A Phase I trial of MGD006 in patients with relapsed acute myeloid leukemia (AML)

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Abstract #: P101

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Background

Acute Myeloid Leukemia (AML)[1]

- Incidence: 3.5 per 100,000 persons per year in United States
- Median age at onset: 67 yrs
- Standard Therapy: 7+3 regimen of cytarabine and doxorubicin induction followed by consolidation[2]
- Only potentially curative therapy is stem cell transplantation
- Limited Survival: 5 year disease free survival 5-10% for those 60 and over[3-5]

Molecular Characteristics

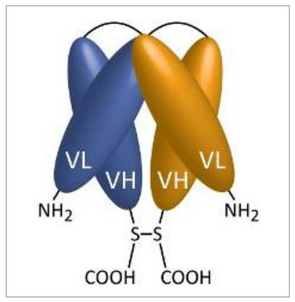
- Leukemic progenitor cells, CD34+, CD38-, proliferate and crowd out normal marrow[6-7]
- Express high levels of CD123 (alpha chain of the interleukin 3 receptor (IL-3Rα))[8]

CD123

- Normally expressed on committed B-cell precursors but not on hematopoietic stem cells or mature B cells[9]
- Normal function in B-cell differentiation and growth
- Expressed on leukemic stem cells (LSCs) often at high levels
- Also expressed in B-cell ALL

DART (Dual-Affinity Re-Targeting) Platform

- Flexible platform for generating stable multi-specific molecules
- Structural features support:
  - Optimal heavy and light chain pairing
  - Predictable antigen recognition
  - Excellent product stability
- Decreased potential for immunogenicity due to minimal linker size and content
- Expression in mammalian or prokaryotic systems feasible (DARTs)
- Multiple approaches to enhance half-life and avidity
- Biological activity demonstrated *in vitro* and *in vivo*

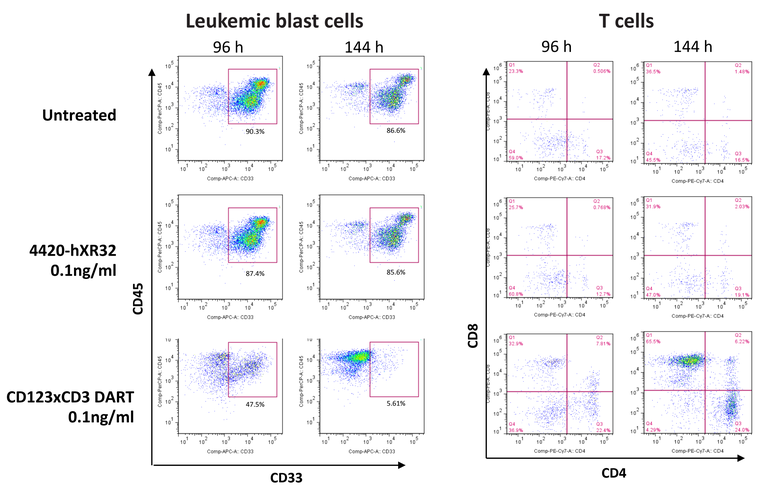


MGD006 DART: CD123 x CD3 DART

- Humanized CD123 x CD3 DART
- Redirected T-cell killing against LSCs mediated by both CD8 and CD4 T-cells
- Mechanism of action associated with up-regulation of granzyme B/perforin; T-cell expansion and activation
- Activity strictly dependent on MGD006-mediated co-engagement of T cells with CD123-expressing target cells

MGD006: *Ex Vivo* Blast Reduction + T-Cell Expansion in AML

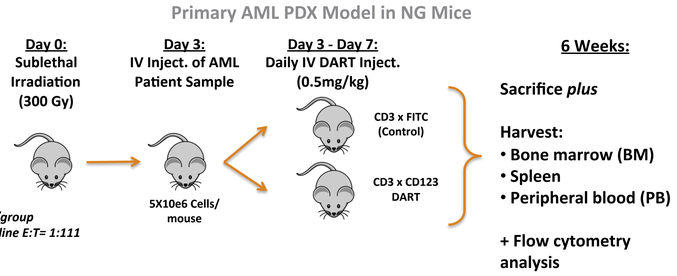
E:T Ratio = ~1:300 (by FACS Analysis)



AML patient PBMC sample with T cells:Blasts ratio of 1:300 as determined by flow cytometry was incubated in presence of MGD006, a control DART that does not bind CD123 (4420-hXR32) or left untreated. As shown by flow cytometry (left panels), leukemic blast population (CD45+CD33+) is eradicated in presence of MGD006 but not by control DART. There is concomitant increase in level of CD4+ and CD8+ T-cells observed in presence of MGD006 (right panels) that is not observed with controls.

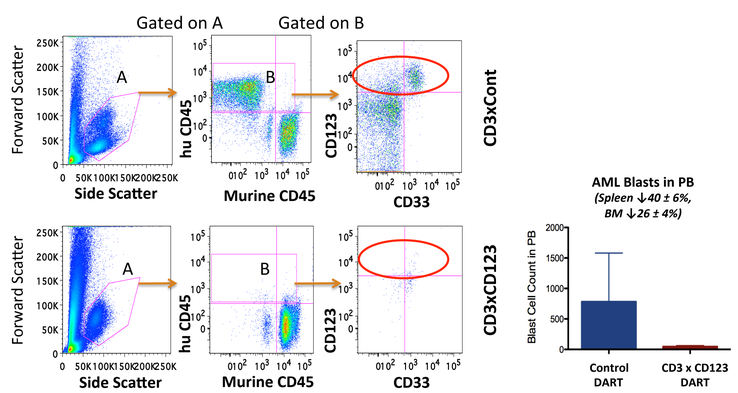
MGD006: Elimination of AML Blasts in PDX

Primary AML PDX Model in NG Mice



MGD006: Elimination of Blasts in AML PDX

Pre-clinical Data Presented at ASH 2013 (from DiPersio Lab at Wash U.)



Irradiated mice are injected with patient-derived AML cells (E:T=1:110) and treated with either MGD006 or an inactive control. Indicated organs and cells are harvested after 7 days and subject to flow cytometry. As seen by flow, MGD006 eliminates human CD123 positive blasts from treated mice.

Study Rationale

- Based on the notion that leukemic stem cells and blasts express greater levels of CD123 compared to normal hematopoietic stem cells, we hypothesize that MGD006 will mediate redirected-killing of leukemic cells by T lymphocytes. Supported by preclinical data demonstrating MGD006-mediated killing of primary leukemic cells expressing CD123 by the patient's own effector population
- Based on the DART mechanism of action, we hypothesize that MGD006 will deliver the biologic activity of a redirected T-cell approach for treatment of AML, without need to manufacture customized T-cell products in real time
- Study CP-MGD006-01 was initiated to determine the safety profile, pharmacokinetics, immune regulatory activity and preliminary anti-leukemic activity of MGD006 in patients with relapsed/refractory AML

Key Study Objectives

Primary Objective

To characterize dose limiting toxicities and determine maximum tolerated dose and schedule for administration of MGD006 in refractory AML

Secondary Objectives

- To characterize preliminary safety profile of MGD006
- To characterize PK and immunogenicity of MGD006
- To describe any evidence of anti-leukemic activity

Key Exploratory Objectives

- To evaluate utility of CD123 expression on leukemic blasts as a biomarker
- To evaluate cytokine production, changes in PBMC, AML, T lymphocyte populations, activation markers, and functional activity over time
- To evaluate bone marrow changes in leukemic cells, leukemic stem cells and normal progenitor cells

References

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Acknowledgements

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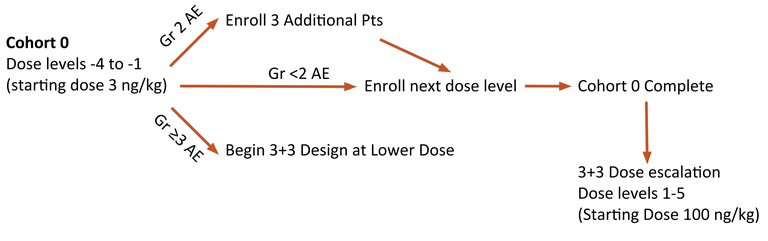
Study Design

- Open-label, multi-dose, single-arm, multi-center, Phase 1, dose-escalation study
- IV infusion
  - 4 Week cycles
- Three segments
  - Single patient dose escalation segment (Cohort 0)
  - Multi-patient dose escalation segment (Cohorts 1-5)
  - Expansion cohort
- Cohort 0
  - Single subject dose escalation starting at 3 ng/kg/day
  - If no Grade ≥2 AEs not related to leukemia, progress to next cohort
  - Expansion to three additional patients for Grade ≥2 AE
- Cohorts 1-5
  - 3+3 cohorts starting at 100 ng/kg/day
  - All patients will receive 100 ng/kg/day for first week
  - Intrapatient dose escalation for Weeks 2-4 for cohorts 2-5
  - Standard 3+3 dose escalation rules for DLTs
- Expansion cohort
  - Expansion to 12 patients at MTD



Patient Evaluations

- Continuous safety monitoring, CTCAE grading
- Bone marrow assessment after 28 days
- Correlative studies performed at Washington University in St Louis

Study Sites

- First patient was enrolled 9 June 2014 at Washington University in St. Louis

Key Inclusion Criteria

- Age ≥18
- Confirmed diagnosis of primary or secondary AML [any subtype except acute promyelocytic leukemia (APL)] according to World Health Organization (WHO) classification
- Must be unlikely to benefit from cytoxic chemotherapy based on at least one of the following criteria:
  - Newly diagnosed leukemia refractory to ≥ 2 induction attempts,
  - Leukemia in 1st relapse with initial CR duration < 6 months,
  - Leukemia in 1st relapse following ≥ 1 unsuccessful salvage attempts, or
  - Leukemia in 2nd or higher relapse
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Life expectancy of at least 4 weeks
- Peripheral blast count ≤20,000/mm3
- Adequate organ function, including normal thyroid function

Key Exclusion Criteria

- Prior history of allogeneic stem cell transplantation
- Prior treatment with an anti-CD123-directed agent
- Need for concurrent cytoreductive chemotherapy
- Any prior history of or suspected current autoimmune disorders
- Second primary malignancy that has not been in remission for greater than 3 years
- Previous treatment with radiotherapy, immunotherapeutic agents or any other investigational agent in 4 weeks prior to study drug administration
- Central nervous system (CNS) leukemia
- Active uncontrolled infection, known human immunodeficiency virus infection, hepatitis B or C infection, Grade 3 or 4 bleeding, significant pulmonary compromise uncontrolled hypertension, significant cardiac disease, stroke or recent pulmonary embolism
- Insulin-dependent diabetes, or non-insulin-dependent diabetes with evidence of small vessel disease

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