

# Bispecific Immune Cell Engagers Built From Harbour HBICE® Platform

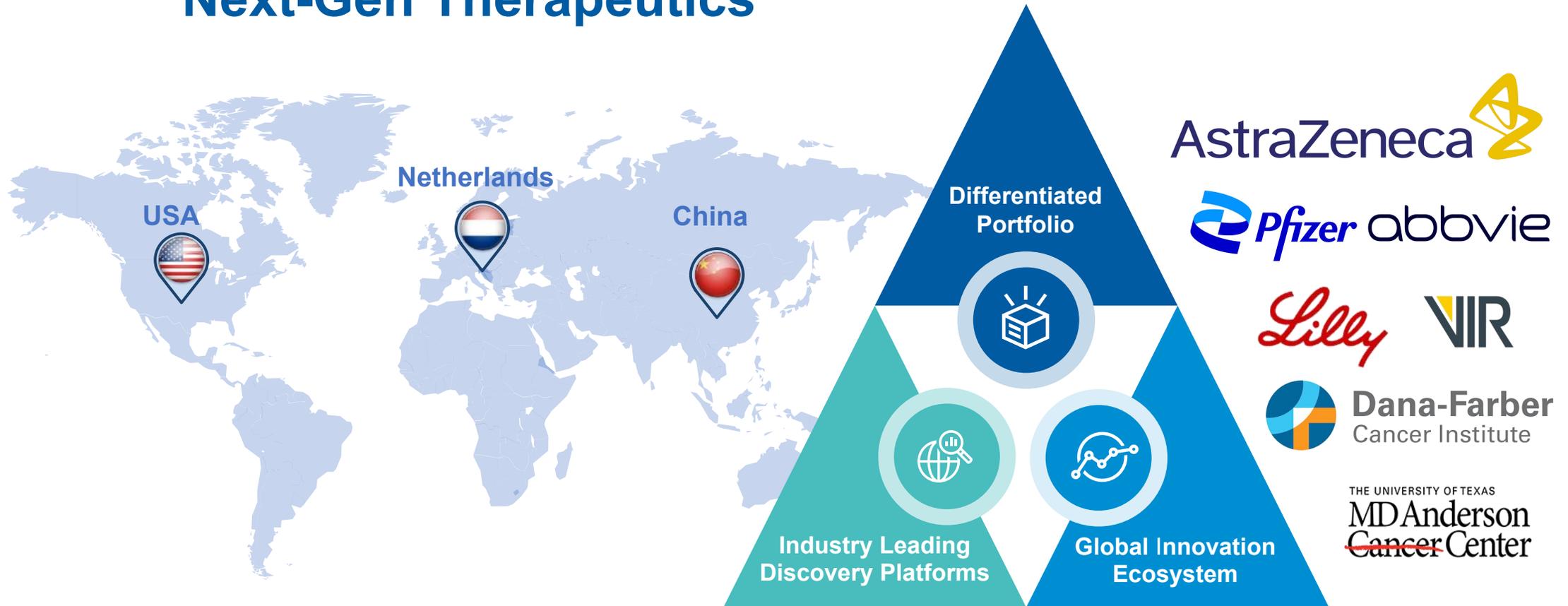
Apr 2022

HBM HOLDINGS-B: 02142.HK

[www.harbourbiomed.com](http://www.harbourbiomed.com)

# Harbour BioMed: A Rapidly Rising Global Innovative Biopharmaceutical Company

## Next-Gen Therapeutics



# Robust Pipeline Combining Advanced Clinical Programs Addressing Highly Unmet Needs and Novel Molecules Leveraging HBM Antibody Platforms

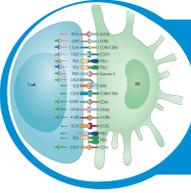
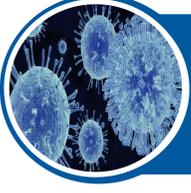
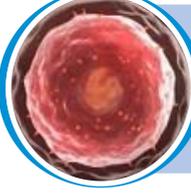
Project	Target	Indication	Commercial Rights	Status						
				Discovery	Pre-Clinical	IND	Phase I	Phase II	Phase III	BLA
• HBM4003	CTLA-4	Solid Tumors <sup>a</sup>	Global	Ph 1b/2						
		Solid Tumors <sup>b</sup>		Combo with PD-1 Ph 1b/2						
		Solid Tumors <sup>c</sup>		Combo with PD-1/PD-1+Chemo Ph 1						
• HBM7008	B7H4x4-1BB	Solid Tumors	Global	IRB approval in Australia <sup>1</sup>						
• HBM9378	TSLP	Asthma	Global	IND approval by NMPA <sup>2</sup>						
• HBM7022	Claudin18.2xCD3	Solid Tumors	License out AstraZeneca 							
• HBM1022	CCR8	Solid Tumors	Global							
• HBM1020	B7H7	Solid Tumors	Global							
• HBM7020	BCMAxCD3	Multiple Myeloma	Ex-Greater China <sup>d</sup>							
• HBM1007	CD73	Solid Tumors	Global							

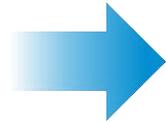
a. Melanoma, HCC, RCC and Other Advanced Solid Tumors  
b. Melanoma, HCC, NEC/NET and Other Advanced Solid Tumors, HCC is in Ph1  
c. NSCLC and Other Advanced Solid Tumors

1. HBM7008 IRB approval in Australia, February 2022  
2. HBM9378 IND approval in China, February 2022

# HBM Global Innovation Ecosystem Leads Next-Gen Therapeutics

## HBM Next-Gen Innovative IO Therapy Strategy

	<b>Immune Cell Engager</b>	HBM7008 HBM7020 ...
	<b>Novel Immune Evasion Pathway</b>	HBM1020 HBM7008 ...
	<b>Treg Depletion</b>	HBM4003 HBM1022 ...
	<b>Innovation in Novel Frontier NK/ADC</b>	Undisclosed ...



### Scientific Strategy is Warranted by Cutting-edge Technologies

1. T/NK cell infiltration/proliferation increasing via immune cell engager (HBICE, SBC, Fc engineering)
2. Innovative targets and pathways of the B7 family (H2L2, HBICE, mRNA/DNA immunization)
3. Depletion of regulatory T cells (eADCC, Afucosylation, HCAb)
4. Innovative products in novel frontier NK/ADC (HBICE, HCAb)



# Overview of HBICE® Technology and Harbour Mice

# Cutting Edge Fully Human Antibody Platforms Enable Sustained Invention of Novel Molecules

## H2L2 – Full IgG Antibody Discovery Platform



-  **HBM1020**  
A fully human antibody against B7 family target for the treatment of solid tumors
-  **HBM9378**  
A fully human antibody against TSLP for severe asthma

Robust and highly efficient, global IP and clinically validated

Ligand



**\$ 178 M**  
Platform only

SANOFI



**\$1.1 B**  
Platform + 1 Ph2 + 1 Ph1

## HCAb – Next-Generation Heavy-Chain-Only Antibody



-  **HBICE®**  
A Unique, HCAb-Based Platform For Immune Cell Engagers
-  **HBM4003**  
A next generation anti-CTLA4 antibody

Unique fully human HCAb, versatile for broad applications

SANOFI



**\$ 4.8 B**  
Nanobody + 1 BLA + 1 Ph2

AMGEN

Teneobio

**\$2.5 B**  
Platform + 1 Ph1

## HBICE® – HCAb-Based Bispecific Platform for Immune Cell Engagers



-  **HBM7020**  
A BCMAxCD3 bispecific antibody
-  **HBM7008**  
A B7H4x4-1BB bispecific antibody

Self-developed, unique geometric flexibility, promising bispecific biology

Lilly

Merus

**\$ 1.6 B**  
3 BsAb slots based on Bionics platform

abbvie

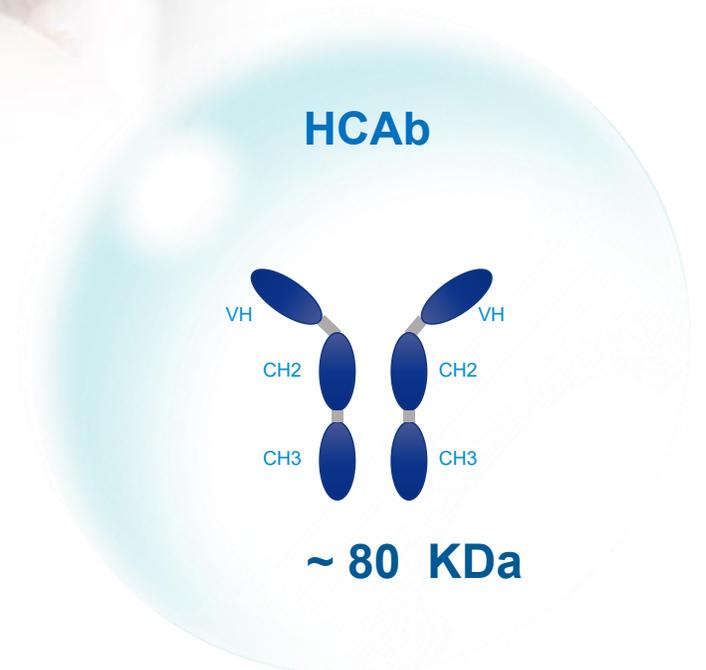
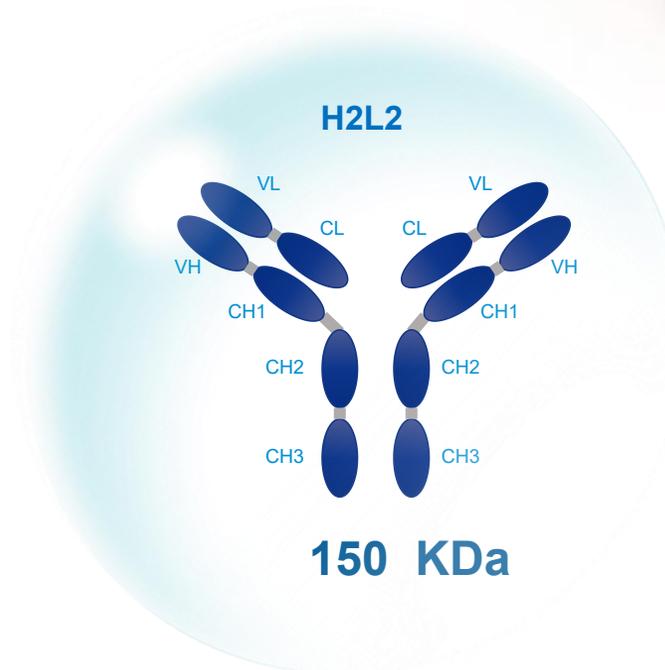
Genmab

**\$ 3.2 B**  
3 BsAb ADC slots based on Duobody platform

# Harbour Mice®: Industry Leading Platform Technology to Generate Fully Human Monoclonal Antibodies

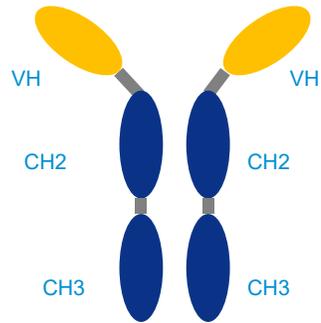
- Worldwide patent protection
- Validated by **45+** industry and academic partners
- **7** projects have entered clinical stage

- ✓ **Human**
- ✓ **Natural**
- ✓ **Optimized**

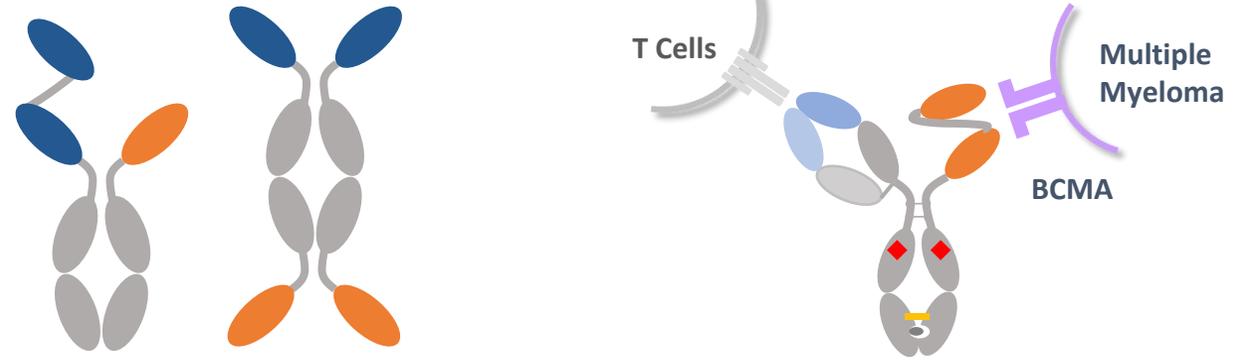


# Fully Human HCAb Has Broad Applications For Bispecifics, CAR-T, Diagnostics, Carrier For Conjugates, Topical Route

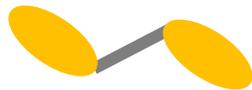
## Monoclonal antibody



## Bispecific antibody



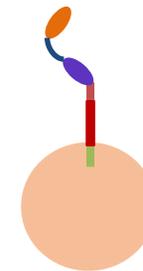
## Nanobody



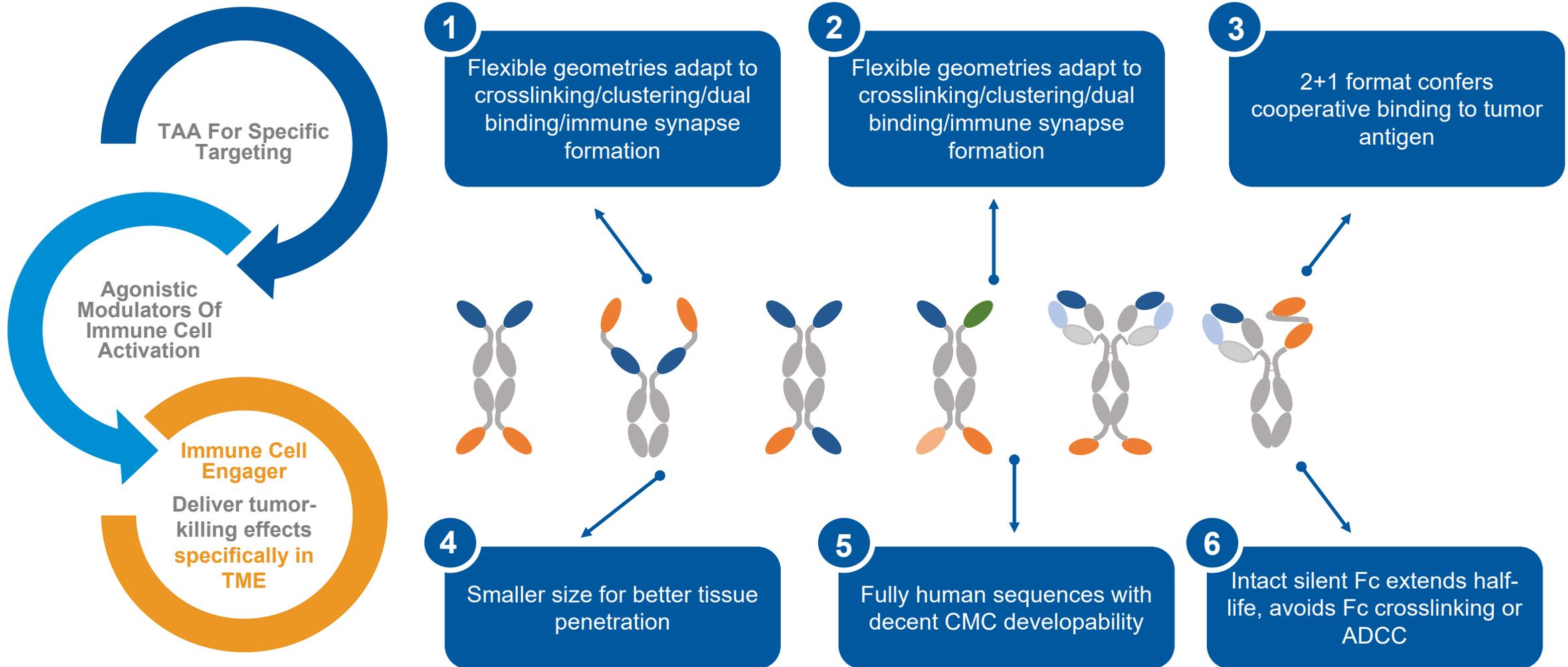
## Diagnostic



## CAR-T



# Harbour HCAb Provides Versatile Geometries to Build Bispecific / Multi-specific Immune Cell Engagers (HBICE®)



TAA: tumor associated antigen  
TME: tumor microenvironment

**Formats and geometries matter!**  
**Developability is the key for bispecific development!**

# Leverage HBM's Efficient Antibody Discovery Engine And Unique HBICE® Platform To Build Innovative Immune Cell Engager Portfolio

## Tumor-associated Antigens For Specific Targeting

A panel of TAAs on various of tumors, e.g. BCMA, TROP2, CLDN18.2, B7H4, ...

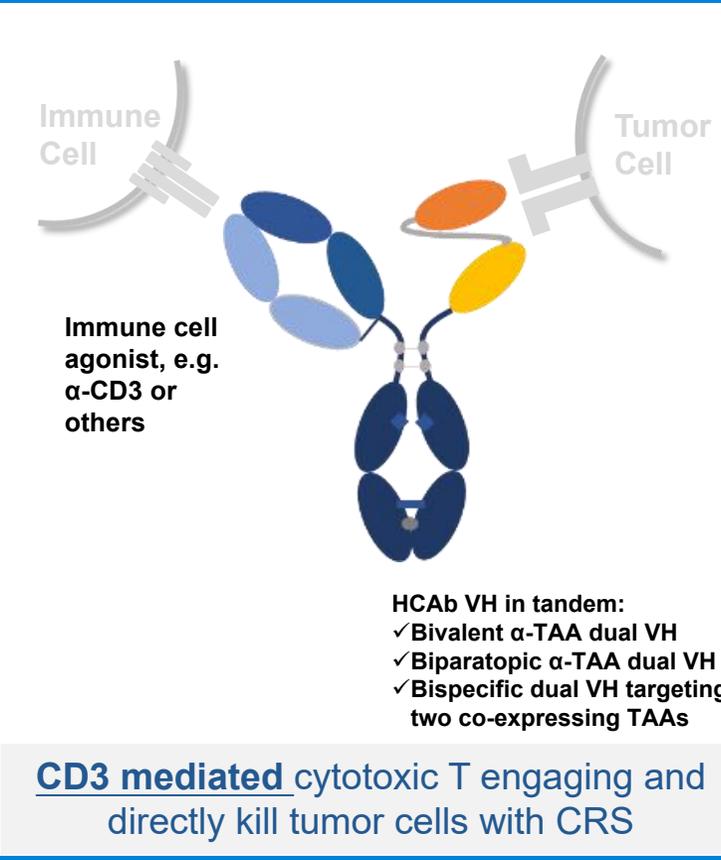
## Agonistic Modules For Immune Cell Activation

A panel of immune cell (T, NK, DC, Mφ) activation or co-stimulatory markers, e.g. CD3, 4-1BB, CD40, ...

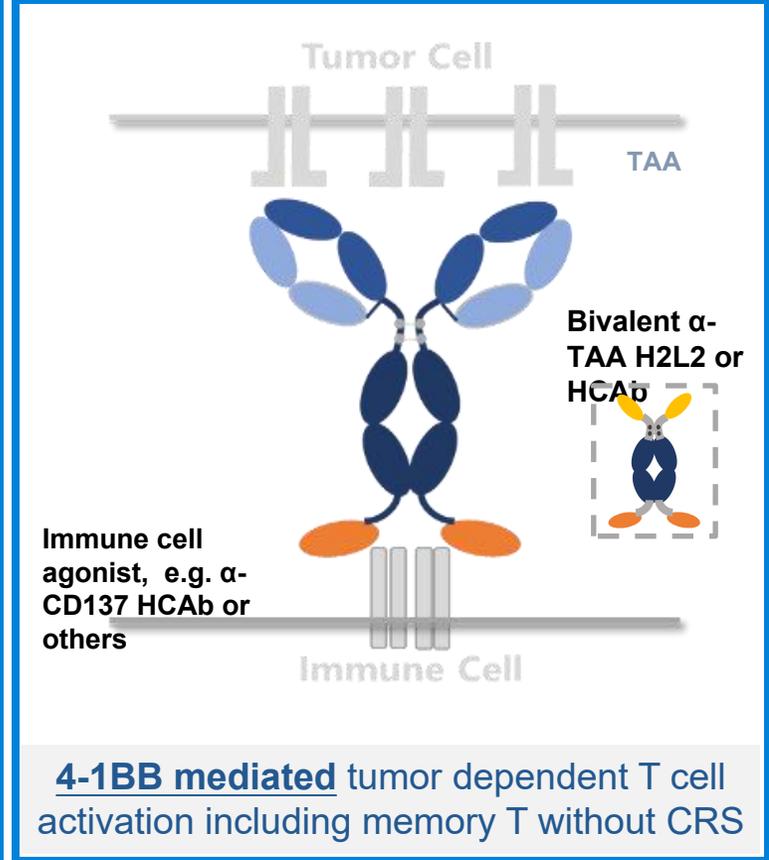
## Immune Cell Engager

Deliver tumor-killing effects unachievable by combination therapies

### '2+1' asymmetric HBICE (A-HBICE)

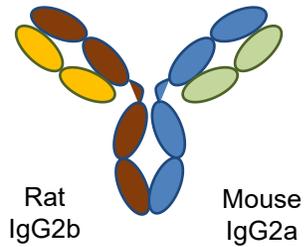


### '2+2' symmetric HBICE (S-HBICE)



# HBM is at the Forefront of New Generation of T-Cell Engager Bispecific Antibodies

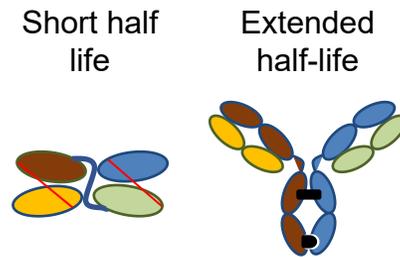
## FcγR engaging



**Catumaxumab**



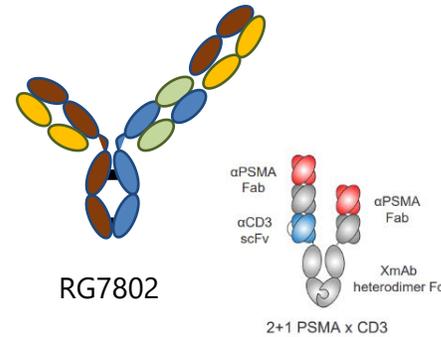
## FcγR-silenced



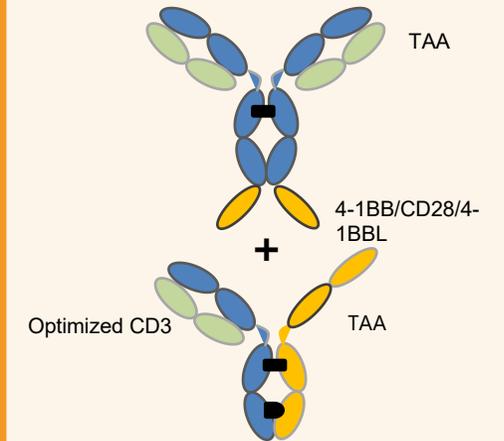
**Blinatumomab**



## Optimized aCD3, 2+1 format

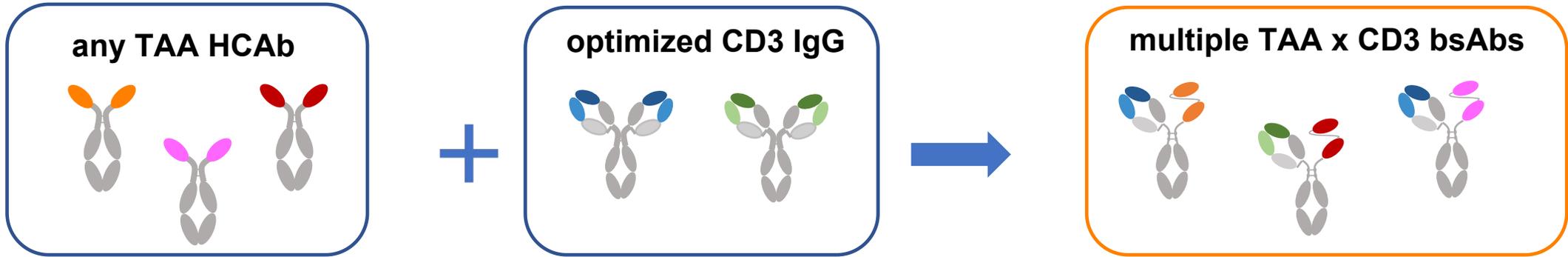


## Trispecific or 2<sup>nd</sup> signal bispecific combination





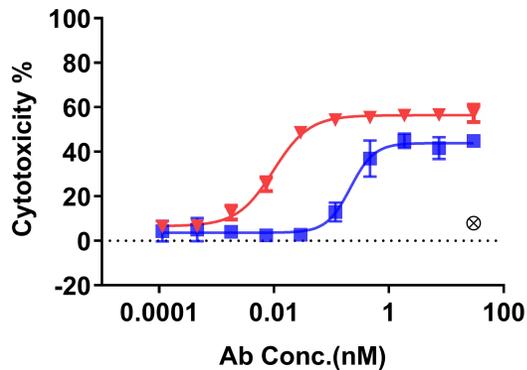
# CD3 HBICE<sup>®</sup> Generated From Fine-Tuned “2+1” Structure



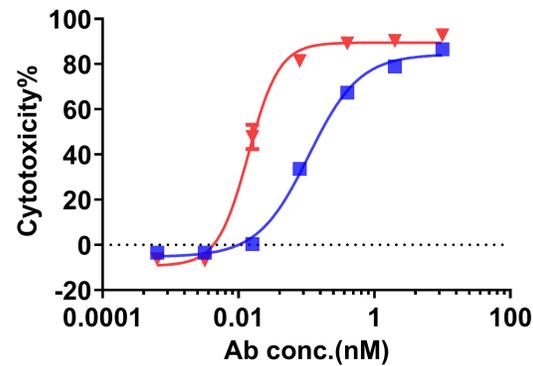
Cytotoxicity to TAA<sup>+</sup> tumor cells

CD3

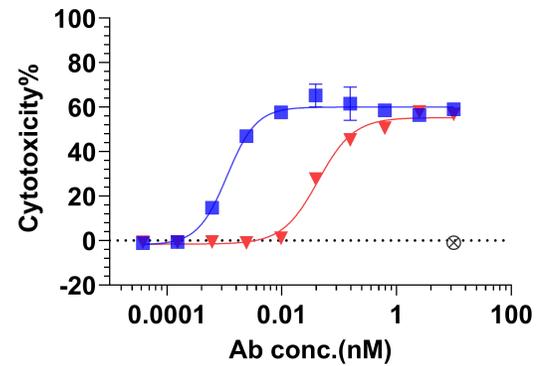
TAA-1



TAA-2

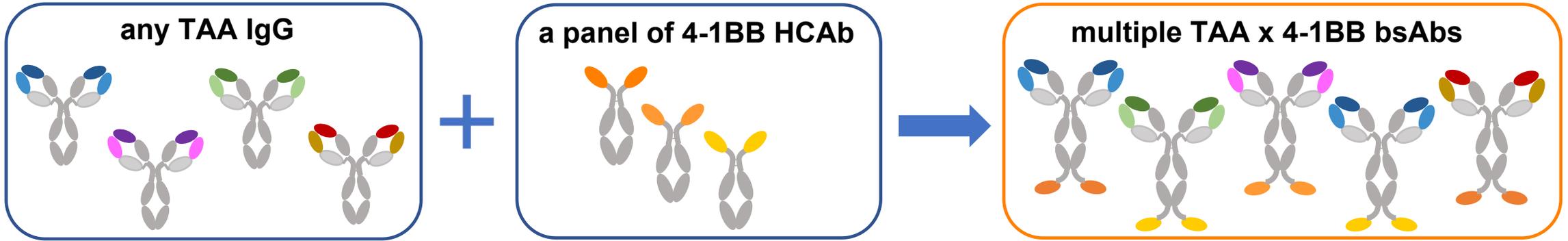


TAA-3



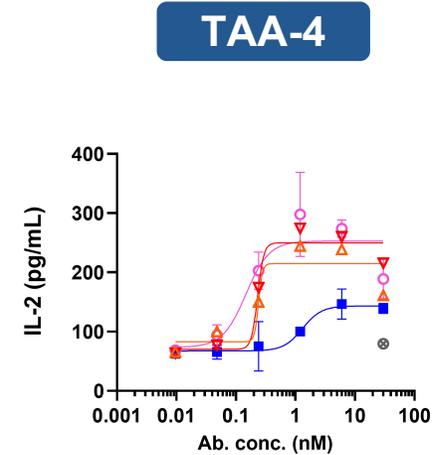
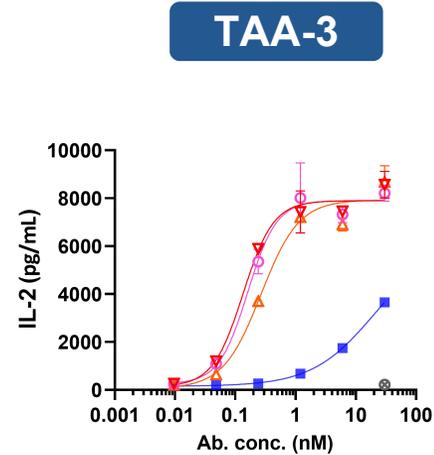
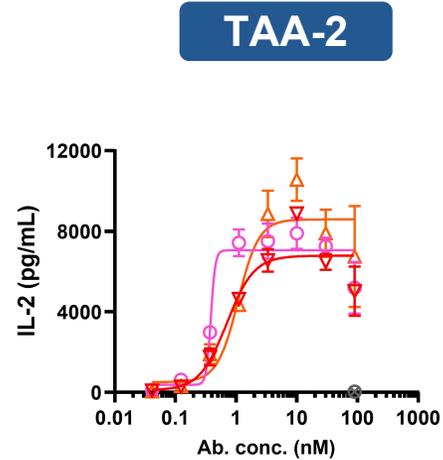
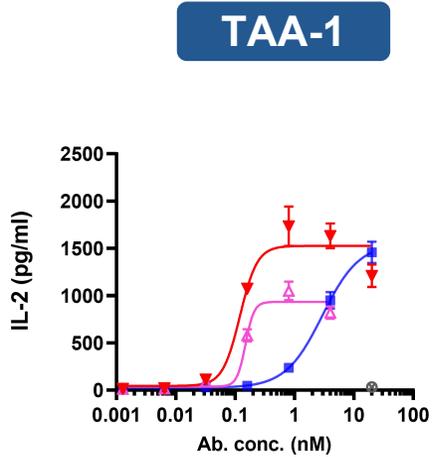
**Figure legends:**  
Benchmark bsAb  
TAA x CD3 '2+1' HBICE  
IgG1 iso

# 4-1BB HBICE<sup>®</sup> Generated from the “Plug & Play” Platform



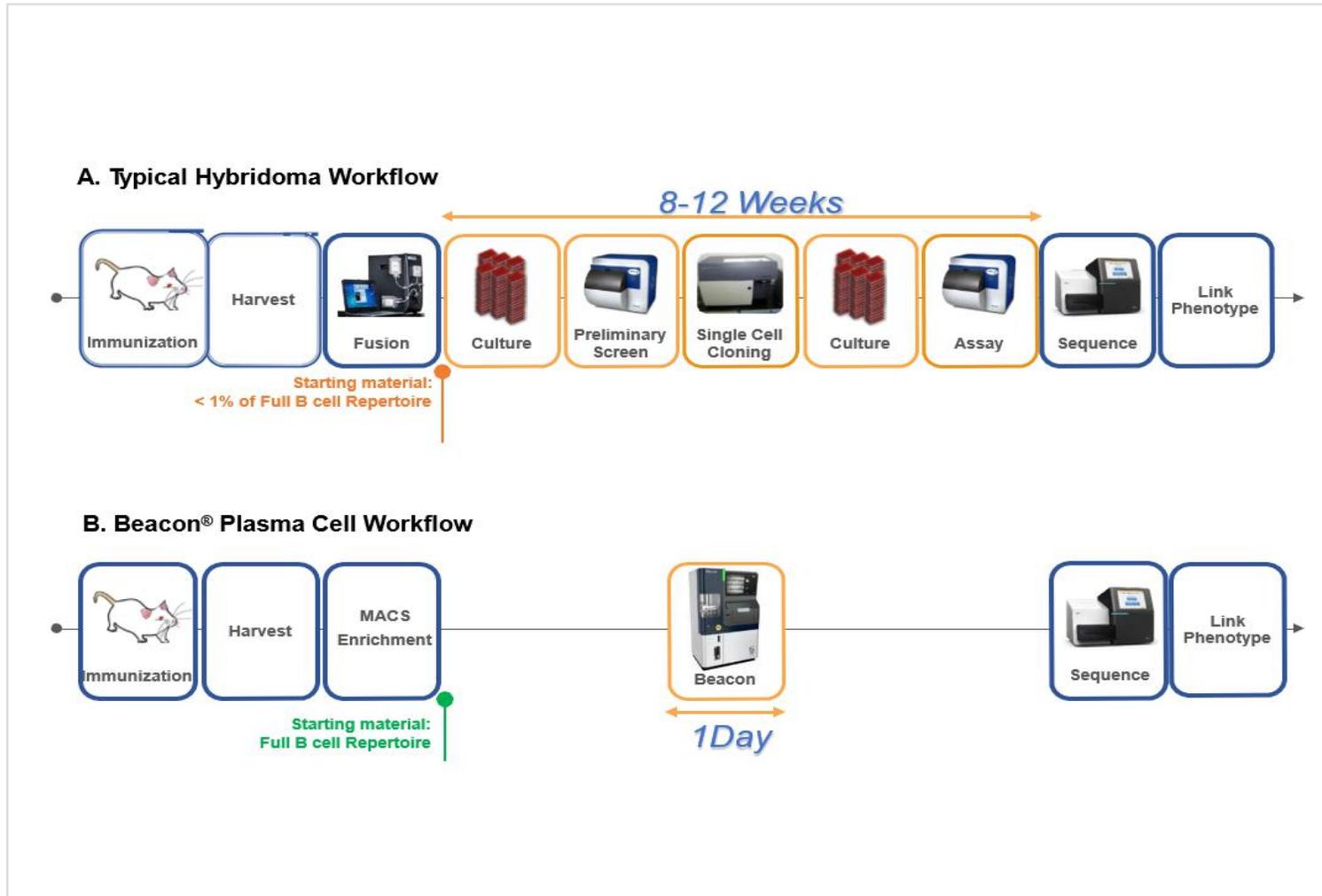
## T activation in the presence of TAA<sup>+</sup> tumor cells

4-1BB



**Figure legends:**  
 Urelumab  
 TAA x 4-1BB bsAb1  
 TAA x 4-1BB bsAb2  
 TAA x 4-1BB bsAb3  
 IgG1 iso

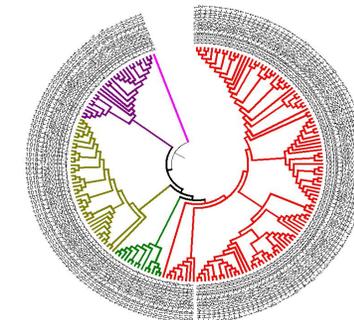
# Single B Cell Technology Accelerates Antibody Screening and Enables “Antibody Mining” for Challenging Targets or Rare Epitopes



## A case study for Mesothelin antibodies

- > 30,000 clones screened in 2-3 days by SBC
- No qualified clone by hybridoma or phage display
- Beacon SBC technology is highly efficient

Mice	Cells screened	Sequences	Antibody produced	Human MSLN-CHOK1 (FACS)	Cyno MSLN-CHOK1 (FACS)
H2L2	33000	161	52	15	9
HCAb	35000	322	65	8	5



Diverse sequences Screened from Beacon



**HBM7022  
(Claudin18.2xCD3)  
Generated from  
HBICE® Technology**

# HBM7022: Novel Bispecific Antibody License-out to AstraZeneca for Global Development

## HBM7022 License-out to AstraZeneca, Validates HBM's Global Vision and Strategy

- HBM7022(CLDN18.2xCD3), developed from HBICE<sup>®</sup>, **pre-clinical** bispecific antibody
- Entered into a global out-license agreement with AstraZeneca in April 2022
- **US\$25 million** upfront payment + **US\$325 million** milestone payment + royalty fee

HARBOUR  
BIOMED



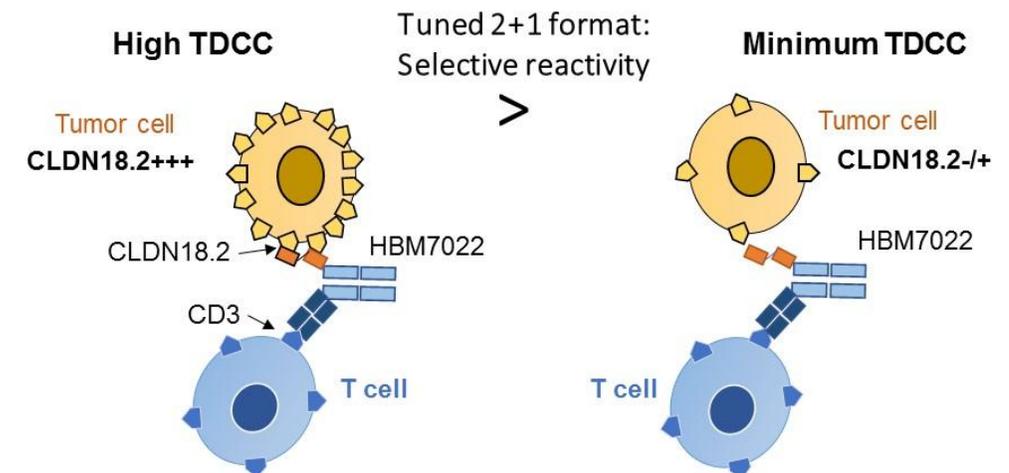
AstraZeneca

### HBM7022 Highlights

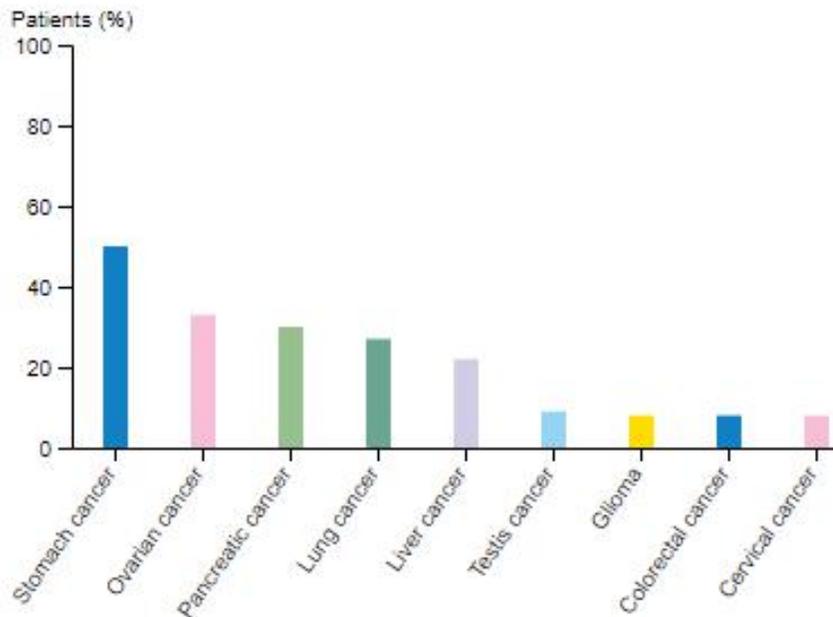
- 2+1 format with better activity and potential larger therapeutic window
- Low CD3 and high CLDN18.2 affinity reduce CRS risk and increase antibody distribution to tumor
- Silent Fc extends half-life, avoids Fc crosslinking and ADCC

HARBOUR  
BIOMED

### MOA of HBM7022



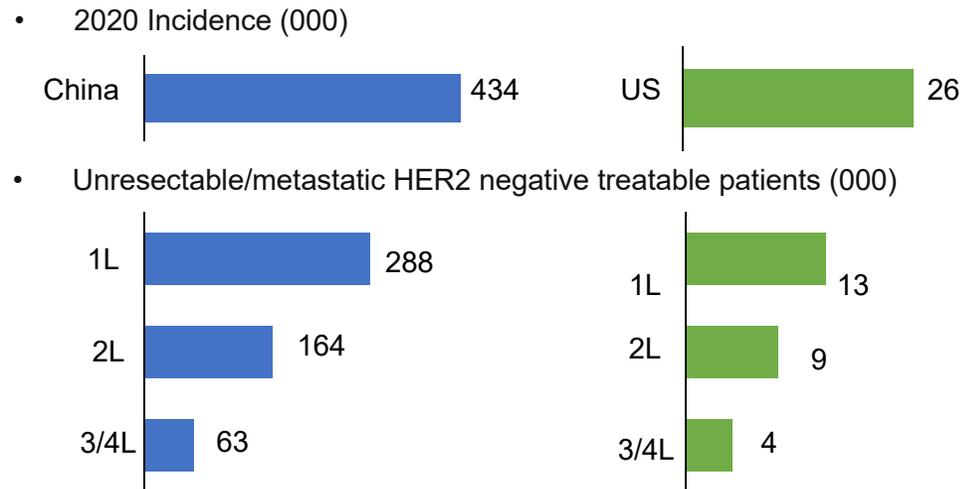
# HBM7022: Targeting Claudin18.2 Positive Solid Tumors with Huge Unmet Medical Needs



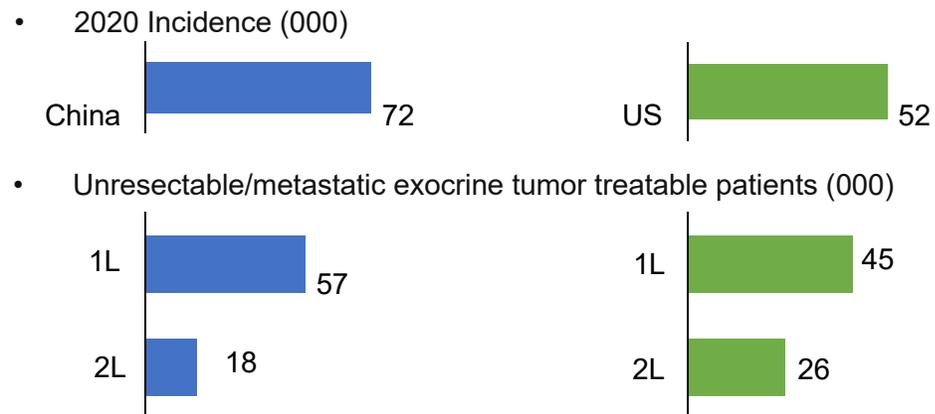
Human protein atlas database

**CLDN18.2 was overexpressed in many types of tumor tissues**, including gastric cancer, gastric and gastroesophageal junction cancer (GC/GEC), pancreatic cancer, bile duct adenocarcinoma, ovarian cancer and non-small cell lung cancer

## Gastric Cancer

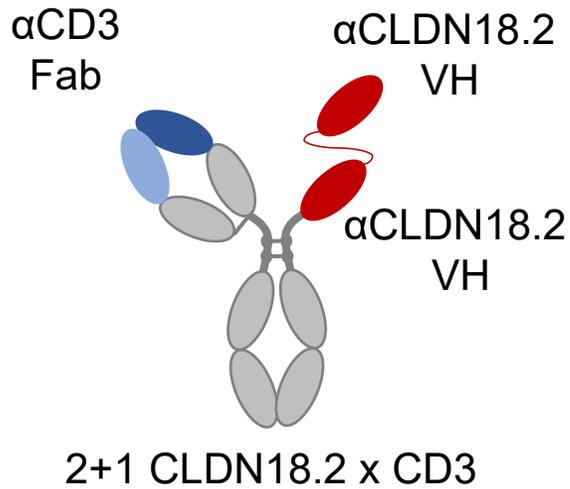


## Pancreatic Cancer



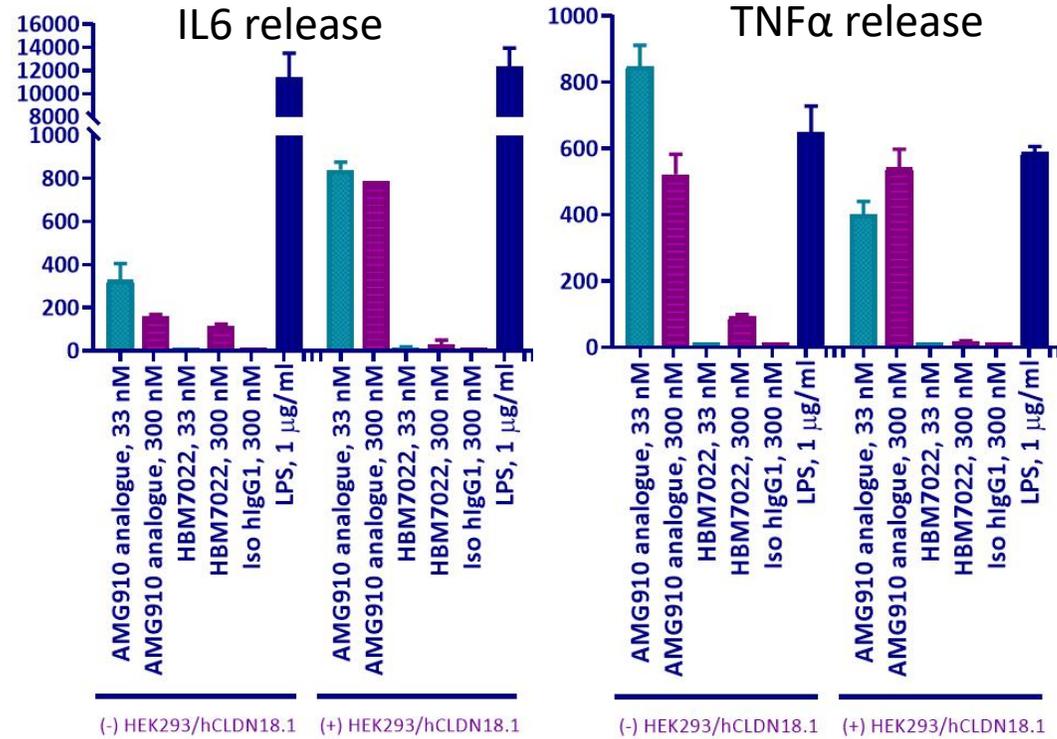
Source: DRG

# HBM7022: Novel Bispecific Antibody License-out to AstraZeneca for Global Development

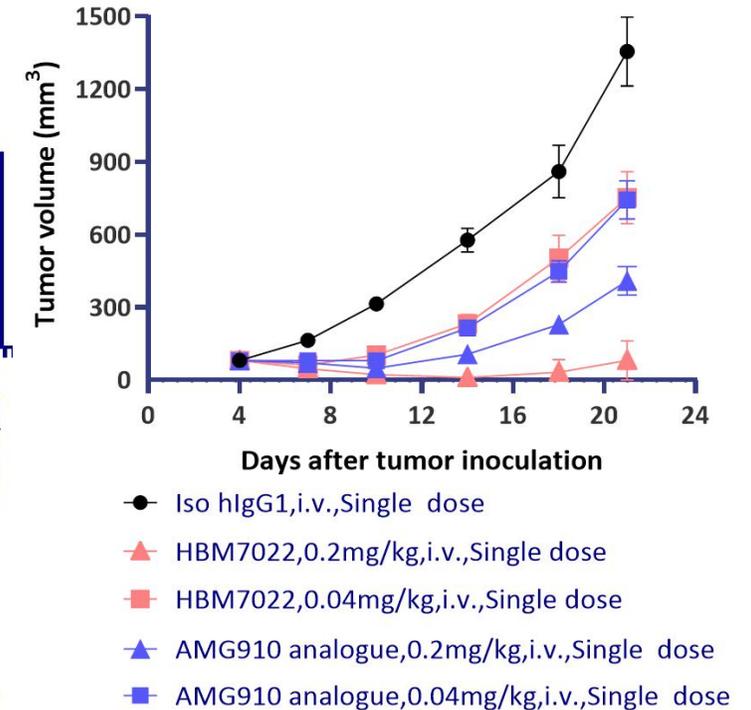


**CLDN18.2 x CD3**  
**HBICE®**

HBM7022 with tuned CD3 activity induces minimal cytokine release in vitro



HBM7022 Showed Potent Tumor Inhibition in Gastric Cancer Model



Antibody Therapeutics & Engineering Europe (June 8-10, 2021)

An aerial view of Europe with a network of white lines and dots overlaid on the map, representing a global or regional network. The background is a dark blue gradient.

# HBM Bispecific Immune Cell Engagers (HBICE®) Portfolio



# HBM's Immune Cell Engager (HBICE<sup>®</sup>) Portfolio

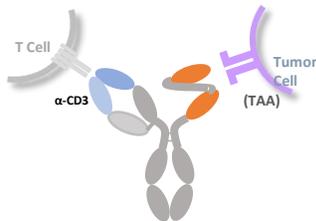
HBICE <sup>®</sup>	Discovery	Pre-clinical	IND	Ph1
<b>B7H4 × 4-1BB</b>	TNBC, ovarian, lung cancers			
<b>BCMA × CD3</b>	Multiple myeloma			
<b>CLDN18.2 × CD3</b>	Gastric, pancreatic cancers			
<b>Undisclosed</b>	Solid tumors			
<b>Undisclosed</b>	Solid tumors			
<b>Undisclosed</b>	Solid tumors			
<b>TAA × 4-1BB</b>	Solid tumors			
<b>NK engager</b>	Solid tumors			



# Representative Assets Generated From Harbour HBICE®

	HBM7022 (Claudin18.2xCD3)	HBM7008 (B7H4 x 4-1BB)	HBM7020 (BCMA x CD3)
Asset Overview	Differentiated 2+1 format CD3 T cell engager for Claudin18.2 positive tumors	B7H4 x 4-1BB HBICE®-based bispecific T cell engager	BCMA x CD3 HBICE®-based bispecific T cell engager
Indication	<b>Solid Tumors</b>	<b>Solid Tumors</b>	<b>Multiple myeloma</b>
Status	<b>Preclinical</b>	<b>Ph1</b>	<b>IND in 2022</b>
Highlights	<ul style="list-style-type: none"> <li>• <b>Unique 2+1 format</b> bispecific T cell engager with <b>optimized anti-CD3 activity</b></li> <li>• Strong <b>VH/HCAb based</b> bivalent binding to Claudin18.2</li> <li>• Potent efficacy, <b>minimal cytokine release</b>, and better safety profile</li> </ul>	<ul style="list-style-type: none"> <li>• <b>First-in-class bispecific</b> based on HBICE® platform</li> <li>• Activate on <b>2<sup>nd</sup> signal</b> stimulation <b>specifically in tumor microenvironment</b> to inhibit tumor growth, and potentially translate to <b>better safety</b></li> </ul>	<ul style="list-style-type: none"> <li>• New generation BCMAxCD3 bispecific with <b>2+1 format</b> and <b>optimized CD3 activity</b></li> <li>• High tumor killing specificity <b>with less cytokine storm risk</b>.</li> </ul>

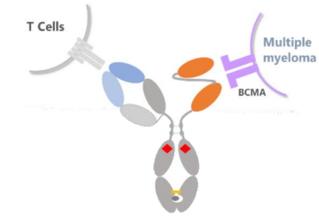
HCAb-based “2+1” format



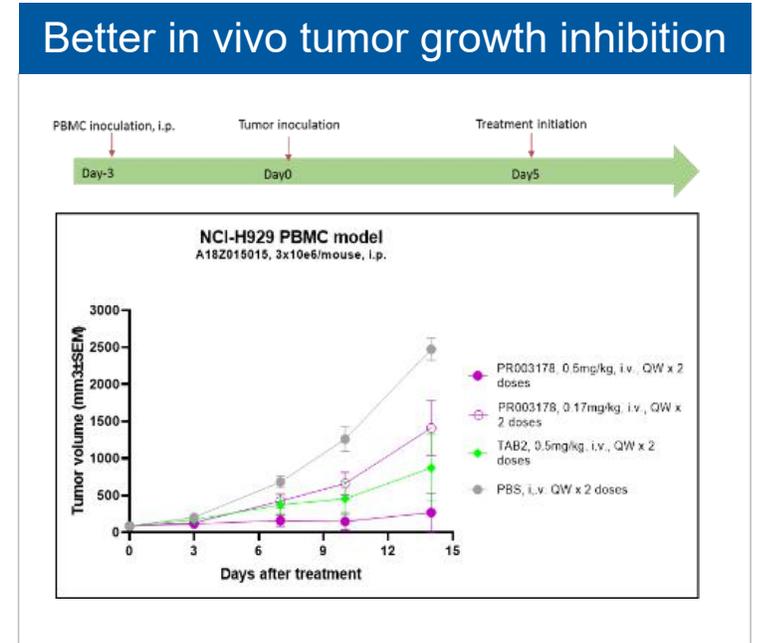
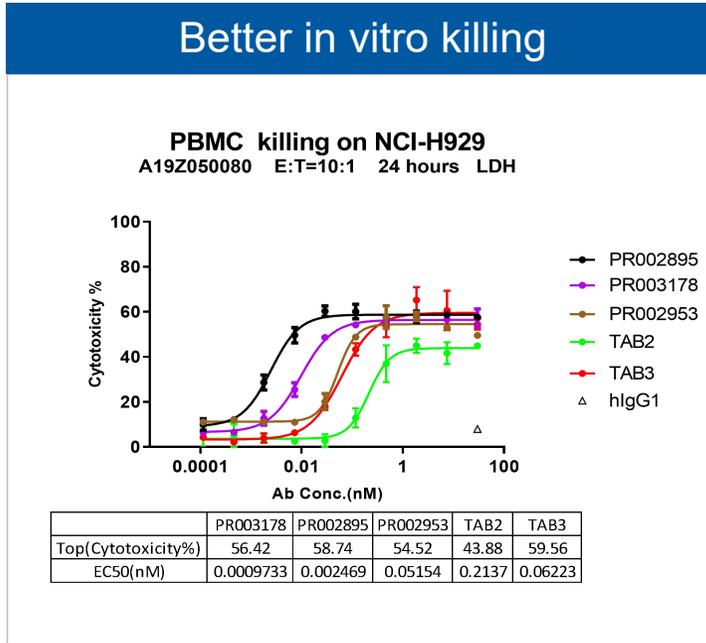
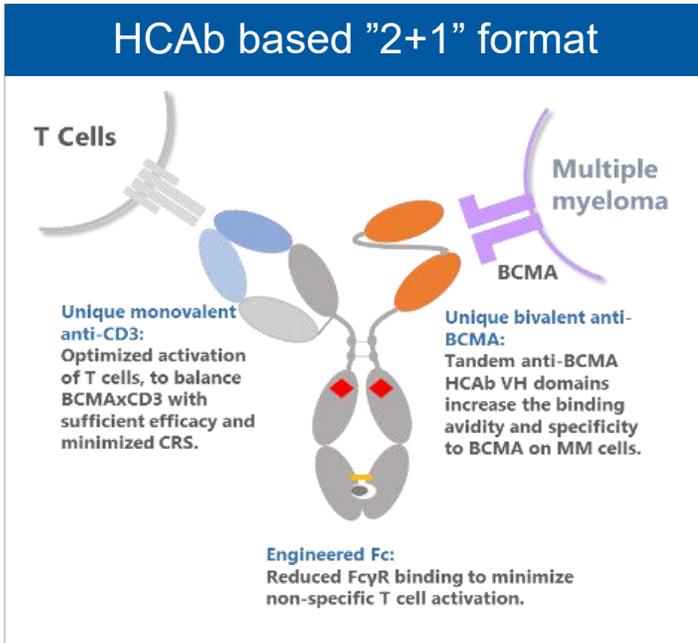
HCAb-based “2+2” format



HCAb-based “2+1” format



# HBM7020: Potential 'Best-in-Class' BCMA×CD3 HBICE® With Improved Therapeutic Window



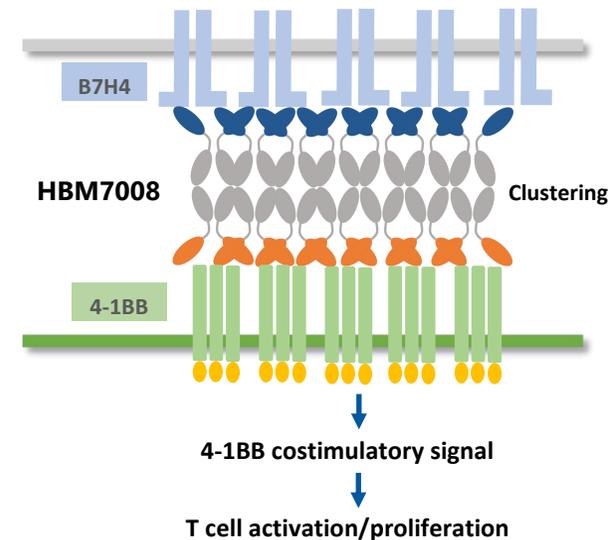
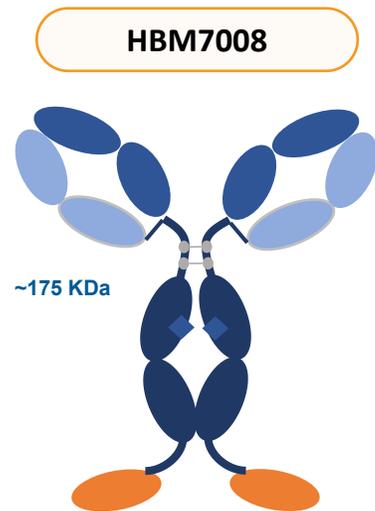
- "2+1" format for better myeloma cell targeting via cooperative binding
- Optimized CD3 activity to minimize CRS
- Silenced Fc for long half-life and less non-specific crosslinking
- Better in-vitro killing, and in-vivo anti-tumor efficacy



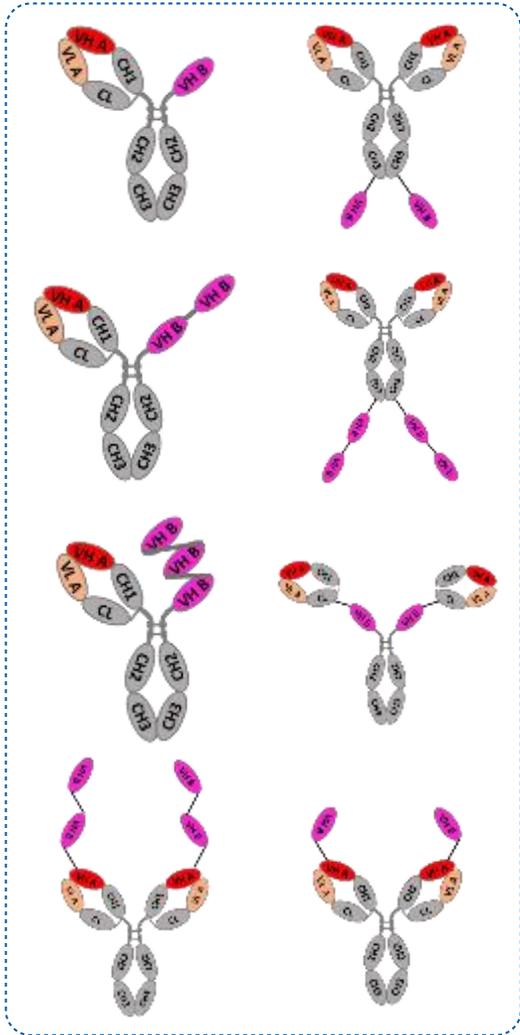
# HBM7008: First-in-Class Bispecific Antibody from the HBICE® Platform

## Highlights:

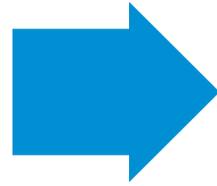
- **MoA:** Crosslinking dependent 4-1BB activation is stringently mediated by B7H4 binding
- **Molecule:** Based on HBICE® platform to optimize the geometry for 4-1BB clustering, T/Tumor cell dual binding
- **Druggability:** Fully human sequences from Harbour mice undergone natural in-vivo selection. Symmetrical format with excellent biophysical properties
- **Indications:** Mutual exclusively expressed with PD-L1, potential for PD1/PD-L1 therapy refractory patients, particularly in multiple gynecological cancers



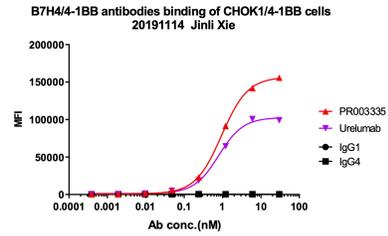
# HBICE® Platform Provides the Best Geometry Design for the MoA of HBM7008



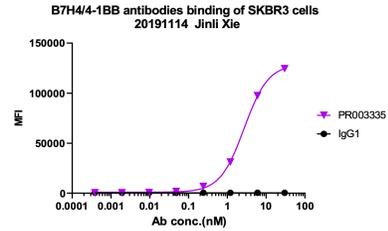
Format Engineering



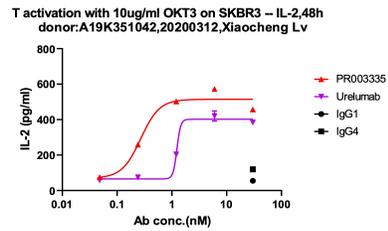
## 4-1BB Binding



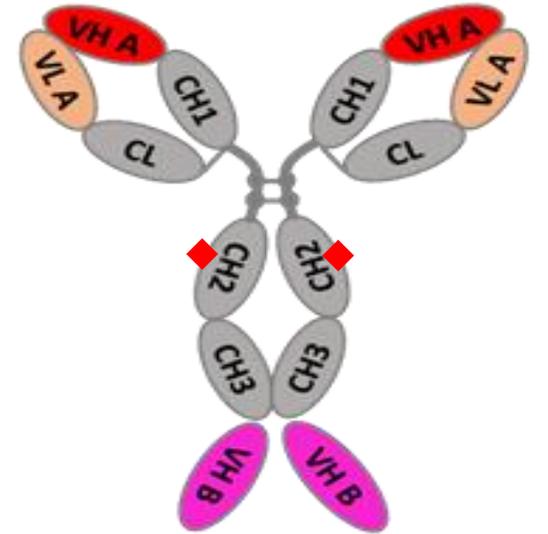
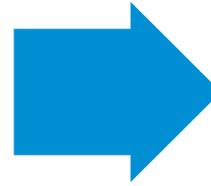
## B7H4 Binding



## T Activation



Linker/  
Sequence Engineering

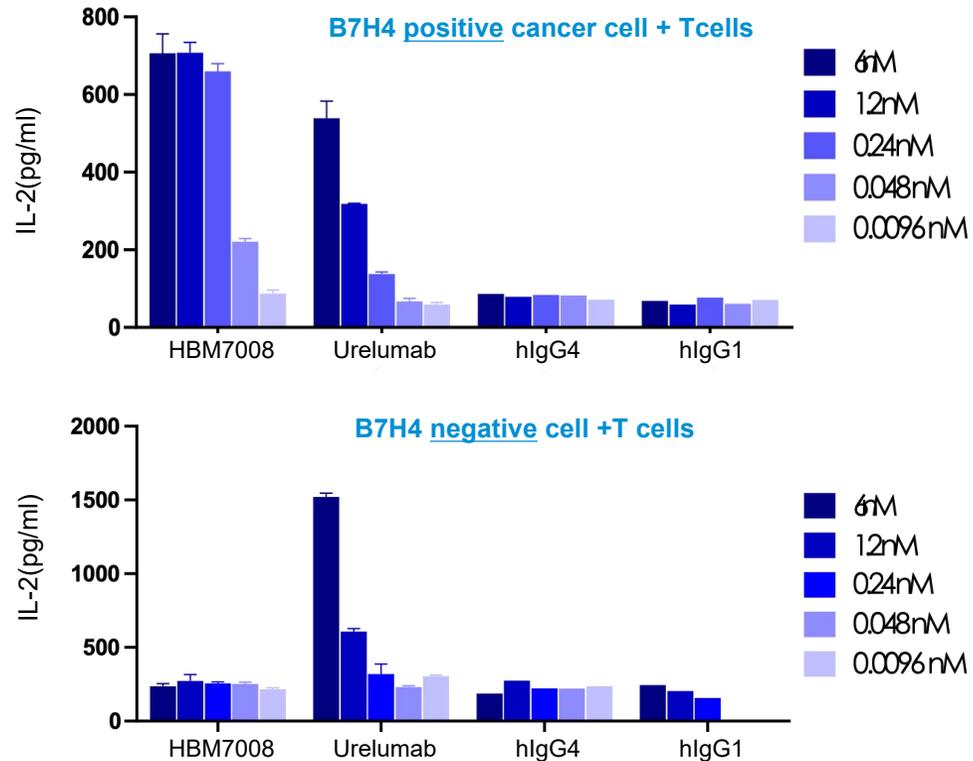




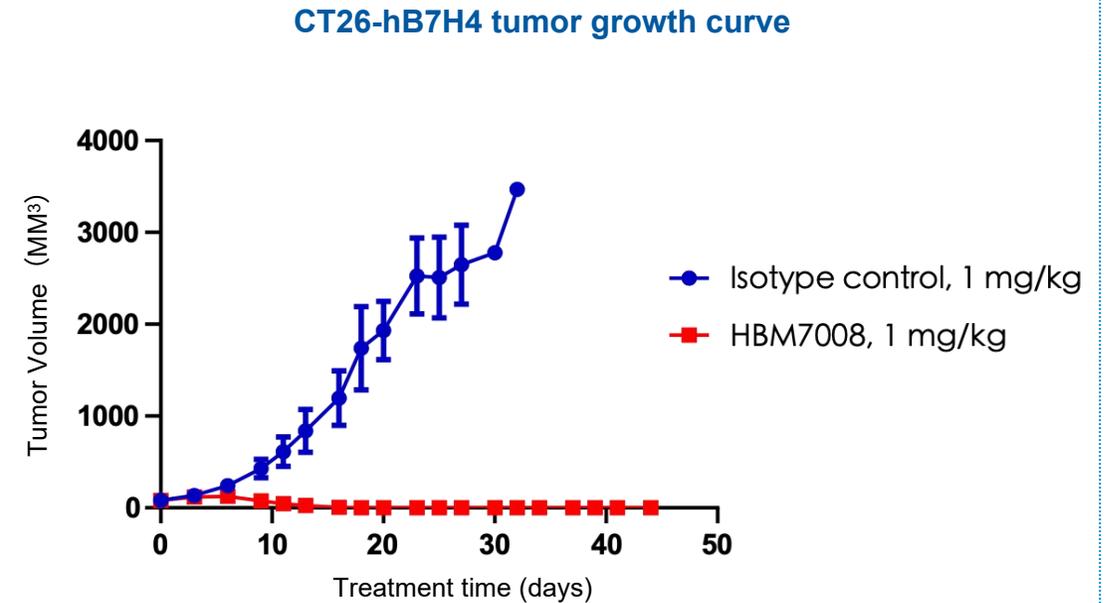
# HBM7008: First-in-Class Bispecific Antibody from the HBICE® Platform

*Encouraging monkey DRF and Tox data also suggest its excellent PK and safety profile*

## B7H4 dependent 4-1BB activation and T cell stimulation

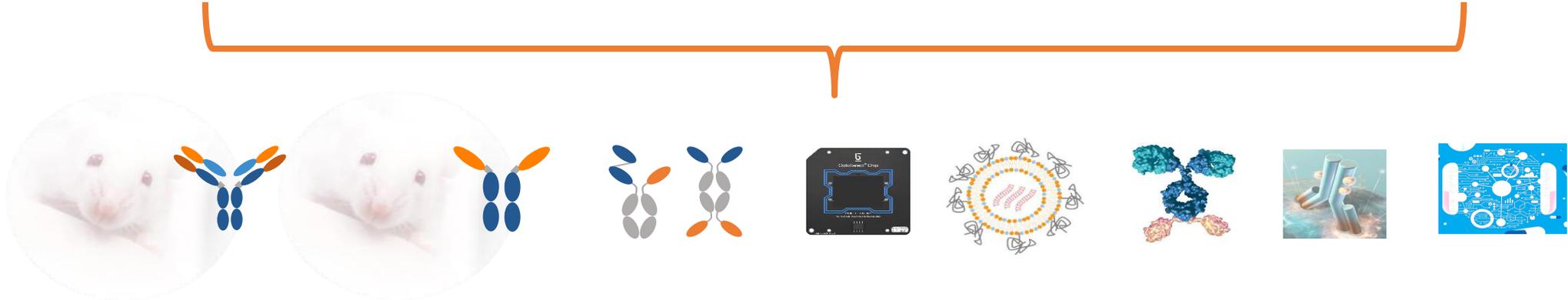
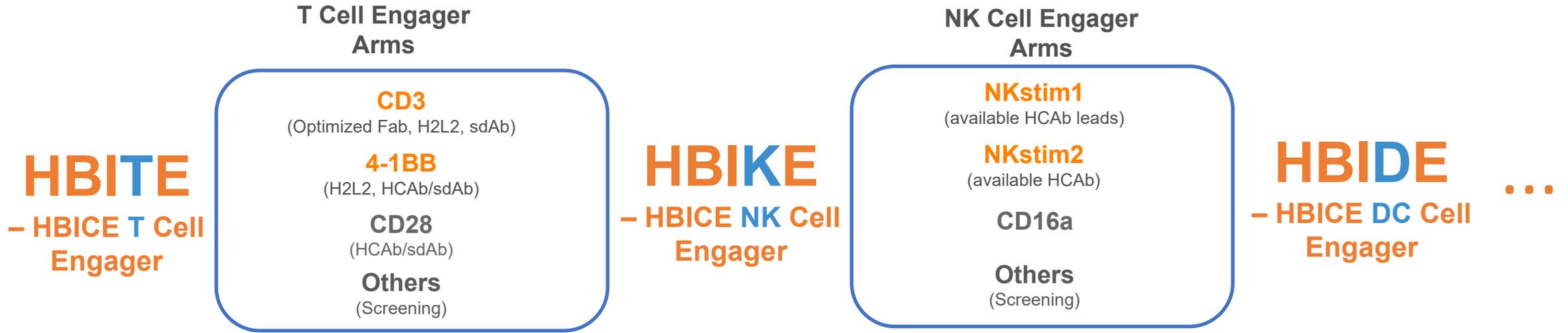


## HBM7008 completely leads tumor regression in B7H4 positive syngeneic model





# HBICE® Portfolio is Continuously Growing, Evolving and Partnering



# Q&A



# THANK YOU



*Harbour BioMed*  
*WeChat Account*

**CONTACT US:**  
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[www.harbourbiomed.com](http://www.harbourbiomed.com)

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