

# Clinical development plan for regenerative therapy in heart failure

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**This editorial refers to ‘Cell-based therapies for cardiac repair: a meeting report on scientific observations and European regulatory viewpoints’<sup>†</sup>, by M. Schüssler-Lenz et al., published in this issue on page 131–139.**

The emerging heart failure pandemic, afflicting nearly 30 million individuals worldwide, underscores the imposing burden of chronic disease on medical and public unmet needs.<sup>1</sup> Tangible achievements in managing acute coronary syndrome have been in part offset by incipient organ failure in patients that survive the initial myocardial insult but ultimately develop an adverse course and require escalation of therapy.<sup>2</sup> Heart failure is a leading indication for repeat hospitalizations across geographies, with poor survivorship halving affected patient populations within 5 years post-onset.<sup>3,4</sup> Identification of actionable strategies to reverse and reduce myocardial injury is a recognized priority in order to avert progressive dysfunction and prevent organ decompensation.<sup>5</sup> The increasingly vulnerable global elderly population necessitates radical advancements in combating heart failure beyond the current standards of care.

Calls for accelerated discovery and development of new therapies have been issued.<sup>6</sup> To address ‘real-life’ patient needs along with the societal quest for ‘health as value’, modern algorithms for clinical development of candidate technology incorporate multidisciplinary assessment by healthcare providers, developers, regulators, and payers.<sup>7</sup> This evolving landscape heralds a shift in the process of development and authorization of novel therapies, from the traditional paradigm zoomed-in on therapeutics, to an increasingly holistic evaluation that integrates the whole patient within a healthcare regimen.

Regenerative technologies exemplify an emerging class of disruptive innovations that are practice-transformative in nature aiming at normative organ restitution in the context of advancing whole-person care.<sup>8</sup> Poised to achieve functional and structural repair, the prospect of regenerative medicine offers

next-generation solutions in promoting wellness while reducing the socio-economic imperative of life-long disease management.<sup>9</sup> Currently, cardiovascular indications account for >25% of all cell-based regenerative medicine products in development.<sup>10</sup> Translation of stem cell technology in clinical trials is increasingly realized across the globe, with initial emphasis on acute/subacute myocardial infarction, and more recently on addressing chronic heart failure. While early post-infarction cell-based interventions aim to limit damage by altering the myocardial response to injury, in advanced heart failure the goal becomes restorative through direct cell-mediated or indirect paracrine-mediated repair mechanisms. Experience to date demonstrates reassuring feasibility and safety, yet indicators of benefit have not been dependably validated, mandating careful assessment of cell therapy practices.<sup>11</sup>

In this issue of the *European Journal of Heart Failure*, a regulatory viewpoint pertinent to development of cell-based therapies for cardiac repair is discussed based on expert opinions convened by the Committee for Advanced Therapies of the European Medicines Agency.<sup>12</sup> Experts acknowledge the general applicability of the existing European Medicines Agency ‘Guideline on human cell-based medicinal products’ as a guiding document that provides fundamental criteria and testing principles for source materials, design and validation of manufacturing, product characterization, quality control, traceability, vigilance, and comparability of stem cells.<sup>13</sup> Central to the established guideline is the identity of the cell population and associated properties including purity, potency, viability, and suitability for intended use. Within a mixed cellular population, subject to inherent variability and diverse biological activities, proper recognition of target cells is a recognized challenge.<sup>12</sup>

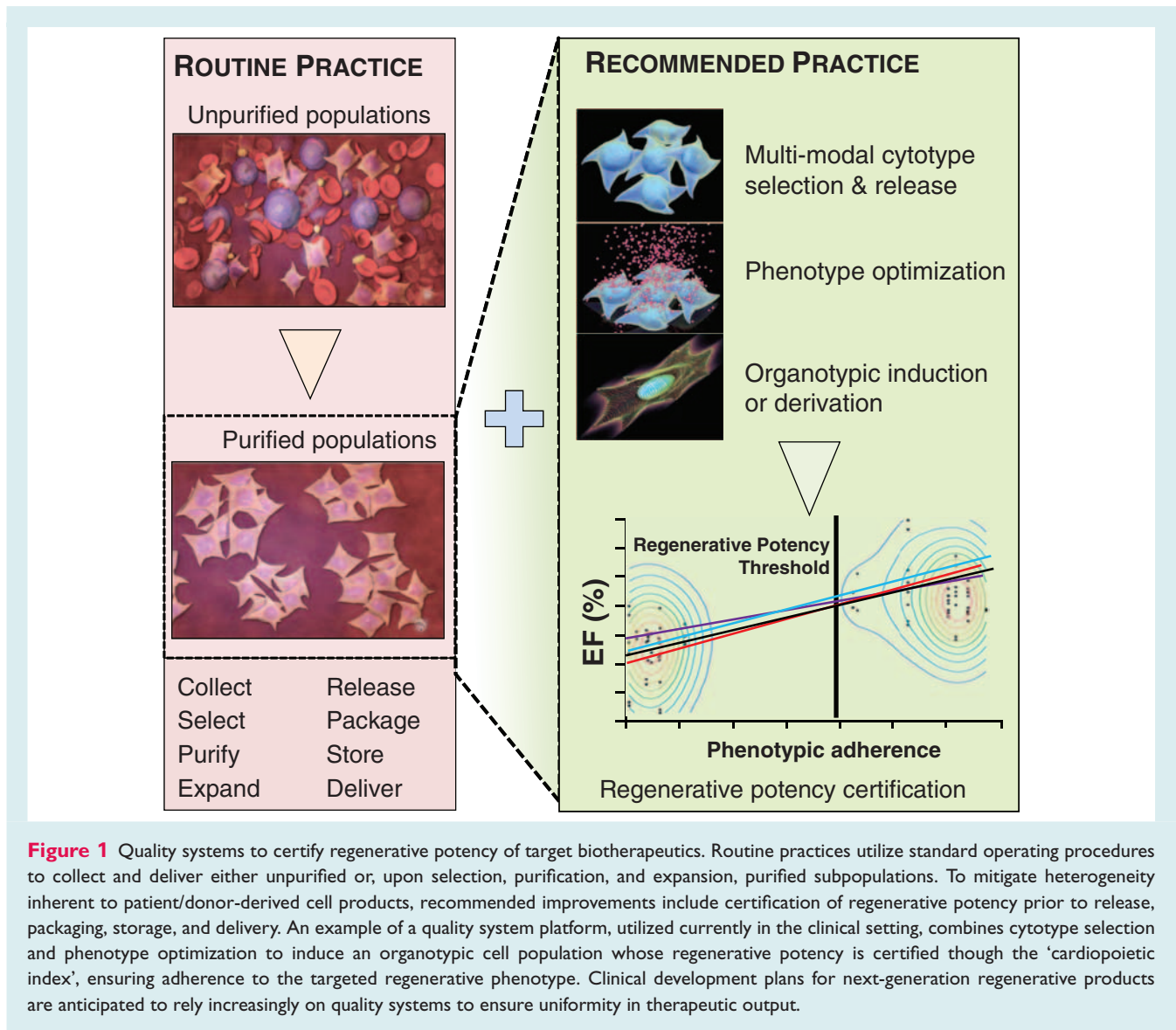
Functionality and purity of a cell-based product are influenced by multiple factors including the starting source, harvesting and isolation techniques, as well as manufacturing. Standardizing the manufacturing process and methods for cell collection, production,

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storage, and delivery is especially important as lack of uniformity in cell procurement and processing compromises clinical outcome, warranting bona fide optimization.<sup>14</sup>

Patient-related modifiers, such as age, gender, and co-morbidities, may further alter stem cell-based repair proficiency. Within stem cell-treated patient cohorts, only rare individuals have been found to harbour stem cells that exhibit a measurable cardio-regenerative aptitude.<sup>15</sup> Therefore, use of suitable potency assays as quantitative measures of biological activity is advocated.<sup>12</sup> Potency assays may be based on the expression of markers, such as cell surface markers or activation markers, or expression patterns of specific genes that correlate with the intended biological activity.

To mitigate product/patient-inherent variability, state-of-the-art initiatives integrate quality systems that certify the regenerative potency of the target biotherapeutics (Figure 1).<sup>15</sup> A prototype—recently reduced to practice—is the ‘cardiopoietic

index’ which provides a quality control standard to forecast stem cell repair potency prior to myocardial delivery.<sup>16</sup> This biomarker-based index relies on a snapshot of canonical cardiac transcription factors employing gene expression profiling as a means to assess the regenerative quotient of patient-derived cells. The ‘cardiopoietic index’ is sensitive and specific in predicting the impact of stem cell benefit on LV function, and has been incorporated into clinical trial settings to upgrade procurement of cardio-reparative cells (Figure 1).<sup>16,17</sup> Indeed, experts conclude that testing for markers indicative of lineage-specific differentiation, such as application of the ‘cardiopoietic index’, constitutes an appropriate potency assay for product release.<sup>12</sup>

Further refinement in assessing cell fitness for heart repair would implicate a comprehensive deconvolution of the biological system regulating regenerative potency. This would probably include information based on dissecting the full transcriptome

and microRNA spectrum (miRNome), but also deciphering the secretome, i.e. the totality of molecules naturally produced and secreted by cells. Indeed, a lack of definite correlation between cell dose and benefit on cardiac repair has prompted the notion that paracrine mechanisms critically contribute to a regenerative outcome.<sup>11</sup> The stem cell secretome would contain the active pro-regenerative ingredients, in essence advancing the concept of acellular tissue repair through induction of a regenerative response. Consideration of 'cell-free' molecule-based regeneration may have manufacturing advantages as an intimate reductionist approach may offer the achievement of therapeutic uniformity in a cost-effective manner.<sup>11</sup>

Regardless of the regenerative platform employed, clinical development plans should include proof-of-principle/proof-of-promise and bio-distribution studies, dose-finding studies, as well as randomized clinical trials to validate safety and efficacy in the target population.<sup>12</sup> The timing/route of cell delivery and disease substrate are also critical considerations. Additional benchmarks—including stratification of patient disease vulnerability—will be essential to inform a more definitive therapeutic outcome. Confirmatory proof-of-efficacy studies should comply with disease-specific guidelines, including the need to select properly the respective target patient population, and the relevance of validated endpoints. Success in the delivery of regenerative medicine procedures will critically depend on the optimal selection of patient populations and the stratification of disease severity.

Multinational experiences suggest that translation of regenerative principles into practice is an achievable enterprise aiming to enrich the current heart failure armamentarium. Adoption of regenerative therapies will require validated clinical evidence, including demonstration of long-term benefit. To approach acceptance, payers will require evidence of safety and efficacy ('validity') until use becomes common ('utility').<sup>18</sup> Inpatient vs. outpatient site of care will impact the reimbursement strategy, as will the designation of technology as a biological, drug, or device. Regulatory designation of regenerative medicine therapies will play a key role in how public and private payers will interpret the therapy for reimbursement purposes, influencing access upon market clearance. Beyond emphasis on the value-added proposition, regenerative solutions will ultimately be tested for their ability to reach broader populations in need.

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## References

1. Terzic A, Waldman S. Chronic diseases: the emerging pandemic. *Clin Transl Sci* 2011;**4**:225–226.
2. Butler J, Gheorghiu M, Kelkar A, Fonarow GC, Anker S, Greene SJ, Papadimitriou L, Collins S, Ruschitzka F, Yancy CW, Teerlink JR, Adams K, Cotter G, Ponikowski P, Felker GM, Metra M, Filippatos G. In-hospital worsening heart failure. *Eur J Heart Fail* 2015;**17**:1104–1113.
3. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. *Eur J Heart Fail* 2015;**17**:884–892.
4. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2015;**131**:e29–e322.
5. Braunwald E. The war against heart failure. *Lancet* 2015;**385**:812–824.
6. *Innovation for Healthier Americans: Identifying Opportunities for Meaningful Reform to Our Nation's Medical Product Discovery and Development*. United States Senate: a 2015 report by Senator Lamar Alexander and Senator Richard Burr. [http://www.help.senate.gov/imo/media/Innovation\\_for\\_Healthier\\_Americans.pdf](http://www.help.senate.gov/imo/media/Innovation_for_Healthier_Americans.pdf) (10 December 10 2015).
7. Pani L, Pecorelli S, Rosano G, Anker SD, Peracino A, Fregonese L, Prasad K, Rasi G. Steps forward in regulatory pathways for acute and chronic heart failure. *Eur J Heart Fail* 2015;**17**:3–8.
8. Terzic A, Harper CM Jr, Gores GJ, Pfenning MA. Regenerative medicine blueprint. *Stem Cells Dev* 2013;**22** Suppl 1:20–24.
9. Terzic A, Nelson TJ. Regenerative medicine primer. *Mayo Clin Proc* 2013;**88**:766–775.
10. Bailey AM, Mendicino M, Au P. An FDA perspective on preclinical development of cell-based regenerative medicine products. *Nat Biotechnol* 2014;**32**:721–723.
11. Behfar A, Crespo-Diaz R, Terzic A, Gersh BJ. Cell therapy for cardiac repair—lessons from clinical trials. *Nat Rev Cardiol* 2014;**11**:232–246.
12. Schüssler-Lenz M, Beuneu C, Menezes-Ferreira M, Jekerle V, Bartunek J, Chamuleau S, Celis P, Doevendans P, O'Donovan M, Hill J, Hystad M, Jovinge S, Kyselovič J, Lipnik-Stangeli M, Maciulaitis R, Prasad K, Samuel A, Tenhunen O, Tonn T, Rosano G, Zeiher A, Salmikangas P. Cell-based therapies for cardiac repair: a meeting report on scientific observations and European regulatory viewpoints. *Eur J Heart Fail* 2016;**18**:131–139.
13. Nelson TJ, Behfar A, Terzic A. Stem cells: biologics for regeneration. *Clin Pharmacol Ther* 2008;**84**:620–623.
14. Terzic A, Behfar A. Regenerative heart failure therapy headed for optimization. *Eur Heart J* 2014;**35**:1231–1234.
15. Behfar A, Terzic A. Stem cell in the rough: repair quotient mined out of a bone marrow niche. *Circ Res* 2014;**115**:814–816.
16. Crespo-Diaz R, Yamada S, Bartunek J, Perez-Terzic C, de Waele P, Mauñ S, Terzic A, Behfar A. Cardiopoietic index predicts heart repair fitness of patient-derived stem cells. *Biomark Med* 2015;**9**:639–649.
17. Bartunek J, Behfar A, Dolatabadi D, Vanderheyden M, Ostojic M, Dens J, El Nakadi B, Banovic M, Beleslin B, Vrolix M, Legrand V, Vrints C, Vanoverschelde JL, Crespo-Diaz R, Homsy C, Tenders M, Waldman S, Wijns W, Terzic A. Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic stem Cell therapy in heart failure) multicenter randomized trial with lineage-specified biologics. *J Am Coll Cardiol* 2013;**61**:2329–2338.
18. Terzic A, Pfenning MA, Gores GJ, Harper CM Jr. Regenerative medicine build-out. *Stem Cells Transl Med* 2015;**4**:1373–1379.