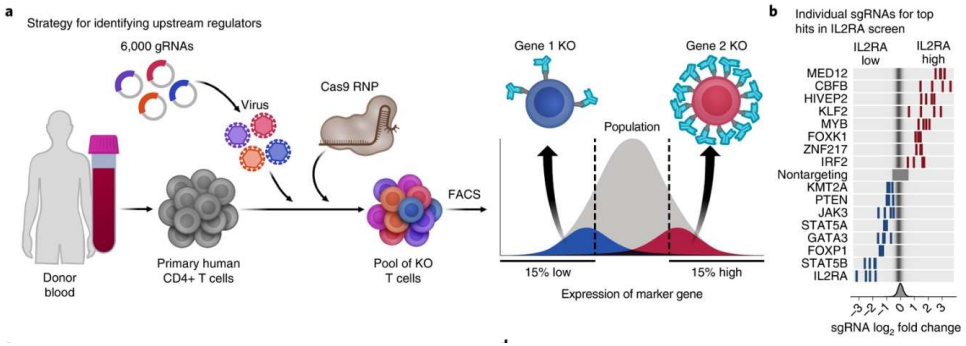
UCSF Startups and Innovation in ***Immunotherapy***

Advanced Genetically Engineered T-Cells for Precision Medicine

Alex Marson, MD, PhD
UCSF Professor; Director of Gladstone-UCSF Institute of Genomic Immunology; PICI Center Director



Discovery of upstream regulators of IL2RA, IL-2 and CTLA4. a, Strategy for identifying upstream regulators. We used SLICE to generate a pool of knocked out (KO) primary human CD4+ T cells. Knockout T cells were sorted into 15% high- or low-expression bins with FACS based on the expression of IL2RA, IL-2 or CTLA4. The sgRNAs in each bin were sequenced to identify positive or negative regulators of IL2RA, IL-2 or CTLA4 levels. **b**, Top, enrichment of individual sgRNAs in the high- or low-expression bins for the top hits in the IL2RA screen. Bottom, distribution of enrichment for all sgRNAs.

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DISEASE/INDICATION: Autoimmune disorders and cancer.

UNMET NEED: Current therapies often involve broad immunosuppression or non-specific immune activation, which can lead to significant side effects and incomplete disease resolution. There is a critical need for more targeted therapies that can selectively modulate the immune system to improve efficacy and reduce adverse effects.

PRODUCT: A population of genetically modified T cells, tailored to either suppress or enhance immune responses in a controlled manner. These cells are engineered through precise genetic modifications to inhibit or overexpress specific nuclear factors, thereby altering the expression of crucial proteins like CTLA4, FOXP3, and IL2RA, which are pivotal in immune regulation.

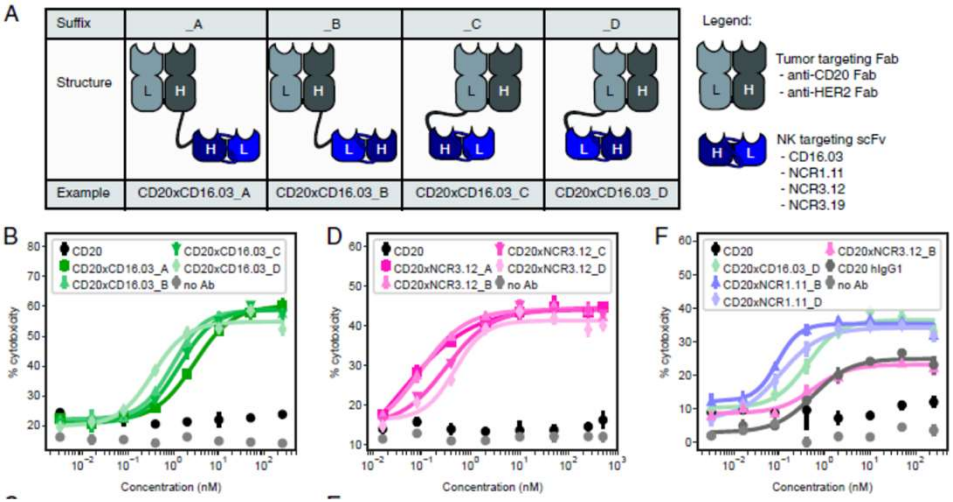
COMPETITIVE ADVANTAGE/DIFFERENTIATION: This technology leverages CRISPR/Cas genome editing to achieve highly specific and customizable modifications in T cells, allowing: 1) Precise manipulation of gene expression, leading to potentially higher efficacy and fewer off-target effects compared to traditional methods; 2) The ability to target a wide range of nuclear factors relevant to various immune pathways, offering broad applicability across different types of immune-related diseases; 3) Flexibility in modulating the immune response, either enhancing or suppressing it, which is crucial for treating different phases or types of diseases such as cancer and autoimmune disorders.

DATA: We developed an approach for systematic discovery of upstream regulators of critical immune factors in primary human T cells. Then, we mapped the network of the target genes of these regulators and putative cis-regulatory elements using CRISPR perturbations, RNA-seq and ATAC-seq. These regulators form densely interconnected networks with extensive feedback loops. Furthermore, this network is enriched for immune-associated disease variants and genes.

Antibodies that stimulate NK Cell-Mediated Cytotoxicity

Lewis Lanier, PhD
UCSF Professor,
Microbiology &
Immunology,
PICI Member

Jim Wells, PhD
UCSF Professor,
Pharmaceutical
Chemistry



Bispecific constructs generated and cytotoxicity induced by bispecific constructs against CD20+ Daudi. (A) Each NK-targeting antibody was converted into an scFv (in blue) and attached to either the light chain (L) or heavy chain (H) of the tumor-targeting Fab (in gray). The tumor antigen was either CD20 or HER2. Cytotoxicity induced by bispecific constructs against CD20+ Daudi. (B) Cytotoxicity induced by PBMCs in the presence of anti-CD20–scFv CD16.03 bispecifics at an Effector-to-target ratio (E:T) of 10:1. (D) Cytotoxicity induced by NCR3+ NK92MI cells in the presence of anti-CD20–scFv NCR3.12 bispecifics at an E:T of 1:9. (F) Comparison of cytotoxicity induced by PBMCs to anti-CD20 human IgG1 mAb.

DISEASE/INDICATION: Various types of cancers, including B cell lymphomas, breast cancer, myeloma, and leukemia.

UNMET NEED: Current cancer therapies often have limitations such as off-target effects, development of resistance, and limited efficacy against certain cancer types. There is a pressing need for therapies that can specifically target cancer cells and enhance the body's natural immune response against these malignant cells.

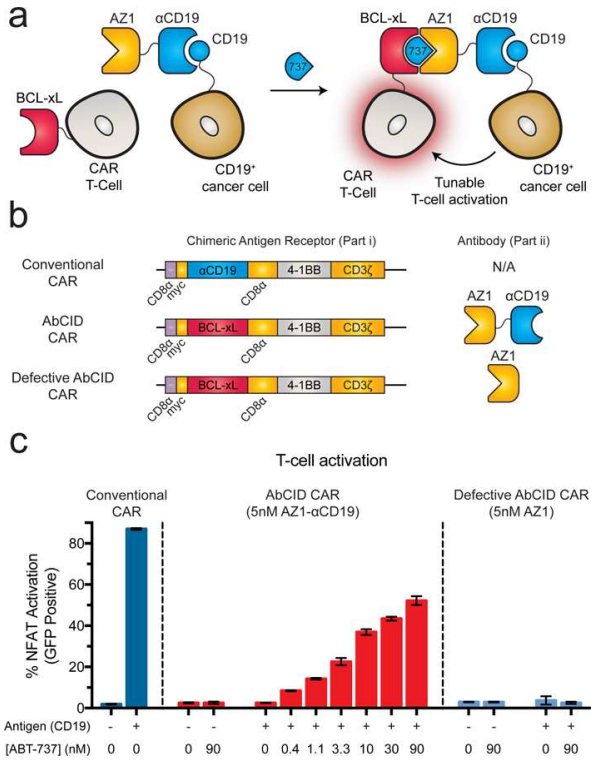
PRODUCT: A bispecific antibody therapy that targets Natural Cytotoxicity Triggering Receptors (NCR1, NCR3) or CD-16 on Natural Killer (NK) cells and a specific antigen on the cancer cell. This therapy will enhance the cytotoxic response of NK cells towards the cancer cells, leading to targeted cell death.

COMPETITIVE ADVANTAGE/DIFFERENTIATION: Bispecific targeting of NCR3 presents a novel opportunity to potently activate NK cells, thereby enhancing the antitumor immune responses.

DATA: The inventors have developed a functional screen to identify antibodies that can activate NK cells. From this screen, antibodies specific for NCR1, NCR3, and CD-16 were identified. These antibodies bound with high affinity to NK cells, and the subsequent development of bispecific antibody constructs showed successful redirection of NK cell-mediated cytotoxicity towards CD20+ B cell lymphomas.

Antibody-Based Chemically Induced Dimerizers (AbCIDs)

Jim Wells, PhD
UCSF Professor, Pharmaceutical Chemistry



AZ1 can be utilized as an extracellular AbCID to regulate CAR T-cell activation. **(a)** Schematic of AbCID-regulated CAR T-cell activation where the CAR contains an extracellular BCL-xL domain in place of the typical scFv. Addition of an AZ1-αCD19 bispecific antibody and various concentrations of ABT-737 results in recruitment to CD19⁺ cancer cells and tunable activation of the CAR T-cells. **(b)** Linear diagrams of the gene constructs used to produce the CARs and schematics of corresponding antibodies for this study. **(c)** Quantification of NFAT-dependent GFP reporter expression 20 hours after initiation of co-culture with either CD19⁺ or CD19⁻ K562 target cells and addition of antibody (5 nM) and varying concentrations of small molecule. Addition of ABT-737 in the presence of CD19⁺ K562 cells and bispecific antibody resulted in dose-dependent activation of the NFAT pathway, but no activation was observed in the absence of ABT-737 or when co-cultured with CD19⁻ K562 cells. The defective AbCID CAR, which lacks the CD19-binding scFv portion of the antibody, resulted in no activation under all conditions.

DISEASE/INDICATION: Cellular therapies, including CRISPRa-mediated gene expression regulation and CAR T-cell activation.

UNMET NEED: Existing chemically induced dimerizers (CID) systems often lack the desired properties for human cell therapy applications and may exhibit toxicity or undesirable pharmacokinetic properties. There is a critical need for novel, human-protein-based CIDs with favorable pharmacokinetics, bioorthogonality, and dose-dependence for effective cell therapy regulation.

PRODUCT: A novel class of human antibody-based chemically induced dimerizers (AbCIDs) derived from known small-molecule-protein complexes. These AbCIDs can be rapidly generated and can regulate human cell therapies, including CRISPRa-mediated gene expression and CAR T-cell activation.

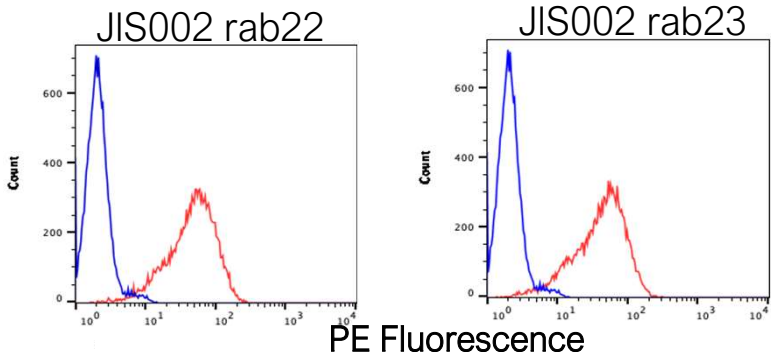
COMPETITIVE ADVANTAGE/DIFFERENTIATION: Unlike traditional CIDs, AbCIDs are derived from human-protein-small-molecule complexes, offering a better safety profile and drug-like properties. Additionally, the small molecules used in AbCIDs demonstrate favorable pharmacokinetics and are well-tolerated. The dose-dependence of AbCIDs and their ability to be incorporated into various cellular signaling pathways highlight their versatility and scope for customization. Furthermore, the AbCIDs can be applied for both intracellular and extracellular regulation of cellular signaling pathways, offering a unique paradigm for the control of immune cell activation.

DATA: The AbCIDs developed showed high selectivity for the BCL-xL/ABT-737 complex over BCL-xL alone. They were successfully used to regulate CRISPRa-mediated gene expression and CAR T-cell activation in living cells, demonstrating their potential utility in regulating cell therapies. Importantly, the concentration of ABT-737 used to activate AbCIDs was far below the concentration at which toxicity was observed in cells, supporting the safety of these novel CIDs.

Anti-CD94 Antibodies for Enhanced Immune Response to Cancer Cells

Lewis Lanier, PhD
UCSF Professor,
Microbiology & Immunology,
PICI Member

Jim Wells, PhD
UCSF Professor,
Pharmaceutical Chemistry



Stained with anti-human CD94 JIS002 rab22 or JIS002 rab23, followed by PE-conjugated anti-human IgG 2nd step

Unstained (stained only with PE-conjugated anti-human IgG 2nd step)

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DISEASE/INDICATION: Various types of cancers, including breast cancer, lung cancer, colon cancer and lymphomas.

UNMET NEED: Current cancer therapies often have limitations such as off-target effects, development of resistance, and limited efficacy against certain cancer types. There is a pressing need for therapies that can specifically target cancer cells and enhance the body's natural immune response against these malignant cells.

PRODUCT: A novel therapeutic approach that uses anti-CD94 antibodies to deplete NK cells in a cancer patient.

COMPETITIVE ADVANTAGE/DIFFERENTIATION: This method enhances the targeting and killing of cancer cells by activated T cells, such as CD8+ effector T cells. The anti-CD94 antibodies can be administered in conjunction with other therapies like checkpoint inhibitors and antigen administration for cancer antigens. The antibodies can also be used to reduce an NK cell-mediated immune response to non-self cells or tissues transplanted in an individual, thereby enhancing the effectiveness of therapies such as CAR T-cell therapy.

DATA: Specific binding regions and potential for high affinity binding to CD94 shown.

ArsenalBio™ — *Programmable Cell Therapy to Defeat Solid Tumors* — UCSF

UCSF Co-founders

Alexander Marson, MD, PhD
Co-founder, ArsenalBio
UCSF Professor and Innovator

Kole Roybal, PhD
Co-founder, ArsenalBio
UCSF Professor and Innovator

PROBLEM:

- Solid tumors are complex and refractory to most treatment regimens.

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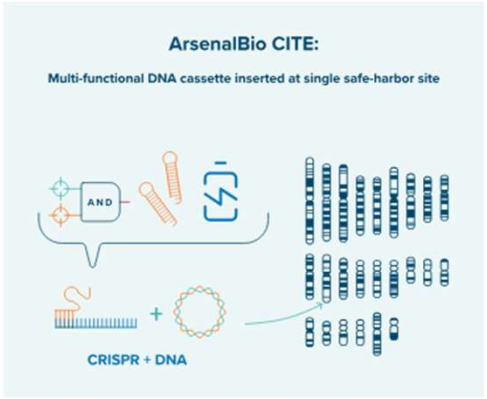
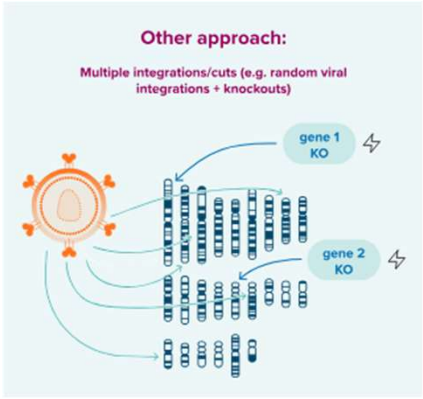




SOLUTION:

- Deploying the combination of CITE editing, a toolkit of synthetic receptors for tumor recognition and a combination of T cell enhancements to improve therapeutic activity.

TRACTION:

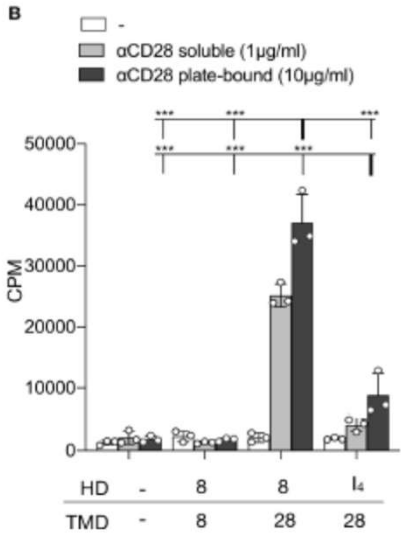
- $325M Series C funding in September 2024
- AB-2100 for treatment of Kidney cancer continues to dose patients in a phase 1 trial. Advancing multiple preclinical candidates for solid tumors, including AB-300 for metastatic prostate cancer.
- Collaborations with BMS and Genentech
- >$500M in Equity Funding and Revenues

LEARN MORE:

CD28 Construct to Enhance Proliferation of CAR-T Cells

Jeff Bluestone, PhD
UCSF Professor Emeritus, School of Medicine

Qizhi Tang, PhD
UCSF Professor, Surgery



Stimulated T cells with a CD28-TMD-containing CAR to see response to anti-CD28 stimulation. The proliferation of purified CAR+ T cells in response to plate-bound or soluble anti-CD28 stimulation.

DISEASE/INDICATION: Oncology

UNMET NEED: Reduction of endogenous CD28 on the cell surface of CAR-engineered cells impacts the expansion and survival of those cells

PRODUCT: CD28 construct containing mutations in the CD28 TMD for Immuno-Oncology Applications

COMPETITIVE ADVANTAGE/DIFFERENTIATION: Reduces dimerization with endogenous CD28, leading to greater CD28 on the cell surface of CAR-T cells, allowing the cells to engage CD28 ligands either during in vitro manufacturing or after infusion into patients (instrumental to cell proliferation & survival)

DATA: In vitro proof of concept

DECIDUOUS THERAPEUTICS

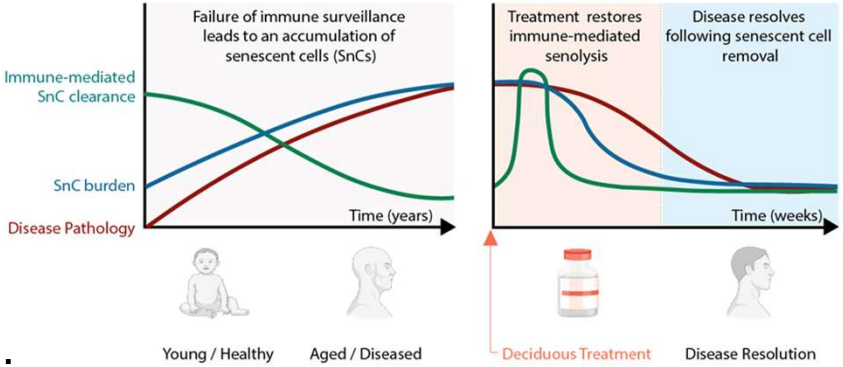
Immune Therapy to Extend Healthspan

UCSF

Anil Bhushan, PhD
Scientific Co-founder, Deciduous Therapeutics
UCSF Professor and Innovator

PROBLEM:

- Killing pathologic senescent cells improves many preclinical age-related disease models.
- Identifying a target that is safe for systemic administration remains a challenge.



SOLUTION:

- Deciduous eliminates senescent cells by re-activating the failed immune system's surveillance mechanism in diseased patients.
- A single systemic dose improves endpoints in a pulmonary fibrosis preclinical model, as well as a diet-induced obesity metabolic disease model in under two weeks.

TRACTION:

- >$18M in funding
- Mechanism discovery published in *Med* titled, "Invariant natural killer T cells coordinate removal of senescent cells"

LEARN MORE:

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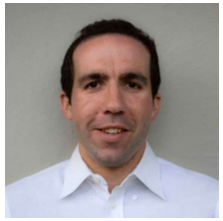
Lung-Targeted Cell-Based Therapies for Inflammatory Disease and Cancer

Wendell Lim, PhD
UCSF Professor, Cellular Molecular Pharmacology

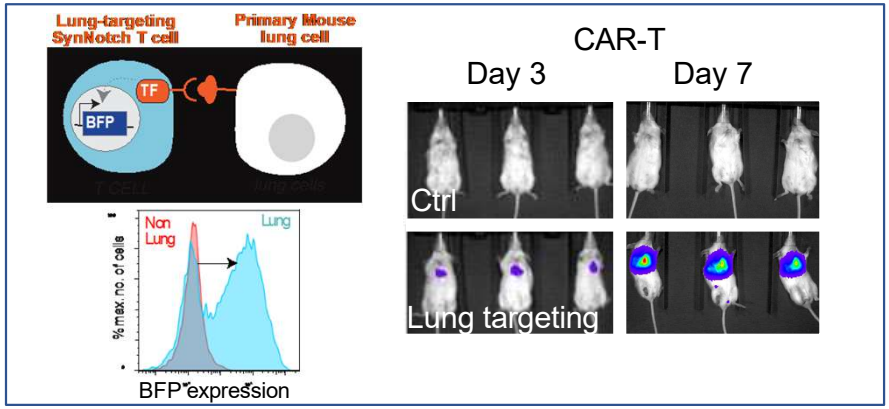
Dean Sheppard, MD
UCSF Professor Medicine



Greg Allen, MD, PhD
UCSF Assistant Professor In Residence, Medicine

Anjali Jacob, MD, PhD
Clinical Fellow, Medicine

Synthetic Receptors activated specifically in the lung



DISEASE/INDICATION: Lung diseases including: acute respiratory distress syndrome (ARDS), idiopathic pulmonary fibrosis (IPF), autoimmune diseases and lung cancer

UNMET NEED:
- ARDS: Mortality rates of 34-58%
- IPF: Median survival 2–5 years

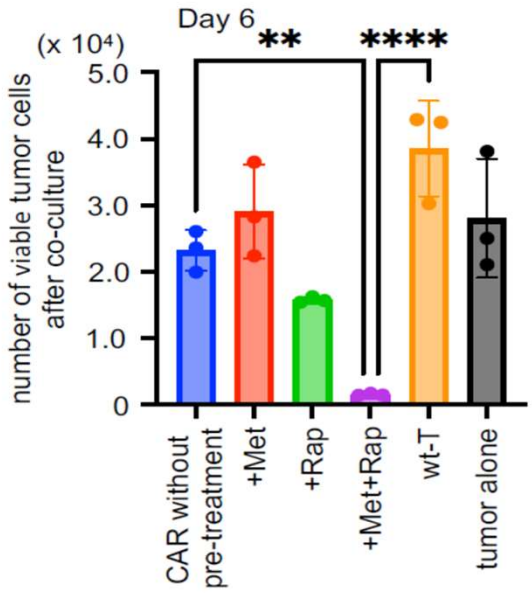
PRODUCTS:
- Lung-targeted chimeric antigen receptor regulatory T-cells (CAR Tregs)
- Lung-specific SynNotch receptor-expressing T cells that deliver genetically encoded therapeutics

COMPETITIVE ADVANTAGE/DIFFERENTIATION:
- Specific targeting of lung tissue
  - Target expression is >100-fold greater in lung tissue vs. other tissues
- Never done before in engineered cells
- Improved safety profile

DATA:
- Demonstrated dramatic, specific expansion of CAR T cells in mouse lung
- Demonstrated specific activation of synthetic circuit by lung antigen
- Evaluation of *in vivo* therapeutic efficacy in progress

Manufacturing Method to Improve CAR-T Cell Survival & Disease Outcomes

Hideho Okada, MD, PhD
UCSF Professor, Neurological Surgery, PICI Member



A combination of Met+Rap promotes the persistent function of CAR-T cells in a hypoxic incubator and decreases the # of viable tumor cells after co-culture

DISEASE/INDICATION: Brain tumors and Solid tumors

UNMET NEED: Limited efficacy of CAR-T cells in brain tumors and solid tumors

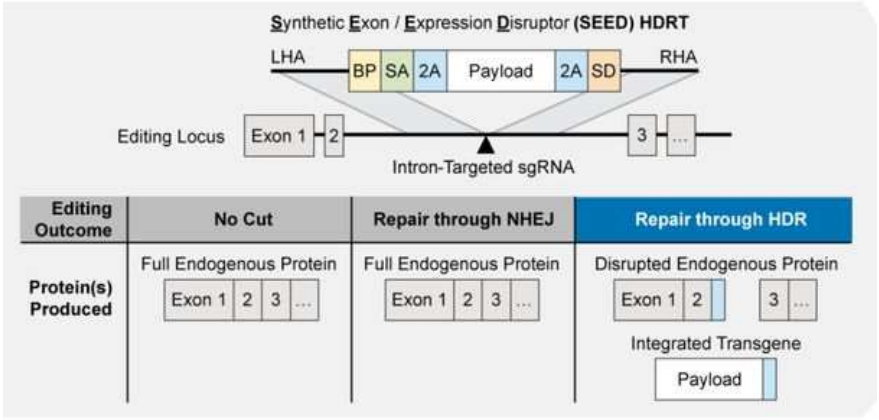
PRODUCT: Method of manufacturing recombinant immune cells by pre-treatment with a combination of small molecules

COMPETITIVE ADVANTAGE/DIFFERENTIATION: Increases the number of CAR-T cells that survive the tumor micro-environment and improves survival time

DATA: Preclinical mouse models of glioma. Potential applications for other solid tumors and for engineered TCRs and NK cells

Manufacturing of Homogeneous T Cells using Synthetic Exon/Expression Disruptors (SEEDs)

Justin Eyquem, PhD
UCSF Assistant Professor, SOM; PICI Member



SEED engineering enables efficient enrichment of cells with transgene integrations
To develop a method that would allow for cells with transgene integrations to be enriched through negative selection, we designed two reagents: (1) a guide RNA (gRNA) targeting an intron of a surface-expressed protein that generates a double strand break (DSB) that minimally impacts expression, and (2) a SEED homology-directed repair template (HDRT) that utilizes synthetic splice acceptor (SA) and splice donor (SD) sequences to introduce an in-frame transgene payload preceded by a P2A sequence at a position that disrupts the target protein

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DISEASE/INDICATION: Diseases that could be treated with engineered T cells such as oncology and autoimmune

UNMET NEED: Current methods of manufacturing T cells produce heterogeneous mixtures of partially engineered T cells

PRODUCT: A one-step process to immunomagnetically deplete non-modified and partially edited T cells, while also reprograming three critical loci encoding T cell specificity, co-receptor expression and MHC expression.

COMPETITIVE ADVANTAGE/DIFFERENTIATION: This strategy produces 98% purity after selection for individual modifications and up to 90% purity for 6 simultaneous edits (3 knock-ins and 3 knockouts). The method is simple, compatible with existing clinical manufacturing workflows and can be readily adapted to other loci to facilitate production of complex gene-edited cell therapies.

DATA: Characterized editing outcomes and transgene function in cells edited with a single or multiple SEEDs and the ability of SEED-selection to enrich for cells with biallelic integrations in a single step. Demonstrate antibody epitope editing enables enrichment of transgenes and facilitates removal of T cells with mispaired TCRs.

MYELOID Therapeutics, Inc.

Next-Generation Immunotherapies Harnessing Myeloid Biology

UCSF

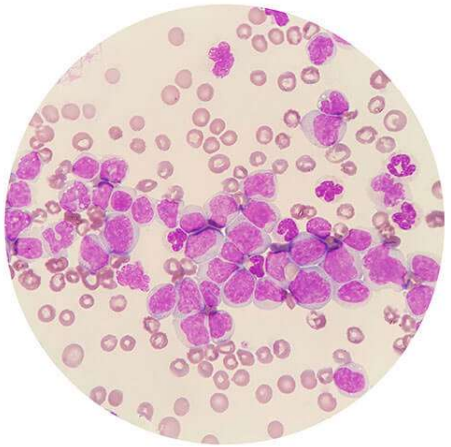
Ron Vale, PhD
Founder, Myeloid Therapeutics
UCSF Professor and Innovator

PROBLEM:

- Sustained medical benefit is still not achieved for majority of patients with advanced solid tumors

SOLUTION:

- Myeloid cells can make up to 75% of tumor mass
- *In-vivo* mRNA delivery platform targeting myeloid cells
- Retrotransposon-mediated gene-insertion technology for delivery of larger genetic sequences



TRACTION:

- Myeloid Therapeutics Initiates Patient Dosing with MT-302, a Novel TROP2-Targeting RNA CAR, in Phase 1 Study for Advanced or Metastatic Epithelial Tumors
- >$120M in Funding

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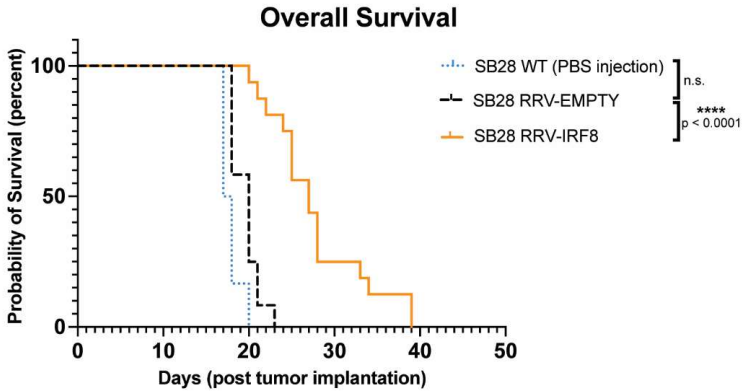
Myeloid Differentiation Factor-Expressing Retroviral Vector for Tumor Therapy

Hideho Okada, MD PhD
UCSF Professor, Neurological Surgery, PICI Member

Noriyuki Kasahara, MD PhD
UCSF Adjunct Professor, Neurological Surgery

Megan Montoya
Grad Student,
BMS Program, UCSF



Transduction with IRF8 *in vivo* suppresses the growth of intracerebral SB28 tumors. SB28 cells were implanted intracerebrally and subsequently injected with control (EMPTY) or IRF8 RRV. Tumor growth kinetics were monitored using bioluminescence (BLI) twice per week until study completion. Tissues were harvested and dissociated into single cells for analysis. Kaplan-Meier showing survival; SB28 WT, SB28 RRV-EMPTY, and SB28 RRV-IRF8.

DISEASE/INDICATION: Brain tumors, particularly Glioblastoma. The potential application extends to a range of solid tumors.

UNMET NEED: Current therapies for GBM and other solid tumors have limitations due to resistance, recurrence, and non-selectivity towards tumor cells, leading to severe side effects. Novel targeted therapies with better efficacy and less toxicity are urgently needed.

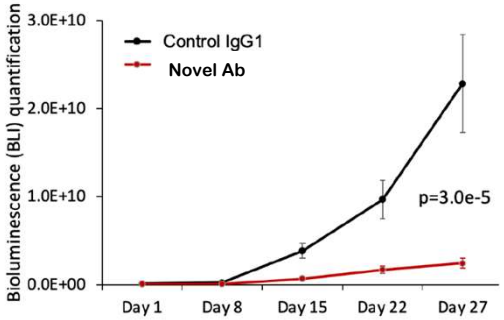
PRODUCT: A retroviral replicating vector (RRV) carrying a transgene that encodes a myeloid/dendritic cell differentiation factor, such as Interferon Regulatory Factor 8 (IRF8). This RRV can be used as a targeted therapeutic agent to increase the killing of tumor cells and reduce tumor burden.

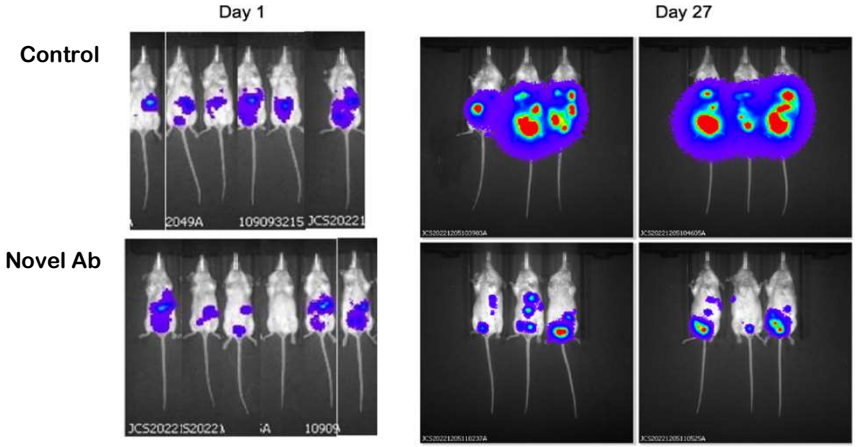
COMPETITIVE ADVANTAGE/DIFFERENTIATION: This approach targets two major hinderances in the anti-tumor immune response: an abundance of immunosuppressive myeloid cells and lack of antigen presenting cells (APCs), which are necessary for T-cell-mediated tumor cell killing. To concurrently address these, an RRV expressing IRF8 was employed to “reprogram” immunosuppressive myeloid cells into APCs, with the goal of both reducing immunosuppression and activating T-cells. The RRV selectively infects and replicates within proliferating tumor and immune cells, causing myeloid-derived suppressor cells to differentiate into potent APCs, increasing cytotoxic T-cell numbers, and enhancing tumor cell killing. This approach leverages the body’s immune system and inherently targets tumor cells, reducing off-target effects.

DATA: Effects of RRV-IRF8 on survival and tumor growth kinetics were examined in the SB28 murine GBM model. Functional immunosuppression and antigen presentation was assayed by *ex vivo* T-cell-myeloid co-culture.

Novel Antibody to Treat Hepatocellular CA and other Common Malignancies

James Rubenstein, MD, PhD
UCSF Professor,
Medicine, PICI Member





Novel mAb delays progression of Hepatocellular Carcinoma (HCC) in mice

DISEASE/INDICATION: Hepatocellular carcinoma, non-small cell lung cancer, multiple myeloma, lymphoma, other cancers.

UNMET NEED: Need for effective therapies for common, high-risk tumors, based on upregulated expression of novel cell surface target by high-risk and/or refractory cancers.

PRODUCT: Novel monoclonal antibody and target

COMPETITIVE ADVANTAGE/DIFFERENTIATION: Potential to be broadly effective as monotherapy and in combinations

DATA: Demonstrated upregulation of the novel target in patients with relapsed CNS lymphoma and in a variety of prognostically poor and common human cancers. Proof of concept studies done *in vitro* and in mouse models of HCC. MOA involves probable ADCC, as well as direct pro-apoptotic effects and possible anti-angiogenic effects.

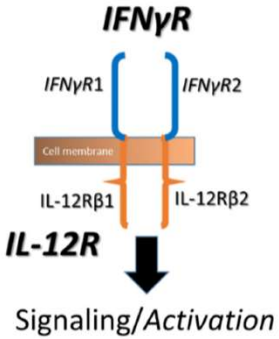
(Initial funding from UCSF Catalyst Program and PICI)

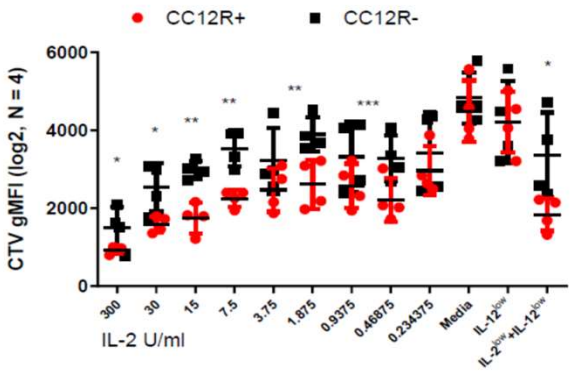
Novel CAR to enhance the proliferation of NK cells

Lewis Lanier, PhD
UCSF Associate Professor, Microbiology & Immunology, PICI Center Director

Avishai Shemesh, PhD
UCSF Associate Specialist, Medicine, PICI Member

Kole Roybal, PhD
UCSF Associate Professor, Microbiology & Immunology, PICI Center Director





Chimeric IFNγR-hIL-12R receptor (CC12R) enhances human primary NK cell proliferation. (A) NK92 cells were cultured in the presence of IL-2 (200 U/ml), IFNγ (100 ng/ml), or without cytokines (media) and measured for (left to right) cell proliferation (CTV gMFI dilution), percentage of live-cell (fixable near-infrared viability dye negative cells), and relative cell numbers (30-s sample acquisition).

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DISEASE/INDICATION: Cancer immunotherapy

UNMET NEED: No CAR NK technologies exist that promote NK growth signals without exogenous IL's, which cause systemic or local toxicity.

PRODUCT: NK cells engineered with a chimeric cytokine receptor that provides autocrine signaling to enhance NK cell proliferation and function.

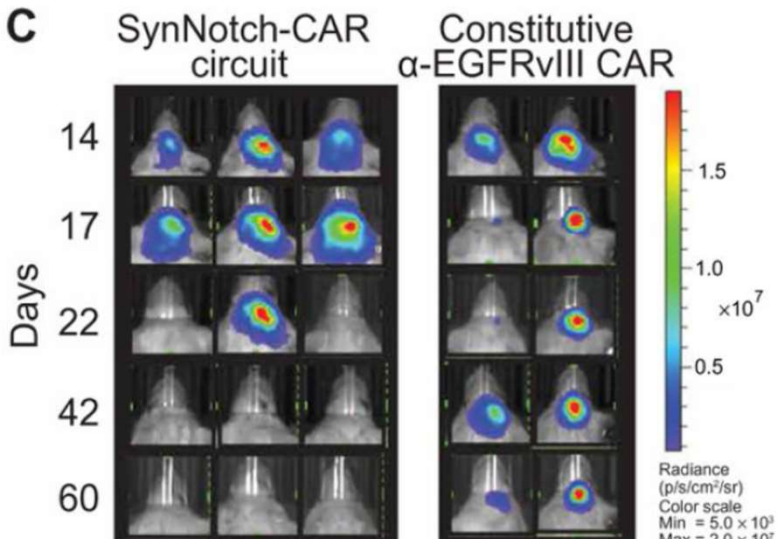
COMPETITIVE ADVANTAGE/DIFFERENTIATION: Potential to overcome expansion issues of NK cells; Reduces sensitivity of NK cells to exogenous IL-2; Eliminates need for expansion of primary NK cells in vitro prior to infusion; Eliminates the need to systemically administer IL-12 thereby reducing toxic effects of IL-12; Targeted NK-cell activation at the tumor site

DATA: In vitro validation showing that Activating NK receptor stimulation promotes differential IL-12 signaling leading to IL-2–primed NK cell expansion.

Novel CAR-T Therapy for Glioblastoma

Wendell Lim, PhD
UCSF Professor, Cellular Molecular Pharmacology

Hideho Okada, MD
UCSF Professor, Neurological Surgery, PICI Member



Longitudinal bioluminescence imaging of GBM6 tumor-bearing mice treated with α-EGFRvIII synNotch–α-EphA2/IL13Rα2 CAR T cells and conventional α-EGFRvIII CAR T cells. Each column represents one mouse over time.

DISEASE/INDICATION: Glioblastoma and other CNS diseases

UNMET NEED:
-No effective therapies currently for GBM. Median survival: < 18months
-Previous studies targeting GBM with anti-EGFRviii CAR: consistent recurrence
-EphA2 and IL13Ra2: widely expressed in GBM but have imperfect specificity

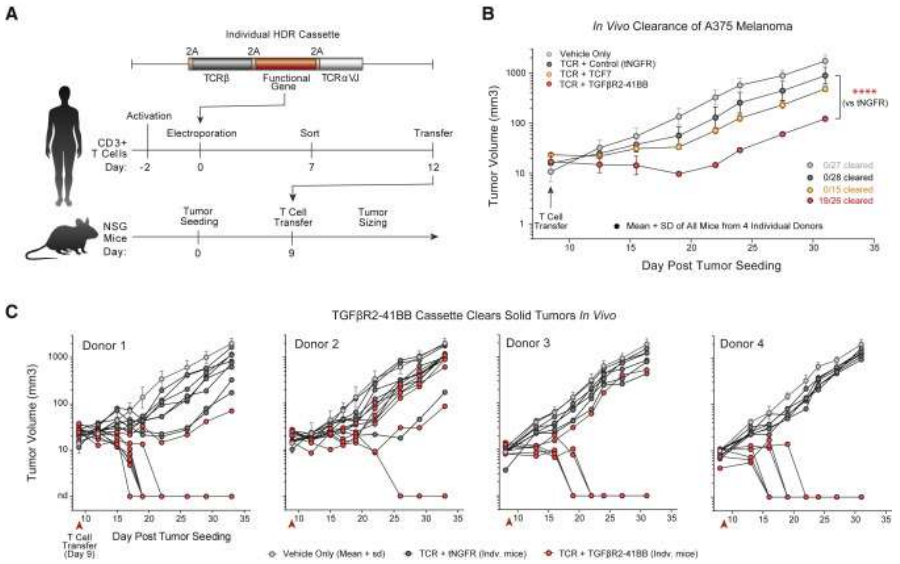
PRODUCT: CAR-T cell therapy that recognizes EGFRviii+ cells and then kills in the presence of EPHA2 or IL13Rα2

COMPETITIVE ADVANTAGE/DIFFERENTIATION: A multi-antigen targeting strategy using synNotch “prime and kill” circuit

DATA: EGFRviii is IND approved with recruitment for phase 1 dose escalation in GBM patients ongoing. Anticipate filing IND for the BCAN approach in Q1 or Q2 2025

Novel TGF-β R2-41BB CAR T Cells to Treat Solid Tumors

Alex Marson, MD, PhD
UCSF Professor; Director of Gladstone-UCSF Institute of Genomic Immunology; PICI Center Director



A Novel TGFβR2-41BB Chimeric Receptor Identified by Pooled Knockin Screening Improved Clearance of an *In Vivo* Solid Tumor Model. (A) Individual constructs nominated by pooled knockin screens and scRNA-seq analyses were adoptively transferred into NSG mice implanted with A375 melanoma tumors. (B) Tumor sizing after adoptive transfer of vehicle alone (saline, gray) or T cells targeted with various polycistrons encoding NY-ESO-1 antigen specificity and potential therapeutic constructs. TGF-βR2-41BB construct performed significantly better than the tNGFR control and was the only construct that resulted in complete tumor clearance (19 out of 26 tumors). (C) Individual *in vivo* tumor growth curves in the A375 melanoma xenograft model are shown for mice treated with T cells with TGF-βR2-41BB and NY-ESO-1 TCR knockin and controls, as in (B).

DISEASE/INDICATION: Cancer.

UNMET NEED: Current cancer immunotherapies often struggle with the immunosuppressive nature of tumor microenvironments, which can significantly limit the efficacy of treatments. Tumors can create hypoxic conditions or express immunosuppressive signals like TGFβ, adenosine, or suppress calcium/calcineurin signaling, effectively evading immune surveillance and destruction.

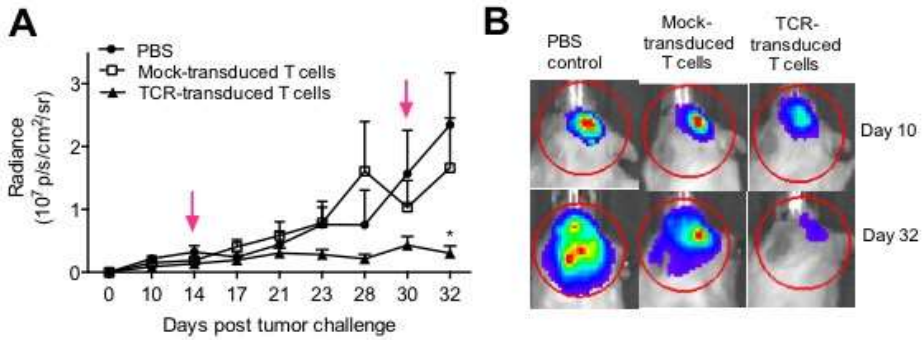
PRODUCT: Our engineered T-cells are designed to resist these immunosuppressive signals by inhibiting specific T-cell negative regulator genes, allowing them to proliferate and exert cytotoxic effects in normally prohibitive tumor microenvironments.

COMPETITIVE ADVANTAGE/DIFFERENTIATION: Unlike traditional therapies that may be generalized or non-specific, our product uses a precision gene editing approach (such as CRISPR, TALENs, or ZFN) to specifically enhance the cytotoxic activity of T-cells against cancer cells. This not only improves the effectiveness of the T-cells but also minimizes potential off-target effects and enhances adaptability to different tumor conditions.

DATA: Our platform nominated a lead hit (TGF-βR2-41BB) that increased T cell fitness in vivo and promoted key effector cytokines including IFNγ. A375 melanoma xenograft model showed mice that received TGF-βR2-41BB cells showed significant reductions in tumor burden. In 19 out of the 26 mice tested with T cells from four different human blood donors, the TGF-βR2-41BB knockin cells cleared the tumor, which was not observed at these doses in any of the control mice.

Novel adoptive TCR therapy to treat patients with H3.3K27M+ diffuse midline glioma

Hideho Okada, MD, PhD
UCSF Professor, Neurological Surgery, PICI Member



Adoptive transfer of TCR-transduced T cells but not mock-transduced T cells results in inhibition of intracranial H3.3K27M+ glioma in NSG mice.

NSG mice bearing intracranial U87H3.3K27M luciferase+ gliomas received intravenous infusion with PBS, mock-transduced T cells or TCR-transduced T cells (including both $CD4^+$ and $CD8^+$ cells). A. Tumor growth is presented as radiance (107 p/s/cm²/sr) using BLI (n = 8 per group). Arrows indicate the days on which mice received treatment. B. Representative BLI images of mice on Day 10 and on Day 32 post-tumor inoculation.

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DISEASE/INDICATION: Diffuse midline glioma (DMG)

UNMET NEED: DMG are aggressive brain tumors characterized by poor prognosis and limited treatment options. The median overall survival for children with DMG is less than one year. Current therapies often result in significant side effects with only marginal efficacy.

PRODUCTS: Autologous TCR cells engineered to target H3.3K27M+ glioma cells; Glioma Vaccine for HLA-A2+ patients

COMPETITIVE ADVANTAGE/DIFFERENTIATION: No adoptive cell therapies targeting this mutation are currently approved. The peptides can be adapted to various delivery methods.

DATA: Preclinical mouse models of glioma. IND approved. Enrolling patients in Phase I clinical trial.

Novel Genome Editing Approach for Autosomal Dominant Diseases

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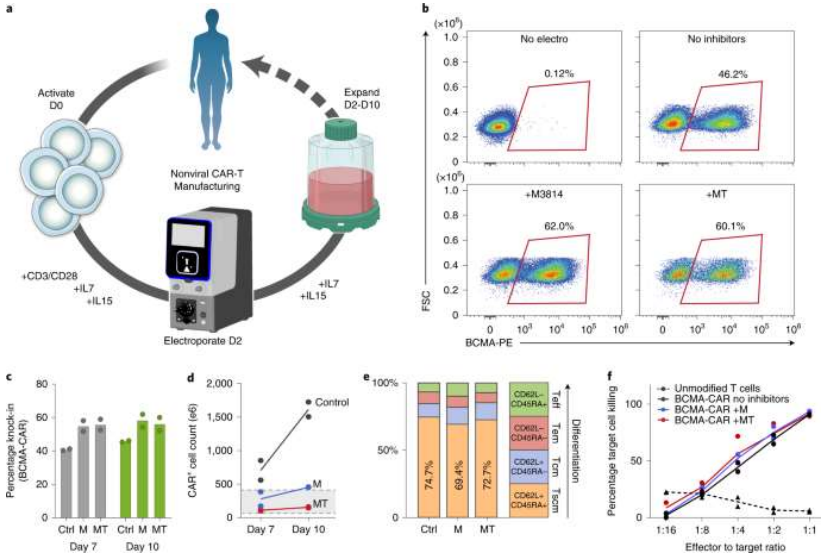
Brian Shy, MD, PhD
UCSF Asst Professor in Residence; Laboratory Medicine



GMP-compatible process for nonviral CAR-T cell manufacturing. **a**, Diagram of nonviral CAR-T cell manufacturing process. T cells are isolated from peripheral blood and activated on day 0 with anti-CD3/anti-CD28 Dynabeads, IL-7 and IL-15. Cells are electroporated using the Maxcyte GTx electroporator on day 2 with Cas9 RNPs+ssCTS HDRTs and then expanded for a total of 7–10 days using G-Rex 100M culture vessels supplemented with IL-7+IL-15. **b**, Representative day 10 flow plots showing BCMA-CAR knock-in for control (no inhibitors), M3814 and MT conditions. **c**, BCMA-CAR knock-in rates on days 7 and 10 for each condition. **d**, Absolute number of CAR+ cells on days 7 and 10. Gray box highlights anticipated patient doses of 50–400 × 106 CAR+T cells. **e**, T cell immunophenotypes on day 10 based on CD45RA and CD62L expression. **f**, In vitro killing of BCMA+MM1S multiple myeloma cell lines in comparison to unmodified T cells from same blood donors.

DISEASE/INDICATION: Autosomal dominant diseases including but not limited to CTLA4 haploinsufficiency.

UNMET NEED: As the gene and cell therapy fields continue to expand, simple, efficient and scalable manufacturing solutions are needed to reduce lead times and treatment costs; and to provide access to more patients.

PRODUCT: Based on CRISPR-Cas9 technology, the product involves a method for precise genome editing where a healthy copy of a gene segment is inserted specifically into the intronic region of the mutated gene in human cells, such as T cells or hematopoietic stem cells. This method ensures that the new gene segment is correctly expressed, replacing the function of the mutated gene.

COMPETITIVE ADVANTAGE/DIFFERENTIATION: Clinical applications with large nonviral DNA templates have been limited by the toxicity of naked dsDNA. Here we report advances that increase both knock-in efficiency and knock-in cell yields with large DNA templates through inclusion of CTS sequences on long ssDNAs, that are less toxic than the previous generation of dsCTS templates.

DATA: We applied these approaches across diverse genetic loci, knock-in constructs and primary hematopoietic cell types to demonstrate broad use for gene correction strategies, disease variant modeling and reprogrammed cell therapy development. We demonstrate a fully nonviral and GMP-compatible CAR-T manufacturing process at clinical ssCTS template generation.

Novel Neoantigen-Based Peptides and TCR for Cancer Immunotherapy

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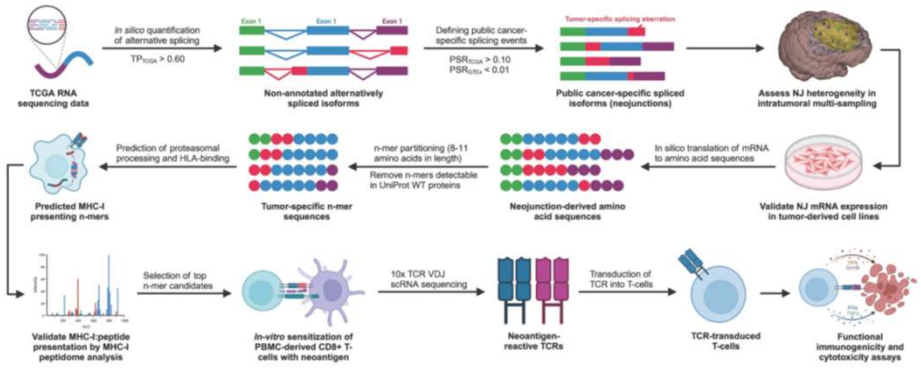
Darwin Kwok, MS
Grad Student, BMS Program, UCSF

Joe Costello, PhD
Professor in Residence, Neurological Surgery



Novel neoantigen discovery pipeline for discovering public and tumor-wide targets for cellular immunotherapy across various cancers. TCGA RNA sequencing data across multiple cancers (n=11) were analyzed for non-annotated, protein-coding, and cancer-specific splicing junctions. The expression of these neojunctions and their peptide derivatives were validated by RNA sequencing and mass spectrometry analysis of patient-derived tumor samples and cell lines. T-cell receptors (TCRs) were cloned and characterized for top predicted candidates through in vitro sensitization of PBMC-derived CD8+ T-cells against the corresponding neoantigen-pulsed antigen-presenting cells and subsequent 10x V(D)J single-cell sequencing. Transduction of these neoantigenreactive TCR sequences in TCR-null Jurkat76/CD8 cells and PBMC-derived CD8+ T-cells allowed the demonstration of neoantigen-specific immunogenicity and tumor-specific killing.

DISEASE/INDICATION: Glioblastoma

UNMET NEED: There is a pressing need for innovative cancer therapeutics that can circumvent cancer cells evading the immune system and resistance to treatment. Conventional “neoantigens” are limited due to the low tumor mutation burden. Tumor-specific alternative splicing events will significantly enhance the repertoire of available antigen targets for effective immunotherapy.

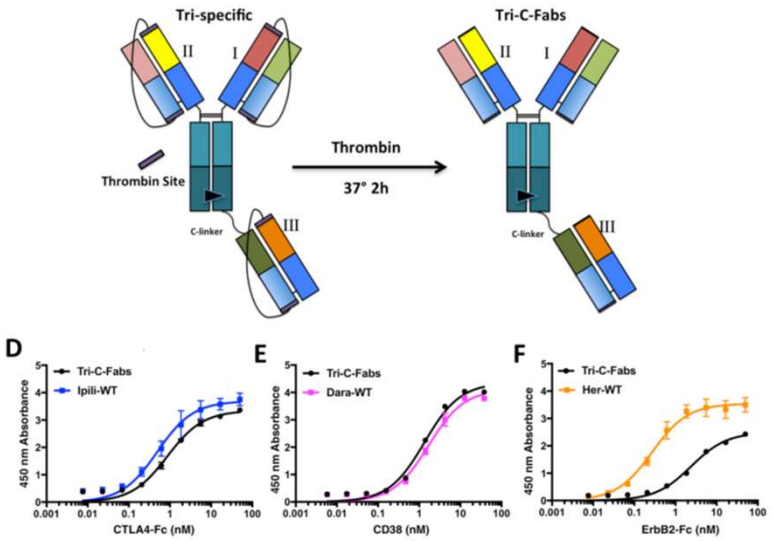
PRODUCT: Our isolated peptides have the potential to be developed into a novel cancer immunotherapeutic. They can be synthesized and modified to enhance stability and biological activity. These peptides can be presented by major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells (APCs), stimulating T cell receptors (TCRs) to induce an immune response

COMPETITIVE ADVANTAGE/DIFFERENTIATION: Our peptides can be modified to enhance their stability and biological activity while preserving their TCR inducibility. Furthermore, they can be used to prime T cells in vitro or in vivo, or used in vaccinations, offering the potential for personalized immunotherapy.

DATA: We identified CD8+ T-cell clones specific for neoantigens derived from tumor-wide and conserved neojunctions in GNAS and RPL22, respectively. TCR-engineered CD8+ T-cells targeting these mutations conferred neoantigen-specific tumor cell eradication.

Platform for construction of bispecific and multi-specific antibodies

Bin Liu, PhD
UCSF Professor, Anesthesia



An example of a tri-N-Fab trispecific against CTLA-4, CD38, and ErbB2

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DISEASE/INDICATION: Platform technology for the development of therapeutics to address a multitude of diseases

UNMET NEED: Multi-specific Abs with an Ig-like architecture are difficult to produce; they suffer from low stability, low efficiency, and contamination by homodimers and improperly paired antibody side-products.

PRODUCT: New approach to produce single-chain IgG with cleavable linkers through commercially available proteases.

COMPETITIVE ADVANTAGE/DIFFERENTIATION: The approach is completely modular, allowing for higher efficiency antibody production and the ability to create multi-specific antibodies in addition to bi-specific antibodies.

DATA: In Vitro proof of concept.

Pooled Knockin Screening for Enhanced Cell Therapies

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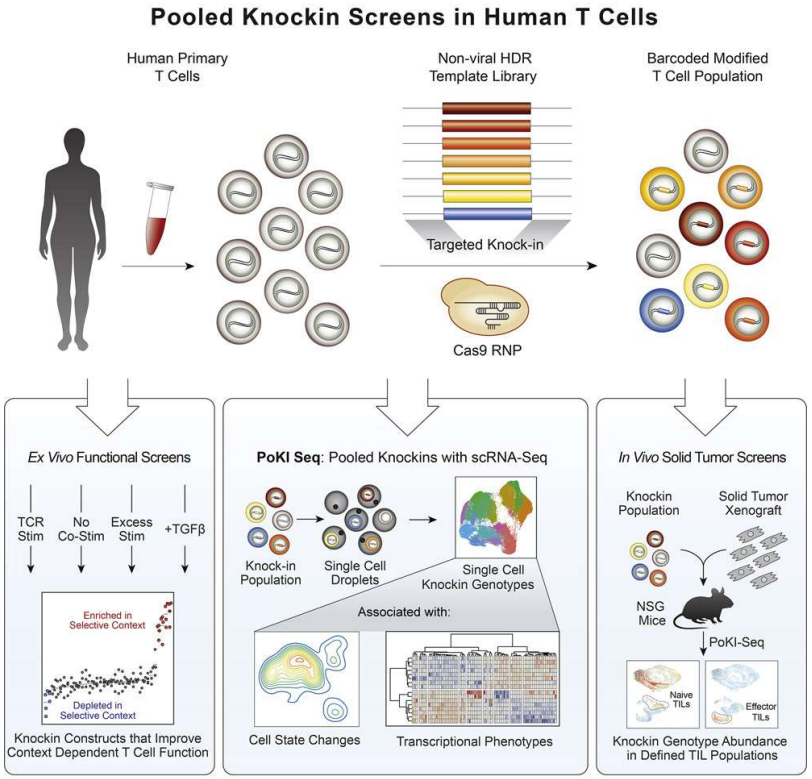

DISEASE/INDICATION: Enhancing T cell functionality can be applied to a host of diseases including cancer and autoimmune disease

UNMET NEED: More high-throughput methods are needed to test which knockin gene constructs most potently enhance primary cell functions in vivo

PRODUCT: DNA constructs to enhance the functionality of genetically modified immune cells

COMPETITIVE ADVANTAGE/DIFFERENTIATION: Unparalleled precision and scalability. By concurrently assessing multiple knockin constructs targeting specific genetic loci, our technology enables rapid identification of the most promising candidates for bolstering T cell function

DATA: In Vitro proof of concept which has provided critical insights into the effects of various transcription factors on T cell function

Precision T Cell Modulation Therapies

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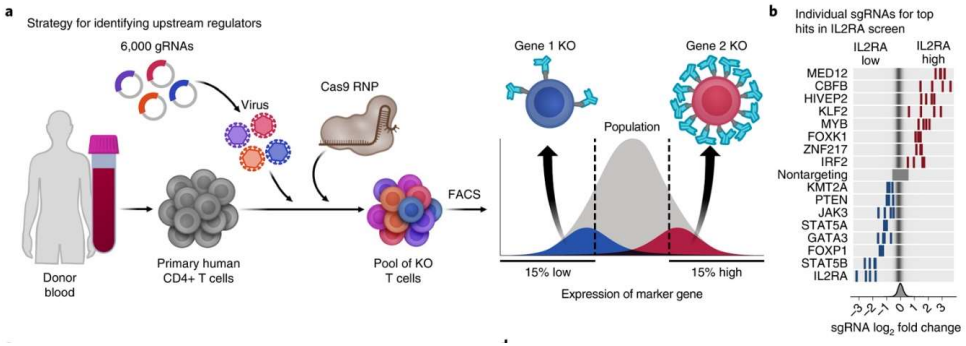

Discovery of upstream regulators of IL2RA, IL-2 and CTLA4. a, Strategy for identifying upstream regulators. We used SLICE to generate a pool of knocked out (KO) primary human CD4+ T cells. Knockout T cells were sorted into 15% high- or low-expression bins with FACS based on the expression of IL2RA, IL-2 or CTLA4. The sgRNAs in each bin were sequenced to identify positive or negative regulators of IL2RA, IL-2 or CTLA4 levels. **b**, Top, enrichment of individual sgRNAs in the high- or low-expression bins for the top hits in the IL2RA screen. Bottom, distribution of enrichment for all sgRNAs.

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DISEASE/INDICATION: Autoimmune disorders and cancer.

UNMET NEED: Current therapies often involve broad immunosuppression or non-specific immune activation, which can lead to significant side effects and incomplete disease resolution. There is a critical need for more targeted therapies that can selectively modulate the immune system to improve efficacy and reduce adverse effects.

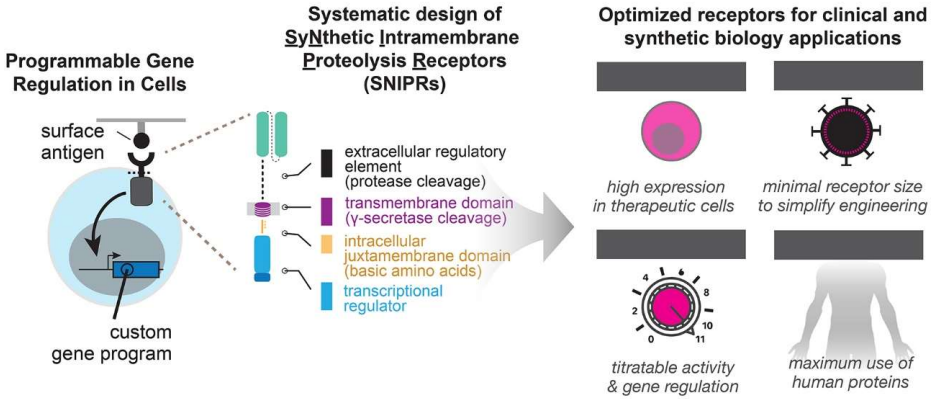
PRODUCT: A population of genetically modified T cells, tailored to either suppress or enhance immune responses in a controlled manner. These cells are engineered through precise genetic modifications to inhibit or overexpress specific nuclear factors, thereby altering the expression of crucial proteins like CTLA4, FOXP3, and IL2RA, which are pivotal in immune regulation.

COMPETITIVE ADVANTAGE/DIFFERENTIATION: This technology leverages CRISPR/Cas genome editing to achieve highly specific and customizable modifications in T cells, allowing: 1) Precise manipulation of gene expression, leading to potentially higher efficacy and fewer off-target effects compared to traditional methods; 2) The ability to target a wide range of nuclear factors relevant to various immune pathways, offering broad applicability across different types of immune-related diseases; 3) Flexibility in modulating the immune response, either enhancing or suppressing it, which is crucial for treating different phases or types of diseases such as cancer and autoimmune disorders.

DATA: We developed an approach for systematic discovery of upstream regulators of critical immune factors in primary human T cells. Then, we mapped the network of the target genes of these regulators and putative cis-regulatory elements using CRISPR perturbations, RNA-seq and ATAC-seq. These regulators form densely interconnected networks with extensive feedback loops. Furthermore, this network is enriched for immune-associated disease variants and genes.

Revolutionizing Therapeutic Cell Control with SyNthetic Intramembrane Proteolysis Receptors (SNIPRs)

Kole Roybal, PhD
UCSF Associate Professor, Microbiology & Immunology, PICI Center Director



Design of Synthetic Intramembrane Proteolysis Receptors. Receptors are comprised of a ligand binding domain (LBD), an extracellular domain (ECD), a transmembrane domain (TMD), a juxtamembrane domain (JMD), and a transcription factor (TF). Receptor circuits are designed to maximize clinical translation potential

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DISEASE/INDICATION: Cancer immunotherapy and autoimmune disease

UNMET NEED: SNIPRs address several unmet needs in the field of cell therapeutics engineering, such as precision & control, immunogenicity concerns, flexibility, versatility, and therapeutic potential

PRODUCT: Optimized engineered cells that are compatible with a range of human and programmable transcription factors

COMPETITIVE ADVANTAGE/DIFFERENTIATION: Through systematic modular engineering, SNIPRs boast tunable sensing and transcriptional response abilities, paving the way for tailored therapeutic interventions

DATA: Humanized SNIPR-CAR circuits exhibit precise dual antigen targeting in preclinical in vivo models of solid tumors

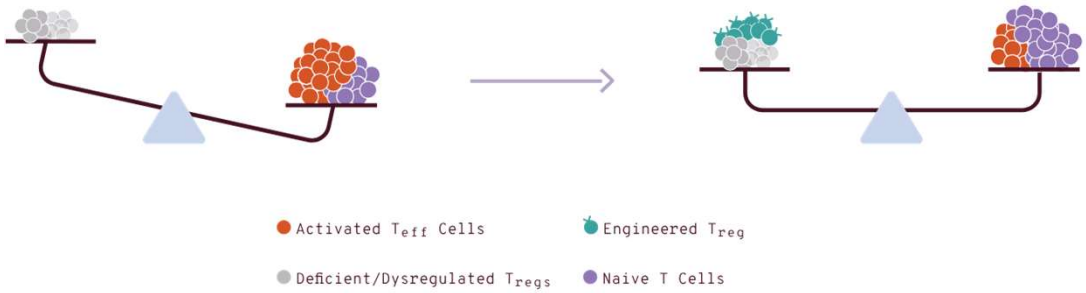
Restoring Balance is Key to Unlocking Cures

Jeffrey Bluestone, PhD
Co-founder, Sonoma Biotherapeutics
CEO, President and Emeritus
UCSF Professor and Innovator

Qizhi Tang, PhD
Scientific Advisor, Sonoma Biotherapeutics
UCSF Professor, Surgery

PROBLEM:

- There are many autoimmune diseases which together account for among the highest rate of medication expenditures in the US.
- RA alone contributes an estimated $22.3B[1].



SOLUTION:

- One time treatment focused on autoimmune and inflammatory diseases.
- A unique platform combining engineered Treg cells with a drug that depletes/deactivates Teff cells at the site of disease.

TRACTION:

- Recent $45M Milestone payment received from Regeneron under ongoing collaboration
- >$450M in Funding

LEARN MORE:

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Unveiling the power of Gamma-Delta T Cells

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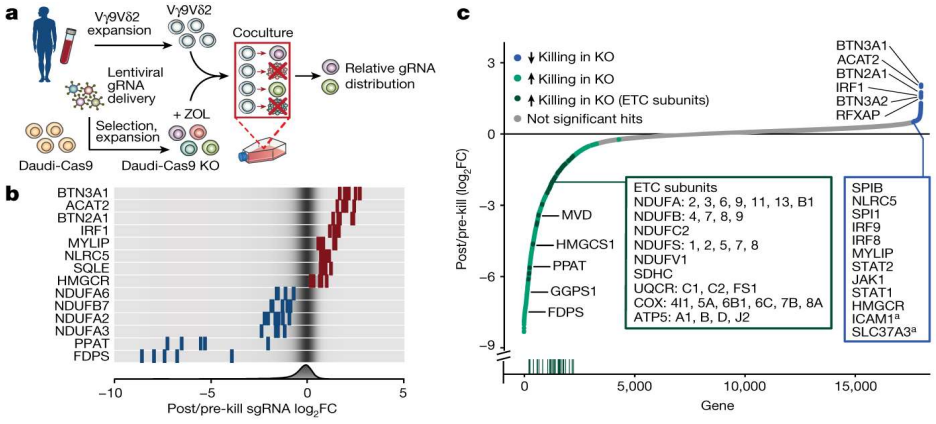

a, Vγ9Vδ2 T cell coculture screen with a genome-wide KO library of Daudi-Cas9 cells. **b**, Enrichment or depletion of individual sgRNAs for a selection of significant hits, overlaid on a gradient showing distribution of all sgRNAs (fold change (FC)). **c**, All 18,010 genes, ranked from negative to positive enrichment of Daudi-Cas9 KOs, that change killing.

DISEASE/INDICATION: Cancer immunotherapy, autoimmune disease and infectious disease

UNMET NEED: The current landscape of cancer treatment faces a significant unmet need in effectively targeting tumors, particularly in cases where patient-specific neoantigens are not readily available. Traditional approaches often fall short in addressing the broad spectrum of cancer types and variations within patients' immune systems

PRODUCT: Screen that decodes cancer cell pathways and leverages the unique ability of gamma delta (γδ) T cells to target tumors broadly, independent of patient-specific neoantigens or human leukocyte antigen background

COMPETITIVE ADVANTAGE/DIFFERENTIATION: Enhanced efficacy and safety profiles of cell therapies

DATA: In vitro proof of concept. The screens showed previously unappreciated multilayered regulation of BTN3A abundance on the cell surface and triggering of γδ T cells through transcription, post-translational modifications and membrane trafficking.