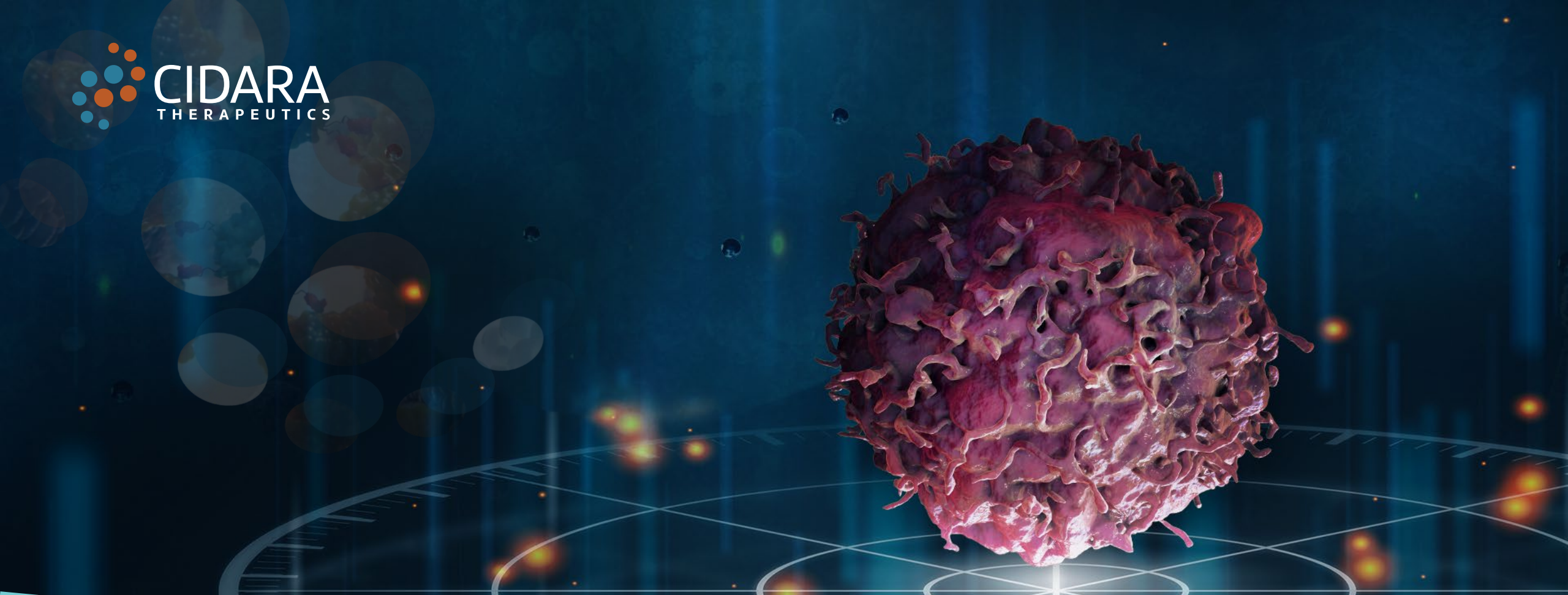
CIDARA THERAPEUTICS



CLOUDBREAK® DFC PLATFORM:
NOVEL THERAPEUTICS FOR IMMUNO-ONCOLOGY

January 2024
NASDAQ: CDTX

FORWARD-LOOKING STATEMENTS

The words “may,” “will,” “estimate,” “plan”, “anticipate,” “expect,” “potential,” “could,” “project,” and similar expressions (including the negative thereof), are intended to identify forward-looking statements. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, statements regarding Cidara’s research and development efforts; preclinical and clinical development activities; plans, projections and expectations for and the potential effectiveness, safety and benefits of, its product candidates, including rezafungin, CD388, and other antiviral and oncology product candidates from the Cloudbreak platform; Cidara’s potential ability to achieve milestones under its respective collaborations with Melinta, Mundipharma and Janssen, and receipt of the related milestone payments; and advancement of its strategic plans.

Projections, assumptions and estimates of the future performance of the markets in which Cidara operates are necessarily subject to a high degree of uncertainty and risk, including, Cidara's ability to obtain additional financing; the success and timing of Cidara’s preclinical studies, clinical trials and other research and development activities; receipt of necessary regulatory approvals for development, as well as changes to applicable regulatory laws in the United States and foreign countries; changes in Cidara's plans to develop its product candidates; Cidara's ability to obtain and maintain intellectual property protection for its product candidates; and the loss of key scientific or management personnel. These and other risks and uncertainties are described more fully in Cidara's Form 10-K as most recently filed with the United States Securities and Exchange Commission ("SEC“’) under the heading “Risk Factors.”

Additional risks and uncertainties may emerge from time to time, and it is not possible for Cidara’s management to predict all risk factors and uncertainties.

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CIDARA THERAPEUTICS HIGHLIGHTS

Platforms	**CLOUDBREAK®:** Novel, proprietary immunotherapy platform with clinical PoC **REZAFUNGIN:** Long-acting antifungal internally developed from preclinical stage to FDA approval
Partnerships	Validating partnerships on both platforms with over **$1.8B** in potential value from existing licenses
Team	Industry veterans with multiple approved products advanced from discovery to approval

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CIDARA CLOUDBREAK® DFC PLATFORM

- Novel immunotherapy platform with applications in antiviral, oncology, and autoimmune therapeutics
- Phase 2a clinical stage program in influenza – CD388
- Best-in-Class and First-in-Class DFC assets

PIPELINE:

Program	Indications	Discovery	Preclinical	IND-Enab.	Phase 1	Phase 2	Collaborations
CD388	Prevention of Seasonal Influenza						janssen (Worldwide License)
CBO-421 (CD73)	(including NSCLC, CRC, Gastric, RCC)						
CD73/PD-1	Solid Tumors						
CCR5	Solid Tumors						

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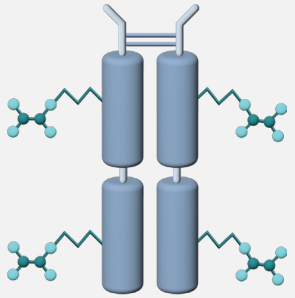
CLOUDBREAK PARTNERING OPPORTUNITIES

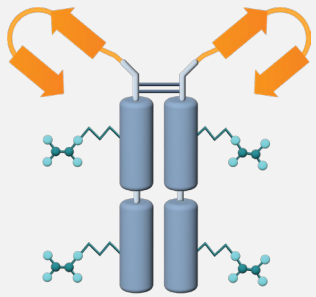
CD73: CBO421 Development Candidate

- Potential Best-in-Class
- Robust tumor control as monotherapy, complete and durable immune response in combination with PD-1 inhibitors
- Excellent safety and COGS, flexible dosing including SC



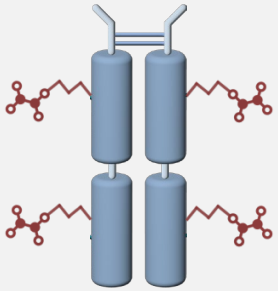
PD-1/CD73 Discovery Program

- First-in-class dual inhibitor of CD73 and PD-1
- Compelling preclinical data
- Potential for more efficient clinical development



CCR5 Discovery Program

- Unexploited target that is an important driver of immune evasion in several difficult-to-treat cancers
- DFCs are an ideal platform to overcome challenges that have impaired development of CCR5 antagonists
- Proof of concept data generated



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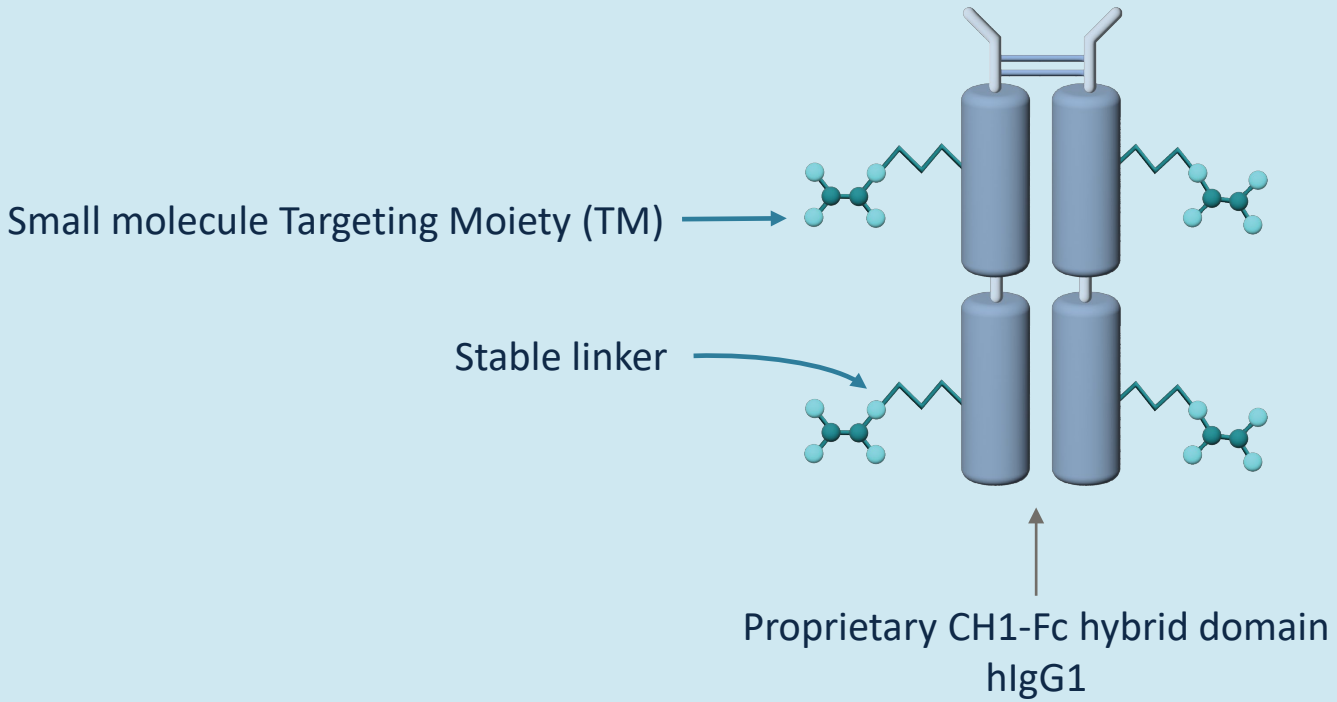
CLOUDBREAK® CREATES A NEW CLASS OF DRUG CONJUGATES: “DFCs”

DRUG Fc CONJUGATE



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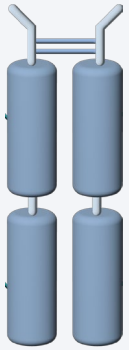
DFCs ADDRESS THE SHORTCOMINGS OF SMALL MOLECULES AND mAbs

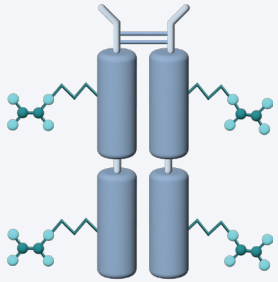
Proprietary Fc can be customized for different target product profiles

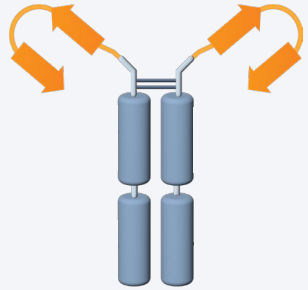


Tunable attributes include:

- Immune effector function
- Half-life extension

Proprietary small molecule and peptidic TMs





All the strengths of mAb therapeutics with several potential advantages:

- Superior targeting of cryptic sites and small molecule receptors
- Tunable valency for better potency
- ~65 kDa vs > 150 kDa for superior tissue/tumor penetration
- Modular – multiple routes to multispecific agents

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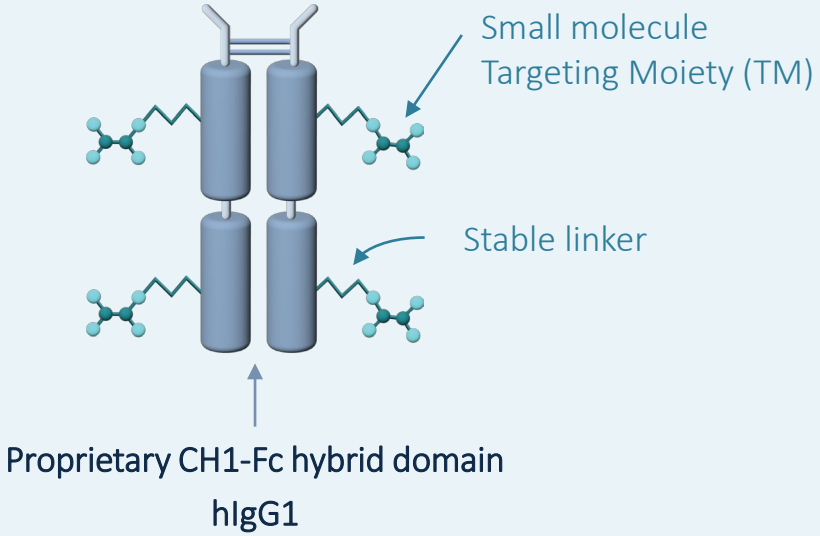
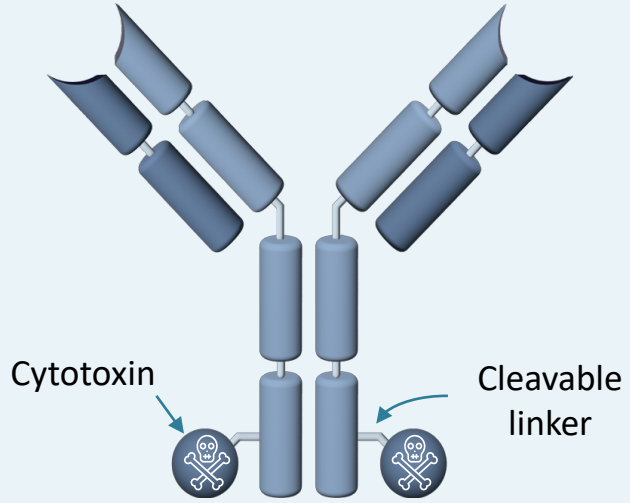
DFCs ARE FUNDAMENTALLY DIFFERENT FROM ADCs

Drug Fc Conjugate (DFC)



- No cytotoxic payload
- Precisely engages immune targets and enhances tumor microenvironment (TME) function
- No premature release of particles in bloodstream

Antibody Drug Conjugate (ADC)



- Acts as chemotherapy with off-target binding, leading to unavoidable toxicity

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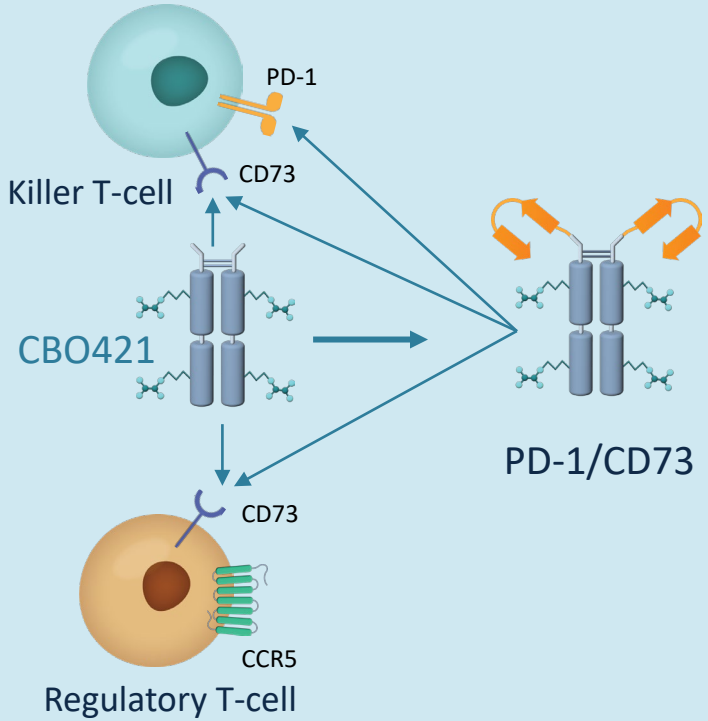
DFCs HAVE BROAD UTILITY ACROSS MULTIPLE THERAPEUTIC AREAS

Modularity and properties of the DFCs allow for the inhibition of multiple tumor immune evasion mechanisms and novel combinations

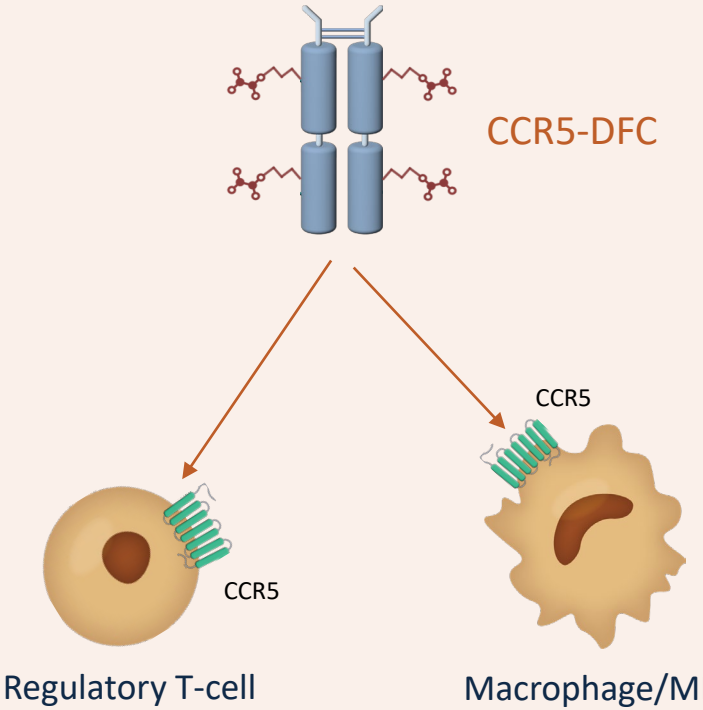
Tumor Microenvironment & Checkpoint Inhibition

CD73 Inhibitors



Immuno-Oncology & Autoimmune Disease

CCR Antagonists



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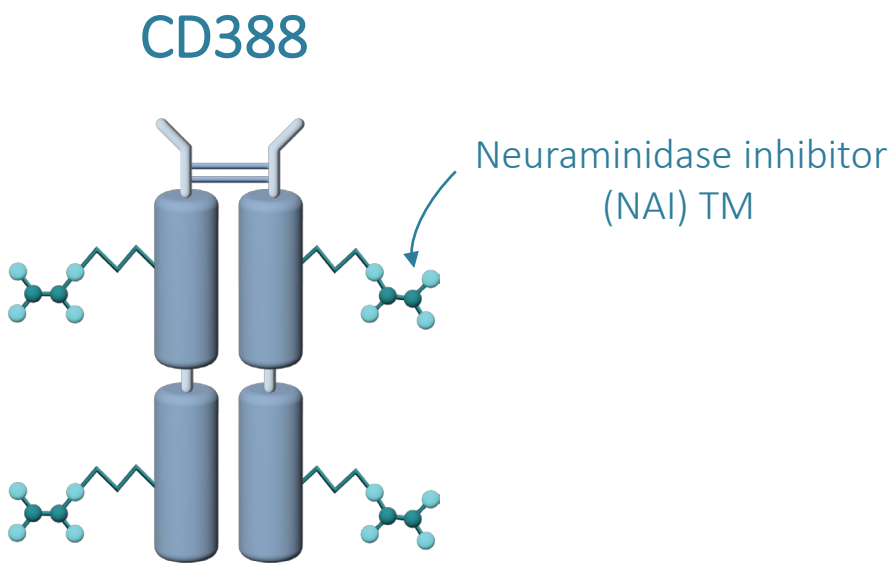
CD388: CLINICAL VALIDATION OF THE UNIQUE STRENGTHS OF DFCs

CD388 has the potential to be the first therapeutic to provide season-long, universal influenza protection



CIDARA THERAPEUTICS | Janssen

- Phase 2a results achieved safety, efficacy and PK objectives
- Universal coverage of ALL seasonal and pandemic strains
- Single SQ or IM dose per flu season
- Streamlined, low-cost manufacturing process, low COGs
- High concentration formulations, compatible with SC or IM dosing
- Low immunogenicity
- Excellent safety/ tolerability profile in Phase 1 and 2a

Phase 2a clinical proof of concept supports expanding the platform to immuno-oncology

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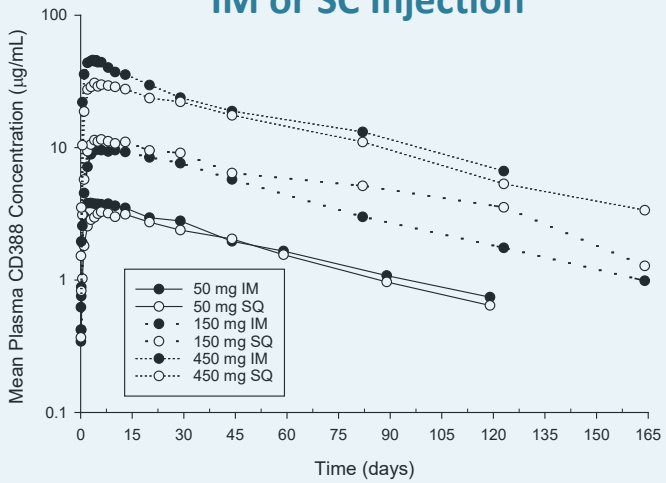
DFC SIZE, STABILITY AND SOLUTION PROPERTIES ALLOW FOR FLEXIBLE DOSING OPTIONS

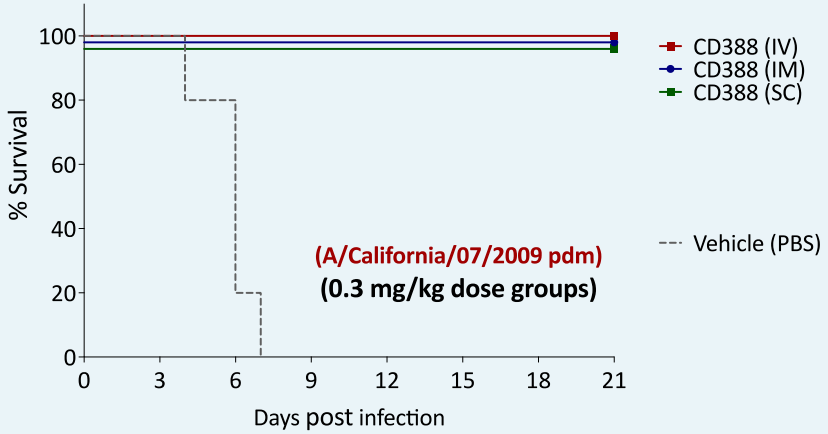
CD388 demonstrates excellent tissue penetration, solubility and bioavailability for subcutaneous (SC) and intramuscular (IM) dosing compatibility

Phase 1 PK: CD388 Administered by IM or SC Injection



- Steady state concentrations of CD388 are similar with SC/IM dosing

CD388 Survival by Dose Route



- Minimum efficacious dose is agnostic of dosing route (mouse)

Bioavailability of multiple formulations highlights potential for SC dosing in oncology indications

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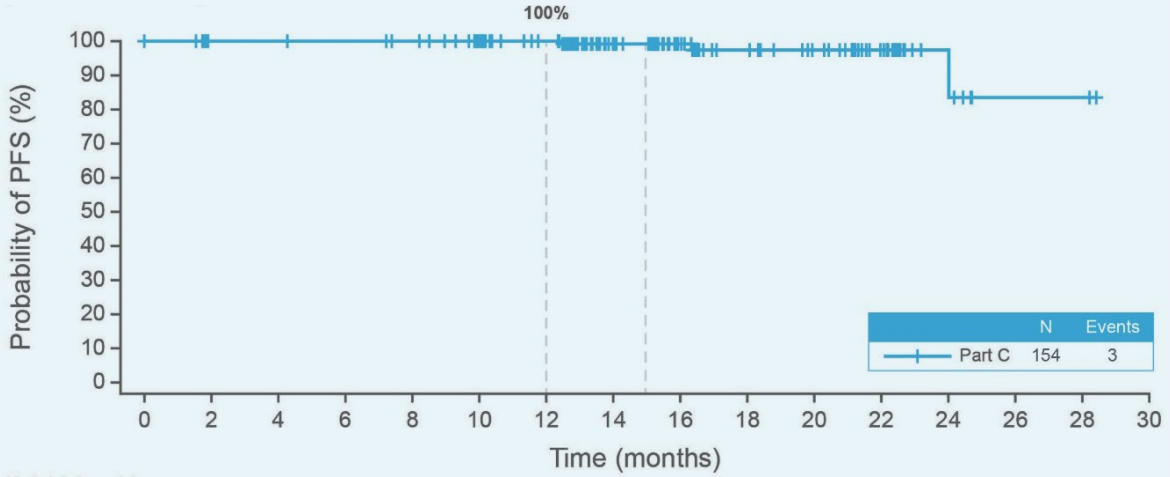
DFCs ADDRESS THE KEY CHALLENGE IN FUTURE ONCOLOGY DRUG DEVELOPMENT: MULTI-DRUG COMBINABILITY

Future oncology landscape requires multi-drug cocktails, e.g. Seagen presents promising 4 drug combo data at ASH 2023 in classical Hodgkins Lymphoma with strong PFS data

Progression-Free Survival in Patients with Early-Stage Classical Hodgkin Lymphoma Treated With Brentuximab, Vedotin, Nivolumab, Doxorubicin, and Dacarbazine (AN+AD) (SGN35-027 Part C)



PFS=progression-free survival

DFCs are designed to meet needs of future oncology therapeutics:

- Demonstrate preclinical complete responses (CRs) vs. tumor stabilization (PR, SD)
- Potential for SubQ formulation which does not require infusion chair time
- Can be combined with Chemotherapy + IO due to reduced toxicity profile and less DDIs
- Tolerability/ safety profile
- Minimal anti-drug antibodies
- Demonstrate activity in tumor areas with limited SOC options and high likelihood of success

Abramson J et al. ASH 2023

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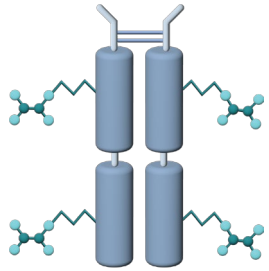
CD73: CBO421 DEVELOPMENT CANDIDATE

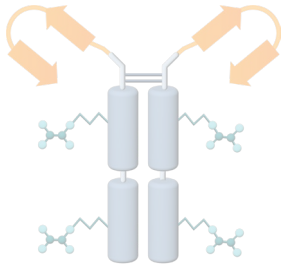
CD73: CBO421 Development Candidate

- Potential Best-in-Class
- Robust tumor control as monotherapy, complete and durable immune response in combination with PD-1 inhibitors
- Excellent safety and COGS, flexible dosing including SC



PD-1/CD73 Discovery Program

- First in class dual inhibitor of CD73 and PD-1
- Compelling preclinical data
- Potential for more efficient clinical development



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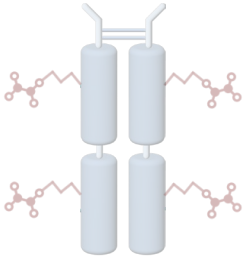

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CD73 IS A VALIDATED TARGET WITH DISAPPOINTING CLINICAL RESULTS

- Dying tumor cells release ATP into the tumor microenvironment (TME), which subsequently gets converted into adenosine by CD73
- Adenosine creates an immune suppressive TME by reprogramming multiple immune cell classes

Tumor Immunosuppression

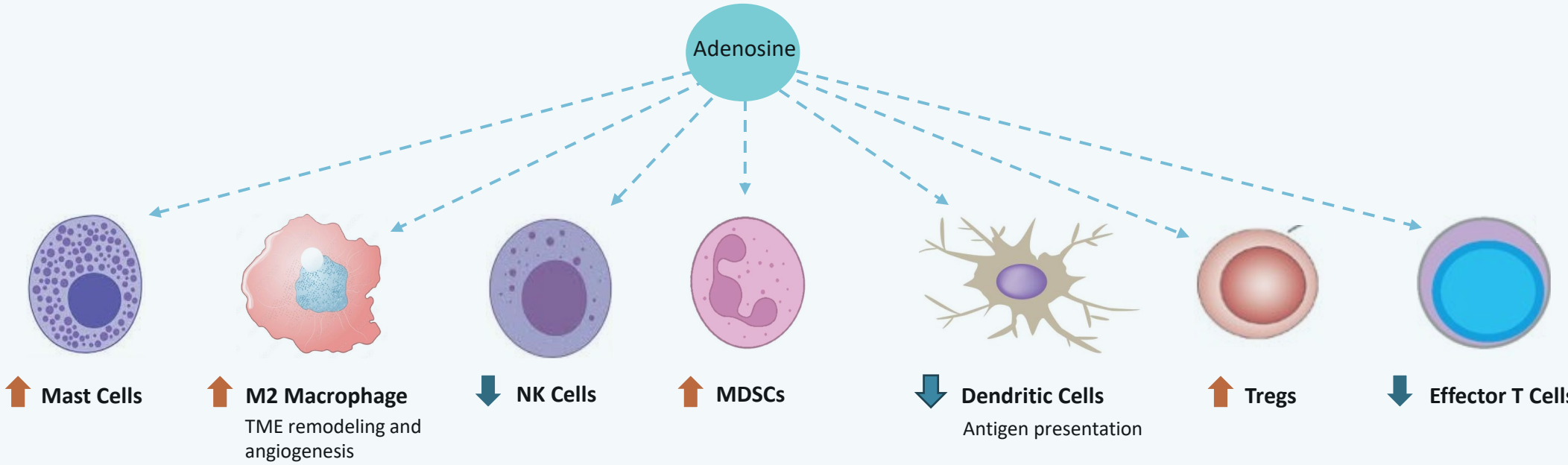

Image reprinted from Harvey JB, Phan LH, Villarreal OE and Bowser JL (2020) CD73's Potential as an Immunotherapy Target in Gastrointestinal Cancers. Front. Immunol. 11:508.

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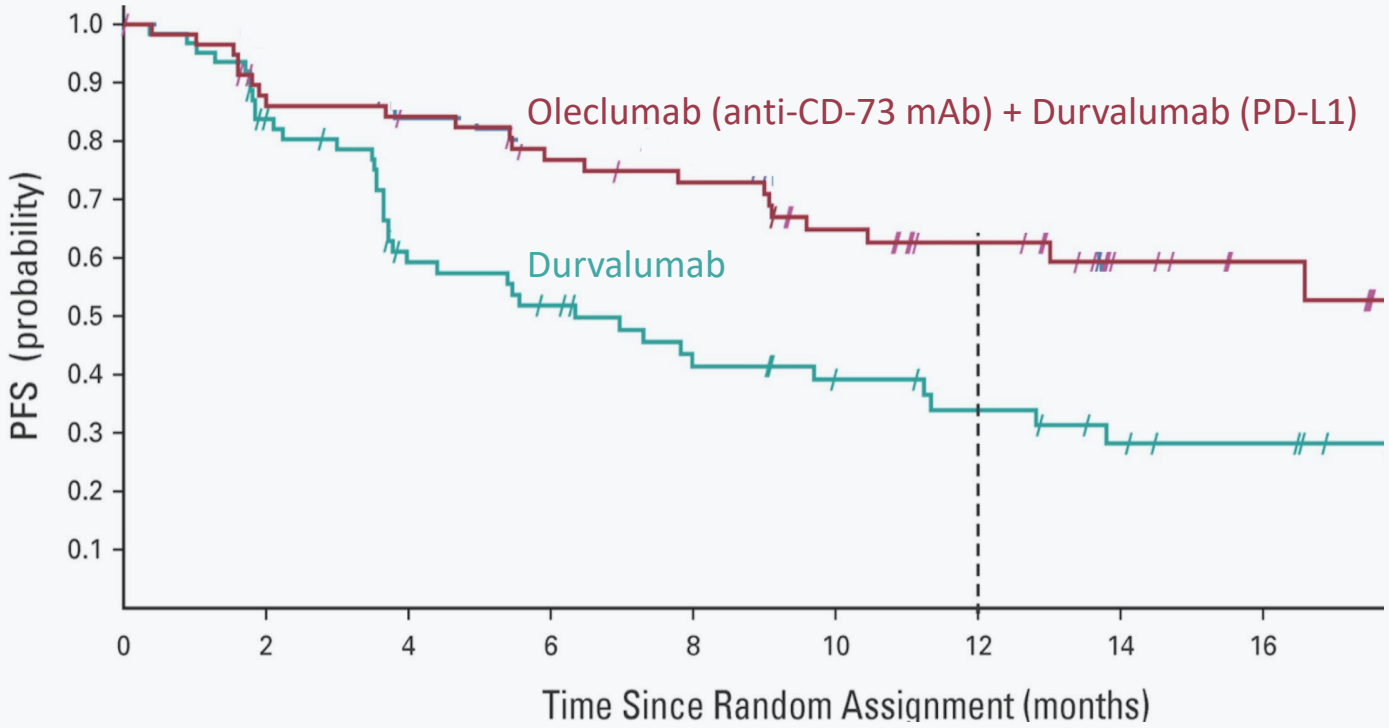
TARGETING CD73 IS CLINICALLY VALIDATED TO ENHANCE ANTI-TUMOR ACTIVITY

In multiple tumor types, inhibition of CD73 enhances activity of PD-1/PD-L1

Ph2 COAST Trial in Stage III NSCLC



Herbst R et al. J Clin Oncol. (2022) Oct 10;40(29).

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HIGH UNMET NEED REMAINS FOR CD73 PATHWAY THERAPIES

- No approved drugs
- Phase 2 results of existing programs have shown no monotherapy activity and minimal Complete Responses (CRs)

- In Phase 1 studies of multiple tumor types, “Oleclumab monotherapy did not show positive clinical responses in any patients …”
  - Kondo S et al. Int. J. Clin. Oncol., 27 (2022), pp. 1795-1804.
- In Phase 2 studies of stage III NSCLC, no additional CRs were achieved with addition of Oleclumab to anti-PD-L1
  - Herbst R et al. J Clin Oncol. (2022) Oct 10;40(29).

Antitumor Activity	Durvalumab (n = 67)	Durvalumab + Oleclumab (n = 60)
Confirmed ORR, % (95% CI)[a] (No.)	17.9 (9.6 to 29.2) (12)	30.0 (18.8 to 43.2) (18)
Difference in confirmed ORR, % (95% CI)[b]	—	12.1 (–2.7 to 26.9)
Best overall response by RECIST,[c,d] No. (%)		
CR	2 (3.0)	1 (1.7)
PR	10 (14.9)	17 (28.3)
SD	37 (55.2)	32 (53.3)
PD	11 (16.4)	6 (10.0)
NE	7 (10.4)	4 (6.7)
DCR at 16 weeks, % (95% CI)[c,e] (No.)	55.2 (42.6 to 67.4) (37)	80.0 (67.7 to 89.2) (48)
Median DoR, months (95% CI)[c] Range	NR (7.4 to NA) 1.9+ to 17.5+	NR (12.9 to NA) 1.8+ to 16.9+

NOTE. Data cutoff: May 17, 2021.

Abbreviations: CR, complete response; DCR, disease control rate; DoR, duration of response; ITT, intent-to-treat; NA NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]95% CI by Clopper-Pearson exact method.

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KEY LIMITATIONS OF mAbs AND SMALL MOLECULE CD73 INHIBITORS ARE LIKELY REDUCING THEIR CLINICAL PERFORMANCE

LIMITATIONS OF mAbS

- Inferior catalytic site inhibition compared with small molecule inhibitors
- Poor tumor penetration
- Poor inhibition of soluble CD73

Oleclumab
Uliledlimab
AK119

LIMITATIONS OF SMALL MOLECULES

- Short half-life, reduced exposures versus mAbs
- Inability to downregulate receptors on tumors via internalization

AB680
Oric-533

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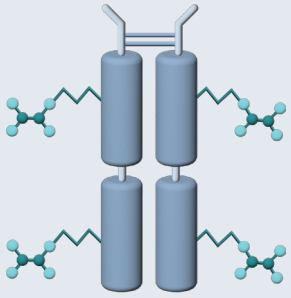
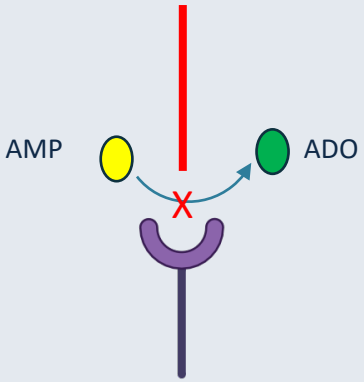
CBO421 DEMONSTRATES OUTSTANDING PRECLINICAL PERFORMANCE

2023 ESMO IMMUNO-ONCOLOGY Annual Congress
GENEVA SWITZERLAND
6-8 DECEMBER 2023

CBO421





DISCOVERY OF CBO421, A FIRST-IN-CLASS DRUG-FC CONJUGATE (DFC), TARGETING CD73 IN CANCER

Simon Döhrmann*, James Levin, Nicholas Dedeic, Amanda Almaguer, Doug Zuill, Elizabeth Abelovski, Joanne Fortier, Qiping Zhao, Maria Hernandez, Karin Amundson, Madison Moniz, Hongyuan Chen, Dhanya Panickar, Thanh Lam, Thomas P. Brady, Allen Borchardt, Jason N. Cole, and Leslie W. Tari.

144P

Cidara Therapeutics, Inc., 6310 Nancy Ridge Drive, Suite 101, San Diego, CA, USA

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BACKGROUND

Dying tumor cells release ATP, which is sequentially converted to adenosine monophosphate (AMP) by CD39 and to adenosine by CD73 (N5TE). By flooding the tumor microenvironment (TME) with immune-suppressive adenosine, where concentrations can reach µM levels, CD73, a rate-limiting enzyme in this process, contributes to immune evasion and drug resistance in solid tumors[1]. Adenosine has been shown to inactivate tumor infiltrating immune cells such as CD8⁺ T cells through its cognate receptor, A2AR, in the TME (**Fig. 1A**).

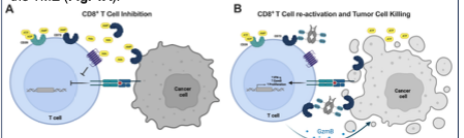

Figure 1. (**A**) CD8⁺ T cell inhibition by the adenosine pathway. (**B**) CBO421-mediated re-activation of CD8⁺ T cells by CD73 inhibition resulting in T cell-induced cancer cell apoptosis.

Furthermore, high CD73 expression levels are correlated with worse prognosis in multiple cancers (e.g. CRC, TNBC). Herein, we describe a CD73 targeting DFC, CBO421, a multivalent conjugate of a potent small molecule CD73 inhibitor stably linked to a proprietary immune-silent human IgG1 Fc. CBO421 combines the strengths of small molecule inhibitors and monoclonal antibodies (mAbs) targeting CD73 with potential best-in-class activity to prevent adenosine-induced inhibition of CD8⁺ T cells (**Fig. 1B**).

METHODS

The activity of CBO421, commercially sourced small molecule inhibitor, AB680 (Quemliclustat), and biosimilar anti-CD73 mAb, Oleclumab (MEDI9447), were investigated. Enzymatic inhibition of CD73 was evaluated using recombinant CD73, in a human breast cancer cell line (MDA-MB-231), a murine breast cancer cell line (EMT-6), or human PBMCs in the presence of AMP. CD73 expression on PBMCs was determined by flow cytometry. Activity of CBO421 was measured in a PBMC re-activation assay in the presence of AMP using flow cytometry (CD25⁺ or GzmB⁺), ELISA (INFγ), or CellTiter-Glo (CD73 inhibition). CD73 internalization was measured in MDA-MB-231 cells using a Fab-ZAP kit (Advanced Targeted System). Tumor spheroid penetration was conducted with MDA-MB-231 cells using confocal microscopy by PhenoVista Biosciences. Efficacy of CBO421 dosed at 10 mg/kg twice a week for two weeks was evaluated in a syngeneic mouse model with the CRC cell line, MC38. On day 18, tumor samples were collected and dissociated by mechanical and enzymatic dissociation (Miltenyi) to obtain single cell suspensions. Tumor infiltrating lymphocytes (TIL) were assessed for CD45⁺, CD3⁺, CD4⁺, CD25⁺, CD8⁺ and FOXP3⁺ staining by flow cytometry and analyzed in FlowJo.

RESULTS

CBO421 is a DFC (**Fig. 2A**) that targets CD73. CD73 is a GPI-anchored ectoenzyme, that forms homodimers and undergoes confirmational changes from an open to a catalytically active closed confirmation to convert substrate, AMP, to adenosine and phosphate (**Fig. 2B**).

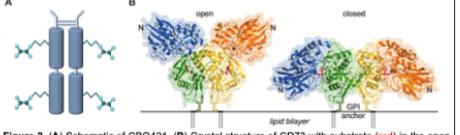

Figure 2. (**A**) Schematic of CBO421. (**B**) Crystal structure of CD73 with substrate (red) in the open and in the catalytically active closed conformation[2]

The first generation anti-CD73 mAb, oleclumab, currently in P2/3 clinical development, is a partial, non-competitive inhibitor that prevents CD73 from adopting the closed, active state[3,4]. CBO421 binds to CD73 expressed on MDA-MB-231 cancer cells with an IC_{50} of 0.17 nM (**Fig. 3A**), and showed a dose-dependent decrease in IC_{50} to 8.61 nM with 1,000 µM AMP (**Fig. 3B**) and to 62.6 nM with 100 nM AB680 (**Fig. 3D**) demonstrating CBO421 is a potent, complete, AMP-competitive and catalytic site inhibitor of CD73. The binding for oleclumab was unaffected by AMP or AB680 (**Fig. 3C, E**). CBO421 demonstrated complete enzyme inhibition with an IC_{50} of 13.8 nM (**Fig. 3F**), comparable to AB680 with an IC_{50} of 4.0 nM (**Fig. 3G**) against soluble CD73. Oleclumab demonstrated weak partial inhibition with hook effect (**Fig. 3H**). For cell-anchored CD73 using MDA-MB-231 cells, CBO421 demonstrated an IC_{50} of 0.77 nM, versus 0.09 nM for AB680 and 0.17 nM for oleclumab (**Fig. 3I**). Similarly, CBO421 demonstrated potent CD73 inhibition with an IC_{50} of 0.77 nM versus 1.06 nM for AB680 and 5.68 nM for oleclumab against CD73 expressing EMT-6 cells (**Fig. 3J**).

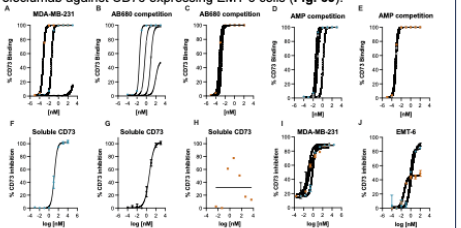

Figure 3. Binding to MDA-MB-231 cells (**A**) alone or with (**B, C**) 10–1,000 µM AMP (grey) or (**D, E**) 1–100 nM AB680 (grey). Soluble (**F-H**) and cell-anchored CD73 inhibition with (I) MDA-MB-231 or (J) EMT-6 cells. CBO421 (blue), AB680 (black), oleclumab (orange) or unconjugated Fc (grey) in **A**

RESULTS

CD73 is predominantly expressed on B cells ($CD3^-CD19^+$) and CD8⁺ T cells in human PBMCs (**Fig. 4A, B**) as shown by tSNE analysis. CBO421 showed complete inhibition of CD73 on human PBMCs with IC_{50}s of 0.62 nM to 1.75 nM, versus 0.02 nM to 0.05 nM with AB680 and 0.37 nM to 5.69 nM with oleclumab at 3h or 24h, respectively (**Fig. 4C-D**). Importantly, CBO421 demonstrated potent re-activation of human PBMCs in the presence of AMP with a median EC_{50} (n = 3) of 12 nM by INFγ (**Fig. 4E**) or 2.6 nM by CD73 inhibition (**Fig. 4F**) similar to AB680 (12 nM (INFγ) or 4.1 nM (CD73 inhibition)) and superior to oleclumab (>1,000 nM (INFγ or CD73 inhibition)) (**Fig. 4E-F**). Similarly, CBO421 demonstrated potent re-activation of CD8⁺ T cells with median EC_{50} of 44 nM by CD25⁺ (**Fig. 4G**) and 34 nM granzyme B⁺ (**Fig. 4H**) comparable to AB680 (11 nM ($CD25^+$) and 54 nM (granzyme B⁺)) and superior to oleclumab (>1,000 nM ($CD25^+$ or granzyme B⁺)).

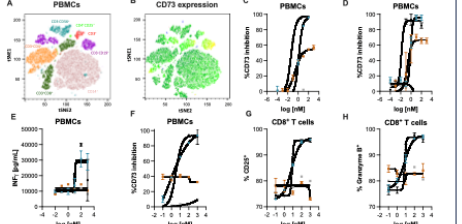

Figure 4. (**A**) Immune subsets of PBMCs and (**B**) relative CD73 expression by tSNE analysis. CD73 inhibition of PBMCs at (**C**) 3 h and (**D**) 24 h. Rescue of AMP-suppressed PBMCs determined by (**E**) INFγ ELISA, (**F**) CD73 inhibition or of CD8⁺ T cells as determined by (**G**) $CD25^+$ or (**H**) granzyme B⁺. CBO421 (blue), AB680 (black), oleclumab (orange), unconjugated Fc (grey)

CD73 internalization via receptor cross-linking is a second mechanism that can be exploited to reduce adenosine production (**Fig. 5A**). CBO421 and oleclumab induced receptor internalization with EC_{50}s of 0.13 nM and <0.03 nM, respectively (**Fig. 5B**). AB680 did not trigger receptor internalization, as expected for a small molecule (**Fig. 5C**).

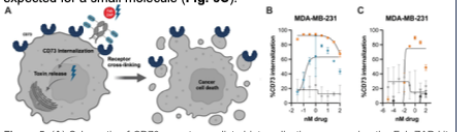

Figure 5. (**A**) Schematic of CD73 receptor-mediated internalization assay using the Fab-ZAP kit. (**B, C**) Receptor internalization in MDA-MB-231 cells at 96 h. CBO421 (blue), AB680 (black), oleclumab (orange), unconjugated Fc (grey)

RESULTS

CBO421 showed complete penetration into MDA-MB-231 spheroids compared to oleclumab, which was unable to reach the core (**Fig. 6A-C**).

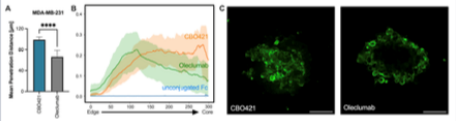

Figure 6. (**A**) MDA-MB-231 spheroid penetration of CBO421 (**A**) mean penetration distance, (**B**) radial plot analysis and (**C**) representative z-stack confocal microscopy images.

CBO421 monotherapy showed robust tumor growth inhibition (TGI) with 27% of mice achieving complete responses[5] in a MC38 mouse model (**Fig. 7A**). This TGI correlated with improved immune cell infiltration (**Fig. 7B-F**) and statistically significant increases in $CD8^+$ T cell:T_{reg} ratio (**Fig. 7G**).

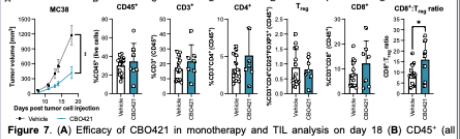

Figure 7. (**A**) Efficacy of CBO421 in monotherapy and TIL analysis on day 18 (**B**) CD45⁺ (all immune cells), $CD3^+$ (T cells), $CD4^+CD25^+FOXP3^+$ regulatory T cells (T_{regs}), CD8⁺ and ratio of CD8⁺ to T_{regs} in a syngeneic MC38 mouse efficacy model; statistical analysis by unpaired t-test.

SUMMARY

In preclinical models, CBO421 outperformed anti-CD73 targeting molecules currently in clinical development. CBO421 combines the potent and complete enzymatic inhibition observed with small molecule inhibitors and targeted receptor internalization seen with the anti-CD73 mAb, oleclumab. The *in vitro* potency of CBO421 translated into robust anti-tumor efficacy in CRC mouse models, that was further improved in combination with an anti-PD-1 mAb[5]. Based on these results and other emerging data, CBO421 is being advanced as a clinical development candidate for treatment of solid tumors.

DISCLOSURE & REFERENCES

All authors are share-holder & employees of Cidara Therapeutics.
*corresponding author: *sdoehrmann@cidara.com*

[1]Allard et al., 2020 PMID: 32514148
[2]Knapp et al., 2012 PMID: 23142347
[3]Geoghegan et al., 2016 PMID: 26854859
[4]Miller et al., 2022 PMID: 36600561
[5]Cidara Therapeutics website

CIDARA THERAPEUTICS

CBO421 OVERCOMES LIMITATIONS OF CLINICAL STAGE CD73 INHIBITORS

Activity	Small molecule (e.g. AB680)	**DFC** (CBO421)	mAb (e.g. Oleclumab)
Soluble CD73 inhibition	+++	+++	–/+
Cell-anchored CD73 inhibition	+++	+++	++
Receptor internalization	–	+++	+++
Half-Life	+	+++	+++
Tissue/tumor penetration	+++	++	+
Potential safety profile*	++	+++	+++
Multispecific targeting	–	+++	+

*mAbs and DFCs do not enter the intracellular space, reducing potential for off-target toxicities

CIDARA THERAPEUTICS

CBO421 HIGHLIGHTS THE IMPORTANCE OF CD73 IN THE ADENOSINE PATHWAY

Inhibition of CD73 restored T cell activation where clinical stage inhibitors against other pathway targets did not

PBMC rescue assay (ATP) vs clinical stage adenosine pathway inhibitors

Test article	Target/Class	EC_{50} [nM]	
		$CD4^+CD25^+$	$CD8^+CD25^+$
CBO421	CD73/DFC	13	51
AB680*	CD73/small molecule	39	73
Oleclumab*	CD73/mAb	>1,000	>1,000
IPH5201*	CD39/mAb	>1,000	>1,000
AB928*	A2AR/BR small molecule	>1,000	>1,000
CPI-444*	A2AR/small molecule	>1,000	>1,000

*IPH5201 – Innate Pharma biosimilar CD39 inhibitor
AB928 – Arcus Biosciences A2AR inhibitor
CPI-444 – Corvus A2AR inhibitor
AB680 – Arcus Biosciences CD73 inhibitor
Oleclumab – Astra Zeneca biosimilar CD73 inhibitor

CIDARA THERAPEUTICS

CBO421 OVERCOMES LIABILITIES OF CLINICAL STAGE CD73 INHIBITORS

PBMC Rescue Assay (ATP) vs Clinical Stage CD73 Inhibitors

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AB680*	CD73/small molecule	39	73
Oleclumab*	CD73/mAb	>1,000	>1,000

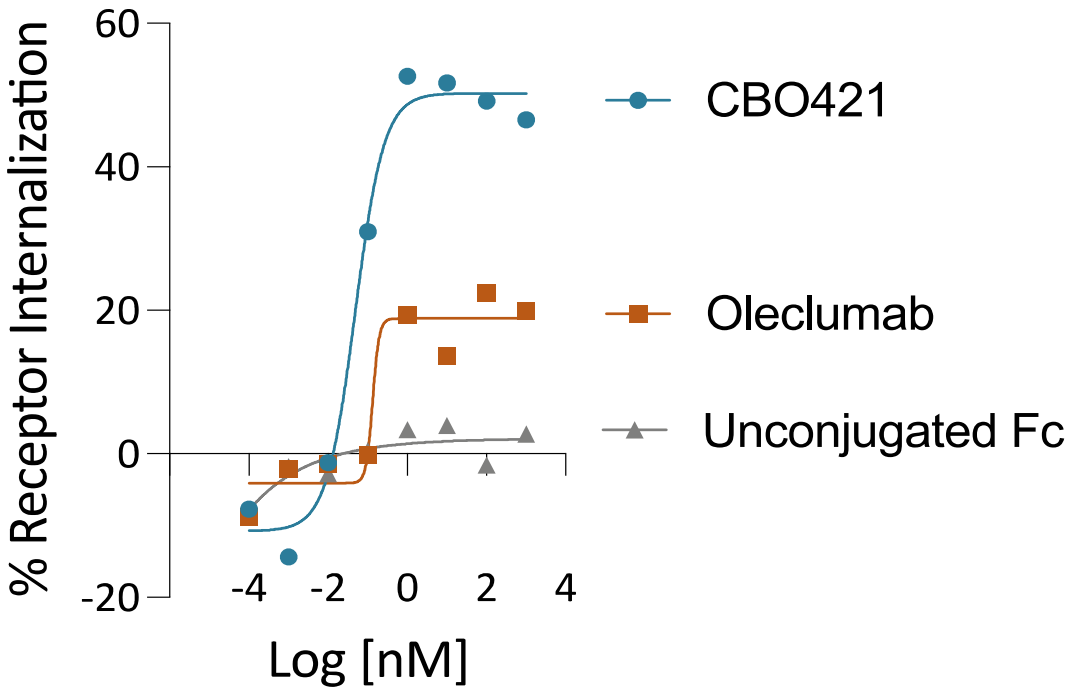
*AB680 – Arcus Biosciences CD73 inhibitor
Oleclumab – Astra Zeneca biosimilar CD73 inhibitor

CBO421 demonstrates potent functional CD73 inhibition and outperforms mAb CD73 inhibitors

CIDARA THERAPEUTICS

CBO421 OVERCOMES LIABILITIES OF CLINICAL STAGE CD73 INHIBITORS IN TNBC CELL LINE

CD73 Internalization on MDA-MB-231 Tumor Cells by Flow Cytometry (4h post-incubation)



CD73 Internalization in MDA-MB-231 Cells

Test article	Target/Class	Maximum % internalization	EC_{50} [nM]
CBO421	CD73/DFC	50	0.049
AB680*	CD73/small molecule	0*	NA
Oleclumab#	CD73/mAb	18	0.13

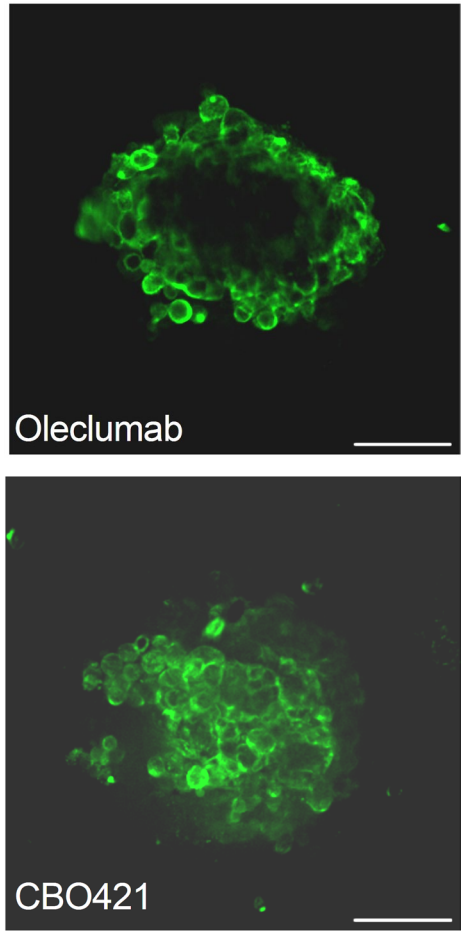
*AB680 – Arcus Biosciences CD73 inhibitor, internalization data not shown
Oleclumab – Astra Zeneca biosimilar CD73 inhibitor

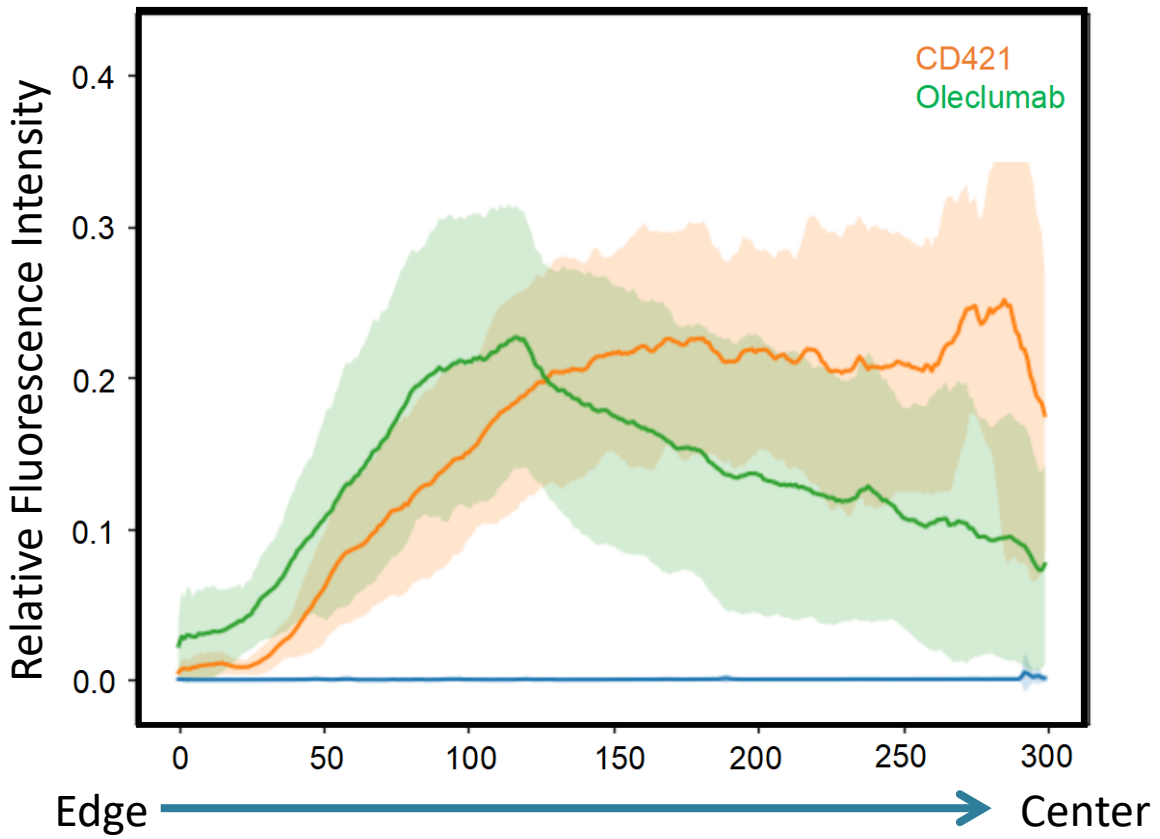
CBO421 demonstrates best in class CD73 downregulation via internalization, which is not achievable with small molecule CD73 inhibitors

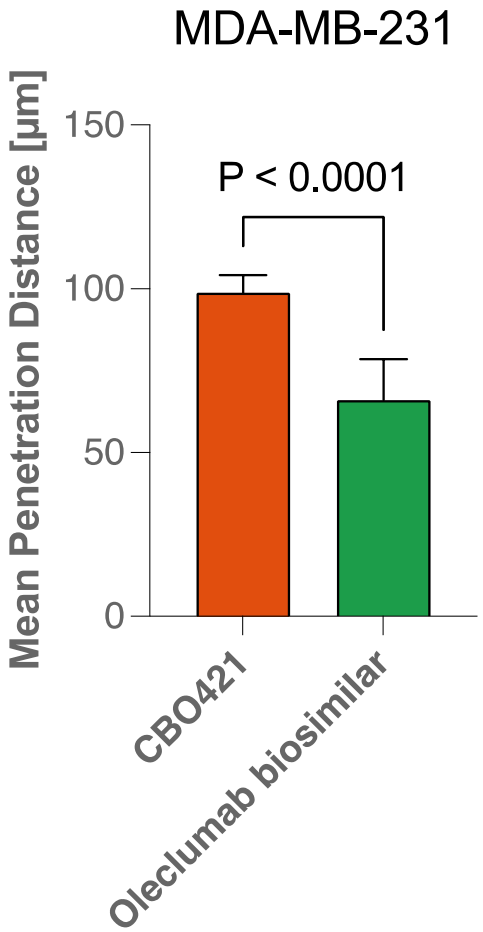
CIDARA THERAPEUTICS

CBO421 EXHIBITS SUPERIOR TUMOR PENETRATION VS. OLECLUMAB BIOSIMILAR

MDA-MB-231 Spheroids





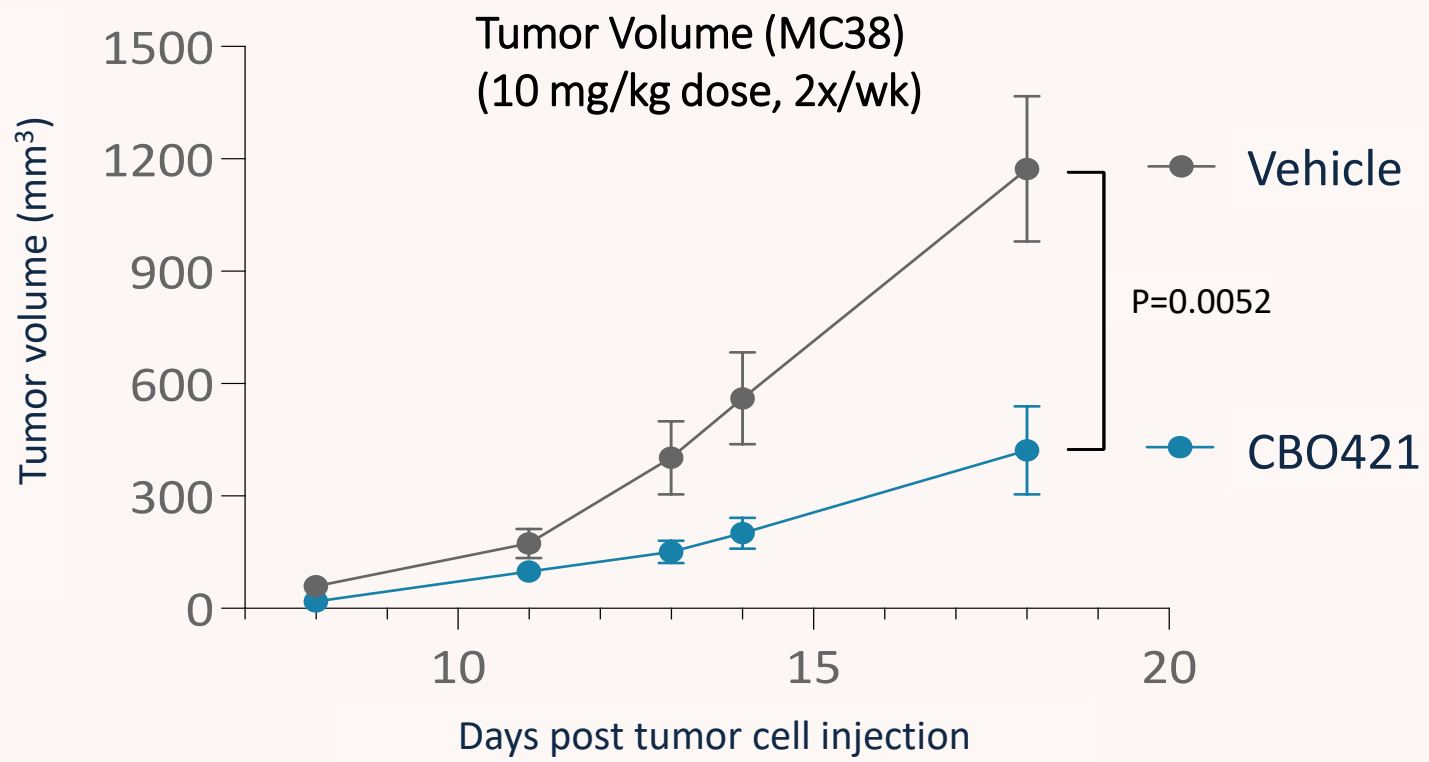


Study conducted by PhenoVista Biosciences

CIDARA THERAPEUTICS

CBO421 ADVANTAGES TRANSLATE TO ROBUST ANTI-TUMOR ACTIVITY

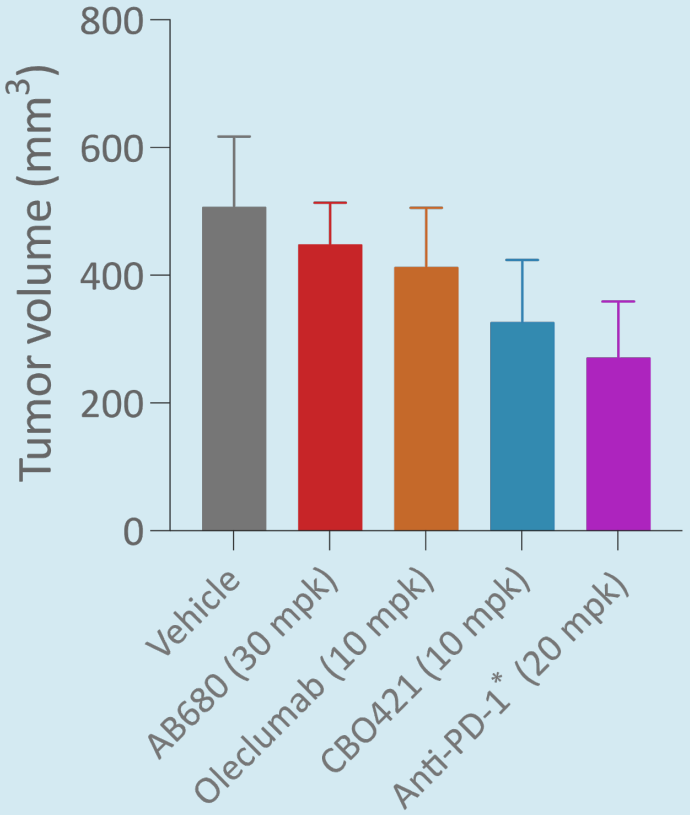
MC38 – murine colorectal carcinoma



CIDARA THERAPEUTICS

CBO421 OUTPERFORMS CLINICAL STAGE COMPARATORS IN EFFICACY MODELS

Tumor Volume (MC38), day 13 post-dosing, BALB/c mice
Biologics dosed 2x weekly, AB680 once daily



Test article	% TGI
CBO421	**36**
Oleclumab	19
AB680	12
Anti-PD-1*	46

*RMP1-14

CIDARA THERAPEUTICS

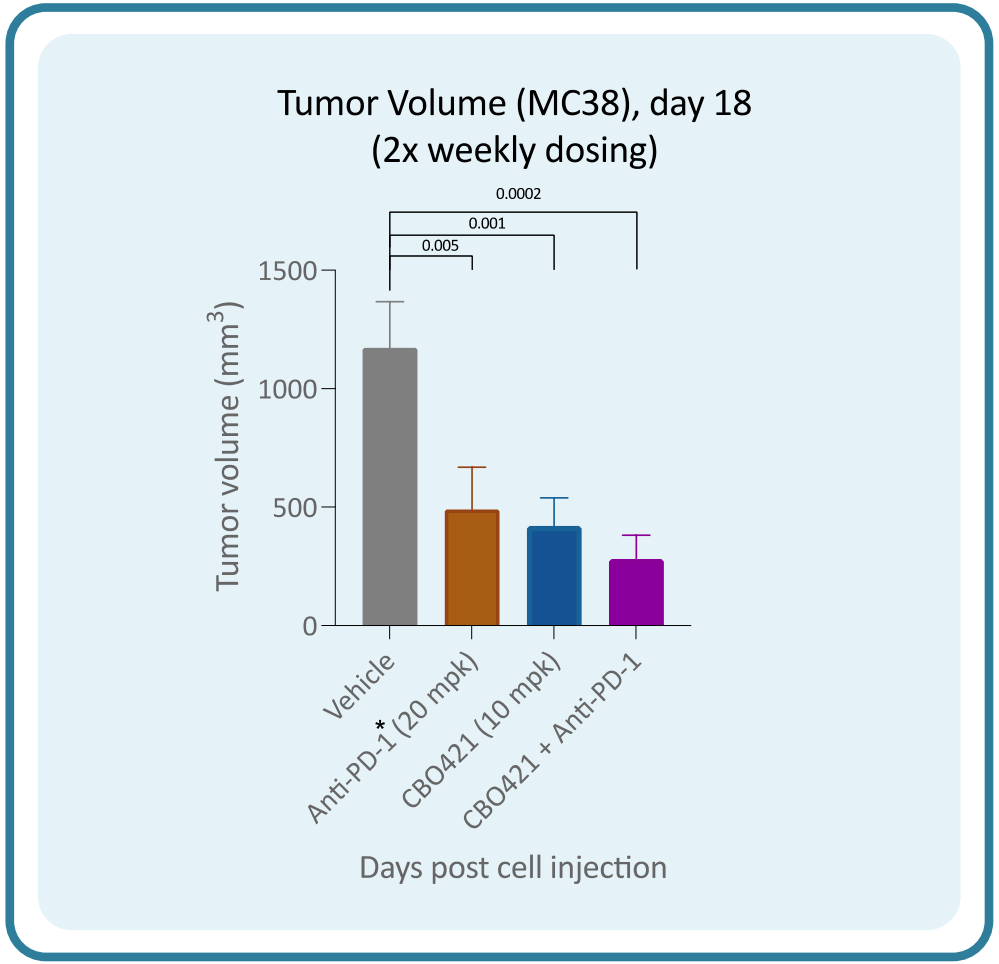
CBO421 ENHANCES ANTI-TUMOR ACTIVITY OF PD-1 INHIBITORS

CBO421 + Anti-PD-1 combination improves response rates versus monotherapy

MC38 – murine colorectal carcinoma

Study Arm	% Responders*
Vehicle	0
CBO421	27
Anti-PD-1	47
CBO421 + Anti-PD-1	60

*Defined as mice that demonstrate cessation of tumor growth or reduction in tumor volume across two or more timepoints



*RMP1-14

CIDARA THERAPEUTICS

CBO421 ELICITS COMPLETE RESPONSES AND IMMUNOLOGIC MEMORY IN COMBINATION WITH PD-1 INHIBITORS

Study start (D+0)

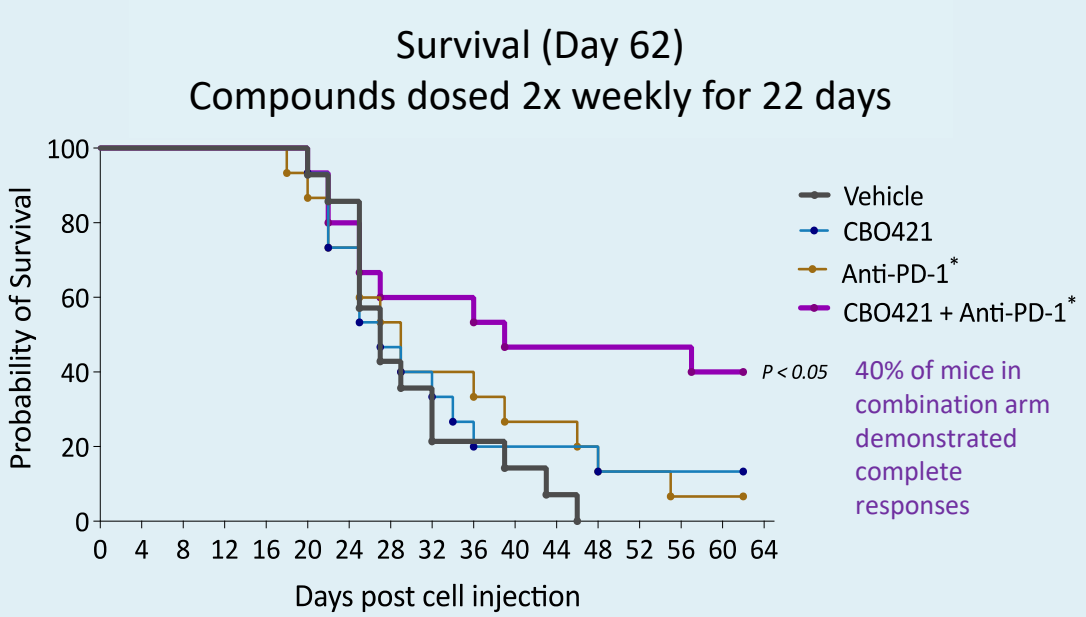
Last dose (D+22)

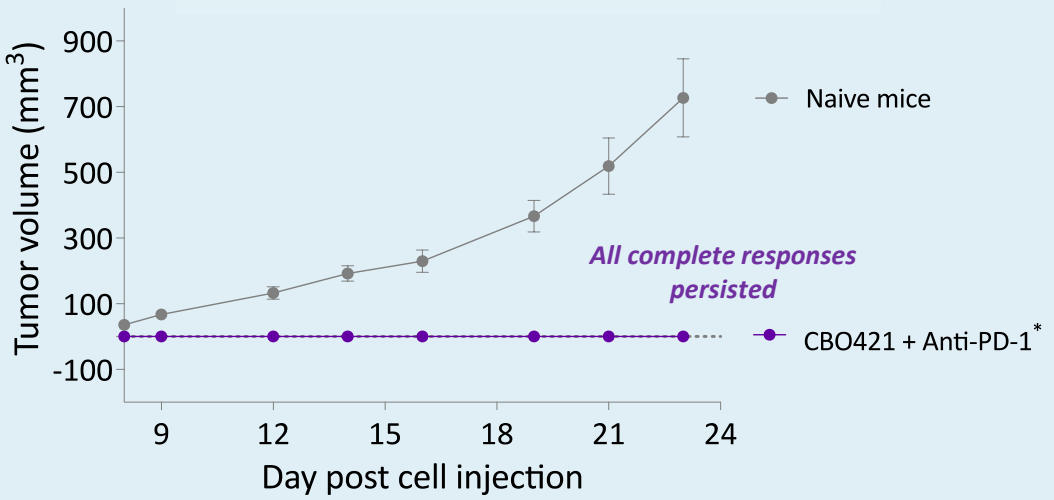
40-day washout period

D+62 (re-challenge)

Study complete (D+73)

EMT6 – murine mammary carcinoma



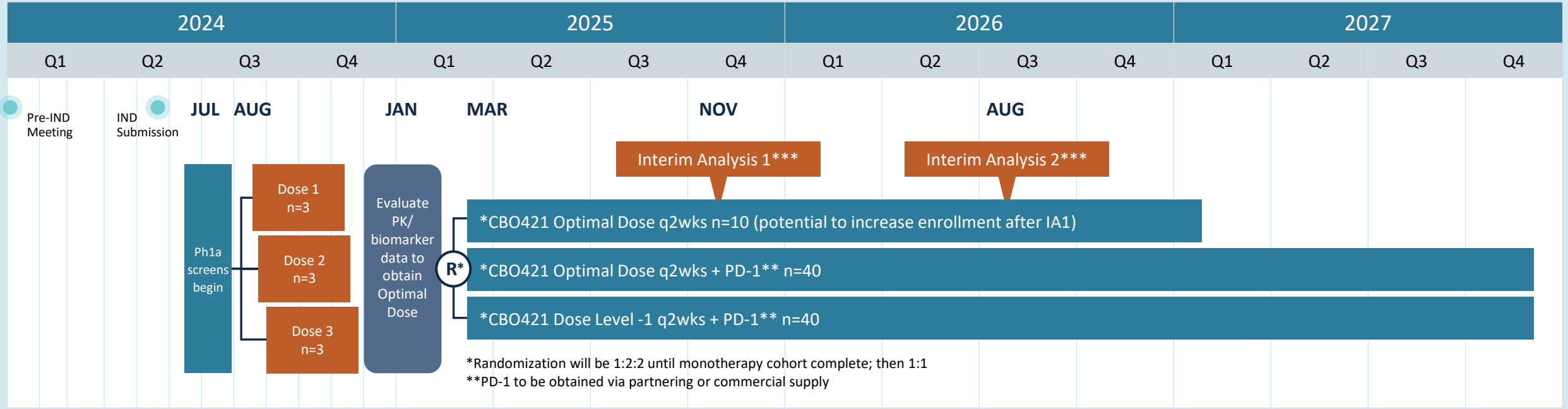


*RMP1-14

CIDARA THERAPEUTICS

CBO421 CLINICAL DEVELOPMENT TIMELINE

Ph1 open-label, dose escalation and expansion studies evaluating the safety, tolerability, and activity of CBO421 alone and in combination with checkpoint inhibition in the treatment of advanced solid tumors (n=99)



Study Phase	Ph1a: SAD Dose Escalation Phase (n=9)	Ph1b: Dose Expansion & Efficacy Phase (n=90) Treat until disease progression, toxicity, or patient discontinues from treatment
Patient Population	Any solid tumor without SOC options	2L+ EGFR mutant NSCLC, MSS CRC, RCC, Gastric CA

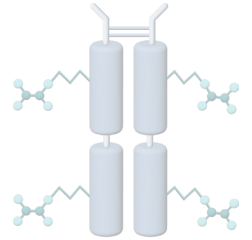
Efficacy Endpoints:	
1EP: ORR	***IA1 & 2 to occur when 20 & 40 pts, respectively, have been randomized in combination arms and followed for ≥16 weeks
2EP: PFS, OS	

CIDARA THERAPEUTICS

CD73/PD-1 MULTI-SPECIFIC DFC

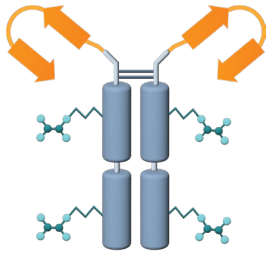
CD73: CBO421 Development Candidate

- Potential Best-in-Class
- Robust tumor control as monotherapy, complete and durable immune response in combination with PD-1 inhibitors
- Excellent safety and COGS, flexible dosing including SC



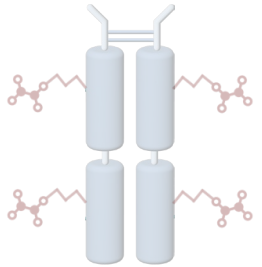
PD-1/CD73 Discovery Program

- First-in-class dual inhibitor of CD73 and PD-1
- Compelling preclinical data
- Potential for more efficient clinical development



CCR5 Discovery Program

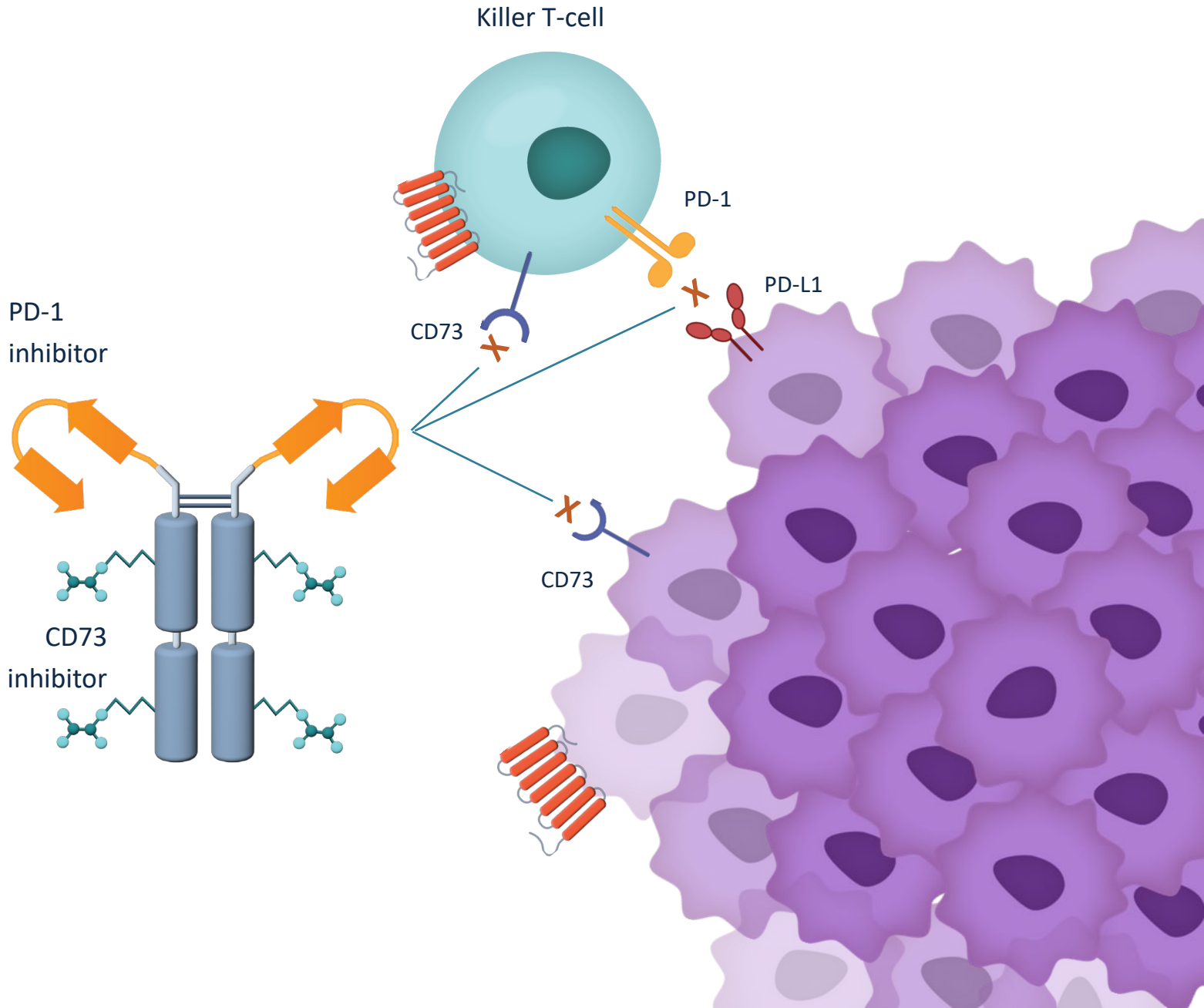
- Unexploited target that is an important driver of immune evasion in several difficult to treat cancers
- DFCs are an ideal platform to overcome challenges that have impaired development of CCR5 antagonists
- Proof of concept data generated



CIDARA THERAPEUTICS

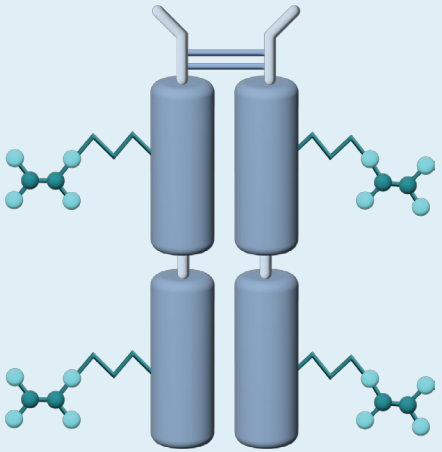
- Cidara's first multispecific DFC (PD-1/CD73) is a **first-in-class** dual inhibitor

- Engineered to improve efficacy by disabling a key resistance mechanism to PD-1 inhibitors



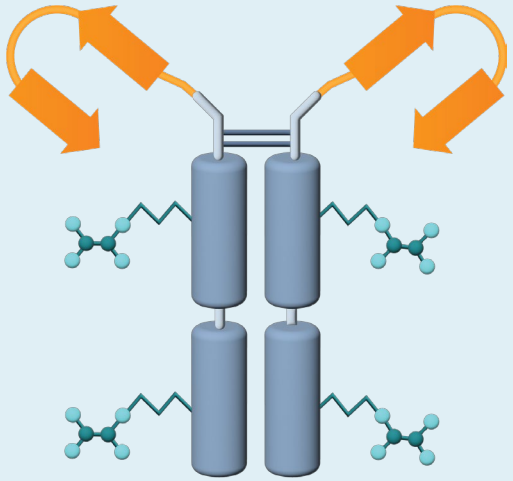
PD-1/CD73 DFC POTENTLY INHIBITS BOTH PD-1 AND CD73 RECEPTORS

CD73 DFC



T-cell reactivation (EC_{50}, nM) – **12**

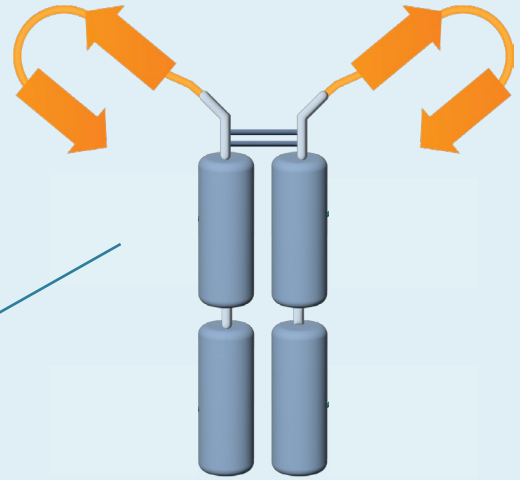
PD-1/CD73 DFC



PD-1 Binding (IC_{50}, nM) – **0.064**

T-cell reactivation (EC_{50}, nM) – **9**

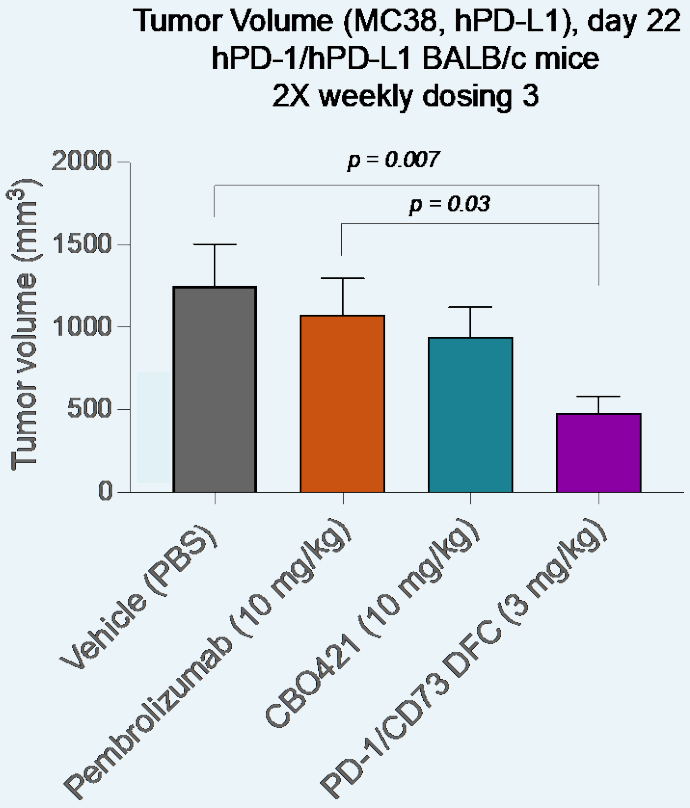
CTP-PD-1

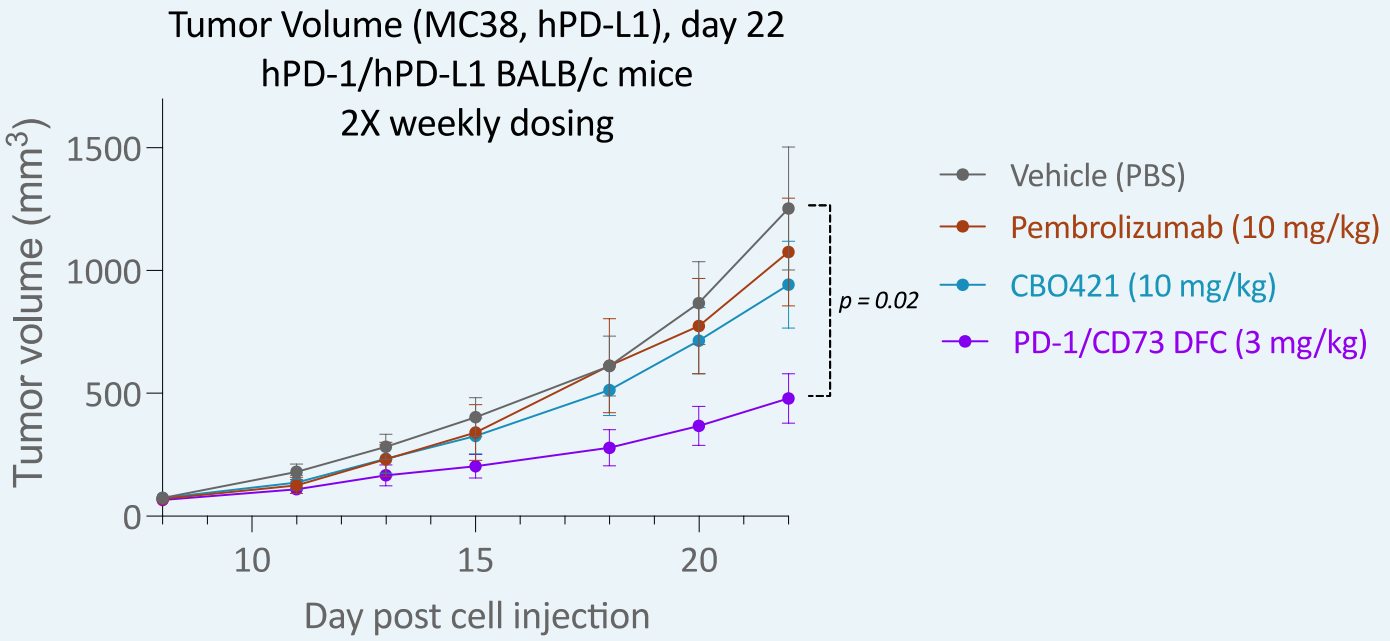


PD-1 Binding (IC_{50}, nM) – **0.056**

CIDARA THERAPEUTICS

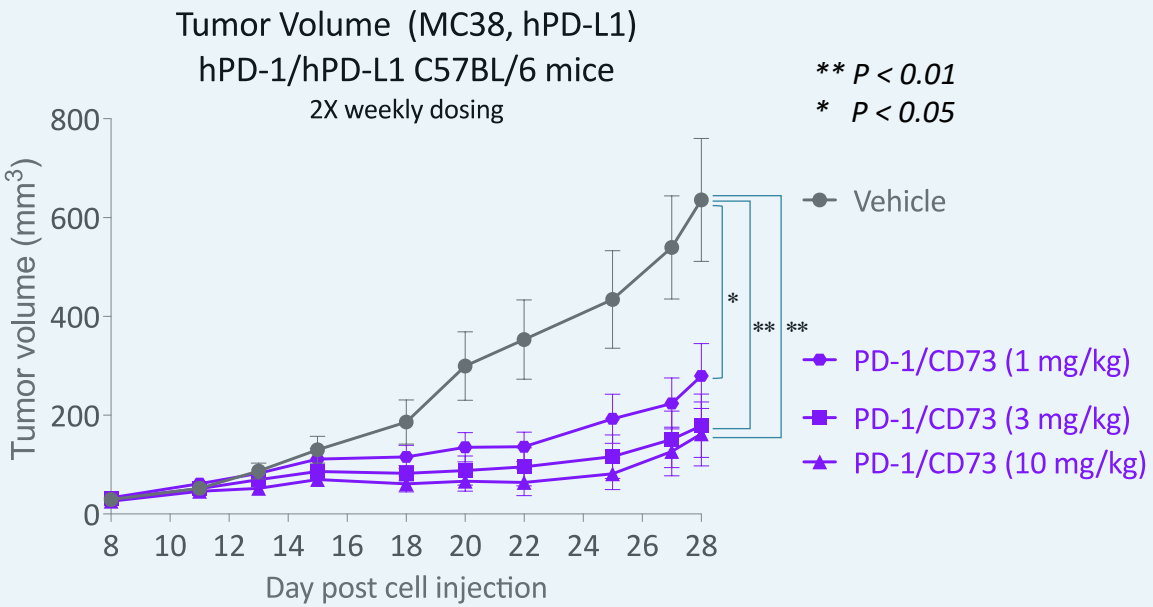
PD-1/CD73 DFC DEMONSTRATES SUPERIOR TUMOR GROWTH INHIBITION OVER MONOTHERAPIES IN HUMANIZED TUMOR MODELS

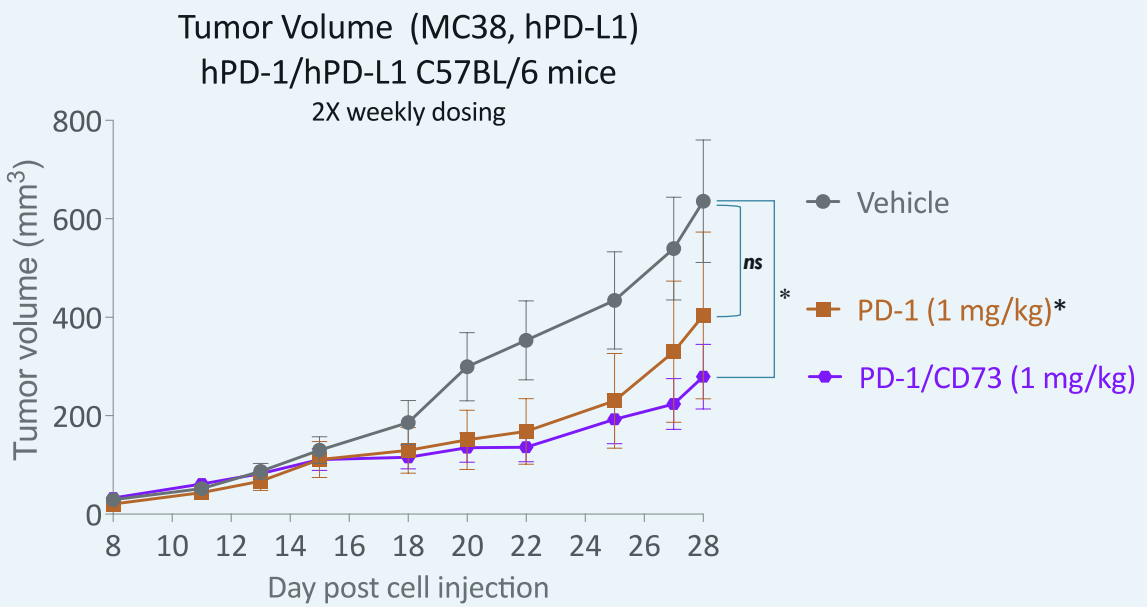




PD-1/CD73 DFC DEMONSTRATES ROBUST TUMOR GROWTH INHIBITION AT LOW DOSES

PD-1/CD73 DFC retains statistically significant tumor growth control at lower doses than its parent PD-1 DFC





*PD-1 is the proprietary PD-1 inhibitor used in the multispecific PD-1/CD73 DFC

CIDARA THERAPEUTICS

CIDARA'S PD-1/CD73 AND PIPELINE OF MULTIPSECIFIC DFCs CARVE OUT UNEXPLORED NICHES

Cidara's DFC and Akeso's bispecific mAb are the only two PD-1/CD73 multispecific agents in development

Stage of Development:
Cidara PD-1/CD73 DFC – Preclinical (IND mid-2025)
Akeso bispecific mAb (AK131) – Phase 1a opened (Dec 2023)

Attribute	PD-1/CD73 DFC	AK131	Potential for differentiation with PD-1/CD73 DFC
Size	< 115 kDa	> 200 kDa	Superior tumor penetration, better potential for high concentration formulations
Inhibition of CD73 catalytic activity	Full	Partial*	Superior inhibition of CD73
Retention of component monotherapy activity in multispecific format	Full	Partial*	Efficacy at lower doses

*Based on data presented in: *Cancer Res* (2022) 82 (12_Supplement): 5526. https://doi.org/10.1158/1538-7445.AM2022-5526

CIDARA THERAPEUTICS

MULTISPECIFIC DFCs OFFER ADVANTAGES OVER BOTH BISPECIFIC mAbs AND ADCs

Attribute	ADC	Bispecific mAb	DFC	Advantage of DFC
Example	Sacituzumab Govitecan Enfortumab Vedotin	PD-1/LAG3 PD-1-CTLA4 PD-1/CD73	PD-1/CD73 PD-1/CCR5	
Size	>150kDa	> 200 kDa	< 115 kDa	Smaller size allows enhanced tumor penetration
Cytotoxic component	Yes	No	No	No chemotherapy component allows enhanced safety profile
Linker	Cleavable	Stable	Stable	MOA not restricted to internalization only Not limited by lower therapeutic efficiency in case of inefficient intracellular trafficking

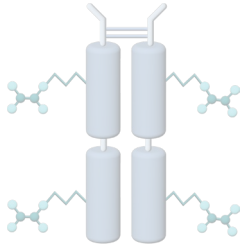
DFCs allow for use of combined targeting modalities (peptides and small molecules) offering unique combinations, smaller size, tunable multivalent binding and enhanced safety

CIDARA THERAPEUTICS

CCR5 DISCOVERY PROGRAM

CD73: CBO421 Development Candidate

- Potential Best-in-Class
- Robust tumor control as monotherapy, complete and durable immune response in combination with PD-1 inhibitors
- Excellent safety and COGS, flexible dosing including sub-Q



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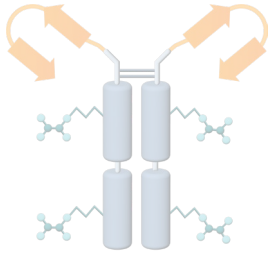

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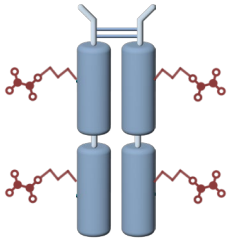
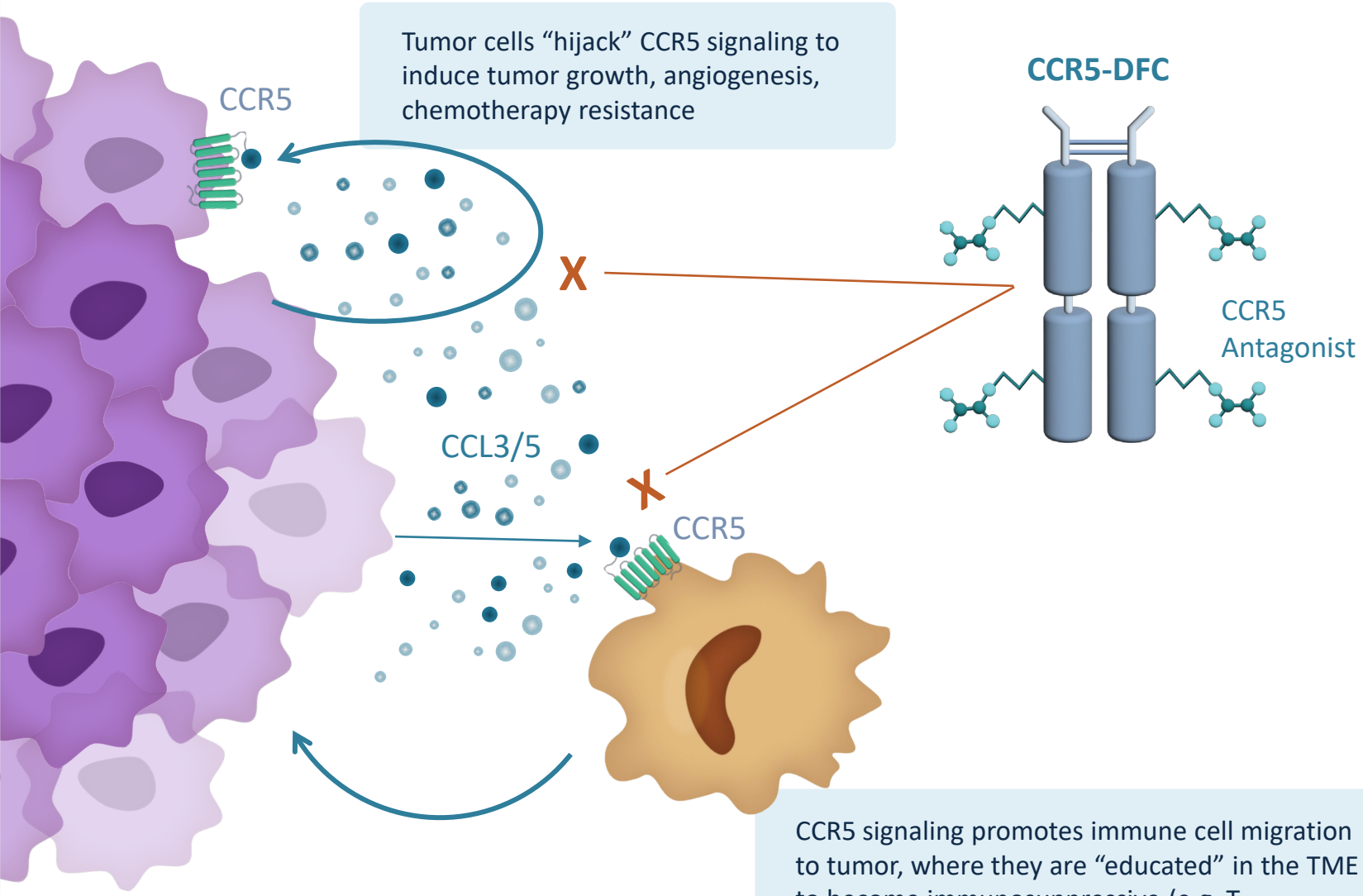
- DFCs are an ideal platform to overcome challenges that have impaired development of CCR5 antagonists
- Proof of concept data generated



CIDARA THERAPEUTICS

CCR5 IS A VALIDATED CANCER TARGET THAT DRIVES PROGRESSION OF HARD-TO-TREAT CANCERS



CCL5/CCR5 is an important driver of tumor growth, immune evasion and metastasis in several difficult-to-treat cancers*

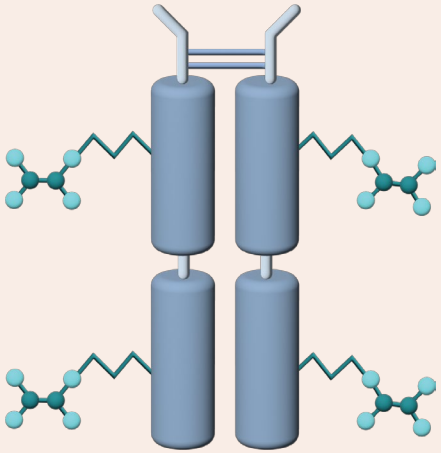
- Breast
- Pancreatic
- Ovarian
- Prostate

*Int. J. Mol. Sci. 2022 https://doi.org/10.3390/ijms232214159

CIDARA THERAPEUTICS

CCR5 IS A CHALLENGING TARGET FOR SMALL MOLECULE DRUG DEVELOPMENT

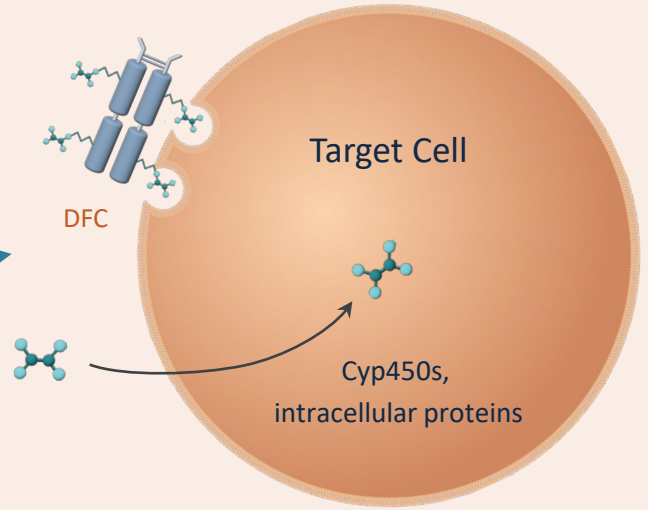
CCR5 DFC
(CCR5-DFC)



Most CCR5 programs have failed to advance due to toxicity and drug-drug interaction potential*

DFCs do not enter cells

DFCs are more selective than SMs



% hERG inhibition @10μM	
Small molecule	40
CCR5-DFC	10

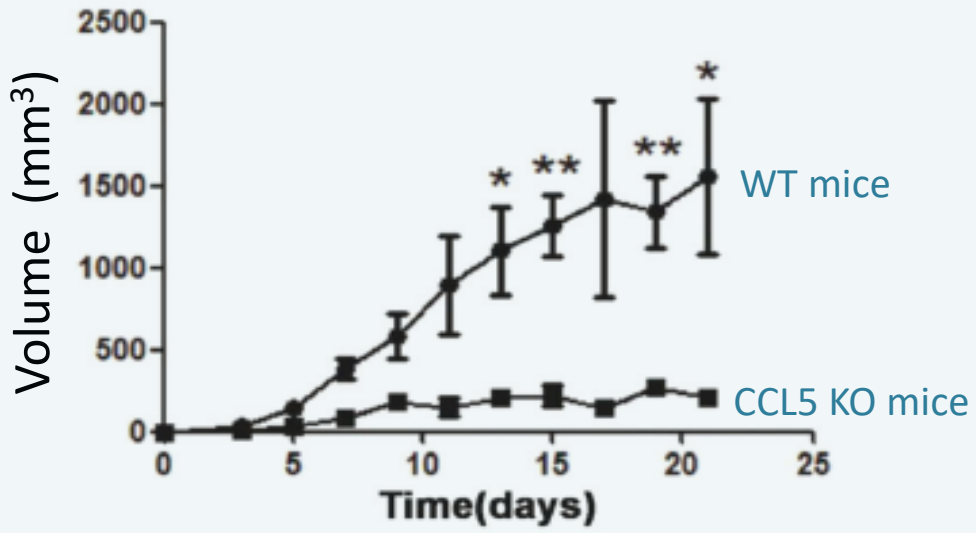
DFCs can uniquely address previously intractable targets

*EXPERT OPINION ON INVESTIGATIONAL DRUGS, 2016 VOL. 25, NO. 12, 1377–1392 http://dx.doi.org/10.1080/13543784.2016.1254615

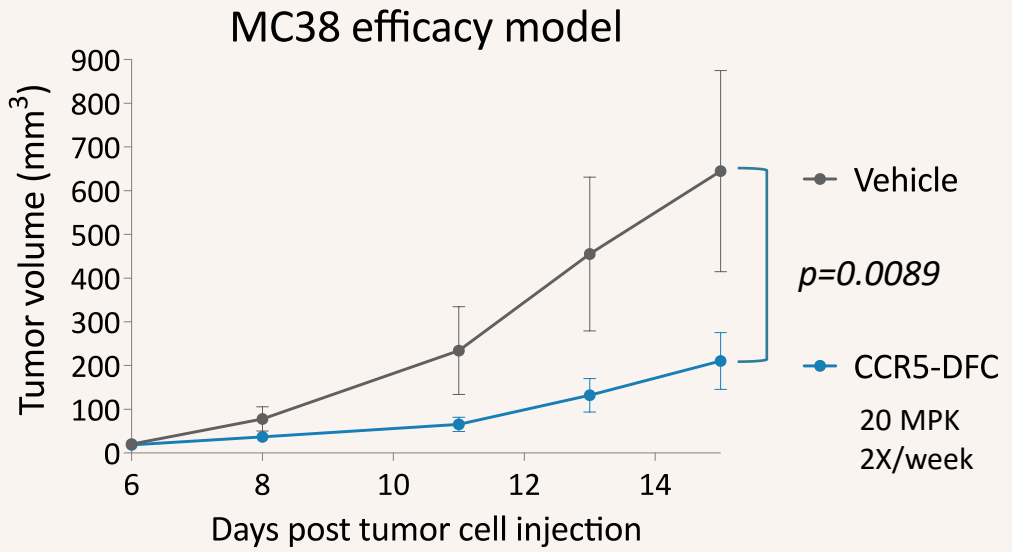
CIDARA THERAPEUTICS

CCR5 DFC INDUCES TUMOR REDUCTION COMMENSURATE WITH A CCL5 KO MODEL IN COLORECTAL CARCINOMA

MC38 tumors are unable to proliferate in CCL5 KO mice (MC38 = murine colorectal carcinoma)



CCR5 DFC treatment potently inhibits tumor growth



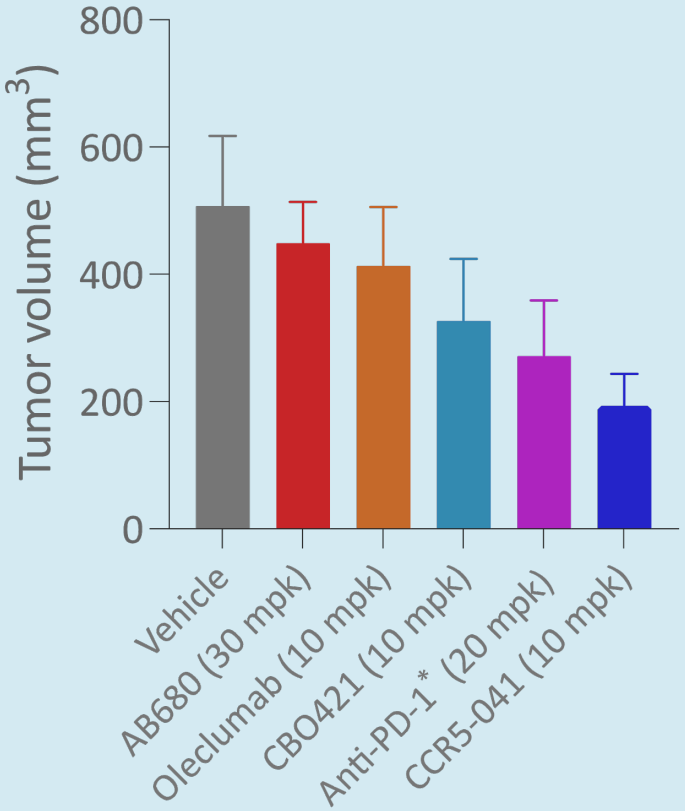
First CCR5 targeting therapy designed for oncology

Zhang et al. Cell Death and Disease (2018) 9:766 DOI 10.1038/s41419-018-0796-2

CIDARA THERAPEUTICS

CCR5 IS A MAJOR DRIVER OF TUMOR PROGRESSION IN CRC MODELS

Tumor Volume (MC38), day 13 post-dosing, BALB/c mice
Biologics dosed 2x weekly, AB680 once daily



Test article	% TGI
CCR5-041	**62**
CBO421	36
Oleclumab	19
AB680	12
Anti-PD-1*	46

*RMP1-14

CIDARA THERAPEUTICS

MULTISPECIFIC DFCs OFFER ADVANTAGES OVER BOTH BISPECIFIC mAbs AND ADCs

Attribute	ADC	Bispecific mAb	DFC	Advantage of DFC
Example	Sacituzumab Govitecan Enfortumab Vedotin	PD-1/LAG3 PD-1-CTLA4 PD-1/CD73	PD-1/CD73 PD-1/CCR5	
Size	>150kDa	> 200 kDa	< 115 kDa	Smaller size allows enhanced tumor penetration
Cytotoxic component	Yes	No	No	No chemotherapy component allows enhanced safety profile
Linker	Cleavable	Stable	Stable	MOA not restricted to internalization only Not limited by lower therapeutic efficiency in case of inefficient intracellular trafficking

DFCs allow for use of combined targeting modalities (peptides and small molecules) offering unique combinations, smaller size, tunable multivalent binding and enhanced safety

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CCR5 COMPETITIVE LANDSCAPE OFFERS SIGNIFICANT POTENTIAL FOR ADVANCEMENT

Anti-CCR5	Drug Class	Clinical Data	Notes
Leronlimab (CytoDyn)	mAb	Pooled analysis 3 studies in combo with chemotherapy TNBC (n=28): mOS 12+ months	2019: Fast Track Designation for TNBC 2022: FDA clinical hold due to CMC and safety concerns
Maraviroc (Pfizer)	Small Molecule	PICASSO-1 ph1b (n=22) in combo with pembrolizumab mCRC: modest efficacy; G3/G4 AEs noted	FDA approved for HIV with black box warning (hepatic tox) No further development planned in oncology

CCR5 DFC

- Significant potential for advancement in oncology due to enhanced safety profile
- MOA and preclinical data support differentiated development plan as monotherapy in areas of highest unmet need: triple negative breast cancer, cervical cancer, gastric cancer, sarcoma, glioblastoma, ALL/AML
- Potential for expedited manufacturing of multispecific PD-1/CCR5 DFC using Cidara's established PD-1 - Fc

CIDARA THERAPEUTICS

UPCOMING CLOUDBREAK AACR PRESENTATIONS

Accepted abstracts below will be presented at the AACR 2024 conference, April 5-10

AACR American Association for Cancer Research ANNUAL MEETING 2024 • SAN DIEGO

ABSTRACT TITLE

Discovery of a multispecific CD73/PD-1 targeting Drug Fc-Conjugate (DFC), which improves tumor reduction compared to PD-1 monotherapy in a humanized mouse model

ABSTRACT TITLE

CBO421: A novel drug Fc-conjugate to prevent tumor immune evasion via the CD73/adenosine pathway

ABSTRACT TITLE

CCR5-001, a novel Drug Fc-Conjugate (DFC) targeting CCR5, demonstrates potent efficacy in a colorectal cancer mouse model

Zhang et al. Cell Death and Disease (2018) 9:766 DOI 10.1038/s41419-018-0796-2

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