Am J Clin Exp Urol 2014;2(3):188-198
www.ajceu.us /ISSN:2330-1910/AJCEU0002032

Review Article

PI-3 kinase p110β: a therapeutic target in advanced prostate cancers

Benyi Li[1,2,3,4], Aijing Sun[3], Wencong Jiang[4], J Brantley Thrasher[1], Paul Terranova[2]

Departments of [1]Urology, [2]Molecular & Integrative Physiology, The University of Kansas Medical Center, Kansas City, KS 66160, USA; [3]Department of Pathology, Shaoxing People's Hospital, Shaoxing 312000, China; [4]Department of Urology, Guangdong Medical College, Zhanjiang 524001, China

Received August 21, 2014; Accepted September 5, 2014; Epub October 2, 2014; Published October 15, 2014

Abstract: Prostate cancers in the castration-resistant stage are life-threatening because they are not curable in clinic. The novel androgen receptor inhibitor Xandi (Enzalutamide) and the new CYP17 inhibitor Zytiga (Abiraterone) prolonged patient survival only a few months in advanced prostate cancers. Therefore, novel therapeutic agents for advanced prostate cancers are urgently needed. PI-3 kinases are major intracellular signaling molecules that regulate multiple signal pathways related to cellular metabolism, cytokinesis, growth and survival. Accumulating evidence in the literature indicates that some isoforms of this kinase family are oncogenic and abnormally expressed in various human cancers, including prostate cancers. Recent extensive studies from our group and others showed that PI-3 kinase p110β is aberrantly overexpressed in advanced prostate cancers and is critical for prostate cancer development and progression as demonstrated in cell-based and animal models. Importantly, novel p110β-specific inhibitors have been developed and are currently been testing in clinical trials. In this article, we will briefly summarize recent developments in this regard.

Keywords: Prostate cancer, p110β, cancer therapy, castration resistance

Introduction

Prostate cancer is the second most diagnosed cancer around the world with about 240K new cases annually in North America [1]. The natural history of prostate cancers varies individually, ranging from microscopic lesions, organ-confined diseases, to aggressive metastatic cancers that ultimately claim patient life [2]. The etiology of prostate cancer and subsequent disease relapse may have various molecular causes, but in each scenario, the androgen receptor (AR) expression is maintained and highly activated [3]. Since the seminal work of Huggins and Hodges in 1941, medical treatment for metastatic prostate cancer has relied heavily on androgen ablation to inactivate the AR [2]. However, most patients treated by androgen ablation ultimately relapse to more aggressive so-called 'castration-resistant prostate cancers' (CRPC) with a highly re-activated AR pathway. Although it is not fully clear how the AR is re-activated after androgen ablation (by either surgical or hormonal castration), accumulating evidence indicated that several intracellular signaling pathways including the phosphoinositide 3-OH kinase (PI-3 kinase, PI3K) family [4-10], mitogen-activated protein kinase family (MAP kinase, MAPK) [11-14] and Src kinase family [15-20] are involved. As a consequence of recent studies, targeting the AR activation pathways is becoming an intensive research topic in prostate cancer [21-27]. Despite recent developments of the novel anti-AR agent Enzalutamide [28-30] and the androgen synthesis enzyme CYP17 inhibitor Abiraterone [31-33], advanced CRPCs remain a fatal with no means of cure in sight [34]. In this mini-review, we will focus our discussion on the role of PI-3 kinase family, especially the class IA isoform p110β, in prostate cancer development and progression, as well as the potential implication of targeting this PI-3 kinase as a novel therapy.

PI-3 kinase family

PI3Ks are a group of major cellular signaling molecules that regulate multiple pathways and

cellular functions [35-37]. In mammalian cells, there are three classes of PI3K isoforms (I, II and III), of which the class I PI3Ks are further divided into two subtypes, IA p110α/β/γ and IB p110γ. Class IA PI3Ks are associated with the p85 regulatory subfamily, while class IB is associated with p101/p84 regulatory subunits. Class I and III but not class II PI3Ks are dual functional kinases, namely lipid kinase and protein kinase. PI3K p110α and p110β are ubiquitously expressed and knocking out either gene in mice results in an embryonic lethal phenotype. In contrast, PI3K p110α and p110β are predominantly expressed in lymphocytes, and knockout animals display immune defects but the mice are viable. There is only one member of the class III PI3K family VPS34, and its major function is regulation of autophagy [38, 39]. Due to the inactivating mutation of PI3K signaling opponent PTEN gene (phosphatase and tensin homologue deleted on chromosome-10) or unknown mechanism after androgen withdrawal, elevated PI3K activity has been proposed as one of the major mechanisms for prostate cancer progression [5, 34].

Property diversity of class I PI-3 kinase isoforms

It is well documented that class I PI3Ks are activated upon hormone and growth factor stimulation through either receptor-tyrosine kinases (RTKs) or G-protein coupled receptors (GPCR). PI3K p110α and p110β share a high similarity in amino acid sequences, expression patterns and regulatory partners. In fact both of them produce the same phospholipid substrate of phosphatidylinositol 3,4,5-trisphosphate (PtdIns (3,4,5) P3), a well-established second messenger for AKT activation. However, these two class I kinases (p110α or p110β) exert distinct preferences in regulation and functionality [40]. The p110α kinase is mostly activated by receptor-tyrosine kinases and small GTPase Ras, while p110β kinase prefers GPCR and Rho GTPase RAC1/CDC42 [41]. GPCR-activated Gβγ subunit interacts with p110β on its C2-helical linker region (^{514}KAAEIASSDSANVSSRGGKKFLPV^{537}) and disruption of this interaction by a decoy peptide derived from this region reduces PTEN-deficient cancer cell growth and invasion [42]. On the other hand, p110 catalytic activity is monitored by the regulatory p85 subunits, of which two inhibitory contacts between p110α C2/kinase domain and p85α nSH2/iSH2 domain whereas three contacts between p110β C2/kinase domain and p85β nSh2/iSH2/cSH2 domain exist to restrict their basal activity [43-45]. These isoform-specific restrictions reflect functional diversity of class I PI-3 kinases in different cell/tissue types.

In terms of functionalities, p110α plays a pivotal role in insulin signaling and glucose metabolism, as well as G1 cycle entry, whereas p110β is important in DNA synthesis/replication and cell mitosis. While p110α is mainly localized in cytoplasm, p110β resides in the nuclear compartment [46]. Although either p110α or p110β is able to sustain cell proliferation and survival as a single viable kinase in immortalized mouse cells [47], there are many differences between these two Class I kinases in human cancer cells. First, their protein levels and corresponding kinase activities are variable in colon/urinary bladder tumor tissues and a significant difference between these two isoforms was found among various colon cancer cell lines [48]. Second, neutralizing antibodies against p110α induced apoptosis in multiple colon cancer cell lines but p110β antibodies only attenuated *de novo* DNA synthesis [48]. This is supported by a recent report [46] that p110β is mostly involved in DNA replication through both kinase-dependent and -independent mechanisms. Third, a nuclear localization sequence (NLS) has been identified in p110β C2 domain (^{310}KVNTTKSTK^{318}) but it is missing in p110α and this nuclear localized p110β is essential for cell survival [49] and chromosome segregation during mitosis [50]. In addition, p110β but not p110α was recently shown to be involved in osteoclastic resorption in bone [51, 52] and in male fertility as evidenced by testicular hypotrophy and impaired spermatogenesis in p110β inactivated mice [53]. Most strikingly, in spite of these diverse differences, a very recent report showed that p110α actually dimerizes with p110β upon serum stimulation in NIH3T3 cells and that their association depends on the p85 regulatory subunit [54]. Further analysis revealed that their kinase activity of this oligomerization in AKT phosphorylation is regulated by PTEN, which is also associated with the dimerized p110α/β complex. These data reflect another layer of PI3K regulation.

Autophagy is an evolutionary mechanism in response to nutritional stress and increased autophagic response is often associated with

cancer progression and treatment resistance in many cancers [55]. Interestingly, in mice with conditional knockout of class I PI3Ks, p110α deletion resulted in a slight increase in autophagic response while p110β deletion resulted in a severe defect in autophagy response [56]. This p110β-mediated promotion of autophagy is associated with increased cellular levels of PtdIns(3)P that is required for the early event in autophagosome formation. Further analysis revealed that p110β kinase activity is not essential in promoting autophagy but its scaffolding property of the kinase protein is involved through its direct interaction with small GTPase Rab5 in responding to growth factor withdrawal [57]. These data provided a strong rationale for targeting p110β as a therapeutic biomarker in cancer management.

Oncogenic role of PI-3 kinase p110β in prostate cancer

It is conceivable that all class I PI-3 kinases are oncogenic when overexpressed or overactivated in mammalian cells [37, 58]. In human cancers, the most common gain-of-function mutations in PI3K family were from *PIK3CA* gene/p110α protein, whereas the los-of-function mutations were from *PTEN* gene/PTEN phosphatase protein [40, 59, 60]. In a small portion of human cancers, gene amplification was seen in *PIK3CB* gene/p110β protein although its wild-type form is also oncogenic [58, 61]. Only one tumor-associated p110β mutant E633K has been reported so far from a HER2-positive breast cancer patient [62]. This E633K mutant p110β had a higher basal activity that activates AKT-S6K1 pathway and promotes tumor cell proliferation/survival.

In prostate cancers, due to a higher prevalence of PTEN loss mutation, aberrant PI3K/AKT activation was proposed to play an important role in disease progression [34, 63]. In animal models, genetic approaches demonstrated that p110β but not p110α activation is required for *PTEN*-deletion or *ERBB2*-driven tumor development in the prostate and breast, respectively [9, 64]. Consistently, overexpression of a constitutive p110β or its downstream kinase AKT protein induces early lesions of prostatic tumor formation in mice [65, 66]. These animal studies were supported by data from cancer cell culture models, in which p110β activity was shown to be critical for cell proliferation and survival in PTEN-null prostate [10] and colon cancers [67]. These findings have been supported by additional animal model-based studies [68-71] and revealed that p110α but not p110β is critical in polyoma middle T antigen (MT) plus HER2-driven breast tumor development [69], PTEN-null derived thyroid tumor [68], or MT/Kras-driven ovarian tumor [70]. Those data indicate that PI3K isoform dependence in tumor development is not tissue- or organ-specific but due to the driving mode of carcinogens [71].

To provide clinical relevance of PI3K involvement in prostate cancers, the expression profiles of class I PI3K family in human were examined. Gene expression of p110β and p85α but not p110α at the mRNA and protein levels were observed to be significantly higher in primary tumors compared to their benign counterparts [4]. These findings are supported by other reports from different groups [72, 73]. PI3K p110β activity and its downstream kinases AKT-SGK1 were found to be involved in AR-dependent gene expression, cell proliferation and survival in prostate cancer cells [74-76]. Most importantly, with a unique inducible AKT activation system [77], AKT activation was capable of driving the castration-resistant progression of prostate cancer in a mouse xenograft model [76]. These studies, together with others, provide a strong clinical rationale for targeting the PI-3 kinase p110β for prostate cancer management.

Isoform-specific p110β inhibitors in prostate cancer

Given the prominent importance of PI-3 kinases in multiple human cancers, targeting this pathway as a novel cancer therapy has drawn extensive attention in recent years as discussed in newly published review articles [34, 63, 78-83]. Most chemical inhibitors currently used in preclinical and clinical studies are targeting PI3K/AKT-mTOR pathways with either mono-, dual- or pan-specificities. The majority of inhibitors target p110α, AKT or mTOR and only two, GSK2636771 and SAR260301 (compound 28, discussed later), are p110β-specific inhibitors currently in early clinical trial [81]. It is obvious that non-isoform selective inhibitors for the PI3K pathway will yield higher efficiency but with severe side effects, while isoform-selective inhibitors definitely have higher toler-

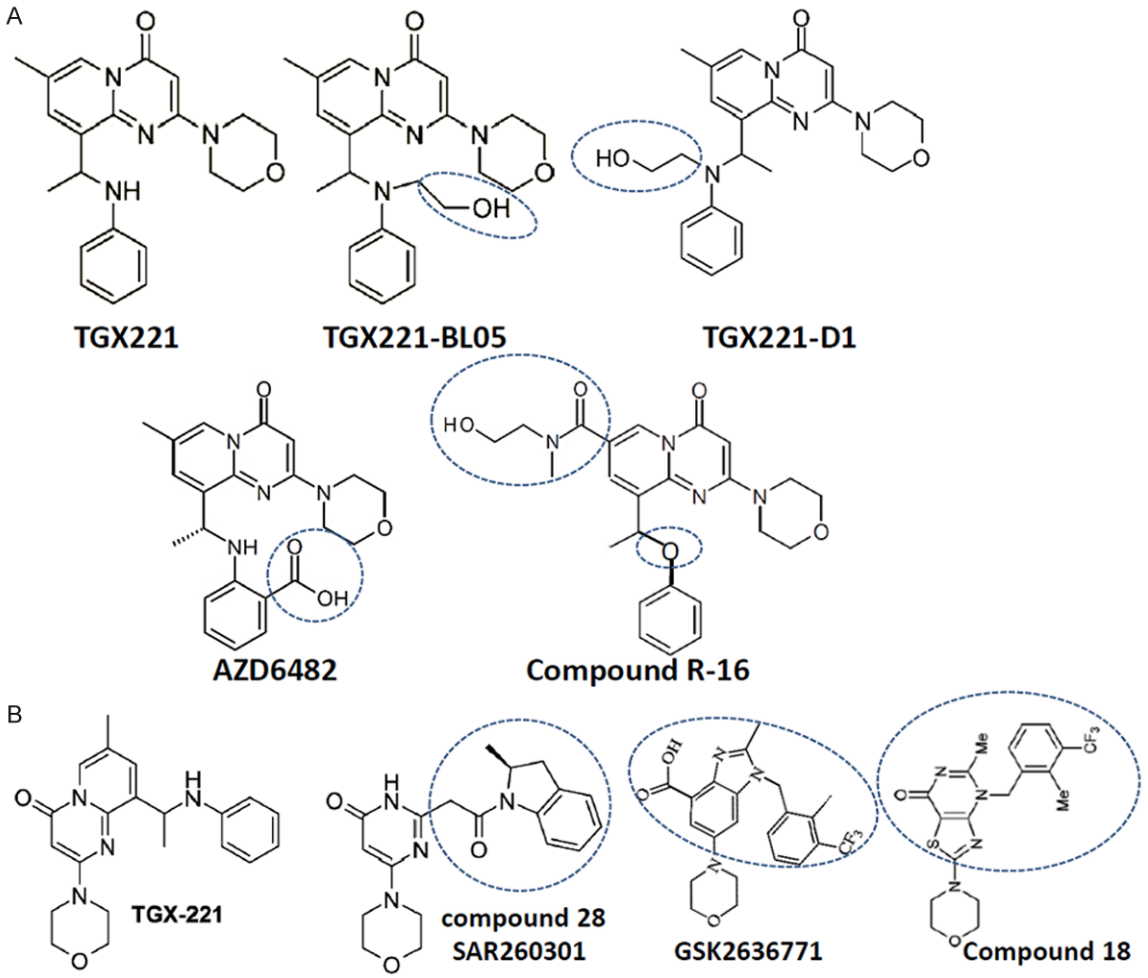

Figure 1. Chemical structures of the TGX221-derived (A) and structurally different (B) p110β-specific inhibitors. Groups circled in dashed lines are the major structural differences compared to TGX221.

able doses with fewer side effects [81]. In the era of personalized medicine, a potent inhibitor with precise target selectivity will be ideal for better patient management.

The first p110β-specific inhibitor TGX221 was reported in 2005 [84] and it is a derivative of the pan-PI3K inhibitor LY294002, which was synthesized in 1994 based on a natural flavonoid compound Quercetin that targets multiple protein kinases [85]. TGX221 has an IC_{50} of 5 nM against p110β, representing a high target selectivity and was initially used as anti-thrombotic agent in animals at 2.5 mg/kg intravenously without cardiovascular side-effect [86]. Due to the concern of its potential bleeding side-effect by inhibiting platelet function [84, 87] and its poor water solubility, a nanoparticle-based approach to specifically deliver TGX221 to cancer cells was designed [88, 89]. The cancer cell-specific targeting is based on a RNA aptamer-mediated binding against prostate-specific membrane antigen (PSMA), a cell surface protein highly expressed on prostate cancer cells [90]. TGX221 was modified (analog BL05, **Figure 1A**) so that the analog could be conjugated with polymers without affecting its inhibitory effect towards p110β/AKT activity. Early experiments in cell and animal models revealed excellent prostate cancer cell-specific uptake kinetics and sustained bioavailability in blood stream [90]. As tested in a nude mouse xenograft model, PSMA-targeted TGX221 nanoparticles dramatically reduced tumor growth of xenografts derived from multiple prostate cancer cells (Li et al, unpublished data highlighted at http://cdmrp.army.mil/pcrp/research_highlights/13li_highlight.shtml).

In addition, an alternative approach to target the TGX221 compound for HER2 overexpressing tumors was developed [89]. A HER2 binding peptide was conjugated to a TGX221 analog (TGX221-D1, **Figure 1A**) with a spacer peptide chain. The TGX-D1 analog was modified from TGX221 so as to be linked to the HER2-targeting peptide without affecting its inhibitory effect towards p110β kinase. To provide a prostate cancer-specific therapeutic effect, a short peptide derived from a substrate of prostate-specific antigen was inserted between HER2-binding peptide and TGX221 analog TGX-D1, so that the final peptide conjugates of TGX221 could be chopped by PSA inside prostate cancer cells after HER2-mediated uptake. The first phase study showed that the TGX221 peptide conjugate has a better prostate cancer cell-specific uptake rate and excellent water solubility compared to the parental compound TGX221 [89]. Further testing in animal models is required to determine its anti-tumor activity in xenograft models.

TGX221 analog KN-309 was synthesized as a racemic mixture in 2004 (described in a patent document of Jackson, et al. WO2004016607). Its active enantiomer AZD6482 (**Figure 1A**) was tested for its anti-thrombotic effect in animals and human volunteers [91]. AZD6482 has an IC_{50} of 10 nM towards p110β and was verified as the first anti-platelet agent in humans without increased bleeding time (clinical trial NCT00688714 and NCT00853450). Interestingly, a different group also identified AZD6482 (named KIN-193) as a potent p110β-specific inhibitor from a collection of 19 PI3K inhibitors [92]. From a panel of 422 human cancer cell lines, AZD6482 (KIN-193)-induced suppression of cell proliferation was associated with PTEN-null status. Intraperitoneal delivery of AZD6482 (KIN-193) at a dose of 20 mg/kg (twice a day) suppressed PTEN-null cancer cell (prostate cancer PC-3 and breast cancer HCC-70)-derived but not PTEN-positive breast HCC-1954 cancer cell-derived xenograft growth in nude mice. These data strongly suggest that targeting PTEN-deficient cancer cells with TGX221 analogs has a bright future as a therapeutic agent in cancer therapy.

Very recently, scientists from Sanofi reported a new series of p110β inhibitory compounds with major structural differences from TGX221 [93]. Compound 28 (SAR260301, **Figure 1B**) exerted preferred drug-like properties, including high water-solubility (0.928 mM), oral bioavailability and low IC_{50} specific to p110β (23 nM) more than 20-fold less compared to other PI-3 kinases. In animal experiments, oral administration of Compound 28 at a dose of 150 mg/kg bidaily suppressed AKT phosphorylation and reduced xenograft tumor growth derived from human prostate cancer PC-3 (PTEN-null) and melanoma UACC-62 (PTEN-null/$BRAF^{V600E}$ mutant) cells. These data provided the biological foundation for compound 28/SAR260301 entering early clinical trials (NCT01673737) as a therapeutic drug for advanced cancers. Meanwhile, research scientists from AstraZeneca also reported a new series of p110β-specific inhibitory compounds that exert better *in vivo* anti-thrombotic effect devoid of bleeding and insulin resistance [94]. Of which Compound R-16 (**Figure 1A**) exerted a reliable oral pharmacokinetic profile and a safe margin towards p100α to avoid interfering insulin pathway. However, its use as anti-tumor agent is currently unknown.

GSK2636771 is a p110β-specific inhibitor developed by GlaxoSmithKline and is now in early phase of clinical trials for PTEN-null cancers (NCT01458067). Like SAR260301, GSK2-63671 is largely different from TGX221 (**Figure 1B**) and has a superb IC_{50} towards to p110β (1.3 nM) [95]. GSK2636771 inhibited cell proliferation and AKT phosphorylation in PTEN-null prostate cancer (PC-3) and breast cancer (BT549 and HCC70) cell lines but not in PTEN-positive breast cancer HCC1954 cells. Also, it had no inhibitory effect on endometrioid endometrial cancer cells, neither PTEN-null nor -positive cells [96]. There is no published data in the literature for its use in animal experiments with human prostate cancer cells.

Based on GSK2636771 and another closely related series of TGX221 analogs [97], a third series of thiazolopyrimidinone compounds were reported as p110β -specific inhibitors [98]. Compound 18 (**Figure 1B**) in this series showed the most preferable properties as an oral anticancer agent, including high specificity against p110β (IC_{50} 0.6 nM), orally bioactive for 6 h suppression of AKT phosphorylation at a dose of 100 mg/kg, and a complete blockage of tumor growth derived from prostate cancer PC-3 cells at both doses of 100 or 300 mg/kg per day in nude mice. These data strongly suggest that

this well-designed small chemical compound with high specificity towards p110β represents a highly effective treatment for advanced prostate cancers.

Conclusion and prospective points

Prostate cancer at the advanced stage is a lethal disease without means to cure in clinic. Extensive studies demonstrated that aberrant activation of the PI3K pathway plays a critical role in disease progression. Current preclinical data suggest that small chemicals specifically targeting PI3K/p110β kinase are capable of suppressing tumor growth. A series of p110β -specific inhibitory compounds were reported in the literature and two of them, SAR260301 and GSK2636771, are in early phase of clinical trials. In this personalized medicine era, prostate cancer-specific targeting of a specific kinase represents the cutting edge trend in drug discovery.

Although current data from animal models did not reveal severe side effects of p110β-specific inhibitors, theoretically, systemic inhibition of p110β kinase might cause dysfunctions in off-target organs or tissues, such as insulin metabolism [64], cardiovascular [83] or brain/neuronal system [99]. Therefore, a tissue-targeted delivery system coupled with a pro-drug strategy as described previously [88, 89] will provide protection from potential systemic side effects. In addition to ATP-competitive inhibitors, alternative strategies to disrupt p110β interaction with its upstream activators like G-protein subunits or p85 proteins [4, 8, 100] will open novel avenues for even better drugs to be developed in the near future.

Acknowledgements

The research in Dr Benyi Li's lab was supported by SWOG HOPE Foundation, DoD PCRP Grants (DAMD17-03-1-0121, W81XWH-04-0214, W81-XWH-07-1-0021, W81XWH-09-1-0455), NIH NCI R21 Grant (1R21CA175279-01A1), NIH-COBRE Grant (1P20RR015563), KU William L. Valk Foundation, KUMC Mason's Foundation and Lied Foundation, as well as Chinese NSF Grant (CNSF#81172427). This work is also partially supported by a NSF Grant from Zhejiang Province of China (Y13H160104) to Dr Aijing Sun.

Address correspondence to: Dr. Benyi Li, KUMC Urology, 3901 Rainbow Blvd, MS 3035, Kansas City, KS 66160, USA. Tel: 913-588-4773; E-mail: bli@kumc.edu

References

[1] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[2] Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. J Clin Oncol 2005; 23: 8253-61.

[3] Yuan X, Cai C, Chen S, Chen S, Yu Z, Balk SP. Androgen receptor functions in castration-resistant prostate cancer and mechanisms of resistance to new agents targeting the androgen axis. Oncogene 2014; 33: 2815-25.

[4] Zhu Q, Youn H, Tang J, Tawfik O, Dennis K, Terranova PF, Du J, Raynal P, Thrasher JB, Li B. Phosphoinositide 3-OH kinase p85alpha and p110beta are essential for androgen receptor transactivation and tumor progression in prostate cancers. Oncogene 2008; 27: 4569-79.

[5] Wang Y, Kreisberg JI, Ghosh PM. Cross-talk between the androgen receptor and the phosphatidylinositol 3-kinase/Akt pathway in prostate cancer. Curr cancer drug targets 2007; 7: 591-604.

[6] Kaarbø M, Mikkelsen OL, Malerød L, Qu S, Lobert VH, Akgul G, Halvorsen T, Maelandsmo GM, Saatcioglu F. PI3K-AKT-mTOR pathway is dominant over androgen receptor signaling in prostate cancer cells. Cell Oncol 2010; 32: 11-27.

[7] Carver BS, Chapinski C, Wongvipat J, Hieronymus H, Chen Y, Chandarlapaty S, Arora VK, Le C, Koutcher J, Scher H, Scardino PT, Rosen N, Sawyers CL. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell 2011; 19: 575-86.

[8] Liu J, Youn H, Yang J, Du N, Liu J, Liu H, Li B. G-protein alpha-s and -12 subunits are involved in androgen-stimulated PI3K activation and androgen receptor transactivation in prostate cancer cells. Prostate 2011; 71: 1276-86.

[9] Jia S, Liu Z, Zhang S, Liu P, Zhang L, Lee SH, Zhang J, Signoretti S, Loda M, Roberts TM, Zhao JJ. Essential roles of PI (3) K-p110beta in cell growth, metabolism and tumorigenesis. Nature 2008; 454: 776-9.

[10] Jiang X, Chen S, Asara JM, Balk SP. Phosphoinositide 3-kinase pathway activation in phosphate and tensin homolog (PTEN)-deficient prostate cancer cells is independent of receptor tyrosine kinases and mediated by the p110beta and p110delta catalytic subunits. J Biol Chem 2010; 285: 14980-9.

[11] Bonaccorsi L, Muratori M, Carloni V, Marchiani S, Formigli L, Forti G, Baldi E. The androgen receptor associates with the epidermal growth factor receptor in androgen-sensitive prostate cancer cells. Steroids 2004; 69: 549-52.
[12] Hong SK, Kim JH, Lin MF, Park JI. The Raf/MEK/extracellular signal-regulated kinase 1/2 pathway can mediate growth inhibitory and differentiation signaling via androgen receptor downregulation in prostate cancer cells. Exp Cell Res 2011; 317: 2671-82.
[13] Carey AM, Pramanik R, Nicholson LJ, Dew TK, Martin FL, Muir GH, Morris JD. Ras-MEK-ERK signaling cascade regulates androgen receptor element-inducible gene transcription and DNA synthesis in prostate cancer cells. Int J Cancer 2007; 121: 520-7.
[14] Gioeli D, Black BE, Gordon V, Spencer A, Kesler CT, Eblen ST, Paschal BM, Weber MJ. Stress kinase signaling regulates androgen receptor phosphorylation, transcription, and localization. Mol Endocrinol 2006; 20: 503-15.
[15] Gelman IH. Androgen Receptor Activation in Castration-Recurrent Prostate Cancer: The Role of Src-Family and Ack1 Tyrosine Kinases. Int J Biol Sci 2014; 10: 620-6.
[16] Ding Y, Wang X, Xu A, Xu X, Tian K, Young CY, Yuan H. Associations of saposin C, Src, and androgen receptor upregulate the expression and function of androgen receptor in human prostate cancer cells. J Cell Biochem 2011; 112: 818-28.
[17] Cai H, Babic I, Wei X, Huang J, Witte ON. Invasive prostate carcinoma driven by c-Src and androgen receptor synergy. Cancer Res 2011; 71: 862-72.
[18] Asim M, Siddiqui IA, Hafeez BB, Baniahmad A, Mukhtar H. Src kinase potentiates androgen receptor transactivation function and invasion of androgen-independent prostate cancer C4-2 cells. Oncogene 2008; 27: 3596-604.
[19] Zou JX, Zhong Z, Shi XB, Tepper CG, deVere White RW, Kung HJ, Chen H. ACTR/AIB1/SRC-3 and androgen receptor control prostate cancer cell proliferation and tumor growth through direct control of cell cycle genes. Prostate 2006; 66: 1474-86.
[20] Migliaccio A, Castoria G, Di Domenico M, de Falco A, Bilancio A, Lombardi M, Barone MV, Ametrano D, Zannini MS, Abbondanza C, Auricchio F. Steroid-induced androgen receptor-oestradiol receptor beta-Src complex triggers prostate cancer cell proliferation. EMBO J 2000; 19: 5406-17.
[21] Thomas C, Lamoureux F, Crafter C, Davies BR, Beraldi E, Fazli L, Kim S, Thaper D, Gleave ME, Zoubeidi A. Synergistic targeting of PI3K/AKT pathway and androgen receptor axis significantly delays castration-resistant prostate cancer progression in vivo. Mol Cancer Ther 2013; 12: 2342-55.
[22] Ravindranathan P, Lee TK, Yang L, Centenera MM, Butler L, Tilley WD, Hsieh JT, Ahn JM, Raj GV. Peptidomimetic targeting of critical androgen receptor-coregulator interactions in prostate cancer. Nat Commun 2013; 4: 1923.
[23] Mitsiades N. A road map to comprehensive androgen receptor axis targeting for castration-resistant prostate cancer. Cancer Res 2013; 73: 4599-605.
[24] Lee SO, Ma Z, Yeh CR, Luo J, Lin TH, Lai KP, Yamashita S, Liang L, Tian J, Li L, Jiang Q, Huang CK, Niu Y, Yeh S, Chang C. New therapy targeting differential androgen receptor signaling in prostate cancer stem/progenitor vs. non-stem/progenitor cells. J Mol Cell Biol 2013; 5: 14-26.
[25] Lallous N, Dalal K, Cherkasov A, Rennie PS. Targeting alternative sites on the androgen receptor to treat castration-resistant prostate cancer. Int J Mol Sci 2013; 14: 12496-519.
[26] Nelson PS. Molecular states underlying androgen receptor activation: a framework for therapeutics targeting androgen signaling in prostate cancer. J Clin Oncol 2012; 30: 644-6.
[27] Culig Z. Targeting the androgen receptor in prostate cancer. Expert Opin Pharmacother 2014; 15: 1427-37.
[28] Berruti A, Generali D, Tampellini M. Enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 2448.
[29] Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, Smith-Jones PM, Yoo D, Kwon A, Wasielewska T, Welsbie D, Chen CD, Higano CS, Beer TM, Hung DT, Scher HI, Jung ME, Sawyers CL. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009; 324: 787-90.
[30] Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187-97.
[31] Raymond LW, Carr JP, Only C. Abiraterone in metastatic prostate cancer. N Engl J Med 2013; 368: 1457-8.
[32] O'Donnell A, Judson I, Dowsett M, Raynaud F, Dearnaley D, Mason M, Harland S, Robbins A, Halbert G, Nutley B, Jarman M. Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br J Cancer 2004; 90: 2317-25.

[33] de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB Jr, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y,Chieffo N, Kheoh T, Haqq CM, Scher HI; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364: 1995-2005.

[34] Edlind MP, Hsieh AC. PI3K-AKT-mTOR signaling in prostate cancer progression and androgen deprivation therapy resistance. Asian J Androl 2014; 16: 378-86.

[35] Martini M, De Santis MC, Braccini L, Gulluni F, Hirsch E. PI3K/AKT signaling pathway and cancer: an updated review. Ann Med 2014; 46: 372-83.

[36] Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. Nat Rev Drug Discov 2014; 13: 140-56.

[37] Vogt PK, Bader AG, Kang S. Phosphoinositide 3-kinase: from viral oncoprotein to drug target. Virology 2006; 344: 131-8.

[38] Russell RC, Yuan HX, Guan KL. Autophagy regulation by nutrient signaling. Cell Res 2014; 24: 42-57.

[39] Yan Y, Backer JM. Regulation of class III (Vps34) PI3Ks. Biochem Soc Trans 2007; 35: 239-41.

[40] Vanhaesebroeck B, Guillermet-Guibert J, Graupera M, Bilanges B. The emerging mechanisms of isoform-specific PI3K signalling. Nat Rev Mol Cell Biol 2010; 11: 329-41.

[41] Fritsch R, de Krijger I, Fritsch K, George R, Reason B, Kumar MS, Diefenbacher M, Stamp G, Downward J. RAS and RHO families of GTPases directly regulate distinct phosphoinositide 3-kinase isoforms. Cell 2013; 153: 1050-63.

[42] Dbouk HA, Vadas O, Shymanets A, Burke JE, Salamon RS, Khalil BD, Barrett MO, Waldo GL, Surve C, Hsueh C, Perisic O, Harteneck C, Shepherd PR, Harden TK, Smrcka AV, Taussig R, Bresnick AR, Nürnberg B, Williams RL, Backer JM. G protein-coupled receptor-mediated activation of p110beta by Gbetagamma is required for cellular transformation and invasiveness. Sci Signal 2012; 5: ra89.

[43] Vogt PK. PI3K p110beta: more tightly controlled or constitutively active? Mol Cell 2011; 41: 499-501.

[44] Zhang X, Vadas O, Perisic O, Anderson KE, Clark J, Hawkins PT, Stephens LR, Williams RL. Structure of lipid kinase p110beta/p85beta elucidates an unusual SH2-domain-mediated inhibitory mechanism. Mol Cell 2011; 41: 567-78.

[45] Dbouk HA, Pang H, Fiser A, Backer JM. A biochemical mechanism for the oncogenic potential of the p110beta catalytic subunit of phosphoinositide 3-kinase. Proc Natl Acad Sci U S A 2010; 107: 19897-902.

[46] Marqués M, Kumar A, Poveda AM, Zuluaga S, Hernández C, Jackson S, Pasero P, Carrera AC. Specific function of phosphoinositide 3-kinase beta in the control of DNA replication. Proc Natl Acad Sci U S A 2009; 106: 7525-30.

[47] Foukas LC, Berenjeno IM, Gray A, Khwaja A, Vanhaesebroeck B. Activity of any class IA PI3K isoform can sustain cell proliferation and survival. Proc Natl Acad Sci U S A 2010; 107: 11381-6.

[48] Benistant C, Chapuis H, Roche S. A specific function for phosphatidylinositol 3-kinase alpha (p85alpha-p110alpha) in cell survival and for phosphatidylinositol 3-kinase beta (p85alpha-p110beta) in de novo DNA synthesis of human colon carcinoma cells. Oncogene 2000; 19: 5083-90.

[49] Kumar A, Redondo-Munoz J, Perez-Garcia V, et al. Nuclear but not cytosolic phosphoinositide 3-kinase beta has an essential function in cell survival. Molecular and cellular biology 2011; 31: 2122-33.

[50] Silio V, Redondo-Munoz J, Carrera AC. Phosphoinositide 3-kinase beta regulates chromosome segregation in mitosis. Mol Biol Cell 2012; 23: 4526-42.

[51] Győri D, Csete D, Benkő S, Kulkarni S, Mandl P, Dobó-Nagy C, Vanhaesebroeck B, Stephens L, Hawkins PT, Mócsai A. The phosphoinositide-3-kinase isoform PI3Kbeta regulates osteoclast-mediated bone resorption. Arthritis Rheumatol 2014; 66: 2210-21.

[52] Shugg RP, Thomson A, Tanabe N, Kashishian A, Steiner BH, Puri KD, Pereverzev A, Lannutti BJ, Jirik FR, Dixon SJ, Sims SM. Effects of isoform-selective phosphatidylinositol 3-kinase inhibitors on osteoclasts: actions on cytoskeletal organization, survival, and resorption. J Biol Chem 2013; 288: 35346-57.

[53] Ciraolo E, Morello F, Hobbs RM, Wolf F, Marone R, Iezzi M, Lu X, Mengozzi G, Altruda F, Sorba G, Guan K, Pandolfi PP, Wymann MP, Hirsch E. Essential role of the p110beta subunit of phosphoinositide 3-OH kinase in male fertility. Mol Biol Cell 2010; 21: 704-11.

[54] Perez-Garcia V, Redondo-Munoz J, Kumar A, Carrera AC. Cell activation-induced phosphoinositide 3-kinase alpha/beta dimerization regulates PTEN activity. Mol Cell Biol 2014; 34: 3359-73.

[55] Honscheid P, Datta K, Muders MH. Autophagy: Detection, regulation and its role in cancer and therapy response. Int J Radiat Biol 2014: 1-8.

[56] Dou Z, Chattopadhyay M, Pan JA, Guerriero JL, Jiang YP, Ballou LM, Yue Z, Lin RZ, Zong WX. The class IA phosphatidylinositol 3-kinase p110-beta subunit is a positive regulator of autophagy. J Cell Biol 2010; 191: 827-43.

[57] Dou Z, Pan JA, Dbouk HA, Ballou LM, DeLeon JL, Fan Y, Chen JS, Liang Z, Li G, Backer JM, Lin RZ, Zong WX. Class IA PI3K p110beta subunit promotes autophagy through Rab5 small GTPase in response to growth factor limitation. Molecular cell 2013; 50: 29-42.

[58] Kang S, Denley A, Vanhaesebroeck B, Vogt PK. Oncogenic transformation induced by the p110beta, -gamma, and -delta isoforms of class I phosphoinositide 3-kinase. Proc Natl Acad Sci U S A 2006; 103: 1289-94.

[59] Ocana A, Vera-Badillo F, Al-Mubarak M, Templeton AJ, Corrales-Sanchez V, Diez-Gonzalez L, Cuenca-Lopez MD, Seruga B, Pandiella A, Amir E. Activation of the PI3K/mTOR/AKT pathway and survival in solid tumors: systematic review and meta-analysis. PLoS One 2014; 9: e95219.

[60] Kan Z, Jaiswal BS, Stinson J, Janakiraman V, Bhatt D, Stern HM, Yue P, Haverty PM, Bourgon R, Zheng J, Moorhead M, Chaudhuri S, Tomsho LP, Peters BA, Pujara K, Cordes S, Davis DP, Carlton VE, Yuan W, Li L, Wang W, Eigenbrot C, Kaminker JS, Eberhard DA, Waring P, Schuster SC, Modrusan Z, Zhang Z, Stokoe D, de Sauvage FJ, Faham M, Seshagiri S. Diverse somatic mutation patterns and pathway alterations in human cancers. Nature 2010; 466: 869-73.

[61] Dbouk HA, Backer JM. A beta version of life: p110beta takes center stage. Oncotarget 2010; 1: 729-33.

[62] Dbouk HA, Khalil BD, Wu H, Shymanets A, Nürnberg B, Backer JM. Characterization of a tumor-associated activating mutation of the p110beta PI 3-kinase. PLoS One 2013; 8: e63833.

[63] Bitting RL, Armstrong AJ. Targeting the PI3K/Akt/mTOR pathway in castration-resistant prostate cancer. Endocr Relat Cancer 2013; 20: R83-99.

[64] Ciraolo E, Iezzi M, Marone R, Marengo S, Curcio C, Costa C, Azzolino O, Gonella C, Rubinetto C, Wu H, Dastrù W, Martin EL, Silengo L, Altruda F, Turco E, Lanzetti L, Musiani P, Rückle T, Rommel C, Backer JM, Forni G, Wymann MP, Hirsch E. Phosphoinositide 3-kinase p110beta activity: key role in metabolism and mammary gland cancer but not development. Sci Signal 2008; 1: ra3.

[65] Lee SH, Poulogiannis G, Pyne S, Jia S, Zou L, Signoretti S, Loda M, Cantley LC, Roberts TM. A constitutively activated form of the p110beta isoform of PI3-kinase induces prostatic intraepithelial neoplasia in mice. Proc Natl Acad Sci U S A 2010; 107: 11002-7.

[66] Majumder PK, Yeh JJ, George DJ, Febbo PG, Kum J, Xue Q, Bikoff R, Ma H, Kantoff PW, Golub TR, Loda M, Sellers WR. Prostate intraepithelial neoplasia induced by prostate restricted Akt activation: the MPAKT model. Proc Natl Acad Sci U S A 2003; 100: 7841-6.

[67] Wee S, Wiederschain D, Maira SM, Loo A, Miller C, deBeaumont R, Stegmeier F, Yao YM, Lengauer C. PTEN-deficient cancers depend on PIK3CB. Proc Natl Acad Sci U S A 2008; 105: 13057-62.

[68] Berenjeno IM, Guillermet-Guibert J, Pearce W, Gray A, Fleming S, Vanhaesebroeck B. Both p110alpha and p110beta isoforms of PI3K can modulate the impact of loss-of-function of the PTEN tumour suppressor. Biochem J 2012; 442: 151-9.

[69] Utermark T, Rao T, Cheng H, Wang Q, Lee SH, Wang ZC, Iglehart JD, Roberts TM, Muller WJ, Zhao JJ. The p110alpha and p110beta isoforms of PI3K play divergent roles in mammary gland development and tumorigenesis. Genes Dev 2012; 26: 1573-86.

[70] Schmit F, Utermark T, Zhang S, Wang Q, Von T, Roberts TM, Zhao JJ. PI3K isoform dependence of PTEN-deficient tumors can be altered by the genetic context. Proc Natl Acad Sci U S A 2014; 111: 6395-400.

[71] Utermark T, Schmit F, Lee SH, Gao X, Schaffhausen BS, Roberts TM. The PI3K isoform dependence of tumor formation is determined by the genetic mode of PI3K pathway activation rather than by tissue type. J Virol 2014.

[72] Ayala G, Thompson T, Yang G, Frolov A, Li R, Scardino P, Ohori M, Wheeler T, Harper W. High levels of phosphorylated form of Akt-1 in prostate cancer and non-neoplastic prostate tissues are strong predictors of biochemical recurrence. Clin Cancer Res 2004; 10: 6572-8.

[73] Hill KM, Kalifa S, Das JR, Bhatti T, Gay M, Williams D, Taliferro-Smith L, De Marzo AM. The role of PI 3-kinase p110beta in AKT signally, cell survival, and proliferation in human prostate cancer cells. Prostate 2010; 70: 755-64.

[74] Liao X, Thrasher JB, Holzbeierlein J, Stanley S, Li B. Glycogen synthase kinase-3beta activity is required for androgen-stimulated gene expression in prostate cancer. Endocrinology 2004; 145: 2941-9.

[75] Shanmugam I, Cheng G, Terranova PF, Thrasher JB, Thomas CP, Li B. Serum/glucocorticoid-induced protein kinase-1 facilitates androgen receptor-dependent cell survival. Cell Death Differ 2007; 14: 2085-94.

[76] Li B, Sun A, Youn H, Hong Y, Terranova PF, Thrasher JB, Xu P, Spencer D. Conditional Akt activation promotes androgen-independent progression of prostate cancer. Carcinogenesis 2007; 28: 572-83.
[77] Li B, Desai SA, MacCorkle-Chosnek RA, Fan L, Spencer DM. A novel conditional Akt 'survival switch' reversibly protects cells from apoptosis. Gene Ther 2002; 9: 233-44.
[78] Porta C, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR Signaling in Cancer. Front Oncol 2014; 4: 64.
[79] Tasian SK, Teachey DT, Rheingold SR. Targeting the PI3K/mTOR Pathway in Pediatric Hematologic Malignancies. Front Oncol 2014; 4: 108.
[80] Houede N, Pourquier P. Targeting the genetic alterations of the PI3K-AKT-mTOR pathway: Its potential use in the treatment of bladder cancers. Pharmacol Ther 2014; [Epub ahead of print].
[81] Dienstmann R, Rodon J, Serra V, Tabernero J. Picking the point of inhibition: a comparative review of PI3K/AKT/mTOR pathway inhibitors. Mol Cancer Ther 2014; 13: 1021-31.
[82] Rodon J, Dienstmann R, Serra V, Tabernero J. Development of PI3K inhibitors: lessons learned from early clinical trials. Nat Rev Clin Oncol 2013; 10: 143-53.
[83] McLean BA, Zhabyeyev P, Pituskin E, Paterson I, Haykowsky MJ, Oudit GY. PI3K inhibitors as novel cancer therapies: implications for cardiovascular medicine. J Card Fail 2013; 19: 268-82.
[84] Jackson SP, Schoenwaelder SM, Goncalves I, Nesbitt WS, Yap CL, Wright CE, Kenche V, Anderson KE, Dopheide SM, Yuan Y, Sturgeon SA, Prabaharan H, Thompson PE, Smith GD, Shepherd PR, Daniele N, Kulkarni S, Abbott B, Saylik D, Jones C, Lu L, Giuliano S, Hughan SC, Angus JA, Robertson AD, Salem HH. PI 3-kinase p110beta: a new target for antithrombotic therapy. Nat Med 2005; 11: 507-14.
[85] Vlahos CJ, Matter WF, Hui KY, Brown RF. A specific inhibitor of phosphatidylinositol 3-kinase, 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one (LY294002). Eur J Pharmacol 1994; 269: 5241-8.
[86] Sturgeon SA, Jones C, Angus JA, Wright CE. Advantages of a selective beta-isoform phosphoinositide 3-kinase antagonist, an antithrombotic agent devoid of other cardiovascular actions in the rat. Eur J Pharmacol 2008; 587: 209-15.
[87] Bird JE, Smith PL, Bostwick JS, Shipkova P, Schumacher WA. Bleeding response induced by anti-thrombotic doses of a phosphoinositide 3-kinase (PI3K)-beta inhibitor in mice. Thromb Res 2011; 127: 560-4.
[88] Zhao Y, Duan S, Zeng X, Liu C, Davies NM, Li B, Forrest ML. Prodrug strategy for PSMA-targeted delivery of TGX-221 to prostate cancer cells. Mol Pharm 2012; 9: 1705-16.
[89] Tai W, Shukla RS, Qin B, Li B, Cheng K. Development of a peptide-drug conjugate for prostate cancer therapy. Mol Pharm 2011; 8: 901-12.
[90] Lupold SE, Hicke BJ, Lin Y, Coffey DS. Identification and characterization of nuclease-stabilized RNA molecules that bind human prostate cancer cells via the prostate-specific membrane antigen. Cancer Res 2002; 62: 4029-33.
[91] Nylander S, Kull B, Björkman JA, Ulvinge JC, Oakes N, Emanuelsson BM, Andersson M, Skärby T, Inghardt T, Fjellström O, Gustafsson D. Human target validation of phosphoinositide 3-kinase (PI3K)beta: effects on platelets and insulin sensitivity, using AZD6482 a novel PI3Kbeta inhibitor. J Thromb Haemost 2012; 10: 2127-36.
[92] Ni J, Liu Q, Xie S, Carlson C, Von T, Vogel K, Riddle S, Benes C, Eck M, Roberts T, Gray N, Zhao J. Functional characterization of an isoform-selective inhibitor of PI3K-p110beta as a potential anticancer agent. Cancer Discov 2012; 2: 425-33.
[93] Certal V, Carry JC, Halley F, Virone-Oddos A, Thompson F, Filoche-Rommé B, El-Ahmad Y, Karlsson A, Charrier V, Delorme C, Rak A, Abecassis PY, Amara C, Vincent L, Bonnevaux H, Nicolas JP, Mathieu M, Bertrand T, Marquette JP, Michot N, Benard T, Perrin MA, Lemaitre O, Guerif S, Perron S, Monget S, Gruss-Leleu F, Doerflinger G, Guizani H, Brollo M, Delbarre L, Bertin L, Richepin P, Loyau V, Garcia-Echeverria C, Lengauer C, Schio L. Discovery and optimization of pyrimidone indoline amide PI3Kbeta inhibitors for the treatment of phosphatase and tensin homologue (PTEN)-deficient cancers. J Med Chem 2014; 57: 903-20.
[94] Giordanetto F, Barlaam B, Berglund S, Edman K, Karlsson O, Lindberg J, Nylander S, Inghardt T. Discovery of 9-(1-phenoxyethyl)-2-morpholino-4-oxo-pyrido[1,2-a]pyrimidine-7-carboxamides as oral PI3Kbeta inhibitors, useful as antiplatelet agents. Bioorg Med Chem Lett 2014; 24: 3936-43.
[95] Sanchez RM, Erhard K, Hardwicke MA, Lin H, McSurdy-Freed J, Plant R, Raha K, Rominger CM, Schaber MD, Spengler MD, Moore ML, Yu H, Luengo JI, Tedesco R, Rivero RA. Synthesis and structure-activity relationships of 1,2,4-triazolo[1,5-a]pyrimidin-7(3H)-ones as novel series of potent beta isoform selective phosphatidylinositol 3-kinase inhibitors. Bioorg Med Chem Lett 2012; 22: 3198-202.

[96] Weigelt B, Warne PH, Lambros MB, Reis-Filho JS, Downward J. PI3K pathway dependencies in endometrioid endometrial cancer cell lines. Clin Cancer Res 2013; 19: 3533-44.

[97] Lin H, Erhard K, Hardwicke MA, Luengo JI, Mack JF, McSurdy-Freed J, Plant R, Raha K, Rominger CM, Sanchez RM, Schaber MD, Schulz MJ, Spengler MD, Tedesco R, Xie R, Zeng JJ, Rivero RA. Synthesis and structure-activity relationships of imidazo[1,2-a]pyrimidin-5(1H)-ones as a novel series of beta isoform selective phosphatidylinositol 3-kinase inhibitors. Bioorg Med Chem Lett 2012; 22: 2230-4.

[98] Lin H, Schulz MJ, Xie R, Zeng J, Luengo JI, Squire MD, Tedesco R, Qu J, Erhard K, Mack JF, Raha K, Plant R, Rominger CM, Ariazi JL, Sherk CS, Schaber MD, McSurdy-Freed J, Spengler MD, Davis CB, Hardwicke MA, Rivero RA. Rational Design, Synthesis, and SAR of a Novel Thiazolopyrimidinone Series of Selective PI3K-beta Inhibitors. ACS Med Chem Lett 2012; 3: 524-9.

[99] Gross C, Bassell GJ. Excess protein synthesis in FXS patient lymphoblastoid cells can be rescued with a p110beta-selective inhibitor. Mol Med 2012; 18: 336-45.

[100] Dbouk HA, Backer JM. Novel approaches to inhibitor design for the p110beta phosphoinositide 3-kinase. Trends Pharmacol Sci 2013; 34: 149-53.