Exploring human stem cell research: separating myth from reality

Dr. Tamra Werbowetski-Ogilvie
Assistant Professor, Regenerative Medicine
Department of Biochemistry & Medical Genetics
University of Manitoba
October 12, 2011
So, what is a stem cell?

Distinguishing and Defining Features of Stem Cells:

1. Self-renewal
2. Developmental Potential
What is so special about stem cells?

Self-renew and differentiate

Differentiate

Expansion (Dysregulated -Cancer)
Adult Stem Cells

Undifferentiated cells found in the differentiated tissue that can renew and mostly produce specialized cell types of tissue from which they originated.
Where are stem cells?

- Neural Stem Cells
- Muscle Stem Cells
- Skin Stem Cells
- Intestinal Stem Cells
- Germ Stem Cells
- Hematopoietic Stem Cells
- Mesenchymal Stem Cells

These stem cells have limited differentiation potential
Pluripotent Stem Cells

Primitive undifferentiated cells that have the potential to become all types of specialized cells that make up the body

Where do they come from? How do we get them?
Human pluripotent stem cells: hPSCs

- Human embryonic Stem Cells (hESCs)
- Induced pluripotent stem cells (iPS cells): skin to stem cell
Where do hESCs come from?

Day 1
- Blastocoel

Day 2
- Zygote divides

Day 3-4
- Trophoderm
- Placenta and other tissues

Day 5: Blastocyst Development
- Inner cell mass
- Cells of the body

Fertilization
- Day 1
- Day 2
- Day 3-4
- Day 5
How do we get them?

Remove ICM

Irradiated Mouse Embryonic Feeders
- Matrigel
- Fibronectin
- Laminin

hES Cell Line
The Controversy, the ethics, and the laws

Departmental

Research Ethics Board (University)

Stem Cell Oversight Committee (SCOC) (Federal-CIHR)

Enforce and oversee Bill C-6 which is now a law

The Agency - Health Canada
Sequential Consent

• Extra embryos become an issue - where do they go from here?

Day 3 or Day 5 pre-implantation embryo/blastocyst

Implant

Freeze those of secondary quality
Consent: level 1 - Where do the embryos go?

- Discard
- Donate
- Subsequent Births
Consent: level 2 - If choose to discard, which way?

- If choose to discard, then destroy or research purposes
Issues with hESCs

• Ethical issue involving the use of embryos
• Use of animal products during derivation
• Cell rejection
From Skin to Stem Cells: iPS cells

Skin cell

Disease Models (chemical + genetic screening)

Sox 2
Oct 3/4
Nanog

Unknown processes

Pluripotent stem cell

“Personalized” Regenerative Medicine (no rejection)

Patent

Reprogramming
Issues with iPSCs

• Generation methods
  • genetically modified cells with viruses
  • genes that promote tumor progression
  • THESE ISSUES HAVE BEEN FIXED

• Efficiency
• Genetic integrity, epigenetic “memory”
• Controlling cells in a dish
• Similarities between pluripotent stem cells and cancer cells
Why study hPSCs?

1. Robust cell proliferation in tissue culture (contrast to adult stem cells)

2. Differentiation potential into many cell types

3. Immune privilege properties (vs. xenotransplantation and immunosuppression)
Why do we need hPSCs?

Hematopoietic reconstitution
(chemotherapy, irradiation, infection (HIV))

Myocardium: Smooth muscle, myocardiocytes, endothelial cells
(Myocardial infarction=Heart attack)

Skeletal Muscle
(Muscular dystrophy)

Neural Cells:
Motor Neurons in ALS, Dopaminergic Neurons in Parkinson’s,
Spinal Cord Injury

Islet Cell Regeneration
(Type I Diabetes)

Cancer
Leukemia and solid tumor cancer stem cells (ie. brain, lung, breast, colon, prostate)
Fundamentally an issue of applying our limited understanding of human developmental biology
Allowing pluripotent stem cell research to continue

• Unpredictable effects of policy, legalities and minority groups on health care in country
• Legislation well established for consent
• Benefits are immense - not only to regenerative medicine but in understanding cancer
Why do I study hPSCs?
Using hESCs as disease models

- Modeling disease in hESCs with p53 KO (Song et al., Cell Stem Cell, 2010)
- hESCs as models of Fanconi anemia (Tulpule et al., Blood, 2010)
- Recently been shown to model cancer and genetic disorders
Interface between human embryonic stem cells and brain tumours

What can we learn about malignant brain tumors from human embryonic stem cells?
Characterization of transformed-human embryonic stem cells (t-hESCs) that display cancer features.

- **Self-renewal/proliferation**
- **ES cell markers**
- **Differentiation**
- **Tumor formation**

hESCs

- TIC: 1:20000

T-hESCs

- TIC: 1:800

Werbowetski-Ogilvie et al., Nature Biotechnology, 2009
Embryonal tumours of the CNS: medulloblastoma and other pediatric tumours

- Presumably originate *in utero* – but not proven
- Few comparative normal counterparts in humans
- Recent studies have linked tumor signaling pathways to proteins associated with embryonic stem cells
- Question: Can we use embryonic stem cells to understand how pediatric neural tumors form?
Cancer-like hESCs in vivo: Infiltration of transformed cells along ventricles and cerebellum

Note: neural rosettes, high nuclear/cytoplasmic ratio and disorganized appearance, staining for neuronal and proliferative markers
The results so far

- Independently confirmed by neuropathologist as classic medulloblastoma/primitive neuroectodermal phenotype – embryonal CNS tumors
- Confirms *in vitro* data demonstrating predominant neuronal marker expression
- Comparative human model system from which to evaluate mechanisms of brain tumorigenesis from a new perspective
Why can’t we use iPS cells from brain tumors?

- Malignant cancer cells are exceedingly difficult to reprogram to iPS (too many genetic changes)
- To date, iPS cells have not been made from malignant brain tumors
- We cannot truly study early events using cancer cells with major genetic abnormalities
What are the stem cell misconceptions?
Discover your body’s own ability to renew itself.
“Stem Cells…”

The Future of Skin Rejuvenation

Über-sophisticated “stem cell creams” really do make you look younger... but can you afford them?

By Tiffany Stoebel

If you haven’t heard that “Stem-Cell” technology is revolutionizing skin care, you’re probably one of those people who...

“Paralyzing injections are so last year... especially when stem cell creams can give you natural-looking skin rejuvenation.”

Tiffany Stoebel Beauty Editor, MyFussDiet.com

“20 and 30 somethings are using these high-tech emulsions so they will always look young... 40 and 50 somethings are using them to look like they’re still in their 20s and 30s.”

Dr. Nathalie Chevreau, Ph.D., P.D.
Director of Women’s Affairs, Voss Laboratories™

Buy Now
StemCellin
Stem Cell Wrinkle Cream

Annual Fall Sale!
20% Off Every Purchase Over $100
Use Coupon code FALL at checkout

Stem Cell Skin Care
2008 Award Winning Ingredient

StemCellin® with 5% PhytoCellTec™:
- Extremely popular in Europe
- Swiss Patented Formula
- Made From Apple Stem Cells
- Enhanced with Vitamin C & E

The future of skin care...Today!

StemCellin® Stem Cell cream Intensive Emulsion
- 4% PhytoCellTec™ stem cell extract
- 2 oz. 90 day supply bottle
- Great light formula
- Made for night use
- Very popular in Europe

StemCellin® Stem Cell Serum
- 5% PhytoCellTec™ stem cell extract
- 2 oz. 90 day supply bottle
- Formulated all natural
- Activated by skin heat
- Made from Apple stem cells

$69.00

$79.00
Stem Cell Treatment - Accepting Patients Now.
www.cellmedicine.com
Medical Information: (800) 980-STEM
Multiple Sclerosis - Spinal Cord Injury - Autism - Rheumatoid Arthritis

Clinic Lemana Switzerland - 50 year cell therapy experience
www.lemana.com
Preserving your health capital.

GMP Cell Therapeutics | GMPbio.org
www.gmpbio.org
Clinical Cell Therapy Production including stem cell therapies

Scholarly articles for stem cell treatments
stem cell transplantation and cell therapy as an ... - Slavin - Cited by 1649
Treatment of severe acute graft-versus-host disease ... - Le Blanc - Cited by 1177
stem cell transplantation for the treatment of severe ... - Buckley - Cited by 414

Stem cell treatments - Wikipedia, the free encyclopedia
en.wikipedia.org/wiki/Stem_cell_treatments
Stem cell treatments. From Wikipedia, the free encyclopedia. Jump to: navigation, search. Stem cell treatments are a type of intervention strategy that introduces ... Current treatments Potential treatments Clinical Trials Stem cell use in animals

Stem Cell Treatment - Stem Cell Therapy - Stem Cell Research
stemcelltreatments.org/Stem_Cell_Treatment - Find comprehensive information regarding current stem cell Therapy. Treatment, Research and where to find a stem cell clinic near you.

Closer Look
www.lascr.org/publicindex.htm
A Closer Look at Stem Cell Treatments ... Clinics all over the world claim to offer stem cell treatments for a wide variety of conditions. But are all of these ...

News for stem cell treatments
What is stem cell therapy?
Culpeper Star Exponent - 10 hours ago
A. The term "stem cell therapy" can be applied to various medical treatments that utilize stem cells to promote healing. Due to the vast potential of stem ... 11 related articles
Stem cells helped heal a dog's crippling injuries - maybe
Philadephia Inquirer - 2 related articles
Injected Stem Cells In ALS Trial Allow Caustious Optimism for ...
Physical Therapy Products

Home - Stem Cell Network
www.stemcellnetwork.ca/
In pursuit of Canadian excellence and global leadership in applied stem cell ... Should the fight against bogus stem cell therapies be turned back to the lab? ...

Can they cure diseases? - Stem Cell Information

Stem Cell Warning
www.rctherapy.net
Read this report before getting Stem Cell treatments!

Stem-Kine
www.stem-kine.com
Natural Product Clinically Proven to Increase Circulating Stem Cells

Leaders in Biobanking
www.healthtech.com/biobanking
International Congress
November 7 - 8, 2011

Top Stem Cell Treatment
www.medra.com/StemCell
Breakthrough Stem Cell Therapy! 2009 Stem Cell Patients Treated

Human Stem Cells
www.neuroomics.com
Pancreas Derived hMSCs-Consistent, Easy to Grow and Reasonably Priced.

ScienceCell - Stem Cell Media
www.sciencecellonline.com
1 (877) 770 2925
Mesenchymal Stem Cell Media Invito - A Specialty Cell Culture Media

StemCell SkinRepair Cream
www.stemcellskincare.com
Anti-Wrinkle Cream As Seen On TV Rejuvenates Skin, Feel Younger!

Cell Therapy Switzerland
www.celltherapyprogram.com
Be 20 yrs younger, more energetic & healthy with Swiss Cell Therapy.

See your ad here »
Delhi stem cell jabs 'help woman walk again'

By Peter Foster in New Delhi and Nic Fleming

Last Updated: 11:55pm BST 14/04/2007

An Australian woman who was told she would never walk again after a car accident has claimed to be on her way to recovery after embryonic stem cell treatment from an Indian doctor.

When Sonya Smith, a 45-year-old mother of three from Brisbane, arrived in New Delhi for the treatment two months ago she was confined to a wheelchair and unable to control the most basic bodily functions.

After eight weeks of injections from Dr Geeta Shroff - a controversial pioneer of embryonic stem-cell research - Mrs Smith says she is able to stand with the aid of callipers and has regained bowel and bladder control.

She also reports recovering "deep sensation" in her thighs and feet and has been able to swing her legs. "When I first moved my toes, I was blown away," Mrs Smith told Sky News.
Human Fetal Stem Cell Therapy

A medical treatment whereby Human Fetal Stem Cells are transplanted into a patient. These cellular building blocks are usually administered intravenously and subcutaneously (under the skin). It is a painless procedure, which takes place in approximately one hour, and has no negative side effects.

The Fetal Stem Cell searches out, detects and then attempts to repair any damage or deficiency discovered, as well as releases growth factors, which stimulate the body’s own repair mechanisms.

Medra’s Medical Director William C. Rader, MD. has treated over one thousand patients with Human Fetal Stem Cells, including children and adults suffering from many of mankind’s most devastating diseases.
Very recent examples...all news outlets
The Reality of Stem Cell Tourism

Korean deaths spark inquiry
Cases highlight the challenge of policing multinational trade in stem-cell treatments.

BY DAVID CHANGWONK IN LOS ANGELES

The controversy over stem-cell tourism, in which patients travel to other countries for unapproved stem-cell treatments, continues to grow. In June, researchers in Thailand reported finding "strange cultures" in a patient who had died following a stem-cell therapy for kidney disease (see Nature 465, 997, 2010). And in August, an 18-month-old Romanian boy died after receiving a brain injection of stem cells.

Now South Korea is trying to crack down on the practice. Following the recent deaths of two Koreans who had received injections of stem cells, the Korea Food and Drug Administration and the health ministry last week launched an investigation into companies offering the treatments. But the latest cases highlight the difficulty of policing these therapies or determining their safety, because some companies are setting up operations around the globe, taking advantage of loopholes in other countries' regulations.

One of the companies under scrutiny is Seoul-based RNL Bio, which formulated the cells used to treat the two Korean patients. The firm prepared stem cells at its processing center in Seoul and shipped them to affiliated clinics in China, Japan and elsewhere. Patients traveled to these clinics to have the injections, which are illegal in South Korea.

RNL Bio is a subsidiary of RNL Life Sciences, which opened an office in California in 2008. Last week, Nature visited the office, situated in a shopping mall called Koreatown Galleria, to learn more about the company's products. Jack Shin, whose business card describes him as a "stem-cell consultant," explained that patients visit an affiliated Los Angeles clinic where a plastic surgeon removes a gram of fat tissue. The sample is sent to the company's Maryland processing center, where mononuclear stem cells — which normally regenerate fat, bone or cartilage in the body — are isolated and sent to Seoul to be cultured. Even the simplest stem-cell treatment, such as those for arthritis, require 100 million cells, says Hong. Preparing and banking these cells for three years costs US$7,000; every subsequent 100 million cells cost an additional $5,000. Standard courses are 600 million cells; see Shin. "The more you use, the better you get," he says.

Shin says that 15,000 patients worldwide, including 1,500 from the United States, have received injections of the firm's stem cells. About half have had facial injections, hoping to rejuvenate their appearance, but the company claims that the cells have been used to treat ailments including Parkinson's disease, kidney failure and diabetes.

STEM-CELL BANKING

Hong admits that there is not yet conclusive clinical trial evidence that the treatment helped these various conditions, although the company is running trials in South Korea. Hong and Shin would start offering a therapy that was proven effective, he says, that the company offers only stem-cell injection and banking services, not stem-cell therapy. "We don't offer therapy," he says. "It's true that we note the potential but we don't make promises.

But Hong and Shin do talk openly about treatments, and the company, for example, proffered details about injection sites and the diseases that could be treated. RNL Bio patients are recommended to go to affiliated clinics such as the RNL Sunrise Regenerative Medicine Center in Yangji, China. And Shin also provided a brochure that describes how a patient recovered from rheumatoid arthritis following treatment. According to the brochure, the patient was "infused by RNL staff" at the "Kang center.

And looking out from the front window of the Los Angeles office, a wide-screen TV broadcasts testimony of patients happy with the results of the company's services.

Stem-cell scientists contacted by Nature are skeptical about the efficacy of RNL preparations. "Stem-cell therapies for Parkinson's disease is biologically unfeasible," says Oliver Cooper, director of the Stem Cell Facility at Harvard University's Center for Neuroregeneration Research in Richmond, Massachusetts. Other scientists echoed his sentiments.

Cooper's team hopes to treat Parkinson's with stem cells. But the researchers will implant the cells only after they have differentiated into neurons. Injecting immature stem cells, he says, "does not provide a long-term treatment for Parkinson's disease, and the risk associated with uncontrolled growth of transplanted stem cells is unacceptable."

Angiomyeloproliferative Lesions Following Autologous Stem Cell Therapy
Dhamnep Thirabansanak,* Kaviatch Tantivongse,† and Paul Scott Thorner*‡

Departments of *Pathology and †Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; ‡Division of Pathology, Hospital for Sick Children, Toronto, Canada; and ‡Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

ABSTRACT

Some reports suggest that autologous hematopoietic stem cell transplantation holds potential for treatment of renal diseases such as lupus nephritis, but the safety of delivering various stem cell types (hematopoietic, mesenchymal, and endothelial precursors) is not well established. Here, we report a case of lupus nephritis treated by direct renal injection of autologous stem cells recovered from peripheral blood. The patient developed masses at the sites of injection and hematuria. We suspected transitional cell carcinoma but nephroscopy revealed that the masses were angiomylolipocytomatous lesions. We believe that this previously undescribed pathologic entity is stem-cell derived or induced. The biologic potential, including the neoplastic potential, of this lesion is unknown. This case illustrates that the development of angiomyeloproliferative lesions is a possible complication of stem cell therapy.

The Reality of Stem Cell Tourism

Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient

Ninette Amariglio\textsuperscript{1,2}, Abraham Hirshberg\textsuperscript{3}, Bernd W. Scheithauer\textsuperscript{4}, Yoram Cohen\textsuperscript{1}, Ron Loewenthal\textsuperscript{5}, Luba Trakhtenbrot\textsuperscript{2}, Nurit Paz\textsuperscript{1}, Maya Koren-Michowitz\textsuperscript{2}, Dalia Waldman\textsuperscript{6}, Leonor Leider-Trejo\textsuperscript{7}, Amos Toren\textsuperscript{6}, Shlomi Constantini\textsuperscript{8}, Gideon Rechavi\textsuperscript{1,6,*}

1 Cancer Research Center, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, 2 Institute of Hematology, Sheba Medical Center, Tel Hashomer, Israel, 3 Department of Oral Pathology, School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel, 4 Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, United States of America, 5 Tissue Typing Laboratory, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, 6 Department of Pediatric Hemato-Oncology, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, 7 Institute of Pathology, Tel Aviv Medical Center, Tel Aviv, Israel, 8 Pediatric Neurosurgery, Dana Children’s Hospital, Tel Aviv Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.
So, what are we doing about it?

- There are a lot of legitimate stem cell clinical trials, under proper control and government regulations (ie. Geron – hESCs for spinal cord injury)
- In Canada, multiple levels of consent and oversight
- ISSCR patient handbook, task force
- Appropriate websites for clinical trials
  - [http://www.cihr-irsc.gc.ca/e/42071.html](http://www.cihr-irsc.gc.ca/e/42071.html)
  - [http://www.closerlookatstemcells.org/Top_10_Stem_Cell_Treatment_Facts.htm](http://www.closerlookatstemcells.org/Top_10_Stem_Cell_Treatment_Facts.htm)
Still have ways to go: major challenges

- Control of differentiation
  - Yield has improved, but purity still an issue
  - Use of animal products *in vitro*
  - Generation methods
- Cell delivery
  - How many cells? Number of sites?
  - Single suspension, aggregates?
  - Optimal site
- Control of immune rejection
Still have ways to go: major challenges

- Preventing infection
- Design of clinical trials
- Ethical and legal considerations: Good manufacturing practice

- hPSCs for replacement therapy not yet a reality
- must not treat patients too soon
Take home messages

• 2 major sources of hPSCs: hESCs and iPS cells
• Ongoing work with hPSCs for transplantation and drug discovery
• Stem Cell Tourism has had a negative impact on public perception of research progress
• Still need more optimization before clinical application
Acknowledgements

- Ludivine Morrison
- Robyn McClelland