Phio PHARMACEUTICALS

Developing the next generation of immuno-oncology therapeutics

Biotech Showcase 2019
January 7th, 2019
San Francisco, CA

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Phio Pharma is working on (Nobel Prize winning science)[2]

The Nobel Prize in Physiology or Medicine 2006

"for their discovery of RNA interference (RNAi) - gene silencing by double-stranded RNA."

Andrew Fire

Craig Mello

X

The Nobel Prize in Physiology or Medicine 2018

"for their discovery of cancer therapy by inhibition of negative immune regulation."

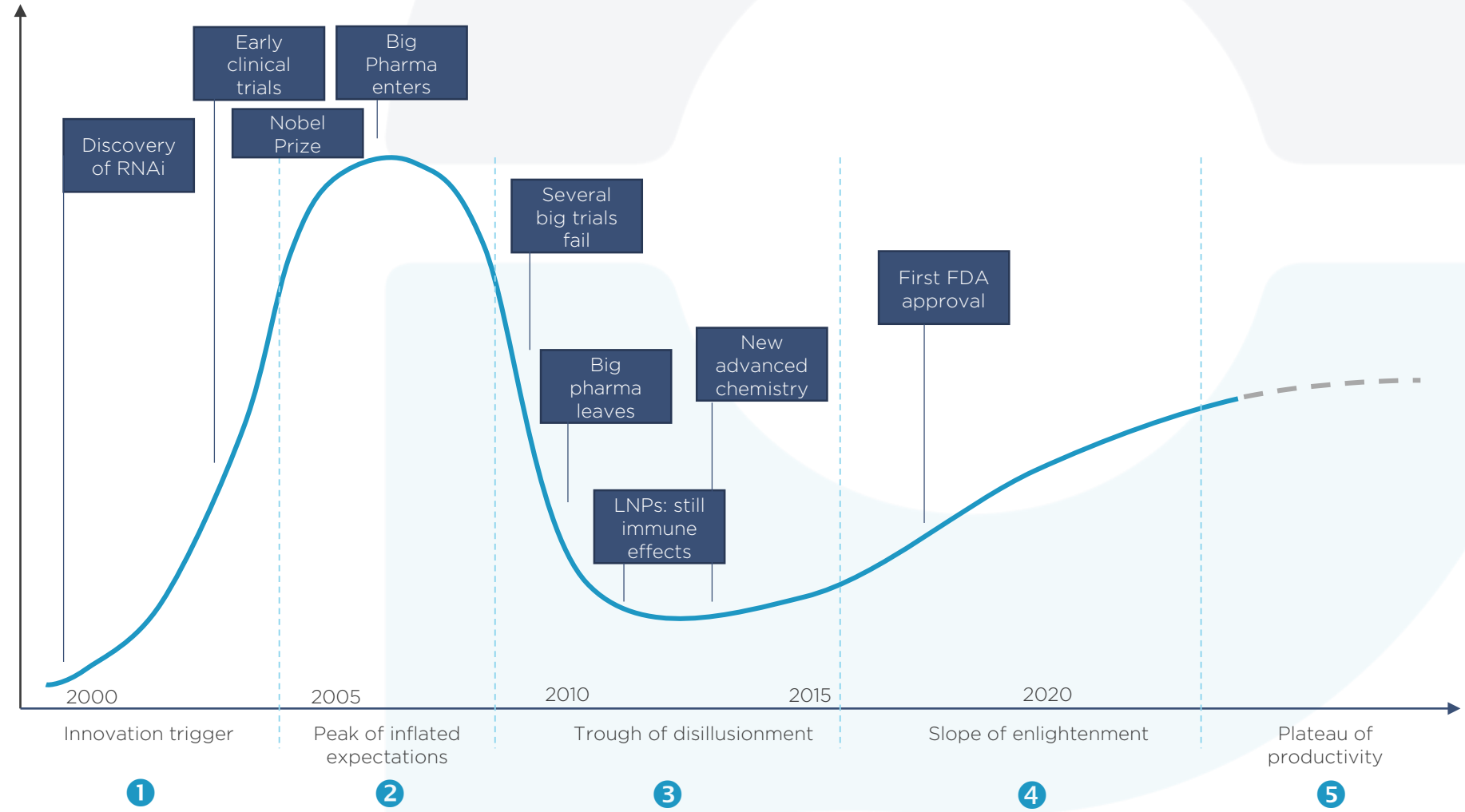
James P. Allison

Tasuku Honjo

=

The Next Generation of Immuno-Oncology Therapeutics

Gartner Hype Cycle - RNAi

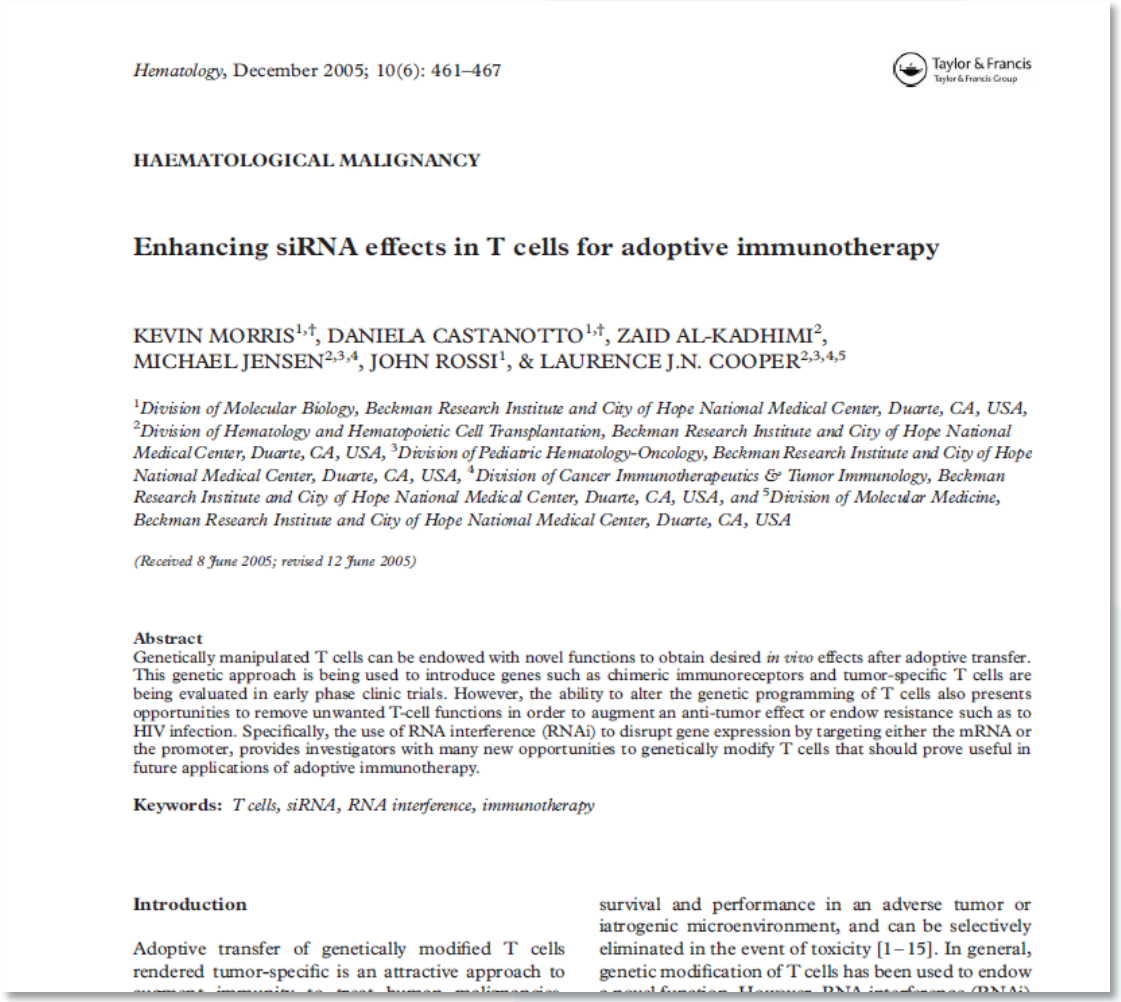


1. RNAi based therapeutics since early 2000s
2. unmodified or minimally modified compounds were rushed to the clinic with significant investment from big pharma
3. dose requirements, side effects and limited clinical efficacy created a dramatically negative view of the technology
4. advancement of core technology (chemical modifications / conjugations) triggering first approvals
5. clinical unmet needs in (cell based) IO provide additional growth platform for self-delivering RNAi

Adapted from: Khvorova & Watts, Nature Biotechnology volume 35, pages 238–248 (2017)

Phio PHARMACEUTICALS

History RNAi and ACT
concept of using siRNA in T cell ACT



Hematology, December 2005; 10(6): 461–467

Taylor & Francis
Taylor & Francis Group

HAEMATOLOGICAL MALIGNANCY

Enhancing siRNA effects in T cells for adoptive immunotherapy

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(Received 8 June 2005; revised 12 June 2005)

Abstract
Genetically manipulated T cells can be endowed with novel functions to obtain desired *in vivo* effects after adoptive transfer. This genetic approach is being used to introduce genes such as chimeric immunoreceptors and tumor-specific T cells are being evaluated in early phase clinic trials. However, the ability to alter the genetic programming of T cells also presents opportunities to remove unwanted T-cell functions in order to augment an anti-tumor effect or endow resistance such as to HIV infection. Specifically, the use of RNA interference (RNAi) to disrupt gene expression by targeting either the mRNA or the promoter, provides investigators with many new opportunities to genetically modify T cells that should prove useful in future applications of adoptive immunotherapy.

Keywords: *T cells, siRNA, RNA interference, immunotherapy*

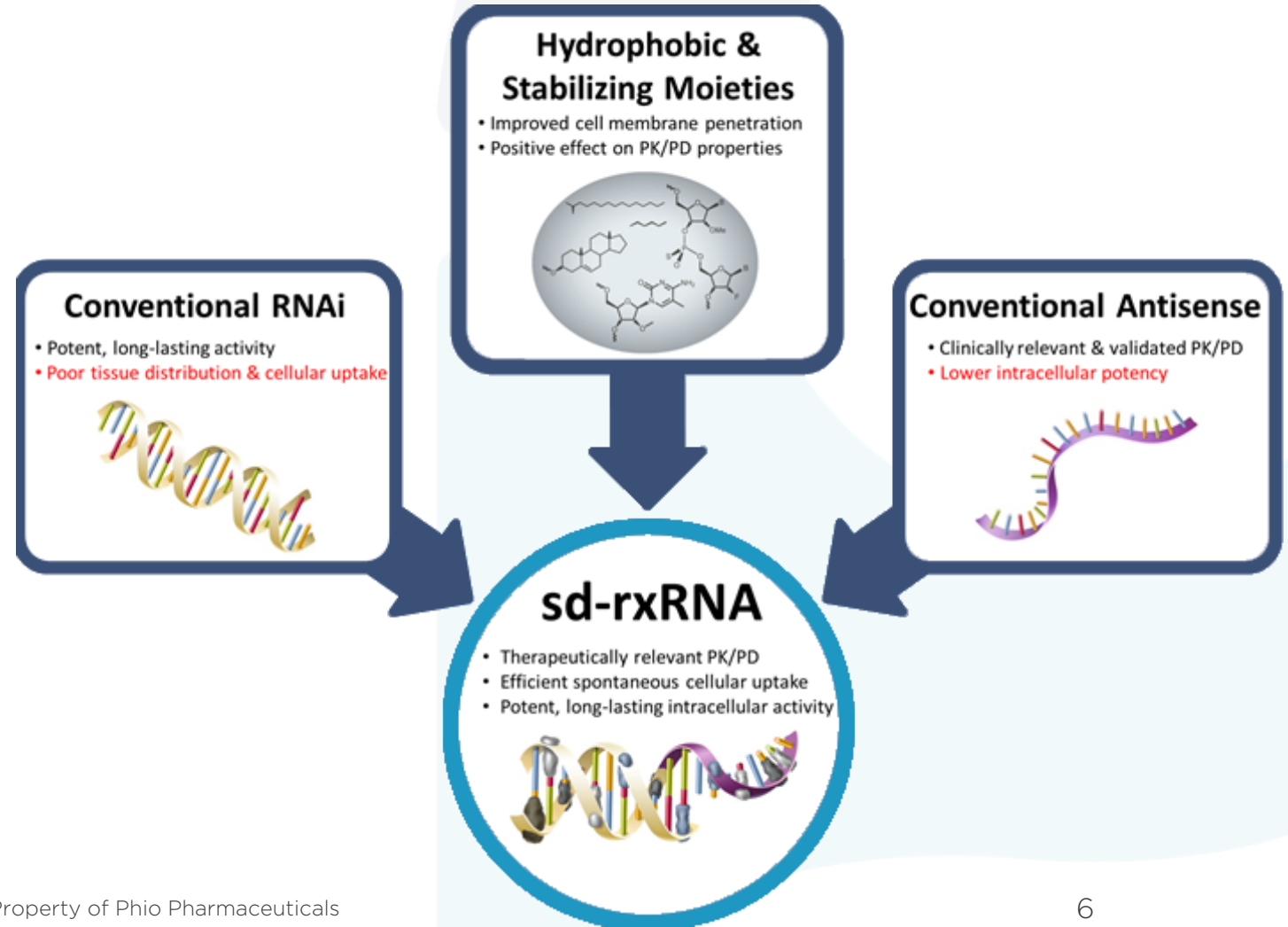
Introduction

Adoptive transfer of genetically modified T cells rendered tumor-specific is an attractive approach to

survival and performance in an adverse tumor or iatrogenic microenvironment, and can be selectively eliminated in the event of toxicity [1–15]. In general, genetic modification of T cells has been used to endow

- Morris et al., 2005:
  - RNA interference [… makes it possible to have…] clinical applications of T cells which are modified to have a desired loss of function to improve their immunobiology.
  - [Use RNAi] for T cell therapy to render T cells functionally resistant to a cytotoxic stimulus, to remove an endogenous inhibitory signal to endow T cells with supra-physiologic function, [and] to generate T cells that can function in an immunosuppressive tumor micro-environment.

self-delivering RNAi (sd-rxRNA®) Therapeutic Platform



- The sd-rxRNA platform is based on extensive chemical modifications of siRNAs
- Such hydrophobically modified siRNA molecules can penetrate all cell types *ex vivo* and *in vivo* and achieve long-lasting specific target gene knockdown
- sd-rxRNA compounds do not require any additional delivery formulations or techniques

sd-rxRNA overcomes limitations & setbacks of conventional siRNA

conventional siRNA

- limited intracellular delivery
- requires use of LNPs* and/or electroporation
- toxicity of LNPs / electroporation
- limited stability and persistence
- LNP / conjugates limit clinical use to certain tissues

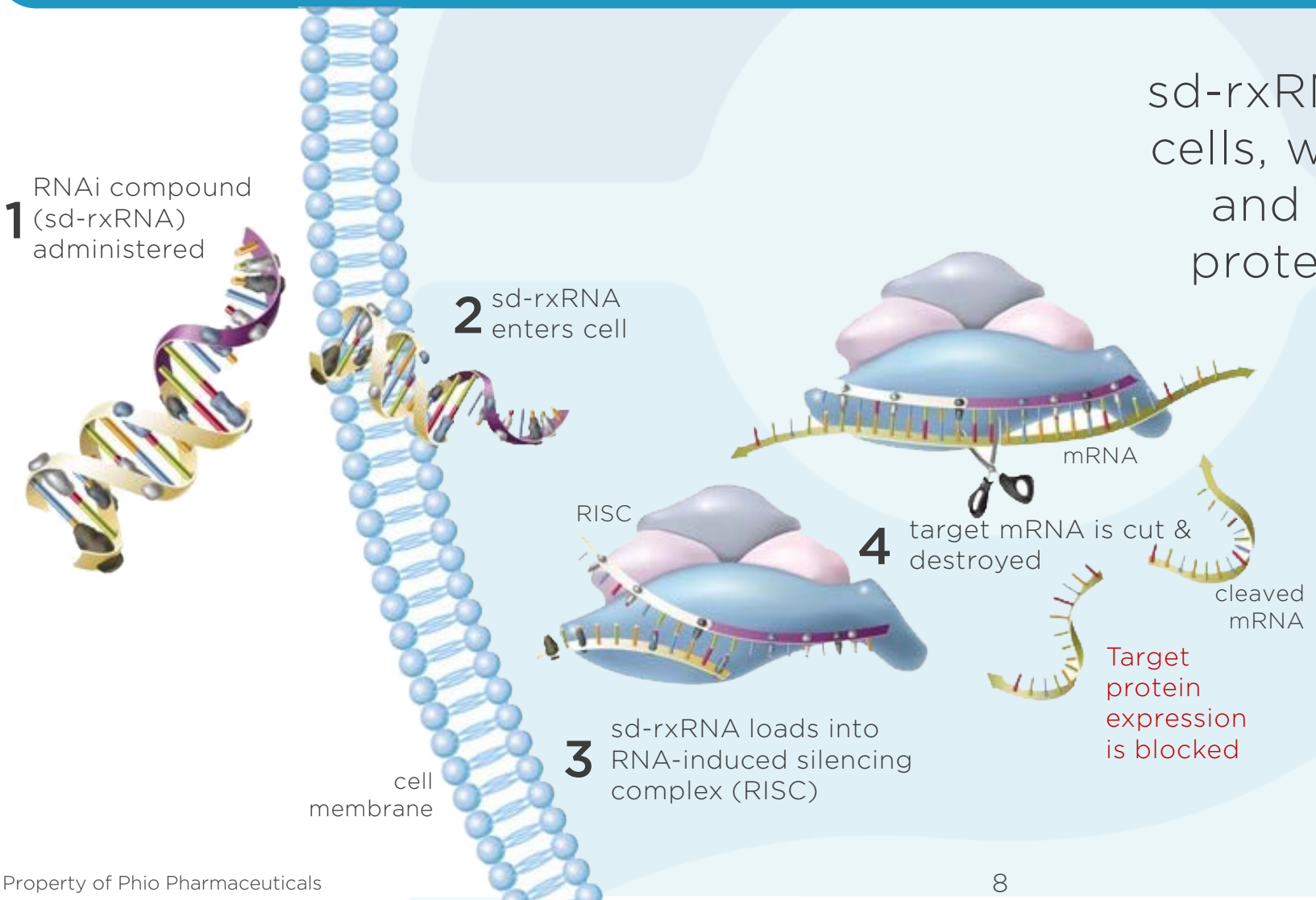
sd-rxRNA

- high spontaneous intracellular delivery
- no need for additional delivery tools
- no toxicity related to delivery
- high stability and persistence
- cell & tissue delivery not restricted

* LNP: lipid nanoparticles

self-delivering RNAi (sd-rxRNA®) Therapeutic Platform

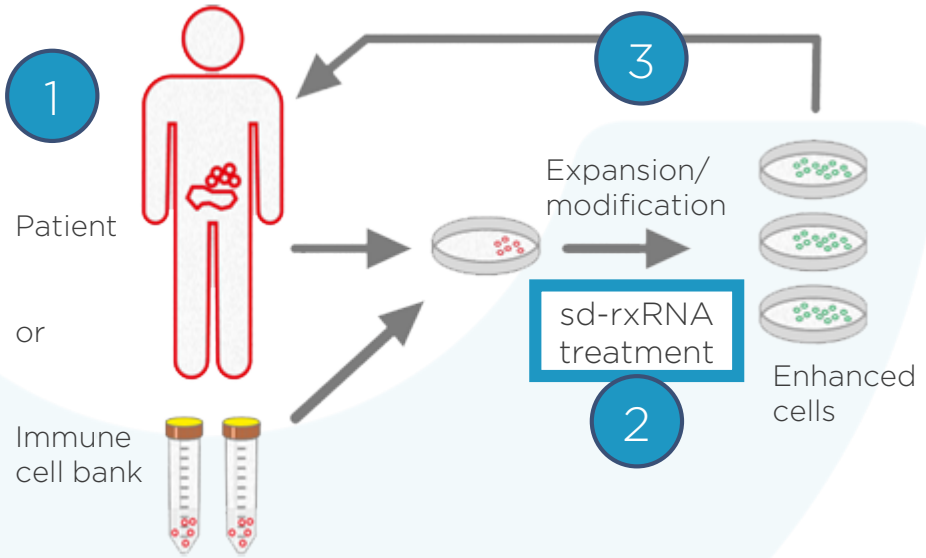
sd-rxRNA can penetrate immune cells, where antibodies fall short, and block the expression of proteins involved in a disease condition



sd-rxRNA in Adoptive Cell Therapy (ACT)
no need for LNPs, electroporation, or cell delivery methods

Using sd-rxRNA in ACT

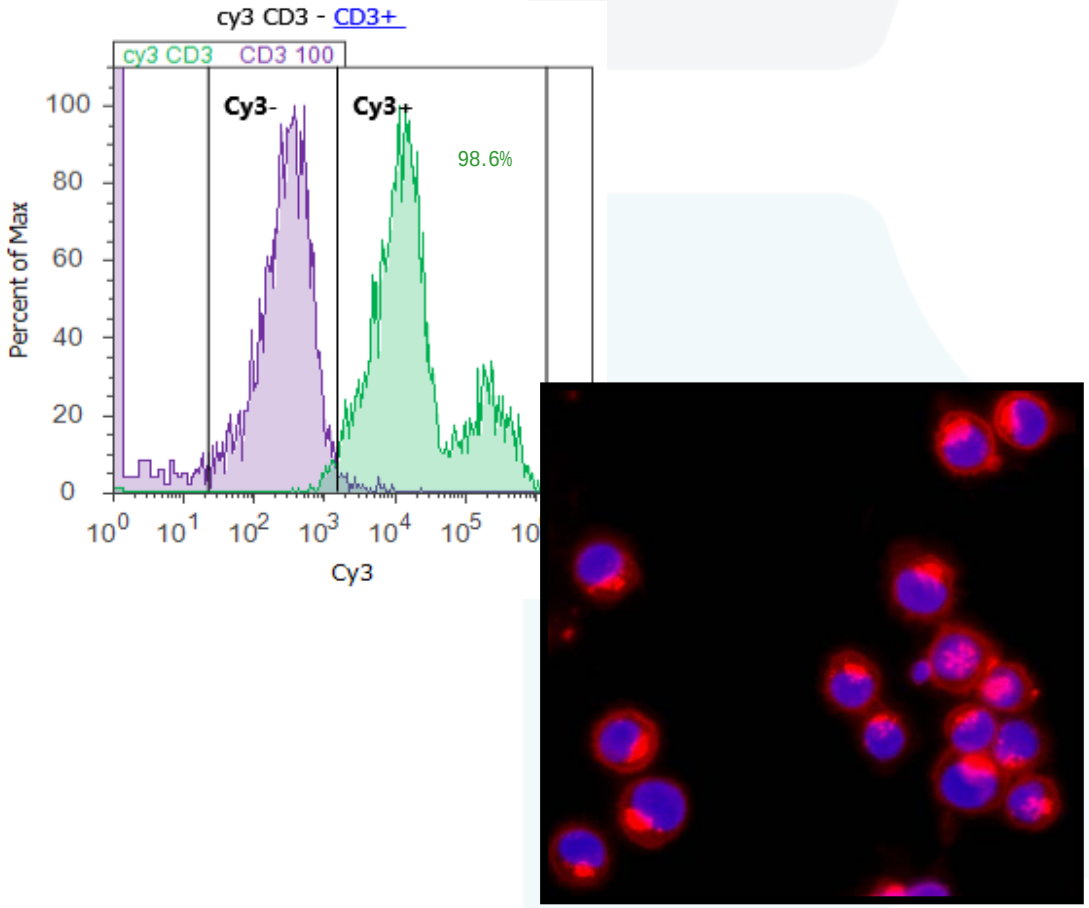
1. T cells are obtained from a patient or immune cell bank
2. Cells are expanded **and treated with Phio's self-delivering RNAi therapeutic compounds (sd-rxRNA)**
3. Enhanced cells are infused back into the patient to attack cancer



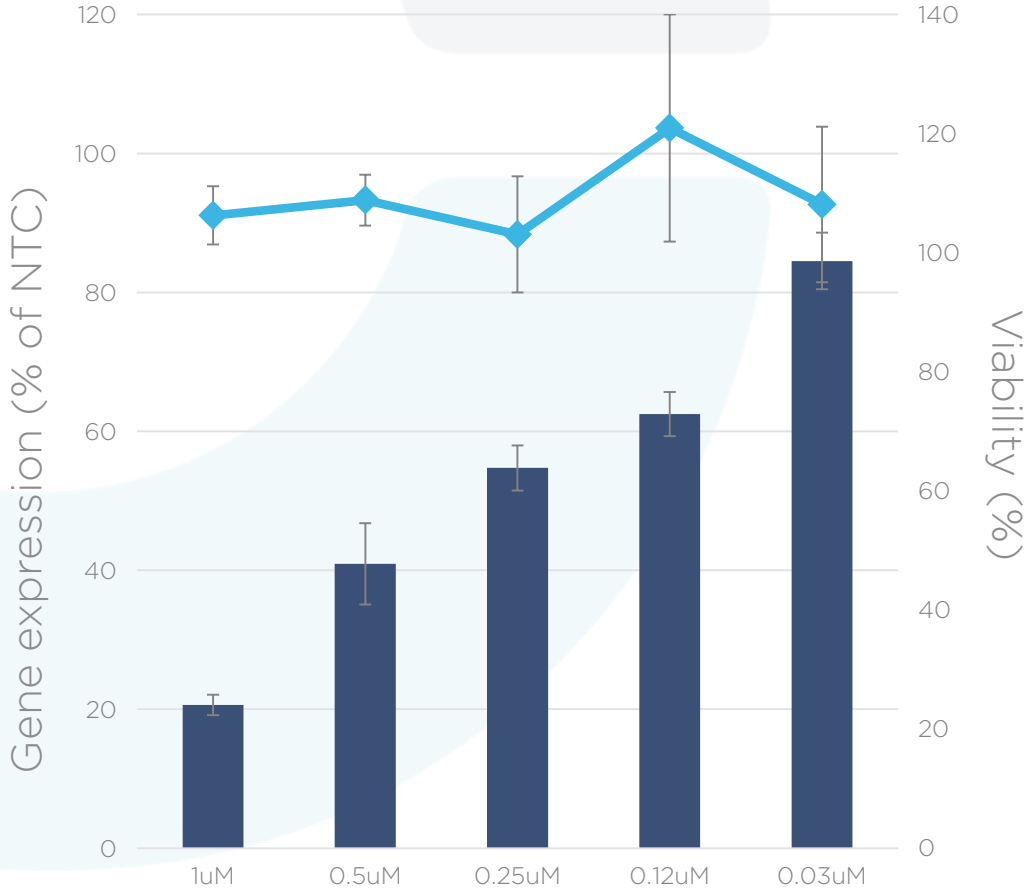
- The sd-rxRNA platform provides an easy way to modify immune cell phenotype used for ACT during the *ex vivo* manufacturing process.
- Pre-treatment of cells with sd-rxRNA compounds can be used to silence one or more genes that restricts its optimal immunobiology (such as PD-1 and other checkpoints).

High transfection efficiency with high cell viability

Nearly 100% transfection efficiency...

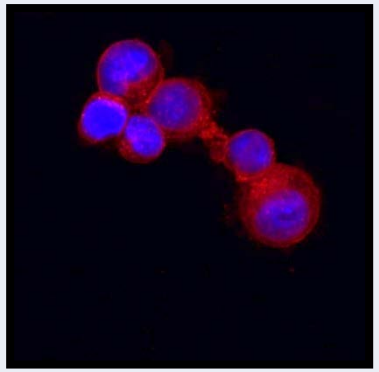


... combined with high cell viability



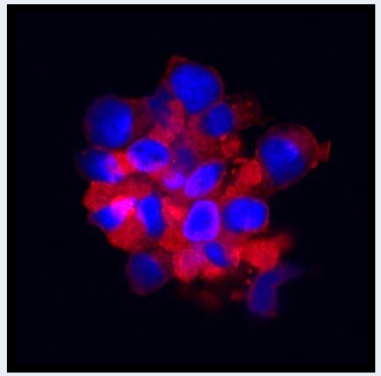
sd-rxRNA use is not limited to specific cells

Human T cells



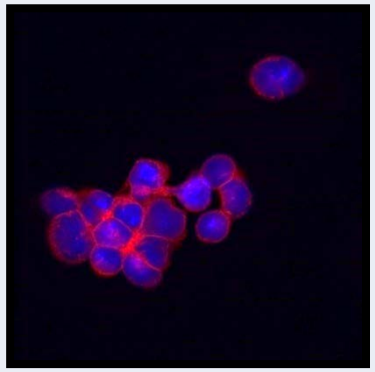
- TILs for ovarian cancer or melanoma
- HSCT for modulation of GvHD
- γ/δ T cells

Engineered T cells



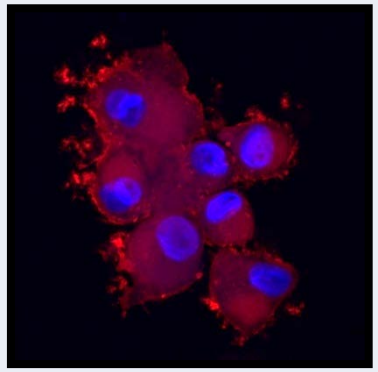
- CAR T
- TCR

Human NK cells



- Autologous or Allogeneic Natural Killer (NK) cells
- Cytokine Induced Killer (CIK) cells
- Engineered NK or CIK

Dendritic cells

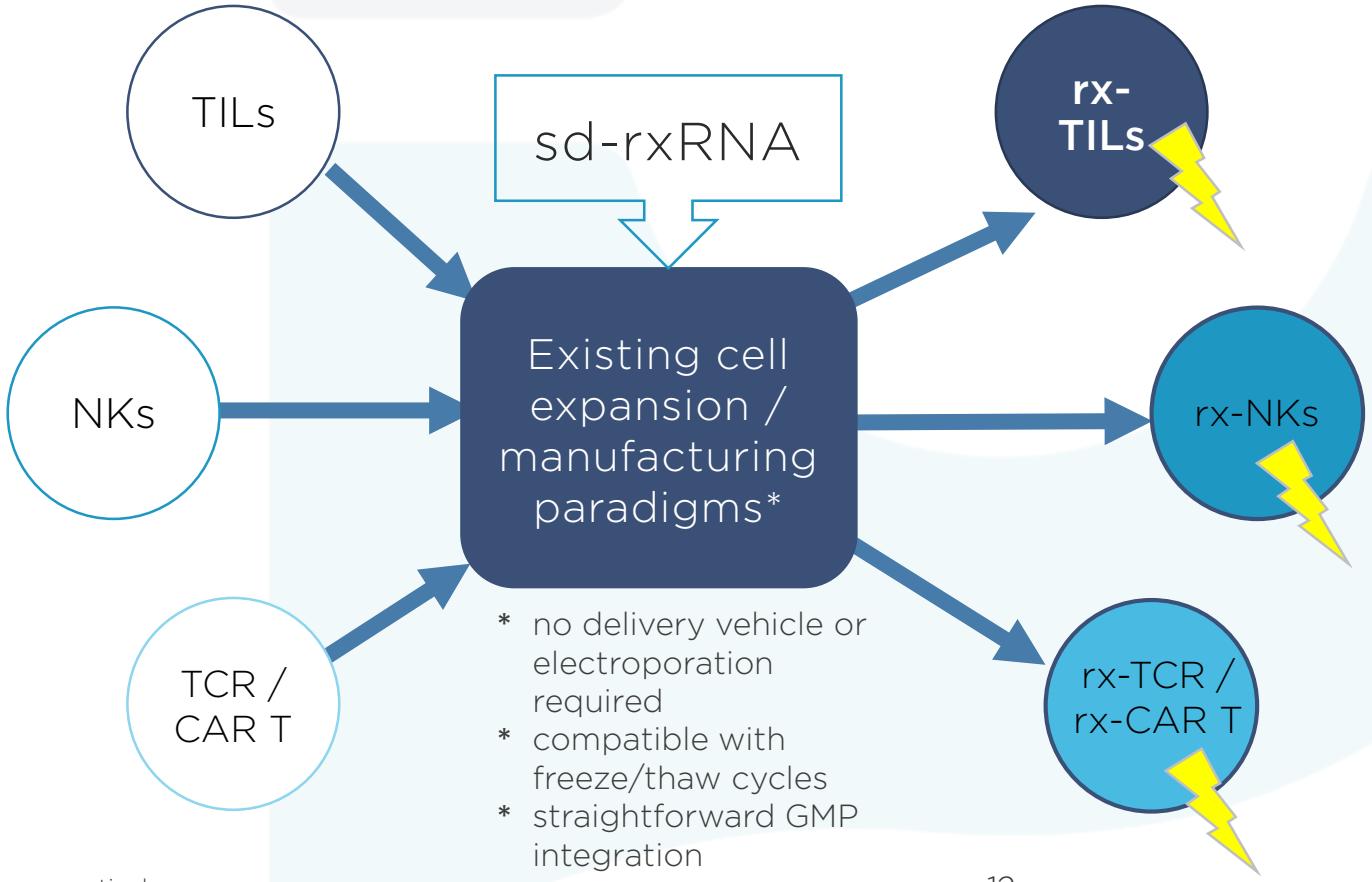


- Dendritic cell cancer vaccines

- Checkpoint inhibition and optimization for persistence and fitness of immune effector cells
- Improve existing clinical treatment paradigms and expand applicability of engineered cells

Broad applicability of sd-rxRNA platform in adoptive cell therapy

ACT Cells → Precise and selective programing of cells for ACT → Optimized cells → Improved cell based immuno-therapy



Immune effector cells that can function in an immunosuppressive tumor micro-environment:

- Checkpoint inhibition
- Enhancing long-term survival and "metabolic fitness"
- Combinations

Self-delivering RNAi can help unlock effective use of ACT in solid tumors

T Cells & Checkpoints

Checkpoint Inhibition

"Release breaks"

- TILs
- Engineered T cells

IOVANCE BIOTHERAPEUTICS

CCIT DANMARK

ACT (T cells and others) cell fitness

Cell Exhaustion / Persistence

"Improve engine and fuel"

- NK cells
- Dendritic cells
- T cells

medigene

UNIVERSITY OF MINNESOTA Driven to Discover℠

Tumor Microenvironment

Reduce TME barriers for immune cells

"Pave the road"

- Undisclosed target cells

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Karolinska Institutet

The self-delivering nature makes sd-rxRNA ideally suited for use with:

- ACT treatments (*ex-vivo* use)
- direct therapeutic use *(in-vivo)*

Pipeline of Therapeutic Development for Immuno-Oncology Therapeutics

TREATMENT	INDICATION	DISCOVERY	PRE-IND	CLINICAL
Checkpoint Inhibition in ACT (TILs)	Melanoma	RXI-762		
Checkpoint Inhibition in ACT (TILs)	Ovarian Cancer	RXI-762		
Checkpoint Inhibition in ACT (TILs)	Head & Neck	RXI-762		
Checkpoint Inhibition in ACT (TCRs)	Other	RXI-762		
Checkpoint Inhibition in ACT (T-cells)	Various	RXI-804		
Checkpoint Inhibition in ACT (other)	Various	RXI-804		
Cell Maturation in ACT	Various	Undisclosed		
Cell Metabolism in ACT	Various	Undisclosed		
Direct Tumor / TME target	Melanoma	Undisclosed		
Direct Tumor / TME target	Various	Undisclosed		
Direct Tumor / TME target	Various	Undisclosed		

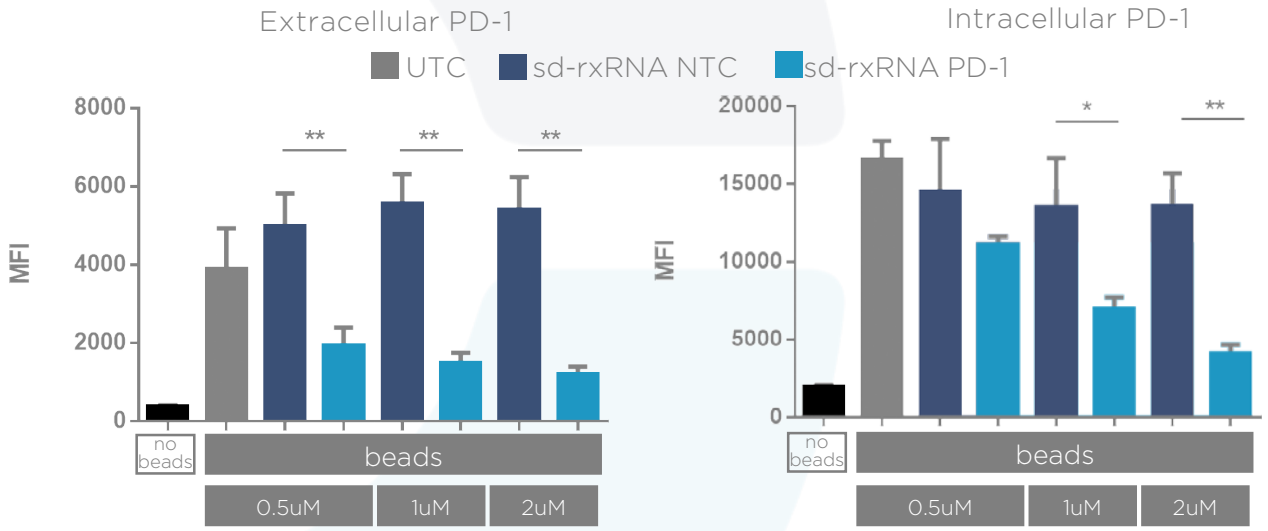
Silencing of PD-1 in T cells by sd-rxRNA - initial proof of concept

PD-1 silencing in healthy T cells by sd-rxRNA

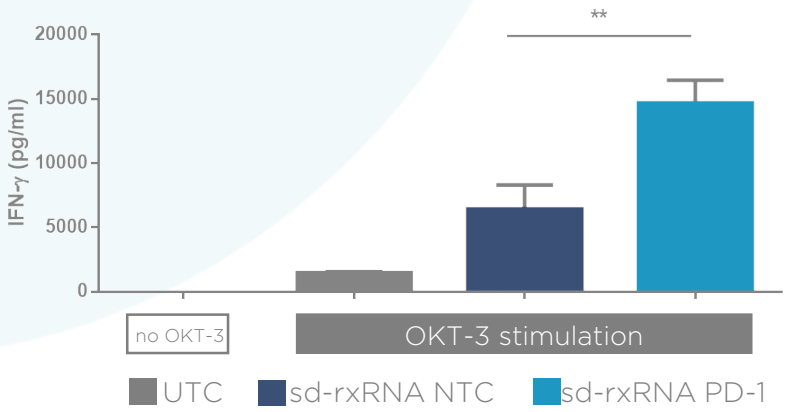
- PD-1 silencing in healthy T cells by using sd-rxRNA led to significant decrease in surface and intracellular levels of PD-1

- Activated PD-1 silenced healthy T cells produce more IFN-γ

Expression of PD-1 as Measured by FACS in Intact and Permeabilized Cells

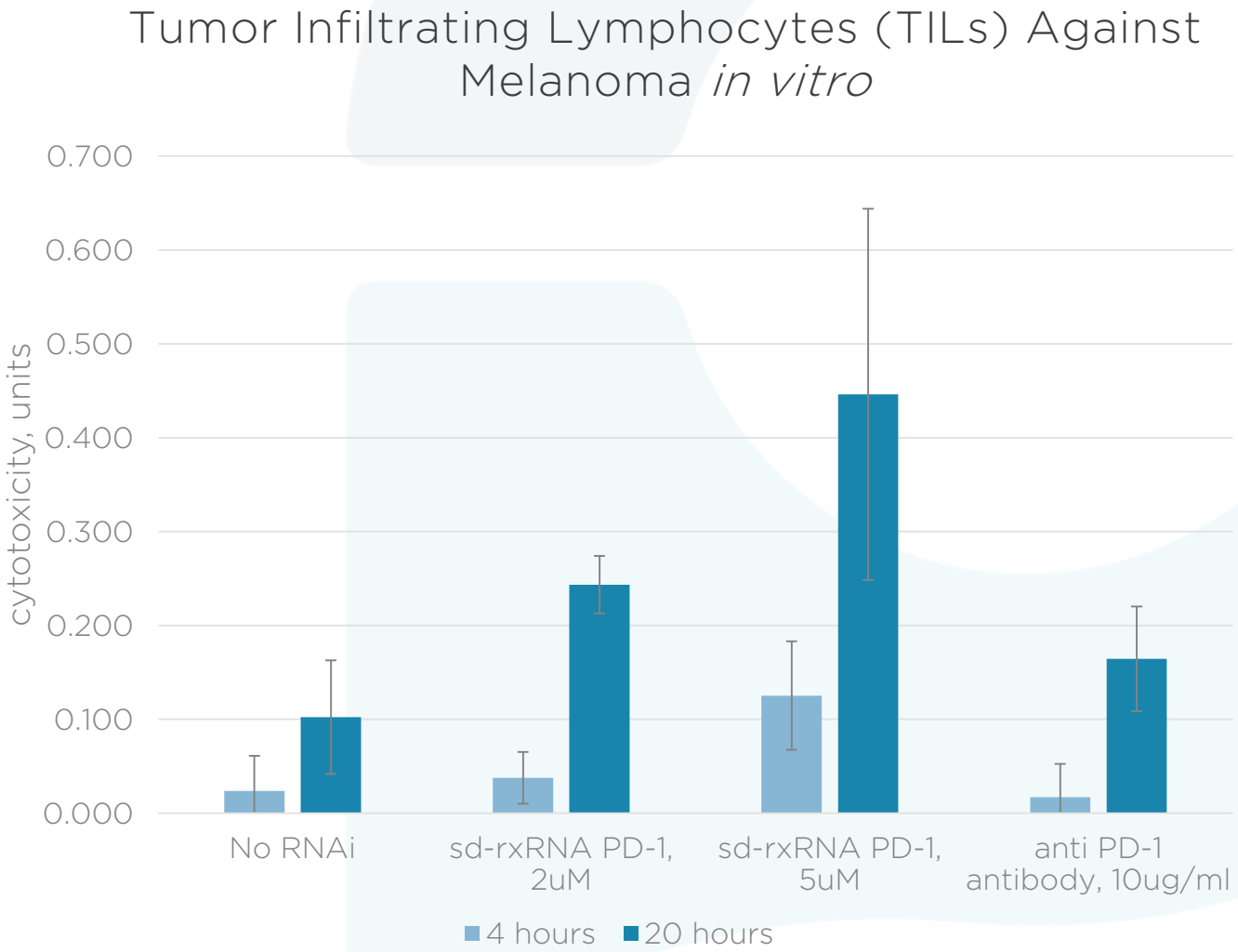


IFN-γ production by activated healthy T cells



Courtesy of R. Kiessling group Karolinska Institute

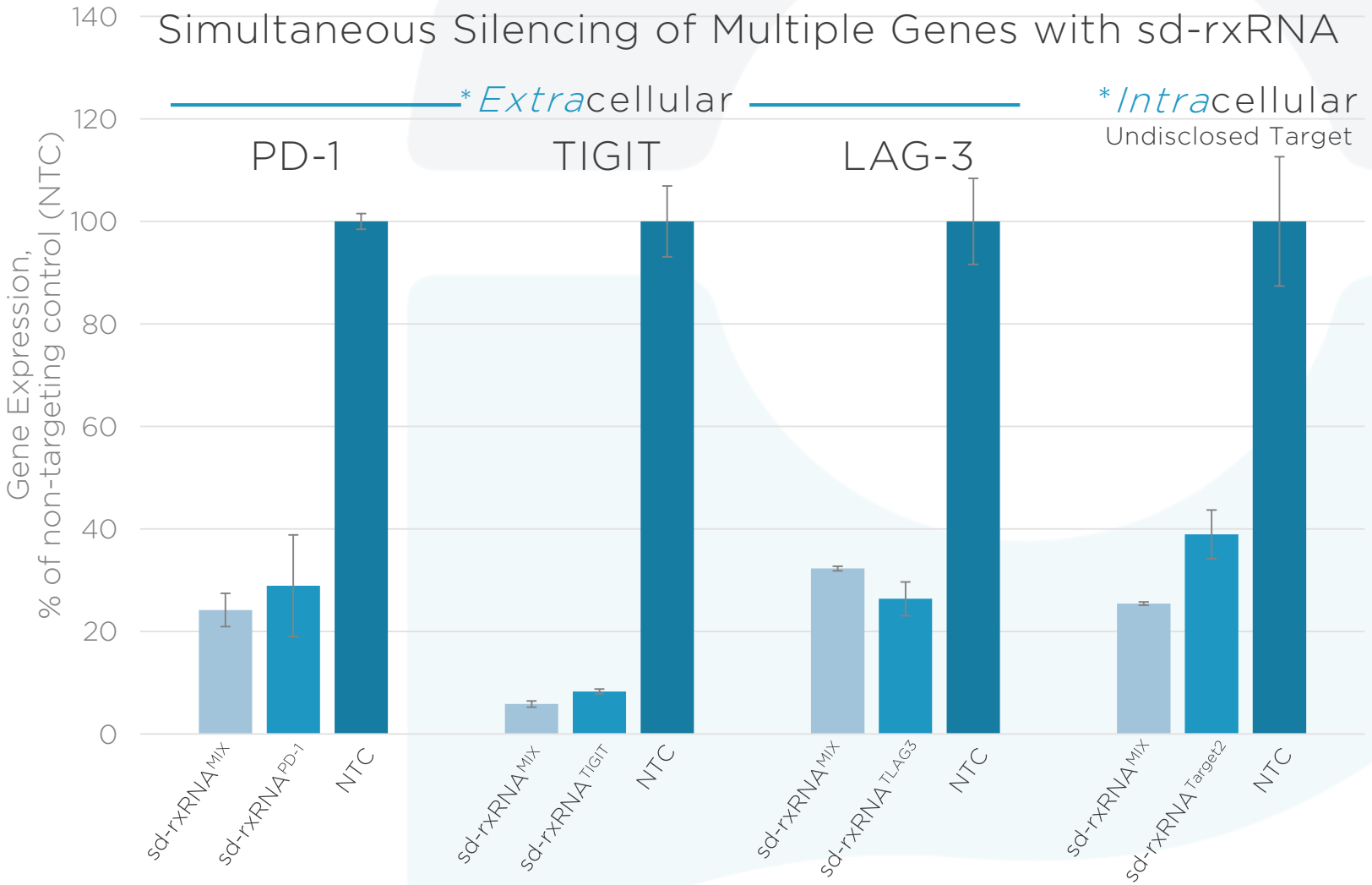
sd-rxRNA Targeting PD-1 in TILs Enhances Killing of Autologous Tumor Cells



- TILs isolated from melanoma patient
- TILs treated with a PD-1 targeting sd-rxRNA in a clinically used Rapid Expansion Protocol (REP)
- Tumor cell killing by TILs was measured by chromium release assay *in vitro*

Ligtenberg et al., Self-Delivering RNAi Targeting PD-1 Improves Tumor-Specific T Cell Functionality for Adoptive Cell Therapy of Malignant Melanoma, Molecular Therapy (2018)

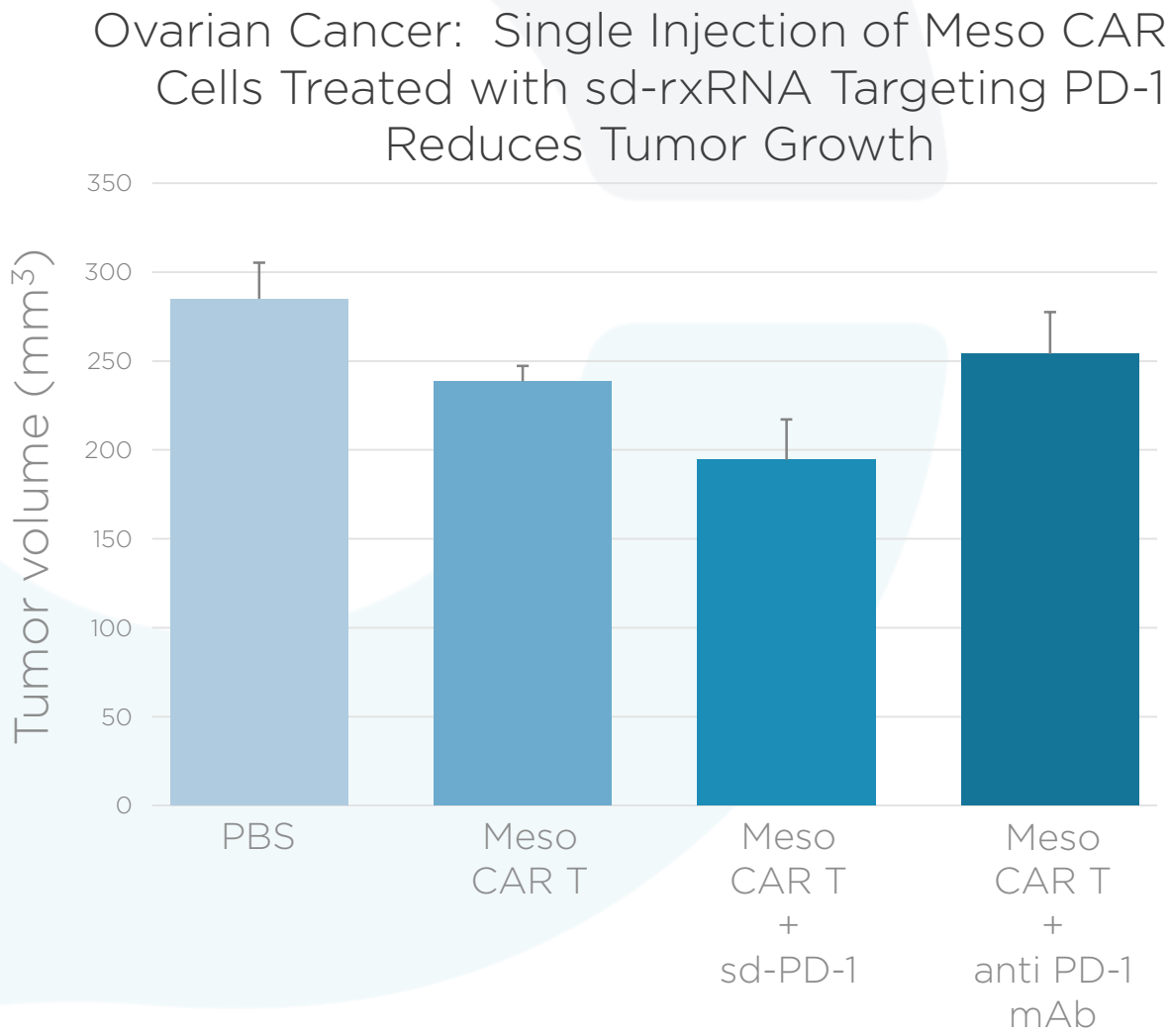
Targeting Multiple Immunosuppression Pathways* in a Single Therapeutic Entity



- Equal levels of silencing of individual protein targets (whether intracellular or extracellular) or in combination can be obtained with sd-rxRNA
- Simultaneous silencing of multiple genes is a major advantage of sd-rxRNA compared to other technologies

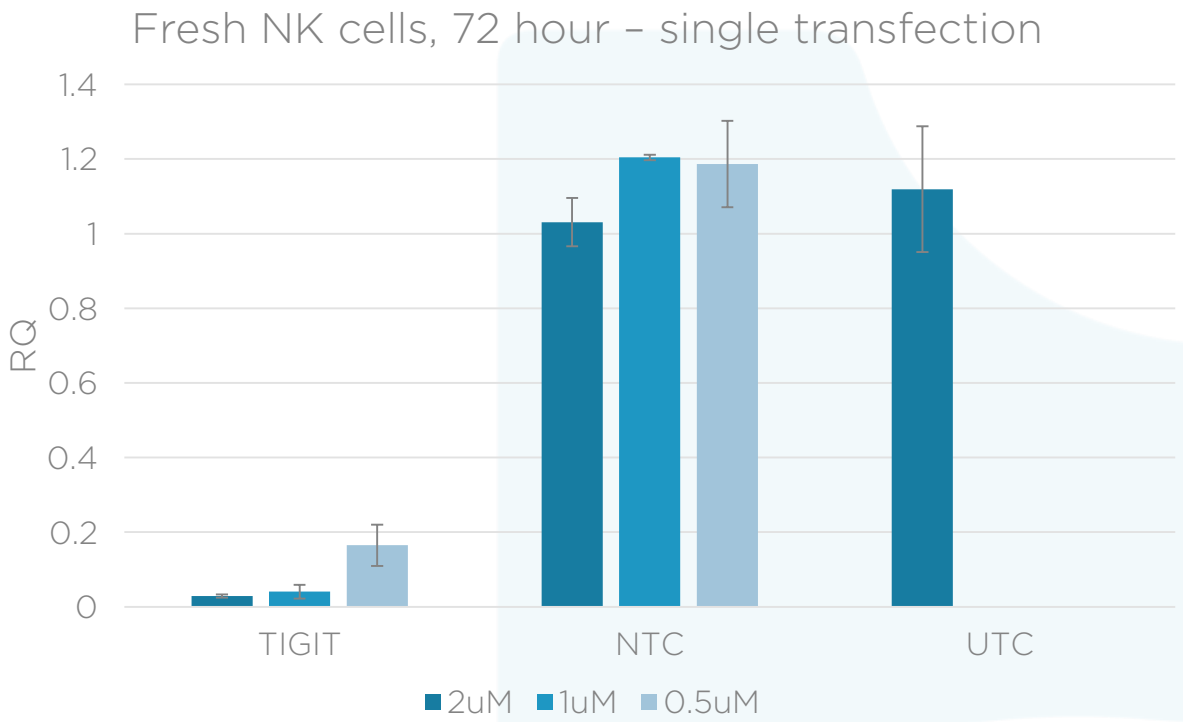
Longevity of sd-rxRNA with ACT *in vivo*

- Mouse xenograft model of ovarian cancer
- Meso CAR T-cells: T cells engineered to target mesothelin, overexpressed on many solid tumors
- Meso CAR T-cells were pre-treated with sd-rxRNA *ex vivo* and injected into human ovarian cancer tumors in mice
- Reduction of tumor growth is significantly improved 1 month after a single injection of anti-PD-1 sd-rxRNA treated Meso CAR T-cells

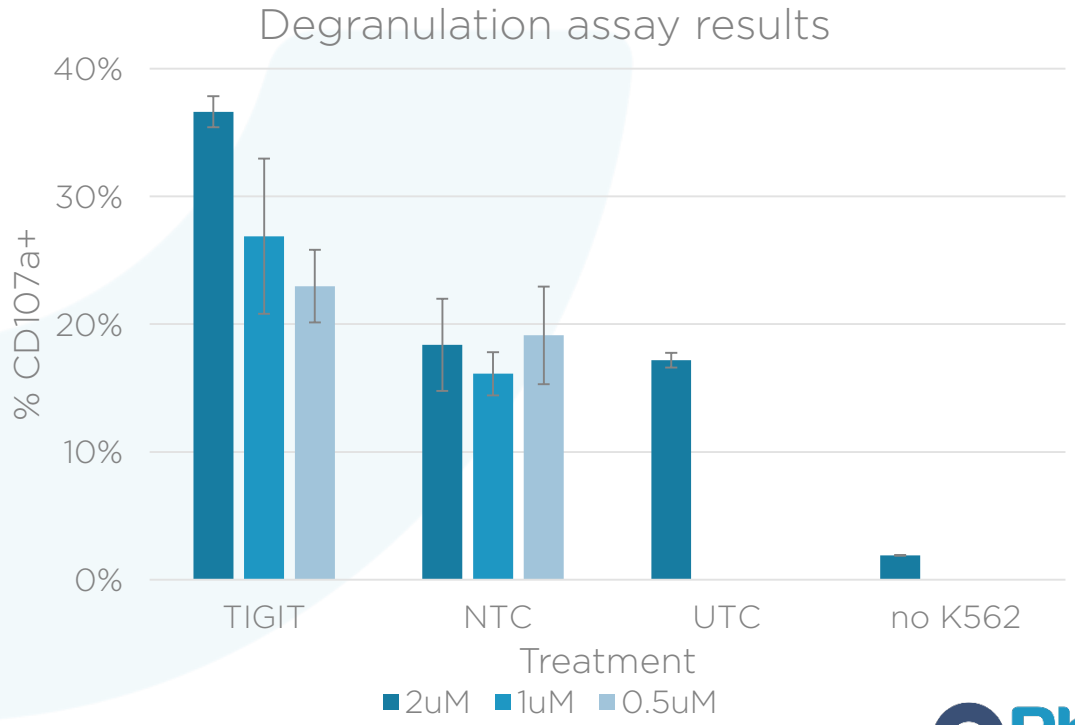


Beyond T cells: Weaponizing of NK cells by using sd-rxRNA

A single dose of TIGIT targeting sd-rxRNA is able to reduce TIGIT mRNA levels by greater than 95% after 72h



A dose dependent reduction of TIGIT protein by TIGIT targeting sd-rxRNA results in a dose dependent increase in cytotoxic capacity of NK cells



Extramural collaborations – TILs and TCRs

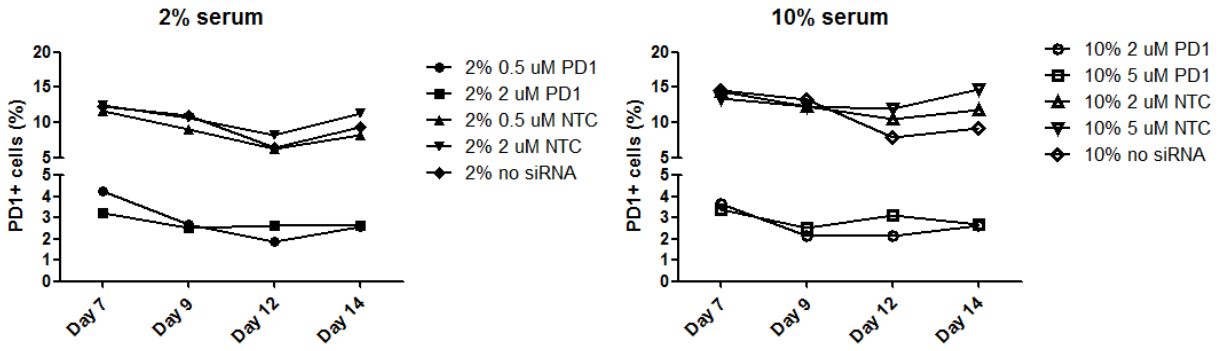
Center for Cancer Immune Therapy (CCIT)

- Evaluating sd-rxRNA compounds targeting immune checkpoints in preclinical screening models of matched TIL/tumor cell pairs from melanoma and ovarian cancer patients

Medigene AG (FRA: MDG1)

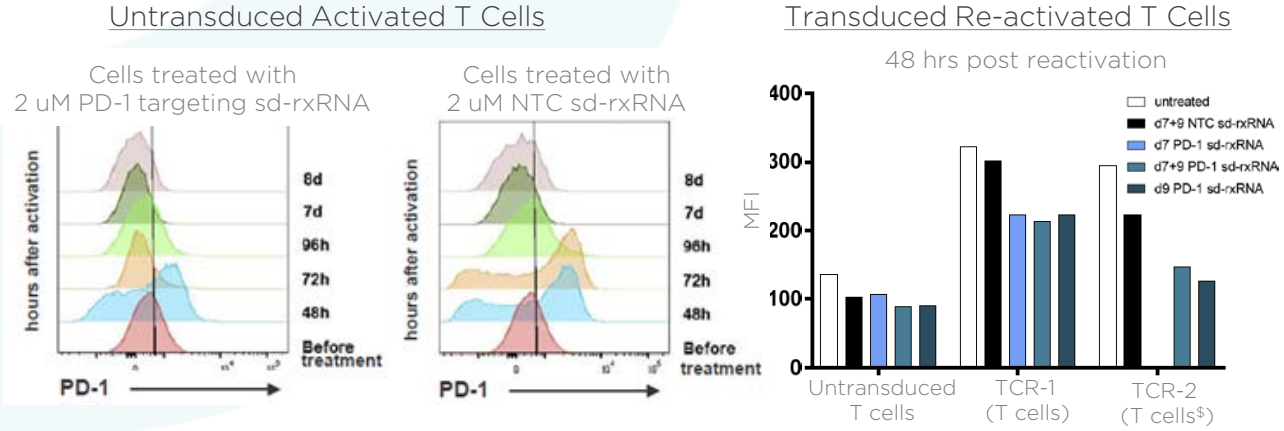
- Evaluating sd-rxRNA compounds targeting immune checkpoints and/or other immuno-suppressive targets in combination with Medigene's recombinant TCRs to develop modified T cells with enhanced efficacy for the treatment of solid tumors.

Marked PD-1 Reduction on Surface of TILs in Pilot Rapid Expansion Protocol



Courtesy of Dr. Özcan Met & Christina Friese – CCIT-DK

Observe reduction* of PD-1 surface Levels in Activated T cells (non-engineered) as well as Transduced (engineered) re-activated T cells

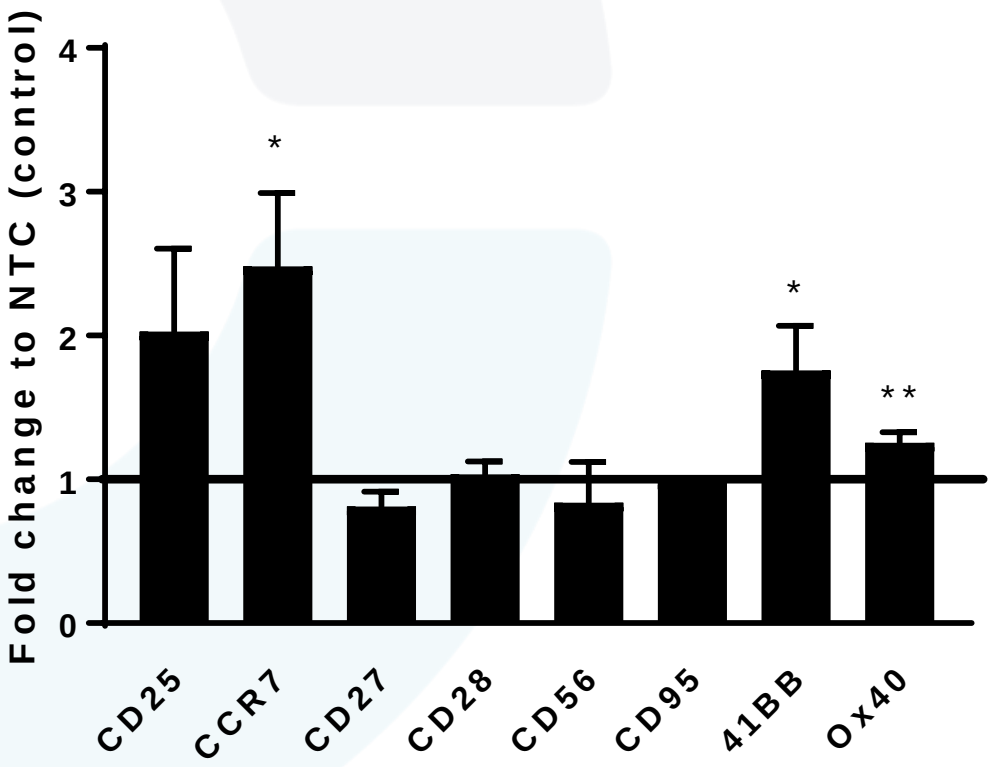


Courtesy of Dr. Manon Weis – Medigene AG

*) silencing activity not optimized for maximal effect
$) Day 7 PD-1 treated TCR-2 cells not measured

Iovance Biotherapeutics collaboration

- Testing of sd-rxRNA mediated gene silencing in Iovance's TIL manufacturing process, evaluating TIL phenotype
- sd-rxRNA-mediated knock down of PD-1 was associated with phenotypic changes indicative of TIL activation
- Next steps include:
  - further evaluation of impact of sd-rxRNA mediated gene silencing on TIL tumor reactivity
  - implementation of optimized silencing protocols and scale-up thereof



PD-1, n>6, preps from pre-REP melanoma/Fresh breast cancer TILs, 2uM sd-rxRNA

Courtesy of Dr. Inbar Alfaguter - Iovance Biotherapeutics, Inc.

sd-rxRNA: Filling the Unmet Need of Other Therapeutic Approaches

Feature / Advantage	sd-rxRNA	Gene editing	Antibodies	Small molecules
Act upstream in protein synthesis	+	+	-	-
Can target intra- & extracellular proteins	+	+	-	+
Can be used for “undruggable” targets	+	+	-	-
Does not permanently change genome	+	-	+	+
Potential for long duration of action	+/-	+	-	-
Can target multiple proteins w/o issues	+	-	-	+/-
Potentially “off-the shelf” / personalized Tx	+	-	+	+
Low regulatory hurdle	+	-	+	+
Low cost of goods	+	-	-	+
Straightforward GMP integration	+	-	+/-	+

Logistical, clinical and commercial benefits

	Consideration	Commentary
Scientific & logistical	Delivery	▪ 100% transfection with ex-vivo use in ACT & no major changes required in current manufacturing approach. ▪ Extensive tissue distribution and cellular uptake with tissue injection but use in IO is limited to injectable tumors
	Safety	▪ Platform with proven safety in preclinical and clinical settings at high doses ▪ Low / no impact on cell viability in ACT setting
	Efficacy	▪ Extending Tx potential of current ACT and other IO therapies ▪ Potential to treat otherwise undruggable targets & ▪ Potential for more personalized treatments
Commercial	Regulatory aspects	▪ FDA & EMA have shown favorable attitudes towards RNAi therapeutics ▪ Clean regulatory track w/ clinical development for non life threatening diseases
	Cost / Pricing	▪ Low intrinsic cost of RNAi molecules (compared to antibodies) ▪ Can lower overall treatment cost (e.g. limit checkpoint antibody use, lower complexity of cell manufacturing)
	Market potential	▪ Approved ASO and RNAi therapeutics (as well as approved cell-based IO therapeutics) have established the commercial potential

Clinical Development Path for Lead Compound

INDICATION
Preclinical data available to support selection of target indication

Complete

MONTH 3

MONTH 6

CLINICAL GRADE SD-RXRNA
Product available and regulatory documentation on manufacturing being compiled

Complete

PHENOTYPIC DATA
In-vitro efficacy and safety data available for regulatory submission

Process underway

MONTH 9

UPSCALED
Cell manufacturing scale-up complete

MONTH 12-15

REGULATORY FILING
Submission to authorities and ethics committee

STUDY START
Approval received for first patient dosing

MONTH 18

Business Objectives 2019

- Develop sd-rxRNA based immuno-oncology therapeutics and promote growth and financial stability by:
  - Entering the clinic with lead product within 12 months
  - Securing a licensing deal(s) in I-O space within 12 months
  - Transition new sd-rxRNA compounds from discovery research to active development within 12 months
    - targets outside checkpoints and/or for other cell types
    - targets for direct intratumoral / intranodal use
  - Expanding external collaborations
  - Finalize partnering / out-licensing of Dermatology and Ophthalmology Franchises

Financial Overview

Cash and cash equivalents* (a/o 12/31/2018)	**~$14.9M**
Burn rate	**$2.0M/quarter**
Cash runway (excluding equity line)	**Q3 2020**
Remaining funds available from equity line	**~$13.3M**
Common shares outstanding (a/o 12/31/2018)	**~18.8M**
Market Cap (a/o 12/31/2018)	**~$6.2M**

* Unaudited