CGCI PROGRAM HIGHLIGHTS

Analysis of Ugandan Cervical Carcinomas Identifies Human Papillomavirus (HPV) Clade-specific Epigenome and Transcriptome Landscapes

The article summarizes results from a study conducted in Ugandan cervical cancer patients as a part of HIV+ Tumor Molecular Characterization Project. The article reports molecular landscapes associated with different human papillomavirus (HPV) clades, influence of HIV status and genetic background in cervical cancer.

CTD² GUEST EDITORIAL

Immunoprofiler Consortium at the University of California, San Francisco (UCSF)

The UCSF Immunoprofiler Consortium aims to understand the nature of immune responses across various cancers and identify biomarkers to discover targets for new therapeutic interventions.

HCMI PROGRAM HIGHLIGHTS

Next-generation Cancer Models Available as a Community Resource

HCMI is an international consortium generating patient-derived next-gen cancer models and case-associated data as a community resource. The article provides updates on the models available through the Searchable Catalog and the models' case-associated data available at NCI's GDC.

CTD² PROGRAM HIGHLIGHTS

Bridging the Gap: CTD² Network Research Findings Undergoing Testing in Clinical Trials

CTD² Network aims to understand cancer metastasis, tumor heterogeneity, and drug resistance, and develop optimal combinations of pharmacologic and immunological agents. The article lists some examples of how CTD² Network research has informed clinical trials for various cancers.

OCG PERSPECTIVE
Dr. Julyann Pérez-Mayoral, a new program manager for the Human Cancer Models Initiative (HCMi) shares her background and aspirations for her new role at the Office of Cancer Genomics.

**CGCI PROGRAM HIGHLIGHTS**

**Analysis of Ugandan Cervical Carcinomas Identifies Human Papillomavirus (HPV) Clade-specific Epigenome and Transcriptome Landscapes**

Nick Griner, Ph.D. and Cindy Kyi, Ph.D.
Office of Cancer Genomics, NCI

Cervical cancer is the leading cause of cancer death among women in Africa. This is largely due to patients being diagnosed at later stages of the disease, leading to poor prognosis. Other factors of poor prognosis include high prevalence of genital human papillomavirus (HPV) infection and limited treatment options. Limited use of vaccine and lack of utilization of *Pap smear* as a form of prevention in developing countries like Uganda are leading to predictions of a 50% increase in cervical cancer mortality by 2040.

Human Immunodeficiency Virus (HIV) infection rate remains relatively high in developing countries. HIV has been classified as an indirect carcinogen through immune suppression that can lead to a number of specific cancers in AIDS patients. HIV is also linked to higher rates of HPV acquisition, and co-infection reduces the likelihood of HPV clearance, leading to increased risk of cervical cancer. It has been found that HPV infection is necessary for cervical cancer, but not sufficient. A number of genomic cervical cancer studies, primarily conducted in non-African patients, have revealed a molecular profile of a number of different pathways involved including copy number amplifications and somatic alterations. However, the role of HIV in these genomic cervical cancer studies has not been adequately addressed.

The HIV+ Tumor Molecular Characterization Project (HTMCP) was initiated by the Office of Cancer Genomics, along with the Office of HIV and AIDS Malignancies, to gain insight into the genetic events driving HIV-associated cancers. A recent HTMCP publication in *Nature Genetics*, describes a large scale genomic and transcriptomic study consisting of 118 tumors from Ugandan patients, 72 of which were HIV+. The results from this study reveals differing HPV clade-specific genomic, epigenome, and transcriptome landscapes in this cohort of samples.
The study consisted of 212 cervical cancer cases, of which 118 were included in discovery cohort and 89 were included in extension cohort for validation of mutations. Whole genome sequencing (WGS) of the 118 HIV+ and HIV- discovery tumor cohort revealed an average of 22,942 somatic mutations per case, of which 311 are coding mutations. APOBEC mutation signature consistent with a mutational process driven by cellular response to viral infections were detected. However, there were no differences in mutation burden \[^3\] or mutation signatures (characteristic combinations of mutation types arising from specific mutagenesis \[^4\] processes) between HIV+ and HIV- cases.

The most recurrent significantly mutated gene (SMG) $\text{PIK3CA}$, was present in a higher proportion of HIV- tumors, and its expression was 1.3 times higher in HIV- tumors compared to HIV+ tumors. Analysis of copy number alterations largely showed similar landscapes between HIV+ and HIV- samples, although HIV+ samples exhibited more unique focal amplifications and deletions. Comparison of the copy number (CN) landscapes between the HIV- samples with those of TCGA cervical cancers revealed some differences. TCGA samples exhibited a larger number of significantly deleted regions, affecting 11 chromosomes while the HIV- samples of this cohort exhibited 3 unique amplified regions. These results suggest genetic background may affect CN differences between the cohort of this manuscript and the largely North American cohort of TCGA.

Analysis of non-coding mutations revealed seven high confidence non-coding “hotspots” including two in $\text{TERT}$ promoter and two in a potential intronic enhancer of $\text{ADGRG6}$ which have been also reported in breast and bladder cancers. All observed hotspots were present in both HIV- and HIV+ cases.

**Identification of HPV clades**

WGS detected 17 HPV types, most of which are highly oncogenic HPV16(clade A9), 18 and 45 (clade
Clade A7 was more prevalent in this cohort compared to TCGA study, particularly among squamous cell carcinomas (SCCs). HPV types between HIV+ and HIV- tumors were similar.

Next, cluster analyses were performed to characterize expression and DNA methylation landscapes correlated with tumor features. Three gene expression clusters enriched for adenocarcinomas, non-keratinizing SCCs and keratinizing SCCs were identified. Two of the DNA methylation clusters distinguished clade A9-infected SCCs from clade A7-infected squamous and non-squamous cell carcinomas.

Differential methylation analysis comparing clade A7-infected samples with clade A9-infected samples detected over a 100,000 differentially methylated probes with different distribution with respect to genomic features and proximity to CpG islands. Clade A9 samples were found to be enriched with keratin family genes which have a role in epithelial differentiation, and production of virus during HPV infection, and directing uncontrolled cell growth. In contrast, clade A7 samples had increased expression of genes linked to extracellular matrix organization, cell adhesion and migration pathways.

Since HPV viral genes regulate epithelial cell differentiation and promote tumorigenesis, unsupervised clustering of viral E1, E2, E6 and E7 RNA transcripts was performed to study their association with different clades. Three clusters with different levels of gene expression and clade-specific enrichment were identified for clade A7-infected samples and A9-infected samples. This suggests that clade-enriched tumor gene expression patterns may be influenced by expression of HPV genes. The more aggressive viral expression profile associated with clade A7 is consistent with the clinical phenotype as A7-infected patients have poorer prognosis compared to A9-infected patients.

Clade-specific nature of DNA methylation results and large number of somatic mutations observed in chromatin modifying genes prompted the HTMCP to investigate clade-specific differences in histone modifications. ChIP-seq and cluster of clusters analyses using histone modification “marks” revealed four clusters that separated clade-specific tumors to mainly two clusters: one enriched in clade A9-infected tumors and the other in clade A7-infected tumors, while the remaining clusters enriched for non-SCC tumors. Differences in abundance of histone marks at active promoter and enhancer regulatory regions were observed between clade A7-infected and clade A9-infected samples, suggesting that DNA methylation and epigenetic modification patterns are altered in an HPV clade-specific manner.

Next, the project identified HPV integration sites into the genome and analyzed association of HPV integration sites with the expression of nearby genes. Clade A7 integration events contained more integration sites per event than clade A9 events, likely resulting in an observed pronounced effect on gene expression in clade A7 samples. Fold changes in histone mark enrichment near integration events were also positively correlated with gene expression changes. Higher number of HPV integration sites were associated with increased expression of nearby genes. These results suggest integration of HPV events in the genomes are associated with altered histone modifications and expression of genes within the proximity of the integration sites.

Nearly a third of integration events in the tumors were not within 10 kb of a protein coding gene. Thus, the HTMCP sought other genomic features influenced by these events and identified endogenous retroviral sequences (ERVs) near 44% of integrations. ERVs are epigenetically silenced in the genome and their reactivation is associated with induction of antiviral pathways. ERV expression near integration events correlated with the number of HPV insertions within the event, and upregulation of ERVs near integration events was associated with histone modification changes. However, increased ERV expression was not associated with immune cell presence in samples with an ERV integration event.

This study outlines genomic, transcriptomic and epigenomic differences between HIV+ and HIV-
samples in Ugandan cervical cancer patients. For the first time, molecular and epigenetic characteristics associated with HPV clades were observed within the A9 and A7-infected tumor samples. Histone modification profiles also distinguished infected samples by HPV clades. Finally, histone modification changes at HPV integration sites were correlated with the upregulation of nearby genes and endogenous retroviruses. Clade-specific differences observed in cervical tumors suggest a model where A7-infected tumors are less differentiated, more likely to have viral transcripts integrated into the genome, and more aggressive with a poor prognosis. In contrast, A9-infected tumors are more epithelial differentiated and have more episomal viral transcripts (less genomic integration), resulting in a better prognosis. The results from this study provides a better understanding of HPV infection-induced genomic, transcriptomic and epigenomic changes in cervical cancers.

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CTD² GUEST EDITORIAL

Immunoprofiler Consortium at the University of California, San Francisco (UCSF)

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Cancer can be seen through a series of lenses. Historically, it was seen through the “tissue-of-origin lens“ in which cancer was classified and treated based on where it had originated, such as in the skin, colon, or the kidneys. Subclassification of tissues-of-origin based on features was also prevalent, although not all were widely adopted. In breast cancer, for example, there are four major molecular subtypes: Luminal A, Luminal B, Triple-negative/Basal-like, and HER2 [11]-enriched. Therapies such as trastuzumab, a monoclonal antibody [12] against HER2-enriched breast cancers, are aimed at these distinctive features. More recently, cancer was seen through the “oncogene lens,” in which specific gene mutations are attributed to uncontrolled cell growth and proliferation observed in cancer. Targeted therapies were developed against oncogenes [13] Such as Ras, Myc, Rb, and BRAF. For example, vemurafenib is a small-molecule inhibitor of BRAF(V600E) kinase that demonstrates exceptional substrate specificity, and profound, yet often transient, effects on tumor size.
In the last few years, new cancer immunotherapy drugs have triggered remarkable and prolonged remissions in a subset of cancer patients. These therapies unleashed the patient’s own immune system to locate and destroy cancer cells. The remarkable success of cancer immunotherapy as well as its limitations have underscored the need to view cancer through a new lens that takes immunology into account. This has led to researchers, like us, to pursue cancer research through an “immunopathology lens”. Through this lens, we've learned that there are also crucial differences among tumors and patients in the strength and durability of the immune response, and that we need a deeper understanding of this new dimension. Thus far, we have yet to fully understand even the most basic questions, including: How many distinct forms of immunopathologies exist in cancer? Do these immunopathologies cross tissue-of-origin and oncogene-driver boundaries? Can you have more than one immunopathology in a tumor? And what are the markers or signatures that identify them?

Through our and the research community's efforts, we are just beginning to reveal some of these distinct forms of immunopathologies in cancers. What we have outlined here are a few of the immunopathologies that may be present in combination within the tumor microenvironment, that we have yet to fully elucidate. “Immune privilege” is a situation in which immune response to pathogens is hindered to protect the organ function from damage by inflammatory immune reactions. A commonly observed “immune privilege” phenomenon in many types of cancers is exclusion of T cells from the vicinity of tumor nests so the tumor cells are protected. Many of these tumors are also poorly antigenic – unable to stimulate a strong T cell response against the tumor. Increasing evidence also suggests that the tumor microenvironment of many cancers potently suppress the immune response by activating multiple regulatory mechanisms such as the presence of inhibitory receptors, overabundance of regulatory T cells (Tregs), and imbalance of myeloid cells. “T cell exhaustion” is a broad term that can describe heterogeneous forms of distinct epigenetic and metabolic states of T cells, including reduced capacity to secrete cytokines and increased expression of inhibitory receptors. Recently, dysfunctional T cells that are chronically stimulated to partial or severe (irreversible) exhaustion were defined; first in chronic viral infections, and then in cancers.

The UCSF Immunoprofiler Consortium was launched with the goal of identifying distinct forms of immunopathologies associated with and across cancers. The Consortium was initially launched in January 2015 by UCSF and, shortly after, involved several large Biopharma companies as partners. The Consortium is presently a six-year initiative, surveying over 600 tumors and has matched adjacent normal tissues across more than 15 different forms of cancer.

The Consortium has also become a model for data sharing between academia and industry in what is now called “precompetitive data sharing”. The data and analysis over the course of this program aims to serve two major roles. First, by providing a better understanding of specific classes of immunopathology, it can guide the selection of patients and indications for existing and novel drugs. If a therapy treats a pathology, knowing which immunopathology is present guides the success of the therapy, especially an immunotherapy. Second, this study aims to discover targets for new therapeutic interventions. The cell types and gene expression that define specific types of tumor immune microenvironments (TIME) will serve to validate and direct new therapeutic efforts.
Figure 1. **Brief Overview of the Immunoprofiler:** The Immunoprofiler seeks to coordinately perform a series of tests on hundreds of human tumor biopsies to reveal immune subset compositions, immune gene-expression analysis, and their spatial organization within the tumor microenvironment. The goal is to understand the nature of the immune response, establish new classes, and identify biomarkers and targets.

The overall scope of the Consortium is to coordinate the handling of valuable human biopsies and surgical resections taken from cancer patients, and to consistently perform multi-scale immunoprofiling assays — a series of tests that determine the tumor-immune composition, single-cell and population-level gene expression, and tumor-immune and immune-immune interaction biology. Shown in Figure 1 is the broad profiling trajectory that maximizes the use of each tumor and adjacent normal tissue. Once a tumor biopsy or surgical resection is removed from a patient, we immediately (<2 hours) transport it to the laboratory for processing. By taking it live and intact, we have the opportunity to study it much more intensely. A sliver or representative pie slice of the tumor is taken immediately for live tumor imaging to study tumor/immune cell interactions, or to be fixed for immunofluorescence imaging to study the spatial mapping of immune cells in tumors. The remaining tumor mass is then gently dissociated into single cells using an optimized standard protocol for digesting tumors to provide quantitative single cell analysis of the TIME. This method has been validated across multiple tumor types and tissues, and the numbers are in accordance with imaging.

The following standardized assays are performed across all tumors:

- Composition analysis based on multi-panel flow cytometry and/or CyTOF to measure the quantities and relative abundance of various cell types
- RNA sequencing of single cells and/or population-level (total live cells, T-cells, T-regs, myeloids, stromal cells [21], and tumor cells) to establish signatures of gene expression in tumors
- Whole exome sequencing to reveal the genetic mutations within tumors, with the aim of discovering genetic factors that may enhance or inhibit the immune response

Another essential component to the Immunoprofiler Consortium is a "human-to-mouse translator" program with the overall goal of providing a rational assignment of mouse models to their human counterparts. While mouse models have advanced our understanding of immune function and disease, they fail to account for the natural diversity in human immune responses. Therefore, we can imagine that a "translation table" between the immune profile of mouse models and their human counterparts will help researchers determine which mouse model to study, including two important environmental conditions: diet and age. First, the immune profiles of tumor models in mice will be benchmarked against data from the human tumor types. Second, mice will be assessed based on their high fat diet regimen and how it alters their antitumor immune response. Third, mice will be assessed based on their aged immune system and how it can impact the systemic and intratumoral [22] immune composition in the host (and whether this brings specific models into greater similarity with specific classes of human disease).

The Consortium is unusual, but beneficial because of an explicit agreement among all members to
share and have real-time access to the complete dataset. In turn, each of the Consortium members contributes a portion of the costs to collect the necessary biopsies and perform subsequent analyses. By sharing data at all levels, from biological discovery to drug development and patient prioritization, our ultimate goal is to accelerate the path to the next cures for all classes of cancer.

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HCMI PROGRAM HIGHLIGHTS

Next-generation Cancer Models Available as a Community Resource

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Overview
The Human Cancer Models Initiative (HCMI) is an international consortium of the National Cancer Institute (NCI), Wellcome Sanger Institute, Cancer Research UK, and Hubrecht Organoid Technology. The goal of the consortium is to generate patient-derived Next-generation Cancer Models (NGCMs) such as organoids, conditionally reprogrammed cells, neurospheres, or optimal growth condition models as a community resource. HCMI aims to provide the models’ case-associated data, which includes quality-checked clinical, biospecimen, and molecular characterization data from the models, the tissues from which they were derived, and normal tissues, when available. NGCM systems present a unique opportunity for the scientific community to study individual human tumors in vitro to further advance knowledge in a variety of research areas such as development of novel cancer therapeutics, cancer biology, biochemistry, and genetics.

HCMI Searchable Catalog
The HCMI models and their case-associated data are available to researchers as a community resource. Available models may be queried through the HCMI Searchable Catalog [28], a continuously updated resource of HCMI models. A summary of currently available models by cancer type, model type, and tissue type is described below (Figure 1).
Within the Catalog, users can filter and identify models by patient demographics, tumor, and model elements including age at diagnosis, sex, treatment information, clinical tumor diagnosis, primary site, clinical stage, and type of model (e.g. 3D-organoid, 2D-conditionally reprogrammed cells), etc. (Figure 2). Users may select specific models and download their associated Catalog data for later use. For additional assistance in navigating the Searchable Catalog, please see the “HCMI Searchable Catalog User Guide” [29]. Each specific model page contains external links to the model distributor and to the model's case-specific data page at NCI's Genomic Data Commons (GDC) which includes all available clinical, biospecimen, and molecular characterization data. New models and data are added to the HCMI Searchable Catalog as they become available.
Figure 2. Snapshot of HCMI Searchable Catalog homepage showing available models with a subset of associated data elements.

HCMI model-associated data

The models’ case-associated clinical, biospecimen, and molecular characterization data are stored at the GDC (Figure 3). NCI’s Clinical Data Center intakes clinical data from the Cancer Model Development Centers (CMDCs), quality checks (QCs), and transfers the data to the GDC. The Biospecimen Processing Center extracts and QCs nucleic acids from the normal and tumor tissues and the derived model for molecular characterization. NCI’s Genomic Characterization Centers perform and QC 15x whole genome sequencing (WGS) and 150x whole exome sequencing (WXS) on DNA from normal tissue, parent tumor, and derived model, and 120 million read RNA sequencing (RNA-Seq) on RNA from the parent tumor and the derived model, when possible. Epigenetic characterization data will be available for some of the HCMI models in the future. While the consortium aims to provide the data described, availability of the models’ case-associated information may differ among the CMDCs. The HCMI models’ case-associated data is submitted to the GDC where additional quality-checks and harmonization of the data are performed through their analytical pipeline [30]. Harmonized HCMI data are available at the HCMI-CMDC page [31] at the GDC data portal. HCMI data at the GDC can be either open-access, which does not require prior permission, or controlled-access, which requires user certification through NCBI’s dbGaP [32]. Open-access data include de-identified clinical data, biospecimen data, and tumor and model associated masked somatic mutation data while controlled-access data include harmonized datasets which may contain germline variants. Read HCMI Model-associated Data Available at NCI’s Genomic Data Commons [33] for more information on HCMI data at the GDC. See “Accessing HCMI Data” [34] page for information on data access. Users may join the GDC User Mailing List [35] to receive email updates on GDC data releases.
HCMI models in precision oncology

HCMI NGCMs serve as innovative research tools to study cancers, disease progression, collect data on accumulation of genetic aberrations, and make clinical correlations. The advantages of using HCMI's NGCMs over traditional cell lines include the availability of clinical data such as patient and tumor clinical information, histopathological biomarkers, and molecular characterization data of the derived model and associated normal and tumor tissues.

More models to be added to the community resource

NCI's commitment to decrease cancer health disparities supports model development from racially and ethnically diverse populations. OCG has partnered with the Center to Reduce Cancer Health Disparities (CRCHD) to collect tumors and clinical data from racial and ethnic minority populations for HCMI NGCM development. The overarching goal of HCMI is to generate 1,000 NGCMs from many human cancer subtypes, including breast, colorectal, glioblastoma, gastroesophageal, lung, melanoma and pancreas. Models from rare adult and pediatric cancers including neuroblastoma, osteosarcoma, Wilms tumor, rhabdomyosarcoma, and Ewing sarcoma have been developed by HCMI. Model generation from new cancer types including kidney, ovarian, and endometrial cancers is currently ongoing. As these models are generated, they will join the collection of HCMI NGCMs. Since HCMI is a highly active program, please check the HCMI Searchable Catalog [28] for current availability of HCMI NGCMs and associated data.

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CTD² PROGRAM HIGHLIGHTS
Bridging the Gap: CTD² Network Research Findings Undergoing Testing in Clinical Trials

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Office of Cancer Genomics

The Cancer Target Discovery and Development (CTD²) initiative aims to not only understand the molecular mechanisms of cancer, but also develop therapies to overcome metastasis, tumor heterogeneity, and drug resistance. CTD² Network Centers utilize advanced computational and systems biology methods, functional genomics and immunological approaches, and small molecule and genetic screens to functionally validate discoveries with preclinical and clinical relevance. Following the vision outlined in its name, the CTD² Network has made many biological discoveries leading to mechanistic, hypothesis-driven, targeted immunotherapies, combinatorial therapies, and window of opportunity clinical trials.

Clinical trials are done in people to answer specific research questions. These trials follow a protocol developed by the researcher or manufacturer and advance through different phases (I, II, and III) to test a treatment. There is a variation in the number of people involved in the different phases of clinical trials. A phase I trial is an early stage, small-scale study, and tests the safety of the treatment, phase II trial tests the effectiveness of the treatment, and a phase III trial is done on large scale to test the safety and effectiveness in different populations. The drug development process can be accelerated by going through only one or two phases of clinical trials when it is being tested for a life-threatening disease (Figure 1).

Figure 1. The drug development and approval process by the Food and Drug Administration (Image downloaded from Wikimedia Commons. Source: U.S. Government Accountability Office from Washington, DC, United States / Public domain)

The following are some examples of how CTD² Network research has informed clinical trials for various cancers:

Small molecule inhibitors

Acute Myeloid Leukemia (AML): AML is one of the most common forms of hematologic malignancies. The Beat AML program is a major collaborative effort led by CTD² scientists at Oregon Health and Science University. The project integrates molecular, drug response, and clinical data for progress
towards individualized therapies for AML. These studies revealed potential novel treatment options that are being tested in clinical trials: a phase II clinical trial of a CSF1R inhibitor and a phase I clinical trial with the combination of ruxolitinib and venetoclax for patients with relapsed/refractory AML.

Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): GEP-NETs are a rare class of tumors arising in the pancreas and gastrointestinal tract. The OncoTreat algorithm developed by CTD² scientists at Columbia University was used to prioritize compounds for treatment. The algorithm predicted entinostat as the most effective treatment for about half (47%) of the metastatic patients. Entinostat also induced significant tumor volume reduction in NET xenograft models. These data led to rapid investigational new drug (IND) approval by the FDA for a phase 2 clinical trial to treat metastatic GEP-NET.

HR-/HER2+ Breast Cancers: HER2-positive breast cancers express higher than normal levels of HER2 protein and make up approximately 25% of breast cancers. CTD² scientists at Columbia University have identified that a combination of HER2 and JAK/STAT3 inhibitors reduced the tumorigenicity in HER2+ breast cancer cell lines. These preclinical findings served as a basis for a phase I/II multicenter clinical trial to investigate the maximum tolerated dose of ruxolitinib in combination with trastuzumab (both FDA-approved drugs) in patients with metastatic HER2+ breast cancer.

Head and Neck Squamous Cell Carcinoma (HNSCC): HNSCC develops in the mucous membranes of the mouth, nose, and throat. Aggressive treatment of HNSCC with surgery, radiation and cisplatin therapies, is disfiguring and induces high-grade toxicities which limit effectiveness of the drug. CTD² scientists at Fred Hutchinson Cancer Research Center have identified WEE1 kinase (a regulator of the cell cycle) as a therapeutic target for the kinase inhibitor MK-1775. This data supported the initiation of a phase I clinical trial of MK-1775 with docetaxel and cisplatin before surgery in patients with Stage III-IVB HNSCC.

Inflammatory Breast Cancers (IBC): IBC is the most lethal form of breast cancer and its treatment options are limited. CTD² researchers at the Columbia University developed new genetic tools, experimental and analytical strategies, and identified that activity of the gene HDAC6 is essential to maintain IBC cells' viability and proliferation. This preclinical data provided a rationale for the initiation of a phase I clinical trial of ricolinostat (ACY1215), an HDAC6 inhibitor, in combination with standard nab-paclitaxel therapy to treat metastatic breast cancer.

Non-Small Cell Lung Cancer (NSCLC): Lung cancer is the leading cause of death in the United States, and NSCLC accounts for 85%-90% of lung cancers which display resistance to chemotherapy. CTD² researchers at University of California San Francisco identified a synthetic lethal interaction between EGFR tyrosine kinase inhibitors and Aurora kinase inhibitors. These findings led to the initiation of a phase I/Ib clinical trial testing the combination of EGFR inhibitor, osimertinib and Aurora kinase inhibitor alisertib.

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In other work, CTD² researchers at University of Texas Southwestern Medical Center identified XPO1, a nuclear export receptor, as an essential gene for survival in KRAS mutant NSCLC. This preclinical study provided supporting evidence for the initiation of a phase 1/2 clinical trial of selinexor with docetaxel.

Multiple Myeloma (MM): MM is an incurable plasma cell neoplasm with a median survival of 3-4 years. CTD² researchers at University of California San Francisco uncovered a network of chaperones and stress-response regulators involved in MM patient response and eventual resistance to carfilzomib, a proteasome inhibitor. Their work suggested a combination of carfilzomib with lenalidomide, an angiogenesis inhibitor, and steroid dexamethasone to treat MM; currently being tested in a phase
Rhabdoid Tumors (RT): RTs are a rare pediatric cancer that usually arise in the kidneys but can also occur in other soft tissues. Genes **MDM2** and **MDM4** were identified as actionable targets in malignant RTs in large-scale genetic and chemical perturbation studies\(^\text{11}\) performed by CTD\(^2\) researchers at Dana-Farber Cancer Institute \(^{54}\). A phase 1 clinical study \(^{55}\) was initiated to examine the effect of the dual MDM2/MDMX inhibitor ALRN-6924 in treatment-resistant solid tumors.

Immunological agents

**Solid Tumors:** Solid tumors are an abnormal clump of cells and are named after the type of cells that form them. CTD\(^2\) scientists at University of California San Diego \(^{56}\) demonstrated that natural killer (NK) cells derived from human-induced pluripotent stem cells \(^{57}\) are effective against refractory cancers \(^{58}\) in a mouse xenograft model\(^{12}\). NK cells may provide an off-the-shelf resource for anti-cancer immunotherapy. NK cells as monotherapy \(^{59}\) and in combination with an immune checkpoint inhibitor (nivolumab, pembrolizumab or atezolizumab) are being assessed in a phase I/II clinical trial \(^{60}\).

Squamous Cell Carcinomas (SCC): SCC is characterized by abnormal, accelerated growth of squamous cells \(^{61}\). CTD\(^2\) scientists at University of California San Francisco \(^{62}\) showed that anti-PD-1 therapy initiates a tumor rejection program and induces a TGF\(\beta\) immune-suppressive program in SCCs with high mutational load\(^{13}\). This study formed the basis for a phase I/Ib clinical trial \(^{63}\) of NIS793 in combination with PDR001 in patients with advanced malignancies.

Data and findings from the CTD\(^2\) Network are made public through the CTD\(^2\) Data Portal \(^{64}\) and Dashboard \(^{65}\), leading to many trials by others in the research community. For example, work by CTD\(^2\) scientists on targeting adaptive responses to PARPi with inhibitors of the AKT (NCT02208375 \(^{66}\)), PI3K (NCT03585661 \(^{87}\)), MEK (NCT03162627 \(^{68}\)), immune checkpoints (NCT03801369 \(^{69}\)), and a novel sequential therapy with a WEE1 kinase inhibitor (NCT04197713 \(^{70}\)) to decrease toxicity has led to numerous clinical trials with the potential to improve patient outcomes.

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Cancer type</th>
<th>Intervention/Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small molecule inhibitor</td>
<td>Acute myeloid leukemia</td>
<td>JNJ-40346527 (inhibitor of CSF1R) (^{39})</td>
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<tr>
<td></td>
<td></td>
<td>Ruxolitinib (JAK inhibitor) + venetoclax (Bcl2 inhibitor) (^{40})</td>
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<td></td>
<td>Gastroenteropancreatic neuroendocrine tumors</td>
<td>Entinostat (deacetylase inhibitor) (^{42})</td>
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<td>HR-/HER2+ breast cancer</td>
<td>Ruxolitinib (JAK inhibitor) + trastuzumab (HER2 receptor antagonist) (^{43})</td>
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<td>Head and neck squamous cell carcinoma</td>
<td>MK-1775 (WEE1 inhibitor) + docetaxel (anti-microtubule agent) + cisplatin (alkylating agent) (^{45})</td>
</tr>
<tr>
<td></td>
<td>Inflammatory breast cancer</td>
<td>Ricolinostat (HDAC6 inhibitor) + nab-paclitaxel (mitotic inhibitor) (^{46})</td>
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<tr>
<td></td>
<td>Multiple myeloma</td>
<td>Carfilzomib (proteasome inhibitor) + lenalidomide (angiogenesis inhibitor) + dexamethasone (anti-</td>
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Table1: List of clinical trials initiated based on the CTD\(^2\) Network research findings
<table>
<thead>
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<th>Therapy type</th>
<th>Cancer type</th>
<th>Intervention/Treatment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Non-small cell lung cancer – EGFR mutant</td>
<td>Osimertinib (EGFR inhibitor) + alisertib (aurora kinase inhibitor) [48]</td>
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<td></td>
<td>Non-small cell lung cancer – KRAS mutant</td>
<td>Selinexor (inhibitor of nuclear export protein, XPO1+) + docetaxel (anti-microtubule agent) [63]</td>
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<td>Rhabdoid tumors</td>
<td>ALRN-6924 (MDM2/MDMX inhibitor) [55]</td>
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<td>Immunological agents</td>
<td>Solid tumors</td>
<td>FT500 (iPSC-derived natural killer cells) [60]</td>
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<td>Squamous cell carcinomas</td>
<td>NIS 793 (anti-TGF beta antibody) + PDR 001 (anti-PD-1 antibody) [63]</td>
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References


**OCG PERSPECTIVE**

**Contributing to Precision Oncology by Expanding Basic Research Capacities Using Next-generation Cancer Models**

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As a basic cancer researcher, I am interested in ways to expand the capacities of researchers to explore new pathways and treatment options that can lead to acceleration of personalized treatments at the bedside. During my last year of postdoctoral training, I realized I wanted to transition to a position where I could capitalize on my experience in cancer genetics to further the scientific enterprise in a larger setting. Thus, I joined the Human Cancer Models Initiative (HCMI) as a program manager to help lead efforts to enrich the available resources such as next-generation cancer models in personalized medicine.

During my undergraduate studies, I was granted the opportunity to participate in the *MARC U*STAR Program [84] at the Pontifical Catholic University of Puerto Rico. It was through this program that I had my first research experience at a NeuroAIDS laboratory. As a Chemistry major, I was excited about this research opportunity since it allowed me to explore other scientific fields such as molecular biology and cell biology. It became the beginning of my strong interest in pursuing a career as a researcher. After graduating in 2006 with a B.S. in Chemistry, I joined the Post-Baccalaureate Research Education Program (PREP) at the University of Rochester [85]. This experience allowed me to develop a bigger research project and fine-tune other skills such as time management, laboratory management and data interpretation. It also prepared me to pursue graduate studies and become a researcher.

After leaving the University of Rochester PREP Program, I returned to Puerto Rico to continue graduate school. I pursued my Ph.D. in Biomedical Sciences at the Ponce School of Medicine and Health Sciences (now Ponce Health Sciences University). My graduate training allowed me to become familiar with the concepts of genetics, cancer biology and population genetics. Furthermore, it allowed me to train in a newly established laboratory where I was able to learn laboratory set-up and fine-tune my organizational and administrative skills. My thesis project focused on DNA repair genes polymorphisms and their association with DNA repair capacity in Puerto Rican women with breast cancer. My research showed that polymorphisms in nucleotide excision repair genes RAD23 homolog B, nucleotide excision repair protein (*RAD23B*) and DNA damage recognition and repair factor (*XPC*) had an additive effect on reducing DNA repair capacity and increasing breast cancer risk in Puerto Rican women. Through my doctoral training, I realized the importance of genetic and genomics in studying cancer and reducing cancer health disparities in underserved populations.

Recently, I finished my postdoctoral training at the University of Puerto Rico Comprehensive Cancer Center. It was during my tenure as a postdoctoral fellow that I learned about patient recruitment, collection of clinical data, database maintenance and design, and biospecimen processing for biobanking. My main postdoctoral project focused on the role of genetic ancestry in association with the risk of developing colorectal cancer and colorectal tumor characteristics. Even though we did not
find that genetic ancestry was associated with colorectal cancer risk, we found that Puerto Ricans with higher than 18% of African ancestry were at higher risk of developing rectal tumors. This research could serve as a steppingstone for personalized interventions for colorectal cancer in Puerto Ricans. In addition, I worked on projects that focused on characterizing the mutational spectrum and clinical features of hereditary colorectal cancer syndromes in Puerto Ricans. I was also involved in a collaborative project with City of Hope Cancer Center which offered research-based genetic testing and counseling to breast cancer patients whose cancer was suspected to be hereditary based on the age of onset and family history of cancer. This project allowed me to expand my knowledge of hereditary cancer by participating in the Intensive Course in Genomic Cancer Risk Assessment [86]. All of these projects during my postdoctoral training required working with an interdisciplinary team to advance the research and to benefit cancer patients in Puerto Rico.

By joining the HCMI, I will be able to use my skills in cancer genetics, molecular biology and management of research projects. The HCMI has the goal of generating human tumor-derived next-generation cancer models from a wide array of cancer subtypes. The HCMI models are characterized and annotated with clinical, biospecimen and molecular data for the scientific community. In my role as a Scientific Program Manager, I will work to ensure that samples from normal, parent-tumor and cancer model are annotated as much as possible. Furthermore, I will collaborate with the teams at Biospecimen Processing Center (BPC), Genomic Characterization Centers (GCCs) and Genomic Data Commons (GDC) to monitor samples and provide support to identify and overcome potential challenges that may arise. This collaborative work serves to ensure that the objective of HCMI to provide high-quality, characterized and annotated next-generation cancer models to the scientific community is met.

As I begin my role as a Scientific Program Manager for the HCMI, I can't help but feel excited about the potential of this program to address many big scientific questions within the field of cancer. The HCMI next-generation models recapitulate tumor biology more accurately than traditional models, hence, paving the way for precision oncology. Our understanding of disease modeling, tumor microenvironment, carcinogenesis pathways, genetic changes, drug screening and treatment outcomes, may grow with the availability of these models. I am honored to be part of an initiative like HCMI where I can use my skills to further the scientific knowledge beyond the bench. It is my hope that the collective effort of HCMI to provide next-generation cancer models can positively impact precision oncology efforts that benefit cancer patients.

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