Editorial

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Right Patient, Right Diagnosis, Right Treatment!

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The 2015 Nobel Prize in Medicine for drugs to fight malaria and other tropical diseases, and in Chemistry for fundamental contributions towards understanding DNA repair and maintaining of genomic integrity in cells, highlights the interdisciplinary approach for maximizing benefits of contemporary science to mankind. The Nobel Prize in Medicine was awarded to William Campbell Ph.D., born in Ireland and migrated to US; Satoshi Omura, Ph.D., from Japan, and Youyou Tu, the first Chinese Nobel laureate. The Nobel laureates – Dr. Campbell and Dr. Omura were cited for their discovery of Avermecitin, derivatives of the drug responsible for decreasing incidence of river blindness and lymphatic filariasis affecting millions in Asia and Africa. Ms. Tu's intensive efforts led to the active compound from the herbal Chinese sweet wormwood plant, giving us the antimalarial drug artemisinin, currently the first line drug for malaria affecting 50% of global population. The Chemistry Nobel acknowledged three scientists for their research in DNA repair, for their intensive work on mapping the process at a molecular level and providing insights into cell functioning and maintenance of genomic stability. The Nobel laureates were Dr. Thomas Lindahl, Ph.D., Francis Crick Institute, London, for his discoveries in base excision repair; Dr. Paul Modrich, Ph.D., Howard Hughes Medical Institute, and Duke University School of Medicine, North Carolina, USA, for the mismatch repair pathway; and Dr. Aziz Sancar, M.D., Ph.D., at the University of North Carolina, USA, for nucleotide excision pathway. The understanding of DNA repair mechanisms in the cells is a breakthrough in understanding how cancer develops and furthers treatment of cancer and also several diseases, much needed for better health management.

Despite the tremendous advances in technology, particularly biotechnology, information technology and imaging technology, cancer development,

progression, response to treatment, and recurrence is still an enigma with several glaring lacunae. It was in 1971, Richard M Nixon, 37th President of US, signed a bill, 'The National Cancer Act', to create new research infrastructure with enormous resources devoted to fighting cancer, and the act was known as 'Nixons war on cancer'. By 2005, NCI spent USD 165 billion, and the outcome was better understanding, and applications of the generated data resulted in reduced mortality from cancer in both men and women. The outcome of genome based screening in Cervical Cancer, Breast Cancer, Colon Cancer and other cancers was early detection, better prognosis and better survival. Genome wide association studies gave us 'Predictive markers', and the whole genome expression studies through transcriptomics, proteomics, metabolomics gave us 'Prognostic Biomarkers' and identified 'Drug Targets' with cutting edge technology. The 'Next Generation Sequencing' with massive parallel sequencing over the past several years, is anticipated to be an invaluable part of clinical medicine.

With the current 1.2 billion population in India, preventive medicine often takes a back seat, although the focus of health management in developed and developing world should be 'Prevention' in monogeneic and multigeneic complex diseases including 'Cancer'. Despite oral cancer ranked as the number one cancer in Indian males and fourth most common cancer in females, contributing 26% of the global oral cancer burden, preventive measures are slow in implementation. Tobacco has been unequivocally established as a high risk factor in oral and lung cancers; however, the role of areca nut is not commonly acknowledged as an important risk factor for oral cancer. In the current issue Dr. Prakash Gupta and Cecily Ray, Healis Sekhsaria Institute for Public Health, Mumbai, in their article on 'Areca nut use and cancer in India', give us a comprehensive review of the evidence for carcinogenicity of areca nut, detail epidemiological and animal studies, and reveal the mechanistic evidence highlighting the causal biochemical and molecular mechanisms of oral submucous fibrosis – a premalignant condition and oral cancer in areca nut chewers. The review emphasizes the necessity for awareness programs for areca nut hazards and control policies on areca nut per se and areca nut products.

Inherent in all health management

programs is the understanding of the mechanisms of diseases using state of the art technology. The concepts of 'Systems Biology' and 'Omics' was knowledge based and advanced applications in clinical medicine. Dr. Rukmini Govekar, Advanced Centre for Treatment, Research and Cancer, Navi Mumbai has lucidly highlighted proteomic technologies and strategies in her article 'Identification of Therapeutic Technologies and Strategies are the Key to Success'. The 'Omics' research has immensely contributed to

'Targeted therapy' in cancer, and is a rapidly resulting in pathology specific therapeutic molecules relevant to an expanding list of tumor types. Thus, the targeted therapy is useful not only in the initially indicated cancer, but is useful in several cancers with identical or similar molecular pathology. The therapy is tailored to the individual patient, with 'Companion Diagnostics' giving a helping hand in the informed decision for the patient. Off label use of targeted therapies will be indicated as confirmed data such as BRCA1/BRCA2 gene mutations as predictive diagnostic test for breast cancer, and hence use of targeted therapy with the specific molecular pathology, is useful in Pancreatic cancers and Non-Small Cell Lung Cancer patients. The recent immune checkpoint blockade therapies, Anti-PDL1, may be used effectively in advanced melanoma or metastatic bladder cancer with impressive clinical responses. A massive effort for high incidence and rare cancers is the NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) Trial, world's largest ever molecular oncology trial, screening 3000 patients for comprehensive molecular pathology, and treated with targeted therapy. Biopsy specimens from tumors will be analyzed for more than 4,000 different variants across 143 genes, regardless of tumor origin. Dr. Pratibha Kadam Amare, Tata Memorial Hospital, Mumbai, gives a snap shot of molecular pathology and targeted therapy in her review on 'Genetic markers and evolution of targeted therapy in cancer'. The author elaborates the cell surface antigens and tyrosine kinase targets identified as pathognomonic in several common cancers, and development of effective inhibitor molecules as small molecules or antibodies for therapy, a must read for our oncologists and basic scientists.

The re-emergence of 'Gene Therapy' recently is obvious. The field has matured, gathering steam and is anticipated to join

mainstream therapy in several monogenic diseases as also complex diseases including cancer, after several years of taking a backseat in both the research realm and clinical applications. The falling precipice in gene therapy truly began in 1999 when 18 year old Jesse Gelsinger died from multiple organ failure four days after treatment for ornithine trans-carboxylase deficiency, the death triggered by severe response to adenoviral carrier. The disenchantment with gene therapy continued when several children developed leukemia like condition after treatment for X-linked severe combined immunodeficiency disease. The current scenario is quite different with several companies conducting clinical trials with gene based therapy using AAV vector, oncolytic viruses, liposomes coated with Polyethylene Glycol, siRNA, etc. And the clinical trials using gene therapy in varied diseases – Parkinson disease, the drug used is Nerologix (Biotech Company); A successful correction of inherited form of blindness has been launched by Spark Therapeutics; Inhalation of normal Cystic Fibrosis CFTR gene copies for improvement in lung function for Cystic fibrosis patients. Gene therapy with siRNA to degrade particular RNA sequences is under investigation for Huntington's disease; and lentivirus based gene transfer to improve efficiency of gene transfer in metachromatic leukodystrophy with the pathology being mutated arylsulfatase A enzyme. The lentivirus vector avoids activation of cancer causing genes by loading the vector with self-inactivating promoter sequences that exclusively induce expression of the therapeutic gene. The advances in gene delivery systems will relegate complex diseases such as cancers to a manageable disease without severe disability, disfigurement and death. Dr. Abhijit De and Shruti Dutta in their article 'Gene therapy for sodium iodide symporter in non-thyroidal cancers' focus on potential suicide genes in cancer supporting diagnosis through imaging of the cancer and therapeutic applications, with emphasis on sodium iodide symporter. The authors emphasize the effectiveness of sodium iodide symporter in non-thyroidal cancers, particularly hormone receptor negative patients.

The technology today facilitates a 'Systems Biology' approach for understanding the role of 'microbiome' at different sites of our body, with emergence of functional metagenomics, to enable a

holistic picture of the beneficial normal microbes. Subtle imbalances in our microbial population can cause diseases, influences our response to drugs, and restore balance between microbial normalcy and pathogenesis, leading to effective cures. Global parameters of microbial communities provide valuable information regarding human health status and disease predisposition. Downstream analyses of the functional interaction between host and the microbiome deciphering the metagenome i.e. the human microbiome and its collective genes, may lead to mechanistic insights into the interaction, with new opportunities for next generation diagnosis, prognosis and treatment of various acute, chronic, localized, systemic, simple and complex diseases. *In vitro* cultivation of the microbiota earlier formed the cornerstone in microbiology, though not possible in densely populated microbial communities. DNA based analyses expands the horizons generating enormous new data sets mined for information. The Human Microbiome Project (by NIH), generated 2.3 terabyte 16S rRNA metagenomics dataset of over 35 billion reads from 690 samples of 300 subjects across 15 body sites. The microbiome and core metagenomics occupies a specific human niche, and varies both by anatomical site and substantial interpersonal variation, with a causal link established between microbiome variation and significant pathology. Dietary changes rapidly cause substantial metagenomic changes. Dr. Abhay Kumar Pandey, Banaras Hindu University, Varanasi, and colleagues succinctly highlight the important role of the microbiome in disease and health in the review 'Microbiota in immune pathogenesis and the prospects for Pre and Probiotic Dietetics in psoriasis'. Psoriasis is a chronic idiopathic, inflammatory dermatologic condition, with the cutaneous microbiome a critical target. The pathogenesis is advanced by genetic predisposition, and a change in the microbiota is observed, with increased ratio of Firmicutes to Actinobacteria. The alterations in commensal microbiome, basis for the changes in disease, and the mechanisms of colonization and host homeostasis is restored, is crucial for manipulating the host microbiota. The authors elaborate the role of dietary prebiotics and probiotics towards healthy host microbiome relationship via dietary probiotics and manipulation of the specific

site and general gut microbiota. It is feasible that the advances in technology facilitating better understanding of disease pathogenesis will prove fruitful and provide optimal benefits and the end of 'Right diagnosis, Right treatment, Right patient,' is in sight, making therapeutics robust and dynamic.