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TITLE: Dissecting the Impact of Mutational Processes on Therapeutic Response in Ovarian Cancer

PRINCIPAL INVESTIGATOR: Dr. Sohrab Shah

CONTRACTING ORGANIZATION: Sloan Kettering Institute for Cancer Research

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14. ABSTRACT

High grade serous ovarian cancer (HGSOC) is the most lethal gynecological malignancy and while treatment with PARP inhibitors has shown some promise for patients with BRCA1/2 mutations these mutations remain an imperfect predictor for response. Our team has established structural variant-associated mutational processes for patient risk stratification: homologous recombination deficient (HRD) tumors, either associated with BRCA1 mutation-linked duplications (HRD-Dup) or BRCA2 mutation-linked interstitial deletions (HRD-Del), have a better prognosis than homologous recombination proficient tumors, including CDK-12 associated tandem duplications (TD) and foldback inversion (FBI) bearing tumors. Our hypothesis is that these **distinct mutational processes confer differential evolutionary capacity** on the malignant cells and impact treatment response.

Aim 1 proposed to *define the contemporary vs vestigial DNA defects resulting from specific structural mutational processes in HGSOC*. Analyzing mutational patterns in >22,000 single cell whole genomes (scDNA) from HRD and FBI tumors we observed widespread aneuploidy and continuous whole genome duplication in HR deficient cancer cells, whereas FBI tumors showed early ploidy fixation and large clone-specific variation in local high-level amplifications with substantial breakpoint variability, often impacting oncogenes and increasing genome plasticity.

In Aim 2 we planned to *define the functional impact of mutational processes on the transcriptome*. To probe the effect of mutational processes on gene expression and cellular phenotype we performed single cell RNA sequencing (scRNA-seq) on 42 HGSOC tumors with different mutational signatures. We observed increased inflammatory signaling and ongoing immunoediting in HRD tumors, while FBI tumors exhibited elevated TGFb signaling and immune exclusion. We also developed a workflow that includes the inference of clone-specific copy number alterations from scRNA data which will make it possible to dissect the clonal structure of tumors from transcription data.

The goal of Aim 3 is *to test structural mutational processes as a determinant of response to genotoxic therapy.* We have begun initial in vitro testing on cells derived from HGSOC PDXs with four classes of genotoxic drug and will continue to measure their effect in PDXs from tumors with different mutational signatures. Comparing genomic and transcriptomic profiles of resistant clones will elucidate the mechanism of resistance.

15. SUBJECT TERMS					
High grade serous ovarian cancer, mutational signatures, copy number variants, single cell genome, single cell transcriptome, drug resistance, tumor evolution					
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Unclassified	Unclassified	Unclassified			

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1. INTRODUCTION:

In this work we will test the hypotheses that the different mutational processes, which stratify HGSOC tumors into distinct subtypes with different prognostic outcomes, confer specific evolutionary capacity on malignant cells, including transcriptional pathway activation unique to each subtype. We will test the response to different classes of genotoxic drugs in PDX models derived from tumor subtypes to understand their specific mechanistic underpinning of drug resistance. The goal of our research is to discover how mutational processes shape tumor evolution and to gain mechanistic insight into the development of drug resistance that will guide targeted treatment options for patients.

2. KEYWORDS:

High grade serous ovarian cancer, mutational signatures, copy number variants, single cell genome, single cell transcriptome, drug resistance, tumor evolution

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aims	Timeline	Milestones achieved
Aim 1 To define the contemporary vs vestigial DNA defects resulting from specific structural mutational processes in HGSOC	Months	
Aim 1.1 Patient accrual and tumor tissue collection (n=50)	5-24	Protocol approved by MSK-IRB; collection from 42 patients
Aim 1.2 Single cell DNA Sequencing	5-24	Data from 42 patients
Aim 1.3 Identify active mutational processes through phylogenetic analysis	7-24	Defined for 36 patients from WGS data
Aim 1.4 Identify clone-specific variation in mutational processes	7-24	Established computational pipeline for allele-specific analysis of clones
Aim 2 To define the functional impact of mutational processes on the transcriptome	Months	
Aim 2.1 Single cell RNA-seq data generation and analytical pre-processing	5-24	scRNA-seq data generated from 41 patients
Aim 2.2 Measure intrinsic cellular variation and stability of activated DNA damage response (DDR) pathways linked to structural mutational processes	7-30	Decomposition of cell-specific DRR activation from scRNA-seq and integration with scDNA-seq
Aim 2.3 Estimate phenotypic diversity within and between genomic clones as a function of mutational signature	10-33	Established tools and pipeline, protocols are in place to analyze HGSOC samples
Aim 3 - Establish structural mutational processes as a determinant of response to genotoxic therapy		
Aim 3.1 Identify the working ranges for index PDX tumors	5-12	8 PDXs were tested with 4 classes of drugs
Aim 3.2 Establish the clonal vs transcriptomic relationships of drug sensitivity/resistance	13-36	ongoing
Aim 3.3 Determine resistance phenotypes and identifying cross resistance	19-30	ongoing
Aim 3.4. Identifying the effects of pairwise drug combinations	21-30	TBD

What was accomplished under these goals?

Aim 1 **To define the contemporary vs vestigial DNA defects resulting from specific structural mutational processes in HGSOC**

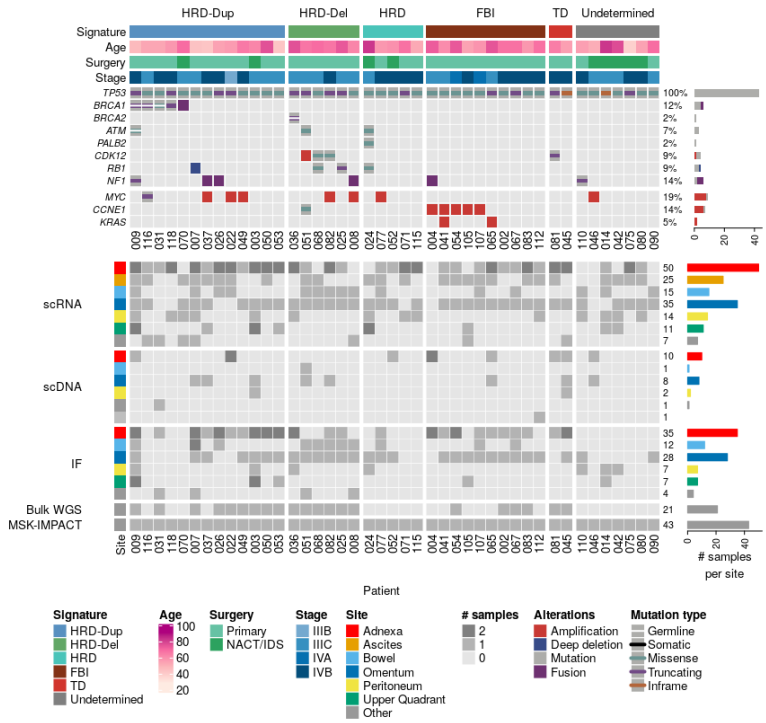

Fig. 1 Cohort overview Top panel: Oncoprint of selected somatic and germline mutations per patient. Bottom panel: sample and data inventory indicating number of co-registered datasets: scDNA-seq, scRNA-seq, bulk WGS and targeted panel sequencing (MSK-IMPACT).

We have collected multi-site tumor biopsies from **42 treatment-naïve HGSOC patients** working closely with the Disease Management Team (DMT) at MSK (see **Fig. 1** for an overview of the data collected for the cohort). For 36 samples we obtained whole genome sequencing (WGS) and employed a method established in the Shah group (*Funnell et al PLoS Comp. Bio. 2019*) to stratify patients by their mutational signatures into prognostically relevant groups: homologous recombination deficient (HRD) subtypes, characterized by BRCA1 mutation linked duplications (HRD-Dup) and BRCA2- variant linked deletions (HRD-Del), both of which are associated with a better prognosis. In contrast, homologous recombination competent groups are characterized by foldback inversion (FBI) and tandem duplications (TD) show worse outcome.

We have acquired scDNA-seq from 42 patients in the present cohort and used our newly developed tools and computational pipeline to reconstruct phylogenetic trees and separate ancestral from clade-specific and cell-specific events, corresponding to the earliest, later and most recent genomic damage. In addition, we designed SIGNALS, a method to quantify allele-specific copy number alterations (CNAs) at 0.5Mb resolution. We demonstrated the robustness of our pipeline on a study of 22,057 single cell genomes of triple negative breast tumors (TNBC) and HGSOCs (*Funnell et al. Nature 2022*). All subtypes displayed extensive subclonal heterogeneity, but FBI tumors showed higher rates of polyploidy and chromosomal missegregation, and they accrued gains at higher rates than HRD-Dup tumors (**Fig. 2**). These data demonstrate that mutational signatures determine the accrual patterns of CNAs with striking differences between HRD and FBI subtypes. One particularly noteworthy type of copy number variation were high-level amplifications (HLAMPs), with 10 or more copies of a segment, often accompanied by extensive variation in breakpoints between cells. This gave rise to a staircase-like pattern which we termed 'serrate structural variation' (SSV). FBI tumors had an almost 2fold higher HLAMP variance than other subtypes and, importantly, these HLAMPs often impacted the expression of known oncogenes (**Fig. 3**). In one example we could show that an HLAMP in a minor clone over the KRAS locus, corresponded to a higher KRAS expression, assessed via scRNA-seq and validated by immunofluorescence imaging on the primary tissue. These observations would not have been possible with bulk sequencing. Notably,

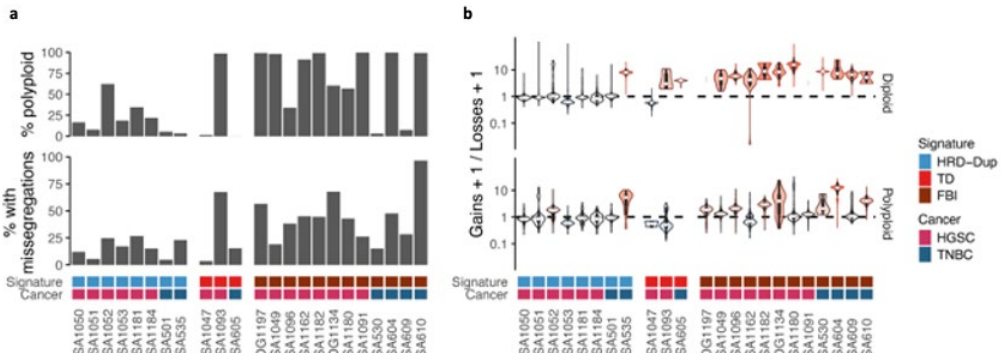

Fig. 2 Single tumor cell genome properties a) % of polyploid cells and missegration events **b)** Ratio of gains vs losses

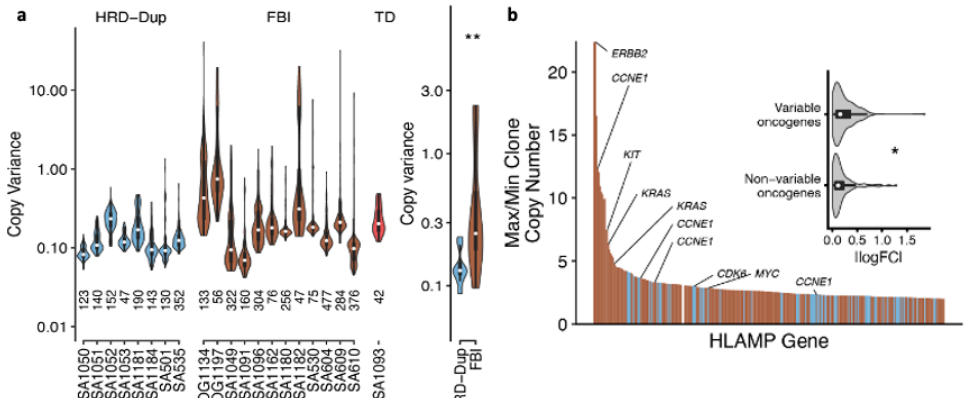

Fig. 3 HLAMP variance a) Copy number variance for HLAMPs **b)** Clone max/min copy number ration of oncogenes overlapping HLAMP regions. Inset shows distribution of gene expression in matched scRNA-seq data for the same genes.

the structural processes leading to the HLAMPs differed between the subtypes: while foldback inversions, as a result of breakage fusion bridge cycles, drove HLAMPs in FBI tumors, in HRD-Dup tumors they were associated with simple tandem duplications. In general, many clone-specific HLAMPs involved complex genomic structures, often involving multiple chromosomes.

Aim 2 **To define the functional impact of mutational processes on the transcriptome**

We obtained scRNA-data from 41 treatment-naïve patients, on flow-sorted cells enriched for either the CD45 negative tumor fraction or CD45 positive immune cells across 156 sites. In addition, we performed bulk whole genome sequencing (WGS) on a single site and FDA-approved clinical sequencing (MSK-IMPACT) (**Fig 1**, cohort overview). Single cell RNA (scRNA-seq) data defined epithelial, lymphoid, myeloid, stromal and tumor cells. Immune cells showed significant differences between anatomic sites, with adnexal samples depleted for T, B and dendritic cells, whereas distal sites were more infiltrated with immune cells (**Fig. 4**). A more granular view of the phenotypic states of immune cell types showed dysfunctional CD4+ and CD8+ T cells enriched in adnexal samples, together with more regulatory T cells, regulatory NK cells and immunosuppressive macrophages, consistent with chronic antigen exposure at the primary tumor site paired with higher immunomodulatory feedback. Focusing on tumor cells we observed increased JAK-STAT signaling in the adnexa of HRD tumors, but not in distal lesions. FBI tumors displayed more prominent TGFβ signaling in non-adnexal sites, compared to the primary tumor, implying that this pathway is activated during metastasis (**Fig. 5A**). Tumor subtypes also differed in their expression of major histocompatibility complex (MHC) genes. MHC class I and II genes were upregulated in HRD relative to FBI adnexal tumors, indicating a possible increase in antigen presentation (**Fig. 5B**).

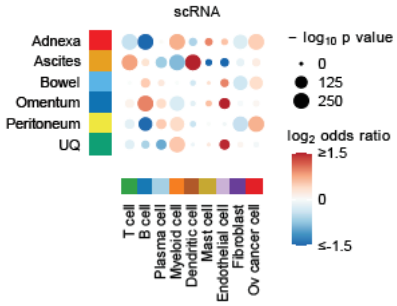

Fig. 4 Tumor microenvironment Site-specific enrichment of cell type composition

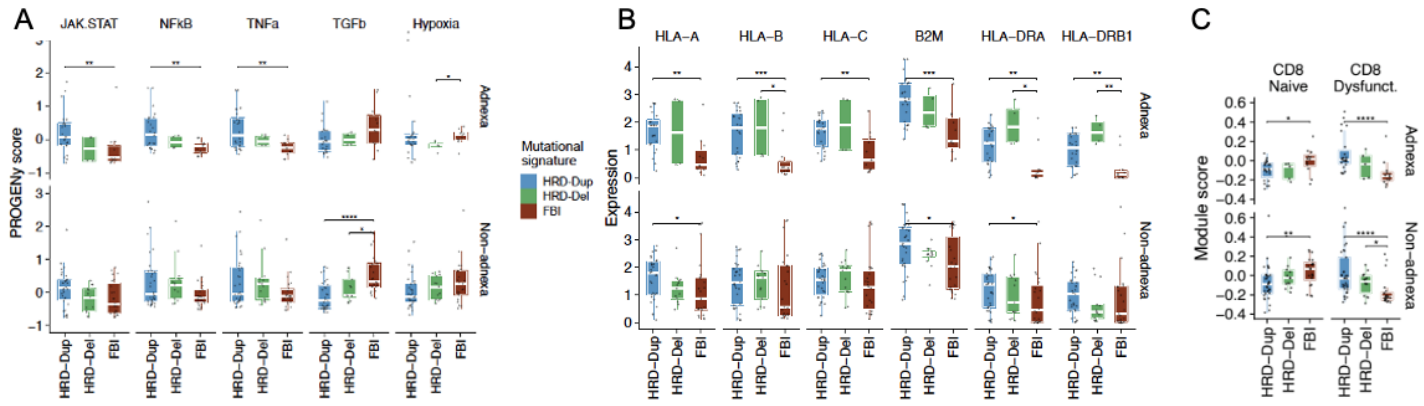

Fig. 5 Immune cell phenotypes as a function of mutational signature A) Signaling pathway activity scores **B)** HLA gene expression **C**) CD8 T cell state module scores.

We observed a compositional difference in the tumor microenvironment (TME) of the different tumor subtypes. FBIs were enriched for naïve/stem like and memory T cells, while depleted for dysfunctional T cells, HRD tumors

on the other hand were enriched for dysfunctional T cells (**Fig. 5C**). To investigate whether the variation in immunophenotypes originated in genomic differences at the HLA locus, we compared the loss of heterozygosity (LOH) at the 6p22.1 locus which encodes HLA class I and II genes, using SIGNALs. We observed frequent clonal LOH of 6p in HRD-Dup tumors, while in FBI patients subclonal LOH events were more common. Our results were recently accepted for publication in Nature (Vasquez-Garcia et al. 2022). Taken together our results provide a phenotypic map of the HGSOC tumor microenvironment that is driven by anatomic site as well as by mutational processes. We outline how HRD and FBI tumors have different mechanisms to evade immune recognition. While HRD tumors are immune infiltrated, they show a high rate of dysfunctional T cells, whereas FBI tumors restrict T cell infiltration and are immune excluded. These observations could prove critically important for treatment since different approaches will need to be taken to either re-activate or engage the immune system.

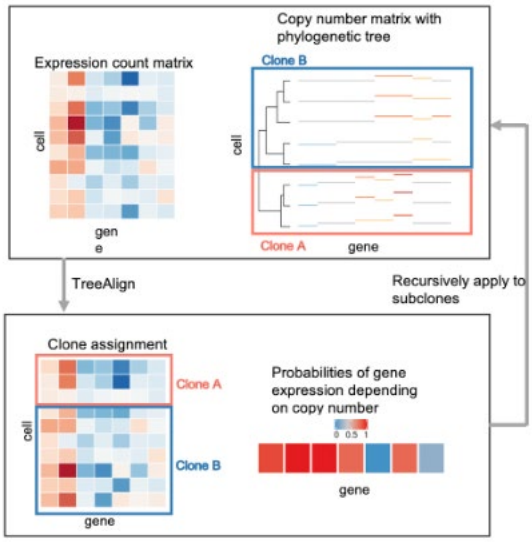

Fig. 6 Overview of `TreeAlign`

In our efforts to investigate individual tumors more in depth and link transcriptional responses to clone-specific copy number alterations (CNA) we developed `TreeAlign`, a modification of `CloneAlign` (Campbell et al Genome Biology 2019). `TreeAlign` combines a single cell expression count matrix with a scDNA-derived phylogenetic tree and its underlying CN matrix to obtain the clone assignment for each cell and derives the probability of CN-dependent gene expression (**Fig.6**). We found accurate predictions of dosage effects in highly expressed genes and saw that only 5-30% of differential gene expression between clones can be attributed to CN dosage effects. Applied to one HGSOC tumor we could delineate clone-specific expression patterns (**Fig. 7A**). By using both total and allele-specific CNA counts of the same tumor for phylogenetic tree reconstruction we were able to resolve allele-specific expression in subclones (**Fig. 7B**). We will now explore the genes that are differentially expressed between subclones and the pathways they belong to.

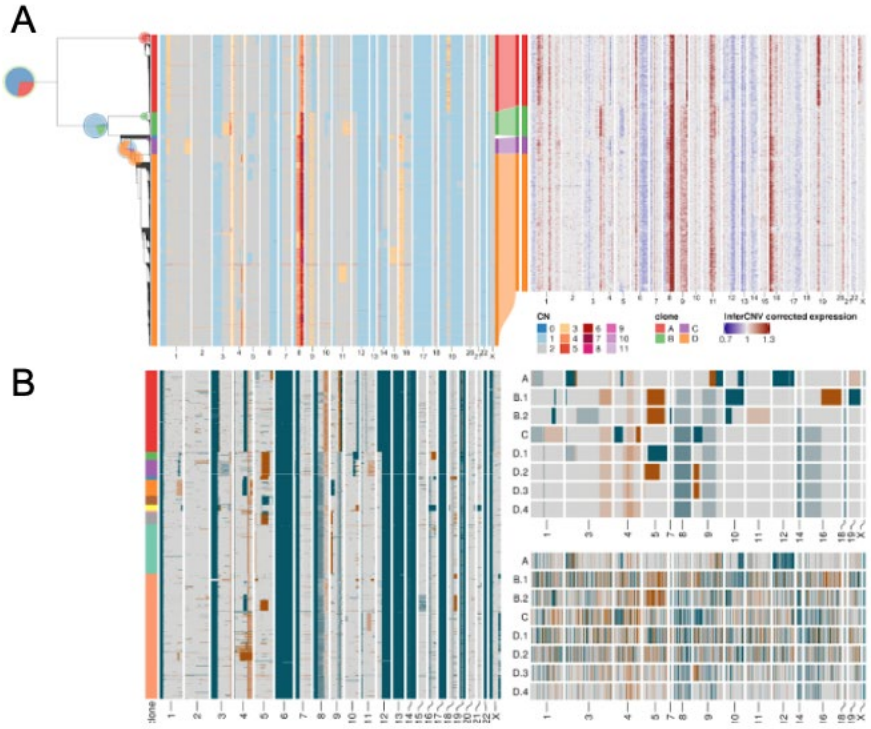

Fig. 7 Inferring clone assignment with `TreeAlign` A) Phylogenetic tree constructed with scDNA-data along with pie charts showing how TreeAlign assigns cell expression profiles to subtrees recursively. The pie charts are colored by the proportions of cell expression profiles assigned to downstream subtrees. The outer ring color of the pie charts indicates the current subtree. Heat maps of copy number profiles from scDNA (left) and InferCNV normalized expression profiles from scRNA (right). The sankey chart in the middle shows clone assignment from expression profiles to copy number based clones by `TreeAlign`. B) Heatmap of B allele frequencies in (left) HGSOC tumor estimated from scDNA data (upper right) subclone scDNA data, (lower right) subclone scRNA data.

Aim 3 **Establish structural mutational processes as a determinant of response to genotoxic therapy**

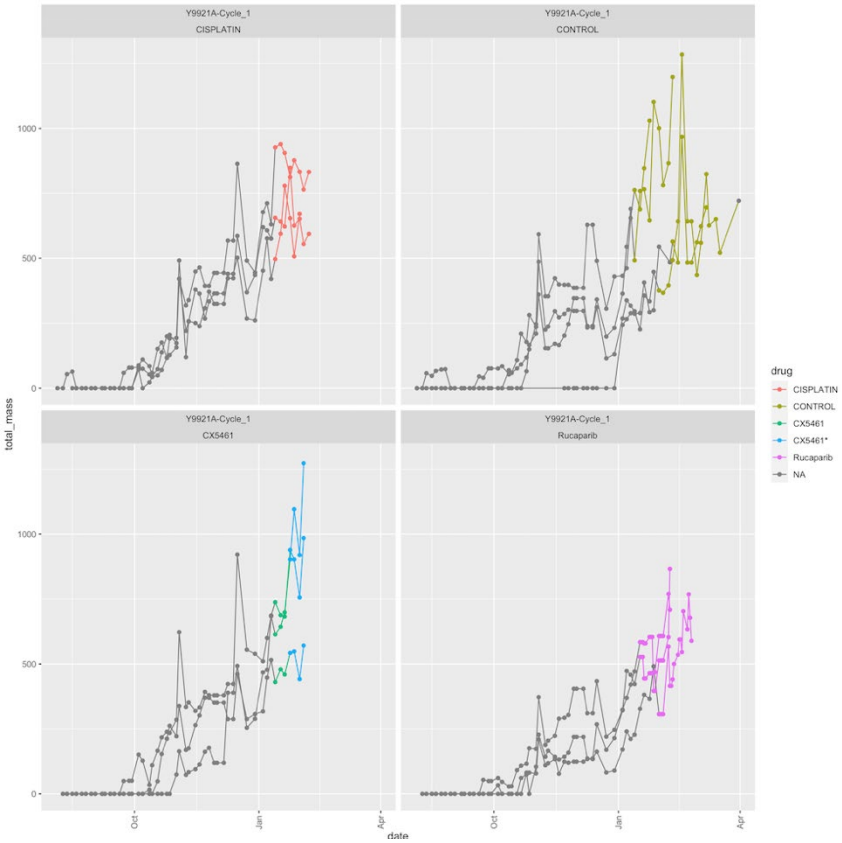

Fig. 7 FBI-derived PDX treated with the indicated drugs

We used our HGSOC-derived PDX collection, representing multi-site sampling from 15 patients, to begin evaluating the impact of mutational processes on the response to four classes of genotoxic drugs. Xenografts were transplanted subcutaneously into NRG mice (n=3 or 4 per group). We measured the tumors twice per week and once they reached ~500mm^3, mice were randomized to receive cisplatin (2mg/kg, intraperitoneal), CX5461 (62.5mg/kg, gavage), Rucaparib (10mg/kg, intraperitoneal) or control. Cisplatin and CX5461 doses were administered once every three days up to 8 doses, Rucaparib was administered daily for 5 days for up to 20 doses. Tumors were measured at each time of dosing. Mice were euthanized if tumors reached 1000mm^3 or following completion of dosing. In agreement with our original hypothesis that FBI tumors will show higher intrinsic resistance to treatment we see that the FBI-PDX tested showed no response to the three drugs (**Fig. 7**). We are in the process of evaluating the results of the PDX derived from HRD tumors.

What opportunities for training and professional development has the project provided?

Dr. Shah holds weekly meetings with all the participants in this grant including technicians, students and the post doctoral fellow. The post doctoral fellow whose work contributed to the goals in this grant presented at the AACR in April 2022, at the Workshop on Mathematical Modeling in Cancer, CIRM, France June 2022 and at Computational Cancer Biology in Bertinoro September 2022.

How were the results disseminated to communities of interest?

Drs. Shah is an active participant in and organizer of scientific meetings (see below for details). In addition, results were shared via BioRxiv preprints prior to publication and software is made available on GitHub.

What do you plan to do during the next reporting period to accomplish the goals?

To advance Aim 1 we will continue to recruit HGSOC patients and collect molecular data including single cell DNA and RNA sequences and WGS. We will determine the mutational signatures and resulting tumor subtypes for all patients from WGS and establish phylogenetic trees for tumors representing the different subtypes based on scDNA-seq. We will then determine the clone specific variation driven by mutational processes to gain insight into the genomic plasticity of each tumor.

For Aim 2 we will analyze scRNA-seq data of all patients to obtain robust transcriptional signatures for each tumor subtype and refine our computational tool to match scRNA-seq data to specific clones. Matching expression with genomic copy number variation in each clone we will be able to determine the impact of

genomic variation on gene expression and separate it from the effect of epigenomic regulators, i.e. factors that are not influenced by structural variations in the genome but could be due to changes in genome architecture.

To ensure progress for Aim 3 we will continue to derive cell lines from HGSOC- PDXs that represent the different subtypes, particularly homologous recombination competent tumors such as FBI and TD. We will then treat these PDX-derived cells with the genotoxic drugs and explore the genome and transcriptome of the resulting clones at the single cell level. These data will provide a view of the resistance phenotype and we will compare the result to the genomic and transcriptomic landscapes we discovered in Aims 1 and 2.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

In the course of this work, we established computational pipelines that will be valuable to basic clinical research beyond ovarian cancer, extending to different diseases. Our tools allow the interrogation of single cells, the basic unit of disease, and will bring to light how changes at the single cell level drive the development of disease and resistance to treatment. Our platforms allow the characterization of cells at the genome level, elucidating how mutations reshape genomic content and the effect this has on the ability of clones to grow. Knowing that genomic changes only account for part of cellular evolution we also profile gene expression at the single cell level and thus provide a framework for the comprehensive analysis of clones. Applied to ovarian cancer our tools and approaches will lead to an in depth understanding of the particular drivers of cancer subtypes and highlight biomarkers that can stratify patients by subtype, each associated with a different risk profile. It will also provide candidates for subtype-specific intervention and a treatment plan that is geared towards the individual molecular makeup of a tumor, exploiting its weaknesses for an improved outlook for patients with high grade serous ovarian cancer.

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?

Upon completion of the project, we will have laid the groundwork for better risk-stratification of high grade serous ovarian cancer patients using genomic changes in tumors as biomarkers. This concept of 'genome as biomarker' will likely impact other diseases that are driven by distinct mutational processes and lead to the development of targeted therapies and more personalized treatment. Work like ours will raise public awareness of the importance of genomic profiling and make a case for incorporating clinical sequencing into standard of care to ensure a more targeted disease management.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

.

While patient accrual was halted during part of 2020 due to Covid, we have resumed recruitment and do not anticipate problems with consenting new patients.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report

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:

- **Publications**

  Journal publications

  Ignacio Vazquez-Garcia,*, Florian Uhlitz,*, Nicholas Ceglia, Jamie L.P. Lim, Michelle Wu, Neeman Mohibullah, Arvin Eric B. Ruiz, Kevin M. Boehm, Viktoria Bojilova, Christopher J. Fong, Tyler Funnell, Diljot Grewal, Eliyahu Havasov, Samantha Leung, Arfath Pasha, Druv M. Patel, Maryam Pourmaleki, Nicole Rusk, Hongyu Shi, Rami Vanguri, Marc J. Williams, Allen W. Zhang, Vance Broach, Dennis Chi, Arnaud Da Cruz Paula, Ginger J. Gardner, Sarah H. Kim, Matthew Lennon, Kara Long Roche, Yukio Sonoda, Oliver Zivanovic, Ritika Kundra, Agnes Viale, Fatemeh N. Derakhshan, Luke Geneslaw, Ana Maroldi, Rahelly Nunez, Fresia Pareja, Anthe Stylianou, Mahsa Vahdatinia, Yonina Bykov, Rachel N. Grisham, Ying L. Liu, Yulia Lakhman, Ines Nikolovski, Daniel Kelly, Jianjiong Gao, Andrea Schietinger, Travis J. Hollmann, Samuel F. Bakhoum, Robert A. Soslow, Lora H. Ellenson, Nadeem R. Abu-Rustum, Carol Aghajanian, Claire F. Friedman, Andrew McPherson, Britta Weigelt, Dmitriy Zamarin, **Sohrab P. Shah**. Immune and malignant cell phenotypes of ovarian cancer are determined by distinct mutational processes (Accepted in principle at Nature) Available from: https://www.biorxiv.org/content/10.1101/2021.08.24.454519.abstract

  Tyler Funnell, Ciara H O'Flanagan, Marc J Williams, Andrew McPherson, Steven McKinney, Farhia Kabeer, Hakwoo Lee, Sohrab Salehi, Ignacio Vázquez-García, Hongyu Shi, Emily Leventhal, Tehmina Masud, Peter Eirew, Damian Yap, Allen W Zhang, Jamie L P Lim, Beixi Wang, Jazmine Brimhall, Justina Biele, Jerome Ting, Vinci Au, Michael Van Vliet, Yi Fei Liu, Sean Beatty, Daniel Lai, Jenifer Pham, Diljot Grewal, Douglas Abrams, Eliyahu Havasov, Samantha Leung, Viktoria Bojilova, Richard A Moore, Nicole Rusk, Florian Uhlitz, Nicholas Ceglia, Adam C Weiner, Elena Zaikova, J Maxwell Douglas, Dmitriy Zamarin, Britta Weigelt, Sarah H Kim, Arnaud Da Cruz Paula, Jorge S. Reis-Filho, Spencer D. Martin, Yangguang Li, Hong Xu, Teresa Ruiz de Algara, So Ra Lee, Viviana Cerda Llanos, David G. Huntsman, Jessica N. McAlpine, IMAXT consortium, **Sohrab P. Shah**, Samuel Aparicio. Single-cell genomic variation induced by mutational processes in cancer. Nature 2022; DOI10.1038/s41586-022-05249-0 https://www.nature.com/articles/s41586-022-05249-0

  Other publications, conference papers and presentations.

Conferences Dr. Shah chaired or co-chaired
1) Panelist, NYSCF Panel Discussion on Women's Reproductive Cancers, March 3, 2022
2) Session Chair: AACR Annual Meeting, Single-cell and Spatial Profiling of Tumor Cells and the Immune Microenvironment, April 11, 2022
3) Vice-chair: Gordon Research Conference: Single-Cell Cancer Biology, Discussion Leader - Computational Methods for Single-cell Analysis, June 12-16, 2022
4) Organizer: Computational Biology Bertinoro Meeting 2022, September 12-16, 2022
5) External Advisory Board Meeting - Fred Hutch Cancer Center Translational Data Science Integrated Research Center, October 18-20, 2022

Dr. Shah's invited presentation
1) "Genomic instability and mutational processes at single cell resolution", UCLA - Leaders in the Field (Virtual), November 18, 2021
2) "Revealing the hidden genomic cell-to-cell variation in cancer", Salk Institute Thursday Seminar Series (Virtual), February 10, 2022
3) "Decoding the hidden states of genome variation cancer cell populations", Princess Margaret Seminar Series (Virtual), February 17, 2022
4) "Cell to cell variation in the context of genomic instability in cancer", University of Toronto – Presentation of Computational Program Students and Faculty, May 20, 2022
5) "Single cell whole genome sequencing to dissect mutational processes and clonal fitness in cancer", EACR Bioinformatics in Cancer, May 19, 2021
6) "The role of genomic instability in shaping immunophenotypes in ovarian cancer", CRUK Symposium of Cancer Evolution, September 2021
7) "Mutational processes as determinants of immunophenotypes in ovarian cancer", AACR Virtual Special Conference, September 2021

- **Website(s) or other Internet site(s)**

  Data will be publicly disseminated upon publication of the results

- **Technologies or techniques**

  To map scRNA-seq data to scDNA-derived clones we modified the tool `CloneAlign` (Campbell et al. Genome Biology 2019) to improve accuracy and the ability to infer gene dosage. The `TreeAlign` tool can be found at Github: ttps://github.com/AlexHelloWorld/clonealign_pyro

- **Inventions, patent applications, and/or licenses**

  Nothing to report

- **Other Products**
  Software: `TreeAlign`

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Dr. Sohrab Shah
Project Role:	Principal Investigator
Researcher Identifier (ORCID):	0000-0001-6402-523X

Nearest person month worked:	0.24
Contribution to Project:	Dr. Shah is leading the overall program and is mentoring the trainees focusing on Aims 1 and 2.
Funding Support:	N/A

Name:	Marc Williams
Project Role:	Post doctoral fellow
Researcher Identifier (ORCID):	0000-0001-5524-4174
Nearest person month worked:	2
Contribution to Project:	Dr. Williams developed the tool for allele-specific CNA analysis and co-directed work in Aim 1 of the project.
Funding Support:	N/A

Name:	Hongyu Shi
Project Role:	Graduate Student
Researcher Identifier (ORCID):	0000-0002-8541-6261
Nearest person month worked:	12
Contribution to Project:	Hongyu Shi leads the analysis of scRNA-seq data generated for Aim 2, she will be supported in the clinical interpretation of the data by Dr. Aghajanian. Ms Shi is fully supported by her PhD program and will base her PhD dissertation on the work described in this proposal.
Funding Support:	N/A

Name:	Juliana Niyazov
Project Role:	Research Technician
Researcher Identifier (ORCID):	N/A
Nearest person month worked:	4
Contribution to Project:	Ms Niyazov was a research technician embedded in the Operating room, receiving samples from the surgeon and processing them under the supervision of Dr. Weigelt.
Funding Support:	

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 the changes in active other support for PI and senior/key personnel attached as appendix.

What other organizations were involved as partners?

Dr. Samuel Aparicio (ORCID: 0000-0002-0487-9599), Head of Molecular Oncology at BC Cancer, Vancouver, Canada, oversees the work in Aim 3 which involves the analysis of previously established patient-derived xenografts (PDXs) from HGSOC patients.

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 SUPPORT

SHAH, SOHRAB
Commons ID: S_SHAH

CURRENT

(NEW)
*Title: Dissecting Ovarian Cancer Tumor-Immune Microenvironments Through 3D In Situ Molecular Profiling
*Major Goals: In this proposal we pursue the hypothesis that the different HGSOC subtypes and the different tumor sites within the same patient create unique microenvironments and tumor architectures that drive the avoidance or inactivation of immune surveillance.
*Status of Support: Active
Project Number: W81XWH-22-1-0759
Name of PD/PI: Shah, S
Source of Support: Congressionally Directed Medical Research Programs
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 9/30/2022 - 9/29/2025
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
1.	2023	0.60 calendar
2.	2024	0.60 calendar
3.	2025	0.60 calendar

Grant official: Juan A. Rodriguez

(NEW)
*Title: Identifying drivers of immune evasion in diffuse-type gastric cancer
*Major Goals: The goals of this proposal are to identify mechanisms of immune evasion in locally advanced and metastatic diffuse-type gastric cancer and to develop a mouse model of diffuser gastric cancer to test whether altering the extracellular metabolic environment can enhance immune surveillance and improve surgical outcomes.
*Status of Support: Active
Project Number: AWD00001736
Name of PD/PI: Vardhana, S
Source of Support: Cycle for Survival
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 4/1/2022 - 3/31/2024
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
1.	2023	0.60 calendar
2.	2024	0.60 calendar

Grant official: Andrew Murphy

(NEW)
*Title: Inferring mutational processes and patient stratification from standard-of-care clinical imaging
*Major Goals: We plan to use data created in the course of routine clinical care, such as histopathological slides of tumor tissue, computed tomography (CT) scans and clinical information to improve the prediction of patient outcome.
*Status of Support: Active

Project Number: 891729
Name of PD/PI: Shah, S
Source of Support: Ovarian Cancer Research Alliance
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 1/1/2022 - 12/31/2024
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
1.	2022	1.20 calendar
2.	2023	1.20 calendar
3.	2024	1.20 calendar

Grant Official: Audra Moran

*Title: Integrating tumor genetics and microenvironment as predictors of response and resistance to immunotherapy in ovarian cancer
*Major Goals: Specific Aim 1: Identify the underlying genomic instability phenotypes in each treatment group and their association with response and resistance to immunotherapy; Specific Aim 2: Define the pathways associated with the respective genomic instability phenotypes and their association with response and resistance to immunotherapy; Specific Aim 3: Define the tumor microenvironment composition and architecture and TCR repertoire parameters associated with the underlying genomic instability phenotype.
*Status of Support: Active
Project Number: W81XWH2110561 (Subaward No. 582539)
Name of PD/PI: Powell, D (site: Zamarin, D)
Source of Support: Univ. of Pennsylvania (Prime: Congressionally Directed Medical Research Programs)
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 8/1/2021 - 7/31/2024
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
2.	2023	0.60 calendar
3.	2024	0.60 calendar

Grant Official: Catherine Sanchez

(NEW)
*Title: Understanding, assessing, and intercepting ovarian carcinogenesis.
*Major Goals: The overall goal of our project is to fully leverage this new paradigm by applying an array of advanced technologies to ask fundamental biological and clinical questions, develop computational methods and new devices, and devise clinical approaches that are specifically tailored to identify, characterize, and intercept these STIC lesions, in both high- and average-risk women, before they disseminate and produce HGSC.
*Status of Support: Active
Project Number: AWD00001704 (MOD)
Name of PD/PI: Aghajanian, C
Source of Support: Break Through Cancer
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 1/1/2022 - 12/31/2024
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
1.	2022	0.60 calendar
2.	2023	0.60 calendar
3.	2024	0.60 calendar

Grant Official: Bill Hulme

(NEW)
*Title: Targeting Ovarian Cancer Minimal Residual Disease (MRD) Using Immune and DNA Repair Directed Therapies
*Major Goals These observations set the stage for this proposal whose overarching aim is to transform the current treatment landscape by developing more effective therapies based on therapeutic vulnerabilities in the MRD phase of ovarian cancer.
*Status of Support: Active
Project Number: AWD00001694 (MRD)
Name of PD/PI: Aghajanian, C
Source of Support: Break Through Cancer
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 1/1/2022 - 12/31/2024
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
1.	2023	0.60 calendar
2.	2024	0.60 calendar
3.	2024	0.60 calendar

Grant Official: Bill Hulme

*Title: Immunotype Identifies Immune Checkpoint Blockade Responders: dissecting the mechanism and understanding the scope and impact of immunotype across diverse cancer patient populations.
*Major Goals: Our overarching aim is to develop a clinical biomarker for patients receiving ICB that will impact patient care and may inform the development of novel immunotherapy treatments or combinations.
*Status of Support: Active
Project Number: T2021-007
Name of PD/PI: Callahan, M
Source of Support: V Foundation for Cancer Research
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 11/1/2021 - 10/31/2024
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
1.	2022	0.21 calendar
2.	2023	0.00 calendar
3.	2024	0.00 calendar

Grant Official: Carole Wegner, PhD

*Title: The MSK Genomic Data Analysis Center for Tumor Evolution
*Major Goals: The MSK Genomic Data Analysis Center for Tumor Evolution will create a software platform for analysis of DNA mutations in cancer to help researchers and clinicians better understand why cancers often relapse. As cancer is a disease that changes at the cellular level over time, with some cells killed by treatment while others survive, we need to understand which mutations lead to treatment failure in specific patients. We expect that with improved tools that can measure, monitor and interpret changes in disease over time, we will make advances that allow for better management of cancer and prevention of relapse.
*Status of Support: Active
Project Number: 1 U24 CA264028-01
Name of PD/PI: Schultz, N / Shah, S

Source of Support: National Institutes of Health
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 9/1/2021 - 8/31/2026
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
1.	2022	0.96 calendar
2.	2023	1.20 calendar
3.	2024	1.20 calendar
4.	2025	1.20 calendar
5.	2026	1.20 calendar

Grant Official: YANG, LIMING

*Title: Dissecting the impact of mutational processes on therapeutic response in ovarian cancer
*Major Goals: We will use single cell whole genome sequencing (scDNA-seq) from n=50 HGSOC to identify clonal populations, their specific copy number architectures and evolutionary properties, and use quantitative approaches to distinguish phylogenetic attributes of contemporary structural alterations to demarcate active mutational processes from vestigial events.
*Status of Support: Active
Project Number: W81XWH-20-1-0565
Name of PD/PI: Shah, S
Source of Support: Congressionally Directed Medical Research Programs
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 9/30/2020 - 9/29/2023
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
2.	2022	0.24 calendar
3.	2023	0.24 calendar

Grant Official: Jennifer Fox

*Title: Diagnosis and Treatment of APOBEC Mutagenesis in Metastatic Breast Cancer (Bioinformatics Core)
*Major Goals: Breast cancers can show various types of unstable genomes that can be readily identified by DNA sequencing. These cancers are the most lethal subtypes of breast cancer at the present time. The SPORE is designed to improve the outcome of patients by using the latest in genomic diagnostic tools and pathological evaluations, plus extend this new knowledge for therapeutic approaches to exploit the underlying genomic instability.
*Status of Support: Active
Project Number: 1P50CA247749-01
Name of PD/PI: Powell, S / Shah, S
Source of Support: National Cancer Institute
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 8/13/2020 - 7/31/2025
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
2.	2022	0.60 calendar
3.	2023	0.60 calendar
4.	2024	0.60 calendar
5.	2025	0.60 calendar

Grant Official: WALTON, TAMARA

*Title: Center for Integrated Cellular Analysis
*Major Goals: We will integrate single cell whole genome data with single cell RNASeq from the same samples in order to assess the impact of tetraploidization and chromosomal missegregation on Type I interferon response mediated via cytosolic DNA sensing pathway activation and adaptive immune response through microenvironment analysis.
*Status of Support: Active
Project Number: 5RM1HG011014-03 (Subaward No. 2019-0014-MSK-01)
Name of PD/PI: Satija, R
Source of Support: National Institutes of Health
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 6/1/2020 - 3/31/2025
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
3.	2023	0.60 calendar
4.	2024	0.60 calendar
5.	2025	0.60 calendar

Grant Official: PAZIN, MICHAEL J

*Title: Profiling co-evolution of ovarian cancer and its immune microenvironment
*Major Goals: Aim 1: Establish how structural mutational processes impact clonal evolution properties in a pre-treatment setting. Aim 2: Establish how structural mutational processes differentially impact innate and adaptive immune responses. Aim 3: Investigate the impact of chemotherapy with or without immunotherapy on coevolution of immune and malignant cells in the periphery and tumor microenvironment.
*Status of Support: Active
Project Number: 648007
Name of PD/PI: Shah, S
Source of Support: Ovarian Cancer Research Fund
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 1/1/2020 - 12/31/2022
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
3.	2022	1.20 calendar

Grant Official: Sarah DeFeo

*Title: LesLois Shaw Foundation Fund
*Major Goals: The objective is to develop and apply advance machine learning and computational techniques to infer three-dimensional properties over time associated with HGSOC diversity derived from multi-modal measurements. This includes properties of malignant clone diversity from single-cell whole-genome sequencing (scWGS) and mutational processes derived from scWGS.
*Status of Support: Active
Project Number: AWD-GC-243310
Name of PD/PI: Shah, S
Source of Support: Philanthropic Funds
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 11/26/2018 - 12/31/2022
*Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
3. 2022 0.24 calendar
Grant Official: Julia Miller Black

*Title: Exploiting new patterns of genome damage in triple negative breast cancer
*Major Goals: We will study how mutations in the DNA of cancer cells in triple negative breast cancer can be used to discover new groups of patients. We will use state-of-the–art DNA sequencing technologies to measure the DNA of individual cancer cells and create an ultra-detailed picture of how these cancers are changing over time in hopes that they will reveal previously unseen patterns of DNA mutations in triple negative breast cancers, thereby providing new directions to pursue treatment approaches.
*Status of Support: Active
Project Number: AWD-GC-260914
Name of PD/PI: Shah, S
Source of Support: Susan G. Komen Breast Cancer Foundation
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 10/1/2018 - 9/30/2022 NCE
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
3. 2022 0.60 calendar
Grant Official: Paula Schneider

*Title: Grand Challenge IMAXT: Imaging and molecular annotation of xenografts and tumors
*Major Goals: Our integrated approach will produce faithful three-dimensional representations of tumours and their host environments, wherein each cell is identified and molecularly annotated. These models will be presented in an interactive, virtual reality (VR) framework.
*Status of Support: Active
Project Number: AWD-GC-243330
Name of PD/PI: Shah, S
Source of Support: Cancer Research UK
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 5/1/2018 - 4/30/2023
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
5. 2023 0.48 calendar
Grant Official: Jess Sutcliffe

INACTIVE

*Title: Gynecological Cancer Center of Excellence
*Major Goals: The Shah Research Team will perform two main areas of data analysis in the context of this subaward: whole genome sequencing analysis and correlative proteomic analysis. Work will be overseen by Dr. Sohrab Shah, Chief Computational Oncology, Memorial Sloan Kettering Cancer Center (MSKCC).
*Status of Support: Completed
Project Number: HU0001-2-02-0033 (sub# 66262)
Name of PD/PI: Casablanca, Y (site: Shah, S)
Source of Support: Henry M. Jackson Foundation/Congressionally Directed Medical Research Programs
Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 5/1/2020-3/31/2022
*Total Award Amount (including Indirect Costs):
Person Months: 0.24 calendar
Grant official: Afrin Khan

*Title: Integration of Radiomic Analysis into the Multi-Modal Profiling of High-Grade Serous Ovarian Cancer
*Major Goals: Our primary objective here is to establish methodology for computing image-based spatial habitats from PET/MRI, and, subsequently, perform hypothesis-generating correlation of image-based features with the richly profiled molecular measures from tissue samples of the same patients.
*Status of Support: Completed
Project Number: MSKCC Society - Nikolovski
Name of PD/PI: Nikolovski, I
Source of Support: MSKCC Society
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 9/1/2019 - 2/14/2022
*Total Award Amount (including Indirect Costs):
Person Months: 0.60 calendar
Grant official: Meg Horovitz

AGHAJANIAN, CAROL
Commons ID: AGHAJANIANCMSKCC

CURRENT

NEW

*Title: Ovarian Cancer - Understanding, Assessing, and Intercepting Ovarian Carcinogenesis
*Major Goals: The overall goal of our project is to fully leverage this new paradigm by applying an array of advanced technologies to ask fundamental biological and clinical questions, develop computational methods and new devices, and devise clinical approaches that are specifically tailored to identify, characterize, and intercept these STIC lesions, in both high- and average-risk women, before they disseminate and produce HGSC.
*Status of Support: Active
Project Number: BTC MOD Award
Name of PD/PI: Aghajanian, C
Source of Support: Break Through Cancer
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 1/1/2022 - 12/31/2024
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.30 calendar
2. 2023	0.30 calendar
3. 2024	0.30 calendar

Grants officer: Bill Hulme

NEW

*Title: Break Through Cancer - Targeting Ovarian Cancer Minimal Residual Disease (MRD) Using Immune and DNA Repair Directed Therapies
*Major Goals: Our goal is to transform the care of women with ovarian cancer by developing unprecedented capabilities for understanding and targeting MRD.
*Status of Support: Active
Project Number: BTC MRD Award
Name of PD/PI: Aghajanian, C
Source of Support: Break Through Cancer
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 1/1/2022 - 12/31/2024
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.30 calendar
2. 2024	0.30 calendar
3. 2024	0.30 calendar

Grants officer: Bill Hulme

*Title: Molecular Profiles of Endometrial Carcinoma in Black Women
*Major Goals: Aim 1: Characterize the histologic and somatic genetic landscape of ECs in black women. Aim 2: Define the frequency of Lynch syndrome in black women with EC. Aim 3: Determine benefit and prognostic
value of genomic profile on survival in black women with EC.
*Status of Support: Active
Project Number: 2020 Cycle for Survival's Equinox Innovation Award in Rare Cancers
Name of PD/PI: Brown, C
Source of Support: Cycle for Survival
Primary Place of Performance: Sloan Kettering Institute For Cancer Research

Project/Proposal Start and End Date (MM/YYYY): 1/1/2021 - 12/31/2022
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
2.	2022	0.24 calendar

Grants officer: Kathleen Bourke

*Title: Dissecting the impact of mutational processes on therapeutic response in ovarian cancer
*Major Goals: We will use single cell whole genome sequencing (scDNA-seq) from n=50 HGSOC to identify clonal populations, their specific copy number architectures and evolutionary properties, and use quantitative approaches to distinguish phylogenetic attributes of contemporary structural alterations to demarcate active mutational processes from vestigial events.
*Status of Support: Active
Project Number: W81XWH-20-1-0565
Name of PD/PI: Shah, S
Source of Support: Congressionally Directed Medical Research Programs
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 9/30/2020 - 9/29/2023
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
2.	2022	0.24 calendar
3.	2023	0.24 calendar

Grants officer: Jennifer Fox

*Title: Profiling co-evolution of ovarian cancer and its immune microenvironment
*Major Goals: Aim 1: Establish how structural mutational processes impact clonal evolution properties in a pre-treatment setting. Aim 2: Establish how structural mutational processes differentially impact innate and adaptive immune responses. Aim 3: Investigate the impact of chemotherapy with or without immunotherapy on coevolution of immune and malignant cells in the periphery and tumor microenvironment.
*Status of Support: Active
Project Number: 648007
Name of PD/PI: Shah, S
Source of Support: Ovarian Cancer Research Fund
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 1/1/2020 - 12/31/2022
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

	Year (YYYY)	Person Months (##.##)
3.	2022	0.24 calendar

Grants officer: Sarah DeFo

*Title: Network Lead Academic Participating Site: Memorial Sloan Kettering Cancer Center
*Major Goals: This goal will be achieved through the continued successful development and execution of definitive, randomized, clinical treatment and advanced imaging trials across a broad range of diseases and diverse patient populations.
*Status of Support: Active
Project Number: 5 UG1 CA233290-04
Name of PD/PI: Aghajanian, C / Lee, N / Morris, M / Tallman, M / Zivanovic, O
Source of Support: National Cancer Institute
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 3/6/2019 - 2/28/2025
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)

4.	2023	1.20 calendar
5.	2024	1.20 calendar
6.	2025	1.20 calendar

Grants officer: Mooney, Margaret M

*Title: Ovarian cancer research
*Major Goals: Our work continues to define how CA125 /MUC16 increases the aggressive nature of ovarian cancer and we have now identified antibodies that can block these effects and increase the lifespan of mice with transplanted ovarian tumors.
*Status of Support: Active
Project Number: AWD-GC-232689
Name of PD/PI: Aghajanian, C
Source of Support: T.J. Martell Foundation
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 7/1/2017 - 12/31/2030
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2030	0.00 calendar

Grants officer: Laura Heatherly

*Title: NRG Gynecologic Cancer Committee Chair
*Major Goals: NRG Oncology seeks to improve the lives of adult patients with gender-specific malignancies (breast, gynecologic, prostate cancers) and/or localized or locally advanced cancer through the development and conduct of a portfolio of timely and relevant clinical trials. NRG uniquely focuses on this large and relatively under-investigated group of cancer patients and has extraordinary scientific accomplishments specific to the group's three specific aims. NRG actively assists in the management of the NCI - National Clinical Trial Network (NCTN) and collaborates with the other NCTN partners in the overall conduct of all NCTN trials.
*Status of Support: Active
Project Number: U10CA180868
Name of PD/PI: Aghajanian, C
Source of Support: NRG Oncology (Prime: National Cancer Institute)
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 4/17/2014 - 2/28/2025
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
9. 2023	1.00 calendar
10. 2024	1.00 calendar
11. 2025	1.00 calendar

Grants officer: Mooney, Margaret M

OVERLAP
None

PREVIOUS
*Title: Novel approaches to locoregional and systemic immunotherapy for ovarian cancer
*Major Goals: In epithelial ovarian cancer (EOC), immunotherapies with PD-1/PD-L1 blocking drugs have been evaluated in preliminary trials with promising response rates. Despite these significant clinical advances, the benefit afforded by PD-1/PD-L1 blockade in ovarian cancer has not been universal, calling for identification of mechanisms of response and resistance to these drugs and development of novel combinatorial approaches.
*Status of Support: Active

Project Number: W81XWH-16-1-0298
Name of PD/PI: Zamarin, D
Source of Support: Congressionally Directed Medical Research Programs
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 9/30/2016 - 9/29/2022 NCE
*Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
5. 2022 0.60 calendar
Grants officer: Lisa Sawyer

*Title: Linking population-based data sources to examine health disparities in clinical trial participation and outcomes
*Major Goals: The purpose of this proposal is to create a national database that will tell us about older adult patients who have participated in clinical trials. This will allow us to answer questions about what kinds of people participate in these trials, where they are treated, what doctors treat them, and the benefits and risks of such participation, which can influence the future of clinical trials research.
*Status of Support: Completed
Project Number: R21 CA235154
Name of PD/PI: Lipitz Snyderman, A / Mailankody, S
Source of Support: National Cancer Institute
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 6/1/2019 - 5/31/2022
*Total Award Amount (including Indirect Costs):
Person Months: 0.60 calendar
Grants officer: CRONIN, KATHLEEN A

*Title: Mechanisms of response and resistance and novel approaches to ovarian cancer immunotherapy*Major Goals: The major objectives of this proposal are to identify the immune-activating and compensatory immunosuppressive mechanisms upregulated in response to immune checkpoint blockade in human ovarian cancer and to develop combinatorial therapeutic approaches targeting these mechanisms using mouse ovarian cancer model.
*Status of Support: Completed
Project Number: GC228959
Name of PD/PI: Zamarin
Source of Support: Cycle for Survival
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 9/1/2015 - 3/31/2020 NCE
*Total Award Amount (including Indirect Costs):
Person Months: 0.60 calendar
Grants officer: Kathleen Bourke

*Title: NCI National Clinical Trials Network (NCTN) – Network Lead Academic Participating Site (LAPS)
*Major Goals: This goal will be achieved through the continued successful development and execution of definitive, randomized, clinical treatment and advanced imaging trials across a broad range of diseases and diverse patient populations.
*Status of Support: Completed
Project Number: U10 CA180791
Name of PD/PI: Aghajanian
Source of Support: NCI
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 4/15/2014-2/28/2019
*Total Award Amount (including Indirect Costs):

Person Months: 2.0 calendar
Grants officer: Mooney, Margaret M

PREVIOUS/CURRENT/PENDING/ SUPPORT
WEIGELT, BRITTA

CURRENT

NEW
OC210081 (PI: Shah) 9/30/2022 - 9/29/2025
Congressionally Directed Medical Research Programs
Title:Dissecting Ovarian Cancer Tumor-Immune Microenvironments Through 3D In Situ Molecular Profiling
Goal: In this proposal we pursue the hypothesis that the different HGSOC subtypes and the different tumor sites within the same patient create unique microenvironments and tumor architectures that drive the avoidance or inactivation of immune surveillance.
Role: Co-Investigator
Contact: Grant official: Juan A. Rodriguez
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY)Person Months (##.##)
1. 2023 0.24 calendar
2. 2024 0.24 calendar
3. 2025 0.24 calendar
Overlap: None

NEW
Title: SRA - PKMYT1 inhibition as a novel targeted for high grade endometrial cancers.
Major Goals: N/A
Status of Support: Active
Project Number: SK2022-0932
Name of PD/PI: Weigelt, B
Source of Support: Repare Therapeutics
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 7/29/2022 - 7/28/2024
Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY)Person Months (##.##)
1. 2024 0.30 calendar
Contact N/A

NEW
Title: Targeting ERBB2 mutations in endometrial carcinoma
Major Goals: To characterize the functional role of the most prevalent variants in contributing to the pathogenesis of EC and provide pre-clinical evidence to evaluate the potential of treating ERBB2-mutated EC with anti-HER2 therapies.
Status of Support: Active
Project Number: Foundation for Women's Cancer
Name of PD/PI: Chui, M
Source of Support: Foundation for Women's Cancer
Primary Place of Performance: Sloan Kettering Institute For Cancer Research
Project/Proposal Start and End Date (MM/YYYY): 4/1/2022 - 3/31/2023
Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
1. 2023 0.12 calendar
Contact: Charles Landen

NEW
FP00002483 (PI: Aghajanian) 1/1/2022 - 12/31/2024

Break Through Cancer
Title: Ovarian Cancer (MOD)
Goal: The overall goal of our project is to fully leverage this new paradigm by applying an array of advanced technologies to ask fundamental biological and clinical questions, develop computational methods and new devices, and devise clinical approaches that are specifically tailored to identify, characterize, and intercept these STIC lesions, in both high- and average-risk women, before they disseminate and produce HGSC.
Role: Co-Investigator
Contact: N/A
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
1. 2022 0.30 calendar
2. 2023 0.30 calendar
3. 2024 0.30 calendar
Overlap: None

NEW
FP00002489 (PI: Aghajanian) 1/1/2022 - 12/31/2024 0.30 calendar
Break Through Cancer
Title: Ovarian Cancer (MRD)
Goal: Our overarching aim is to transform the current treatment landscape by developing more effective therapies based on therapeutic vulnerabilities in the MRD phase of ovarian cancer.
Role: Pathologist
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY)Person Months (##.##)
1. 2022 0.30 calendar
2. 2023 0.30 calendar
3. 2024 0.30 calendar
Overlap: None
Grants officer: Bill Hulme

NEW
BCRF-20-135 (PI: Reis-Filho) 10/1/2016 - 9/30/2022
Breast Cancer Research Foundation
Title: Devising a molecular taxonomy for rare special types of breast cancer
Goal: To define the drivers of rare types of breast cancer, in particular of subtypes of triple-negative disease.
Role: Co-PI
Contact: Lisa Risi _____
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
6. 2022 0.60 calendar
Overlap: None

648007 (PI: Shah) 1/1/2020 - 12/31/2022
Ovarian Cancer Research Fund
Title: Profiling co-evolution of ovarian cancer and its immune microenvironment
Goal: The aims are to establish how structural mutational processes impact clonal evolution properties in a pre-treatment setting and differentially impact innate and adaptive immune responses.
Role: Co-PI
Contact: Natalie Alvarado
Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY) Person Months (##.##)
3. 2022 1.20 calendar
Overlap: None

GC243301 (PI: Friedman) 1/1/2018 - 11/30/2022 NCE
Stand Up To Cancer
Title: Connecting Immune Health and Tumor Biology in Gynecologic Cancers
Goal: To test how tumor-intrinsic factors predispose to response or resistance to checkpoint blockade, and to define how on treatment blood markers may reflect the tumor-immune interaction.
Role: Investigator
Contact: Lauren S Miller
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
3. 2022 1.20 calendar
Overlap: None

W81XWH 20 1 0565 (PI: Shah) 9/30/2020 - 9/29/2023
Congressionally Directed Medical Research Programs
Title: Dissecting the impact of mutational processes on therapeutic response in ovarian cancer
Goal: To identify clonal populations in ovarian cancer, their specific copy number architectures and evolutionary properties, and use quantitative approaches to distinguish phylogenetic attributes of contemporary structural alterations to demarcate active mutational processes from vestigial events.
Role: Co-Investigator
Contact: Jennifer Fox
Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
2. 2022 0.24 calendar
3. 2023 0.24 calendar
Overlap: None

GC261061 (PI: Brown) 1/01/2021-12/31/2022
Cycle for Survival:
Title: Molecular Profiles of Endometrial Carcinoma in Black Women
Goal: To characterize the histologic and genetic landscape of ECs occurring in black women, and to determine the prognostic value of genomic profile on survival.
Role: Co-PI
Contact: Kathleen Bourke
Person Months (Calendar/Academic/Summer) per budget period:
Year (YYYY)Person Months (##.##)
2. 2022 0.60 calendar
Overlap: None

GC241384 (PI: Weigelt) 10/1/2018 - 12/31/2022 NCE
Cycle for Survival
Title: Mechanisms of immune recognition of ovarian small cell carcinoma of hypercalcemic type
Goal: The goal of this project is to define the mechanisms behind immune recognition of small cell carcinomas of hypercalcemic type and identify predictors of response to PD-1 blockade in these patients.
Role: PI
Contact: Kathleen Bourke

Person Months (Calendar/Academic/Summer) per budget period.
Year (YYYY) Person Months (##.##)
2. 2022 0.60 calendar
Overlap: None

P50 CA247749-02 (PI: Powell) 4/1/2020 - 3/31/2025
NCI/ MSK SPORE in Genomic
Instability in Breast Cancer
Title: Non-coding mutations in triple-negative breast cancers.
Goal: To develop and apply a novel computational approaches to identify drivers of TNBCs in promoters, enhancers and non-coding (nc)RNAs, and their functional validation.
Role: Leader of a Developmental Research Project (1-year project - 01/01/2021-12/31/2022) (in kind)
Contact: Joyann Courtney
Year (YYYY) Person Months (##.##)
1. 2021 0.60 calendar
2. 2022. 0.60 calendar

PREVIOUS (last 5 years):

GC259055 (PI: Kim) 04/1/2020 - 06/30/2022 NCE
Foundation for Women's Cancer
Title: Mutation and HPV tracking in cervical cancer patients using circulating cell free DNA
Goal: To assess whether HPV and repertoire of somatic mutations present in the tumors can be captured by cfDNA sequencing, and whether mutation/ c-HPV detection in cfDNA can be used for disease-monitoring.
Role: Co-Investigator (in kind)
Contact: Anil K. Sood
Year (YYYY) Person Months (##.##)
1. 2022 0.60 calendar
Overlap: None

GC ID: 220180
Susan G Komen Breast (PI: Hicks) 10/22/2013-10/21/2017
Cancer Foundation
Title: Molecular markers for progression from in situ to invasive breast cancer.
Goal: The goal of this project is to use a combination of cutting edge sequencing approaches to determine the genetic basis of DCIS, whether these lesions are composed of populations of cells that are heterogeneous in their repertoire of genetic aberrations, and whether progression to IBC would be the result of clonal selection.
Role: Co-Investigator
Contact: Ruta Lendins
Year (YYYY) Person Months (##.##)
1. 2017 0.60 calendar

GC ID: 225894 9/1/2014-8/31/2017
Cycle for Survival (PI: Park)
Title: Genomic and clinico-pathologic characterization of human papillomavirus-negative endocervical adenocarcinomas.
Goal: The aims of this study are to perform a genomic and clinico-pathologic characterization of human papillomavirus-negative endocervical adenocarcinomas.
Role: Co-Investigator

Contact: Christina Malinda Puglisi
Year (YYYY) Person Months (##.##)
1. 2017 0.60 calendar

R21 CA195365-01 (PI: Shen) 6/1/2015-5/31/2018
NIH/NCI
Title: Defining a novel subtype of luminal-TP53 mutant breast cancer with poor prognosis.
Goal: This project aims to characterize a novel breast cancer subtype identified on the basis of an integrated genomics-transcriptomics-proteomics analysis and validate functionally its driver genetic alterations.
Role: Co-PI
Contact: Funmi Elesinmogun
Year (YYYY) Person Months (##.##)
1. 2018 0.60 calendar

GC ID: 231675 (PIs: Ellis, Lewis, Welm & Reis-Filho) 9/1/2014 –6/30/2019
Breast Cancer Research Foundation
Title: Investigation of the genomics and biology of metastasis using patient-derived xenografts
Goal: The aim of this project is to investigate the genomics and biology of metastasis using patient-derived xenograft models.
Role: Co-Investigator
Contact: Leanne B. Scott
Year (YYYY) Person Months (##.##)
1. 2019 1.20 calendar

GC ID: 235334 (PIs: Weigelt & Andreasen) 10/1/2018-03/31/2021
Adenoid Cystic Carcinoma Research Foundation
Title: Minimally invasive detection of metastatic adenoid cystic carcinoma in circulating tumor DNA: a proof-of-concept study.
Goal: The aim of this pilot project is to develop a customized sequencing-based assays for the detection of AdCC-specific fusion genes in primary tumors and cfDNA.
Role: PI
Contact: Jeffrey Kaufman
Year (YYYY) Person Months (##.##)
1. 2021 0.00 calendar

W81XWH 17 1 0580 04 (PI: Schiff) 9/15/2017 - 9/14/2021
Congressionally Directed Medical Research Programs
Title: A new paradigm for de escalation of treatment in HER2 positive breast cancer: revolutionizing care with more effective and less toxic therapy
Goal: To define, and functionally characterize, mechanisms of resistance to dual anti HER2 therapy, and to develop a multi parameter classifier to assign patients into therapeutic groups on a prospective clinical trial.
Role: Co-Investigator
Contact: Leanne B. Scott
Year (YYYY) Person Months (##.##)
1. 2021 0.90 calendar

CURRENT/PENDING/PREVIOUS SUPPORT
APARICIO, SAMUEL

CURRENT:

7/1/2016 - 6/30/2023 1.20 calendar

Aparicio S
Canadian Institutes of Health Research (CIHR)
Title: Targeting the dynamics and genomics of clonal evolution in cancer patients
Goals: Support for research program
Aims: N/A
Contact: Dale A. Dempsey Role: PI
Overlap: None

7/1/2016 - 6/30/2023 0.12 calendar

Bénard F
Canadian Institutes of Health Research (CIHR)
Title: Targeted radiopharmaceuticals to improve cancer diagnosis and treatment
Goals: To develop novel imaging and therapeutic agents, which have radioactive tags ("radioisotopes") that bind to markers found specifically at the surface of cancer cells.
Aims: To develop novel imaging agents.
Contact: Dale A. Dempsey
Role: Co-PI
Overlap: None

3/1/2017 - 2/28/2027 0.12 calendar

Aparicio S
The University of British Columbia (UBC)
Title: Distinguished University Scholar
Goals: Research Award and Salary Support.
Aims: N/A
Contact: 604 822 2211
Role: PI
Overlap: None

5/1/2017 - 4/30/2023 1.20 calendar

Hannon G
Cancer Research UK
Title: IMAXT, Imaging and Molecular Annotation of Xenografts and Tumours
Goals: To develop and combine precise, 3D maps of tumours and their environment in a virtual reality experience, allowing researchers to ‘walk around’ inside a tumour, visualising how individual cells adapt to their environment.
Aims: Deploy existing and develop new methods (MerFISH, and 3D Virtual Reality) for making single-cell measurements and place these within the context of a faithful, interactive, three-dimensional map of the entire tumour, presented with sub-cellular resolution.
Contact: Lucy Shaw
Role: Co-PI
Overlap: None

2/1/2018 - 1/31/2023 1.20 calendar

Aparicio S
Canadian Cancer Society
Title: Decoding clonal dynamics and evolution in breast cancers at single cell resolution: improving diagnostics and expanding treatment approaches
Goals: To find new therapies for triple-negative breast cancer (TNBC) by exploiting the observation that TNBC may differ in the way that the tumour genomes become unstable.

Aims: (1) Integrated measurements of genome, epigenome and transcriptome for assessment of TNBC. (2) Linking TNBC clonal genotypes and epigenotypes to molecular determinants of clonal fitness. (3) Prediction of disease trajectory in TNBC patients and PDX model systems.
Contact: Sherri Huys
Role: PI
Overlap: None

2/1/2018 - 1/31/2023 0.12 calendar

Shah S
Canadian Cancer Society
Title: The determinants of drug response in high grade serous ovarian cancer: a single cell population genetics approach
Goals: To unlock the biological reasons for treatment failure in ovarian cancer and provide the basis for a practical test that can be administered at the point of diagnosis to better guide clinicians and ovarian cancer patients onto more effective therapies.
Aims: (1) Determine the relative evolutionary properties of FBI and HRD HGSC over disease natural history prior to diagnosis. (2) Determine the FBI- and HRD- dependent drug response profiles of HGSC under platinum, PARPi and investigational compounds. (3) Develop a genome-signature based tool for use in routine HGSC pathology materials to direct patient management.
Contact: Sherri Huys
Role: Co-applicant
Overlap: None

7/1/2018 - 03/31/2025 0.60 calendar

Huntsman D
Terry Fox Research Institute (TFRI)
Title: The Terry Fox New Frontiers Program Project Grant in New Vistas on Cancer Biology and Treatment: Conceptual Advancements from the Frome Fruste Project
Goals: To understand how mutations, particularly the mutations we discovered in our past studies, interact with non-mutational features to promote tumour development, progression, and metastasis in order to develop new diagnostic and therapeutic opportunities that target both the mutations and the mechanisms through which they operate.
Aims: Project #1 will study how cell context contributes to the development of cancer. Project #2 will study how adaptations to stress in the translatome contrubutes to neoplastic behaviour. Project #3 will study how the context-specific interplay between epigenomic changes in the transcriptional enhancer landscape and cell type specific transcription factors promote cellular transformation. Project #4 will use single cell measurements and functional interventions to study the clonal fitness associated with specific genomic or epigenomic changes. Project #5 will access the data sets generated by P1-P4 to develop predictive computational models to predict tumour behaviour.
Contact: Russell Watkins
Role: Co-PI
Overlap: None

4/1/2020 - 3/31/2025 0.12 calendar

Satija R
National Institutes of Health
Title: Center for Integrated Cellular Analysis
Goals: Goals: The major goals of this project are to understand how the molecular components, inherited lineage, and spatial milieu of single cells dictate function in health and disease remains a key outstanding challenge in genomics. The overarching goal of our Center for Integrated Cellular Analysis is to develop methods to simultaneously assess these multimodal cellular properties, develop tools to harmonize them to allow inferential assessment of cell identity based on partial phenotyping, and share these developments with the broad scientific community while encouraging community engagement through education and outreach.

Success in our strategy will facilitate deep, multi-omic phenotyping of single cells for basic research and clinical applications.
Role: Significant Contributor
Contact: N/A
Overlap: None

6/01/2020 - 03/31/2023 0.36 calendar

Aparicio S, Chia S (New)
Terry Fox Research Institute and BC Cancer Foundation
Title: Precision Medicine in Breast Cancer (B-PRECISE): Managing residual disease and drug resistance in breast cancer
Goals: To address residual disease after therapy and emergence of drug resistance in breast cancer through the development of multimodal genomic, imaging and pathology based tools, developed from retrospective and prospective clinical cohorts of breast cancer patients. Our goal is to develop sensitive whole genome assays for residual circulating tumour DNA in plasma and other fluids and combine these with digital imaging and digital pathology, to identify patients at high risk of early relapse.
Aims: 1) Minimal residual disease management in ER+ and HER2+ breast cancer patients 2) Targeting drug resistance in triple negative breast cancers (TNBC)
Contact: Russell Watkins
Role: Principal Investigator
Overlap: None

9/30/2020 - 9/29/2023 0.24 calendar

Shah S (This award)
Congressionally Directed Medical Research Programs (CDMRP)/US Department of Defense (US DOD)
Title: Dissecting the impact of mutational processes on therapeutic response in ovarian cancer
Goals: To identify contemporaneous impacts of genome damage and active pathways in high-grade serous ovarian cancer (HGSOC) associated with structural variation mutational processes using single cell sequencing.
Aims: To pursue deeper characterization of the signatures using a multi-faceted single cell sequencing approach of both transcriptomes and genomes, comparing DNA damage profiles (Aim 1) activated pathways (Aim 2) and drug response characteristics (Aim 3) of tumors bearing the distinct structural mutational processes.
Contact: Karen Wylie
Role: Co-PI
Overlap: None

4/1/2021 - 3/31/2026 0.60 calendar

Aparicio S
BC Cancer, part of the Provincial Health Services Authority/ BC Cancer Foundation (BCCF)
Title: Breast cancer evolution and therapeutics program, Nan & Lorraine Robertson Chair in Breast Cancer Research (Core programme in breast cancer research)
Goals: Salary/ Research Support
Contact: N/A
Role: PI
Overlap: None

4/1/2021 - 3/31/2024 0.60 calendar

Aparicio S
Canada Foundation for Innovation
Title: Cancer Single Cell Dynamics Observatory
Goals: To develop infrastructure for leading edge method development in single-cell genomics as well as critically required new capacity for training.
Contact: N/A
Role: PI

Overlap: None

10/1/2021 - 09/30/2024 0.36 calendar

Hannon G
Wellcome Leap
Title: Predicting treatment induced state changes in triple-negative breast cancer
Goals: To define the tissue states of triple-negative breast cancer (TNBC) and understand how they change in response to treatment.
Contact:
Role: Co-Investigator
Overlap: None

4/1/2022 - 3/31/2029 0.36 calendar

Aparicio S (new)
Canada Research Chairs
Title: Canada Research Chair in Molecular Oncology (Tier 1)
Goals: Salary Support
Aims: N/A
Contact: Tri-agency Institutional Programs Secretariat
Role: PI
Overlap: None

10/1/2022 - 9/30/2023 0.60 calendar

Aparicio S (new)
Breast Cancer Research Foundation
Title: Developing predictive biomarkers for genome targeting agents in TNBC, to single cell resolution
Goals: To test whether fold back inversion and non-fold back inversion subgroups of triple negative breast cancer tumors predict sensitivity/resistance to genome targeting agents.
Aims: 1) Define FBI, HRD and other patterns at single cell resolution in TNBC PDX. Co-map scRNA-seq in the same populations. Determine the timing of patterns in subclones. 2) Determine the clonal and sub-clonal response patterns of FBI and HRD pattern TNBC treated with platinum salts, PARPi, CX-5461. Contrast clonal drug responses with transcriptome derived measures and RAD51 focus formation. 3) Validation of clonal response pathways through in vivo sgRNA library-drug interactions.**Contact:** Lisa Risi

Role: PI
Overlap: None

5/2/2022 - 5/1/2026 0.36 calendar

Sweet-Cordero EA (new)
Alex's Lemonade Stand Foundation
Title: Defining and exploiting novel vulnerabilities for the treatment of metastatic osteosarcoma
Goals: To identify novel potential therapies for osteosarcoma (OS) that are informed by its genomic characteristics and complexity, and to understand what drives therapy resistance and metastasis.
Aims: 1) Test the hypothesis that metastatic capacity in OS is an innate, subclonal phenotype promoted by MYC expression. 2) Test the hypothesis that translational control through eIF4A plays a critical role in adaptation to stress in the metastatic niche in OS. 3) Identify mechanisms of resistance to conventional and targeted therapies in OS and test combinatorial drug approaches in vivo.
Contact:
Role: Co-investigator
Overlap: None

11/1/2022 - 10/31/2025 0.60 calendar

Brugges J (new)
Gray Foundation

Title: Breast Pre-cancer Atlas Proposal
Goals: To profile epithelial, stromal and immune cells in breast tissues from women who carry pathogenic variants in BRCA1 or BRCA2, comparing them to a matched set of
breast tissues from women with wild-type BRCA1/2.
Aims: To provide an atlas of information, shareable with the broader scientific community, invaluable for many different studies centered on understanding how mutations in BRCA1 and BRCA2 and other variables affect the breast tissue structure and function of the cells within. Ultimately, this information is intended to facilitate the development of strategies to prevent cancer development and facilitate early detection.
Contact:
Role: Co-investigator
Overlap: None

PREVIOUS:

12/1/2014 - 3/31/2022 0.00 calendar
Bénard F
Canadian Institutes of Health Research (CIHR)
Title: Integrating Quantitative Imaging Methods and Genomic Biomarkers to Assess the Therapeutic Response of Cancers
Goals: To improve existing methods to measure tumor volume and accurately measure the accumulation of PET radiotracers, and relate the total viable tumor mass to the amount of circulating tumor DNA (ctDNA) present in the blood.
Aims: (1) Improve image reconstruction and processing methods for PET/CT to accurately quantify tumor burden and relative radiotracer uptake in lesions across metastatic sites and over time. (2) Correlate established and novel surrogate image-based indicators of tumor burden with circulating tumor DNA (ctDNA) levels at baseline and as a function of response to treatment. (3)Compare genome-wide mutational profiles obtained from exome-wide and transcriptome sequencing of human tumors with treatment resistance and discordant responses to therapy based on early PET/CT imaging.
Contact: Marilyn Desrosiers
Role: Co-Investigator
Overlap: None

4/1/2015 - 3/31/2022 0.00 calendar
Aparicio S
Canada Research Chairs
Title: Canada Research Chair in Molecular Oncology (Tier 1)
Goals: Salary Support
Aims: N/A
Contact: Tri-agency Institutional Programs Secretariat Role: PI
Overlap: None

3/1/2013 - 2/28/2021 0.00 calendar
Aparicio S
BC Cancer, part of the Provincial Health Services Authority/ BC Cancer Foundation (BCCF)
Title: Breast cancer evolution and therapeutics program, Nan & Lorraine Robertson Chair in Breast Cancer Research (Core programme in breast cancer research)
Goals: Salary/ Research Support
Contact: N/A
Role: PI
Overlap: None

5/1/2016 - 4/30/2020 0.00 calendar
Morin G, Aparicio S
Congressionally Directed Medical Research Programs (CDMRP)/US Department of Defense (US DOD)

Title: Mechanistic Investigation of Breast Cancer Synthetic Lethality Through Inhibition of CDK12
Goals: To understand how CDK12 controls the alternative splicing of genes involved in DNA repair pathways, and to determine which breast cancer types containing mutations in DNA damage repair pathways will be killed by drugs targeting CDK12.
Aims: 1) Characterize the genome-wide regulation of mRNA processing by CDK12 after DNA damage. 2) Determine the molecular mechanisms underlying regulation of gene transcription by CDK12. 3) Investigate the molecular mechanisms underlying regulation of mRNA processing by CDK12. 4) Identify tumor genomic backgrounds sensitive to CDK12 inhibition.
Contact: N/A
Role: Co-PI
Overlap: None

3/1/2017 - 2/28/2022 0.12 calendar

Hirst M, Marra M, Jones S
Canadian Institutes of Health Research (CIHR)/ The Canadian Epigenetics, Environment and Health Research Consortium (CEEHRC)/Genome British Columbia
Title: Centre for Epigenome Mapping Technologies
Goals: To renew the CIHR Canadian Epigenetics, Environment and Health Research Consortium (CEEHRC) Platform Centre and maintain and continue to develop the Centre for Epigenome Mapping Technologies (CEMT).
Aims: (1) Community Access to Reference Epigenome Mapping. (2) Epigenomic Mapping of selected tissues and cells. (3) Epigenome Mapping Technology Development.
Contact: Dale A. Dempsey
Role: Co-applicant
Overlap: None

2/1/2017 - 1/31/2019 0.00 calendar

Steidl C, Shah S
Canadian Cancer Society Research Institute (CCSRI)
Title: Deciphering the cellular crosstalk in the tumour microenvironment of classical Hodgkin lymphoma
Goals: To reveal how changes in the genetic material of tumour cells associate with the cellular composition and functional properties of the microenvironment.
Aims: (1) Characterize the phenotypic and functional properties of the tumour microenvironment on a single cell level. (2) Describe the mutational landscape of enriched Reed-Sternberg (HRS) cells and decipher tumour microenvironment crosstalk.
Contact: Sherri Huys
Role: Co-PI
Overlap: None

4/1/2018 - 3/31/2022 0.12 calendar

Stein L
Canada Foundation for Innovation
Title: The Cancer Genome Collaboratory
Goals: This project will accelerate research for effective treatment of cancer by providing researchers with access to the world's largest open cancer genomics dataset.
Aims: Activity 1: To enhance the core software and data infrastructure of the Cancer Genome Collaboratory (CGC). Activity 2: To package software developed within the CGC with selected genome analysis software developed by leading groups in cancer genome analysis. Activity 3: To exploit the unprecedented size of the CGC data to implement computational methods that address challenges of variant calling and consequence prediction. Activity 4: To develop a comprehensive software toolbox encompassing implementations of new algorithms to drive biological interpretation from the new era of single cell cancer genomics.
Contact: Dr. Cecile Lacombe

Role: Co-PI
Overlap: None

8/1/2018 - 7/31/2020 0.00 calendar

Marra M
Canadian Cancer Society
Title: Dissecting tumour heterogeneity using single cell genomics, epigenomics and transcriptomics
Goals: To develop ground breaking methods to study thousands of individual cancer cells to enable insights into how tumours evolve, both as disease progresses and in response to treatments
Aims: Aim 1: Optimization of nuclear disaggregation and suspension for fresh and fixed samples Aim 2: Full length RNA seq Aim 3: miRNAseq in single cells Aim 4: ATACseq and Bisulfite in single cells Aim 5: Labeling single cells prior to sequencing Aim 6: Combinatorial methods to increase cell numbers Aim 7: Development of novel single cell analysis methods
Contact: Sherri Huys
Role: Co-PI
Overlap: None

10/1/2018 - 9/30/2020 0.00 calendar

Chia S, Aparicio S
British Columbia Cancer Foundation
Title: New Frontiers in Breast Cancer Research + Care: Harnessing the Power of Circulating Tumour DNA
Goals: The goals of this project is to establish a novel ctDNA research facility to transform breast cancer care.
Aims: Aim #1: Create a multi-disciplinary hub and a novel research facility at BC cancer to prove the effectiveness of ctDNA for breast cancer within the next two years. Aim #2: Collect and store of ctDNA from all breast cancer patients in the province. Aim #3: Development of cloud compute models for ctDNA analysis and training.
Contact: Siok Gan
Role: Co-PI
Overlap: None

10/1/2018 - 9/30/2021 0.00 calendar

Shah S
Susan G. Komen Breast Cancer Foundation
Title: Exploiting new patterns of genome damage in triple negative breast cancer
Goals: To bring together the discovery power of whole genome sequencing, single cell sequencing, and advanced machine learning tools to decipher new biological and clinically relevant sub-groups of TNBC.
Aims: Aim 1 will determine the mutational processes active in TNBCs. Aim 2 will determine the evolutionary features and active DNA repair mechanisms of distinct mutational
Contact: Amy Dworkin
Role: Co-PI
Overlap: None

1/1/2019 - 12/31/2021 0.00 calendar

Sonenberg N and Pollak M
American Association for Cancer Research International
Title: Targeting mRNA translation to effectively treat metastatic breast cancer
Goals: An integrated team of Canadian researchers, recognized as global leaders in their fields, have been assembled to conduct a phase 1b clinical trial of a novel drug candidate eFT508 in patients with metastatic breast cancer, and to study innovative pharmacodynamics as well as clinical endpoints of this trial.
Aims: AIM 1. Clinical trial of the MNK inhibitor eFT508 in patients with metastatic breast cancer. AIM 2: Pharmacodynamic studies of the MNK inhibitor eEFT508 in patients with metastatic breast cancer
Contact: Jayashree Karar
Role: Co-applicant

Overlap: None

9/18/2019 - 9/17/2022 0.00 calendar

Brugge JS, Aparicio S
Gray Foundation
Title: Development of strategies to track and prevent breast cancer development in BRCA mutation carriers
Goals: To decipher in detail why BRCA mutations cause *BRCA1/2* cells to accumulate, and to expose vulnerabilities that could lead to new strategies for their elimination. The ultimate objective of the proposed studies is to develop strategies to track and eliminate pre-malignant cells in breasts from BRCA1/2 mutation carriers.
Aims: Aim#1: Investigate whether BL and LUM cells contribute directly or indirectly to cancer development in *BRAC1/2* mutation carriers Aim #2: Elucidate the mechanisms underlying the accumulation of the BRCA1/2mut/+-enriched subpopulations. Aim #3: Develop methodologies to track the in vivo expansion of premalignant cells in BRCA1/2 mutation carriers in order to inform the timing of prophylactic interventions. Aim #4: Develop strategies to block development or progression of breast cancer in BRCA1/2mutation carriers.
Role: Co-applicant
Contact: Dana Zucker 70 E 55th Street, 14th Floor New York, NY 10022
Overlap: None

10/1/2018 - 9/30/2022 0.00 calendar

Aparicio S
Breast Cancer Research Foundation
Title: Developing predictive biomarkers for genome targeting agents in TNBC, to single cell resolution
Goals: To analyze drug sensitivity in mouse models of four TNBC types displaying distinct patterns of chromosome shuffling. To also study whether the patterns predict tendency to metastasize.
Aims: Aim 1: Define FBI, HRD and other patterns at single cell resolution in TNBC PDX. Co-map scRNA-seq in the same populations. Determine the timing of patterns in subclones Aim 2: Determine the clonal and sub-clonal response patterns of FBI and HRD patttern TNBC treated with platinum salts, PARPi, CX5461. Contrast clonal drug responses with transcriptome derived measures and RAD51 focus formation. Aim 3: Validation of clonal response pathways through in vivo sgRNA library-drug interactions. Aim 4: Anticipated outcomes, future directions.
Contact: Lisa Risi
Role: PI
Overlap: None

2/1/2021 - 08/31/2022 0.00 calendar

Huntsman D (New)
The University of British Columbia
Title: Molecular and Advanced Pathology Core (MAPcore): a Translational Research Core Platform for UBC
Goals: To establish MAPcore as a powerful UBC core platform to further fuel the success of omics and other discovery research by translating these findings to clinical utility.
Contact: n/a
Role: Co-applicant
Overlap: None

2/1/2021 - 07/31/2022 0.00 calendar

Roth A, Ha G, Hunter N, Aparicio S (New)
Microsoft, BC Cancer Foundation, The University of British Columbia
Title: Monitoring breast cancer: Bringing single-cell and liquid biopsy analysis to the cloud
Goals: The goal of this study is to develop and apply novel computational approaches for integrating single cell DNA and circulating tumour DNA sequencing to track disease burden in breast cancer.
Contact: Katie Smolnycki
Role: Co-PI

Overlap: None