

Stem Cells and Cancer Stem Cells 10
Therapeutic Applications in Disease and Injury

M.A. Hayat
Editor

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Volume 10

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Although touched by technology, surgical pathology always has been, and remains, an art. Surgical pathologists, like all artists, depict in their artwork (surgical pathology reports) their interactions with nature: emotions, observations, and knowledge are all integrated. The resulting artwork is a poor record of complex phenomena.

Richard J. Reed, MD

One Point of View

All small tumors do not always keep growing, especially small breast tumors, testicular tumors, and prostate tumors. Some small tumors may even disappear without a treatment. Indeed, because prostate tumor grows slowly, it is not unusual that a patient may die at an advanced age of some other causes, but prostate tumor is discovered in an autopsy study. In some cases of prostate tumors, the patient should be offered the option of active surveillance followed by PSA test or biopsies. Similarly, every small kidney tumor may not change or may even regress. Another example of cancer or precancer reversal is cervical cancer. Precancerous cervical cells found with Pap test may revert to normal cells. Tumor shrinkage, regression, dormancy, senescence, reversal, or stabilization is not impossible. Can prosenescence therapy be an efficient alternative strategy to standard therapies for cancer prevention and treatment?

Another known example of cancer regression is found in pediatric neuroblastoma patients. Neuroblastoma shows one of the highest rates of spontaneous regression among malignant tumors. In addition to the well-known spontaneous regression in stage 4S disease, the high incidence of neuroblastoma remnants found during autopsy of newborns suggest that localized lesions may undergo a similar regression (Guin et al. 1969). Later studies also indicate that spontaneous regression is regularly seen in infants with localized neuroblastoma and is not limited to the first year of life (Hero et al. 2008). These and other studies justify the “wait and see” strategy, avoiding chemotherapy and radiotherapy in infants with localized neuroblastoma, unless *MYCN* gene is amplified. Infants with nonamplified *MYCN* and hyperdiploidy can be effectively treated with less intensive therapy. Infants with disseminated disease without *MYCN* have excellent survival with minimal or no treatment. Another example of spontaneous shrinkage and loss of tumors without any treatment is an intradural lipoma (Endoh et al. 1998).

Although cancers grow progressively, various lesions such as cysts and thyroid adenomas show self-limiting growth. Probably, cellular senescence occurs in many organ types following initial mutations. Cellular senescence, the growth arrest seen in normal mammalian cells after a limited number of divisions, is controlled by tumor suppressors, including p53 and p16, and so this phenomenon is believed to be a crucial barrier to tumor development. It is well-established that cell proliferation and transformation induced by oncogene activation are restrained by cellular senescence.

Metastasis is the main cause of death from cancer. Fortunately, metastasis is an inefficient process. Only a few of the many cancer cells detached from the

primary tumor succeed in forming secondary tumors. Metastatic inefficiency varies depending on the location within an organ, but the malignancy may continue to grow preferentially in a specific tissue environment. Some of the cancer cells shed from the primary tumor are lost in the circulation due to hemodynamic forces or the immune system, macrophages, and natural killer cells.

Periodic rejection of a drug by FDA, which was previously approved by the FDA, is not uncommon. Most recently, the FDA ruled that Avastin should not be used to treat advanced breast cancer, although it remains on the market to treat other cancers, including colon and lung malignancies. Side-effects of Avastin include high blood pressure, massive bleeding, heart attack, and damage to the stomach and intestines.

Unwanted side effects of some drug excipients (e.g., propylene glycol, menthol) may also pose safety concerns in some patients. Excipients are defined as the constituents of the pharmaceutical formulation used to guarantee stability, and physicochemical, organoleptic, and biopharmaceutical properties. Excipients frequently make up the majority of the volume of oral and parenteral drugs. Not all excipients are inert from the biological point of view. Although adverse drug reactions caused by the excipients are a minority of all adverse effects of medicinal products, the lack of awareness of the possible risk from excipients should be a concern for regulatory agencies, physicians, and patients (Ursino et al. 2011). Knowledge of the potential side effects of excipients is important in clinical practice.

It is known that chemotherapy can cause very serious side-effects. One most recent example of such side-effects was reported by Rubsam et al. (2011). Advanced hepatocellular carcinoma (HCC) induced by hepatitis C virus was treated with sorafenib. It is an oral multikinase inhibitor that interferes with the serine/threonine kinases RAF-1 and B-Raf and the receptor tyrosine kinases of the vascular endothelial growth factor receptors and the platelet-derived growth factor receptor-beta. Although sorafenib is effective in regressing HCC, it shows serious side-effects including increasingly pruritic and painful skin changes (cutaneous eruption).

An example of unnecessary surgery is the removal of all the armpit lymph nodes after a biopsy when a sentinel node shows early stage breast cancer; removal of only the sentinel node may be needed. Limiting the surgery to the sentinel node avoids painful surgery of the armpit lymph nodes, which can have complications such as swelling and infection (such limited surgery is already being practiced at the Memorial Sloan-Kettering Cancer Research Center). Radiation-induced second cerebral tumors constitute a significant risk for persons undergoing radiotherapy for the management of cerebral neoplasms. High-grade gliomas are the most common radiation-induced tumors in children (Pettorini et al. 2008). The actual incidence of this complication is not known, although it is thought to be generally low.

Medical Radiation

Chromosome aberrations induced by ionizing radiation are well-known. Medical radiation-induced tumors are well-documented. For example, several types of tumors (sarcomas, meningiomas) can develop in the CNS

after irradiation of the head and neck region (Parent 1990). Tumorigenic mechanisms underlying the radiation therapy of the CNS are discussed by Amirjamshidi and Abbassioun (2000) (See below).

Radiation therapy is commonly used to treat, for example, patients with primary and secondary brain tumors. Unfortunately, ionizing radiation has limited tissue specificity, and tends to damage both neoplastic and normal brain tissues. Radiation-induced brain injury, in fact, is a potential, insidious later cerebral side-effect of radiotherapy. Most commonly it consists of damage in small arteries and capillaries, resulting in secondary processes of ischemia.

After radiation therapy, imaging techniques (CT, MRI, SPECT) can be used to assess treatment response and detect radiation-induced lesions and recurrent tumors. Optical spectroscopy has also been used for detecting radiation damage (Lin et al. 2005). The F_{500} nm spectral peak allows accurate selection of tissues for biopsy in evaluating patients with new, contrast enhancing lesions in the setting of previous irradiation. This peak is highly correlated with a histological pattern of radiation injury. Deep lesions require a stereotactic biopsy to be conclusive. Also, much of the radiation effect is mediated by acute and chronic inflammatory cellular reactions. Biopsy samples supplement pathological differentiation of radiation effect from tumor progression. It should be noted that most of the biopsies show radionecrosis as well as scattered tumor cells.

Women treated with therapeutic chest radiation may develop cancer. This possibility becomes exceedingly serious considering that 50,000–55,000 women in the United States have been treated with moderate to high-dose chest radiation (~20 Gy). This possibility is much more serious for pediatric or young adult cancer patients, because these women are at a significantly increased risk of breast cancer and breast cancer mortality following cure of their primary malignancy (Martens et al. 2008). A recent study also indicates that such young women develop breast cancer at a young age, which does not appear to plateau (Henderson et al. 2010). In this high-risk population, ironically there is a benefit associated with early detection. In other words, young women with early stage breast cancer following chest radiation have a high likelihood for favorable outcome, although life-long surveillance is needed.

Presently, although approximately 80 % of the children with cancer are cured, the curative therapy could damage a child's developing organ system; for example, cognitive deficits following cranial radiotherapy are well known. Childhood survivors of malignant diseases are also at an increased risk of primary thyroid cancer (Sigurdson et al. 2005). The risk of this cancer increases with radiation doses up to 20–29 Gy. In fact, exposure to radiation therapy is the most important risk factor for the development of a new CNS tumor in survivors of childhood cancer, including leukemia and brain tumors. The higher risk of subsequent glioma in children subjected to medical radiation at a very young age reflects greater susceptibility of the developing brain to radiation. The details of the dose-response relationships, the expression of excess risk over time, and the modifying effects of other host and treatment factors have not been well defined (Neglia et al. 2006).

A recent study indicates that childhood brain tumor survivors are at an increased risk of late endocrine effects, particularly the patients treated with cranial radiation and diagnosed at a younger age (Shalitin et al. 2011). Among children with cancer, the application of radiotherapy, therefore, should not be taken lightly, and it should be administered only when absolutely necessary to successfully treat the primary tumor. When radiotherapy is administered, use of the minimum effective dose tends to minimize the risk of second CNS neoplasms (late effect). Prolonged follow-up of childhood cancer survivors (particularly those treated with radiation) is necessary because of the long period between treatment and the development of malignancy. This practice should be a part of the effective therapy of the primary disease.

It is well established that radiation doses are related to risk for subsequent malignant neoplasms in children with Hodgkin's disease. It has been reported that increasing radiation dose was associated with increasing standardized incidence ratio ($p = 0.0085$) in survivors of childhood Hodgkin's disease (Constine et al. 2008). Approximately, 75 % of subsequent malignancies occurred within the radiation field. Although subsequent malignancies occur, for example, in breast cancer survivors in the absence of radiotherapy, the rise increases with radiation dose.

The pertinent question is: Is it always necessary to practice tumor surgery, radiotherapy, chemotherapy, or hormonal therapy or a combination of these therapies? Although the conventional belief is that cancer represents an "arrow that advances unidirectionally," it is becoming clear that for cancer to progress, it requires cooperative microenvironment (niche), including immune system and hormone levels. However, it is emphasized that advanced (malignant) cancers do not show regression and require therapy. In the light of the inadequacy of standard treatments of malignancy, clinical applications of the stem cell technology need to be expedited.

Prostate Cancer

There were an estimated 217,730 new cases of prostate cancer in the United States in 2010 with 32,050 deaths, making it the second leading cause of cancer deaths in men. Currently, there are more than 2,000,000 men in the United States who have had radical or partial prostate surgery performed. Considering this huge number of prostate surgeries and the absence of a cumulative outcome data, it seems appropriate to carefully examine the benefits of radical surgery, especially in younger men.

Clinical prostate cancer is very rare in men of the ages younger than 40 years. In this age group the frequency of prostate malignancy is 1 in 10,000 individuals. Unfortunately, the incidence of malignancy increases over the ensuing decades, that is, the chance of prostate malignancy may reach to 1 in 7 in men between the ages of 60 and 79 years. Reactive or aging-related alterations in the tumor microenvironment provide sufficient influence, promoting tumor cell invasion and metastasis. It has been shown that

nontumorigenic prostate epithelial cells can become tumorigenic when cocultured with fibroblasts obtained from regions near tumors (Olumi et al. 1999).

Prostate cancer treatment is one of the worst examples of overtreatment. Serum prostate specific antigen (PSA) testing for the early detection of prostate cancer is in wide use. However, the benefit of this testing has become controversial. The normal cut-off for serum levels of PSA is 4 ng/ml, so a man presenting with a PSA above this level is likely to require a rectal biopsy, but only in 25 % of men with serum levels of PSA between 4 ng and 10 ng/ml have cancer (Masters 2007). The PSA threshold currently being used for biopsy ranges between 2.5 and 3.4 ng/ml. Up to 50 % of men presenting with prostate cancer have PSA levels within the normal range. It is apparent that screening of prostate cancer using PSA has a low specificity, resulting in many unnecessary biopsies, particularly for gray zone values (4–10 ng/ml). According to one point of view, the risks of prostate cancer overdetection are substantial. In this context, overdetection means treating a cancer that otherwise would not progress to clinically significant disease during the lifetime of the individual. Overdetection results in overtreatment. The advantages and limitations of PSA test in diagnosing prostate cancer were reviewed by Hayat (2005, 2008).

Androgen deprivation therapy (ADT) is an important treatment for patients with advanced stage prostate cancer. This therapy is carried out by blocking androgen receptor or medical or surgical castration. Although ADT is initially very effective, treated tumors inevitably progress to androgen-independent prostate cancer (AIPC), which is incurable. One possible mechanism responsible for the development of AIPC is modulation of the tissue microenvironment by neuroendocrine-like cancer cells, which emerge after ADT (Nelson et al. 2007).

Recently, Pernicova et al. (2011) have further clarified the role of androgen deprivation in promoting the clonal expansion of androgen-independent prostate cancer. They reported a novel linkage between the inhibition of the androgen receptor activity, down-regulation of S-phase kinase-associated protein 2, and the formation of secretory, senescent cells in prostate tumor cells. It is known that several components of the SASP secretome, such as IL-6, IL-8, KGF, and epidermal growth factor, are capable of transactivating androgen receptor under androgen-depleted conditions (Seaton et al. 2008). It needs to be pointed out that androgen deprivation therapy, used in high-risk patients with prostate cancer, may cause reduced libido, erectile dysfunction, fatigue, and muscle loss; osteoporosis is also a late complication. Therefore, periodic bone density scanning needs to be considered.

Recently, the FDA cleared the use of NADiA (nucleic acid detection immunoassay) ProsVue prognostic cancer test. This proprietary nucleic acid detection immunoassay technology identifies extremely low concentrations of proteins that have not been routinely used as a diagnostic or prognostic aid. It is an *in vitro* diagnostic assay for determining the rate of change of serum total PSA over a period of time. The assay can quantitate PSA at levels <1 ng/ml. This technique can be used as a prognostic marker, in conjunction with clinical evaluation, to help identify patients at reduced

risk for recurrence of prostate cancer for years following prostatectomy. It targets the early detection of proteins associated with cancer and infectious diseases. This technique combines immunoassay and real-time PCR methodologies with the potential to detect proteins with femtogram/ml sensitivity (10–15 g/ml). Additional clinical information is needed regarding its usefulness in predicting the recurrence.

A significant decrease in the risk of prostate cancer-specific mortality is observed in men with few or no comorbidities. Indeed, active surveillance in lieu of immediate treatment (surgery or radiation, or both) is gaining acceptance. Most men with prostate cancer, even those with high-risk disease, ultimately die as a result of other causes (Lu-Yao et al. 2009). Debate on this controversy is welcome, but narrow opinions and facile guidelines will not lead to facts and new information – men worldwide deserve it (Carroll et al. 2011). Automatic linking of positive diagnosis with treatment, unfortunately, is a common clinical practice. Unfortunately, even men who are excellent candidates for active surveillance in the United States often undergo some treatment. Deferment of treatment is advised in men with low-risk disease, especially of a younger age.

Active surveillance is proposed for patients with low-risk prostate cancer in order to reduce the undesirable effects of overdiagnosis. Prostate specific antigen serum level lower than 10 ng/L and Gleason score lower than 7 are the main criteria to select patients for active surveillance. The correct use of these two criteria is essential to differentiate between aggressive and nonaggressive prostate cancer. Autopsy studies indicate that approximately one out of three men older than 50 years show histological evidence of prostate cancer (Klotz 2008). Thus, a large proportion of prostate cancers are latent, never destined to progress, or affect the life of the patient. It is estimated that the percentage of low-risk prostate cancer is between 50 and 60 % of newly diagnosed cases. A large number of patients die having prostate cancer, but not because of this cancer (Filella et al. 2011).

First whole genome sequences of prostate tumors were recently published online in *Nature* journal (vol. 470: 214–220, 2011). This study revealed that rather than single spelling errors, the tumor has long “paragraphs” of DNA that seem to have broken off and moved to another part of the genome (rearrangement of genes), where they are most active. These portions of DNA contain genes that help drive cancer progression. The mutated genes involved include *PTEN*, *CADM2*, *MAG12*, *SPOP*, and *SPTA1*. This information may lead to the development of more efficient, less invasive ways to diagnose and treat this cancer. Such information, in addition, should lead to personalized therapeutics according to sequencing results of different gene mutations or chromosomal rearrangements. The urgent need of such studies becomes apparent considering the huge number of new cases of prostate problems reported every year.

In contrast to prostate cancer, cardiovascular disorders take the heavier toll of life. In other words, the risk of death for men in the United States between the ages of 55 and 74 years due to cardiovascular disease surpasses that of prostate cancer. Cardiovascular disease is the most common of the chronic non-communicable diseases that impact global mortality.

Approximately, 30 % of all deaths worldwide and 10 % of all healthy life lost to disease are accounted for by cardiovascular disease alone.

In conclusion, initial treatment with standard surgery, irradiation, chemotherapy, or hormonal therapy, or combination of these protocols can result in both local and systemic sequelae. Therefore, surveillance for late recurrence and secondary primary malignancies is recommended for most cancer patients. Patients with breast, lung, prostate, colorectal, and head and neck cancers constitute the largest groups requiring long-term monitoring and follow-up care.

Eric Hayat

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Preface

Stem Cells are nature's indispensable gift to multicellular organisms, including humans.

This is volume 10 of the 14-volume series, *Stem Cells and Cancer Stem Cells: Therapeutic Applications in Disease and Tissue Injury*. A stem cell is defined as a cell that can self-renew and differentiate into one or more specialized cell types. A stem cell may be pluripotent, which is able to give rise to the endodermal, ectodermal, and mesodermal lineages; an example is embryonic stem cells. A stem cell may be multipotent, which is able to give rise to all cells in a particular lineage; examples are hematopoietic stem cells and neural stem cells. A stem cell may be unipotent, which is able to give rise to only one cell type; an example is keratinocytes.

A cancer stem cell is a cell type within a tumor that possesses the capacity of self-renewal and can give rise to the heterogeneous lineages of cancer cells that comprise the tumor. In other words, a cancer stem cell is a tumor initiating cell. A unique feature of cancer stem cell is that although conventional chemotherapy will kill most cells in a tumor, cancer stem cells remain intact, resulting in the development of resistance of therapy. All of these types of stem cells are discussed in this series.

By bringing together a large number of experts (oncologists, neurosurgeons, physicians, research scientists, and pathologists) in various aspects of this medical field, it is my hope that substantial progress will be made against terrible human disease and injury. It is difficult for a single author to discuss effectively the complexity of diagnosis, therapy, including tissue regeneration. Another advantage of involving more than one author is to present different points of view on a specific controversial aspect of cancer cure and tissue regeneration. I hope these goals will be fulfilled in this and other volumes of the series. This volume was written by 66 contributors representing 13 countries. I am grateful to them for their promptness in accepting my suggestions. Their practical experience highlights their writings, which should build and further the endeavors of the readers in these important areas of disease and injury. I respect and appreciate the hard work and exceptional insight into the nature of cancer and other diseases provided by these contributors. The contents of the volume are divided into five subheadings: Mesenchymal Stem Cells, Induced Pluripotent Stem Cells, Neural Cells and Neural Stem Cells, Role of Stem Cells in Disease, and Stem Cell Transplantation for the convenience of the readers.

It is my hope that subsequent volumes of the series will join this volume in assisting in the more complete understanding of the causes, diagnosis, and cell-based treatment of major human diseases and debilitating tissue/organ injuries. There exists a tremendous, urgent demand by the public and the scientific community to address to cancer diagnosis, treatment, cure, and hopefully prevention. In the light of existing cancer calamity, government funding must give priority to eradicating deadly malignancies over military superiority.

I am thankful to my students for their help in many ways in completing this project.

M.A. Hayat

Contents

Part I Mesenchymal Stem Cells

1 Mesenchymal Stem Cells in Bone Regeneration	3
Sebastian Fischer, Matthias Schulte, Tobias Hirsch, Marcus Lehnhardt, and Björn Behr	
2 Experimental (Preclinical) Studies and Clinical Trials of Adipose Tissue-Derived Mesenchymal Stem Cells for Autoimmune Diseases	13
Eun Wha Choi	
3 Validity of Markers for Epithelial Cells and Mesenchymal Cells	23
Jianyuan Chai	
4 Mesenchymal Stem Cell Survival in Infarcted Myocardium: Adhesion and Anti-death Signals	35
Woochul Chang, Byeong-Wook Song, and Ki-Chul Hwang	
5 Hepatogenic Differentiation: Comparison Between Adipose Tissue-Derived Stem Cells and Bone Marrow Mesenchymal Stem Cells	45
María José Gómez-Lechón and Laia Tolosa	
6 Fibrin for Encapsulation of Human Mesenchymal Stem Cells for Chondrogenic Differentiation	59
Tamer A.E. Ahmed and Maxwell T. Hincke	
7 Differences Between Adipose Tissue-Derived Mesenchymal Stem Cells and Bone Marrow-Derived Mesenchymal Stem Cells as Regulators of the Immune Response	71
Dobroslav Kyurkchiev, Ekaterina Ivanova-Todorova, Ivan Bochev, Milena Mourdjeva, and Stanimir Kyurkchiev	
8 Transforming Growth Factor-Beta Induced Chondrogenic Differentiation of Bone Marrow-Derived Mesenchymal Stem Cells: Role of Smad Signaling Pathways	85
Peter M. van der Kraan	

Part II Induced Pluripotent Stem Cells

- 9 Drug Discovery Using Human iPSC Based Disease Models and Functional Hepatic Cells**..... 95
Su Mi Choi, Yonghak Kim, and Yoon-Young Jang
- 10 Generation of Antigen-Specific T Lymphocytes from Induced Pluripotent Stem Cells for Adoptive Immunotherapy**..... 105
Fengyang Lei, Rizwanul Haque, Xiaofang Xiong, and Jianxun Song

Part III Neural Cells and Neural Stem Cells

- 11 Genetic Identification of Human Embryonic Stem Cell-Derived Neural Cell Types Using Bacterial Artificial Chromosomes**..... 125
Zeynep Tokcaer-Keskin and Dimitris G. Placantonakis
- 12 Moderate Low Temperature Preserves the Stemness of Neural Stem Cells (Methods)** 137
Kosuke Saito, Noboru Fukuda, and Nariyuki Hayashi

Part IV Role of Stem Cells in Disease

- 13 High-Dose Chemotherapy with Autologous Stem Cell Support in the Treatment of Transformed B-Cell Non-Hodgkin's Lymphomas**..... 149
Marianne Brodtkorb Eide and Harald Holte
- 14 The Wnt/ β -Catenin Pathway as a Potential Target for Drug Resistant Leukemic Stem Cells** 163
Tsz Kan Fung, Anskar Y.H. Leung, and Chi Wai Eric So
- 15 Bone Marrow Stem Cell Therapies for Diabetes Mellitus and Its Complications** 173
Ming Li and Susumu Ikehara
- 16 Thyroid Cancer Stem Cells – Strategies for Therapeutic Targeting**..... 181
Reigh-Yi Lin, William Sewell, Kyle Spradling, Ashley N. Reeb, and Wen Li
- 17 Role of Cancer Stem Cell in Mammary Carcinogenesis and Its Clinical Implication**..... 189
Yajing Liu and Suling Liu
- 18 Critical Analysis of Parkinson's Disease Models and Cell-Based Therapy** 199
Amit K. Jaiswal and Asok Mukhopadhyay
- 19 Presence of an Early Lineage Stem Cell Phenotype in Meningioma-Initiating Cells**..... 211
Prakash Rath, James M. Wilson, and Huidong Shi

20 Isolation and Characterization of Cancer Stem Cells from Dog Glioblastoma	219
George Stoica and Gina Lungu	
21 Role of Stem Cell Niche in the Development of Bone Metastases (An Update).....	229
Nadia Rucci and Anna Teti	
22 Treatment of Hemophilia A Using B Cell-Directed Protein Delivery	239
Ali Ramezani and Robert G. Hawley	
Part V Stem Cell Transplantation	
23 Reduction in the Risk Invasive Fungal Infection Relapse in Patients Undergoing Allogeneic Stem Cell Transplantation Using Caspofungin Secondary Prophylaxis.....	253
Paolo de Fabritiis	
24 Hematopoietic Stem Cell Transplantation in Elderly Patients with Myelodysplastic Syndrome and Acute Myelogenous Leukemia: Use of Busulfan/Fludarabine for Conditioning	263
Nelson Hamerschlag, Marcos de Lima, and Fábio Kerbauy	
25 Co-transplantation of Islets with Mesenchymal Stem Cells Improves Islet Revascularization and Reversal of Hyperglycemia.....	271
Aileen King and Chloe Rackham	
26 Significance of Interleukin-7 Receptor Alpha Polymorphisms in Allogeneic Stem Cell Transplantation.....	283
Klaus Müller, Zaiba Shamim, and Lars P. Ryder	
Index	291

Contents of Volume 1

- 1 Pluripotent Human Stem Cells: An Overview**
- 2 Complexity of Tumor Angiogenesis and Stem Cells**
- 3 Stem Cells Like Astrocytes: Various Roles**
- 4 Neural Crest Cell-Derived Tumors: An Overview**
- 5 Therapeutic Neural Stem Cells for Brain Tumor Therapy**
- 6 Brain Tumors: Role of Neural Cancer Stem Cells**
- 7 Targeting Cancer Stem Cells with Phytochemicals: Inhibition of the Rat C6 Glioma Side Population by Curcumin**
- 8 Glioma Patients: Role of CD133 Stem Cell Antigen**
- 9 Cancer Stem Cells in Brain Gliomas**
- 10 Primary Glioma Spheroids: Advantage of Serum-Free Medium**
- 11 Tumorigenesis of Glioma-Initiating Cells: Role of Sox11**
- 12 Glioma-Initiating Cells: Interferon Treatment**
- 13 Is CD133 the Appropriate Stem Cell Marker for Glioma?**
- 14 Cancer Stem Cells in Glioblastoma**
- 15 Glioblastoma-Derived Cancer Stem Cells: Treatment with Oncolytic Viruses**
- 16 Cancer Stem Cells in Medulloblastoma**
- 17 Transplantation of Embryonic Stem Cells Results in Reduced Brain Lesions**
- 18 Allogenic Hematopoietic Stem Cell Transplantation Followed by Graft-Versus-Host Disease: Role of Adenosine A_{2A} Receptor**
- 19 Umbilical Cord Blood and Alpha-3 Fucosyl Transferase-Treated Haematopoietic Stem Cells for Transplantation**
- 20 Bone Marrow-Derived Stem Cell Therapy for Myocardial Infarction**
- 21 The Use of Mesenchymal Stem Cells in Orthopedics**

Contents of Volume 2

- 1 Isolation of Bone Marrow Stromal Cells from Bone Marrow by Using a Filtering Device (Method)**
- 2 Hematopoietic Stem Cell Frequency Estimate: Statistical Approach to Model Limiting Dilution Competitive Repopulation Assays**
- 3 Characteristics of Cord Blood Stem Cells: Role of Substance P (SP) and Calcitonin Gene-Related Peptide (CGRP)**
- 4 A New Concept of Stem Cell Disorders, and the Rationale for Transplantation of Normal Stem Cells**
- 5 Differentiation of Human Embryonic Stem Cells into Functional Hepatocyte-Like Cells (Method)**
- 6 Stem Cell Mobilization: An Overview**
- 7 Status and Impact of Research on Human Pluripotent Stem Cells: Cell Lines and Their Use in Published Research**
- 8 Gliosarcoma Stem Cells: Glial and Mesenchymal Differentiation**
- 9 Generation of Induced Pluripotent Stem Cells from Mesenchymal Stromal Cells Derived from Human Third Molars (Method)**
- 10 Self-renewal and Differentiation of Intestinal Stem Cells: Role of Hedgehog Pathway**
- 11 Hematopoietic Stem Cell Repopulation After Transplantation: Role of Vinculin**
- 12 Static and Suspension Culture of Human Embryonic Stem Cells**
- 13 Generation of Marmoset Induced Pluripotent Stem Cells Using Six Transcription Factors (Method)**
- 14 MYC as a Multifaceted Regulator of Pluripotency and Reprogramming**
- 15 Human Thyroid Cancer Stem Cells**
- 16 Tumor Stem Cells: CD133 Gene Regulation and Tumor Stemness**
- 17 Cripto-1: A Common Embryonic Stem Cell and Cancer Cell Marker**

-
- 18 **Treatment of Heart Disease: Use of Transdifferentiation Methodology for Reprogramming Adult Stem Cells**
 - 19 **Rat Mesenchymal Cell CD44 Surface Markers: Role in Cardiomyogenic Differentiation**
 - 20 **Stroke Therapy Using Menstrual Blood Stem-Like Cells: Method**
 - 21 **Spontaneous Cerebral Stroke in Rats: Differentiation of New Neurons from Neural Stem Cells**
 - 22 **Neurogenesis in the Cerebral Cortex After Stroke**
 - 23 *Ex Vivo* **Expanded Hematopoietic Stem Cells for Ischemia**
 - 24 **Breast Cancer Risk: Role of Somatic Breast Stem Cells**
 - 25 **Cellular Replacement Therapy in Neurodegenerative Disease Using Induced Pluripotent Stem Cells**
 - 26 **Treatment of Graft-Versus-Host Disease Using Allogeneic Mesenchymal Stem Cells**
 - 27 **Adult Neurogenesis in Etiology and Pathogenesis of Alzheimer's Disease**
 - 28 **Generating Human Cardiac Muscle Cells from Adipose-Derived Stem Cells**
 - 29 **Mesenchymal Stem Cells and Mesenchymal-Derived Endothelial Cells: Repair of Bone Defects**
 - 30 **Omentum in the Repair of Injured Tissue: Evidence for Omental Stem Cells**
 - 31 **Human Embryonic Stem Cells Transplanted into Mouse Retina Induces Neural Differentiation**
 - 32 **Stem Cells to Repair Retina: From Basic to Applied Biology**
 - 33 **Heterogeneous Responses of Human Bone Marrow Stromal Cells (Multipotent Mesenchymal Stromal Cells) to Osteogenic Induction**
 - 34 **Adipose-Derived Stem Cells and Platelet-Rich Plasma: Implications for Regenerative Medicine**
 - 35 **Skeletal Muscle-Derived Stem Cells: Role in Cellular Cardiomyoplasty**
 - 36 **Cardiac Regenerative Medicine Without Stem Cell Transplantation**
 - 37 **Allogeneic Transplantation of Fetal Membrane-Derived Mesenchymal Stem Cells: Therapy for Acute Myocarditis**
 - 38 **Patients with Cancer or Hematopoietic Stem Cell Transplant: Infection with 2009 H1N1 Influenza**

Contents of Volume 3

- 1 Introduction**
- 2 Diversity Oriented Fluorescence Library Approach for Stem Cell Probe Development**
- 3 Isolation of Mesenchymal Stem Cells from Umbilical Cord (Method)**
- 4 Mesenchymal Stem Cell Isolation and Expansion Methodology**
- 5 Hair Follicle Stem Cells**
- 6 Rat Embryonic Cortical Neural Stem Cells: Role of Hypoxia on Cell Proliferation and Differentiation**
- 7 Human Cord Blood-Derived Hematopoietic Stem and Progenitor Cells: From Biology to Medicine**
- 8 Proteomic Characterization of Mesenchymal Stem Cell-Like Populations Derived from Various Tissue Types**
- 9 The Roles of Nanog During Early Embryonic Development and Primordial Germ Cell Migration**
- 10 Human Embryonic Stem Cells in Serum-Free Media: Growth and Metabolism**
- 11 Evolutionary Dynamics of Mutations in Hematopoietic Stem Cells and Beyond**
- 12 Isolated Corneal Epithelial Stem Cells Derived from Limbal Biopsies: Use of Lectin as a Marker for Identifying Transient Amplifying Cells**
- 13 Stem Cell Distribution and Mgmt Expression in Glioblastoma: Role of Intratumoral Hypoxic Gradient**
- 14 Initiation of Human Tumourigenesis: Upregulation of Foxm1 Transcription Factor**
- 15 Role of Cancer Stem Cells of Breast, Colon, and Melanoma Tumors in the Response to Antitumor Therapy**
- 16 Cell-Based Regenerative Therapies: Role of Major Histocompatibility Complex-1 Antigen**

-
- 17 **Mesenchymal Stem Cells for Cellular Therapies**
 - 18 **Radiation Burns and Mesenchymal Stem Cell Therapy**
 - 19 **Mesenchymal Stem Cells: Role of Mechanical Strain in Promoting Apoptosis and Differentiation**
 - 20 **Human Mesenchymal Stem Cells: Melatonin as a Potential Anti-osteoporosis Drug**
 - 21 **Applications of Human – Induced Pluripotent Stem Cell Derived Hepatocytes**
 - 22 **Stem Cells and Gastric Carcinogenesis: From Mouse to Human**
 - 23 **Gain and Loss of Cancer Stem Cells: Effect on Metastatic Efficiency and Treatment Response**
 - 24 **Treatment of Ischemia/Reperfusion Injury of the Kidney with Mesenchymal Stromal Cells**
 - 25 **Mesenchymal Stem Cells: Role for Delivering Nanoparticles to Brain Tumors**
 - 26 **Human Induced Pluripotent Stem Cells: Role in Patient Specific Drug Discovery**
 - 27 **Biomedical Applications of Induced Pluripotent Stem Cells**
 - 28 **Duchenne Muscular Dystrophy: Isolation of CD133-Expressing Myogenic Progenitors from Blood and Muscle of DMD Patients**
 - 29 **Human Fetal Mesenchymal Stem Cells for Prenatal and Postnatal Transplantation**
 - 30 **Protection of Mice from Stroke Using Hematopoietic Stem Cell Transplantation**
 - 31 **Neonatal Hypoxic-Ischemic Encephalopathy: Neural Stem/Progenitor Cell Transplantation**
 - 32 **Mesenchymal Stem Cell-Dependent Formation and Repair of Tendon-Done Insertions**
 - 33 **Cartilage Injuries: Role of Implantation of Human Stem/Progenitor Cells**
 - 34 **Bone Marrow-Derived Very Small Embryonic-Like Cells: β -Cell Regeneration in Pancreatic Tissue**
 - 35 **Engineering Stem Cell Niche: Regulation of Cellular Morphology and Function**
 - 36 **Embryonic Stem Cells: The Role of Nitric Oxide in Regulating Cell Differentiation, Self-renewal, and Apoptosis**
 - 37 **Induction of Apoptosis in Human Keratinocyte Stem Cells: The Role of Hydrogen Sulfide**

Contents of Volume 4

- 1 Neural Stem/Progenitor Cell Proliferation and Differentiation:
Role of Sonic Hedgehog and Wingless/Int-1 Proteins**
- 2 Sensitivity of Hematopoietic and Leukemic Stem Cells
to *Hoxa* Gene Levels**
- 3 Maintenance of Neural Stem Cells in the Brain:
Role of Notch Signaling**
- 4 Maintenance of Hematopoiesis: Role of Early B Cell Factor 2**
- 5 Differentiation of Periodontal Stem/Progenitor Cells:
Roles of TGF- β 1**
- 6 Induced Pluripotent Stem Cells from Human Extra-Embryonic
Amnion Cells: Role of DNA Methylation in Mainting Stemness**
- 7 Smooth Muscle Cell Differentiation from Embryonic Stem Cells:
Role of HDAC7 and PDGF-BB**
- 8 Adult Neural Stem Cells; Identity and Regulation**
- 9 Tendon Injury: Role of Differentiation of Adult and Embryonic
Derived Stem Cells**
- 10 The Potential of Stem Cells and Tissue Engineered Scaffolds
for Repair of the Central Nervous System**
- 11 Improving the Efficacy of Diabetes Mellitus Treatment
by Combining Cell Replacement Therapy
with Immune Correction**
- 12 Induced Pluripotent Stem Cell Production and Characterization:
An Overview of Somatic Cell Reprogramming**
- 13 Proliferation of Bone Marrow-Derived Human Mesenchymal
Stem Cells: Role of Enamel Matrix Proteins**
- 14 Pluripotent Cell-Derived Glial Precursor Cells for the Delivery
of Therapeutic Proteins to the Central Nervous System**
- 15 Cellularized Scaffolds: New Clothes for Cardiac Regenerative
Medicine**

-
- 16 Microencapsulation Procedures for the Immunoisolation of Wharton's Jelly Mesenchymal Stem Cells: A Review**
 - 17 Human Hair Follicular Stem Cells: Markers, Selection and Perspective Clinic Application**
 - 18 Adipose-Derived Stem Cells: Therapy Through Paracrine Actions**
 - 19 Mesenchymal Stem Cell-Natural Killer Cell Interactions**
 - 20 Malignant Gliomas: Treatment Using Genetically-Modified Neural Stem Cells**
 - 21 The Cancer Stem Cell Hypothesis and Its Impact on the Design of New Cancer Therapies**
 - 22 Breast Cancer Stem Cell: Translating to the Clinic**
 - 23 Enhanced Growth and Metastasis of Colon Cancer: Role of Mesenchymal Stem Cells**
 - 24 Proteomic Characterization of Mesenchymal Stem Cell-Like Populations Derived from Various Tissue Types**
 - 25 Severe Combined Immunodeficiency Patients: Immune Recovery After Stem Cell Transplantation**
 - 26 Transplanted Mesenchymal Stem Cells Aid the Injured Brain Through Trophic Support Mechanisms**

Contents of Volume 5

- 1 Signaling Pathways in Cancer Stem Cells: Therapeutic Implications**
- 2 Inhibition of Telomerase with Imetelstat Causes Depletion of Cancer Stem Cells**
- 3 Targeting Self-renewal Pathways in Cancer Stem Cells**
- 4 Detection of Cancer Stem Cells Using AC133 Antibody**
- 5 Peripheral Nerve Regeneration After Traumatic Injury and Stem Cell Therapy**
- 6 Neural Stem Cell Proliferation Surrounding the Area of Traumatic Brain Injury: Role of Exercise Therapy**
- 7 Mesenchymal Stem Cell Treatment for Ischemic Brain Injury**
- 8 Role of Neuropeptide Y on the Maintenance of Self-renewal and Proliferation of Human Embryonic Stem Cells**
- 9 Differentiation of Human Adipose-Derived Stem Cells into Cardiomyocytes**
- 10 Cellular Cardiomyoplasty: Arterial Cells-Stem Cells Transplantation**
- 11 Cardiac Stem Cells Derived from Epithelial-Mesenchymal Transition of the Epicardial Cells: Role in Heart Regeneration (Method)**
- 12 Allogenic Mesenchymal Stem Cells in Experimental Ischaemic Stroke: Translation to the Clinic?**
- 13 Bone Reconstruction Utilizing Mesenchymal Stem Cell Sheets for Cell Delivery**
- 14 Dental Implants Application Using Tissue Engineering Technology**
- 15 Dental Stem Cells: Regeneration of Dentin Upon Tooth Injury**
- 16 Scaffolds for Human Dental Stem Cells to Regenerate Cementum**