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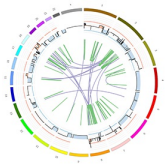

TARGET PROGRAM HIGHLIGHTS

TARGET Reveals the Genomic Characteristics of Multiple Childhood Cancers

The Therapeutically Applicable Research to Generate Effective Treatments (TARGET), a large-scale pediatric genomic characterization initiative, continues to demonstrate the importance of integrative analyses using comprehensive data and metadata generated from high-quality

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CTD² PROGRAM HIGHLIGHTS

Studying Human Cancer Invasion and Metastasis in Real-Time in the Laboratory

A large majority of cancer deaths are attributable to metastasis, the process by which cancer cells spread throughout the body to form new tumors in distant vital organs1. Despite its central importance to patient outcomes, the cellular and molecular basis of metastasis is incompletely understood.

CGCI PROGRAM HIGHLIGHTS

Challenging Experiences in Expanding Opportunities: The Burkitt Lymphoma Genome Sequencing Project in Brazil

Burkitt Lymphoma (BL) is an aggressive B-cell lymphoma involving

dysregulation of the MYC oncogene by chromosomal translocations. It is most common in children but also affects adults and occurs in sporadic, endemic, and HIV-associated forms.

OCG PERSPECTIVE

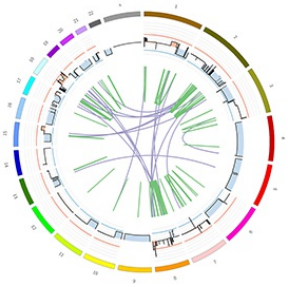
Understanding the Other Side of Research

For over seven years, the Office of Cancer Genomics (OCG) has supported recent doctoral graduates through internship and fellowship programs.

TARGET PROGRAM HIGHLIGHTS

TARGET Reveals the Genomic Characteristics of Multiple Childhood Cancers

Jaime M. Guidry Auvil, Ph.D., Malcolm A. Smith, M.D., Ph.D., and Daniela S. Gerhard, Ph.D.



The Therapeutically Applicable Research to Generate Effective Treatments [2] (TARGET), a large-scale pediatric genomic characterization initiative, continues to demonstrate the importance of integrative analyses using comprehensive data and metadata generated from high-quality patient tissues in both solid and hematologic cancers. March is National Kidney Cancer Awareness month, and a good time to reflect on the successes of TARGET in renal tumors, such as Wilms tumor (WT) and other childhood cancers. TARGET investigators published papers in 2017 integrating the genomic and clinical data of cases with high-risk subsets of WT and cases with acute myeloid leukemia (AML) and in February 2018 published an analysis across the spectrum of childhood cancers studied to date. These publications (and previous reported findings from TARGET [3]) proved what many oncologists suspected: many pediatric cancers have distinctive molecular characteristics from adults, and therefore it will likely be important to develop specific treatments for these childhood cancers.

The TARGET initiative's approach is to provide molecular characterization of each patient's tumor genome, transcriptome, and epigenome through analysis of both primary and, when available, relapsed tumor tissues together with their matched normal tissue. The TARGET project teams (PTs) had access to cases for which both tumor and normal tissues were available along with the patient's clinical and outcome data, predominantly from clinical or biological studies run through the Children's Oncology Group (COG). The PTs integrated the molecular and clinical data to discover mechanisms of disease development and potential areas for improved therapeutic intervention strategies substantiating the critical need for large-scale research studies of similar design for the pediatric cancer community. Here we summarize some of the results recently published.

Wilms tumor [4] **(WT)** – the most common kidney cancer in children – harbors genetic mutations across a number of genes that are important in two major cellular processes that occur early in kidney development: one pathway regulates miRNA biogenesis and another interferes with normal maturation of the kidney (induction) by regulating gene transcription. The WT PT studied patients who were defined as "high-risk", including tumors with diffuse anaplastic (DA) histology and tumor with favorable histology (FH) that recurred predominantly within 5 years of initial treatment. A WT PT paper published August 2017, as well as the 2 previous manuscripts[1,2], suggest that targeting these pathways may provide viable therapeutic opportunities for high-risk Wilms tumors. Key findings from this paper include:

- The genes most commonly mutated in the TARGET WT cohort are *TP53* (47.5% DA, 1.7% FH), *CTNNB1* (13.5%), *DROSHA* (10.1%), and *FAM123B* (13.5%), most of which were already known to be associated with WT.
- Novel genes uncovered included certain miRNA processing, transcription, and renal development genes [e.g. *DGCR8* (4.5%), *XPO5* (1.5%), *DICER1* (2.5%), *SIX1* (3.8%), *SIX2* (2.9%), and *MLLT1* (3.7%)].
- Other mutated genes with novel association to WT included *BCOR* (2.6%), *BCORL1* (3.8%), *NONO* (2%), *MAX* (1.7%), *COL6A3* (3.2%), *ASXL1* (1.7%), *MAP3K4* (1.7%), and *ARID1A* (1.8%).
- The WT PT also reported that chromosome copy number changes were found in a number of discovery cases [e.g., recurrent 1q gain (56/117 patients; 47.9%), *MYCN* amplification (19/117 patients; 16.2%), *LIN28B* gain (24.8% in discovery cohort), and loss of *MIRLET7A* family members (5.1%-22%; up to 4x more prevalent in DA than FH)].
- Germline mutations were found in about 10% of the WT high risk cases studied as well (*PALB2* (1.2%) and *CHEK2* (1.2%) being novel).

Given the relatively high number of genes with candidate driver mutations, future treatment protocols targeting the common processes or pathways affected by the gene mutations may be more efficient than focusing on individual gene mutations.

Acute myeloid leukemia [5] **(AML)** – a blood cancer arising in the bone marrow with 50% treatment failure rate – occurs in patients of all ages. The TARGET AML PT published in December 2017 the first large-scale study establishing the prevalence of and relationships among recurrent, somatic genetic and epigenetic alterations in pediatric AML, including how the frequency of these mutations changed as the patients' age of AML onset increased. The AML PT observed several features common to pediatric and adult AML, including low overall rate of mutation compared to other cancers and overlap of some recurrently mutated genes. Fewer than 40 genes were mutated in more than 2% of cases.

Pediatric and young adult AML exhibit critically important molecular characteristics that are distinct in three age-related groups (≤2yrs, 3-14yrs, and 15-39yrs). TARGET investigators identified novel gene fusions, many involving known partner *NUP98* and focal deletions (*MBNL1, ZEB2,* and *ELF1*) that were more prevalent in young individuals as compared to adults. In addition, novel variants in *GATA2, FLT3,* and *CBL*, along with recurrent mutations in *MYC, NRAS, KRAS,* and *WT1* appeared more frequently in pediatric AML. In contrast, targetable *IDH* mutations that are relatively

common in adult AML are practically nonexistent in the childhood disease, reducing the potential role of IDH inhibitors for pediatric AML. Similarly, mutations in other genes commonly observed in adult AML such as *DNMT3A* and *TP53* were nearly absent in pediatric cases.

The AML PT discovered that certain combinations of variants affect patient prognosis, for example *FLT3-ITD* in combination with a mutation in *NPM1* confers a probability of improved survival. *FLT3 ITD* by itself, or even in combination with other mutations (which are important in AML on their own), are associated with highly aggressive disease. The TARGET PT further found that certain deletions, mutations, and hypermethylation of promoter DNAs cooperatively impacted key signaling pathways in growth, immunity, and alternate splicing that can lead to leukemogenesis. These results suggest that the development of future therapeutic strategies may benefit through an age-tailored, targeted approach to the treatment of pediatric AML.

In February 2018, the first **trans-TARGET** study[3] of somatic alterations in 1,699 pediatric leukemia and solid tumors across six histotypes was published online. The analyses were performed on samples from young patients (most ≤20yrs and enrolled on COG trials). The manuscript was published back-to-back with a study from German investigators analyzing European childhood cancer cohorts. The studies were complementary inasmuch TARGET's cohort was >50% hematologic cancers, while the European cohort included >50% brain cancers. The molecular characterization details were not identical, but the "big picture" conclusions agreed remarkably well. Here we summarize the TARGET results.

The trans-TARGET study found that 142 genes in the pediatric cancers studied had mutation frequencies high enough to declare that these are "driver" genes. Interestingly, only 45% matched potential cancer drivers found in adult tumors, providing additional support to the findings highlighted above that pediatric cancers can have different initiation and progression processes than adult cancers. The trans-TARGET study confirmed that:

- The median somatic mutation rates among all TARGET pediatric cohorts generally range from 0.17 per million bases (MB) to 0.7/MB and are substantially lower than those observed in common adult cancers (1-10/MB).
- The frequency of germline variants which are risks for tumor development are ~10%.

In addition, the trans-TARGET study found that:

- Somatic copy number alternations (sCNAs) and structural variations (SV) comprised the majority (62%) of events observed, specifically single nucleotide mutations or small indels were less frequent. This finding provided strong support to the initial design of the project, to utilize whole genome sequencing whenever possible, since whole exome sequencing would not have allowed detection of sCNAs and SVs mutations. In many patients these genomic alterations are the driver events.
- The genomes of 11% of TARGET patients revealed chromothripsis (i.e. massive rearrangements caused by a single catastrophic event).
- Analyses revealed a large number of low frequency drivers within and among disease cohorts.

- Driver gene alterations produced disruptions in pathways that may be targetable with existing treatments. Specifically, TARGET investigators found 21 biologic pathways disrupted by driver alterations, across cancers (i.e. cell cycle, epigenetic regulation) or histotype-specific (i.e. *JAK-STAT*, Wnt/ β-catenin, and *NOTCH* signaling).
- Of clinical significance, the genes mutated in shared or separate pathways were different among histotypes. Certain signaling pathways (*RAS*, *JAK-STAT*, and *PI3K*) show distinctive somatic alterations between solid tumors (primarily *ALK*, *NF1*, and *PTEN*) and leukemias (nearly all mutations in *FLT3*, *PIK3CA*, *PIK3R1*, and *RAS* genes).
- The somatic alterations with highest prevalence across certain disease groups occurred in *CDKN2A* (predominantly as deletions): mostly affecting T-ALL (78%), B-ALL (42%), and OS (11%).
- Over half of the pediatric driver genes observed across TARGET cohorts were specific to a single histotype (e.g. *TAL1* for T-ALL and *ALK* for NBL).
- The trans-TARGET analyses outlined some known and novel, statistically significant co-occurrences (e.g., *USP7*, *TAL1* in T-ALL; *ETV6*, *IKZF1* in AML, and *CREBBP*, *EP300* in B-ALL) or mutual exclusivities (e.g. *MYCN*, *ATRX*, or *SHANK2* in NBL; *PAX5*, *TP53* in B-ALL) among more than 300 gene-pairs.
- TARGET findings further indicate that subclonal mutations could be contributing to tumorigenesis in various childhood cancers, with nearly half of point mutations in leukemia and NBL driver genes showing low mutant allele frequencies (*MAFs*, <0.3).

The TARGET initiative and other large-scale genomics projects are transforming precision oncology for childhood cancers by identifying therapeutic strategies based on insights that can only be gleaned through high-quality, large-scale integrative data analyses. By creating a comprehensive molecular compendium of molecular alterations from large cohorts of cancer patients and by making these data available for investigators who will continually improve upon the knowledge base of these cancers, more effective classification and treatment strategies can be developed. Additional integrative manuscripts will be published for TARGET in the coming months, and the community is encouraged to use and follow-up on those important observations as they become available. For more information, including additional TARGET publications [3] and data used for these analyses, please visit and explore the TARGET website [2] and Data Matrix [6] at the Office of Cancer Genomics [7].

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CTD² PROGRAM HIGHLIGHTS

Responses to Cancer Therapies are Complex

Matthew J. Hangauer, Ph.D.

Patient clinical responses and changes in tumor burden during treatment reflect the cumulative effects of diverse phenomena that occur at the cellular level. Therefore, it is useful to describe treatment responses at the level of patients, tumors and cells. Here, we will discuss the terminology that is used to describe the drug responses at each of these levels with a focus on heterogeneity between individual cancer cells.

Clinical responses for patients with solid tumors are judged based on changes in tumor sizes compared to a pretreatment baseline. Depending on cumulative changes across all measurable tumors, patients are judged to have a complete response [11] (CR), partial response [12] (PR), stable disease [13] (SD), or progressive disease [12] (PD). Each of these response categories apply to a single time point during treatment and can subsequently change. For example, a patient who experiences a CR or PR may subsequently relapse into PD. Also, distinct tumors within the same patient may respond differently. During treatment, tumors can undergo shrinkage, stasis, or growth. Tumors shrink if they are composed primarily of drug-sensitive cancer cells. However, a shrinking tumor may contain a minority of surviving non-proliferative or actively proliferating cells embedded in a larger population of drug-sensitive dying cells, giving the appearance of tumor shrinkage. Tumor stasis, or lack of change in size, can result from a bulk population of non-responsive and non-proliferative cells, an equilibrium state of dying and proliferating cells, or a mixture of these two scenarios. A related but not an identical term is tumor dormancy which is used to refer to cancer cells which disseminate throughout the body and remain undetected in microscopic groups or as single cells for months or years. These so called dormant “disseminated tumor cells” are thought to be the source of tumor recurrence in the cases where tumors reemerge years after cessation of therapy.

Individual cells within a tumor can have drastically different responses to therapy regardless of whether the overall tumor in which the cells reside is shrinking, static or growing. This cellular phenotypic heterogeneity can arise from genetic or non-genetic

variations between cells. Drug resistance-conferring genetic mutations can preexist prior to treatment or can be acquired during treatment, and can cause resistance by activating, deactivating, or altering the structure of genes and pathways in cancer cells. DNA mutations are irreversible, and therefore if a cancer cell has a drug resistance-conferring mutation its daughter cells upon cell division will also be drug-resistant. This is a common and widely appreciated mechanism by which cancer cells survive

Alternatively, cancer cells can have variable drug response due to non-genetic mechanisms. Distinct from genetic mutations, non-genetic mechanisms of drug resistance are transient and reversible. The clinical observation of secondary responses in patients who have been treated with the same drug they developed resistance to, after a temporary period of time without treatment (drug holiday), supports the concept that reversible, non-genetic mechanisms of drug resistance play an important role in tumors. At the cellular level, emerging evidence indicates that a subpopulation of tumor cells can reversibly enter a non-proliferative (quiescent) “persister” cell state with decreased sensitivity to a range of cancer therapies. These persister cells are affected by drug treatment and stop proliferating, but do not die, hence they are referred to as drug-tolerant rather than drug-resistant. Persister cells have been found to have increased stemness, or capacity to regenerate new tumors, highlighting their potentially important role in tumor regrowth and dissemination after an initial therapeutic response. Recent evidence also indicates that persister cells have increased DNA mutation rates, possibly serving as a cell reservoir from which drug-resistant mutant cells with distinct mutations may emerge during treatment. If this occurs in patients, then a clinical approach to prevent the formation or elimination of persister cells before resistance-conferring mutations are acquired may be essential to achieve durable responses.

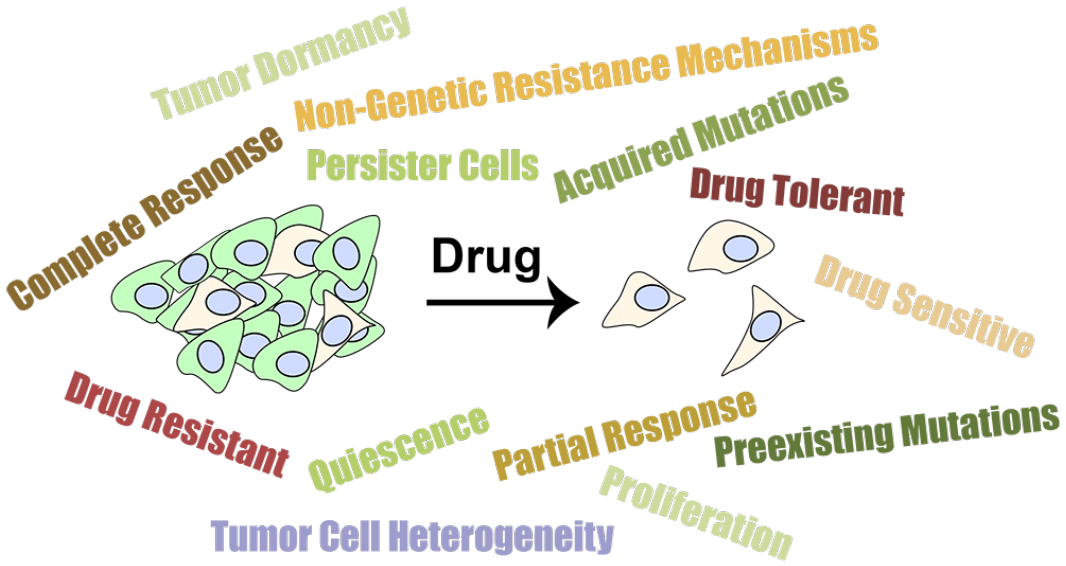

Figure: Tumor heterogeneity and drug responses.

This discussion has focused on responses to small molecule drugs in solid tumors. Relative to our understanding of responses to small molecules, our understanding of the intricacies of responses to immunotherapy is at its infancy. However, it is likely that similar principles apply to antibody- and cell-based immunotherapies. Cell to cell

genetic or non-genetic heterogeneity is likely to contribute to the emergence of drug-tolerant or drug-resistant cancer cells which are not recognized by or do not respond to effector immune cells. Therefore, continued efforts to characterize responses to therapy are important to identify approaches to overcome drug resistance and provide patients with durable responses from a variety of treatment modalities.

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CTD² PROGRAM HIGHLIGHTS

Studying Human Cancer Invasion and Metastasis in Real-Time in the Laboratory

Andrew J. Ewald, Ph.D. and Joel S. Bader, Ph.D.

A large majority of cancer deaths are attributable to metastasis, the process by which cancer cells spread throughout the body to form new tumors in distant vital organs[1]. Despite its central importance to patient outcomes, the cellular and molecular basis of metastasis is incompletely understood. Surprisingly, metastatic cancer has also been relatively understudied compared to earlier, more treatable stages of the disease[2]. This discrepancy may in part be attributable to metastasis involving the entire body, occurring deep inside the patient over long periods, and involving many different cells types and molecular pathways in complex combinations. These challenges come together to make metastasis difficult to study in the laboratory.

There has therefore been an urgent need to develop model systems that enable the analysis of key processes in metastasis at cellular and molecular resolution[3]. We set out to solve this problem inspired by progress with tissue organoid assays originally developed to study normal mammary gland development[4,5]. The essential concept is to surgically remove a portion of an organ, mechanically disrupt it with a scalpel, digest with enzymes, and then process by centrifugation to separate single cells from the tissue pieces or organoids. The single cells consist mostly of immune cells or fibroblasts and can be included or excluded from the culture as desired. Organoids usually consist of 100-500 epithelial cells. Our approach contrasts with the stem cell organoids pioneered by Hans Clevers: our tissue organoids are freshly isolated, are not generally expanded, do not require Wnt ligands for short term culture, and are available for immediate use. The basic approach of mechanical and enzymatic processing to generate tissue organoids is very flexible, and we have adapted it for use with normal mammary glands, primary breast tumors, and metastatic site breast tumors. We have also extended these methods to liver, pancreas, and lung tumors and can start from fresh human tumors, patient derived xenografts (PDXs), or genetically engineered mouse models (GEMMs). We routinely generate ~2,000 organoids per clinical sample, ~20,000 per PDX tumor, and ~200,000 per GEMM model. Accordingly, we can explant organoids from the same sample into a wide

range of experimental conditions. We have applied this approach both to understand molecular pathways in the cancer cell and also to interrogate the functional role of specific elements of the tumor microenvironment[6,7,8,9].

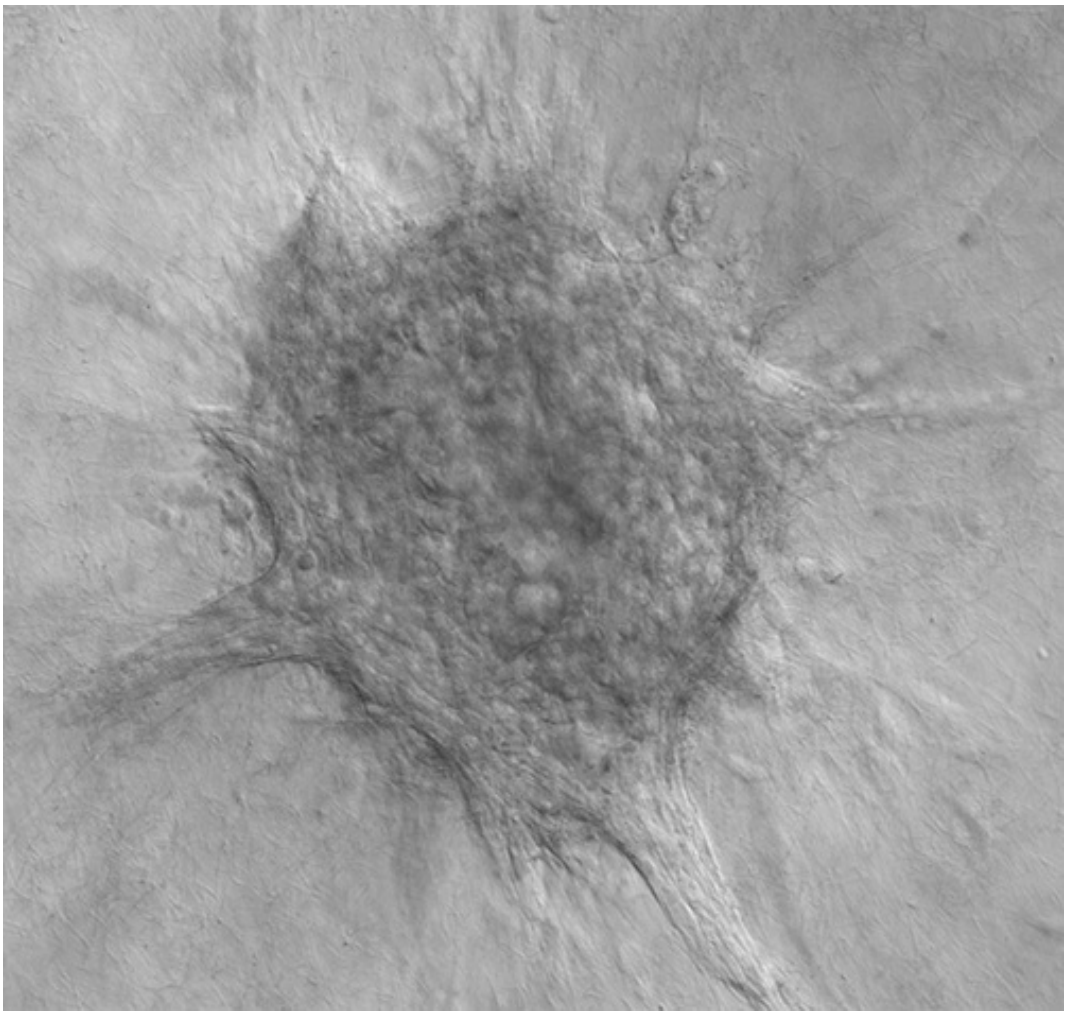

Figure: Human breast tumor organoid invades collectively into a 3D collagen I microenvironment.

One of the main advantages of our approach is the ability to maintain a tumor's cellular and phenotypic diversity in convenient, multi-well plate compatible assays. Metastasis requires many steps, each of which poses quite distinct challenges for the cancer cell. Accordingly, we have developed a range of assays modeling primary tumor growth, invasion, dissemination, intravasation, and secondary tumor formation. We use highly automated microscopy to image the behavior of cancer cells at subcellular resolution in these assays, which enables us to develop hypotheses for how these processes take place at the cellular level. To understand the underlying molecular regulation, we can introduce signaling perturbations, shRNA, CRISPR, inducible gene expression, or Cre-lox based gene deletion. We have also optimized nucleotide and protein-based molecular analyses in these cultures, enabling mechanistic dissection of the molecular basis of phenotypes. We then integrate the results of the experimental interventions using network analysis and computational modeling. We have projects analyzing the molecular basis of normal, primary tumor, and metastatic site growth and motility that enable us to identify the truly cancer-specific processes.

Our newly launched Center for Cancer Target Discovery and Development [14] (CTD^2) builds on our track record of success and provides substantial new resources to exploit these model systems to develop novel therapeutic targets. Breast cancer is particularly challenging in exhibiting a very wide range of suspected driver mutations, with relatively few present in large percentages of patients[10,11]. Accordingly, the understanding of which genes are the most important for breast tumor initiation and particularly for metastasis remains largely incomplete. The key insight guiding our CTD^2 Center is that quantitative analysis of phenotypes within these 3D organoid assays enables us to adopt the mathematical framework of population genetics to identify genes and mutations responsible for breast cancer growth, invasion, and metastasis. The large number of organoids isolated, combined with quantitative imaging and applied mathematics, enables us to systematically analyze the molecular basis of variation among different clones within the same tumor and between tumors from different individuals. Based on our previous analyses of molecular programs driving collective invasion in breast cancer[6] and our past work in population genetics[12,13], we anticipate that our approach will enable us to appreciate the underlying molecular logic of metastasis. We will then use techniques from network analysis and graph theory[14,15] to prioritize targets for intervention.

Our goals are to understand metastasis at the molecular level, to apply these insights to identify patients at the greatest risk of metastatic recurrence, and ultimately to improve patient outcomes by identifying new anti-metastatic therapies. Past and current support from the BCRF, the JKTG Foundation, and the National Cancer Institute has been critical to the development of these techniques and to their current application in translational cancer research.

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CGCI PROGRAM HIGHLIGHTS

Challenging Experiences in Expanding Opportunities: The Burkitt Lymphoma Genome Sequencing Project in Brazil

Stella Maris Pereira Sobrinho Rodrigues, Ana Raquel Viana de Godoy, and Jeffrey M. Bethony

Jeffrey M. Bethony, Ph.D.

Burkitt Lymphoma (BL) is an aggressive B-cell lymphoma involving dysregulation of the *MYC* oncogene by chromosomal translocations. It is most common in children but also affects adults and occurs in sporadic, endemic, and HIV-associated forms. The Epstein-Barr virus-associated BL (eBL) endemic subtype is the most common pediatric cancer in equatorial Africa but also occurs in other parts of the world (e.g. the rainforest of Brazil).

The National Cancer Institute (NCI) established a collaboration with the Foundation for Burkitt Lymphoma Research [29] to develop a genomic databank for BL. One goal of the Burkitt Lymphoma Genome Sequencing Project [30] (BLGSP) is to conduct comprehensive molecular characterization of BL by sequencing DNA and RNA from a large BL cohort–including endemic, HIV-associated, sporadic, pediatric, and adult cases–in order to define the genetic and phenotypic features that drive these cancers. These data will be analyzed and published; the goals are to develop new therapeutic strategies that can be deployed worldwide.

BL in Brazil is characterized by geographically distinct clinical and pathologic features[1]. In central and southern Brazil, adult BL cases occur with similar diagnosis as in the United States and western Europe. In the northeastern and Amazonian regions of Brazil, eBL-associated infections overlap with either *Plasmodium falciparum* or *Plasmodium vivax* malaria similar to cases in equatorial Africa. Intensive chemotherapy is effective, but the associated toxicity requires supportive care that is not readily available in resource-poor regions.

Clinical Research in Brazil: The Ethical Approval for the BLGSP was Among the First to Use a New Federal Regulation Process

NCI's Office of Cancer Genomics [7] (OCG) identified, after extensive search, the Hospital das Clinicas da Universidade Federal de Minas Gerais (HdC-UFMG) as a potential tissue source site in Brazil and became a member of the project working group (WG). The regulatory process was initiated in November 2013, and all necessary documents (e.g. protocol, informed consent form, etc.) were submitted to the local Institutional Review Board (IRB). Ethical approval was obtained in March 2014; however, the challenge arose because the BLGSP is an internationally-sponsored project involving sample storage and shipping outside of Brazil, and a national IRB approval for biobanking and biorepository (CONEP) was requested. This was a newly developed process, and therefore required extensive (two year) to- and from- exchange to ensure that all required materials were provided in the right format. The approval was obtained in July 2016.

Brazil BLGSP Tissue Source Sites (TSS)

Once we had the approval in hand, Dr. Frederico Melo (a pathologist), the principal investigator (PI), and staff evaluated the availability of cases at the HdC-UFMG in the spring of 2017. It was decided that to ensure the accrual of the promised number of cases, a partnership with the Instituto Nacional do Cancer (INCA), with PI Dr. Fabio Leal, was established.

Standard Operating Procedures (SOPs)

The BLGSP utilizes SOPs to enhance the ability to integrate results for tissues obtained across multiple collection sites. The TSS are required to collect and store the tissues, perform site-capable pathology analysis to determine the BL diagnosis, and provide the BLGSP-required clinical data. Based on the SOPs, an overview flowchart was developed by the TSS coordinator in Brazil to understand the process. A challenge for the TSS in Brazil was to develop mechanisms and strategies to identify retrospective samples which was successfully overcome at both sites. Below we describe what was done at HdC-UFMG.

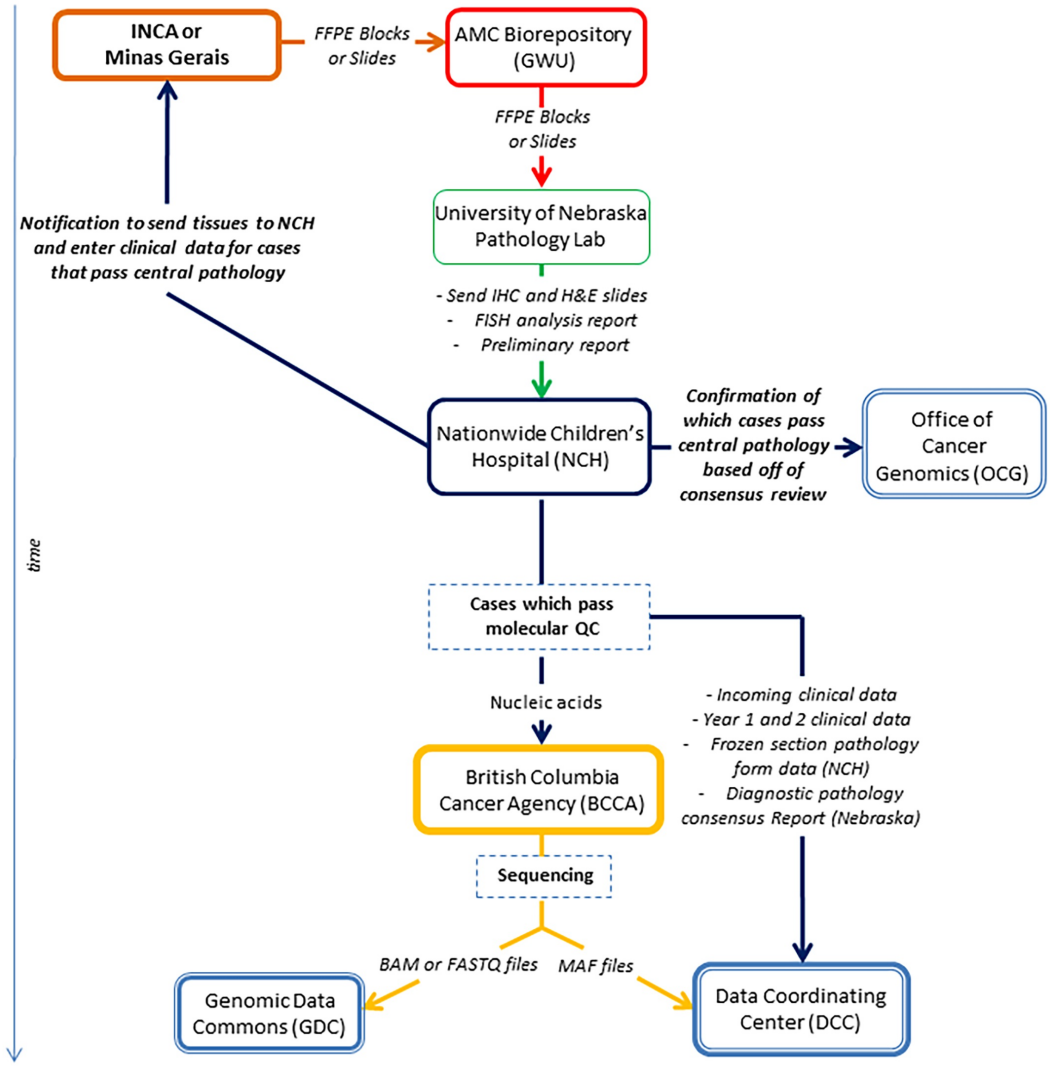

Figure. Outline of the Brazil BLGSP Flowchart.

The BL case biobank of retrospective samples is located at the Anatomy and Pathology Unit at UFMG. The Unit has a large bank of samples and diagnostic reports for patients diagnosed from 2005 to 2017. The PI and staff first developed preliminary inclusion criteria to be: (i) patients diagnosed with BL confirmed through laboratory results (i.e. histopathological and immunochemistry exams); (ii) patients with "possible BL" (i.e. B-cell lymphoma in germinal center where turnover cells Ki67 >95% are searched); and (iii) patients with other types of lymphoma (e.g. B-cell with low turnover, T-cell, gray zone, anaplastic large cell, mucosa-associated lymphoid

tissue, mantle cell).

The identification process starts with reading the clinical reports, selecting the patients with a positive diagnosis for lymphoma, and identifying the sample in the biobank. Clinical report forms for each case are available as paper copies, and cases which match the inclusion criteria are selected. Then, the patient ID code, formalin-fixed paraffin-embedded (FFPE) tissue block number, and the slice number are recorded. This information is vital to facilitate initial contact with the patient and obtain informed consent to get permission to use their tumor and normal samples in the study. Finally, the samples, which were selected by the Anatomy and Pathology Unit staff, are confirmed to match the BLGSP SOPs by the PI.

To date at both sites, 26 cases of BL in Brazil have been submitted to BLGSP, of which seven cases have both tumor and germline paired-samples. Currently, eight cases have passed diagnostic pathology review, three did not pass, and 15 are still being analyzed.

Next Steps

Challenges of the Brazil TSS have been the identification of prospective BL cases, which require logistical steps and complex operational procedures carried out by clinical staff and a study team involved at the hospital. The TSS have now improved the identification process for the retrospective BL cases from the past 12 years through expanding the search of diagnostic reports and FFPE blocks stored in the Anatomy and Pathology Unit at HdC-UFMG. The TSS are learning about the technical issues with molecular characterization data, and they can continue to use what they have learned today, from identifying the retrospective cases, to improve the collection process of prospective BL cases. Additionally, young investigators in the research community will use the molecular characterization data from BL patients identified through BLGSP to better understand the molecular alterations of BL in Brazil. This breakthrough has steered the TSS teams to improve the operational procedures in Brazil that have led to the current success of the BLGSP.

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OCG PERSPECTIVE

Understanding the Other Side of Research

Pamela C. Birriel, Ph.D.

For over seven years, the Office of Cancer Genomics [7] (OCG) has supported recent doctoral graduates through internship and fellowship programs. This past September, I became the newly appointed Health Communications Fellow for OCG through a Cancer Research Training Award under the Health Communications Internship Program [32] (HCIP). The HCIP provides highly qualified graduate students and recent graduate degree recipients the opportunity to participate in vital health and science communications projects through host offices at the National Cancer Institute [33] (NCI). Applicants are required to have some science background and experience and/or education in at least one of the following areas: public health, epidemiology, public relations, health education, communications, science writing, statistics, social marketing, and/or journalism. After the eight-week selection process, fellows are offered either a six-month or one-year full-time internship with the possibility of renewal for a second-year term.

HCIP offers enrichment opportunities through a professional development series of events. Trainings include *Managing Up: How to Be Effective with Your Boss*, *Giving and Receiving Feedback Effectively*, and *To the Point: Make an Impact by Saying Less*. 'Brown Bags' are also held throughout the first year as networking events providing the opportunity to interact in a casual environment with individuals from the NCI Presidential Management Fellows program. As part of the HCIP, I was assigned a mentor and a supervisor within OCG, who function as an advisor and day-to-day point of contact, respectively—both also sharing their knowledge and setting fellowship performance expectations that help progress towards my defined goals and objectives at the NCI.

Before coming to the NCI, I had recently earned my Ph.D. degree in Public Health and, prior to that, received an M.P.H. in Global Health Practice with a graduate certificate in Disaster Management from the University of South Florida in Tampa. I also received a B.S. in Exercise Science from Florida State University in Tallahassee and became a Certified Health Education Specialist in 2015. My doctoral dissertation focused on understanding Latina breast cancer survivors' perceptions of the importance of diet and nutrition in helping them cope with the effect of cancer treatment and survivorship. My research study revealed unmet information needs; Latina breast cancer survivors relied on organizational and online nutrition-related resources but identified a gap in culturally and linguistically tailored information related to diet and nutrition following diagnosis. Understanding the limitations that individuals face in their ability to function in daily life roles through cancer survivorship heightened my interest and influenced my decision to come to the NCI.

While in the doctoral program, I was also employed as Project Coordinator of the Florida Maternal, Infant, and Early Childhood Home Visiting (MIECHV) program evaluation. The Florida MIECHV initiative is funded by a grant from the Health Resources and Services Administration with the goal of improving health and developmental outcomes for at-risk children through evidence-based home visiting programs. Our evaluation team was required to collect data and submit quarterly performance reports which served to assist the Maternal and Child Health Bureau in monitoring our grant and providing oversight. Throughout my four years working on the MIECHV program evaluation, I came to understand how organizations apply for,

meet the requirements of, and report on federal research funding and competitive grants. My current position at the NCI now affords me a glimpse of how the National Institutes of Health (NIH) award and monitor the success of grants and contracts distributed to the extramural research community and help to disseminate the information achieved through such awards—the other side of the spectrum. As part of the OCG team, I currently collaborate with OCG program managers in supporting innovative scientific programs.

OCG aims to advance the molecular understanding of cancer by funding and managing national and international cancer genomics and translational research programs, with the goal of improving clinical outcomes, and thereby contributing to precision medicine. OCG currently supports four collaborative programs: the Cancer Genome Characterization Initiative [34] (CGCI), Therapeutically Applicable Research to Generate Effective Treatments [2] (TARGET), Cancer Target Discovery and Development [14] (CTD^2), and the Human Cancer Models Initiative [35] (HCMI). My responsibilities as Health Communications Fellow include managing and creating website content; collaborating with OCG program managers on updating guidelines and manuals; interpreting website engagement analytics; and developing topics, writing articles, and editing the OCG e-Newsletters [36]. I also collaborate with the Center for Cancer Genomics [37] (CCG) Communications team regarding the development of video tutorials, tweets for the NCI Genomics Twitter page [38], and posts for the Insights and Innovations Blog [39].

Throughout the past seven months, I have become actively involved in assisting with communications initiatives for the CTD^2 program. CTD^2 is a collaborative Network of 12 research teams called Centers [40]. Through robust cross-Network collaborations, the Network Centers use a combination of computational and experimental approaches to advance cancer research by translating large-scale genomic datasets into clinically-relevant information. For this program, I attend monthly steering committee teleconferences where presentations are given by each Center on a rotating basis to provide updates on their research. I also work closely with the CTD^2 Dashboard [41] and Data Harmonization Informatics Portal working groups. Through my OCG tasks and communications activities, I have come to better understand extramural federal grants from the award and management end.

My passion in the field of public health stemmed from my drive to help underserved and vulnerable populations through culturally and linguistically tailored health education programs. From my experience so far as part of the OCG team, my future career goals entail working in a government research-entity, ideally NIH, that would provide me the opportunity to develop targeted research and subsequently implement and manage specific programs. My current 12-month Health Communications Fellowship is just a starting off point to improving my understanding of cancer genomics research, bioinformatics, and precision medicine. It is important for me, through the HCIP, to build upon the community-based and analytic research skills I have attained as an evaluator in Florida and apply that knowledge to my work and collaboration activities at the OCG. I am now eager to continue contributing to research that will ultimately improve the health of the people in the cancer community for years to come.

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