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Digest

Recent progress towards clinically relevant ATP-competitive Akt inhibitors

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ABSTRACT

The frequency of PI3K/Akt/mTOR (PAM) Pathway mutations in human cancers sparked interest to determine if the pathway is druggable. The modest clinical benefit observed with mTOR rapalogs (temsirolimus and everolimus) provided further motivation to identify additional nodes of pathway inhibition that lead to improved clinical benefit. Akt is a central signaling node of the PAM pathway and could be an ideal target for improved pathway inhibition. Furthermore, inhibitors of Akt may be especially beneficial in tumors with Akt1 mutations. Recently, multiple ATP-competitive Akt inhibitors have been identified and are currently in clinical development. This review details the medicinal chemistry efforts towards identification of these molecules, highlights relevant preclinical data supporting clinical evaluation, and summarizes current clinical development plans.

Introduction to the PAM pathway

The PI3K/Akt/mTOR (PAM) Pathway regulates essential cellular functions; including, metabolism, growth, and survival (Fig. 1). It is therefore unsurprising that genomic alterations of the PAM pathway are frequently observed in human cancers.[1] Furthermore, misregulation of the PAM pathway is a common mode of resistance to cancer therapeutics; including resistance to both targeted agents and chemotherapy.[2] The most frequently observed PAM pathway alterations are mutations (PIK3CA, Akt1, PTEN), gene amplification (PIK3CA, Akt1, and Akt2), and loss of expression of the tumor suppressor PTEN. Cancer indications with the highest prevalence of PAM pathway mutations include breast cancer, endometrial cancer, head and neck cancer, and glioblastoma.[3]

The high frequency of PAM pathway alterations in many types of human cancers led to the evaluation as to whether the pathway was druggable. Initial success in targeting the PAM pathway was achieved with several mTOR rapalogs (everolimus and temsirolimus). Everolimus is approved as monotherapy in pancreatic neuroendocrine tumor, renal cell carcinoma, and renal AML-TSC, and in combination with exemestane in HR+ breast cancer; while temsirolimus is approved as monotherapy in renal cell carcinoma and mantle cell lymphoma.[4–7] Unfortunately, clinical benefit derived from mTOR inhibitors can be short lived as resistance through the activation of negative compensatory PAM pathway feedback loops is observed.[8]

While the approval of mTOR rapalogs validated the druggability of the PAM pathway, the short lived clinical responses sparked efforts to identify if additional modes of PAM pathway inhibition could provide improved clinical benefit. Cumulatively, these efforts led to a comprehensive investigation of a variety of modes of PAM pathway inhibition; and include: pan-PI3K inhibitors, α-selective PI3K inhibitors, β-selective PI3K inhibitors, dual PI3K/mTOR inhibitors, mTOR kinase inhibitors[9], ATP-competitive Akt inhibitors, allosteric Akt inhibitors, and p70S6K inhibitors.[3]

Inhibition of Akt

Akt is an AGC-family kinase and a central, integral signaling node of the PAM pathway. There are three Akt isozymes, Akt1, Akt2 and Akt3. Small-molecule inhibitors of Akt1 could be especially useful to target tumors with a high prevalence of Akt1 E17K activating mutations, which is observed in 4–6% of breast cancers and 1–2% of colorectal cancer.[3]

Akt consists of three conserved domains (Fig. 2**a**): an N-terminal pleckstrin homology domain (PH domain); an ATP binding kinase domain (KD), and a C-terminal regulatory hydrophobic motif (HM).[10] Spatial orientation of these domains plays an important role in the regulation of the Akt kinase activity. The X-ray crystal structure of Akt1 (PDB 5KCV) revealed that under basal conditions, productive interactions between the PH and KD domains keep Akt1 in an autoinhibited, inactive form (PH-in

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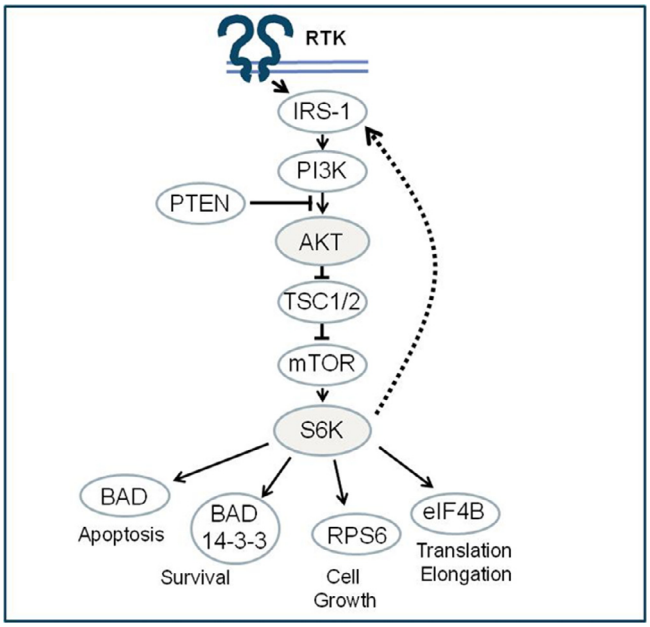

Fig. 1. The PI3K/Akt/mTOR (PAM) pathway.

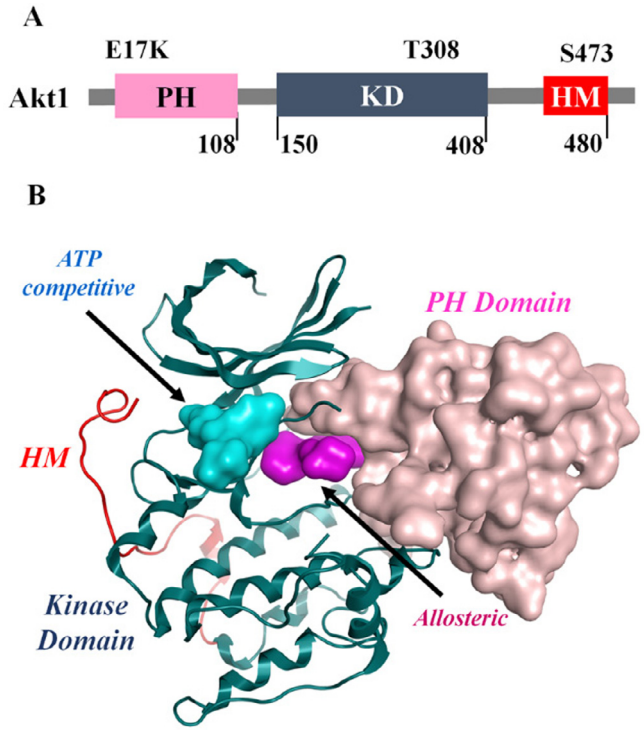

Fig. 2. a. Schematic representation of Akt functional and structural domains, consisting of the *N*-terminal pleckstrin homology (PH) domain, followed by the kinase domain (KD), and the hydrophobic motif (HM). Phosphorylation sites T308 and SD473 and activating mutation E17K are labeled. **b**. Overall structure of Akt1 showing the orientation of the PH domain relative to the KD. PH domain is rendered as a surface colored in light pink. KD is shown as a ribbon colored in teal. Allosteric binding sites located at the interface of the PH and KD is shown as a magenta surface. ATP binding region within the KD is highlighted as a turquoise surface. HM is shown in red.

conformation) (Fig. 2**b**). In this autoinhibited conformation, PDK1 in unable to phosphorylate Thr308 or Ser473 of Akt1. Upon upstream signaling or activating mutations, Akt undergoes a conformational switch from the autoinhibited PH-into open PH-out conformation, leading to Akt phosphorylation and activation.

Research towards Akt inhibition has focused on inhibition of two distinct binding sites: (1) the allosteric pocket of the inactive enzyme, and (2) the ATP binding site. Allosteric Akt inhibitors, highlighted by MK-2206, have been extensively evaluated in a clinical setting (Fig. 3). While monotherapy treatment of MK-2206 was well tolerated, impact on patient benefit has been minimal.[11,12] Due to the acceptable tolerability profile, MK-2206 has been evaluated in combination with other oncology agents to further improve patient benefit.[13] Recently, additional allosteric Akt inhibitors have been identified. ARQ-092, is a potent pan-Akt inhibitor which can inhibit tumor growth preclinically, and is currently in Phase I clinical studies.[14] BAY1125976 is an allosteric Akt 1,2 inhibitor, and also displays efficacy in preclinical tumor models.[15] TAS-117 is another allosteric Akt inhibitor, and is reported to demonstrate combination benefit with molecular targeted drugs in a preclinical setting.[16] It remains to be seen if any of these recent allosteric Akt inhibitors will provide additional clinical benefit over MK-2206.

Current ATP-competitive Akt inhibitors in clinical development

The remainder of this review will focus on recent efforts towards ATP-competitive Akt inhibitors. The recent gains in structure-based drug discovery have led to the identification of multiple ATP-competitive kinase inhibitors with proven clinical benefit.[17,18] Therefore, it should also be possible to identify selective ATP-competitive Akt inhibitors. Overall, the three Akt isozymes possess high ATP-binding site homology. Other kinases with high overall ATP-binding site homology (>70%) include: S6K1, PKA, PKC, SGK, PRKX, PKN1, and Aurora A (Table 1).

The first ATP-competitive Akt inhibitor evaluated in the clinic was GSK690693 (Fig. 4).[19] GSK690693 is a potent, pan-Akt inhibitor with modest kinase selectivity, and poor oral bioavailability. Clinical development of this molecule was suspended due to significant adverse events; including, hyperglycemia.

Subsequent efforts towards 2nd generation ATP-competitive Akt inhibitors focused on optimization of kinase selectivity with an eye towards an improvement in patient tolerability. Recently, multiple compounds from this class have been described in the literature and are currently under clinical evaluation; including, GDC-0068 (ipatasertib), AZD5363, AT13148, GSK2110183 (afuresertib), and GSK2141795 (uprosertib) (Fig. 5). This review provides an overview of (1) medicinal chemistry optimization, (2) binding mode structural analysis (if available), (3) molecular pharmacology, (4) preclinical pharmacology, and (5) clinical development of these ATP-competitive Akt inhibitors.

GDC-0068: medicinal chemistry optimization

Efforts towards GDC-0068 were initiated with the identification of racemic hit molecule **1** (Akt1 IC_{50} = 2.1 μM) from a high throughput screen (Scheme 1).[20] Drug discovery efforts focused on exploration of hinge-binding motifs, and led to molecule **2** which had improved enzyme potency (Akt1 IC_{50} = 3 nM). While **2** had improved enzyme activity, it suffered from poor rodent tolerability which was thought to originate from sub-optimal kinase selectivity. Kinase selectivity was the featured parameter to guide further compound optimization (focusing on selectivity over AGC-family kinase PKA) and yielded lead molecule **3**.[21] This molecule introduced a novel dihydrothienopyrimidine hinge-binding motif which improved PKA/Akt selectivity to >35×. Further optimization of the hinge-binding scaffold via structure-based drug discovery led directly to GDC-0068 which has a PKA/Akt selectivity ratio of 620×.[22]