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Associate Professor of Medicine
Dallas Heart Ball Endowed Chair in Cardiac Research
University of Texas, Southwestern Medical Center
March 15th, 2013

This is to acknowledge that Dr. Schneider has disclosed a financial relationship with LoneStar Heart, Inc. (UT Southwestern BioCenter) related to this program, and that he will be discussing off-label uses in his presentation.

BIOGRAPHY:

Dr. Schneider earned his M.D./Ph.D. degrees in the Medical Scientist Training Program at Yale University School of Medicine and Graduate School. He completed his internal medicine and cardiovascular diseases training at Brigham and Women's Hospital while doing post-doctoral research at Harvard Medical School (Brigham and Women's Hospital, Children's Hospital and Dana Farber Cancer Institute). He was on staff at Brigham and Women's Hospital and the West Roxbury VA Medical Center in Boston until moving to UT Southwestern Medical Center in Dallas in 2003. He is currently tenured Associate Professor of Medicine at UT Southwestern Medical Center. His area of interest is chemical biology and drug discovery/development with focus on stem cell-modulator small-molecules that regulate heart repair, adult neurogenesis and pancreatic β cell function. With Drs. Eric Olson and Joseph Hill, Dr. Schneider is co-PI/co-director of three large national or Texas-wide consortium grants focused on developing novel therapeutics for heart repair after ischemic or cancer chemotherapy related heart injury (AHA-DeHaan Cardiac Myogenesis Research Center, NIH/NHLBI U01 Progenitor Cell Biology Consortium Hub and CPRIT MIRA). Recently, Dr. Schneider was appointed to the "Dallas Heart Ball Endowed Chair in Cardiac Research," established in 1997 from proceeds of the "Dallas Heart Ball" to promote research, treatment and cure of heart disease.

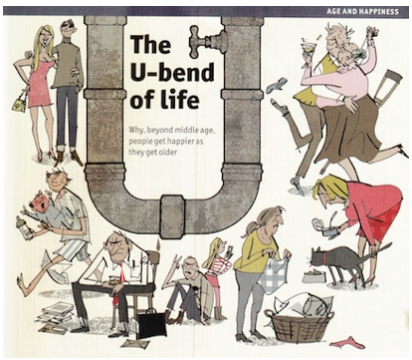
LEARNING OBJECTIVES:

1. To understand the biological and political distinctions between embryonic and adult stem cells.
2. To gain an appreciation of how regenerative medicine is impacting global healthcare.
3. To provide an educational foundation for distinguishing meaningful scientific and clinical advances from the hype and hyperbole in stem cell and regenerative medicine news media.
4. To establish a concrete basis for addressing our patient's questions regarding stem cell clinical trials and tourism.

OVERVIEW:

This is "The Aging Century (*1*)." Over the past 150 years, mankind has defeated his natural enemies and doubled his longevity. The price to pay for extending life beyond the human body's teleological design limit is progressive wear-and-tear and degeneration of cells, tissues and organs, compounded by withering atherosclerotic vascular supplies. Certain tissues like blood, skin and gastrointestinal epithelium undergo constant renewal; other tissues like brain, spinal cord and heart are terminally differentiated, permanent and non-renewable structures. Despite high-tech highly debated evidence for microscopic cellular turnover, brain and heart in particular can only repair themselves through astrogliosis or fibrosis – there are no natural regenerative injury repair mechanisms for these critical adult tissues. Clinical success with rescue and emergency medical care, defibrillators, cath labs, thrombolysis and ICUs have created an

escalating epidemic of heart attack and stroke survivors with seriously damaged hearts and brains. The American Heart Association estimates that in the next several decades, as Baby Boomers enter their Golden Years, cardiovascular disease (with heart failure leading the way) will cost over $1 Trillion per year in U.S. health care expenditures and lost productivity. Cardiovascular disease threatens to bankrupt health systems globally.



The Happily Aging Century. The joy of growing old (or why life begins at 46), The Economist, December 2010.

The myth of Prometheus. The liver's regenerative ability enabled Prometheus' everlasting torture.

Yet, "The Aging Century" is aging happily. Objective evidence, published in the *Proc. Natl. Acad. of Sci. USA*, has demonstrated that quality-of-life ("happiness") increases with advancing aging. Indeed, there is a "U-bend of life" with a nadir in happiness around age 50 in both men and women, and a steady upward trend in happiness from there on out towards elder-hood (*2*), despite degenerating organ systems and tissues.

To capitalize on the aging population's state of well being (and decrease health care expenditures), regenerative medicine seeks to convert "The Aging Century" into "***The Regenerating Century***," replacing or regenerating human cells, tissue or organs, restoring or establishing normal function. Regenerative medicine integrates two distinct areas of science: stem cell biology and tissue engineering. The goal is to regenerate critical cell types like neurons, cardiomyocytes and β cells, and have them functionally integrate into pre-existing tissues or engineer entirely new tissues. Integration must be seamless and regenerated cells must be directly connected to vascular supplies and associated with cells that provide trophic support (e.g., fibroblasts or glial cells). Within the next decade or two, regenerative therapies (of some sort) will become standard-of-care for the treatment of many of today's otherwise untreatable or incurable illnesses of aging.

Although regenerative medicine has been around for thousands of years, since the days of Prometheus (8th Century B.C.), it has now become a worldwide billion dollar enterprise comprised of hardcore basic scientists rooted in mechanistic developmental biology and physicians and allied health care providers sincerely seeking to alleviate patient's pain and suffering through cell-based therapies. There is, however, a darker side, populated by "money-grubbing snake oil-salesmen," preying on hapless patient's fears of death and disability to sell unproven and possibly worthless therapies. There is a myriad of fascinating biological, ethical, political and biotech economical issues surrounding regenerative medicine.

While we commonly think of Prometheus' regenerating liver as a life saving phenomenon, it was actually part of the Zeus' punishment, enabling everlasting torture by the voracious eagle – Prometheus was immortal anyway.

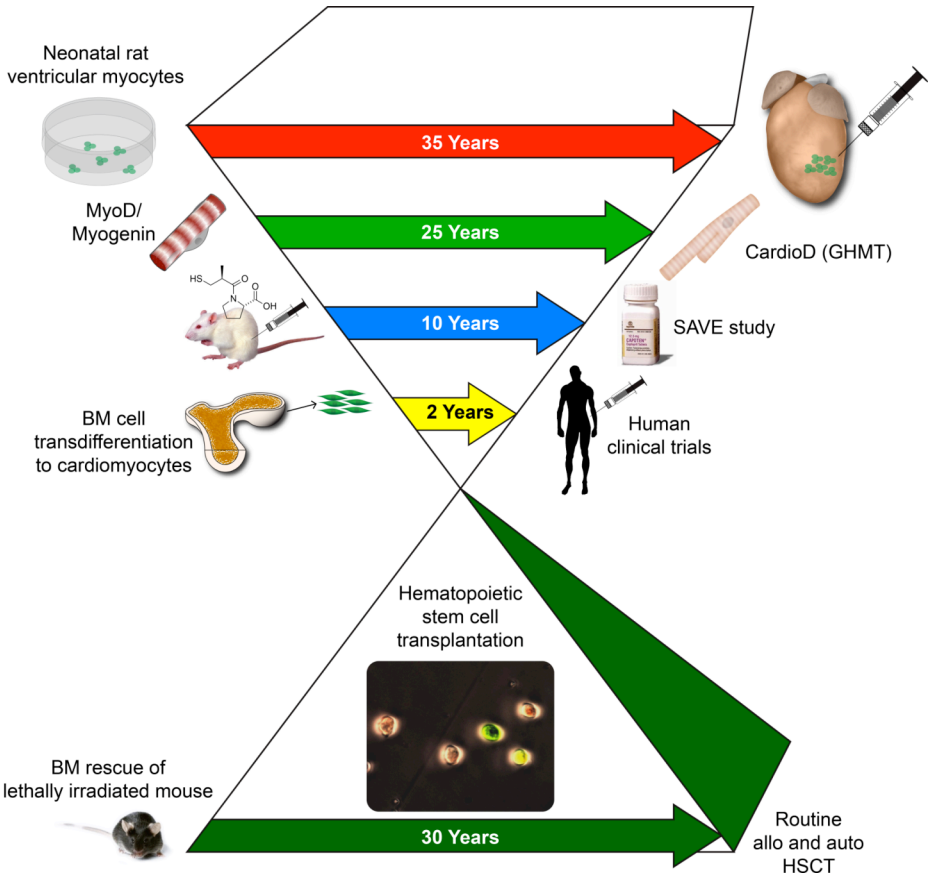
This Internal-Medicine Grand Rounds will focus on the stem cell aspects of regenerative medicine, cell therapy, in particular. Fifteen years after the creation of the first human embryonic

stem cells capable of differentiating into any and all of the 210 different cell lineages that comprise the human body, regenerative medicine is at an important crossroads. This field remains highly polarized. Taking cardiac cell therapy for an example, after the first decade of clinical trials that produced slight but non-zero improvement over standard-of-care (*vide infra*), there are two equally defensible viewpoints, championed by equally prominent scientists and clinicians.

Two opposing viewpoints regarding stem cell therapy:

The Skeptic	**The Optimist**
Cell therapy has failed because it was rushed to clinic, placing the clinical cart before the scientific horse. It needs to return to the lab bench for a mechanistic overhaul to understand issues like homing, engraftment, cell number expansion, cell survival, immunity and rejection. Pre-clinical studies in rodents have been misleading. It's unconscionable to treat patients with (and charge patients for) a therapy that has no concrete rationale and no evidence for efficacy, even if safe. It's probably safe because it doesn't do anything and all the injected cells just die and disappear!	These are very early days. As long as cell therapy is not overtly harmful and adds even minor clinical benefit to standard-of-care, as shown by anecdotal and meta-analysis studies of large clinical trials, we should push onward. It would be unconscionable to withhold potentially beneficial or even life-saving therapy from desperate patients who may have no other options, just because we don't understand exactly how it works or don't believe animal studies. If patients have to pay out-of-pocket, stem cell tourism is their individual right and prerogative. Cell therapy provides hope in otherwise hopeless situations and will ultimately provide cures.

There is a common ground between these two viewpoints. Clinically, it is necessary to re-set less magical and more realistic goals of tissue rebuilding and repair. Scientifically, it is necessary to interpret the animal, especially mouse, studies more cautiously and make more reserved inferences that fuel translational medicine. While it is certainly true that cell therapy was fast-tracked into human clinical trials, it was built upon a strong foundation of hematopoietic stem cell research and medicine. Nonetheless, the pace of scientific advancement in regenerative medicine, particular in the cardiovascular area, is mind-boggling.



The accelerating pace of cardiovascular research and translation. It took 35 years from the time we could first study cardiomyocytes in culture until we had the courage to inject these cells into the beating rodent heart; it took 25 years to discover CardioD (GHMT: Gata4, Hand2, Mef2c and Tbx5) from the time we discovered MyoD; it took 10 years to go from captopril studies in rats to SAVE; but it only took less than two years to go from bone marrow cell-to-cardiomyocyte transdifferentiation studies, which were later disputed, to human clinical trials. In contrast, it took 30 years to develop hematopoietic stem cell transplantation as a routine life-saving therapy.

The goal of this UT Southwestern Medical Grand Rounds is to provide an awareness of the hype, hyperbole and dangers and the current and future possibilities of curing mankind's most devastating medical conditions with stem cells. The take home message will be that ***the future of regenerative medicine is today*** and all physicians need to become aware of the promise and perils of this new field.

FOUR REGENERATIVE MEDICINE CLINICAL VIGNETTES:

Mushrooms in the MICU

1990. Brigham and Women's Hospital, Boston. An Asian American family – the father, mother and a daughter – are admitted to the MICU in fulminate liver failure. They just returned from Northern California where their vacation included a mushroom hunting expedition into a Sierra Mountain forest. All three are critically ill in multisystem organ failure. The 2nd child, the son, hates mushrooms and he is fine. The liver transplant team is called.

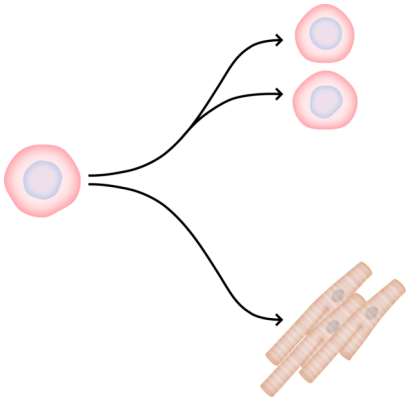
From stem cell pioneer to plaintiff
2003. Beaumont Hospital, Royal Oak, Michigan. A rambunctious teen is horsing around with his friend in his father's construction site. His friend accidentally shoots him in the chest with a nail gun. The 3-inch nail lodges in his chest, piercing the right and entering the left ventricular myocardium, narrowly missing the left anterior descending coronary artery. Surviving, he is taken to emergency cardiac surgery and the nail is successfully removed. Post-operatively, his ventricular function plummets and it is feared he will die. In the absence of cardiac transplant options, an experimental bone marrow stem cell transplant is contemplated (to be done under the hospital's compassionate/emergent-use protocol) with full consent of the teenager's parents.

The importance of hope in medicine
"A hundred years ago." Los Angeles, California. A 55-year old asymptomatic high-spirited woman is admitted because of a coin lesion in the right upper lobe of the lung discovered by routine chest X-ray. Bronchoscopy fails to identify neoplastic cells and she is taken to the OR for thorascopic exploration.

Strange lesions in the kidney
2006. Bangkok, Thailand. A woman with lupus nephritis undergoes a procedure at a private clinic in which her own hematopoietic stem cells are injected directly into her kidneys in hopes of defeating the immune system's attack on kidney function. Six months later she develops hematuria and imaging studies reveal a 4 cm mass on the left kidney; there are additional smaller masses in the left kidney, the adrenal gland and the liver. The left kidney is removed for analysis and hemodialysis is initiated.

WHAT IS A STEM CELL?

The term "stem cell" means many different things, biologically and politically, and is often used imprecisely and inaccurately.



A "stem cell" is defined by its behavior in culture or *in vivo*; there is no specific biochemical marker that defines whether a cell is a stem cell or not. To qualify as a stem cell, a cell must self-renew (meaning make ***exact*** replicas of itself) and its immediate progeny must be capable of differentiating into functionally specialized cells like cardiomyocytes, neurons or pancreatic β islet cells. Generally, stem cells are inconspicuous, immature little cells with a gigantic nucleus and a thin rim of pale cytoplasm, just enough mitochondria to maintain anaerobic glycolytic metabolic homeostasis and sustain a meager quiescent existence in a hypoxic microenvironment (or niche). Although they are "undifferentiated," this doesn't mean they do not have specialized cellular functions. Indeed, their most specialized function is to protect the genome, maintaining the pristine epigenetic state of pluripotency. Embryonic-like stem cells, including induced pluripotent stem cells (iPSCs) divide ceaselessly, zipping through G1 and G2 phases. An important concept is that self-renewal or quiescence and differentiation are mutually exclusive; in fact, the mechanics of stem cell cycles (either embryonic cell cycles lacking G1 and G2 phases or long-term quiescence in tissue-resident stem cells) actively prevent differentiation.

Embryonic stem cells (ESCs) are what most people think of as "stem cells," yet, paradoxically, ESCs are purely an artifact of cell culture and do not exist as a biological entity *in vivo*, in any animal. "Adult stem cell" is political term intended to convey ***that human embryos were not***

destroyed to produce them. Indeed, some adult stem cells, like inducible pluripotent stem cells (iPSCs) are (for the most part) functionally indistinguishable from embryo-derived ESCs. Additionally, human iPSCs and ESCs should, in principle, be equally competent for cloning a human being (although this would be immoral & unethical).

For a whirlwind tour of stem cells and regenerative medicine, here is a partial summary. To gauge the magnitude of activity in this field, as of Spring 2013, there are 471 studies listed on ClinicalTrials.gov using search terms "heart" and "stem cells," and 167 of these studies are actively recruiting patients.

Types of human stem cells and clinical utilities

Type	Embryonic, fetal or adult	Source	Advantages	Disadvantages	Clinical trial examples (ClinicalTrials.gov identifier)	Ref.
Human embryonic stem cells (hESCs)	Embryonic	The inner cell mass of discarded IVF human embryos; note that hESCs can be generated without "killing" the embryo (3)	Pluripotent, unlimited supply of cells, can be genetically modified	Allogeneic rejection, efficient multi-lineage differentiation, teratoma formation, ethical constraints	Macular dystrophy and degeneration (NCT01345006); spinal cord injury (NCT01217008)	(4)
Human fetal brain	Fetal	Mesencephalon of aborted human fetuses	Rich source of dopaminergic neurons	Poor availability of human fetuses, lack of standardization of protocol, allogeneic rejection, ethical constraints	Parkinson's disease (NCT00190450)	(5)
Somatic cell nuclear transfer (SCNT) stem cells	Adult	Transfer of a somatic cell nucleus into an enucleated human oocyte	Autologous, pluripotent (strategy for creating Dolly), unlimited supply of cells, can be genetically modified	Ethical liabilities due to human egg donation (or purchase)	Human SCNT stem cell experiments unsuccessful thus far (vide infra, Korean fraud)	(6)
Human induced pluripotent stem cells (iPSCs)	Adult	Adult skin fibroblasts, peripheral blood cells, shed urine cells, others…	Pluripotent, autologous, patient-specific mutations	Low induction efficiency, multi-lineage differentiation, teratoma formation, viral oncogenesis, induced histo-***in***compatability (7)	None, yet	(8)
Hematopoietic stem cells (HSCs)	Adult	Bone marrow aspiration or peripheral blood harvest	Multipotent, paracrine effects, autologous, can be mobilized by drugs and growth factors, automated GMP isolation, track record of success	Susceptibility to autologous pathology (e.g., diabetes, aging, etc.), poor survival and engraftment in extramedullary niches,	Myocardial infarction (REPAIR-AMI-NCT00279175); heart failure (CCTRN-FOCUS-NCT00824005); type 1 diabetes mellitus	(9)

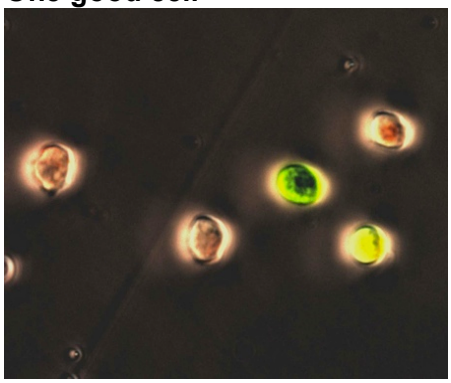
				hematopoietic differentiation only	(NCT01121029); myasthenia gravis (NCT00424489); multiple sclerosis (NCT00273364); sarcoidosis (NCT00282438); ischemic stroke (NCT01518231); primary biliary cirrhosis (NCT00393185); systemic lupus erythematosus (NCT00750971)	
Mesenchymal stem cells (MSCs)	Adult	Bone marrow aspiration, tissue biopsies, unlimited availability (one donor can generate enough cells for 10,000 “doses”)	Multipotent, paracrine effects, autologous or universal histo-compatable allogeneic donor source	Susceptibility to autologous pathology (e.g., diabetes, aging, etc.), low trans-differentiation potential, poor survival and engraftment in tissues	Chronic graft versus host disease (NCT01526850); amyotrophic lateral sclerosis/Lou Gehrig’s disease (NCT01609283); heart failure (PROMETHEUS-NCT00587990); systemic lupus erythematosus (NCT00698191); Parkinson’s disease (NCT00976430);	(10)
Cord blood stem cells	Adult	Discarded umbilical cord	Multipotent, paracrine effects, autologous	Too late for most of us!	Critical limb ischemia (NCT01019681); autism (NCT01638819); pediatric stroke (NCT01700166); epidermolysis bullosa (NCT01033552);	(11)
Endothelial progenitor cells (EPCs)	Adult	Peripheral blood harvest	Unipotent, autologous, paracrine effects, mobilized by tissue injury	Susceptibility to autologous pathology (e.g., diabetes, aging, etc.)	Ischemic stroke (NCT01468064); myocardial infarction (NCT00936819); liver cirrhosis (NCT01333228);	(12)
Menstrual fluid stem cells	Adult	Collected menstrual fluid	Availability, autologous	Phenotype undefined, excludes males of human species	Liver cirrhosis (NCT0148324 8); type 1 diabetes mellitus (NCT01496339); critical limb ischemia (NCT01558908)	(13)
Tissue-specific precursors (cardiac stem cells, neural	Adult	Tissue biopsy and *ex vivo* culture	Uni- or multipotent, autologous, paracrine effects, transdifferentiation	Susceptibility to autologous pathology (e.g., diabetes, aging, etc.), difficult to	Amyotrophic lateral sclerosis (NCT01348451); myocardial infarction	(14)

stem cells, skeletal myoblasts, adipose-derived stem cells, etc.)			potential *in vivo* uncertain	obtain, undefined phenotypes, exposure to xenogeneic serum components	(CADUCEUS-NCT00893360); Parkinson's disease (NCT01453803); Crohn's fistula (NCT01440699); chronic obstructive pulmonary disease (NCT01559051)	
Germ stem cells	Adult	Testis or ovary	Multipotent, autologous	Difficult to obtain	Generation of haploid stem cells from human sperm (NCT01454765)	(15)
Parthenogenic stem cells	"Non-embryonic" stem cells	Uniparental parthenogenic blastocysts	Pluripotent	Requires blastocyst (from in vitro fertilization)	Pre-clinical	(16)

SOME HIGHLIGHTS OF REGENERATIVE MEDICINE'S RECENT HISTORY:

I have selected a few topics from this fascinating field to discuss.

One good cell



Human Cd34^{+} hematopoietic stem cells (green), courtesy of the NHLBI Progenitor Cell Biology Consortium.

Building on earlier milestone studies demonstrating that a single self-renewing leukemia cell could transmit cancer to a host animal (Furth, J. & Kahn, M. C. The transmission of leukaemia of mice with a single cell. *Am J. Cancer* **31**, 276–282 (1937), recent work has demonstrated that a single human hematopoietic stem cell can fully reconstitute the lymphomyeloid system of recipient animals (*17, 18*). The HSC is the champion of all adult stem cells. This experiment, I believe, above all others, demonstrates the unbelievable power of stem cells.

Dolly the Sheep and a Second Chance for Texas

Everyone knows "Dolly the Sheep." She was the first animal to be cloned through somatic cell nuclear transfer (SCNT) of an adult mammalian cell nucleus (a breast epithelial cell, hence the slightly perverted name, "Dolly" for Dolly Parton). Dr. Ian Wilmut's landmark reproductive cloning of Dolly the sheep at the Roslin Institute near Edinburgh, Scotland, was not his original intention, rather he had set out to genetically modify sheep so they would produce recombinant α-1 antitrypsin and secrete it into their milk for isolation as a human therapeutic agent.

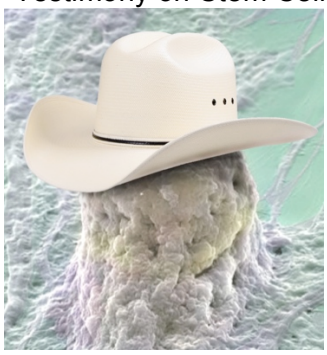
Dolly was generally healthy but died of a viral pulmonary infection and was thought to perhaps have an underlying immune dysfunction. Preserved by taxidermy, Dolly's remains are on display

at the National Museum of Scotland (http://www.nms.ac.uk/our_collections/highlights/dolly_the_sheep.aspx) (*19*). Someday I go visit her.

Not to be outdone, Texas A&M also successfully cloned a 21 year old celebrity Brahman bull named "Chance" (who had to be neutered at age 17 because of an infection), producing "Second Chance" from skin cells taken shortly before Chance died. Texas A& M has also cloned goats, pigs and dogs. Will there be a "Third and Final Chance," probably?

Human embryonic stem cells

Although later eclipsed by the iPSC phenomenon, James Thomson's generation of human ESCs was a fundamental breakthrough that suddenly made everything possible. Indeed, on the eve of Dr. Thomson's 1998 report in *Science* of the first continuous lines from human pluripotent stem cells derived from IVF embryos, Dr. Varmus (the NIH Director at the time), stated in his "Testimony on Stem Cells" before the Senate Appropriations Committee that:

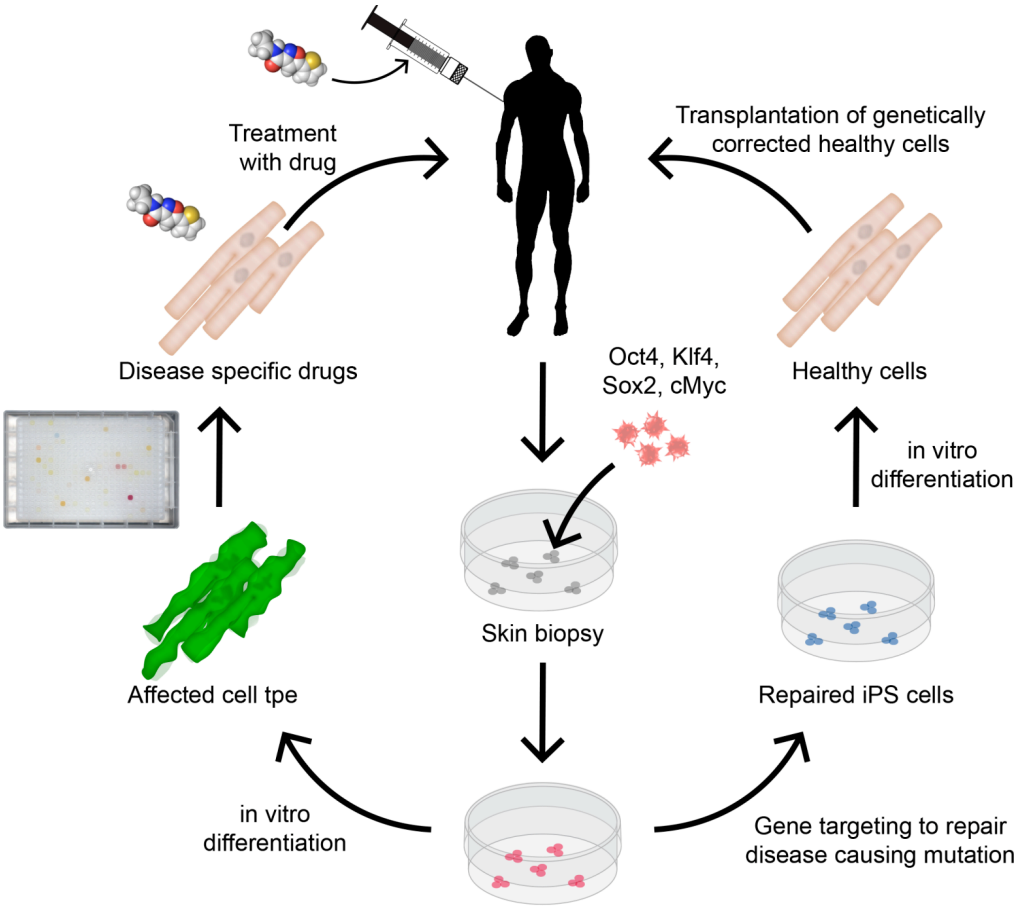


"The development of cell lines that may produce almost every tissue in the human body is an unprecedented scientific breakthrough. It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life." (http://www.hhs.gov/asl/testify/t981202a.html)

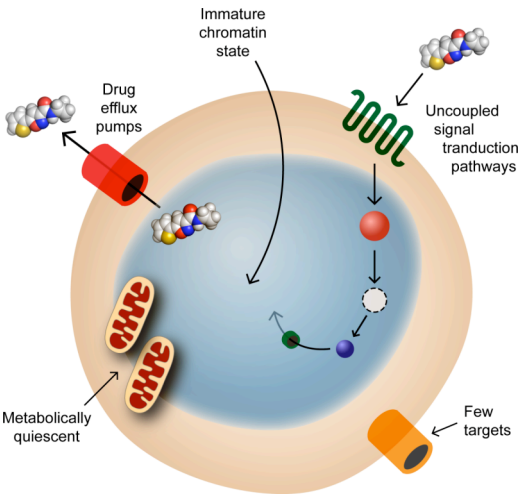
With human ESCs, it became possible for the first time to make human cardiomyocytes for mechanistics studies *in vitro*. Some people, especially residents of the Wisconsin, feel that Dr. Thomson's achievements should have been recognized along with Sir John Gurdon and Shinya Yamanaka by the 2012 Nobel Prize in Physiology or Medicine.

Inducible pluripotent stem cells

Recognized by the 2012 Nobel Prize, reprogramming a differentiated fibroblast into an undifferentiated pluripotent stem cell – induced pluripotent stem cell – by over-expression of 4 pluripotency genes, Oct4, Klf4, cMyc and Sox2, forever changed the stem cell landscape (*20*). Mechanisms and new strategies for transcriptionally inducing pluripotency is a major focus of our NHLBI Progenitor Cell Biology Consortium.



In principle, patient specific iPSCs can be used to both model human disease and discover disease specific drugs or other therapeutics (left hand side of panel) or patient specific iPSCs can be used to generate healthy, genetically corrected cells for transplantation (right hand side of panel).



It turns out that trans-differentiating iPSCs into desirable lineages (and avoiding undesirable lineages) is a lot tougher than making ordinary cells pluripotent. Although progress has been made, it is still not possible to make iPSCs with chemicals (small-molecules) alone (*21*). Small-molecules and iPSCs (indeed, all stem cells) have a unique and unfriendly relationship, largely due to the immaturity of stem cells (lack of drug targets) and the presence of drug efflux pumps. Developing stem cell-modulator small-molecules as future regenerative therapeutics is the research focus of my laboratory at UT Southwestern Medical Center.

Therapeutic cloning, Gangnam style

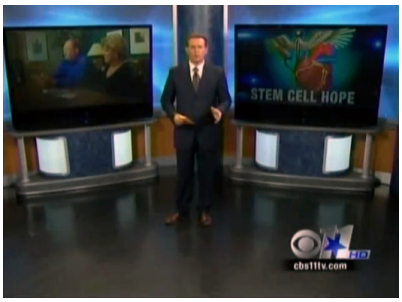
Stem cell hero (and his lab) turned criminal.

Therapeutic cloning involves the transfer of somatic cell (e.g., skin fibroblast) nuclei into enucleated oocytes to create pluripotent stem cells. The importance of these cells, called somatic cell nuclear transfer (SCNT) stem cells, has been eclipsed by the iPSC phenomenon, but there is still great interest in human SCNT stem cells. Human therapeutic cloning by SCNT has never been successfully achieved and remains an important bugaboo in the field. It is problematic because of the difficulty of obtaining human oocytes, which are essential starting material and can't be substituted by other species. Human oocytes can only be obtained from female volunteers (or paid mercenaries) who undergo hormonal stimulation and laparoscopic harvest of oocytes similar to IVF procedure.

In 2004-2005, two papers were published in the journal *Science* from the laboratory of Dr. Hwang Woo Suk in South Korea claiming to have produced the first human SCNT adult stem cells. These papers were highly acclaimed as scientific breakthroughs until it was discovered that the results were incorrect, perhaps even fraudulent, and that many of cell lines were the result of parthenogenesis (meaning they were actually derived from an unfertilized egg whose nucleus had not been properly removed) rather than successful SCNT. The papers were retracted and Dr. Hwang Woo Suk, initially a national hero (given lifetime 1st class tickets on Korean Airlines), was disgraced, sentenced to two years suspended sentence in Korean prison for embezzlement and fraud (*22, 23*). He still gets scientific credit for cloning the first dog, "Snuppy."

Stem cell tourism

Americans are spending millions of out-of-pocket health care dollars overseas on unproven stem cell therapies. Internet sites offer help for people suffering from an impressive catalog of serious conditions, including: Alzheimer's disease, amyotrophic lateral sclerosis, atherosclerosis, autism, brain damage, cancer, cerebellar ataxia, cerebral palsy, chronic obstructive pulmonary disease, Crohn's disease, diabetes mellitus, diseases of the eye, genetic disorders, Huntington's disease, kidney disease, systemic lupus erythematosus, multiple sclerosis, muscular dystrophy, Parkinson's disease, rheumatoid arthritis, spinal cord injury, spinal muscular atrophy, stroke, Tay-Sachs disease, among many others. There are stem cell tourism clinics all around the world but the leaders are in China, India, the Caribbean, Latin America, and nations of the former Soviet Union. The concerns are that these clinics offer therapies and promise results without scientific validity; moreover, stem cell tourism threatens the legitimacy of scientific stem cell research, which produces less spectacular results.



Thailand offers stem cell hope for Joe, a Texan.

This story is summarized in Dallas Channel CBS11 KTVT news story/interview called "**Stem Cell Hope**" (http://www.youtube.com/watch?v=ZqptGkqf7vo). This story, which featured my laboratory at UT Southwestern Medical Center, was nationally syndicated on the major networks. In retrospect, I didn't much like my comments, too negative, but I didn't get to edit the piece.

I recently met with Joe Woolfolk and his wife Judy to obtain a follow-up on how he is doing. Joe is now a UT Southwestern Medical Center Heart Failure and Arrhythmia Service clinic patient (and he loves his UT Southwestern doctors) and he is doing quite well, playing golf regularly. His defibrillator has rescued him from VT 9 times. He has lost 30 pounds and is on an optimized medical regimen. At the time of his stem cell therapy, Joe's EF was ~12% and he was in decompensated heart failure, able to walk only a few yards (he didn't think he'd survive the trip to Thailand). Post-cell therapy, his EF peaked at ~40%, but it has now declined again to ~20%. His bypass grafts are patent. ***Joe firmly believes that he is alive today because of his stem cell therapy in Thailand.*** He recalls the details of how 6.2 million peripheral blood mononuclear cells returned from Israel as in the video were injected into thirty ventricle sites through a lateral thoracotomy. Joe has already donated his body to UT Southwestern; he and I are formalizing arrangements so that upon his unexpected death or in the case of a heart transplant, his heart will go to my to my lab for detailed molecular and histological analysis, perhaps even for the generation of iPSCs and cardiomyocytes. In a curious twist, Joe recalls that he was given Halcion on the day after surgery and this gave him a vivid & prescient dream that he was a bullfrog. The bullfrog's heart undergoes seasonal cycle of cardiomyocyte degeneration (when buried in the cold mud for the winter) and regeneration (upon warming in the spring) that involves fascinating disassembly and reassembling of myofibrils and other key cellular structures. This phenomenon was originally characterized through detailed electron microscopic studies in the 1960's and 70's by the Russian biologist, P.P. Rumyantsev (*24*). Joe also doesn't understand why many doctors are reticent to talk about his stem cell therapy experience in Thailand. It makes him feel like this is "a deep dark secret." He wants us to learn from his experience and his heart muscle in any way possible. If Joe could afford it or if he would be eligible for a clinical trial he would eagerly have cardiac cell therapy again.

Texas stem cell rules and outlaws

Stem cell therapy has become a cottage industry in Texas. Although Texas is generally viewed as a highly conservative state when it comes to stem cell issues, it has paradoxically become the Wild Wild West of stem cell therapies. In fact, Texas is the country's leading "destination state" for American stem cell tourism. A group of orthopedic surgeons in the Houston area formed a company called ***Celltex Therapeutics*** that developed stem cell treatments for a variety of orthopedic conditions, multiple sclerosis, Parkinson's disease and other conditions. Celltex licensed the stem cell technology from a South Korean company called ***RNL***, which claims to have successfully treated tens of thousands of patients with stem cells. RNL recruits patients through "stem cell boutiques" in shopping centers around the world. Interestingly, because stem cell therapy is illegal in South Korea, RNL must send patients to Japan or China (or now Texas) for treatment. Governor Rick Perry is among Celltex's high-profile celebrity stem cell patients.

The problem is that Celltex is selling a form of therapy that has unproven efficacy and has not been approved by the FDA. Celltex maintains that autologous mesenchymal stem cells derived from bone marrow or fat are harvested from and then returned to patients in "minimally altered form," so, in principle, it's just like rearranging the patient's own cells, almost like no therapy at all. To avoid legal issues, Celltex (somehow) mobilized the **Texas Medical Board** to consider the issue of stem cell therapy in Texas. I was the UT Southwestern faculty member representing Dr. Podolsky at the TMB Stem Cell Stakeholder's Meeting in Austin. This meeting was confrontational and heated debate attended by many prominent and influential Texas stem cell scientists, physicians and politicians. Still on the trail for his presidential campaign at this time, Governor Perry could not attend this meeting, although he sent a letter to the committee before the meeting:

OFFICE OF THE GOVERNOR

RICK PERRY
GOVERNOR

July 25, 2011

Irvin E. Zeitler, Jr., D.O.
Chairman
Texas Medical Board
P.O. Box 2018
Austin, Texas 78768-2018

Dear Dr. Zeitler:

As the Texas Medical Board considers new rules regarding adult stem cell research and treatments, I would ask you and your colleagues to recognize the revolutionary potential that adult stem cell research and therapies have on our nation's health, quality of life and economy. Adult stem cells have many proven medical benefits and many uses yet to be found. It is my hope that Texas will become the world's leader in the research and use of adult stem cells.

Autologous adult stem cells have shown promise in the treatment of arthritis, orthopedic conditions, cardiovascular disease and diabetes. Other adult stem cell therapies have been used to treat autoimmune diseases, leukemia, and other types of cancer.

I appreciate the board's responsibility to protect patients. As you meet with stakeholders, I urge you to recognize the sound science and good work that is already being done, and will continue to be done in the future, in this field. We need to ensure that physicians in this state can continue to pursue new technologies and treatments that will benefit all Texans.

Texas is a leader in innovation in many fields. It is critical that we continue to foster an environment that encourages technological advancement in the health care arena. With the right policies in place, we can lead the nation in advancing adult stem cell research that will treat diseases, cure cancers and, ultimately, save lives.

I look forward to continuing this dialogue with you. As always, thank you for your service to the State of Texas.

Sincerely,

Rick Perry

Rick Perry
Governor

RP:bdp

cc: Texas Medical Board Members

Although the intention of this committee, however convened, was laudable – to protect patients by preventing the spread of "illegal" stem cell therapies in Texas – yet, the TMB had only limited authority. The end result was two rules:

1. To perform stem cell therapy in Texas, you must be a TMB licensed physician.
2. In lieu of FDA approval, you can perform stem cell therapy in Texas as long as you have approval from a "qualified" IRB.

Although on the one hand, Texas should be applauded for being the first state in the country to establish stem cell therapy rules, on the other hand, these rules caused international outrage because of the perception that Texas IRBs could supercede the authority of the FDA, which has not formally acted upon stem cell therapies done outside of clinical trials (*25, 26*). In September 2012, Celltex Therapeutics received a reprimand from the FDA in the form of an "advisory opinion letter." In response, after respectfully and publically disagreeing with the letter, Celltex re-defined itself a stem cell *banking* as opposed to a stem cell *therapeutics* company (http://celltexbank.com/advantage/). Texas is considered a rogue state, the Wild Wild West of American stem cell tourism (*27*).

Sean Morrison weighed-in on this issue, interviewed for an editorial piece in *Science* (*28*):

Sean Morrison, an International Society for Stem Cell Research member at the University of Texas Southwestern Medical Center in Dallas, says the Texas board cannot require FDA oversight, noting that many legitimate U.S. clinical trials test treatments that don't meet FDA's definition of a regulated product. But the draft rule wouldn't stop FDA from stepping in, Morrison says, because "federal laws trump state laws. Morrison does share concerns that the draft rule's requirements for IRB review are "weak." ***But he says the medical board "should be congratulated for trying to impede the proliferation of unproven stem cell therapies." Texas, he says, "has done more to address this problem than most other states."***

Just this week, a new bill was been introduced in the Texas State Senate relating to the research, collection and use of adult stem cells. The bill aims to establish an adult stem cell research consortium, coordinating board, program guidelines & procedures. This would be very important step for stem cells in Texas.

By: Zedler H.B. No. 2342

A BILL TO BE ENTITLED
AN ACT

relating to the research, collection, and use of adult stem cells.

BE IT ENACTED BY THE LEGISLATURE OF THE STATE OF TEXAS:

SECTION 1. Subtitle H, Title 3, Education Code, is amended by adding Chapter 156 to read as follows:

CHAPTER 156. ADULT STEM CELL RESEARCH PROGRAM

Sec. 156.001. DEFINITIONS. In this chapter:

(1) "Adult stem cell" means an undifferentiated cell that is:

(A) found in differentiated tissue; and

(B) able to renew itself and differentiate to yield all or nearly all of the specialized cell types of the tissue from which the cell originated.

(2) "Consortium" means the Texas Adult Stem Cell Research Consortium.

(3) "Institution of higher education" means an institution of higher education as defined by Section 61.003 or a private college or university that receives state funds.

(4) "Program" means the adult stem cell research program established under this chapter.

(5) "Research coordinating board" means the Texas Adult Stem Cell Research Coordinating Board.

http://www.legis.state.tx.us/tlodocs/83R/billtext/html/HB02342I.htm

Geron "bails" on human ESCs

In January 2009, the FDA approved the Investigational New Drug application of Geron Corporation, a small California-based biopharmaceutical company, to initiate a first-in-human (FIH) Phase I clinical trial to assess "GRNOPC1" human embryonic stem cell-derived oligodendrocyte progenitor cells in severe spinal cord injury (http://cell-therapies.geron.com/grnopc1_pipeline). Geron had helped pioneer human ESC work by supporting James Thomson at University of Wisconsin, Madison, and has exclusive license for a number of human ESC patents. ***GRNOPC1 was the world's first human ESC clinical trial, designed to treat 8 patients with spinal cord injury.*** After 4 patients had been treated with human ESCs, Geron stopped the trial (although they'll continue to follow and report on the 4 treated patients), giving-up more than $20M of CIRM (California Institute for Regenerative Medicine) support. Geron's decision to abandon the human ESC business (http://news.sciencemag.org/scienceinsider/2011/11/geron-bails-out-of-stem-cells.html) sent shockwaves through the field.

WHACKY STEM CELL "SCIENCE"

Your monthly miracle

The "curse" of menstruation has been lifted because now you can bank menstrual fluid for extracting stem cells (http://www.cryo-cell.com/menstrual-stem-cell-banking) or for generating iPS cells (*29*). Even further, you can now generate brain cells from urine (*30*).

The stem cell bra

Yes, a woman's brassiere that recruits stem cells to the breast and promotes growth is in Phase III clinical trials (http://www.stemcellbra.com). This high tech bra's mechanism-of-action, seriously, involves: (1) an initial electrical signal that triggers release of SDF-1 (a homing signal protein) by breast cells, causing stem cells from bone marrow, fat tissue and circulating blood to home to the breasts; (2) after stem cell recruitment, the electrical signal converts to "proliferation mode" and promotes

stem cell proliferation, further enhancing breast volume; and finally, (3) a 3rd third signal that promotes angiogenesis in breast tissue, ensuring that the newly created breast tissue is well fed to maintain survival. Interesting…see the article, "All Natural: Why Breasts Are the Key to the Future of Regenerative Medicine," by Sharon Begley in Wired Magazine (http://www.wired.com/magazine/2010/10/ff_futureofbreasts/all/). No authentic science references are provided. Replacing the stem cell bra with stem cell-modulator small-molecules is an interesting possibility.

RE-FOCUSING ON CELL THERAPY FOR HEART REPAIR

Where are we after a decade of cardiac cell therapy?

Mega-meta-analysis of adult bone marrow cell therapy in the heart

Confirming a previous meta-analysis that concluded that functional changes after cell therapy were comparable to those achieved with reperfusion therapy, pharmacotherapeutic interventions influencing the renin-angiotensin-aldosterone pathway, and beta-blockers after acute myocardial infarction (*31*), cardiac cell therapy is now considered to confer clinical benefit beyond current standard of practice, which is already pretty good. Indeed, Recent meta-analysis of 50 studies (enrolling 2,625 patients in randomized controlled and cohort studies) demonstrated the following small but significant changes in functional and clinical parameters in bone marrow cell versus control subjects. These results persisted in long-term follow-up irrespective of whether adult one marrow cell therapy was done for acute myocardial infarction of chronic ischemic heart disease (*32*).

Functional parameters:

- Improved LV function (EF increased by 3.96%)
- Decreased infarct size (decreased by 4%)
- Favorable remodeling (decreased LV-EDV by 5 ml and LV-ESV by 8 ml)

Clinical outcomes:

- Reduced incidence of death (OR 0.39) (all cause mortality)
- Reduced recurrent myocardial infarction (OR 0.25)
- Reduced stent thrombosis (OR 0.34)
- With trends towards reduced heart failure incidence and stroke
- No change in in-stent restenosis, target vessel revascularization or ventricular arrhythmias

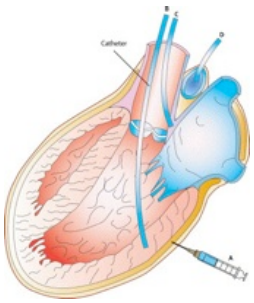
This is considered a landmark study that provides conclusive evidence from a decade of clinical studies that adding cardiac cell therapy is favored over standard-of-care, although, admittedly, optimization is needed.

How does cardiac cell therapy really work?

Accepting that cardiac cell therapy is effective – meaning that it confers some clinical and/or functional benefit beyond standard-of-care – how does it work? The initial simplistic explanation that injected stem cells transdifferentiated into cardiomyocytes proved naïve (wishful thinking or perhaps artifact) (*33, 34*). Nonetheless, preclinical scientific evidence supports a number of alternative hypotheses that do not require muscle differentiation of injected stem cells.

Mechanistic hypotheses for how non-regenerating stem cells can nonetheless promote cardiac regeneration:

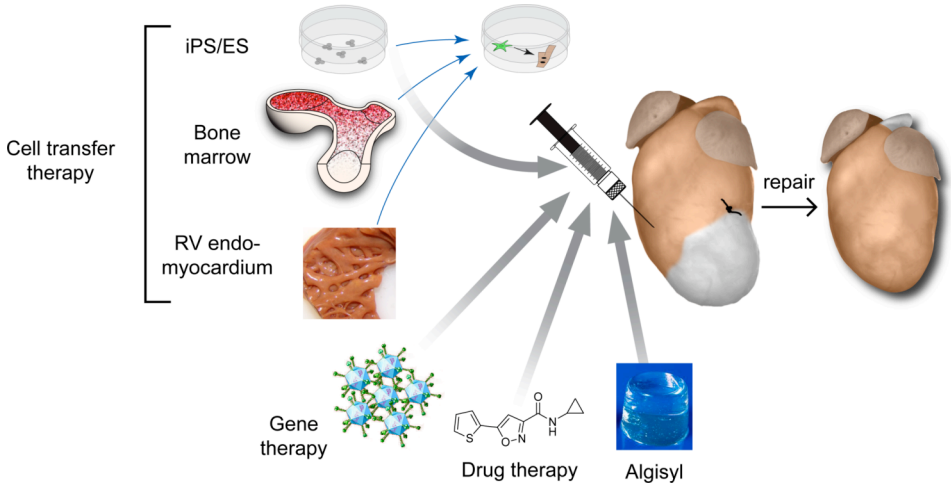
1. **Double paracrine hypothesis**: through release of **primary paracrine factors**, injected stem cells trigger endogenous cardiac progenitor-like cells to produce **secondary paracrine factors** that promote cardiomyocyte replication or survival or enhance cardiomyogenesis from native or recruited progenitor cells or promote angiogenesis (*35-37*).
2. **Dead stem cell hypothesis**: dying (or dead) stem cells injected into the injury border zone release cellular materials that buffer oxidative stress or attenuate extracellular matrix degradation, block fibrosis (through MMPs) or neutralize "negative" cytokines, or, through cell-cell fusion, transfer organelles, substrates or other cellular constituents that rescue ischemic cardiomyocytes (*38, 39*). Live cells are better than dead cells, but dead cells work too (*40, 41*).
3. **Immune modulation hypothesis**: injected stem cells promote regenerative-repair processes by "fine tuning " normal inflammatory and immune responses that salvage myocardial function (*42*).
4. **Extramedullary hematopoiesis**: injected stem cells create hematopoietic stem cell micro-niches that locally produce hematopoietic cell lineages that favorably regulate native myocardial repair/regeneration processes (*43*).
5. **Metabolic rescue**: injected stem cells prevent dilation (bulging) of the infarct border zone, decreasing wall stress by the Law of Laplace, thereby improving border zone myocardial energetics (*44*).



Modes of stem cell delivery to the heart:
This is a giant topic and area of intense research and development within the cardiology and cardiac surgery fields. Given limitations of time, it will not be presented in detail in this grand rounds, suffice it to say that options are being developed to deliver stem cells via (A) direct intramyocardial injection through the epicardium; (B) direct intramyocardial injection through the endocardium; (C) intracoronary injection; and (D) retroperfusion via the cardiac veins (*45*).

The next frontier: the LoneStar Heart platform for cardio-regenerative therapies

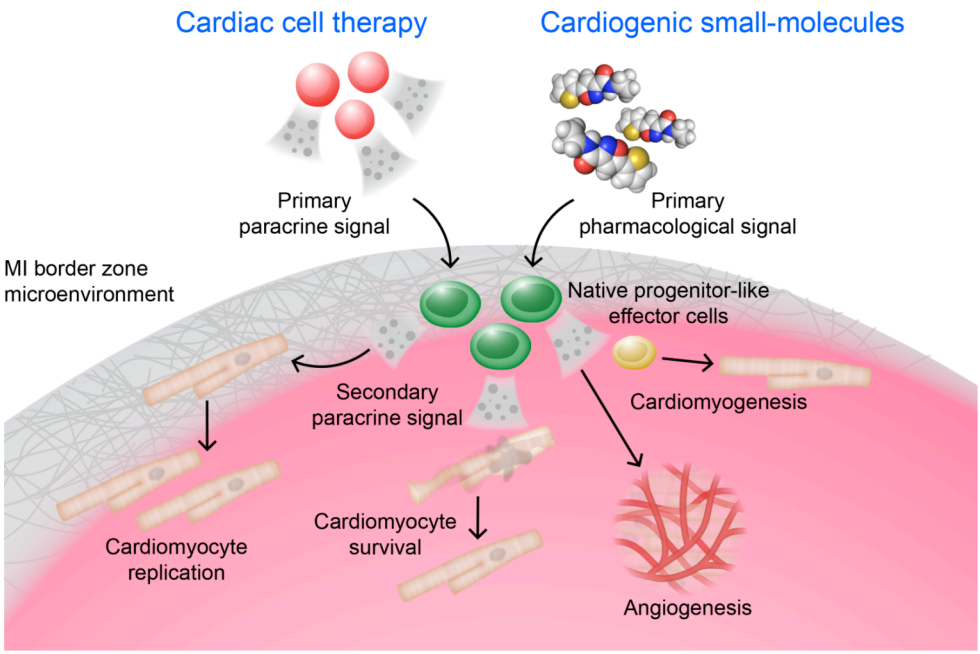
This final part of the talk will discuss three "outside-of-the-box" molecular-genetic approaches to heart repair and regeneration being developed at LoneStar Heart, Inc. (UT Southwestern BioCenter): **small-molecules**, **large-molecules** (transcription factor gene therapy) and **gigantic-molecules** (Algisyl biopolymers).



Small-molecules

Our cardiogenic small-molecule drug discovery/development program builds upon the mechanistic foundations of cardiac cell therapy. As described above in the "double paracrine hypothesis," the current consensus working model for how cardiac cell therapy actually works is that bone marrow-derived or other cells injected into myocardium do not become functional cardiomyocytes themselves, rather they transiently produce and secrete signaling molecules that act in a paracrine manner upon native progenitor-like effector cells pre-existing in or recruited to the myocardial microenvironment. This is the ***primary paracrine signal***. In response to the primary paracrine signal, native progenitor-like cells (most likely a cell type called "multipotent stromal cells") produce a ***secondary paracrine signal*** that promotes cardiomyocyte replication and survival, angoiogenesis and cardiomyogenesis from native precursor cells. Converging evidence suggests that all of these processes are involved in and required for effective regenerative heart repair in the border zone of myocardial infarction.

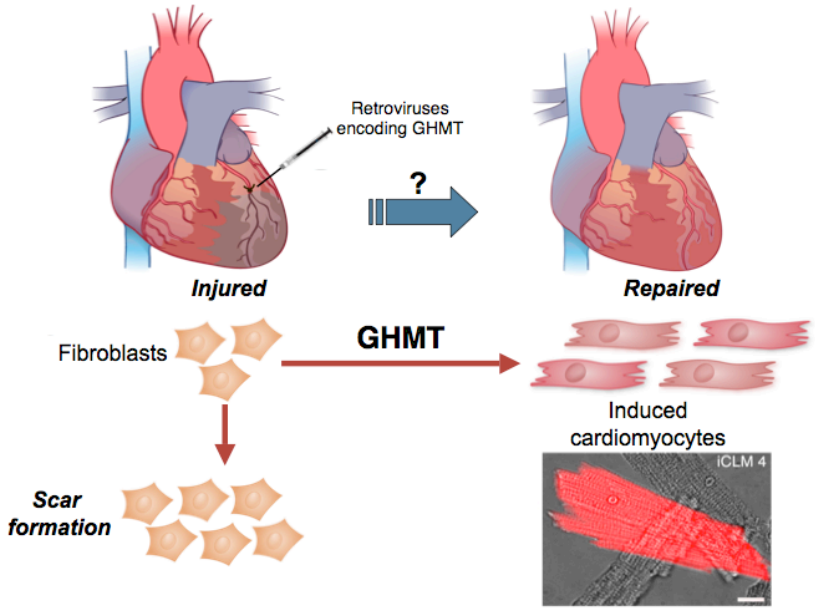
We have identified synthetic small-molecules in a stem cell-based high throughput screen of the UT Southwestern chemical compound library that can target the heart's native repair-effector cells directly, *in vivo*, inducing these cells to trigger a native heart repair response that includes improvements in metabolic and contractile function (50-52). Indeed, in several different small-animal models, these small-molecule drugs enhance survival after serious heart injury. We are currently moving these studies to pigs. Although it is ambitious, perhaps unrealistic, to propose that a single simple synthetic small-molecule administered systemically or locally to the heart can substitute for an injected stem cell, which is by far the most complex "drug" ever developed, our results provide an excellent starting point.



Replacing cardiac cell therapy with cardiogenic small-molecules that target native progenitor-like effector cells *in vivo* triggering endogenous regenerative heart repair processes like cardiomyocyte replication and enhanced survival, angiogenesis and cardiomyogenesis from endogenous precursors. Ultimately, small-molecule drugs will obviate the need for or act as adjuncts to cardiac cell therapy.

Large-molecules

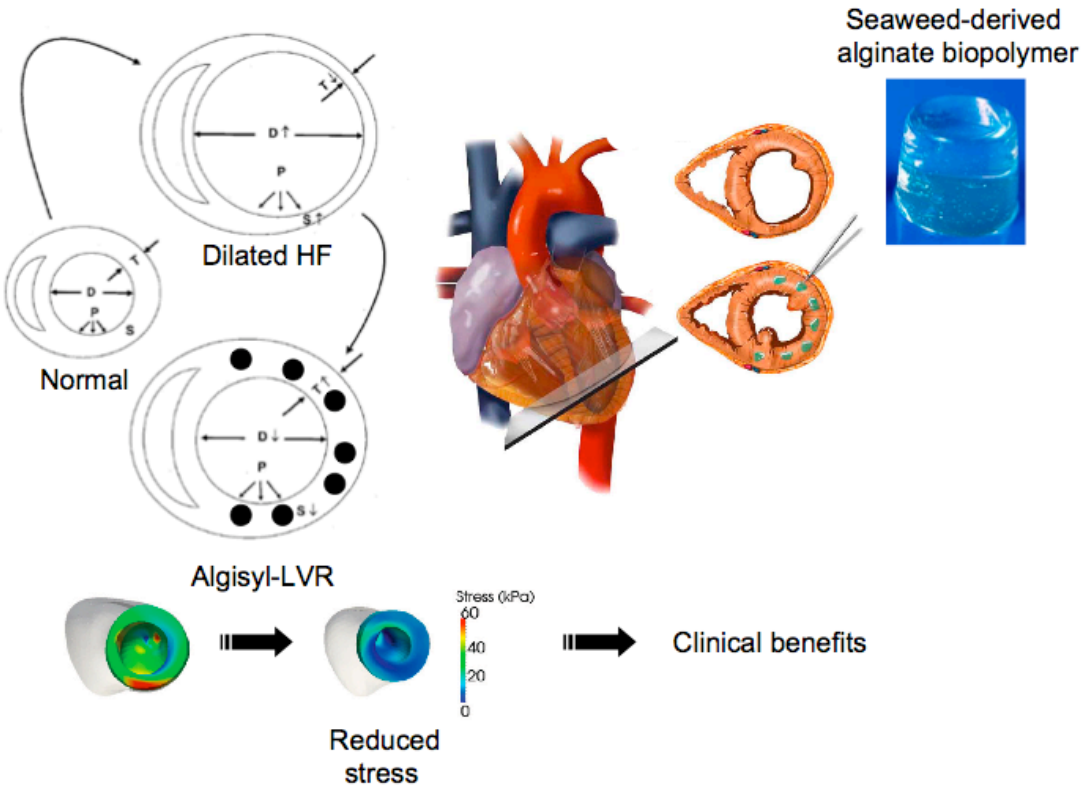
The identification of "CardioD" as a team of four cardiac transcription factors ("GHMT" for Gata4, Hand2, Mef2c and Tbx5) that can transdifferentiate fibroblasts into spontaneously beating cardiomyocytes (*46*) is a discovery that eluded scientists for more than 35 years, ever since Hal Weintraub's transformative discovery of MyoD. Eric Olson's discovery of CardioD was inspired by Shinya Yamanaka Nobel Prize winning observation that ESC-enriched transcription factor teams (Oct4, Klf4, Sox2 and cMyc) could reprogram fibroblasts into pluripotent stem cells (iPSC). The efficiency of fibroblast conversion to cardiomyocytes by GHMT viruses is very low *in vitro*, not surprisingly. Importantly, however, when GHMT viruses are injected into the injured mouse heart *in vivo* there is a dramatic enhancement in fibroblast-to-cardiomyocyte conversion. Presumably, native microenviromental signals can bolster the transdifferentiation process and, perhaps most importantly, couple it to angiogenesis, producing new fully functional replacement myocardium. Removing the liability of viral-mediated transcription factor gene therapy, future studies will strive to replace the viruses with safer gene delivery methods like modified-RNAs or even small-molecules.



Direct reprogramming of fibroblasts to cardiomyocytes *in vivo* in the injured mouse heart by a team of retroviruses encoding 4 transcription factors (Gata4, Hand2, Mef2c and Tbx5) holds tremendous promise for heart repair, obviating the need for cell therapy. Courtesy of Eric Olson.

Gigantic-molecules

Reducing left ventricular wall stress (afterload) is a cornerstone of heart failure therapies. Evidence from animal studies indicates that injection of non-contractile material can reduce elevated myocardial fiber stress, conferring functional benefits to the heart through Laplace Law therapeutics (increasing wall thickness reduces wall stress). LoneStar Heart has developed a proprietary biopolymer called Algisyl derived from Norwegian seaweed. Liquid outside of the body, this biopolymer gels after injection into the heart where it forms a small (~100μL) space-filling implant that is permanent. A fibrous cap, part of a benign foreign body reaction, is generated around, insulating, the Algisyl implant. The Algisyl implant is non-arrhythmogenic and is considered a "device" rather than a drug or biological by the FDA. Two clinical trials are currently underway in Europe, **Algisyl-LVR (FIM) (NCT00847964)** and **AUGMENT-HF (NCT01311791)** and early results confirm safety and signal positive efficacy (*47, 48*). My vision is to treat the first U.S. patients with Algisyl implants at UT Southwestern Medical Center.



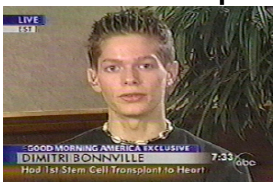
A seaweed-derived biopolymer called “Algisyl” or “Alginate,” produced under GMP conditions in Scandinavia, is injected, through specially designed catheters, into human myocardium at thoracotomy. This space-occupying “bulking” therapy improves myocardial mechanics and energetics by the Law of Laplace, reducing myocardial stress/afterload, and this translates into functional and clinical benefits. Algisyl provokes a benign foreign body reaction and becomes encapsulated by fibroblasts, although its potential interaction with the heart’s stem cell compartment is poorly understood at this time.

RETURN TO THE FOUR REGENERATIVE MEDICINE CLINICAL VIGNETTES:

Mushrooms in the MICU

Three members of the family, the mother, the father and one of the children, were in fulminant liver failure due to Amanita phalloides (death cap) poisoning. Transplants were not necessary for these patients because, like Prometheus’, their otherwise healthy livers were expected to regenerate over time. Liver lobules or triads are functionally independent, e.g., you can survive, the remainder of the liver functions autonomously as liver mass is regenerated; this is very different from the heart, which is a functional syncytium, making myocardial regeneration more problematic.

From stem cell pioneer to plaintiff



The first US cardiac stem cell patient.

Turns out, Dimitri’s anterior wall was only stunned by the impaling nail, not infarcted; ventricular functional would have very likely recovered spontaneously (without the historic stem cell therapy). Unfortunately, Dimtri’s parents decided to sue William Beaumont Hospital, James Robbins (the trauma surgeon who removed the nail), and Srinivas Dukkipati (the cardiology fellow who evaluated Dimitri after surgery), claiming that it was the negligence of his initial care, and not the

severity of his heart injury, that made the stem cell transplant necessary (http://www.the-scientist.com/?articles.view/articleNo/16419/title/Use-stem-cells--get-sued/).

The importance of hope in medicine

Lessons From the Practice

The Importance of Hope

ALEXANDRA M. LEVINE, MD, *Los Angeles*

A hundred years ago, when I was a medical student on the general medicine wards, a 55-year-old woman was admitted to my service with a coin lesion in the right upper lobe of the lung. She was basically well and asymptomatic and spent the next week undergoing diagnostic studies—bronchoscopy and so forth. During that time, I got to know her and like her. She was a real dynamo, vigorous and friendly. She became the extra pair of hands on the ward, helping to pass the meal trays, running minor errands. We all came to love her. When the diagnostic tests came back nondiagnostic, the patient was transferred to the surgery service and underwent an open thoracotomy. At operation, she was found to have a squamous cell carcinoma that had already invaded the mediastinal nodes, such that the tumor was not resectable. A biopsy was taken, and the incision was closed.

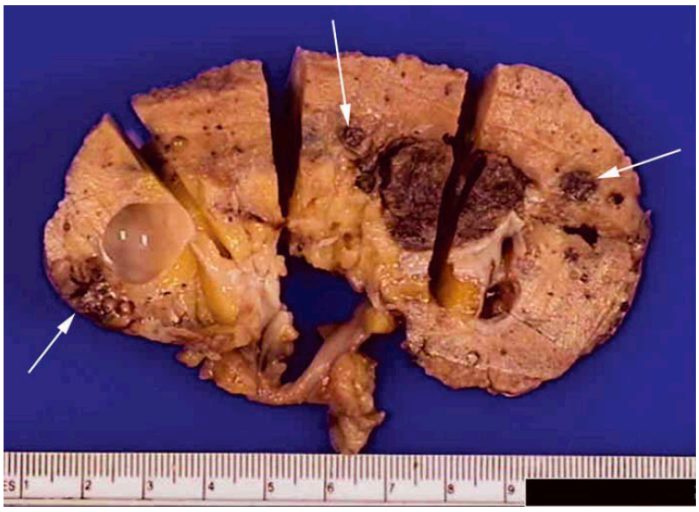
suggested in any sense that there was any other treatment that could be used. His words took away her hope, and I honestly believe, as crazy as it may seem, that those words took away some of her potential lifetime.

Should he have lied to the patient? No, I don't think so, but I do think that we can be sensitive to the effect of our words, and that it might be acceptable to state the facts in such a way that we do not take away all possibility of hope. For example, why couldn't the resident have said that he removed some of the tumor but could not remove all of it, and, therefore, that further therapy would be required. That's all; that's not a lie. It states the facts as they occurred but still allows the patient some space in which to work, some possibility of life ahead.

Let me give one more example of this concept of hope, to

Every physician should read this story of lost hope and death in medicine (*49*)

Strange lesions in the kidney

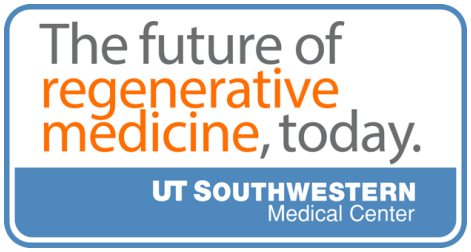


Strange angiomyeloproliferative lesions in the kidney after autologous stem cell transplant (*50, 51*).

Good stem cells, in principle, should do bad things, as they did in this unfortunate woman's case. She died from renal failure complications and is the first stem cell therapy-related death to be reported in the literature.
There are now hundreds of ongoing allogeneic mesenchymal stem cell (MSC) clinical trials and thousands of stem cell tourism programs throughout the world, yet there has been only one published autopsy study (by Dr. Katarina Le Blanc from the Karolinska Instituet) to explore where these cells go after intravenous infusion (*52*). They examined autopsy material from 18 patients who had received human leukocyte antigen (HLA)-mismatched MSCs, and 108 tissue samples from 15 patients were examined by PCR. No signs of ectopic tissue formation or malignant tumors of MSC-donor origin were found on macroscopic or histological examination. MSC donor DNA was detected in one or several tissues including lungs, lymph nodes, and intestine in eight patients but there was no correlation between MSC engraftment and treatment response. They concluded that MSCs function through a "hit and run" mechanism and that MSC is safe in part because there is little sustained engraftment.

CONCLUDING REMARKS:
UT Southwestern Medical Center patients are becoming increasingly aware of adult stem cell therapies from the popular media and internet sources and from their friends and colleagues, and many of our patients are asking whether stem cell therapy options exist for their own conditions or diseases, either at UT Southwestern Medical Center or elsewhere in the U.S., or even abroad. In case you haven't perused the internet regarding stem cell therapies, the hype is pervasive and testimonials quite convincing, compelling our patients to spend tens of thousands of (cash) health care dollars to travel for stem cell therapies not available to them locally. As physicians of "The Regenerating Century" we are obligated to provide our patients with answers to their questions (or they'll go to less reliable sources for answers). Patients specifically seek academic medical center physicians like us expecting for us to be the "knowledgeable voice of scientific reason." It is important for us to balance our skepticism based on the lack of scientific data and medical commonsense with realistic but not oversold optimism and, most importantly, compassion, so as not to defeat our patient's hopes, rather to give them realistic expectations. It is important to recognize that saying "forget it, it doesn't work" is equally erroneous as saying "it does work, it's a miracle cure-all," we just don't know yet. Only scientific research will answer this question and thousands of legitimate studies (costing billions of dollars -- it can cost up to $100K to support a patient through an FDA-approved clinical trial) are underway, around the world; many thousands of patients have generously enrolled in trials to help us address these questions. Most commonly, patients ask questions about heart disease, neurodegenerative diseases and diabetes, but other rare diseases as well. For heart disease, compelling meta-analysis data from thousands of patients demonstrates non-zero clinical and functional benefit when added to standard-of-care. Even if these improvements are small, they're undeniable, and 5 or 10 years into the future after cardiac cell therapies have been optimized the benefits may be substantial and stem cell therapy will become the new standard-of-care. The future of regenerative medicine really is now, get ready.

Maybe it's time for UT Southwestern Medical Center to establish a Regenerative Medicine Consult Service or even a Center for Regenerative Science and Medicine…



I have assembled a series of typical questions that your patients might ask you about stem cell therapy and regenerative medicine. Of course, the answers are personal opinions and you may feel differently or know otherwise.

FAQS:

1. Are stem cells drugs?

Yes, as far as the FDA is concerned, stem cells are drugs. As living cells, they are in fact the most complex drugs ever developed. Unlike other drugs, we don't even know what the "active ingredient" of stem cell therapy really is; every "dose" of stem cells is biologically different, even if they are prepared the same way. It is important to keep in mind that we don't know what happens to stem cells when they are injected into your body, they are not metabolized like other drugs, they may die or stick around in their new locations for the rest of your life, and if they behave badly, which they sometimes do, there is no way for your doctor to stop them or remove them.

2. Do stem cell treatments produce side effects?

Yes, like all medicines (even aspirin), stem cell treatments will cause side effects. Generally, these side effects are mild, yet stem cells can behave in unpredictable ways.

3. Has anyone ever died from stem cell treatment?

Yes, deaths have been reported in patients undergoing stem cell therapy abroad (stem cell tourism in Asia), fortunately rarely. In all cases, it is difficult to conclude with certainty how the stem cell treatments contributed to the patient's death.

4. Why hasn't the FDA approved stem cell treatments and what does this really mean?

The only stem therapy that the FDA has approved is bone marrow transplantation (BMT) and BMT has saved or prolonged hundreds of thousands of lives around the world. BMT helps to cure very serious diseases like leukemia. The fact that stem cell treatments are not yet FDA approved technically means that unless they are part of an FDA-approved clinical trial, they are "illegal" in the U.S. and may in fact be dangerous. The job of the FDA is to protect you. The FDA has no authority over stem cell tourism and most other countries have little or no oversight like the FDA. Stem cell tourism is *caveat emptor* (buyer beware).

5. If I venture outside of the U.S. for stem cell treatment, will my doctor be mad or think I'm foolish?

No, it is critically important that a knowledgeable physician in the U.S. guides you through your stem cell tourism experience and follows-up on how you are doing afterwards. Stem cell treatments are added-to not substituted-for standard therapies. Your doctor will never be mad, that's unethical. You may have a difficult time finding U.S. physicians knowledgeable about stem cell therapy but ask at major academic centers. Some centers, like the Mayo Clinic in Rochester, MN, have a "Regenerative Medicine Consult Service" that is specifically designed to answer all of your questions and concerns, and to guide you through your experience. Importantly, they may be aware of traditional non-stem cell therapies or clinical trials that you have not tried yet and that you might be a candidate for. You can also ask stem cell scientists, they'll point you in the right direction.

6. Can stem cells really cure terrible diseases like cerebral palsy, autism, etc.?

Not likely, we are all very excited about the potential of stem cells to treat many types of conditions and diseases, but for most of these, at this time, there is no scientific proof of efficacy. Keep in mind when you read testimonials on Facebook or Google or elsewhere that

only “success stories” from satisfied (or ecstatic) patients get published; treatment failures get buried, no one wants to hear about these, and they may be the majority. For certain diseases, like heart disease, scientific evidence suggests that most patients do better with cardiac cell therapy than without it, but the improvement is small (yet for some patients highly significant).

6. What about the celebrities, Rick Perry, Peyton Manning, etc., they must have really smart doctors?
Probably, but don’t let celebrities be your guide to medical care. Certainly, the number of musicians, politicians, sports stars and other famous people who get stem cell therapy is increasing, but they may have more money than sense, and they are sometimes reckless or desperate when it comes to taking care of their bodies. However, as far as I know, Keith Richards (The Rolling Stones) hasn’t had cell therapy yet.

7. Why does stem cell therapy overseas cost so much money, $50,000 or more?
The simple answer is that people selling non-FDA approved stem cell treatments want your money; they are making a profit from your fear and hope. They will try their best to convince you that their treatment is safe and effective. This is a stem cell “sell” not science. It is important to recognize that even if you are paying for this type of therapy you are still part of an “experiment” because we don’t really know whether and, if so, how it works.

8. If I enroll in an FDA-approved clinical trial, is it true that I might be tricked and get placebo instead of stem cells?
Yes, but it’s not a trick, some but not all FDA-approved clinical trials are “blinded” meaning that you and maybe even your doctor won’t know whether you got stem cells or not. You have to understand that a clinical trial is designed to answer a scientific question for all of mankind not just you. We are grateful that you consent to participate in this important activity. If you do get “the short end of the stick,” in most trials you can later on crossover to the stem cell treatment arm of the study. Stem cell tourism has no control groups because no one is going to ask you to pay $50,000 for nothing.

9. What questions should I ask when I’m evaluated for stem cell tourism?
You should discuss this with your doctor before you go and have a set of questions ready. The International Society for Stem Cell Research has prepared some questions for you (see: http://www.isscr.org/home/publications/ClinTransGuide). You should be highly skeptical if your stem cell tourism doctors claim to have all the answers, but don’t show you any data meaning numbers of patients treated, success rates, failure rates, etc., or claim that their version of cell therapy is already proven save and effective – it may be relatively safe but efficacy is unproven except for bone marrow transplantation in cancer patients. They should explain all the risks. If they criticize the FDA or scientific clinical trials this is a red flag warning that they are snake oil salesman and don’t understand the process of medical discovery.

RECOMMENDED (EASY READING) BOOKS:

1. ***STEM CELLS: A Very Short Introduction*** by Jonathan Slack. Oxford University Press, 2012.
2. ***THE STEM CELL HOPE: How Stem Cell Medicine Can Change Our Lives*** by Alice Park. Hudson Street Press/Penguin, 2011.

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