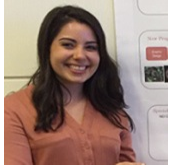




Issue 15 : October, 2016



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PRECISION ONCOLOGY

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Precision medicine is an approach to disease prevention, diagnosis, and treatment, which takes into account an individual's genes, background, lifestyle, and physical characteristics.

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The field of immunotherapy is rapidly advancing and genomics techniques are being incorporated to add a “precision” approach. OCG spoke with two CTD2 investigators from the Fred Hutchinson Cancer Research Center (FHCRC) about new advances in immunotherapy.

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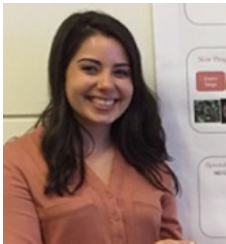
From the Bench to the Clinic Part 2: Edus "Hootie" Warren Provides Perspective on the Clinical Impact and Potential of Immunotherapy

Immunotherapy is a promising approach to cancer treatment. The field of immunotherapy is rapidly advancing and genomics techniques are being incorporated to add a “precision” approach.

OCG PERSPECTIVE

Cheering for Team Science

Nadia Jaber



As a graduate student, my PhD thesis focused on the function of a single human gene, within a genome of some 20,000 genes. Although this sometimes made my work seem insignificant, I was reminded of how important one small piece of a large puzzle can be when I discovered all the ways the gene knockout cells were disadvantaged. Studying the basic biology of our cells made me appreciate the beautiful complexity of human biology.

Nadia Jaber, Ph.D. While I enjoyed my time discovering the inner workings of our cells, I ultimately discovered that I preferred talking and writing about science to pipetting. I took multiple courses from the Alan Alda Center for Communicating Science at Stony Brook University, worked as a guest writer whenever I had the chance, and challenged myself to multiple public speaking events. After earning my PhD from Stony Brook University, I had the incredible opportunity to join the world’s leaders in cancer research at the National Cancer Institute.

As a Health Communications Fellow for the Office of Cancer Genomics I found impactful research and inspiring opportunities. I was introduced to the world of cancer genomics, and become enveloped by the promising concepts of team science and precision medicine. After I became familiar with OCG’s mission and collaborative research projects I developed a “Visibility Plan” to enhance the dissemination of data generated by OCG-supported research programs to the cancer research community, a key component of OCG’s mission. As part of this plan I helped OCG establish a presence on [Twitter](#) [2], sharing research updates alongside the Cancer Genome Atlas(TCGA). This opened the door for OCG to participate in an NCI-hosted Twitter chat about #cancergenomics. In addition, I had the wonderful opportunity to attend

the annual AACR conference in New Orleans, where I presented a poster that detailed OCG-supported datasets and resources. I was able to interact with researchers from around the globe and inform them about OCG's research and available data; many of these researchers can use this data to advance their own research. In addition, I attended fascinating lectures, from which there was a general consensus that we are at a critical turning point in cancer medicine. The experience was galvanizing.

While these were rewarding experiences, the most influential aspect of my fellowship was being exposed to the collaborative research approach used by OCG. OCG-supported research programs bring together acclaimed investigators from institutions around the world for a common goal: to fight cancer. Compared to investigator-initiated research grants (e.g., R01) most scientists are familiar with, OCG research programs are funded by cooperative agreements (e.g., U01) and contracts. Under a cooperative agreement, competitively selected investigators conduct research that supports specific goals which require collaboration and team work.

This "team science" model is a refreshing approach to research, and has clear advantages. Regular team meetings keep projects on track, generates accountability, and creates an external push towards progress. Team meetings also allow research questions to be debated from multiple angles and perspectives, which leads to creative problem solving. In addition, regular data presentation at monthly meetings provides a platform for feedback and criticism, which often leads to higher quality data.

Another advantage of team science is the opportunity to share ideas, data, and reagents. By sharing unpublished data, team members are able to work with and build upon new findings immediately, rather than waiting long periods until the work is published. Although the publication of negative data is largely discouraged (by most journals), team members are able to share negative data during meetings which saves other researchers in the group from repeating the same experiments. Sharing fledgling hypotheses and burgeoning research stories allows the team to provide critical feedback and sometimes even supporting evidence from independent research work. In addition, sharing reagents and technical expertise is a definite cost-savings approach which allows team members to focus time and funds on additional experiments.

Finally, one of the most influential aspects of team science is the opportunity for collaboration. During my fellowship I witnessed first-hand the generation of collaborations between scientists from different institutions and areas of focus. Through monthly meetings each team member becomes familiar with the strengths and expertise of the others, thus allowing the team to explore new ways to leverage their abilities; this expands the depth and strength of data produced by the team. Through these aspects of team science (regular meetings, sharing, and collaboration) research progress is greatly accelerated.

The collaborative science approach was applauded at the Precision Medicine Initiative Summit when chief of the Urologic Oncology branch at NCI, Dr. W. Marston Linehan, said we "shouldn't be surprised the progress people can make, working together, if you're not quite so concerned about who gets the credit ... I think we can

change the culture.” I believe that as we are propelled forward into the era of precision medicine, we will quickly realize the tremendous benefits of the team science, and it will become a key weapon in our fight against cancer. With collaborative research projects like those supported at OCG, and others like the Ras initiative and the Precision Medicine Initiative, I’m excited to witness and be a part of the advances that the cancer research community will make over the next several years.

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TARGET PROGRAM HIGHLIGHTS

TARGET-Inspired Clinical Trials

Jaime Guidry Auvil, Malcolm Smith, Nadia Jaber, Jessica Mazerik

Since its inception in 2009, the Office of Cancer Genomics’ Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative has generated volumes of genomic characterization data for multiple high risk and/or hard-to-treat pediatric cancers*. Disease-specific project teams are studying subtypes of acute lymphoblastic and myeloid leukemias, neuroblastoma, osteosarcoma, and select kidney tumors. One of TARGET’s primary goals is to translate this genomic information into new or more effective treatment strategies for children; this aim is being fulfilled progressively as datasets are completed. Through a collaboration with the Children’s Oncology Group (COG), TARGET’s identification of distinct cancer subtypes and novel cancer targets have influenced clinical and biological studies. TARGET research-inspired trials in these areas have the potential to impact treatment strategies and change the clinical landscape of pediatric oncology.

Identifying distinct cancer subtypes

In the clinical setting, cancer subtypes are generally identified by histopathology and tumor behavior. However, further classification of cancers by genetic characteristics may provide more accurate diagnoses, prognoses, and treatments. As an example, breast cancers are divided into different subtypes based on the presence or absence of certain molecular markers such as hormone receptors and receptor tyrosine kinases. This subdivision informs patient prognosis and subsequent treatment regimens. No such stratification mechanism currently exists to distinguish pediatric clear cell sarcoma of the kidney (CCSK) from other kidney tumor types. However, researchers analyzing data from TARGET and other studies identified internal tandem duplications in the BCL6 co-repressor (*BCOR*) gene^{1,2} in patients with CCSK. *BCOR* is a subunit in a complex that silences genes through chromatin regulation and is known to regulate tumor suppressor genes³. Roy and colleagues found that the mutated *BCOR* protein was expressed and transcript levels were upregulated in CCSK as compared to other renal tumor types. In addition, transcriptome analysis revealed that *BCOR*-related targets were enriched in *BCOR*-mutant tumors, suggesting a potential pathogenic mechanism. Independent research subsequently identified internal tandem duplications in *BCOR* in other cancer types including pediatric and adult central nervous system neuroepithelial tumors and infant undifferentiated

round cell sarcoma^{4,5}. Although these findings have not yet been applied in the clinic, the presence of the genetic lesion in kidney tumors that were previously difficult to distinguish from other kidney cancers, and in diseases that were previously considered unrelated, could change the way clinicians diagnose or treat these cancer subtypes.

Finding genomic alterations for targeted therapies

Additional analyses of TARGET data have led to the identification of key oncogenic drivers that have the potential to be exploited via targeted therapies. For example, TARGET data revealed genetic drivers and a potential treatment strategy for children and young adults with the *BCR-ABL1*-like (“Ph-like”) subtype of acute lymphoblastic leukemia (ALL). *BCR-ABL1* ALL [also known as Philadelphia chromosome-positive (Ph⁺) ALL] is characterized by the presence of the “Philadelphia chromosome”, a translocation between chromosomes 9 and 22. The translocation results in a fusion of breakpoint cluster region (*BCR*) and Abelson murine leukemia viral oncogene homolog 1 (*ABL1*), and generates *BCR-ABL1*, an oncoprotein that can be targeted with tyrosine kinase inhibitors. *BCR-ABL1*-like ALL has a molecular profile similar to *BCR-ABL1* ALL, but lacks the Philadelphia chromosome. However, genomic profiling of 15 tumors by TARGET researchers revealed that Janus kinases (*JAK1*, 2, and 3) are mutated and JAK kinase signaling is dysregulated in *BCR-ABL1*-like ALL, suggesting that these patients may also benefit from treatment with tyrosine kinase inhibitors⁶ (also see the [TARGET Program Highlight](#) [3]). As such, pediatric patients with relapsed leukemia were enrolled in a Phase 1 clinical trial testing the best dose of JAK inhibitor ruxolitinib/INCB18424 (COG ADVL1011, [NCT01164163](#) [4])⁷. The trial established that ruxolitinib was well tolerated in patients, and warrants further investigation of ruxolitinib plus chemotherapy as a combination treatment approach in Ph-like ALL⁸.

The TARGET ALL project team went on to analyze a larger number of genomically characterized *BCR-ABL1*-like ALL cases and identified a broad spectrum of activating alterations in multiple kinase genes. They reported kinase-activating alterations in 91% of *BCR-ABL1*-like ALL patients, 62% of which were gene rearrangements leading to potentially actionable fusion proteins⁹. These rearrangements involved several different kinase, cytokine, or cytokine-receptor genes. When expressed in a murine pre-B cell line, all six of the gene fusions tested induced cytokine-independent proliferation and were sensitive to treatment with tyrosine kinase inhibitors that matched their respective mutated signaling pathways. These results suggest that tyrosine kinase inhibitors are a plausible targeted therapeutic strategy for *BCR-ABL1*-like ALL. This research led to another clinical trial in which a diagnostic test, called a Low Density Array (LDA) gene expression card¹⁰, is being used to identify potential *BCR-ABL1*-like ALL patients who may have alterations that can be targeted using kinase inhibitors. After LDA screening, specific alterations are identified by targeted gene sequencing. This approach can determine the most appropriate kinase inhibitor to add to standard chemotherapy for patients with *BCR-ABL1*-like ALL (COG AALL1131, [NCT01406756](#) [5])¹¹.

The TARGET neuroblastoma (NBL) project team has also identified genetic drivers that could potentially be treated by targeted therapy. High-risk neuroblastoma tumors are characterized by few recurrent mutations and are therefore challenging

to treat using precision medicine approaches. TARGET researchers analyzed high-risk metastatic neuroblastoma by whole exome and/or whole genome sequencing with the goal of identifying recurrent, potentially actionable somatic mutations. Their analysis of this dataset confirmed the recurrence of activating somatic mutations in the anaplastic lymphoma kinase (*ALK*) gene in NBL¹². Among other studies, this research contributed to the rationale for a clinical trial to test the therapeutic efficacy of an *ALK* inhibitor, crizotinib, in children with relapsed or refractory tumors, including NBL (COG ADVL0912, [NCT00939770](#) [6])¹³. Crizotinib is already approved for treatment of adults with non-small cell lung cancer; the purpose of this ongoing study is to determine best dose and effectiveness in young patients. Crizotinib will also be studied in combination with standard of care chemotherapy in a clinical trial for children newly diagnosed with *ALK*-mutated neuroblastoma.

TARGET has helped shape the pediatric clinical oncology field by providing high quality genomic datasets and analyses of high-risk pediatric cancers that have led to clinical trials and generation of new therapeutic strategies. A critical component to the clinical translation of TARGET research is its partnership with the Children's Oncology Group, an NCI-funded clinical trials group and the world's largest organization devoted solely to childhood and adolescent cancer research. In addition, the nature of the pediatric oncology field has also influenced these successes. For example, childhood cancers are rare diseases, and the small sample size of pediatric cancer subtypes biases the research culture toward high clinical trial participation and collaboration between investigators. These unique qualities of the pediatric oncology field accelerate the pace of pediatric cancer research and translation of findings into the clinic, making it a good model for the oncology field as a whole.

*TARGET data are available at the [Genomic Data Commons](#) [7] and the [TARGET Data Matrix](#) [8].

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DATA CORNER

Introducing the Genomics Data Commons

Nadia Jaber

As genomics studies progress and datasets become larger and more complex, the ability of the research community to access and analyze genomic data is hindered by several limitations, including the size of data files, cost of storage, and difficulty accessing various portals. To address these challenges, the [Center for Cancer Genomics](#) [10] launched the [Genomics Data Commons](#) [11] (GDC) as part of the [National Cancer Moonshot Initiative](#) [12]. The GDC is a unified data sharing platform which enables data sharing across the entire cancer research community, to ultimately support precision medicine in oncology.

As a secure data storage network, the GDC provides investigators with a single portal to access genomic characterization datasets including The Cancer Genome Atlas (TCGA [13]) and Therapeutically Applicable Research to Generate Effective Treatments (TARGET [14]). In the future, other datasets, including the Cancer Genome Characterization Initiative (CGCI [15]), the Cancer Cell Line Encyclopedia (CCLE [16]), and the Human Cancer Models Initiative (HCMI) will be added. In addition, the molecular information company Foundation Medicine, Inc., which has already pledged to add data from 18,000 adult cancer patients.

For the community of researchers that contribute to and follow OCG research programs, the launch of the GDC means that data from TARGET and CGCI (but not CTD²) will be accessible through the GDC in addition to their designated data matrices [17]. The raw data files used to produce the analyzed data accessible from the OCG matrices are the same as those stored in the GDC. The GDC will use 17 different analytical pipelines to analyze the TARGET data and will map the sequences to the latest version of the human genome reference sequence. Therefore, re-aligned and re-analyzed data in the GDC may be different from those accessible through the OCG data matrices. Additionally, the data access sites differ in their user interfaces and interactive applications. In the OCG matrices, data are separated by program and further delineated by project and tissue type. In the default setting for the GDC data are not separated by any factors, so all programs and tissue types are displayed. However, data can be sorted by program (such as TARGET), primary site (such as kidney), disease type (such as high-risk Wilms Tumor), data category (like transcriptome profiling), or experimental strategy (like whole exome sequencing). For example, users can view, download, and analyze TARGET's dataset on its own, or in conjunction with other datasets. It should be noted that although the datasets are intermingled, users will need a separate data use certification (DUC) to access each program's data.

Another advantage of the GDC is that data are harmonized (meaning uniformly analyzed) which enables the direct comparison and analysis of datasets from different sources in ways that were not possible before. Data harmonization allows investigators to carry out analyses on cases from multiple studies, thereby enhancing statistical power and increasing the depth of investigation. This is especially important for rare and understudied cancers, such as those studied by TARGET and CGCI.

The GDC also holds clinical information associated with the molecular data, and a long-term goal of the GDC is for physicians to use it as a tool for precision oncology. In addition, GDC users have the ability to upload genomic data, increasing the breadth of data and allowing for more comparisons. Alternatively, a provider could possibly determine the best course of treatment to match the specific genetic vulnerabilities of the patient's tumor by looking at the associated clinical information, such as treatment regimen and outcome, from other patients with the same alterations. A cancer "knowledge bank" containing both genomic and clinical data will be a critical component of precision oncology strategies, and the GDC has the potential to be one component.

The GDC will continue to grow with data, tools, and resources, and has the potential

to transform the use of OCG and other genomic datasets.

For more details about the GDC:

- View the GDC [website](#) [11]
- Launch the GDC [Data Portal](#) [7]
- Read the [press release](#) [18]
- Visit the [NCI News Note](#) [19]
- Check out the GDC [fact sheet](#) [20]
- Watch an introductory [video](#) [21] featuring Dr. Louis Staudt, Director of the Center for Cancer Genomics
- Browse the University of Chicago's [GDC FAQ](#) [22]
- Visit the GDC [About the Data](#) [23] page
- Read about the addition of data from [Foundation Medicine, Inc.](#) [24]
- For questions and feedback, email the [support team](#) [25]
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PRECISION ONCOLOGY

OCG Contributions to Precision Oncology: From Discovery to Clinical Development

Nadia Jaber and Jessica Mazerik

Precision medicine is an approach to disease prevention, diagnosis, and treatment, which takes into account an individual's genes, background, lifestyle, and physical characteristics. Genomics has taken center stage as a key component of this precision medicine approach, which is being accelerated by new technology and methods. Cancer arises as a result of multiple genetic mutations, the precision medicine approach in oncology has the potential to offer many advantages including better response rates and avoidance of unnecessary or ineffective treatments.

Precision oncology research can be thought of as a gear-powered machine where each cog represents a category of precision oncology research (Figure 1). Data and information from patient tumors act as the input. Like a gear set, the research

components interact and set one another into motion. Movement by each individual “cog” contributes to the motion of the entire gear set and moves the machine forward towards precise approaches for cancer prevention, diagnosis, and treatment.

The Office of Cancer Genomics (OCG) contributes to cancer research that moves precision oncology toward standard clinical practice. OCG supports four collaborative research initiatives that utilize the latest technologies in genomics, bioinformatics, functional biology, small molecule screening, and other approaches to advance the study of cancer. In this article, we highlight different areas of precision oncology research (the “cogs”) and discuss the unique and complimentary ways in which OCG initiatives contribute to the movement of each cog.

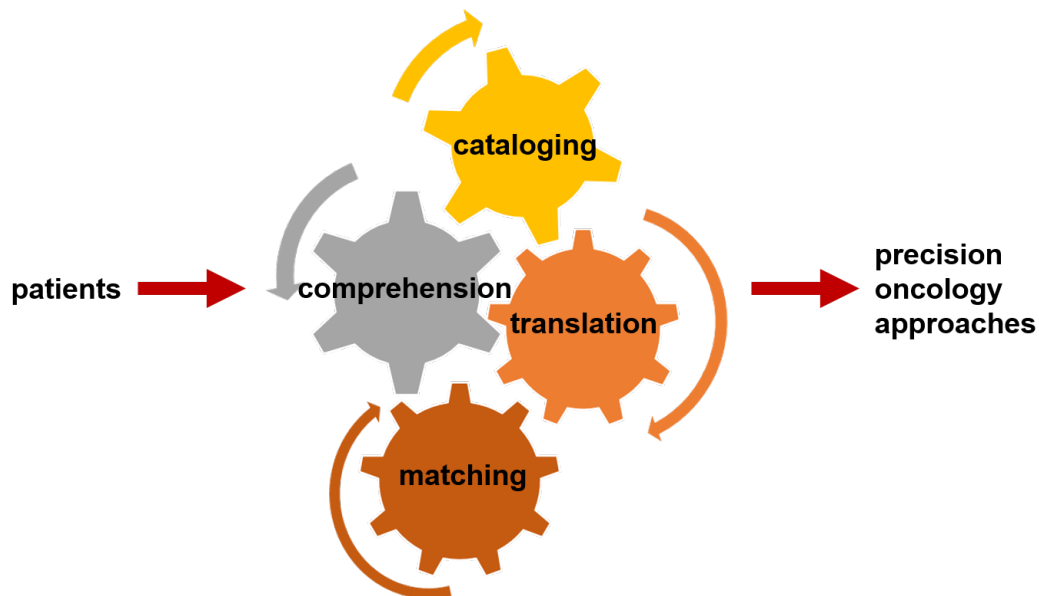


Figure 1: Each area of research acts as a cog, and information from patients acts as the input. Like individual cogs contribute to the movement of a gear set, advances in each area power the forward movement of precision oncology.

CATALOGING the genetic alterations found in all cancer types, including genetic mutations, chromosomal rearrangements, and epigenomic changes; specific focus is placed on identifying genetic differences between cancer subtypes

The Cancer Genome Characterization Initiative (CGCI) and the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative are large-scale cancer genome sequencing and characterization programs, which contribute to the *cataloging* component of precision oncology. CGCI and TARGET researchers carry out comprehensive DNA and transcriptome profiling (for example, using whole genome and/or exome sequencing, and sequencing of mRNA and miRNA), copy number analysis, and epigenomic (methylation) characterization of high-quality matched tumor and normal tissue samples. Genomic sequencing and characterization by CGCI and TARGET provide information about the underlying genetic and molecular causes of the cancer subtypes being studied, which includes

cancers that are more prevalent in HIV-positive individuals and hard-to-treat pediatric cancers.

The Human Cancer Models Initiative (HCMI), a component of the NCI's Precision Medicine Initiative in Oncology, aims to generate cancer culture models that are representative of human tumors by using new technologies such as conditionally reprogrammed cells and organoids. The initiative will generate new models from patient tumor tissue; the resulting models, the originating tumor, and case-matched normal tissue will be characterized by whole genome and whole exome sequencing. The transcriptomes of the models and tumors from which they are derived will also be sequenced. As such, HCMI contributes to the *cataloging* component of precision oncology by identifying genetic abnormalities associated with different tumor subtypes. HCMI aims to generate models from tumor tissue of underrepresented minorities. Increasing the molecular characterization data available for these populations is an important contribution to this component of precision oncology because it will help provide a more extensive view of cancer biology.

COMPREHENDING how the genetic characteristics of cancer contribute to cancer biology, and determining which characteristics are the most influential and clinically actionable

Sequencing initiatives such as CGCI and TARGET have revealed that each tumor contains numerous distinct genetic mutations; if and how each alteration contributes to the cancerous phenotype must be determined through validation, including functional experiments. In addition to genomic characterization, TARGET researchers analyze the genomic data they generate and investigate the biological function and consequences of observed genetic alterations, thus contributing to the *comprehension* component.

Another OCG-supported program, the Cancer Target Discovery and Development (CTD²) initiative, utilizes genomic data from programs like CGCI, TARGET, and The Cancer Genome Atlas (TCGA) to validate and determine the biological function of key mutations and abnormalities. CTD² also aims to identify approaches to target these cancer-causing alterations, either directly or indirectly by modulating an affected pathway. By identifying oncogenes, biomarkers, and vulnerabilities among the vast array of mutations in cancer genomes, and elucidating their roles in the complex landscape of cancer biology, CTD² investigators build a basis on which they and other researchers can further develop their findings into therapeutic interventions. Therefore, the major goals of CTD² contribute to the *comprehension* component.

HCMI will also facilitate the discovery of relationships between cancer genotypes and phenotypes. The models generated through HCMI will be available worldwide through a distributor, and the genomic and clinical data will be available through the Genomic Data Commons and other databases. Access to the models and data will allow researchers around the globe to use the models for various areas of research, which will advance the *comprehension* of cancer biology.

TRANSLATING the findings related to genetic alterations and biological abnormalities of cancer into biomarkers, targeted therapies, and better treatment strategies

A pivotal aspect of precision oncology research is translating genomic discoveries into clinical relevance; this is another main goal of the CTD² initiative. CTD² research has led to the discovery of small molecules to target specific genetic alterations and biomarkers of drug sensitivities or resistance. Another way that CTD² contributes to this component of precision oncology research is by making Network-generated data and results available through the [CTD² Dashboard](#) [28], an interactive open-access site for straightforward browsing and comprehension of CTD²-generated conclusions (more information on the CTD² Dashboard [here](#) [29]). Observations and conclusions in the CTD² Dashboard are designated with a “[Tier](#) [30]” value, which indicates the extent of characterization associated with a finding. As the Tier value goes up, it indicates an increased probability that the observation is relevant, and upon further study may lead to clinically relevant discoveries. Thus, the CTD² Network aims to advance the *translation* of genomic findings into therapies, biomarkers, and treatment strategies for cancer.

In addition, analysis of TARGET data has revealed key findings which, through a collaboration with the Children’s Oncology Group, has led to clinical trials and influenced new treatment strategies for certain pediatric cancers (discussed in more detail [here](#) [31]). Contributions to the *translation* component of precision oncology will likely continue as TARGET data are further analyzed and interpreted.

MATCHING each patient with the most effective and appropriate targeted therapies

The crux of the precision medicine approach is precise matching of treatment and therapies to each individual patient’s complete biological makeup. A cancer knowledge network is necessary to help clinicians determine the most appropriate treatment, and many data repositories and software tools are contributing to this goal. The Genomic Data Commons (more information on the GDC [here](#) [32]) acts as a repository for cancer genomic and related clinical data, and could potentially contribute to a knowledge network for precision oncology in the clinic. Researchers and clinicians are able to upload patient data to the GDC and perform comparisons between the patient’s tumor genome and characterized genomes stored in the GDC. Data generated by CGCI and TARGET are stored in the GDC, along with TCGA and other CCG initiatives, contributing to the depth of this repository. In addition, some clinical and biological trials inspired by TARGET discoveries contribute to the *matching* component: they are tailoring potential treatments to patients with certain subtypes or specific tumor genome alterations.

In the future, clinical screens or panel tests that match a patient’s tumor genome

with the most precise treatment will also be a key tool for precision oncology. Many screens and tests of this sort are in development and use in the clinic. Similarly, knowledge gained from HCMI could potentially lead to development of methods to grow short-term patient-derived cancer models that can be used to test a panel of therapeutic options and inform treatment decisions for individual patients.

While the concept of individualized medical treatment has been in practice for many years, new technologies and methods are allowing therapies and approaches to become even more precisely tailored to each individual patient. President Obama's Precision Medicine Initiative and the National Cancer Moonshot Initiative are supporting the National Cancer Institute's efforts to advance knowledge into precision oncology approaches and treatments that help more patients achieve remission. While precision medicine approaches are becoming more advanced, more progress is still needed in order to make it the standard of care for cancer patients. Multiple research components act as the cogs that power the forward movement of precision oncology. The Office of Cancer Genomics has and will continue to support genomics research, turning the gears and accelerating precision oncology into standard clinical practice.

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FEATURED RESEARCHERS

From the Bench to the Clinic Part 1: Martin McIntosh, Ph.D., Introduces His Lab's Immunotherapy Research

Edited by Nadia Jaber and Jessica Mazerik

The field of immunotherapy is rapidly advancing and genomics techniques are being incorporated to add a "precision" approach. OCG spoke with two CTD² investigators from the Fred Hutchinson Cancer Research Center (FHCRC) about new advances in immunotherapy. For the first article of this two-part series, we interviewed Martin McIntosh, Ph.D., member of the Fred Hutchinson Translational Research program and previously Program Head in Computational Biology at FHCRC/University of Washington Comprehensive Cancer Center. He gives his perspective of immunotherapy approaches and describes his laboratory's translational research efforts.

Can you describe the different types of immunotherapy approaches?

In broad terms, there are several classes of immunotherapies. All tumors are thought to adopt strategies that interfere with normal T cell function. One class of immunotherapy tries to overcome obstacles to T cell efficacy that are present in the tumor. These treatments are predicated on the notion that an effective anti-cancer immune response is already present within a patient. Agents that block T cell inhibitory pathways, including anti-PDL1 (programmed death ligand 1) and anti-PD1 (programmed cell death protein 1) are examples of this class. Unlike conventional therapies, the agents are not necessarily directed to the tumor cells; instead, they block signals within the tumor microenvironment that inhibit T cell function.

Adoptive cellular therapies are another class of immunotherapy. For these therapies, a patient's T cells are removed from circulation and expanded *ex vivo* in the presence of a tumor antigen [33], then re-infused into the patient. This allows any existing anti-tumor T cells to divide, amplify, and affinity mature*. The result is a super-charged population of T cells that are ready to attack any cells that express the antigen. Adoptive therapies may have been the first and may possibly still be the only truly personalized cancer therapy; T cell expansion can be performed in the presence of tumor material obtained from a patient's biopsy, or by using a synthetic antigen identified by genomic or proteomic interrogation of a biopsy sample.

A third class combines adoptive cellular therapy with cellular engineering to target cancer cells that express a shared tumor antigen**. During the *ex vivo* expansion step of adoptive cellular therapy, a patient's T cell receptors (TCR) are modified to express a high-affinity T cell receptor or Chimeric Antigen Receptors (CARs) that are specific to a shared tumor antigen. For CAR T cells, the TCR is replaced with a modified B cell receptor that recognizes a tumor-specific antigen. The CARs and TCRs used in these approaches can be obtained from unrelated individuals, including healthy individuals, whose immune cells have been observed in the laboratory to recognize a tumor. Because they recognize shared antigens, a CAR identified for one patient can be used to engineer CAR T cells for unrelated patients.

**Editor's Note: Affinity maturation is accomplished by starting with T cells that harbor a receptor that recognizes a target antigen to some degree and systematically mutating it to increase avidity.*

***Editor's Note: A shared tumor antigen is one that is present in a significant number of patients' tumors.*

How does your laboratory research fit into these immunotherapy approaches?

Our role is to identify target antigens that can be used for adoptive T cell therapy approaches with or without engineered T cells. Most tumors have antigens that are the products of mutated genes, which are identifiable through conventional exome sequencing. To be practical for therapy, the mutated gene must give rise to a product that is processed by the proteasome, presented on the surface of cancer cells, and recognized by T cells. Most mutated genes do not meet these criteria. Also, mutations are rarely shared between patients, so they are useful only for precision approaches and are not yet viable candidates for engineered therapies. This means each patient would require a unique T cell immunotherapy. We are testing approaches to rapidly identify large numbers of polypeptides that are highly immunogenic and expected to be shared in most tumors. The ultimate goal is to find an immunogenic polypeptide that is shared by multiple tumor types so that a single therapy would be efficient for all, or many, people.

Which tumor types are you studying?

We have done most of our work in ovarian tumors and cell lines, but we also reproduce all experiments using pancreatic and lung tumors and cell lines to ensure that what we are seeing is not idiosyncratic to a single cancer type. We also conduct extensive mining of public data sources that profile normal tissues, specifically the

Genotype-Tissue Expression ([GTEx](#) [34]) project, to ensure that we are identifying tumor-specific variants.

How can immunotherapy approaches be tailored to each patient?

Antigens that are expressed uniquely in each patient's tumor can be used to generate personalized adoptive cellular therapies. Additionally, each patient is thought to have different combinations of immune-suppressive factors that inhibit T cell function, and these same factors can also inhibit engineered T cells. Identifying immune-suppressive factors in tumors is a necessary part of our effort, but we rely heavily on our collaborators within the Fred Hutch who are doing the leading work here. We can identify factors that may be at play, but the immune system is complex and dynamic. Predicting the outcome of circumventing any apparent barrier has not been solved at this time. In principle, with the large and growing number of FDA-approved immune-modulatory agents, one can imagine using a unique combination of drugs to steer each patient's tumor away from its immune-suppressive state.

What do you perceive as the key advantages of immunotherapy?

One is that T cells are self-renewing and non-limiting. Thus, once tumor-specific T cells are established they can survive for years and fight off the tumor if it recurs. From a personal perspective, what drew me to this area is the time frame for making an impact. For conventional therapy, the time frame from identifying a target to testing in humans is long and reliant on factors entirely out of the control of a researcher, such as investment by pharmaceutical companies. In contrast, our institute and our collaborators' institute, the University of Texas MD Anderson Cancer Center, have in-house facilities to develop adoptive T cell therapies. These are most often used in patients who have failed all other therapies, so time is of the essence. For example, we are piloting work with a collaborator at MD Anderson (Dr. Cassian Yee) to determine whether we can rapidly and consistently identify immunogenic polypeptides and use them for immunotherapies. We will first test these antigens in human immune cells *in vivo*, of course, and if the results are promising, Dr. Yee could use the antigens we identify to treat very ill patients. It is very motivating and rewarding to know that what we do today could possibly impact patient care in a time frame that one can see.

What are the shortcomings of immunotherapy approaches?

I see two shortcomings that I think can be overcome. One is that tumors evolve with treatment and they can simply adopt different mechanisms to evade the immune system. The other is that T cells are self-renewing and non-limiting; I noted this as an advantage, but it is also a disadvantage because if the T cells used for therapy recognize healthy cells, they can attack and damage healthy organs. Mechanisms to cope with these obstacles are currently being tested.

How has being involved in the CTD² Network affected your lab's experimental scope and design?

The CTD² Network defined "Tiers" to describe the extent to which CTD²-generated results have been validated. The Tiers start with *in vitro* observations and advance to *in vivo* confirmation. We changed our approach to follow the principle of the Tiers

more closely.

Other influential aspects of CTD² are the diverse research focuses of the Network and the collaborations that merge these different areas of research. Many CTD² researchers use functional biology approaches to identify critical molecules or pathways in cancer cells and therapeutic agents to target them. In developing these as potential therapies, one consideration is, how can we deliver those agents specifically to cancer cells? What I recognized is that the part of our CAR T cell identification efforts could be used to assist with the problem of drug delivery, which may often require targeting a receptor on the surface of cancer cells to help internalize the drug. To do this, we have made our approach more general by focusing on more than just T cell targets and considering all surface antigens. I think there are many valuable resources generated by CTD², like data and methods, but the real value of the Network lies in the less tangible aspects, like shared ideas and collaborations. I have learned a great deal from the Network. The group meetings are dynamic. I leave every group meeting with new ideas that we incorporate into our effort. I think members from other Centers feel the same way.

Stay tuned for the next installment of "From the bench to the clinic part II" in our eNewsletter.

To learn more about Dr. McIntosh's research, visit the [Fred Hutchinson Cancer Research Center \(2\) CTD² Center description](#) ^[35]n. Visit the [National Cancer Institute's website](#) ^[36]_[36] to read more about immunotherapy.

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FEATURED RESEARCHERS

From the Bench to the Clinic Part 2: Edus "Hootie" Warren Provides Perspective on the Clinical Impact and Potential of Immunotherapy

Edited by Nadia Jaber and Jessica Mazerik



Edus Warren MD, Ph.D.

Immunotherapy is a promising approach to cancer treatment. The field of immunotherapy is rapidly advancing and genomics techniques are being incorporated to add a "precision" approach. OCG spoke with two CTD² investigators at the Fred Hutchinson Cancer Research Center about different immunotherapy approaches and new advances. For the second part of this two-part series, Edus "Hootie" Warren, M.D., Ph.D., Member, Program in Immunology, Clinical Research Division, provides a clinical perspective of immunotherapy.

What immunotherapy approaches does your laboratory study?

Most tumors express antigens that can be recognized by the immune system. However, tumors learn to evade or disable the immune system in order to grow. One way they do this is through exploitation of immune checkpoint pathways, and blocking these pathways is an effective immunotherapy approach. One of the major foci right now in the lab is studying the mechanisms of tumor regression in patients who are treated with immune checkpoint inhibitors. We want to know which immune responses are important in eliminating tumors, so perhaps we can make it happen more often in other patients who do not experience the same positive outcome. We do molecular analysis of T and B cells from patients who are treated with immune checkpoint inhibitors. For those that have responded, we want to know, what antigens on the tumor cells are recognized to enable tumor elimination? For patients that do not respond, we want to know why an effective anti-tumor response did not occur, if there was a response that proved inadequate, if the tumor mutated to evade the immune response, or all of the above.

How do immune checkpoint inhibitors initiate tumor regression?

There is speculation, and now an increasing body of evidence suggesting, that regression occurs because the immune checkpoint inhibitors rejuvenate an immune response directed at neoantigens ^[37] expressed by the tumor cells. There is a lot of exciting research aimed at trying to strengthen the rejuvenated immune response to these neoantigens.

Is there any evidence that memory T cells are induced by immunotherapy and can prevent cancer recurrence?

Researchers have engineered highly potent CAR-T ^[37] cells against CD19, an antigen that is expressed on normal B cells and a large fraction of B cell lymphomas and B cell cancers. These CAR-T cells have been used as an immunotherapy approach in patients with CD19-positive malignancies, and it is clear that the persistence of the CAR-T cells is very closely correlated with freedom from relapse. The converse observation is also quite frequent: patients are more likely to relapse when the CAR-T cells disappear.

What causes CAR-T cells to not persist?

There are many different explanations. Sometimes the CAR-T cells are genetically engineered with synthetic molecules that contain murine amino acid sequences, so they can trigger a host immune response against them. Sometimes the lack of persistence is due to the fact that the T cells get exhausted, meaning they lose the ability to keep proliferating. Immune checkpoint pathways can also get activated and block the CAR-T cells. One very active area of research right now is combining CD19 CAR-T cells with immune checkpoint inhibitors as a treatment method for lymphoma.

Can traditional treatments like chemotherapy or targeted therapies be combined with immunotherapy?

Synergy between conventional cytotoxic chemotherapy and immunotherapy is quite

likely, and there is already good evidence for it. A very important principle of immunotherapy is that it works best when the tumor burden is low. Combining conventional chemotherapy that can reduce the tumor burden by 90-99%, with an immunotherapy component which can mop up the last 1-10%, could lead to complete tumor elimination.

Why are certain cancer types less sensitive to immunotherapy?

Ovarian cancer and pancreatic cancer are far less sensitive to immunotherapy than other tumor types. It is thought that in pancreatic cancer, part of the problem is that immune cells don't have good access to the tumor because it is embedded in a dense stroma. If we could modify the vasculature and improve the infiltration of immune cells, immunotherapy approaches would probably be more effective. That is being actively explored in both preclinical and clinical settings. Ovarian cancers tend to have more copy number alterations and whole scale losses of genomic regions, and so they may evade the immune system by losing expression of molecules that are required for T cell or CAR-T cell recognition. However, with so much exciting research going on in this area, one of the great hopes is that we will learn how to develop effective immunotherapy for these refractory tumor types.

Are there any other areas of immunotherapy that are up-and-coming?

Although I do not have any direct involvement with it, I think an exciting new area is oncolytic viruses. One can engineer a virus in the following ways: (1) change the cellular tropism* so that viruses are more likely to infect cancer cells than normal cells; (2) take out the normal viral genes and add genes encoding immune stimulators. It's kind of like a Trojan horse design. When these oncolytic viruses are used as therapy, virus particles associate with and preferentially infect tumor cells. Then the immune-stimulating genes get transcribed and translated, and the resulting proteins recruit immune cells which contribute to tumor elimination. Some tumor death also comes from viral infection and lytic viral replication. A group at Duke University has developed an oncolytic virus for the most lethal form of brain cancer, called glioblastoma, and last year the US Food and Drug Administration (FDA) approved an oncolytic virus for the treatment of melanoma.

*Editor's note: Tropism refers to modification of the virus to preferentially infect tumor cells.

What do you think makes immunotherapy so impressive?

I think immunotherapy is impressive because, although it still only works in a minority of patients, some patients achieve durable (*i.e.* we hope permanent) elimination of otherwise very chemotherapy-refractive tumors. For example, one of the patients we are studying with our CTD² project had end-stage metastatic lung cancer, and achieved a virtually miraculous complete remission with a combination of radiation and immunotherapy. That kind of response is not very common in any treatment setting, so when it does occur it's very noteworthy. I've been a practicing oncologist for 23 years and immunotherapy is transforming the practice of oncology. It is one of the biggest advances, in addition to the development of targeted small molecule therapies. There are now FDA-approved immune checkpoint therapeutics for the treatment of melanoma, kidney cancer, non-small cell lung cancer, bladder

cancer, Hodgkin lymphoma, and likely very soon, head and neck cancer, as well as a very rare but incredibly refractory skin cancer called Merkel cell carcinoma. And the sky is the limit; this is just the beginning.

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