Writer #1

Writer #1 has a PhD in medicinal chemistry from the State University of NY at Buffalo, a BS in Pharmacy from Rutgers University, and over ten years of experience in the pharmaceutical industry in drug discovery. In the pharmaceutical industry, she was involved in multiple drug discovery projects primarily focused on oncology. She has authored 17 peer-reviewed manuscripts, 11 patents and patent applications, and several dozen presentations and posters. With a background in Pharmacy, she has extensive knowledge of medicines and has taken numerous continuing education classes. Currently, this writer is splitting her time between work in a compounding pharmacy and medical writing.

Writing Sample:

This writing sample contains the introduction for a peer-reviewed published invited review.

**Inhibitors of anaplastic lymphoma kinase: a patent review**

**Importance of the field:** Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that belongs to the insulin receptor superfamily. Aberrant ALK activity has been implicated in the oncogenesis of human cancers as a fusion protein in anaplastic large cell lymphoma, inflammatory myofibroblastic tumor, diffuse large B-cell lymphoma, systemic histiocytosis and NSCLC or through mutations in the full length protein in hereditary familial neuroblastoma. Thus, abrogation of ALK signaling through direct kinase inhibition has become an attractive therapeutic intervention point for a subset of genetically defined human cancers.

**Areas covered in this review:** This manuscript provides a comprehensive review of the patent literature pertaining to ALK inhibitors and outlines their potential as anticancer therapeutic agents.

**What the reader will gain:** The reader will gain an understanding of the major structural classes of ALK inhibitors and insights into the future of this class of drugs.

**Take home message:** Multiple small-molecule ALK inhibitors have been reported with diverse chemical architecture, potency, kinase selectivity profiles and activity against potential resistance. The breadth of inhibitors combined with the recent discoveries of the involvement of ALK in lung, breast and colorectal cancers has kept the field advancing at a rapid pace.

Keywords: ALK, cancer, IGF-1R, IGF receptor, receptor tyrosine kinase, small-molecule kinase inhibitor

Anaplastic lymphoma kinase (ALK) was identified as the fusion partner of nucleophosmin (NPM) in the oncogene NPM-ALK resulting from a t(2;5) chromosomal translocation in anaplastic large cell lymphoma (ALCL). ALK is a receptor tyrosine kinase and belongs to the insulin receptor (IR) superfamily, which includes IGF-1 receptor (IGF-1R), insulin related receptor and leukocyte tyrosine kinase. Though the normal function of ALK is not completely understood, ALK is implicated in the physiological development and function of the nervous system. Of note, though ALK knockout mice have a full life-span and have no overt abnormalities, behavioral and neurochemical alterations were observed in ALK deficient mice. The characterization of ALK’s role in oncogenesis of various
cancer types, however, has been widely documented. ALK forms various fusions, almost all containing the intracellular kinase domain of ALK. ALK fusion genes were subsequently detected in ALCLs, inflammatory myofibroblastic tumor, diffuse large B-cell lymphoma, systemic histiocytosis, and most notably, in NSCLC, resulting in the generation of oncogenic ALK fusion proteins with constitutive phosphorylation/activation of ALK. Recently, germ-line mutations in ALK have been reported to be the cause of most hereditary neuroblastoma cases and ALK activation by mutation and/or gene amplification is functionally relevant in high-risk sporadic neuroblastoma. Recently, mutations in ALK have been found to be implicated in atypical juvenile myelomonocytic leukemia and acute myeloid leukemia as well [1]. For more complete coverage of the biology of ALK and its role in cancer, please refer to several excellent recent reviews on the topic [2-5].

With the strong link between aberrant expression and activation of ALK with the onset and progression of ALK-positive ALCL, NSCLC and neuroblastomas, ALK has emerged as an attractive target for small-molecule therapy with the potential of enhancing the clinical outcome of patients with well-defined ALK mediated cancers. Thus, a heightened interest in small-molecule ALK inhibitors has emerged with a variety of unique chemical architectures recently being reported. The inhibitors reported to date appear to be all ATP-competitive inhibitors binding in the DFG-in mode (type I inhibitors). Recently, the crystal structure of ALK with small-molecule inhibitors bound was reported [6,7]. For further information regarding the recent development of small-molecule inhibitors of ALK, please refer to two comprehensive reviews of the ALK literature [8,9].

The ALK patent literature contains three distinct approaches for ALK inhibition: anti-ALK antibodies, ALK vaccines and small molecules. Not only are ALK fusion proteins required for the development of ALCL, they are also antigenic: patients with ALCL mount ALK specific T- and B-cell responses. These two characteristics make ALK a unique target for vaccine therapy. Inghirami and co-workers vaccinated BALB/c mice with a DNA plasmid which coded for a large portion of the intracytoplasmic domain of ALK. Mice were then treated with syngeneic ALK positive lymphoma cells. Untreated mice developed lymphoma, while ALK-vaccinated mice did not. In another study, mice were pretreated with a low tumor load of lymphoma cells. Administration of the ALK vaccine provided protection to these mice as well. Combination therapy with chemotherapeutics provided an additional benefit [10-13].

In the second approach to ALK inhibition, an anti-ALK antibody may inhibit either ALK kinase activity or inhibit its ability to bind to fusion proteins. Both Esbatech [14,15] and Medimmune [16] have published patent applications claiming the utility of anti-ALK antibodies.

The third approach for ALK inhibition is the use of small molecule inhibitors.

**Bibliography**

The following abstract and introduction are taken from a published peer-reviewed manuscript.

**Improvement in oral bioavailability of 2,4-diaminopyrimidine c-Met inhibitors by incorporation of a 3-amidobenzazepin-2-one group**

**Abstract:**
The hepatocyte growth factor (HGF)-c-Met signaling axis is involved in the mediation of many biological activities, including angiogenesis, proliferation, cell survival, cell motility, and morphogenesis. Dysregulation of c-Met signaling (e.g., overexpression or increased activation) is associated with the proliferation and metastasis of a wide range of tumor types, including breast, liver, lung, colorectal, gastric, bladder, and prostate, among others. Inhibiting the HGF-c Met pathway is predicted to lead to anti-tumor effects in many cancers. Elaboration of the SAR around a series of 2,4-diaminopyrimidines led to a number of c-Met inhibitors in which pharmaceutical properties were modulated by substituents appended on the C2-benzazepinone ring. In particular, certain-3-amidobenzazepin-2-one analogs had improved oral bioavailability and were evaluated in PK/PD and efficacy models. Lead compounds demonstrated tumor stasis with partial regressions when evaluated in a GTL-16 tumor xenograft mouse model.

Under normal physiological conditions, during embryonic development, and hepatic and cardiac injury repair, the c-Met receptor tyrosine kinase and its high affinity ligand hepatocyte growth factor (HGF, also known as scatter factor) mediate a variety of cellular processes including
proliferation, invasion, and angiogenesis. \(^1\)–\(^4\) In tumor cells, the activation of c-Met triggers a series of signaling cascades that results in cell growth, invasion, proliferation, and protection from apoptosis.\(^5\),\(^6\) The over-expression of HGF and c-Met is associated with more aggressive tumors and poor patient prognosis.\(^7\) Tumor biopsies of many solid tumors indicate expression of c-Met and HGF, and c-Met signaling has been noted in a wide range of malignancies, including breast, liver, lung, colorectal, gastric, bladder, prostate, head and neck, renal, pancreatic, sarcomas, thyroid, melanoma, and hematopoietic malignancies.\(^5\),\(^8\),\(^9\)

Activating mutations of c-Met have been identified in patients with hereditary forms of cancer, which directly implicates c-Met activation in human tumorogenesis.\(^10\),\(^11\) Inhibition of c-Met kinase activity by small molecules would likely have broad therapeutic utility due to the prevalence of Met amplification/overexpression and mutations in a variety of human malignancies.\(^12\) Many reports have indicated that the inhibition of c-Met kinase activity blocks tumor cell growth and invasion in both in vitro and in vivo systems.\(^13\)–\(^17\) There are many c-Met inhibitors in various stages of development.\(^18\),\(^19\) Initial clinical results indicate that targeting the c-Met-HGF axis is tolerated and can lead to efficacious results either as single agent therapy or when combined with other tyrosine kinase inhibitors.\(^20\),\(^21\)

References and notes