

## STATE-OF-THE-ART REVIEW

# Priorities in Cardio-Oncology Basic and Translational Science

## GCOS 2023 Symposium Proceedings: JACC: CardioOncology State-of-the-Art Review

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## ABSTRACT

Despite improvements in cancer survival, cancer therapy-related cardiovascular toxicity has risen to become a prominent clinical challenge. This has led to the growth of the burgeoning field of cardio-oncology, which aims to advance the cardiovascular health of cancer patients and survivors, through actionable and translatable science. In these Global Cardio-Oncology Symposium 2023 scientific symposium proceedings, we present a focused review on the mechanisms that contribute to common cardiovascular toxicities discussed at this meeting, the ongoing international collaborative efforts to improve patient outcomes, and the bidirectional challenges of translating basic research to clinical care. We acknowledge that there are many additional therapies that are of significance but were not topics of discussion at this symposium. We hope that through this symposium-based review we can highlight the knowledge gaps and clinical priorities to inform the design of future studies that aim to prevent and mitigate cardiovascular disease in cancer patients and survivors. (J Am Coll Cardiol CardioOnc 2023;■:■-■) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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**ABBREVIATIONS  
AND ACRONYMS****AIC** = anthracycline-induced cardiotoxicity**CHIP** = clonal hematopoiesis of indeterminate potential**CTR-CVT** = cancer therapy-related cardiovascular toxicity**CV** = cardiovascular**CVD** = cardiovascular disease**DOX** = doxorubicin**HF** = heart failure**ICI** = immune checkpoint inhibitor**LVEF** = left ventricular ejection fraction

In recent years, the longevity and quality of life of cancer survivors have dramatically improved in large part due to the development of new anticancer therapeutic options.<sup>1</sup> While this approach has increased the number of cancer survivors, it has also increased the incidence and prevalence of cancer treatment-related toxicities. Cancer therapy-related cardiovascular toxicity (CTR-CVT) has become a frequent challenge faced by patients and clinicians alike.<sup>2,3</sup>

One of the pillars of modern medicine is that clinical practice should be evidence based. However, translating preclinical knowledge to direct patient care can be

challenging. In 2022, the European Society of Cardiology published the first cardio-oncology guidelines in collaboration with the European Hematology Association, the European Society for Therapeutic Radiology and Oncology, and the International Cardio-Oncology Society.<sup>4</sup> This document provided a comprehensive overview on modern cardio-oncology practice including precise recommendations on cancer treatment monitoring and CTR-CVT risk stratification, prevention and management.<sup>4</sup> However, due to the complexity of cancer treatments, most of the recommendations are based on expert consensus.

**HIGHLIGHTS**

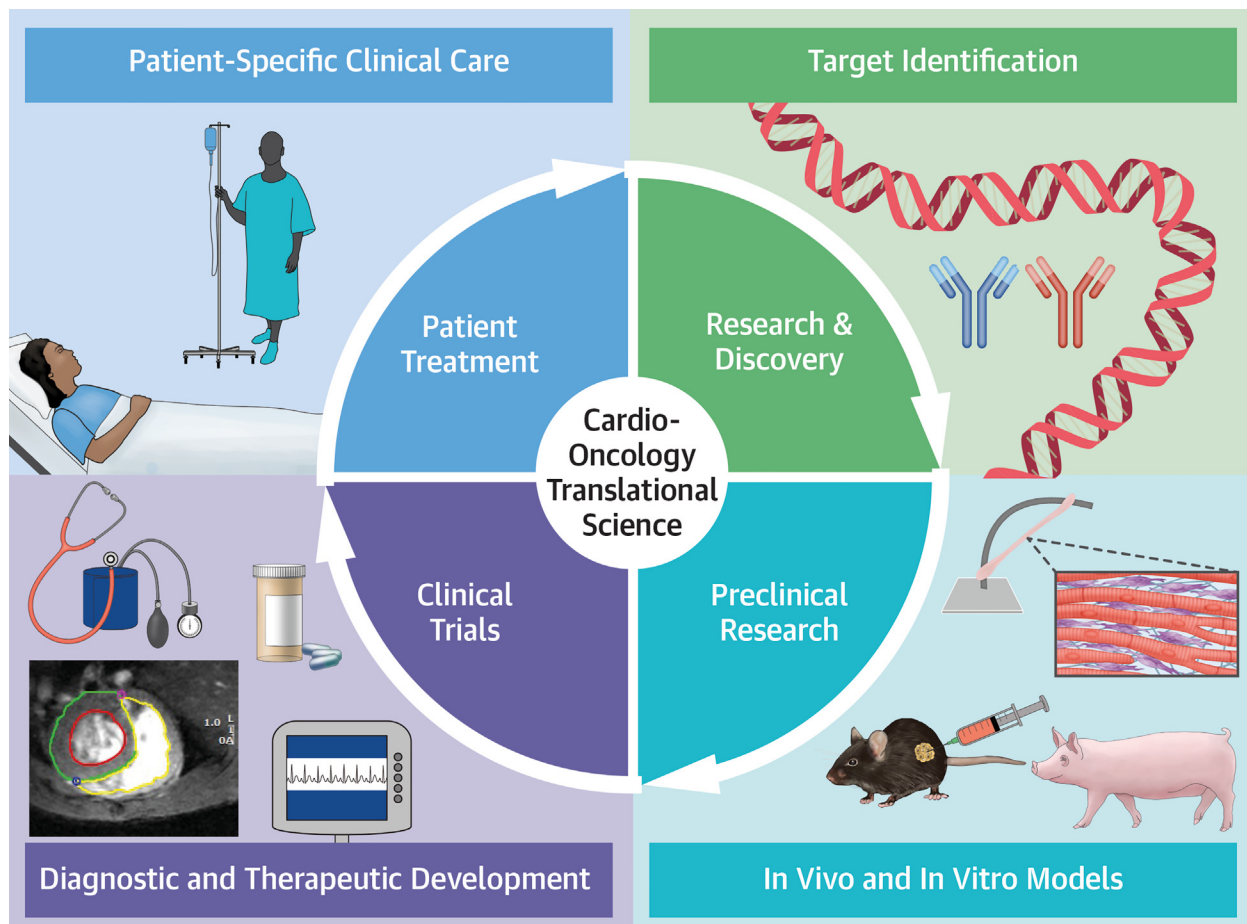
- Translational research is essential to guide genetic and pharmacologic cardioprotective approaches in cancer patients.
- DOX enhances heart cell senescence via DNA damage, oxidative stress, and mitochondrial dysfunction.
- CD8<sup>+</sup> T cells play a critical role in ICI-related cardiotoxicity.
- Mechanistic-based risk prediction models are needed to further advance our understanding of the strategies to prevent cancer and CV diseases.

To further advance the field of cardio-oncology and help resolve many of the clinical questions in diagnosing and managing CTR-CVT, translational research is essential. It is critical that productive, multidisciplinary crosstalk between clinicians and translational scientists occurs to ensure that science continues to inform clinical care (**Central Illustration**). This collective effort can eradicate the barriers between preclinical research and clinical practice using robust in vitro and in vivo models that can accurately recapitulate the pathophysiology of CTR-CVT. These

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

**CENTRAL ILLUSTRATION** Schematic Representation of the Basic/Translational Scientific Approach

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Research and discovery of new targeted therapies and testing in a preclinical model of human disease are essential phases for designing a comprehensive clinical trial. The information obtained from both preclinical and clinical studies can inform physicians and researchers in a bidirectional approach on the future steps to develop patient care planning and improve the quality of life in cancer survivors.

platforms can enable investigations into new genetic or pharmacologic cardioprotective approaches that aim to improve the quality of life in cancer survivors. In response to this important need, the International Cardio-Oncology Society and the Global Cardio-Oncology Symposium Committee convened a symposium dedicated to basic and translational science, focused on highlighting some of the ongoing international collaborative research network in cardio-oncology and discussing new mechanisms in cardio-oncology science that is primarily performed by the participants in this symposium. This paper summarizes the most novel aspects presented during this scientific meeting, but it is important to note that

there are many other important active areas of basic and translational research in cardio-oncology that are not included in this review, including cardiotoxic drugs (ie, MEK inhibitors and HER2 targeted therapies) and radiation therapy.<sup>5,6</sup>

#### INTERNATIONAL COLLABORATIVE EFFORTS TO ADDRESS AN UNMET CLINICAL NEED IN UNDERSTANDING AND MITIGATING ANTHRACYCLINE CARDIOTOXICITY

Although anthracycline-induced cardiotoxicity (AIC) has been recognized for many decades, the mechanisms responsible for this have not been fully

**TABLE 1** Mechanisms of Cancer Therapy-Related Cardiovascular Toxicity Discussed at the Global Cardio-Oncology Symposium 2023 Scientific Symposium

Anthracyclines	Immune Checkpoint Inhibitors	Bruton Tyrosine Kinase Inhibitors
<ul style="list-style-type: none"> <li>Mitochondrial dysfunction:               <ul style="list-style-type: none"> <li>Activation of PI3K-<math>\gamma</math> reduces mitophagy</li> <li>Loss of PI3K-C2<math>\alpha</math> triggers premature cardiomyocytes senescence</li> </ul> </li> <li>Endothelial/microcirculation damage through ROS generation and inflammation</li> <li>Senescence via DNA damage, oxidative stress, and mitochondrial dysfunction</li> <li>CHIP</li> <li>DNA damage</li> <li>Dysregulation of iron metabolism</li> <li>Oxidative stress</li> </ul>	<ul style="list-style-type: none"> <li>CD8<sup>+</sup> T cell-driven ICI-mediated myocarditis and atherosclerosis</li> <li><math>\alpha</math>-MyHC-specific autoreactive T cell-driven ICI-mediated myocarditis</li> <li>PD-1/PD-L1 down-regulation in contributes to AF pathogenesis</li> </ul>	AF related to: <ul style="list-style-type: none"> <li>Reduction in PI3K-Akt pathway signaling</li> <li>Inhibition of C-terminal Src kinase</li> </ul>
<small><math>\alpha</math>-myHC = <math>\alpha</math>-myosin heavy chain; AF = atrial fibrillation; CHIP = clonal hematopoiesis of indeterminate potential; ICI = immune checkpoint inhibitor; PD-1 = programmed cell death 1; PD-L1 = programmed cell death-ligand 1; PI3K = phosphoinositide 3-kinase; ROS = reactive oxygen species.</small>		

elucidated (Table 1).<sup>7</sup> Several multinational collaborative efforts have come together to address this issue. Two of the largest endeavors in this regard are the Leducq foundation-funded Targeted Approaches for Prevention and Treatment of Anthracycline-Induced Cardiotoxicity and the European Commission-funded RESILIENCE (REmote iSchemic condItioning in Lymphoma PatIents REceiving ANthraCyclinEs) project. Here, we summarize the main objectives of these endeavors.

**ELUCIDATING THE ROLE OF MITOCHONDRIAL DYSFUNCTION.** Doxorubicin (DOX) irreversibly binds to cardiolipin in the inner mitochondrial membrane, generating structural and functional damage to mitochondria. Because mitochondria cannot be generated de novo and the mitochondrial population is regulated by fusion and fission of pre-existing units,<sup>8</sup> when a critical mitochondrial mass is damaged by DOX, the heart can become severely and irreversibly injured. It is hypothesized that DOX leads to an iron-mediated increase in the levels of mitochondria-driven reactive oxygen species (ROS).<sup>9,10</sup>

As a defense mechanism against DOX, the cell promotes selective mitophagy to eliminate “toxic” (ROS-generating) organelles. This mitophagy results in intra-cardiomyocyte edema, that can be tracked by noninvasive cardiac magnetic resonance (CMR).<sup>11</sup> Mitophagy seems to be a therapeutic target, as its enhancement, either by injection of dexrazoxane or by execution of remote ischemic conditioning (RIC), can alleviate AIC.<sup>12</sup>

Members of the Leducq consortium have demonstrated that phosphoinositide 3-kinase (PI3K)- $\gamma$  acts as a stress kinase that is activated by the mitochondrial damage elicited by DOX. This process involves the recognition of mitochondrial DNA by Toll-like

receptor 9. Downstream of Toll-like receptor 9, PI3K- $\gamma$  initiates an Akt/mTOR/Ulk-1 signaling cascade. PI3K- $\gamma$  promotes feedback inhibition of the mitophagy process involved in the disposal of damaged mitochondria. In addition, PI3K- $\gamma$  directs a metabolic switch of cardiomyocytes towards a more glycolytic metabolism. Accordingly, genetic or pharmacologic PI3K- $\gamma$  loss of function approaches resulted in increased mitophagy and protection against AIC.<sup>13</sup> Investigators from the consortium recently pinpointed a key function for the class II PI3K isoform, PI3K-C2 $\alpha$ , in the control of cellular senescence by showing that loss of PI3K-C2 $\alpha$  triggers premature senescence.<sup>14</sup> The potential role of PI3K-C2 $\alpha$  in DOX-induced senescence in cardiomyocytes is currently being studied.

**DAMAGE TO THE CARDIAC MICROCIRCULATION.** Endothelial dysfunction is a hallmark of cardiovascular disease (CVD) and is associated with impaired vascular function, increased vascular inflammation and oxidative stress.<sup>15</sup>

Experimental studies have shown that DOX treatment induces a decrease in cardiac capillary density, nitric oxide production, and impaired endothelium-dependent vasodilation in the coronary arteries.<sup>16,17</sup> Furthermore, prospective, and cross-sectional human studies in cancer patients have shown a detrimental effect of anthracyclines on cardiac perfusion measured by positron emission tomography and CMR during and after chemotherapy treatment.<sup>18-20</sup> The mechanism of such a subclinical effect on the microcirculation is not entirely known. It is speculated that anthracyclines induce direct damage to the endothelial cells through ROS generation, causing regulated cell death. Inflammation in the heart could also contribute to microvascular damage because anthracycline treatment has been shown to activate

inflammatory cells such as macrophages and neutrophils,<sup>21</sup> which can damage arterioles and capillaries.

**REFINEMENT OF ANIMAL MODELS OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY.** The translation of experimental studies into effective clinical trials is limited by the lack of animal models that accurately mimic the clinical scenario, including the presence of cancer and other comorbidities that have a clear impact on outcomes.<sup>22-26</sup>

To develop a clinically translatable murine cancer model, members of the Leducq consortium have established a reversible B16F10 melanoma mouse model, modified via a lentiviral transduction of a suicide gene inducing cell death upon exposure to ganciclovir.<sup>27,28</sup> This model enables studies into the long-term effects of advanced cancer on the cardiovascular (CV) system. As an example, upon chemotherapy-free tumor elimination of cancer in this murine model, most cardiac morphological, functional, metabolic, and molecular changes spontaneously recovered, and exposure to additional pathophysiologic stress, such as increases in blood pressure, did not result in worse cardiac performance compared with control animals. In contrast, DOX treatment resulted in permanent, long-term molecular alterations in the heart, including those of the circadian rhythm pathway, which can influence cardiac repair mechanisms. It has been hypothesized that these changes may render the heart more susceptible to additional stress over the course of life and thus contribute, at least in part, to late cardiotoxicity.<sup>28,29</sup>

The RESILIENCE consortium has focused on the development of AIC pig models. These pigs are followed up in the long-term (>4 months) by multimodality imaging, including CMR, positron emission tomography-computed tomography, and ultrasound. Severe AIC, mimicking heart failure (HF) with reduced left ventricular ejection fraction (LVEF), is induced by intracoronary infusions of DOX.<sup>11</sup> After the fourth dose, a progressive decline in systolic function was observed, resulting in severe HF in the long-term.<sup>11</sup> Moderate reduction in LVEF is achieved by injections of low doses of DOX with left ventricular pressure overload, resulting in a moderate reduction in LVEF. These models are ideal for identifying new early markers of AIC (such as early cardiac edema as detected by CMR),<sup>16</sup> and for testing novel interventions, such as RIC.<sup>12</sup>

**EARLY DETECTION OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY BY CMR.** The RESILIENCE consortium is prospectively validating the CMR-based biomarker T2 relaxation time prolongation as the

earliest marker of AIC in a multinational study. Intracardiomyocyte edema is the earliest phenomenon occurring in the myocardium, long before any contractile defect becomes apparent.<sup>11</sup> Leveraging the RESILIENCE trial, the consortium will validate this novel marker of early cardiotoxicity in humans. To facilitate the implementation of CMR in daily practice, investigators of the RESILIENCE trial have developed a new CMR sequence (based on ESSOS [Enhanced SENSE by Static Outer volume Subtraction]) allowing an ultrafast CMR scan (scan time <1 minute) with comparable results to the classical scan.<sup>30</sup>

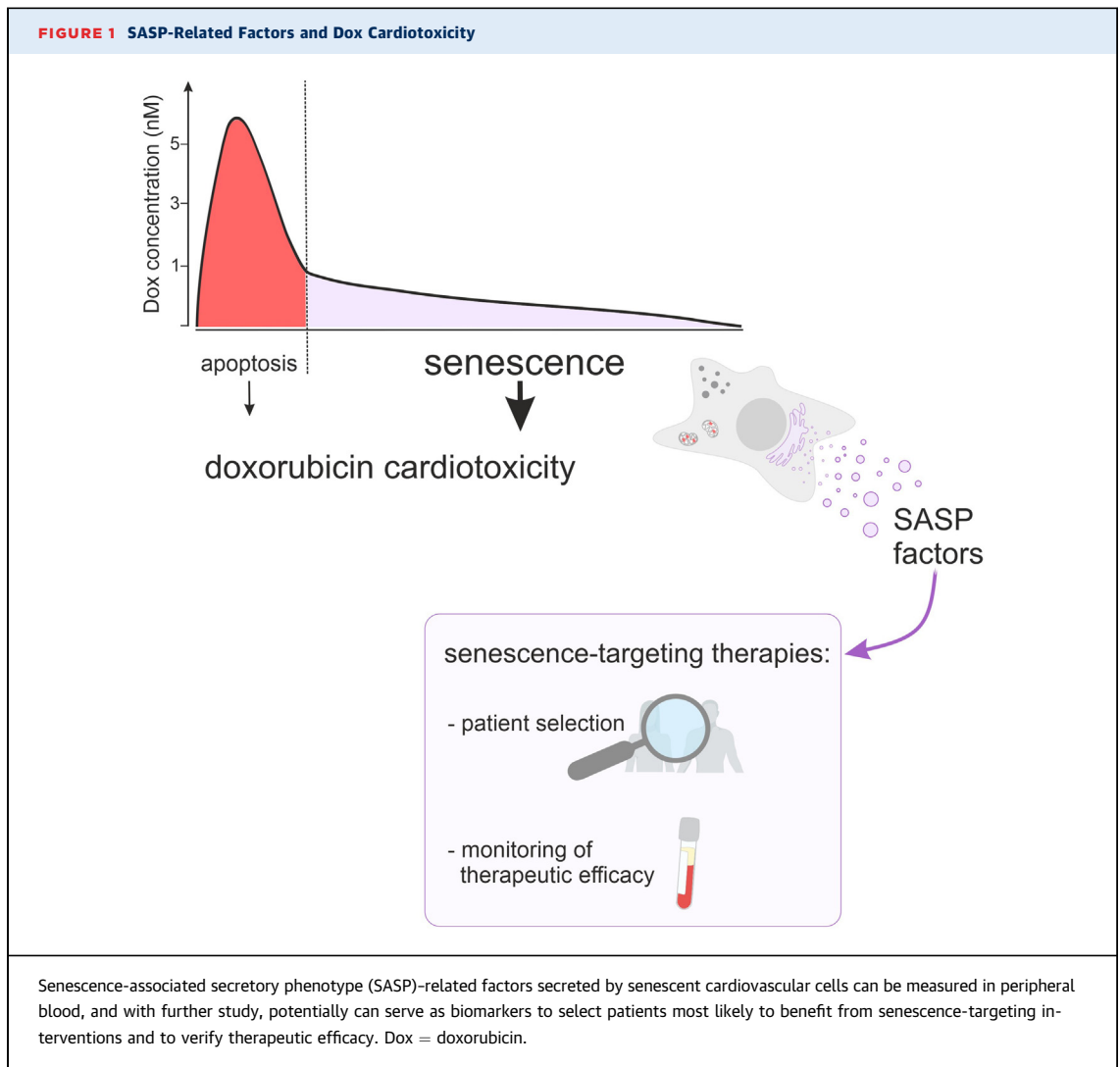
#### **REMOTE ISCHEMIC CONDITIONING TO PREVENT ANTHRACYCLINE-INDUCED CARDIOTOXICITY.**

RIC is an intervention designed to produce brief episodes of ischemia and reperfusion in an organ (usually the arm or leg) that confers protection to distant organs (the heart in this case).<sup>31</sup> The benefit of this strategy in certain clinical scenarios, such as myocardial ischemia, can be limited because RIC is initiated after the onset of damage, weakening the cardioprotection afforded by this intervention compared with its application prior to injury as observed in experimental models.<sup>31</sup> Indeed, RIC performed before each DOX administration in a pig model resulted in robust protection against LVEF reduction through a mechanism involving mitochondrial protection via enhanced mitophagy.<sup>16</sup> These results form the premise for the ongoing RESILIENCE randomized clinical trial.<sup>32</sup> Lymphoma patients enrolled in the RESILIENCE trial are randomized to weekly RIC or sham during the entire duration of chemotherapy (approximately 4 months). RIC is achieved by several cycles of ischemia-reperfusion inflating an arm blood pressure cuff above the systolic pressure. The primary outcome is the change in the incidence of LVEF decline.<sup>4</sup> This study will also validate T2 mapping as an early marker of cardiac dysfunction<sup>11</sup> and the ultrafast CMR sequence ESSOS in this vulnerable population.<sup>37</sup>

#### **NEW MECHANISMS IN CARDIO-ONCOLOGY**

This section aims at highlighting key areas of research within the broad spectrum of the current science in cancer therapeutics. The covered topics span recent insights into additional mechanisms accounting for AIC, the role of genetics in CTR-CVT, and the effects and mechanisms of immune and targeted therapies on the CV system.<sup>33</sup>

**THE ROLE OF SENESCENCE IN CTR-CVT.** Senescent cells are characterized by cell cycle arrest, altered vulnerabilities to cell death, and the elaboration of a complex secretome referred to as senescence-



associated secretory phenotype (SASP), which includes the release of core factors that are consistently secreted irrespective of the pro-senescence stimulus.<sup>34</sup>

Several studies have shown that DOX elicits senescence of cultured cardiac cells.<sup>35,36</sup> Interestingly, cardiomyocytes also acquire the hallmarks of senescence when incubated with DOX, although almost all are postmitotic and, therefore, non-proliferating.<sup>37,38</sup> It is noteworthy that the concentrations of DOX that cause senescence in cardiac cell cultures are in the range of 50 to 500 nM, and DOX is detected at these levels in blood and tissues for most of the time after intravenous infusion.<sup>39,40</sup> By contrast, higher concentrations, which typically initiate apoptosis *in vitro*, correspond to the peak reached only shortly after intravenous

administration.<sup>39,40</sup> Hence, it has been hypothesized that senescence of cardiac cells, rather than cell death, underlies AIC in patients. Confirmation that cardiac cell senescence is central to the development of AIC has been obtained by using mouse models, in which senescent cells can be tracked and selectively killed.<sup>41</sup> Treatment of p16-3MR transgenic mice with DOX resulted in left ventricular dysfunction and a significant increase in the number of senescent cells in the heart. Moreover, targeted elimination of senescent cells prevented the decline in left ventricular systolic contraction induced by DOX.<sup>42</sup>

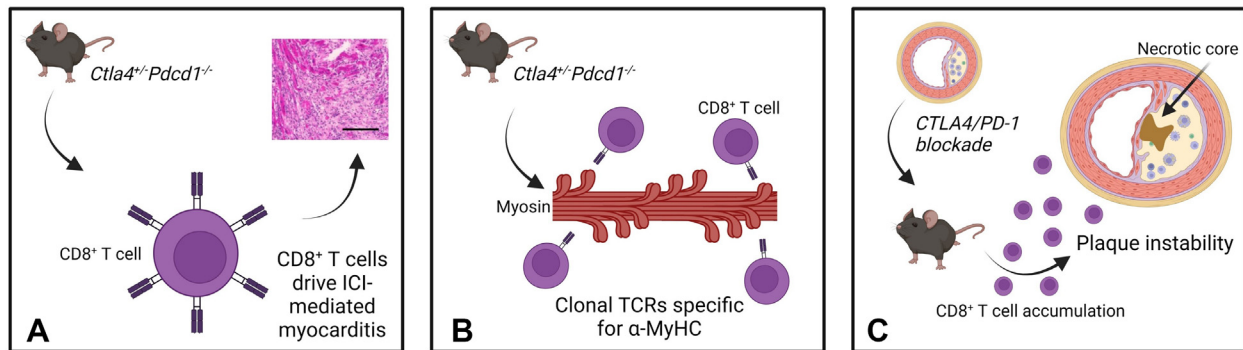
DOX promotes senescence via DNA damage, oxidative stress, and mitochondrial dysfunction.<sup>43</sup> Recently, Linders et al<sup>44</sup> demonstrated that the cardiac tissue of patients with severe AIC (requiring heart transplantation or left ventricular assist device

implantation) had a 15-fold increase in senescent cardiomyocytes compared with control tissue. Three-dimensional (3D) dynamically loaded engineered heart tissue models were then constructed to better understand the functional consequences of senescence in heart tissue and to provoke a phenotype that might be translatable to clinical HF.<sup>45,46</sup> Exposure of dynamically loaded engineered heart tissue to DOX resulted in progressive dilatation, reduced contractile force, and more senescent cells without an increase in cell death. Prevention of senescence in these tissue constructs, however, did not improve function and resulted in more cell death and fibrosis.

Cardiac (and vascular) senescence upon cancer treatment other than DOX has been poorly investigated. Limited data are available for selected therapies, such as radiotherapy,<sup>47</sup> although these are areas of active investigation. In this regard, it is noteworthy that SASP-associated factors secreted by senescent CV cells can be measured in peripheral blood and with further study, potentially serve as biomarkers to select patients most likely to benefit from senescence-targeting interventions and to verify therapeutic efficacy (Figure 1). For instance, growth differentiation factor 15 (GDF-15) is a SASP core protein and is synthesized by cardiomyocytes and endothelial cells undergoing senescence upon incubation with DOX and radiation, respectively.<sup>38,47</sup> In addition, GDF-15 concentrations increase in the months after DOX chemotherapy in women with breast cancer,<sup>48</sup> although the origin of GDF-15 is not yet clear.

**THE ROLE OF GENETICS IN CTR-CVT.** Clinical risk prediction for CTR-CVT remains imperfect at present. Some older patients treated with maximum doses of chemotherapy retain normal cardiac function, whereas other young patients develop fulminant cardiac toxicity with standard cancer treatment regimens. This phenotypic variability has led to an increasing recognition of the role of genetics and other heritable traits (eg, circulating proteins and metabolites) in cardio-oncology. Prior studies have focused primarily on genetic variants associated with CV toxicity in children and adults treated with anthracyclines, in which blood samples and serial assessment of cardiac function are most readily available.<sup>49</sup> For other antitumor agents, detailed CV phenotyping has not been routinely incorporated into cancer clinical trials and cohort studies. Metrics used to define CV toxicity, including the timing and modality of cardiac imaging or biomarker assessment, vary markedly from one study to another. The few cohorts designed specifically to assess CTR-CVT have

been limited by small sample size. To date, genetic studies in cardio-oncology have therefore focused on validation of molecular mechanisms discovered in preclinical models, including oxidative stress, topoisomerase 2 $\beta$  signaling, dysregulation of iron metabolism, pharmacokinetic and drug transport pathways, and sarcomeric mutations such as titin-truncating variants.<sup>50-54</sup> Discovery studies using human genetics have been hindered by the absence of large, prospectively enrolled cohorts in which analyses can achieve sufficient statistical power to uncover new biology. Existing population-based cohorts generally lack data on cancer therapeutics, dosing, and the chronological sequence of various cancer treatments, although recent studies in childhood cancer survivors have uncovered novel and intriguing information in this space.<sup>55,56</sup> Moving forward, further development of multicenter or population-based cohorts focused on cardio-oncology variables and endpoints would enable the integration of clinical information with different -omics such as genomics, transcriptomics, epigenomics, proteomics, and metabolomics. Multiomics datasets, when combined with statistical approaches such as Mendelian randomization and colocalization, could lead to the discovery of new genetic biomarkers that contribute to CTR-CVT these genetic variants can provide information on the underlying mechanisms and new targets for drug development. Also, combination models, including genetic variants, clinical, biomarker, genetic, and epigenetic data can contribute to the calculation of risk scores, helping in the identification of patients at high risk of develop CTR-CVT and those who are at low risk. In designing such large cohorts in cardio-oncology, several points merit consideration. First, should patients be stratified by cancer type or treatment? Some cancer treatments exert their effects through tumor-independent mechanisms, such as immune checkpoint inhibitors. On the other hand, the tumor type and stage may influence the severity of CTR-CVT. Second, what are the best ways to incorporate the rapidly changing landscape of cancer treatment into data analysis? Third, is a biorepository format the most efficient way to enroll patients, or will focused, hypothesis-driven studies be more likely to yield new mechanistic insights? Fourth, what is the optimal method to validate genetic variants associated with CTR-CVT phenotypes? Fifth, are genetic variants that confer an increased risk of CRT-CVT also associated with cancer outcomes, either directly through shared biological pathways or indirectly by mitigating the delivery of effective cancer treatment? In summary, genetic risk

**FIGURE 2 Immune Therapy**

**(A)** Preclinical immune checkpoint inhibitor (ICI)-mediated myocarditis model that recapitulates the clinical setting revealed a CD8<sup>+</sup> T cell-driven mechanism. **(B)** A preclinical ICI-mediated myocarditis model uncovered  $\alpha$ -myosin heavy chain ( $\alpha$ -MyHC)-specific autoreactive T cells. **(C)** Immune checkpoint blockade in murine models prone to atherosclerosis displayed accumulation of CD8<sup>+</sup> T cells in the plaques, which was associated with increased necrotic core size and plaque instability. TCR = T cell receptor.

prediction of CTR-CVT represents a promising avenue of research that will be critical in providing personalized treatment to the individual cancer patient maximizing efficacy and minimizing drug toxicity.

#### IMMUNE THERAPY AND MECHANISMS OF MYOCARDITIS.

Co-inhibitory molecules found on immune cells, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death-ligand 1 (PD-L1), play a crucial role in regulating T cell responses to prevent uncontrolled immune reactions within an organism.<sup>57,58</sup> Immune checkpoint inhibitors (ICIs) overcome cancer cells' ability to evade immune surveillance.<sup>59</sup> The clinical success of ICIs has been remarkable, leading to the approval of an increasing number of these agents for the treatment of diverse tumor types over the past decade. Unfortunately, the nonspecific activation of the immune system can lead to a wide range of immune-related adverse events.<sup>33,60</sup> Among these various toxicities, myocarditis is an uncommon toxicity (range 0.75%-1.7%), although early studies have noted a high fatality rate (20%-50%).<sup>61-63</sup> ICI-induced myocarditis can be a difficult diagnosis to make,<sup>64</sup> resulting in a challenge to establish a consensus on an effective approach to manage this condition.<sup>65,66</sup>

Limited knowledge is available on the underlying pathophysiologic mechanisms of ICI-related CV toxicity. Recent preclinical and translational research has proposed different potential mechanisms of ICI-related cardiotoxicity (Table 1, Figure 2). Studies with animal, primarily murine models, and clinical

data have provided insights on the cellular mediators involved,<sup>67</sup> the pathogenic soluble factors such as cytokines and chemokines, and T cell receptor (TCR) clonality and specificity.<sup>67</sup>

In animal models, activated effector CD8<sup>+</sup> T cells and proliferating CD8<sup>+</sup> T cells are enriched and key in ICI myocarditis relative to controls.<sup>68</sup> Specifically, administration of CD8<sup>+</sup> T cell-depleting antibodies conferred fatal myocarditis to the receiving mice.<sup>68</sup> In clinical studies, using peripheral blood mononuclear cells in ICI myocarditis patients,<sup>69</sup> cytotoxic CD8<sup>+</sup> T cell population was expanded in the blood.<sup>69</sup> The effect of immunosuppressive therapy on the cellular mediators is unclear; however, it is possible that immune suppression, with corticosteroids for example, may alter that cellular landscape and increase the role of B cells and explain the occasional positive effect of therapies with intravenous immunoglobulin in these patients.

Infiltrating effector T cells are a central feature of myocarditis, and the antigens responsible for their response have been a central focus of research. In mouse models, provoked by the repeated administration of anti-PD-1 antibodies to immunocompetent A/J mice,<sup>70</sup> CD4<sup>+</sup> and CD8<sup>+</sup> T cells carrying TCRs specific for  $\alpha$ -myosin were detected in the hearts with ICI myocarditis. These  $\alpha$ -myosin-specific T cells expressed higher levels of PD-1 compared with the remainder of the T cells. Additionally, using a genetic mouse model *Ctla4<sup>+/-</sup>Pdc1<sup>-/-</sup>*, 3 distinct  $\alpha$ -myosin-specific TCRs were identified.<sup>68</sup> In humans, the first proposed mechanism was molecular mimicry between cancer cells and cardiac tissue, which suggests



that T cells recognizing tumor antigens may also react against antigens in cardiac tissue.<sup>71</sup> This hypothesis was supported by TCR genotyping, which identified the expansion of similar T cell clones in both tumor tissue and myocardium in a patient with myocarditis.<sup>71</sup> In a second analysis of TCR- $\beta$  sequences from the heart, liver, and a lung metastasis of an ICI myocarditis patient,<sup>72</sup> 33% were shared with lung metastasis, 4% with those from the liver and 3% were shared across all 3 tissues. In addition,  $\alpha$ -myosin is expressed by some tumors,<sup>68</sup> supporting the hypothesis that a shared antigen (or shared epitope) drives T cell responses in the tumor and the heart in ICI myocarditis.

The identification of  $\alpha$ -myosin-specific T cells in the hearts with ICI myocarditis leads to the question of how such autoreactive T cells could escape mechanisms of central tolerance. Autoreactive T cells to the  $\alpha$ -myosin heavy chain ( $\alpha$ -MyHC) can escape from central tolerance and be naturally present in the periphery of healthy mice and humans due to a lack of representation of this antigen in the medullary thymic epithelial cell.<sup>73</sup> This is significant, as the thymus is responsible for negative selection, a process in which autoreactive T cells are eliminated to prevent autoimmune reactions. The absence of  $\alpha$ -MyHC epitope in the thymus allows autoreactive T cells specific to cardiac tissues to evade negative selection and persist in the peripheral circulation of healthy individuals. Additionally,  $\alpha$ -myosin-specific T cells could be expanded from the blood of healthy donors and of patients with ICI myocarditis. The  $\alpha$ -myosin-expanded TCRs overlapped with TCR repertoires in the diseased hearts and skeletal muscle of 3 patients with ICI myocarditis.<sup>68</sup> The breakdown of peripheral tolerance due to the action of ICIs would allow those autoreactive cells induce cytotoxic damage to heart.<sup>74</sup> Further study of this novel mechanism has the potential to inform risk factors for ICI-related CV toxicity.

Finally, as ICI therapy is increasingly used as adjuvant therapy in tumor-free patients after surgical resection, it remains to be elucidated whether the incidence or characteristics of immune-related adverse events vary in comparison to patients with high tumor burden. This could shed light on the potential differences in immune response and subsequent development of CV toxicities.

**ATHEROSCLEROSIS AND ICI THERAPY.** Atherosclerotic plaque develops through lipid accumulation in the vessel intima and plaque growth is perpetuated by leukocyte-driven chronic inflammation. Polarization of T helper cells toward T helper 1 and T helper 17

lineages has been associated with aggravated atherosclerosis, whereas regulatory T cells limit plaque development.<sup>75</sup> Recent advances have shown that T cells in human atherosclerotic plaques are phenotypically diverse and include locally expanded clones, possibly responding to both viruses and autoantigens.<sup>76</sup>

Immune checkpoint receptors play an important role in providing immune homeostasis by restricting T cell activation. Recent work has detailed a potential link between atherosclerotic CVD and ICI therapy,<sup>77</sup> including a retrospective study of cancer patients treated with ICIs that demonstrated a 3-fold increased incidence of CV events.<sup>78</sup> Other studies have replicated these observations,<sup>78</sup> albeit some reports have failed to observe any increased risk for CVD in patients receiving ICI therapy.<sup>79</sup>

While T cells play a fundamental role in myocarditis, some novel experimental data have emerged suggesting their potential role in atherosclerosis. Studies of genetically modified atherosclerosis-prone mice have demonstrated a role for PD-1,<sup>80</sup> CTLA-4,<sup>81</sup> and LAG3<sup>82</sup> in regulating plaque growth and T cell accumulation in lesions. Likewise, hypercholesterolemic mice administered anti-PD1 and anti-CTLA-4 antibodies displayed increased accumulation of CD8<sup>+</sup> T cells in plaques associated with increased necrotic core size,<sup>83</sup> a feature associated with plaque instability. Supporting a cardioprotective role for PD-1 signaling, the treatment of atherosclerotic mice with monoclonal agonistic anti-PD-1 antibodies led to reductions in plaque burden.<sup>84</sup> Despite these studies, the underlying mechanism causing plaque inflammation and increased CV risk is unclear. Studies in tumor-bearing mice have shown that the T-cell subset that primarily responds to ICI therapy is progenitor-exhausted T cells, characterized by expression of PD-1 and SLAMF6 along with the transcription factor TCF1.<sup>85</sup> Interestingly, autoreactive CD8<sup>+</sup> T cells exhibiting a similar phenotype (TCF1<sup>+</sup>PD1<sup>+</sup>) were recently reported to promote autoimmune type 1 diabetes,<sup>86</sup> indicating that this subset may be important in other autoimmune or autoinflammatory diseases such as atherosclerosis. Further studies are required to define the phenotype of T cells mediating the proatherogenic effects of ICI therapy and to formulate strategies to limit ICI-induced plaque inflammation without hampering antitumor efficacy.

**CANCER, CANCER THERAPY, AND ARRHYTHMIAS.** Arrhythmias are an increasingly recognized toxicity of cancer therapeutics with a significant impact on patient morbidity and mortality.<sup>87</sup> Although almost all types of arrhythmias have been described in

patients with cancer, atrial fibrillation (AF) represents the most common and clinically relevant arrhythmic comorbidity.<sup>87</sup> Several studies have shown an increased risk of AF in cancer patients, with the highest incidence in advanced stages and in some types of cancer (ie, multiple myeloma).<sup>88-90</sup> This relationship has also been demonstrated in reverse; patients affected by AF have an increased risk of developing cancer compared with the general population.<sup>91</sup> While this may be due to detection bias, AF and cancer share several modifiable risk factors, and cancer-related systemic inflammation may also play a role in the development of both conditions.<sup>64</sup>

During cancer therapy, an increased risk of AF has been associated with anticancer drugs<sup>92</sup> or in patients with CTR-CVT (ie, HF or ischemia). Atrial arrhythmias are most seen with the first generation Bruton tyrosine kinase (BTK) inhibitors, compared with the second- and third-generation inhibitors.<sup>93</sup> One proposed mechanism suggests AF may be related to on-target effects via reduction in PI3K-Akt pathway signaling, a downstream target of BTK (Table 1). Additionally, off-target inhibition of C-terminal Src kinase was the attributable arrhythmogenic mechanism for ibrutinib-associated AF, which is not affected by subsequent generations of BTK inhibitors.<sup>94</sup> Initially the arrhythmogenic potential of BTK inhibitors was not considered to be a class related effect; however, with increased experience and monitoring, rates of arrhythmias with these agents are also increasing. As such, it is imperative to better understand the mechanism of arrhythmogenesis to provide patients with better prevention and treatment strategies.

Atrial arrhythmias have typically considered a consequence of the underlying myocardial inflammation in patients treated with ICIs; however, more recent evidence suggests that the burden of arrhythmias exceeds that of myocarditis and that ICIs may also confer a direct arrhythmogenic effect.<sup>95,96</sup> In a study by Liu et al,<sup>97</sup> the expression of PD-1 on CD4<sup>+</sup> T cells in patients with AF is down-regulated when compared with healthy volunteers, and more so in those patients with persistent vs paroxysmal AF. As such, it appears that PD-1/PD-L1 down-regulation in AF patients promotes T cell function and may contribute to AF pathogenesis.

Although ventricular arrhythmias (VAs) are far less common than atrial arrhythmias in patients with cancer, their impact on morbidity and mortality can be substantial.<sup>98</sup> VAs may occur because of cancer therapy-induced QT prolongation<sup>99</sup> or new CTR-CVT, such as ischemia, or may be caused by a permanent arrhythmogenic substrate related to cancer.<sup>100</sup> Primary ventricular arrhythmias, unrelated to QT

prolongation, are an increasingly recognized phenomenon.<sup>87</sup> For patients treated with BTK inhibitors, this is an issue of particular interest. VA are a class-related effect and may be dose-dependent<sup>79,101-103</sup>; however, the mechanisms underlying VA in BTK inhibitors are not well understood and are essential for moving the field forward.

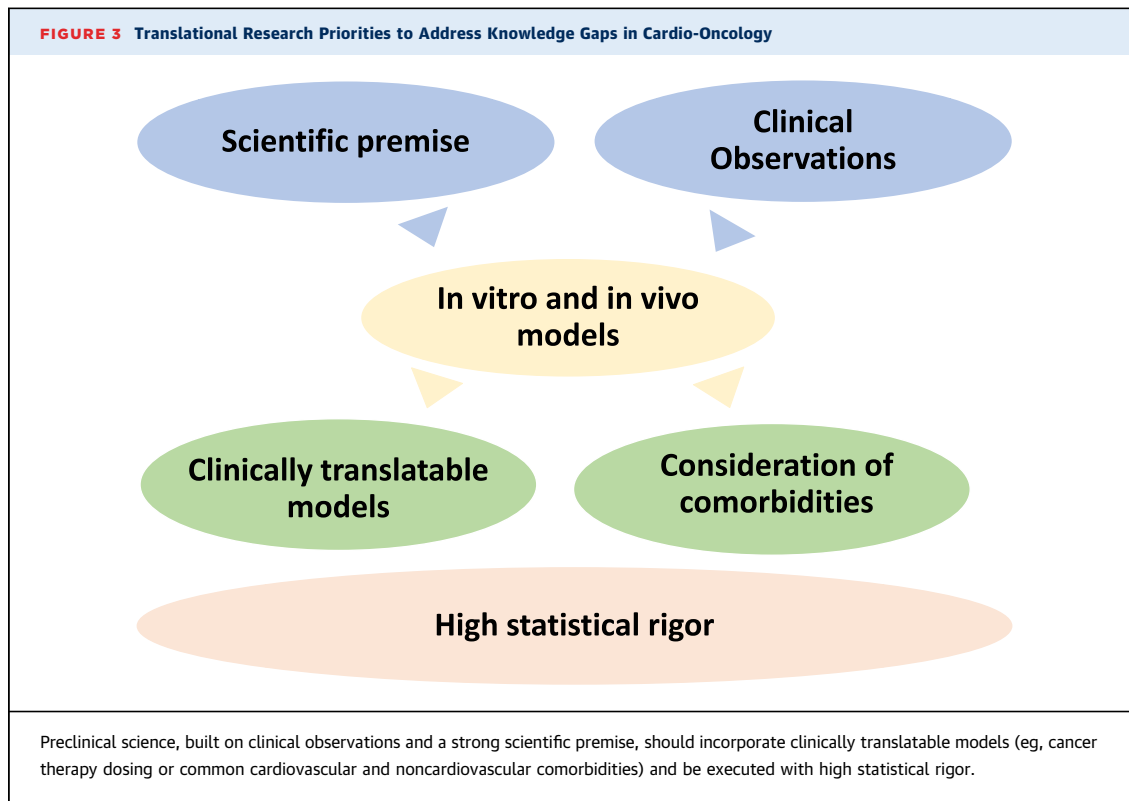
## THE INTERSECTION BETWEEN CANCER AND CVD

The basic and translational cardio-oncology field has broadened its scope to study other aspects of the interplay between CVD and cancer, including the pathways driving the development of both conditions as well as the potential tumorigenic effects of established CVD.<sup>104</sup> In the last decade, there has been mounting evidence that cancer and CVD often coincide. There are some obvious explanations, such as shared risk factors.<sup>105-107</sup> However, in the last years, it has also been noted that CV risk factors and CVD are associated with an increased risk of cancer.<sup>105,108,109</sup> Moreover, acquired somatic mutations in hematopoietic stem cells leading to clonal hematopoiesis are emerging as an area of increasing research interest in cardio-oncology due to their potential role as a shared risk factor for cancer and CVD.<sup>110</sup>

### THE ROLE OF CLONAL HEMATOPOIESIS IN THE INTERPLAY BETWEEN CANCER AND CVDs.

Clonal hematopoiesis occurs when an acquired mutation provides a selective advantage to the hematopoietic stem cell that carries it, leading to its progressive clonal expansion and the propagation of the mutation among the progeny of hematopoietic stem cells, including immune cells.<sup>111,112</sup> When clonal hematopoiesis is driven by mutations in genes related to hematological malignancies, and more than 4% of cells harbor the mutation, the condition is frequently referred to as clonal hematopoiesis of indeterminate potential (CHIP). Although closely linked to hematological cancer, CHIP has also emerged as a risk factor for CVD, as studies in humans and animal models suggest that certain CHIP mutations contribute to the development of CV disorders such as coronary artery disease, peripheral artery disease, and HF.<sup>111-113</sup> Elevated cytokine levels, dysfunctional macrophage activity, and activation of the inflammasome suggest that a vicious cycle of chronic inflammation and clonal expansion represents the major functional link.<sup>114</sup>

Two main lines of evidence indicate that CHIP may be particularly relevant in the setting of cardio-oncology. First, human sequencing studies suggest that CHIP mutations are common in patients with nonhematological cancers, with approximately 25%



of patients with solid tumors carrying CHIP mutations at diagnosis.<sup>113</sup> The high prevalence of CHIP, along with the close association between CHIP and CVD, suggests that CHIP may contribute to the heightened risk of CVD in these patients. Second, studies in humans and animal models indicate that cytotoxic cancer therapies, such as radiation or platinum-based drugs, facilitate the clonal expansion of hematopoietic cells carrying certain CHIP mutations. This phenomenon, referred to as cancer therapy-related clonal hematopoiesis, is mainly driven by mutations in DNA damage response genes such as TP53 or PPM1D, which are markedly over-represented in cancer patients treated with cytotoxic drugs.<sup>110,113</sup> Although still untested in large cohorts of non-hematological cancer patients, carrying mutations in these genes is associated with a higher risk of CVD in cancer-free individuals.<sup>115</sup> Experimental studies in mice also suggest that these mutations accelerate the development of CVD in various settings.<sup>115,116</sup>

Supporting the clinical relevance of CHIP in cancer patients, recent research shows that CHIP mutations, particularly those affecting TP53, are associated with a higher risk of developing CV complications in patients treated with intensive chemotherapy for acute myeloid leukemia.<sup>117</sup> However, sequencing studies in large populations of cancer patients/survivors will be

required to elucidate the interplay between cytotoxic therapies, CHIP and CVD in a comprehensive manner. Hagiwara et al<sup>118</sup> recently demonstrated that 15% of long-term survivors of childhood cancer have a mutation in clonal hematopoiesis genes, most of which are associated with exposure to alkylating agents, radiotherapy, and bleomycin.

Despite this need for further research, the field may evolve into the development of clinical programs that facilitate the identification of patients who carry CHIP mutations and may benefit from more intensive monitoring of CV health and hematological parameters. Supporting this possibility, some CHIP clinics have been established in institutions that routinely use next-generation sequencing panels to examine tumor and blood samples from cancer patients.<sup>119</sup> Such clinics may facilitate the multidisciplinary care required for the proper clinical management of patients with CHIP. However, it must be noted that there are currently no evidence-based interventions to mitigate the heightened CV risk associated with CHIP, either in the general population or in cancer patients, emphasizing the need for continuous research in the field.

**THE ROLE OF HF IN CANCER PATHOGENESIS.** There are strong signals from epidemiological cohorts that

patients with prevalent HF are prone to develop cancer.<sup>104,108,120</sup> This has been described in various cohorts in multiple countries, and signals are robust for lymphoma, colorectal cancer, urogenital cancer, and breast cancer. Also, subclinical heart disease, for example, as detected by N-terminal pro-B-type natriuretic peptide<sup>121</sup> or abnormal stress echocardiography,<sup>122</sup> is associated with higher rates of incident cancer. The underlying mechanisms have been studied and described in some detail.<sup>107,123</sup> HF is a systemic disorder associated with numerous pathophysiological changes that could explain this relation. It has been shown in experimental settings that circulating factors associated with and elevated in HF have pro-oncogenic effects.<sup>121</sup> Moreover, immunological changes that are commonly observed in HF have been linked to tumor growth. Some of these changes are relevant for circulating immune cells, whereas others may give rise to CHIP mutations in the bone marrow, and both are linked to incident HF and cancer. Inflammatory factors that are well known to be increased in HF are causative for incident cancer. Finally, several metabolic changes in heart disease may be a liability for tumor growth.<sup>34</sup>

### RESEARCH PRIORITIES AND GAPS IN KNOWLEDGE

Further basic and translational research is needed to provide a better understanding of both the underlying mechanisms linking CVD and cancer and the pathogenesis of CTR-CVT, and potentially actionable pathways for therapeutic discovery. For example, there remain important questions related to whether senescent CV cells are long-lived, if and how they affect contiguous cells, and whether they are cleared by the immune system. Translational research on the role of genetics is required to refine CTR-CVT risk stratification scores. Despite the recognition of the increased risk of arrhythmias, a comprehensive understanding of the arrhythmogenesis of cancer therapies remains incomplete and represents an area of opportunity to advance the field.

Moreover, several areas of translational research must be improved to successfully bridge knowledge gaps in cardio-oncology (Figure 3): the first is creation of reproducible and relevant models including genetically modified animals and various cardiac cell types differentiated from patient-derived human induced pluripotent stem cells (iPSCs), as well as bioengineered 3D human CV tissues and organoids.<sup>124-126</sup> The conjunction of human iPSCs CV phenotypes with bioengineered-based strategies can provide important translational knowledge. Although seminal work has shown the predictive capacity of

human cardiomyocytes derived from iPSCs,<sup>127,128</sup> organoids<sup>129</sup> can generate small replicas of the tissue of choice and have been used to model the enhanced sensitivity of the human ischemic heart to AIC.<sup>130</sup> Recent technical advances,<sup>131</sup> including 3D bioprinting, can provide potential strategies to generate human-engineered myocardium ex vivo, at different scales and with the concomitant presence of different CV phenotypes.<sup>132,133</sup> Microfabrication technologies have also proven to be valuable by generating microfluidic devices relying on extremely low amounts of cells, materials, and drugs while incorporating sensing features.<sup>134</sup> Additional scientific needs include: 1) accurate recapitulation in animal models of the route of administration, the dosing, and the frequency and duration of cancer treatment regimens<sup>135</sup>; 2) incorporation of statistical rigor and adequate power in preclinical studies; and 3) a strong scientific premise and design, including an awareness of species-specific differences in immunogenicity and drug-binding targets.<sup>136,137</sup>

In addition to the considerations noted previously, it is important to consider the impact of CV comorbidities, such as coronary artery disease, hypertension, obesity, dyslipidemia, and diabetes,<sup>138</sup> that can influence the pathophysiology of cancer and CVD. These comorbidities share many risk factors (ie, smoking, inactivity, poor nutrition, and psychosocial stress) and pathophysiologic processes (ie, alterations in inflammation and in oxidative-nitrosative stress) that can also foster tumorigenesis. Therefore, having preclinical models that can broadly reproduce many aspects of modern human lifestyles will offer the best preclinical investigative platform that can facilitate the translation of basic research findings to carefully designed clinical trials.

We have summarized in this review many of the molecular events and pathophysiological mechanisms that contribute to the onset of CTR-CVT following cancer therapies; however, many aspects in patients remain unappreciated, especially pertaining to the impact of social determinants of health on CVD.<sup>139</sup> For example, chronic psychosocial stress (CPS) involves experiences and exposure to life challenges (early-life adversities, low socioeconomic status, caregiving, discrimination, low social support, etc.) to which an individual faces difficulty in adapting or coping.<sup>139</sup> CPS has been recently found to correlate with increases in morbidity and mortality and early onset of CVD.<sup>140</sup> Extensive and longstanding literature has been published describing the association between chronic stress and CVD risk, including progression from stage A (at risk for developing HF) to more advanced stages B through

D.<sup>141</sup> While the progression to more advanced stages of HF related to CPS often occurs over several years in the setting of conventional CVD risk factors, the presence of a cancer diagnosis and its treatment provide an acute cardiotoxic event that accelerates the process.

Sex-based, racial, and ethnic disparities play a key role in the overall outcomes in the field of cardio-oncology. To this end, greater efforts should be made by the scientific community to encourage and support clinical trials that improve the representation of women and racial/ethnic minorities, who unfortunately often have a higher inherent propensity to multiple comorbidities.<sup>142,143</sup> In addition, knowledge of the impact of individual genetic predisposition on the risk of developing cancer and CTR-CVT remains in its infancy for meaningful use as a risk prediction tool. Opportunities for improvement will become available from more broad studies that employ genomics to predict and potentially prevent cancer therapy-associated cardiotoxicity, enabling clinicians to tailor cancer treatment based on individual susceptibility for developing CTR-CVT. Such risk prediction models have the potential to be further applied to combination models utilizing clinical, biomarker, genetic and epigenetic data.

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**KEY WORDS** anthracyclines, basic research, cancer, cardiac arrhythmias, cardio-oncology, cardiotoxicity, chemotherapy, immunotherapy, translational research