PENNINGTON
BIOMEDICAL RESEARCH CENTER

Adult Stem Cell Workshop
Part 1 – The Big (& Muddy!) Picture

July 27, 2010

Oklahoma Center for Stem Cell Research

Oklahoma City, OK

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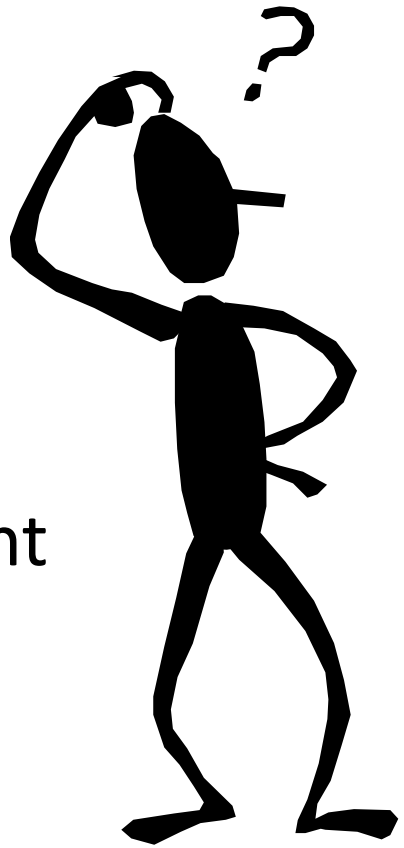
Process guidelines & disclosures

- Remember, this is for you.
- Interrupt with questions at any time!
- Most of what you hear is just common sense
- But remember to distinguish facts vs opinion - everything you hear will reflect my unabashed "adult stem cell" bias from the perspective of practical & clinical considerations
- In the event that this is a problem, just substitute "stromal cell" for "stem cell" where ever the term is used!

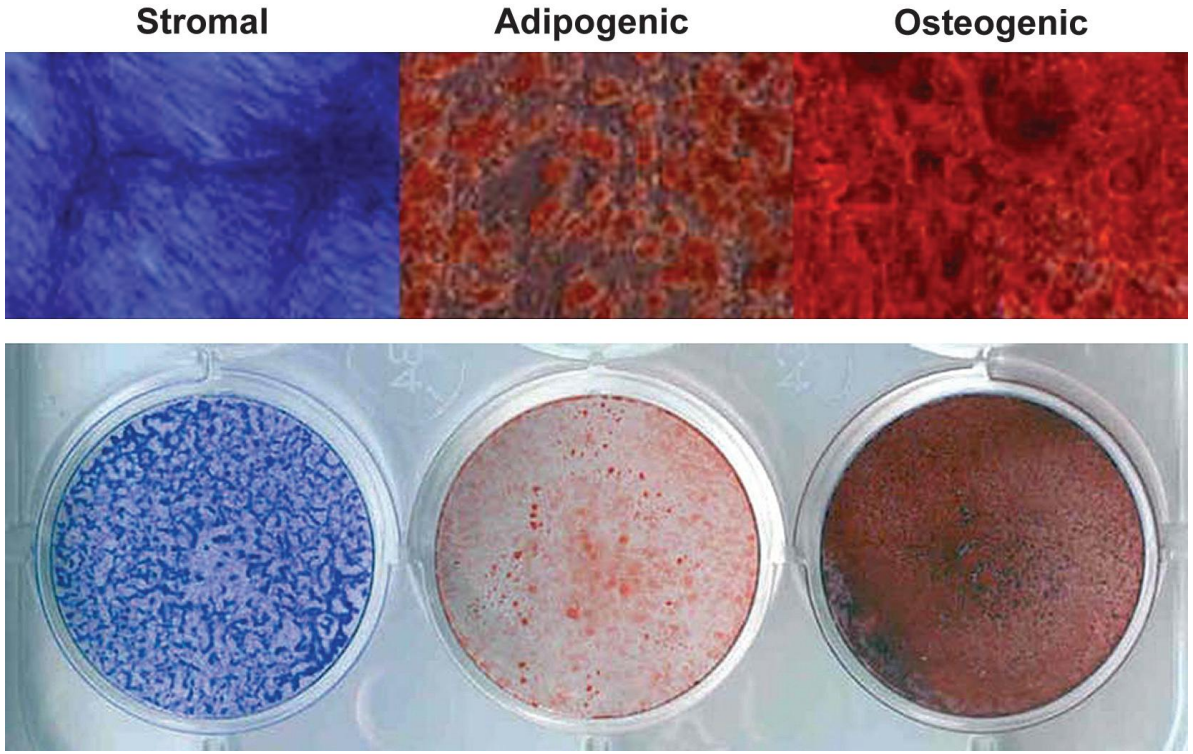
What will we cover? General Themes



- What are stem cells?
- What are the research considerations?
- What are the applications and treatment opportunities?
- What are the expectations and funding opportunities?
- What are relevant societies and organizations?
- What does it take to make it all work?
- What are the major concerns?

What will we cover?
Specific Themes (as time permits!)

- Details of adipose-derived stem cells (ASC) as a representative example for general themes.



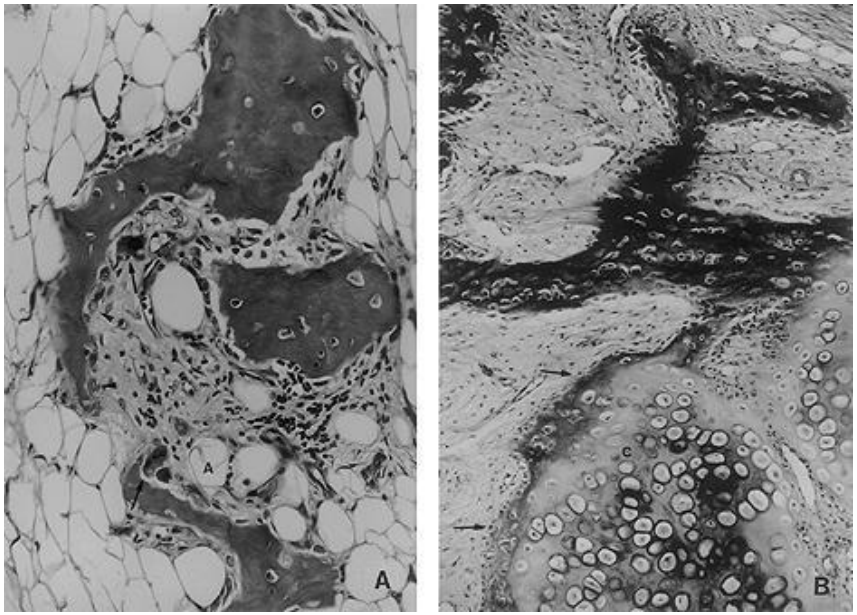
Paradigm shift in cell biology

- The concept that stem cells existed in multiple organs/tissues was heresy 20 years ago
- Tissues were composed of “committed” progenitors whose lineage was “restricted” at birth
- Tissue regeneration in adulthood was a rare and unreliable event

Clues for the existence of stem cells

Physiology **vs** **Pathology**

- Recovery of neurological function in stroke patients
- Regeneration of liver following resection of multiple lobes
- Origin of multi-lineage cancer cells
- Inborn disorders such as paroxysmal osseous heteroplasia (POH) & fibrosis ossificans progressiva (FOP)



POH

Emerging Concept (circa 1990)

- That adult tissues contain stem cells characterized by self renewal, multiple lineage differentiation potential, and retention of these properties with serial transplantation
- Historically, only **hematopoietic stem cells** (HSC) of bone marrow origin had been thought to display such features
- Arnold Caplan (Case Western University) had the "chutzpah" to begin describing bone marrow stromal cells as "**mesenchymal stem cells** (MSC)"

What are stem cells?

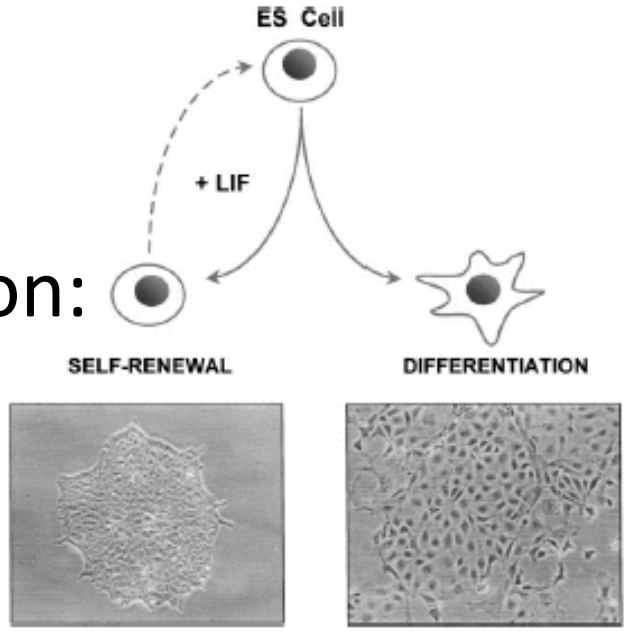
- Categories of stem cells based on sources :
  - Embryonic
  - Fetal
  - Neonatal
  - Adult
  - Induced pluripotent stem cells (iPS cells)

What are stem cells?

- Categories of stem cells based on potency:
  - Unipotent
  - Multipotent
  - Pluripotent
  - Totipotent

In vitro vs *in vivo* documentation of stem cell functionality

- Original "sine qua non" definition (pre 2005):
  - Self renewal
  - Multilineage differentiation potential
- Recent "sine qua non" definition:
  - Transplantability?
  - Trackability?

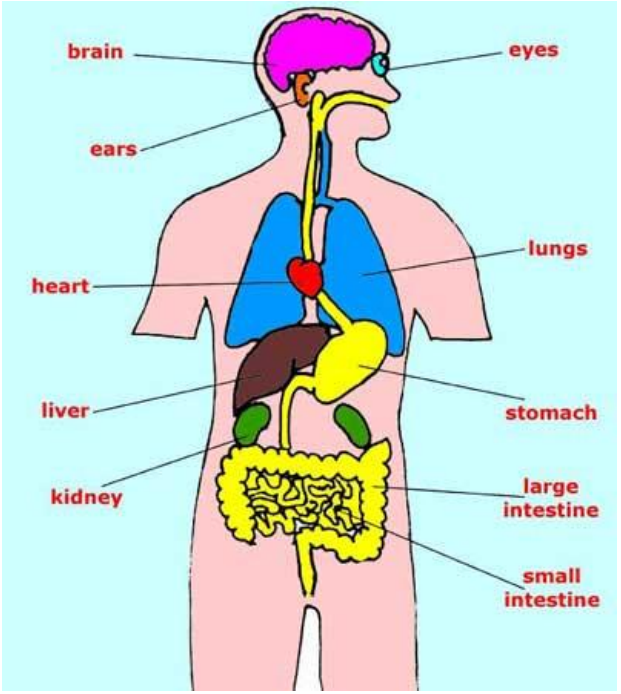


Mechanisms of action

- Differentiation capacity (original favorite)
- Paracrine actions (recent favorite)
- Reactive oxygen specie (ROS) scavenger
- Immunomodulator & immunosuppressor
- Cell fusion (fusion confusion)
- Other?
  - Modification by genetic engineering
  - Modification by scaffold combination

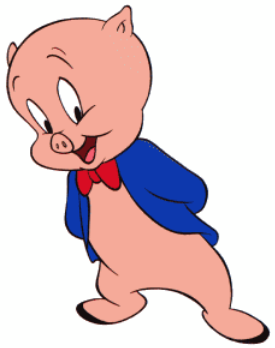
What are the research considerations?

- Pros & cons of primary cultures vs cell lines
  - Access to primary tissue
  - Risk of infectious agents
  - Impact of immortalization



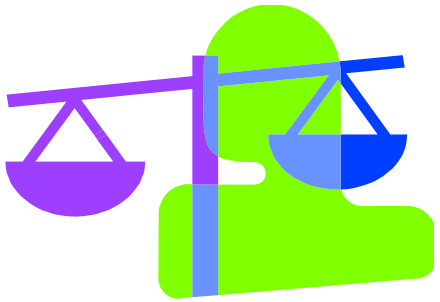
What are the research considerations?

- Human vs animal models:
  - Small animals (mouse, rat, rabbit)
  - Large animals (dog, sheep, goat, pig, horse)
  - Non human primates
  - Clinical studies

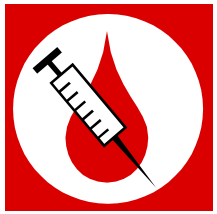


What are the research considerations?

- Issues
  - IACUC approval
  - IRB approval
  - Legal issues
  - Availability of species specific research reagents
    - Advantages of murine & human models
    - Disadvantages of other species



Safety issues - Personnel protection



- Universal precautions
- Blood borne pathogen training
- Hepatitis vaccine & immunization testing
- Personnel serum sample storage (?)
- Standard Operating Procedures (SOP) for:
  - Adverse event algorithm (needle stick precautions)
  - Live cell flow cytometry guidelines & procedures
  - Waste handling
  - Cell culture procedures
  - Transport of tissues in public
  - Monitoring for infection

Safety - Tissue acquisition & processing

- IRB approval – inclusion/exclusion criteria, consent form, donor anonymity
- HIPAA training and certification for personnel
- Human subject training and certification
- Association with clinical investigator, clinical department & hospital collaborators

Product safety concerns

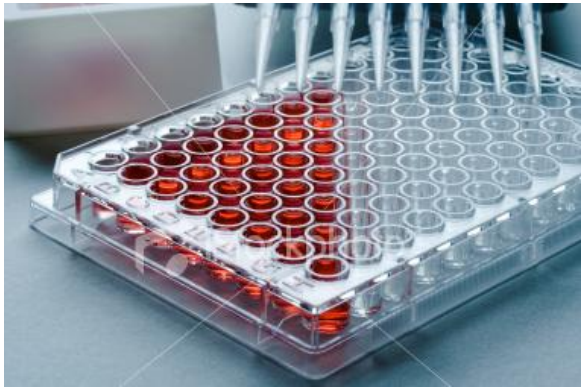
- Tumorigenesis – safety studies *in vitro* & *in vivo* as a function of cell passage, differentiation, and manipulation/combination
- Contamination of cells – mycoplasm, endotoxin, bacterial (aerobic/anaerobic), viral
- Minimal manipulation
- Migration of cells post implantation (tracking methods)
- Combination products (gene transduction, scaffolds & biomaterials)

Efficacy

- *In vitro* biochemical differentiation
- Cytokine production
- Cell fusion
- Immunomodulatory function (immunosuppression, immune response to stem cells)
- Reactive oxygen specie scavenger
- Combination products (genetically engineered cells, scaffold combinations)
- *In vitro* vs *in vivo* considerations (need for early *in vivo* data in today's landscape)
- Cell tracking methods and approaches

Efficacy – beyond discovery

- Assays used to document efficacy will serve to document final product quality control parameters & lot release criteria



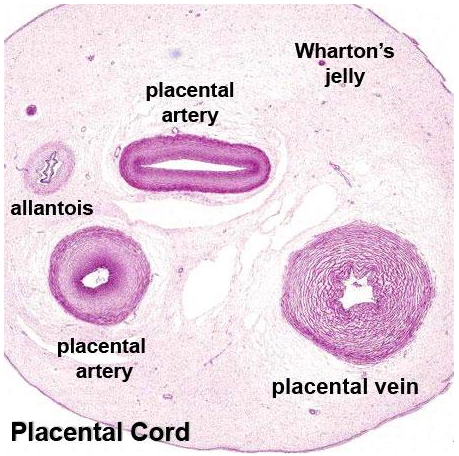
Access to source tissue

Fetal or embryonic tissues

- Legal / ethical restrictions & concerns

Single time access for harvest

- Umbilical cord blood
- Placenta
- Wharton's jelly



Access to source tissue

Multiple time availability

- Blood (renewable, accessible)
- Marrow (renewable, painfully accessible, limited volume)
- Adipose (renewable, accessible, abundant)
- Muscle (accessible, limited volume)
- Skin (accessible, limited volume)
- Brain and nervous system (inaccessible, available in theory only)
- Teeth (accessible, removable, available in childhood only)
- Liver (difficult access, limited volume available)
- Pancreas (difficult access, limited volume available)

Access to source tissue

Additional issues

- Storage at time of harvest
- Storage during transport to laboratory (temperature, medium, length of time until processing)
- Shipping via air courier

IRB Considerations

Institutional Review Board (IRB)

- Inclusion – all ages, genders, ethnicities
- Exclusion – infectious disease status, oncology status, metabolic disease status, age considerations (pediatric age group)
- Anonymity
- Consent completion prior to collection (recommended that this be performed even with "discarded waste tissues without identifiers")

IRB Considerations

- Serum sample for analysis
  - Cytokine profile
  - Metabolites (triglycerides, cholesterol, metabolome, etc)
  - Demographics (age, body mass index, blood pressure, waist circumference, DEXA/bone mineral density, MRI)
- Genetic testing language for current and future studies particularly if developing tissue bank
- Medical history issues (osteoporosis, diabetes, osteoarthritis) depending on study intent

Storage issues for cell products

- Temperature control of tissue between time in OR until lab processing (wet ice, dry ice, liquid nitrogen, “room temp”)
- Cryopreservation
  - Optimization
  - Removal of animal products
  - Cryoprotective agent selection & compatability with patient safety & comfort
  - Achieving and documenting viability, reproducibility, utility, ease of use of in clinical setting

Regulatory concerns/issues

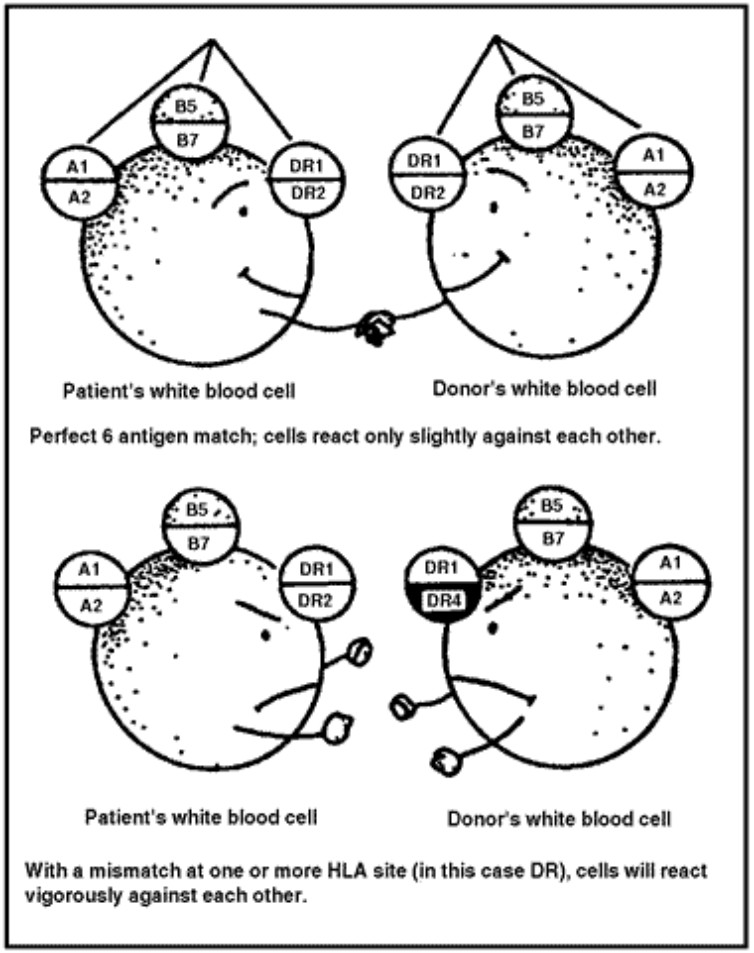
- Infectious agents and contamination
- Lot variability
- Definition of product by multiple quantitative parameters
  - FACS definition
  - Secreted proteins
  - –Omics approaches
  - Destruction of product
  - In process testing
  - Final product testing and timing relative to delivery
  - Lot tracking methods (bar code)

Regulatory Concerns

- Quality assurance /quality control (QA/QC)
- Animal protein free product
  - Xenovirus & Bovine Spongiform Encephelopathy
  - FDA vs EMEA – serum irradiation, BSE free herds of livestock certification
  - Non-animal sources of trypsin
- Cytokine and medium product sourcing and validation testing for potency and action
- Collagenase – Endotoxin testing, sterility, functionality, cost, final product testing for residual levels

Autologous vs Allogeneic Cell Applications

- HLA donor matching in BMT
- Not required for MSC applications
- Current Phase I/II studies underway with FDA approval using allogeneic cell transplantations (Osiris Therapeutics, Baltimore, MD)



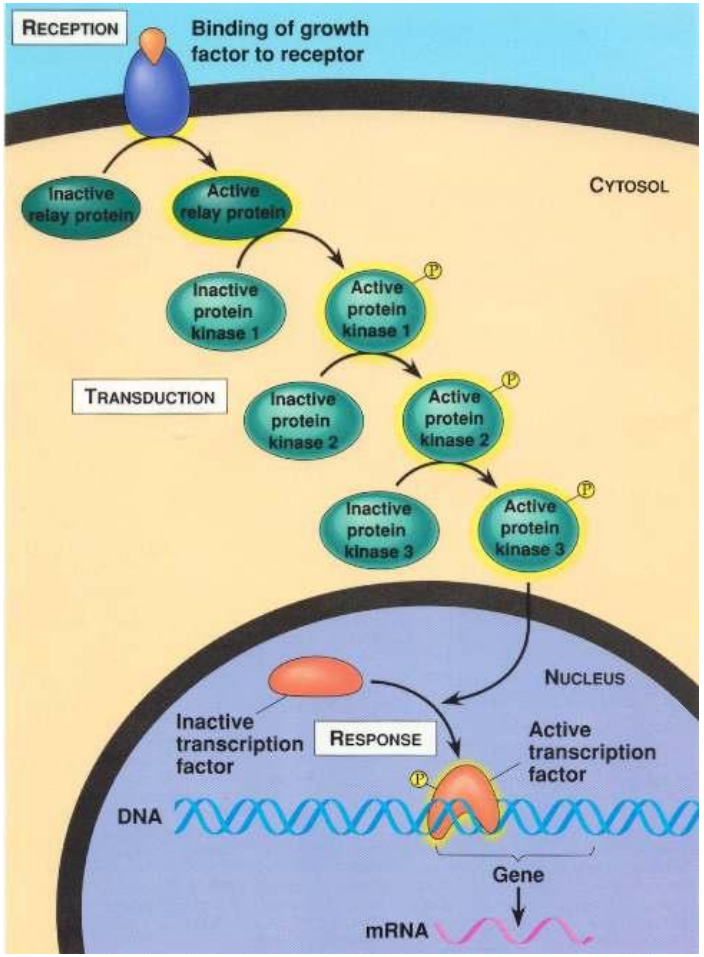
Stem Cell Legal Limitations

- Embryonic stem cell (ESC) – national vs state vs institutional restrictions
- Fetal tissue – national vs state vs institutional restrictions
- Somatic cell nuclear transfer (SCNT) – Illegal in Louisiana as a criminal act (fines, jail time)
- Induced pluripotent stem cells (iPS cells) – future issues looming in gamete research

What are the applications and treatment opportunities?

Basic Research Opportunities

- Signal transduction pathway analysis
  - Drug discovery
  - Metabolic pathways
- –Omics approaches
- Circadian mechanisms
- Mechanobiology mechanisms



Pre-clinical and Translational Research Acute Disease Models

- Fractures
- Ischemic Models (Stroke, MI, bowel ischemia 2^{o} to volvulus or intusception, renal ischemia)
- Trauma (TBI, spinal cord, burn, chemical exposure, radiation exposure, knife & gun wound)

Center for the Intrepid
Brook Army Medical Center

Pre-clinical and Translational Research Chronic Disease Models

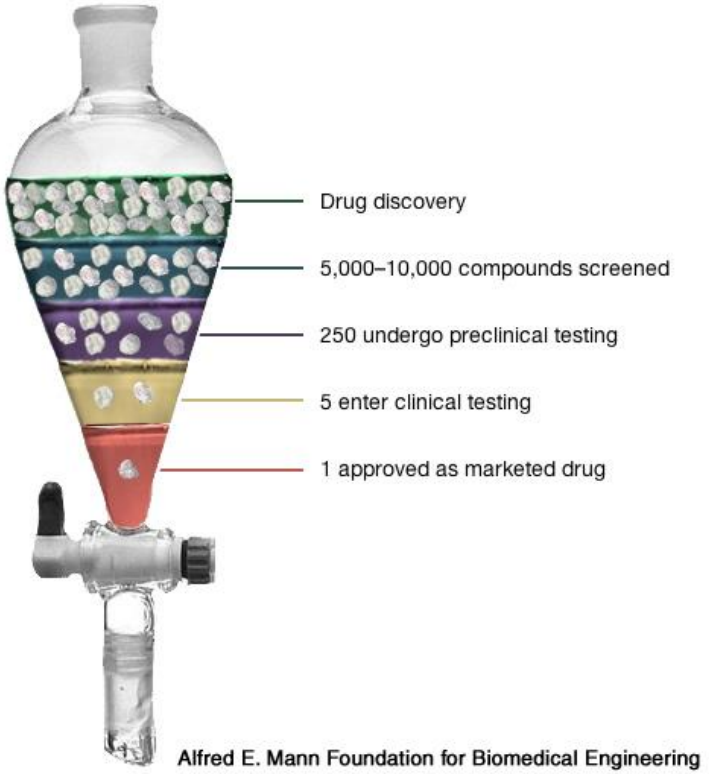
- CNS – Parkinson Disease, Alzheimers Disease, Multiple Sclerosis, Leukodystrophies
- Metabolic – Diabetes Mellitus, Osteoporosis, Obesity, Lipodystrophy, Neuropathy, Retinopathy)
- Cardiovascular Disease – CHF, claudication
- Decubiti Ulcers

Pre-clinical and Translational Research

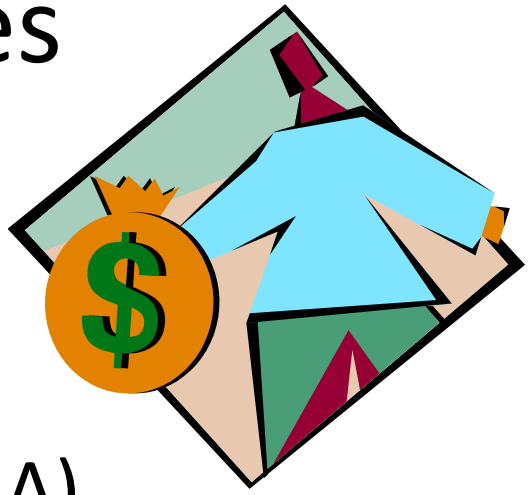
- In vitro Models
- In vivo Pre-clinical Models
- Small animals (rodents, rabbits)
- Large animals (canine, ovine, caprine)
- Non human primates

Pre-clinical and Translational Research

- Clinical Trials – FDA approved IND or BLA (investigator initiated vs industry sponsored project)
- BLA = Biological License Application
- IND = Investigational New Drug



Funding Sources



- NIH
- DoD
- Private foundations (JDRF, AHA)
- Device companies (JNJ, Smith & Nephews, Medtronic, Stryker, Zimmer)
- Pharmaceutical companies (1^{o} focus on drug discovery tools)
- State funding mechanisms (OK is lucky!)

Funding Sponsor Expectations

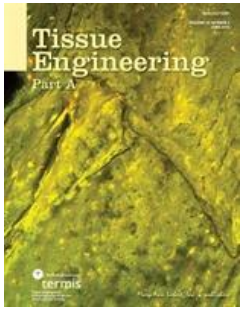
- Dependent on the funding source
- Safety, efficacy, cures
- Quantitative metrics of success
- Milestone parameters
  - Publications
  - Leveraged national funding
- Investigator accountability
  - Quarterly or annual reports

Journal Expectations

Mesenchymal stem cell example

- Multiple differentiation potential (adipo-, chondro-, osteo-)
- FACS profile & immunophenotype
- Purification & enrichment scheme
- Donor demographics

- Mechanism – signal transduction pathway (journal dependent)



- Utility – in vivo data & documentation (journal and reviewer dependent)
- Human & animal in vitro & in vivo data (highest impact journals)

What are relevant societies and organizations (*journals*)?

International Societies

- American Society for Bone and Mineral Research ASBMR *(Journal of Bone & Mineral Research*)
- American Association of Immunologists AAI *(Journal of Immunology*)
- American Society of Hematology ASH *(Blood*)
- International Federation for Adipose Therapy and Science IFATS (Dallas TX Oct 22-24) (*Stem Cells*)
- International Society for Cell Therapy ISCT (*Cytotherapy*)
- International Society for Bone and Mineral Research ISBMR *(Bone*)
- International Society for Stem Cell Research ISSCR (*Cell Stem Cell*)
- Orthopedic Research Society ORS (*Journal of Orthopedic Research*)
- Plastic Surgical Society (*Plastic and Reconstructive Surgery*)
- Tissue Engineering and Regenerative Medicine International Society TERMIS (*Tissue Engineering*)

Additional Journals

- Cells Tissues Organs
- Experimental Hematology
- Journal of Cellular Biochemistry
- Journal of Cellular Physiology
- Journal of Tissue Engineering & Regenerative Medicine
- Regenerative Medicine
- Stem Cells & Development
- Stem Cells International
- And, of course, Cell, Nature & Science!

State Stem Cell Initiatives with Peer Reviewed Granting Mechanisms

- CIRM – California
- Maryland
- New York Stem Cell Society
- New Jersey (discontinued due to budget issues)
- Pennsylvania
- Oklahoma
  - (often run by American Institute for Biological Sciences, AIBS)

What does it take to make it all work?

Team Approach

- Basic Research
  - Multiple Disciplines & Technologies
- Clinical Scientists/Medical Discipline
- Manufacturing
- Engineering
- Legal – Intellectual Property
- Business
- Venture Capital & Seed Money Opportunities for Investment

Academic/Private/Corporate Partnerships

Oklahoma Health Science Center has a record of success and the necessary infrastructure to support and grow such enterprise. In addition, it has serial entrepreneurs on site who can help direct such activities to a successful outcome.

What are the major concerns?

- Inadequate safety considerations. For example, a contaminated cell product in a clinical trial would have the same impact as the Geisinger/adenoviral contamination issue had on the gene therapy field.

What are the major concerns?

- Tumor formation. An Israeli report linked a rare brain tumor in a child directly to implanted fetal/embryonic cell therapy provided by a laboratory in the Ukraine. Pre-clinical animal studies have reported sarcoma formation by multiple passaged adipose stromal/stem cells and bone marrow mesenchymal stem cells.

Amariglio et al. PloS Medicine 17: 6 (2) 1000029, 2009

What are the major concerns?

- Hype and hope. It is better to under promise & over perform, not the other way around. The field does not do this consistently.
- Balancing risk and reward. Is the medical discovery process, particularly in the US, handicapped by fear of litigation and over-cautious regulatory concerns?

What are the major concerns?

- Secondary immune responses. Will repeat applications of stem cell therapy in a single recipient lead to secondary immune responses and rejection?

What are the major concerns?

- Lack of defined international standards (harmonization). Studies underway in Asia and Europe with protocols that may or would not meet FDA regulatory guidelines are being conducted by US and international companies for a variety of reasons.

Before we break…

- Let's take a 10 minute recess and then come back to use work on adipose-derived stem cells (ASC) as an example for further discussion and questions……

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Adult Stem Cell Workshop
Part 2 – A Historical Perspective & Adipose-derived Stem Cells (ASC)

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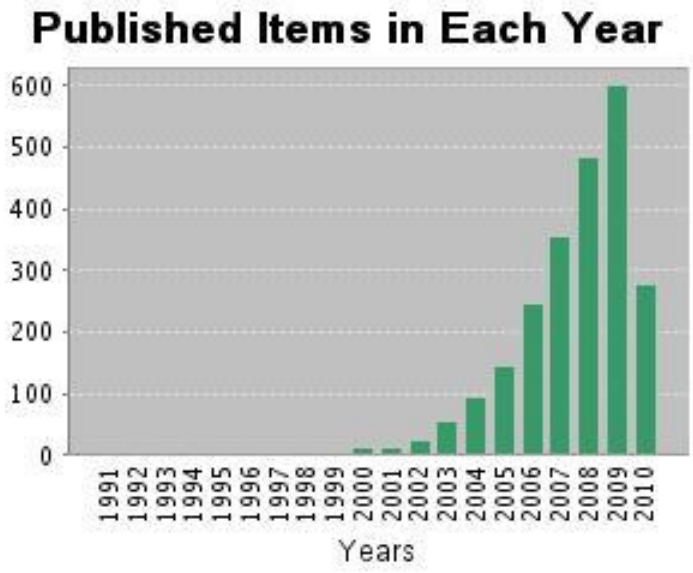
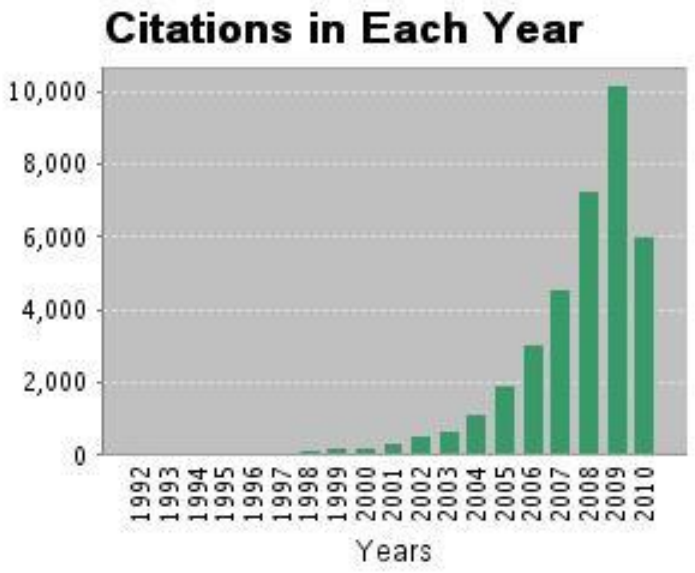
Where do we stand with ASC?

- Interest in adipose stem cells (ASC) has grown exponentially within the last decade





Challenges

- Regulatory hurdles & safety concerns
- Perceptions of hype vs hope
- Understanding mechanism of action
- Manufacturing methods & standard operating procedures
- Point of care & hospital based banking

Is this truly new territory?

- Bone marrow mesenchymal stem cells (BMSC) provide a similar model that is currently being employed in hundreds of FDA registered autologous & allogeneic clinical trials
- But blood products & hematopoietic stem cells are the most widely used clinical cell therapeutics world wide.
- What can we learn from their history?

History of Blood Transfusions

- 1665 – 1st recorded transfusion (UK)
- 1667 – Sheep to human transfusions (FR)
- 1678 – Paris outlaws transfusions due to complications (FR)
- 1818 – 1st successful human transfusions (US)
- 1901 – Landsteiner defines 1st blood groups
- 1907 – 1stdonor/recipient cross matching
- 1908 – Carrel develops anti-clotting methods
- 1914 – Anticlotting & blood preservation reagents developed
- 1926 –1st blood transfusion service (British Red Cross)
- 1932 – 1st hospital blood bank (Leningrad, Russia)
- 1937 - 1st US hospital blood bank (Cook County)
- 1940 – Drew develops method for long term blood storage

www.bloodbook.com

History of Blood Transfusions

- 1943 – Transfusion hepatitis 1st reported
- 1949-50 – 1500 hospital blood banks, 46 community blood centers, & 31 Red Cross regional blood centers in US
- 1951 – American Association of Blood Banks as clearinghouse
- 1953 – Refrigerated centrifuge
- 1959 – Structure of hemoglobin revealed
- 1962 – Antihemophiliac factor developed
- 1962 – 4400 hospital blood banks, 123 community blood centers, & 55 Red Cross Regional blood centers in US
- 1964 – Plasmapheresis introduced
- 1967 – Hepatitis B Ag testing introduced
- 1980's – Blood transfusion as medical specialty
- 1985 – 1st screening tests for HIV contamination
- 1990 – Hepatitis C testing introduced
- 1999 – PCR testing introduced

www.bloodbook.com

The bottom line on blood….

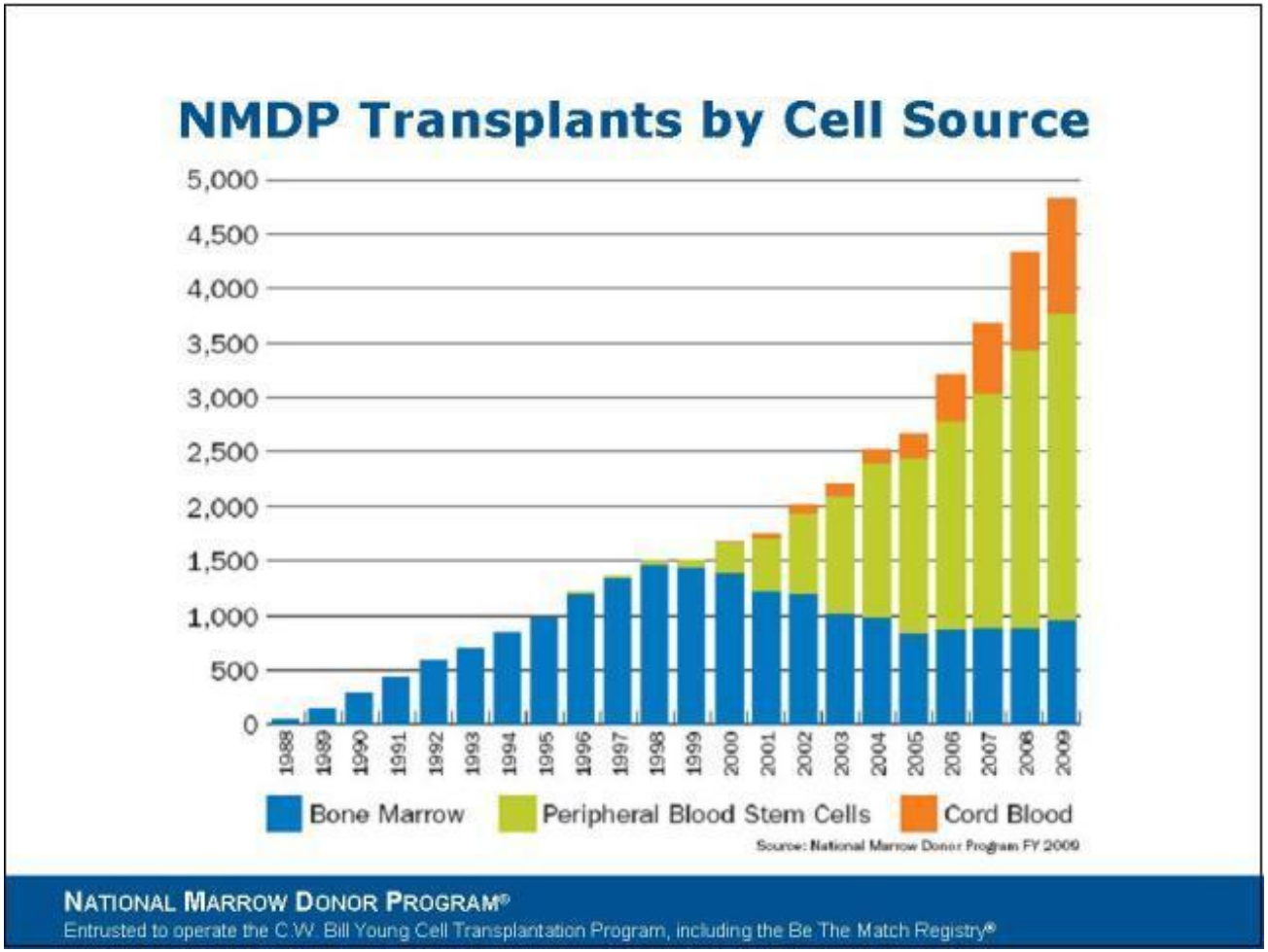
- Millions of blood & blood product transfusions have been performed successfully
- Risk remains but is minimized through federal & industry regulation
- Blood banking is a multi-billion $$$ international public/private enterprise encompassing academic, non-profit & for-profit entities

History of Hematopoietic Stem Cell (HSC) Transplantation

- Late 1950's – First identical twin bone marrow transplant (BMT)
- 1973 – First unrelated BMT
- 1986 – National Bone Marrow Registry established with federal funding
- 1988 - First cord blood transplant (CBT)
- 1998 – Carolinas Cord Blood Bank opened at Duke Univ withNHLBI support
- 2010 – 100's of public/private cord blood banks world wide

www.fhcrc.org

National Marrow Donor Program Annual Statistics



http://www.marrow.org/

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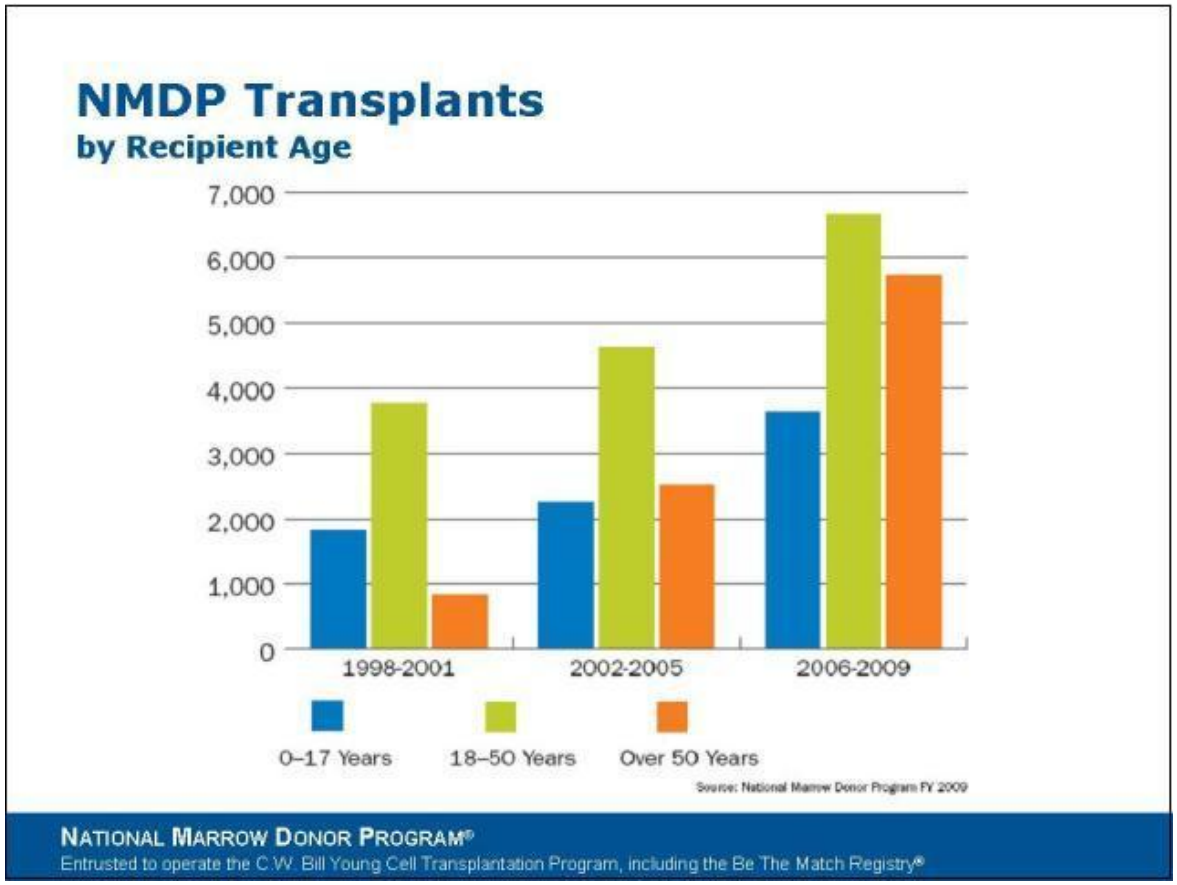
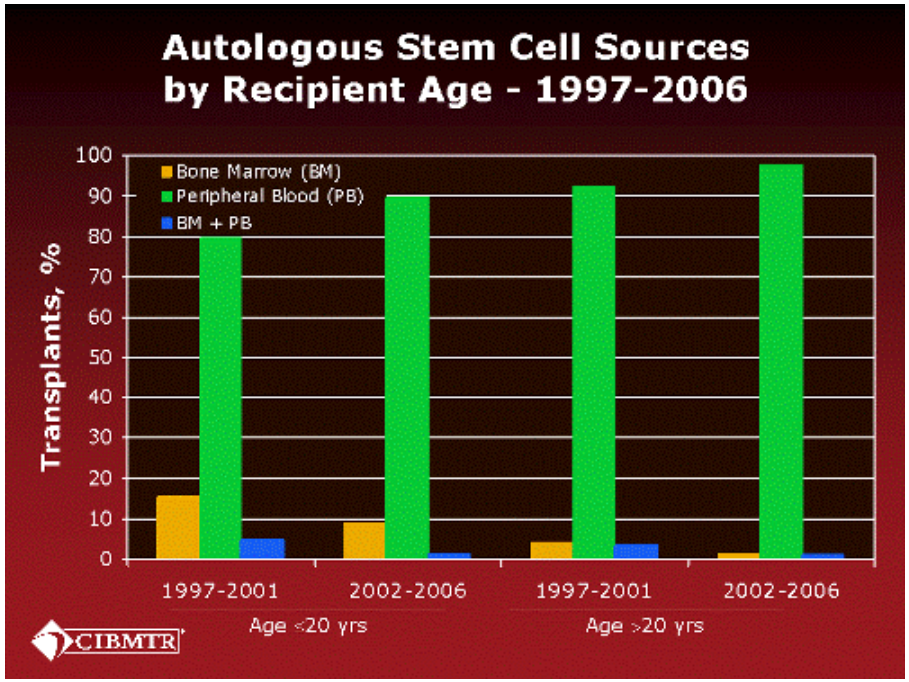
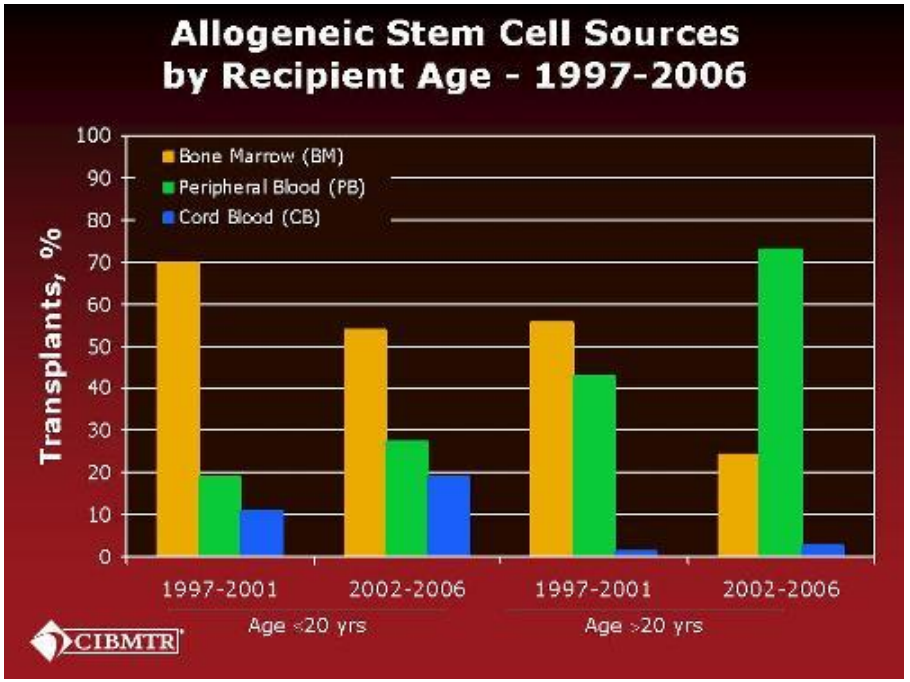


http://www.marrow.org/

NMDB Transplant of Autologous & Allogeneic Cells



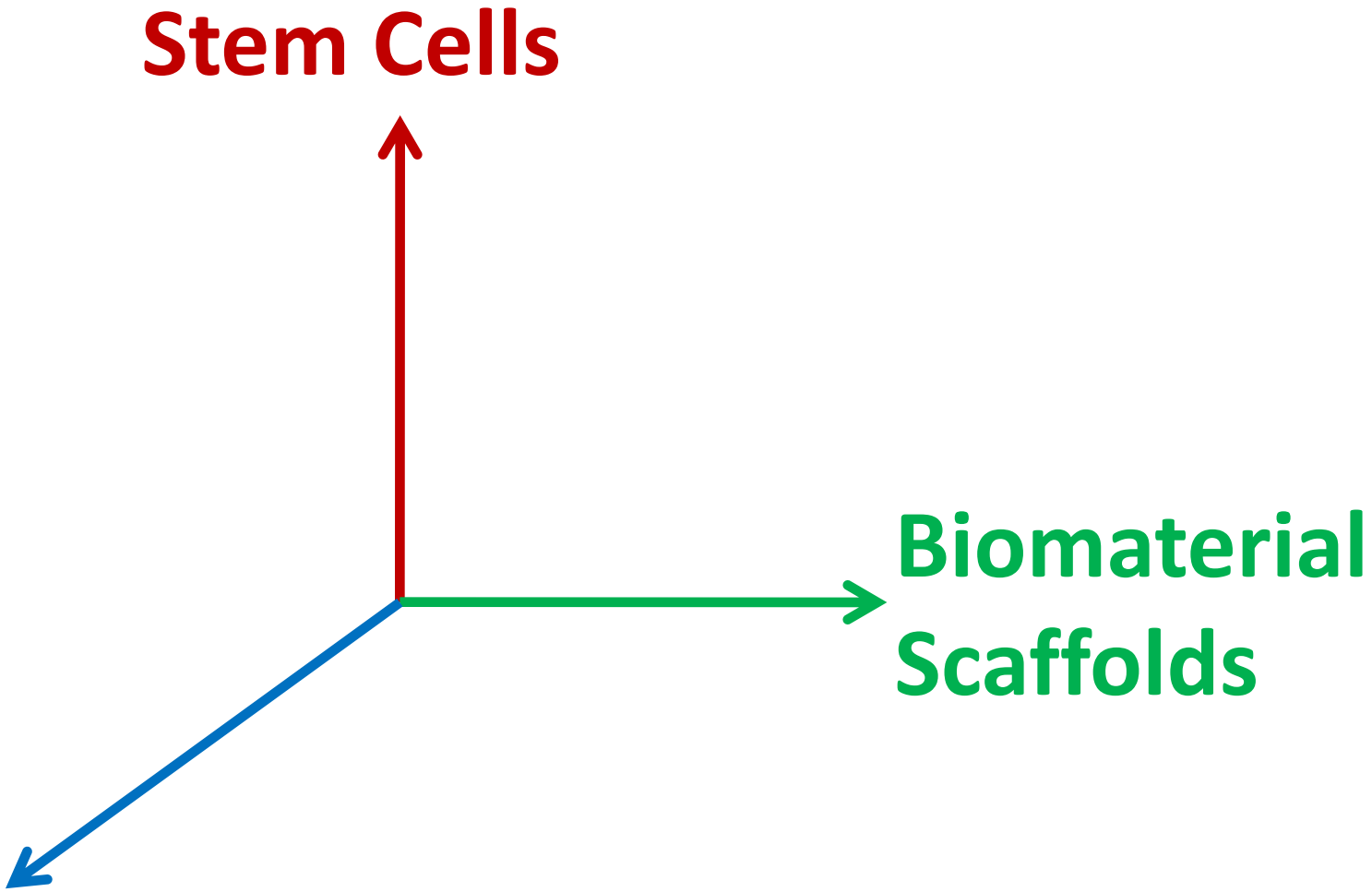


http://www.marrow.org/

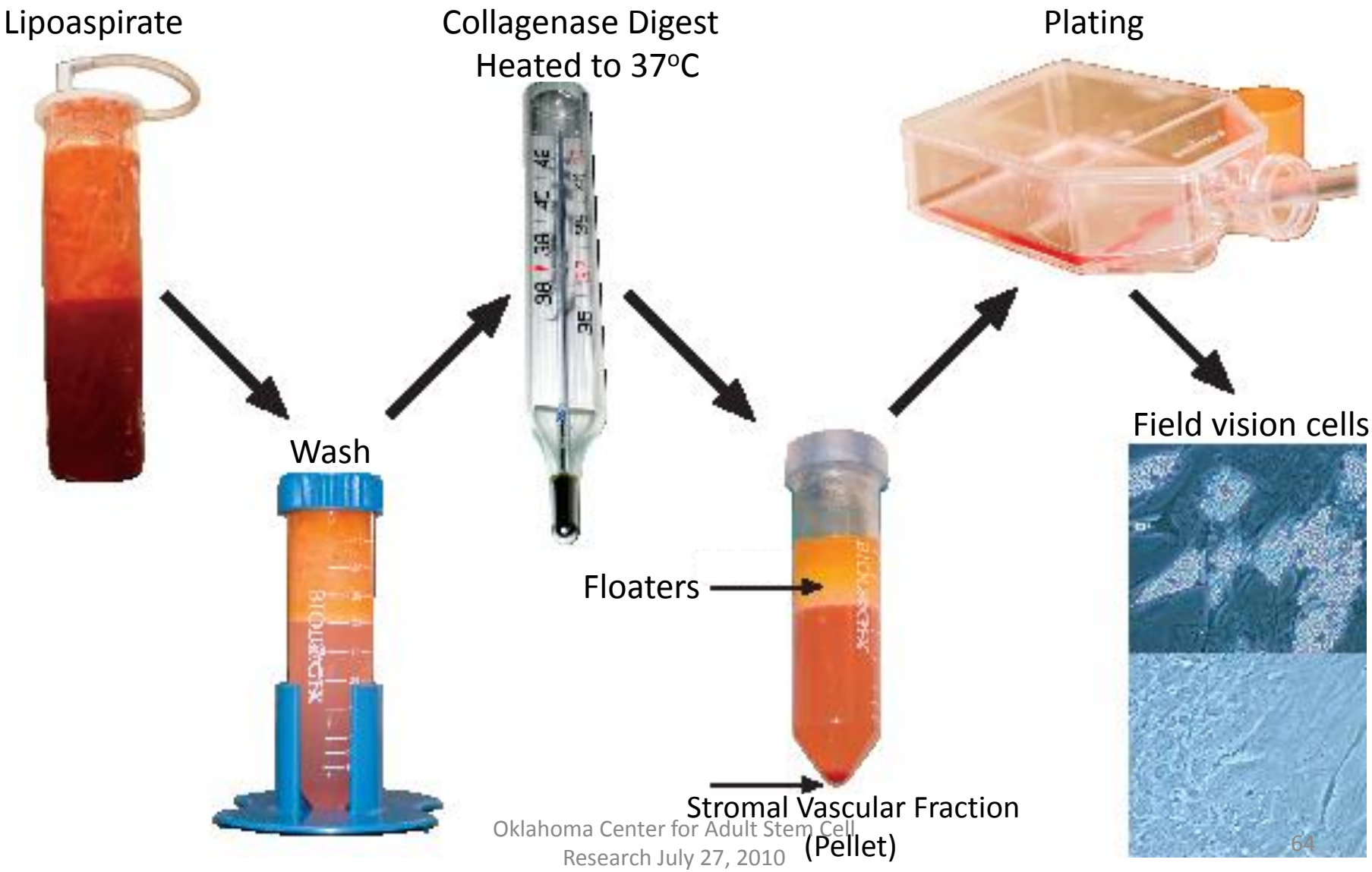
The bottom line on BMT…

- Procedure has been practiced for >60 yrs
- Recipients numbers are multiples of 10^4 patients annually (at most)
- Procedures have only recently been accepted under health insurance policies
- Cost per patient for care remains high
- Indications are exclusively life threatening diseases

So what is the bottom line on ASC & SVF cells?



Cell Isolation from Liposuction Adipose Tissue



Adipose-derived Cell Types

- Stromal Vascular Fraction (SVF) Cells
  - Freshly isolated
  - Heterogeneous
  - Suspended, not adherent
- Adipose-derived Stem Cells (ASC)
  - Culture expanded
  - Plastic adherent
  - Relatively homogeneous relative to SVF cells

ASC Yield

- Recent PBRC Experience
- Culture period 4.1 ± 0.7 d
- Cells/ml tissue = 375 K ± 147 K
- Mean Age, 43.6 ± 11.1
- Mean BMI, 27.0 ± 3.8
- Subjects, n = 64

Yu et al Cytotherapy In Press

- Prior PBRC Experience
- Culture period 6.0 ± 2.4 d
- Cells/ml tissue = 247 K ± 136 K
- Cells/cm^2, 38.4 K ± 21.2 K
- Mean age, 41 ± 10
- Mean BMI, 26.1 ± 4.8
- Subjects, n = 44

Mitchell et al Stem Cell 2006

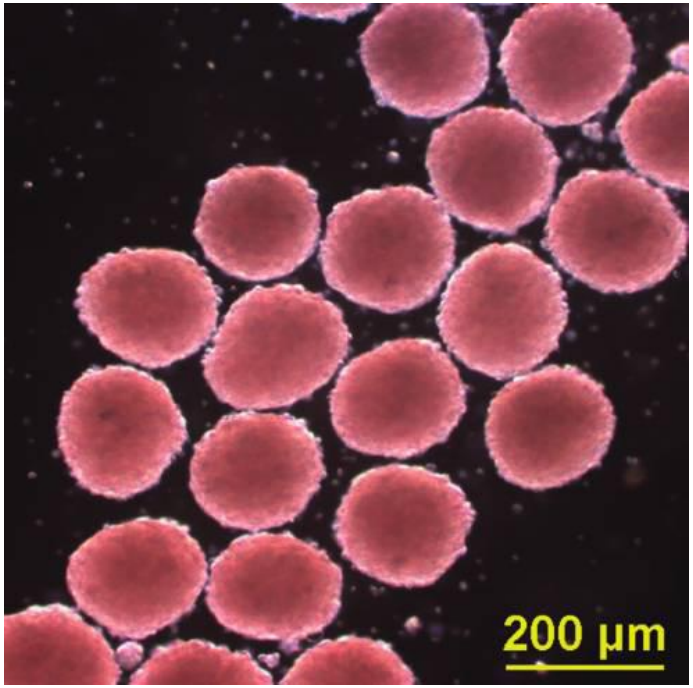
ASC & BMSC Cytokine Production

- Adipokines – Adiponectin, Leptin
- Angiogenic – HGF, VEGF
- Hematopoietic – Flt3 Ligand, G-CSF, GM-CSF, M-CSF, IL-7, IL-12, SCF
- Pro-Inflammatory – IL-6, IL-8, IL-11, LIF, TNFα
- Others – BMP2, BMP4

Kilroy et al. J Cell Physiol. 212:70, 2007
Miranville et al; Rehman et al: Planat-Bernard et al Circulation 2004

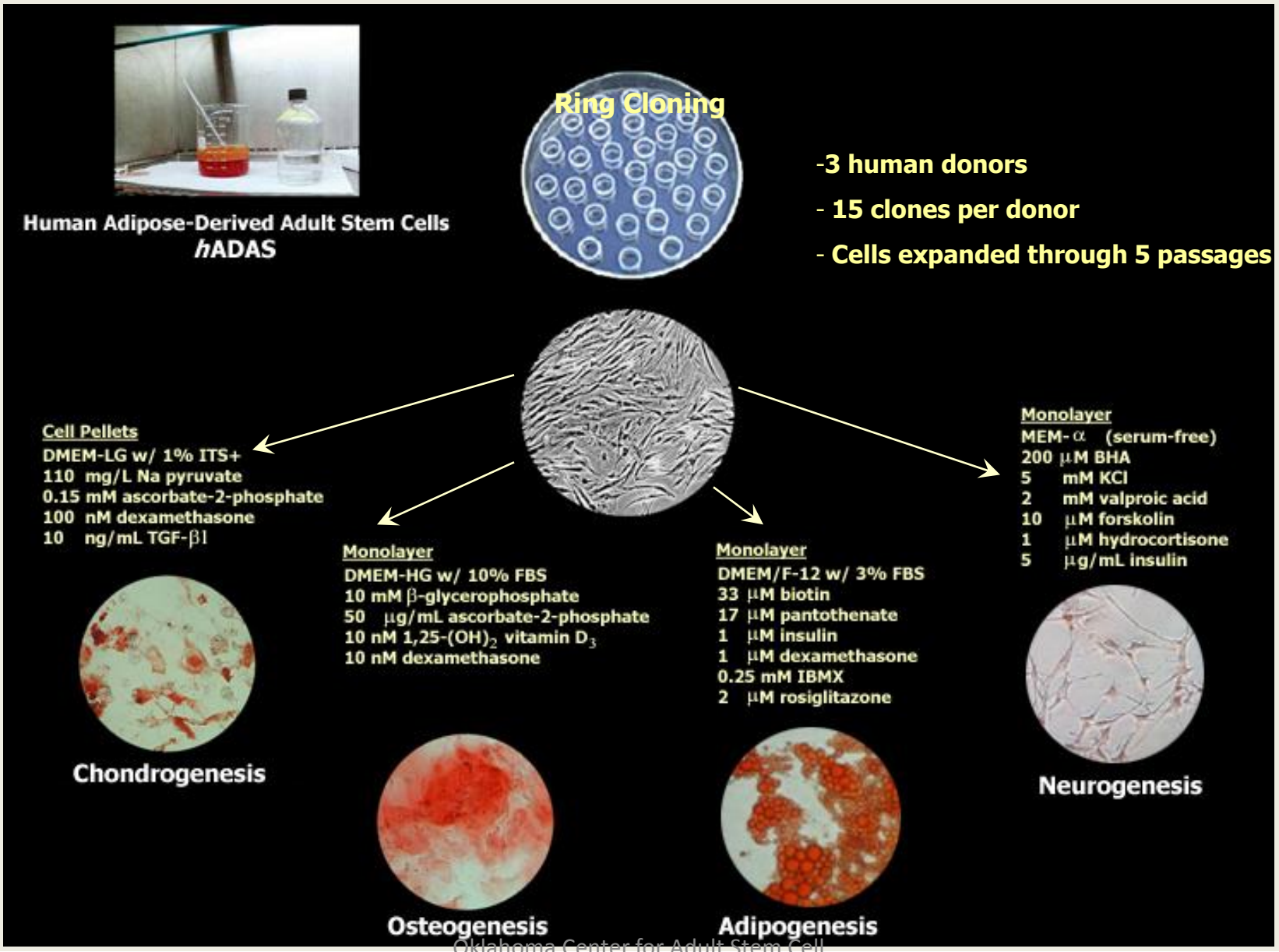
Multicellular Aggregates

- Culture of ASC as hanging drops
- Generation of uniform 25,000 cell/MA
- Increased secretion of angiogenic and reparative factors
- Acceleration of skin wound healing in *db/db* diabetic mice in dose dependent manner



Amos et al. Tissue Engineering 16:1595, 2010

ASCs Are Multipotent

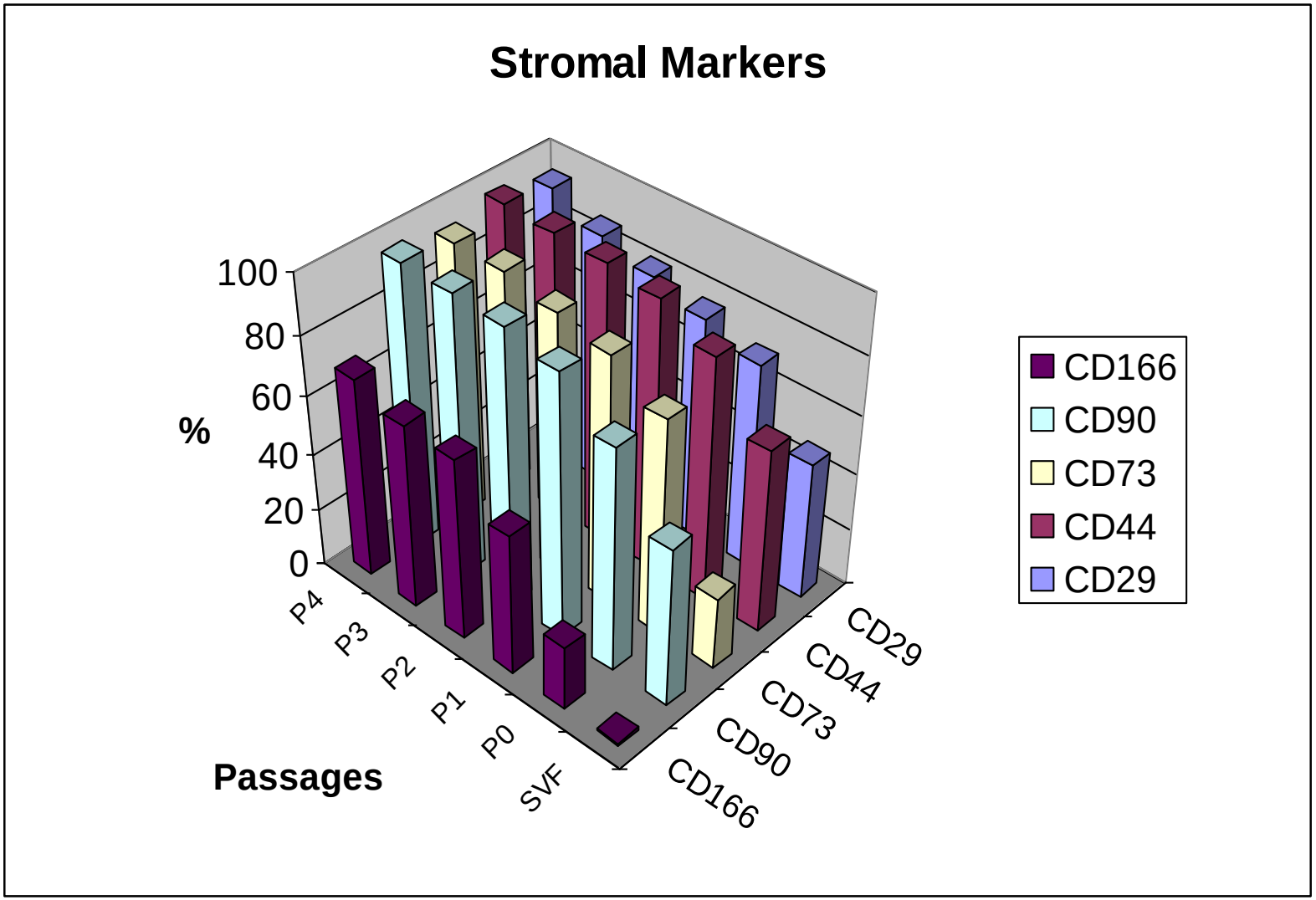


Guilak et al J Cell Physiol 2006

ASC Differentiation Potential

- Adipocytes
- Chondrocyte
- Cardiomyocyte
- Endothelial cell
- Epithelial cell
- Hematopoietic supporting cell
- Hepatocyte
- Neuronal cell
- Osteoblast
- Smooth muscle cell
- Skeletal myocyte
- Tendon cell
- Others????

Immunophenotype & Passage



Mitchell et al Stem Cells 2006

ASC Immunophenotype

- **Positive Markers:**
  - Adhesion Molecules: CD9
  - Integrins: CD29, CD49
  - Metalloproteinases: CD10, CD13
  - Receptors Hyaluronate CD44, ICAM-1 CD54, Endoglin CD105, Muc-18 CD146, ALCAM CD166
  - Stromal: 5' Ecto Nucleotidase CD73, Thy 1 CD90
  - HLA: Class I HLA-ABC
  - Stem Cell: CD34, ALDH*, ABCG2*

- **Negative Markers:**
  - Adhesion: PECAM CD31, ICAM 3 CD50, E Selectin CD62e
  - Integrins: CD11b, CD18
  - Hematopoietic: CD14, CD45
  - HLA: Class II HLA-DR

Gronthos et al., J. Cell. Physiol. 189:54, 2001; Zuk et al, MBC 13:4279, 2002; Mitchell et al, Stem Cells, 2006

Acellular Adipose Matrices

- Freeze/thaw, polar solvent or salt extraction, enzymatic digestion employed
- Protein content includes collagen IV, laminin, nidogen, fibronectin, growth factors (FGF)
- Promotes ASC adipogenesis in 2-D & 3-D

Flynn et al. Biomaterials 31:4715, 2010
Uriel et al. Biomaterials 29:3712, 2008

ASC & BMSC Immunogenicity

- Passaged allogeneic cells do not elicit an immune response *in vitro* (mixed lymphocyte reaction)
- Passaged allogeneic cells suppress a T cell immune response to potent stimulator cells *in vitro* through release of PGE2
- Implication – Allogeneic transplantation and off the shelf products are feasible!

Bartholomew Exp Hematol 30:42, 2002
Puissant Br J Hematol 129:118, 2005
McIntosh et al. Stem Cell 24:1246, 2006
Cui et al. Tissue Engineering 13:1185, 2007
McIntosh et al. Tissue Engineering 15:2677, 2009

Potential Mechanisms of Action

- Differentiation to tissue of interest
- Paracrine actions via cytokine release
- Antioxidant actions
- Immune decoys
- Cell fusion

Potential Pitfall

- Human ASCs maintained in continuous culture for > 3-4 months
- Developed karyotypic abnormalities
- Caused tumors as xenografts in mice
  - *Rubio et al Cancer Research 2005*

Distribution of ASCs

- Provided to over 50 laboratories over past 6 years under NIDDK support (P0 cells)
- Characterized by donor BMI, age, gender
- New information will include immunophenotype, serum profile, HOMA-IR, adipokine level, differentiation potential
- Commercial production by LaCell LLC with distribution through a corporate partner

Pre-Clinical Animal Models

Tissue Type	Defect	Specie	Ref.
Adipose/Soft Tissue	Fat Pad Generation Lipodystrophy Burn/Radiation Trauma	Murine, Rat, Ovine Murine	45-54 55, 56 57-59
Bone	Critical Sized Defect Craniofacial Critical Sized Defect Long Bone Spinal Fusion	Murine, Rat Murine Rat	60, 61 62 63, 64
Cardiac	Myocardial Infarction	Murine, Rat	37, 38, 65, 66
Central Nervous System	Vascular Injury/Stroke Spinal Cord Trauma Multiple Sclerosis	Murine, Rat Rat Murine	39, 41, 67 42 68
Gastrointestinal Tract	Crohn's Disease/IBS	Murine	69
Hematopoiesis	Bone Marrow Transplantation	Murine	70, 71
Joint	Osteoarthritis	Canine, Caprine, Equine	72-75
Liver	Acute Toxicity/Regeneration	Murine	76-84
Pancreas	Type 1 Diabetes Mellitus	Murine, Rat	56, 85, 86
Renal	Acute Ischemia	Rat	(J.M.G.)
Skin	Wounds, Burns	Murine, Porcine	57, 59, 87
Tendon	Tendonitis	Equine	88
Urinary Bladder	Incontinence	Rat	89
Vascular	Hind Limb Ischemia	Murine, Rat	31, 36, 40

Gimble, Guilak & Bunnell Stem Cell Therapy & Research In Press

Clinical Arena

Where is the soft tissue engineering field moving?

- Intra-operative approaches with reduced regulatory oversight
- Mechanical closed systems for lipoaspiration and tissue processing
- Use of “minimally manipulated” stromal vascular fraction cells
- Combinations of SVF cells with lipoaspirates for cosmesis and reconstructive surgery
- Generation of acellular tissue extracts

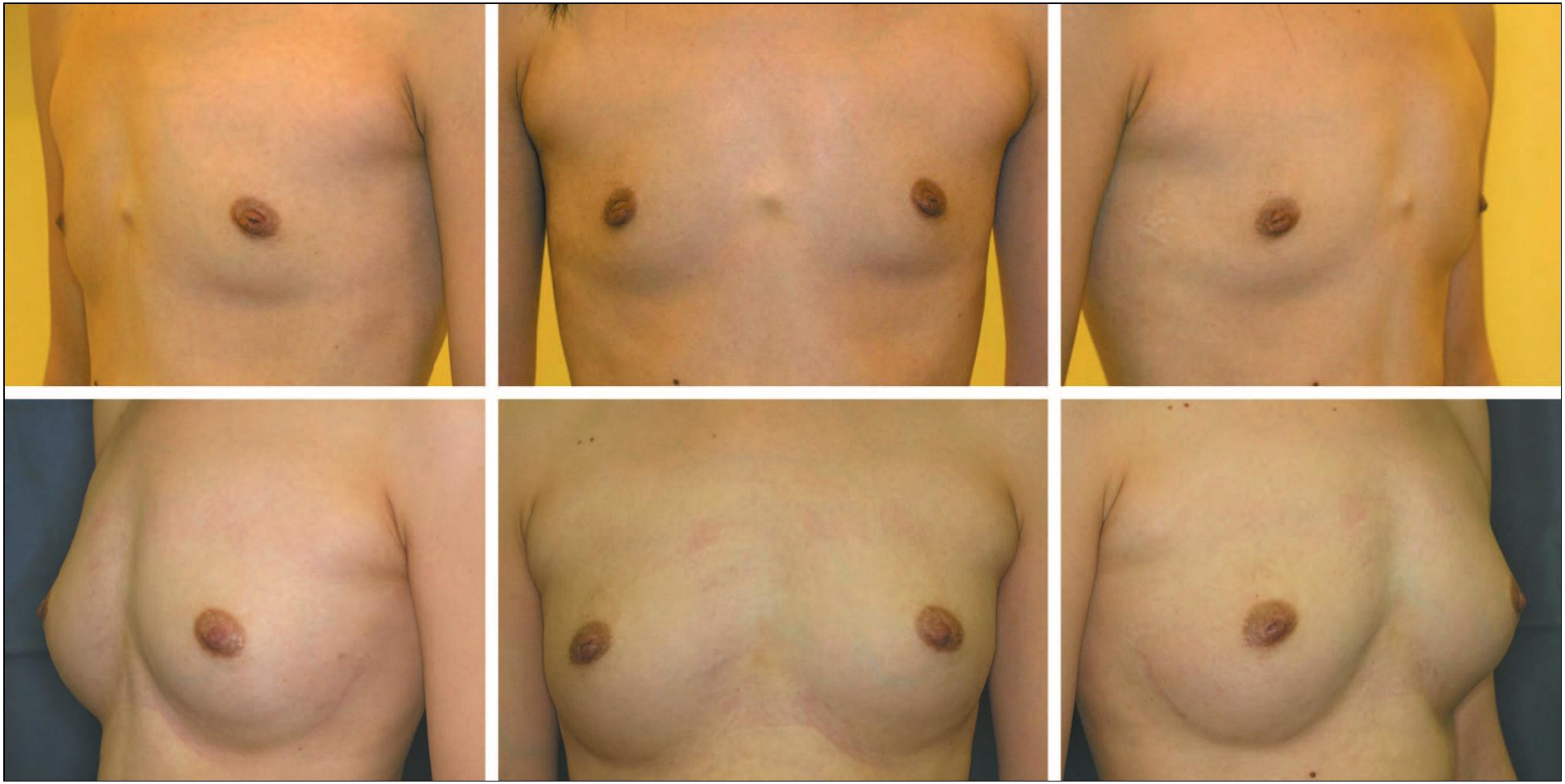
Cytori Therapeutics/GE Celution™ 700

Available in Europe and Asia; US/FDA Approval Pending

Reported Clinical Applications

- Breast & soft tissue reconstruction (Japan, Europe)
- Post-irradiation skin fibrosis (Italy)
- Vocal cord reconstruction (Italy)
- Cranial bone regeneration (Germany, Finland)
- Crohn's disease fistula repair (Spain)

Clinical Application – 1 Yr Follow-up (from Yoshimura, Tokyo, Japan)



Moseley et al. Plast Reconstr Surg.:121S, 2006
Matsumoto et al. Tissue Eng. 12:3375, 2006

Questions?

- Longevity of implants?
- Calcification and/or cyst formation?
- Tumor promotion or suppresion?
- Any other safety or efficacy issues?

Hard Tissue Reconstruction

Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells

K. Mesimäki, B. Lindroos, J. Törnwall, J. Mauno, C. Lindqvist, R. Kontio, S. Miettinen, R. Suuronen: Novel maxillary reconstruction with ectopic bone formation by GMP adipose stem cells. Int. J. Oral Maxillofac. Surg. 2009; 38: 201–209.

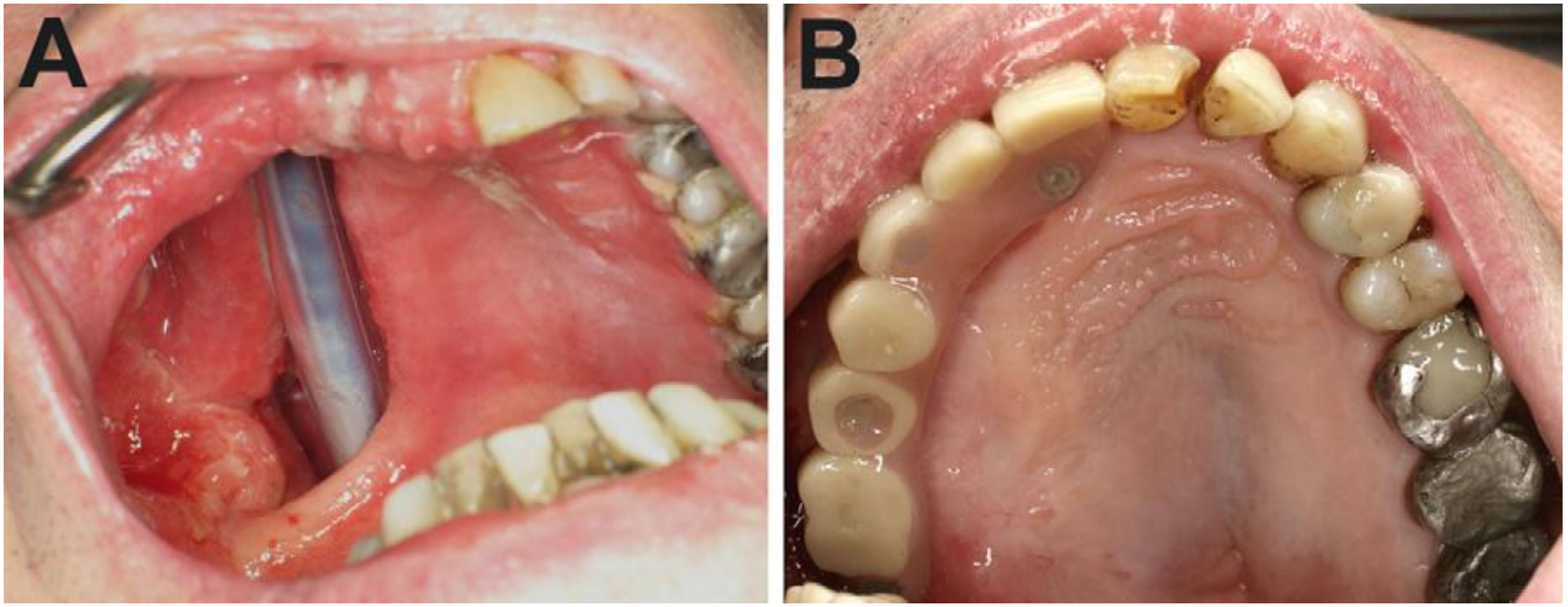
REGEA Institute, Tampere, & University of Helsinki, Finland

Clinical Approach

- 65 yr old male 28 months post hemimaxillectomy for keratocyst
- Harvest autologous adipose tissue and expand ASC in autologous serum
- Mix with HA/TCP and BMP2 inside titanium cage
- Implant in rectus abdominis muscle above epigastric artery for 6-8 months
- Transfer as free flap to repair palatal defect with anastomosis to facial artery
- Subsequent dental implants
- Success out to 1.5 year follow up

Repair of Soft Palate Defect (one of 14 patients)

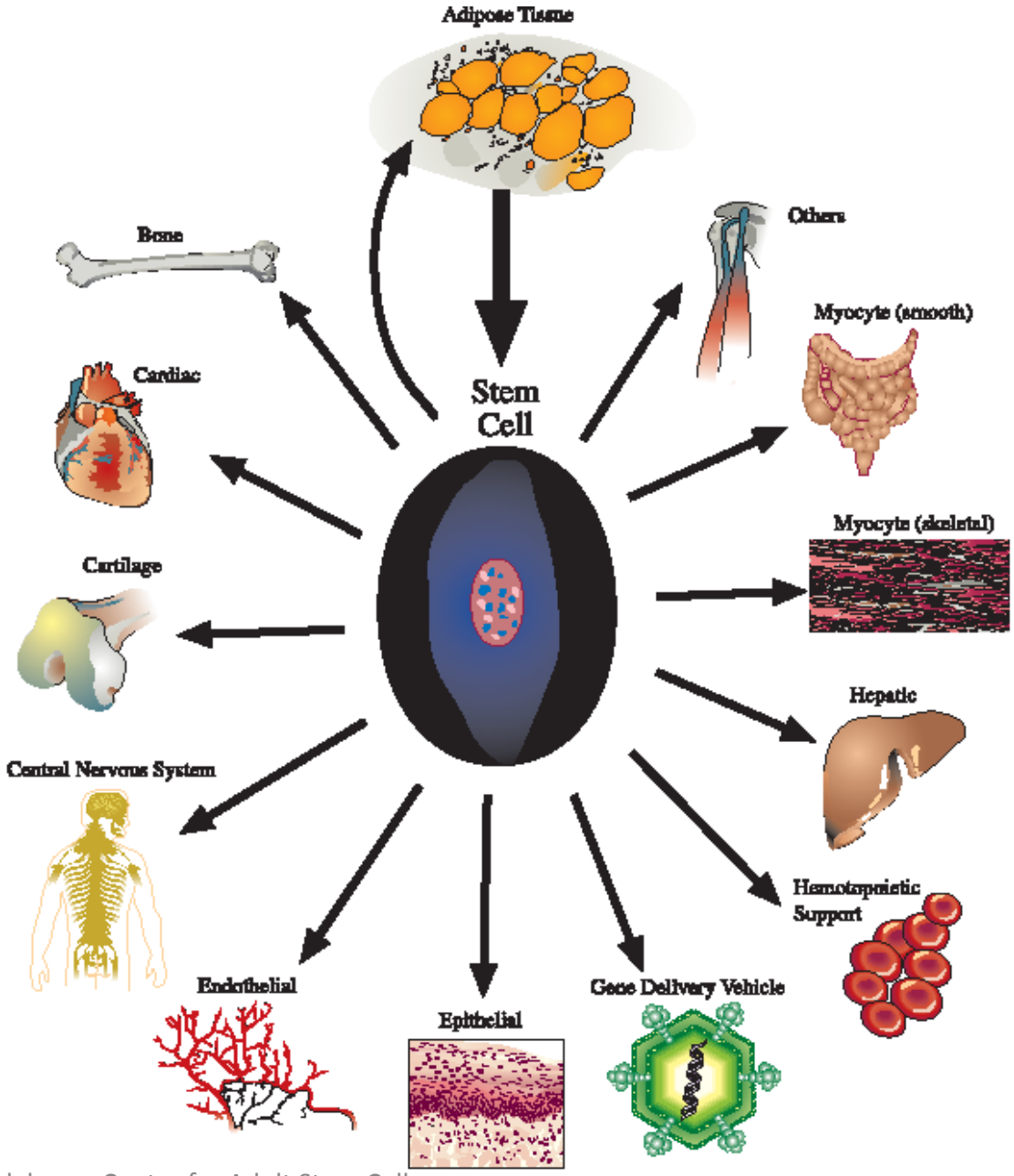
Before **After**



Mesimäki et al. Int J Oral Maxillofacial Surg 38:201, 2009

The Future

- Will we be using stem cells the way we currently use small molecules?
- Will stem cell therapeutics augment and enhance the current level of care we can offer to patients?
- Will it be cost effective?



Bottom line on ASC…

- Clinical landscape for ASC development faces more complex regulatory oversight than blood or BMT
- More information is known today about ASC than was available on blood or BMT at time of their initial clinical application
- ASC will be applied to both life-threatening & non-life threatening conditions
- Paradigms from blood & BMT have relevance to ASC development programs
- Public/private partnerships will be critical its success

Questions for the Audience

- What are your specific challenges & hurdles?
- What are the infrastructure needs you can identify that will make you more competitive?
- What are the relationships that can exist across the OUHSC/OMRF/OU/OSU campuses that can accelerate adult stem cell research?
- In other words, now you need to “pick my brain” before we end……

Thanks for your attention & hospitality!