MSCs: the New Medicine.

Regenerative Medicine

ARNOLD I. CAPLAN, PhD
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Case Western Reserve University
Cleveland, Ohio
Disclosure Information:

1. Osiris Therapuetic, Inc. :
   Former Officer and Founder
   *Current status: NO association or equity; receive royalties thru CWRU.*

2. Consulting Service :
   Provide advice globally within the Regenerative Medicine space.
How Stem Cells Are Changing the Way We Think About Disease

BY ALICE PARK

TREATING DISEASE IS ABOUT FIXING BROKEN PARTS—about replacing cells that no longer work as they should, repairing tissues that falter and boosting systems that fail. But curing disease is a different matter. To cure disease, you have to do all of that and more. You have to remove the pathological cause of the problem and to ensure that it doesn’t return. This requires teasing out where rogue cells went wrong and finding a way to nurture healthier ones to replace them.

That’s where the promise of stem cells lies. As the mother cells of every tissue in the body, they are the biological ore from which the body emerges. All cells can trace their provenance to a stem cell, to the embryo and the first days after fertilization when such cells form. It’s now possible to grow stem cells in a lab, not just from embryonic tissue but also by turning back the clock on an already developed cell like one from the skin, bypassing the embryo altogether with four important fountain-of-youth genes that rework the skin cell’s DNA machinery and make it stemlike again.

These biological wonders are transforming the way we treat disease as well as how we think about unhealthy states and even

MSCs: The New Medicine
Regenerative Medicine:

Stem Cells

PRP
2013: Before the start of the season, Kobe (34 yrs old) had amassed more than 48,000 minutes of playing time in the NBA, placing him 16th on the all time most active list.
The Injury Response Cascade

ADULT

Inflammation

“Regeneration”

Fibrosis

Acute Injury

Scar Complete

Magnitude

Time
The Injury Response Cascade

Inflammation

"Regeneration"

Magnitude

Acute Injury

Scarless Regeneration
The Injury Response Cascade

- **Acute Injury**
  - IL-1α, IL-1β, TNF-α, IFN-γ, MCP-1, TGF-β...
  - IL-6, MMP-7, VEGF, BDNF, Endothelin, Angiogenin...

- **Scarless Regeneration**
  - FGFs, TGF-β3, Type 1 Collagen, HA...

- **hMSC Rx**

Magnitude
Regenerative Medicine

- Engineering of tissue in vitro for subsequent implantation in vivo, or
- Regeneration of tissue directly in vivo.

Innate Regen. Potential for the purpose of repairing, replacing, maintaining, or enhancing organ function that has been lost due to congenital abnormalities, injury, disease, or aging.
Every second, 15 million blood cells expire and are replaced in the human body.
Adult Bone Marrow

Hematopoietic Stem Cell

HSC

MSC

MESENCHYMAL STEM CELLS

ALL BLOOD CELLS
MSC

Reproductive Medicine

1988
CURRENT HYPOTHESIS:

MSCs

“Mesenchymal Stem Cells”
and
Regenerative Medicine.
Pericytes: cells on capillaries and microvessels.

ALL MSCs are PERICYTES!

modified by
BRUNO PEault
from
http://www.geocities.co.jp/HeartLand-Suzuran/9389/kekkan
PROPOSED SEQUENCE OF CHANGE DUE TO INJURY:

INJURY → PERICYTE → MSC → ACTIVATED MSC → REGENERATIVE MSC
natural INJURY RESPONSE

IMMUNOMODULATORY

Trophic

Anti-Apoptotic

Anti-Scarring

Angiogenic

Mitotic

Regenerative Micro-environment

MSC = pericyte

T-cells, B-cells, Dendritic cells, T-regs, etc
MSC = Medicinal Signaling Cell.
(the injury-specific DRUG STORE)
PROLIFERATION: Female versus Male marrow donor MSCs.

Fetal Calf Serum = ESTROGEN.
Disease Models (rodent) for Adult MSC Cell-Therapy at CWRU:

- Miller: MS, mechanism and cure.
- Bonfield: CF-Knockout and antibiotic proteins.
- Hijaz: Urinary Incontinence.
- Penn: Acute MI and SDF-1.
- Bonfield: Asthma, acute & chronic.
- Correa: Metastases. MSC the Gatekeeper.
- Dennis: IBD; osteoporosis and complement.
MSC/Perivascular Niche, Homing, and Serial Transplantation.

**In Vivo – Injury model**

- Infusion

1 hour, Day 2, Day 7, Day 21

- Local injury
  - Radiation

Intra-arterial Infusion of transduced MSCs (BMC9)

Non irradiated

Irradiated

ab-luciferase IHC

MSC-based Therapies:

MSCs dock at sites of broken or inflamed blood vessels.

*MSC-action*: An Immuno-component. A Regenerative component.
425+ MSC-CLINICAL TRIALS, 10-2014:

4636 Studies for “Stem Cells”
Clinical Conditions for MSC-therapy: ~25% autologous.

Ulcerative Colitis, Diabetes Mellitus, Type 1, Liver Cirrhosis, Nonunion Fractures, Diabetic Foot, Critical Limb Ischemia, Dilated Cardiomyopathy, Autoimmune Diseases; Nervous System Diseases; Immune System Diseases; Demyelinating Diseases; Nervous System Diseases; Demyelinating Autoimmune Diseases, CNS; Autoimmune Diseases of the Nervous System (MS), Sjogren's Syndrome, Graft Versus Host Disease; Chronic and Expanded Graft Versus Host Disease, Middle Cerebral Artery Infarction, Osteoarthritis, Aplastic Anemia, Maxillary Cyst; Bone Loss of Substance, Spinal Cord Injury, Parkinson's Disease, Crohn's Disease, Acute Myocardial Infarction, Multiple Sclerosis, Hematological Malignancies, Organ Transplantation, Ischemia; Stroke, Systemic Sclerosis, Chronic Allograft Nephropathy, Degenerative Arthritis; Chondral Defects; Osteochondral Defects, Progressive Multiple Sclerosis; Neuromyelitis Optica, Primary Biliary Cirrhosis, Osteonecrosis of the Femoral Head, Penum Chest Surgery for Programmes Coronary Bypass, Lupus Nephritis, Wilson's Disease, Multiple System Atrophy, Burns, Intervertebral Disc Disease, Lower Back Pain; Articular Cartilage Lesion of the Femoral Condyle, Osteoporotic Fractures, Bone Neoplasms, Solid Tumors; Acute Kidney Injury, Cerebellar Ataxia, Primary Disease, Autism, Limbus Corneae Insufficiency Syndrome, Wound Healing, Dementia of the Alzheimer's Type, Myelodysplastic Syndrome, ST-Elevation Myocardial Infarction, Pulmonary Disease, Chronic Obstructive; Pulmonary Emphysema; Chronic Bronchiitis, Lower Back Pain; Disc Degeneration, Plantar Fasciitis, Bursitis, Achilles Tendinitis, Achilles Tendon Rupture, Plantar Fasciitis, Achilles Tendinitis, Achilles Tendon Rupture; AMI, Chronic Heart Failure; Atherosclerosis, Multivessel Coronary Artery Disease, Osteogenesis Imperfecta, Emphysema, Progressive Hemifacial Atrophy; Romberg's Disease, Complex Perianal Fistula, Multiple Trauma, Osteodysplasia, Tibiotalar Arthrodesis; Subtalar Arthrodesis; Calcaneocuboid Arthrodesis, Talonavicular Arthrodesis, Double Arthrodesis (i.e. Calcaneocuboid and Talonavicular); Triple Arthrodesis (i.e. Subtalar, Calcaneocuboid, and Talonavicular), Recto-vaginal Fistula, Peripheral Vascular Diseases, Prostate Cancer; Erectile Dysfunction, Diabetic Wounds; Venous Stasis Wounds, Ovarian Cancer; Sarcoma; Small Intestine Cancer.
Cystic Fibrosis

- Known to be inherited in an autosomal recessive pattern, located on chromosome 7.
- Gene defect is in the cystic fibrosis transmembrane conductance regulator (CFTR).
- Mutations in the gene result in dysfunction of the epithelia resulting in inefficient sodium and chloride transport.
Cystic Fibrosis (CF)

- *Lung* disease is the major cause of morbidity and mortality in CF.
- Airway inflammation plays a central role in the progression of CF lung disease.
- CF has been characterized as a perpetuating cycle involving airway obstruction, chronic bacterial infection and robust inflammatory response.
Knock-out mCF Gene:

- Wild type mice + *P. aeruginosa* = most alive at day 7.
- CF Knock-out + *P. aeruginosa* = all dead by day 7.
- **CF Knock-out + P. aeruginosa + (day 2) hMSCs** = 70% alive at day 7.
Antibacterial Effects of hMSCs

- The human cathelicidin antimicrobial peptide, hCAP-18/LL37, is secreted by hMSCs.
- In vivo hMSCs effect sepsis induced by bacterial infection.
INNATE MSC FUNCTIONS:

- **ANTI-MICROBIAL**
  - Anti-Scarring
  - Anti-Apoptotic
  - Angiogenic
  - Mitogenic
  - IL-6, IL-8, IL-10, IL-1RA, PGE2, IDO, TGF-β1, HGF, TSG-6, STNF-R, NO, sHLA-G5
  - LL-37, IDO

- **IMMUNOMODULATORY**
  - Anti-Apoptotic
  - Angiogenic
  - Mitogenic
  - IL-6, IL-8, IL-10, IL-1RA, PGE2, IDO, TGF-β1, HGF, TSG-6, STNF-R, NO, sHLA-G5

- **TROPHIC**
  - Anti-Scarring
  - Angiogenic
  - Mitogenic
  - IL-6, IL-8, IL-10, IL-1RA, PGE2, IDO, TGF-β1, HGF, TSG-6, STNF-R, NO, sHLA-G5
  - LL-37, IDO

- **REGENERATIVE MICROENVIRONMENT**
  - Anti-Apoptotic
  - Angiogenic
  - Mitogenic
  - IL-6, IL-8, IL-10, IL-1RA, PGE2, IDO, TGF-β1, HGF, TSG-6, STNF-R, NO, sHLA-G5
  - LL-37, IDO
The Businesses of Regenerative Medicine
MSCs and OA
Adult Human Mesenchymal Stem Cells (MSCs) Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy: A Randomized, Double-Blind, Controlled Study.

C. Thomas Vangsness, Jr., MD1; Jack Farr, II, MD2; Joel Boyd, MD3; David T. Dellaero, MD4; C. Randal Mills, PhD5; Michelle LeRoux-Williams, PhD5


Methods: 55 patients at 7 institutions underwent a partial medial meniscectomy. A single superolateral knee injection was given within 7 to 10 days after the meniscectomy. Patients were randomized to 1 of 3 treatment groups: Group A, in which patients received an injection of $50 \times 10^6$ allogeneic MSCs; Group B, $150 \times 10^6$ allogeneic MSCs; and the Control Group, a sodium hyaluronate (hyaluronic acid/hyaluronan) vehicle control.

Results: No ectopic tissue formation or clinically important safety issues were identified. There was significantly increased meniscal volume (defined a priori as a 15% threshold) determined by quantitative MRI in 24% of patients in Group A and 6% in Group B at 12 months post meniscectomy ($p = 0.022$). No patients in the Control Group met the 15% threshold for increased meniscal volume. Patients with osteoarthritic changes who received MSCs experienced a significant reduction in pain compared with those who received the control, on the basis of visual analog scale assessments.

Conclusions: Meniscus regeneration and improvement in knee pain following treatment with allogeneic human MSCs.

OSIRIS THERAPUETICS FUNDED
A) **Reduction in mean pain score:** While mean pain scores, as measured by a Visual Analog Scale (VAS), were similar for all four groups at baseline (67 points for saline, 72 points for HA, 70 points for 6M MPC, 72 points for 18M MPC), at 12 months MPC treatment resulted in significantly greater pain reduction than was seen in controls. Mean pain reduction at 12 months was **40 points for the 18M MPC group, 37 points for the 6M MPC group, 27 points for HA controls, and 27 points for saline controls** (p=0.046 and p=0.11, respectively, for 18M MPC and 6M MPC vs. pooled controls).

B) **Increased proportion of patients achieving >50% reduction in pain score:** Achieving more than 50% reduction in low back pain at 12 months is considered by many patients and physicians as a key target. A significantly greater proportion of MPC-treated patients achieved at least a 50% reduction in low back pain at 12 months, as measured by VAS, compared to controls (6M MPC 69%, 18M MPC 62%, HA 35%, saline 31%, p=0.036 between groups). Both MPC dose groups had a significantly greater proportion of patients with 50% or more reduction in back pain from baseline compared to the pooled controls (6M, p=0.009, 18M p=0.038).

C) **An increased proportion of patients achieving minimal residual back pain:** Minimal residual back pain at 12 months was considered if the VAS score was <20. A significantly greater proportion of MPC-treated patients achieved minimal residual back pain at 12 months than controls (6M group 52%, 18M group 42%, pooled controls 18%, p=0.01 and p=0.05, respectively).

D) **Reduced opioid use for pain relief:** At 12 months, mean daily use of opioid medications for back pain was reduced by as much as 42% in the 18M MPC group compared with the saline control group (p=0.17). Mean opioid use was 1.00 tablet/day saline group, 0.94 tablet/day HA group, 0.77 tablet/day 6M MPC group, and 0.58 tablet/day 18 MPC group. Mean opioid use was also over two-fold higher in saline and HA controls achieving **50% reduction in pain score than in MPC-treated patients**, indicating that pain reduction in the controls may have been due to high opioid intake rather than to any biologic effect (mean opioid use 1.3 and 1.2 tablets/day in saline and HA controls compared with 0.7 and 0.6 tablets/day for the 6M and 18M MPC groups).

E) **Reduced need for additional surgical and non-surgical interventions for persistent pain:** MPC-treated patients had a significantly reduced need for additional interventions at the treated disc level, including surgical intervention (spine fusion, discectomy or artificial disc replacement) or injection (epidural steroid injection, rhizotomy or transforaminal injections), than saline controls. By 12 months, 25% saline controls had undergone an additional intervention, compared with 10% HA controls, 6.9% of 6M MPC and only 3.3% of 18M MPC-treated patients. By Kaplan-Meier analysis of time to a first additional treatment intervention, **treatment with either 6M or 18M MPC significantly reduced the need for additional interventions** compared with saline treatment (p=0.024 and p=0.010, respectively).
TROPHIC

CELL-PRODUCED, BIOACTIVE FACTOR-MEDIATED REGENERATIVE MILIEU.

**MSCs as regulated multi-drug delivery vehicles.**

MSCs as **DRUG STORES.**
PROPOSED SEQUENCE OF CHANGE DUE TO INJURY:
IMMUNO-MODULATORY

Trophic
Anti-Apoptotic

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Regenerative Micro-environment

MSC = pericyte

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2014 natural INJURY RESPONSE
MSC Transitions:
Osteogenic, Trophic and Immunomodulatory.

Pericyte

MSC

Activated MSC

MSC

Osteo-progenitor

Secretory Osteoblast

PRP

VEGF

BMP

PDGF

PDGF

Trophic

Immunomodulatory

MEDICINAL
MSCs are NOT stomal cells:

- Stroma is a generic term for connective tissue found in and around almost all organs and tissues.
- MSCs are found as perivascular cells and, even in large vessels, in the adventitia but, again, not in the generic connective tissue.
- To best understand the native, functional properties of MSCs, think PERICYTES.
- Huge # of MSCS in Menstrual flow.
MSC = Medicinal Signaling Cell.
CELL-BASED THERAPY: Where are we?

“This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning”

W Churchill, 10 November 1942
THE FIFTH BIANNUAL

MSC 2015

• Join us August 18-20, 2015
• Michael Gilkey meg14@case.edu

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