Meeting Report

The Global Cancer Genomics Consortium: Interfacing Genomics and Cancer Medicine#

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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 on the 9th to the 11th of November 2011. The symposium showcased international next generation sequencing efforts that explore cancer specific transcriptomic changes, single nucleotide polymorphism, copy number variations in various types of cancers, as well as 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 multi-disciplinary 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.
One of the major determinants that enable the cancer cells to acquire malignant traits is genomic diversity and instability. Understanding the genomic abnormalities and its influence on the onset of cancer has 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 cancer genome offers incredible promises towards unraveling the evolutionary history of cancer and the basis of tumor responsiveness or resistance to a given treatment modality. More importantly, the trickling of such cancer genomic progress is slowly arriving into patient care but the full potential of the cancer genomics (i.e. the personalized oncomedicine) still remains to be realized (10, 11). Therefore, the crusade against cancer and the march towards effective translational outcomes from genomics continues. In this context, one of the obvious missions is to catalyze our international efforts to utilize shared resources to better understand and translate the fruits of the post-genomic era for clinical benefits (12).

**GCGC – A Focused International Cancer Genomic Partnership**

In late 2010, a Global Cancer Genomics Consortium (GCGC) was set up between like-minded cancer scientists and oncologists from six complementing medical institutions and five countries. The overarching mission of GCGC is to develop an effective, new global way to collaborate between participating institutions, which will address specific cancer research challenges and stimulate younger investigators. These young investigators will employ high throughput genomics approaches to solve complex, high-value, translational research questions using tumor specimens. The GCGC connects six complementary translational groups from the Tata Memorial Center, Mumbai, India, the Rajiv Gandhi Centre for Biotechnology,
Thiruvananthapuram, India, the Kyoto University Graduate School of Medicine, Kyoto, Japan, the Institute of Molecular Medicine, Lisbon, Portugal, The George Washington University, Washington, DC, USA, and the Structural Genomic Consortium at the Oxford University, Oxford, UK. The clinical partnership with the Oncology Division at Hospital de Santa Maria, Lisbon and the Tata Memorial Hospital (TMC), Mumbai offers a unique insight from two different continents, allowing us to evaluate current cancer therapeutic options and identify major global cancer treatment conundrums and bottlenecks. The group is mandated to identify and address one or two 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 on November 9th to 11th at the Advanced Centre for Treatment Research and Education in Cancer (ACTREC), Tata Memorial Center, Mumbai, India. The primary purpose of the meeting was to integrate the strengths of the GCGC partners, evaluate the progress of the first year, and to outreach and steer the young Indian scientific community towards the field of next generation sequencing and computational genomics. India is emerging as a world leader in the field of information technology; therefore, they 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 (13, 14). 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 towards cancer genomics research.

**Focus on the Cancer Translational Landscape**

The meeting fused together speakers from three 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 half days including eight sessions, each comprised of two to three 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 three 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, Mumbai, India) opened the session with a welcome message, followed by Dr. Rakesh Kumar (The George Washington University, Washington, DC, USA) explaining the genesis of GCGC and how this connects the cohesive multi-disciplinary teams from the U.S., Europe and India. He also highlighted the role of the international collaborative funding body, the Prime Ministers Initiative 2 Connect from the British Council, UK, which immediately recognized the strength of the GCGC scientists and awarded a collaborative grant. This allowed GCGC to further strengthen the research partnership, initiate the first year translational research and educational questions and the student-faculty exchange.
between the UK, U.S., and India. Next, Dr. Rajendra Badwe (Tata Memorial Hospital, Mumbai, India) 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 of the first year GCGC study that investigated the transcriptional regulation of breast cancer through massively parallel mRNA sequencing (15). Using the 1.2 billion reads generated from 17 individual human tissues belonging to 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 between the three 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. Jeyanthi Eswaran (MGPC, The George Washington University, Washington, DC, USA) discussed specific steps involved in the mRNA gene expression study, identification of novel splicing variants and previously unknown SNPs 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 employed at every stage of this study, which provided the overview of various aspects of mRNA sequencing.
To compare the wealth of the 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 (The George Washington University, Washington, DC, USA). He presented data that showed the mediatory role of voltage gated anionic and cationic channels in cancer phenotypes (14). 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 its 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, Navi Mumbai, India) 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 loco-regional recurrence and shorter survival. Dr. Kumaravel Somasundaram (Indian Institute of Science, Bengaluru, India) presented the clinical cohort study of 154 glioma patients 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, Navi Mumbai, India). The SNPs were selected from the exome capture and sequencing studies using advanced cervical cancer patient samples. The area of microRNA was covered by Dr. Ramkumar Hariharan (Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, India). He highlighted the significance of microRNA and small non-coding RNAs that are involved in post-transcriptional 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 Non-metastatic 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 (NIDDK, National Institutes of Health, Bethesda, MD, USA) 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 playing significant roles (16). Dr. Raja Mazumder (The George Washington University, Washington, DC, USA) 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 employed 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, Oxford, UK) presented the showcase studies that demonstrate the development of the “chemical probe” against the epigenetic family using structural and chemical genomics approaches (17). He also shared recently developed new specific probes that could intervene cancers at the level of epigenetic reader where specific post-translational 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 (18). In the same topic of targeting human kinome, Dr. Amit Dutt (ACTREC, Navi Mumbai, India) presented recent work on targeting EGFR beyond lung cancer. The higher incidences of EGFR mutations were found among East Asian ethnicity than Caucasian populations of European descent. This study profiled actionable mutations, including EGFR mutations from formalin fixed paraffin embedded clinical specimens derived from lung cancer patients of Indian origin using Raindance Technologies’ microfluidic based approach followed by next generation sequencing. Further, 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. Jeyathany 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 (19, 20).

II. Molecular Cancer Therapeutics

Intrinsic subtype classification has been incorporated into clinical practice of breast cancer treatment, particularly for primary breast cancer patients. Dr. Masakazu Toi (OOTR and Kyoto University Medical Center, Japan) illustrated the complexities involved in therapeutic decision-making in breast cancer (21). The rapid developments in the genomics field enabled the use of various new diagnostic tools in breast cancer treatment. For instance, multi-gene assays are available broadly to predict the prognosis of estrogen receptor in positive breast cancer patients treated by hormone therapy alone and prediction of chemosensitivity. Likewise, in the case of anti-HER2 therapy, various approaches including anti-angiogenesis therapy and anti-mTOR therapy are tested in order to predict the response to anti-HER2-therapy and survival. However, the study Dr. Masakazu Toi shared clearly highlighted the dire clinical scenario of breast cancer and the recurrence, which still warrants 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 since 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 (University of Lisbon Medical Center, 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 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 and that could explain why the current bone targeted therapy, which
includes Bisphosphonates and a monoclonal antibody against RANKL (Denosumab), unfortunately have had little impact on the disease progression and patient survival. Dr. Costa also discussed the use of AZD0530 (a src inhibitor) over zoledronic acid in phase II clinical trials, thus emphasizing the need to focus on MMPs 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 in the molecular triad RANK-RANKL-MMP1, specially aiming for an anti-tumoral 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 the computational genomics. To address the central issues that might impact the data analysis, several dedicated computational genomics groups are trying to optimize genomics algorithms and improve consistency between programs, 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, Iowa, USA), Randeep Singh (Philips Research Asia, Bengaluru, India), Uday Deshpande (Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, 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. Srinivas Aluru. The latest developments in
the computational genomics are promising and the presentations of the comparisons of algorithms by Drs. Binay Panda and Srinivas Aluru addressed the complexities involved in the understanding of mRNA sequencing and systems biology. In keeping with this, Dr. Raja Mazumder also demonstrated the downstream analysis, which interprets the functions of protein through evolutionary conservations 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, this theme of speakers provided an overview on current bioinformatics challenges and recent cutting edge developments that are in place to overcome several of these critical practical issues.

**Conclusion 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 employ 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 included the identification (and validation using GCGC sites) of specific splice variants and SNPs associated with TNBC, Non-TNBC and HER2-positive breast cancers (13) and to expend the significance of these alterations to other cancer-types. In addition, a new GCGC collaborative project is also planned to identify “saintly signature” that results from pre-operative progesterone treatment, which might be a component of the recently reported enhanced survivals of breast cancers patients (21). The group now wishes to perform the whole transcriptome analysis of the paired tumor samples from TMC tumor bank. There is also a lot 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 the 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.

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