Meeting Report

Cancer Research

The Global Cancer Genomics Consortium: Interfacing Genomics and Cancer Medicine

The Global Cancer Genomics Consortium

Abstract

The Global Cancer Genomics Consortium (GCGC) is an international collaborative platform that amalgamates cancer biologists, cutting-edge genomics, and high-throughput expertise with medical oncologists and surgical oncologists; they address the most important translational questions that are central to cancer research and treatment. The annual GCGC symposium was held at the Advanced Centre for Treatment Research and Education in Cancer, Mumbai, India, from November 9 to 11, 2011. The symposium showcased international next-generation sequencing efforts that explore cancer-specific transcriptomic changes, single-nucleotide polymorphism, and copy number variations in various types of cancers, as well as the structural genomics approach to develop new therapeutic targets and chemical probes. From the spectrum of studies presented at the symposium, it is evident that the translation of emerging cancer genomics knowledge into clinical applications can only be achieved through the integration of multidisciplinary expertise. In summary, the GCGC symposium provided practical knowledge on structural and cancer genomics approaches, as well as an exclusive platform for focused cancer genomics endeavors. *Cancer Res; 72(15); 3720–4. ©2012 AACR.*

Introduction

Among the major determinants that enable cancer cells to acquire malignant traits are genomic diversity and instability. Genomic abnormalities and their influence on the onset of cancer have fascinated cancer researchers for more than a century (1–3). The genomic research empowerment began after the complete characterization of the draft human genome in 2000 at high resolution (4, 5). The subsequent arrival of the second-generation sequencing technologies further accelerated the progress of the cancer genomics (6–9). The wealth of the high-throughput information from the cancer genome offers incredible promise toward unraveling the evolutionary history of cancer, the basis of tumor responsiveness and resistance to a given treatment modality. More importantly, the trickling of such cancer genomic progress is slowly making its way into patient care, but the full potential of cancer genomics (i.e., personalized oncomedicine) still remains to be realized (10, 11). Therefore, the crusade against cancer and the march toward effective translational outcomes from genomics continue. In this context, one of the obvious missions is to catalyze our international efforts to use shared resources to better understand and translate the fruits of the postgenomic era for clinical benefits.

GCGC–A Focused International Cancer Genomic Partnership

In late 2010, the Global Cancer Genomics Consortium (GCGC) was set up between like-minded cancer scientists and oncologists from 6 complementing medical institutions and 5 countries. The overarching mission of GCGC is to develop an effective, new global way to collaborate among participating institutions, which will address specific cancer research challenges and stimulate younger investigators. These young investigators will use high-throughput genomics approaches to solve complex, high-value, translational research questions using tumor specimens. The GCGC connects 6 translational groups from the Tata Memorial Centre (TMC, Mumbai, India), the Rajiv Gandhi Centre for Biotechnology (Thiruvananthapuram, Kerala, India), the Kyoto University Graduate School of Medicine (Kyoto, Japan), the Institute of Molecular Medicine (Lisbon, Portugal), The George Washington University (Washington, DC), and the Structural Genomic Consortium at Oxford University (Oxford, UK). The clinical partnership with the Oncology Division at Hospital de Santa Maria in Portugal and the Tata Memorial Hospital in India offers unique insight from 2 different continents, allowing us to evaluate current cancer therapeutic options and identify major global cancer treatment conundrums and bottlenecks. The group

Note: Presented at Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre, Mumbai, India; November 9–11, 2011. Members of the Global Cancer Genomics Consortium who contributed to this meeting report are Jeyanthy Eswaran (The George Washington University, Washington, DC), Sudeep Gupta (Tata Memorial Centre, Mumbai, India), Amit Dutt (Tata Memorial Center), Masakazu Toi (Kyoto University Graduate School of Medicine, Kyoto, Japan), M. Radhakrishna Pillai (Rajiv Gandhi Center for Biotechnology, Kerala, India), Luis Costa (Hospital de Santa Maria and Institute of Molecular Medicine, Lisbon, Portugal), Stefan Knapp (Structural Genomic Consortium, University of Oxford, Oxford, UK), Rajendra Badwe (Tata Memorial Centre), and Rakesh Kumar (The George Washington University).

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is mandated to identify and address 1 or 2 significant cancer patient–centered questions each year using shared resources, such as tumor specimens and the experimental and analytical strength of the members in structural and functional genomics.

Why GCGC-TMC Symposium at Mumbai?

The first meeting of GCGC was held in India from November 9 to 11, 2011, at the Advanced Centre for Treatment Research and Education in Cancer (ACTREC), TMC. The primary purpose of the meeting was to integrate the strengths of the GCGC partners, evaluate the progress of the first year, and provide outreach to the young Indian scientific community and steer them toward the field of next-generation sequencing and computational genomics. India is emerging as a world leader in the field of information technology; therefore, researchers are well equipped to resolve challenges and contribute to the field of computational genomics. The ever-growing ancient fascination with fundamental sciences, along with the highest number of young people skilled in "contemporary sciences" (such as computational sciences, systems biology, and bioinformatics) makes India an attractive location for genomics endeavors (12, 13). Therefore, it is an appropriate time to set the stage to celebrate the first year of the GCGC with a meeting in Mumbai and to orient the multidisciplinary scientific talent in India toward cancer genomics research.

Focus on the Cancer Translational Landscape

The meeting fused together speakers from 3 broad themes who covered emerging cancer genomics knowledge, molecular therapeutics, and developments and challenges in genomics technologies. There were 190 registered participants from 42 Indian National Institutes. The symposium was conducted for two and a half days including 8 sessions, each composed of 2 to 3 invited speakers followed by a poster session. In addition, vibrant panel discussions examined strategies that are essential for the tackling of current translational cancer medicine challenges, such as the study design, high-throughput genomics data analysis, interpretation, and what are normal variations of the human genome. This report discusses the above-mentioned 3 themes and the overall scientific highlights and emphasis of the GCGC meeting.

I. Emerging global cancer genomics knowledge

The first session of the meeting discussed the goals, objectives, and working plans of the GCGC. Dr. Sudeep Gupta (Tata Memorial Hospital) opened the session with a welcome message, followed by Dr. Rakesh Kumar (The George Washington University) explaining the genesis of GCGC and how this connects the cohesive multidisciplinary teams from the United States, Europe, and India. He also highlighted the role of the international collaborative funding body, the Prime Minister's Initiative 2 Connect from the British Council, which immediately recognized the strength of the GCGC scientists and awarded a collaborative grant. This allowed GCGC to further strengthen the research partnership, initiating the first-year translational research and educational questions and student–faculty exchange among the United Kingdom, United States, and India. Next, Dr. Rajendra Badwe (Tata Memorial Hospital) discussed the current problems in cancer diagnostics and therapeutic decision making and how he envisions genome-centered translational research might contribute to the day-to-day treatment challenges of clinicians in years to come.

Exploring Cancer Gene Expression Signatures through mRNA Sequencing and Microarray

Dr. Rakesh Kumar presented the discoveries revealed in the first-year GCGC study that investigated the transcriptional regulation of breast cancer through massively parallel mRNA sequencing (14). Using the 1.2 billion reads generated from 17 individual human tissues belonging to triple-negative breast cancer (TNBC), non-TNBC, and HER2-positive breast cancers, the comprehensive digital transcriptome was determined for the first time. The comparative transcriptomic analyses elucidated the transcriptional regulatory elements and differentially expressed transcripts among the 3 breast cancer groups. This study opens previously unexplored niches for a better understanding of breast cancer and the development of new breast cancer therapy. In the same theme, Dr. Jeyanthy Eswaran (George Washington University) discussed specific steps involved in the mRNA gene expression study, identification of novel splicing variants, and previously unknown single-nucleotide polymorphisms (SNP) that are specific to each breast cancer type. The impact of the SNPs was studied using protein functional motifs and structure-based analysis, a strength of the GCGC network. There has been a specific effort from the GCGC team to illustrate the individual steps and strategies used at every stage of this study, which provided the overview of various aspects of mRNA sequencing.

To compare the wealth of knowledge acquired through microarray and next-generation sequencing, research on the identification of novel druggable targets in the area of colon cancer and cancer in general was discussed by Dr. Norman Lee (George Washington University). He presented data that showed the mediatory role of voltage-gated anionic and cationic channels in cancer phenotypes. More interestingly, alternative mRNA splicing components identified through microarray studies were attributed to be the possible cause of the cancer burden seen in different races, such as African Americans and Caucasian Americans.

Investigating the Cancer Genome–Specific Variants and Their Functional Implications

The genomics research field in India is vibrant, with a focus on several cancers; the highlights presented here include the progress on oral tongue cancers, cervical cancers, lung cancer, and glioma malignancies. Dr. Abraham Moni Kuriakose (Mazundar-Shaw Cancer Center, Bengaluru, India) presented the current status of the Indian Oral Cancer Genome Sequencing Project. In the same area, Dr. Manoj Mahimkar (ACTREC/TMC) shared the emerging SNP and structural variation studies of oral cancers that led to the identification of chromosomal gain of region 11q22.1–q22.2 and losses of 17p13.3 and 11q23–q25 to be associated with locoregional

recurrence and shorter survival. Dr. Kumaravel Somasundaram (Indian Institute of Science, Bengaluru, India) presented the clinical cohort study of 154 patients with glioma and the investigation that explored the possibility of methylation signatures as predictors of glioma tumor stages. The role of RNA-binding proteins in glioma was also studied using high-throughput methodologies such as siRNA, which led to the identification of new diagnostic targets. Currently, the targeted sequencing of these candidates in the glioma patient group is ongoing. Similar clinical validation for SNPs is also reported for advanced cervical cancer in India by Dr. Rita Mulherkar (ACTREC). The SNPs were selected from the exome capture and sequencing studies using advanced cervical cancer patient samples. The area of miRNA was covered by Dr. Ramkumar Hariharan (Rajiv Gandhi Centre for Biotechnology). He highlighted the significance of miRNA and small noncoding RNAs that are involved in posttranscriptional regulation of different types and stages of prostate and ovarian carcinoma. In the same topic of oncogenic regulation, Dr. Shantanu Chowdhury (Institute of Genomics and Integrative Biology, Delhi, India) presented recent findings on focal adhesion marker as transcriptional target of nonmetastatic 2 (nme2), a suppressor of metastasis in lung cancer using ChIP-seq and transcriptome analysis. Together, the current cancer genomics projects in India open promising new diagnostic options; however, the discussion after these presentations emphasized the need to establish natural variations specific to the Indian community.

Away from the direct cancer patient sample sequencing studies, Dr. Brian Oliver (National Institute of Diabetes and Digestive and Kidney Diseases, NIH) discussed the significance of using model systems such as Drosophila to understand gene copy number variations. In terms of interpreting the influence of genomics changes on functionality of the pathways, structural bioinformatics and systems biology are playing significant roles (15). Dr. Raja Mazumder (George Washington University) elaborately illustrated this notion with examples from his recent work on the changes in *N*-glycosylation sites in the human proteome. In the same vein, Dr. Ashok S. Kolaskar (KIIT University, Bhubaneswar, India) put forward strategies that could be used in the analysis of large-scale "omics" data. Dr. Rajendra Joshi (Center for Development and Advanced Computing, Pune, India) and Dr. Supratik Chakraborty (IIT, Mumbai, India) further discussed and highlighted various challenges and design of high-throughput data analysis. Thus, these sessions tackled various necessary aspects for proper interpretation of emerging large volumes of cancer genomics data.

Enriching Cancer Therapeutic Targets through Structural and Functional Genomics

Dr. Stefan Knapp (Oxford University) presented the showcase studies that show the development of the "chemical probe" against the epigenetic family using structural and chemical genomics approaches (16). He also shared recently developed new specific probes that could intervene in cancers at the level of epigenetic reader where specific posttranslational modifications in histones are recognized and targeted. In the kinase area, the study focused on specific "lead compound" (dichloroindolyl enaminonitrile KH-CB19) development to regulate the activity of novel protein kinases that control RNA splicing, such as CDC2 kinase isoforms 1 and 4 (17). On the same topic of targeting the human kinome, Dr. Amit Dutt (ACTREC) presented recent work on targeting *EGFR* beyond lung cancer. Higher incidences of *EGFR* mutations were found in East Asian ethnicity compared with Caucasian populations of European descent. This study profiled actionable mutations, including *EGFR* mutations from formalin-fixed, paraffin-embedded clinical specimens derived from patients of Indian origin with lung cancer using Raindance Technologies' microfluidic-based approach followed by next-generation sequencing. Furthermore, the possibility of using erlotinib-sensitive *EGFR* mutation in other human cancers such as advanced endometrial cancer were also shared by Dr. Dutt. When the various approaches that identify new targets across various types of cancer are explored, Dr. Eswaran highlighted the significance of atypical kinases and GTPases. She discussed the recent structural studies that revealed the unique characters of atypical kinases such as VRK3, CASK, STRADα, and ILK and atypical GTPases (RGKs and centaurins) that prompted the drug target hunting studies to shift their focus on these unusual members of the family (18).

II. Molecular cancer therapeutics

Intrinsic subtype classification has been incorporated into clinical practice of breast cancer treatment, particularly for patients with primary breast cancer. Dr. Masakazu Toi (Organisation for Oncology and Translational Research and Kyoto University Medical Center, Japan) illustrated the complexities involved in therapeutic decision making in breast cancer (19). The rapid developments in the genomics field enabled the use of various new diagnostic tools in breast cancer treatment. For instance, multigene assays are available broadly to predict the prognosis of estrogen receptor in patients with breast cancer treated by hormone therapy alone and for prediction of chemosensitivity. Likewise, in the case of anti-HER2 therapy, various approaches, including antiangiogenesis therapy and anti-mTOR therapy, are tested as a means to predict the response to anti-HER2 therapy and survival. However, the study Dr. Toi shared clearly highlighted the dire clinical scenario of breast cancer and its recurrence, which still warrant a clear molecular-level understanding of cancer evolution. He put forward reasons that support the need to define the genetic identities of circulating primary and secondary tumor cells through genomics with the GCGC, as this knowledge will offer critical details that will be helpful in breast cancer therapy. In the same area of breast cancer recurrence, Dr. Luis Costa (Hospital de Santa Maria and Institute of Molecular Medicine, Lisbon, Portugal) presented new therapeutic possibilities in bone metastasis particularly when it happens due to the recurrence of breast cancer (20). Dr. Costa presented data on the use of bisphosphonates or denosumab as bone-targeted therapy based on the concept that the cancer cells in bone promote bone destruction through osteoclast activation. However, recent studies show this might be happening independent of osteoclast activation, which could

explain why current bone-targeted therapy, which includes bisphosphonates and a monoclonal antibody against RANKL (denosumab), unfortunately has had little impact on disease progression and patient survival. Dr. Costa also discussed the use of AZD0530 (an src inhibitor) over zoledronic acid in phase II clinical trials, thus emphasizing the need to focus on matrix metalloproteinases (MMP) and a genomic fingerprinting of recurrence and bone metastasis, and presented data with combined use of zoledronic acid and AZD0530 as a new approach to target MMP1 in bone metastases. In this perspective, Dr. Costa also discussed the new therapeutic possibilities based on the molecular triad RANK-RANKL-MMP1, specially aiming for an antitumoral effect that could improve patients' overall survival rate.

III. Developments and challenges in genomics technologies

The backbone of large data-centered genomics studies continues to be bioinformatics and computational resources. Incredible progress has been made in computational genomics. To address the central issues that might have an impact on these data analyses, several dedicated computational genomics groups are trying to optimize genomics algorithms and improve consistency between programs as a means to minimize the computing power. Dr. Binay Panda (Ganit Labs, Bengaluru, India) presented the much-needed data that compared various current mRNA sequencing analysis programs. In addition, Drs. Srinivas Aluru (Iowa State University, Ames, IA), Randeep Singh (Philips Research Asia, Bengaluru, India), Uday Deshpande (Rajiv Gandhi Institute of Information Technology and Biotechnology, Pune, India), and Shubha Srinivasan (The Institute of Bioinformatics and Applied Biotechnology, Bengaluru, India) discussed the availability of a diverse set of genomics technology platforms and training opportunities. Merits and demerits of various evolving computational environments, such as multicores, cloud computing, clusters, and super computer setups, as well as new sequencing technologies of Ion Torrent, PacBio, 454, Solid, and illumina platforms were discussed by Dr. Aluru. The latest developments in computational genomics are promising and the presentations of the comparisons of algorithms by Drs. Panda and Aluru addressed the complexities involved in the understanding of mRNA sequencing and systems biology. In keeping with this, Dr. Raja Mazumder also showed the downstream analysis, which interprets the functions of protein through evolutionary conservation and comparative genomics studies. He emphasized the need for the computational set-up [high-performance integrated virtual environment cloud (HIVE)] for integrative genomics and proteomics resources. Together, the speakers on this theme provided an overview of current bioinformatics challenges and recent cutting-edge developments that are in place to overcome several of these critical practical issues.

Conclusions and Future GCGC Translational Endeavors

In conclusion, the GCGC meeting enabled the participants to discuss the issues that lie at the heart of the translation of genomics knowledge into cancer therapeutics and provide the basic knowledge needed to use next-generation sequencing as part of regular laboratory experiments. Using the established multifaceted strengths of GCGC, the team explored the possible second-year translational questions. These include identification (and validation using GCGC sites) of specific splice variants and SNPs associated with TNBC, non-TNBC, and HER2-positive breast cancers and expanded analyses of these alterations to assess their application to other cancer types. In addition, a new GCGC collaborative project is also planned to identify "saintly signature" that results from preoperative progesterone treatment, which might be a component of the recently reported enhanced survivals of patients with breast cancer (21). The group now wishes to conduct the whole transcriptome analysis of the paired tumor samples from the TMC tumor bank. There is also a lot of excitement in the GCGC membership to reveal the genomic basis of generally observed gradation in hormonal sensitivity of breast tumors. In summary, the GCGC symposium provided an overview of structural and functional research, and it set the stage to ask focused translational questions that could unravel the riddles of cancer genomics through international collaborations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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