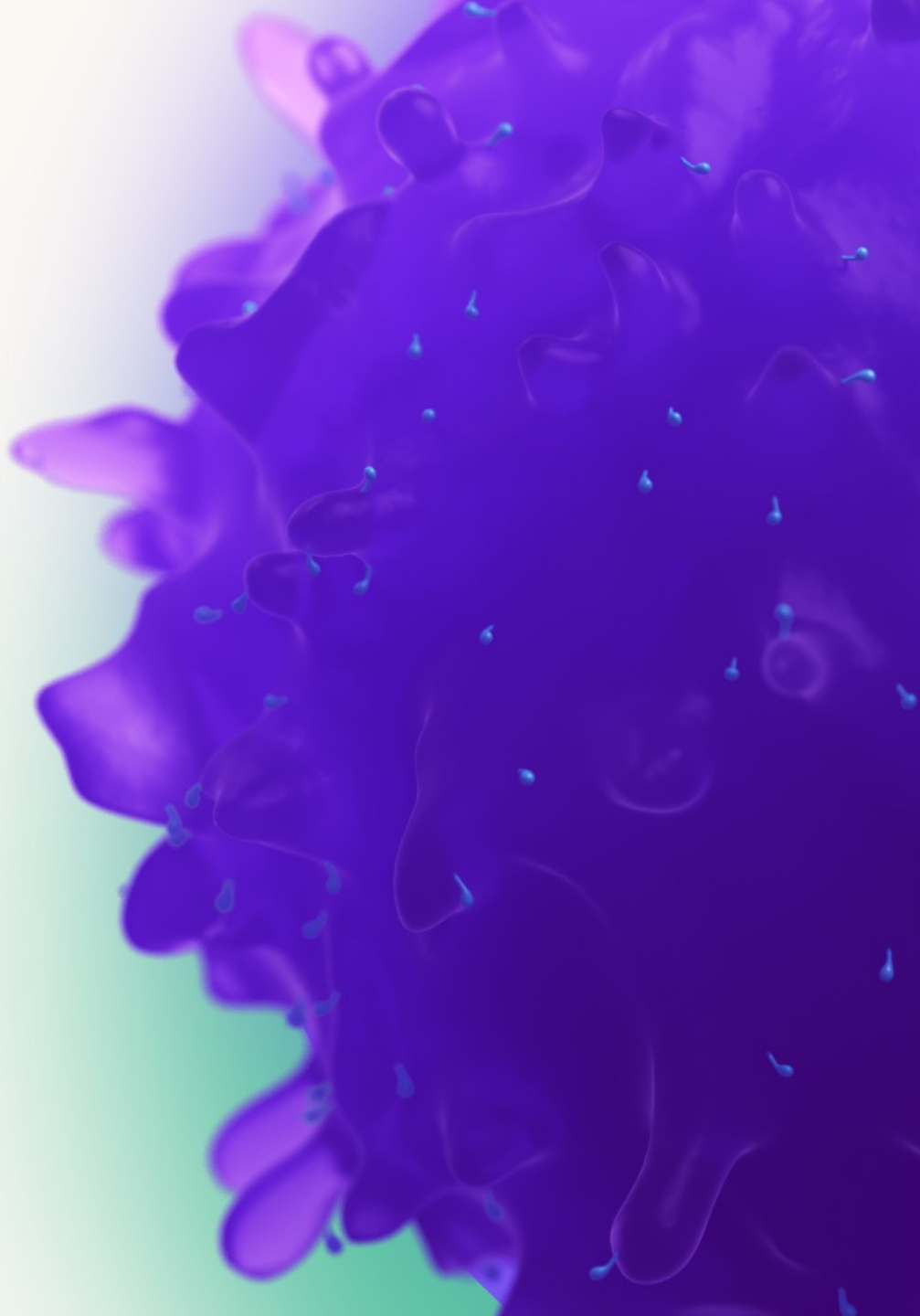
Lyell

Enhancing the Extraordinary

TCELL



Lyell Immunopharma — February 28, 2024

Forward Looking Statement

Certain matters discussed in this presentation are "forward-looking statements" of Lyell Immunopharma, Inc, Inc. (hereinafter referred to as the "Company," "we," "us," or "our") within the meaning of the Private Securities Litigation Reform Act of 1995 (the "PSLRA"). All such written or oral statements made in this presentation, other than statements of historical fact, are forward-looking statements and are intended to be covered by the safe harbor for forward-looking statements provided by the PSLRA. Without limiting the foregoing, we may, in some cases, use terms such as "predicts," "believes," "potential," "continue," "estimates," "anticipates," "expects," plans"," "intends," "forecast," "guidance," "outlook," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes and are intended to identify forward-looking statements. Forward-looking statements are based on assumptions and assessments made in light of management's experience and perception of historical trends, current conditions, expected future developments and other factors believed to be appropriate. Forward looking statements in this presentation are made as of the date of this presentation, and we undertake no duty to update or revise any such statements, whether as a result of new information, future events or otherwise. Forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and other factors, many of which are outside of our control, that may cause actual results, levels of activity, performance, achievements, timelines and developments to be materially different from those expressed in or implied by these forward-looking statements. Important factors that could cause actual results, developments and business decisions to differ materially from forward-looking statements are described in the sections titled "Risk Factors" in our filings with the Securities and Exchange Commission (the "SEC"), and include, but are not limited to, the following substantial known and unknown risks and uncertainties inherent in our business related to: the effects of geopolitical instability; macroeconomic conditions and the lingering effects of the COVID-19 pandemic; our ability to initiate or progress our current and planned clinical trials or to submit planned INDs on the anticipated timelines, if at all; our limited experience as a company in enrolling, conducting or completing clinical trials; our ability to manufacture and supply our product candidates for our clinical trials; the nonclinical profiles of our product candidates not translating in clinical trials; the potential for results from clinical trials to differ from nonclinical, early clinical, preliminary or expected results; significant adverse events, toxicities or other undesirable side effects associated with our product candidates; the significant uncertainty associated with our product candidates ever receiving any regulatory approvals; our ability to obtain, maintain, or protect intellectual property rights related to our product candidates; implementation of our strategic plans for our business and product candidates; the sufficiency of our capital resources and the need for additional capital to achieve our goals; other risks, including general economic conditions and regulatory developments, not within our control; and those risks described under the heading "Risk Factors" in our SEC filings, including our Annual Report on Form 10-K for the quarter ended December 31, 2023 and subsequent filings with the SEC.

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People with cancer need better therapies

90%
Cancer deaths caused by solid tumors

<3 Years
Most patients with metastatic cancer live after diagnosis

<2 Years
Before cancer progression

seer.cancer.gov; Deaths (Estimated 2021);
Survival Rates by Time Since Diagnosis, 2000-2017.
CDC Nat'l Ctr for Health Statistics, Mortality in the US, 2020.

Advancing T-cell Therapies for Solid Tumors

Wholly-owned product candidates addressing large patient populations

Expanding clinical pipeline; data from two programs in 2024

LYL797

ROR1-targeted CAR T cells for TNBC, NSCLC, and other solid tumors

Ph 1 clinical & translational data from 20+ patients in 1H24

LYL845

Tumor Infiltrating Lymphocytes (TIL) for melanoma, NSCLC, and CRC

Ph 1 clinical & translational data in 2H24

LYL119

ROR1-targeted CAR T cells for ROR1+ solid tumors

IND filing in 1H24

Scientific expertise, capabilities and capital to drive continuous innovation and ability to scale

Multiple genetic and epigenetic technology platforms to improve the function of T cells

- Designed to generate T cells that resist exhaustion and have durable stemness

Executing a scalable manufacturing strategy

- Lyell LyFE center producing clinical supply
- Shorten TIL manufacturing time in 2024
- Cellares collaboration to automate and scale manufacturing

Strong balance sheet

- ~$563 million of cash*
- Runway into 2027 through multiple clinical readouts

*Cash, cash equivalents and marketable securities as of 12/31/2023

Abbreviations: CAR, chimeric antigen receptor; CRC, colorectal cancer; IND, investigational new drug; NSCLC, non-small cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1; TIL, tumor-infiltrating lymphocytes; TNBC, triple-negative breast cancer.

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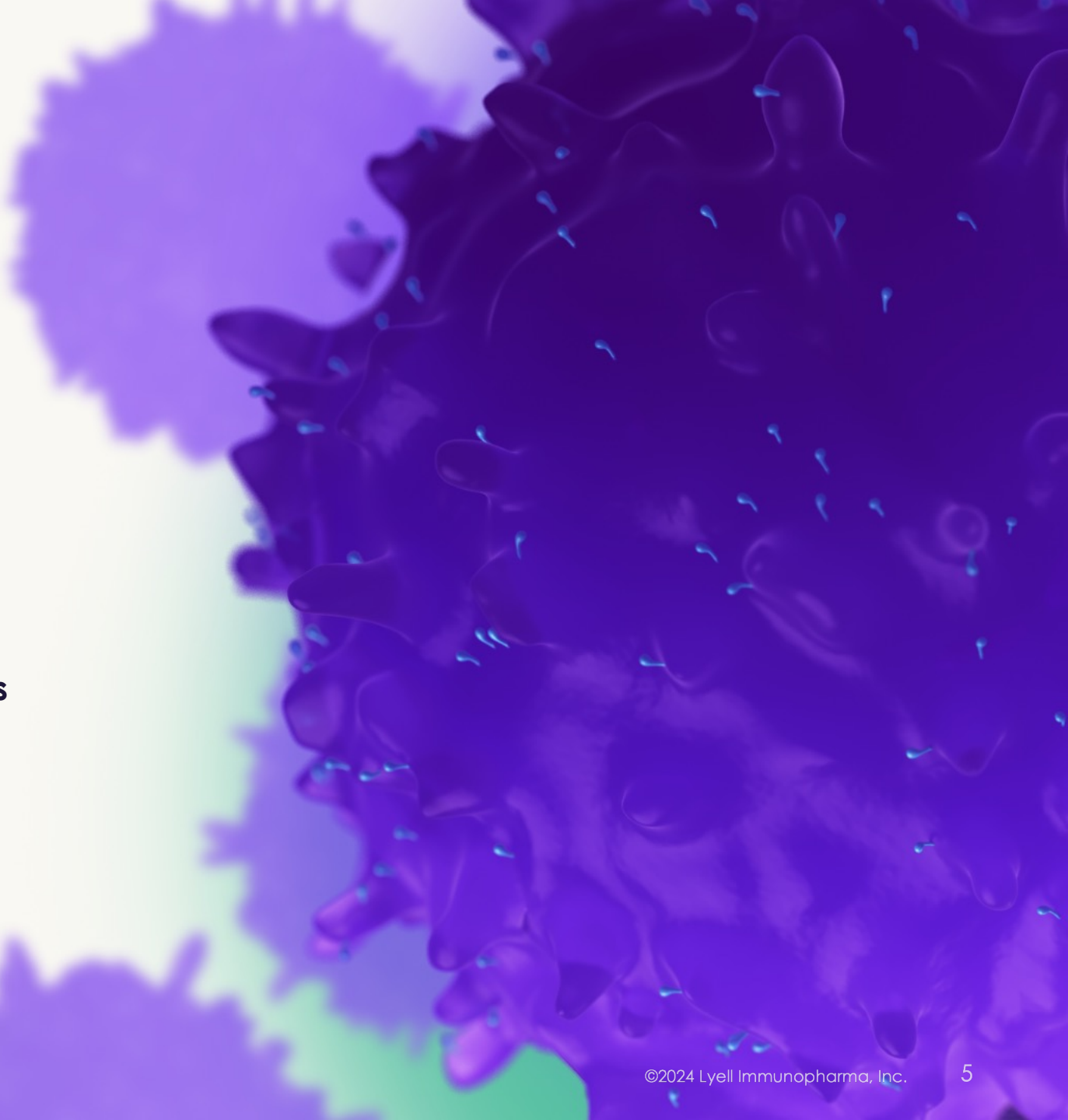
It’s All About the Cells

We are developing **next-generation T-cell reprogramming technologies** to overcome two primary barriers to successful therapies in malignant solid tumors. We are generating T cells that **resist exhaustion** and **have durable stemness**



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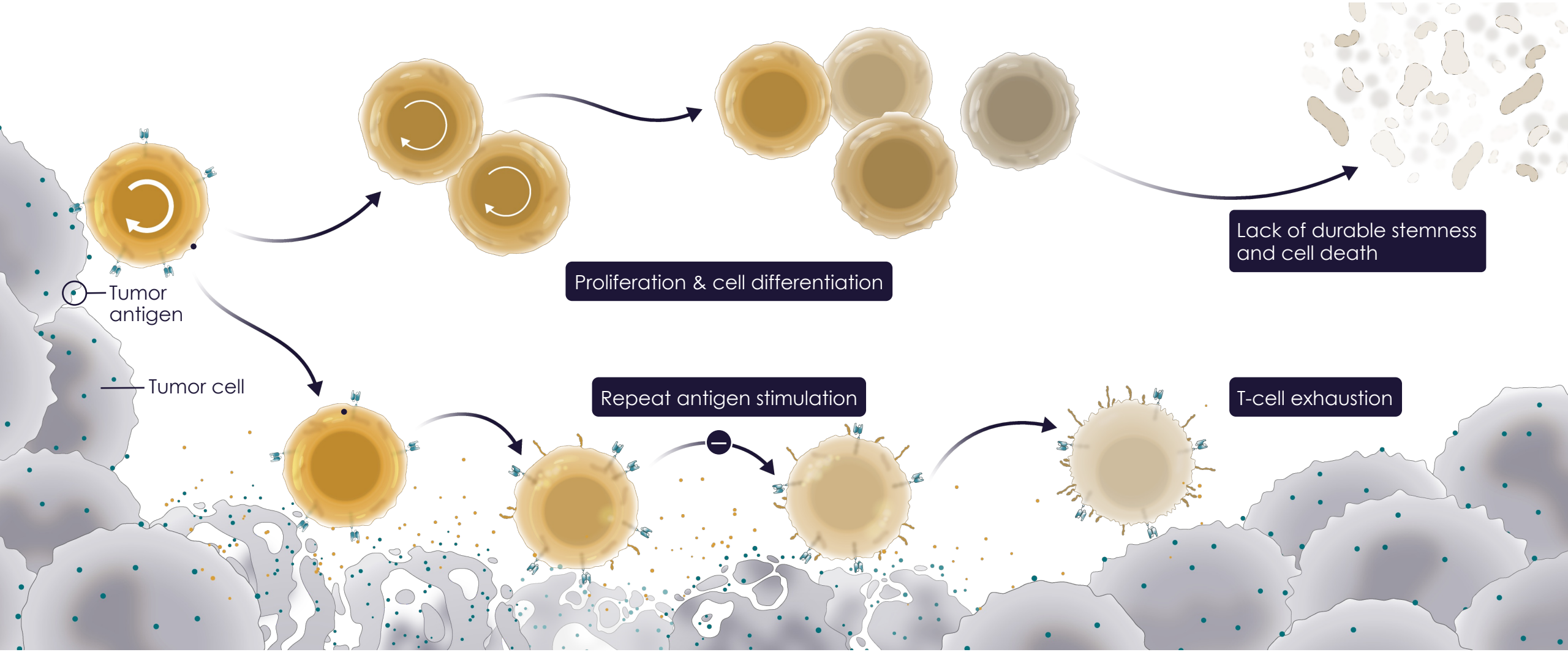
Cell Therapies for Solid Tumors Must Overcome Two Primary Barriers: T-cell Exhaustion and Lack of Durable Stemness



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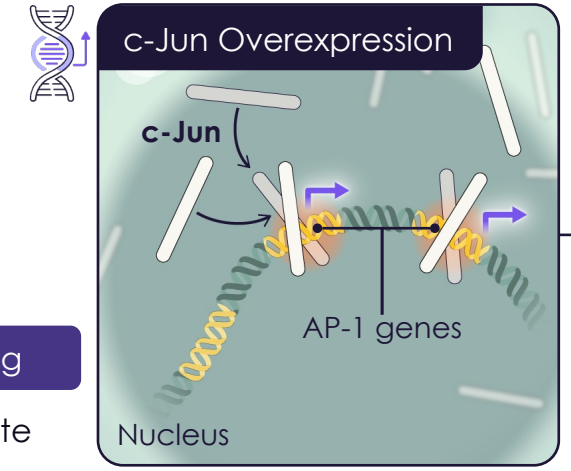
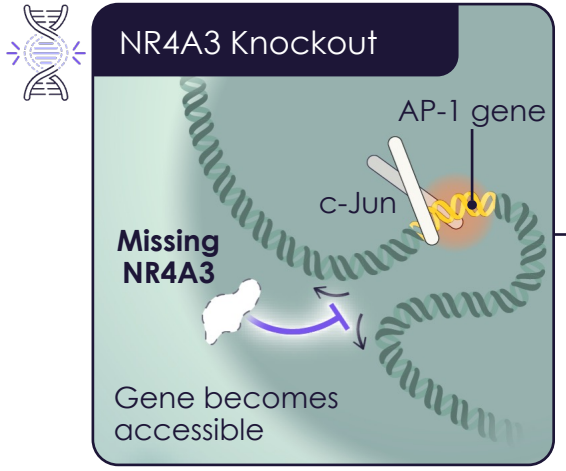
Lyell's T-cell Reprogramming Technologies

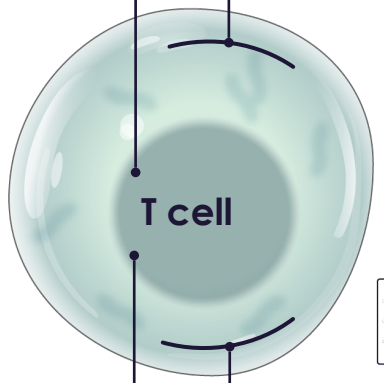
Designed to maintain cancer cell killing in the immunosuppressive tumor microenvironment while increasing ability to self-renew and persist to drive durable tumor cytotoxicity

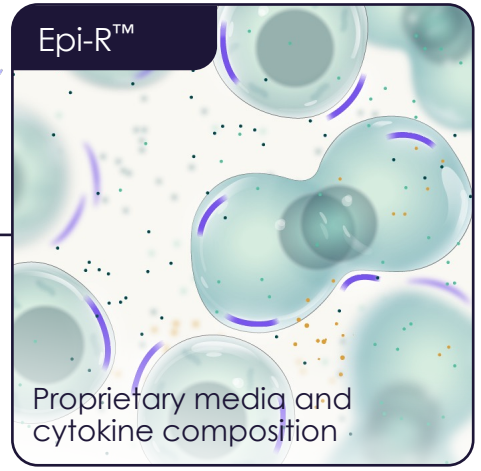
Genetic Reprogramming

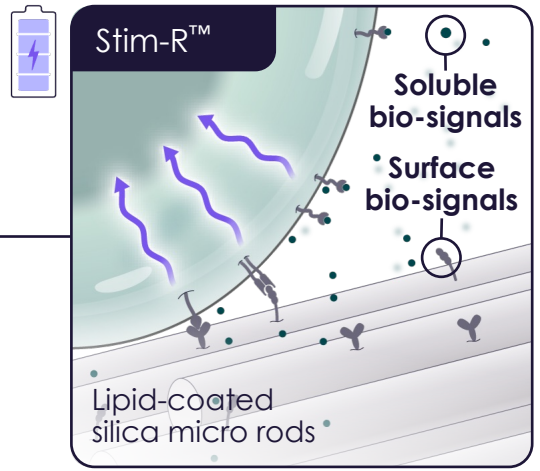
c-Jun and NR4A3 regulate the AP-1 transcription factor pathway, which plays a key role in T-cell effector function











Epigenetic Reprogramming

Manufacturing protocols that generate more stem-like cells that self renew and persist despite repeat antigen stimulation

Lynn, R. et al., *Nature*, 2019; Chen, J. et al., *Nature*, 2019.
Abbreviations: AP-1, activator protein 1; NR4A3, Nuclear receptor 4A3; TME, tumor microenvironment.

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A Robust Pipeline of T-cell Therapies for Solid Tumors

Product	Target	Reprogramming				Target Indications	Preclinical	Phase 1	Phase 2/ Pivotal	Next Milestone
		Genetic		Epigenetic						
		c-Jun	NR4A3	Epi-R™	Stim-R™					
LYL797 CAR T cell	ROR1	✓		✓		TNBC, NSCLC, other ROR1+ solid tumors				Initial data on 20+ patients in 1H24
LYL119 CAR T cell	ROR1	✓	✓	✓	✓	ROR1+ solid tumors				Submit IND 1H24
LYL845 TIL	Multiple antigens			✓		Melanoma (Orphan Drug Designation), CRC, NSCLC				Initial data 2H24
2nd Gen TIL	Multiple antigens	Genetic and Epigenetic Reprogramming				Solid tumors				

Abbreviations: CAR, chimeric antigen receptor; CRC, colorectal cancer; IND, investigational new drug; NSCLC, non-small cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1; TIL, tumor-infiltrating lymphocytes; TNBC, triple-negative breast cancer.

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Lyell Product Candidates Target Large Unmet Needs

~500K new US cases annually[1]
~180K US deaths annually[1]

LYL797

Triple-negative Breast Cancer

- 15% of breast cancer diagnoses in the US each year
- ~40K new cases | ~10K deaths

LYL797 LYL845

Non-small Cell Lung Cancer

- 84% of new lung cancer diagnoses each year
- ~200K new cases | ~110K deaths

LYL845

Melanoma

- 80% of all skin cancer-related deaths
- ~100K new cases | ~8K deaths

LYL845

Colorectal Cancer

- 3rd most common form of cancer
- ~150K new cases | ~53K deaths

[1]National Cancer Institute and the American Cancer Society and are based on US cases (2022).

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Reprogramming T Cells to Target Aggressive Cancers

LYL797

A genetically and epigenetically reprogrammed ROR1 CAR T-cell product candidate designed for differentiated potency and durability

LYL119

Innovative ROR1 CAR T-cell product candidate designed for enhanced cytotoxicity

Abbreviations: CAR, chimeric antigen receptor; ROR1, receptor tyrosine kinase-like orphan receptor 1.

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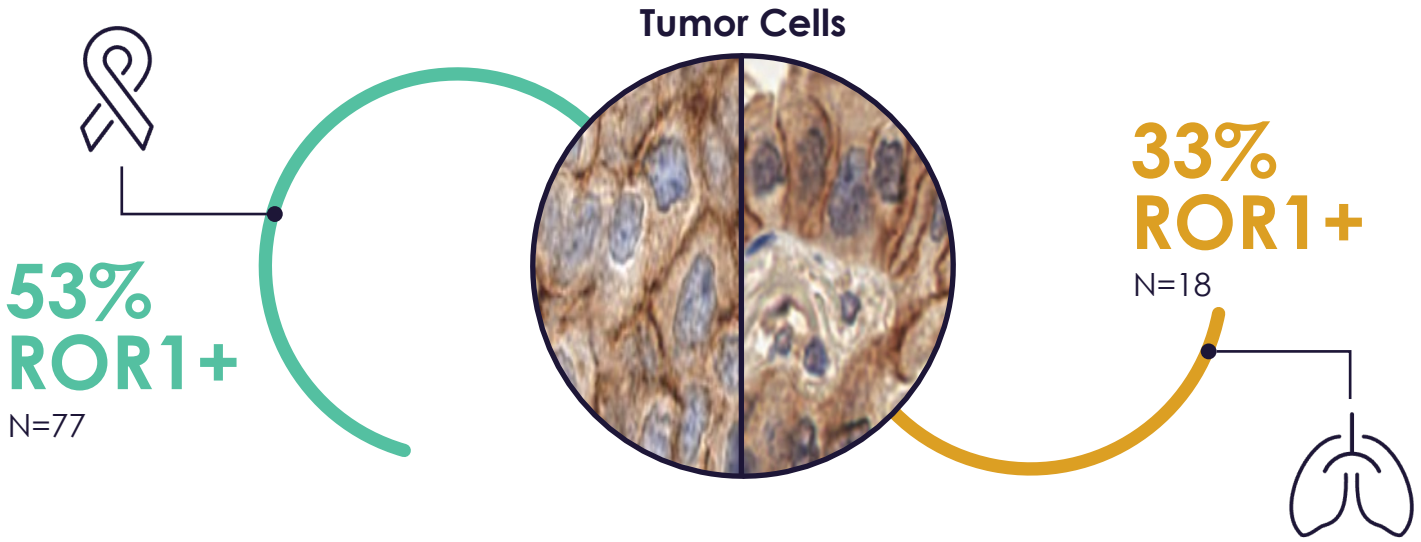
Lyell's ROR1 Assay and Screening Program Support Current and Future Clinical Trials

Screening data with Lyell's assay consistent with ROR1 expression in the literature



Triple-negative Breast Cancer[1]

- 15% of breast cancer diagnoses/year
- ~40K new cases; ~10K deaths

Non-small Cell Lung Cancer[1]

- 84% of new lung cancer diagnoses/year
- ~200K new cases; ~110K deaths

[1]National Cancer Institute and the American Cancer Society and are based on US cases (2022).
Published literature: Balakrishnan et al, Clin Cancer Res, 2017, TNBC ~60%, NSCLC ~40%
Abbreviations: ROR1, receptor tyrosine kinase-like orphan receptor 1.

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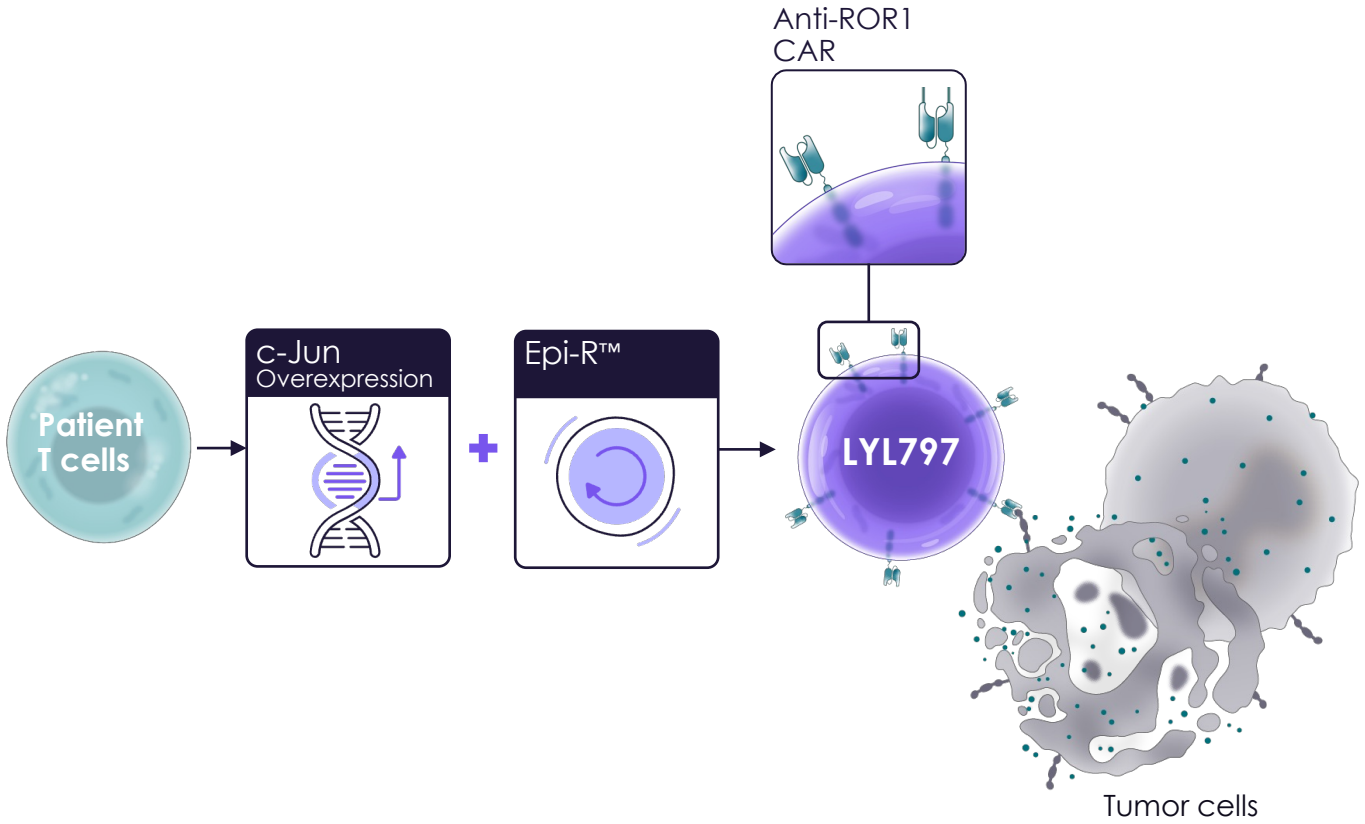
LYL797: Clinical Program Supported by Robust Preclinical Data

ROR1 CAR T cell + c-Jun + Epi-R



Key Differentiators

Tumor reduction, enhanced cytokine production, and tumor infiltration in aggressive NSCLC syngeneic model with c-Jun CAR T cells

Stem-like phenotype, durability, and enhanced cytotoxicity with Epi-R technology

Prolonged survival by combining c-Jun and Epi-R technologies (LYL797) in xenograft NSCLC animal model

Abbreviations: CAR, chimeric antigen receptor; NSCLC, non-small cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1.

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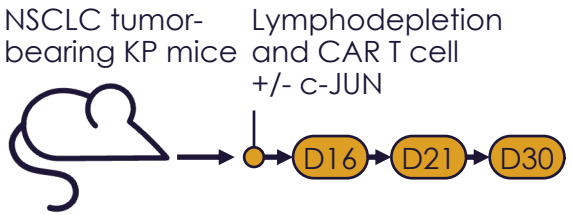
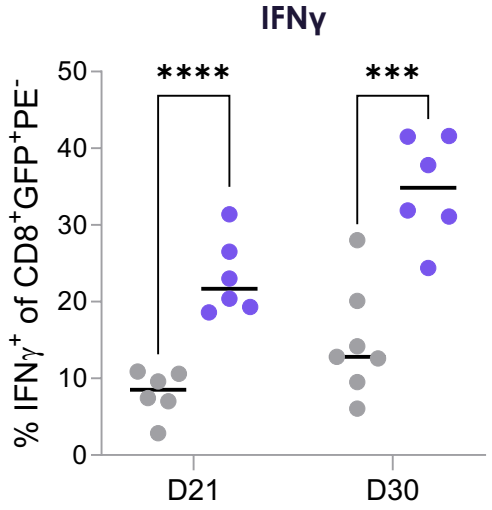
LYL797: Superior Preclinical Efficacy Demonstrated With c-Jun Overexpressing ROR1 CAR T Cells in Aggressive NSCLC Model

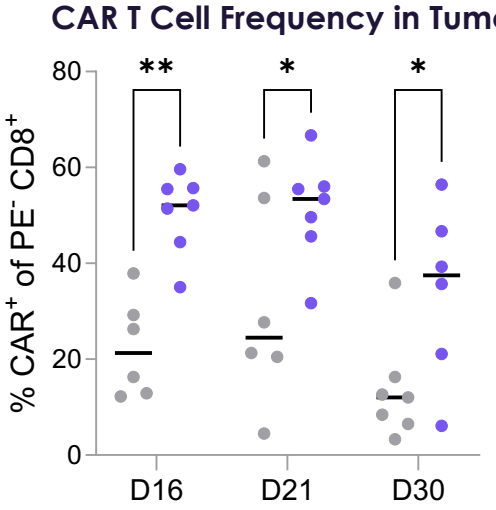


- Syngeneic KRAS/p53 model that recapitulates human NSCLC
- Multifocal tumors and suppressive microenvironment that are similar to human NSCLC
- Tumor regression rarely achieved in this model

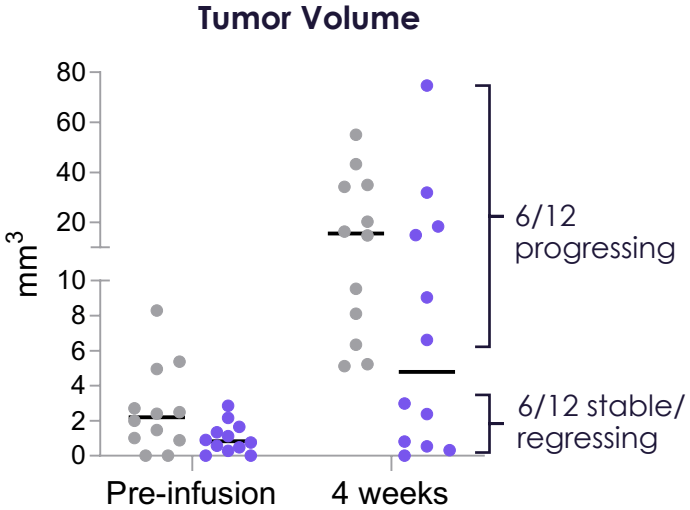
Enhance Intratumoral Function



Enhanced Infiltration



Tumor Control in 50% of Mice



WT ROR1 CAR T cells
c-Jun ROR1 CAR T cells

WT CAR T cell-treated mice
c-Jun ROR1 CAR T cell-treated mice

Riddell Lab, Fred Hutch, unpublished data. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001
Abbreviations: CAR, chimeric antigen receptor; D, day; NSCLC, non-small cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1.

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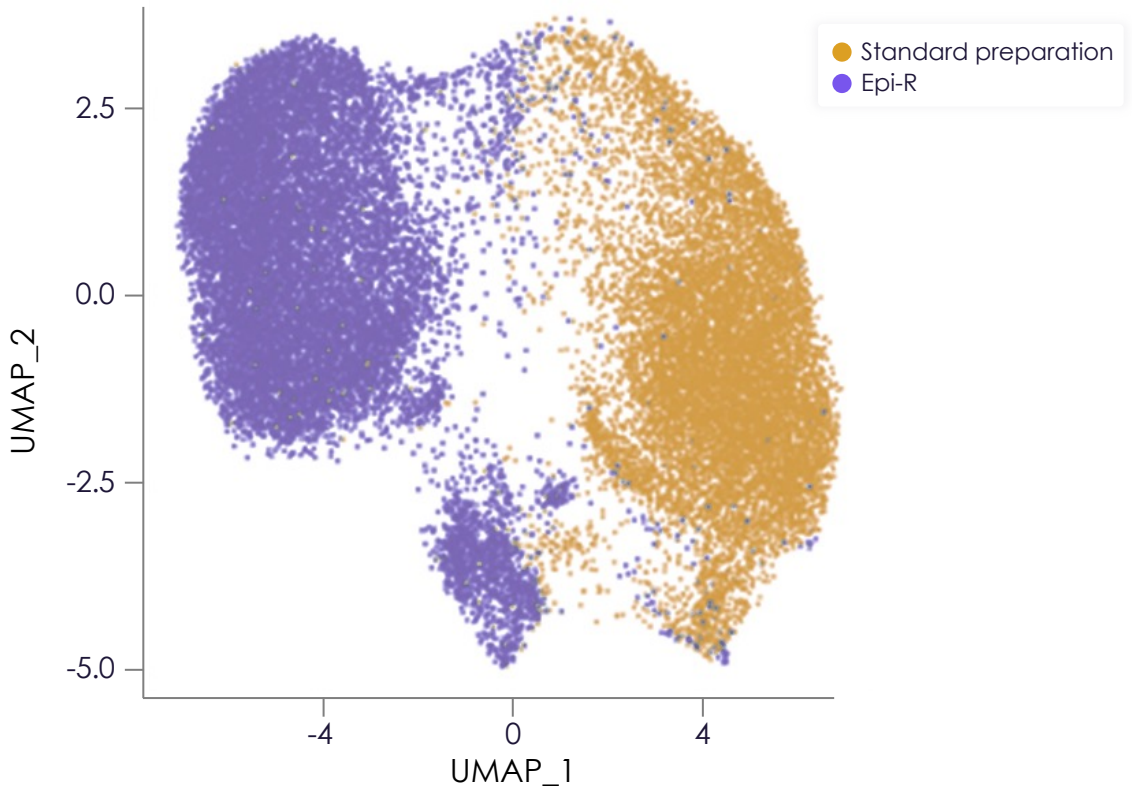
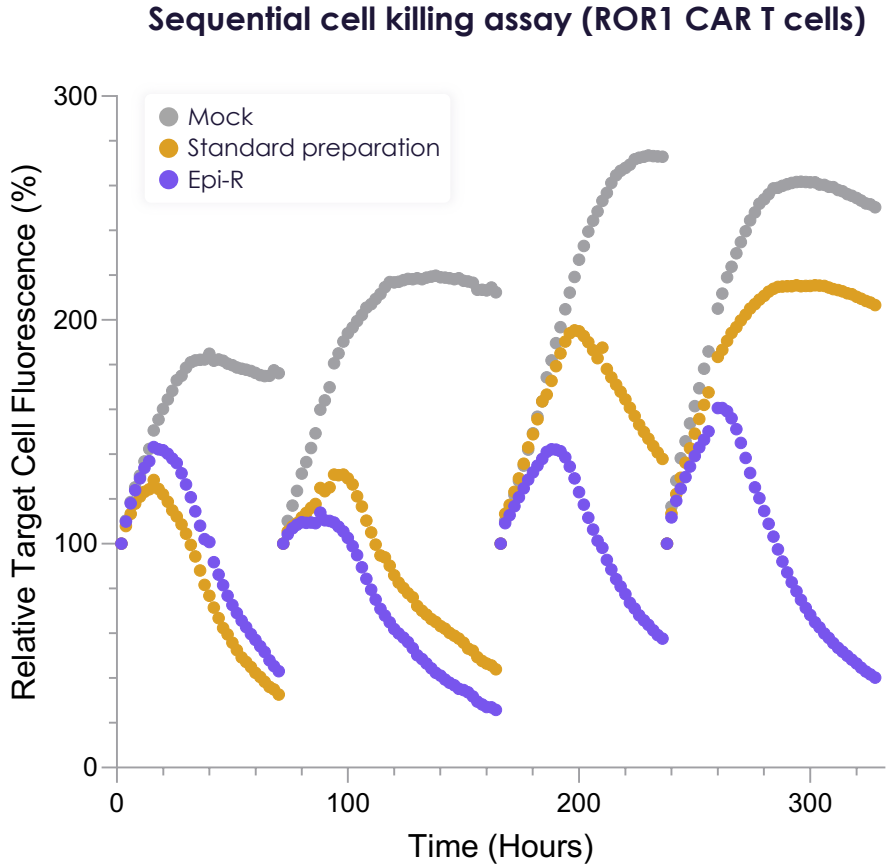
Epi-R Technology Produces Transcriptionally Distinct Populations of T Cells that Resist Exhaustion and Maintain Cytotoxicity

Distinct Gene Expression Profile of Epi-R Expanded Cells vs. Standard Preparation



Epi-R Expanded Cells Demonstrate Prolonged Cytotoxicity After Removal From Epi-R Conditions



Left graph: Park et al., AACR 2022. Right graph: Tumor target: H1975.
Abbreviation: UMAP: Uniform manifold approximation and projection.

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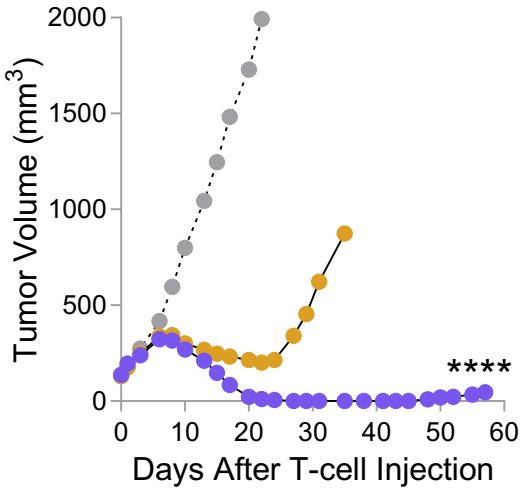
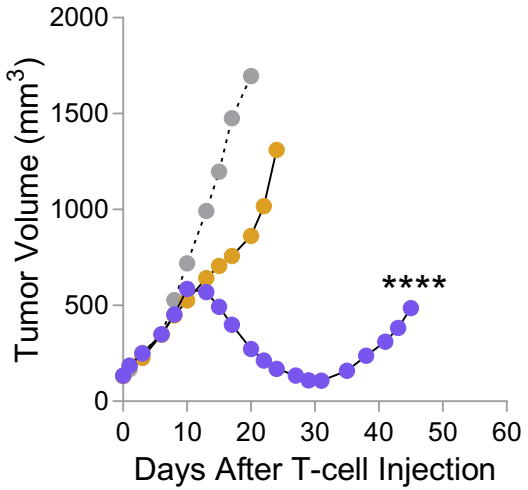
LYL797: Combining c-Jun and Epi-R Reprogramming Technologies Prolongs Survival in NSCLC (H1975) Xenograft Model

LYL797 Reduces Tumor Burden

High Dose
5 x 10^6 CAR T cells

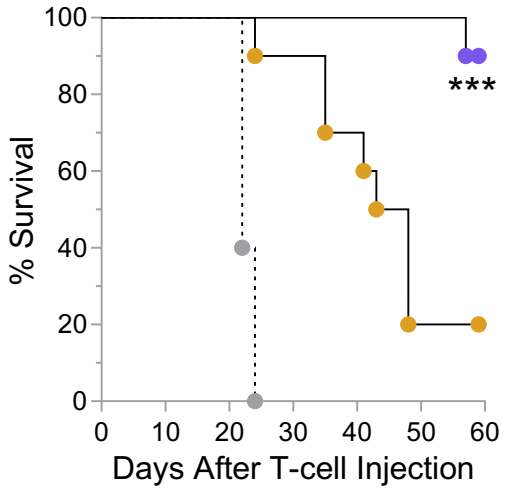


Low Dose
2.5 x 10^6 CAR T cells

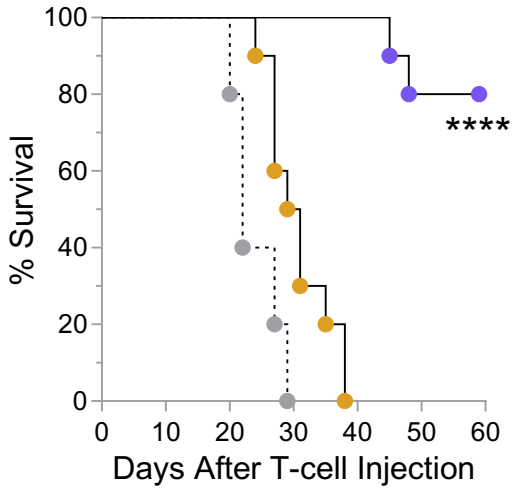


LYL797 Prolongs Survival

High Dose
5 x 10^6 CAR T cells



Low Dose
2.5 x 10^6 CAR T cells



Mock Control ROR1 CAR T LYL797

Park et al., ASGCT 2022. *P<0.05, ***P<0.001, ****P<0.0001
Abbreviations: CAR, chimeric antigen receptor; NSCLC, non-small cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1.

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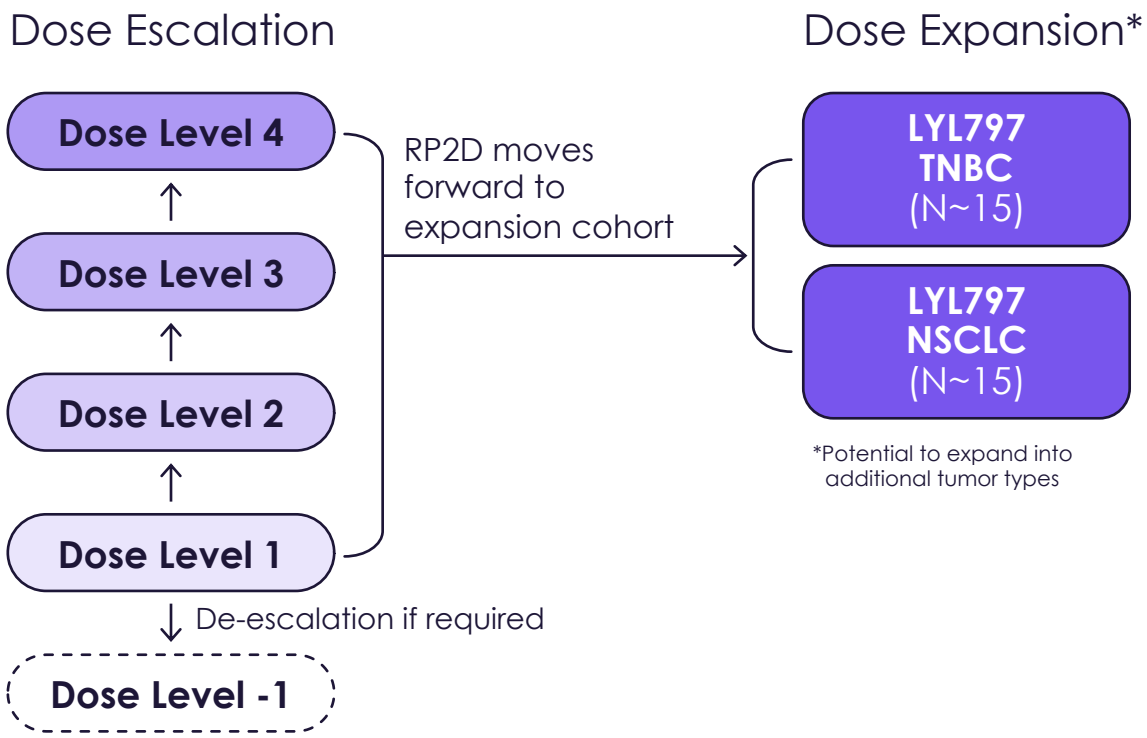
LYL797: CAR T-cell Phase 1 Trial Design

NCT05274451

Clinical Trial Design (mTPI-2)



Patient Population

- Relapsed/refractory TNBC patients who have failed two lines of therapy
- Relapsed/refractory NSCLC patients who have failed one line of therapy
- ROR1 positive

Study Objectives

- Patient safety and tolerability
- Overall response rate and durability
- Recommended Phase 2 dose
- CAR T-cell pharmacokinetics
- Assessment of cytotoxicity and duration of T-cell function

Spigel et al, SITC 2023

Abbreviations: ROR1, receptor tyrosine kinase-like orphan receptor 1; CAR, chimeric antigen receptor; m-TPI-2, Modified Toxicity Probability Interval; NSCLC, non-small cell lung cancer; RP2D, Recommended phase 2 dose; TNBC, triple-negative breast cancer.

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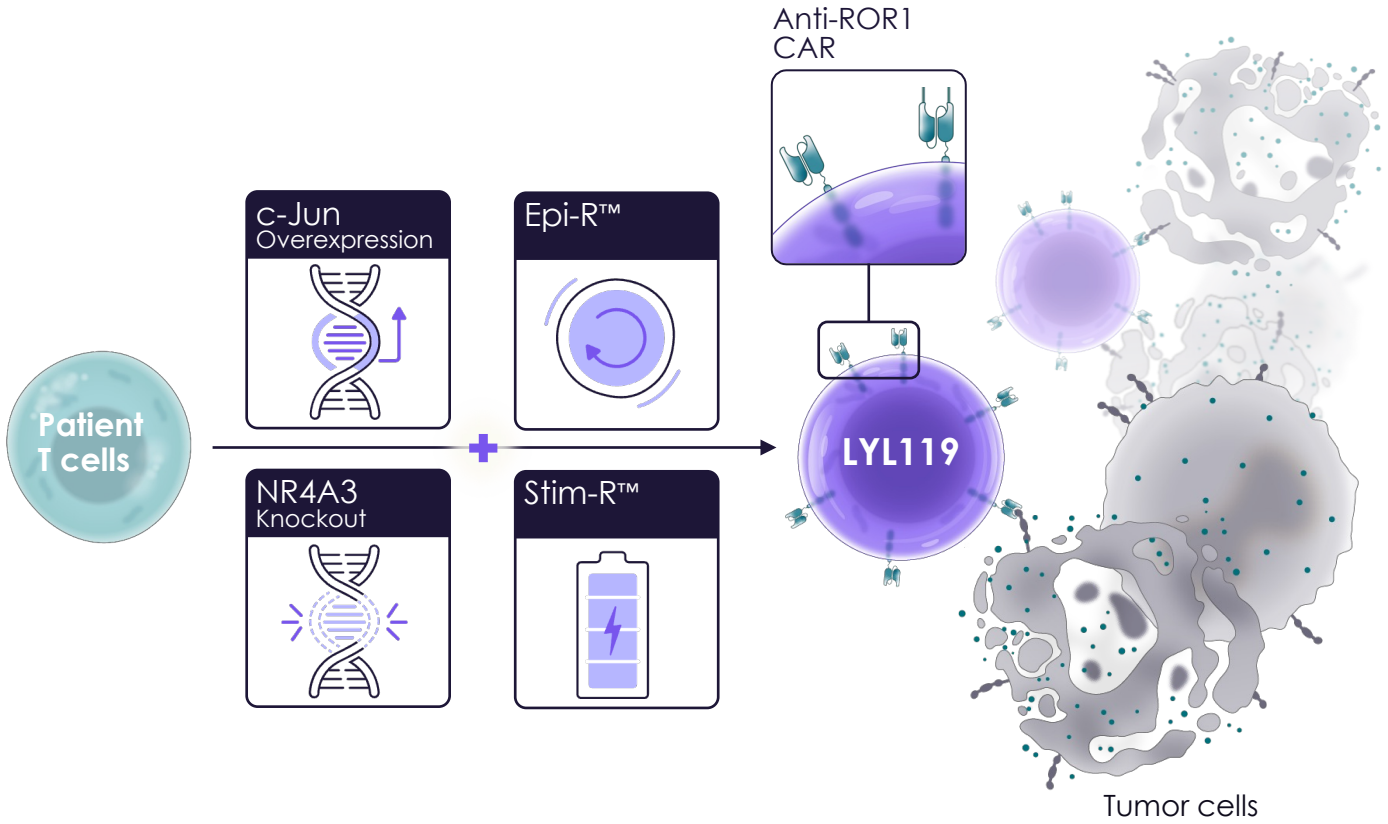
LYL119: Incorporates Novel Stackable Technologies Designed to Improve Potency and Cytotoxicity

ROR1 CAR T cell + c-Jun + NR4A3 KO + Epi-R + Stim-R



Key Differentiators

Combining NR4A3 knockout and c-Jun overexpression further reduces T-cell exhaustion and enhances cytotoxicity in preclinical models:

- Reducing NR4A expression enhances T-cell function associated with increased expression of AP-1–regulated genes
- NR4A family transcription factors contribute to T-cell exhaustion by restraining c-Jun/ AP-1 activity

Stim-R CAR T cells demonstrate prolonged persistence and enhanced cytotoxicity in response to serial antigen stimulation in preclinical models

Lam et al., SITC, 2023. Chen J, et al. *Nature*. 2019; Tirosh I, et al. *Science*. 2016; Liu X, et al. *Nature*. 2019; Odagiu I, et al. *Proc Natl Acad Sci USA*.
Abbreviations: AP-1, activator protein 1; CAR, chimeric antigen receptor; NR4A3, The nuclear receptor 4A3; NSCLC, non-small cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1.

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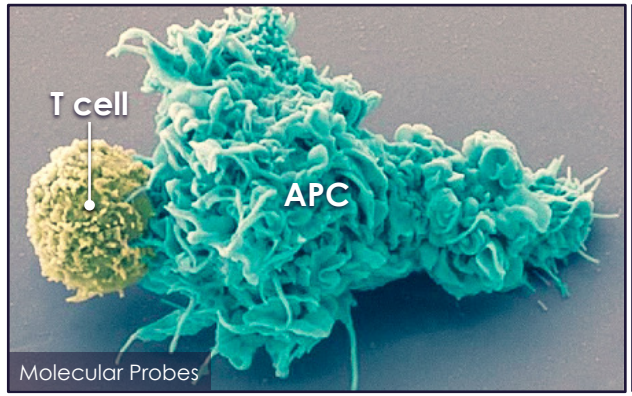
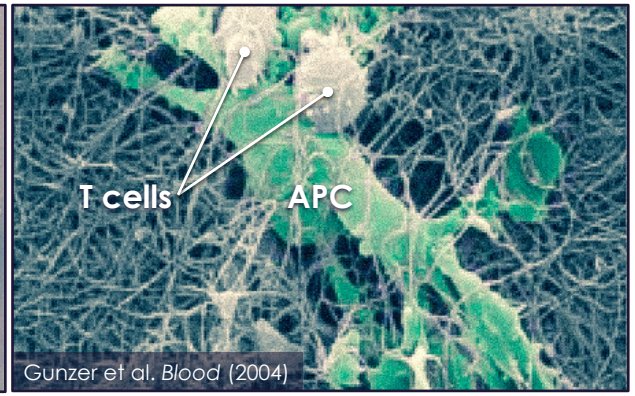
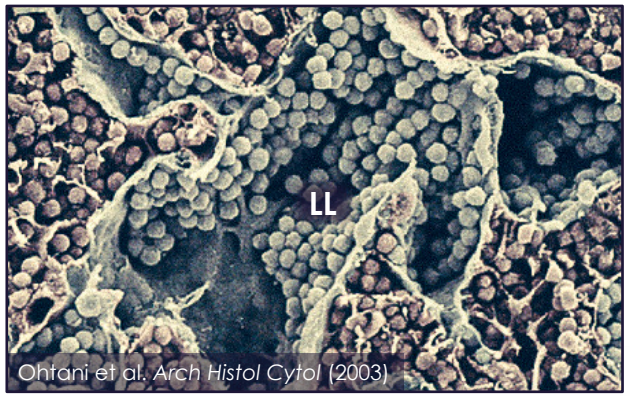
LYL119: Stim-R Closely Emulates Natural Antigen Presentation

Breakthrough in T-cell Activation Technology

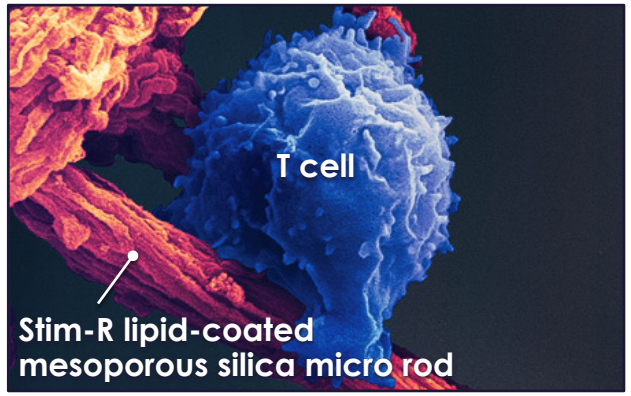
Natural Antigen Presentation

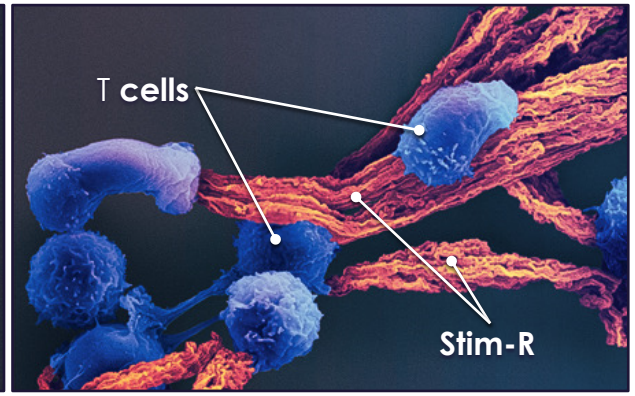


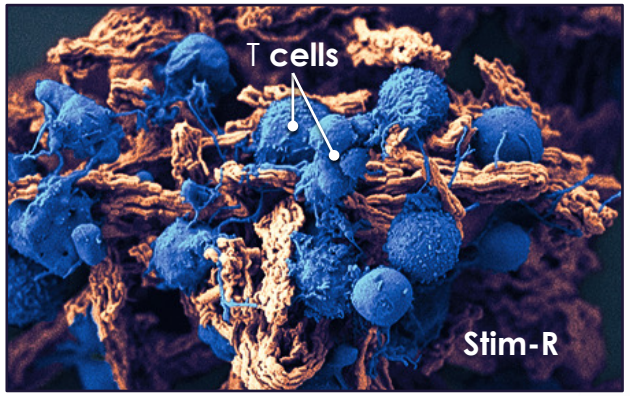




Stim-R







Cheung et al.
Nature Biotech (2018)

Abbreviations: APC, antigen presenting cell; LL, lymphatic labyrinths.

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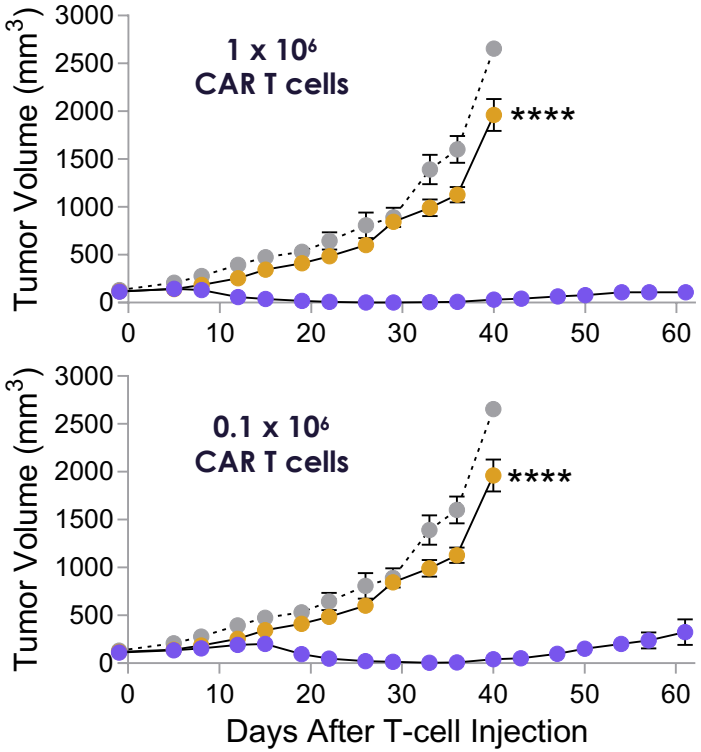
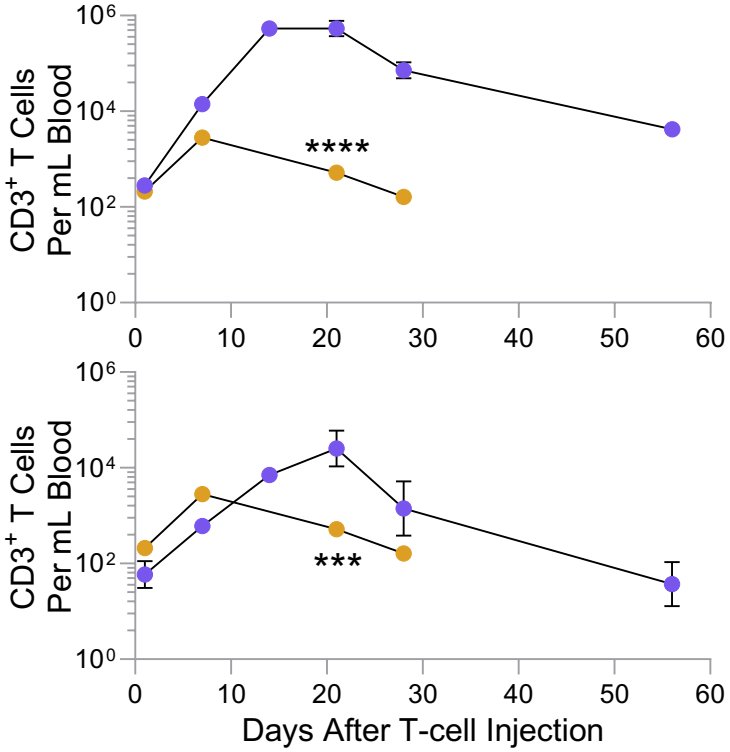
LYL119: Eliminated H1975 (NSCLC) Xenograft Tumors and Improved Survival, Even at Low Doses

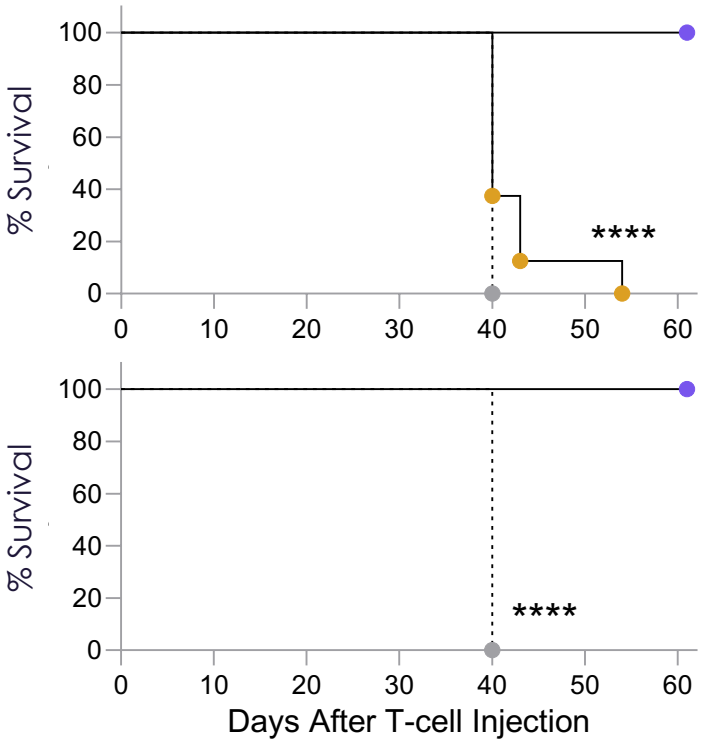
Elimination of Xenograft Tumors at Low and Lower CAR T-cell Doses



Superior T-cell Expansion In Vivo



Significantly Improved Animal Survival at the Lower 0.1 x 10⁶ CAR T-cell Dose



PBS Mock non-transduced (Epi-R + Stim-R) 1.42 x 10⁶ cells LYL119 (NR4A3 KO + c-Jun + Epi-R + Stim-R)

Lam et al., SITC, 2023
*P<0.05, **P<0.01, ****P<0.0001
Abbreviations: CAR, chimeric antigen receptor; NSCLC, non-small cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1.

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Harnessing Tumor Infiltrating Lymphocytes (TIL) to Fight Cancer

LYL845

A novel epigenetically reprogrammed TIL product candidate designed for differentiated potency and durability

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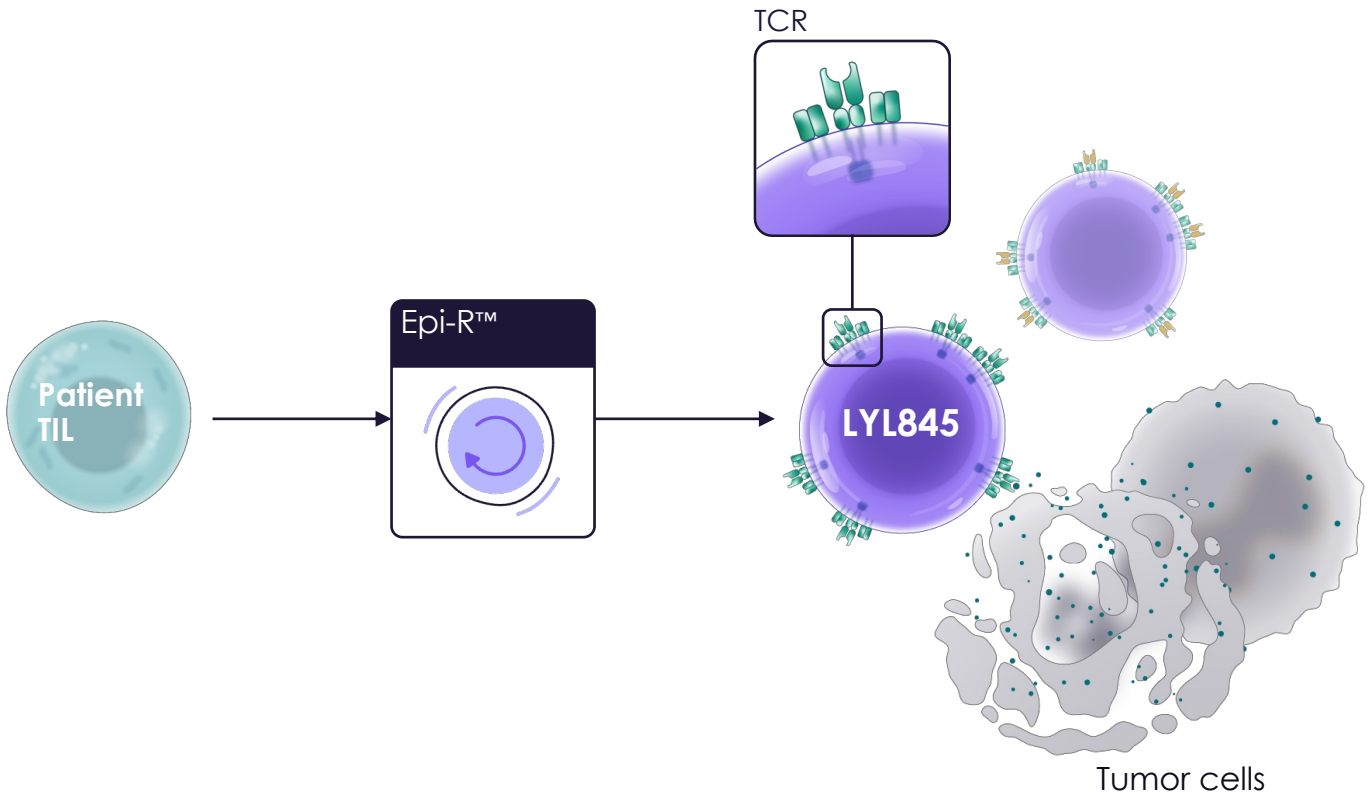
LYL845: Clinical Program Supported by Robust Preclinical Data



Key Differentiators

Robust TIL expansion across both immunologically hot and cold tumors

Phenotypes (stemness markers and cytotoxic cells) associated with clinical responses

Preserved polyclonal tumor reactive cells

Improved tumor cell killing in vivo

Abbreviations: TCR, T-cell receptor; TIL, tumor-infiltrating lymphocytes.

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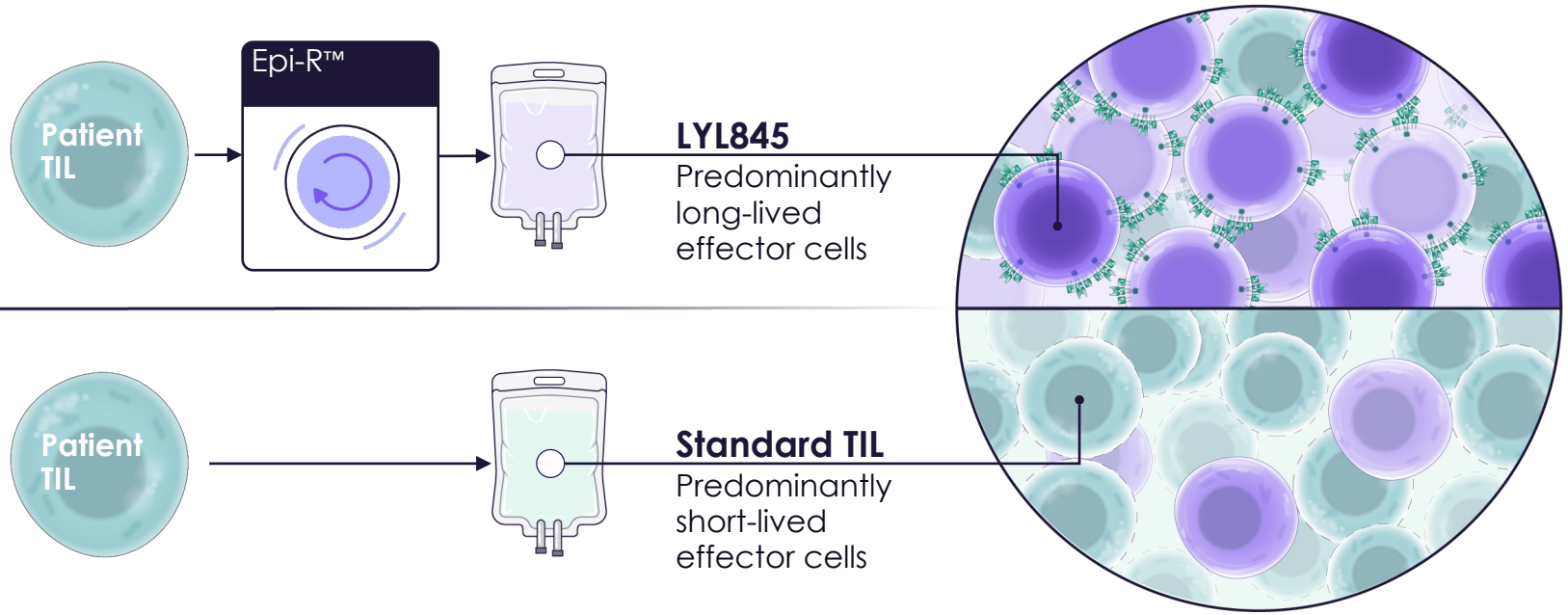
LYL845: A Novel and Differentiated TIL Product Candidate

Lyell Epi-R Protocol Comprises

- ✓ Proprietary media
- ✓ Optimized cytokine compositions
- ✓ Well-defined cell activation and expansion protocols



Abbreviations: TIL, tumor-infiltrating lymphocytes.

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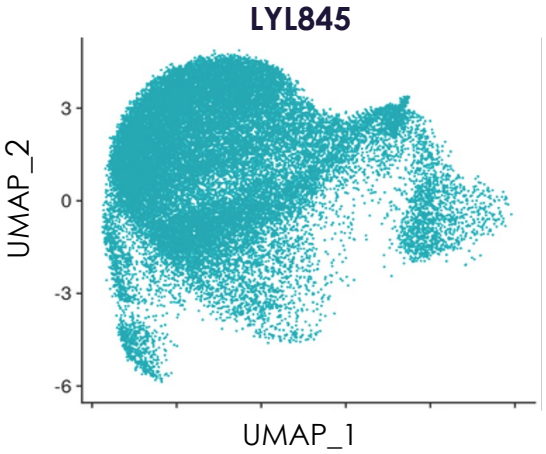
LYL845: Enriched for Stem-like TIL

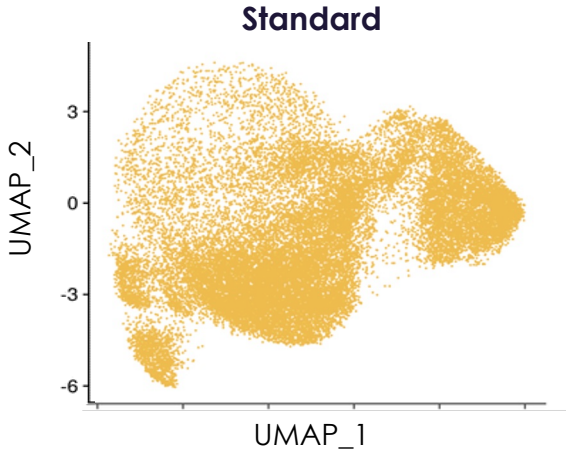
Transcriptomic data of TIL generated from 5 donor tissues using either standard or LYL845 Epi-R process (4 melanoma and 1 NSCLC)

LYL845

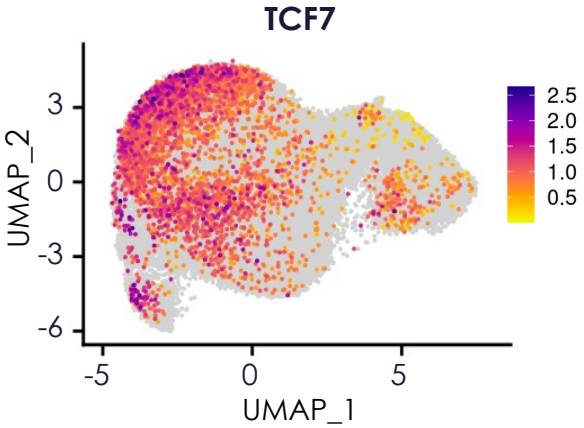


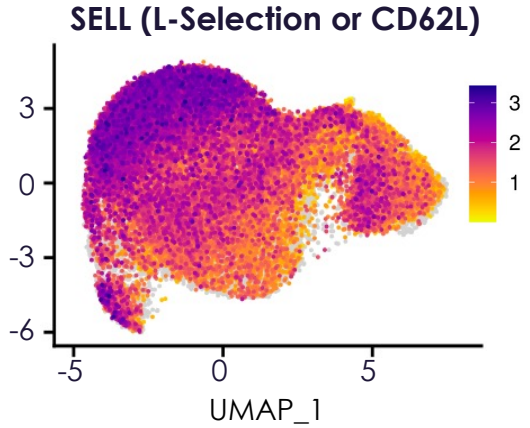
- LYL845 TIL express genes associated with stem-like phenotype (TCF7 and SELL)

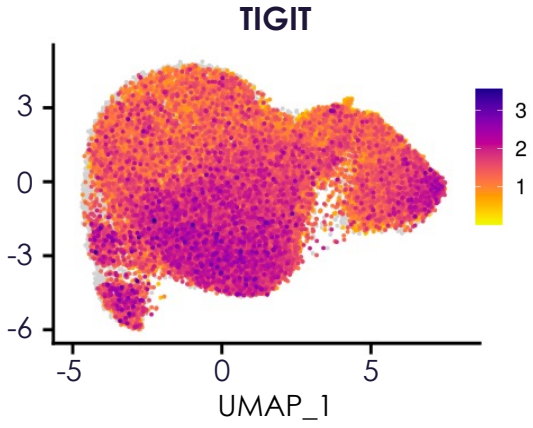
Standard TIL

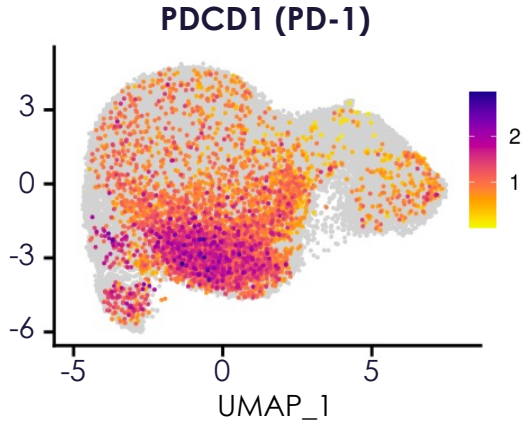


- Standard TIL express genes associated with exhaustion (TIGIT and PD-1)









Lyell data on file
Abbreviation: UMAP: Uniform manifold approximation and projection.

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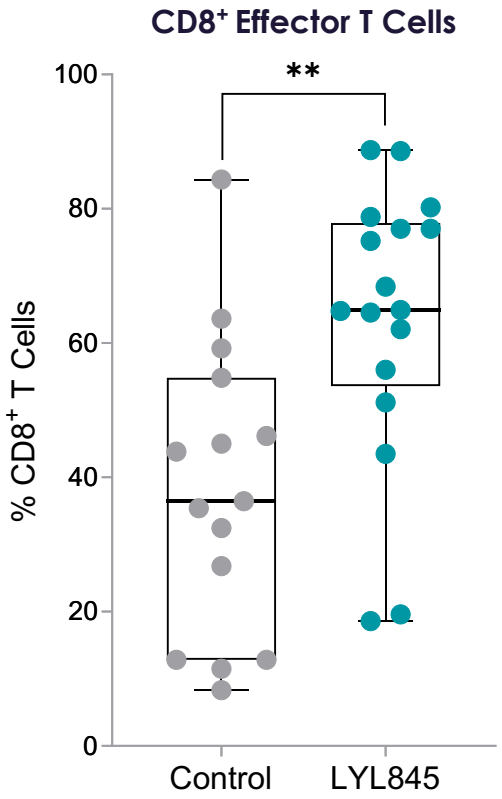
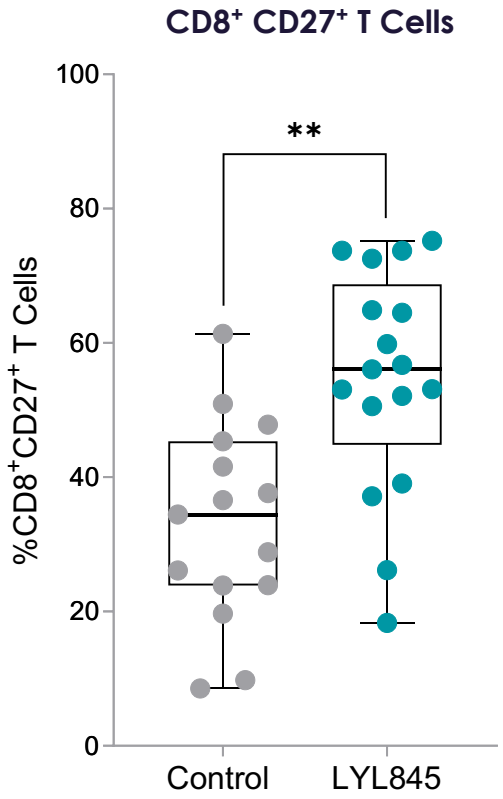
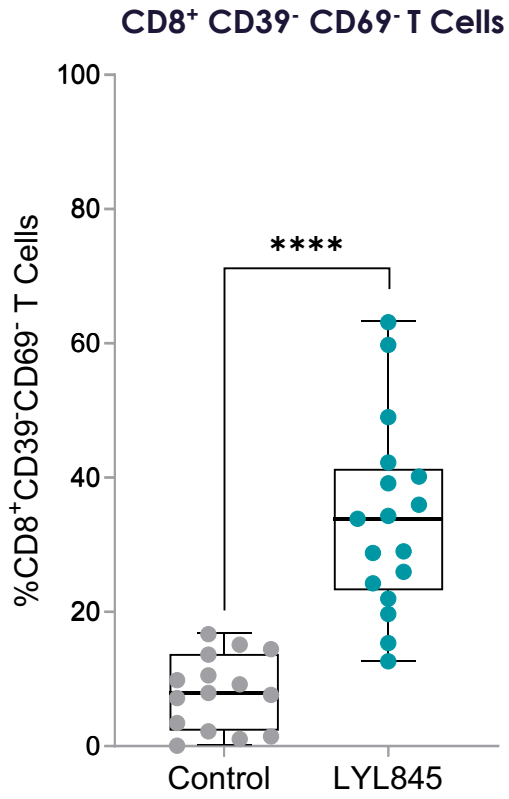
LYL845: Enriched for Cells With Characteristics Associated With Improved Clinical Outcomes from the Literature

Increased % of Cytotoxic Cells



Increased % of Stem-like T Cells





Krishna et al., *Science* Dec. 2020. Patel et al., SITC 2022.
*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001

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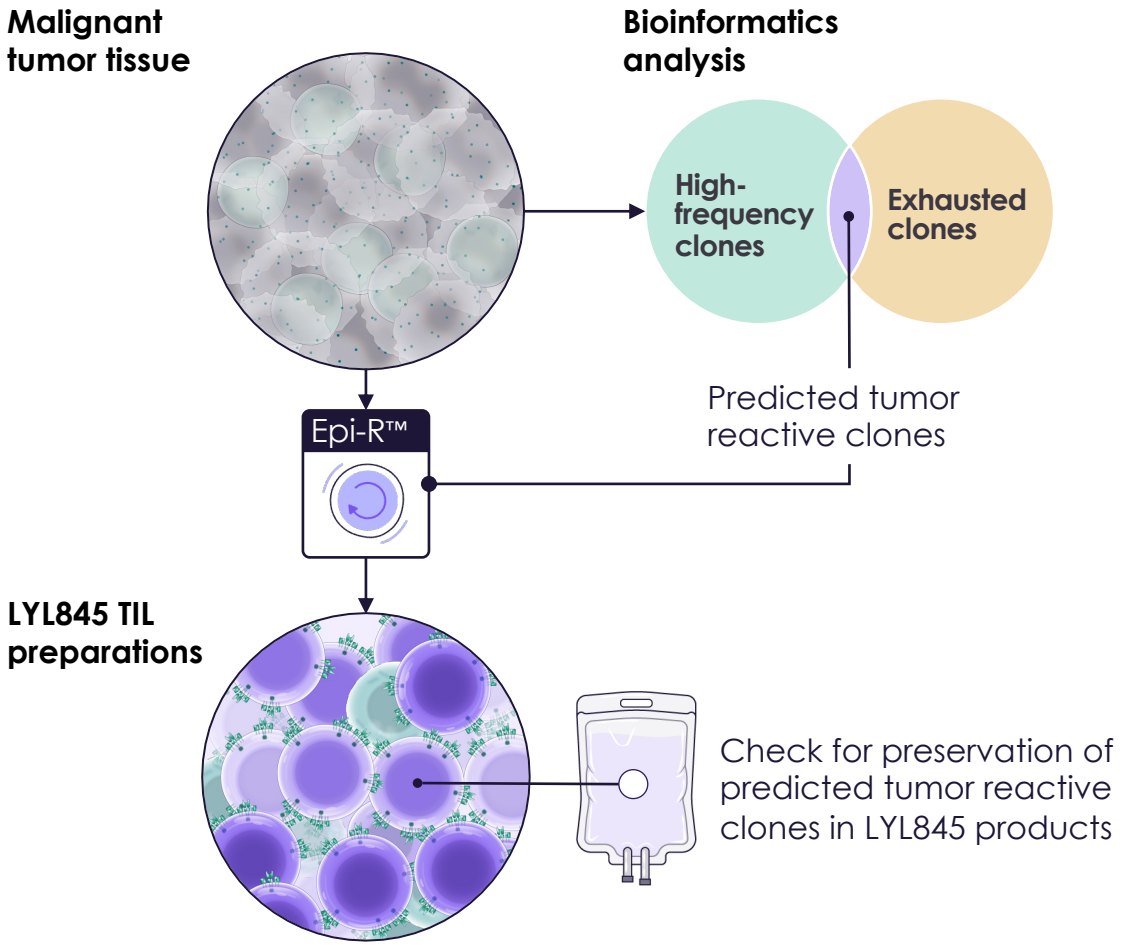
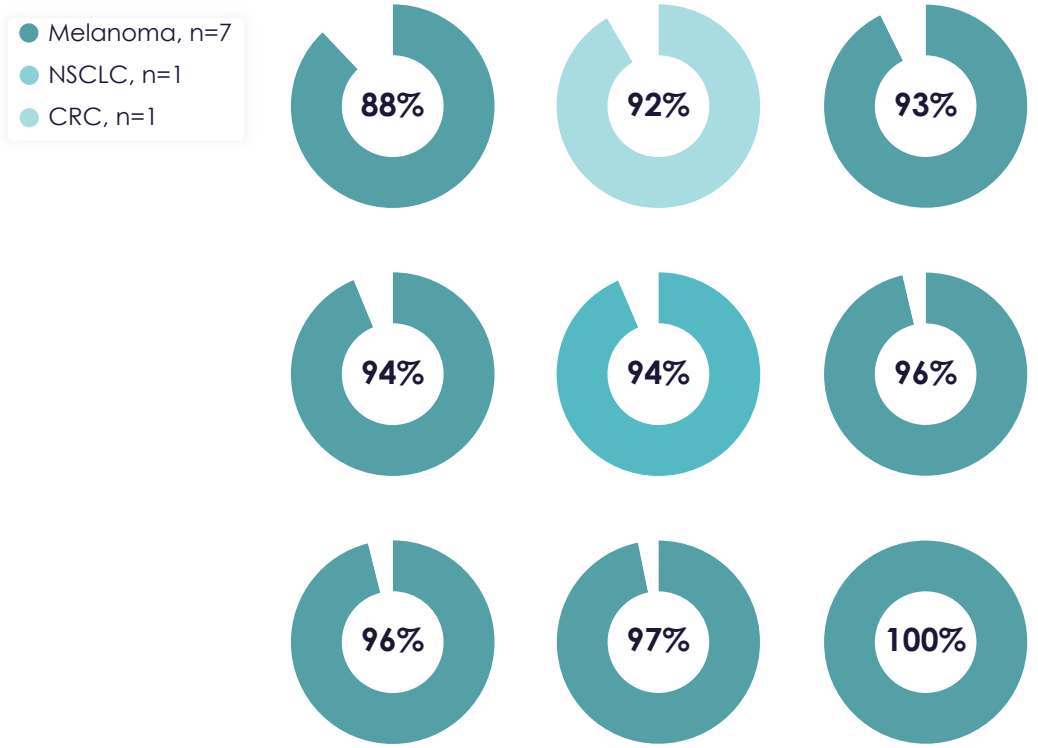
LYL845 TIL Preserve ~94% of Predicted Tumor-reactive Clones to Enable Targeting of Heterogeneous Solid Tumors



% of Tumor-reactive Clones Preserved in Clinical Scale TIL Products

Donor, N=9



Harris et al., SITC 2022. Pasetto et al., *CIR* 2016. Lowrey et al., *Science* 2022, Oliveira et al., *Nature* 2021.
Abbreviations: CRC, colorectal cancer; NSCLC, non-small cell lung cancer; TIL, tumor-infiltrating lymphocytes.

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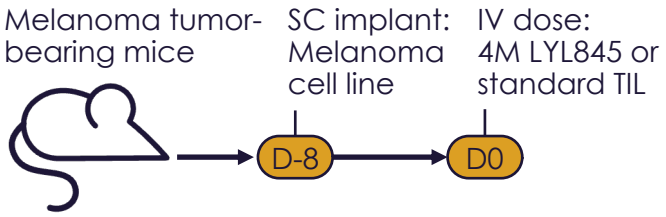
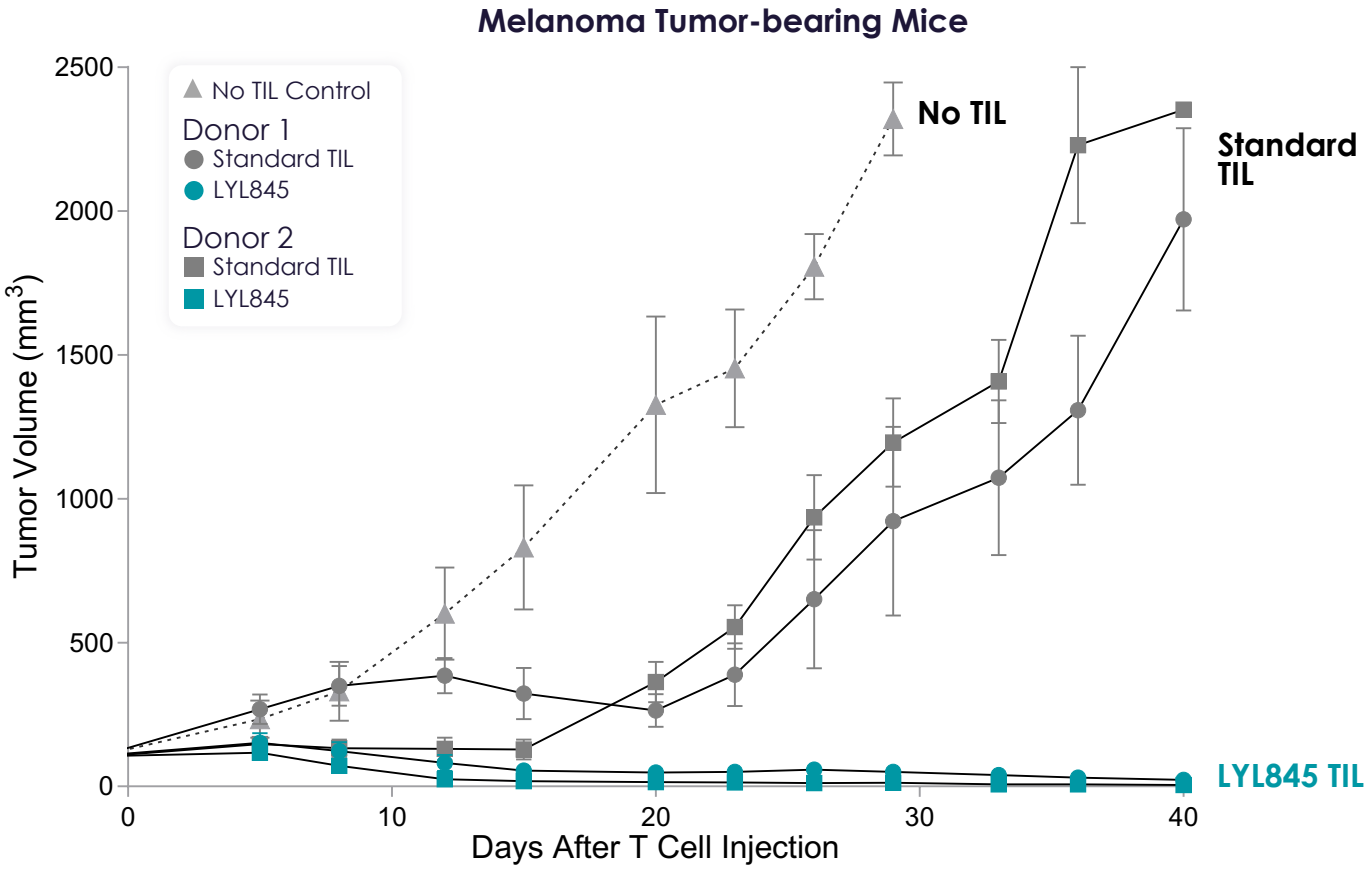
LYL845: In Vivo Efficacy is Superior With LYL845 TIL Using Epi-R Process Compared to TIL Using Standard Process in Novel Model



- Two refractory melanoma donor samples were collected
- TIL products were generated from each sample using the standard or Lyell Epi-R (LYL845) process

LYL845 Eliminated Tumor Growth



Lyell data on file.
Abbreviations: IV, intravenous; M, million; SC, subcutaneous; TIL, tumor-infiltrating lymphocytes.

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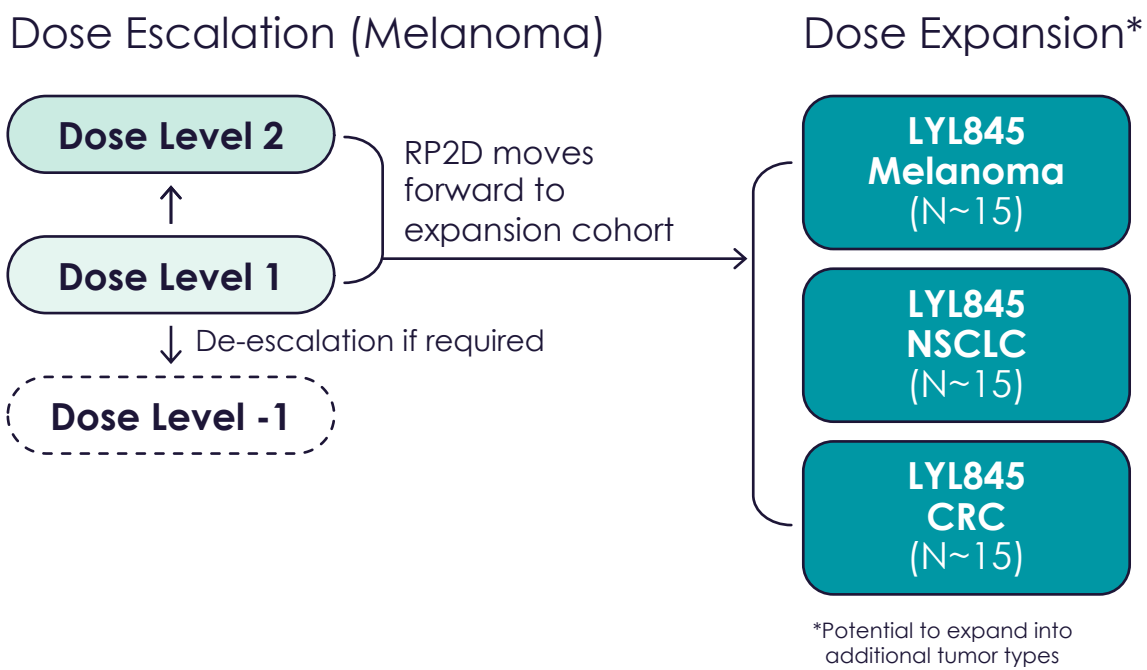
LYL845: TIL Phase 1 Trial Design

NCT05573035

Clinical Trial Design (mTPI-2)



Patient Population

- Relapsed/refractory metastatic or locally advanced solid tumors:
  - Melanoma
  - NSCLC
  - CRC

Study Objectives

- Patient safety and tolerability
- Overall response rate and durability
- Recommended Phase 2 dose
- Evaluation of expansion, phenotype, clonal diversity, and persistence

Samhouri et al, SITC 2023.
Abbreviations: CRC, colorectal cancer; m-TPI-2, Modified Toxicity Probability Interval; NSCLC, non-small cell lung cancer; RP2D, Recommended phase 2 dose; TIL, tumor-infiltrating lymphocytes.

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Advancing manufacturing strategy to deliver for the future

Lyell is currently producing Phase 1 clinical supply at LyFE manufacturing center

Capabilities include CAR T cell, TIL, GMP vector, and a capacity for ~500 doses/year depending on product mix

Partnered with Cellares

Automated manufacturing processes to rapidly and cost-effectively scale to meet anticipated patient demand for our CAR T-cell product candidates

Proof of concept tech transfer for the manufacture of LYL797 CAR T-cell therapy

Single Cell Shuttle capacity of up to ~800 LYL797 cell doses/year

Abbreviations: CAR, chimeric antigen receptor; GMP, good manufacturing practice; TIL, tumor-infiltrating lymphocytes.

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Advancing T-cell Therapies for Solid Tumors

Wholly-owned product candidates addressing large patient populations

Expanding clinical pipeline; data from two programs in 2024

LYL797

ROR1-targeted CAR T cells for TNBC, NSCLC, and other solid tumors

Ph 1 clinical & translational data from 20+ patients in 1H24

LYL845

Tumor Infiltrating Lymphocytes (TIL) for melanoma, NSCLC, and CRC

Ph 1 clinical & translational data in 2H24

LYL119

ROR1-targeted CAR T cells for ROR1+ solid tumors

IND filing in 1H24

Scientific expertise, capabilities and capital to drive continuous innovation and ability to scale

Multiple genetic and epigenetic technology platforms to improve the function of T cells

- Designed to generate T cells that resist exhaustion and have durable stemness

Executing a scalable manufacturing strategy

- Lyell LyFE center producing clinical supply
- Shorten TIL manufacturing time in 2024
- Cellares collaboration to automate and scale manufacturing

Strong balance sheet

- ~$563 million of cash*
- Runway into 2027 through multiple clinical readouts

*Cash, cash equivalents and marketable securities as of 12/31/2023

Abbreviations: CAR, chimeric antigen receptor; CRC, colorectal cancer; IND, investigational new drug; NSCLC, non-small cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1; TIL, tumor-infiltrating lymphocytes; TNBC, triple-negative breast cancer.

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It’s all about the cells.

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