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CARDIOPULSE

Back to square one

The future of stem cell therapy and regenerative medicine after the recent events

In the old days medicine provided tender loving care, later gave pain relief and then gradually developed effective remedies for an increasing number of illnesses. However, up until today curing remains an unfulfilled vision for most conditions. For certain diseases, e.g. end-stage heart failure, a new organ is often the only remedy and transplantation surgery has provided such an option. However, transplantation is associated with numerous hurdles and requires lifelong immune suppression with its own problems in most patients.

The myth of Prometheus

In Greek mythology, the Titan Prometheus gave mankind the gift of fire and the skill of metalwork, a treason for which Zeus chained him to a Caucasian rock.[1] To eternally perpetuate his suffering Zeus further ensured that every day an eagle, the emblem of Zeus, ate his liver. Of note, his liver continuously regrew—the first description of organ regeneration (*Figure 1*). Ever since, organ regeneration was a dream and indeed certain animals truly have such capacity. For instance, amphibia such as reptiles, and lizards are able to regrow a lost tail and even parts of their legs and the Zebra fish can even regrow parts of its heart.[2] So why should we not achieve this in patients with failing organs? And indeed, modern medicine confirmed the capacity of the liver to regenerate resected tissue after surgery.[3]

The vision of regenerative medicine

The discovery of pluripotent cells in our body and their creation by defined transcription factors from dermal fibroblasts[4] created a lot of enthusiasm and hopes for a clinical application in regenerative medi-

Figure 1 The Titan Prometheus chained to a Caucasian rock and the eagle eating his liver.

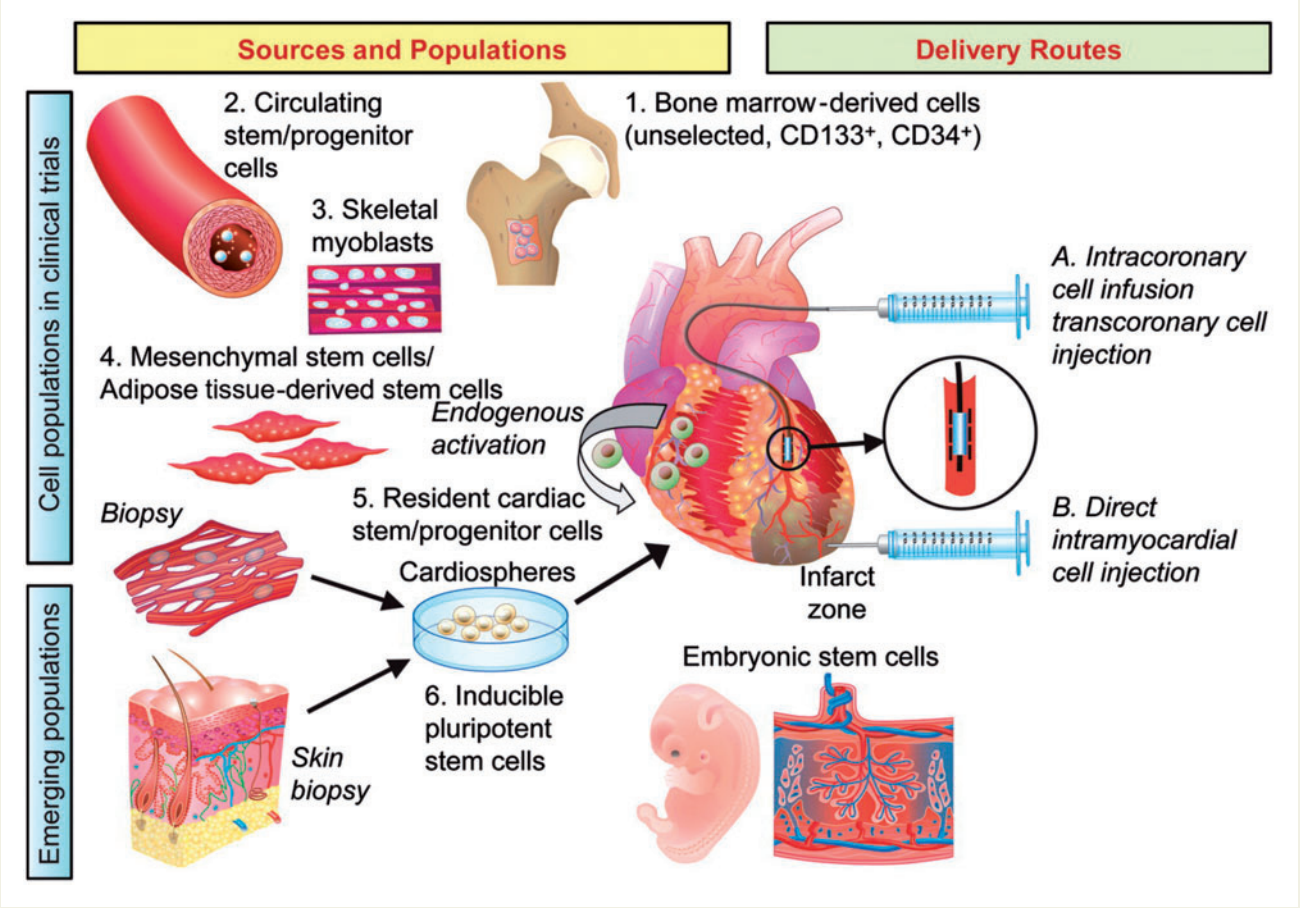

Figure 2 Clinically examined as well as emerging stem and progenitor containing cell populations, and their delivery routes for the treatment of ischaemic heart disease. From: Stem and progenitor cell-based therapy in ischaemic heart disease: promise, uncertainties, and challenges. Eur Heart J 2011;32(10):11971206. doi:10.1093/eurheartj/ehr018.

cine (*Figure 2*). At first in haematology stem cells became an established treatment in patients with different forms of leukaemia for bone marrow transplantation—and soon became a role model for other medical specialties.[5] Thus, it seemed logical that in fatal end-stage heart failure, for instance, after a large myocardial infarction, regeneration of lost myocardial tissue using progenitor cells would soon enter clinical practice.

The experimental evidence

Cardiovascular research was truly stimulated by such a promise and in fact in numerous animal models of infarction it seemed to work.[6] Scientific journals embraced such studies no less enthusiastically than the submitting authors and the field grew exponentially. And indeed, some even claimed that bone marrow cells can regenerate myocardial cells.[7] In no time, there were clinical proof-of-concept studies started, followed by larger trials.[8] Such trials mainly used bone marrow derived progenitor cells and injected such cells intracoronary mostly in patients who had recently experienced a myocardial infarction and had been revascularized. The results were initially very promising, but later it became obvious that the cells would not, or only to a small extent, remain at the injection site within the heart, nor would they transmigrate to form new blood vessels or even myocardial tissue. Indeed, most of injected progenitor or early outgrowth cells were found in the reticuloendothelial system, i.e. in liver, spleen, and lymph nodes. Accordingly, the effects on left ventricular ejection fraction turned out to be marginal[9] or absent.[10,11]

Nevertheless, the enthusiasm continued, and resident stem cells were found in the heart and other organs.[12] It appeared that they would have regeneration capability and as they were also found in the heart, a trial using such c-kit$^+$ lineage-negative cardiac stem cells was immediately designed. The SCIPIO trial using such cells recruited only 16 patients (!) with myocardial infarction.[13] At the *American Heart Association Scientific Sessions* in November 2011 in Los Angeles, a main session was devoted to stem cell therapy and a number of trials including SCIPIO were presented. Most of them, among them the SWISS-AMI trial, reported neutral or marginally positive effects on ejection fraction, while the last trial presented by Roberto Bolli revealed impressive effects. Indeed, in the 14 of the 16 patients analysed the ejection fraction increased by an impressive 8%. Accordingly, the paper was swiftly published in the *Lancet*.

Raising concerns

Not only at the clinical level, but also in basic science doubts increased whether regenerative cardiovascular medicine would work as easily as

anticipated. Many studies published with great enthusiasm could not be reproduced and in fact, the results of an increasing number of papers came into question. On 15 October 2018, an investigative committee of Harvard Medical School looked at a large number of stem cell studies from their own institution and concluded that the results of 31 papers could not be confirmed with certainty and its members therefore recommended retraction of these manuscripts. Such an earthquake has rarely, if ever, shattered a research field and thus the *European Heart Journal* editors felt that it would be worthwhile to discuss the incident and the lessons thereof by experts in the field.

Lessons from the earthquake

The lessons are indeed important for both stem cell research and medicine and science at large:

(1) Scientists are commonly excited about their own hypothesis and they search to confirm their expectations—and rightly so: Without such enthusiasm nothing would have been discovered in human history!

(2) The principle of science, however, is conjectures and refutations:
- as Sir Karl Popper put it[14]; 'only scientists that listen to their experiments and accept their answers even when they disprove their expectations are good scientists'.
- Of note, Thomas Huxley crisply stated: '*The tragedy of scientific inquiry is that a beautiful hypothesis may be slain by an ugly fact*'. This is hard to swallow but is at the base of any scientific discovery.

(3) Good science requires time: If we rush to conclusions before we have finished all the necessary control experiments, have obtained the proper amount of data to allow for confirmatiion of the conclusions reached, assured and excluded any cognitive bias, we are likely to eventually fail.
Undoubtedly, the pressure is on. If a new field opens; everybody wants to be the first; but we need to take the necessary time to produce reproducible results. Contrary to some initiatives to shorten the time from bench to publication further and further,[15] such a hasty research strategy is likely to produce irreproducible results. Indeed, we should not be working towards the end of journals as Harlan M. Krumholz has suggested but should rather take the time for proper peer review, and indeed, should even improve peer review further, to avoid such catastrophes as we have just had to experience.

(4) If we jump too early from basic observations to clinical application, we may fail.

Rodents are widely used animal models, but they share only around 80% of their genes with us, their hearts are much smaller and their infarctions are usually induced in young and healthy animals, while patients with myocardial infarction, are on average around 65 years of age, have multiple risk factors and comorbidities[16] and their progenitor cells are commonly dysfunctional—they are as old as the patient.[17] Therefore, translating results from the mouse to humans must be done with caution.

In this issue of the *European Heart Journal* a number of experts in the field discuss stem cell research and the future of regenerative medicine in the context of the recent events. Not everything in science, not even all results from the best laboratories or research groups are reproducible as biology and experimental conditions are influenced by an overwhelming number of known and unknown factors.

But if things go out of hand, we have to push the reset button and evaluate how to revive the dream of regenerative medicine.

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References

References are available as supplementary material at *European Heart Journal* online.

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Regeneration for All: An Odyssey in Biotherapy

Authors from the Mayo Clinic discuss the evolution of the regenerative paradigm and look to the future

Origins

Two decades ago, if you were to ask a scientist what it would mean to regenerate the heart, you would regularly hear about the power of developmental biology in decoding the intricacy of organogenesis and the plasticity of stem cells recognized as nature's ultimate 'building blocks'. The conversation would then delve into the merits and drawbacks of embryonic stem cell technology, presented as the quintessential regenerative phenotype.

With an ever-broader scholarly engagement and a growing public awareness, the academic intrigue of stem cell-based therapy was exponentially fuelled by the practicality of mining adult stem cell reservoirs out of bone marrow and adipose tissue. Universally, this multinational transdisciplinary endeavour captured the imagination of patients and physicians/scientists alike, while recognizing the ensuing medical, ethical and societal opportunities, and potential risks.

The prospect of pioneering a change in disease management propelled this maturing field from science fiction to the rigor of the scientific bench and onwards to randomized clinical trials. Here, the tantalizing concept of rebuilding the body to reverse underlying pathology, as opposed to a battle to palliate disease, emerged as a paradigm shift. In parallel, the notion of a curative intervention held the promise