AWARD NUMBER: W81XWH-21-1-0634

TITLE: Optimizing Treatment for NF1-Deficient Metastatic ER+ Breast Cancers

PRINCIPAL INVESTIGATOR: Dr. Eric Chang

CONTRACTING ORGANIZATION: Baylor College of Medicine, Houston, TX

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Fort Detrick, Maryland 21702-5012

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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. The parent grant has led to the discovery that NF1 has a GAP-independent activity by functioning also as a transcriptional co-repressor for estrogen receptor α (ER) in ER+ breast cancer. Our data support the hypothesis that loss of a single tumor suppressor NF1 can enhance signaling activities from both the Ras and ER pathways, which must be properly co-targeted for efficient tumor inhibition. In this expansion award, our goal is to improve diagnose of NF1 loss in clinical samples in order to expand eligibility criteria for trials targeting ER+ breast cancer with NF1 loss. The specific aims are:

AIM 1: To orthogonally validate genomic evidence for NF1 loss by develop a precise mass spectrometry (MS)-based diagnostic approach to accurately assess NF1 protein levels in core needle biopsy samples. The objective is to improve the diagnosis of NF1low state in the absence of detectable NF1 FS/NS mutation.

AIM 2: To functionally characterize missense NF1 mutants recently identified in an adjuvant endocrine therapy trial as associated with poor prognosis to determine whether they should be included in the eligibility criteria for the present or future trials designed to improve outcomes in ER+ NF1low breast cancer.

15. SUBJECT TERMS
None taken.

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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. The parent grant has led to the discovery that NF1 has a GAP-independent activity by functioning also as a transcriptional co-repressor for estrogen receptor α (ER) in ER^+ breast cancer. Our data support the hypothesis that loss of a single tumor suppressor NF1 can enhance signaling activities from both the Ras and ER pathways, which must be properly co-targeted for efficient tumor inhibition. In this expansion award, our goal is to improve diagnose of NF1 loss in clinical samples in order to expand eligibility criteria for trials targeting ER^+ breast cancer with NF1 loss. The specific aims are:

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KEYWORDS

AI, Aromatase inhibitor
E2, estrogen/estradiol
ER, estrogen receptor-α
FS, frameshift
GAP, GTPase Activating Protein
IHC, immunohistochemistry
KI, knock-in
KM, Kaplan-Meier
KO, knock-out
MEKi, MEK inhibitor.
MS, mass spectrometry
NF1, Neurofibromatosis type 1
NS, nonsense
PDX, patient-derived xenograft

ACCOMPLISHMENTS

For Year-1, we have made great progress to accomplish Goal-1, see below. We will pursue Goal-2 in the next project year.

NF1 binding to the drug beads is selective (Goal 1-1).

Our preliminary data show that NF1 protein was pull down by kinase inhibitor conjugated beads before being measured by mass spectrometry (MS). We call this MS platform KIPA for kinase inhibitor pull-down assay. We tested the binding between purified NF1 and the bead conjugated to each individual kinase inhibitor and found that NF1 bound strongly to crizotinib- and palbociclib-conjugated beads (Figure 1). The latter targets CDK4/6, which were strongly pull-down in addition to NF1 in this assay, as expected. In contrast, beads that

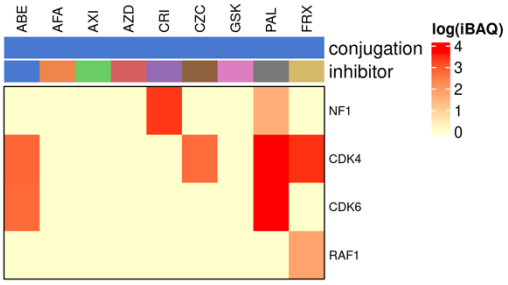

Figure 1. NF1 binding to bead conjugated to individual kinase inhibitor. After pull-down the amount of NF1 in terms of iBAQ score on the bead was measured by MS.

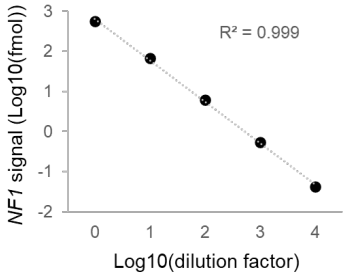

Figure 2. MS can detect NF1 with great sensitivity and linearity. NF1 protein was serially diluted and measured by MS.

conjugated with abemaciclib, another approved CDK4/6 inhibitor, pulled-down CDK4/6, but not NF1. In addition, since neither crizotinib- nor palbociclib-conjugated bead bound Raf, it is unlikely that NF1 bound to the beads indirectly through binding of this Ras-associated protein kinase.

Detect NF1 by MS with heavy isotope label peptide spiked-in (Goal 1-2).

We have identified an NF1 peptide that is well detected by MS and labeled it with a heavy isotope. When this labeled NF1 peptide with known quantity was spiked into a solution with purified NF1, it would allow the MS to more efficiently detect endogenous NF1. We call this approach SureQuant. By comparing the signal from the endogenous NF1 peptide to the labeled peptide with known quantity, the amount of endogenous NF1 can be revealed. As shown in Figure 2, we can detect NF1 at fmol levels with remarkable linearity.

Measure NF1 levels in PDX models by MS (Goal 1-3).

We first measured all the PDXs by KIPA without heavy peptide spike in. As shown in Figure 3, there is a good agreement between NF1 protein levels detected by KIPA, mRNA, and gene copy number (Figure 3). We then applied SureQuant to determine the amount of NF1 in six of our PDX models, which as assessed by genomics and KIPA can be classified as NF1^{high} (WHIM37 and WHIM43) and NF1^{low} (WHIM16, WHIM9, WHIM24, and WHIM40). By SureQuant, these models were further divided into 3 groups with respect to NF1 levels: high (WHIM37 and WHIM43), medium (WHIM9 and WHIM40), and low (WHIM16 and WHIM24).

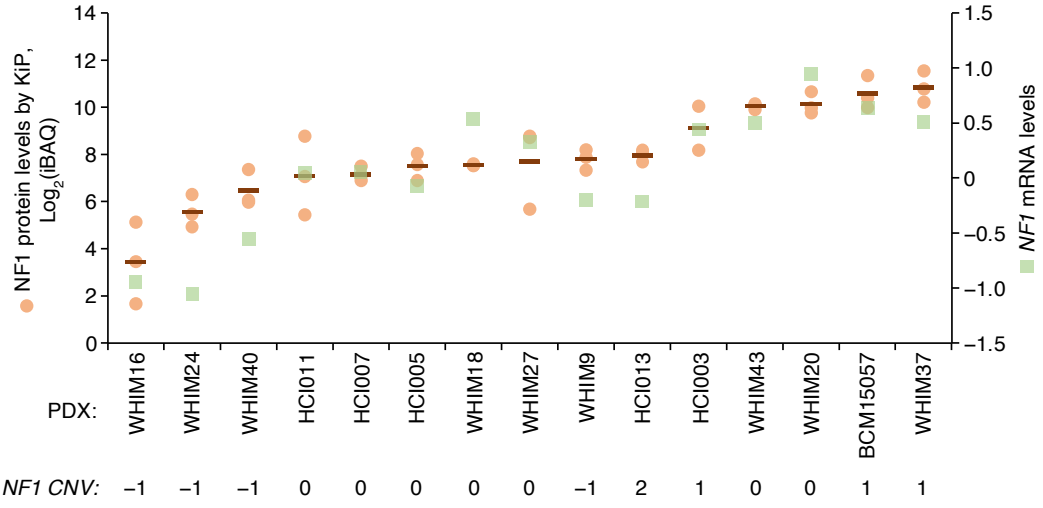

Figure 3. NF1 protein levels as measured by KIPA agree with mRNA and copy number measurements in selected ER$^+$ PDX models. NF1 protein levels as determined by KIPA (orange dot), *NF1* mRNA levels as measured by RNA-seq (green dot), and NF1 copy number as deduced from whole exome sequencing from each PDX model were plotted to show a general good agreement between these measurements.

In the next project year we will treat these PDX models with fulvestrant and binimetinib to see which of these models will respond to assess how NF1 levels can predict treatment response. Also next year, we will be ready to analyze NF1 protein levels in patient samples (Goal 1-4).

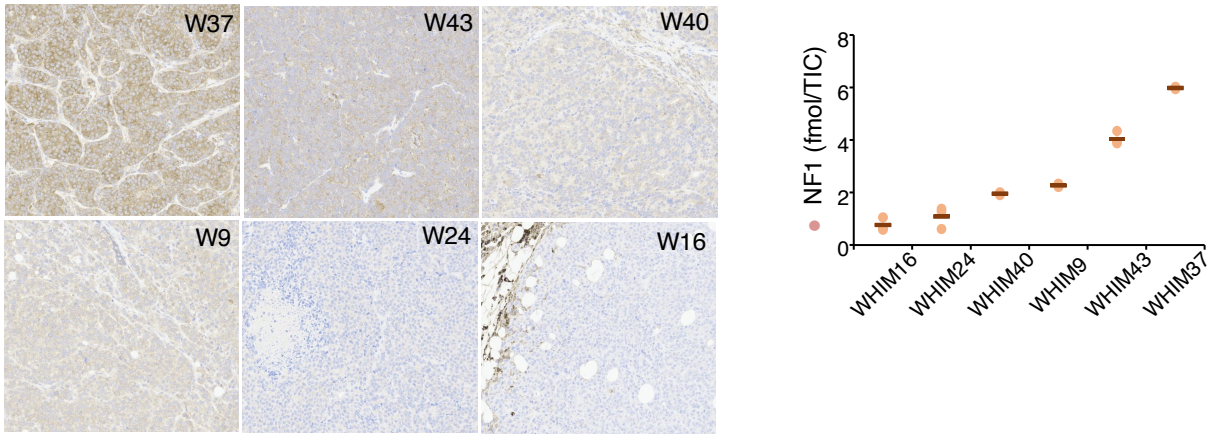

Figure 4. SureQuant can more precisely measure NF1 protein levels in tumors. We selected 6 models and measured NF1 levels with by IHC (left) or by SureQuant (right). The SureQuant can quantitatively separate these models into 3 groups.

IMPACT

For targeted therapy to work, we must be able to accurately measure the biomarker, NF1, driving the treatment strategy. Given the importance of NF1, there is currently no robust diagnoses to assess the loss of NF1 protein. In this one project we have demonstrated that NF1 protein levels in tumors can be measured by two approaches, IHC and MS. The former is ready to be deployed to study clinical FFPE samples while the latter is very quantitative. How these methods can be used to study clinical samples will be a key test for the next project year.

CHANGES/PROBLEM

We had to make the transition earlier this year when the original PI on the grant, Dr. Matthew Ellis departed for a position at Astra Zeneca. Since then we have addressed the issue by requesting Dr. Chang, a co-PI and a long time collaborator with Dr. Ellis to take over the leadership as the PI. We have also added Dr. Bora Lim, a physician scientist, and our clinical research director as a co-I on the grant to continue providing clinical supervisions for this project. We do not believe there will be any major disruptions going forward, and we have been productive in Year-1 of our study.

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). 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 Q3 of 2022 as one of the ten inaugural trials. 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.

Publication:

While working hard on this project, we have been also productive on another related project in which we found that when the activity of a Ras protein increases during a premalignant state called DCIS, these mostly

ER+/luminal lesion can evolve into a basal-like state, which can be invasive. We have submitted a paper describing this, which was invited for revision.

Ze-Yi Zheng, Hanan Elsarraj, Jonathan T. Lei, Yan Hong, Meenakshi Anurag, Long Feng, Hilda Kennedy, Yichao Shen, Flora Lo, Zifan Zhao, Bing Zhang, Xiang H. -F. Zhang, Fariba Behbod, Eric C. Chang. Elevated *NRAS* expression during DCIS is a potential driver for progression to basal-like properties and local invasiveness. *Breast Cancer Res.* Invited for revision.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name	**Project role**	**ORCID ID**	**Person Mon Worked (Time Period worked 08/01/21-07/31/22)**	**Project contribution**	**Funding support**
Eric Chang	PI**	0000-0002-1375-5088	3.15 CM	Design and execute all the studies in this project, and will write the pa-per.	This grant.
Zeyi Zheng	Instructor	0000-0001-6536-4874	2.4 CM	Assist Dr. Chang in the design and execution of all the studies in this project, and supervise Ms. Kenney	This grant.
Hilda Kennedy	Tech	NA	2.4 CM	Provide technical support on all projects.	This grant
Beom-Jun Kim	Co-Investigator	0000-0003-3109-8170	2.4 CM	Performed MS related experiments.	This grant
Bora Lim	Co-Investigator	0000-0002-4182-6058	1.2 CM	Supervise all experimental design to ensure clinical significance.	This grant

Meenakshi Anurag	Co-Investigator	0000-0003-4379-5192	1.2CM	Bioinformatic and biostatistical analyses.	This grant

**** PI was changed to Dr. Eric Chang from Dr. Matthew Ellis from 03/07/2022.**

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.

CHANG, ERIC

ACTIVE

W81XWH-19-1-0527 09/01/19 – 08/31/22 (NCE) 0.24CM (2%)**
Department of Defense
Project Title: Direct regulation of estrogen receptor transcription activity by NF1
Grants Contact: Henry Nothnagel- henry.j.nothnagel.civ@mail.mil
Role: Principal Investigator
Major Goals: The objective of this project is to define NF1's role in bone metastasis in order to establish a strategy to stop it
Specific Aims

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.
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 metas-tasis in ER^+ $NF1^-$ cancer.

** The effort of DOD W81XWH-19-1-0527 reduced to 2% from 03/07/2022.

P50CA186784 (Zhang) 08/01/20 – 07/31/25 3.0 CM (25%)

NIH/NCI

Project Title: Translational Research in Breast Cancer

Grant Contact: Funmi Elesinmogun - elesinmf@mail.nih.gov

Project 1: Basic Co-Leader – 1.8 CM (15%)

The objectives of this project are thus to identify treatment-resistance drivers in ER+ breast cancer and to target their therapeutic vulnerabilities.

Core C Admin: Core Lead – 1.2 CM (10%)

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.

W81XWH-21-1-0106 03/15/21-03/14/24 4.2CM (35%)

Department of Defense
Project Title: Therapeutic Targeting of Nuclear Hormone Receptors in Neurofibromin/NF1-Depleted Breast Cancer
Role: Initiating PI
Major Goals: The overall objective of this project is to assess what therapeutic opportunities are associated with neurofibromin loss in patients.
Specific Aims

1. We will perform molecular biology experiments to determine whether neurofibromin-loss causes AR activation in both ER+ and ER– breast cancer cells.
2. We will determine whether ER+ NF1– breast cancer is more sensitive to an AR-activating agent, or 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.

W81XWH-21-1-0634-***This grant*** 08/01/21 – 07/31/23 4.2 CM (35%)**
Department of Defense
Project Title: Optimizing Treatment for NF1-Deficient Metastatic ER+ Breast Cancers (Expansion Award)
Role: Principal Investigator
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
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
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.

**PI changed from Dr. Matthew Ellis to Dr. Eric change on 03/07/2022 and Dr. Chang's effort increased from 20% to 35% at the same time.

PENDING
None

COMPLETED IN LAST 5 YEARS

RP180844 (Chang) 08/31/18 - 08/31/21(NCE) 1.20 CM(10%)
CPRIT – HI/HR
Project Title: Regulating androgen receptor as a co-repressor by neurofibromin (NF1)
Grant Contact: Patty Moore - pmoore@cprit.texas.gov
Role: Principal Investigator
Major Goals: This project will investigate the hypothesis that NF1 is a co-repressor for AR as well as ER, so that its loss may increase AR (as well as ER) transcriptional activities in breast cancer cells
Specific Aims
1. We will assess whether NF1 functionally acts as an AR co-repressor by measuring AR transcriptional activity after *NF1*-silencing *in vitro*
2. We will assess the roles of anti-AR agents in treating NF1-deficient breast cancer by determining whether its growth can be pharmacologically blocked *in vitro*, as well as *in vivo* using xenograft mouse models

W81WH-16-1-0538 (Chang) 09/30/16-09/29/20(NCE) 3.24 CM(27%)
Department of Defense
Project Title: Direct Regulation of Estrogen Receptor Transcriptional Activity by NF1
Grants Contact: Jamie A. Shortall – Jamie.a.shortall.civ@mail.mil
Role: Initiating PI
Major Goals: The key objectives of this proposal are to define NF1's role in the control of ER's transcriptional activity and to assess the clinical significance of this finding by focusing on designing treatment strategies
Specific Aims
1. To define how NF1 regulates expression of ER target genes by investigating a direct interaction between NF1 and canonical ER transcriptional co-regulators
2. To establish a strategy to treat NF1-deficient ER^+ breast cancers by rationally combining anti-Ras and anti-ER approaches.

1R21CA226567-02 (Chang) 06/04/18 - 05/31/21(NCE) 1.8 CM(15%)
NIH
Project Title: A Novel N-Ras Pathway DCIS to Basal-like Breast Cancer
Grant Contact: Viviana Knowles – Viviana.knowles@nih.gov

Role: Principal Investigator
Major Goals: Our overall research goal is to show that BLBC evolves from luminal cells during DCIS, driven by N-Ras.
Specific Aims
1. To assess whether BLBCs indeed evolve from luminal breast cancers, and whether this is driven by NRas in DCIS, studying both previously established DCIS cell lines and *patient-derived* primary DCIS cells both *in vitro* and *in vivo* using MIND xenografts
2. To assess whether formation of BLBC can be blocked early during DCIS by inhibiting the JAK2-STAT5-IL8 pathway downstream of N-Ras, using small molecule inhibitors in xenograft models

(Chang) 3/1/2016 – 2/28/2017 2.4CM(20%)
Willa and Ella Owen Medical Research Foundation
Project Title: Target Ras for Destruction as a Novel Treatment for Cancer
Grant Contact: Nancy Davis, Davis, ndavis@bcm.edu, 713-798-6194.
Role: Principal Investigator
Major Goals: This project is to assess the possibility that the stability of Ras proteins can be targeted by small molecule compounds that can later be developed into therapeutic agents.
Specific Aims
1. To use various mouse models to test whether flunarizine treatment can inhibit the growth and/or metastasis of basal-like breast cancer overexpressing N-Ras.
2. To define the mechanism by which flunarizine controls Ras degradation, by analyzing the interaction between Ras and key components involved in selective autophagy

1P50CA186784 (Osborne-PI; Chang-Project Leader) 3/1/15-8/31/16 0.12CM(1%) NIH
Project Title: Target N-Ras for treating basal-like breast cancer- SPORE Developmental Project
Grant Contact: Viviana Knowles, viviana.knowles@nih.gov;
Role: Pilot project leader
Major Goals: The objective of this project is to seek means to target N-Ras in order to ultimately treat Basal-like Breast Cancer.
Specific Aims

1. To directly test whether FLN can be used to treat BLBC in vivo using mouse models
2. To fully investigate the mechanism that induces N-Ras degradation by examining the role of autophagy

SAC140059 Komen Leadership Grant (Ellis) 06/23/15-06/22/16 3CM(25%)
Susan G. Komen for the Cure
Project Title: Mechanisms of Endocrine Resistance in Estrogen Receptor Positive Breast Cancer
Grant contact: Jerome Jourquin, JJourquin@komen.org
Role: Co-Investigator
Major Goals: This project is to target aberrant cell survival mechanisms in ER+ breast cancer that permit late relapse by using genome matched pharmacological approaches, causing ER+ tumors to permanently regress.
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.

RP130135 (Chang) 06/01/13/-11/30/15 1.2 CM(10%)
Cancer Prevention and Research Institute of Texas

Project Title: Comprehensive identification of all human Ras effectors to define mechanisms of Ras-induced malignancy and potential drug targets.
Grant Contact: Michael Brown, mbrown@cprit.state.tx.us
Role: Principal Investigator
Major Goals: The major goal is to use a new technology to isolate all human Ras effectors and test them for relevance to tumor formation.

Specific Aims
1. To construct new Gateway compatible libraries from the ORFeome collection to ultimately cover the whole human genome.
2. To screen for new Ras effectors using N-Ras and K-Ras-4B as baits in live human cells.
3. To functionally validate the isolated Ras effectors for their roles in tumorigenesis.

Overlap:
None

ANURAG, MEENAKSHI

ACTIVE

U01CA214125 (Anurag/Carr) 06/01/2017 – 05/31/2023 (in NCE) 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 (Kaochar) 09/20/2018 – 06/30/2023 1.83 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

Adrienne Helis Malvin Medical Research Foundation (Foulds) 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.

BCC Philanthropic Project (Learner) 08/01/20 – 7/31/25 1.16 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

P50 CA186784 (Zhang) 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

P50 CA186784 (Zhang)-*New* 08/01/22 – 07/31/23 0.24 CM
NIH/NCI
Project Title: Translational Research in Breast Cancer – Development Research Project
Contact: Funmi Elesinmogun; Email: elesinmf@mail.nih.gov
Role: PI
Major Goals: (SPORE DRP) Through the funding of pilot projects, we broaden the scope of research, and allow exploration of high-risk ideas that have the potential for high yields in treatment, prevention, or basic biology of breast cancer. We also attract new investigators with a wide variety of special expertise to apply their expertise to problems and questions in breast cancer research, and we catalyze productive collaborations in which individual skills and approaches combine to create progress that no single investigator could achieve alone.
Specific Aims (individual awardee Aims): Aim 1: to determine the effect of LIG1 loss in HR deficient TNBC models. Aim 2: To guide targeted-therapies based on LIG1 and HRD status in TNBC cell lines.

W81XWH-21-1-0634 (Chang)-*This grant* 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) 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) 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.

R01 CA271498 (Li/Zhang)-*New* 03/14/2022 – 03/13/2027 1.00 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

R01 CA269783 (Echeverria) 09/01/2022 – 08/31/2027 0.60 CM NIH
Project Title: Metabolic Adaptation in Triple Negative Breast Cancer Residual Disease Following Chemotherapy
Role: Co-Investigator
Major Goals: Chemoresistance in triple negative breast cancer (TNBC) leads to extremely poor patient outcomes and there are no approved targeted therapies with which to treat residual tumors that persist following chemotherapy. Based on our preliminary findings that TNBCs rely on mitochondrial metabolism to evade chemotherapy, we now aim to delineate the functional role of mitochondrial structural dynamics in TNBC metabolic adaptations and chemoresistance. Our long-term goal is to therapeutically target regulators of mitochondrial structure in chemo refractory TNBCs.
Specific Aims: Aim 1. Determine if mitochondrial fusion is responsible for NACT-induced oxphos in TNBC. Aim 2. Genetically and pharmacologically target and quantify mitochondrial fusion in residual TNBC mouse models and serial patient biopsies.
Overlap: None

COMPLETED

P50 CA186784 (Ellis) 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

SAC190059 – Leadership Grant (Ellis) 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

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
Overlap: None

SUPPORT
LIM, BORA

Current

0021150030 (Lim)-***New*** 05/2022 – 04/2025 0.60 CM
AbbVie Inc
Project Title: Proteogenomic Analysis of Treatment Refractory Cancers
Contact: Michelle A. Parks, J.D. - michelle.parks@abbvie.com
Role: PI
Major Goals: We will perform three pilot studies of proteogenomics as a prelude to larger studies and for proof of the principle that we can conduct proteogenomic analysis during cancer clinical trials.

W81XWH-21-1-0107 (Lim) 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.

T2021-018 (Hoyos)-***New*** 11/2021 – 11/2024 0.24 CM
V Foundation
Project Title: 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"
Contact: info@v.org
Role: Co-Investigator
Major Goals/*Specific Aims*: 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.

W81XWH-21-1-0634 (Chang)-***This grant*** 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
Major 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.

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

R01 CA262623 (Han) 07/01/21 – 06/30/26 0.30 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.

CZF2019-002432 (Navin) 12/07/2020 – 02/28/2023 NCE 1.68 CM
Chan Zuckerberg Foundation
Project Title: Human Breast Cell Atlas Seed Network
Contact: Jennifer Weaver (MD Anderson Cancer Center) JMWeaver@mdanderson.org
Role: Co-Investigator
Major 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.

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

P50CA186784 (Zhang) 08/01/20 – 07/31/25 0.60 CM
NIH/NCI
Project Title: Translational Research in Breast Cancer
Contact: Funmi Elesinmogun - elesinmf@mail.nih.gov
Role: 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

P50CA186784 (Zhang) 08/01/20 – 07/31/25 1.20 CM
NIH/NCI
Project Title: Translational Research in Breast Cancer- Project 1
Contact: Funmi Elesinmogun - elesinmf@mail.nih.gov
Role: 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

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
Contact: Alissa Adams (Jackson Laboratory) Alissa.adams@jax.org
Major 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.

U54CA233223 (Mitsiades) 09/2018 – 06/2023 1.20 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
Grant Contact:
Role: Project 2 Leader
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.

Pending

R01CA255080 (Ling) 07/2022 – 06/2027 1.01 CM
NIH/NCI
Project Title: Systematic Targeting Small Nucleolar RNA Augments Immunotherapeutic Efficacy
Role: Co-Investigator
Major goals: The major goal of this study is to demonstrate the molecular mechanism of Immune check point inhibitor resistance of TNBC, which could be alleviated by novel targeted therapy towards small nucleolar RNA, SNORD46.

R01CA269783 (Echeverria) 09/2022 – 08/2027 0.36 CM
NIH/NCI
Project Title: Metabolic Adaptation in Triple Negative Breast Cancer Residual Disease Following Chemotherapy
Role: Co-Investigator
Major Goals: Our long-term goal is to therapeutically target regulators of mitochondrial structure in chemo refractory TNBCs.

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