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# MOLECULAR TARGETS AND CANCER THERAPEUTICS

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## **CS5001, a novel ROR1-targeting antibody drug conjugate (ADC) armed with tumor-cleavable $\beta$ -glucuronide linkers and pyrrolobenzodiazepine (PBD) prodrugs for hematological and solid malignancies**

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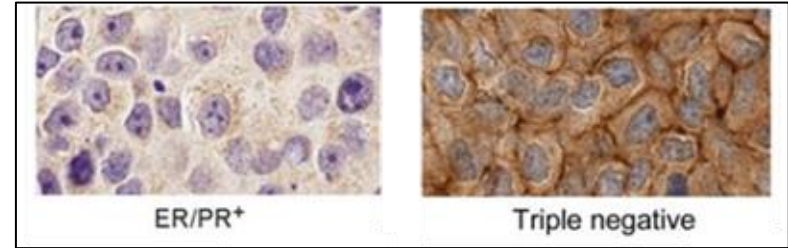
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## Archie N.Tse

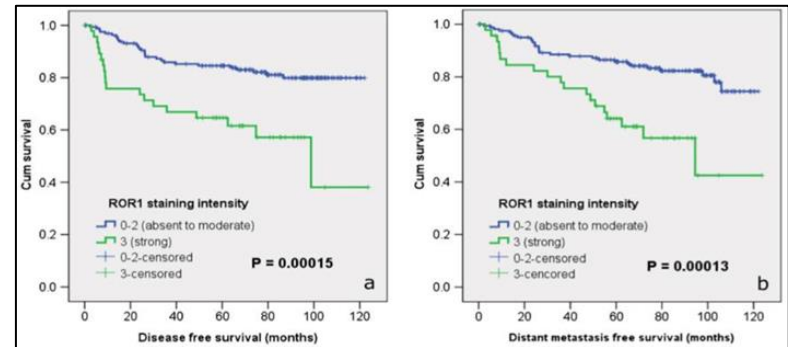
- I have the following financial relationships to disclose
  - Stockholder in: CStone Pharmaceuticals
  - Employee of: CStone Pharmaceuticals
  
- I will not discuss off label use and/or investigational use in my presentation

# Receptor Tyrosine Kinase-Like Orphan Receptor 1 (ROR1)

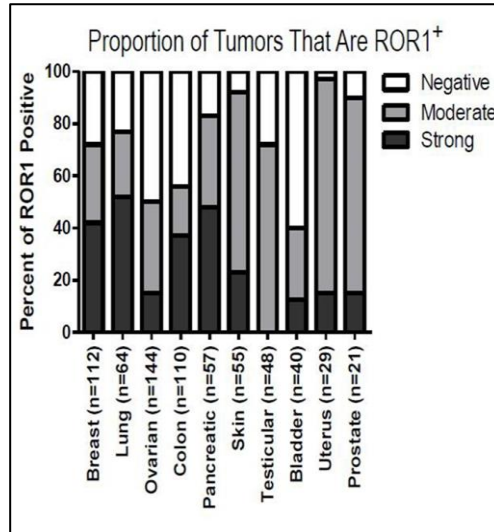
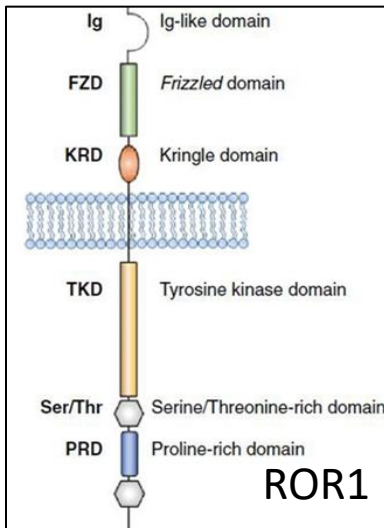
- Broad expression of ROR1 in both solid and hematological malignancies (TNBC, lung cancer, pancreatic cancer, CLL, MCL, etc.)
- Largely absent from normal blood lymphocytes and adult tissues



High expression in TNBC



ROR1 expression confers a poor prognosis in TNBC



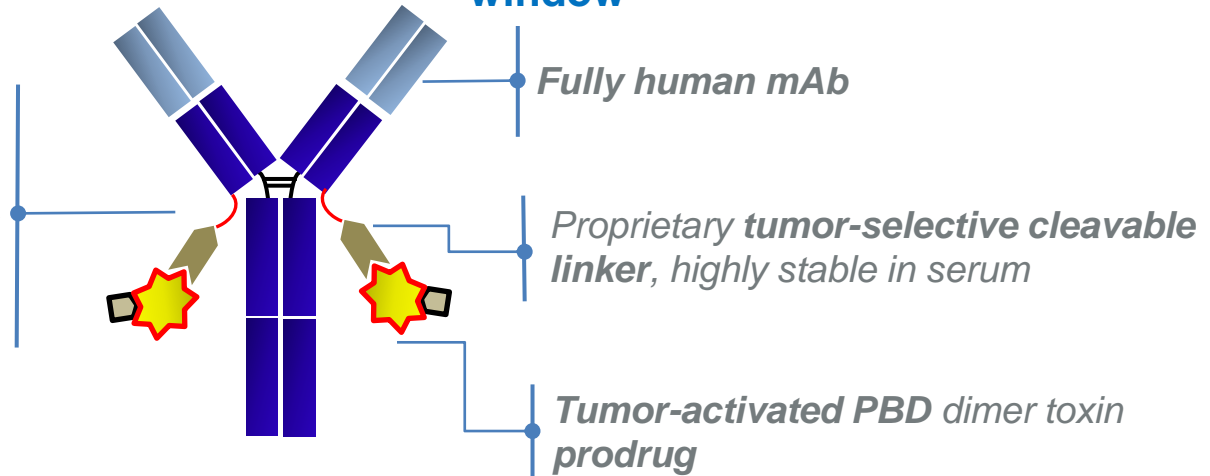
(2012) Am J Pathol 181(6)1903-10 (2012) PLoS One 7(3)e31127

# CS5001: Potentially FIC/BIC ROR1 ADC with differentiated features

Potentially **wider therapeutic window**

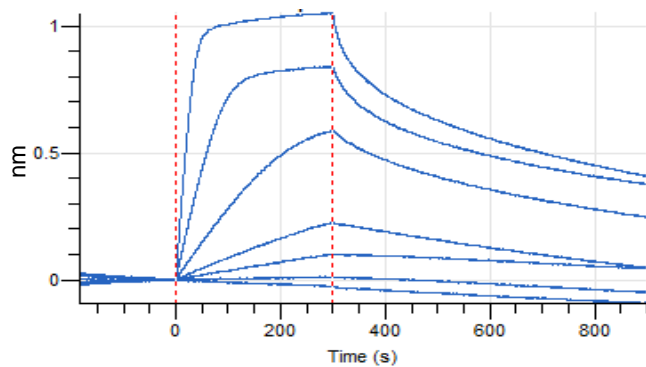
**Controllable quality and production**

Site-specific conjugation for a **homogeneous drug antibody ratio (“DAR”)** (**DAR=2**)

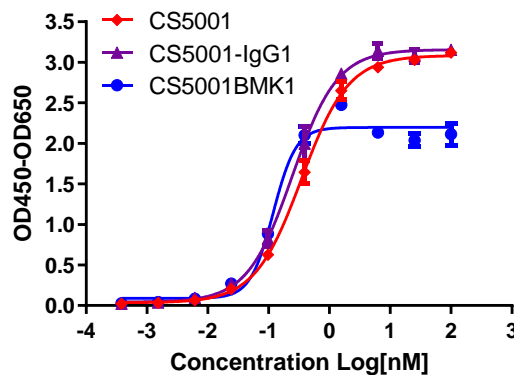


# CS5001 potently binds to human ROR1 but not ROR2

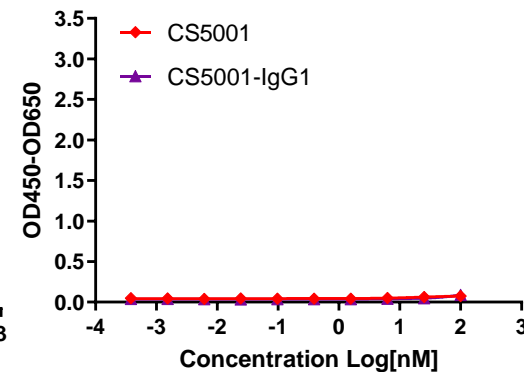
Human ROR1



Human ROR1



Human ROR2



Sample	ka (1/Ms)	kd (1/s)	KD (M)
CS5001	1.59E+06	2.19E-03	1.38E-09

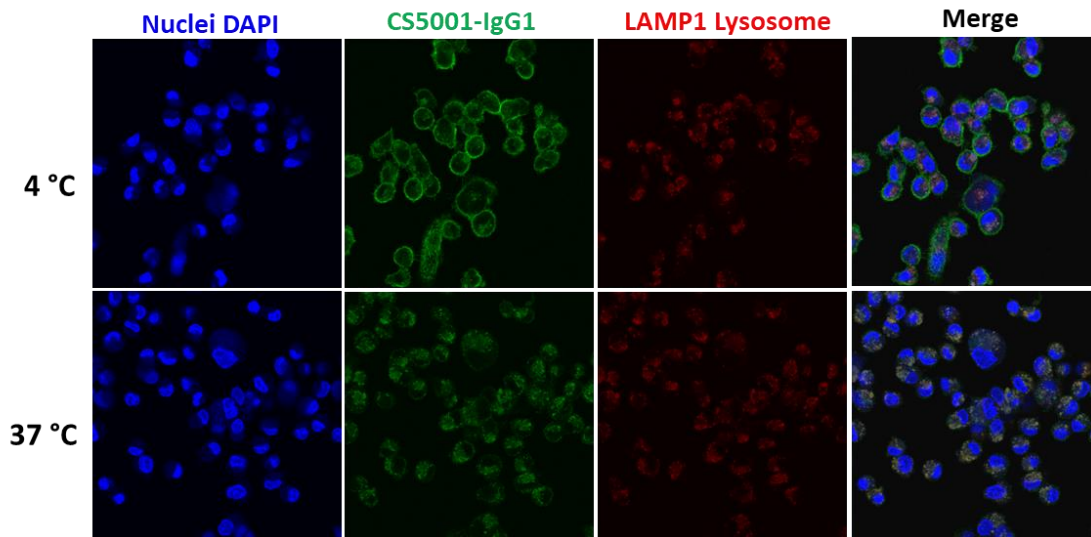
	Human ROR1	Human ROR2
CS5001 (EC <sub>50</sub> , nM)	0.347	No binding
CS5001-IgG1 (EC <sub>50</sub> , nM)	0.245	No binding
CS5001BMK1 (EC <sub>50</sub> , nM)	0.119	-

CS5001-IgG1: mAb of CS5001

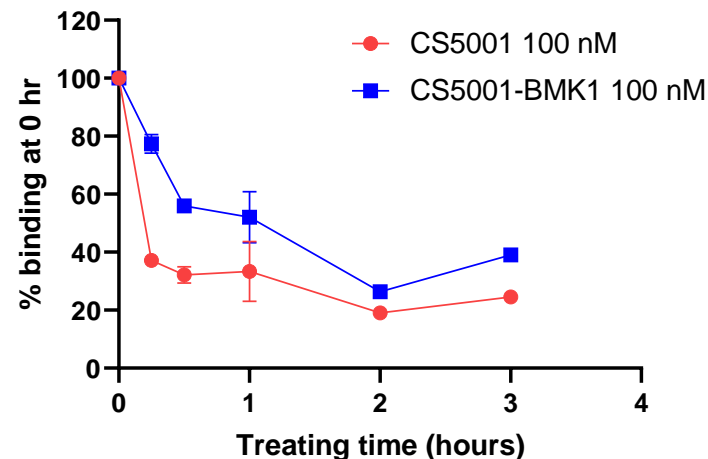
CS5001-BMK1: benchmark, an MMAE-based ROR1 ADC

# Rapid internalization of CS5001 by ROR1-expressing cells

## Internalization and intracellular trafficking of CS5001-IgG1

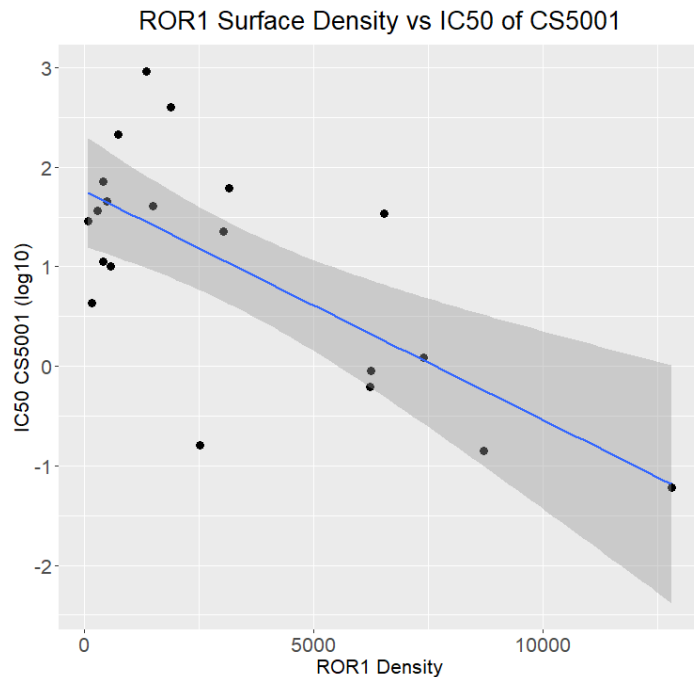


## Internalization of CS5001



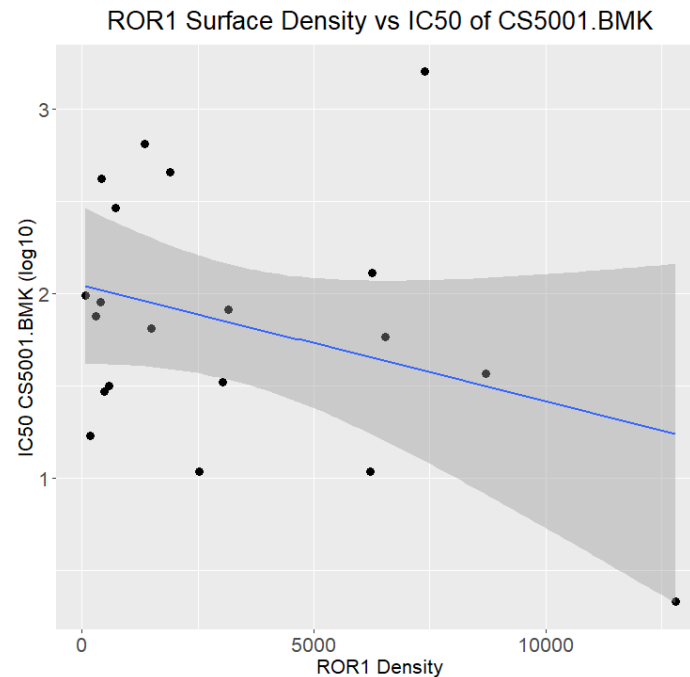
MDA-MB-231 cells were treated with ROR1 mAb or ADC at 4°C or 37°C and were examined using confocal microscope or flowcytometry.

# ROR1 surface density correlates with sensitivity to CS5001 in a 20-cell line panel



Rho = -0.465, P = 0.0405

R = -0.697, P = 0.000640



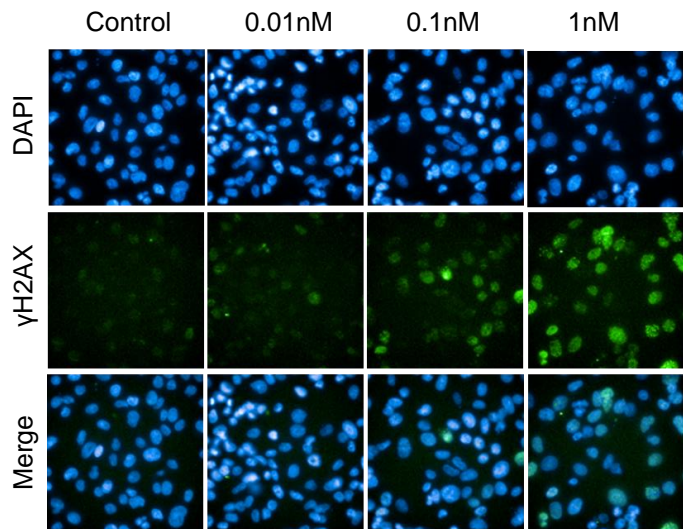
Rho = -0.139, P = 0.56

R = -0.326, P = 0.16

*In vitro* cytotoxicity was evaluated by CellTiter-Glo (CTG) assay after a 6-day continuous exposure of ADCs in 20 human cancer cell lines.

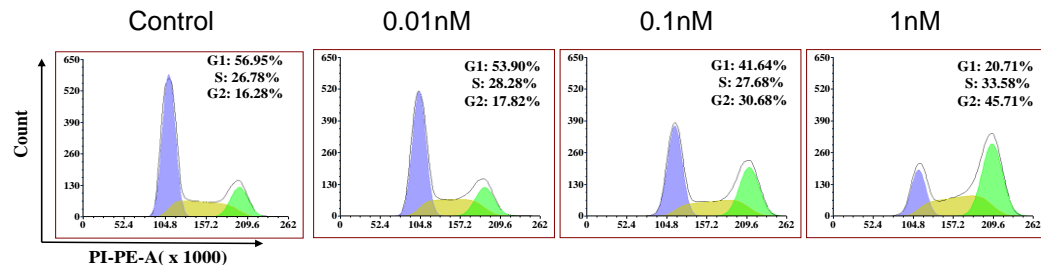
# CS5001 potently induces DNA damage, G2-M cell cycle arrest, and apoptosis

## DNA damage

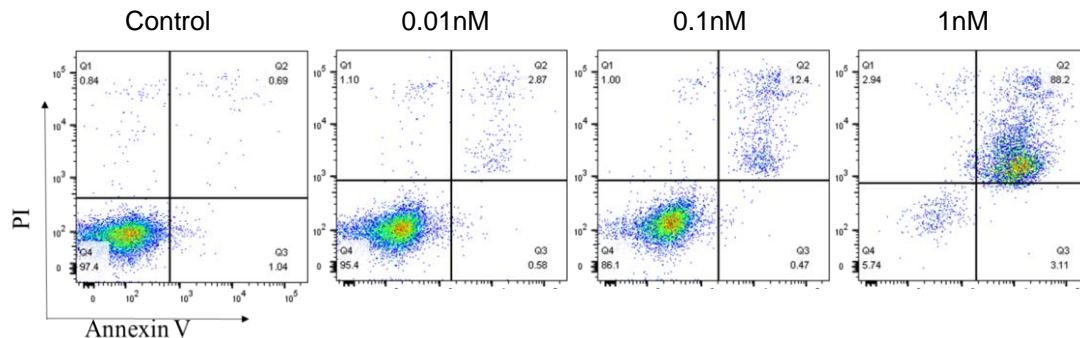


γH2AX: a DNA damage response biomarker

## G2-M cell cycle arrest

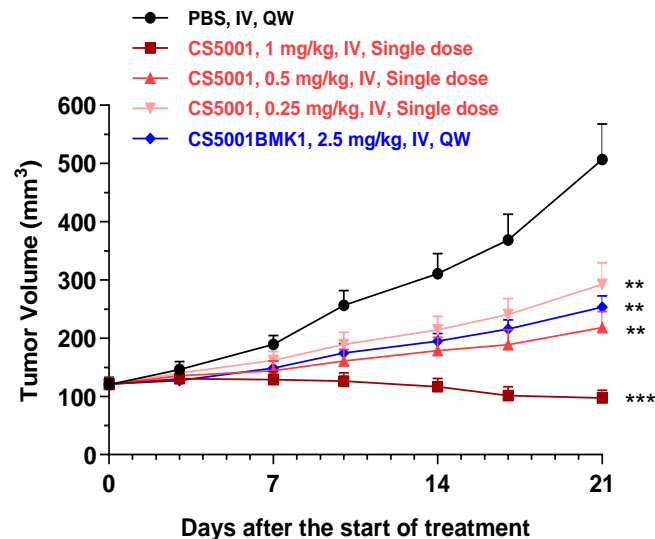
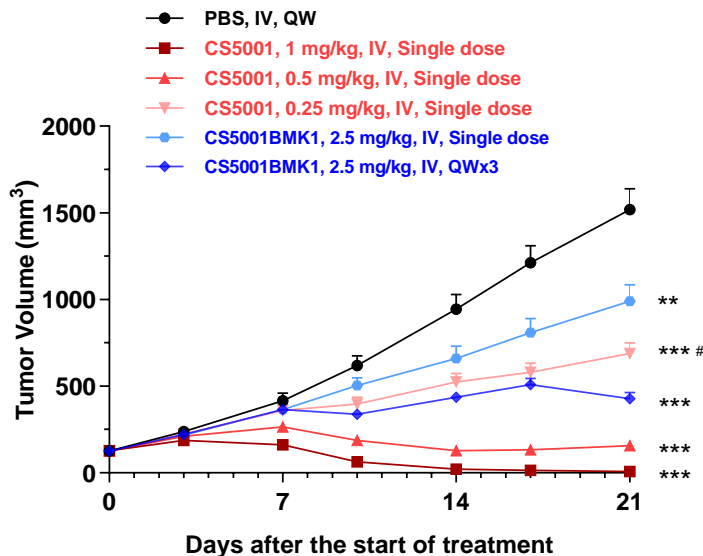


## Apoptosis induction





# In vivo efficacy of CS5001 in Jeko1 (MCL) and MDA-MB-231 (TNBC) xenografts



Treatment	TGI %	CR
CS5001, 1 mg/kg, Single dose	109	2/8
CS5001, 0.5 mg/kg, Single dose	98	0/8
CS5001, 0.25 mg/kg, Single dose (1/20 MTD)	60	0/8
CS5001BMK1, 2.5 mg/kg, Single dose (1/20 MTD)	38	0/8
CS5001BMK1, 2.5 mg/kg, QWx3	78	0/8

Treatment	TGI %
CS5001, 1 mg/kg, Single dose	106
CS5001, 0.5 mg/kg, Single dose	75
CS5001, 0.25 mg/kg, Single dose	55
CS5001BMK1, 2.5 mg/kg, QWx3	68

Note: p<0.01, \*\*\*, p<0.001 vs PBS; #, p<0.05, vs CS5001BMK1 single dose; MCL, mantle cell lymphoma; TGI: tumor growth inhibition; CR: complete regression is defined as  $\leq 13.5 \text{ mm}^3$  for three consecutive measurements.

# Conclusion

- CS5001 exhibits potent and selective cytotoxicity to a variety of ROR1-expressing cell lines and shows remarkable *in vivo* antitumor activity
- ROR1 cytometric density predicts sensitivity to CS5001 *in vitro*
- CS5001 is a promising therapeutic candidate for ROR1-expressing hematological and solid malignancies with precision medicine potential

# Thanks!