

The background features a dark blue gradient with white technical diagrams. On the left, there is a large circular scale with markings from 140 to 260. Several concentric circles and dashed lines with arrows are scattered across the slide, suggesting a technical or scientific theme.

*2016 UPDATE:*  
**THE USE OF STEM CELLS  
IN  
IROM**

*(INTERVENTIONAL REGENERATIVE ORTHOPEDIC MEDICINE)*

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# GOALS & OBJECTIVES

- **GOALS:**

- To define and describe the various types of “stem cells” being used in IROM.
- Describe safety data to date
- List various Orthopedic/MSK conditions being treated.
- Review the available evidence

- **OBJECTIVES**

- By the end of this session, you should be able to:
- Discuss the various types of stem cells used in IROM.
- Discuss how they are used in different MSK conditions.
- Describe the available research in the field

# “STEM CELLS” USED IN IROM

- **Adult Stem Cells: autologous, multipotent cells**
  - “Mesenchymal Stem Cells”
    - What is “Mesenchyme”?
  - BMAC
  - BD-MSCs
  - Fat Graft
  - SVF
  - AD-MSCs
- Embryonic Stem Cells
- Many others...

# ADULT STEM CELLS USED IN IROM

- **MSCs “Mesenchymal Stem Cells”**
- *“Mesenchyme” = a tissue meshwork within the Mesoderm of a developing human embryo which gives rise to mainly mesodermal connective tissues (fascia, muscle, tendons, ligaments, capsules, bone, and cartilage), but also to blood vessels and lymphatics.*
- **Two Main Types / Sources of Adult-MSCs:**
- **Bone-Marrow**
  - “BMAC” (Bone-Marrow Aspirate Concentrate)
  - BM-MSCs (Bone-Marrow derived MSCs)
  - Culture-expanded, BM-MSCs = grown in-vitro to “expand” the number of MSCs.
- **Fat/Adipose Tissue**
  - “Fat-Graft” = unprocessed “lipo-aspirate”
  - AD-MSCs / “SVF” = lipo-aspirate which has been processed via enzymatic digestion or mechanically to release MSCs.
  - Culture-expanded, AD-MSCs = grown in-vitro to “expand” the number of MSCs.

# WHICH ORTHOPEDIC CONDITIONS?

- ***OSTEOARTHRITIS***
  - *Knee*
  - Hip
  - Ankle
  - *Shoulder*
  - Basal joint/Thumb
- AVN (AVASCULAR NECROSIS) / HIP
- DISCOGENIC DISEASE / DDD of the SPINE
- ACL / KNEE
- ***ROTATOR CUFF / SHOULDER***
- Others..

STEM CELLS??.....MUTANT ZOMBIES!!??

***ARE STEM CELLS SAFE?***



# STEM-CELL EBM: *SAFETY DATA*

- *Is the use of Autologous, Adult-Mesenchymal Stem Cells in patients SAFE?*
- **2016: Centeno et al...Bond** (*International Orthopedics*)
- *“A Multi-center Analysis of adverse events amount 2,372 adult patients undergoing Adult Autologous Stem Cell therapy for Orthopedic conditions”*
  - Total of 3,012 in **2,372 patients over 9-years**: knee, hip, foot/ankle, hand/wrist, elbow, shoulder and spine.
  - Adverse events in 10% (325 patients), majority of which were post-procedure pain – self limiting.
  - 7 cases of reported neoplasm – which is LOWER than the general population!
  - Lowest rate of Adverse events with BMC vs highest rate of AE with BMC+Adipose+Cx-cells, which is explained by nature of treatment and longer follow-up.
  - No evidence that treatment with MSCs increases risk of neoplasm....?protective?
- ***ANSWER....YES!! THE USE OF ADULT, AUTOLOGOUS, BD-MSCs ARE SAFE.***

# STEM-CELL EBM: *SAFETY DATA*

- **2013: Pak et al** (BMC Musculoskeletal Disorders)
  - *“Safety reporting on implantation of autologous adipose tissue-derived stem cell with platelet-rich plasma into human articular joints”*
- 91 patients with Knee OA
- Injected with “Non-culture-expanded ADSCs”(SVF) + PRP
- No serious side effects or cancer at 36months out; a few “minor” episodes of “swelling and tendonitis”
- Efficacy: “65% at 3months and beyond”
- ***Conclusion: ADSCs/SVF + PRP in OA-Knees safe and well-tolerated***



# STEM-CELL EVIDENCE: “EARLY WORK”

- 2009: International Journal of Oral Maxillofacial Surgery, by Mesimaki et al
- *“Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells”*
- Case report: patient with very large maxillary osteoid keratocyst requiring hemi-maxillectomy.
  - Liposuction / lipo-aspirate – to GMP-level lab; grown in concert with beta-tricalcium phosphate & BMP-2 (bone morphogenetic protein-2) x 8months.
  - Re-implanted into patient as a microvascular flap with developed bone structure and vascular supply.
  - Post-op: patient did well with filling of defect.

# EVIDENCE FOR STEM CELL USE IN ORTHOPEDICS

- Studies have focused on...
  - ***The use of MSCs as an “add-on” to surgical intervention***  
Or
  - Using MSCs independently as the treatment intervention itself:
    - ---example: Knee OA

# STEM-CELL EBM: SURGERY ADD-ON – *THE KNEE*

- Level-I Evidence: none...pending...
- Level-II Evidence:
- **Wong et al (Arthroscopy 2013):**
  - *“Injectable C-BD-MSCs in Varus Knees with cartilage defects undergoing HTO: a prospective, RCT with 2-years’ follow up”*
  - *HTO+MFX, HA post-inject at 3 wks---versus--- HTO+MFX, HA+CBDMSCs post-inject at 3weeks: better pain/function/MRI scores.*
- **Koh et al (Arthroscopy 2016):**
  - *“AD-MSCs + Microfracture vs Microfracture alone: 2-year follow-up of a Prospective Randomized Trial”*
  - *MFX+ADSCs >> MFX alone in terms of pain/symptom subscores (KOOS) but no different in sports or QOL subscores.*
- **Gobbi et al (AJSM 2016):**
  - *“One-stage Cartilage repair using a HA-based Scaffold with activated BMMSCs compared with Microfracture: 5-year follow-up.”*
  - *Fibrin-glue activated BM-MSCs in a HA-based scaffold >> MFX at 2-years: IKDC score “normal” - 100% vs 64%!*
  - *At 5 years: IKDC normal scores: 100%-to-100% (BM-MSCs+HA-scaffold) vs. 64%-to-28% (MFX group)!*

# STEM CELL EBM: SURGERY ADD-ON, *SHOULDER*

- Majority of EBM: animal data...
- **2014: Hernigou et al** (International Orthopedics):
- ***“Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: a case-controlled study”***
  - *45 patients received on average 51,000 MSCs as an adjunct to single-row Rotator Cuff repair.*
  - *45 matched-controls (single-row RCR but no MSCs)*
  - *US performed every month, MRIs at 3months and 6months*
  - ***Results: 100%! (45/45) of MSC+ patient healed RCT by 6months vs. 67% (30/45) of control group!***

# EBM: STEM CELL USE IN ORTHOPEDICS

- Studies have focused on...
  - The use of MSCs as an “add-on” to surgical intervention  
Or
  - ***Using MSCs independently as the treatment intervention itself:***
    - ***---example: Knee OA***

# STEM-CELL EBM: OSTEO-ARTHRITIS, *KNEE*

- **2013: Koh et al (*Knee*): “Infrapatellar fat pad-derived MSC therapy for Knee OA”**
  - 25 patients, OA+Meniscal pathology --- nonrandomized, retrospective, comparative study
  - 3 months: improvements in all measures with no major AEs + meniscal improvement on 3-month MRI.
- **2014: Jo et al (*Stem Cells*): IA injection of MSCs for the treatment of OA of the Knee: a proof of concept”**
  - Double-blind, RCT of 18 patients: Cx-expanded-ADSC suspended in 3ml NS – 3 different dosages: Low(10M), Medium(50M), High(100M) - --- after 1<sup>st</sup> 9patients in High group showed MRI and Arthroscopic increases in hyaline cartilage, remaining 9 patients switched to the High-dose group.
  - No PRP or HA used in this study – thus, MSCs alone led to regrowth of cartilage!
  - The more MSCs used, the better the regeneration of the cartilage!
- **2015: Koh et al (*Knee Sugery, Sports Traumatology, Arthroscopy*): “Clinical results and 2<sup>nd</sup>-look arthroscopic findings after treatment with ADSCs for knee osteoarthritis”**
  - 30 patients --- 120g liopaspirate = SVF + PRP into knees via arthroscopy after lavage --- 2-years later, underwent “2<sup>nd</sup>-look”
  - All patient had clinical improvement, and of the “2<sup>nd</sup>-look” group (16), 10/16(63%) had visual improvement, 4/10(25%) had maintained cartilage, and 2 patients (12%) had failed to heal prior cartilage defects.
  - 120g Lipoaspirate = 4M ADSCs ----- 1<sup>st</sup> study to show direct arthroscopic evidence via 2<sup>nd</sup>-look for regrowth with SVF+PRP

# STEM-CELL EBM: OSTEO-ARTHRITIS, *KNEE*

- **2015: Centeno et al..Bond** (IOF Registry Data): Intermittent Data Report
- **1,825** patient-procedures: Regenexx-SD procedure = “Same-Day” stem cell procedure = BM-MSCs.
- 48 month / 4-year follow-up
- No severe AEs or Cancer.
- **Results:**
- *No differences observed between outcomes for age, sex, BMI or condition treated.*
- **Percent of patients with >50% improvement (avoiding TKA) at:**
  - **1-year: 68%**
  - **2-years: 68%**
  - **3-years: 70%**
  - **4-years: 76%**

# STEM-CELL EBM: OSTEO-ARTHRITIS, *KNEE*

- **2015: Emadedin et al** (*Archives Iranian Medicine*)
- ***“Long-Term Follow-up of Intra-articular Injection of Autologous MSCs in patients with Knee, Ankle or Hip OA”***
  - 18 patients, 30-month follow-up
  - *Results:* MSCs are “safe and therapeutically beneficial” – but “further study needed” “larger trials”
- **2016: Filardo et al** (*Journal Orthopedic Surgery Research*)
- ***“Stem Cells in Articular Cartilage Regeneration”***
  - **Review Article: 60 selected studies** – 7 RCTs, 13 comparatives, 31 case series, and 9 case reports.
  - 37 studies = BD-MSCs or AD-MSCs; 16 studies = BMAC
  - **Results:**
  - Using MSCs is safe!
  - *Improvements in outcome reported across the board* – regardless of stem cell source or method of administration.
  - **Better outcomes with younger age, lower OA grade, lower BMI.**



# STEM-CELL EBM: OSTEO-ARTHRITIS, *KNEE*

- 2016-2017: Michalek et al: (*Cell Transplantation*)
  - ***“Autologous, Adipose-tissue derived SVF cells application in patients with Osteoarthritis”***
- *Prospective, Multinational/Multicenter (Czech,Slovakia,Lithuania,US) trial of 1,114 patients.*
- *Lipoaspirates 20-90grams --- SVF alone (no PRP or HA used); ADSCs estimated 100K – 18M.*
- *No serious AEs or Cancer at 12months.*
- **Results:**
- *12 months: 91% of patients treated (1013/1114) reported >50% symptom improvement scores.*
- *12 months: 63% of patients treated (701) reported >75% symptom improvement scores.*
- *Conclusions: “results are encouraging”*

# STEM-CELL EBM: *SHOULDER, OA & RC*

- 2015: Centeno et al ...Bond (Journal of Pain Research)
- *“A Prospective, Multi-Site, Registry study of a specific protocol of Autologous, Bone Marrow Concentrate for the treatment of Shoulder Rotator Cuff Tears and Osteoarthritis”*
  - 115 shoulders treated with BMAC under US-guidance; all with dx of OA, +/- RC tears.
  - Data collected: Age, sex, BMI, condition type (OA vs RC vs both)
  - Outcomes measured: DASH (Disabilities of Arm, Shoulder, Hand), VAS/NPS, and subjective improvement.
- Results:
  - Statistical improvement of DASH & VAS/NPS
  - Patient-reported subjective improvement in 48.8%
  - *No differences observed between outcomes for age, sex, BMI or condition treated.*

# MSC USE IN ORTHOPEDICS: SUMMARY

- ***General Concepts / Perspectives of MSC use in Orthopedic Medicine***

- The use of Autologous, MSCs from Bone Marrow and/or Adipose tissue is SAFE.
- Although more study is needed, the use of MSCs from BM and/or Adipose is EFFICACIOUS.
- In general, MSCs are efficacious used alone or in combination with activated PRP and HA.
- In general, Culture-expanded MSCs with very high MSC counts, ex. > 100 Million cells seem to be more efficacious and effective than non-Culture expanded MSCs (with lower counts).
- Culture-expanded MSCs with very high MSC counts alone have been shown to regenerate hyaline cartilage in the knee.
- In general, the higher the MSC count the more effective at regenerating hyaline cartilage in the knee, as evident by 2<sup>nd</sup>-look arthroscopy and follow-up MRI.
- Data regarding the effect of gender, age, weight and comorbid conditions on MSCs is currently conflicting.

# MSC USE IN ORTHOPEDICS: SUMMARY

- ***MSCs as Surgical Add-ons:***

- **Knee**: MSCs in addition to cartilage surgery in the knee >> without; & protective at 5 years! (Gobbi)
- **Shoulder**: Add-on RC repairs: MSCs augment RC repair with >> outcomes. (Hernigou)

- ***MSCs as Stand-Alone Procedures:***

- **Knee OA**: MSCs – from BM or Adipose –are efficacious, whether alone or in combination with PRP and/or HA.
- **Shoulder OA & RC**: MSCs from BM are somewhat effective in Shoulder OA / RC, more studies needed.

# THANK YOU!

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# **AAOM Educational Opportunities**

***Hands-On Patient Treatment Workshops***

***Guadalajara, Mexico: November 5<sup>th</sup> – 12<sup>th</sup>, 2016***

***Cancun, Mexico: February 4<sup>th</sup> – 11<sup>th</sup>, 2017***

***34<sup>th</sup> AAOM Annual Meeting & World Congress on IROM***

***Seattle, Washington, USA***

***4/19/2017 – 4/22/2017***