GenScript
Make Research Easy

Make Your Immunology Research Easy

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Associate Director of Marketing Division,
GenScript

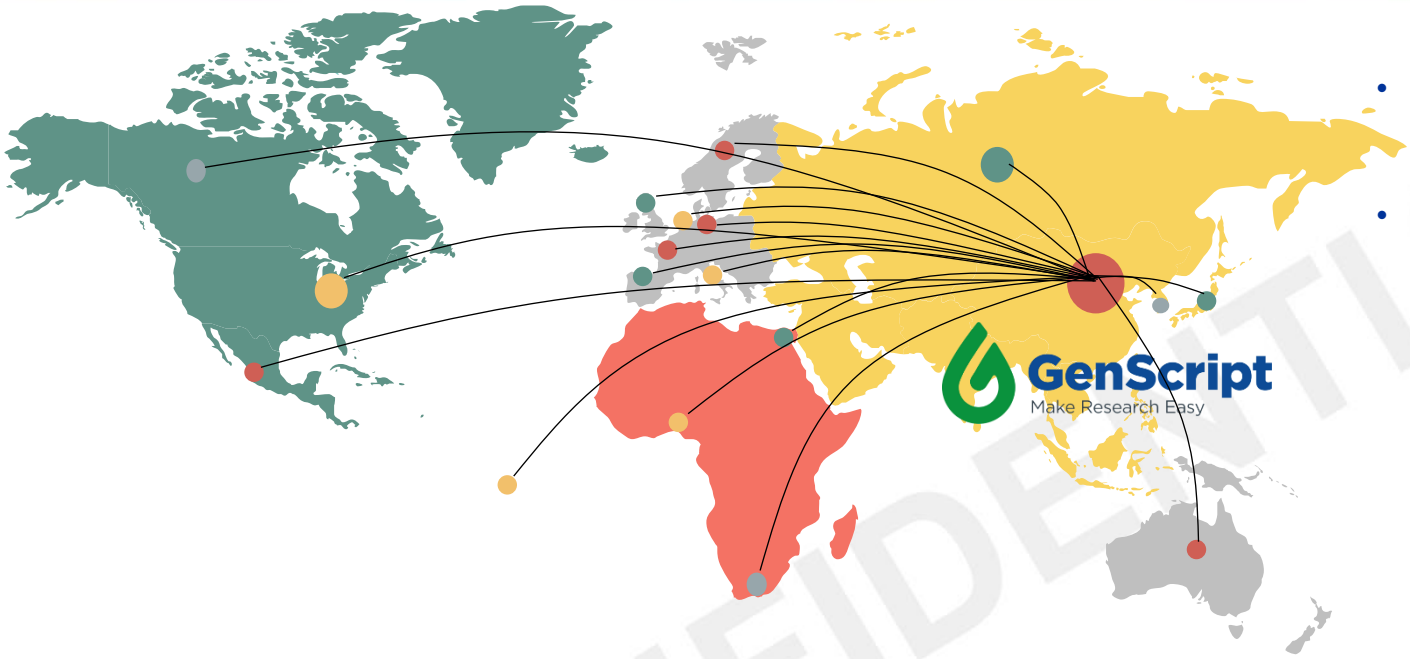
GenScript Overview

Headquarter, New Jersey, US

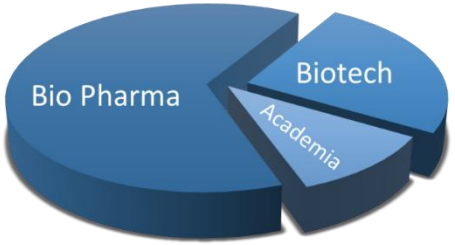
- Founded in **2002**
- Headquarters in **Piscataway, NJ**
- Facilities and branches: **Europe, Japan, China**
- **1,700** employees
- **Leading CRO** (Contract Research Organization)
  - 2014/2015 CRO Leadership Award

Production Center, Nanjing, China

Customer Composition



- 30,000 customers in 90+ countries
- Including big bio pharma and famous scientific research institutions



MERCK · GlaxoSmithKline · Pfizer · Johnson & Johnson · ThermoFisher SCIENTIFIC The world leader in serving science · genzyme · HARVARD UNIVERSITY · UNIVERSITY OF OXFORD

Lilly · Abbott A Promise for Life · NOVARTIS · Wyeth · Genentech IN BUSINESS FOR LIFE · AstraZeneca · COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK · UNIVERSITY OF CAMBRIDGE

Bayer · Roche · Schering-Plough · sanofi aventis Because health matters · Fermentas Part of Thermo Fisher Scientific · AMGEN · PRINCETON UNIVERSITY · Yale University

Antibody Capacity at GenScript

- AAALAC International and OLAW accredited animal facility
  - 6,000 sq.m, hosting more than **8,000 rabbits and 12,000 rodents**
  - Providing a broad range of antibody services from individual cases to **bulk orders**
- High volume output and track record

Polyclonal Antibody Project	⇨	500-800/Month
Monoclonal Antibody Project	⇨	50-100/Month
Antibody Related Project	⇨	50/Month

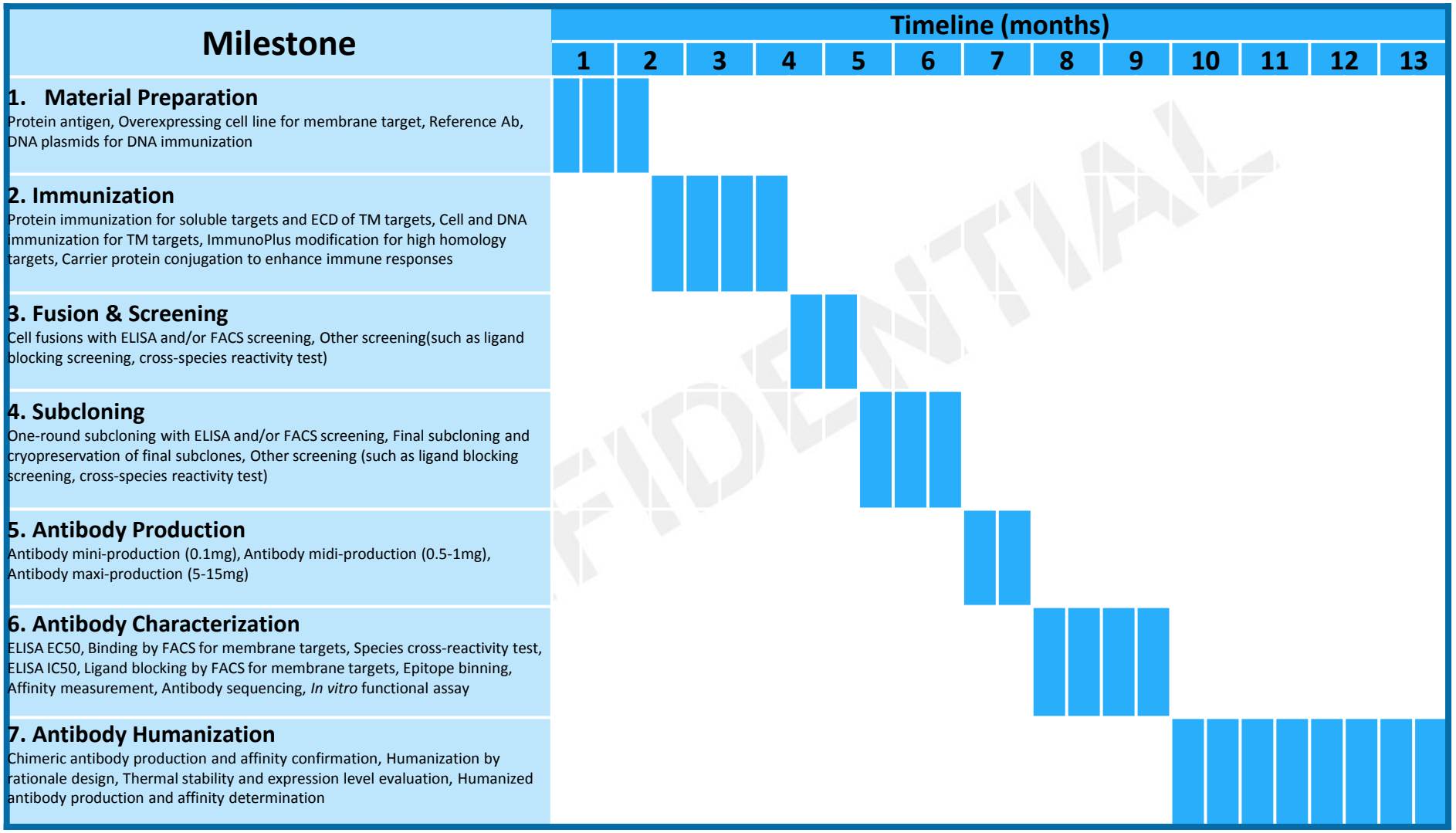
  - >100,000 pAb projects
  - >10,000 mAb projects (delivered ~ 1 million monoclones)
  - >200 therapeutic lead generation projects
  - >60 lead optimization projects

Therapeutic Antibody Discovery

Hybridoma Technology–Old but Powerful

- By 2016, FDA has approved over 62 therapeutic antibody drugs.
- Over 50 were derived from hybridoma technology, 8 from phage-display technology.
- The hybridoma technology generates high market value.

Discovery Roadmap

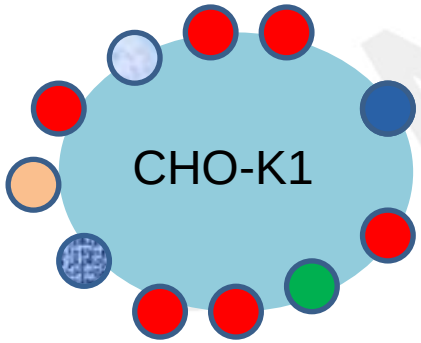


Hybridoma Platform for Lead Generation

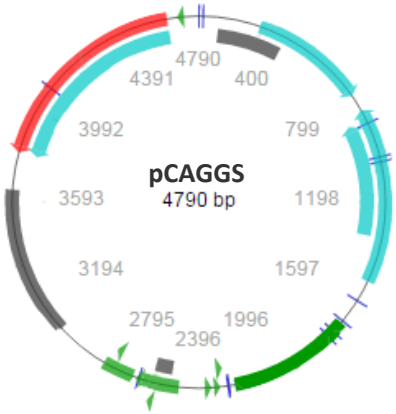
Conventional Hybridoma Generation Procedures	GenScript's Expertise
Immunogen Preparation	Multiple approaches on immunogen preparation
Immunization	Variety of choices on host animals Optimized adjuvant and immunization schedule ImmunoPlus™ to break immune tolerance
Fusion Screening	Electro-fusion with high fusion efficiency
Subcloning and Stabilization	High throughput screening for the binders against the most native epitopes
Antibody Production	High quality, multi-scale (serum free, Low endotoxin)
Antibody Characterization	Multiple characterization tools to narrow down the hits list for lead selection

Multiple Immunogen Designs

- **DNA immunization** to deliver the target DNA plasmid into the host animals and make protein of interest expressed *in vivo*
- **Peptides** designed by OptimumAntigen™ design tool
- **Recombinant proteins** secreted proteins, extracellular domain of membrane proteins, membrane preps
- **Whole cell** Receptors including GPCRs; surface antigens including immune checkpoint proteins, ion channels and transporters
- **Virus like particle (VLP)** that contains enriched membrane protein
- **Combination** of the above



Target transfected cell

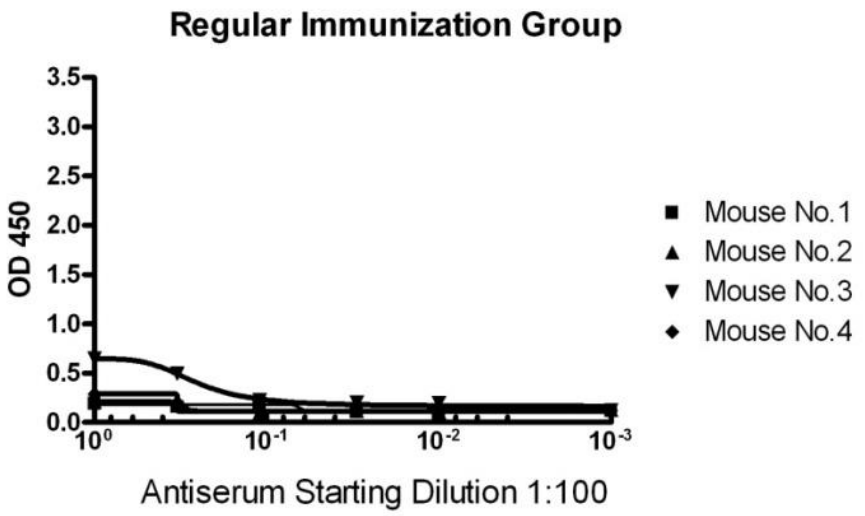


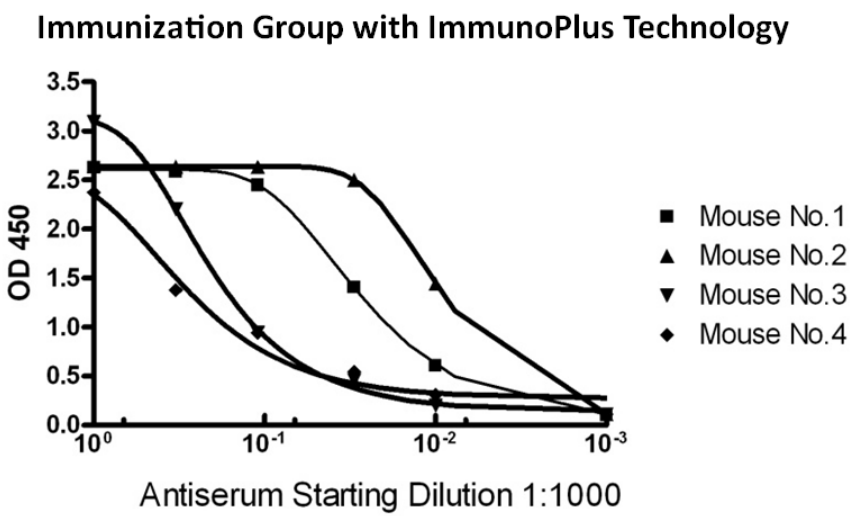
Target expression plasmid

Gene Gun

ImmunoPlus™ Break Immune Tolerance

- **ImmunoPlus™**: A powerful tool to break immune tolerance and enhance Antigenicity
- Ideal for raising antibodies against antigens of high degree of homology between human and rodent counterparts



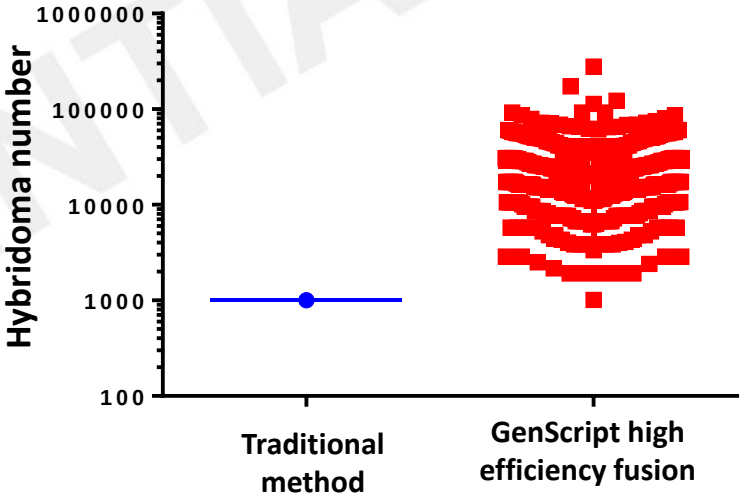


Case: an Ag, human/mouse seq identity: **96%**

Surrogate Ab of 'mouse against mouse' or 'rat against rat' can be generated, which have great utility in drug validation and development.

Immunization and Hybridoma Fusion

- Multiple choices of animal strains
  - ✓ Mouse: Balb/c, C57Bl/6, MRL, C3H/He, SJL and GANP transgenic mouse
  - ✓ Rat: Wistar and Sprague Dawley
  - ✓ Rabbit: MonoRab™ platform
  - ✓ H2L2 Transgenic mouse from Harbour

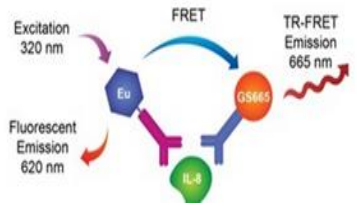


- Reproducible high-titer in most cases
  - ✓ By average >1:512,000

- Electrofusion
  - ✓ High cell-fusion efficiency to increase the size of library

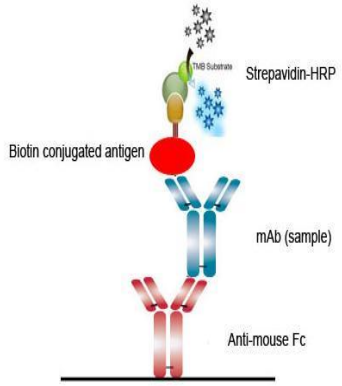
High-Throughput Binder Screening

- Natural epitope-based
  - ✓ Soluble target: ELISA (capture and indirect), TR-FRET
  - ✓ Membrane target: FACS and FMAT



Homogeneous (HT March™)

BD FACSCalibur with HTS loader



NativeSelect™ screening

HTS iQue™ Screening System

Lead Characterization

- Therapeutic antibody discovery aims to identify highly specific functional clones as the leads for downstream antibody drug development, and therefore multiple antibody characterizations are needed.

- **A pack of tools:**

- ELISA, WB, DOT, IP, FACS
- Binding activity (EC50)
- Ligand blocking activity (IC50)
- Species cross-reactivity and family member specificity
- Epitope binning (ELISA or SPR based)
- Affinity measurement (Kd by Biacore T200)
- Cell-based functional assays (EC50 or IC50)
- Antibody sequencing

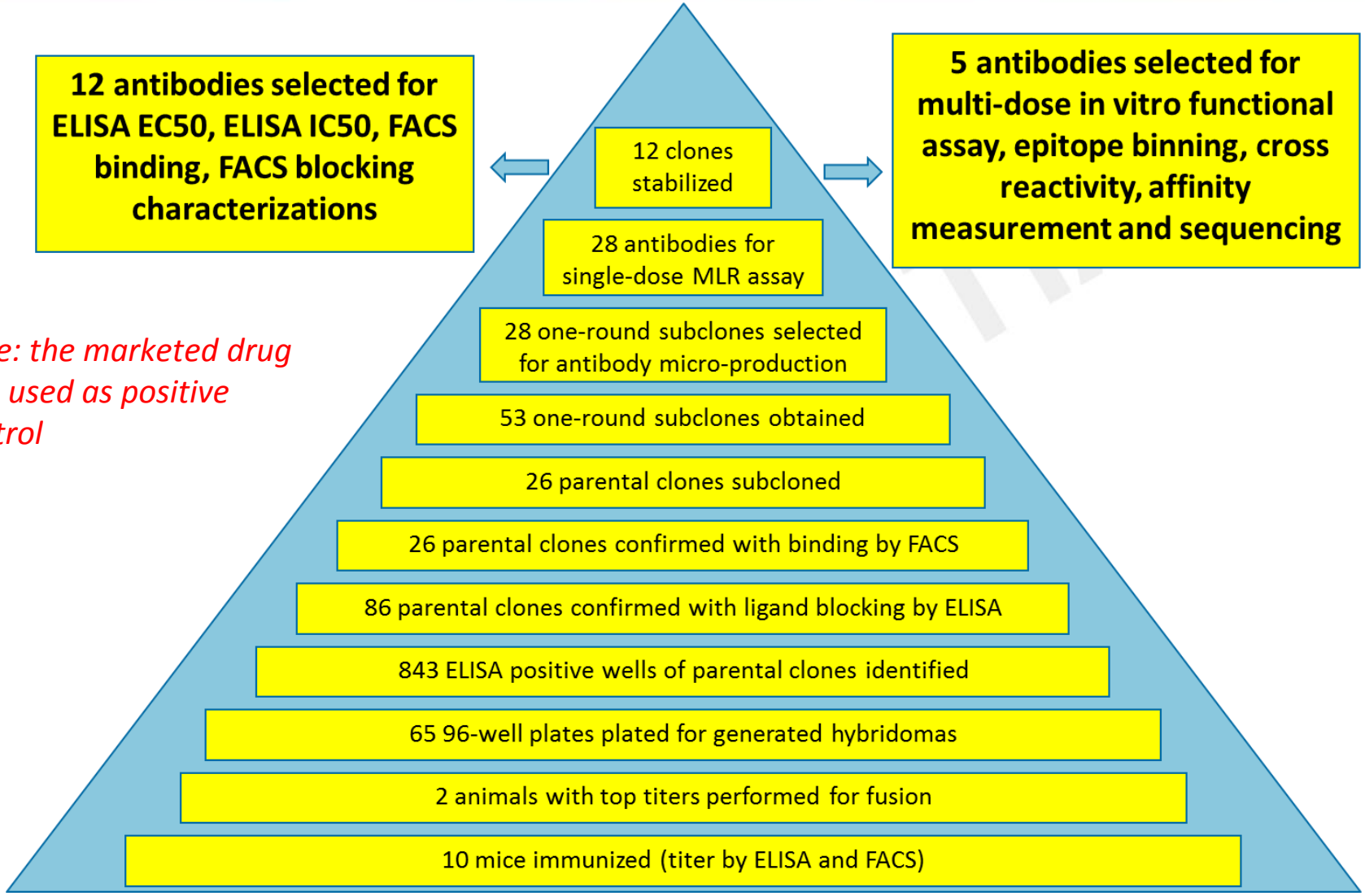
Case Study: Anti-Immune Checkpoint Lead Identification

GenScript

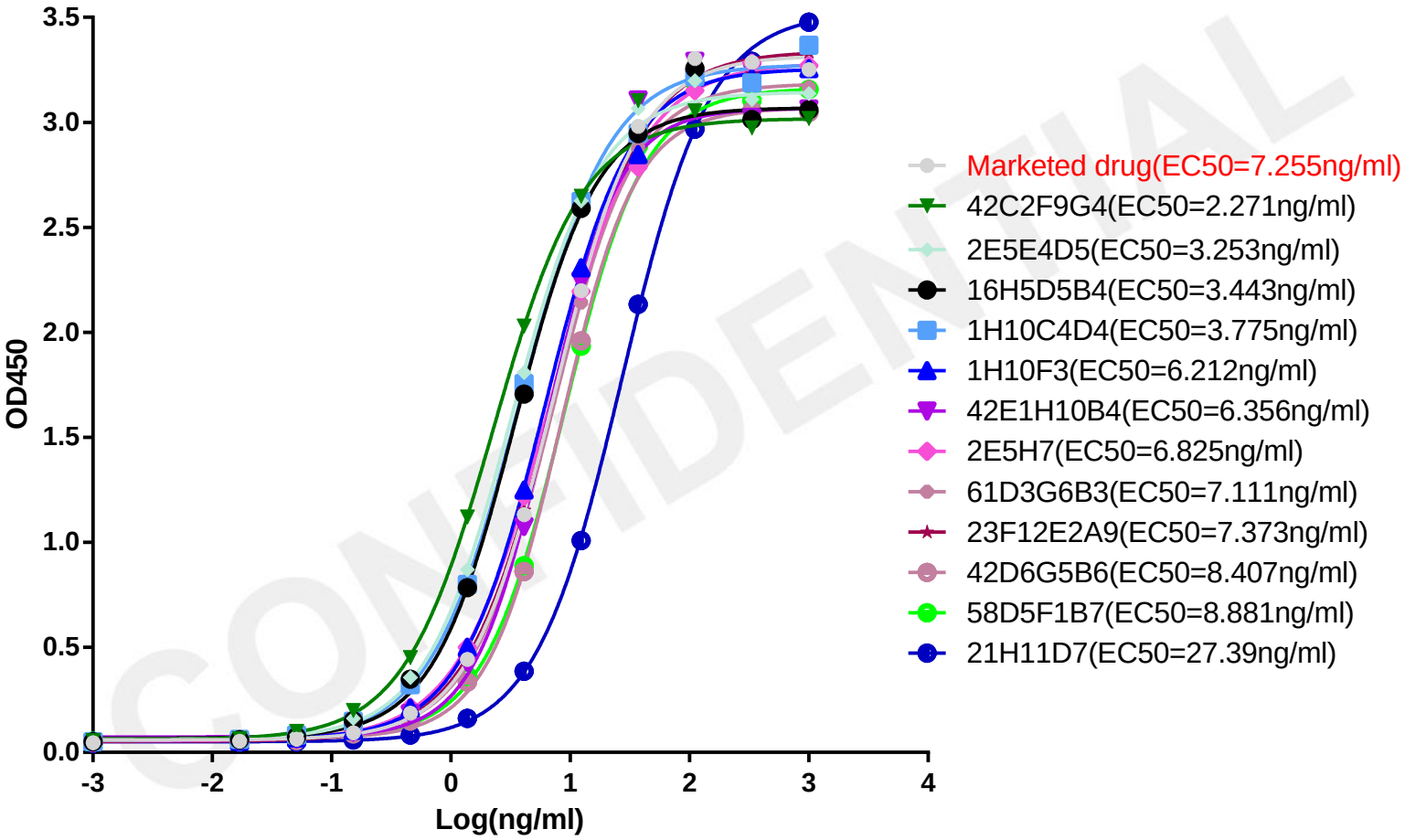
12 antibodies selected for ELISA EC50, ELISA IC50, FACS binding, FACS blocking characterizations

5 antibodies selected for multi-dose in vitro functional assay, epitope binning, cross reactivity, affinity measurement and sequencing

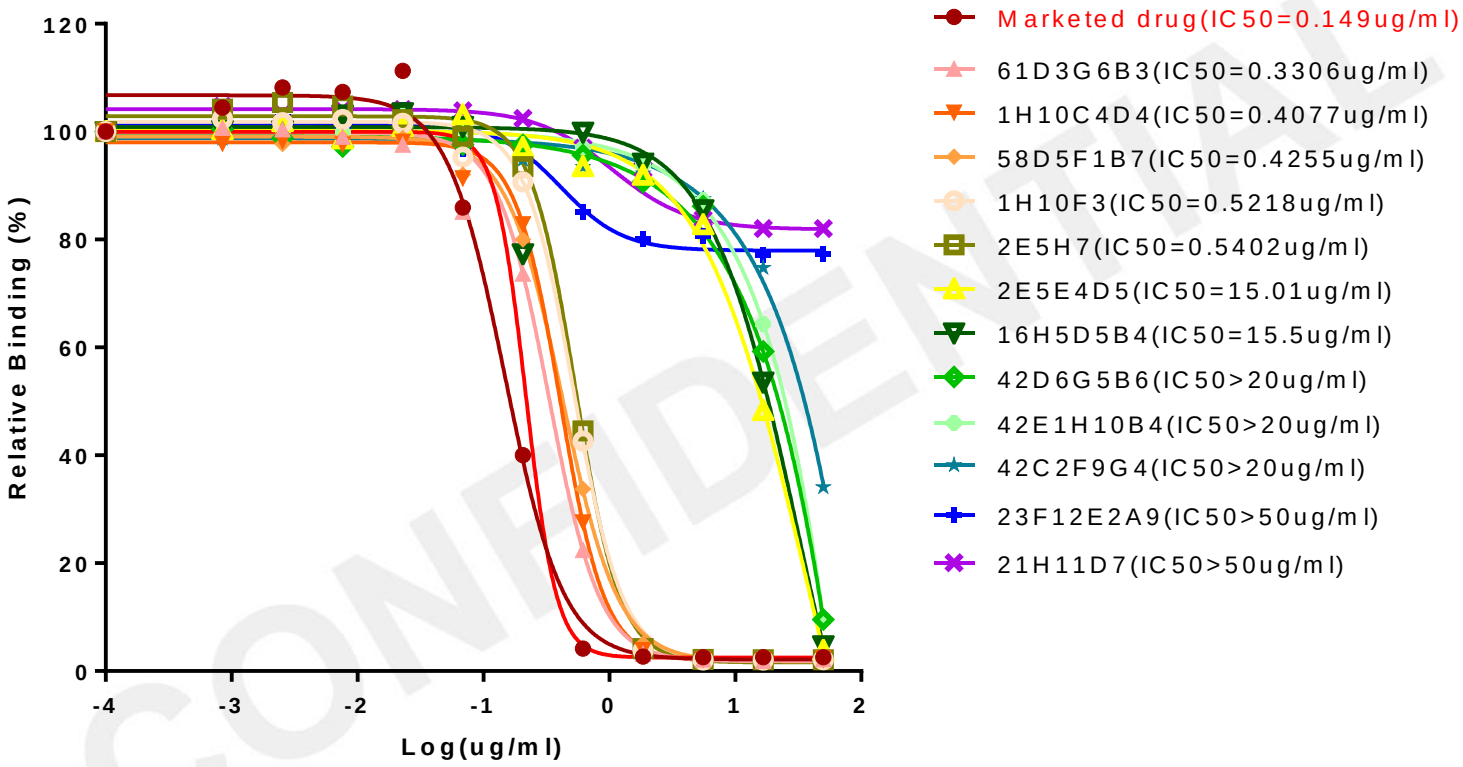
Note: the marketed drug was used as positive control



12 Antibodies ELISA EC50

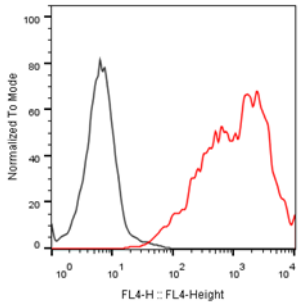


12 Antibodies ELISA IC50



12 Antibodies FACS Binding

1H10F3



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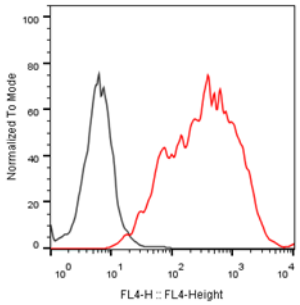
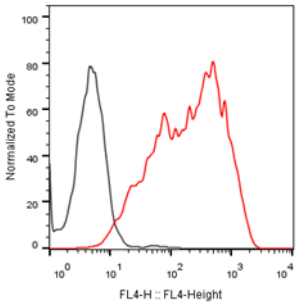


21H11D7



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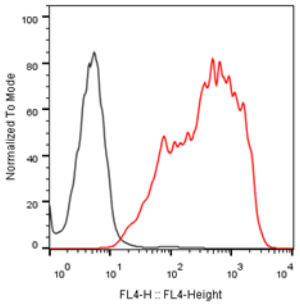

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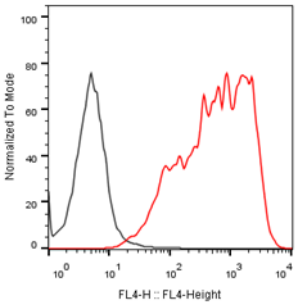

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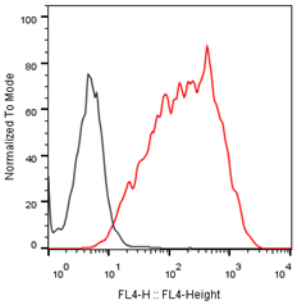

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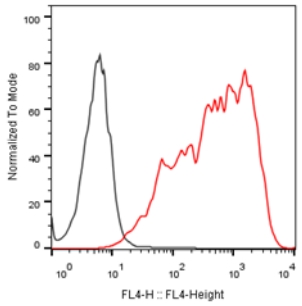

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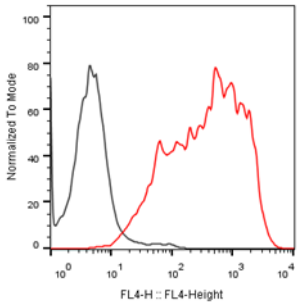

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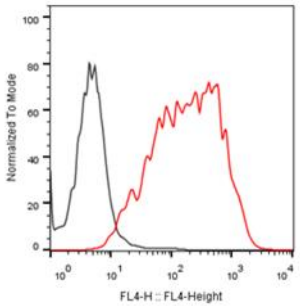

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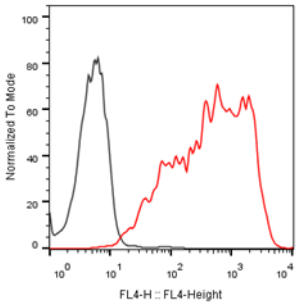

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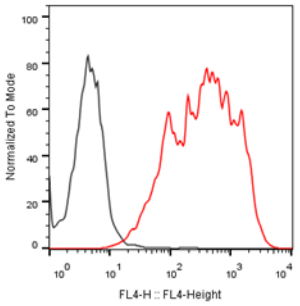

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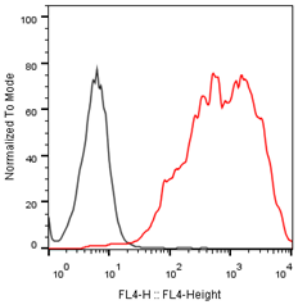
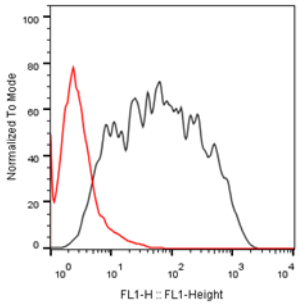


Black: negative cell line + purified antibody + secondary antibody
Red: Positive cell line + purified antibody + secondary antibody

12 Antibodies FACS Blocking

1H10F3



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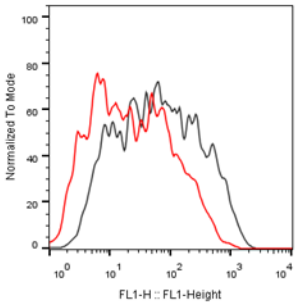

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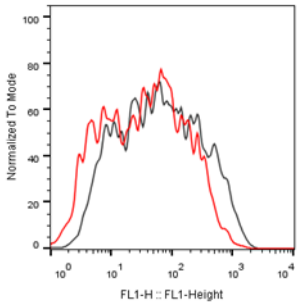

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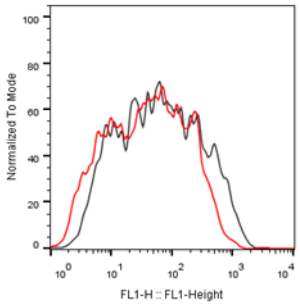

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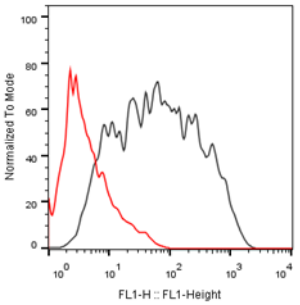

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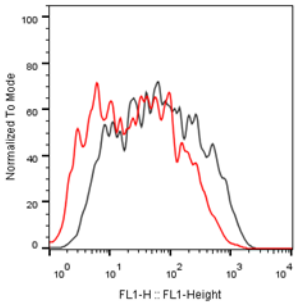

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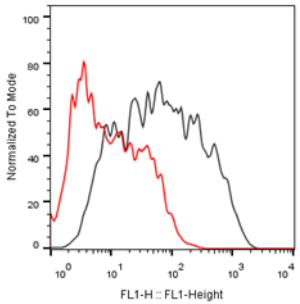

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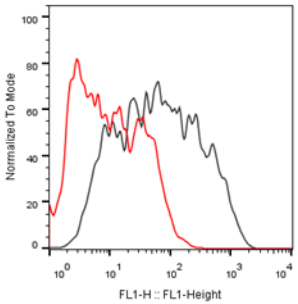

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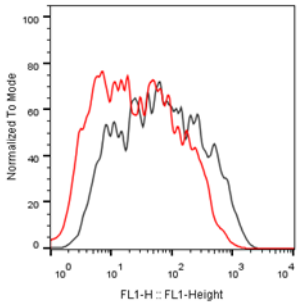

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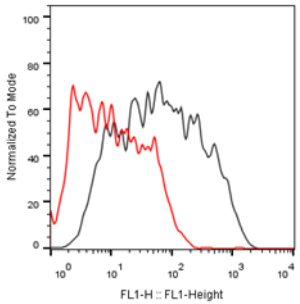
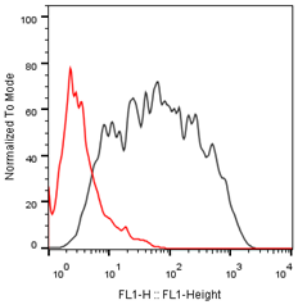
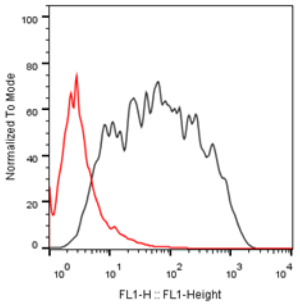


16H5D5B4

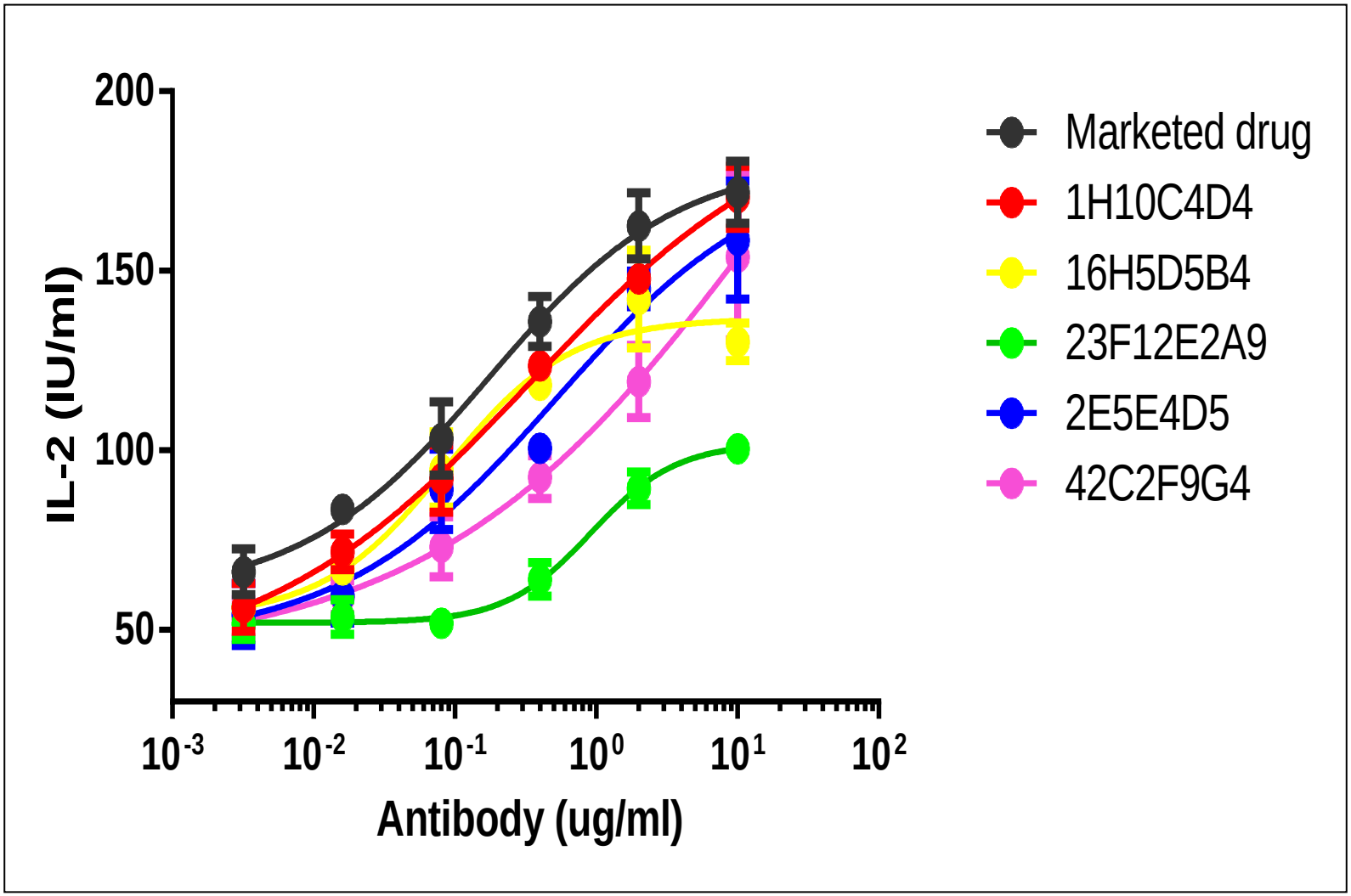


1H10C4D4



Black: Positive cell line + PBS + ligand protein + secondary antibody
Red: Positive cell line + purified antibody + ligand protein + secondary antibody

5 Antibodies Multi-dose MLR



5 Antibodies Epitope Binning

	Marketed Drug-biotin	1H10C4D4-biotin	23F12E2A9-biotin	42C2F9G4-biotin	16H5D5B4-biotin	2E5E4D5-biotin
control	2.024	2.568	1.008	1.398	2.446	1.116
Marketed drug	0.082	1.371	0.842	0.145	1.229	0.183
1H10C4D4	0.118	0.102	0.812	0.083	0.094	0.059
23F12E2A9	1.811	2.432	0.058	1.462	2.374	1.08
42C2F9G4	0.655	1.713	0.984	0.134	1.485	0.23
16H5D5B4	0.142	0.116	0.905	0.076	0.097	0.056
2E5E4D5	0.24	0.307	0.884	0.08	0.236	0.064

- The epitope of 23F12E2A9 is different with other antibodies
- 1H10C4D4 and 16H5D5B4 may have stronger affinity than marketed drug to the same epitope on the target

Track Records

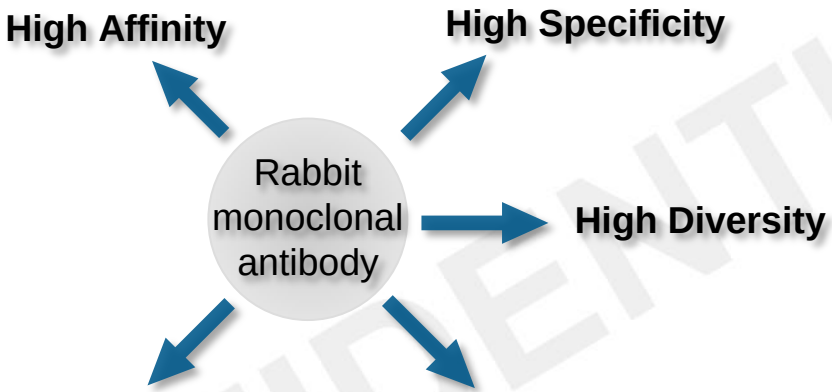
In the past 3 years (by Mar, 2017)

- GenScript has delivered more than **200** antibody lead generation projects.
- GenScript has delivered **60** antibody lead optimization projects.
- GenScript has delivered **12** biologics CMC projects.
- **3** of them were/ will be moved forwards to IND filing stage before the end of 2017.

Diagnostic Antibody Development

GenScript MonoRab™ Technology

- Kd typically at the picomolar (10^{-12}) level [mouse mAbs: Kd at nanomolar (10^{-9}) level]
- Permit higher working dilutions (5 -10 times)
- Able to distinguish between very similar proteins or sequences
- Lower cross reaction



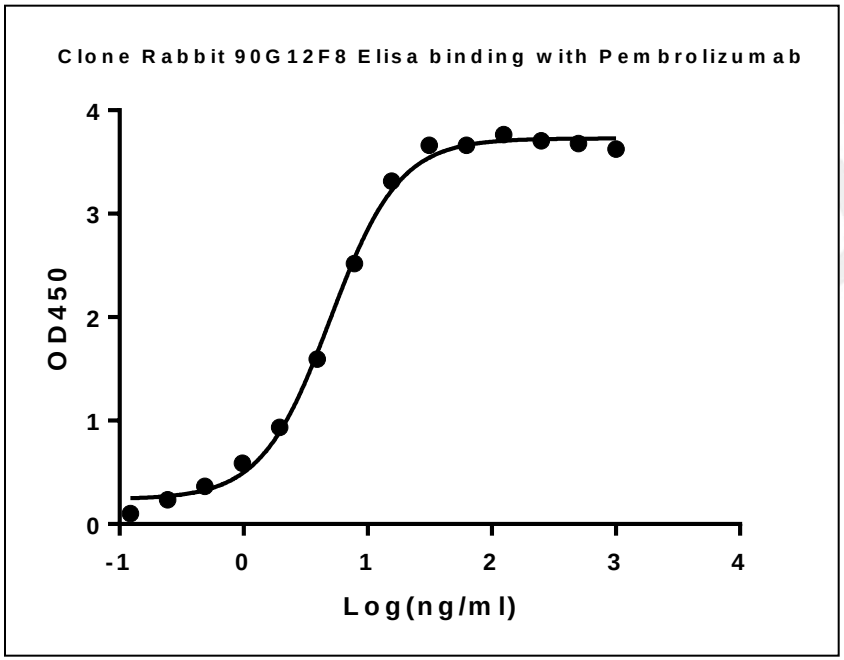
- Recognizes wider range of epitopes, novel epitopes
- More immuno-responsive to small epitopes (<1kDa)
- bigger spleen
- Against antigens that are not immunogenic in mice

- ELISA, Westerns, FACS, IP, ICC…
- Excellent results in IHC
- Good for IVD/anti-idiotype Ab…

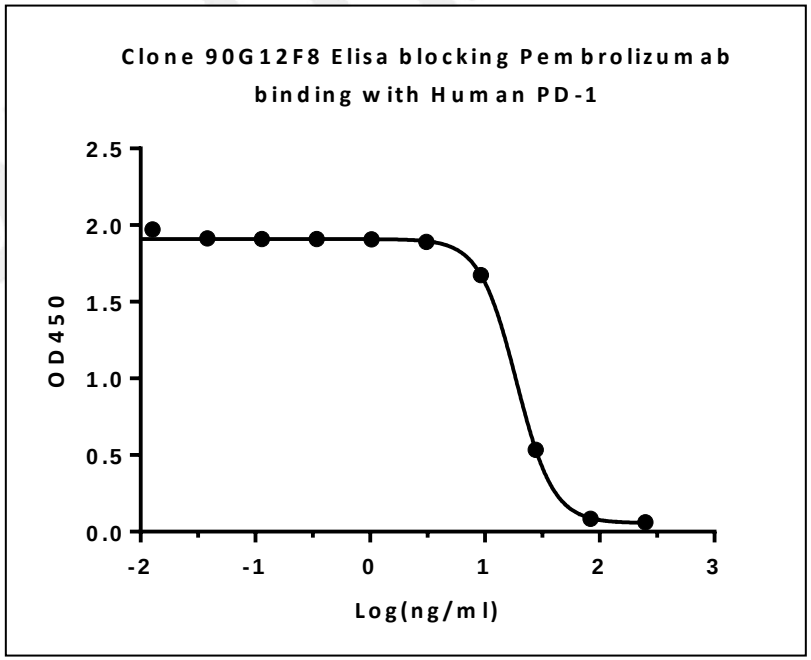
- GenScript developed the Rabbit-Mouse (Rb-Ms) chimeric hybridoma technology
- We have studied extensive cases against idiotypes, small molecules, receptors, epigenetic modifications for various applications.

Case Study: Anti-Pembrolizumab idiotype Rb mAb

- High affinity: Kd ≈ 10^{-11}M
- High specificity: lower cross reactivity
- Inhibitory function: high antigen blocking activity
- Diversity: more suitable candidates for PK and ADA assay development



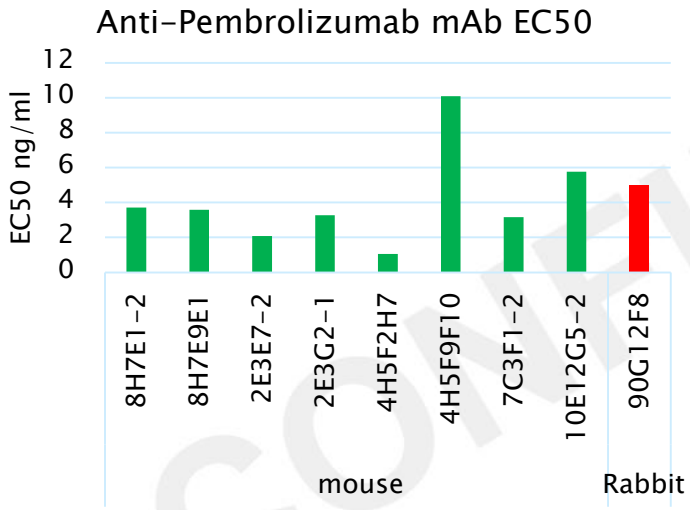
EC50=5.001ng/ml



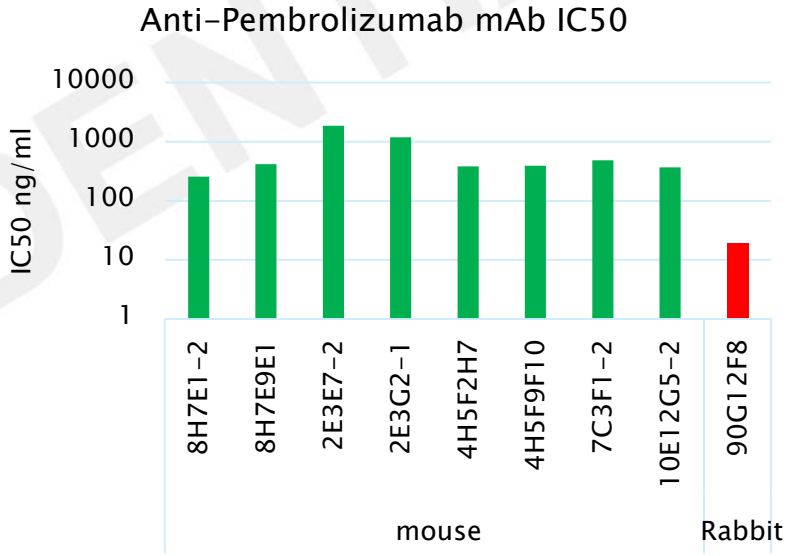
IC50=18.8ng/ml

Anti-Pembrolizumab idiotype Rb mAb

The affinity and specificity of rabbit monoclonal Anti-Pembrolizumab antibody is equal to mouse monoclonal antibody. While the blocking function of rabbit monoclonal Anti-Pembrolizumab antibody is much better than mouse monoclonal antibody.



EC50 comparison

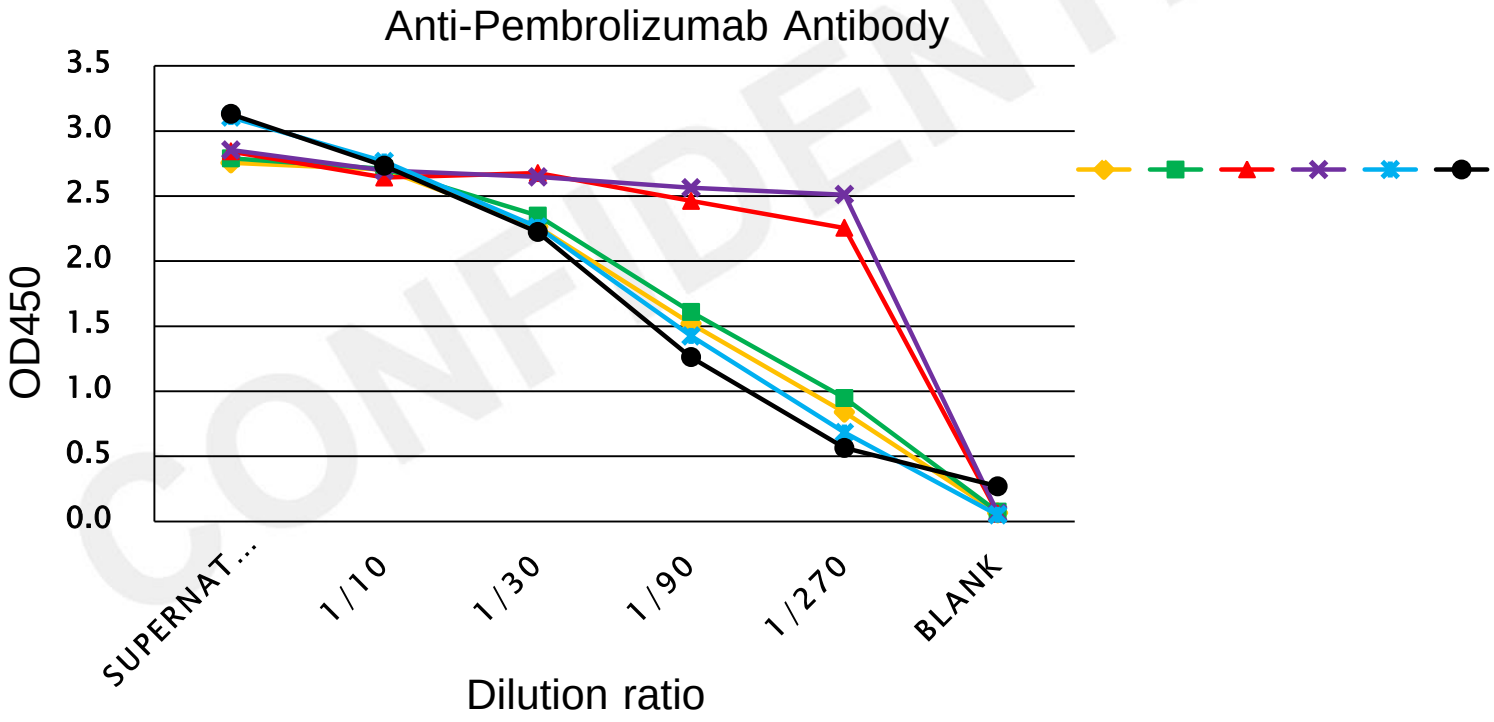


IC50 comparison

Anti-Pembrolizumab idiotype Rb mAb

Hybridoma Production vs Recombinant Production

- Ab sequencing and express 3 clones in mammalian cells
- The sensitivity and affinity of the anti-Pembrolizumab antibody produced by recombinant expression or hybridoma cells is equal to each other.



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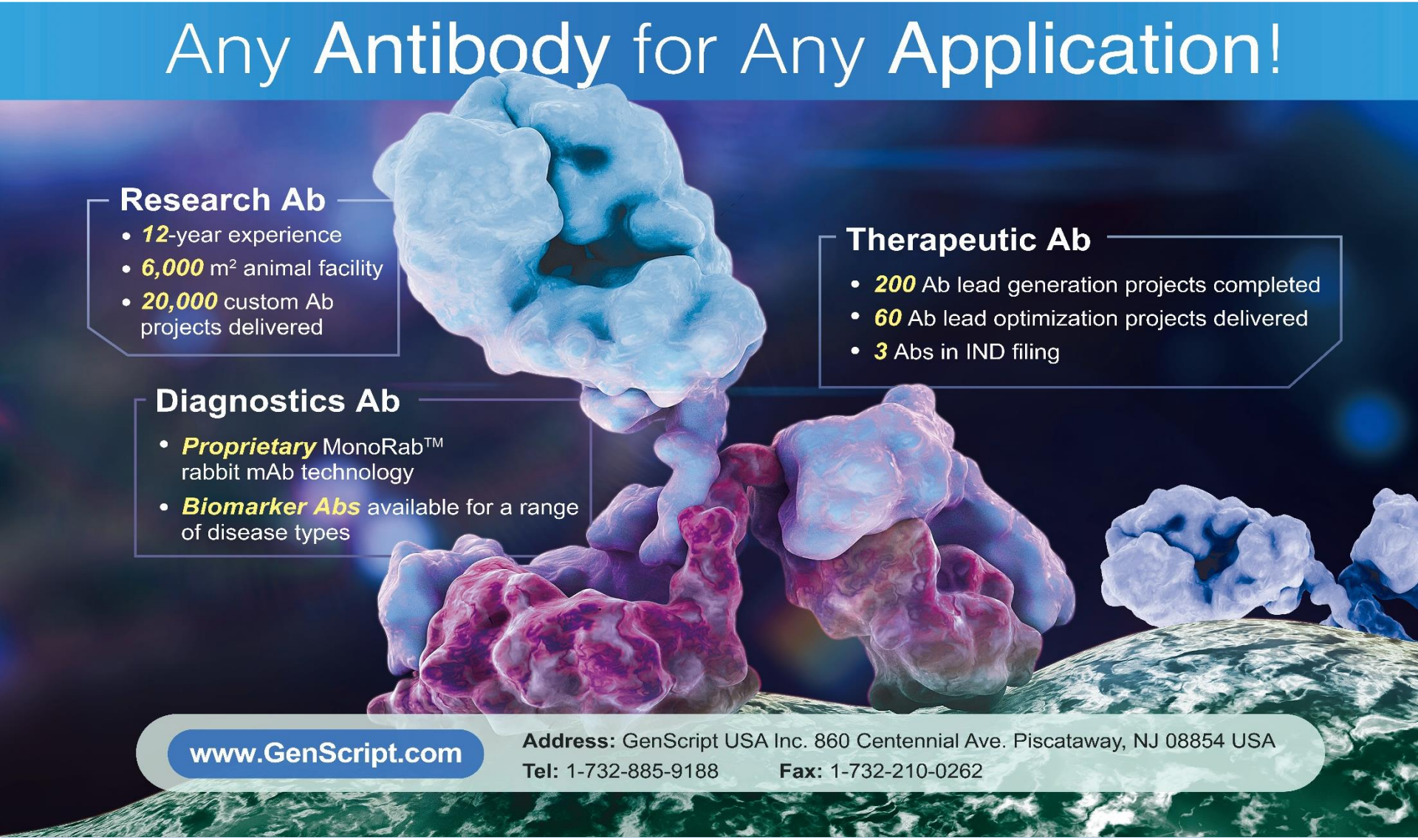

Research Ab

- ***12***-year experience
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Therapeutic Ab

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