TECHNOLOGY

Total and Phosphorylated IL-1 Receptor-Associated Kinase-1 (IRAK-1) and -4 (IRAK-4) as a Biomarker for Cancer Progression and Chemotherapy Resistance.

OVERVIEW

UMB inventors have identified two proteins active in the TNF receptor-associated factor (TIRAF)/MyD88 pathway, Interleuken-1 Receptor-Associated Kinase (IRAK)-1 and -4, as potential targets for combinatorial therapy reducing chemotherapy resistance in multiple cancer cell lines. IRAK is a signal transducer for the Toll-like receptor (TLR)/Interleukin-1 (IL-1) family of proteins and play a role in cancer, inflammatory and autoimmune diseases. This technology is a method of administering IRAK-1 and IRAK-4 inhibitors to patients expressing phosphorylated IRAK in melanoma or T-cell acute lymphoblastic leukemia (T-ALL). The inventors have identified IRAK-1 and -4, in the TLR-NF-KappaB signaling pathway, whose total and phosphorylated expression may be targeted for combinatorial therapy in cancers. Studies with chemotherapeutic resistant melanoma cell lines found that 42% of the melanoma lines tested expressed phosphorylated IRAK-1 (p-IRAK-1) and 85% expressed variable levels of p-IRAK-4 in the absence of TLR agonists. In mouse models, treatment with small-molecule IRAK-1 and -4 inhibitors were found to reduce NF-KappaB activation. In xenograft mouse models, established human melanoma tumors treated with IRAK-1 and -4 inhibitors combined with vinblastine (a microtubule-inhibiting anti-cancer drug) increased mean survival to 38 days over 19 days with inhibitor alone, and 22 days with vinblastine alone**.** Potential also exists for use of total and phosphorylated expression as the first biomarker for cancer progression and chemotherapy resistance in melanoma.

APPLICATIONS

Signaling through the TLR family has been well characterized in the induction of innate and adaptive immunity. The expression of different TLRs on various cancer cell lines are speculated to signal through the TIRAF/MyD88 pathway resulting in the activation of NF-KappaB aiding in cancer survival and growth. No IRAK inhibitor currently exists on the market though several are in development. In Phase 1 clinical trials is Pfizer's PF-06650833 pursued for the treatment of Lupus. Nimbus Therapeutics who uses computer modeling to identify potential leads exclusively licensed its IRAK4 program to Genentech in 2015 and is currently under development.

ADVANTAGES

- **Commercial inhibitors available**: full scale drug development program is not necessary

- **Conserved Targets:** reduced chance for the development of drug resistance

- **Potential biomarker:** biomarker for cancer progression and chemotherapy resistance in cancers

STAGE OF DEVELOPMENT

- In vivo and in vitro studies conducted

(MB- As of 6/12/17)

R&D REQUIRED

Proof of concept and clinical trials.

LICENSING POTENTIAL

UM seeks to develop and commercialize by an exclusive or non-exclusive license agreement and/or sponsored research with a company active in the area.

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Additional Information

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PATENT STATUS

US Patent 9,464,326 issued 10/11/2016

LICENSE STATUS

Available for licensing

CATEGORIES

- Therapeutics

INVESTIGATOR(S)

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ATTACHMENTS

- Download ED-2012-072 - final.pdf

EXTERNAL RESOURCES

- Inhibition of IRAK1/4 sensitizes T cell acute lymphoblastic leukemia to chemotherapies
- IL-1 receptor-associated kinase signaling and its role in inflammation, cancer progression, and therapy resistance
- Augmentation of Therapeutic Responses in Melanoma by Inhibition of IRAK-1, -4

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