Poster Number
5307

CD180-Targeting ADCs with a Topoisomerase I Inhibitor Payload Achieve Strong Efficacy in AML Tumors

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ABSTRACT

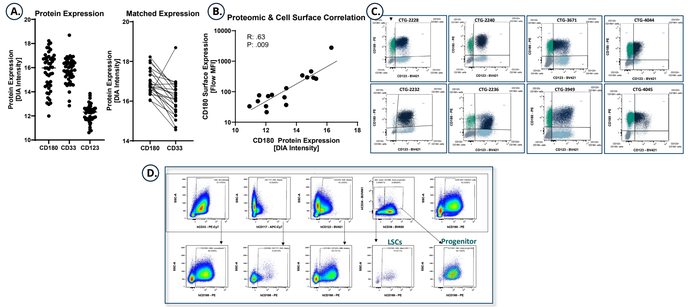
- CD180 (RP105) is a type I single-pass transmembrane protein that heterodimerizes with MD-1 or MD-2 for stable cell surface expression. Characterized as an orphan Toll-like receptor, predominantly expressed on mature B cells, dendritic cells, and macrophages, CD180 is also upregulated in multiple hematologic malignancies, including diffuse large B-cell lymphoma, mantle cell lymphoma and acute myeloid leukemia (AML). Here, we identify CD180 as a novel and promising therapeutic target for AML and describe the development of CO-ADC-004, a CD180-directed antibody–drug conjugate (ADC), along with its biochemical properties, antitumor activity across AML models, and pharmacokinetic and safety profiles in non-human primates.
- Consistent with emerging datasets, we observed high, homogeneous CD180 expression on AML blasts, including leukemic stem cells (LSCs) and progenitor compartments, across a large cohort of primary AML specimens, with minimal to no expression on healthy hematopoietic stem cells (HSCs), common myeloid progenitors (CMPs), or normal tissues. We generated a fully human monoclonal antibody with high-affinity, selective binding to the human and cynomolgus CD180/MD-1 complex and no cross-reactivity to rodent CD180.
- This antibody was conjugated to two payloads: (1) the pyrrolobenzodiazepine (PBD) dimer Tesirine at a DAR of 2 (CO-ADC-001), and (2) the topoisomerase I inhibitor Deruxtecan at a DAR of 8 (CO-ADC-004), selected for its high potency and favorable stability profile in hematologic malignancies. Both ADCs showed rapid internalization, high specificity for CD180-expressing cells, and potent cytotoxicity in AML cell lines, primary ex vivo samples, and patient-derived xenograft (PDX) models, with therapeutic response strongly correlating with CD180 expression levels.
- In a single-dose exploratory toxicity study in cynomolgus monkeys (10, 30, and 60 mg/kg), CO-ADC-004 was well tolerated, with no target-related toxicities or cytopenias observed at any dose. All clinical and histopathological findings were mild and reversible, establishing a maximum tolerated dose (MTD) of 60 mg/kg. CO-ADC-004 also demonstrated excellent physicochemical stability and developability. Together, these findings support the advancement of CO-ADC-004 into clinical development for patients with CD180-positive AML.

MATERIALS & METHODS

- CO-mAb-020 is a proprietary fully human IgG1 antibody targeting CD180.
- CO-ADC-004 is an ADC comprising CO-mAb-020 linked to deruxtecan (DAR 8).
- CO-ADC-001 is an ADC comprising CO-mAb-020 linked to tesirine (DAR 2).
- All AML patient samples were sourced from Champions Oncology.
- *In vivo* studies were conducted using systemic engraftment tumor models. CO-ADC-004 was administered at 5 mg/kg (single dose) in MV4-11 and at 5 mg/kg (single dose or q14d ×2) in disseminated primary AML models.
- Pharmacokinetic studies were performed in cynomolgus monkeys following administration of CO-ADC-004 at 3 mg/kg.
- Maximum tolerated dose (MTD) toxicity studies were conducted in cynomolgus monkeys, with evaluations over 21 days after dosing at 10, 30, or 60 mg/kg of CO-ADC-004.

RESULTS

Figure 1: CD180 Expression in AML Samples. (A) Protein intensity in AML patient samples using whole cell proteomics. **(B)** A correlation analysis of proteomic intensity and surface expression as determined by flow cytometry. **(C)** Flow cytometry analysis of AML patient samples. **(D)** Flow cytometry analysis of different cell populations in AML patient samples.



RESULTS

Figure 1, Continued: CD180 Expression in AML Samples. (E) CD180 receptor density in AML patient samples. **(F)** CD180 expression by karyotype from the TCGA dataset. **(G)** CD180 expression pre/post Venetoclax treatment from GO Accession GSE270621. **(H)** CD180 expression pre/post 7+3 or Venetoclax from the BEAT AML dataset. **(I)** CD180 expression in de novo vs R/R AML tumors from the BEAT AML dataset.

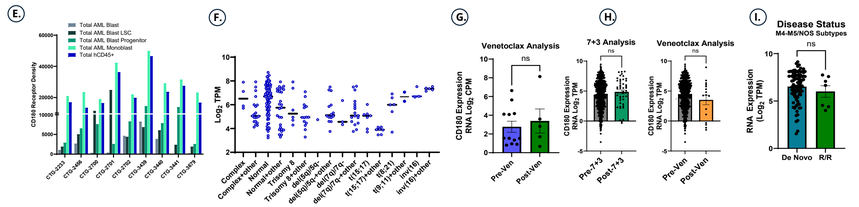


Figure 2. CD180 Expression in AML Normal Tissue. (A) Representative flow analysis of bone marrow from healthy donors. **(B)** CD180 receptor density in PBMC and bone marrow samples from healthy donors. **(C)** CD180 expression throughout hematopoiesis from 20 b determined by scRNAseq of bone marrow samples from healthy donors; GSE120221 dataset.

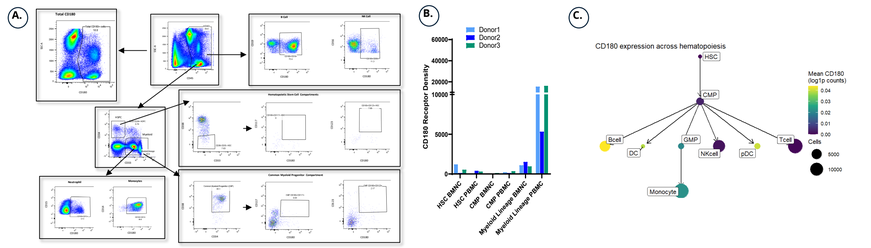
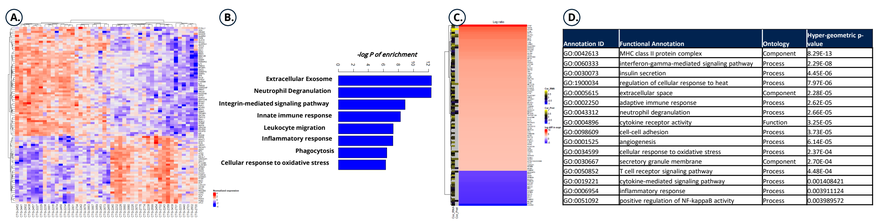
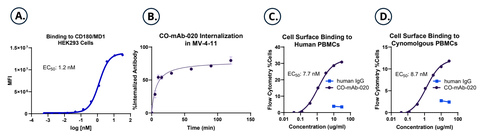


Figure 3. CD180 Drives Inflammatory Signaling. . (A) Clustering of CD180 alongside the most positively and negatively correlated genes across AML patient samples. **(B)** Gene set enrichment analysis (GSEA) of genes most positively correlated with CD180 expression in AML patient samples. **(C)** Top enriched and depleted genes following ectopic expression of CD180 in HEK293 cells. **(D)** Summary table of GSEA results samples from figure 3C.



Annotation ID	Functional Annotation	Ontology	Hyper-geometric p-value
GO:0042613	MHC class II protein complex	Component	8.29E-13
GO:0060333	interferon-gamma-mediated signaling pathway	Process	2.29E-08
GO:0030073	insulin secretion	Process	8.45E-06
GO:1900034	regulation of cellular response to heat	Process	7.97E-06
GO:0005615	extracellular space	Component	7.28E-05
GO:0002250	adaptive immune response	Process	2.62E-05
GO:0043312	neutrophil degranulation	Process	2.66E-05
GO:0004896	cytokine receptor activity	Function	3.25E-05
GO:0098609	cell-cell adhesion	Process	1.71E-05
GO:0001525	angiogenesis	Process	8.14E-05
GO:0034599	cellular response to oxidative stress	Process	2.37E-04
GO:0030667	secretory granule membrane	Component	2.70E-04
GO:0050852	T cell receptor signaling pathway	Process	6.48E-04
GO:0019221	cytokine-mediated signaling pathway	Process	0.001408421
GO:0006954	inflammatory response	Process	0.003911124
GO:0051092	positive regulation of NF-kappaB activity	Process	0.003989572

Figure 4. Pre-CMC of CD180 Therapeutic. (A) Cell surface binding of CO-mAb-020. **(B)** Internalization of CO-mAb-020. **(C)** Cell surface binding of Co-mAb-020 on human PBMCs and **(D)** Cyno PBMCs. **(E)** Pre-CMC summary of CD180 ADC, CO-ADC-004.



- **Concentration:** No aggregation/degradation observed at 5 mg/mL, 10 mg/mL or 14.5 mg/mL.
- **Freeze/Thaw:** No aggregation/degradation observed after 1 F/T or 5 F/T cycles at 5 mg/mL and 10 mg/mL
- **Thermal Stability:** No aggregation/degradation observed under the following conditions:
  - 4°C for 1, 4, and 7 days at 5 mg/mL and 10 mg/mL
  - 37°C for 1, 4, and 7 days at 5 mg/mL and 10 mg/mL

RESULTS

Figure 5: *In vitro Analysis of* **CO-ADC-004.** **(A)** Correlation analysis of CO-ADC-004 *in vitro* IC_{50} and CD180 protein expression in AML patient samples. **(B)** Representative *in vitro* cytotoxicity results in AML patient samples.

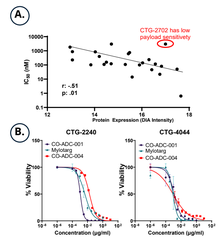


Figure 6. *In vivo* **Analysis** *of* **CO-ADC-004 In MV4-11. (A)** Quantitation of luciferase tagged MV4-11 tumor growth *in vivo*. **(B)** Luminescence images of animals in different treatment groups.

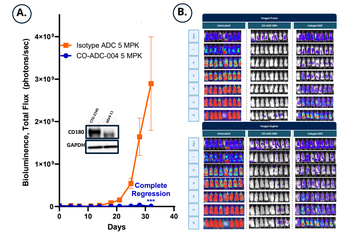


Figure 7. *In vivo* **Analysis** *of* **CO-ADC-004 in Disseminated Models of Primary AML.**
In vivo efficacy of CO-ADC-004 in systemic primary AML models, along with corresponding cytograms showing CD180 expression for each tumor.

CTG-2240	
Gender	Male
Subtype	NOS; MLL fusion
Cytogenetics	46, XY, t(9;11)(p22;q23),
Mutation Status	FLT3 WT, NPM WT

CTG-2232	
Gender	Female
Subtype	NOS
Cytogenetics	Normal
Mutation Status	FLT3 ITD, NPM mut

CTG-2228	
Gender	Female
Subtype	M5
Cytogenetics	Normal
Mutation Status	FLT3 ITD, NPM mut

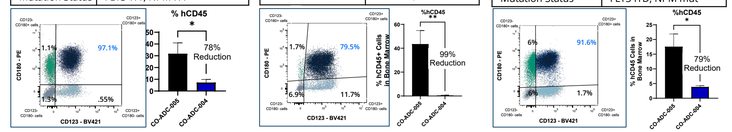
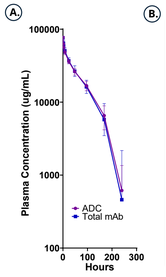


Figure 8. Pharmacokinetics and toxicity profile of CO-ADC-004 in cynomolgus monkeys.
(A) PK analysis after CO-ADC-004 is dosed at 3 mg/kg. **(B)** Toxicity results summarized after animals were dosed with 10 mg/kg, 30 mg/kg or 60 mg/kg)



B.

Parameter Category	Key Observations	Dose Level(s)	Reversibility	Toxicologic Significance
Hematology	↑ WBC in females at 10 & 60 mg/kg on Day 22 (reactive leukocytosis).• No decreases in platelets, RBC, or HGB.• Bone marrow smears: no drug-related suppression.	10 & 60 mg/kg (females)	Returned to normal trends before necropsy	**Low**
Clinical Chemistry	Minor ALT increases in:– Male at 10 mg/kg (Day 22)– Female at 60 mg/kg (Days 4 & 15)• No AST or ALP changes consistent with toxicity.• No bilirubin increases.• All changes judged not biologically significant.	10–60 mg/kg (sporadic)	Fully reversible	**Low**
Coagulation	Slight ↑ APTT in animals at ≥30 mg/kg, noted at Day 22.• No PT changes.	≥30 mg/kg	Reversible	**Low**
Body Weight	Weight loss:– 30 mg/kg: −4.6% (M), −3.7% (F)– 60 mg/kg: −6.1% (M only)• All animals recovered prior to necropsy.	30 & 60 mg/kg	Reversible	**Low–Moderate**
Food Consumption	No test-article–related decreases. All animals scored "good" throughout.	None	Not applicable	**None**
Clinical Signs	Soft stool at 10 & 60 mg/kg.• Loose feces at 60 mg/kg.• No tremors, no reduced activity, no morbidity.	10 & 60 mg/kg	Resolved during study	**Low**
Organ Weights	No liver, kidney, or spleen changes.• Single ↓ testes/epididymis weight at 10 mg/kg male—non-dose-related, judged unrelated.	None dose-related	Not applicable	**None**
Gross Pathology	Sporadic findings (tongue discoloration, thymus small) without dose pattern and judged not significant.	None dose-related	Not applicable	**None**
Bone Marrow	No drug-related cytologic changes.• Some lineage variations attributed to individual baseline differences.	None	Not applicable	**None**

SUMMARY

- CD180 is a novel target in AML, exhibiting upregulated and homogeneous expression.
- CD180 is not expressed in hematopoietic stem cells (HSCs) or common myeloid progenitors (CMPs).
- CD180 undergoes rapid internalization and drives inflammatory signaling.
- The novel CD180-targeted ADC, CO-ADC-004, demonstrates an excellent CMC profile.
- CO-ADC-004 shows potent anti-tumor activity both in vitro and in vivo.
- CO-ADC-004 has a favorable safety profile, with dosing up to 60 mg/kg in cynomolgus monkeys without irreversible effects.

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