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How to facilitate seamless translation from basic concepts to new heart failure drugs.

A scientific statement of the Heart Failure Association of the ESC

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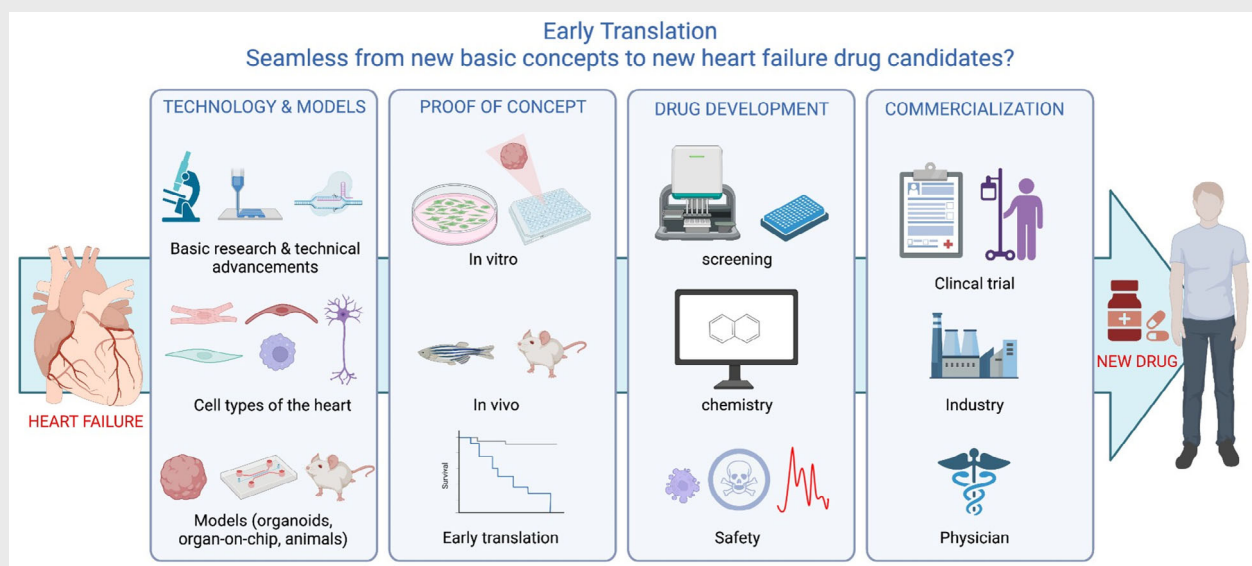
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A rift has opened and is widening between basic research (bench) and clinical research and patients (bed) who need their new treatments, diagnostics and preventive strategies. This problem involving the ‘translation’ of basic scientific findings into clinical applications and potential treatments or biomarkers for a condition like heart failure is widely recognized both in academia and industry. Despite the attempts that have been made by both sides to improve this situation, the high attrition rates of drug development and the problem with reproducibility and translatability of preclinical findings to human applications still persist. As a result, the return on investment of basic research has been limited in terms of clinical impact. In this scientific statement we describe and discuss various issues with relevance to this theme and try to dissect how to move our field towards the development of more effective heart failure drugs. We zoom in on facilitating the process of heart failure drug development, the unnecessary gaps (‘valley of death’) between the critical steps in heart failure drug development, validation and de-validation of new concepts as early as possible (‘rigorous translation’). We describe forums on how to stimulate cross-talk and interaction between clinician-scientists, basic heart failure researchers, biotech and industry, and how to enable them to speak the same language, and lessons learned from successes outside the heart failure field.

Graphical Abstract



Seamless translation from basic concepts to new heart failure drugs.

Keywords

Heart failure translational research • New drugs • Valley of death

Introduction

During the last decades, the heart failure (HF) community has been successful in addressing some bona fide targets (with a certain amount of serendipity), including the renin–angiotensin system (RAS), the sympathetic nervous system, and, more recently, the sodium–glucose cotransporter 2 (SGLT2). Neuroendocrine

activation is a hallmark of HF and it is effectively targeted by classic therapeutic approaches in HF such as RAS inhibitors (including angiotensin receptor–neprilysin inhibitors) and beta-blockers.¹ In some cases, the discovery of underlying pathophysiological pathways did not always precede the development of these drugs, an example being the discovery of SGLT2 inhibitors (SGLT2i),^{1–3} whose efficacy became apparent through U.S. Food

and Drug Administration (FDA)/European Medicines Agency (EMA) mandated cardiovascular outcome trials in diabetes.

Despite these advances, HF remains one of the leading causes of mortality and hospitalization worldwide. There is thus a pressing need to develop novel drugs directly targeting the relevant pathophysiological mechanisms in each HF phenotype, going beyond mitigating symptoms and systemic alterations. Unfortunately, different recent preclinical developments have been lost in the translation to the clinical setting (e.g. phosphodiesterase 5 inhibitors, stem cells), while some of the most successful treatments have been discovered first in clinics, which mandates the need to 'reverse-translate' in order to explain how they actually work (SGLT2i). This review will address some of the difficulties found in the translation from preclinical studies to the clinic and propose some avenues for improvement.

Examples of translational challenges in heart failure concepts

Clinical and preclinical studies have taught us that the pathophysiology of HF is extremely heterogeneous and complex, and many potential targets are available that are not touched by currently available therapies.⁴ Disappointing as it is, it is not that no attempts have been made to target the possibilities that have been left untreated. For instance, oral inotropes target impaired contractility, a phenomenon central in many forms of HF, and a large number of compounds and trials have not made it into the clinical arena.^{5,6} In the event oral inotropes were evaluated in the clinical arena, several turned out to have a poor performance, which mostly was explained by the intrinsic pro-arrhythmogenic side-effects that most inotropes have. Only in recent times a novel modified inotrope, omecamtiv mecarbil, has been designed and showed to improve contractility in the absence of adverse effects like calcium overload and ventricular arrhythmia.^{5,6} However, the FDA declined approval end of February 2023 because a large randomized clinical trial showed very modest benefit. Post-hoc analysis suggested that in patients with very poor contractility (left ventricular ejection fraction <20%) the drug may be advantageous, but it is unclear if a specific trial in this patient group will be launched.⁷

Myocardial fibrosis is another unsuccessfully touched target,⁸ despite the well-described anti-fibrotic potential of mineralocorticoid receptor antagonists⁹ and the promising results of transforming growth factor- β -interfering drugs such as pirfenidone.¹⁰ There are several examples of unsuccessful translational attempts to mitigate myocardial fibrosis, including targeting collagen cross-linking with advanced glycation end-products breakers¹¹ or antibodies against lysyl oxidase like-2, which were effective in preclinical studies but failed to show clear benefits in clinical trials,^{12,13} dampening the enthusiasm and expectations on this approach. Importantly, fibrosis is a consistent hallmark in HF of various aetiologies, and the dynamics and complexities related to the diverse underlying pathophysiological mechanisms afford several opportunities to intervene, ranging from engineered CAR-T cells¹⁴ to epigenetic regulators¹⁵ or metabolic modulators.¹⁶ Therefore, designing new

trials will require precision medicine, where the specific players and culprits are targeted, rather than global inhibition of e.g. myofibroblasts or collagen products, as discussed in detail elsewhere (Figure 1).

The mechanisms at the basis of the success of the above-mentioned protective effects of SGLT2i have yet to be fully elucidated and involve – next to blood pressure lowering, weight losing, and diuretic effects – several other effects in the tissue, such as lower levels of reactive oxygen species, improved mitochondrial dysfunction as well as increased circulating ketone levels and ketogenesis.^{4,17–19} Evidence in support of beneficial effects of SGLT2i on increasing ketone levels in HF is a matter of an ongoing debate including the role of skeletal muscle,^{18–20} but the shift towards increased ketone utilization in HF is considered as adaptive and remains a promising target for future studies.²¹ Yet, metabolism has certainly been a difficult target in HF therapeutics.²² In parallel with myocardial fibrosis, the 'myocardial metabolism' is a gross oversimplification of the very complex and dynamic metabolism of the cardiac muscle. As a result, global one-size-fits-all interventions of cardiac metabolism have proven mostly neutral. For instance, supplementation of propionyl-L-carnitine failed to achieve efficient effects in a large multicentre study already in the 1990s,²³ with strategies to increase glucose oxidation or inhibit fatty acid oxidation either lacking efficiency or resulting in serious side-effects.²⁴ Furthermore, perhexiline inhibits carnitine palmitoyl transferase 1, an enzyme involved in the transport of fatty acids across the mitochondrial membrane shuttle, and improved energy deficiency, as well as improved exercise capacity in a small study in patients with hypertrophic cardiomyopathy (HCM) prompting further studies in HCM.^{24,25} However, while improving left ventricular function on the one hand, hepatic and neural toxicity prevented a broad use for HF treatment on the other hand.²²

Inflammation and immunity have been recognized since decades to be involved in HF pathophysiology, but the translation from basic studies into clinical success has been problematic. In the '90s, the potential role of inflammation and inflammatory cytokines^{26,27} was under intense study.²⁸ This ultimately resulted in a trial evaluating the efficacy of the tumour necrosis factor- α receptor blocker etanercept in HF with reduced ejection fraction, that was neutral.²⁹ This clearly dampened the interest in inflammation as a target. However, more recent basic research provides several clues as to why this initial approach may have been unsuccessful,²⁹ and deeper insights into the aetiology of myocardial inflammation, the specific immune cells, inflammatory cytokines, and their temporal dynamics have provided more detailed knowledge,³⁰ allowing new and more targeted trials,^{31,32} with some examples of success targeting interleukin-1 and the inflammasome as potential therapeutic targets.^{27,33} For instance, the inflammasome inhibitor colchicine reduced the risk of ischaemic cardiovascular events in patients with a recent myocardial infarction, although it increased the risk of pneumonia.³⁴ Interestingly, the CANTOS clinical trial, performed in over 10 000 patients who had suffered a myocardial infarction, showed that canakinumab, a monoclonal antibody targeting interleukin-1 β , was able to reduce cardiovascular events.²⁶ Currently, the interleukin-6 antibody ziltivekimab is being evaluated

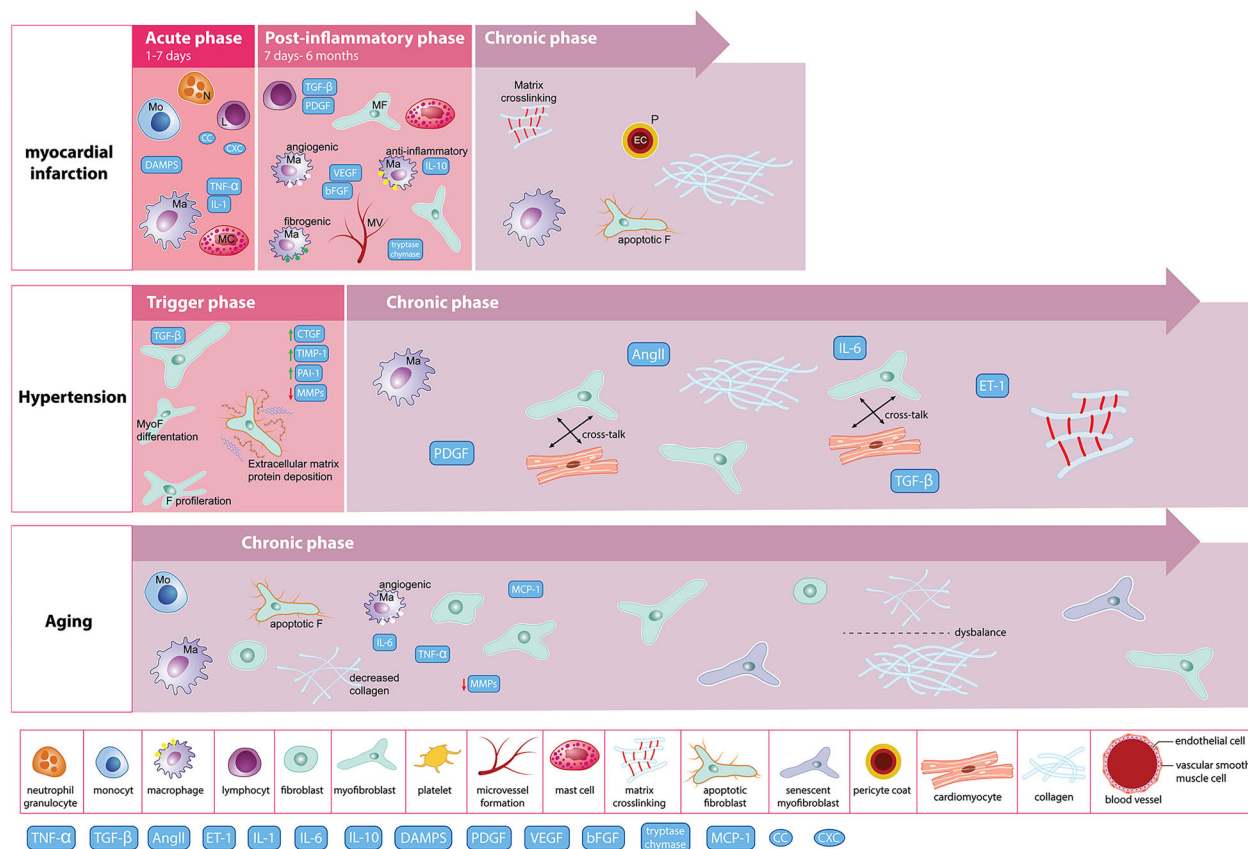


Figure 1 Graphical depiction of time-dependent fibrosis formation in the heart after acute injury such as myocardial infarction, longstanding injury such as hypertension, and intrinsic tissue changes during ageing and senescence. The aetiological factors underpinning fibrosis, as well as the (physiological) need for a fibrotic reparative response will dictate the extent and timing of the fibrotic process. (Illustration: Maartje Kunen, Medical Visuals). AngII, angiotensin II; bFGF, basic fibroblast growth factor; CTGF, connective tissue growth factor; DAMPs, danger-associated molecular patterns; ET-1, endothelin-1; IL, interleukin; L, lymphocyte; Ma, macrophage; MC, mast cell; MCP-1, monocyte chemoattractant protein-1; MF/MyoF, myofibroblast; MMP, matrix metalloproteinase; MV, microvessel; N, neutrophil; PAI, plasminogen activator inhibitor; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor. Reproduced with permission from de Boer et al.⁸

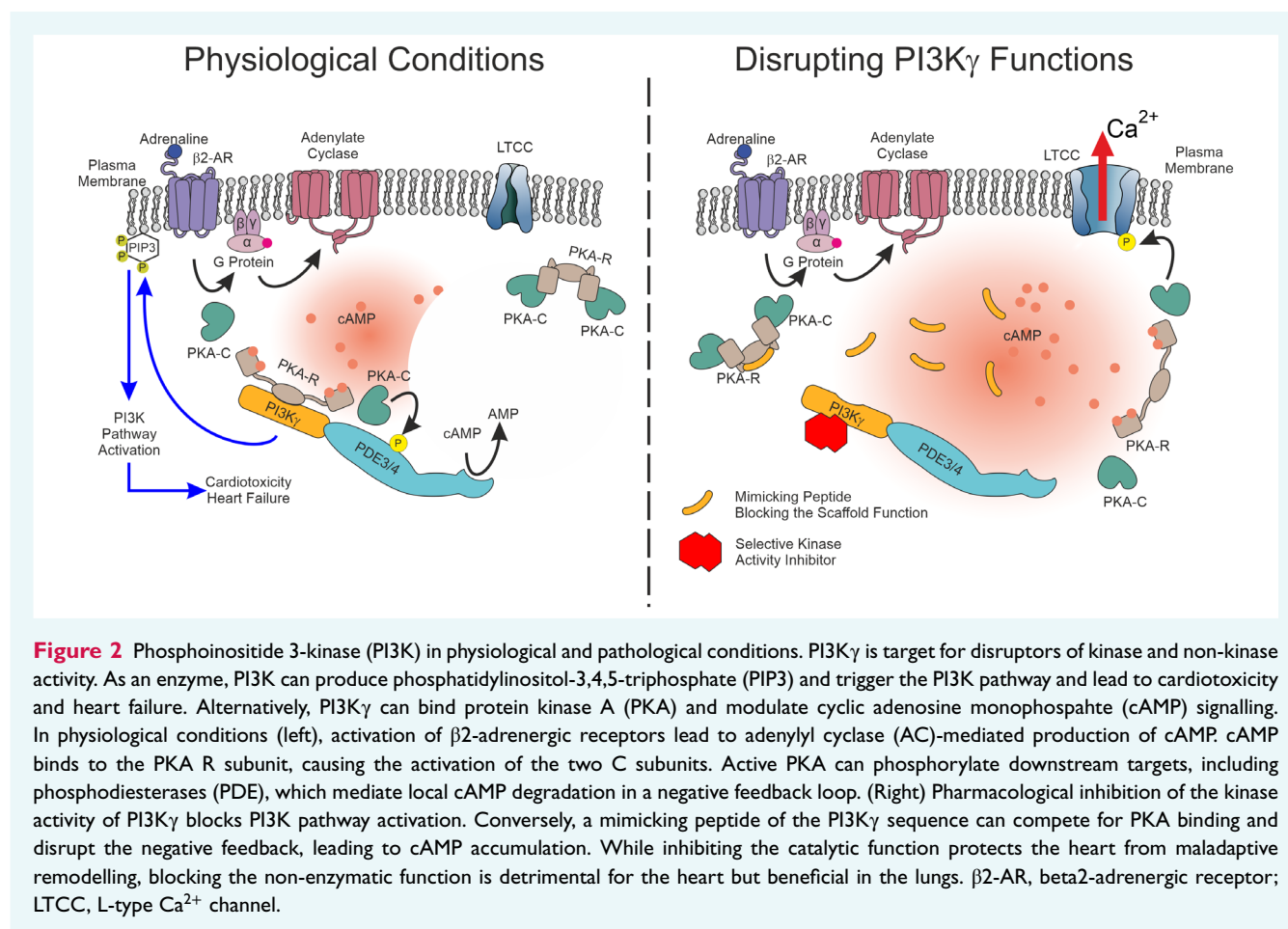
in HF with mid-range/preserved ejection fraction (HERMES trial, ClinicalTrials.gov NCT05636176).

Another field of extensive research with gaps in its clinical translation is cell therapy. For almost two decades, cell therapy has been promised as a solution for cardiac disease. Though, legacies of hype, scientific misconduct and neutral results have led to prevailing scepticism.³⁵ However, due to more rigorous studies, further mechanistic understanding and promising clinical data, clinical progress in cell therapy continues.³⁶

New diagnostics (e.g. scRNAseq, omics, etc.) and therapeutics (e.g. targeted drugs such as biologicals, specific kinase inhibitors) may enable future drug development. For instance, phosphoinositide 3-kinase-γ (PI3Kγ), which expression is mainly restricted to leucocytes, is an attractive molecule for cardiovascular research: its catalytic subunit is up-regulated in the heart after different stress stimuli, leading to maladaptive remodelling of cardiac tissue and, ultimately, to HF³⁷ (Figure 2). Interestingly, experimental evidence pointed out that the pharmacological inhibition of the catalytic

activity of PI3Kγ can boost the antineoplastic activity of chemotherapy agents, such as doxorubicin, while preventing their cardiotoxic effect.³⁸ Unfortunately, although the selective inhibition of PI3Kγ offers an attractive strategy in cardio-oncology, none of the numerous inhibitors developed in the last years have been approved for clinical translation. Further studies are ongoing to develop novel isoform-selective inhibitors specifically targeting PI3Kγ for clinical use against HF. These inhibitors should be specifically designed to inhibit the catalytic activity without affecting the non-catalytic function of the enzyme, which is essential to control β-adrenergic signalling and myocardial contractility.³⁹

All the aforementioned pathophysiological mechanisms are differentially involved in HF, depending on aetiology, precipitant factors, and comorbidities. Hence, there is a call to action to better phenotype and genotype patients, integrating omics technologies, which will hopefully lead to better targeted therapies.⁴⁰ Ageing as a major contributor to heart dysfunction should also be part of the work-up.⁴¹



Unraveling the molecular and cellular mechanisms responsible for ageing as a major driver of chronic diseases, in an attempt to reverse the processes of ageing, will ameliorate or simultaneously prevent several age-related diseases and conditions.^{42–45} The conceptual and therapeutic approach towards ageing and disease may significantly benefit from observing, extending and harnessing our knowledge regarding embryonic development, and by utilizing these findings thorough our adult life to re-enhance the regenerative potential of the human body⁴⁶ (Figure 3). This concept is recapitulated by a 43 amino acid secreted peptide, thymosin beta-4, which is not only expressed and significantly influences the development of the embryonic heart,⁴⁷ but is also equally capable of re-activating these processes in adults.⁴⁸

Animal models in cardiovascular research: relevance and limitations

One of the explanations for the fact that the significant progress that has been made in understanding HF pathophysiology has not been paralleled by novel treatments is the lack of proper models that can be used to faithfully recapitulate the pathophysiological mechanisms and the response to new drugs. Animal models have

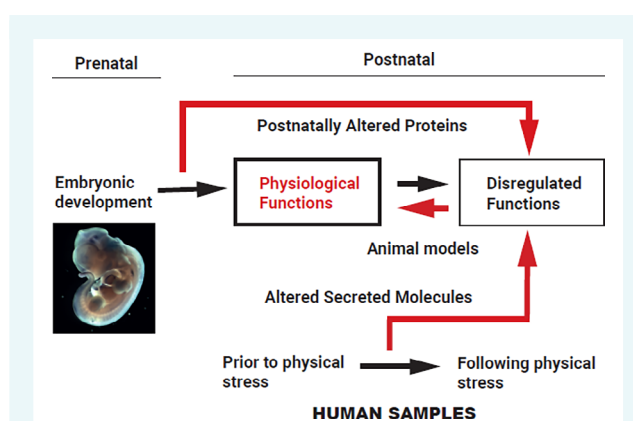


Figure 3 Potential directions regarding therapeutic candidate search to reinvigorate physiological organ function.

provided remarkable contributions in elucidating key biochemical and physiologic processes of cardiovascular diseases (CVDs).⁴⁹ Indeed, our modern understanding of cardiovascular medicine is largely based on the use of animals as surrogate for patients in the evaluation of novel diagnostic tools and therapeutic cardiovascular drugs/devices.^{49–52}

The need of using animal models in cardiovascular research depends largely on the complexity of the cardiovascular system. CVDs are the results of disruption of a complex interplay between haemodynamic, neuro-hormonal, metabolic, and immunologic processes, involving a plethora of different cells. This by itself illustrates how difficult it is to model this in cell assays or other *in vitro* systems, in the absence of loading conditions, cell–cell interactions, and an interstitial space filled with cells and proteins. Hence, animals more readily represent a valid biological model system that can recapitulate such complexity and can be of value to understand the underlying mechanisms of CVDs as well as to identify novel therapies.^{49–51} However, HF characteristics seen in mammalian preclinical models often also do not entirely resemble human HF due to the inherited differences in physiological – not only cardiovascular – parameters across species.^{52,53} If we consider for instance mice and humans, then one paradigmatic example is the difference in heart rate, but other well-known differences between mice and humans are differences in contractile proteins (with a shift in alpha-to-beta myosin heavy chain proteins), different calcium handling, relative resilience to arrhythmia, and differences in natriuretic peptide release (more atrial natriuretic peptide than B-type natriuretic peptide in mice and vice versa in humans).⁵⁴ It is more and more appreciated that the quality of animal models can substantially be improved by adding comorbidities, which are common in human disease but often lack in animal models.⁵⁵ Similar differences as observed in mice, albeit to a lesser extent, exist between rats, pigs or goats and humans. Primates clearly are closer to humans, but ethical restraints are also far more severe. A final important consideration to explain the apparent discrepancy between (successful) pharmacological studies in animals that cannot be replicated in humans is that animal studies often do not include background HF therapy, while human randomized clinical trials usually test newer drugs on top of standard medication, which clearly reduces the possibility of an incremental benefit.

Despite a number of limitations, the use of animal models in cardiovascular research still is the best available option to study underlying molecular mechanisms. However, the systematic application of the 3Rs principle – replace, reduce, refine –, the recognition of proper preclinical modelling of CVDs and the use of alternative, cell/tissue-based approach as well as more advanced computational approaches⁵¹ will be instrumental to ultimately improve the translational relevance of preclinical cardiovascular research. Once *in vivo* experiments prove successful, the molecular mechanisms should be tested in more complex tissue culture environments and clarify whether drug candidates can be declared as candidates to potential human studies. Occasionally, investigations also include large animal studies, in the case of the heart, usually a porcine model (Figure 4).

Using technology and human model systems

A worthy alternative is initiating drug candidate screening in human samples, while employing animal models to effectively match symptoms and disease based on observations seen in man.⁵⁶ Once a

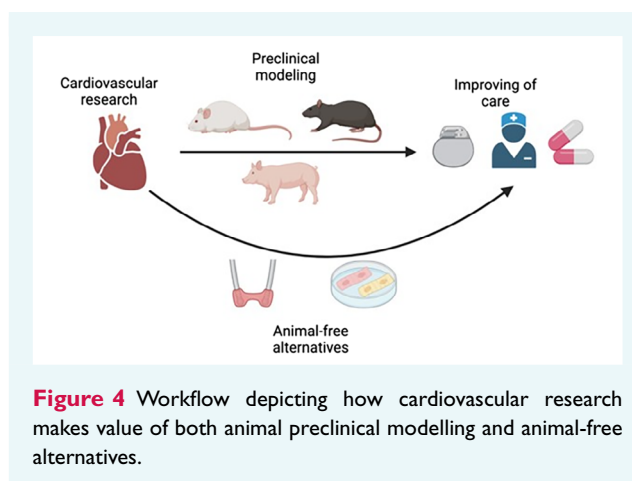


Figure 4 Workflow depicting how cardiovascular research makes value of both animal preclinical modelling and animal-free alternatives.

matching model becomes established, the potential mechanisms may be further investigated and confirmed under tissue culture conditions. Myocardial cells differentiated from human induced pluripotent stem cells (hiPSC) generated from patients with specific conditions may be appropriate for *in vitro* drug testing candidates towards achieving success.⁵⁷ This ‘reverse order’ hypothesis is supported, for instance, by experiments utilizing various peptide candidates to restore post-hypoxic cardiac function in mice.⁵⁸ In addition, utilization of body fluid samples harvested from healthy recreational athletes to identify various target molecules to inhibit cellular and organ degeneration revealed exciting novel candidates to reverse ageing and accelerate performance and recovery.⁴⁶

Beside the practical approach, we believe it is equally essential to comprehensively grasp which aspects of the human pathology should be simultaneously and ultimately targeted to effectively improve organ function. For instance, the combined or independent inhibition of initial myocyte death, suppression of inflammation and activation of coronary vessel growth *per se*, may be satisfactory in mice following hypoxia, but appears to be insufficient in large mammals, such as pigs, while screening for the state of cardiomyocyte communication, in particular for connexin-43 expression and phosphorylation in rodent models, proved indeed informative and revealed to be equally critical to predict post-ischaemic functional improvement among larger sized mammals.⁵⁸

The development of multiple high throughput ‘omic’ technologies has enabled obtaining a more comprehensive view of the specific mechanisms and pathways involved in HF progression, becoming a major source for predictive phenotype modelling, and facilitating the identification of novel targets for precision medicine approaches.⁵⁹ Implementation of machine learning strategies are needed to manage the enormous amount of data generated and to extract meaningful information and clinically relevant phenogroups and specific targets.^{60,61}

The development, application, and implementation of novel human models provide the opportunity to overcome some of the issues described above.

Primary heart tissue still is an invaluable source of knowledge to identify pathological and maladaptive changes. Human heart tissue slices are indeed a valuable *in vitro* cardiac model of intermediate

complexity that can be used for cardiac research. For instance, fibrotic remodelling in response to mechanical load was studied by stretching failing and non-failing human heart slices.⁶²

In addition, de-cellularized tissue slices from failing and non-failing human hearts, re-populated with hiPSC-derived cardiomyocytes were used to identify how the changes in extracellular matrix composition can influence cardiomyocyte morphology and function.⁶³

The hiPSC-based models⁶⁴ of the heart are experiencing a strong drive, thanks to technological advancements in gene editing, microfluidic and chip design, and protocols to differentiate hiPSCs into many of the different cell types and subtypes that are present in the human heart. Patient-specific hiPSCs allow capturing the genetic background of the patient; alternatively, different mutations can be introduced into one wild-type hiPSC line of interest, therefore eliminating the confounding factors of variation in the individual genetic settings. This versatility is unique to hiPSC technology and allows working under genetically-controlled conditions.

Here below we list some relevant examples of models that were able to capture physiological and pathological relevant parameters. As an example, recapitulation of haemodynamic load was recently achieved with the hiPSC-based dynamic engineered heart format able to model both preload and afterload.⁶⁵ This format

can be used to identify adaptive and maladaptive changes of the heart. Cardiac microtissues were built by combining in defined ratios hiPSC-derived cardiomyocytes, cardiac fibroblasts, and cardiac endothelial cells; this format proved crucial in promoting hiPSC-derived cardiomyocyte maturation and also in identifying the contribution of non-cardiomyocytes to human disease.⁶⁶ An oxygen-diffusion gradient coupled with cardiac organoids was used to mimic myocardial infarction and study the consequent remodelling.⁶⁷ Finally, self-organizing cardiac organoids showed chamber-like structures that so far have been used for modelling chamber formation defects⁶⁸ but we cannot exclude they will assist identification of pathological changes in heart chamber function in the near future.

These examples nicely illustrate the opportunities that human-based *in vitro* models offer,⁶⁹ however, it is important to realize that still some challenges remain to be addressed (Figure 5).

Some intrinsic limitations include the lack of immune system in the current models, which is instead present in patients and animals. Also, although the simplification of the *in vitro* models allows for a neater identification of cause–effects, the more complex – and still physiologically and pathologically relevant – mechanisms of multi-organ communication cannot be recapitulated and captured. We expect that the development of more

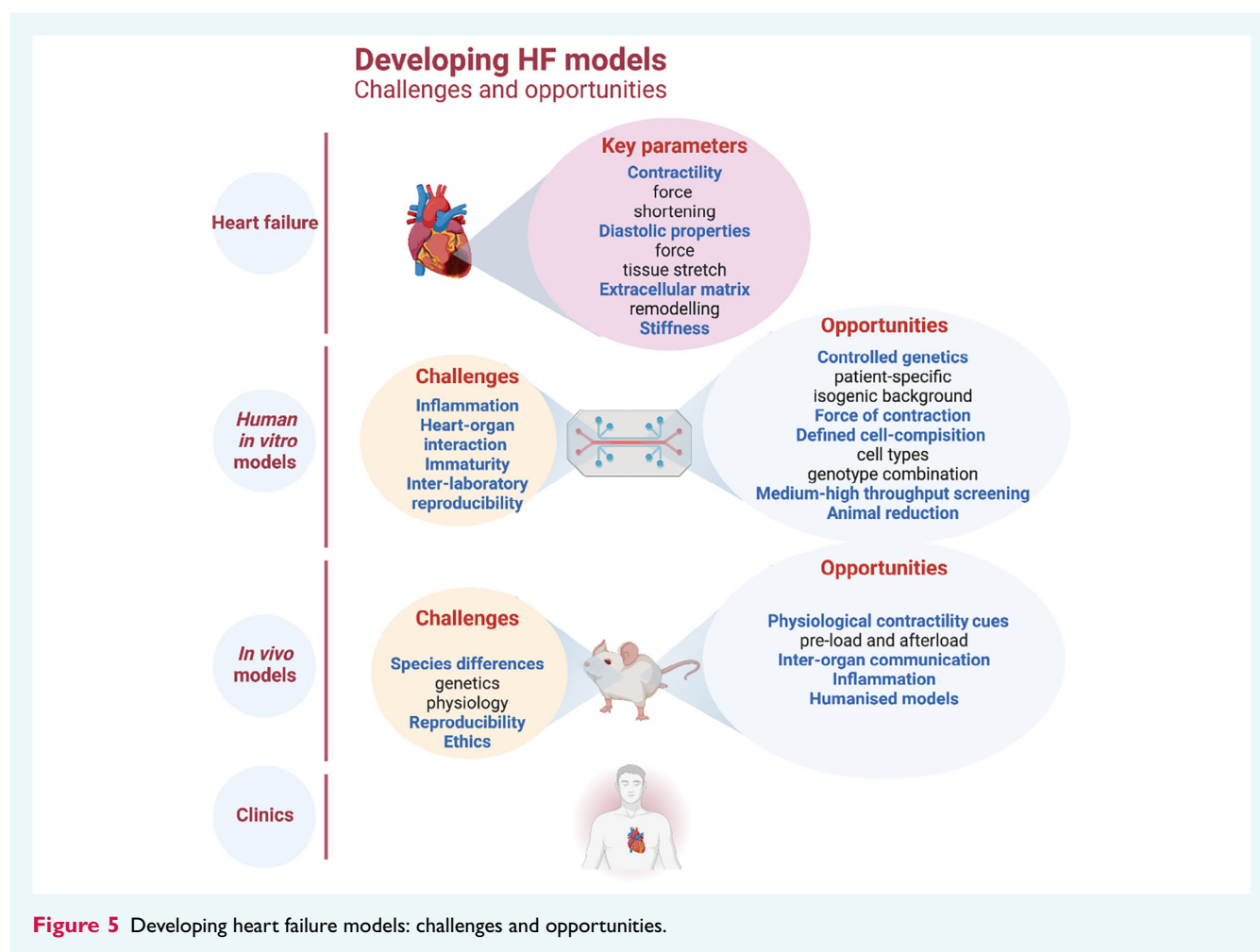


Figure 5 Developing heart failure models: challenges and opportunities.

complex organ-on-chip platforms and systems, along with their complementation with paralleled advancement in animal models (e.g. humanized mice) will lead to more efficient identification and validation of new drugs and treatments for HF.

Three-dimensional (3D) cellular systems are emerging among *in vitro* and *ex vivo* platforms to recapitulate and study the complexities of the human heart. These 3D models are being constantly developed for easy, cost-efficient and high-throughput approaches. Multicellular methods, cardiac spheroids, organoids, engineered cardiac microtissues, myocardial organ slicing, and bioprinting approaches are useful for personalized disease models and *in vivo* similar characteristics, paving the way towards translational approaches. These methods are also useful to reduce animal models for assessing compound effects, including cardiotoxicity, and cardiac pathology as well as in patient-specific regenerative approaches.

Nevertheless, relevant issues still need to be addressed in order to standardize 3D cell culture. Already existing production, analysis and high-throughput methods should be improved and reconsidered to eliminate too complex, too cost-intensive and non-translatable methods for a wider application and a better comparison of *in vitro* and *ex vivo* studies.⁶⁹ Furthermore, given sex- and racial/ethnic-based differences and disparities in HF,^{70,71} *in vitro* model systems with cells from patients with different sex and ethnical background are needed.

Digital methods

Digital methodologies are revolutionizing preclinical research, drug discovery and development by improving efficiency, accuracy, and predictive capabilities, ultimately bridging the translational gap between preclinical research and clinical application. Coupled with machine learning and deep learning, artificial intelligence (AI) has shown to play a pivotal role in this transformation. Digitization as a whole empowers researchers to employ advanced computational methods, machine learning algorithms, statistical tools, and data visualization techniques for comprehensive analysis and interpretation of preclinical research data. Integration of digital technologies and tools to transform how data are collected, stored, analysed, and shared, streamline data management workflows, enhance data quality, improve accessibility, and enable more efficient and informed decision-making.⁷²

AI-driven analysis of large-scale biological datasets, including genomics (UK Biobank, Broad L1000, etc.), proteomics, and transcriptomics, facilitates the identification of novel drug targets and biomarkers. AI-driven network analysis further enables the prediction of disease-associated molecular interactions, enhancing target selection and prioritization.⁷³

In the domain of drug design and discovery, AI-augmented molecular docking techniques can accurately predict the binding interactions between potential drug candidates and target proteins. Deep learning algorithms further contribute by generating drug-like molecules with optimized pharmacological properties, thereby expediting the identification of promising therapeutic compounds, ultimately reducing costs and time-to-market for new therapies.⁷² Additionally, AI-driven models are instrumental in predicting pharmacokinetic properties, including absorption, distribution, metabolism, excretion, and toxicity (ADMET), allowing for the early elimination of unsuitable compounds and streamlining the drug development pipeline.⁷³

Digital twins, which are *in silico* replications of an individual and its environment, have advanced clinical decision-making and prognostication in cardiovascular medicine. This technology enables personalized simulations of clinical scenarios, prediction of disease outcomes, and strategies for clinical trial augmentation and drug repurposing. Incorporation of AI-generated virtual patient cohorts minimize the need for extensive control groups, thereby accelerating the regulatory approval process. Current applications of cardiovascular digital twins have integrated multi-modal data into mechanistic and statistical models to build physiologically accurate cardiac replicas to enhance disease phenotyping, enrich diagnostic workflows, and optimize procedural planning.^{74,75} Moreover, AI enables the extraction of insights from wearable devices, electronic health records, and multi-omics data, contributing to the refinement of clinical trial design and execution. Finally, the integration of multi-omics data – including genomics, proteomics, and metabolomics – via AI enhances the development of personalized treatment strategies, enabling precision medicine approaches tailored to individual patient profiles.

While drugs designed and their properties predicted by AI still require validation through wet lab studies, and human oversight remains essential in guiding AI research and application, the continuous expansion of AI capabilities, the rapid pace of advancements, and the open-sourcing of large models underscore AI's potential to accelerate drug development and bridge the gap between preclinical and clinical research.⁷³ It also accentuates the raising need for educating translational scientists in AI.

Research integrity and scientific reproducibility

Another obstacle in translating experimental results into the clinical arena is the reward system that applies within academic research, and that sometimes risks providing perverse incentives that may reward flashy science with not enough control of its quality, robustness or reliability in some cases. That includes papers published in the 'top tier' journals resulting in some of those papers being irreproducible.^{76–78} These publications may fail to be reproduced e.g. because experiments were not performed by blinded investigators, relevant controls were not used, experiments were not repeated, reagents were not validated, data were highly selected ('cherry-picking'), and data analysis was inappropriate.^{79,80} Over recent years, positive steps have been taken to begin to address this issue with some funding agencies and several journals seeking to improve their processes, but the principal responsibility for addressing this problem rests with investigators and research institutions.⁸¹

Researchers themselves can take important steps to actively foster quality research. For example, as scientists, we should actually care more for quality than for quantity of our published papers, read papers before citing them, refuse to cite poor quality papers (even from famous laboratories/investigators), refuse to accept the journal as a surrogate for quality, and of course, do things properly ourselves.

Institutions should create an 'Office of Research Integrity', with responsibility for conducting random laboratory audits, compulsory methods training, ensuring compliance with agreed guidelines.⁸¹ Institutions could also more honestly disclose the

implications of a piece of research rather than claiming each new study as a potential ‘cure’ that will be available in the near future. Failure of researchers and institutions to comply should be associated with real consequences. Publication of negative or neutral results should be encouraged by the institutions, but also the journals and funding agencies.

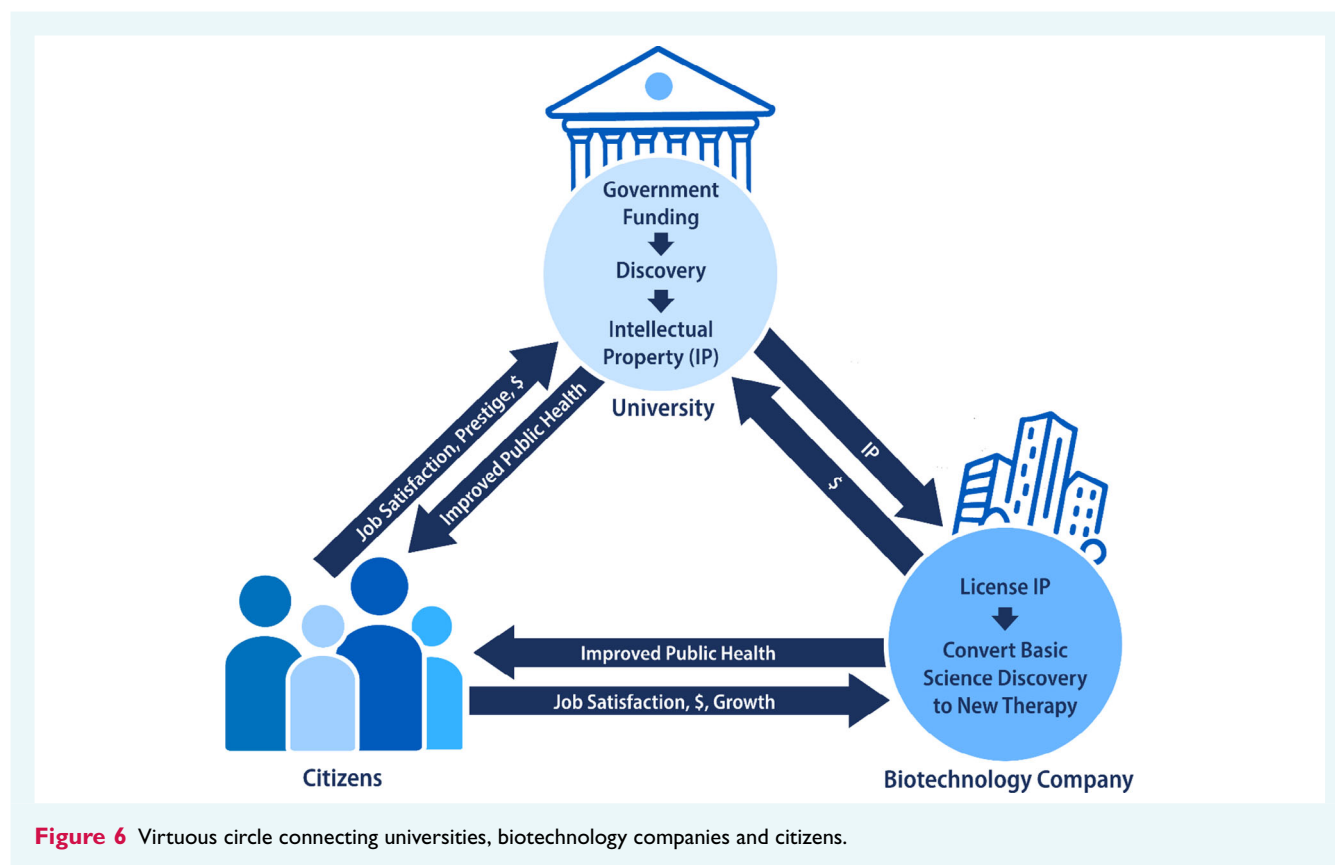
Funding agencies, journalists and the public could further reinforce the importance of research quality rather than quantity. This could be achieved by ensuring that the focus is on the methods (blinding, repeating experiments, lack of ‘cherry picking’, use of validated reagents, appropriate data analysis, data management, etc.) when research is conducted and whenever a new research finding is highlighted. Application of the ARRIVE guidelines 2.0 and use of online tools such as those introduced for preregistration should become standard for planning and conduction of animal experiments.^{82,83} In addition, data management of future high-quality studies should be based on the FAIR principles—findability, accessibility, interoperability, and reusability—that serve to guide data producers and publishers.⁸⁴

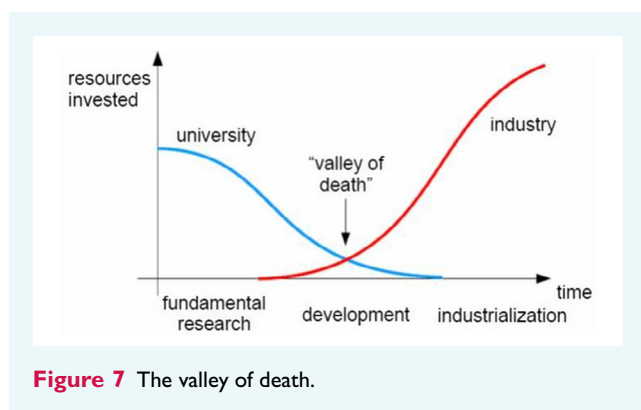
Drug development

The 1980 passing of the Bayh-Dole Act in the United States allowed non-profit institutions, such as universities, to own inventions developed from federally sponsored research, thereby promoting commercialization of university-developed technology.⁸⁵ One outcome of this act was to trigger creation of ‘spinoff’ biotechnology

companies that were founded based on licensing university-owned intellectual property (IP).^{86,87} Formation of such start-up companies is potentially financially beneficial to the university and the faculty member(s) who developed the IP, but more importantly, allows the academic researchers to be directly involved in the advancement of their science into commercial development. As envisioned by the framers of the Bayh-Dole Act, commercialization of technology originating from universities has the potential to lead to the development of innovative therapies to treat devastating human medical conditions, thus ultimately benefiting the taxpayers who supported the federally funded research (Figure 6).

An interesting example is provided by the specific case of Myogen, that was founded in 1996 in Denver, Colorado, USA, by Dr. Michael Bristow from the University of Colorado School of Medicine. Drs. Leslie Leinwand (University of Colorado – Boulder) and Eric Olson (University of Texas Southwestern Medical Center) were subsequently brought on as scientific co-founders. One arm of Myogen was designed to convert seminal HF-related basic science discoveries/IP from the founders’ laboratories into small molecule drug discovery programmes, with high throughput screening as a starting point.^{88–92} Another key component of this programme was exclusive licensing of the University of Colorado human heart tissue bank by Myogen. Funding for Myogen’s drug discovery operation was initially provided by venture capital investors, later through Small Business Innovation Research (SBIR) grants from the National Institutes of Health, and ultimately through a 5-year collaboration with Novartis. Myogen was acquired





by Gilead in 2006. The second arm of Myogen's business plan was to identify novel therapeutics that could be in-licensed and developed through innovative trial designs against novel cardiovascular targets within unmet need areas. Gilead's Letairis/ambisentan, a highly selective endothelin A receptor antagonist devoid of liver toxicity that had hindered this class of compounds, is a first-line therapy for pulmonary arterial hypertension, and was developed at Myogen. Additional programmes emanating from Myogen's drug discovery unit are in various stages of clinical development.

Many scientific papers begin and/or end with a discussion of how the current findings could lead to a new therapy, but sadly, there is often little follow through on these statements. The path from therapeutic hypothesis to successful development is long and arduous, but involvement in start-up entrepreneurial endeavours by scientists who generate the basis for the hypothesis can increase the probability of success. The Myogen story is an excellent example of how entrepreneurial pursuits by academic investigators, resulting in commercialization of university-developed technology, can have a major impact on society through the development of transformative therapies for human disease.

To facilitate the process of conversion of new targets and mechanisms into starting points for drug discovery, it is important that research scientists may rely on entities that cooperate with academic partners and offer a fully integrated incubator structure for all stages of drug discovery in order to identify novel first-in-class treatments, and after reaching initial *in vivo* proof of concept, start to identify commercial partners for these assets to secure further development. These entities (such as the Lead Discovery Center in Germany) can be effective instruments to bridge the 'valley of death' – that is the usual funding gap between basic research and commercial application (Figure 7).

The need for commercialization – successful partnering with industry

The traditional (and still current) template for success in pharmaceuticals development describes a trajectory in which a drug is considered 'successful' not only when it passes through the regulatory process, but when it is launched and commercialized, becomes a

useful and trusted tool in its therapeutic area through the accrual of real-world data, and gets the expected/required return on investment, thus reinforcing further efforts in the research area (a process which in industry is called 'internal trust'). This general pattern is broadly applicable, notwithstanding that there are big differences between the United States, the European Union, Japan, and other countries on issues such as time protection from me-too competitors and generics, and opportunities for patent strategies or repurposing.

Concerning the benefits of a successful drug, current trends in pharma include not only statistically significant and clinically relevant signs of efficacy and safety, but also pharmaco-economic and health economic values from the perspective of the payers (individual or institutional). On top of it, the field is shifting towards a new 'personalized health' paradigm, and, in this emerging era of ultra-detailed patient characterization and real-time monitoring, it may transpire that fitting the right drug to the right patient translates in practice to each new drug being appropriate for a small number of patients. Taking chronic HF as an example, new insights into pathophysiology may plausibly transform the syndrome into a myriad of orphan drug indications. The implications of such a change on both the conduct of clinical trials and even more so on commercial profitability and/or drug acquisition costs will be evident.⁹³

However, an even better example of complex therapeutic field is acute HF which includes many clinical manifestations characterized by different symptoms, signs, and markers, with different aetiologies, and different courses, also due to overlapping morbidities and to a variety of chronic medications.⁹⁴ Paradoxically, while use of current treatments for chronic HF does prolong life, the number of acute HF hospitalizations is still increasing⁹⁵: in fact, currently nothing helps avoiding an acute or final HF stage in the increasingly elderly population. It appears that clinical and industrial trialists had too high expectations in the development of drugs for acute HF.⁹⁶ For a successful breakthrough, the scientific community, the industrial partners, and the regulatory authorities should refine their comprehension and focus their resources by embracing new definitions for multifaceted syndromes such as acute HF.⁹⁷

On the other hand, the question arises as to how to translate scientific advances and new diagnostic and/or therapeutic development to the approval by regulatory bodies and marketing stages in the shortest time possible. There are many paths open to the innovator of new technology to accomplish this end, with various approaches for commercialization of new technology, but we will emphasize on the strategy for starting up a new company.^{98,99} As a general rule, the more optimized a technology is, the greater the probability of success and the shorter the time to market. An approximate categorization of technology status as it relates to drug discovery would be: (1) preliminary data with no IP or *in vivo* animal proof of concept (aPOC) present a very low likelihood of success; (2) identified target with IP and aPOC completed and non-optimized chemical starting point in-hand still has a low chance of success; (3) advanced IP and optimized molecule in-hand will increase the probability to 1–5%; (4) once the preclinical development is completed and clinical Phase I results are available, the success rate is between 10% to 20%; (5) when clinical Phase II

studies are completed, the likelihood of success can reach 30–50%. However, even with clinical stage technologies, development costs to market are still very high and risk of failure is substantial.

It has to be considered that the greatest cost in the development of new therapeutics occurs during the clinical development stage. These clinical studies are required for regulatory approval and registration of new medicines. Thus, early-stage discoveries and opportunities without clinical data have the least amount of inherent value to the innovator and sponsoring institution because development costs and risk of failure are very high. In addition, there is a long development time to marketing approval. Preliminary stage opportunities could best be served by continued research to establish IP. Early-stage discoveries (with IP and aPOC) are best licensed out or partnered with pharma or biotech companies, which are better positioned to optimize the technology for commercial success. An alternative to this would be to add value to the early-stage technology with the support of public programmes aimed at enabling small companies to explore their technological potential and facilitate the commercialization of their products such as the SBIR and Small Business Technology Transfer (STTR) grants in the United States or their equivalent in other international funding schemes. Discoveries and targets that have an optimized molecule in-hand and have advanced to first clinical studies constitute the basis for start-up companies, and have a reasonable chance of success. However, the cost and time for development to marketing stage is still quite high and time of development is long. With a start-up company,¹⁰⁰ once the senior management and support staff is in place, with a clear business plan, the key is acquiring funding to advance the technology. Here again, government-funded programmes may be useful, especially for preclinical research. Key funding milestones for venture capital, or pharma company investment or acquisition will be successful completion of clinical studies, especially Phase II clinical proof-of-concept studies and Phase III clinical results. A start-up company with a preclinical stage opportunity should thus focus its activity on obtaining clinical data and should conduct only the animal studies that are absolutely required for achieving this goal. Finally, the artificial and often erroneous and unjust calculation of cost of life-year or quality-adjusted-life saved in different therapeutic fields (e.g. oncology vs. cardiology) – derived mostly by not standardized social and economic considerations¹⁰¹ – must be also considered as a reason why investments in drug discovery, translation, and development are often favouring some fields over others.

Conclusions

Pharmacologic treatment of HF has advanced substantially in the last decades; however, residual morbidity and mortality remain high and constitute one of the largest unmet medical needs. Novel therapeutic agents targeting the relevant pathophysiological mechanisms in different phenotypes within the HF syndrome are needed to advance towards the implementation of precision medicine in the cardiovascular field. Several recent developments have been disappointing, being lost in translation from preclinical studies to the clinical arena and have dampened the expectations in the field.

In order to improve the chances of success, we call for increasing the quality of preclinical studies, for the need to be aware of the limitations of animal models to recapitulate some of the key features of the complex clinical syndrome of HF, to take advantage of novel technical developments in integrative -omics analyses (e.g. RNAseq, proteomics, genomics, metabolomics) to deeply phenotype disease subtypes and enable personalized strategies, and to apply tissue engineering, hiPSCs, AI and bioprinting to establish models arising from human tissue and biological samples to test the pathways and targets of interest. Conversely, to close the gap between basic science research and commercial developments, we need a closer interaction between academic researchers and specialized entities, including government-funded agencies and biotechnological and pharmaceutical companies, that offer support for all stages of drug discovery to identify and develop novel first-in-class treatments.

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