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TITLE: Prospectively Randomized, Placebo-Controlled Phase 3 Study to Determine the Effect of Denosumab on Breast Cancer Prevention in BRCA1 Mutation Carriers

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14. ABSTRACT

In Europe and the USA, more than 1.3 million women are estimated to carry a germline mutation in the BRCA1 or BRCA2 genes. These women have up to 87% lifetime risk of developing breast cancer, with tumors usually developing at an early age. Currently, prophylactic surgery is the only proven procedure that significantly reduces breast cancer risk, and this can be associated with postoperative complications and a suboptimal cosmetic outcome. Medical prevention, if effective, could present a non-invasive alternative to mastectomy, but would need to be started relatively in early adulthood and has potentially to be offered beyond menopause. This strategy could also 'buy time' for women considering prophylactic mastectomy. There is accumulating evidence that the RANK/RANKL signaling pathway plays a pivotal role in breast tumorigenesis, particularly in the development of BRCA1-mutated tumors. Targeting the RANK pathway has been shown to attenuate breast epithelial proliferation in vitro and in vivo, and to profoundly reduce mammary tumor formation in mouse models.

In addition, since BRCA germline (gBRCA) mutations confer an increased risk for ovarian cancer, the vast majority of gBRCA women undergo prophylactic bilateral salpingo-oophorectomy (PBSO) at a young age. This has been shown to reduce ovarian cancer risk, but can significantly compromise bone, sexual and potentially cardiovascular and cognitive health. Many women who undergo PBSO therefore receive some kind of osteoprotective therapy. Current medical breast cancer prevention strategies for gBRCA mutation carriers involve the use of tamoxifen or aromatase inhibitors, which - at least in the case of aromatase inhibitors - may further compromise bone health.

The RANKL inhibitor Denosumab is potentially an ideal chemopreventive agent for women with a BRCA1 germline mutation because it: (a) could potentially reduce breast cancer risk, and (b) concomitantly protect bone health in those women who have already undergone PBSO or in naturally postmenopausal women. It has already been shown to have a positive benefit-risk profile in the treatment and prevention of bone loss in post-menopausal patients undergoing endocrine therapy for breast cancer.

15. SUBJECT TERMS

BRCA1; Breast Cancer; Bone Health; Breast Density; Clinical Trial; Collaboration; Correlative Science; Denosumab; DNA; Imaging; Mammogram; International; Multicenter; Mutation; Prevention; Phase III; Translational Science; Quality of Life; Xtreme CT HR-pQCT

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose, and scope of the research.*

   The BRCA-P/ ABCSG 50 Study is a randomized, double-blinded, placebo-controlled, multi-center, international phase 3 trial, which examines the preventive effect of denosumab on breast cancer, as well as ovarian cancer and other cancer types in women, who have a *gBRCA1* mutation. One in 400 women in the industrialized world carries the *BRCA1* mutation, which entails a 60-87% risk to develop breast cancer and a 50% risk to develop ovarian cancer throughout the lifetime. Denosumab is already approved for the treatment of various medical indications, for example, prevention of skeletal complications (pathological fracture, radiation of the bone, spinal cord compression or bone surgery) in adults with bone metastases due to solid tumors.
   denosumab is not yet approved as a breast cancer prevention drug for people carrying the *BRCA1* mutation. The main objective of this prevention study is to determine whether the study medication, denosumab can reduce the risk to develop breast cancer in women with a *BRCA1* mutation or possibly even prevent it.

   Participants will be randomized 1:1 into one of 2 treatment arms (Arm A or Arm B).

   - TREATMENT ARM A

   Study medication Denosumab 120 mg as a subcutaneous injection every 6 months for 5 years.

   - TREATMENT ARM B

   Placebo as a subcutaneous injection every 6 months for 5 years.

   The study will be conducted in seven countries and 2918 women in total will participate.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

   BRCA1; Breast Cancer; Bone Health; Breast Density; Clinical Trial; Collaboration; Correlative Science; Denosumab; DNA; Imaging; Mammogram; International; Multicenter; Mutation; Prevention; Phase III; Translational Science; Quality of Life; Xtreme CT HR-pQCT

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

   Please refer to the tables below.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Site 1	Site 2	Site 3
Dana-Farber Cancer Institute 450 Brookline Avenue Boston, MA For the Alliance for Clinical Trials in Oncology, Chicago, IL	Austrian Breast & Colorectal Cancer Study Group* Nussdorfer Platz 8 1190 Vienna, Austria **with national Sponsors in UK, Germany, Israel, Spain (where applicable)*	Australia/ New Zealand Breast Cancer Trials Group Level 4, 175 Scott St Newcastle, NSW 2300
PI: Judy E. Garber MD MPH, CO-PI: Chair, Steering Cmte	PI: Christian Singer, MD Overall PI, BRCA-P	Geoffrey Lindeman, MD PhD Global PI, BRCA-P

Aims and Tasks	Timeline Months	Site 1	Site 2	Site 3	Completion Date / % Complete
Specific Aim 1: To evaluate the reduction in the risk of breast cancer (Invasive and DCIS) in women with germline *BRCA1* mutation treated with Denosumab compared to Placebo					
Major Task 1: Approval of trial protocol and initiation of BRCA-P					
Preparation and submission of core Clinical Trial application forms to IRB's/Ethical committees	1-3	X	X	X	**Site 1**: The ABCSG-Alliance Country Sponsor Agreement and MoU was fully executed as of 11/17/2021, which allowed us to receive final approval from the NCI Division of Cancer Prevention (DCP) on 11/17/2021. On 12/10/2021, we received the NCI CIRB continuing review approval for the protocol. The HRPO protocol review application was submitted to the DoD on 12/23/2021. An Activation Amendment was submitted and approved on 2/1/2022 and 2/8/2022 by the NCI CIRB and NCI DCP respectively. An Update #01 was submitted, and we received final approval for the US group specific appendix of the protocol from the NCI CIRB on 09/22/2022 and from the NCI DCP on 09/23/2022. % Complete: 100% preparation; 100% complete

					Site 2 and 3: This was achieved in all countries (Australia, Austria, UK, Spain, Israel, Germany). **Site 2 and 3:** % Complete: 100%
Complete and finalize revisions of the main protocol document to include the scientific projects and additional image and specimen collection. Include modifications necessitated by DOD funding for the correlative science aims.	1-3	X	X	X	**Site 1:** The approved version of the US group specific appendix (Version Date 08/26/22) of the protocol includes all the correlative science aims. Global protocol v2.0 changes were included in Update #01 for the US sites. **Site 2 and 3:** It was agreed by HRPO, that no changes in language regarding the Research Monitor have to be implemented in the protocol or other trial documents (such as ICF). Main protocol submitted in all 6 countries and approved in 4 countries (Austria, Australia, Spain and Israel, partially approved also in Germany); approval for UK is pending, amendment see above **Post-reporting period note:** Approvals for UK were obtained on 20-Sep-2022. **Site 2 and 3:** % Complete: 95% preparation. 100%
Submit revised protocol document for review at participating IRBs and US CIRB.	1-3	X	X	X	**Site 1:** On 09/22/2022, we received the NCI CIRB approval for Update #01 of the protocol. All participating sites continue to submit the protocol document to site-level IRBs as part of the activation process. **Site 1:** % Complete: 100% Complete **Site 2 and 3:** Main protocol

					document complete, amendment see above **Site 2 and 3:** % Complete: 90% preparation. 90% complete
Submit revised protocol document for review at HRPO/DOD.	1-6	X	X		**Site 1:** The HRPO protocol review application was submitted to the DoD on 12/23/2021. A protocol activation amendment was submitted to the NCI DCP for review and approval on 11/18/2021. All approved applications and protocol revisions have been shared with the DoD. **Site 1:** % Complete: 100% preparation; 100% complete **Sites 2 and 3:** It was agreed by HRPO, that no changes in language regarding the Research Monitor have to be implemented in the protocol or other trial documents (such as ICF). Main protocol submitted in all 6 countries and approved in 4 countries (Austria, Australia, Spain and Israel, partially approved also in Germany); approval for UK is pending, amendment see above **Post-reporting period note:** Approvals for UK were obtained on 20-Sep-2022. **Site 2 and 3:** % Complete: 100% preparation. 95% complete
Obtain IRB approval from all international IRBs and US-CIRB following submission of required revisions.	3-6	X	X	X	**Site 1:** NCI CIRB: as above **Site 1:** % Complete: 100% **Site 2 and 3:** The global BRCA-P protocol version 2.0 was amended to take queries from various regulatory bodies into account. The global protocol was submitted to the DoD and reviewed by

					HRPO, the official approval notification will follow as soon as the EC/ CA approvals are reviewed by HRPO. Global Protocol v2.0 approvals were already obtained in countries such as Austria, Spain, and Israel and partially in Australia. **Site 2 and 3:** % Complete: 90% preparation. 90% complete
Finalize systems for drug distribution and AE reporting	1-6	X	X		Achieved for **site 1, 2, 3:** Those systems are set-up centrally by ABCSG for all sites. The IxRS system is live and running (used for international drug supply). (S)AE reporting is outlined in the global Study Manual and associated documents. % complete: 100% complete **For Site 1:** The Alliance has worked with the ABCSG to harmonize US procedures in line with local/NCI regulations and manufacturer specifications. In addition to the SAE and drug distribution systems set up centrally by ABCSG for all sites, the Alliance, as a grantee of the NCI, will use NCI's electronic reporting system, the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS), for SAE reporting. As the US IND holder, Alliance shall comply with all applicable safety reporting requirements involving the Study Drug, including the requirements set forth in 21 C.F.R. § 312.32.
Post study on ClinicalTrials.gov/EMA registry	4-6	X	X		**Site 1:** ClinicalTrials.gov entry for A211801 was approved on 01/14/2021. The NCT ID is

					NCT04711109. Local sites for the study will be updated on the ClinicalTrials.gov website once they begin accrual. **Site 1**: % Complete: 100% preparation, 100% complete **Site 2:** The Study was activated on 25-Jun-2018 (Competent Authority approval date of the first participating EU country, which is Austria) in the EU Clinical Trials Register. **Site 2:** % Complete: 100% preparation. 100% complete. .
Initiate enrolment at 64 total sites	4-10	X	X	X	**Site 1:** All 34 sites are in the process of study initiation activities including completing study training and fulfilling local institutional requirements for site activation. So far, 23 out of the 34 sites have completed or are in the process of completing the study specific training. Access to training is only granted once sites receive site specific NCI CIRB approval by submitting the study specific worksheet. As of 12-Oct-2022, 110 personnel across 23 sites have been trained to conduct the BRCA- P study in the US. Enrolment will begin as start-up activities are completed at each respective site. **Site 1:** % Complete: 100% preparation **Site 2 and 3:** As of 14-Sep-2022, 4 sites in Austria, 14 sites in Australia, 5 sites in Spain and 1 site in Israel are activated. All planned sites are active in Austria,

					Australia, and Spain. One additional site in Israel was submitted to the EC, once approved the site will be initiated and activated. Approvals are pending for Germany and UK. **Post-reporting period note:** Approvals for UK were obtained on 20-Sep-2022, additional site was approved in Israel on 02-Oct-2022. **Site 2 and 3: %** Complete: 100% preparation. 80% complete
Coordinate with sites for material transfer agreements	4-10	X	X	X	**Site 1:** An umbrella MTA has been signed to designate Massachusetts General Hospital (MGH) as the data coordinating centre for all images collected for the bone density sub-study. MGH will receive only de-identified images for the purpose of the bone density measurement sub-study. These images will be collected and analysed by MGH. Since the trial is being coordinated by the Alliance in the US, no individual site level MTAs will be required for the transfer of biospecimens from recruiting sites to Alliance Biorepository at Mayo Clinic (ABMAYO). **Site 1:** % Complete: 100% complete **Site 2:** Most countries do not have central biobanks in place and store samples locally. **Site 3:** Australia is already shipping material to their central biobank. **Site 2 and 3:** % Complete: 100%

					preparation. 100% complete
Recruit 2918 women to protocol BRCA-P	6-30	X	X	X	**Site 1:** An elaborate recruitment plan has been devised to invite eligible women to participate in the US. Enrolment will begin as start-up activities are completed at each respective site. **Site 2 and 3:** As of 14-Sep-2022, 147 participants have been randomized to the BRCA-P study. Due to COVID-19 pandemic, recruitment was impaired, as was already communicated by ABCSG to DoD on 19-Mar-2020 and more recently during the Milestone Meetings in November 2020 and 2021 and it cannot be foreseen how long the situation might have an impact on study progress. Therefore, support / endorsement from all partner organizations as well as Amgen has been granted for enrolment extension until end of 2023.
Develop and implement systems for paying sites for subject recruitment with NCORP	4-8	X			**Site 1:** Systems are in place to reimburse sites per participant recruitment based on standard NCORP/NCI procedures. **Site 1:** % Complete: 100% complete
Major Task 2: Implement blood specimen, image, and PRO data collection/storage systems N = 1000 participants					
Formalize procedures for kit assembly and distribution, return to repositories	1-3	X	X	X	**Site 1:** For US sites, a detailed Correlative Science Procedure Manual (CSM) has been prepared including detailed instructions for collection, local and central processing, storage, and shipment of all protocol-specified samples, for all relevant projects. Instructions for sharing images are included in the US Specific Appendix.

					Site 1: % Complete: 100% complete **Site 2 and 3:** Achieved in Australia, where a central laboratory is in place. For other countries samples are stored locally at site. Handling of mandatory (and optional samples) is outlined in Australia specific Manual as well as global Study Manual. An update of the global Study Manual, including more detailed instructions for sample handling, has been meanwhile released by ABCSG. **Site 2 and 3:** % Complete: 100% preparation. 100% completion
Finalize plans for image collection and storage in existing data centers	1-4	X	X	X	**Site 1:** Procedures for US sites are finalized in the CSM. **Site 1:** % Complete: 100% complete **Site 2 and 3:** Imaging necessary for enrollment in the BRCA-P trial is stored in the respective Investigator Site Files at the sites. Additional imaging for exploratory research not applicable at all sites. **Site 2 and 3:** % Complete: 100% preparation. 100% completion
Finalize plans for QOL instrument collection in US, UK, and Australia and data transmission to study team in Australia	1-4	X	UK only	X	**Site 1,2 and 3:** QoL questions are finalized, available in English (limited to English-speaking participants only) and already implemented in the BRCA-P eCRF and are thus centrally collected using electronic submission systems.

					% Complete: 100% complete
Implement specimen, imaging and QOL instrument collection to repositories.	6-48	X	X	X	**Site 1:** The Alliance and ABMAYO has finalized plans for specimen collection, management, and storage in established repositories in the US using standardized procedures. To avoid material expiration, storage tubes and materials will be acquired closer to the activate date. **Site 1:** % complete: 100% preparation; 100% complete **Site 2 and 3:** Australia has central lab in place for samples; other countries store samples at sites directly. At site 2 and 3 QoL is only applicable in Australia and UK (already finalized eCRF for collection). Images are stored locally and data in general for all sites are stored centrally on eCRF at ABCSG (MACRO). **Site 2 and 3:** % Complete: 100% preparation. 100% complete
Implementation of overall site monitoring programs	7-48	X	X	X	**Site 1:** A preliminary local site monitoring plan has been developed by the Alliance based on the basic criteria for monitoring shared by ABCSG. Support to implement the monitoring plan has been secured and the Alliance is working to hire a monitor for this trial. **Site 1:** % complete: 100% preparation. **Site 2 and 3:** Implementing Site monitoring programs is the responsibility of every Country Sponsor. As only Australia,

					Austria, Spain, and Israel have active sites so far, site monitoring is in place in these countries. For Austria a Trial Monitoring Plan is in place and the basic criteria for monitoring have been shared by ABCSG with all global partners who need it for their set up. Training for all assigned Site Monitors was provided by ABCSG. **Site 2 and 3:** 100 % complete in active countries
Specific Aim 2: We will investigate whether treatment with denosumab alters serum OPG, RANKL or progesterone levels in pre- and postmenopausal *BRCA1* carriers in **1000** participants					
Collection of blood specimens for measurement of RANKL, OPG, Estradiol, Progesterone levels and repository at baseline and months 12, 24, 36, 48	7-48	X	X	X	**Site 1:** Specimen collection will begin once participants are enrolled onto the study. **Site 2 and 3:** (Optional) blood samples are collected and stored at site in Austria, Spain, and Israel, whereas in Australia blood samples are shipped to the central laboratory. Complete: Sampling is ongoing, however testing will be performed later on for most countries **Site 2 and 3:** % Complete: 100% in active countries
Optimize measurement of biomarkers with specified kits	7-9		X		**Site 1:** Specimen collection will begin once participants are enrolled onto the study. **Site 2**: Information on which samples to collect and how to proceed with them (including preferable kits) has been shared with active sites. Detailed instructions are also outlined in the Study Manual.
Optimize systems for de-identifying specimens for analysis (protect treatment arm and tumor v none)	4-6	X	X	X	**Site 1,2 and 3:** A detailed Study Manual has been prepared with instructions to de-identify

					specimens for analysis. % Complete: 100% preparation. 100% complete
Batch analyses of serum specimens for circulating biomarkers as above	13-48	X	X	X	**Site 1,2 and 3:** Analysis will be performed at a later stage of the trial.
Specific Aim 3: To evaluate the change in mammographic breast density (MBD) in premenopausal *BRCA1* mutation carriers (g*BRCA1*m) from baseline to 12 months of denosumab versus placebo. **N= 268 participants (134 per arm)**					
Optimize collection of digital mammogram images and storage all sites	7-12	X	X	X	**Site 1:** Procedures for US sites are finalized in the U.S. Specific Protocol Appendix. **Site 1:** % Complete: 100% preparation; 100% Complete **Site 2 and 3:** Imaging is performed as per local standard (MG is performed where feasible. However, this is only mandatory at baseline). Where image is collected, the respective data is documented in the database. Participants where data is available are considered for this Aim. **Site 2 and 3:** % Complete: 100% preparation; 100% Complete
Optimize collection of breast MRI images and storage all sites	7-12	X	X	X	**Site 1:** Procedures for US sites are finalized in the CSM. **Site 1:** % Complete: 100% preparation; 100% Complete **Site 2 and 3:** Imaging is performed as per local standard (MRI is performed where feasible. However, this is not mandatory). Where image is collected, the respective data is documented in the database. Participants where data is available are considered for this Aim. **Site 2 and 3:** % Complete: 100% preparation; 100% Complete

Analysis of digital mammogram images using Cumulus software*	7-48	X			**Site 1:** Analysis will begin once all images are collected. % Complete: 100% preparation
Analysis of digital mammogram images using semi-automated system*	7-48	X			**Site 1:** Analysis will begin once all images are collected. % Complete: 100% preparation
Specific Aim 4: To investigate the impact of denosumab use in women with a *BRCA1* germline mutation on health-related quality of life (HRQoL), controlling for potential confounders such as menopausal status and age. **N = 400 participants**					
Optimize systems for collection of QOL instruments from English speaking enrolled participants	4-6	X	UK only	X	**Site 1:** QoL questions are agreed on, available in English (they will be provided to English-speaking participants only) and already implemented in the BRCA-P eCRF and are thus centrally collected using electronic submission systems. **Site 1:** % Complete: 100% preparation; 100 % complete **Site 2 and 3:** QoL is documented for English speaking countries centrally at ABCSG eCRF and as Australia already has participants randomized, they already perform this task. UK is not yet active. **Site 2 and 3** 100% complete as system is active
Collection of completed instruments at baseline and months 6, 12 and 24 for English-speaking subjects	7-42	X	UK only	X	**Site 2:** Only applicable for UK – since UK has no active sites yet, no collection of QoL questionnaires could be performed. **Site 3:** QoL questionnaires are being collected
Specific Aim 5: To characterize changes in bone density, microarchitecture, microstructure, and bone strength in premenopausal and early postmenopausal women receiving denosumab 120 mg and placebo **Enrollment 150 participants: with dropout, analysis 100 participants**, scans at 0, 12 and 24 months.					
Finalize recruitment of sites with ScanCo Xtreme CT HR-pQCT in proximity to active BRCA-P sites+	4-12	X	X	X	**Site 1, 2, 3:** The team at MGH has collaborated with ScanCo to identify Xtreme CT HR-pQCT

					sites in proximity to confirmed BRCA-P sites in the US and globally. The team has connected with international sites to finalize site participation. **Site 1,2 and 3:** % Complete: 100% preparation; 50% complete
Optimize systems for image sharing with MGH and site reimbursement for Xtreme HR-pQCT imaging+	4-12	X	X	X	**Site 1:** A contract has been signed to designate MGH as the data coordinating site to optimize image sharing by US participating sites with MGH. MGH will work with the ABCSG to optimize image transfer from global sites to MGH. MGH has refined procedures internally to reimburse sites for Xtreme HR-pQCT imaging in the US and globally. **Site 1:** % Complete: 100% preparation; 25% complete **Site 2 and 3:** await system optimization of site 1
Collection of de-identified HR-pQCT images (protection of denosumab vs placebo assignment)	7-48	X	X	X	**Site 1,2, 3:** Teams at MGH will work with participating sites to ensure collection of de-identified images. **Site 1,2, 3:** % Complete: 100% preparation
Specific Aim 6: In exploratory studies, we will examine tumors arising and prophylactic mastectomy specimens from trial participants and conduct phenotypic (including TIL scoring) and molecular characterization, comparing DNSB to controls. The effect on peripheral blood immune cell subsets will also be characterized and cfDNA collected and studied as a potential screening strategy for women with a germline *BRCA1* mutation. **see Peer/Programmatic responses: ~100 participants per subaim**					
Collection of tumor tissue developing in women on the BRCA-P trial	7-48	X	X	X	**Site 1:** Our team has worked out material collection and transfer processes with ABMAYO. Additional guidance on sample processing and shipment is available in the CSM. **Site 1:** % Complete: 100% preparation

					Site 2 and 3: Guidance is in place in case of tumor occurrence. Sites are advised to collect the respective tumor tissue and document this occurrence accordingly in the eCRF system. **Site 2 and 3:** % Complete: 100% preparation
Collection of prophylactic mastectomy specimens from women who drop out of the BRCA-P trial	7-48	X	X	X	**Site 1:** Our team has worked out material collection and transfer processes with ABMAYO. Additional guidance on sample processing and shipment is available in the CSM. **Site 1:** % Complete: 100% preparation **Site 2 and 3:** Guidance is in place should participants drop out. **Site 2 and 3:** % Complete: 100% preparation
Tissue immune phenotyping	7-48			X	**Site 1:** Materials will be sent to Site 3 for analysis. **Site 3:** Analysis will be performed at a later stage of the trial. % Complete: 100% preparation
Tissue molecular phenotyping and immunohistochemistry	7-48			X	**Site 1:** Materials will be sent to Site 3 for analysis **Site 3:** Analysis will be performed at a later stage of the trial. % Complete: 100% preparation
cfDNA specimens collected from central repositories	7-36	X	X	X	**Site 1:** Use of standardized material transfer practices have been agreed upon to transfer specimens to Site 3. **Site 1:** % Complete: 100% preparation; 0% Complete **Site 2 and 3:** Guidance on collection of cfDNA specimens at sites was developed and

					distributed to active sites.
cfDNA analyses	7-42			X	**Site 1:** Materials will be sent to Site 3 for analysis **Site 1:** % Complete: 100% preparation **Site 3:** Analysis will be performed at a later stage of the trial.

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Please refer to the table above.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Global
The trial was presented at the ASCO conference 2022, which also enabled a lively exchange not only with participating investigators but also with interested parties.
Furthermore, the upcoming annual ABCSG meeting will provide an opportunity to present the trial to an audience of approximately 300 participants.
Last but not least, the main Project Manager at site 2 (and responsible for global coordination as well as establishing recruitment materials) completed a course on "patient involvement on clinical trials".

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Global

This trial is currently in the recruitment phase, and no results are available at this time. However, the PI of site 2 participated in various interviews in local Austrian broadcasts together with a BRCA-P participant (prior consent and IRB approval were obtained) to raise awareness about breast cancer prevention and the BRCA-P study to reach prospective participants. Site 3 has also shared interviews with participating women sharing their experiences on the trial. These interviews are available on social media channels. Further, also the PI in Spain broadcasted a live interview on the social media platform Instagram in cooperation with a patient advocacy group to raise awareness for the trial and to also reach a wide range of women.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Global

In the next reporting period, it is anticipated to receive full regulatory approval for the trial in the last remaining country Germany (Post-reporting period note: UK approvals were obtained since the cut-off date for this report). All planned sites are already active in Australia, Austria and Spain. In Israel a second site will be activated. Further, also Spain is exploring their options regarding initiation of additional sites. In view of two additional countries activating their sites and various additional sites getting activated in already active countries in the next reporting period, it can be expected to see an increase in recruitment numbers.

Promotional campaigns are planned to be launched or were already launched in active countries and strategies to raise interest in trial participation are discussed on an ongoing basis. All materials are shared among the countries and are available for use. We are simultaneously working on clarifying the last pending queries from the German Ethics Committee , in order to receive final approval and start recruitment at 6 sites in Germany.

It should be noted that the COVID-19 pandemic remains unpredictable and might still slow processes down, starting from EC/CA approvals to be received to enrollment of new participants (as these are healthy women, they often times are advised not to enter a hospital in these times).

However, the local sponsors and ABCSG are following up and supporting local teams as necessary and as possible. ABCSG is working together with local country sponsors on strategies how to increase enrollment by regular Investigator calls and implementation of advertisement campaigns and recruitment materials.

Ongoing regular contact has been established (e.g., via teleconferences and harmonized documents) with all participating countries in order to support their current tasks, as well as with representatives of patient advocacy, and will be further maintained to achieve the set goals. Efforts to harmonize systems for registration and drug distribution between US and ABCSG were finalized, allowing the US sites to actively recruit participants.

United States

Last month, we received all our anticipated regulatory approvals that allowed participating sites to submit updated study protocol and relevant documents to their respective institutional scientific and ethical review boards. During the next report period, we anticipate that all of our sites would have been on-boarded. This includes receiving ethical and scientific approvals from all institutions.

In preparation for study activation in the US, the teams at DFCI, Alliance, and ABCSG have worked together to streamline training modules and processes for confirmed sites. In collaboration with the NCI's Cancer Trials Support Unit (CTSU), our team have made all training materials available through the Compliance, Learning, and SOP Solutions (CLASS) website for site level training. Our teams will use the CTSU system to work with participating sites to securely submit regulatory materials to ensure timely study activation. So far, 23 out of the 34 sites have completed or are in the process of completing the study specific training. Access to training is only granted once sites receive site specific NCI CIRB approval by submitting the study specific worksheet. As of now, 110 personnel across 23 sites have been trained to conduct the BRCA- P study in the US. We anticipate that all site personnel at each participating site will complete study related training and submit all regulatory documents to ensure study activation and participant enrolment at their site. Currently, three (3) sites have fully activated in the US and are actively reaching out to prospective participants with the intention to enroll them. We anticipate that in the next reporting period, all sites will be fully activated and actively reach out to prospective participants. If any site is not able to do so in the coming weeks, we plan to replace them with another site.

The US team has drafted a local study monitoring and safety plan. We anticipate rolling out the local study monitoring and safety plan for all US sites.

The US team will continue its collaboration with the ABCSG to harmonize participant registration systems and drug distribution processes. During the next reporting period, we will ensure that all active sites have the logistic and operational capabilities to use these complex systems and are able to randomize and register participants onto the study.

We have made significant progress on developing our participant recruitment material with plans in place to encourage diversity in recruitment and ensuring inclusion of minorities in our trial. All trial relevant participant-facing promotional materials have received the NCI DCP, the NCI CIRB approvals. During the next reporting period, we hope that all local site IRBs will approve the materials to be used at local sites. To promote the trial, our team has developed recruitment materials focused on the providers, participants, and partners. Our promotional materials include an elaborate BRCA-P study website (containing a study summary, call to action, and contact sheet in Spanish), shareable social media graphics (in English and Spanish), flyers (in English and Spanish), and study summary sheets (in English and Spanish). To promote diversity in our trials, we have partnered with two patient advocacy organizations (FORCE and TigerLily Foundation) who focus

on providing information on cancer prevention and upcoming clinical trials to minority populations. In the next reporting period, we plan to promote the BRCA-P study at the Annual FORCE conference. This conference will allow our team to introduce the study to conference participants which includes *BRCA1* mutation carriers and medical professionals who interact with individuals with genetic mutations. Our team will also roll out our social media collaborations with the Alliance, TigerLily, and FORCE which includes a series of social media posts, and one-on-one interactions with advocacy groups that will be broadcasted widely.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Breast cancer prevention for *BRCA1/2* mutation carriers has predominantly focused on surgical strategies, such as bilateral prophylactic mastectomy (BPM) and endocrine ablation by premenopausal bilateral salpingo-oophorectomy (PBSO). These procedures are associated with a substantially reduced risk of breast cancer. Of note, prophylactic BSO (PBSO) had initially been shown to reduce breast cancer risk by 50%, irrespective of whether the *BRCA1* or *BRCA2* genes are affected. More recently, however, a thorough re-analysis which has addressed potential biases that had previously not been considered, has suggested that there may not be a preventive effect of PBSO on breast cancer risk in *BRCA1* mutation carriers, and in *BRCA2* carriers older than 50 years. Only *BRCA2* mutation carriers who are younger than 50 appear to have some benefit from PBSO but the preventive effect is weaker than shown earlier. Similar findings have been observed by other groups.
In addition, in many countries the uptake of these highly effective prevention strategies is low and is compromised by a high rate of postoperative complications and sub-optimal cosmetic outcome for bilateral prophylactic mastectomy. This highlights the need for additional, nonsurgical alternatives for breast cancer prevention particularly for *BRCA1* mutation carriers.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

This trial is currently in the recruitment phase and no results are available at this moment. However, mutations in *BRCA1* or *BRCA2* affect at least one in 400 women in the industrialized world. They are associated with up to 87% lifetime risk for the development of breast cancer, and a 15% to 50% lifetime risk for the development of ovarian cancer. There is now a widespread awareness that a positive family history of breast and/or ovarian cancer, particularly when early onset, could be due to the presence of a deleterious *BRCA1* or *BRCA2* germline mutation. As a result, affected women with a family history now commonly receive genetic testing. This is also being increasingly performed for women diagnosed before age 60 where their tumors exhibit 'BRCA-like' features, such as a TNBC phenotype. Genetic testing is increasingly relevant for their medical management, due to important therapeutic options that include consideration of mastectomy and incorporation of platin-based chemotherapy or PARP inhibitors.
Importantly, the identification of a mutation usually leads to 'cascade testing' of unaffected relatives to ascertain whether they harbor a pathogenic BRCA mutation. This has substantially increased the numbers of *BRCA1/2* mutation carriers who are as yet unaffected by cancer.

Since both ovarian cancer and breast cancer can occur at a young age, carriers are usually advised to undergo prophylactic bilateral salpingo-oophorectomy (PBSO) at about age 40 (after completion of their family) in order to prevent ovarian cancer and to possibly reduce their risk of breast cancer. However, early PBSO compromises bone health and may require ongoing monitoring of bone mineral density throughout life and treatment with bone-protective therapies. Available non-surgical chemopreventive options such as aromatase inhibitors (AIs) are often associated with significant menopausal symptoms, and a further decline in bone health. Alternative, non-hormonal chemopreventive strategies are thus urgently required.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are*

significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

On 19-Mar-2020 ABCSG proactively informed the DoD, that processes of the BRCA-P trial such as the active recruitment in our global sites may be substantially impaired due to COVID-19 and that participating sites are working on rescheduling all avoidable appointments (e.g., trial specific site visits) in order to allocate their resources to emergency and critical patient care and to keep trial participants save.
It was also emphasized that at that point the extent of the impact on trial recruitment cannot be foreseen as it was and still is dependent on how the situation in Europe and in other continents further evolves.
Although the situation slightly improved in the last reporting period, the COVID-19 pandemic might still have an impact on enrollment in the next reporting period and has certainly delayed the activations and impaired enrollment which is one of the reasons we are lagging behind in terms of the enrollment figures.

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Extension of recruitment period until December 2023 – This change was also part of the global Protocol amendment v2.0, that was shared with HRPO 2/25/2022.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Global
- Slow recruitment at some activated sites: proactive measures to motivate sites to enroll participants, such as communication via trial PI and mail-out letters to *BRCA1* mutation carriers to raise interest in the trial and overcome potential concerns. Additionally, in Australia multiple recruitment campaigns using public and social media were initiated to draw attention to the trial and thus boost enrollment. The materials were shared with all other participating countries and may be used as applicable according to the local laws and regulations. Also, in Spain a social media campaign was launched in March. In Austria, various public awareness strategies were submitted to the EC/CA. Since approvals were obtained, those strategies are going to launch in the next reporting period. Further, in Austria the national Coordinating Investigator (PI, Dr Singer) is following up personally with the Austrian sites to discuss potential issues and solutions. On a global level, ABCSG has held multiple dedicated meetings such as an Investigator Meeting and an Investigator emergency teleconference (TC) to discuss the lack of enrollment and to underline the crucial point of getting enrollment started or increased. Further, PIs, Drs. Singer and Garber, contacted each national PI to discuss recruitment challenges and to offer assistance, followed by a Trial Principal Investigator call to define corrective actions and mitigation strategies, resulting in new enrollment tools and considerations that should be adopted on country and site level. The Steering Committee Meeting was held and was mainly focused on enrollment strategies. The enrollment is also being discussed on a regular basis during the Status Calls, which are scheduled monthly. All country

sponsors and Investigators are aware of the situation and are very involved in following up to address the respective local situation.

- The ongoing COVID-19 pandemic results in limited on-site staff, monitor and research team availability which may lead to a slowdown in site activation for countries coming on board in the next reporting period.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

There have been no changes in use or care of human subjects.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

This trial is currently in the recruitment phase and no results are available at this moment. The trial was presented at a poster session during the Annual ASCO Meeting 2022.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

This trial is currently in the recruitment phase and no results are available at this moment. Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

The trial was presented at a poster session during the Annual ASCO Meeting 2022.

- **Website(s) or other Internet site(s)**
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

This trial is currently in the recruitment phase and no results are available at this moment. Nonetheless, the trial is being described on the ABCSG (https://www.abcsg.org/), BCT (https://www.breastcancertrials.org.au/home) and EMA (https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002505-35/AT) homepages. Participant recruitment website is in development in the US.

- **Technologies or techniques**
Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**
Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**

  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

  Data and research material: For already randomized participants: Medical history, demographic & lifestyle data, physical examination including ECOG, dental status, weight, and height (baseline), clinical breast examination, concomitant medications collection, MRI or Mammogram, Breast Ultrasound (if performed), Bone Density Scan, Pregnancy test, Menopausal status, Blood samples, Bone Turnover Markers, QoL Questionnaires (where applicable), and biological samples.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name: **Judy E. Garber, MD MPH**
Project Role: Principal Investigator
No change

Name: **Nizar Bhulani, MD MPH**
Project Role: Research Scientist/Project Manager – Dana-Farber Cancer Institute
No change

Name:	**Marie Wood, MD**
Project Role:	Site Principal Investigator – University of Colorado
Research Identifier:	
No change	

Name:	**Geoffrey Lindeman, MBBS PhD**
Project Role:	Principal Investigator – ANZ Clinical Trials
No change	

Name:	**Sarah-Jane Dawson, PhD**
Project Role:	Co-Investigator – ANZ Clinical Trials
No change	

Name:	**Bianca Capaldo**
Project Role:	Research Officer – ANZ Clinical Trials
No change	

Name:	**Elliot Surgenor**
Project Role:	Research Assistant– ANZ Clinical Trials
No change	

Name:	**Joy Tsai, MD**
Project Role:	Co-Investigator – Massachusetts General Hospital
No change	

Name:	**Benjamin Leder, MD**
Project Role:	Co-Investigator – Massachusetts General Hospital
No change	

Name:	**Hang Lee, PhD**
Project Role:	Co-Investigator – Massachusetts General Hospital
No change	

Name:	**Savannah Ryan**
Project Role:	Research Assistant – Massachusetts General Hospital
No change	

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

What other organizations were involved as partners?

Organization Name: Amgen Limited
Location of Organization: 240 Science Park, Milton Road, Cambridge, CB4 OWD, UK
Partner's contribution: Financial support, In-kind support (drug provider)

Organization Name: Alliance for Clinical Trials in Oncology
Organization Location: Chicago, IL
Partner's Contribution: The Alliance has worked with Dana-Farber Cancer Institute and other partner organizations like ABCSG to streamline processes for trial activation and set up in the US.

Organization Name: Mayo Clinic
Organization Location: Rochester, MN
Partner's Contribution: The Mayo Clinic will serve as a central repository for all the human tissue and specimens collected during the trial in the US.

Organization Name: Forms Vision
Organization Location: Hollandse Kade 13, 1391 JD Abcoude, Netherlands
Partner's Contribution: Implementation of an XML Web Service which enables ABCSG-50 study sites to complete randomization of subjects in ABCSG-50 through the US based RandoNode system.

Organization Name: FORCE: Facing Our Risk of Cancer Empowered
Organization Location: Tampa, FL
Partner's Contribution: Force is a patient advocacy organization that would support participant recruitment by sharing trial relevant information on their platform.

Organization Name: TigerLily Foundation
Organization Location: Stone Ridge, VA
Partner's Contribution: TigerLily Foundation is a patient advocacy organization that would support participant recruitment by sharing trial relevant information on their platform.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

9. **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

PREVIOUS/CURRENT/PENDING SUPPORT
JUDY GARBER, MD MPH: PRINCIPAL INVESTIGATOR
DANA-FARBER CANCER INSTITUTE

PREVIOUS (Last 5 Years)

NO GRANT NUMBER (Garber) 10/01/2017-09/30/2022 0.30 CM
Breast Cancer Research Foundation (BCRF)
Clonal Hematopoiesis (CHIP) and Breast Cancer
Aim 1 To estimate the prevalence of clonal hematopoiesis of indeterminate significance (CHIP) at breast cancer diagnosis and to examine factors that may predict for its observation, including age, breast cancer subtype, treatment, and presence/absence of germline mutations in DNA repair genes (BRCA1/2, TP53, PALB2, Fanconi anemia genes). Aim 2 To compare the rate of CHIP after adjuvant chemotherapy to the rate among women following 6 months of adjuvant hormonal therapy without chemotherapy. Aim 3 To explore the effect of CHIP on breast cancer outcome, both treatment-related myeloid malignancy and time to recurrence.
POC: Margaret Flowers, PhD, Managing Director, Research Program, E-Mail: MFlowers@bcrf.org; Address: 28 W. 44th Street, Suite 609, New York, NY 10036
Role: Principal Investigator

5500021820, Collaboration Agreement (Baker, Laurence) 09/01/2021 – 09/30/2022 0.12 CM
University of Michigan Subcontract
Leiomyosarcoma (LMS): New Targets, New Therapies, New Models
A major objective is to better define the true risk of TP53 germline mutation as well as other DNA repair genes such as RB and DNA-PK. This study will contrast the clinical course of patients with a somatic mutation with the course of those with germline mutation and propose a panel to recommend how TP53 germline mutant patient will undergo annual screening (whole body MR) in an older population than newly identified Li Fraumeni individuals. In addition, we will propose to integrate screening studies currently in place to detect cancer. The Administrative Core provides linkage to all projects and is responsible for facilitating meetings, overseeing progress and assisting with addressing obstacles that arise. This core will house our External Advisory Board and our Executive committee which will be chaired by Judy Garber and include a leader from each project and Cores. The Executive Committee will meet at least every three months.
POC: Kelly Pavlica, Procurement Agent; E-Mail: kelpav@umich.edu; Address: University of Michigan Procurement Services, 7071 Wolverine Tower, 3003 South State Street, Ann Arbor, MI 48109-1282
Role: Project Lead – Project 2; Chair, Administrative Core

R01CA207365 (Rebbeck) 09/18/2017-08/31/2022 0.60 CM NIH/NCI
Precision Assessment and Delivery of Cancer Risks in BRCA 1/2 Mutation Cancers
Optimize risk assessment by estimating individualized (precision) breast and ovarian cancer absolute risks by estimating precision cancer absolute risks by age, mutation and risk modifiers.
Develop a web-based tool of precision absolute risks for use in clinical counseling.
POC: Wendy Nelson, PhD, MPH, Program Director, Basic Biobehavioral and Psychological Sciences Branch (BBPSB), NCI/NIH; E-Mail: wendy.nelson@nih.gov; Address: BG 9609 Room 3E106, 9609 Medical Center Drive, Rockville, MD 20850
Role: Co-Investigator

HHSN26100013 (Brown) 08/21/2017-09/20/2021
NIH/NCI – MD Anderson Cancer Center Subcontract 0.0 CM*
Pilot Study of Denosumab in BRCA1/2 Mutation Carriers Scheduled for Risk-Reducing Salpingo-Oophorectomy (TO 13) (Project 00006260)

This study will consist of a presurgical 2-arm pilot study to evaluate the effect of 3-4 monthly doses of denosumab on proliferation of fallopian tube epithelial cells in pre-menopausal women carrying a BRCA1/2 mutation.
POC: Lana A. Vornik, MS, MHA, CCRC, Associate Director, Research Planning and Development Clinical Cancer Prevention, MD Anderson Cancer Center; E-Mail: lavornik@mdanderson.org; Address: 1515 Holcombe Boulevard, Houston, TX 77030
Role: Site Principal Investigator

NO GRANT NUMBER (Garber) 02/15/2018-02/14/2021 0.60 CM
V Foundation
2017 BRCA 1,2 Research Collaborative Grants
Development of Effective Hormonal Chemoprevention for BRCA2 Carriers
Specific Aim 1: Conduct a randomized phase II study in BRCA2 mutation carriers beginning 4-6 weeks following premenopausal RRSO (baseline), comparing a 3-month course of CE 0.45mg daily with the approved HRT combination: BZA 20mg plus CE 0.45mg daily (Duavee®). Specific Aim 2. To investigate the impact of CE, BZA and BZA/CE on ER signaling in normal mammary epithelial cells from BRCA2mutation carriers.
POC: Carole Wegner, PhD, Vice President of Research and Grants Administration; E-Mail: grants@jimmyv.org; Address: 14600 Weston Parkway, Cary, NC 27513
Role: Principal Investigator
Overlap: None.

N01-CN-2012-00034 (Brown) 09/15/2015-09/14/2020 0.0 CM* NIH/
NCI – MD Anderson Cancer Center Subcontract
Cancer Prevention Agent Development Program: Early Phase Clinical Research Consortium
VADIS Trial: Phase II trial of the E75 Peptide Vaccine in Women with DCIS Breast Cancer
This is a mechanism for the conduct of early phase clinical trials of agents for prevention of diverse cancers. The current portfolio targets breast cancer with a trial of DHA, and a trial of a HER2-targeted vaccine trial has been approved and is in development for DCIS.
POC: Lana A. Vornik, MS, MHA, CCRC, Associate Director, Research Planning and Development Clinical Cancer Prevention, MD Anderson Cancer Center; E-Mail: lavornik@mdanderson.org; Address: 1515 Holcombe Boulevard, Houston, TX 77030
Role: Site Principal Investigator
*Clinical Trial; Dr. Garber did not have measurable effort on this project.

HeritX (Garber) 02/01/2018-01/31/2020 0.60 CM
Prevent Inherited BCRA Cancer Immunoprevention
of BRCA1-Associated Breast Cancer
The primary objectives of this award were (1) to demonstrate that the acquisition of *TP53* missense mutations precedes progression to invasive breast cancer in *BRCA1* mutation carriers; (2) to test whether these events induce p53-specific adaptive immune responses in *BRCA1* carriers and (3) to identify any immunosuppressive conditions in the microenvironment that might facilitate immune escape.
POC: Thomas Bock, MD MBA, Chief Executive Officer; E-Mail: info@HeritX.org; Address: 1217 Wilshire Blvd., #3390, Santa Monica, CA 90403
Role: Principal Investigator

NO GRANT NUMBER (Garber) 10/01/2011-09/30/2018 0.12 CM
Breast Cancer Research Foundation (BCRF)
Project I. Neoadjuvant Cisplatin vs Doxorubicin/Cyclophosphamide ("AC") in Women with Newly Diagnosed Breast Cancer and Germline BRCA Mutations INFORM/TBCRC 031
The goal of this project is to better establish whether aggressive breast cancers in women with BRCA mutations are sensitive to platinum agents because of their specific deficiencies in DNA-repair.

POC: Margaret Flowers, PhD, Managing Director, Research Program, E-Mail: MFlowers@bcrf.org;
Address: 28 W. 44th Street, Suite 609, New York, NY 10036
Role: Principal Investigator

CURRENT

W81XWH1910780 (Garber) 09/15/2019-09/14/2023 1.80 CM
Department of Defense (DoD)
Breast Cancer Breakthrough Award
Prospectively Randomized, Placebo-Controlled Phase III Study to Determine the Effect of Denosumab on Breast Cancer Prevention
The primary objective of the BRCA-P phase III randomized placebo-controlled chemoprevention trial is to evaluate the reduction in risk of any BC (invasive or DCIS) in women with a gBRCA1m treated with DNSB compared to placebo.
POC: JoAnn L. Martin, Grants Management Specialist Assistance Agreements Branch 3; E-Mail: joann.l.martin2.civ@mail.mil; Address: U.S. Army Medical Research Acquisition Activity; 820 Chandler Street, Fort Detrick, MD 21702-5014
Role: Principal Investigator
Overlap: None.

R01HG011928 (Rana) 09/22/2021 – 06/30/2026 0.30 CM
NIH/NHGRI
A Stakeholder Informed Randomized Trial of Pretest Video Education vs Standard Genetic Counseling for Cancer Patients: Evaluating the Impact on Patients, Providers and Practices
This proposal is relevant to public health because it will optimize the delivery of genetic testing and counseling services to cancer patients who are otherwise undertested and underdiagnosed with cancer predisposition. We will compare behavioral, and patient reported outcomes of pretest Video Education with Result Dependent DIsclosure (VERDI) vs standard genetic counseling, to provide an evidence-based approach to modern cancer genetics care. We will evaluate the evolving role of genetic counselors as vital stakeholders in ensuring widespread implementation to expand access to genetics care.
POC: Laura Eisenman, NHGRI, E-Mail: laura.eisenman@nih.gov;
Role: Co-Investigator
Overlap: None.

1U2CCA252974-01 (Wagle) 09/01/2020-08/31/2025 0.60 CM
NIH/National Cancer Institute
Broad Institute Subcontract
Count Me In: Partnering with Patients to Define the Clinical and Genomic Landscape of Rare Aggressive Sarcomas in Children and Adults
The project is expected to engage patients directly and perform at least WES, RNA-seq, and low pass WGS in tumor samples (plus appropriate germline). The goal of the research is to generate a new knowledge from the genomic characterization. Return of actionable tumor and germline results from the WES is required but is not intended to be the focus of the research.
POC: (NIH contact not assigned yet) Mr. Sharmarke Osman, Manager, Research Administration, Signing Official (SO); Authorized Official (AO) - NIH eRA Commons, The Broad Institute of MIT and Harvard; E-Mail: sosman@broadinstitute.org; Address: Office of Sponsored Research, 415 Main Street, Cambridge, MA 02142
Role: Co-Investigator
Overlap: None.

R01CA242218 (Gruber/Garber/Amos) 09/18/2019-08/31/2024 1.20 CM
NIH/NCI – City of Hope Subcontract

Precision Approaches to Refining TP53-Associated Cancer Risk
The specific aims of this project are to, 1. Characterize TP53-related cancer risk and penetrance in a large collection of families with TP53 mutations, exploiting more agnostic multi-gene panel testing ascertainment strategies. 2. Evaluate molecular genetic modifiers of TP53-related penetrance across the full spectrum of ascertainments and phenotypes. 3. Determine the prevalence and clinical implications of ACE and TP53 mosaicism.
POC: Melissa Rotunno PhD; Program Director, Genomic Epidemiology Branch (GEB) of the Epidemiology and Genomics Research Program (EGRP), NCI Division of Cancer Control and Population Sciences; E-Mail: melissa.rotunno@nih.gov; Address: BG 9609, Room 4E548, 9609 Medical Center Drive, Rockville, MD 20850
Role: Principal Investigator (MPI)
Overlap: None.

1U01CA243688-01 (Mack) 09/18/2019-08/31/2024 0.12 CM NIH/ National Cancer Institute
The AYA-RISE Intervention: Risk Information and Screening Education for Adolescents and Young Adults with Cancer Predisposition Syndromes
The proposed study will develop and test a novel, patient- and family-centered model for cancer risk communication and decision-making to meet the unique needs of AYAs.
POC: Wendy Nelson PhD, Program Director, NCI Basic Biobehavioral & Psychological Sciences Branch; E-Mail: wendy.nelson@nih.gov; Address: BG 9609, Room 3E106, 9609 Medical Center Drive, Rockville, MD 20850
Role: Co-Investigator
Overlap: None.

Gray Foundation (Brugge) 08/01/2019-07/31/2024 0.12 CM
Basser Initiative @ Gray Foundation Team Science Grant
Harvard Medical School Subcontract
Development of Strategies to Track and Prevent Breast Cancer Development in BRCA Mutation
It has been difficult to track and prevent breast cancer in BRCA1/2 mutation carriers because we do not yet understand how their cancers begin and progress. To address this challenge, we have assembled an internationally recognized team of basic and clinical scientists, who will build on exciting new findings that have identified the earliest changes in cells from ostensibly normal tissues from BRCA1/2-mutation carriers, to understand how they progress, and devise clinically applicable approaches to track and suppress progression. The proposed work could transform both our understanding of breast carcinogenesis in BRCA1/2 mutation carriers, and our ability to predict and prevent it.
POC: Elizabeth Tran-Nguyen, HMS Senior Grants and Contracts Officer/AOR; E-Mail: elizabeth_tnguyen@hms.harvard.edu; Address: Harvard Medical School, Office of Research Administration, 1635 Tremont Street, Boston, MA 02120
Role: Co-Investigator
Overlap: None.

P50CA168504-06A1 (Polyak, Shapiro, Lin) 07/05/2019-05/31/2024 0.60 CM NIH/ NCI (CEP)
Dana-Farber/ Harvard Cancer Center SPORE in Breast Cancer – Career Enhancement Program (CEP)
The purpose of the Career Enhancement Program (CEP) is to attract junior investigators in basic, clinical, and, particularly, translational research to breast cancer research. By providing research support and exposure to the Breast SPORE investigators, we hope to promote the independent research careers of junior faculty. The SPORE CEP strives to attract minority and female investigators to the field of breast cancer research. By its very nature, translational research is multidisciplinary, and we strive to support and bring together new investigators in multiple disciplines, including surgeons, oncologists, tumor biologists, and epidemiologists. The

CEP will be co-directed by Judy Garber, MD and Rulla Tamimi, ScD. They will work with a standing committee made up of SPORE and DF/HCC investigators to review applications.
POC: Joyann Courtney, Program Director, Division of Cancer Treatment and Diagnosis Office of the Director, NCI Translational Research Program; E-Mail: joyann.rohan@nih.gov; Address:
BG 9609 RM 3W206, 9609 Medical Center Drive, Rockville, MD 20850
Role: Co-Director, CEP
Overlap: None.

R01CA239342 (Wang) 04/01/2019-03/31/2024 0.15 CM NIH
– MD Anderson Cancer Center Subcontract
Statistical Methods and Tools for Cancer Risk Prediction in Families with Germline Mutations in TP53
The major goal of this project is to improve the clinical management of individuals with a family history of early-onset cancers by developing mathematical models to assess 1) germline mutation carrier probability prior to TP53 testing and 2) the absolute lifetime risk of developing cancers in individuals with TP53 mutations.
POC: Huann-Sheng Chen, PhD, NCI Statistical Research and Applications Branch; E-Mail: huann-sheng.chen@nih.gov; Address: BG 9609, Room 4E542, 9609 Medical Center Drive, Rockville, MD 20850
Role: Co-Investigator
Overlap: None.

NO GRANT NUMBER (Garber) 10/01/2021-09/30/2023 0.36 CM
Breast Cancer Research Foundation (BCRF)
Assessing Hormone Dependence and DNA Repair Deficiency in ER+ BRCA1/2-Associated Breast Cancer: Can We Distinguish Tumors That Will and Will Not Benefit From PARP Inhibitors?
A significant subset of BRCA1/2-associated BC are hormone-receptor positive (HR+). PARP inhibitors (PARPi) are active treatment against some HR+ BRCA1/2-tumors in metastatic and now neo(adjuvant) trials. We seek to study HR+ BRCA1/2-associated BC to characterize their HR+ biology and try to distinguish those dependent on their DNA repair deficiencies who will respond to PARPi from those who are not dependent and are unlikely to respond, to spare patients an inactive and expensive therapy.
POC: Margaret Flowers, PhD, Managing Director, Research Program, E-Mail: MFlowers@bcrf.org; Address: 28 W. 44th Street, Suite 609, New York, NY 10036
Role: Principal Investigator
Overlap: None.

NO GRANT NUMBER (Maitra) 02/01/2018-07/31/2023 0.60 CM
Pancreatic Cancer Interception
SU2C Lustgarten Foundation Dream Team Grant
Intercepting Pancreatic Cancer in High Risk Cohorts
The objectives are to produce end results that have relevant clinical impact for pancreatic cancer interception including the identification of high risk cohorts for pancreatic imaging, immune based interception via a vaccine trial, and biomarker studies to develop assays for use in cohorts with inherited cancer predisposition.
POC: Catherine Higgins, PhD, Director of Scientific Program Management; E-Mail: info@su2c.org; Address: P.O. Box 843721
Los Angeles, CA 90084-3721
Role: Co-Investigator
Overlap: None.

ACTIVE CLINICAL TRIALS*
Each active clinical trial below has a varying need of effort dependent upon the type of activity currently in progress and is assigned to members of the study team performing the work. Dr. Garber does not have measurable effort except as indicated otherwise.

1R01CA249437-01A1 (Fabian) 02/01/2022 – 01/31/2026 0.00 CM*
NIH/NCI – The University of Kansas Medical Center
Research Institute Subcontract
Biomarker-Based Phase IIB Trial of (Bazedoxifene-Conjugated Estrogen) To Reduce Risk for Breast Cancer
To conduct a Phase IIB clinical trial of Duavee as a potential breast cancer prevention agent.
POC: Mario Medina, PhD; E-Mail: spa@kumc.edu; Address: 3901 Rainbow Blvd., MSN 1039, Kansas City, KS 66160 - 8500
Role: Other Significant Contributor – Site Lead
Overlap: None.

N01-CN-2012-00034 (Brown) 09/19/2016-09/18/2023 0.0 CM*
NIH/NCI – MD Anderson Cancer Center Subcontract
MD Anderson Cancer Center Subcontract
Cancer Prevention Agent Development Program: Early Phase Clinical Research Consortium
A Randomized, Double-Blind, Placebo-Controlled Study of 4-Hydroxtamoxifen Topic Gel in Women With Mammographically Dense Breasts - T011
This is a mechanism for the conduct of early phase clinical trials of agents for prevention of diverse cancers. The current portfolio targets breast cancer with a trial of DHA, and a trial of a HER2-targeted vaccine trial has been approved and is in development for DCIS.
POC: Lana A. Vornik, MS, MHA, CCRC, Associate Director, Research Planning and Development Clinical Cancer Prevention, MD Anderson Cancer Center; E-Mail: lavornik@mdanderson.org; Address: 1515 Holcombe Boulevard, Houston, TX 77030
Role: Site Principal Investigator
Overlap: None.

R01 CA218436 (Kulkarni) 08/01/2017-07/31/2023 0.30 CM*
NIH/NCI – Northwestern University Subcontract
Evaluating the protective effect of a tissue selective estrogen complex (TSEC) in women with newly diagnosed ductal carcinoma in situ
We propose to conduct a randomized placebo-controlled window of opportunity trial with CE/BZA in 140 postmenopausal women with ER + DCIS.
POC: Brandy Heckman-Stoddard, PhD, MPH, Chief, Division of Cancer Prevention, NCI/NIH; E-Mail: heckmanbm@mail.nih.gov; Address: BG 9609 Room 5E334, 9609 Medical Center Drive, Rockville, MD 20850
Role: Co-Investigator
Overlap: None.

PENDING

Grant ID: Pending (Baker, Laurence) 07/01/2022-06/30/2027 1.50 CM NIH – U of Michigan Subcontract
P50 CA272170
Genetics and Genomics of Leiomyosarcoma (LMS): Improved Understanding of Cancer Biology and New Approaches to Diagnosis and Treatment
Dr. Garber is the Clinical Co-Leader of Project 2. Dr. Garber will assist with Aim 1B (LFS-based) which will estimate percentage of individuals with LFS who develop LMS using this LFS-specific registry, including clinical features and genotype-phenotype correlations. Individuals with known PVs in TP53 will be identified from several source including the LFS registries at each participating institution and from the LiFE Consortium based at the City of Hope. She will also participate in manuscript preparation and weekly conference calls.
POC: Shane Woodward, National Cancer Institute (NCI); E-Mail: woodwars@mail.nih.gov
Role: Clinical Co-Leader, Project 2; and Co-Investigator, Administrative Core
Overlap: None.

1R01CA269684-01 (Syngal) 04/01/2023 – 03/31/2028 0.60 CM NIH
Development and Validation of a Prediction Model for Identifying Inherited Cancer Predisposition Through Integrated Analyses of Tumor Mutational Profiling, Clinical, Family History, and Ancestry data
The results of this effort will lead to the development and validation of a comprehensive risk assessment model that will predict the likelihood of carrying a germline cancer susceptibility variant on multigene testing. The model will be based on a combination of statistical approaches, building on the individual approaches of the team's collaborators, and will integrate data relevant to germline status, including somatic data, ancestry, personal and cancer family history, as well as demographic data, to predict the status of 19 genes implicated in hereditary cancers. The resulting risk assessment tool will be a comprehensive and integrated approach for use in a variety of clinical settings to guide multigene panel testing for targeted cancer treatments and surveillance of patients and their family members.
Role: Co-Investigator
POC: (not assigned) Email:GrantsInfo@nih.gov;
Overlap: None.

IN-KIND RESOURCES

- ***Dr. Renata Lazari Sandoval - Research Fellow/Visiting Scientist***
  Dr. Sandoval will work with Dr. Garber on cancer predisposition syndrome studies.
  Source of Support: In-Kind through Hospital Sirio-Libanes, Brazil
  In Kind Start and Projected End Date: 01/18/2022 – 12/31/2022
  Value of in-kind support:

I, Judy E. Garber, MD PI/or other senior/key personnel, certify that the current and pending support provided herein is current, accurate, and complete. I agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award. I have been made aware of the requirements under Section 223(a)(1) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021. I am aware that false, fictitious, or fraudulent statements or claims may result in criminal, civil, or administrative penalties.

Signature: Judy Garber *Electronically signed by: Judy Garber Reason: I'm an approver Date: Oct 12, 2022 15:58 EDT*

Date: Oct 12, 2022

PREVIOUS/CURRENT/PENDING SUPPORT
GEOFFREY LINDEMAN, MBBS FRACP PHD – SUBCONTRACT SUB-INVESTIGATOR THE WALTER AND ELIZA HALL INSTITUTE OF MEDICAL RESEARCH

PREVIOUS (Last 5 Years)

GRANT NUMBER: 1040978 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: National Health and Medical Research Council (Australia)
PROJECT DATES: 01/01/2012-12/31/2017
PROJECT TITLE: The Australian Centre for Translational Breast Cancer Research: from discovery to better health outcomes
DESCRIPTION OF PROJECT/AIMS:
This grant provides support for personnel to enable early phase clinical studies, focused on the clinical transfer of promising laboratory discoveries.
POC: Research Administration Section, National Health and Medical Research Council, Email: postaward.management@nhmrc.gov.au, Address: GPO Box 1421, Canberra City ACT 2601, Australia
ROLE: PI
DOLLAR AMOUNT: AUD
TIME COMMITMENT: 10% effort per year
OVERLAP STATEMENT: None.

GRANT NUMBER: NT-13-06 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: National Breast Cancer Foundation (Australia)
PROJECT DATES: 07/01/2013-06/30/2018
PROJECT TITLE: Targeting the BCL-2 pro-survival pathway in breast cancer – translating discovery to the clinic
DESCRIPTION OF PROJECT/AIMS:
This project was focused on pre-clinical and early phase studies of BH3 mimetics distinct subtypes of breast cancer
POC: Dr Samantha Oakes, Director of Research Investment; Email: samantha.oakes@nbcf.org.au; Address: Lvl9, 10 Barrack St, Sydney NSW 2000, Australia.
ROLE: PI
DOLLAR AMOUNT: AUD
TIME COMMITMENT: 10% effort per year
OVERLAP STATEMENT: None.

FUNDER/SPONSOR NAME: Victorian Cancer Agency – Translational Research Project grant
PROJECT DATES: 05/01/2014-04/30/2017
PROJECT TITLE: BH3-mimetics in rational combination therapies to overcome treatment-resistant cancers
DESCRIPTION OF PROJECT/AIMS:
This project was focused on pre-clinical and early phase studies of BH3 mimetics in a variety of cancer types, including breast cancer (9 co-PIs). Lindeman focused on breast cancer.
POC: Dayna Swiatek, Victorian Cancer Agency. Email: victorian.canceragency@dhhs.vic.gov.au, Address: GPO Box 4057 (Level 15), Melbourne, VIC 3001, Australia
ROLE: co-PI
DOLLAR AMOUNT:
TIME COMMITMENT: 5% effort per year
OVERLAP STATEMENT: None.

GRANT NUMBER: 1086727 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: National Health and Medical Research Council (Australia)
PROJECT DATES: 01/01/2015-12/31/2017
PROJECT TITLE: Elucidating the *in vivo* role of the pro-survival gene Mcl-1 in mammary gland development and breast cancer.
DESCRIPTION OF PROJECT/AIMS:
This project was focused on studying the in vivo role of Mcl-1 in mammary development and cancer POC: Research Administration Section, National Health and Medical Research Council, Email: postaward.management@nhmrc.gov.au, Address: GPO Box 1421, Canberra City ACT 2601,

Australia
ROLE: PI
DOLLAR AMOUNT:
TIME COMMITMENT: 10% effort per year
OVERLAP STATEMENT: None.

GRANT NUMBER: 1078730 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: National Health and Medical Research Council (Australia)
PROJECT DATES: 01/01/2015-12/31/2019
PROJECT TITLE: Not applicable
DESCRIPTION OF PROJECT/AIMS:
This is a Senior Principal Research Fellowship that supports the salary of the PI
POC: Research Administration Section, National Health and Medical Research Council, Email: postaward.management@nhmrc.gov.au, Address: GPO Box 1421, Canberra City ACT 2601, Australia
ROLE: PI
DOLLAR AMOUNT:
TIME COMMITMENT: not applicable (this grant provided salary support)
OVERLAP STATEMENT: None.

GRANT NUMBER: PS-17-011 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: National Breast Cancer Foundation (Australia)
PROJECT DATES: 01/01/2017-12/31/2018
PROJECT TITLE: Optimising breast cancer prevention strategies for BRCA1 mutation carriers
DESCRIPTION OF PROJECT/AIMS:
This project focused on gaining further insights into RANK signaling in BRCA1 mutation carriers. Specific aims were to compare oophorectomy, tamoxifen and RANKL inhibition as chemoprevention strategies using Brca1/p53 mouse models. RANK expression in human fallopian tube and ovary was also examined. The project also provided support for the development of the BRCA-P clinical trial protocol
POC: Dr Samantha Oakes, Director of Research Investment; Email: samantha.oakes@nbcf.org.au; 4828; Address: Lvl9, 10 Barrack St, Sydney NSW 2000, Australia.
ROLE: PI
DOLLAR AMOUNT:
TIME COMMITMENT: 10% effort per year
OVERLAP STATEMENT: None

GRANT NUMBER: IIRS-20-080 Mann, Bruce (PI)
FUNDER/SPONSOR NAME: National Breast Cancer Foundation (Australia)
PROJECT DATES: 01/01/2020-12/31/2021
PROJECT TITLE: Precision genomic medicine in breast cancer: synergizing somatic and germline mutation testing
DESCRIPTION OF PROJECT/AIMS:
This project focused on testing the effectiveness of universal germline and tumor sequencing of the breast cancer tumor in women who are newly diagnosed with invasive breast cancer.
POC: Dr Samantha Oakes, Director of Research Investment; Email: samantha.oakes@nbcf.org.au; Address: Lvl9, 10 Barrack St, Sydney NSW 2000, Australia.
ROLE: CIC
DOLLAR AMOUNT:
TIME COMMITMENT: 5% effort per year
OVERLAP STATEMENT: None

CURRENT

GRANT NUMBER: 1113133 Strasser, Andreas (PI)
FUNDER/SPONSOR NAME: National Health and Medical Research Council (Australia)
PROJECT DATES: 01/01/2017-12/31/2022
PROJECT TITLE: Apoptosis and stem/progenitor cells in the development and treatment of cancer
DESCRIPTION OF PROJECT/AIMS:

This program grant supports 10 principal investigators. The research focus is to understand the role of apoptosis in normal development and cancer.
POC: Research Administration Section, National Health and Medical Research Council, Email: postaward.management@nhmrc.gov.au, Address: GPO Box 1421, Canberra City
ACT 2601, Australia
ROLE: PI
DOLLAR AMOUNT:
TIME COMMITMENT: 5% effort per year
OVERLAP STATEMENT: None.

GRANT NUMBER: BCRF-22-182 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: Breast Cancer Research Foundation (USA)
PROJECT DATES: 10/01/2022-09/30/2023
PROJECT TITLE: Boosting tumor response to conventional therapy in ER-positive breast cancer
DESCRIPTION OF PROJECT/AIMS:
This grant is to conduct translational studies on targeting BCL-2 and CDK4/6 in ER-positive breast cancer.
POC: Ashley Marion, Senior Manager, Email: grants@bcrf.org,
28 West 44th Street, Suite 609, New York, NY 10036
ROLE: PI
DOLLAR AMOUNT:
TIME COMMITMENT: 10% effort per year
OVERLAP STATEMENT: None

GRANT NUMBER: HHSN26100009 Brown, Powell (PI)
FUNDER/SPONSOR NAME: NIH PREVENT Cancer Program
PROJECT DATES: 09/17/2018-03/16/2023
PROJECT TITLE: Preclinical efficacy and intermediate endpoint biomarkers: RANK ligand inhibition – a potential chemoprevention strategy for women at high genetic risk of breast cancer
DESCRIPTION OF PROJECT/AIMS:
Investigation of RANKL inhibition in Brca2 mouse mammary tumor models. The aims of the project are to analyze a Brca2-deficient mouse mammary tumor model and to determine whether Rankl inhibition can delay or prevent tumor development. POC: Nicole Belanger, Contract Officer NCI, Email: belangern@mail.nih.gov, Address:
2115 East Jefferson St, MSC 8500, Room 4B-432, Bethesda, MD 20892
ROLE: Contracting investigator to NIH through Dr Powell Brown at MD Anderson.
DOLLAR AMOUNT:
TIME COMMITMENT: 10% effort per year
OVERLAP STATEMENT: None. This project is solely focused on Brca2 in pre-clinical models.

GRANT NUMBER: 1140715 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: National Health and Medical Research Council (Australia)
PROJECT DATES: 01/01/2018-12/31/2022
PROJECT TITLE: BRCA-P: An international randomized phase III study evaluating the RANK ligand inhibitor denosumab for the prevention of breast cancer in BRCA1 mutation carriers
DESCRIPTION OF PROJECT/AIMS:
The objective of this project is to conduct 'BRCA-P', a double blind randomised controlled phase III international prevention study comparing denosumab to placebo in BRCA1 mutation carriers.
POC: Research Administration Section, National Health and Medical Research Council, Email: postaward.management@nhmrc.gov.au, Address: GPO Box 1421, Canberra City
ACT 2601, Australia
ROLE: PI
DOLLAR AMOUNT:
TIME COMMITMENT: 5% effort per year
OVERLAP STATEMENT: This grant provides some support the core/operational running costs for BRCA-P in Australia and New Zealand. There is no overlap with the funding request to DoD, which would support the Quality of Life analysis and exploratory translational research studies to be conducted in Australia: studies on breast tissue in women who withdraw from study and undergo mastectomy, phenotypic characterization (including TIL scoring) and molecular characterization of tumors that arise on DNSB therapy (vs controls), study peripheral blood immune cell subsets, collect and study cfDNA as a potential screening strategy for gBRCA1m women.

GRANT NUMBER: 1153049 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: National Health and Medical Research Council (Australia)
PROJECT DATES: 10/01/2017-09/30/2022
PROJECT TITLE: Centre for Translational Breast Cancer Research (TransBCR): delivering laboratory studies to the clinic
DESCRIPTION OF PROJECT/AIMS:
This grant provides support for personnel to enable early phase clinical studies, focused on the clinical transfer of promising laboratory discoveries.
POC: Research Administration Section, National Health and Medical Research Council, Email: postaward.management@nhmrc.gov.au,Address: GPO Box 1421, Canberra City ACT 2601, Australia
ROLE: PI
DOLLAR AMOUNT:
TIME COMMITMENT: 5% effort per year
OVERLAP STATEMENT: None

GRANT NUMBER: IIRS-19-004 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: National Breast Cancer Research Foundation
PROJECT DATES: 01/01/2019-12/31/2022
PROJECT TITLE: Targeting BCL-2 pro-survival proteins in breast cancer – transferring benchside discovery to the clinic.
DESCRIPTION OF PROJECT/AIMS:
This is a translational research project aimed at exploring the role of different BH3 mimetics in the treatment of breast cancer. Its aims include pre-clinical studies using PDX models, syngeneic mouse models and the development and implementation of two clinical trials using the BCL-2 inhibitor venetoclax in patients with metastatic breast cancer.
POC: Dr Samantha Oakes, Director of Research Investment; Email: samantha.oakes@nbcf.org.au; Address: Lvl9, 10 Barrack St, Sydney NSW 2000, Australia.
ROLE: PI
DOLLAR AMOUNT:
TIME COMMITMENT: 10% effort per year
OVERLAP STATEMENT: None

GRANT NUMBER: 1165878 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: Cancer Australia
PROJECT DATES: 04/29/2019-12/31/2022
PROJECT TITLE: Targeting BCL-2 in estrogen receptor positive breast cancer
DESCRIPTION OF PROJECT/AIMS:
This project aims to use preclinical models in parallel with early phase clinical trial to test the effectiveness of combining ventoclax with the current 'gold-standard' breast cancer therapy.
POC: Dr Samantha Oakes, Director of Research Investment; Email: samantha.oakes@nbcf.org.au; Address: Lvl9, 10 Barrack St, Sydney NSW 2000, Australia, Melbourne VIC 3001
ROLE: PI
DOLLAR AMOUNT:
TIME COMMITMENT: 10% effort per year
OVERLAP STATEMENT: None

GRANT NUMBER: W81XWH19107080 Garber, Judy (PI)
FUNDER/SPONSOR NAME: DOD
PROJECT DATES: 09/15/2019- 09/14/2023
PROJECT TITLE: BRCA-P: Prospectively Randomized, Placebo-Controlled Phase III Study to Determine the Effect of Denosumab on Breast Cancer Prevention in BRCA1 Mutation Carriers
DESCRIPTION OF PROJECT/AIMS:
AIM 1**:** To evaluate the reduction in the risk of breast cancer (Invasive and DCIS) in women with germline BRCA1 mutation treated with Denosumab compared to Placebo
AIM 2**:** Investigate whether treatment with denosumab alters serum OPG, RANKL or progesterone levels in pre- and postmenopausal *BRCA1* carriers in 1000 patients
AIM 3: To evaluate the change in mammographic breast density (MBD) in premenopausal *BRCA1* mutation carriers (g*BRCA1*m) from baseline to 12 months of denosumab versus placebo
AIM 4: Investigate the impact of denosumab use in women with a *BRCA1* germline mutation on health-related

quality of life (HRQoL), controlling for potential confounders such as menopausal status and age
AIM 5: Characterize changes in bone density, microarchitecture, microstructure, and bone strength in premenopausal and early postmenopausal women receiving denosumab 120 mg and placebo
AIM 6: In exploratory studies, we will examine tumours arising and prophylactic mastectomy specimens from trial participants and conduct phenotypic (including TIL scoring) and molecular characterization, comparing DNSB to controls. The effect on peripheral blood immune cell subsets will also be characterized and cfDNA collected and studied as a potential screening strategy for women with a germline *BRCA1* mutation.
POC: Soozy J Smith, CEO Breast Cancer Trials, Level 4 175, Scott Street, Newcastle NSW 2300 Australia Email soozy.smith@bctrials.org.au
ROLE: Co-PI
DOLLAR AMOUNT:
TIME COMMITMENT: 10% effort per year
Overlap: None

GRANT NUMBER: IIRS-20-022 Visvader, Jane (PI)
FUNDER/SPONSOR NAME: National Breast Cancer Research Foundation
PROJECT DATES: 01/01/2020-12/31/2022
PROJECT TITLE: Exploiting single-cell platforms to provide a breast cancer cell atlas and potential biomarkers
DESCRIPTION OF PROJECT/AIMS:
This project aims to unravel the behavior of single cells (both epithelial tumor and surrounding immune cells) within individual to open up new treatment strategies and improve outcomes for patients with the most aggressive and resistant forms of breast cancer.
POC: Dr Samantha Oakes, Director of Research Investment; Email: samantha.oakes@nbcf.org.au; Address: Lvl9, 10 Barrack St, Sydney NSW 2000, Australia, Melbourne VIC 3001
ROLE: CIC
DOLLAR AMOUNT:
TIME COMMITMENT: 5% effort per year
OVERLAP STATEMENT: None

GRANT NUMBER: 1175960 Lindeman, Geoffrey (PI)
FUNDER/SPONSOR NAME: National Health and Medical Research Council (Australia)
PROJECT DATES: 01/01/2020-12/31/2024
PROJECT TITLE: Exploiting breast stem cell research discoveries for transfer to the clinic
DESCRIPTION OF PROJECT/AIMS:
This is a Leadership 3 Fellowship that supports the salary of the PI
POC: Research Administration Section, National Health and Medical Research Council, Email: postaward.management@nhmrc.gov.au, Address: GPO Box 1421, Canberra City ACT 2601, Australia
ROLE: PI
DOLLAR AMOUNT:
TIME COMMITMENT: not applicable (this grant provides salary support)
OVERLAP STATEMENT: None

PENDING

None

PREVIOUS/CURRENT/PENDING SUPPORT
JOY TSAI, MD – SUBCONTRACT (MGH) PRINCIPAL INVESTIGATOR

PREVIOUS (Last 5 years)

Title: (5K23AR068447-04) Effect of anabolic and antiresorptive therapy on bone quality in osteoporosis
Level of Effort: 9.00 CM
Funding agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Contact: Mark E. Langer, Grants Mgt. Specialist; mark.langer@nih.gov; 301-451-8216
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance period: 9/1/15-8/31/20
Level of funding: $157,500
Brief description of the project's goals: By studying how anabolic and antiresorptive osteoporosis therapy affects skeletal health, the proposed research will increase our understanding of how fracture reduction is achieved and how the different agents interact.
Specific Aims: Aim 1: To characterize changes in bone density, microarchitecture, microstructure and bone strength in postmenopausal women receiving denosumab and high dose teriparatide. Aim 2: To characterize changes in bone strength due to changed material properties of bone using *in vivo* novel techniques in postmenopausal women receiving denosumab and high dose teriparatide. Aim 3: To compare skeletal microarchitecture, microstructure, and estimated bone strength in women at high fracture risk who have been previously exposed to bisphosphonates with bisphosphonate-naïve women matched for age and areal BMD (aBMD).
Role: PI

Title: (R21AR069871-03) Consolidating skeletal benefits after short-term combination osteoporosis therapy: The DATA-EX study
Level of Effort: 0.96 CM (subsumed by K23AR068447)
Funding agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Contact: Teresa Do, Grants Mgt. Specialist, Teresa.Do@nih.gov; 301-480-5450
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance period: 5/1/16-4/30/19
Level of funding: $110,000
Brief description of the project's goals: Extension of a proof-of-principle clinical trial evaluating the efficacy of short-term therapy with a novel combination of osteoporosis medications followed by a single dose of a long-acting bisphosphonate.
Specific Aims: To test the following hypotheses: Hypothesis 1: In postmenopausal women with osteoporosis, the large increases in cortical and trabecular bone density achieved with combined denosumab and standard or high-dose teriparatide will be maintained and extended for up to 27-months by a single administration of an intravenous bisphosphonate (zoledronic acid). Hypothesis 2: In postmenopausal women with osteoporosis, the extensive improvement in bone quality achieved with combined denosumab and standard or high-dose teriparatide therapy will also be maintained and extended for up to 27-months by a single dose of zoledronic acid.
Role: Co-I

Title: (BA058-05-020) An open-label, single-arm, multicenter study to evaluate the early effects of abaloparatide on tissue-based indices of bone formation and resorption
Level of Effort: 0.12 CM

Funding Agency: Radius Health Inc. (Industry)
Contact: Sherita Hall, Sr. Director Clinical Operations; shall@radiuspharm.com; 617-444-5000
950 Winter Street
Waltham, MA 02451
Performance period: 10/2/18-10/1/23
Level of funding: $25,404
Brief description of the project's goals: This open-label, single-arm, multicenter study will assess the early effects of abaloparatide in postmenopausal women with osteoporosis using tissue-based indices of bone metabolism obtained by iliac crest bone biopsy after quadruple tetracycline labeling and will relate these indices to biochemical markers of bone turnover.
Specific Aims: 1. Demonstrate the early effects of abaloparatide on tissue-based bone formation and resorption indices 2. Assess the degree to which increased bone formation is achieved by modeling, remodeling, and overflow bone formation 3. Relate the early indices of tissue-based bone formation and bone resorption to those measured using biochemical markers of bone turnover.
Role: Co-I

Title: (1R34AR074114-01) Combination osteoporosis therapy and fracture reduction
Level of Effort: 0.96 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Contact: Teresa Do, Grants Mgt. Specialist, Teresa.Do@nih.gov; 301-480-5450
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance period: 9/1/18-8/31/20
Level of funding: $168,743
Brief description of the project's goals: Aim is to plan a clinical trial assessing the efficacy of combination therapy on fracture
Role: PI

CURRENT

Title: (20187074) Comparative antiresorptive efficacy of alendronate or raloxifene following discontinuation of denosumab
Level of Effort: 0.12 CM
Funding agency: Amgen Inc. (Industry)
Contact: Julie Marvin-Craig, Mgr. Investigator-Sponsored Studies; jmarvinc@amgen.com; 402-506-6887
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Performance period: 9/21/18-9/20/23
Level of funding: $1,310,337 Total Award Amount
Brief description of the project's goals: This investigator-initiated open-label, single center randomized controlled trial will assess the relative efficacy of two oral antiresorptives (alendronate and raloxifene) in preventing the rebound increase in bone turnover that occurs after denosumab discontinuation in postmenopausal women with osteoporosis.
Specific Aim: To test the hypothesis that in postmenopausal women with osteoporosis who received denosumab 60 mg every 6 months for one year, alendronate will more fully inhibit the post-denosumab increase in bone resorption compared to raloxifene.
Role: Co-I
Overlap: None

Title: (5R01AR073191-04) Mechanisms Underlying the Bone Modeling Effects of Combined Anabolic/Antiresorptive Administration
Level of Effort: 0.48 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Contact: Teresa Do, Grants Mgt. Specialist, Teresa.Do@nih.gov; 301-480-5450
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance period: 4/1/19-3/31/23
Level of funding: $2,247,416 Total Award Amount
Brief description of the project's goals: To define cellular and molecular mechanisms that underlie the efficacy of combination antiresorptive and anabolic osteoporosis therapy.
Role: Co-I
Overlap: None

Title: (BC181146 Garber) Prospectively Randomized, Placebo-Controlled Phase III Study to Determine the Effect of Denosumab on Breast Cancer Prevention in BRCA1 Mutation Carriers
Breast Cancer Research Program (BCRP) Breakthrough Award
Level of Effort: 2.04 CM
Funding Agency: Department of Defense (DoD)
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Contact: Jamie A. Shortall. Grants Officer, jamie.a.shortall.civ@mail.mil; 301-619-2393
W03J USA Med Research MAT CMD
1077 Patchel Street, Fort Detrick, MD 21702
Performance Period: 10/1/2019-9/30/2023
Level of Funding: $1,086,251 Total Award Amount
The primary objective of the BRCA-P phase III randomized placebo-controlled chemoprevention trial is to evaluate the reduction in risk of any BC (invasive or DCIS) in women with a gBRCA1m treated with DNSB compared to placebo.
Role: Subaward PI
Overlap: None

Title: (5R21AR079718-02) Limited-duration anabolic therapy in postmenopausal osteoporosis
Level of Effort: .60 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Fay Chen, Program Official, chenf1@mail.nih.gov, 301-594-5055
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance Period: 09/20/2021 - 08/31/2024
Level of Funding: $626,036 Total Award Amount
The major goal of this project is to assess the efficacy of short-term anabolic therapy in postmenopausal women with osteoporosis.
Role: Co-I
Overlap: None

PENDING

Title: (P50AR080596-01) Project 1: The role of osteoblast progenitors in response to bone anabolic agents
Level of Effort: 2.40 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Victoria Matthews, Grants Management Specialist, 301-594-5032, victoria.matthews@nih.gov
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance Period: 04/01/2022 - 03/31/2027
Level of Funding: $2,847,934 Total Cost Amount
The goal of this center of research translation (CORT) is to understand how bone-building osteoporosis medications work in order to develop 'next generation' strategies to treat this disease. To accomplish this goal, we will apply cutting-edge methods to study the effects of such medications on key cell types in bone: stem cells and osteocytes.
Role: Co-I

Signature: Joy Tsai
Joy Tsai (Sep 20, 2022 16:12 EDT)

Date: Sep 20, 2022

PREVIOUS/CURRENT/PENDING SUPPORT

Wood, Marie E.

PREVIOUS (ending within last 5 years)

5UG1CA189823-04 (Buckner, PI)
08/2017 – 06/2018
NIH/NCI
Grants Officer Contact Information: Edward M. Todd, Mayo Clinic, 200 First Street SW, Rochester, MN 55905:
Role: Subaward PI
Effort: 0.6 calendar

total award amount
Title: Analysis of Primary Endpoint Data and Preparation of Primary Endpoint Manuscript for Study C70806 Goals/Aims: The goal of this project was to complete writing a protocol for this study.
Overlap: None

No Award Number (Wood, PI)
09/2018 08/2019
Northern New England Clinical Oncology Society (NNECOS)
Grants Officer Contact Information: PO Box 643 Sandown, NH 03873-0643 603-887-1948, info@nnecos.org
Role: PI
Effort: 0 calendar
total award amount
Title: DNA Repair Landscape of Discordant Sibling Pairs
Goals/Aims: The goal of this project was to try and identify additional genes associated with hereditary breast cancer through examination of discordant sibling pairs from breast cancer families
Overlap: None

CURRENT-

UG1CA189823 (Bertagnolli, Monica M., PI)
08/2021 – 07/2025
ALLIANCE NCTN FOUNDATION
Grants Officer Contact Information: Sabrina Kvasnicka, Grant Program Coordinator, 815-761-0240, researchadministration@alliancenctn.org
Role: Co-Investigator
Effort: 2.4 calendar
Award amount: 20% of Dr. Wood's salary, fringe, and F&A.
Title: Alliance NCORP Research Base
Goals/Aims: The Alliance NCI Community Oncology Research Program (NCORP) Research Base conducts research in cancer prevention, cancer symptom control, and cancer care delivery with a special emphasis on minority, underserved, and older patients and with a strong commitment to building collegial relationships with NCORP Community sites and Minority/Underserved Community sites. The Alliance NCORP seeks to continue its mission into the next grant cycle of generating practice-changing research that directly and favorably impacts the lives of cancer patients and those at risk for cancer
Overlap: None

037270 (Wood, Greenblatt, PI)
01/2020 – 12/2023
University of Vermont Cancer Center

Grants Officer Contact Information: 802-656-4414, cancer@uvmcc.med.uvm.edu
Role: PI
Effort: 0.12 calendar
total award amount
Title: Point of Care (POC) Testing for Patients with Advanced Cancer (PoC-TAC): A feasibility study
Goals/Aims: The major goal of this project is to test the feasibility of a novel approach to genetic testing for patients with newly diagnosed metastatic cancer.
Overlap: None

W81XWH1910780 (Garber, Judy, PI)
09/2019 – 09/2023
Department of Defense (DoD) Breast Cancer Breakthrough Award
Grants Officer Contact Information: JoAnn Martin, 301-619-2594, joann.l.martin2.civ@mil
Role: Co-Investigator
Effort: 0.6 calendar
total award amount
Title: Prospectively Randomized, Placebo-Controlled Phase III Study to Determine the Effect of Denosumab on Breast Cancer Prevention in BRCA1 Mutation Carriers
Goals/Aims: The primary objective of the BRCA-P phase III randomized placebo-controlled chemoprevention trial is to evaluate the reduction in risk of any BC (invasive or DCIS) in women with a gBRCA1m treated with DNSB compared to placebo.
Overlap: None

PENDING-
None

DocuSigned by:
Marie Wood
4352B97347564FC...

October 3, 2022 | 8:15:23 PM MDT

PREVIOUS/CURRENT/PENDING SUPPORT

SARAH-JANE DAWSON – PRINCIPAL INVESTIGATOR
PETER MACCALLUM CANCER CENTRE

PENDING

None

CURRENT

Grant number: W81XWH19107080 Garber, Judy (PI)
Funder/Sponsor: DOD
Type: Sub Award
Amount:
Period: 09/15/2019- 09/14/2023
BRCA-P: Prospectively Randomized, Placebo-Controlled Phase III Study to Determine the Effect of Denosumab on Breast Cancer Prevention in BRCA1 Mutation Carriers
DESCRIPTION OF PROJECT/AIMS:
AIM 1**:** To evaluate the reduction in the risk of breast cancer (Invasive and DCIS) in women with germline BRCA1 mutation treated with Denosumab compared to Placebo
AIM 2**:** Investigate whether treatment with denosumab alters serum OPG, RANKL or progesterone levels in pre- and postmenopausal *BRCA1* carriers in 1000 patients
AIM 3: To evaluate the change in mammographic breast density (MBD) in premenopausal *BRCA1* mutation carriers (g*BRCA1*m) from baseline to 12 months of denosumab versus placebo
AIM 4: Investigate the impact of denosumab use in women with a *BRCA1* germline mutation on health-related quality of life (HRQoL), controlling for potential confounders such as menopausal status and age
AIM 5: Characterize changes in bone density, microarchitecture, microstructure, and bone strength in premenopausal and early postmenopausal women receiving denosumab 120 mg and placebo
AIM 6: In exploratory studies, we will examine tumours arising and prophylactic mastectomy specimens from trial participants and conduct phenotypic (including TIL scoring) and molecular characterization, comparing DNSB to controls. The effect on peripheral blood immune cell subsets will also be characterized and cfDNA collected and studied as a potential screening strategy for women with a germline *BRCA1* mutation.
POC: Soozy J Smith, CEO Breast Cancer Trials, Level 4 175, Scott Street, Newcastle NSW 2300 Australia Ph 02 49 255 255 Email soozy.smith@bctrials.org.au
Role: Co-Principal Investigator
Time commitment: 10% effort per year
Overlap: None

Grant number: 2014291 (OVERALL PI)
Funder/Sponsor: Cancer Council of Victoria Grant in Aid
Type: NGO (non-profit)
Amount: AUD
Period: 1/2022-12/2024
Early detection and monitoring of hepatocellular carcinoma using liquid biopsies
AIM 1: To develop a novel ctDNA based analysis approach in HCC
AIM 2: To characterise the clinical applications of ctDNA based approaches in HCC
POC: Ms Amy Shelly, Head-Research Governance & Optimal Care, Cancer Council Victoria, 615 St Kilda Road, Melbourne, VIC 3004. Ph (03) 9514 6200 Email grants@cancervic.org.au
Role: Principal Investigator
Time commitment: 0.2 CM
Overlap: None

Grant number: CCR ID663175 (OVERALL PI)
Funder/Sponsor: Cancer Australia/Susan G. Komen Career Catalyst Research Grant
Type: NGO (non-profit)
Amount: AUD
Period: 1/2020-12/2022
Genomic and epigenomic monitoring of residual disease using liquid biopsies
AIM 1: Development of a multimodality ctDNA MRD assay for BC detection
AIM 2: Validation of the sensitivity and specificity of the ctDNA MRD assay
AIM 3: Characterisation of disease at relapse to guide patient management
POC: Dr Christopher Poon, Senior Project Officer-Research, Cancer Australia Knowledge Management, Level 8, 595 Collins St, Melbourne VIC 3000 GPO Box 1756, Melbourne VIC 3001 P: 03 8539 8085
E. Christopher.Poon@canceraustralia.gov.au
Role: Principal Investigator
Time commitment: 0.4 CM
Overlap: None

Grant number: ASP-Fall21-0000000030 (OVERALL PI)
Funder/Sponsor: The MARK Foundation Aspire Phase 1 application
Type: NGO (non-profit)
Amount: AUD
Period: 1/2022-12/2022
Circulating tumour DNA to serially assess in vivo transcriptional evolution in cancers
AIM 1: Optimisation of the SNIPER methodology across multiple malignancies
AIM 2: Studying genomic and non-genomic resistance mechanisms during cancer therapy
POC: Irena Ivanovska, Senior Scientific Director, The Mark Foundation for Cancer Research, 1350 Avenue of the Americas, Suite 2902 New York, NY 10019 Email: iivanovska@themarkfoundation.org
Role: Principal Investigator
Time commitment: 0.4 CM
Overlap: None

Grant number: MRFF 2008726 (OVERALL PI)
Funder/Sponsor: Medical Research Future Fund
Type: MRFF Research Grant
Amount: AUD
Period: 1/2021-12/2025
Novel predictive disease modelling using liquid biopsies to improve outcomes in melanoma
AIM 1: Development of a multimodal ctDNA MRD assay for melanoma detection
AIM 2: Investigate the role of the novel ctDNA ssay to detect. MRD in early stage melanoma
AIM 3: Validate the clinical performance of the assay and impact on survival outcomes
POC: Alan Singh, Executive Director-Research Translation Branch, MRFF/National Health and Medical Research Council, GPO Box 1421 Canberra City ACT 2601 Email: mrff.postaward@nhmrc.gov.au
Role: Principal Investigator
Time commitment: 0.4 CM
Overlap: None

Grant number: APP1153049 (Geoff Lindeman, PI)
Funder/Sponsor: National Health and Medical Research Council (NHMRC) Centre of Research Excellence
Type: Research Centre Grant
Amount: AUD
Period: 1/2018-12/2022
Centre for Translational Breast Cancer Research (TransBCR): delivering laboratory discoveries to the clinic

AIM 1: Stream 1 – Clinical trials: implementing novel targeted therapies
AIM 2: Stream 2 – Breast biomarker project: selecting the correct target for the right patient
POC: Dr Tony Willis, Executive Director, Research Programs NHMRC, GPO Box 1421, Canberra ACT 2600, Australia, tony.willis@nhmrc.gov.au
Role: Co-Principal Investigator
Time commitment: 0.1 CM
Overlap: None

Grant number: APP1196755 (OVERALL PI)
Funder/Sponsor: National Health and Medical Research Council (NHMRC)
Type: Investigator Grant
Amount: AUD6
Period: 1/2021-12/2025
Circulating tumour DNA for precision medicine
AIM 1: Clinical translational of circulating tumour DNA analysis
AIM 2: Discovery and innovation through circulating biomarker research
POC: Dr Tony Willis, Executive Director, Research Programs NHMRC, GPO Box 1421, Canberra ACT 2600, Australia, tony.willis@nhmrc.gov.au
Role: Principal Investigator
Time commitment: 0.8 CM
Overlap: None

Grant number: N/A (OVERALL PI)
Funder/Sponsor: CSL Centenary Fellowship
Type: Fellowship
Amount: AUD
Period: 1/2018-12/2022
Circulating tumour DNA for precision medicine
AIM 1: Clinical translation of circulating tumour DNA analysis
AIM 2: Discovery and innovation through circulating biomarker research
POC: Lina Papalia, Senior Manager, Portfolio Planning & Partnerships CSL Limited, 45 Poplar Road, Parkville, VIC 3052, Australia Email: lina.papalia@csl.com.au
Role: Principal Investigator
Time commitment: 0.8 CM
Overlap: None

Grant number: APP1158345 (OVERALL PI)
Funder/Sponsor: National Health and Medical Research Council (NHMRC)
Type: Project Grant
Amount: AUD
Period: 1/2019-12/2022
Monitoring evolutionary trajectories in non-small cell lung cancer to improve treatment outcomes
AIM 1: To prospectively characterise ctDNA dynamics within the OSCILLATE clinical trial
AIM 2: To understand clonal evolution patterns and mechanisms of resistance in patients receiving alternating EGFR TKI therapy
AIM 3: To model optimal treatment strategies with novel schedules of EGFR TKI therapy in *EGFR* mutant NSCLC
POC: Dr Tony Willis, Executive Director, Research Programs NHMRC, GPO Box 1421, Canberra ACT 2600, Australia, tony.willis@nhmrc.gov.au
Role: Principal Investigator
Time commitment: 0.2 CM
Overlap: None

Grant number: IIRS-18-025 (OVERALL PI)
Funder/Sponsor: National Breast Cancer Foundation (NBCF)
Type: Investigator Initiated Research Scheme
Amount: AUD
Period: 1/2018-12/2022
Tracking residual disease using circulating tumour DNA in high risk early stage breast cancer
AIM 1: Define the frequency of circulating tumour DNA detection post adjuvant therapy in women with high-risk early stage BC
AIM 2: Evaluate the relationship between MRD identified through ctDNA analysis and clinical relapse following adjuvant therapy for high-risk early stage BC.
AIM 3: Determine the feasibility of identifying treatment targets in MRD identified through ctDNA analysis and develop a platform that provides downstream linkage to novel clinical trials.
POC: Chris Pettigrew, Director, Research Investment, National Breast Cancer Foundation, Level 9, 50 Pitt Street, Sydney NSW 2000, Australia, +61 2 8098 4800, info@nbcf.org.au
Role: Principal Investigator
Time commitment: 0.4 CM
Overlap: None

Grant number: APP1143025 (OVERALL PI)
Funder/Sponsor: National Health and Medical Research Council (NHMRC)
Type: Project Grant
Amount: AUD
Period: 1/2018-12/2022
CAPTURE; Circulating tumour DNA assessment of PIK3CA to guide treatment response
Primary Aim: To test the role of *PIK3CA* mutant ctDNA testing to guide treatment selection in women with endocrine resistant ER+, HER2- MBC through a multicentre, randomized, phase II clinical trial
POC: Dr Tony Willis, Executive Director, Research Programs NHMRC, GPO Box 1421, Canberra ACT 2600, Australia, tony.willis@nhmrc.gov.au
Role: Principal Investigator
Time commitment: 0.4 CM
Overlap: None

Grant number: CCV GIA – Francis (Prue Francis, PI)
Funder/Sponsor: Cancer Council of Victoria Grant in Aid
Type: NGO (non-profit)
Amount: AUD
Period: 1/2021-12/2023
Understanding response to neoadjuvant therapy in hormone receptor positive breast cancer; a correlative analysis of the ELIMINATE trial
AIM 1: To characterise the baseline genomic landscape of the patients enrolled in the ELIMINATE study through analysis of both tumour, and matched plasma samples and investigate associations with clinico-pathologic outcomes.
AIM 2: To compare the dynamic molecular changes using paired tumour samples following NAT from baseline to week 6 in those who achieve down staging (RCB 0-1) and those that do not (RCB 2-3).
AIM 3: To investigate the dynamics of ctDNA during treatment and characterise the relationship between changes in ctDNA levels and treatment response. We plan to assess the dynamics of ctDNA in relation to NAT, using our targeted sequencing ctDNA assay described above, in aim 1.2. For this ctDNA will be analysed from serial samples at baseline, week 6, post NAT (pre-operative), and post surgery.
POC: Alysha Cameron**,** Research Governance Lead, Research Governance & Optimal Care, 615 St Kilda Rd, Melbourne Vic 3004 Australia E: CancerCouncilGrants@cancervic.org.au T**:** 03 9514 6200
Role: Co-Principal Investigator

Time commitment: 0.2 CM
Overlap: None

PREVIOUS (Last 5 Years)

Grant number: APP1107126 (OVERALL PI)
Funder/Sponsor: National Health and Medical Research Council (NHMRC)
Type: Project Grant
Amount: AUD
Period: 1/2016-12/2019
Circulating tumour DNA as a noninvasive biomarker in melanoma
AIM 1: Utilise ctDNA in patients with Stage III melanoma to identify minimal residual disease and predict early relapse
AIM 2: Utilise ctDNA in patients with Stage IV melanoma to monitor treatment responses to targeted and immune therapies
AIM 3: Investigate the utility of ctDNA to study intratumoural heterogeneity in melanoma
AIM 4: Utilise ctDNA to study acquired treatment resistance to targeted therapies
AIM 5: Utilise ctDNA to study mutational load and predict treatment response to immunotherapies
POC: Dr Tony Willis, Executive Director, Research Programs NHMRC, GPO Box 1421, Canberra ACT 2600, Australia, tony.willis@nhmrc.gov.au
Role: Principal Investigator
Time commitment: 0.6 CM
Overlap: None

Grant number: APP1104549 (OVERALL PI)
Funder/Sponsor: National Health and Medical Research Council (NHMRC)
Type: Project Grant
Amount: AUD
Period: 1/2016-12/2018
Circulating tumour DNA to monitor treatment response and resistance in chronic lymphocytic leukaemia
AIM 1: Utilise ctDNA to monitor treatment responses to novel therapeutic agents in CLL
AIM 2: Compare and contrast the utility of ctDNA analysis with the current gold standard of flow-cytometry for identifying minimal residual disease (MRD) following treatment in CLL
AIM 3: Utilise ctDNA to study acquired treatment resistance in patients receiving ibrutinib and/or ABT-199 for relapsed / refractory CLL
POC: Dr Tony Willis, Executive Director, Research Programs NHMRC, GPO Box 1421, Canberra ACT 2600, Australia, tony.willis@nhmrc.gov.au
Role: Principal Investigator
Time commitment: 0.6 CM
Overlap: None

Grant number: APP1128984 (Mark Dawson, PI)
Funder/Sponsor: National Health and Medical Research Council (NHMRC)
Type: Project Grant
Amount: AUD
Period: 1/2017-12/2019
Clonal evolution in myelodysplasia and acute myeloid leukaemia following azacitidine
AIM 1: To analyse clonal composition and clonal evolution in malignant cells from patients with MDS / AML receiving azacitidine based therapies
AIM 2: To characterise the cellular and molecular events that influence clonal evolution in the context of azacitidine treatment.

AIM 3: To assess the role of cell free circulating tumour DNA (ctDNA) as a novel biomarker to noninvasively monitor therapeutic response and clonal evolution in MDS / AML
POC: Dr Tony Willis, Executive Director, Research Programs NHMRC, GPO Box 1421, Canberra ACT 2600, Australia, tony.willis@nhmrc.gov.au
Role: Co-Principal Investigator
Time commitment: 0.6 CM
Overlap: None

Grant number: APP1085014 (OVERALL PI)
Funder/Sponsor: National Health and Medical Research Council (NHMRC)
Type: Project Grant
Amount: AUD
Period: 1/2015-12/2017
Circulating tumour DNA of acquired treatment resistance in breast cancer
AIM 1: Quantify ctDNA levels in serial plasma from women receiving taxane treatment for MBC.
AIM 2: Perform genome-wide exome sequencing of selected serial plasma samples, to identify candidate mutations enriched following the selective pressure of taxane-based treatment.
AIM 3: Validate candidate mutations across the series using targeted deep sequencing.
AIM 4: Perform functional analyses of selected mutations to determine their role in the development of acquired treatment resistance to taxanes
POC: Dr Tony Willis, Executive Director, Research Programs NHMRC, GPO Box 1421, Canberra ACT 2600, Australia, tony.willis@nhmrc.gov.au
Role: Principal Investigator
Time commitment: 0.6 CM
Overlap: None

Grant number: 0862-15 (OVERALL PI)
Funder/Sponsor: The Leukaemia and Lymphoma Society (LLS)
Type: Quest for Cures Grant
Amount: AUD
Period: 1/2015-12/2016
Circulating tumour DNA to monitor response and resistance in mantle cell lymphoma
AIM 1: To use ctDNA for molecular monitoring of treatment response and MRD in mantel cell lymphoma
AIM 2: To use ctDNA for detecting the emergence of treatment resistance in mantel cell lymphoma
POC: Nikay Thomas, The Leukemia & Lymphoma Society, 3 International Drive, Suite 200, Rye Brook NY 10573, researchprograms@lls.org, Nikay.Thomas@lls.org
Role: Principal Investigator
Time commitment: 0.6 CM
Overlap: None

Grant number: IN-15-054 (OVERALL PI)
Funder/Sponsor: National Breast Cancer Foundation (NBCF)
Type: Innovation Grant
Amount: AUD
Period: 1/2015-12/2016
Circulating tumour DNA to monitor response to neoadjuvant therapy in women with HER2 overexpressing breast cancer
Primary Aim: To determine if women with ER positive, HER2 negative metastatic breast cancer and increasing levels of *PIK3CA* mutant ctDNA 3 weeks after commencement of paclitaxel benefit from the addition of a PI3K inhibitor, through improvement in progression free survival (PFS).
POC: Chris Pettigrew, Director, Research Investment, National Breast Cancer Foundation, Level 9, 50 Pitt Street, Sydney NSW 2000, Australia, info@nbcf.org.au

Role: Principal Investigator
Time commitment: 0.6 CM
Overlap: None

27 September 2022
Professor Sarah-Jane Dawson 

OTHER SUPPORT
PREVIOUS/CURRENT/PENDING SUPPORT
BENJAMIN Z. LEDER – SUBCONTRACT (MGH) CO-INVESTIGATOR

PREVIOUS (Last 5 years)

Title: (No grant number) Teriparatide resistance: Investigation of potential mechanisms and therapeutic options
Level of Effort: .12 CM Funding Source: Mass General Hospital; Dart Family Foundation Award
Contact: Mass General Development Office; mghdevelopment@partners.org; 617-726-2200
125 Nashua Street, Suite 540
Boston, MA 02114-1101
Performance period: 9/1/13-9/01/17
Level of funding:
Brief description of the project's goals: The goals of the animal studies in this proposal are to determine the mechanism(s) responsible for the waning of the anabolic effects of long-term daily teriparatide administration and of the marked reduction in the anabolic response to teriparatide re-treatment. The aim of the human study is to determine whether teriparatide resistance can be overcome by administering a higher dose of teriparatide together with denosumab.
Role: PI

Title: (5K24AR067847-05) Novel combination therapies in the treatment of osteoporosis
Level of Effort: 6.00 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Contact: Aleisha James, Grants Mgt. Specialist, aleisha.james@nih.gov
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance period: 5/1/15-4/30/20
Level of funding:
Brief description of the project's goals: To assess the efficacy of high dose teriparatide in combination with RANKL inhibition in postmenopausal women with osteoporosis.
Role: PI

Title: (5R21AR069871-03) Consolidating skeletal benefits after short-term combination osteoporosis therapy: The DATA-EX study
Level of Effort: 0.96 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Contact: Teresa Do, Grants Mgt. Specialist, Teresa.Do@nih.gov;
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance period: 5/1/16-4/30/20 (NCE)
Level of funding:
Brief description of the project's goals: Extension of a proof-of-principle clinical trial evaluating the efficacy of short-term therapy with a novel combination of osteoporosis medications followed by a single dose of a long-acting bisphosphonate.
Specific Aims: To test the following hypotheses: Hypothesis 1: In postmenopausal women with osteoporosis, the large increases in cortical and trabecular bone density achieved with combined denosumab and standard or high-dose teriparatide will be maintained and extended for up to 27-months by a single administration of an intravenous bisphosphonate (zoledronic acid). Hypothesis 2: In postmenopausal women with osteoporosis, the

extensive improvement in bone quality achieved with combined denosumab and standard or high-dose teriparatide therapy will also be maintained and extended for up to 27-months by a single dose of zoledronic acid.
Role: PI

Title: (BA058-05-020) An open-label, single-arm, multicenter study to evaluate the early effects of abaloparatide on tissue-based indices of bone formation and resorption
Level of Effort: 0.06 CM
Funding Agency: Radius Health Inc. (Industry)
Contact: Sherita Hall, Sr. Director Clinical Operations; shall@radiuspharm.com;
950 Winter Street
Waltham, MA 02451
Performance period: 10/2/18-10/1/23
Level of funding:
Brief description of the project's goals: This open-label, single-arm, multicenter study will assess the early effects of abaloparatide in postmenopausal women with osteoporosis using tissue-based indices of bone metabolism obtained by iliac crest bone biopsy after quadruple tetracycline labeling and will relate these indices to biochemical markers of bone turnover.
Specific Aims: 1. Demonstrate the early effects of abaloparatide on tissue-based bone formation and resorption indices 2. Assess the degree to which increased bone formation is achieved by modeling, remodeling, and overflow bone formation 3. Relate the early indices of tissue-based bone formation and bone resorption to those measured using biochemical markers of bone turnover.
Role: PI

Title: (5K23AR068447-04) Effect of anabolic and antiresorptive therapy on bone quality in osteoporosis
Level of Effort: 0.06 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Contact: Mark E. Langer, Grants Mgt. Specialist; mark.langer@nih.gov;
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance period: 9/1/15-8/31/20
Level of funding:
Brief description of the project's goals: By studying how anabolic and antiresorptive osteoporosis therapy affects skeletal health, the proposed research will increase our understanding of how fracture reduction is achieved and how the different agents interact.
Specific Aims: Aim 1: To characterize changes in bone density, microarchitecture, microstructure and bone strength in postmenopausal women receiving denosumab and high dose teriparatide. Aim 2: To characterize changes in bone strength due to changed material properties of bone using *in vivo* novel techniques in postmenopausal women receiving denosumab and high dose teriparatide. Aim 3: To compare skeletal microarchitecture, microstructure, and estimated bone strength in women at high fracture risk who have been previously exposed to bisphosphonates with bisphosphonate-naïve women matched for age and areal BMD (aBMD).
Role: Mentor

Title: (1R34AR074114-02) Combination osteoporosis therapy and fracture reduction
Level of Effort: 1.81 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Contact: Teresa Do, Grants Mgt. Specialist, Teresa.Do@nih.gov;
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772

Performance period: 9/1/18-8/31/20
Level of funding: $168,743
Brief description of the project's goals: Aim is to plan a clinical trial assessing the efficacy of combination therapy on fracture
Role: PI

Title: Mechanisms Underlying the Bone Modeling Effects of Combined Anabolic/Antiresorptive Administration
Level of Effort: 1.80 CM
Funding Agency: Massachusetts General Hospital ECOR
Performance Period: 4/1/2018-3/31/2019
Level of Funding: $75,000
The goal of this proposal is to identify the cellular and molecular basis for the dramatic increase in bone observed with administration of combined anabolic/antiresorptive therapies. Subjects will be administered two fluorochromes prior to and after three months of therapy. Histomorphometric analyses will examine modeling vs remodeling-based bone formation. Bone marrow stromal cells will be isolated for molecular analyses and CFU assays.

CURRENT

Title: (5R01AR073191-04) Mechanisms Underlying the Bone Modeling Effects of Combined Anabolic/Antiresorptive Administration
Level of Effort: 4.08 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Fay Chen, Program Official, chenf1@mail.nih.gov, 301-594-5055
National Institute of Arthritis and Musculoskeletal and Skin Diseases/National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance period: 4/1/19-3/31/23
Level of funding: $2,247,416 Total Award Amount
Brief description of the project's goals: To define cellular and molecular mechanisms that underlie the efficacy of combination antiresorptive and anabolic osteoporosis therapy.
Role: PI
Overlap: None

Title: (20187074) Comparative antiresorptive efficacy of alendronate or raloxifene following discontinuation of denosumab
Level of Effort: 0.12 CM
Funding Agency: Amgen Inc. (Industry)
Contact: Julie Marvin-Craig, Mgr. Investigator-Sponsored Studies; jmarvinc@amgen.com; 402-506-6887
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Performance period: 9/21/18-9/20/23
Level of funding: $1,310,337 Total Award Amount
Brief description of the project's goals: This investigator-initiated open-label, single center randomized controlled trial will assess the relative efficacy of two oral anti-resorptives (alendronate and raloxifene) in preventing the rebound increase in bone turnover that occurs after denosumab discontinuation in postmenopausal women with osteoporosis.
Specific Aim: To test the hypothesis that in postmenopausal women with osteoporosis who received denosumab 60 mg every 6 months for one year, alendronate will more fully inhibit the post-denosumab increase in bone resorption compared to raloxifene.
Role: PI
Overlap: None

Title: (BC181146 Garber) Prospectively Randomized, Placebo-Controlled Phase III Study to Determine the Effect of Denosumab on Breast Cancer Prevention in BRCA1 Mutation Carriers
Breast Cancer Research Program (BCRP) Breakthrough Award
Level of Effort: 0.24 CM
Funding Agency: Department of Defense (DoD)
Name and address of the Funding Agency's Procuring Contracting/Grants Officer:
Contact: Jamie A. Shortall. Grants Officer, jamie.a.shortall.civ@mail.mil; 301-619-2393
W03J USA Med Research MAT CMD
1077 Patchel Street, Fort Detrick, MD 21702
Performance Period: 10/1/2019-9/30/2023
Level of Funding: $1,086,251 Total Award Amount
The primary objective of the BRCA-P phase III randomized placebo-controlled chemoprevention trial is to evaluate the reduction in risk of any BC (invasive or DCIS) in women with a gBRCA1m treated with DNSB compared to placebo.
Role: Subaward Co-I
Overlap: None

Title: (5R21AR079718-02) Limited-duration anabolic therapy in postmenopausal osteoporosis
Level of Effort: 2.40 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Fay Chen, Program Official, chenf1@mail.nih.gov, 301-594-5055
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance Period: 09/20/2021 - 08/31/2024
Level of Funding: $626,036 Total Award Amount
The major goal of this project is to assess the efficacy of short-term anabolic therapy in postmenopausal women with osteoporosis.
Role: PI
Overlap: None

PENDING
Title: (P50AR080596-01) Project 1: The role of osteoblast progenitors in response to bone anabolic agents
Level of Effort: 2.40 CM
Funding Agency: NIH/NIAMS
Name and address of the Funding Agency's Procuring Contracting/Grants Officer: Victoria Matthews, Grants Management Specialist, 301-594-5032, victoria.matthews@nih.gov
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
6701 Democracy Blvd; Suite 800
Bethesda, MD 20892-4772
Performance Period: 04/01/2022 - 03/31/2027
Level of Funding: $2,847,934 Total Cost Amount
The goal of this center of research translation (CORT) is to understand how bone-building osteoporosis medications work in order to develop 'next generation' strategies to treat this disease. To accomplish this goal, we will apply cutting-edge methods to study the effects of such medications on key cell types in bone: stem cells and osteocytes.
Role: Co-I

Signature: Benjamin Leder
Benjamin Leder (Sep 20, 2022 13:04 EDT)

Date: Sep 20, 2022

Current, Pending and Previous Support for Lee Hang, Ph. D

POSITIONS AND APPOINTMANTS	
2018-Present	Associate Professor of Medicine, Harvard medical School and MGH Biostatistics Center, Boston, MA
2001 – 2017	Assistant Professor of Medicine, Harvard Medical School and MGH Biostatistics Center, Boston, MA
1998 – 2001	Director of Biostatistics, UCLA Center for Vaccine Research, Torrance, CA
1998 – 2001	Assistant Professor, UCLA School of Medicine, Los Angeles, CA
1996 – 2006	Statistical Consultant, College Alcohol Study, Department of Society, Human Development, and Health, Harvard School of Public Health, Boston, MA
1996 – 1998	Statistical Consultant, Behavioral Science Research Program Frontier Science and Technology Research Foundation, Chestnut Hill, MA
1996 – 1998	Instructor in Psychiatry, Harvard Department of Psychiatry, Boston, MA
1994 – 1996	Research Fellow in Biostatistics, Harvard School of Public Health, Boston, MA
1987 – 1994	Biostatistician, Univ. of Southern California School of Medicine, Los Angeles, CA

CURRENT	
Title:	Cancer Center Support Grant (Biostatistics CORE)
Effort:	2.5% (0.30 CM)
Supporting Agency:	NIH-NCI National Cancer Institute
Grant Officer:	Krzysztof Ptak| krzysztofptak@ninds.nih.gov
Address:	6116 Executive Blvd, Rm 7004 Rockville, MD 20852
Performance Period:	12/22/2016 – 11/30/2022
Funding Amount:	
Project Goals:	The major goals of this project are to support CORE activities that represent shared resources used by a variety of investigators in different labs throughout the DF/HCC. This is a subcontract through the Dana-Farber Cancer Institute.
Specific Aims:	1) foster inter-disciplinary interactions and collaborations 2), utilize CCSG Developmental Funds to recruit new investigators, encourage translational research Programs, and develops new Shared Resources (Cores) to Support KCI members
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Novel PET/CT and Treatment Strategies to reduce PTS following DVT
Effort:	3% (0.36 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Andrei Kindzelski, M.D., Ph.D.| kindzelskial@nhlbi.nih.gov
Performance Period:	07/15/2017 – 05/31/2023
Funding Amount:	
Project Goals:	This clinical, molecular imaging, and biological research proposal seeks to: (1) establish the relationship between DVT and inflammation and risk of subsequent development of post – thrombotic syndrome and (2) develop novel anti-inflammatory therapies to reduce DVT complications.
Specific Aims:	1) to perform a first-in-human clinical trial assessing DVT-based inflammation using FDG- PET/CT to predict the risk of subsequent PTS in patients independently and in multivariate analyses. 2) to develop three new Anti-inflammatory pharmacotherapeutic Strategies to reduce vein wall scarring in experimental DVT
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Nutrition Obesity Research Center at Harvard (NORCH)
Effort:	2.5% (0.30 CM)
Supporting Agency:	NIDDK
Grant Officer:	Kristy Nicks, Ph.D.| nickskm@mail.nih.gov
Address:	6701 Democracy Boulevard | Building: Democracy I, Suite: 800 Bethesda MD 20892-4872
Performance Period:	08/01/2017 – 07/31/2022
Funding Amount:	
Project Goals:	This Center grant supports the Nutrition Obesity Research Center at Harvard (NORC-H), the goals of which are to provide critical support to research in nutrition and obesity throughout the Harvard community, to facilitate novel directions in nutrition and obesity research through pilot funding and scientific exchange, to promote interactions and collaborations among investigators to advance the science of nutrition and obesity, and to foster the development of junior faculty in these research areas.
Specific Aims:	Our goals are to promote novel cutting edge research in nutrition and obesity, while promoting a new generation of researchers interested and retained in the field, to promote the engagement of a wide spectrum of the research community, through comprehensive peer review of submitted proposals, active monitoring of results and publications, and enrichment, through organized symposia highlighting the work of the successful grantees and engaging these researchers in successful collaborations, to facilitate the success of our grantees grants through: 1) the use of shared core resources, made uniquely accessible to grantees through an incentives and a weighed system of charge back subsidies to P&F winners 2) provision of consultations in model development for specific experimental strategies, and 3) specific statistical support to P&F applicants and ongoing support to awardees to facilitate optimal study design.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Harvard Clinical and Translational Science Center
Effort:	10%. (1.20 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Mary E. Purucker, M.D., Ph.D.| puruckerm@mail.nih.gov
Performance Period:	05/01/2018 – 04/30/2023
Funding Amount:	
Project Goals:	Provide enriched resources to educate and develop the next generation of researchers trained in the complexities of translating research discoveries into clinical trials and ultimately into practice. Design new and improved clinical research informatics tools for analyzing research data and managing clinical trials. Support outreach to underserved populations, local community and advocacy organizations, and health care providers. Assemble interdisciplinary teams and forge new partnerships with private and public health care organizations.
Specific Aims:	1) Workforce Development will support the broadly defined educational needs of the present and future CT workforce inclusive of all CT research domains, disciplines, medical and graduate students, post-graduate trainees, investigators, multi-disciplinary team members, and communities of collaborators. 2) Research Methods and Processes will provide "everything necessary" to execute CT research including methods, processes, workflows, pilot grants, novel technologies, and integrated data sets necessary for investigators and their teams to succeed locally and in collaboration with communities and the CTSA consortium. 3) Integration will ensure that translational science is interconnected across all T domains and is inclusive of the

	needs of special populations and individuals across their entire lifespan. 4) Collaboration and Engagement will promote team science by extending the CT research community beyond its traditional academic borders. It engages and partners with our patients, communities, and our diverse ecosystem to participate in prioritization decisions and gap analysis. 5) Informatics respond to the needs of CT investigators, teams, patients, and communities by providing enabling processes, methodologies, and tools.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Growth Hormone Releasing Hormone Analog to Improve Nonalcoholic Fatty Liver Disease and Associated Cardiovascular Risk
Effort:	3% (0.36 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Edward Doo, MD | edward.doo@nih.gov
Performance Period:	05/15/2018 – 04/30/2023
Funding Amount:	
Project Goals:	The major goals of this project are to investigate whether growth hormone releasing hormone, a treatment that increases growth hormone secretion, will reduce liver fat, liver damage, and cardiovascular disease risk in patients with NAFLD.
Specific Aims:	Aim 1: Compared to placebo, GHRH will significantly decrease hepatic fat as measured by MRS (primary endpoint) and improve liver histology as assessed by reduction in NAFLD activity score and its individual components. Aim 2: GHRH will alter hepatic lipid metabolism by decreasing hepatic de novo lipogenesis and increasing expression of lipolytic genes, and will also reduce the hepatic expression of lipogenic, pro- inflammatory and fibrogenic genes. Aim 3: Finally, given that cardiovascular disease is the leading cause of death in NAFLD, and that preliminary data strongly suggest a benefit of GHRH to reduce subclinical atherosclerosis, we hypothesize that GHRH will decrease coronary artery calcium scores and overall plaque burden and will improve lipids and circulating markers of cardiovascular disease. If these hypotheses are correct, the proposed studies will represent significant progress toward the development of therapies for NAFLD in obesity.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	The Role of Estrogen in the Neurobiology of Eating Disorders: A Study of Cognitive Flexibility and Reward in Eating Disorders
Effort:	3% (0.36 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Mark Chavez, Ph.D.| mchavez1@mail.nih.gov
Performance Period:	03/08/2019 – 12/31/2023
Funding Amount:	
Project Goals:	Adolescence and young adulthood are often a time for the onset of eating disorders, as well as a key window of neurocognitive development and hormone changes. Estrogen dysregulation is common in eating disorders and is associated with impaired cognitive flexibility and altered reward responsiveness and valuation, which in turn, may play a mechanistic role in the onset and course of eating disorders. This proposal utilizes physiologic estrogen as a probe, studying its role in cognitive flexibility, reward responsiveness and valuation, and in turn, eating disorder psychopathology, in eating disorders
Specific Aims:	We will randomize 120 hypoestrogenemic females with ED-R/E (ages 16-26) to a 12-week challenge of physiologic estrogen or placebo to evaluate: effects on RDoC subconstructs (Updating, Representation and Maintenance i.e. Cognitive Flexibility; Initial Response to Reward; and Delay) at 8 weeks; ED pathology at 12 weeks; and

	determine whether 8-week changes in RDoC subconstructs mediate the 12-week improvement in ED pathology. We hypothesize that in ED-R/E, correcting estrogen deficiency will improve Cognitive Flexibility, Initial Response to Reward and Delay, and ED pathology; and that improvement in ED pathology will be mediated by changes in these RDoC subconstructs.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Mechanisms Underlying the Bone Modeling Effects of Combined Anabolic/ Antiresorptive Administration
Effort:	4% (0.48 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Faye H. Chen, PhD | chenf1@mail.nih.gov
Address:	6701 Democracy Boulevard | Building: Democracy I, Suite: 800 Bethesda MD 20892-4872
Performance Period:	04/01/2019 – 03/31/2023
Funding Amount:	
Project Goals:	Osteoporosis is a large and growing public health concern that affects over 20 million Americans. While no single medication is able to restore skeletal health in most patients with severe disease, one specific drug combination has recently been shown to increase bone mass more than any available agent. This proposal aims to define the mechanisms that underlie the efficacy of this drug combination and thus support the optimization of combination osteoporosis therapy. Such an advance has the potential to fundamentally improve osteoporosis management.
Specific Aims:	Aim 1: To directly assess the ability of teriparatide to stimulate modeling-based bone formation when bone resorption is blocked by denosumab. Aim 2: To define the cellular and molecular mechanisms by which this combination achieves its efficacy.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Prevention of post-therapy breast cancer metastasis
Effort:	3 % (0.36 CM) Years 4&5
Supporting Agency:	NCI- National Cancer Institute
Grant Officer:	Dr. Mansoor M Ahmed | ahmedmm@mail.nih.gov
Address:	9609 Medical Center Dr., MSC 9727 Bethesda, MD 20892-9727
Performance Period:	04/12/2019 – 03/31/2025
Funding Amount:	
Project Goals:	This grant proposal aims at eradicating the source of metastasis, namely breast cancer stem cells through repurposing a FDA approved drug Disulfiram (known for chronic alcoholism treatment) in combination with standard chemo- and radiation- therapy to prevent post-therapy breast cancer metastasis.
Specific Aims:	In Aim1, we will assess the therapeutic efficacy of IR and/or chemo combined with DSF/Cu on preventing metastasis of patient breast cancer-derived xenograft (PDX) and MMTV-PyMT transgenic mammary tumors in an adjuvant setting. In Aim2, we will assess the therapeutic efficacy of chemo combined with DSF/Cu on preventing metastasis of PDX and MMTV-PyMT tumors in a neoadjuvant setting. In Aim3, we will analyze the mechanisms by which DSF/Cu systemically targets BCSC via induction of ICD and modulation of IR-induced immune response
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Arterial Inflammation and Coronary Microvascular Dysfunction among Women with HIV: Missing Pieces to the MI Risk Puzzle
Effort:	5% (0.60 CM)

Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Dr Erin Jane Iturriaga | erin.iturriaga@nih.gov
Address:	6705 Rockledge Dr.| BG RKL1 RM 309-G1 Bethesda, MD. 20817
Performance Period:	08/09/2019 – 07/31/2023
Funding Amount:	
Project Goals:	The major goals of this study are to characterize novel physiologic mechanisms underlying increased HIV-attributable myocardial infarction risk among women.
Specific Aims:	Through this proposal, our interdisciplinary team will combine state-of-the-art non-invasive CV imaging with detailed molecular immune cell and endothelial cell phenotyping to define mechanisms predisposing WHIV to MI. Studying a prospectively recruited cohort of WHIV vs. non-HIV-infected women, we will explore a well-substantiated central hypothesis: Among women, HIV infection prompts systemic monocyte activation and endothelial cell pathology, predisposing to increased arterial inflammation. Arterial inflammation and endothelial cell pathology, in turn, promote not only non-calcified epicardial artery plaque but also coronary microvascular dysfunction. We plan to show that arterial inflammation and coronary microvascular dysfunction represent thus far neglected but potentially critical mechanisms of HIV-attributable MI risk among women – missing puzzle pieces (Aims 1-2). We also aim to delineate - on a molecular level - how circulating monocyte and vascular endothelial cell phenotypes differ among WHIV vs. non-HIV-infected women. Finally, we will investigate how pathologic monocyte/endothelial cell phenotypes may engender arterial inflammation, non-calcified epicardial artery plaque, and/or coronary microvascular dysfunction among WHIV (Aim 3).
Project Overlap	No overlap with any currently funded or pending projects.

Title:	ADMINISTRATIVE Core (Core A) - Hormonal Control of Calcium Metabolism
Effort:	3% (0.36 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Saul N. Malozowski M.D. PhD| saul.malozowski@nih.gov
Performance Period:	09/05/2019 – 06/30/2024
Funding Amount:	
Project Goals:	The support of our Administrative Core is essential to the integration of work on all projects and cores including financial management, compliance with regulatory and reporting requirements, recruiting and hiring, monitoring of employee performance and salaries and organization of activities that encourage the sharing of information both within the Endocrine Unit and with other groups of Scientists with similar interests.
Specific Aims:	This Program Project "Hormonal Control of Calcium Metabolism" brings together a group of highly productive investigators who work closely together, as they have for years, supported by the project and stimulated by the environment of the Endocrine Unit. Powerful research tools feature the approaches of chemical and molecular biology and a number of carefully designed genetically modified animals to evaluate bone and renal cell biology as well as mineral metabolism.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Impact of Depression on Alzheimer's disease: Prenatal Immune Origins and Shared Impact of Sex
Effort:	3.80% (0.46 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Luci Roberts | roberlu@mail.nih.gov |

Performance Period:	09/15/2019 – 05/31/2024
Funding Amount:	
Project Goals:	The major goals of this project are: Major depressive disorder (MDD), which has twice the risk in women than men, is a risk factor of Alzheimer's disease (AD). Further, both disorders are highly related to vascular compromise and neurovascular dysfunction. However, despite the strong comorbidity between MDD, AD, and neurovascular dysfunction, little is known about the shared pathophysiology that underlies these prominent disorders. We will test the hypothesis that sex differences in AD pathology and neurovascular dysfunction are, in part, mediated by MDD through dysregulation of shared immune and stress pathways beginning in fetal development.
Specific Aims:	We will test the hypothesis that this shared risk has fetal origins that involve abnormalities in immune-stress and vascular pathways with sex-dependent consequences. we will test whether associations between prenatal inflammatory biomarkers and sex- dependent AD risk and neurovascular dysregulation are mediated by sex-dependent risk for MDD. Our lifespan perspective is an innovative approach that will identify potential therapeutic targets for AD associated with MDD and vascular function that are sex-dependent and can be applied to early periods for intervention prior to disease onset.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Glioma SPORE Core B Biostatistics and Computational Biology
Effort:	5% (0.60 CM)
Supporting Agency:	NCI-National Cancer Institute | (Subcontract PI)
Grant Officer:	Leah Hubbard Ph.D | leah.hubbard@nih.gov
Address:	9609 Medical Center Drive, Room 3W212 MSC 9726 Bethesda, MD 20892
Performance Period:	09/17/2019 – 08/31/2024
Funding Amount:	
Project Goals:	The mission of the Biostatistics and Computational Biology Core of this glioma SPORE is to foster rigor and reproducibility. Towards this end, the core will work with project leaders to insure statistical integrity in the design of their experiments and interpretation of their data.
Specific Aims:	The work proposed for Project One has the potential to deliver brain-penetrant targeted therapies for these tumors. Primary brain tumors, including high-grade gliomas are the third most common cause of cancer-related death in persons ages 15-39 years (http://www.CBTRUS.org). In the fullness of time, the work proposed for Projects Two and Three could change the standard of care and improve patient outcomes for these tumors via highly selective "synthetic lethal" therapeutic modalities (Project Two) or small molecule adjuvants to immunotherapy (Project Three). Project Four addresses a unique feature in the biology of high-grade gliomas. These tumors occur within the context of the brain microenvironment. Preliminary studies have shown that neuronal activity within the glioma microenvironment secrete a factor (NLGN3) that promotes the growth of these tumors in adults and also in children. The study plan for this project will explore a novel therapeutic opportunity embedded within the NLGN3 requirement.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Stimulation of Dendritic Cell Recruitment and Differentiation to Improve the Treatment of Metastatic Breast Cancer
Effort:	2% (0.24 CM)
Supporting Agency:	U.S. Army Medical Research Acquisition Activity

Performance Period:	12/01/2019 – 11/30/2022
Funding Amount:	
Project Goals:	In this study, we will test the hypothesis that the intravenous delivery of oncolytic herpes simplex virus encoding XCL1 and FLT3L will increase the intratumoral recruitment of dendritic cells and activity of natural killer cells and T cells, and anti-tumor activity in metastatic breast cancer.
Specific Aims:	Aim 1a: Establish in lung models of MBC whether ganetespib increase the vascular leakiness of nanoparticles and intratumoral distribution of oncolytic HSV injected intravenously. Our in vitro results suggest that the ganetespib-induced increase in endothelial permeability of NPs is due to an increase phosphorylation of VE-CAD. However, it is unknown whether ganetespib affects the phosphorylation of VECAD (phospho-VE-CAD) in tumors. We will measure in tumor vessels VE-CAD and phospho-VE-CAD expression and assess if the accumulation of NPs in the peri-vascular space is linked to phospho-VE-CAD. Aim 1b: Determine in lung models of MBC the effect of ganetespib combined with oHSV on virus replication, lung metastasis formation and mouse survival. Aim 2a. To stimulate the infiltration of cDC1 in MBC, we will engineer oHSV expressing XCL1 and FLT3L. We will then determine how oHSV encoding XCL1 and FLT3L affect the expression / secretion of XCL1 and FLT3L in MBC cells. We will use culture supernatants to determine the activity (e.g. chemotaxis assay, differentiation of bone marrow cells into cDC1s) of transgene products. Aim 2b. Determine whether the IV injection of oHSV-XCL1, oHSV-FLT3L or oHSV-XF with or without the administration of ganetespib enhances the expression of XCL1 and FLT3L. Aim 3a. Determine whether the IV injection of oHSV-XCL1, oHSV-FLT3L or oHSV-XF with or without the administration of ganetespib improves the infiltration of cDC1, and activity of NK cells and T cells in MBC. We will also assess how the ectopic expression of XCL1 and FLT3L affects the intratumoral accumulation of other innate and adaptive immune cells. However, we will focus mostly on CD103+ cDCs, CD8+T cells and NK cells because the following important questions related to these cells in MBC remain unaddressed: i) Are CD103+ cDC1 required for tumor infiltration and activity of CD8+ T cells or NK cells? ii) Will the addition of ganetespib before the IV injection of oHSV enhance in MBC the access of oHSV, expression of XCL1 and FLT3L, and the accumulation of CD103+ cDC1s? Aim 3b. Establish the therapeutic efficacy of oHSV-XCL1, oHSV-FLT3L or oHSV-XF combined with ganetespib. In lung models of MBC, we will measure treatment effects on lung weight, metastasis formation and mouse survival. We will also perform mechanistic experiments to assess if the anti-tumor response is due to the activity of cDC1, CD8+ T cells or NK cells.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Avoiding (Heart) Failure: Physiologic-Based Targeting of the RAAS to Treat Subclinical HFpEF among PWH
Effort:	3% (0.36 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Fassil Ketema | fassil.ketema@nih.gov
Performance Period:	01/15/2020 – 12/31/2024
Funding Amount:	
Project Goals:	These studies led by an early stage investigator and team of experts in HIV-associated CVD, CV imaging, HFpEF phenotyping, CV biomarker science, and CV endocrinology will provide key insight on two neurohormonal systems critical to CV health, RAAS-NP, and test whether targeted manipulation of these systems can reduce subclinical HFpEF risk in HIV.

Specific Aims:	We aim to investigate the cardiac phenotype associated with reduced NP among PWH compared to uninfected individuals utilizing advanced CV imaging techniques (cardiac MRI, cardiac TTE) and circulating myocardial biomarkers to comprehensively assess myocardial inflammation, structure, and function. This novel proposal represents a substantial departure from the typically well-studied HF patients with relatively higher NP and may uncover a large class of newly-identified inflammatory-prone or metabolically-deranged patients deserving of more clinical attention in the HF realm. We will also determine the effect of sacubitril/valsartan, a dual angiotensin II receptor antagonist and neprilysin inhibitor, vs. placebo on longitudinal changes in myocardial inflammation, structure and function among PWH in a 6-month randomized controlled trial.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Sex Differences in Major Depression: Impact of Prenatal Stress-Immune and Autonomic Dysregulation
Effort:	3.8% (0.46 CM), 7.5% (0.90 CM) in Years 4&5
Supporting Agency:	NIMH/ORWH
Grant Officer:	Jovier D Evans, Ph.D. | je180t@nih.gov
Address:	6001 Executive Boulevard, Room 7113, MSC 9637 Bethesda, MD 20892-9663
Performance Period:	02/01/2020 – 12/31/2024
Funding Amount:	
Project Goals:	This U54, a Specialized Center of Research Excellence on Sex Differences (SCORE), will conduct a set of basic science and clinical studies that are synergistic for understanding the risk for sex differences in major depression and comorbidity with autonomic dysregulation, a risk factor for CVD. We will identify stress-immune pathways, beginning in fetal development, that will lead to translation into sex-dependent therapeutics, and we will train the next generation to incorporate knowledge of sex differences into how we treat disorders of the brain and their impact on general medicine.
Specific Aims:	The SCORE Aims are specifically to: 1: Facilitate transdisciplinary, translational collaboration among basic and clinical investigators to enhance our understanding of the impact of sex on MDD and central and peripheral autonomic function; 2: Translate this knowledge into "sex-selective" therapeutics; 3: Serve as an interdisciplinary resource to train scientists, clinicians and policy makers; and 4: Disseminate findings about sex differences in depression and autonomic dysregulation to the scientific and medical communities, policy makers, and the public .
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Longitudinal neuroprotective effects of periconceptional folic acid supplements in help-seeking youth with psychiatric symptoms and healthy controls
Effort:	1% (0.12 CM), 1.7% (0.20 CM) Years 3-5
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Julia Zehr, Ph.D. | zehrj@mail.nih.gov
Performance Period:	08/01/2020 – 05/31/2025
Funding Amount:	
Project Goals:	This is a longitudinal, observational study of youth at low versus high risk for psychiatric disorders. We will determine whether exposure to folic acid supplements early in pregnancy associated with differential clinical, cognitive, and MRI outcomes.
Specific Aims:	Aim 1: To determine whether PFAS protects against dimensional psychopathology in adolescence. Aim 2: To evaluate a mechanistic model of PFAS effects on cortical

	development in adolescence. Aim 3: To determine whether PFAS buffers adverse effects of genetic load on clinical outcomes
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Alignment of cortical development trajectories with emergent dimensional psychopathology and related risk factors among early adolescents in the ABCD Study
Effort:	2.5% (0.30 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Julia Zehr, Ph.D. | zehrj@mail.nih.gov
Performance Period:	09/15/2020 – 07/31/2025
Funding Amount:	
Project Goals:	To use brain imaging, clinical, environmental, and genetic data from the ongoing U.S.-based Adolescent Brain Cognitive Development Study to identify patterns of brain maturation that predict emergence of psychiatric illness in adolescence.
Specific Aims:	AIM 1: To assign emergent dimensional symptoms to spatiotemporally specific cortical trajectories AIM 2: To evaluate and parse genomic mediation of symptom-specific thinning trajectories AIM 3: To evaluate and parse exposomic mediation of symptom-specific thinning trajectories
Project Overlap	No overlap with any currently funded or pending projects.

Title:	SWAN: Aging: The Impact of Midlife on Early Old Age
Effort:	8% (0.96 CM)
Supporting Agency:	NIH/NIA (Subaward w/ Univ. of Pittsburgh)
Grant Officer:	Chhanda Dutta, PhD,| duttac@mail.nih.gov
Performance Period:	09/30/2020 – 03/31/2024
Funding Amount:	
Project Goals:	Determine the impact of midlife health indicators and menopause transition characteristics on the preservation of cognitive, physical, sexual, and psychosocial function and risk of adverse health outcomes in early old age.
Specific Aims:	This project will build upon the resources of the Study of Women's Health Across the Nation (SWAN) to quantify the impact of ovarian aging, the MT and the midlife on successful aging. Aim 1: Determine the impact of MT characteristics and trajectories of midlife health indicators on the preservation of cognitive, physical, sexual, and psychosocial function. This includes identifying modifiable factors that promote functional resilience; i.e., the ability to maintain or regain function in later life despite adverse midlife changes in health and functioning. Aim 2: Determine the impact of MT characteristics and trajectories of midlife health indicators on risk of adverse health outcomes including falls, osteoporosis and fractures, poor cardiac function, cardiovascular events, genitourinary dysfunction, poor sleep and early mortality. This includes identifying modifiable factors that promote health resilience; i.e., the ability to avoid adverse health outcomes in later life despite adverse midlife changes in health and functioning. Aim 3: Determine if racial/ethnic disparities in later life health and functioning are attributable to midlife racial/ethnic differences in MT characteristics and trajectories of midlife health indicators. Aim 4: Expand the translation of SWAN findings to women and their health care providers
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Delineating mechanisms of skeletal fragility in older adults with Type 1 Diabetes
Effort:	5% (0.60 CM) Years 3-5
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Eunica Hayes | haynese@mail.nih.gov
Address:	6707 Democracy Blvd.

	Bethesda, MD 20892
Performance Period:	02/01/2021 – 01/31/2026
Funding Amount:	
Project Goals:	The major goals of this project are: (1) to determine in vivo bone structure, density and quality in adults with T1D, (2) to associate bone endpoints with diabetic complications, and (3) to examine bone material properties in ex vivo femoral specimens from adults with T1D
Specific Aims:	Aim 1 (in vivo): Compare 3D bone density, structure and strength of the hip and age-related changes in these outcomes in older adults with T1D to nondiabetic controls. Aim 2 (in vivo): Determine the influence of glycemic control, microvascular disease, and AGE accumulation on changes in femoral bone density, structure, and strength in older adults with T1D. Aim 3 (ex vivo): Determine the effect of long duration T1D on bone AGE content, composition and quality.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Reprogramming the tumor microenvironment to improve immunotherapy of glioblastoma by co-targeting VEGF and Ang2
Effort:	3% (0.36 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Fountain, Jane W. | fountai@ninds.nih.gov
Performance Period:	05/01/2021 – 02/28/2026
Funding Amount:	
Project Goals:	This R01 grant will test the hypothesis that the abnormal vasculature within the unique environment of brain tumors and the resulting immunosuppression cause resistance to the novel immunotherapies. Our findings will provide unprecedented insights into the mechanisms of resistance to immunotherapy in glioblastoma (GBM), and a novel strategy to overcome this resistance while addressing putative adverse effects, which will inform the design of clinical trials of glioma patients.
Specific Aims:	Hypothesis 1: aA2V improves tumor vessel function and enhances anti-tumor immunity especially with aPD1. Aim 1a: To test if aA2V+aPD1 improves CTL infiltration and distribution in GBM via vascular normalization. Aim 1b. To test if aA2V+aPD1 enhances intratumor CTL function via enhanced tumor cell recognition. Hypothesis 2: aA2V "normalizes"aPD1-aggravated abnormal tumor vasculature and microenvironment. Aim 2: To test if ADCC mediates aPD1-induced edema and if aA2V mitigates it. Hypothesis 3: To determine memory responses following aA2V+aPD1 after SoC therapy. Aim 3a: To test whether aA2V+aPD1 therapy enhances survival in mice and improves the outcome of SoC. Aim 3b: To determine memory responses following aA2V+aPD1 after SoC therapy.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Improving treatment of HER2+ breast cancer brain metastasis by targeting lipid metabolism
Effort:	3% (0.36 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Hatch, Christopher L.| ch29v@nih.gov
Performance Period:	05/01/2021 – 04/30/2026
Funding Amount:	
Project Goals:	The major goals of this project are to demonstrate that (a) de novo lipid synthesis as a novel therapeutic target for HER2+ breast cancer brain metastases and (b) targeting lipid metabolism improves the treatment outcome. Our findings will directly inform the design and interpretation of future clinical trials using agents that target lipid

	metabolism to improve treatment of patients with HER2+ breast cancer brain metastases
Specific Aims:	Aim 1: Determine the cell extrinsic mechanism(s) by which cancer cells upregulate de novo lipid synthesis to proliferate in the brain microenvironment. Aim 2: Determine whether de novo lipid synthesis is required for breast cancer proliferation in the brain. Aim 3: Develop clinically translatable strategies to target de novo lipid synthesis in BCBM.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Impact of sex differences in immune function on shared risk for cardiometabolic disorder & Alzheimer's disease
Effort:	5% (0.60 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Jean Yuan, Ph.D. | xin.yuan@nih.gov
Performance Period:	09/30/2021 – 08/31/2024
Funding Amount:	
Project Goals:	Alzheimer's disease (AD) is one of the most important public health challenges of our time, with women disproportionately impacted. We will uniquely examine whether sex differences in immune pathophysiology, in part, underlies the sex-dependent impact of cardiometabolic dysfunction on AD risk in midlife. Understanding this shared etiology could provide insights into development of sex-dependent early interventions to prevent AD or attenuate disease burden.
Specific Aims:	We will test the hypothesis that sex differences in immune pathophysiology, in part, underlies the sex-dependent impact of cardiometabolic dysfunction on AD risk in midlife. We propose to recruit 240 people, ages 50- 75, equally divided by sex, that are "high and low risk" (HR & LR) for AD, defined as those with genetic risk and CMD vs. those without. Currently, we are recruiting 100 people (ages 50-70), whom we will re-recruit in the current study at ages 55-75. We will develop a general AD polygenic risk score (PRS) and a sex-stratified PRS to select HR and LR individuals along with presence or absence of CMD. We are conducting extensive in-clinic assessments to characterize structural and functional MRI (s/fMRI), cognitive function, hormone and immune profiling, cardiophysiology, neurovascular structure/function, genotype, RNA transcription and cell metabolism of monocyte cells, Aβ PET imaging, and AD blood-based biomarkers. Here, we propose to recruit an additional 140 HR and LR subjects, equally divided by sex, in order to obtain adequate statistical power to test for the shared sex-dependent impact of immune dysregulation underlying the association between CMD and AD- related pathology. Further, we will follow the current 100 subjects to evaluate the longitudinal impact of immune dysregulation on 5-year change in AD-related pathology by sex. Further, we predict immune dysregulation will mediate (i.e., in part, explain) the relationship between HR vs. LR and AD-related pathology, and that this mediation will be stronger (larger effect sizes) in postmenopausal women versus men. Finally, in exploratory analyses, we predict that the presence of CMD will exacerbate the effects of genetic risk alone on AD-related pathology, with women experiencing worse outcomes than men.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	PET Imaging of Thrombus
Effort:	8% (0.96 CM)
Supporting Agency:	NIH-NHLBI National Heart, Lung, and Blood Institute
Grant Officer:	Andrei Kindzelski, M.D., Ph.D. | kindzelskial@nhlbi.nih.gov
Performance Period:	02/10/2022 – 01/31/2026

Funding Amount:	
Project Goals:	To detect thrombus in the heart, veins, and arteries in the context of stroke: to apply PET-CT imaging with a new molecular probe that can detect blood clots in the heart, arteries, or veins, and to determine if it can effectively identify the source of ischemic stroke in patients.
Specific Aims:	Aim 1 of the proposal we will validate the ability of PET-CT of 64Cu-FBP8 to detect thrombus in hospitalized patients. In Aim 2 we will use the agent in subjects with acute stroke of known origin, and in Aim 3 we will study subjects with cryptogenic stroke. Execution of the study will provide important insights and lay the foundation for the use of 64Cu-FBP8 in the prevention and management of stroke.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Reprogramming the Tumor Microenvironment to Improve Immunotherapy of Glioblastoma
Effort:	2% (0.24 CM)
Supporting Agency:	NIH-NCI National Cancer Institute
Grant Officer:	Lillian S. Kuo, Ph.D. | lillian.kuo@nih.gov
Performance Period:	04/01/2022 – 03/31/2027
Funding Amount:	
Project Goals:	The goal of the project is to provide insights into the mechanisms of response and resistance to combined Wnt signaling inhibition and αPD1, and utilize losartan, an angiotensin receptor blocker, to alleviate edema and resistance to this combination and thereby improve outcome of αPD1 in GBM
Specific Aims:	Our overarching hypothesis is that Wnt signaling reprograms the GBM tumor microenvironment from immune suppressive to immune stimulatory, thus potentiating αPD1 therapy, and adding losartan further enhances the outcome by overcoming treatment resistance mechanisms, and reducing edema. We will test this hypothesis by examining the function of (a) antigen cross-presenting DCs and (b) decreased gMDSCs in mediating the response to WNT974 and αPD1 (Aim 1). We will also test the hypothesis that resistance to WNT974+αPD1 is caused by (a) increased mMDSCs and (b) lack of T cell infiltration and function (Aim 2). In Aim 3, we will test the hypothesis that the combination of losartan with Wnt-inhibition and αPD1 will (a) reduce mMDSCs infiltration and increase T cell infiltration and effector function and (b) alleviate edema and provide durable responses in GBMs that are refractory to WNT974+αPD1. If successful, our results will inform the design of future GBM clinical trials to improve the outcome of ICBs using agents currently in clinical trials for non-CNS tumors (WNT974: e.g., NCT01351103; and losartan: NCT03563248).
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Stable and dynamic neurobehavioral phenotypes of social isolation and loneliness in serious mental illness
Effort:	10% (1.20 CM) **Year 5**
Supporting Agency:	NIH-NIMH National Institute of Mental Health
Grant Officer:	David I. Leitman, Ph.D. | david.leitman@nih.gov
Performance Period:	03/15/2022 – 01/31/2027
Funding Amount:	
Project Goals:	We plan to demonstrate that fundamental neural and behavioral processes drive momentary variation in the experience of social isolation and loneliness, impacting quality of life in SMI.
Specific Aims:	Aim 1 of the proposed project, we will show that the higher levels of social isolation and loneliness in SMI are linked to shared and distinct neural responses to social

	stimuli, with deficient responses of social perception-related circuitry (medial temporal lobe regions) linked to social isolation, and deficient responses of reward-related circuitry (basal ganglia regions) linked to loneliness. In Aim 2, we will measure transient changes in social isolation and loneliness with smartphone assessments using a longitudinal "burst" design. Lastly, in Aim 3, we will determine how the quantitative markers of social isolation and loneliness identified in Aims 1 and 2 predict indices of cardiometabolic health, measuring the stability of these associations over time.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Using Wearable Technology to Assess Recovery and Detect Post-Operative Complications Following Cardiothoracic Surgery
Effort:	5% (0.60 CM)
Supporting Agency:	NIH-NHLBI National Heart, Lung, and Blood Institute
Grant Officer:	N/A |PI: Yang, Chi-fu J| 1R01HL159170-01A1
Performance Period:	07/01/2022 – 06/30/2027
Funding Amount:	
Project Goals:	The overarching goal of this research is to use machine learning analysis of data—collected by wearable technology—of cardiothoracic surgical patients to predict and detect complications early
Specific Aims:	TBD
Project Overlap	No overlap with any currently funded or pending projects.

PENDING	
Title:	Manipulating energy availability to expose individual and sex-based predictors of multi-stressor effects on cognitive function, performance, and health
Effort:	5% (0.60 CM)
Supporting Agency:	DoD/ Pennsylvania State University
Grant Officer:	N/A | Nancy Williams, Sc.D. (Submitting PI) and Franziska Plessow, Ph.D. (Co-PI)
Performance Period:	07/01/2023 – 06/30/2027
Funding Amount:	
Project Goals:	This project will investigate nutrition optimization during prolonged stress exposure and as part of the recovery from sustained stress exposure + energy restriction as a novel intervention to counteract stress-induced decrements in cognitive function, physical performance, and health. An additional goal is to identify critical determinants of (1) individual susceptibility to periods of severe energy restriction and need for sustained energy availability and (2) individual recovery rate and magnitude after cessation of prolonged stress + energy restriction.
Specific Aims:	1) Determine the beneficial effects of meeting full energy needs (vs. energy restriction) on cognitive function, physical performance, and biological indicators of health during prolonged multi-stress exposure and identify critical determinants of individual susceptibility to periods of severe energy restriction and the need for sustained meeting of energy needs. (2) Determine the effects of refeeding level (100 vs. 75 vs. 50%) on cognitive function, physical performance, and biological indicators of health after cessation of prolonged multi-stress exposure with severe energy restriction and define critical determinants of recovery rate and magnitude.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Comparative Effectiveness of Combined Anabolic Therapy in Established Osteoporosis
Effort:	7.5% (0.90 CM)

Supporting Agency:	Patient Centered Outcomes Research Institute
Grant Officer:	N/A, PI: Leder, Benjamin Z
Performance Period:	11/01/2022 – 10/31/2027
Funding Amount:	
Project Goals:	The major goal is to assess the comparative effectiveness of combined anabolic therapy in postmenopausal osteoporosis.
Specific Aims:	TBD
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Exercise alleviates immunosuppression and sensitizes metastatic breast cancers to immunotherapy
Effort:	2% (0.24 CM)
Supporting Agency:	Department of Defense-Congressionally Directed Medical Research Programs
Grant Officer:	N/A | DoD BCRP BTA Level, BC200978 (PI, Fukumura)
Performance Period:	12/01/2022-12/31/2024
Funding Amount:	
Project Goals:	This project will bring new insights on how optimized exercise training can improve breast cancer tumor microenvironment and immunotherapy as a non-pharmacological, adjuvant intervention. This is an uncharted area of breast cancer research that has a potential for rapid translation. Dissection of mechanisms will also help future expansion of the proposed treatment approach.
Specific Aims:	Hypothesis 1: Exercise training promotes anti-tumor immunity and reduces metastatic BC progression. Aim 1a. Determine the effect of ExTr on metastatic BC progression. Aim 1b. Determine the effect of ExTr on immune microenvironment. Aim 1c. Verify the association of physical activity and adiposity with human BC immune profile. Hypothesis 2: Exercise training potentiates immunotherapy for metastatic breast cancer. Aim 2a. Determine the effect of ExTr on immune checkpoint blockade therapy in metastatic BC.Aim 2b. Determine the effect of ExTr on immune microenvironment under ICB treatment.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Delineating mechanisms of skeletal fragility in older adults with Type 1 Diabetes
Effort:	5% (0.60 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Saul Malozowski, M.D., Ph.D., M.B.A. | saul.malozowski@nih.gov
Performance Period:	09/01/2022 – 01/31/2026
Funding Amount:	
Project Goals:	This proposal will define the skeletal mechanisms underlying this increased fracture risk with comprehensive assessments of hip bone structure, quality, and strength among older adults with T1D. Further identification of the glycemic factors that contribute to skeletal fragility will allow clinicians to develop rational approaches to prevent fractures in patients with T1D.
Specific Aims:	Aim 1 will evaluate prospective changes in bone density, structure, strength, and cortical bone quality in postmenopausal women and men age 50 years with T1D as compared to nondiabetic controls. Aim 2 will investigate the potential contributions of diabetic complications, such as glycemic profiling (using continuous glucose monitoring), advanced glycation endproducts (AGEs) and microvascular disease, to skeletal endpoints and age-related bone loss. Finally, Aim 3 will utilize ex vivo

	femoral specimens to directly assess femoral bone composition and biomechanical strength among adults with longstanding T1D.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Penicillin Allergy Evaluation to Reduce Surgical Site Infections
Effort:	0% (0.0 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	N/A | PI: Blumenthal, Kimberly G
Address:	
Performance Period:	09/01/2022 – 08/31/2027
Funding Amount:	
Project Goals:	This project includes patient cohort and simulation model studies to achieve the overall goal of increasing first-line perioperative antibiotic prophylaxis as a strategy to reduce surgical site infections.
Specific Aims:	TBD
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Targeting lymph node metastases to prevent cancer progression
Effort:	3% (0.36 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Elizabeth Snyderwine, Ph.D | snyderwe@mail.nih.gov
Performance Period:	09/01/2022 – 08/31/2027
Funding Amount:	
Project Goals:	Successful completion of this project will help evaluate this risk and give the basis for new therapeutic regimens to eradicate disease from lymph nodes and restore anti-tumor immune responses.
Specific Aims:	We will test the hypotheses that lymph node metastases disseminate to distant sites (Aim 1) and inhibit the ability of the immune system to develop and maintain anti-tumor immunity (Aim 2). We will accomplish our goals using innovative animal models that allow state-of-the-art intravital microscopy of spontaneous lymph node metastasis. In Aim 1, we will determine whether cancer cells utilize the fibroblastic reticular cell-lined conduit system in lymph nodes to home to blood vessels and spread to distant sites. We will attempt to block this process. In Aim 2, we will determine whether metastatic lymph nodes retain the ability to initiate immune responses to new antigens.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	A miRNA biomarker panel for clinical prognostic and novel therapeutic stratification in osteosarcoma
Effort:	5% (0.60 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	N/A| PI: Spentzos, Dimitrios
Performance Period:	09/01/2022 – 08/31/2027
Funding Amount:	
Project Goals:	The goals of this project are to develop and validate a miRNA assay for risk based stratification of patients with osteosarcoma and study its relevance for selecting appropriate tailored therapies.
Specific Aims:	TBD
Project Overlap	No overlap with any currently funded or pending projects.

Title:	In Silco Modeling of Heterogeneity and Host Resilience in the Acute Respiratory Distress Syndrome

Effort:	5% (0.60 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	N/A | PI: Hardin, Charles C
Performance Period:	09/01/2022 – 08/31/2026
Funding Amount:	
Project Goals:	In Silico Modeling of Heterogeneity and Host Resilience in the Acute Respiratory Distress Syndrome seeks to gain new insight into the mechanistic basis of heterogenous immune responses in ARDS using mathematical modeling and clinical biomarker profiling.
Specific Aims:	TBD
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Targeting Activin Type II Receptor and HIF-1α Pathways in Skeletal Muscle Improves Survival and Prevents Muscle Wasting in Sepsis
Effort:	5% (0.60 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	N/A| PI: Kaneki, Masao
Performance Period:	09/01/2022 – 08/31/2027
Funding Amount:	
Project Goals:	To test the hypothesis that crosstalk between activin type II receptor and HIF-1α pathways in skeletal muscle plays an important role in sepsis development and immune dysfunction as well as muscle wasting and the Warburg effect in sepsis
Specific Aims:	TBD
Project Overlap	No overlap with any currently funded or pending projects.

COMPLETED	
Title:	Reprogramming PDAC Tumor Microenvironment to Improve Immunotherapy
Effort:	4% (0.48 CM)
Supporting Agency:	NIH-NCI National Cancer Institute
Grant Officer:	Peter Ujhazy, M.D., Ph.D. | ujhazyp@mail.nih.gov
Address:	9609 Medical Center Drive, Room 3W106 MSC 9726 Bethesda, MD 20892
Performance Period:	09/01/2020 – 08/31/2022
Funding Amount:	
Project Goals:	The goal of this U01 is to provide novel mechanistic insights into reprogramming the immunosuppressive tumor microenvironment of PDAC into an immunostimulatory one. Our approach to achieve this will be to use widely prescribed and inexpensive inhibitors of the angiotensin II signaling.
Specific Aims:	1) Uncover how losartan combined with cytotoxic agents alters tumor microenvironmental components (ECM, blood vessels, hypoxia) and immune cells, in locally advanced PDAC patients; 2) Dissect the causal role of drug- induced adaptive and innate immune cells in the anti-tumor response in orthotopic (implanted and genetically engineered) PDAC models in mice; and 3) Evaluate whether combining ASI-induced tumor microenvironment reprogramming along with cytotoxic therapies enhances the efficacy of immune checkpoint blockers
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Evaluation of small-fiber polyneuropathy in youth
Effort:	2% (0.24 CM) in Year 2
Supporting Agency:	NIH-National Institutes of Health

Grant Officer:	Durga Mohapatra, Ph.D. | dp.mohapatra@nih.gov
Performance Period:	09/15/2020 – 05/31/2025
Funding Amount:	
Project Goals:	(1) To adapt validated metrics for small-fiber neuropathy (SFN) for external use, (2) To correlate whole genome sequences with metrics to identify risk-modifying variants for SFN, (3) Collaboration with FDA to optimize skin-biopsies for SFN diagnosis in adults and children
Specific Aims:	Aim 1 proposes to use Registry participants plus new patients and healthy volunteers to adapt and validate the SSS and MAGNET for general medical use by any doctor and for use in children. Aim 2 will collaborate with the Food and Drug Administration's Biomarker Qualification Program to obtain an FDA ruling on lab requirements to improve the quality and accuracy of skin biopsy testing. Aim 3 begins whole-genome study of causes and risks for SFN. It recruits Registry patients with CONCEPPT-defined SFN and adds more via the lab's NeuropathyCommons website and its global collaborators.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Biomechanical mechanisms underlying skeletal fragility in older adults with Type 1 diabetes
Effort:	2% (0.24 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Saul Malozowski, M.D., Ph.D., M.B.A. | saul.malozowski@nih.gov
Performance Period:	09/12/2019 – 08/31/2022
Funding Amount:	
Project Goals:	To investigate biomechanical mechanisms of skeletal fragility in postmenopausal women and men age > or = to 50 years with T1D. We will compare tissue level bone biomechanical properties and bone composition using ex vivo femoral specimens from adults with longstanding T1D (50+ year duration) and matched nondiabetic controls, as well as from adults with and without T1D who are undergoing surgical repair of hip fracture
Specific Aims:	We will compare tissue level bone biomechanical properties and bone composition using ex vivo femoral specimens from adults with longstanding T1D (50+ year duration) and matched nondiabetic controls, as well as from adults with and without T1D who are undergoing surgical repair of hip fracture. Using state-of-the-art methods, successful completion of our proposed aims will provide novel insights about the alterations in bone structure and quality that contribute to skeletal fragility in older adults with T1D, in whom fracture risk is highest. In addition, our findings will clarify the impact of diabetic history and accumulation of advanced glycation end-products on skeletal fragility in T1D. Addressing these critical gaps in knowledge will ultimately allow clinicians to develop rational approaches to prevent fractures in patients with T1D.
Project Overlap	No overlap with any currently funded or pending projects.

Title:	Oxytocin as a Neuroendocrine Therapy for Obesity in Youth
Effort:	3% (0.36 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Osganian, Voula | voula.osganian@nih.gov
Performance Period:	09/17/2020-06/30/2025
Funding Amount:	

Project Goals:	This randomized placebo-controlled investigation will study the effects and underlying mechanisms of twelve weeks of intranasal oxytocin on weight and metabolic risk markers in adolescents with obesity 12-18 years old. This study will be the first to systematically investigate the efficacy and safety of OXT as a novel therapeutic agent to induce weight loss and improve indicators of cardiometabolic risk in youth with obesity.
Specific Aims:	AIM 1: Effects on body weight. Hypothesis 1: OXT administration will result in (A) reduced BMI-SDS, consequent to (B) decreased caloric intake in the fasting state (assessed using a breakfast test meal) and in the absence of hunger (assessed using the Cookie Taste Test), and (C) increased resting energy expenditure and diet induced thermogenesis (measured by indirect calorimetry). Both (B) and (C) will be mediated in part by reduced measures of hypothalamic inflammation (MRI). AIM 2: Effects on metabolic risk. Hypothesis 2: OXT administration will result in (A) reduced visceral and intrahepatic fat with relative preservation of lean/muscle mass (measured by MRI/1H-MRS and whole body DXA) associated with (B) reduced systemic inflammation (IL-6, TNF-α, hsCRP), and (C) improved lipid profile (serum lipids, lipoproteins).
Grant Number:	1R01DK124223-02

Title:	Evaluation of small-fiber polyneuopathy as a cause of chronic widespread pain in youth
Effort:	2% (0.24 CM)
Supporting Agency:	NIH- National Institutes of Health
Grant Officer:	Durga Prasanna Mohapatra, dp.mohapatra@nih.gov
Performance Period:	09/01/2020-07/31/2025
Funding Amount:	
Project Goals:	The major goals of this project are:(1) To adapt validated metrics for small-fiber neuropathy (SFN) for external use, (2) To correlate whole genome sequences with metrics to identify risk-modifying variants for SFN, (3) Collaboration with FDA to optimize skin-biopsies for SFN diagnosis in adults and children
Specific Aims:	Aim 1 proposes to identify the best objective tests for early onset SFPN in young patients with CWP and in positive and negative controls recruited from the community. We will focus on the recommended tests, autonomic function testing and skin biopsy, but will also investigate less invasive or cheaper tests such as in vivo corneal confocal microscopy, the Minor starch-iodine sweat test, a new questionnaire, and Sudoscan, a new sweat-measuring device. The goal is to develop the best tests that can be applied in diverse circumstances, including low-resource settings. Aim 2 will more rigorously define the medical causes of SFPN using laboratory blood tests and dermatopathologic study of skin biopsies in community-based cohorts. We will also see if these tests support our prior finding that half of people with early-onset uCWP have evidence of SFPN. Aim 3 will apply the questionnaire and best tests developed above at defined intervals to prospectively track SFPN patients with various causes being treated in different ways, and will also follow untreated SFPN patients to gather the first natural history data about early-onset SFPN. This should provide the information needed to plan for future clinical trials of promising treatments.
Grant Number:	5R01NS093653-07

Title:	Prospectively Randomized, Placebo-controlled Phase III Study to Determine the Effect of Denosumab on Breast Cancer Prevention in BRCA1 Mutation Carriers
Effort:	4% (0.48 CM)

Supporting Agency:	U.S. Army Medical Research Acquisition Activity subcontract Dana Farber Cancer Institute
Grant Officer:	N/A (PI: Tsai Joy)
Performance Period:	09/15/2019-09/14/2023
Funding Amount:	
Project Goals:	The major goals of this project are to investigate whether denosumab versus placebo can prevent breast cancer in BRCA1 mutation carriers (3,000 enrolled internationally) over 4 years with a 6-year follow-up period. Our substudy consists of HR-pQCT imaging on a subset of subjects (150 total) over 4 years to examine the effect of denosumab versus placebo on bone microarchitecture.
Specific Aims:	To characterize changes in bone density, microarchitecture, microstructure, and bone strength in premenopausal and early postmenopausal women receiving denosumab 120 mg.
Grant Number:	W81XWH1910780

Title:	Effect of Mineralocorticoid Receptor Blockade on Coronary Vasculature and Myocardial Structure in HIV
Effort:	3% (0.36 CM)
Supporting Agency:	NIH-National Institutes of Health
Grant Officer:	Dr Andrew Alan Bremer | andrew.bremer@nih.gov
Address:	6710B Rockledge Dr. | RM 2444 Bethesda, MD 20817
Performance Period:	09/01/2016-08/31/2021
Funding Amount:	
Project Goals:	This study is being conducted to test the efficacy of a selective mineralocorticoid blocker, eplerenone, on improving coronary flow, myocardial fibrosis, and atherosclerotic plaque in HIV patients with excess visceral adiposity.
Specific Aims:	**1)** quantify baseline risk of Coronary flow reserve, Myocardial Inflammation and fibrosis, and Coronary plaque and assess longitudinal changes in these indices with MR Blockade. Information regarding the natural history of these subtypes of CVD is limited among the HIV Population, and thus, these studies will also inform us as to the progression of disease pathology in the Coronary Vasculature and myocardium in HIV. **2)** evaluate biomarkers of vascular Dysfunction, Inflammation, and fibrosis to understand the effects of MR blockade on these indices in relation to radiological assessment of cardiac Structure and function
Grant Number:	5R01DK049302-24

Title:	SPORE: Targeted Therapies for Glioma (Core B)
Effort:	2.5% (0.30 CM)
Supporting Agency:	NIH-NCI
Grant Officer:	Julia Arnold, jarnold@mail.nih.gov
Performance Period:	07/01/2013-06/30/2019
Funding Amount:	
Project Goals:	The Core provides shared resources of statistical and related expertise for long-term collaboration and short-term consultation with SPORE investigators in the research and developmental projects.
Specific Aims:	1) target the tumor vascular system and will test the hypothesis that responses to VEGF pathway inhibitors can be augmented by concurrent or sequential suppression of the angiopoietin-2 signal transduction pathway. 2) target the PI3K signaling axis - a signaling pathway that is activated in ~50% of glioblastomas. 3) target the IDH pathway and test the hypothesis that non-invasive measurement of 2-HG levels can

	serve as a surrogate for IDH mutant enzyme activity, and that targeting of IDH mutation and 2-HG can afford a breakthrough treatment for malignant Glioma patients. 4) attack the Olig2 transcription factor and test the hypothesis that suppression of Olig2 will enhance radiation sensitivity of the major population of glioblastomas (~75%) that retain a structurally intact p53 gene
Grant Number:	4P50CA165932-05

Title:	Metabolomic Profiling in the Prediction of Gestational Diabetes Mellitus
Supporting Agency:	NIH/NIDDK
Grant Officer:	Kevin McBryde, mcbrydekd@nidcr.nih.gov
Performance Period:	09/01/2012-07/31/2015
Funding Amount:	
Project Goals:	The purpose of this study is to employ an emerging technology, metabolomic profiling, in existing study cohorts to further characterize women at increased risk for developing GDM and T2DM.
Specific Aims:	**1)** will examine a cohort of women followed during pregnancy for the development of GDM. **2-4)** will examine the cohort of women within the Diabetes Prevention Program (DPP) with a History of GDM for the development of T2DM while examining the effects of study Intervention and race on the outcome.
Grant Number:	5R03DK096152-03

Title:	Fat Mediated Modulation of Reproductive and Endocrine Function in Young Athletes
Supporting Agency:	NIH/NICHD/NIDDK
Grant Officer:	Karen Winer, winek@mail.nih.gov
Performance Period:	09/10/2009-06/30/2014
Funding Amount:	
Project Goals:	This study will determine the predictors of hypogonadotropic hypogonadism in adolescent and young adult female athletes and the response of bone density and bone structural parameters to physiological estrogen replacement.
Specific Aims:	Determine a better understanding of the pathophysiology of Reproductive Dysfunction that is critical to develop therapeutic strategies that will normalize the Reproductive axis and bone accrual
Grant Number:	5R01HD060827-05

Title:	Course and predictors of depressive relapse during IVF
Supporting Agency:	NIMH
Grant Officer:	Peter R Muehrer, pmuehrer@mail.nih.gov
Performance Period:	08/01/2012-07/31/2014
Funding Amount:	
Project Goals:	This is a longitudinal naturalistic study of women with histories of major depressive episodes undergoing IVF, to assess course of illness and risk factors for depressive relapse. Relationships between depression and stress will be examined, with assessments of biomarkers of stress.
Specific Aims:	**1)** to delineate the clinical predictors of depressive relapse in women with histories of depression across a period of six months while they are undergoing IVF including: antidepressant continuation or discontinuation, previous Course of depressive illness, duration of attempt to conceive, and partner support, **2)** to describe the trajectory of depressive symptoms over the Course of IVF cycles, and **3)** to explore biological markers of the stress response, including those pertaining to HPA axis dysregulation and inflammation associated with depressive relapse and stress during IVF treatment.
Grant Number:	5R21MH096006

Title:	Physiological, Metabolic and Cardiovascular Effects of GHRH in HIV infected patients
Supporting Agency:	NIH
Grant Officer:	Saul Malozowski, malozowskis@extra.niddk.nih.gov
Performance Period:	08/01/2008-07/31/2013
Funding Amount:	
Project Goals:	The major goals of this project are to determine the significance and durability of the effects of GHRH on endogenous GH pulse dynamics, long term cardiovascular and body composition endpoints among HIV-infected patients with central fat accumulation
Specific Aims:	1) study and determine how the secretion of Growth Hormone is regulated in HIV patients. 2) investigate whether the use of a secretory factor that induces the body to makes its own GH, Growth Hormone releasing hormone, will improve Cardiovascular risk endpoints, including abdominal fat, Insulin, and carotid IMT.
Grant Number:	5R01DK063639-08

Title:	MRI Studies of folate –related genes, diet and development: Promise for psychosis
Effort:	3% (0.36 CM)
Supporting Agency:	NIH/NIMH
Grant Officer:	Stacia Friedman, friedmans@mail.nih.gov
Performance Period:	08/01/2013 - 04/30/2018
Funding Amount:	
Project Goals:	This study will examine neural effects of genetic variation throughout the folate metabolic pathway, in concert with dietary folate measures, in healthy adults and adolescents.
Specific Aims:	1) we will leverage a large, existing collection of MRI data and DNA (>3,300 subjects) to conduct novel, polygene-score based analyses of genetic variation throughout the folate metabolic pathway. 2) we will recruit individuals across a range of polygene scores to determine how folate intake influences high-resolution structural and functional MRI indices. Using the same MRI measures, 3) will leverage a recent large-scale public health intervention to examine effects of in utero folate exposure in two age-matched cohorts of healthy adolescents: one group will have gestated before mandatory folate fortification of grain products was implemented in 1998, and the other will have gestated after this intervention. This multi-tiered approach will allow us to comprehensively evaluate genomic (Aim 1), environmental (Aim 2), and neurodevelopmental (Aim 3) aspects of folate effects on the brain, both separately and in combination with each other.
Grant Number:	5R01MH101425-05

Title:	Immune Checkpoints and HPV-associated Head and Neck Cancers
Effort:	5% (0.60 CM)
Supporting Agency:	NIH/NIDCR
Grant Officer:	Chiayeng Wang, chiayeng.wang@nih.gov
Address:	
Performance Period:	07/01/2015-06/30/2018
Funding Amount:	
Project Goals:	The major goal of this project is to identify other immune checkpoint pathways, in addition to the PD-1:PD-L1 pathway, which can be targeted in HPV-associated head and neck cancers.
Specific Aims:	1), quantify and geographically localize the expression of these proteins in a separate cohort of HPV-HNSCC patients using quantitative PCR and multiplex biomarker

	imaging and quantitative analysis. Subsequently, we will assess the efficacy of blocking in vivo either the IL10 and/or IDO1 pathway alone or in combination with anti-PD1 in a murine HPV tumor model. 2) correlate expression of these markers with clinical response to anti-PD-1 monotherapy in Head and Neck cancer patients.
Grant Number:	5R01DE025340-02

Title:	Skeletal fragility and fracture risk after bariatric surgery
Effort:	3% (0.36 CM)
Supporting Agency:	Doris Duke Clinical Scientist Development Award
Grant Officer:	Linda Diamond, ldiamond@ddcf.org|
Address:	Doris Duke Charitable Foundation | 650 5th Ave, New York, NY 10019
Performance Period:	07/01/2016–06/30/2019
Funding Amount:	
Project Goals:	Goals are to evaluate long-term (≥10 years) risks of bariatric surgery on skeletal fragility and fracture risk

Title:	Bone Metabolism in Adolescents Undergoing Bariatric Surgery
Effort:	3**% (**0.36 CM)
Supporting Agency:	NIH
Grant Officer:	Saul Malozowski, malozowskis@extra.niddk.nih.gov
Performance Period:	08/06/2015-07/31/2020
Funding Amount:	
Project Goals:	The proposal will examine the impact of RYGB and VSG on bone density, structure and strength over a two-year period in morbidly obese adolescents undergoing surgery compared to non-surgical obese adolescents.
Specific Aims:	**1)** comprehensively evaluate skeletal health over 2 years in morbidly obese Adolescents Undergoing RYGB and VSG compared with matched non-surgical obese controls **2)** investigate mechanisms that contribute to deleterious changes in Bone Metabolism following Bariatric Surgery
Grant Number:	5R01DK103946-05

Title:	Interdisciplinary Study of Marrow Adiposity, Mineral Metabolism and Energy Balance
Effort:	5% (0.60 CM)
Supporting Agency:	NIH/NIDDK
Grant Officer:	Carol Haft, carol_haft@nih.gov
Performance Period:	09/01/2015-08/31/2020
Funding Amount:	
Project Goals:	Marrow adipocytes have been identified as a component of the bone marrow micro-environment; their function, relevance to mineral metabolism and relationship to energy homeostasis has only recently been examined. We will use in vivo and in vitro systems to develop experimental paradigms for investigating this topic.
Specific Aims:	**1)** To determine how nutrient changes affect skeletal remodeling and MAT in rodents and humans. This will be accomplished through 3 sub aims: 1st, we will Study the skeletal effects of a HFD in four mouse models with different Marrow adiponectin levels; 2nd, we will examine how high fat feeding and fasting affects skeletal remodeling and MAT in humans; 3rd, we will investigate mechanisms for regulating lipid saturation within MAT depots, and whether secretion of palmitate and other saturated lipids from regulated MAT is detrimental to bone; in addition, we will develop animal models to specifically and inducibly modulate genes within MAT. **2)** To define the adipocyte progenitor in mouse and human MAT. This will be achieved

	by studies in mice and man using double reporter models to delete specific genes within the Marrow, and human bone Marrow aspirates to definitively identify the Marrow adipocyte progenitor (MAP). In summary, in this proposal we will use an integrated approach and team science for these two aims to define the functional significance and origin of MAT.
Grant Number:	5R24DK092759-09

Title:	Consolidating skeletal benefits after short-term combination osteoporosis therapy: The DATA-EX study
Effort:	1.5% (0.18 CM)
Supporting Agency:	NIH/NIAMS
Grant Officer:	D. Lee Alekel, lee.alekel@nih.gov
Performance Period:	05/01/2016-04/30/2020
Funding Amount:	
Project Goals:	Extension of a proof-of-principle clinical trial evaluating the efficacy of short-term therapy with a novel combination of osteoporosis medications followed by a single dose of a long-acting bisphosphonate.
Specific Aims:	**1)** evaluate a rational and cost-effective approach to this consolidation by testing the hypotheses that in postmenopausal women with osteoporosis, the large increases in bone density and improvements in bone quality achieved with combined denosumab/teriparatide therapy will be maintained and extended by a single administration of an intravenous bisphosphonate
Grant Number:	5R21AR069871-03

Title:	SWAN: The Study of Women's Health Across the Nation V
Effort:	5% (0.60 CM)
Supporting Agency:	NIH/NIA
Grant Officer:	Winifred Rossi, rossiw@nia.nih.gov
Performance Period:	08/15/2019-03/31/2020
Funding Amount:	
Project Goals:	SWAN is a multicenter, longitudinal cohort study of women belonging to multiple racial and ethnic groups as they traverse the menopause. Topics to be studied include bone loss, cardiovascular risk factors, psychological changes, symptoms, hormonal profiles, bleeding patterns, sexuality, health care utilization, non-Western health practices, diet, exercise, and body composition.
Specific Aims:	1) complete the characterization of the natural history of reproductive aging through the late PM; 2), evaluate the impact of reproductive aging through the late PM on health outcomes clinically relevant to women in their 60s and 70s, including: cognitive and physical function, psychological well-being, sleep, bone and cardiometabolic health, urogenital symptoms, sexual function and vaginal health. 3) identify potential underlying mechanisms linking reproductive aging and health by assessing the relation of inflammation, hemostasis and adipokines to the occurrence and progression of biological, functional and clinical outcomes and delineating the interrelationships of body size and composition, race/ethnicity and socioeconomic status with these outcomes.
Grant Number:	3U01AGO12531-25S1

I, PI or other senior/key personnel, certify that the current and pending support provided herein is current, accurate, and complete. I agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award. I have been made aware of the requirements under Section 223(a)(1) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021. I am aware that false, fictitious, or fraudulent statements or claims may result in criminal, civil, or administrative penalties.

Signature: Hang Lee Digitally signed by Hang Lee Date: 2022.09.21 17:36:44 -04'00'

Date: _____