

## IN THE SPOTLIGHT

## Beta-Testing of PI3-Kinase Inhibitors: Is Beta Better?

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**Summary:** Although it has been known for some time that PTEN-null tumors require expression of the p110 $\beta$  isoform of phosphoinositide 3-kinase for growth, the corollary demonstration that small-molecule inhibitors of p110 $\beta$  are effective drugs for such tumors has not been shown. This has now been rectified by the demonstration that the TGX221 analogue KIN-193 is effective in mouse xenografts of HCC70 and PC3 human tumor cell lines. *Cancer Discov*; 2(5); 393-4. ©2012 AACR.

Commentary on Ni et al., p. 425 (9).

Phosphatidylinositol-3-kinases (PI3K) were discovered more than 20 years ago, and it was soon apparent that they were members of a small family of kinases that included not only lipid kinases but also some protein kinases such as mTOR. The family is subdivided into 4 classes, and it was clear quite quickly that the 4 members of the class I PI3K (p110 $\alpha$ , p110 $\beta$ , p110 $\gamma$ , and p110 $\delta$ ) were activated downstream of receptor tyrosine kinases and G protein-coupled receptors, the latter being via allosteric effects of  $\beta\gamma$  subunits of heterotrimeric G-proteins (1). This results in increased production of the membrane lipid phosphatidylinositol 3,4,5-triphosphate (PIP<sub>3</sub>), which in turn activates a wide range of cellular responses that promote cell growth and reduce apoptosis. The importance of PI3K in such cell signaling pathways raised interest from cancer researchers, which increased greatly when it was found that more than 15% of all tumors contain activating mutations in the *PIK3CA* gene, which codes for p110 $\alpha$  (2). In addition, PTEN—the phosphatase thought to be responsible for degrading PIP<sub>3</sub>—is a very common tumor suppressor gene. As a result, there has been intense activity in developing inhibitors of PI3K as potential anticancer drugs, and a number of such molecules are currently in clinical trials.

One important question is how each of the PI3K isoforms contributes to tumor development and whether isoform-selective therapies might be able to achieve therapeutic effects while minimizing potential side effects caused by inhibiting all isoforms. The most obvious target isoform is p110 $\alpha$ . Indeed, inhibiting p110 $\alpha$  alone can reduce the growth of tumors containing *PIK3CA* mutations (3), but this approach is not effective in all solid tumors. No oncogenic mutations have been identified in the other class I PI3K isoforms; however, p110 $\delta$ -selective inhibitors have proven effective in the clinic in certain forms of leukemia (4).

There is less evidence that inhibiting p110 $\beta$  might be therapeutically beneficial in treating cancer, although this isoform

is interesting because it can be activated by both growth factor receptors and G protein-coupled receptors and its overexpression is capable of transforming cells (5). Knockdown of *PIK3CB* (coding for p110 $\beta$ ) has been shown to block transformation of cells, although this was only observed in PTEN-deficient cell types (6). In agreement with this, reduction in functional p110 $\beta$  reduces the incidence of tumors in PTEN-deficient mice (7). Previous biochemical studies have also shown that the known p110 $\beta$ -selective inhibitor TGX-221 blocks activation of PKB/Akt in PTEN-deficient cells (6, 8). In this issue of *Cancer Discovery*, Ni and colleagues (9) have obtained similar results by using the compound KIN-193, which they also show is highly selective for p110 $\beta$  over all other kinases tested. This finding is perhaps not surprising, given that it only differs from the previously described p110 $\beta$  inhibitor TGX221 by a single carboxyl group. They also demonstrate a significant correlation between PTEN mutations and sensitivity to KIN-193 in a large (422-member) panel of cell lines, although exceptions in both directions were seen.

If a p110 $\beta$ -selective inhibitor were active *in vivo* as an antiproliferative agent, it would potentially minimize the side effects caused by pan-PI3K inhibitors and p110 $\alpha$ -selective inhibitors (10). However, although sub-nM and 30- to 50-fold selective inhibitors of p110 $\beta$  enzyme have been described (6-8), they have not shown high antiproliferative potency in cell line assays, and, to date, no one has shown that a p110 $\beta$  inhibitor can be effective in an animal cancer model. Ni and colleagues (9) now show that KIN-193 has very good pharmacokinetic properties and as such is suitable for *in vivo* xenograft studies, in which they demonstrate for the first time that a small-molecule p110 $\beta$  inhibitor can block the progression of tumors derived from cell lines deficient in PTEN. The cytostatic effect is similar to that seen with p110 $\alpha$  inhibitors in xenografts of *PIK3CA* mutant cells and the result adds to the growing evidence that inhibiting different PI3K isoforms has different effects in different tumor types.

However, there are still a number of questions remaining. For example, why are very high levels of KIN-193 required to achieve a therapeutic effect? Similar observations have been made with the use of p110 $\beta$ -selective inhibitors in other PTEN-deficient cell models (6, 8, 9, 11). One explanation for this is crossover with other targets for the drugs, as is suggested in the work of Ni and colleagues (9). In support of this, it has been shown that the combination of a p110 $\beta$  inhibitor with a p110 $\delta$ -selective inhibitor can together block activation of Akt in some PTEN-deficient

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cell lines when neither inhibitor alone is capable of doing this (3). Together, this suggests that the effect of inhibiting combinations of class I PI3K warrants further investigation. Also, it is important to note that inhibition of p110 $\beta$  alone is not able to block activation of Akt in all PTEN-negative cell lines (3). The reason for this discrepancy with KIN-193 remains to be resolved, but it is notable that all the cell lines that responded to KIN-193 not only lacked PTEN but were also deficient for p53 ([www.sanger.ac.uk/genetics/CGP/cosmic/](http://www.sanger.ac.uk/genetics/CGP/cosmic/)), raising the possibility that more than simple loss of PTEN might be required to make cells responsive to p110 $\beta$  inhibitors. Although much remains to be learned, the beta-testing performed by Ni and colleagues (9) is likely to revive interest in p110 $\beta$  inhibitors as potential anticancer agents.

### Disclosure of Potential Conflicts of Interest

Both P.R. Shepherd and W.A. Denny have served as consultants to Pathway Therapeutics.

### Authors' Contributions

**Writing, review, and/or revision of the manuscript:** P.R. Shepherd, W.A. Denny

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