Lecture #20:
Stem Cell Therapies
Embryonic and Adult Stem Cells

THE SUPPLY CHAIN
Embryonic and adult stem cells as a source of new tissue.

Egg → Zygote → Blastocyst → Gastrula

- Ectoderm
- Mesoderm
- Endoderm

Embryonic stem cells
- Self renewal
- Differentiation signals
  - Endoderm
  - Mesoderm
  - Ectoderm

Somatic stem cells
- Self renewal
- Differentiation signals
  - Cell types restricted to organ source
  - Any cell type?
## Adult Stem Cells

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Stem cell location</th>
<th>Niche components</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tissues with constant turnover</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematopoietic system</td>
<td>Bone marrow</td>
<td>Macrophages*, T&lt;sub&gt;reg&lt;/sub&gt; cells*, osteoblasts, adipocytes, nestin* MSCs, CAR cells, glia</td>
</tr>
<tr>
<td>Intestine</td>
<td>Fast-cycling: base of crypt Slow-cycling: '+4 position'</td>
<td>Paneth cells*, mesenchymal cells</td>
</tr>
<tr>
<td>Interfollicular epidermis</td>
<td>Basal layer of epidermis</td>
<td>Dermal fibroblasts</td>
</tr>
<tr>
<td>Hair follicle</td>
<td>Bulge</td>
<td>K6&lt;sup&gt;+&lt;/sup&gt; bulge*, dermal papilla, adipocyte precursor cells, subcutaneous fat, dermal fibroblasts</td>
</tr>
<tr>
<td><strong>Tissues with low or no turnover</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>Subventricular zone, subgranular zone</td>
<td>Ependymal cells, vasculature</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Between the basement membrane and the muscle fibres</td>
<td>Myofibres* (?)</td>
</tr>
</tbody>
</table>

*Hsu and Fuchs, Nature Rev Mol Cell Biol, 2012*
Adult Stem Cell Therapies

- Bone marrow transplants to rebuild immune system (HSC)
- Skin grafts for burns or other injuries (skin stem cells)
* There are examples of intertissue plasticity- but likely happens at very low frequency under normal physiologic conditions
Cell Fusion as Possible Mechanism after Transfer

Umbilical-Cord Blood Transplantation

- Less restrictive HLA-compatibility requirements, can be provided quickly
- Variable volume, can have fewer cells than typical BM
- Public vs. private banking
Mesenchymal Stem Cells

MSC Therapies
Example: Myocardial Infarction

Ranganath et al, Cell Stem Cell, 2012
MSC Therapies
Example: Myocardial Infarction

Table 1. Ongoing MSC-Based Clinical Trials for Cardiovascular Diseases Registered at clinicaltrials.gov

<table>
<thead>
<tr>
<th>Clinical Trial ID</th>
<th>Phase</th>
<th>Condition</th>
<th>No. of Patients</th>
<th>Outcome Measure</th>
<th>Cell Delivery Route</th>
<th>Basis of Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01394432</td>
<td>III</td>
<td>AMI</td>
<td>50</td>
<td>LVSV</td>
<td>endocardial</td>
<td>reduction in scar formation and increased reverse remodeling</td>
</tr>
<tr>
<td>NCT00877903</td>
<td>II</td>
<td>MI</td>
<td>220</td>
<td>ESV, LVEF, infarct size</td>
<td>intravenous</td>
<td>improvement in myocardial remodeling and reduction in incidence of CHF</td>
</tr>
<tr>
<td>NCT00790764</td>
<td>II</td>
<td>SCI</td>
<td>60</td>
<td>safety</td>
<td>intracoronary and transendocardial</td>
<td>development of mature and stable vessels and improved cardiac function via combinatorial effect of BM-MNCs and MSCs</td>
</tr>
<tr>
<td>NCT00555828</td>
<td>I/II</td>
<td>MI</td>
<td>25</td>
<td>safety, feasibility</td>
<td>transendocardial</td>
<td>transdifferentiation of mesenchymal precursor cells (MPCs) into cardiomyocytes</td>
</tr>
<tr>
<td>NCT00672222</td>
<td>I</td>
<td>AMI</td>
<td>28</td>
<td>safety, efficacy</td>
<td>space surrounding target vessel (perivascular)</td>
<td>improvement in cardiac function via MSC paracrine actions</td>
</tr>
<tr>
<td>NCT01291329</td>
<td>II</td>
<td>AMI</td>
<td>160</td>
<td>myocardial metabolism, perfusion, LVEF</td>
<td>intracoronary</td>
<td>transdifferentiation of MSCs into cardiomyocytes</td>
</tr>
<tr>
<td>NCT00768066</td>
<td>I/II</td>
<td>IHF</td>
<td>60</td>
<td>safety</td>
<td>transendocardial</td>
<td>stimulation of endogenous cardiac stem cells by the transplanted MSCs</td>
</tr>
<tr>
<td>NCT00644410</td>
<td>I/II</td>
<td>CHF</td>
<td>60</td>
<td>LVEF</td>
<td>intramyocardial</td>
<td>development of new myocardium and blood vessels</td>
</tr>
<tr>
<td>NCT00587990</td>
<td>I/II</td>
<td>LVD</td>
<td>45</td>
<td>safety, LVEF, infarct size, ESV</td>
<td>intramyocardial</td>
<td>combinatorial effects of bypass surgery and MSC transplantation</td>
</tr>
<tr>
<td>NCT00721045</td>
<td>II</td>
<td>HF</td>
<td>60</td>
<td>safety, efficacy</td>
<td>transendocardial</td>
<td>MPC-induced large blood vessel formation and cardiac repair</td>
</tr>
<tr>
<td>NCT00418418</td>
<td>II</td>
<td>MI</td>
<td>60</td>
<td>LVEF, safety</td>
<td>intramyocardial</td>
<td>combinatorial effects of bypass surgery and MSC transplantation</td>
</tr>
<tr>
<td>NCT00883727</td>
<td>I/II</td>
<td>MI</td>
<td>20</td>
<td>myocardial perfusion, infarct size</td>
<td>intravenous</td>
<td>transdifferentiation of MSCs into cardiomyocytes and production of new blood vessels</td>
</tr>
<tr>
<td>NCT01687996</td>
<td>I/II</td>
<td>LVD, MI</td>
<td>30</td>
<td>safety, efficacy</td>
<td>transendocardial</td>
<td>neo-myogenesis induced by transplanted allogenic and autologous MSCs</td>
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<tr>
<td>NCT00176920</td>
<td>I/II</td>
<td>MI, LVD</td>
<td>10</td>
<td>safety, efficacy</td>
<td>transendocardial</td>
<td>transdifferentiation of MSCs to produce new blood vessels</td>
</tr>
<tr>
<td>NCT01449032</td>
<td>II</td>
<td>CMI</td>
<td>60</td>
<td>safety, efficacy</td>
<td>not specified</td>
<td>angiogenesis</td>
</tr>
<tr>
<td>NCT01442129</td>
<td>II</td>
<td>HF</td>
<td>30</td>
<td>safety, efficacy</td>
<td>intramyocardial</td>
<td>MPC-induced angiogenesis via paracrine signaling combined with LVAD implantation</td>
</tr>
<tr>
<td>NCT01392625</td>
<td>I/II</td>
<td>NDC</td>
<td>36</td>
<td>safety, efficacy</td>
<td>transendocardial</td>
<td>neomyogenesis via MSC-CSC interaction</td>
</tr>
<tr>
<td>NCT01270139</td>
<td>I/II</td>
<td>CAD</td>
<td>180</td>
<td>plaque volume</td>
<td>stenting</td>
<td>functional restoration of blood vessels via nanoburning and MSC paracrine effects</td>
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<tr>
<td>NCT01436123</td>
<td>I</td>
<td>CAD</td>
<td>120</td>
<td>plaque volume</td>
<td>stenting</td>
<td>reduction of plaque via paracrine signaling in combination with burning effects from Si-Fe NPs</td>
</tr>
</tbody>
</table>

LVSV, left ventricular systolic volume; SCI, severe coronary ischemia; IHF, ischemic heart failure; CHF, congestive heart failure; LVD, left ventricular dysfunction; ESV, end systolic volume; LVEF, left ventricular ejection fraction; CMI, chronic myocardial ischemia; LVAD, left ventricular assist device; NDC, nonischemic dilated cardiomyopathy; CAD, coronary artery disease.

Ranganath et al, Cell Stem Cell, 2012
Question: Should Stem Cell Treatments Be Regulated As Drugs?
Directed Differentiation

Cohen & Melton, Nat Rev Genet, 2011
### Directed Differentiation

<table>
<thead>
<tr>
<th>Molecule name</th>
<th>Function</th>
<th>Effect/use</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid</td>
<td>Not known</td>
<td>Dopamine and motor neuron differentiation</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac differentiation</td>
<td>34</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>Not known</td>
<td>Retinal pigment epithelium differentiation</td>
<td>84</td>
</tr>
<tr>
<td>Retinoic acid</td>
<td>Endogenous small molecule</td>
<td>Neuronal protocols</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinal protocols</td>
<td>35</td>
</tr>
<tr>
<td>Taurine</td>
<td>Endogenous small molecule</td>
<td>Retinal differentiation</td>
<td>35</td>
</tr>
<tr>
<td>PD173074</td>
<td>FGF inhibitor</td>
<td>Blocks endogenous caudalizing signals in motor neuron differentiation</td>
<td>86</td>
</tr>
<tr>
<td>SU5402</td>
<td>FGF inhibitor</td>
<td>Blocks otic induction</td>
<td>19</td>
</tr>
<tr>
<td>Hh.Agf.3</td>
<td>Hedgehog agonist</td>
<td>Induces motor neurons</td>
<td>24</td>
</tr>
<tr>
<td>C61414</td>
<td>Hedgehog antagonist</td>
<td>Blocks motor neuron induction</td>
<td>86</td>
</tr>
<tr>
<td>KAAD-cyclopamine</td>
<td>Hedgehog antagonist</td>
<td>Induces pancreatic cells from endoderm</td>
<td>20,31</td>
</tr>
<tr>
<td>LY294002</td>
<td>Phosphoinositide 3-kinase inhibitor</td>
<td>Enhances activin A signalling to generate endoderm</td>
<td>29,33</td>
</tr>
<tr>
<td>Indolactam V</td>
<td>Protein kinase C inhibitor</td>
<td>Induces pancreatic progenitors from endoderm</td>
<td>31</td>
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<tr>
<td>ALK inhibitor</td>
<td>TGFβ signalling inhibitor</td>
<td>Neuron and hepatocyte differentiation</td>
<td>27–29</td>
</tr>
<tr>
<td>(SB-431542)</td>
<td>(inhibitor of activin/Nodal signalling)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIS3</td>
<td>TGFβ signalling inhibitor</td>
<td>Otic induction</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>(inhibits SMAD3)</td>
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</table>

ALK, activin receptor-like kinase; FGF, fibroblast growth factor; KAAD, 3-keto-N-(aminoethyl-aminocaproyl-dihydrocinnamoyl); SIS3, specific inhibitor of SMAD3; TGF, transforming growth factor.

Cohen & Melton, Nat Rev Genet, 2011
Directed Differentiation- β cells

ES/iPS → endoderm → pancreas → endocrine → insulin

Sox17 → Pdx1 → Ngn3

IDEs, indolactam V

Melton D A Phil. Trans. R. Soc. B 2011;366:2307-2311
How can you obtain pluripotent stem cells (ES cells) from a particular patient?
Reprogramming of Somatic Cells

• Somatic Cell Nuclear Transfer, i.e. Cloning

Reprogramming of Somatic Cells

- Somatic Cell Nuclear Transfer, i.e. Cloning

http://www.pbs.org/wgbh/nova/body/cloning-process.html
Reprogramming of Somatic Cells

- Induced Pluripotent Stem Cells (iPS)

Skin fibroblasts

Retroviral transfection of 4 transcription factors: Oct-4, Sox2 (pluripotency); c-Myc, Klf-4 (proliferation)

Select Nanog+ cells

iPS cells
Highly Efficient Reprogramming to Pluripotency and Directed Differentiation of Human Cells with Synthetic Modified mRNA

Luigi Warren,1,7 Philip D. Manos,3,4,7 Tim Ahfeldt,4,6,7,8 Yin-Han Loh,8,9,10 Yiu Li,11,12,13 Frank Lau,4,10 Wataru Ebina,1
Panaj K. Mandal,1 Zachary D. Smith,14 Alexander Meissner,4,14 George Q. Daley,3,4,6,15,16 Andrew S. Brack,5,7
James J. Collins,11,12,13 Chad Cowan,4,5,13 Thorsten M. Schlaeger,2,8 and Derrik J. Ross11,5,10,*

1Immune Disease Institute, Program in Cellular and Molecular Medicine
2Stem Cell Program
3Manton Center for Orphan Disease Research
4Children’s Hospital Boston, Boston, MA 02115, USA
5Department of Stem Cell and Regenerative Biology
6Harvard Stem Cell Institute
7Harvard University, Cambridge, MA 02138, USA
8Center of Regenerative Medicine, Massachusetts General Hospital, 185 Cambridge Street, Boston, MA 02114-2790, USA
9Department of Biochemistry and Molecular Biology II, Molecular Cell Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
10Division of Pediatric Hematology/Oncology, Children’s Hospital Boston and Dana-Farber Cancer Institute, Boston, MA 02115, USA
11Department of Biological Chemistry and Molecular Pharmacology
12Department of Pathology
13Harvard Medical School, Boston, MA 02115, USA
14Department of Biomedical Engineering and Center for BioDynamics, Boston University, Boston, MA 02215, USA
15Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA 02115, USA
16Stowers Medical Institute, 185 Cambridge Street, Boston, MA 02114, USA
17Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA
18Howard Hughes Medical Institute
19Division of Hematology/Oncology, Brigham and Women’s Hospital, Boston, MA 02115, USA
20These authors contributed equally to this work
21These authors contributed equally to this work

Correspondence: rossi@hms.harvard.edu
DOI 10.1016/j.stem.2010.08.012

## Best Method?

<table>
<thead>
<tr>
<th></th>
<th>ES</th>
<th>ES/SCNT</th>
<th>iPS</th>
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<tr>
<td>Immune</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compatibility</td>
<td></td>
<td></td>
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<tr>
<td>Yield</td>
<td></td>
<td></td>
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<tr>
<td>Expansion</td>
<td></td>
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<tr>
<td>Affordability</td>
<td></td>
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<tr>
<td>Tumors</td>
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<tr>
<td>Ethics</td>
<td></td>
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</table>
## Best Method?

<table>
<thead>
<tr>
<th></th>
<th>ES</th>
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<th>iPS</th>
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<tr>
<td><strong>Immune Compatibility</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Yield</strong></td>
<td>+</td>
<td>--</td>
<td>- ... +</td>
</tr>
<tr>
<td><strong>Expansion</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Affordability</strong></td>
<td>-</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Ethics</strong></td>
<td>-</td>
<td>--</td>
<td>+</td>
</tr>
</tbody>
</table>

*(After Differentiation OK- All will Form Teratomas if Not Differentiated)*

Approx. $5,000, But decreasing
iPS- Disease Models

Melton D A Phil. Trans. R. Soc. B 2011;366:2307-2311
A Screen For Neuronal-Fate-Inducing Factors

Transfect with a panel of 19 neuronal genes

Vierbuchen et al, Nature 2010
Defining a Minimum Pool for Neuronal Induction

A, Ascl1; B, Brn2; M, Myt1l; O, Olig2; Z, Zic1

Vierbuchen et al, Nature 2010
Direct Conversion of Cardiofibroblasts to Cardiomyocytes

Ieda et al, Cell 2010
Direct Conversion *In Vivo*

**In vivo reprogramming of adult pancreatic exocrine cells to β-cells**

Qiao Zhou¹, Juliana Brown², Andrew Kanarek¹, Jayaraj Rajagopal¹ & Douglas A. Melton¹

One goal of regenerative medicine is to instructively convert adult cells into other cell types for tissue repair and regeneration. Although isolated examples of adult cell reprogramming are known, there is no general understanding of how to turn one cell type into another in a controlled manner. Here, using a strategy of re-expressing key developmental regulators *in vivo*, we identify a specific combination of three transcription factors (*Ngn3* (also known as *Neurog3*) *Pdx1* and *Mafa*) that reprograms differentiated pancreatic exocrine cells in adult mice into cells that closely resemble β-cells. The induced β-cells are indistinguishable from endogenous islet β-cells in size, shape and ultrastructure. They express genes essential for β-cell function and can ameliorate hyperglycaemia by remodelling local vasculature and secreting insulin. This study provides an example of cellular reprogramming using defined factors in an adult organ and suggests a general paradigm for directing cell reprogramming without reversion to a pluripotent stem cell state.
As is the case for embryo-derived stem cells, application of reprogrammed human induced pluripotent stem cells is limited by our understanding of lineage specification. Here we demonstrate the ability to generate progenitors and mature cells of the haematopoietic fate directly from human dermal fibroblasts without establishing pluripotency. Ectopic expression of OCT4 (also called POU5F1)-activated haematopoietic transcription factors, together with specific cytokine treatment, allowed generation of cells expressing the pan-leukocyte marker CD45. These unique fibroblast-derived cells gave rise to granulocytic, monocytic, megakaryocytic and erythroid lineages, and demonstrated in vivo engraftment capacity. We note that adult haematopoietic programs are activated, consistent with bypassing the pluripotent state to generate blood fate: this is distinct from haematopoiesis involving pluripotent stem cells, where embryonic programs are activated. These findings demonstrate restoration of multipotency from human fibroblasts, and suggest an alternative approach to cellular reprogramming for autologous cell-replacement therapies that avoids complications associated with the use of human pluripotent stem cells.
ES/iPS Clinical Therapies

• Advanced Cell Technology
  Macular degeneration- less rejection (BBB)
  Clinical Assessment tools, animal models
ES/iPS Clinical Therapies

• Advanced Cell Technology
  Macular degeneration- less rejection (BBB)
  Clinical Assessment tools, animal models

• Geron
  Clinical trial- human ES-derived oligodendrocytes to treat spinal cord injuries
ES/iPS Clinical Therapies

- Advanced Cell Technology
  Macular degeneration- less rejection (BBB)
  Clinical Assessment tools, animal models

- Geron
  Clinical trial- human ES-derived oligodendrocytes to treat spinal cord injuries

But....
Geron Study- Nov ’11

REGENERATING MUSCLE

Stem-cell pioneer bows out

Geron halts first-of-its-kind clinical trial for spinal therapy.

BY HONYA BAKER

The field of stem cell therapy has become a major focus in the medical community, with many companies and research institutions working to develop new therapies for a wide range of diseases. However, one of the pioneers in the field, Geron, has announced that they will be halting their first-of-its-kind clinical trial for spinal therapy.

Geron, based in Menlo Park, California, announced on November 14, 2011, that they had met an important benchmark in their drug development process but that they did not meet an important clinical endpoint. This means that the drug, which was being tested for the treatment of spinal cord injury, did not achieve the desired level of effectiveness.

The decision was based on data from a Phase II clinical trial, which had been ongoing since 2006. The data showed that the drug did not meet the primary endpoint of improving motor function as measured by the American Spinal Injury Association Impairment Scale (ASIA). While there were some positive trends in secondary endpoints, the primary endpoint was not met.

Geron’s decision to halt the trial is a significant setback for the company, which had been working on this technology for over a decade. The company had invested over $1 billion in the development of the drug, and the decision to halt the trial will likely have a significant financial impact.

Geron’s decision comes after a series of other setbacks for the company, including the loss of several key researchers and the departure of its CEO in 2010. The company has been struggling to find new sources of funding, and the decision to halt the trial is a further blow to its already strained financial situation.

The impact of the decision on the field of stem cell therapy is likely to be significant. Geron was one of the pioneers in the field, and their work had been a key driver of progress in the development of stem cell therapies for spinal cord injury. The decision to halt the trial will likely delay the development of new therapies for this condition and could have implications for the development of other stem cell therapies.

Geron’s decision is also likely to have implications for the broader field of stem cell therapy. The company had been working on a range of other therapies, including treatments for age-related macular degeneration and heart failure. The decision to halt the spinal cord injury trial may signal a shift in the company’s focus, with a greater emphasis on other areas of research.

Geron’s decision is likely to be met with mixed reactions from the scientific community. While some may view the decision as a necessary step to ensure the safety and efficacy of new therapies, others may see it as a missed opportunity for the company to make significant progress in the field.

Overall, Geron’s decision to halt the spinal cord injury trial is a significant event in the field of stem cell therapy. The impact of the decision is likely to be felt for years to come, and it will be interesting to see how the company moves forward in the years ahead.
Important Current Questions and Research Areas

- Engraftment (what happens to transplanted stem cells?)
- Safety (ensure that stem cell treatments do not cause cancer or other diseases)
- iPS vs. ES (can iPS be used instead of ES)
- Immunological tolerance
- Adult stem cells in other tissues? (optimize expansion and function)
Regulation
Should Stem Cell Treatments Be Regulated As Drugs?
Regulation
Should Stem Cell Treatments Be Regulated As Drugs?

THIS WEEK

The darker side of stem cells

An investigation by Nature has found that patients in Texas are receiving unproven stem-cell treatments. The state and the company involved need to ensure that they follow FDA guidelines.

Stem cells offer the hope that one day they will be able to cure a huge range of disorders. But too many people are promising those cures to patients now, long before there is any evidence that they work. These claims are potentially misleading at best, and at worst could be downright harmful.

This week, Nature raises important questions about one company that works with adult stem cells: Celltex Therapeutics in Houston, Texas. Nature's investigation, reported on page 13, suggests that the company has supplied adult stem cells to Texas doctors who offer unproven treatments to patients, and that the company is involved in these treatments. One doctor claims that the treatments are part of a clinical study run by Celltex and that the company pays him US$500 a time to inject the cells into patients, who are charged up to $25,000 for a course. The US Food and Drug Administration (FDA) considers it to be a crime to inject unapproved adult stem cells into patients. David Eller, chief executive of Celltex, denies that the company is involved in treatment procedures, but would not comment on Nature's findings about how its cells are used or answer questions about them.

Celltex has the backing of state governor Rick Perry, who has tried adult-stem-cell treatments himself. And the company recently recruited Glenn McGee, editor-in-chief of the American Journal of Bioethics, to be its president of ethics and strategic initiatives. McGee, whose move they are akin to simple skin grafts from one part of the body to another, which do not require validation in an FDA-approved clinical trial.

The FDA can help to clarify these matters. A sensible first step in the new state regulations would be a requirement for any firm that plans to inject processed stem cells into patients to contact the FDA, which can advise on whether federal rules — the same federal rules that have already been used to arrest stem-cell practitioners and to stop a company pushing unapproved treatments elsewhere — apply to what they are doing. Once past that step, Texas could move on to develop its own safety regulations.

If the Texas Medical Board were to act according to its stated pledge to protect patients, then it would make clear the need for clinical validation of adult stem cells before use and would rescind the medical licences of any doctors in breach of rules on using unapproved treatments. If Celltex truly wants to help patients, then it should refuse to supply stem cells for medical procedures until those procedures are properly proven to be effective. And if the company is serious about demonstrating clinical effectiveness itself, then it should start by contacting the FDA about what needs to be done.

http://www.nature.com/nature/journal/v483/n7387/pdf/483005a.pdf
Controversial stem-cell company moves treatment out of the United States

Celltex to send patients to Mexico.

David Cyranoski
30 January 2013

US citizens who had pinned their hopes on a company being able to offer stem-cell treatments close to home will now need to travel a little farther. Celltex Therapeutics of Houston, Texas, stopped treating patients in the United States last year following a warning from regulators. A 25 January e-mail to Celltex customers indicates that the firm will now follow in the footsteps of many other companies offering unproven stem-cell therapies and send its patients abroad for treatment — but only to Mexico.

The stem-cell treatments offered by Celltex involved extracting adult stem cells from a patient, culturing them and then reinjecting them in a bid to replenish damaged tissue. It had been offering the treatment for more than a year — with one of its high-profile customers being Texas governor, Rick Perry — when the US Food and Drug Administration (FDA) wrote to the company on 24 September 2012 advising it that the stem cells it harvested and grew were more than "minimally manipulated" during Celltex’s procedures. As such, the FDA regarded the cells as
Regulation
Should Stem Cell Treatments Be Regulated As Drugs?

Patients Beware: Commercialized Stem Cell Treatments on the Web

A report by the International Society for Stem Cell Research (ISSCR)’s Task Force on Unproven Stem Cell Treatments outlines development of resources for patients, their families, and physicians seeking information on stem cell treatments.