

Meeting Report

Leaders in Translational Cancer Research Meet in Udaipur, a Historical Town of India: An International Symposium on Translational Cancer Research: Cancer Prevention. Udaipur, Rajasthan, India, December 16-19, 2011

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Abstract. *Like most countries in the Western world, most non-communicable diseases, such as cancer, are very much on the rise. Extensive research suggests that cancer is a preventable disease that requires a major change in lifestyle. The fourth International Translational Cancer Research Symposium on Cancer Prevention was convened from Dec. 16th through Dec. 19th, 2011 in Udaipur, Rajasthan, the largest state located on the northwestern side of India. Scientists, clinicians, and trainees from different countries participated in this conference to discuss biological processes involved in cancer and various avenues to prevent cancer. It became clear from this conference that tobacco use, alcohol consumption, diet and obesity, radiation, and pollution may account for many carcinomas.*

During the past half a century, there have been major advances in our understanding of cancer biology. Yet the prevention and treatment of cancer remain challenging. According to the World Health Organization, the incidence of cancer is expected to double within next 20 years. Most of this doubling is expected to come from India and China, where the overall lifestyle is becoming increasingly westernized. Thus it is quite appropriate that the conference Translational Cancer Research: Cancer Prevention was focused on discussing these developments.

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The prior three conferences organized in India had focused on different aspects of Translational Cancer Research (1, 2). The fourth conference focused on cancer prevention (3). The symposium was initiated by a plenary presentation by Dr. Margaret Foti, the President of the American Association for Cancer Research (AACR, Philadelphia, PA, USA). She was introduced by Dr. Varsha Gandhi (MD Anderson Cancer Center, Houston, TX, USA). Dr. Foti discussed incidences of cancer in the USA and different activities of the AACR and how they are relevant to prevention and treatment of cancer. Just prior to this conference, the AACR had their first meeting in India in New Delhi which clearly indicated association's interest in reaching out to Indian cancer researchers.

Starting the following morning and for the next three days, attendees participated in 10 different scientific sessions in the main symposium. To set the pace and to understand the gravity of the situation, the inaugural talk of the first session on cancer prevention was on the topic "Cancer in India – How bad it is?" by Dr. R. K. Grover (Delhi State Cancer Institute, Delhi, India). Not only is the incidence of cancer changing, but also the disease site. At present, among the 1.3 billion population of India, 1.3 million individuals suffer from cancer. It is expected that by 2035, the population in India will increase to 1.6 billion and a soaring 5 million people will be inflicted with this disease. In major metropolitan cities such as Delhi, Mumbai, Bangalore, breast cancer incidence is overtaking that of cervical cancer. The statistics are overwhelming and underscore an immediate need for translational cancer research and clinical cancer research in India.

Dr. Oliver Bogler (Global Academic Program, MD Anderson Cancer Center, Houston, TX, USA) recognized that >40% of the present population will be affected by cancer. This pandemic is not only an Indian issue, but also a global

problem. Importantly, the solution is also global. The complexity of cancer will require collaborative and complementary effort worldwide. With that in mind, MD Anderson Cancer Center has created a Global Academic Program under the umbrella of the Center for Global Oncology. This academic program spans over 23 sister institutions in several countries. These efforts foster collaborative interactions worldwide in cancer diagnosis, prevention, and treatment. Epidemiological investigators will determine the diversity of cancer and its relation to genetics, epigenetics, environment and lifestyles of different countries. The role of epidemiology, locally and globally, for cancer was further elucidated by Dr. Xifeng Wu (MD Anderson Cancer Center, Houston, TX, USA) who focused on translational epidemiology in cancer risk assessment and prevention. Novel molecular epidemiological approaches integrated with basic analytical, translational, and clinical research are allowing for identification, testing and establishment of predictors for disease development, treatment, response, quality of life, and cancer survivorship.

The final talk in this session was delivered by Dr. Cherie-Ann Nathan (Louisiana State University Health Science Center City, Shreveport, LA, USA) and focused on head and neck cancers in India and other countries. She enumerated the risk factors for these malignancies that include (i) tobacco use, (ii) inadequate diet, (iii) lack of physical activity, (iv) exposure to radiation and occupational carcinogens, (v) infections and inflammation, and (vi) lack of treatment or treatment failure. Fortunately many of these risk factors are preventable, illustrating a general need for educating the public. She further reinforced that 40% of all cancer deaths are preventable; therefore cancer prevention is an essential and integral component of cancer control.

The second session revolved around inflammation and cancer under the overall theme of cancer prevention. The primary presentation was delivered by Dr. Raymond DuBois (MD Anderson Cancer Center, Houston, TX, USA), who focused on crosstalk between inflammatory modulators and their role in colorectal cancer. He informed us that this type of cancer is a major cause of morbidity. For example, 150,000 cases are diagnosed per year and 50,000 of these patients succumb to death annually. While a sedentary lifestyle, consumption of unsaturated fat and red meat, inherited/somatic mutations in key tumor-suppressor genes, and epigenetic changes increase the risk, and use of non-steroidal anti-inflammatory drugs (NSAIDs) and estrogens lower the risk. Lifestyle and diet can easily be controlled. He reviewed a series of research projects that suggest that there is a crosstalk between prostaglandin E2, a pro-inflammatory mediator involved in tumor progression, and the peroxisome proliferator-activated receptor family that regulate the catabolism of dietary fats and play a pivotal role between colonic inflammation and colorectal cancer progression.

Focusing on the gastrointestinal disease site, Dr. C.V. Rao (Center for Chemoprevention and Cancer Drug Development, Oklahoma Cancer Center Oklahoma City, OH, USA) presented lipoxygenase-cyclooxygenase (Lox-Cox) pathways as potential targets for pancreatic cancer prevention and treatment. He discussed the evidence that a Lox/Cox inhibitor, licofelone, suppresses the progression of pancreatic intra-epithelial neoplasia to pancreatic ductal adenocarcinoma. Furthermore, the activity of pancreatic stem cell marker enzyme was suppressed by licofelone. Such approaches concurred with the overall theme of cancer prevention even for this difficult disease. Carcinoma of the gallbladder, another gastrointestinal disease, not that common globally, is the third most common type of cancer in India. Dr. Vijay K. Shukla (Banaras Hindu University, Varanasi UP, India) illustrated that incidence of this cancer is specifically high in Northern India, especially in Uttar Pradesh and Bihar states. He highlighted that the river Ganges passes through these states and its water is used for human consumption. He mentioned that heavy metals, especially cadmium present in the Ganges water may be a primary reason for the increased incidence of gallbladder cancer in these states. Removal of the heavy metals and establishment of other water sources are needed as gallbladder carcinoma prevention strategies. The role of the diet in cancer of another common site, breast, was highlighted by Dr. Kotha Subbaramaiah (Weill Cornell Cancer Center, New York, NY, USA). He emphasized that obesity is associated with inflammation and increased aromatase activity in breast cancer tissues of women. Estrogen production is catalyzed by aromatase, linking obesity and increased breast cancer risk.

The afternoon session (#3) focused on a well-established chemotherapy agent, taxol, which originates from a tree. Dr. Susan B. Horwitz (Albert Einstein College of Medicine, Bronx, NY, USA) systematically described the identification of taxol, its development, mechanism of action, clinical progress, and second-generation taxol analogs. This originally natural product has become among the most used chemotherapy agents. While Dr. Horwitz's talk reviewed the mechanism of action of taxol, Dr. Mansukh C. Wani (RTI International, Research Triangle Park, NC, USA) described the discovery and development of taxol. His talk entitled "From Bark to Bedside: A Personal History of the Discovery and Development of the Plant-derived Anticancer Agent, Taxol" focused primarily on the isolation of this compound from crude plant material and its chemistry, and summarized 30 years of effort to revolutionize the use of taxol for treatment of many solid tumor types. Dr. Richard Eckert (University of Maryland, Baltimore, MD, USA) elucidated the role of Activator protein one (AP1) transcription factors in epidermis. AP1 factors are a family of transcription regulators. Upstream of these factors are the RAS and MAP kinase pathway.

Helicobacter pylori-associated gastric cancer was summarized by Ki-Baik Hahm (Gachon Graduate School of

Medicine, Seoul, Korea). This presentation illustrated key molecular players that link *H. pylori*-mediated inflammation to gastric carcinogenesis. Connected with such inflammation was the fact that several plant products prevent or reduce this tumorigenic process.

The last session (#4) of the first day started with an informative presentation by Dr. John Mendelsohn (MD Anderson Cancer Center, Houston, TX, USA). His talk entitled "Personalized Cancer Therapy" identified factors in individualized treatment of patients that include identification of genetic changes involved in the pathogenesis of disease, differences in cancer cells from their normal counterparts, heterogeneity of disease in the same patient, complexity in trial design (including regulatory issues and ethical issues), operational issues and costs. He exemplified the importance of genetics by describing epidermal growth factor receptor (EGFR) inhibitors and factors such as EGFR mutations that were associated with responders. In contrast, mutations in *K-RAS* or *B-RAF* genes were related to non-responders.

Dr. Young-Joon Surh (Seoul National University, Seoul, South Korea) devoted his presentation to the modulation of redox signaling by anti-inflammatory plant products. He summarized some of the transcription factors as targets for chemoprevention by anti-inflammatory and antioxidant strategies. These transcription factors and regulators include p53, NF- κ B, NRF2 and STAT3. His model system included colorectal and pancreatic carcinomas. Focusing on colorectal carcinomas, Dr. Rashmi Sinha's (National Cancer Institute, Rockville, MD, USA) presentation provided evidence for increased risk of cancer in populations that consumed red and processed meat, heme iron, nitrate-nitrite and heterocyclic amines. This large prospective study (number of subjects=566,402) also identified consumption of coffee as a risk-reducing factor for this cancer.

Dr. Gopal Kundu (National Center for Cell Science, Pune, India) highlighted the impact of the stromal microenvironment on tumor maintenance and progression. In particular, signaling induced by osteopontin, which is derived from both tumor- and stroma-controlled expression of effector genes, contributes to tumor progression and angiogenesis.

The most studied and established substance correlated with cancer is tobacco. This was the topic for the first session of Day two (session 5), where researchers focused on the power of prevention by smoking cessation programs. Dr. Ellen R. Gritz (MD Anderson Cancer Center, Houston, TX, USA) emphasized on tobacco control efforts in India. This is particularly important because India is the second largest consumer of tobacco products. This is further enhanced by the fact that incidence of tuberculosis is highest in India. Emphasis on education of tobacco-addicted individuals of tobacco-mediated effects and on steps to eradicate its use are not only important, but are also essential.

Jennifer Grandis (University of Pittsburgh, Pittsburgh, PA, USA) focused on pathways that are activated in head and neck squamous cell carcinoma (HNSCC). In particular, STAT3, a transcription factor is induced in HNSCC. While STAT3 appears to be a target, it is difficult to target it. Targeting this transcription factor by small molecules or a 15-mer double-stranded decoy appears to be an approach that her group has advanced to the clinic. Cellular biomarkers during this early clinical trial suggest that inhibition of this transcription factor and down-regulation of target genes can be achieved.

Marc Diederich (Luxembourg Medical Center, Luxembourg City, Luxembourg) introduced a novel chemopreventive drug, cinnamic acid. This compound inhibits the expression of COX2 which is an important mediator of inflammation. In a non-carcinogenic breast cell line, COX-2 was induced by phorbol ester, while cinnamic acid inhibited this regulation.

Dr. A. Rangarajan (India, Institute of Science, Bangalore, AP, India) illustrated novel breast cancer models by exploiting the mammosphere model system. These mammospheres contain primitive mammary stem/progenitor cells. Manipulation of these cells by SV40 early region and hTERT resulted in a new cell line which not only served as a model system *in vitro* but also resulted in invasive ductal adenocarcinoma in immune-compromised mice. These cells exhibited stemness properties, self-renewal capability and transformation to malignant state.

Session 6 on day 2 focused on ageing and cancer. Ageing is associated with de-regulated cellular pathways. Dr. Curtis Harris (National Cancer Institute, Bethesda, MD, USA) exemplified age-associated cellular senescence and asymmetric cell division in human cancer. In lung cancer cell lines, the asymmetric cell division of template DNA was investigated. This was also noticed in short-term cultures of primary lung tumor. Mechanisms controlling these events in cancer cells are being identified to develop novel targets for cancer therapy.

STAT3 as a chemoprevention target was again recognized in hepatocellular carcinomas by Dr. Gautam Sethi (National University of Singapore, Singapore, Singapore). Sorafenib is a STAT3 inhibitor and was tested in a model system of hepatocellular carcinoma. A novel plant product called butein inhibited STAT3 phosphorylation and activity. Acetylation of STAT3 is reduced by garcinol, another natural compound. This inhibition prevents dimerization of the STAT3 protein and hence down-stream signaling.

A great example of cancer prevention strategy is human papilloma virus (HPV) testing and immunization for cervical cancer. This was emphasized and established by Dr. R. Sankaranarayanan (International Agency for Research on Cancer, Lyon, France). He has conducted several large studies in India to demonstrate that visual screening and a single round of HPV testing was associated with a significant reduction in the number of cases of advanced cervical cancer.



Figure 1

Dr. Omer Kucuk (Emory University, Atlanta, GA, USA) used soy isoflavones to inhibit AKT and NF- κ B in prostate cancer cells. Genistein, derived from soybeans, was found to inhibit cancer cell growth, as well as to induce apoptosis. These inhibitory actions were synergistic with established chemotherapeutic agents such as cisplatin and docetaxel.

Session seven was inaugurated by Dr. Lorenzo Cohen (MD Anderson Cancer Center, Houston, TX, USA) who focused on alternative approaches for cancer prevention. Chronic stress promotes tumor formation in female mice by affecting the neuroendocrine system. Yet, he emphasized that healthy nutrition could reverse this role. For example, vegetable uptake inhibited breast cancer development in women. Surprisingly, this was observed even in these BRCA-1 positive tumors.

Dr. Lalit Kumar (All India Institute Medical Science, Delhi, India) reviewed multiple myeloma pathogenesis in the Indian population. While the incidence is lower in India (2-3/100,000 people versus 6/100,000 individuals in the Western world), it is increasing. Treatment approaches have dramatically changed during the past decade, and agents such as thalidomide, bortezomib, lenalidomide, promalidomide, and carfilzomib are being used in combination with standard chemotherapeutic agents for this disease.

Dr. Kasturi Datta (Jawaharlal Nehru University, New Delhi, India) discussed hyaluronan which is a family of proteins on chromosome 13 and which plays a major role in cancer metastasis. Using the stably transfected cell line F-HABP07 that overexpresses human hyaluronan binding protein-1 (HABP1) in murine fibroblasts, they tested several natural compounds. Their studies demonstrated that serpentine, one of the active components from the roots of *Rauwolfia serpentina* inhibited metastatic potential of this protein. The final talk in this session was by Dr. Rajesh Agarwal

(University of Colorado, Denver, CO, USA) who also emphasized the role of diet in cancer prevention. He focused on prostate cancer and the role of inositol hexaphosphate (IP-6), a dietary constituent. Constitutive activation of PI3K-AKT pathway transmits signals that are essential in survival and proliferation of tumor cells. In prostate cancer cell lines, IP-6 treatment inhibited survival, induced apoptosis, and prevented tumor formation.

Session eight was chaired by Dr. Susan Horwitz and Dr. Sunil Krishnan (MD Anderson Cancer Center, Houston, TX, USA). The first talk in this session was delivered by Dr. Nadir Arber (Integrated Cancer Prevention Center, Tel-Aviv University, Tel-Aviv, Israel) who emphasized on early detection and prevention strategies for cancer. The Integrated Cancer Prevention Center offers comprehensive early cancer detection and prevention services, including instruction on maintaining a healthy lifestyle and minimizing cancer risk. Through scientific and clinical cancer research, the center develops and implements innovative technologies and approaches for cancer prevention and early detection.

The best example for cancer prevention in the recent history of cancer is vaccination against HPV to prevent cervical cancer. Two different countries are making giant efforts in promoting this program. Dr. Surendra Shastri (Tata Memorial Hospital, Mumbai, India) explained the process of identification of appropriate candidates, Long-term follow-up of these will direct policy on cervical screening in India. Dr. Fregnani from Barretos, a city of 110,000 citizens in Brazil elucidated efforts that have been taken to implement vaccination of young girls against this virus. More than 1,500 girls attending the 6th and 7th grades participated in this clinical trial in the town of Barretos. The session was concluded with a presentation by Dr. H. K. Na (Sungshin Women's University, Seoul, South Korea)

who described the role of the garlic compound diallyl trisulfide in breast cancer prevention.

Session nine was chaired by Dr. Sadhan Majumder (MD Anderson Cancer Center, Houston, TX, USA) and Dr. Girish Maru [Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Navi Mumbai]. The lead speaker was Dr. Banavali an expert in childhood leukemias from Tata Memorial Hospital, Parel, Mumbai, India. Focusing on pediatric acute leukemia, Dr. S.D. Banavali illustrated the use of metronomic chemotherapy, which is based on chronic low-dose administration of therapy that targets not only tumor, but the immune system, microenvironment and angiogenesis. He further compared treatment of childhood acute lymphoblastic leukemia in the United States (St. Jude Children's research hospital) with that in India. Dr. Michael Andreeff (MD Anderson, Houston, TX, USA) another expert in leukemia (adult acute leukemia) elucidated the role of mesenchymal stem cells as a protective microenvironment for leukemia cells. This is further complicated by hypoxia generated in these microenvironment niches. He discussed the rationale for therapeutic interventions that use hypoxia in activating agents.

Dr. Sunil Saini from Cancer Research Institute (Dehradun, Uttarakhand, India) provided a clinician's perspective regarding integration of complementary therapies. Specifically these alternate therapies could replace or compliment palliative care.

Session ten - the last session of the meeting was chaired by Drs. Richard Eckert and Subhash Chauhan (Sanford School of Medicine, University of South Dakota.

Cancer Biology Research Center, Sioux Falls, SD, USA). Dr. S. Nagini (Annamalai University, Annamalaiagar, Tamil Nadu, India) discussed uses of neem (*Azadirachta indica*) in cancer prevention. Dr. Yogeshwar Shukla (Indian Institute of Toxicology Research, Lucknow, UP, India) emphasized on the use of nanoparticles in delivering cancer drugs even cancer preventive agents. Dr. Girish Maru reported that black tea has catechins which are chemopreventive agents. Going in the same direction, the last talk of this session and the meeting was by Dr. Nihal Ahmed (University of Wisconsin, Madison, WI, USA) who presented his work on green tea and resveratrol. Importantly, other natural products, such as piperine (present in black pepper) synergistically affected agents such as curcumin, resveratrol, and green tea. Several of these agents affect COX2 activity and inhibit colon cancer growth.

In addition to these major symposia, nearly fifty investigators presented their findings in four mini symposia that concentrated on halting cancer through therapeutics and natural products. These parallel symposia provided

opportunities for young scientists and local scientists from India to discuss their work to an international audience. Similarly, more than fifty students, fellows, and other trainees participated in poster sessions that were attended by all participants. The conference was well-attended, and all enjoyed the location (Figure 1). Please visit the website (3) to review previous meetings and to obtain updates and additional information for future conferences.

Conflicts of Interest

There is no potential conflict of interests.

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We apologize to those speakers whose work is not discussed owing to space limitations.

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