Editorial: Contemporary Cancer Therapy

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On the Public Health scenario globally the major issues in provision of effective care from ‘Precision Medicine to Precision Care’ that need urgent solutions include ‘Antimicrobial resistance to negate the estimated death of 10 million individuals annually due to Antimicrobial Resistance by 2050’, and ‘Understanding of Cancer Biology with consequent complete cure in Cancer’ and translation care with patient centered approach. Besides an impetus for prioritising ‘Preventive Medicine’ in both communicable and non-communicable diseases is needed. The laudable 'Sustainable Development Goal target' of reducing maternal mortality to 70/100,000 live births by 2030 from the current 216/100,000 is feasible due to collective efforts. We look forward to similarly tackling both the problems of antimicrobial resistance and cancer cure. In the editorial we focus on the success of Contemporary approach to Cancer Care for individual patients indicating the use and efficacy of US FDA approved and globally implemented targeted treatment. Cancer is still an enigma both to the patients and to a considerable extent to the oncologists, due to its biological complexity and extreme heterogeneity in treatment responses in patients. The bane of cancer is metastasis of the cancer cells to distant organs introducing uncertainties in cancer cure.

Over the past several years, a next generation of cancer treatment targeted to the molecular pathology of cancer has made a difference in cancers of lung, colorectal, breast, pancreas, brain, gastrointestinal, head and neck cancers including oral cancer, kidney, lymphoma, melanoma, mesothelioma, prostate, thyroid, leukemia and myeloma, tailored to an individual patient's tumor. The approach takes into account individual variability in the genes, environment and lifestyle, and this will enhance evidence informed decision making. Targeted molecular therapy is designed to treat cancer by interrupting unique molecular abnormalities that drive cancer growth. The drugs used in targeted therapy are designed to interfere with a specific biochemical pathway central to the development, growth and spread of the
particular cancer. Although targeted therapy minimises adverse side effects, not all cancers and patients respond to targeted therapy, and stratification of the patients through molecular biomarkers is mandatory. Besides, in several countries the medicines are hard to access, expensive, not yet developed for all types of cancer, and sometimes available only in clinical trials. The main types of successful targeted cancer therapy are small molecule inhibitors and monoclonal antibodies. To facilitate cancer cure and survival, a representative list of targeted drugs approved by USA Food and Drug Administration, and used in treatment of cancers is highlighted.

Small Molecule Inhibitors (SMI)/ Monoclonal Antibodies (Mab):
The growth of cancer cells are responsive to growth factors, which bind to the receptors on the cell surface and trigger downstream pathways functional in cancer cell proliferation. The inhibitors and the monoclonal antibodies work by blocking signals within cancer cells, preventing proliferation of cancer cells. Representative cancer, specific targets and SMI/Mab agents in treatment are cited.

**Breast Cancer**
Mab – Her2/neu: Trastuzumab, Pertuzumab, Ado-Trastuzumab, emtansine

**Lung Cancer**
SMI – Anaplastic Lymphoma Kinase (ALK): Crizotinib, Ceritinib, Alectinib; Epidermal Growth Factor Receptor (EGFR): Erlotinib, Gefitinib, Afatinib dimaleate, Osimertinib
Mab – VEGFA: Bevacizumab; VEGFR2: Ramucirumab; EGFR: Nacitumumab; PD-1: Nivolumab, Pembrolizumab

**Melanoma**
SMI – BRAF: Vemurafenib, Darafenib; MEK1/MEK2: Trametinib; MEK/BRAF – Cobimetinib
Mab – CTLA4: Ipilimumab; PD-1: Pembrolizumab, Nivolumab

**NHL/Anaplastic large cell lymphoma** – CD30: Brentuximab vedotin

**NHL (R)** – CD20: Ibritumomab tiuxetan, Rituximab

**Multicentric Castleman Disease** – IL-6: Siltuximab

**Renal Cancer**
SMI – VEGFR/ PDGFR/ BRAF: Sorafenib; Mets: VEGFR/ PDGFR/ Kit/ RET: Sunitinib; Adv.: VEGFR/PDGFR/ FGFR/ Kit: Pazopanib; mTOR: Temsirolimus; Res.: VEGFR/ PDGFR/ Kit:
Axitinib; mTOR: Everolimus
Mab – Res.: VEGFA: Bevacizumab; Pralatrexate; Phosphoinositide 3-kinase (PI3K): Idelalisib
Adv: PD-1: Nivolumab
CML – SMI: Tyrosine Kinase: Imatinib mesylate, Bosutinib, Nilotinib; Mab: CD20 – Ofatumumab
Subependymal Astrocytoma – SMI – AML, CML, ALL – SMI: Tyrosine Kinase: Dasatinib
mTOR: Everolimus
CML – SMI: Tyrosine Kinase: Imatinib mesylate, Bosutinib, Nilotinib; Mab: CD20 – Ofatumumab
Liver Cancer – SMI – VEGFR/ PDGFR/BRAF: Sorafenib
Ovarian Cancer (BRCA1/2) – SMI – CML, CLL, NHL – SMI: PI3K: Idelalisib
Poly ADP Ribose Polymerase (PARP): Olaparib
Cervical Cancer – Mab: VEGFA: Leukaemia – Mab: CD20: Rituximab
Bevacizumab
Head and Neck Cancers – Mab: CD52: Alemtuzumab
EGFR: Cetuximab
Lung (NSCLC) – Mab: CD20: Obinutuzumab
Bevacizumab; VEGFR2: Ramucirumab; Multiple Myeloma – SMI: 26S Proteasome: Bortezomib; 20S Proteasome: Carfilzomib; Ixazomib citrate
EGFR: Necitumumab; PD-1: Nivolumab, Pemrolizumab
Thyroid Cancer – SMI: VEGFR/ PDGFR/BRAF: Sorafenib; Mets: Melanoma (Met) – Mab: CTLA4: Ipilimumab; PD-1: Pembrolizumab, Nivolumab
PDGFR2/R: Lenvatinib mesylate
Medullary Thyroid Carcinoma (MTC) – SMI: met/VEGFR2: Cabozantinib; Multiple myeloma – Mab: CD319: Elotuzumab; Res: CD38: Daratumumab
– SMI: met/VEGFR2: Cabozantinib; Glioblastoma – Mab: VEGFA: Bevacizumab
Mets: VEGFR/EGFR/RET: Vandetanib
Pancreatic (Neuroendocrine) – SMI: Neuroblastoma – Mab: GD2: Dinutuximab
mTOR: Everolimus; PDGFR/VEGFR/ Kit, RET: Sunitinib; Mets: EGFR: Erlotinib
Prostate/Met/Hor-R/Chemo-R – SMI: Besides, targeted Mabs and SMIs, Microtubule: Cabazitaxel; Androgen Histone Deacetylase Inhibitors such as Receptor: Enzalutamide; CYP17: Belinostat, Vorinostat, Romidepsin, Abiraterone acetate Recombinant IL-2-Diphertheria toxin, third generation retinoid and All-transretinoic acid constitute targeted therapy in several
Lymphoma/leukemia – SMI: 26S Proteasome: Bortezomib; Folate:
hematopoietic cancers. The succeeding years will provide exhaustive information on cancer biology leading to addition of diverse categories of drugs with better prognosis, overall survival and cure for cancers.

Cancer treatment in various cancer types is well streamlined with tremendous experience and expertise in patient management, yet patients with the same cancer with respect to histopathology, tumor staging, nodal metastasis and distant metastasis do not respond similarly to treatment. Cancer is a complex biological process, and it seems a long way to win the war on cancer. The major bane of cancer in patient management is metastasis to distant organ and innate or eventual drug resistance, and the article by Dr. Madhumita Roy and colleagues focuses on an unconventional approach for treatment of leukemias in the article ‘Drug resistance in leukemia: remediation by natural means’. The authors from the prestigious Chittaranjan National Cancer Institute, Kolkata, expand on the mechanisms of drug resistance, adverse effects of the conventional cytotoxic drugs and introduce the concept of use of herbal phytochemicals or natural products exploiting the diverse mechanisms of reversal of drug resistance using in vivo models and in vitro cell lines. The influx and efflux of drugs through the cancer cell membranes is elaborated indicating transporter molecules such as adenosine triphosphate binding cassette protein including P-glycoprotein, multidrug resistance associated protein, solute carrier transporter protein, lung cancer resistance protein, breast cancer resistance protein; and different modalities of drug resistance via drug inactivation, alteration of drug targets, inhibition of cell death, epigenetic regulation, well explained. The envisaged plant products, their anticancer activities and mechanisms in reversal of drug resistance are elaborated by the authors and include the alkaloids, phenols, phenolic products, flavonoids isoflavones, isothiocyanates, capsaicinoids, carotenoids, coumarin and several additional compounds, with appropriate examples of Apigenin isolated from chamomile, active ingredient Quercitin from turmeric, and Resveratrol are cited to convince the potential of phytochemicals in treatment and reversal of drug resistance in cancers.

Cellular senescence, a growth-arrest program that limits the lifespan of mammalian cells and prevents unlimited cell proliferation, is attracting considerable interest because of its links to tumour suppression. Cellular
senescence is a defining feature of Ras-initiated premalignant tumours, which may prove valuable in the diagnosis and prognosis of cancer. Dr. Shilpee Dutt and colleagues from Advanced Centre for Treatment, Research and Education in Cancer, Mumbai, have analysed a different aspect of senescence in cancer in their article ‘Therapy Induced Senescence and its Implications in Cancer’, dealing with therapeutic agents inducing senescence in cancer cells, therapy induced senescence reversal, mechanisms underlying the phenomenon and implications of senescence reversal in cancers, imparting pertinent information in multiple fields. Senescence in cancers is a relatively recent field and better understanding of the phenomenon is critical, particularly in light of senescence reversal in cancer cells that have evolved to abrogate senescence and resume proliferation. Thus, the favourable and unfavourable outcomes as a result of senescence in cancer patients needs extensive investigations.

The next two articles have highlighted on Nanoparticles (NPs) for drug delivery to overcome limitations in conventional chemotherapy in cancer and abrin toxicity. The NPs are of significant interest as these can be tailored to simultaneously carry drugs and as imaging probes specifically targeted to diseased tissues. The earliest clinical trials on Nanoparticle use for anti-cancer drug delivery were conducted in 1980s, and the first nanoparticles with encapsulated doxorubicin was marketed by the Pharmaceutical Industry in 1995. Numerous nanoparticles for cancer drug delivery have been approved and/or are currently under development due to advantages of enhancing solubility of hydrophobic drugs, prolonging circulation time, minimizing nonspecific uptake, preventing undesirable off-target and side effects, improving intracellular penetration, and specific targeting. Drs. Barick, Hassan, Gawali and Dutta from Bhabha Atomic Research Centre, Mumbai, in the article ‘Surface Engineering of Iron Oxide Nanoparticles for Cancer Therapy’, review the recent developments in the field of functionalization, coating for increased biocompatibility and uptake, and potential diagnostic and therapeutic applications in cancer. The review cites several state-of-the-art references convincing the future in Nanoparticles as smart drug delivery and diagnostic system.

On the other hand, Dr. Karande and her group at Indian Institute of Science, Bangalore, elaborate on Nanoparticle delivery in abrin toxicity, in the article ‘Nanocarrier Mediated Intracellular
Delivery of Neutralizing Antibodies for the Management of Abrin Lethality. Abrin is a toxic protein which inhibits protein synthesis of eukaryotic cells. It is similar in structure and properties to ricin, although its toxicity is 75 times higher than ricin in mice, with an estimated human fatal dose of 0.1–1 g/kg, causing death after accidental and intentional poisoning. In the current environment of global discontent and fear of terrorism in countries, abrin represents potential biological warfare agent exploitable for terrorist attack. Gastric emptying techniques, including induced emesis, activated charcoal, gastric lavage and whole bowel irrigation, may be useful treatment modalities for abrin toxicities. Dr. Karande and team analysed abrin antibody-nanocarrier conjugate in protecting cells from abrin-mediated toxicity several hours prior to and an hour post abrin exposure, using two delivery systems comprising an inorganic nanoparticle (silica) and a biomolecular nanocarrier (chimeric Sesbania mosaic virus like particle) for intracellular delivery of neutralizing monoclonal antibodies to abrin. Further, the authors demonstrated that neither of the conjugates were cytotoxic to the cells, and SiNP-mAb D6F10 protected the cells from abrin mediated inhibition of protein synthesis, thus neutralizing abrin toxicity. The utility of the approach for military personnel and security forces facing adversaries with toxins in their arsenal, is a valuable addition. A must read article in the biomedical research arena.

The research article by Dr. Kale and her team at National Centre for Cell Science, Pune, on ‘Determination of Hyperglycaemia-induced EPC Dysfunction Using a Panel of Cellular Assays: Validation of Experimental Murine and Human Model Systems’ discusses the concept of glycemic memory. The study indicates progression of diabetic vascular complications linked to uncontrolled glycemia early in the disease despite a significant follow-on period of improved glycemic control. It also relates to the association between tight glycemic control early in the course of disease and prevention of progression to late macrovascular, retinopathic and neuropathic complications, independent of future glycemic control strategies. Thus, the vascular complications of diabetes significantly impact quality of life and mortality in diabetic patients, impacting multiple organ systems despite later glucose control. Several of these complications are linked to impairment in vasculogenesis, with circulating and bone marrow-derived endothelial progenitor cells (EPCs) contributing to
new vessel formation. Experimentally, impairments in EPC function prevents new blood vessel growth and are potentially reversible by manipulations to decrease reactive oxygen species (ROS). Novel strategies aimed at reducing hyperglycemia-induced ROS may be a useful adjuvant to antihyperglycemic therapies in the prevention of diabetic complications. Hence, it is imperative to analyse EPC dysfunction using universal detection test systems. The authors have analysed responses to high glucose via several tests including colony formation and cell adhesion assays, proliferation and viability tests for evaluation of responses in EPCs in Murine and Human systems. Besides, functional assays of tubule formation, chemotactic migration assay, CXCR4 and VEGFR mRNA expression were analysed to demonstrate the effect of high glucose in vitro and diabetes in vivo. The study enhances accuracy of endothelial progenitor cell dysfunction tests in human and murine systems, and the standardised tests will enable comparison of data enhancing uniformity across data sets.

The final article on ‘Investigation of Action Potential Propagation in a Syncytium’, by Drs. Appukuttan, Brain and Manchanda, from Indian Institute of Technology, Mumbai, and University of Birmingham, UK, is a computational study on action potential to explain functioning of syncytial tissues. The detrusor smooth muscle (DSM) of the urinary bladder, exhibits a variety of spikes that differ markedly in their amplitudes and time courses, and the origin of the diversity is often attributed to the syncytial nature of smooth muscle and its distributed innervation. The normal process of excitation of DSM involves propagation of action potentials through different intrinsic membrane properties by the propagation of action potentials through electrically coupled cells that have differing anatomical patterns of connections and intrinsic membrane properties. The current knowledge of either the pattern of cell–cell coupling or of the regional variation in intrinsic membrane properties is far from complete. The authors have investigated the extent of electrical coupling between cells, the size of the network, arrangement of cells in the network, and location of the cell within the network, thus providing a better understanding of functioning of syncytial tissues.