



Stem Cells: the State of the Art

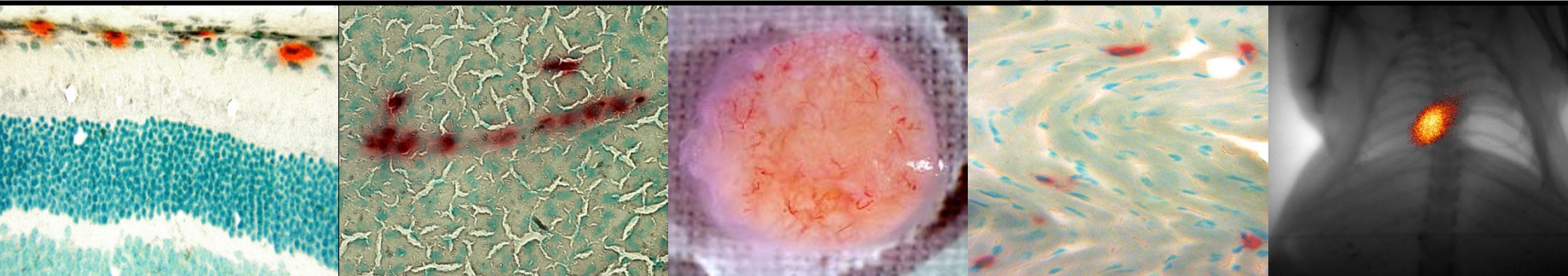
Jan A. Nolte, Ph.D., Professor and Director, UC Davis Stem Cell Program

Historic arches at the entrance to UC Davis/CIRM Institute for Regenerative Cures

UC Davis Stem Cell Program Disease Teams-

145 Basic, Translational, and Clinical Investigators working together toward stem cell cures

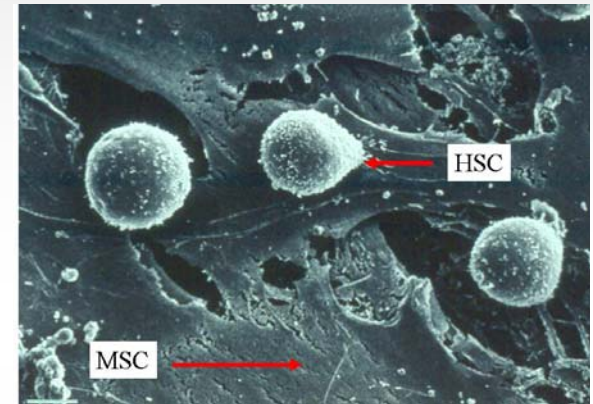
- Liver repair and regeneration, bioengineered livers
- Peripheral artery disease: revascularization to prevent amputation
- Eye degeneration/blindness
- Lung disease, lung repair and regeneration
- Skin: Non-healing ulcers, burn repair
- Bone repair, osteoporosis, cartilage regeneration
- Heart disease, 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

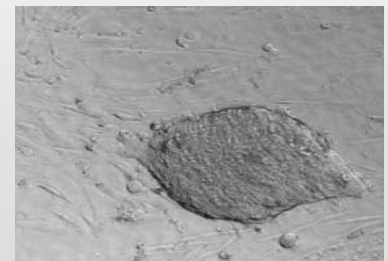
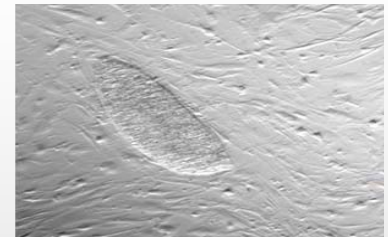
- **Adult stem cells:**

- Hematopoietic = blood-forming
- Mesenchymal = supporting cells and generate bone and cartilage

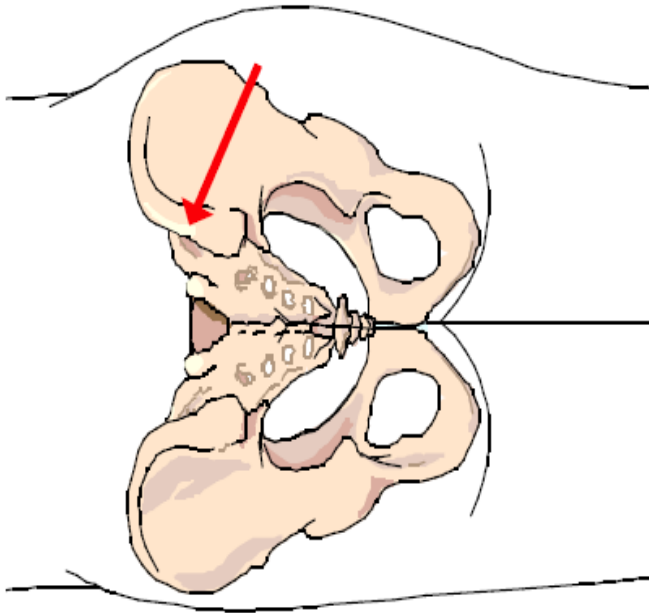


- **Pluripotent cells:**

- Embryonic stem cell lines
- Induced pluripotent stem cells

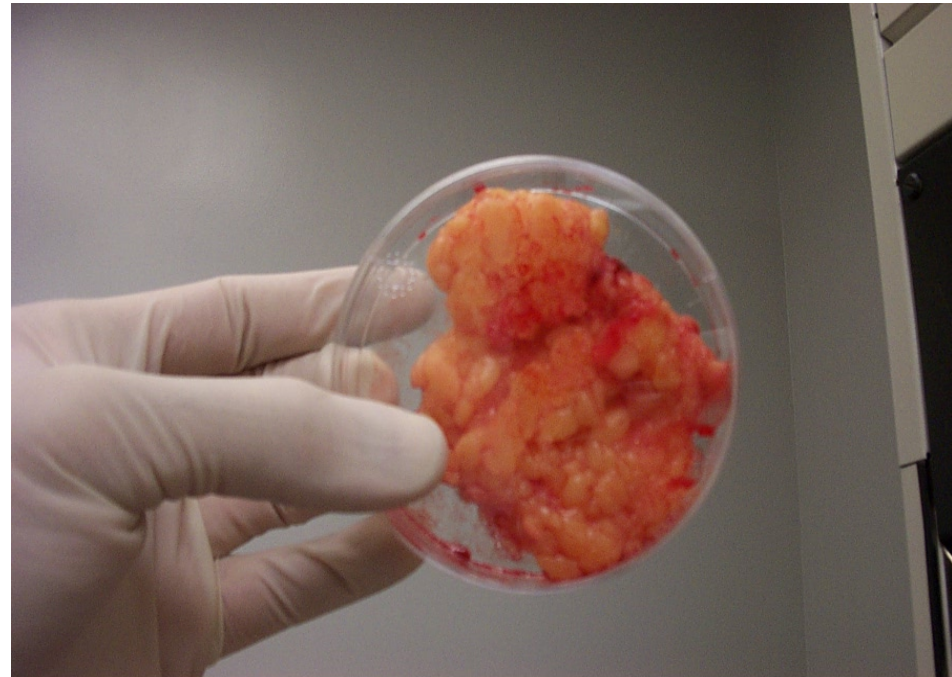


Sources of MSC



Bone Marrow

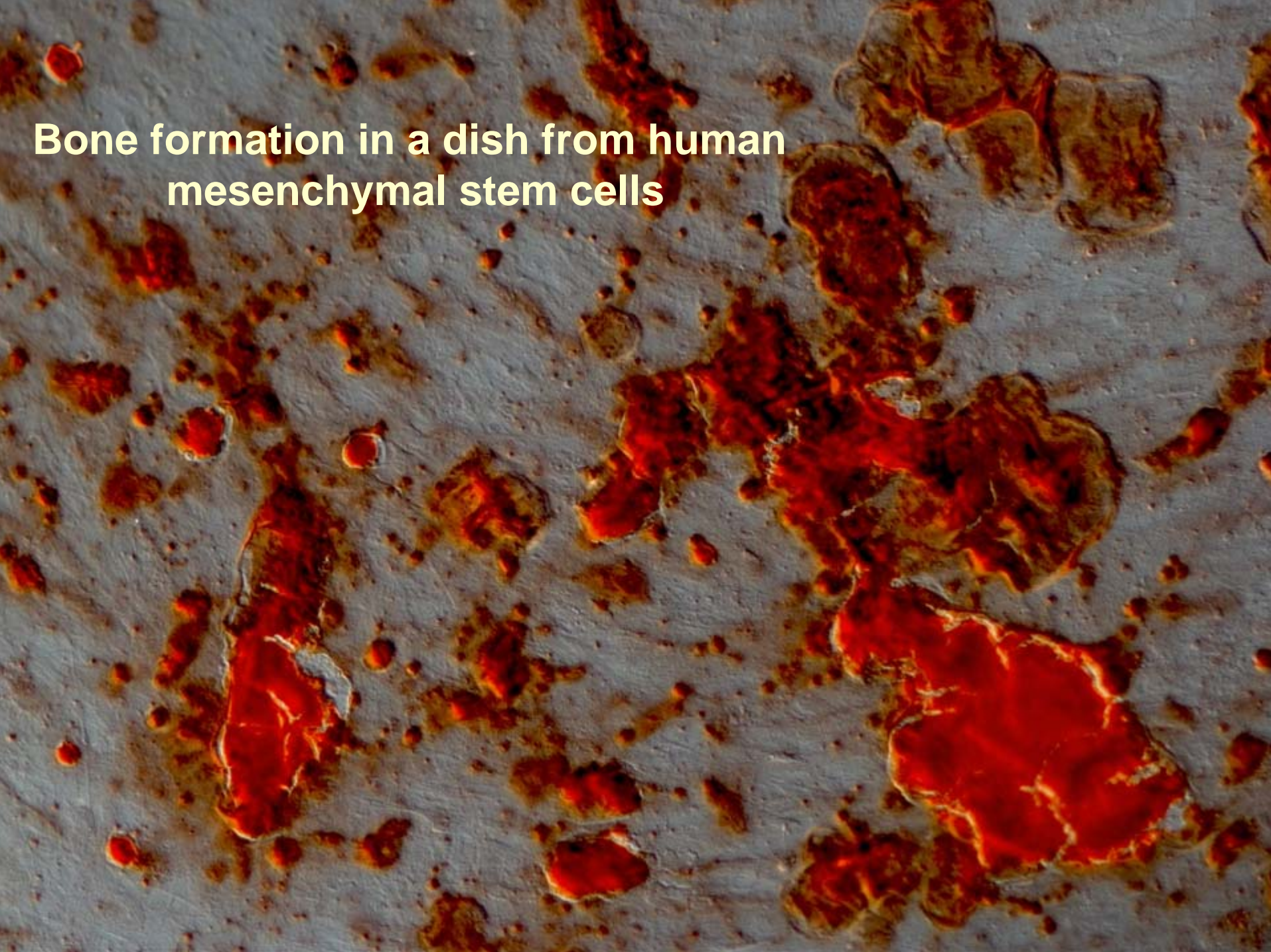
**Harvested from
brave donors**



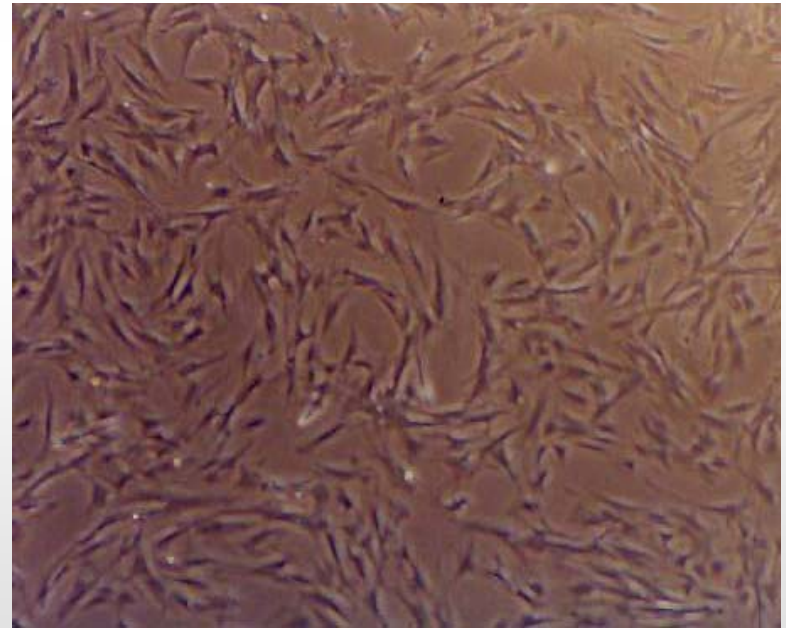
Adipose tissue

**Liposuction – to obtain
subcutaneous fat or gastric
bypass surgery – to obtain
omental fat**

Bone formation in a dish from human mesenchymal stem cells

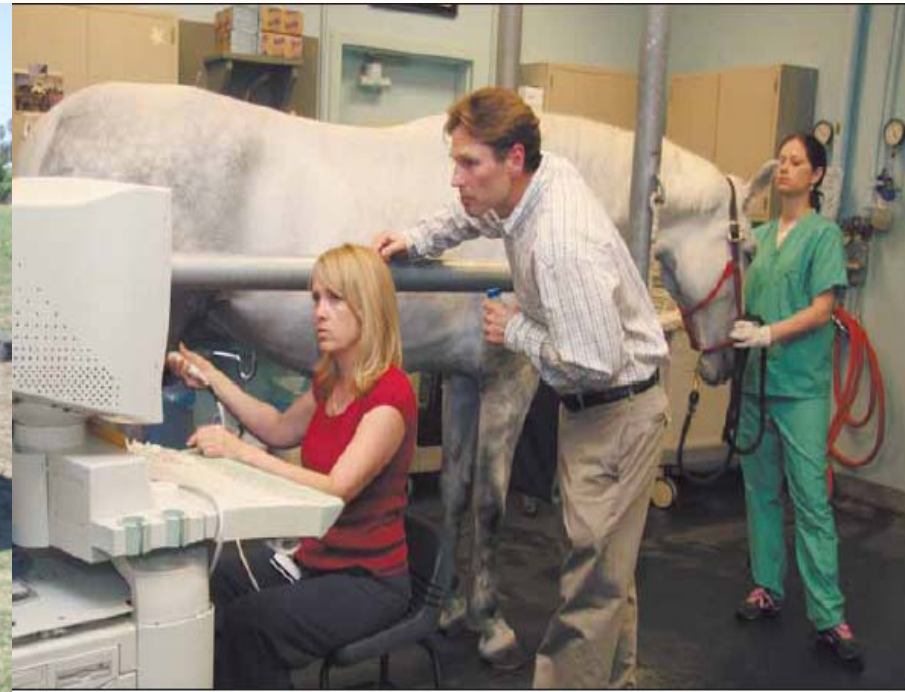


- At UC Davis our patients needing faster/better bone repair are human, canine, and equine.
- The use of autologous MSC for each patient population is currently under development or in practice at UCD.
- Allogeneic sources are under consideration for traumatic injuries, since MSC need to be expanded 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



Nature Reviews Immunology 8, 165 (March 2008)

Stem cells: Immunosuppression by mesenchymal stem cells

Elaine Bell

Mesenchymal stem cells (MSCs) are fibroblast-like cells that can develop into several types of tissue. MSCs have been shown to have immunosuppressive functions in various settings, including autoimmune diseases and transplantation, but the mechanisms by which MSCs suppress immune responses have not been clearly defined.

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.](http://www.nuvasive.com)

[URL:http://www.nuvasive.com](http://www.nuvasive.com)

Condition **Intervention** Degenerative Disc Disease, Back Pain
biologic, 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).



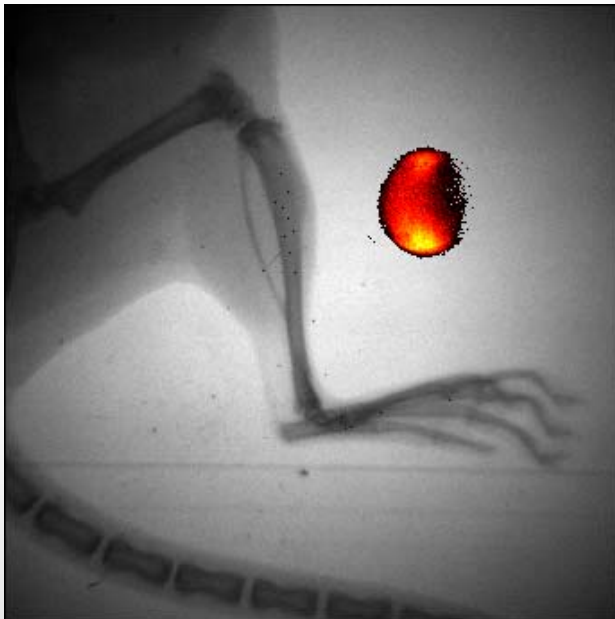
Cinicaltrials.gov



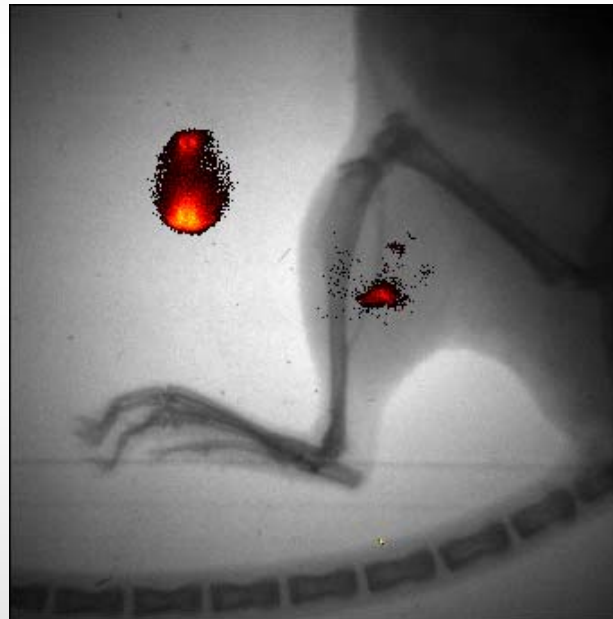
Fluorescent Iron nanoparticle-loaded human stem cells are recruited to the site of ischemic injury within 12 hours

Tail vein injection of 5×10^5 human stem cells at T = 0 hours

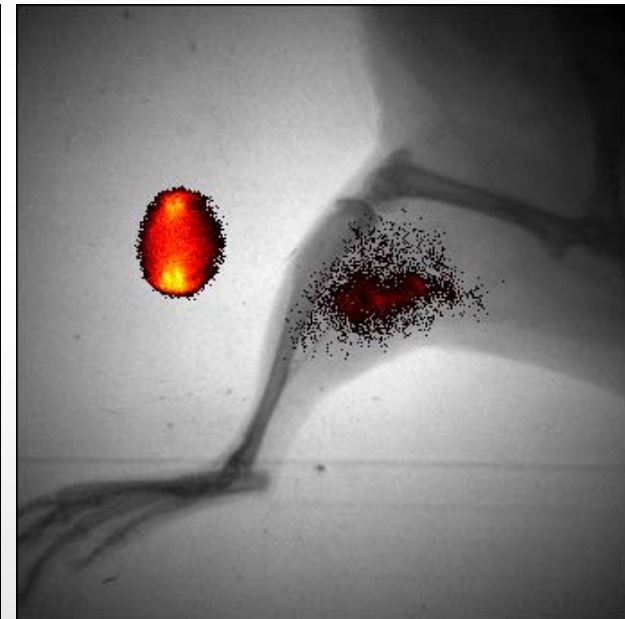
Non-ischemic Limb - 12 hours



Ischemic Limb - 12 hours



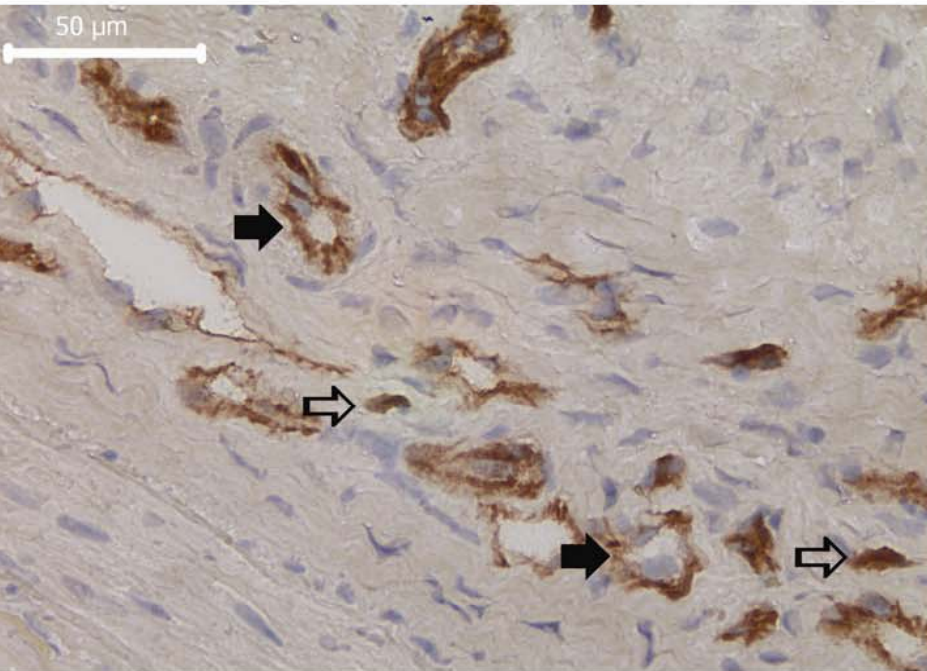
Ischemic Limb - 48 hours



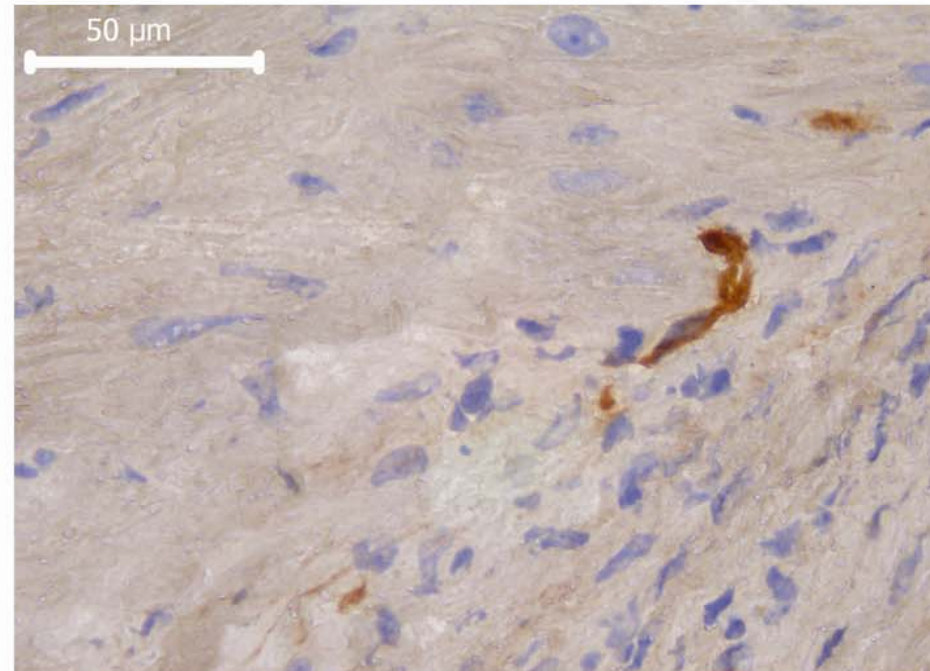
Capoccia et al., Nolta lab, Blood, 2009

Increased vascular density in the infarct zone of NOD/SCID B2M null mice with AMI four weeks after transplantation of ALDH^{hi}Lin⁻ (A), but not ALDH^{lo}Lin⁻ (B), sorted human UCB cells

A



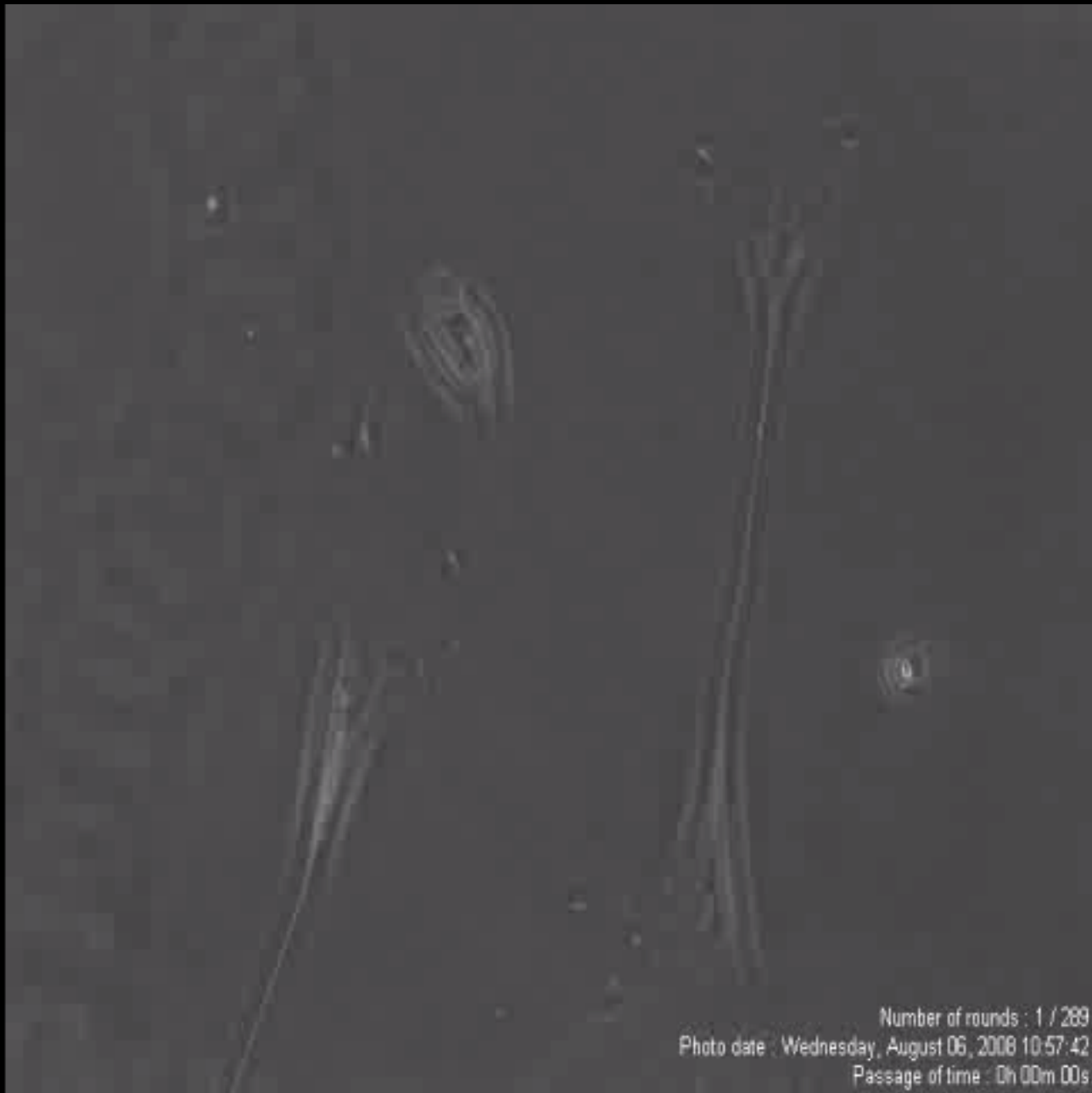
B



Nolta JA
Figure 6

Staining = anti-mouse CD31

Sondergaard et al, in press 2010



Mesenchymal stem cell migration

UC Davis Institute for Regenerative Cures

Proposed Auditorium

Shell space-

Shell space

Toxicology testing

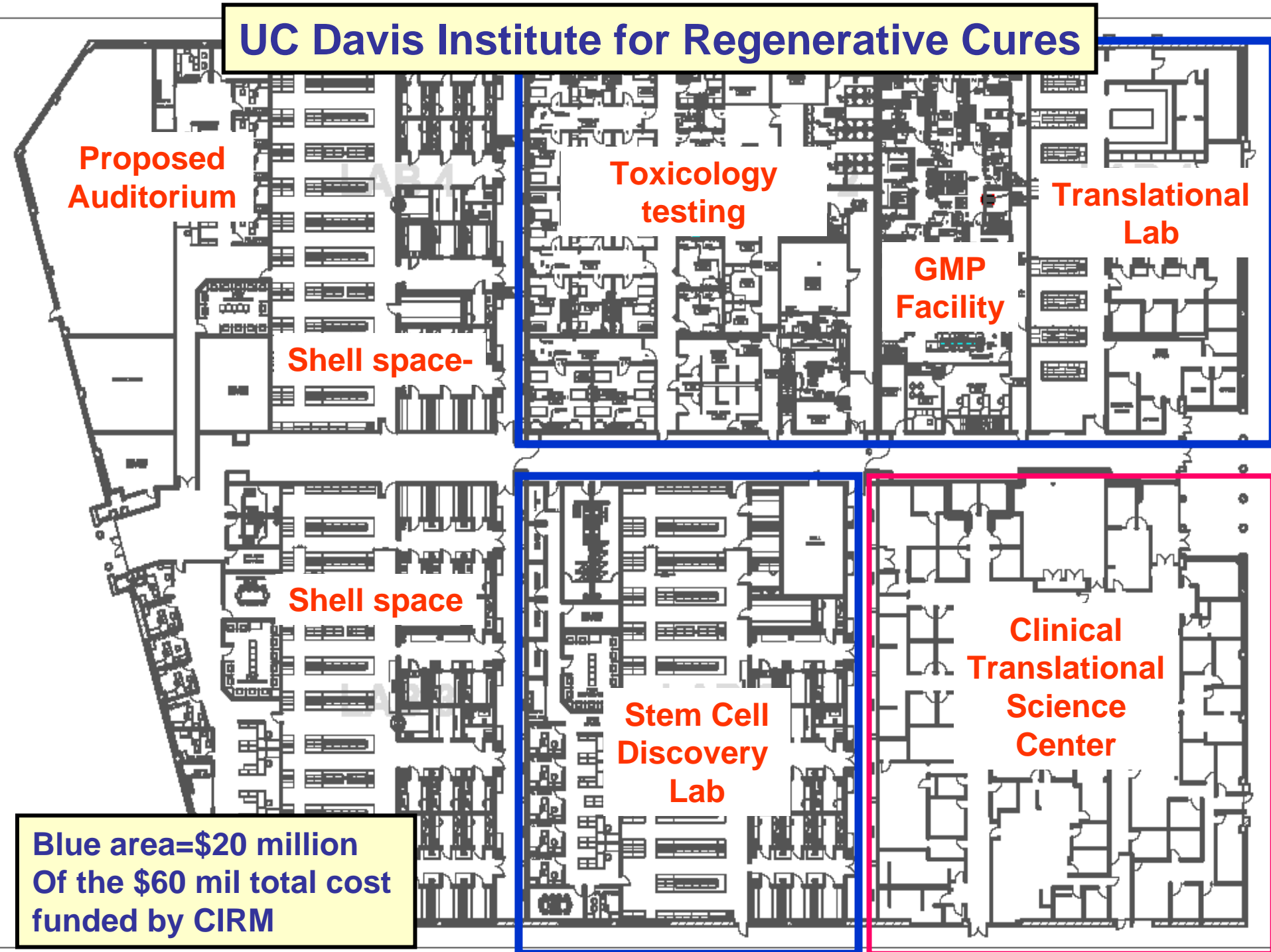
GMP Facility

Translational Lab

Stem Cell Discovery Lab

Clinical Translational Science Center

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

