Innovative B7H4 x CD3 & B7H4 x 4-1BB Bispecifics for Solid Tumor Therapies

Musheng Bao, Ph.D.

Harbour BioMed

HBM HOLDINGS-B: 02142.HK

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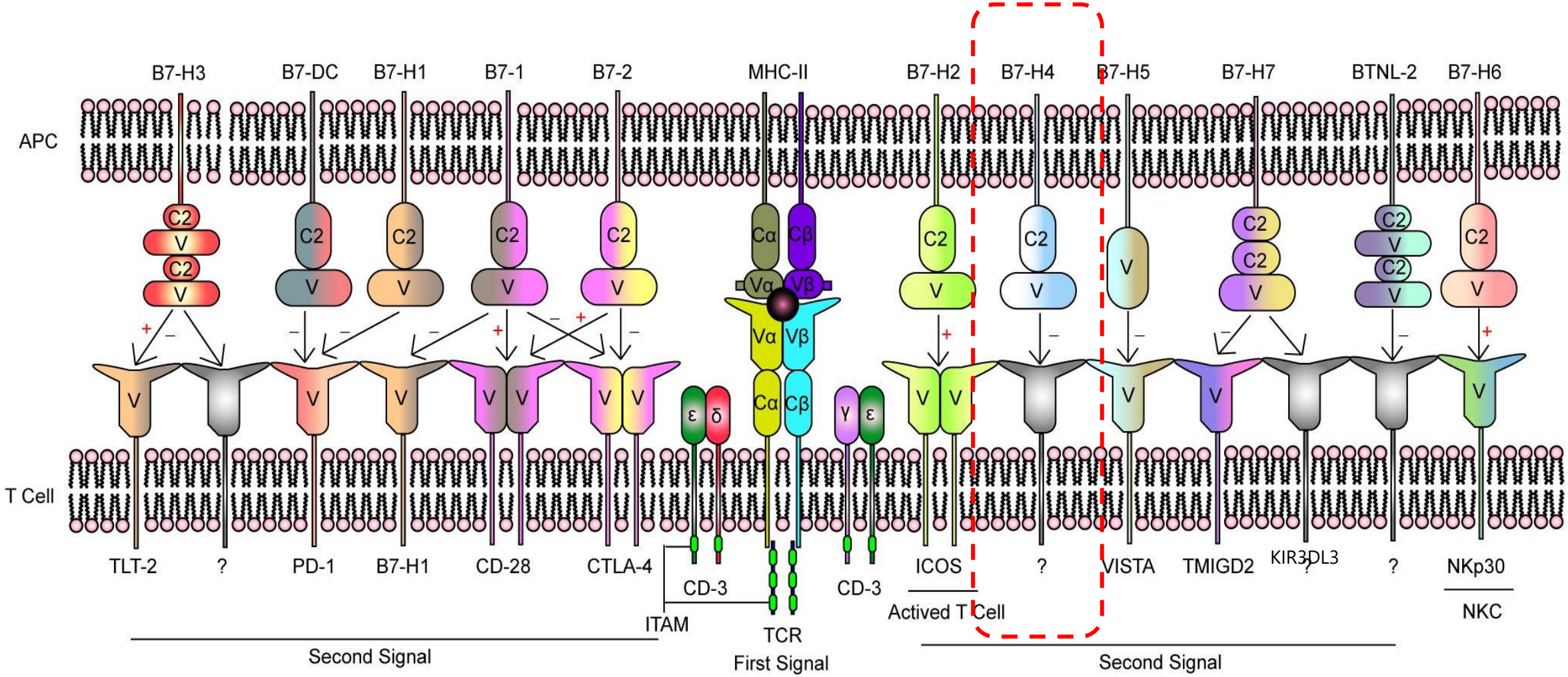
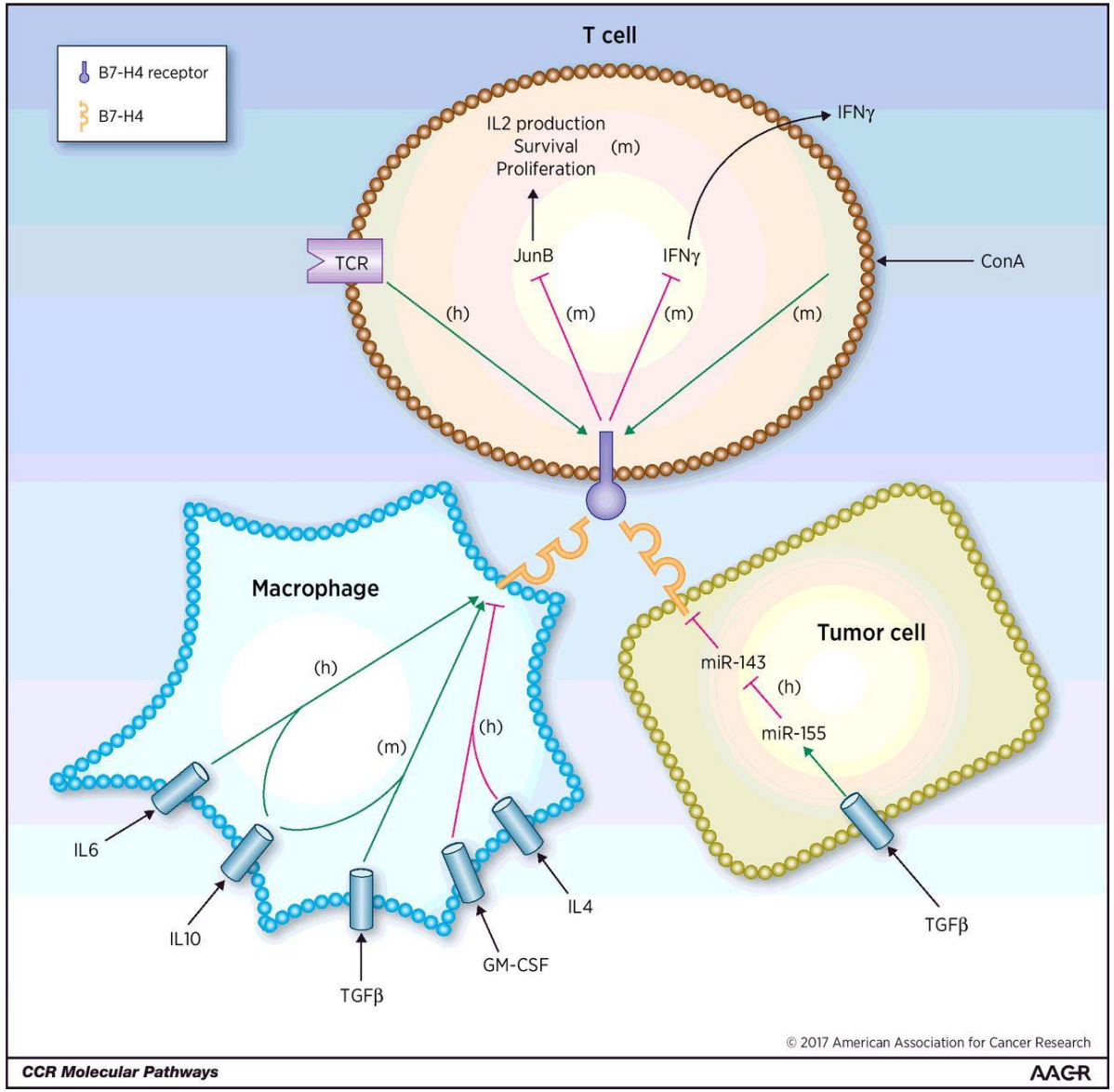
B7 family molecules



Front Immunol. 2020; 11: 458

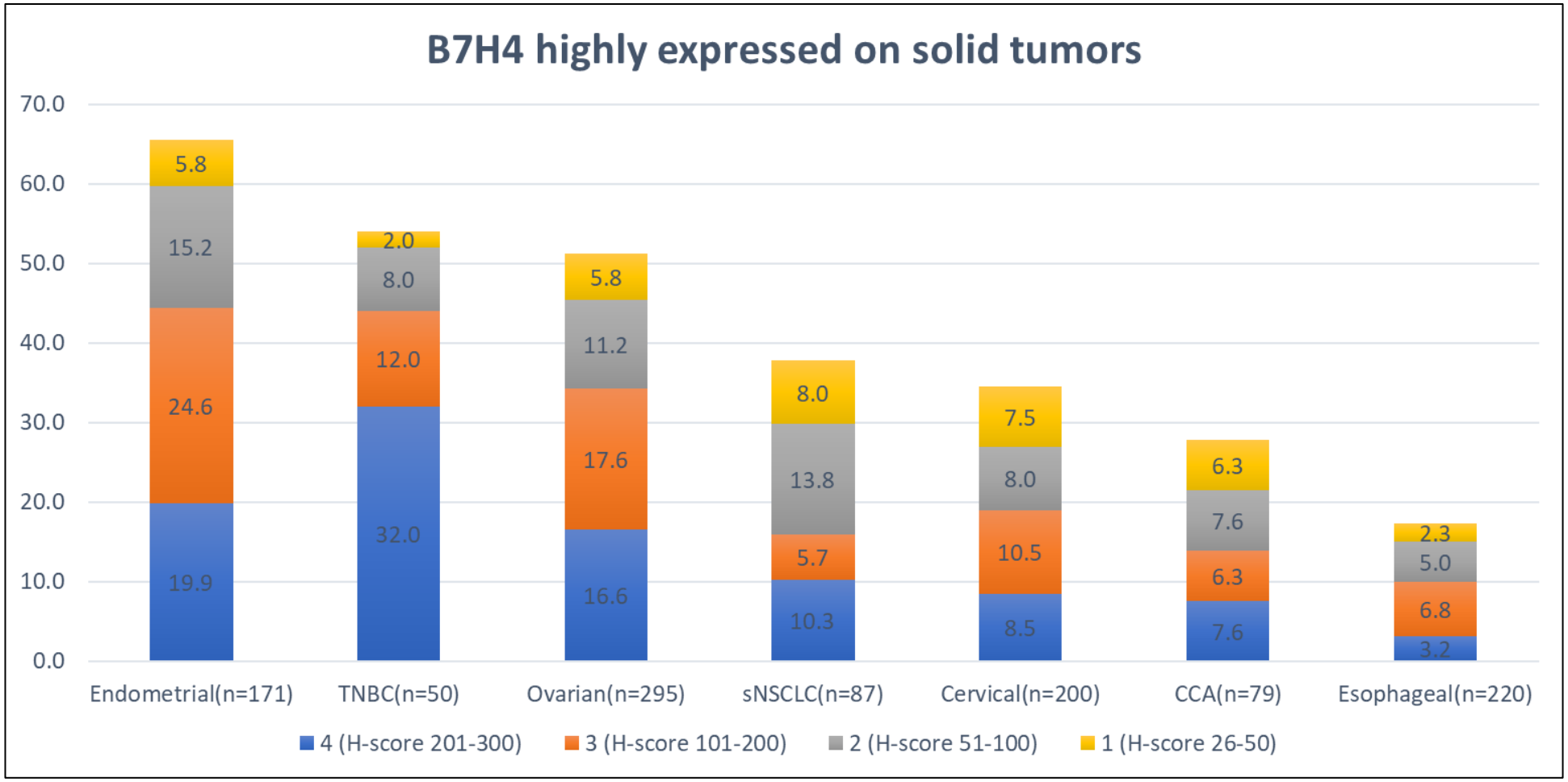
B7H4 acts as both a TAA and an immune checkpoint



- B7H4 is highly expressed on tumor cells and tumor associated macrophages.
- B7-H4 inhibits immune responses via unknown receptor(s) on T cells.
- Mutually exclusive expression of B7H4 and PDL1

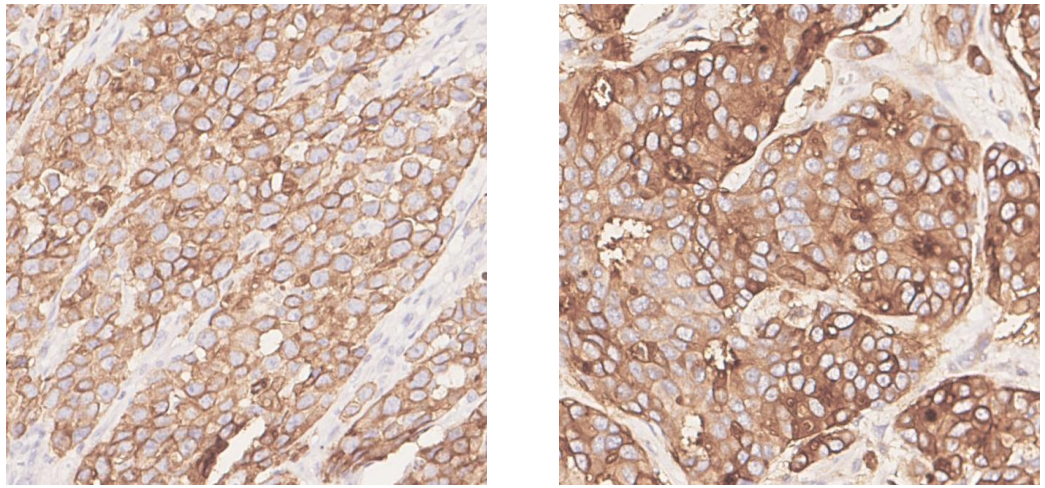
Clin Cancer Res. 2017 Jun 15;23(12):2934-2941

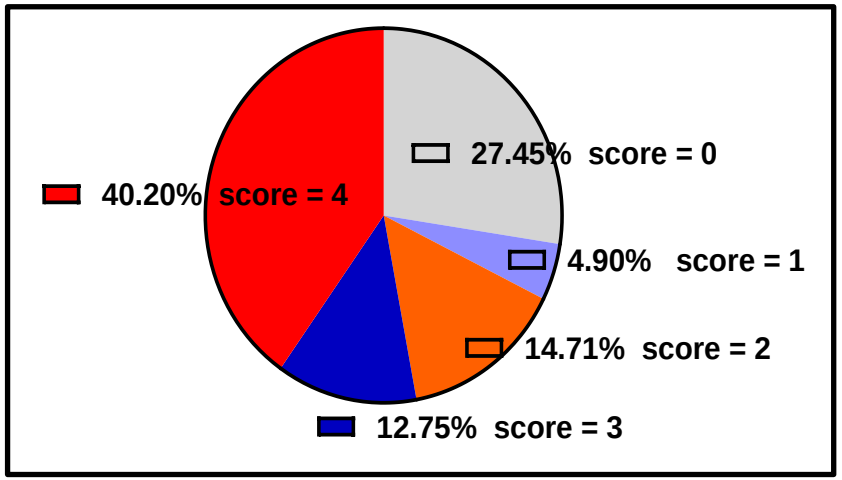
B7H4 is highly expressed in multiple solid tumors

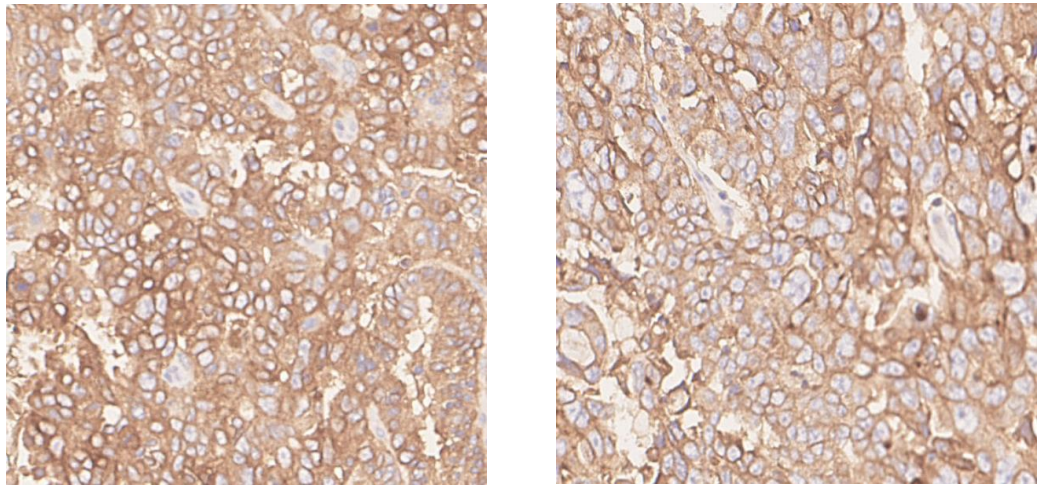


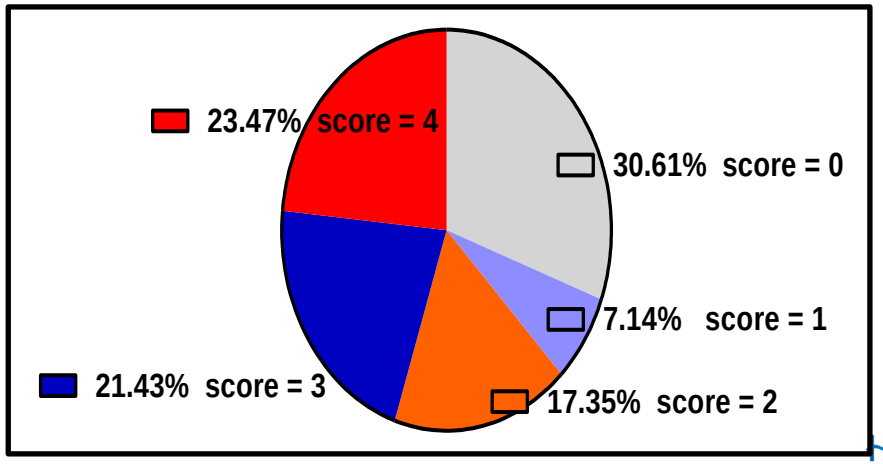
B7H4 is highly expressed in breast and endometrial cancers

Breast Cancer	Endometrial Cancer









B7-H4 exhibits mutually exclusive expression pattern with PD-L1

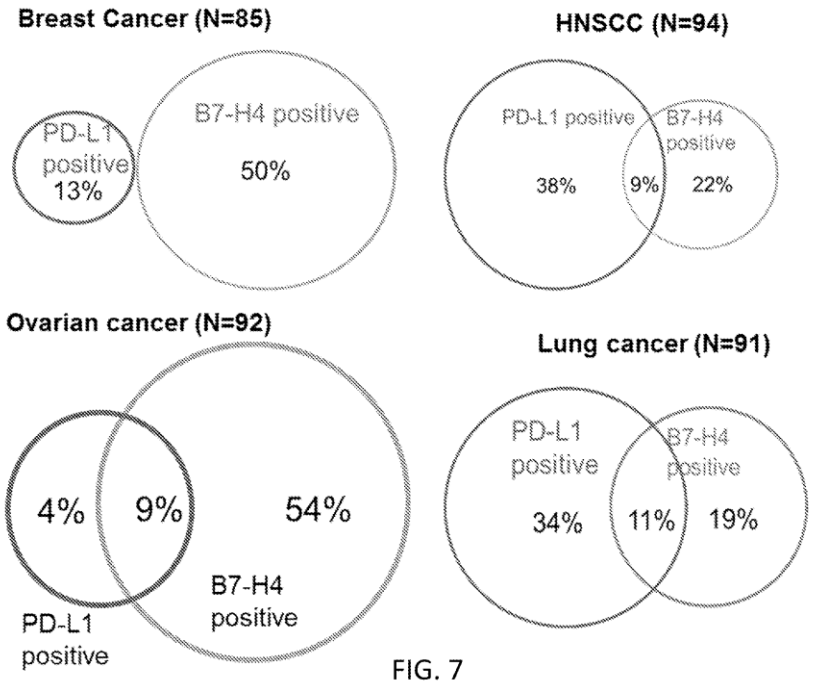


FIG. 7

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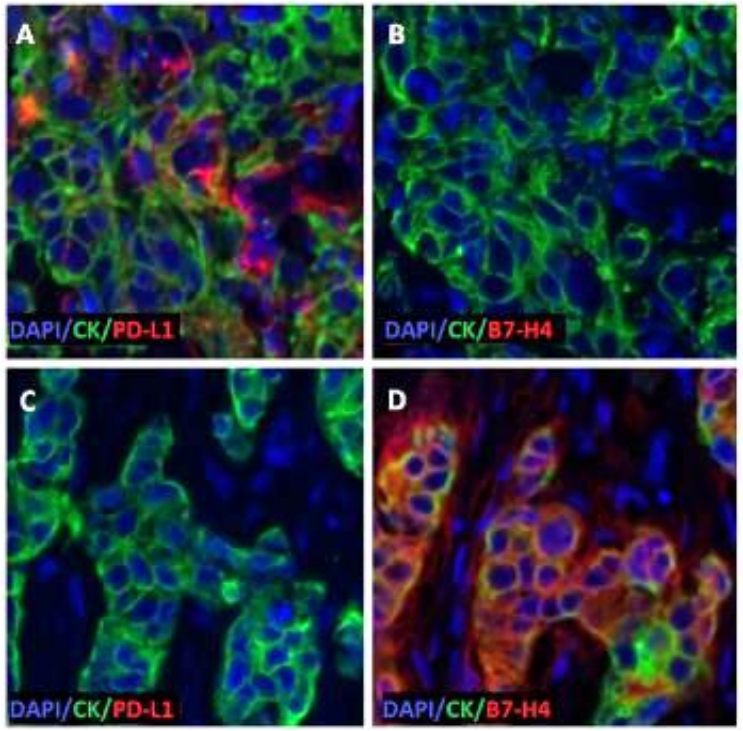


NPJ Breast Cancer (2018) 4:40

B7H4 and 4-1BB fully human antibodies generation: Harbour Mice®

H2L2
(traditional antibodies)

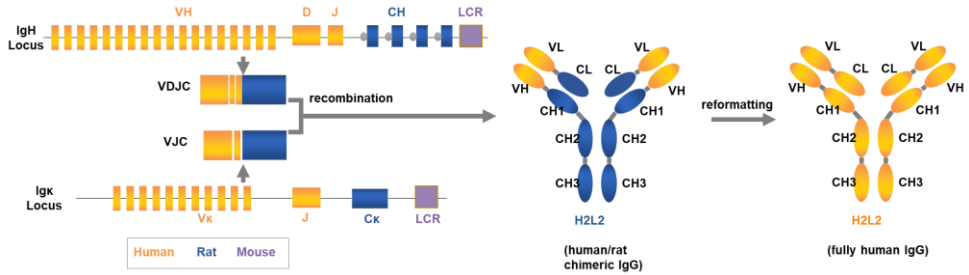
150 KDa

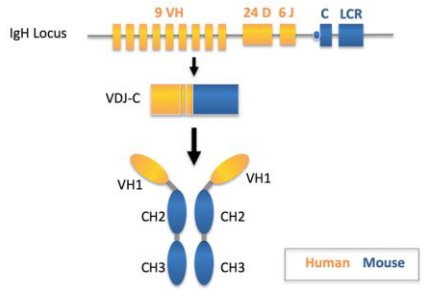
B7H4

HCAb
(**H**eavy **C**hain only **A**nti**b**ody)

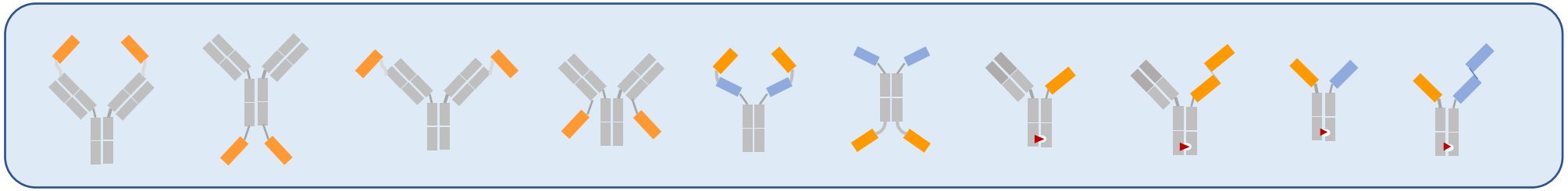
~80 KDa

- **B7H4**
- **4-1BB**

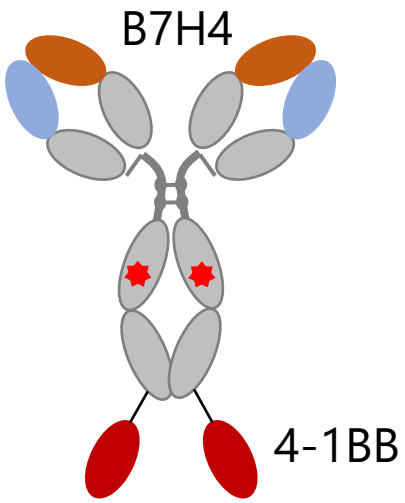




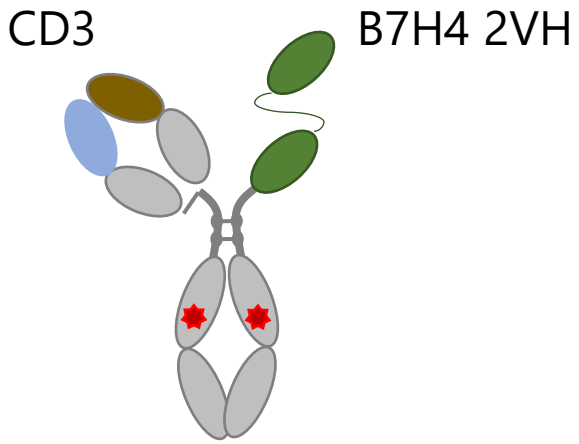
HBICE® (HCAb Based Immune Cell Engagers) platform



B7H4 x 4-1BB

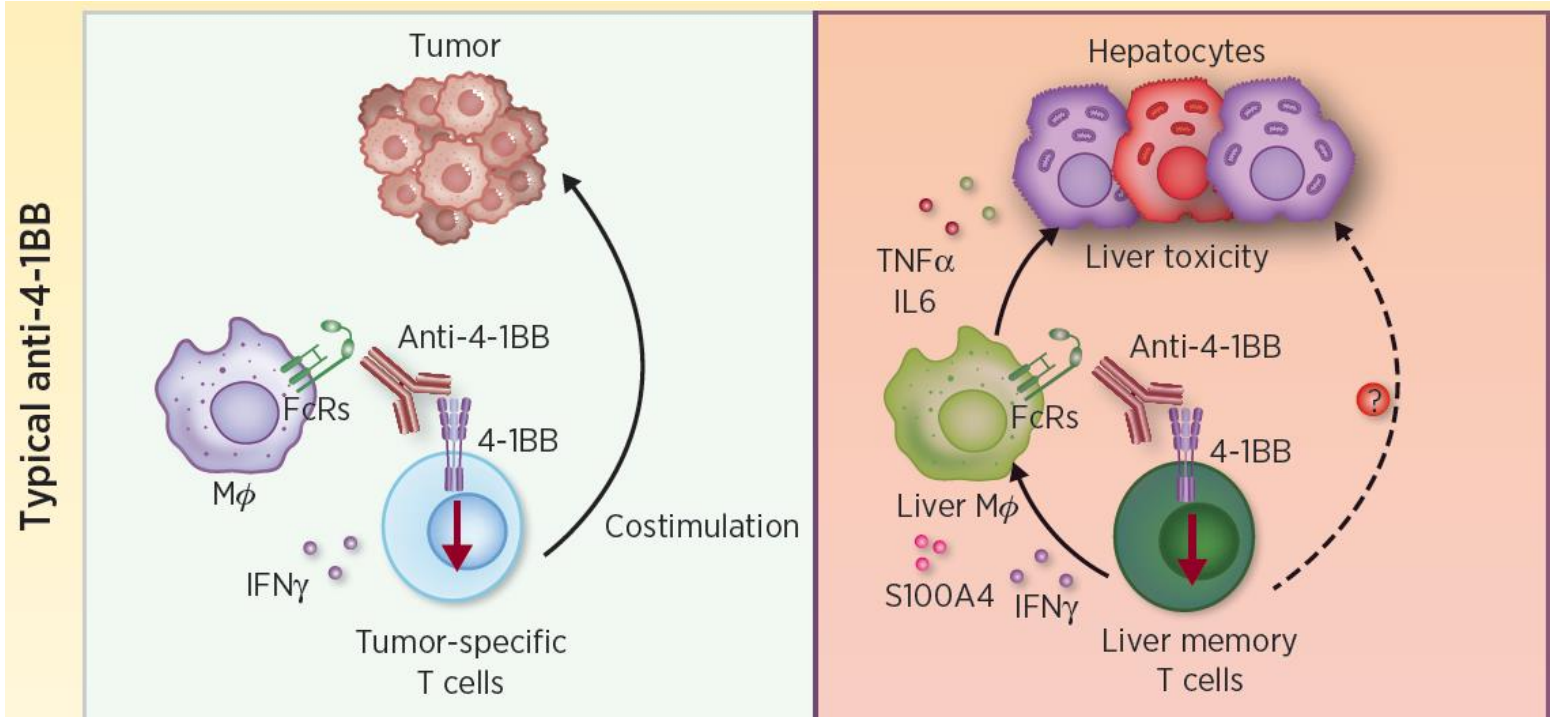


B7H4 x CD3



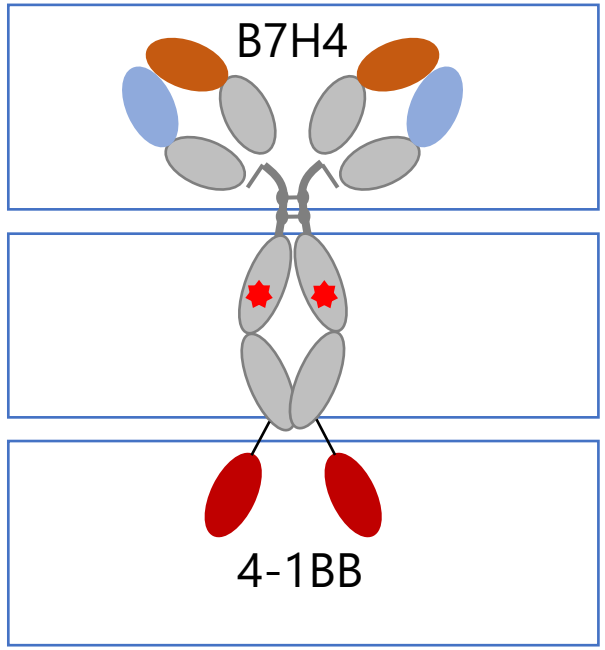
HBM7008 (B7H4 x 4-1BB)

4-1BB (CD137) is the key costimulatory molecule



	Urelumab (BMS-663513)	Utomilumab (PF-05082566)
Format	Fully human IgG4 antibody, does not block the interaction of 4-1BB with its ligand.	humanized IgG2 antibody, activates 4-1BB while blocking binding to endogenous 4-1BBL
Toxicity	MTD is 0.1 mg/kg every three weeks due to tendency to elevate transaminase level.	Up to 10 mg/kg every four weeks without hepatotoxicity
Clinical activity		in solid tumors (3.8 % Objective Response Rate (ORR)) and Merkel cell carcinoma (13.3 % ORR) as a single agent

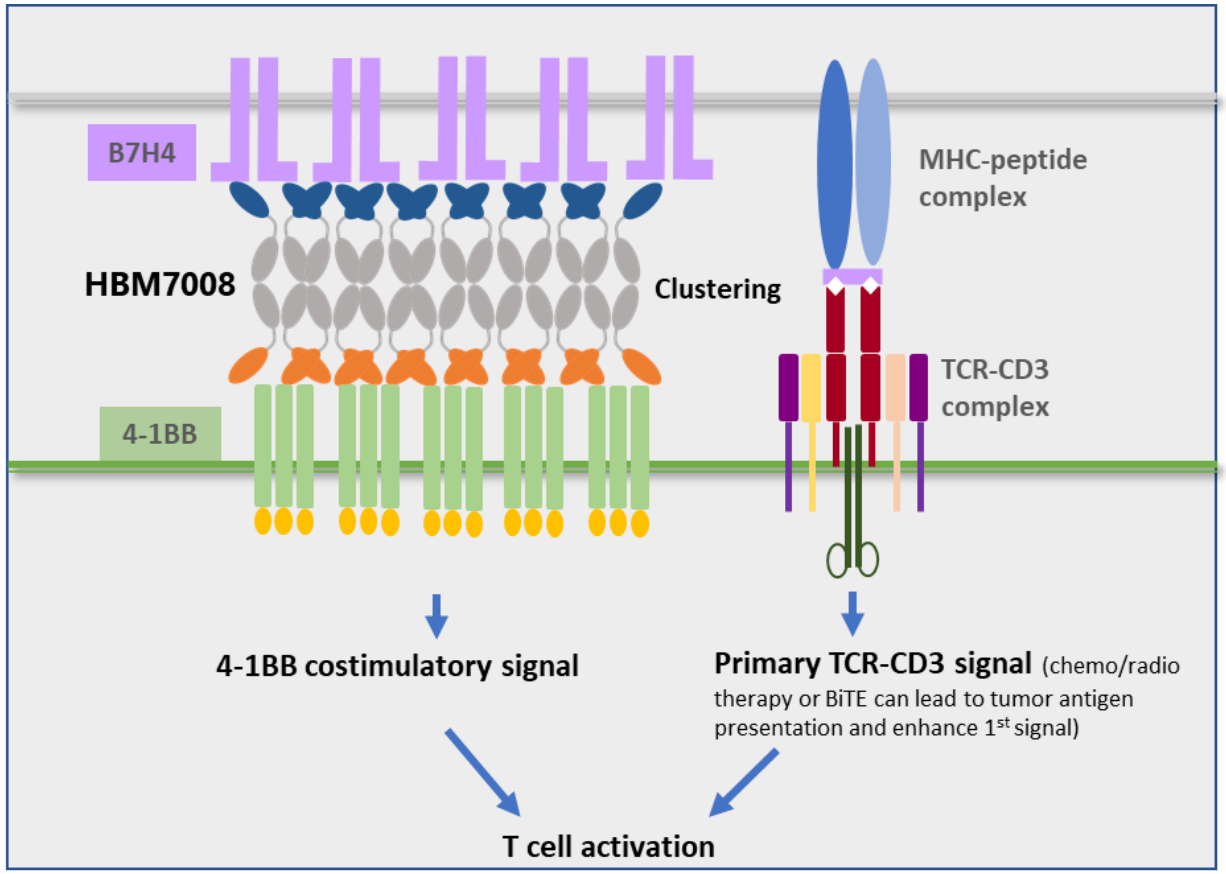
HBM7008 (B7H4 x 4-1BB) design



- High binding affinity to human B7H4
- Reduce FcγR-mediated binding
- Crosslinking dependent 4-1BB activation

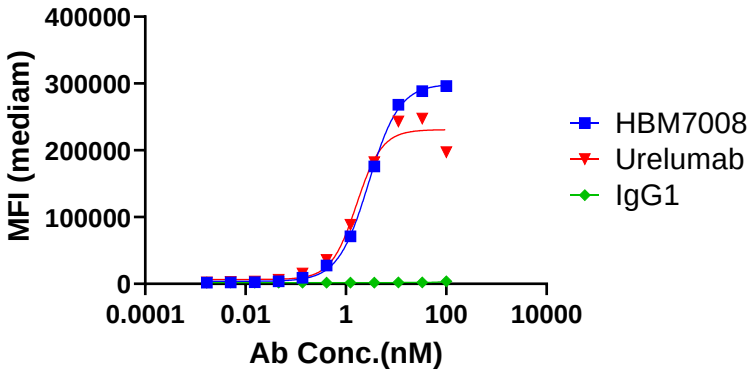
HBM7008 MOA

Selectively activate 4-1BB signaling in B7H4 positive tumor microenvironment

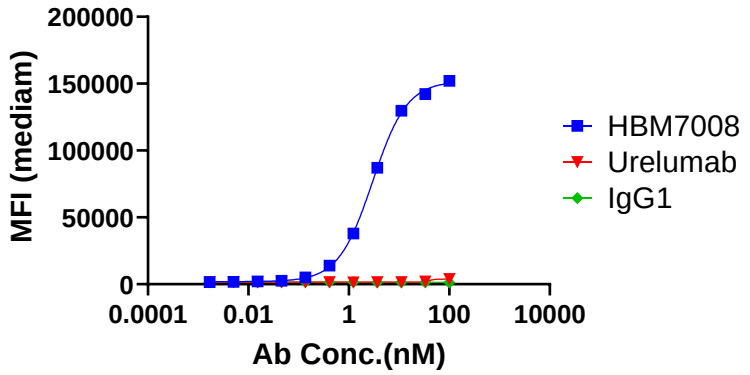


HBM7008 binds to human/cyno 4-1BB, not mouse 4-1BB

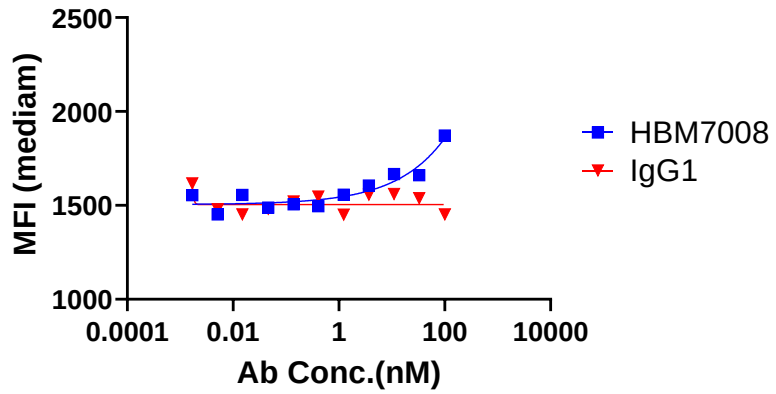
CHO-K1/h4-1BB



CHO-K1/cyno4-1BB

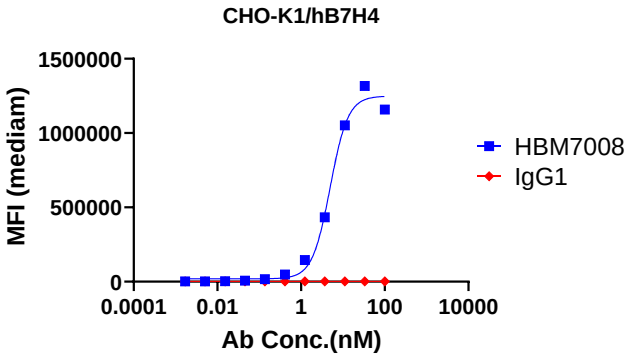


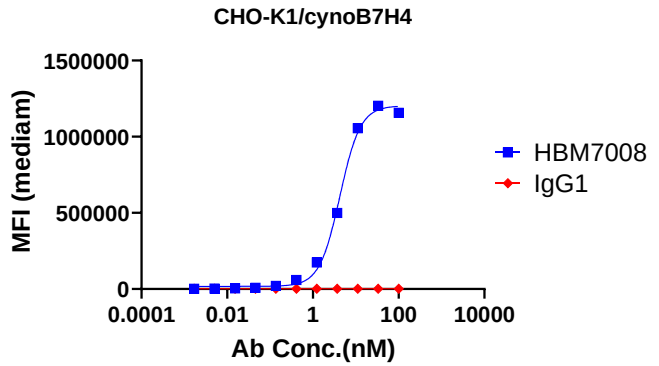
CHOK1/m4-1BB

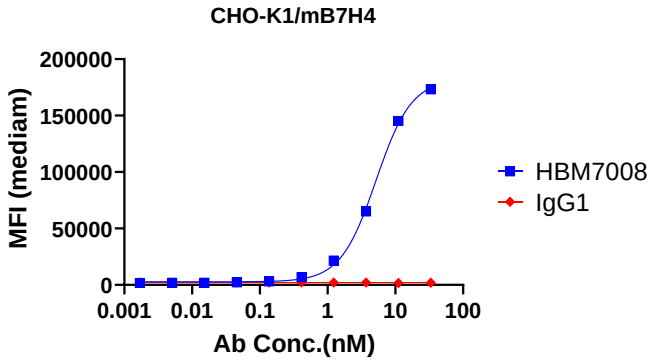


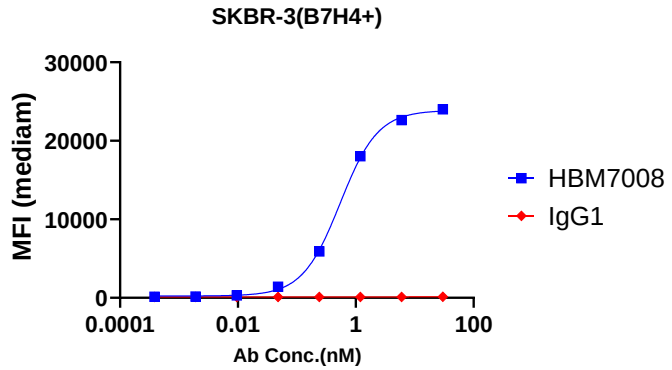
	CHO-K1/h4-1BB EC50(nM)	CHO-K1/cyno 4-1BB EC50(nM)
HBM7008	2.851	2.990

HBM7008 binds to human/cyno/mouse B7H4





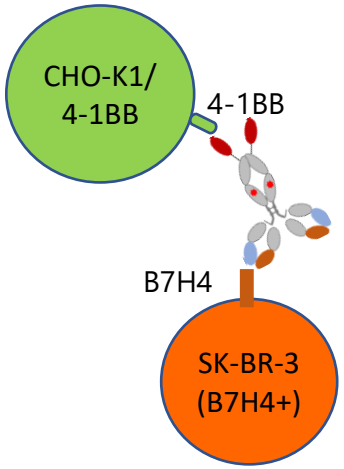


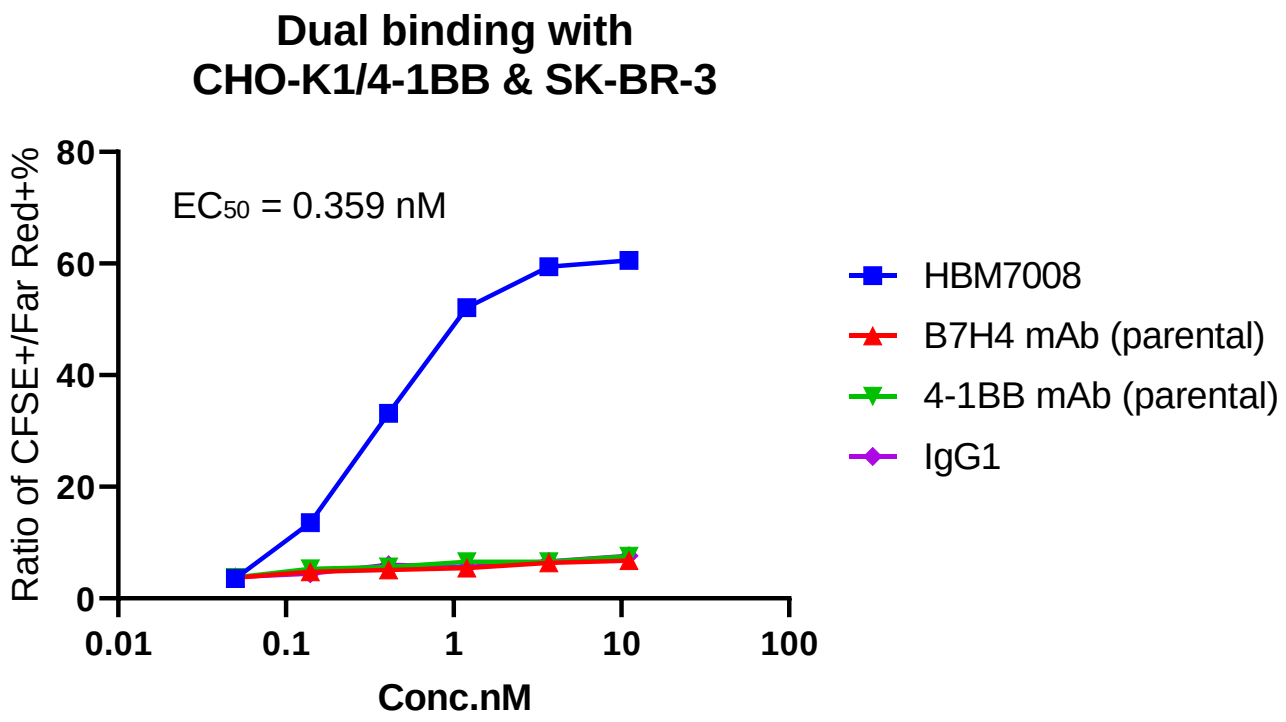


Ab Name	CHO-K1/hu B7H4 EC50(nM)	CHO-K1/cyno B7H4 EC50(nM)	CHO-K1/m B7H4 EC50(nM)	SKBR3 EC50(nM)
HBM7008	4.961	4.272	5.192	0.5444

HARBOUR BIOMED

HBM7008 engages 4-1BB expressing cells & B7H4 expressing cells

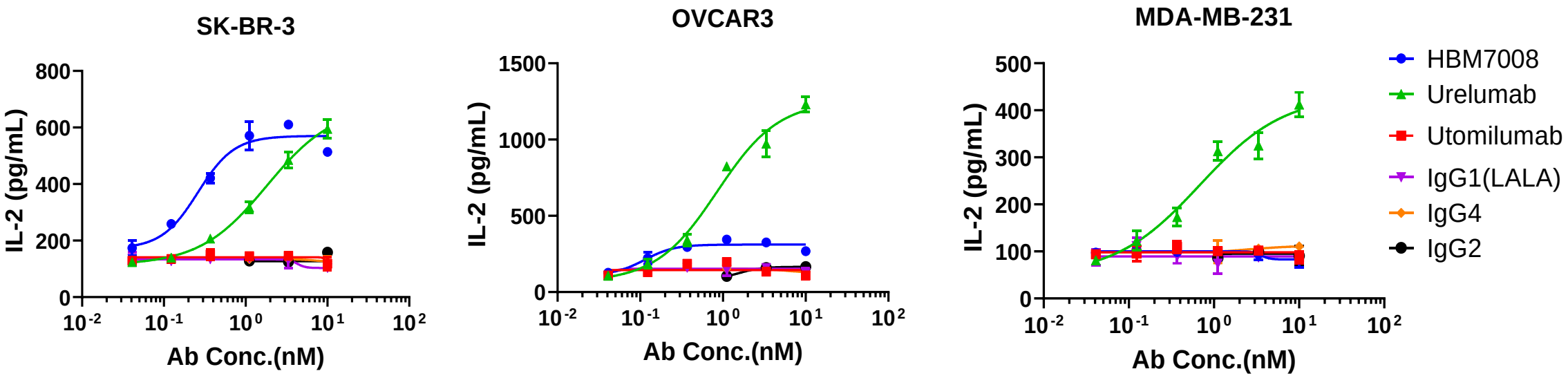




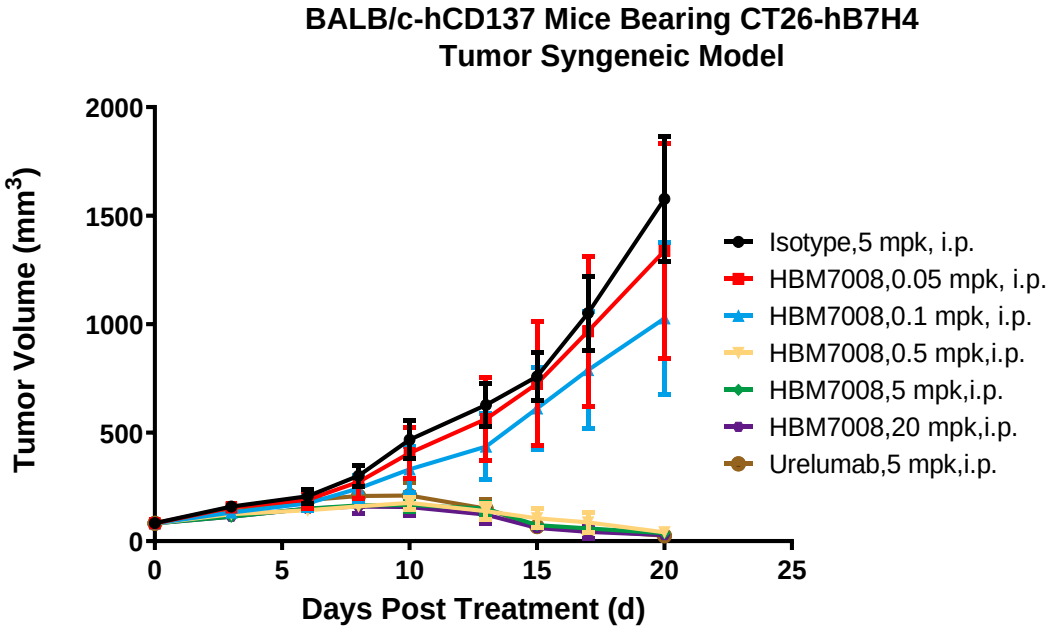
Dual binding data suggests that B7H4x4-1BB can engage T cells to tumor cells.

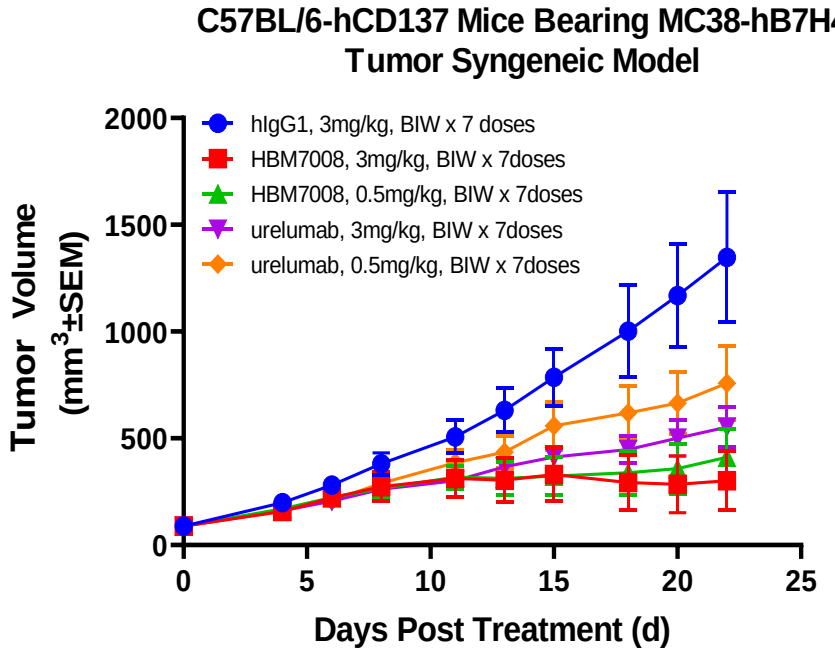
HBM7008 Activates Human T Cells in a B7H4 Crosslinking Dependent Manner

B7H4 ++	B7H4 +	B7H4 -



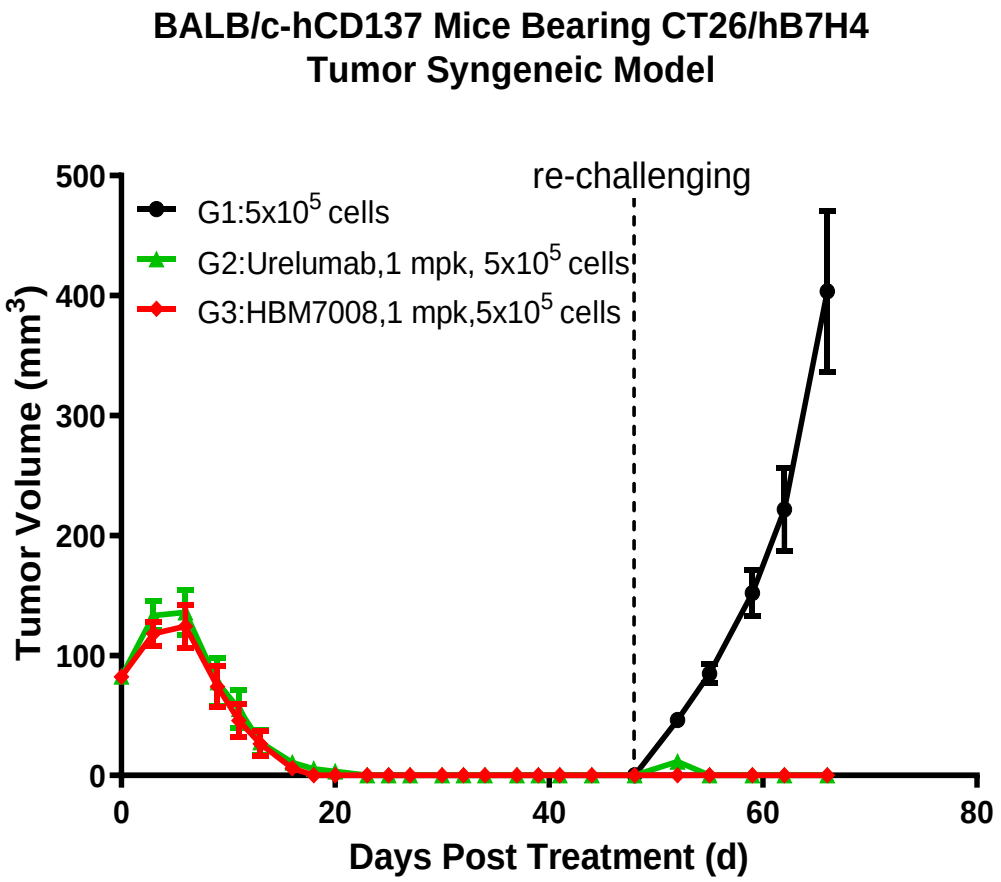
HBM7008 Shows Potent in vivo Anti-tumor Efficacy



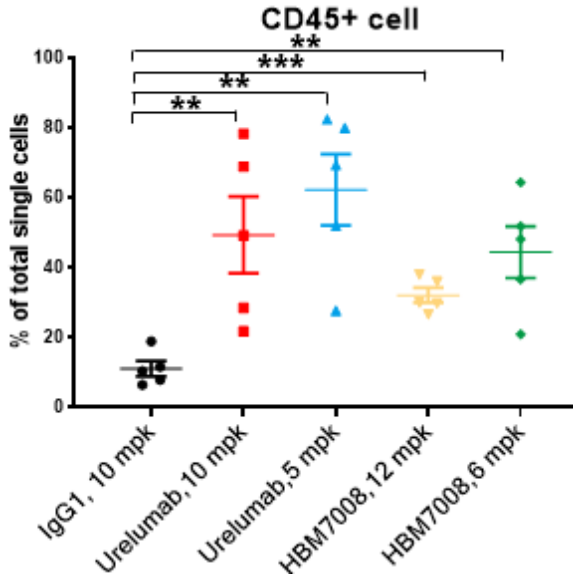


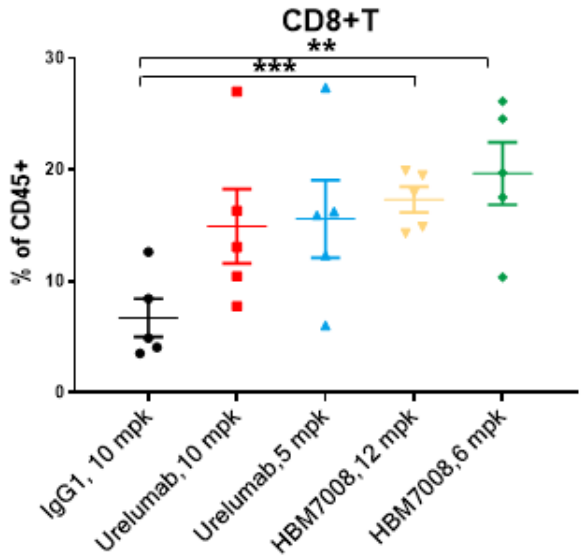
HARBOUR BIOMED

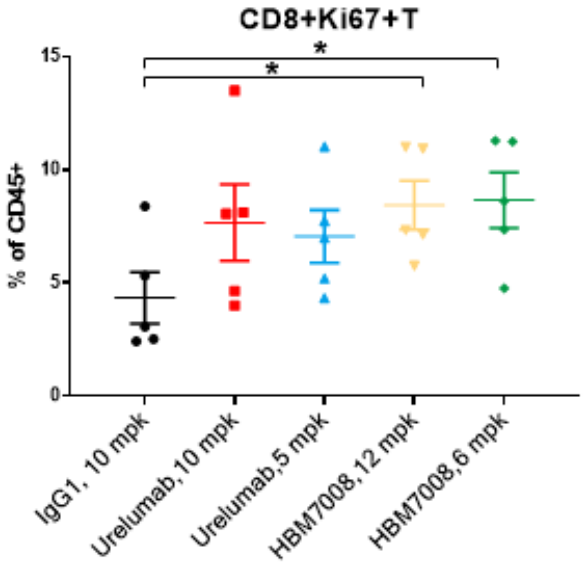
Mice Treated With HBM7008 Developed Long-Lasting Antitumor Immunity



HBM7008 significantly increased infiltration of lymphocytes and proliferation of CD8+T cells in TME



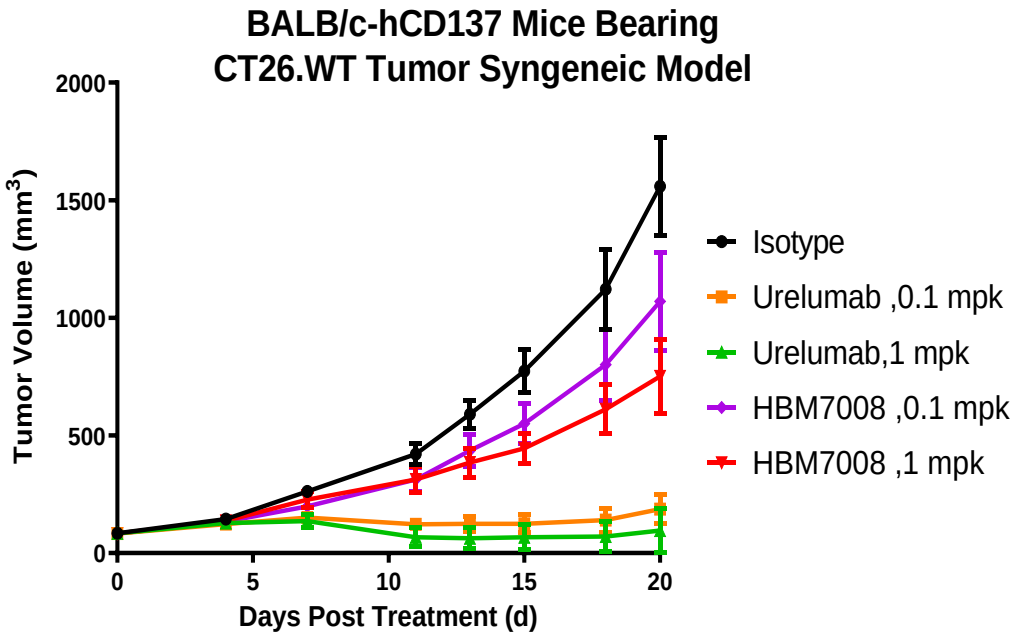




HARBOUR BIOMED

HBM7008 showed limited efficacy in B7H4- tumor

CT26 CDX model in 4-1BB KI mice
(B7H4 negative cell line)



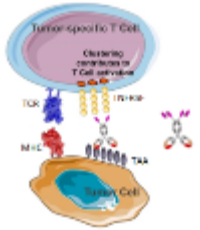
HBM7008 Dose-Range-Finding Study

Purposes:
To assess maximum tolerable dose and evaluate liver as the target for 4-1BB related toxicity

Study design:
0, 3, 30, 60, 100 mg/kg, 1M/1F/dose QW (total 5 doses); Assessment focused on liver functions, structure and systemic cytokine release

Conclusions:
1. HBM7008 was well tolerated at 3, 30, 60 up to 100 mg/kg following 5 weekly doses
2. No noteworthy findings in liver enzymes (ALT/AST) and no changes in liver structure based on histopathology examination
3. No detectable systemic cytokine release
4. R7008 showed IgG-like PK profiles in Cynomolgus monkeys, with half-life of 3-6 days in monkeys at the doses ranging 1-60 mg/kg

Highlights of First in Class HBM7008



MoA:

Crosslinking dependent 4-1BB activation to avoid systemic toxicity

Molecule:

Fully human bispecific (HBICE® platform)

Druggability:

No toxicity issues

Good biophysical properties

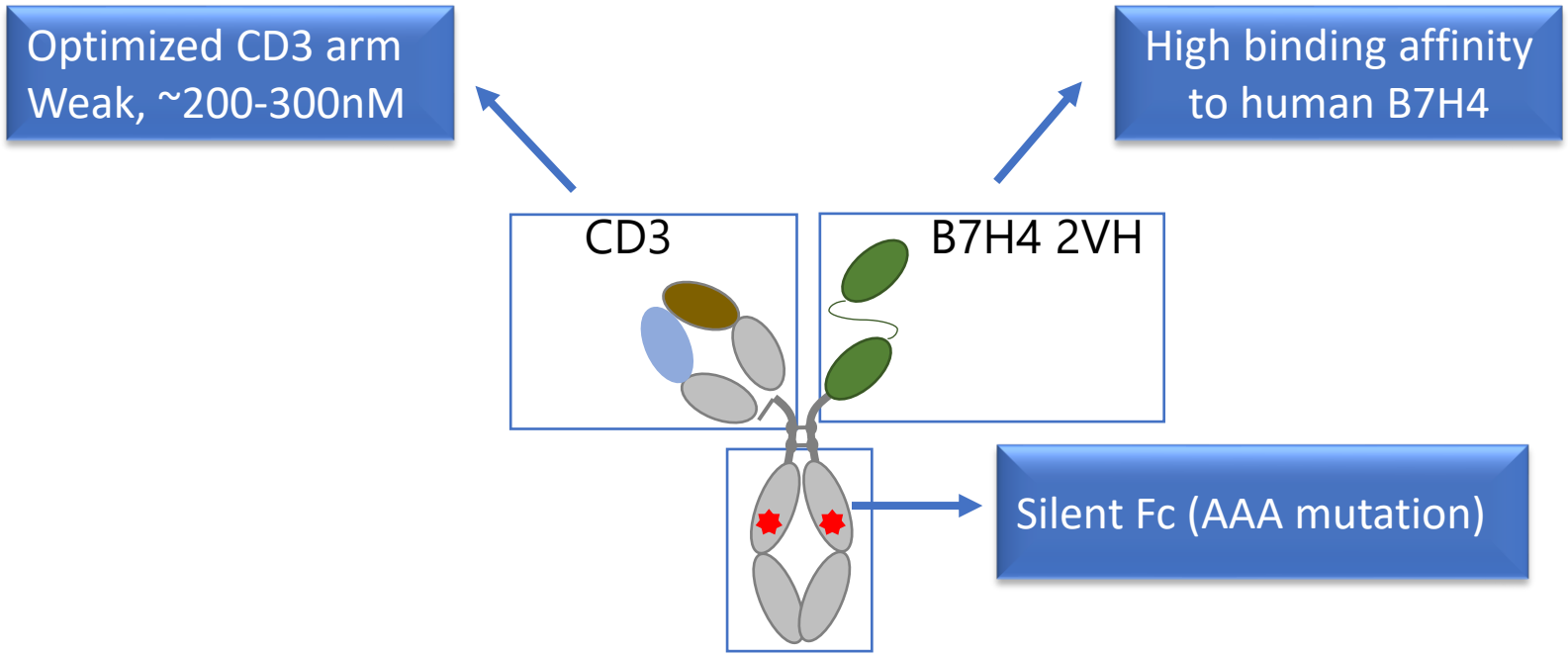
Indications:

B7H4+ patients, gynecological cancers

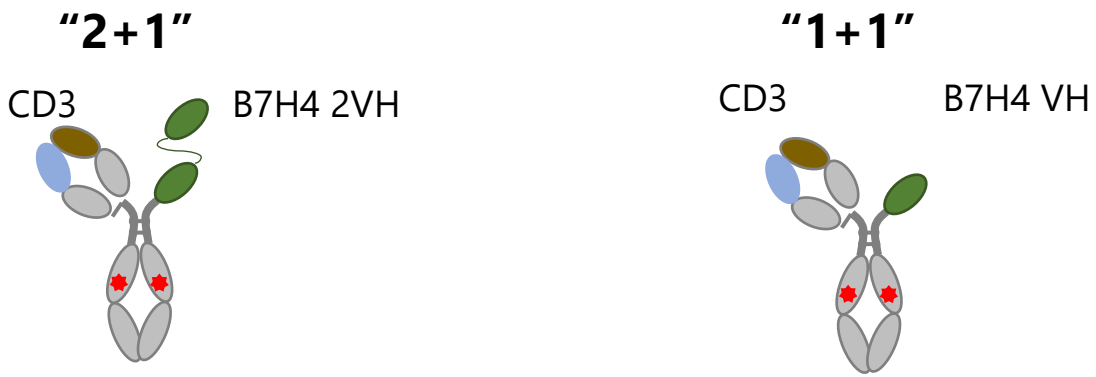
Combine with other therapies (ICIs, CD3 T cell engager etc.)

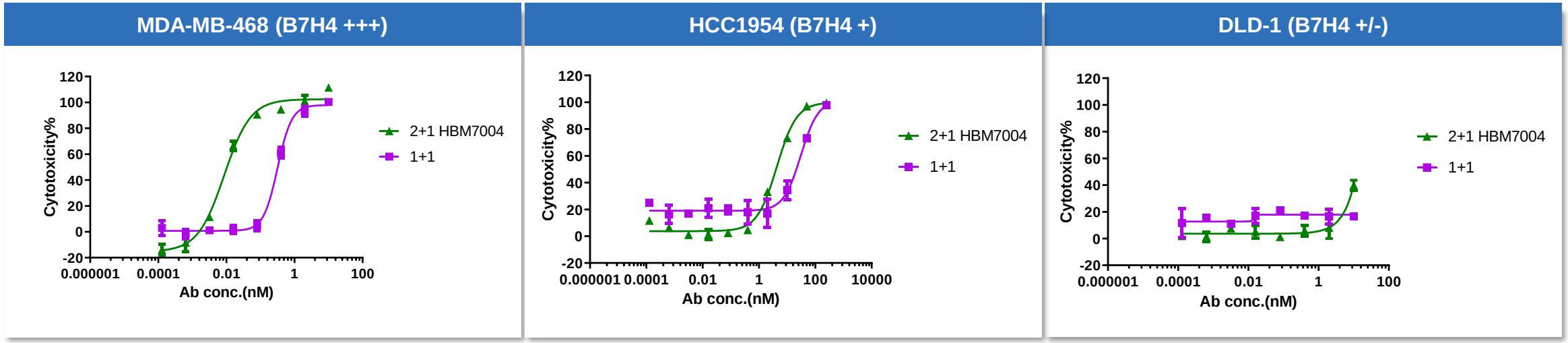
HBM7004 (B7H4 × CD3)

HBM7004 (B7H4 x CD3) design

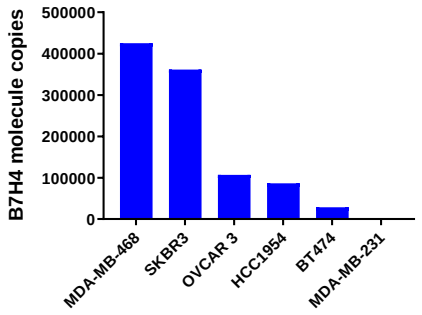


2+1 Format Shows Stronger Efficacy than 1+1 Format

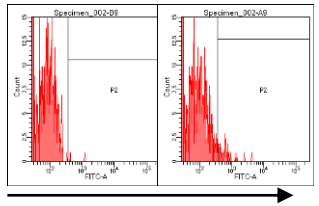




HBM7004 Shows B7H4 Dependent in vitro Cytotoxicity

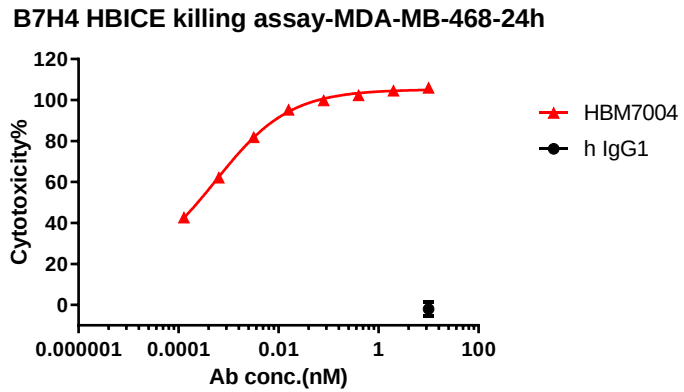


B7H4 expression on tumor cell lines

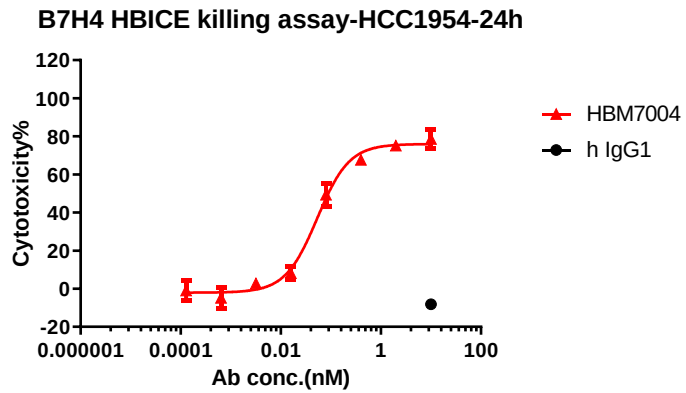


B7H4 expression on DLD-1

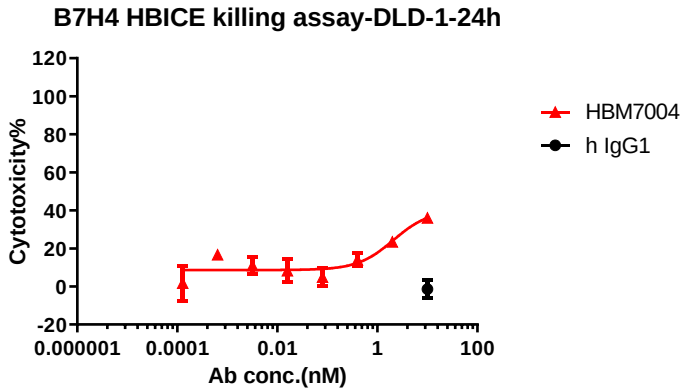
MDA-MB-468 (B7H4 +++)



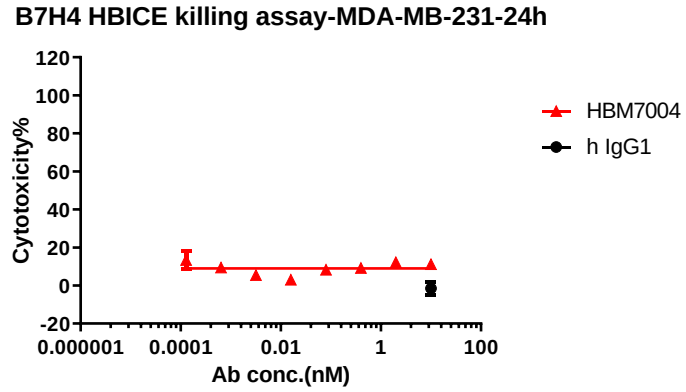
HCC-1954 (B7H4 +)



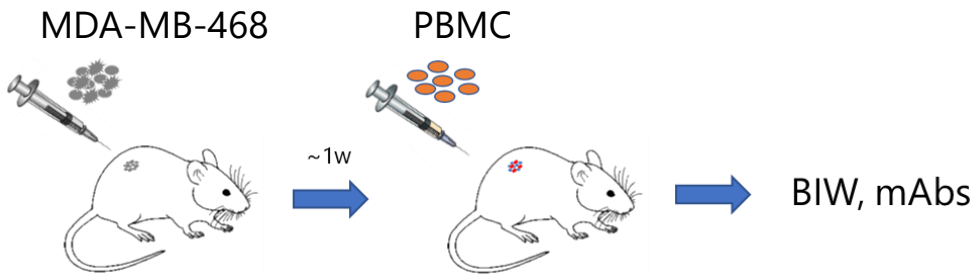
DLD-1 (B7H4 +/-)

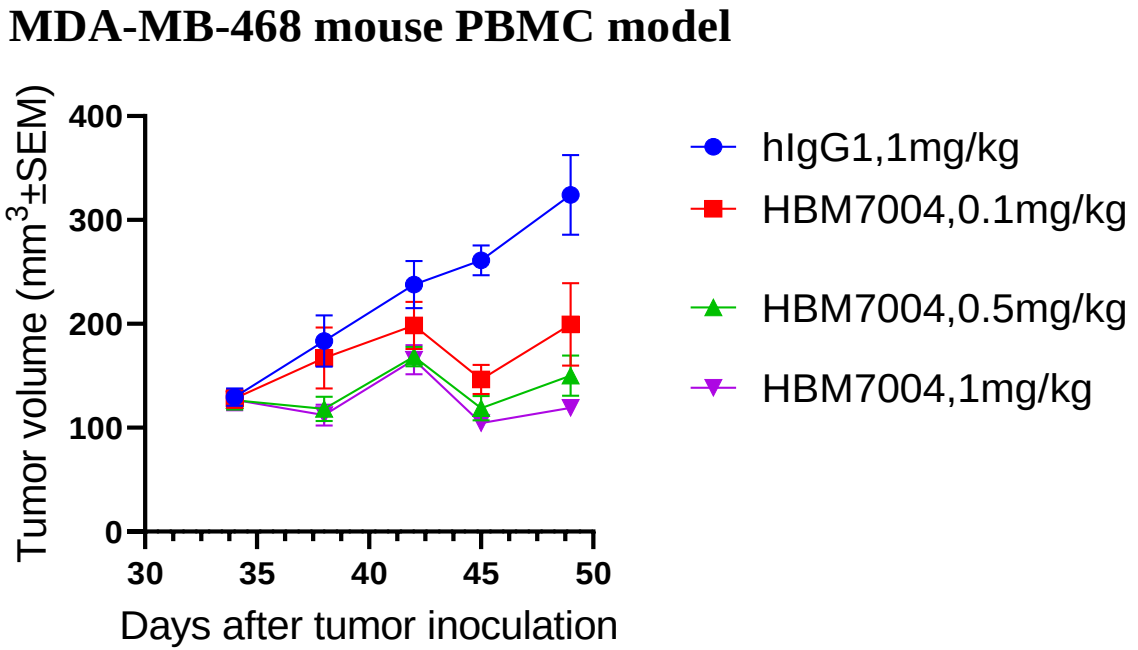


MDA-MB-231 (B7H4 -)



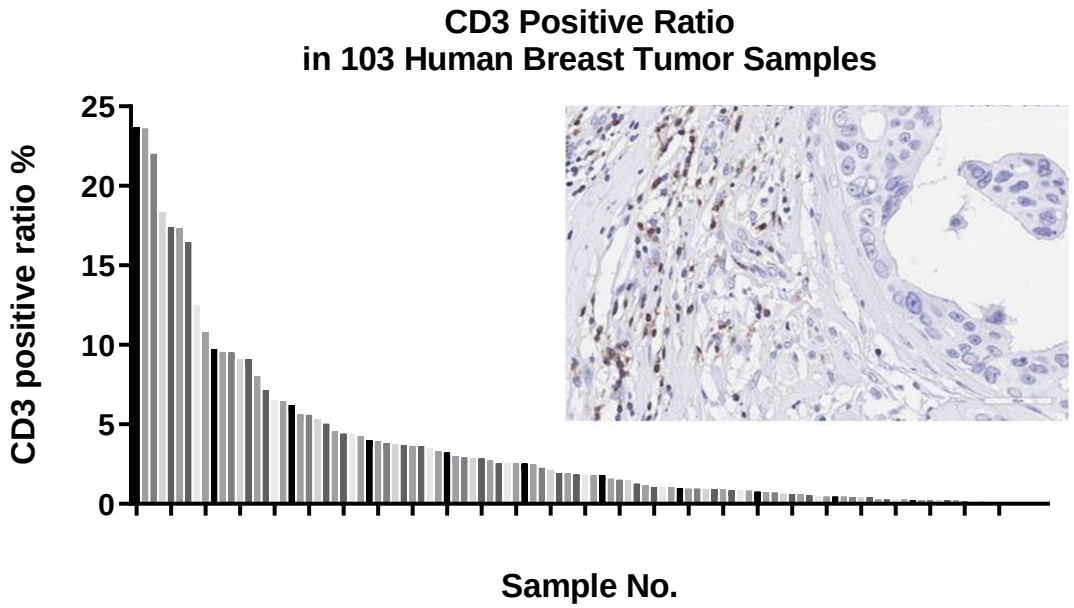
HBM7004 Shows Potent in vivo Anti-tumor Efficacy



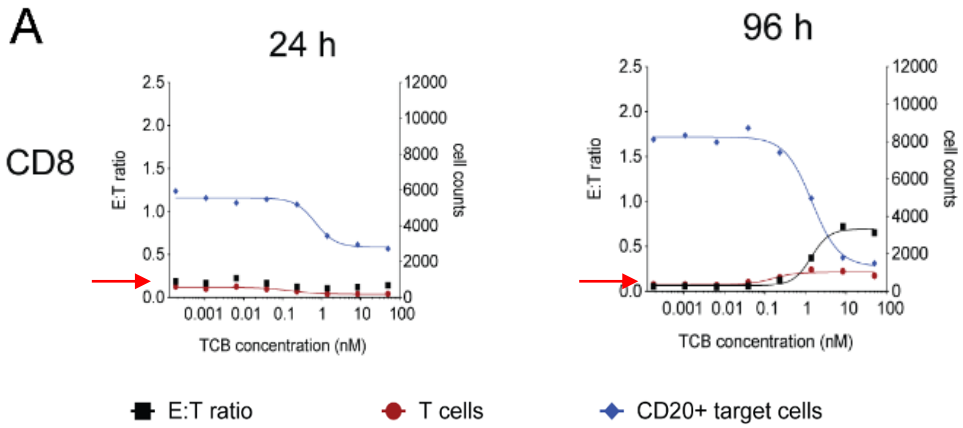


Low Effector:Target Cell Ratio in Tumor May Result in Poor Efficacy in Patients

Most of breast cancers have <10% CD3 T infiltration.



- Low E:T Ratio (~1:10) primary bone marrow aspirates from patients with lymphoma and leukemia.
- T cell ratio increased after BITE treatment



Clin Cancer Res. 2018; 24(19):4785-4797. (Roche)

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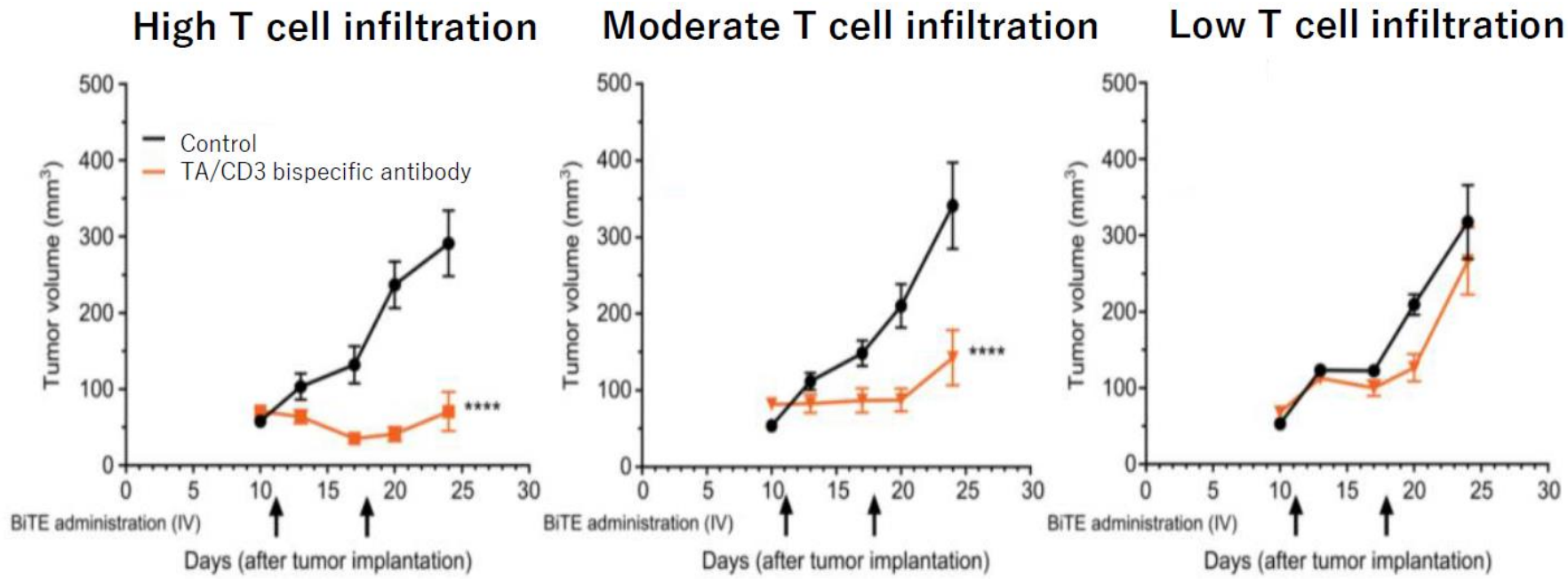
Low Anti-tumor Efficacy Correlates with Low T Cell Infiltration

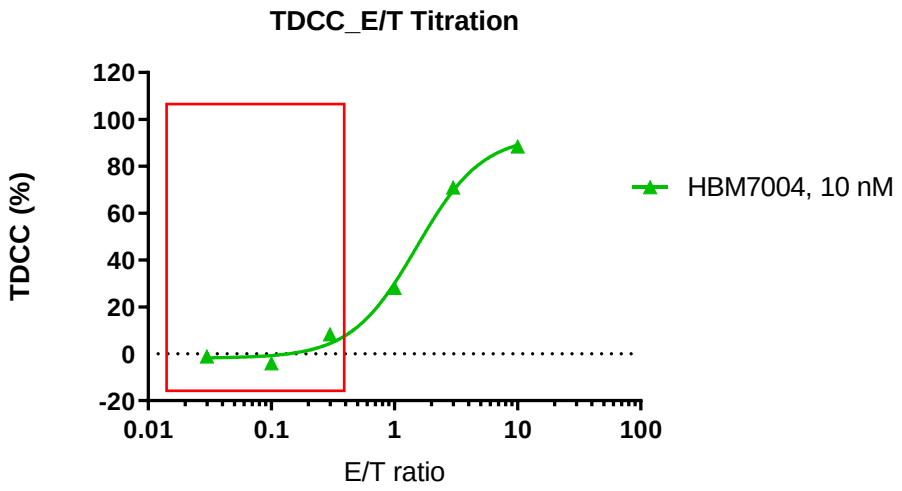


Belmontes B, Sci Transl Med. 2021 Aug 25;13(608).

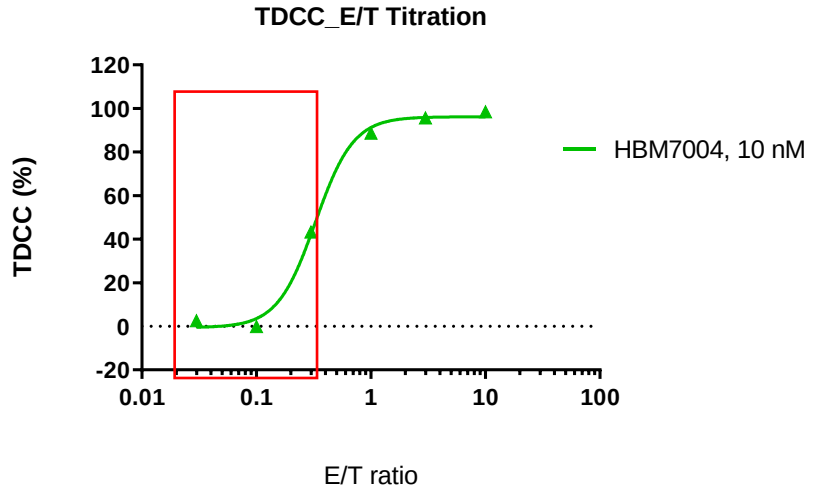
B7H4 x CD3 Shows limited Cytotoxicity at Low E:T ratio

E:T ration titration
Saturated antibody concentration: 10nM

24h



96h



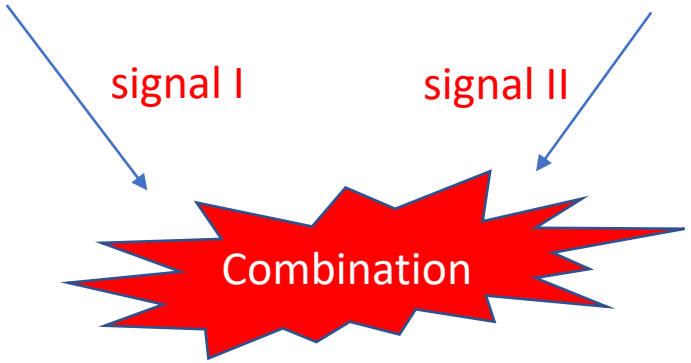
➢ No cytotoxicity at low E:T ratio

HBM7008(B7H4 × 4-1BB) and HBM7004(B7H4 × CD3) combination

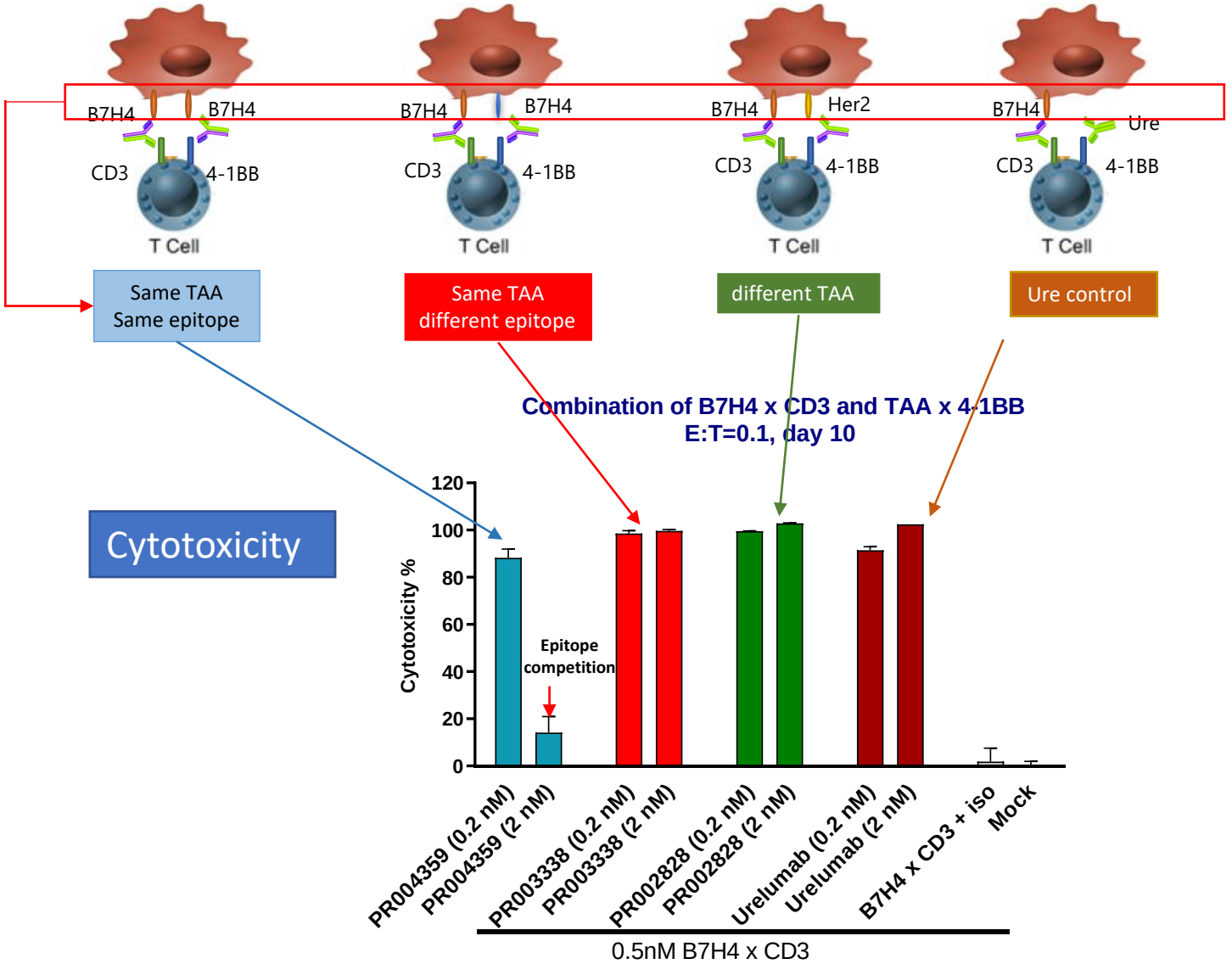
Combination of CD3 and 4-1BB Based T Cell Engagers Provides Both Signal I and II to fully activate T Cells

	CD3 T cell engager	4-1BB co-stimulator
pros	Strong signal I for T cell activation (non-MHC restricted, independent of antigen presenting, polyclonal T-cell response)	Activate/maintain pre-existing T cell clones activity
cons	Signal I only may cause T cell exhaustion/anergy	Depend on pre-existing signal I

Rationale



Combination of TAA x CD3 with TAA x 4-1BB



- Target cell: SKBR3 (B7H4+, Her2+)
- E:T ratio: 1:10
- 10 days

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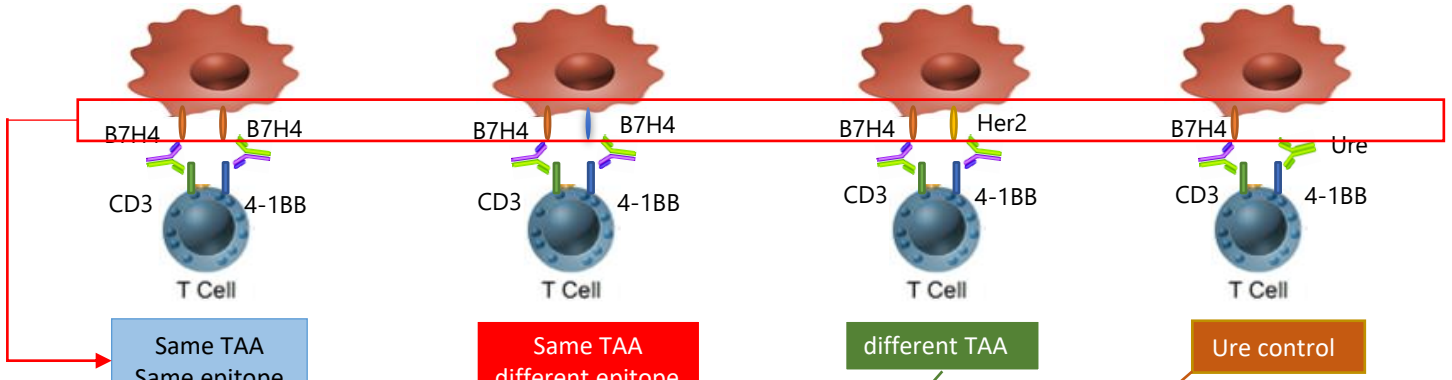
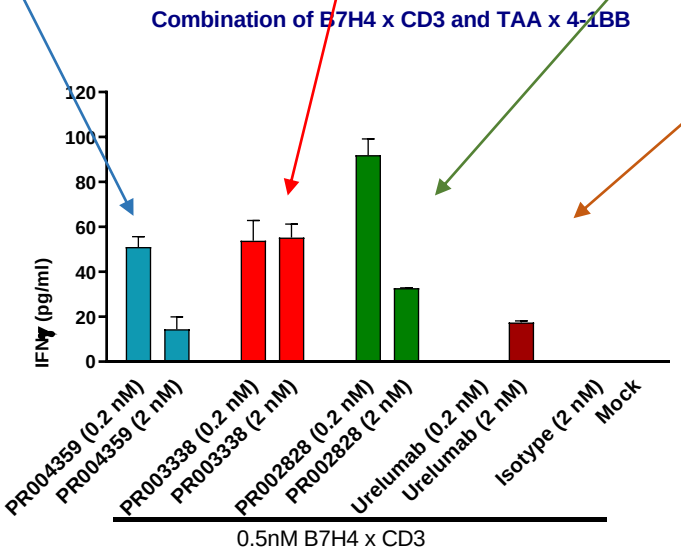
Combination of TAA x CD3 with TAA x 4-1BB

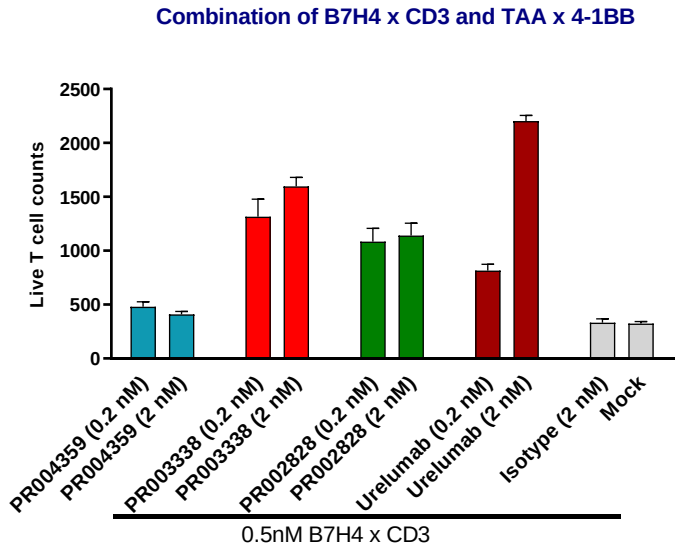


- Target cell: SKBR3 (B7H4+, Her2+)
- E:T ratio: 1:10
- 10 days

IFN-γ



Live T cell count



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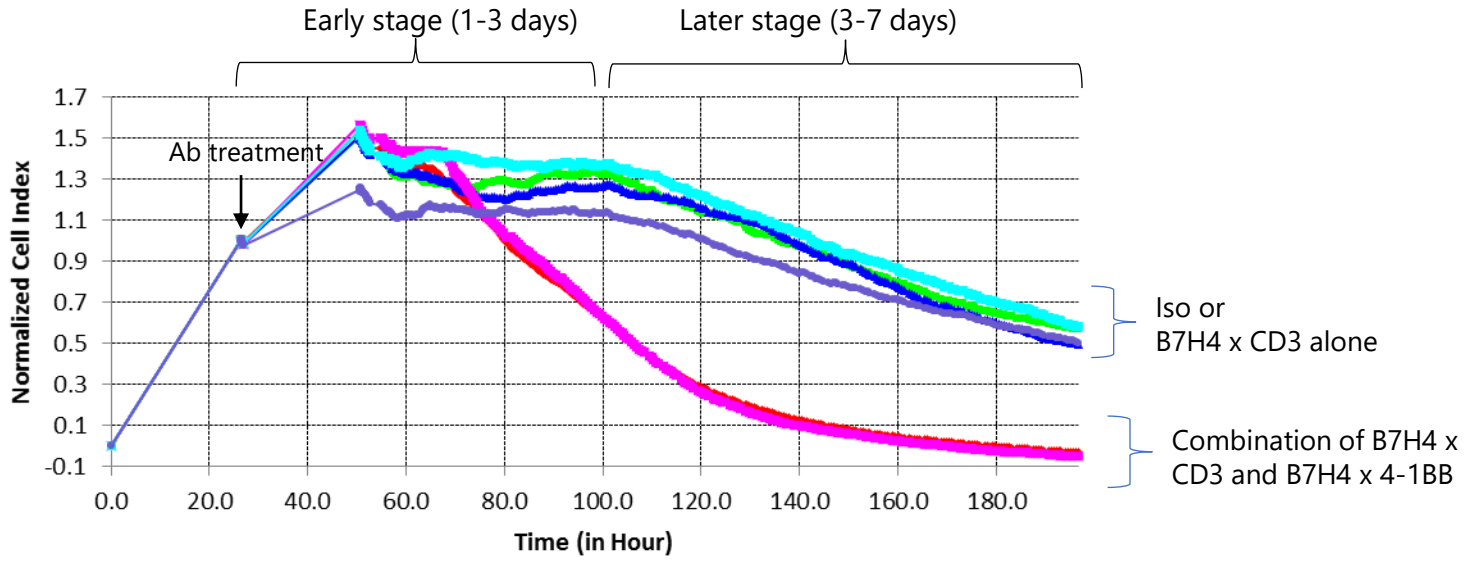
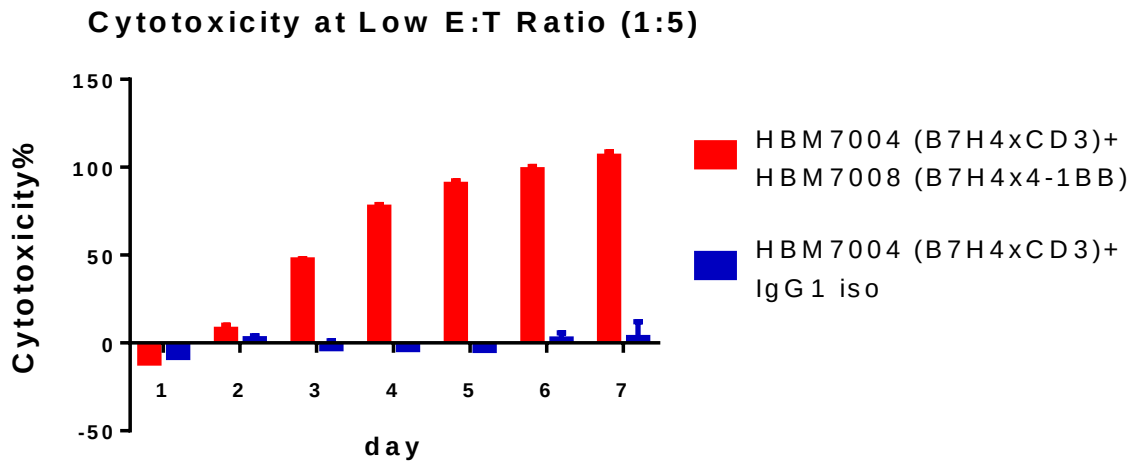
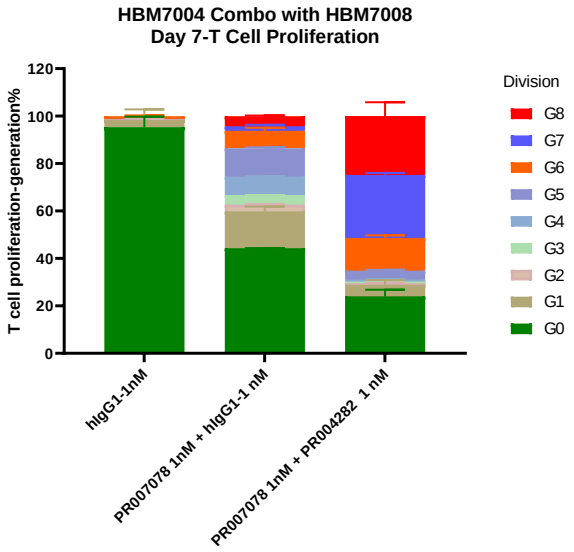
Dynamics of Target Cell Cytotoxicity of Combination of HBM7004 and HBM7008

Y-axis represent target cell number

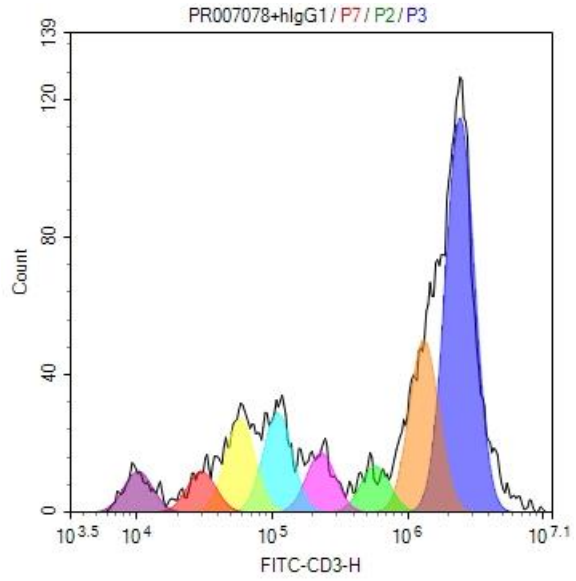




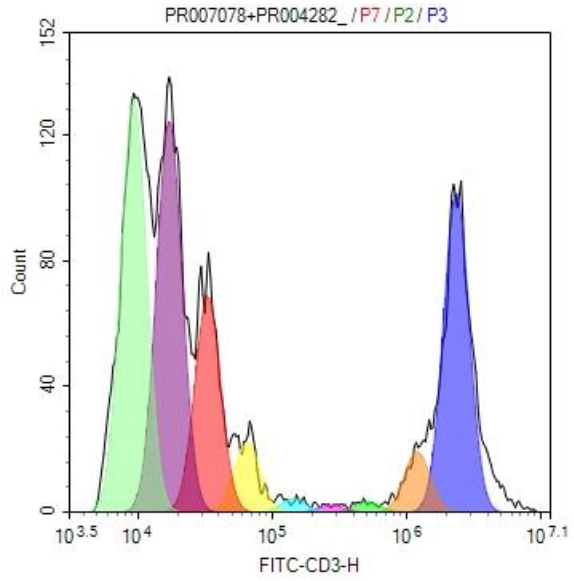
Combination of B7H4 x CD3 with B7H4 x 4-1BB Greatly Promotes T Cell Proliferation



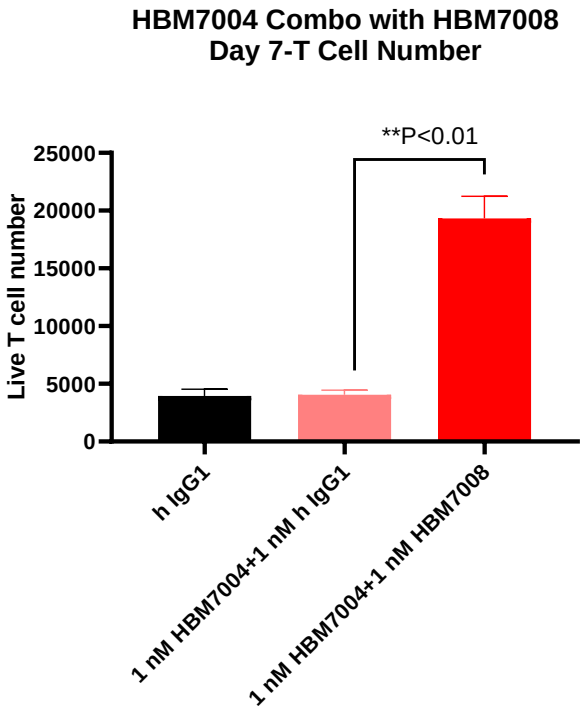
B7H4 x CD3 alone

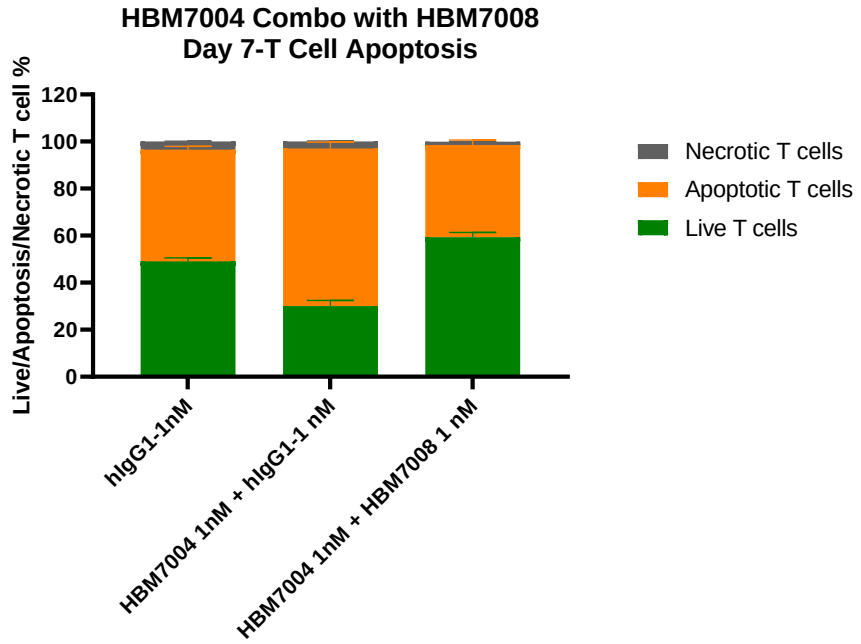


B7H4 x CD3 + B7H4 x 4-1BB

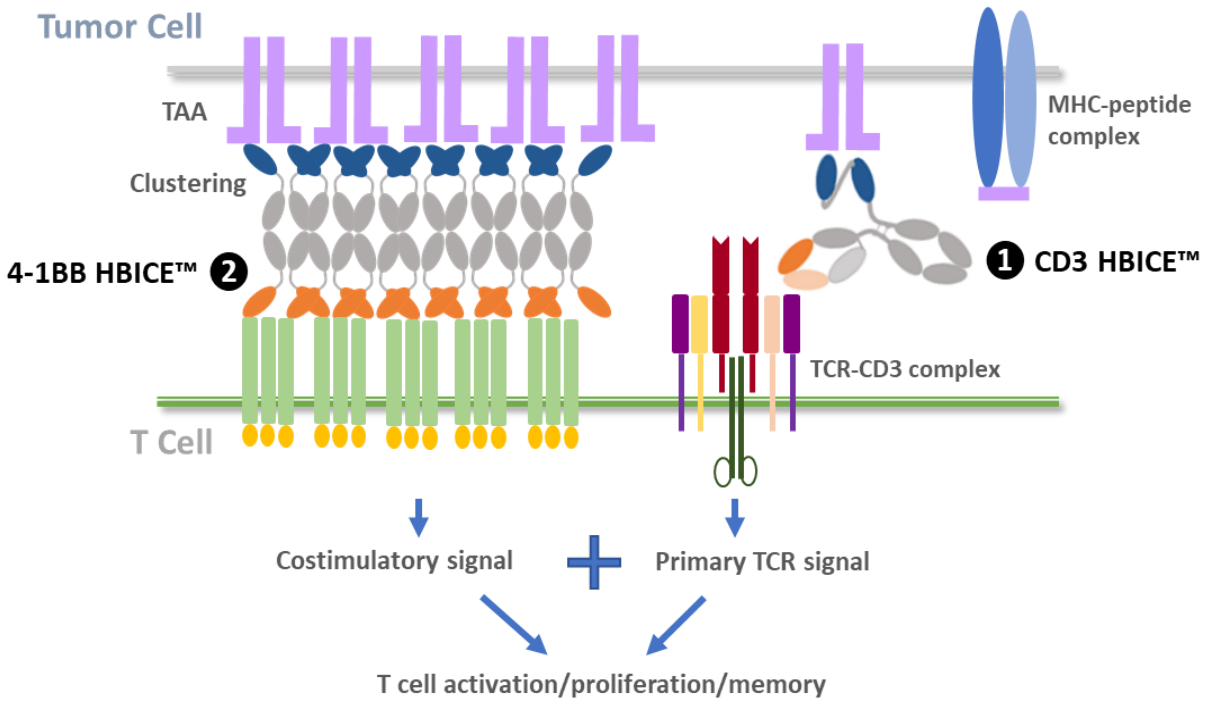


Combination of B7H4 x CD3 with B7H4 x 4-1BB Increases T Cell Number and Decrease Apoptosis





Summary



- B7H4 x CD3 shows limited cytotoxicity at low E:T ratio.
- Combination with 4-1BB BsAb can restore T cell cytotoxicity at low E:T ratio.
- Combination with 4-1BB can reduce T cell apoptosis and increase T cell proliferation.
- Combination with 4-1BB BsAb can reduce T cell exhaustion.
- Flexible combination of TAA x CD3 and TAA 4-1BB

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Acknowledgement

HBICE design and optimization
Yun He, Yongqiang Wang, Lei Shi

***In vitro* functional assay**
Xiaodong Wu, Bing Huang, Chen Zhong, Gezi Jia, Tina Du

***In vivo* functional assay**
Fei Chen, Lei Niu, Yuetao Wu

Monkey toxicity study
Izzie Wang, Joanne Wang