City of Temples Discusses Signaling Templates in Cancer Cells. Third International Symposium on Translational Cancer Research: Cell Signaling & Cancer Therapy
Bhubaneswar, Orissa, December 18th through 21st, 2009

VARSHA GANDHI¹, KAPIL MEHTA¹, SEN PATHAK², BALACHANDRAN RAVINDRAN³, SANDIP MISHRA³ and BHARAT B. AGGARWAL¹

¹Department of Experimental Therapeutics and ²Department of Genetics, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, U.S.A.; ³Institute of Life Sciences, Bhubaneswar, Orissa, India

Abstract. The third International Translational Cancer Research symposium on “Cell Signaling and Cancer” was recently (from Dec. 18th through Dec. 21st, 2009) convened in Bhubaneswar, Orissa, which lies along the eastern shores of India, just south of Bengal. Overall, the meeting provided a platform for scientists from different nations to discuss emerging ideas that focused on cell signaling in cancer. This third in a row symposium tried to bridge the gap not only between basic research and clinical trials, but also between developed nations and developing countries. With the continuing success of these meetings, the fourth International Translational Cancer Research Meeting is slated to be in December 2011. Please contact us if you are interested in participating, presenting, or supporting the next conference.

The recent estimates from World Health Organization indicates that both cancer incidence and cancer-related deaths are expected to double by 2030; and most of this doubling is going to come from developing countries. While the cancer rate is stabilizing in the developed countries, it is on the increase in developing countries such as India. Chemists, biologists, immunologists, and clinicians have been underscoring the importance of translational research to diagnose, prevent, treat, and perhaps even to cure cancer. While the concept of translating research from the bench to the bedside has become a norm in developed countries such as the United States, education and training are required to perpetuate this notion in developing countries, such as India. Specifically for cancer, research-driven patient care is the only way to make a difference. With this in mind, in 2005 four American scientists of Indian origin from the University of Texas M.D. Anderson Cancer Center decided to form an International Society of Translational Cancer Research with a primary goal of biannually organizing a symposium in India and inviting the leaders from all over the world to discuss latest developments in cancer research. Special emphasis and encouragement are provided to students and trainees in India to attend these meetings and to network with the leaders in the field.

The first such symposium was conducted in 2005 in the city of Thiruvananthapuram (Trivandrum), Kerala, which is the southernmost state of India and is thought to have been created by Parsuram, the legendary Brahmin “protector”. The focus of the first meeting was “Apoptosis and Cancer”. This symposium was inaugurated by the then President of India, Dr. A.P.J Abdul Kalam with Dr. John Mendelsohn, the President of M. D. Anderson, as the keynote speaker. A detailed meeting report was published (1).

The second International symposium on “Natural Products and Cancer” was organized in 2007 in the western region of India in Lonavala, a hill station close to Mumbai, the economic and entertainment capital of India, in the state of Maharashtra. Ayurveda, the science of long life, and a goldmine for natural products for cancer, is still being used

Correspondence to: Varsha Gandhi, Ph.D., Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, Unit 71, 1515 Holcombe Boulevard Houston, TX 77030, U.S.A. Tel: +1 7137922989, Fax: +1 7137924316, e-mail: vgandhi@mdanderson.org

Key Words: Stem cells, cell cycle, education, cooperation, natural products.
for all ailments in India. Whether it is vincristine, vinblastin or flavopiridol for cancer, they have their origin from Ayurveda. This symposium was inaugurated by the Director of the Tata Memorial Cancer Center, Dr. Katayan Dinshaw, from Mumbai with Dr. John Milner from the National Cancer Institute as a Keynote speaker.

The third International symposium on “Cell Signaling and Cancer” was recently (from Dec. 18th through Dec. 21st, 2009) convened in Bhubaneswar, Orissa, which lies along the eastern shores of India, just south of Bengal. Bhubaneswar is the capital of this tropical state and is loaded with history. This is the city where the great Indian emperor Ashoka, almost 265 B.C. ago, dropped weapons in a famous Kalinga war and adopted Buddhism. This city of Bhubaneswar is full of temples with unique architecture; it is nicknamed as “the city of one thousand temples”. The modern city was designed by the German architect Otto Königsberger in 1946. Only 40 miles away on the seashore is Puri, also a city of temples and Konark (Sun temple) – a must-see marvelous example of art and architecture.

In this city with 3000 years of history, about 300 scientists from more than 15 nations gathered to discuss cell signaling and cancer therapy. During recent years, it has been recognized that identification of pathways that lead to maintenance, survival, and/or proliferation of tumor tissue is needed to understand pathophysiology of the disease and importantly identification of drugable targets based on this pathophysiology. Drugs, such as gleevec, that target the biology of the disease has become the poster child of how cancer could be treated, controlled, or cured.

The objective of the 3½-day conference was to bring together laboratory and clinical scientists from developed and developing nations to share current knowledge and future strategies for understanding signaling from malignant cells and to target the pathways that manifest cancer cell survival. The format of the meeting was the daily major symposium, parallel mini symposia, and poster sessions.

Dr. Naveen Patnaik, Chief Minister of the State of Orissa, inaugurated the meeting by lighting a candle (a reflection of spreading the knowledge by enlightenment). He emphasized the importance of research in general and translational research in particular for controlling cancer. Dr. Axel Ulrich (Max Planck Institute, Martinsried, Germany) set the scientific stage with his keynote speech that focused on his journey of identifying signaling pathways and developing and discovering drugs such as herceptin. He reviewed thirty years of molecular medicine that evolved from oncogenomics and is leading us to develop novel targeted therapeutics. His presentation also emphasized that while targets could be identified and specific drugs could be developed, in many cases resistance develops to the therapy, which poses new challenges.

Starting next day, attendees participated in nine different scientific sessions that focused on various themes in cell signaling. Every session was introduced by a chairperson presenting an overview of the topic, opportunities to intervene, and challenges that are obvious. The first session was introduced by Dr. Varsha Gandhi (M.D. Anderson Cancer Center, Houston, TX, USA), on cell cycle kinases. While cyclin dependent kinases accompanied with their respective cyclins drive the cell cycle machinery of tumor cells and were discussed by several speakers in this session, the keynote presentation for the session was by Dr. Subrata Sen (M.D. Anderson cancer Center, Houston, TX, USA). His research and presentation concentrated on genes that regulate mitosis, the last step in cell cycle resulting in cytokinesis and formation of new cells. He spotlighted that mitotic regulatory genes, which included Aurora kinases, are involved in complex functional networks with oncogenes and tumor suppressor genes in regulating mitotic checkpoint response. Abnormal regulation of these functional networks contributes towards chromosomal instability and aneuploidy, a common feature observed in tumor cells. Aberrantly expressing mitotic regulatory genes are potential novel therapeutic target for cancer and therapeutic targeting of signaling pathways may be more effective when done in combination with targeting mitotic regulatory genes associated with mitotic checkpoint response.

Dr. Bharat Aggarwal (M.D. Anderson Cancer Center, Houston, TX, USA), chaired the second session on inflammation and cancer and elucidated three chronic ailments – aging, obesity, and cancer – that originate from inflammation. He described that these diseases could be preventable or manageable. He illustrated the ground work that is ongoing in identifying downstream molecules, genes, and pathways that originate from inflammation and travel toward tumorigenesis. These include transcription factors, cytokines, angiogenesis inducers, and proteins that promote tumor survival, maintenance, and development of chemoresistance. Dr. Sankar Ghosh (Columbia University, New York, USA) described the key role of nuclear factor kappa B in the inflammatory and immune responses. He concluded that understanding the mechanisms that lead to activation of this transcription factor is critical. Additional major presentations in this session from Drs. Surh from Korea, Murakami from Japan, and Agrawal from the USA, centered on phytochemicals that can abrogate or attenuate the process of inflammation. These scientists concurred that natural products could act as potential drugs to target inflammation and cancer. Several key molecules were identified that are attacked by these plant products including nuclear factor kappa B, Cox-2, and transcription factors.

The afternoon session on the first day was devoted to microenvironment and cancer. Dr. Dharamrajan (Perth, Australia), who chaired the session, set up the stage by providing the foundation for the role of microenvironment in
promoting survival, maintenance, and proliferation of tumor cells. His introductory talk highlighted types of tissues that form microenvironment, mechanisms through which these cells provide survival benefit to tumor, and opportunities to interfere with the cross-talk between malignant cells and their surrounding environment. In a plenary lecture, Dr. Varsha Gandhi (M.D. Anderson Cancer Center, Houston, TX, USA), explained the connection between microenvironment and chronic lymphocytic leukemia. Her talk paid attention to factors initiated through bone marrow stroma cells or nurse-like cells that affect survival of CLL lymphocytes by inducing Bcl-2 family anti-apoptotic proteins in tumor cells. She ended her presentation by providing a list of emerging therapeutics that affect prosurvival function of Bcl-2 anti-apoptotic proteins.

The final session on the first day was devoted to coding and non-coding RNA and chromatin modifiers which are involved in cancer causation and progression. Drs. Somasundaram and Wesley provided a list of miRNAs that have been identified in glioblastoma and neuroblastoma, respectively. While Dr. Sandip Mishra (Institute of Life Sciences, Bhubaneswar, India) in his keynote lecture emphasized epigenetic changes that are identified in breast cancer cells. The core of his presentation addressed histone acetylasles and deacetylases that regulate silencing or expression of genetic code. Dr. R. K. Grover (Delhi State Cancer Institute, Delhi, India), in his chairmanship remarks, introduced the audience to a new cancer center, Delhi State Cancer Institute. He highlighted that it is essential to develop a facility with international standards to provide a comprehensive and most modern set-up for the diagnosis and treatment of all types of cancer; and to serve as a ‘role model’ for health care by amalgamating the academic skills of the universities, clinical acumen of the “super-specialists”, research skills of the international institutions, managerial skills of the corporate world and technological development skills of the industry.

The first morning session on the second day (Session 5) concentrated on apoptosis and cancer. Dr. P. Krammer (Tumor Immunology Program, Heidelberg, Germany) presented a keynote lecture on apoptosis and the immune system. His talk reviewed the fundamentals on cell death phenomenon and highlighted how apoptosis leads to the elimination of cells via a complex but highly defined cellular process. Both in autoimmune disease and in cancer, this process is deregulated. He introduced the topic by describing his last three decades of pioneering work on understanding the processes involved in apoptosis. He ended his presentation by providing examples of how this deregulated pathway could be intervened in cancer by small molecules such as wogonin. This ground work set the stage for Marc Diederich (Luxembourg, Luxembourg) to present his research focus on chemotherapy-induced cell death.

Building on the idea of apoptosis resistance, other pathways affecting tumor cytotoxicity were discussed. For example, angiogenesis and drug resistance was the topic for the second session of this morning. The topic was introduced by Dr. K. Mehta (M.D. Anderson Cancer Center, Houston, TX, USA) who also discussed various mechanisms implicated in the development of chemoresistance in cancer cells in his keynote address. One culprit of chemoresistance is the enzyme transglutaminase II (TG2), whose expression in tumor cells is associated with poor patient survival. TG2-regulated pathways which promote drug resistance in cancer cells were discussed. Dr. N. Singh (New Delhi, India) summarized the results of a randomized clinical trial evaluating curcumin as adjuvant with radio-chemotherapy in advanced cervical carcinoma. Dr. A. Dharmrajan (Perth, Australia) presented data supporting antiangiogenic effect of the secreted frizzled-related protein 4, both in vitro and in animal models. Dr. A. Jaiswal (Bethesda, MD, USA) summarized the signaling pathways associated with Nrf2 activation and the impact of these events in acquired resistance to chemotherapy by cancer cells.

Dr. Sen Pathak (M.D. Anderson Cancer Center, Houston, TX, USA) and Dr. Madan M. Chaturvedi (Delhi University, India) Chaired Session 7 on stem cells and cancer. This topic was introduced by Dr. Pathak who presented an overview and the current definition of not only normal stem cell (NSC) but also of cancer stem cell (CSC). Three most important characteristics of NSCs and CSCs involving – (a) self renewal, (b) migration, and (c) differentiation were discussed in greater details. He also presented historical evidence to support the idea that cancer originates in the organ- and tissue-specific stem cells. The keynote speaker of the session, Dr. Sharmila Bapat (National Centre for Cell Science, Pune University, India), presented her talk on cancer stem cells as determinants of tumor dormancy. She outlined the relationship between quiescent cancer stem cells and dividing progenitor cells. Cancer stem cells contribute to tumor dormancy and present great difficulty in the successful treatment of cancer patients. Her group has been able to isolate two types of quiescent cells: (i) stem-like cells and (ii) aneuploid cells. The stem-like cells express a reversibility of quiescence by retention of functionality and also exhibit aneuploid features. The aneuploid cells either remain quiescent or are under proliferation arrest. Under selective pressure of chemotherapy, a fraction of these cells may acquire the potential to proliferate and acquire stem-like characteristics. From these findings, she concluded that tumor-derived CSCs and aneuploid cell population contribute to drug resistance and tumor dormancy in cancer progression. The role of Notch signaling in human cervical cancer treatment was presented by another speaker. Dr. P.K. Lala (University of Western Ontario, London, Canada) presented challenges and opportunities on the molecular targets for lymphatic metastasis in human breast cancer.
Continuing the theme of cancer progression, tumor promotion and progression was the focus of the penultimate session on the last day of the meeting. Dr. Kondaiah (Indian Institute of Sciences, Bangalore, India) demonstrated the role of IGFBP isoforms in tumor promotion while Dr. Sinha (All India Institute of Medical Sciences, New Delhi, India) elucidated mechanisms that lead to genomic instability under adverse growth conditions. In his plenary talk, Dr. S. Sahoo (Institute of Life Sciences, Bhubaneswar, India) provided examples of nanoparticle delivery of several established and experimental chemotherapeutic agents to inhibit tumor promotion and progression.

The last session (#9) was “Cancer Diagnosis and Treatment” that was chaired by Dr. Sunil Saini from Himalayan Institute of Molecular Medicine in Dehradun and Dr. Pramod Rath from Jawaharlal Nehru University, New Delhi. The keynote speaker in this session was Dr. Yong-Sang Song (Seoul National University Hospital, Korea) who discussed the clinical implications of COX2 in gynecologic cancer. This was followed by Dr. Lalit Kumar, a hematological medical oncologist from All India Institute of Medical Sciences, New Delhi, who talked about the impact of disease biology on treatment outcome. Then Dr. Sunil Saini discussed the role of natural products in cancer treatment. Finally Dr. Moni Kuriakose, a surgeon from Bangalore, summarized the role of HPV in oral cancer, the most common form of cancer in Indian men.

Close to fifty investigators presented at minisymposia that concentrated on cell signaling and therapeutics including 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 two poster sessions that were attended by all participants. Please visit the website (2) to review previous meetings and to obtain updates and additional information for future conference.

Disclosure of Potential Conflicts of Interest

There is no potential conflict of interests.

Acknowledgements

The Authors appreciate the funding provided by B. D. Biosciences, Care Stream Molecular Imaging, Hemlata Hospital and Research Center, Indo-US Foundation, Institute of Life Sciences, Imgenex, McCormick Spices, Ottogi, and Mr. Naresh Sharma that allowed us to convene this conference. We thank Chitra Sundaram for assisting the US organizers. We apologize to those speakers whose work is not discussed owing to space limitations.

References

2 www.istcr.org

Received March 15, 2010
Accepted May 11, 2010