Multi-targeted Approach to Cancer Treatment: An International Translational Cancer Research Symposium

KAPIL MEHTA1, VARSHA GANDHI1, SEN PATHAK2, BHARAT B. AGGARWAL1 and RAJESH K. GROVER3

Departments of 1Experimental Therapeutics and 2Genetics, The University of Texas MD Anderson Cancer Center, Houston, TX, U.S.A.; 3Delhi State Cancer Institute, Dilshad Garden, Delhi, India

Abstract. Whether it is chronic myeloid leukemia, ALK-expressing malignancies, or HER2-positive breast cancer, targeted-therapies for treatment of human cancers have shown great promise. However, as they hit a single molecule expressed in neoplastic cells, their use is frequently associated with development of resistance. In cancer cells many signaling pathways operate in parallel, hence the idea of multi-targeted therapy is prevailing. The Society of Translational Cancer Research held its biennial meeting in the capital city of India, Delhi from February 6th through 9th, 2014 to discuss ‘Multi-targeted Approach to Treatment of Cancer’. Over 200 scientists, clinicians, trainees, and industry representatives from different countries gathered in Vigyan Bhavan, the hotspot of Delhi for four days to talk and discuss on a variety of topics related to multi-targeted therapeutic approaches. Talks were presented by leaders in the cancer research field from various countries. It became clear from this conference that coupling multiple targeted-agents or using an agent that hits an individual target in several independent locations in the disease-causing pathway(s) may be the best approach to treat different cancers.

Just prior to this conference (July 6-9, 2014), a report compiled by more than 250 scientists from over 40 countries was released on the eve of World Cancer Day (February 4, 2014) (1). The report alluded to some staggering estimates that globally new cases of cancer will rise from 14 million in 2012 to 21.6 million per year by the year 2030. Similarly, cancer deaths will likely rise from 8.2 million to 13 million per year. The report also reflected some demographic bias: more than 60 percent of the world’s cancer cases and 70 percent of deaths occurred in Africa, Asia and Central and South America. Almost half of the new cases diagnosed in 2012 were in Asia, most of them in China. Europe had nearly a quarter of cases, the Americas about a fifth, and Africa and the Middle East just over eight percent. But when it came to deaths, Asia’s share jumped to more than 50% and that of Africa and the Middle East to nearly 10%, while the Americas’ share shrank to under 16% and that of Europe to 21.4%.

According to another magazine (India Today) published to commemorate World Cancer Day, cancer is tightening its grip on India (2). In India, lung and oral cancers are the most common among men while cervix and breast cancer are strikingly more frequent in women. Cancer is one of the leading causes of deaths in India, which has nearly three million patients suffering from the disease. Nearly, 500,000 people die of cancer every year in this country and this number is expected to rise to 700,000 by 2015. According to the report - of more than 300 cancer Centers in India, 40% are not adequately equipped for advanced cancer care. India will need at least 600 additional cancer centers by 2020 to meet cancer care demands.

With these facts in mind, we have been holding biennial Translational Cancer Research meetings in India to promote cancer awareness, education, and exchange of information for fostering collaborative efforts among researchers and clinicians from East and West. As with the current symposium, previous four conferences were organized under the umbrella of the Society of Translational Cancer Research. The venue changes for each conference as well as the scientific focus of the meeting (3-5). This fifth conference concentrated on ‘Multi-targeted approaches to Treatment of Cancer’ and was held during February 6-9, 2014 at the state-of-the-art conference facility, Vigyan Bhavan in Delhi (6).
The meeting started with a ‘Public Forum’ that was open to general public and college and high school students to educate them about causes and prevention of cancer. This was followed by release of hot air balloons and gas balloons - carrying messages on cancer awareness. In the evening, Hon’ble Vice President of India, Mr. Hamid Ansari, inaugurated the meeting. In his inaugural address, he welcomed delegates and invited them to enjoy the rich traditions and culture of India. He emphasized the importance of joint efforts to find cost-effective and safer drugs for cancer. He strongly endorsed the need to increase education and awareness about cancer in India. To commemorate the occasion, he released a book titled–Nature – a collection of paintings complied by Mrs. Elizabeth Anthony (wife of Defense Minister of India) whose proceeds will go to support the cancer patients. The Evening ended with a Keynote Lecture by Dr. Oliver Bogler (Global Oncology Program, MD Anderson Cancer Center, Houston, TX, USA). Dr. Bogler recognized that the complexity of cancer would require collaborative and complementary effort worldwide. He discussed the Global Academic Program of MD Anderson Cancer Center that was created under the umbrella of the Center for Global Oncology (www.mdanderson.org/gap). This academic program consists of 30 sister institutions from 20 countries in Asia, Latin America, and Europe, including the Tata Memorial Center (Mumbai) and Delhi State Cancer Institute (Delhi) from India. The sister institutions carry out collaborative work in cancer diagnosis, prevention, and treatment. “Epidemiological investigators are studying the diversity of cancer and its relation to genetics, epigenetics, environment and lifestyles in different countries”, he said. He then discussed the need and strategies to promote global collaborations to find safe and effective treatments for cancer. The evening concluded with a Sarod recital (an Indian musical instrument) by legendary Maestro, Ustad Anjaj Ali Khan.

The meeting started with an early morning session ‘Meet the Professor’ where senior faculty interacted with students and trainees under informal settings and shared their experiences and answered questions related to successful careers in cancer research, education and treatment. After sunrise sessions, two Plenary Sessions were organized, each day before lunch break.

The first Plenary Session on ‘Tumor Microenvironment’ was co-chaired by Drs. R.K. Grover (Delhi State Cancer Institute, Delhi) and Sen Pathak (MD Anderson Cancer Center, Houston, USA). First speaker in this session, Dr. Alberto Mantovani (Univ of Milan, Italy) discussed the evidence that tumor associated macrophages (TAMs) play fundamental roles in promoting tumor progression and presented data to support the benefit of targeting TAMs for treating human cancer. Next, Dr. Anirban Maitra (Houston, TX) presented an overview of some natural products and their potential for multi-targeted therapy. Because of high lipophilic nature of these compound and poor bioavailability, he presented data supporting that the use of drug delivery systems, particularly nanoparticles, is an effective way to circumvent this problem. Last speaker in this session, Dr. Caroline Dive (University of Manchester, UK), discussed recent advances on circulating tumor cells (CTCs) and their relevance in diagnosis of cancer and intratumoral heterogeneity. She shared information on molecular profiling of CTCs from human small cell lung carcinoma and discussed CTC-derived mouse models for lung cancer.

The second Plenary Session was dedicated to Gastroesophageal Cancers (GECs) and co-chaired by Drs. Anil Agarwal (GB Pant Hospital, Delhi) and Kapil Mehta (MD Anderson Cancer Center, Houston, USA). Dr. Jeff Ajani (MD Anderson Cancer Center, USA), the first speaker in this session discussed the heterogeneity in GECs. He shared the view that protein overexpression or gene amplification may not be sufficient to target and treat GECs rather taking advantage of the host immune system to identify and destroy GEC may be the frontier that should be considered. Dr. VK Kapoor (Sanjay Gandhi, Postgraduate Institute of Medical Sciences, Lucknow, India) discussed the incidence, biology, and challenges in treating and early diagnosis of gallbladder cancer (GBC). He emphasized the need to identify biomarkers that can be used to screen asymptomatic persons with gallbladder stones, a major risk factor in GBS etiology. Next speaker, Dr. Milind Javle (MD Anderson Cancer Center, Houston, USA) discussed data on genomic analysis of cholangiocarcinoma (CCA) patients and concluded that mutations in chromatin modulating genes, ERRB2 and FGFR are most common in this subset of patients.

The third Plenary Session ‘Targeting DNA and RNA machinery’ was held next day morning and Co-chaired by Drs. SD Banavali (Tata Memorial Cancer Center, Mumbai, India) and Varsha Gandhi (MD Anderson Cancer Center, Houston, USA). Dr. Bill Plunkett (MD Anderson, Houston, USA) - the first speaker in this session discussed approaches of inhibiting DNA damage repair pathways in tumors that lacked compensatory homologous repair pathways. He presented data on a nucleoside analogue, Sapacitabine that generates a genetic lesion similar to that caused by PARP inhibitors. Hence, this nucleoside analogue could sensitize the viability of cells that lack essential elements of homologous DNA repair such as ATM, BRCA-1 or BRCA-2. He summed-up the ongoing clinical studies with Sapacitabine in patients with mutations in these DNA repair genes. Dr. Yves Pommier (NCI, Rockville, USA) presented evidence that PARP inhibitors act as cytotoxic anticancer agents by trapping PARP-DNA complexes and discussed the rationale for combining PARP inhibitors with topoisomerase I inhibitors. Last speaker in this session, Dr. William Beck.
(University of Illinois, Chicago, USA) discussed the role of splicing factors in drug resistance and their therapeutic implications in cancer. Specifically, he presented evidence that knockdown of PTPB1 splicing factor in ovarian cancer cells could inhibit the cell growth, decrease invasiveness, and alter expression of more than 1,000 genes. Importantly, this inhibition sensitized cancer cells to chemotherapeutic drugs.

Fourth Plenary session on day three was co-chaired by Drs. Gopal Kundu (National Center for Cell Sciences, Pune, India) and Caroline Dive (University of Manchester, UK) and was focused on the theme of Targeted Therapies. First speaker, Dr. Nitin Jain (MD Anderson Cancer Center, Houston, USA) discussed some targeted-therapies that are underway to improve disease outcome in patients with relapsed chronic lymphocytic leukemia (CLL). Some examples included the CD20 monoclonal antibodies, CD52 monoclonal antibodies, immunomodulatory drug (lenalidomide), B-cell receptor inhibitors (ibrutinib, idelalisib, CC-292) and Bcl-2 antagonist (ABT-199). The data he presented on Ibrutinib as monotherapy, is able to induce an overall response rate of 75% in relapsed/refractory CLL patients, while additional 13% patients achieved partial response. Next speaker, Dr. Sachin Jain (Quest Diagnostic, India) discussed the problems associated with molecular monitoring of chronic myeloid leukemia in response to targeted tyrosine kinase inhibitor. He emphasized the need for using the ratio of BCR-ABL1 transcript to ABL1 transcripts or other internationally recognized control transcript as Standard International Scale to evaluate responses in CML patient to allow timely decisions with regard to therapeutic strategy. Last speaker of this session, Dr. Sapna Patel (MD Anderson Cancer Center, Houston, USA) discussed molecular analysis of Leptomeningeal Carcinomatosis Melanoma –a highly aggressive stage of metastatic melanoma. She shared data on a small cohort of patients (n=38) with the disease which received intrathecal IL-2 at MD Anderson and were analyzed for mutations. Of the 25 evaluable patients, 68% (n=17) showed BRAF and 28% (n=7) showed NRAS mutation. Of the total IL-2 treated patients, 24 were confirmed diseased, 16 of which had the mutation (63% with BRAF and 31% NRAS mutation). ‘Larger cohort of patients are needed to validate these findings and to determine if NRAS/BRAF targeted therapies can be effective in these patients’, she emphasized.

The next day, fifth Plenary Session was dedicated to Signaling Biomarkers and was co-chaired by Drs. V. Gupta (AIIMS Delhi, India) and Bill Plunkett (MD Anderson Cancer Center, Houston, USA). In an opening lecture Dr. Gyatri Rath (Safdarjung Hospital, New Delhi, India) presented data on HPV infections in cervical cancer patients from India. HPV-16 was most prevalent affecting almost 100% patients in CIN group. Importantly, HPV infection was associated with activation of Wnt/β-catenin signaling pathway and inactivation of glycogen synthase kinase 3β in squamous cell carcinoma, suggesting a synergistic role of HPV with Wnt/β signaling due to glycogen synthase kinase 3β inactivation in the disease progression. Next speaker, Dr. Sunita Saxena (National Institute of Pathology-ICMR, Delhi, India) discussed genomic approaches to identify molecular signatures and biomarkers for esophageal cancer in India. In a cohort of 16 non-familial tobacco-chewing patients, 127 genes were found differentially regulated (87 up-regulated and 40 down-regulated). Based on known functions of these dysregulated genes, four molecular functional pathways (MAPK, G-protein couples receptor family, ion transport activity, and serine threonine kinases) were up-regulated and six pathways (structural constituents of ribosome, endopeptidase inhibitor activity, constituents of cytoskeleton,
antioxidant activity, acyl- group transferase activity, translational elongation factor activity) were down-regulated. Interestingly, the gene profiles of familial and non-familial esophageal cancers were significantly different. Data on novel SNPs and their deleterious effect on some key genes were presented. Last speaker in this session Dr. Ravi Mehrotra (Institute of Cytology and Preventive Oncology, Noida, India) discussed in detail the feasibility and implementation of various cost-effective integrated programs for screening preventable cancers (breast, head and neck and cervical cancers) in India.

The last and sixth Plenary Session of this meeting was appropriately focused on Integrative Medicine and co-chaired by Drs. BB Aggarwal (MD Anderson Cancer Center, Houston, USA) and CV Rao (Oklahoma State University, USA). The first speaker, Dr. Shripad Banavali (Tata Memorial Center, Mumbai, India) discussed his metronomic therapy experiences in refractory and early stage cancer patients at the Tata Memorial Cancer Center. He emphasized that these therapies target not only the tumor but also its microenvironment, which may lead to superior control and cure rates. There is a need for more scientific research and systematic clinical studies to validate the benefits of metronomic therapies as these therapies cost a fraction of what the conventional therapies cost and at the same time give cancer patients an excellent quality of life.

The next speaker, Dr. Massimo Bonucci (Outpatient Laboratory Oncology, Rome, Italy) shared with the audience clinical experience of using combinations of natural compounds with radiation and chemotherapies for treatment of cancer. The data presented suggest that such drug-natural compounds combinations are safe, cost-effective and active in management of certain types of cancers. Continuing on the theme of Integrative Medicine, Dr. Seong W. Yoon (University Korean Medicine Hospital, Seoul, Republic of Korea) discussed the importance of Traditional Korean Medicines in prevention and treatment of cancer. He alluded to the belief that cancer is an outcome of imbalance of body, mind, and spirit hence it requires a multimodal treatment approach that involves changes in lifestyle, use of herbs, acupuncture, and exercise to restore the balance. Complementary to this theme, the next speaker Dr. H.R. Nagendra (Yoga University, Bangalore, India), discussed principles of Yoga (part of Indian traditional medicine) in control and treatment of cancer. “While radiation, chemotherapies and surgery can control the symptoms - management of cancer should also involve balancing the mind and spiritual status of the body” he said. He presented evidence that Yoga as an add-on therapy using techniques offered at five different levels, were effective in improving the immune status, ability to cope up with the toxic effects of chemotherapy, and improve general health of cancer patients. Last speaker, Dr. P. Banerji (Banerji Homeopathic Research Foundation, Kolkata, India) discussed his experiences in treating Glioblastoma (GBM) patients using homeopathic medicine-based regimen. Out of the 37 patients treated with homeopathic medicines alone, the mean survival rate was 48 months while those treated with homeopathic medicines along with conventional therapy had a mean survival of 30 months. Like other speakers, he highlighted the fact that these medicines are free of toxicity, inexpensive and can be utilized in an outpatient clinic setting. He invited clinical researchers to conduct clinical trials with these safer protocols in their respective institutions.

In addition to these major symposia, nearly sixty researchers presented their research in eight mini-symposia that were focused on similar topics as plenary sessions in the morning. These parallel mini-symposia provided an excellent platform for many local students and young scientists from India to discuss their research to an international audience. Similarly, more than seventy students, trainees and fellows presented their research in two Poster Sessions that were attended by all the participants. Highlight of Poster sessions was - interactive media where each presenter could show the video of their data on a large LCD screen using PC computer. Another highlight of the meeting was Panel Discussion sessions. A total of five such sessions were held that focused on different topics of general interest. Each Panel Discussion Session comprised of two moderators and 4-6 panelists who raised highly relevant questions/issues related to that topic and audience were invited to give their feedback. The conference was well attended (Figure 1) and everyone enjoyed the hospitality, venue, and cultural programs that were held every evening during dinner. The meeting concluded with a vote of thanks from the organizers and announcement for next – 6th Translational Cancer Research Conference: Cancer Resistance and Metastasis –to be held in Ahmadabad (Gujarat) from February 4-7, 2016. Please visit the website (6) to review previous meetings and to stay tuned for updates for next meetings.

Conflicts of Interest
Authors have no potential conflicts of interest.

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We apologize to many speakers whose work could not be discussed in this report.

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