# Bispecific Immune Cell Engagers Built From Harbour HBICE® Platform

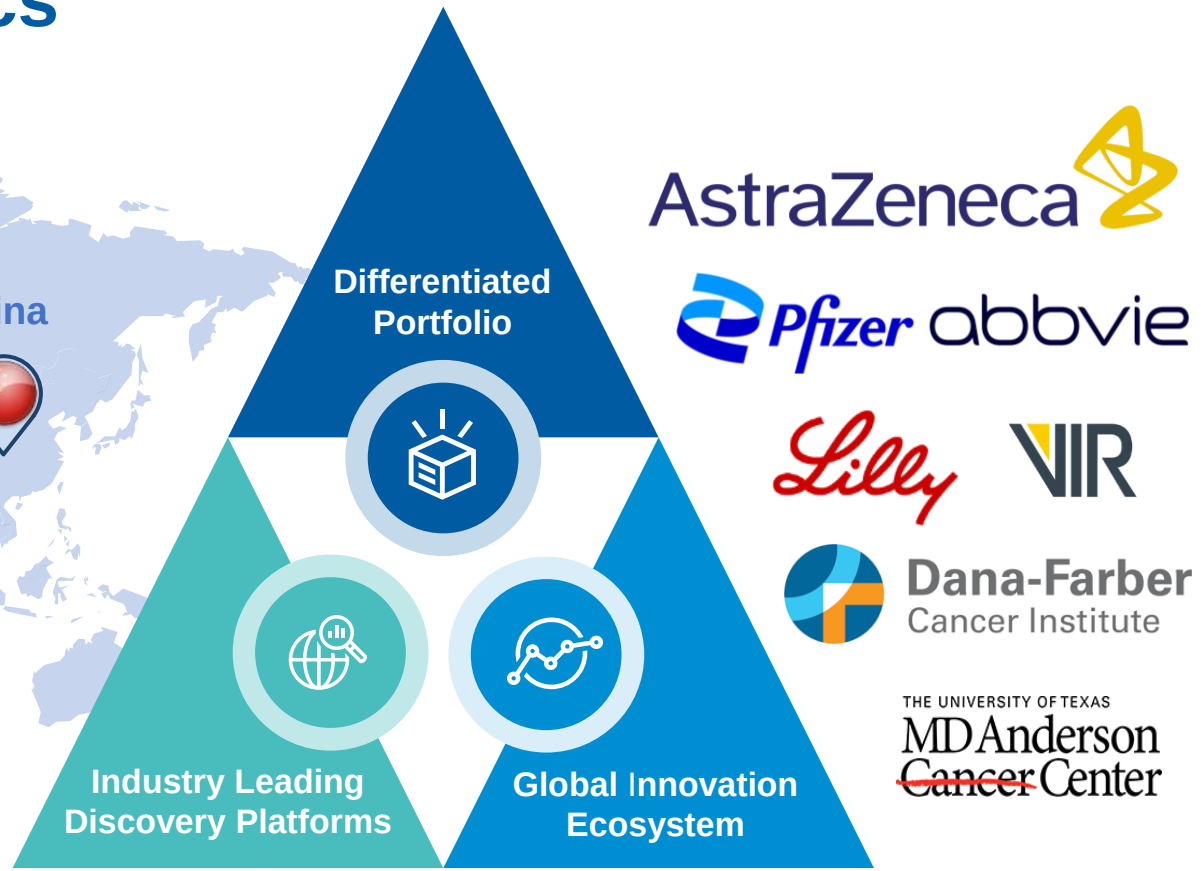
**Apr 2022**

**HBM HOLDINGS-B: 02142.HK**

www.harbourbiomed.com

# Harbour BioMed:
# A Rapidly Rising Global Innovative Biopharmaceutical Company

## Next-Gen Therapeutics


AstraZeneca

Pfizer abbvie

Lilly VIR

Dana-Farber Cancer Institute

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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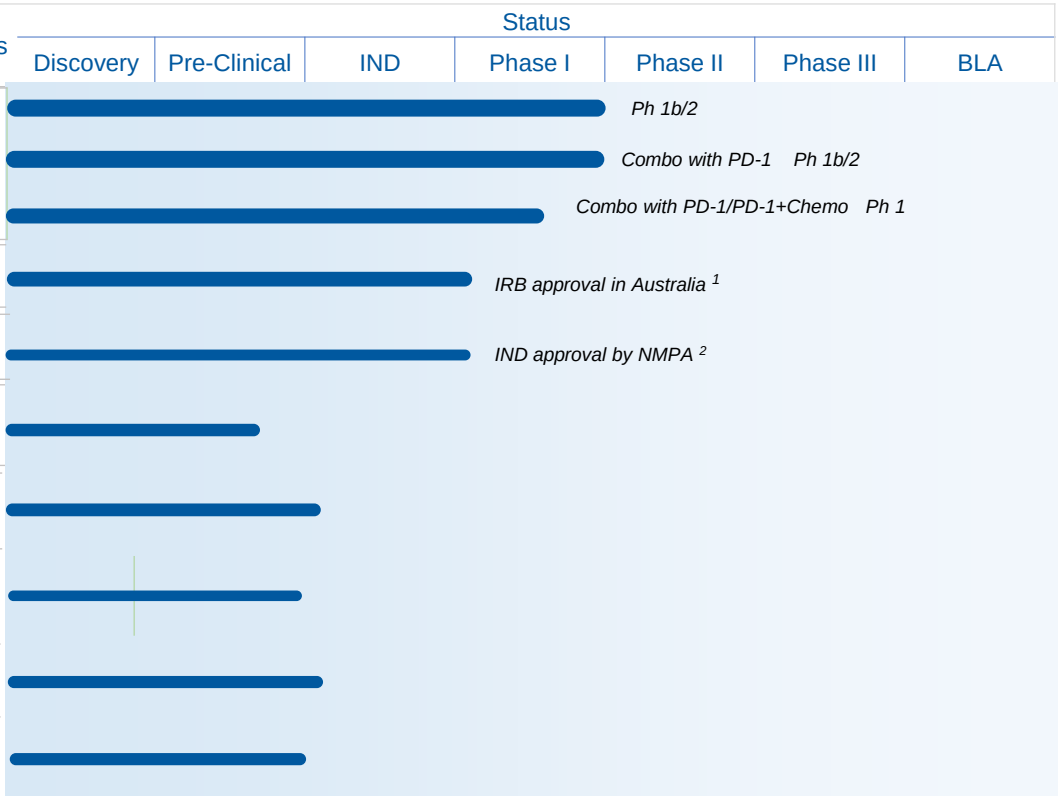
# Robust Pipeline Combining Advanced Clinical Programs Addressing Highly Unmet Needs and Novel Molecules Leveraging HBM Antibody Platforms

| Project | Target | Indication | Commercial Rights |
|---|---|---|---|
| HBM4003 | CTLA-4 | Solid Tumors [a] | Global |
| | | Solid Tumors [b] | |
| | | Solid Tumors [c] | |
| HBM7008 | B7H4×4-1BB | Solid Tumors | Global |
| HBM9378 | TSLP | Asthma | Global |
| HBM7022 | Claudin18.2xCD3 | Solid Tumors | License out AstraZeneca |
| HBM1022 | CCR8 | Solid Tumors | Global |
| HBM1020 | B7H7 | Solid Tumors | Global |
| HBM7020 | BCMA×CD3 | Multiple Myeloma | Ex-Greater China [d] |
| 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

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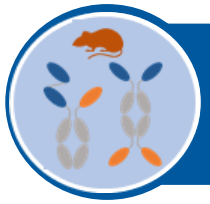
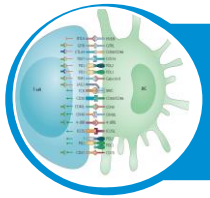
# HBM Global Innovation Ecosystem Leads Next-Gen Therapeutics

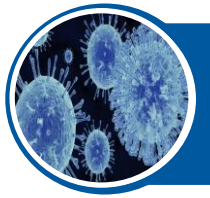
## HBM Next-Gen Innovative IO Therapy Strategy



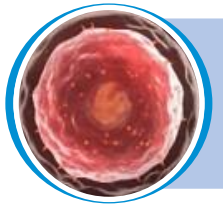
**Immune Cell Engager** — HBM7008, HBM7020, …



**Novel Immune Evasion Pathway** — HBM1020, HBM7008, …



**Treg Depletion** — HBM4003, HBM1022, …



**Innovation in Novel Frontier NK/ADC** — 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)



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# Overview of HBICE® Technology and Harbour Mice

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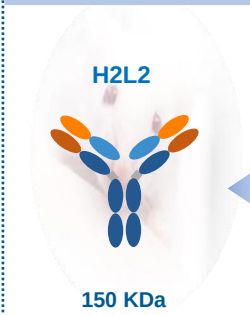
# Cutting Edge Fully Human Antibody Platforms Enable Sustained Invention of Novel Molecules

## H2L2 – Full IgG Antibody Discovery Platform




**HBM1020**

A fully human antibody against B7 family target for the treatment of solid tumors

**HBM9378**

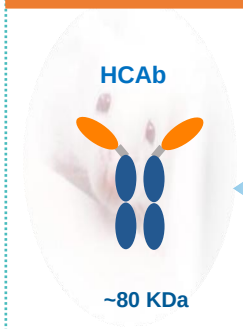
A fully human antibody against TSLP for severe asthma

Robust and highly efficient, global IP and clinically validated

Ligand / MT — **$ 178 M** — Platform only

SANOFI / kymab — **$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 / Ablynx — **$ 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 B7H4×4-1BB bispecific antibody

Self-developed, unique geometric flexibility, promising bispecific biology

Lilly / Merus — **$ 1.6 B** — 3 BsAb slots based on Biclonics platform

abbvie / Genmab — **$ 3.2 B** — 3 BsAb ADC slots based on Duobody platform

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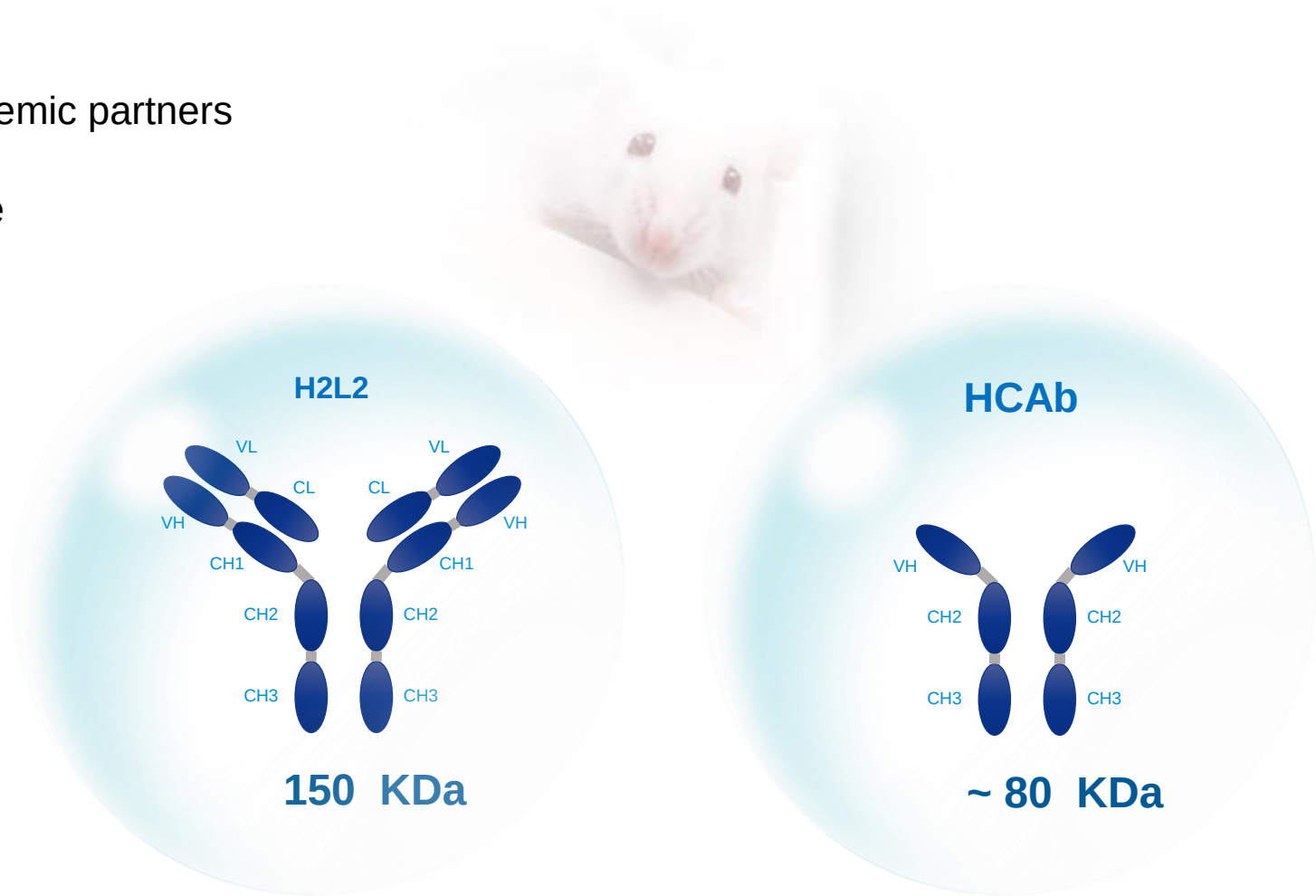
# Harbour Mice®: Industry Leading Platform Technology to Generate Fully Human Monoclonal Antibodies

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

**Human**
**Natural**
**Optimized**

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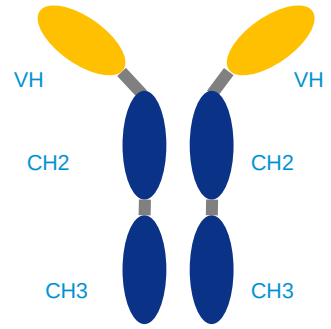
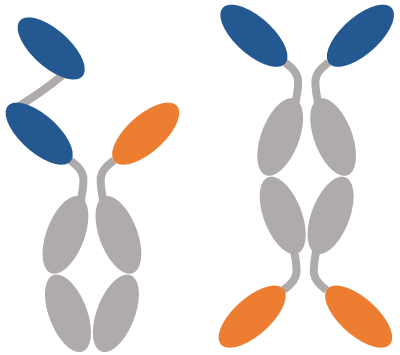
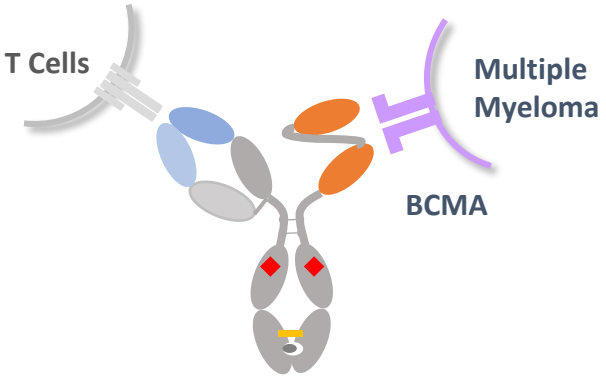
# Fully Human HCAb Has Broad Applications For Bispecifics, CAR-T, Diagnostics, Carrier For Conjugates, Topical Route

## Monoclonal antibody




## Bispecific antibody

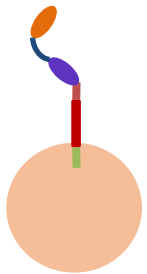





## Nanobody

## Diagnostic

## CAR-T



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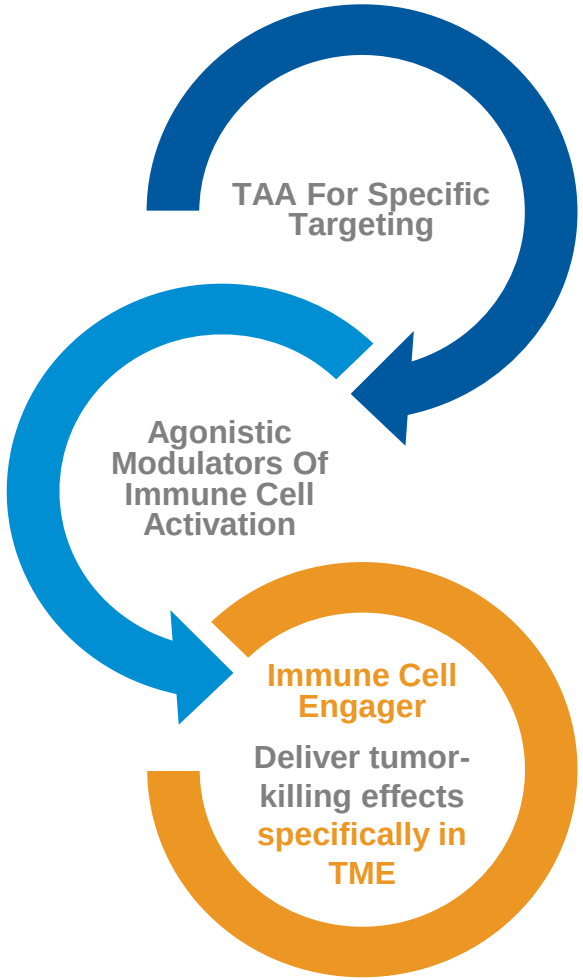
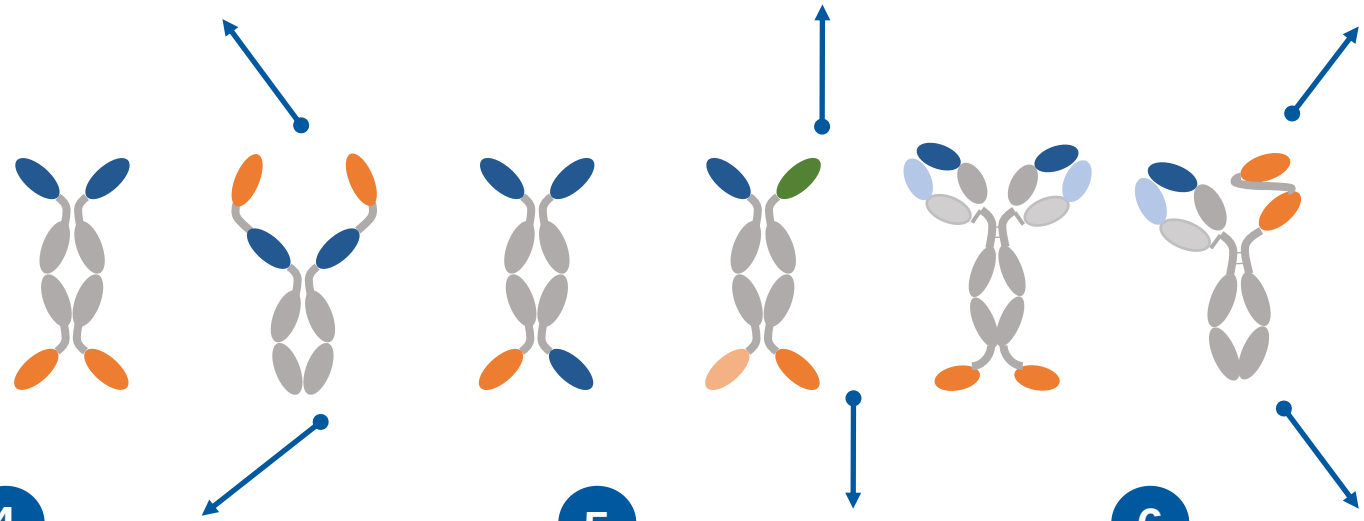
# Harbour HCAb Provides Versatile Geometries to Build Bispecific / Multi-specific Immune Cell Engagers (HBICE®)




TAA: tumor associated antigen
TME: tumor microenvironment

1. Flexible geometries adapt to crosslinking/clustering/dual binding/immune synapse formation
2. Flexible geometries adapt to crosslinking/clustering/dual binding/immune synapse formation
3. 2+1 format confers cooperative binding to tumor antigen



4. Smaller size for better tissue penetration
5. Fully human sequences with decent CMC developability
6. Intact silent Fc extends half-life, avoids Fc crosslinking or ADCC

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

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# 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, …

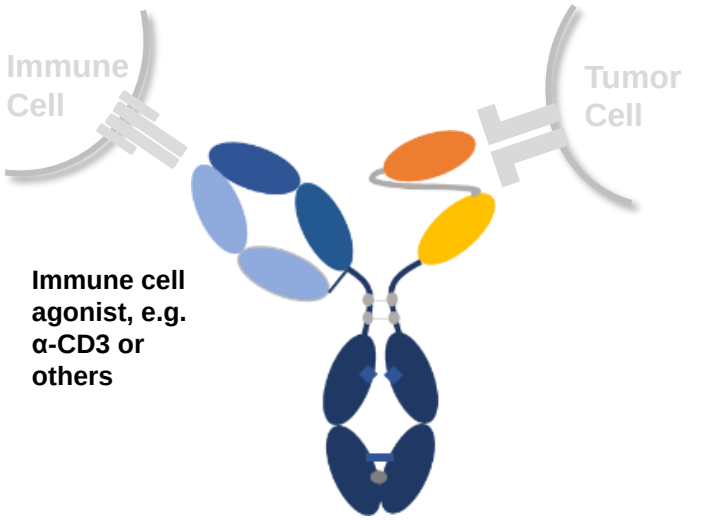
**Agonistic Modules For Immune Cell Activation**

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

**Immune Cell Engager**

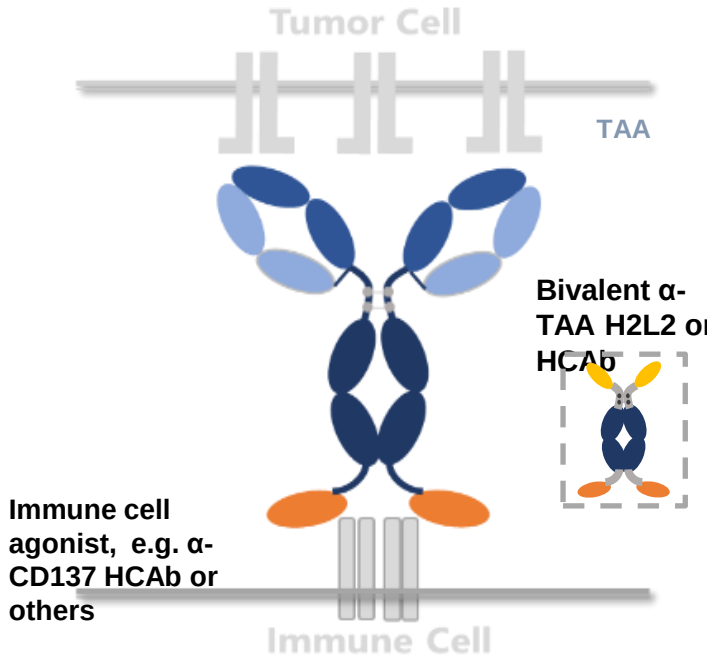
Deliver tumor-killing effects unachievable by combination therapies

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




**CD3 mediated** cytotoxic T engaging and directly kill tumor cells with CRS

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




**4-1BB mediated** tumor dependent T cell activation including memory T without CRS

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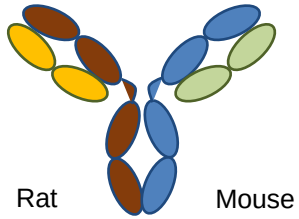
# HBM is at the Forefront of New Generation of T-Cell Engager Bispecific Antibodies

## FcyR engaging

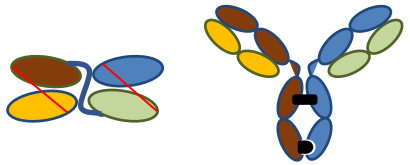



**Catumaxumab**

## FcyR-silenced

Short half life

Extended half-life



**Blinatumomab**

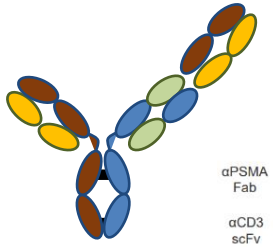
AMGEN

MacroGenics

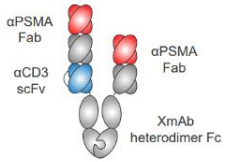
Genmab

...

## Optimized aCD3, 2+1 format



RG7802




2+1 PSMA x CD3

Roche

xencor

abbvie

Teneobio

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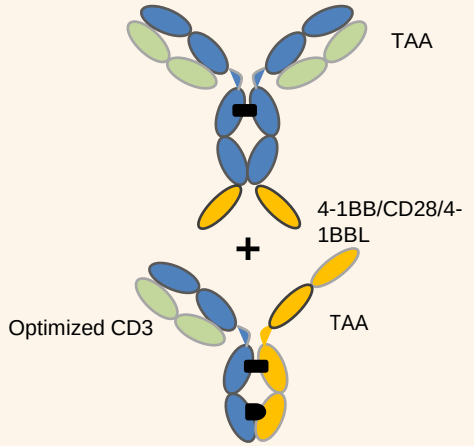
## Trispecific or 2nd signal bispecific combination




Roche

SANOFI

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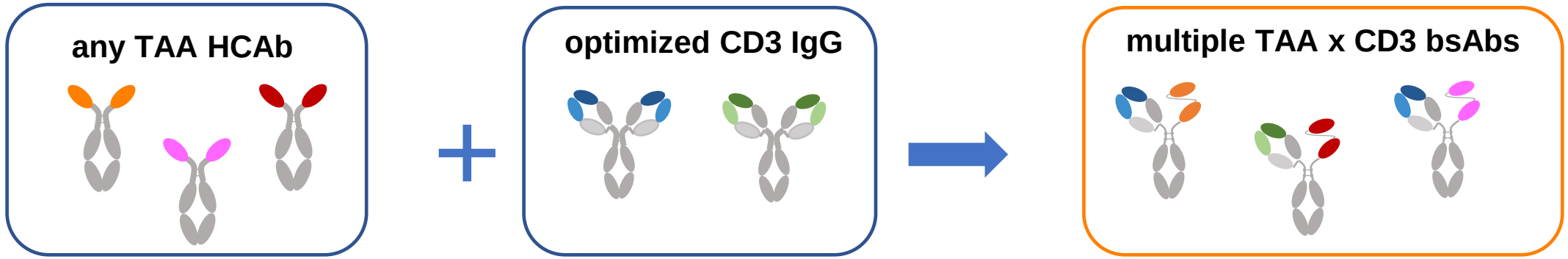
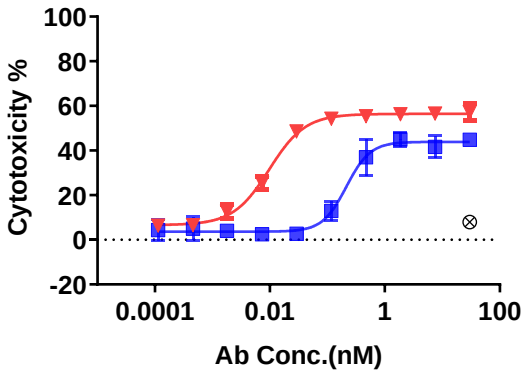
# CD3 HBICE® Generated From Fine-Tuned “2+1”Structure



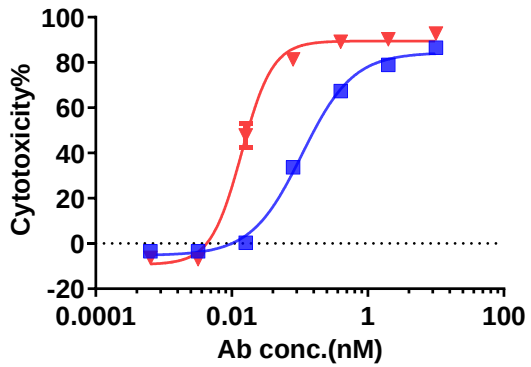

## Cytotoxicity to TAA⁺ tumor cells

CD3

TAA-1




TAA-2




TAA-3

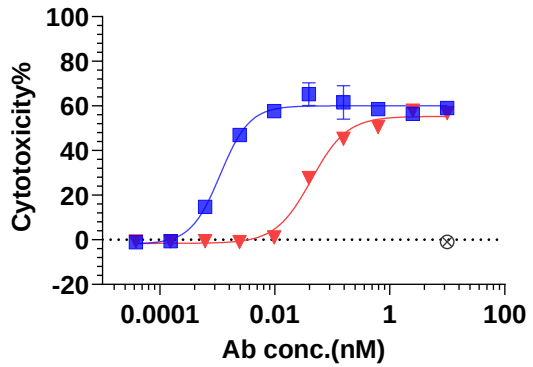



***Figure legends:***
***Benchmark bsAb***
***TAA x CD3 ‘2+1’ HBICE***
***IgG1 iso***

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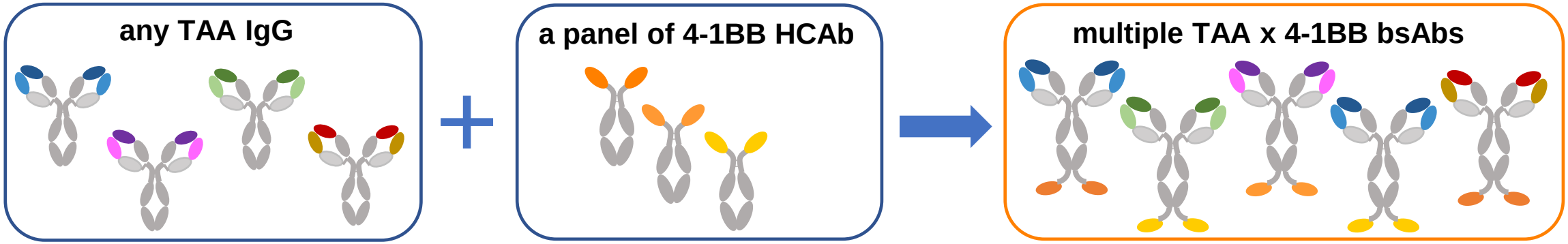
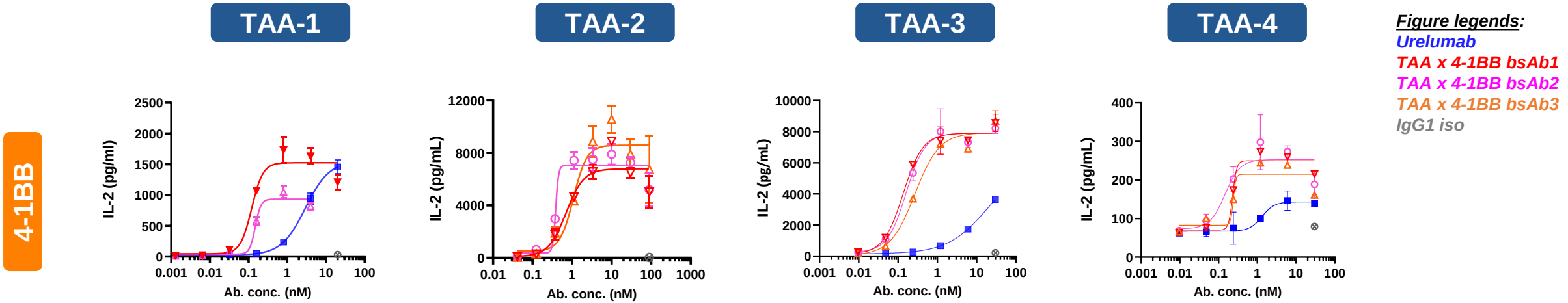
# 4-1BB HBICE® Generated from the "Plug & Play" Platform




## T activation in the presence of TAA+ tumor cells

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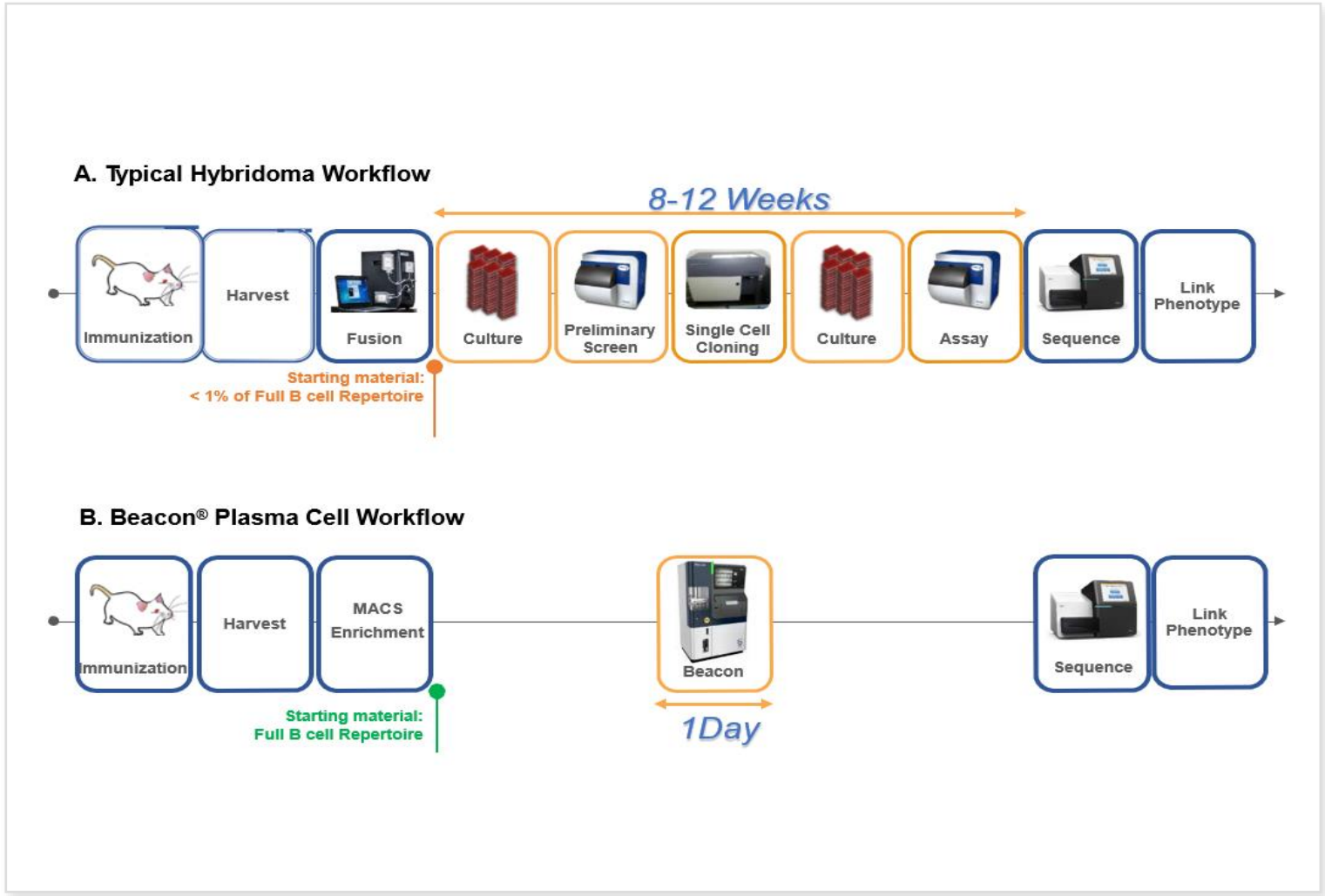
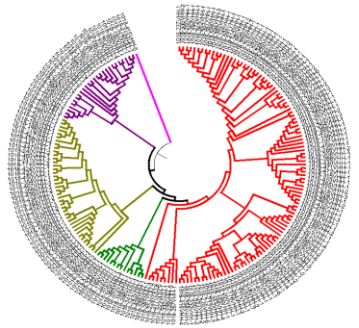
# Single B Cell Technology Accelerates Antibody Screening and Enables "Antibody Mining" for Challenging Targets or Rare Epitopes




## 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

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

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# 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® , **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

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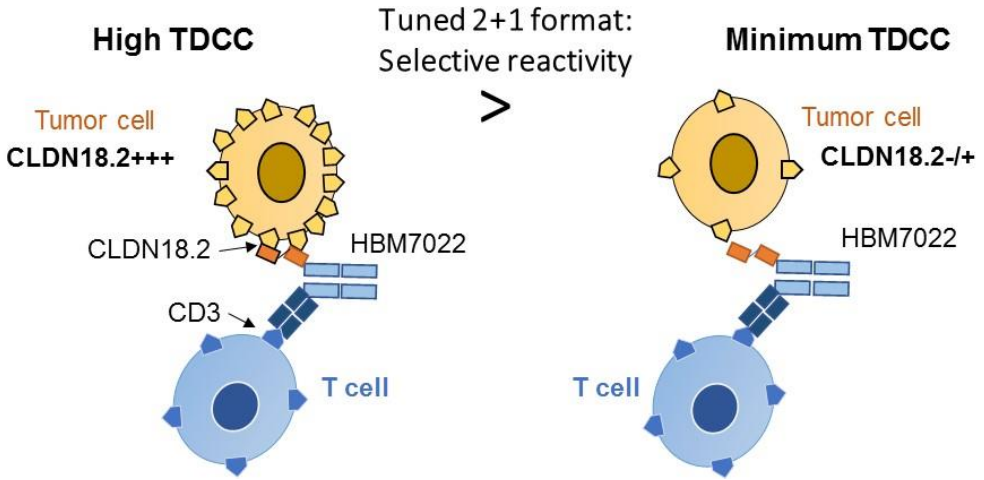
AstraZeneca

### 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

### MOA of HBM7022

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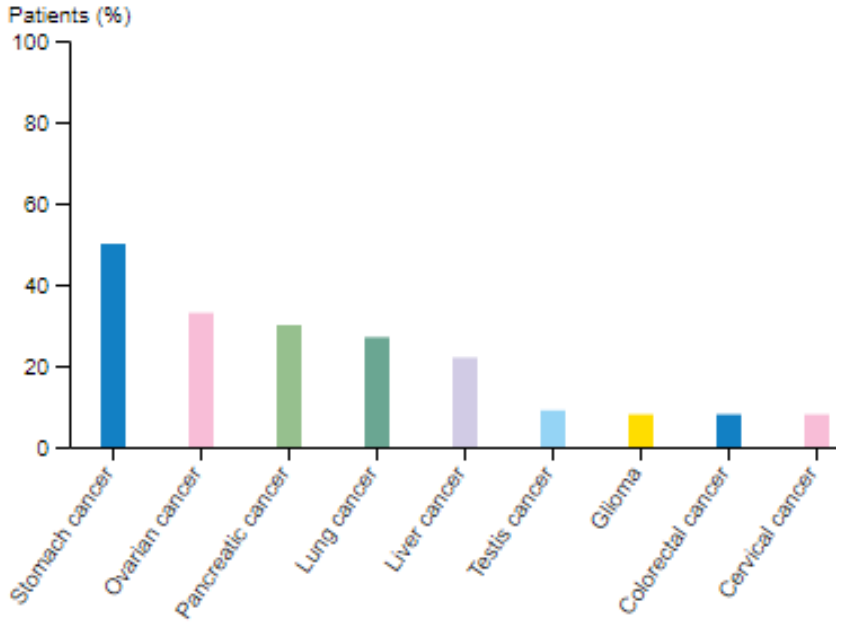
# HBM7022: Targeting Claudin18.2 Positive Solid Tumors with Huge Unmet Medical Needs



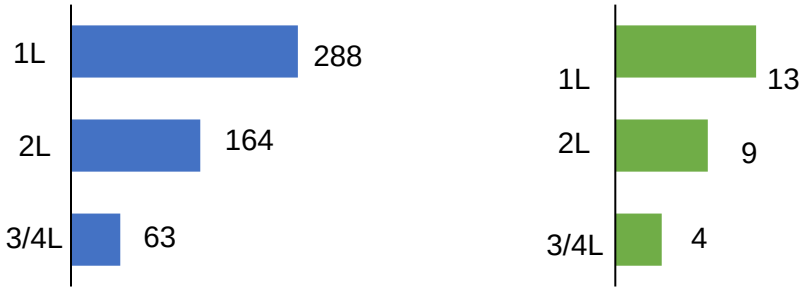

*Human protein atlas database*

**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***

- 2020 Incidence (000)


- Unresectable/metastatic HER2 negative treatable patients (000)




***Pancreatic Cancer***

- 2020 Incidence (000)


- Unresectable/metastatic exocrine tumor treatable patients (000)


*Source: DRG*

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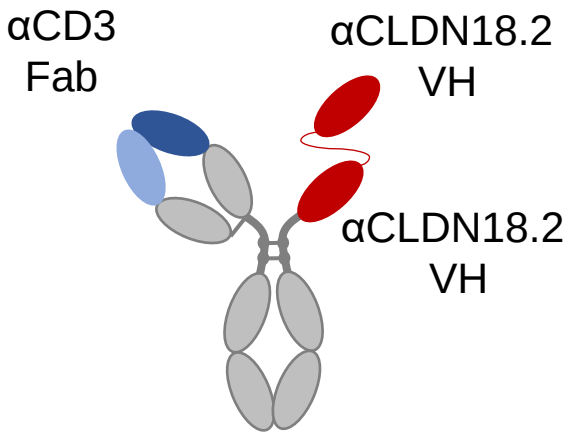
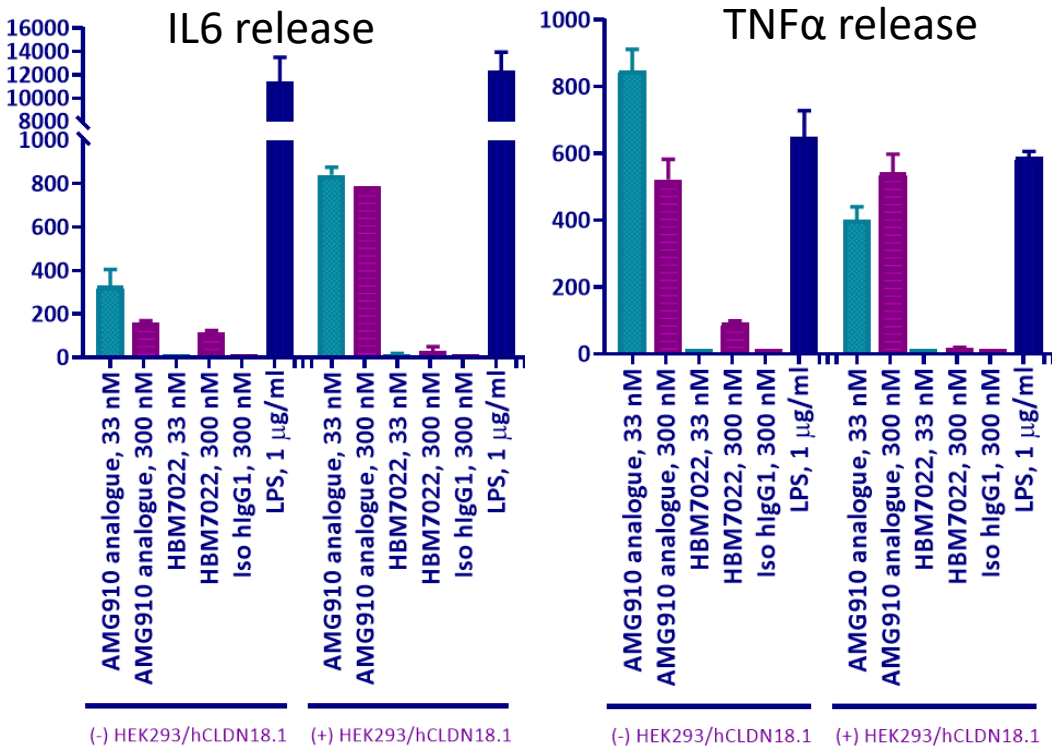
# HBM7022: Novel Bispecific Antibody License-out to AstraZeneca for Global Development



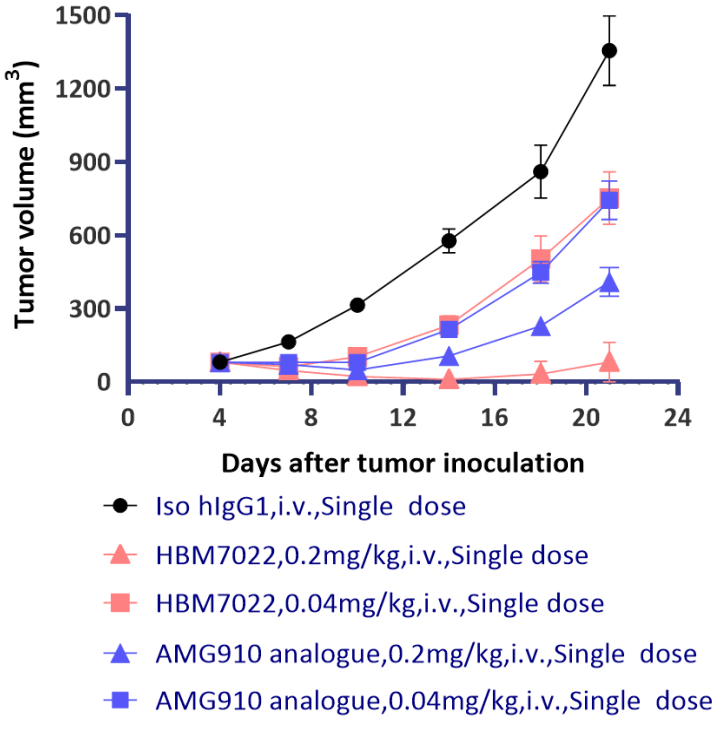

2+1 CLDN18.2 x CD3

**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)*

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# HBM Bispecific Immune Cell Engagers (HBICE®) Portfolio

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# HBM's Immune Cell Engager (HBICE®) Portfolio

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

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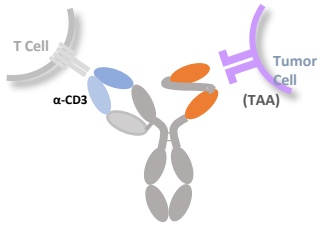
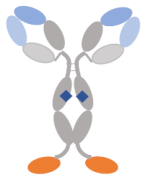
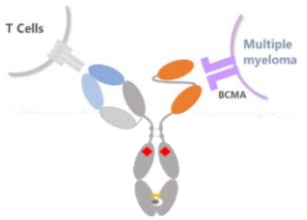
# Representative Assets Generated From Harbour HBICE®

| | 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 | **Solid Tumors** | **Solid Tumors** | **Multiple myeloma** |
| Status | **Preclinical** | **Ph1** | **IND in 2022** |
| Highlights | • Unique 2+1 format bispecific T cell engager with optimized anti-CD3 activity<br>• Strong VH/HCAb based bivalent binding to Claudin18.2<br>• Potent efficacy, minimal cytokine release, and better safety profile | • **First-in-class bispecific** based on HBICE® platform<br>• Activate on **2nd signal** stimulation **specifically in tumor microenvironment** to inhibit tumor growth, and potentially translate to **better safety** | • New generation BCMAxCD3 bispecific with **2+1 format** and **optimized CD3 activity**<br>• High tumor killing specificity **with less cytokine storm risk.** |
| | **HCAb-based "2+1" format** | **HCAb-based "2+2" format** | **HCAb-based "2+1" format** |
| |  |  |  |

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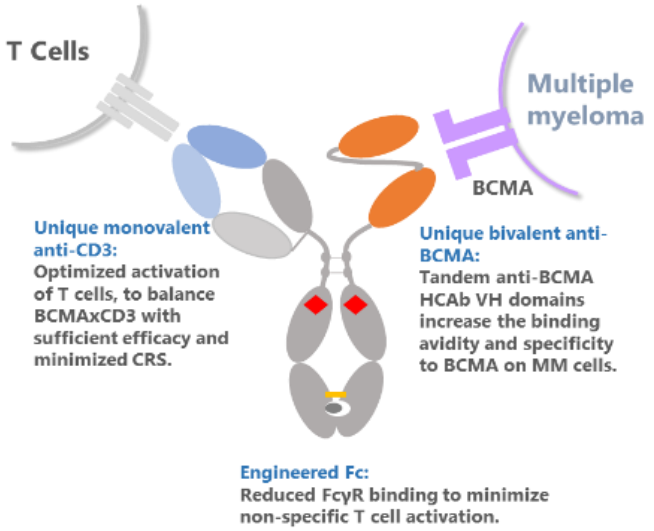
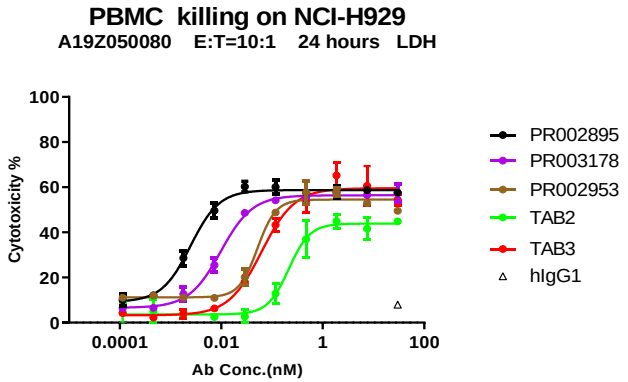
# HBM7020: Potential ‘Best-in-Class’ BCMA×CD3 HBICE® With Improved Therapeutic Window

## HCAb based ”2+1” format

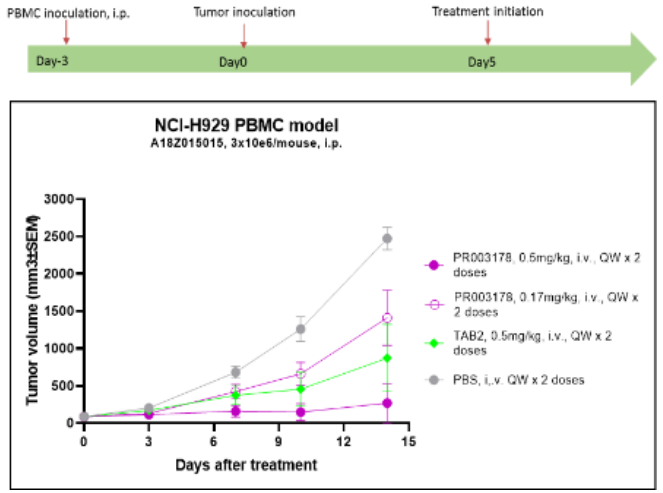



## Better in vitro killing




| | PR003178 | PR002895 | PR002953 | TAB2 | TAB3 |
|---|---|---|---|---|---|
| Top(Cytotoxicity%) | 56.42 | 58.74 | 54.52 | 43.88 | 59.56 |
| EC50(nM) | 0.0009733 | 0.002469 | 0.05154 | 0.2137 | 0.06223 |

## Better in vivo tumor growth inhibition



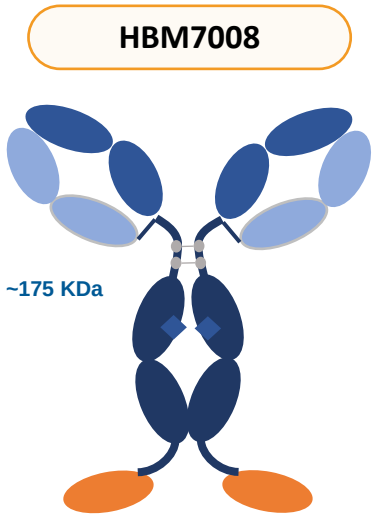

- “2+1” format for better myeloma cell targeting via cooperative binding
- Optimized CD3 activity to minimize CRS
- Silenced Fc for long half-life and less non-specific crosslinking
- Better in-vitro killing, and in-vivo anti-tumor efficacy

HARBOUR BIOMED

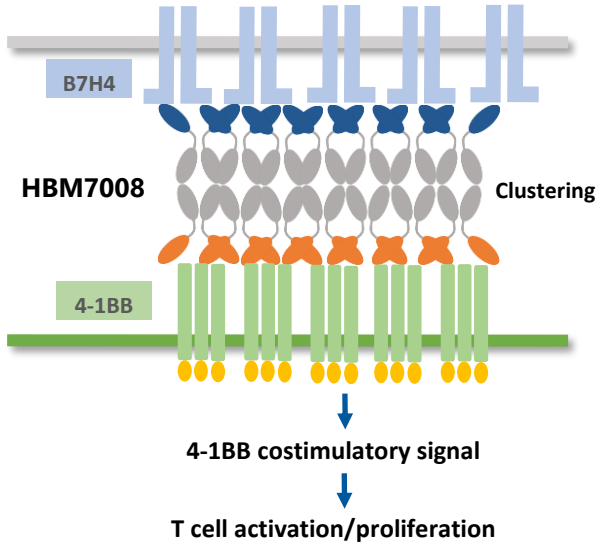
# HBM7008: First-in-Class Bispecific Antibody from the HBICE® Platform

## 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





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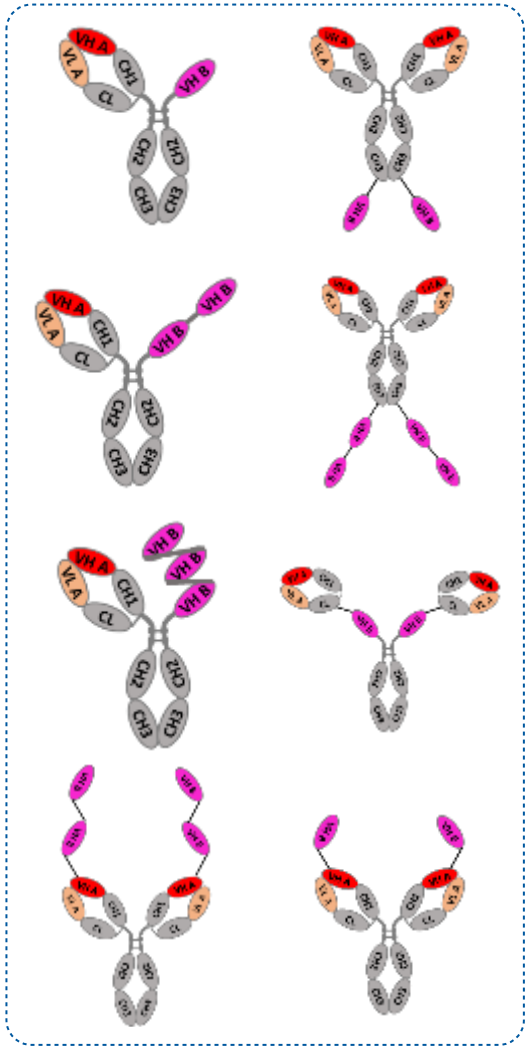
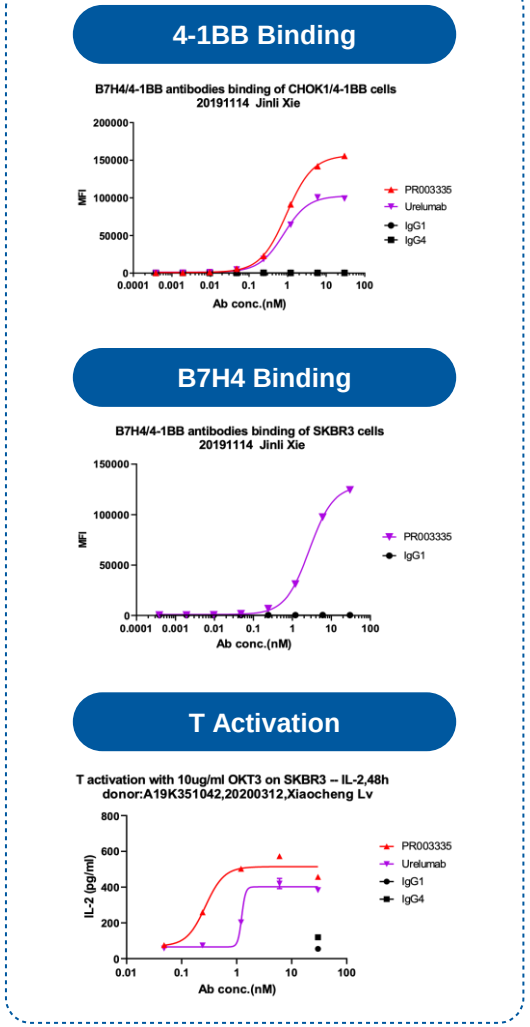
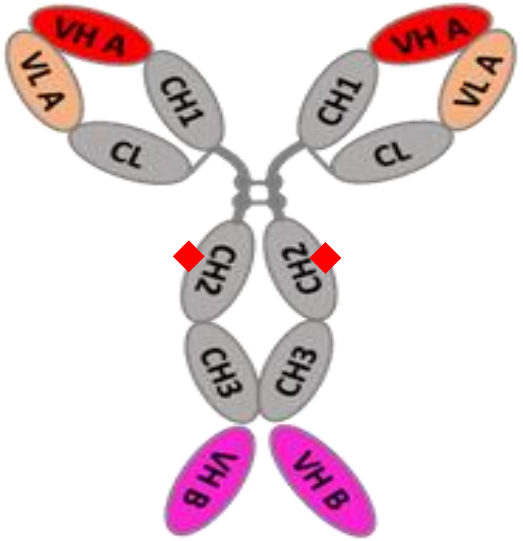
# HBICE® Platform Provides the Best Geometry Design for the MoA of HBM7008



Format Engineering




Linker/ Sequence Engineering

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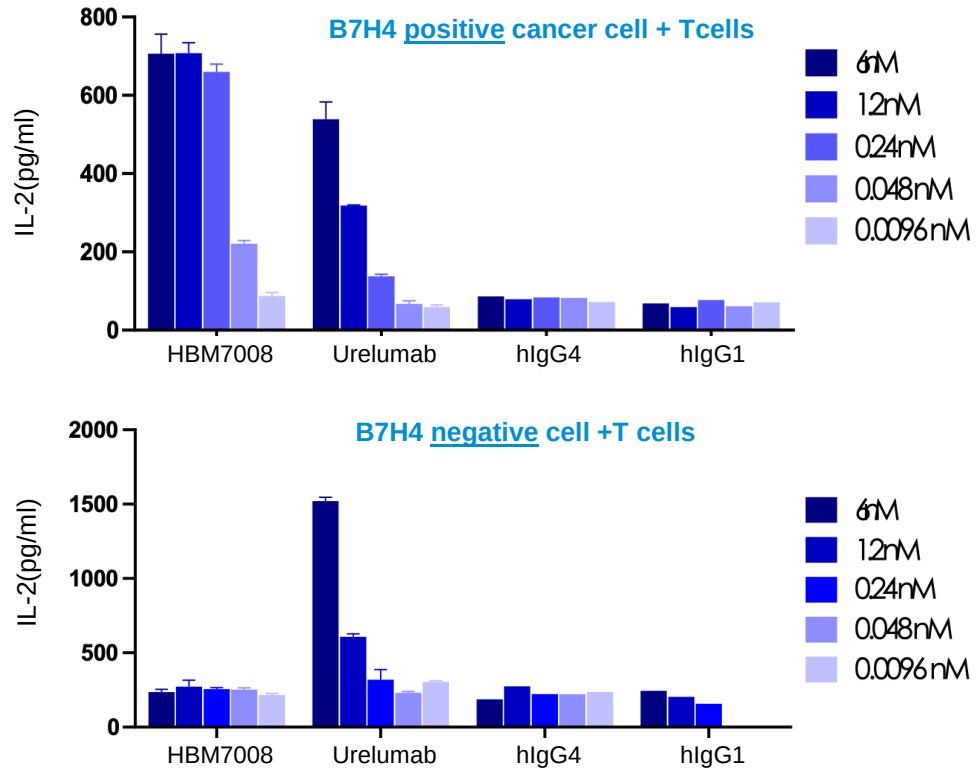
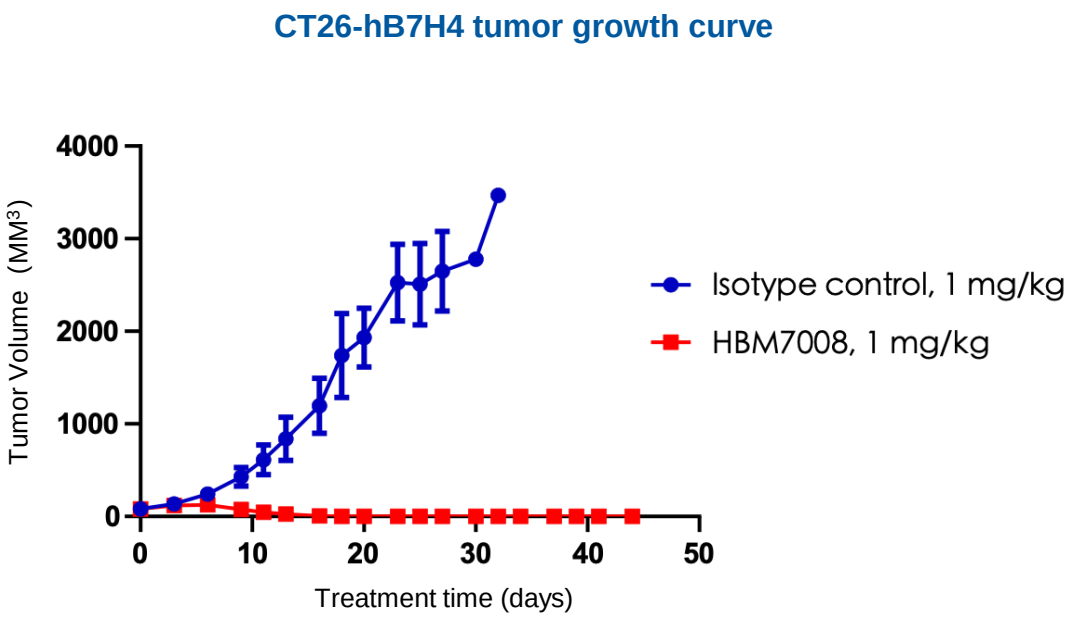
# HBM7008: First-in-Class Bispecific Antibody from the HBICE® Platform

*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

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# HBICE® Portfolio is Continuously Growing, Evolving and Partnering

**HBITE**
**– HBICE T Cell Engager**

**T Cell Engager Arms**

**CD3**
(Optimized Fab, H2L2, sdAb)

**4-1BB**
(H2L2, HCAb/sdAb)

**CD28**
(HCAb/sdAb)

**Others**
(Screening)

**HBIKE**
**– HBICE NK Cell Engager**

**NK Cell Engager Arms**

**NKstim1**
(available HCAb leads)

**NKstim2**
(available HCAb)

**CD16a**

**Others**
(Screening)

**HBIDE**
**– HBICE DC Cell Engager**

**…**

# Q&A

# THANK YOU

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