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TITLE: Somatic mutation rate as determinant of breast cancer penetrance in BRCA1/2 familial cases

PRINCIPAL INVESTIGATOR: Jan Vijg

CONTRACTING ORGANIZATION: Albert Einstein College of Medicine, Bronx, NY

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**14. ABSTRACT**

Analysis of how mutations accumulate in pretumor tissue, although widely presumed to occur, has been extremely difficult to study. This is principally because, with most such mutations being unique to individual cells within a tissue, their detection is technically challenging. In this study we propose to apply "Single Cell Multiple Displacement Amplification (SCMDA)" that we recently developed for high accuracy detection of a spectrum of mutations from single nucleotide substitutions to indels and aneuploidy in individual cells within pre-tumor tissues of women who inherited mutations in the *BRCA1* or *BRCA2* genes. We hypothesize that mutations from single nucleotide substitutions to indels, large genomic rearrangements, and aneuploidy accumulating as consequence of defects in homology dependent DNA repair in mammary epithelial cells are the underlying cause of increased cancer risk in these women. We further hypothesize that estrogen, which is known to generate metabolites that directly damage DNA, mechanistically acts as a modifier.

**15. SUBJECT TERMS**
None listed.

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| Unclassified | Unclassified | Unclassified | Unclassified | 11 | 19b. TELEPHONE NUMBER *(include area code)* |

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## 1. INTRODUCTION:

Cancer is a genetic disease caused by mutations that accumulate in somatic cells during aging, environmental exposure or other endogenous factors. How these somatic mutations acquired by cells transform them into tumors remains largely unknown. This is due, in part, to the technical difficulties of studying non-clonal casual mutations accumulated in tissues before transformation. In this application we will test the hypothesis that mutations accrued as consequence of endogenous DNA damage caused by high estrogen levels cause increased breast cancer risk. By leveraging *in house* generated approaches including "Single Cell Multiple Displacement Amplification (SCMDA)" we aim to map all forms of mutations from single nucleotide substitutions to indels, large genomic rearrangements, and aneuploidy using as a model woman who inherited germline mutations in *BRCA1* or *BRCA2* because of their intrinsic defect in the homologous repair (HR) pathway which greatly increase their susceptibility to develop tumors. We hypothesized that estrogen, from endogenous production, contraceptives, pregnancy, hormone replacement therapy, which is known to generate metabolites that directly damage DNA, mechanistically acts as a modifier of *BRCA1/2* cancer penetrance by working in concert with the HR repair defects to increase the somatic mutation rate in the cells of *BRCA1/2* mutation carriers. Our hypothesis is being tested along two specific aims: in Aim 1, we apply SCMDA to test if mutation frequency in normal mammary epithelial cells is increased in *BRCA1/2* mutation carriers relative to age-matched control women undergoing reduction mammoplasty purely for cosmetic reasons. In Aim 2 we define how the hormonal microenvironment of the mammary epithelium influence genomic instability to promote transformation by acquisition of a cascade of genetic event increasing the risk for tumor transformation. To do so we established a unique collection of primary organoids obtained from *BRCA1/2* mutation carriers or age matched controls which we exposed to estrogen levels mimicking those found in the mammary gland.

## 2. KEYWORDS:

Breast cancer, *BRCA1*, *BRCA2*, germline mutations, mutations, genomic instability, transformation, estrogen, 17b estradiol, inherited cancer, DNA damage

## 3. ACCOMPLISHMENTS:

### 3A Major goals of the project

**Specific Aim 1: Test if mutation frequency in normal mammary epithelial cells is increased in *BRCA1/2* carriers.**

**Major Task 1: to collect and isolate mammary epithelial cells from *BRCA1/2* mutation carriers and controls** During this funding period we completed the collection of tissues from women undergoing prophylactic risk-reducing mastectomy in women diagnosed with pathogenic germline mutations in *BRCA1* or *BRCA2* for the work proposed in Specific Aim 1 (**Table 1**).

***Table 1: Task 1 - Clinical characteristics of study subjects (Aim 1)***

| ID | Type | Age | Race | BMI | Co morbidities | Prior cancer history | Path report | parity |
|---|---|---|---|---|---|---|---|---|
| **M05** | *BRCA1+* | 39 | W | unk | BRCA1+ | no | Benign breast | n=3 fT |
| **M08** | | 42 | W | unk | BRCA1+ | no | Benign breast | n=2 fT |
| **M21** | | 42 | W | 29.8 | BRCA1+ | no | No gross lesions | unk |
| **M23** | | 37 | A | unk | BRCA1+ | | unk | unk |
| **M24** | | 45 | B | 39.8 | HTN, obesity, BRCA1+ | Uterine cancer | L/benign fibroadipose tissue | unk |
| **M27** | | 44 | W | unk | BRCA1+ | no | Benign breast | n=1 fT |
| **M07** | *BRCA2+* | 38 | W | unk | Personal history of cancer | yes | DCIS | 0 |
| **M28** | | 42 | W | unk | Personal history of cancer | yes | unk | n=3<br>n=2 ft<br>n=1<br>pre T |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **M01** | Control | 28 | W | 25.8 | no | no | No gross lesions | unk |
| **M10** | | 46 | W | 25.6 | no | no | No gross lesions | unk |
| **M20** | | 43 | W | 52.1 | HTN, obesity, GERD | no | No gross lesions | unk |
| **M22** | | 35 | B | 32.8 | Obesity | no | No gross lesions | unk |
| **M25** | | 33 | W | 28.1 | no | no | No gross lesions | unk |
| **M26** | | 47 | W | 32.6 | obesity | no | R/ focal papillary apocrine metaplasia; negative for atypical ductal hyperplasia or malignancy. L/mammary parenchyma with dilated benign ducts/cysts, papillary apocrine metaplasia; negative for atypical ductal hyperplasia or malignancy. | unk |
| **M31** | | 48 | W | 25.5 | no | no | No gross lesions | unk |
| | | | | | | | | |
| ***BRCA1+*** | | 41.5+/-3 | W=4 B=1 A=1 | 34.8+/-7 | no=0 yes=6 | no=4 yes=1 | | |
| ***BRCA2+*** | | 41+/-2 | W=2 | unk | no=0 yes=2 | no=0 yes=2 | | |
| **Controls** | | 40+/-7.9 | W=5 B=1 | 31.79+/-9.5 | no=4 yes=3 | no=7 yes=0 | | |
| | | **n.s.** | **n.s.** | **n.s.** | | **n.s.** | | |

**Major Task 2: to perform whole genome single cell sequencing with the goal to establish if mammary epithelial cells of *BRCA1/2* carriers have increased genomic instability relative to age matched controls**

We enrich for luminal or basal mammary epithelial cells after staining single cells with antibodies against CD49f and CD326 (EpCAM) as well as lineage specific markers CD31, CD45, CD235a, CD140b followed by sorting to separate basal epithelial cells (Lin- CD49f+/high EpCAM-/low) and luminal epithelial cells (Lin- CD49f-/low EpCAM+/high) into single cells. Globally we successfully amplified and sequenced 64 single cells in total from 15 individuals of which 31 cells were obtained from 8 women diagnosed with a *BRCA1/2* germline mutation. Libraries from each single cell were sequenced along patient matched bulk DNA used as a reference genome.

**Major Task 3: to run analytical pipelines and biostatistical analyses to evaluate genomic instability index across all experimental groups**

The raw sequencing reads were trimmed to remove adapter and low-quality nucleotides, aligned to the human reference genome (GRCh37 with decoy) using BWA. To correct mapping errors made by genome aligners, the known indels and SNPs were collected from the 1000 Genomes Project (phase I) and dbSNP (build 144). Then indels realignment and base quality score recalibration were performed based on known indels and SNPs via Genome Analysis Toolkit (GATK, version 3.5.0). Somatic mutations between each single cell and the corresponding bulk were identified by SCcaller (version 2.0.0) developed by Dr. Vijg's laboratory. The frequency of somatic SNVs per cell was estimated after normalizing genomic coverage and calling sensitivity: frequency of somatic SNVs per cell =( # somatic SNVs )/( (surveyed genome)/( total size of genome)*sensitivity). To identify mutation signature, we used non-negative matrix factorization (NMF) and confirmed the results with hierarchical Dirichlet process (hdp).

**Specific Aim 1 accomplishments**

Specific Aim 1 is nearly completed and a manuscript describing the findings has been submitted "*Single-cell analysis on somatic mutation burden in mammary cells of pathogenic BRCA1/2 mutation carriers*" (Journal of Clinical Investigation #148113-JCI-CC-1).

**Specific Aim 2: Determine the effects of estrogen (E2) exposure on mutation rate in *BRCA1/2* mutant cells.**

**Major Task 1: to establish an in-culture model of 3D mammary organoids exposed to 17β estradiol**

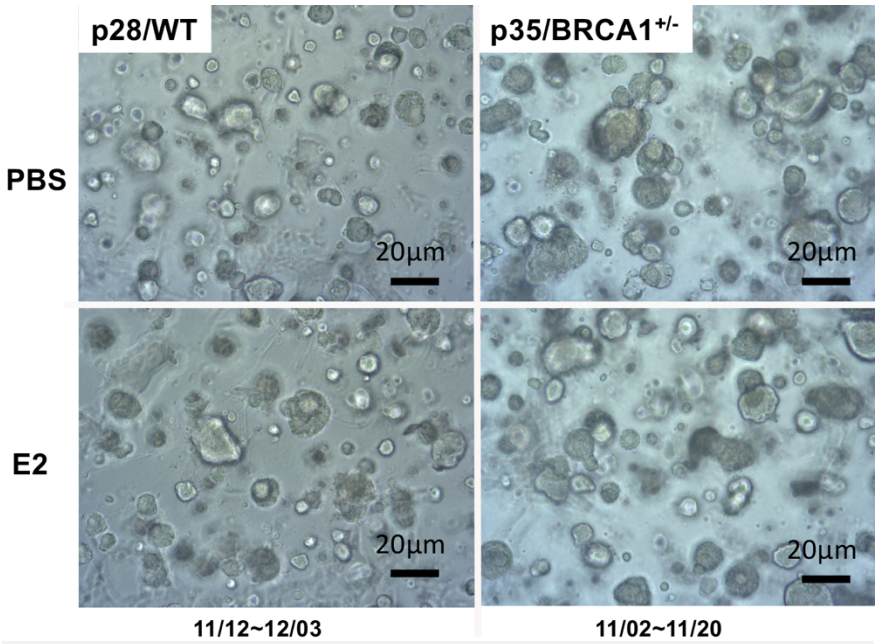


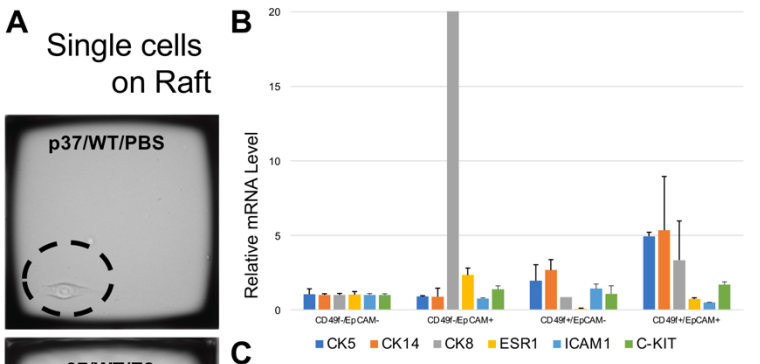

**Figure 1: In culture E2 exposure of primary mammary organoids.** Representative images of primary mammary organoids established from control women undergoing reduction mammoplasty for cosmetic reasons (left) or from prophylactic risk-reducing mastectomy because of a pathogenic germline mutation in *BRCA1* (right). Top panels depict organoids grown in control culture conditions; bottom panel depict organoids exposed to 20mM E2 for two weeks.

For establishing mammary organoids, we tested two 3D models: mammary organoids in which partially digested mammary epithelial tree tissue is embedded in extracellular matrix hydrogel (Matrigel) and spheroids organized from patients derived dissociated single cells grown in Matrigel. We opted to implement mammary spheroids for aim 2 because these cultures are established from a defined mixture of enriched mammary luminal and basal cells (ratio of 1:1) which greatly limits confounding factors due to patient-to-patient variability in cell type composition. In addition, we are able to culture the mammary spheroids over several passages and maintain their viability in culture for over 1 month, which allows for long term hormonal exposure this be needed to study the effect of 17β estradiol (E2) on genomic instability and transformation of mammary epithelial cells of *BRCA1/2* mutation carriers.

Mammary spheroids are being exposed to 20mM E2 reflecting the local levels estimated in the mammary tissue; this concentration remains within the physiological range detected in the blood of women in the third trimester of pregnancy (**Figure 1**).

**Major Task 2: Sequencing and QC of 3D organoids exposed to 17 β estradiol (E2) established from *BRCA1/2* carriers versus control**

Our pipeline for establishing the 3D organoid model of E2 exposure is now fully established and we have collected 12 samples for specific aim 2 (**Table 2**); efforts are continuing to expand the cohort. We were able to establish viable organoids form all the samples and those are currently at different stages of E2 treatment, which we maintain for 2 weeks with change of media every 48hrs. We demonstrated the ability to enrich for basal or luminal subtypes at the end of the E2 regimen and isolate single cells for SCMDA which is performed as described for specific aim 1 (**Figure 2**).




| CD49f/EpCAM pattern | Cell subtype | Marker genes |
|---|---|---|
| CD49f⁻/EpCAM⁻ | Stromal | N/A |
| CD49f⁻/EpCAM⁺ | LM | Ck8, ESR1 |
| CD49f⁺/EpCAM⁻ | Basal | CK5, CK14 |
| CD49f⁺/EpCAM⁺ | LP | ICAM1, c-kit |

**Figure 2: QC of mammary epithelial cells obtained from mammospheres post E2 exposure. A)** Single cells isolated from mammospheres plated on a cell raft retain viability. **B-C)** Expression levels from bulk RNA of markers specific to basal, luminal or stromal cells indicates that during the E2 regimen the mammospheres retain a composition of cells with a diverse lineage similar to what observed at plating.

**Major Task 3: LOH analysis to establish clonal evolution pattern of mutations in cells with wt and deleted *BRCA1* or *BRCA2* alleles.**

*Table 2: Task 1 - Clinical characteristics of study subjects (Aim 2)*

| ID | Type | Age | Race | Co morbidities | Prior cancer history | Path report |
|---|---|---|---|---|---|---|
| **O_M01** | *BRCA1* | 35 | W | BRCA1+ | no | Benign mammary parenchyma |
| **O_M02** | | 38 | B | BRCA1+ | no | |
| **O_M03** | | 37 | B | BRCA1+ | no | |
| **O_M04** | *BRCA2* | 26 | W | BRCA2+ | no | |
| **O_M05** | | 39 | W | BRCA2+ | no | |
| **O_M06** | Control | 23 | W | Obesity | no | |
| **O_M07** | | 42 | W | no | no | |
| **O_M08** | | 37 | B | no | no | |
| **O_M09** | | 28 | W | no | no | |
| **O_M10** | | 50 | B | no | no | |
| **O_M11** | | 22 | W | no | no | |
| **O_M12** | | 28 | B | no | no | |
| ***BRCA1*** | | 36.6+/-1.5 | W=1 B=2 | no=0 yes=3 | | |
| ***BRCA2*** | | 32.5+/-5 | W=2 B=0 | no=0 yes=3 | | |
| **Controls** | | 32.8+/-10.4 | W=4 B=3 | no=6 yes=1 | | |
| | | **n.s.** | **n.s.** | | | |

We performed preliminary analysis of MCF10A and htert-immortalized mammary epithelial cells (htert-IMEC) parental lines and isogenic clones containing the founder *BRCA1* pathogenic mutation 185delAG mapping to exon 2. We established that introduction of 185delAG increase the mutation frequency as measured by SCMDA. In order to study LOH of the wt allele in *BRCA1* heterozygous mutant cells under estrogen exposure parental and mutant isogenic clones have been exposed to 20mM E2 for three weeks and prepared for Fluorescent *in situ* Hybridization (FISH) analysis using custom probes mapping to *BRCA1*, *c-MYC*, *TERC* and *TP53*.

## 3B Opportunities for training and professional development

The analysis of the samples collected to complete specific aim 1 provided a new dataset to apply and develop analytical tools for students and postdoctoral trainees in the Dr. Vijg laboratory. Collection of primary mammary tissues provided postdoctoral trainees in Dr. Montagna's laboratory opportunities to master new protocols for 3D grow of primary mammary epithelial cells.

## 3C Dissemination of results of interest

Nothing to report.

## 3D Goals for next reporting period

**Specific Aim 1: Test if mutation frequency in normal mammary epithelial cells is increased in *BRCA1/2* carriers.**

The goal is to publish and disseminate to the scientific community the findings obtained from specific aim 1.

**Specific Aim 2: Determine the effects of estrogen exposure on mutation rate in *BRCA1/2* mutant cells.**

The primary mammary spheroids cultures are at different stages of the E2 regimen. For some cultures (n=4) we have already collected single cells from both mock treated and E2 exposed culture and library construction by SCMDA is underway. We anticipate submitting the libraries for sequencing in the next 2-4 months. We continue the collection of tissues from new patients with the goal to expand the cohort. Data analysis will follow as described for aim 1.

Evolution of clones with copy number alterations (CNAs) in candidate oncogenes or tumor suppressor genes (*BRCA1*, *c-MYC*, *TERC* and *TP53)* will be evaluated by FISH.

## 4. IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**
  Nothing to Report
- **What was the impact on other disciplines?**
  Nothing to Report
- **What was the impact on technology transfer?**
  Nothing to Report

- **What was the impact on society beyond science and technology?**
  Nothing to Report

## 5. CHANGES/PROBLEMS:

There were no major changes to the experimental approach.
In the previous reporting period, we encountered substantially delays as consequence of the pandemic caused by SARS-CoV-2. We were unable to collect primary tissues as originally proposed and therefore we were restricted in performing sequencing as planned. As elective surgeries have resumed across the United States, we have been able to complete the collection of samples proposed in Specific Aim 1; all libraries were prepared and submitted for sequencing. Likewise, tissue collection resumed for preparing organoids as proposed in Aim 2. Culture of organoids is now underway, and we do not anticipate major delays.

## 6. PRODUCTS:

Nothing to Report

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name: Jan Vijg
Project Role: PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-8457-9595
Nearest person month worked: 1.2
Contribution to Project: Dr. Vijg supervised the single cell experiments studies and closely interacted with Dr. Montagna to ensure the timely progress of the project. Dr. Vijg oversees the development and application of analytical tools for whole genome data analysis.

Name: Yujue Wang
Project Role: Computational Analyst
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 6.0
Contribution to Project: Dr. Wang is responsible for running the analytical pipelines for whole genome sequencing data and SCMDA analysis and perform QC on the data generated as part of aims 1 and 2.

Name: Moonsook Lee
Project Role: Research Tech
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 6.0
Contribution to Project: Mrs. Lee is responsible for isolation of single cells for SCMDA as well as whole genome amplification and QC to ensure that the DNA used for analysis retains unbiased amplification. She is also responsible for coordinating the shipment of samples for sequencing and ensure that the delivery of the sequencing data is timely.

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

  Yes, attached.

- **What other organizations were involved as partners?**

  Nothing to Report

## 8. SPECIAL REPORTING REQUIREMENTS

Nothing to Report

## 9. APPENDICES

## OTHER SUPPORT

**VIJG, JAN**

ACTIVE

2P30AG038072-13 (Barzilai) 08/15/20-05/31/25 0.48 calendar
NIH 4% effort
Einstein's Nathan Shock Center of Excellence in Basic Biology of Aging
The major goals are (1) to provide expert advice in the design, implementation and data analysis of high-throughput genomics experiments in aging, (2) performing special applications of high-throughput sequencing, such as single cell analysis, (3) higher-order modeling of aging-related data sets, and (4) the generation of a database of high-throughput genomics data relevant to aging research.
Role: Core Leader (Human Multi-Omics Core)

5P01AG047200-08 (Gorbunova) 05/01/19-04/30/24 0.6 calendar
NIH 5% effort
Comparative Genomics of Longevity
The major goal of this project is to study the possible effect of several potential mutation rate suppressors and study age-related mutation accumulation in liver and spleen of a short- and long-lived rodent species.
Role: Project 3 Project Leader

5P01AG017242-25 (Vijg) 04/01/99-04/30/24 1.8 calendar
NIH (entire) 15% effort
DNA Repair, Mutations and Cellular Aging
The goals of this project are to coordinate interaction between five well-established and well-funded research groups with complementary backgrounds, to focus upon the role of genome stability mechanisms in longevity and aging as possible sources of intervention.
Role: PI

3P01AG017242-25S1 (Vijg) 08/01/20-04/30/24 0.6 calendar
NIH 5% effort
DNA Repair, Mutations and Cellular Aging – Supplement (Project 2)
Title: Chromosome instability of glial cells in aging and Alzheimer's disease brain
The goal of this supplement is to use spatially-resolved transcriptomics to study genomic instability in the context of the brain microenvironment in the AD and control transentorhinal cortex (TEC) is to greatly increase our understanding of the mechanisms and consequences of genomic instability in aging.

3P01AG017242-25S2 (Vijg) 08/01/20-04/30/24 0.0 calendar
NIH 0% effort
DNA Repair, Mutations and Cellular Aging – Supplement (Project 1)
Title: Age-related transcription stress as novel underlying cause of Alzheimer's disease
The goal of this project is to test the hypothesis that human AD suffers from enhanced transcription stress by analyzing brains of normal and accelerated aging mice and in available transcriptomics datasets of AD patients to better understand the contribution of aging as the main risk factor for the onset of neurodegeneration, most notably protein aggregation.

(Barzilai) 06/01/16-05/31/23 0.12 calendar
The Glenn Foundation for Medical Research No salary support
The Paul F. Glenn Center for the Biology of Human Aging
This award is to support research into the basic biology of normal aging with the objective of developing interventions to delay its onset and progression thereby extending the healthy years of human life. This is a renewal application.
Role: Co-Project Leader

5R01AG053269-05 (Neretti/Secombe) 09/01/17-04/30/22 0.12 calendar NIH 1% effort
Activation of Endogenous Transposable Elements by Myc During Aging
The goal of this proposal is to determine the functional link between activation of endogenous TEs by the transcription factor Myc and changes to lifespan and aging.
Role: Co-I

5U19AG056278-06 (Vijg/Robbins) 09/15/17-04/30/22 1.92 calendar NIH (total) 16% effort
Genetic variant-based drug discovery targeting conserved pathways of aging
Project 1: Identification of rare variants and miRNAs associated with human longevity
The proposed project should greatly increase our understanding of the importance of the conserved pro-longevity pathways, identified and thus far mostly studied in model organisms, for human aging.
Role: PI

3U19AG056278-06S1 (Vijg/Robbins) 08/01/20-04/30/22 0.00 calendar NIH 0% effort
Genetic variant-based drug discovery targeting conserved pathways of aging – Supplement (Project 2)
Title: Altered IGF-1R as a potential therapeutic target for treatment of Alzheimer's disease
The proposed experiments will reveal if systemic aging (progeria) exacerbates AD and whether a sequence variant in IGF-1R identified in centenarians attenuates this.
Role: PI

3U19AG056278-06S1 (Vijg/Robbins) 08/01/20-04/30/22 0.00 calendar NIH 0% effort
Genetic variant-based drug discovery targeting conserved pathways of aging – Supplement (Project 2)
Title: SIRT6 as a potential therapeutic target for treatment of Alzheimer's Disease
These proposed experiments will document that increasing SIRT6 expression or ribosylation activity is therapeutic for AD and lead to the development of novel approaches to prevent or treat the disease. Role: PI

5U01ES029519-04 (Vijg/Spivack) 08/15/18-05/31/23 1.38 calendar NIH year 11.5% effort
Assessing genome sequence integrity in normal human cells
We propose to integrate, further optimize and validate these assays into the first next-generation sequencing-based mutation analysis system that provides comprehensive insight in genome sequence integrity in normal human cells.
Role: PI

3U01ES029519-04S1 (Vijg) 09/09/20-05/31/23 0.30 calendar s NIH /year 2.5% effort
Assessing genome sequence integrity in normal human cells – Supplement
Title: Cross-Validation of Genome Integrity Assays in Primary Human Cells
The major goal of this supplement is to test three assays and provide a robust approach to test the pitfalls in the original project and to delineate potential sources of error in our measurements and to establish a powerful platform for measuring genome integrity accurately.
Role: PI

3U01ES029519-04S2 (Vijg) 09/10/20-05/31/21 0.30 calendar NIH /year 2.5% effort
Assessing genome sequence integrity in normal human cells - Supplement
Title: Cost-effective assessment of somatic mutational load
The major goal of this supplement is to fill the gap in genetic toxicology methodology and will provide a practical tool for accurate cost-effective genome-wide assessment of somatic mutational load in a high throughput manner.
Role: PI

5U01HL145560-03 (Spivack) 01/01/19-12/31/22 1.8 calendar
NIH/NCI 15% effort Integrative, age-related changes in genome and epigenome in human lung in relation to smoking The major goal of this project is to comprehensively analyze human lung bronchial epithelium for both stochastic and adaptive changes in the genome, epigenome and transcriptome.
Role: Co-I

BC180689P1 (Montagna/Vijg) 05/01/19-04/30/22 1.18 calendar
DOD /year 9.86% effort
Somatic mutation rate as determinant of breast cancer penetrance in BRCA1/2 familial cases
Role: Partnering PI

1UH2AG064704 (Sebastiani and Perls) 07/01/19-06/30/24 0.6 calendar NIH
/year 5% effort
(No salary support)
Identifying protective omics profiles in centenarians and translating these into preventive and therapeutic strategies
Role: Co-Investigator

1RF1AG068908-01 (Montagna/Campisi) 09/30/20-08/31/24 0.30 calendar
NIH /year 2.5% effort
Genomic Instability-Induced Senescence in Brain Aging and Alzheimer's Disease
The goal of this project is to study genomic instability in non-neuronal cells of the cerebral cortex to understand how age-related accumulation of genomic instability contributes to Alzheimer's Disease.
Role: Co-I

No agency number 01/01/21-12/31/21 1.21 calendar
Albert Einstein College of Medicine 10.14% effort
Lola and Saul Kramer Chair in Molecular Genetics Endowed Fund
Salary support for Chairman of the Department from endowment funding.
Role: PI

<u>PENDING</u>
2P01AG017242-S3 05/01/22-04/30/23 0.12 calendar
NIH /year 1% effort
No salary support
DNA Repair, Mutations and Cellular Aging – Supplement (Project 2)
Title: Reimplementation and cloud deployment of software pipelines for age-related RNA and DNA changes
The overall objective of this proposed supplemental work by the Bioinformatics Core is to enhance the design, implementation, and deployment of SCcaller and iRAT.
Role: PI

<u>OVERLAP</u>
None.