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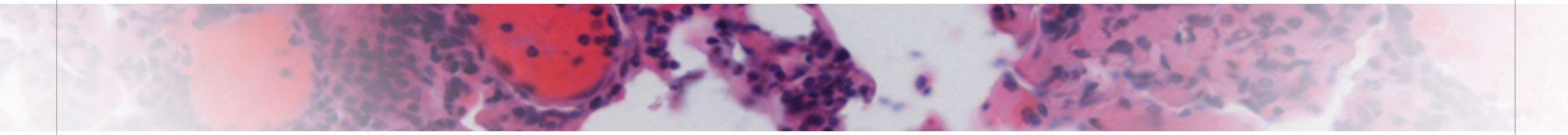

2863: A Phase 1, Open Label Dose Escalation Trial Evaluating the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of Orally Administered CA-4948 in Patients with Acute Myelogenous Leukemia or Myelodysplastic Syndrome

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Introduction/Background

- IRAK4 kinase plays an essential role in toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling pathways. These pathways are frequently dysregulated in Non-Hodgkin Lymphomas (NHL) and AML/MDS. [1] Oncogenic IRAK4- L, which is driven by spliceosome mutation (including SF3B1 and U2AF1), is preferentially expressed in >50% of AML/MDS patients [2,3].

- CA-4948 is a novel small molecule oral inhibitor of interleukin-1 receptor associated kinase 4 (IRAK4)

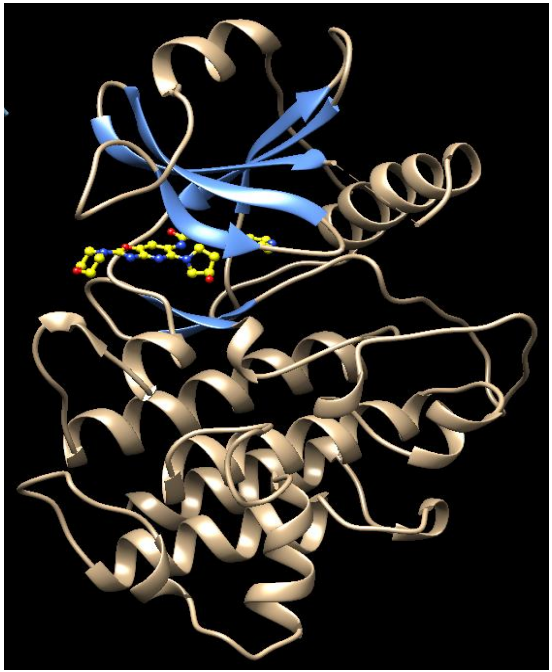
- Orally bioavailable; moderate plasma binding (77% human)
    - Stable in plasma, liver microsomes, hepatocytes
    - No inhibition of 7 major CYP450s
    - No significant metabolism *in vitro*

- CA-4948 inhibits a defined subset of malignancies that are driven by over-activity of the TLR/IL-1R pathway, which is dependent on IRAK4

- Activated IRAK4 identified as a driver of adaptive resistance in AML and other tumors [4]

- CA-4948 not only strongly inhibits IRAK4, but also FLT3 in vitro and in-vivo models

IRAK4/CA-4948 Co-crystal Structure



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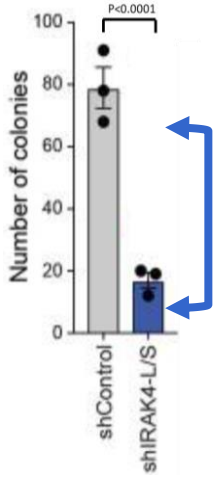
Genetic Mutation Expression: Long IRAK4 Isoform (IRAK4-L)

Spliceosome mutations (incl. SF3B1 and U2AF1) drive expression of IRAK4-L in >50% of AML/MDS

IRAK4-L is Oncogenic

IRAK4-L provides a genetic link to oncogenic immune signaling in AML/MDS

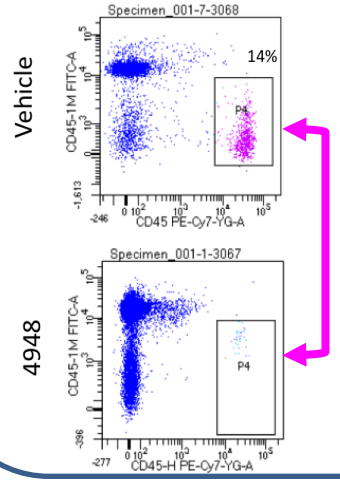


Blocking IRAK4-L reduces the formation of leukemia colonies in preclinical studies

Smith et al. Nat Cell Biol. 2019

CA-4948 Directly Targets IRAK4

Direct inhibition of IRAK4 is associated with disease

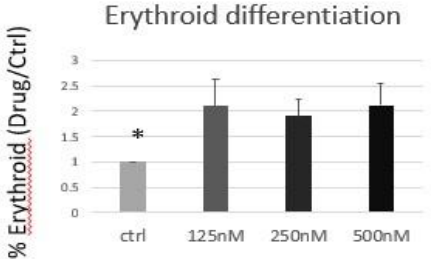


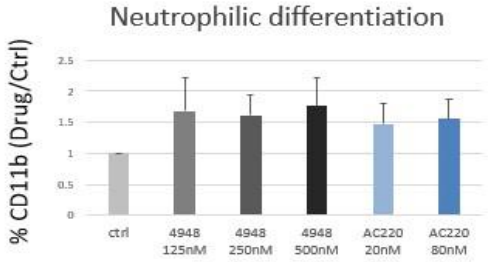
CA-4948 treatment reduces leukemic blasts in patient-derived xenografts

Choudhary et al. AACR 2017

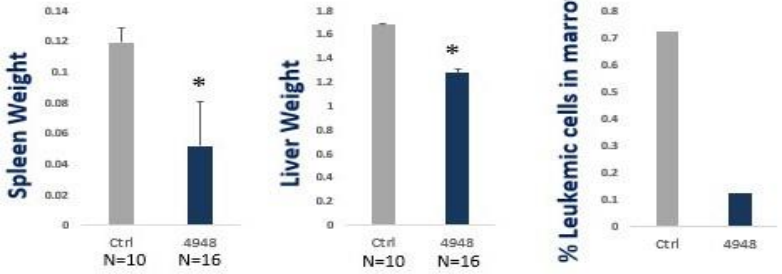
CA-4948

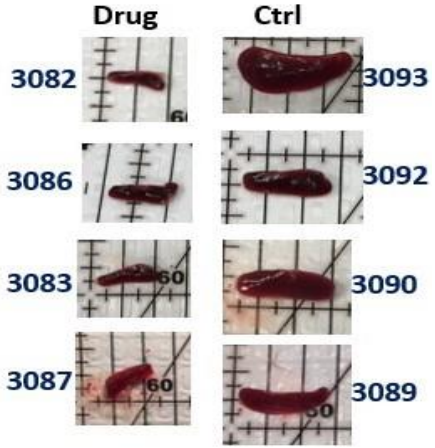
Increases Cell Differentiation from Primary MDS/AML HSPCs





Decreases Disease Burden in THP-1 Xenografts





6 weeks of treatment at 12.5mg/kg

Ulrich Steidl Lab (Albert Einstein) collaboration

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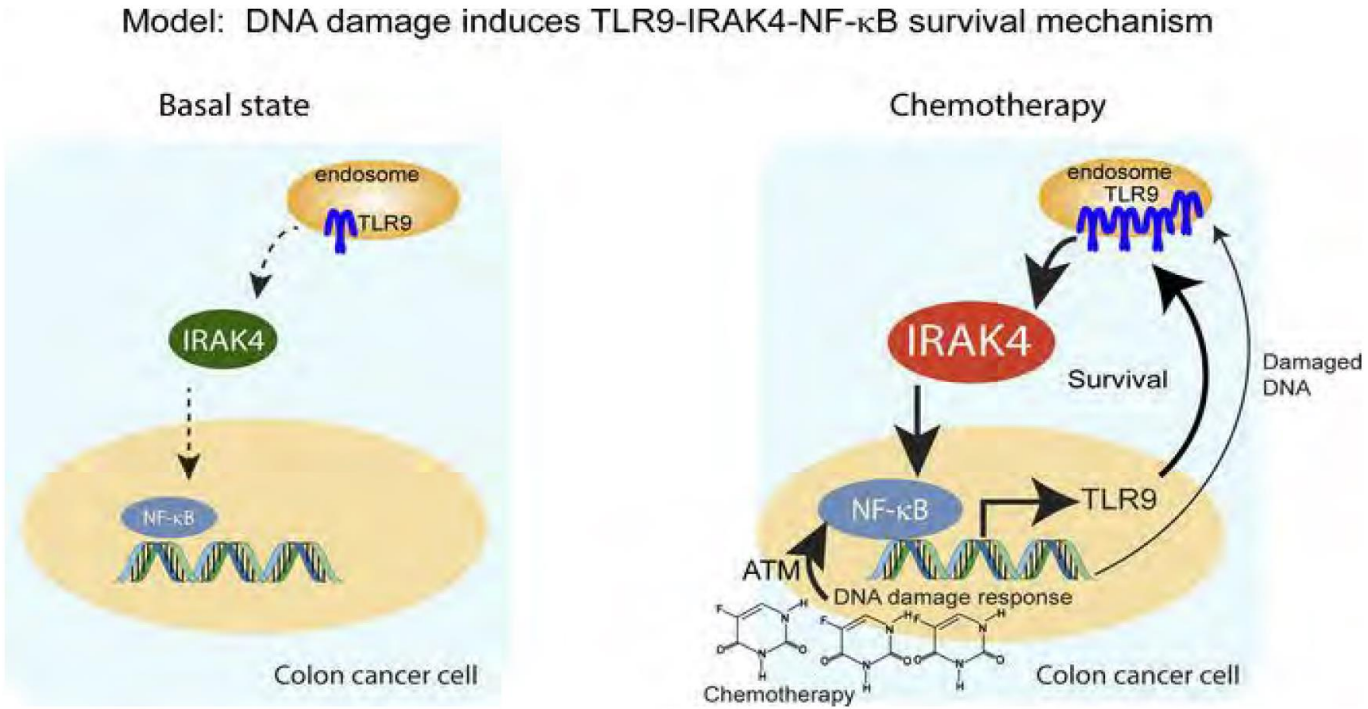
IRAK4 Inhibition May Inhibit Adaptive Malignancy Resistance



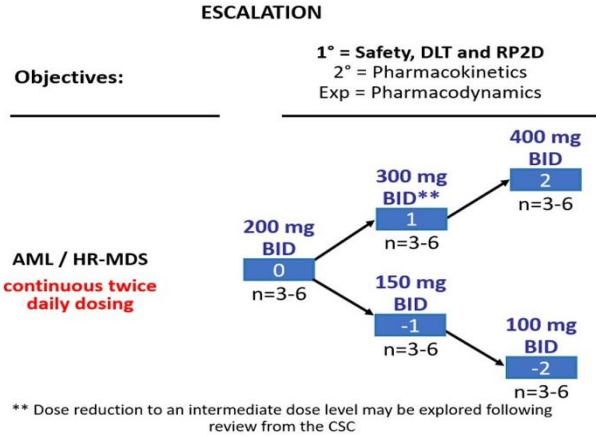
Q Li et al, JCI Insight 2019

CA-4948

Study Design and Methods

- This is a multicenter, open-label, single arm Phase 1 dose escalation study of orally administered CA-4948 monotherapy in adult patients with AML or high risk MDS *(NCT04278768)*

- Each treatment cycle of CA-4948 will be 28 days in length and repeated in the absence of unacceptable toxicity or disease progression



Primary Objective:

- To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) for CA-4948 based on the safety and tolerability, DLTs and PK/PD findings

Secondary Objective

- Characterization of the pharmacokinetic (PK) parameters and preliminary efficacy

Exploratory objective:

- To assess the potential association between target-related biomarkers (including IRAK4-L and downstream signaling parameters), selected genetic mutations (including spliceosome mutations), gene expression signatures, cell of origin, or other molecular classification subtypes and anti-leukemic activity (including central morphology review)
- To assess the pharmacodynamic effects of CA-4948 on selected biomarkers in peripheral blood and bone marrow

CA-4948

Inclusion and Exclusion Criteria

Inclusion:

- Males and females ≥18 years of age
- Cytomorphology-based confirmed diagnosis of MDS or AML (per the WHO 2016 classification) with the following characteristics:
    a. Relapsed or refractory AML (primary or secondary, including treatment-related); OR
    b. High/very high risk relapsed/refractory MDS (IPSS-R criteria), following at least 6 cycles of hypomethylating agents (HMA) or evidence of early progression

Exclusion:

- Patients diagnosed with acute promyelocytic leukemia (APL, M3)
- Blast phase of CML
- Allogeneic hematopoietic stem cell transplant (Allo-HSCT) within 60 days of the first dose of CA-4948, or clinically significant graft-versus-host disease (GVHD) requiring ongoing up-titration of immunosuppressive medications prior to start of CA-4948

CA-4948-102

Trial in Progress: Monotherapy in R/R High-Risk MDS and AML

Cohort 1 (200mg BID; cycle duration 4 weeks):

- 3 patients with hr-MDS; all with ongoing treatment (currently 2-4 cycles)
- **No DLT** in 1st cycle

Cohort 2 (300mg BID):

- 4 patients (3 AML, 1 hr-MDS), all with ongoing treatment (currently 1-2 cycles)
- **No DLT** in first 3 patients; 4th patient too early (will complete 1st cycle mid Nov)

Cohort 3 (400mg BID):

- Open for enrollment

Conclusion and References

- 200mg and 300mg cohorts fully enrolled
- Clinical update to be reported Dec 7-8, 2020
- After RP2D is determined, the study may be amended to include patient selection criteria, as well as combination therapy in a controlled design

References:

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3. Smith MA. et al., 2019 Nat Cell Biol. 21(5): 640–650
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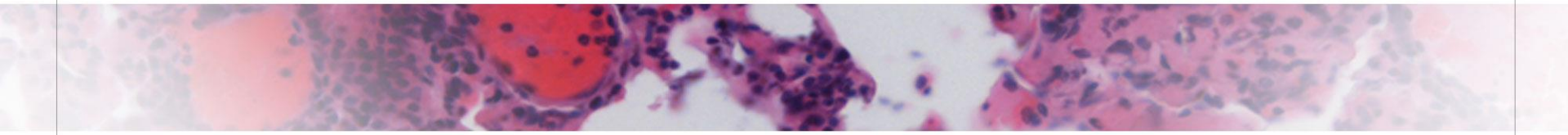

Thank you

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