TARGET PROGRAM HIGHLIGHT
Genomic Discoveries in Pediatric Mixed Phenotype Acute Leukemia Inform Therapeutic Approaches

The principal subtypes of acute leukemia are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). These are driven by distinct mutational profiles and arise from different developing blood cells.

CTD² GUEST EDITORIAL
CytoScreen: A Miniaturized Imaging Platform to Develop Combinatorial Therapies

Hematologic malignancies represent the fifth most common type of cancer and fourth most common form of cancer-related death. More than 1 million people in the U.S.

DATA CORNER
OCG’s Data Coordinating Center: Facilitating the Sharing of Data Generated by the Office’s Initiatives

Today, cancer research studies by different research groups produce vast amounts of data in widely varying formats.

CGCI PROGRAM HIGHLIGHT
OCG’s Efforts in the Discovery and Validation of Tissue Samples for the HIV+ Tumor Molecular Characterization Project (HTMCP)

The success of antiretroviral therapy and prevention education has led to a dramatic decrease in new HIV (human immunodeficiency virus) positive cases in the United States (U.S.) since the 1980s.

OCG PERSPECTIVE
From Bench to Desk: Transitioning from the Laboratory to Project Management

My name is Eva Tonsing-Carter, and I recently became the Scientific Program Manager for the Human Cancer Models Initiative (HCMI) in the Office of Cancer Genomics (OCG) within the National Cancer Institute (NCI).
The principal subtypes of acute leukemia are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). These are driven by distinct mutational profiles and arise from different developing blood cells. The treatment for these diseases involves contrasting combinations and schedules of drugs. Exploring the biology of these leukemia subtypes has improved disease classification and clinical management. However, these advances have not carried over to patients diagnosed with mixed phenotype acute leukemia (MPAL), a subtype of acute leukemia of ambiguous lineage (ALAL) and a disease characterized by features of both ALL and AML.

MPAL carries a poor prognosis and accounts for about 3 percent of the estimated 4,000 cases of pediatric acute leukemia diagnosed annually in the U.S. The biology driving this complicated leukemia subtype, and the optimal treatment, are largely undefined, leaving physicians and patients with limited information to help guide therapy. The recent study in Nature by Alexander et al explored the biology of pediatric ALAL, mostly MPAL, by genomic interrogation, analysis of multiple leukemia cell subpopulations within each patient sample, and in vivo xenograft models. The investigation provided conceptual insights into the cell of origin of each subtype of MPAL and the genetic alterations that drive them, as well as the basis for the unusual, aberrant immunophenotype. These insights provide a framework for future preclinical research, as well as clinical trials and therapeutic decisions for patients with MPAL. The research was a combined effort of many clinicians and researchers. Thirteen institutions or consortiums provided samples to create a large cohort of 115 cases.

MPAL includes multiple subtypes, defined by immunophenotype, that have distinct genetic features driving leukemia biology. The most common subtypes are B/Myeloid (B/M) and T/Myeloid (T/M) (Figure 1). B/M MPAL has immunophenotypic features of both B-cell ALL (B-ALL) and AML, and similarity to B-ALL in both the DNA mutation profile of transcription factor genes ETV6, PAX5, IKZF1 and patterns of gene expression. Rearrangements of the transcription factor gene ZNF384, which have also been observed in B-ALL, were present in nearly half of the cases analyzed by RNA-sequencing and this fusion has been well-characterized in B-ALL. These biological features support ALL directed therapy as the appropriate initial therapeutic choice for B/M MPAL, consistent with recent clinical studies. T/M MPAL shares features with a subtype of ALL called early T-cell precursor (ETP) ALL. Both T/M MPAL and ETP-ALL have frequent alterations in FLT3 (tyrosine kinase receptor gene), WT1 (tumor suppressor gene), and developmental pathway genes RUNX1 and ETV6. The gene expression profiles of both T/M MPAL and ETP-ALL are in between T-ALL and AML. Previously, ETP-ALL was shown to have a poor prognosis with some investigators advocating for incorporation of AML-directed therapy. However, recent trials have demonstrated improved prognosis of ETP-ALL when patients are treated on response-adapted ALL protocols.

The similarities between T/M MPAL and ETP-ALL suggest that ALL therapy may be appropriate for many T/M MPAL patients.
MPAL cases often present with multiple distinct populations; some cells express predominantly myeloid features, some lymphoid only, some cells with features of both, and some cells with no lineage-defining features (Figure 1). In the current study, mutational analysis of purified progenitor subpopulations demonstrated the presence of hallmark mutations in progenitor cells. Conversely, distinct immunophenotypic populations of leukemia cells within individual cases typically harbored the same mutations. In addition, when immunophenotypically distinct subpopulations from several MPAL cases were inoculated into immunocompromised mice, the engrafted leukemias typically recapitulated the full phenotypic spectrum of each primary patient sample. These findings support the notion that causal mutations arise in early hematopoietic cells that have the potential for either lymphoid or myeloid differentiation, rather than mutational evolution determining the final phenotype (Figure 2).
These findings have multiple conceptual and clinical implications. Nearly half of the cases of T/M MPAL contained FLT3 alterations, and half of the B/M cases contained ZNF384 rearrangements which result in high levels of FLT3 expression even in the absence of FLT3 mutations. Hence, possibilities for translational approaches come to the forefront, e.g. inhibition of FLT3. Another translational challenge is to identify the optimal methods for monitoring dynamics of responses to therapy in MPAL, which is complicated by the unusual phenotype. Copy number analysis revealed rearrangements of immunoglobulin [6] (Ig) and T-cell receptor [7] (TCR) in MPAL cases. The potential for utilizing sequence-based methods to track MPAL responses to therapy using Ig/TCR rearrangements as a clonal marker remains to be explored. Finally, converging evidence supports ALL therapy as an appropriate choice in a majority of cases of MPAL. This evidence has contributed to the important decision of the Children's Oncology Group to include patients with MPAL on an arm of the upcoming frontline ALL clinical trial (AALL1732, activation anticipated 2019).

The work was led by authors Charles G. Mullighan and Hiroto Inaba. The study's co-first authors were Thomas B. Alexander, Zhaohui Gu, and Ilaria Iacobucci, with key contributions from the Children's Oncology Group [8] and the Therapeutically Applicable Research to Generate Effective Treatments [9] (TARGET) initiative of the National Cancer Institute.

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CTD² GUEST EDITORIAL

CytoScreen: A Miniaturized Imaging Platform to Develop Combinatorial Therapies
Hematologic malignancies represent the fifth most common type of cancer and fourth most common form of cancer-related death. More than 1 million people in the U.S. suffer from a hematologic malignancy; every year, another 150,000 patients are diagnosed with lymphoma, leukemia or myeloma. Targeted therapies have been a recent focus of drug development, but the majority of patients eventually develop resistance even to these new drugs. As a result, many leukemia patients eventually succumb to their diseases due to resistance to both conventional chemotherapies and newer targeted agents. Hence, there is an urgent need to better understand the pathways underlying drug resistance and to identify novel drugs or combinations of drugs that can effectively inhibit these pathways.

Major efforts are underway to develop combinatorial therapies that can target multiple biological pathways for effective synergistic cell killing that can help decrease the risk of cancer relapse. A major technical challenge is the lack of screening platforms that allow assessment of optimal combinations of drug conditions directly in primary patient cells. Flow cytometry is a widely-used option, however the amount of sample required limit the number of drug combinations that can be tested. Other ex vivo screening platforms lack single cell granularity and hinder the detection of cells that are resistant to drug treatments. Moreover, many protein targets (e.g. phosphoproteins, immune modulatory molecules induced via inflammation) may often be present at low levels. Hence, negative detection cannot be conclusively interpreted, and it is difficult to discriminate the signal from diffuse background noise. To address these issues, Drs. Tania Vu and Thomas Jacob at the Knight Cancer Center, Oregon Health and Science University (OHSU) have developed a single cell imaging platform, the CytoScreen. The CytoScreen is a miniaturized assay platform performed in multi-well imaging chambers that allows testing of drug combinations in primary patient cells with single cell granularity and at high detection sensitivity. In this assay, protein levels are quantified by digitized, discrete counting of fluorophore-tagged proteins. This molecular digital detection imparts amplification-free detection sensitivity and provides significant improvement in protein quantification over current methods that quantify the total diffuse fluorescence per cell (Figure 1). This is an ultrasensitive system and scales down the amount of sample required to perform the assay in patient samples. This assay offers new capabilities for profiling the therapeutic effect of multiple protein targets in different cell subpopulations that were previously challenging to measure.
In collaboration with Drs. Jeffrey Tyner, Evan Lind, Brian Druker and others at the OHSU’s Knight Cancer Center and Dr. Jody Martin at Becton Dickinson, the team has customized CytoScreen assays for the identification of effective new treatment options—especially those that address combination immunotherapies and drug-resistance. This assay allows testing a panel of drug combinations with multi-parameter readouts of T-cell activation and tumor-cell killing as well as readouts of stem/progenitor cell phosphoactivation with single cell granularity (Figure 2). The system has been used to assess drug response from acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL) patients.

The Beat AML study is a groundbreaking collaborative clinical study characterizing the molecular characteristics and drug exposure response for clinically annotated adult AML cases. The Beat AML is the world’s largest AML cohort, and the goal of this study is to evaluate investigational or combinatorial therapies to advance precision oncology. The CytoScreen assay system is adapted to identify small molecule/immune checkpoint combinations that can operate synergistically to boost anti-tumor immune response and kill tumor cells in AML samples. The combinations of small molecule/immune checkpoint inhibitors that can overcome resistance are computationally predicted using RNA-seq and ex vivo small molecule sensitivity data from the Beat AML cohort. This initial screen showed that mucin-domain containing protein 3 (TIM3) and mitogen-activated protein kinase kinase (MEK) inhibitors can have synergistic effects on T-cell immunoglobulins. The CytoScreen studies also showed that in certain patients, TIM3 in combination with certain MEK inhibitors can elicit more effective T-cell proliferation than the single immune checkpoint agent alone (Figure 2).
Figure 2: CytoScreen platform screening of immune/small molecule therapeutics in leukemia patient cells. (a) Multiplexed readouts of proliferation, death, and activated phosphoprotein levels in single immune T-cell and myeloid cell. (b) Single cell quantification in an AML patient sample shows increased T-cell proliferation (CD3+ Ki67+) by TIM3 (left) and increased AML cell death (CD33+ cPARP+) by MEK inhibitors combined with TIM3.

New technical capabilities – including increased multiplexing, profiling function and pathway activity not only of single leukemic cells but also T-cells and stem cell subpopulations as well as directly in individual patient samples – are currently in progress. Cancer Target Discovery and Development (CTD²) Center at OHSU is using this platform to screen combinations of targeted pathways and immune-modulating therapies in hematologic malignancies. The team at the Knight Cancer Research Center is optimistic that the integrations of technologies like this, along with other ex vivo functional technologies and predictive computation tools, will enable them to uncover effective drug combinations that can be advanced to clinical trial testing to improve therapy not only for AML and CLL patients but also for other leukemias in the near future.

In conclusion, the CytoScreen is a new assay platform that addresses issues in sample requirement and molecular detection sensitivity. This assay facilitates routine assessment of single-cell drug target effects in most leukemia patient samples and provides multiplexed readouts of specific cell subpopulations (T-cells, stem cells, leukemic cells) as well as their functional status (death, phosphoactivity, proliferation state) with quantitative accuracy.

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DATA CORNER

OCG’s Data Coordinating Center: Facilitating the Sharing of Data Generated by the Office’s Initiatives

Patee Gesuwan, B.S. and Yiwen He, Ph.D.

Today, cancer research studies by different research groups produce vast amounts of data in widely varying formats. In order to continuously improve our understanding of cancer mechanisms which in turn could improve patient outcomes, it is important for these data to be effectively analyzed, interpreted, and utilized by other studies according to the FAIR (findable, accessible, interoperable, and reusable) principles throughout the life of each study. The Office of Cancer Genomics’ (OCG) Data Coordinating Center (DCC) is responsible for managing the flow of data within each of OCG’s programs: Therapeutically Applicable Research to Generate Effective Treatments (TARGET), Cancer Genome Characterization Initiative (CGCI), Cancer Target Discovery and Development (CTD²) Network, and Human Cancer Models Initiative (HCM). The DCC’s major goals are to collect the multiple datasets generated within each program, check submitted data files for
quality (QC), assist in harmonizing the data into standard formats, and perform or facilitate distribution of the data to other centralized repositories such as the National Cancer Institute’s (NCI) Genomics Data Commons \[28\] (GDC) and National Center for Biotechnology Information’s (NCBI) Sequence Read Archive \[29\] (SRA).

While most raw sequencing data such as FASTQ\(^2\) and BAM\(^3\) files are submitted by sequencing centers directly to GDC (previously to SRA), clinical, biospecimen, and higher level (analyzed) data are submitted to the DCC. The DCC then submits the clinical and biospecimen data to the other repositories mentioned above, and also makes each project’s data files available for download from the DCC’s servers.

Project team members work directly with the DCC to obtain user accounts in order to submit (upload) data to or download data from the DCC’s servers via a secure file transfer protocol (sFTP). The DCC stores the data for collaborators to use while the studies are in progress, and depending on the dataset, releases the data to the public or to dbGaP-approved, controlled-access users once a related research paper has been accepted for publication. The Guide to Accessing Data \[30\] provides a visual and interactive overview on how to obtain approval to view controlled-access datasets. Once datasets are released at the DCC, OCG provides several tools to help users navigate and understand the data associated with each study.

Navigating Through CGCI and TARGET Projects at the DCC

The CGCI Data Matrix \[31\] and the TARGET Data Matrix \[32\] provide centralized starting points to the data types available for each project, and to navigate those datasets that are stored at the DCC. The data matrices direct users to specific locations from which it is possible to download the dataset of interest. In general, data stored at the DCC is organized within directories that correspond to the types of analysis, levels of data, and the names of centers that submitted a particular type of data when there are multiple data-submitting centers (Figure 1).
Users can download the data via links provided in the data matrices or via Unix by using commands such as `wget` and `curl`. Description on how to use the data can be found on the Using CGCI Data \[^{33}\] and Using TARGET Data \[^{34}\] webpages. The DCC also provides users with more in-depth information on data availability for each project within TARGET and CGCI in the form of Sample Matrices.

**CGCI and TARGET Sample Matrices**
Sample matrices, available in each project’s SAMPLE_MATRIX download directory at the DCC, specify the type of data available for each patient/case for each cancer type within the CGCI and TARGET programs. Depending on the study, each row of a sample matrix may correspond to either a single case or sample, and the columns within a row show availability of data from different analyses (e.g. either chip-based or sequence based characterization of RNA, genome, exome, targeted capture or epigenome), as well as data levels for the corresponding case/sample (Figure 2). A “Comments” column provided at the end of each row may contain additional information that is important to note for a particular case/sample.

Figure 2: Screenshot of a TARGET project sample matrix.

CGCI and TARGET Analysis Metadata

Metadata files, including MAGE-TAB [36]-formatted SDRF and IDF files, map cases within a study to related data files produced by the project. These files can be found in the METADATA directory of each type of analysis (Figure 1).
CTD² Data Resources

CTD² is a “community resource project”, meaning members of the Network are required to release data to the research community. The release of CTD² data to the scientific community is intended to maximize the impact of the findings. Data generated by the Network can be accessed through two resources: CTD² Data Portal [37] and CTD² Dashboard [38].

CTD² Data Portal

The CTD² Data Portal is an open-access resource which hosts raw/analyzed primary data generated from different types of experimental and computational approaches. The data can be sorted by Center or the method used to generate the data. Along with the Data Harmonization Informatics Portal team (comprising at least one member from each Center), the DCC is responsible for quality assurance and usability of the data submissions. The DCC currently supports data from 15 Centers. In the near future, data from Network Centers’ collaborations will be listed under “Cross-Center Projects” and will be noted with an asterisk. Data stored at the DCC can be accessed through the “Raw/Analyzed Data” link on each project page on the Data Portal. Sequence data that are categorized by the Centers’ Institutional Review Boards as “open access” are stored at NCBI’s Gene Expression Omnibus (GEO) (Figure 3).

Figure 3. Screenshot of the CTD² Data Portal. Broad Institute is highlighted under the Centers and associated projects are displayed in the right column. Brief description of the project, links to data, point of contact, etc. are listed under the table for the highlighted project.
**CTD² Dashboard Data**

The CTD² Dashboard is an open-access web interface with observations compiled from the data generated by various types of biological and analytical approaches by the CTD² Centers. The DCC is responsible for maintaining the website and creating monthly releases of the Dashboard to update the observations when the Centers submit them. Some projects on the Data Portal have a link to the corresponding Dashboard submissions.

**Conclusion**

In summary, the DCC provides bioinformatic support for the OCG cancer research programs. The DCC supports OCG by receiving and formatting genomics data, transferring data to GDC, maintaining web applications, and coordinating with NIH’s Center for Information Technology regarding security, storage space, and web hosting. The DCC plays a key role in ensuring that the standardized genomic data from the OCG programs can be systematically accessed by the cancer research community and that the process adheres to the FAIR principles.

**References**


**CGCI PROGRAM HIGHLIGHT**

**OCG’s Efforts in the Discovery and Validation of Tissue Samples for the HIV+ Tumor Molecular Characterization Project (HTMCP)**

Nicholas Griner, Ph.D.

The success of antiretroviral therapy and prevention education has led to a dramatic decrease in new HIV (human immunodeficiency virus) positive cases in the United States (U.S.) since the 1980s. The HIV+ patients, who have been successfully treated for AIDS (acquired immunodeficiency syndrome), are now reaching the stage in their lives when cancer incidence increases. Understanding the mechanisms of how AIDS-defining cancers arise in patients is critical in the treatment of these patients.

Epidemiology studies found that AIDS-defining cancer rates have remained steady since the early 2000s. Early detection of cancer has greatly improved the prognosis of
HIV+ patients with cancer. Many HIV+ patients who present with malignancies are prescribed chemotherapy and other tumor treatment regimens that damage the DNA of the tumor cells. When these tissues are used for genomic/transcriptomic sequencing, the genetic somatic aberrations present in the tumor prior to treatment as well as those arising from chemotherapies make the former hard to identify.

The HiP+ Tumor Molecular Characterization Project (HTMCP) is a joint effort by the Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) to identify, accrue, and fully characterize common malignancies that occur in patients who were previously treated with antiretroviral therapy because they were HIV+. HTMCP studies the most common malignancies associated with HIV including diffuse large B-cell lymphoma (DLBCL), cervical cancer, and non-small cell lung cancer (NSCLC). HTMCP requires cooperation between multiple participating sites to identify, acquire, and process tissues for molecular characterization as these tumors are relatively rare. Since 2012, a large majority of samples acquired for HTMCP have originated from Sub-Saharan Africa, specifically, the Uganda Cancer Institute (UCI) (see e-News: Issue 13).

Because genetic risk-factors can influence the development and/or progression of cancers among the different populations around the world, the project characterizes tumors which develop in cancer patients with and without a history of HIV infection. The diagnosis of each tumor is confirmed by a group of expert pathologists who work together to achieve consensus. Once diagnosis is confirmed, the tumor and normal tissues are processed into nucleic acids and fully molecularly characterized by whole genome and whole transcriptome sequencing. The sample processing is done by a single site to reduce technical variability of sequencing due to protocol variability. The clinical data is collected from each patient at the time of diagnosis and one- and two-year follow-up, if available.

Within the Cancer Genome Characterization Initiative (CGCI) projects, the process of tissue accrual for some cancers present more challenges than others. The accrual of DLBCL and NSCLC have proven much more difficult than that of cervical cancer. For example, some tissue sites are challenged with pathological diagnosis while others are challenged with inadequate sample amount since tissue samples were collected with fine needle biopsies. It is important that the amount of tissue removed for pathological diagnosis is sufficient for the projects’ needs as the prescribed chemotherapy will lead to damaged genetic material, eliminating the option of additional biopsy. Tissue biopsy methods have also changed as technology continues to improve. Fine needle biopsies allow clinical centers to perform minimally invasive procedures to remove malignant tissue for analysis. However, the amount of tissue removed from the biopsies is generally much less than the amount needed for the project’s whole genome/transcriptome sequencing. An additional challenge is obtaining detailed clinical data information of the patient receiving treatment. This clinical data and subsequent follow-up data is critical to the project in comparing molecular data from patients with both differing genetic and treatment backgrounds.

In order to address some of these challenges, OCG established standard operating procedures (SOPs) with the help of OHAM. The SOPs were updated when it was clear that certain tissue source sites (TSSs) in different countries could not provide fresh frozen tissues and could not perform pathology analyses to the extent possible in the U.S. In addition, OCG worked with certain TSSs that already had a study protocol in place to adapt the project requirements to optimize the tissue accrual process for the HTMCP. Furthermore, the AIDS Malignancy Consortium (AMC) has protocols for clinical trials and tissue procurement to address these challenges. The AMC represents a group of hospitals, universities, clinicians, and researchers who are investigating new treatments and prevention interventions for malignancies in people living with HIV. One protocol, AMC-083, was started in 2012 concurrently with HTMCP, and represents AMC’s efforts to accrue and contribute tissues for molecular characterization. There are currently 11 TSSs within the U.S. who activated this protocol and are currently active in accruing tissues for this study. The Emmes Corporation coordinates with different TSSs in the accrual of both tissues and clinical data for AMC-083. To date, AMC-083 has accrued a number of cases which match the HTMCP requirements and continues to identify more. Additional AMC TSSs are being investigated for case accruals, including international sites. Both DBLCL and NSCLC projects are accruing cases from Africa and the U.S. while adapting protocol specifics so as to optimize case accruals without sacrificing data quality.

As a result of all the hard work of team members involved in the projects over the past six years, HTMCP has recently achieved its goal of acquiring 100 UCI cervical cancer cases that are currently undergoing molecular characterization and analyses. The OCG was successful in accruing and fully molecularly characterizing an initial cohort of DLBCL and NSCLC cases and continues to search for additional sites which can donate cases that match the project requirements. OCG will continue to work closely with the AMC to accrue sufficient cases and publish results of molecular characterization of DLBCL and NSCLC cases similar to the completed cervical cancer
My name is Eva Tonsing-Carter, and I recently became the Scientific Program Manager for the Human Cancer Models Initiative (HCMI) in the Office of Cancer Genomics (OCG) within the National Cancer Institute (NCI). HCMI is an international consortium that is developing next-generation human tumor-derived culture models that will better represent patients. The goal of HCMI is to find more clinically accurate and precise cancer treatments. Coming from the background of basic and translational cancer research in the laboratory, I wanted to further pursue research where findings at the bench lead to new therapies at the bedside. For this reason, managing clinical research projects at the OCG as the program manager for HCMI was an exciting subsequent step for me.

Throughout my adult life, I have always had a strong desire to understand the ‘how’ and the ‘why’. I completed my undergraduate studies in 2008 at Saint Mary’s College in Notre Dame, IN, where I earned a B.S. in Biology with a concentration in Molecular Cell Biology. It was during my senior year that I was able to conduct my first independent research project. I learned a lot during this period including time management skills, wet lab techniques, experimental design, and data interpretation. My project focused on characterizing erythogenic toxin gene expression in Streptococcus pyogenes, the bacteria that causes strep throat and scarlet fever. I examined patient samples to see if there was any correlation between erythogenic toxin gene expression and scarlet fever cases during the sample procurement time. As I learned my way around the lab and how to interpret experimental results, I gained invaluable experience that led me to pursue a Ph.D. in pharmacology.

In my quest to continue learning, I pursued my Ph.D. in Pharmacology at Indiana University-Purdue University, Indianapolis. The Indiana BioMedical Gateway Program allowed me to explore several specialty programs, and I chose to complete my Ph.D. training in the Department of Pharmacology and Toxicology. Throughout my coursework, I learned how and why drugs affect the body as well as how and why the body affects drugs. My research focused on the combination treatment of a standard of care chemotherapeutic drug, carboplatin, with a protein-protein interaction inhibitor, nutlin-3a, in triple-negative breast cancer models. I found that nutlin-3a led to potentiation of the carboplatin-mediated damage leading to increased cell death in vitro and decreased xenograft tumor growth and metastasis in an in vivo mouse model. I showed that this potentiation was in part dependent on p73, a family member of the well-known p53 protein family. My experience in this basic science laboratory sparked my interest in clinical research.

After completing my Ph.D. in 2014, I pursued further learning through postdoctoral training at The University of Chicago. The principal investigator of my postdoctoral laboratory is a medical oncologist who regularly sees and treats breast cancer patients. Many projects in the lab have resulted in the design of clinical trials and the research projects have also been influenced by clinical findings and questions. My lab had previously made an observation that in estrogen receptor positive (ER+) patients, high tumor expression of glucocorticoid receptor (GR) was associated with a relatively improved, relapse-free survival compared to patients with low GR tumor expression. My project focused on understanding how and why patients with ER+ breast cancer and high tumor GR expression may have an improved outcome compared to those patients with low tumor GR expression. Our laboratory found that GR modulation slows ER-mediated proliferation in vitro and associates with a decrease in ER-mediated, pro-proliferative gene expression. Utilizing chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq) and ChIP followed by quantitative polymerase chain reaction, I found that the crosstalk between GR and ER receptors results in altered ER chromatin association in regulatory regions of genes that are important in cell proliferation. My hope is that the information gained through my research will be
taken to the clinic to test GR modulators in ER+ breast cancer patients.

As I was considering the next step in my career, I wanted to expand my skills and knowledge in a larger context with broader impact. The HCMI project piqued my interest, and I joined the OCG this summer. Since starting my new position, I have transitioned from utilizing research tools to helping to create new research tools. My role with HCMI started by continuing to develop the case report forms for cancer types in which models are being developed. This role utilizes my research skills in learning more about a specific cancer type including clinical attributes, clinical biomarkers, and treatments. The clinical data is compiled, reviewed, and discussed with clinical collaborators to define which data elements are important to capture for all the researchers who may utilize the data generated through the HCMI program. The clinical data will be available alongside the sequencing data from the matched normal, primary tumor, and cancer model.

While the models are developed and expanded in the laboratory, the associated clinical data and sequencing data from the matched normal, primary tumor, and models are collected and submitted, quality checked, and harmonized for international accessibility. We are working to facilitate the development of the ‘HCMI Searchable Catalog’ where 1,000 models from a wide variety of cancer types including rare and pediatric, together with a subset of clinical data, will be searchable. Links to the models’ associated full clinical and sequencing data at the NCI Genomic Data Commons [28], as well as purchasing information from the third-party distributor, American Type Culture Collection, will be included in the catalog. Our goal is to launch the HCMI Searchable Catalog in early 2019. These next-generation in vitro models will allow for many downstream applications including high-throughput drug or CRISPR screens where other types of models have proven difficult (e.g. patient-derived xenografts). This process is a highly collaborative effort between all participants of the HCMI program including clinicians, scientists, data analysts, software developers, and project/program managers.

Additionally, NCI has a strong commitment to expanding racially and ethnically diverse research programs with the goal to decrease cancer health disparities. OCG has partnered with the Center to Reduce Cancer Health Disparities to fund several research supplement awards to allow for collection of tumors and generation of models from racial and ethnic minority cancer populations.

So far, my experience in OCG, albeit short, has already taught me so much not only about cancer and developing cancer models but also how to facilitate discussions across a broad range of contributors in large-scale program management. My background gives me a unique perspective as I was once someone who would have been utilizing the tools like the ones developed by the HCMI. Now, I am involved in helping to develop such tools and resources for the broader research community.

I am excited to see how HCMI continues to grow and expand. The next-generation in vitro models generated through the HCMI program have been created to provide more clinically relevant and representative cancer models than the traditional cancer cell lines. The HCMI models may provide better tools to understand how and why a cancer either responds or fails to respond to therapeutics. Expanding the types of cancer models, as well as increasing the number of models from racial and ethnic minorities, will further expand the breadth and scope of knowledge gained by the research community. My hope is that the information gained from utilizing the HCMI models will be taken from the bench back to the bedside and provide better treatment strategies for all patients.

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