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# Toward precision cardiovascular medicine: progressing basic and translational science

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KEYWORDS

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A Viewpoint on the Frontiers in Science Lead Article
Precision cardiovascular medicine: shifting the innovation paradigm

## Key points

- Precision cardiovascular medicine requires new experimental models that better mimic human diseases.
- Target definition must be adequately cell type-specific, as proteins can exert different functions in different cells.
- New treatments also need cell type-specific delivery approaches and methods to better understand and predict off-target effects.

In their excellent lead article "Precision cardiovascular medicine: shifting the innovation paradigm," Aikawa et al. (1) highlight that, in addition to cardiovascular risk management, new and more effective therapies are needed to treat complex and heterogenous cardiovascular diseases (CVDs) to reduce overall morbidity and mortality among patients. There is no doubt that "precision medicine" has the potential to achieve such a goal in the near future. However, this will require progress in several aspects of basic and translational science (Figure 1), i.e., the creation of adequate animal models mimicking the complexity of human diseases, better definition of the time course and specific cells involved in disease development or progression, and improvement of cell type-specific targeting of therapeutic approaches and understanding of potential off-target effects.

## Adequate experimental models

While "big" clinical data are required to discover and test novel preventive and curative therapies for CVDs, new experimental models that better recapitulate human diseases are just as important. Translating basic science into clinical practice is challenging, especially for complex conditions such as CVDs, which often result from multiple risk factors and comorbidities. In the coming years, animal models need to be further refined and made

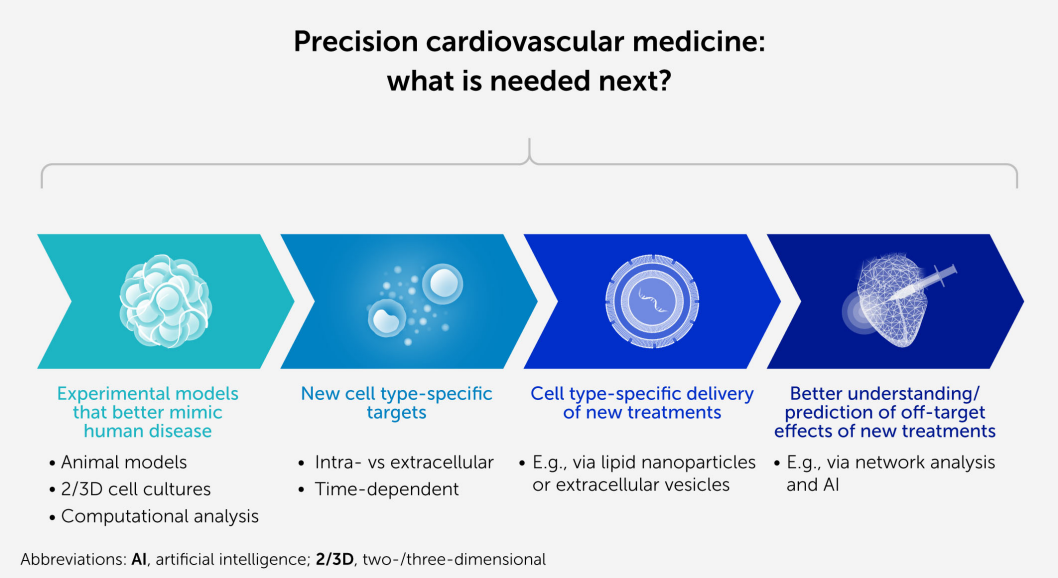


FIGURE 1
Progress in several aspects of basic and translational science is necessary to enable precision cardiovascular medicine.

more "human-like" using big datasets from human studies (2, 3). As well as predicting efficacy, it is also important to identify uncommon or "hidden" cardiotoxic effects of treatment modalities, which currently are often detected only after market launch when large numbers of patients are exposed to treatment (4). As CVD mechanisms and treatment responses potentially differ between males and females, the effect of the patient's sex should also be considered in the design of experimental studies (5). Novel *in vitro* technologies, such as inducible pluripotent stem cells in two- or three-dimensional (so-called organoid) cultures or human slices and advanced computational analyses, will improve our experimental designs and better capture human pathophysiology —thereby reducing the number of laboratory animals required.

## Adequate target definition

Different cell types might behave differently during disease development. This can be because a certain protein might have different functions:

(i) Within or outside the cell. For example, intracellular deletion of proprotein convertase subtilisin kexin type 9 (PCSK9) using genetic approaches reduced infarct sizes *ex vivo*, but inhibition of extracellular PCSK9 using antibodies did not (6). Thus, exact understanding of the intra- and extracellular function of a protein is required before target definition.

(ii) In different cell types. For example, uncoupling protein 2 contributes to the formation of reactive oxygen species (ROS) in many cell types, potentially causing harm under pathophysiological conditions. However, this is not the case in cardiomyocytes (7), where uncoupling protein 2 most likely functions by modifying substrate transport and usage and is potentially important for maintaining cardiomyocyte function. Therefore, targeting all cell types at once does not necessarily improve disease development and/or progression. This is seen on a larger scale when comparing the two sides of the heart during disease development: recent studies suggest that regulation of ROS formation, which is involved in many cardiovascular pathologies, differs in the left and right ventricle (8). Thus, any modification of the function of a target protein has to be cell-type-specific.

(iii) At different time points during disease development and/or progression. Time-dependent effects, either beneficial or detrimental, have been described for fibrosis development following myocardial infarction. Early interference with fibrosis development will cause harm due to the potential of increased ventricular rupture, while later inhibition will potentially attenuate heart failure development. Thus, the time course, rather than a snapshot in time, is required to understand protein function in disease development and progression.

(iv) Within subpopulations of the same cell type. Single-cell analyses of genetic, epigenetic, or proteome changes indicate that there are subpopulations within a given cell type (for example, cardiomyocytes or β cells) that behave differently during disease development. Here, a better understanding of the contribution of these different subpopulations of cells is required for adequate therapeutic target prediction.

## Cell type-specific delivery of new treatments

Lipid nanoparticles (LNP) have been synthesized to protect messenger RNA (mRNA) therapeutic agents from degradation and, with adequate composition of the bilayer membrane, facilitate uptake into specific cellular compartments. However, even though there might be a certain cell-type specificity, LNPs are taken up to a small extent by almost every cell, raising the potential for adverse effects of the mRNA-encoded protein and/or protein inhibition (9). Moreover, LNPs might induce immune responses and local inflammation due to their synthetic components. Extracellular vesicles, which play an essential role in intercellular communication by facilitating the transport of bioactive molecules, may offer advantages over LNPs as delivery vehicles, being naturally derived and thus less likely to elicit immune responses. However, far more research is needed to develop standardized techniques for their isolation and purification, and to explore their therapeutic use (10).

## Safety of new therapeutic approaches

Small interfering RNAs (siRNAs), microRNAs (miRNAs), and the RNA subtype of antisense oligonucleotides offer advantages over small-molecule drugs. These small RNAs can target any gene product, offering new, effective, and safe therapeutic approaches for a wide range of diseases. However, the use of these agents faces important challenges. Hybridization-dependent off-target effects remain a major hurdle, for example, as no established, standard methodology exists to minimize these, and the various proposed methods have limitations. Here, the inclusion of new techniques (including network theoretical algorithms and artificial intelligence) in the development process would enable examination of the entire, complex regulatory network—allowing more accurate prediction of potential off-target effects and more precise sequence design (11).

## Conclusion

Taken together, precision medicine has enormous potential to improve therapy for CVDs and reduce patients' morbidity and mortality. However, further research using a new generation of adequate experimental models is needed if we are to develop and deliver new, effective, and safe cell type-specific therapies.

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RS: Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

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