Stem Cells: the State of the Art

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Historic arches at the entrance to UC Davis/CIRM Institute for Regenerative Cures
Liver repair and regeneration, bioengineered livers
Peripheral artery disease: revascularization to prevent amputation
Eye degeneration/blindness
Lung disease, lung repair and regeneration
Skin: Non-healing ulcers, burn repair
Bone repair, osteoporosis, cartilage regeneration
Heart disease, infarction repair and stroke
Neurodegenerative (Parkinsons, Huntingtons, Alzheimers, ALS)
Neurodevelopmental disorders (Autism spectrum, FX-TAS, others)
Kidney repair and regeneration
Bioengineered bladders, tracheas, and other tissues and organs
Blood disorders, autoimmune disorders (Scleroderma, MS)
HIV treatment using gene-modified stem cells
Hearing, inner ear cilia repair
Tumor stem Cells, Cell-based immunotherapy for Cancer
Stem cell types

- **Adult stem cells:**
  - Hematopoietic = blood-forming
  - Mesenchymal = supporting cells and generate bone and cartilage

- **Pluripotent cells:**
  - Embryonic stem cell lines
  - Induced pluripotent stem cells
Sources of MSC

Bone Marrow
Harvested from brave donors

Adipose tissue
Liposuction – to obtain subcutaneous fat or gastric bypass surgery – to obtain omental fat
Bone formation in a dish from human mesenchymal stem cells
• At UC Davis our patients needing faster/better bone repair are human, canine, and equine.
• The use of autologous MSC for each patient population is currently under development or in practice at UCD.
• Allogeneic sources are under consideration for traumatic injuries, since MSC need to be expanded for several weeks in vitro prior to use.
Horses with athletic injuries, seen in the UC Davis School of Veterinary Medicine’s Center for Equine Health, are now being successfully treated with their own expanded mesenchymal stem cells

- Important collaborations for vascular disease, knee, tendon and bone repair, offering team training opportunities
Commonly, MSC are transplanted between patients with zero regard to tissue matching. To ensure safety the MSC product does need to be FDA-approved: lacking antigenic cells
Osiris Therapeutics clinical trials with MSC

Crohn's Disease Phase II trial results:
• Every patient evaluated in the trial had a statistically significant reduction in disease severity. Improvement was rapid with a reduction in disease severity on day 7.

32 pts treated for GvHD, phase II:
• 94% of evaluable patients responded after receiving two infusions of PROCHYMAL. 74% of evaluable patients achieved a complete response (meaning that the patients had experienced total clinical resolution of the disease). Patients experiencing a complete response rate by day 28 had a statistically significant improvement in survival.

53 pts treated for MI, phase II:
• PROCHYMAL patients with major "anterior wall" heart attacks had a statistically significant 7.0 point (24%) improvement in ejection fraction at three months and a 7.3 point (25%) improvement at six months over baseline (p less than 0.05), while similar patients receiving placebo did not have significant improvement.

And 55 for knees, phase II –
• About 30% of patients treated with CHONDROGEN demonstrated an improvement in their baseline cartilage or joint condition, while no patients in the placebo group demonstrated similar improvement.
Commercially available allogeneic MSC/scaffold/growth factor product: Osteocel

**CELLS**

Osteocel Plus contains living bone cells, including *mesenchymal stem cells*. These bone cells are naturally present in our bodies and are essential for bone tissue formation and healing.

Osteocel Plus retains mesenchymal stem cells from *adult* tissue donors, avoiding the concerns associated with embryonic cells.

**SIGNALS**

Mesenchymal stem cells and other elements of Osteocel Plus are able to send signals to the body's own cells to involve them in bone formation.

**Scaffold**

Osteocel Plus also provides a scaffold, or support structure, for new bone to grow on and through.
Osteocel® Plus in extreme Lateral Interbody Fusion (XLIF®) (NUVA OC 0801)

Label: NuVasive, Inc.

URL: http://www.nuvasive.com

**Condition**  
Degenerative Disc Disease, Back Pain

**Intervention**  
bio logic, Osteocel Plus

Subjects will receive Osteocel Plus during their XLIF operation. Subjects will be followed for 24-months post-op to determine mean time to fusion. This data will be compared to published and/or retrospective data for autograft, synthetic ceramics and Bone Morphogenetic Protein (BMP).
Fluorescent Iron nanoparticle-loaded human stem cells are recruited to the site of ischemic injury within 12 hours

Tail vein injection of $5 \times 10^5$ human stem cells at $T = 0$ hours

Capoccia et al., Nolta lab, Blood, 2009
Increased vascular density in the infarct zone of NOD/SCID B2M null mice with AMI four weeks after transplantation of ALDHhiLin- (A), but not ALDHloLin- (B), sorted human UCB cells

Nolta JA
Figure 6

Staining = anti-mouse CD31

Sondergaard et al, in press 2010
Mesenchymal stem cell migration
Blue area=$20 million
Of the $60 mil total cost funded by CIRM
Good Manufacturing Practice ("clean room") Facility

- High flexibility, versatility
  - 6 manufacturing labs
  - 3 intermediate labs
- Nolta and Bauer: two decades of experience with cell therapy trials
  - 18 trials since 1994

Currently establishing contracts with Stanford, Industry, and other Institutions

MSC expansion is underway for phase 1 trials
UC Davis GMP facility - 6 suites
Stem Cell Clinical Trials Ongoing/Pending at UC Davis

- Non-union bone fractures (Lee, Jamali, Dwyre: human trials, also done in Center for equine health) *Started in 2008*

- Cardiac infarction (Southard and UCD cardiovascular team) *Started Sept. 2009*

- Peripheral vascular disease caused by diabetes or other causes of poor circulation (Laird, UC Davis Vascular Center) *2010*

- Retinal Occlusion, causing blindness (Park, Telander, Bauer, Nolta) *pending, IND is with the FDA*

- Gene-Modified MSC for Huntington’s Disease (Wheelock, Nolta, HD team) *pending, IND is in process* and ALS – Lou Gehrig’s disease (Oskarsson, Joyce)

- MSC to secrete enzymes in lysosomal storage and other disorders (multiple PIs)

- Liver disease, when a suitable donor organ is not available (Zern, Tarantal, Nolta, and Liver Disease Team members)
Nolta lab tour guides at Institute for Regenerative Cures Grand Opening Event