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## **INTERNAL**

## ***2022 - 2023***

**Elucidating the Roles of Ubiquitination in Homologous Recombination**
[George Burslem, PhD](https://hosting.med.upenn.edu/epigenetics/faculty-member/george-burslem-ph-d/), is the Principal Investigator on this study intended to explore the loss of ubiquitination signals required for efficient repair of double strand DNA breaks via homologous recombination. Loss of DNA repair associated with BRCA1 variants results in a higher incidence of cancer. Ubiquitin signaling has been challenging to observe, due its complexity and the lack of appropriate tools available. This study will develop new technology—a chemical biological methodology—to explore the roles of ubiquitin in DNA damage response, to better understand what is necessary for homologous repair.

**PARP1-Targeted [18F]FTT PET/CT as an Imaging Biomarker to Select for PARPi Therapy in Patients with Metastatic Castrate-Resistant Prostate Cancer**
Principal Investigator [Neil Taunk, MD, MSCTS](https://www.pennmedicine.org/providers/profile/neil-taunk), leads this study examining the use of Poly (ADP-ribose) polymerase (PARP) inhibitor drugs (PARPi) as a therapeutic treatment for metastatic castrate-resistant prostate cancer in patients with mutations in DNA-damage response. While this represents nearly 20% of metastatic castrate-resistant prostate cancer patients, PARPi response rates are variable and it is difficult to determine who would best benefit from this therapy. Building on successful work with [18F]FTT, a PARP imaging biomarker, in breast and ovarian cancer, this study will use [18F]FTT in a larger, randomized study to predict who may optimally respond to PARPi therapy.

## ***2021 – 2023***

**Leveraging the Electronic Health Record to Promote Guideline-Recommended Cancer Risk Management in BRCA1/2 Carriers**
This early career award for Principal Investigator [Kelsey Lau-Min, MD](https://ldi.upenn.edu/expert/kelsey-lau-min-md), supports a study intended to develop strategies to standardize the uptake of guideline-recommended cancer risk management in BRCA1/2 carriers—a critical need for patient care. Clinical decision support (CDS) systems embedded in the electronic health record (EHR) have emerged as effective tools in standardizing health care processes. However, these are ineffective unless they are seamlessly integrated into routine clinical practice. The study aims to identify barriers, facilitators, and supports needed to leverage the EHR to promote guideline-recommended cancer risk management in BRCA1/2 carriers, to ultimately develop an innovative EHR-based tool that will have an immediate and direct impact on patient care.

**The Role of Pattern Recognition Receptor-Driven Inflammation in BRCA-Deficient HGSOC**
[Timothy Lippert, PhD](https://www.med.upenn.edu/greenberglab/team.html), is the lead investigator on this early career award that explores the treatment of high-grade serous ovarian cancer (HGSOC), a tumor type that accounts for 50% of all ovarian cancer-related deaths. This is due to the late diagnosis in most cases, when the cancer is already metastatic and tumors develop resistance to therapy easily. This is particularly found in cases of BRCA-related HGSOC, where tumors are not inflamed and have no immune cells. This study aims to explore how immune pattern-recognition receptors (PRRs) could trigger inflammation and recruitment of immune cells, rending the tumor susceptible to immune checkpoint inhibitors, making treatment with combination therapy effective.

**Risk Stratification Among Known BRCA1/2 Mutation Carriers Using Polygenic Risk Scores and Imaging Biomarkers**
Principal Investigators [Anne Marie McCarthy, ScM, PhD](https://www.med.upenn.edu/apps/faculty/index.php/g275/p3348), and [Despina Kontos, PhD](https://www.med.upenn.edu/apps/faculty/index.php/g5455356/p8123294), lead this study funded to better estimate individualized risk for BRCA mutant cancers, which could help women make more informed decisions about undergoing prophylactic surgeries and intensive screening. This study will combine advances in genetics and imaging, which may provide new information by which to stratify individual breast cancer risk. Polygenic risk scores, which combine genetic variants known as single nucleotide polymorphisms (SNPs) into a score that has recently been shown to stratify breast cancer risk, including among women with BRCA1/2 mutations, will be examined alongside dynamic contrast-enhanced MRI (DCE-MRI) imaging of breast tissue. DCE-MRI may provide a more sensitive biomarker of breast cancer risk compared to conventional mammographic density. The study proposes to combine polygenic risk scores and DCE-MRI imaging to improve breast cancer risk assessment among BRCA1/2 carriers, and help guide precision-based recommendations for risk-reducing interventions.

**Molecular Mechanisms That Regulate PARP-1 and Impact its Effective Targeting in Homologous Recombination Deficient Cancers**
This early career award funds Nootan Pandey, PhD, Principal Investigator on this study focusing on PARP-1, a key player in DNA repair pathways. Inhibiting PARP-1 catalytic activity that prevents the recruitment of DNA repair proteins to DNA lesions results in “trapped PARP-1 complex.” Trapped PARP-1 complex creates a toxic lesion in cancer cells, destroying them. However, the molecular basis for differential trapping and variable efficacy for cancer cell killing remains unclear. The team’s recent work provided key molecular insights on why small molecule PARP inhibitors (PARPi) have variable clinical effectiveness and can be modified to improve their efficacy for PARP-1 trapping and tumor cell killing. This study aims to uncover the molecular underpinnings of PARP-1 activation, which will provide useful fundamental insights to develop effective PARPi molecules for homologous recombination deficient cancers.

**Insurance Barriers to PARP Inhibitors in Women with BRCA1/2 and Ovarian Cancer**
Principal Investigator [Anna Jo Smith, MD, MPH, MSc](https://pc3i.upenn.edu/people/anna-jo-smith-md-mph-msc/), is funded in this early career award to lead a study exploring insurance barriers to PARP inhibitor usage as treatment for BRCA-related ovarian cancer. While PARP inhibitors have been shown to improve survival substantially in BRCA-related breast and ovarian cancer, little is known about the uptake of PARP inhibitors in clinical practice, and substantial concerns have been raised about insurance barriers to, and financial toxicity of, these new therapies for patients. This study will provide a first look at real-world utilization of PARP inhibitors and insurance barriers to use among women with BRCA-related ovarian cancer, in the setting of a large academic gynecologic oncology practice, with the hypothesis that Medicare causes greater delays in care and financial burdens than private insurance.

# Regulation of IFN-γ Signaling in *BRCA1*-Loss Dependent Breast Cancer

Gather Thacker, PhD, is the Principal Investigator in this early career award funded study exploring under-examined functions of *BRCA1* in breast cancer, such as regular mechanisms based on posttranslational modification of proteins. The group’s preliminary studies show higher expressions of interferon gamma receptor IFNGR1 and interferon gamma inducible p-STAT1 suggesting enhanced IFN-γ signaling could be applicable to several *BRCA1* associated tumors. Based on preliminary data, the study proposes to elucidate the precise molecular mechanism controlling the stability of IFNGR1 by E3 ubiquitin ligase FBXW7 and determine if sustained IFN-γ signaling through IFNGR1 promotes cancer stem cell function of BRCA1 associated tumors. This enhanced understanding will enlighten new avenues for future targeted therapy.

## ***2018 - 2020***

# PARPi Resistance Mutations of PARP-1 in *BRCA1/2* Mutant Cancers

Principal Investigator [Ben Black, PhD,](https://www.med.upenn.edu/apps/faculty/index.php/g275/p8128470) is funded to explore the mechanistic underpinnings of how mutations in the PARP-1 enzyme generate resistance to PARP inhibitors (PARPi) as has been observed in the clinic during the treatment of breast and ovarian cancer. Using expertise in studying protein/DNA complexes with hydrogen/deuterium exchange coupled to mass spectrometry (HXMS) and a longstanding and productive collaboration with the world-leading PARP crystallographer (John Pascal, Université de Montréal) and establishing a new collaboration with an expert in PARPi strategies in *BRCA1/2* deficient cancers (Chris Lord, ICR, London), the study will now determine the physical basis for PARP-1 PARPi resistance driver mutations. Specifically, the focus will be on mutations that are likely to involve disruption of the PARP-1 allosteric network. This mechanism of resistance is particularly relevant to the many *BRCA1/2* deficient breast and ovarian tumors where residual *BRCA1* activity allows resistance mutations of PARP-1 where its activity is lowered and/or eliminated.

**Core Resource for Clinical Studies of PET Imaging of PARP-1 to Direct Targeted Cancer Therapy**
Principal Investigators [Mehran Makvandi, PharmD,](https://www.med.upenn.edu/apps/faculty/index.php/g334/p8681271) and [Austin Pantel, MD,](https://www.med.upenn.edu/apps/faculty/index.php/g334/p8474863) are funded to develop a shared resource for clinical studies of PET (positron emission tomography) imaging of PARP-1 (Poly [ADPribose] polymerase 1) to direct targeted cancer therapy. This resource provides common services and infrastructure to support ongoing PARP imaging projects in breast, ovarian, pancreatic, and prostate cancer, and will assist with translational research and the data management of clinical trials. This resource will enable multiple research teams to work together to answer fundamental questions to evaluate [18F]FTT as a biomarker to predict and monitor response to chemotherapy and PARPi. This shared resource will provide support for radiotracer production, image analysis, clinical data mining, and data analysis for the existing projects in this space.

# Implication of Gleason Score for the Precision Medicine Treatment of Patients with Localized Prostate Cancer

[Kara Maxwell, MD, PhD,](https://www.med.upenn.edu/apps/faculty/index.php/g348/p8474927) is the Principal Investigator on this study funded to investigate alterations in *BRCA1/2*-related prostate cancer. This study aims to utilize the robust resources of the Penn Medicine Biobank and PennOmics to study the relationship of *BRCA1/2* mutations to Gleason score in prostate cancer patients at Penn Medicine. Genomic predictors of response to DNA damaging agents, specifically measures of homologous recombination deficiency, and mutational signatures suggestive of tumor etiology will be analyzed in the prostate tumors of patients with *BRCA1/2* mutations. Concurrently, specimens from all Gleason 9-10 prostate cancer patients with *BRCA1/2* mutations undergoing radical prostatectomy will be prospectively collected for the development of a tumor organoid bank to study therapy response. The results of this study will further clarify the role of *BRCA1/2* in the development of prostate cancer and may directly inform the precision medicine treatment of patients with localized prostate cancer.

# DDR-Inhibitor Combinations for the Treatment of *BRCA1/2* Germline Carriers

Principal Investigators [Fiona Simpkins, MD,](https://www.med.upenn.edu/apps/faculty/index.php/g275/p8676551) and [Eric Brown, PhD,](https://www.med.upenn.edu/apps/faculty/index.php/g275/p2585468) are funded to explore preliminary findings that distinct combinations of PARPi, ATRi and WEE1i differ in treatment effectiveness depending on BRCA status in high-grade serous ovarian cancers (HGSOC). The aims of the study include determining the most effective combination strategies for *BRCA1/2* germline carriers using patient-derived xenograph models and identifying both mechanisms of response and resistance with state-of-the-art proteomic and genomic technologies. These studies will determine how best to implement these next-generation treatment combinations in the clinic in a manner that is customized to the genetics of the HGSOC.

## ***2014 – 2017***

# Optimizing Access to Genetic Services for *BRCA1/2* Mutation Carriers

In this Outreach and Implementation Science Award, principal investigator [Angela Bradbury, MD](http://www.med.upenn.edu/apps/faculty/index.php/g275/p8527609) was funded for three years to test the effectiveness of TeleGenetics (telephone or videoconferencing) to provide cancer risk counseling and cancer genetic testing to individuals in communities with limited access to genetic services. Patients were randomly selected to receive remote genetic services at their community provider’s site by telephone or videoconferencing with a Penn genetic counselor or a usual care arm, where they received information on resources for genetic services in their area. The project aims to expand access to expert genetic providers in geographically and socio-demographically diverse populations with limited access to genetic services, improving the delivery of information and expanding the population of people who can benefit from learning about *BRCA1/2*-associated cancer risk.

# Targeting the ATR/CHK1 Pathway in Treatment

Principal investigators [Eric Brown, PhD](http://www.med.upenn.edu/apps/faculty/index.php/g275/p2585468) and [Fiona Simpkins, MD](http://www.med.upenn.edu/apps/faculty/index.php/g275/p8676551) and co-investigators [Rugang Zhang, PhD](http://www.med.upenn.edu/apps/faculty/index.php/g306/c425/p27113) and [Mark Morgan, MD](https://cancer.pennmedicine.org/providers/profile/mark-morgan) were funded for two years for this Breakthrough Science Team Award to determine if ovarian and pancreatic *BRCA2*-deficient cancers can be treated by targeting the ATR/CHK1 pathway as a primary line of therapy, or be used secondarily following the development of PARPi resistance. This study may lead to the development of new therapeutic strategies for patients with *BRCA1/2*-deficient cancers and could spur future Phase I/II trials evaluating ATR/CHK1 inhibition as an alternative primary treatment or secondary treatment for *BRCA1/2*-mutation carriers.

# Molecular Determinants of Chemo-Responsiveness of BRCA Mutant Cancers

For this three-year Breakthrough Science Team Award, principal investigators [Roger Greenberg, MD, PhD,](http://www.med.upenn.edu/apps/faculty/index.php/p8145566) [Lin Zhang,MD,](http://www.med.upenn.edu/apps/faculty/index.php/g275/p7157) [Andy Minn, MD, PhD,](http://www.med.upenn.edu/apps/faculty/index.php/g20000320/p8382979) and [Warren Pear, MD, PhD](http://www.med.upenn.edu/apps/faculty/index.php/g20000341/p8944) collaborated with basic and clinical investigators from four core laboratories, including [Wei Tong, PhD,](http://www.med.upenn.edu/apps/faculty/index.php/g20000320/p8146029) [Robert Mach, PhD](http://www.med.upenn.edu/apps/faculty/index.php/g275/p8658246)[, David Mankoff, MD, PhD,](http://www.med.upenn.edu/apps/faculty/index.php/g275/p6549765) and [Angela DeMichele, MD, MSCE](https://cancer.pennmedicine.org/providers/profile/angela-demichele) to study the molecular basis of cell intrinsic and extrinsic mechanisms that dictate chemo-responsiveness of BRCA mutant cancers, and identify novel strategies that overcome common mechanisms of resistance.

# Vaccination to Prevent *BRCA1/2*-Related Cancer

In this Breakthrough Science Team Award, principal investigators [Robert Vonderheide, MD,](http://www.med.upenn.edu/apps/faculty/index.php/g20000341/p1073)

[DPhil](http://www.med.upenn.edu/apps/faculty/index.php/g20000341/p1073) and [David Weiner, PhD](http://www.med.upenn.edu/apps/faculty/index.php/p10392) and co-investigators [Daniel Powell, PhD](https://www.med.upenn.edu/apps/faculty/index.php/g5455356/p8186734)[, Andrea Facciabene, MD, PhD,](http://www.med.upenn.edu/apps/faculty/index.php/g275/p8133929) [Katherine Nathanson, MD,](https://cancer.pennmedicine.org/providers/profile/katherine-nathanson) [E. John Wherry, PhD,](http://www.med.upenn.edu/wherrylab/) and [Ben Stanger, MD, PhD](http://www.med.upenn.edu/apps/faculty/index.php/g275/p8139400) were funded for three years to study the development of a novel vaccine that prevents *BRCA1/2*-related cancer in healthy individuals who carry *BRCA1/2* mutations. As a first step toward this overall goal, this study worked to determine the clinical and immunological impact of vaccinating high-risk patients in remission after adjuvant therapy using TERT DNA with or without IL-12 DNA; optimize the generation of anti-tumor immunity in genetic mouse models of *BRCA1/2*-related cancers using prophylactic DNA-based vaccines; and discover new T cell antigens based tumor mutations in *BRCA1/2* cancers.

## ***2013***

# REACH: Research to Evaluate Adolescents and Early Communication of Hereditary Risk

In this Communication and Risk Assessment Award, [Dr. Angela Bradbury](https://www.pennmedicine.org/providers/profile/angela-bradbury) was awarded funding to study communication about hereditary cancer risk within families, with a focus on adolescents. Her work aimed to inform interventions that increase preventative behaviors and minimize adverse psychological outcomes in adolescents and young adults from BRCA families. To date, Dr. Bradbury's team reached 141 interviews with parents reporting on communication with 287 children, and also enrolled girls aged 1119 years for interviews on knowledge and beliefs about breast cancer risk. During this grant cycle, Dr. Bradbury's team aimed to complete recruitment, analyze the relationship between what parents tell their children and the psychosocial adjustment of children, and begin to develop psychosocial interventions.

# Effects of AURKA and BRCA1 Dysregulation on Replication Fork Stability and Cell Survival Upon ATR/CHK1 Inhibition

[Eric Brown, PhD](https://www.med.upenn.edu/apps/faculty/index.php/g275/p2585468) was funded for this Cancer Therapy Targets and Predictors of Therapy Response Award to study pathways involved in the development and drug-susceptibility of cancers that are related to *BRCA1*. AURKA and ATR/CHK1 are both pathways that are highly relevant in breast cancers. By studying the role of different pathways, Dr. Brown's team aims to translate their findings into potential uses of pathway-inhibitors in breast cancers that are *BRCA1*-deficient.

# Development of Molecular Imaging of Tumor Vasculature for the Early Detection of Hereditary Ovarian and Breast Cancer

For this Early Detection Award, Drs. [George Coukos](https://www.cancerresearch.org/scientists/clinical-accelerator/leadership/scientific-advisory-committee/george-coukos) and [Chungsheng Li](https://www.med.upenn.edu/apps/faculty/index.php/g361/p8125284) investigated innovative molecular imaging techniques that visualize the tiny veins that grow to feed cancers which could lead to better methods for early detection of *BRCA*-related cancers.

**Minimizing Adverse Outcomes Following RRSO in *BRCA1/2* Mutation Carriers**
In this Cancer Risk Reduction and Prevention Award, [Susan Domchek, MD](https://www.pennmedicine.org/providers/profile/susan-domchek) was funded to comprehensively investigate the effect of risk-reducing oophorectomy (RRSO) on a variety of health outcomes. Findings from this study will be helpful in advising patients on the best timing for oophorectomy and in establishing whether interventions to treat side effects are needed. To date, Dr. Domchek's team developed an interdisciplinary and international project to prospectively study BRCA carriers undergoing RRSO and have recruited 231 women into an extensive survey study of RRSO effects for women who have already undergone the procedure. In this grant cycle, Dr. Domchek's team began prospective recruitment and increased the survey study response rate to 500.

# Predictors of Healthy Mood and Memory After Oophorectomy

[C. Neill Epperson, MD](https://www.med.upenn.edu/apps/faculty/index.php/g275/p8336338) was funded to study mood and memory in BRCA carriers before and after oophorectomy to determine who is at risk for adverse responses to the surgery and to determine ways to target prevention and treatment for mood and memory problems post-oophorectomy. For this Cancer Risk Reduction and Prevention Award, Dr. Epperson performed two randomized clinical trials to test hormone replacement therapy and a psychostimulant medication in women who were undergoing risk-reducing oophorectomy and women who had already undergone oophorectomy.

# Development of Vaccine Targeting the Tumor Vasculature for the Prevention of BRCA-Deficient Tumors

In this Cancer Risk Reduction and Prevention Award, [Andrea Facciabene, PhD](https://www.med.upenn.edu/apps/faculty/index.php/g361/p8133929) worked to develop a potential vaccine for BRCA-related cancers that may teach the immune system to react to and destroy cancerous tissue. To date, Dr. Facciabene's lab identified the device needed to deliver the vaccine to humans, developed new DNA vectors for the vaccine to perform studies necessary to submit to FDA for trials in humans, and completed all pre-IND (investigational new drug) documentation necessary to submit to FDA. Dr. Facciabene's lab performed safety studies in an animal model in preparation for submitting an IND to FDA for clinical trials in humans.

# AFFIRM: Assessment of Fertility and Factors Influencing Reproduction and Menopause in BRCA Mutation Carriers

[Clarisa Gracia, MD, MSCE](https://www.pennmedicine.org/providers/profile/clarisa-gracia) was funded for this Communication and Risk Assessment Award to study the impact of carrying a BRCA mutation on fertility and reproductive decisions. BRCA mutation carriers and a control group of *BRCA1/2* negative women will be recruited to provide a blood spot for hormone level testing and to complete a questionnaire on fertility and the impact of BRCA on reproductive decision-making.

# Chromatin Modifying Factors and *BRCA1/2*

For this Cancer Therapy Targets and Predictors of Therapy Response Award, [Roger Greenberg, MD, PhD](http://www.med.upenn.edu/apps/faculty/index.php/p8145566) was funded to study other DNA errors present in BRCA-related cancers to determine if these errors predict response to certain therapies, towards the end of developing better chemotherapy approaches based on the specific genetic changes in BRCA-related cancers. To date, Dr. Greenberg's lab has identified molecular mechanisms that influence DNA damage responses to clinically important therapies and discovered a new *BRCA1*-related syndrome. In this grant cycle, Dr. Greenberg's lab will work to identify additional molecular mechanisms by which *BRCA1* functions that may offer new targets for enhancing sensitivity to chemotherapies in BRCA-related cancers.

# Imaging Biomarkers for Risk Reduction Management of *BRCA1/2* Carriers

In this Early Detection Award, [Despina Kontos, PhD](https://www.med.upenn.edu/apps/faculty/index.php/g5455356/p8123294) was funded to study whether dynamic contrastenhanced MRI (DCE-MRI) provides useful information about the actual effect of risk-reducing methods on breast cancer risk. If DCE-MRI helps to predict which women are benefiting from each risk-reducing intervention, Kontos' team will provide new clinical decision-aid tools for improving risk-reduction and quality of life for BRCA carriers.

# Next Generation Tomosynthesis Imaging for *BRCA1/2* Carriers

[Andrew Maidment, PhD, FAAPM](https://www.med.upenn.edu/apps/faculty/index.php/g334/p232524) was funded for this Early Detection Award to study digital breast tomosynthesis (DBT), a novel imaging modality that may replace mammography in the future. DBT is currently limited to the detection of non-calcified lesions which is problematic because many cancers detected in *BRCA2* carriers have cancers that present as calcified lesions. Dr. Maidment's team aimed to develop the next generation of DBT systems that may benefit BRCA mutation carriers by increasing early detection of BRCA-related breast cancers.

# Interferon-Related DNA Damage Resistance Signature (IRDS) in BRCA Mutant Tumor

[Andrew Minn, MD, PhD](https://www.med.upenn.edu/apps/faculty/index.php/g20000320/p8382979) was funded for this Cancer Therapy Targets and Predictors of Therapy Response Award to study how cells that surround cancers can play an important role in shaping cancer behavior. Dr. Minn's project aims to identify and understand signals that are sent from non-cancer cells to cancer cells that contribute to therapy resistance. To date, Dr. Minn's lab has uncovered how pathways that normally respond to viral infection can control treatment resistance, particularly in *BRCA1-*related breast cancers, and how inhibiting these pathways can improve the effectiveness of therapies. In this grant cycle, Dr. Minn will study these pathways and test a hypothesis that a step of this pathway is a potential drug target for addressing therapy resistance.

# Whole Genome Sequencing of Breast and Ovarian Cancers Associated with *BRCA1/2* Mutations

[Kate Nathanson, MD,](https://www.med.upenn.edu/apps/faculty/index.php/g275/p9542) was funded for this Cancer Therapy Targets and Predictors of Therapy Response Award to sequence the DNA of breast and ovarian tumors for *BRCA1/2* carriers to understand the molecular changes that may represent new targets for treatment or predict drug sensitivity or resistance to current regimens. To date, Dr. Nathanson's lab has identified multiple changes in 48 known cancer genes that are likely driving the growth of BRCA-related tumors and changes which suggest sensitivity to a range of experimental drugs. In the next cycle, Dr. Nathanson's lab will expand their analysis to explore thousands of gene mutations in BRCA-related tumors in the hopes of identifying novel pathways and drug targets in *BRCA1* and *BRCA2* mutated tumors.

# A Zebrafish Mutagenesis Screen to Identify Genes, Promote Initiation and Progression of *BRCA2* Associated Ovarian Cancer

For this Cancer Risk Reduction and Prevention Award, [Michael Pack, MD](https://www.med.upenn.edu/apps/faculty/index.php/g275/p12874) was funded to identify and study mutations that occur in the development of *BRCA2*-related ovarian cancers in a zebrafish model. In addition to providing insight into BRCA2's role in the development of ovarian cancer, the mutations identified in the development of ovarian cancer may help define risk factors for the development of ovarian cancer in carriers, identify novel targets for anti-cancer drugs, and alter our approach to detection and treatment of *BRCA2*-related ovarian cancer.

# A Fully Optimized CAR RNA T Cell-based Therapy for BRCA Cancer Treatment

[Daniel Powell, PhD](http://www.med.upenn.edu/apps/faculty/index.php/g275/p8186734) was funded to further develop a potent immune-based therapy for BRCA-related breast cancers that teaches the immune system's T-cells to attack the cancer for this Cancer Risk Reduction and Prevention Award. Dr. Powell's laboratory focused on developing this potential therapy for trial in the clinic by exploring possible allergic responses and by developing a vector for delivering the therapy to humans in a future pilot study.

# Eating and Exercise for BRCA+ Survivors: Addressing Heart and Bone Health

[Kathryn Schmitz, PhD](https://www.med.upenn.edu/apps/faculty/index.php/g275/p5294028) was funded to study the efficacy of a commercially available web-based nutrition and exercise program on a novel population of breast cancer survivors who have undergone riskreducing oophorectomy under age 45 and who have not been on hormone replacement therapy for at least two years. For this Cancer Risk Reduction and Prevention Award, Dr. Schmitz studied cardiovascular and bone outcomes in order to provide a balanced understanding of the potential benefits of nutrition and exercise on these outcomes.

# The Role of *BRCA1* and Genomic Instability in Pancreatic Cancer Metastasis

[Ben Stanger, MD, PhD](https://www.med.upenn.edu/apps/faculty/index.php/g275/p8139400) was funded for this Cancer Therapy Targets and Predictors of Therapy Response Award to study the role of *BRCA2* in the development of pancreatic cancers, specifically the role of *BRCA2* in metastatic disease. Dr. Stanger's team will use mice models to study the role of *BRCA2* in pancreatic cancer and to determine whether *BRCA2* mutations and mutations in a related gene called *PALB2* increase sensitivity to inhibitors of other molecular pathways.

# The Stone Family Award in BRCA Prevention Research: Telomerase Vaccination to Prevent BRCA1/2 Related Cancer

[David Weiner, PhD](https://www.med.upenn.edu/apps/faculty/index.php/p10392) and [Robert Vonderheide, MD, DPhil,](https://www.pennmedicine.org/providers/profile/robert-vonderheide) were funded to study a prevention vaccine aimed at reducing the risk of cancer is BRCA mutation carriers for this Cancer Risk Reduction and Prevention Award. Using an enzyme called hTERT, Drs. Weiner and Vonderheide aimed to develop a vaccine that teaches the body's immune system to fight BRCA-related cancers. They performed a series of preclinical studies using several mouse models of immune-prevention that were designed to prove the immunological concept, optimize the vaccine, and provide necessary data to file an investigational new drug application with FDA, the first step towards studying the vaccine in humans. Drs. Weiner and Vonderheide's work has been made possible by the Stone Family Award, created by Norman L. Stone, W'52 and Carol Stone to advance prevention research on *BRCA1/2*.

# Functional Genetic Approached to Identify MicroRNAs Regulating BRCAness in Breast and Ovarian Cancer

For this Cancer Therapy Targets and Predictors of Therapy Response Award, [Lin Zhang, MD](https://www.med.upenn.edu/apps/faculty/index.php/g275/p7157) was funded to study the role of microRNA's, which are molecules that affect the action of genes, in the development of cancer and the sensitivity of cancers to chemotherapies. Dr. Zhang's team aims to identify the microRNAs present that make cancers exhibit features of BRCA-related cancers ("BRCAness"), to predict sensitivity to chemotherapies including PARP inhibitors and to develop well-annotated databases of breast and ovarian cancers for BRCA researchers.

## **EXTERNAL**

## ***2021 – 2023***

# Identifying the Role of *BRCA1* in the Mammary Gland Thus Leading to Therapeutic Targets

[Alexander Bishop, DPhil,](https://www.uthscsa.edu/academics/biomedical-sciences/faculty/profile/1AS0YZ49K/Bishop%252C-Alexander-James-Roy) of the University of Texas Health Science Center at San Antonio, is Principal Investigator on this study funded to explode why *BRCA1*, a gene expressed in all cells of the body, confers a predisposition to breast cancer in particular when *BRCA1* is mutated. The study will investigate the normal function of *BRCA1* in the mammary gland, presumably beyond promoting DNA repair, and apparently during pregnancy, which may provide novel insights into *BRCA1* biology and potential novel therapeutic strategies. This will build off recent work considering the roles of *BRCA1* beyond DNA repair, particularly the *BRCA1:NRF2* interaction. Preliminary data indicates *BRCA1* supports NRF2 transactivation of lactase expression in the mammary gland and in basal type breast cancer cell lines. The study proposes to validate *BRCA1* control of lactase production and ask whether modulating this pathway in TNBCs augments PARP1 inhibitor sensitivity in a *BRCA1* dependent manner.

# Re-Purposing a Potassium Channel Inhibitor Identified by Genome-Wide Association Studies for Breast Cancer Prevention and Treatment

Principal Investigators [Kara Britt, PhD,](https://www.petermac.org/users/assoc-prof-kara-britt) [Georgia Chenevix-Trench, PhD,](https://researchers.uq.edu.au/researcher/7231) and [Jane Visvader, PhD, FAA, FRS,](https://royalsociety.org/people/Jane-Visvader-25404/) of the University of Melbourne, are funded to the study the application of a potassium channel KCNN4 inhibitor, Senicapoc, can be applicable for breast cancer, particularly *BRCA1*-related breast cancer. There is an urgent need to develop more risk-reducing medications for *BRCA1* mutation carriers as the uptake and adherence to endocrine therapy is very low, and prophylactic surgery is an unpalatable option for many women. Senicapoc is well tolerated and is orally bioavailable. Preliminary prevention/early therapy studies in mice have shown Senicapoc may delay tumor onset, inhibit tumor growth, and increase survival.

# Understanding Breast Cancer Driver Mechanisms in *BRCA2* Mutation Carriers

Principal Investigator [Aura Carreira, PhD,](https://science.curie.fr/members/aura-carreira/) of the Institut Curie Research Center in Paris is funded to explore what drives tumorigenesis in *BRCA2* mutation carriers down to the molecular level. The study hypothesizes that *BRCA2* heterozygous cell lines may display distinct phenotypes that could mimic precancerous lesions. The team will use preliminary functional, transcriptomic, and whole-genome sequencing data on two isogenic gene-edited breast epithelial cell lines carrying two of the most common pathogenic truncating mutations in *BRCA2* to determine which mutations lead to driving mechanisms of tumor formation and sensitivity to various treatments.

# Characterizing a New Mouse Model of Fanconi Anemia

[Neil Johnson, PhD,](https://www.foxchase.org/neil-johnson) from the Research Institute of Fox Chase Cancer Center is the Principal Investigator on this study funded to uncover the molecular perturbations that might result in BRCA-related Fanconi anemia (FA). The study will use a new, specially developed FA mouse model, which is driven by a 3-amino acid deletion in the coiled-coil domain of *BRCA1*, which specifically disrupts the *BRCA1-*

*PALB2* association, resulting in loss of *RAD51* and HR deficiency, mimicking the conditions of FA in humans. These unique mouse models will provide a new tool to gain insight into the biological pathways that underpin FA etiology.

# Vaccination as a Strategy to Prevent or Treat Drug Resistance Caused by BRCA Reversions

Principal Investigators [Stephen Pettitt, PhD,](https://www.icr.ac.uk/our-research/researchers-and-teams/dr-stephen-pettitt) [Christopher Lord, DPhil,](https://www.icr.ac.uk/our-research/researchers-and-teams/professor-chris-lord) and [Andrew Tutt, PhD, FRCR, MRCP, MB, ChB,](http://theharleystreetbreastclinic.co.uk/team/andrew-tutt) of the Institute of Cancer Research in London are funded to study a unique amino acid sequence found within PARP-resistant mutant BRCA tumors that differs from sequences found in other BRCA type proteins. Their research suggests that this novel out of frame sequence often constitutes a potential tumor neoantigen, opening the possibility that PARP inhibitor resistant cancers could be targeted by exploiting the presentation of a BRCA reversion neoantigen. The study will test this hypothesis by using mouse models to test an anticancer vaccine and immune checkpoint inhibition to assess whether this may represent a viable therapeutic strategy.

# Defining the Contribution of BRCA Mutations to the Presence and Function of Tumor-Infiltrating Nerves in Ovarian Cancer

[Paola Vermeer, PhD,](https://www.usd.edu/faculty-and-staff/Paola-Vermeer) of the University of South Dakota, is the Principal Investigator in this study funded to explore the effectiveness of nerve-targeted therapy on BRCA-related ovarian cancer. Tumor-infiltrating nerves are critical components of the tumor microenvironment (TME). While nerves actively contribute to cancer initiation and progression, a clear understanding of how they impact disease is lacking. The team found that high-grade serous ovarian carcinomas (HGSOCs) are innervated, with BRCA-mutated HGSOCs being more innervated than their BRCA wildtype counterparts. Their electrophysiologic studies indicate that HGSOCs harbor electrical activity which can be pharmacologically attenuated. The study will explore whether BRCA mutations potentiate HGSOC innervation making them particularly vulnerable to nerve-targeted therapy. Positive outcomes will fuel future in vivo studies to define if blocking intratumoral electrical activity attenuates tumor growth and improves survival of BRCA-mutated HGSOC.

# Structure-Function Relationships of *BRCA1-BARD1* Mutations and Relevance to Cancer Progression

Principal Investigator [Elton Zeqiraj, PhD,](https://biologicalsciences.leeds.ac.uk/molecular-and-cellular-biology/staff/161/dr-elton-zeqiraj) of the University of Leeds, is funded to study the relationship between *BRCA1* and its obligate partner, *BARD1*, in order to understand more about the biological functions of *BRCA1* and more about its multifunctional enzyme machinery works. Additionally, the molecular basis by which many mutations lead to cancer predisposition, progression and resistance to current therapeutics cannot be fully explained without a 3- dimensional structure, which includes Exon 11. Importantly, multiple reversion mutations to existing cancer therapies occur in the Exon 11 region and other *BRCA1* regions, and elucidating these precise molecular mechanisms of resistance is important to future therapeutics. The study will optimize cryo-EM analyses to obtain high-resolution models, resolve *BRCA1-BARD1* inter and intra-molecular contacts and determine the Exon 11 location relative to the previously characterized RING and BRCT domains—leading to a significant advancement in understanding *BRCA1* roles in cancer.

## ***2018 - 2020***

# Quantitative Proteomics to Identify Mediators of Therapy Response in BRCA-Cancer

Principal Investigator [Sharon B. Cantor, PhD,](https://www.umassmed.edu/mccb/faculty-MCCB/faculty-MCCB/faculty-profile-pages/cantor-sharon/) of University of Massachusetts, is funded to define the protein landscape of therapy, sensitive vs. resistant hereditary breast cancer to predict therapy response. and define targets to disrupt resistance mechanisms. The goal of the study is to comprehensively reveal how genetic loss of the BRCA- pathway alters the proteome by utilizing quantitative mass-spectrometrybased proteomics to first gain an unbiased examination of protein machinery in BRCA mutant and proficient cancer cells. Second, by comparing cisplatin sensitive vs. resistant BRCA cancer cells, to unmask proteomic changes that favor chemoresistance. Collectively, the grant aims to provide critical new selective targets that could be used in conjunction with current therapies to prevent chemoresistance.

# Variable Number Tandem Repeats (VNTRs) as modifiers of *BRCA1* risk

Principal Investigator [Eitan Friedman, MD, PhD,](https://www.shebaonline.org/doctor/eitan-friedman/) of Sheba Medical Center in Israel is funded to conduct the first comprehensive analysis of variable-number tandem repeats (VNTRs) in exons, promoters, and UTRs of genes in the human genome, focusing on Jewish women who carry the same *BRCA1* mutation. The lack of an accurate, personalized risk estimate makes it exceedingly difficult for an individual to decide on a course of action regarding the timing and type of risk reduction. Genetic modifiers—primarily single-nucleotide polymorphisms (SNPs)—explain only a portion of the variation in risk. This study proposes a new paradigm of genetic modifiers—VNTRs—that govern the penetrance of mutant *BRCA1* alleles and hypothesize that they act as modifiers of risk of developing breast cancer in women carrying pathogenic BRCA mutations. This information will provide women at high risk with more precise estimates of their personal risks, and will allow them to make more informed decisions on the use and timing of preventive options, thus reducing the uncertainty, comorbidities, and mortality associated with breast cancer.

# A Randomized Controlled Trial to Enhance the Use of Genetic Counseling and Testing in Latina Women at Risk of Hereditary Breast and Ovarian Cancer

[Alejandra Hurtado de Mendoza Casaus, PhD,](https://fishercenter.georgetown.edu/hurtado-de-mendoza/) of Georgetown University is leading this study that is funded to explore how to increase awareness and use of genetic counseling and testing services among Latina women at risk of hereditary breast and ovarian cancer using a culturally targeted narrative video to enhance genetic counseling and testing uptake and psychosocial outcomes. This study aims to conduct a two arm randomized controlled trial (RCT) to compare the impact of two brief interventions (video vs. fact sheets) on genetic counseling and testing uptake. The study will conduct a mixed methods hybrid effectiveness-implementation design to assess the impact of the interventions while gathering data on implementation outcomes. All participants will receive referrals to free telephone genetic counseling in Spanish to address cost, logistic, and language barriers. The primary outcome is genetic counseling uptake at three months post-intervention.

# Defining the Molecular Mechanisms Underlying BRCA2 and RAD51 PARP Lesion Processing

[Ryan B. Jensen, PhD,](https://medicine.yale.edu/therapeuticradiology/research/radiobiology/people/ryan_jensen.profile) of Yale University is funded to lead a study exploring resistance to PARP inhibitors, namely the need to elucidate how PARP inhibitors (PARPi) cause cell death in BRCA mutant but not normal cells. The study will also seek to define how individual PARPi may act through distinct mechanisms, either by “trapping” PARP-DNA complexes or by inhibiting repair of (single-stranded DNA (ssDNA) nicks that are subsequently converted to double-stranded breaks (DSBs). The study will interrogate the explicit biochemical function(s) compromised by pathogenic *BRCA2* mutations. Sensitivity to various PARPi will be assessed with strong, intermediate, or weak trapping activity (e.g. talazoparib, olaparib, and veliparib, respectively), and the function(s) reconstituted by “reversion” mutations identified in patients with PARPi-resistant tumors will be investigated with the goal of identifying functional attributes necessary for PARPi sensitivity.

# Identifying Drivers of BRCA2 Mutation Associated Predisposition to Cancer

For this study, Principal Investigator [Shailja Pathania, PhD,](https://www.umb.edu/academics/csm/faculty_staff/shailja_pathania) University of Massachusetts, is funded to examine the molecular origins of *BRCA2* mutant cancer, particularly the identification of genetic changes that drive normal heterozygous cells in *BRCA2* mutation carriers (*BRCA2*mut/+) to become tumor cells. Preliminary data that shows that (*BRCA2*mut/+) breast cells are sensitive to replication stress (RS) inducing DNA damage. The study hypothesizes that the tumors that eventually arise from *BRCA2*mut/+ cells must tolerate the RS inherent to oncogenic transformation. This tolerance might be dependent on acquisition of additional modifications like loss of p53 and/or other genes and/or pathways. To identify additional genes and pathways that allow *BRCA2*mut/+ cells to survive RS, a genome-scale screening approach will be utilized, and then human tumors can be queried for mutations or altered expression of the genes discovered in the screen. Identification of such genetic changes will provide insight into the first step/s that occur in the path to tumor formation in cells of *BRCA2* mutation carriers.

**Evaluating R-Loop Dynamics as an Indicator of Cancer Vulnerability in *BRCA1* and *BRCA2* Mutant Cancers**
Principal Investigator [Kavitha Sarma, PhD,](https://wistar.org/our-scientists/kavitha-sarma) of The Wistar Institute, is funded to examine R-loop dynamics in *BRCA1/2* deficient cancers. Mutations in *BRCA1/2* that are associated with breast, ovarian and prostate cancers result in the accumulation of three-stranded nucleic acid structures that contain a DNA:RNA hybrid and a displaced single strand of DNA called R-loops. R-loops are associated with changes in gene expression, increased DNA damage and genome instability, and are consequently thought to increase the incidence of mutations in cancers. The study hypothesizes that R-loop formation at specific genome locations contributes to cancer vulnerability and that R-loops formed upon *BRCA1/2* loss dictate the location of mutations that arise, and pathways that are deregulated, in these cancers. The study hopes to gain a comprehensive view of R-loop dynamics in *BRCA1/2* deficient cancers that can ultimately facilitate the use of R-loops for novel diagnostic and therapeutic applications.

# Interaction Between FANCM and *BRCA1* in Cancer Therapy

Principal Investigator [Ralph Scully, PhD,](https://www.dfhcc.harvard.edu/insider/member-detail/member/ralph-scully-mbbs-phd/) of Beth Israel Deaconess Medical Center/Harvard Medical School is funded to expanded on a previous study on the use of the Escherichia coli Tus/Ter replication fork barrier and FANCM on the repair of stalled replication forks in mammalian cells. *BRCA1* mutant cells respond to the Tus/Ter block by forming small (<10 kb) tandem duplications (TDs), mimicking a rearrangement signature observed in *BRCA1* mutant cancers. FANCM acts in synergy with *BRCA1* to suppress TDs. This study will define the genetic interactions between *BRCA1* and FANCM in synthetic lethality and will lay the groundwork for the development of small molecule inhibitors of FANCM as novel “synthetic lethal” therapeutics in *BRCA1* mutant cancer.

# Modeling Early Detection and Prevention of *BRCA1*-Related Breast Cancer

Principal Investigator [Hui Zong, PhD,](https://med.virginia.edu/faculty/faculty-listing/hz9s/) of University of Virginia is funded to explore the development of breast cancer in women with *BRCA1* mutations. A significant gap in knowledge regarding the progressive kinetics of pre-malignant mutant cells makes it virtually impossible to precisely determine when to intervene, which is a particular challenge for women who want to maintain their fertility. This study seeks to tackle this problem using a mouse model called MADM (mosaic analysis with double markers), which is ideal for studying tumor initiation because the model mimics the clonal origin of cancer in human patients and the direct comparison between mutant and wildtype cells allows the detection of even the subtlest anomalies at early stages. The model will have two specific aims: to take advantage of the single-cell resolution provided by MADM to thoroughly characterize tumor initiation stage, focusing on early progression kinetics, varied susceptibility of different cell types, and spatial heterogeneity of progression in the mammary gland; and to quantitatively evaluate whether the synthetic lethality of PARP-1 inhibitor in *BRCA1*-mutant cells could exert tumor-prevention activity.

## ***2014 – 2017***

# BRCA Mutant Cancer

In this Basser Team Science Award, principal Investigator [Junjie Chen, PhD (](http://faculty.mdanderson.org/Junjie_Chen/)MD Anderson Cancer Center) led a multi-institutional team funded for two years to study novel mechanisms of chemotherapy responsiveness in BRCA mutation-related cancers and overcoming therapy resistance arising from these mechanisms. These studies were performed at the level of basic laboratory investigation, using clinical samples from BRCA mutant breast and ovarian cancers that are naïve to therapy and in those that have acquired resistance. Achieving these objectives allowed for the development of more efficacious treatment strategies for BRCA patients.

# When Numbers Matter: Decision Support for BRCA Genetic Testing

Principal Investigator [Katherine Crew,](http://www.cumc.columbia.edu/hematology-oncology/about_us/katherine_crew) MD (Columbia University) was funded to develop a program to screen underserved communities for BRCA mutations in the New York City area.

**Development of a Culturally-Tailored Decision Aid on BRCA Genetic Testing for Orthodox Jews**
While it is known that 1 in 40 people of Ashkenazi Jewish descent carry a *BRCA1* or *BRCA2* gene mutation, the Orthodox Jewish community remains an under-studied population. Principal investigator [Katherine Crew, MD](http://www.cumc.columbia.edu/hematology-oncology/about_us/katherine_crew) (Columbia University) was funded for one year to develop a web-based decision aid, RealRisks, which is designed to improve genetic testing knowledge and accuracy of breast cancer risk perceptions, as well as self-efficacy to engage in a collaborative dialogue about BRCA genetic testing. The goal of this work was to develop a culturally-tailored decision aid for Orthodox Jewish women to enhance informed decision-making regarding BRCA genetic testing.

# Towards Selective PARP Inhibitors

For this Basser Innovation Award, principal investigator [Sonia Franco,](http://www.hopkinsmedicine.org/radiation_oncology/about_us/our_team/bios/sonia_franco.html) MD, PhD (Johns Hopkins University) was funded to employ a genetic approach to test the hypothesis that PARP2 has PARP1independent functions in the suppression of genomic instability in BRCA-deficient backgrounds. This will help define the mechanisms of action for PARPi in BRCA cells, setting the stage for future development of biomarkers and more specific PARP inhibitors.

# Determine the Role of Dormant Origin Firing in Modulating *BRCA1* Haploinsufficiency

For this one year study, principal investigator [Tony T. Huang, Ph.D.](https://med.nyu.edu/faculty/tony-t-huang) from New York University School of Medicine was funded to determine causes of haploinsufficiency, a condition that arises where the function of a gene is reduced resulting in abnormalities. The study focused on *BRCA1* mutations and looked to prevent instability in the chromosomes as cells are replicating. The study looked at a recent discovery of a protein implicated in a type of anemia known as Fanconi anemia that may have a positive impact. The study also mapped locations where the gene doesn’t replicate properly using an innovative deep sequencing technique that compares normal human mammary (breast) epithelial cells with *BRCA1* mutations carriers.

# The Role of *BRCA1* Isoforms in PARP Inhibitor and Platinum Resistance

Principal investigator [Neil Johnson,](http://www.fccc.edu/research/pid/johnson-n/index.html) PhD (Fox Chase Cancer Center) was funded for this Basser Innovation Award to identify and characterize *BRCA1* isoforms that are capable of contributing to DNA repair and drug resistance. This characterization could be useful for predicting which patients will have lasting responses to PARP inhibitor or platinum therapy based on establishing relationships between specific *BRCA1* mutations and the likelihood of expressing particular *BRCA1* isoforms.

# Targeting Familial Breast Cancer with RAD52 Inhibitors

In this Basser Innovation Award, principal investigator [Alexander Mazin,](https://www.drexelmed.edu/Home/AboutOurFaculty/AlexanderMazin.aspx) PhD (Drexel University) was funded to analyze the effect of RAD52 inhibitors in *BRCA1/2* cells alone and in combination with therapeutic drugs, analyze the mechanism of RAD52 inhibition in vitro, and develop more effective analogs of RAD52 inhibitors through a medicinal chemistry approach.

# Analysis of *BRCA1* Missense Variants in DNA Repair

This basic science project, headed by [Jeffrey D. Parvin, M.D., Ph.D.](https://medicine.osu.edu/bmi/people/jeffrey_parvin/pages/index.aspx) of Ohio State University, was funded for one year and focused on the impact of missense alterations on the *BRCA1* protein function in DNA repair. In collaboration with the University of Washington, a novel approach was used to analyze thousands of genetic variations in *BRCA1*. The study was intended to have an immediately translatable clinical use, as the results from the functional assay can be combined with information in order to advise women with a *BRCA1* variant of unknown significance on their likely breast cancer predisposition. Additionally, there is a basic science impact in terms of understanding the structure-function relationships of *BRCA1* at very high resolution.

**Targeting DNA Polymerase θ for Precision Medicine in BRCA Deficient Cancers**

In a collaboration between Temple and Stanford Universities, this study, led by principal

investigator [Richard T. Pomerantz, Ph.D.,](https://medicine.temple.edu/richard-pomerantz) was funded for one year and explored the use of targeting DNA polymerase theta (Polθ), which is highly upregulated in breast and ovarian cancers and corresponds to a poor clinical outcome for breast cancer patients. Recent groundbreaking studies have demonstrated a synthetic lethal relationship between Polθ and the BRCA pathway of homologous recombination, and strongly indicates that inhibition of Polθ will selectively kill BRCA deficient cancer cells. Because BRCA deficient cells often become resistant to Poly (ADP-ribose) polymerase (PARP) inhibitors the development of promising new DNA repair drug targets, such as Polθ, is important for identifying personalized non-toxic treatments for patients with BRCA deficient cells.

# Using PARP Inhibitors in the Treatment of Cancer

PARP inhibitors are a promising class of cancer treatment drugs. However, some cancers are resistant to PARP inhibitors while others can become resistant to PARP inhibitors over time. CDK12 is a protein that appears to help the cancer cell resist the beneficial effects of PARP inhibitors. So, stopping CDK12 might stop the cell’s ability to resist treatment. One way to stop CDK12 could be to promote THZ-5-31-1, which is a protein that inhibits CDK12. For this Basser Innovation Award, principal investigator [Geoffrey Shapiro, MD, PhD](http://doctors.dana-farber.org/directory/profile.asp?pict_id=0000294) (Dana-Farber Cancer Institute) was funded for one year to assess how promoting THZ5-31-1 might stop the body from accidentally repairing breast cancer cells. Also, he explored if pairing THZ-5-31-1 with a PARP inhibitor could stop a tumor from growing.

# Roles of BRCA1 in RAD51-Mediated Homologous Recombination and Tumor Suppression

Principal investigator [Patrick Sung, DPhil](https://medicine.yale.edu/lab/sung/members/patrick_sung-2.profile) of Yale University was funded for one year to explore deeper molecular understandings of the genes *BRCA1* and *BARD1* and their role in homologous recombination (a natural process cells use to accurately repair harmful breaks in strands of DNA) to better develop strategies for the treatment of cancer stemming from BRCA mutations. To overcome the difficulties of working with BRCA *in vitro*, the team has developed a system to obtain soluble,

monodispersed *BRCA1* (in combination with *BARD1*) in large quantities for this two part study, which includes: the generation and testing of *BRCA1* mutations in various cell-based assays to assess biological significance of protein-ligand interactions; and deciphering how *BRCA1-BARD1* impacts different stages of homologous recombination.

# Predicting the Best Treatment for Each Patient

Knowing the protein make-up of a tumor can help doctors predict how an individual patient will respond to different types of cancer treatments. For this Basser Innovation Award, principal investigator [Zoltan Szallasi, MD](http://www.dfhcc.harvard.edu/insider/member-detail/member/zoltan-szallasi-md/) (Boston Children’s Hospital) was funded for one year to establish a profile of the 53BP1 and Ku70 proteins that will help doctors predict how individual people with BRCA-associated cancers would respond to PARP inhibitors and platinum-based therapy. This defined a mutational profile measuring the relative activity of 53BP1 and Ku70 in BRCA mutant tumors, which will be an important step towards establishing a robust biomarker that reliably predicts response to platinum or PARP inhibitor based therapy in BRCA mutation carriers.

# Mechanism Based Strategies to Overcome Resistance and Augment Response to Targeted Therapy in

# Inhibiting SIRT2 Activity to Inhibit BRCA Activity

BRCA proteins, which are made from BRCA genes, typically help in the repair of DNA damage that occurs in a cell’s life. There are other proteins, like SIRT2, that regulate how BRCA proteins perform this role in the cell. For this Basser Innovation Award, principal Investigator [David Yu, MD, PhD](http://radiationoncology.emory.edu/people/physicians/yu-david.html) (Emory University) was funded for one year to determine the significance of SIRT2’s regulation over *BRCA1* protein activity and to determine if inhibiting SIRT2 might kill cells and tumors with *BRCA1/BRCA2* dysregulation.

## ***2013***

**Analyses of the Genetic Interaction Between PARP2 and the *BRCA1/BRCA2* Tumor Suppressors:**

# Comprehensive Evaluation of Cancer Risk Modifiers in *BRCA1/2* Mutation Carriers

Timothy Rebbeck, PhD was awarded funding to study factors that modify *BRCA1/2* cancer risks in carriers to provide information that may aid women and their providers in making optimal decisions about cancer prevention strategies in this Cancer Risk Reduction and Prevention Award. Dr. Rebbeck will further focus these studies on under-represented groups. To date, Dr. Rebbeck's team has undertaken a comprehensive synopsis of factors that modify *BRCA1/2*-associated cancer risks such as reproductive history, exposures, and modifying genes. In this grant cycle, Dr. Rebbeck's team will extend the above analyses and focus on the recruitment and analyses of these parameters in underrepresented populations.

# Blood-borne Biomarkers of Dysplasia and Early Cancer in Patients with BRCA Mutations

[Dr. Andrew Rhim's](https://gsbs.uth.edu/faculty/faculty-directory/faculty-profiles.htm?id=a72366b4-034d-4c5c-941a-21a8eb65dfd1) laboratory recently found that cells from the pancreas (and other organs) can enter the bloodstream when a pre-cancerous lesion is present but long before a tumor has formed. For this Early Detection Award, Dr. Rhim's work focused on applying this discovery of circulating epithelial cells (CEC's) to develop a screening method for detecting BRCA-related cancers early. To date, Dr. Rhim has initiated serial blood sampling in BRCA carriers treated at the Basser Center and has detected CEC's in BRCA mutation carriers without clinical diagnoses of cancer. In this grant cycle, Dr. Rhim continued to follow BRCA carriers with serial blood sampling to determine if CEC's can be used to identify patients with early cancer. In addition, Dr. Rhim's team profiled the genetic make-up of these cells to gain more information about their potential to develop into cancer.