INTEGRATION OF STEM CELLS IN PAIN MANAGEMENT

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Financial Disclosure

- Founding member of Cell Surgical Network of Florida, the first stem cell treatment and research facility in North Florida.
STEM CELLS: DEFINITION

- Cells which have the capacity to divide symmetrically to expand their numbers and asymmetrically to self renew and give rise to a differentiated progeny.
TYPES OF STEM CELLS

1. Germ cells - most primitive cells of the body, truly pluripotent and can give rise to identical cells and can also produce differentiated cell lines.

2. Embryonic Stem cells (ESc) - derived from the fetus; pluripotent and can differentiate to any tissue type. Cells are derived from the human embryo, aborted or left over from in vitro fertilization.

4. Mesenchymal stem cells (MSCs) - derived from adults
   - a. Bone marrow Aspirate
   - b. Adipose Tissue
   - c. Amnion
   - d. Cord Blood/Placenta
   - e. periosteum
   - f. synovial membrane
   - g. dental pulp

5. Induced Pluripotent Stem Cells (iPS) - derived from non-pluripotent somatic cells such as dermal fibroblasts, which then transformed and genetically engineered into a pluripotent state.
EMBRYONIC STEM CELLS

- **PLURIPOTENTIAL**
- **DERIVED FROM HUMAN EMBRYO**
- **ABORTED OR LEFT OVER FROM IN VITRO FERTILIZATION**
- **CONTROVERSIAL DUE TO MORAL AND ETHICAL ISSUES**
- **DIFFERENT DNA FROM THE HOST**
- **FORMATION OF TERATOMAS**
- **TRANSPLANT REJECTION**
MESENCHYMAL STEM CELL PROPERTIES

1. Multi-lineage differentiation capacity.

2. Preferential accumulation to the site of injury and inflammation - requires the presence of migration factors.


4. Possess hypoimmunogenic and immunosuppressive activity, inhibiting the proliferation of CD4+, CD8 T cells, B-cells and natural killer cells - allogeneic use does not require HLA matching.
MESENCHYMAL STEM CELLS
MESENCHYMAL STEM CELLS

- First described as fibroblast precursors within the bone marrow in 1966.

- Adult stem cells - do not show unlimited self-renewal capacity and cannot be maintained and expanded indefinitely in vitro.

- Display fibroblast like morphology, most are adherent to plastic, and can form colonies from single cell
THE MESENGENIC PROCESS

The above diagram shows the thinking on how Mesenchymal Stem Cells go through steps to help accomplish repair. Please use caution in looking at this diagram since it is simplistic in nature.
STEM CELL THERAPY

Ability to replace cells lost from aging or tissue injury.

Can be either autologous (derived from the same donor) or allogenic (obtained from another donor)

Able to differentiate to myoblasts, chondrocytes, adipocytes, osteocytes, tenocytes, nerve cells and hepatocytes
Activated Stem Cells Go To Work Healing, Building, Repairing Damaged Tissue
STEM CELL THERAPY

- Scaffolds and biologic matrix are used to enhance cellular differentiation

- Biomaterials available include poly-lactic-glycolic acid sponge, fibrin gel, TGF-B (transforming growth factor-Beta), PRP (platelet rich plasma)
METHODS OF STEM CELL DELIVERY

- Soft Tissue injection
- Intra-articular injection
- Intramedullary delivery
- Intradiscal delivery
- Intravenous infusion
- Intrathecal administration
- Intraventricular delivery either by direct injection or via the Ommaya pump
Therapeutic Applications

- Pain Management
- Bone Defects
- Soft Tissue Repair / Regeneration
- Tissue / Nerve Preservation
- Ocular Defects
- Advanced Dermal Wound Care Management
STEM CELLS AS POTENTIAL THERAPY FOR CHRONIC PAIN

- A third of the US population report chronic pain every year
- Continues to be a poorly treated disease
- Recalcitrant chronic nociceptive and neuropathic pain may be responsive to stem cell therapy
- The anti-inflammatory properties of mesenchymal cells makes it an attractive treatment option in ameliorating pain.
CHRONIC PAIN CONDITIONS POTENTIALLY RESPONSIVE TO STEM CELL THERAPY

- Osteoarthritis
- Intervertebral Disc Disorder
- Diabetic Neuropathy
- Spinal Cord Injury
- Trigeminal Neuralgia
- Chronic pain associated with degenerative neurologic disorders
- Complex regional pain syndrome
STEM CELL THERAPY IN OSTEOARTHRITIS

- Osteoarthritis - slow, progressive condition seen in the ageing population, resulting in hyaline cartilage destruction associated with chronic pain and reduced functioning.

- Risk factors: increasing age, genetic predisposition, hereditary factors, obesity, mechanical injuries and joint trauma.

- Affects all joints especially weight bearing

- Associated with neuropathic pain, depression and sleep disorders

- NO APPROVED MEDICAL TREATMENT REVERSES ARTICULAR CARTILAGE DESTRUCTION!!!!
STEM CELL THERAPY IN OSTEOARTHRITIS

- Standard treatment including physical therapy, pain control with steroid, NSAIDs, opioids, viscosupplementation with hyaluronic acid and surgery can impact pain but do not prevent progression.

- Cellular therapy with chondrocyte implantation can repair and restore cartilage but requires surgery, is a slow process and leads to insufficient results due to poor renewal and regeneration potential of chondrocytes.

- STEM CELLS ARE SHOWN TO IMPROVE PAIN CONTROL, FUNCTION AND REGENERATE FULL THICKNESS ARTICULAR CARTILAGE.
STEM CELL THERAPY IN OA: CLINICAL INVESTIGATION

- Worldwide studies on the therapeutic efficacy and safety of stem cell therapy using bone marrow, adipose derived or allogenic

- First reported use of MSCs to repair cartilage damage in humans was in 1998 (Wakitani et al, 2004)

- Better physical role functioning and greater improvement over time in autologous MSC treated vs. autologous chondrocyte implantation (Nejadnik et al, 2010)

- Improved clinical symptoms and cartilage repair confirmed by MRI and histopathologic studies (Wakitani et al, 2007)

- Consistent improvement in pain score, improvement in cartilage regeneration and physical function after intra-articular knee injection in OA patients two years after injection (Vangsness et al, 2007)
STEM CELL THERAPY IN OA: CLINICAL INVESTIGATION

- One Step Repair Technique - combined bone marrow MSCs with standard knee arthroscopy at the same time

- Patients reported improvement in pain scores, OA severity and MRI confirmed repair of cartilage defect (Buda et al, 2010; Gobbi et al, 2011, 2014)

- Drawback: Hard to estimate the number of MSCs, making standard treatment with consistent results more difficult
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STEM CELL THERAPY IN OA: CLINICAL INVESTIGATION

Microfracture technique - small holes were drilled into the subchondral bone marrow during arthroscopic knee surgery.

Allowed bone marrow MSCs to migrate to target site.

Follow up arthroscopy confirmed articular cartilage regeneration and hyaline cartilage formation. (Goyal et al, 2013; Saw et al 2013)
Autologous adipose derived MSCs injected into the knee after arthroscopy showed significant reduction in pain, increased quality of life and MRI confirmed articular cartilage regeneration (Koh et al, 2012, 2013).

Method is simple, cost effective and requires no hospitalization.

Cells were harvested and injected the same day.

Drawback: cell population were not confirmed as MSCs.
First dose dependent study on direct intra-articular injection of autologous adipose derived MSCs was published in 2014 (Jo et al, 2014)

Patients were divided into three categories:
- a) low dose (1 million cell count)
- B) mid dose (5 million cell count)
- C) high dose (10 million cell count)
OPTIMAL DOSE IN STEM CELL THERAPY

Results:

- Significant improvement in joint function and pain reduction observed in the low and mid dose group.

- The size of cartilage defect was significantly reduced in the mid and high dose while it increased in the low dose group.

- Thick hyaline-like cartilage covered the defect site in the high dose group as confirmed by arthroscopy and histologic staining.

- No adverse effect was reported in all groups.

Conclusion: High dose injection (10 million or more cell count) are more beneficial and improved knee function by forming cartilage in the defect site.

- Abdominal subcutaneous fat is a superior source of MSC compared to other fat pads since 100 times more cells were harvested.
AUTOLOGOUS MESENCHYMAL STEM CELL SOURCES FOR CARTILAGE REPAIR

- Bone marrow MSCs - most common source for treating cartilage damage

  Collected easily without causing tissue defects by drilling into the bone and aspirating the bone marrow.

- Most common harvest sites: iliac crest, tibia and femur

- Bone marrow MSC Concentration
  - Newborn- 1/10,000
  - Teen- 1/100,000
  - 50 year old- 1/400,000
INTERVERTEBRAL DISC DISORDER

- Low back pain is the leading cause of disability in the developed world

- Annual health care and economic burden in the US is estimated at 500 billion dollars; second most common reason for sick leave

- 75-80% will experience low back pain
- Prevalence ranged from 15 to 45%

- 5th most common reason for physician’s visit

- Severe degenerative disc disease is associated with two fold increase in chronic low back pain
CURRENT TREATMENT MODALITIES FOR IVD DISEASE

- Conservative non-surgical treatment - is the preferred treatment, including pharmacotherapy, physical therapy, minimally invasive procedures and injections, and lifestyle adjustment.

- Surgical intervention including fusion, discectomy, disc implant.

- Neither treatment correct nor prevent further disc degeneration.
STEM CELL THERAPY IN IVD DISEASE: CLINICAL INVESTIGATION

- 28 patients undergoing microdiscectomy with back pain had percutaneous injection 12 weeks post-surgery using cultured disc chondrocytes - resulted in reduced back pain at 2 years and increased MRI T2 signals of treated and adjacent discs (Meiser et al, 2007)

- 10 patients with DDD underwent percutaneous injection of autologous MSCs resulted in clinical improvement in back and leg pain, and disability (Orozco et al, 2011)

- 2 patients with back pain, sciatica and radiologic evidence of spinal stenosis and disc disease underwent percutaneous injection of autologous bone marrow MSCs within a collagen sponge- resulted in increased MRI T2 signal, less instability and clinical improvement in both patients (Yoshikawa et al, 2010)
STEM CELL THERAPY AND NEUROPATHIC PAIN

- Stem cell therapy may offer palliative and curative potential in patients with neuropathic pain from multiple etiologies.
- Stem cells reverse and repair the pathology that underlies the genesis and propagation of damage within the somatosensory system.
- Stem cells can replace damaged neuronal tissue, protect against progressive nerve damage, and release soluble factors to facilitate neuronal repair.
INITIAL SAFETY STUDY
1,000 PATIENTS

- 1-3 year follow up
  No serious adverse events related to SVF cells in deployment
- Tumors - none
- Emboli - None
- Death - 3 patients - determined non-related
- Hospitalization - 1- overnight observation in ICU following pulmonary congestion - cleared and breathing improved within 12 hours
- Infection - - intradiscal - oral pathogen
EVALUATION OF SERIOUS EVENTS

► Deaths - non-related
► Pulm Fibrosis patient - very ill, died after flying to Israel for further treatment
► Pulm Fibrosis patient - several days after SVF hospitalized for bowel obstruction, not treated, died
► ALS patient- hospitalize 2 weeks post SVF for recurrent pneumonia, DVT and PE-died
EVALUATION OF SERIOUS EVENTS

- Hospitalized - COPD patient admitted for pulmonary congestion - cleared - bacteriostatic saline as the cause
- Infection - intradiscal - history of dental infection - yield oral pathogen
NON-SERIOUS ADVERSE EVENTS

- Joint swelling increase - resolved in 24 hours
- Flu like symptoms - 4 patients - resolved in 24 hours
- Pain during liposuction
  None/Slight - 72%
  Moderate - 17%
  Severe - 2%
- Pain at liposuction site one week later
  None/little - 82%
  Moderate - 17%
  Severe - 1%
- Infection at lipo site - 1 pt - cleared in a week
- Superficial skin blister - reaction to prep solution
CLINICAL TRENDS -> 1600 PATIENT PROCEDURES
% POSITIVE RESPONSES

- Orthopedic cases - 80%
- Cardiac - 68%
- Pulmonary - 57%
- Auto-immune - 75%
- Neuro-degenerative - 63%
- Urologic: Interstitial Cystitis - 84%
- Peyronies - 73%
- Erectile Dysfunction - 63%
- Miscellaneous - 80%
ORTHOPEDIC SUCCESS

- Patients reported 3-4 years pain free
- Avoid morbidity and mortality associated with total joint replacement
- Knees may improve in 2 months
- Shoulders can take up to 3 months to improve
- CMC joint can be better overnight
- Backs tend to improve in week or more
Note increased space
3 years PO
Thank you