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# Inhibition of IRAK-1/4 to enhance the efficacy of chemotherapeutic drugs in melanoma and T-cell acute lymphoblastic leukemia (T-ALL).


## Summary

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).



## Key Investigator

Eduardo Davila


## Field

Immunology
Oncology

## Technology

Method of enhancing the efficacy of chemotherapeutic drugs

## Technology Status

In vivo and in vitro studies conducted

## Status

Available for licensing
Available for sponsored research

## Patent Status

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

## UMB Docket Reference

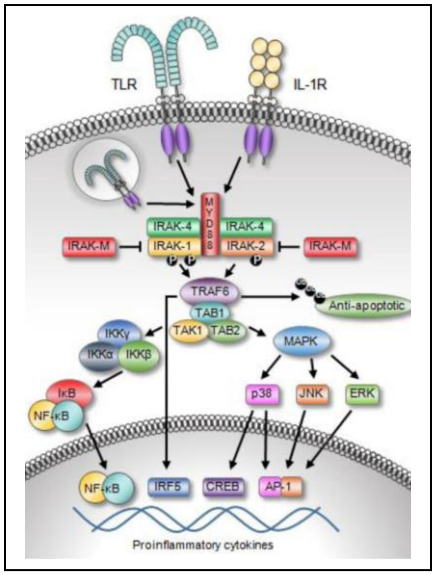
ED-2012-072

## External Reference

- J Clin Invest. 2015 Mar 2;125(3): 1081-97
- Front Immunol. 2014 Nov 17;5:553
- Cancer Res. 2012 Dec 1;72(23):3209

## Market

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 it's IRAK4 program to Genentech in 2015 and is currently under development.




## Technology

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.

## 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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