Forward-looking Statements

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,” “forecasts,” “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 submit planned INDs or initiate or progress clinical trials 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 Quarterly Report on Form 10-Q for the quarter ended September 30, 2023 and subsequent filings with the SEC.
Advancing T cell therapies for solid tumors
Clinical data from two lead programs in 2024

Two clinical programs: wholly-owned, addressing large patient populations

LYL797: ROR1 targeted CAR T cell
• 1H2024: P1 clinical & translational data from 20+ patients
• TNBC, NSCLC

LYL845: Tumor Infiltrating Lymphocyte (TIL)
• 2024: P1 clinical & translational data
• Melanoma, NSCLC, CRC

Executing a scalable manufacturing strategy

Lyell’s LyFE center producing current clinical supply
• 2024: Epi-R P2 process to shorten TIL manufacturing time without impacting cell number and phenotype

Planning for the future
• CAR T cell proof-of-concept collaboration with Cellares to build scale and reduce cost

Portfolio of novel reprogramming platform technologies

• 1H2024: IND filing for LYL119, ROR1 targeted CAR T cell designed for enhanced potency and durability; using four of our technologies

~$598 million in cash

• Runway into 2027

ROR1, receptor tyrosine kinase-like orphan receptor 1; TNBC, triple-negative breast cancer; NSCLC, non-small-cell lung cancer; CRC, colorectal cancer; P1, Phase 1
Lyell is developing two types of personalized cell therapy:
Focused on getting the T-cells right

**OUR GOAL: Reprogram T cells to defeat solid tumors**

- **CAR T cells**
  - Resist exhaustion
  - Durable cytotoxicity
  - Self-renewal
  - Persistence

- **Tumor-infiltrating lymphocytes**
  - Durable cytotoxicity
  - Maintain polyclonality
  - Right phenotype
  - Hot and cold tumors

**CAR, chimeric antigen receptor**

CAR, chimeric antigen receptor
Lyell’s T-cell reprogramming technologies are designed to address primary barriers to success in solid tumors

TO ACHIEVE SUCCESS IN SOLID TUMORS, CELL THERAPY MUST:

RESIST EXHAUSTION, RETAIN FUNCTION

Maintain cancer cell killing in the immunosuppressive tumor microenvironment

ENHANCE DURABLE STEMNESS

Increase ability to self-renew and persist to drive durable tumor cytotoxicity
Solid tumors drive T cells down a path to exhaustion

Hematologic malignancy

Adequate cell expansion, persistence, and tumor killing

Inadequate expansion, driven to exhaustion, and lack of durability

Tumor cell clearance

Lack of T-cell function; cancer cells persist

Infusion

Autologous CAR T cell

Riddell et al, Keystone, 2020
Stackable technologies designed to generate potent T cells with durable function

**GENETIC REPROGRAMMING**
- c-Jun overexpression
- NR4A3 knockout

C-Jun and NR4A3 regulate the activator protein 1 (AP-1) transcription factor pathway, which plays a key role in T-cell effector function.

**EPIGENETIC REPROGRAMMING**
- Epi-R™
- Stim-R™

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

A clinical-stage company with a growing pipeline of novel therapies for solid tumors

<table>
<thead>
<tr>
<th>Product Candidate/ Modality</th>
<th>Target</th>
<th>Genetic Reprogramming</th>
<th>Epigenetic Reprogramming</th>
<th>Target Indications</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2 / Pivotal</th>
<th>Next Expected Milestone</th>
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<td>LYL797 CAR T Cell</td>
<td>ROR1</td>
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<td>TNBC, NSCLC</td>
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<td></td>
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<td>Initial data from 20+ patients in 1H 2024</td>
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<td>Other Solid Tumors</td>
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<td>LYL119 CAR T Cell</td>
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<td>ROR1+ Solid Tumors</td>
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<td>Submit IND in 1H 2024</td>
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<tr>
<td>LYL845 TIL</td>
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<td>Melanoma, CRC, NSCLC</td>
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<td>✓ ✓ ✓ ✓ ✓ ✓</td>
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<td>Initial data in 2024</td>
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<tr>
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</tbody>
</table>

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

90% Cancer deaths caused by solid tumors

<2 Years before cancer progresses

<3 Years most metastatic cancer patients live after diagnosis

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
Lyell product candidates target large unmet needs
~500K new cases and ~180K US deaths annually

<table>
<thead>
<tr>
<th>Condition</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIPLE-NEGATIVE BREAST CANCER</td>
<td>15% of breast cancer diagnoses in the US each year, ~40,000 new cases, ~10,000 deaths</td>
</tr>
<tr>
<td>NON-SMALL CELL LUNG CANCER</td>
<td>84% of new lung cancer diagnoses each year, ~200,000 new cases, ~110,000 deaths</td>
</tr>
<tr>
<td>MELANOMA</td>
<td>80% of all skin cancer-related deaths, ~100,000 new cases, ~8,000 deaths</td>
</tr>
<tr>
<td>COLORECTAL CANCER</td>
<td>3rd most common form of cancer, ~150,000 new cases, ~53,000 deaths</td>
</tr>
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LYL797
LYL797 & LYL845
LYL845
LYL845

National Cancer Institute and the American Cancer Society and are based on US cases. (2022)
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
LYL797 CAR T cell Phase 1 trial design

- **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
  - Assessment of cytotoxicity and duration of T-cell function
  - Overall response rate and durability
  - Recommended phase 2 dose
  - CAR T cell pharmacokinetics

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**CLINICAL TRIAL DESIGN (mTPI-2)**

- **Dose Escalation**
  - Dose Level 1
  - Dose Level 2
  - Dose Level 3
  - Dose Level 4

- **Dose Expansion**
  - LYL797 TNBC (N = ~15)
  - LYL797 NSCLC (N = ~15)

- The RP2D moves forward to expansion cohort.
- Potential to expand into additional tumor types: NCT05274451

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Spigel et al, ESMO 2022
mTPI-2, modified toxicity probability interval 2; NSCLC, non-small-cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1; TNBC, triple-negative breast cancer; RP2D, recommended Phase 2 dose
ROR1 is highly expressed in many human cancers and correlates with a poor prognosis

ROR1 expression

- **~60%** Triple-negative breast cancer
- **~50%** Ovarian cancer
- **~40%** Non-small cell lung cancer
- **~95%** Chronic lymphocytic leukemia

In previous clinical trials and a non-human primate ROR1 CAR T cell toxicity study, no on-target off-tumor toxicity from ROR1-targeted therapies have been reported.

ROR1, receptor tyrosine kinase-like orphan receptor 1
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**

- 15% of breast cancer diagnoses/year
- ~40,000 new cases / ~10,000 deaths

**NON-SMALL CELL LUNG CANCER**

- 84% of new lung cancer diagnoses/year
- ~200,000 new cases / ~110,000 deaths

ROR1, receptor tyrosine kinase-like orphan receptor 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%
LYL797 clinical program supported by robust preclinical data

**Key differentiators**

- **Tumor reduction, enhanced cytokine production and tumor infiltration** in aggressive NSCLC syngeneic animal model with c-Jun

- **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
Superior preclinical efficacy demonstrated with c-Jun overexpressing ROR1 CAR T cells in aggressive NSCLC model

- Syngeneic Kras/p53 model that recapitulates human NSCLC
- Also recapitulates the barriers in treating human NSCLC with the ROR1 CAR T cells
- Extremely difficult model in which to achieve tumor regression

Enhanced intratumoral function

Enhanced infiltration

Tumor control in 50% of mice

Riddell Lab, Fred Hutch, unpublished data
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

Sequential cell killing assay (ROR1 CAR T cells)

Tumor target: H1975
LYL797 combines c-Jun and Epi-R™ reprogramming technologies to prolong survival in NSCLC (H1975) xenograft model

**LYL797 reduces tumor burden**

![Graph showing tumor volume (mm³) vs. days after T-cell injection for different CAR T doses (5 x 10^6 and 2.5 x 10^6) with and without LYL797. The graph indicates a significant reduction in tumor volume with LYL797 treatment.]

*** is p<.001    **** is p<.0001

**LYL797 prolongs survival**

![Graph showing % survival vs. days after T-cell injection for different CAR T doses (5 x 10^6 and 2.5 x 10^6) with and without LYL797. The graph shows a significant improvement in survival with LYL797 treatment.]

*** is p<.001    **** is p<.0001

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Park et al., ASGCT 2022
Novel stackable technologies designed to improve potency and durability

LYL119: Innovative ROR1 CAR T cell product candidate designed for enhanced cytotoxicity
LYL119 incorporates novel stackable technologies designed to improve potency and durability

**Key Differentiators**

- Combining NR4A3 knockout and c-Jun overexpression further **reduces T cell exhaustion and enhances cytotoxicity**
  - Reducing NR4A expression enhances T-cell function associated with increased expression of AP-1–regulated genes
  - NR4A family transcription factors may contribute to T-cell exhaustion by restraining c-Jun activity

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

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Lam et al., SITC, 2022
Li et al., SITC 2022
Stim-R technology mediates precise signal-molecule presentation during T-cell activation

- Stim-R technology mimics physiologic presentation:
  - Multiple signals presented in precise densities and stoichiometries
  - Controlled presentation of both soluble and surface signals

**Stim-R technology is a programmable cell-signaling platform**

Li et al., SITC 2022
LYL119 is potent and eliminated H1975 (NSCLC) xenograft tumors and improved survival even at low doses of CAR T cells.

Elimination of xenograft tumors at both low and high CAR T cell doses

Superior T cell expansion in vivo

Significantly improved animal survival at the low $0.1 \times 10^6$ CAR T-cell dose

**LYL119 (NR4A3 KO + c-Jun + Epi-R + Stim-R)**

Mock non-transduced (Epi-R + Stim-R)

PBS

1.42 $\times 10^6$ mock T cells injected per mouse

Lam et al., SITC, 2023
Harnessing tumor-infiltrating lymphocytes to fight cancer

LYL845: A novel epigenetically reprogrammed TIL product candidate designed for differentiated potency and durability
LYL845 TIL Phase 1 trial design

• Patient population
  – Relapsed and/or refractory metastatic or locally advanced solid tumors:
    – Melanoma
    – Non-small cell lung cancer
    – Colorectal cancer

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

*Potential to expand into additional tumor types

mTPI-2, modified toxicity probability interval 2; NSCLC, non-small-cell lung cancer; RP2D, recommended Phase 2 dose
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

Key differentiators:

- **Phenotypes** (stemness markers and cytotoxic cells) associated with clinical responses
- **Preserved polyclonal** tumor reactive cells
- Robust TIL expansion across both hot and cold tumors
LYL845 is enriched for cells with characteristics associated with improved clinical outcomes

**Increased % of cytotoxic cells**

**Increased % of stem-like T cells**

- **% CD8+ T cells**
- **% CD8+CD27+ T cells**
- **% CD8+CD39-CD69+ T cells**

* is p<.05    ** is p<.01    *** is p<.001    **** is p<.0001

Krishna et al., Science Dec. 2020
Patel et al., SITC 2022
LYL845 TIL preserve ~94% of predicted tumor reactive clones to enable targeting of heterogeneous solid tumors

Malignant tumor tissue

Bioinformatics analysis

HIGH FREQUENCY CLONES

EXHAUSTED CLONES

Predicted tumor reactive clones

Check for preservation of predicted tumor reactive clones in LYL845 products

LYL845 T-Cell preparations

LYL845 TIL clinical scale runs

% of predicted tumor reactive clones

0 25 50 75 100

Donor

Melanoma NSCLC CRC

Harris et al., SITC 2022
Pasetto et al., CIR 2016, Lowrey et al., Science 2022, Oliveira et al., Nature 2021
In vivo efficacy is superior with LYL845 TIL using our Epi-R process compared to TIL using standard conditions in novel model

In this study:
- Two refractory melanoma donor samples were collected.
- Samples were split processed to generate TIL products using either the Epi-R (LYL845) or the standard process.
- Mice were implanted with subcutaneous melanoma cell line on day -8.
- 4 million LYL845 or standard TIL were dosed intravenously on day 0.
Epi-R P2 is a new manufacturing process designed to shorten product delivery time to patients

- Compared to Epi-R, Epi-R P2:
  - Does not compromise yield, stemness phenotype or tumor reactive clones
  - Reliably produces 10+ billion cells in substantially shorter manufacturing time

- Expect to implement Epi-R P2 into our TIL manufacturing in 2024

<table>
<thead>
<tr>
<th></th>
<th>Epi-R™</th>
<th>Epi-R™ P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>10+ billion cells</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Maintains stem-like qualities and tumor killing functionality</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Preserves tumor reactive clones</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Manufacture time</td>
<td>~24 days</td>
<td>~16 days</td>
</tr>
</tbody>
</table>
Epi-R and Epi-R P2 processes demonstrate comparable product profiles across CD8 cells

Comparable % of cytotoxic cells

Comparable % of stem-like T cells

N=21 include metastatic melanoma, lung cancer and colorectal cancers

Patel et al., SITC, 2023
Epi-R P2 preserves and allows expansion of tumor reactive TIL

In this study:

- T-cell receptor (TCR) sequencing was performed across Day 0 tumor, and TIL samples to assess retention of tumor reactive clones in products.
- T cell clones that are more highly represented in the Day 0 tumor sample (e.g., top 50 or top 100 in frequency) are more likely to be tumor reactive.
- We also experimentally confirmed several top frequency TCR clones to be tumor reactive (shown in purple).

Patel et al., SITC, 2023
Manufacturing
Advancing manufacturing strategy to deliver for the future

- Currently producing Phase 1 clinical supply
- Capabilities include CAR T cell, TIL and GMP vector
- Capacity for up to ~500 doses/year depending on product mix

CAR T, chimeric antigen receptor T cell; TIL, tumor infiltrating lymphocytes; GMP, good manufacturing practice

- Automated manufacturing processes to rapidly and cost-effectively scale to meet anticipated patient demand for our CAR T-cell product candidates
- Proof-of-concept technology transfer for the manufacture of LYL797 CAR T-cell therapy
- Single Cell Shuttle capacity of up to ~800 LYL797 cell doses/year
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**Two clinical programs: wholly-owned, addressing large patient populations**

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IT’S ALL ABOUT THE CELLS