

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<sup>14</sup>; ‘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 confirmation 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,<sup>15</sup>

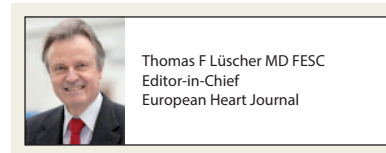
such a hasty research strategy is likely to produce irreproducible results. Indeed, we should not be working towards the end of journals as Harlan M. Krumholz has suggested but should rather take the time for proper peer review, and indeed, should even improve peer review further, to avoid such catastrophes 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<sup>16</sup> and their progenitor cells are commonly dysfunctional—they are as old as the patient.<sup>17</sup> 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.

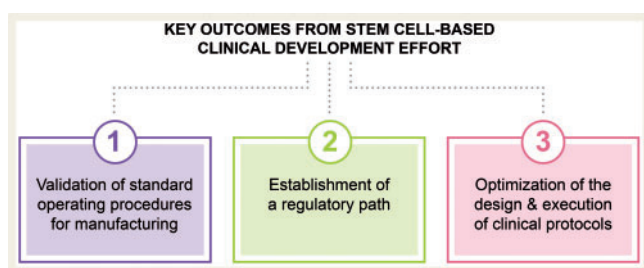
The prospect of pioneering a change in disease management propelled this maturing field from science fiction to the rigor of the scientific bench and onwards to randomized clinical trials. Here, the tantalizing concept of rebuilding the body to reverse underlying pathology, as opposed to a battle to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

of altering the economics of chronic disease management, relieving the health care system of the cost burden associated with an ageing population vulnerable to degenerative disease.

## Reflection

To date, the key outcomes from the collective cardiovascular clinical development effort have been:

- i. validation of standard operating procedures needed for stem cell derivation and manufacturing;
- ii. establishment of a regulatory path including the FDA 'Expedited Programs for Regenerative Medicine Therapies for Serious Conditions'; and
- iii. optimization of the design and execution of clinical protocols for cell-based therapy.



Accordingly, the safety and feasibility of applying adult stem cell therapy to patients with cardiovascular disease have been repeatedly attained and independently documented. Mechanistic insights into how stem cells behave and influence the heart are also increasingly elucidated. With enrolment of patients into larger clinical trials, stratification criteria for selection of patient populations most likely to benefit has become progressively clearer. However, used as an investigational new drug stem cells in practice departed from traditional pharmacodynamics, introducing an increased complexity in the therapeutic paradigm. Moreover, even with efforts to ensure potency, purity, and homogeneity, dose-to-dose variance in outcomes precluded standardized regimens amenable for early adoption.

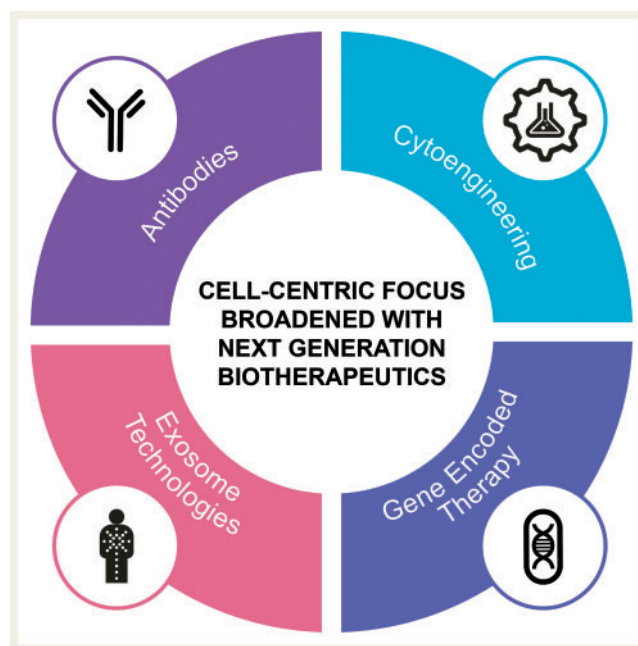
As we approach 2020, and despite significant clinical experience with thousands of patients treated globally, there is still no specific cell type registered definitively for use in cardiovascular practice.

## Journey

The odyssey to achieve reproducible cardiac regeneration in a clinically meaningful manner is reminiscent of the efforts to develop vaccines for cancer. The notion that the immune system can be sensitized to eliminate cancer from the body was heralded for decades as the Holy Grail in oncology, elevating the armamentarium of care with introduction of a 'fourth modality', beyond the traditional triad of chemotherapy, surgery and radiation. Yet, in initial clinical applications, promising pre-clinical data did not materialize, yielding little reduction in tumour load and failure to prevent metastatic progression. Destined to remain on the side-lines of care, cancer immunotherapy did eventually attain dramatic breakthroughs. Catalysed by robust public/private partnerships, immunotherapies today are transforming daily oncological practice.

## Blueprint

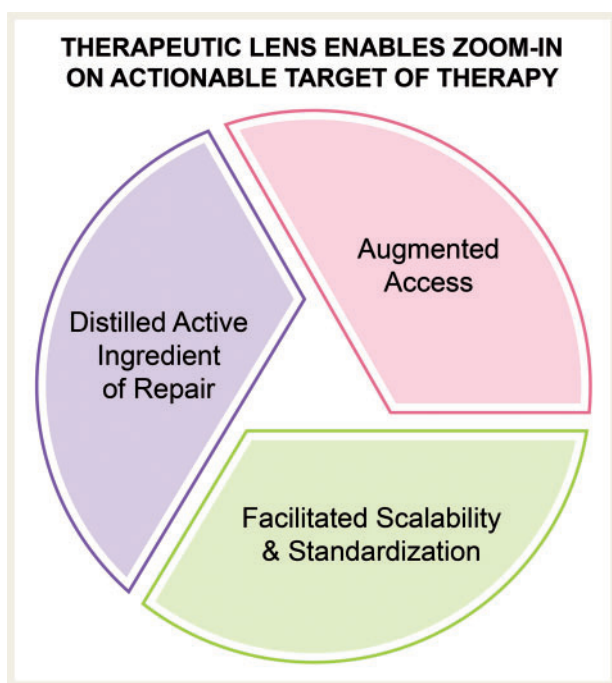
Highlighted by targeted antibodies and engineered chimeric antigen receptor (CAR) T-cell therapy, the era of biologics-based treatment is realized as a revolutionary advance in managing select refractory cancers. For the cardiac regeneration space, the playbook gathered from decades of trial and error in immunotherapy can in turn serve as a progressive blueprint towards realizing novel cardiovascular solutions. The culture of establishing the molecular basis underpinning clinical outcomes provides a remarkable inroad to identify the determinants of prospective benefit, and thus creates an informed framework to drive the success of novel therapies. If this iterative tactic holds true for improved cardiovascular disease management, the current cell-centred focus will likely be broadened to encompass next generation advances in the science of biotherapeutics, including antibodies, cytoengineering, gene encoded therapy, and exosome technologies.



## Fitness

Although naïve T-cells are not primed to treat cancer, CAR engineering allows for a curative result. Likewise, stem cells utilized as a reparative measure in the heart, show among others, anti-inflammatory and provasculogenic properties, which are serendipitously relied upon to achieve regenerative outcomes. Use of emergent molecular platforms, exemplified by gene encoded technology and exosome science, creates a therapeutic lens enabling to zoom-in on the actionable target of therapy.

Mounting clinical experience in cardiovascular regeneration streamlines the mechanistic understanding of benefit to distil the active ingredient of repair. Scientific, scalability and standardization barriers, which at present have marred progress and exposed scepticism, are poised to be breached, thanks to an expanding knowledge base and adoption of the increasingly precise, target-costumed toolkit that provides a new level of regenerative fitness.



## Imagine

Imagine a potassium channel selective antibody that can restore heart rhythm, while avoiding the long-term hazards of amiodarone. Or, a cell engineered to specifically secrete endothelial nitric oxide synthase, hence enhancing microvascular efficiency. How about tissue engineering for scar revision leveraging induced pluripotent stem cell-derived cardiac scaffolds? Or, gene encoded therapy for discriminate reversal of genetic lesions causing cardiomyopathies in no option patients or in order to postpone organ transplantation in others.

Furthermore, a refined understanding of cell-to-cell communication has emerged with the exploration of extracellular vesicles, often referred to as exosomes. Use of derived exosomes has the potential to harness salient features driving benefit from cell therapy, while concentrating the resolved active ingredient to endow flexibility of dosing biopotency in a ready-to-use product. If successfully derived and formulated, exosome-based therapies would eliminate the need for ensuring cell survival, freeze-thaw issues and could overall simplify the skillset and infrastructure needed in the application of biologics-based therapies.

If non-cellular biologics are realized as an off-the-shelf platform, suddenly therapy at the time of acute syndromes, such as a heart attack or stroke, would become a feasible indication for point-of-care regenerative medicine not necessarily limited to tertiary care centres.

Thus, milestones achieved over the 20-year odyssey of cardiac regeneration have brought us ever closer to the prospect of reaching a 'therapeutic Ithaca' with adoption of advances in biologic modalities championing a wave of synergistic innovation to complete this journey aimed at the wellbeing of patients.



Atta Behfar, MD, PhD  
Associate Professor of Medicine &  
Assistant Professor of Pharmacology  
Director, Van Cleave Cardiac  
Regenerative Medicine Program  
Braswell Deputy Director of Translation  
Center for Regenerative Medicine  
Mayo Clinic, Rochester, Minnesota, USA

## Access

As cardiology gradually adopts therapeutic capabilities stemming from biologics, there is an added opportunity not only to achieve the full potential of disruptive therapies, but also to evade major costs inherent to latest generation technologies. With introduction of biologics in the oncology space, a reset in the norms of how much can be charged for a dose of a transformative or curative therapy has arisen. One may ask, if organ transplant to save a life costs in excess of \$500 000, why cannot a cure for cancer or heart failure be as costly?

The approach to scientific advance is often achieved in the laboratory without a conscious decision or the know-how necessary to design cost-effective processes that would limit manufacturing and delivery costs. The objective of the discovery process is to prove a paradigm, not necessarily figure out how to achieve scale-up or proper dosing. Yet, both components are critical in advancing practice utilization. And if successful and exciting, the momentum of getting the technology ready for the clinic typically impedes *post hoc* introduction of cost efficiency and seamless delivery.

Although a technology can save lives in its current state, it is important to also ask how many lives can it save. A very large global population suffers from cardiovascular disease accounting for one-third, or nearly 20 million of all deaths worldwide. A large portion responsible for this staggering epidemiology occurs in emerging economies, where individuals in the most productive years of their lives suffer from debilitating heart attacks or strokes. Thus, in order to be impactful, not only does the next decade of efforts in cardiac regeneration need to overcome efficacy hurdles of the past; but also, there is a pressing need to build and apply technologies that fiscally and logistically are realistic on a global scale ensuring both validity and utility.

## Horizon

To safeguard from healthcare disparities, it behoves the whole community of practice to utilize discovery not only as an engine to achieve translational and ultimately therapeutic success—but importantly, to embed innovation stringency as a means to break or prevent socioeconomic divides, augment access and level the playing field of care. In principle, biotherapies manufactured and delivered at a low cost of goods, as a room temperature stable product, would provide the unique ability to offer a generation of therapies across diverse environments and even for emerging nations.

If we could advance far enough where the need for a living therapeutic entity is no longer a pre-requisite to achieve regeneration, then suddenly new horizons of innovation and implementation would open-up. Achieving cell-free biologics to feature the ease of use and uniform benefit is an exciting evolution towards regeneration for all.

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Andre Terzic, MD, PhD, FAHA  
Professor of Medicine and Pharmacology  
Marriott Family Professor of Cardiovascular Research  
Michael S. and Mary Sue Shannon Director,  
Center for Regenerative Medicine  
Marriott Family Director of Comprehensive  
Cardiac Regenerative Medicine  
Mayo Clinic, Rochester, Minnesota, USA  
Corresponding author: terzic-andre@mayo.edu  
Tel: 1-507-2845514