NOVEL RNA THERAPEUTICS THAT TARGET RIG-I

MARTIN DRISCOLL
MDRISCOLL@RIGIMMUNE.COM
Anna Marie Pyle, PhD
Anna Marie Pyle, PhD is a Yale Sterling Professor, in the Department of Molecular, Cellular and Developmental Biology and Department of Chemistry. She is an HHMI investigator since 1997. Dr. Pyle is a co-discoverer of the RIG-I receptor family. She conducted many of the first structural and biochemical investigations on RIG-I.

Akiko Iwasaki, PhD
Akiko Iwasaki, PhD is Waldemar Von Zedtewitz Professor of Immunobiology and Professor of Molecular, Cellular and Developmental Biology at Yale University. She is an HHMI Investigator and was elected to the National Academy of Sciences in 2018. She has shown how RIG-I functions as an immunomodulator.

• Formed a Delaware Corp. in 2020
• Exclusive option to license extensive IP from Yale University
• Launched a Seed Round effort in April ‘21 with a $5 million goal
Company Overview

RIGImmune

Biopharmaceutical research company developing immunomodulatory therapies against the cytosolic RNA sensor RIG-I

Stem Loop RNA Therapeutics (SLRs)
A New Class of Therapeutic Oligonucleotides for Diseases Caused by RNA Viruses

- Antitumor Immune Response Induction
- Internal platform for small molecule RIG-I agonist & antagonist development
Key Investment Highlights

• Developing a novel class of host-targeted agents that activate the body’s innate and adaptive immune capability for antiviral defense and antitumor response
• Lead development product, SLR-14, could be in the clinic before YE’22
• Pan-viral benefit - demonstrated efficacy in multiple models for diseases caused by RNA viruses
• SLR-14 demonstrated treatment & prevention effects for serious viral respiratory diseases
• SARS-CoV-2, influenza
• Capability for development as a vaccine adjuvant
• Antitumor immune response POC in multiple oncology models
• Demonstration of abscopal effect, immune memory, and additive benefit with checkpoint inhibition
• Significant interest with potential support from Gates Foundation and NIAID
• Experienced leadership team to execute the development programs
• Future internal capability to develop RIG-I agonists & antagonists
• Interferonopathies, inflammatory-mediated diseases
Influenza A virus (flu) epidemics occur annually*

3 – 5 million severe cases annually

~ 500,000 deaths worldwide each year

HPIV3 & RSV cause severe respiratory disease in infants and children

SARS & MERS have caused significant morbidity and mortality

SARS-CoV-2 has infected >180 million people globally thus far

* Prevalence substantially lower in 2020-21 season

Novel immune-therapeutics could play an essential role in the enhancement of response rates & durability of the responses to checkpoint inhibitors for a broad range of cancers
RIG-I Activation Triggers a Multifaceted Innate Immune Response

Triggered by double stranded RNA from virus or SLR mimic
Central role in innate immunity and antiviral response

RIG-I – the first line of defense against RNA viral pathogens

- Coronaviruses (COVID-19, SARS, MERS)
- Influenza, RSV
- Ebola
- Flaviviruses (Dengue)

By harnessing and controlling RIG-I, we can create new immunomodulatory therapies for...

- Viral Respiratory Diseases
- Oncology
- Viral Hemorrhagic Fevers
- Inflammatory Diseases
## Product Development Pipeline

<table>
<thead>
<tr>
<th>Product Candidate</th>
<th>Indication</th>
<th>Discovery</th>
<th>Lead</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR-14</td>
<td>Influenza, vaccine adjuvant RNA viral prophylaxis, pan-viral tx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pursue FIH Trial &amp; Vaccine adjuvant</td>
</tr>
<tr>
<td>SLR-14S18</td>
<td>Cancer Immunotherapeutic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Seek partnerships w/ novel delivery systems</td>
</tr>
<tr>
<td>RIG-I antagonist</td>
<td>Interferonopathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Internalize validated platform</td>
</tr>
<tr>
<td>MDA5 agonist</td>
<td>Infectious diseases and cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Selectively implement discovery programs to fund internally and partner others</td>
</tr>
<tr>
<td>LGP2 agonist</td>
<td>Infectious diseases and cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

©2021 RIGImmune
• Notable human respiratory diseases caused by RNA viruses
  • COVID-19, SARS, MERS, Influenza, RSV
  • SLRs - a role in managing the next respiratory disease outbreak?

- Pan-viral – immediate tx upon symptoms
- Prophylaxis
- Vaccine adjuvant
- Favorable solubility profile allows for direct mucosal delivery - intranasal
I.V. SLR14 protects C57BL/6J mice from influenza infection

**Figure legend.** SLR14 intravenous treatment protects C57BL/6J mice from influenza virus infection. A. Naïve C57BL/6J mice (male, 8 weeks) received SLR14 intravenous (i.v.) treatment 5 hours before (pre-treated) or after (post-treated) intranasal (i.n.) challenge with PR8. The mice treated intravenously with vehicle (jetPEI) were used as controls. B. Body weight loss in SLR14- or vehicle-treated mice after PR8 challenge. C. The survival of SLR14- or vehicle-treated mice after PR8 challenge.
SLR14 treatment of persistent infection and long COVID

*Rag1<sup>−/−</sup>* mice lack T and B cells and suffer from persistent SARS-CoV-2 infection

Intranasal infection of 10<sup>6</sup> PFU SARS-CoV-2 in AAV-hACE2 transduced C57BL/6J and *Rag1<sup>−/−</sup>* mice
SLR14 treatment in tumor-bearing mice pre- & post-SARS-CoV-2 infection

BWL and survival of tumor-bearing mice after SARS-CoV-2 i.n. infection

- Treatment groups:
  - K18-hACE2
  - YUMMER1.7
  - SARS-CoV-2 (5x10^6 PFU in 50uL)

Graphs showing:
- % of starting weight over time
- % survival over time

BWL and survival of tumor-bearing mice with SLR14 tx 12 hours before or after SARS-CoV2 i.n. infection

- Treatment groups:
  - vehicle
  - pre-treated
  - post-treated

Graphs showing:
- % of initial weight over days after SARS-CoV2 challenge
- Percent survival over days after SARS-CoV2 challenge

1. pre-treated: 25 ug SLR14 12 hours before PR8 challenge
2. post-treated: 25 ug SLR14 12 hours after PR8 challenge
3. vehicle: vehicle 12 hours before PR8 challenge
Tumor Growth Inhibition in Pan02 Syngeneic Pancreatic Cancer Model

- **Vehicle Control**
- **αPD1**
- **SLR14**
- **SLR14 + αPD1**

### Tumor Volume (mm$^3$)

- **Study Day**
  - 0  2  4  6  8  10  12  14  16  18  20  22  24  26  28  30

### % Growth Inhibition (Normalized to Control)

- **Vehicle Control**
- **SLR14**
- **SLR14 + αPD1**
- **αPD1**
SLR14 Recruits the Adaptive Immune System

**SLR14 induces robust abscopal effect**

Growth of untreated (left) tumor is inhibited by SLR14 injection into treated (right) tumor

B16-ova Melanoma

![Graph showing tumor volume over days after tumor cell inoculation for treated (vehicle), distant (vehicle), treated (SLR14), and distant (SLR14) groups.](image)
SLR14 Induces Immune Memory

Tumors implanted in mice previously cured with SLR14 do not grow

C57BL/6 (male) B16-ova (5x10^5, s.c.) treatment (SLR14) B16-ova (5x10^5, s.c.)

Days after tumor cell inoculation

B16-Ova Melanoma

Tumor volume (mm^3)

Percent survival

Days after tumor cell inoculation
SLR-14 Protects Against Rift Valley Fever Mortality

- RIG-I shown to be receptor that responds to flaviviral & HCV infection
- SLR compounds shown to be effective, prophylactically and post-infection, in three viruses completely different in composition and biological mechanisms
  - Influenza viruses, bunyaviruses and coronaviruses

### Rift Valley Fever Bunyavirus Study
Utah State
SLR14 Compound Administered subQ

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Protection (% Survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infected Controls</td>
<td>100</td>
</tr>
<tr>
<td>25 µg SLR14</td>
<td>100</td>
</tr>
<tr>
<td>5 µg SLR14</td>
<td>90</td>
</tr>
<tr>
<td>1 µg SLR14</td>
<td>90</td>
</tr>
<tr>
<td>10 µg Poly(I:C)</td>
<td>40</td>
</tr>
<tr>
<td>Vehicle Placebo</td>
<td>30</td>
</tr>
</tbody>
</table>
Use of Proceeds & Near-Term Plans

Build a biopharma development company with a platform capability to develop differentiated RIG-I agonist & antagonist compounds

Pre-Seed Round (Completed)
Management Investment + CT Innovations $300k

Seed Round Goal: $5 million

- IND-enabling efforts for SLR-14 for FIH Influenza Challenge
- Additional MOA, Nonclinical POC & co-formulation w/ vaccine
- Formulate the SLR-14S18 for IV ROA as adjunct to checkpoint inhibitors

Further Synthesis & Formulation Optimization
Intranasal delivery
Co-formulation with flu vaccine

Research collaborations related to immuno-oncology

Potential FIH Trial Initiation YE’22
Potential FIH Trial Initiation 2023
RIGImmune Leadership Team

**Martin Driscoll**
**Chair**
OncoNano Medicine, Inc. CEO & Director
- Former CEO & Director at Spring Bank Pharmaceuticals (NASDAQ:SBPH)
- Former CEO & Director at Javelin Pharmaceuticals (NYSE Euronext: JAV)

**Dov Goldstein MD**
**Director**
Indapta Therapeutics CFO, CBO & Director
- Former CFO at Vicuron Pharmaceuticals (NASDAQ: MICU)
- Former CFO Loxo Oncology (NASDAQ:LOXO)

**Tom Smart**
**Director**
Gravitas Therapeutics, Inc.
**Board Chair & CEO**
- Former Chair and CEO of AnaptysBio (NASDAQ: ANAB)
- Extensive fund-raising and corporate partnering transaction experience

**Donald Corcoran**
**Current Advisor & Future CEO**
- Former CEO at Methlygene and Cyteir Therapeutics
- Head of Business Development & Alliance Mgmt for Epi-Cure Pharma
- Chief of Staff & Head of Operations for AstraZeneca Boston R&D
- Multiple prior and current board roles

**Kris Iyer, PhD**
**Chief Scientific Officer**
- Previously CSO Spring Bank
- >40 yrs oligonucleotide research
- Advanced multiple therapeutics to clinical development
- Former NIH

**Akansha Bhargava, MD MS**
**Blavatnik Fellow, Yale OCR**
- Former Head of Clinical Development Soleno Therapeutics.

**Anna Marie Pyle, PhD**
Anna Marie Pyle, PhD is a Yale Sterling Professor, in the Department of Molecular, Cellular and Developmental Biology and Department of Chemistry. She is an HHMI investigator since 1997. Dr. Pyle is a co-discoverer of the RIG-I receptor family. She conducted many of the first structural and biochemical investigations on RIG-I.

**Akiko Iwasaki, PhD**
Akiko Iwasaki, PhD is Waldemar Von Zedtwitz Professor of Immunobiology and Professor of Molecular, Cellular and Developmental Biology at Yale University. She is an HHMI Investigator and was elected to the National Academy of Sciences in 2018. She has shown how RIG-I functions as an immunomodulator.

**Anna Marie Pyle, PhD**
Anna Marie Pyle, PhD is a Yale Sterling Professor, in the Department of Molecular, Cellular and Developmental Biology and Department of Chemistry. She is an HHMI investigator since 1997. Dr. Pyle is a co-discoverer of the RIG-I receptor family. She conducted many of the first structural and biochemical investigations on RIG-I.

**Akiko Iwasaki, PhD**
Akiko Iwasaki, PhD is Waldemar Von Zedtwitz Professor of Immunobiology and Professor of Molecular, Cellular and Developmental Biology at Yale University. She is an HHMI Investigator and was elected to the National Academy of Sciences in 2018. She has shown how RIG-I functions as an immunomodulator.

**Anna Marie Pyle, PhD**
Anna Marie Pyle, PhD is a Yale Sterling Professor, in the Department of Molecular, Cellular and Developmental Biology and Department of Chemistry. She is an HHMI investigator since 1997. Dr. Pyle is a co-discoverer of the RIG-I receptor family. She conducted many of the first structural and biochemical investigations on RIG-I.

**Akiko Iwasaki, PhD**
Akiko Iwasaki, PhD is Waldemar Von Zedtwitz Professor of Immunobiology and Professor of Molecular, Cellular and Developmental Biology at Yale University. She is an HHMI Investigator and was elected to the National Academy of Sciences in 2018. She has shown how RIG-I functions as an immunomodulator.

**Anna Marie Pyle, PhD**
Anna Marie Pyle, PhD is a Yale Sterling Professor, in the Department of Molecular, Cellular and Developmental Biology and Department of Chemistry. She is an HHMI investigator since 1997. Dr. Pyle is a co-discoverer of the RIG-I receptor family. She conducted many of the first structural and biochemical investigations on RIG-I.

**Akiko Iwasaki, PhD**
Akiko Iwasaki, PhD is Waldemar Von Zedtwitz Professor of Immunobiology and Professor of Molecular, Cellular and Developmental Biology at Yale University. She is an HHMI Investigator and was elected to the National Academy of Sciences in 2018. She has shown how RIG-I functions as an immunomodulator.

**Anna Marie Pyle, PhD**
Anna Marie Pyle, PhD is a Yale Sterling Professor, in the Department of Molecular, Cellular and Developmental Biology and Department of Chemistry. She is an HHMI investigator since 1997. Dr. Pyle is a co-discoverer of the RIG-I receptor family. She conducted many of the first structural and biochemical investigations on RIG-I.

**Akiko Iwasaki, PhD**
Akiko Iwasaki, PhD is Waldemar Von Zedtwitz Professor of Immunobiology and Professor of Molecular, Cellular and Developmental Biology at Yale University. She is an HHMI Investigator and was elected to the National Academy of Sciences in 2018. She has shown how RIG-I functions as an immunomodulator.

**Anna Marie Pyle, PhD**
Anna Marie Pyle, PhD is a Yale Sterling Professor, in the Department of Molecular, Cellular and Developmental Biology and Department of Chemistry. She is an HHMI investigator since 1997. Dr. Pyle is a co-discoverer of the RIG-I receptor family. She conducted many of the first structural and biochemical investigations on RIG-I.

**Akiko Iwasaki, PhD**
Akiko Iwasaki, PhD is Waldemar Von Zedtwitz Professor of Immunobiology and Professor of Molecular, Cellular and Developmental Biology at Yale University. She is an HHMI Investigator and was elected to the National Academy of Sciences in 2018. She has shown how RIG-I functions as an immunomodulator.
Contacts for Further Information

Marty Driscoll
mdriscoll@rigimmune.com

Anna Marie Pyle
Anna.pyle@yale.edu

Kris Iyer, PhD
kiyer@rigimmune.com

Akiko Iwasaki, PhD
Akiko.iwasaki@yale.edu