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## Emerging Paradigms in Cardiomyopathies Associated with Cancer Therapies

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### Abstract

The cardiovascular care of cancer patients (“Cardio-Oncology”) has emerged as a new discipline in clinical medicine given recent advances in cancer therapy, and is driven by the cardiovascular complications that occur as a direct result of cancer therapy. Traditional therapies, such as anthracyclines and radiation, have been recognized for years to have cardiovascular complications. Less expected were the cardiovascular effects of “targeted” cancer therapies, which were initially felt to be specific to cancer cells and would spare any adverse effects on the heart. Cancers are typically driven by mutations, translocations, and/or over-expression of protein kinases. The majority of these mutated kinases are tyrosine kinases, though serine/threonine kinases also play key roles in some malignancies. Several agents were developed to target these kinases, but many more are in development. Major successes have been largely restricted to agents targeting Her2 (mutated or over-expressed in breast cancer), BCR-ABL (CML and some cases of ALL), and c-Kit (gastrointestinal stromal tumor). Other agents targeting more complex malignancies such as advanced solid tumors have had successes, but have not extended life to the degree seen with CML. Years before the first targeted therapeutic, Judah Folkman correctly proposed that to address solid tumors, one had to target the inherent neo-angiogenesis. Unfortunately, emerging evidence confirms that angiogenesis inhibitors cause cardiac complications, including hypertension, thrombosis, and heart failure. And therein lies the Catch 22. On the other hand, cardiomyopathies that arise unexpectedly from such targeted therapies can provide key insights into the normal function of the heart.

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**Nonstandard Abbreviations and Acronyms:** None

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## Keywords

Cancer; Chemotherapies; Cardiomyopathy; Cardio-Oncology; HER2 targeted therapies; Angiogenesis Inhibitors; Anthracyclines

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## Introduction

There has been an explosion in cancer drug development over the last two decades. An early so-called targeted agent, and still one of the most effective, was the monoclonal antibody, trastuzumab, that targets Her2 (Human epidermal growth factor receptor-2), which is mutated or over-expressed, in about 20% of breast cancers. It was approved in 1998 with the hope that trastuzumab would have very few side effects because of the selectivity of the antibody and of data in early clinical studies showing minimal serious adverse events. However, this turned out not to be the case with a significant incidence of LV dysfunction, especially when combined with anthracyclines.<sup>1, 2</sup> Subsequently, significant cardiotoxicity with LV dysfunction and chamber dilatation was seen in mice with a cardiac-specific deletion of the Her2 gene, confirming a central role of Her2 in maintaining cardiac homeostasis.<sup>3</sup> In this review, we will attempt to shed light on the molecular mechanisms driving the cardiotoxicity seen with an ever-increasing number of Her2 targeted agents.

A number of reviews have been published on this topic,<sup>4-6</sup> and the reader is urged to read those by way of background, because herein we will focus on recent findings, particularly on 1) novel molecular mechanisms underlying anthracycline cardiotoxicity<sup>7</sup>, 2) mechanisms of cardiotoxicity of what appears to be the most problematic “class” of agents targeting VEGF and VEGFRs<sup>6, 8, 9</sup>, 3) A surprising toxicity (severe pulmonary hypertension) with dasatinib<sup>10, 11</sup>, an agent that has been in use for several years, 4) potential concerns over nilotinib, a derivative of imatinib, in possibly promoting peripheral vascular disease<sup>12</sup>; and 5) the “other side of the Her2 coin,”-the potential of developing novel biomarkers of cardiotoxicity, and of employing ligands of the Her2 receptor (neuregulins) to not only better understand mechanisms of cardiotoxicity, but also to potentially treat patients with heart failure.<sup>13, 14</sup> It is hoped that this “update” will pique the interest of heart failure physicians and lead them to learn more about these very unique and fascinating forms of heart failure that tell us much about the critical pathways regulating cardiac homeostasis.

## Novel mechanisms of anthracycline cardiotoxicity are identified

Since the successful introduction of daunorubicin in the early 1950s, anthracyclines continue to be the most commonly used chemotherapeutic agents.<sup>15</sup> The chemical structure of anthracyclines consists of a tetracyclic aglycone linked to an amino sugar, daunosamine. The chemical structure of doxorubicin differs from daunorubicin only by a single hydroxyl group but has somewhat distinct patterns in metabolism, pharmacokinetics and spectrum of antitumor activity. The original paper describing daunorubicin's anti-tumor activity reported heart failure as a potential complication.<sup>16</sup> A decade later, von Hoff and colleagues published a landmark paper correlating the incidence of congestive heart failure (HF) with the cumulative dose of anthracyclines.<sup>17</sup> More recent clinical studies using cardiac imaging show that the estimated incidence of HF was 5%, 26%, and 48% at 400 mg/m<sup>2</sup>, 550 mg/m<sup>2</sup>,

and 700 mg/m<sup>2</sup>, of doxorubicin respectively.<sup>18</sup> Importantly, patients can develop HF years after anthracycline-containing chemotherapy. This may be due to subclinical myocardial damage that was exacerbated by a newly added stress such as hypertension or coronary artery disease.

Endomyocardial biopsy was considered to be the most sensitive approach for detecting anthracycline-induced cardiac damage prior to the use of biomarkers or left-ventricular strain. Given the invasive nature of this procedure, cardiac biopsy is not often employed nor is it necessary in the diagnosis of LV dysfunction associated with anthracycline therapy.<sup>19</sup> Typical pathological changes include myofibrillar disarray and myocyte drop out, mitochondrial inclusions, vacuolar degeneration and interstitial fibrosis. The pathological changes in myocardial tissue can be detected even before the patients develop symptoms or changes in LV function.<sup>20</sup>

Anthracyclines can affect the cardiovascular system in a variety of ways.<sup>21</sup> Acute cardiac manifestations include transient ECG changes, dysrhythmias, and in rare instances, myocarditis and pericarditis. The subacute and late onset LV dysfunction is clinically significant and often limits the use of anthracyclines.<sup>22</sup> Traditional teaching with anthracycline-induced cardiomyopathy suggests that cardiac function rarely returns to baseline and some cancer survivors may eventually require heart transplantation.<sup>23</sup> However, a recent study suggests cardiac recovery if cardiac dysfunction is recovered early and cardioprotective medications started.<sup>24</sup> Moreover, clinical severity of LV dysfunction also varies greatly among individuals, which cannot be explained by the cumulative dose. Thus, genetic variation and underlying cardiac risk factors in each individual could play a central role in developing anthracycline-induced cardiomyopathy.<sup>25</sup>

Despite decades of research, the mechanisms of anthracycline-induced cardiotoxicity remain unclear. A widely accepted paradigm attributes anthracycline-induced cardiotoxicity to reactive oxygen species (ROS) formation. Once administered, anthracyclines enter cells via passive diffusion, and can accumulate to several hundred times greater concentrations than in the extracellular compartment. The “redox-cycling” of anthracyclines can generate a large amount of intracellular superoxide radicals. Semiquinone, O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub> and other reactive oxygen species can increase intracellular free iron load by various mechanisms, including reductive release of iron from ferritin, an important iron storage protein, as well as from cytoplasmic aconitase.<sup>26, 27</sup> Accumulation of free iron can lead to DNA damage and lipid peroxidation by converting O<sub>2</sub><sup>-</sup> and H<sub>2</sub>O<sub>2</sub> into hydroxyl radical (OH<sup>-</sup>), one of the most potent oxidants, contributing to oxidative stress and cytotoxicity.<sup>28</sup> Anthracyclines cause uncoupling of the electron transport chain in the mitochondria, impairing oxidative phosphorylation and adenosine triphosphate (ATP) synthesis, making cells more vulnerable to ROS.

A variety of antioxidants have been studied in animal models and clinical trials, including probucol, vitamin E, and N-acetylcysteine. However, these have failed to provide cardioprotection against anthracycline chemotherapy.<sup>29</sup> The only FDA approved agent for preventing cardiomyopathy associated with anthracycline chemotherapy is dexrazoxane, a neutral pro-drug analog of the tetra-acid metal chelation ethylenediaminetetraacetic acid

(EDTA).<sup>30</sup> The initial proposed mechanism for its cardio-protective effect was the iron chelating property similar to EDTA. Dexrazoxane quickly distributes intracellularly to remove Fe<sup>3+</sup> from the Fe<sup>3+</sup>-anthracycline complex or binds to free iron in the cell, thus reducing the production of ROS. However other iron chelating agents such as deferasirox and ICRF-161 failed to provide cardioprotection against doxorubicin in mouse models.<sup>31, 32</sup>

The failure of antioxidant or Fe-chelation to ameliorate anthracycline-induced cardiotoxicity further emphasized the critical need for a new paradigm and understanding of doxorubicin cardiotoxicity. An important clue came from the ability of dexrazoxane to directly interfere with the formation of Topoisomerase 2 (Top2) cleavage complexes raising the intriguing possibility that the cardioprotective effect of dexrazoxane was dependent on its ability to inhibit Top2. Indeed, anthracyclines are Top2 poisons.<sup>33</sup> Top2 is a crucial enzyme in DNA transcription, replication, and recombination by transiently breaking the DNA backbone to allow DNA strands to pass through one-another and untangle the supercoiled DNA complex.<sup>34</sup> As an intercalating agent, a planar aglycone moiety of anthracycline inserts between adjacent DNA base pairs and forms a ternary Top2-doxorubicin-DNA cleavage complex. The formation of anthracyclines with the DNA complex inhibits the re-ligation of the broken DNA strands, leading to DNA double-strand breaks and cell death. There are two types of Top2 isozymes, Top2 $\alpha$  and Top2 $\beta$ .<sup>35</sup> These two isoforms are encoded by different genes with variable tissue expression.<sup>36</sup> Top2 $\alpha$  expression level is higher in proliferating tissues including bone marrow, spleen and tumor cells.<sup>37</sup> In contrast, Top2 $\beta$  is widely distributed in quiescent or terminally differentiated tissue such as brain or liver. Interestingly, adult mammalian cardiomyocytes only expressed Top2 $\beta$ , but not Top2 $\alpha$ .<sup>38</sup> Previously, it was shown that doxorubicin-induced DNA double strand breaks were greatly reduced in Top2 $\beta$  knockout mouse embryonic fibroblasts when compared with Top2 $\beta$  wild type.<sup>31</sup> Thus, Top2 $\beta$  may play an important role in anthracycline-induced cardiotoxicity.

To test the hypothesis that Top2 $\beta$  was critical to anthracycline-induced cardiotoxicity, a conditional, cardiomyocyte-specific Top2 $\beta$  knockout mouse (Top2 $\beta$ <sup>-/-</sup>) was generated. These mice had no identifiable abnormalities at 10 months of age and ejection fraction (EF) was preserved, suggesting that Top2 $\beta$  is not required in the non-stressed adult heart. However, following acute challenge with a relatively high single dose of doxorubicin, hearts from Top2 $\beta$ <sup>-/-</sup> mice had a marked reduction in DNA double strand breaks and apoptotic nuclei as compared to wild-type. Thus, Top2 $\beta$  alone is a key driver of cell death resulting from doxorubicin administration.

If Top2 $\beta$  in cardiomyocytes is sufficient for doxorubicin to induce DNA double strand breaks and apoptosis, is there still a role for the ROS hypothesis? Of note, generation of ROS was reduced by 70% in doxorubicin-treated Top2 $\beta$ <sup>-/-</sup> mice as compared to Top2 $\beta$ <sup>+/+</sup> mice. Striking ultrastructural changes were also present in doxorubicin-treated wild type mice including mitochondrial damage and vacuolization. Oxygen consumption rate was significantly reduced in doxorubicin-treated wild type mice, but not in Top2 $\beta$ <sup>-/-</sup> mice, consistent with mitochondrial dysfunction. Expression of genes involved in mitochondrial and oxidative phosphorylation pathways were down regulated in Top2 $\beta$  wild type, but not Top2 $\beta$ <sup>-/-</sup> mice. In addition, quantitative PCR analysis showed down-regulation of *PGC-1 $\alpha$*  and *PGC-1 $\beta$*  transcripts. Given their crucial role in regulating cellular energy metabolism

and mitochondrial biogenesis, this may be a key mechanism driving cardiotoxicity. The reduction of PGC-1 $\alpha$  also led to a decrease in the critical anti-oxidant, superoxide dismutase, possibly explaining in part the increase in ROS formation after anthracycline treatment. These data suggest that ROS generation after anthracycline treatment is a result of a change in the transcriptome affecting mitochondria and oxidative phosphorylation rather than redox cycling of doxorubicin as previously proposed.

Finally, the effect of longer-term doxorubicin administration on LVEF, mimicking the clinical scenario more closely, showed no significant change in LVEF after chronic administration of doxorubicin in Top2 $\beta$ <sup>-/-</sup> mice. In contrast, EF deteriorated significantly in wild type mice. These results support the critical concept that doxorubicin-induced cardiotoxicity is mediated by Top2 $\beta$  in cardiomyocytes.<sup>39</sup> (Figure 1)

The elucidation of the molecular mechanism of anthracycline-induced cardiotoxicity could be useful for predicting and preventing LV dysfunction. For example, developing Top2 $\alpha$ -specific drugs that have no Top2 $\beta$  activity could be myocardial-sparing. This is predicated on the assumption that Top2 $\beta$  does not have a major role in doxorubicin's anti-cancer effects. One might also be able to use Top2 $\beta$  expression level to stratify risk of developing anthracycline-induced cardiotoxicity. Thus patients with low Top2 $\beta$  expression in the heart could be less susceptible to anthracyclines. It has been reported that Top2 $\beta$  levels in peripheral blood are correlated with the apoptotic response of leukocytes to doxorubicin in humans.<sup>39</sup> Hence, the Top2 $\beta$  level in peripheral blood may be useful as a surrogate marker for susceptibility to anthracycline-induced cardiomyopathy. However, this remains to be proven in clinical studies. Clearly, if we are able to predict which patients are more susceptible to anthracycline-induced cardiotoxicity before treatment, oncologists could select a less cardiotoxic drug, monitor the patient more closely, or provide early cardiac protection with dexrazoxane. Currently, ACE inhibitors or  $\beta$ -Blockers have been recommended for cardio-protection after detection of cardiotoxicity through biomarkers or with a clear decrease in ejection fraction (Ann. Oncology 23 (supplement 7, Vii155-Vii166, 2012). The identification of the molecular basis of anthracycline-induced cardiotoxicity appears to be one more example in an age where genetic profiling could be used to provide personalized cardiac protection similar to the concept of personalized cancer therapy.

### **A remarkable beginning for small molecule kinase inhibitors**

Imatinib, the first small molecule kinase inhibitor to reach the market, revolutionized the treatment of patients with CML. Imatinib inhibits the kinase activity of the BCR/Abl fusion protein that arises from the balanced translocation that creates the Philadelphia chromosome. This accounts for the vast majority of cases of CML and about 20% of cases of ALL. Imatinib is generally well-tolerated and since treatment is life-long, that is critical.

The success of imatinib led to the development of similar agents targeting CML- nilotinib and dasatinib- and hopes were high that toxicity would be uncommon with these as well. In large part that has been the case, but concerns have recently surfaced. Most notably, a group in France identified very significant pulmonary hypertension in some CML patients treated with dasatinib. Although this side effect appears to be uncommon, dasatinib has been largely

relegated to third line treatment in France, and is primarily used after failure with imatinib and nilotinib.

Less clear, but of concern, several recent abstracts and papers (e.g.<sup>12</sup>) suggested that nilotinib might increase risk of peripheral vascular disease. Although not definitive, and mechanisms are entirely unclear, this may be one more example of the unpredictability of kinase inhibitors.

Why might dasatinib use be associated with pulmonary hypertension whereas imatinib use is not? The most likely answer is that dasatinib is a promiscuous kinase inhibitor, inhibiting many more kinases than imatinib. If any of these kinases play a key role in the heart, cardiotoxicity could result. Of note, identifying the kinase (s), inhibition of which leads to toxicity, could allow re-design of dasatinib to no longer inhibit the kinase that is critical to the heart.<sup>40</sup>

### **Cardiomyopathy associated with small molecule angiogenesis inhibitors**

Although initially proposed by Dr. Judah Folkman over 40 years ago, inhibiting angiogenesis by targeting specific circulating pro-angiogenic factors or their receptors has become a major focus of cancer drug development in the last decade.<sup>41</sup> Angiogenesis is mediated by the stabilization of the master transcription factor - Hypoxia-Inducible Factor- $\alpha$  (HIF- $\alpha$ ) - leading to the transcription of a number of pro-tumorigenic factors, including Vascular Endothelial Growth Factor (VEGF) and Platelet-Derived Growth Factor (PDGF). This system has been best described in clear cell renal cell carcinoma where sporadic mutations in the gene encoding for the von Hippel-Lindau protein (pVHL) play a causal role in tumorigenesis. pVHL is the substrate recognition component of an E3 ubiquitin ligase complex that targets HIF $\alpha$  for degradation with VHL mutations leading to inappropriate stabilization (and hence activation) of HIF (specifically HIF2 $\alpha$ ) and induction of VEGF and other HIF targets.<sup>42</sup> This model probably explains why renal cell carcinoma has been the main focus for FDA approval of angiogenesis inhibitors and why renal cell carcinoma remains the one cancer type where angiogenesis inhibitors are approved as single therapy and lead to modest benefit.<sup>41, 42</sup>

Bevacizumab (Avastin), the first FDA approved drug in this class, is a monoclonal antibody targeting the soluble VEGF protein and is given intravenously. However, the newer FDA approved drugs targeting angiogenesis (and the many currently in clinical trials) are given orally and target the tyrosine kinase receptors for VEGF, PDGF and other factors. Examples include sunitinib (Sutent), sorafenib (Nexavar) and pazopanib (Votrient). Because VEGF inhibition is a central feature, the class of drugs are generally referred to as VEGF signaling pathway (VSP) inhibitors; however, with respect to the tyrosine kinase inhibitors in this class, the term “VSP inhibitor” is a bit misleading given the drugs' relative promiscuity. The latter serves as a double edge sword both allowing the drugs to be approved for a wide range of cancers but also has implications for toxicity. For example, sunitinib targets several tyrosine kinases receptors including all three VEGF receptors (VEGFR1, VEGFR2, VEGFR3), PDGF receptors  $\alpha$  and  $\beta$ , KIT, and FLT3 and has been approved for the treatment of gastrointestinal stromal tumor, advanced renal cell carcinoma, and advanced

pancreatic neuroendocrine tumors. In this regard, it may be simplistic to generalize the cardiotoxicities in this section as a “class effect” since each drug has selective targets. (See Figure 2) VSP inhibitors represent arguably the fastest growing class of drugs for cancer therapy with the number of FDA approved drugs nearly doubling in 2012 alone with many more drugs in this class currently awaiting FDA approval.<sup>6</sup>

Clinical trials involving VSP inhibitors have not included routine screening for clinical heart failure or left ventricular dysfunction. As a result, the emerging recognition of cardiomyopathy with VSP inhibitors is mostly based on retrospective analyses where there is potential for misclassification bias. A meta-analysis assessing five clinical trials (and involving 3,784 patients with breast cancer) showed an incidence of high-grade congestive heart failure (CHF) to be 1.6% in patients treated with bevacizumab compared to 0.4% in the control or placebo groups, resulting in an overall RR of developing high-grade CHF of 4.74.<sup>43</sup> Another meta-analysis assessing the propensity of patients receiving sunitinib to develop CHF (involving 6,935 patients from 16 studies) suggested an overall incidence of all-grade and high-grade CHF of 4.1% and 1.5%, respectively; treatment with sunitinib was associated with an increased relative risk of developing all-grade and high-grade CHF (RR of 1.81 and 3.30, respectively).<sup>44</sup> Single-institution studies suggest an incidence anywhere between 2.7% to 15% in patients on sunitinib having symptomatic CHF (and attributed to sunitinib).<sup>45-47</sup>

Observational data from individual trials involving sunitinib suggest a higher incidence of asymptomatic cardiomyopathy. Among 75 patients with imatinib-resistant gastrointestinal stromal tumor in a phase I/II trial of sunitinib, 28% of patients had an absolute decrease in ejection fraction of at least 10 percent.<sup>8</sup> An observational study of patients with metastatic renal cell carcinoma treated with sunitinib or sorafenib found that 33% of patients had a “cardiac event,” although “cardiac event” in this study ranged from an asymptomatic increase in cardiac enzymes to new left ventricular dysfunction requiring intensive care.<sup>9</sup>

The above studies, however, probably underestimate the true incidence of cardiomyopathy in the setting of VSP inhibitor treatment for several reasons. First, as stated above, none of clinical trials involving VSP inhibitors prospectively monitored cardiac function, thus relying heavily on investigator judgment of clinical heart failure. Second, reporting of heart failure using NCI's Common Terminology Criteria of Adverse Events (CTCAE) can be confusing given the various definitions for cardiomyopathy.<sup>48</sup> Third, diagnosis of heart failure in cancer patients can be difficult given the often non-specific symptoms that can arise with malignancy (such as fatigue or peripheral edema). Fourth, cardiomyopathy can present as asymptomatic left ventricular dysfunction, thus underscoring the necessity of cardiac imaging in clinical trials. Fifth, long term cardiac consequences of VSP inhibitors are completely unknown. Sixth, early clinical trials with novel cancer therapies usually exclude patients with a history of significant heart failure, uncontrolled hypertension, or other risk factors whereas these exclusions do not always apply to the general population once a drug is FDA-approved. Finally, due to the relative promiscuity of novel VSP inhibitors, it is unclear if the early observations regarding the incidence and prognosis of cardiomyopathy associated with sunitinib extend to newer drugs in this class. In the future, prospective studies using close clinical and imaging follow-up of patients treated with VSP



inhibitors are needed to get a better estimate of patients who develop left ventricular dysfunction.<sup>6</sup>

There have been several proposed mechanisms for VSP inhibitor-associated heart failure. The most intriguing model that examines this is a mouse expressing a “tunable” transgene encoding a VEGF trap (in a sense recapitulating the effects of bevacizumab). In this model, the induction of the VEGF trap leads to decreased myocardial capillary density (“capillary rarefaction”), induction of hypoxia and hypoxia-inducible genes in the myocardium, and cardiac dysfunction, which is reversible upon removal of the transgene.<sup>49</sup> Similarly, mice in which PDGF receptor  $\beta$  is genetically deleted in the heart have decreased capillary density, increased myocardial hypoxia and accentuated heart failure after transverse aortic constriction (TAC).<sup>50</sup> These two studies suggest the intriguing possibility that induction of hypoxia and hypoxia-inducible genes in the heart (as may occur as a result of inhibition of angiogenesis in the heart after treatment with VSP inhibitors) may lead to cardiomyopathy. In keeping with this model, stabilization of Hypoxia-Inducible Factor- $\alpha$  (HIF $\alpha$ ) in the heart is sufficient to induce reversible cardiomyopathy in mice.<sup>51, 52</sup> While these pre-clinical models are intriguing, it remains to be seen whether myocardial hypoxia (as a result of capillary rarefaction) plays a causal role in cardiomyopathy associated with VSP inhibitors in humans. Nevertheless, these mouse models predict that VSP inhibitor-associated cardiomyopathy would lead to myocardial hibernation rather than myocardial death and that they would be reversible. Indeed, several studies suggest that sunitinib- and sorafenib-induced cardiomyopathy may be reversible.<sup>8, 53</sup> Moreover, sunitinib-induced cardiomyopathy in both mouse and man show similar ultrastructural changes – including mitochondrial alterations - that are reversible after discontinuation of treatment.<sup>54</sup> (See Figure 3).

Despite the increasing recognition of heart failure, hypertension is by far the most common cardiovascular toxicity associated with VSP with an incidence of hypertension of 19-25% with these class of agents.<sup>6, 55</sup> Newer VSP inhibitors such as axitinib and cediranib probably cause an even higher incidence of hypertension. For example, a recent trial with cediranib showed that 87% of the patients had hypertension.<sup>56</sup> Blood pressure increase is rapid in most patients after initiation of treatment with VSP inhibitors and can be reversible once chemotherapy is stopped. There have been several proposed mechanisms for VSP inhibitor-associated hypertension. Both functional (inactivation of endothelial nitric oxide synthase and production of vasoconstrictors such as endothelin-1) and anatomic (“capillary rarefaction”) changes in the endothelium have been proposed as mechanisms of VSP inhibitor-associated hypertension.<sup>57</sup> Interestingly, the resultant hypertension after initiation of VSP inhibitors is probably mediated via VEGF signaling and not due to an “off-target” effect. Consistent with this model, there is emerging evidence that elevations in blood pressure may predict superior tumor outcomes.<sup>57</sup> Finally, interesting similarities exist between VSP inhibitor-associated hypertension and pre-eclampsia, a syndrome of hypertension and proteinuria affecting 5% of all pregnancies, which also probably results from dysregulation of VEGF signaling.<sup>6, 57, 58</sup>

In the absence of prospective studies detailing the extent of cardiomyopathy, we suggest a low threshold for assessing cardiac dysfunction after initiation with VSP inhibitors. Baseline

echocardiogram to assess for structural heart disease should be considered, especially in patients with cardiac risk factors. Risk factors including hypertension should be aggressively treated during therapy and a repeat echocardiogram be done if the patient has symptoms concerning for heart failure. Upon detection of cardiomyopathy, VSP inhibitor treatment should be stopped and patients should be started on cardioprotective medications including beta-blockers and ACE inhibitors. Given the potential reversibility of this class of cardiomyopathy<sup>53</sup>, a repeat echocardiogram after stopping the VSP inhibitor is necessary. Less clear is whether the patient can be re-challenged with the same or another VSP inhibitor.

In addition, in all patients considered for VSP inhibitor treatment, blood pressure needs to be aggressively managed prior to initiation of chemotherapy and in keeping with JNC7 guidelines. Because VSP inhibitors have been associated with proteinuria, testing for urine proteins should be performed before and after initiation of treatment and select patients should be referred to a nephrologist. We advocate angiotensin-converting enzyme inhibitors and dihydropyridine calcium channel blockers as first- and second-line therapy for hypertension, respectively. Finally, because of the reversibility of VSP-inhibitor-induced hypertension, blood pressure medications may need to be titrated during chemotherapy “holiday,” such as in the 4 weeks-on/2 weeks-off schedule of sunitinib. The management of hypertension is important in this population because it is possible that hypertension promotes the development of cardiomyopathy. Less clear is whether hypertension plays a role in the increased incidence of thrombosis in this population.<sup>59</sup> A multidisciplinary approach including the treating oncologist and cardiologist will provide highly specialized care that will lead to early detection and prevention of potential cardiovascular events.<sup>55</sup>

## Understanding Her2 inhibitors and agonists

### Trastuzumab

More than 20% of breast carcinomas overexpress HER2/neu (also known as Epidermal growth factor receptor B2 or ErbB2 in the mouse). Trastuzumab (Herceptin®) is a humanized monoclonal antibody that targets the extracellular domain (ECD) of the Her2 receptor and is used widely to treat HER2+ breast cancer. Currently one of the few approved therapies for patients with early stage and metastatic HER2+ disease, this agent has dramatically altered the landscape of breast cancer therapy.<sup>60</sup>

Trastuzumab binds to the  $\beta$ -hairpin region of domain II of the HER2 receptor in tumor cells. There are multiple proposed mechanisms of trastuzumab's actions.<sup>61</sup> These include the following: 1) antibody-dependent cellular cytotoxicity (ADCC); 2) inhibition of ErbB2 ECD cleavage and the expression of the constitutively active fragment; 3) inhibition of ligand-independent ErbB2 receptor hetero-dimerization; 4) inhibition of angiogenesis; 5) induction of cell-cycle arrest, and 6) interference with DNA repair. The ability of trastuzumab to inhibit the formation of the ErbB2-ErbB3 complex in cancer cells, and downstream activation of the PI3K/Akt pathway is believed to be a particularly potent mechanism of action of this agent.

Although trastuzumab has demonstrated remarkable efficacy in the treatment of HER2 positive breast cancer, there is a clinically significant incidence of cardiotoxicity. A portion of patients experience an important, but primarily reversible cardiotoxic effect manifest as a decline in LVEF.<sup>62</sup> Experience from large clinical trials demonstrate an approximate 9.8% incidence of left ventricular (LV) dysfunction and 2.7% incidence of severe, symptomatic heart failure.<sup>2, 63</sup> However, when used in combination with anthracyclines, the incidence of cardiac dysfunction increases to 16-20%, with a 7-fold increased risk of heart failure or cardiomyopathy.<sup>2</sup> Although clinical experience suggests that recovery of LVEF occurs in the majority of patients within the 1<sup>st</sup> year after exposure, either with temporary cessation of trastuzumab or in combination with standard heart failure therapy, not all patients experience recovery of cardiac function.<sup>2</sup>

In addition to prior anthracycline exposure, there are a number of clinical risk factors for cardiotoxicity including hypertension,<sup>1</sup> suggesting that the risk of cardiotoxicity with trastuzumab increases with additional cardiac stress, potentially indicative of a two-hit model of trastuzumab-induced cardiotoxicity, in which trastuzumab somehow interferes with the cardiac stress response.<sup>64</sup> However, the pathogenesis of trastuzumab-induced cardiotoxicity is still unclear, and remains an area of active investigation.

One central hypothesis for the pathophysiology of trastuzumab cardiotoxicity is related to alterations in the neuregulin (NRG) and ErbB pathway, which is established as a critical pathway in fetal heart development and the maintenance of adult cardiac function.<sup>3, 65, 66</sup> NRG1 is a signaling protein released from microvascular endothelial cells that acts in a paracrine and juxtacrine fashion to activate the ErbB family of tyrosine kinase receptors expressed in cardiac myocytes.<sup>67</sup> In adult cardiomyocytes, NRG1 binds the ErbB4 receptor, resulting in ErbB4/ErbB4 homodimerization or ErbB4/ErbB2 heterodimerization. In response, the PI3-K/Akt, and MEK/ERK pathways, as well as Src/focal adhesion kinase (FAK) and nitric oxide (NO) synthase are activated and regulate cardiac stress responses.<sup>67, 68</sup> Recent data also demonstrate that stimulation of the NRG1/ErbB4 signaling pathway induces cell-cycle reentry of differentiated cardiomyocytes, cardiomyocyte proliferation, and promotion of cardiac repair.<sup>13</sup> Furthermore, in vitro and in vivo models support a cardioprotective role for endogenous, endothelial cell-derived NRG and ErbB4 in response to hypoxic/ischemic injury.<sup>69</sup>

The NRG-1/ErbB ligand-dependent signaling pathway is believed to be crucial in the adaptive response to cardiac stress, as NRG-1/ErbB deficient animals develop a dilated cardiomyopathy phenotype, increased susceptibility to cardiac injury and to anthracycline exposure, and decreased survival.<sup>3, 70</sup> Basic science evidence and early translational studies in both animals and humans suggest that augmentation of the NRG/ErbB signaling pathway through exogenous delivery is beneficial and results in substantial improvements in cardiac function and survival in cardiomyopathy models.<sup>14, 71</sup>

Although it is tempting to speculate that trastuzumab-related cardiac damage may be, at least in part, related to the inhibition of the NRG1/ErbB4/ErbB2 pathway in cardiomyocytes, the precise mechanisms are unknown, and direct causal relationships and downstream mediators have not been defined.<sup>72</sup> We hypothesize that NRG/ErbB inhibition

has important effects on cardiomyocyte growth; angiogenesis; and maintenance of myofibrillar structure through PI3Kinase/Akt and MEK/Erk signaling, and suggest these areas should be a continued focus of further study. Similarly, the potential relevance of associated ligands such as heparin-binding epidermal growth factor (HBEGF) and receptors such as ErbB3, both of which may have a role in the cardiovascular system, remain to be elucidated in trastuzumab cardiotoxicity.<sup>73, 74</sup>

An improved mechanistic understanding could be translated into strategies to improve risk stratification and develop new therapies for cardiac repair. Several groups have been actively studying the role of circulating factors reflective of the NRG/ErbB signaling pathway in identifying patients at risk for adverse cardiovascular outcomes in heart failure and with exposure to doxorubicin and trastuzumab. In studies done in 899 patients with chronic heart failure, serum NRG-1b was significantly elevated in patients with NYHA Class IV heart failure with a median value of 6.2ng/ml versus 4.4ng/ml for Class I HF patients (p=0.002). There was also an increased risk of death or cardiac transplantation over a median follow-up of 2.4 years (adjusted HR 1.58 [95% CI 1.04-2.39, p=0.03] comparing 4<sup>th</sup> versus 1<sup>st</sup> NRG-1 $\beta$  quartile).<sup>75</sup> Similarly, a small case-control study of chronic heart failure patients found increased levels of circulating ErbB2 in the serum of heart failure patients (n=50) versus age and gender-matched controls (n=15), possibly indicative of increased shedding of ErbB2 into the circulation in heart failure.<sup>76</sup>

In breast cancer patients undergoing chemotherapy, initial observations suggest that exposure to anthracyclines result in a significant reduction in circulating NRG-1 $\beta$  levels. This was postulated to be indicative of endothelial dysfunction and, potentially, downregulation or dysfunction of this pathway. Other groups have corroborated these findings in independent cohorts, and also suggested there may be correlations between NRG-1 $\beta$  levels and changes in LVEF.<sup>77</sup> More precise phenotyping of the time-course of NRG-1 expression during exposure to cancer therapy and how this may relate to subsequent cardiotoxicity are topics of active investigation, as the potential adaptive activation and maladaptive depression of NRG/ErbB signaling may be relevant to trastuzumab, as well as doxorubicin cardiotoxicity. This additional work will also clarify the role of NRG-1 as a biomarker for risk prediction in cancer therapy-induced cardiotoxicity.

### Novel Her2 Therapies for Breast Cancer

The success of trastuzumab in the treatment of both early and metastatic breast cancer has led to the development of a number of other agents targeting the Her2 receptor. Although early studies suggest that these novel agents may be less cardiotoxic than trastuzumab, the complexity here is underscored by the fact that these novel agents are being tested *in combination* with, rather than as an alternate to, trastuzumab. (See Figure 4)

**Lapatinib**—Lapatinib is a small-molecule dual tyrosine kinase inhibitor (TKI) of EGFR1 and ErbB2 that competes with ATP for binding to the ATP pocket of the kinase. If ATP cannot access the pocket, downstream targets of EGFR and ErbB2 cannot be phosphorylated and thus cannot be activated. Consequently, downstream targets that promote cancer growth and/or angiogenesis will be blocked.<sup>78</sup> Lapatinib is believed to enhance trastuzumab's

effects in a synergistic fashion, and as such, dual targeting of HER2-positive tumors with trastuzumab and lapatinib is being employed given the primary and acquired resistance of these agents when used as monotherapy.<sup>79</sup> While trastuzumab inhibits ligand-independent ErbB2 and ErbB3 dimerization and acts via ADCC, lapatinib blocks ligand-dependent heterodimer signaling and prevents signaling of the truncated version of the HER2 receptor. Therefore, lapatinib may also enhance trastuzumab-dependent ADCC through the accumulation of HER2 at the cell surface<sup>36</sup>.

In recent Phase II and III clinical trials, the rates of cardiotoxicity with lapatinib have been reported to be low, on the order of 1.5 to 2.2%.<sup>80</sup> Nevertheless, the generalizability and interpretation of such early studies with lapatinib, with respect to cardiotoxicity, is limited given patient enrollment is restricted to those without cardiovascular disease and the various definitions used to define cardiotoxicity. Interestingly, in many of these published studies comparing lapatinib and trastuzumab, the rates of cardiotoxicity observed with trastuzumab alone have also been less than that reported in retrospective analyses of non-clinical-trial populations.<sup>81</sup> The true incidence of cardiotoxicity will likely be revealed with continued experience with these agents.

Interestingly, recent in vitro data suggest that EGFR/ErbB2 inhibition may result in a different cardiac safety profile as compared to trastuzumab. In human cardiomyocytes, administration of GW2974, an equipotent inhibitor of EGFR/ErbB2, resulted in increased levels of activated AMP kinase in a calcium-dependent, Akt-independent fashion.<sup>82</sup> AMPK, a well-known master regulator of metabolic processes particularly in the setting of stress, was critical in maintaining human cardiomyocyte survival, and resulted in reduced cellular lipid content, increased fatty acid oxidation, and increased production of ATP.<sup>82</sup> In contrast, there was no evidence for AMPK activation in trastuzumab-treated human cardiomyocytes.

However, other studies show, like trastuzumab, EGFR/ErbB2 inhibition via intracellular tyrosine kinase inhibition is associated with myofibrillar disarray in adult rat ventricular cardiomyocytes, with worse damage observed in combination with doxorubicin.<sup>83</sup> Furthermore, inhibition of EGFR/ErbB2 also inhibits phosphorylation of Erk1/2, which may also be important in modulating trastuzumab cardiotoxicity.

**Pertuzumab**—Pertuzumab is a recombinant humanized monoclonal antibody that targets an epitope near the center of the extracellular domain II of ErbB2 and sterically inhibits ErbB2 homo- and heterodimerization.<sup>61, 79</sup> Inhibition of ErbB2 dimerization by pertuzumab has been shown to block subsequent activation of Akt and ERK1/2.

Clinical experience with pertuzumab is growing, and rates of cardiotoxicity have not yet fully been established. In Phase II studies of pertuzumab use as monotherapy in patients with Her2 negative breast cancer with prior exposure to anthracycline-containing chemotherapy, 10% of patients experienced a decline in LVEF of at least 10% to less than 50% that occurred at a median time frame of 100 days. All patients who experienced cardiotoxicity had borderline normal LVEF and again, again, there was a reversible component.<sup>84</sup> Similar findings were observed in additional cohorts,<sup>85, 86</sup> where cardiac events typically occurred in patients with a prior cardiovascular disease history.<sup>87</sup> Finally, a

pivotal study combining pertuzumab, trastuzumab and docetaxel, showed similar rates of cardiac dysfunction, as placebo, trastuzumab and docetaxel, for first-line treatment of HER2-positive metastatic breast cancer, while significantly prolonging progression-free survival.<sup>88</sup>

Basic mechanisms of pertuzumab-associated cardiac dysfunction as well as the true incidence of cardiotoxicity remain to be elucidated. Again, alterations in NRG1 and ErbB signaling that occur with this agent, as well as the relevance of circulating NRG1 levels as a biomarker of pertuzumab cardiotoxicity, are areas of active investigation. Overall, clinical studies to date suggest that in patients with normal baseline cardiac function and without any cardiovascular disease history, the selective use trastuzumab and pertuzumab in combination will likely have a low incidence of cardiotoxicity. However, the applicability of these findings to non-clinical-trial populations and in patients with pre-existing cardiovascular disease and an enhanced risk factor profile remains to be determined.

**Trastuzumab emtansine (T-DM1)**—Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that incorporates trastuzumab with the cytotoxic activity of the microtubule-agent - DM1 - via a stable linker, covalently binding these components.<sup>61</sup> A recently pivotal study randomized patients with HER2-positive advanced breast cancer that had previously been treated with a taxane and trastuzumab, to T-DM1 or lapatinib and capecitabine. Here, 8 of 481 patients treated had an LVEF of less than 50% that was at least 15% below baseline (and comparable to the lapatinib and capecitabine group). Three of the 481 had an LVEF decline to less than 40%.<sup>89</sup> While in this study the incidence of cardiotoxicity appears to be low, additional experience is necessary before establishing any conclusions.

### What can Cardio-Oncology teach us about heart failure?

Understanding the mechanisms behind the cardiomyopathies that arise as a result of targeted cancer therapies and developing strategies to treat these complications are important for the cardiovascular care of the cancer patient. Understanding these cardiomyopathies may also have implications for more common types of heart failure and may provide unexpected insights into the biology of the heart. For example, the understanding that HER2 signaling plays a critical role in cardiovascular homeostasis has possible implications for prognosis and treatment for more common forms of heart failure.<sup>90</sup> As described above, circulating levels of NRG1 (the agonist for HER2 in the heart) correlate with disease severity and the risk of death.<sup>75</sup> In addition, recombinant NRG1 is now under investigation as a therapeutic molecule in severe heart failure.<sup>91</sup> Likewise, emerging data over the past year suggest that VSP-inhibitor associated cardiomyopathy may have implications for peri-partum cardiomyopathy, where impaired VEGF signaling probably plays a causal role.<sup>58</sup> In this regard, with the explosion of novel cancertherapeutics being tested in clinical trials, we may just be observing the tip of the iceberg. For example, both mTOR inhibitors and PI3K inhibitors are being tested in breast cancer trials (and often in combination with anthracyclines and HER2 targeted therapies). While there remains a dearth of data with respect to the possible cardiovascular sequelae of these agents, biologically plausible mechanisms suggest adverse cardiovascular and metabolic consequences.

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***Circulation Research* Compendium on Heart Failure**

Research Advances in Heart Failure: A Compendium

Epidemiology of Heart Failure

Genetic Cardiomyopathies Causing Heart Failure

Non-coding RNAs in Cardiac Remodeling and Heart Failure

Calcium Cycling in Heart Failure

Heart Failure Gene Therapy: The Path to Clinical Practice

Cardiac Metabolism in Heart Failure

Integrating the Myocardial Matrix into Heart Failure Recognition and Management

The Adrenergic Nervous System in Heart Failure: Pathophysiology and Therapy

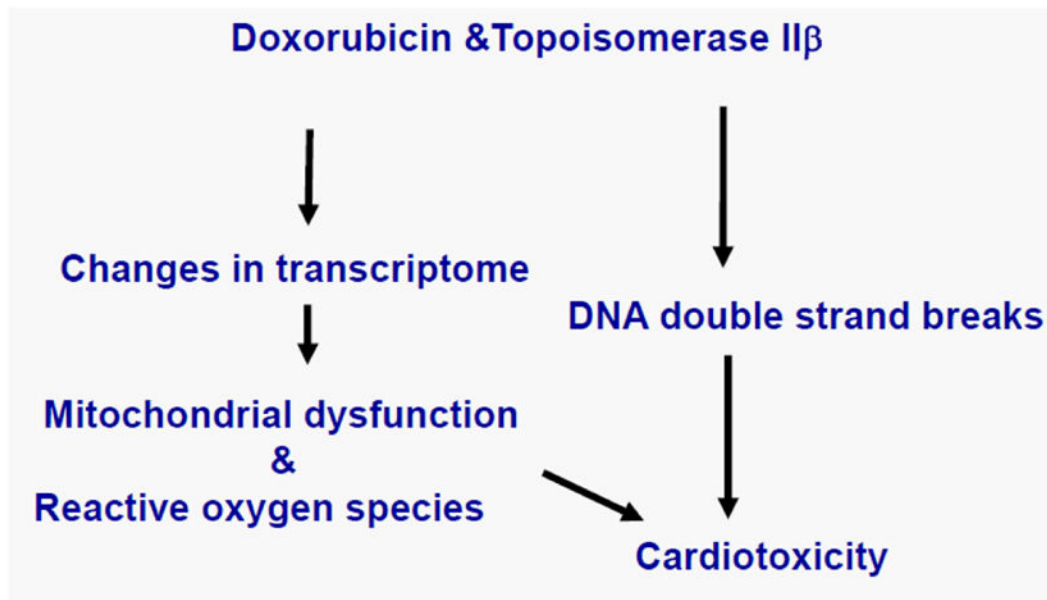
Emerging Paradigms in Cardiomyopathies Associated with Cancer Therapies

Dyssynchronous Heart Failure: Pathophysiology, Recognition, and Management

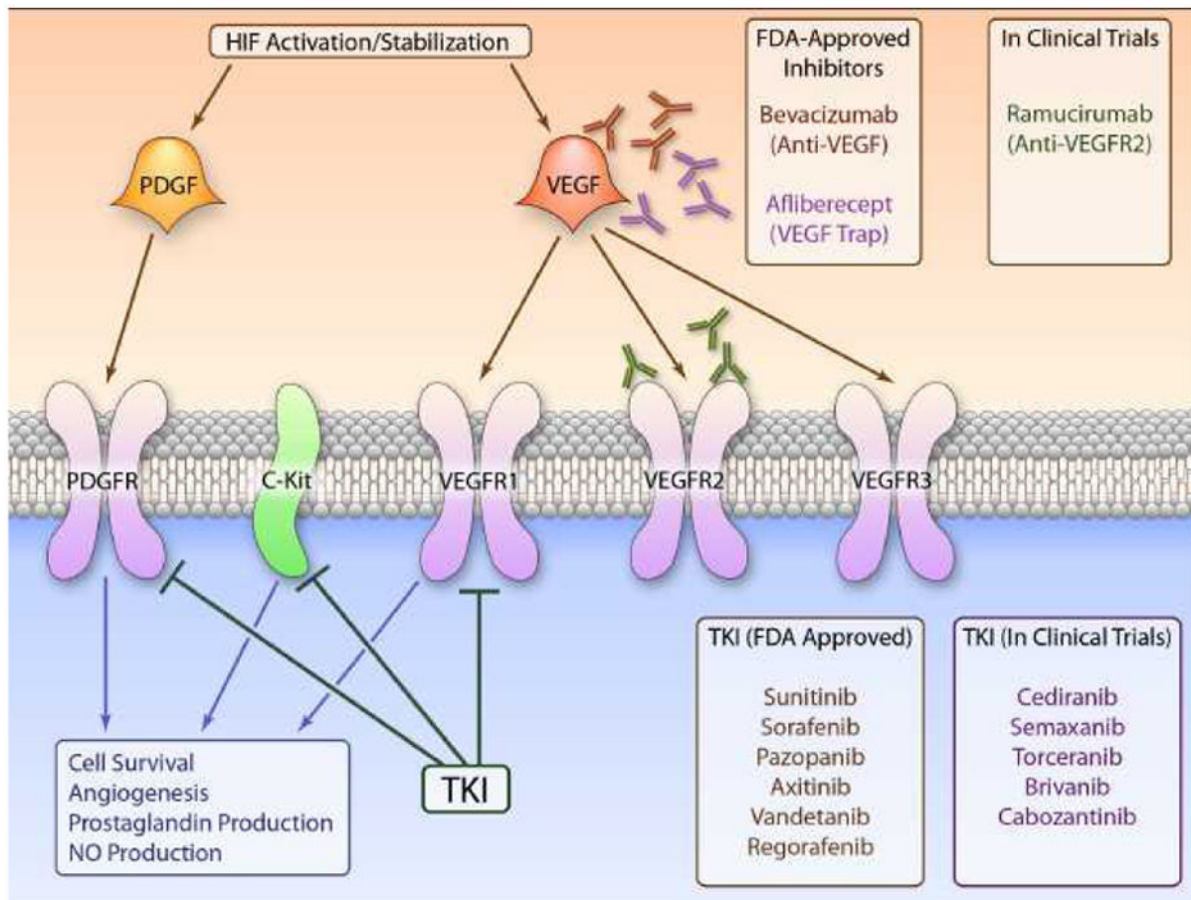
Molecular Changes Following Left Ventricular Assist Device Support for Heart Failure

Cell Therapy for Heart Failure

***Eugene Braunwald, Editor***



**Figure 1.** Schematic of the mechanisms of doxorubicin-mediated cardiomyopathy. See text for details.

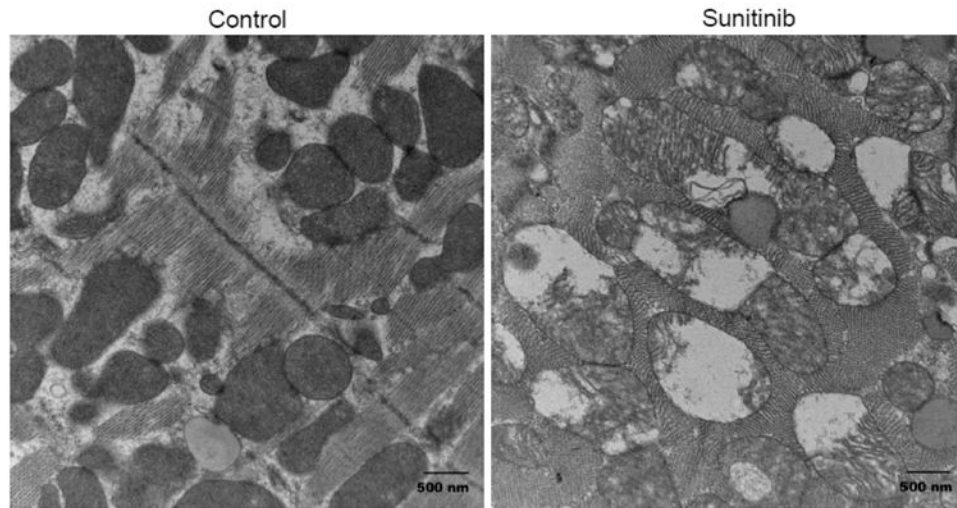


**Figure 2.**

Angiogenesis Inhibitors (VSP Inhibitors) being tested in human cancer trials. While these agents are being referred to as VEGF Signaling Pathway (VSP) inhibitors, drugs such as sunitinib inhibit many other receptor tyrosine kinases allowing them to be approved for the treatment of other cancers while at the same time creating the possibility for a wide range of “off-target” toxicities. (Illustration Credit: Ben Smith).

3A

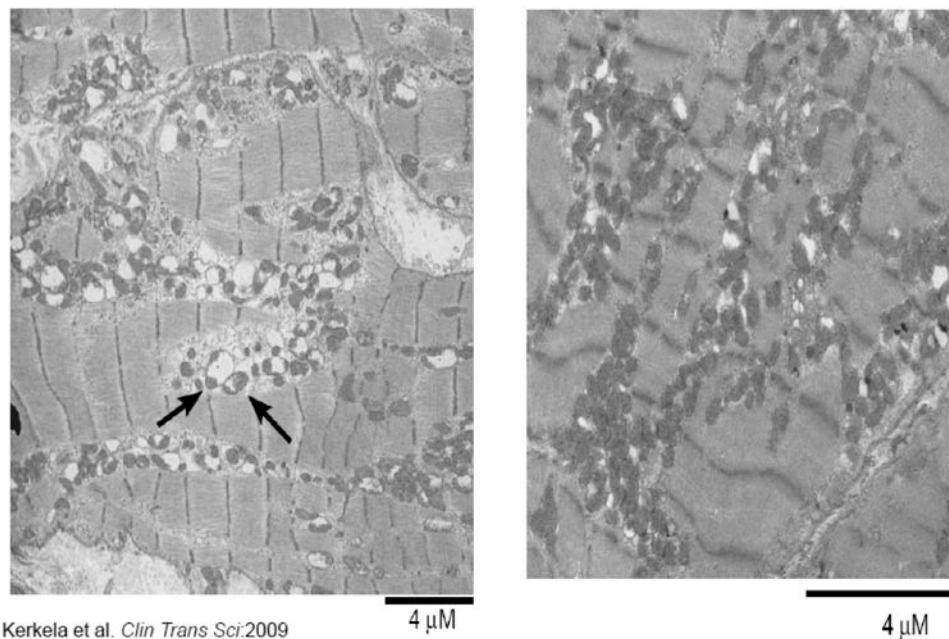
### Mitochondrial damage in sunitinib-treated mice



Chu et al. *Lancet*:2007

3B

### Resolution of cardiotoxicity at the ultrastructural level

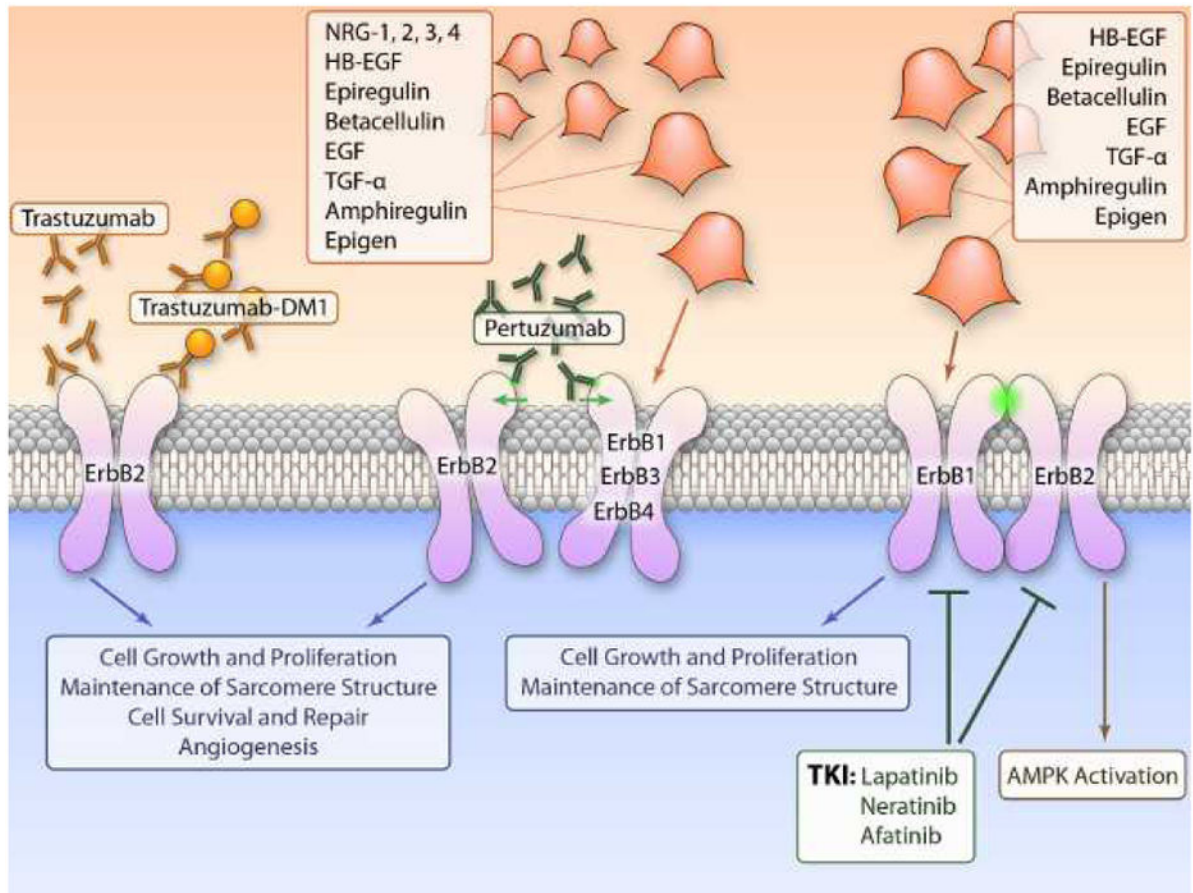


Kerkela et al. *Clin Trans Sci*:2009

**Figure 3.** Ultra-structural evidence of mitochondrial injury in mice treated with the VSP inhibitor sunitinib (A), and significant reversibility of that injury in a patient after withdrawal of sunitinib (B). A. Mice were treated with doses of sunitinib that would mimick levels in



humans. Note the mitochondrial injury on transmission EM (right panel). B. Left: Transmission EM images from a patient who developed profound heart failure while receiving sunitinib. Note the marked mitochondrial injury. Right: Repeat biopsy showing marked resolution of injury one month after discontinuation of sunitinib and addition of standard heart failure treatment.



**Figure 4.** Novel FDA-approved and investigational HER2 targeted agents being used for the treatment of breast cancer (Illustration Credit: Ben Smith).