Mesenchymal Stem/Stromal Cell (MSC) Therapies

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UC Davis Stem Cell Program and
Institute for Regenerative Cures

Editor, Stem Cells
Mesenchymal Stem/Stromal Cells (MSC)

Expansion of MSC from bony spicules/trabeculae since 1987

Techniques detailed in:

Genetic Engineering of Mesenchymal Stem Cells. Kluwer
Nolta JA (Editor). Feb 2006
MSC Mechanism of Action

• In areas of tissue damage, MSCs secrete factors that:
  - Stimulate revascularization
  - Recruit organ-specific stem cells and prevent cell apoptosis in the damaged region
  - Keep the immune system at bay during tissue remodeling
  - Reduce inflammation

• In most cases MSCs are not “becoming” the damaged tissue, but act through their effects on other cells.
MSCs – Statistically Significant Successes in Human Clinical Trials:

- Heart attack and critical limb ischemia - revascularization
- Orthopedics and spine fusion
- Cartilage repair (knee)
- Graft vs. Host disease after transplant (liver and gut)
- Autoimmune disorders (lupus)
- Crohn’s disease - related fistula
- Arthritis
- Stroke

Reviewed in: Murphy, Moncivais and Caplan, Exp. Mol. Medicine 2013
Injectable Bone Tissue Engineering Using Expanded Mesenchymal Stem Cells

Yoichi Yamada, Sayaka Nakamura, Kenji Ito, Eri Umemura, Kenji Hara, Tetsuro Nagasaka, Akihiro Abe, Shunsuke Baba, Yasushi Furuichi, Yuichi Izumi, Ophir D. Klein, Toshihiko Wakabayashi
MSCs can be engineered to secrete copious amounts of protein and other factors for delivery to target cells and tissues in the body ("supercharged drugstores")
Human MSC migrate rapidly and interact robustly, directly infusing damaged cells with protein, RNA and other factors

Funding; NIH Transformative Grant (Nolta)

Narrated video on: http://vimeo.com/46898303 courtesy of Gene Veritas
### Funded Projects

#### Disease Team Therapy Development Awards

<table>
<thead>
<tr>
<th>Number</th>
<th>PI</th>
<th>Title</th>
<th>Institution</th>
<th>Committed funds</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR2A-05415</td>
<td>Vicki Wheelock</td>
<td>MSC engineered to produce BDNF for the treatment of Huntington's disease</td>
<td>University of California, Davis</td>
<td>$18,950,061</td>
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<tr>
<td>DR2A-05309</td>
<td>Antoni Ribas</td>
<td>Genetic Re-programming of Stem Cells to Fight Cancer</td>
<td>University of California, Los Angeles</td>
<td>$19,999,563</td>
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<tr>
<td>DR2A-05302</td>
<td>Nancy Lane</td>
<td>Treatment of osteoporosis with endogenous Mesenchymal stem cells</td>
<td>University of California, Davis</td>
<td>$19,999,867</td>
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<tr>
<td>DR2A-05423</td>
<td>John Laird</td>
<td>Phase I study of IM Injection of VEGF-Producing MSC for the Treatment of Critical Limb Ischemia</td>
<td>University of California, Davis</td>
<td>$14,184,595</td>
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<tr>
<td>DR2A-05736</td>
<td>Nobuko Uchida</td>
<td>Neural stem cell transplantation for chronic cervical spinal cord injury</td>
<td>StemCells, Inc.</td>
<td>$20,000,000</td>
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<tr>
<td>DR2A-05394</td>
<td>Robert Robbins</td>
<td>Human Embryonic Stem Cell-Derived Cardiomyocytes for Patients with End Stage Heart Failure</td>
<td>Stanford University</td>
<td>$19,999,899</td>
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<tr>
<td>DR2A-05320</td>
<td>Clive Svendsen</td>
<td>Progenitor Cells Secreting GDNF for the Treatment of ALS</td>
<td>Cedars-Sinai Medical Center</td>
<td>$17,842,617</td>
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<tr>
<td>DR2A-05365</td>
<td>Judith Shizuru</td>
<td>A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants</td>
<td>Stanford University</td>
<td>$20,000,000</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
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</table>

http://www.cirm.ca.gov/PressRelease_2012-07-26
PRE-CELL

A pre-cellular therapy observational study in early Huntington's Disease
UC Davis Health System

What is the PRE-CELL Study?
PRE CELL is an observational study (no intervention). A group of up to 40 patients with early-stage Huntington's Disease (HD) will be enrolled in this observational trial to establish a baseline and study changes over time in measures of movement, thinking, behavior, brain imaging, blood and spinal fluid markers. The information from the study assessments will help Dr. Wheelock and the research team learn more about the rate of change in these measures in people with early-stage HD. Participants enrolled in this study may be eligible to participate in a future planned study of stem cell therapy for Huntington's Disease.

Who Can Participate?
- People over 18 years of age that have tested positive for the HD gene expansion (CAG repeat number 38 and above)
- Early stage Huntington's Disease with some movement changes, but stable mood and thinking skills
- Must have a caregiver or informant willing to come to all study visits and complete observations forms
- Women and men with childbearing potential must agree to adequate birth control measures for the length of the study
- Additional study criteria apply that can be discussed with the study coordinator

What are the study procedures?
If you are interested in participating, Dr. Wheelock and the research team will first have to determine if you are eligible. That will be done by reviewing your medical records and performing a research screening visit. There will be physical and neurological examinations, and written and verbal tests to assess your mood and thinking skills. There will also be rating scales to measure your ability to function in day to day life. A brain scan, heart rhythm test, chest X-ray, spinal tap, and blood tests will be scheduled to make sure there are no underlying medical problems that would make it unsafe for you to participate. These tests will be repeated at 6 month intervals. You will be enrolled in the study for 12-18 months.

What are the risks associated with participating?
- Some people experience emotional discomfort when being observed for symptoms of HD
- Some people feel claustrophobic having a brain scan
- There may be minor pain and the possibility of bruising from blood draws, and the lumbar puncture
- There is the potential for a headache after a spinal tap
- Exposure to a minimal amount of radiation from the chest X-ray

What are the benefits to me if I decide to participate in PRE-CELL?
There will be no direct benefit to you in this observational trial, however you will be contributing to the growing knowledge of Huntington's Disease. Subjects who successfully complete PRE-CELL and meet future study eligibility criteria will be considered for a planned stem cell therapy trial in HD.

How do I learn more about PRE-CELL?
Contact:
Terry Tempkin, NP-C, MSN
(916) 734-6276
Teresa.Tempkin@ucdmc.ucdavis.edu

This study is approved by the Internal Review Board that monitors all research activities at UC Davis Health System. Funding provided by the California Institute of Regenerative Medicine (www.CIRM.ca.gov) DR2A-06416

We Can Do It!
PRE CELL

A Pre Cellular Therapy Observational Study in Early Huntington’s Disease

Case Report Form Subject Binder
UC Davis stem cell research team visit study partners in Spain

(SACRAMENTO, Calif.) — The UC Davis Health System research team that is working to speed therapies to people suffering from critical limb ischemia (CLI) recently returned from visiting its collaborative partners in Spain.

The collaboration between UC Davis and researchers in Cordoba began last year following an agreement between Spain’s Andalusian Initiative for Advanced Therapies and the California Institute for Regenerative Medicine (CIRM). It complements a $14.1 million CIRM grant to John Laird, professor of cardiovascular medicine and director of the UC Davis Vascular Center and Jan Nolta, director of the UC Davis Institute for Regenerative Cures, who are the co-principal investigators on a research project that includes human clinical trials for CLI in 2015.

The research effort involves using bioengineered mesenchymal stem cells to produce a revascularizing factor to restore blood flow and avoid the possible amputation that patients often face when they suffer from the devastating disease impacts of CLI. For the UC Davis study, cells will be injected into the legs of CLI patients to migrate to low-oxygen areas in the patient’s diseased limbs.

The five-person delegation, led by Laird, met with their research partners at the University Hospital Reina Sofia in Cordoba, where they visited the Maimonides Institute for Biomedical Research Córdoba and held meetings with teams of cardiovascular surgery, radiology and vascular cell therapy experts. The two teams are working in parallel on a phase I clinical trial of stem cell and gene therapy for CLI, in which genetically modified mesenchymal stem cells will be used to restore blood flow to the feet and legs of diabetic patients.

“Thanks to the collaborative work between the two centers it will be possible to compare the same therapy administered in two different ways,” said UC Davis researcher Fernando Fierro during an interview with the Córdoba Journal, the local Spanish newspaper that covered the group’s visit. “In California, it will be done intra-muscularly. In Cordoba, it will be done intra-arterially, so that way we can analyze which of the two stem cell routes are safer and show more effectiveness.”
From the lab to the patient
UC Davis Good Manufacturing Practice Facility

Cellular product manufacturing for clinical trials/regulatory agency approvals
Current Human Stem Cell Clinical Trials at UC Davis

- Peripheral artery disease
- Non-healing ulcers, burns and wounds
- Non-union bone fractures
- Heart disease; cardiac infarction
- Blood and autoimmune disorders
- Traumatic brain injury
- Chronic pain – spine
- Disc degeneration
- Eye degeneration

- Plus another 18 in the “pipeline”
Approved therapy: BMT, organ transplant, Skin expansion/grafting, Cord Blood transplant
UC Davis CTSC Clinical Research Center (CCRC)

Devoted to conducting novel clinical trials, and is assisting with those described today

Forms the template for our planned UC Davis Stem Cell Therapy Alpha Clinic
Not just for humans- clinical trials of stem cell therapy are also ongoing at the UC Davis School of Veterinary Medicine to treat dogs, cats, horses, and other companion animals.

Daisy received stem cells in her eye for our vision trial.

Whiskey had his jaw rebuilt after cancer, using tissue engineering.

Bailey was injected with her own stem cells to treat lameness.

(AND we have a Cord blood bank for horses!)

Mojito can swallow again thanks to Dr. Belafsky, lasers, and tissue engineering.