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OCG PERSPECTIVE

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PEDIATRIC CANCER RESEARCH

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Molecular Signatures as Potentially Effective Screening Tools in the Prognosis and Treatment of Pediatric Acute Lymphoblastic Leukemia (ALL)

Dr. Richard Harvey, a TARGET investigator studying high-risk acute lymphoblastic leukemia, is a research professor in the Department of Pathology at the University of New Mexico's School of Medicine.

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Targeted Cancer Therapies: Molecular Insight Driving a New Generation of Drugs

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EXPLORING CANCER GENOMES

Open-Access Cancer Genomics Tools: the UCSC Cancer Genomics Browser

The completion of the Human Genome Project sparked a revolution in high-throughput genomics applied towards deciphering genetically complex diseases, like cancer. Now, almost 10 years later, we have a mountain of genomics data on many different cancer types and subtypes that is rapidly expanding.

OCG PERSPECTIVE

Using Genomics to Accelerate Science into the Clinic: Reflections on the American Association of Cancer Research (AACR) Annual Meeting 2012

Jaime M. Guidry Auvil, Ph.D.

April Fools' Day ironically found me among some of the most brilliant minds in cancer research and medicine while attending the American Association of Cancer Research (AACR) Annual Meeting 2012 in beautiful downtown Chicago. The theme of this year's gathering was "Accelerating Science: Concept to Clinic" with a special focus on the integration of basic, clinical and translational research that is driving discovery in the oncology field. For those unfamiliar with the AACR conference, roughly 16,000 investigators across a wide variety of disciplines in academia, government and industry come together to network and learn from their colleagues. Advances from all spectrums of cancer research are highlighted through daily plenary sessions, major and mini-symposia, forums, educational sessions, methods workshops, and poster sessions.

I attended the AACR conference primarily to chair and speak at an "NCI/NIH-sponsored" session on one of the Office of Cancer Genomics' (OCG) [2] pediatric cancer initiatives, Therapeutically Applicable Research to Generate Effective Treatments (TARGET) [3]Opens in a New Tab. These sessions are endorsed by the National Institutes of Health (NIH) and serve to provide conference attendees with information on a variety of topics that are central to the mission of the National Cancer Institute (NCI) and NIH as a whole. TARGET is a comprehensive molecular characterization initiative to identify genes that drive the development and progression of the most prevalent childhood cancers. Further, TARGET seeks to rapidly advance those discoveries toward targeted therapies in the clinic. The TARGET session at the AACR Annual Meeting served to both inform investigators about the genomic data this ground-breaking initiative is producing as well as how to access it through NIH databases.

The TARGET session began with a general overview of the initiative, its history and goals, followed by individual project team reviews. Team leaders representing each of the 5 major disease groups studied in TARGET provided a description of their project, the progress made to date, challenges resolved and the lessons learned, as well as ongoing and future data generation and analysis. A detailed outline of the mechanics to access TARGET genomics data stored in NCIOpens in a New Tab [4] and NCBIOpens in a New Tab [5] databases was presented for the research community. The session concluded with presentations describing specific protocols for obtaining these datasets, their location, and the process of applying for access to protected data.

In attending other symposia at the AACR conference, one recurrent theme was that successful cancer treatment requires targeting of multiple drivers within a tumor. Cancer is a disease of the genome; therefore understanding the genetic basis of an individual tumor, the principal goal of OCG initiatives, is essential to the formulation of treatments that can be tailored to an individual and translated to improved patient outcomes. Identifying drivers in molecular pathways within a tumor is a critical step to finding better treatments for cancer. By mapping significant driver mutations in various tumor types, genomics research efforts like those of TARGET and other OCG initiatives are laying the groundwork for the development of enhanced cancer therapies.

The wealth of ground-breaking and inspirational findings presented at the AACR Annual Meeting 2012 allowed me to reflect on the importance of genomics in cancer research, various aspects of which are highlighted in this issue (#7) of the OCG e-News [6]. There are several articles relating specifically to TARGET research projects: an interview with Dr. Peter Adamson [7] (the Chair of the Children's Oncology Group; COG) about current issues in pediatric cancer research; a discussion by TARGET investigator, Dr. Paul Meltzer [8], on how genomics research will help reveal the underlying biology of sarcomas and provide an approach to new therapeutic strategies; and an informative review by TARGET investigator, Dr. Richard Harvey [9], on the discovery of molecular signatures as the most effective means of diagnosing a difficult-to-treat subtype of childhood acute lymphoblastic leukemia (ALL). Also in this issue are two inaugural articles, each launching a new educational series for the OCG e-News. One piece discusses the concepts of targeted cancer therapies [10], the first in a collection of articles that seeks to educate a broader audience on various aspects

of cancer genomics research. The second is largely directed towards researchers and presents a brief history of the UCSC Cancer Genome Browser [11] before surveying some of its many useful features. It is part of a specialized e-News series that will explore an array of the freely available web tools designed to visualize, analyze, and integrate various cancer genomics data.

As highlighted in the e-News, OCG initiatives and the collaborators driving them are using genomics research to better define cancer at a molecular level, ultimately contributing to more effective clinical treatments. Attending the AACR conference helped reinforce a key role of large-scale genomics efforts like TARGET in the future of cancer research: the fact that once all tumor types have been sequenced and significant mutations mapped across critical pathways, then therapeutic targeting using existing and/or novel drugs can be properly implemented. I have returned to Bethesda from the Windy City energized and ready to contribute to the OCG mission of improving cancer care.

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PEDIATRIC CANCER RESEARCH

An Interview with Dr. Peter Adamson, the Chair of the Children's Oncology Group

Shannon Behrman, Ph.D.; Malcolm A. Smith, M.D., Ph.D.

Supported in part by the National Cancer Institute (NCI), the Children's Oncology GroupOpens in a New Tab [12] (COG) is the world's largest organization dedicated to pediatric cancer research. Since 1955, the COG has made tremendous advances in reducing pediatric cancer mortality through highly-collaborative translational and clinical research. The Office of Cancer Genomics [2] (OCG) is currently working with COG investigators through the Therapeutically Applicable Research to Generate Effective TreatmentsOpens in a New Tab [3] (TARGET) initiative. For this issue of OCG's e-News, we asked the Chair of COG, Dr. Peter Adamson, to comment on the current status of pediatric cancer research and what COG is doing to build upon its successes over the last 50 years in childhood cancer cure rates.

About Dr. Peter Adamson

Aside from his COG Chair responsibilities, Dr. Peter Adamson is a pediatric oncologist and investigator at the Children's Hospital of Philadelphia (CHOP). Dr. Adamson currently heads a clinical pharmacology laboratory at CHOP that seeks to find new drugs for childhood cancers using pre-clinical and early-phase clinical trial research. Prior to his election to COG Chair in 2011, he served as the Director of the Office for Clinical and Translational Research and Chief of the Division of Clinical Pharmacology and Therapeutics at CHOP. Dr. Adamson received an M.D. from Cornell University Medical College before he received his pediatric oncology training, as well as his research training in drug development and clinical pharmacology, at the NCI. Read his interview below.

Can you describe the childhood cancer clinical trial process and how it compares to the adult cancer process?

What is distinctive about pediatric oncology is that the large majority of children with cancer participate in clinical research. Over 60 percent of children who are newly-diagnosed with cancer will enroll in a clinical trial, in contrast to only 2-3 percent of newly-diagnosed adults. Pediatric oncology is a unique subspecialty where close partnerships with children and their families go hand-in-hand with clinical practice and research.

Despite its widely collaborative approach to clinical trials research, the COG faces many specific challenges. To begin, childhood cancers occur infrequently when compared to adult cancers, so they are considered to be rare tumors. Furthermore, the majority of childhood cancers are curable, leaving a small population of children with cancers that are resistant to treatment and who are appropriate for early phase clinical trials of novel agents. The low frequency of these particularly serious cancers makes studying them especially difficult, despite needing the greatest improvements in outcome.

Phase III trials are largely available to most newly-diagnosed patients. However, with few exceptions, Phase I and II trials primarily enlist children with relapsed or resistant cancers. The cooperative infrastructure of the COG allows us to maximize our ability to conduct these studies, but small cohorts remain a challenge.

Additionally, drug companies develop novel drugs almost exclusively for adult rather than childhood cancers, which is an understandable market-based decision. We get around this limitation by using adult clinical trials to inform the design of pediatric trials. Even though drugs behave differently in children than adults, we can learn from adult Phase I trials which new drugs have the most potential to be efficacious in treating childhood cancers as well. Of note, developing appropriate dosages for children of various sizes and stages of development is not a trivial task. Growth and development of children have considerable impact on the clinical pharmacology of a drug, how we dose that drug and what interactions we might see.

There are many shared challenges among pediatric and adult cancer research, especially in Phase II clinical trials. In general, we study new drugs in patients whose tumors have recurred and are, therefore, more likely to be resistant to multiple forms of therapy. In treating these cancers, some drugs may be efficacious only when combined with other cytotoxic drugs or other targeted agents, making the design of those trials much more difficult.

Are targeted therapies having an impact on treating pediatric cancers?

Imatinib (Gleevec) has made a dramatic impact on the outcome of children with Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL), but we are still evaluating the efficacy of most targeted therapies in the pediatric population, particularly in the Phase I/II trial stage. Consequently, it’s too early to know if others will significantly reduce mortality, but I do think there will be subsets of patients that will benefit.

How does COG work with TARGET and other genomics research programs to

fulfill its mission?

Programs like TARGET are accelerating our ability to hone our clinical trial decisions and prioritize new therapeutic agents in the treatment of certain pediatric cancers. COG is so tightly integrated with TARGET that any new discoveries are quickly translated into clinical trials. The most recent advances include the identification of a subpopulation of ALL patients with mutations in the Janus kinase (JAK) pathway, where JAK inhibitors may prove successful in treating that disease. When the JAK story broke from TARGET, COG was well-positioned to rapidly begin pediatric Phase I testing of the first JAK inhibitor already available in the clinic for adult cancers. TARGET research is helping to define both biologically compelling and druggable targets.

Genomics research has proven useful in understanding, classifying and treating many cancers, but now we are finding many genomic alterations don't lead to obvious treatments (either no known drugs are available or they don't provide a straightforward targeting strategy). How is COG addressing this issue?

We do not have a magical solution. Fortunately, the prevalence of mutation in many pediatric cancers (especially those arising early in development) is low, making development of targeted agents against childhood cancers easier than in adult cancers, where the mutation rate is usually high. However, there are some childhood cancers, such as osteosarcoma, with very complicated genomic abnormalities, and therapeutic targeting is therefore more complicated. Despite this hurdle, we think there is likely to be continued value in these genomic studies. Some insights and discoveries that emerge from childhood cancer research are applicable in the adult population. The classic example is retinoblastoma and the Rb gene. Aside from its involvement in an extremely rare childhood cancer, we now know it also plays a role in the malignant transformation of a number of adult cancers.

Genomic research is uncovering the immense molecular complexities of cancer, sub-dividing each cancer type into ever smaller subtypes. How is the discovery of smaller molecular subtypes affecting clinical outcomes and the projected rate of decline of pediatric cancer mortality? What is COG doing to address this challenge in the design of its clinical trials research?

In order to make advances, we must balance the need for improved efficiency with the potential for risk to the patient. Our strategy is to have platforms and protocols that allow for continuous evaluation of novel therapeutics. To that end, we are comparing the efficacy of new targeted therapies in combination with standard cytotoxic drugs to that of standard drugs alone. So, in evaluating treatment of a number of relapsed cancers, we begin with the standard cytotoxic "backbone" of chemotherapies and then integrate a range of targeted agents either in a randomized or sequential fashion. We keep these backbone studies open and ongoing, so that whenever a new targeted therapy arises, we are ready to implement it into a clinical trial. This trial design gives us the flexibility to evaluate different types of agents as quickly as possible for their effect on clinical outcome.

We are also beginning to look at approaches that others have taken with adult cancers. One good example is I-SPY 2 (investigation of serial studies to predict

therapeutic response with imaging and molecular analysis) and its application of the Bayesian predictive probability model. The goal of the I-SPY 2 trial is to improve the efficiency in identifying better treatments for patient subpopulations using distinct molecular signatures.

What factors contributed to the success in greatly reducing pediatric cancer mortality over the last 50 years? And, what is COG focusing on now to continue to reduce pediatric cancer mortality, despite the recent plateau in improvement?

The fundamental factors contributing to our success are collaboration and the importance of research. Fifty years ago, the predecessors of the COG set the stage for the field of pediatric oncology by developing a cooperative group system, where a culture of collaborative research flourished. Now, most children diagnosed with cancer today are offered an opportunity to participate in research.

The drugs that we use now to treat most cancers cure approximately 4 out of 5 children. However, most of these drugs were approved in the 1950s – 1970s. We've learned how to use these chemotherapies better over time, but I think we've gotten as much mileage as we can from them. Now, there is a pressing need to develop novel therapeutics. COG is moving in this direction by studying the biology of tumors and linking that to outcome. At COG sites, we see about 90 percent of newly-diagnosed children in the US. So, in a population-based way, we have an opportunity to capture the biology and outcome through well-annotated clinical biospecimens for every cancer – even rare or relapsed cancers or cancers refractory to current treatment. We are putting our greatest investment into researching the population of tumors in children where current treatments have not proven curative. Through well-annotated biospecimens and translational research of hard-to-treat cancers, we are setting the stage for the next era of discovery.

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FEATURED RESEARCHERS

Sarcomas: An Ongoing Challenge in Pediatric Oncology

Paul Meltzer, M.D., Ph.D.

Dr. Paul Meltzer researches sarcomas and other cancers as Senior Investigator and Chief of the Genetics Branch in the Center for Cancer Research at the National Cancer Institute. As a TARGET investigator, Dr. Meltzer uses genomics analyses to study a type of sarcoma called osteosarcoma.

Pediatricians understand that children are not little adults. This is apparent across a range of medical fields, including pediatric oncology. Fortunately, cancers are rare in the pediatric population. When they do occur, the majority are quite different from the common cancers of adults. Brain tumors, Wilms tumors, neuroblastomasOpens in a New Tab [13] and sarcomasOpens in a New Tab [14] are the dominant types of solid tumorsOpens in a New Tab [15] (as opposed to blood cancers) diagnosed in pediatric

patients. Sarcomas are tumors of the connective tissues of the body such as muscle or bone. Sarcomas that typically manifest in children include rhabdomyosarcoma (related to muscle), osteosarcoma (related to bone), and Ewing's sarcoma, a mysterious tumor possibly derived from early connective tissue stem cells. In addition to these three, there are numerous other tumors occurring at an even lower frequency. Although there is some variation, the majority of pediatric sarcomas are aggressive tumors which call for intense multimodality therapy including surgery, radiation and chemotherapy. While these rigorous treatments are often helpful and can be curative, many pediatric sarcoma patients cannot be cured with current approaches. Progress in improving outcomes for this difficult group of tumors remains an important priority for pediatric cancer research.

Researchers studying these diseases are examining sarcoma tumor genomesOpens in a New Tab [16] in hopes of finding keys to unlock their underlying biology and open new possibilities for treatment. Previous research has shown that sarcomas (both adult and pediatric) broadly fall into two categories based on the degree and types of abnormalities in their genomes. The first category, exemplified by Ewing's sarcoma and alveolar rhabdomyosarcoma, contains specific fusion genesOpens in a New Tab [17] composed of segments from two genes which have been juxtaposed by a chromosome translocationOpens in a New Tab [18]. Often these are transcription factors which are thought to drive tumor growth by disturbing the normal pattern of gene expression. Dozens of fusion genes are known in various sarcomas, and new ones are discovered with some regularity. The second category of sarcomas, exemplified by osteosarcoma, lacks fusion genes and typically has a highly rearranged genome with many structural and numerical changes distributed across the genome. This category also tends to occur in older patients and contain mutationsOpens in a New Tab [19] in the tumor suppressor gene TP53Opens in a New Tab [20].

The ability to profile genome structure and function through the advent of powerful new sequencing technologies and microarrayOpens in a New Tab [21] methods has opened up the possibility of providing a truly comprehensive description of the sarcoma genome. There are a number of specific questions which investigators hope to answer using this modern approach. For example, do translocation-bearing sarcomas carry additional mutations which contribute to tumor growth? What mutations occur in genetically complex tumors, such as osteosarcoma? Are there recurrent mutations in genes or pathways which will reveal the mechanisms of tumor formation? It is hoped that addressing these questions could lead directly to new treatments for sarcomas. Supporting this notion, previous research revealed that most adults with the sarcoma gastrointestinal stromal tumor (GIST) have tumors with activating mutations in one of the receptor tyrosine kinasesOpens in a New Tab [22], KIT or PDGFRA. By targeting these kinases with therapies in the appropriate individuals, survival rates have significantly increased for GIST patients. Additionally, activating mutations in the growth factor receptor FGFR4 were recently discovered in some cases of rhabdomyosarcoma. This raises the possibility of developing novel therapies for patients with this disease, as therapeutic strategies targeting this receptor are currently being explored. Even in the absence of identified targets, such as growth factor receptors, describing sarcoma genomes will provide a firm basis for future research on these diseases.

At this time, large-scale sequencing projects are underway for the pediatric sarcomas: rhabdomyosarcoma, Ewing's sarcoma and osteosarcoma. Under the Therapeutically Applicable Research to Generate Effective TreatmentsOpens in a New Tab [3] (TARGET) initiative, osteosarcoma is being intensively investigated. In addition to sequencing tumor genomes and transcriptomes, investigators are also studying the pattern of gene copy number alterations, the status of DNA methylationOpens in a New Tab [23], and the expression of micro-RNAs in the tumor genome. Interestingly, alterations in micro-RNAs, a fascinating new class of small RNAs which regulate the expression of protein-coding genes, are emerging as important regulators of tumor biology in cancers, including osteosarcoma. Taken together, the various genomics methods of the TARGET initiative will build on the understanding of how gene expression is altered in osteosarcoma and how it contributes to tumor development. The results of these studies will fill critical gaps in our knowledge and are sure to alter thinking about the best way to approach the development of new treatments not just for osteosarcomas, but for other pediatric sarcomas as well.

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TARGET PROGRAM HIGHLIGHTS

Molecular Signatures as Potentially Effective Screening Tools in the Prognosis and Treatment of Pediatric Acute Lymphoblastic Leukemia (ALL)

Richard Harvey, Ph.D.

Dr. Richard Harvey, a TARGET investigator studying high-risk acute lymphoblastic leukemia, is a research professor in the Department of Pathology at the University of New Mexico's School of Medicine.

The seminal discovery in 1960 of the Philadelphia chromosomeOpens in a New Tab [24] (Ph+) in chronic myelogenous leukemia was a catalyst for decades of research that has resulted in the discovery of hundreds of unique genomic alterations in human cancer. In Ph+ patients with the tumor-specific *BCR-ABL1* fusion product, the aberrant expression of the fused Abl tyrosine kinase has proven to be an initiating genomic event in the development of leukemia.[1] Similar gene perturbations, whether by deregulation or modification (e.g., rearrangement, alternative splicing or mutation), have subsequently been shown to be recurring events in many leukemias.[2] Successful therapies directed against these initiating genomic events (such as the tyrosine kinase inhibitor, imatinib, for *BCR-ABL1*) have begun to refocus the field from simply identifying genomic alterations as potential screening tools, to understanding their functional consequences and applying appropriate targeted therapies [10]. In parallel with developing these new therapies, it remains crucial that we continue to focus our efforts on identifying effective diagnostic markers. Predicting an accurate prognosisOpens in a New Tab [25] and assigning an appropriate treatment regimen through diagnostic screening tools can reduce both the burden of uncertainty and cost in cancer management. Together,

diagnostic markers and targeted therapies will help to revolutionize cancer outcomes.

As part of the Therapeutically Applicable Research to Generate Effective Treatments (TARGET)Opens in a New Tab [3] high-risk acute lymphoblastic leukemiaOpens in a New Tab [26] (ALL) project, our research group seeks to cure pediatric high-risk ALL by employing and integrating a variety of molecular approaches. Our initial gene chip analysis in these patients revealed clearly distinct signatures of gene expressionOpens in a New Tab [27], several of which were characteristic of previously identified chromosomal translocationsOpens in a New Tab [18] (e.g., *TCF3-PBX1*, *MLL*, *ETV6-RUNX1*). We also observed a novel signature comprised of a group of highly expressed genes that had previously been identified as overexpressed in many Ph+ ALL patients.[3] Curiously, none of the patients in our high-risk ALL patient cohort harbored the Ph+ translocation, yet patients with this signature had a similarly poor prognosis. Concurrent with the expression analysis, our colleagues in this project performed a detailed analysis of the DNA in these patients and found they also exhibited deletions within the *IKZF1* gene, another hallmark of ALL patients with Ph+ translocations.[4] Because of the extensive molecular similarities with Ph+ patients, we refer to this group of ALL patients as Philadelphia chromosome-like, or “Ph-like.”

With these results in hand, we performed more in depth genomic analysis of the Ph-like ALL patients in order to uncover the inherent biology and to identify, if possible, candidate therapeutic targets. Our analysis revealed that this subset of patients had an overall similar gene expression signature, yet was comprised of numerous subgroups with different underlying genomic features. Approximately half of the Ph-like patients harbor a cryptic translocation or rearrangement of the type I cytokine receptor subunit gene (*CRLF2*), with about half of these *CRLF2* subtypes also harboring activating mutations of *JAK1* or *JAK2* tyrosine kinasesOpens in a New Tab [22].[5] Most recently, sequencing of RNA and DNA from a dozen of these Ph-like cases has shown that essentially all of them have cryptic translocations involving tyrosine kinases (*ABL1*, *JAK2*), tyrosine kinase receptors (*PDGFRB*), cytokine receptors (*CRLF2*, *EPOR*) and/or deletions involving *IKZF1* and mutations of *JAK2*.[6] Recurrence testing is ongoing to determine the relative frequency of each of these other translocations, however it is quite apparent that the vast majority of the Ph-like cases share a common underlying theme of tyrosine kinase gene/pathway deregulation.

Despite the absence of the *BCR-ABL1* fusion, the repeated involvement of tyrosine kinase genes in Ph-like cases (including other translocations of *ABL1* itself) strongly suggest they will be amenable to similar therapeutic approaches targeting their aberrant tyrosine kinase pathways. As mentioned previously, adding the kinase inhibitor, imatinib, to an intensive chemotherapy regimen in children with Ph+ ALL dramatically improved their outcomes.[7] Recently, we have begun pre-clinical studies using xenograftOpens in a New Tab [28] mouse models that mimic a variety of Ph-like cases in an effort to identify therapeutic agents that might be effective in patients with the Ph-like signature. In parallel with these studies, we continue to focus on developing and improving screening methods to identify these patients at the time of diagnosis. Although their full characterization required gene expression, copy number analysis, cytogenetic analysis and sequencing, identification of the Ph-like gene expression signature alone appears to be sufficient as an initial first

screening.[8] Because the core of the signature is comprised of just a couple of dozen genes, it is quite amenable to rapid and relatively inexpensive clinical platforms for quantitative gene expression analysis. Subsequent characterization of the exact underlying lesions, if necessary, will likely require additional targeted sequencing or PCR analysis.

Through collaborative and integrated molecular evaluations of gene expression, mutations, copy number alterations, functional analysis and related methods, we have found that many of the high-risk pediatric ALL patients with the poorest outcome share perturbations of common pathways. It is imperative that we quickly translate this information into the clinic for the benefit of all patients that suffer from this disease. It is now possible to rapidly identify patients with the Ph-like signature at the time of diagnosis and stratify them into appropriate therapeutic regimens targeted for their particular underlying lesions. The general perturbation of common tyrosine kinase pathways in these patients is encouraging from a therapeutic perspective. Rather than having to target tumor-specific events (such as fusion genes) individually, it bodes well for targeting therapy towards a common aberrant pathway across these poor-outcome leukemias.

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EDUCATIONAL SERIES

Targeted Cancer Therapies: Molecular Insight Driving a New Generation of Drugs

Shannon Behrman, Ph.D.

In the context of finding new and improved cancer treatments, cancer genomics researchers often talk about identifying “molecular targets” and developing “targeted therapies”, but what exactly do these terms mean? In this article, we explore these concepts and reveal how they are transforming the way we treat cancer. This article is the first installment of a series of educational pieces that will explore various aspects of cancer genomicsOpens in a New Tab [29] research.

In the 1940s and 1950s, patients had little chance of surviving cancer even with early advancements in surgical and radiation therapies. Frustrated with continually fighting a losing battle, physicians decided to take an entirely different approach to treatment: chemotherapyOpens in a New Tab [30]. They knew very little about the disease and its origins, except that cancer cells divide faster than their normal counterparts. Armed with this observation, physicians tested the efficacy of a variety of toxic compounds (ones that generally target rapidly dividing cells) in treating different types of cancers in human patients. This empirical approach to medicine ultimately proved quite successful and, consequently, many of these compounds were approved for clinical use. Today, these drugs or their derivatives remain part of the standard chemotherapy regimen used to treat most cancers.

Chemotherapies have dramatically reduced cancer deaths over the last 50 years. However, the need for novel, more effective drug therapies is imminent. Chemotherapies are poisons by nature and work by indiscriminately killing *all* rapidly dividing cells, including both cancer and normal cells. Consequently, they are very harmful to the human body and can produce lasting adverse side effects. Furthermore, many of the improvements to the survival rates of certain cancers are starting to plateau. In 1975, acute lymphoblastic leukemiaOpens in a New Tab [26] (ALL) patients under the age of 65 had a 43% 5-year survival rate. Now, the 5-year survival rate is ~70%, where it has hovered since 1996. More than 1 out of every 4 ALL patients die within 5 years of their initial diagnosis, and current therapies have not shown significant progress in recent years. As Dr. Peter Adamson, Chair of the Children’s Oncology Group, stated in this issue’s interview, “We’ve learned how to use these chemotherapies better over time, but I think we’ve gotten as much mileage as we can from them.”

As our knowledge of the underlying biology of cancer expands, investigators are discovering novel ways to specifically target cancer cells with minimal damage to healthy tissue. Research since the 1960s has generated enormous insight into the genetic origin and molecular biology of cancer. Thanks to seminal work from Drs. Michael Bishop, Harold Varmus, and others, we know that cancer is caused by changes in our own genes. Genes produce molecules that participate in a wide array of cellular processes that are tightly controlled in normal cells, such as cell growth and survival. In cancer cells, however, changes (e.g. mutations) in genes that play a

key role in cell growth and survival disrupt the normal function and regulation of these processes. The result is the uncontrolled growth of cancer cells at the expense of normal cells. By targeting the rogue molecules born from these genetic changes, investigators ascertained they could interfere with their tumor-promoting activity and effectively stop tumor growth. Drugs that are designed to selectively bind to these vulnerable “molecular targets” and stop their cancer-causing activity are called “targeted therapies.” Because targeted therapies preferentially block the growth of cancer cells over normal cells, they are more effective and less toxic than standard chemotherapies.

Most targeted therapies come in one of two forms: monoclonal antibodies or small-molecule inhibitors. Unable to cross the cell membrane barrier, monoclonal antibodies bind molecular targets outside the cancer cell (e.g. growth factors) or on the cell surface (e.g. growth factor receptors). They block their target’s activity by providing a physical obstruction, delivering a toxin or radioactive molecular “bomb,” or flagging the attention of the immune system. More diminutive in size, small-molecule inhibitors can pass through cell membranes and target molecules inside the cancer cell as well as on the cell surface. They wedge themselves into the structures of their targets, such as enzymesOpens in a New Tab [31], ultimately inhibiting its activity.

Identifying a “good” molecular target is crucial in developing a successful targeted therapy. Rather than using a classical genetics approach to look for candidate targets one gene at a time, investigators are employing modern genomicsOpens in a New Tab [29] methods (as well as other “-omics”) to view hundreds or thousands of genes all at once. Thus, modern genomics is akin to the invention of electricity. Instead of using a gas lamp to find a set of lost keys in a house, you are now able to illuminate most of the house by turning on the overhead lights. An example of a common high-throughput genomics approach is DNA sequencing. Investigators use sequencing to read the complete genetic code, or genome, of tumors. Applying careful computational analyses, investigators compare the genomes of tumors to those of normal tissue in order to identify mutations that are unique to the tumors studied. Because not all mutations have functional consequences, investigators separate the wheat from the chaff through a series of experiments that help reveal whether the mutations contribute to the initiation, progression and/or metastasis of tumors. If a molecular change resulting from a mutation demonstrates functional ties to tumor biology, then it may prove useful in detecting and treating the disease. In other words, it may constitute a “good” target. One classic example of a good molecular target is the *BCR-ABL1* kinaseOpens in a New Tab [22], which is present in most cases of chronic myelogenous leukemiaOpens in a New Tab [32] (CML). *BCR-ABL1* is a fusion geneOpens in a New Tab [17] that results when two segments of separate chromosomes (chromosomes 9 and 22) abnormally trade places. The resulting *BCR-ABL1* molecule perpetually activates the proliferation of white blood cells, leading to the formation of CML. Researchers developed a kinase inhibitor, imatinib (Gleevec), which targets the *BCR-ABL1* kinase and stops the proliferation of these cancerous cells. The success of imatinib in treating CML patients paved the way for the development of other similar targeted therapies.

As we continue to uncover the immense genetic complexity and heterogeneity of tumors, it is clear there will be no “magic bullet.” However, using the genetic

makeup of hard-to-treat tumors to design targeted therapies signifies progress in the area of cancer research and exemplifies the newly-emerging form of medicine called “precision medicine.” For instance, research demonstrates that a breast cancer patient may have one of many tumor subtypes, each defined by the presence or absence of certain molecular features, such as high levels of the estrogen receptor or the human epidermal growth factor 2 (HER-2). The overabundance of HER-2 promotes the rapid growth of breast cancer cells, and so HER-2-positive patients historically have very poor prognosesOpens in a New Tab [25] even after standard chemotherapy treatment. Fortunately, targeting HER-2 with trastuzumab (Herceptin) has shown tremendous success in treating this disease since its FDA-approval in 1998. Identifying which subtype a breast cancer patient has is, thus, essential in providing the correct therapy.

Rather than relying on the traditional trial-and-error approach to cancer drug development, investigators are using insights into the molecular underpinnings of cancers to develop a new generation of more effective, less toxic drugs. Some FDA-approved targeted therapies, such as imatinib and trastuzumab, have already revolutionized treatment of certain cancers. With many in the clinical trial pipeline, the pool of targeted therapies approved by the FDA is growing. All in all, targeted therapies show great promise in increasing the chance of survival and improving the quality of life for many cancer patients – especially for those where current chemotherapies are inadequate at treating their disease.

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EXPLORING CANCER GENOMES

Open-Access Cancer Genomics Tools: the UCSC Cancer Genomics Browser

Shannon Behrman, Ph.D.

The completion of the Human Genome Project sparked a revolution in high-throughput genomics applied towards deciphering genetically complex diseases, like cancer. Now, almost 10 years later, we have a mountain of genomics data on many different cancer types and subtypes that is rapidly expanding. From gene expression to copy number analysis to DNA sequencing, each type of genomic data helps investigators determine the molecular causes of tumor biology and certain clinical outcomes. How we integrate the data to make it meaningful is a daunting computational challenge in genomics research – one that may be facilitated through the use of visualization. Understanding the power of pictures in data interpretation, several innovative groups of bioinformaticians have designed web-based tools that allow investigators to graphically explore and interact with the different forms of data from various cancer genomics studies (and, some tools even allow users to explore their own data).

In this series of articles, we survey a selection of open-access cancer genomics tools to highlight their genesis, features and utility to the research community. In this first article, we present the University of California, Santa Cruz (UCSC) Cancer Genomics

Browser.

The UCSC Cancer Genomics BrowserOpens in a New Tab [33] was constructed by the group that developed the UCSC Human Genome BrowserOpens in a New Tab [34]. The importance of UCSC scientists in the history of the assembly and public accessibility of human genome sequences cannot be overstated. A consortium led by UCSC scientists assembled the first preliminary rough draft, or “working draft,” of the human genome sequence and published it on the web at https://genome.ucsc.eduOpens in a New Tab [34] in July 2000. Subsequently, it would take three years of refining and filling in the gaps to complete the sequence. Aside from providing the long list of As, Ts, Gs and Cs that comprise the human body, the goal of the UCSC-led team was to aid the progress of biomedical research by creating a browser that visually translates the human genome into relevant and useful information that is searchable.

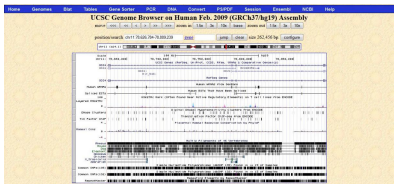

Figure 1Opens in a New Tab [35]

Officially launched in September 2000, the UCSC Human Genome Browser was (and still is) at its core a user-friendly program that displays any part of the genome on multiple scales – from the chromosome down to the DNA sequence. There were only two other publicly available genome browsers developed around that time which facilitated the search and display of the human genome: the European Molecular Biology Laboratory’s Ensembl and the National Center for Biotechnology Information’s MapViewer. The graphical interface of the UCSC Human Genome Browser is dynamic, allowing users to zoom in/out or move along the various levels of the genome (see figure 1Opens in a New Tab [35]). It offers a range of “track” annotations that are stacked vertically to help refine an inquiry about a genomic region. These tracks may be turned on or off in the display and may include links to deeper information about a select region from external databases, such as RefSeq gene predictions and descriptions. One widely used track, the conservation track, aligns a select human genome sequence with annotated genome sequences from other species, both closely and distantly related. The degree of sequence conservation across species provides clues in determining the functional significance of certain genomic elements. All of its features combined, the UCSC Human Genome Browser is a “one-stop-shop” for investigators forming and verifying phenotype-related hypotheses in scientific research.

The UCSC bioinformatics group is dedicated to keeping up with the ever-changing needs of the research community. After more than a decade in operation, the UCSC Genome Browser has undergone several updates, leading to the expansion of its capabilities – the addition of more tracks, more links to databases and more genomes of different species. Part of this drive in evolution spawned a few complementary offshoot web projects, including the UCSC Cancer Genomics Browser.

The UCSC bioinformatics group developed an open-access visual tool, the UCSC Cancer Genomics Browser, to improve medicine by facilitating the ability to link genomic information to cancers. This browser helps investigators find patterns in clinical and genomic data from large-scale genomic studies. The browser includes 25 different cancer type projects, and more will be added when data becomes available. Publicly-available datasets for each project may be comprised of gene expression,

DNA copy number, DNA methylation, miRNA or somatic mutation tracks, along with associated clinical data. For security reasons, it is not currently possible to upload data onto the cancer browser on the web. However, investigators may install the browser locally to access their own data. Contact genome-cancer@soe.ucsc.edu [36] for more information.

Various kinds of projects and datasets are curated and hosted on the UCSC Cancer Genomics BrowserOpens in a New Tab [33]. Take note that the cancer browser supports Firefox, Safari or Chrome web browsers, but not Internet Explorer. For first-time users, there are a number of resources available to help navigate this sophisticated package of tools: a tutorial, a user guide and a FAQ. The authors highly recommend reviewing the tutorial to facilitate the use of the browser. It covers many more of the intricate and customizable features not reviewed in this article.

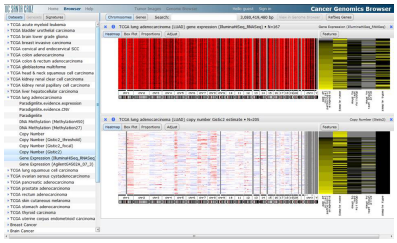

Figure 2Opens in a New Tab [37]

The main “Cancer Genomics Browser” page has a multi-paneled graphical interface that is highly interactive (see figure 2Opens in a New Tab [37]). The panel on the left (for a close-up view, see figure 3Opens in a New Tab [38]) contains a list of all of the projects and corresponding datasets that the user may choose to select for display. The larger panel on the right (for close-up view, see figure 4Opens in a New Tab [39]) displays the genomic and associated clinical datasets as heatmaps (or box plots or proportions), side-by-side, to facilitate comparison. Each row represents one sample and is ordered based on the leftmost column in the clinical heatmap. Users may change the sample order based on customizable criteria. For example, users may sort samples based on adherence to a specific gene expression signature or to a set of hand-picked clinical parameters, such as gender and age at initial diagnosis. Click on “Signatures” or “Features,” respectively, to activate these features.

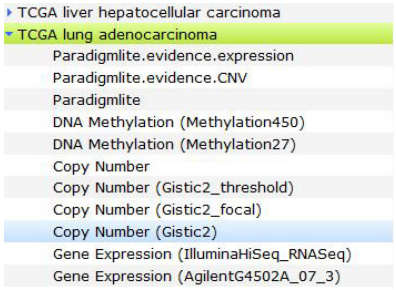

Figure 3Opens in a New Tab [38]

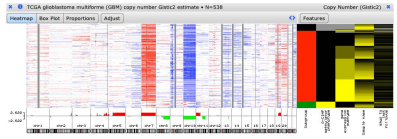

Figure 4Opens in a New Tab [39]

The genome-based experimental datasets are aligned above an up-to-date reference genome (as of this publication, Human March 2006 – NCBI36/hg18) for genomic context. Facilitating the integration of multiple datasets, heatmaps stack on top of one another and are synchronously aligned to the reference genome for vertical comparison. Users can manipulate the focus on the genome-oriented heatmaps by zooming in and out of a genomic region. If more information regarding a specific chromosomal region is needed, the UCSC Genome Browser may be accessed through a “Genome Browser” tab at the top of the page.

Figure 5Opens in a New Tab [40]

A common approach to cancer genomic data analysis is to look for the presence or absence of genes and pathways that are frequently disrupted in cancers. To view specific sets of genes in the heatmaps, turn

on the “Genes” mode and select either a predefined or user-defined “Geneset” (see figure 5Opens in a New Tab [40]). For computational pathway analysis, UCSC developed a program called PARADIGM that the browser publicly hosts. Currently, this feature is only available for The Cancer Genome Atlas’ glioblastoma multiforme and ovarian cystadenocarcinoma projects.

In summary, the UCSC Cancer Genomics Browser is a user-friendly interactive online tool that makes the vast assortment of data on cancer genomes accessible to the research and medical community. It allows investigators to visualize, integrate, and analyze genomic and clinical datasets in a variety of juxtaposing formats. To learn more, please visit https://xena.ucsc.edu/welcome-to-ucsc-xena/ [33].ens in a New Ta [33]

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