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Translational considerations in the development of CS5001, a PBD-based ADC against ROR1, a tumor-specific target

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CStone Pharmaceuticals

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A fully integrated biopharma with end-to-end capabilities

5.5 years from inception to the first commercial launch

RESEARCH

Clinical insight driven modular R&D model

10+ Discovery Projects

45+ IND approvals

DEVELOPMENT

Efficient, high-quality and innovative clinical dev. engine

10 NDA approvals

40+ Data presentations /publications

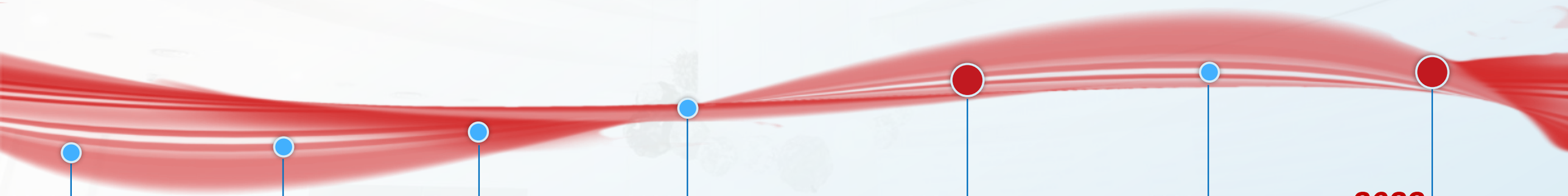
COMMERCIAL

Full capability of in-house commercialization

4 commercialized products

6 indications approved

3 territories covered



2016 *CStone Inception*

2018 *Record Setting Series B Funding of $260m*

2019 *IPO at SEHK*

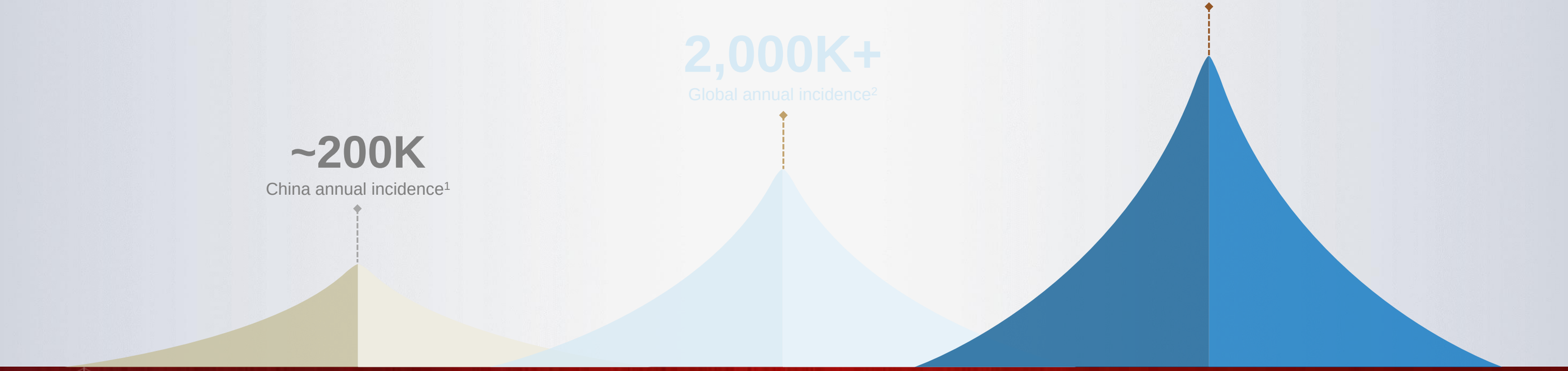
2020 *Global Strategic Partnership with Pfizer & EQRx*

2021 *Approval and launch of Gavreto®, Ayvakit®, Cejemly®,* ***Fully integrated biopharma***

2022 *Approval and launch of Tibsovo®*

2023 *All 5 Registrational Studies of Sugemalimab succeed, overseas launch expected*

CStone's innovative assets with magnificent commercial value



Precision Medicine

- **Pralsetinib**
  FIC RET inhibitor
- **Avapritinib**
  FIC KIT/PDGFRA inhibitor
- **Ivosidenib**
  FIC and the only IDH1 inhibitor
- **Lorlatinib**
  ROS1/ALK, co-dev with Pfizer

Immuno-oncology

- **Sugemalimab**
  PD-L1, the only PD-(L)1 approved for SIII/IV NSCLC all comer
- **Nofazinlimab**
  PD-1, front runner in PD-(L)1 + Lenvatinib for 1L HCC
- **CS1002**
  CTLA4, co-dev with Hengrui

Pipeline 2.0

- **CS5001**
  ROR1-ADC in leading position worldwide
- **CS2006**
  Potential BIC 4-1BB agonist and next generation PD-(L)1 inhibitor
- **10+ Discovery projects**
  FIC/BIC assets with global rights

Data source: 1.2.3. Clarivate DRG, 2025

ROR-1 – Receptor tyrosine kinase-like orphan receptor 1 (ROR1)

An ADC target for both hematological malignancies and solid tumors

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- Embryotic protein over-expressed by many hematological malignancies especially B-cell lymphomas [1,2]
- Largely absent in normal blood lymphocytes and adult tissues [3~5]
- Broadly expressed by solid tumors such as TNBC, ovarian cancer, and adeno-NSCLC [4,6~13]
- Being explored clinically as a tumor-specific target for mAb, ADC, CAR-T and bi-specific

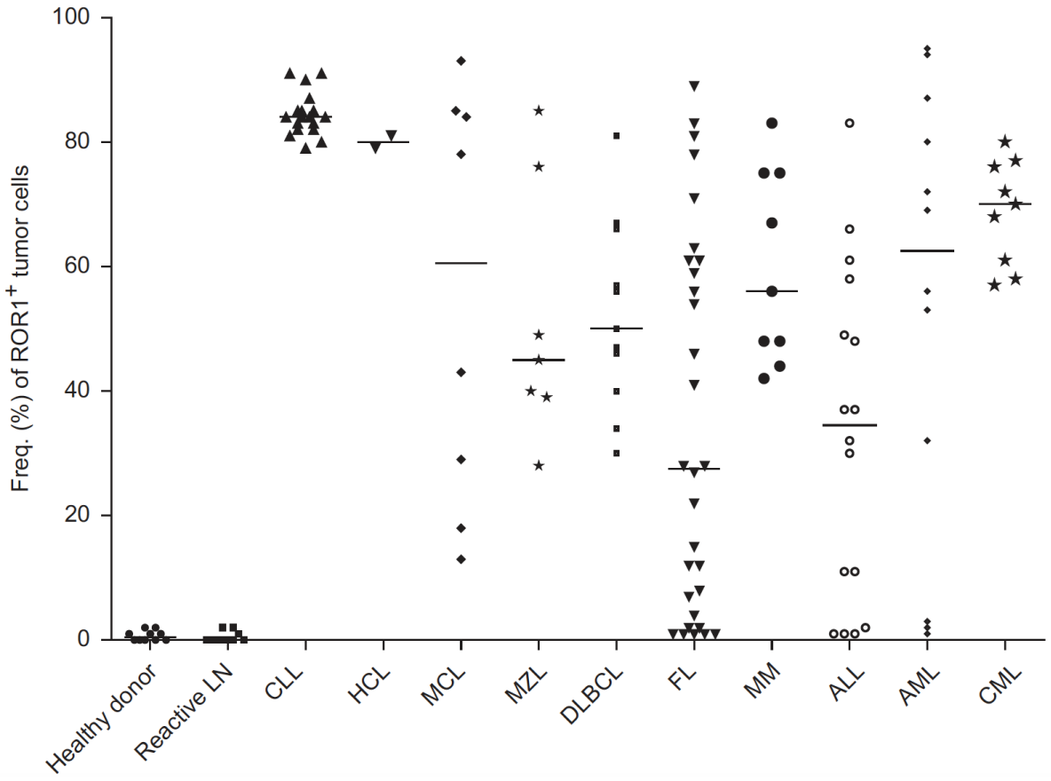
IHC Abs	Scor-ing	% of ROR1 positive by IHC				
		TNBC	Ovarian	Adeno-NSCLC	Endo-metrial	CRC
Clone 6D4 [4]	mb only	**57%** (n=60)	**50%** (n=159)	**42%** (n=76)	--	--
Clone 4A5 [6]	mb + cyto	--	**54%** (n=144)	**93%** (n=29)	**95%** (n=360)	**57%** (n=110)
Abcam [7~13]	mb + cyto	**44%** (n=210)	**71%** (n=185) **55%** (n=100)	**94%** (n=232) **65%** (n=37)	**97%** (n=87)	**94%** (n=186)

[1] Borcherding *et al*, Protein Cell 2014, 5(7):496–502; [2] Daneshmanesh *et al*, Leukemia & Lymphoma 2013,54(4): 843–850; [3] Baskar *et al*, Clin Cancer Res 2008,14(2); [4] Balakrishnan *et al*, Clin Cancer Res 2017 23(12); [5] Uhrmacher *et al*, Leukemia Research 35 (2011) 1360; [6] Zhang *et al*, PLoS ONE 2012 7(3): e31127; [7] Chien *et al*, Virchows Arch 2016, 468(5):589-95; [8] Henry *et al*, Transl Oncol. 2017, 10(3):346-356; [9] Zhang et al, Sci Rep. 2014, 24(4):5811; [10] Zheng *et al*, Sci Rep. 2016, 10(6):36447; [11] Liu *et al*, PLoS One. 2015,10(5):e0127092; [12] Henry *et al*, Gynecol Oncol. 2018, 148(3):576-584; [13] Zhou *et al*, Oncotarget 2017, 8(20):32864-32872

ROR1 in hematologic malignancies

Clinical efficacy observed with with ROR1-targeting ADC

- Homogenous expression across various hematologic malignancies



Daneshmanesh *et al*, Leukemia & Lymphoma 2013,54(4): 843–850

- Similar density to most targets of clinically approved ADCs in hematologic malignancies

Table 1. ABC of B-CLL cell surface ROR1

B-CLL sample	ABC for CD5	ABC for ROR1
1	Not determined	7,090*
2	8,872	4,551
3	14,720	2,773
4	16,002	3,993
5	7,362	3,315
6	21,002	4,164

Baskar *et al*, Clin Cancer Res 2008;14(2)

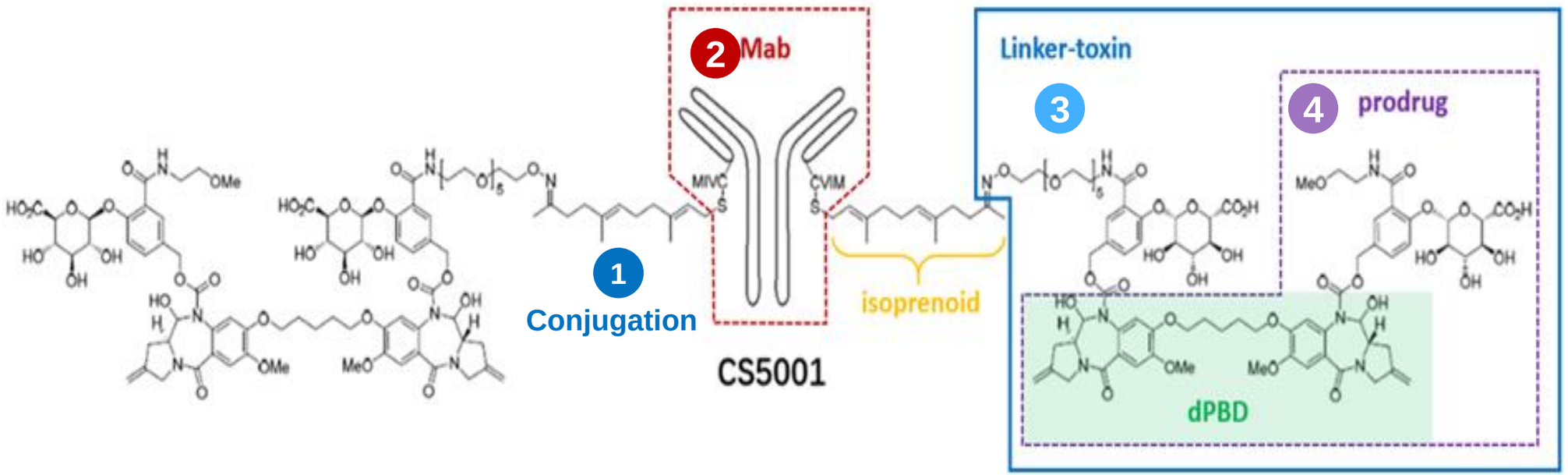
FDA-approved ADCs targeting hematologic malignancies

	Besponsa	Mylotarg	Blenrep	Zynlonta
Target	**CD22** [1]	**CD33** [2]	**BCMA** [3]	**CD19** [4]
Surface density (receptors/cell)	**10^3~10^4**	**10^3~10^4**	**10^3~10^4**	**10^4~10^5**
Payload	Calicheamicin		MMAF	PBD

[1] Haso *et al*, Blood 2013, 121(7):1165-74; [2] Sutherland *et al*, Blood 2013, 122(8):1455-63; [3] Figueroa-Vazquez *et al*, Mol Cancer Ther 2021, 20(2):367-378; [4] Zammarchi *et al*, Blood 2018, 131(10):1094-1105

CS5001 – armed with an ultrapotent PBD payload to maximize tumor cell killing

4 key differentiators



Controllable quality and production

1 *Proprietary **site-specific conjugation** for a **homogenous drug antibody ratio (DAR=2)***

Potentially less immunogenicity

2 ***Fully human mAb** v.s. humanized mAb of other ROR1-ADCs*

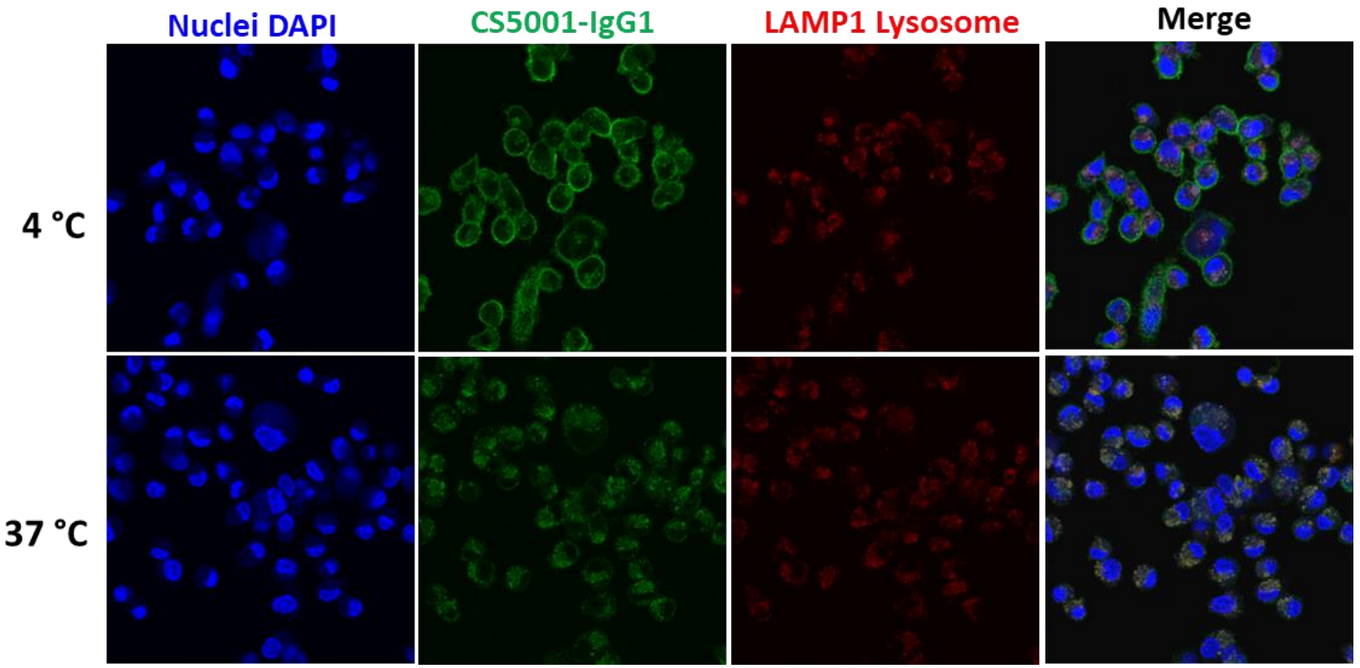
Potentially wider therapeutic window

3 *Proprietary **tumor-selective cleavable linker**, highly stable in serum*

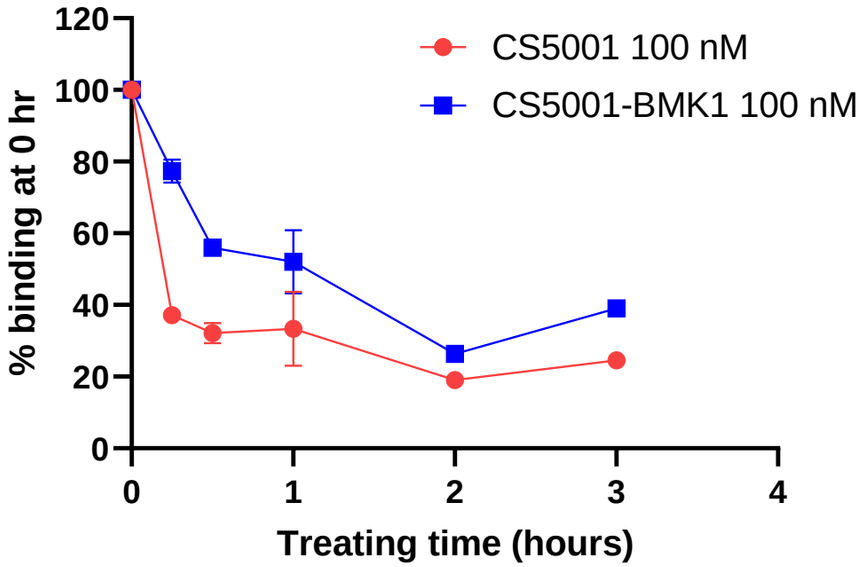
4 *Proprietary t**umor-activated PBD** dimer toxin **prodrug***

Rapid internalization of CS5001 by ROR1-expressing cells

Internalization and intracellular trafficking of CS5001-IgG1



Internalization of CS5001



MDA-MB-231 cells were treated with ROR1 mAb or ADC at 4℃ or 37℃ and were examined with confocal microscopy or flow cytometry

CS5001-IgG1: mAb of CS5001
CS5001-BMK1: benchmark, an MMAE-based ROR1 ADC

ROR1-dependent cytotoxicity – blocking of ROR1 binding significantly attenuates CS5001 cytotoxicity in ROR1-expressing cell lines

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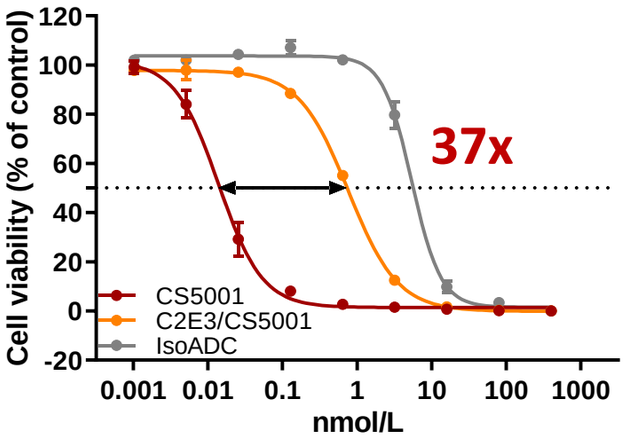
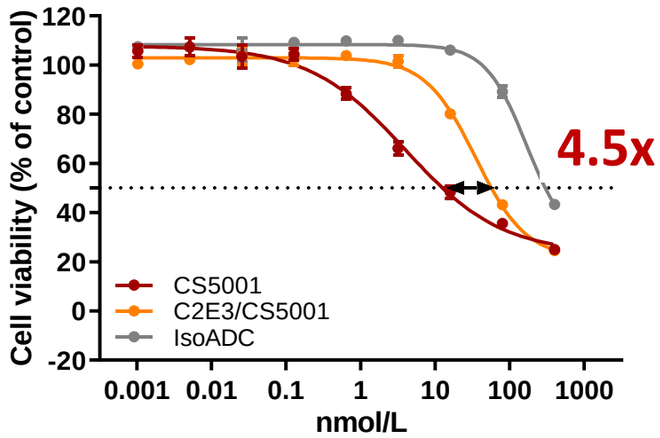
ROR1-high

PA-1

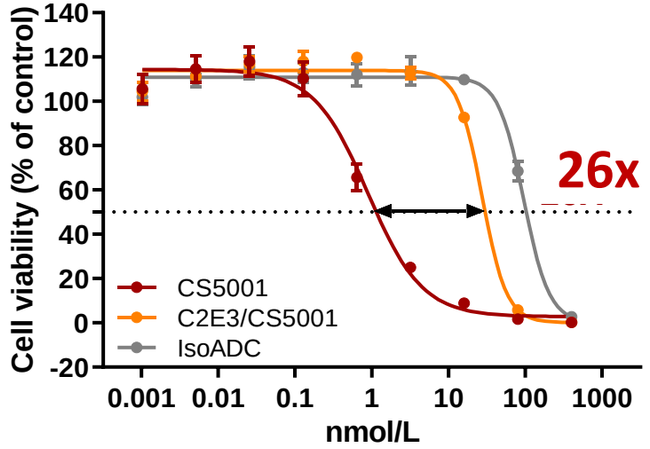


ROR1-moderate

MDA-MB-231

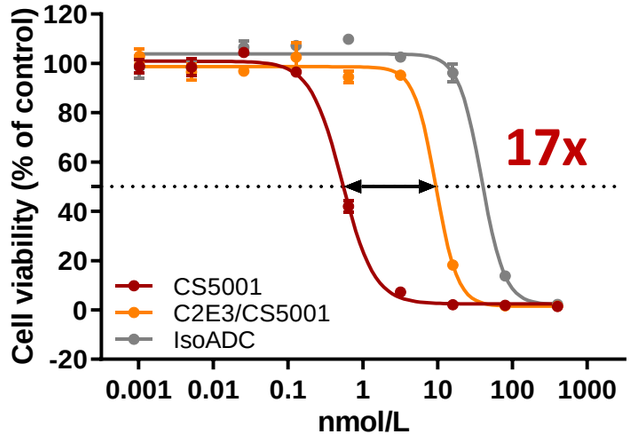


Jeko-1

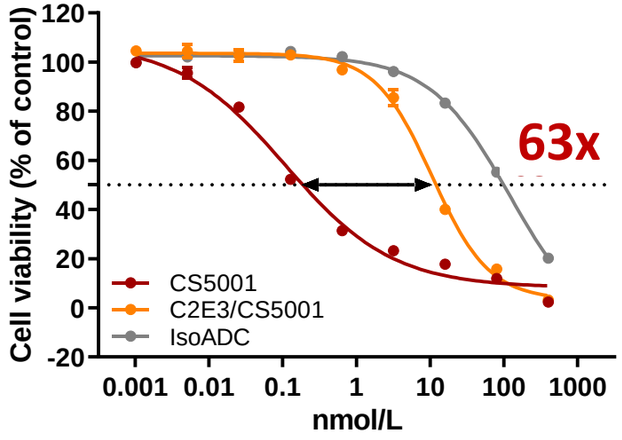


ROR1-low

HGC-27

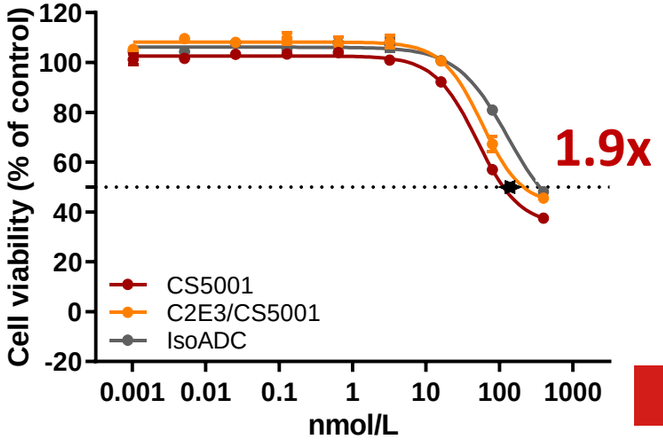


NCI-H2087



ROR1-negative

MCF-7

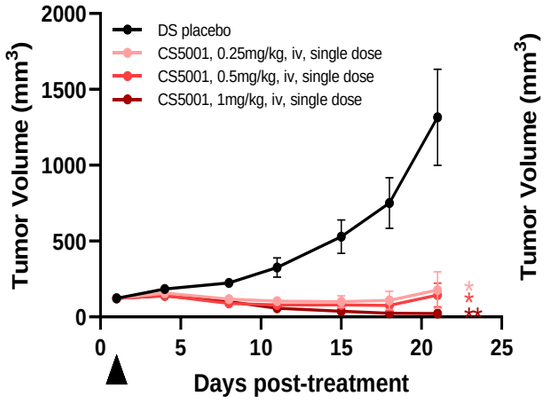


ROR1-dependency of *in vivo* efficacy – Trend of more significant TGI in mouse xenografts of solid tumors with higher ROR1 expression

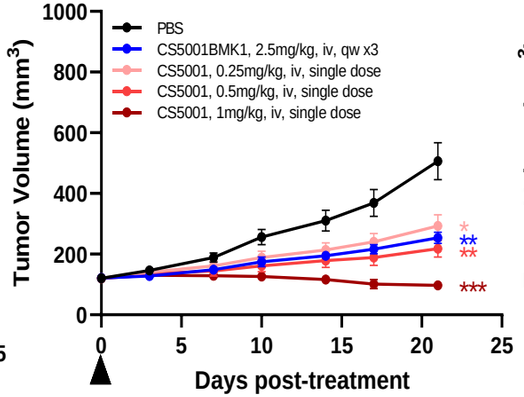
- **MED 0.25 mg/kg, single dose** in PA-1, an ovarian cancer model with the highest ROR1 expression

ROR1-high | **ROR1-moderate** | **ROR1-low** | **ROR1-negative**

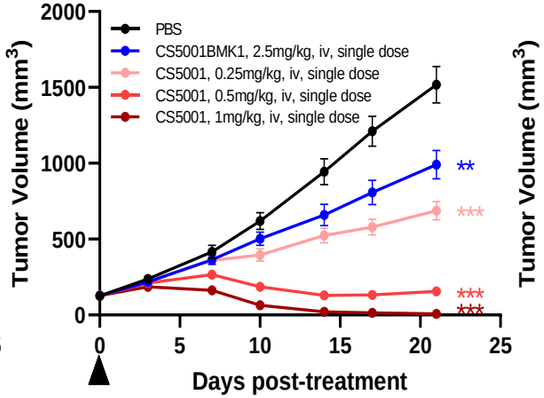
PA-1



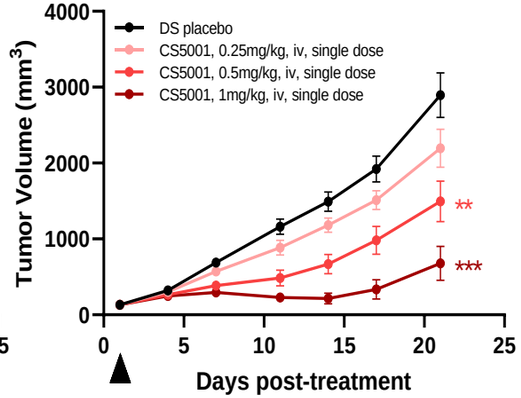
MDA-MB-231



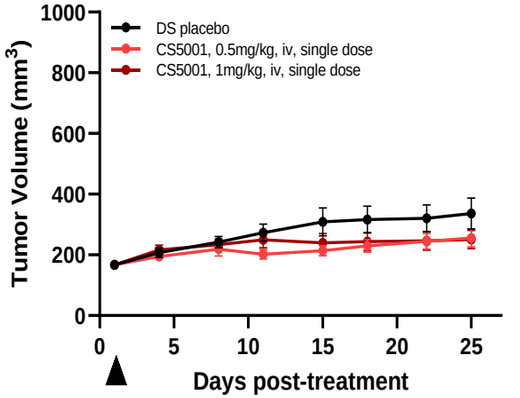
Jeko-1



HGC-27



MCF-7

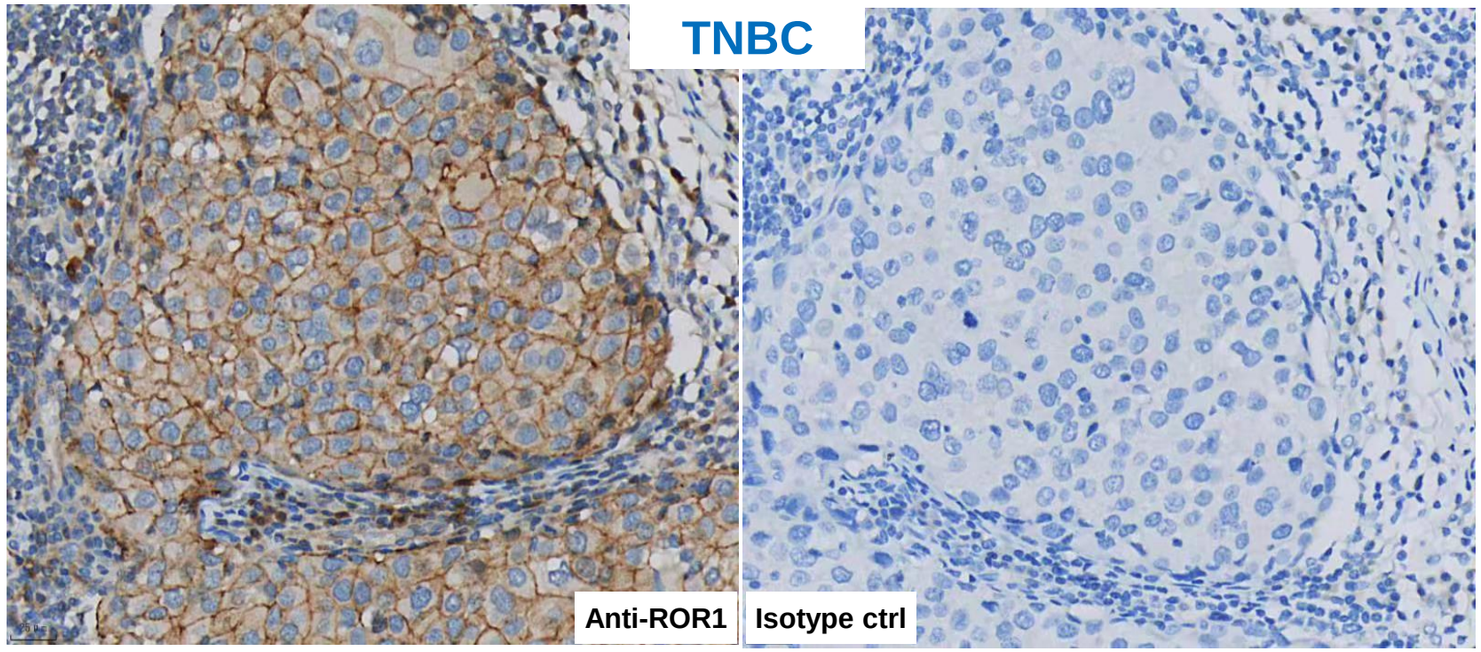


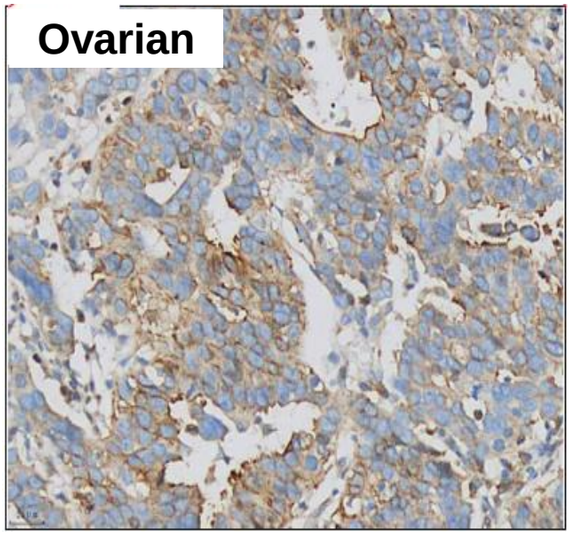
Treatment	PR	CR	TGI (%)	PR	CR	TGI (%)	PR	CR	TGI (%)	PR	CR	TGI (%)	PR	CR	TGI (%)
0.25 mg/kg	6 / 8	0	95	0	0	55	0	0	60	0	0	25	--	--	--
0.5 mg/kg	6 / 8	1 / 8	98	0	0	75	0	0	98	0	0	51	0	0	48
1 mg/kg	8 / 8	2 / 8	108	0	0	106	6 / 8	2 / 8	109	0	0	80	0	0	51
BMK1, 2.5mg/kg	--	--	--	0	0	66	0	0	38	--	--	--	--	--	--

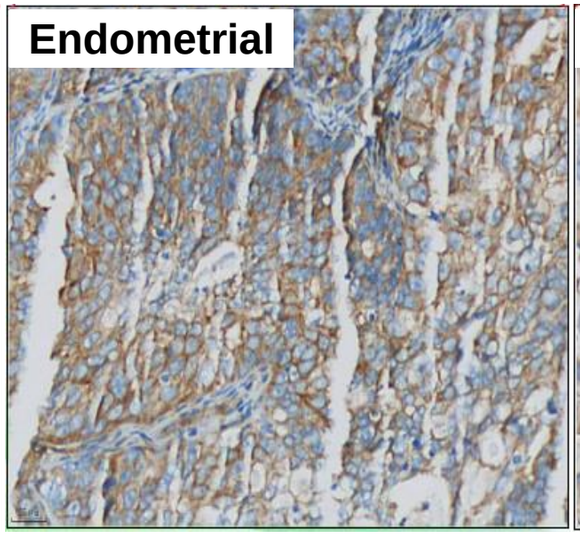
p<0.05, ** p<0.005, *** p<0.001; TGI: tumor growth inhibition; PR: partial regression, defined as -30% of baseline tumor volume ; CR: complete regression, defined as ≤ 13.5 mm^3 for three consecutive measurements

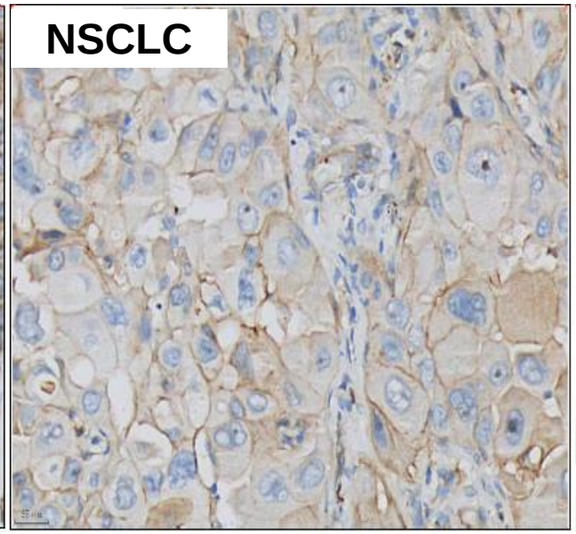
ROR-1 expression in human tumor tissues – A proprietary IHC assay being developed

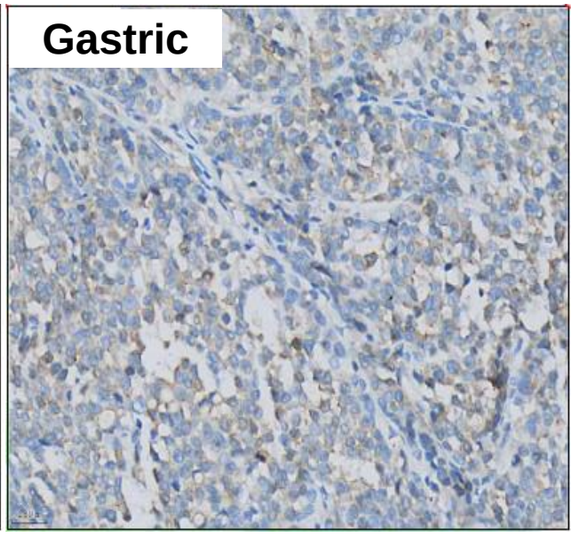
Specific membrane staining on tissues of various human solid tumors





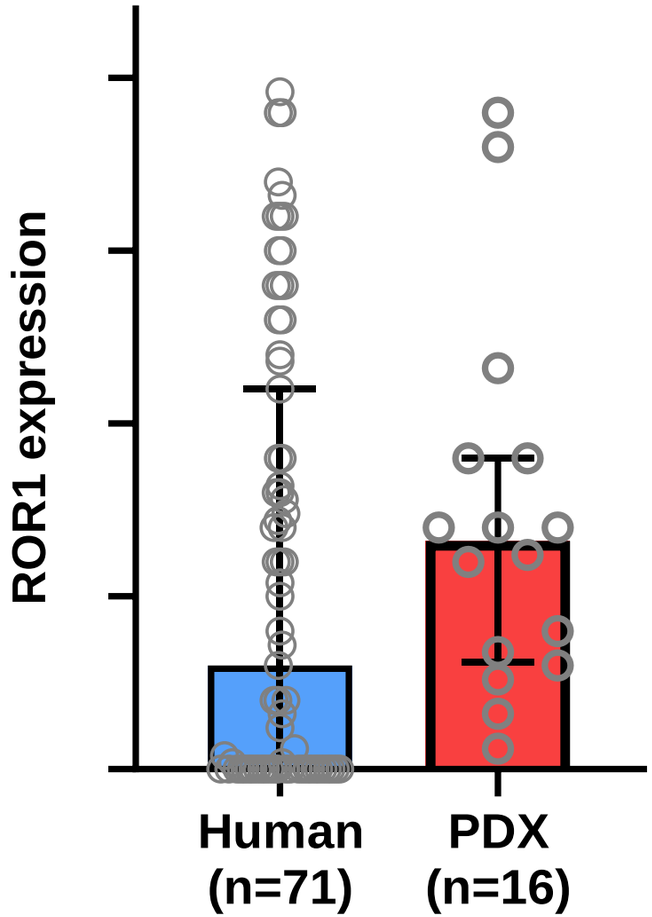






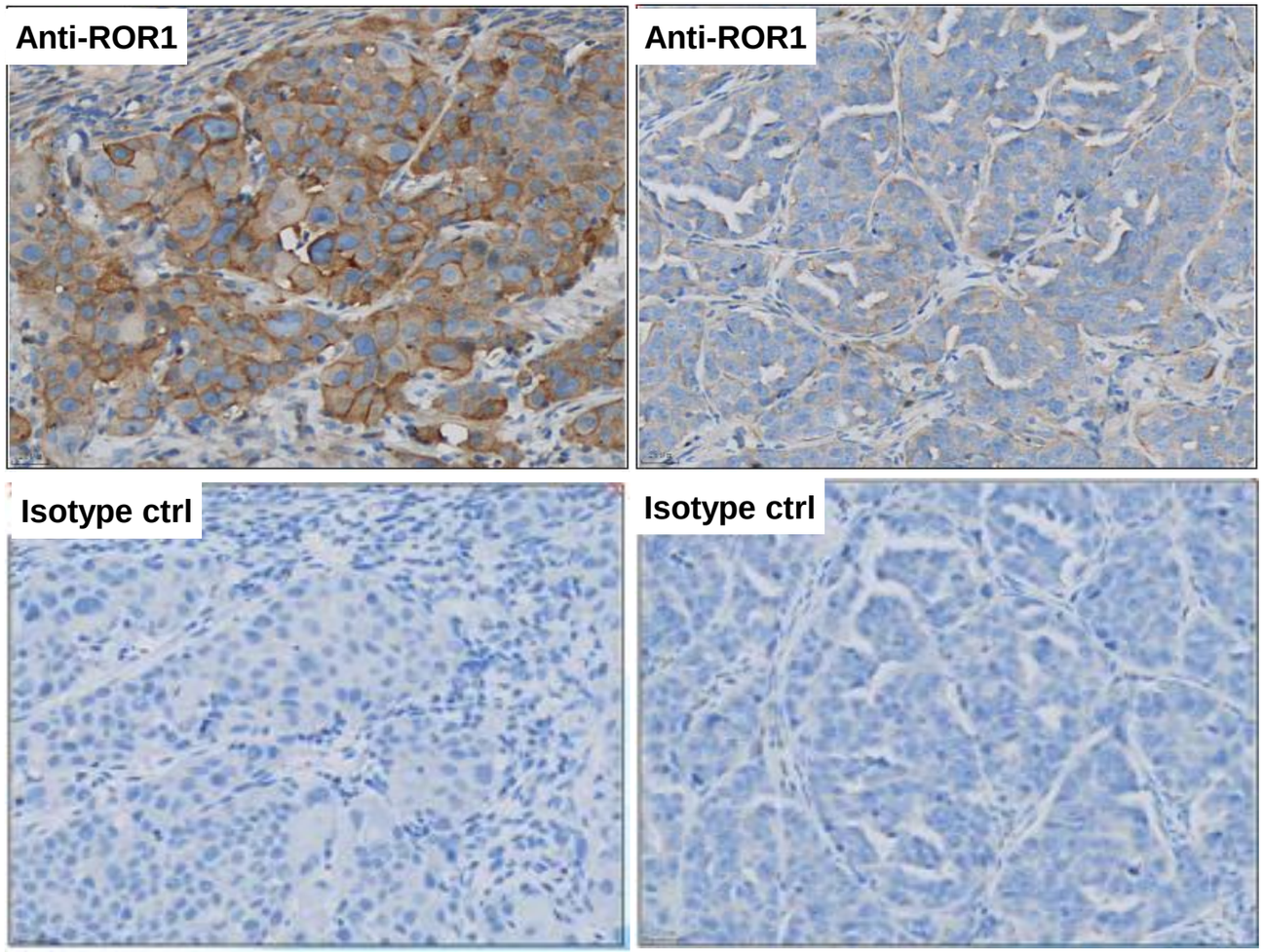
CS5001 efficacy in human TNBC PDX models – characterization of ROR1 expression

PDX models with levels of ROR1 relevant to human expression



BR1282
Moderate

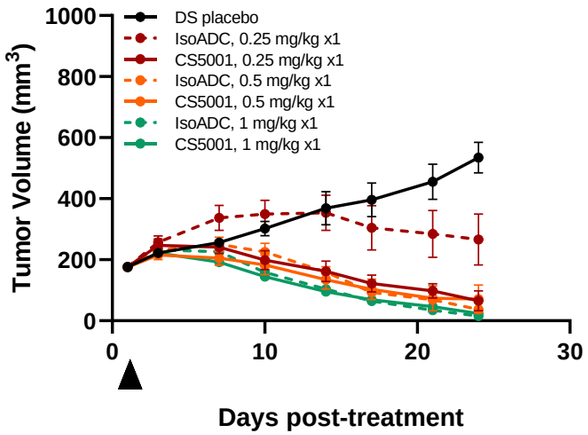
BR5010
Low



CS5001 in human TNBC PDX models – ROR1-dependent TGI only in ROR1-expressing models (preliminary data)

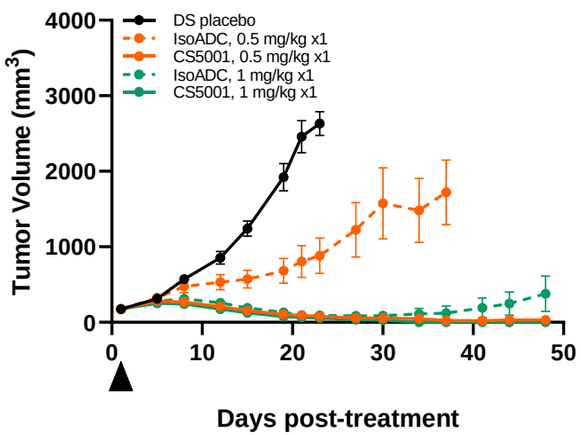
ROR1 high

BR1474



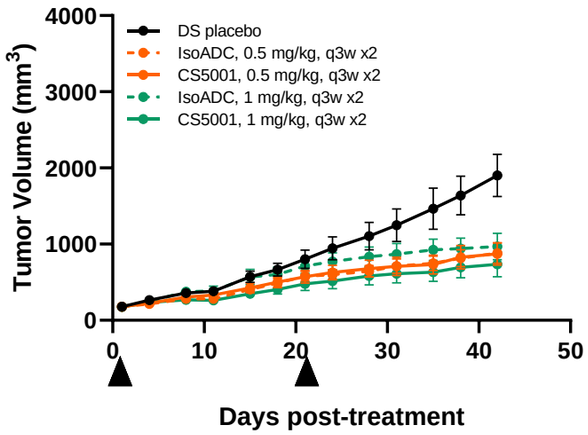
ROR1 moderate

BR1282

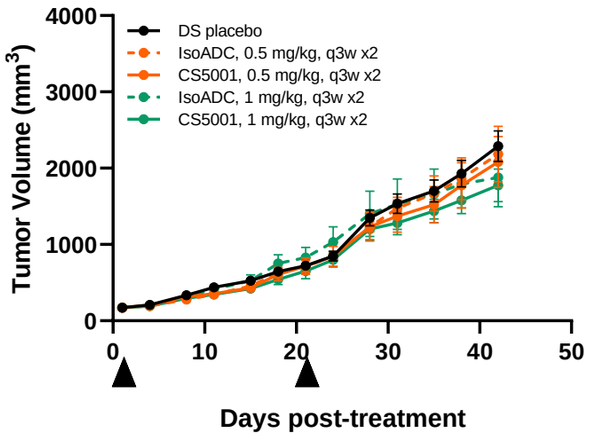


ROR1 low

BR9465



BR5010



	0.25 mg/kg		0.5 mg/kg		1 mg/kg		0.5 mg/kg		1 mg/kg		0.5 mg/kg x2		1 mg/kg x2		0.5 mg/kg x2		1 mg/kg x2	
	Iso ADC	CS 5001	Iso ADC	CS 5001	Iso ADC	CS 5001	Iso ADC	CS 5001	Iso ADC	CS 5001	Iso ADC	CS 5001	Iso ADC	CS 5001	Iso ADC	CS 5001	Iso ADC	CS 5001
CR	0	**4/8**	3/8	3/8	5/8	3/8	0	**5/6**	2/6	**6/6**	0	0	0	0	0	0	0	0
TGI (%)	75	**131**	139	129	145	142	71	**104**	104	105	59	60	54	68	5	10	30	24

CR: complete regression, defined as ≤ 13.5 mm^3 for three consecutive measurements ; TGI: tumor growth inhibition

PDX *in vivo* efficacy data integration – ROR1 expression vs. efficacy vs. dose

Lower requirement on ROR1-expression at higher dose for meaningful target-dependent efficacy

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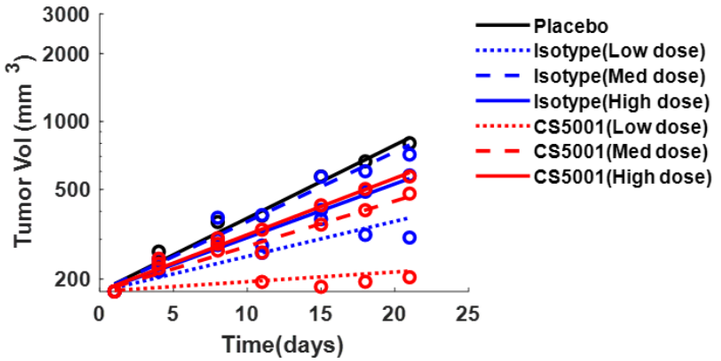
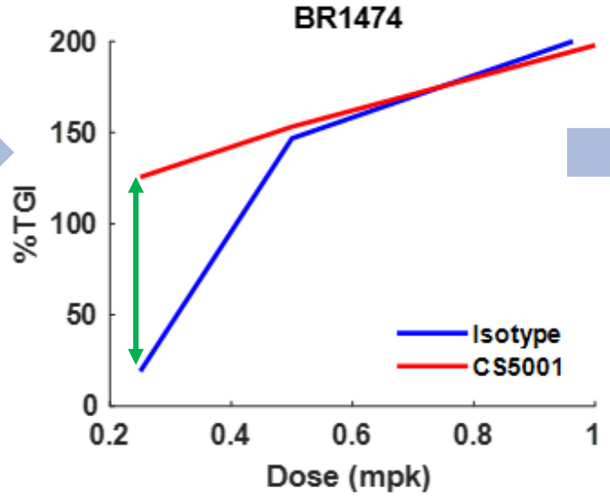
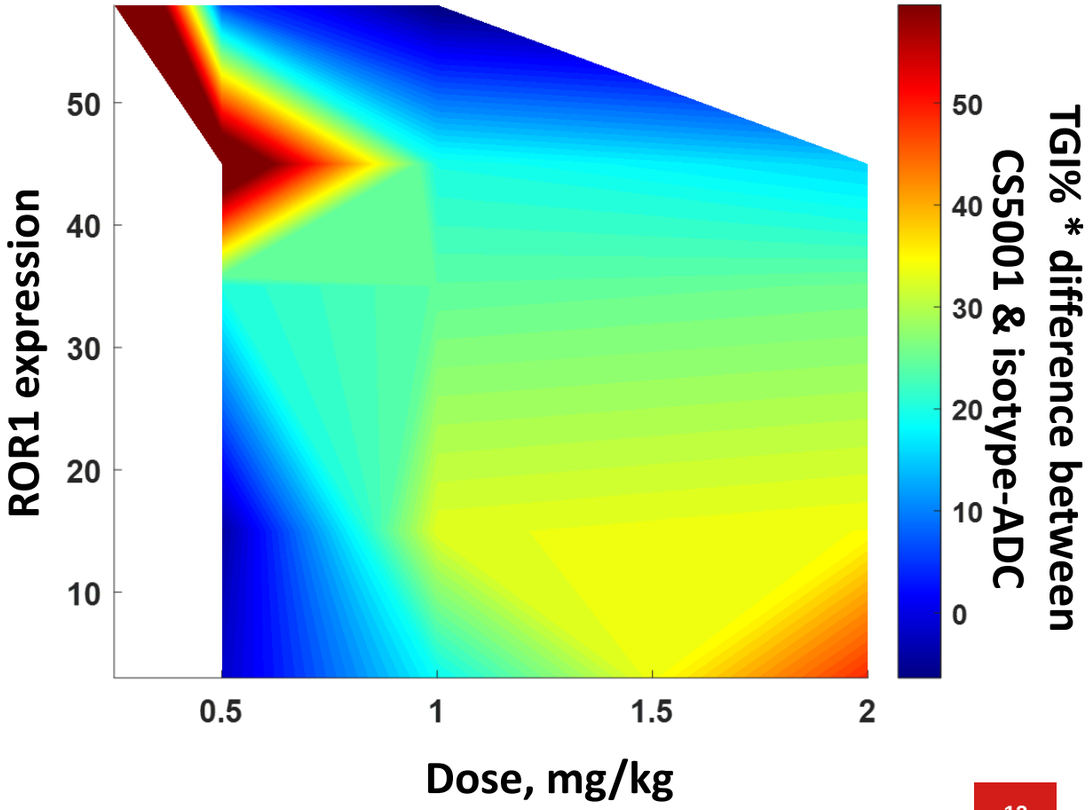
%TGI* – defined using the tumor growth rate of 21-day tumor profile



Target-dependent efficacy – using %TGI difference between CS5001 & Isotype ADC



ROR1 expression vs. dose vs. Target-dependent efficacy



$$\%TGI = \frac{kgexp_{vehicle} - kgexp\_CS5001(or\ Isotype)}{kgexp\_vehicle}$$

CS5001 currently under Phase I clinical investigation

In both hematologic malignancies and solid tumors

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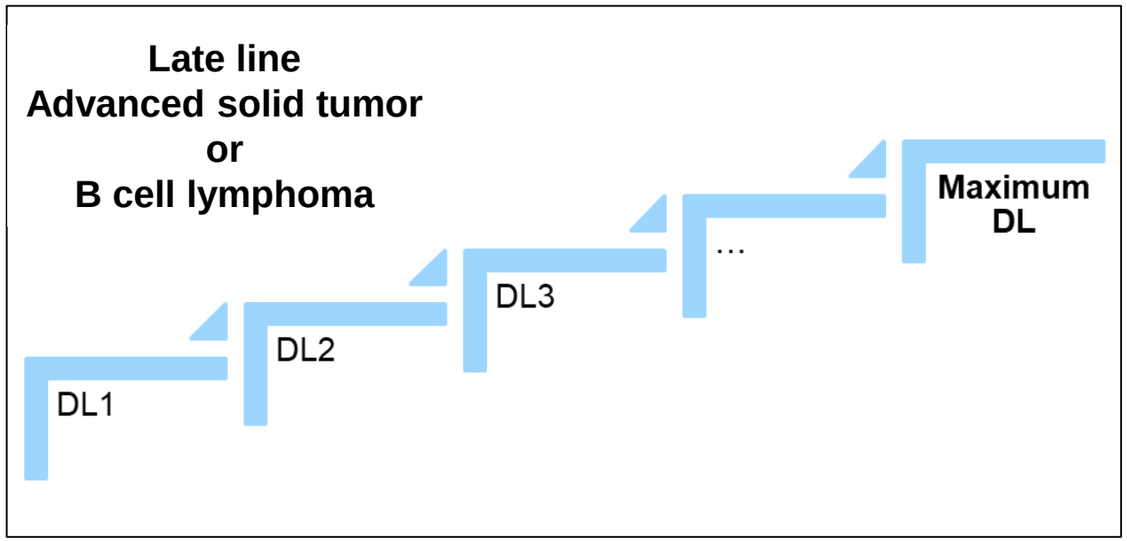
Phase 1a Dose Escalation



RP2D

Phase 1b Dose Expansion

Arm A: r/r MCL, ≥ 3L

Arm B: r/r DLBCL, ≥ 3L

Arm C: advanced ROR1+ solid tumor arms including TNBC and others (NSCLC, Ovarian, Gastric, etc)

Phase I ongoing in US, Australia, and China

Summary

- ROR1 is an ADC target for both hematological malignancies and solid tumor
- CS5001 is a ROR1 ADC designated to maximize ROR1-mediated tumor cell killing with an ultra-potent PBD payload
- CS5001 showed potent and ROR1-dependent *in vitro* cytotoxicity and *in vivo* efficacy against various mouse xenografts of solid tumors, demonstrating potential as a therapeutic for human solid tumors
- ROR1 expression can a potential predictive biomarker for CS5001 and will be further investigated in the ongoing PhI study

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