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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

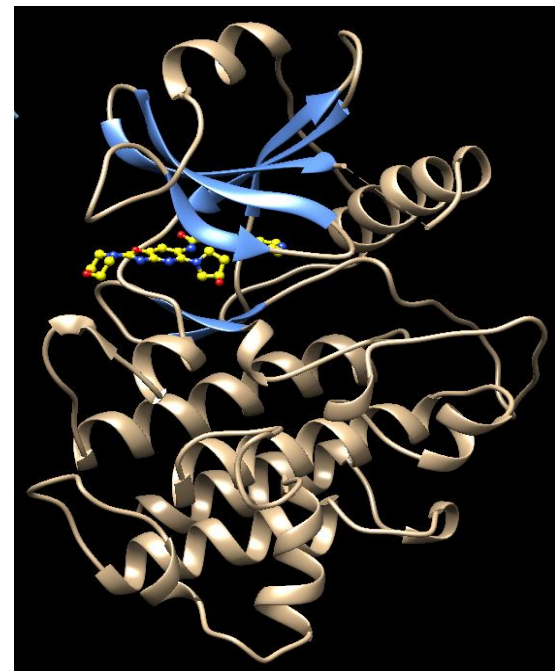
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# Introduction/Background

- 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



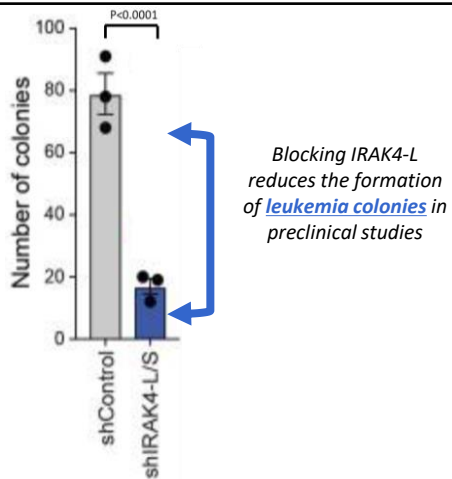
# CA-4948

## 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

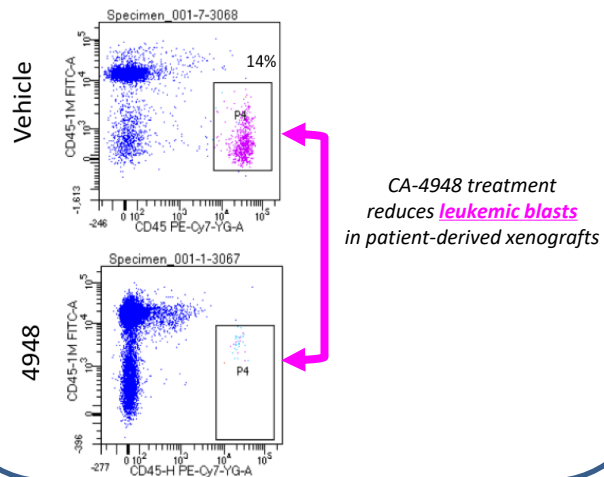
IRAK4-L provides a genetic link to oncogenic immune signaling in AML/MDS



Smith et al. Nat Cell Biol. 2019

### CA-4948 Directly Targets IRAK4

Direct inhibition of IRAK4 is associated with disease

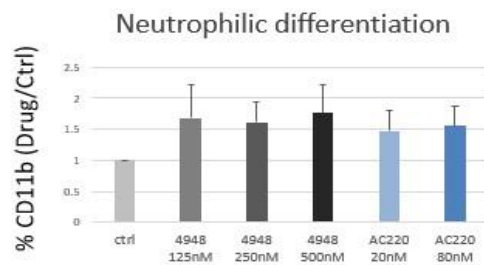
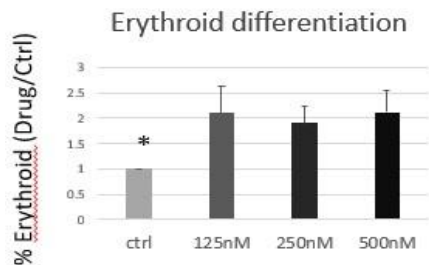


Choudhary et al. AACR 2017

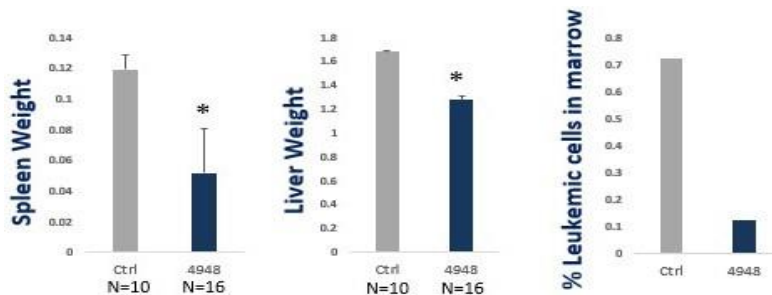


# CA-4948

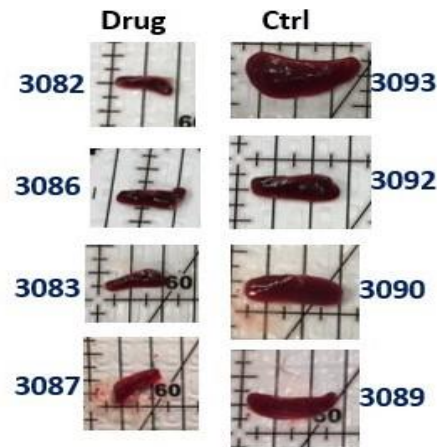
## Increases Cell Differentiation from Primary MDS/AML HSPCs



## Decreases Disease Burden in THP-1 Xenografts



6 weeks of treatment at 12.5mg/kg



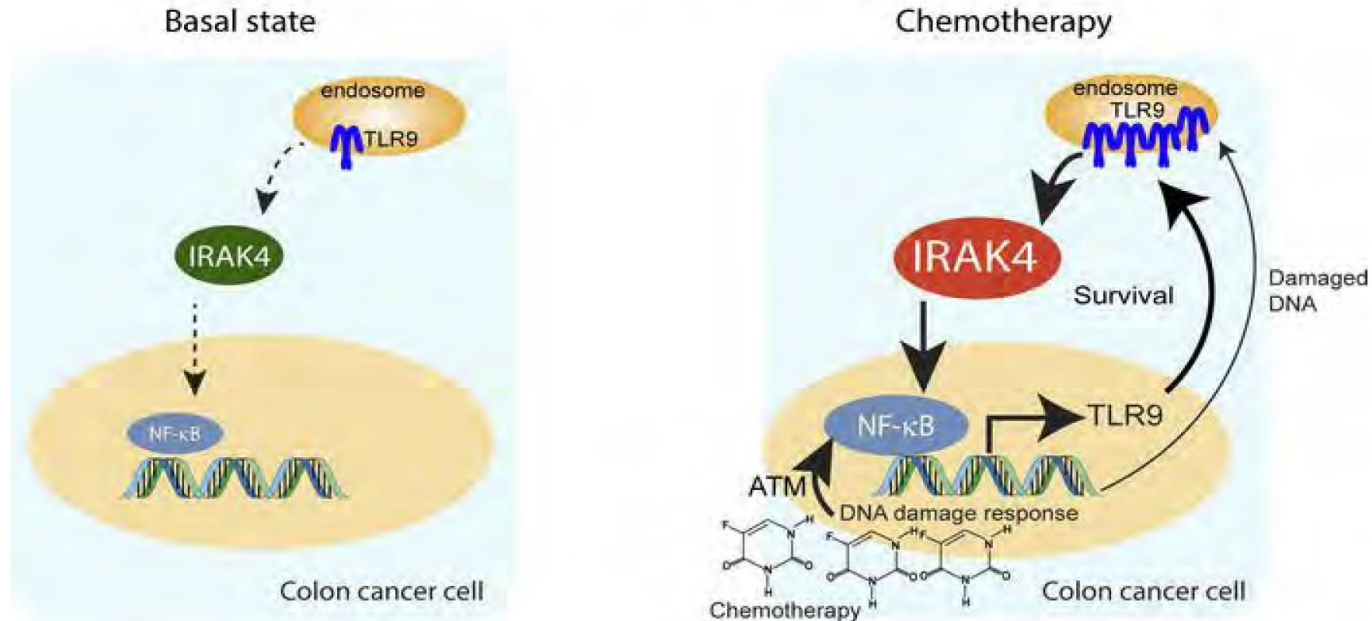
Ulrich Steidl Lab (Albert Einstein) collaboration



# CA-4948

## IRAK4 Inhibition May Inhibit Adaptive Malignancy Resistance

Model: DNA damage induces TLR9-IRAK4-NF- $\kappa$ B survival mechanism



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:

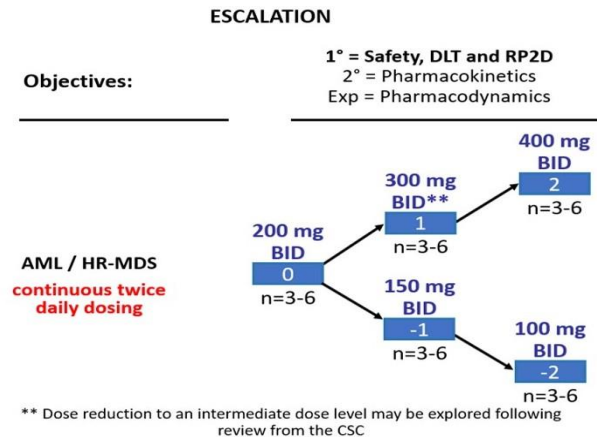
- To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) for CA-4948 based on the safety and tolerability, DLTs and PK/PD findings

### 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  $\geq 18$  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 1<sup>st</sup> 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; 4<sup>th</sup> patient too early (will complete 1<sup>st</sup> 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:

1. Rhyasen, GW, Starczynowski DT, 2015. Brit J Cancer 112, 232–237
2. Choudhary G et al. 2019. Blood 134 (Suppl 1): 4224.
3. Smith MA. et al., 2019 Nat Cell Biol. 21(5): 640–650
4. Melgar, K. et al., 2019. Sci Transl Med, 11: eaaw8828
5. Booher R. et al.: 2019: EHA Annual Meeting, Abstr. PS991





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## Thank you

Thanks to the participating trial investigators, clinical staff, the patients and their families.

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