UNIVERSITI PUTRA MALAYSIA

REPLACEMENT OF DEGRADED ARTICULAR CARTILAGE USING STEM CELL-BASED THERAPY IN RABBIT MODEL OF OSTEOARTHRITIS

MARWAN TAHER M. ABOFILA

FPV 2012 14

REPLACEMENT OF DEGRADED ARTICULAR CARTILAGE USING STEM CELL-BASED THERAPY IN RABBIT MODEL OF OSTEOARTHRITIS

By

MARWAN TAHER M. ABOFILA

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Veterinary Science

October 2012

In the name of Allah, Most Gracious, Most Merciful

DEDICATION

To

My parents, lecturers, family, relatives, friends and to my country at large

Abstract of thesis presented to the Senate of Universiti Putra Malaysia
in Fulfillment of the Requirement for the Degree of Master of Veterinary Science

REPLACEMENT OF DEGRADED ARTICULAR CARTILAGE USING STEM CELL-BASED THERAPY IN RABBIT MODEL OF OSTEOARTHRITIS

By

MARWAN TAHER M. ABOFILA

October 2012

Chairman: Associate Professor Shanthi Ganabadi, PhD

Faculty : Veterinary Medicine

Osteoarthritis (OA) is a degenerative disease of the joint characterized by the degradation of articular cartilage, with loss of matrix, and cyst and osteophyte formation. Osteoarthritis is the most common form of arthritis, and mostly results in physical disability. Treatments of osteoarthritis with stem cells appear to be a practical and effective, resulting in enhanced repair of damaged tissues. *In vivo* systems, the ability of autologous mesenchymal stem cells, in both humans and animals, to regenerate lost articular cartilage in OA has clearly been proven.

The general aim of this study was to evaluate the effectiveness of rabbit bone marrow-derived stem cell (allogeneic stem cells) and human umbilical cord-derived stem cell (xenogeneic stem cell) therapies in comparison with sodium hyaluronate, as potential replacements for degraded articular cartilage in monosodium iodoacetate-induced osteoarthritic rabbit models. Assessment parameters included

clinical signs, radiographic and histopathological evaluation of affected joints, gross assessment of muscle and joints, and cytokine levels (IL-1, IL-4, IL-10 and TNFα) in plasma and serum.

Thirty male New Zealand white rabbits were used in this study. OA was induced by a single intra-articular injection of 2.5 mg of monosodium iodoacetate (MIA) / 0.3 ml normal saline (NS). Five milliliters of bone marrow were aspirated from the rabbit's iliac crest and cultured in vitro. The rabbits were divided into five groups (n=6); 1. Human stem cell-treated group (HSTG), 2. Rabbit stem cell-treated group (RSTG), 3. Sodium hyaluronate-treated group (SHTG), 4. Media stem cell-treated group (MSTG), and 5. Normal saline-treated group (NSTG).

The results showed that there were significant differences ($P < 0.05$) in body weights, voluntary movement and size of joints among all groups at week 20 post OA induction (16 weeks post injection treatments). In terms of clinical outcomes, treatment with rabbit bone marrow-derived stem cells (allogeneic stem cells) and human umbilical cord-derived stem cells (xenogeneic stem cells) produced better outcomes, and treatment with sodium hyaluronate was not as effective. Treatments with the media and normal saline were the least effective in this regard. There was significant suppression of catabolic cytokines in the RSTG ($P < 0.05$) compared to other groups, which showed no significant differences ($P > 0.05$), at 12, 16 and 20 weeks. Furthermore, there were significant differences ($P < 0.05$) among all groups in the radiological scoring of affected stifle joints of rabbits at week 20. Results of radiographical scoring for the treated stifle joint were best in the RSTG and HSTG, which showed healing and a reversal to normal appearance. That of the SHTG revealed slow OA progression, while MSTG and NSTG scored the worst. There

were significant differences ($P < 0.05$) among all groups in the grading of gross lesions in the OA stifle joints of rabbits at week 20. The degree of OA grading was best for the RSTG, which revealed normal (no change) to mild changes in stifle joint structures while the HSTG showed mild to moderate changes in the joint structures. The SHTG on the other hand showed moderate changes and the MSTG and NSTG had the most severe gross lesions as demonstrated by severe to very severe pathological changes in joint structures. The differences in sizes and masses of the quadriceps femoris muscles between treated and untreated contra-lateral joints were significantly different ($P < 0.05$) among all groups at week 20. Disuse atrophy of the affected joints was obvious in the MSTG and NSTG, while only slight atrophy was noted in SHTG, and no atrophy was noted in both the RSTG and HSTG. Histopathological scoring on the stifle joints at week 20 showed significant differences ($P < 0.05$) between all the groups. The RSTG showed the best histopathological scoring, followed by the HSTG and SHTG, while the MSTG and NSTG showed the worst scores. In conclusion, single intra-articular injection of rabbit bone marrow-derived stem cells (allogeneic stem cells) or human umbilical cord-derived stem cells (xenogeneic stem cells) could promote the regeneration of damaged articular cartilage in OA as evidenced by improved radiological and pathological outcomes, with resultant improvements in general mobility, and relief of symptoms and pain.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Master Sains Verterinar

PENGGANTIAN RAWAN ARTIKULAR YANG ROSAK DENGAN MENGGUNAKAN TERAPI BERASASKAN SEL STEM DALAM MODEL OSTEOARTRITIS PADA ARNAB

Oleh

MARWAN TAHER M. ABOFILA

Oktober 2012

Pengerusi: Profesor Madya Shanthi Ganabadi, PhD

Fakulti : Perubatan Veterinar

Osteoartritis (OA) adalah penyakit degeneratif di mana tulang rawan akan kehilangan tisu matriks, bersama dengan pembentukan sista dan osteofit. Osteoartritis merupakan penyakit artritis yang paling kerap dijumpai dan ianya mengakibatkan kehilangan keupayaan fisikal. Rawatan OA dengan sel stem didapati adalah efektif kerana ianya dapat membaikpulih kerosakan tisu. Secara in vivo, keupayaan sel stem autologous (sel daripada pesakit sendiri) untuk membaikpulih tulang rawan artikular yang rosak telah terbukti bagi kedua dua haiwan dan manusia.

Kajian ini bertujuan menguji keberkesanan terapi menggunakan sel stem dari pada arnab (sel stem alogenik) dan sel stem manusia daripada tali pusat (sel stem xenogenik) berbanding dengan terapi menggunakan sodium hyaluronate bagi membaikpulih tulang rawan artikular yang rosak, dalam model OA pada arnab yang diaruh oleh monosodium iodoacetate (MIA). Parameter yang dikaji termasuk

petanda klinikal, pemerhatian secara radiografik dan histopatologikal atas sendi, pemerhatian kasar ke atas sendi dan otot, serta tahap sitokin (IL-1, IL-4, IL-10 and TNFα) dalam plasma dan serum.

Sebanyak tiga puluh arnab New Zealand White jantan telah digunakan dalam kajian ini. Osteoartritis adalah diaruh dengan satu injeksi "monosodium iodoacetate" (MIA) dengan kepekatan 2.5 mg / 0.3 ml larutan garam 0.9% sodium klorida (NaCl). Sebanyak lima milliliter sum-sum tulang disedut daripada tulang pinggung arnab dan seterusnya dikultur secara in vitro. Arnab kajian dibahagi kepada lima kumpulan dengan enam sekumpulan (n=6) iaitu; 1. Kumpulan dengan rawatan sel stem manusia (HSTG), 2. Kumpulan dengan rawatan sel stem arnab (RSTG), 3. Kumpulan dengan rawatan sodium hyaluronate (SHTG), 4. Kumpulan dengan rawatan media dari kultur sel stem (MSTG), dan 5. Kumpulan dengan rawatan larutan garam 0.9% sodium klorida (NaCl).

Keputusan kajian kami menunjukkan bahawa terdapat perbezaan yang signifikan dalam berat badan, pergerakan sukarela serta dan saiz sendi antara kumpulan pada minggu ke-20 selepas aruhan OA (iaitu 16 minggu selepas rawatan) ($P < 0.05$). Dari segi petanda klinikal, keputusan HSTG dan RSTG adalah paling baik diikuti oleh SHTG, MSTG dan akhirnya NSTG. Tahap antagonis bagi sitokin katabolic dalam RSTG naik secara signifikan berbanding dengan kumpulan lain pada minggu 12, 16 dan ke-20 ($P < 0.05$), manakala tiada perbezaan dalam tahap sitokin katabolic antara kumpulan dikesan ($P > 0.05$). Terdapat perbezaan yang signifikan antara kumpulan dalam skor radiografik atas sendi arnab yang dirawat pada minggu ke-20 ($P < 0.05$). Skor radiografik adalah paling baik bagi RSTG dan HSTG di mana pemulihan sepenuh atau hampir sepenuh dicapai, dan diikuti oleh SHTG di mana OA berlaku

dengan lebih lambat. MSTG dan NSTG pula menunjukkan skor radiografik yang paling teruk. Perbezaan yang signifikan antara kumpulan juga dikesan bagi gred OA atas sendi arnab yang dirawat pada minggu ke-20 ($P < 0.05$). Gred OA adalah paling baik bagi RSTG di mana tiada atau sedikit perubahan dikesani pada struktur sendi. HSTG menunjukkan perubahan struktur sendi yang sedikit atau sederhana. SHTG pula menunjukkan perubahan yang sederhana dan akhirnya, MSTG dan NSTG menunjukkan kerosakan tisu yang paling teruk di mana terdapatnya perubahan yang amat besar dalam struktur sendi. Perbezaan saiz dan berat otot peha antara kaki yang dirawat dengan kaki kontralateral yang normal adalah berbeza secara signifikan antara kumpulan pada minggu ke-20 ($P < 0.05$). Kehilangan otot pada otot yang dirawat adalah ketara bagi MSTG dan NSTG manakala ini tidak dapat dikesani dalam RSTG dan HSTG. Kehilangan otot yang sedikit telah dikesani bagi SHTG. Pemerhatian histopatologi ke atas sendi yang dirawat pada minggu ke-20 mempamerkan perbezaan yang signifikan antara kumpulan ($P< 0.05$). RSTG menunjukkan skor histopatologi yang paling baik, diikuti oleh HSTG, kemudiannya SHTG, manakala MSTG dan NSTG menunjukkan skor yang paling teruk. Secara rumusan, satu injeksi sel stem arnab (sel stem alogenik) mahupun manusia (sel stem xenogenik) secara intra-artikular dapat membaikpulih tulang rawan rosak yang disebabkan oleh OA dan pembaikkan dari segi pergerakan, pemerhatian radiografik dan patologi, serta petanda klinikal dan kesakitan.

ACKNOWLEDGEMENTS

First and foremost, all praise and thanks to Allah, the Almighty, for gracing me with the strength to complete my thesis.

I would like to express my deepest gratitude to my supervisory committee members, Dr. Angela Ng Min Hwei, Dr. Rajesh Ramasamy, Dr. Chen Hui Cheng, and Assoc. Prof. Dr. Shanthi Ganabadi for their guidance, advice and encouragement throughout the completion of my thesis.

My gratitude also goes to the members of the Anatomy Laboratory and staff of the Veterinary Pre-clinical Sciences Department, for their assistance and contribution to my thesis, and to all of my friends for their moral support throughout my study in Universiti Putra Malaysia.

Finally, I would like to express my sincere thanks to my family for being patient and supportive throughout my study. Without their support and help, I would not have made it to the end.

I certify that a Thesis Examination Committee has met on 18-10-2012 to conduct the final examination of Marwan Taher Moloud Abofila on his thesis entitled "Replacement of Degraded Articular Cartilage Using Stem Cell-Based Therapy in Rabbit Model of Osteoarthritis" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Veterinary Science.

Members of the Thesis Examination Committee were as follows:

Mohd Hair Bejo, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Md Zuki bin Abu Bakar @ Zakaria, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Internal Examiner)

Noordin bin Mohamed Mustapha, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Internal Examiner)

Srihadi Agungpriyono, PhD
Professor
Faculty of Veterinary Medicine
Bogor Agricultural University
Indonesia
(External Examiner)

SEOW HENG FONG, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 26 February 2013

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Veterinary Science. The members of the supervisory committee were as follows:

Shanthi Ganabadi, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Chen Hui Cheng, DVSc
Senior Lecturer
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Rajesh Ramasamy, PhD
Faculty of Medicine
Universiti Putra Malaysia
(Member)

Angela Ng Min Hwei, PhD
Faculty of Medicine
Universiti Kebangsaan Malaysia
(Member)

BUJANG BIN KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
University Putra Malaysia

Date:

DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

MARWAN TAHER M. ABOFILA

Date: 18 / October / 2012

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACL	Anterior Crucial Ligament
ACLT	Anterior Cruciate Ligament Transection
ACUC	Animal Care and Use Committee
APC	Antigen Presenting Cells
ALT	Hepatic Alanine Aminotransferase
ANOVA	Analysis of Variance
Anti-CALLA	Antibody of Common Acute Lymphoblastic Leukemia Antigen
ASCs	Adult Stem Cells
BDNF	Brain-Derived Neurotrophic Factor
bFGF	Basic Fibroblast Growth Factor
BM	Bone Marrow
BM-MSCs	Bone Marrow Mesenchymal Stem Cells
BMP-2	Bone Morphogenetic Protein 2
BMP-4	Bone Morphogenetic Protein 4
BMP-6	Bone Morphogenetic Protein 6
BMP-7	Bone Morphogenetic Protein 7
BMP-9	Bone Morphogenetic Protein 9
BMP-13	Bone Morphogenetic Protein 13
BV	Bee Venom
^{o}C	Degree Celsius
C.C	Chondrocytes Colony
CCLT	Cranial Cruciate Ligament Transection
CD	Cluster of Differentiation = Cluster of Designation
C.F	Cyst Formation
C.L	Chondrocyte Loss = Cellular Loss

cm^2	Centimeter Squared
cm^3	Cubic Centimeter
CO_2	Carbon Dioxide
COL	Collagenase
COL9A1	Collagen Gene IX
COX-2	Cyclooxygenase-2
C shape	Crescent Shape
CTLA4	Cytotoxic T-Lymphocyte Antigen 4
CT scan	Computed Tomography = X-ray Computed Tomography
D	Sample Dilution
DEX	Dexamethasone
DMEM	Dulbecco's Modified Eagle's Medium
DMEM F12	Dulbecco's Modified Eagle's Medium Ham's F12
DMOADs	Disease Modifying OA Drugs
DMSO	Dimethyl Sulfoxide
D.O	Chondrocytes Disorganization
ECM	Extracellular Matrix
EDTA	Ethylene Diamine Tetra-acetic Acid
EGF	Epidermal Growth Factor
ELISA	Enzyme Linked Immunosorbent Assay
ESCs	Embryonic Stem Cells
F	Fibrillation
F.F	Fibrosis Formation
FACS	Fluorescence-Activated Cell Sorting
FBS	Fetal Bovine Serum
FGF-2	Fibroblast Growth Factor 2
FGF-4	Fibroblast Growth Factor 4
FGF-8	Fibroblast Growth Factor 8
Fig	Figure

FITC	Fluorescent Isothiocyanate
FSCs	Foetal Stem Cells
FVM	Faculty of Veterinary Medicine
G	Gram
GAGs	Glycosaminoglycans
GDNF	Glial Cell-Derived Neurotrophic Factor
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
H	Hypertrophy
HA	Hyaluronan = Hyaluronate = Hyaluronic Acid
H & E Stain	Hematoxylin and Eosin Stain
HGF	Hepatocyte Growth Factor
HSTG	Human Stem Cells Treated Group
ICM	Inner Cell Mass
ICRS	International Cartilage Repair Society
IFN-γ	Interferon-Gamma
IGF-1	Insulin-Like Growth Factor 1
IGFBP	Insulin-Like Growth Factor Binding Protein
IgG	Immunoglobulin G
IL-1	Interleukin-1
IL-1Ra	Interleukin 1 Receptor Antagonist
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-7	Interleukin-7
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-11	Interleukin-11
IL-12	Interleukin-12
IL-13	Interleukin-13

IL-14	Interleukin-14
IL-15	Interleukin-15
IL-17	Interleukin-17
IL-18	Interleukin-18
iNOS	Nitric Oxide Synthase
IPFP	Infra-Patellar Fat Pad
IRAP	Interleukin Receptor Antagonist Protein
KGF	Keratinocyte Growth Factor
Kg	Kilogram
LIF	Leukemia Inhibitory Factor
M	Molarity = Molar
mM	MilliMolar
µM	Micrometer
Mg	Milligram
Ml	Milliliter
ml/kg	Milliliter/kilogram
MCP	Macrophage Chemotactic Protein
M-CSF	Macrophage-Colony Stimulating Factor
MHC	Major Histocompatibility Complex
MIA	Monosodium Iodoacetate
Min	Minute
MIP-1β	Macrophage Inflammatory Protein-1β
MLC	Mixed Lymphocyte Culture
MMP	Matrix Metalloproteinase
MMP-13	Matrix Metalloproteinase-13 gene
MRI	Magnetic Resonance Imaging
MSCs	Mesenchymal Stem Cells = Mesenchymal Stromal Cells
MSTG	Media Stem Cells Treated Group

N	Necrosis/Degenerative
N	Number
N_2	Liquid Nitrogen
Na-HA	Sodium Hyaluronate
NC	Number of Count Vital Cells
NE	Nor Epinephrine
Ng	Nanogram
ng /ml	Nanogram/Milliliter
NGF	Nerve Growth Factor
NO	Nitric Oxide
Non-ESCs	Non-Embryonic Stem Cells
NS	Normal Saline
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NSTG	Normal Saline Treated Group
OA	Osteoarthritis
OSM	Oncostatin M
P0	Initial Passage
P1	Primary Passage
P2	Secondary Passage
P3	Third Passage
P4	Fourth Passage
P5	Fifth Passage
P α-hydroxy E	Poly Alpha-*H*ydroxy Esters
PBS	Phosphate Buffer Saline
PDGF	Platelet-Derived Growth Factor
PG	proteoglycan
pg/ml	Pico gram/Milliliter
Pg	Pico gram

PGA	Poly Glycolic Acid
PGE2	Prostaglandin E2
PGP 9.5	Protein Gene Product 9.5
pH	Hydrogen Ions Concentration
PLA	Poly Lactic Acid
PLc-GA	Poly Lactic Co-Glycolic Acid
PST	Plasma Separator Tube
Q	Number of Squares Used in Haemocytometer
Rpm	Revolute Per Minute
RSTG	Rabbit Stem Cells Treated Group
RT-PCR	Real Time-Polymerase Chain Reaction
SCF	Stem Cell Factor
SCs	Stem Cells
SD	Standard Deviation
SDF	Stromal Derived Factor
SEM	Standard Error of Mean
SHTG	Sodium Hyaluronate Treated Group
sIL-4R	Serum Interlukeins-4 Receptor
SPSS	Statistical Package for the Social Sciences
SST	Serum Separator Tube
Stro-1	Stromal Marker 1
T25	Tissue Culture Flask 25 Centimeter Squared
T75	Tissue Culture Flask 75 Centimeter Squared
TEC	Tissue Engineered Construct
TGF-β	Transforming Growth Factor Beta
TGFβ1	Transforming Growth Factor Beta 1
TGFβ2	Transforming Growth Factor Beta 2
TGFβ3	Transforming Growth Factor Beta 3

TIMP	Tissue Inhibitor of Metalloproteinase
TNFα	Tumor Necrosis Factor Alpha
TNFR	Tumor Necrosis Factor Receptor
TNFR-I	Tumor Necrosis Factor Receptor 1
TNFR-II	Tumor Necrosis Factor Receptor 2
TMJ	Temporomandibular Joint
UC-MSC	Umbilical Cord-Derived Mesenchymal Stem Cells
UPM	Universiti Putra Malaysia
USA	United State of America
VEGF	Vascular Endothelial Growth Factor
W	Week
WHO	World Health Organization
%	Percentage

CHAPTER 1

INTRODUCTION

A synovial joint is the place at which two bones or more make contact. It provides mechanical support, stability to the body during weight bearing, and allow movement (Standring and David, 2005). The normal movements of the joint are essential for performance of daily living activities (Leach, 2004). The articular cartilage, which is a crucial part of the joint, is a unique, avascular (not supplied by blood vessels) and aneural (not innervated by nervous tissue) connective tissue which provides covering for the osseous component of synovial joints (Martel-Pelletier *et al.*, 2008).

The unique properties of articular cartilage are related to the composition and structure of its extracellular matrix (ECM), and population of cells, known as chondrocytes. These cells are responsible for the synthesis and maintenance of the extracellular matrix, and are arranged in four zones with different functions (Venn, 1979). The articular cartilage allows for frictionless motion of the joint. Moreover, it serves as a load-bearing material by absorbing impact, and is capable of sustaining shearing forces. The articular cartilage may be degraded or lost due to arthritis (Martel-Pelletier *et al.*, 2008).

Arthritis refers to joint inflammation, which is an important innate defense response against injury or disease, characterized by swelling, pain, and stiffness (Percival, 1999). Arthritis is commonly used to describe a group of conditions involving damage to the joints of the body. It is the most common cause of disability in the

world, which limits human and animal capabilities by restricting their normal physical activities (Lorig *et al.*, 1987).

The incidence and prevalence of arthritis are variable. Lack of correct information limits an exact knowledge of the true incidence and prevalence, with wide variations in reported estimates from different sources (Woolf and Pfleger, 2003). The economic implications of the diseases are dire, with significant mortality and severe morbidity (Kramer *et al.*, 1983). There are over 200 different forms of arthritis, the most common form of which is osteoarthritis (OA) (Arnett *et al.*, 1988).

The word "osteoarthritis" was derived from the Greek medical term "osteo" meaning "of the bone", "arthro" meaning "joint", and "itis" meaning "inflammation" (Martin, 1994). OA belongs to a group of degenerative joint diseases, which encompass mechanical abnormalities entailing degradation of joints, including articular cartilage and its subchondral bone (Ehrlich, 1972). Degenerative joint disease is a more appropriate and accurate term based on the putative pathogenesis. Other common synonyms include osteoarthrosis and degenerative arthropathy (Thompson *et al.*, 2007).

Degenerative joint disease is not a specific entity, but a common sequel to various forms of joint injury and includes the interaction between biologic and mechanical factors on articular cartilage (Dumbleton, 1981). Degenerative arthropathy affects major weight bearing joints leading to pain, physical incapacity and reduced quality of life (Wolfe *et al.*, 1990). Most researchers conform to the view that the disease is primarily degenerative in nature and the inflammatory changes are secondary. There is convincing evidence that the chondrocytes of articular cartilage play an important role in the early stages of the disease development (Thompson *et al.*, 2007).

OA can be classified into primary OA and secondary OA. Primary degenerative joint disease refers to those cases, which have no apparent predisposing factor and commonly occur in older humans or animals. Secondary degenerative joint disease refers to those cases, which have an apparent predisposing factor (Thompson *et al.*, 2007). OA is multifactorial in origin and normally does not have a single cause or factor that could be used to explain why OA does not behave in the same way over the world (Farooqi, 2008). The occurrence and clinical presentation of degenerative joint disease vary between the developed and developing countries due to geo-ethnic differences in lifestyle and many other factors such as nutritional, genetic, gender, cultural and occupational. Besides that, poor health and nutritional awareness are other factors that might affect both the occurrence and clinical presentation of OA (Chopra *et al.*, 1997; Muirden, 2005).

OA affects a large number of humans and animals at different ages. It commonly affects horses, dogs, and cats. At least, 80% of joint problems are classified as degenerative joint disease (McDougall, 2006). The diagnosis of OA is made by obtaining a detailed history about the age and secondary cause or predisposing factors, and by conducting a complete physical examination with a detailed radiographic assessment of the affected joint. Radiographical features of OA include osteophytes, cyst formation, subchondral sclerosis, reduced joint space and joint misalignment (Ness, 2007). The major problem affecting the treatment of OA is the late presentation of cases and/or difficulty of diagnosis at earlier stages of the diseases. The diagnosis of the disease is normally confirmed only when the symptoms have progressed (alterations in the joints have led to pain) and radiographically detectable changes are pronounced (Lorenz and Richter, 2006).

There are several drug classes available for OA management in both humans and animals. Most of these drugs are limited to pain control, symptom alleviation, delayed progression of the disease, and improving general mobility and exercise tolerance as well as eliminating the risk factors (Felson *et al.*, 2000b). OA drug treatments include non-steroids such as diclofenac, ibuprofen, naproxen, and ketoprofen, as well as corticosteroids, narcotic as morphine and hyaluronic acid (Taylor *et al.*, 2008). The efficiency of these treatments is still controversial because unfavorable gastrointestinal complications have been reported (Papaioannou *et al.*, 2007).

Pharmacological treatment options for OA are still very limited (Baltzer *et al.*, 2009), making the search for more options worthwhile. Recently, attention has been focused on agents that could stimulate the endogenous production of cytokines that can arrest the disease and, in some cases; help rebuild the cartilage in joints that have been damaged by the disease (Selfe and Innes, 2009).

Bajada *et al.* (2008) reported that replacement of either lost or defective tissues can be achieved with the assistance of regenerative medicine when current therapies are inadequate. Regenerative medicine comprises the use of tissue engineering and stem cell technology. Specifically, stem cells are suitable and effective biological agents that can help damaged tissues to regenerate, because of their ability to grow and differentiate into all types of body tissues such as bones, heart, liver, muscles, and under the influence of growth factors, but by a process yet undefined. The two main types of stem cells depending on their sources of origin are embryonic stem cells and non-embryonic stem cells (adult stem cells).

In 2004, Joanne *et al.*, reported that autologous adult stem cells are a much better potential source of cells than mature chondrocytes, because of their better compatibility and less likelihood of provoking an immune rejection. Furthermore, mesenchymal stem cells (MSCs) have been shown to treat degenerative joint disease, influence regeneration of articular cartilage and slow the progression of the disease (Murphy *et al.,* 2003). Transplantation of MSCs to affected discs in stifle joints of rabbits showed proliferation and differentiation into cells expressing regeneration of affected joints (Daisuke *et al.,* 2005).

Thus, it is evident that previous studies on management of degenerative joint disease using autologous stem cells have shown promising results. In this study, we investigated the possibility of using allogeneic and xenogeneic stem cells as therapy for OA to study healing of the joints and articular cartilage following experimentally induced OA. Successful use of both allogeneic and xenogeneic stem cells therapies to replace degraded articular cartilage will provide an opportunity to reduce the cost, time and effort that are involved currently in the treatment of OA in humans and large animals such as sport horses, which are susceptible to joint disease.

Hypothesis

The replacement of degraded articular cartilage using stem cells therapy provides a useful alternative approach in the treatment of degenerative joint disease.

Objectives

General Objective of This Study Was:

- To explore the potential of allogeneic and xenogeneic stem cells in the treatment of osteoarthritis.

Specific Objectives of This Study Were:

1. To isolate and characterize rabbit bone marrow derived mesenchymal stem cells for the treatment of OA.
2. To evaluate the usefulness of rabbit bone marrow derived mesenchymal stem cell (allogeneic stem cell) and human umbilical cord-derived mesenchymal stem cell (xenogeneic stem cell) therapies in comparison with sodium hyaluronate in the replacement of degraded articular cartilage.

REFERENCES

Adams, K. E., Cohen, M. H., Eisenberg, D., & Jonsen, A. R. (2002). Ethical considerations of complementary and alternative medical therapies in conventional medical settings. *Annals of Internal Medicine, 137*(8), 660.

Adams, M., & Pelletier, J. (1988). The canine anterior cruciate ligament transection model of osteoarthritis. *Handbook of Models for Arthritis Research. CRC Press, Boca Raton, FL, USA*, 265-297.

Adriaansen, J., Vervoordeldonk, M., & Tak, P. (2006). Gene therapy as a therapeutic approach for the treatment of rheumatoid arthritis: innovative vectors and therapeutic genes. *Rheumatology, 45*(6), 656.

Agarwal, S., Long, P., Gassner, R., Piesco, N., & Buckley, M. (2001). Cyclic tensile strain suppresses catabolic effects of interleukin 1 in fibrochondrocytes from the temporomandibular joint. *Arthritis and Rheumatism, 44*(3), 608-617.

Agung, M., Ochi, M., Yanada, S., Adachi, N., Izuta, Y., Yamasaki, T., et al. (2006). Mobilization of bone marrow-derived mesenchymal stem cells into the injured tissues after intraarticular injection and their contribution to tissue regeneration. *Knee Surgery, Sports Traumatology, Arthroscopy, 14*(12), 1307-1314.

Aigner, T., Cook, J., Gerwin, N., Glasson, S., Laverty, S., Little, C., et al. (2010). Histopathology atlas of animal model systems-overview of guiding principles. *Osteoarthritis and Cartilage, 18*, S2-S6.

Aigner, T., Fundel, K., Saas, J., Gebhard, P. M., Haag, J., Weiss, T., et al. (2006). Large-scale gene expression profiling reveals major pathogenetic pathways of cartilage degeneration in osteoarthritis. *Arthritis and Rheumatism, 54*(11), 3533-3544.

Al-Saffar, F., Ganabadi, S., & Fakuraz, S. (2011a). Response of Channa striatus Extract Against Monosodium Iodoacetate Induced Osteoarthritis in Rats. *Journal of Animal and Veterinary Advances, 10*(4), 460-469.

Al-Saffar, F., Ganabadi, S., Fakurazi, S., Yaakub, H., & Lip, M. (2010). Chondroprotective Effect of Zerumbone on Monosodium Iodoacetate Induced Osteoarthritis in Rats. *Journal of Applied Sciences Research, 10*(4), 248-260.

Al-Saffar, F., Ganabadi, S., Yaakub, H., & Fakurazi, S. (2009). Collagenase and sodium iodoacetate-induced experimental osteoarthritis model in sprague dawley rats. *Asian Journal of Scientific Research, 2*, 167-179.

Al-Saffar, F. J. T., Ganabadi, S., Fakurazi, S., & Yaakub, H. (2011b). Zerumbone improved immunoreactivity of neuropeptides in monosodium iodoacetate induced knee osteoarthritis in rat. *African Journal of Biotechnology, 10*(18), 3646-3653.

Al-Timmemi, H., Ibrahim, R., Al-Jashamy, K., Zuki, A., Azmi, T & Ramassamy, R. (2011a). Neurobiology observation of bone marrow mesenchymal stem cell in vitro and invivo of injuried sciatic nerve in rabbit. *Journal of Animal and Veterinary Advances, 10:*, 686-691.

Al-Timmemi, H., Ibrahim, R., Al-Jashamy, K., Zuki, A., Azmi, T & Ramassamy, R. (2011b). Identification of adipogenesis and osteogenesis pathway of differentiated bone marrow stem cells in vitro in rabbit. *Annals of Microscopy, 11:*, 23-29.

Alaaeddine N, D. J., Pelletier JP, et al. (1999). Inhibition of tumor necrosis factor-α-induced prostaglandin E2 production by anti-inflammatory cytokines interleukin-4, interleukin-10 and interleukin-13 in osteoarthritis synovial fibroblasts: distinct targeting in the signal pathway. *Arthritis Rheumatol Review, 42*, 710-718.

Alam, T., & Sollinger, H. W. (2002). Glucose-regulated insulin production in hepatocytes. *Transplantation, 74*(12), 1781-1787.

Alfaqeh, H. B. H. (2011). Cell based therapy for Osteoarthritis in sheep model, PhD Thesis, University Kebangsaan Malaysia.

Alfaqeh, H., Norhamdan, M., Chua, K., Chen, H., Aminuddin, B., & Ruszymah, B. (2008). Cell based therapy for osteoarthritis in a sheep model: gross and histological assessment. *The Medical Journal of Malaysia, 63*, 37-38.

Allan, G. (2002). Radiographic signs of joint disease. *Textbook of Veterinary Diagnostic Radiology, 3*, 169-188.

Alrowayeh, H. N., Sabbahi, M. A., & Etnyre, B. (2005). Soleus and vastus medialis H-reflexes: Similarities and differences while standing or lying during varied knee flexion angles. *Journal of Neuroscience Methods, 144*(2), 215-225.

Altman, R., & Gold, G. (2007). Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis and Cartilage, 15*, A1-A56.

Altman, R. D., & Dean, D. D. (1990). Osteoarthritis research: animal models. Arthritis and Rheumatism, 19(4), pp. 21-25.

Ameye, L. G., & Young, M. F. (2006). Animal models of osteoarthritis: lessons learned while seeking the'Holy Grail'. *Current Opinion in Rheumatology, 18*(5), 537.

Amiel, D., Toyoguchi, T., Kobayashi, K., Bowden, K., Amiel, M., & Healey, R. (2003). Long-term effect of sodium hyaluronate (Hyalgan®) on osteoarthritis progression in a rabbit model. *Osteoarthritis and Cartilage, 11*(9), 636-643.

Anderson, J. J., & Felson, D. T. (1988). Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). *American Journal of Epidemiology, 128*(1), 179.

Andersson, K. E., & Christ, G. J. (2007). Regenerative pharmacology: The future is now. *Molecular Interventions, 7*(2), 79.

Andréasson, A., Arborelius, L., Erlanson-Albertsson, C., & Lekander, M. (2007). A putative role for cytokines in the impaired appetite in depression. *Brain, Behavior, and Immunity, 21*(2), 147-152.

Angoulvant, D., Clerc, A., Benchalal, S., Galambrun, C., Farre, A., Bertrand, Y., et al. (2004). Human mesenchymal stem cells suppress induction of cytotoxic response to alloantigens. *Biorheology, 41*(3-4), 469-478.

Anoldi, C., Lemperg, R.K., & Linderholm, H. (1975). Intrasseous hypertension and pain in the knee. *Journal Bone Joint Surgery, 57B*, 360-363.

Appell, H., Duarte, J., & Soares, J. (1990). Muscle atrophy following immobilization. *International Journal Sports Medicine, 10*, 42-58.

Arai, F., Ohneda, O., Miyamoto, T., Zhang, X. Q., & Suda, T. (2002). Mesenchymal stem cells in perichondrium express activated leukocyte cell adhesion molecule and participate in bone marrow formation. *The Journal of Experimental Medicine, 195*(12), 1549-1563.

Arnett, F., Edworthy, S., Bloch, D., Mcshane, D., Fries, J., Cooper, N., et al. (1988). The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and Rheumatism, 31*(3), 315-324.

Arokoski, M. H., Arokoski, J. P. A., Haara, M., Kankaanpää, M., Vesterinen, M., Niemitukia, L. H., et al. (2002). Hip muscle strength and muscle cross sectional area in men with and without hip osteoarthritis. *The Journal of Rheumatology, 29*(10), 2185-2195.

Aston, J. E., & Bentley, G. (1986). Repair of articular surfaces by allografts of articular and growth-plate cartilage. *Journal of Bone and Joint Surgery-British Volume, 68*(1), 29-35.

Athanasiou, K., Korvick, D., & Schenck Jr, R. (1997). Biodegradable implants for the treatment of osteochondral defects in a goat model. *Tissue Engineering, 3*(4), 363-373.

Attur MG, D. M., Akamatsu M, Katoh M, & Amin AR. (2003). Osteoarthritis or osteoarthrosis: the definition of inflammation becomes a semantic issue in the genomic era of molecular medicine. *Osteoarthritis Cartilage, 10*, 1-4.

Aung, A., Gupta, G., Majid, G., & Varghese, S. (2011). Osteoarthritic chondrocyte–secreted morphogens induce chondrogenic differentiation of human mesenchymal stem cells. *Arthritis and Rheumatism, 63*(1), 148-158.

Aydelotte, M. B., & Kuettner, K. E. (1993). Heterogeneity of articular chondrocytes and cartilage matrix. In Joint Cartilage Degradation: Basic and Clinical Aspects, ed. Woessner, J. J., Howell, D. S., pp. 37 – 65. New York, Marcel Dekker Inc.

Bajada, S., Mazakova, I., Richardson, J. B., & Ashammakhi, N. (2008). Updates on stem cells and their applications in regenerative medicine. *Journal of Tissue Engineering and Regenerative Medicine, 2*(4), 169-183.

Balazs, E. A., & Denlinger, J. L. (1993). Viscosupplementation: A new concept in the treatment of osteoarthritis. *The Journal of Rheumatology. Supplement, 39*, 3.

Baltzer, A. W., Moser, C., Jansen, M.D & R. Krauspe. (2009). Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. *Osteoarthritis and Cartilage, 17*, 152-160.

Banfi, A., Muraglia, A., Dozin, B., Mastrogiacomo, M., Cancedda, R., & Quarto, R. (2000). Proliferation kinetics and differentiation potential of ex vivo expanded human bone marrow stromal cells:: Implications for their use in cell therapy. *Experimental Hematology, 28*(6), 707-715.

Barry, F., Boynton, R. E., Liu, B., & Murphy, J. M. (2001). Chondrogenic differentiation of mesenchymal stem cells from bone marrow: differentiation-dependent gene expression of matrix components. *Experimental Cell Research, 268*(2), 189-200.

Bartholomew, A., Sturgeon, C., Siatskas, M., Ferrer, K., McIntosh, K., Patil, S., et al. (2002). Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. *Experimental Hematology, 30*(1), 42-48.

Bendele, A. (2001). Animal models of osteoarthritis. *Journal Musculoskelet Neuronal Interact, 1*(4), 363-376.

Bennett, D., & Whittick, W. (1990). Joints and joint diseases. *Canine Orthopedics.*, 761-853.

Berg, H., Larsson, L., & Tesch, P. (1997). Lower limb skeletal muscle function after 6 weeks of bed rest. *Journal of Applied Physiology, 82*(1), 182-188.

Berry, C. R. (1992). Radiology corner evaluation of the canine elbow for fragmented medial coronoid process. *Veterinary Radiology and Ultrasound, 33*(5), 273-276.

Beyreuther, B., Callizot, N., & Stohr, T. (2007). Antinociceptive efficacy of lacosamide in the monosodium iodoacetate rat model for osteoarthritis pain. *Arthritis Research and Therapy, 9*(1), 14 - 22.

Black, L. L., Gaynor, J., Adams, C., Dhupa, S., Sams, A. E., Taylor, R., et al. (2008). Effect of intraarticular injection of autologous adipose-derived mesenchymal stem and regenerative cells on clinical signs of chronic osteoarthritis of the elbow joint in dogs. *Veterinary Therapeutics, 9*(3), 192-200.

Black, L. L., Gaynor, J., Gahring, D., Adams, C., Aron, D., Harman, S., et al. (2007). Effect of Adipose-Derived Mesenchymal Stem and Regenerative Cells on Lameness in Dogs with Chronic Osteoarthritis of the Coxofemoral Joints: A Randomized, Double-Blinded, Multicenter Controlled Trial. *Veterinary Therapeutics, 8*(4), 272-284.

Bodeker, G., & Kronenberg, F. (2002). A public health agenda for traditional, complementary, and alternative medicine. *American Journal of Public Health, 92*(10), 1582.

Bora Jr, F., & Miller, G. (1987). Joint physiology, cartilage metabolism, and the etiology of osteoarthritis. *Hand Clinics, 3*(3), 325-326.

Bosnakovski, D., Mizuno, M., Kim, G., Ishiguro, T., Okumura, M., Iwanaga, T., et al. (2004). Chondrogenic differentiation of bovine bone marrow mesenchymal stem cells in pellet cultural system. *Experimental Hematology, 32*(5), 502-509.

Bosnakovski, D., Mizuno, M., Kim, G., Takagi, S., Okumura, M., & Fujinaga, T. (2006). Chondrogenic differentiation of bovine bone marrow mesenchymal stem cells (MSCs) in different hydrogels: influence of collagen type II extracellular matrix on MSC chondrogenesis. *Biotechnology and Bioengineering, 93*(6), 1152-1163.

Bove, S., Calcaterra, S., Brooker, R., Huber, C., Guzman, R., Juneau, P., et al. (2003). Weight bearing as a measure of disease progression and efficacy of anti-inflammatory compounds in a model of monosodium iodoacetate-induced osteoarthritis. *Osteoarthritis and Cartilage, 11*(11), 821-830.

Boulocher, C. B., Viguier, E. R., Cararo, R. D. R., Fau, D. J., Arnault, F., Collard, F., et al. (2010). Radiographic assessment of the femorotibial joint of the CCLT rabbit experimental model of osteoarthritis. *BMC Medical Imaging, 10*(1), 3.

Braga-Silva J, G. D., Roman JA, Menta C, Atkinson EA, Machado DC, et al. (2006). Bone marrow stem cells and platelet-rich plasma effects on nervous regeneration and functional recovery in an acute defect model of rats' peripheral nerve. *The Acta Ortopédica Brasileira Journal. 14(5)*, 273-275.

Brandt, K., & Mankin, H. (1991). Pathogenesis of osteoarthritis. *Rheumatol Review, 1*, 3-11.

Brandt, K. D. (1994). Insights into the Natural History of Osteoarthritis Provided by the Cruciate Deficient Dog. *Annals of the New York Academy of Sciences, 732*(1), 199-205.

Brittberg, M., Aglietti, P., Gambardella, R., Hangody, L., Hauselmann, H., & Jakob, R. (2000). Cartilage injury evaluation package *ICRS Cartilage Injury Evaluation Package*. Journal of Bone and Joint Surgery, American Volume, 85(suppl 2):58-69

Brenner, S. S., Klotz, U., Alscher, D. M., Mais, A., Lauer, G., Schweer, H., et al. (2004). Osteoarthritis of the knee–clinical assessments and inflammatory markers. *Osteoarthritis and Cartilage, 12*(6), 469-475.

Buckbinder, L., Talbott, R., Velasco-Miguel, S., Takenaka, I., Faha, B., Seizinger, B. R., et al. (1995). Induction of the growth inhibitor IGF-binding protein 3 by p53. *Arthritis Rheumatol Review, 36*, 1709–1717.

Buckland-Wright, C. (1997). 6 Current status of imaging procedures in the diagnosis, prognosis and monitoring of osteoarthritis. *Baillière's Clinical Rheumatology, 11*(4), 727-748.

Buckwalter, J. (1992). Mechanical injuries of articular cartilage. *The Iowa Orthopaedic Journal, 12*, 50.

Buckwalter, J. (1998). Articular cartilage: injuries and potential for healing. *The Journal of Orthopaedic and Sports Physical Therapy, 28*(4), 192-202.

Buckwalter, J., & Mankin, H. (1998). Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. *Instructional Course Lectures, 47*, 487-504.

Buckwalter, J. A., & Lohmander, S. (1994). Operative treatment of osteoarthrosis. Current practice and future development. *The Journal of Bone and Joint Surgery. American Volume, 76*(9), 1405-1418.

Buckwalter, J. A., Mankin, H. J., & Grodzinsky, A. J. (2005). Articular cartilage and osteoarthritis. *Instructional Course Lectures, 54*, 465-480.

Bukowski, E. L., Conway, A., Glentz, L. A., Kurland, K., & Galantino, M. L. (2006). The effect of iyengar yoga and strengthening exercises for people living with osteoarthritis of the knee: a case series. *International Quarterly of Community Health Education, 26*(3), 287-305.

Burgeson, R. (1982). Articular cartilage, intervertebral disc, synovia. *Collagen in Health and Disease. JB Weiss and MIV Jayson, editors. Churchill Livingstone, Edinburgh, 335*, 361.

Butnariu-Ephrat, M., Robinson, D., Mendes, D. G., Halperin, N., & Nevo, Z. (1996). Resurfacing of goat articular cartilage by chondrocytes derived from bone marrow. *Clinical Orthopaedics and Related Research, 330*, 234-243.

Buttle, D., Bramwell, H., & Hollander, A. (1995). Proteolytic mechanisms of cartilage breakdown: a target for arthritis therapy? *Clinical Molecular Pathology, 48*(4), M167.

Cao, Y., Vacanti, J., Ma, X., Paige, K., Upton, J., Chowanski, Z., et al. (1994). Generation of neo-tendon using synthetic polymers seeded with tenocytes. *Transplant Proceedings Journal, 26*, 3390-3392.

Caplan, A. I., & Dennis, J. E. (2006). Mesenchymal stem cells as trophic mediators. *Journal of Cellular Biochemistry, 98*(5), 1076-1084.

Carlo Jr, M. D., & Loeser, R. F. (2003). Increased oxidative stress with aging reduces chondrocyte survival: correlation with intracellular glutathione levels. *Arthritis & Rheumatism, 48*(12), 3419-3430.

Carrig, C. B. (1997). Diagnostic imaging of osteoarthritis. *The Veterinary clinics of North America. Small Animal Practice, 27*(4), 777-814.

Carroll, G. L., & Simonson, S. M. (2005). Recent developments in nonsteroidal antiinflammatory drugs in cats. *Journal of the American Animal Hospital Association, 41*(6), 347-354.

Carter, D. R., Orr, T. E., Fyhrie, D. P., & Schurman, D. J. (1987). Influences of mechanical stress on prenatal and postnatal skeletal development. *Clinical Orthopaedics and Related Research, 219*, 237.

Castillo, M., Liu, K., Bonilla, L., & Rameshwar, P. (2007). The immune properties of mesenchymal stem cells. *International Journal Biomedical Science, 3*(100), 100-104.

Cavarretta, I. T., Altanerova, V., Matuskova, M., Kucerova, L., Culig, Z., & Altaner, C. (2009). Adipose Tissue–derived Mesenchymal Stem Cells Expressing Prodrug-converting Enzyme Inhibit Human Prostate Tumor Growth. *Molecular Therapy, 18*(1), 223-231.

Cawston, T., & Wilson, A. (2006). Understanding the role of tissue degrading enzymes and their inhibitors in development and disease. *Best Practice and Research Clinical Rheumatology, 20*(5), 983-1002.

Chambers, M., Bayliss, M., & Mason, R. (1997). Chondrocyte cytokine and growth factor expression in murine osteoarthritis*. *Osteoarthritis and Cartilage, 5*(5), 301-308.

Chen, F. H., & Tuan, R. S. (2008). Mesenchymal stem cells in arthritic diseases. *Arthritis Research Therapy, 10*(5), 223-234.

Chen, Y., Liu, W., Li, W., & Gao, C. (2010). Autologous bone marrow mesenchymal cell transplantation improves left ventricular function in a rabbit model of dilated cardiomyopathy. *Experimental and Molecular Pathology, 88*(2), 311-315.

Chikanza, I. C., & Fernandes, L. (2000). Novel strategies for the treatment of osteoarthritis. *Expert Opinion on Investigational Drugs,* 9(7), 1499-1510.

Chopra A, P. J., Billampelly V., et al. (1997). The Bhigwan (India) copcord: methodology and first information report. *The Journal of Rheumatology, 1*, 145–151.

Clarke, S., Mellor, D., Clements, D., Gemmill, T., Farrell, M., Carmichael, S., et al. (2005). Prevalence of radiographic signs of degenerative joint disease in a hospital population of cats. *Veterinary Record, 157*(25), 793-799.

Coleman, C. M., Curtin, C., Barry, F. P., O'Flatharta, C., & Murphy, J. M. (2010). Mesenchymal stem cells and osteoarthritis: remedy or accomplice? *Human Gene Therapy, 21*(10), 1239-1250.

Coleman, R. M., Case, N. D., & Guldberg, R. E. (2007). Hydrogel effects on bone marrow stromal cell response to chondrogenic growth factors. *Biomaterials, 28*(12), 2077-2086.

Colombo, C., Butler, M., O'Byrne, E., Hickman, L., Swartzendruber, D., Selwyn, M., et al. (1983). A new model of osteoarthritis in rabbits. *Arthritis and Rheumatism, 26*(7), 875-886.

Conget, P. A., & Minguell, J. J. (1999). Phenotypical and functional properties of human bone marrow mesenchymal progenitor cells. *Journal of Cellular Physiology, 181*(1), 67-73.

Cooper, C. (1995). Radiographic atlases for the assessment of osteoarthritis. *Osteoarthritis and cartilage/OARS, Osteoarthritis Research Society, 3*, 1.

Crawford, T., Adams, D., Sande, R., Gorham, J., & Henson, J. (1980). The connective tissue component of the caprine arthritis-encephalitis syndrome. *The American Journal of Pathology, 100*(2), 443.

Creamer, P., Lethbridge Cejku, M., & Hochberg, M. (2000). Factors associated with functional impairment in symptomatic knee osteoarthritis. *Rheumatology, 39*(5), 490.

Cuevas, P., Carceller, F., Garcia-Gomez, I., Yan M. & Dujovny, M. (2004). Bone marrow stromal cell implantation for peripheral nerve repair. *Neurology Research 26: ,* 230-232.

Curry, S. L., Cogar, S. M., & Cook, J. L. (2005). Nonsteroidal antiinflammatory drugs: a review. *Journal of the American Animal Hospital Association, 41*(5), 298-309.

D'Anjou, M. A., Moreau, M., Troncy, E., Martel-Pelletier, J., Abram, F., Raynauld, J. P., et al. (2008). Osteophytosis, subchondral bone sclerosis, joint effusion and soft tissue thickening in canine experimental stifle osteoarthritis: comparison between 1.5 T magnetic resonance imaging and computed radiography. *Veterinary Surgery, 37*(2), 166-177.

Daisuke, S. M., Joji Mochida MD, Toru Iwashina, MD, & Takuya Watanable. (2005). Differentiation of mesenchymal Stem cells transplanted to a Rabbit Degenerative Disc Model. *Lippincott Williams., Vol. 30,* pp 2379-2387.

Dambisya, Y. M., Lee, T. L., Sathivulu, V., & Mat Jais, A. M. (1999). Influence of temperature, pH and naloxone on the antinociceptive activity of Channa striatus (haruan) extracts in mice. *Journal of Ethnopharmacology, 66*(2), 181-186.

Dantzer, R. (2001). Cytokine-induced sickness behavior: mechanisms and implications. *Annals of the New York Academy of Sciences, 933*(1), 222-234.

Dantzer, R., & Kelley, K. W. (2007). Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity, 21*(2), 153-160.

De Passillé, A. M., Rushen, J., & Martin, F. (1995). Interpreting the behaviour of calves in an open-field test: a factor analysis. *Applied Animal Behaviour Science, 45*(3), 201-213.

De Ugarte, D. A., Alfonso, Z., Zuk, P. A., Elbarbary, A., Zhu, M., Ashjian, P., et al. (2003). Differential expression of stem cell mobilization-associated molecules on multi-lineage cells from adipose tissue and bone marrow. *Immunology Letters, 89*(2-3), 267-270.

Deans, R. J., & Moseley, A. B. (2000). Mesenchymal stem cells:: Biology and potential clinical uses. *Experimental Hematology, 28*(8), 875-884.

Deek JJ., S. L., Bradley MD. (2002). Efficacy, tolerability and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis:Systematic review of randomised control trials. *British Medical Journal,* (325), 619-623.

Desechenes, M. R., Britt, A.A., & Chandler, W.C. (2001). A comparison of the effects of unloading in young adult and aged skeletal muscle. *Medicine and Science in Sports & Exercise, 33*(9), 1477.

Deshmukh-Phadke, K., Lawrence, M., & Nanda, S. (1978). Synthesis of collagenase and neutral proteases by articular chondrocytes: stimulation by a macrophage-derived factor. *Biochemical and Biophysical Research Communications, 85*(1), 490-496.

Deyo R, S. K., Moyer J., et al. (1989). Nimodipine Ameliorates Aging-Related Changes in Open-Field Behaviors of the Rabbit. *Expermental Aging Research, 15*, 169-175.

Di Nicola, M., Carlo-Stella, C., Magni, M., Milanesi, M., Longoni, P. D., Matteucci, P., et al. (2002). Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood, 99*(10), 3838-3843.

Dieppe, P. (1978). Inflammation in osteoarthritis. *Rheumatology, 17*(suppl), 59.

Dougados, M., Nguyen, M., Listrat, V., & Amor, B. (1993). High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. *Osteoarthritis and Cartilage, 1*(2), 97-103.

Dumbleton, J. H. (1981). Tribology of natural and artificial joints. Tribology Series, 3. Amsterdam: Elsevier Scientific Publishing Company. pp. 47-49. , Morrey B., editor. Chap 6. New York: Churchill Livingstone

Dumond, H., Presle, N., Terlain, B., Mainard, D., Loeuille, D., Netter, P., et al. (2003). Evidence for a key role of leptin in osteoarthritis. *Arthritis and Rheumatism, 48*(11), 3118-3129.

Dyce, K. M., Sack W.O., & Wensing, C.J.G. (1996) *Some Basic Facts and Concepts. In TextBook of Veterinary Anatomy* (2nd ed., pp. 14-21).

Ehrlich, G. (1972). Inflammatory osteoarthritis: The clinical syndrome. *Journal of Chronic Diseases, 25*(6-7), 317-322.

Eisenberg, D. M. (1997). Advising patients who seek alternative medical therapies. *Annals of Internal Medicine, 127*(1), 61.

Elliott, R., & Gardner, D. (1979). Changes with age in the glycosaminoglycans of human articular cartilage. *Annals of the Rheumatic Diseases, 38*(4), 371.

Ely, L., & Mensor, M. (1933). Studies on the immobilization of the normal joints. *Surgery, Gynecology and Obstetrics, 57*, 212-215.

Endres, M., Andreas, K., Kalwitz, G., Freymann, U., Neumann, K., Ringe, J., et al. (2010). Chemokine profile of synovial fluid from normal, osteoarthritis and rheumatoid arthritis patients: CCL25, CXCL10 and XCL1 recruit human subchondral mesenchymal progenitor cells. *Osteoarthritis and Cartilage, 18*(11), 1458-1466.

Ettinger Jr, W. H., Burns, R., Messier, S. P., Applegate, W., Rejeski, W. J., Morgan, T., et al. (1997). A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. *The Journal of the American Medical Association, 277*(1), 25-31.

Eustace, S., DiMasi, M., Adams, J., Ward, R., Caruthers, S., & McAlindon, T. (2000). In vitro and in vivo spin echo diffusion imaging characteristics of synovial fluid: potential non-invasive differentiation of inflammatory and degenerative arthritis. *Skeletal Radiology, 29*(6), 320-323.

Evans, C., Gouze, J., Gouze, E., Robbins, P., & Ghivizzani, S. (2004). Osteoarthritis gene therapy. *Gene Therapy, 11*(4), 379-389.

Evans, H. E. (1993). Miller's Anatomy of the dog (3rd ed., pp. 246 - 252): W. B. Saunders Company.

Farooqi A, K. S. (2008). Osteoarthritis. *Best Practice and Research Clinical Rheumatology, 22*(4), 657–675.

Fassbender, H. (1994). 9. Inflammatory Enactions in Arthritis. *Immunopharmacology of Joints and Connective Tissue*, 165.

Feldmann, M., & Maini, S. (2008). Role of cytokines in rheumatoid arthritis: an education in pathophysiology and therapeutics. *Immunological Reviews, 223*(1), 7-19.

Felson, D. T. (2005). The sources of pain in knee osteoarthritis. *Current Opinion in Rheumatology, 17*(5), 624-637.

Felson, D. T., & Chaisson, C. E. (1997). 2 Understanding the relationship between body weight and osteoarthritis. *Baillière's Clinical Rheumatology, 11*(4), 671-681.

Felson, D. T., Lawrence, R. C., Dieppe, P. A., Hirsch, R., Helmick, C. G., Jordan, J. M., et al. (2000a). Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Annals of Internal Medicine, 133*(8), 635-646.

Felson, D. T., Lawrence, R.C., Hochberg, M.C., McAlindon, T., Dieppe, P.A., Minor M.A., et al. (2000b). Osteoarthritis: new insights. Part 2: treatment approaches. *Annals of Internal Medicine, 133*, 726-737.

Felson, D. T., & Zhang, Y. (1998). An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis and Rheumatism, 41*(8), 1343-1355.

Fernandes, J. C., Martel-Pelletier, J., & Pelletier, J. P. (2002). The role of cytokines in osteoarthritis pathophysiology. *Biorheology, 39*(2), 237-246.

Fife, R. S., Brandt, K. D., Braunstein, E. M., Katz, B. P., Shelbourne, K. D., Kalasinski, L. A., et al. (1991). Relationship between arthroscopic evidence of cartilage damage and radiographic evidence of joint space narrowing in early osteoarthritis of the knee. *Arthritis and Rheumatism, 34*(4), 377-382.

Fink, B., Egl, M., Singer, J., Fuerst, M., Bubenheim, M., & Neuen-Jacob, E. (2007). Morphologic changes in the vastus medialis muscle in patients with osteoarthritis of the knee. *Arthritis and Rheumatism, 56*(11), 3626-3633.

Fischer, B. A., Mundle, S., & Cole, A. A. (2000). Tumor necrosis factor-α induced DNA cleavage in human articular chondrocytes may involve multiple endonucleolytic activities during apoptosis. *Microscopy Research and Technique, 50*(3), 236-242.

Fisher, A. (1922). A Contribution to the pathology and etiology of osteo-arthritis: With observations upon the principles underlying its surgical treatment. *British Journal of Surgery, 10*(37), 52-80.

Fleming, K., & Hubel, A. (2006). Cryopreservation of hematopoietic and non-hematopoietic stem cells. *Transfusion and Apheresis Science, 34*(3), 309-315.

Foo, H., Crabtree, K., Thrasher, A., & Mason, P. (2009). Eating is a protected behavior even in the face of persistent pain in male rats. *Physiology and Behavior, 97*(3-4), 426-429.

Fosang, A., Last, K., & Maciewicz, R. (1996). Aggrecan is degraded by matrix metalloproteinases in human arthritis. Evidence that matrix metalloproteinase and aggrecanase activities can be independent. *Journal of Clinical Investigation, 98*(10), 2292.

Foster, N. E., Thomas, E., Barlas, P., Hill, J. C., Young, J., Mason, E., et al. (2007). Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. *British Medical Journal, 335*(7617), 436.

Frandson, R. D. (1974). Stifle joint Anatomy and Physiology of farm animals. *Lea and Febiger, Publisher, Philadelphia.* (pp. 133-134).

Freed, L., & Vunjak-Novakovic, G. (1997). Tissue culture bioreactors: chondrogenesis as a model system. *Principles of Tissue Engineering*, 151-165.

Freed, L., Vunjak-Novakovic, G., & Langer, R. (1993). Cultivation of cell-polymer cartilage implants in bioreactors. *Journal of cellular biochemistry, 51*(3), 257-264.

Frenkel, J. (1969). *Choice of animal models for the study of disease processes in man. Federation Proceedings Journal,* 28: 160 - 161

Freshney, I. (2001). Application of cell cultures to toxicology. *Cell Biology and Toxicology, 17*(4), 213-230.

Frisbie, D. D., & Stewart, M. C. (2011). Cell-based Therapies for Equine Joint Disease. *Veterinary Clinics of North America: Equine Practice, 27*(2), 335-349.

Galli, R., Borello, U., Gritti, A., Minasi, M. G., Bjornson, C., Coletta, M., et al. (2000). Skeletal myogenic potential of human and mouse neural stem cells. *Nature Neuroscience, 3*(10), 986-991.

Gamble, R., Wyeth-Ayerst, J., Johnson, E. L., Searle, W. A., & Beecham, S. K. (2000). Recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis and Rheumatism, 43*(9), 1905-1915.

Gardner, D. (1960). The experimental production of arthritis. *Annals of the Rheumatic Diseases, 19*(4), 297-317.

Gartner. L. P., & Hiatt. J. L. (2007). Cartilage and bone. *Color textbook of histology,* (3th ed., pp. 131-156): Elsevier Health Science.

Gastel, J. A., Muirhead, W. R., Lifrak, J. T., Fadale, P. D., Hulstyn, M. J., & Labrador, D. P. (2001). Meniscal tissue regeneration using a collagenous biomaterial derived from porcine small intestine submucosa. *Arthroscopy: The Journal of Arthroscopic and Related Surgery, 17*(2), 151-159.

Ge, Z., Hu, Y., Heng, B. C., Yang, Z., Ouyang, H., Lee, E. H., et al. (2006). Osteoarthritis and therapy. *Arthritis Care and Research, 55*(3), 493-500.

Ghannam, S., Bouffi, C., Djouad, F., Jorgensen, C., & Noël, D. (2010). Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. *Stem Cell Research and Therapy, 1*(1), 2.

Ghosh, P. (1994). The role of hyaluronic acid (hyaluronan) in health and disease: interactions with cells, cartilage and components of synovial fluid. *Clinical and Experimental Rheumatology, 12*(1), 75-82.

Ghosh, P., Read, R., Armstrong, S., Wilson, D., & Marshall, R. (1993). The effects of intraarticular administration of hyaluronan in a model of early osteoarthritis in sheep I. Gait analysis and radiological and morphological studies. *Arthritis and Rheumatism, 22*(6), 18-30.

Ghosh, P., Shimmon, S., & Whitehouse, M. (2006). Arthritic disease suppression and cartilage protection with glycosaminoglycan polypeptide complexes (Peptacans) derived from the cartilage extracellular matrix: a novel approach to therapy. *Inflammopharmacology, 14*(3), 161-168.

Gibbons, S., Macias, C., Tonzing, M., Pinchbeck, G., & McKee, W. (2006). Patellar luxation in 70 large breed dogs. *Journal of Small Animal Practice, 47*(1), 3-9.

Gietzen, D. W., & Magrum, L. J. (2001). Molecular mechanisms in the brain involved in the anorexia of branched-chain amino acid deficiency. *The Journal of Nutrition, 131*(3), 851S-855S.

Gimeno, M., Maneiro, E., Rendal, E., Ramallal, M., Sanjurjo, L., & Blanco, F. (2005). Cell therapy: a therapeutic alternative to treat focal cartilage lesions. *Transplant Proceedings Journal, 37*(9), 4080-4083.

Glennie, S., Soeiro, I., Dyson, P. J., Lam, E. W. F., & Dazzi, F. (2005). Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. *Blood, 105*(7), 2821-2827.

Godfrey, D. (2005). Osteoarthritis in cats: a retrospective radiological study. *Journal of Small Animal Practice, 46*(9), 425-429.

Goldberg, V., & Caplan, A. (1999). Biologic resurfacing of articular surfaces. *American Academy Orthopaedic Surgeons Instructional Course Lectures, 48*(4), 623-627.

Goldring, M. B. (1999). The role of cytokines as inflammatory mediators in osteoarthritis: lessons from animal models. *Connective Tissue Research, 40*(1), 1-11.

Goldring, M. B. (2000). Osteoarthritis and cartilage: the role of cytokines. *Current Rheumatology Reports, 2*(6), 459-465.

Goldring, S. R., & Goldring, M. B. (2004). The role of cytokines in cartilage matrix degeneration in osteoarthritis. *Clinical Orthopaedics and Related Research, 427*, S27.

Goodrich, L. R., & Nixon, A. J. (2006). Medical treatment of osteoarthritis in the horse-a review. *The Veterinary Journal, 171*(1), 51-69.

Gotoh, S., Onaya, J., Abe, M., Miyazaki, K., Hamai, A., Horie, K., et al. (1993). Effects of the molecular weight of hyaluronic acid and its action mechanisms on experimental joint pain in rats. *Annals of the Rheumatic Diseases, 52*(11), 817-822.

Goupille, P., Jayson IV, M., Valat, J., & Freemont, A. (1998). Matrix metalloproteinases: the clue to intervertebral disc degeneration? *Spine, 23*(14), 1612.

Grande, D., Halberstadt, C., Naughton, G., Schwartz, R., & Manji, R. (1997). Evaluation of matrix scaffolds for tissue engineering of articular cartilage grafts. *Journal of Biomedical Materials Research, 34*(2), 211-220.

Greco, S. J., & Rameshwar, P. (2008). Microenvironmental considerations in the application of human mesenchymal stem cells in regenerative therapies. *Biologics: Targets and Therapy, 2*(4), 699.

Greenwel, P., Tanaka, S., Penkov, D., Zhang, W., Olive, M., Moll, J., et al. (2000). Tumor necrosis factor alpha inhibits type I collagen synthesis through repressive CCAAT/enhancer-binding proteins. *Molecular and Cellular Biology, 20*(3), 912-918.

Grigolo, B., Lisignoli, G., Desando, G., Cavallo, C., Marconi, E., Tschon, M., et al. (2009). Osteoarthritis treated with mesenchymal stem cells on hyaluronan-based scaffold in rabbit. *Tissue Engineering Part C: Methods, 15*(4), 647-658.

Grosvenor, P. W., Gothard, P. K., McWilliam, N. C., Supriono, A., & Gray, D. O. (1995). Medicinal plants from Riau Province, Sumatra, Indonesia. Part 1: uses. *Journal of Ethnopharmacology, 45*(2), 75-95.

Grunstein, R. (2011). Plenary Sessions. *Sleep and Biological Rhythms, 9*, 194-253.

Guenechea, G., Gan, O. I., Dorrell, C., & Dick, J. E. (2001). Distinct classes of human stem cells that differ in proliferative and self-renewal potential. *Nature Immunology, 2*(1), 75-82.

Guilak, F., Meyer, B. C., Ratcliffe, A., & Mow, V. C. (1994). The effects of matrix compression on proteoglycan metabolism in articular cartilage explants. *Osteoarthritis and Cartilage, 2*(2), 91-101.

Guillemot, F., Souquet, A., Catros, S., & Guillotin, B. (2010). Laser-assisted cell printing: principle, physical parameters versus cell fate and perspectives in tissue engineering. *Nanomedicine, 5*(3), 507-515.

Gunnar, K., Lars, E., Tom, C., Jon Olav, D., Torbjørn, G., Eirik, S., et al. (2004). Autologous Chondrocyte Implantation Compared with Microfracture in the KneeA Randomized Trial. *The Journal of Bone and Joint Surgery (American), 86*(3), 455-464.

Gustafson, S., Trotter, G., Norrdin, R., Wrigley, R., & Lamar, C. (1992). Evaluation of intra-articularly administered sodium monoiodoacetate-induced chemical injury to articular cartilage of horses. *American Journal of Veterinary Research, 53*(7), 1193.

Haapala, J., Arokoski, J., Rönkkö, S., Ågren, U., Kosma, V., Lohmander, L., et al. (2001). Decline after immobilisation and recovery after remobilisation of synovial fluid IL1, TIMP, and chondroitin sulphate levels in young beagle dogs. *Annals of the Rheumatic Diseases, 60*(1), 55-60.

Harari J. (1997). Clinical evaluation of the osteoarthritic patient. *Veterinary Clinics North America: Small Animal Practice Journal*, *27*(4), 725-734.

Hayami, T., Pickarski, M., Wesolowski, G. A., Mclane, J., Bone, A., Destefano, J., et al. (2004). The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. *Arthritis and Rheumatism*, *50*(4), 1193-1206.

Hedbom, E., & Häuselmann, H. (2002). Molecular aspects of pathogenesis in osteoarthritis: the role of inflammation. *Cellular and Molecular Life Sciences*, *59*(1), 45-53.

Henderson, B., Revell, P., & Edwards, J. (1988). Synovial lining cell hyperplasia in rheumatoid arthritis: dogma and fact. *Annals of the Rheumatic Diseases*, *47*(4), 348.

Hickman, I., Jonsson, J., Prins, J., Ash, S., Purdie, D., Clouston, A., et al. (2004). Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut*, *53*(3), 413-419.

Hill, C. L., LaValley, M. P., & Felson, D. T. (2002). Secular changes in the quality of published randomized clinical trials in rheumatology. *Arthritis and Rheumatism*, *46*(3), 779-784.

Hochberg, M. (1991). Epidemiologic considerations in the primary prevention of osteoarthritis. *The Journal of Rheumatology*, *18*(10), 1438.

Hochberg, M. C. (2000). *Role of intra-articular hyaluronic acid preparations in medical management of osteoarthritis of the knee*. *Arthritis and Rheumatism*, 30 (2 suppl 1): 2-10

Holland, T., Jones, R., Basford, A., Child, T., & Smith, A. (2000). An intra-articular method for assessing topical application to a synovial joint. *Laboratory Animals*, *34*(3), 298-300.

Honczarenko, M., Le, Y., Swierkowski, M., Ghiran, I., Glodek, A. M., & Silberstein, L. E. (2006). Human bone marrow stromal cells express a distinct set of biologically functional chemokine receptors. *Stem Cells*, *24*(4), 1030-1041.

Honsawek, S., & Chayanupatkul, M. (2010). Correlation of plasma and synovial fluid adiponectin with knee osteoarthritis severity. *Archives of Medical Research*, *41*(8), 593-598.

Hortobagyi, T., Dempsey, L., Fraser, D., Zheng, D., Hamilton, G., Lambert, J., et al. (2000). Changes in muscle strength, muscle fibre size and myofibrillar gene expression after immobilization and retraining in humans. *The Journal of Physiology, 524*(1), 293-304.

Hou, Y., Li, T., Zhang, C., Yan, X., Zhu, Z., Gao, Y., et al. (2011). Effect of hypoxia treatment by CoCl_2 on the expression of vascular growth factor in UC-MSCs. *Chinese Heart Journal*. 1: 59-64.

Huang, G. T. J. (2008). A paradigm shift in endodontic management of immature teeth: conservation of stem cells for regeneration. *Journal of Dentistry, 36*(6), 379-386.

Hudson, J., Chen, N., Song, S., Walczak, P., Jendelova, P., Sykova, E., et al. (2004). Green fluorescent protein bone marrow cells express hematopoietic and neural antigens in culture and migrate within the neonatal rat brain. *Journal of Neuroscience Research, 76*(2), 255-264.

Hui, J., Azura, M., & Lee, E. (2009). Review Article: Stem Cell Therapy in Orthopaedic Surgery: Current Status and Ethical Considerations. *Malaysian Orthopaedic Journal 3*(1), 4-12.

Hunziker, E. B. (1999). Articular cartilage repair: are the intrinsic biological constraints undermining this process insuperable? *Osteoarthritis and Cartilage, 7*(1), 15-28.

Hunziker, E. B. (2002). Articular cartilage repair: basic science and clinical progress. A review of the current status and prospects. *Osteoarthritis and Cartilage, 10*(6), 432-463.

Hurley, M. V. (1999). The role of muscle weakness in the pathogenesis of osteoarthritis. *Rheumatic Disease Clinics of North America, 25*(2), 283-298.

Hurley, M. V., Scott, D. L., Rees, J., & Newham, D. J. (1997). Sensorimotor changes and functional performance in patients with knee osteoarthritis. *Annals of the Rheumatic Diseases, 56*(11), 641-648.

Ikeda, S., Tsumura, H., & Torisu, T. (2005). Age-related quadriceps-dominant muscle atrophy and incident radiographic knee osteoarthritis. *Journal of Orthopaedic Science, 10*(2), 121-126.

Ikeda, T., Mabuchi, A., Fukuda, A., Kawakami, A., Yamada, R., Yamamoto, S., et al. (2002). Association Analysis of Single Nucleotide Polymorphisms in Cartilage Specific Collagen Genes With Knee and Hip Osteoarthritis in the Japanese Population. *Journal of Bone and Mineral Research, 17*(7), 1290-1296.

Im, G. I., Kim, D. Y., Shin, J. H., Hyun, C. W., & Cho, W. H. (2001). Repair of cartilage defect in the rabbit with cultured mesenchymal stem cells from bone marrow. *Journal of Bone and Joint Surgery-British Volume, 83*(2), 289.

Immelmann, K., & Beer, C. (1989). *A dictionary of ethology*. Cambridge: Harvard Univ. Press.

Indrawattana, N., Chen, G., Tadokoro, M., Shann, L. H., Ohgushi, H., Tateishi, T., et al. (2004). Growth factor combination for chondrogenic induction from human mesenchymal stem cell. *Biochemical and biophysical research communications, 320*(3), 914-919.

Innes, J., Costello, M., Barr, F., Rudorf, H., & Barr, A. (2004). Radiographic progression of osteoarthritis of the canine stifle joint: a prospective study. *Veterinary Radiology & Ultrasound, 45*(2), 143-148.

Iqbal, J., Dudhia, J., Bird, J. L. E., & Bayliss, M. T. (2000). Age-Related Effects of TGF-[beta] on Proteoglycan Synthesis in Equine Articular Cartilage. *Biochemical and Biophysical Research Communications, 274*(2), 467-471.

Islam, N., Haqqi, T. M., Jepsen, K. J., Kraay, M., Welter, J. F., Goldberg, V. M., et al. (2002). Hydrostatic pressure induces apoptosis in human chondrocytes from osteoarthritic cartilage through up-regulation of tumor necrosis factor-α, inducible nitric oxide synthase, p53, c-myc, and bax-α, and suppression of bcl-2. *Journal of Cellular Biochemistry, 87*(3), 266-278.

Ismail, S. N. (2001). *Clinicopathological Changes in Adjuvant Induced Arthritis in Canine Stifle Joint,* Master Thesis, Universiti Putra Malaysia.

Iyer, S. S., & Rojas, M. (2008). Anti-inflammatory effects of mesenchymal stem cells: novel concept for future therapies. *Expert Opinion on Biological Therapy*, 569-581.

Jais, A. M. M., McCulloch, R., & Croft, K. (1994). Fatty acid and amino acid composition in haruan as a potential role in wound healing. *General Pharmacology: The Vascular System, 25*(5), 947-950.

Janszky, I., Lekander, M., Blom, M., Georgiades, A., & Ahnve, S. (2005). Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease. *Brain, Behavior, and Immunity, 19*(6), 555-563.

Jefferson, R., Collins, J., Whittle, M., Radin, E., & O'Connor, J. (1990). The role of the quadriceps in controlling impulsive forces around heel strike. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 204*(1), 21-28.

Jezierski, T., Scheffler, N., Bessei, W., & Schumacher, E. (2005). Demand functions for cage size in rabbits selectively bred for high and low activity in open-field. *Applied Animal Behaviour Science, 93*(3), 323-339.

Jiang, Y., Jahagirdar, B. N., Reinhardt, R. L., Schwartz, R. E., Keene, C. D., Ortiz-Gonzalez, X. R., et al. (2002). Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature, 418*(6893), 41-49.

Jiang, Y., Vaessen, B., Lenvik, T., Blackstad, M., Reyes, M., & Verfaillie, C. M. (2002). Multipotent progenitor cells can be isolated from postnatal murine bone marrow, muscle, and brain. *Experimental Hematology, 30*(8), 896-904.

Jing, X., Yang, L., Duan, X., Xie, B., Chen, W., Li, Z., et al. (2008). In vivo MR imaging tracking of magnetic iron oxide nanoparticle labeled, engineered, autologous bone marrow mesenchymal stem cells following intra-articular injection. *Joint Bone Spine, 75*(4), 432-438.

Joanne reghonath, H. J. S., Kevin M Sales, Peter E Butler & Alexander M Seifalian. (2004). Advance Cartilage Tissue engineering: the application of stem cell technology. *Current Opinion in Biotechnology., Vol 16*, p503-509.

Johnson, D. L., Urban, W. P., Caborn, D. N. M., Vanarthos, W. J., & Carlson, C. S. (1998). Articular cartilage changes seen with magnetic resonance imaging-detected bone bruises associated with acute anterior cruciate ligament rupture. *The American Journal of Sports Medicine, 26*(3), 409.

Johnson, J. M., & Johnson, A. L. (1993). Cranial cruciate ligament rupture. Pathogenesis, diagnosis, and postoperative rehabilitation. *The Veterinary Clinics of North America. Small Animal Practice, 23*(4), 717-733.

Johnston, S. A. (1997). Osteoarthritis. Joint anatomy, physiology, and pathobiology. *The Veterinary clinics of North America. Small Animal Practice, 27*(4), 699-723.

Jones, A. C., Pattrick, M., Doherty, S., & Doherty, M. (1995). Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. *Osteoarthritis and Cartilage, 3*(4), 269-273.

Jorgensen, C., Djouad, F., Bouffi, C., Mrugala, D., & Noël, D. (2008). Multipotent mesenchymal stromal cells in articular diseases. *Best Practice and Research Clinical Rheumatology, 22*(2), 269-284.

Joy, J. E., Watson, S. J., & Benson, J. A. (1999). *Marijuana and medicine: assessing the science base*: National Academies Press. Pp. 137-192. Washington DC.

Jubb, K. A. (2007). Locomotor System. In: Maxie MG, editor. Jubb, Kennedy, and Palmer's Pathology of Domestic Animals. 5. Vol. 2. (pp. 148 -158). Edinburgh: Elsevier.

Kacena, M. A., Merrel, G. A., Konda, S. R., Wilson, K. M., Xi, Y., & Horowitz, M. C. (2001). Inflammation and bony changes at the temporomandibular joint. *Cells Tissues Organs, 169*(3), 257-264.

Kandel, R., Renlund, R., & Cheng, P. (1983). Calcium pyrophosphate dihydrate crystal deposition disease with concurrent vertebral hyperostosis in a Barbary ape. *Arthritis and Rheumatism, 26*(5), 682-687.

Karlson, E. W., Mandl, L. A., Aweh, G. N., Sangha, O., Liang, M. H., & Grodstein, F. (2003). Total hip replacement due to osteoarthritis: the importance of age, obesity, and other modifiable risk factors* 1. *The American journal of Medicine, 114*(2), 93-98.

Karp, J. M., & Leng Teo, G. S. (2009). Mesenchymal stem cell homing: the devil is in the details. *Stem Cell, 4*(3), 206-216.

Kealy, J. McAllister, 2000. *Diagnostic Radiology and Ultrasonography of the Dog and Cat. 3rd Ed, Saunders Elsevier*, 96-97.

Kemper, F., Gebhardt, U., Meng, T., & Murray, C. (2005). Tolerability and short-term effectiveness of hylan G-F 20 in 4253 patients with osteoarthritis of the knee in clinical practice. *Current Medical Research and Opinion, 21*(8), 1261-1269.

Kersten, A., Meijsser, F., & Metz, J. (1989). Effects of early handling on later open-field behaviour in rabbits. *Applied Animal Behaviour Science, 24*(2), 157-167.

Kikuchi, T., Sakuta, T., & Yamaguchi, T. (1998). Intra-articular injection of collagenase induces experimental osteoarthritis in mature rabbits. *Osteoarthritis and Cartilage, 6*(3), 177-186.

Kim, S. B., Lee, K. W., Ha, N. J., Lee, J. H., Kim, Y. D., Joe, Y. L., et al. (2008). Comparison of the Effects between Growth Hormone and Hyaluronic Acid on Degenerative Cartilage of Knee in Rabbit. *Journal of Korean Academy of Rehabilitation Medicine, 32*(3), 247-252.

Kimura, T., Yasui, N., Ohsawa, S., & Ono, K. (1984). Chondrocytes embedded in collagen gels maintain cartilage phenotype during long-term cultures. *Clinical Orthopaedics and Related Research, 186*, 231-239.

Klyushnenkova, E., Mosca, J. D., Zernetkina, V., Majumdar, M. K., Beggs, K. J., Simonetti, D. W., et al. (2005). T cell responses to allogeneic human mesenchymal stem cells: immunogenicity, tolerance, and suppression. *Journal of Biomedical Science, 12*(1), 47-57.

Knecht, S., & Vanwanseele, B. (2006). A review on the mechanical quality of articular cartilage-implications for the diagnosis of osteoarthritis. *Clinical Biomechanics, 21*(10), 999-1012.

Knight, A. O., & Levick, J.R. (1983). The Density and Distribution of Capillaries Around a Synovial Cavity. *Journal of Experimental Physiology, 68*, 629-644.

Kobayashi, K., Matsuzaka, S., Yoshida, Y., Miyauchi, S., Wada, Y., & Moriya, H. (2004). The effects of intraarticularly injected sodium hyaluronate on levels of intact aggrecan and nitric oxide in the joint fluid of patients with knee osteoarthritis. *Osteoarthritis and Cartilage, 12*(7), 536-542.

Kobayashi, k., R. Imaizumi, H. Sumichika, H. Tanaka, M. Goda, A. Fukunari & H. Komatsu. (2003). sodium iodoacetate-induced experimental osteoarthritis and associated pain model in rat. Journal of Veterinary Medical Science, (65:), 1195-1199.

Koga, H., Shimaya, M., Muneta, T., Nimura, A., Morito, T., Hayashi, M., et al. (2010). Local adherent technique for transplanting mesenchymal stem cells as a potential treatment of cartilage defect. *Arthritis Research and Therapy, 10*(4), 84.

Kopen, G. C., Prockop, D. J., & Phinney, D. G. (1999). Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. *Proceedings of the National Academy of Sciences, 96*(19), 10711-10716.

Koshino, T., Wada, S., Ara, Y., & Saito, T. (2003). Regeneration of degenerated articular cartilage after high tibial valgus osteotomy for medial compartmental osteoarthritis of the knee. *The Knee, 10*(3), 229-236.

Kotton, D. N., Ma, B. Y., Cardoso, W. V., Sanderson, E. A., Summer, R. S., Williams, M. C., et al. (2001). Bone marrow-derived cells as progenitors of lung alveolar epithelium. *Development, 128*(24), 5181-5188.

Kramer, J., Yelin, E., & Epstein, W. (1983). Social and economic impacts of four musculoskeletal conditions. *Arthritis and Rheumatism, 26*(7), 901-907.

Krampera, M., Glennie, S., Dyson, J., Scott, D., Laylor, R., Simpson, E., et al. (2003). Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. *Blood, 101*(9), 3722-3729.

Krause, D. S., Theise, N. D., Collector, M. I., Henegariu, O., Hwang, S., Gardner, R., et al. (2001). Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. *Stem Cell, 105*(3), 369-377.

Kreuz, P., Steinwachs, M., Erggelet, C., Krause, S., Konrad, G., Uhl, M., et al. (2006). Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthritis and Cartilage, 14*(11), 1119-1125.

Kuroda, R., Ishida, K., Matsumoto, T., Akisue, T., Fujioka, H., Mizuno, K., et al. (2007). Treatment of a full-thickness articular cartilage defect in the femoral condyle of an athlete with autologous bone-marrow stromal cells. *Osteoarthritis and Cartilage, 15*(2), 226-231.

Kwon, Y., Pittler, M., & Ernst, E. (2006). Acupuncture for peripheral joint osteoarthritis. *Rheumatology, 45*(11), 1331.

Kwon, Y. B., Lee, H. J., Han, H. J., Mar, W. C., Kang, S. K., Yoon, O. B., et al. (2002). The water-soluble fraction of bee venom produces antinociceptive and anti-inflammatory effects on rheumatoid arthritis in rats. *Life sciences, 71*(2), 191-204.

Langley-Hobbs, S., & Straw, M. (2005). An anatomical study with relevance to external skeletal fixator and intramedullary pin placement. *Veterinary and Comparative Orthopaedics and Traumatology Journal, 18*, 1-6.

Lanzer, W. L., & Komenda G. (1990). Changes in articular cartilage after meniscectomy. *Clinical Orthopaedics and Related Research, (252*): 41-48.

Lark, M., Bayne, E., Flanagan, J., Harper, C., Hoerrner, L., Hutchinson, N., et al. (1997). Aggrecan degradation in human cartilage. Evidence for both matrix metalloproteinase and aggrecanase activity in normal, osteoarthritic, and rheumatoid joints. *Journal of Clinical Investigation, 100*(1), 93.

Lascelles, B. D. X. (2007). Nonsteroidal anti inflammatory drugs in cats: a review. *Veterinary Anaesthesia and Analgesia, 34*(4), 228-250.

Lascelles, B. D. X. (2010). Feline degenerative joint disease. *Veterinary Surgery, 39*(1), 2-13.

Lavernia, C. J., & Guzman, J. F. (1995). Relationship of surgical volume to short-term mortality, morbidity, and hospital charges in arthroplasty. *The Journal of Arthroplasty, 10*(2), 133-140.

Lavik, E., & Langer, R. (2004). Tissue engineering: current state and perspectives. *Applied Microbiology and Biotechnology, 65*(1), 1-8.

Le Blanc, K., Rasmusson, I., Götherström, C., Seidel, C., Sundberg, B., Sundin, M., et al. (2004). Mesenchymal Stem Cells Inhibit the Expression of CD25 (Interleukin-2 Receptor) and CD38 on Phytohaemagglutinin-Activated Lymphocytes. *Scandinavian Journal of Immunology, 60*(3), 307-315.

Le Blanc, K., & Ringden, O. (2007). Immunomodulation by mesenchymal stem cells and clinical experience. *Journal of Internal Medicine, 262*(5), 509-525.

Le Blanc, K., Tammik, C., Rosendahl, K., Zetterberg, E., & Ringdén, O. (2003). HLA expression and immunologic propertiesof differentiated and undifferentiated mesenchymal stem cells. *Experimental Hematology, 31*(10), 890-896.

Le Blanc, K., Tammik, L., Sundberg, B., Haynesworth, S., & Ringden, O. (2003). Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. *Scandinavian Journal of Immunology, 57*(1), 11-20.

Leach, D., Jacobs, K., & Whittick, W. (1990). Normal arthrology. *Canine Orthopedics.* 42-58.

Leach, R. (2004). The chiropractic theories—a textbook of scientific research. 4th ed. Baltimore: Lippincott Williams and Wilkins. 207(34), 251-68.

Leach, R. E., Baumcard, S., & Broom, J. (1973). Obesity: its relationship to osteoarthritis of the knee. *Clinical Orthopaedics and Related Research, 93*, 271.

LeBlanc, A., Rowe, R., Evans, H., West, S., Shackelford, L., & Schneider, V. (1997). Muscle atrophy during long duration bed rest. *International Journal of Sports Medicine, 18*(S 4), S283-S285.

Lee, E., & Hui, J. (2006). The potential of stem cells in orthopaedic surgery. *Journal of Bone and Joint Surgery-British Volume, 88*(7), 841-853.

Lee, K. B. L., Hui, J. H. P., Song, I. C., Ardany, L., & Lee, E. H. (2007). Injectable mesenchymal stem cell therapy for large cartilage defects—a porcine model. *Stem Cells, 25*(11), 2964-2971.

Lee, S., Park, D., & Chmell, S. J. (2004). Viscosupplementation with Hylan GF 20 (Synvisc): pain and mobility observations from 74 consecutive patients. *Journal of Knee Surgery, 17*, 73-78.

Leroux, M., Cheung, H., Bau, J., Wang, J., Howell, D., & Setton, L. (2001). Altered mechanics and histomorphometry of canine tibial cartilage following joint immobilization. *Osteoarthritis and Cartilage, 9*(7), 633-640.

Leslie, I. (1994). Surgical Treatment of Osteoarthritis *In Doherty M (ed); Color Atlas and Text of Osteoarthritis* (pp. 171): Nottingham, UK. Wolfe.

Liechty, K. W., MacKenzie, T. C., Shaaban, A. F., Radu, A., Moseley, A. M. B., Deans, R., et al. (2000). Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after in utero transplantation in sheep. *Nature Medicine, 6*(11), 1282-1286.

Linch, D., Knott, L., Patterson, K., Cowan, D., & Harper, P. (1982). Bone marrow processing and cryopreservation. *Journal of Clinical Pathology, 35*(2), 186.

Lipowitz, A. J., & Newton, C. D. (1985). Degenerative joint disease and traumatic arthritis. In D. M. Nunamaker (Ed.), *Textbook of small animal orthopaedics, International Veterinary Information Service, Ithaca* (pp. 1122): J.B. Lippincott Company.

Listrat, V., Ayral, X., Patarnello, F., Bonvarlet, J. P., Simonnet, J., Amor, B., et al. (1997). Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan®) in osteoarthritis of the knee*. *Osteoarthritis and Cartilage, 5*(3), 153-160.

Lodie, T. A., Blickarz, C. E., Devarakonda, T. J., He, C., Dash, A. B., Clarke, J., et al. (2002). Systematic analysis of reportedly distinct populations of multipotent bone marrow-derived stem cells reveals a lack of distinction. *Tissue Engineering, 8*(5), 739-751.

Loeser Jr, R. (2004). Aging cartilage and osteoarthritis--what's the link? *Science of Aging Knowledge Environment: SAGE KE, 2004*(29), pe31.

Lohmander, L., Neame, P., & Sandy, J. (1993). The structure of aggrecan fragments in human synovial fluid. Evidence that aggrecanase mediates cartilage degradation in inflammatory joint disease, joint injury, and osteoarthritis. *Arthritis and Rheumatism, 36*(9), 1214-1222.

Lohmander, L. S., Dalen, N., Englund, G., Hämäläinen, M., Jensen, E., Karlsson, K., et al. (1996). Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. *Annals of the Rheumatic Diseases, 55*(7), 424-431.

Lorenz, H., & Richter, W. (2006). Osteoarthritis: Cellular and molecular changes in degenerating cartilage. *Progress in Histochemistry and Cytochemistry, 40*(3), 135-163.

Lorig, K., Konkol, L., & Gonzalez, V. (1987). Arthritis patient education: A review of the literature* 1. *Patient Education and Counseling, 10*(3), 207-252.

Lozito, T. P., & Tuan, R. S. (2011). Mesenchymal stem cells inhibit both endogenous and exogenous MMPs via secreted TIMPs. *Journal of Cellular Physiology, 226*(2), 385-396.

Luard, L. D. (2003). The Skeleton *The Anatomy and Action of the Horse* (pp. 6 - 108): Dover Pubns.

Lukoschek, M., Schaffler, M., Burr, D., Boyd, R., & Radin, E. (1988). Synovial membrane and cartilage changes in experimental osteoarthrosis. *Journal of Orthopaedic Research, 6*(4), 475-492.

Lum ZP, H. B., Mort JS, & Recklies AD. (1996). Modulation of the catabolic effects of interleukin-1 beta on human articular chondrocytes by transforming growth factor-beta. *Journal Cell Physiology*, (166), 351–359.

Lust, G., Beilman, W.T., & Dueland, S.J. (1980). Intra-articular Volume and Hip Joint Instability in Dogs with Hip Dysplasia. *American Journal Bone and Joint Surgery, 62:*, 576-582.

Ma, Y., Xu, Y., Xiao, Z., Yang, W., Zhang, C., Song, E., et al. (2006). Reconstruction of chemically burned rat corneal surface by bone marrow–derived human mesenchymal stem cells. *Stem Cells, 24*(2), 315-321.

Maccoux, L. J., Salway, F., Day, P. J. R., & Clements, D. N. (2007). Expression profiling of select cytokines in canine osteoarthritis tissues. *Veterinary Immunology and Immunopathology, 118*(1), 59-67.

Maitra, B., Szekely, E., Gjini, K., Laughlin, M., Dennis, J., Haynesworth, S., et al. (2004). Human mesenchymal stem cells support unrelated donor hematopoietic stem cells and suppress T-cell activation. *Bone Marrow Transplantation, 33*(6), 597-604.

Majumdar, M. K., Thiede, M. A., Mosca, J. D., Moorman, M., & Gerson, S. L. (1998). Phenotypic and functional comparison of cultures of marrow-derived mesenchymal stem cells (MSCs) and stromal cells. *Journal of Cellular Physiology, 176*(1), 57-66.

Malemud, C. J. (1999). Fundamental pathways in osteoarthritis: an overview. *Frontier Biosciences, 4*, d659-d661.

Malemud, C. J. (2004). Cytokines as therapeutic targets for osteoarthritis. *Biodrugs Journal, 18*(1), 23-35.

Malemud, C. J. (2010). Anticytokine therapy for osteoarthritis: evidence to date. *Drugs and Aging Journal, 27*(2), 95-115.

Malemud, C. J., Islam, N., & Haqqi, T. M. (2003). Pathophysiological mechanisms in osteoarthritis lead to novel therapeutic strategies. *Cells Tissues Organs, 174*(1-2), 34-48.

Manan Mat Jais, A. (2007). Molecular Size of the Bio-active Components from Haruan Channa striatus Extract. *Journal of Applied Sciences, 7*, 2198-2199.

Mankin, H. J., & Radin, E. (1997). Structure and function of joints. *Arthritis and Allied Conditions*, 175-191.

Manton, K. G., Corder, L. S., & Stallard, E. (1993). Estimates of change in chronic disability and institutional incidence and prevalence rates in the US elderly population from the 1982, 1984, and 1989 National Long Term Care Survey. *Journal of Gerontology, 48*(4), S153-S166.

Marion, N. W., & Mao, J. J. (2006). Mesenchymal stem cells and tissue engineering. *Methods in Enzymology, 420*, 339-361.

Martel-Pelletier, J. (2004). Pathophysiology of osteoarthritis. *Osteoarthritis and Cartilage, 12*, 31-33.

Martel-Pelletier, J., Alaaeddine, N., & Pelletier, J. P. (1999a). Cytokines and their role in the pathophysiology of osteoarthritis. *frontier biosciences, 4*, D694-703.

Martel-Pelletier, J., Boileau, C., Pelletier, J., & Roughley, P. (2008). Cartilage in normal and osteoarthritis conditions. *Best Practice and Research Clinical Rheumatology, 22*(2), 351-384.

Martel-Pelletier, J., Di Battista, J., & Lajeunesse, D. (1999b). Biochemical factors in joint articular tissue degradation in osteoarthritis. *Osteoarthritis: Clinical and Experimental Aspects. Berlin: Springer*, 156-187.

Martel-Pelletier, J., Lajeunesse, D., Reboul, P., & Pelletier, J. (2007). 2 The Role of Subchondral Bone in Osteoarthritis. *Osteoarthritis: a Companion to Rheumatology*, 15.

Martel-Pelletier, J., & Pelletier, J. P. (2003). The Cytokine Network in Osteoarthritis. *Reumatology, 19*(2), 89-92.

Martin, E. (1994). The Oxford Medical Dictionary: Oxford University Press.

Martin, G. R. (1981). Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. *Proceedings of the National Academy of Sciences, 78*(12), 7634-7638.

Martin, J. A., & Buckwalter, J. A. (2002). Aging, articular cartilage chondrocyte senescence and osteoarthritis. *Biogerontology, 3*(5), 257-264.

Mary Murphy, D. J. F., Ernst B. H., & Frank P. (2003). Stem cells therapy in a caprine model of osteoarthritis. *Arthritis and Rheumatism, 48(12)*, 3464-3474.

Masoro, E. J. (1990). Animal models in aging research. *Handbook of the Biology of Aging*, 72-94.

Mastrogiacomo, M., Cancedda, R., & Quarto, R. (2001). Effect of different growth factors on the chondrogenic potential of human bone marrow stromal cells. *Osteoarthritis and Cartilage, 9*, S36-S40.

Mat Jais, A. M., Dambisya, Y. M., & Lee, T. L. (1997). Antinociceptive activity of Channa striatus (Haruan) extracts in mice. *Journal of Ethnopharmacology, 57*(2), 125-130.

May, S. A., Mcllwraith C. W., & Trotter G. W. (1996). Animal models and other experimental system in the investigation of equine arthritis. *Joint disease in the horse. W. B. Saunders Company*, pp: 421-437.

McClain, S. A., Simon, M., Jones, E., Nandi, A., Gailit, J. O., Tonnesen, M. G., et al. (1996). Mesenchymal cell activation is the rate-limiting step of granulation tissue induction. *The American Journal of Pathology, 149*(4), 1257-1270.

McDevitt, C., Gilbertson, E., & Muir, H. (1977). An experimental model of osteoarthritis; early morphological and biochemical changes. *Journal of Bone and Joint Surgery-British Volume, 59*(1), 24.

McDougall, J. (2006). Pain and OA. . *Journal of Musculoskeletal and Neuronal Interactions, 6(4)*, 385.

Mcllwraith, C. W. (1996). General Pathology of The Joint and Response to Injury. In C. T. Mcllwraith, Trotter, G.W (Ed.), *Joint Disease in Horse* (pp. 40-69): W.B Sanuders Com.

Meijsser, F., Kersten, A., Wiepkema, P., & Metz, J. (1989). An analysis of the open-field performance of sub-adult rabbits. *Applied Animal Behaviour Science, 24*(2), 147-155.

Merali, Z., Brennan, K., Brau, P., & Anisman, H. (2003). Dissociating anorexia and anhedonia elicited by interleukin-1β: antidepressant and gender effects on responding for" free chow" and" earned" sucrose intake. *Psychopharmacology, 165*(4), 413-418.

Meyer-Carrive, I., & Ghosh, P. (1992). Effects of tiaprofenic acid (Surgam) on cartilage proteoglycans in the rabbit joint immobilisation model. *Annals of the Rheumatic Diseases, 51*(4), 448-455.

Mi, Z., Ghivizzani, S. C., Lechman, E. R., Jaffurs, D., Glorioso, J. C., Evans, C. H., et al. (2000). Adenovirus-mediated gene transfer of insulin-like growth factor 1 stimulates proteoglycan synthesis in rabbit joints. *Arthritis and Rheumatism, 43*(11), 2563-2570.

Miao, Z., Jin, J., Chen, L., Zhu, J., Huang, W., Zhao, J., et al. (2006). Isolation of mesenchymal stem cells from human placenta: comparison with human bone marrow mesenchymal stem cells. *Cell Biology International, 30*(9), 681-687.

Michael, U. V., Maloney, M. D., Goater, J. J., Søballe, K., Goldring, M. B., O'Keefe, R. J., et al. (2002). Light activated gene transduction enhances adeno associated virus vector–mediated gene expression in human articular chondrocytes. *Arthritis and Rheumatism, 46*(8), 2095-2104.

Michelle, N. Y. T., Shanti, G., & Loqman, M. (2004). Effect of orally administered Channa striatus extract against experimentally-induced osteoarthritis in rabbits. *International Journal of Applied Research in Veterinary Medicine, 2*, 171-175.

Mignatti, P., & Rifkin, D. (1999). Nonenzymatic interactions between proteinases and the cell surface: novel roles in normal and malignant cell physiology. *Advances in Cancer Research, 78*, 103-157.

Mihara, M., Higo, S., Uchiyama, Y., Tanabe, K., & Saito, K. (2007). Different effects of high molecular weight sodium hyaluronate and NSAID on the progression of the cartilage degeneration in rabbit OA model. *Osteoarthritis and Cartilage, 15*(5), 543-549.

Milgram, J. W. (1983). Morphologic Alterations of the Subchondrall Bone in Advanced Degenerative Arthritis. *Clinical Orthopaedics and Related Research, 173*, 293.

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological Psychiatry, 65*(9), 732-741.

Miller, L. E., Justen, H. P., Scholmerich, J., & Straub, R. H. (2000). The loss of sympathetic nerve fibers in the synovial tissue of patients with rheumatoid arthritis is accompanied by increased norepinephrine release from synovial macrophages. *The Journal of the Federation of American Societies for Experimental Biology, 14*(13), 2097.

Minas, T. (1999). The role of cartilage repair techniques, including chondrocyte transplantation, in focal chondral knee damage. *Instructional Course lectures, 48*, 629-643.

Moreland, L. W. (2003). Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Research and Therapy, 5*(2), 54-67.

Morgan, J. (1969). Radiological pathology and diagnosis of degenerative joint disease in the stifle joint of the dog. *Journal of Small Animal Practice, 10*(9), 541-544.

Moskowitz, R. (2006). Osteoarthritis cartilage histopathology: grading and staging. *Arthroscopy: The Journal of Arthroscopic and Related Surgery, 14*(1), 1-2.

Moskowitz, R., & Goldberg, V. (1987). Studies of osteophyte pathogenesis in experimentally induced osteoarthritis. *The Journal of Rheumatology, 14*(2), 311.

Moulharat, N., Lesur, C., Thomas, M., Rolland-Valognes, G., Pastoureau, P., Anract, P., et al. (2004). Effects of transforming growth factor-β on aggrecanase production and proteoglycan degradation by human chondrocytes in vitro. *Osteoarthritis and Cartilage, 12*(4), 296-305.

Moxley, G., Meulenbelt, I., Chapman, K., van Diujn, C., Eline Slagboom, P., Neale, M., et al. (2010). Interleukin-1 region meta-analysis with osteoarthritis phenotypes. *Osteoarthritis and Cartilage, 18*(2), 200-207.

Müller, P., Bulnheim, U., Diener, A., Lüthen, F., Teller, M., Klinkenberg, E. D., et al. (2008). Calcium phosphate surfaces promote osteogenic differentiation of mesenchymal stem cells. *Journal of Cellular and Molecular Medicine, 12*(1), 281-291.

Muirden, K. (2005). Community Oriented Program for the Control of Rheumatic Diseases: studies of rheumatic diseases in the developing world. *Current Opinion in Rheumatology, 17*(2), 153.

Muramatsu, T., Nakamura, A., & Park, H. M. (1998). Basics and Applications of Gene Transfer in Animal Cells and Tissues for Production and Therapeutics. *Journal of Mammalian Ova Research, 15*(1), 1-16.

Murphy, J. M., Dixon, K., Beck, S., Fabian, D., Feldman, A., & Barry, F. (2002). Reduced chondrogenic and adipogenic activity of mesenchymal stem cells from patients with advanced osteoarthritis. *Arthritis and Rheumatism, 46*(3), 704-713.

Murphy, J. M., Fink, D. J., Hunziker, E. B., & Barry, F. P. (2003). Stem cell therapy in a caprine model of osteoarthritis. *Arthritis and Rheumatism, 48*(12), 3464-3474.

Mustafa, Z., Chapman, K., Irven, C., Carr, A., Clipsham, K., Chitnavis, J., et al. (2000). Linkage analysis of candidate genes as susceptibility loci for osteoarthritis—suggestive linkage of COL9A1 to female hip osteoarthritis. *Rheumatology, 39*(3), 299.

Nagase, H., & Kashiwagi, M. (2003). Aggrecanases and cartilage matrix degradation. *Arthritis Research and Therapy, 5*(2), 94-103.

Nakagami H, M. R., Maeda K, Kikuchi Y, Ogihara T, & Kaneda Y. (2006). Adipose Tissue-Derived Stromal Cells as a Novel Option for Regenerative Cell Therapy. *Journal of Atherosclerosis and Thrombosis, 13*(2), 77-81.

Namiki, O., Toyoshima, H., & Morisaki, N. (1982). Therapeutic effect of intra-articular injection of high molecular weight hyaluronic acid on osteoarthritis of the knee. *International Journal of Clinical Pharmacology, Therapy, and Toxicology, 20*(11), 501-507.

Nathan, S., De, S. D., Thambyah, A., Fen, C., Goh, J., & Lee, E. H. (2003). Cell-based therapy in the repair of osteochondral defects: a novel use for adipose tissue. *Tissue Engineering, 9*(4), 733-744.

Ness, T. J. (2007). Models in pain research. Molecular Pain. *Springer Link Date*, 425-439.

Newman, P. (1971). Development of total hip replacement. *Total Hip Replacement. Jayson, M.(Editor). J.B. Lippincott*, 13-25.

Ng, M. Y. T. (2003). *Effect of Channa Striatus and Curcuma Longa in Experimentally-Induced Osteoarthritis in Rabbits,* Master Thesis, Universiti Putra Malaysia.

Nuki, G. (2002). Osteoarthritis: risk factors and pathoenesis. *Arthritis Research Campanign*, 134-141.

Nuttall, M. E. (2001). Drug discovery and target validation. *Cells Tissues Organs, 169*(3), 265-271.

Nyangoga, H., Aguado, E., Goyenvalle, E., Baslé, M. F., & Chappard, D. (2010). A non-steroidal anti-inflammatory drug (ketoprofen) does not delay [beta]-TCP bone graft healing. *Acta Biomaterialia, 6*(8), 3310-3317.

O'Driscoll, S. W. (1998). The healing and regeneration of articular cartilage. *Journal of Bone and Joint Surgery. American volume, 80*(12), 1795-1812.

O'Connell, J. X. (2000). Pathology of the synovium. *American Journal of Clinical Pathology, 114*(5), 773.

O'Regan, R. M., & Gradishar, W. (2001). Selective estrogen-receptor modulators in 2001. *Oncology, 15*(9), 1177-1194.

O'Reilly, S. C., Muir, K. R., & Doherty, M. (1999). Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial. *Annals of the Rheumatic Diseases, 58*(1), 15-19.

Olsson, S. (1971). Degenerative joint disease (osteoarthrosis): A review with special reference to the dog. *Journal of Small Animal Practice, 12*(6), 333-342.

Owens, J., & Ackerman, N. (1978). Roentgenology of arthritis. *The Veterinary Clinics of North America, 8*(3), 453.

Ozlem Nisbet, H., Ozak, A., Yardimci, C., Nisbet, C., Yarim, M., Koray Bayrak, I., et al. (2011). Evaluation of bee venom and hyaluronic acid in the intra-articular treatment of osteoarthritis in an experimental rabbit model. *Research in Veterinary Science*, 1-6.

Palmoski, M. J., & Brandt, K. D. (1982). Immobilization of the knee prevents osteoarthritis after anterior cruciate ligament transection. *Arthritis and Rheumatism, 25*(10), 1201-1208.

Papaioannou, N. A., Triantafillopoulos, I.K., Khaldi, L & Galanos, A. . (2007). Effect of calcitonin in early and late stages of experimentally induced osteoarthritis. A histomorphometric study. *Osteoarthritis and Cartilage, 15*, 386-395.

Park, R., Steyn, P., & Wrigley, R. (1996). Imaging techniques in the diagnosis of equine joint disease. *Joint Disease in the Horse. Philadelphia, WB Saunders, USA*, 145-164.

Payne, J. T., & Constantinescu, G.M. (1993). Stifle joint anatomy and surgical approaches in the dogs. *The Veterinary Clinics of North America: Small Animal Practice* (Vol. 23, pp. 691-701).

Payne, R., Hutchinson, J., Robilliard, J., Smith, N., & Wilson, A. (2005). Functional specialisation of pelvic limb anatomy in horses (Equus caballus). *Journal of Anatomy, 206*(6), 557-574.

Pease, A. P. (2000). *Novel approaches to evaluate osteoarthritis in the rabbit lateral meniscectomy model*, Master Thesis, Virginia Polytechnical Institute and State University.

Pei, M., He, F., Boyce, B., & Kish, V. (2009). Repair of full-thickness femoral condyle cartilage defects using allogeneic synovial cell-engineered tissue constructs. *Osteoarthritis and Cartilage, 17*(6), 714-722.

Pelletier, J., Martel Pelletier, J., & Abramson, S. (2001). Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. *Arthritis and Rheumatism, 44*(6), 1237-1247.

Peng, L., Jia, Z., Yin, X., Zhang, X., Liu, Y., Chen, P., et al. (2008). Comparative analysis of mesenchymal stem cells from bone marrow, cartilage, and adipose tissue. *Stem Cells and Development, 17*(4), 761-774.

Pennington, R. (1971). Biochemical aspects of muscle disease. *Advances in Clinical Chemistry, 14*, 409-451.

Percival, M. (1999). Understanding the Natural Management of Pain and Inflammation. *Clinical Nutrition Insights, Advanced Nutrition Publications, Inc*. 1-5.

Peretti, G. M., Gill, T. J., Xu, J. W., Randolph, M. A., Morse, K. R., & Zaleske, D. J. (2004). Cell-based therapy for meniscal repair. *The American Journal of Sports Medicine, 32*(1), 146-158.

Peretti, G. M., Xu, J. W., Bonassar, L. J., Kirchhoff, C. H., Yaremchuk, M. J., & Randolph, M. A. (2006). Review of injectable cartilage engineering using fibrin gel in mice and swine models. *Tissue Engineering, 12*(5), 1151-1168.

Perry, R. (1993). Principles of conventional radiography and fluoroscopy. *The Veterinary clinics of North America. Small Animal Practice, 23*(2), 235.

Peterson, M., Hollenberg, J., Szatrowski, T., Johanson, N., Mancuso, C., & Charlson, M. (1992). Geographic variations in the rates of elective total hip and knee arthroplasties among Medicare beneficiaries in the United States. *The Journal of Bone and Joint Surgery. American Volume, 74*(10), 1530-1539.

Petrella, R. J., DiSilvestro, M. D., & Hildebrand, C. (2002). Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. *Archives of Internal Medicine, 162*(3), 292.

Petsatodis, G. E., Antonarakos, P. D., Christodoulou, A. G., Pappas, L. S., & Pournaras, J. D. (2009). Cementless Total Hip Arthroplasty for Osteonecrosis of the Femoral Head After Allogenic Bone Marrow Transplantation. *The Journal of Arthroplasty, 24*(3), 414-420.

Phillips, R. H. (2001). Osteoarthritis - an overveiw. *Coping with osteoarthritis: sound, compassionate advice for people dealing with the challenges of osteoarthritis* (pp. 3-15): Avery Pub Group.

Phinney, D. G., & Prockop, D. J. (2007). Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair—current views. *Stem Cells, 25*(11), 2896-2902.

Pidd, J., Gardner, D., & Adams, M. (1988). Ultrastructural changes in the femoral condylar cartilage of mature American foxhounds following transection of the anterior cruciate ligament. *The Journal of Rheumatology, 15*(4), 663.

Pittenger, M. F., Mackay, A. M., Beck, S. C., Jaiswal, R. K., Douglas, R., Mosca, J. D., et al. (1999). Multilineage potential of adult human mesenchymal stem cells. *Science, 284*(5411), 143-147.

Pomonis, J. D., Boulet, J. M., Gottshall, S. L., Phillips, S., Sellers, R., Bunton, T., et al. (2005). Development and pharmacological characterization of a rat model of osteoarthritis pain. *Pain, 114*(3), 339-346.

Poole, C. A. (1997). Review. Articular cartilage chondrons: form, function and failure. *Journal of Anatomy, 191*(1), 1-13.

Poole, C. A., Flint, M. H., & Beaumont, B. W. (1987). Chondrons in cartilage: ultrastructural analysis of the pericellular microenvironment in adult human articular cartilages. *Journal of Orthopaedic Research, 5*(4), 509-522.

Potian, J. A., Aviv, H., Ponzio, N. M., Harrison, J. S., & Rameshwar, P. (2003). Veto-like activity of mesenchymal stem cells: functional discrimination between cellular responses to alloantigens and recall antigens. *The Journal of Immunology, 171*(7), 3426–3434.

Preston, S., Alison, M., Forbes, S., Direkze, N., Poulsom, R., & Wright, N. (2003). The new stem cell biology: something for everyone. *Molecular Pathology, 56*(2), 86.

Prisco, M., Hongo, A., Rizzo, M. G., Sacchi, A., & Baserga, R. (1997). The insulin-like growth factor I receptor as a physiologically relevant target of p53 in apoptosis caused by interleukin-3 withdrawal. *Molecular and Cellular Biology, 17*(3), 1084-1092.

Pritzker, K. (1994). Animal models for osteoarthritis: processes, problems and prospects. *Annals of the Rheumatic Diseases, 53*(6), 406-420.

Pritzker, K., Chateauvert, J., Grynpas, M., Renlund, R., Turnquist, J., & Kessler, M. (1989). Rhesus macaques as an experimental model for degenerative arthritis. *Puerto Rico Health Sciences Journal, 8*(1), 99-102.

Pritzker, K., Gay, S., Jimenez, S., Ostergaard, K., Pelletier, J. P., Revell, P., et al. (2006b). Osteoarthritis cartilage histopathology: grading and staging1, 2. *Osteoarthritis and Cartilage, 14*(1), 13-29.

Prockop, D. J. (1997). Marrow stromal cells as stem cells for nonhematopoietic tissues. *Science, 276*(5309), 71-74.

Puelacher, W., Kim, S., Vacanti, J., Schloo, B., Mooney, D., & Vacanti, C. (1994). Tissue-engineered growth of cartilage: the effect of varying the concentration of chondrocytes seeded onto synthetic polymer matrices. *International Journal of Oral and Maxillofacial Surgery, 23*(1), 49-53.

Puhl, W., Bernau, A., Greiling, H., Köpcke, W., Pförringer, W., Steck, K. J., et al. (1993). Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. *Osteoarthritis and Cartilage, 1*(4), 233-241.

Puzas, J. E., Landeau, J. M., Tallents, R., Albright, J., Schwarz, E. M., & Landesberg, R. (2001). Degradative pathways in tissues of the temporomandibular joint. *Cells Tissues Organs, 169*(3), 248-256.

Qin, L., Leung, K. S., Chan, C. W., Fu, L. K., & Rosier, R. (1999). Enlargement of remaining patella after partial patellectomy in rabbits. *Medicine and Science in Sports and Exercise, 31*(4), 502.

Radin, E. L., & Paul, I. L. (1970). Does cartilage compliance reduce skeletal impact loads?. the relative force attenuating properties of articular cartilage, synovial fluid, periarticular soft tissues and bone. *Arthritis and Rheumatism, 13*(2), 139-144.

Radin, E. L., & Rose, R. M. (1986). Role of subchondral bone in the initiation and progression of cartilage damage. *Clinical Orthopaedics and Related Research*, (213), 34.

Radin, E. L., Yang, K. H., Riegger, C., Kish, V. L., & O'Connor, J. J. (1991). Relationship between lower limb dynamics and knee joint pain. *Journal of Orthopaedic Research, 9*(3), 398-405.

Rainsford, K., Ying, C., & Smith, F. (1997). Effects of meloxicam, compared with other NSAIDs, on cartilage proteoglycan metabolism, synovial prostaglandin E2, and production of interleukins 1, 6 and 8, in human and porcine explants in organ culture. *Journal of Pharmacy and Pharmacology, 49*(10), 991-998.

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology, 27*(1), 24-31.

Rasmusson, I., Ringdén, O., Sundberg, B., & Le Blanc, K. (2003). Mesenchymal stem cells inhibit the formation of cytotoxic T lymphocytes, but not activated cytotoxic T lymphocytes or natural killer cells. *Transplantation, 76*(8), 1208-1213.

Rasmusson, I., Ringdén, O., Sundberg, B., & Le Blanc, K. (2005). Mesenchymal stem cells inhibit lymphocyte proliferation by mitogens and alloantigens by different mechanisms. *Experimental Cell Research, 305*(1), 33-41.

Ratcliffe, A., Shurety, W., & Caterson, B. (1993). The quantitation of a native chondroitin sulfate epitope in synovial fluid lavages and articular cartilage from canine experimental osteoarthritis and disuse atrophy. *Arthritis and Rheumatism, 36*(4), 543-551.

Ravaud, P., Giraudeau, B., Auleley, G., Chastang, C., Poiraudeau, S., Ayral, X., et al. (1996). Radiographic assessment of knee osteoarthritis: reproducibility and sensitivity to change. *The Journal of Rheumatology, 23*(10), 1756-1764.

Rayman, M., & Callaghan, A. (2008). Current management of osteoarthritis and rheumatoid arthritis. *Nutrition and Arthritis* (pp. 61-62): Blackwell-Wiley Online Library.

Reali, C., Scintu, F., Pillai, R., Cabras, S., Argiolu, F., Ristaldi, M. S., et al. (2006). Differentiation of human adult CD34+ stem cells into cells with a neural phenotype: role of astrocytes. *Experimental Neurology, 197*(2), 399-406.

Redman, S., Oldfield, S., & Archer, C. (2005). Current strategies for articular cartilage repair. *European Cell Materials, 9*, 23-32.

Rehman, J., Traktuev, D., Li, J., Merfeld- Clauss, S., Temm-Grove, CJ, Bovenkerk, J. E., Pell, CL, Johnstone, BH, Considine, RV, & March, KL. (2004). Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. *Circulation*, (109), 1292–1298.

Relic, B., Guicheux, J., Mezin, F., Lubberts, E., Togninalli, D., Garcia, I., et al. (2001). IL-4 and IL-13, but not IL-10, protect human synoviocytes from apoptosis. *The Journal of Immunology, 166*(4), 2775.

Resnick, D. (1988). Common disorders of synovium-lined joints: pathogenesis, imaging abnormalities, and complications. *American Journal of Roentgenology, 151*(6), 1079.

Richards, M., Fong, C. Y., Chan, W. K., Wong, P. C., & Bongso, A. (2002). Human feeders support prolonged undifferentiated growth of human inner cell masses and embryonic stem cells. *Nature Biotechnology, 20*(9), 933-936.

Richardson, J. M. (1984). Global modeling in the 1980's. In J. Richardson (Ed.) Models of reality: Shaping thought and action. Mount Airy, Maryland. Lomond Books (pp. 115-129).

Robbins, P. D., & Ghivizzani, S. C. (1998). Viral vectors for gene therapy. *Pharmacology and Therapeutics, 80*(1), 35-47.

Robinson, A. (2000). Use of a Rush pin to repair fractures of the distal femur in cats. *Veterinary Record, 146*(15), 429.

Robinson, D., Guetsky, M., Halperin, R., Schneider, D., & Nevo, Z. (2002). Articular cartilage reconstruction using xenogeneic epiphyses slices. *Cell and Tissue Banking, 3*(4), 269-277.

Rodeo, S. A. (2001). Meniscal allografts—where do we stand? *The American Journal of Sports Medicine, 29*(2), 246-261.

Rodriguez, A. M., & Vacanti, C. A. (1998). Tissue engineering of cartilage (pp. 400–409): Pergamon, Amsterdam.

Røgind, H., Bibow-Nielsen, B., Jensen, B., Møller, H. C., Frimodt-Møller, H., & Bliddal, H. (1998). The effects of a physical training program on patients with osteoarthritis of the knees. *Archives of Physical Medicine and Rehabilitation, 79*(11), 1421-1427.

Rørvik, A., & Teige, J. (1996). Unstable stifles without clinical or radiographic osteoarthritis in young goats: an experimental study. *Acta veterinaria Scandinavica, 37*(3), 265.

Rosenberg, L. C., Choi, H., Tang, L., Johnson, T., Pal, S., Webber, C., et al. (1985). Isolation of dermatan sulfate proteoglycans from mature bovine articular cartilages. *Journal of Biological Chemistry, 260*(10), 6304.

Ross. M. H., Romrell, L. J., & Kaye. G. I. (1995). Cartilage *Histology a text and atlas* (3th ed., pp. 130-149): Lippincott Williams and Wilkins.

Rydell, N., & Balazs, E. A. (1971). Effect of intra-articular injection of hyaluronic acid on the clinical symptoms of osteoarthritis and on granulation tissue formation. *Clinical Orthopaedics and Related Research, 80*, 25.

Ryu, J., Saito, S., & Yamamoto, K. (1997). Changes in articular cartilage in experimentally induced patellar subluxation. *Annals of the Rheumatic Diseases, 56*(11), 677-681.

Salasznyk, R. M., Williams, W. A., Boskey, A., Batorsky, A., & Plopper, G. E. (2004). Adhesion to vitronectin and collagen I promotes osteogenic differentiation of human mesenchymal stem cells. *Journal of Biomedicine and Biotechnology, 2004*, 24-34.

Sato, T., Konomi, K., Yamasaki, S., Aratani, S., Tsuchimochi, K., Yokouchi, M., et al. (2006). Comparative analysis of gene expression profiles in intact and damaged regions of human osteoarthritic cartilage. *Arthritis and Rheumatism, 54*(3), 808-817.

Schiavinato, A., Lini, E., Guidolin, D., et al. (1989). Intra-articular sodium hyaluronate injections in the pond-nuki experimental model of osteoarthritis in dogs. *Clinical Orthopaedics and Related Research, 241*, 286–299.

Schilke, J. M., Johnson, G. O., Housh, T. J., & O'Dell, J. R. (1996). Effects of muscle-strength training on the functional status of patients with osteoarthritis of the knee joint. *Nursing Research, 45*(2), 68.

Sedgwick, A., Willoughby, D., Dale, M., Foreman, J., & Fan, T. (1994). Animal models for testing immunopharmacological agents (pp. 279–288): Blackwell, Oxford, UK.

Sedgwick, A. D., & Edwards, J. C. W. (1994). immunopharmacology of the microcirculation. In 2 (Ed.), *Animals Models of Inflammation* (pp. pp. 190-205): San Diego, Academic Press.

Selfe, T., & Innes, K. (2009). Mind-Body Therapies and Osteoarthritis of the Knee. *Current Rheumatology Reviews, 5*(4), 204-211.

Setton LA, Mow VC, Muller FJ, Pita JC, & DS., H. (1994). Mechanical properties of canine articular cartilage are significantly altered following transection of the anterior cruciate ligament. . *Journal Orthopaedic Research, 12*, 451- 463.

Shangkai, C., Naohide, T., Koji, Y., Yasuji, H., Masaaki, N., Tomohiro, T., et al. (2007). Transplantation of allogeneic chondrocytes cultured in fibroin sponge and stirring chamber to promote cartilage regeneration. *Tissue Engineering, 13*(3), 483-492.

Shapiro, F., Koide, S., & Glimcher, M. (1993). Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. *The Journal of Bone and Joint Surgery. American Volume, 75*(4), 532-553.

Sharma, L., Pai, Y. C., Holtkamp, K., & Rymer, W. Z. (1997). Is knee joint proprioception worse in the arthritic knee versus the unaffected knee in unilateral knee osteoarthritis? *Arthritis and Rheumatism, 40*(8), 1518-1525.

Shimomura, K., Ando, W., Tateishi, K., Nansai, R., Fujie, H., Hart, D. A., et al. (2010). The influence of skeletal maturity on allogenic synovial mesenchymal stem cell-based repair of cartilage in a large animal model. *Biomaterials, 31*(31), 8004-8011.

Shin, S.-S., Leung, G. . (1986). Blood Supply of the Knee joint. Amicroangiographic Study in Childern and Adult. *Clinical Orthopaedics and Related Research, 208:*, 119-125.

Shur, I., Marom, R., Lokiec, F., Socher, R., & Benayahu, D. (2002). Identification of cultured progenitor cells from human marrow stroma. *Journal of Cellular Biochemistry, 87*(1), 51-57.

Silvestri, T., Pulsatelli, L., Dolzani, P., Facchini, A., & Meliconi, R. (2006). Elevated serum levels of soluble interleukin-4 receptor in osteoarthritis. *Osteoarthritis and Cartilage, 14*(7), 717-719.

Simmons, P. J., & Torok-Storb, B. (1991). Identification of stromal cell precursors in human bone marrow by a novel monoclonal antibody, STRO-1. *Blood, 78*(1), 55-62.

Simon, S. R. (1985). Biomechanics of The Joints. In H. E. D. In Kelly W.N., Ruddy S., Sledge C.B. (Ed.), *Textbook of Rhematology* (Vol. 1., pp. 317-336): Philadelphia, WB Saunders.

Simpkin, P. A. (1993). Synovial Physiology. In K. W. J. In McCarty D.J. (Ed.), *Arthritis and Allied Conditions, A Textbook of Rheumatology* (Vol. 1, pp. 199-212): Philadelphia, Lea & Febiger.

Sledge, C., Reddi, A., Walsh, D., & Blake, D. (2001). Biology of the normal joint. *Kelley's textbook of rheumatology. 6th ed. Philadelphia: WB Saunders*, 9-13.

Slemenda, C., Brandt, K. D., Heilman, D. K., Mazzuca, S., Braunstein, E. M., Katz, B. P., et al. (1997). Quadriceps weakness and osteoarthritis of the knee. *Annals of Internal Medicine, 127*(2), 97-104.

Slemenda, C., Heilman, D. K., Brandt, K. D., Katz, B. P., Mazzuca, S. A., Braunstein, E. M., et al. (1998). Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? *Arthritis and Rheumatism, 41*(11), 1951-1959.

Smith, H. A., Jones, T.C., Hunt, R.D. (1974). Veterinary Pathology. Text book of Pathology. (pp. 1072-1083).

Smith Jr, G. N., Myers, S. L., Brandt, K. D., & Mickler, E. A. (1998). Effect of intraarticular hyaluronan injection in experimental canine osteoarthritis. *Arthritis and Rheumatism, 41*(6), 976-985.

Snibbe, J. C., & Gambardella, R. A. (2005). Use of injections for osteoarthritis in joints and sports activity. *Clinics in Sports Medicine, 24*(1), 83-91.

Snyderman, R. (1986). Mechanisms of inflammation and leukocyte chemotaxis in the rheumatic diseases. *The Medical clinics of North America, 70*(2), 217.

Sokoloff, L. (1960). Comparative pathology of arthritis. *Advances in Veterinary Science, 6*, 193-250.

Solchaga, L. A., Dennis, J. E., Goldberg, V. M., & Caplan, A. I. (1999). Hyaluronic acid-based polymers as cell carriers for tissue-engineered repair of bone and cartilage. *Journal of Orthopaedic Research, 17*(2), 205-213.

Somchit, M. N., Solihah, M. H., Israf, D. A., Zuraini, A., Arifah, A. K., & Mat Jais, A. M. (2009). Effects of three local Malaysian Chauna spp. fish on chronic inflammation. *Oriental Pharmacy and Experimental Medicine, 4*(2), 91-94.

Sommer, O. J., Kladosek, A., Weiler, V., Czembirek, H., Boeck, M., & Stiskal, M. (2005). Rheumatoid Arthritis: A Practical Guide to State-of-the-Art Imaging, Image Interpretation, and Clinical Implications1. *Radiographics, 25*(2), 381.

Sordi, V., Malosio, M. L., Marchesi, F., Mercalli, A., Melzi, R., Giordano, T., et al. (2005). Bone marrow mesenchymal stem cells express a restricted set of functionally active chemokine receptors capable of promoting migration to pancreatic islets. *Blood, 106*(2), 419-427.

Spector, T. D., & MacGregor, A. J. (2004). Risk factors for osteoarthritis: genetics1. *Osteoarthritis and Cartilage, 12*, 39-44.

Speer, D. P., Chvapil, M., Vorz, R. G., & Holmes, M. D. (1979). Enhancement of healing in osteochondral defects by collagen sponge implants. *Clinical Orthopaedics and Related Research, 144*, 326-335.

Standring S., H. E., David H. (2005). *Gray's anatomy: the anatomical basis of clinical practice* (39th ed.): St. Louis, Mo: Elsevier Churchill Livingstone.

Steadman, J. R., Rodkey, W. G., & Rodrigo, J. J. (2001). Microfracture: surgical technique and rehabilitation to treat chondral defects. *Clinical Orthopaedics and Related Research, 391*, S362-S369.

Steadman, J. R., Rodkey, W. G., Singleton, S. B., & Briggs, K. K. (1997). Microfracture technique forfull-thickness chondral defects: Technique and clinical results. *Operative Techniques in Orthopaedics, 7*(4), 300-304.

Stein B., A. C. (2006). Patellofemoral Disorders. *Sports Medicine*, 391-415.

Stock, U. A., & Vacanti, J. P. (2001). Tissue engineering: current state and prospects. *Annual Review of Medicine, 52*(1), 443-451.

Stockwell, R. (1987). Structure and function of the chondrocyte under mechanical stress. *Joint loading: biology and health of articular structures*, 126–148.

Stockwell, R. A. (1979). *Biology of cartilage cells* (Vol. 7): 31-45. Cambridge Univ Press.

Suarez, S. D., & Gallup, G. G. (1981). An ethological analysis of open-field behavior in rats and mice. *Learning and Motivation, 12*(3), 342-363.

Suh, J. K. F., Youn, I., & Fu, F. H. (2001). An in situ calibration of an ultrasound transducer a potential application for an ultrasonic indentation test of articular cartilage. *Journal of Biomechanics, 34*(10), 1347-1353.

Sun, Y., Cheung, J. M., Martel-Pelletier, J., Pelletier, J. P., Wenger, L., Altman, R. D., et al. (2000). Wild type and mutant p53 differentially regulate the gene expression of human collagenase-3 (hMMP-13). *Journal of Biological Chemistry, 275*(15), 11327-11332.

Sutton, S., Clutterbuck, A., Harris, P., Gent, T., Freeman, S., Foster, N., et al. (2009). The contribution of the synovium, synovial derived inflammatory cytokines and neuropeptides to the pathogenesis of osteoarthritis. *The Veterinary Journal, 179*(1), 10-24.

Tanaka, T., Shimizu, M., Kohno, H., Yoshitani, S., Tsukio, Y., Murakami, A., et al. (2001). Chemoprevention of azoxymethane-induced rat aberrant crypt foci by dietary zerumbone isolated from Zingiber zerumbet. *Life Sciences, 69*(16), 1935-1945.

Taylor, R., Zacher, J., Altman, R., Bellamy, N., Brühlmann, P., Da Silva, J., Huskisson, E. (2008). Topical diclofenac and its role in pain and inflammation: An evidence-based review. *Current Medical Research and Opinion®, 24*(4), 925-950.

Temenoff, J. S., & Mikos, A. G. (2000). Review: tissue engineering for regeneration of articular cartilage. *Biomaterials, 21*(5), 431-440.

Thompson K, M. M., Jubb, Kennedy, & Palmer's. (2007). Degenerative disease of joints in Pathology of domestic animal. *Elsevier Saunders*, Pp:148 - 158.

Thomson, J. A., Itskovitz-Eldor, J., Shapiro, S. S., Waknitz, M. A., Swiergiel, J. J., Marshall, V. S., et al. (1998). Embryonic stem cell lines derived from human blastocysts. *Science, 282*(5391), 1145-1147.

Thomson, R., Wake, M., Yaszemski, M., & Mikos, A. (1995). Biodegradable polymer scaffolds to regenerate organs. *Biopolymers Ii*, 245-274.

Todhunter, R., & Lust, G. (1990). Pathophysiology of synovitis: clinical signs and examination in horses. *The Compendium on continuing education for the practicing veterinarian (USA)*. 12: 980-992.

Todhunter, R. J. (1996). Anatomy and Physiology of Synovial joints *In Joint Disease in Horse* (pp. 1-28): Saunders Company.

Toghraie, F., Chenari, N., Gholipour, M., Faghih, Z., Torabinejad, S., Dehghani, S., et al. (2011). Treatment of osteoarthritis with infrapatellar fat pad derived mesenchymal stem cells in Rabbit. *The Knee, 18*(2), 71-75.

Toh, E., Prasad, P., & Teanby, D. (2002). Correlating the efficacy of knee viscosupplementation with osteoarthritic changes on roentgenological examination. *The Knee, 9*(4), 321-330.

Toma, C., Pittenger, M. F., Cahill, K. S., Byrne, B. J., & Kessler, P. D. (2002). Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. *Circulation, 105*(1), 93-98.

Tong, C. K., Vellasamy, S., Chong Tan, B., Abdullah, M., Vidyadaran, S., Fong Seow, H., et al. (2011). Generation of mesenchymal stem cell from human umbilical cord tissue using a combination enzymatic and mechanical disassociation method. *Cell Biology International, 35*(3), 221-226.

Tosun, N., Ug˘ras, S., & Akpınar, F. (1997). The effect of intra-articular exogenous hyaluronic acid injection on the healing of traumatic cartilage damage An experimental study on rabbits. *The Journal of Bone and Joint Surgery, 3*, 96–98.

Trostel, C. T., McLaughlin, R. M., & Pool, R. R. (2002). Canine lameness caused by developmental orthopedic diseases: Osteochondrosis. *Compendium, 24*, 836-854.

Trotter, G. W., Yovich, J. V., McIlwraith, C., & Norrdin, R. W. (1989). Effects of intramuscular polysulfated glycosaminoglycan on chemical and physical defects in equine articular cartilage. *Canadian Journal of Veterinary Research, 53*(2), 224.

Troyer, H. (1982). Experimental models of osteoarthritis: a review. *Arthritis and Rheumatism, 11*(3), 362-374.

Tsai, M. S., Lee, J.L., Chang, Y.J. & Hwang, S.M. . (2004). Isolation of human multipotent mesenchymal stem cells from second-trimester amniotic fluid using a novel two-stage culture protocol. *Human Reproduction, 19:* 1450–1456.

Tschope, C., Miteva, K., Schultheiss, H. P., & Van Linthout, S. (2011). Mesenchymal Stromal Cells: A Promising Cell Source for the Treatment of Inflammatory Cardiomyopathy. *Current Pharmaceutical Design, 17*(30), 3295-3307.

Tse, W. T., Pendleton, J. D., Beyer, W. M., Egalka, M. C., & Guinan, E. C. (2003a). Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. *Transplantation, 75*(3), 389–397.

Tse, W. T., Pendleton, J. D., Beyer, W. M., Egalka, M. C., & Guinan, E. C. (2003b). Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. *Transplantation, 75*(3), 389-397.

Tuli, R., Seghatoleslami, M. R., Tuli, S., Wang, M. L., Hozack, W. J., Manner, P. A., et al. (2003). A simple, high-yield method for obtaining multipotential mesenchymal progenitor cells from trabecular bone. *Molecular Biotechnology, 23*(1), 37-49.

Uccelli, A., Moretta, L., & Pistoia, V. (2008). Mesenchymal stem cells in health and disease. *Nature Reviews Immunology, 8*(9), 726-736.

Unden, A., Andréasson, A., Elofsson, S., Brismar, K., Mathsson, L., Ronnelid, J., et al. (2007). Inflammatory cytokines, behaviour and age as determinants of self-rated health in women. *Clinical Science, 112*, 363-373.

Updike, S. J., & Diesem, C.D. (1980). Vascular Supply of The Equine Stifle Joint. *American Journal of Veterinary Research, 11:*, 362-374.

Urso, M., Clarkson, P., & Price, T. (2006). Immobilization effects in young and older adults. *European Journal of Applied Physiology, 96*(5), 564-571.

Vacanti, C., & Vacanti, J. (1997). Bone and cartilage reconstruction. *Principles of Tissue Engineering. RG Landes Company., Austin, Texas, USA*, (pp. 619-631).

Vachon, A., Bramlage, L., Gabel, A., & Weisbrode, S. (1986). Evaluation of the repair process of cartilage defects of the equine third carpal bone with and without subchondral bone perforation. *American Journal of Veterinary Research, 47*(12), 2637 - 2645.

Vegad, J. L., Katiyar, A. K. . (2004). Textbook of Veterinary Systemic Pathology (pp. 439-445).

Venn, G., Billingham, M., & Hardingham, T. (1995). Increased proteoglycan synthesis in cartilage in experimental canine osteoarthritis does not reflect a permanent change in chondrocyte phenotype. *Arthritis and Rheumatism, 38*(4), 525-532.

Venn, M. (1979). Chemical composition of human femoral and head cartilage: influence of topographical position and fibrillation. *Annals of the Rheumatic Diseases, 38*(1), 57.

Vernal, R., Velásquez, E., Gamonal, J., Garcia-Sanz, J. A., Silva, A., & Sanz, M. (2008). Expression of proinflammatory cytokines in osteoarthritis of the temporomandibular joint. *Archives of Oral Biology, 53*(10), 910-915.

Verwer, C. M., van Amerongen, G., van den Bos, R., & Hendriksen, C. F. M. (2009). Handling effects on body weight and behaviour of group-housed male rabbits in a laboratory setting. *Applied Animal Behaviour Science, 117*(1-2), 93-102.

Vignon, E., Bejui, J., Mathieu, P., Hartmann, J., Ville, G., Evreux, J., et al. (1987). Histological cartilage changes in a rabbit model of osteoarthritis. *The Journal of Rheumatology, 14*, 104 - 106.

von Schroeder, H. P., Kwan, M., Amiel, D., & Coutts, R. D. (1991). The use of polylactic acid matrix and periosteal grafts for the reconstruction of rabbit knee articular defects. *Journal of Biomedical Materials Research, 25*(3), 329-339.

Vuolteenaho, K., Moilanen, T., Knowles, R., & Moilanen, E. (2007). The role of nitric oxide in osteoarthritis. *Scandinavian Journal of Rheumatology, 36*(4), 247-258.

Wagner, W., Wein, F., Seckinger, A., Frankhauser, M., Wirkner, U., Krause, U., et al. (2005). Comparative characteristics of mesenchymal stem cells from human bone marrow, adipose tissue, and umbilical cord blood. *Experimental Hematology, 33*(11), 1402-1416.

Wakitani, S., Goto, T., Pineda, S. J., Young, R. G., Mansour, J. M., Caplan, A. I., et al. (1994). Mesenchymal cell-based repair of large, full-thickness defects of articular cartilage. *The Journal of Bone and Joint Surgery. American Volume, 76*(4), 579-592.

Wakitani, S., Goto, T., Young, R. G., Mansour, J. M., Goldberg, V. M., & Caplan, A. I. (1998). Repair of large full-thickness articular cartilage defects with allograft articular chondrocytes embedded in a collagen gel. *Tissue Engineering, 4*(4), 429-444.

Wakitani, S., Imoto, K., Yamamoto, T., Saito, M., Murata, N., & Yoneda, M. (2002). Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. *Osteoarthritis and Cartilage, 10*(3), 199-206.

Wakitani, S., Mitsuoka, T., Nakamura, N., Toritsuka, Y., Nakamura, Y., & Horibe, S. (2004). Autologous bone marrow stromal cell transplantation for repair of full-thickness articular cartilage defects in human patellae: two case reports. *Cell Transplantation, 13*(5), 595-600.

Walsh, D., Sledge, C., & Blanke, D. (2008). Biology of the normal joint. *Textbook of Rheumatology, 1*, 1-26.

Wang, C. T., Lin, J., Chang, C. J., Lin, Y. T., & Hou, S. M. (2004). Therapeutic Effects of Hyaluronic Acid on Osteoarthritis of the KneeA Meta-Analysis of Randomized Controlled Trials. *The Journal of Bone and Joint Surgery (American), 86*(3), 538-545.

Watt, F. M., & Hogan, B. L. (2000). Out of Eden: stem cells and their niches. *Science, 287*(5457), 1427-1430.

Watt, I. (1994). Radiology and imaging. *Osteoarthritis, a colour atlas and text. Wolfe Medical Imaging, London*, 85-114.

Webb, G. R., Westacott, C. I., & Elson, C. J. (1997). Chondrocyte tumor necrosis factor receptors and focal loss of cartilage in osteoarthritis. *Osteoarthritis and Cartilage, 5*(6), 427-437.

Wei, O. Y., Xavier, R., & Marimuthu, K. (2010). Screening of antibacterial activity of mucus extract of snakehead fish, Channa striatus (Bloch). *European Review for Medical and Pharmacological Sciences, 14*(8), 675-681.

Weissmann, G., Pras, M., & Rosenberg, L. (1967). Arthritis induced by filipin in rabbits. *Arthritis and Rheumatism, 10*(4), 325-336.

Wessler, S. L. (1976). Animal model of thrombosis and hemorrhagic disease (2nd ed.): USA. Department of Health, Education, and Welfare. Publications. Pp. 76-982.

West, S. G. (2002). Final secrets- complementary and alternative medicine, *rheumatology secrets* (pp. 647-653): Elsevier Health Sciences.

Westacott, C. I., & Sharif, M. (1996). Cytokines in osteoarthritis: mediators or markers of joint destruction. Seminars in Arthritis and Rheumatism, *25*(4), 254-272.

Westminster, C., Westminister, C., Vail, C., & Busse, D. (2008). Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. *Pain Physician, 11*(3), 343-353.

Wexler, S. A., Donaldson, C., Denning-Kendall, P., Rice, C., Bradley, B., & Hows, J. M. (2003). Adult bone marrow is a rich source of human mesenchymal 'stem'cells but umbilical cord and mobilized adult blood are not. *British Journal of Haematology, 121*(2), 368-374.

Whittick, W., & Simpson, S. (1990). Examination of the orthopedic patient. *Canine Orthopedics.*, 61-95.

Widmer, W. R., Buckwalter, K. A., Braunstein, E. M., Hill, M. A., O'Connor, B. L., & Visco, D. M. (1994). Radiographic and magnetic resonance imaging of the stifle joint in experimental osteoarthritis of dogs. *Veterinary Radiology and Ultrasound, 35*(5), 371-384.

Williams, A., Newell, R.L., & Patricia, S.S. (2005). Pelvic Gridle and lower limb *Gray's Anatomy " The Anatomy Basis of Clinical Practice"* (39th ed., pp. 1474 - 1487).

Williams, J. M., & Brandt, K. D. (1984). Exercise increases osteophyte formation and diminishes fibrillation following chemically induced articular cartilage injury. *Journal of Anatomy, 139*(Pt 4), 599.

Williams, J. M., & Brandt, K. D. (1985). Triamcinolone hexacetonide protects against fibrillation and osteophyte formation following chemically induced articular cartilage damage. *Arthritis and Rheumatism, 28*(11), 1267-1274.

Williams, V. S. (2007). Intraarticular hyaluronic acid supplementation in the horse: The role of molecular weight. *Journal of Equine Veterinary Science, 27*(7), 298-303.

Wirth, C. J., & Rudert, M. (1996). Techniques of cartilage growth enhancement: a review of the literature. *Arthroscopy: The Journal of Arthroscopic and Related Surgery, 12*(3), 300-308.

Wluka, A. E., Cicuttini, F. M., & Spector, T. D. (2000). Menopause, oestrogens and arthritis. *Maturitas, 35*(3), 183-199.

Wolfe, F., Smythe, H., Yunus, M., Bennett, R., Bombardier, C., Goldenberg, D., et al. (1990). The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis and Rheumatism, 33*(2), 160-172.

Woolf, A., & Pfleger, B. (2003). Burden of major musculoskeletal conditions. *Bulletin of the World Health Organization, 81*, 646-656.

Wu, J., Herzog, W., & Epstein, M. (2000). Joint contact mechanics in the early stages of osteoarthritis. *Medical engineering and physics, 22*(1), 1-12.

Wu, P., Tarasenko, Y. I., Gu, Y., Huang, L. Y. M., Coggeshall, R. E., & Yu, Y. (2002). Region-specific generation of cholinergic neurons from fetal human neural stem cells grafted in adult rat. *Nature Neuroscience, 5*(12), 1271-1278.

Xie, T., Guo, S., Zhang, J., Chen, Z., & Peavy, G. (2006). Determination of characteristics of degenerative joint disease using optical coherence tomography and polarization sensitive optical coherence tomography. *Lasers in Surgery and Medicine, 38*(9), 852-865.

Yagi, R., McBurney, D., Laverty, D., Weiner, S., & Horton Jr, W. E. (2005). Intrajoint comparisons of gene expression patterns in human osteoarthritis suggest a change in chondrocyte phenotype. *Journal of Orthopaedic Research, 23*(5), 1128-1138.

Yang, Y. G. (2004). *Application of xenogeneic stem cells for induction of transplantation tolerance: present state and future directions*. *Springer Seminars in Immunopathology*, 26(1-2):187-200

Ye, J., Yao, K., & Kim, J. (2005). Mesenchymal stem cell transplantation in a rabbit corneal alkali burn model: engraftment and involvement in wound healing. *Eye, 20*(4), 482-490.

Yeh, T. T., Wen, Z. H., Lee, H. S., Lee, C. H., Yang, Z., Jean, Y. H., et al. (2008). Intra-articular injection of collagenase induced experimental osteoarthritis of the lumbar facet joint in rats. *European Spine Journal, 17*(5), 734-742.

Young, A. A., Smith, M. M., Smith, S. M., Cake, M. A., Ghosh, P., Read, R. A., et al. (2005). Regional assessment of articular cartilage gene expression and small proteoglycan metabolism in an animal model of osteoarthritis. *Arthritis Research Therapy, 7*(4), R852-R861.

Young. B, L. J. S., Stevens A, & Heath J. W. (2006). Skeletal tissue *Wheater's Functional Histology A text and colour atlas* (5th ed., pp. 186-206): Churchill Livingstone Elsevier.

Yovich, J., Trotter, G., McIlwraith, C., & Norrdin, R. (1987). Effects of polysulfated glycosaminoglycan on chemical and physical defects in equine articular cartilage. *American Journal of Veterinary Research, 48*(9), 1407.

Zakaria, Z., Somehit, M., Sulaiman, M., & Universiti Putra Malaysia, S. (2004). Preliminary investigation on the antinociceptive properties of haruan (Channa striatus) fillet extracted with various solvent systems. *Pakistan Journal of Biological Sciences, 7(10), 1706-1710*.

Zeb, S., & Edwards, L. (1998). Osteoarthritis: nonpharmacologic therapy. *Clinical Review Journal*, 14–17.

Zhao, L. R., Duan, W. M., Reyes, M., Keene, C. D., Verfaillie, C. M., & Low, W. C. (2002). Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. *Experimental Neurology, 174*(1), 11-20.

Zhou, G., Liu, W., Cui, L., Wang, X., Liu, T., & Cao, Y. (2006). Repair of porcine articular osteochondral defects in non-weightbearing areas with autologous bone marrow stromal cells. *Tissue Engineering, 12*(11), 3209-3221.

Zwingmann, J., Mehlhorn, A. T., Südkamp, N., Stark, B., Dauner, M., & Schmal, H. (2007). Chondrogenic differentiation of human articular chondrocytes differs in biodegradable PGA/PLA scaffolds. *Tissue Engineering, 13*(9), 2335-2343.