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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, New York, NY

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6. AUTHOR(S)
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5e. TASK NUMBER

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1275 York Avenue New York, NY
10065-6007

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13. SUPPLEMENTARY NOTES

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 an increased neoantigen burden, inflammatory signaling and ongoing immunoediting in HRD tumors, while FBI tumors exhibited elevated TGFβ signaling. 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 9 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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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 each tumor subtype 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 39 patients
Aim 1.3 Identify active mutational processes through phylogenetic analysis	7-24	Defined for 30 patients from WGS data
Aim 1.4 Identify clone-specific variation in mutational processes	7-24	Established computational pipeline and analyzed 22 HGSOC samples
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 39 patients
Aim 2.2 Measure intrinsic cellular variation and stability of activated DNA damage response (DDR) pathways linked to structural mutational processes	7-30	Preliminary decomposition of cell-specific DRR activation from scRNA-seq and integration with scDNA-seq achieved for 4 samples
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	TBD
Aim 3.3 Determine resistance phenotypes and identifying cross resistance	19-30	TBD
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**

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 30 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 with a better prognosis and HR competent groups characterized by foldback inversion (FBI) and tandem duplications (TD) with worse outcome. Sample collection is ongoing to reach our projected goal of 50 patients.

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

The Shah team recently published a statistical modeling framework for scalable phylogenetics of single cell genomes to identify clones and model clonal fitness from time series data (*Salehi et al Nature 2021*). We have acquired scDNA-seq from 39 patients in the present cohort and will use our platform to reconstruct phylogenetic trees based on single cell copy number profiles to separate ancestral from clade-specific and cell-specific events, corresponding to the earliest, later and most recent genomic damage. We have recently completed a study on > 22,000 single cell whole genome sequences from HGSOC and triple negative breast cancer (TNBC) patients that demonstrates the robustness of our pipeline and the valuable insights that emerge. Comparing cell-to-cell structural genomic variation we found widespread aneuploidy and continuous whole genome duplication in HRD tumors whereas FBI tumors showed early ploidy fixation paired with variation in local high-level amplifications (**Fig. 2**).

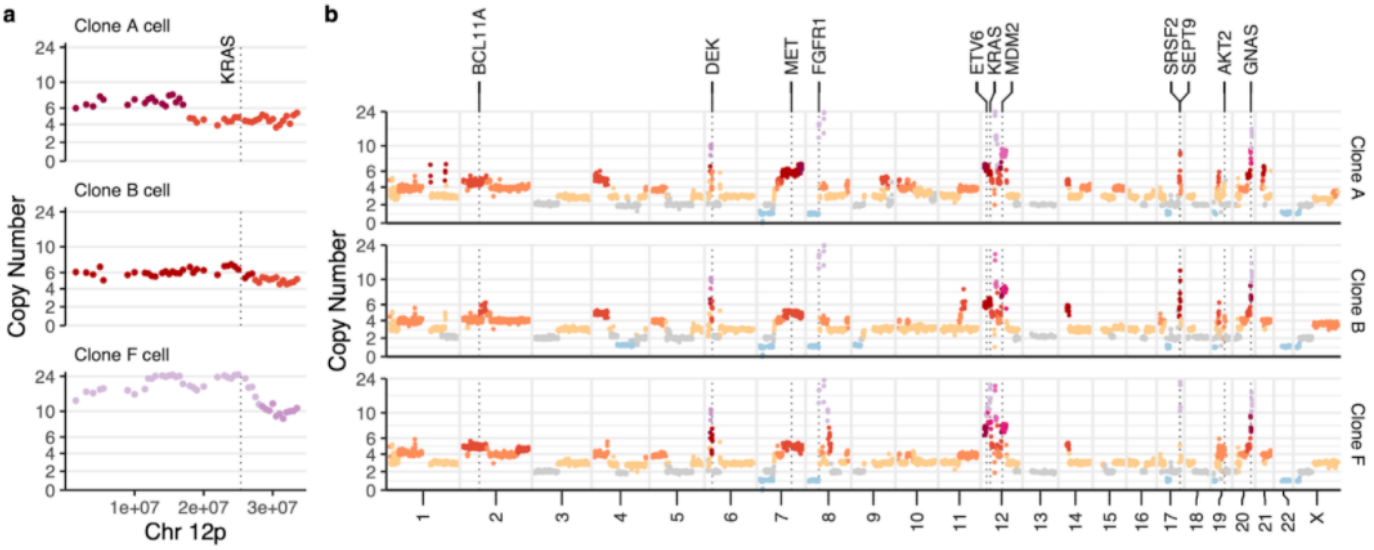

Fig. 2 Variance in high level amplifications in a HGSOC tumor a) Chromosome 12p copy number for 3 cells from clones A, B, and F, with *KRAS* gene locus indicated with dotted line b) Clone whole genome consensus copy number profiles for clones A, B, and F. Selected genes overlapping HLAMP regions indicated with dotted lines.

We noted additional genomic diversification in FBIs in the form of high break-point variability around the amplifications (*Funnell et al under revision at Nature*). We will employ the same analysis pipeline on our present HGSOC cohort to reveal clone specific genomic plasticity driven by mutational signatures.

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

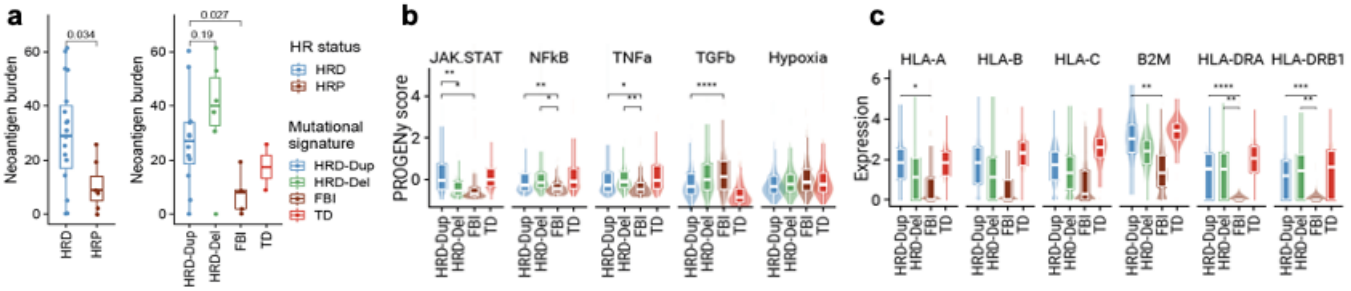

Fig. 3 Cancer cell characterization with respect to mutational signatures a) Comparison of neoantigen burden b) Signaling pathway activity scores c) Distributions of HLA gene expression; * indicate pairwise Wilcoxon rank sum test

We obtained scRNA-data from the same 39 patients as analyzed in Aim 1, enriched for either the CD45 negative tumor fraction or CD45 positive immune cells, and employed our computational pipeline to data processing and cell type identification. In the cancer cells we found distinct gene signature enrichments associated with mutational subtypes (**Fig. 3**): JAK-STAT signaling was increased in BRCA1-mutation linked HRD tumors, which TGFb signaling was higher in FBI patients (**Fig. 3b**). HRD tumors showed an upregulation of immune-activating and immune-inhibitory targets, indicating that the different mutational processes shape immune recognition and escape (**Fig. 3a,c**) (*Vazquez-Garcia et al under revision at Nature*). We will then link transcriptional responses to clone-specific mutational signatures by deploying our *Clonealign* tool that facilitates the mapping of scRNA-seq data to distinct genomic clones (*Campbell et al Genome Biology 2019*). By exploring differential gene expression in the different clones we will be able to distinguish the contributions of the genome and the epigenome to tumor plasticity and assess the overall phenotypic variation in a tumor driven by mutational processes.

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

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. We harvested PDX tumors following subcutaneous engraftment, dissociated them into single cells and cultured them in 3D in vitro. Organoids were treated with increasing concentrations of cisplatin, the G quadruplex stabilizer CX5461, PARP inhibitors olaparib and rucaparib, or CDK12 inhibitors THZ531 and T836 for 96hrs, with 5 replicates per data point. Viability was measured using Cell Titre Glo 3D and IC50s were determined from resulting response curves (**Fig. 4**). We are in the process of testing additional FBI PDXs. We will use our recently published statistical models to infer phylogenetic clones and dissect the fitness trajectories of the individual clones. By combining clonal genotypes with

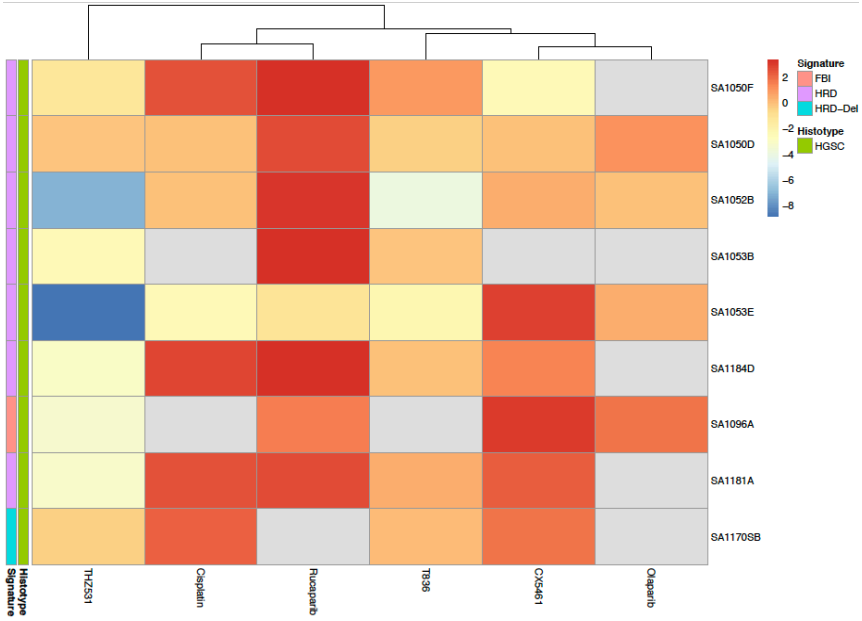

Fig. 4 3D culture of PDX-derived cells after drug treatment. Heatmap shows the IC50 values after treatment with the indicated drugs.

scRNA-seq data we will be able to distinguish the impact of genome and transcriptome on clonal fitness and drug resistance.

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. Due to covid post docs were limited in their opportunities to give talks at conferences, but these will be resumed next year. In addition, Dr. Shah gave a lecture entitled "Cancer biology at single cell resolution" for the MSKCC Computational Biology Summer Program interns.

How were the results disseminated to communities of interest?

Dr. Shah chaired sessions in five scientific conferences during the first year of this grant, all focused on either cancer evolution or computational oncology (see below for details).

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 his 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, conference papers, and presentations**

Journal publications

Salehi S, Kabeer F, Ceglia N, Andronescu M, Williams MJ, Campbell KR, Masud T, Wang B, Biele J, Brimhall J, Gee D, Lee H, Ting J, Zhang AW, Tran H, O'Flanagan C, Dorri F, Rusk N, de Algara TR, Lee SR, Cheng BYC, Eirew P, Kono T, Pham J, Grewal D, Lai D, Moore R, Mungall AJ, Marra MA; IMAXT

Consortium, McPherson A, Bouchard-Côté A, Aparicio S, **Shah SP**. Clonal fitness inferred from time-series modelling of single-cell cancer genomes. Nature. 2021 Jul;595(7868):585-590. (yes)

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 (under review at Nature) Available from: https://www.biorxiv.org/content/10.1101/2021.08.24.454519.abstract (yes)

Tyler Funnell, Ciara H O'Flanagan, Marc J Williams, Andrew McPherson, Steven McKinney, Farhia Kabeer, Hakwoo Lee, Tehmina Masud, Peter Eirew, Damian Yap, Allen W Zhang, Jamie L P Lim, Beixi Wang, Jazmine Brimhall, Justina Biele, Jerome Ting, 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, J Maxwell Douglas, Dmitriy Zamarin, Britta Weigelt, Sarah H Kim, Arnaud Da Cruz Paula, Jorge S. Reis-Filho, Yangguang Li, Hong Xu, Teresa Ruiz de Algara, So Ra Lee, Viviana Cerda Llanos, IMAXT consortium, **Sohrab P. Shah**, Samuel Aparicio. The impact of mutational processes on structural genomic plasticity in cancer cells (under review at Nature) Available from:bioRxiv https://doi.org/10.1101/2021.06.03.446999 (yes)

Marc J Williams, Tyler Funnell, Ciara H O'Flanagan, Andrew McPherson, Sohrab Salehi, Ignacio Vázquez-García, Farhia Kabeer, Hakwoo Lee, Tehmina Masud, Peter Eirew, Damian Yap, Beixi Wang, Jazmine Brimhall, Justina Biele, Jerome Ting, Sean Beatty, Daniel Lai, Jenifer Pham, Diljot Grewal, Douglas Abrams, Eliyahu Havasov, Samantha Leung, Viktoria Bojilova, Adam C Weiner, Nicole Rusk, Florian Uhlitz, Nicholas Ceglia, IMAXT consortium, Samuel Aparicio, Sohrab P. Shah Evolutionary tracking of cancer haplotypes at single-cell resolution (under review at Nature) Available from: bioRxiv https://doi.org/10.1101/2021.06.04.447031 (yes)

Other publications, conference papers and presentations.

Conferences Dr. Shah chaired or co-chaired
1) Mechanisms and Models of Cancer Conference, Dr. Shah Session Chair, (Virtual), August 11-14, 2020
2) MSK MIND Symposium, MSKCC (Virtual), Dr. Shah Chair, December 2020
3) EACR Bioinformatics in Cancer (Virtual), Dr. Shah Session Chair, May 18, 2021
4) AACR Virtual Special Conference: Ovarian Cancer, Dr. Shah Session Moderator, September 2021

Dr. Shah's invited presentation (all virtual)
1) Keynote Speaker: "Single Cell Whole Genome Sequencing for Studying Cancer Evolution" Midatlantic Bioinformatics Conference November 2, 2020
2) "Single Cell RNA Sequencing and Clinical Applications", Princess Margaret's 2020 Cancer Genomics and Tumor Immunotherapy Symposium , November 11, 2020
3) "Investigating co-evolution of mutational processes and immune response in ovarian cancer at single cell resolution", GSK Opportunities in Ovarian Cancer, January 14, 2021

4) Multimodal integration and results on clone fitness/ovarian cohorts", Cancer Grand Challenges Summit, March 1, 2021
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 CloneAlign 2.0 tool can be found at Github: ttps://github.com/AlexHelloWorld/clonealign_pyro

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

  Nothing to report

- **Other Products**
  Software: CloneAlign 2.0

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:	Juliana Niyazov
Project Role:	Technician
Researcher Identifier (ORCID):	N/A
Nearest person month worked:	1
Contribution to Project:	Ms Niyazov is embedded in the OR to receive tissue for processing; she generates single cell suspensions and submits samples for sequencing to the Integrated Genomics Operation core facility.
Funding Support:	N/A

Name:	Jaime Lim

Project Role:	Technician
Researcher Identifier (ORCID):	N/A
Nearest person month worked:	2
Contribution to Project:	Ms Lim is embedded in the OR to receive tissue for processing; she generates single cell suspensions and submits samples for sequencing to the Integrated Genomics Operation core facility.
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 rully supported by her PhD program and will base her PhD dissertation on the work described in this proposal.
Funding Support:	N/A

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:

QUAD CHARTS:

9. APPENDICES:

SHAH, SOHRAB

ACTIVE

(NEW)
V Foundation Translational Cancer Research Grant Program- Callahan (PI: Callahan) 11/1/2021 - 10/31/2024 0.21 calendar
V Foundation for Cancer Research
Immunotype Identifies Immune Checkpoint Blockade Responders: dissecting the mechanism and understanding the scope and impact of immunotype across diverse cancer patient populations
Role: Collaborator

1 P50CA247749-01 (PI: Powell / Powell) 8/13/2020 - 7/31/2025 0.60 calendar
National Cancer Institute
MSK SPORE in Genomic Instability in Breast Cancer (Bioinformatics Core)
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.
Role: PD/PI

(NEW)
1 U24 CA264028-01 (PI: Schultz / Shah) 9/1/2021 - 8/31/2022 0.96 calendar
National Institutes of Health
Analysis of copy number variation, SVs and SNVs in cell free, single cell and bulk tumor genomes & transcriptomes and their impact on pathway analysis
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.
Role: PD/PI

AWD-GC-240388 (PI: Shah) 6/1/2020 - 3/31/2025 0.60 calendar
National Institutes of Health
Center for Integrated Cellular Analysis
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.
Role: PD/PI

AWD-GC-243330 (PI: Shah) 5/1/2018 - 4/30/2023 0.48 calendar
Cancer Research UK
Grand Challange IMAXT: Imaging and molecular annotation of xenografts and tumors
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.
Role: PD/PI

W81XWH-20-1-0565 (PI: Shah) 9/30/2020 - 9/29/2023 0.24 calendar
Congressionally Directed Medical Research Programs
Dissecting the impact of mutational processes on therapeutic response in ovarian cancer
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.
Role: PD/PI

648007 (PI: Shah) 1/1/2020 - 12/31/2022 1.20 calendar
Ovarian Cancer Research Fund
Profiling co-evolution of ovarian cancer and its immune microenvironment
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.
Role: PD/PI

AWD-GC-243310 (PI: Shah) 11/26/2018 - 12/31/2021 0.24 calendar
Philanthropic Funds
LesLois Shaw Foundation Fund
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.
Role: PD/PI

582539 (PI: Zamarin) 8/1/2021 - 7/31/2024 0.00 calendar
Congressionally Directed Medical Research Programs
Integrating tumor genetics and microenvironment as predictors of response and resistance to immunotherapy in ovarian cancer
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.
Role: Co-Investigator

INACTIVE

None

AGHAJANIAN, CAROL

ACTIVE

5 UG1 CA233290-03 (PI: Aghajanian / Lee / Morris / Tallman / Zivanovic) 3/6/2019 - 2/28/2025 0.00 calendar
National Cancer Institute
Network Lead Academic Participating Site: Memorial Sloan Kettering Cancer Center
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.
Role: PD/PI

(NEW)
2020 Cycle for Survival's Equinox Innovation Award in Rare Cancers (PI: Brown) 1/1/2021 - 12/31/2022 0.24 calendar
Cycle for Survival
Molecular Profiles of Endometrial Carcinoma in Black Women
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.
Role: Co-Investigator

5 R21 CA235154-02 (PI: Lipitz Snyderman / Mailankody) 6/1/2019 - 5/31/2022 NCE 0.60 calendar
National Cancer Institute
Linking population-based data sources to examine health disparities in clinical trial participation and outcomes
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.
Role: Co-Investigator

W81XWH-20-1-0565 (PI: Shah) 9/30/2020 - 9/29/2023 0.24 calendar
Congressionally Directed Medical Research Programs
Dissecting the impact of mutational processes on therapeutic response in ovarian cancer
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.
Role: Co-Investigator

648007 (PI: Shah) 1/1/2020 - 12/31/2022 0.24 calendar
Ovarian Cancer Research Fund
Profiling co-evolution of ovarian cancer and its immune microenvironment
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.
Role: Co-PD/PI

W81XWH-16-1-0298 (PI: Zamarin) 9/30/2016 - 9/29/2022 NCE 0.60 calendar
Congressionally Directed Medical Research Programs
Novel approaches to locoregional and systemic immunotherapy for ovarian cancer
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.
Role: Mentor

INACTIVE:

None

WEIGELT, BRITTA

ACTIVE:

(NEW)
2020 Cycle for Survival's Equinox Innovation Award in Rare Cancers (PI: Brown) 1/1/2021 - 12/31/2022 0.60 calendar
Cycle for Survival
Molecular Profiles of Endometrial Carcinoma in Black Women
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.
Role: Co-PD/PI

W81XWH-20-1-0565 (PI: Shah) 9/30/2020 - 9/29/2023 0.24 calendar
Congressionally Directed Medical Research Programs
Dissecting the impact of mutational processes on therapeutic response in ovarian cancer
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.
Role: Co-Investigator

648007 (PI: Shah) 1/1/2020 - 12/31/2022 1.20 calendar
Ovarian Cancer Research Fund
Profiling co-evolution of ovarian cancer and its immune microenvironment
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.
Role: Co-PD/PI

GC238479 (PI: Wherry) 1/1/2018 - 12/31/202 1.20 calendar Stand Up To Cancer
Connecting Immune Health and Tumor Biology in Gynecological Cancers
Specific Aim 1: Test how tumor-intrinsic factors predispose to response or resistance to checkpoint blockade, Specific Aim 2: Test how baseline immune function and quality affects response to checkpoint blockade, Specific Aim 3: Define how on treatment blood markers may reflect the tumor-immune interaction.
Role: Investigator

INACTIVE:

BCRF-17-133 (PI: Reis) 10/1/2016 - 9/30/2019 1.20 calendar
Breast Cancer Research Foundation, The
Devising a molecular taxonomy for rare special types of breast cancer
We posit that by studying special types of breast cancer using a comprehensive whole genome sequencing approach, including non-protein coding regions, as well as methylation analysis, we would have a unique opportunity to identify the drivers of these rare cancer types and provide an approach that is complementary to that offered by large scale sequencing endeavors for the identification of novel breast cancer driver genetic alterations.
Role: Co-PI

CURRENT/PENDING/PREVIOUS SUPPORT
APARICIO, SAMUEL

CURRENT:

Bénard F — 12/1/2014 - 3/31/2022 — CAD — 0.12 calendar
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 613-948-2893
Role: Co-Investigator
Overlap: None

Aparicio S — 4/1/2015 - 3/31/2022 — CAD — 0.36 calendar
Canada Research Chairs
Title: Canada Research Chair in Molecular Oncology (Tier 1)
Goals: Salary Support
Aims: N/A
Contact: Tri-agency Institutional Programs Secretariat 613-996-0239 information@chairs-chaires.gc.ca
Role: PI
Overlap: None

Aparicio S — 7/1/2016 - 6/30/2023 — CAD — 1.20 calendar
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 613-944-4624 dale.dempsey@chairs-chaires.gc.ca
Role: PI
Overlap: None

Bénard F — 7/1/2016 - 6/30/2023 — CAD — 0.12 calendar
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 613-944-4624 dale.dempsey@chairs-chaires.gc.ca
Role: Co-PI
Overlap: None

Aparicio S — 3/1/2017 - 2/28/2022 — CAD — 0.12 calendar
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

3/1/2017 - 2/28/2022 0.12 calendar
Hirst M, Marra M, Jones S CAD
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 613-944-4624 dale.dempsey@chairs-chaires.gc.ca
Role: Co-applicant
Overlap: None

5/1/2017 - 4/30/2023 1.20 calendar
Hannon G GBP
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 grandchallenge@cancer.org.uk
Role: Co-PI
Overlap: None

2/1/2018 - 1/31/2023 1.20 calendar
Aparicio S CAD
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 416-934-5313 sherri.huys@cancer.ca
Role: PI
Overlap: None

2/1/2018 - 1/31/2023 0.24 calendar
Shah S CAD
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 416-934-5313 sherri.huys@cancer.ca
Role: Co-applicant
Overlap: None

Stein L — 4/1/2018 - 3/31/2022 — 0.12 calendar
CAD
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 778 698-9909
Role: Co-PI
Overlap: None

Huntsman D — 7/1/2018 - 03/31/2025 — 0.60 calendar
CAD
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 rwatkins@tfri.ca 604-675-8000
Role: Co-PI
Overlap: None

Shah S — 10/1/2018 - 9/30/2021 — 0.24 calendar
USD
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 614-297-8155
Role: Co-PI
Overlap: None

10/1/2018 - 9/30/2024 0.60 calendar
Aparicio S USD
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 bcrf@bcrf.org 646-497-2600
Role: PI
Overlap: None

1/1/2019 - 12/31/2021 0.12 calendar
Sonenberg N and Pollak M CAD
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 (215) 440-9300
Role: Co-applicant
Overlap: None

9/18/2019 - 9/17/2022 0.60 calendar
Brugge JS, Aparicio S USD
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

4/1/2020 - 3/31/2025 0.60 calendar
Satija R (New) USD
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

9/30/2020 - 9/29/2023 0.24 calendar
Shah S (This award) USD
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 karen.m.wylie.civ@mail.mil
Role: Co-PI
Overlap: None

4/1/2021 - 3/31/2026 0.60 calendar
Aparicio S (New) CAD
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 - 3/318/2026 1.20 calendar
Aparicio S (New) CAD
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

2/1/2021 - 1/31/2022 0.36 calendar
Roth A, Ha G, Hunter N, Aparicio S (New) CAD
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 cascadia@fredhutch.org
Role: Co-PI
Overlap: None

2/1/2021 - 08/31/2022 0.12 calendar
Huntsman D (New) CAD
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

10/1/2021 - 09/30/2024 0.60 calendar
Hannon G (New) USD
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: deltatissue@wellcomeleap.org
Role: Co-Investigator
Overlap: None

PREVIOUS:

3/1/2013 - 2/28/2021 .00 calendar
Aparicio S CAD
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 .00 calendar
Morin G, Aparicio S USD
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

2/1/2017 - 1/31/2019 .00 calendar
Steidl C, Shah S CAD
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 sherri.huys@cancer.ca
Role: Co-PI
Overlap: None

8/1/2018 - 7/31/2020 .00 calendar
Marra M CAD
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 416-934-5313 sherri.huys@cancer.ca
Role: Co-PI
Overlap: None

10/1/2018 - 9/30/2020 .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 604 675-8242
Role: Co-PI
Overlap: None

W81XWH-20-1-0565: Dissecting the impact of mutational processes on therapeutic response in ovarian cancer

PI: Dr. Sohrab Shah, Sloan Kettering Institute for Cancer Research, NY **Budget:** $760,667

Topic Area: Cancer Evolution **Mechanism:** FY19 OCRP-Investigator-Initiated Research Award

Research Area(s): 0200, 1500 **Award Status:** 30 Sep. 2020- 29 Sep. 2023

Study Goals: In this work we plan to discover how mutational processes shape tumor evolution and to gain mechanistic insight into the development of drug resistance. Our long-term goal is for our findings to guide targeted treatment options for high grade serous ovarian cancer (HGSOC) patients.

Specific Aims:

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

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

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

Key Accomplishments and Outcomes:

Publications:

1) Salehi, S., Kabeer, F., et al. Clonal fitness inferred from time-series modelling of single-cell cancer genomes. Nature. 2021 Jul;595(7868):585-590

2) Vazquez-Garcia, I., Uhlitz, F. et al. Immune and malignant cell phenotypes of ovarian cancer are determined by distinct mutational processes (under review at Nature) Available from: https://www.biorxiv.org/content/10.1101/2021.08.24.454519.abstract

3) Funnell, T., O'Flanagan, C., et al. The impact of mutational processes on structural genomic plasticity in cancer cells (under review at Nature) Available from:bioRxiv https://doi.org/10.1101/2021.06.03.446999

4) Williams, M., Evolutionary tracking of cancer haplotypes at single-cell resolution (under review at Nature) Available from: bioRxiv https://doi.org/10.1101/2021.06.04.447031

Patents: none to date

Funding Obtained: none to date