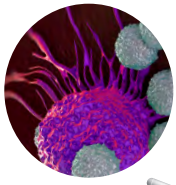

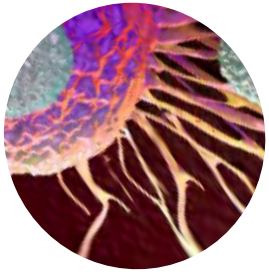

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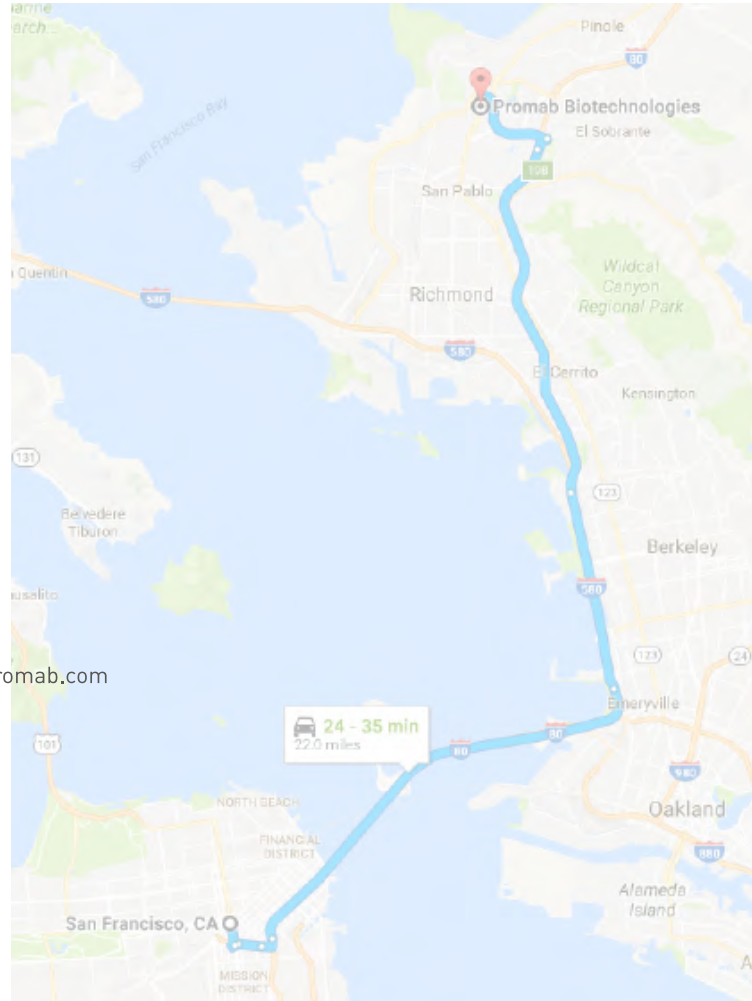
CAR-T ANIMAL STUDIES

CONTENT

BETTER SCIENCE
BETTER LIFE

MISSION

PROMAB BIOTECHNOLOGIES DEVELOPS ANTIBODIES AND NOVEL IMMUNOTHERAPIES WITH A MISSION TO CURE CANCER PATIENTS AND IMPROVE HEALTH.



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2600 Hilltop Drive Richmond, CA 94806 866.399.0871 | www.promab.com

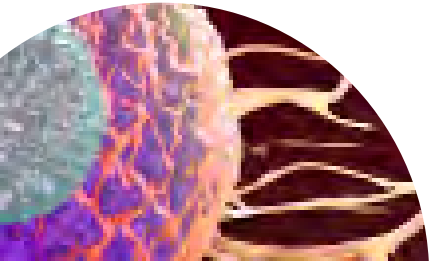
PRODUCTS & SERVICES LIST

PRODUCTS

- CAR-T CELLS
- MRNA / LNP
- MONOCLONAL ANTIBODIES
- LENTIVIRAL PARTICLES
- RECOMBINANT PROTEINS
- CAR-NK CELLS
- CAR-MACROPHAGE CELLS
- ENGINEERED CELL LINES
- CANCER STEM CELLS
- NON-TRANSDUCED T- CELLS
- HUMAN PRIMARY CELLS
- SARS-COV-2 (COVID-19)
- NATURAL PROTEINS
- CELL MEDIA

SERVICES

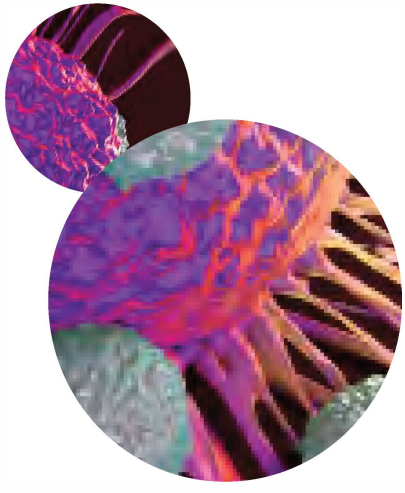
- CUSTOM CAR-T CELL DEVELOPMENT
- MRNA / LNP PRODUCTION
- HUMAN MONOCLONAL ANTIBODIES
- MOUSE MONOCLONAL ANTIBODIES
- BISPECIFIC ANTIBODIES
- RECOMBINANT ANTIBODIES
- ANTIBODY PRODUCTION
- LENTIVIRUS PRODUCTION
- CUSTOM CAR-NK CELL DEVELOPMENT
- CUSTOM CAR-MACROPHAGE DEVELOPMENT
- ANIMAL RESEARCH
- STABLE CELL LINE DEVELOPMENT
- CANCER STEM CELL SERVICES
- PEPTIDE SYNTHESIS
- GENE SYNTHESIS



ABOUT US

ProMab's CAR-T service is a completely inclusive *in vitro* and *in vivo* testing service, from generating a monoclonal (using our rabbit, mouse and human antibody generation platforms) to your novel fluid, or solid-tumor target antigen. Once antigen-binding of your scFv has been validated, it will be incorporated into a lentiviral CAR construct, and T-cells will be activated, transduced and expanded to produce a CAR-T population. Following verification of CAR-T function by Real-time cytotoxicity assay, and cytokine secretion, cells will be delivered to you, or Promab will move directly into an animal study to confirm *in vivo* functionality.

ProMab recently added an *in vivo* animal facility with three imaging systems to test CAR-T *in vivo* efficacy using xenograft NSG mice models. Different cancer cell lines can be tested with your CAR-T: solid cancer-ovarian, cervical, colon, prostate, liver, lung, melanoma and hematological cancer: leukemia, lymphoma, multiple myeloma and other. We have several luciferase-positive cell lines that can be analyzed using IVIS imaging systems together with your CAR-T. In addition, we can do toxicology, PK/PD and IHC (immunohistochemical staining) of xenograft tumor samples with antibodies of your choice. The CAR-T animal studies were successfully conducted with several different CAR-T cells targeting different tumor antigens.



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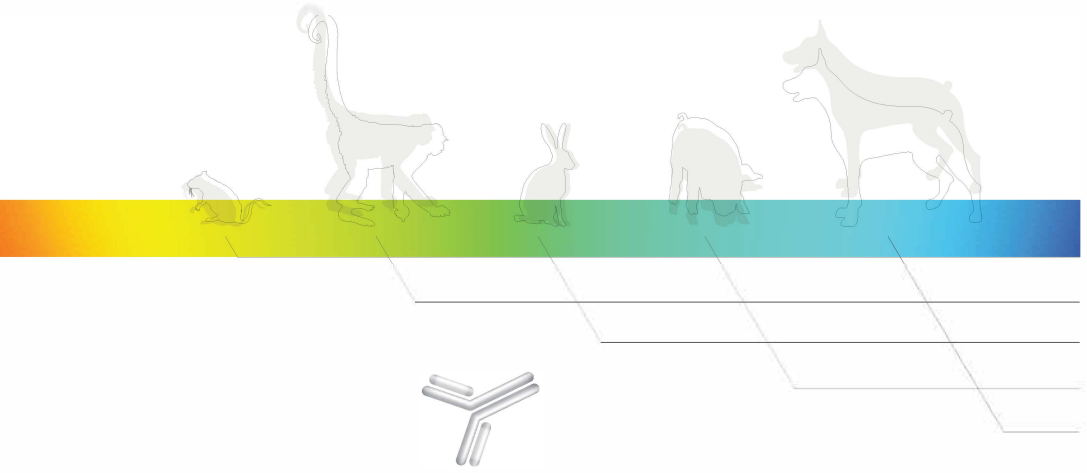


Animal Facility is located in Richmond (San Francisco Bay Area) CA

ANIMAL MODELS AVAILABLE:

1. Rodents
2. Rabbits
3. Nonhuman primates
4. Guinea pigs & Mini pigs
5. Dogs

ONCOLOGY PARAMETERS:

// **Clinical signs:** Weight, food consumption, behavior, mortality.

// **Tumor volume and weight:** Tumor volume with caliper measurements, tumor growth rate, tumor weight.

// **Histopathology:** Tumor cell apoptosis, IHC for biomarkers: Ki-67, etc.

// **Genomic:** Gene expression profiles, RT-PCR.

ONCOLOGY ANIMAL MODELS:

// Patient-derived xenograft models

// Subcutaneous xenograft tumor models

// Intravenous v tumor models

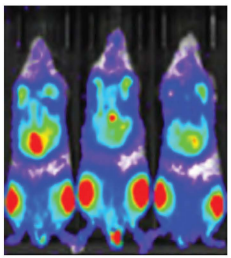
// Orthotopic xenograft tumor models

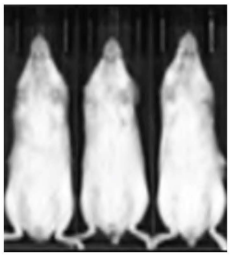
// Intracranial xenograft tumor models

// Syngeneic tumor models

// Cancer stem cell xenograft tumor models

Promab Biotechnologies has developed patient-derived xenograft models of different types of cancer to validate your CAR-T efficacy. This enables us to study the efficacy of the CAR-T against tumors and the tumor microenvironment.





CAR-T ANIMAL STUDY

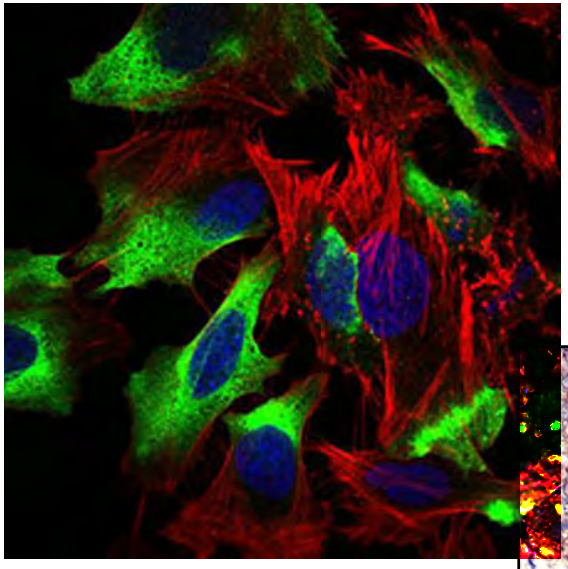
Promab recently added an *in vivo* animal facility with three imaging systems to test CAR-T *in vivo* efficacy using xenograft NSG mice models. The imaging systems can detect luciferase-positive and GFP-positive cells.

DIFFERENT CANCER CELL LINES CAN BE TESTED WITH YOUR CAR-T:
solid cancer-ovarian, cervical, colon, prostate, liver, lung, melanoma and hematological cancer-leukemia, lymphoma, multiple myeloma & other.

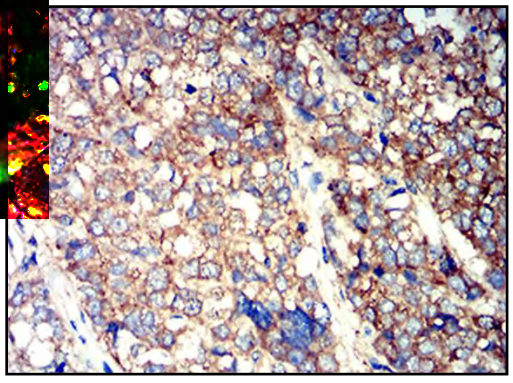
ROUTES OF ADMINISTRATION:

1. ORAL
2. DERMAL
3. PARENTERAL
    a. Intramuscular
    b. Intraperitoneal
    c. Intravenous
    d. Subcutaneous
    e. Intratumoral
4. OTHER

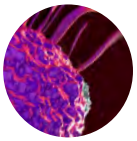
(IMMUNOHISTOCHEMICAL STAINING)



In addition, we can do toxicology, [PK/PD pharmacokinetics/ pharmacodynamics) and IHC (immunohistochemical staining) of xenograft tumor samples with antibodies of your choice.

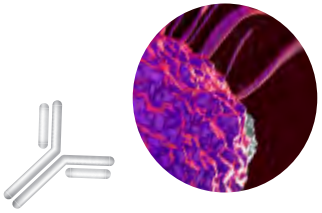


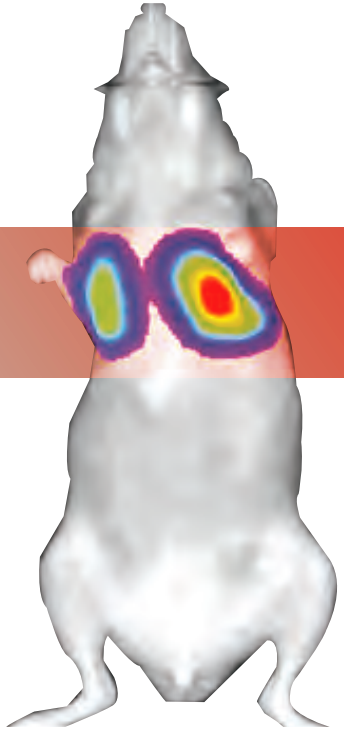
IHC



WE HAVE SEVERAL LUCIFERASE-POSITIVE CELL LINES THAT CAN BE ANALYZED USING IVIS IMAGING SYSTEMS TOGETHER WITH YOUR CAR-T CELLS:

4T1-luc+
Raji-luc+-GFP+
HCT116-luc+
HT29-luc+
PANC02-luc+
U87-luc+-GFP+
PC3M-luc+
A549-luc+
B16/F10-luc+



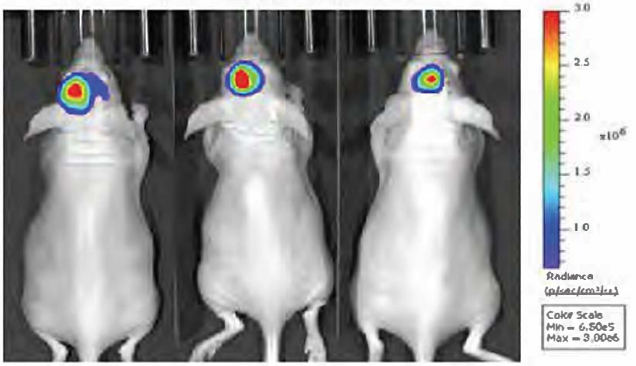


Any customized luciferase-positive stable cell lines can be generated in our Facility.

// Industry standard *in vivo* imaging system.
// Scientific grade 1 CCD camera, back-thinned, back-illuminated, cooled to -70C.
// Light tight imaging chamber with a high collection lens, 50mm, f/0.95-f/8.
// Integrated isoflurane gas anesthesia system.

IMMUNOHISTOCHEMICAL STAINING

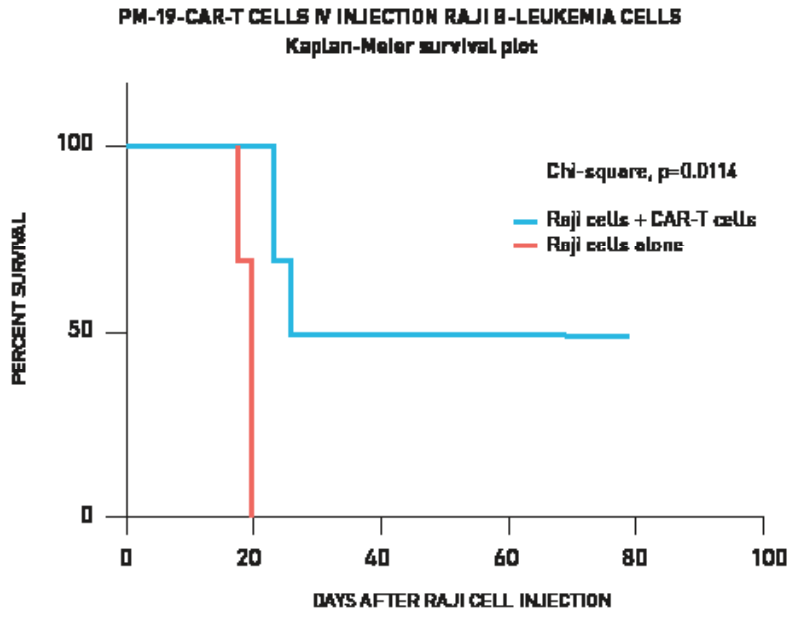
U87-luc Glioma



Female nu/nu mice with orthotopic U87-luc.
Day 6 Post Implant of $1x10^6$ cells

THE IMAGING SYSTEM DETECTS LUCIFERASE-POSITIVE CELLS IN MICE XENOGRAFTS:

The IVIS imaging system detects tumors in orthotopic intracranial U87-luc cell injection with lucifearin as a substrate. The quantification is done in photons/sec units and tumor growth curves are generated. Different luciferase-positive cell lines are available for CAR-T cell efficacy studies. In addition, customized luciferase-positive cell lines can be generated for testing the efficacy of CAR-T cells.



CAR-T SIGNIFICANTLY PROLONGED MICE SURVIVAL IN RAJI MICE MODEL:

The Raji leukemia cells were intravenously (iv) injected into immunodeficient NOG mice, and the next day PM-19-CAR-T cells that were validated *in vitro* using real-time cytotoxicity and cytokine assays were injected by iv. The survival was monitored using a Kaplan-Meier survival plot. CAR-T cells significantly prolonged survival of Raji cells.

FIGURE CAR-T significantly prolong survival of immunodeficient mice in Raji xenograft model.

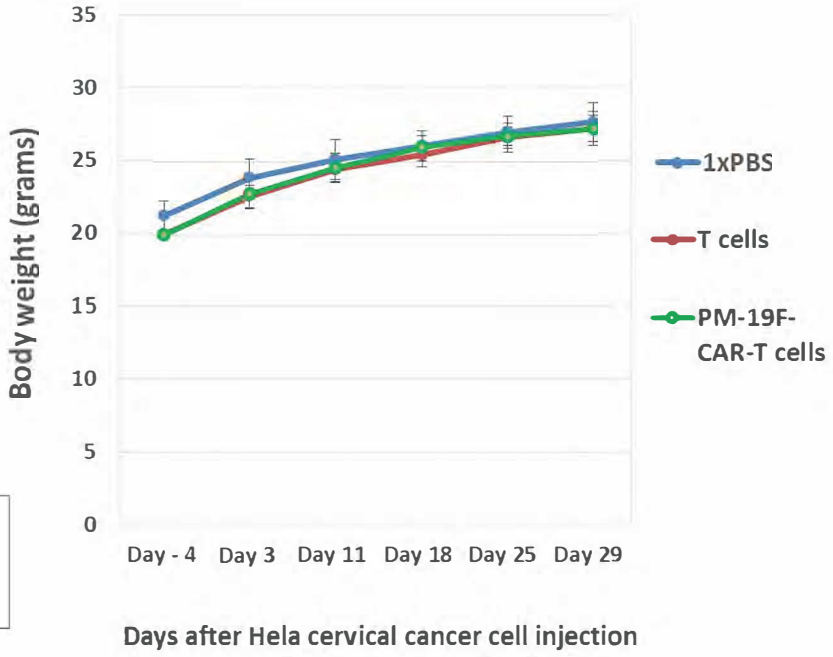


FIGURE Mice body weight is not decreased by CAR-T cell treatment.

CD19F-CAR-T IS NOT TOXIC TO MICE (NO LOSS OF MOUSE BODY WEIGHT):

The mouse weight is measured in parallel with tumor growth. The mouse weight is not decreased by CAR-T cell treatment, suggesting that CAR-T cells are not toxic to mice. The imaging system detects luciferase-positive cells in mouse xenografts.

CAR-T MICE DATA

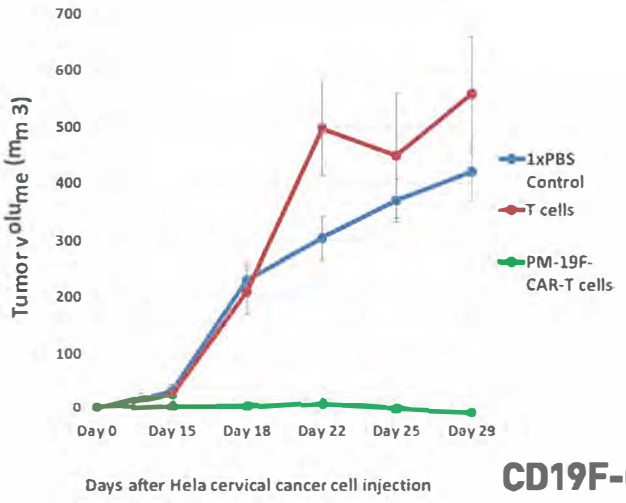


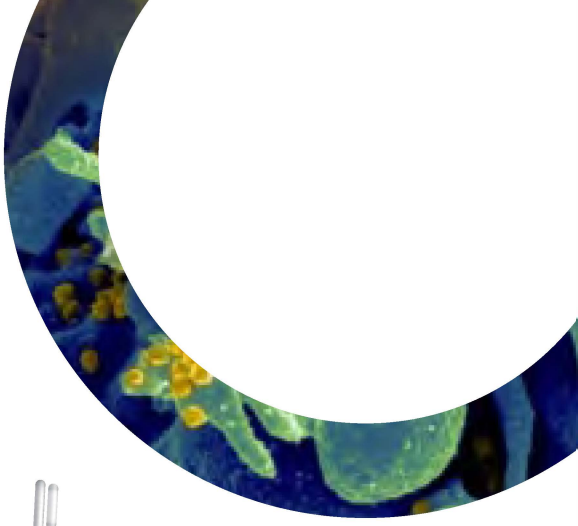
FIGURE Legend PM-19F-CAR-T cells significantly decreased Hela-CD19 xenograft tumor growth. *p↓0.05 PM-19F-CAR-T cells versus 1xPBS control & T cell.

CD19F-CAR-T SIGNIFICANTLY DECREASES XENOGRAFT TUMOR GROWTH:

CD19- Flag CAR-T (PM-CD19F-CAR-T) cells were validated *in vitro* to kill ProMab's engineered cervical cancer cell line (HeLa-CD19) which overexpresses CD19 tumor antigen, and to secrete cytokines IL-2 and INF-gamma. The validated *in vitro* CD19-CAR-T cells were injected intravenously into NSG mice with HeLa-CD19 cell xenografts.

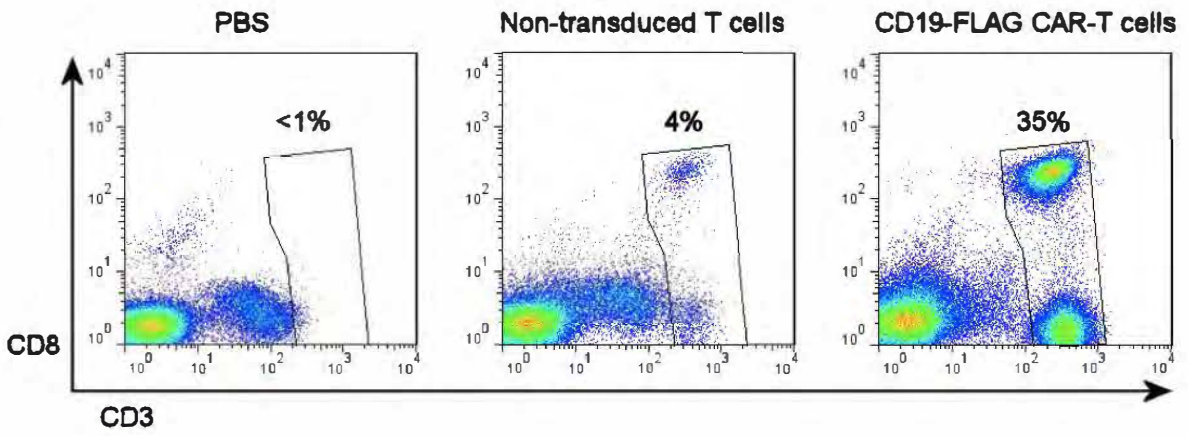
THE TUMORS WERE MEASURED WITH CALIPERS AND TUMOR VOLUME WAS CALCULATED USING THE FOLLOWING FORMULA:

Tumor volume= (length x width^2)/2, where length represents the longer diameter of the tumor, and width the shorter diameter of the tumor.



CAR-T CELL MICE HAVE INCREASED % HUMAN T-CELLS AND INCREASED % OF HUMAN CD8+ T CELLS:

The blood is collected from mice and can be analyzed by flow cytometry for the presence of human T cells and CD4+, CD8+ T cell subtypes. CAR-T-treated groups have increased levels of CD8+ cells suggesting proliferation and activation of CAR-T cells *in vivo*. The representative flow cytometry plots with CD3 and CD8 antibodies are shown below.



CAR-T CELL MICE HAVE INCREASED % HUMAN T CELLS AND INCREASED % OF HUMAN CD8+ T CELLS:

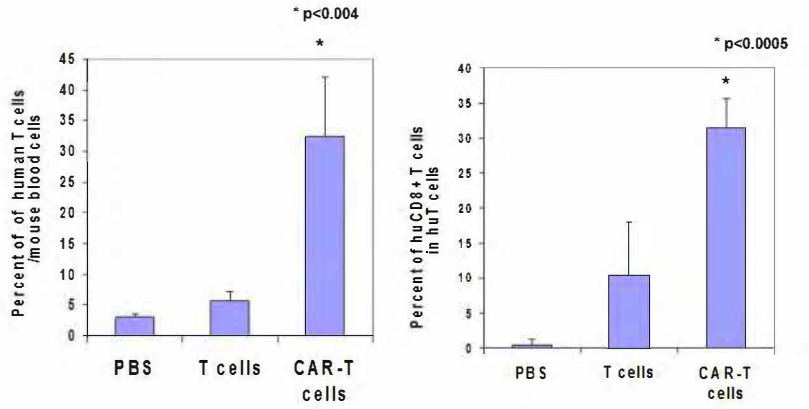


FIGURE Left panel: Analysis of blood leukocytes from HeLa-CD19 mouse study. Blood samples of mice were collected on day 29 and stained with anti-human CD3 and anti-human CD8 antibodies. Representative human CD3 vs human CD8 flow cytometry plots from each mice group show that in the mice treated with CD19-FLAG CAR-T cells, almost one-third of the leukocytes were human T cells. In the mice treated with non-transduced T cells, only ~4% of the leukocytes were human T cells. Right panel: Quantification of human T and CD8+ T cells demonstrate increased percent of human T and CD8+ cells in CAR-T cell treated group.

IHC WITH KI-67 ANTIBODY DETECTS DECREASED KI-67 STAINING IN CAR-T-TREATED XENOGRAFT TUMORS IN MICE:

The tumor samples are collected at the end of the experiment, and tumor samples are either snap frozen or fixed in 10% formaldehyde, 4% paraformaldehyde, or 10% formalin. The immunohistochemical staining can be done with CD3, Ki67, caspase-3 or other tumor-related or immunological markers.

STAINING WITH CD3 ANTIBODY DETECTS CAR-T CELLS:

The IHC with CD3 antibody showed increased CD3 staining in CAR-T-treated xenograft tumors supporting activation of CAR-T cells.

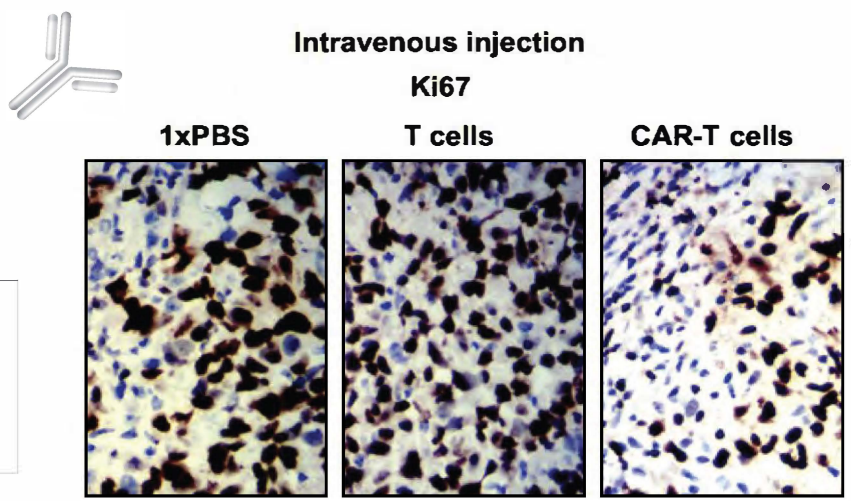
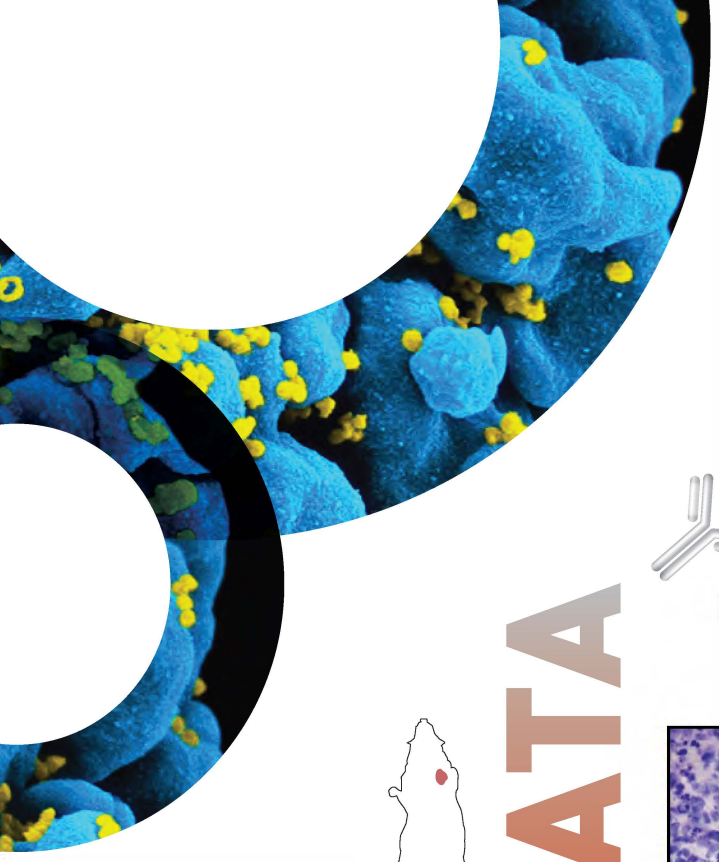
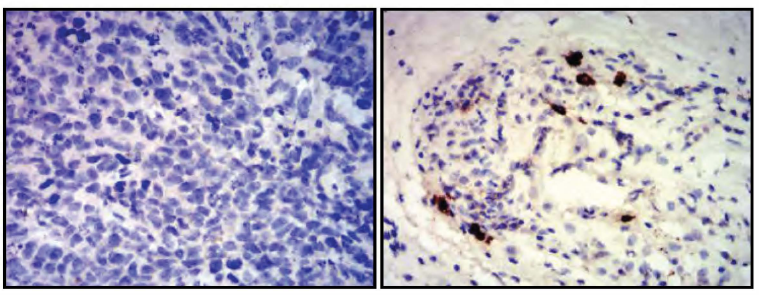


FIGURE shows that CAR-T cells decreased Ki67 staining (marker of proliferation) in CD19-treated xenograft Hela-CD19 samples.



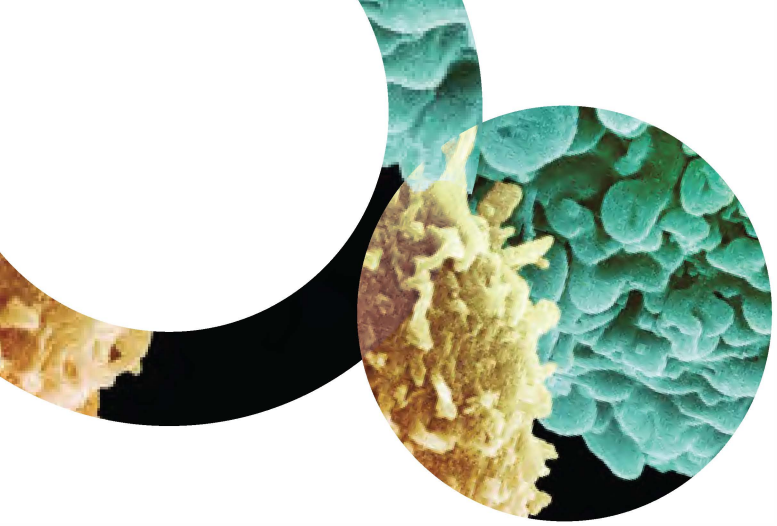
CAR-T MICE DATA

Intra-tumoral CD-19-CAR-T cell injection



The frozen tumor samples can be used for RT-PCR, genomics and proteomics studies to understand deeper CAR-T cell biology and anti-cancer mechanisms.

In conclusion, Promab has developed a pre-clinical platform for testing the safety, efficacy, toxicity, and pharmacodynamic properties of CAR-T cells which is critical for future clinical studies.



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ProMab Biotechnologies seeks partnership with academic researchers, and biotechnology and pharmaceutical companies around the world. We seek to achieve a distinguished global ranking within the scientific community by building a superior reputation for quality, reliability, promptness, and cost-effective products and services.


BETTER SCIENCE
BETTER LIFE
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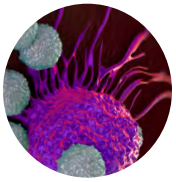

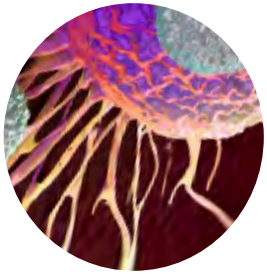

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