

Advances in Biotechnology and Implications in Clinical Medicine

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We continue with the theme of contemporary topics in this issue with articles in stem cell research which has undoubtedly evolved as the most fascinating area of science in the last decade. The current issue initiates an invited editorial on technology with Dr. Tania Fernandez, earlier a Director on the Board of Burill and Company, USA, and currently the Founder and CEO of DreamCatcher Ventures, USA, with her expertise in assessment of biotechnology advances and applications for venture funding, bridging the gap of current state of art technology, scientific basic research and clinical applications, and highlighting translational research from 'Bench to Bedside'. The importance of technology in today's biomedical research is apparent. The 2014 Nobel Prize winners, Eric Betzig, William Moerner and Stefan Hall, were awarded the prize for use of fluorescence to magnify microscopic images to visualize molecules inside living cells. The applications of the technology developed by the nobel laureates enabled a paradigm shift in microscopy to nanoscopy with immense applications including detailed working of cells such as synapses between brain cells,

macromolecular aberrations in diseases at cellular level, tracking functioning of cells. The super resolution microscopy/nanoscopy has revolutionised imaging. The current Next Generation Sequencing (NGS) with its myriad applications in disease transmission, epidemiology and clinical applications available and affordable for Predictive, Diagnostic, Prognostic, the right drug and right dosage for individual patients, taking us rapidly into personalized medicine, may be another such technology. We do see the flip side today including finding the needle in a haystack with the NGS mega data analysis; ethical dilemmas of 'To tell or not to tell' with inherent socio-psychological issues; counseling the patients and care givers. A close connect between clinicians requesting tests and answers, and the lab Director providing the tests, for appropriate interpretations has to be mandatory; and the correct pricing in the market for affordability by a patient. Dr. Fernandez takes us through these facets in her editorial. The current opinion is NGS will practically take us into expanded genetic testing in the real world and soon.

We have excellent review articles, and a

method to refrain from use of animal fetal bovine serum for maintenance and proliferation of stem cells for clinical use. Stem cells in regenerative medicine have been a perennial topic for intense discussion and debate around the world. The enormous potential of stem cells in replacement of damaged and diseased tissues in several areas including cardiovascular diseases, neurological diseases, spinal injuries, geriatric diseases like Parkinsons and Alzheimers, genetic diseases, and cancer, makes it feasible to finding cures and treatments for several as yet 'Uncurable' diseases. The regenerative stem cell treatment in the near future is a hope for better quality of prolonged life for the suffering millions. Recently, with the advent of the somatic cell reprogramming technology, the path-breaking noble prize winning work of John Gurdon and Shinya Yamanaka has opened avenues for customized stem cell based therapies. The methodology has obviated the need to use supernumerary embryos, an ethical issue in human embryonic stem cell research.

Despite the tremendous progress in stem cell research and therapy, certain challenges need to be overcome for realizing the ultimate potential of the highly specialized and unique stem cells. This includes improper differentiation to relevant cell types, need for suitable biocompatible matrices to support cell growth, guided delivery of the cells, and mechanisms to comprehend stem cell fate

decisions in biological systems. A critical aspect of regenerative medicine should include the stem cell niche and its implications in harnessing endogenous stem cells for successful therapeutic purposes. To address these challenges, interdisciplinary bioengineering strategies for stem cell differentiation; synthesis of novel biocompatible biomaterials for clinical use; sensitive biomedical imaging techniques, are a dire need of the hour.

The review presented in the current issue of the journal by Kanitkar and Kale, discusses the progress in the field of stem cells and tissue engineering. The authors discuss the importance of maintenance of a suitable environment that mimics the *in vivo* natural milieu, for proper differentiation and preservation of the architecture of the cells. Thus, taking cues from the natural environment, generation of mature cell types would depend on a combination of cells, growth factors and a suitable three dimensional (3D) environment to maintain functionality. Scaffolds are biomaterials that are seeded with cells and provide a provisional 3D physical template upon which the seeded cells build new 'Extracellular Matrix' (ECM) and form the regenerated tissue. The ECM of mammalian tissues performs a variety of functions including anchoring of cells, providing a structural support and is supercritical for tissue development, homeostasis and repair. Thus, a key goal to

success in tissue engineering is to effectively emulate several aspects of normal tissue development and remodeling. The article provides a comprehensive review of the various ECMs/scaffolds used for differentiation and growth of stem cells for treatment of a number of medical conditions. Every tissue and organ including bone marrow, have a defined microenvironment or niche that regulates quiescence, proliferation and/or differentiation of the cells within. The authors speculate on the role of 'cellular secretome' for therapeutic purposes, during construction of an artificial niche in their review.

The article by Raut and Khanna reviews the progress in understanding the role of microRNAs (miRNAs), an innate regulatory group of molecules in somatic cell reprogramming. The article briefly describes various approaches used for derivation of induced pluripotent stem cells (iPSCs), and the limitations in existing methods viz., low efficiency of reprogramming, use of harmful oncogenes, and viral vectors for reprogramming. The authors elaborate distinct sets of miRNAs expressed in the early stage and late stage of reprogramming, which play key functions in the reprogramming event. Further the authors highlight the role of miRNAs *per se* in reprogramming, which may culminate in a safe, effective method for efficient reprogramming, moving closer to clinical translation.

An important consideration for translating stem cell therapy to clinics is to avoid use of animal proteins and other macromolecules in processing the cells. The article by Limaye and co-workers, indicates alternative, inexpensive use of cord blood plasma (CBP) as a substitute to the often used fetal bovine serum (FBS) for cultivation of mesenchymal stem cells (MSCs) derived from cord tissue. Normally, cell culture procedures utilize FBS as cell culture supplement to isolate and expand MSCs. However, the individual variability in each batch, and the undefined factors coupled with xenogeneic conditions, necessitates use of 'humanized' cell culture protocols, to facilitate clinical translation of MSCs. An acceptable substitute is cord blood derived AB positive plasma (CBP). The authors describe the *ex vivo* expansion of cord derived MSCs with CBP. MSCs derived from cord tissue represent a promising source for clinical applications. A critical concern in applications of umbilical cord blood derived MSC is development of a consistent and reproducible method for in vitro expansion of the cells. The authors demonstrate that MSCs cultured using CBP retain their phenotype, characteristics and differentiation potential. Thus, the authors convincingly demonstrate CBP as a promising alternative to FBS and provide a GMP-compliant protocol.

The stem cell series of articles culminate with Dr. Pandey and his colleagues synthesizing the implications of cancer stem

cells in radiotherapy in cancer, highlighting the tangible reality of clinical applications of stem cell therapy. The review focuses on the critical role of Cancer Stem Cells (CSCs) during radiotherapy. Since irrefutable proof of existence of CSCs has been demonstrated in several cancers, research is directed to this population of stem cells, in an effort to better understand the mechanism of recurrence of tumors after surgery and chemo/radio-resistance. The review also highlights prospects for targeting the CSCs for sensitization during cancer radiotherapy for better prognosis of the disease.

An often neglected area in medicine globally, and in India with a large population of 1.2 billion, is 'Prevention'. With exception of common pediatric vaccines for polio, diphtheria, pertussis, small pox, measles and mumps, disease prevention is not a common practice in India. Further, 'Preventive Medicine in Cancer' is also rarely practiced, despite the consistent increase in the incidence and prevalence of the various cancers. Screening through 'Primary Prevention' including activities that prevent diseases from occurring, and 'Secondary Prevention' that includes screening for diseases at early stages

to reduce mortality and improve the quality of life, is a fairly difficult proposition as a systematic, planned program in countries with a large population. Despite availability of tests for screening the normal population and predicting risk for cancers, availability of screening tests and vaccines unequivocally associated with cancers – cervical and hepatic cancers, use of the preventive measures is not a well accepted and also not a feasible proposition, regret to add in India as well. Dr. Maru gives a comprehensive review on 'Cancer Prevention Approaches'. He succinctly puts forth facts such as a majority of cancers are caused, mediated and modified by environmental and lifestyle factors. Changes in lifestyle habits and socially accepted customs, reducing use of tobacco, alcohol, overweight and obesity, have met with limited success and perhaps limited efforts, despite great potential. On the other hand, the numbers of chemopreventive agents and approaches have been limited. The review is a must read for all. The take home message is a healthy lifestyle, use of vaccines where available and appropriate, and regular clinical check-ups to prevent almost 50% of all adult cancers.