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各　　位

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FLT3 阻害剤に関する研究結果の学会発表のお知らせ

当社は、FLT3 遺伝子変異陽性の急性骨髄性白血病（Acute Myeloid Leukemia; AML）の治療を目的とした FLT3 阻害剤の研究結果を米国がん学会年次総会（American Association for Cancer Research (AACR) Annual Meeting 2022）においてポスター発表しましたので、その概要をお知らせいたします。

演題：
Discovery of OTS447, a highly potent and selective inhibitor of FLT3 for the treatment of AML patients with FLT3-ITD/TKD mutations（FLT3-ITD/TKD 変異陽性 AML 患者の治療のための強力かつ選択的な FLT3 阻害剤 OTS447 の発見）
概要：
FLT3 は、急性骨髄性白血病患者において、高頻度に変異が出現し、予後不良と関連する遺伝子の一つです。現在、FLT3 遺伝子変異陽性の急性骨髄性白血病患者の治療薬として複数の FLT3 阻害剤が承認され、以前の治療方法と比較して高い治療効果を発揮しておりますが、薬剤耐性変異の出現による再発などの課題が残されております。当社では、この薬剤耐性変異の課題を克服すべく、自社所有化合物ライブラリのスクリーニングを実施し、FLT3 に対して高い阻害活性と選択性を有する化合物として OTS447 を発見いたしました。OTS447 は、FLT3 遺伝子変異陽性の急性骨髄性白血病患者に由来する培養細胞株を死滅させるだけでなく、再発の原因として報告のある薬剤耐性変異を導入した培養細胞株も死滅させました。さらに、OTS447 は、急性骨髄性白血病細胞株を移植したマウスにおいて、体重減少を引き起こすことなく顕著な腫瘍増殖抑制効果を示しました。

今後、この化合物の最適化を進め、早期の臨床試験候補化合物の取得を目指します。

なお、本件による 2023 年 3 月期当社業績への影響は軽微であります。

【発表概要 原文】

Discovery of OTS447, a highly potent and selective inhibitor of FLT3 for the treatment of AML patients with FLT3-ITD/TKD mutations

FMS-like tyrosine kinase 3 (FLT3) is one of the most frequently mutated genes in acute myeloid leukemia (AML), and its activating mutations including internal tandem duplications (ITDs) and missense point mutations in the tyrosine kinase domain (TKD) are found in approximately 30% of AML patients. Although the patients initially well responded to FLT3 inhibitors such as gilteritinib, the most cases relapsed within a few months after the initiation of treatment. For these patients who relapsed after FLT3 inhibitor-based therapy, no effective treatment is available. Mechanisms of resistance are not fully elucidated, but FLT3-ITD-TKD double mutant is considered as one of possible mechanisms. We have discovered a novel FLT3 inhibitor OTS447 that shows the potent and selective inhibition in both FLT3-ITD and FLT3-ITD-TKD double mutants.

OTS447 was identified through the screening of our in-house proprietary compound library. It showed potent inhibitory activity against FLT3 with an IC_{50} value of 0.19 nM. The selectivity of OTS447 was investigated by human kinase profile assay. Among 371 human kinases tested, there were only seven (including FLT3) whose activity were inhibited by 80% or more at 5 nM of OTS447. We then examined the anti-proliferative effects in FLT3-ITD and -wild type (WT) AML cell lines. The proliferation of FLT3-ITD cell lines, MV4-11 and MOLM13, was more strongly suppressed than that of FLT3-WT cell lines. We also investigated the inhibitory effects to FLT3-ITD-TKD double mutants using Ba/F3 cells. FLT3-ITD-D835Y mutant was inhibited as strongly as FLT3-ITD mutant, and FLT3-ITD-F691I mutant was more strongly inhibited than Ba/F3 parental cells. These data suggest that OTS447 has selective inhibitory activity against FLT3 mutants. To confirm that FLT3 inhibition by OTS447 leads to the anti-proliferative effect, FLT3 autophosphorylation and phosphorylation of downstream molecules such as STAT5, ERK and AKT were examined. Both autophosphorylation of FLT3 and phosphorylation of downstream molecules were decreased by OTS447 in dose-dependent manner. Moreover, treatment of OTS447 induced the apoptosis and increased sub-G1 population in MV4-11 cell. Finally, we tested OTS447 anti-tumor effect using MV4-11 mouse xenograft model. OTS447 showed potent growth inhibition against MV4-11 tumor in dose-dependent manner.

In summary, we discovered OTS447, a potent and selective FLT3 inhibitor, that can inhibit not only ITD mutation but also ITD-TKD mutations of the *FLT3* gene. OTS447 possesses cytotoxic activity induced by inhibition of FLT3 signaling pathway and has anti-tumor activity in mouse xenograft model. We are pursuing further optimization of the inhibitor aiming for the effective treatment of AML patients with several types of FLT3-activating mutations.

参照 URL: https://www.abstractsonline.com/pp8/#!/10517/presentation/17687
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以上