Editorial

Precision/Personalized Medicine in Cancer

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Recent technological advances have provided unprecedented opportunities to develop platforms for implementing 'Precision/Personalized Medicine', with confluence of medicine and technology making significant advances in treatment. The Cancer Genome Atlas (TCGA), a large scale initiative started in 2006, to generate a comprehensive landscape for identification of alterations in tumor types with a view to develop better therapies, is on a wind down. The next phase is use of the information generated for 'Precision/Personalized Medicine'. Implementation of 'Precision/Personalized Medicine' requires understanding of the biology of each cancer type with precise definition of the cancer genome. The different genome alterations will identify the 'Founder Mutations' involved in the early phase, but may not be associated with a fully transformed phenotype; 'Driver Mutations' required for fully transformed phenotype; and 'Passenger Mutations' considered as collateral damage. Treatment against key oncogenic driver mutations in individual cases with targeted drugs will be the benefit of the 'Precision Medicine' approach. Rational choices for treatment have to be preceded by full genomic data and expression data, facilitating combination therapy decisions. Thus, advanced technology including 'Next Generation Sequencing' (NGS) with both availability and affordability will enable understanding of cancer and other diseases, a feasible proposition.

Next Generation Sequencing is massively parallel sequencing enabling rapid sequencing of the entire genome or exome sequencing on whole genome or cDNA (RNA-Seq), builds on the concept of 'NGS taking us into expanded genomic testing for risk prediction, diagnosis, prognosis, treatment response and disease free survival or overall survival in real time'. The understanding of the mechanisms and processes in cancer with single aberrations or cumulative alterations including mutations, rearrangements, amplifications, deletions, insertions and other alterations in cancer will be discerned. It is important to remember that several countries have initiated studies in this direction. Prime Minister David Camerno, UK, endorsed the 'Genomes Project' for collection of data for whole genome sequences from 100,000 individuals, to be completed by 2017, sanctioning USD 475 million for sequencing studies, with a view to better understand complex diseases including cancer. Barack Obama, President, USA, launched the 'Precision Medicine' initiative.
with a USD 215 million for genomic data on one million volunteers to accelerate patient powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge and therapies for individual patients. A result of better understanding of cancer, is the current repertoire of targeted therapy drugs and personalized medicine on the global scene.

In the past decade the advent of targeted therapy and new tailored drugs has led to a revolution in treatment of lung cancer, with larger benefit, lower toxicity and better quality of life for the patient. The treatment is often based on molecular profiling of individual patients with identified cancer, as also indicated in other cancers with a similar molecular profile. Thus, Tyrosine kinase inhibitors including Erlotinib, Gefitinib, Afatinib targeting epidermal growth factor receptors (EGFR), and ALK Inhibitors including Crizotinib, Ceritinib are beneficially used in patients with aberration of the genes in Non-small cell lung cancer, and indicated for additional cancers with the appropriate molecular profile. Involvement of Kras, EGFR, ALK, HER2, Braf, MET, AKTI, MAP2KI, PI3KC genes have been identified in lung cancers, opening possibilities of targeted therapy with consequential benefits. Thus, an additional aspect which has emerged is combination therapy using two or more targeted drugs, or targeted drugs plus the conventional chemotherapeutic drugs. A few examples are targeted drugs Dabrafenib and Trametinib, mitogen activated protein kinase 1/2 (MAPK1/2) for melanoma with BRAFV600E/K; angiogenesis inhibitor, Bevacizumab, against vascular endothelial factor A is a targeted therapy in cancers of the colon, lung, breast, kidney and brain; whereas Ramicirumab, a monoclonal antibody against vascular endothelial growth factor receptor 2, is used in gastric cancer and Non-small cell lung cancer, and in combination with Docetaxel improves outcomes in bladder cancer. HER2 gene antibody – Herceptin, shows substantial survival benefits in all newly diagnosed and recurrent breast cancer patients with amplification and over-expression of the gene. Development of companion diagnostics indicating the pathogenic molecular alterations and new targeted drugs go hand-in-hand, and guidelines for several molecular diagnostic tests are available. Thus, ‘Precision/Personalized Medicine’ will enable the current oncologists to ‘Win the War against Cancer’.

The current issue includes a review paper and an original article on glioblastoma multiforme (GBM), one of the most aggressive brain tumor, a cancer with bad prognosis and median survival of 15 months. The conventional treatment of GBM using the strategy of surgery, radiation and chemotherapy, has advanced only incrementally in the last 30 years. With the advent of molecular biology and consequent
improved understanding of basic tumor biology, targeted therapies have become cornerstones for cancer treatment. Several signaling pathways including RTKs/PI3K/AKT/mTOR/VEGF/VEGFR are deregulated in GBM, playing a major role in tumorigenesis, treatment resistance and progression of GBM. Dr. Anita Tandle and colleagues from National Cancer Institute, Bethesda, Maryland, USA, discuss the Omics of GBM and applications in novel therapies, in the article, ‘Advances in Omics technologies in GBM’. The authors survey the technologies of genomics, transcriptomics, epigenomics, proteomics, metabolomics and post transcriptional modifications of microRNAs in GBM. A comprehensive information in GBM will lead to better understanding of the cancer, highlight the various signal transduction pathways, and identify key molecules associated with the pathogenesis, culminating in development of new drugs and 'Personalized treatment'. The original article by the group, ‘EGFR 2, EGFR and HDAC triple inhibitor CUDC-101 enhances radiosensitivity of GBM cells’, convincingly shows enhancement of in vitro radiosensitivity of GBM and breast cancer cell lines selectively, with no effect on normal human lung fibroblast cell line. The radiosensitization of the cancer cell lines was attributed to inhibition of DNA double stranded break repair and modulation of cell cycle. A better understanding of the cancer will open avenues for better contemporary treatment.

Nanomaterials and nanoparticles including dendrimers, polymers, nanotubes, oxides, and enzymes and their hybrids as catalysts for various sensors such as glucose sensors, DNA sensors, neurotransmitters sensors, are another facet of technological advances with tremendous applications in health sciences. Dendrimers are synthetic nanoscale compounds with unique properties, resulting in biomedical and industrial applications. Dendrimers have a number of features that make them ideally suited for sensor applications, such as, its high surface area, high reactivity, easy dispersability and rapid fabrication. Dr. Saumya Nigam and Dr. Dhirendra Bahadur, Indian Institute of Technology Bombay, Mumbai, along with Dr. Sudeshna Chandra, NMIMs (Deemed-to-be) University, present a review on ‘Dendrimers based electrochemical biosensors’. The review highlights the advanced development of effective, rapid and versatile electrochemical biosensors based on dendrimers. A must read review for all to understand the technology.

The concept of cancer stem cells (CSC) proposed earlier in the year 2000, are now well accepted to play a critical role in cancers. The CSCs are more of an enigma and relatively more difficult to decode the biology of CSCs. The conserved Wnt/β-Catenin, Notch and Sonic Hedgehog pathways regulate stem cell pluripotency and cell fate decisions during...
normal embryonic development and adult tissue homeostasis, and aberrant activity within these pathways is displayed in several cancers. Human cancers contain a relatively dormant cell population, CSCs, with characteristics similar to normal stem cells. Convincing evidence indicates that CSCs are responsible for chemotherapy/radiation therapy resistance, maintenance and consequent recurrence of the cancer. The roles of Wnt, Notch and Hedgehog pathways in cancers and their deregulation are of critical significance, directly linked to CSCs. In order to target the CSCs therapeutically, it is imperative to understand the molecular mechanisms regulating CSCs responsible for maintenance and recurrence of cancer, and develop combination therapies to target CSCs inhibiting the cumulative action of the deregulated genes. Dr. Sanjeev Waghmare and his colleagues from Advanced Centre for Treatment, Research and Education in Cancer, Navi Mumbai, succinctly review the intricately complex signalling cascades of Wnt, Notch and Hedgehog genes, regulation and maintenance of normal developmental processes, and their association in cancer, in the article, ‘Developmental signalling in maintenance and regulation of cancer stem cells’. Whereas, the article, ‘Phenotypic and functional characterization in the maintenance and regulation of a marrow-derived stromal cell line, M210B4 and its comparison with primary marrow stromal cells’ by Dr. Vaijayanti Kale and colleagues from the National Centre for Cell Science, Pune, emphasizes importance of alternative systems for investigating regulation of hematopoietic stem cells (HSCs). The authors showed that the cell line M210B4 unequivocally differentiated towards adipogenic lineage, and exhibited a higher HSC-supportive ability and conclude that the cell line M210B4 is an appropriate substitute to study HSC regulation in vitro.

The transcription factor Nrf2 containing the conserved basic leucine zipper structure belongs to the Cap ‘N’ Collar family, and plays a critical role in cell defense and survival pathways. Nrf2 often protects cells and tissues from toxicants and carcinogens via transcription of cytoprotective genes, and hence considered chemopreventive, protecting against redox-mediated injury and carcinogenesis. Paradoxically, the flip side of Nrf2 is protection of cancer cells from chemotherapeutic agents and/or radiotherapy resulting in resistance to the therapy and cancer progression. Nrf2 is aberrantly upregulated in several cancer types, and associated with poor prognosis in cancer patients. The dilemma of the dual action of Nrf2 has been well reviewed in the article, ‘Divergent role of Nrf2 in cancer progression and prevention’ by Dr. Santosh Sandur and colleagues from Bhabha Atomic Research Centre, Mumbai. The review indicates a wider approach with better...
comprehension of the mechanisms of action of Nrf2 and consequent design and development of drugs to handle the upregulation or downregulation of Nrf2 in the preventive, protective or destructive niche of normalcy and diseases. Thus, 'One fit for all' is not a feasible solution in all conditions indicating importance of 'Precision/Personalized Medicine'.

The mechanisms of embryo implantation and development resulting in pregnancy are comparable to cancer with respect to the growth processes and mechanisms of development. A receptive endometrium, normal blastocyst, cross talk between fetal and maternal compartments remodeling uterine vasculature, and selector activity comprise innate requirements for successful pregnancy. Adverse events such as preeclampsia, infertility and intra-uterine growth retardation are minimized or avoided in normal fetal growth. The highly orchestrated embryo-endometrial cross talk involves a plethora of molecules including hormones, cytokines, growth factors, specific immune modulating factors, to create the appropriate micromilieu for establishing pregnancy. Dr. Deepak Modi and Mr. Pradeep Bhartiya from the National Institute for Research in Reproductive Health, Mumbai, take us through the 'Physiology of embryo-endometrial cross talk' lucidly highlighting the various processes and interactions. The networking interactions and intricate physiology in a pregnancy is very well explained. The applications in a clinical scenario for successful implantation, infertility treatment and development of contraceptive drugs are discussed.