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TITLE: A Multi-Omics Approach to Overcome Resistance in Infant Leukemia by Identifying Immune Therapy Failure Mechanisms

PRINCIPAL INVESTIGATOR: **Patrick Brown**

CONTRACTING ORGANIZATION: **JOHNS HOPKINS UNIVERSITY**

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5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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Kathrin Bernt (submitting PI)
Erin Guest (co-PI),

E-Mail:

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5e. TASK NUMBER

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JOHNS HOPKINS UNIVERSITY
BALTIMORE MD 21218-2608

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Approved for public release; distribution is unlimited

13. SUPPLEMENTARY NOTES

14. **ABSTRACT**

Despite advances in curing children over 1 year of age with acute lymphoblastic leukemia (ALL) children under 1 year of age face grim survival rates of around 35%. Infants with ALL often experience on therapy relapses. Bone marrow transplant has persistently failed to improved outcomes. The goal of this proposal is to use a single cell multi-omic approach to better understand the biology of infant ALL, particularly with respect to immune mechanisms, as a prerequisite to develop better therapies including novel immunotherapy approaches.

15. SUBJECT TERMS

NONE LISTED

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1. INTRODUCTION:

Despite advances in curing children over 1 year of age with acute lymphoblastic leukemia (ALL) children under 1 year of age face grim survival rates of around 35%. Infants with ALL often experience on therapy relapses. Bone marrow transplant has persistently failed to improved outcomes. The goal of this proposal is to use a single cell multi-omic approach to better understand the biology of infant ALL, particularly with respect to immune mechanisms, as a prerequisite to develop better therapies including novel immunotherapy approaches

2. KEYWORDS:

Infant acute lymphoblastic leukemia, MLL, KMT2A, lineage switch

3. ACCOMPLISHMENTS:

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

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Specific Aim 1	Months	Site
IRB approvals (with annual renewals)	-12 to -6	All
Major task 1: RNA-Seq and whole genome bisulfite sequencing of bulk leukemia	1-18	Dr. Bernt/Tan, Dr. Brown
Major task 2: scRNA-Seq and scATAC-Seq of leukemia	1-18	Dr. Bernt/Tan
Major task 3: snmC sequencing	1-18	Dr. Bernt/Wu
Major task 4: Subclone analysis and identification of antigens and epigenetic programming related to lineage switch	12-36	Dr. Tan, Dr. Bernt
Milestones achieved: identification of iALL subclones, antigen identification, final data analysis	18-36	All
Specific Aim 2		
Major task 1: RNA-Seq and whole genome bisulfite sequencing of bulk T cells	1-18	Dr. Bernt/Tan,
Major task 2: scRNA-Seq and scATAC-Seq of T cells	1-18	Dr. Bernt/Tan,
Major task 3: snmC sequencing of T cells	1-18	Dr. Bernt/Wu
Major task 4: T cell pathway analysis, exhaustion profiling and correlation with CAR potential	18-36	Dr. Tan
Milestone(s) Achieved: identification of pathways to be targeted to improve infant T cell CAR performance, final data analysis	18-36	All

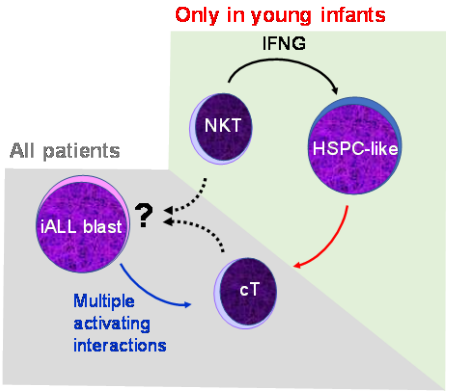
What was accomplished under these goals?

1) major activities: we proposed to profile 30 infant ALL (iALL) samples using sc-RNA-Seq, sc-ATAC-Seq and sn-mC-Seq. We have completed a total of 16 samples. We also had proposed to profile several patients who underwent lineage switch under the pressure of immunotherapy. We identified two such patients, and completed the analysis of tumor evolution through serial samples. Progress was somewhat slower than anticipated due to delays in all aspects of this project due to COVID19.

2) specific objectives:

- define mechanisms of drug resistance and poor outcome
- define immune mechanisms that impact outcome
- interrogate tumor evolution through lineage switch.

3): preliminary analysis of the infant cohort revealed 3 key insights:
3.1 Infants less than 6 months of age, who have a much inferior outcome, tend to have ALL that is characterized by greater developmental and lineage plasticity. In particular, younger infants (< 6 months) often have leukemic cells that transcriptionally and phenotypically map onto hematopoietic stem and early progenitor cells.
3.2 The leukemic clone of infants less than 6 months of age contains a subpopulation that expresses reduced levels of the steroid receptor NR3C1 and steroid response genes. High dose steroids induce apoptosis in ALL cells and are a key component of ALL therapy. This feature may explain why infant ALL tends to be more upfront resistant that other subtypes of ALL.
3.3 we inferred a provocative immune interaction that is specifically found in infants less than 6 months, whereby immature NKT cells produce interferon gamma, which acts on the most immature blasts within the leukemic clone. In turn, highly immature cells in the blood of young infants (< 6 mo) are predicted to undergo immune inhibitory interactions with cytotoxic T-cells. If confirmed, this data will be critical for developing immunotherapy approaches in infants.



Inferred immune interactions in infants < 6 and > 6 months of age.

3.4. Analyzing two patients with KMT2A (MLL) rearranged leukemia whose leukemia underwent a lineage switch (from ALL to AML) after B-cell directed immunotherapy revealed a pre-existing myeloid biased population that expanded under selective pressure.

A preprint report of our findings is available at
https://www.biorxiv.org/content/10.1101/2020.12.06.413930v1.full

Opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

- A preprint report of our findings on the first 50% of samples is available here: https://www.biorxiv.org/content/10.1101/2020.12.06.413930v1.full
- We are in the process of functionally validating some of our insights and preparing a manuscript for submission.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Currently we are in the process of putting together a confirmatory cohort. This will consist in samples from the AALL0632 clinical trial – these samples are in the hands of Dr. Brown and will be enough to complete the proposed sample set of 20 samples, and have outcomes data available and will allow us to ask whether and which features we identified correlate with poor outcome. Future studies will include second set from AALL15P1 – this cohort will be larger, confirm outcomes relations in the discovery data set, and is currently at the Children's Oncology Group (COG) repository. Drs. Bernt and Guest are applying for release of these samples for this program.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

We have known for a long time that infants less than one year of age face dismal odds of survival if they are diagnosed with ALL. This is in contrast to older children, who are much more likely to be cured. Our data points to several reasons why infants face worse outcomes – some long suspected, and some unexpected and novel. Understanding why our traditional approaches fail to cure infants with ALL is the first critical step in developing more effective therapies.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Our combined transcriptomic and epigenomic single cell analysis longitudinally over the course of tumor evolution is quite novel and will likely encourage other researchers to use similar approaches to understand dynamic tumor evolution.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*

- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:
- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Dr. Barrett, who was the submitting PI for this project, left CHOP to move to industry. Dr. Bernt, who had worked closely with Dr. Barrett on this project, and is co-PI with Dr. Tan on several similar projects for older children, took over as coordinating PI for Dr. Barrett. The DOD was notified immediately, and all regulatory and rebudgeting requirements were fulfilled prior to Dr. Barrett's departure.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

COVID 19 considerably slowed the progress of all collaborative projects between Dr. Bernt and Tan, since these experiment required sorter time, and cores were shut down for several months. Furthermore, Dr. Barrett left CHOP, and his collaborator Dr. Bernt took over the role of PI. Finally, Dr, Gao left, with Drs. Uzun and Alikarami taking on extra effort temporarily while a search for a replacement us under way. Despite these challenges, we are slightly ahead of schedule, and have generated intriguing results with the first set of samples. We are now fully open, and are working with Dr. Brown on putting together our outcomes cohort.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Since multiple programs were affected, this led to an underuse of already purchased library prep and sequencing kits which were about to expire. These about to expire kits were used once operations were able to resume, leading to a large carryover on the budget.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

All aspects of the experimental pipeline were modified and re-certified by our biosafety committee granting us permission to use COVID19+ samples should the need arise. This is not likely to be relevant given the currently targeted samples that were collected in the pre-COVID19 era.

PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

  Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

https://www.biorxiv.org/content/10.1101/2020.12.06.413930v1.full

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report (We plan to eventually upload the generated data sets to make the publicly available in a deidentified manner)

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

During the first year, Dr. Barrett left CHOP, and Dr. Bernt assumed the role of overall PI for this study effective 11/10/2020. This included some minor adjustments in effort for other personnel. These were in part driven by cost of living increases as well as a substantial change in position for Dr. Gao, who was promoted to staff scientist during year 1 with the commensurate increase in pay. **All changes were already executed at the time of the transition. No further changes are made or planned at the time of this report.** The already executed changes are summarized below:

Name:	**David M. Barrett, MD/PhD**
Project Role:	Principal Investigator.
Researcher Identifier:	ORCID ID: 0000-0003-0993-7919
Nearest Person Month worked:	(planned effort: 2.4 calendar months, 20% effort. This was adjusted to 0 when Dr. Barrett left the institution.)
Contribution to Project:	Kickstarted the project, facilitated initiation collaboration with Hopkins and Kansas sites.
Funding Support:	N/A
Name:	**Kathrin Bernt, MD**
Project Role:	New Principal Investigator (previously: co-I)
Researcher Identifier:	ORCID ID: 0000-0002-0691-356X
Nearest Person Month worked:	adjusted effort year 1: 3 calendar months 25% effort (to facilitate transition), year 2&3: 2.7 calendar months, 22.5% effort. (initially planned effort: 1.2 calendar months, 10% effort. This was adjusted when Dr. assumed the position of PI.)
Contribution to Project:	Worked with Dr. Tan on performing single cell multi-omic analysis of a first cohort of infant ALL samples. Worked with Drs. Guest and Brown to set up two second cohorts originating from studies AALL0631 and AALL15P1.
Funding Support:	N/A

Name:	**Kai Tan, PhD**
Project Role:	co-Investigator
Researcher Identifier:	ORCID ID: 0000-0002-9104-5567
Nearest Person Month worked:	0.6 calendar months, 5% effort Years 1-3
Contribution to Project:	Worked with Dr. Bernt on performing single cell multi-omic analysis of a first cohort of infant ALL samples. Oversaw development of analytic algorithms, data analysis and interpretation
Funding Support:	N/A
Name:	**Fatemeh Alikarami, PhD**
Project Role:	postdoctoral fellow, Bernt lab
Researcher Identifier:	ORCID ID: N/A
Nearest Person Month worked:	2.4 calendar months, 20% effort, for most of the year. Of note, effort was temporarily decreased to 17% 11/1/2020 – 3/30/2021.
Contribution to Project:	Dr. Alikarami oversees the sample processing and planning of experiments for the multi-omic analysis of infant ALL cells, including coordination with collaborating groups. Dr. Alikarami is involved in data interpretation, and downstream validation experiments.
Funding Support:	N/A
Name:	**Yasin Uzun, PhD**
Project Role:	research scientist, Tan lab
Researcher Identifier:	ORCID ID: 0000-0003-3478-3499
Nearest Person Month worked:	6 calendar months, 50% effort for most of the year. 11/1/2020 – 3/30/2021 Planned effort: 5.4 calendar months, 45% effort Years 2&3
Contribution to Project:	Dr. Uzun conducted most of the data analysis of the first cohort, including analysis and integration of scRNA-Seq, scATAC-Seq data. After Dr. Gao left, Dr. Uzun became the primary interface between the Bernt and Tan labs, and CHOP and CMH/JHU labs for data analysis. Since submission of the original budget, Dr. Uzun has received a cost of living increase which is reflected in the increased base salary of the revised budget
Funding Support:	N/A
Name:	**Peng Gao, PhD**
Project Role:	research scientist, Tan lab
Researcher Identifier:	ORCID ID: N/A
Nearest Person Month worked:	4.32 calendar months, 34% effort Year 1,
Contribution to Project:	Dr. Gao coordinated with Dr. Alikarami the single cell sorting techniques, and generated scRNA-Seq and scATAC-Seq data. He was promoted to the rank of staff scientist during Year 1. He left CHOP towards the end of year 1Q3. A search for a replacement is ongoing.
Funding Support:	N/A

Name:	**Erin Guest, MD**
Project Role:	Co-Principal Investigator
Researcher Identifier:	ORCID ID: 0000-0003-2482-5608
Nearest Person Month worked:	1.8 calendar months, 15% effort Years 1-3
Contribution to Project:	Worked with Drs. Bernt, Brown, and Tan to analyze data from first cohort of samples originating from studies AALL0631 and AALL15P1. Prepared an application to Children's Oncology Group to obtain additional AALL15P1 samples for sequencing.
Funding Support:	N/A

Name:	**Patrick Brown, MD**
Project Role:	Co-Principal Investigator
Researcher Identifier:	ORCID ID: 0000-0002-8653-1069
Nearest Person Month worked:	0.12 calendar months, 1% effort Years 1-3
Contribution to Project:	Oversee primary patient sample identification, selection, approval for use and shipment to the appropriate laboratories. Help design and supervise the bioinformatics analytics of the WGBS and other data, help integrate the data generated by the collaborating laboratories, and ensure key findings are efficiently translated into clinical trials.
Funding Support:	N/A

Name:	**Rumen Kostadinov, PhD**
Project Role:	Biostatistician/Research Associate, Brown lab
Researcher Identifier:	ORCID ID: N/A
Nearest Person Month worked:	6 calendar months, 50% effort Years 1-3
Contribution to Project:	Create and apply data analytics for the WGBS and other sequencing data to be generated in this project. (NOTE: Dr. Kostadinov recently left the Brown lab for a job in industry; a full time replacement is pending, but the work continues using biostatistical support available through core services at the Johns Hopkins Kimmel Cancer Center.)
Funding Support:	N/A

Name:	**Hao Wu, PhD**
Project Role:	co-Investigator
Researcher Identifier:	ORCID ID: 0000-0003-4395-6929
Nearest Person Month worked:	0.6 calendar months, 5% effort Years 1-3
Contribution to Project:	Worked with Dr. Bernt on performing single cell DNA methylome analysis of a first cohort of infant ALL samples.
Funding Support:	N/A

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Changes to Other Support:

Kathrin M. Bernt, MD, PI:
The following awards closed in the last reporting period:

*Title: The role of H3K79 methylation in IDH-mutant leukemia
Major Goals: This project aimed at establishing the histone methyltransferase Dot1l as a therapeutic target in AML with IDH mutations, and at discovering the demethylase for H3K79 methylation.
*Status of Support: Completed
Project Number: R01CA201230
Name of PD/PI: Kathrin Bernt
*Source of Support: NIH/NCI
*Primary Place of Performance: Children's Hospital of Philadelphia
Project/Proposal Start and End Date: (MM/YYYY) (if available): 12/2015-04/2021 (NCE)
* Total Award Amount (including Indirect Costs): N/A
* Person Months (Calendar/Academic/Summer) per budget period. N/A

*Title: HOXA cluster alterations in angiosarcoma
Major Goals: Investigate whether HOXA cluster overexpression induces similar transcriptional changes in angiosarcoma and AML, and whether HOXA9 overexpression in an embryonic hemagioendothelial precursor will yield a novel angiosarcoma model.
*Status of Support: Completed
Project Number: N/A
Name of PD/PI: Kathrin Bernt
*Source of Support: University of Pennsylvania/Emerson Collective Cancer Research Fund
*Primary Place of Performance: Children's Hospital of Philadelphia
Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/2019-02/2021 NCE
* Total Award Amount (including Indirect Costs): N/A
* Person Months (Calendar/Academic/Summer) per budget period. N/A

*Title: A single cell atlas of childhood hematopoietic development
Major Goals: The goal of this project was to develop the most detailed map of blood development during childhood available today. This map was made available to researchers around the globe, and advance leukemia research worldwide
*Status of Support: Completed
Project Number: N/A

*Name of PD/PI: Kathrin Bernt
*Source of Support: University of Pennsylvania/Emerson Collective Cancer Research Fund
*Primary Place of Performance: Children's Hospital of Philadelphia
Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/2018-07/2020
* Total Award Amount (including Indirect Costs): N/A
* Person Months (Calendar/Academic/Summer) per budget period. N/A

<u>The following awards are newly active since the last reporting period:</u>

*Title: Understanding mechanisms and developing therapies for MN1-driven leukemia
Major Goals: In this proposal, we will evaluate molecular mechanisms of MN1 - driven leukemic transformation and investigate new therapeutic approaches.
*Status of Support: Active
Project Number: N/A
Name of PD/PI: Kathrin Bernt
*Source of Support: Cookies for Kids' Cancer
*Primary Place of Performance: Children's Hospital of Philadelphia
Project/Proposal Start and End Date: (MM/YYYY) (if available): 01/2021-12/2022
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.

*Title: Targeting MN1 in Hard-To-Treat Cancer
Major Goals: MN1 overexpression in AML is associated with poor prognosis. The goal of this project is to conduct translational studies identifying and testing targeted therapeutic approaches.
*Status of Support: Active
Project Number: N/A
Name of PD/PI: Kathrin Bernt
*Source of Support: Children's Cancer Research Fund
*Primary Place of Performance: Children's Hospital of Philadelphia
Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2021-03/2023
*Total Award Amount (including Indirect Costs):
*Person Months (Calendar/Academic/Summer) per budget period.

Kai Tan, PhD
*Title Center for Developmental Mapping of Heart and Bone Tissues
Major Goals: The overarching goal of our mapping effort is to capture the molecular and cellular heterogeneity and cellular spatial organization of bone and heart.
*Status of Support: Active
Project Number: NIH U54HL156090
Name of PD/PI: Kai Tan
*Source of Support: NIH/NHLBI
*Primary Place of Performance: Children's Hospital of Philadelphia
Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/01/2020-08/31/2022
*Total Award Amount (including Indirect Costs): annual total costs
*Person Months (Calendar/Academic/Summer) per budget period.

Hao Wu, PhD (UPENN):
No changes

Patrick Brown, MD (JHU):
No changes

Erin Guest, MD (CMH):
The following awards are newly active in the last reporting period:
*Title: Free the Data: Open Sharing of Comprehensive Genomic Childhood Cancer Datasets
*Status of Support: Active
Project Number: N/A
Name of PD/PI: Midhat Farooqi, MD, PhD
*Source of Support: National Cancer Institute, Childhood Cancer Data Initiative, Administrative Supplement for the NCI P30 Cancer Center Support Grant
*Primary Place of Performance: Children's Mercy Kansas City
Project/Proposal Start and End Date: 07/2020 – 06/2021
Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period: 0.36 calendar months

*Title: Centromeric DNA instability as a biomarker in Acute Lymphoblastic Leukemia
*Status of Support: Active
Project Number: N/A
Name of PD/PI: Erin Guest, MD
*Source of Support: University of Kansas Cancer Center, Cancer Biology Program, Clinical/Basic Science Translational Research Pilot Grant Award
*Primary Place of Performance: Stowers Institute for Medical Research
Project/Proposal Start and End Date: 01/2021 – 12/2021
Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period: 0.12 calendar months

*Title: Next Generation Sequencing to Detect Minimal Residual Disease in Infant ALL
*Status of Support: Active
Project Number: 1UG1CA233249-01 Sub-award
Name of PD/PI: Erin Guest, MD
*Source of Support: Children's Oncology Group (COG) Hematopoietic Malignancies Integrated Translational Science Center (HM-ITSC) Grant
*Primary Place of Performance: Children's Mercy Kansas City
Project/Proposal Start and End Date: 07/2020-06/2021
Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period: 0.36 calendar months

The following awards are pending in the last reporting period:

*Title: Identifying genomic biomarkers of resistance to therapy in infant acute lymphoblastic leukemia
*Status of Support: Pending Sponsor Review
Project Number: N/A
Name of PD/PI: Erin Guest, MD
*Source of Support: Hyundai Hope on Wheels
*Primary Place of Performance: Children's Mercy Kansas City
Project/Proposal Start and End Date: 12/2021 – 12/2023
Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period: N/A

*Title: Novel Structural Variant Discovery and Minimal Residual Disease Detection in Infant Leukemia
*Status of Support: Pending Sponsor Review
Project Number: N/A
Name of PD/PI: Midhat Farooqi, MD, PhD
*Source of Support: V Foundation
*Primary Place of Performance: Children's Mercy Kansas City
Project/Proposal Start and End Date: 09/2021 – 09/2023
Total Award Amount (including Indirect Costs):
Person Months (Calendar/Academic/Summer) per budget period: N/A

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization Name: University of Pennsylvania
Location of Organization: (if foreign location list country): Philadelphia, PA
Partner's contribution to the project : collaboration

Beyond the 3 main sites (CHOP/Kansas Mercey/ Johns Hopkins), Hao Wu at the University of Pennsylvania is a collaborator for this award. Dr. Wu completed the single cell DNA-methylation analysis for this project.

6. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *N/A*

QUAD CHARTS: *N/A*

7. APPENDICES: *N/A*