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IRAK4 Modulators for Treatment of Hematologic Malignancies

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Abstract

Interleukin-1 Receptor-Associated Kinase 4 (IRAK4) plays an important role in Toll-Like Receptor (TLR) signalling and activation of innate immune responses. Impairment of the innate immunity is known to be associated with different inflammatory conditions and cancer. Although there had been significant progress in evaluation of IRAK4 modulators in clinic for the treatment of various inflammatory pathologies, there had been only limited exploration so far for evaluation of these agents for the treatment of cancers. Recent updates on the profile of some of these compounds have demonstrated that IRAK4 could be a fascinating and important target for the treatment of certain life-threatening cancers. In this brief review article, we have compiled all the known IRAK4 modulators which are being actively developed to specifically address the unmet medical need in cancer.

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TLRs play vital role in the innate immune system [1] and IRAK4 is an important signalling member in the TLR immune response pathway. Recruitment and activation of IRAK4 upon TLR stimulation is facilitated by a protein called Myeloid Differentiation Primary Response 88 (MYD88) adaptor [2]. MYD88 in complex with IRAK4 further activates another isoform of IRAK (IRAK1) leading to the stimulation of TRAF6 (TNF receptor-associated factor 6) and NF-kB (Nuclear factor of kappa light polypeptide gene enhancer in B-cells) [3]. Certain mutations in MYD88 are known to stimulate the NF-kB signalling leading to different oncogenic pathologies like Waldenstrom's Macroglobulinemia (WM) and Diffuse Large B Cell Lymphomas (DLBCLs) [4,5]. TLRs and associated signalling partners like IRAK4 are also frequently over expressed and activated in cancers including Myelodysplastic Syndromes (MDS), Acute Myeloid Leukaemia (AML) etc. and known to correlate with poor prognosis [6,7]. Therefore, IRAK4 could be an attractive molecular target for the treatment of such haematological malignancies.

Leveraging the role of IRAK4 in up regulation of NF-kB signalling and activation of inflammatory cytokines, a few novel IRAK4 inhibitors have been evaluated in clinical trials for the treatment of conditions including rheumatoid arthritis, hidradenitis suppurativa, psoriasis, atopic dermatitis, and other autoimmune disorders. These IRAK4 targeted agents include Pfizer's PF-06650833, Bayer's BAY-1830839, BAY-1834845, Rigel's R-835 and Kymera's novel IRAK4 degrader, KT-474 [8-14]. Nevertheless, there had been only limited success so far for such inhibitors in the clinic for the treatment of life-threatening haematological conditions. This short review mainly highlights all the publicly known active oncology programmes in this target space as of date and progress made in the direction of finding novel therapeutics.

The earliest known IRAK4 inhibitor explored for the treatment of haematological cancers is ND-2158 (Figure 1), developed by Nimbus Therapeutics and Schrödinger Inc. ND-2158 is a highly potent and selective inhibitor of IRAK4. ND-2158 was shown to be effective in reducing proliferation of Activated B-Cell (ABC)-DLBCL cell lines with MYD88 L265P mutation but not Germinal Center B-Cell (GCB)-DLBCL cell-lines, thereby implicating that ABC-DLBCL with activating mutations in MYD88 likely to be dependent on IRAK4 signalling. ND-2158 also demonstrated synergistic blockade of ABC-DLBCL proliferation when combined with different B Cell Receptor (BCR) signalling inhibitors both in vitro and in vivo [15-17]. However, further development of this compound presumed to have been discontinued since there are neither any public updates on this compound since June 2019 [18] nor the websites of ND-2158 developers feature these compounds anymore. Like ND-2158, few other IRAK4 inhibitors including Astra Zeneca's AZ1495 (Figure 1), Rigel's R191, LG0250276 and LG0224912 from Ligand Pharma and TG Therapeutics were also shown to be efficacious in haematological cancer models [19-21] but there are no updates available on further progress of these compounds since last several years. There was also a disclosure on in vivo efficacy of BAY-1830839 in pre-clinical ABC-DLBCL models [22] but intriguingly Bayer's oncology pipeline does not showcase this compound in any stage of discovery or development. Kymera disclosed an orally bio available degrader of IRAK4 viz. KYM-001 couple of years back. The compound showed robust efficacy in a MYD88-driven lymphoma model, both alone and in combination with a BTK inhibitor [23]. Although this compound per se does not feature in the developer's website but there is another IRAK4 degrader being projected as in active development for treatment of DLBCL [24], which will be discussed in the following section.

To the best of our knowledge, as of date there are only three IRAK4 inhibitors/degraders which are known to be still actively undergoing preclinical and clinical development for the treatment of haematological malignancies and these are KT-413 (KTX-120), KM-10544 and CA-4948, discovered by Aurigene and licensed to Curis Inc for global development.

Kymera's KT-413 is an orally bio available dual degrader of IRAK4 and Immuno-Modulatory Imide Drug (IMiD) substrates. The compound demonstrated significant potency in MYD88^{MT} DLBCL cell-lines and tumour regression via intermittent dosing in relevant Patient Derived Xenograft (PDX) and Cell line-Derived Xenograft (CDX) tumour models. PK - PD analysis showed >80% degradation

of the target proteins which correlated well with observed tumour regression. KT-413 is also known to inhibit both MYD88-dependent NF-kB signalling as well as up regulates Type 1 IFN pathways, consistent with dual-targeting activity of this molecule. As per the interim data shared by Kymera recently, their other clinical stage degrader KT-474 has demonstrated satisfactory IRAK4 degradation in the isolated PBMC of healthy volunteers in a randomized Phase 1 clinical trial. However, KT-413 is expected to enter clinical trials by 2H 2021 [24-27].

Next one is the IRAK4 inhibitor KM-10544 from Kainos Medicine and Emmaus Life Sciences. The collaborating parties have disclosed that they will be evaluating the efficacy of this compound in solid cancers, blood cancers and lymphoma in a recent press release [28]. However, there are no other information on either the current stage of development or the profile of this compound disclosed in the public domain so far.

Lastly and notably, the most advanced compound in this target space explored for treatment of haematological cancers is CA-4948, currently in clinical development by Curis Inc. The structure and pre-clinical profile of this compound was published last year by our groups at Aurigene [29]. CA-4948 is an orally bioavailable selective IRAK4 inhibitor that demonstrated enhanced efficacy in multiple ABC vs GCB DLBCL PDX tumor models both as single agent and in combination with Ibrutinib (BTK inhibitor) or Venetoclax (BCL2 inhibitor) [30]. CA-4948 is currently in Phase 1/2 clinical trials. A very recent press release disclosed remarkable interim clinical efficacy observed with this compound in an ongoing phase 1/2 study evaluating monotherapy in patients with relapsed or refractory AML and MDS. The study results showed that the treatment with CA-4948 leads to marrow blast reductions in 10 out of 12 patients and 5 objective responses including 1 complete remission [31].

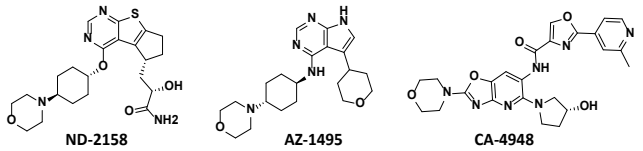

Figure 1: Publicly disclosed structures of selective IRAK4 inhibitors investigated for the treatment of haematological cancers [17,29,32].

Innate immune response coordinated through TLR is vital for body's primary defence against external antigens, while their malfunctioning is associated with certain inflammatory conditions, including cancer. The encouraging clinical data with CA-4948, a first-in-class IRAK4 inhibitor in cancer has established that specific malignancies with overactive TLR pathway can be addressed effectively with IRAK4 inhibitors either alone or in combination with other agents. Kymera's IRAK4 degrader has demonstrated attractive preclinical profile, and the efficacy and tolerability of such bifunctional degraders in clinical setting are eagerly awaited. We hope the emerging data from CA-4948 and other novel IRAK4 targeted therapeutics in haematological cancers with unmet medical need will inspire identification of other exciting clinical opportunities for these agents. Approval and clinical success of an inhibitor of IRAK4 as cancer treatment should be an appropriate outcome of the extensive research on this target since its discovery in the year 2002 [33,34].

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