DOX), cells can grow better at sub-optimal DHT concentrations as compared to their $NF1^+$ counterparts (Figure 4).

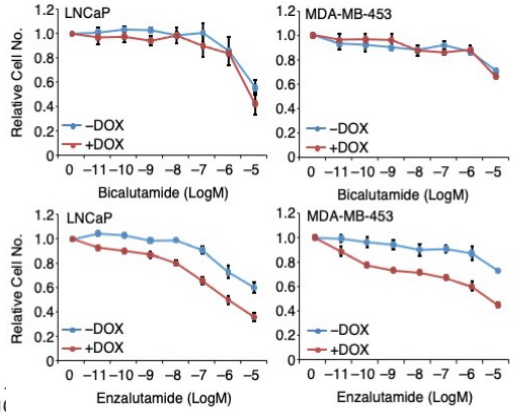

Figure 5. NF1 silencing induced differential responses to anti-AR agents. AR^+ LNCaP and MDA-MB-435 cells carrying the DOX-inducible NF1 shRNA were seeded in the presence of various of concentration of two anti-AR agents, and the cell growth was measured by the MTS assay 7 days later. The data show that NF1-depleted cells are more sensitive to enzalutamide.

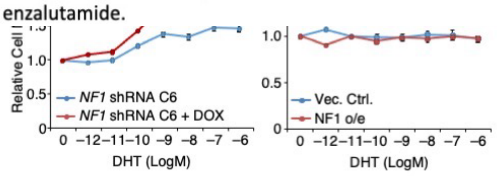

Figure 4. NF1 silencing enhanced sensitivity to AR agonist. AR^+ LNCaP and MDA-MB-435 cells carrying the DOX inducible NF1 shRNA were seeded in the presence of various of concentration of DHT and the cell growth was measured by the MTS assay 7 days later. The AR^- MDA-MB-231 cells were examined as the control which do not respond to DHT. Western blot shows that *NF1* silencing enhanced DHT responsiveness without increasing AR levels.

<u>NF1-depletion affects cellular responses to anti-AR therapeutics (Aim 2A)</u>. As discussed above, we have evidence that NF1-depletion can enhance AR-dependent transcriptional activities. This change in AR signaling may reduce the efficacy of anti-AR agents that have weak agonist activities. To investigate this possibility and to seek a more appropriate drug to treat NF1-depleted AR^+ tumor cells, we treated NF1 wild type or NF1-depleted AR^+ cancer cells with several AR agonists and then measured the impacts on cell growth. Bicalutamide is an AR antagonist with weak agonist activity, and as shown in Figure 5, NF1-silenced AR^+ breast and prostate cancer cells were insensitive to this agent. In contrast, these cells were more sensitive to enzalutamide which mainly blocks AR from entering the nucleus and is not known to have agonist activity.

<u>Adding a MEK inhibitor enhances the treatment efficacy of AR inhibitor, enzalutamide in treating NF1-depleted AR^+ cancer cells (Aim 2A)</u>. We hypothesize that loss of NF1 can turn on not only AR but the Ras-Raf signaling pathways as previously shown in ER^+ breast cancers. Therefore, we postulated that a MEK inhibitor (MEKi) such as binimetinib can block the latter, thereby co-inhibition can more effectively inhibit the NF1-depleted AR^+ cancers. Indeed, our data show that NF1-depleted AR^+ prostate and breast cancer cells are more sensitive to the enzalutamide + binimetinib combination compared to the $NF1^+$ counterparts (Figure 6). Based on this, we will further assess whether blocking another Ras pathway, e.g., that of the PI3K pathway, may more efficiently inhibit or possibly kill NF1-depleted AR^+ cells in the presence of enzalutamide. This will be important for future therapeutic strategy development strategies.

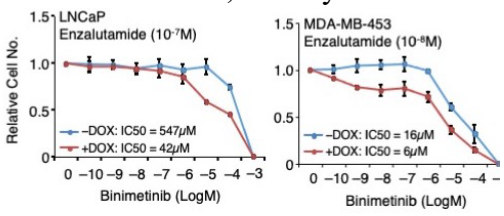

Figure 6. Adding a MEKi enhances enzalutamide efficacies when treating NF1-depleted AR^+ cancer cells. Indicated cells carrying the DOX-inducible shRNA against NF1 were seeded in the presence of a single concentration of enzalutamide plus various concentrations of a MEKi, binimetinib. Cell numbers were assessed by the MTS assay one week later. These data show that NF1-knock down cells are more sensitive to binimetinib.

CHANGES/PROBLEMS

Dr. Matthew Ellis is a physician-scientist who was the original partnering PI on this proposal responsible for therapeutic related studies in Aim 2. He has left Baylor College of Medicine for AstraZeneca where he is now the Senior VP of Early Oncology. We have requested to change the partnering PI to Dr. Bora Lim, who is also a clinician-scientist, and the Director of Translational Research for the Breast Cancer Research Program in the Dan L. Duncan Comprehensive Cancer Center. Dr. Lim is able to assume the 3% Partnering PI effort to provide the clinical expertise/translational input on this project. The Aims of the grant will not change, and she will be able to successfully complete this grant without any increase in funds.

Our project has also been facing many challenges caused by COVID-19, which has led to greatly limited lab access, and animal work was nearly shut down completely. In the next project period, we believe these limitations will be mostly behind us and will allow us to more efficiently conduct experiments requiring animals (Aim 2). NF1 ChIP-seq as proposed in Aim 1 is a challenging experiment due to the fact that NF1's binding to the DNA is through the binding to ER, which directly binds DNA. In addition, we are limited by the toolset of ligands that promote NF1 binding to the DNA. We are in the process of optimizing the cross-linking protocol to increase/stabilize the portion of DNA bound by NF1 to improve the sequencing performance.

PRODUCTS

Clinical Trial: Based on our compelling pre-clinical data, we were able to design a two-cohort phase II study of fulvestrant-binimetinib combination in patients with metastatic ER^+ breast cancers in collaboration with the NCI Combo MATCH program (Protocol #EAY191-N2; Figure 7 for a schema). This trial is approved by NCI Cancer Therapy Evaluation Program (CTEP) as one of the ComboMATCH therapeutic protocols and the final protocol has been developed and submitted to the CTEP during Q1 of 2022. The ComboMATCH is a highly competitive program designed to study rationally combinatorial therapeutics in advanced cancers, based on robust predictive biomarkers-guided selection of the target population.

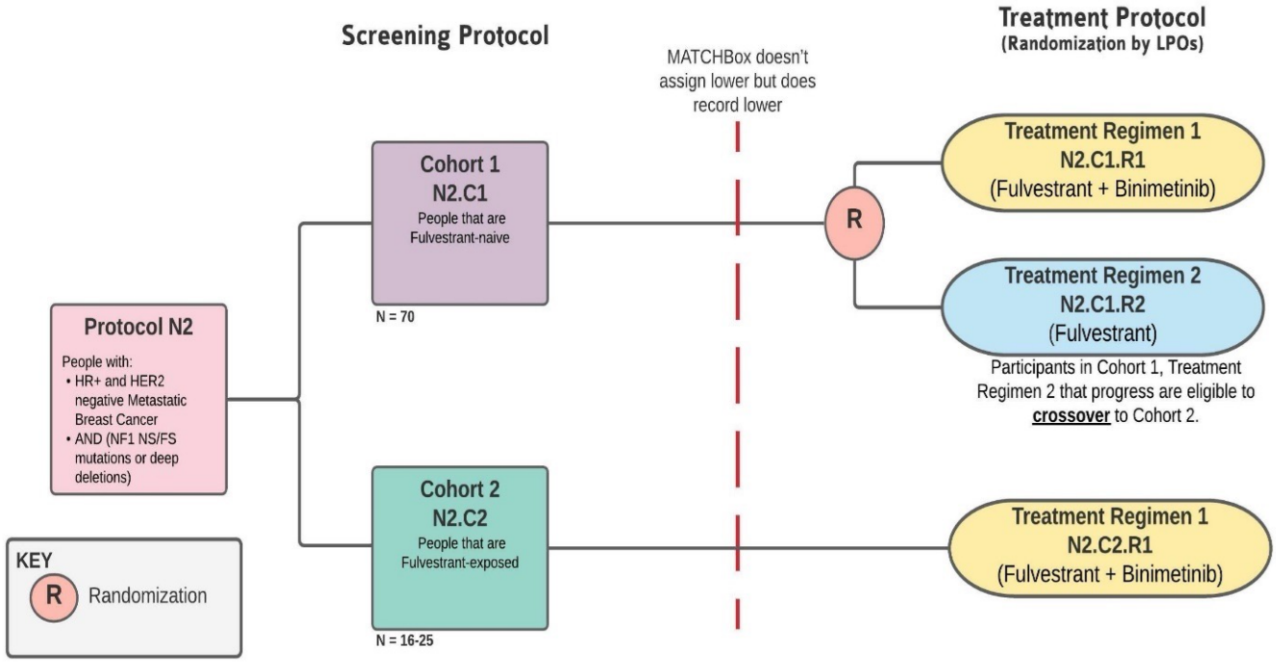

Figure 6. Schema of EAY191-N2
This is a phase II study of binimetinib in combination with fulvestrant in patients with metastatic hormone receptor-positive HER2 negative breast cancers with a non-functional mutation (frameshift or nonsense or genomic deletion) in NF1.
This trial includes two cohorts: the fulvestrant naïve cohort (Cohort 1: randomized) and the fulvestrant resistant cohort (Cohort 2: single arm).

Other Grant awarded with support by this grant:

Our parent grant's partnering PI (Ellis) has submitted an Expansion award to better study other aspects of NF1's properties and got funded. The PI on this grant (Chang) is a co-PI on that grant:

****Title: Optimizing Treatment for NF1-Deficient Metastatic ER+ Breast Cancers (Expansion Award)**

Major Goals: The major goal is to further interrogate approaches to diagnose NF1 loss in clinical samples in order to expand eligibility criteria for trials targeting ER+ breast cancer with NF1 loss.

Project Number: BC201666/ W81XWH-21-1-0634

Project/Proposal Start and End Date: 09/01/2021-08/31/2023

Total Award Amount (including Indirect Costs):

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name	**Project role**	**ORCID ID**	**Person Mon Worked (Time Period worked 08/01/21-03/14/22)**	**Project contribution**	**Funding support**
Ellis, Matthew	Partnering PI from 08/01/21 – 03/06/2022	**0000-0002-8467-8534**	0.18	provide clinical expertise and preclinical therapeutic experiments	This grant.
Lim, Bora	Partnering PI from 03/07/22	**0000-0002-4182-6058**		provide clinical expertise and preclinical therapeutic experiments	This grant.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Updated Other Support Attached.

SUPPORT
LIM, BORA

Current

W81XWH-21-1-0107 (Lim) This Award 03/15/21 – 03/14/24 0.36 CM
Department of Defense
Project Title: BC200589P1 - Therapeutic Targeting of Nuclear Hormone Receptors in Neurofibromin/NF1-Depleted Breast Cancer
Contact: Jamie A. Shortall – Jamie.a.shortall.civ@mail.mil
Role: Partnering PI
Major goals: The overall objective of this project is to investigate this hypothesis in order to assess what therapeutic opportunities are associated with neurofibromin loss in patients
Specific Aims:
Aim 1: we will define how neurofibromin and AR interact by investigating the role of neurofibromin as an AR co-repressor. We will measure direct ligand-dependent interaction between neurofibromin and AR on the DNA, and the consequence on gene expression when neurofibromin is lost in AR^+ ER^+, as well as ER^-, breast cancer cells –
Aim 2: we will study how AR antagonists (e.g., enzalutamide) or less virilizing Selective Androgen Receptor Modulators (e.g., ostarine/enobosarm) can impact the growth of breast cancer cells upon neurofibromin-depletion using cell line and PDX models.

R01 CA262623 (Han) New 07/01/21 – 06/30/26 0.36 CM
NIH/NCI
Project Title: Systematic Characterization of Small Nucleolar RNAs in Cancer
Contact: Julie Bishop (PRIME Institution) jbishop@tamu.edu
Role: Consortium PI
Major Goals: The goal of this project is to conduct a pragmatic, and systemic approach to characterize the snRNA and their roles in the cancer biology. We will characterized the impact of snoRNA expression on drug response in patients to facilitate the clinical utility of snoRNAs in cancer, using a data platform, such as GPSno (http://hanlab.uth.edu/GPSno), with multiple modules for researchers to visualize, browse, and download multi-dimensional data.

RP210227 (Edwards) New 08/2021 – 08/2026 0.60 CM
CPRIT
Project Title: Proteomics and Metabolomics Core Facility
Contact: Patty Moore – pmoore@cprit.texas.gov – 512-305-8491
Role: Co-Investigator
Major Goals: The overarching goal of the Core Facility is to support cancer researchers with state-of-the-art proteomics and metabolomics technologies for discovery of proteins and metabolic pathways that underline important cancer research and clinical problems. These include, but are not limited to, identification of drivers of different cancer molecular subtypes, resistance mechanisms to enable development of alternative therapies to combat resistance, identification of biomarkers for diagnosis and guiding therapy choices, and new targets for drug development

T2021-018 (Hoyos) New 11/2021 – 11/2024 0.24 CM
V Foundation
Selectively targeting myeloid derived suppressor cells (MDSCs) through TRAIL receptor 2 to enhance the efficacy of CAR T cell therapy for treatment of breast cancer"
Major Goals: Aim1. Incorporate cytokine signaling into HER2CAR.TR2BB T cells to optimize therapy for breast cancer Aim2. Evaluate the safety and activity of escalating doses of HER2CAR.TR2BB T cells in

patients with metastatic breast cancer. Aim3. Analyze the fate of HER2CAR.TR2BB T cells and their ability to eliminate MDSCs.

R37CA23730701 (Ren) 02/04/2020 – 01/31/2025 0.60 CM
NIH/NCI
Project Title: The Role of Lung Resident Mesenchymal Stem Cells in Post-chemotherapy Lung Metastases of Breast Cancer
Grant Contact: Alissa Adams (Jackson Laboratory) Alissa.adams@jax.org
Project Goals**:** To define the function of lung resident mesenchymal stem cells (MSCs) in posttherapy lung metastatic relapse in breast cancer.
Specific Aims**:** The specific aims of this study are to determine how chemotherapeutic drugs cisplatin and doxorubicin modulate the lung resident MSCs using our newly established endogenous MSC modeling platform in mice, to delineate the molecular mechanisms underlying drug- activated lung resident MSCs to support metastatic tumor growth in the lung, with a focus on the TLR4 signaling pathway and the key wound healing cytokine osteopontin (OPN), and to define the translational potential of stroma targeting approaches using both patient-derived xenograft models and breast cancer patient specimen analyses.

CZF2019-002432 (Navin) 12/07/2020 – 06/30/2022 1.68 CM
Chan Zuckerberg Foundation
Project Title: Human Breast Cell Atlas Seed Network
Grant Contact: Jennifer Weaver (MD Anderson Cancer Center) JMWeaver@mdanderson.org
Project Goals: To apply single cell RNA and Epigenomic sequencing technologies and spatial genomic methods to establish a reference of normal cell types and cell states in normal human breast tissues.
Specific Aims: The specific aims of this study are to generate a large-scale human breast atlas of cell types and states, spatial genomic analysis of cell type neighborhoods in human breast tissues, and functional mapping of breast cell type interactions and differentiation trajectories.

W81XWH-21-1-0634 (Ellis/Chang) 09/01/2021 – 08/31/2023 1.20 CM
DOD
Project Title: Optimizing Treatment for NF1-Deficient Metastatic ER+ Breast Cancers (Expansion Award)
Contact: Jamie A. Shortall – Jamie.a.shortall.civ@mail.mil
Project Goals: To further interrogate approaches to diagnose NF1 loss in clinical samples in order to expand eligibility criteria for trials targeting ER+ breast cancer with NF1 loss.
Specific Aims: The specific aims of this study are to assess whether this MS-based diagnostic approach can adequately assess NF1 protein levels in patients who will be selected first by DNA sequencing, and to functionally characterize these NF1 mutants to assess whether they should be included in future trials because, despite being mis-sense they disrupt NF1 function in a manner that sensitizes to the fulvestrant/binimetinib combination.

P50CA186784 (Ellis) 08/01/20 – 07/31/25 0.60 CM
NIH/NCI
Project Title: Translational Research in Breast Cancer
Grant Contact: Funmi Elesinmogun - elesinmf@mail.nih.gov
Core C Admin: Core Investigator
Major Goals: The overall goal of the Administrative Core is to consolidate common support and administrative functions for improved efficiency, to assure quality control in record-keeping, services, and compliance issues, and to support the Director and Executive Committee in maintaining integration and communication among the components and individual investigators involved in the SPORE effort

BCRF-21-042 (Ellis) 10/01/20-09/30/22 0.36 CM
BCRF

Project Title: Circulating Tumor DNA Based-Monitoring in Early Stage and Advanced Breast Cancer
Contact: Sarah Boll; Email: sboll@bcrf.org
Role: Co-Investigator
Major Goals: This application requests continued support for our interrogation of the clinical value of circulating tumor DNA assays (ctDNA). There are a number of proposed uses for ctDNA analysis and several technical approaches are under investigation. There remains no consensus as to the best approach, but we remain committed to the accumulation of appropriate blood samples from cooperative group trials so that the most technically appropriate test can be evaluated when these trials are complete.
Specific Aims:
1. To accrue serial ctDNA blood samples from patient enrolled on the BR003 Trial.
To develop a ctDNA monitoring approach for the management of advanced breast cancer

Pending

P50CA186784 (Ellis) Pending NIH Approval for Project Change 08/01/20 – 07/31/25 1.20 CM
NIH/NCI
Project Title: Translational Research in Breast Cancer- Project 1
Grant Contact: Funmi Elesinmogun - elesinmf@mail.nih.gov
Core C Admin: Core Investigator
Major Goals: the objectives of this project are thus to identify treatment-resistance drivers in ER+ breast cancer and to target their therapeutic vulnerabilities.

Previous
Title: Identification of Therapeutic molecular targets that enhance anti-tumor activity of neratinib in breast cancer
Time Commitments: 0.12 calendar
Supporting Agency: PUMA Biotechnology, Inc.
Address:
10880 Wilshire Blvd., Suite 2150,
Los Angeles, CA 90024
Contracting/Grants Officer: n/a
Performance Period: 4/20/2017-12/02/2020
Level of funding:
Project Goals: To identify the optimal target disease subtype and synergistic partner to maximize neratinib's anti-tumor effect in breast cancer cells in vitro and in vivo.
Specific Aims: The specific aims of this study are to identify molecules that enhance the anti-metastasis and anti-proliferative activity of neratinib in vitro via high-throughput SIRNA library screening and proteomics analysis and to determine the in vivo anti-tumor activity of neratinib in combination with other cancer therapeutic drugs in xenograft models.
Overlap: none

Title: A phase Ib/II study of safety and efficacy of MLN0128 (Dual TORC 1/2 Inhibitor) in combination with exemestane or fulvestrant therapy in postmenopausal women with ER+/HER2-advanced or metastatic breast cancer that has progressed on treatment with everolimus in combination with exemestane or fulvestrant
Time Commitments: 0.12 calendar
Supporting Agency: Millenium Pharmaceuticals
Address: n/a
Contracting/Grants Officer: n/a
Performance Period: 12/03/2013-12/02/2020
Level of funding:
Project Goals: To determine the efficacy of dual TORC 1 and 2 inhibitor MLN0128 in patients with metastatic hormone receptor positive breast cancer (both everolimus sensitive/resistant)

Specific Aims: n/a
Overlap: none

Title: A preclinical and clinical research protocol of KAPt project
Time Commitments: 0.12 calendar
Supporting Agency: Nittobo Medical Co LTD
Address:
Shiojima Fukuhara Fukuyama
Koriyama Fukushima-Pre, 963- 8061
Contracting/Grants Officer: Hideki Ishihara
Performance Period: 08/27/2015-12/02/2020
Level of funding:
Project Goals: To develop PI3K and MAPK pathway interrogating protein assay
Specific Aims: The specific aims of this study are the collection of TNBC cell lines samples, and the collection of PDX tissue samples.
Overlap: none

Title: A phase II study of anti-PD-1 (pembrolizumab) in combination with hormonal therapy in patients with hormone eceptor (HR)-positive localized inflammatory breast cancer (IBC) who did not achieve a pathological complete response (pCR) to neoadjuvant chemotherapy
Time Commitments: 0.6 calendar
Supporting Agency: Merck
Address:
2000 Galloping Hill Road,
Kenilworth, JN 07033
Contracting/Grants Officer: n/a
Performance Period: 09/09/2016-12/02/2020
Level of funding:
Project Goals: To determine the role of additive check point inhibitor using anti-PD-1 therapy in combination with endocrine therapy to prolong the progression free survival of hormone receptor positive inflammatory breast cancer.
Specific Aims: n/a
Overlap: none

Title: A Phase II Trial of Panitumumab, Carboplatin and Paclitaxel (PaCT) in Patients with Localized Triple-Negative Breast Cancer (TNBC) with Tumors Predicted Insensitive to Standard Neoadjuvant Chemotherapy
Time Commitments: 0.6 calendar
Supporting Agency: Amgen
Address:
One Amgen Center Drive
Thousand Oaks, CA 91320
Contracting/Grants Officer: n/a
Performance Period: 05/23/2016-12/02/2020
Level of funding:
Project Goals: To determine the efficacy of combination of panitumumab, and carboplatin + paclitaxel in patients with TNBC who has resistance to anthracycline based chemotherapy
Specific Aims: n/a
Overlap: none

Title: A Phase II Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy for Metastatic Triple-Negative Breast Cancer (nIBC) (KEYNOTE-086)
Time Commitments: 0.12 calendar

Supporting Agency: Merck
Address:
2000 Galloping Hill Road,
Kenilworth, JN 07033
Contracting/Grants Officer: n/a
Performance Period: 07/03/2015-12/02/2020
Level of funding:
Project Goals: To determine the efficacy of anti-PD1 antibody in patients with metastatic triple negative breast cancer patients
Specific Aims: n/a
Overlap: none

Title: A Phase II study of triple combination of atezolizumab, cobimetinib, eribulin (ACE) in patients with chemo resistant IBC
Time Commitments: 0.12 calendar
Supporting Agency: Genetech
Address: n/a
Contracting/Grants Officer: n/a
Performance Period: 08/02/2016-12/02/2020
Level of funding:
Project Goals: To determine clinical efficacy of triple combination: atezolizumab, cobimetinib, eribulin (ACE) followed by AC combination only for metastatic inflammatory breast cancer after 1st line
Specific Aims: n/a
Overlap: none

Title: A phase 1b study of neratinib, pertuzumab and trastuzumab with taxol (3HT) in metastatic and locally advanced breast cancer, and phase II study of 3HT followed by AC in HER2 + primary IBC, and neratinib with taxol (NT) followed by AC in HR+ /HER2- primary IBC
Time Commitments: 0.36 calendar
Supporting Agency: PUMA Biotech
Address:
10880 Wilshire Blvd., Suite 2150,
Los Angeles, CA 90024
Contracting/Grants Officer: n/a
Performance Period: 01/30/2017-12/02/2020
Level of funding:
Project Goals: To determine the role of pan-HER2 inhibitor neratinib to improve the response to neoadjuvant therapy in both ER/PR positive and HER2 negative, HER2 positive inflammatory breast cancers
Specific Aims: n/a
Overlap: none

Title: Determine in vitro and in vivo anti-tumor activity of naclynamide in inflammatory breast cancer
Time
Commitments: 0.6 calendar
Supporting Agency: Therimunex
Address:
5110 Campus Drive, Suite 180,
Plymouth Meeting, PA 19462
Contracting/Grants Officer: James D. Thacker
Performance Period: 04/28/2016-12/02/2020
Level of funding:
Project Goals: To determine a biological role of a novel peptide Naclynamide, a major component to maintain a

balance within the regulation of inflammasome, and its contribution to the tumor growth and survival
Specific Aims: The specific aims of this study are to determine the in vivo anti-tumor activity of Naclynamide and the inflammasome/caspase-1 actibity in IBC cells, and to determine the in vivo anti-tumor activity of Naclynamide combined with chemo reagent or other cancer therapeutic drugs using xenograft or PDX animal models.
Overlap: none

Title: Delineating the Evolution of Multi-Organ Metastasis in Breast Cancer with Single Cell Genomics
Time
Commitments: 0.12 calendar
Supporting Agency: Emerson Collective
Address: n/a
Contracting/Grants Officer: Maria Gelormini
Performance Period: 11/01/2018-10/31/2020
Level of funding:
Project Goals: To establish a post-mortem tissue collection program to collect multi-organ tissues from metastatic breast cancer patients to study the evolution of metastatic disease using single cell sequencing methods.
Specific Aims: The specific aims of this study are to delineate the genomic evolution of metastatic clones across multiple organ sites, and to investigate metastatic phenotypes and stromal cells in different metastatic niches.
Overlap: none

Title: A phase I study of OTS167PO, a MELK inhibitor, to evaluate safety, tolerability and pharmacokinetics in patients with advanced breast cancer and dose-expansion study in patients with triple negative breast cancer and dose-expansion
Time Commitments: 0.12 calendar
Supporting Agency: Oncotherapy
Address:
3-2-1 Sakado, Takatsu, Kawasaki,
Kanagawa, 213- 0012 Japan
Contracting/Grants Officer:
Performance Period: 04/26/2017-12/02/2020
Level of funding:
Project Goals: To determine the role of MELK inhibition in metastatic triple negative breast cancer after the progression on chemotherapy.
Specific Aims: n/a
Overlap: none

Title: Enhancing anti-EGFR Therapeutic Efficacy in Inflammatory Breast Cancer
Time Commitments: 0.12 calendar
Supporting Agency: NCI
Address: n/a
Contracting/Grants Officer: Leslie Hickman
Performance Period: 03/15/2017-12/02/2020
Level of funding:
Project Goals: To determine how the EGFR pathway promotes the progression of IBC and, through understanding the pathway, to identify novel therapeutic targets that could enhance the efficacy of EGFR targeted therapy
Specific Aims: The specific aims of this study are to determine how the EGFR/COX-2 signaling axis regulates the cancer stem-like cell population in IBC cells and to determine predictive biomarkers of response to EGFR targeted therapy in patients with IBC.

Overlap: none

Title: A phase IIB study of neoadjuvant ZT regimen (enzalutamide therapy in combination with weekly paclitaxel) for androgen receptor (AR)-positive triple- negative breast cancer
Time Commitments: 0.12 calendar
Supporting Agency: Astellas Pharma Global
Address:
1 Astellas Way,
Northbrook, Illinois 60062
Contracting/Grants Officer: Hong Tang
Performance Period: 06/14/2016-12/02/2020
Level of funding:
Project Goals: To evaluate the pCR and RCB-I rates of patients with TNBC who were non- responders to initial anthracycline and cyclophosphamide chemotherapy and who were treated with ZT regimen (enzalutamide in combination with weekly paclitaxel) in the neoadjuvant setting.
Specific Aims: n/a
Overlap: none

Title: Identification of molecules that enhance anti-tumor activity of eribulin in metastatic breast cancer cell lines
Time Commitments: 0.12 calendar
Supporting Agency: EISAI, Inc.
Address:
155 Tice Blvd.,
Woodcliff Lake, New Jersey 07677
Contracting/Grants Officer: n/a
Performance Period: 08/14/2017-12/02/2020
Level of funding:
Project Goals: To identify the patient population that will benefit from eribulin and to identify a synergistic partner for the anti-tumor effect of eribulin.
Specific Aims: The specific aims of this study are to identify molecules that enhance anti-proliferative and anti-metastasis activity of eribulin, and the validation of target molecules and determine the therapeutic efficacy of eribulin as combination agent in TNBC and IBC cell lines.
Overlap: none

Title: A Multi-ctr, Ph 2 study of the Glutaminase inhibitor CB-839 in combination with Paclitaxel in patients with advanced TNBC including patients of african ancestry and non-african ancestry (CX-839-007)
Time Commitments: 0.12 calendar
Supporting Agency: Calithera
Address: n/a
Contracting/Grants Officer: n/a
Performance Period: 05/17/2018-12/02/2020
Level of funding:
Project Goals: To evaluate the overall response rate (ORR) of patients treated with CB-839 plus paclitaxel (Pac-CB) for metastatic TNBC
Specific Aims: n/a
Overlap: none

Title: Determining the anti-tumor efficacy of DS-8201a or patritumab based on novel HER2 targeted drug resistant HER2 positive breast cancer cell lines
Time Commitments: 0.12 calendar
Supporting Agency: Daiichi Sankyo

Address:
399 Thornall Street,
Edison, New Jersey 08837
Contracting/Grants Officer: n/a
Performance Period: 08/12/2016-11/11/2020
Level of funding:
Project Goals: To determine the mechanism of resistance to HER2-targeted drugs (T-DM1, and Pertuzumab/Trastuzumab) in HER2 positive breast cancer cell lines; and whether DS-8201a or patritumab can induce anti-tumor efficacy in HER2-targeted drugs resistant cell lines.
Specific Aims: The specific aims of this study are the characterization of HER2-targeted drug-resistant cell lines by protein and gene expression profiling and evaluation of the efficacy of DS-8201a or patritumab in the HER2-targeted drug-resistant HER2-positive breast cancer cell lines.
Overlap: none

Title: Study 2: Identify molecules that enhance anti-tumor activity of EP-100 in ER- positive, triple-negative and inflammatory breast cancer cells lines
Time Commitments: 0.12 calendar
Supporting Agency: Esperance Pharmaceuticals
Address:
340 East Parker Boulevard,
Baton Rouge, LA 70803
Contracting/Grants Officer: Hectory Alila
Performance Period: 08/06/2015-08/29/2018
Level of funding:
Project Goals: To identify best target group and synergistic partner of anti-tumor effect of EP-100 in breast cancer cells via pre-clinical study
Specific Aims: The specific aims of this study are to determine the therapeutic efficacy of EP-100 in different subtype of breast cancer cell lines, to identify molecules that enhance anti-proliferative and anti- metastasis activity of EP-100 using a high-throughput siRNA library screening, and to determine the in vivo anti-tumor activity of EP-100 combined with other cancer therapeutic drugs using both xenograft and PDX animal models
Overlap: none

Title: Determining the Anti-tumor Efficacy of DS-8201a Based on Novel HER2-Targeted Drugs-resistant HER2-Positive Breast Cancer Cell Line Panel
Time Commitments: 0.12 calendar
Supporting Agency: Daiichi Sankyo
Address:
399 Thornall Street, Edison,
New Jersey 08837
Contracting/Grants Officer: Contract Management Legal Operations
Performance Period: 11/05/2015-11/04/2016
Level of funding:
Project Goals: The major goals of this project is to evaluate Inflammasome/Caspase-1 pathway and its contribution to aggressive behavior and survival of inflammatory breast cancer
Specific Aims: n/a
Overlap: none

Title: Single cell transcriptome of IBC cells and surrounding microenvironment
Time Commitments: 0.12 calendar
Supporting Agency: SWOG Hope Foundation ITSC
Address:
24 Frank Lloyd Wright Drive

P.O. Box 483 (Suite 3600A)
Ann Arbor, Michigan 48105
Contracting/Grants Officer: n/a
Performance Period: 03/01/2018-02/29/2020
Level of funding:
Project Goals: To determine the Role of Genomics in Tumor Emboli and Microenvironment in IBC
Specific Aims: n/a
Overlap: none

Title: Human Cell ATLAS project – breast
Time Commitments: 0.12 calendar
Supporting Agency: Silicon Valley Community Foundation
Address:
2440 West El Camino Real, Suite 300
Mountain View, California 94040-1498
Contracting/Grants Officer: n/a
Performance Period: 09/01/2017-02/28/2019
Level of funding:
Project Goals: To delineate the role of normal cell types and states in Breast Cancer Progression, via studying normal contralateral breast cells
Specific Aims: This project will determine 'best practices' for tissue sources, dissociation, storage and genomic profiling methods for breast tissues (aim 1). Using an optimized approach, we will perform unbiased single cell RNA, epigenomic and proteomic profiling to identify cell types and generate the first draft human breast cell atlas (HBCA) (aim 2).
Overlap: none

Title: In vitro anti-tumor and in vivo anti-metastatic effect of E6201
Time Commitments: 0.12 calendar
Supporting Agency: Strategia Therapeutics
Address:
14 Union Wharf,
Boston, MA 02109
Contracting/Grants Officer: Linda J. Paradiso, DVM, MBA
Performance Period: 04/21/2016-03/31/2019
Level of funding:
Project Goals: To define the in vitro anti-tumor and in vivo anti-metastatic efficacy of E6201 in TNBC
Specific Aims: The specific aims of this study are to determine in vitro anti-tumor activity of E6201 in TNBC cell lines and to determine anti-metastasis activity of E6201 in TNBC using in vivo metastasis model.
Overlap: none

Title: A Phase II Study of BIBF 1120 (Nintedanib) for Patients with HER2 Normal Metastatic Inflammatory Breast Cancer (IBC)
Time Commitments: 0.12 calendar
Supporting Agency: Boehringer Ingleheim
Address:
900 Ridgebury Road,
Ridgefield, CT 06877
Contracting/Grants Officer: Mary Alice Norrison
Performance Period: 03/01/2015-12/31/2020
Level of funding:
Project Goals: The primary goal of this study is to clinical benefit rate (CBR) of BIBF-1120 in Metastatic Inflammatory Breast Cancer (IBC)

Specific Aims: n/a
Overlap: none

Title: Determination of the anti-tumor and anti-metastatic effect of OR-S2, a EXH1/2 dual inhibitor, in metastatic breast cancer
Time Commitments: 0.12 calendar
Supporting Agency: Daiichi Sankyo
Address:
99 Thornall Street, Edison,
New Jersey 08837
Contracting/Grants Officer: n/a
Performance Period: 08/15/2017-08/14/2020
Level of funding:
Project Goals: To determine the effect of OR-S2 on breast cancer growth and metastasis through modulation of the tumor microenvironment and cancer stem cells.
Specific Aims: The specific aims for this study are to determine the in vitro anti-tumor effect of OR-S2 in TNBC and IBC cell lines, and to investigate the effect of OR-S2 on metastasis, the tumor microenvironment, and cancer stem cells in TNBC using an immunocompetent mouse model.
Overlap: none

ANURAG, MEENAKSHI

ACTIVE

U01 CA214125 (Anurag/Carr) Now PI 06/01/2017 – 05/31/2022 2.16 CM NIH/ NCI
Project Title: (MPI) Microscaled Proteogenomics for Cancer Clinical Trials (CPTAC)
Contact: Viviana Knowles; Email: Viviana.Knowles@nih.gov
Role: Bioinformatician
Major Goals: The overall goal of our proposal leverages state-of-the-art quantitative discovery proteomics and phosphoproteomics as well as targeted assays to measure the kinome and chromatin modifications. These sensitive and reproducible pipelines will be used to analyze preclinical models, well-annotated cohorts and clinical trial samples in an iterative design. A robust proteogenomics pipeline developed by our group will be used to analyze and visualize the data.
Specific Aims:
1. Determine the adequacy of our microscaled proteomic pipelines and PDX resources in revealing tumor biology.
2. Develop a prioritization scheme for clinical trial sample analysis using Tier 2 (core needle biopsies from small-scale neoadjuvant studies samples)
3. Determine interactions between the proteogenome, drug response and outcomes in breast cancer neoadjuvant clinical trials.
Overlap: None

U54CA233223 (Mitsiades) Reduced effort 09/20/2018 – 06/30/2023 2.16 CM NIH/ NCI
Project Title: Minority PDX Development and Trial Center: Baylor College of Medicine and MD Anderson Cancer Center Collaboration in Mechanistic Studies to Dissect and Combat Health Disparities in Cancer RP2: Targeting Estrogen receptor and DNA damage repair disparities in African American and Hispanic/Latino breast cancer using Patient- Derived Breast Cancer Xenografts
Contact: Ashley Salo - ashley.salo@nih.gov
Role: Bioinformatician
Major Goals: The objective of this study is to characterize the genome, transcriptome and kinome of 100 breast cancer PDX lines, >70% of which are derived from patients of African American or Hispanic/Latino ethnicity. By understanding fundamental cancer pathways specific to these minority groups this study will delineate efficacy of pre--existing, CTEP--approved therapies in minority ethnicities.
Specific Aims:
1. Systematically characterize estrogen receptor (ER) signaling and response to endocrine treatment in PDX lines derived from AA and Hispanic breast cancer patients.
2. Characterize DNA repair profiles of ER+ and triple negative PDX lines across ethnic groups.
3. Generate -omics' based network profiles specific for Hispanic, AA and CA PDXs.
Overlap: None

SAC190059 – Leadership Grant (Ellis)Reduced effort 06/01/19 – 12/31/2021 0.12 CM
Susan G Komen Foundation
Project Title: Proteogenomics of Endocrine Therapy Resistance
Contact: Amy Dworkin; Email: Adworkin@komen.org
Role: Co-Investigator
Specific Aims:
1. Conduct Tandem-Mass Tag (TMT) quantitative proteomic and phosphoproteomic analysis of ER+ PDX grown in the presence and absence of estradiol supplementation. Informatic tools will be applied to contrast estradiol-dependent and independent models and metastatic and non-metastatic models

2. Tractable therapeutic hypotheses that are specific to pathways that are active in the hormone independent state will be identified. We will conduct proof of principle therapeutic experiments in endocrine therapy resistant PDX models to achieve validation of the predictive properties of proteogenomic analyses conducted in Aim 1.
Overlap: None

Adrienne Helis Malvin Medical Research Foundation (Foulds) New 10/01/20 – 09/30/23 0.12 CM

Project Title: Kinase inhibition for ESR1 fusion-driven breast cancer
Contact: Kimberlee Townsend ktownsend@helisoil.com
Role: Co-Investigator
Major Goals: This proposal provides strong evidence that *ESR1* translocation events are an emerging class of recurrent somatic mutations that lead to not only therapeutic drug resistance but also lethal metastasis in a subset of patients with ER+ breast cancer, a disease not previously considered to be driven by gene fusions. *These ESR1 fusions cannot be treated with the current standard-of-care ET, as they produce proteins lacking the ERα LBD.* However, we will define gene expression patterns that classify pathogenic *ESR1* fusion proteins and their downstream activated kinases to allow new therapeutics to be developed to treat *ESR1* translocated breast tumors. Results of this study will also shed new mechanistic insight into how ER+ breast cancer becomes ET-resistant and metastatic, a lethal process that is still poorly understood.

P50 CA186784-06 (Ellis) 08/01/20 – 07/31/25 1.20 CM NIH/ NCI
Project Title: Translational Research in Breast Cancer
Contact: Funmi Elesinmogun; Email: elesinmf@mail.nih.gov
Role: Co-Director – Biostatistics, Information, and Computational Biology (Core B)
This Core provides comprehensive and essential statistical, bioinformatics, medical informatic and data management support to all projects, to the DRP and CEP and to the other Cores. Our mission is to bring the best possible methods to bear, and to help ensure that the translational goals of the SPORE will be met while making efficient use of resources.
Specific Aims:
1. Comprehensive biostatistical consultation, experimental design, data analysis and reporting;
2. Integrative proteome-genomic bioinformatic consultation, experimental design, data analysis and reporting;
3. Development, customization, integration and maintenance of databases and data management systems to support data management needs of SPORE projects and cores.

Overlap: None

BCC Philanthropic Project (Learner) New 08/01/20 – 7/31/25 0.96 CM BCM Partnership for Bladder Cancer Research
Project Title: Translational Bladder Cancer Research
Contact: Karoline Kremers; Email: Karoline.Kremers@bcm.edu
Role: Bioinformatics
Vision for the Bladder Cancer Program at Baylor College of Medicine is to accelerate innovation in research and treatment and invent the future of personalized precision care for bladder cancer patients
Specific Aims:
1. Comprehensive characterization 350 NMIBC including 100 low risk (Ta low grade), 100 intermediate risk (multifocal and/or recurrent Ta low grade), and 150 high risk (Ta or T1HG, Tis) divided equally between treatment naïve and previously treated.
2. Comprehensive characterization of carcinoma in situ: up to 100 samples stratified between treatment naïve and recurrence post BCG.
3. Functional validation a) miRNA project; b) pre-clinical models – PDX; organoids; c) Phase O platform for evaluating novel agents and biomarkers

4. Comprehensive integrated bioinformatics and biobanking

W81XWH-21-1-0634 (Chang) New 08/01/21 – 07/31/23 1.20 CM
Department of Defense
Project Title: Optimizing Treatment for NF1-Deficient Metastatic ER+ Breast Cancers (Expansion Award)
Contact: Amanda Carrera - amanda.c.carrera.civ@mail.mil
Role: Co-Investigator - W81XWH-20-BCRP-EA
Major Goals: The major goal is to further interrogate approaches to diagnose NF1 loss in clinical samples in order to expand eligibility criteria for trials targeting ER+ breast cancer with NF1 loss.
Specific Aims:
Aim 1: we will further assess whether this MS-based diagnostic approach can adequately assess NF1 protein levels in patients who will be selected first by DNA sequencing.
Aim 2: we will functionally characterize these NF1 mutants to assess whether they should be included in future trials because, despite being mis-sense they disrupt NF1 function in a manner that sensitizes to the fulvestrant/binimetinib combination.

W81XWH-21-1-0119 (Foulds) New 03/15/21 – 03/14/24 1.80 CM
Department of Defense
Project Title: Proteogenomic approaches for finding therapeutic vulnerabilities to treat breast tumors expressing transcriptionally active ESR1 fusions.
Contact: Jamie A. Shortall – Jamie.a.shortall.civ@mail.mil
Role: PI
Major goals: Our proposed research will promote the ability to diagnose active *ESR*1 fusions accurately in the clinic (by developing an "active *ESR1* gene fusion signature") and will reveal specific kinase and coactivator inhibitor- based therapeutic vulnerabilities for the treatment of *ESR1* fusion-driven metastatic breast cancer. Our pre-clinical therapeutic data will support the development of future clinical trials for patients expressing active *ESR1* fusions that cannot be treated by existing endocrine therapies.
Specific Aims:
Aim 1: To establish functional rules that predict which ESR1 fusions are active drivers of drug resistance and metastasis
Aim 2: To investigate ESR1 fusion-activated downstream kinases for therapeutic targeting
Aim 3: To identify common coactivators recruited by ESR1 fusions as therapeutic targets

W81XWH-21-1-0107 (Lim) This Award 03/01/21 – 12/31/24 0.60 CM
Department of Defense
Project Title: Therapeutic Targeting of Nuclear Hormone Receptors in Neurofibromin/NF1-Depleted Breast Cancer
Contact: Amanda Carrera - amanda.c.carrera.civ@mail.mil
Role: Co-Investigator
Major Goals: The overall objective of this project is to investigate this hypothesis in order to assess what therapeutic opportunities are associated with neurofibromin loss in patients
Specific Aims:
Aim 1: we will define how neurofibromin and AR interact by investigating the role of neurofibromin as an AR co-repressor. We will measure direct ligand-dependent interaction between neurofibromin and AR on the DNA, and the consequence on gene expression when neurofibromin is lost in AR+ ER+, as well as ER–, breast cancer cells
Aim 2: we will study how AR antagonists (e.g., enzalutamide) or less virilizing Selective Androgen Receptor Modulators (e.g., ostarine/enobosarm) can impact the growth of breast cancer cells upon neurofibromin-depletion using cell line and PDX models.

P50 CA186784 (Ellis) New 07/01/21 – 06/30/22 0.48 CM NIH/ NCI
Project Title: Translational Research in Breast Cancer – Career Enhancement Program (CEP)
Contact: Funmi Elesinmogun; Email: elesinmf@mail.nih.gov
Role: PI
Major Goals: Career Enhancement Program (CEP). The central goal of our translational research is to get the most up to date laboratory research and the most current clinical experience to talk productively to each other, for the most rapid and efficient progress toward controlling and eliminating breast cancer. Thus we have designed this career enhancement program to expose young researchers to the full range of the breast cancer research experience in a vigorously translational environment, whatever their initial training was, as they move towards research independence

R01 CA271498 (Li/Zhang) New 03/14/2022 – 03/13/2027 1.20 CM NIH
Project Title: Next Generation Rat Models of ER+ Breast Cancer
Contact: Shakeeya Mone Eaddy; Email: shakeeya.eaddy@nih.gov
Role: Co-Investigator
Major Goals: The major goal of this proposal is to develop and credential rat models of ER+ breast cancer for studying ER+ breast cancer progression, metastasis and therapeutic resistance.
Specific Aims: (1) To characterize early progression of ER+ BCa in RIIM models.
(2) To characterize the metastatic behaviors of ER+ BCa in RIIM models. (3) To credential ER+ RIIM models in recapitulating therapeutic responses
Overlap: None

PENDING

None

Overlap:
None

COMPLETED
W81XWH-19-1-0527 – BC181527 (Chang) 09/01/19 – 08/31/2021
Department of Defense
Project Title: Direct Regulation of Estrogen Receptor Transcription Activity by NF1 (Expansion Award)
Contact: Jodi Cardoza; Email: Jodi.l.cardoza.civ@mail.mil
Role: Bioinformatician
Specific Aims:
AIM 1: To define the full range of NF1 transcriptional activity in ER+ breast cancer cells by identifying key metastasis-driving genes that are directly regulated by NF1.
AIM 2: To assess the impact of NF1 depletion on bone metastasis using BICA (bone in culture assay) in vitro and IIA (intra iliac artery) injection in vivo, and how to block these activities in order to reduce metastasis in ER+ NF1– cancer.
Role: Bioinformatician

SAC170059 – Leadership Grant (Ellis) 02/20/2017 – 02/19/2019 3.0 CM Susan G. Komen
Project Title: Somatic Mutation and Recurrence Risk for Early Stage Estrogen Receptor Positive Breast Cancer
Contact: Jerome Jourquin; Email: JJourquin@komen.org
Role: Biostatician

Major Goals: The primary objective of this proposal is to establish relationships between somatic mutations in significantly mutated or druggable genes in breast cancer and outcomes for patients receiving adjuvant endocrine therapy.
Specific Aims:
1. We will establish the cell line models to define the molecular activities caused by NF1 inactivation.
2. We will use cell lines identified in Aim 1, as well as ER+ PDXs (patient-derived xenografts) that have NF1 mutations, to investigate whether greater efficacy in standard endocrine therapy can be achieved by also targeting the NF1-dependent Ras pathways.
Overlap: None

RR140033 (Ellis) 06/01/2014 – 11/30/2019 NCE 2.68 CM
CPRIT
Established Investigator Recruitment Award
Project Title: Proteogenomic and genomic analysis of luminal and triple negative breast cancer for targeted therapeutics discovery.
Contact: Michael Brown; Email: mbrown@cprit.state.tx.us
Role: Bioinformatician
Specific Aims:
1. Develop a mechanism-based classification of endocrine therapy resistant ER+ HER2- breast cancer and translate these findings into improved clinical outcomes through clinical trials in the neoadjuvant and metastatic settings
2. Develop a mechanism-based classification of chemotherapy resistant ER- HER2- breast cancer and translate these findings into improved clinical outcomes through clinical trials in the neoadjuvant and metastatic settings
3. Serve goals 1 and 2 through the development of clinically actionable CLIA and/or FDA approved tests based on the measurement of critical DNA, RNA, protein and post-translational modifications that define druggable biology
Overlap: None

W81XWH-19-1-0527 – BC181527 (Chang) 09/01/19 – 08/31/2021 0.6 CM
Department of Defense
Project Title: Direct Regulation of Estrogen Receptor Transcription Activity by NF1 (Expansion Award)
Contact: Jodi Cardoza; Email: Jodi.l.cardoza.civ@mail.mil
Role: Bioinformatician
Specific Aims:
AIM 1: To define the full range of NF1 transcriptional activity in ER+ breast cancer cells by identifying key metastasis-driving genes that are directly regulated by NF1.
AIM 2: To assess the impact of NF1 depletion on bone metastasis using BICA (bone in culture assay) in vitro and IIA (intra iliac artery) injection in vivo, and how to block these activities in order to reduce metastasis in ER+ NF1– cancer.
Role: Bioinformatician

SUSAN HILSENBECK

ACTIVE

U54CA233223 (Mitsiades) 09/20/18 – 06/30/23 1.20 CM NIH
Project Title: Minority PDX Development and Trial Center: Baylor College of Medicine and MD Anderson Cancer Center Collaboration in Mechanistic Studies to Dissect and Combat Health Disparities in Cancer RP2: Targeting Estrogen receptor and DNA damage repair disparities in African American and Hispanic/Latino breast cancer using Patient- Derived Breast Cancer Xenografts
Contact: Ashley Salo - ashley.salo@nih.gov
Role: Co-Investigator
Major Goals: The objective of this study is to characterize the genome, transcriptome and kinome of 100 breast cancer PDX lines, >70% of which are derived from patients of African American or Hispanic/Latino ethnicity. By understanding fundamental cancer pathways specific to these minority groups this study will delineate efficacy of pre--existing, CTEP--approved therapies in minority ethnicities.
Specific Aims:
1. Systematically characterize estrogen receptor (ER) signaling and response to endocrine treatment in PDX lines derived from AA and Hispanic breast cancer patients.
2. Characterize DNA repair profiles of ER+ and triple negative PDX lines across ethnic groups.
3. Generate -omics' based network profiles specific for Hispanic, AA and CA PDXs.

Overlap: None

R01AR072018 (Park, D) 07/09/18 - 06/30/23 0.60 CM NIH
Project Title: Defining periosteal skeletal stem cells and novel migration mechanisms in bone regeneration and repair in vivo
Contact: Fei Wang; Email: wangf@mail.nih.gov
Role: Co-Investigator
The major goal of this project is to define in vivo function of periosteal SSCs and the mechanisms that regulate P-SSCs in bone regeneration and repair. These studies will further define new therapeutic targets for reversing bone diseases and defects.
Specific Aims:

1. Determine whether inflammatory stimuli such as CCL5 are necessary for P-SSC migration and bone healing in vivo.
2. Test whether local ablation of P-SSCs or CCR5 deletion in P-SSCs affect bone healing in vivo.
3. Determine whether local provision of CCL5 accelerates healing of aged-bone defect with increased P-SSC recruitment but decreased osteoclast activity.

Overlap: None

W81XWH-17-1-0579 (Rimawi) 09/15/17 - 09/14/22 0.60 CM DOD
Project Title: A New Paradigm for De-escalation of Treatment in Her2 Positive Breast Cancer: Revolutionizing Care with More Effective and Less Toxic Therapy
Contact: Elayne Seiler; Email: Elayne.K.Seiler.civ@mail.com; Phone:
Role: Co-Investigator
Major Goals: The overall objective of this proposal is to define, and functionally characterize, mechanisms of resistance to dual anti-HER2 therapy, and use this information to develop a multi-parameter classifier to assign patients into distinct therapeutic groups on a prospective clinical trial.
Specific Aims:
1. To identify and validate additional genes/pathways and genomic alterations associated with resistance (LTR)

2. To conduct a clinical trial that will test the feasibility and provide early results of a next generation clinical trial design that uses tumor characteristics to successfully perform a molecular triage that identifies patients who can benefit from anti-HER2 therapy alone without chemotherapy

Overlap: None

U54CA224076 (Welm/Lewis) 09/01/17 - 08/31/22 0.33 CM NIH
Project Title: (MPI) PDX Trial Center for Breast Cancer Therapy
Contact: Jacquelyn Saval Email: boudjedaj@mail.nih.gov Phone:
Role: Co-Investigator
Major Goals: The proposed Patient-derived Xenograft Development and Trials Center (PDTC) will be a multi-institutional Center comprising three well-established research groups: two from the Huntsman Cancer Institute (HCI), and one from Baylor College of Medicine (BCM). The scientific premise of this study is that breast PDX models represent the diversity of human breast tumors, and can be feasibly utilized to test new drugs and drug combinations to find therapeutic approaches that match with molecular features of various tumor types. The goal of our PDTC is to obtain preclinical data that will facilitate prioritization of drugs to be tested in clinical trials at the National Cancer Institute (NCI). Toward this goal, our PDTC focuses on testing drugs that are already available through the NCI as NCI-IND agents with the Experimental Therapeutics Clinical Trials Network (ETCTN).
Overlap: None

R01MD013715 (Montealegre) 04/16/19 – 12/31/23 0.60 CM NIH
Project Title: A Randomized Controlled Trial of Mail-Self Stamped HPV Testing to Increase Cervical Cancer Screening Participation Among Minority/Underserved Women in an Integrated Safety Net Healthcare System
Contact: Carla Griffith; Email: griffithcp@mail.nih.gov; Phone:
Role: Co-Investigator
The major goal of the project is to create a process for cost-effective strategies to improve existing screening programs that involve testing self-collected cervicovaginal samples for HR-HPB to overcome the multiple barriers to clinic-based screening.
Specific Aims:

1. Compare the effectiveness of mailed self-sample HPV testing alone and in combination with patient navigation to increase primary screening participation (primary outcome) and clinical follow-up (secondary outcome).
2. Describe attitudes and experiences toward screening among women who receive mailed self-sampling kits and toward clinical follow-up among those who test positive for HR-HPV.
3. Evaluate the cost-effectiveness of mailed self-sample HPV testing alone and in combination with patient navigation to increase screening participation and reduce cervical cancer risk in safety net health systems.

Overlap: None

RP190398 (Schiff) Now at NCE 03/01/19 – 02/28/23 NCE 0.12 CM
CPRIT
Project Title: Targeting the Mechanism of Hyperactive FOXA1 in Transcriptional Reprogramming Toward Endocrine Resistance and Metastasis in Breast Cancer
Grant Contact: Jim Willson; jwillson@cprit.texas.gov
Role: Co-Investigator
Specific Aims:
1. Investigate and establish the role of H-FOXA1/AP-1 and ER and identify the key AP-1 components involved in promoting EndoR and metastatic propensities, using our diverse preclinical EndoR models.
2. Determine the mechanism by which H-FOXA1/AP-1 and ER form a core-regulatory circuit to amplify

transcriptional programs in EndoR and metastatic breast cancer.
3. Explore the therapeutic potential of targeting FOXA1/FRA1, and evaluate clinical importance of FOXA1/AP-1 and ER-dependent signatures in EndoR and metastatic ER+ breast cancer.
Overlap: None

U01 CA214125 (Anurag/Carr) 06/01/17 – 05/31/22 0.48 CM
NIH/NCI
Project Title: (MPI) Microscaled Proteogenomics for Cancer Clinical Trials (CPTAC)
Contact: Viviana Knowles; Email: Viviana.Knowles@nih.gov
Role: Co-Investigator
Major Goals: The overall goal of our proposal leverages state-of-the-art quantitative discovery proteomics and phosphoproteomics as well as targeted assays to measure the kinome and chromatin modifications. These sensitive and reproducible pipelines will be used to analyze preclinical models, well-annotated cohorts and clinical trial samples in an iterative design. A robust proteogenomics pipeline developed by our group will be used to analyze and visualize the data.
Specific Aims:
1. Determine the adequacy of our microscaled proteomic pipelines and PDX resources in revealing tumor biology.
2. Develop a prioritization scheme for clinical trial sample analysis using Tier 2 (core needle biopsies from small-scale neoadjuvant studies samples)
3. Determine interactions between the proteogenome, drug response and outcomes in breast cancer neoadjuvant clinical trials.
Overlap: None

Scalp Cooling Alopecia Prevention Trial H-33692 11/13/13 - 12/31/22 0.12 CM
Paxman Coolers Limited
Project Title: *Scalp* cooling for alopecia prevention (scalp)
Contact: Richard Paxman; Email: RichardPaxman@paxman-coolers.co.uk; Phone:
Role: Co-Investigator
Major Goal: The primary goal of this project is to demonstrate that the Orbis Paxman Hair Loss Prevention System is safe and effective in reducing chemotherapy-induced alopecia in woman with breast cancer undergoing neoadjuvant or adjuvant chemotherapy.
Specific Aim: Determine device is safe and effective at reducing chemotherapy-induced alopecia in women with breast cancer undergoing neoadjuvant or adjuvant chemotherapy
Overlap: None

P50CA126752 (Heslop/Brenner) 09/01/17 – 08/31/22 0.12 CM NIH-
NCI
Project Title: SPORE in Lymphoma – Competing Renewal
Contact: Viviana Knowles; Email: Viviana.knowles@nih.gov
Role: Core D – Co-Investigator
The overarching goal of this SPORE renewal proposal is to devise and test novel forms of cellular immunotherapy mediated by T cells and NKT cells to treat non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL).
Specific Aims:
1. To use highly specific T and NKT cellular immunotherapies to target multiple lymphoma antigens.
2. To increase the potency of the T and NKT cell immunotherapies for lymphoma.
3. Overcome the immune evasion tactics of lymphoma cells and their microenvironment.
4. To make T and NKT cell immunotherapy for lymphoma more broadly available.
Overlap: None

P50 CA186784 (Ellis) 08/01/20 – 07/31/25 1.20 CM
NIH/NCI
Project Title: Translational Research in Breast Cancer
Contact: Funmi Elesinmogun; Email: elesinmf@mail.nih.gov
Role: Core Director - Informatics and Statistics Core (Core B)
This Core provides comprehensive and essential statistical, bioinformatics, medical informatic and data management support to all projects, to the DRP and CEP and to the other Cores. Our mission is to bring the best possible methods to bear, and to help ensure that the translational goals of the SPORE will be met while making efficient use of resources.
Specific Aims:
1. Comprehensive biostatistical consultation, experimental design, data analysis and reporting;
2. Integrative proteome-genomic bioinformatic consultation, experimental design, data analysis and reporting;
3. Development, customization, integration and maintenance of databases and data management systems to support data management needs of SPORE projects and cores.

Overlap: None

U54CA254569 (Allen/Scheurer) 07/25/20 – 06/30/25 0.90 CM NIH
Project Title: Pediatric HIV/AIDS & Infection-Related Malignancies Research Consortium for Sub-Saharan Africa (PARCA)
Contact: Funmi Elesinmogun; Email: domingug@mail.nih.gov
Role: Co-Leader
Major Goals: The goal of this proposal is to establish PARCA, a collaborative clinical and translational research framework designed with the overarching goal to improve the current unacceptably poor outcomes of children with HIV-associated malignancies in sub-Saharan Africa (SSA).
Specific Aims:

1. Define the descriptive epidemiology and infectious exposures related to pediatric malignancies in SSA.
2. Conduct transformative inter-disciplinary collaborative research to reduce the burden of KS and lymphoma among children and adolescents in SSA.
3. Support the formation of a multi-national collaborative resource in clinical and translational research, training, and career development for African scientific leaders in HIV and pediatric cancer.

Overlap: None

P42-ES027725 (Moorthy) New 02/28/20 – 01/31/25 0.42 CM
NIH
Project Title: SUPERFUND: Polycyclic Aromatic Hydrocarbons: Ultrasensitive Detection, Early Life Exposures-Clinical Outcomes (Preterm Births, Chronic Lung Disease, and Neurocognitive Deficits), Prevention and Remediation
Contact: James R. Williams; Email: williamsjr@nieh.nih.gov; Phone:
Role: Core Leader
Major Goals: The over-arching hypothesis of the BCM-Rice SRP is that early life exposure to PAHs, which are present in superfund sites, increases the risk of PTBs and incrementally augments major morbidities such as (BPD and neurocognitive deficits.
Specific Aims:
1. To develop ultrasensitive detection and identification strategies (e.g., surface-enhanced Raman Spectra (SERA) and surface-enhanced Infrared Absorption spectroscopy (SEIRA) for primary and secondary PAH-based compounds in air, water, and soil based on optically active engineered nanomaterials (project 1).
2. To determine molecular mechanisms by which early life exposure to PAH mixtures increases the risks for preterm births, which in turn leads to BPD and neurocognitive deficits.
3. To develop novel remediation technologies to treat sediments contaminated with PAHs in a manner that completely removes the health risks while adding value to the impacted media.

4. To develop novel strategies to prevent and reduce the health burden associated with PAHs present in superfund sites through our Community.

Overlap: None

P30CA125123 (Heslop) New 07/01/2020 – 06/30/2025 0.85 CM
NIH/NCI
Project Title: Baylor College of Medicine Cancer Center: Biostatistics and Data Management Core
Contact: Funmi Elesinmogun; email: elesinmf@mail.nih.gov
Role: Quantitative Science Shared Resource and QSSR Core Leader
Major Goals: The overall goal is to unify and organize strong, independent scientific programs into a well-functioning Cancer Center.
Specific Aims:

1. To facilitate collaborative multidisciplinary research and patient care among our Members from different Departments and Centers by establishing Integrated Research Programs.
2. To translate our basic discoveries to the clinic to impact morbidity and mortality from cancer in our Catchment Area and globally.
3. To provide infrastructure support for the conduct of our basic, translational, clinical, and population science research.
4. To promote implementation science research and outreach programs through Community Outreach and Engagement (COE) to reduce the cancer burden in our CA.
5. To establish an effective cancer education program (CRCE) that is integrated with our research to spawn the next generation of scientists and physicians.

Overlap: None

U01-HG006485 (Plon) New 08/01/2020 – 05/31/2022 0.54 CM NIH
Project Title: (MPI) Evaluating Utility and Improving Implementation of Genomic Sequencing for Pediatric Cancer Patients in the Diverse Population and Healthcare Setting of Texas: The KIDSCANSEQ Study
Contact Zephuan Harvey; Email: harveyz@mail.nih.gov
Through this Clinical Sequencing Evidence-Generating Research (CSER2) with Enhanced Diversity project we will complete a trial (The Texas KidsCanSeq Study) comparing the results of targeted cancer panel sequencing versus genome-scale testing in pediatric cancer patients across diverse clinical settings
Role: Co-Investigator
Major Goals: The goal of the project is to determine the relative utility of more focused panel testing versus genome-scale testing including exome and RNA sequencing in the care of the childhood cancer patients across the diverse Texas population.
Specific Aims:

1. We will assess clinical utility of these tests by measuring the frequency of diagnostic and/or actionable germline and tumor findings and the effect on treatment decisions
2. We will compare uptake by first degree relatives for familial genetic testing and recommended cancer surveillance by race, ethnicity and clinical settings
3. We will describe perceived utility (clinical, psychological, and pragmatic) by surveying and interviewing parents and participating pediatric oncologists
4. We will create and evaluate the use of culturally sensitive educational materials, including videos in English and Spanish, improved integrated genomic test reports and counseling materials, and will compare in-person versus telemedicine exome results disclosure

Overlap: None

R01CA250905 (Rosenberg) New 07/01/2020 – 06/30/2025 0.00 CM
NIH
Project Title: Mechanisms of Endogenous DNA Damage Promotion

Contact: Funmi Elesinmogun; Email: elesinmf@mail.nih.gov
Role: Significant Contributor
Major Goals: This project uses the E. coli model to uncover both mechanisms that generate spontaneous endogenous DNA damage, and the functions and mechanisms of DNA-damage promotion by bacterial and human DDPs, to understand how many cancer-promoting proteins drive cancers, which may potentially enable universal, economical cancer/disease screening, and novel anti-cancer drug targets.
Specific Aims:
1. Mechanisms of endogenous DNA-damage promotion by dysregulated E. Coli DDPs.
2. Mechanistic studies of DNA-damage promotion by dysregulated human DNMT1, TFs, and others.
3. Connecting DDP activities to mutation mechanisms and cancer signatures.

Overlap: None

1R21NS123589 (Rao) New 07/01/2021 – 02/28/2023 0.24 CM NIH
Project Title: Laser Interstitial Thermal Therapy for the Treatment of Glioblastoma
Contact: Jeannette Gordon; Email: jeannette.gordon@nih.gov
Role: Co-Investigator
Major Goals: Determine the effects on the brain tumor microenvironment after treatment with laser interstitial ther-mal therapy. And to determine how laser interstitial thermal therapy can augment the efficacy of chemotherapy-laden na-noparticles for the treatment of intracranial tumors
Specific Aims:

1. Determine the longitudinal effects on the tumor microenvironment after LITT examining treated mice for the influx of immune cells and genetic changes using NanoString.
2. Determine the efficacy of thermally-released doxorubicin from nano-particles on improving survival in tumor bearing mice.

Overlap: None

P01-AG066606 (Zheng) New 06/01/2021 – 02/28/2026 0.24 CM NIH
Project Title: Lysosome Regulation and Signaling in Aging and Alzheimer's Disease
Contact: Jermain Cooper; Email: jermain.cooper@nih.gov
Role: Co-Investigator
Major Goals: The overarching goal of this Program Project Grant application is to investigate the lysosome-to-nucleus signaling pathways regulating lysosomal homoeostasis in aging and AD, with a focus on tau pathology. Our central hypothesis is that the lysosome is an integrative sensor of cellular stress capable of nuanced communication with the nucleus to activate a range of transcriptional programs that are governed through unique post-translational modifications of signaling molecules and chromatin structural elements.
Specific Aims:
1. Determine how lysosomal properties change as a function of aging and tauopathy, and upon modification of TFEB or TMEM106B.
2. Quantify the impact of aging and tauopathy on PTM patterns of TFEB and TMEM106B.
3. Define how PTM changes regulate lysosome-to-nucleus signaling and target activation.

Overlap: None

RSG-21-182-01-CDP (Sandulache) New 01/01/2022 – 12/31/2025 0.36 CM
American Cancer Society
Project Title: Determining the Impact of Ancestry on Oropharyngeal Cancer Biology and Treatment Response
Contact: Lynne Elmore; Email: lynne.elmore@cancer.org
Role: Co-Investigator
Major Goals: Appropriate staging and treatment paradigm development for OPSCC patients with smoking histories mandates a better understanding of 1) how tobacco exposure interacts with HPV status to modulate

prognosis and 2) identification of biological mechanisms leading to decreased treatment response and poor prognosis in HPV+ smokers.
Specific Aims: 1) how tobacco exposure interacts with HPV status to modulate prognosis and
2) identification of biological mechanisms leading to decreased treatment response and poor prognosis in HPV+ smokers.
Overlap: None

R01 CA271498 (Li/Zhang) New 03/14/2022 – 03/13/2027 0.48 CM NIH
Project Title: Next Generation Rat Models of ER+ Breast Cancer
Contact: Shakeeya Mone Eaddy; Email: shakeeya.eaddy@nih.gov
Role: Co-Investigator
Major Goals: The major goal of this proposal is to develop and credential rat models of ER+ breast cancer for studying ER+ breast cancer progression, metastasis and therapeutic resistance.
Specific Aims: (1) To characterize early progression of ER+ BCa in RIIM models.
(2) To characterize the metastatic behaviors of ER+ BCa in RIIM models. (3) To credential ER+ RIIM models in recapitulating therapeutic responses
Overlap: None

W81XWH-21-1-0119 (Foulds) New 03/15/21 – 03/14/24 0.24 CM Department of Defense
Project Title: Proteogenomic approaches for finding therapeutic vulnerabilities to treat breast tumors expressing transcriptionally active ESR1 fusions.
Contact: Jamie A. Shortall – Jamie.a.shortall.civ@mail.mil
Role: Co-Investigator
Major goals: Our proposed research will promote the ability to diagnose active *ESR*1 fusions accurately in the clinic (by developing an "active *ESR1* gene fusion signature") and will reveal specific kinase and coactivator inhibitor- based therapeutic vulnerabilities for the treatment of *ESR1* fusion-driven metastatic breast cancer. Our pre-clinical therapeutic data will support the development of future clinical trials for patients expressing active *ESR1* fusions that cannot be treated by existing endocrine therapies.
Specific Aims:
Aim 1: To establish functional rules that predict which ESR1 fusions are active drivers of drug resistance and metastasis
Aim 2: To investigate ESR1 fusion-activated downstream kinases for therapeutic targeting
Aim 3: To identify common coactivators recruited by ESR1 fusions as therapeutic targets

W81XWH-21-1-0107 (Lim) This Award 03/15/21 – 03/14/24 0.66 CM Department of Defense
Project Title: BC200589P1 - Therapeutic Targeting of Nuclear Hormone Receptors in Neurofibromin/NF1-Depleted Breast Cancer
Contact: Amanda Carrera – amanda.c.carrera.civ@mail.mil
Role: Co-Investigator
Major goals: The overall objective of this project is to investigate this hypothesis in order to assess what therapeutic opportunities are associated with neurofibromin loss in patients
Specific Aims:
Aim 1: We will perform molecular biology experiments to determine whether neurofibromin-loss causes AR activation in both ER+ and ER breast cancer cells, agreeing with its role as an AR repressor.
Aim 2: we will determine whether ER+ NF1 breast cancer is more sensitive to an AR-activating agent SARM, while ER NF1+ breast cancer is more sensitive to an anti-AR agent (enzalutamide), and finally whether adding a MEKi can greatly increase treatment efficacies.

Adrienne Helis Malvin Medical Research Foundation (Foulds) New 10/01/20 – 09/30/23 0.12 CM
Project Title: OPTIMISE: A Shared Care Approach for Improving Comprehensive Care of Cancer Patients with Comorbidities in A Safety-Net System
Contact: Funmi Elesinmogun; elesinmf@mail.nih.gov
Role: Co-Investigator
Major Goals: This proposal provides strong evidence that *ESR1* translocation events are an emerging class of recurrent somatic mutations that lead to not only therapeutic drug resistance but also lethal metastasis in a subset of patients with ER+ breast cancer, a disease not previously considered to be driven by gene fusions. *These ESR1 fusions cannot be treated with the current standard-of-care ET, as they produce proteins lacking the ERα LBD.* However, we will define gene expression patterns that classify pathogenic *ESR1* fusion proteins and their downstream activated kinases to allow new therapeutics to be developed to treat *ESR1* translocated breast tumors. Results of this study will also shed new mechanistic insight into how ER+ breast cancer becomes ET-resistant and metastatic, a lethal process that is still poorly understood.

R01 CA258040 (Badr) New 06/01/2021 – 05/31/2026 0.60 CM NIH
Project Title: Next Generation Rat Models of ER+ Breast Cancer
Contact: Sundaresan Venkatachalam; sundarv@nih.gov
Role: Co-Investigator
Major Goals: Patients receiving UMC will receive their cancer treatment, as directed by their oncologist, a survivorship care plan (SCP) at the end of active treatment, and surveillance visits with their oncologist based on national guidelines. Patients in OPTIMISE will 1) have an oncology nurse navigator assigned to their care team at diagnosis to facilitate oncologist-PCP communication and continuity of care; 2) receive coordinated care between their oncologist and PCP throughout cancer treatment.
Specific Aims: AIM 1 evaluates the impact of OPTIMISE on patient chronic disease self-management (primary outcome) and quality of life (secondary outcome). Aim 2 explores the effects of OPTIMISE on healthcare use and patient unmet needs during and after active cancer treatment. Aim 3 examines the effects of OPTIMISE on oncologist and PCP attitudes and coordination of care. Aim 4 seeks to elucidate patient- and system-level factors that may influence implementation outcomes.
Overlap: None

R01 CACA252685 (Ripley) New 08/01/2021 – 07/31/2023 0.12 CM NIH
Project Title: Dynamic BH3 Profiling with Patient Derived Organoids of Esophageal Cancer and Mesothelioma Enable Precision-Based Targeting of the Mitochondrial Apoptotic Pathway
Contact: Shakeeya Mone Eaddy; Email: shakeeya.eaddy@nih.gov
Role: Co-Investigator
Major Goals: Our goal is to disrupt the mitochondrial balance that enables carcinogenesis but blocks apoptosis by directly targeting the proteins responsible for resistance.
Specific Aims: Aim 1 We will establish a biochemical toolkit to predict treatment response in esophageal cancer and mesothelioma by utilizing a DBP-PDO model.
Overlap: None

VAMC Assignment Agreement (Yao) New 08/01/2021 – 07/31/2023
Michael E. DeBakey VA Medical Center 0.24 CM
Project Title: VA-Stratification of Pancreatic Cancer Subpopulation for Effective Immunotherapy
Contact: Qizhi Yao; qizhiyao@bcm.edu
Role: Co-Investigator

Major Goals: The major goal of this project is to determine and characterize PDAC subtypes that are sensitive to combination immunotherapy using MSLN VLPs vaccine plus immune checkpoint inhibitor in preclinical animal models.
Specific Aims: Aim 1: Determine whether the immunogenic subtype of PDAC is responsive to MSLN-VLP vaccine in PDX-hu-NSG model. Aim 2: Determine whether combination therapy with anti-PD-1 Ab enhances MSLN-VLP vaccine responses and efficacy in onco-humice model
Overlap: None

Pending

U24-CA271076 (Zhang) 09/01/2022 – 03/31/2027 0.24 CM
NIH
Project Title: iPGDAC, An Integrative Proteogenomic Data Analysis Center for CPTAC
Contact:
Role: Co-Investigator
Major Goals: To analyze CPTAC proteogenomic data to reveal biological and clinical insights.
Specific Aims: (2) To advance data analysis through computational tool development. (3): To identify candidate biomarkers for targeted protein assays.
Overlap: None

R01 CA262437 (Yun) 04/01/2022 – 03/31/2027 0.24 CM
NIH
Project Title: Role of SORD in Sugar-Mediated Cancer Metastasis
Contact:
Role: Co-Investigator
Major Goals: The major aims of this proposal are 1) Determine how SORD accelerates Colorectal cancer (CRC) motility in the HFCS condition.
Specific Aims: 2)Determine how SORD increases CRC motility in the high-glucose condition. 3) Understand the role of SORD in CRC metastasis in vivo.
Overlap: None

COMPLETED IN LAST 5 YEARS
R01CA207270 (Fuqua) 03/07/17 - 02/28/22 0.24 CM
NIH
Project Title: Mechanisms of AR-ER Collaboration In Hormone Resistance and Metastasis of Breast Cancer
Contact: Barbara Hodgkins; Email: barb.hodgkins@nih.gov; Phone:
Role: Co-Investigator
Specific Aims:
1. To determine if receptor crosstalk (WT or mutant ER with AR) is a mechanism of resistance to hormonal agents.
2. To determine whether AR employs novel nuclear receptor interactions to drive hormone resistance.
3. To determine AR and ESR1 mutant effects on invasion and metastasis.
Overlap: None

R01CA205594 (Li) 02/01/17 - 01/31/22 0.36 CM NIH
Project Title: Ruxolitinib for Preventing Breast Cancer in Women on Neuroleptics
Contact: Viviana Knowles, viviana.knowles@nih.gov, (240)276-5157
Role: Co-Investigator
The overall goal of this proposal is to test a novel concept in breast cancer prevention for women on antipsychotic dopamine antagonists.

Specific Aims:
1. To determine whether in rodent models bearing mammary early lesions, dopamine-antagonizing neuroleptics activate STAT5 and STAT3 in these early lesions, suppress apoptosis, and accelerate progression to cancer.
2. To determine whether in early lesion-bearing rodents on dopamine-antagonizing neuroleptics, genetic ablation of STAT5 and/or STAT3 restores apoptosis in these early lesions and slows the progression to cancer, and to discover the molecular mechanism by which neuroleptic treatment activates STAT3.
3. To determine whether in early lesion-bearing rodents on dopamine-antagonizing neuroleptics, short-term or intermittent treatment to block STAT5/3 activity prevents mammary tumors.
Overlap: None

R01CA204926 (Li) 02/01/17 - 1/31/22 0.36 CM NIH
Project Title: Novel LGR4 Oncogenic Signaling in Breast Cancer Progression and Metastasis
Contact: Viviana Knowles, viviana.knowles@nih.gov, (240)276-5157
Role: Co-Investigator
The overall goal of this proposal is to show that LGR4 binds CBL and prevents it from targeting pEGFR for ubiquitin-mediated proteasomal degradation, leading to sustained EGFR signaling, and that this novel LGR4-CBL-EGFR signaling pathway, together with LGR4-stimulated Wnt signaling, promotes BLBC invasion and metastasis.
Specific Aims:

1. To elucidate the novel interaction between LGR4 and CBL in relation to EGFR activation.
2. To establish LGR4 roles in breast cancer metastasis using mouse models and patient-derived xenografts (PDXs).
3. To determine in mouse models, PDX, and human clinical samples whether both EGFR and Wnt signaling play critical roles in breast cancer metastasis stimulated by LGR4.
Overlap: None

CCR185478284 (Roarty) 08/21/18 – 08/20/21 0.12 CM
Susan G Komen
Project Title:WNT Pathway Regulation of Metastatic Progression in TNBC
Contact: ResearchPrograms@komen.org
Role: Co-Investigator
Major Goals: The ultimate goal of the proposed studies will be to discover novel molecular and cellular interactions facilitating the cooperation and plasticity between these cell entities and leverage these findings to render metastatic progression of TNBCs therapeutically vulnerable. Disrupting these cellular interactions by selective targeting of Wnt signaling at key stages of disease, either alone or in combination with other therapies, may block progression and reduce metastatic burden to help improve TNBC patient outcome.
Overlap: None

RP170172 (Rosen) 08/31/20 -08/31/21 (NCE) 0.24 CM
CPRIT
Project Title: Targeting Therapy Resistance using Epithelial to Mesenchymal Transition (EMT) Pathways in Preclinical Claudin Low Breast Cancer Models
Role: Co-Investigator
The overall goal of this project is to have a significant impact on therapy for triple-negative and claudin-low breast cancers as well as potentially other solid cancers, such as pancreatic and colon cancer that have TICs as potential crucial cells involved in both drug resistance as well as metastatic capacity. Competitive renewal of previous CPRIT grant.
Specific Aims:

1. To identify the role of EMT in breast cancer response to chemotherapy in both the primary and metastatic setting using unique basal and claudin-low mouse and human breast cancer models and the Z-cad sensor to detect dynamic transitions between the epithelial and mesenchymal states.
2. To elucidate the response of primary and metastatic breast cancer to epigenetic and other targeted therapies that promote the EMT to MET transition.
3. To determine the efficacy of these therapies, which alter the EMT status of breast cancer in enhancing the response to adjuvant chemotherapy treatment in both the primary and metastatic setting with an emphasis on the treatment of established metastatic disease.
Overlap: None

Cancer Prog M-2018 (Rosen) 04/01/18 – 03/31/21 0.12 CM
Adrienne Helis Malvin Medical Research Foundation
Project Title: Overcoming the Roadblocks for Breast Cancer Immunotherapy
Role: Co-Investigator
Specific Aims:
1. Determine if TIN functionally mediate de novo and acquired resistance against immunotherapies including ICBT and CAR-T.
2: Determine if ED and/or anti-Jag1 treatment increases the efficacy of ICBT and CAR-T in TIN-enriched, ERmammary tumor models, Mammary tumor models.
Overlap: None

BCRF-19-055 (Fuqua) 10/01/18 – 0.36 CM
09/30/20 Breast Cancer Research Foundation
Project Title: Role of ESR1 mutations in breast cancer progression
646-497-2611 Role: Co-Investigator
Specific Aims:

1) To conduct sensitive retrospective ESR1 mutation sequence detection and quantitation using an established digital drop BioRad QX100 PCR assay to determine ESR1 mutation frequency, and address whether ESR1 mutations confer resistance to select hormonal therapies
2) To evaluate subclonal evolution and metastatic dissemination of ESR1 mutants, and determine whether a dominant ESR1 mutation phenotype drives distant metastasis.
3) To identify and validate biologic targets activated by ESR1 mutations by identifying paracrine mechanisms, such as secretion of cytokines and growth factors, and genomic changes using ChIPSeq coupled with RNASeq technologies on stable mutant-expressing clones
Overlap: None

U01CA214172 (Paulovich/Lewis) 09/19/16 - 08/31/21 0.21 CM NIH
Project Title: (MPI) A Unique Approach Combining Avatar Mice and Targeted Mass Spectrometry to Identify Blood Biomarkers For Early Detection of Breast Cancer
Contact: Grants Management Specialist: Justin Birken Email: birkenjg@mail.nih.gov Phone: Role: Co-Investigator
Major Goals: The major goal of this grant is to identify plasma biomarkers that could be used in conjunction with mammography (±ultrasound) to improve the sen-sitivity and specificity of breast cancer screening programs, facilitating early detection and thereby reducing breast cancer mortality.
Overlap: None

W81XWH-18-1-0040 (Kavuri) 02/15/18 - 02/14/21 0.24 CM
Department of Defense, Level 2
Project Title: Targeting DDR1 Aberrations in Metastatic ER+ Breast Cancer

Grant Contact: Nicholas E. Simon, nicholas.e.simon2.ctr@mail.mil
Role: Co-Investigator
Major Goals: The AIMS of this project are to 1) Determine the effect of DDR1 overexpression on metastasis in ER+ in vivo models;2) Determine the functional impact of DDR1 somatic mutations on tumor growth and metastasis in ER+ in vitro and in vivo models, and 3) Establish a strategy to effectively treat DDR1 overexpressed and activating mutant breast cancers.
Specific Aims:
1. Determine the effect of DDR1 overexpression on metastasis in ER+ in vivo models.
2. Determine the functional impact of DDR1 somatic mutations on tumor growth and metastasis in ER+ in vitro and in vivo models.
3. Establish a strategy to effectively treat DDR1 overexpressed and activating mutant breast cancers.

Overlap: None

U01HG006485 (Plon) 08/01/12 - 05/31/21 0.60 CM
NHGRI
Project Title: Incorporation of Genomic Sequencing into Pediatric Cancer Care
Contact: Lucia Hindorff; E-mail: hindorffl@mail.nih.gov
Role: Co-Investigator
Major Goals: The goal of this Exploratory Clinical Sequencing project is to integrate CLIA-certified germline and tumor exome sequencing information generated by the Whole Genome Laboratory into the care of childhood cancer patients with high-risk solid tumors and brain tumors of the Texas Children's Cancer Center.
Overlap: None

(Stevens) 07/01/18 - 06/30/19 0.24CM Cure
Childhood Cancer
Project Title: A Trial of Atovaquone with Conventional Chemotherapy for Pediatric AML (Atacc Aml)
Role: Co-Investigator
Major Goals: In this project we hope to develop a multi-institutional clinical trial that will test atovaquone - a well-tolerated agent in combination with traditional cytotoxic chemotherapy for pediatric AML.
Overlap: None

CCR16380599 (Kavuri) 09/15/17 - 09/14/19 0.24CM
Susan. G. Komen Career Catalyst award
Project Title: Career Catalyst - Kinome Analysis to Rationalize Targeting HER2 and DDR1 Breast Cancer Mutations
Grant Contact: Jamie Stanford – jstanford@komen.org
Role: Co-Investigator
Major Goals: The main goal of this project is to understand resistance to HER2-targeted therapy arising through kinome reprogramming
Specific Aims:
1. Aim-1. Determine kinome reprogramming in response to HER2-targeted drugs in HER2-amplified breast cancer PDX models.
2. Aim-2. Determine kinome reprogramming in response to HER2 oncogenic mutations in the context of endocrine therapy resistance in ER+ breast cancers.
3. Aim-3. Determine the impact of HER2-targeted drugs on “phospho-HER2-enriched” basal-like subtype breast cancer models.

Overlap: None

(Lerner) 08/15/17 - 08/14/19 0.12CM
Bladder Cancer Advocacy Network (BCAN)

Proteogenomic characterization of muscle invasive bladder cancer to identify mechanisms of resistance and targets for therapy
The aims are genomic and proteomic characterization of pre-treatment muscle invasive bladder tumors to determine profiles associated with treatment response and resistance and to validate therapeutic compounds derived from the discovery based proteogenomic studies in Aim 1 in PDX models and in naturally occurring bladder cancer in pet dogs.
Role: Co-Investigator
Overlap: None

W81XWH-16-1-0620 (Li) 09/15/16 - 09/14/19 0.36CM
DOD
Project Title: Beyond Apoptosis, Bcl-xL in Breast Cancer Metastasis
Contact: Grants administrator: Chris Meinberg, (301) 619-2657
Role: Co-Investigator
Major Goals:The overall goal of this proposal to determine the mechanisms by which Bcl-xL promotes migration and invasion in breast cancer cell lines and mouse models, and explore targeting Bcl-xL in preventing and treating breast cancer metastasis in mouse models and PDX models.
Aims
1) To investigate molecular mechanisms by which Bcl-xL promotes breast cancer metastasis using breast cancer cell lines
2) To establish whether nuclear Bcl-xL drives breast cancer metastasis in vivo using cell line xenografts, genetically engineered mouse models, and PDXs
3) To determine whether full suppression of Bcl-xL or blockade of nuclear roles of Bcl-xL prevent or treat metastatic breast cancer in mouse models
Overlap: None

R01CA072038 (Fuqua) 09/01/14 - 08/31/19 0.36CM
NIH
Project Title: Integration of Predictive Biomarkers of Hormone Resistance in Breast Cancer
Contact: Rosemary Ward; Email: wardros@mail.nih.gov; Phone:
Role: Co-Investigator
Specific Aims:
1) To identify and validate new clinical targets of resistance to antiestrogens, such as tamoxifen (Tam) and aromatase inhibitors (AIs
2) To integrate the classification of resistance targets and determine how they impact on ERα function.
3) To target resistance mechanisms to prevent the development of resistance and to restore hormone sensitivity, and validate selective candidates for their ability to predict resistance to Tam.
Overlap: None

BCRF-18-055 (Fuqua) 10/01/14 – 09/30/19 0.36CM
Breast Cancer Research Foundation
Project Title: Role of ESR1 mutations in breast cancer progression
Contact: Margaret Flowers; Email: mflowers@bcrfcure.org; Phone: Role: Co-Investigator
Specific Aims:
1) To conduct sensitive retrospective ESR1 mutation sequence detection and quantitation using an established digital drop BioRad QX100 PCR assay to determine ESR1 mutation frequency, and address whether ESR1 mutations confer resistance to select hormonal therapies
2) To evaluate subclonal evolution and metastatic dissemination of ESR1 mutants, and determine whether a dominant ESR1 mutation phenotype drives distant metastasis.

3) To identify and validate biologic targets activated by ESR1 mutations by identifying paracrine mechanisms, such as secretion of cytokines and growth factors, and genomic changes using ChIPSeq coupled with RNASeq technologies on stable mutant-expressing clones
Overlap: None