# Solutions for Immune Cell Therapy Development

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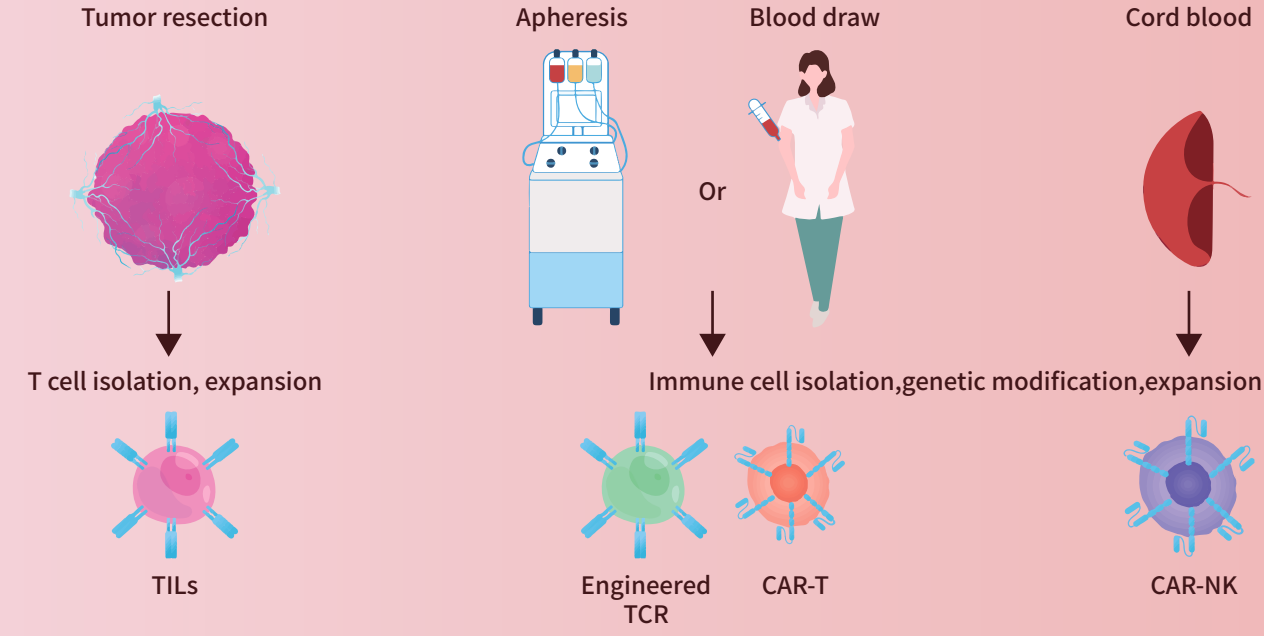
BIOSYSTEMS Acro

# Background

With the continuous development of tumor biology and immunology in recent years, immune cell therapy has developed into an exciting new field of tumor treatment.

Immune cell therapy refers to isolating the patient's own or donor-derived immune cells, which are modified *in vitro* and then reinfused into the patient's body. These modified immune cells are better able to identify and kill tumor cells and generate a memory-type immunity. The described process creates a significant advantage in preventing tumor recurrence and metastasis. The most common immune cell therapy modalities include CAR-T, TCR-T, TIL, and CAR-NK. These therapies have their advantages in different types of tumors and immune fields.

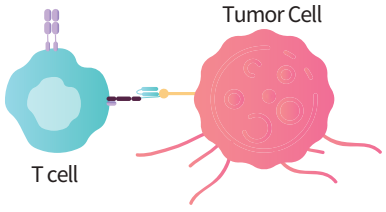
## Schematic diagram of immune cell therapy




Contents

# Types of Immune Cell Therapy Techniques

## Chimeric Antigen Receptor T Cell Therapy (CAR-T)




**Principle:** The Chimeric Antigen Receptor (CAR) consists of an antibody-derived targeting domain fused with T-cell signaling domains. It is expressed by a T-cell, endows the T-cell with antigen specificity as determined by the targeting domain of the CAR.

**Manufacturing process:** The production of autologous CAR T cells is carried out by various manufacturing approaches, all comprising the same common steps. First, the patient's white blood cells (WBCs) are isolated by leukapheresis, washed, and then T cells are isolated. The T cells are then activated, transduced with the CAR transgene, expanded to the required cell numbers for therapy, formulated, and filled. After quality control testing and preparatory lymphoid-depleting chemotherapy for the patient, the product is injected.

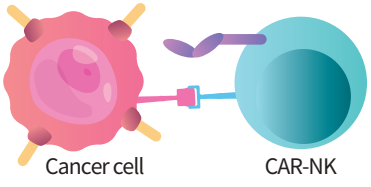
**Representative products:**

At present, there are 7 approved CAR-T cell therapies globally, including Novartis' Kymriah, Gilead's Yescarta, and so on. In addition, 1007 CAR-T projects are currently at the clinical research stage (Clinical Trials.gov, October 25, 2021).

**Kymriah(Novartis):** CAR-T cell therapy targeting CD19, a drug used to treat children and adolescents with acute lymphoblastic leukemia (ALL). This drug is the world's first FDA-approved CAR-T cell therapy product.

**Yescarta(Gilead):** CAR-T cell therapy targeting CD19 to treat adult patients with recurrent or refractory large B-cell lymphoma (LBCL).

## Chimeric antigen receptor natural killer cell therapy (CAR-NK)




**Principle:** CAR-NK cell strategy involves isolating a patient's own NK cells, engineering these NK cells to express CAR, which recognizes the tumor-specific target.

**Manufacturing process:** Primary NK cells can be isolated directly from peripheral blood mononuclear cells (PBMCs) of healthy donors or umbilical cord blood (UCB) and induced pluripotent stem cells (iPSCs). Isolated primary NK cells can be activated genetically engineered with CAR-expressing vectors (e.g., lentivirus [LVs] or retrovirus [RVs]). After the CAR-NK cells are amplified in vitro, they can be transfused back into the patient.

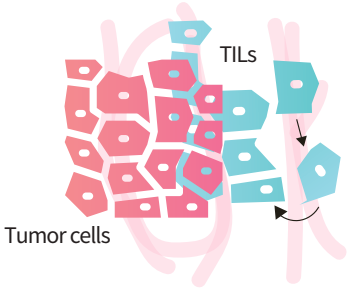
**Representative products:**

**NKX101 (Nkarta Therapies):** An "off-the-shelf" CAR-NK cell therapy targets NKG2D. It is composed of NK cells engineered to express a chimeric NKG2D receptor that targets a tumor cell's NKG2D ligands and a membrane-bound interleukin-15 to increase persistence. Compared with non-engineered NK cells, NKX101's ability to recognize and kill tumor cells in preclinical models has been significantly improved.

**FT596 (Fate Therapies):** Spot-type, iPSC-derived CAR-NK therapy. Among the 14 patients who received a dose of FT596 with more than 90 million cells, 10 (71%) out of 14 patients achieved objective remission, of which 7 (50%) achieved complete remission.

It is not currently approved for the market.

## Tumor-infiltrating lymphocyte therapy (TIL)




**Principle:** Tumor-infiltrating lymphocyte (TIL) therapy is a type of adoptive cellular therapy achieved by harvesting infiltrated lymphocytes from tumors, culturing and amplifying them in vitro, and, then infusing them back into patients. Some of these lymphocytes are T cells that target tumor-specific mutant antigens. They are immune cells that can penetrate deep into the tumor and exhibit the most effect.

**Manufacturing process:** The most used widely TIL production method is to isolate infiltrating lymphocytes from tumor tissues and then culture and expand these cells *in vitro*. The patient's tumor cells can then interact with the enlarged TIL cells to screen effector TIL cells that can kill tumor cells. Dendritic cells loaded with tumor-specific antigen (DC) are used for further amplification and cultivate tumor-specific TIL.,Finally, cells are transfused back into patients for treatment.

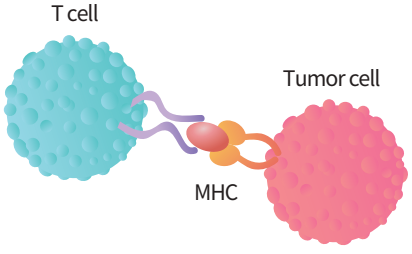
**Representative products:**

**LN-145 (Lovance Biotherapeutics):** A TIL therapy developed to treat metastatic non-small cell lung cancer. LN-145 monotherapy has achieved a total remission rate of 21.4% and a disease control rate (DCR) of 64.3%.

**ITIL-168 (Instil Bio):** ITIL-168 was developed to treat melanoma, with an overall objective response rate of 67%. Among them, the complete remission rate (CR) was 19%, the partial remission rate (PR) was 48%, and the disease control rate (DCR) was as high as 86%.

It is not currently approved for the market.

## T cell antigen receptor T cell therapy (TCR-T)




**Principle:** T-cell receptor (TCR)-based adoptive therapy employs genetically modified lymphocytes directed against specific tumor markers. T cells (or heterologous T cells), derived from the patient's peripheral blood, are modified via genetic engineering by adding identified TCR sequences. These TCR sequences can specifically bind to target antigens. The modified T cells are then transfused back into the patient's body to recognize and kill tumor cells expressing the antigen specificity.

**Manufacturing process:** The manufacturing process for TCR therapy is virtually the same as the one for CAR T cell therapy. T lymphocytes must be collected from the patient and purified. After purification, the sample is expanded, drastically increasing the number of TCR-T cells, and then transfused back into the patient.

**Representative products:**

KIMMTRAK (Immunocore) is the first FDA-approved treatment for unresectable or metastatic uveal melanoma. It is also the first regulatory approved T cell receptor (TCR) therapy and the first FDA-approved bispecific T cell connector to treat solid tumors.

# Comparison of different immune cell therapies

| | CAR-T/UCAR-T | CAR-NK | TIL | TCR-T |
|---|---|---|---|---|
| **Description** | Isolated T cells from peripheral blood are reinfused after introducing the CAR genes that specifically recognize tumor antigens | Introduction of CAR gene into NK cells from different sources and transfusion | Tumor-infiltrating T cells are amplified in vitro and then reinfused into the body | Transfusions of TCR genes specific for tumor antigen recognition into T cells isolated from peripheral blood |
| **Main targets** | Tumor cell surface proteins, such as CD19, BCMA | Tumor cell surface proteins, such as CD19, HER2 | There are no requirements for the target. Anti-tumor effect of multiple targets can be stimulated at the same time | Recognition of MHC antigen-peptide complexes after processing and presentation of tumor surface and internal antigens, such as MAGE-A1, NY-ESO-1, WT1 |
| **Characteristics** | Haematoma is highly effective, with severe side effects | Powerful anti-hematomas, side effects, and solid tumor efficacy need more research. | The intensity and incidence of side effects are the lowest; almost no non-target tissue side effects occur in the target | There are strong non-target tissue side effects on the target, and the effect on solid tumors has yet to be tested |
| **Hurdles** | CAR gene transduction /HLA gene knockout, cell sorting | CAR gene transduction | TIL cell sorting/expansion culture | TCR screening/gene transduction |
| **Indications** | Mainly for haematoma, such as Hodgkin lymphoma, lymphocytic leukemia, etc. | Hematologic malignancies and solid tumors, such as lymphocytic leukemia, mammary cancer, glioblastoma, etc. | Solid tumors, cervical cancer, melanoma, lung cancer, etc | Hematologic Malignancies and solid tumors, such as lymphocytic leukemia, synovial sarcoma, etc. |
| **Number of products listed** | 7 | 0 | 0 | 1 |
| **Representative enterprise** | Novartis、Gilead | Nkarta Therapeutics, Fate Therapeutics | Lovance Biotherapeutics, InstilBio | Immunocore |

**The cut-off time for the above data is Feb 1,2022.*

# Regulatory Requirements for R&D, Manufacture, and Clinical Research of Immune Cell Therapy

Immune cell therapy drugs had developed rapidly since 2017 when two CAR-T cell therapy drugs were approved by FDA. However, quality research and quality control are more complicated due to the large heterogeneity in the cell source, type, and in vitro operation of immune cell therapy products.

In July 2018, the US Food and Drug Administration (FDA) issued six scientific guidelines on human gene therapy products to standardize the research and development of cell therapy products and improve their safety, effectiveness, and quality controllability. As the cornerstone of a modern and comprehensive regulatory framework, these guidelines provide a strong reference for developing new products in this field following the FDA's safety and efficacy pathway. These guidelines cover a series of regulatory issues and special requirements for different gene therapy products. In addition, the EMA (European Medicines Agency) defines cell therapy products as advanced therapeutic products (ATMPs). The EMA has corresponding principles for ATMPs from non-preclinical research and clinical trials to industrial production. It includes the clinical trial quality management specification (GCP) for cutting-edge drugs, the quality management specification (GLP) for non-clinical research of cutting-edge drugs, and the production quality management specification (GMP) for cutting-edge drugs.

## FDA\EMA Immune Cell Therapy Regulations

| Publishers | File name | Time of publication |
|---|---|---|
| FDA | Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) | 2020 |
| FDA | Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up | 2020 |
| FDA | Long Term Follow-Up After Administration of Human Gene Therapy Products | 2020 |
| FDA | Human Gene Therapy for Retinal Disorders | 2020 |
| FDA | Human Gene Therapy for Rare Diseases | 2020 |
| FDA | Human Gene Therapy for Hemophilia | 2020 |
| FDA | Recommendations for Microbial Vectors used for Gene Therapy | 2016 |
| FDA | Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products | 2015 |
| FDA | Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products | 2015 |
| FDA | Preclinical Assessment of Investigational Cellular and Gene Therapy Products | 2013 |
| FDA | Potency Tests for Cellular and Gene Therapy Products | 2011 |
| EMA | Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials | 2019 |
| EMA | Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products | 2017 |

Scan the QR code for the FDA\EMA guidelines package

## Immune Cell Therapy Development Process (take CAR-T cell drugs as an example)

| | Early drug discovery | Manufacture/Quality control | Non-clinical studies | Clinical research |
|---|---|---|---|---|
| **Research Content** | • Targets identification and selection.<br>• Preparation and screening of scFv or sdAb (single domain antibody).<br>• Design and optimization of CAR structure. | • Selection of raw materials<br>• Preparation of Gene vector.<br>• Preparation of CAR-T cell therapy products. | • Selection of animal models.<br>• Pharmacodynamic studies.<br>• Pharmacokinetics.<br>• Non-clinical safety. | Exploratory Clinical Trials<br>• Safety and tolerability.<br>• Assessment of activity in vivo. Confirmatory clinical trials.<br>• Clinical efficacy and safety. |
| **Solutions and Products** | 50 + CAR-T Target Products: Suitable for multiple scenarios such as immunology, single-domain antibody or scFv screening, CAR affinity detection, and species cross-validation. | Raw materials: Anti-CD3/CD28 antibody-coupled magnetic beads, cytokines, GENES™Nuclease, and other products. For quality control release testing: fluorescent-labeled proteins | Pharmacokinetic study: Highly sensitive and specific fluorescent-labeled CAR-T target proteins, anti-idiotypic antibodies.<br>For immunogenicity evaluation: anti-idiotypic antibodies, such as rabbit Anti-FMC63 scFv polyclonal antibody and murine Neutralizing Anti-FMC63 scFv monoclonal antibody;<br>ACROBiosystems can provide customized anti-idiotypic antibody services to meet customers' demands. | |

## Manufacture and quality control of gene vector substances

The quality control of gene vector substances is an important upstream link in the production of CAR-T cell drugs. The three most commonly used gene vector substances are lentiviral vectors, retroviral vectors, and plasmid vectors. Among them, lentiviral vectors are the most widely used. The determination of viral vector transfer titers is one of the key indicators of lentiviral vector quality control.

## Determination of viral vector transfer titer

The ability to transfer cells is usually used as the titer of the viral vector. After the viral vector is transferred to sensitive cell lines (such as 293T cells, HT-1080 cells, etc.) or primary cells (such as PBMC), the positive CAR expression rate or CAR gene copy number of the cell is detected, and the transfer titer (TU/ml) is calculated.

## Quality control of CAR-T cell products

For CAR-T cells, the active ingredients that play a tumor-killing role are CAR-positive T cells. The packaging specifications and clinical dosage of CAR-T cell products are based on the number of CAR-T-positive cells. Therefore, detecting the positive rate of CAR transfection is one of the key indicators for CAR-T quality control.

**The detection of positive CAR transfer and transfection positivity rate:**
Flow cytometry usually is used to detect the positive rate of CAR transfection. There are some methods for CAR detection, such as CD19 antigen or anti-scFv antibody for CAR antigen-binding sites, anti-Fab antibody, or Protein L for light chain or hinge regions. Among these choices, target antigens are widely considered the best option because they offer high specificity and minimal background staining.

## Non-clinical research

Non-clinical research, using suitable subjects and animal models to carry out *in vivo* and in vitro pharmacodynamic, pharmacokinetic, and non-clinical safety research, can provide a supporting basis for follow-up clinical trials.

### ▶ Pharmacokinetic study of CAR-T cells

The pharmacokinetic research of CAR-T cells mainly focuses on the proliferation level, distribution, and survival time of target cells *in vivo*. Optional detection techniques are imaging techniques, flow cytometry, immunohistochemistry techniques, quantitative PCR, etc. Different methods are suitable for detection of different samples and detection purposes.

- **Imaging method:** The in vivo distribution of CAR-T cells can be visually detected. Cell labeling for *in vivo* imaging can be achieved by a variety of methods, such as radioisotope labeling of cells, genetic modification (e.g., expression of a green fluorescent protein or luciferase) labeling, and nano-particle labeling (e.g., iron-dextran nano-particles), etc.
- **Flow cytometry:** Can detect CAR-T cells in animal blood, bone marrow, and spleen.
- **Immunohistochemistry method**: CD3+cells or CAR+ T cells in the spleen or other organs can be detected to indicate the distribution and accumulation of human T cells in animal organs.
- **Quantitative PCR method:** It can detect CAR-T cells' DNA or RNA levels in all types of samples. The PCR method recommends CAR instead of CAR-T cells as the specific detection target.

## Pharmacodynamic study of CAR-T cells

Bioluminescent Imaging (BLI) technology is the most intuitive and commonly used method for studying the pharmacodynamic effects of CAR-T cells. This method detects tumor cells expressing luciferase and uses fluorescence intensity to indicate the tumor load. It is currently one of the main techniques for evaluating the pharmacodynamic effects of CAR-T cell products *in vivo*.

Flow cytometry can detect the number of tumor cells in animals.

Immunological methods such as flow cytometry, ELISA, and MSD detect changes in tumor-related cytokines in serum, thereby indirectly reflecting pharmacodynamic results.

Conventional pharmacological or pathological methods detect tumor-related parameters (such as tumor volume, tumor weight, colonization site of tumor cells in animals) and the median survival period of animals.

## Indicators of non-clinical immunotoxicity of CAR-T cells

- **Cytokine storm (CRS):** Use flow cytometry, Luminex, MSD electrochemical luminescence, and other methods to detect serum cytokine levels (such as IL-2, IL-4, IL-6, IL-10, INF-γ, TNF-α, etc.)

# Clinical research

Clinical research is divided into exploratory and confirmatory clinical trials. The exploratory clinical trial phase focuses on the safety and tolerance of cell therapy products. The biological activity range or optimal effective dose of cell therapy products is determined through dose exploration. Another purpose in the exploratory clinical trial phase is to conduct a preliminary evaluation of product activity, such as cell proliferation, survival, and biological distribution in vivo (such as pharmacokinetics), pharmacodynamic activity (such as cytokine levels after product infusion), immunogenicity, and efficacy such as tumor remission or other types of clinical improvement, etc.

The purpose of confirmatory clinical trials is to confirm the efficacy and safety of preliminary indications in exploratory studies and to provide key benefit/risk assessment evidence for registration.

## Pharmacokinetic (PK) evaluation method of CAR-T cell products

For clinical PK studies of CAR-T cell products, real-time fluorescence quantitative polymerase chain reaction (qPCR) and flow cytometry are usually used for PK analysis. The measurement of exogenous gene copies and changes in the number of CAR positive cells helps to verify the reliability of the detection method with each other. The amplification and survival of the product can be more comprehensively analyzed in vivo.

## Immunogenicity evaluation method for CAR-T cell products

Immunogenicity research investigates the correlation between anti-drug antibodies (ADA) produced by cell therapy drugs and pharmacokinetic/pharmacodynamic, efficacy, and safety. Its research content mainly focuses on the detection and characterization of drug-resistant antibodies. Data on drug-resistant antibodies' incidence, titer, survival time, and neutralization ability should be obtained.

Commonly used detection methods: Direct/indirect ELISA, bridged ELISA, electrochemiluminescence (ECL/MSD), radioimmunoprecipitation test (RIPA), surface plasma resonance (SPR), cell-level test (Cell-based assay), and Competitive Ligand Binding Assay (Competitive Ligand Binding Assay).

# Immune Cell Therapy Development and Evaluation Solutions

## Early discovery of immune cell products

### Early discovery for CAR-T cell therapy

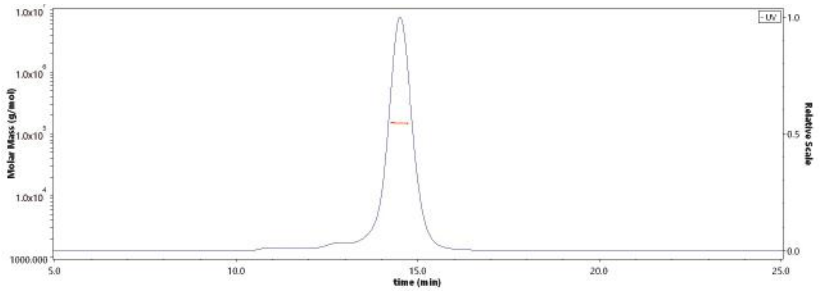
ACROBiosystems has developed more than 50 CAR-T targets, including CD19, BCMA, CD22, MSLN, and GPC3 using professional protein research and development to support the CAR-T cell drug development research platform.

### Product features

- 50+ CAR-T targets
- PE/FITC/Biotin/Unconjugated forms available
- Variety of tags including His Tag/Human IgG1 Fc Tag/Mouse IgG2a Fc Tag/Llama IgG2b Fc Tag
- Human, Cynomolgus, mouse, and more species
- Suitable for various application scenarios such as immunization, antibody screening, antibody affinity measurement, and species cross-verification.
- Some products have completed the FDA DMF filing (DMF number: 034936), which can support your IND, NDA, and BLA.

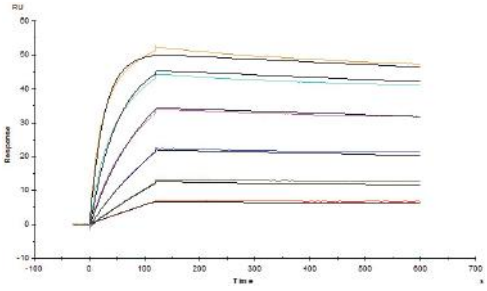
### Star product – CD19

**>>> High purity verified by HPLC-MALS**



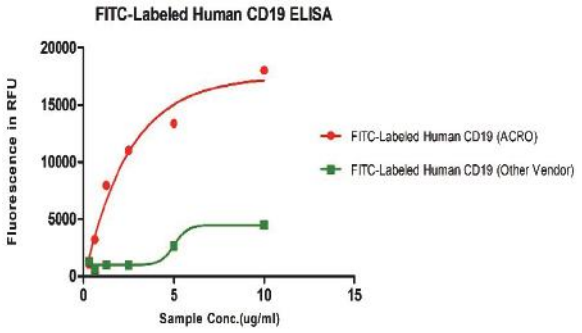

*The purity of Human CD19 (20-291), Fc Tag (Cat. No. CD9-H5251) was more than 95% and the molecular weight of this protein is around 140-160 kDa verified by HPLC-MALS.*

**>>> High affinity verified by SPR**

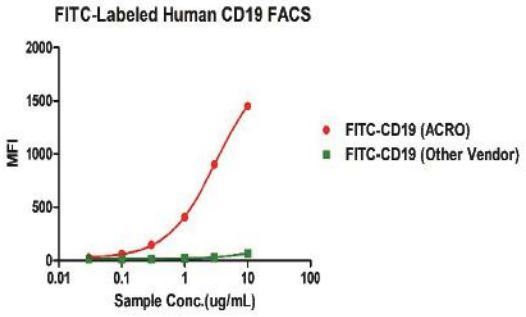



*Human CD19 (20-291), Fc Tag (Cat. No. CD9-H5251) captured on CM5 chip via Anti-Human IgG Fc antibodies surface, can bind FMC63 MAb (Mouse IgG2a) with an affinity constant of 0.17 nM as determined in a SPR assay (Biacore T200) (Routinely tested).*

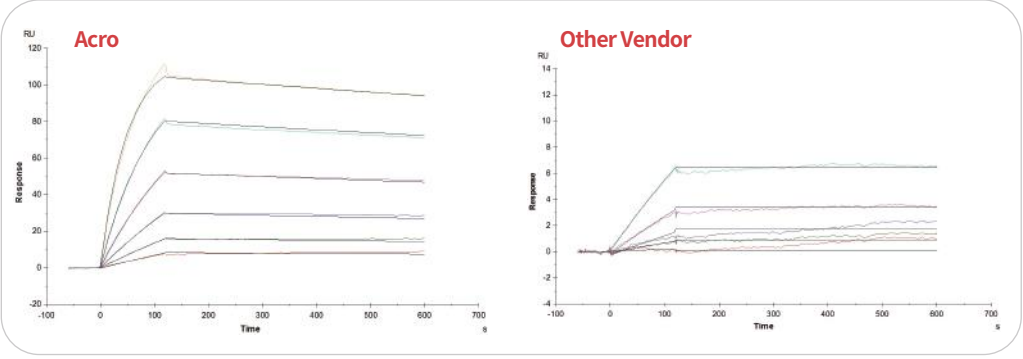
## >>> Higher binding activity compared to that of other competitors




Binding activity of FITC-Labeled Human CD19, His Tag from two different vendors were evaluated in the ELISA analysis against FMC63 Mab. The result showed that ACRO's FITC-Labeled Human CD19, His Tag has a much higher binding activity than that of the other vendor.




Binding activity of FITC-Labeled Human CD19, His Tag from two different vendors were evaluated in the flow cytometry analysis against anti-CD19-CAR-293 cells. The result showed that ACRO's FITC-Labeled Human CD19, His Tag has a much higher binding activity than that of the other vendor.




*Binding activity of Human CD19, His Tag from two different vendors were evaluated by SPR assay against FMC63 mAb. The result showed that ACRO's Human CD19, His Tag can bind FMC63 mAb with an affinity constant of 2.95 nM which is much higher than that of the other vendor.*

## ▶ Hot CAR-T targets at ACROBiosystems

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CD19 | BCMA | CD22 | CD20 | CD123 | CD33 | CD30 | CD38 | CS1 |
| CD138 | CD37 | CD4 | CD5 | CD56 | CD7 | CD72 | CD99 | CLL-1 |
| GPRC5D | LILRB4 | HER2 | MSLN | EGFR | GPC3 | PSMA | EBV | B7-H3 |
| CAIX | CD147 | CD47 | CEA | CLDN18 | DLL3 | EGFRVIII | EpCAM | FAP |
| FOLR1 | GUCY2C | HER3 | HGFR | IL13RA2 | MUC16 | Nectin-4 | PSCA | uPAR |
| VEGFR2 | CD171 | MUC-1 | NKG2D | CD133 | CD70 | ROR1 | PD-L1 | |

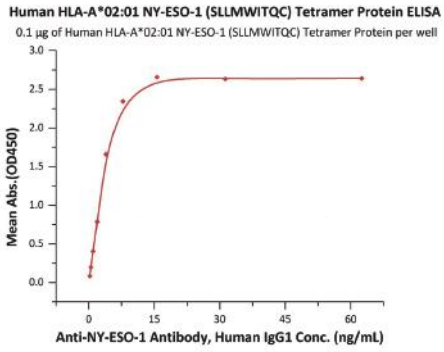
The red background represents blood tumor markers, the pink background is for solid while the others are common markers for both.

## ■ Early discovery for TCR-T cell therapy

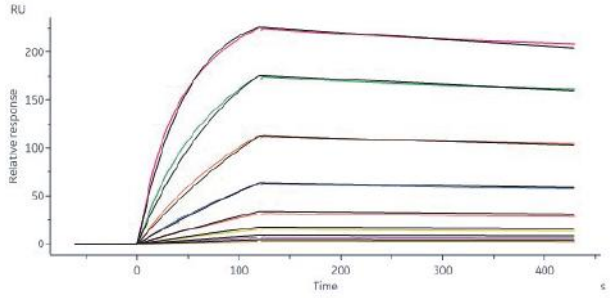
ACROBiosystems provides a series of MHC-polypeptide complex proteins with natural conformation and complete glycosylation modification, including monomer, tetramer forms, etc., to meet the requirements of TCR screening and detection in the development of TCR-T cell therapy.

## ▶ Star product - Human HLA-A*02:01 NY-ESO-1 (SLLMWITQC) Complex Protein

★ High bioactivity of Human HLA-A*02:01 NY-ESO-1 (SLLMWITQC) Tetramer Protein




*Immobilized Human HLA-A*02:01 NY-ESO-1 (SLLMWITQC) Tetramer Protein (Cat. No. HL1-H52E8) at 1 μg/mL (100 μL/well) on streptavidin (Cat. No. STN-N5116) precoated (0.5 μg/well) plate can bind Anti-NY-ESO-1 Antibody, Human IgG1 with a linear range of 0.2-8 ng/mL (QC tested).*




*Anti-NY-ESO-1 antibody captured on CM5 chip via Anti-human IgG Fc antibodies surface can bind Human HLA-A0201 NY-ESO-1 (SLLMWITQC) Tetramer Protein (Cat. No. HL1-H52E8) with an affinity constant of 1.35 nM as determined in an SPR assay (Biacore 8K) (QC tested).*

# Raw materials for immune cell products

| Raw materials at ACROBiosystems | Application |
|---|---|
| Cytokines（e.g. IL-2, IL-7, IL-15, IL-21） | Activation and amplification of T/NKcells |
| Anti-CD3/CD28 coupled Magnetic Beads and related antibodies products | Activation and amplification of T cells |
| GENIUS™Nucleas | Nucleic acid removal in the lentivirus purification process |
| CRISPR-Cas Nuclease | Gene edition |

## ▶ Star product - GMP Human IL-15

**>>> Product Features**


★ Strict Quality Control Standards

- 16 quality control standards.
- Excellent safety profile (testing for sterility, mycoplasma, endotoxin, and residual impurities).
- High stability and batch-to-batch consistency.

## ★ GMP Grade Quality Management System

- ISO 5 cleanrooms used for filling.
- Raw and packing materials are registered.
- Facilities are available for online and on-site audits.

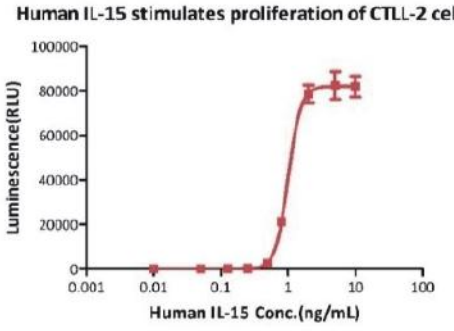
## ★ Accelerating Global Regulatory Approval of Biological Products

- A comprehensive set of regulatory documents is available.
- Validation reports for analysis methods are available on request.
- FDA DMF filing is in progress.

## ★ Automatic filling equipment


## ★ Sterilization equipment

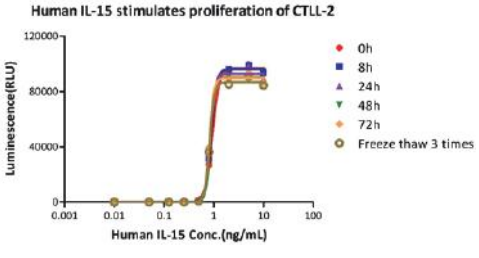
## >>> High bioactivity




*GMP Human IL-15 (Cat. No. GMP-L15H13) stimulates the proliferation of CTLL-2 cells. The EC50 for this effect is 1.004 ng/mL, corresponding to a specific activity of > 0.8 x 10^7 IU/mg, which is calibrated against human IL- 15 WHO International Standard (NIBSC code: 95/554).*

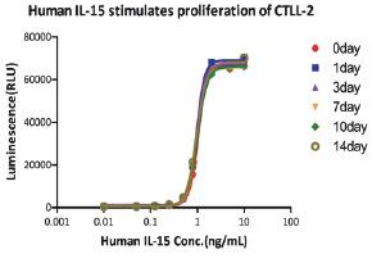
## >>> High stability

## ★ Validation of accelerating and freeze-thaw stability



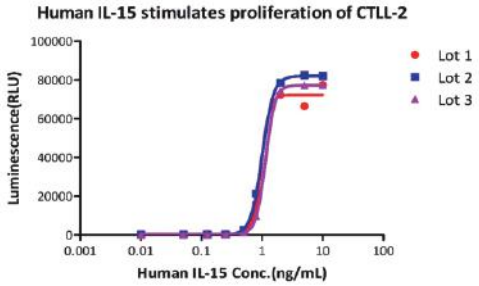

GMP Human IL-15 (Cat. No. GMP-L15H13) is stable in undiluted samples at 25℃ for 72 hours and freeze-thaw 3 times without performance reduction.

## ★ Long-term stability testing（4°C）




GMP Human IL-15 (Cat. No. GMP-L15H13) is stable in undiluted samples at 4 ℃ for 14 days without performance reduction.

### >>> High batch-to-batch consistency



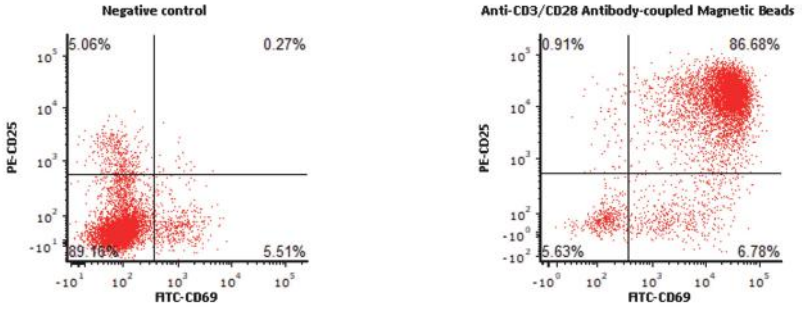

*Bioactivity of three different lots of GMP Human IL-15 (Cat. No. GMP-L15H13) verified by cell-based assay, and the result shows very high batch-to-batch consistency.*

## ▶ Star product- Anti-CD3/CD28 coupled Magnetic Beads

### >>> Product Features

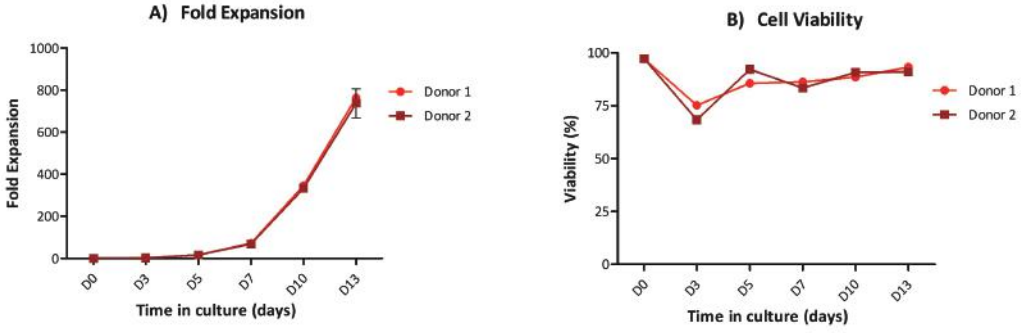
- Microbial testing and ultra-low endotoxin（<2 EU/mg）
- Efficient activation and expansion
- High batch-to-batch consistency
- Highly stable and convenient for storage and transportation in lyophilization

### ★ Activation of the purified human T Cells




*The purified human T cells were activated using Anti-CD3/CD28 Antibody-coupled Magnetic Beads (Cat. No. MBS-C001) at a ratio of 1:1 beads-to-cells for 24 hours alongwith RPMI1640 supplemented with 10% of FBS. The negative control experiment was performed by adding the Negative Control Beads coupled HSA. Cells were fluorescently stained using PE-labeled anti-human CD25 antibody and labeled FITC anti-human CD69 antibody and analyzed by flow cytometry.*

### >>> Purified human T Cells expansion




*The purified human T cells were stimulated using Anti-CD3/CD28 Antibody-coupled Magnetic Beads (Cat. No. MBS-C001) at a ratio of 1:1 beads-to-cells. Cells were expanded in a T cell culture medium supplemented with 4ng/mL of rhIL-2 Protein (Acrobiosystems, Cat. No. IL2-H4113). Activated Cells were expanded for up to 13 days (A) with high cell viability (B).*

## ▶ Star product - GENIUS™ Nuclease

### >>> Product Features

- **High purity, high activity** (Purity > 95%, specific activity > 1.5 x $10^6$ unit/mg)
- **Tag Free, Close to the natural state, High enzyme activity** (Enzyme activity≥250 U/μl)
- **High specificity and sensitivity** (No protease activity)
- **The reaction conditions are broader** (Optimum temperature 35 °C -42 °C, optimum pH 8.0 - 8.5)

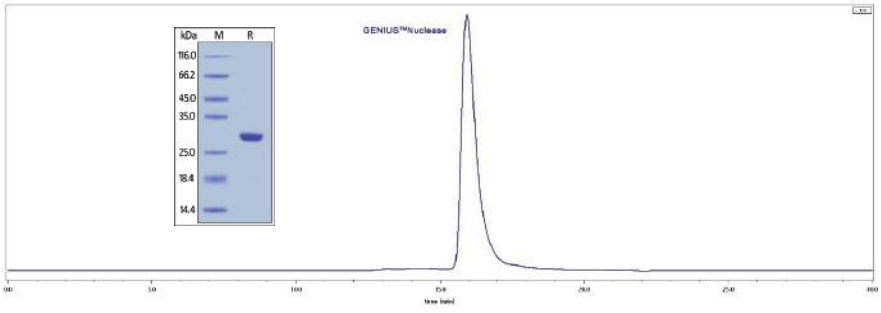

**GMP grade GENIUS™ Nuclease is coming soon !**

### >>> GENIUS™Nuclease Applicable conditions

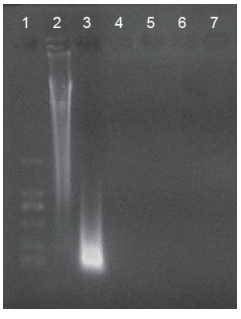
| Reaction parameters | Optimal condition | Valid conditions |
|---|---|---|
| $Mg^{2+}$ | 1-2 mM | 1-10 mM |
| pH | 8.0 - 8.5 | 6 - 10 |
| Temperature | 35-42°C | 0-42°C |
| DTT | 0-100 mM | > 100 mM |
| Mercaptoethanol | 0-100 mM | > 100 mM |
| Univalent cations | 0-20 mM | 0-150 mM |
| Phosphate anion | 0-10 mM | 0-100 mM |

*An enzyme activity unit is defined as the digestion of ultrasound-treated salmon sperm DNA into acid-soluble oligonucleotides after reaction for 30 minutes at pH 8.0, 37 °C. DeltaA260 is 1.0 (equivalent to 37 μg DNA fully digested), corresponding to Genius TM Nucleus.*

★ GENIUS™Nuclease (Cat. No: **BEE-N3116**), The high purity verified by SDS-PAGE & HPLC



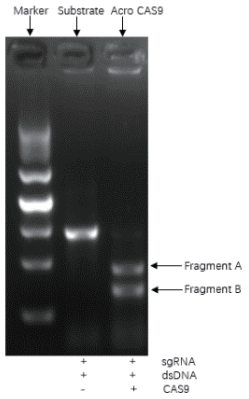

★ GENIUS™Nuclease (Cat. No: **BEE-N3116**) can completely remove DNA from the system




*Line 1: Marker, MD114 (100-2000bp)*
*Line 2: Ultrasound (unsonicated) DNA*
*Line 3: Post-ultrasound DNA*
*Line 4-7: Post-ultrasound DNA + GENIUS™Nuclease*

## Star product – Cas 9

- High enzyme activity: improve the cutting efficiency to 90% and make it easier to edit gene by CRISPR
- High purity verified by SDS-PAGE(>90%) and SEC-MALS(>95%)
- Bioactivity verified by *in vivo*/ *in vitro* assay: gene knockout activity ***in vivo*** and fragment cleavage activity *in vitro*
- Low endotoxin less than 0.1 EU/ug


*Measured by its ability to cleave a targeted DNA substrate. Cas9 (Cat. No. CA9-S5149) achieves >90% substrate cleavage.*

# Quality control of CAR-T cell products

The detection of the positive rate of CAR transfection is a key test indicator for the quality control of CAR-T cell products. Regulatory authorities recommended flow cytometry to test CAR antigen-binding sites, such as target antigen. However, there is a lack of stable products suitable for this application in the market.

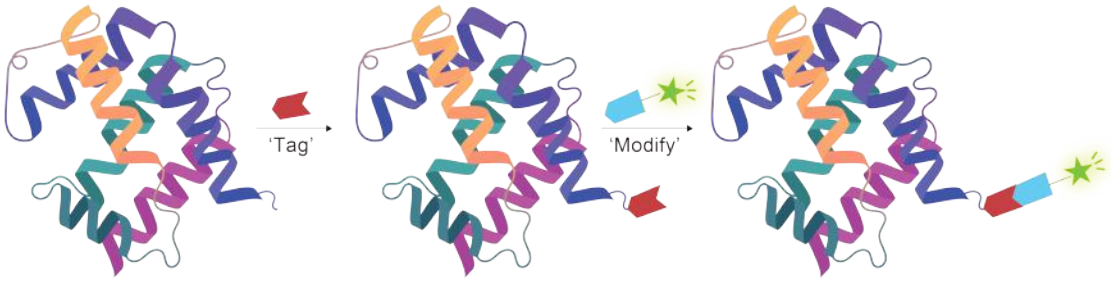
ACROBiosystems has used its professional protein research and development platform, a new fluorescent targeted labeling platform, a stable cell line development platform, and a cell-based assay platform to develop more than 50 kinds of Fluorescent-labeled CAR target antigens. These antigens are verified by flow cytometry to ensure high batch-to-batch consistency and stability.

## Product features

- 50+ CAR-T targets
- PE/FITC/APC/ Alexa Fluor 647/488/555/Biotin/Unconjugated forms.
- High batch-to-batch consistency and stability to meet CAR-T cell drugs' strict quality control requirements.
- Suitable for CAR detection with high sensitivity and specificity.
- Some products have completed the FDA DMF filing (DMF number: 034936), which can support your IND, NDA, and BLA.

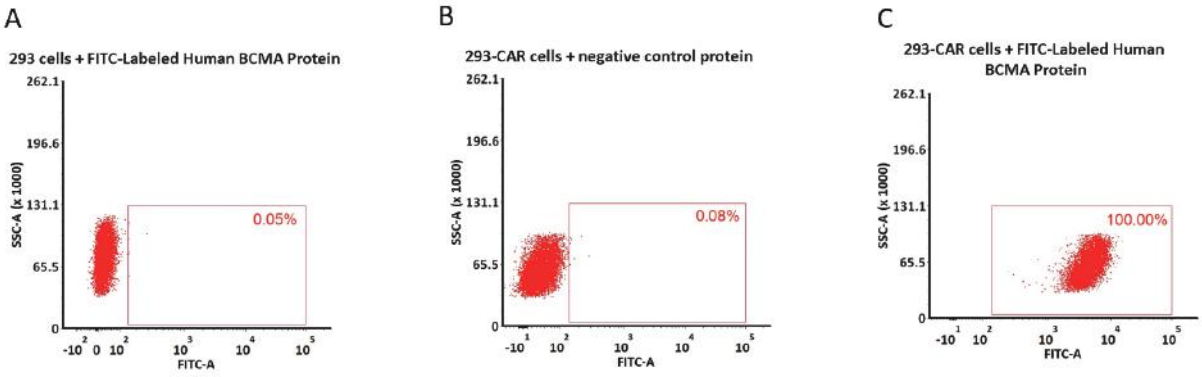
## ▶ Star products——Star Staining FITC-labeled Human BCMA, His Tag

### >>> New generation labeling technology to maintain high bioactivity.



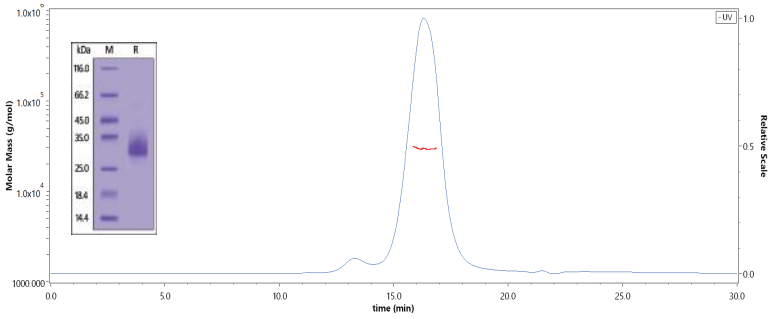

### >>> Suitable for CAR detection by flow cytometry

★ FACS Analysis of Anti-BCMA CAR Expression



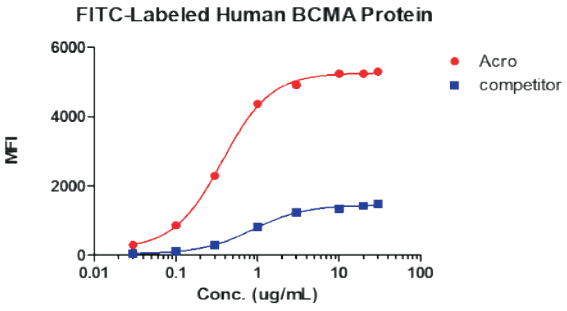

*2x10⁵ of 293 CAR cells transfected with anti-BCMA-scFv were stained with 100 µL of 1 µg/mL of FITC-Labeled Human BCMA, His Tag (Cat. No. BCA-HF2H3) and negative control protein respectively (Fig. C and B), and non-transfected 293 cells were used as a control (Fig. A). FITC signals were used to evaluate the binding activity (QC tested).*

### >>> High purity is more than 90% as verified by HPLC-MALS



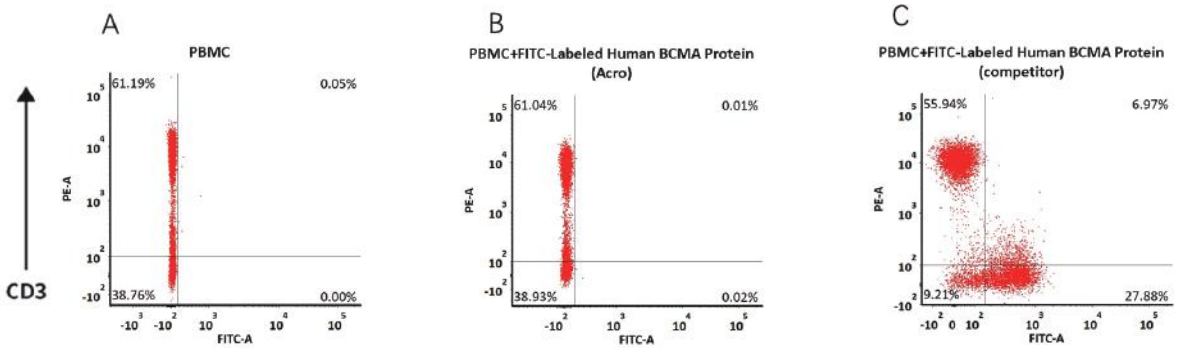

*The purity of FITC-Labeled Human BCMA, His Tag (Cat. No. BCA-HF2H3) was more than 90%, and the MW of this protein is around 24-34 kDa as verified by HPLC-MALS.*

### >>> Higher binding activity as compared to that of other competitors




*The binding activity of FITC-Labeled Human BCMA protein from AcroBiosystems and a competing vendor was evaluated by FACS analysis. The result showed that ACRO's Star Staining FITC-Labeled Human BCMA (Cat. No. BCA-HF2H3) protein has a much higher binding activity as compared to competitors.*

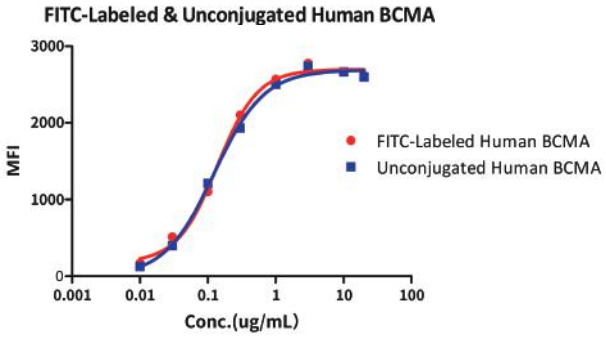
## >>> No non-specific binding to non-transduced PBMCs



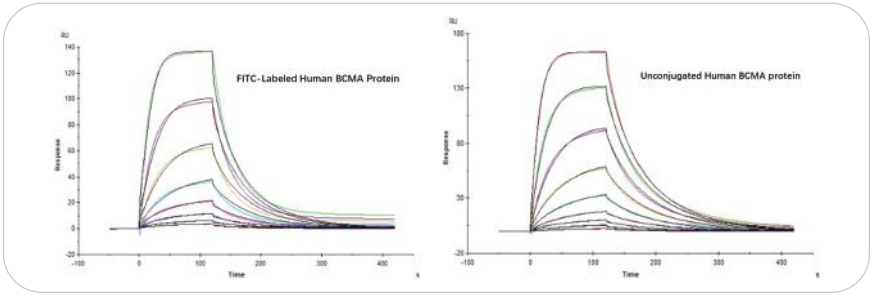

*Non-specific binding to non-transduced PBMCs between FITC-Labeled Human BCMA Protein of Acro and competitor. 5e5 of non-transduced PBMCs were stained with FITC-Labeled Human BCMA Protein and anti-CD3 antibody, washed and then analyzed with FACS. PE signal was used to evaluate the expression of CD3+ T cells in non-transduced PBMCs, and FITC signal was used to evaluate the non-specific binding activity to non-transduced PBMCs.*

## >>> Maintain natural bioactivity

★ High binding capacity before and after conjugation, as verified by FACS and SPR



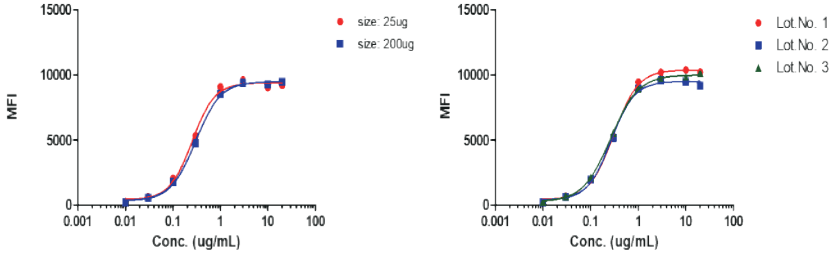

*The binding activity of the Human BCMA before and after FITC labeling was evaluated in the above FACS analysis. The result shows that FITC-Labeled BCMA (Cat. No. BCA-HF2H3) and unconjugated Human BCMA have similar levels of binding activity.*




*Binding affinity of the Human BCMA before and after FITC labeling was evaluated in the above SPR analysis (Biacore T200). The result shows that FITC-Labeled (Cat. No. BCA-HF2H3) and unconjugated Human BCMA, His Tag have almost the same level of affinity.*

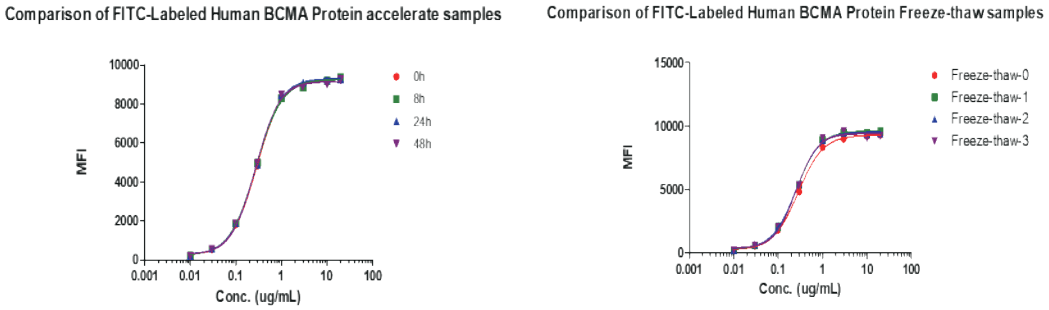
## >>> High batch-to-batch consistency

★ FACS verified the binding activity of different lots of FITC-labeled Human BCMA protein




*Binding activity of two different sizes (left) and three different lots (right) of FITC-Labeled Human BCMA (Cat. No. BCA-HF2H3) against anti-BCMA CAR-293 cells was evaluated by flow cytometry. The result shows very high batch-to-batch consistency.*

### >>> High stability




*FITC-Labeled Human BCMA (Cat. No. BCA-HF2H3) kept at different concentrations at 25℃ for 48 hours and undergoing multiple freeze-thaw cycles shows no stability issue or performance reduction.*

## Preclinical and clinical pharmacokinetics (PK) research

The purpose of preclinical and clinical PK research on CAR-T cell products is to analyze the amplification and survival of CAR-T cells in vivo. Real-time fluorescence quantitative polymerase chain reaction (qPCR) and flow cytometry are usually used for such analysis, and the changes in exogenous gene copies and the number of CAR-positive cells are measured separately.

However, due to the complex cell composition of preclinical and clinical samples, low CAR-T cell content and strong non-specific background, currently available flow detection reagents cannot readily meet the needs of PK research.

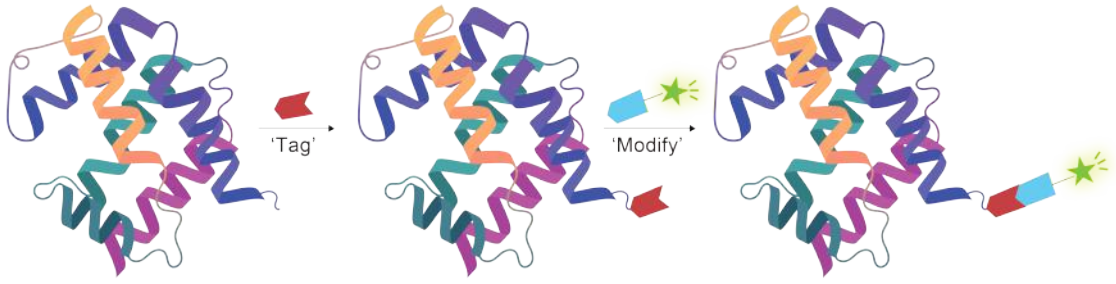
To solve this problem, ACROBiosystems has developed a series of high-sensitivity and high-specificity CAR-T target proteins and anti-unique antibodies, which are suitable for flow cytometry to detect CAR-T preclinical and clinical samples.

### ▶ Product features

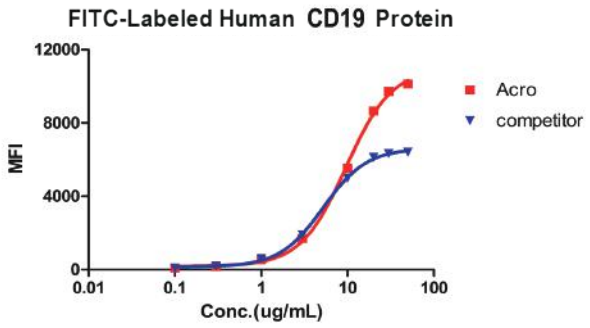
- 50+ CAR-T targets
- PE/FITC/APC/ Alexa Fluor 647/488/555 forms
- High sensitivity and specificity verified by FACS
- Nonspecific binding to non-transduced PBMCs
- High batch-to-batch consistency and stability that meet the requirements of clinical sample analysis
- Some products have completed FDA DMF filing (DMF number: 034936), which can be used to support your IND, NDA, and BLA.

### ▶ Star products——Star Staining FITC-labeled Human CD19, His Tag

**>>> New generation labeling technology to maintain high bioactivity**

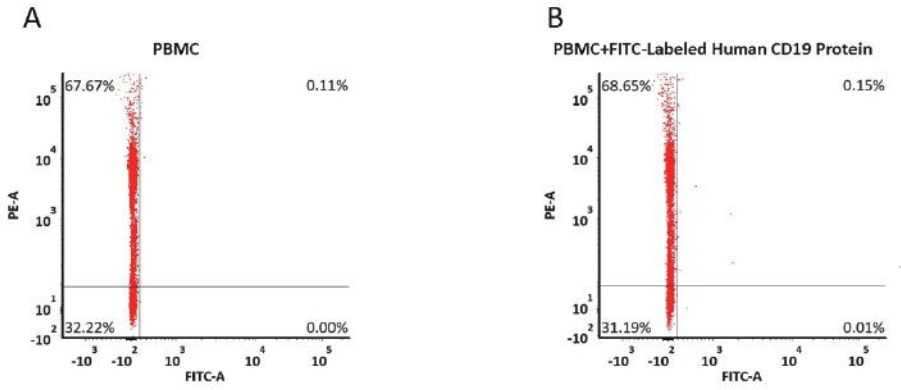


### >>> Higher binding activity as compared to that of other competitors




*The FACS analysis evaluated the binding activity of FITC-Labeled Human CD19 protein from two different vendors. The result shows that ACRO's Star Staining FITC-Labeled Human CD19 (Cat. No. CD9-HF2H3) protein has a much higher binding activity than other competitors'.*

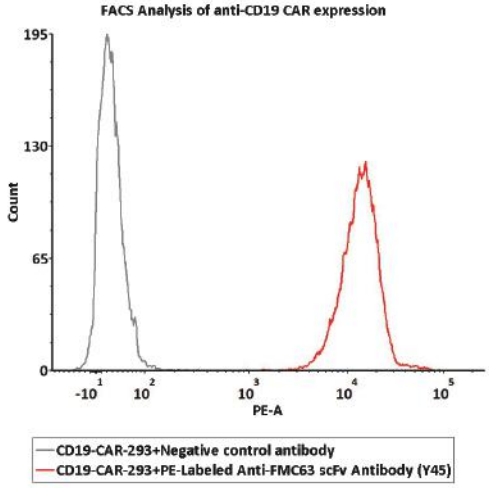
### >>> No non-specific binding to non-transduced PBMCs




*5e5 PBMCs were stained with FITC-Labeled Human CD19 (20-291), His Tag (Cat. No. CD9-HF2H3), and anti-CD3 antibody, washed and then analyzed with FACS. PE signal was used to evaluate the expression of CD3+ T cells in PBMCs. FITC signal was used to evaluate the nonspecific binding activity to PBMCs (QC tested).*

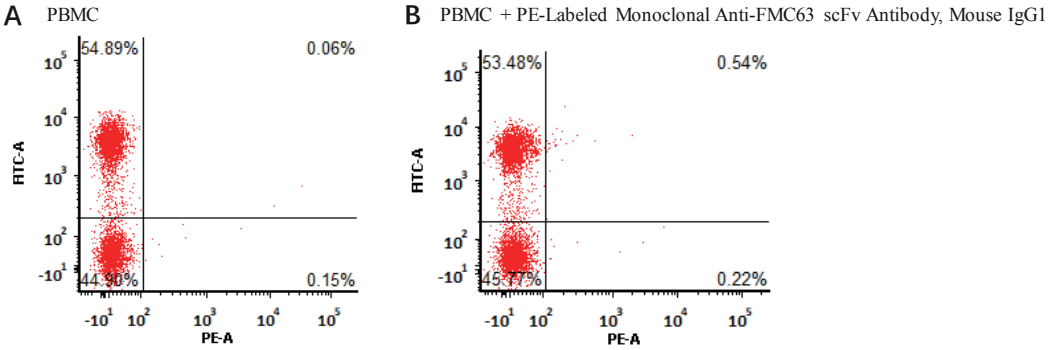
## ▶ Star products——PE-Labeled Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Y45)

### >>> High sensitivity validated by FACS



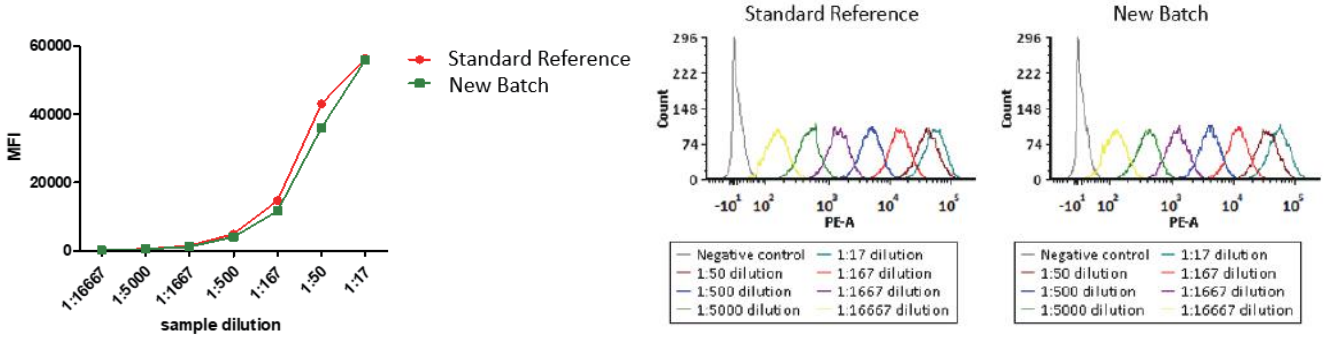

*1e6 of the Anti-CD19 CAR-293 cells were stained with 100 μL of 1:50 dilution (2 μL stock solution in 100 μL FACS buffer) of PE-Labeled Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Cat. No. FM3-HPY53) and negative control antibody respectively. PE signal was used to evaluate the binding activity (QC tested).*

### >>> No non-specific binding to non-transduced PBMCs

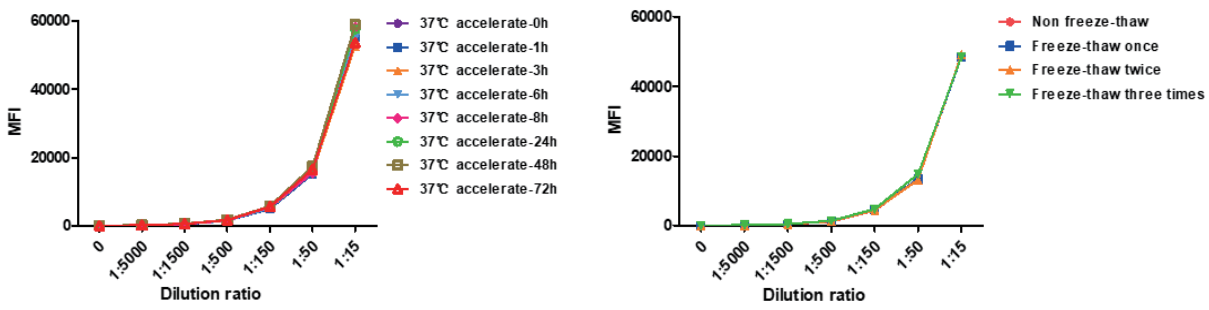



*5e5 PBMCs were stained with PE-Labeled Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Cat. FM3-HPY53), and anti-CD3 antibody, washed followed by FACS analysis. FITC signal was used to evaluate the expression of CD3+ T cells in PBMCs, and PE signal was used to evaluate the nonspecific binding activity to PBMCs.*

### >>> High batch-to-batch consistency and stability meet the requirements of clinical sample analysis




*The binding activity of two different batches of PE-Labeled Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Cat. No. FM3-HPY53) against anti-CD19 CAR-293 cells was evaluated by flow cytometry. The result shows very high batch-to-batch consistency.*




*PE-Labeled Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Cat. No. FM3-HPY53) were tested in different concentrations at 37℃ for 72 hours with repeated freeze-thaw cycles and found to be stable without performance reduction.*

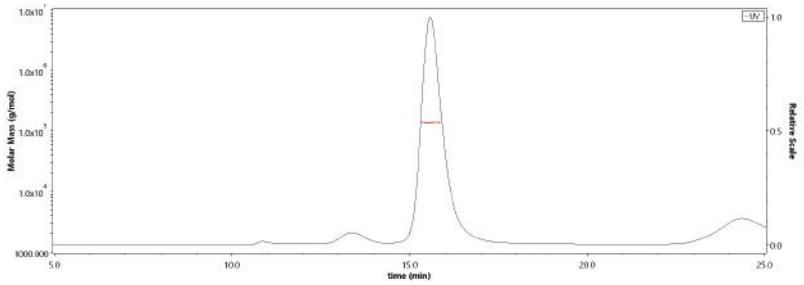
## Preclinical and clinical immunogenicity evaluation

Immunogenicity is a key indicator in CAR-T cell therapy non-clinical and clinical safety research. It is mainly used to investigate the correlation between Anti-drug antibodies (ADA) produced by cell therapy drugs and pharmacokinetics, efficacy, and safety. The research content mainly focuses on the detection and characterization of anti-drug antibodies. Data on anti-drug antibodies' incidence, titer, survival time, and neutralization ability should be obtained.

Using a professional anti-idiotypic antibody research platform, ACROBiosystems has developed anti-idiotypic antibody products such as Anti-FMC63 scFv antibodies that can evaluate CAR-T cell drugs and provide customized ADA services.

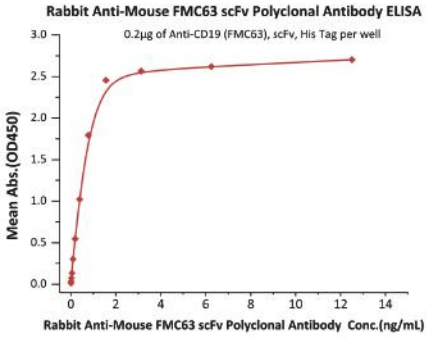
## ▶ Star products——Rabbit Anti-Mouse FMC63 scFv Polyclonal Antibody

### >>> High purity is more than 90%

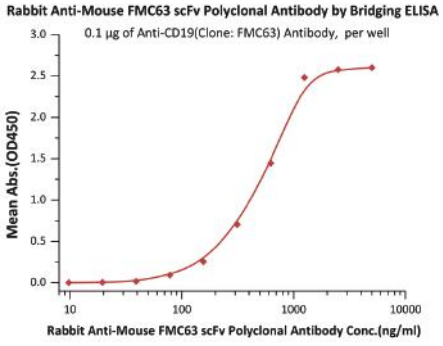



*The purity of Rabbit Anti-Mouse FMC63 scFv Polyclonal Antibody (Cat. No. FM3-S93) was more than 90%, and the molecular weight of this protein is around 130-145 kDa, as verified by HPLC-MALS.*

### >>> Suitable for ADA assay development



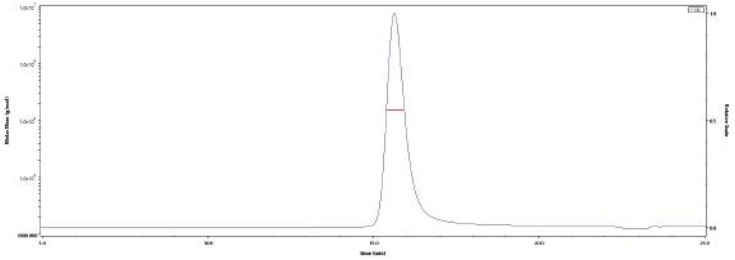

Immobilized FMC63 scFv at 2 μg/mL (100 μL/well) can bind Rabbit Anti-Mouse FMC63 scFv Polyclonal Antibody (Cat. No. FM3-S93) with a linear range of 0.098-0.78 ng/mL (QC tested).




Immobilized anti-CD19 antibody (Clone: FMC63) at 1 μg/mL, add increasing concentrations of Rabbit Anti-Mouse FMC63 scFv Polyclonal Antibody (Cat. No. FM3-S93) and then add Biotinylated anti-CD19 antibody (Clone: FMC63) at 2 μg/mL. Detection was performed using HRP-conjugated streptavidin with sensitivity of 78 ng/mL (QC tested).

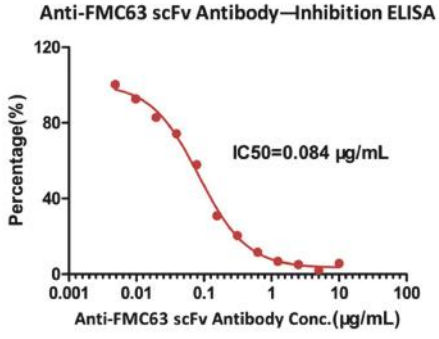
## ▶ Star products——Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Y45) (Carrier-free)

### >>> >95% purity as verified by SEC-MALS



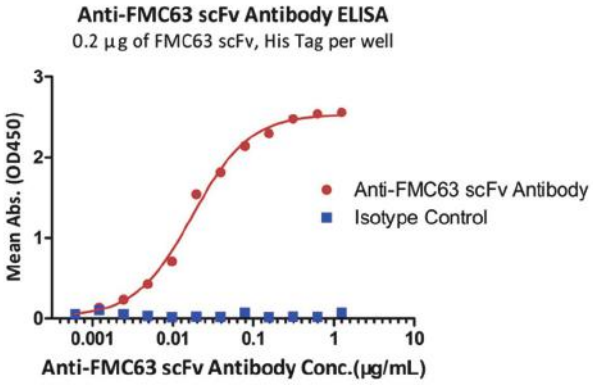
*The purity of Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Carrier-free) (Cat. No. FM3-Y45A1) was more than 95%, and the molecular weight of this protein is around 140-160kDa as verified by SEC-MALS.*

### >>> Competitive inhibition ELISA verified Anti-FMC63 antibodies neutralizing activity. Suitable for development of Neutralising ADA Detection Assay



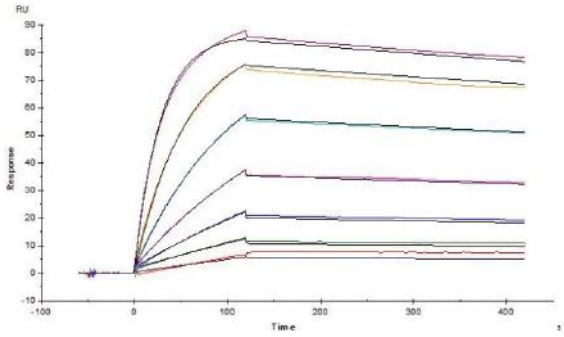

*ELISA analysis shows that the binding of Human CD19, Fc Tag (Cat. No. CD9-H5251) to FMC63 scFv, His Tag was inhibited by increasing concentration of Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Clone Y45). The concentration of Human CD19, Fc Tag used is 5 μg/mL (100 μL/well). The IC50 is 0.084 μg/mL (Routinely tested).*

## >>> Binding activity and specificity verified by Indirect ELISA




*Immobilized FMC63 scFv, His Tag at 2 μg/mL (100 μL/well) can bind Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Clone Y45) with a linear range of 1-19 ng/mL. Anti-DNP antibody, mouse IgG1 (Cat. No. DNP-M1) was used as an isotype control (QC tested).*

## >>> High affinity verified by SPR



*Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Cat. No. FM3-Y45) captured on CM5 chip via anti-mouse antibodies surface can bind FMC63 scFv with an affinity constant of 1.08 nM as determined in an SPR assay.*

***ACRO provides cell therapy researchers with one-stop services from antigen preparation to polyclonal anti-idiotype antibody and immunogenicity test kit developments.***

# Product list

## GMP Grade Cytokines

| Molecule | Cat.No. | Product Description |
|---|---|---|
| IL-15 | GMP-L15H13 | GMP Human IL-15 |
| IL-7 | GMP-L07H14 | GMP Human IL-7 *Coming soon* |
| IL-21 | GMP-L21H18 | GMP Human IL-21 *Coming soon* |

## Star Staining New Generation Fluorescent-labeled Products

| Molecule | Cat.No. | Product Description |
|---|---|---|
| BCMA | BCA-HF2H3 | FITC-Labeled Human BCMA / TNFRSF17 Protein, His Tag *Star Staining* |
| CD19 | CD9-HF2H3 | FITC-Labeled Human CD19 (20-291) Protein, His Tag *Star Staining* |
| Mesothelin | MSN-HF2H3 | FITC-Labeled Human Mesothelin / MSLN (296-580) Protein, His Tag *Star Staining* |
| Siglec-2 | SI2-HF2H4 | FITC-Labeled Human Siglec-2 / CD22 Protein, His Tag *Star Staining* |
| FMC63 | FM3-FY57P1 | FITC-Labeled Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Y45) *Star Staining* |
| CD19 | CD9-HP2H5 | PE-Labeled Human CD19 (20-291) Protein, His Tag *Star Staining* |
| BCMA | BCA-HP2H7 | PE-Labeled Human BCMA / TNFRSF17 Protein, His Tag *Star Staining* |
| Mesothelin | MSN-HP2H8 | PE-Labeled Human Mesothelin / MSLN (296-580) Protein, His Tag *Star Staining* |
| CD19 | CD9-HA2H9 | APC-Labeled Human CD19 (20-291) Protein, His Tag *Star Staining* |
| BCMA | BCA-HA2H4 | APC-Labeled Human BCMA / TNFRSF17 Protein, His Tag *Star Staining* |
| Mesothelin | MSN-HA2H6 | APC-Labeled Human Mesothelin / MSLN (296-580) Protein, His Tag *Star Staining* |

## ★ More Star Staining Products

### >>> FITC Label

Glypican 3 | HER2 | CD7 | Siglec-3 | CD30 | EGF R
EGFRVIII | GUCY2C | NKG2D | FAP | Nectin-4 | CD37
protein L

### >>> PE Label

Glypican 3 | NKG2D | FAP | Nectin-4 | CD37 | protein L
CD147 | CD300e | HER2 | Siglec-2 | Siglec-3 | PD-1
OX40 | MUC-1 | TSLP R

### >>> APC Label

Glypican 3 | CD147 | CD300e | HER2 | Siglec-2 | Siglec-3
PD-1 | OX40 | MUC-1 | TSLP R

### >>> Alexa Fluor 647 Label

BCMA | CD19 | Mesothelin | Glypican 3 | CD147 | CD300e
HER2 | Siglec-2 | Siglec-3 | PD-1 | OX40 | MUC-1
TSLP R

### >>> Alexa Fluor 555 Label

| | | | | | |
|---|---|---|---|---|---|
| BCMA | CD19 | Mesothelin | Glypican 3 | NKG2D | FAP |
| Nectin-4 | CD37 | protein L | | | |

### >>> Alexa Fluor 488 Label

| | | | | | |
|---|---|---|---|---|---|
| BCMA | CD19 | Mesothelin | Glypican 3 | CD147 | CD300e |
| HER2 | Siglec-2 | Siglec-3 | PD-1 | OX40 | MUC-1 |
| TSLP R | | | | | |

## ▶ Targets for Cell Therapy

### >>> Blood tumor

| | | | | | |
|---|---|---|---|---|---|
| BCMA | CD19 | CD123 | CD138 | CD20 | CD22 |
| CD30 | CD33 | CD37 | CD38 | CD4 | CD5 |
| CD56 | CD7 | CD72 | CD99 | CLL-1 | CS1 |
| GPRC5D | LILRB4 | CD123 | CD138 | CD20 | CD22 |

### >>> Solid tumor

| | | | | | |
|---|---|---|---|---|---|
| VEGF R2 | uPAR | ROR1 | PSMA | PSCA | NKG2D |
| Nectin-4 | MUC16 | MUC1 | MSLN | IL13RA2 | HGF R |
| HER3 | HER2 | GUCY2C | GPC3 | FOLR1 | FAP |
| EpCAM | EGFRVIII | EGFR | EBV | DLL3 | CLDN18 |
| CEA | CD70 | CD47 | CD147 | CD133 | CAIX |
| B7-H3 | | | | | |

### >>> TCR-T Targets

| |
|---|
| NY-ESO-1 |

## ▶ Anti-idiotypic Antibodies

| Cat.No. | Species | Product Description | Application |
|---|---|---|---|
| FM3-Y45 | Mouse | Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Y45) DMF Filed | CAR expression by flow cytometry in preclinical and clinical samples |
| FM3-FY45 | Mouse | FITC-Labeled Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Y45) DMF Filed | |
| FM3-BY45 | Mouse | Biotinylated Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Y45) DMF Filed | |
| FM3-Y45P1 | Mouse | Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Y45) (HEK293) DMF Filed | |
| FM3-HPY53 | Mouse | PE-Labeled Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Y45) (Site-specific conjugation) DMF Filed | |
| FM3-BY54 | Mouse | Biotinylated Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1, Avitag™ (Y45) DMF Filed | |
| FM3-FY45P1 | Mouse | FITC-Labeled Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Y45) (HEK293) | |
| FM3-Y45A1 | Mouse | Monoclonal Anti-FMC63 scFv Antibody, Mouse IgG1 (Y45) (Carrier-free) (recommended for ADA assay) DMF Filed | ADA assay development |
| FM3-S93 | Rabbit | Rabbit Anti-Mouse FMC63 scFv Polyclonal Antibody (recommended for ADA assay) (MALS verified) | |

## Magnetic Beads

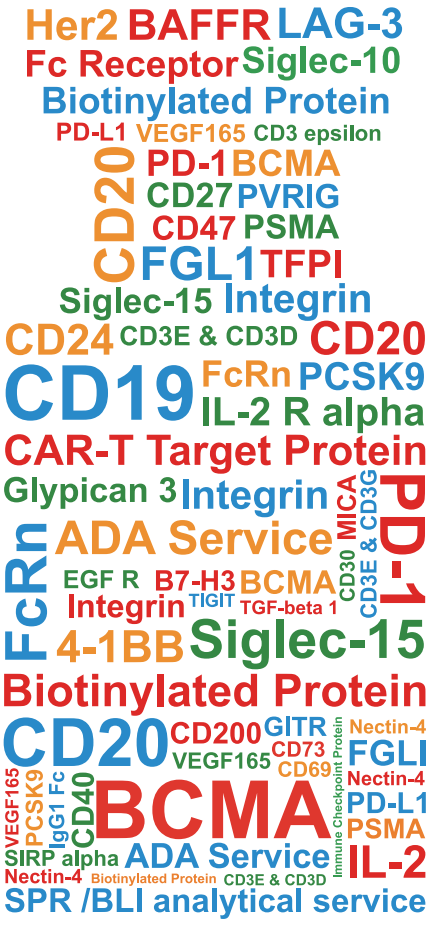
| Cat.No. | Product Description | Application |
|---|---|---|
| MBS-C001 | Anti-CD3/CD28 Antibody-coupled Magnetic Beads | Cell activation and expansion |

## Nucleases

| Molecule | Cat.No. | Product Description |
|---|---|---|
| Cas9 | CA9-S5149 | NLS-Cas9 Nuclease |
| Cas12a | CAA-L5149 | NLS-Cas12a Nuclease |
| BenzNuclease | BEE-N3116 | GENIUS™Nuclease DMF Filed |

## Cytokine ELISA Kits

| Molecule | Cat.No. | Product Description |
|---|---|---|
| IFN-γ | CRS-A001 | Human Interferon-γ(IFN-γ) ELISA Kit |
| TNF-α | CRS-A002 | Human Tumor Necrosis Factor Alpha(TNF-α) ELISA Kit*coming soon* |
| IL-2 | CRS-A003 | Human Interleukin-2(IL-2) ELISA Kit*coming soon* |
| IL-4 | CRS-A004 | Human Interleukin-4(IL-4) ELISA Kit*coming soon* |
| IL-6 | CRS-A005 | Human Interleukin-6(IL-6) ELISA Kit*coming soon* |
| IL-7 | CRS-A006 | Human Interleukin-7(IL-7) ELISA Kit*coming soon* |
| IL-8 | CRS-A007 | Human Interleukin-8(IL-8) ELISA Kit*coming soon* |
| IL-10 | CRS-A008 | Human Interleukin-10(IL-10) ELISA Kit*coming soon* |
| IL-15 | CRS-A009 | Human Interleukin-15(IL-15) ELISA Kit*coming soon* |
| IL-21 | CRS-A010 | Human Interleukin-21(IL-21) ELISA Kit*coming soon* |
| IL-12 p70 | CRS-A011 | Human Interleukin-12 p70(IL-12 p70) ELISA Kit*coming soon* |
| IL-1 beta | CRS-A012 | Human Interleukin-1 beta(IL-1 beta) ELISA Kit*coming soon* |
| GM-CSF | CRS-A013 | Human Macrophage Colony Stimulating Factor 2(GM-CSF) ELISA Kit*coming soon* |

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