REALIZING THE POWER OF RED™
A NEW ERA IN CELLULAR MEDICINE

DECEMBER 2020
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Strong Execution of Key Priorities

**DELIVERING ON CRITICAL MILESTONES**

- **Completed dosing of 4 cohorts** in Phase 1/2 RTX-240 solid tumor clinical trial; generating clinical data
- **Dosing patients** in Phase 1 arm of RTX-240 clinical trial in relapsed/refractory acute myeloid leukemia (AML)
- **RTX-321 IND cleared** for treatment of HPV+ cancers; includes frozen drug substance with potential shelf of up to several years
- Fully owned manufacturing enables execution of clinical trials; **conducting cGMP runs** for RTX-240 and RTX-321 clinical trials
- **Presented preclinical oncology data** at SITC, FOCIS & AACR supporting lead oncology programs

*As of November 9, 2020*
Red Cell Therapeutics™: The Future of Cellular Therapy

POTENTIALLY TRANSFORMATIVE CELLULAR THERAPIES

LEVERAGE HISTORY OF ADMINISTERING RED BLOOD CELLS

MODULAR PLATFORM THAT MIMICS IMMUNE BIOLOGY

BROAD PIPELINE

ADVANTAGEOUS TOLERABILITY

SCALABLE OFF-THE-SHELF
The Promise of the RED PLATFORM®

**Features**
- Consistent product design and discovery approach
- Only modification from product to product is added gene or genes via lentivirus
- Universal, scalable, reproducible

**Benefits**
- Leverages common CMC, toxicology data packages, reducing development timelines
- Shorter timeline to lead candidate compared with traditional drug discovery
- Efficient cost structure
BROAD IMMUNE SYSTEM STIMULATION

Stimulate adaptive and innate immunity through **immune cell agonists**
- Presentation of synergistic co-stimulatory ligands and cytokines
- Biodistribution may reduce toxicities
- Potential broad therapeutic window

Realize the power of immune agonists

ANTIGEN-SPECIFIC IMMUNE STIMULATION

Drive unique, *in vivo* **antigen-specific and antigen-spreading** responses
- Direct MHC I antigen presentation
- Co-stimulatory ligand induces significant quantity of CD8+ T cells
- Cytokine potently stimulates desired quality of killer T cells

Unlock the potential of cancer vaccines

AUTOIMMUNE DISEASES

**TARGETING THE APC**

Induce immune tolerance
- Autoantigen delivery and presentation of inhibitory molecules
- May create tolerogenic APCs that promote regulatory CD4 cells

Induce immune tolerance in high-potential indications
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Potential to Unlock Platform Value with Clinical Data from Lead Oncology Program

ACCELERATING CLINICAL DEVELOPMENT

RTX-240
Broad Immune Stimulation
Advanced Solid Tumors

RTX-240
Broad Immune Stimulation
R/R Acute Myeloid Leukemia

RTX-321
Antigen-Specific Immune Stimulation
Advanced HPV 16+ Cancers

RTX-224
Broad Immune Stimulation
Advanced Solid Tumors

IND Enabling
Preclinical
Second aAPC
Discovery
Future Opportunities

CANCER

In the Clinic
IND Filed
RTX-240: BROAD IMMUNE SYSTEM STIMULATION
The Untapped Potential of Immune Agonists

**BLOCKING IMMUNE CHECKPOINTS WORKS**

- Checkpoint inhibitors (CPIs) release the “brakes” in cancer immunity
- Costimulatory and proinflammatory cytokine pathways push the “accelerator”
- CPIs are limited to certain cancers; most patients do not benefit and rapid disease progression is common
- Harnessing the immune system to treat cancer works
- New combinatorial approaches with CPIs are needed

**STRONG BIOLOGIC RATIONALE FOR AGONISTS**

- 80 agents in development targeting stimulatory pathways, such as 4-1BB, OX40, GITR, CD27, IL-15, IL-12, and IL-2
- Anti-4-1BB mAbs showed promise in solid tumors (utomilumab), but potent approaches (urelumab) have had toxicity
- IL-15 agonist (ALT-803) showed promise in AML Phase 1 study
  - Multiple other approaches being explored in combo
- These potent approaches limited by severe toxicities

- 4-1BB and IL-15 are promising pathways
- Clinical utility limited by toxicity, particularly in combination therapy
RTX-240: Enrolling Phase 1/2 Clinical Trial in Advanced Solid Tumors & Phase 1 Arm in Relapsed/Refractory AML

BROAD IMMUNE SYSTEM STIMULATION

POTENTIAL BENEFITS:
• Activates existing agonist pathways leading to enhanced potency
• Improved anti-tumor activity
• Overcomes resistance to immunotherapy
• Reduced toxicity given biodistribution

RTX*-240 | (4-1BBL + IL-15TP)

STIMULATE ADAPTIVE AND INNATE IMMUNE CELL AGONIST PATHWAYS

IL-15TP
4-1BBL
T CELL

IL-15TP
4-1BBL
NATURAL KILLER (NK) CELL

*Rubius Therapeutics Terminology: RTX – Red Cell Therapeutic product candidate; mRBC – mouse surrogate model; RCT – experimental construct
Proposed Mechanism of RTX-240

1. Activation and 2. expansion of immune cells

3. Trafficking to tumor

4. Tumor killing

Potential for enhanced efficacy and safety by confining RTX-240 to the vasculature
The Biodistribution of RBCs can be Exploited to Limit the Toxicity of Effective Targets
mRBC-240 Results in No Liver Toxicity Compared to Anti-4-1BB mAb

SERUM ALT

LIVER HISTOLOGY

Normal mice; 4 Doses, 1x10⁹ cells day 0, 3, 7, 10; Sacrifice day 18

Dugast, et. al., American Association for Cancer Research; Poster #3272, 2019
TREATMENT WITH mRBC-240 EXPANDS CD8 AND NK CELL NUMBERS IN SPLEEN AND BLOOD

Normal mice; 4 doses, 1x10^9 cells at days 0, 3, 7, 10; Sacrifice day 14
mRBC-240 Significantly Inhibits Tumor Growth as Monotherapy or in Combination with Anti-PD-1 mAb

mRBC-240 reduced tumor burden and was equivalent to anti-4-1BB mAb

mRBC-240 + anti-PD-1 mAb reduced tumor burden vs. anti-PD-1 mAb alone
RTX-240 Stimulated Potent Activation of Immune System

RTX-240 is ~10-Fold Superior to 4-1BB Agonist Antibody in Preclinical Models

Dugast, et. al., American Association for Cancer Research; Poster #3272, 2019
RTX-240 Promotes Expansion and Activation of Cells Driving Innate and Adaptive Immunity

Dugast, et. al., American Association for Cancer Research; Poster #3272, 2019
# RTX-240 Clinical Development Plan

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<th>RTX-240</th>
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<td>Relapsed/Refractory or Locally Advanced Solid Tumors</td>
<td><strong>ENROLLING:</strong> Phase 1: Monotherapy Dose-Escalation 4-6 cohorts</td>
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<td>Relapsed/Refractory Acute Myeloid Leukemia</td>
<td><strong>Phase 2: Tumor-Specific Expansion Cohort #1</strong></td>
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<td><strong>ENROLLING:</strong> Phase 1: Monotherapy Dose-Escalation 4 cohorts, initially transplant ineligible with potential for post-transplant</td>
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## Phase 1 Objectives:
- Determine safety and tolerability, maximum tolerated dose, recommended Phase 2 dose and dosing interval of RTX-240
- Assess pharmacodynamics of RTX-240 as measured by changes in T and NK cell number and function relative to baseline
- Measure anti-tumor activity by Overall Response Rate (ORR)
- Assess pharmacokinetics of RTX-240
Assessing Potential Pharmacodynamic Effects and Overall Response Rate

**Level One:** Target Cell Activation

**Level Two:** Target Cell Proliferation

**Level Three:** Target Cell Trafficking

**Level Four:** Tumor Reductions
NK cells generate potent **cytolytic activity** and regulate **immune responses** against cancer cells.

- NK cells play a key role in the development and eradication of **myeloid malignancies**
  - AML tumor-associated mechanisms often suppress proper NK cell function to avoid immune system recognition.
  - Loss of NK activation receptor ligands is a hallmark of leukemia blasts and stem cells.
    - Results in AML cells evading the immune system.
  - Reconstitution of NK cells post high-dose chemo or transplant are **strong prognostic indicators** of overall survival.

**NK Cells in AML**

**NK Cell Interactions**

RTX-240 is designed to induce NK cell proliferation and activation, leading to the killing of AML cells.
RTX-240 Induces Activation and Proliferation of NK Cells that are Effective Against a Myeloid Leukemia Cell Line In Vitro

- RTX-240 induces both proliferation and activation of NK cells in vitro
- These activated NK cells are effective in killing the myeloid leukemia cell line K562

Dugast, et. al., Society for Immunotherapy of Cancer; Poster #144, 2020
RTX-321: ANTIGEN-SPECIFIC IMMUNE STIMULATION
Untapped Potential of Cancer Vaccines Hindered by Potency and Antigen Spread

Rubius approach has the potential to overcome challenges associated with cancer vaccines

**CHALLENGES WITH OTHER VACCINE APPROACHES**

- Autologous cellular vaccines are associated with significant manufacturing delays impacting timing of treatment of patients
- Peptide or DNA/RNA vaccines may not provide the full three signals that are required for optimal quantity and quality of T cells
- In cancer patients, both T cells and dendritic cells (DCs) are immunosuppressed and cancer vaccines could be limited by impaired DC function

**RUBIUS aAPCs MAY OVERCOME CHALLENGES**

- Rubius aAPCs are designed to directly activate anti-tumor T cells, while vaccines target DCs which in turn activate T cells
- aAPCs can be administered repeatedly, whereas for viral-based vaccines, the immune response to the viral vector may preclude repeat usage
- aAPCs promote epitope spreading, broadening the immune response against the tumor
Rubius’ First Engineered aAFC will Target HPV+ Tumors – IND Cleared with Frozen Drug Substance

Replicating immune system function to activate and expand antigen-specific T cells for a potent anti-tumor effect
The risk of cancer is strongly associated with HPV infection.

High-risk strain HPV 16 accounts for approximately 70% of all cervical cancers and 80% of head and neck cancers associated with HPV infection.

Critical need for new and innovative treatment options for advanced HPV 16-associated cancers.
Rubius’ aAPCs Demonstrate Rapid and Direct Cell-to-Cell Interaction with Target T cells

SIGNIFICANT OT1-mRBC DOUBLETS OBSERVED BY FLOW WITH aAPCs

- mRBC-CTRL
- mRBC-4-1BBL-IL-12
- mRBC-OVA-4-1BBL
- mRBC-OVA-4-1BBL-IL-12

mRBCs labeled with CTFR injected at time 0
At 1h and 17h splenocytes harvested
Evaluated flow for double positive signals
- OT-1 gate X CTFR

Increase in labeled mRBC-OVA-4-1BBL-IL-12 cells in OT-1 gate observed with aAPCs indicates direct cell-to-cell interaction
Rubius’ aAPC Approach Drives Tumor Regressions in Vivo

**TUMOR CONTROL**

**EG7.OVA MODEL**

**TUMOR REgressions AND CELL DOSE**

CTRL

→ 0/8 regressions

mRBC – OVA + 4-1BBL at 1 x 10⁹

→ 2/8 regressions

mRBC – OVA + 4-1BBL + IL-12 at 6.3 x 10⁷

→ 5/8 regressions; 16-fold lower dose

mRBC – OVA + 4-1BBL + IL-12 at 2.5 x 10⁸

→ 7/8 regressions; 4-fold lower dose

MODEL DETAILS:
EG7.OVA is a lymphoma cell line that expresses OVA (antigen from chicken ovalbumin)
OT-1 cells are T cells that recognize OVA

Zhang, et. al., Society for Immunotherapy of Cancer; Poster #P233, 2019
Re-challenge of Cured Mice Demonstrates Memory and Epitope Spreading

**EG7.OVA RE-CHALLENGE**

- **mRBC-OVA-4-1BBL-IL-12 previously cured (n=7)**
- **OT-1 (5E5) naive group**

**EL4 CHALLENGE**

- **mRBC-OVA-4-1BBL-IL-12 previously cured (n=7)**
- **OT-1 (5E5) naive group**

**Re-challenge with original tumor**

Re-challenge with EL4, the “parental” line of EG7.OVA. EL4 expresses other tumor antigens, but not OVA, the antigen that was presented by the aAPC.

Nixon, et. al., American Society of Gene & Cell Therapy; Poster #32, 2020
Rubius’ aAPC Approach Harnesses Endogenous T cells to Control Tumors

mRBC OVA-4-1BBL-IL-12 EXPANDS BOTH ADOPTIVELY TRANSFERRED AND ENDOGENOUS ANTIGEN-SPECIFIC T CELLS

OVA specific T cell expansion
Day 10 (blood)

OT-1
Endogenous OVA specific T cells

CD45.2: OT1

OVA tetramer

Endogenous cells alone can control tumor growth

Tumor volume mm$^3$

Days after inoculation

NOTE: No transfer of OT-1 cells
mRBC-aAPC (gp100) Nearly Eliminates Lung Metastases in Melanoma Model

Model Details:
B16 is melanoma cell line carrying the tumor associated antigen gp100. Pmel T cells recognize gp100.

Zhang, et. al., Society for Immunotherapy of Cancer; Poster #P233, 2019
RTX-321 Activates and Expands HPV-Specific Human T Cells

**HPV-SPECIFIC T CELL EXPANSION**

**LEGEND**

- **RTX-CTRL**
- **RTX-HPV**
- **RTX-HPV-4-1BBL**
- **RTX-321**
- **RTX-CMV-4-1BBL-IL-12**

**IFNγ SECRETION**

**MODEL:**

CD8 T cells are transduced with a TCR specific for HPV E7 cultured for 10 d with aAPCs. ~20% of the cells are HPV tet+ at the start of the culture, i.e., they have the TCR recognizing HPV.
UPCOMING CATALYSTS
Anticipated Upcoming Milestones

Unlocking the potential of the RED PLATFORM in cancer and autoimmune disease
Strong financial position with cash runway into 2022
REALIZING THE POWER OF RED™
A NEW ERA IN CELLULAR MEDICINE