NATIONAL CANCER INSTITUTE
Office of Cancer Genomics

Published on *Office of Cancer Genomics* (https://ocg.cancer.gov)

Issue 5 : September, 2011

OCG PERSPECTIVE

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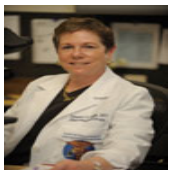

FEATURED RESEARCHERS

From Bedside to Bench: A Career in Pathology

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CONNECTING THE DATA

Wading Through a Deluge of Data: An Interview with Bioinformatician Ryan Morin

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NCI GENOMIC PROGRAM HIGHLIGHTS

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OCG PERSPECTIVE

Is There More to AIDS Malignancies than Immunosuppression?

Jean C. Zenklusen, Ph.D.

Caused by infection with human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS) is a complex and devastating disease brought about by the systematic destruction of a person's immune response. A weakened immune system can lead to a variety of opportunistic infections in affected persons, as well as a distinct spectrum of tumors known as AIDS-defining cancers. Some of these malignancies, such as Kaposi sarcoma, are also observed in other immunocompromised populations, while others are seen at increased rates only in AIDS patients. Since the advent of highly active antiretroviral therapy (HAART) in 1996, the rates of AIDS-defining cancers in HIV+ patients have steadily declined, suggesting that restoration of the immune response enables the body to return to effective immunosurveillance. This can result in a reduced ability of the AIDS-defining malignancies to develop.

While there has been a decrease in the incidence of AIDS-defining cancers, there is, however, an increase in the incidence of other forms of common cancers in HIV-infected individuals. For a number of the more common cancers, such as lymphoma and lung adenocarcinoma, the use of HAART has not made a difference, suggesting that HIV infection has the capacity to increase the risk of cancer beyond its immunosuppressive properties. These other mechanisms by which HIV infection augments an individual's susceptibility to subtypes of cancers are presently unknown. To gain insight into these mechanisms, the Office of Cancer Genomics in collaboration with the Office of HIV and AIDS MalignanciesOpens in a New Tab [2] has initiated the HIV+ Tumor Molecular Characterization Project (HTMCP)Opens in a New

Tab [3].

The goals of the HTMCP are to:

- Determine, through full genomic and transcriptomic sequencing, if the alterations found in cancers arising in HIV+ patients are different when compared to the same tumor type in non HIV-infected persons;
- Investigate if tumors in HIV+ patients express hereto undiscovered viral etiological agents that are enabled through the immunosuppressive phenotype of AIDS;
- Discover, through analysis of transcriptome sequencing, the role of the immunosuppressive phenotype, if any, on the increased incidence and morbidity observed in HIV-infected cancer patients.

Based on their incidence and morbidity, the HTMCP advisory group selected three tumor types for evaluation: diffuse large B-cell lymphomas, lung cancers, and cervical cancer. An additional component critical to the selection of these cancers stems from the need for comparison of tumor tissue with normal tissue from control populations with similar ethnic and regional background. Thus, the availability of preexisting data from large-scale genomic initiatives characterizing these same tumor types in non-HIV patients was needed. These large-scale genomic initiatives include the Cancer Genome Anatomy Characterization Initiative (CGCI)Opens in a New Tab [4] and The Cancer Genome Atlas (TCGA)Opens in a New Tab [5].

Accrual of cases for these tumor types has begun, as well as the full molecular characterization by the Genome Science Centre, British Columbia Cancer Agency in Vancouver, Canada. There are, however, hurdles that often accompany large-scale genomic projects. These include identifying tissues of good quality and quantity, obtaining patient-matched normal samples, and accessing associated clinical data. This is particularly true in the HTMCP as HIV+ patients are not considered "cancer" patients by their primary caregivers. These patients only come to central oncology institutions after the tumors have been biopsied or excised, making adequate preservation of the tissues a challenge.

Through the efforts of HTMCP, we hope to shed light on the molecular causes of HIV-related cancers. These molecular insights hold potential for the development of effective therapies for patients doubly afflicted with both HIV and cancer.

Should you have any interest in participating in the project or desire additional information, please contact the project director zenklusj@mail.nih.gov [6].

Back to Top

FEATURED RESEARCHERS

From Bedside to Bench: A Career in Pathology

Elaine S. Jaffe, M.D.

Dr. Elaine Jaffe is Head of the Hematopathology Section in the Laboratory of Pathology at the NCI's Center for Cancer ResearchOpens in a New Tab [7]. A remarkably well-accomplished pathologist, she has contributed significantly to our pathological and molecular understanding of malignant lymphomas, including follicular lymphomas. Her work focuses on the critical first steps in elucidating the mechanisms of cancer pathogenesis: disease discovery and disease definition. Dr. Jaffe was an editor for the "WHO Classification of Tumours of the Hematopoietic and Lymphoid Tissues," initially published in 2001 and revised in 2008. As Series Editor for the WHO Classification of Tumours, she is working to implement a new taxonomy that embraces traditional pathology and genomics for all types of malignancy. More recently, she was elected to the Institute of Medicine of the National Academies in 2008. Dr. Jaffe serves as a member of the Pathology Review Committee for the Office of Cancer Genomics' newest initiative, the Burkitt Lymphoma Genome Sequencing Project [8]. Here, she writes about her work as a pathologist, emphasizing both its clinical and molecular implications.

The drive to classify is intrinsic to science and medicine, and classifications are the language of disease. The use of uniform and precise terminology is essential for appropriate patient care and an essential part of the investigational process. Clinicians, in analyzing data from clinical trials, must be assured that the patient cohorts in different studies from around the world are comparable. Similarly, scientists studying tumors at the genomic level require tissue samples that accurately represent the disease process. The responsibility to precisely diagnose specimens in the clinical and research arena falls to the pathologist.

My destiny to pursue a career in pathology was determined early in my medical career. As a medical student, I found that the microscope opened up a whole new world. By examining cells and tissues – healthy and diseased – we can see with our own eyes disruptions in normal physiology and function. Certainly, we can later pursue these at the biochemical or molecular level, but it is careful analysis of the diseased tissues that often provides the first insight or glimpse of the problem. Careful examination of a microscopic section can tell a whole story, revealing the patients signs, symptoms, and expected clinical course. In some ways, it is like reading tea leaves, only much more reliable as a predictive tool. The pathologist is somewhat like a detective, deciphering the morphological clues. Still today, making a difficult diagnosis provides me with great satisfaction.

However, as a diagnostic pathologist, my goal has not been just to arrive at the correct diagnosis so that the patient can receive proper treatment. It's also been to discern from the microscopic changes in the tissue something about the pathophysiology and pathogenesis of the disease process. Ideas for research projects often come from the observations that we make at the microscope. In medicine today, it is popular to talk about "Bench to Bedside Research," in which advances at the laboratory bench can be translated into improved treatments. However, I would characterize my research endeavors as "Bedside to Bench." Through astute clinical observations, we gain insight into the basic nature of disease, and these observations can point the way towards laboratory studies to further resolve pathogenesis. The microscope can serve as a tool, not only for diagnosis, but also for disease discovery.

A principal focus of my work has been relating lymphomas to the normal immune system. In many instances, lymphomas represent caricatures of the normal cells of the immune system. The neoplastic cells recapitulate the phenotypic and functional properties of normal immune cells, and the clinical features we encounter at the bedside reflect the function of the tumor cells *in vivo*. These studies can explain why some patients, but not others, have depressed levels of immunoglobulins and are prone to infection, as an example. Additionally, the clinical patterns of tumor spread are not random but reflect the homing patterns of normal and neoplastic lymphoid cells. Even at the microscopic level, at the earliest stages of involvement, the tumor cells occupy the normal compartment of their precursors. By this approach, we can gain insight – not only into the lymphoma cells – but also their normal counterparts, as the neoplastic cells represent a clonal expansion of cells often frozen at a particular stage of differentiation and function.

Careful pathological studies can lead to new insights. In 2002, we described "follicular lymphoma *in situ*". These lymph nodes histologically looked normal, but upon closer inspection, the follicles contained a small population of cells with the *BCL2/IGH* translocation associated with follicular lymphoma. Remarkably, the vast majority of these patients do not go on to develop clinical lymphoma. These cases are providing a window into the earliest stages of lymphomagenesis, and we are learning that the *BCL2/IGH* translocation is necessary but not sufficient for tumor development. Secondary genetic events are required for the development of clinically significant follicular lymphoma. Importantly, the B-cells carrying the *BCL2/IGH* translocation continue to function in many respects like normal B-cells. They can circulate through the normal lymphatic system and home to germinal centers, where they take up residence. They also respond to perturbations in the immune system and may expand in response to antigenic stimulation.

Novel molecular insights like these expand our understanding of malignancies and can lead us to improved therapies. In this way, pathologists can serve a vital role in bridging the gap between patients and researchers.

Back to Top

CONNECTING THE DATA

Wading Through a Deluge of Data: An Interview with Bioinformatician Ryan Morin

Ryan Morin

Ryan Morin is a bioinformatics graduate student in Dr. Marco Marra's lab at the British Columbia Cancer Agency's Genome Sciences Centre in Vancouver. Ryan develops tools and assembles pipelines to reconstruct the genomic events that contribute to cancer pathogenesis. He takes an integrated approach, employing a variety of next generation sequencing technologies such as RNA seq, genome and exome sequencing. Although juggling several projects, his main focus has been uncovering genes and pathways implicated in non-Hodgkin Lymphoma (NHL), and more recently, Acute

Lymphoblastic Leukemia (ALL). Both of these projects are sponsored by the NCI's Office of Cancer Genomics (OCG) through the auspices of the Cancer Genome Characterization Initiative (CGCI)Opens in a New Tab [4] and Therapeutically Applicable Research to Generate Effective Treatments (TARGET)Opens in a New Tab [9]. After sequencing over 100 NHL tumors, Ryan and colleagues discovered a novel role for chromatin modification, a global form of gene regulation, in the development of this disease. More specifically, they observed the recurrence of mutations in several histone-modifying genes, including the two methyltransferases, *EZH2* and *MLL2*. These findings are well documented in two recent publications in *Nature Genetics* (2010)Opens in a New Tab [10] and *Nature* (2011)Opens in a New Tab [11].

Last year, Ryan contributed an article to the July 2010 [12] issue of the OCG e-newsletter. In the article, he discussed his overall experience – both the toil and the reward - as a bioinformatician dealing with the deluge of data from genomic sequencing. One year later, this genomic information remains unrelenting for researchers like Ryan. Take, for example, the $1,000 genome project, in which researchers are encouraged to bring the cost of genome sequencing down to $1,000 or less by rapidly improving the technologies. This project, funded by the National Human Genome Research Institute (NHGRI)Opens in a New Tab [13], has incredible potential for accelerating our understanding and treatment of cancer as well as other diseases. NHGRI Director Eric Green said, "As genome sequencing costs continue to decline, researchers and clinicians can increase the scale and scope of their studies." This increase in the scale and scope of genomic data, however, brings certain challenges.

To gain more insight into this issue, we decided to bring Ryan back for an interview to get an up-to-date and more in depth perspective. We also asked him to look towards the future and project where he thinks the field of cancer genomics is going. And, finally, we asked him to share what he's doing currently to follow up on his NHL story.

What are the specific challenges you face as a bioinformatician studying the cancer genome in this era of rapidly advancing sequencing technologies?

I think the big issue right now is that you can sequence a genome fairly cheaply and quickly, but once you get the results, the accuracy, sensitivity, and specificity of picking up mutations are still questionable. We have a sense for how many of the mutations are real, and it's not 100%. This is a problem, especially in a clinical setting. You have to sequence more deeply to capture the mutations, which can help increase the sensitivity. It's known there are spots in the genome we can't sequence efficiently. This is due to nucleotide sequences that are very rich in guanines (G) and cytosines (C) or, alternatively, adenines (A) and thymines (T). This results in reduced sequence coverage for the first exons of many genes, because they are often rich in Gs and Cs. There have been solutions proposed for ameliorating this problem, for instance, capturing just the GC-rich exon on a separate array and then sequencing the exon. Additionally, the sensitivity is worse for exome sequencing. There are certain genes that were omitted from the original exome design, like *MLL2* for example, which is possibly due to technical issues and restrictions of the design process itself.

Finally, you can get a genome sequenced in less than a month, but you then have to

go through a second round of verification to improve the confidence in your results. The downside to this second round of verification is that it can take much longer than the original sequencing experiment.

What does the second round of verification entail?

Either targeted capture or PCR (polymerase chain reaction), depending on the scale of your study. Targeted capture uses a set of "baits" to pull down regions of the genome that are then sequenced or validated. It is very useful for looking at hundreds of mutations. For smaller studies, where the number of mutations is much less, PCR allows you to amplify and sequence specific regions of the genome where the mutations are present. Unfortunately, PCR doesn't always work the first round and may require multiple rounds of optimization.

Both capture and PCR can become an iterative process. I don't see it improving much in the near future. Hopefully, some of these rapid turnaround sequencers, such as MiSeq and Ion Torrent, along with streamlined library construction will accelerate the verification stage.

How would MiSeq and Ion Torrent speed up verification?

MiSeq is designed to perform sequencing faster and at a smaller scale. With less surface area and imaging time, there are fewer reagents, so the cost is less. Essentially, MiSeq compressed the entire sequencing schedule, so you can run a sample in a matter of a few days. Ion Torrent is even faster, because it uses different chemistry and doesn't use any fluorescence or imaging. Its sequencing runs are on the order of 2 hours. As these tools emerge, this second round of verification will hopefully become a final step, done quickly.

You've discussed the technical challenges, but what about the analytical challenges like distinguishing between a driver mutation (a mutation that 'drives' the cancer event) and a passenger mutation (a mutation that doesn't play a role in cancer)? What do you do to overcome these issues?

Analytical challenges are big problems. When you sequence a genome, you don't necessarily know how to distinguish the importance of the somatic events. I think the cancers that have very high mutation rates are going to be difficult. Diffuse Large B-cell Lymphoma (a type of NHL) doesn't have a high mutation rate, if you compare it to the spectrum of other cancer genomes. But, there are still passenger mutations present. Just because you see a mutation in *EZH2*, doesn't mean that it's a driver. At the end of the day, it will come down to doing *in vitro* experiments, where individual mutations will have to be explored.

We are at the discovery stage now, trying to create a working parts list of cancer. We have statistical tools that are intended to model the mutation pattern and identify the genes being selected beyond chance. There are commonly mutated drivers that are seen in 10%-50% or more of patients, and other mutations seen in a very small percentage of patients, which are still important. Will these genes mutated at lower incidence be important from a clinical standpoint for a drug target? Probably not. But if they are in a common pathway, then perhaps we can target that pathway, and that is important.

Any surprise advances that have facilitated analysis in the field of cancer genomics?

I'm amazed by how big the community around next generation sequencing has become. There is a lot more sharing of software these days. There are numerous short-read aligners that people have written, made open-source, and put online, such as the various tools for SNP calling and for finding structural alterations. Some examples of these open source tools are Samtools, BWA, Picard, GATK, and Galaxy. For bioinformaticians, these tools are facilitating data analysis, leaving more room to address biological questions from our data. I'm impressed by how much the community tackles these problems.

Where do you see the field going? Where would you like it to go?

It's really hard to say. I hope that people create tool kits, so you are not reinventing the wheel again and again. People have generated enough of these tools that could be placed into an analytical pipeline, making the analysis fairly automated. This automated analysis would allow one to ask specific questions of the cancer genome, such as 'What is common or different?' without having to fully understand the analysis itself. This is the model we hope to see from the genome sequencing and analysis company, Complete Genomics, which now offers structural rearrangements, somatic mutations, and SNP calls as part of its services. Ideally, that is what people are going to want.

What are you doing to follow up on your NHL story? Is there a drug in the pipeline?

Two papers from last year, one from our group and one from a company, showed the mutant *EZH2* (Tyr641) might actually have enhanced enzymatic activity in the presence of the wild type enzyme, making it a possible gain-of-function mutation. These two studies demonstrated that mutant *EZH2* has reduced function in catalyzing the first methylation step, but enhanced function in catalyzing the subsequent two methylation steps. The reason we didn't detect that in our original paper is because we only tested *EZH2* (Tyr641) alone, without the wild type protein present. Now that it's been shown to be a gain-of-function mutation, *EZH2* (Tyr641) is being pursued as a drug target in NHL here at the Cancer Agency, by Epizyme and potentially other companies. The Cancer Agency is looking at mouse models with the *EZH2* (Tyr641) mutation and asking whether they get lymphoma. Once/if they develop lymphomas, we plan to inject them with small molecules that are predicted to inhibit this protein and look for a response. Also, we have a much larger list now of genes predicted to be under selection in NHL that we are currently following up on.

Back to Top

NCI GENOMIC PROGRAM HIGHLIGHTS

Epidemiology of Burkitt Lymphona in East African Children and Minors (EMBLEM)

Sam Mbulaiteye, M.D.

In the April 2011 issue [14] of the Office of Cancer Genomics (OCG) e-Newsletter, Burkitt lymphoma (BL) was introduced as the newest cancer to be studied as part of OCG's Cancer Genome Characterization InitiativeOpens in a New Tab [4]. The Burkitt Lymphoma Genome Sequencing Project (BLGSP) will develop a genomic databank for the main types of BL, including endemic. To obtain tissues from patients with endemic BL, the BLGSP is collaborating with another NCI study, Epidemiology of Burkitt Lymphoma in East African Children and Minors (EMBLEMOpens in a New Tab [15]). Dr. Sam Mbulaiteye, EMBLEM's principal investigator, shares more about the study and what it aims to accomplish to improve the lives of those with BL.

Led by investigators in the Infections and Immunoepidemiology BranchOpens in a New Tab [16] of the Division of Cancer Epidemiology and GeneticsOpens in a New Tab [17] at the National Cancer Institute (NCI), EMBLEM is a multi-country, multiyear case-control study of childhood Burkitt lymphoma in Uganda, Kenya, and Tanzania. The study will enroll 1500 patients with BL and 3000 age-, sex-, and residence-matched controls. The scientific objectives of EMBLEM are to measure the contribution of malaria, Epstein-Barr virus (EBV), and genetic variation to the development of Burkitt lymphoma in East African children.

Understanding the etiology of Burkitt lymphoma is critical for scientific advances needed for improved therapeutic development and for public health. Historically, the study of Burkitt lymphoma has led to seminal discoveries, including insights into the viral and molecular basis of cancer. In Africa where it is considered endemic, Burkitt lymphoma is the most common childhood tumor, accounting for 50-75% of the cancers diagnosed in children in some countries. It is thought that the high incidence, or endemicity, of Burkitt lymphoma in Africa is attributable to repeated infections of very young children with immature immune systems with malaria and EBV. The scientific evidence for this thinking is, however, still ambiguous. Correlation studies conducted in the 1960s prompted investigators to propose the malaria hypothesis. Case-control studies conducted recently have provided some support for the hypothesis that children with Burkitt lymphoma are more likely to have higher anti-malaria antibodies than children without. However, concerns that results of anti-malaria antibodies measured after onset of disease may be the consequence, not determinant of disease, mar the interpretation of these results.

Through the application of genomic technologies, the EMBLEM study will address this age-old question of malaria's role in the genesis of Burkitt lymphoma. Because malaria causes high mortality, populations exposed to very high levels of malaria have developed genetic mutations that confer resistance to severe forms of malaria (e.g., the sickle cell gene). More than 40 functional malaria-resistance mutations have been characterized in more than 25 genes. By comparing and contrasting carriage of these malaria resistance genotypes in BL patients and controls, EMBLEM investigators hope to obtain robust evidence to better understand malaria's contribution, if any, to Burkitt lymphoma. In addition, other questions, including those

regarding the nature (molecular pathology) and the role of rare EBV variants, can be addressed through the EMBLEM project.

EMBLEM began accruing cases in Uganda in November 2010 and will start accruing cases in Kenya and Tanzania beginning in the fall of 2011 until 2015. The study is collecting detailed questionnaire data on malaria and other disease exposures, along with blood and saliva samples for DNA extraction from both Burkitt lymphoma patients and matched controls. Because EMBLEM operates in very poor countries, the study has to address unique challenges, such as the lack of standard diagnosis and treatment for patients with Burkitt lymphoma. Through unique collaborations, such as with the International Network of Cancer Treatment and Research (INCTR)Opens in a New Tab [18], protocol-based treatment of Burkitt lymphoma is being availed to patients at no cost to them. Also of note, EMBLEM's collaboration with the Sub-Saharan Lymphoma ConsortiumOpens in a New Tab is working to improve pathologic diagnosis of Burkitt lymphoma.

Like the BLGSP, EMBLEM not only aims to improve the understanding and treatment of patients with Burkitt lymphoma, but also to provide a bridge between cancer researchers in East Africa and NCI.

Back to Top

PATIENT PERSPECTIVE

Engagement, Education, Trust: Three Key Elements Needed for Disparities and Genomic Research Progress

Phyllis Pettit Nassi, MSW

Phyllis Pettit Nassi works in Prevention & Outreach as Manager of Special Populations and Native American Outreach at Huntsman Cancer Institute in Salt Lake City, Utah. As a cancer advocate for underserved communities, Phyllis uses outreach to raise awareness of cancer, cancer research, and clinical trials within poor communities. Her efforts cross a wide spectrum, from providing patients and their families with easy-to-understand educational materials to bringing the underserved patients' perspective to the realm of cancer research by sharing their collective issues with researchers and legislators. In the April 2011 [14] issue of Office of Cancer Genomics e-News, Phyllis contributed her perspective on a studyOpens in a New Tab [19] by TARGET pediatric researchers which uncovered a link between Native American ancestry and increased risk of relapse of childhood acute lymphoblastic leukemia. Her writing is a reflection of her experience working as the Manager of Special Populations and Native American Outreach and serving on various committees, but does not reflect the views of the Huntsman Cancer Institute.

In his commentaryOpens in a New Tab [20] in *Nature* (2004) on the "Human Genome Variations and 'Race:' The State of Science" meeting, Dr. Francis S. Collins, director of the National Institutes of Health, poses a number of important questions.

Included among them are:

- "What does the current body of scientific information say about the connections among race, ethnicity, genetics and health?"
- "…will [genetics] explain a substantial proportion of health disparities for most common diseases…?"
- "What additional research is needed?"

Seven years later, I realize that we remain far from clear-cut answers to these questions, particularly as I ponder how they relate to health disparities in cancer research. I believe one key reason why we are without answers is because unfortunately, most clinical trials are conducted in patient populations that don't reflect the full range of ethnic and socioeconomic backgrounds.

Including underserved communities in cancer genomics research is oftentimes challenging, but it is most certainly possible. In my experience with Native American outreach, the willingness to take the time to engage tribal nations -- or any underserved population for that matter — as true research partners is invaluable. We must invite these populations to be at the table from the very beginning and continuously provide them with services throughout.

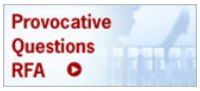
Many underserved patients lack the exposure and education needed to understand basic biological concepts. During my time working with Native American cancer patients and their extended network of family and health care professionals, I found that few know what a gene is, let alone a genome. Understandable information about all major aspects of the cancer research project is critical to educating these underserved populations. With this knowledge, they are empowered to make informed choices about participation in research and treatment options. In order for minority populations to reap the desired the therapeutic benefits of advances in genomics and pharmacogenomics cancer research, educational programs must be targeted to reach them. They desire the beneficial outcomes of new research findings after learning of them but cannot ask for something they aren't aware of.

Lastly, we must establish a relationship of trust by encouraging researchers to focus on how research findings may impact cultural and societal aspects of tribal nations or other underserved populations. This trust benefits the underserved and ultimately the research, which will in turn, eventually lead us to the answers we have been awaiting.

Back to Top

NCI FUNDING OPPORTUNITY

Provocative Questions: Identifying Perplexing Problems to Drive Progress Against Cancer



NCI has released two new funding announcementsOpens in a New Tab [21] entitled "Research Answers to NCI's Provocative Questions."

RFA-CA-11-011Opens in a New Tab [22]
RFA-CA-11-012Opens in a New Tab [23]

The provocative questions (PQ) project was established in 2010 to provide the research community an opportunity to assemble a collection of questions to stimulate new and imaginative ways to study cancer. The research community responded by participating in workshops throughout the country to bring to the forefront some of the more perplexing cancer-related questions and by submitting questions online.

Of the numerous PQs submitted, 24 were selected for inclusion in this funding opportunityOpens in a New Tab [21]. The PQs cover a broad range of topics, including cancer genomics. All investigators with appropriate expertise are invited to submit a proposal.

Key Dates

- Posted Date: August 25, 2011
- Open Date (Earliest Submission Date): October 14, 2011
- Letter of Intent Due Date: October 14, 2011
- Application Due Date(s): November 14, 2011, by 5:00 PM local time of applicant organization
- Scientific Merit Review: March/April 2012
- Advisory Council Review: May 2012
- Earliest Start Date(s): July 2012
- Expiration Date: November 15, 2011

Back to Top

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Links
[1] https://ocg.cancer.gov/printpdf/taxonomy/term/60 [2] https://www.cancer.gov/about-nci/organization/oham [3] https://ocg.cancer.gov/programs/cgci/projects/HTMCP [4] https://ocg.cancer.gov/programs/cgci [5] https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga [6] mailto:zenklusj@mail.nih.gov [7] https://ccr.cancer.gov/ [8] https://ocg.cancer.gov/news-publications/e-newsletter-issue/issue-4#128 [9] https://ocg.cancer.gov/programs/target [10] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2850970/ [11] https://www.nature.com/articles/nature10351 [12] https://ocg.cancer.gov/news-publications/e-newsletter-issue/issue-2 [13] https://www.genome.gov/ [14] https://ocg.cancer.gov/news-publications/e-newsletter-issue/issue-4 [15] https://emblem.cancer.gov [16] https://dceg.cancer.gov/about/organization/tdrp/iib?redirect=true [17] https://dceg.cancer.gov/?redirect=true [18] http://www.inctr.org [19] https://pubmed.ncbi.nlm.nih.gov/21297632/ [20] https://www.genome.gov/pages/news/documents/raceandgeneticscommentary.pdf [21] https://provocativequestions.cancer.gov/ [22] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-11-011.html [23] https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-11-012.html