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Editorial: Recent advances in cardiotoxicity testing, volume II

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Editorial on the Research Topic
Recent advances in cardiotoxicity testing, volume II

Over the years, there has been a notable rise in the number of cardiovascular complications associated with various therapeutic interventions, particularly in the domain of cancer treatment (Abdul-Rahman et al., 2023; Pawar et al., 2024). Drug-induced cardiotoxicity poses a significant challenge, often leading to market withdrawals and detrimental health outcomes (Destere et al., 2023). This surge in cardiotoxicity cases underscores the necessity for robust preclinical screening strategies to mitigate risks before advancing to human clinical trials. Traditional screening methods heavily relied on animal models, which, albeit valuable, possess limitations in accurately reflecting human cardiac responses and high financial burden. Consequently, the quest for more reliable and cost-effective alternatives has led to a paradigm shift towards innovative *in vitro* models (Asnani et al., 2021). In recent years, significant strides have been made in leveraging human induced pluripotent stem cell-derived cardiomyocytes (hiPS-CMs), organoids, and human heart slices as promising tools for cardiotoxicity assessment (Miller et al., 2020; Ou et al., 2020; Meki et al., 2021; Rothbauer et al., 2021; Miller et al., 2022; Zhu et al., 2024). These models offer a more physiologically relevant platform, exhibiting high sensitivity and specificity towards diverse therapeutic interventions while faithfully replicating human cardiac physiology and pathophysiology (Wang et al., 2008).

In this Research Topic, "*Recent Advances in Cardiotoxicity Testing, Volume II*," we present a compilation of eight manuscripts comprising four review articles and four original research articles. Each manuscript delves into the latest breakthroughs in cardiotoxicity testing, encompassing a spectrum of innovative methodologies and insights. This collection serves as a comprehensive resource, shedding light on the cutting-edge strategies and advancements shaping the landscape of cardiotoxicity assessment.

(Altrocchi et al., 2023) described the development and validation of a novel assay utilizing human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) to assess both acute and delayed drug-induced cardiotoxic effects of reference compounds with known cardiac outcomes. The assay, conducted on 48-well multielectrode array (MEA) plates, evaluated functional-electrophysiological parameters and viability over 4 days. Testing of various compounds, including tyrosine-kinase inhibitors, classic cardiac toxic drugs, ion-channel trafficking inhibitors, and compounds without known cardiotoxicity, revealed the assay's ability to recapitulate different cardiotoxicities, such as prolongation of field potential, changes in beating rate, arrhythmic events, and impedance reduction. Additionally, fluorescence- and luminescence-based plate reader assays confirmed cytotoxic effects linked to changes observed in the MEA assay. The study underscores the importance of chronic drug evaluation in identifying cardiotoxic effects,

emphasizing the potential of this hiPSC-CMs assay to contribute to early compound de-risking and optimize drug development processes.

Similarly (Arefin et al., 2023), investigated the stability and reproducibility of engineered heart tissues (EHTs) derived from human pluripotent stem cell (hPSC)-differentiated cardiomyocytes for cardiac contractility assays in drug development. Utilizing EHTs from different tissue casting batches and hPSC-cardiomyocyte lines, the researchers assessed contractile outputs using a video-optical assay and compared them with monolayer cultures. Drug-induced variations were tested with compounds known for their cardiac effects or cardiotoxicity, alongside analyses of intracellular calcium transients. Establishing quality control criteria based on excitation-contraction coupling, the study identified suitable EHTs for analysis. Results indicate comparable drug-induced contractile responses between EHTs and monolayers, with a close correlation between contractile output and calcium kinetics. The study emphasizes the importance of reproducibility in assessing drug-induced effects in EHTs, suggesting potential future applications with additional mechanistic criteria for specific contexts of use.

In another context (Advani et al., 2023), aimed at replicating the most common genetic associations of chemotherapy-related cardiotoxicity in the adjuvant NSABP B-31 clinical trial. Using genotyping data from 993 patients, TRPC6 rs77679196 and CBR3 rs1056892 (V244M) were found to be linked to doxorubicin-induced cardiac events in both NCCTG N9831 and NSABP B-31. However, other variants previously reported to be linked to trastuzumab-related decline in LVEF failed to replicate between these studies. In an effort to develop cardioprotective peptides (Zerihun and Qvit, 2023), used computational methods to develop peptides that inhibit mitochondrial fission 1 (Fis1)/mitochondrial dynamics 51 kDa (Mid51) protein-protein interactions to reduce the cellular damage that can lead to cardiotoxicity. They identified two peptides, CVP-241 and CVP-242, and characterized their binding dynamic both *in silico* and *in vitro*.

In this Research Topic (Xiao et al., 2023), provided a bibliometric and knowledge-Map analysis from 2010 to 2022 to spot the light on the hotspots and emerging trends of cardiotoxicity (Lee et al., 2024). provided a perspective regarding the use of iPSC-cardiomyocytes in the preclinical prediction of candidate pharmaceutical toxicity. They explored compared and contrasted the electrophysiology, calcium handling, cellular signaling, contractile machinery, and metabolism between iPSC-CMs and adult CMs. As well they highlighted the methodologies when using iPSC-CMs to ensure a more representative phenotype of the adult human CM. On the other hand (Wu et al., 2023), reviewed the pathogenic mechanism of Immune checkpoint inhibitors-induced cardiotoxicity and evaluated the commonly used cardio-protective drugs. Finally (Zhang et al., 2023), reviewed the gut microbiota product, trimethylamine oxide (TMAO), and its link to cardio pathology, renal pathology, and cardio-renal syndrome.

As this field of research is evolving rapidly, the present volume of the Research Topic provides an update on the mechanisms of chemotherapy-induced cardiotoxicities, genetic variants related to them, possible modifiers and targets including peptides and metabolites, and testing platforms.

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Conflict of interest

TM holds equities in Tenaya Therapeutics.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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