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Aims and scope

Expert Opinion on Therapeutic Patents is a peer-reviewed, international journal publishing review articles on recent pharmaceutical patent claims, providing expert opinion the scope for future development, in the context of the scientific literature.

The Editors welcome:

- *Reviews* covering recent patent claims on compounds or applications with therapeutic potential, including biotherapeutics and small-molecule agents with specific molecular targets; and patenting trends in a particular therapeutic area
- *Patent Evaluations* examining the aims and chemical and biological claims of individual patents
- *Perspectives* on issues relating to intellectual property

The audience consists of scientists, managers and decision-makers in the pharmaceutical industry and others closely involved in R&D.

Editorial policy

Articles published in *Expert Opinion on Therapeutic Patents* are commissioned by the Editor in collaboration with the Section Editorial Board. Authors who wish to contribute should contact the Editor. All reviews are subject to peer-review.

Editorial boards

The Advisory Panel and Editorial Board are composed of Senior Scientists involved in drug research and development. The Advisory Panel is responsible for the development of the journal, whereas the Section Editors are responsible for selecting authors and topics for review to ensure comprehensive coverage of subjects in each therapeutic area.

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Forthcoming articles

- Biologicals targeting survivin: a patent review
- Inhibitors of Anaplastic Lymphoma Kinase: a patent review
- Spiro azepane-oxazolidinones as Kv1.3 potassium channel blockers – WO2010066840
- Thirteen compounds promoting oligodendrocyte progenitor cell differentiation and remyelination for treating multiple sclerosis

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Expert Opinion on Therapeutic Patents is grateful and indebted to the reviewers of all the above articles

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Bruton's tyrosine kinase as a molecular target in treatment of leukemias and lymphomas as well as inflammatory disorders and autoimmunity

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Importance of the field: Bruton's tyrosine kinase (BTK) has emerged as a new anti-apoptotic molecular target for the treatment of B-lineage leukemias and lymphomas. Preclinical and early clinical results indicate that BTK inhibitors may be useful in the treatment of leukemias and lymphomas. BTK inhibitors may also be helpful in prevention and treatment of thromboembolic complications as well as inflammatory disorders.
Areas covered in this review: We provide a comprehensive review of the target diseases for which the use of BTK inhibitors may be helpful as well as the activity profiles of BTK inhibitors.
What the reader will gain: We review the currently available translational research, biomarker as well as patent literature regarding BTK molecular target and BTK inhibitors.
Take home message: BTK inhibitors may provide the foundation for therapeutic innovation against B-lineage leukemias/lymphomas, inflammatory disorders and autoimmunity.

Keywords: Bruton's tyrosine kinase, graft-versus-host disease, inflammatory disorders, leukemia, lymphoma, rational drug design, thromboembolism

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1. Protein tyrosine kinases as molecular targets for new drugs

More than 200 member genes of the protein kinase complement of the human genome – 'kinome' – have been mapped to disease loci or cancer amplicons [1,2]. Among the kinases encoded by the 'kinome', ~ 100 are protein tyrosine kinases (PTK) that play important regulatory roles in intracellular signal transduction pathways affecting survival, proliferation and chemotherapy sensitivity of cancer cells. Small molecule inhibitors of these PTK have emerged as promising new anticancer drug candidates [3-8]. There is a wealth of crystal structure information of protein kinase and inhibitor complexes that provides the basis for the structure–activity relationships of kinase inhibitors [3-8]. **Figure 1A** shows the binding modes of small-molecule protein kinase inhibitors in relationship to the hinge regions of the ATP-binding site in view with the N-lobe on the top and the C-lobe in the background, based on corresponding crystal structures (taken from the coordinates with PDB access codes: 1fvt, 1a9u, 1fpu, 2csn, 1ian, 1di8, 1aq1, 1ckp, 1bl6, 1bl7, 1k2p). **Figure 1B** shows a model of the ternary complex

Article highlights.

- BTK has emerged as an upstream activator of multiple anti-apoptotic signaling molecules and networks.
- A meta-analysis of cancer-associated gene expression changes revealed a marked enrichment of the most discriminating BTK-dependent anti-apoptotic gene targets for human leukemias and lymphomas.
- The availability of the coordinates of the BTK kinase domain X-ray crystal structures supports the development of rationally designed BTK inhibitors.
- BTK inhibitors show potential as anti-leukemic agents with apoptosis-promoting and chemosensitizing properties.
- BTK inhibitors also show potential as immunomodulatory agents for treatment of autoimmune diseases, inflammatory disorders, graft-versus-host disease in hematopoietic stem cell transplantation and treatment/prevention of thromboembolism.

This box summarizes key points contained in the article.

of Bruton's tyrosine kinase (BTK) (blue), ATP (multiple colors) and a peptide substrate (white) derived from the crystal structure of the BTK kinase domain. **Figure 1C** is a schematic illustration of the active site. There are two hydrogen acceptors and one hydrogen donor from the backbone carbonyl and amide groups of the hinge region, potentially forming hydrogen bonds with the inhibitors (as indicated by arrows in B) which, aligned with the ATP-binding cleft, determine the orientation of protein kinase inhibitors. Many derivatives of tyrosine kinase inhibitors that contain the same core groups would be expected to adopt one of these binding modes with 1 – 3 hydrogen bonds with the protein backbone.

2. BTK

BTK is a member of the SRC-related TEC family of cytoplasmic PTK [9-11]. TEC family kinases are activated downstream of many cell–surface receptors, including receptor tyrosine kinases, cytokine receptors and integrins [12]. Well established as critical for the full activation of phospholipase-C γ (PLC-γ) and MAPK as well as calcium mobilization downstream of antigen receptors [12], TEC kinases were recently described in actin reorganization and cell polarization, as well as transcriptional regulation, cell survival and cellular transformation [12-14]. TEC family members share significant structural and sequence homology, including the presence of distinct proline-rich (PR) regions as well as N-terminal pleckstrin homology (PH) and TEC homology (TH) domains. The exceptions to this classification are Rlk, which contains PR regions but not TH or PH domains, and Bmx that does not contain PR regions [12]. The PH domain is not found in other cytoplasmic PTK and plays an essential role in the regulation and function of the BTK. The PH domain is the site of activation by phosphatidylinositol phosphates and G-protein βγ subunits as well as inhibition by PKC [15-20]. Multiple partners and signaling pathways have been implicated for BTK and other TEC family kinases. TEC family kinases play central and diverse modulatory roles in various cellular processes. They participate in signal transduction in response to virtually all types of extracellular stimuli, which are transmitted by growth factor receptors, cytokine receptors, G-protein receptors, antigen receptors and integrins and are regulated by non-receptor tyrosine kinases such as SRC, JAK, SYK and FAK family kinases. In turn, they regulate many major signaling pathways including those of PI3K, PLC-γ and PKC [12,21-24]. These pathways play multiple roles in growth, differentiation and apoptosis. Recently, a new role for this family of kinases in cytoskeletal reorganization and cell motility was discovered. The actin cytoskeleton plays an essential role in a variety of cellular processes including cell division, cell shape, motility and chemotaxis. BTK is known to colocalize with actin fibers on stimulation of mast cells by the high affinity IgE receptor in a PH domain-dependent manner [25]. The PH domain of BTK has also been shown to promote actin filament bundle formation *in vitro* [25]. These and other observations suggest the possibility that on stimulation BTK kinase is able to translocate to the actin cytoskeleton where BTK and its downstream targets may work coordinately to reorganize the cytoskeleton in response to stimuli.

Genetic evidence supports a critical role for BTK in multiple hematopoietic signaling pathways including the B-cell antigen receptor (BCR), several cytokine receptors and a potential novel role in heterotrimeric G-protein-associated receptor signaling [9,10,26-28]. In B-lineage lymphoid cells, as an essential component of the B-cell signalosome, BTK is intimately involved in multiple signal transduction pathways regulating survival, activation, proliferation, maturation and differentiation [9,10]. The recognition of an antigen by the BCR triggers a signal transduction cascade that culminates in activation of multiple genes controlling activation, proliferation, differentiation and survival of B cells. As such, alteration of BCR signaling is crucial for the survival of lymphoma cells [29]. As compared to non-tumor cells, BTK-mediated signaling through the BCR was found to occur more swiftly with increased levels of sustained cellular signaling in B-follicular lymphoma cells [12]. Recent observations also suggest the involvement of BTK in signal transduction pathways affecting gene transcription [30,31]. BTK is essential for the BCR-mediated activation of the NF-κB/Rel family of transcription factors, which in turn regulates genes controlling B-cell growth [32]. BTK has also been shown to regulate the nuclear localization and transcriptional activity of the ubiquitously expressed multifunctional transcription factor BAP-135/TFII-I [33-35]. BAP-135/TFII-I is capable of binding to several promoter elements, including initiator elements (e.g., VpreB, TdT and possibly RAG, CD5, Bcl-2 and

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