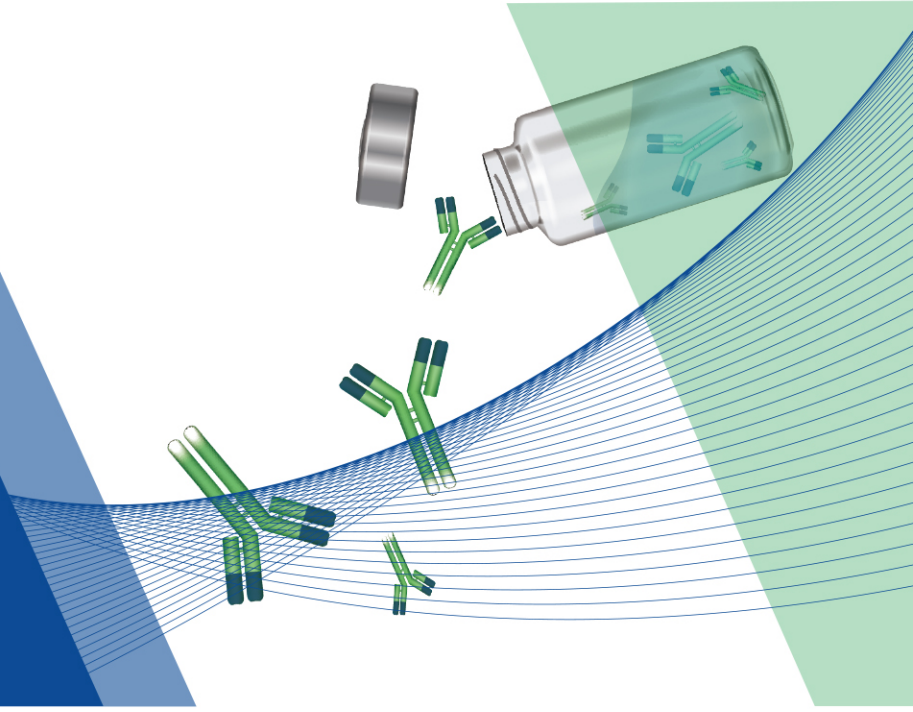
GenScript PROBIO

ANTIBODY DRUG DISCOVERY SERVICES



Inspire, Accelerate & Co-create Biomedical Innovation

GenScript ProBio

GenScript ProBio is the bio-pharmaceutical CDMO segment of the world's leading biotech company GenScript Biotech Corporation (Stock Code: 1548.HK). Founded in 2002 in New Jersey, GenScript started business from gene synthesis. Now, GenScipt 's businesses encompass four major categories based on its leading gene synthesis technology, including operation as a Life Science CRO, enzyme and synthetic biology products, biologics development and manufacturing, as well as cell therapy.

In Jan 2019, GenScript established the Biologics Development Business Unit (BDBU) which is the predecessor of GenScript ProBio.

The name of "ProBio" indicates 3 core philosophies - being PROACTIVE, PROFESSIONAL and PROCESS-oriented. GenScript ProBio shows our dedication to proactively provide end to end service (discovery to commercialization) with professional solutions, and efficient process to accelerate drug development for customers.

GenScript ProBio provides an integrated biologics discovery & development solution from target to IND. With our cutting-edge technology platforms in therapeutic antibody discovery & development, GenScript is able to deliver functional antibody lead with good developability and safety in discovery phase, as well as reliable, productive and regulatory-compliant process & drug product for IND filing in development phase, which significantly save client's time and cost.

Lead Generation

- Hybridoma generation
- Human naïve library & Synthetic library
- Single B cell cloning
- SMAB bispecific antibody discovery

Lead Optimization

- Antibody humanization
- Affinity maturation
- Developability assessment
- Bioassay & Bioanalytics

Biologics Development

- Cell line development
- Process development
- Analytical development
- Clinical batch supply

GMP Plant #1
Nanjing, China

GMP Plant #2
Nanjing, China

GMP Plant #3
Zhenjiang, China

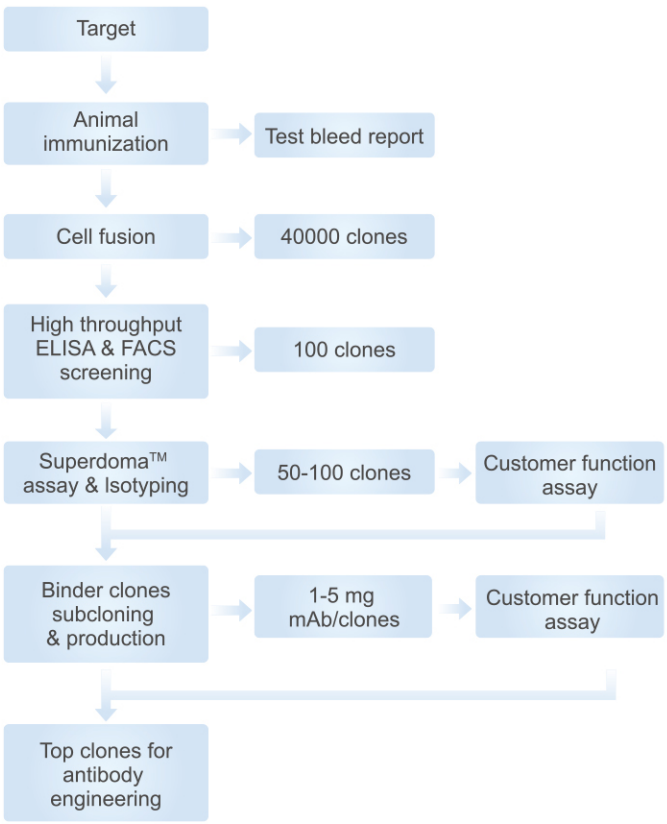
- Leading Therapeutic Antibody CDMO
- From Target to Market Solutions
- 500+ Employees, 40+ Experts with extensive experiences in industry
- cGMP compliant Mammalian Cell Culture Facility
- Comprehensive Analytics Platform

Hybridoma Antibody Drug Discovery

GenScript's 13 years of custom antibody generation experience can deliver a panel of hybridomas under 4 months with our standard protocol.

We Provide

- **A full spectrum of immunization approaches:** Protein, peptide, whole cells and DNA. OptimumAntigen™ Design Tool guarantee results.
- **Optimized immunization:** Transgenic mice* generate human antibodies. Proprietary adjuvant and immunogen modification breaks immunological tolerance for superior immune response.
- **Complete service:** From antigen production to hybridoma development and characterization.
- **High throughput:** High efficiency screening. Proprietary NativeSelect™ ELISA for soluble targets. iQue HT Screener, and BD FACS Calibur with HT loader for membrane targets.
- **Comprehensive functional assays:** Validated functional assay platforms provide reliable *in vitro* screening.
- **Readily integrated with other drug discovery services:** Antibody sequencing, antibody humanization, recombinant antibody production and anti-idiotype antibody generation.



Note:

1) We can customize your project based on your specific requirement.

2) We provide free cell line storage service for 6 months from the date of cell freezing.

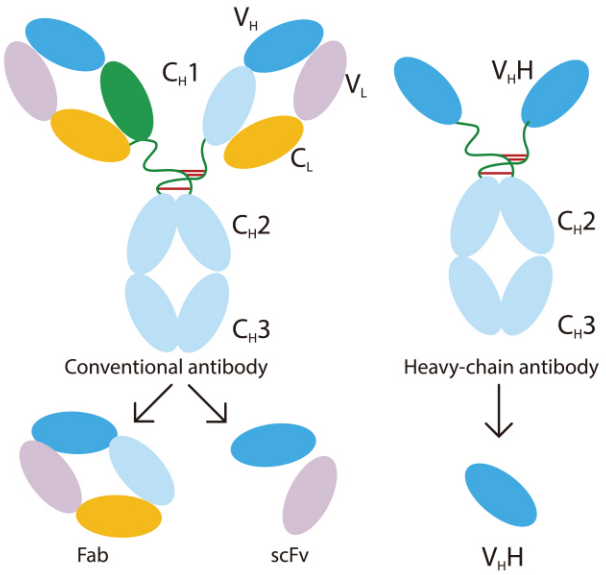
3) We recommend GenScript provides immunogen for highest quality .

* OmniAb ALLOY THERAPEUTICS 重庆金迈博生物科技有限公司 CHONGQING CAMAB BIOTECH LTD

Single Domain Antibody Discovery

The Status of sdAb as Therapeutics

sdAb is a promising next-generation therapeutic antibody technology for cancer immunotherapy and other applications.



- Efficacy and safety validated in clinical studies
- Easy to modify for specific applications
- Relative-short discovery cycle
- Pursued by main-stream pharmaceutical companies
- Cost-effective in manufacturing

SdAb Naïve Library Service

Llama naïve library → Phage bio-panning for 2-3 rounds and screening → Antibody production and characterization

SdAb Immunized Library Service

Preparation of immunogen → Llama/Camel immunization → Phage display library construction → Phage biopanning for 2-3 rounds and screening → FASEBA HTS to identify best binders → Antibody production and characterization

Service highlights

SdAb Immune Library

- **Using non-immunized Alpaca/Llama for each project**
- **20+ projects delivered, 100% success rate**

SdAb Naïve Library

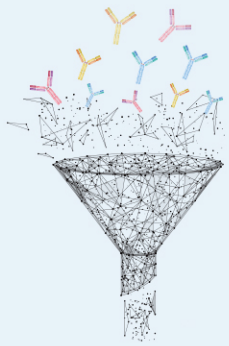
- **Library Size:$1.02*10^{11}$ (300 donors)**
- **Quality of Library**
  - **In frame rate/ORF rate: >95%**
  - **Diversity: Normal Distribution of CDR3 diversity**
- **As fast as 2 weeks to deliver single domain antibody sequences**
- **Diversified panning & screening strategies to ensure diversity & affinity**
- **Single Domain Antibody leads with high affinity (10^{-9}~10^{-10} or better) generated in case study**

Single B Cell Screening for Antibody Drug Discovery

Finish Antibody Screening within 24 hours

Single B cell screening platform, also known as single B cell cloning technology, is a microsystem based screening method. This platform conducts isolation, screening and evaluation on the B cells, avoiding the cell fusion and the library construction step. Also, single B cell screening platforms usually integrate high throughput platforms, therefore assays could be carried out in a highly efficient manner.

GenScript ProBio has built our own single B cell platform by using Beacon™, a micro-chamber based platform. With dozens years of experience on antibody discovery and cell manipulation, GenScript ProBio now provides a one-stop solution on antibody discovery using single B cell screening technology.

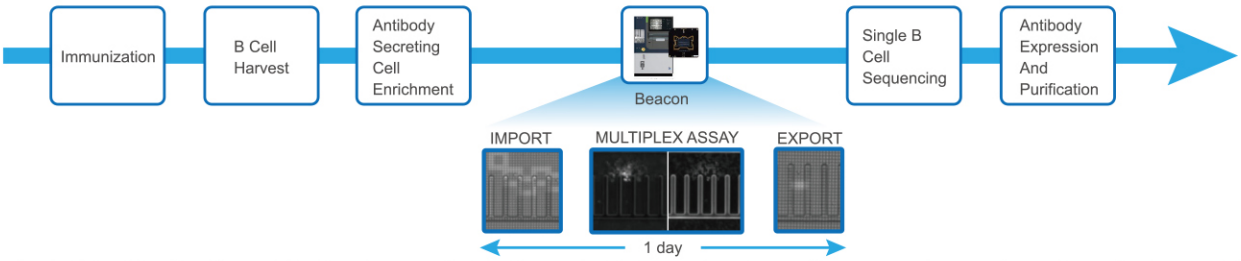


Service Features

EXPEDITED TIMELINE
Screening completed in 1 day
As fast as 1 month to get functional sequences

MAXIMIZED DIVERSITY
Minimal diversity loss, forward functional screening

INTRINSIC ADVANTAGE for CHALENGING TARGET
High hit rate: multiple screening/assay method to select functional leads at earlier stage
Low hit rate: limited B cell repertoire due to fusion loss



GenScript ProBio ProSpeed™ Service: suitable for soluble targets, single transmembrane targets and also multiple transmembrane targets. Human PBMC samples could also be used as starting material.

Phase	Item	TAT
Materials Preparation	Antigen preparation	
Pilot Experiment	Antigen ligand (positive control antibody) binding/blocking with ELISA and/or FACS, EC50 measurement, optimize antigen concentration and/or secondary antibody concentration	
	Option 1: Immunization with protein (regular animals)	8-14 Weeks(Standard) 2 Weeks(Express)
	Option 2: Immunization with protein (Transgenic animals*)	
Assay on Single B System: Beacon	Protein-based IgG Protein-based antigen specific binding Cell based assays(epitope mapping, antigen binding, ligand blocking, etc)	***1 Day***
Sequencing	Desirable single B cells (given the selection criteria) will be exported for total cDNA recovery and single cell VH/VL sequencing	1 Week
Recombinant Antibody Production	Ab expression & purification	1-2 Weeks

* OmniAb ALLOY THERAPEUTICS 重庆金迈博生物科技有限公司 CHONGQING CAMAB BIOTECH LTD

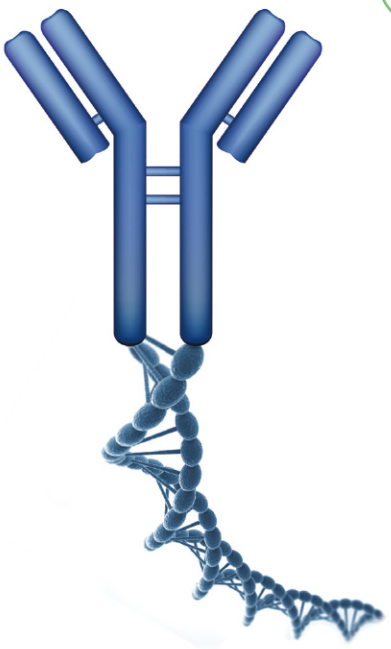
Antibody Sequencing

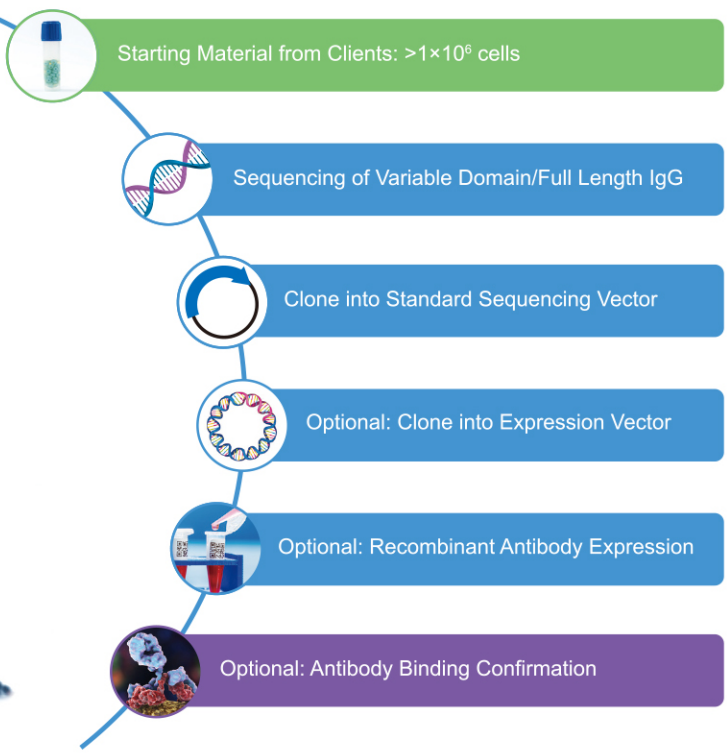
Our Experienced Hands, Your Unique Sequence

GenScript ProBio offers first generation sequencing and high-throughput sequencing services of antibody variable regions to fully address your antibody sequencing needs for different types of samples.

First generation Sequencing

General Workflow



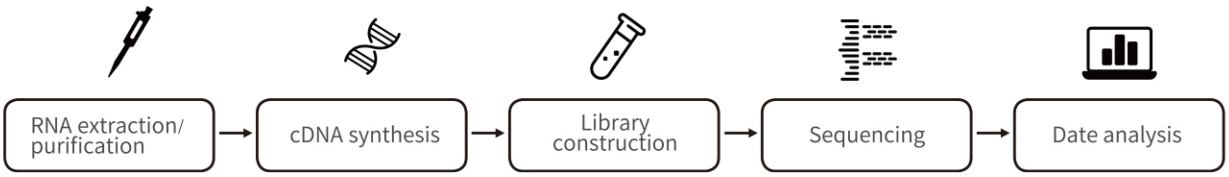


Value and Speed

Within duration as short as 6 days, GenScript delivers the data needed with your intellectual property being protected. Sequencing of antibody binding regions also sheds light upon further development such as humanization and recombinant antibody production.

High-throughput Sequencing

General Workflow



General Workflow

- Guaranteed 100% hybridoma sequencing accuracy
- Suitable for single B cell sequencing
- Validated by multiple species: human, mouse, rat, hamster, rabbit, goat, llama, and alpaca
- As fast as 1 week to get antibody sequences
- Starting from $53/clone for bulk samples

Antibody Humanization

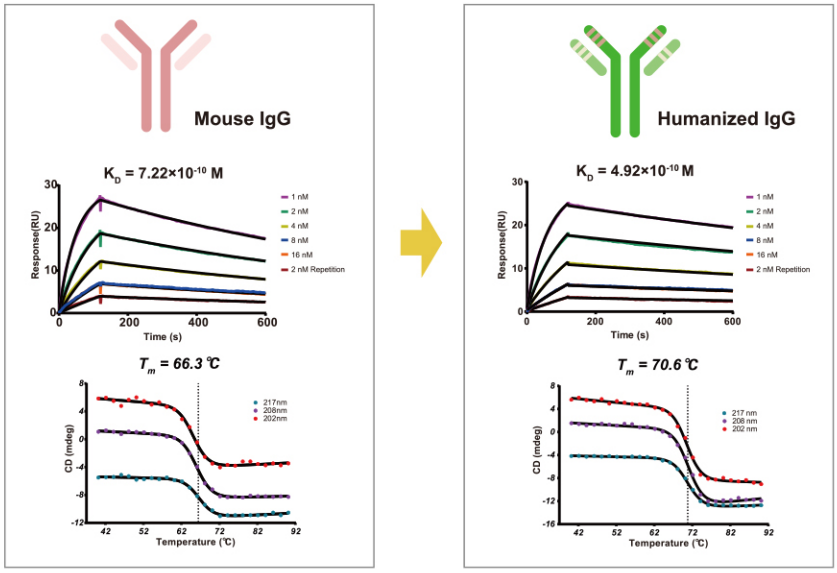
Reduce the Immunogenicity, Keep the Accuracy

Replacing everything but the complementarity determining region (CDR) reduces the degree to which an antibody drug itself acts as an immunogen. Immunization against an antibody drug lowers efficacy through reduction in circulating half-life and/or neutralization.

Our Strategy

- **CDR-grafting**
- **Patented** library based “framework assembly”
- **FASEBA:** FAst Screening for Expression level, Biophysical properties, and Affinities

Case Study



The engineering and screening procedures are integrated, allowing for simultaneous antibody humanization and stabilization. We even **guarantee the affinity of the humanized antibody,** which will be equal to or higher than the affinity of your parental antibody.

Service	Milestone	Deliverables	Turnaround
Express Humanization	Chimeric antibody production and binding confirmation PTM analysis（optional） Express humanization by rational design and sequence synthesis Humanized antibody production and affinity ranking Humanized antibody production and affinity determination	• Sequence, DNA and chimeric Ab & top 3 humanized Abs (0.5 mg) • Guarantee at least 1 Ab with affinity comparable with parental Abs	8 Weeks
Deluxe Humanization	Chimeric antibody production and Binding confirmation Sequence PTM analysis, Back mutation library design and library construction Humanized antibody selection Humanized antibody production and characterization	• Sequence, DNA and chimeric Abs & top 3 humanized Abs (0.5 mg) • Guarantee at least 1 Abs with affinity comparable with parental Abs	11 Weeks

Affinity Maturation

5-100 fold of Affinity Maturation

Affinity is one of the key parameters of an antibody drug, which will affect the function and efficacy of the antibody. Generally, antibody candidates from hybridoma platform has already acquired high affinity, but it may not exactly fit in the practical needs in research.

GenScript ProBio provides Affinity Maturation Service, which will help to improve the antibody affinity as you desired.

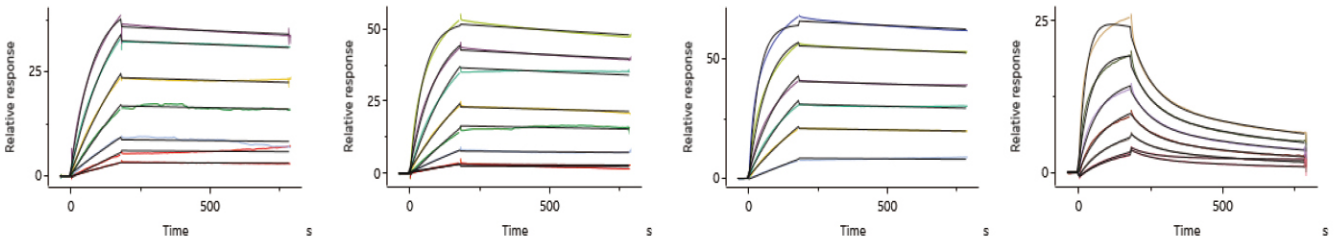
Core Advantages

- Guarantee the 5-10 fold increase
- Application of FASEBA High Throughput platform, in which affinity, expression level and thermal stability are screened simultaneously.

Service Details	Deliverables	Timeline
Antibody sequencing and sequence analysis Paratope mapping, library design and HTP screening	• Antibody and sequence and report analysis • Top 5 clones • Guarantee 5-10 fold affinity improvement	20-24 weeks

Case Study

Affinity maturation was performed for the Wild Type IgG and 3 positive clones were found, with Clone 1 showing highest fold increase(751 fold increase).



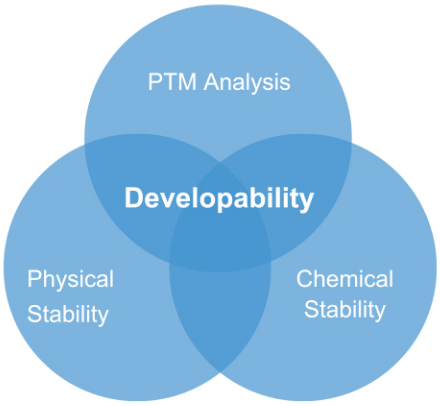
	Analyte	ka (1/Ms)	kd (1/s)	KD (M)	Rmax	Chi² (RU²)	Fold Increase
Before	Wild Type	8.15E+04	9.88E-03	1.21E-07	18.3	7.63E-02	NA
After	Clone 1	5.31E+05	8.54E-05	1.61E-10	35.4	1.62E-01	751
	Clone 2	4.32E+05	1.24E-04	2.87E-10	49.1	3.11E-01	421
	Clone 3	2.91E+05	8.85E-05	3.04E-10	64.1	5.45E-01	398

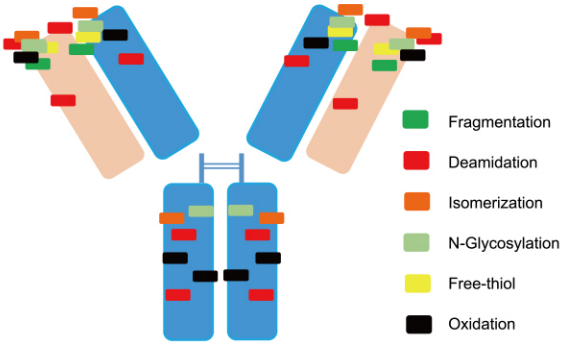
Preliminary Developability Assessment

Seamless Connection from Antibody Discovery to Preclinical CMC Development

Some antibody candidates discovered in early stage will involve issues such as post translational modification (PTM) hotspots or poor physiochemical stability, which will lead to potential risk during preclinical CMC development, resulting in huge time and financial loss to researchers.

Taking advantage of bioinformatics tools and a series of quality study instruments, GenScript ProBio introduces Developability Assessment Service to identify the inherent risk in antibody discovery stage, which seamlessly connects antibody discovery with preclinical CMC development.



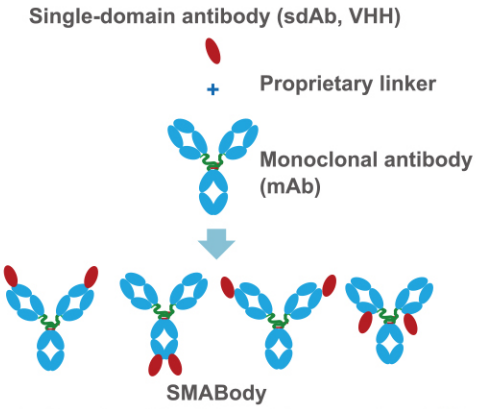


PTM Hotspots

Service Package	Service Content	Timeline
Physiochemical assessment	Thermostability	8 weeks
	Aggregation	
	Hydrophobicity	
	Molecular weight (de-glycosylated and glycosylated)	
	Stability (Freeze-thaw cycle, low pH, 40℃ accelerated degradation, matrix effect)	
PTM hotspot identification & validation	Asparagine deamidation	8-10 weeks
	Aspartate isomerization	
	Tryptophan oxidation	
	Hydrolysis	
	N-glycosylation	

SMABody—Bispecific Antibody Platform

GenScript Proprietary Bispecific Antibody Platform——SMABody

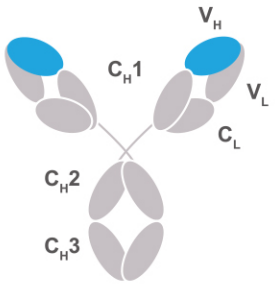


Bispecific antibodies (bsAb) have become a focus of interest for therapeutic applications with nearly 85 commercial candidates entering the clinical trials and 3 having been approved to market.

GenScript ProBio SMABody (**S**ingle-domain antibody fused to **m**onoclonal **Ab**) platform naturally combines the single domain antibody and the monoclonal antibody to make a bispecific antibody in symmetric format. With the design concept of "Keeping Natural", SMABody platform gives good developability and biosuperiority which are comparable to monoclonal antibody.

Why Single Domain Antibody?

- Potential ability to bind "hidden" epitopes
  GPCR, ion channel, etc.
- High affinity: can reach pM range
- Favorable biophysical properties
- Flexibility in modality design
  Bivalent, trivalent, tetravalent



Core Advantages of SMAB

Unique Molecular Flexibility

- Flexibility to modulate dual target effect to achieve best potency
- Possibility on ADCC/CDC enhancement
- Uniqueness of sdAb to target to "hidden" epitope

Exceptional Developability

- CLD titer > 2 g/L
- Yield > 60%
- One step protein A purity > 95%
- Solubility > 25 mg/ml
- Stability > 95% after 5 times freeze-thaw
- PK half life 2-3 weeks
- Low immunogenicity risk

Efficient Development

- 3-5 months for SMAB molecule development
- 10 months for preclinical development
- 1 plasmid system for CLD
- No additional purification
- No post-production process

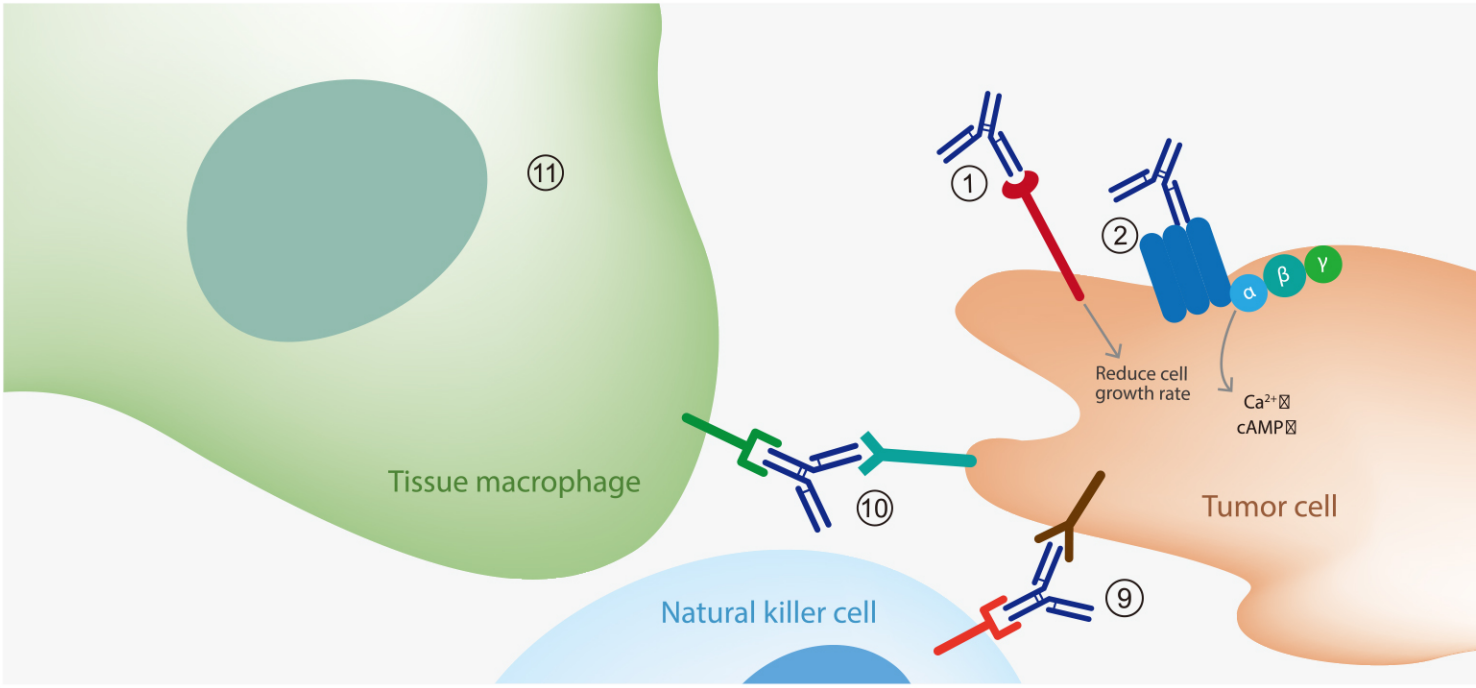
Our clients include *:

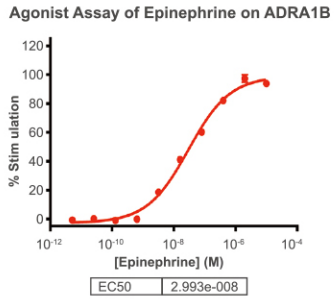
*Disclosed partners.

In vitro Cell-based Bioassay

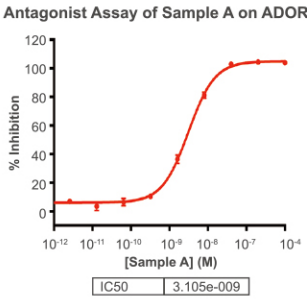
Comprehensive *in vitro* Cell-based Bioassay Platforms

Antibody drugs exert their therapeutic effect through different mechanisms of action (MOAs) in human body. Validation of these MOAs *in vitro* during early discovery is prerequisite to further drug development. GenScript ProBio has developed various *in vitro* cell-based bioassay platforms to accommodate such needs in both academia and industry. Assay methods are readily available for more than 30 hot immune-oncology targets and 9 Fc-γ-Receptors. IND-filing standard can be fulfilled upon request.

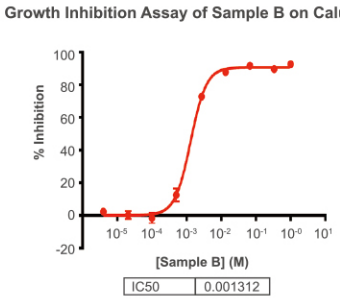




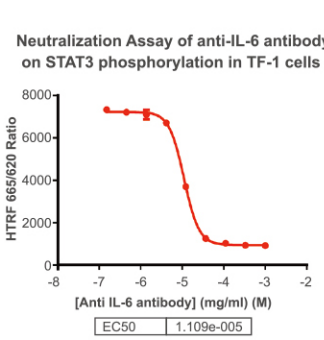
GPCR agonist assay



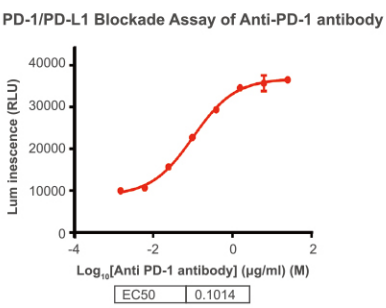
GPCR antagonist assay



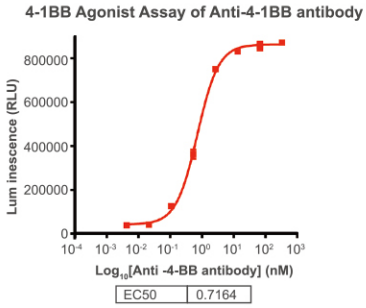
Growth inhibition assay



Neutralization assay

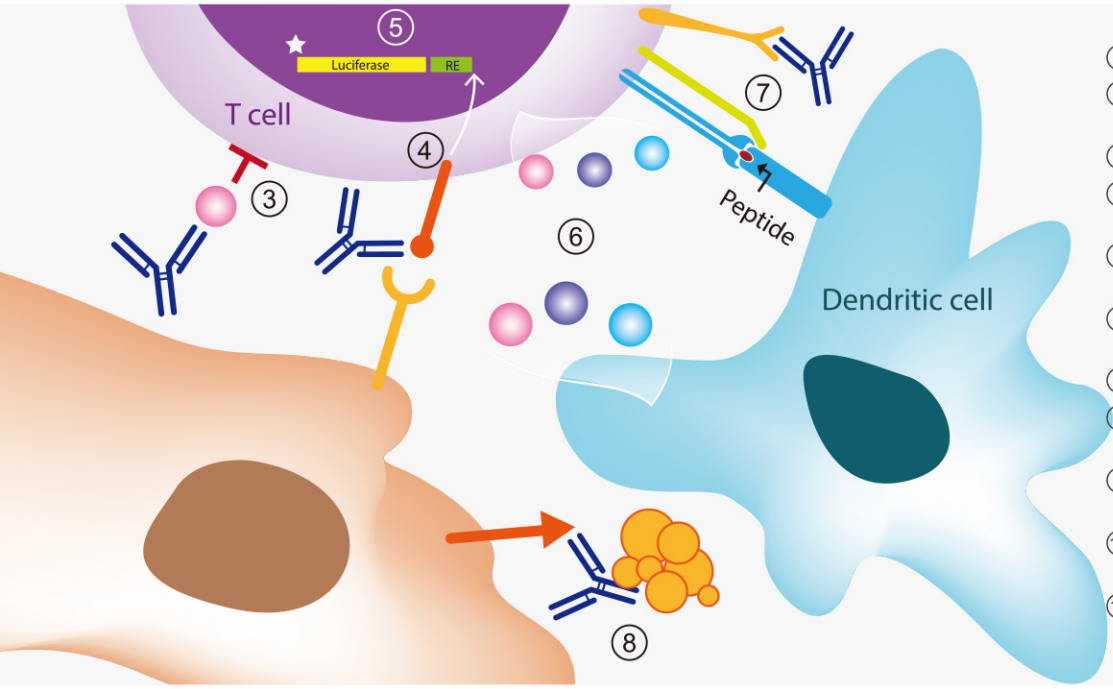


Immune checkpoint blockade reporter assay



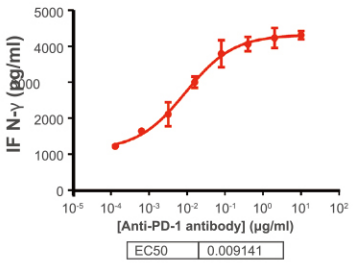
Immune checkpoint agonist reporter assay

In vitro
Cell-based Bioassay



1. Growth inhibition assay
2. GPCR-targeted agonist/antagonist assay
3. Neutralization assay
4. Immune checkpoint-targeted reporter gene assay
5. Customized functional assay cell line construction
6. Immune cell stimulation and multiplex cytokine release assay
7. Mixed lymphocyte reaction
8. Complement-dependent cytotoxicity assay
9. Antibody-dependent cell cytotoxicity assay
10. Antibody-dependent cellular phagocytosis assay
11. Cellular characterization assay by flow cytometry

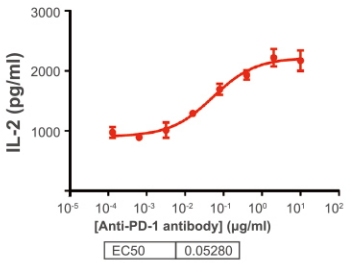
IFN-γ Release in MLR Assay of anti-PD-1 antibody



EC50	0.009141

MLR assay IFN-γ release

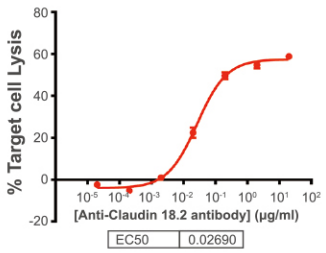
IL-2 Release in MLR Assay of anti-PD-1 antibody



EC50	0.05280

MLR assay IL-2 release

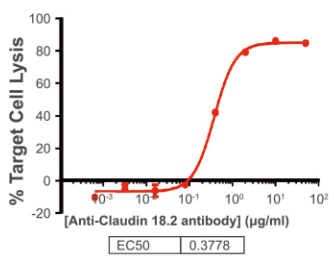
ADCC Assay of anti-Claudin 18.2 antibody



EC50	0.02690

ADCC assay

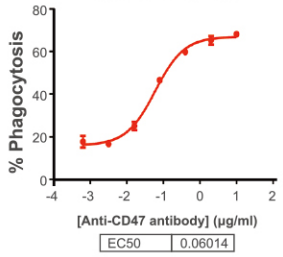
CDC Assay of anti-Claudin 18.2 antibody



EC50	0.3778

CDC assay

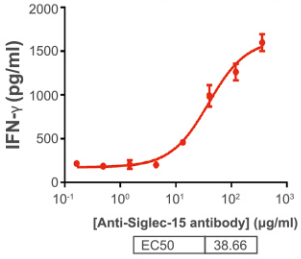
Cellular Phagocytosis Assay of anti-CD47 antibody against HL-60 cells



EC50	0.06014

Cellular phagocytosis assay

IFN-γ Release from PBMC stimulation assay of anti-Siglec-15 antibody



EC50	38.66

PBMC stimulation assay

Anti-Idiotype Antibody Generation & Immunoassay Development

One Stop Solution from Anti-idiotype Antibody to Immunoassay Development

An anti-idiotype antibody (anti-ID Ab) binds to the idiotype (specific combination of idiotopes present within an antibodies complement determining regions) of another antibody, usually an antibody drug. As anti-id Abs specifically bind to therapeutic antibodies, they act as a powerful tool for antibody drug pharmacokinetics (PK) and studies. Anti-ID Abs are also commonly used as a reference standard for anti-drug antibodies (ADAs) in antibody drug immunogenicity (immune response, IG) studies.

As a critical reagent used in IND filing and clinical trials, the batch variation of anti-idiotype antibodies significantly affects the performance of following PK/ADA assay. Particularly in long-term clinical use, it is critical to ensure batch-to-batch consistency. GenScript ProBio provides the best practice and compliance in anti-ID antibody manufacturing and PK/ADA kit development.

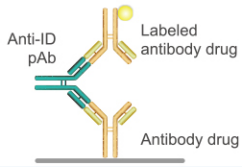
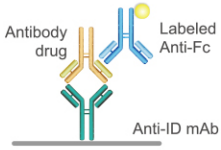
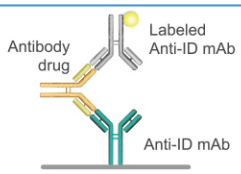
Features of GenScript ProBio Anti-ID Antibodies Service

Application tailored anti-ID mAb
Fit for immunoassay development

Fast delivery for anti-ID pAb
As fast as 8 weeks with guaranteed quantity

High success rate
>98% success rate with > 400 projects

Anti-ID Antibodies Package Details

Package	Typical Application	Starting Material	Time (weeks)	Deliverable
Anti-id mAb Golden Package for Capture ELISA		• ≥ 2 mg target antibody drug • 0.5 mg isotype control or human IgG	21-27	• 1-2 mL supernatant/parental clone • 5 mL final supernatant/subclone • 3-5 Hybridoma cell lines • 3-5 purified Ab/clone, 2-5 mg/clone • Pilot sensitivity report (optional) • COA report
Anti-id mAb Deluxe Package for Sandwith ELISA		• ≥ 2 mg target antibody drug • 0.5 mg isotype control or human IgG	21-29	• 1-2 mL supernatant/parental clone • 5 mL final supernatant/subclone • 5-10 Hybridoma cell lines • 5-10 purified Ab/clone, 2-5 mg/clone, • Anti-id mAb pair and pilot sensitivity report (optional) • COA report
Anti-id pAb Guranteed Package		• ≥ 45 mg target antibody drug • ≥ 30 mg isotype control or human IgG	Human IgGl: 8-12 Other type#: >13	• Small scale affinity purification (optional) • Affinity purified pAb • Pilot sensitivity report (optional) • COA report
PK ELISA Kit Development	As detection reagent: • Measure antibody drug concentration in patient serum samples	• ≥ 0.5mg antibody drug • ≥1mg detecting antibody • ≥ 1mg capture antibody	8-12	• Report of feasibility analysis • Final report of kit development • Labelled anti-ID antibody • Analytical methods and key reagent instructions
ADA ELISA Kit Development	As positive control: • Measure·ADA concentration in patient serum samples. • Measure the level of neutralization antibody, analyze the affect of efficacy	• ≥ 1mg antibody drug • ≥ 1mg Anti-ID antibody	8-12	

Note: #Other type: including but not limited to peptide, protein, ADC, SvFv & bispecific antibody.

Compliance Requirements for Anti-idiotype Antibodies

- Data integrity
  Data is preserved in paper and electronic forms for client to audit
- Record
  Operations are recorded in notebook/controlled coding paper
- Instrument
  Certified, calibrated, periodically maintained
- Document (Standard Management Process)
  Fully controlled SMP system
- Facility
  Continuous environmental monitoring
  Preventive maintenance

Inspire, Accelerate and Co-create Biomedical Innovation

Email: cdmo@genscript.com
Toll-Free: 1-877-436-7274
Tel: 1-732-885-9188
Fax: 1-732-210-0262