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Digest

Small molecule immuno-oncology therapeutic agents

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ABSTRACT

Treatment of cancer by activation of an antitumor immune response is now a widely practiced and well-accepted approach to therapy. However, despite dramatic responses in some patients, the high proportion of unresponsive patients points to a considerable unmet medical need. Although antibody therapies have led the way, small molecule immuno-oncology agents are close behind. This perspective provides an overview of some of the many small molecule approaches being explored. It encompasses small molecule modulators of validated targets such as programed cell death 1 (PD-1) as well as novel approaches still to be proven clinically.

Immuno-oncology seeks to enlist the body's immune system to combat the growth of malignant tumors.[1] The approval and launch of protein drugs that act to release tumor-imposed suppressive mechanisms, so called checkpoint inhibitors, has provided ample validation that this strategy can produce curative results in a subset of patients.[2–4] The success of checkpoint inhibitors such as antibodies targeting CTLA4, PD1 or PD-L1 has led to a large and rapid shift of emphasis in cancer research. Along with the next generation of large molecule immunotherapy agents, there is a growing focus on the discovery of small molecule drugs targeting the same pathways as well as less validated targets.[5–8] At the same time, there is increased appreciation for the notion that many existing small molecule cancer therapies also affect cells of the immune system and thus can influence the antitumor immune response.[8–12] For instance, imatinib, originally developed as a bcr-abl inhibitor, suppresses the expression of indoleamine 2,3-dioxygenase (IDO) through its inhibition of a kinase known as c-KIT. The nucleoside analog gemcitabine selectively kills myeloid derived suppressor cells, a subset of immunosuppressive cells that can promote tumor growth. The immune-based mechanisms of existing targeted and cytotoxic chemotherapeutics have been reviewed elsewhere.[13] This perspective will focus on new potential drugs and selected drug targets still at various stages of preclinical and early clinical research and development. It is intended to complement existing literature and where applicable the reader is directed to recent reviews for more detail.

Targeting the tumor microenvironment

Indoleamine 2,3-dioxygenase and tryptophan dioxygenase

The metabolic enzymes IDO and TDO (tryptophan dioxygenase) catalyze the conversion of tryptophan to kynurenines and further metabolites. Both tryptophan depletion and elevated levels of kynurenine can exert a suppressive effect on the immune system.[14–16] Tryptophan is an essential amino acid for T cell proliferation, and kynurenine binds to the aryl hydrocarbon receptor and promotes regulatory T cell (Treg) generation. The two known isoforms of IDO, IDO1 and IDO2, differ in their amino acid sequence and expression pattern. TDO is a functionally similar but structurally unrelated enzyme expressed primarily in the liver. IDO expression in human cancer is generally associated with a worse prognosis[14]; an increased ratio of kynurenine to tryptophan is associated with poorer outcomes in patients with AML.

Animal studies in mice have demonstrated antitumor activity for small molecule IDO inhibitors either as a single agent or in combination with cytotoxic agents or checkpoint inhibitors. Several companies have programs to identify and develop inhibitors of IDO and/or TDO and there are multiple small molecule IDO inhibitors currently in clinical trials (Fig. 1).[15] Compounds early in development include a preclinical IDO1 inhibitor (EOS-200,271/PF-06,840,003) from iTeos therapeutics/Pfizer as well as NLG919 (navoximod) from NewLink Genetics, currently in a phase 1 trial in combination with atezolizumab, a checkpoint inhibitor targeting PD-L1. Newlink Genetics is also developing two other IDO/TDO pathway inhibitors, indoximod (NLG-8189: D-1-methyltryptophan) and an indoximod prodrug, NLG802. Indoximod is currently

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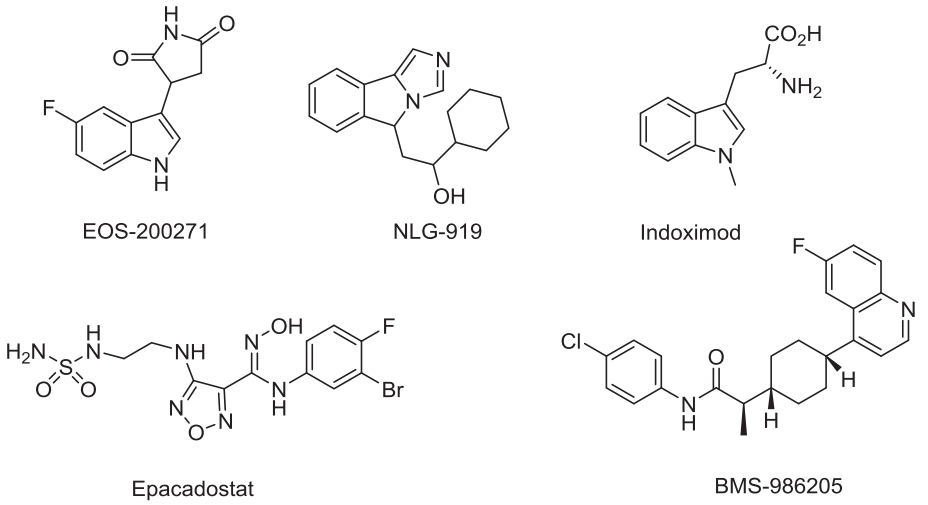

Fig. 1. Inhibitors of IDO and the IDO pathway.

being studied in 5 clinical trials including studies in combination with cytotoxic agents. Results from a phase 2 combination study in metastatic pancreatic cancer are expected in the first half of 2018. BMS is developing BMS-986,205 from Flexus Pharmaceuticals with a Phase I/II trial ongoing.

The IDO inhibitor that has progressed furthest in development is Incyte's epacadostat (Fig. 1), an orally bioavailable IDO1 inhibitor.[17,18] This compound and other IDO inhibitors have been well described elsewhere.[8,12] Epacadostat has been combined with the checkpoint inhibitors ipilimumab, nivolumab or pembrolizumab. These combinations appear to be well tolerated. In an alternative approach to modulating the same pathway, Kyn Therapeutics is developing drugs to inhibit the immunosuppressive effects of kynurenine through its enzymatic degradation.

Arginase and nitric oxide synthase

Another essential amino acid is arginine. The manganese metalloenzyme arginase metabolizes the conversion of arginine to ornithine and urea. In the tumor microenvironment, arginase is secreted by myeloid-derived suppressor cells (MDSCs) leading to a local depletion of arginine, which limits T cell proliferation. Thus, inhibitors of arginase activity may be expected to exert a beneficial immunomodulatory effect in cancer patients.[19] While various compounds have been described possessing inhibitory activity vs arginase, many of them are weakly potent with IC_{50} values in the microMolar range or higher. The hydroxyguanidine nor-NOHA (Fig. 2) is one of the more potent inhibitors to have been described (K_d/Ki = 47/51 nM vs arginase I and arginase II respectively). Moreover, this compound is 100% orally bioavailable in rats, although its half-life is short, between 15 and 30 min. Nor-NOHA was well tolerated in atherosclerotic or hypertensive rats for 9 or 10 weeks respectively, as well as in small scale clinical studies in patients with various cardiovascular diseases,[20,21] suggesting the potential of testing nor-NOHA clinically for cancer.

Other metal binding groups that have been investigated for arginase inhibition include boronic acid derivatives of alpha amino acids (for example compound 10, Fig. 2).[22] Calithera's CB-1158 (IC_{50} = 98 nM),[23] which displays single agent antitumor activity in a Lewis Lung carcinoma model, is being evaluated for treating cancer both as a single agent and in combination with nivolumab.

A competing metabolic pathway for arginine is its conversion to citrulline and nitric oxide (NO) by the action of nitric oxide synthases.[24] The important role of NO as a second messenger and the implication of NO in the pathology of a wide variety of conditions including hypertension, schizophrenia and asthma have prompted considerable efforts towards the development of NOS inhibitors, and Ronopterin (Fig. 2) is currently in phase III clinical trials for the treatment of traumatic brain injury. NO is implicated as a pro-growth signal for tumor cells and preclinical studies of specific NOS inhibitors have demonstrated an antitumor effect.[25,26] In one example, N^G-nitro-L-arginine methyl ester (L-NAME, Fig. 2) was demonstrated to improve the response to irradiation of a syngeneic squamous cell carcinoma in mice. No such improvement was observed in nude mice, implicating a role for the immune system, and L-NAME treatment was associated with an increase in interferon-γ (IFNγ) and a decrease in IL-10 consistent with a pro-inflammatory response.

General control non-repressible 2 (GCN2)

Amino acid metabolism in the tumor microenvironment can lead to the accumulation of uncharged tRNAs, which induces a stress signal alerting cells to place a hold on protein synthesis and ramp up amino acid synthesis/acquisition.[27–29] Excess uncharged tRNA binds to and activates the 187 KDa stress control protein General Control Non-repressible 2 (GCN2), a kinase that phosphorylates Serine 51 on protein synthesis initiation factor eIF2α.[30] It has been reported that activation of GCN2 following hypoxia or UV stress is similarly mediated by the binding of uncharged tRNA.[31] Phosphorylation of eIF2α generally inhibits protein synthesis with the exception of specific proteins required for activation of amino acid synthesis such as ATF4, and is broadly immunosuppressive. Inhibition of GCN2 is anticipated to counter the immunosuppressive effect of amino acid deficiency in the tumor microenvironment that arises as a result of IDO, arginase and iNOS activity. In addition, GCN2 may be a direct antitumor target since its inhibition may abrogate the ability of tumor cells to tolerate stress signals.[30]

Inhibitors of GCN2 have been described by several groups.[32] Robert and coworkers identified three inhibitors from a library of known kinase inhibitors.[33] Merck GMBH has published a series of patents claiming GCN2 inhibitors including triazolopyrimidines,[34–36] triazolopyrazines (Fig. 3)[37,38] and aminopurine derivatives.[39] The most potent GCN2 inhibitors described exhibit IC_{50} values for GCN2 enzyme inhibition <0.3 μM and some of these compounds inhibit eIF2α phosphorylation in cells. However, the triazolopyrimidines appear to be more potent inhibitors of SYK