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Julie R. McMullen

*Baker Heart Research Institute*

Patrick Y. Jay

*Washington University School of Medicine in St. Louis*

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## Perspective

# PI3K(p110 $\alpha$ ) Inhibitors as Anti-Cancer Agents

## Minding the Heart

Julie R. McMullen<sup>1,\*</sup>

Patrick Y. Jay<sup>2</sup>

<sup>1</sup>Experimental Cardiology and Heart Failure Division; Baker Heart Research Institute; Melbourne, Victoria, Australia

<sup>2</sup>Washington University School of Medicine; Departments of Pediatrics and Genetics; St. Louis, Missouri USA

\*Correspondence to: Julie R. McMullen; PO Box 6492; St. Kilda Road Central; Melbourne Victoria 8008 Australia; Tel.: +61.3.85321194; Fax: +61.3.85321100; Email: Julie.mcmullen@baker.edu.au

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### ABSTRACT

The central role of phosphatidylinositol 3-kinase (PI3K, p110 $\alpha$ ) signaling in allowing cancer cells to bypass normal growth-limiting controls has led to the development of PI3K(p110 $\alpha$ ) inhibitors. A challenge in targeting PI3K(p110 $\alpha$ ) relates to the diverse actions of the PI3K pathway in numerous cell types. Recent findings in mice deficient in PI3K(p110 $\alpha$ ) activity in the heart, demonstrate the critical role of this pathway in protecting the heart against pathological insults. Mice deficient in PI3K(p110 $\alpha$ ) displayed accelerated heart failure in response to dilated or hypertrophic cardiomyopathy. These results help explain the association of cardiomyopathy in cancer patients given tyrosine kinase inhibitors and raise concerns for the use of PI3K(p110 $\alpha$ ) inhibitors in cancer patients with cardiovascular risk factors. Interestingly, an inhibitor of the mammalian target of rapamycin (a downstream effector of PI3K), did not have adverse effects on the heart. A more complete understanding of the complex arms and interactions of the PI3K pathway will hopefully lead to the development of anti-cancer agents without cardiac complications.

### THE PHOSPHATIDYLINOSITOL 3-KINASE SIGNALING PATHWAY

Phosphatidylinositol 3-kinases (PI3Ks) are a family of lipid kinases that phosphorylate the hydroxyl group at position 3 of phosphatidylinositol (4,5) biphosphate (PIP<sub>2</sub>) to produce the second messenger phosphatidylinositol (3,4,5) trisphosphate (PIP<sub>3</sub>).<sup>1,2</sup> PI3K isoforms are divided into three classes (I, II, III) and composed of several subunits.<sup>1,2</sup> Class I PI3Ks are the best characterized and are subdivided into class I<sub>A</sub> and I<sub>B</sub>. Class I<sub>A</sub> PI3Ks consist of a catalytic subunit (p110 $\alpha$ , p110 $\beta$  and p110 $\delta$ ) and a regulatory subunit (p85 $\alpha$ , p55 $\alpha$ , p50 $\alpha$ , p85 $\beta$ , and p55 $\gamma$ ). They are activated by receptor tyrosine kinases e.g., insulin and insulin-like growth factor 1 receptors (IGF1R; Fig. 1). Other tyrosine kinase receptors like BCR-ABL and ErbB2, which new anti-cancer drugs target, also signal through the PI3K pathway.<sup>3,4</sup> Class I<sub>B</sub> PI3K consists of the p110 $\gamma$  catalytic subunit and the p101 regulatory subunit and is activated by G-protein-coupled receptors (GPCRs; Fig. 1). Class I PI3Ks produce PIP<sub>3</sub>, a lipid second messenger that controls a wide range of cellular responses.<sup>5</sup> Phosphatase and tensin homolog (PTEN) negatively regulates PI3K signaling by dephosphorylating PIP<sub>3</sub> to PIP<sub>2</sub>. Akt is activated downstream of PIP<sub>3</sub> to mediate physiologic processes. Substantial crosstalk exists with other signaling networks at all levels of the PI3K pathway.<sup>6</sup>

### THE CENTRAL ROLE OF PI3K SIGNALING IN CARCINOGENESIS

It has been suggested that malignant growth requires six essential changes in cell physiology including self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis.<sup>7</sup> Mutations in the PI3K signaling pathway play critical roles in at least two of these oncogenic phenotypes (i.e., self-sufficiency in growth signals and evasion of apoptosis). Many inherited and acquired oncogenic mutations in PI3K signaling have been identified.<sup>6</sup> For example, loss-of-function mutations of the tumour suppressor PTEN, are found in Cowden disease, a familial cancer syndrome, and a significant percentage of spontaneous cancers, leading to constitutive activation of class I PI3Ks.<sup>8,9</sup> Activating mutations of PI3K(p110 $\alpha$ ) have also been associated with diverse forms of cancer at high frequency.<sup>10,11</sup> Thus, uncontrolled activation of the PI3K(p110) pathway is a critical molecular mechanism by which cancer cells bypass normal growth-limiting controls. Consequently, the therapeutic potential of PI3K(p110 $\alpha$ ) inhibitors has generated great

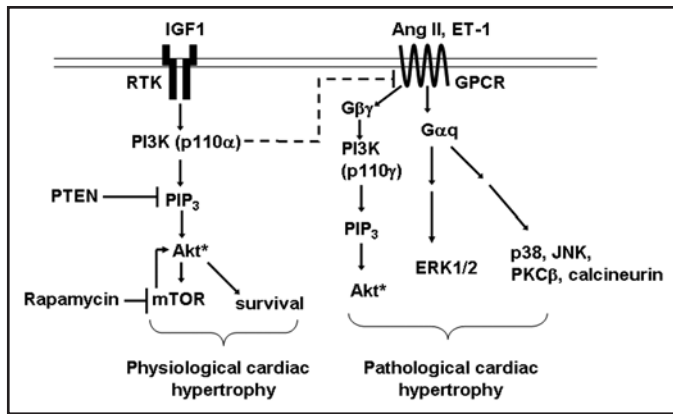


Figure 1. Schematic of signaling cascades in the heart. PI3K is activated by receptor tyrosine kinases (RTK) and G-protein-coupled receptors (GPCRs). In the heart, PI3K activated by RTK induces physiological cardiac hypertrophy, whereas PI3K activated by GPCRs participates in the depressed cardiac function associated with pathological hypertrophy. IGF, insulin-like growth factor 1; Ang II, angiotensin II; ET-1, endothelin 1; mTOR, mammalian target of rapamycin; ERK, extracellular responsive kinase; PKC, protein kinase C.

interest.<sup>12-15</sup> A challenge in targeting PI3K(p110 $\alpha$ ), however, relates to the diverse actions of the PI3K(p110 $\alpha$ ) pathway in numerous cell types and the theoretical off-site effects. One such concern was the risk of diabetes because PI3K is a downstream effector of the insulin receptor. Later reports suggested that unmanageable metabolic disturbances may not be a major concern.<sup>13</sup> On the other hand, the risk of cardiomyopathy may be significant, based on studies in mouse models and clinical experience with tyrosine kinase inhibitors.

### NOT ALL GROWTH IS BAD: PI3K(P110 $\alpha$ ) MEDIATES PHYSIOLOGIC HEART GROWTH AND PROVIDES PROTECTION FROM PATHOLOGIC STRESS

Growth of the heart is broadly classified as either pathological (“bad”) or physiological (“good”).<sup>16</sup> Cardiac growth in response to pathologic stimuli like hypertension is a poor prognostic sign because of its association with the development of heart failure.<sup>17,18</sup> This form of growth is referred to as pathologic hypertrophy. Signaling cascades downstream of GPCR have been implicated in inducing pathologic cardiac hypertrophy. Cardiac specific overexpression of G $\alpha$ q,<sup>19</sup> PKC $\beta$ <sup>20</sup> and calcineurin<sup>21</sup> lead to hypertrophy, heart failure and premature death in transgenic mice. (Fig. 1). An exception to the association of heart failure with hypertrophy is the cardiac muscle growth that occurs in athletes. Physiologic growth includes developmental and exercise-induced heart growth and is regulated by the IGF1R-PI3K(p110 $\alpha$ ) pathway (Fig. 1).<sup>22-24</sup> Physiological cardiac hypertrophy is associated with normal or enhanced cardiac function, and is not associated with heart failure and increased mortality.<sup>16,25</sup>

In a cardiac-specific transgenic mouse model expressing a constitutively active (ca) PI3K(p110 $\alpha$ ) mutant, PI3K(p110 $\alpha$ ) activity was elevated 6.5-fold, heart size was increased by approximately 20%, and cardiac function and lifespan were normal.<sup>22</sup> In contrast, in a cardiac-specific mouse model expressing a dominant negative (dn) PI3K(p110 $\alpha$ ) mutant, PI3K(p110 $\alpha$ ) activity was reduced by 77% and hearts were approximately 20% smaller. Under basal conditions, cardiac function in dnPI3K transgenics was not significantly different to that of control animals.<sup>22</sup> This suggests that PI3K(p110 $\alpha$ ) inhibitors may be safe in the heart under normal conditions.

### INHIBITING PI3K(P110 $\alpha$ ) IN A SETTING OF HEART DISEASE

Cardiac function was not compromised in mice deficient in PI3K(p110 $\alpha$ ) under basal conditions, but the critical role of PI3K(p110 $\alpha$ ) in regulating physiological heart growth led us to believe that inhibiting PI3K(p110 $\alpha$ ) in the heart may have an adverse effect in the presence of pathologic stimuli. To test this hypothesis, we recently studied dnPI3K(p110 $\alpha$ ) transgenic mice in a setting of dilated or hypertrophic cardiomyopathy.<sup>26</sup> DnPI3K(p110 $\alpha$ ) transgenic mice were genetically crossed to a transgenic mouse model of dilated cardiomyopathy (DCM)<sup>27</sup> or subjected to pressure overload for 1 week (a surgically placed constriction of the ascending aorta increases the pressure work of the heart to induce hypertrophic cardiomyopathy).<sup>28</sup> The transgenic mouse model of DCM has a mean lifespan of approximately 80 days in males. In a setting of reduced PI3K(p110 $\alpha$ ) activity, lifespan in the DCM model was reduced dramatically to ~40 days.<sup>26</sup> In the model of pressure overload, cardiac function was significantly depressed in dnPI3K(p110 $\alpha$ ) transgenic mice but not control (non-transgenic) animals (Fig. 2A).<sup>26</sup> These data suggest that PI3K(p110 $\alpha$ ) is essential for maintaining cardiac function in response to a pathological cardiac insult and raises concerns for the use of PI3K(p110 $\alpha$ ) inhibitors in cancer patients with cardiovascular risk factors.

PI3K(p110 $\alpha$ ) induced “good” physiological cardiac growth also appears to inhibit “bad” pathological growth and to protect the heart from failing. In contrast to the accelerated heart failure observed in dnPI3K transgenics subjected to dilated or hypertrophic cardiomyopathy, caPI3K transgenic mice with increased physiological heart growth were significantly protected in these models.<sup>26</sup> Transgenic expression of caPI3K increased the lifespan of mice with dilated cardiomyopathy by 15–20%. The increase was comparable to that found using angiotensin-converting enzyme inhibitors, a mainstay of clinical heart failure management.<sup>27</sup> The caPI3K transgenics also displayed a blunted hypertrophic response to pressure overload and less pathology than control mice.<sup>26</sup>

To understand how physiological signaling/growth inhibits pathological growth, we isolated myocytes from non-transgenic, caPI3K transgenic and dnPI3K transgenic hearts. caPI3K myocytes showed a blunted response to GPCR stimulation whereas dnPI3K myocytes showed an exaggerated response.<sup>26</sup> These data suggest that PI3K(p110 $\alpha$ ) can inhibit signaling molecules downstream of GPCR, and explains how inhibition of PI3K(p110 $\alpha$ ) could accentuate the unhealthy response to pathologic stimuli.

### PARADOXICAL EFFECTS OF MAMMALIAN TARGET OF RAPAMYCIN (mTOR) INHIBITION IN THE HEART

Inhibitors of mTOR, a downstream target of PI3K/Akt and effector of the growth response, are also being developed as anti-cancer drugs. Encouraging results from clinical trials of mTOR inhibitors have emerged.<sup>29</sup> Somewhat surprisingly, rapamycin, an inhibitor of mTOR, had an opposite effect on cardiac function to that observed in PI3K deficient mice (i.e., dnPI3K). Rapamycin improved cardiac function in a setting of left ventricular hypertension and cardiac dysfunction<sup>30</sup> (Fig. 2B). Furthermore, rapamycin reduced cardiac fibrosis in response to pressure overload,<sup>31</sup> whereas inhibition of PI3K(p110 $\alpha$ ) resulted in more fibrosis, which adversely increases the stiffness of the myocardium.<sup>26</sup> The opposite effects of reductions in PI3K or mTOR activity on cardiac function highlight the biological complexity of targeting this pathway. While these results seem

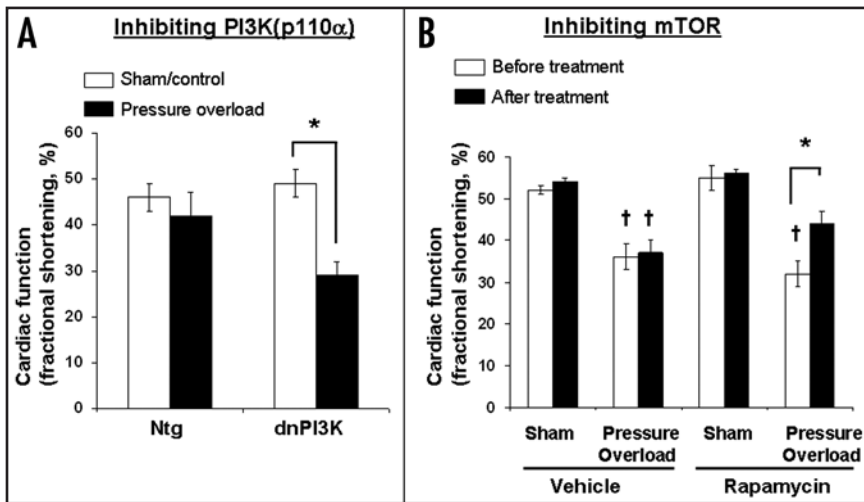


Figure 2. (A) Cardiac function in non-transgenic (Ntg) or dnPI3K transgenic mice in response to a moderate model of pressure overload or the sham operation for 1 week. Cardiac function was assessed non-invasively by echocardiography by measuring fractional shortening. Moderate pressure overload does not induce cardiac dysfunction in Ntg after a period of one week. Data taken from McMullen et al.<sup>26</sup> (B) Cardiac function in Ntg mice subjected to a severe model of pressure overload or the sham operation for 1 week. Mice were then treated with an mTOR inhibitor (rapamycin) or vehicle for 1 week. The severe model of pressure overload induces cardiac dysfunction in mice after 1 week. \* $P < 0.05$ , † $P < 0.05$  compared with sham. Data taken from McMullen et al.<sup>30</sup>

contradictory, it may be due to feedback mechanisms when inhibiting mTOR. Inhibiting mTOR has been reported to result in feedback on Akt (Fig. 1), resulting in increased or decreased Akt activation depending on the exposure time.<sup>32,33</sup> Interestingly, Akt appears to be differently regulated in the heart. Myostatin, an inhibitor of cardiac growth, inhibited GPCR induced Akt phosphorylation but not receptor tyrosine kinase induced phosphorylation.<sup>34</sup> Finally, Akt1 and 2, the predominant isoforms in the heart may mediate separate physiologic processes induced by PI3K. Akt1 seems to effect physiologic growth and the anti-hypertrophic response to pressure overload, whereas Akt2 may effect anti-apoptotic pathways in the heart.<sup>35,36</sup> Rapamycin might affect a very specific arm of the PI3K signaling pathway that leaves intact the salutary effects of PI3K activation in the heart.

## THE PROMISE OF A GOOD LIFE AFTER THE CANCER IS CURED

An incredible demand is placed upon the mammalian heart to pump an entire lifetime without any significant mechanism to replace injured or dead cells. Therefore, a robust mechanism must exist to ensure survival of cardiac myocytes when they are stressed. It is not surprising then, that cancer cells and the heart share the PI3K pathway as a molecular survival mechanism. Considered in this context, the association of heart failure in cancer patients given tyrosine kinase inhibitors, like trastuzumab and imatinib mesylate, is understandable. Trastuzumab-related cardiomyopathy has been linked with downregulation of ErbB2 signaling, and imatinib mesylate is thought to promote apoptosis and heart damage by inhibiting the non-receptor tyrosine kinase c-Abl.<sup>37,38</sup> Obviously, one should not have to trade one disease for another that often has a worse prognosis.

Since dnPI3K transgenic animals have normal cardiac function until stressed, it seems prudent to minimize stressors on the heart in cancer

patients given tyrosine kinase or PI3K inhibitors. These stressors might include comorbid diseases like hypertension or other chemotherapeutic drugs with cardiotoxic effects. In this regard, the incidence of cardiomyopathy has declined substantially in breast cancer patients given trastuzumab when such issues were addressed.<sup>39</sup> Inhibition of maladaptive neurohormonal responses mediated by GPCR in the stressed heart during induction of chemotherapy could also yield important long term benefits.<sup>40</sup>

One might also prevent cardiomyopathy with individualized or combination strategies. Clearly, PI3K signaling is activated via multiple receptor types in the heart. Why then do some patients given tyrosine kinase inhibitors develop heart failure but others do not? Perhaps these patients have deficiencies in alternative pathways for PI3K activation or are unusually dependent on the specific pathway being inhibited by the prescribed tyrosine kinase inhibitor. If the mechanism in patients at risk could be defined, one might be able to supplement the alternative pathway in the heart without driving the oncogenic pathway. Alternatively, it has been suggested that concurrent inhibition of PI3K(p110 $\alpha$ ) and mTOR may be required for complete growth inhibition.<sup>12</sup> To date, the effects of this treatment combination on the heart have not been comprehensively addressed, but experimental animal models offer the promise that adding an mTOR inhibitor may actually benefit the stressed heart.

In summary, recent findings in mice with deficient or supranormal PI3K(p110 $\alpha$ ) activity in the heart demonstrate the vital role of this pathway in normal growth and protection against pathologic stress. The data explain the association of cardiomyopathy in patients given tyrosine kinase inhibitors as cancer chemotherapy and raise the concern that future PI3K(p110 $\alpha$ ) inhibitors may cause an even higher incidence of heart failure. Fortunately, as the complex arms and interactions of the PI3K pathway are better understood, hope is raised that the deleterious cardiac complications can be avoided. Thus, patients may be offered the dual promise of a cure for their cancer and a good life.

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