

# The Potential Role of Aerobic Exercise to Modulate Cardiotoxicity of Molecularly Targeted Cancer Therapeutics

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Disclosures of potential conflicts of interest may be found at the end of this article.

**Key Words.** Exercise • Cardiotoxicity • Molecular therapeutics • Solid malignancies

## ABSTRACT

Molecularly targeted therapeutics (MTT) are the future of cancer systemic therapy. They have already moved from palliative therapy for advanced solid malignancies into the setting of curative-intent treatment for early-stage disease. Cardiotoxicity is a frequent and potentially serious adverse complication of some targeted therapies, leading to a broad range of potentially life-threatening complications, therapy discontinuation, and poor quality of life. Low-cost pleiotropic interventions are therefore urgently required to effectively prevent and/or treat MTT-induced cardiotoxicity. Aerobic exercise therapy has the unique capacity to modulate, without toxicity,

multiple gene expression pathways in several organ systems, including a plethora of cardiac-specific molecular and cell-signaling pathways implicated in MTT-induced cardiac toxicity. In this review, we examine the molecular signaling of antiangiogenic and HER2-directed therapies that may underpin cardiac toxicity and the hypothesized molecular mechanisms underlying the cardioprotective properties of aerobic exercise. It is hoped that this knowledge can be used to maximize the benefits of small molecule inhibitors, while minimizing cardiac damage in patients with solid malignancies. *The Oncologist* 2013;18:221–231

**Implications for Practice:** Cardiotoxicity, a frequent and devastating adverse complication of some molecularly targeted therapies (MTTs), can lead to potentially life-threatening cardiovascular complications, therapy discontinuation, and poor quality of life. In non-cancer patients with left ventricular dysfunction and heart failure, aerobic exercise is one of the mainstay clinical interventions for the prevention and treatment of cardiovascular disease. However, few studies have investigated the efficacy of aerobic exercise in the prevention and/or treatment of MTT-induced cardiac injury. This topic is of particular importance because cardiac function is a strong predictor of cardiovascular and all-cause mortality, quality of life, and fatigue, and maybe even cancer-specific mortality. Here, we provide a comprehensive overview of cardiac molecular and cell-signaling pathways specific to MTT-induced cardiac toxicity. This review also outlines many pertinent aerobic exercise-induced molecular signaling pathways that may uniquely prevent and/or treat MTT cardiac injury. Overall, information presented in this review provides critical information for basic scientists, clinicians, and exercise oncology researchers who are investigating the application of exercise in cancer control.

## INTRODUCTION

The emergence of molecularly targeted therapeutics (MTTs) has revolutionized the management of solid malignancies. Antiangiogenic and human epidermal growth factor receptor 2 (HER2)-directed MTTs are approved by the U.S. Food and Drug Administration (FDA) for the treatment of several solid malignancies, either as monotherapy or in combination with standard chemotherapy [1, 2]. The biologic selectivities of these drugs were expected to substantially reduce off-target toxicity, although it is now apparent that MTTs cause adverse cardiovascular consequences, such as hypertension and progressive left ventricular (LV) dysfunction, ultimately leading to symptomatic heart failure.

Several excellent reviews have described the biologic and molecular mechanisms underlying MTT-induced cardiotoxicity and risk for cardiotoxicity [1–8]; however, comparably little attention has been focused on strategies to prevent and/or mitigate anticipated injury. MTTs target multiple cellular pathways including highly coordinated myocardial molecular signaling. Pleiotropic interventions will therefore be required to effectively prevent and/or treat MTT-induced cardiotoxicity. Aerobic exercise therapy has the unique capacity to modulate, without toxicity, multiple gene expression pathways in several organ systems, including a plethora of cardiac-specific molecular and cell-signaling pathways implicated in MTT-in-

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duced cardiac toxicity. Here we review molecular signaling of antiangiogenic and HER2-directed therapies that may underpin cardiac toxicity and the hypothesized cardioprotective properties of aerobic exercise.

### THE BIOLOGY OF TYROSINE KINASES

Receptor tyrosine kinases (RTKs) are enzymes that act as critical mediators of normal cellular signal transduction and regulate diverse cellular processes including cell cycle progression, metabolism, transcription, and apoptosis (reviewed extensively elsewhere [9, 10]). All RTKs are embedded in plasma membranes and consist of an extracellular ligand-binding domain and an intracellular kinase domain. RTKs are not only key regulators of normal cellular processes, but they also are central to malignant transformation and tumor proliferation when constitutively activated via gene amplification, overexpression, or mutations [11]. Strategies for the prevention or interception of deregulated RTK signaling include the development of selective agents that target either the extracellular ligand-binding domain or the intracellular tyrosine kinase binding region [2, 4]. Monoclonal antibodies (mAbs) are designed to inhibit kinase activation by binding to the extracellular portion of RTKs or by binding to growth factor ligands that activate RTKs. Mechanistically, anti-RTK mAbs block the ligand-receptor interaction, thus inhibiting activation of the tyrosine kinase domain, and/or induce downregulation of receptor expression [12]. In contrast, small-molecule tyrosine kinase inhibitors (TKIs) bind to the intracellular portion of RTKs, thereby inhibiting the phosphorylation of downstream substrates.

### MECHANISMS OF HER2-DIRECTED THERAPY CARDIAC INJURY

Overexpression and/or gene amplification of the RTK HER2 (also known as ErbB2) is present in approximately 20% of women with breast cancer [13], as well as approximately 10% and 5% of patients with non-small cell lung cancer, [14] and gastric cancer, respectively [15]. Randomized trials demonstrate that HER2-directed agents cause significant improvements in disease-free survival and overall survival among women with early [16, 17] and metastatic [18] HER2-positive breast cancer. However, trastuzumab (the first FDA-approved HER2-directed mAb) and pertuzumab (a newer mAb in phase III testing) are associated with cardiac toxicity (Table 1).

### HER2-DIRECTED THERAPY INHIBITION OF CARDIAC MOLECULAR SIGNALING

We focus here on the putative role of ErbB2 and transforming growth factor  $\beta$  (TGF $\beta$ ) signaling as major pathways mediating anti-ErbB2 cardiotoxicity (Fig. 1).

#### ErbB2

ErbB2 belongs to the family of human epidermal growth factor (EGF) receptors comprised of the EGF receptor (ErbB1), ErbB2, ErbB3, and ErbB4 [19]. Hyperactivation of the ErbB2/ErbB3/PI3K complex in tumor cells leads to upregulation of the phosphatidylinositol 3-kinase (PI3K)-Akt pathways resulting in cellular proliferation [20], increased mitogen-activated protein kinase (MAPK) activity causing protein hypertrophy [21], and reduced cytoskeleton via CCAAT/enhancer-binding protein

(C/EBP $\beta$ ) [22]. The antiproliferative activity of HER2-directed therapy is therefore based on disruption of the ErbB2-ErbB3 complex in tumor cells, thus reducing intracellular Akt activity [19, 23] and MAPK signaling [24]. Conversely, HER2-directed therapy dramatically alters cardiomyocyte function and/or survival via inhibition of Nrg1/ErbB/Akt signaling.

The essential role of ErbB2 signaling for cardiomyocyte proliferation was first revealed through germline deletion of ErbB2 receptors in mice, which proved lethal in mid gestation with failure of proper ventricle formation [25]. Transgenic mice with cardiac-specific deletion of ErbB2 after cardiac development survive embryogenesis [25] but develop progressive cardiomyopathy in adulthood [16]. In the healthy heart, neuregulin-1 $\beta$  (Nrg1) is released by endocardial and myocardial endothelial microvascular cells and binds to ErbB4 on cardiomyocytes leading to activation of the ErbB2/ErbB4/PI3K/Akt complex. HER2-directed agents inhibit Nrg1 release [26] and significantly decrease both total and phosphorylated Akt in neonatal rat cardiomyocytes [27], thus potentially limiting cell growth, glucose uptake, and protein regulation [28–30] and ultimately triggering the progression of heart failure [31].

#### TGF $\beta$

During carcinogenesis, TGF $\beta$  signaling initially prevents malignant progression via the small mother against decapentaplegic (Smad) pathway [32]. Eventually, malignant cells overexpressing ErbB2 circumvent the growth-suppressive effects of TGF $\beta$  by downregulating TGF $\beta$  receptors or altering downstream pathways [22]. In the heart, TGF $\beta$  regulates ventricular remodeling (cardiomyocyte hypertrophy) via activation of the Smad/3 and 4 complexes and matrix metalloproteinases [33]. Inhibition of ErbB2 signaling with trastuzumab also activates TGF $\beta$  and C/EBP $\beta$  signaling in breast cancer cells [22]. Whether trastuzumab induces TGF $\beta$  and C/EBP $\beta$  signaling in cardiomyocytes is unknown; however, increased cardiac TGF $\beta$  and C/EBP $\beta$  expression results in pathological remodeling [34].

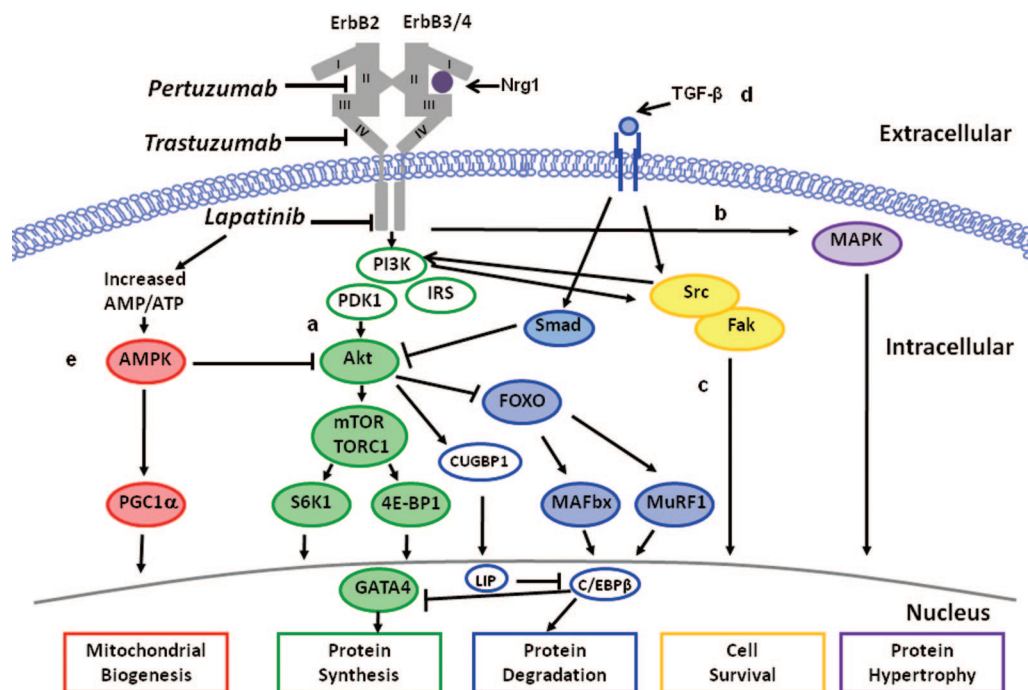
### AEROBIC EXERCISE-INDUCED CARDIOPROTECTION FROM HER2-DIRECTED AGENTS

Figure 2 outlines the modulation of ErbB and TGF $\beta$  signaling through aerobic exercise. The cardioprotective properties of increased Nrg1/ErbB signaling are well described [26, 29]. For example, drug-induced enhancement of myocardial Nrg1/ErbB signaling significantly improved both cardiac performance and survival in four different rodent models of LV failure [31] and induced differentiated cardiomyocytes to proliferate [35]. In vitro studies in isolated cardiac endothelial cells (the main source of Nrg1 in the heart) show that mechanical strain increases endothelial Nrg1 synthesis and release [36], whereas Nrg1 release is directly inhibited by angiotensin II and adrenergic agonists [37]. Aerobic exercise increases endocardial mechanical strain [38] with a concomitant reduction in angiotensin II [39]. Interestingly, Lebrasseur et al. [40] found that resistance or aerobic exercise increased proteolytic processing of mature Nrg1 transmembrane protein to soluble Nrg1 in rat skeletal muscle. Thus, we contend that increased Nrg1 synthesis in the ventricle in response to exercise-induced mechanical stress will evoke suppression of neurohormonal factors, leading to cardioprotection.

**Table 1.** Incidence of cardiotoxicity in HER2-directed and angiogenesis inhibitor clinical trials

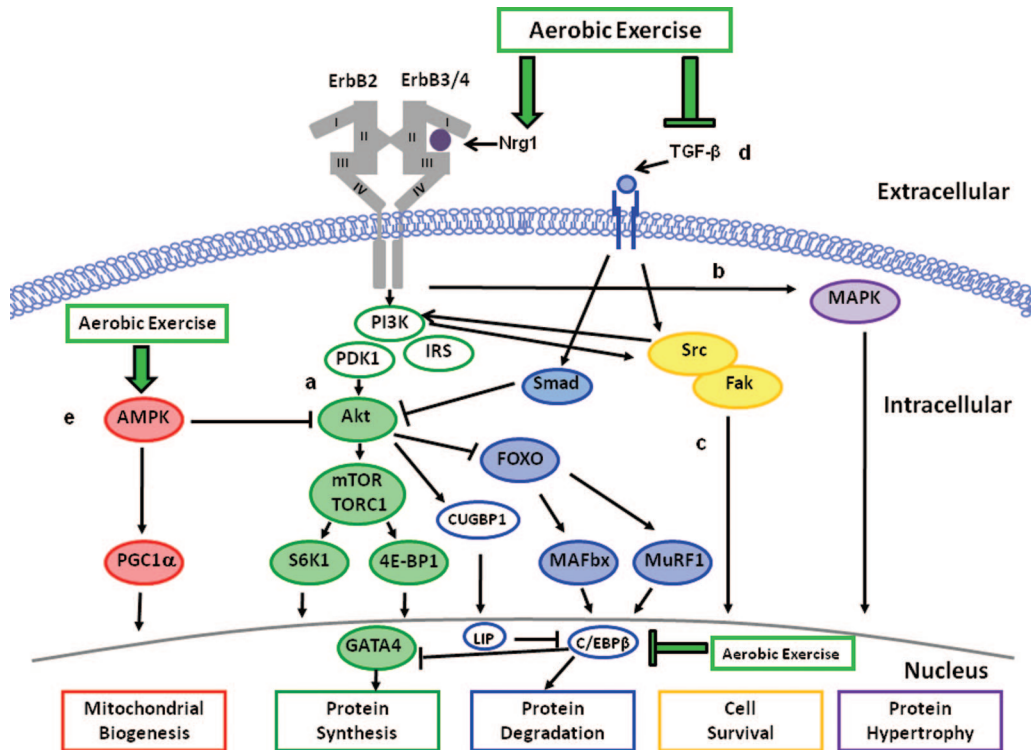
Agent	Class	Target	Malignancy	Heart failure	Subclinical decline in ejection fraction ( $\geq 10\%$ )	Hypertension ( $\geq$ grade I)
<b>HER2-directed</b>						
Trastuzumab	mAb	ErbB2	ErbB2+ breast cancer, MGC (phase III)	1.7%–4% (early) [89, 90] 8.3%–20% (advanced) [16, 91–95]]	2.1%–14% (early) [89] 16%–18% (advanced) [16, 92–96]	NA
Lapatinib	TKI	ErbB1, ErbB2	ErbB2+ breast cancer, NSCLC (phase II)	0.2% (advanced) [97]	1.4%–5% (advanced) [97, 98]	4% (advanced) [99]
Pertuzumab	mAb	ErbB2	ErbB2+ breast cancer (phase II)	9% (advanced) [100]	1.2%–54% (advanced) [91, 100–102]	NA
<b>Angiogenesis inhibitors</b>						
Bevacizumab	mAb	VEGF	RCC, NSCLC, glioblastoma, CRC, breast	2.2%–3% (advanced) [103, 104]	2%–14% (early) [105–107] 0.8%–23.5% (advanced) [103, 104, 108]]	2%–12% (early) [106, 109] 17.9%–35% (advanced) [103, 104, 110]
Ramucirumab	mAb	VEGFR	RCC (phase II), breast (phase III)	NA	NA	13.5% (advanced) [111]
Sunitinib	TKI	VEGFR 1–3, c-kit, PDGFR	RCC, GIST	2.7%–11% (advanced) [62, 112]	4%–47% (advanced) [62, 112]	5%–47% (advanced) [62, 113, 114]
Sorafenib	TKI	VEGFR 2, PDGFR, Raf1	RCC, melanoma	NA	18.9% (advanced) [115]	7.2%–43% (advanced) [116–119]
Pazopanib	TKI	VEGFR, c-kit, PDGFR	RCC, breast (phase II)	NA	NA	14%–40% (advanced) [120, 121]
Cediranib	TKI	VEGFR 1–3, c-kit	RCC, breast, and liver (all phase II)	NA	NA	21%–81% (advanced) [122–124]
Vandetanib	TKI	VEGFR, EGFR	MTC, NSCLC (phase III), mHRPC (phase II)	NA	NA	14%–29% (advanced) [125–127]
Motesanib	TKI	VEGFR, PDGFR, c-kit	MBC (Phase II)	NA	9% (advanced) [128]	12% (advanced) [128]
Axitinib	TKI	VEGFR, PDGFR, c-kit	Pancreatic, (phase III), MBC (phase II)	NA	1.8% (advanced) [129]	7%–27.9% (advanced) [129, 130]

Abbreviations: CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; HF, heart failure; mAb, monoclonal antibody; MBC, metastatic breast cancer; MGC, metastatic gastric cancer; mHRPC, metastatic hormone-refractory prostate cancer; MTC, metastatic medullary thyroid cancer, NA, not available; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.



**Figure 1.** Mechanisms underlying HER2-directed therapy cardiotoxicity. Inhibition of ErbB receptors with HER2-directed therapies impacts numerous signaling pathways resulting in suppression of myofilament protein synthesis via the PI3K-Akt pathway (pathway A), suppression of protein hypertrophy via the MAPK pathway (pathway B), suppression of cell survival via Src/Fak pathway (pathway C), suppression of myofilament protein synthesis and upregulation of protein degradation via TGF-β1 and C/EBPβ signaling (pathway D), and alterations in cardiac energy metabolism via downregulation of AMPK (pathway E).

Abbreviations: AMPK, AMP-activated protein kinase; C/EBPβ, CCAAT/enhancer binding protein; Fak, focal adhesion kinase; MAPK, mitogen-activated protein kinase; Nrg1, Neuregulin-1β; PI3K, phosphatidylinositol 3-kinase; Smad, small mother against decapentaple β; TGFβ, transforming growth factor β.



**Figure 2.** Mechanisms underlying modulation of HER2-directed therapy cardiotoxicity through aerobic exercise. Aerobic exercise induces cardioprotection via upregulation of Nrg1 synthesis and release, thus activating pathways A–C; inhibition of TGF- $\beta$ 1 and C/EBP $\beta$  signaling and upregulation of GATA4 (pathway D); and activation of AMPK expression (pathway E).

Abbreviations: AMPK, AMP-activated protein kinase; C/EBP $\beta$ , CCAAT/enhancer binding protein; Fak, focal adhesion kinase; MAPK, mitogen-activated protein kinase; Nrg1, Neuregulin-1 $\beta$ ; PI3K, phosphatidylinositol 3-kinase; Smad, small mother against decapentaplegic; TGF $\beta$ , transforming growth factor  $\beta$ .

Aerobic exercise may also modulate a number of myocardial intracellular processes, thus overcoming HER2-inhibitor receptor blockade. McMullen et al. [41, 42] elegantly demonstrated that exercise increases myocardial Akt, with subsequent attenuation of pathologic LV remodeling, fibrosis, and protein degradation. Whether similar processes occur during administration of targeted cancer therapeutics has not been investigated; however, exercise training increases myocardial PI3K activity [43] with an effective reduction in infarct size and cardiomyocyte apoptosis in rats subjected to myocardial ischemia reperfusion [44], as well as improves lifespan in mice with dilated cardiomyopathy [45]. These investigations provide evidence for the protective effects of PI3K/Akt signaling in settings of targeted therapy-induced cardiac stress.

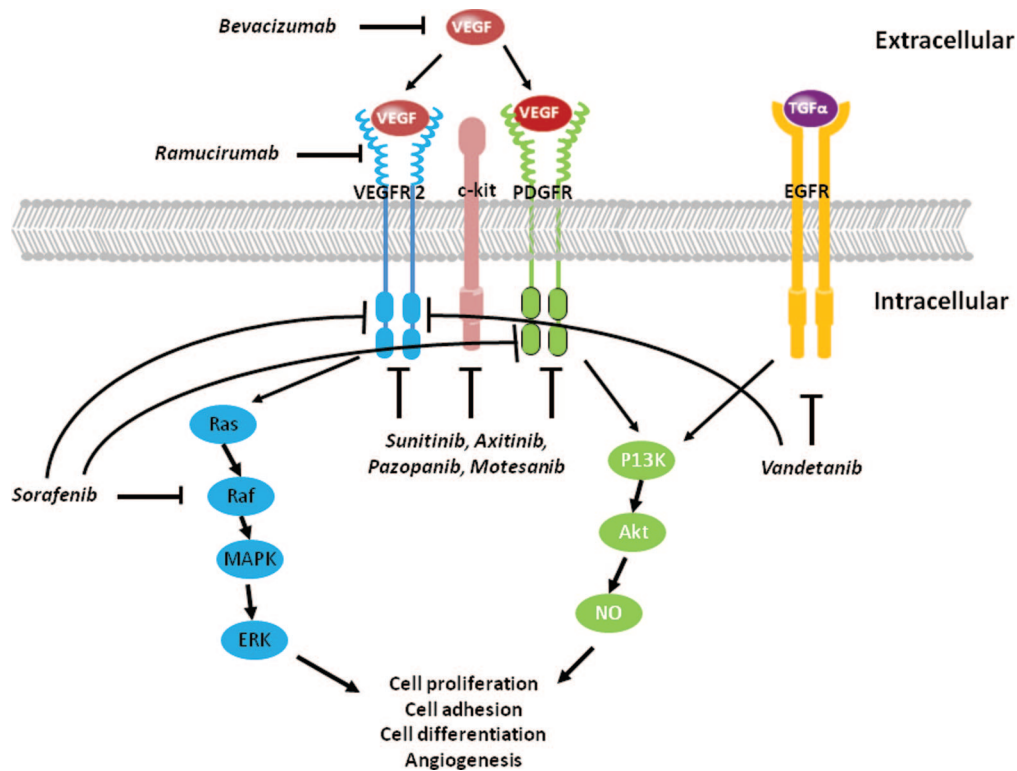
Finally, aerobic exercise inhibits TGF $\beta$  and C/EBP $\beta$  signaling to effectively prevent and/or attenuate pathological cardiac hypertrophy in various mouse models. For instance, aerobic exercise attenuates isoprenaline-induced increases in myocardial levels of TGF $\beta$  and C/EBP $\beta$  mRNA, with parallel inhibition of pathological myocardial hypertrophy [34]. Exercise-induced reduction of TGF $\beta$  and C/EBP $\beta$  expression, in turn, increases both cardiomyocyte size and cell division resulting in physiological hypertrophy [34]. Interestingly, exercise or experimental downregulation of C/EBP $\beta$  expression has also been shown to upregulate GATA4, a regulator of cardiomyocyte proliferation during myocardial regeneration in zebrafish [46]. These data indicate that aerobic exercise inhib-

its TGF- $\beta$ 1 and C/EBP $\beta$  expression and upregulates GATA4, ultimately leading to modulation of protein degradation and upregulation of protein synthesis.

In the only human study examining MTTs and exercise to date, our group found that 16 weeks of supervised aerobic training failed to attenuate trastuzumab-induced LV dilation and reduced ejection fraction in patients with HER2-positive operable breast cancer [47]. This observation is in contrast to work by us and others demonstrating that aerobic training can reverse LV remodeling in patients with stable heart failure [48, 49]. These discordant findings were likely due to the fact that participants in the trastuzumab trial attended an insufficient number of training sessions and did not receive a high enough training stimulus to achieve beneficial adaptations.

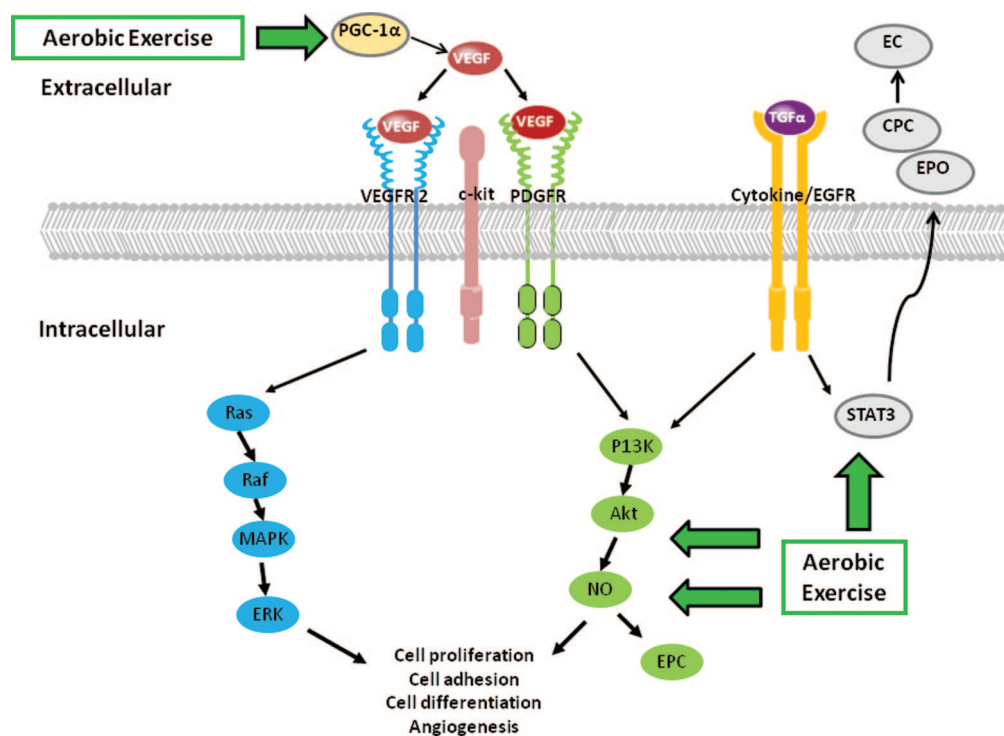
### MECHANISMS OF ANGIOGENESIS INHIBITION DIRECTED THERAPY-INDUCED CARDIAC INJURY

Angiogenesis, the formation of new capillary blood vessels, is predominantly regulated via vascular endothelial growth factor (VEGF) and is fundamental for both physiologic and pathologic processes (reviewed extensively in references [50, 51]). VEGF inhibition, alone or in combination with conventional chemotherapy, is now approved by the FDA as first-line therapy for a broad range of advanced solid malignancies [50]. The incidence and magnitude of cardiac injury with multitargeted TKIs is particularly high, whereas treatment with monoclonal mAbs appears to cause comparably less injury (Table 1).



**Figure 3.** Mechanisms underlying anti-angiogenic therapy cardiotoxicity. Inhibition of VEGF signaling with tyrosine kinase inhibitor-directed therapies impacts numerous signaling pathways resulting in inhibition of angiogenesis, and protein synthesis and degradation via the PI3K-Akt-NO pathway; and inhibition of cell proliferation and differentiation via the MAPK-ERK pathway. Monoclonal inhibitors include bevacizumab and ramucirumab; multikinase inhibitors include sunitinib, axitinib, pazopanib, motesanib, vandetanib, and sorafenib.

Abbreviations: MAPK, mitogen-activated protein kinase; NO, nitric oxide; PI3K, phosphatidylinositol 3-kinase; VEGF, vascular endothelial growth factor.



**Figure 4.** Mechanisms underlying anti-angiogenic therapy cardiotoxicity through aerobic exercise. Aerobic exercise induces cardioprotection via upregulation of VEGF expression; a nitric oxide-dependant increase in endothelial progenitor cells; and activation of STAT3 resulting in erythropoietin secretion and binding to cardiac progenitor cells, causing differentiation into endothelial cells.

Abbreviations: CPC, cardiac progenitor cells; MAPK, mitogen-activated protein kinase; NO, nitric oxide; PI3K, phosphatidylinositol 3-kinase; EC, endothelial cell; EPO, erythropoietin; VEGF, vascular endothelial growth factor.

**Table 2.** Potential future research directions to assess modulation of molecularly targeted therapeutic cardiotoxicity with aerobic exercise**Underlying mechanisms of MTT-related cardiotoxicity**

- Elucidate the specific actions of HER2-inhibitors on myocardial Nrg1 release and ErbB downstream pathways
- Examine whether anti HER2 agents upregulate myocardial TGF $\beta$  and C/EBP $\beta$  signaling and consequently downregulate GATA4 signaling
- Determine the effects of anti-angiogenic agents on myocardial and vascular VEGF expression and VEGFR signaling
- Examine the impact of MTT on other tissues, such as skeletal muscle
- Delineate the longitudinal cardiac consequences in patients receiving MTTs

**Underlying mechanisms of aerobic exercise-induced cardioprotection**

- Perform translational exercise-cardiotoxicity studies to elucidate whether aerobic exercise:
  - Upregulates myocardial Nrg1 and PGC1- $\alpha$  expression
  - Decreases myocardial TGF $\beta$  and C/EBP $\beta$  signaling and increases GATA4 signaling
  - Increases myocardial downstream effector signaling (e.g., endothelial progenitor cell, cardiac progenitor cell)
- Evaluate aerobic exercise intensity required to prevent/treat cardiotoxicity
- Establish most effective timing (before, during, or following therapy) to perform aerobic exercise training
- Examine whether integrating resistance and aerobic exercise can protect peripheral as well as central factors
- Monitor antineoplastic indices during aerobic exercise training to ensure antineoplastic goals of MTTs are met

**Potential Research Models**

- Neonatal rat ventricular myocytes  
Model should be used to examine molecular mechanisms underlying cardiomyocyte hypertrophy, stress, and failure as a result of MTT-induced toxicity
- Zebrafish  
Ideal for cardiotoxicity-aerobic exercise studies given that the underlying cardiac development, patterning, genes, functions, and disease characteristics are similar to humans, and has recently been established as novel exercise model
- Knockout/transgenic rodents  
Genetically downregulated or upregulated pathways in rodents should be used to establish exercise-induced cardioprotective signaling pathways
- Patient populations  
Adequately powered multicenter RCTs with appropriate cardiac endpoints are required to evaluate the relative efficacy of aerobic exercise training to prevent/treat cardiotoxicity

Abbreviations: MTT, molecularly targeted therapeutic; RCT, randomized controlled trial.

### ANTIANGIOGENIC THERAPY INHIBITION OF CARDIAC AND VASCULAR MOLECULAR SIGNALING

Putative pathways underlying the cardiotoxic properties of monoclonal and multitargeted agents are illustrated in Figure 3.

#### Monoclonal Inhibition

Circulating VEGF binds to its receptors platelet derived growth factor receptor (PDGFR), VEGFR1 (also known as Flt-1), and VEGFR2 (also known as Flk-1 or KDR). Monoclonal therapeutic inhibition of the VEGF pathway is achieved via antibodies targeting a VEGF ligand (e.g., bevacizumab binding to VEGF), decoy receptors for VEGF (e.g., aflibercept), or antibodies targeting the extracellular domain of VEGFRs (e.g., ramucirumab binding to VEGFR2), thus limiting endothelial cell sprouting, migration, proliferation, and tube formation [52]. Of importance, suppression of VEGF/VEGFR signaling causes pathological alterations in cardiac and vascular tissues [53, 54]. For instance, global VEGF knockout in rodents causes embryonic lethality [55], whereas postnatal murine downregulation of myocardial VEGF expression initiates a cascade of events leading to progressive diastolic and systolic LV dysfunction [43]. Cardiac-specific VEGF knockout mice display abnormal cardiac muscle capillarity number [56] and classic features

of cardiomyopathy (i.e., reduced cardiac output, fractional shortening, decreased dP/dt) [57]. Physiologically, cardiomyocyte binding of VEGF activates Akt, initiating signaling pathways regulating nitric oxide (NO) synthase, angiogenesis, and progenitor cell differentiation into cardiomyocytes [58–60]. Anti-VEGF agents likely inhibit vascular NO release, thus promoting vasoconstriction, increased peripheral resistance, and increased blood pressure, [53], as well as limiting endothelial progenitor cell (EPC) [59] and cardiac progenitor cell (CPC) [61] development and ultimately restraining cardiomyocyte differentiation. Unfortunately, limited clinical data and mechanistic information are available to substantiate these potential pathways.

#### Multitargeted Inhibition

Multitargeted TKIs may lead to a greater incidence and magnitude of cardiotoxicity due to binding of multiple proteins and/or downstream pathways (Table 1). For instance, Chu et al. [62] demonstrated that sunitinib, which targets VEGFR1–3, c-kit, and PDGFR, leads to profound structural and functional abnormalities in cardiomyocyte mitochondria, leading to a decrease in ATP production. In addition, blockade of VEGFR2 with TKIs decreases endothelial nitric oxide synthase (eNOS)

**Table 3.** Future challenges for research investigating the effects of and mechanisms of aerobic exercise in MTT-induced cardiac toxicity**Preclinical studies**

- Many of the available MTTs are humanized agents. Thus, whether the cardiotoxic mechanistic action of these agents is the same in rodent models is questionable. Investigators should strive to test the murine versions of selected agents whenever possible.
- Within available rodent models, strains have inherently different exercise capacities which may also contribute to distinct cardiac adaptations to exercise training [131, 132]. These disparities may account for discordant findings between investigations.
- Cardio-oncology investigations often use either male or female animals only. However, there are sexually dimorphic cardiovascular adaptations to exercise training in both mice and rats [133–135], which limits mechanistic implications for either male or female patients.
- Mechanistic investigations are often conducted in animals that are young and otherwise healthy. In contrast, cancer patients are typically older with the presence of concomitant comorbidities which exacerbate treatment-induced cardiotoxicity [136].
- No threshold of exercise intensity for inducing observable cardiac adaptations has been identified in any clinical disease [137]. Most animal cardio-oncology exercise studies utilize continuous treadmill running characterized by fixed speed, inclination, and duration [138]. Elucidation of the dose-response relationship of exercise on cardiac function in rodents and how this translates to the clinical setting are urgently required.

**Clinical studies**

- Overt cardiac events are relatively uncommon in cancer patients receiving MTTs; asymptomatic events are more frequent. Nevertheless, given the current event rate with standard detection techniques, large trials will be required to examine the effect of exercise on reducing the event rate. This issue could be somewhat addressed using biomarker enriched trials in which patients only at high-risk of events are recruited. Established biomarkers to identify such high-risk patients are not yet available but currently under investigation [8].
- Cancer patients typically receive MTTs in combination with other agents, particularly cytotoxic agents, possibly confounding the effects of exercise on MTT-induced cardiotoxicity [139], making interpretation challenging.
- Although numerous studies have demonstrated excellent adherence and safety profiles with moderate intensity exercise [140], no studies to date have examined whether patients receiving MTTs can successfully adhere or tolerate structured exercise training prescriptions incorporating moderate or high intensity training.
- The clinical impact of exercise on the antitumor efficacy of MTTs in patients is unknown. Investigations determining the interaction between exercise and tumor outcomes are critical in both rodent and human studies [141].

Abbreviations: MTT, molecularly targeted therapeutic.

activation and NO release, promoting vasoconstriction and increased blood pressure [63]. Of significance, the combined cardiac and vascular injury may enhance the severity of cardiac injury. Izumiya et al. [64] demonstrated that VEGF inhibition contributed to progression from compensatory cardiac hypertrophy to LV failure under hypertensive conditions. Chronic hypertension ultimately leads to a compensatory increase in myocardial muscle mass to maintain normal cardiac output [65]. In both hypertensive and pre-hypertensive states, there is slow but steady hypertrophy of the LV [66], leading to a decreased ability to relax initially during exercise and subsequently at rest [67]. Whether concentric remodeling occurs in patients receiving antiangiogenic therapies has not been investigated.

#### **AEROBIC EXERCISE-INDUCED CARDIOPROTECTION FROM ANGIOGENESIS INHIBITION**

Aerobic exercise-induced increase in vascular and myocardial VEGF/VEGFR signaling may prevent/treat antiangiogenesis-induced cardiotoxicity. These conceptual pathways are illustrated in Figure 4. Upregulation of myocardial VEGF using naked DNA gene therapy enhances capillary density and decreases endothelial cell and cardiomyocyte apoptosis, leading to improvements in cardiac function in a diabetic rat model [43]. Aerobic exercise augments the aging-induced [68] and infarct-induced [69] decrease in VEGF mRNA and protein expression in murine cardiac tissue. Increased VEGF expression occurs via upstream peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) through the transcription factor estrogen-related receptor- $\alpha$  and is independent of

hypoxia-inducible factor 1 $\alpha$ -induced VEGF expression [70]. Aerobic exercise rapidly upregulates PGC-1 $\alpha$  mRNA in skeletal muscle, with a concomitant increase in mitochondrial content leading to resistance to fatigue and a higher number of oxidative fibers [71]. Thus, because PGC-1 $\alpha$  is obligatory for the exercise-induced increase in VEGF expression, it is evident that PGC-1 $\alpha$  has a particularly prominent role in regulating training-induced VEGF expression.

An additional putative cardioprotective mechanism is exercise-induced augmentation in the production and mobilization of CPCs and EPCs via acute increases in interleukin-6 (IL-6), NO, and VEGF-dependent mechanisms [72–74]. Aerobic

Aerobic exercise rapidly upregulates PGC-1 $\alpha$  mRNA in skeletal muscle, with a concomitant increase in mitochondrial content leading to resistance to fatigue and a higher number of oxidative fibers. Thus, because PGC-1 $\alpha$  is obligatory for the exercise-induced increase in VEGF expression, it is evident that PGC-1 $\alpha$  has a particularly prominent role in regulating training-induced VEGF expression.

exercise leads to an NO-dependent increase in circulating EPCs in mice and humans [72], thus contributing to neovascularization and vascular repair, leading to improved endothelial function and myocardium recovery after ischemia [75–78]. IL-6 also plays multiple functions in angiogenesis and vascular

remodeling and may stimulate EPC proliferation, migration, and tube formation following exercise [73, 79].

Importantly, this upregulation in EPCs and CPCs has been implicated in cardiomyocyte healing processes. Kolwicz et al. [80] found that exercise increased CPC proliferation by ~200% and augmented the presence of KIT-positive cells (a stem cell factor crucial for the mobilization of progenitor cells to sites of injury) in the heart. Together with signal transducer and activator of transcription 3 (STAT3), this exercise-induced increase in CPC proliferation may play a key role in cardiomyocyte proliferation, differentiation, and survival [81]. STAT3 activation has been shown to mediate cardiac hypertrophy and protect cells in response to cardiomyopathy induced by ischemia or drug treatment [82–84]. Significantly, exercise increases STAT3 activation [85, 86], causing release of erythropoietin into the cardiac microenvironment that, in turn, binds to CPCs, causing differentiation into endothelial cells [87]. Presumably, these endothelial cells can then be activated by VEGF to express matrix metalloproteinases, which degrade the vascular basement membrane to form new capillary networks [88]. Collectively, we speculate that aerobic exercise may increase PGC-1 $\alpha$  and VEGF secretion and STAT3 activation, with the resultant release, mobilization, and homing of CPCs during angiogenesis inhibitor therapy.

## CONCLUSION

Molecularly targeted therapeutics are the future of cancer systemic therapy; they have already moved from palliative therapy for advanced solid malignancies into the setting of curative-intent treatment for early-stage disease. Cardiotoxicity is a frequent and potentially serious adverse complication of some targeted therapies, leading to a broad range of potentially life-threatening complications, therapy discontinuation, and poor quality of life. Low-cost, multitargeted interventions are therefore urgently required to mitigate these adverse consequences. Evidence reviewed here indicates that aerobic exercise is a nontoxic, pleiotropic therapy that affects diverse cardiac signaling pathways implicated in the cardiotoxicity induced by anti-HER2 and antiangiogenic therapy. It is important to stress that the current evidence base is emergent with

a small number of studies; many areas of MTT-induced cardiotoxicity remain to be defined and addressed. A summary of future investigations needed to define the nature and magnitude of the cardioprotective effects of exercise in the setting of MTT is provided in Table 2. Future challenges for research investigating the effects of aerobic exercise in MTT-induced cardiac toxicity are provided in Table 3.

Although clinical and research interest in aerobic exercise has increased dramatically over the past decade, a more thorough understanding of the myocardial signaling pathways activated by exercise will be needed to improve cardiovascular outcomes. Collectively, such research will lead to mechanistically driven clinical trials. Importantly, adequately powered multicenter randomized controlled trials are required to evaluate the relative efficacy of aerobic exercise training to prevent/treat cardiotoxicity. These investigations, in turn, will inform exercise prescription rehabilitation guidelines for patients with cancer, whereby the most effective exercise intensity and timing (before, during, or following therapy) are established. We anticipate that exercise will complement molecularly targeted therapeutics to improve the health and longevity of patients with solid malignancies.

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## DISCLOSURES

**John R. Mackey:** Roche Oncology; **Pamela S. Douglas:** Atritech/Boston Scientific, Edwards Lifesciences (RF); CardioDX, Universal Oncology (OI). The other authors indicated no financial relationships.  
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