Stem cell therapy for heart failure: Ensuring regenerative proficiency

Andre Terzic, MD, PhD\textsuperscript{a,b,c,*} and Atta Behfar, MD, PhD\textsuperscript{a,b,c,d}

\textsuperscript{a}Center for Regenerative Medicine, Mayo Clinic, Rochester, MN
\textsuperscript{b}Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN
\textsuperscript{c}Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN
\textsuperscript{d}Center for Transplantation and Clinical Regeneration, Mayo Clinic, Rochester, MN

A B S T R A C T

Patient-derived stem cells enable promising regenerative strategies, but display heterogenous cardiac reparative proficiency, leading to unpredictable therapeutic outcomes impeding practice adoption. Means to establish and certify the regenerative potency of emerging biotherapies are thus warranted. In this era of clinomics, deconvolution of variant cytoreparative performance in clinical trials offers an unprecedented opportunity to map pathways that segregate regenerative from non-regenerative states informing the evolution of cardio-regenerative quality systems. A maiden example of this approach is cardiopoiesis-mediated lineage specification developed to ensure regenerative performance. Successfully tested in pre-clinical and early clinical studies, the safety and efficacy of the cardiopoietic stem cell phenotype is undergoing validation in pivotal trials for chronic ischemic cardiomyopathy offering the prospect of a next-generation regenerative solution for heart failure.

Key words: Cardiovascular disease, Cardiopoiesis, Cardiopoietic stem cell, Clinical trial, Clinomics, Epidemic, Health care, Myocardial infarction, Next generation, Regenerative medicine, Quality, System.

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Heart failure paradox

Scientific advances profoundly impact evidence-based systems of cardiovascular care [1]. In acute myocardial infarction, coronary reperfusion along with adjuvant pharmacotherapy has helped to ensure a \( \geq 96\% \) in-hospital survival offering a contemporary exemplar of improved outcomes [2]. Despite reduced early mortality, 12% of patients die within 6 months post-infarction and 25% of infarction survivors progressively develop organ failure [3]. Hence, the emerging heart failure epidemic is regarded as a paradox of medical success (Fig. 1) [4].

Chronic heart failure affects up to 30 million people worldwide and highlights the growing burden of degenerative diseases at a global scale [5]. About 1–2\% of adults in developed countries suffer from heart failure, with prevalence rising to \( \geq 10\% \) in persons 70 years of age or older. Liable for \( \geq 2 \) million yearly hospitalizations in the United States and Europe, heart failure is a primary indication for repeated in-hospital care across geographies [6]. Survival does not exceed 1 in 3 patients at 5-year follow-up [7]. These staggering trends underscore pressing unmet needs of a vulnerable aging population in spite of a generalized decline in cardiovascular mortality rates.

Coronary artery disease underpins two-thirds of all systolic heart failure—the best-known form of disease associated with reduced ejection fraction. In patients who overcome acute ischemic insult, initial survival is offset by progressive organ failure requiring therapy escalation. As focus of therapy shifts from mortality to consequences of survival, the quest for treatments that reduce myocardial injury/limit...
adverse remodeling and restore parenchymal integrity/preserve ventricular function is paramount [8].

Disease reversal goals

Heart failure therapy entails syndrome relief, prevention of hospital admission, and mortality reduction [9]. To impact quality of life and survival, disease management relies largely on optimal titration of pharmacotherapy (i.e., beta blockers, angiotensin-converting enzyme inhibitors, aldosterone antagonists, and neprilysin inhibition), and use of cardiac resynchronization as appropriate. Infarct size, however, remains the main determinant of adverse post-infarction aftermath, including a particularly poor clinical outcome in worsening heart failure [10]. Current approaches fail to address the fundamental issue of myocyte loss that underlies incipient cardiomyopathy. In end-stage disease, mechanical circulatory support, and organ transplantation are extraordinary life-extending measures limited by cost and access. To enhance standard of care, innovative treatments aim to fundamentally alter the course of disease, and avert end-stage deterioration and need for transplantation [11].

The U.S. Department of Health and Human Services perspective, “2020: A New Vision,” singles out regenerative medicine at the core of health care innovation [12]. Exemplified by curative therapies offered in transfusion medicine and in defined hematological malignancies, regenerative technologies incorporate transplant of healthy tissues, induction of a healing response in diseased tissues, and/or implement tissue engineering to manufacture new tissue [13,14]. Regenerative innovations are introduced across medical and surgical specialties aiming at normative organ restitution integrated in whole-person care. With the prospect of functional and structural repair, regenerative solutions strive to achieve disease reversal goals reducing medical and societal imperatives of life-long disease management [15].

Regenerative equation

The notion of the heart as an organ permissive of regeneration is central in the rollout of regenerative paradigms applied to cardiovascular medicine. Traditionally referred as a post-mitotic, terminally differentiated organ, newer evidence supports a dynamic view of the human heart. Cell death versus renewal incorporates vital components governing cardiac homeostasis, aging, and disease [16]. During a person’s life, revitalizing mechanisms—particularly operational at a younger age—contribute to ongoing renewal of the heart mass, securing physiological tissue safeguard [17]. Regenerative reserve reflects the ability to maintain homeostasis through self-reparative mechanisms [18]. In disease, this innate propensity becomes inadequate to cope with cardiomyocyte loss and ultimately fails to restore organ performance. In particular, with aging, the rejuvenative reserve is compromised as decline in tissue health is compounded with accrual of senescent cells [19]. Clearance of senescent cell pools improves tissue function, yet falls short at restoring pre-aging status [20]. In a permissive myocardial environment, regenerative therapy is thus conceived as a boost to the innate repair capacity aiming to restore regenerative fitness.

Within a diverse and evolving regenerative toolkit that includes standalone or combination techniques relying on cells/tissues/biomaterials, and/or molecules, stem cells and derivatives are the most commonly tested active ingredient [21–23]. Use of stem cells to buttress the regenerative fortitude of ailing hearts leverages a presumed capacity to recreate tissue and/or promote repair, and represents 25% of all clinical development efforts in cell-based therapies [24]. Stem cells, envisioned to fulfill a building-block role to rebuild compromised heart muscle, are increasingly thought to actually stimulate a multifaceted regenerative response, leading to an overhaul of the disease substrate within the host myocardium. Indeed, a science that was initially highly cell centric has undergone a fundamental re-examination, moving away from the premise of a direct exogenous stem cell-mediated regeneration toward the currently prevailing hypothesis that therapeutic activity reflects primarily an indirect, paracrine effect of delivered cells interacting with the diseased myocardium to trigger an endogenous regenerative cascade. Multimodal repair mechanisms, implicating...
both exogenous and endogenous progenitors, have been proposed in this regard [25].

Post-infarction, cell-based interventions aim at regenerative prophylaxis of fragile injured hearts, that is, to limit early damage by altering the myocardial response to injury, averting adverse remodeling, and avoiding or delaying organ failure [26]. Beyond acute/subacute cardioprotection, in advanced heart failure associated with protracted systolic decompensation, the goal becomes cardioresorative aimed at reversal of contractile dysfunction, structural restoration, and scar reduction [27]. Proposed strategies are supported by wide-ranging pre-clinical proof-of-concept studies that serve as a launch pad for testing in humans [28].

As a result, over the last decade, translation of stem cell technology in clinical trials has been increasingly realized. Across the cardiovascular disease spectrum, numerous phase I and a growing number of phase II clinical trials have been completed, testing various cell types and delivery protocols. Accumulating data from early phase clinical experience documents safety and feasibility of delivering autologous or allogeneic therapies in a range of cardiovascular conditions, and importantly provides a foundation to define parameters of clinical efficacy that justify further investigation in larger clinical trials [29]. Clinical progress in developing convincing and successful therapies, although steady, has been modest in part attributed to rather small, underpowered trials using surrogate end points and open-label treatment approaches carrying the risk of bias [30]. A recent meta-analysis focused on heart failure reflects on the state-of-the-art [31]. This comprehensive study analyzed systematically 31 clinical trials including over 1500 total participants (882 cell-treated and 639 control patients). Collectively, these trials encompass an assortment of tested cell products ranging from bone marrow-derived mononuclear cells, including granulocyte-colony stimulating factor (G-CSF) mobilized sub-populations, and bone marrow-derived mesenchymal stem cells to cardiac stem cells, skeletal myoblast, and adipose tissue-derived cells [31]. Supporting the safety record of cell-based therapies, this meta-analysis underscores overall safety with minimal major intervention-related adverse effects and no increase in the incidence of arrhythmias [31]. Moreover, reduction in mortality and re-hospitalization caused by worsening heart failure during long-term follow up, along with moderate improvement of left ventricular ejection fraction and improved heart failure symptoms including exercise capacity were documented. However, performance/selection bias was deemed considerable as only half of the analyzed trials reported blinding of participants/clinicians, and roughly, half failed to report methods of allocation concealment [31]. In fact, when only double-blind studies were selected, the meta-analysis did not reveal statistical difference between cell-treated versus control groups [30,31]. Thus, encouraging feasibility and safety profiles observed repeatedly in clinical testing have yet to materialize into broadly validated clinical benefit, dictating the need for vigilant assessment of cell therapy practices [32]. In this regard, it should be noted that the presumed biological activity of a cellular product might greatly differ depending on the cell source, cell preparation, and/or cell administration. Moreover, among a number of variables, the state of the target cardiac micro-environment dictates the efficacy of mechanisms contributing to ultimate functional regeneration [30]. New emphasis is thus placed on establishing quality control procedures through development of standard operating practices for the harvesting, isolation, and expansion of cell populations. Insights into the composition of stem cell sources have, for example, paved the way toward approaches that would eliminate non-regenerative cells to expand cell populations that display multipotent traits possibly predicting regenerative potency before intervention [32].

**Problem statement**

Regenerative science must achieve “validity” (potential effectiveness) and “utility” (likelihood of improved outcome) in clinical settings to extend current care models, and provide a value-added benefit for patients and society at large [33]. Build-out of regenerative service lines is predicated on effective clinical-grade biotherapies suitable for scale-up and standardized production and application. A viable supply chain requires quality-controlled manufacturing and delivery of products that fulfill patient specifications [33]. At present, an essential point of vulnerability that constrains translational readiness and practice adoption is the inherent idiosyncrasy and aleatory bioactivity of stem cell populations (Fig. 2) [34].

Patient modifiers—such as age, sex, morbidities, and concomitant therapies—impact regenerative fitness. Cell performance is also subject to influences during procurement, production, and/or delivery [35]. In fact, not all individuals harbor stem cells with a uniform reparative capacity. Systematic analysis of national trial experience reveals that, in patient cohorts, the incidence of reparative stem cells with a clinically measurable cardio-regenerative aptitude is quite rare—in the order of 5% [36]. The inconsistency in stem cell effectiveness mandates means that would ensure consistent efficacy of treatment, including quantitative surrogates to reliably predict the intended biological activity [37].

**Informing biotherapy evolution**

Clinical trial experience provides an irreplaceable avenue to inform the evolution of cardio-regenerative stem cell therapies [30]. "First-generation" therapies are typically comprised of mixed cell populations that generated largely mixed results [38,39]. Heterogeneous clinical outcomes offer, however, a unique opportunity to delineate molecular underpinnings of true responders from non-responders (Fig. 2). Surface markers alone may provide insufficient resolution to forecast cellular repair aptitude. Rather, regenerative from non-regenerative cytotypes are segregated based on distinctive molecular pathways that are starting to be elucidated through high-throughput clinomics approaches leveraging clinical trial specimens cross-referenced with individual patient outcomes [36,40]. Non-regenerative cells remain confined to a state of perpetual stemness [39]. In contrast, rare regenerative counterparts are milieu responsive, plastic, with a definitive inclination for differentiation—traits of regenerative proficiency [40,41].
Accordingly, “next-generation” therapies are designed to ensure that therapeutic stem cells will reliably function in the target organ [42]. This requirement can, in principle, be achieved through multiple strategies, including habituation of the myocardial environment to improve on stem cell homing upon delivery [43], anatomic matching of cell source with target organ relying on resident stem cell pools [44], or combined cell therapy [e.g., mesenchymal stem cells along with c-kit(+) cells] for synergistic effects that leverage cooperative cell-to-cell communication according to organ needs [45,46]. We here zoom in on an alternative prototype platform—cardiopoiesis—developed to mitigate variability inherent to cell products/patients and integrate a quality system that certifies regenerative proficiency of a biotherapy candidate.

Cardiopoiesis fundamentals

Cardiopoiesis imposes a lineage-specifying program on stem cells to reinvigorate function and promote cardioreparative proclivity [40,41]. Cardiopoiesis guides stem cells to (re)activate cellular plasticity, (re)engage into cardiovascularogenesis, and (re)set an active aptitude for repair (Fig. 3). This conditioning paradigm draws from embryonic signals that instruct precardiac mesoderm to commit into the cardiomyogenic fate [47]. Cues germane to the ventral endoderm of a developing embryo guide, the anterolateral mesoderm ensuring definitive cardiac program engagement, and avoidance of alternative fates or uncontrolled growth [48]. Narrow windows defining developmental stages dictate the delicate nature in which cardiogenic cues need to be introduced to promote cardiogenesis from an embryonic stem cell source, exemplified in the complex dynamics of TGF-β superfamily signaling guiding pluripotent stem cell fate choices [49,50]. A systems biology-resolved cardiopoietic atlas revealed an integrated and tractable molecular network fundamental to lineage specification [51]. Using endodermal cell lines, the cardio-inductive aptitudes of secreted cytokines and growth factors have been screened—a process facilitated by the stress cytokine TNF-α that spikes the cardiogenicity of the endodermal secretome [52]. Resolving the unprimed endodermal secretome vis-à-vis that of the TNF-α-enhanced endoderm enabled dissection of molecules that coax stem cells into cardiac fate. Through this approach, a cocktail of critical factors was formulated to recapitulate required cardiogenic cues [53]. An initial version included TGF-β1, BMP-2/4, FGF-2/4, IL-6, IGF-1/2, VEGF-A, EGF, and Activin-A, where staged factor combinations created a synergistic environment, which promotes the upregulation and nuclear translocation of cardiac transcription factors, including homeobox transcription factor Nxk2.5, zinc finger-containing transcription factor GATA-4, and myocyte enhancer factor MEF2C. Directed differentiation allows lineage mapping of embryonic stem cells, as they transition from pluripotency to a cardiogenically oriented multipotent fate. The distinguishing feature of the derived intermediate cell phenotype, termed cardiopoietic stem cell, is the capacity to uniquely yield cardiovascular lineages [40,48,53]. Cardiopoietic stem cells are defined by nuclear translocation of cardiac transcription factors (low in unguided stem cells) and absence of sarcomerogenesis (typical of mature cardiomyocytes). In density gradients, sarcomere-poor cardiopoietic stem cells are readily separated from cardiomyocytes. A low-density cardiopoietic stem cell culture (1500 cells/cm²) placed in the cardiogenic cocktail yields a 10%, 30%, and 65% population of cardiomyocytes by 3, 6, and
10 days, respectively [41]. In this way, cardiopoiesis enables targeted generation of lineage-specified stem cells [54].

Translating cardiopoiesis

Principles discovered in embryonic platforms are translatable into clinically apt practices (Fig. 4). A cardiogenic cocktail-rich milieu can guide patient-derived adult stem cells to acquire a repair potential associated with cardiac transcription factor expression [40,54]. Adult stem cells suffering from sequestered plasticity are resuscitated by priming with recombinant factors TGF-β, BMP-4, Activin-A, IGF-1, IL-6, FGF-2, thrombin, and retinoic acid that mimic signals and pathways activated in natural cardiogenesis. Of note, however, the biological outcome of cardiopoiesis applied to an adult stem cell population should be distinguished from that of pluripotent counterparts, as it intends to achieve a regenerative paracrine function in the heart rather than to recapitulate embryonic cardiomyogenesis [40,48]. The first clinically tested example of such an approach is lineage specification through conditioning of bone marrow-derived mesenchymal stem cells from patients with ischemic heart failure to yield the cardiopoietic stem cell phenotype [40,41,54]. In mesenchymal stem cells, simultaneous activation with TGF-β, BMP-4, and Activin-A along with retinoic acid induces cytosolic expression of cardiac transcription factors, while IGF-1 and IL-6 prompt their nuclear translocation (Fig. 3). Such co-stimulation typically results in cell cycle arrest of primed mesenchymal stem cells precluding cell propagation to achieve a therapeutic dose needed in man. To this end, FGF-2 and thrombin are utilized to maintain cell cycle activity (Fig. 3). Compared to lineage-unspecified mesenchymal stem cells, delivery of derived cardiopoietic stem cells into an infarcted failing heart demonstrates improved therapeutic impact on follow-up [40]. Limited cell grafting detectable long-term contrasts the maintained functional benefit, implicating indirect mode of action that harnesses endogenous

Fig. 4 – Cardiopoiesis platform: translating discovery into application. Deconvoluted molecular events underlying cardiogenesis guided translation and scale-up of lineage-specified stem cells manufactured for clinical application.
repair pathways [40,55]. Although rare, head-to-head studies of different transplanted cell types indicate functional superiority of those whose phenotype is close to that of the target tissue, that is, cells committed toward a cardiac lineage [55]. Pre-emptive cardiopoietic conditioning could thus serve to expand the number of patients potentially benefiting from stem cell therapy by converting the naive, typically non-reparative, source into a reparative cytotype [56,57].

A biomarker-based measure to anticipate therapeutic efficacy of adult stem cells prior to transplantation was in accordance developed. The “cardiopoietic index” employs a gene-expression profiling as a means to assess the regenerative quotient of patient-derived cells [58]. The index reflects an integrated readout, based on the messenger RNA expression of cardiogenic transcription factors Nkx2.5, MEF2c, Gata-4, Gata-6, Fog-1, MESP1, and Tbx5. Application of this quality control standard allows pre-assessment of repair potential at time of cell harvest predicting individuals harboring stem cells with an innate capacity for repair versus those with non-reparative cells, where switch-on of pro-regenerative signaling is needed. The cardiopoietic index is a gauge of functional benefit (measured as ejection fraction change) with a reported sensitivity and specificity of 91% and 95%, respectively [58].

Ensuring a robust cardiopoietic yield would be valuable, particularly in conditioning stem cells derived from elderly patients. An example of strategy currently investigated to maintain youthful status is the titration of nucleostemin functionality. This nucleolar stress sensor works by stabilizing stemness gene programs through pro-survival pathways with nucleostemin overexpression reducing senescent traits in support of tissue youth [59], thus providing a means to meet purity, potency, and sterility metrics. Manufactured cardiopoietic stem cells require a multitier release schedule, which first establishes homogeneity of the mesenchymal stem cell source through cell surface marker profiling. This is followed by establishment of purity through gene profiling to ensure that the therapeutic formulation is devoid of divergent, non-cardio-regenerative contaminants. Finally, documented nuclear translocation of a select cardiopoietic index marker ensures potency (Fig. 9).

The impact of cardiopoietic stem cells on patients with established ischemic heart failure was investigated in the C-CURE trial (Cardiopoietic stem Cell therapy in heart failure; ClinicalTrials.gov Identifier: NCT00810238; Fig. 6). This phase II, randomized, and prospective multicenter study evaluated the feasibility and safety of the cardiopoiesis-based technology in patients with chronic heart failure of ischemic origin while monitoring for efficacy signals [62]. Cardiopoietic stem cells were implanted, using direct endomyocardial delivery [63], on average 1500 days after myocardial infarction. Patients were randomized to receive cardiopoietic stem cells plus standard of care, in the therapy arm, versus standard of care alone in the control arm. Following the cardiopoiesis algorithm, the C-CURE trial pre-emptively treated patient-derived mesenchymal stem cells with the cardiogenic cocktail to achieve guidance toward a lineage specified state [62]. There was no evidence of cardiac or systemic toxicity induced by cardiopoietic cell therapy. In addition, left ventricular ejection fraction was improved in the cardiopoietic stem cells therapy arm compared to standard of care alone, and associated with reduction in left ventricular end-systolic volume. A favorable impact on global parameters such as 6-min walk distance was also noted, along with benefit in a composite clinical score encompassing cardiac as well as general wellness parameters [62].

These results serve to support further investigation [64], including a multinational phase III clinical trial, named CHART-1 (Congestive Heart Failure Cardiopoietic Regenerative Therapy), currently in the follow up phase [65]. Patients with chronic heart failure secondary to ischemic heart disease, reduced left ventricular ejection fraction (<35%), and at high risk for recurrent heart failure-related events, were randomized in CHART-1 to receive 600 × 10⁶ bone marrow derived and lineage-directed autologous cardiopoietic stem cells (administered via a retention-enhanced intra-myocardial injection catheter [66]) or a sham procedure (ClinicalTrials.gov Identifier: NCT01768702). The primary efficacy end point of the CHART-1 study is a hierarchical...

**Cardiopoiesis in the clinic**

To achieve clinical application of a stem cell-based technology, scalable standard operating procedures are utilized. Proper dose ramp up, in tandem with suitable bio-distribution, are some of the basic requirements for safety and efficacy to reflect pre-clinical data [60,61]. The stringency of good manufacturing practice is employed to ensure clinical-grade manufacturing of derived cellular products that must meet purity, potency, and sterility metrics. Manufactured cardiopoietic stem cells require a multitier release schedule, which first establishes homogeneity of the mesenchymal stem cell source through cell surface marker profiling. This is followed by establishment of purity through gene profiling to ensure that the therapeutic formulation is devoid of divergent, non-cardio-regenerative contaminants. Finally, documented nuclear translocation of a select cardiopoietic index marker ensures potency (Fig. 9).

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composite of mortality, worsening heart failure, Minnesota Living with Heart Failure Questionnaire score, 6-min walk test, left ventricular end-systolic volume, and left ventricular ejection fraction at 9 months [65]. The secondary efficacy end point is the time to cardiovascular death or worsening heart failure at 12 months. Safety end points include mortality, readmissions, aborted sudden deaths, and serious adverse events at 12 and 24 months. The CHART-1 clinical trial is powered to examine the therapeutic impact of lineage-directed stem cells as a strategy to achieve cardiac regeneration in heart failure populations [65]. On completion, the CHART-1 trial is designed to offer a definitive evaluation of

Fig. 6 – Clinical implementation of the lineage-guidance paradigm in cell therapy. The C-CURE (Cardiopoietic stem Cell therapy in heart failURE) trial was conducted in patients with ischemic heart failure. Bone marrow was harvested (step 1) and isolated mesenchymal stem cells (step 2) lineage specified by cardiogenic cocktail priming (step 3). Cardiopoietic stem cells meeting release criteria were delivered by endomyocardial injections (step 4). On follow-up, signs of efficacy were documented (step 5).

Fig. 7 – Clinomics-based optimization algorithm informs next-generation regenerative biotherapies. Mixed outcomes documented in cardiovascular clinical trials underscore a limitation of first generation stem cell regimens. High-throughput clinomics strategies provide the opportunity to delineate the molecular underpinnings of responders versus non-responders informing next-generation strategies. Use of a priming platform to guide patient-derived stem cells into a pro-reparative phenotype exemplifies such an optimizing approach aimed to ensure benefit in heart failure patient populations.
the efficacy and safety of cardiopoietic stem cells in the treatment of chronic ischemic heart failure [67].

## Outlook

Standard of care in heart failure aims to reverse disease course and reduce adverse outcomes. Countering post-infarction parenchymal loss, patients display different trajectories of disease progression [68] compounded by age-mediated cardiac vulnerability [69]. Introduction of regenerative regimens in management algorithms is conceived to complement, and potentially transform the available armamentarium. Early experience in clinical cardiac regeneration supports the compatibility of stem cell-based therapies as adjuvants to established practice [70]. However, lack of therapeutic consistency inherent to patient-derived stem cell populations remains a central hurdle limiting adoption.

The regenerative capacity of stem cells is influenced by multiple factors dictating the proclivity for tissue health restoration [71]. Importantly, therapeutic inconsistency in clinical trials provides a kaleidoscope of biological systems activity across the range of observed regenerative benefit (Fig. 7). Leveraging clinomics-based interrogation, biological deconvolution informs the development of new high-fidelity protocols endowed with a resolution needed to ensure cell repair potency prior to application. A prototype approach is cardiopoiesis that inculcates lineage specification, conditioning stem cells with recombinant cardiogenic cues to endow therapeutic proficiency in heart failure. Accordingly, a multitier quality system to verify homogeneity, purity, and potency-associated markers for release of manufactured clinical-grade cardiopoietic stem cells has been rolled-out. The cardiopoietic stem cell phenotype is currently tested in the laboratory. Drs. Terzic and Behfar are listed as co-inventors on patents US 20080019944 and US 20120100533.

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