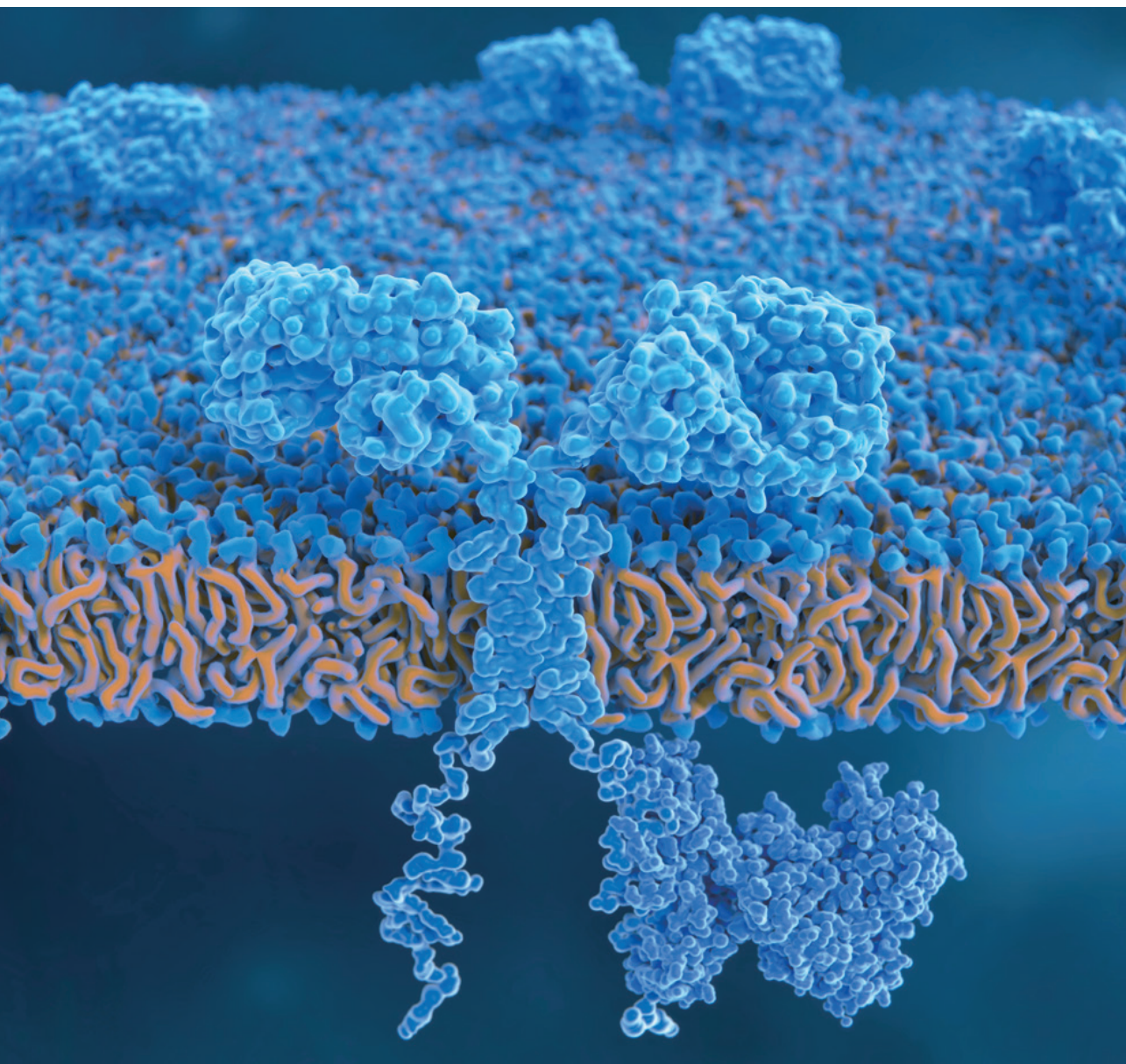
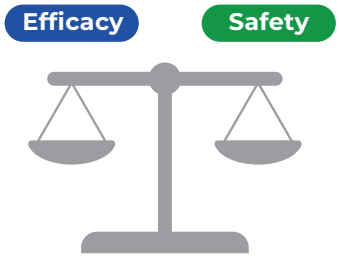
GenScript
PROBIO

Well-suited Antibody Discovery Strategy for CAR T Cell Therapy

One-stop CAR-T Discovery Solution
From Target to CAR-T Preclinical Candidates (PCC)



Begin with The End in Mind
Balance the Drug Efficacy and Safety



CAR T cell therapy faces many challenges in the R&D stage, such as CAR-T cell-associated toxicities, on-target off-tumor effects, antigen escape, etc. These issues can be addressed through the rational design of CAR leads, such as altering CAR structure to ameliorate toxicity, modifying CAR transduced T cells and neuro-toxicity, targeting multiple antigens (dual or tandem CARs), and so on.

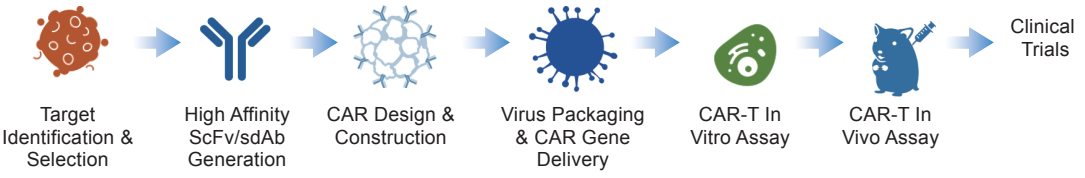
During the CAR lead design phase, it is crucial to consider the balance between efficacy and safety to ensure the success of the drug in the clinical stage.

Well-suited Antibody Discovery Strategy for CAR Leads

GenScript ProBio offers a comprehensive antibody discovery platform that is exceptionally well-suited for CAR lead discovery. What sets our CAR lead discovery platform apart is its diverse array of customized antibody discovery strategies, in-depth in vitro bioassays, and comprehensive in vivo pharmacology studies. **Our goal is to assist you in identifying fully-validated antibody candidates with desirable affinity, epitope and sequence diversity, while minimizing the risks associated with developability, immunogenicity, and thermostability.**

One-stop CAR-T Discovery Solution

From Target to CAR-T Preclinical Candidates (PCC)



Excellence Proven by Impressive Track Record

20
years of expertise in antibody drug discovery

1200
lead generation projects

610
lead generation projects

1
Most advanced project for CAR discovery has been marketed

Statistics by Apr. 2024

Bring Together Various Technology Platforms Under One-roof and Maximize the PCC Success Rate

Two sdAb Lead Generation Approaches

sdAb Naïve Library

Faster timeline
Higher diversity

- **300** Alpaca donors;
- Library size: **2×10^{11}**
- In frame rate/ORF rate: **>95%**

1.5-2 months

sdAb Immunized Library

Higher affinity
Higher positive hit rate

- Easy access to Alpaca farm
- Using **only naïve Alpaca** for each project

3 -4 months

SPSSdAb™ Platform

Soluble supernatant based Phage Screening for SdAb Discovery

- 2 antibody formats expressed during the phage display screening phase: phage expression & soluble expression
- Extremely high affinity of SASA tag to allow high throughput affinity ranking by SPR
- Further elimination of false positive clones by SPR ranking

3 scFv Lead Generation Approaches

Powerdoma™ Hybridoma Discovery Platform

- **Proven Excellence**
- **800+ Projects Completed**
- **14 Projects Advanced to Clinical Trials**
- Elimination of cumbersome subcloning steps
- Conducting high-throughput assays with hybridoma supernatant for rapid, reliable results

2 months

ProSpeed™ Single B Cell Screening Platform

- **Extremely Fast, Minimal Diversity Loss**
- **110+ Projects Completed**
- Integration of the ProSpeed™ expression with Beacon® platform to allow fast and cost-effective discovery of functional Ab leads

1 months

Human Fab Naïve Library

- **High Capacity Exceeding 10^{11},**
- **High Diversity, High Quality**
- The high-quality naïve library increases the probability of screening the high-potential Ab leads
- The diverse panning and screening strategy ensures affinity and diversity of Ab leads

1 months

Accelerating the Discovery of “Me-better” CAR Lead Candidates

Functionality Optimization

Antibody affinity maturation
10-fold affinity improvement guaranteed

Fc engineering
ADCC, CDC, ADCP enhancement , STR Fc silencing technology and half-life extension

Developability Optimizations

Antibody Humanization
Industry-leading timeline **in 2.5 weeks**

Antibody Developability
Prediction, optimization, and assessment

All-inclusive Bioassay Services from Vector Construction to Functional Assay

Generation of CAR encoding vector

- FTO CAR vector

T cell activation and transduction

- Non–virus transfection
- Lentivirus
- Retrovira

Expansion of CAR-T cells

- High–fold expansion

Functional assay for cytotoxicity and cytokine release

- Time–based killing assay
- Cancer cell lines
- Overexpression cell lines
- Luciferase target cells

CAR-T In Vivo Pharmacology Services that Span the Entire Drug Discovery and Development

Milestone 1: Efficacy
(TGI,T/C,Survival)

- Cell line screening based on IHC panel or FACS
- Tumorigenic or pilot experiment (benchmark)
- In vivo efficacy including screening/dose-response finding

Milestone 2:PK study
(Circulating & Infiltrated)

- CAR+/Total T cell detection method (FACS or PCR)
- Circulating CAR-T cell persistence
- Tumor CAR-T cell infiltration

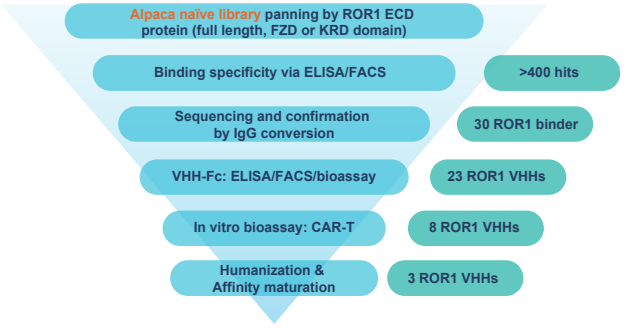
Milestone 3:Toxicity
(ex vivo & In vivo)

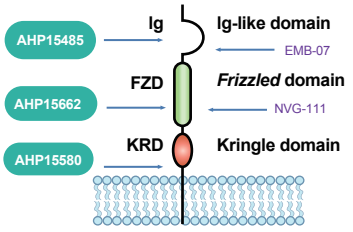
- Early TCR study(human/monkey/rat/mice)
- Single dose toxicity based on xenograft mice(or WT mice)
- General observation, temperature, pathological etc.

Case Study

Utilization of naïve VHH phage display library & integrated antibody engineering platform to generate antibody leads for CAR-T therapy

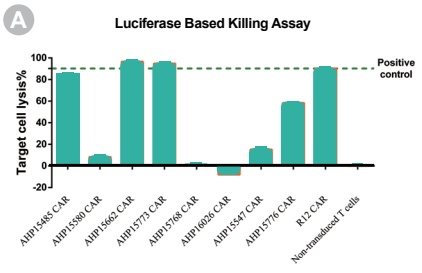
In this case study, an alpaca naïve VHH library was panned and screened by ROR1 proteins of 3 different ECDs and CHO-K1/ROR1 cell line to identify ROR1 VHH candidates. These VHH candidates were used to construct CAR-T cells and further evaluated by vitro functional assays, based on which final leads were selected for optimization by affinity maturation and ready for the development of CAR-T therapies.



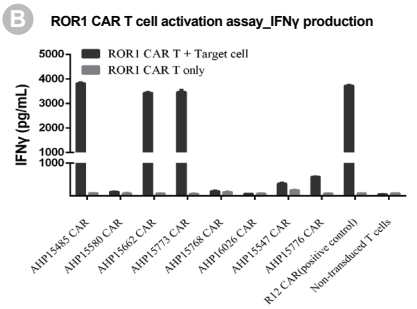


VHH candidates against three different ECD domains were obtained by differential panning/screening strategy

Functional evaluation of ROR1 VHHs in a CAR-T setting in vitro. CAR-T cells was constructed by transduction of primary T cells with CAR constructs containing relevant VHH candidates, and evaluated by in vitro function assays.

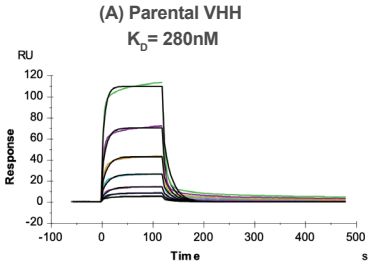


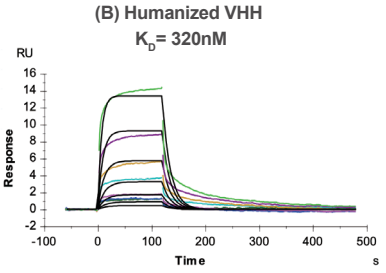
(A) Cytotoxicity assay was performed after co-incubation of CAR-T cells (effectors) and CHO-K1/ROR1/Luc for 24 hours. The percentage of target cell lysis was calculated per luminescence signal

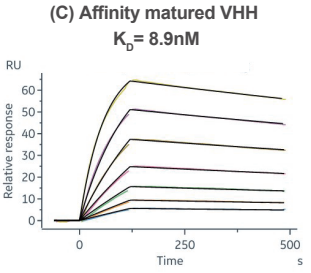


(B) The release of representative cytokines (IFN-γ) by ROR1 CAR-T cells in response to co-incubation with target cells was measured by ELISA assays

Full kinetic SPR analysis revealed that the affinity of a top candidate (AHP15485) was maintained after humanization, and greatly improved after affinity maturation (> 30 fold).







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