STEM CELL THERAPY FOR VASCULAR REGENERATION
VASCULAR REGENERATION

- RESTORATION OF NORMAL VASCULAR FUNCTION & STRUCTURE
- REVERSAL OF VASCULAR SENESCENCE
- GROWTH OF NEW BLOOD VESSELS
- ANGIOGENESIS, VASCULOGENESIS, ARTERIOGENESIS
VASCULAR REGENERATION
THERAPEUTIC APPLICATIONS

• RELIEVING SYMPTOMS OF CLAUDICATION, ISCHEMIA, REST PAIN, CLI, & GANGRENE
• PREVENTING TARGET-ORGAN DAMAGE DUE TO HYPOXIA
• REPERFUSION
• AVOIDANCE OF CARDIOVASCULAR CATASTROPHES (ACUTE THROMBOSIS, EMBOLISM, PLAQUE RUPTURE & DISSECTION)
STEM CELL-BASED APPROACHES (SCB)

• EFFORTS SHIFTED TOWARDS SCB APPROACHES GIVEN THEIR "THEORETICAL" CAPACITY TO REPLICATE, DIFFERENTIATE, & FORM NEW BLOOD VESSELS IN A DIRECTED FASHION

• INITIAL STUDIES EVALUATED PLURIPOTENT EMBRYONIC STEM CELLS (ESC) & MORE LINEAGE-COMMITTED "ADULT" STEM CELLS WHICH INCLUDE ENDOTHELIAL PROGENITOR CELLS (EPC) FOUND WITHIN BONE MARROW
STEM CELL REGENERATION (IPSC)

- Scientific interest shifted to a newly described class of stem cell – induced pluripotent stem cell (IPSC)
- Derived from terminally differentiated adult somatic cells which are "reprogrammed" to an embryonic-like state
- IPSC are "autoologous" (do not require immunosuppression)
- IPSC have "pluripotent" characteristics (can differentiate into tissue from each of the 3 germline lineages)
- IPSC are noncontroversial (derived from adult tissue)
STEM CELLS
GENERAL PROPERTIES

• CAPACITY FOR BOTH "SELF-RENEWAL" & DIRECTED DIFFERENTIATION
• TWO BROAD CATEGORIES (ESC) & ADULT STEM CELLS
STEM CELLS

EMBRYONIC STEM CELLS (ESC)

• REPLICATE VIA MITOTIC DIVISION
• RETAIN THEIR "UNDIFFERENTIATED" STATE
• DIFFERENTIATE INTO LINEAGE-SPECIFIC CELLS UNDER APPROPRIATE STIMULI
• PLURIPOTENT
STEM CELLS
ADULT STEM CELLS

• PARTIALLY LINEAGE-COMMITTED
• CAPACITY TO GIVE RISE ONLY TO CELLS OF A GIVEN GERM LAYER
• MULTI POTENT
STEM CELLS (IPSC)

- IPSC resemble ESC having the potential to differentiate into any adult cell
- May represent the most "attractive" cellular approach for regenerative medicine
Characterization of iPSCs. iPSCs derived from human fibroblast reprogrammed with lentiviral vectors expressing Oct-3/4, Sox2 and Klf4 maintain colony morphology characteristic of ESC (A: 4X, B: 20X), demonstrate alkaline phosphatase activity (C) and express pluripotency markers as detected by immunocytochemistry including Nanog (D), TRA-1-81 (E) and SSEA-4 (F). For panels D-F pluripotency markers were
AUTOLOGOUS STEM CELL THERAPY TRIALS

• PRECLINICAL STUDIES ESTABLISHING BONE MARROW DERIVED MONONUCLEAR CELLS (BM-MNC) INCLUDING ENDOTHELIAL PROGENITOR CELLS (EPC) INTO ISCHEMIC LIMBS PROMPTED INVESTIGATORS TO EXPLORE FEASIBILITY OF CELL THERAPIES FOR PAD

• FIRST LARGE SCALE REPORT UTILIZING BM-MNC IN LIMB ISCHEMIA WAS THE THERAPEUTIC ANGIOGENESIS BY CELL TRANSPLANTATION (TACT) BY TATEISHI-YUYAMA ET AL (2002)
AUTOLOGOUS STEM CELL TRIAL TACT (TATEISHI-YUYAMA ET EL)

• PROTOCOL OPEN PILOT STUDY OF EFFICACY & SAFETY OF AUTOLOGOUS IMPLANTATION OF BM-MNC ESTABLISHED VS PERIPHERAL BLOOD (PB-MNC) TREATMENT

• PTS WITH BILATERAL LEG ISCHEMIA WERE RANDOMLY INJECTED WITH BM-MNC IN ONE LEG (ACTIVE TX) OR WITH PB-MNC INTO THE OTHER (CONTROL)
TACT AUTOLOGOUS TRIAL

• AT 4 WEEKS, ABI SHOWED SIGNIFICANT IMPROVEMENT IN LEGS INJECTED WITH BM-MNC COMPARED TO THOSE TX WITH PB-MNC

• SIMILAR IMPROVEMENTS SEEN TCO2, REST PAIN, & CLAUDICATION FREE AMBULATION

• LEGS INJECTED WITH PB-MNC SHOWED MUCH SMALLER INCREASES IN ABI & TCO2

• CONCLUSION: HIGHER EFFICACY USING BM-MNC WAS DUE TO EPC & MULTIPLE ANGIogenic FACTORS
CLINICAL TRIALS IM INJECTION BM-MNC FOR PAD, CLI, RP

• HIGASHI ET AL (2004) – IMPROVEMENT IN MEAN LEG BLOOD FLOW IN RESPONSE TO ACETYLCHOLINE INFUSION FROM 19.3 – 29.6 ML/MIN

• SAGAWA ET AL (2004) – IMPROVEMENT IN MEAN ABI FROM 0.54 – 0.61 & IMPROVEMENT IN MEAN TC02 FROM 28.4 – 37.1

• MIYAMOTO ET AL (2006) – IMPROVEMENT IN VISUAL ANALOG PAIN SCALE SCORE FROM 5.1 – 2.3
CLINICAL TRIALS IA INJECTION BM-MNC FOR PAD

• COBELLIS ET AL (2008) – IMPROVEMENT IN ABI SEEN IN 80% OF EXPERIMENTAL GROUP (NO IMPROVEMENT IN CONTROL GROUP)

• WALTER ET AL (2011) – NO IMPROVEMENT IN ABI. MINIMAL IMPROVEMENT IN WOUND HEALING
CLINICAL TRIALS USING COMBINED IM & IA INJECTION PAD

• BARTSCH ET AL (2007) – DEMONSTRATED 3.4 FOLD INCREASE IN PAIN FREE WALKING DISTANCE (NO IMPROVEMENT IN CONTROLS)

• VAN TONGEREN ET AL (2008) – NO STATISTICALLY SIGNIFICANT DIFFERENCE IN LIMB SALVAGE AMONGST TWO GROUPS. SLIGHT IMPROVEMENT IN ABI FROM 0.52 – 0.66

• FRANZ ET AL (2009) – IMPROVEMENT IN ABI SEEN IN 44% PATIENTS. IMPROVEMENT IN REST PAIN SYMPTOMS 83% PATIENTS
INVESTIGATIONAL CLINICAL TRIAL
FREDERICK MEIJER INSTITUTE
SPECTRUM HEALTH

• TESTING THE SAFETY & EFFECTIVENESS OF A NEW TREATMENT STRATEGY DESIGNED TO IMPROVE BLOOD FLOW VIA ANGIOGENESIS

• INVOLVES EXTRACTING BM-MNC & IM INJECTIONS INTO INNER & OUTER CALF REGION

• CLINICAL TRIAL WILL HELP DETERMINE IF STIMULATING NEW BLOOD VESSEL GROWTH WILL IMPROVE WOUND HEALING, DECREASE PAIN & DECREASE NEED FOR AMPUTATION
PATIENT SELECTION CRITERIA

INCLUSION CRITERIA

• UNILATERAL OR BILATERAL LOWER EXTREMITY ISCHEMIA DUE TO ADVANCED PAD

• NON-CANDIDATES FOR SURGICAL BYPASS OR PERCUTANEOUS ANGIOPLASTY & STENTING (NON-RECONSTRUCTABLE)

• UNDERGOING MAXIMAL MEDICAL THERAPY FOR CLI AS DEFINED BY RUTHERFORD CATEGORY 5 (MINOR TISSUE LOSS OF INDEX LIMB)

• ISCHEMIC REST PAIN OF INDEX LIMB (RUTHERFORD CATEGORY 4)

• NO CURRENT OR PREVIOUS MALIGNANCY
PATIENT SELECTION CRITERIA
EXCLUSION CRITERIA

- MAJOR TISSUE LOSS OF THE INDEX LIMB (RUTHERFORD CATEGORY 6)
- HGA1C > 10% & HISTORY OF PROLIFERATED RETINOPATHY IN DIABETIC PATIENTS
- RENAL DISEASE (CREATININE > 2.5MG/DL OR CHRONIC HEMODIALYSIS)
- UNCOMPENSATED CHF &/OR OTHER CONDITIONS THAT PRECLUDE GENERAL ANESTHESIA
- MYOCARDIAL INFARCTION OR STROKE WITHIN LAST 90 DAYS
CONCLUSIONS

• MOST CLINICAL TRIALS OF CELL THERAPY FOR PAD HAVE CONSISTED OF UNCONTROLLED PATIENT SERIES, WITH A FEW RANDOMIZED, PROPERLY CONTROLLED STUDIES

• SAMPLE SIZES ARE RELATIVELY SMALL, WITH MOST STUDIES ENROLLING FEWER THAN 50 PATIENTS

• VARYING DEGREES OF PAD SEVERITY HAVE BEEN INCLUDED, RANGING FROM INTERMITTENT CLAUDICANTS TO THOSE WITH CRITICAL LIMB ISCHEMIA
CONCLUSIONS

• THERAPEUTIC PRODUCT FOR NEARLY ALL TRIALS HAS BEEN BM-MNC AND/OR PB-MNC HARVESTED WITH OR WITHOUT GRANULOCYTE COLONY-STIMULATING FACTOR MOBILIZATION

• CELLS DELIVERED BY DIRECT IM INJECTION AT MULTIPLE SITES OF THE AFFECTED LIMB OR BY IA INJECTION VIA FEMORAL ARTERY

• REPORTED ENDPOINTS OF THESE STUDIES INCLUDED ABI, TC02, & ANGIOGRAPHY EXAMINED AT BASELINE & FOLLOWING CELL THERAPY
CONCLUSIONS

• AVERAGE FOLLOW-UP PERIOD OF 6 TO 12 MONTHS
• SUBJECTIVE OUTCOMES HAVE BEEN REPORTED TO INCLUDE PATIENT PERCEIVED REST PAIN & PAIN-FREE WALKING TIME OR DISTANCE
• COLLECTIVELY, RESULTS FROM STUDIES, INCLUDING WOUND HEALING AND LIMB SALVAGE, ARE ENCOURAGING, BUT THE NUMBER OF PATIENTS STUDIED IS SMALL IN MOST TRIALS
• PROCEDURES ASSOCIATED WITH CELL THERAPY, SUCH AS BM ASPIRATION & INJECTION NOT GENERALLY WELL TOLERATED

DAD! Knock it off!
That's Bruce Jenner!