The Global Cancer Genomics Consortium's Second Annual Symposium: Genomics Medicine in Cancer Research

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Rakesh Kumar^{1,2}, Anelia Horvath^{1,2}, Raja Mazumder², Masakazu Toi³, Fumiaki Sato³, M. Radhakrishna Pillai⁴, Luis Costa⁵, Maria Carmo-Fonseca⁵, Stefan Knapp⁶, Amit Dutt⁷, Sudeep Gupta⁷, and Rajendra Badwe⁷

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Abstract

The Second Annual Symposium of the Global Cancer Genomics Consortium (GCGC) was held at the Tata Memorial Center in Mumbai, India, from November 19 to 20, 2012. Founded in late 2010, the GCGC aims to provide a platform for highly productive, collaborative efforts on next-generation cancer research through bridging the latest scientific and technology developments with clinical oncology challenges. This year's presenters brought together highly innovative interdisciplinary views and strategies to meet major challenges in cancer research. The symposium featured 3 major themes: OMICS approaches toward the identification of cancer molecular drivers, single-cell analysis in cancer, and clinical and translational genomics. Each theme was represented in presentations of new findings, with an obvious implication in cross-disciplinary components of OMICs and an overwhelming participation by students. In summary, the GCGC symposium provided a discussion and congregation of the latest advances in basic and translational cancer research and offered the participants with a highly cooperative network environment for future collaboration.

Keywords

genomics medicine, anticancer target, cancer therapy

Introduction

Initially formed between 6 leading clinical and research institutions from 5 countries, the Global Cancer Genomics Consortium (GCGC) is a constantly expanding initiative, connecting a growing number of members and meeting participants.¹ This year's GCGC symposium attracted 210 participants, accommodating 25 invited platform speakers and 50 poster presenters. The overarching goal of the GCGC is to disseminate cutting-edge ideas and knowledge on basic and translational cancer research, aiming to meet the challenges in cutting-edge cancer medicine.

In the post-genome-sequencing era, next-generation approaches aiming to decipher the human genome, transcriptome, and proteome are increasingly finding potential roles in the diagnostics, prevention, and treatment of cancer. This in turn is contributing to an unprecedented increase in the demand for formal educational training to appreciate this growing area of science. The GCGC initiated a large-scale effort to provide a collaborative networking platform for the congregation of real-time, up-to-date technological advances, scientific discoveries, and clinical challenges. The Second Annual Symposium featured a highly stimulating educational and professional environment, accommodating a broad array of clinical and research specialists, from students and young scientists to commercial technology developers and leading international experts. Impressive progress in the involvement of the young Indian

scientific community in the next-generation sequencing efforts was evident through multiple, creatively displayed student projects.

Focus on Cancer's Translational Landscape

The major priority of the meeting was to facilitate the knowledge and technologies in the post-genomic era toward anticancer translational strategies and platforms. The symposium was opened by Dr. Rajendra Badwe from

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¹The Global Cancer Genomics Consortium, the McCormick Genomic and Proteomic Center

²Department of Biochemistry and Molecular Medicine, the George Washington University, Washington, DC, USA

³Kyoto University Graduate School of Medicine, Kyoto, Japan

⁴Rajiv Gandhi Center for Biotechnology, Kerala, India

⁵Hospital de Santa Maria and Institute of Molecular Medicine, Lisbon, Portugal

⁶Structural Genomic Consortium, University of Oxford, Oxford, UK

⁷Tata Memorial Centre, Mumbai, India

Corresponding Author:

Rakesh Kumar, Department of Biochemistry and Molecular Medicine, The School of Medicine and Health Sciences, The George Washington University, 2300 Eye Street Northwest, Ross 530, Washington, DC 20037
(Email: bcmrxk@gwu.edu).

the Tata Memorial Center, and the introductory remarks were made by Dr. Rakesh Kumar from the George Washington University. Drs. Badwe and Kumar shared the message of the Annual GCGC Symposium, emphasizing the importance of disseminating ideas, knowledge, expertise, and resources for the faster development of effective diagnostic and therapeutic outcomes. The meeting was organized into 8 platform sessions followed by an extended discussion on the platforms' concurrent poster exhibition and was concluded with a short communication of emerging breakthrough findings under the session "Yet to Be Reported Discoveries."

The symposium focused on 3 major scientific and clinical themes: 1) OMICS approaches to identify cancer-causing drivers that can be potentially used as therapeutic targets; 2) single-cell analysis in cancer; and 3) cancer genomics, transcriptomics, and proteomics in the clinic. In addition, the need for efficient data exploration through data integration and multiplatform alignment was constantly emphasized throughout the meeting to achieve a high-value collaborative project.

OMICS Approaches to Identify Anticancer Targets

High-throughput search for molecular targets. OMICS-based approaches to identify anticancer targets occupied a majority of the discussion foci, with a special emphasis on transcriptomics. The subject was introduced by the opening keynote lecture of Dr. Maria Carmo-Fonseca from the Institute of Molecular Medicine. Dr. Carmo-Fonseca focused on high-throughput identification of splicing factors deregulated in cancer that can lead to the expression of cancer-specific splice variants, potentially contributing to the tumor initiation, progression, and response to therapy. As a major challenge in the field, Dr. Carmo-Fonseca highlighted the ability to accurately distinguish driving and growth advantage—providing splice isoforms, which can be potentially used as anticancer targets.² On the note of splicing, alternative splice variants that can distinguish breast cancer subtypes, such as HER2-positive, ER-positive, and triple-negative breast cancer (TNBC), were discussed in the presentation of Dr. Anelia Horvath from The George Washington University, who demonstrated examples of analytical strategies to identify biologically significant splice isoforms using the datasets generated from whole transcriptome sequencing.³ Further, transcriptome-based strategies to distinguish breast cancer subtypes were explored by Dr. Rakesh Kumar. He presented a creative approach to outline the unique molecular features of the therapeutically challenging TNBC through a generation of isogenic clones expressing HER2 and ER α receptors in a TNBC background. The confidence of the unique TNBC expression

signature was facilitated through the generation of HER2 and ER α isogenic clones in different TNBC breast cancer cell lines. Another creative OMICS-based approach to precisely differentiate precancerous and early stages from advanced tumor lesions was presented by Dr. Binay Panda from Ganit Laboratories. Dr. Panda is attempting to identify genome, transcriptome, and epigenome features, distinguishing normal tissue from oral tongue squamous cell carcinoma.⁴ The power of integrative genomics was further exemplified in the presentation of Dr. Murali Bashyam from the Center for DNA Fingerprinting and Diagnostics, whose presentation was focused on the identification and characterization of novel pancreatic cancer genes.⁵

A combined genomics-proteomics approach to follow the expression of ion channels in the progression of epithelial-derived human cancers was presented by Dr. Norman Lee from the George Washington University. Decreased anionic and increased cationic channel expression was found to recurrently correlate with the progression of prostate, colon, breast, and liver cancers, and the role of these ion channels was assessed in xenograft mouse models. The tumors exhibited decreased growth and metastatic potential when treated with compounds affecting ion channel expression, among which were commonly used in noncancer-related drugs, such as neurosteroids and flecainide. Dr. Lee also discussed the potential repurposing of such compounds to anticancer therapy.⁶ An innovative proteomics-based strategy, phosphoproteomics, was presented by Dr. Akhilesh Pandey from the Institute of Bioinformatics, who shared the importance of individual patterns of phosphorylated kinase signatures in different subsets of patients with breast and pancreatic cancers and discussed the potential applications of such kinase phosphorylation profiling for personalizing therapy.⁷ Dr. Pandey also presented a draft map of the human proteome studies carried out in his laboratory and showed a surprising expression and translation of more than 400 pseudogenes using an elegant multi-Omics analysis (from genome to proteome) at the "Yet to Be Reported Discoveries" session.

Cancer mechanisms discovered through OMICS approaches. In terms of novel molecular mechanisms, the DNA damage repair (DDR) pathway in cancer was discussed in several presentations. Dr. Rameshwar Bamezai from the National Center for Applied Human Genetics highlighted the importance of understanding the genetic variations and microRNA regulation in the DDR pathway in cancer susceptibility.⁸ On the same note, Dr. Sunita Saxena from the Safdarjung Hospital reported an association between the breast cancer risk and genetic variants in DDR and the cell cycle pathway in the context of betel quid chewing.⁹ Dr. Indraneel Mitra from the Tata Memorial Center discussed the potential activation of the DDR pathway as a key element of the

biological effects of the extracellular nucleic acids.¹⁰ In addition to the DDR pathway, a novel mechanism of AP-1-mediated up-regulation of inflammatory pathways in glioma was shared by Dr. Subrata Sinha from the National Brain Research Institute.¹¹

A major finding in cancer biology was presented by Dr. Kumar in the breakthrough session “Yet to be Reported Discoveries.” Dr. Kumar shared recent results from his team, showing a novel model of dynamic co-repressor/co-activator regulation of chromatin signaling through alteration of the methylation status of the MTA1 master co-regulator. The discovery of the MTA1 methylation/demethylation as a molecular switch toward opposite biological functions changes the current understanding of static chromatin regulation and opens new venues in chromatin dynamics. He further discussed the significance of these findings in modifying the genome-wide targets of MTA1 and its impact on biological processes.¹²

OMICS in cancer epidemiology. The OMICS-triggered advances in cancer epidemiology were presented by Dr. Uwe Völker from the Ernst-Moritz-Arndt-Universität and Dr. Rajesh Dikshit from the Tata Memorial Center. Dr. Völker highlighted the role of novel population-based strategies, including plasma proteomic and metabolomic database generation, to set reference values for an expanded comparative platform.¹³ Dr. Dikshit focused on the advantages provided through high-throughput studies to address the classic cancer epidemiology challenges such as weak effects, complex phenotypes, and environmental exposure. Both presentations underlined the importance of population-based genomic platforms.¹⁴

Single-Cell Approaches in Cancer

The necessity in understanding the intracellular processes underlying cancer biology was acknowledged throughout the entire meeting, and several breakthrough methodological reports discussed the advantages of single-cell analysis to digest subcellular cancer features. Dr. Akos Vertes from the George Washington University presented 2 cutting-edge mass spectroscopy applications, employing new ion sources to study single-cell metabolomics developed in his laboratory. Silicon nanopore arrays (NAPAs) were generated to serve as an ultrasensitive ionization platform in laser desorption ionization mass spectroscopy. NAPAs exhibited unique ion production properties, extending their sensitivity to an approximately 800-zmol range, which enables the analysis of a single-cell yeast. The second technique, laser ablation electrospray ionization (LAESI) mass spectroscopy, employs ultra-sharp optical fibers to deliver a laser pulse with less than a 3- μ m wavelength, causing the water content of the cell to undergo phase explosion and to

produce a plum of particulates, which is intercepted by an electrospray to produce sample-specific ions. Combining fiber-based LAESI with microdissection on the cellular level enables the analysis of subcellular compartments.¹⁵

Another advanced single-cell methodology was presented in the session “Yet to be Reported Discoveries” in which Dr. Carmo-Fonseca shared a unique novel approach, allowing real-time following of the splicing dynamics through creative visualizing of the order of intron removal at the level of a single molecule using different fluorescent dyes. Dr. Carmo-Fonseca discussed the broad potential of the approach to investigate how specific regulatory sequence motifs and splicing factors influence intron dynamics and impinge on splicing decisions.

In the field of analytical and computational strategy toward deciphering single-cell features, an advanced analytical strategy, high-dimensional computational cytomics, was presented by Dr. Saumyadipta Pyne from the Advanced Institute of Mathematics, Statistics and Computer Sciences. Dr. Pyne’s group applies high-resolution single-cell multi-marker analysis to classify specific cellular subpopulations within complex mixtures, such as cancer, an approach of tremendous significance in the characterization of intertumor and intratumor heterogeneity¹⁶

Cancer Genomics, Transcriptomics, and Proteomics in Clinics

The application of high-throughput approaches in clinics covered a broad spectrum of developments from basic scientific studies on the effect of therapeutic strategies on cancer growth and invasion through pure clinical assessments of the results of treatment.

Scientific developments toward therapy. The theme was opened by Dr. Stefan Knapp from the University of Oxford, who shared a strategy to modulate cancer transcription by highly selective targeting of epigenetic effectors such as bromodomains (BRDs).¹⁷ Dr. Knapp presented the current progress on the development of specific chemical probes against certain BRDs, whose modulation exerts either strong antitumor or tumor growth-promoting effects. Another basic research strategy on targeting cancer was presented by Dr. Sorab Dalal from the Advanced Centre for Treatment, Research and Education in Cancer–Tata Memorial Center, whose group is focused on centrosomal amplification as a mechanism triggering cellular transformation. Dr. Dalal demonstrated that activation of CDC25C can lead to the disruption of centrosomal amplification, resulting in chromosomal clustering and inhibition of neoplastic transformation.¹⁸ Transcription targeting of the human papillomavirus oncogene by curcumin (diferuloylmethane) used in traditional medicine was presented by Dr. Bhudev Das from

the University of Delhi. Dr. Das presented data, establishing that both native curcumin and its hydrophilic folic acid derivative selectively down-regulate the transcription of both HPV18 and host cell transcription factor AP-1.¹⁹ Dr. Das further discussed the potential application of the approach against cervical cancer, for which, despite successful vaccine developments, no treatment is currently available. The role of traditional medicine and dietary components in cancer management was further explored in the presentation of Dr. Suman Kapur from the Birla Institute of Technology and Science, who discussed the scientific evidence for anticancer properties of bioactive food and herb compounds provided by high-throughput methylation studies.

Estimation of treatment response. The emerging impact of genomic approaches on improved clinical outcomes was demonstrated through several studies on the effect of anti-cancer treatment. Dr. Fumiaki Sato from Kyoto University demonstrated the feasibility of microRNA assessment to predict the effect of trastuzumab therapy in HER2-positive breast cancer.²⁰ The strong practical potential application of Dr. Sato's studies was seen in the demonstrated ability to analyze microRNAs from FFPE blocks, a development with tremendous impact due to the broad availability of such material used historically as a major preservation approach.²¹ The presentation of the genomic applications in cancer clinics was offered in the talk "Making Head and Tale of Genomics in Clinics" by Dr. Rajendra Badwe. He presented an ongoing clinical trial, estimating the effect of progesterone infusion prior to the surgical removal of breast cancer tumors. The molecular effects of progesterone are being studied through transcriptome sequencing and aligned to the clinical outcome for the development and optimization of personalized therapy platforms.²²

Integration of Resources and Efforts to Facilitate Discovery and Education

The versatile applications of OMICS in cancer were illustrated in the talk of Dr. Amit Dutt from the Advanced Centre for Treatment, Research and Education in Cancer-Tata Memorial Center, who presented an integrated analysis using next generation sequencing platforms and SNP arrays on cancer specimens of Indian ethnicity with strong focus on in-house informatics pipeline and functional validation of the alternations. Project themes covered a broad array of interests; a significant proportion aimed at defining the molecular landscape of highly prevalent endemic cancers, head and neck cancer, lung and breast cancers. Another major direction was the implementation of high-throughput approaches in practical clinical applications such as determining the pharmacogenetics/pharmacokinetics of commonly used anticancer drugs and the feasibility of screening

buccal mucosal cells for the diagnostics of lung and other upper aerodigestive tract cancers. Strong bioinformatic subsistence was evident across the presentations, and several specialized groups reported novel computational biology approaches to increase the efficiency of the analyses and to facilitate discovery. The need for gathering the resources for more efficient data analysis and information extraction was further illustrated in the talk of Dr. Raja Mazumder from the George Washington University. Dr. Mazumder presented exciting data on the high-throughput estimation of the effect of protein-altering changes through multiplatform data integration and emphasized the need for modern educational approaches to attract a high number of young scientists to the emerging and promising field of OMICS.²³

The Next Step

The meeting concluded with the much anticipated session on "Yet to be Reported Discoveries" by speakers as briefly highlighted in the preceding sections. Dr. Kumar presented his thoughts about the dynamic evolution of this forum since the last year and the value of moving them each year. He also extracted the high points from various sessions via a common thread - how to position the on-going revolution in Genome Medicine for the benefits of mankind in addition to advancing the knowledge base. Dr. Kumar also pointed out an obvious success of the meeting as judged by the number of participating students, the posters presented, the burning questions from the floor, and the blocks of active discussions by students in corridors of the venue during breaks and poster viewing periods. Drs. Carmo-Fonseca and Kumar concluded the meeting by announcing that the next GCGC meeting will be held in Lisbon, Portugal and invited all to Lisbon in September 2013.

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