Repare Therapeutics

Insight that enriches. Precision that empowers.
Introduction

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Lloyd M. Segal, President & CEO, Repare Therapeutics

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Mike Zinda, PhD, EVP & CSO, Repare Therapeutics

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Maria Koehler, MD, PhD, EVP & CMO, Repare Therapeutics & Dr. Timothy Yap, MBBS, PhD, FRCP, Principal Investigator, MYTHIC Trial

Lunresertib ongoing combination trials
Mike Zinda, PhD, EVP & CSO, Repare Therapeutics & Maria Koehler, MD, PhD, EVP & CMO, Repare Therapeutics

Conclusions
Lloyd M. Segal, President & CEO, Repare Therapeutics & Maria Koehler, MD, PhD, EVP & CMO, Repare Therapeutics

Q&A
Repare participants

Lloyd M. Segal  
President & CEO

Mike Zinda, PhD  
Chief Scientific Officer

Maria Koehler, MD, PhD  
Chief Medical Officer

Steve Forte  
Chief Financial Officer
Statements contained in this presentation regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. Words such as "anticipates," "believes," "expects," "intends," "potential," "projects," "would" and "future" or similar expressions are intended to identify forward-looking statements. Each of these forward-looking statements involves substantial risks and uncertainties that could cause actual results to differ significantly from those expressed or implied by such forward-looking statements. Forward-looking statements contained in this presentation include, but are not limited to, statements regarding the initiation, timing, progress and results of our current and future preclinical studies and clinical trials, including specifically our clinical trials of lunaresertib and camonsertib; the expected timing of program updates and data disclosures; and the therapeutic potential of our product candidates, including lunaresertib (RP-6306) and camonsertib.

These forward-looking statements reflect our current beliefs and expectations. Many factors may cause differences between current expectations and actual results, including the evolving impact of macroeconomic events, including the COVID-19 pandemic, rising inflation, the U.S. Federal Reserve raising interest rates, recent disruptions in access to bank deposits or lending commitments due to bank failures and the Russia-Ukraine war, on our business, clinical trials and financial position, unexpected safety or efficacy data observed during preclinical or clinical studies, clinical site activation rates or clinical trial enrollment rates that are lower than expected, changes in expected or existing competition, changes in the regulatory environment, and unexpected litigation or other disputes. These and other risks are described more fully in our filings with the Securities and Exchange Commission (“SEC”), including the “Risk Factors” section of our Annual Report for the year ended December 31, 2022 filed with the SEC and the AMF on February 28, 2023, our most recently filed Quarterly Report on Form 10-Q, and other documents we subsequently filed with or furnished to the SEC. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Except as required by law, we assume no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

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Solely for convenience, the trademarks and trade names in this presentation may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert their rights thereto.
Leading precision oncology company focused on synthetic lethality

Lunresertib (RP-6306), a first-in-class, oral PKMYT1 inhibitor, drives genomic instability in CCNE1-amplified tumors with Ph 1 monotherapy and multiple combination trials ongoing.

Camonsertib (RP-3500 / RG6526), a potential best-in-class ATR inhibitor with durable responses and clinical benefit in Ph 1/2 and strategic validation through Roche partnership.

Robust pipeline of SL-based therapeutic opportunities, including Polθ and a pipeline of advanced preclinical opportunities.

Proprietary genome-wide CRISPR-enabled SNIPRx platform, focused on genomic instability and DNA damage repair, enabling novel target identification and differentiated patient selection insights.

Balance Sheet of $314M funds Repare through multiple value-creating milestones into 2026.
Lunresertib (RP-6306) exploits vulnerabilities caused by increases in \textit{CCNE1}, not previously considered a druggable target

Potent and well tolerated, first in class inhibitor with anti-tumor activity especially in combination

Many affected tumor types, including gynecological and gastrointestinal malignancies

Synthetic lethal combinations with \textit{CCNE1} amplified, \textit{FBXW7} or \textit{PPP2R1A} loss, and other \textit{STEP}\textsuperscript{2} genes aid in patient selection
Background on Lunresertib

*Preclinical data and rationale for clinical investigation*
CCNE1 amplification drives genome instability

Cyclin E-overexpression drives premature entry into S-phase and overloads the DNA replication machinery, resulting in genome instability.
PKMYT1: Strong hit in a CCNE1-O/E SL screen

Genome-wide CRISPR screen

PKMYT1

Highest scoring druggable hit
Also high scoring hit in the DepMap
FBXW7 and PP2A Phosphatase Sensitizers

**FBXW7**

The E3 ubiquitin ligase FBXW7 targets proteins, such as cyclin E, for proteasomal degradation. Therefore, inactivating mutations can increase cyclin E levels and replication stress.

**PPP2R1A**

The PP2A phosphatase is critical in the response to replication stress. Therefore, hotspot inactivating mutations can increase replication stress.
Initial lunresertib addressable patient populations

Top tumor types with highest prevalence of CCNE1 amplification or inactivating mutations in FBXW7 and PPP2R1A include ~65K US+UK/EU4 patients eligible for treatment annually, or ~90K across cancer types.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Prevalence of genes of interest</th>
<th>Eligible patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine</td>
<td>3.8% 12.9% 7.6% 4.7%</td>
<td>28.9% 7,000</td>
</tr>
<tr>
<td>Ovarian</td>
<td>19.0% 20.0%</td>
<td>6,300</td>
</tr>
<tr>
<td>Stomach</td>
<td>10.2% 6.4% 17.7%</td>
<td>9,000</td>
</tr>
<tr>
<td>Colorectal</td>
<td>13.1% 14.7%</td>
<td>24,500</td>
</tr>
<tr>
<td>Bladder</td>
<td>5.8% 6.3% 12.2%</td>
<td>6,200</td>
</tr>
<tr>
<td>Cervical</td>
<td>9.1% 11.8%</td>
<td>1,300</td>
</tr>
<tr>
<td>Esophageal</td>
<td>7.1% 3.3% 11.5%</td>
<td>4,500</td>
</tr>
<tr>
<td>Sarcoma¹</td>
<td>7.1% 7.8%</td>
<td>1,200</td>
</tr>
<tr>
<td>Lung Squamous²</td>
<td>4.7% 7.6%</td>
<td>5,300</td>
</tr>
</tbody>
</table>

These lesions are largely mutually exclusive and represent distinct patient populations.

* Based on estimated number of pts treated in 1st line, advanced setting for diagnosed and new recurrent patients (CancerMPact®, Treatment Architecture, United States, 2021; accessed 5/19/23) and lesion prevalence (TCGA). ¹ Soft Tissue Sarcoma only; ² Squamous subtype of Non-Small Cell Lung Cancer only.
Lunresertib inhibits growth of CCNE1 amplified xenograft tumors

HCC1569 Breast Cancer CDX Model

Robust tumor growth inhibition (TGI) observed at well tolerated doses and exposures. Intermittent dosing delivers equivalent TGI as continuous dosing.
Lunresertib leads to CDK1 activation and induction of DNA damage *in vivo*

- PD biomarkers tested across *CCNE1* amplified and *FBXW7* mutant CDX and PDX *in vivo* models
- ~50% CDK1 dephosphorylation (IHC) and a ~2-fold γH2Ax increase was required for maximal anti-tumor activity across models. Comparable induction observed with DDR targeting agents (e.g., ATRi, PARPi).
- Lunresertib MOA to be confirmed in paired tumor biopsies collected in Phase 1
Lunresertib initial global clinical trial program

Key inclusion criteria:
- Recurrent solid tumors with CCNE1 amplification or PPP2R1A FBXW7 inactivating mutations

Monotherapy: Lunresertib
- Initiated April 2021

Combinations:
- Lunresertib + Gemcitabine: MAGNETIC: Initiated Dec 21
- Lunresertib + Camonsertib: MYTHIC: Initiated May 22
- Lunresertib + FOLFIRI: MINOTAUR: Initiated Aug 22
- Lunresertib + CCTG ¹: IST: Enrolling
- Lunresertib + Carbo/paclitaxel ²: IST: Expected 2023

Dose escalation
Dose & schedule

Determine RP2D dose / schedule
Progress to POC trials

Selected tumors with amplified CCNE1

Selected tumors with FBXW7 Loss

Tumors with high rate of sensitivity genes

Basket trial

FDA/EMA consultation re: further development

¹ Canadian Clinical Trial Group (CCTG) collaborations include NCT05605509 and NCT05601440.
² SOC for 1st line ovarian cancer is carbo/paclitaxel (6 cycles) + PARPi maintenance therapy or carbo/paclitaxel with bevacizumab + bev maintenance therapy; this IST supports future potential 1st line combination studies as triplet therapy in patients with CCNE1 amplified tumors.
Study Principal Investigator: Timothy Yap, MBBS, PhD, FRCP

Medical Oncologist and Physician-Scientist at the University of Texas, MD Anderson Cancer Center

- Associate Professor, Department for Investigational Cancer Therapeutics
- Medical Director of the Institute for Applied Cancer Science
- Associate Director of Translational Research in the Institute for Personalized Cancer Therapy
- Primary research focuses on the first-in-human and combinatorial development of molecularly targeted agents and immunotherapies, and their acceleration through clinical studies using novel predictive and pharmacodynamic biomarkers
- Main interests include the targeting of the DNA damage response with novel therapeutics, such as ATR and PARP inhibitors, as well as the development of novel immuno-therapeutics
- BSc degree in Immunology and Infectious Diseases and MD from Imperial College London, UK
I have the following financial relationships to disclose:

**Employment**

University of Texas MD Anderson Cancer Center, where I am Medical Director of the Institute for Applied Cancer Science, which has a commercial interest in DDR and other inhibitors (IACS30380/ART0380 was licensed to Artios)

**Grant/Research support (to the Institution)**

Acrivon, Artios, AstraZeneca, Bayer, Beigene, BioNTech, Blueprint, BMS, Boundless Bio, Clovis, Constellation, Cyteir, Eli Lilly, EMD Serono, Forbiius, F-Star, GlaxoSmithKline, Genentech, Haihe, Ideaya ImmuneSensor, Ionis, Ipsen, Jounce, Karyopharm, KSQ, Kyowa, Merck, Mirati, Novartis, Pfizer, Ribon Therapeutics, Regeneron, Repare, Rubius, Sanofi, Scholar Rock, Seattle Genetics, Tesaro, Vivace and Zenith

**Consultant for**


**Stockholder in**

Seagen
Lunresertib Preliminary Monotherapy Clinical Trial Results
First-in-human biomarker-driven Phase 1 MYTHIC trial of PKMYT1 inhibitor lunresertib (RP-6306) in patients with advanced solid tumors harboring \textit{CCNE1} amplification or \textit{FBXW7} or \textit{PPP2R1A} genomic alterations

Timothy A. Yap, MBBS, PhD, FRCP
University of Texas MD Anderson Cancer Center, Houston, TX;

On behalf of MYTHIC study Investigators
**First-in-human MYTHIC study**

**PKMYT1 InHIbition for the treatment of Cancers: study design**

**Phase 1 MYTHIC study NCT04855656 (accruing)**

- **Inclusion criteria:**
  - Pts ≥12yo with solid tumors resistant or intolerant to standard therapy
  - Tumors centrally reviewed* with CCNE1 amplification**, deleterious FBXW7 or PPP2R1A alterations
  - ECOG 0, 1 or 2
  - Hgb ≥9.0 g/dL
  - Platelets ≥100 K/uL
  - ANC ≥1.5 K/uL

- **Module 1:**
  - Single agent lunresertib
  - N=63 pts enrolled
  - Study is ongoing

- **Primary endpoints:**
  - Safety and tolerability
  - Recommended phase 2 dose (RP2D), schedule

- **Other endpoints:**
  - Pharmacokinetics
  - Pharmacodynamics in paired tumor biopsies
  - Preliminary antitumor activity
  - Kinetics of circulating tumor DNA (ctDNA)

- **Initiated:** 28 April 2021
- **Data cut-off date:** 28 April 2023

*Central review by Precision Oncology Decision Support (PODS) Group at MDACC
**CCNE1 amplification (Copy number ≥6)
Comprehensive biomarker analyses for first in class PKMYT1i

- Thorough understanding of predictive biomarkers for lunresertib
- Assessment of PK/PD relationship
- Early efficacy readout via ctDNA

Targeting 3 genes

Proof of principle - DNA damage

Molecular response monitoring (ctDNA)

Copy Number alterations and mutation profile

Proof of mechanism - PKMYT1 inhibition evidence
FIH Phase 1 MYTHIC study N=63, tumors and genotypes

Tumor types:

- Endometrial: 31.7%
- Colorectal: 17.5%
- Ovarian: 15.9%
- Breast: 4.8%
- Head and neck: 4.8%
- Esophageal: 3.2%
- Sarcoma, Soft tissue: 3.2%
- Others*: 19%

Most common genotypes:

- **CCNE1** amplification: 46.0%
- **FBXW7**: 31.7%
- **PPP2R1A**: 17.5%
- **FBXW7/PPP2R1A**: 1.6%

Endometrial cancer without above mutations: 3.2%

* Uterine Carcinosarcoma, Bladder, Brain, Cervical, Gastroesophageal Junction, Gastrointestinal, Melanoma, Gallbladder, Vulvar, Sarcoma
Single agent lunresertib tested at multiple doses/schedules

- Adaptive BOIN design and sufficient cohort sizes to ensure robust MTD/RP2D decision
  - Continuous daily 240mg QD and 80-100mg BID intermittent weekly schedules proposed for future combination use
- DLT: Reversible rash
- Rash any grade reported in 36.5% of patients (7.9% grade 3)
- Well managed with dose modification, topical steroids, emollients and oral antihistamines
- Rechallenge at reduced dose well tolerated, intermittent schedule prevents G3 rash

Investigation of the mechanism of rash ongoing.
MTD: maximum tolerated dose, RP2D: recommended Phase 2 dose
Human PK achieves preclinical target coverage at recommended doses

- Human lunresertib PK is linear up to daily doses of 160-240 mg with a half-life of ~9 hours
- Exploration of QD and BID regimens to maximize target coverage
Clinical mechanism of action confirmed in paired biopsies

**pCDK1-Thr14**  
(Direct Target Inhibition)

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment (n=17)</th>
<th>On-treatment (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td><strong>0.001</strong></td>
</tr>
</tbody>
</table>

**γH2Ax**  
(Induction of DNA Damage)

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment (n=25)</th>
<th>On-treatment (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td><strong>0.022</strong></td>
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</table>

Preclinical PD targets that drive maximal activity (~50% CDK1 dephosphorylation and ~2-fold induction of γH2AX) achieved in paired tumor biopsies acquired pre- and post- lunresertib treatment.
### Lunresertib related Treatment Emergent Adverse Events

**Distinct profile from cell cycle inhibitors currently in clinic: limited myelotoxicity**

All grades, occurring in ≥10% of patients

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All Grades (%)</th>
<th>G3 (%)</th>
<th>G4 (%)</th>
<th>All Grades (%)</th>
<th>G3 (%)</th>
<th>G4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash*</td>
<td>36.5%</td>
<td>7.9%</td>
<td>0</td>
<td>47.1%</td>
<td>5.9%</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>33.3%</td>
<td>1.6%</td>
<td>0</td>
<td>29.4%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23.8%</td>
<td>1.6%</td>
<td>0</td>
<td>29.4%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>20.6%</td>
<td>6.3%</td>
<td>0</td>
<td>23.5%</td>
<td>11.8%</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15.9%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Safety profile unremarkable**
- **Favorable tolerability profile:**
  - manageable adverse events
  - events of interest: rash, nausea/vomiting
  - grade 3 toxicity infrequent
  - no grade 4 toxicity

Proposed dose/schedule and food mitigated both rash and nausea/vomiting

* Rash terms included: Rash Maculopapular, Pruritis, Rash, Skin Exfoliation, Erythema, Dermatitis Contact, Eczema, Flushing, Rash Erythematous, Rash Pruritic
Tumor response to lunresertib monotherapy at intermittent RP2D

- Female
- 73 years old
- Metastatic recurrent uterine carcinosarcoma
- FBXW7 & PPP2R1A
- Received 3 prior lines of therapy

- Overall response: cPR (RECIST)
- Max. tumor burden decrease - 41%
- On therapy 7+ months *

Several patients with <30% tumor shrinkage and long stable disease ongoing up to >11 months

* As of June 1, 2023
Lunresertib: preliminary MYTHIC trial monotherapy conclusions

- Proof of concept established in clinic
- Monotherapy appears safe and well tolerated
  - Potentially suitable for maintenance therapy
- Preliminary antitumor activity observed, including:
  - Confirmed RECIST partial response
  - Several patients with <30% tumor shrinkage and long stable disease ongoing up to >11 months
- Preclinical findings translated into the clinic
  - Confirmed PKMYT1 inhibition and DNA damage at active doses
- Intermittent & continuous schedules enable combinations

Achieved monotherapy objectives and continuing to move forward on monotherapy and combination opportunities
Lunresertib initial global clinical trial program

Key inclusion criteria:

Recurrent solid tumors
- CCNE1 amplification or
- PPP2R1A FBXW7 inactivating mutations

Monotherapy: Lunresertib
- Initiated April 2021

Combinations:
- Lunresertib +
  - Gemcitabine
  - Camonsertib
  - FOLFIRI
  - CCTG
  - Carbo/paclitaxel

Preliminary data today

Selected tumors with amplified CCNE1

Selected tumors with FBXW7 Loss

Tumors with high rate of sensitivity genes

Basket trial

Determine RP2D dose / schedule Progress to POC trials

FDA/EMA consultation re: further development

1 Canadian Clinical Trial Group (CCTG) collaborations include NCT05605509 and NCT05601440.
2 SOC for 1st line ovarian cancer is carbo/paclitaxel (6 cycles) + PARPi maintenance therapy or carbo/paclitaxel with bevacizumab + bev maintenance therapy; this IST supports future potential 1st line combination studies as triplet therapy in patients with CCNE1 amplified tumors.
Lunresertib Ongoing Combination Trials

*Preclinical rationale for testing lunresertib with camonsertib*
Replication stress caused by CCNE1 overexpression engages ATR

- **CCNE1** amplification activates the ATR pathway
- ATR (CHK1-mediated inhibition of CDC25) and PKMYT1 inhibition result in inactive CDK1
- These findings provide a rationale for combination of ATR and PKMYT1 inhibition
Addition of camonsertib to lunresertib exacerbates premature mitosis
Camonsertib synergizes with lunresertib in tumor models with CCNE1 amplification, FBXW7 or PPP2R1A loss
Lunresertib + camonsertib drives regression in \textit{FBXW7 KO} models

Lunresertib + camonsertib combination leads to significant tumor regressions at doses showing minimal single-agent activity
MYTHIC Module 2: Lunresertib with Camonsertib

Brief preview of clinical data
Monitoring of Molecular Response

Analysis of ctDNA changes at baseline, 3 weeks, 6 weeks (interim trial data)

MYTHIC Module 1: Lunresertib monotherapy

MYTHIC Module 2: Lunresertib + camonsertib

Greater depth and higher frequency of ctDNA changes in combination vs. monotherapy are expected to predict similar trend in clinical results in combination therapy
Lunresertib + camonsertib case studies: confirmed responses

66 y.o. Female
Endometrial adenocarcinoma with **FBXW7** & **PPP2R1A** mutation (MSS)
- Perirectal implant
- Overall response: cPR (RECIST)
- Max tumor burden decrease: -56%
- On therapy for 7 months *

67 y.o. Female
Cholangiocarcinoma with **CCNE1** amplification
- Liver segment VIII
- Overall response: cPR (RECIST)
- Max tumor burden decrease: -35%
- On therapy for 6 months *

63 y.o. Male
CRC with **FBXW7** mutation
- Left para-aortic lymph node
- Overall response: cPR (RECIST)
- Max tumor burden decrease: -43%
- On therapy for 5+ months *

Confirmed RECIST responses observed across genotypes and tumor types for lunresertib + camonsertib combination

* As of June 1, 2023
Conclusions from today’s presentation

- Potent and well tolerated, first in class PKMYT1 inhibitor
- Proof of concept established in clinic
- Monotherapy tolerability differentiated from WEE1 and CDK2 inhibitors
- Early efficacy signals in monotherapy and combinations
  - Monotherapy cPR and several patients with long stable disease >11+ months
  - Combination cPRs, including in tumors not expected to respond to ATR inhibition
- Recommended range of monotherapy doses and schedules

Clear clinical understanding of the PKMYT1 target and lunresertib performance

Substantial evidence to support ongoing combinations to be presented in Q4 2023
**Near-term guidance:**

- MYTHIC (+ camonsertib) and MAGNETIC (+ gemcitabine) planned disclosure in 4Q 23
- MINOTAUR (+ FOLFIRI) to be disclosed subsequently
- Princess Margaret Cancer Center sponsored study start 2023 (lunresertib + carboplatin/paclitaxel)\(^1\) in recurrent *TP53* mutated ovarian and uterine cancer
- Canadian Cancer Trials Group sponsored Phase 2 Basket Study is enrolling and second study of lunresertib + gemcitabine in patients with CDK4/6 inhibitor treated ER+/HER2- metastatic breast cancer is active
- WEE1 combination – evaluating *in vitro* and *in vivo* data to assess combination potential

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\(^1\) SOC for 1st line ovarian cancer is carbo/paclitaxel (6 cycles) + PARPi maintenance therapy or carbo/paclitaxel with bevacizumab + bev maintenance therapy; this IST supports future potential 1st line combination studies as triplet therapy in patients with CCNE1 amplified tumors
Q&A