DOWNLOAD PDF STEM CELLS AND MYOCARDIAL AGING ROBERTO BOLLI, PIERO ANVERSA

Chapter 1 : Stem Cells and Cardiac Aging â€" Johns Hopkins University

The recent explosion of the field of stem cell biology, with the recognition that the possibility exists for extrinsic and intrinsic regeneration of myocytes and coronary vessels, necessitates reevaluation of cardiac homeostasis and myocardial aging.

Features Hearts on Trial As researchers conduct the most rigorous human trials of cardiac cell therapies yet attempted, a clear picture of whether these treatments actually work is imminent. Nurses pivot carefully around a table laden with sterile instruments while a trio of physicians fusses over a catheter inserted into the groin of cardiac patient Ken Anderson. Amidst the hubbub, only the patient is still, occasionally answering questions from a nurse about his level of comfort. All at once, everything stops. Michelle Domingo, the study coordinator for the experimental cell therapy Anderson is about to receive, counts down from five, then shouts: The cells, called cardiosphere-derived cells, originated from an organ donor whose heart was not suitable for transplant. Anderson, who had refused a heart transplant, flew to Los Angeles from Missouri to take part in this experimental treatment, hoping it would help his damaged heart become more effective at pumping blood. Why should they put a heart in me? On the other hand, negative results could spell the end of the approach altogether. Anderson is one of thousands of patients who have had cells injected into their hearts over the past 10 years. Like any new branch of medicine, cardiac cell therapy has progressed in fits and starts. Most cardiologists remain underimpressed, says Anthony Mathur, the director of cardiology at Barts Health NHS Trust and the head of an ongoing Phase 3 trial in Europe that involves injecting bone marrow cells into heart attack patients. But the cells used in the therapies that are now moving into Phase 3 trials all originate in the bone marrow, and include mesenchymal stem cells as well as other cell types. Yet no one knew how the cells worked. At the time, the prevailing thought was that stem cells took up residence in the heart and proliferated to produce new tissue. But this idea has since become a matter of debate. While some researchers claim the cells can form new cardiac muscle, others assert that the cells only very rarely differentiate into cardiomyocytes and instead support cardiac regeneration by other means. On its own, the heart regenerates about one percent of its tissue per year via the division of cardiomyocytes; perhaps cell therapies simply boost that normal behavior. The absence of a concrete mechanism of action has been one of the main criticisms of the field. And with no cure for heart damage yet available, patients like Anderson are willing to try experimental treatments. But I understand why there was an explosion [of clinical trials]â€"because there is such a need. Congestive heart failure patients enrolling in the congestive heart failure cardiopoietic regenerative therapy CHART -1 study in Europe and Israel will receive mesenchymal stem cells derived from their bone marrow. And in another congestive heart failure study in the U. These studies are the most scientifically rigorous human experiments to date in the field of cardiac cell therapy. The BAMI trial is the simplest of the three, with mononuclear cells extracted from the bone marrow delivered directly into the heart with no manipulation. Investigators will measure whether patients randomly assigned to receive the cell therapy have a reduced chance of dying over the next two years than patients receiving a placebo. One of the criticisms of the BAMI approach is that the cellular mixture administered to patients contains very few stem cells and a slew of other cell types, including lymphocytes and monocytes. The trial will track several outcomes, including exercise capacity and subsequent heart events, in addition to survival. In the search for an optimal cardiac cell therapy, researchers have delivered a variety of cell types with regenerative or reparative potential into the hearts of patients with heart damage. In most cases the cells are taken from patients, expanded in culture, and returned to them. In a few cases, the cells have come from the bone marrow or hearts of donors. In this trial, the researchers are using cells collected from donated bone marrow, rather than from the patients themselves, paving the way to creating an off-the-shelf product. Results from each of these trials are expected in the next one to two years. In the meantime, researchers are concocting even more refined versions of cardiac cell therapies, including the cells Anderson received, which are derived from donor hearts.

Benefit and bias While early-stage research continues to hammer out which type of cell is optimal for repairing heart damage, a bigger question faces the field: Do cardiac cell therapies even work? Studies have found a range of results, from no benefit to substantial therapeutic effects, and research in the field has been plagued by a couple of high-profile scandals surrounding studies that made the biggest claims about heart regeneration. More recently, the work of Anversa, now at Harvard, has come under scrutiny. Beginning last year, his lab has been the subject of an institutional investigation into potential scientific misconduct. One of his papers, describing the regenerative capacity of the human heart, has been retracted, 2 while another has received an Expression of Concern from journal editors at The Lancet, where it was published in Anversa declined to comment. It has been a very long journey of one disappointment after another, where the clinical trial results have been less than overwhelmingly positive. He says the scandals in the field have given cardiac cell therapy a bad rap. Combing through 49 clinical trials of cardiac cell therapies, Francis and his colleagues exposed some inconsistencies and reporting errors, including conflicts between figures and raw data, and impossible time linesâ€”such as dead patients continuing to produce clinical data. Interestingly, the number of discrepancies Francis found in a clinical trial correlated with the reported benefit of the treatment: Francis says that poring over the cardiac cell therapy studies has soured him on the approach, and he expects that none of the therapies currently being studied will pan out. Several other meta-analyses have also yielded cautionary results. But if they are negative, then I think we are failing as a clinical scientific community if we do not thoroughly explore how it is that we got our entire clinical research field into this colossally expensive dead end. In his gloved hands are pieces of the heart of a young woman who recently passed away. Her donated organ made it here to a laboratory at Capricor Therapeutics , the biotechnology firm that is sponsoring the trial Ken Anderson is participating in. They will instead be used for preclinical research. One of the big questions the Capricor team would like to answer is which cells pack the most regenerative punch. When infused into 17 heart attack patients in a Phase 1 study, the cells caused a reduction in scarring and regrowth of heart muscle. Preclinically, other cell types are stirring up excitement. In this case, no one disputes the regenerative capacity of embryonic stem cells, but some have cautioned that their safety has not yet been sufficiently vetted to try them out in humans. Jalees Rehman at the University of Illinois at Chicago says cell therapy patches lined with regenerative cells such as induced pluripotent stem cells or embryonic stem cells are another possible route to cardiac regeneration. Other teams are looking to introduce growth factors, cytokines, or genes to induce the heart to fix itself. In the original version of this article we stated that BAMI is a double-blind study. It is actually an open label clinical trial.

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Chapter 2 : - NLM Catalog Result

Stem Cells and Cardiac Aging. / Bolli, Roberto; Anversa, Piero. Cardiovascular Regeneration and Stem Cell Therapy. Blackwell Publishing Ltd, p.

The team has had a paper in Circulation retracted , and a paper in The Lancet subject to an expression of concern. In echoes of the Fazlul Sarkar case , in which a scientist is suing PubPeer commenters because of an allegedly rescinded job offer: Sinai was actively pursuing Drs. The University of Miami was also pursuing Drs. Harvard had promised Dr. But the lawsuit is not about money, of course: And for alerting the journals to the investigation we applaud Dean Brodnicki and Harvard â€" whom, we should note, we have found less than forthcoming in other cases. With the way some of these investigations drag on â€" and then come to mealy conclusions â€" waiting for them to be over just wastes money others are spending on trying to replicate or advance the work. It also reminds us that we were recently forced to ask whether lawyers are ruining science. Dean Brodnicki did not obtain the consent of Drs. Why did she need to? Perhaps so they would have time to file a lawsuit to block it? See comments on They are, after all, the authors. The suit claims that Drs. But the Anversa lab, according to an account supplied to us by a former research fellow there, was not an environment that encouraged the kind of skeptical thinking that should be the hallmark of science. Beyond the science, ironically, a certain braggadocio also existed surrounding this hypothesis. Anyone who attended the pertinent sessions at the American Heart Association Scientific Sessions could attest to this. In essence, to Dr. For one within the group to dare question the central hypothesis, or the methods used to support it, was a quick ticket to dismissal from your position. We do get a brief mention in the suit. The researcher Anversa and Leri blame for the misconduct was not even named in any of the Boston Globe stories, and was only identified as a co-author in the blog Retraction Watch.

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Chapter 3 : SCIPIO Trial Shows Cardiac Stem Cell Benefits for Heart Failure Patients | DAIC

The existence of a cardiac stem cell (CSC) has also been described, which has the ability to generate new cardiac myocytes and blood vessels, raising the possibility of rebuilding a damaged heart.

The paper published Wednesday shows that these stem cells normally generate new cardiac muscle cells at a glacial rate in mice, and the authors said this suggests the stem cells alone would be unlikely to contribute significantly to regeneration of muscle in heart-disease patients. Do the cells in the heart do this themselves? Sign Up Thank you for signing up! Sign up for more newsletters here The research is the latest salvo in the heart stem cell wars â€" and will further roil a deeply divided field that owes many of its foundational ideas to Dr. Anversa was already controversial because his results were often in conflict with those of other researchers in the field. Brigham researcher facing new questions after retraction Many credit Anversa for the dogma-challenging insight that the heart has the capacity to regenerate itself. That broad notion is now accepted, but the field has since split into two camps over how â€" and how much â€" the heart regenerates. Figuring out how to harness that regenerative potential as a therapy depends on the answers. For a number of outside scientists, the new work brings clarity: The heart can regenerate, but at a very low rate. Jonathan Epstein, a professor of cardiovascular research at the University of Pennsylvania Perelman School of Medicine. He emphasized that multiple animal studies suggest infusing c-kit stem cells into the heart is beneficial. Bolli led an early-stage safety trial of infusing c-kit cells into the hearts of heart disease patients and found no adverse effects. Several independent laboratories could not replicate the results, but the technique was tried â€" many think too hurriedly â€" in patients, first in Europe and then in the United States. For years, scientists have debated the role those cells play in regenerating heart muscle, with studies providing evidence for both sides. Advertisement The new paper used a method that genetically tags c-kit cells so that they glow green â€" as will any heart muscle cells created by those cells. The scientists looked in newborn and adult mice, and injured mouse hearts and found only a tiny percentage of muscle cells glowed â€" three cells in 10, Anversa said by e-mail that his own lab is working with the same technique, with results pending. The important thing, they say, is that it happens at all. But a leading stem cell scientist disagreed. Joshua Hare of the University of Miami School of Medicine said that he has received FDA-approval for a trial that will combine two types of stem cells, including c-kit stem cells. Further complicating the field is the fact that it is rife with potential conflicts of interest. Eduardo Marban, director of Cedars-Sinai Heart Institute was a coauthor of the paper and provided external verification of the results in the new paper. His lab was sent specimens of heart to count the number of new cardiac muscle cells, and were blinded as to what the specimens were. Critics point out he has a company called Capricor that is trying to commercialize a different stem cell approach. Hare, in Miami, founded a company called Vestion Pharma that is focused on commercializing a combination of c-kit and another type of stem cells based on the insights from his laboratory. Johnson can be reached at cjohnson globe. Follow her on Twitter carolynyjohnson.

Chapter 4 : Myocardial aging: A stem cell problem â€" Johns Hopkins University

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Chapter 5 : Cardiac stem cells and myocardial disease â€" Italian Ministry of Health

Piero Anversa MD Dr. Anversa is Director of the Cardiovascular Research Institute at New York Medical College, and is the founder of the field of stem cell therapy and regenerative cardiovascular medicine. In recognition of his contributions, Dr. Anversa received the Distinguished Scientist Award of the American Heart Association.

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Chapter 6 : Rationale for using stem cells to repair the heart questioned by new study - The Boston Globe

Conversely, the regeneration of the skin, bone marrow, and skeletal muscle is regulated by activation of skin stem cells, hematopoietic stem cells (HSCs), and satellite cells, respectively.

Chapter 7 : Hearts on Trial | The Scientist MagazineÂ®

The paradigm that the heart is a postmitotic organ incapable of regenerating parenchymal cells was established in the s, and this dogma has profoundly conditioned basic and clinical research in cardiology for the last 3 decades.