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TITLE: Comprehensive Evaluation of Immune Function in Patients Receiving Multimodal Therapy for High-Risk Neuroblastoma

PRINCIPAL INVESTIGATOR: Dr. Kai Tan, PhD

CONTRACTING ORGANIZATION: Children's Hospital of Philadelphia

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14. ABSTRACT Children with high-risk neuroblastoma undergo intensive multimodality treatment. Despite this, only ~50% of patients are cured, highlighting a need for improved therapies. Because ~90% of patients with neuroblastoma are diagnosed before the age of 5 years, the impact of improved therapy selection has the potential to not only improve survival, but also impact the quality of the many years of life survivors of this disease may have. Unfortunately, we currently lack accurate methods to identify patients who are most likely to benefit from specific therapeutic modalities and those for whom new treatments are needed. Prior research has revealed that immune cells such as T cells play an essential role in killing cancer cells, but we know very little about how their functions change over the course of various components of neuroblastoma therapy. This proposal will focus on using new and highly detailed techniques to study malignant cells from patients and simultaneously study immune cell function from the same patients. Our twin goals are to identify biomarkers that can be used clinically to predict therapy response to optimize treatment selection, and to understand immune cell response during therapy in order to develop novel therapies.					
15. SUBJECT TERMS Neuroblastoma, multimodal therapy, sequencing and profiling techniques, dynamics of immune function					
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1. INTRODUCTION:

High-risk neuroblastoma is an aggressive childhood malignancy that accounts for a disproportionate number of childhood cancer deaths. In recent years, immunotherapy approaches have shown significant activity both for children with newly diagnosed disease and for patients with relapsed or refractory disease. In this context, there are important gaps in our knowledge of the immune microenvironment of these tumors at diagnosis and over time in response to high-risk therapy. Moreover, the humoral immune response to these tumors at diagnosis and over time has not been fully characterized. In this Translational Team Science Award, the multidisciplinary team is working to address these gaps in our knowledge by characterizing the immune profile of high-risk neuroblastoma patients participating in Children's Oncology Group (COG) trial ANBL1531. By embedding this work within the ANBL1531 trial, the immune profiling can be linked to the rich clinical annotation from this large phase 3 clinical trial. Moreover, the effects on the immune profile of the specific targeted therapies (¹³¹I-MIBG and the ALK inhibitor lorlatinib) under investigation in this trial can be studied.

2. KEYWORDS:

Neuroblastoma, immune microenvironment, 131I-MIBG, lorlatinib, single-cell sequencing, imaging, cytokines, immune repertoire, T cell receptor, B cell receptor, circulating tumor DNA

3. ACCOMPLISHMENTS:

Specific Aims (specified in proposal)	Timeline	Site 1	Site 2	Site 3	% completion
Specific Aim 1	Months				
IRB approvals (with annual renewals)	-12 to -6	Dr Bagatell	Dr Pugh	Dr DuBois	100%
HRPO review and approval	0-3	Dr Tan, Dr Bagatell, Dr Naranjo	Dr Pugh	Dr Dubois	100%
Major task 1: Identify ANBL1531 patients with available paired frozen tumor samples and serial blood samples; distribute samples from COG and CHOP banks	3-6	Dr Tan, Dr Bagatell, Dr Naranjo		Dr DuBois, Dr Collins	20%
Major task 2: snRNA-Seq on paired samples	9-30	Dr Tan			0%
Major task 3: scATAC-Seq on paired samples	9-30	Dr Tan			0%
Major task 4: CODEX on paired samples	15-36	Dr Tan			0%
Major task 5: CyTOF on serial PBMC samples	9-18			Dr Collins	0%
Major task 6: Luminex on serial plasma samples	15-24			Dr Collins	0%
Major task 7: Data analysis focused on immune cell landscape, immune-tumor cell interactions, transcriptional regulatory and signaling pathways as well as circulating immune markers in specimens from patients on each treatment arm	16-42	Dr Tan, Dr Naranjo			0%

Major task 8: Data analysis focused on clinical associations with immune cell landscape, immune-tumor cell interactions, transcriptional regulatory and signaling pathways in tumors and with circulating immune markers	40-48	Dr Tan, Dr Bagatell, Dr Naranjo			0%
Major task 9: Translate key findings from Aim 1 into successor COG high-risk neuroblastoma trials and/or COG neuroblastoma classification system	42-48	Dr Bagatell, Dr Naranjo			0%
Major task 10: Manuscript preparation	42-48	All	All	All	0%
Milestones achieved: Identify treatment arm-specific cellular and molecular signatures; identify associations between cellular and molecular signatures and clinical outcomes	40-48	All	All	All	0%
Specific Aim 2					
Major task 1: Identify ANBL1531 patients with available serial cell-free DNA samples and receive sequencing libraries from Dana-Farber	4-10	Dr Naranjo	Dr Pugh	Dr DuBois Dr Crompton	25%
Major task 2: Data generation (CapTCR/BCR-Seq on serial cfDNA libraries, PBMC sample processing, library generation and CapTCR/BCR-Seq)	9-18		Dr Pugh		0
Major task 3: Quality control (data assessment and library reprocessing if needed)	18-21		Dr Pugh		0%
Major task 4: Data analysis focused on immune cell repertoires, overall diversity, common clonotypes, tracking clones over time, defining clone specificity groups	21-36		Dr Pugh		5%
Major task 5: Correlative analysis of peripheral immune repertoire with tumor-infiltrating immune cells from Aim 1	36-48	Dr Tan	Dr Pugh		0%
Major task 6: Correlative analysis of peripheral immune repertoire with immune phenotypes and cytokine profiles from Aim 1	36-48		Dr Pugh	Dr Collins	0%
Major task 7: Clinical associations of overall diversity, TCR/BCR specificity groups and clonotype behaviors	36-48	Dr Bagatell, Dr Naranjo	Dr Pugh	Dr DuBois, Dr Crompton	0%
Major task 8: Integrate findings from Aim 2 with other ANBL1531 genomic efforts, including germline, somatic, and ctDNA sequencing	36-48	All	All	All	0%
Major task 9: Translate key findings from Aim 2 into successor COG high-risk neuroblastoma trials and/or COG neuroblastoma classification system	42-48	Dr Bagatell, Dr Naranjo		Dr DuBois	0%
Major task 10: Manuscript preparation	42-48	All	All	All	0%

Milestones achieved: Determine temporal patterns of peripheral immune repertoire specific to treatment arms, identify tumor-specific immune cells and their clinical significance, identify associations between shifts in immune repertoire and therapy response	36-48	All	All	All	0%
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What was accomplished under these goals?

1. We have completed all of the regulatory and administrative steps needed to conduct this collaborative research (Major Task 1, Aims 1 and 2). Specifically, all IRB and HRPO approvals are in place. Moreover, all material transfer agreements are in place that will allow samples and data to flow between collaborating researchers. Completion of these steps required substantial effort on behalf of the whole team.
2. We have established quarterly team meetings to track progress and discuss any intervening issues. Increasingly, these meetings will focus on scientific rather than administrative components of this project.
3. The parent clinical trial (COG ANBL1531) upon which this research is based has continued to show outstanding patient accrual (Major Task 1, Aims 1 and 2). As of September 1st, we have enrolled 698 patients with newly-diagnosed high-risk neuroblastoma, making this now the largest COG trial ever conducted for patients at time of initial diagnosis. Of these 698 patients, 487 out of 500 planned have been randomized as part of the ¹³¹I-MIBG randomized portion of the trial and 72 patients are participating in the non-randomized portion of the trial focused on treatment of patients with *ALK* aberrant tumors with the *ALK* inhibitor lorlatinib. As seen in **Figure 1**, accrual to the randomized portion of the trial (Arm A vs. Arm B) is proceeding ahead of schedule. This robust accrual will enable the immune profiling work embedded in the trial and funded by this award.

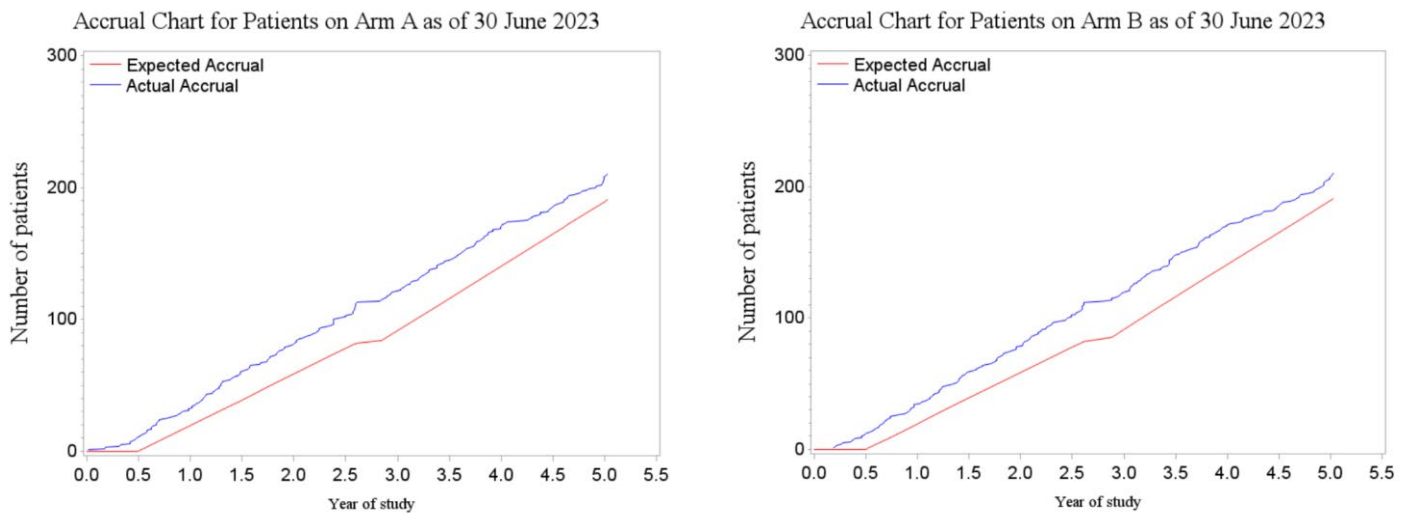


Figure 1. Actual vs. expected accrual to Arms A and B of the ANBL1531 clinical trial.

4. We have established parameters and workflows for identifying patients from ANBL1531 to be included in the cohort of patients who will be profiled as part of this project (Major Task 1, Aims 1 and 2). It was anticipated that paired frozen tumor samples with adequate viable tumor material from diagnosis and second look surgical resection would be the most limiting biospecimen for the project. We have started to build our cohort based upon patients already identified to have adequate viable tumor. Using this approach, we have identified an initial group of 18 patients with samples being pulled for shipment from the Biopathology Center to the Tan laboratory. These patients also have the appropriate peripheral blood samples to support work based upon circulating biomarkers. We identified another 9 patients with adequate viable tumor seen at second look surgical resection who did not have a baseline Streck tube available for analysis. We are holding these patients' samples in reserve

for now while we prioritize patients for the cohort who have both frozen tumor (from both timepoints) and Streck tubes available to allow integrated immune profiling.

We recently completed another batch of pathology reviews that yielded 4 more patients with paired baseline frozen and second look surgical samples and Streck tubes as well as 2 more patients with inventory pending for Streck tube and baseline frozen material.

5. We have identified a cohort of 15 ANBL1531 patients for analysis of serial cell-free DNA (Major Task 1, Aim 2). These 15 patients have samples collected from multiple sources and timepoints (see Figure 2 below). One of these patients (PAZNRG) also has matching 30x WGS data.

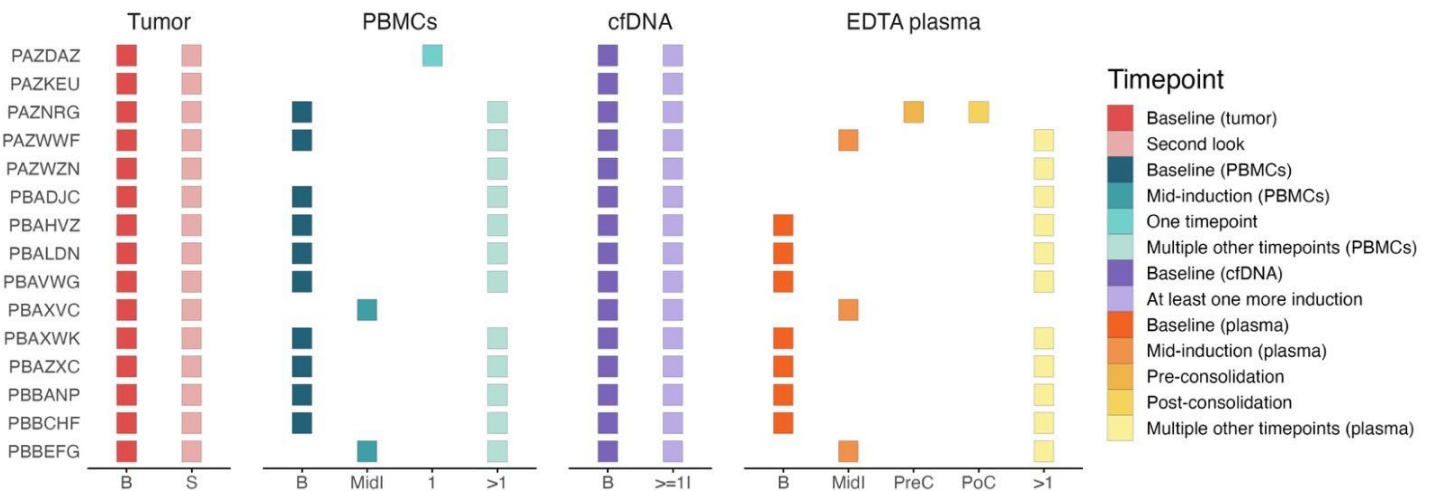


Figure 2. First ANBL1531 patient cohort with multiple sample types and timepoints.

So far, we have received 14 baseline and one C3 cfDNA samples from the Crompton lab, from the following patients in cohort 1: PAZDAZ, PAZKEU, PBAHVZ, PAZWZN, PAZWWF, PBAZXC, PBAXWK, PBALDN, PBBCHF, PBAXVC and PBBEFG. One of these samples (PAZDAZ-BL) also has matching 30x WGS data.

We are currently deep-sequencing the 15 cfDNA samples mentioned above using CapTCR/BCR-Seq.

6. We have performed bioinformatics analysis to determine if TCRs and BCRs can be detected from 30X WGS data (Major Tasks 2 and 4, Aim 2). We used MiXCR4.0.2 and TRUST4 on three samples: PAZSKT-baseline (BL), PBAXSX-BL and PBAXSX-relapse (RL). MiXCR was unable to detect any TCRs and BCRs, and TRUST4 found very few functional BCRs, most of which lack J-gene information (see Figure 3 below for TRUST4 result for PBAXSX-BL). We thus concluded that we cannot detect TCRs and BCRs at 30x.

#count	frequency	CDR3nt	CDR3aa	V	D	J	C	cid	cid_full_length
40	0.163265300	TGTATGATCGAGCACAGCAGAGCTTCTCATGCTGACAC...	CMIEHSRASHADTHRW	IGLV5-45*01	.	.	.	assemble123	0
36	0.149918400	TGTATGATTTGGCACAGCAGCGCTTCTCACAGTGACAC...	CMIWHSSASHSDTHRW	IGLV5-45*01	.	.	.	assemble378	0
36	0.146938800	TGTATGATTTGGCCAAGCAATGCTTCTCACAGTGACAC...	CMIWPSNASHSDTHRW	IGLV5-37*01	.	.	.	assemble185	0
27	0.111306100	TGTATGATTTGGCACAGCAGTGCTTCTCACAGTGACAC...	CMIWHSSASYSDTHRW	IGLV5-45*01	.	.	.	assemble378	0
10	0.044530610	TGTGCCATTTGGTACAGCAGCACTTCTCACAGTGACAC...	CAIYSSYSHSDHTHW	IGLV5-39*01	.	.	.	assemble1340	0
3	0.012244900	TGTATGATTTGGCACAGCAGTGCTTCTCACAGTGACAC...	CMIWHSSASYSDTHRW	IGLV5-48*01	.	.	.	assemble3104	0
3	0.333333300	TGTGACAATAACAATGACATGCGCTTT	CDNNNDMRF	.	.	TRAJ43*01	TRAC	assemble2106	0
2	0.008163265	TGTATCATTTGGCACAGCAGCGCTTCTCACAGTGACAC...	CIWHSSASHSDHTHW	IGLV5-45*01	.	.	.	assemble378	0
1	0.004448980	TGTGTCAATTTGGTACAGCAGCACTTCTCACAGTGACAC...	CVIYSSYSHSDHTHW	IGLV5-39*01	.	.	.	assemble1340	0
1	0.004081633	TGTCAACAGTATGATAATCTCTTT	CQQYDNLF	IGKV1-33*01	.	IGKJ4*01	IGKC	assemble4179	0
1	0.004081633	TGTACCATTTGGCACAGCAGCGCTTCTCACAGTGACAC...	CTIWHSSASHSDHTHW	IGLV5-39*01	.	.	.	assemble1340	0

Figure 3. BCR sequence analysis using TRUST4 and patient PBAXSX-BL WGS data.

Subsequently, we conducted copy number analysis on the same three samples using ichorCNA. We were able to recapitulate the high tumor burden and copy number finding originally reported by the Crompton lab (see Figure 4 below).

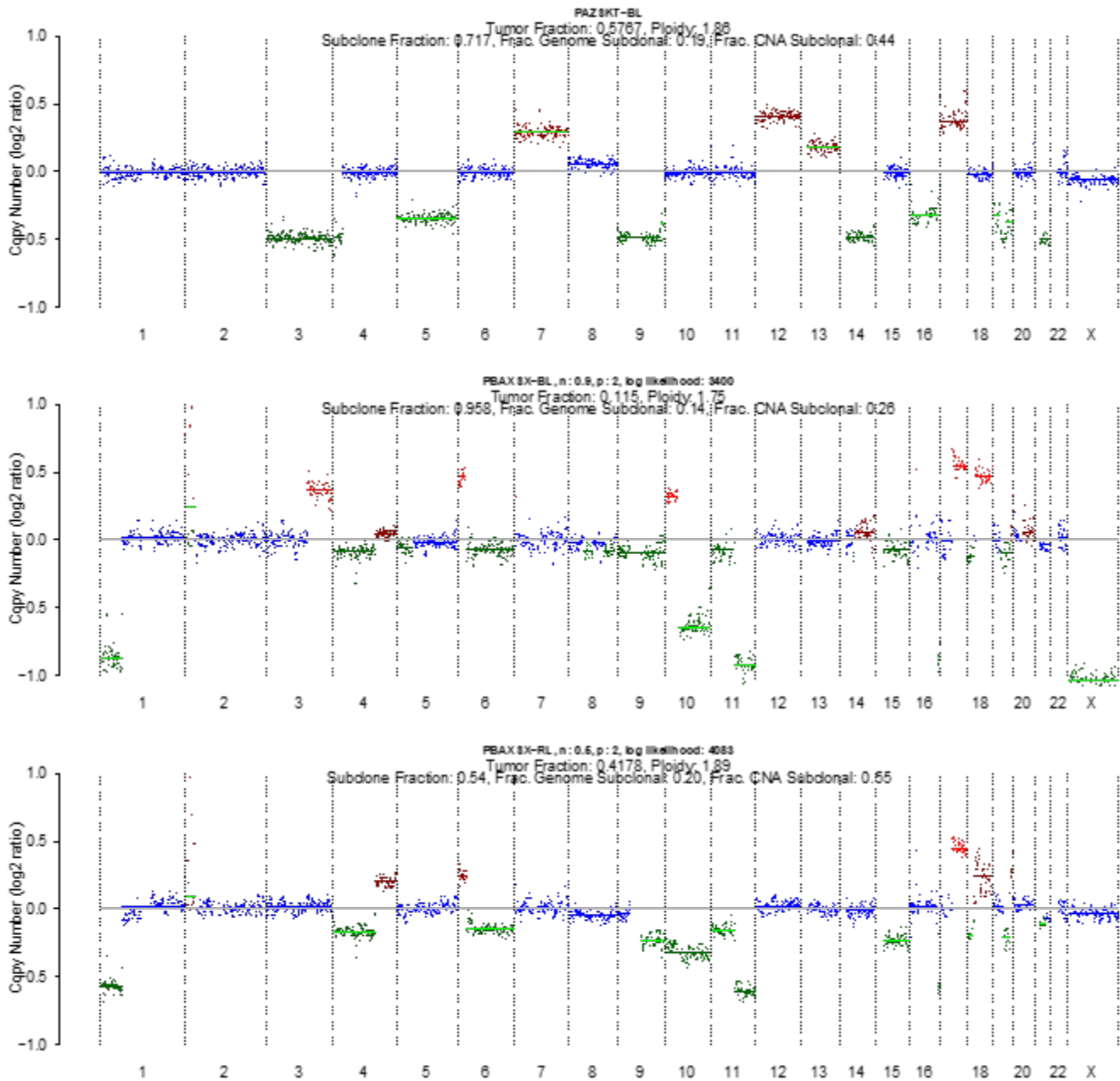


Figure 4. Copy number analysis using ichorCNA on three patient WGS datasets.

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

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

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

1. **Complete Accrual to ANBL1531 (Major Task 1, Aims 1 and 2, DuBois, Bagatell, Naranjo):** The ANBL1531 clinical trial will reach a major milestone during the upcoming reporting period. The trial will reach 500 randomized patients in October or November 2023 and will close to further accrual at that time.

2. **Continue to Collect Biospecimens for Analysis (Major Task 1, Aims 1 and 2, DuBois, Bagatell, Naranjo):** While accrual to the ANBL1531 clinical trial will end, patients will continue to be treated for approximately 18 months from time of enrollment. Moreover, patients previously treated on the trial remain at risk for relapse events. Peripheral blood samples for immune biomarkers and circulating tumor DNA analysis will continue to be collected during this next reporting period. Likewise, paired tumor specimens from diagnosis and second look surgical resection will continue to be collected. As above, the study team reminds the local enrolling institution about the importance of submitting baseline Streck tubes and paired frozen tissue to support the funded work.
3. **Continue to Add Patients to the Cohort (Major Task 1, Aims 1 and 2, DuBois, Bagatell, Naranjo):** As above, we now have an established workflow for performing pathology review of second look surgical samples to identify patients with sufficient viable material for immune profiling following initial induction chemotherapy. We will continue this work during the upcoming reporting period and add patients to the cohort as they are identified.
4. **Continue to Collect Clinical Data for the Project (Major Task 1, Aims 1 and 2, DuBois, Bagatell, Naranjo):** In parallel with biospecimen collection, the study team continues to collect and clean the clinical data that will be essential for the final planned clinical correlations. Key outcomes of interest include response at end-induction using the International Neuroblastoma Response Criteria and survival endpoints, including relapse/disease progression and death.
5. **Generate single-nucleus RNA-Seq and ATAC-Seq data (Major Tasks 2 and 3, Aim 1, Tan):** We will make significant progress on data generation using the two types of assays. We will be able to get additional tumor samples from cohort 1 and finalize additional cohorts.
6. **Generate CODEX data (Major Task 4, Aim 1, Tan):** We will make significant progress on data generation using the two types of assays. We will be able to get additional tumor samples from cohort 1 and finalize additional cohorts.
7. **Perform initial analysis of single-nucleus RNA-Seq, ATAC-Seq and CODEX Data (Major Task 7, Aim 1, Tan):** We will focus on annotating immune cell landscape, identifying immune-tumor cell interactions, transcriptional regulatory and signaling pathways.
8. **Continue to generate serial cfDNA sequencing and CapTCR/BCR-Seq data (Major Tasks 2 and 3, Aim 2, Pugh):** We will make significant progress on data generation using the two types of assays. We will be able to get additional samples (cfDNA, PBMCs and tumor resections) from cohort 1, and finalize additional cohorts. We will sequence these additional samples using CapTCR/BCR-seq and perform quality control assessment once they get shipped to our lab.
9. **Continue to perform data analysis of the immune repertoire specificity and diversity of the sequenced samples (Major Task 4, Aim 2, Pugh):** We will use multiple analytical tools including MiXCR, TRUST4, GLIPH2, iNEXT to determine the overall TCR/BCR clonal diversity, common clonotypes, tracking clones over time, defining clone specificity groups.

4. IMPACT

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

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

There are no significant changes proposed for the coming reporting period.

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

The number of patients to date with pathology confirmation of sufficient frozen tumor material to support single-cell sequencing is lower than anticipated at this point in the project. This issue is delaying final determination of our cohort for this project. We are addressing this issue in several ways:

- Continue to accrue and treat new patients on the ANBL1531 clinical trial: We expect that all patients on the trial will be through second look surgical resection by May 2023. Therefore, new samples continue to be received by our Biopathology Center for tissue triage.
- Continue to remind enrolling centers of the importance of submitting frozen tumor material from the second look surgical resection: With each enrollment to the trial, staff at the enrolling center receive an email reminding them of the importance of submitting frozen tumor material from second look surgery. Moreover, the study team reminds participating investigators and clinical research coordinators about these samples at our twice yearly Children's Oncology Group meetings.
- Continue pathology reviews of second look surgical cases: We have an established workflow for obtaining pathology expert review of second look surgical cases to confirm adequate viable tumor available to justify detailed immune profiling.

Changes that had a significant impact on expenditures

Due to the delay in identifying patients for the cohort as described above, there have been delays in the execution of assays and the expenditures related to these assays. Our expectation is that in the next reporting year patient identification will be increased and therefore so will expenditures related to the proposed assays.

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

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals.

Not applicable to this award

Significant changes in use of biohazards and/or select agents

Not applicable to this award

6. PRODUCTS

Publications, conference papers, and presentations

Journal publications

Nothing to report

Books or other non-periodical, one-time publications

Nothing to report

Other publications, conference papers and presentations

Jiang, Y., Pugh T. J. (May 2023). Understanding the relationship between T- and B-cell repertoire and therapy response in patients with high-risk neuroblastoma. Poster presented at the 2023 James Lepock Memorial Symposium, University of Toronto, ON, Canada.

Biyik Sit, R., Uzun, Y., Chen, C., Thadi, A., Wu, C., Surrey, L., Gao, P., Martinez, D., Patel, T., Qiu, Q., Yu, W., Chen, C., Hu, Y., Chen, G., Hogarty, M., Bernt, K., Zhang, N., Maris, J.M., Tan, K. (June 2023). Identification and validation of intrinsic and extrinsic factors of neuroblastoma therapy resistance. Oral presentation at the 2023 NCI Cancer Moonshot Human Tumor Atlas Network Semi-annual Meeting, Cambridge, Massachusetts, USA.

Website(s) or other Internet sites(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Children's Hospital of Philadelphia personnel

Name: Kai Tan, PhD

Project Role: Initiating PI

Researcher Identifier (ORCID ID): 0000-0002-9104-5567

Nearest person month worked: 1

Contribution to project: He leads a laboratory focused on utilizing single cell sequencing approaches to understand pediatric cancers, including the tumor microenvironment. He is responsible for overall

oversight of the project. He is also responsible for the scientific conduct of the genomic and imaging studies included in Aim 1.

Name: Rochelle Bagatell, MD

Project Role: Co-investigator

Researcher Identifier (ORCID ID): 0000-0002-5729-8819

Nearest person month worked: 1

Contribution to project: She is a pediatric oncologist and clinical investigator. She is an international expert in the clinical care of children with neuroblastoma. She is the co-chair of the ANBL1531 clinical trial that forms the basis for the project and the chair of the COG Neuroblastoma Committee. She is providing her expertise in immunotherapy for neuroblastoma, and she is responsible for translating the findings from the current study into subsequent national and international frontline neuroblastoma studies.

Name: Anusha Thadi

Project Role: Research Assistant

Researcher Identifier (ORCID ID): 0000-0002-1271-0398

Nearest person month worked: 1

Contribution to project: Ms. Thadi is responsible for generating snRNA-Seq, scATAC-Seq data and CODEX data along with Ms. Joshi. She will work closely with Mr. Zhang and bioinformatician for QC and downstream data analysis.

Name: Zhan Zhang

Project Role: Graduate student

Researcher Identifier (ORCID ID): N/A

Nearest person month worked: 6

Contribution to project: Mr. Zhang is responsible for all data analysis described in Aim 1. Specifically, he will be responsible for integration of snRNA-Seq, scATAC-Seq data, and CODEX data. He will also work with other bioinformatics researchers from DFCI and University of Toronto for integrative analysis of data from Aims 1 and 2. Mr. Zhang will also work closely with the biostatistics team led by Dr. Naranjo for correlative analysis of omics data and clinical data

Name: Apoorva Joshi

Project Role: Research Assistant

Researcher Identifier (ORCID ID): 0000-0003-4867-0057

Nearest person month worked: 1

Contribution to project: Ms. Joshi is responsible for generating snRNA-Seq, scATAC-Seq data and CODEX data along with Ms. Thadi. She will work closely with the graduate student and bioinformatician for QC and downstream data analysis.

Name: Jessica Perazzelli

Project Role: Research Lab Manager

Researcher Identifier (ORCID ID): 0000-0003-0983-7854

Nearest person month worked: 1

Contribution to project: Ms. Perazzelli is responsible for receiving fresh samples from the participating sites on trial ANBL1531 and performing the initial processing of the received samples. She logs and freezes down the processed samples for use by the investigators involved in this project.

Funding support: Ms. Perazzelli is supported by the Children's Hospital of Philadelphia Cellular & Immunotherapy Fund

University of Florida personnel

Name: Arlene Naranjo, PhD

Project Role: Co-investigator

Researcher Identifier (ORCID ID): 0000-0001-7737-4324

Nearest person month worked: 1

Contribution to project: She is the lead biostatistician for the COG Neuroblastoma Committee and the lead biostatistician for the COG ANBL1531 clinical trial. The current application provides additional effort to enable her to perform the statistical analyses to determine whether there are tumor-intrinsic and microenvironment (extrinsic) markers that define patient subgroups with differential probabilities of clinical benefit following therapy. She is supervising and directing a master's level statistician in this capacity. Dr. Naranjo will interact closely with Drs. Tan, DuBois, and Bagatell throughout the award period.

Name: Brian LaBarre

Project Role: Masters Statistician

Researcher Identifier (ORCID ID): 0009-0001-6566-6861

Nearest person month worked:1

Contribution to project: Mr. LaBarre is a master's level statistician at the COG Statistics and Data Center office at the University of Florida. He is working on this project under the supervision of Arlene Naranjo, Ph.D. and is responsible for reviewing and formatting the immune function and clinical data to enable statistical analyses. He will also program the statistical software needed to conduct the described and will generate reports, data summaries, and figures to support the project.

Dana-Farber Cancer Institute personnel

Name: Steven DuBois, MD, MS

Project Role: Partnering PI

Researcher Identifier (ORCID ID): 0000-0003-0882-738X

Nearest person month worked: 1

Contribution to project: He is a pediatric oncologist and clinical investigator. He leads an active clinical research program focused on the development of novel agents and biomarkers relevant to children with advanced neuroblastoma. He is the chair of the Children's Oncology Group (COG) ANBL1531 clinical trial that forms the basis for this project. He is working with Drs. Collins and Crompton to oversee the activities described in Aims 1 and 2. He is contributing his clinical expertise relevant to neuroblastoma and will provide access to clinical data derived from the ANBL1531 trial.

Name: Natalie Collins, MD, PhD

Project Role: Co-investigator

Researcher Identifier (ORCID ID): 0000-0003-2980-9244

Nearest person month worked: 1

Contribution to project: She is a pediatric oncologist with a translational research program focused on pediatric solid tumor immunology. She has expertise in tumor microenvironment and immunotherapies relevant to neuroblastoma. She is responsible for coordinating the peripheral blood immune markers included in Aim 1.

Name: Brian Crompton, MD

Project Role: Co-investigator

Researcher Identifier (ORCID ID): 0000-0001-9404-6621

Nearest person month worked: 1

Contribution to project: He is a pediatric oncologist with a laboratory focused on utilizing genomic technologies to identify and validate new therapeutic targets for pediatric solid tumors, to develop non-invasive biomarkers of treatment response, and to study mechanisms of treatment resistance in these diseases. He has dedicated expertise in the development of liquid biopsy approaches relevant to pediatric solid tumors. He is responsible for sharing ctDNA data and sequencing libraries from ANBL1531 to inform the work being led by Dr. Pugh on Aim 2.

University Health Network personnel

Name: Trevor Pugh, PhD

Project Role: Partnering PI

Researcher Identifier (ORCID ID): 0000-0002-8073-5888

Nearest person month worked: 1

Contribution to project: His laboratory is focused on developing and applying novel sequencing approaches to understand human cancers, including changes in immune repertoire over time. He has extensive experience studying the genomics of neuroblastoma. He is responsible for the scientific conduct of the work included in Aim 2.

Funding support: Canada Research Chair in Translational Genomics and a Senior Investigator Award from the Ontario Institute for Cancer Research.

Name: Yiyue Jiang

Project Role: Graduate student

Researcher Identifier (ORCID ID): 0000-0001-5488-9763

Nearest person month worked: 12

Contribution to project: Yiyue Jiang is a PhD student with experience in immunology and genome biology. She is responsible for performing bioinformatic analysis of immune repertoire and cell-free DNA data sets, including integration with single cell RNA-seq data. She will also coordinate data generation and delivery to the core sequencing lab, working with the technician and scientific associate.

Name: Arash Nabbi, PhD

Project Role: postdoctoral fellow

Researcher Identifier (ORCID ID): 0000-0002-3195-7361

Nearest person month worked: 12

Contribution to project: He is a senior postdoctoral fellow with extensive experience in pediatric cancer research and immunogenomics. He is responsible for performing bioinformatic analysis of immune repertoire and cell-free DNA data sets, including integration with single cell RNA-seq data. The

postdoctoral fellow will also coordinate data generation and delivery to core sequencing lab, working with the technician and scientific associate

Name: Stephanie Pedersen

Project Role: Lab Technician

Researcher Identifier (ORCID ID): 0000-0002-4525-371X

Nearest person month worked: 1

Contribution to project: Ms. Pedersen is responsible for processing the blood samples from the clinical trial and performing all CapTCR-seq laboratory experiments

Funding support: The Terry Fox New Frontiers Program Project Grant funded by the Terry Fox Research Institute, New Frontiers Program

Name: Jeffrey Bruce

Project Role: Bioinformatician

Researcher Identifier (ORCID ID): 0000-0001-5509-9990

Nearest person month worked: 1

Contribution to project: Mr. Bruce supports the execution of standardized pipelines, sharing data through the cloud-based TCR repertoire analysis system and public repositories, performing data quality reviews, integrating mutation calls from the Crompton lab, and supporting statistical analysis.

Funding support: The Princess Margaret Cancer Consortium. Gold cohort case and infrastructure support, funded by the Terry Fox Research Institute - Marathon of Hope Cancer Centres Network; Ontario Institute for Cancer Research Senior Investigator Award, funded by the Ontario Institute for Cancer Research (OICR)

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

Kai Tan

Completed funding since previous submission

Title: A systems approach to the genetic study of alcohol dependence

Role: MPI (Shizhong Han/Kai Tan MPI)

Time commitment: 7.5%, 0.9 cal mos

Supporting agency: NIH/NIAAA R01AA024486

Funding Agency Grant Officer: Abbas Parsian, Program Officer, 6700B Rockledge Dr, BG 6700B RM 1338, Bethesda MD 20817

Period of performance: 03/01/2017-02/28/2022 (NCE)

Level of funding: subcontract annual directs

Brief description of the project's goals: The goal of this project is to employ a systems biology approach to identify regulatory variants and gene networks underlying alcohol dependence.

List of specific aims:

Aim 1: Identify gene subnetworks underlying AD through integrated analysis of GWAS with brain-specific DCNs;

Aim 2: Identify regulatory risk variant sets through integrated analysis of GWAS with brain-specific TRNs

Aim 3: Evaluate the function of identified gene subnetworks and regulatory variants using existing imaging genetics data.

Overlap: None

Title: Mechanisms of endothelial-to-hemogenic transition mediated by Runx1

Role: MPI (Kai Tan/Nancy Speck PI)

Time commitment: 5%, 0.60 cal mos

Supporting agency: NIH/NICHD R01HD089245

Funding Agency Grant Officer: James Coulombe, Program Officer, 6710B Rockledge Drive, BG 6710B Room 2442, Bethesda, MD 20817

Period of performance: 07/01/2017-05/31/2022

Level of funding: annual direct costs

Brief description of the project's goals: The goal of this project is to apply systems biology approaches to study the transcriptional regulatory network controlling hemogenic endothelial specification, mediated by Runx1 and additional transcription factors that cooperate with Runx1.

List of specific aims:

Aim 1: Identify Runx1 target genes in embryonic endothelial cells that are competent to respond to Runx1, and examine the genome-wide chromatin modifications and gene expression changes that take place when Runx1 binds its target genes.

Aim 2: Develop an advanced graph-theoretic method to identify key TFs that cooperate with Runx1 in embryonic endothelial cells to induce HE and form blood.

Overlap: None

Title: Tools for annotating mutations in the 3D cancer genome

Role: PI

Time commitment: 8.7%, 1.04 cal mos

Supporting agency: NIH/NCI U01CA226187

Funding Agency Grant Officer: Jerry Li, Program Officer, BG 9609 RM 6W336 9609 Medical Center Dr. Rockville, MD 20850

Period of performance: 04/19/2018-03/31/2022 (NCE)

Level of funding: annual direct costs

Brief description of the project's goals: The goal of this project is to develop a suite of bioinformatics tools to predict the hierarchy of 3D genome organization and use such information to interpret and identify causal noncoding mutations.

List of specific aims:

Aim 1: Develop a method for identifying mutations that disrupt chromatin domain and subdomain boundaries in cancers.

Aim 2: Use disease-relevant enhancer- promoter network for prioritizing mutations that disrupt enhancer function.

Aim 3: Develop a 3D cancer genome database for curating, querying and visualizing chromatin interaction data together with transcriptomic, epigenomic, and mutation data.

Overlap: None

Title: Single-cell Analysis to Study Mechanisms of Pediatric Cancer and Developmental Disorders

Role: PI

Time commitment: 1%, 0.12 cal mos

Supporting agency: Pennsylvania Department of Health (SAP#4100083086)

Funding Agency Grant Officer: Susan Guy, Public Health Program Administrator, Room 833 Health and Welfare Building, 625 Forster Street, Harrisburg, PA 17120-0701

Period of performance: 06/01/2019 – 05/31/2023

Level of funding: annual direct costs

Brief description of project's goals: The overarching goal of this project is to harness the power of single-cell technology to better understand the transcriptomic, epigenomic, and tissue-microenvironmental heterogeneity in pediatric sarcoma, childhood epilepsy, and premature birth. Novel gene markers and therapeutic targets derived from the single-cell studies will be tested using cell line and animal models. List of specific aims:

Aim 1: Determine the molecular basis of the heterogeneity of three major types of pediatric sarcomas, Ewing's sarcoma (ES), rhabdomyosarcoma (RMS), and osteosarcoma (OS)

Aim 2: Determine transcriptomic and epigenomic signatures of defined subsets of neurons in pediatric epilepsy syndromes across development to inform novel therapeutic approaches

Aim 3: Link the transcriptomic and epigenomic signatures of the cord blood immune cell population to adverse outcomes in preterm infants.

Overlap: None

Title: A Crohn's disease epithelial stem cell atlas: pediatric to adult continuum

Role: MPI (Hamilton/Tan/Legner/Kelsen/Bewtra MPI)

Time commitment: 3%, 0.36 cal mos

Supporting Agency: The Leona & Harry B. Helmsley Charitable Trust 2008-04062

Funding Agency Grant Officer: Laurie Churchill, Program Officer (PO), 230 Park Avenue, Suite 659, New York, NY 10169

Period of performance: 12/01/2019 – 11/30/2022

Level of funding: direct costs

Brief description of project's goals: The overall goal of this project is to generate a comprehensive map of intestinal stem cells and their cellular signaling pathways in healthy versus Crohn's disease biopsies from children and adult

List of specific aims:

Aim 1: Determine the cellular composition of terminal ileal and ascending colonic mucosal biopsies.

Aim 2: Define transcriptional regulatory and signaling pathways within and between ISCs and niche cells

Aim 3: Evaluate epithelial stem cells signatures that persist in 3D enteroid/colonoid culture.

Overlap: None

Title: Center for Developmental Mapping of Heart and Bone Tissues

Role: MPI (Kai Tan/Kathrin Bernt/Liming Pei MPI)

Time commitment: 8%, 0.96 cal mos

Supporting agency: NIH U54HL156090

Funding Agency Grant Officer: Kevin Heath, Grants Management Specialist, 6701 Rockledge Drive, RKL1 200-E, Bethesda, MD 20892

Period of performance: 09/01/2020-08/31/2022

Level of funding: annual total costs

Brief description of the project's goals: The overarching goal of our mapping effort is to capture the molecular and cellular heterogeneity and cellular spatial organization of bone and heart.

List of specific aims:

Aim 1: To procure, bank and annotate high-quality bone and heart biospecimens to be used by our center and the larger research community. We will optimize tissue handling, biobanking, and processing protocols that are compatible for the range of molecular assays proposed in this project.

Aim 2: To profile bone and heart specimens across the lifespan using a set of robust and scalable imaging and single-cell omics assays, including MERFISH, CODEX, snRNA-Seq and scATAC-Seq. We will integrate existing and new multidimensional phenotyping and computational modeling to further define both the "normalcy" and diversity of high quality human bone and heart tissues with aging.

Aim 3: To deploy robust and scalable computational pipelines and algorithms for atlas construction. The multi-dimensional atlases will be anchored on a common coordinate framework and contain the following components: cell-molecule maps, spatial distribution patterns of chromatin, RNA, protein and cells in the tissue microenvironment, cell-specific transcriptional regulatory pathways, and signal transduction pathways mediating cell-cell crosstalk in the tissue microenvironment. Open-source software and an interactive database will be developed to facilitate data sharing and in-depth analyses.

Aim 4: To collaborate with other Human Biomolecular Atlas Program Centers to identify organ-specific and common mechanisms for the organization of tissue microenvironment and cell-cell communications.

Overlap: None

Title: Identification of Biomarkers and Mechanisms of Response in Pre- and Post-KTE-C19 Manufacturing T Cells

Role: Co-investigator (Stephan Grupp/Jos Melenhorst MPI)

Time commitment: 3%, 0.36 cal mos

Supporting agency: Kite Pharma, Inc.

Funding Agency Grant Officer: Sophia Doak, Translational Medicine Management Associate, 1800 Stewart St. Santa Monica, CA 90404

Period of performance: 04/07/2020-04/06/2023

Level of funding: total costs

Brief description of the project's goals: The main focus of this proposal is on the biomarker discovery in pre- and post-manufacturing T cells and post-infusion CAR T cells.

List of specific aims:

Aim 1: Determine whether the same biomarkers and mechanisms previously identified for another CART19 product discriminate between responders and non-responders to KTE-C19

Aim 2: Deep molecular, biochemical and cellular characterization of pre- and post-manufacturing patient T cells to identify biomarkers and mechanisms of response to KTE-C19

Aim 3: Test the hypothesis that the anti-tumor effect of KTE-C19 is induced and maintained by discrete but long-term persisting CAR-engineered T cells

Overlap: None

New funding since previous submission

Title: Regulation of innate immune signaling by RUNX1

Role: Co-Investigator (Nancy Speck PI)

Time commitment: 5% effort, 0.60 cal mos

Supporting agency: NIH R01HL161221-01A1

Funding Agency Grant Officer: Shaheed Michael Ziyout, Grant Management Specialist, 6705 Rockledge Dr. RK1 Rm 202-D Bethesda, MD 20817 Period of Performance: 07/01/2022 – 06/30/2027

Level of funding: annual direct costs

Brief description of the project's goals: The goal of this proposal is to understand how the transcription factor RUNX1 restrains inflammatory cytokine production by neutrophils.

List of specific aims:

Aim 1: Determine in which hematopoietic stem or progenitor population RUNX1 function is required to restrain inflammatory cytokine/chemokine production by neutrophils

Aim 2: Determine if RUNX1 directly regulates the transcription of inflammatory cytokine/chemokine genes.

Aim 3: Determine the mechanism underlying increased TLR4 pathway activity in neutrophils lacking RUNX1

Overlap: None

Title: Center for multi-dimensional atlas of the human heart

Role: MPI (Kai Tan, Liming Pei, Jeffrey Moffitt)

Time commitment: 10% effort, 1.20 cal mos

Supporting agency: NIH U54HL165442-01

Funding Agency Grant Officer: Raj K Krishnaraju, Scientific Review Officer, 6701 Rockledge Dr. RK2 Room 903-D Bethesda, MD 20817

Period of Performance: 07/01/2022 – 06/30/2026

Level of funding: annual directs

Brief description of the project's goals: Map molecular and cellular changes in heart tissues over the course of human lifespan using comprehensive multi-dimensional single-cell and imaging technologies List of specific aims:

Aim 1: Organ Atlases: spatially resolved atlases will provide a highly user friendly, publicly available, searchable database of the most comprehensive multi-omic, single cell analysis of the heart. Molecular data will be richly annotated with additional clinical and epidemiological data.

Aim 2: Computational methods: in addition to the data, the critical computational tools and pipelines developed in this project will be available to the research community. These include methods and pipelines for processing multi-omics and imaging data, inference of cell-specific regulatory and signaling pathways, correlation of mesoscale imaging and molecular imaging features, as well as database algorithms for the query, exploration and visualization of highly complex data.

Aim 3: Access to biospecimens for follow-up studies: biospecimens collected in this project will be banked and made available to the biomedical research community.

Overlap: None

Title: Comprehensive evaluation of immune function in patients receiving multimodal therapy for high risk neuroblastoma

Role: MPI (Kai Tan/Steven DuBois/Trevor Pugh)

Time commitment: 5% effort, 0.60 cal mos

Supporting agency: Department of Defense CA210953P1

Funding Agency Grant Officer: Amie Bunker, U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702-5014 Period of performance: 09/01/2022 – 08/31/2026

Level of funding: annual direct costs

Brief description of project goals: We will test the novel hypothesis that markers reflective of immune cell profile and interaction with malignant cells during the course of therapy can guide treatment of children with NBL

List of specific aims:

Aim 1: Identify tumor-derived and circulating biomarkers predictive of response to therapy in patients with high-risk neuroblastoma using single cell profiling and proteomic analyses

Aim 2: Define the breadth and dynamics of T- and B-cell diversity at diagnosis, during treatment, and at remission in patients with high-risk neuroblastoma

Overlap: None

Title: Repressing TGFbeta family signaling to promote hematopoietic stem cell formation in the embryo

Role: Co-Investigator (Nancy Speck PI)

Time commitment: 5% effort, 0.60 cal mos

Supporting agency: NIH R01HL163265-01

Funding Agency Grant Officer: Brian C Bai, Program Official, 6705 Rockledge Dr. RK1 Rm 202-D Bethesda, MD 20817

Period of Performance: 04/01/2022 – 02/28/2025

Level of funding: subcontract

Brief description of the project's goals: The goal of this proposal is to understand how transforming growth factor beta (TGFb) family signaling regulates the formation of hematopoietic stem cells (HSCs) in the embryo

List of specific aims:

Aim 1: To determine at what step of HSC formation or function the restraint of TGFb family signaling by

SMAD7 is required (pre-HSC formation, pre-HSC to HSC maturation, HSC self-renewal)

Aim 2: To determine which TGFb family signaling pathway SMAD7 restrains to allow HSCs to form in the embryo or function in the adult.

Overlap: None

Title: CART38: A Novel therapy for T-ALL

Role: Co-Investigator (David Teachey PI)

Time commitment: 1% effort, 0.12 cal mos

Supporting agency: Children's Hospital of Philadelphia (CHOP) Cell & Gene Therapy Seed Grant

Funding Agency Grant Officer: Robert DeNight, Assistant Director, Research Business Operations, Period of Performance: 07/01/2022 – 06/30/2024

Level of funding:

Brief description of the project's goals: The goal of the proposed work will be to evaluate the safety and efficacy of CART38 for T-ALL, and to compare the biology of CRS and ICANS following CART19, CART22 and CART38

List of specific aims:

Aim 1: Establish the safety and efficacy of CART38 for T-ALL

Aim 2: Identify the antigen specific variations in CRS and ICANS and identify targeted therapies

Overlap: None

Title: Center for multi-dimensional atlas of the human heart

Role: MPI (Kai Tan, Liming Pei, Jeffrey Moffitt)

Time commitment: 10% effort, 1.20 cal mos

Supporting agency: NIH U54HL165442-01

Funding Agency Grant Officer: Raj K Krishnaraju, Scientific Review Officer, 6701 Rockledge Dr. RK2 Room 903-D Bethesda, MD 20817

Period of Performance: 08/01/2022 – 07/31/2026

Level of funding:

Brief description of the project's goals: Map molecular and cellular changes in heart tissues over the course of human lifespan using comprehensive multi-dimensional single-cell and imaging technologies

List of specific aims:

Aim 1: Organ Atlases: spatially resolved atlases will provide a highly user friendly, publicly available, searchable database of the most comprehensive multi-omic, single cell analysis of the heart. Molecular data will be richly annotated with additional clinical and epidemiological data.

Aim 2: Computational methods: in addition to the data, the critical computational tools and pipelines developed in this project will be available to the research community. These include methods and pipelines for processing multi-omics and imaging data, inference of cell-specific regulatory and signaling pathways, correlation of mesoscale imaging and molecular imaging features, as well as database algorithms for the query, exploration and visualization of highly complex data.

Aim 3: Access to biospecimens for follow-up studies: biospecimens collected in this project will be banked and made available to the biomedical research community.

Overlap: None

Title: Understanding Differences between T-cell Acute Lymphoblastic Leukemia & Lymphoma

Role: Co-Investigator (David Teachey PI)

Time Commitment: 1% effort, 0.12 cal mos

Supporting Agency: Hyundai Motor America - Hope on Wheels 993259

Funding Agency Grant Officer: John Guastaferro, Executive Director, 10550 Talbert Ave. Fountain Valley, CA 92708

Performance Period: 12/1/2022 - 12/1/2024

Level of funding:

Brief description of project's goals: To understand of T-ALL and T-LL disease biology and define intrinsic and extrinsic biologic factors that distinguish T-ALL and T-LL. We will identify which T-ALL and T-LL patients are at high-risk for relapse and should be treated with alternative therapies. Finally, we will identify novel targets for the translation of new therapies for the next generation of clinical trials.

Specific Aims:

Aim 1: Investigate intrinsic biologic differences in T-ALL and T-LL

Aim 2: Define Microenvironmental differences in T-ALL and T-LL

Overlap: None

Title: Improving risk allocation and developing novel therapies for children with T-ALL

Role: Co-Investigator (David Teachey PI)

Time Commitment: 1% effort, 0.12 cal mos

Supporting Agency: NIH 2R01CA193776-06

Funding Agency Grant Officer: Alice Chi Wong, 9609 Medical Center Drive West Tower, 2nd floor Rockville MD 20850

Performance Period: 10/1/2022-9/30/27

Level of funding:

Brief description of project's goals: To understand differences in intrinsic tumor biology and the microenvironment in patients with T-cell acute lymphoblastic leukemia and T-cell acute lymphoblastic lymphoma

Specific aims:

Aim 1: Investigate intrinsic biologic differences between T-ALL and T-LL

Aim 2: Define mechanisms of sensitivity and resistance to corticosteroids in T-ALL and T-LL

Aim 3: Delineate mechanisms of sensitivity and resistance to proteasome inhibitors (PI) in TALL and T-LL

Overlap: None

Title: Interrogating Mechanisms of Anti-Tumor Immunity in Human Subjects and Murine Models of IDH-Mutant Glioma Treated with All-Trans Retinoic Acid and PD-1 Inhibition

Role: Co-Investigator (Nduka Amankulor PI)

Time Commitment: 3%, 0.36 cal mos

Supporting Agency: NIH

Funding Agency Grant Officer: N/A

Performance Period: 07/1/2023 – 06/30/2028

Level of funding: (subcontract)

Brief description of project's goals: To interrogate mechanisms of anti-tumor activity of all-trans retinoic acid and PD-1 inhibition treated humans and mouse models

Specific aims:

Aim 1: To Identify effector immune cellular and transcriptional mediators of ATRA-induced tumor immunity in IDHm glioma

Aim 2: To investigate the hypothesis that single dose ATRA/PD1i induces response-predictive immune biomarkers in a syngeneic murine glioma model.

Aim 3: To validate correlative immunologic signatures associated with therapeutic response in human subjects receiving neoadjuvant ATRA/PD1i followed by resection.

Overlap: None

Title: Genomic and Immunomic Mechanisms of Resistance During Daratumumab Post Stem Cell Transplantation in Patients with Poor Risk T-cell Lymphoblastic Lymphoma/Leukemia

Role: Co-investigator (David Teachey PI)

Time Commitment: 5% effort, 0.60 cal mos

Supporting Agency: US Department of Defense CA220666P1

Funding Agency Grant Officer: Amie Bunker, U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702-5014 Performance Period: 09/01/2023 – 08/31/2027

Level of funding:

Brief description of project's goals: To understand the genomic and immunomic mechanisms of resistance in poor risk T-cell lymphoblastic lymphoma/leukemia patients with daratumumab post stem cell transplantation.

Specific aims:

Aim 1: To determine the safety, pharmacokinetics and pharmacodynamics of daratumumab post-HSCT and detection and changes in minimal residual disease (MRD) post-HSCT DARA in PAYA patients with T-LL/T-ALL in CR2.

Aim 2: To investigate the impact of DARA on clonal evolution and tumor microenvironment after AlloHSCT and post-HSCT DARA in PAYA patients with T-LL/T-ALL in CR2.

Aim 3: To measure changes in T-cell adaptive immunity following HSCT and post-HSCT DARA and correlation with the risk of acute GVHD and relapse post-HSCT DARA in PAYA patients with T-LL/T-ALL in CR2.

Overlap: None

Pending awards since previous submission

Title: Targeting Therapy-Resistant Mechanisms in Pediatric B-ALL at a Single-Cell Level

Role: Co-Investigator (Sarah Tasian PI)

Time Commitment: 3.5%, 0.42 cal mos

Supporting Agency: Pennsylvania Department of Health

Funding Agency Grant Officer: Susan Guy, Public Health Program Administrator, Room 833 Health and Welfare Building, 625 Forster Street, Harrisburg, PA 17120-0701

Performance Period: 08/1/2023 – 07/31/2027

Level of funding:

Brief description of project's goals: To use results from preclinical single-cell analysis systems biology approaches and patient-centered clinical immunotherapy correlative analyses to develop 'next-generation' clinical trials of precision medicine targeted therapies and immunotherapies for children and adolescents with B-ALL

Specific aims:

Aim 1: To identify and target rare, therapy-resistant cell populations in high-risk genetic subtypes of pediatric B-cell acute lymphoblastic leukemia (B-ALL)

Aim 2: To develop biologically-optimized CD19-directed cellular immunotherapies based upon lessons learned from treated patients.

Overlap: None

Title: Hematopoietic stem cell ontology

Role: Co-investigator (Nancy Speck PI)

Time Commitment: 5.8% effort, 0.70 cal mos

Supporting Agency: NIH, R35

Funding Agency Grant Officer: N/A

Performance Period: 12/1/2023-11/30/2030

Level of funding: subcontract

Brief description of project's goals: The major goal of this R35 is to identify, understand, and classify hematopoietic stem cells.

Specific aims:

Aim 1: The R35 mechanism does not require specific aims.

Overlap: None

Rochelle Bagatell

Completed funding since previous submission

Title: ALK Testing as an Integral Biomarker on COG ANBL1531

Role: Study PI (Doug Hawkins, PI)

Time commitment: 1%, 0.12 cal mos

Supporting agency: NIH/NCI BQSF, U10CA180886

Funding Agency Grant Officer: Margaret Mooney, Program Officer, BG 9609 RM 5W412 9609

Medical Center Dr. Rockville, MD 20850

Period of performance: 04/01/2018-03/31/2023

Level of funding: annual direct costs

Brief description of the project's goals: BQSF funding will allow testing of tumor specimens from patients enrolled on the COG ANBL1531 trial for aberrations in the ALK gene. This will facilitate treatment assignment on the study

List of specific aims:

Aim 1: To identify patients on COG ANBL12P1 with activating ALK tyrosine kinase domain mutations, via Sanger sequencing analysis.

Aim 2: To identify patients on COG ANBL12P1 with ALK gene amplification via FISH testing

Overlap: None

Title: MYC and MYCN as Integrated Biomarker on COG ANBL1531

Role: Study PI (Doug Hawkins, PI)

Time commitment: 1% 0.12 cal mos

Supporting agency: NIH/NCI BQSF, U10CA180886

Funding Agency Grant Officer: Margaret Mooney, Program Officer, BG 9609 RM 5W412 9609

Medical Center Dr. Rockville, MD 20850

Period of performance: 04/01/2018-03/31/2023

Level of funding: annual direct costs

Brief description of the project's goals: BQSF funding will allow testing of MYC and MYCN protein levels in tumor specimens from patients enrolled on the COG ANBL1531. Expression of MYC/MYCN proteins may be prognostic in newly diagnosed children with this disease

List of specific aims:

Aim 1: Evaluate the role of MYC (c-myc) protein and MYCN protein levels as biomarkers in patients with neuroblastoma.

Overlap: None

Title: Clinical Trial Decision Aid (DECIDES) for Adolescents and Young Adults with Cancer and their Caregivers

Role: Co-Investigator (Lamia Barakat PI)

Time Commitment: 1%, 0.12 cal mos

Supporting Agency: Andrew McDonough B+ Foundation

Funding Agency Grant Officer: Joe McDonough, President, 101 Rockland circle Wilmington, DE 19803

Period of performance: 01/01/2020-12/31/2022

Level of funding: annual direct costs

Brief description of the project's goals: The proposed study aims to assess acceptability and feasibility and evaluate preliminary efficacy of a theoretically informed, developmentally appropriate, web-based decision support intervention (DECIDES = AYA Deciding about Enrolling on a Clinical Intervention Trial: Decision Aid for Education and Support) to increase AYA involvement in clinical trials decision-making and improve decision processes for AYA and primary caregivers

List of specific aims:

Aim 1: To assess the acceptability and feasibility of DECIDES using mixed methods and use results to evaluate an implementation strategy

Aim 2: To evaluate preliminary efficacy of DECIDES using a randomized trial.

Overlap: None

Title: Next Generation Sequencing to Identify *MYCN* Amplification in Neuroblastoma

Role: PI

Time Commitment: 1% 0.12 cal mos, no sal support

Supporting Agency: Children's Oncology Group

Funding Agency Grant Officer: Daniel Woods, Operations Manager, COG Foundation, 3501 Civic Center Blvd, Philadelphia, PA 19104

Period of performance: 07/01/2020-06/30/2022

Level of funding: annual direct costs

Brief description of the project's goals: This project is designed to evaluate the performance characteristics of a next-generation sequencing approach to identify neuroblastoma tumors that harbor amplification of the *MYCN* oncogene. This project represents a step toward improved identification of patients with a poor prognosis using current technology.

List of specific aims:

Aim 1: To determine the sensitivity and specificity of a tumor/normal exome NGS assay for identifying *MYCN* amplification compared to the gold standard of *MYCN* FISH. Banked tumor and /or bone marrow samples previously tested using FISH will be evaluated using NGS.

Aim 2: To use a tumor/normal exome NGS assay to test prospectively collected neuroblastoma tumor and/or tumor-containing bone marrow samples as well as associated comparator normal samples to determine turnaround time and potential barriers to real time reporting of *MYCN* status.

Aim 3: : To describe other genomic features detected by this tumor/normal exome NGS assay, including copy number alterations at recurrently altered loci and aberrations in genes implicated in neuroblastoma that also are used to risk stratify and triage patients to therapeutic arms of high risk neuroblastoma clinical trials (e.g., ALK and MAPK pathway genes).

Overlap: None

New funding since previous submission

Title: Comprehensive evaluation of immune function in patients receiving multimodal therapy for high-risk neuroblastoma

Role: Co-Investigator (Kai Tan/Steven DuBois/Trevor Pugh)

Time commitment: 2% effort, 0.24 cal mos

Supporting agency: Department of Defense

Funding Agency Grant Officer: Amie Bunker, U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702-5014 Period of performance: 09/01/2022 – 08/31/2026

Level of funding: annual direct costs

Brief description of project goals: We will test the novel hypothesis that markers reflective of immune cell profile and interaction with malignant cells during the course of therapy can guide treatment of children with NBL

List of specific aims:

Aim 1: Identify tumor-derived and circulating biomarkers predictive of response to therapy in patients with high-risk neuroblastoma using single cell profiling and proteomic analyses

Aim 2: Define the breadth and dynamics of T- and B-cell diversity at diagnosis, during treatment, and at remission in patients with high-risk neuroblastoma

Overlap: None

Pending awards since previous submission

none

Arlene Naranjo

Completed funding since previous submission

Title: Tumor and Host Markers of Clinical Outcomes after MIBG Therapy in Neuroblastoma

Role: Co-Investigator & PI on the subcontract to University of Florida

Time commitment: 3.5%, 0.42 calendar months

Supporting agency: NIH/NCI 9609 Medical Center Drive Rockville, MD 20892

Funding Agency Grant Officer: Sumana Mukherjee Dey

Period of performance: 04/15/2018–03/31/2022

Level of funding: subcontract annual direct costs

Brief description of the project's goals: To determine whether biologic and genomic features of neuroblastoma patients can predict response and toxicity from I-131 MIBG therapy after induction chemotherapy in patients with high-risk newly diagnosed neuroblastoma in a large COG phase III randomized trial.

List of specific aims:

1. Study features of neuroblastoma tumors that may predict outcome after I-131 MIBG.
2. Evaluate host factors that may influence survival and toxicity related to I-131 MIBG therapy.

Overlap: None

Title: Statistical Analysis for COG Neuroblastoma Committee Projects

Role: Principal Investigator

Time commitment: 1%, 0.12 calendar months

Supporting agency: Seattle Children's Hospital 4800 Sand Point Way NE, Seattle, WA 98105

Funding Agency Grant Officer: Mr. Erik Lausund

Period of performance: 08/01/2019–07/31/2022

Level of funding: annual direct costs

Brief description of the project's goals: To support the data management and clean-up, statistical programming and analytic support, data exports, and other neuroblastoma projects of the COG.

List of specific aims:

1. Manage data file systems from clinical trials and bio-specimen banks
2. Develop programs for the selection of patient cohorts from COG clinical trials with specified inclusion criteria requiring bio-specimens from the COG biobank
3. Conduct statistical analyses correlating results from biology assays with clinical data from COG trials and prepare technical reports to be used as precursors for full manuscripts
4. Programmatically conduct regular checks on the trial data, identify data inconsistencies, and work to resolve the data issues with participating sites
5. Prepare draft semi-annual study progress reports and data safety monitoring committee reports using existing templates
6. Understand and implement protocol-specified interim monitoring and final analytic plan
7. Interpret results for assigned clinical trials by employing various statistical data analyses methodologies
8. Assist in abstract, presentation, and manuscript preparation related to projects

9. Conduct requested ad-hoc analyses and prepare summary reports

Overlap: None

Title: Statistical analysis for COG Neuroblastoma Committee projects

Role: Principal Investigator

Time commitment: 1%, 0.12 calendar months

Supporting agency: University of Chicago 6054 South Drexel Avenue Chicago, IL 60637

Funding Agency Grant Officer: Michael R. Ludwig

Period of performance: 08/01/2020–07/31/2022 with no cost extension

Level of funding: annual direct costs

Brief description of the project's goals: To support the data management and clean-up, statistical programming and analytic support, data exports, and other neuroblastoma projects of the COG.

List of specific aims:

1. Manage data file systems from clinical trials and bio-specimen banks
2. Develop programs for the selection of patient cohorts from COG clinical trials with specified inclusion criteria requiring bio-specimens from the COG biobank
3. Conduct statistical analyses correlating results from biology assays with clinical data from COG trials and prepare technical reports to be used as precursors for full manuscripts
4. Programmatically conduct regular checks on the trial data, identify data inconsistencies, and work to resolve the data issues with participating sites
5. Prepare draft semi-annual study progress reports and data safety monitoring committee reports using existing templates
6. Understand and implement protocol-specified interim monitoring and final analytic plan
7. Interpret results for assigned clinical trials by employing various statistical data analyses methodologies
8. Assist in abstract, presentation, and manuscript preparation related to projects
9. Conduct requested ad-hoc analyses and prepare summary reports

Overlap: None

Title: Alternate Telomere Maintenance Mechanisms in High-Risk Neuroblastoma as Prognostic Indicators and Therapeutic Targets

Role: Co-Investigator & PI on the subcontract to the University of Florida

Time commitment: 5%, 0.6 calendar months

Supporting agency: NIH/NCI 9609 Medical Center Drive Bethesda, MD 20892

Funding Agency Grant Officer: Crystal Wolfrey

Period of performance: 6/18/2021- 7/31/2022

Level of funding: subcontract annual direct costs

Brief description of the project's goals: To determine whether telomere maintenance mechanism status can identify patient subsets within the high-risk group that have divergent outcomes.

List of specific aims:

1. To utilize the RNA sequencing data on tumors from ANBL1531 patients to identify tumors which have low and high expression of the telomerase gene TERT.
2. To compare RNA sequencing data of tumors from ANBL1531 patient tumors with RNA sequencing data of patient-derived cell lines (PDCLs) and patient-derived xenografts (PDXs) that have been grown from patients enrolled on ANBL1531 in which samples were provided via the ANBL0B1 study and sent to the Reynolds lab to establish PDCLs and PDXs.

Overlap: None

New funding since previous submission

Title: Statistical Support for COG Neuroblastoma Projects

Role: Principal Investigator on the subcontract to University of Florida

Time commitment: 1%, 0.12 calendar months

Supporting agency: Children's Hospital of Philadelphia Research Institute 2716 South Street, 17th Floor Philadelphia, PA 19146-2305

Funding Agency Grant Officer: Jeannine Voll

Period of performance: 01/01/2022-12/31/2026

Level of funding: subcontract annual direct costs

Brief description of the project's goals: To support the data management and clean-up, statistical programming and analytic support, data exports, and other neuroblastoma projects of the COG.

List of specific aims:

1. Manage data file systems from clinical trials and bio-specimen banks
2. Develop programs for the selection of patient cohorts from COG clinical trials with specified inclusion criteria requiring bio-specimens from the COG biobank
3. Conduct statistical analyses correlating results from biology assays with clinical data from COG trials and prepare technical reports to be used as precursors for full manuscripts
4. Programmatically conduct regular checks on the trial data, identify data inconsistencies, and work to resolve the data issues with participating sites
5. Prepare draft semi-annual study progress reports and data safety monitoring committee reports using existing templates
6. Understand and implement protocol-specified interim monitoring and final analytic plan
7. Interpret results for assigned clinical trials by employing various statistical data analyses methodologies
8. Assist in abstract, presentation, and manuscript preparation related to projects
9. Conduct requested ad-hoc analyses and prepare summary reports

Overlap: Effort overlaps with Children's Oncology Group Statistics and Data Center Award

Title: Novel Health Equity Intervention to Improve Pediatric Oncology Outcome Disparities: Targeting Poverty and Psychosocial Stress

Role: Principal Investigator on the subcontract to the University of Florida

Time commitment: 5%, 0.6 calendar months

Supporting agency: NIH/NCI 9609 Medical Center Drive Rockville, MD 20892

Funding Agency Grant Officer: Crystal Wolfrey

Period of performance: 03/01/2022-02/29/2026

Level of funding: subcontract annual direct costs

Brief description of the project's goals: To apply a novel health equity intervention (HEI) for parents of children with high-risk neuroblastoma that combines an intervention targeting household material hardship and a novel resilience resource intervention to reduce poverty associated disparities.

List of specific aims:

1. Identify HEI efficacy in improving parent-centered outcomes.
2. Explore the impact of the HEI on child-centered outcomes.

Overlap: None

Title: Comprehensive Evaluation of Immune Function in Patients Receiving Multimodal Therapy for High-Risk Neuroblastoma

Role: Principal Investigator on the subcontract to University of Florida

Time commitment: 1%, 0.12 calendar months

Supporting agency: U.S. Army Medical Research Acquisition Activity 820 Chandler St Fort Detrick MD 21702-5014

Funding Agency Grant Officer: Danielle L. Reckley

Period of performance: 09/01/2022-08/31/2026

Level of funding: subcontract annual direct costs

Brief description of the project's goals: To learn about the immune response in patients with high-risk neuroblastoma and test our hypothesis that tumor-intrinsic and microenvironment (extrinsic) markers define patient subgroups with differential probabilities of clinical benefit following therapy on ANBL1531.

List of specific aims:

1. Apply single cell and imaging techniques to define the tumor microenvironment and identify malignant cell phenotypes associated with neuroblastoma treatment response.
2. Define the breadth and dynamics of T- and B-cell diversity at diagnosis, during treatment, and at remission in patients with high-risk neuroblastoma.
3. Discover circulating biomarkers of the tumor immune microenvironment and that are associated with response to therapy.

Overlap: None

Pending awards since previous submission

Title: Tumor GD2 Expression as a Biomarker for Neuroblastoma Responsiveness to Immunotherapy

Role: Principal Investigator on the subcontract to University of Florida

Time commitment: 5%, 0.6 calendar months

Supporting agency: NIH/NCI 9609 Medical Center Drive Rockville, MD 20892

Funding Agency Grant Officer: Shane Woodward

Period of performance: 07/01/2023-06/30/2028

Level of funding: subcontract annual direct costs

Brief description of the project's goals: The goals of this project are to provide data to inform optimal integration of dinutuximab with chemotherapy and provide a predictive biomarker to identify patients not likely to benefit from anti-GD2 based therapy.

List of specific aims:

1. Using a multicolor flow cytometry assay we will quantify dinutuximab binding to tumor cells in bone marrow from neuroblastoma patients to determine the frequency of low GD2 expression and the relationship to clinical response in patients receiving chemoimmunotherapy.
2. Define molecular mechanisms of low and high GD2 expression in neuroblastoma.
3. Determine the relationship of levels of GD2 expression to anti-tumor activity of dinutuximab combined with temozolomide + irinotecan in neuroblastoma PDCLs and PDXs.

Overlap: None

Title: Assessing and Overcoming Resistance to Chemoimmunotherapy for Neuroblastoma

Role: Principal Investigator on the subcontract to University of Florida

Time commitment: 5%, 0.6 calendar months

Supporting agency: NIH/NCI 9609 Medical Center Drive Bethesda, MD 20892

Funding Agency Grant Officer: Crystal Wolfrey

Period of performance: 09/01/2023-08/31/2028

Level of funding: subcontract annual direct costs

Brief description of the project's goals: To provide data to inform optimal integration of dinutuximab with chemotherapy and provide a predictive biomarker to identify patients not likely to benefit from anti-GD2 based therapy.

List of specific aims:

1. Using a multicolor flow cytometry assay we will quantify dinutuximab binding to tumor cells in bone marrow from neuroblastoma patients to determine the frequency of low GD2 expression and the relationship to clinical response in patients receiving chemoimmunotherapy.
2. Define molecular mechanisms of low and high GD2 expression in neuroblastoma.
3. Determine the relationship of levels of GD2 expression to anti-tumor activity of dinutuximab combined with temozolomide + irinotecan in neuroblastoma PDCLs and PDXs.

Overlap: None

Title: Immune Landscape Predictors of Dinutuximab Response in Neuroblastoma

Role: Principal Investigator on the subcontract to University of Florida

Time commitment: 1%, 0.12 calendar months

Supporting agency: NIH/NCI 9609 Medical Center Drive Rockville, MD 20892

Funding Agency Grant Officer: Shane Woodward

Period of performance: 12/01/2023-11/30/2028

Level of funding: subcontract annual direct costs

Brief description of the project's goals: To establish race-associated biomarkers to identify which patients will benefit from chemoimmunotherapy and thus improve outcomes, narrow the disparity gap, and facilitate future personalized immunotherapy regimens.

List of specific aims:

1. Characterize tumor immune landscapes contributing to differences in high-risk neuroblastoma survival.
2. Determine circulating patient immunophenotypes contributing to differences in high-risk neuroblastoma survival.

3. Explore the associations between tumor and host immune landscapes with parent-reported race and adverse social determinants of health (including income poverty and household material hardship) and with child DNA-based genetic ancestry.

Overlap: None

Steven Dubois

Completed funding since previous submission

Title: Phase 1 Study of the Dual MDM2/MDMX Inhibitor ALRN-6924 in Pediatric Cancer

Role: PI

Time commitment: 0.6 calendar months

Supporting agency: Team Connor Childhood Cancer Foundation

Funding Agency Grant Officer: Kathryn Copple, Two Lincoln Center, 5420 LBJ Freeway, Ste. 1300, Dallas, TX 75240,

Period of performance: 01/01/2019-12/31/2020 (NCE)

Level of funding: annual direct costs

Project Goals: The goal of this project is to evaluate the side effect profile and optimal dosing of ALRN-6924 by investigating the anticancer activity of ALRN-6924 in pediatric cancers and study the effects of ALRN-6924 on blood markers.

List of specific aims:

Aim 1: To describe the toxicity, antitumor activity, and pharmacokinetics of ALRN-6924 in children with cancer.

Aim 2: To describe pharmacodynamic effects and potential resistance mechanisms of ALRN-6924 when administered to children with cancer

Overlap: None

Title: Predictors of IGF1-R Resistance in Metastatic Ewing Sarcoma

Role: PI

Time commitment: 0.12 calendar months

Supporting agency: V Foundation / Quad W Foundation

Funding Agency Grant Officer: Kameko Owoeye, 14600 Weston Parkway Cary, NC 27513

Period of performance: 10/01/2015-09/30/2022 (NCE)

Level of funding: annual direct costs

Project Goals: This foundation grant supports novel correlative biology studies embedded in a national clinical trial of an IGF-1 R monoclonal antibody added to conventional chemotherapy for patients with metastatic Ewing sarcoma.

List of specific aims:

Aim 1: To determine if event-free survival differs based on serum markers of the IGF-1 pathway in patients with newly diagnosed metastatic Ewing sarcoma treated with multiagent chemotherapy with and without the addition of an anti-IGF-1R monoclonal antibody.

Aim 2: To determine if event-free survival differs based on level of surface IGF-1R expression on bone marrow tumor cells in patients with newly diagnosed metastatic Ewing sarcoma treated with multiagent chemotherapy with and without the addition of an anti-IGF-1 R monoclonal antibody.

Aim 3: To determine if event-free survival differs based on expression of IGF-1R, phospho-AKT, and related pathway proteins in primary tumor samples from patients with newly diagnosed metastatic Ewing sarcoma treated with multiagent chemotherapy with and without the addition of an anti-IGF-1 R monoclonal antibody.

Overlap: None

Title: Targeting Epigenetic Dysregulation in Pediatric Cancer

Role: Team Co-Leader and Leader of the clinical Trial

Time commitment: 0.6 calendar months

Supporting Agency: Stand Up to Cancer

Funding Agency Grant Officer: Cathryn Dhanatya, 10880 Wilshire Boulevard, Suite 1400, Los Angeles, CA 90024

Period of Performance: 01/01/2018-12/31/2022

Level of Funding: annual direct costs

Project goals: This Pediatric Catalyst proposal brings together a unique team of accomplished investigators with complementary expertise in basic, translational, and clinical cancer research, with specific expertise in neuroblastoma, Ewing, and other sarcomas, and brain tumors in order to bring new therapies to children with cancer most in need. Specifically, we propose to test Bristol-Myer Squibb's BET inhibitor in children with cancer in the first pediatric clinical trial of BET inhibitors. In parallel, we will perform laboratory research to identify novel drugs that when combined with the BET inhibitor will lead to even better anti-cancer activity, which will lay the foundation for new drug combinations to treat children with cancer in second-generation clinical trials.

List of specific aims:

Aim 1: Conduct a phase 1 clinical trial testing BMS BETi BMS-986158 in children with cancer

Aim 2: Test rational drug combinations with BMS-986158 in preclinical models of pediatric cancer

Aim 3: Identify novel drug combinations with BMS-986158 through genomic-scale CRISPR-Cas9 synergy screens

Overlap: none

Title: Tumor and host markers of clinical outcomes after MIBG therapy in neuroblastoma

Role: Co-PI

Time commitment: 1.2 calendar months

Supporting agency: National Cancer Institute/NIH/DHHS

Funding Agency Grant Officer: Sumana Mukherjee Dey, Program Officer, 9609 Medical Center Dr. Rockville, MD 20850 Period of performance: 04/15/2018-03/31/2023

Level of funding: annual direct costs

Project Goals: The goal of this project is to conduct a phase III clinical trial, ANBL 1531, to compare survival inpatients with newly diagnosed high-risk neuroblastoma after randomization to standard therapy with or without the addition of the radiopharmaceutical I-MIBG.

List of specific aims:

Aim 1: To identify tumor biological features that influence the likelihood of clinical benefit after 1311-MIBG therapy.

Aim 2: To evaluate host factors associated with differential likelihood of clinical benefit and toxicity after treatment with I-MIBG

Overlap: None

Title: Serum Markers of the IGF-IR Pathway in Metastatic Ewing Sarcoma

Role: PI

Time commitment: 0.6 calendar months

Supporting agency: The Children's Oncology Group Foundation, Inc.

Funding Agency Grant Officer: Deborah Crabtree, 3501 Civic Center Blvd. CTRB 10062 Philadelphia, PA 19104

Period of performance: 06/01/2019-05/31/2023

Level of funding: annual direct costs

Project Goals: The goal of this project is to determine whether a panel of promising blood markers related to the IGF-1 pathway are predictive of clinical outcomes in patients with metastatic Ewing sarcoma treated with an IGF-IR inhibitor by evaluating peripheral blood markers at baseline and after initiation of treatment. List of specific aims:

Aim 1: To determine if event-free survival differs based on baseline serum markers of the IGF-IR pathway inpatients with newly diagnosed metastatic Ewing sarcoma treated with multiagent chemotherapy with and without the addition of an anti-IGF-1 R monoclonal antibody.

Aim 2: To determine if event-free survival differs based on changes in serum markers of the IGF-IR pathway inpatients with newly diagnosed metastatic Ewing sarcoma treated with multiagent chemotherapy with and without the addition of an anti-IGF-IR monoclonal antibody.

Overlap: None

New funding since previous submission

Title: Comprehensive evaluation of immune function in patients receiving multimodal therapy for high-risk neuroblastoma

Time Commitment: 0.6 calendar months

Supporting Agency: DOD W81XWH-20-I-0813 TTSA

Funding Agency Grant Officer: Abigail Strock, Grants Officer

Level Of Funding: (total costs)

Performance Period: 09/01/2022 - 08/31/2026

Project Goals: Children with high-risk neuroblastoma undergo intensive multimodality treatment. Despite this, only ~50% of patients are cured, highlighting a need for improved therapies. Our twin goals are to identify biomarkers that can be used clinically to predict therapy response to optimize treatment selection, and to understand immune cell response during therapy in order to develop novel therapies. The results from the currently proposed studies will guide the development of new treatments for children with high-risk neuroblastoma.

Specific Aims:

Aim 1: Identify tumor-derived and circulating biomarkers predictive of response to therapy in patients with high-risk neuroblastoma using single cell profiling and proteomic analyses.

Aim 2: Define the breadth and dynamics of T- and B-cell diversity at diagnosis, during treatment, and at remission in patients with high-risk neuroblastoma

Overlap: none.

Pending awards since previous submission

Title: Prospective Validation of a Prognostic Liquid Biopsy Approach for Pediatric Ewing Sarcoma Time

Commitment: 0.3 calendar months

Supporting Agency: Pediatric Cancer Research Foundation

Agency's Contracting/Grants Officer: Jeri Wilson, Executive Director

Level of Funding: (total costs)

Performance Period: 01/01/2024 - 12/31/2025

Project Goals: In this proposal, we aim to validate a new assay that detects tumor DNA from a simple peripheral blood draw as a surrogate for tumor burden in patients with Ewing sarcoma.

Specific Aims:

Aim 1: Demonstrate that the commercial Foundation One Liquid CDx provides equivalent results to a previously validated laboratory research assay for detection of ctDNA in patients with EWS

Aim 2: Identify mechanism of tumor evolution that contribute to the development of treatment resistant relapse in EWS.

Overlap: None.

Natalie Collins

Completed funding since previous submission

Title: Dana-Farber/Children's Hospital Cancer Center (DF/CHCC) Developmental Therapeutics Center of Excellence

Time Commitment: 3.4 calendar months

Supporting Agency: Alex's Lemonade Stand Foundation

Funding Agency Grant Officer: Elexis Andruzzi, 111 Presidential Blvd., Suite 203, Bala Cynwyd, PA 19004

Period Of Performance: 01/01/2013-12/31/2021

Level Of Funding: annual direct costs

Project Goals: The major goal of this award is to sustain and enhance the infrastructure of the DF/CHCC Developmental Therapeutics Center of Excellence, and to provide training support for junior investigators

(ALSF Scholars in Developmental Therapeutics) who will become the future leaders in pediatric cancer developmental therapeutics.

List Of Specific Aims:

Aim 1: To create a Developmental Therapeutics Unit (DTU), including the creation of a new position, the Developmental Therapeutics Clinical Research Manager (DTCRM).

Aim 2: To provide patients with increased access to clinical trials of novel agents, and provide treating physicians with increased awareness of existing/open clinical trials of novel agents at DF/HCC.

Aim 3: To facilitate collaboration among the sites of the ALSF COEs, and increase the number of innovative

phase I and II clinical trials for rare pediatric cancers.

Aim 4: To build a Pediatric Oncology Developmental Therapeutics Training Program at DP/HCC.

Overlap: none

Title: A cellular atlas of fusion oncoprotein driven pediatric cancer

Time Commitment: 1.2 calendar months

Supporting Agency: Children's Cancer Research Fund

Agency's Contracting/Grants Officer: Haivy Thompson Vice President of Mission and Marketing, 7301 Ohms Lane, Suite 355 Minneapolis, MN 55439

Level Of Funding: (total costs)

Performance Period: 09/01/2019- 09/30/2021

Project Goals: The goal of this project is to perform single cell profiling on tumor samples from children with fusion-positive sarcoma in order to create the first tumor atlases in pediatrics.

Specific Aims:

Aim 1: To describe the tumor and immune microenvironment in fusion positive pediatric sarcoma using single cell technologies.

Aim 2: To define the T cell receptor (TCR) repertoire in fusion positive sarcoma.

Aim 3: To correlate heterogeneity of fusion protein expression with tumor cell state.

Overlap: none.

Title: Single Cell Pediatric Cancer Atlas

Time Commitment: 1.2 calendar months

Supporting Agency: Alex's Lemonade Stand Foundation

Funding Agency Grant Officer: Elexis Andruzzi, 111 Presidential Blvd., Suite 203, Bala Cynwyd, PA 19004

Level Of Funding: (total costs)

Performance Period: 09/01/2019- 10/15/2021

Project Goals: The goal of this project is to build a cellular atlas of pediatric osteosarcoma to 1) describe the tumor and immune microenvironment of osteosarcoma using single cell technologies, 2) analyze individual circulating tumor cells (CTCs) by single cell sequencing to describe their phenotypic and phylogenetic relationship to primary and metastatic disease and 3) to correlate tumor and immune single cell gene expression patterns with clinical behavior and biologic features such as genomic alterations.

Specific Aims: We aim to build a cellular atlas of pediatric osteosarcoma to

Aim 1: Describe the tumor and immune microenvironment of osteosarcoma using single cell technologies

Aim 2: Analyze individual circulating tumor cells (CTCs) by single cell sequencing to describe their phenotypic and phylogenetic relationship to primary and metastatic disease

Aim 3: To correlate tumor and immune single cell gene expression patterns with clinical behavior and biologic features such as genomic alterations.

Overlap: None.

Title: SARC031: A Phase 2 Trial of the MEK inhibitor selumetinib (AZD6244 hydrogen sulfate) in combination with the dual mTOR inhibitor sirolimus for patients with unresectable or metastatic malignant peripheral nerve sheath tumors

Time Commitment: 0.6 calendar months

Supporting Agency: Department of Defense / Sarcoma Alliance For Research Through Collaboration

Agency's Contracting/Grants Officer: Denise Reinke, 24 Frank Lloyd Wright Drive PO Box 406, Ann Arbor MI 48195-0406.

Level Of Funding: (total costs)

Performance Period: 10/01/2019- 09/30/2022

Project Goals: To conduct a Phase 2 Trial of the MEK Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Combination with the mTOR Inhibitor Sirolimus for Patients with Unresectable or Metastatic Malignant Peripheral Nerve Sheath Tumors

Specific Aims: To determine the clinical benefit rate of selumetinib in combination with sirolimus in patients with unresectable or metastatic NFI associated or sporadic MPNST

Overlap: None.

New funding since previous submission

Title: Comprehensive evaluation of immune function in patients receiving multimodal therapy for high risk neuroblastoma

Time Commitment: 0.6 calendar months

Supporting Agency: DOD W81XWH-20-I-0813 TTSA

Funding Agency Grant Officer: Abigail Strock, Grants Officer

Level Of Funding: (total costs)

Performance Period: 09/01/2022 - 08/31/2026

Project Goals: Children with high-risk neuroblastoma undergo intensive multimodality treatment. Despite this, only ~50% of patients are cured, highlighting a need for improved therapies. Our twin goals are to identify biomarkers that can be used clinically to predict therapy response to optimize treatment selection, and to understand immune cell response during therapy in order to develop novel therapies. The results from the currently proposed studies will guide the development of new treatments for children with high-risk neuroblastoma.

Specific Aims:

Aim 1: Identify tumor-derived and circulating biomarkers predictive of response to therapy in patients with high-risk neuroblastoma using single cell profiling and proteomic analyses.

Aim 2: Define the breadth and dynamics of T- and B-cell diversity at diagnosis, during treatment, and at remission in patients with high-risk neuroblastoma

Overlap: none.

Pending awards since previous submission

Title: Fusion oncoproteins in pediatric sarcomas as targets for adoptive T cell therapeutics

Time Commitment: 1.8 calendar months

Supporting Agency: Kid's Beating Cancer

Agency's Contracting/Grants Officer: TBD

Level Of Funding: (total costs)

Performance Period: 10/01/2023 - 09/30/2025

Project Goals: The goal of this project is to 1) overcome the current technical limitations in neoantigen and TCR identification in fusion positive sarcomas and 2) optimize the development of TCR transduced adoptive T cell therapies.

Specific Aims:

Aim 1 : Identification of immunogenic fusion protein specific neoepitopes.

Aim 2: Generation and functional validation of fusion protein specific T cells for pediatric sarcomas.

Overlap: None.

Brian Crompton

Completed funding since previous submission

Title: Prospective Validation of a Prognostic Liquid Biopsy Approach for Pediatric Ewing Sarcoma Time commitment: 1.2 calendar months

Supporting Agency: Pediatric Cancer Research Foundation Basic Research Grant

Agency's Contracting/Grants Officer: Jeri Wilson, Executive Director, PCRFB

Level Of Funding: (total costs)

Performance Period: 01/01/2019 – 12/31/2021

Project Goals: To validate the measurement of circulating tumor DNA assays (also known as liquid biopsies) obtained from blood samples as a biomarker of poor outcome for patients with Ewing sarcoma. Specific Aims:

Aim 1: To validate that pre-treatment ctDNA is prognostic in localized Ewing sarcoma

Aim 2: To determine if changes in ctDNA levels during therapy are associated with outcome and reveal patterns of tumor evolution and treatment resistance.

Overlap: None.

Title: Prospective Validation of a Prognostic Liquid Biopsy Approach for Pediatric Ewing Sarcoma Time

Commitment: 1.2 calendar months

Supporting Agency: Pediatric Cancer Research Foundation

Agency's Contracting/Grants Officer: Jeri Wilson, Executive Director, PCRFB

Level Of Funding: (total costs)

Performance Period: 01/01/2022 – 12/31/2023

Project Goals: We aim to validate a new assay that detects tumor DNA from a simple peripheral blood draw as a surrogate for tumor burden in patients with Ewing sarcoma.

Specific Aims:

Aim1: To validate that pre-treatment ctDNA is prognostic in localized Ewing sarcoma.

Aim2: To determine if changes in ctDNA levels during therapy are associated with outcome and reveal patterns of tumor evolution and treatment resistance.

Overlap: None.

Title: Targeting Kinase Signaling in Preclinical Models of Ewing Sarcoma

Time Commitment: 0.6 calendar months

Supporting Agency: Rally Foundation

Agency's Contracting/Grants Officer: Leigh Anna Lang, Grant Administrator,

Level Of Funding: (total costs)

Performance Period: 07/01/2021 – 06/30/2022

Project Goals: In this proposal, we plan to take three new approaches to identify and validate a larger collection of combination targeted therapy options for Ewing sarcoma in order to increase our chances of identifying candidate therapeutic combinations that utilize anti-cancer drugs that eventually reach approval.

Specific Aims:

Aim 1: Does EWS/FLI transcriptional reprogramming sensitize Ewing sarcoma cells to AURKB inhibition?

Aim 2: Do novel combinations of cell-cycle inhibitors and proliferative signaling pathway inhibitors have synergistic anti-Ewing sarcoma activity? (3) Can circulating tumor cells be used to detect responses and resistance mechanisms of Ewing sarcoma cells to pan-tyrosine kinase inhibitor therapy?

Overlap: None.

Title: Development of a Circulating Tumor DNA Assay for Early Cancer Detection in Children with Li-Fraumeni Syndrome

Time Commitment: 0.42 calendar

Supporting Agency: BCH Translational Research Program

Agency's Contracting/Grants Officer: Paul M. Santos, Manager, OSP, Boston Children's Hospital, osp@childrens.harvard.edu. Level Of Funding:(total costs)

Performance Period: 07/01/2019 – 06/30/2022 (NCE)

Project Goals: In this proposal, we plan to develop a "blood biopsy" assay that can detect cancer in the blood of patients with predisposition syndromes at a very early stage of cancer development. We believe this test could drastically improve outcomes for these patients.

Specific Aims:

Aim 1: Design a novel hybrid-capture next-generation sequencing assay that detects chromosomal copy number changes.

Aim 2: Validate the assay in a collection of plasma samples from patients with LFS and cancer.

Overlap: None.

Title: Profiling Circulating Tumor DNA to Inform Rhabdomyosarcoma Prognosis and Tumor Evolution

Time Commitment: 0.6 calendar

Supporting Agency: Hyundai Hope on Wheels

Agency's Contracting/Grants Officer: Zafar Brooks, Executive Director, Hyundai Hope on Wheels,

Level Of Funding: (total costs)

Performance Period: 12/01/2019 – 06/30/2022

Project Goals: Alveolar rhabdomyosarcoma is an aggressive pediatric soft-tissue sarcoma. Outcomes for this disease have changed very little in the last 30 years. In this study, we will leverage new blood biopsy technologies to identify patients with high-risk of relapse and determine what patterns of mutations give rise to relapsed disease

Specific Aims:

Aim 1: Are ctDNA levels and detected patterns of copy-number alterations prognostic in aRMS?

Aim 2: Can liquid biopsies detect patterns of tumor evolution that give rise to relapse?

Overlap: None.

Title: Leiomyosarcoma (LMS): New Targets, New Therapies, New Models

Time Commitment: 0.3 calendar months

Supporting Agency: Regents of the University of Michigan

Agency's Contracting/Grants Officer: Jeff Kolodica, Financial Senior Manager, Divisions of Hematology/Oncology and Genetic Medicine, 24 Frank Lloyd Wright Drive, Ann Arbor, MI 48109-5750.

Level Of Funding: (total costs)

Performance Period: 09/01/2021 – 09/30/2022

Project Goals: The major goal of Project 3 is a 40-patient study of patients with a localized LMS that is at high risk of recurrence and or distant metastasis. Investigators will measure impact of surgery, then adjuvant radiotherapy and then systemic adjuvant chemotherapy using the cell free DNA (ctDNA) assay developed by Dr. Crompton.

Specific Aims:

Aim 1: To apply liquid biopsy technologies to detect clinical response and mechanisms of resistance in treatment of LMS.

Overlap: None.

Title: Translocation Assessment of Ewing Sarcoma Cases Enrolled on COG Clinical Group Trials Time Commitment: 0.24 calendar

Supporting Agency: COG Foundation

Agency's Contracting/Grants Officer: Daniel T. Woods, Operations Manager, Children's Oncology Group (COG) Foundation

Level Of Funding: (total costs)

Performance Period: 01/01/2018 – 12/31/2022 (NCE)

Project Goals: To profile a large cohort of patients treated on multiple previous Ewing sarcoma clinical trials to identify the specific translocation in each sample and determine the mutations status of STAG2 and TP53 using customized DNA and RNA sequencing techniques.

Specific Aims:

Aim 1: Evaluate the feasibility of performing molecular translocation detection from tumor tissue collected by COG from patients with a diagnosis of Ewing Sarcoma.

Aim 2: Determine the frequency of patients enrolled on Ewing-specific COG studies with classic Ewing translocations, Ewing-like translocations, or non-Ewing translocations.

Aim 3: Determine the frequency of STAG2 and TP53 mutations in tumors obtained from patients enrolled in Ewing sarcoma COG studies.

Overlap: None.

Title: Clinical Trial of SP-2577 (Seclidemstat) in Patients with Relapsed or Refractory Ewing Sarcoma

Time Commitment: 0.12 calendar months

Supporting Agency: National Pediatric Cancer Foundation

Agency's Contracting/Grants Officer: Margaret J. Fonner, Director, Office of Sponsored Research, H. Lee Moffitt Cancer Center, 12901 Magnolia Drive, Tampa, FL

Level Of Funding: (total costs)

Performance Period: 07/01/2019 – 06/30/2023

Project Goals: This funding supports Dr. Crompton's participation on this clinical trial as part of the National Pediatric Cancer Foundation's "Sunshine Project," which implements a novel collaborative approach that will accelerate the development of new drugs and therapies leading to the prevention and cure of pediatric cancers.

Specific Aims:

Aim 1: In this study, Dr. Crompton will analyze plasma samples from patients enrolled on a trial testing the safety and efficacy of SP-2577, a novel LSD1 inhibitor, for patients with Ewing sarcoma, to assess circulating tumor DNA.

Overlap: None.

Title: BIQSFP Supplement: Circulating Tumor DNA to Evaluate Translocation Status, Prognosis, and Treatment Resistance in Patients with Metastatic Ewing Sarcoma

Time Commitment: 0.12 calendar

Supporting Agency: NIH/NCI

Agency's Contracting/Grants Officer: Margaret M. Mooney, MD, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD, 20850

Performance Period: 03/01/2020 – 02/01/2023

Project Goals: Through a Children's Oncology Group randomized phase 3 trial (AEWS1221), we have assembled the largest known collection of clinically annotated serial plasma samples from patients with newly diagnosed metastatic Ewing sarcoma.

Specific Aims:

Aim 1: For this project we will evaluate this resource using a fit-for-purpose assay designed to detect, quantify, and characterize circulating tumor DNA (ctDNA) in metastatic Ewing Sarcoma.

Overlap: None.

Title: BIQSFP Supplement, ARST1431: Validation of genomic risk-stratification for patients with intermediate risk rhabdomyosarcoma

Time Commitment: 1.2 calendar

Supporting Agency: NIH/NCI 3U10 CA180886-08S1

Agency's Contracting/Grants Officer: Margaret M. Mooney, MD, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD, 20850

Performance Period: 03/01/2021 – 02/28/2023

Project Goals: In this study, we plan to profile tumor, germline, and plasma collected prior to the initiation of treatment for up to 90% of the 300 patients enrolling on the COG trial AST1431.

Specific Aims:

Aim 1: DNA extraction of plasma samples for profiling.

Overlap: None.

New funding since previous submission

Title: BIQSFP Supplement: ctDNA Profiling in Patients with High-Risk Neuroblastoma on COG Trial ANBL1531

Time Commitment: 0.6 calendar months

Supporting Agency: NIH/NCI 3U10 CA180886-10

Agency's Contracting/Grants Officer: Margaret M. Mooney, MD, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD, 20850

Level Of Funding: (total costs)

Performance Period: 03/01/2023 – 02/28/2024

Project Goals: To complete ctDNA profiling of serial plasma samples from the full ANBL1531 cohort (over 600 cases) and for deeper sequencing that will address our specific aims.

Specific Aims:

Aim 1: To determine the association between ctDNA levels during initial chemotherapy and event-free survival (EFS) in patients with HRNB

Aim 2: To prospectively validate the prognostic impact of genomic RAS/MAPK pathway variants on EFS in patients with HRNB.

Overlap: None.

Title: Prospective Validation of a Prognostic Liquid Biopsy Approach for Pediatric Ewing Sarcoma

Time Commitment: 0.6 calendar months

Supporting Agency: Pediatric Cancer Research Foundation

Agency's Contracting/Grants Officer: Jeri Wilson, Executive Director, PCRFB

Level Of Funding: (total costs)

Performance Period: 01/01/2024 - 12/31/2025

Project Goals: In this proposal, we aim to validate a new assay that detects tumor DNA from a simple peripheral blood draw as a surrogate for tumor burden in patients with Ewing sarcoma.

Specific Aims:

Aim 1: Demonstrate that the commercial FoundationOne Liquid CDx provides equivalent results to a previously validated laboratory research assay for detection of ctDNA in patients with EWS

Aim 2: Identify mechanism of tumor evolution that contribute to the development of treatment resistant relapse in EWS.

Overlap: None

Title: Liquid biopsy approaches to inform neuroblastoma prognosis and disease monitoring

Time Commitment: 0.3 calendar months

Supporting Agency: NIH / NCI R37 CA262781

Agency's Contracting/Grants Officer: Percy Thomas III, Grants & Contracts Administrator, Department of Pediatrics, The University of Chicago & Biological Sciences, 5837 S. Maryland Ave., Chicago, IL 60637.

Level Of Funding: (total costs)

Performance Period: 04/11/2022 – 03/31/2027

Project Goals: The goal of this R01 is to use and compare complimentary ctDNA approaches to enhance the prognostic and biologic information obtained from liquid biopsy samples collected on this prospective study.

Specific Aims:

Aim 1: As a co-investigator on this project, Dr. Crompton will work on Specific Aim 2: Prospectively identify minimal residual disease and predict relapse from cfDNA 5hmc profiles collected serially from patients enrolled on ANBL1531.

Overlap: None.

Title: Genetics and Genomics of Leiomyosarcoma (LMS): Improved understanding of cancer biology and new approaches to diagnosis and treatment

Time Commitment: 1.2 calendar months

Supporting Agency: NIH / NCI SPORE 5P50 CA22170-02

Agency's Contracting/Grants Officer: Amy Albert, Project Senior Manager, Internal Medicine Hematology/Oncology, Michigan Medicine. Level Of Funding: (total costs)

Performance Period: 09/16/2022 – 08/31/2027

Project Goals: Project 3: Applying liquid biopsy technologies to detect clinical response and mechanisms of resistance in the treatment of LMS

Specific Aims:

Aim 1: To determine the association of ctDNA levels and recurrent copy-number alterations with outcome in patients with metastatic LMS.

Aim 2: To characterize and validate recurrent patterns of tumor heterogeneity and tumor evolution in patients with metastatic LMS undergoing palliative therapy.

Overlap: None.

Title: Genetics and Genomics of Leiomyosarcoma (LMS): Improved understanding of cancer biology and new approaches to diagnosis and treatment

Time Commitment: 0.12 calendar months

Supporting Agency: NIH / NCI SPORE 5P50 CA22170-02

Agency's Contracting/Grants Officer: Amy Albert, Project Senior Manager, Internal Medicine Hematology/Oncology, Michigan Medicine. Level Of Funding: (total costs)

Performance Period: 09/16/2023 – 08/31/2027

Project Goals: Project 2: Genomic Sequencing

Specific Aims:

Aim 1: To facilitate and oversee the germline sequencing of 200 patient samples collected from the prospective study developed for Project 3 of this SPORE.

Overlap: None.

Title: Lurbinectedin in FET fusion tumors (LiFFT)

Time Commitment: 1.2 calendar months

Supporting Agency: Stand Up to Cancer #CT6330 Catalyst Ò Research Team Grant

Agency's Contracting/Grants Officer: Jeannine Voll, CRA, Manager, Sponsored Projects, Roberts Center for Pediatric Research, 2716 South Street, 17th Floor, Philadelphia, PA 19146-2308.

Level Of Funding: (total costs)

Performance Period: 07/01/2022 – 06/30/2025

Project Goals: The goal of these studies will be to identify association between changes in the ctDNA and CTC profiles with responses the therapy.

Specific Aims:

Aim 1: Dr. Crompton's laboratory at Dana-Farber Cancer Institute will be responsible for the proposed liquid biopsy studies in this trial. Serial blood samples collected from enrolled patients will be shipped to the Crompton laboratory for circulating tumor DNA (ctDNA) and circulating tumor cell (CTCs) identification and profiling.

Overlap: None.

Title: Comprehensive evaluation of immune function in patients receiving multimodal therapy for high risk neuroblastoma

Time Commitment: 0.24 calendar months

Supporting Agency: Department of Defense

Agency's Contracting/Grants Officer: Abigail Stroock, Grants Officer

Level Of Funding: (total costs)

Performance Period: 09/01/2022 – 08/31/2026

Project Goals: Children with high-risk neuroblastoma undergo intensive multimodality treatment. Despite this, only ~50% of patients are cured, highlighting a need for improved therapies. Our twin goals are to identify biomarkers that can be used clinically to predict therapy response to optimize treatment selection, and to understand immune cell response during therapy in order to develop novel therapies. The results from the currently proposed studies will guide the development of new treatments for children with high-risk neuroblastoma.

Specific Aims:

Aim 1: Identify tumor-derived and circulating biomarkers predictive of response to therapy in patients with high-risk neuroblastoma using single cell profiling and proteomic analyses.

Aim 2: Define the breadth and dynamics of T- and B-cell diversity at diagnosis, during treatment, and at remission in patients with high-risk neuroblastoma.

Overlap: None.

Title: Interrogating a multi-parameter liquid biopsy diagnostic in osteosarcoma

Time Commitment: 0.12 calendar months

Supporting Agency: American Cancer Society RSG-23-1029535-01-CDP

Agency's Contracting/Grants Officer: Shauna Gaffny, Pre-Award Research Administrator, Tufts University OVPR, 136 Harrison Avenue, Boston, Mass. 02111.

Level Of Funding: (total costs)

Performance Period: 09/01/2023 – 08/31/2027

Project Goals: The goal of this application is to characterize how complex structural variants alter the methylome in osteosarcoma, and leverage this information to credential a multi-parameter liquid biopsy based diagnostic using canine osteosarcoma as a model system.

Specific Aims:

Aim 1: The team at DFCI will provide critical intellectual contributions to the work through their expertise in pediatric oncology and liquid biopsy. Dr. Crompton is a co-investigator on this project.

Overlap: None.

Pending awards since previous submission

Title: Radiation Oncology at the Interface of Pediatric Cancer Biology and Data Science: Project 2 Time

Commitment: 0.3 calendar months

Supporting Agency: NIH 1U54 CA274516-01A1

Agency's Contracting/Grants Officer: To be determined.

Level Of Funding: (total costs)

Performance Period: 07/01/2023 – 06/30/2028

Project Goals: Project 2 will deeply characterize samples, imaging, and data from a cohort of children with high-risk neuroblastoma treated with the targeted radiopharmaceutical 131I-MIBG.

Specific Aims:

Aim 1: To test the prediction that pretreatment intra-tumoral heterogeneity of high-risk neuroblastoma tumors regulate differential radiation responses to 131I-MIBG therapy

Aim 2: To test the prediction that dynamic changes in markers of tumor heterogeneity from longitudinal samples obtained following 131I-MIBG therapy will define tumors with favorable versus unfavorable responses to 131I-MIBG therapy

Aim 3: To test the prediction that markers of host heterogeneity can predict key late effects of 131I-MIBG therapy.

Overlap: None.

Title: Tumor markers of clinical outcomes after MIBG therapy in neuroblastoma

Time Commitment: 1.2 calendar months

Supporting Agency: NIH/NCI R01 CA285681

Agency's Contracting/Grants Officer: To be determined.

Level Of Funding: (total costs)

Performance Period: 09/01/2023 – 08/31/2028

Project Goals: The major goal of this project is to validate circulating biomarkers for patients with neuroblastoma who are receiving combination therapy.

Specific Aims:

Aim 1: Detection of ctDNA, changes in ctDNA levels, and evolution of somatic mutations are associated with response and treatment resistance to 131I-MIBG-based therapy in NBL

Aim 2: Vorinostat therapy induces recurrent on target patterns of chromatin changes in NBL which can be detected in serial liquid biopsy samples

Aim 3: Response and resistance to dinutuximab-containing treatment combinations are associated with pre-treatment GD2 antigen levels and changes in GD2 expression during therapy.

Overlap: None.

Title: Cancer screening with cell-free DNA in Li-Fraumeni Syndrome: Feasibility study prior to national trial

Time Commitment: 0.24 calendar months

Supporting Agency: NIH: R34: PAR-22-173

Agency's Contracting/Grants Officer: To be determined.

Level Of Funding: (total costs)

Performance Period: 12/01/2023 – 11/31/2025

Project Goals: The goal of this project is to perform a feasibility study prior to a national trial.

Specific Aims:

Aim 1: Dr. Crompton will work directly with the clinical research coordinators supported by this project to ensure enrollment of patients with Li-Fraumeni Syndrome (LFS) on a local banking study.

Overlap: None.

Title: Prospective Validation of a Prognostic Liquid Biopsy Approach for Pediatric Ewing Sarcoma

Time Commitment: 0.6 calendar months

Supporting Agency: Pediatric Cancer Research Foundation

Agency's Contracting/Grants Officer: Jeri Wilson, Executive Director, PCRFL Level Of Funding: (total costs)

Performance Period: 01/01/2024 - 12/31/2025

Project Goals: In this proposal, we aim to validate a new assay that detects tumor DNA from a simple peripheral blood draw as a surrogate for tumor burden in patients with Ewing sarcoma.

Specific Aims:

Aim 1: Demonstrate that the commercial FoundationOne Liquid CDx provides equivalent results to a previously validated laboratory research assay for detection of ctDNA in patients with EWS

Aim 2: Identify mechanism of tumor evolution that contribute to the development of treatment resistant relapse in EWS.

Overlap: None.

Title: Profiling circulating tumor DNA to inform rhabdomyosarcoma prognosis and relapse

Time Commitment: 1.2 calendar months

Supporting Agency: Children's Cancer Research Fund

Agency's Contracting/Grants Officer: To be determined

Level Of Funding: (total costs)

Performance Period: 01/01/2024 – 12/31/2025

Project Goals: In this project, we propose to profile tumor and plasma tissue from patients to validate ctDNA is a prognostic biomarker of outcome for patients with IR RMS and to identify recurrent patterns of tumor evolution in patients who experience disease progression during or after therapy.

Specific Aims:

Aim 1: Are pre-treatment and on-treatment levels of ctDNA prognostic in patients with IR RMS?

Aim 2: Can liquid biopsies detect patterns of tumor evolution that give rise to relapse?

Overlap: None.

Trevor Pugh

Completed funding since previous submission

Title: Establishment and genome characterization of PNET mouse models

Time Commitments: 0.3 Calendar

Supporting Agency: Neuroendocrine Tumour Research Foundation Address: 31 St. James Avenue, Suite 365 Boston, MA 02116

Contracting/Grants Officer: NA

Performance Period: 2021/01-2022/01

Level of funding: USD

Project Goals: To characterize the sequence of mutations that trigger genomic instability and allow for further molecular screening and drug development that will inform future patient studies.

Specific Aims:

Aim 1: Establishing a versatile CRISPR/Cas9 PanNET mouse model platform

Aim 2: Cross-species comparison of genetic alterations driving aggressive PanNETs

Overlap: none

Title: Molecular Predictors of Response of Maintenance Poly (ADP-ribose) Polymerase Inhibition (PARPi) in Serous or p53 Abnormal Endometrial Cancer After Chemotherapy: Randomized Phase II Trial

Time Commitments: 0.1 Calendar

Supporting Agency: Canadian Cancer Society Research Institute Address: 55 St Clair Avenue West, Suite 500, Toronto, Ontario M4V 2Y7

Contracting/Grants Officer: NA

Performance Period: 2020/09-2022/09

Level of funding: CAD

Project Goals: To determine if HRD in serous/p53mut EC is a predictive tumour biomarker of response to maintenance PARPi after chemotherapy.

Specific Aims:

Aim 1: to determine whether having HRD can predict response (decrease recurrence or progression of cancer) to niraparib in women with serous/p53mut EC

Aim 2: can we use this tumour test to determine who should receive this drug

Overlap: none

Title: NCI Experimental Therapeutics-Clinical Trials Network with Phase I Emphasis (ETCTN) (UM1) North American Star Consortium (NASC) (2UM1-CA186644-06)

Time Commitments: 0.1 calendar

PREVIEW Date: Aug 18, 2021

Supporting Agency: National Cancer Institute (NCI) Address: 9609 Medical Center Drive West Tower, 2nd floor Rockville MD 20850

Contracting/Grants Officer: Mohammed Kurtom

Performance Period: 2020/03-2023/03

Level of funding: USD

Project Goals: To conduct innovative, coordinated, efficient, regulatory-compliant and high impact early phase clinical trials in experimental therapeutics, which are designed to address important questions that do not duplicate research supported by the pharmaceutical industry or other sources

Specific Aims:

Aim 1: To conduct innovative, coordinated, efficient, regulatory-compliant and high impact early phase clinical trials in experimental therapeutics, which are designed to address important questions that do not duplicate research supported by the pharmaceutical industry or other sources

Aim 2: To adopt a team science interdisciplinary approach with internal and external collaborations to enhance the optimal evaluation of novel anticancer agents alone or in combination

Aim 3: To accelerate biomarker development and correlative sciences research through comprehensive molecular characterization of tumors obtained from patients enrolled on ET-CTN trials to elucidate mechanism of action, as well as predictors of therapeutic response and/or resistance

Aim 4: To emphasize training and education to foster career development of junior investigators

Overlap: none

Title: Reimagining glioblastoma as a consequence of aberrant neural tissue repair

Time Commitments: 1 calendar

Supporting Agency: Canadian Cancer Society, Impact Grant Address: 55 St Clair Avenue West, Suite 500, Toronto, Ontario M4V 2Y7

Contracting/Grants Officer: NA

Performance Period: 2020/2 – 2023/01

Level of funding: CAD

Project Goals: To perform a functional follow-up of glioblastoma stem cell biology found by single cell RNA-seq

Specific Aims:

Aim 1: We will use multi-omics computational drug and mechanism prediction methods to identify drugs and novel drug combinations designed to simultaneously target all cell populations present in GBM, and we will evaluate these using in vitro and in vivo models.

Aim 2: Determine the role of injury or inflammation in GBM genesis and phenotype.

Overlap: none

Title: Early detection of cancer in Hereditary Breast and Ovarian Cancer patients and Lynch syndrome patients using cell-free DNA

Time Commitments: 1 Calendar

Supporting Agency: TD Ready Challenge Address: 161 Bay St., Toronto, ON M5J 1C4

Contracting/Grants Officer: Marcellus Arokium, Manager Research Financial Reporting, OICR

Performance Period: 2020/01-2023/01

Level of funding: CAD

Project Goals: To expand our national network of hereditary cancer clinics and samples for profiling
Specific Aims:

Aim 1: develop a screening test that will detect cancer cell at an early stage of development

Aim 2: guide more personalized management of carriers

Aim 3: provide better screening and care to all patients, especially in remote areas

Overlap: none

Title: Early detection of cancer in high-risk patients through profiling of circulating tumour DNA.

Time Commitments: 1 calendar

Supporting Agency: Canadian Institutes of Health Research (CIHR) Address: 160 Elgin Street, 9th Floor
Ottawa ON K1A 0W9

Contracting/Grants Officer: Martine Lafrance, Ph.D., Manager, Project Grant Program Program
Design and Delivery Branch

Performance Period: 2018/7 – 2022/7

Level of funding: CAD

Project Goals: to better understand the role that the tumour immune microenvironment (TIME) plays in the evolution/progression of pre-malignant disease states in multiple myeloma (MM).

Specific Aims:

Aim 1: Define TIME cell populations and transcriptional programs associated with distinct stages of MM disease evolution

Aim 2: Characterize temporal evolution of the TIME in MM using serial samples

Aim 3: Nominate novel TIME-associated mechanisms of MM evolution

Overlap: none

Title: Defining Optimal Tumor, Host, and Microbiome Signatures For Immunotherapeutic Eradication of Myeloma.

Time Commitments: 0.25 calendar

Supporting Agency: Multiple Myeloma Research Foundation, Immunotherapy Initiative Address: 383
Main Ave, 5th Floor, Norwalk CT, 06851

Contracting/Grants Officer: NA

Performance Period: 2018/7 – 2023/7

Level of funding: USD

Project Goals: We will harness the diverse experience within our network to characterize the tumour and host phenotypes associated with response, durability, toxicity, or escape from immunotherapeutic interventions in myeloma

Specific Aims:

Aim 1: Develop and manage an infrastructure of coordinated analyses of individual patient data derived from state of the art assays to characterize tumor/host genomes, immunophenotype, microbiome and seromic response in the bone marrow and peripheral blood from healthy donors, and MM patients with early and advanced relapsed disease in order to obtain a baseline characterization and gain an understanding of the common immune disturbances as MM progresses to the multiply relapsed/refractory setting.

Aim 2: Apply these assays to serial patient samples from checkpoint blockade and CAR T cell trials to discover predictive markers for response and toxicity.

Aim 3: Use the resources of the network to develop a murine model for the in vivo study of primary MM, including the MM microenvironment, and study in cell culture or murine models, overcoming specific resistance mechanisms to immunotherapies.

Overlap: none

Title: The Terry Fox New Frontiers Program Project Grant in Li-Fraumeni Syndrome.

Time Commitments: 0.5 calendar

Supporting Agency: Terry Fox Research Institute, New Frontiers Program Address: 7624 675 West 10th Avenue (14th floor) Vancouver, BC V5Z 1L3

Contracting/Grants Officer: Russell Watkins, Senior Research Programs Manager, Performance Period: 2018/7 – 2023/7

Level of funding: CAD

Project Goals: to improve early detection and clinical management of cancer in people with Li-Fraumeni Syndrome by developing a safe, effective, and non-invasive cfDNA screening test that can detect early cancer onset and predict tissue-of-origin.

Specific Aims:

Aim 1: Tailor a sensitive ctDNA sequencing assay to detect somatic mutations in blood plasma of LFS patients with known cancers

Aim 2: Develop the cfMeDIP-seq assay for epigenetic signature analysis of ctDNA in LFS patients with known cancers

Aim 3: Utilize ctDNA mutational profiling and cfMeDIP-seq to validate detection of early tumour development in a murine model of LFS.

Aim 4: Compare longitudinal ctDNA mutational profiling and cfMeDIP-seq against current imaging/biochemical based surveillance modalities (Toronto protocol) in LFS patients.

Overlap: none

Title: Molecular evolution of myeloma from precursor through to relapsed disease

Time Commitment: 0.3 calendar

Supporting Agency: Canadian Institutes of Health Research (CIHR), Project Grant Address: 160 Elgin Street, 9th Floor Ottawa ON K1A 0W9

Contracting/Grants Officer: Martine Lafrance, Ph.D., Manager, Project Grant Program Program Design and Delivery Branch

Performance Period: 2018/7 – 2022/7

Level of Funding: CAD

Project Goals: to better understand the role that the tumour immune microenvironment (TIME) plays in the evolution/progression of pre-malignant disease states in multiple myeloma (MM).

Specific Aims:

Aim 1: Define TME immune cell populations and transcriptional programs associated with distinct stages of MM disease evolution

Aim 2: Characterize temporal evolution of the TIME in MM using serial samples

Aim 3: Nominate novel TIME-associated mechanisms of MM evolution

Overlap: none

New funding since previous submission

Title: Early cancer detection in children and adults with familial cancer syndromes across Canada

Time Commitments: 0.25 calendar months

Supporting Agency: Canadian Cancer Society (CCS) and Canadian Institutes of Health Research (CIHR) Address: CCS: 55 St Clair Ave W Suite 500, Toronto, ON M4V 2Y7 / CIHR: 160 Elgin Street, 9th Floor Ottawa ON K1A 0W9

Contracting/Grants Officer: Christian Brochu, Manager, Program Design and Delivery Research Programs Portfolio

Performance Period: 2023/1-2028/12

Level of Funding:

Project Goals: The major goal of this project is to conduct a prospective clinical trial to establish whether cell-free DNA (cfDNA) whole genome sequencing can detect high-fatality cancers at the same time, or before, conventional annual medical exams for (FCS) carriers.

Specific Aims:

Aim 1: Testing of cfDNA more frequently than the current imaged-based screening protocols will result in detection of more cancers at earlier stages and improve medical management and quality of life for carriers with FCS.

Aim 2: A programmatic approach to cfDNA testing will increase quality of life including: patient empowerment and decrease distress, uncertainty, and anxiety among carriers with FCS.

Overlap: none

Title: Multiple myeloma surveillance using plasma cell free whole genome sequencing

Time Commitments: 0.5 calendar months

Supporting Agency: Princess Margaret Cancer Foundation (Paula and Roger Riney Foundation Award)

Address: 610 University Ave, Toronto, ON M5G 2C4

Contracting/Grants Officer: David Taylor, Senior Associate, Agreements & Knowledge Management, The Princess Margaret Cancer Foundation

Performance Period: 2022/10-2024/10

Level of Funding:

Project Goals: The major goal of this project is to improve on the sensitivity of the MYLESTONE tests by deploying blood plasma WGS. WGS detects myeloma at its earliest stages and improves surveillance of minimal residual disease (MRD) following treatment.

Specific Aims:

Aim 1: Demonstrate that blood plasma WGS can detect both active myeloma and MRD.

Aim 2: Test whether longitudinal plasma WGS testing can confirm sustained MRD or detect early relapse.

Aim 3: Assess whether plasma WGS of MGUS patients can identify those at risk to progress to myeloma.

Overlap: none

Title: An integrated approach to characterize high-risk disease in myeloma at Princess Margaret.

Time Commitments: 0.5 calendar months

Supporting Agency: Princess Margaret Cancer Foundation (Helga and Antonio De Gasperis Grand Challenge in Myeloma Research) Address: 610 University Ave, Toronto, ON M5G 2C4

Contracting/Grants Officer: Cameron Sharpe, Planning Associate, Beyond Chemotherapy Strategic Pillar at UHN, The Princess Margaret Cancer Foundation

Performance Period: 2023/01-2025/01

Level of Funding:

Project Goals: The major goal of this project is to develop and assess a framework for improved identification and management of HR MM, we propose an integrated assessment of HR features in a uniformly-treated transplant-eligible patient cohort.

Specific Aims:

See Project Goals.

Overlap: none

Title: Cure leukemia, lymphoma, hodgkin's disease and myelome and improve the quality of life of patients and their families.

Time Commitments: 0.25 calendar months

Supporting Agency: The Leukemia & Lymphoma Society Specialized Center of Research Program Grant Address: 2 Lansing Square, Suite 601 Toronto, ON M2J 4P8

Contracting/Grants Officer: Paul O'Connell, Research Program Lead

Performance Period: 2022/10-2027/9

Level of Funding:

Project Goals: The major goal of this project is to combine and synergize our efforts to define the genetic, molecular, cellular, and niche/TME events leading from the initial transformation of a cell to full-blown tumorigenesis.

Specific Aims:

Aim 1: We will examine epigenetic/somatic HLA loss/mutation in AML and DLBCL patient samples, extending this study to other host protein alterations enabling tumor cells to escape immunosurveillance.

Aim 2: We will identify peptides bound to HLA molecules that are expressed by AML and DLBCL cells and recognized by T cells in the TME, focusing first on peptides derived from CTAs.

Aim 3: We will profile non-transformed lymphoid lineage cells within AML and DLBCL samples to identify gene expression changes in various subsets that contribute to resistance to immunosurveillance.

Overlap: none

Title: The EBioPortal for Cancer Genomics

Time Commitment: 0.25 calendar months

Supporting Agency: Subgrant Agreement: Original Agency National Institutes of Health, Sustained Support for Informatics Resources for Cancer Research and Management (U24), Pass-Through Entity: Sloan Kettering Institute for Cancer Research Address: NIH - 9000 Rockville Pike Bethesda, Maryland 20892 301-496-4000 Sloan Kettering Institute for Cancer Research: 1275 York Ave New York, NY 10065
Contracting/Grants Officer: NIH : Michael Raymond Kluk, Grants Management Specialist, National Cancer Institute Annmarie L. Pacchia, PhD, Sloan Kettering Institute for Cancer Research

Performance Period: 2022/9- 2027/8

Level of Funding:

Project Goals: The major goals of this project are to establish a multi-institutional software development network, which will coordinate and drive the future development of the software and associated data pipelines.

Specific Aims:

Aim 1: Evolve the core cBioPortal technology platform.

Aim 2: Implement new features with a focus on cancer genomics and precision medicine

Aim 3: Build a vibrant open source community to continually develop the cBioPortal.

Aim 4: Expand community outreach, user support and training, and documentation

Overlap: none

Title: The Brain Single Cell Initiative (+UHN Matching account)

Time Commitments: 0.5 calendar months

Supporting Agency: Brain Canada Foundation Platform Support Grant; UHN Matching Funds Address: 1200 McGill College Avenue Suite 1600, Montreal, Quebec H3B 4G7 Contracting/Grants Officer: Melissa Russo, Program Manager

Performance Period: 2022/11-2025/10

Level of Funding:

Project Goals: The major goal of this project is to deploy new assays that make available the latest generation single-cell genomics technologies in a variety of areas to brain researchers.

Specific Aims:

Aim 1: Sustain and enhance existing single cell RNA-seq services

Aim 2: Evaluate and deploy new multi-omic single cell technologies

Aim 3: Establish a brain-focused single cell data analysis, integration, and sharing service

Overlap: none

Title: Enabling non-invasive measurement of the immune microenvironment of glioblastoma and meningioma: from single cells to liquid biopsy.

Time Commitments: 0.5 calendar months

Supporting Agency: Princess Margaret Cancer Centre (Yamana Gold Discovery to Impact Fund) Address: 7-504, 610 University Avenue Toronto, Ontario M5G 2M9

Contracting/Grants Officer: Patrick Yau, Business Manager, Research

Performance Period: 2022/10-2024/9

Level of Funding: CAD

Project Goals: We propose to identify immune subtypes at population scale across a diverse range of histologies and attempt to establish an orthogonal and clinically actionable immune grading system. We will then attempt novel immune deconvolution of cfDNA from CSF and plasma, paving the way towards simultaneous diagnosis/subtyping, treatment monitoring, and immune grading from a single non-invasive blood test.

Specific Aims:

Aim 1: Generate reference cell-type specific methylomes of CNS tumours and TIME.

Aim 2: Deconvolute the TIME of tumour and liquid biopsy.

Aim 3: Identify clinically relevant immunologic clusters of CNS tumours.

Overlap: none

Title: Phenomic Liquid Biopsy Resource

Time Commitments: 0.1 calendar months

Supporting Agency: Canadian Cancer Society, Data Transformation Grant Address: 55 St Clair Ave W Suite 500, Toronto, ON M4V 2Y7

Contracting/Grants Officer: Stephanie Bazinet, Research Partnerships & Engagement Senior Coordinator

Performance Period: 2022/3-2024/3 (includes 1 year automatic NCE)

Level of Funding: CAD

Project Goals: To improve the accessibility of liquid biopsy data, and in particular fragmentomic profiling data, we propose to develop the Phenomic Liquid Biopsy Resource (PLBR). The PLBR will act as a centralized repository for fragmentomic data, thereby decompartmentalizing the currently disjointed landscape of cfDNA screening data and allowing researchers to quickly and easily share this valuable data with their colleagues.

Specific Aims:

Aim 1: Design a backend database schema that reflects the needs of the liquid biopsy research community.

Aim 2: Build a front-end web application infrastructure to enable identification and export of reference fragmentomic profiles.

Aim 3: Use PLBR in a pilot study to integrate data from sporadic cancers to detect early breast and prostate cancer in patients with hereditary cancer.

Overlap: none

Title: Comprehensive evaluation of immune function in patients receiving multimodal therapy for high risk neuroblastoma

Time commitment: 5% effort, 0.60 cal mos

Supporting agency: Department of Defense CA210953P1

Funding Agency Grant Officer: Jamie A. Shortall, U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick, MD 21702-5014 Period of performance: 2022/09 – 2026/08

Level of funding:

Brief description of project goals: We will test the novel hypothesis that markers reflective of immune cell profile and interaction with malignant cells during the course of therapy can guide treatment of children with NBL

List of specific aims:

Aim 1: Identify tumor-derived and circulating biomarkers predictive of response to therapy in patients with high-risk neuroblastoma using single cell profiling and proteomic analyses

Aim 2: Define the breadth and dynamics of T- and B-cell diversity at diagnosis, during treatment, and at remission in patients with high-risk neuroblastoma

Overlap: None

Title: Implementation of serological and molecular tools to inform COVID-19 patient management (GENCOV)

Time Commitments: 0.5 Calendar months

Supporting Agency: Subgrant Agreement: Original Agency: Canadian Institutes of Health Research (CIHR) Subgrant Agency: Sinai Health System Address: CIHR: 160 Elgin Street, 9th Floor Ottawa ON KIA 0W9 Sinai Health: Office of Technology Transfer and Industry Liaison, Mount Sinai Hospital, 600 University Avenue, Room 843, Toronto, Ontario M5G 1X5

Contracting/Grants Officer: CIHR: Martine Lafrance, Ph.D., Manager, Project Grant Program Program Design and Delivery Branch Sinai Health: Dee Perera, VP Finance & CFO, Sinai Health System Performance Period: 2021/5-2023/12

Level of funding:

Project Goals: Differential outcomes to COVID-19 infection may be influenced by differences in short and long-term immune response, acute physiological response to infection, genetic variation or viral strain. By linking these variables to patient characteristics (sex, age, ancestry, symptom severity, comorbidities) and patient outcomes we hope to identify characteristics of patients that result in poor or favourable response to infection.

Specific Aims:

1. Identify the characteristics of the antibody response that result in maintained immune response and better patient outcomes.
2. Determine impact of genetic differences on COVID-19 infection severity and immune response.
3. Determine impact of different viral strains on antibody response and patient outcomes.

Overlap: None

Title: Senior Investigator Award

Time Commitment: 1 calendar months

Supporting Agency: Ontario Institute for Cancer Research (OICR) Address: 661 University Ave Suite 510, Toronto, ON M5G 0A3

Contracting/Grants Officer: Lincoln Stein, Head of Adaptive Oncology Performance Period: 2019/5-2024/3

Level of Funding:

Project Goals: to leverage both UHN appointment and independent research program at the University of Toronto to successfully deliver a full translational genomic program for Ontario and beyond

Specific Aims:

1. To expand the translational and clinical mandate of OICR Genomics
2. To integrate OICR's internal genomic enterprise with outward-facing data policy, analysis, and sharing initiative
3. To strengthen and embed collaborative programs with external institutions and investigators from across Ontario

Overlap: none

Pending awards since previous submission

Title: Improving Patient Matching to Therapy (PMATCH): streamlining clinical trial criteria to guide precision oncology

Time Commitments: 0.25 calendar months

Supporting Agency: Genome Canada and University Health Network Address: 150 rue Metcalfe Ste. 2100 Ottawa CA K2P 1P1

Contracting/Grants Officer: Bettina Hamelin, Ontario Genomics Administrative Centre

Performance Period: 2023-2026

Level of Funding:

Project Goals: The goal of this project is to facilitate accurate, real-time matching of cancer patients to clinical trials based on their genomic, clinical, pathology, and imaging data.

Specific Aims:

Aim 1: Automating matching based on eligibility criteria.

Aim 2: Developing a pilot federated network for trial matching.

Aim 3: Deployment for clinical and research uses.

Overlap: none

What other organizations were involved as partners?

Organization name: University of Florida

Location of Organization: Gainesville, FL

Partner's contribution to the project: Collaboration.

In addition to the 2 partnering institutions (DFCI and UHN), Dr. Arlene Naranjo at the University of Florida is a collaborator for this award. Dr. Naranjo is the lead statistician for ANBL1531, the parent clinical trial upon which this project's aims are based. She will perform the statistical analyses to determine whether there are tumor-intrinsic and microenvironment (extrinsic) markers that define patient subgroups with differential probabilities of clinical benefit following therapy.

8. SPECIAL REPORTING REQUIREMENTS

The study team acknowledges the collaborative awards requirements and independent reports are being submitted with this progress report.

9. APPENDICES

None