DRUG DEVELOPMENT INSTITUTE (DDI) TECH BRIEF

The James
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

DHODH Inhibitors for the Treatment of Hematological Malignancies

Recent research has demonstrated the potential to treat hematologic malignancies through inhibition of dihydroorotate dehydrogenase (DHODH). The Ohio State University, in collaboration with Hendrix College, is developing DHODH inhibitors for the treatment of hematological malignancies, including acute myeloid leukemia (AML).

Applications

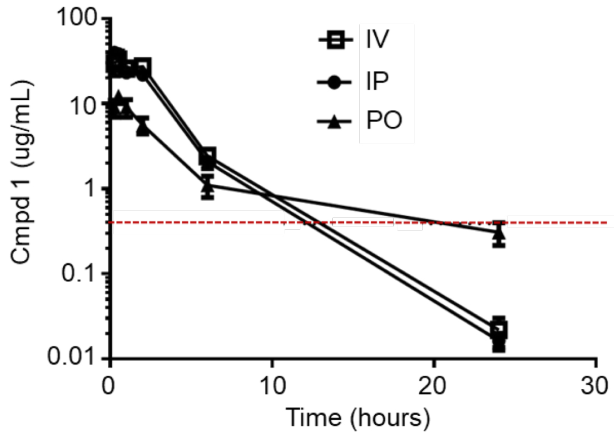
- AML, MDS and CMML
- Follow-on indications - Undisclosed hematological malignancies

Advantages

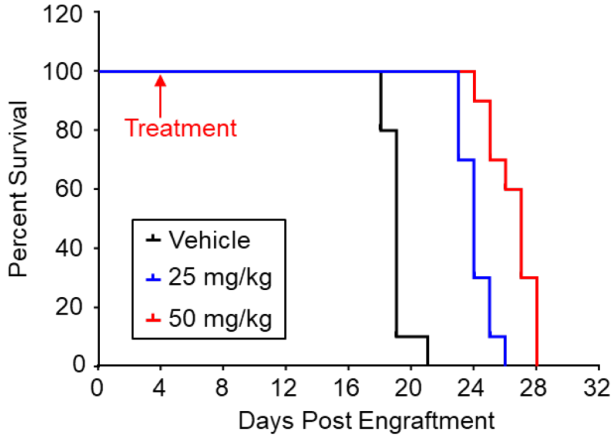
- More potent than Brequinar in AML cell lines (Brequinar is in early clinical trials for AML.)
- Differential growth inhibition compared to Brequinar in murine AML models with defined genetic phenotype.
- Patent protection for chemical composition

Stage of Development: Lead Optimization

- **Known Characteristics of Compound 1:**
  - Biochemical IC_{50} of 43 nM
  - Dose linear oral bioavailability in mice
  - Clean kinome screen
  - *In vitro* ADME (no major concerns)
- **Next Steps:**
  - Efficacy of Compound 1 in PDX
  - Rat and Dog PK of Compound 1
  - Pilot toxicity of Compound 1
  - Evaluate follow-on compounds



Favorable Oral PK: Single dose (10 mg/kg) in WT B6 mice (N=4 per route). Plasma was sampled by repeat blood draw.



Daily Oral Administration of Compound 1 Produces Dose Dependent Increased Survival in Disseminated MOLM-13 Murine Model
Vehicle vs. 25 and 50 mg/kg of Compound 1; each $p < 0.001$. ↑ = treatment start.

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Rationale for Targeting DHODH

DHODH is a rate-limiting enzyme in *de novo* pyrimidine synthesis. Rapidly dividing cancer cells are therefore sensitive to blockade of this pathway. New research has shown DHODH inhibition can induce differentiation in AML cell lines, translating to increased survival in animal models. There is also evidence that DHODH inhibitors can produce cytotoxic effects through p53 upregulation and mitochondrial effects.

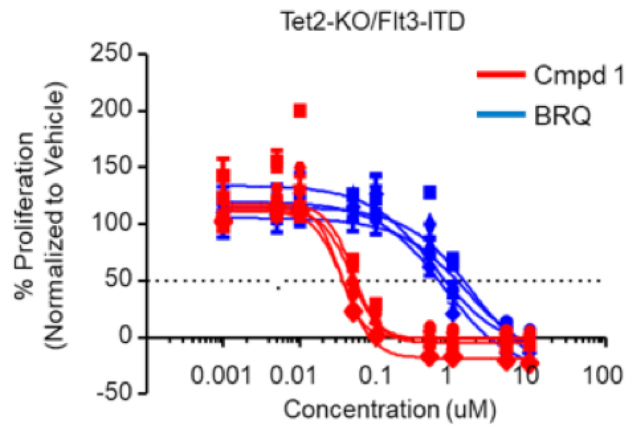
AML affects more than 21,000 people annually in the United States. The prevalence of AML in this country is estimated to be over 60,000 people. Hematopoietic stem cell transplantation is still the most successful therapy; however, the five-year survival remains less than 30%. Patients ineligible for stem cell transplant have < 10% cure rate.

Publications

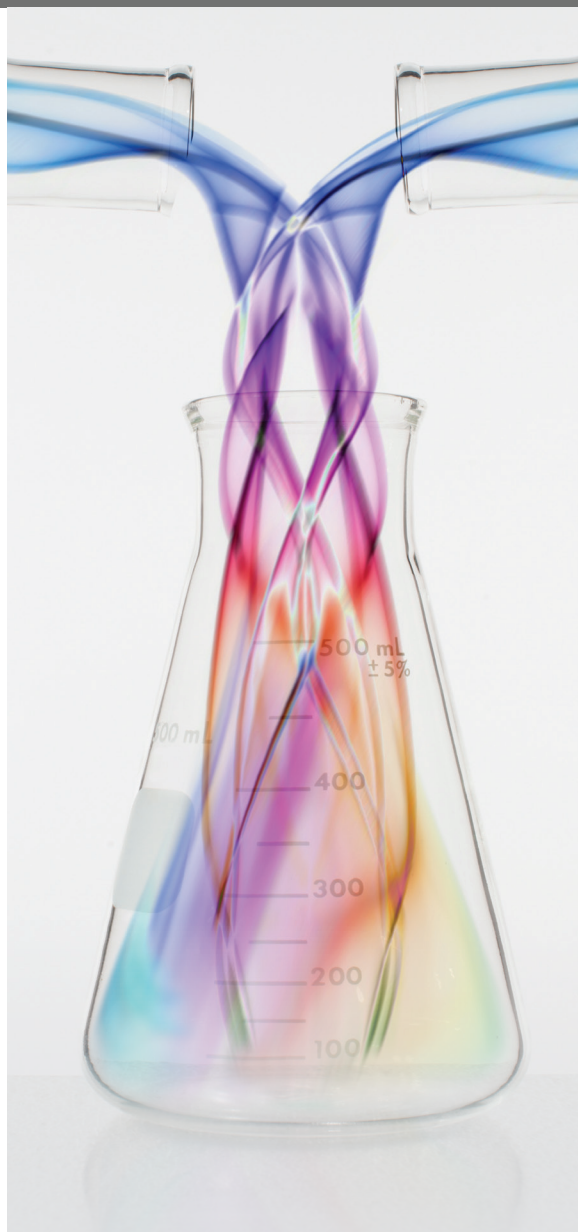
No information has been published concerning the compounds being developed.

IP Landscape

Patent Application: Provisional to convert on June 22, 2019
Priority Date: June 22, 2018



More potent growth inhibition compared to Brequinar: Murine splenocytes isolated from leukemic Tet2-KO/Flt3-ITD mice (N=7) were treated *ex vivo* with Compound 1 or Brequinar (dose range 0 – 10 uM). Cell growth was determined at 96 hours relative to the vehicle (DMSO) control using an MTS assay.



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