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Bone and Cartilage Regeneration Cartilage Regeneration Frontiers in Stem Cell and Regenerative Medicine Research Is the Articular Cartilage Regeneration Approachable Through Mesenchymal Stem Cells Therapies Articular Cartilage Regeneration with Stem Cells Stem Cell Therapy *Directing the Paracrine Actions of Adipose Stem Cells for Cartilage Regeneration* Stem Cell and Tissue Engineering A Tissue Regeneration Approach to Bone and Cartilage Repair *Mesenchymal Stem Cells Bone Marrow Aspirate Concentrate and Expanded Stem Cell Applications in Orthopaedics* Stem Cell and Growth Factor Delivery Vehicles for Cartilage Repair *Mesenchymal Stem Cells as Trophic Mediators in Cartilage Regeneration* Mesenchymal Stem Cells and Skeletal Regeneration **Elucidating and Empowering Stem Cell-chondrocyte Interactions for Cartilage Tissue Regeneration** *Mesenchymal Stem Cell Derived Exosomes* **Strategies for Cartilage Regeneration Cartilage Repair Using Stem Cells Regenerative Medicine and Cell Therapy Regenerative Medicine and Plastic Surgery Mesenchymal Stem Cell Therapy Investigation of Mesenchymal Stem Cells for Cartilage Repair Innovations in Molecular Mechanisms and Tissue Engineering Stem Cell and Regenerative Medicine** Articular Cartilage Tissue Engineering **Tissue Engineering and Cell Therapy for Cartilage Restoration** Ovine Bone Marrow Mesenchymal Stem Cells **From Fat to Cartilage Cartilage Developmental Biology and Musculoskeletal Tissue Engineering Engineering Stem Cells For Tissue Regeneration** Techniques in Cartilage Repair Surgery **A Multiscale Approach to Stem Cell-Based Chondrogenesis for Cartilage Repair** *Evaluation of the Potential for Repair of Degenerate Hyaline Cartilage in the Osteoarthritic Knee by Cartilage Stem Cells Regenerative Medicine: Laboratory to Clinic* **Engineered Cartilage Composed of Mesenchymal Stem Cell Condensates as Modules with Controlled Shape and Size for Multi-tissue Type Constructs, as Materials for Chondroconductive Scaffolds and as Mechanoresponsive Tissues** *Cartilage and Osteoarthritis* Replacement of Degraded Articular Cartilage Using Stem Cell-based Therapy in Rabbit Model of Osteoarthritis *Regenerative Medicine for Spine and Joint Pain* **Orthobiologics**

The aim of the thesis project was to identify a growth factor that would enhance the in vitro chondrogenesis of the equine mesenchymal stem cell (MSC) and subsequently to assess the capacity of the growth factor expressing MSC to improve cartilage repair and osteoarthritis (OA) prevention in vivo. Previous efforts on MSC enhanced cartilage repair have focused on implantation of MSCs to articular cartilage defects. This approach is only applicable to acute and focal articular cartilage injury and does not apply to the OA joint. Global joint disease, as in OA, is far more common than focal cartilage injury and no disease modifying therapies of regenerative therapies are currently available. Short term tracking studies of intra-articular injection of autologous MSCs were performed as part of this dissertation. Studies revealed that MSCs efficiently engraft the synovial membrane but not articular cartilage, whether normal or diseased. Differing three-dimensional culture systems were tested for suitability as a system to study in vitro chondrogenesis of MSCs. In chondrogenic media, fibrin alginate culture and pellet culture (500,000 cell pellets) were superior for chondrogenic induction to agarose, alginate alone and 250,000 cells pellets. For in vitro MSC chondrogenesis, supplementation with an isoform of transforming growth factor beta (TGF-[beta]) is required. TGF-[beta]1, -[beta]2 and -[beta]3 have been used and although TGF-[beta]1 is the most frequently reported both in vitro and in vivo, it is not clear which is superior for chondrogenic

induction and prevention of hypertrophy. The chondrogenic effect of the 3 isoforms was tested in MSC pellet culture. All 3 isoforms resulted in MSC chondrogenesis, however, TGF-[beta]3 had clear enhancement of prevention of hypertrophy. Growth factor supplementation in vivo is difficult to maintain because of the short halflife of injected or implanted growth factors. Gene therapy techniques to induce growth factor expression by injected or implanted MSCs would allow for continuous growth factor supplementation to the joint. Adenoviral vectors for expression of TGF-[beta]1, -[beta]2 and -[beta]3 were constructed and tested in MSC pellet culture to confirm transgene expression and efficacy for chondrogenic induction in long term 3-dimensional culture. Adenoviral transgene expression of TGF-[beta]3 resulted in chondrogenic induction and reduced progression toward hypertrophy compared to Ad TGF-[beta]1 and -[beta]2. Given the synovial distribution of MSCs injected to the arthritic joint, injection of growth factor enhanced and anti-catabolic MSCs to the middle carpal joint of horses in the osteochondral fragmentation model of OA was tested. This resulted in improved control of joint disease evidenced by improved effusion scores and range of motion in the week following treatment injection, reduced cartilage MMP13 and synovial IL1b expression, reduced synovial fibrosis and a strong trend of increased cartilage glycosaminoglycan content. This invaluable resource discusses clinical applications with effects and side-effects of applications of stem cells in bone and cartilage regeneration. Each chapter is contributed by a pre-eminent scientist in the field and covers such topics as skeletal regeneration by mesenchymal stem cells, clinical improvement of mesenchymal stem cell injection in injured cartilage and osteoarthritis, Good manufacturing practice (GMP), minimal critera of stem cells for clinical applications, future directions of the discussed therapies and much more. Bone & Cartilage Regeneration and the other books in the Stem Cells in Clinical Applications series will be invaluable to scientists, researchers, advanced students and clinicians working in stem cells, regenerative medicine or tissue engineering. Reviewing exhaustively the current state of the art of tissue engineering strategies for regenerating bones and joints through the use of biomaterials, growth factors and stem cells, along with an investigation of the interactions between biomaterials, bone cells, growth factors and added stem cells and how together skeletal tissues can be optimised, this book serves to highlight the importance of biomaterials composition, surface topography, architectural and mechanical properties in providing support for tissue regeneration. Maximizing reader insights into the importance of the interplay of these attributes with bone cells (osteoblasts, osteocytes and osteoclasts) and cartilage cells (chondrocytes), this book also provides a detailed reference as to how key signalling pathways are activated. The contribution of growth factors to drive tissue regeneration and stem cell recruitment is discussed along with a review the potential and challenges of adult or embryonic mesenchymal stem cells to further enhance the formation of new bone and cartilage tissues. This book serves to demonstrate the interconnectedness of biomaterials, bone/cartilage cells, growth factors and stem cells in determining the regenerative process and thus the clinical outcome. This book focuses on cartilage defects and new mesenchymal stem cell-based treatments for their repair and regeneration. Early chapters provide a review of current etiological findings and repair methods of cartilage defects. The next chapters discuss fundamental concepts and features of MSCs, including their proliferation, differentiation, migration and immunomodulatory effects. The discussion also includes clinical applications of MSCs in cartilage tissues, especially with regards to various animal models, biomaterials and transferring techniques. Cartilage Regeneration focuses on the biology of MSCs and their possible applications in cartilage reconstruction, with the goal of bringing new insights into regenerative medicine. It will be essential reading for researchers and clinicians in stem cells, regenerative medicine, biomedical engineering and orthopedic surgery. Tissue engineering is a possible method for long-term repair of cartilage lesions, but current tissue-engineered cartilage constructs have inferior mechanical properties compared to native cartilage. This problem may be due to the lack of an oriented structure in the constructs at the microscale that is present in the native tissue. In this study, we utilize contact guidance to develop constructs with microscale architecture for improved chondrogenesis and function. Stable channels of varying microscale dimensions were formed in

collagen-based and polydimethylsiloxane membranes via a combination of microfabrication and soft-lithography. Human mesenchymal stem cells (hMSCs) were selectively seeded in these channels. The chondrogenic potential of hMSCs seeded in these channels was investigated. We demonstrate selective seeding of viable hMSCs within the channels. hMSC aligned and produced mature collagen fibrils along the length of the channel in smaller linear channels of widths 25-100 æm compared to larger linear channels of widths 500-1000 æm. Further, substrates with microchannels that led to cell alignment also led to superior mechanical properties compared to constructs with randomly seeded cells or selectively seeded cells in larger channels. The ultimate stress and modulus of elasticity of constructs with cells seeded in smaller channels increased by as much as four folds. Furthermore, we extended the 2-dimensional finding and successfully created 3-dimensional large scale constructs (3.5 mm in diameter {u00D7} 18 mm in length) with microscale architecture for in vivo applications. Histology and immunohistochemistry indicated extensive GAG and collagen type II production in 3-dimensional construct, which are both indicative of chondrogenesis. Our results show that the microscale guidance channels incorporated within the 3-dimensional cartilage constructs lead to the production of aligned cell-produced collagenous matrix and enhanced mechanical function. The tissue modulus of elasticity of 3-dimensional cartilage constructs containing guidance increased by as much as six times compared to constructs without channels. Overall, these findings offer new insight into how microscale guidance channel regulates matrix deposition and long term construct development. This book presents the evidence related to the use of injectable biologics to provide faster and better healing for musculoskeletal lesions and conditions. The authors discuss approaches, such as blood derivatives and cell concentrates, applied to lesions of muscles, ligaments, tendons, bones, meniscus and cartilage, as well as osteoarthritis. Chapters are written by some of the most influential opinion leaders in the field, with up-to-date review of the current literature, where the authors explore both the potential and the limitations of these minimally invasive and promising treatments. The first section is devoted to the formulations and rationale for the use of injectable orthobiologics, while the second section reviews current treatment methods applied to specific joints and pathologies – ranging from tendinopathies through non-unions to articular degenerative processes – as well as the results of these treatment approaches. The third section explores future perspectives, such as pluripotent stem cells, gene therapy, and the stimulation of intrinsic stromal cell niches. Appealing to a broad readership, this book will be of interest to both laboratory research scientists and clinicians, including orthopedists, sports physicians, physiatrists, and regenerative medicine experts. Current cartilage repair methods are ineffective in restoring the mechanical and biological functions of native hyaline cartilage. Therefore, using the paracrine actions of stem cell therapies to stimulate endogenous cartilage regeneration has gained momentum. Adipose stem cells (ASCs) are an attractive option for this endeavor because of their accessibility, chondrogenic potential, and secretion of factors that promote connective tissue repair. In order to use the factors secreted by ASCs to stimulate cartilage regeneration, the signaling pathways that affect postnatal cartilage development and morphology need to be understood. Next, approaches need to be developed to tailor the secretory profile of ASCs to promote cartilage regeneration. Finally, delivery methods that localize ASCs within a defect site while facilitating paracrine factor secretion need to be optimized. The overall objective of this thesis was to develop an ASC therapy that could be effectively delivered in cartilage defects and stimulate regeneration via its paracrine actions. The general hypothesis was that the secretory profile of ASCs can be tailored to enhance cartilage regeneration and be effectively delivered to regenerate cartilage in vivo. The overall approach used the growth plate as an initial model to study changes in postnatal cartilage morphology and the molecular mechanisms that regulate it, different media treatments and microencapsulation to tailor growth factor production, and alginate microbeads to deliver ASCs in vivo to repair cartilage focal defects. Mesenchymal stem cell-derived exosomes are at the forefront of research in two of the most high profile and funded scientific areas – cardiovascular research and stem cells. Mesenchymal Stem Cell Derived Exosomes provides insight into the biofunction and molecular mechanisms, practical tools for research, and a look toward the

clinical applications of this exciting phenomenon which is emerging as an effective diagnostic. Primarily focused on the cardiovascular applications where there have been the greatest advancements toward the clinic, this is the first compendium for clinical and biomedical researchers who are interested in integrating MSC-derived exosomes as a diagnostic and therapeutic tool. Introduces the MSC-exosome mediated cell-cell communication Covers the major functional benefits in current MSC-derived exosome studies Discusses strategies for the use of MSC-derived exosomes in cardiovascular therapies Tissue engineering integrates knowledge and tools from biological sciences and engineering for tissue regeneration. A challenge for tissue engineering is to identify appropriate cell sources. The recent advancement of stem cell biology provides enormous opportunities to engineer stem cells for tissue engineering. The impact of stem cell technology on tissue engineering will be revolutionary. This book covers state-of-the-art knowledge on the potential of stem cells for the regeneration of a wide range of tissues and organs and the technologies for studying and engineering stem cells. It serves as a valuable reference book for researchers and students. In three Volumes this mini book series presents current knowledge and new perspectives on cartilage as a specialized yet versatile tissue. This third volume provides insight into current and future treatment strategies for repair of cartilage lesions. This book addresses Professors, researchers and PhD students who are interested in musculoskeletal and cartilage pathobiology and tissue-engineering. This book discusses the two different cellular approaches that are pursued in regenerative medicine: cell therapy and tissue engineering. It examines in detail the therapeutic application of hematopoietic stem cells in marrow regeneration, multi-potent mesenchymal stem cells (MSCs), also referred to as mesenchymal stromal cells. The interest in MSCs can be seen in more than 150 clinical trials, some of which have progressed to Phase III, despite the cells' limited differentiation potential. The book also explores how embryonic stem (ES) cells, being pluripotent in nature, can resolve some of the problems associated with adult stem cells, yet entail other challenges like risks of teratoma formation and immune rejection. A separate chapter deals with the role of noncoding RNAs in neuronal commitment of induced pluripotent stem (iPS) cells. Chapters like "Cord blood banking in India and the global scenario"; "3D bioprinting of tissue" and others will make this book an extremely interesting read for all students, researchers and clinicians working in the area of regenerative medicine/stem cells. The book is broadly divided into two parts, the first of which is devoted to basic information on stem cells, and the second of which addresses potential clinical applications in the areas of hematology, cardiology, orthopedic and immune suppression, etc. This book covers our current understanding of the role of mesenchymal stem cells (MSCs) and other mesenchymal progenitors in skeletal regeneration, encompassing bone, cartilage and whole joint regeneration. The expansion reflects developments in the field to include data on the use of MSCs in drug development, growth factors, scaffolds and biomechanical manipulations for skeletal trauma and diseases, including osteoporosis and arthritis. Written for an audience of clinicians and young researchers who are exposed to MSCs in their work, this work summarizes recent findings pertaining to the definition and characterization of MSCs in skeletal tissues and discusses the mechanisms of their actions in regeneration of bone in vivo. The authors describe recent findings pertaining to the efficacy of MSC therapies in animal models and in human clinical trials and bring together literature showing that the ways MSCs are extracted, expanded and implanted can considerably affect bone formation outcomes. Finally, it presents the latest knowledge on the nature of native MSCs in skeletal tissues, which provide a platform for novel in situ tissue regeneration approaches for systemic bone disease such as osteoporosis. Focuses specifically on the use of stem cells in skeletal tissue generation for a broad audience of stem cell, cancer, and bone biologists, orthopedists, oncologists, and regenerative medicine specialists Provides a short historical 'detour' and foundational information on founding concepts, discoveries and personalities in MSC research Assists a new generation of scientists and clinicians in digesting the multitude of journal articles on the topic by providing easily-absorbed and condensed foundational context This book marries stem cell biology, tissue engineering, and regenerative biology into a single, interdisciplinary volume. The chapters also explore embryonic stem cells, induced pluripotent stem cells, cardiovascular

regeneration, skeletal development, inflammation, polymeric biomaterials, neural injury, cartilage regeneration, regeneration in ambystoma, models for regeneration using salamander and zebrafish, and more. The volume also discusses recent advances and their potential in developing future therapies. Innovations in Molecular Mechanisms and Tissue Engineering combines perspectives from the biomedical, bioengineering, and medical fields to present a cutting-edge, multifaceted picture of the tissue engineering and regenerative medicine fields. This installment of Springer's Stem Cell Biology and Regenerative Medicine series is ideal for scientists, clinicians, and researchers in the fields of stem cell biology, regenerative medicine, biomedical engineering, and tissue engineering. Articular Cartilage Regeneration with Stem Cells. Developmental Biology and Musculoskeletal Tissue Engineering: Principles and Applications focuses on the regeneration of orthopedic tissue, drawing upon expertise from developmental biologists specializing in orthopedic tissues and tissue engineers who have used and applied developmental biology approaches. Musculoskeletal tissues have an inherently poor repair capacity, and thus biologically-based treatments that can recapitulate the native tissue properties are desirable. Cell- and tissue-based therapies are gaining ground, but basic principles still need to be addressed to ensure successful development of clinical treatments. Written as a source of information for practitioners and those with a nascent interest, it provides background information and state-of-the-art solutions and technologies. Recent developments in orthopedic tissue engineering have sought to recapitulate developmental processes for tissue repair and regeneration, and such developmental-biology based approaches are also likely to be extremely amenable for use with more primitive stem cells. Brings the fields of tissue engineering and developmental biology together to explore the potential for regenerative medicine-based research to contribute to enhanced clinical outcomes Initial chapters provide an outline of the development of the musculoskeletal system in general, and later chapters focus on specific tissues Addresses the effect of mechanical forces on the musculoskeletal system during development and the relevance of these processes to tissue engineering Discusses the role of genes in the development of musculoskeletal tissues and their potential use in tissue engineering Describes how developmental biology is being used to influence and guide tissue engineering approaches for cartilage, bone, disc, and tendon repair Mesenchymal Stem Cells: Isolation, Characterization, and Applications thoroughly presents the isolation, characterization, and some applications of mesenchymal stem cells in the clinic. The book has two parts: "Isolation and Characterization" and "Clinical Perspectives and Applications." In Part I, the subsequent chapters introduce some techniques in isolation, characterization, and purification of mesenchymal stem cells in different tissues. In Part II, some applications of mesenchymal stem cells in the popular diseases, which include cartilage regeneration, spinal cord injury, and osteoarthritis, are discussed. This book provides a succinct yet comprehensive overview of mesenchymal stem cells for advanced students, graduate students, and researchers. Tissue engineering integrates knowledge and tools from biological sciences and engineering for tissue regeneration. A challenge for tissue engineering is to identify appropriate cell sources. The recent advancement of stem cell biology provides enormous opportunities to engineer stem cells for tissue engineering. The impact of stem cell technology on tissue engineering will be revolutionary. This book covers state-of-the-art knowledge on the potential of stem cells for the regeneration of a wide range of tissues and organs, including cardiovascular, musculoskeletal, neurological and skin tissues. The technology platforms for studying and engineering stem cells, such as hydrogel and biomaterials development, microfluidics system and microscale patterning, are also illustrated. Regulatory challenges and quality control for clinical translation are also detailed. This book provides an comprehensive update on the advancement in the field of stem cells and regenerative medicine, and serves as a valuable resource for both researchers and students. Contents: Tissue Engineering: From Basic Biology to Cell-Based Applications (R M Nerem)Recent Advances and Future Perspectives on Somatic Cell Reprogramming (K-Y Kim & I-H Park)Hematopoietic Stem Cells (J J Trowbridge)Mesenchymal Stem Cells for Tissue Regeneration (N F Huang & S Li)Delivery Vehicles for Deploying Mesenchymal Stem Cells in Tissue Repair (M S Friedman & J K Leach)Stem Cells for Cardiac Tissue Engineering (J L

Young et al.)Cardiovascular System: Stem Cells in Tissue-Engineered Blood Vessels (R Sawh-Martinez et al.)Stem Cells for Vascular Regeneration: An Engineering Approach (L E Dickinson & S Gerecht)Stem Cells and Wound Repair (S H Ko et al.)Engineering Cartilage: From Materials to Small Molecules (J M Coburn & J H Elisseeff)Adult Stem Cells for Articular Cartilage Tissue Engineering (S Saha et al.)Stem Cells for Disc Repair (A A Allon et al.)Skeletal Tissue Engineering: Progress and Prospects (N J Panetta et al.)Clinical Applications of a Stem Cell Based Therapy for Oral Bone Reconstruction (B McAllister & K Haghighat)Therapeutic Strategies for Repairing the Injured Spinal Cord Using Stem Cells (M S Beattie & J C Bresnahan)Potential of Tissue Engineering and Neural Stem Cells in the Understanding and Treatment of Neurodegenerative Diseases (C Auclair-Daigle & F Berthod)High-Throughput Systems for Stem Cell Engineering (D A Brafman et al.)Microscale Technologies for Tissue Engineering and Stem Cell Differentiation (J W Nichol et al.)Quality Control of Autologous Cell- and Tissue-Based Therapies (N Dusserre et al.)Regulatory Challenges for Cell-Based Therapeutics (T McAllister et al.) Readership: Life science scientists; biomedical researchers; cell biologists; academics, postgraduate students and advanced undergraduate students in cell biology, biochemistry and genetics; surgeons; clinicians; biotechnology and pharmaceutical industry professionals. Keywords: Stem Cells;Tissue Engineering;Regenerative Medicine;Biotechnology;Cell EngineeringReview:0 Osteoarthritis (OA) is a highly prevalent, debilitating disease affecting many joints including the knee. Despite the involvement of several tissues, it is believed that the articular cartilage is the primary site of pathogenesis in humans. Within this study, a new scoring system of OA was devised, incorporating the articular cartilage and underlying bone, aimed at providing a more comprehensive means of grading the severity of tissue damage. We examined changes progressively from mild to severe and were able to deduce from the scoring system that bone changes may precede those of the overlying cartilage. Immunohistochemistry was used to assess stem cell marker expression, proliferation and progressive changes within the extracellular matrix of sectioned osteochondral plugs, however no distinct pattern of change could be extrapolated, highlighting the variable nature of this taxing disease. Previous studies have demonstrated the presence of a sub-population of chondroprogenitor cells present in normal hyaline cartilage. We demonstrated in this study that a similar group of cells reside in osteoarthritic articular cartilage. We were able to isolate and expand clonally derived primary cell lines to beyond 50 population doublings whilst maintaining a chondrogenic phenotype, and demonstrated the tri-lineage potential of these cells. That said, a significant amount of variation was observed and it was, therefore, postulated that there may be a smaller cohort of viable cells within this sub-population isolated from osteoarthritic cartilage. A preliminary study was also carried out comparing chondroprogenitors from normal articular cartilage to those isolated from OA tissue. Heterogeneity was again encountered, suggesting that there was a group of OA chondroprogenitors with similar characteristics to the normal cells, which differed from the other less metabolically active cells. This finding was agreeable with the aforementioned postulation. Data from our preliminary integration study was promising as we demonstrated the potential for using these chondroprogenitor cells in combination with other cells whilst achieving successful integration. However, further work is necessary to distinguish between the cell lines with the potential for integration from those that lacked this ability, thereby eliminating the heterogeneity. The presence of viable chondroprogenitor cells in OA tissue challenges the dogma that the tissue is irrecoverable, and opens the scope for regenerative medicine using resident progenitor cells. This is an exciting prospect that could significantly contribute to articular cartilage repair. "The potential use of stem cells in transplantation for the purpose of tissue regeneration is an exciting area of research currently undergoing rapid development. Implantation of human embryonic or autologous, ex vivo-expanded adult stem cells, particularl" Regenerative medicine (RM) is a rapidly expanding topic within orthopedic and spine surgery, sports medicine and rehabilitation medicine. In the last ten years, regenerative medicine has emerged from the fringes as a complement and challenge to evidence-based medicine. Both clinicians and patients alike are eager to be able to offer and receive treatments that don't just surgically replace or clean old joints or inject away inflammation or work

as a stop-gap measure. Regenerative medicine encompasses everything from the use of stem cells and platelet-rich plasma (PRP) to prolotherapy, viscosupplementation and beyond. This book will provide healthcare practitioners dealing with spine and joint pain with the most current, up-to-date evidence-based information about which treatments work, which treatments don't, and which are on the horizon as potential game changers. Chapters are arranged in a consistent format and cover the spine, shoulder, elbow, hand and wrist, hip, knee, and foot and ankle, providing a thorough, top-to-bottom approach. A concluding chapter discusses current and future directions and applications of RM over the next decade or two. Timely and forward-thinking, Regenerative Medicine for Spine and Joint Pain will be a concise and practical resource for orthopedists, spine surgeons, sports medicine specialists, physical therapists and rehabilitation specialists, and primary care providers looking to expand their practice. This book presents the latest advances in the field of regenerative medicine in plastic surgery. It is the first authoritative reference documenting all the ways that plastic surgical practice and regenerative medicine science overlap or provide a road map for the future of both specialties. The Editors have provided a valuable service by gathering in one place the leading voices in these two fields in clear and concise manner.The first part introduces readers to essential principles of skin and soft tissue regeneration, e.g. the possibility of using mesenchymal stem cells for wound healing. Since bone serves as a supportive tissue in most of the body, bone regeneration is an important aspect of regenerative medicine; accordingly, the second part discusses the novel bone implants, activated bone grafts and bone tissue engineering. The book’s third part, focusing on cartilage regeneration, includes chapters on e.g. stem cells and ear regeneration. In turn, part four addresses muscle and tendon regeneration: from tendon to bone and tendon to muscle, as well as aging in the realm of muscle regeneration. Lastly, part five highlights nerve regeneration, deepening surgeons’ knowledge to help them successfully treat injuries to the peripheral neural system. Written by leading experts this book is an invaluable resource for researchers, students, beginners and experienced clinicians in a range of specialties. "With beautiful clinical images and artwork, this book will be a central companion to both practicing plastic surgeons who wish to remain abreast of oncoming technologic advances and regenerative medicine researchers who wish to understand the current state of the art of surgical reconstruction." - Geoffrey C. Gurtner, MD, FACS Johnson and Johnson Distinguished Professor of Surgery Professor (by courtesy) of Bioengineering and Materials Science Inaugural Vice Chairman of Surgery for Innovation Stanford University School of Medicine There is a critical need for cartilage regeneration therapies. Not only is cartilage necessary for proper joint function, as deterioration of cartilage leads to osteoarthritis, but it also serves important roles in other places in the body, like in the trachea. Specifically in the articular and tracheal niches, replacement cartilage should have adequate mechanical properties and specific geometries to restore native function. To address these needs, novel strategies to engineer high-density human mesenchymal stem cell (hMSC)-derived cartilage tissues are presented in this dissertation. Bioactive microspheres loaded with chondrogenic transforming growth factor beta 1 (TGF-ß1) were incorporated within some of these tissues for enhanced chondrogenesis. First, scaffold-free cartilage rings and tubes with controlled dimensions were successfully fabricated using custom-made culture wells and a ring-to-tube assembly approach, respectively. The use of TGF-ß1 microspheres in the hMSC rings and tubes significantly improved the quality and quantity of generated cartilage tissue. Next, localized TGF-ß1 presentation within cartilaginous tissues facilitated organized fusion and culture of cartilage tissue building blocks with engineered epithelial and prevascular tissues. Successful development and/or maintenance of tissue-specific phenotypes in this co-culture approach with localized presentation of cues guiding cell differentiation is a promising step toward engineering a functional replacement trachea. Next, extracellular matrix (ECM) scaffolds fabricated from high-density hMSC condensates with and without TGF-ß1 microspheres were shown to support chondrogenesis of re-seeded hMSCs. Importantly, addition of microspheres to hMSC condensates significantly enhanced ECM production and consequently yielded 50% more scaffolds. Additionally, ECM scaffolds were demonstrated to drive chondrogenesis when TGF-ß1 was loaded into them, which suggests improved potential for clinical translatability of this off-the-shelf cartilage

regeneration product. Lastly, three different types of bioreactors were designed and engineered or modified for the application of hydrostatic pressure, magnetic bead-induced micromechanical stress and compressive stress to scaffold-free hMSC condensates with the goal to improve the functionality of the engineered cartilage. Stimulation with hydrostatic pressure showed promising evidence of enhanced chondrogenesis in hMSC-derived cartilage, while micromechanical stresses did not improve cartilage tissue formation. Additional studies may further elucidate the impact of each type of stimulus on chondrogenesis. Taken all together, this dissertation developed many strategies and technologies that help advance the field of cartilage tissue engineering. Most human tissues do not regenerate spontaneously. Cell therapy and tissue engineering, which involve collecting cells from either the patient or a donor and introducing them into injured tissues or organs, sometimes after modifying their properties, offer promising solutions for regenerative medicine. Indeed, so promising are these therapies that current research has shifted from organ growth to cell therapy. The range of therapeutic applications is wide, including cardiac insufficiency, atherosclerosis, cartilage defects, bone repair, burns, diabetes and liver or bladder regeneration.This book, whilst not covering all aspects Cartilage loss is a leading cause of disability among adults and represents a huge socioeconomic burden. Articular cartilage has limited self-repair potential and damage is often irreversible. Tissue engineering holds great promise for cartilage repair using a combination of cells, biomaterials and/or biological factors. However, one of the key barriers is the lack of abundant cell sources that can effectively regenerate articular cartilage. Conventional tissue engineering strategies for cartilage repair often utilize adult chondrocytes, which is limited by donor site morbidity, the need for multiple surgeries, and tendency to de-differentiate during in vitro expansion. Unlike adult chondrocytes, neonatal chondrocytes (NChons) are highly proliferative, immune-privileged, and can readily produce abundant extracellular matrix with retained articular cartilage phenotype. However, donor availability for NChons is scarce, which greatly hinders their broad application. The goal of this thesis is to examine the potential of ADSCs to catalyze cartilage tissue formation by NChons in 3D hydrogels. Specifically, we explored the feasibility of substituting the majority of NChons with ADSCs, an abundant autologous cell source that can be obtained in a minimally invasive manner. Using three different co-culture models, we demonstrated that the effects of co-culture on cartilage tissue formation were highly dependent on intercellular distance and cell distribution in 3D. Unexpectedly, increasing ADSC ratio in mixed co-culture led to increased synergy between NChons and ADSCs, and robust cartilage formation could be achieved using as few as 2% NChons in the mixed cell population. Cell tracking indicated that the newly formed cartilage was contributed by NChons alone, whereas ADSCs catalyzed such cartilage formation via paracrine signaling. We then demonstrated that catalyzed cartilage formation was retained under hypoxia, supporting the feasibility of translating such therapy for repairing cartilage tissue in situ. Furthermore, we examined the effects of transient priming of ADSCs with transforming growth factor (TGF)-beta on their ability to catalyze cartilage formation by NChons. Our results showed that ADSCs with short-term TGF-beta priming led to optimal catalyzed cartilage formation. Finally, we validated the efficacy of utilizing a mixed population of ADSCs with a small number of NChons for cartilage regeneration in vivo with robust hyaline cartilage formation over 12 weeks. In summary, the findings of this thesis raise the potential of utilizing stem cells to catalyze tissue formation by NChons, which may accelerate the broad translation of NChons for cartilage repair by alleviating donor scarcity limitation. Furthermore, the concept of harnessing paracrine signaling between two or more cell types in 3D scaffolds to catalyze tissue formation may be broadly applicable to regenerating other tissue types. This reference presents insights into the development of bone marrow aspirate stem cell (BMAC) technology and the potential role of stem cell expansion in the regeneration of damaged and deficient musculoskeletal tissues. The book features valuable contributions from stem cell therapy experts from around the world. The authors explain the production, proliferation, differentiation into various tissues, and medical applications of stem cells. In addition to work on the use of stem cells in the treatment of non-unions and bone defects, the book explores the potential for articular cartilage regeneration, repair of tendon injuries, the

treatment of degenerative joint disease, revascularization of bone and regeneration of damaged nerves as well as spinal cord injury. The authors also explain ethical challenges faced by researchers and public authorities working on stem cells and the varying constraints on the development of this technology around the world. Scientists and surgeons, alike, who are involved in the fields of orthopaedics, rheumatology, stem cell and regenerative medicine will benefit from the illuminating snapshot of the applications of BMAC stem cell expansion presented in the volume. What Is Stem Cell Therapy The use of a patient's own stem cells, either to cure or prevent a disease or condition, is the practice known as stem-cell therapy. As of the year 2016, hematopoietic stem cell transplantation is the only treatment that has been shown to be effective employing stem cells. The transplantation of bone marrow is the most common method used for this procedure; however, the cells may also be extracted from umbilical cord blood. Research is now being conducted to establish diverse sources for stem cells and to use stem-cell therapies for neurodegenerative disorders and ailments such as diabetes and heart disease. Additionally, research is being conducted to generate new stem cell sources. How You Will Benefit (I) Insights, and validations about the following topics: Chapter 1: Stem-cell therapy Chapter 2: Stem cell Chapter 3: Bone marrow Chapter 4: Hematopoietic stem cell transplantation Chapter 5: Embryonic stem cell Chapter 6: Regenerative medicine Chapter 7: Cell therapy Chapter 8: Cord blood Chapter 9: Adult stem cell Chapter 10: Stem-cell line Chapter 11: Knee cartilage replacement therapy Chapter 12: Cardiomyoplasty Chapter 13: Stem cell transplantation for articular cartilage repair Chapter 14: Mesenchymal stem cell Chapter 15: Clinical uses of mesenchymal stem cells Chapter 16: Muse cell Chapter 17: Guo Mei Chapter 18: Spinal cord injury research Chapter 19: Stem cell secretome Chapter 20: Shimon Slavin Chapter 21: Stem cell fat grafting (II) Answering the public top questions about stem cell therapy. (III) Real world examples for the usage of stem cell therapy in many fields. (IV) 17 appendices to explain, briefly, 266 emerging technologies in each industry to have 360-degree full understanding of stem cell therapy' technologies. Who This Book Is For Professionals, undergraduate and graduate students, enthusiasts, hobbyists, and those who want to go beyond basic knowledge or information for any kind of stem cell therapy. Is the Articular Cartilage Regeneration Approachable Through Mesenchymal Stem Cells Therapies. Osteoarthritis (OA), the most common form of arthritis, is generally characterized by a slowly progressive degeneration of articular cartilage, particularly in the weight-bearing joints. It has a stronger prevalence in women, and its incidence increases with age. OA is a major and growing health concern in developed countries, owing to steadily increasing life expectancy and the demand for better quality of life. Because of its chronic nature and nonfatal outcome, OA affects the growing population of the elderly over an increasing time span. Moreover, despite its relatively benign character, OA is one of the most disabling diseases; it is responsible for increasing financial and social burdens in terms of medical treatments, forced inactivity, loss of mobility, and dependence. Despite a growing awareness of OA as a medical problem that has yet to reach its maximum impact on society, there is a surprising absence of effective medical treatments beyond pain control and surgery. So far, only symptom-modifying drugs are available, while there remains a major demand for disease-modifying treatments of proven clinical efficacy. This demand will hopefully be met in the future by some of the drugs that have been pressed into development and are now at different stages of clinical investigation. Nevertheless, the current lack of effective treatments reflects a still insufficient knowledge of cartilage with respect to its metabolism, interactions with other joint tissues, and causes and mechanisms (possibly of very different nature) leading to failure of its turnover. Cells are social, and dynamic interactions among cells play an important role in tissue development. While stem cells are widely known for their potential to differentiate directly into a variety of cell types, stem cells can also support tissue regeneration by secreting trophic factors to stimulate other cells. Using a 3D hydrogel co-culture model, our lab has previously reported that adipose-derived stem cells (ADSCs) can substantially enhance cartilage tissue regeneration by juvenile chondrocytes, making them become "super chondrocytes", through cell-cell communications. This finding is significant, as it aids in overcoming donor scarcity associated with chondrocytes by mixing them with ADSCs, an abundantly available autologous cell

source. However, the molecular mechanisms through which chondrocytes become "super chondrocytes" remain unknown. Furthermore, while using a mixed cell population overcomes the cell source problem, the resulting cartilage remains mechanically weak, with a compressive modulus an order of magnitude lower than that of native cartilage. My thesis seeks to overcome the above two key challenges by: (1) Identifying the key molecular signal changes that drive the "super chondrocyte" phenotype during co-culture, and (2) Improving the mechanical properties of engineered cartilage during co-culture by developing novel 3D scaffolds. Using RNA microarray technology, I compared the gene expression changes during co-culture vs. mono-culture and identified top candidate genes (up-regulation and down-regulation) associated with the "super chondrocyte" phenotype. These targets offer potential new ways to produce "super chondrocytes" via genetic modification, thereby removing the need for co-culture. To further enhance the mechanical properties of tissue engineered cartilage, I developed a new composite scaffold made of macroporous gelatin-based microribbon (μRB)s as well as a rapidly degradable hydrogel. The scaffold was optimized to support initial retention of paracrine signals required for synergistic ADSC-chondrocyte co-culture, but also provide macroporosity to facilitate new tissue formation. When implanted in vivo using a mouse model, the composite scaffold led to a rapid increase in mechanical properties of cartilage produced by mixed ADSCs and chondrocytes, yet minimal increase was observed using conventional hydrogels. Together, the findings from this thesis fill the gap of knowledge of how stem cells catalyze cartilage formation by chondrocytes during co-culture, and will accelerate the translation of using mixed cell populations for cartilage regeneration with enhanced mechanical functions. Stem cell and regenerative medicine research is a hot area of research which promises to change the face of medicine as it will be practiced in the years to come. Challenges in the 21st century to combat diseases such as cancer, Alzheimer and related diseases may well be addressed employing stem cell therapies and tissue regeneration. Frontiers in Stem Cell and Regenerative Medicine Research is essential reading for researchers seeking updates in stem cell therapeutics and regenerative medicine. The seventh volume of this series features reviews on roles of mesenchymal stem cells and biomaterials in cartilage regeneration in vivo, liver regeneration, cardiogenesis and magnetic nanoparticles for regenerative therapy. Over the past decade, significant efforts have been made to develop stem cell-based therapies for difficult to treat diseases. Multipotent mesenchymal stromal cells, also referred to as mesenchymal stem cells (MSCs), appear to hold great promise in regards to a regenerative cell-based therapy for the treatment of these diseases. Currently, more than 200 clinical trials are underway worldwide exploring the use of MSCs for the treatment of a wide range of disorders including bone, cartilage and tendon damage, myocardial infarction, graft-versus-host disease, Crohn’s disease, diabetes, multiple sclerosis, critical limb ischemia and many others. MSCs were first identified by Friendenstein and colleagues as an adherent stromal cell population within the bone marrow with the ability to form clonogenic colonies in vitro. In regards to the basic biology associated with MSCs, there has been tremendous progress towards understanding this cell population’s phenotype and function from a range of tissue sources. Despite enormous progress and an overall increased understanding of MSCs at the molecular and cellular level, several critical questions remain to be answered in regards to the use of these cells in therapeutic applications. Clinically, both autologous and allogenic approaches for the transplantation of MSCs are being explored. Several of the processing steps needed for the clinical application of MSCs, including isolation from various tissues, scalable in vitro expansion, cell banking, dose preparation, quality control parameters, delivery methods and numerous others are being extensively studied. Despite a significant number of ongoing clinical trials, none of the current therapeutic approaches have, at this point, become a standard of care treatment. Although exceptionally promising, the clinical translation of MSC-based therapies is still a work in progress. The extensive number of ongoing clinical trials is expected to provide a clearer path forward for the realization and implementation of MSCs in regenerative medicine. Towards this end, reviews of current clinical trial results and discussions of relevant topics association with the clinical application of MSCs are compiled in this book from some of the

leading researchers in this exciting and rapidly advancing field. Although not absolutely all-inclusive, we hope the chapters within this book can promote and enable a better understanding of the translation of MSCs from bench-to-bedside and inspire researchers to further explore this promising and quickly evolving field. Cartilage defects are common. Cartilage repair surgery is not only fascinating but also surgically challenging. There are books dealing with basic science and some surgical aspect. This book fills a gap in surgical techniques for cartilage repair. All of the surgical chapters are logically organised, covering patient selection, patient setup/positioning, surgical approach, potential complications and troubleshooting. An attempt is made to compare with various surgical techniques. This book also covers anaesthesia, postoperative follow-up, pain management and rehabilitation. Both the editors and the authors are renowned experts in the field. This book will be invaluable for orthopaedic and sports medicine surgeons (consultants and training doctors) and is also of potential interest to physiotherapists, medical students, general practitioners, physical medicine and rehabilitation specialists and rheumatology specialists. The growth plate is a cartilaginous structure located at the proximal and distal ends of immature long bones, which contributes to longitudinal growth through the process of endochondral ossification. Cartilage has a limited ability to regenerate and in children, injury to the the growth plate can result in limb length discrepancies and angular deformity, due to formation of a bone bridge at the damaged site which disturbs structure and function of the growth plate. Current treatments of the abnormalities arising from growth plate arrest involve surgical correction once the deformities have manifested. To date, there is no biological based therapy for the repair of injured/damaged growth plate cartilage. Mesenchymal stem cells (MSC) are self renewable mulitpotential progenitor cells with the capacity to differentiate toward the chondrogenic lineage. Since their discovery, significant interest has been generated in the potential application of these cells for cartilage regeneration. In this study, the ability of autologous bone marrow mesenchymal stem cells to regenerate growth plate cartilage in a sheep model was examined. Cartilage injuries in children and adolescents are increasingly observed, with roughly 20% of knee injuries in adolescents requiring surgery. In the US alone, costs of osteoarthritis (OA) are in excess of $65 billion per year (both medical costs and lost wages). Comorbidities are common with OA and are also costly to manage. Articular cartilage's low friction and high capacity to bear load makes it critical in the movement of one bone against another, and its lack of a sustained natural healing response has necessitated a plethora of therapies. Tissue engineering is an emerging technology at the threshold of translation to clinical use. Replacement cartilage can be constructed in the laboratory to recapitulate the functional requirements of native tissues. This book outlines the biomechanical and biochemical characteristics of articular cartilage in both normal and pathological states, through development and aging. It also provides a historical perspective of past and current cartilage treatments and previous tissue engineering efforts. Methods and standards for evaluating the function of engineered tissues are discussed, and current cartilage products are presented with an analysis on the United States Food and Drug Administration regulatory pathways that products must follow to market. This book was written to serve as a reference for researchers seeking to learn about articular cartilage, for undergraduate and graduate level courses, and as a compendium of articular cartilage tissue engineering design criteria. Table of Contents: Hyaline Articular Cartilage / Cartilage Aging and Pathology / In Vitro / Bioreactors / Future Directions

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