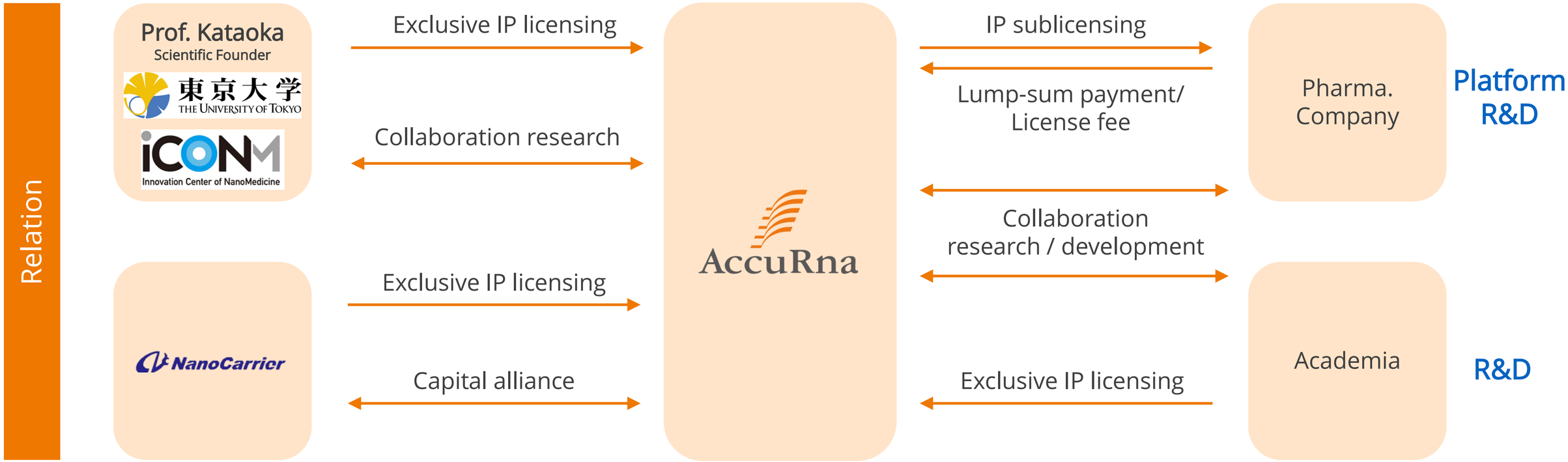
AccuRna

Corporate Overview

May 2018 AccuRna Inc.

Business scheme (Strategic Alliance to advance new therapy)

AccuRna can collaborate with Pharmaceutical companies based on DDS technologies invented by Prof. Kataoka



Role

- Academic technology development
- Introduction of alliance partner
- Technical advice

- Commercialization of technology
- Project management
- IP management

Overview of the market

Nucleic acid medicine with many benefits are expected to rapidly expand the market

Summary of the world market of nucleic acid medicine

Merits

- Target molecules that low molecular and antibody drugs cannot reach can be a target for drug discovery.
- A fundamental treatment for lethal genetic diseases (incurable or rare diseases) can be achieved.

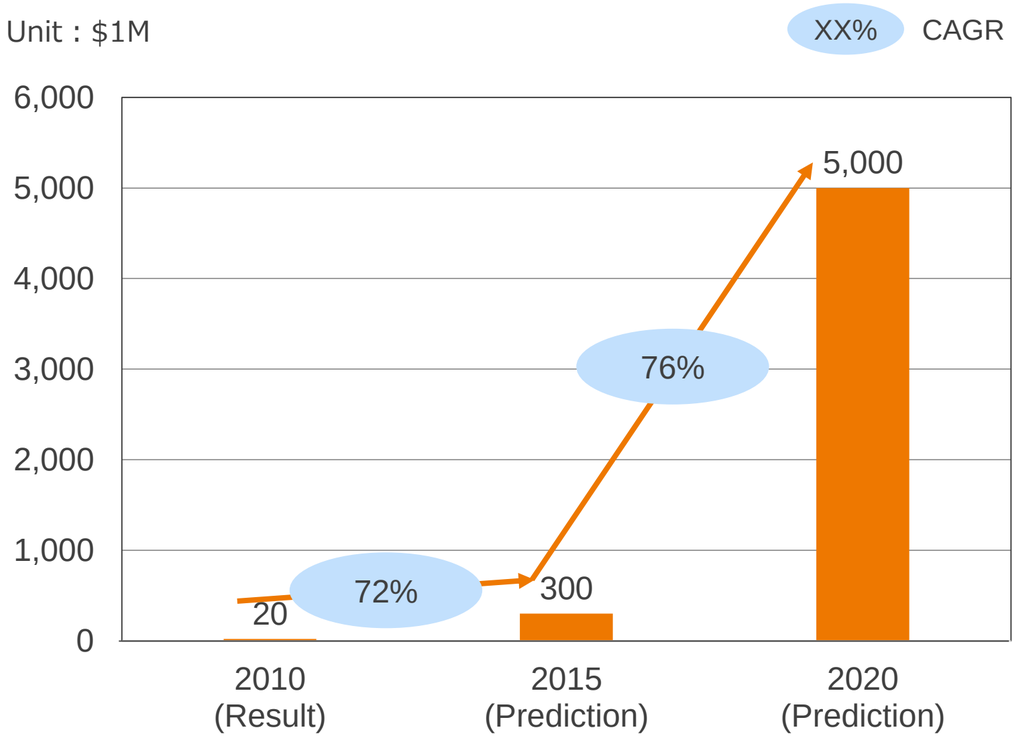
Challenges

- Low delivery efficiency to target organs and tissues due to low stability in the body
- Inflammation induction

Trend / Scale

- The application has been expanded to cancer, infectious and genetic disease
- Over 140 clinical trials has been conducted in the world and 5 product has been launched
- The market is expected to become bigger after 2020 (right figure)

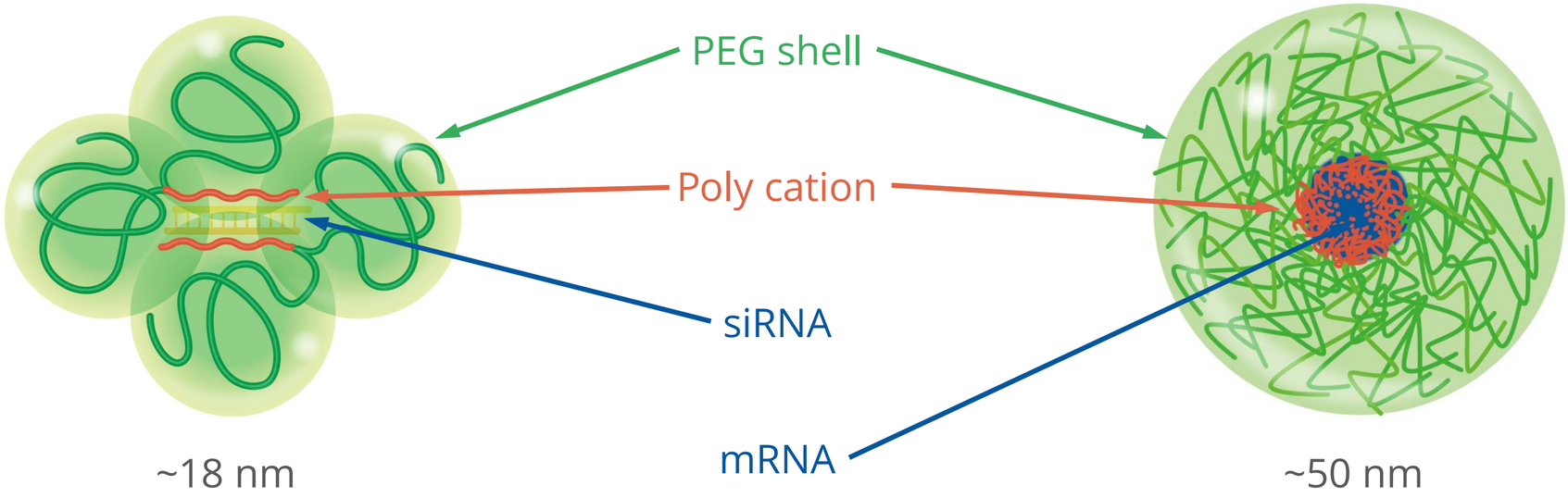
The world market scale of nucleic acid medicine



”Preliminary survey toward the establishment of a co-production facility for nucleic acid drugs,”
Seed Planning, Inc., 2011

Solution

AccuRna's two DDS can contribute to the market expansion of nucleic acid medicine and create great economic value



unit poly ion complex (uPIC) for Short chain

uPIC is as simple solution for DDS of short chain nucleic acid therapeutics

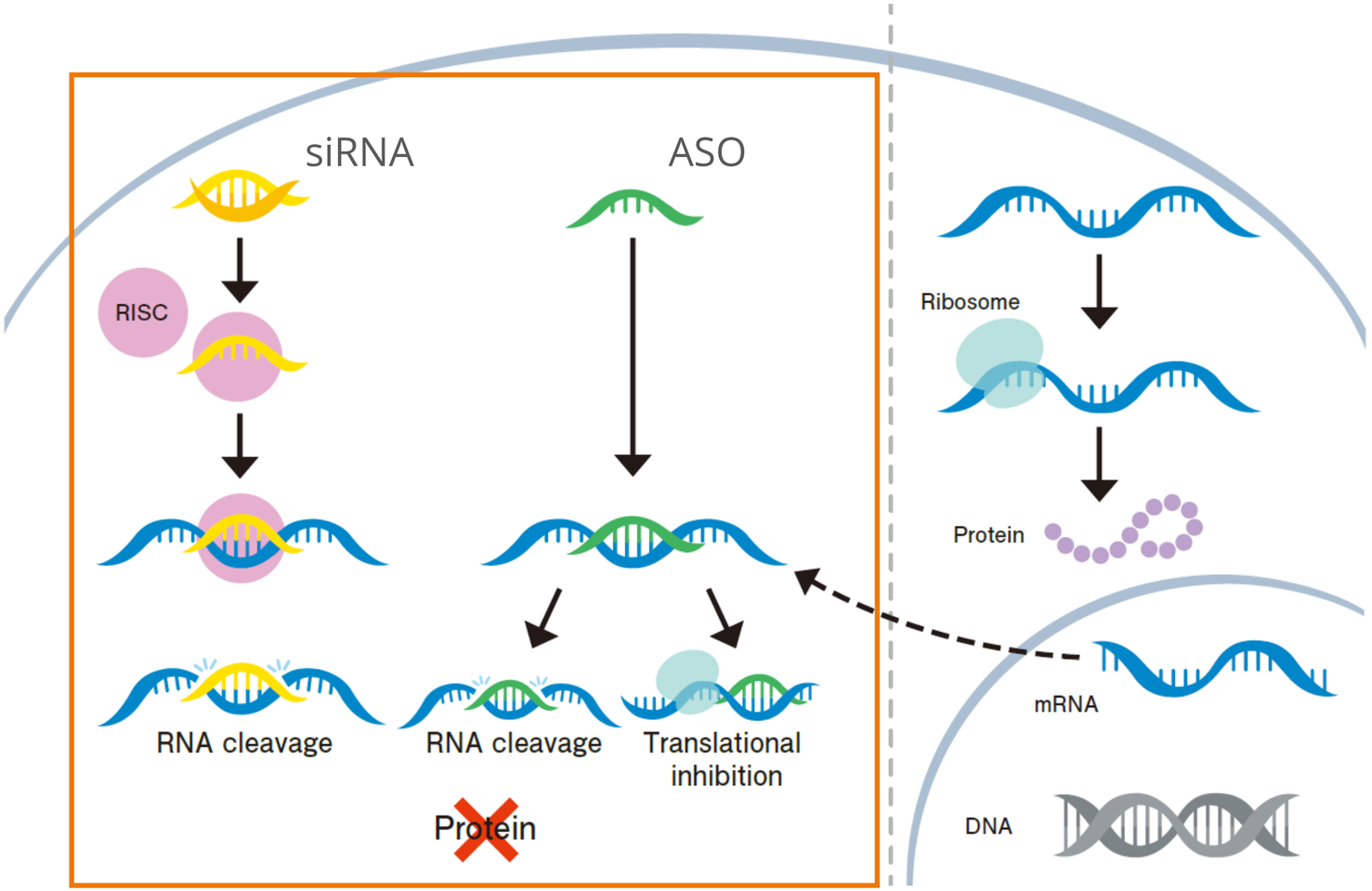
Polyplex micelle for long chain

Our polyplex micelle enables development of mRNA therapeutics

AccuRna’s unique DDS for Short Chain Nucleic Acid Therapeutics

- Antisense Oligonucleotide (ASO)
- Short Interfering RNA (siRNA)
- Micro RNA mimic (miRNA)

Mechanism of action for ASO and siRNA



Merits

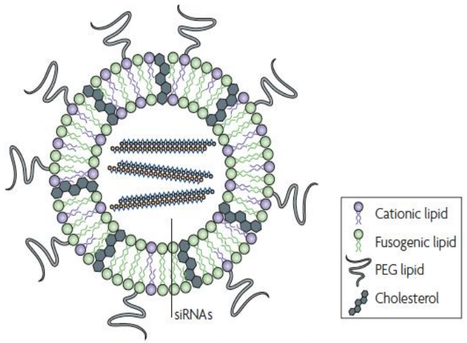
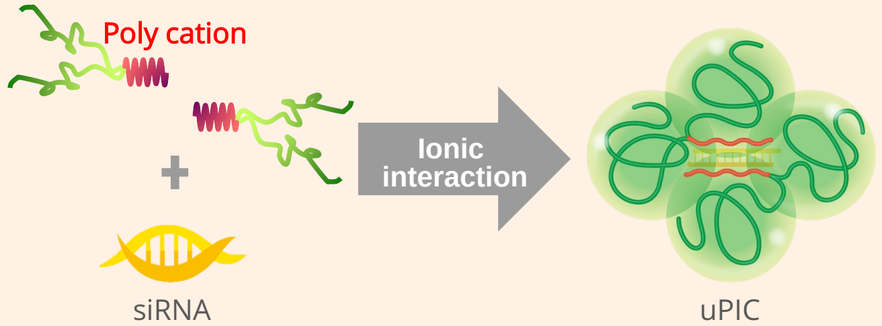
- Sequence-specific suppression of gene expression
- No genome damage
- Broad target selection
- Applicable to ncRNA

Challenges

- Unstable in blood (Nuclease attack)
- Low cell permeability
- Immunogenicity
- Poor delivery to target organ
- DDS System

Novel DDS technology: unit Poly Ion Complex (uPIC)

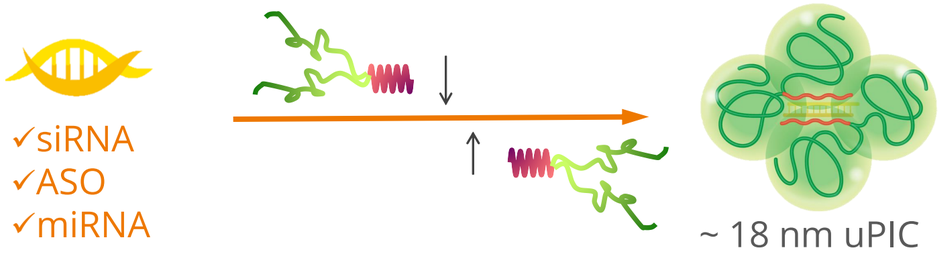
uPIC is a simple solution for DDS of short chain nucleic acid therapeutics as siRNA, ASO and miRNA

	Conventional Technology (LNP)	AccuRna's technology (uPIC)
Diagram		
Size	~ 90 nm	~ 18 nm
Delivery	Accumulation into liver and tumor	Accumulation into tumor
Production	Mixture of several components	Electrostatic complex formation
Human experiences in oncology	3 trials for siRNA have been discontinued ➢ POC has been established but not much enough activity + liver toxicity	No human experience so far ➢ GLP toxicology studies were conducted with a given siRNA towards P1 in 2019

Novel DDS technology: unit Poly Ion Complex (uPIC)

uPIC stabilizes nucleic acid therapeutics in mice body thus achieving improved retention in blood, accumulation into a tumor and greater antitumor effects (Data from Kataoka Lab., iCONM)

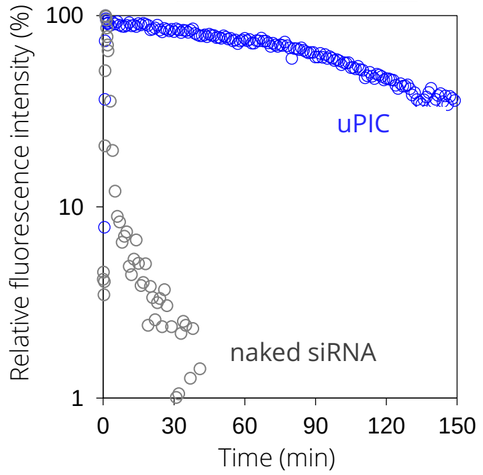
Formulation of uPIC



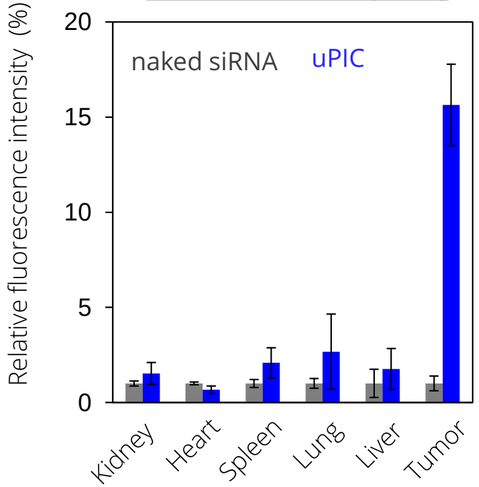
Characteristics of uPIC

- Simple preparation
- Electrostatic interaction of polycation with negatively charged nucleic acids
- Improved retention in blood
- Accumulation of nucleic acid medicines into a tumor

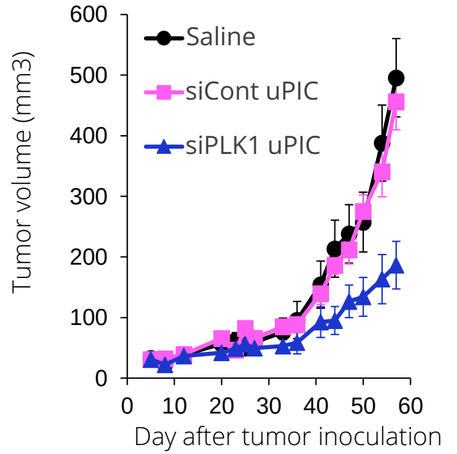
Blood circulation



Biodistribution (48 h)



Antitumor effect in a pancreas cancer model

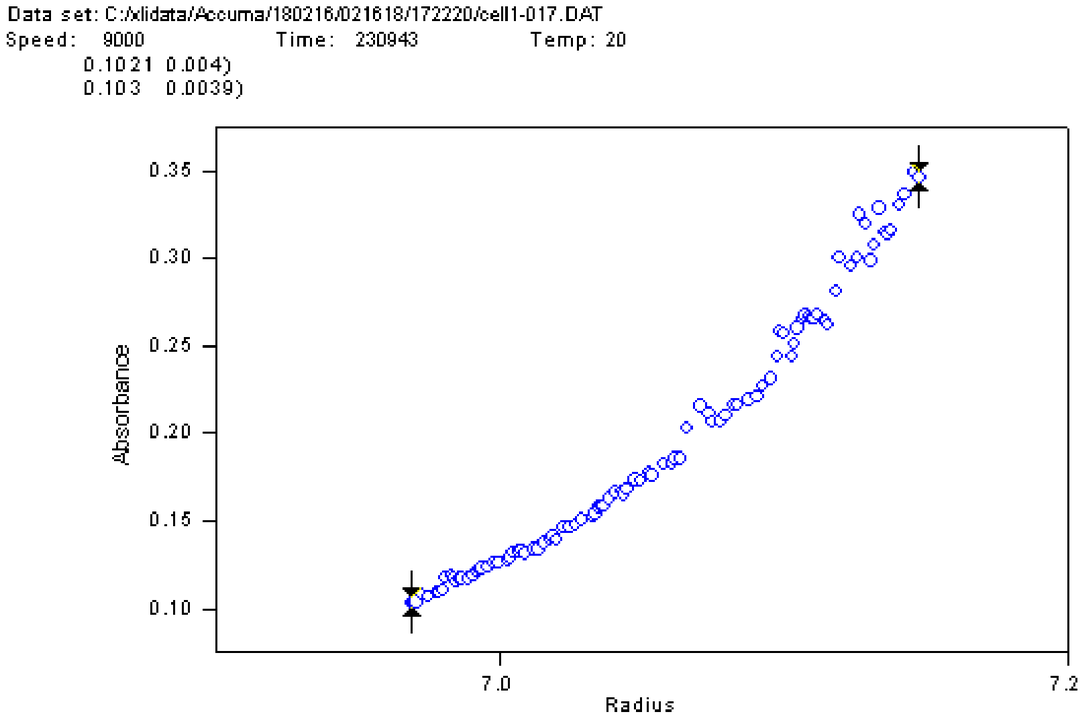


Novel DDS technology: unit Poly Ion Complex (uPIC)

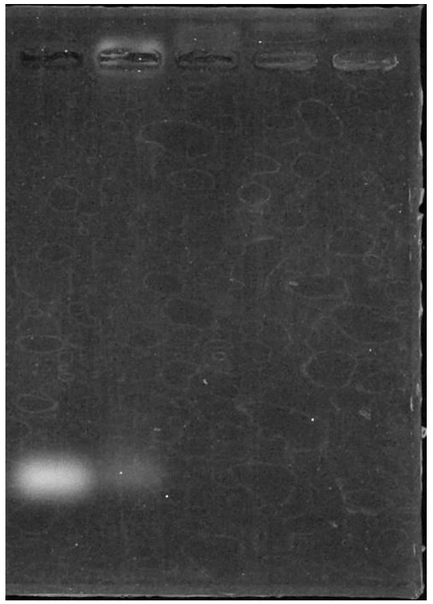
Characterization data; uPIC with a short chain RNA

Ultracentrifugation

XXRNA Mw: XXX, Polymer Mw: 76,300



Agarose gel electrophoresis

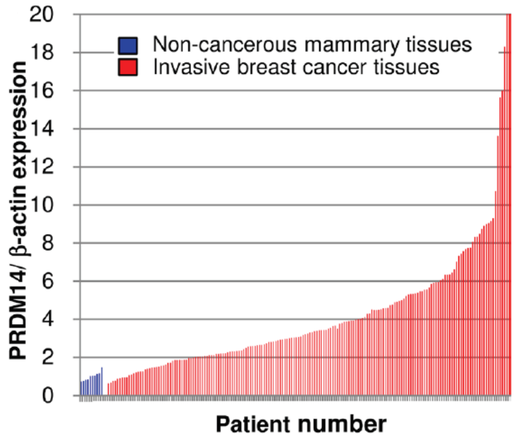


1: Naked short chain RNA
2: N/P=0.5
3: N/P=1
4: N/P=3
5: N/P=5

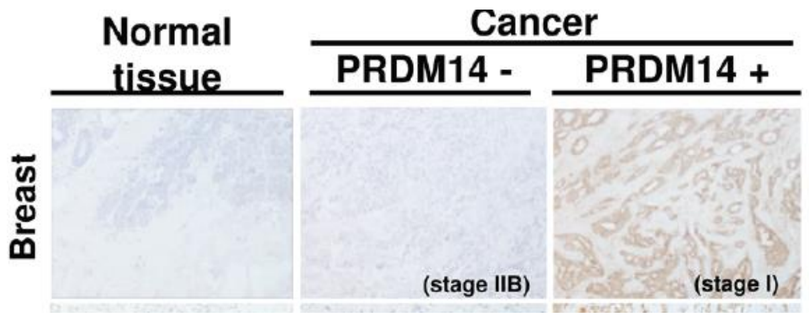
Development of PRDM14 siRNA/uPIC in MBC

PRDM14, a transcriptional factor, is a putative “oncogene” for Metastatic Breast Cancer (MBC)

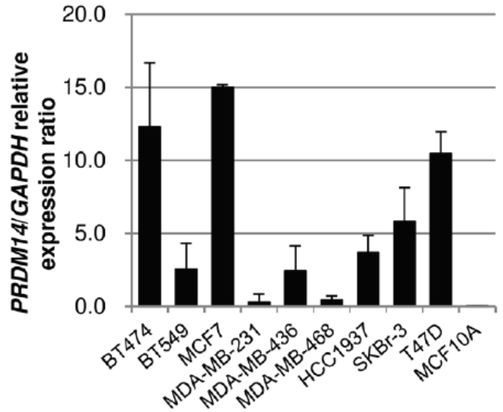
mRNA expression in MBC tissues



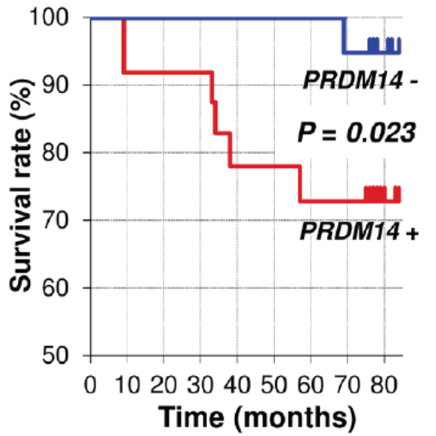
IHC analysis in MBC



mRNA expression in MBC cell lines



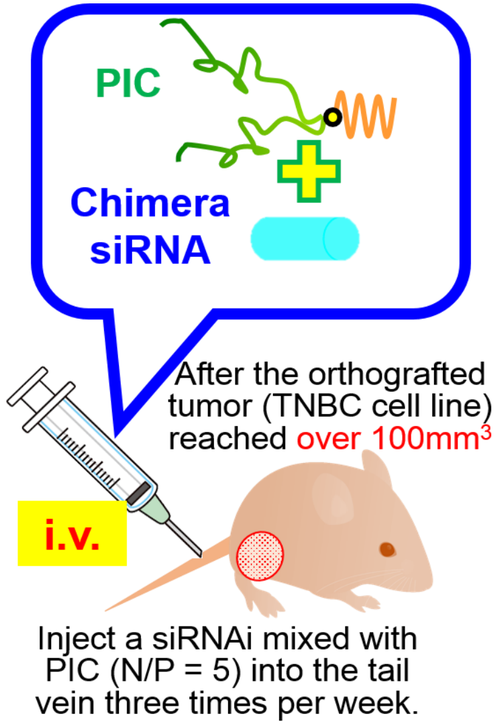
PRDM14 is a worse prognosis factor

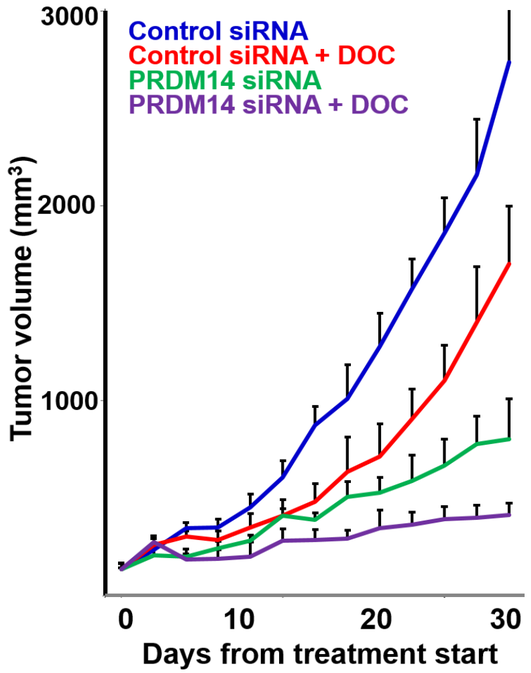


H Taniguchi et al, *Oncotarget 2017 8(29) 46856-46874*

Development of PRDM14 siRNA/uPIC in MBC

PRDM14-specific chimera siRNA/uPIC decreased PRDM14^{+} TNBC tumor size





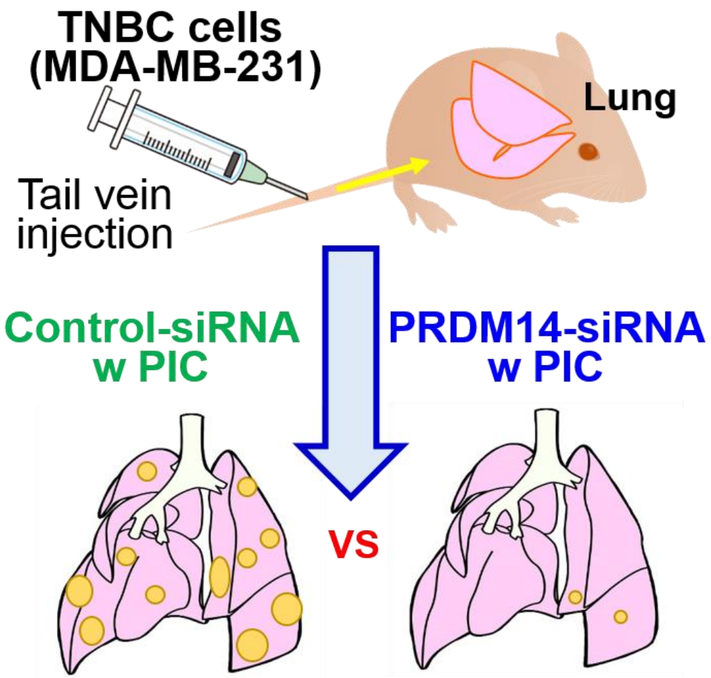
I. PRDM14-specific chimera siRNA (1mg/kg) mixed with a PIC nanocarrier (N/P ratio = 5) was injected into mice tail vain 3 times a week for a month, after the HCC1937 tumor reached over 100mm^3

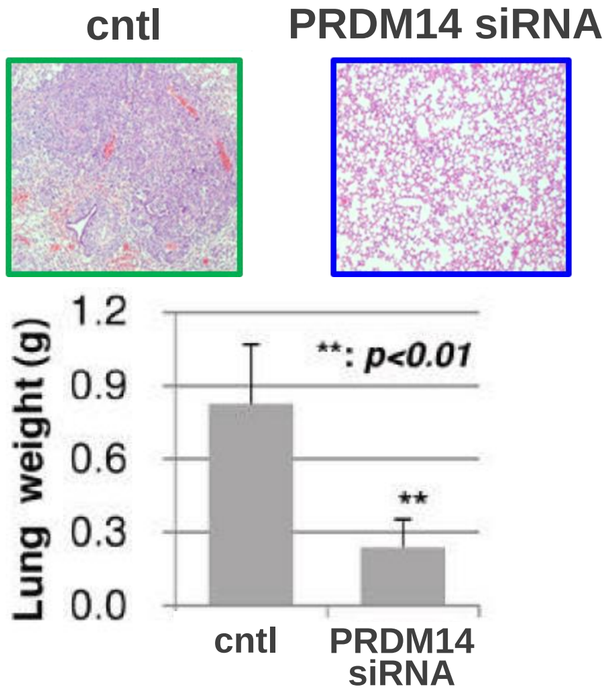
II. This treatment caused 50.3% reduction of mean relative tumor volume, 98% reduction by synergistic effect with docetaxel (3.0mg/kg).

H Taniguchi et al., AACR 2018 #3959

Development of PRDM14 siRNA/uPIC in MBC

Pulmonary metastases formed in the controls but not in PRDM14-specific chimera siRNA with PIC nanocarrier-treated mice





I. PRDM14+ TNBC cells (MDA-MB-231) were injected into mice via the tail vein.

II. 3 days later from cell injection, we start to treat with chimera RNAi against PRDM14 with a PIC nanocarrier.

III. After approximately 45 days, pulmonary metastases formed in the controls but not in PRDM14 siRNA-treated mice, clearly.

H Taniguchi et al., AACR 2018 #3959

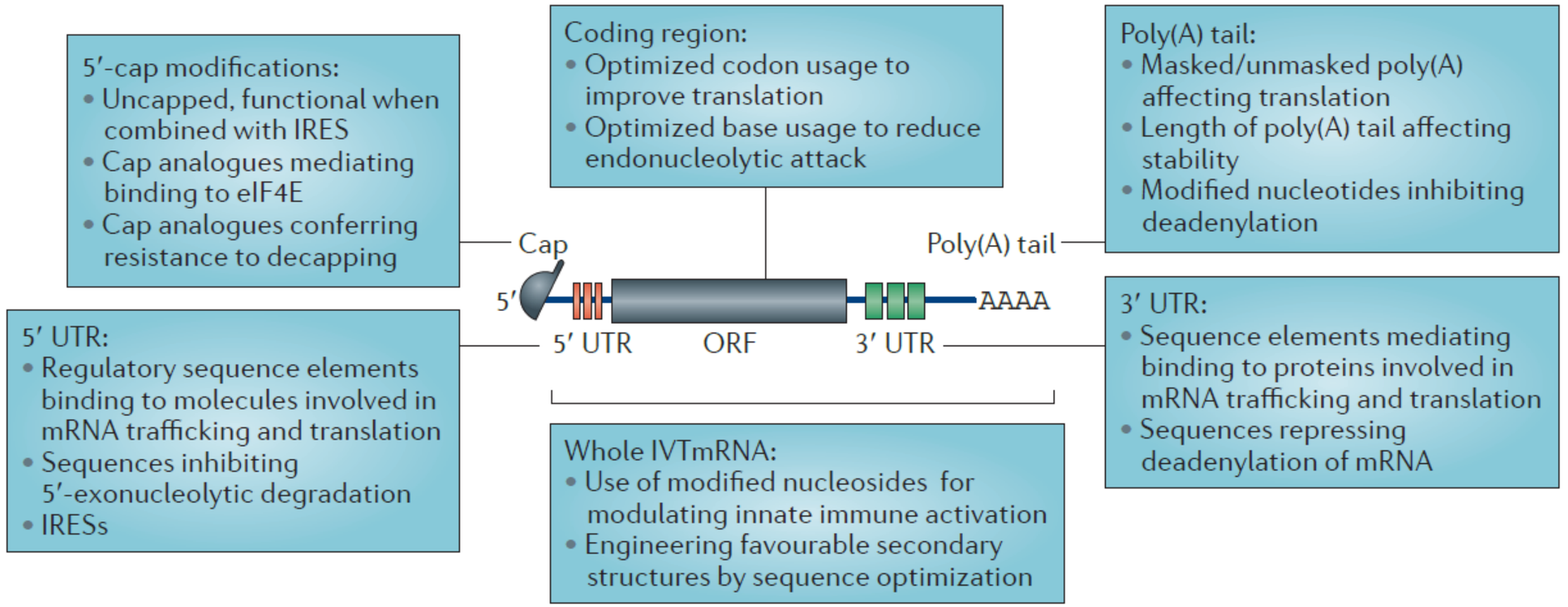
AccuRna's unique DDS for ling Chain Nucleic Acid Therapeutics
-mRNA as a therapeutic drug-

- Alternative for enzyme replacement therapy or gene therapy
- Vaccine for infectious disease or cancer

mRNA therapeutics

Prof . Sahin (Mainz Univ. and BioNTech) has wrote a “Bible paper” for mRNA Therapeutics in Nature Drug Discovery 2014

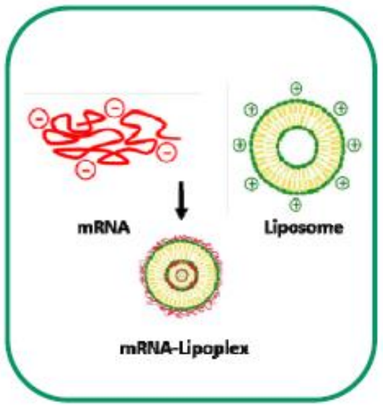
a Structural modifications for tuning mRNA pharmacokinetics

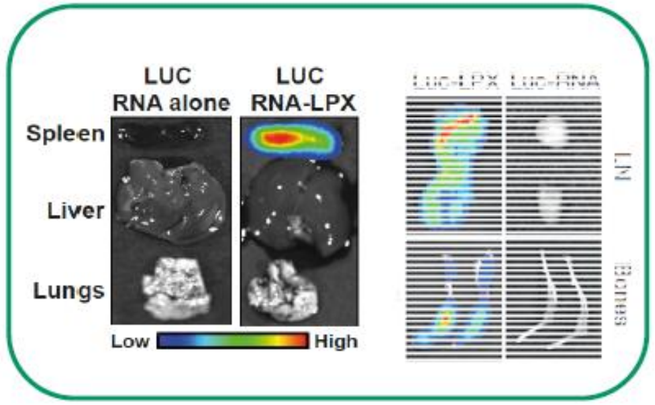


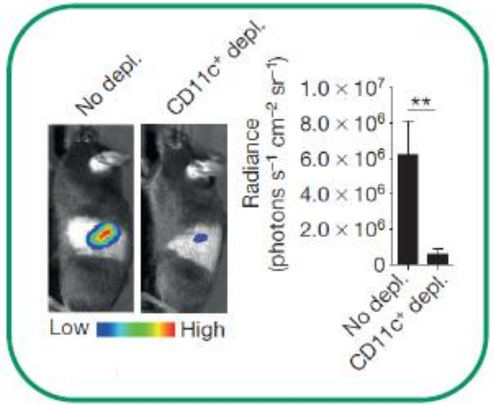
NATURE REVIEWS | DRUG DISCOVERY VOLUME 13 | OCTOBER 2014 | 759

Quote from BioNTech's work

Outlook: Systemic RNA delivery to DCs via RNA-lipoplexes

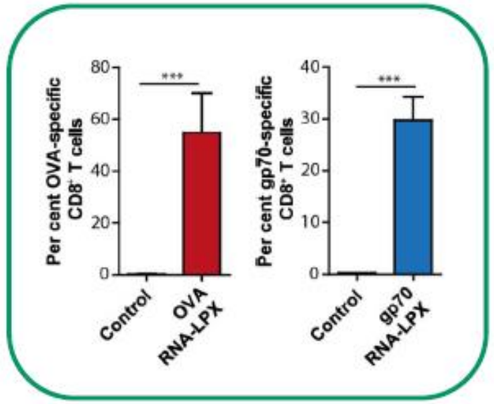






RNA-lipoplexes i.v.

- Selective expression in CD11c$^+$ DCs in the spleen, lymph nodes and bones
- High frequency of antigen-specific T cells



Kranz LM, et al.: **Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy.** *Nature* 2016, **534**:396–401.

BIONTECH
RNA Pharmaceuticals

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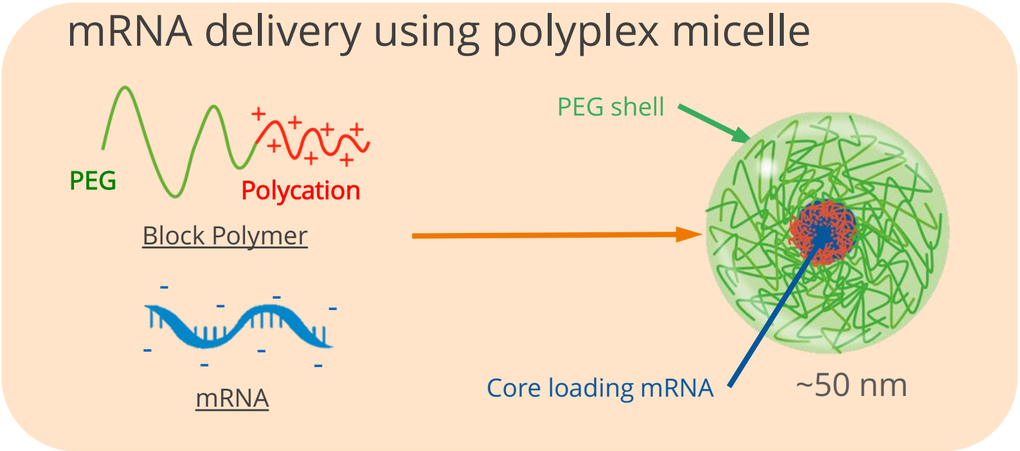
Novel DDS technology: Polyplex micellar nanosystems

Our polyplex micelle is a solution to the issues in mRNA delivery

Issues in mRNA delivery

1. Instability under physiological condition due to RNase attack
2. Immunogenicity due to recognition by Toll-Like Receptors

Solution

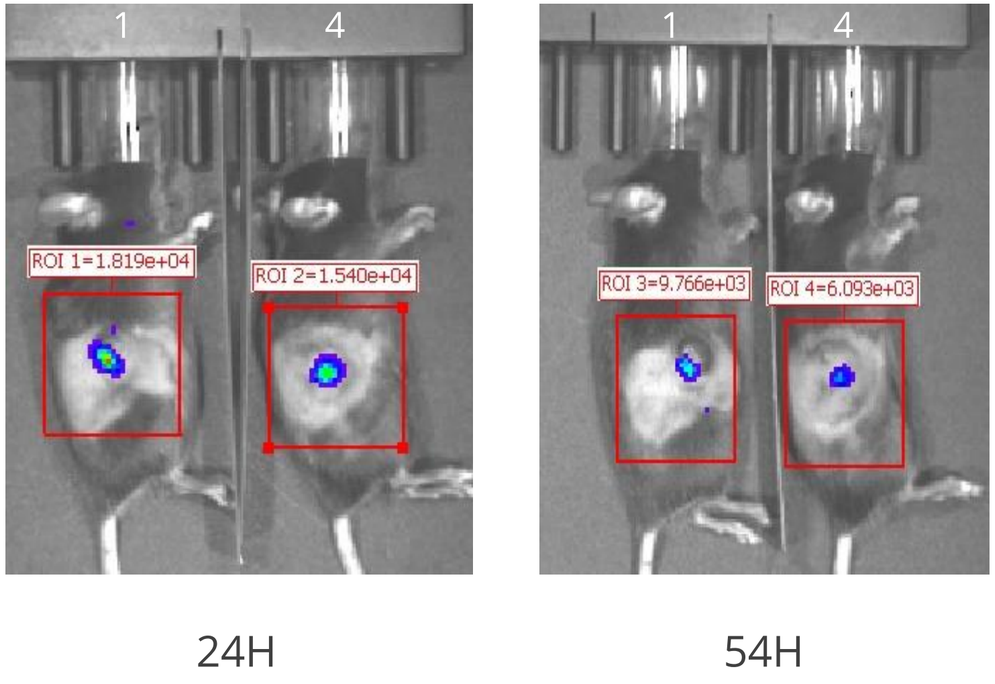


- Increased tolerability of mRNA against RNase attack
- Bypassing immune recognition by stealth PEG shell

Polyplex micelle with a Luc mRNA

In house data

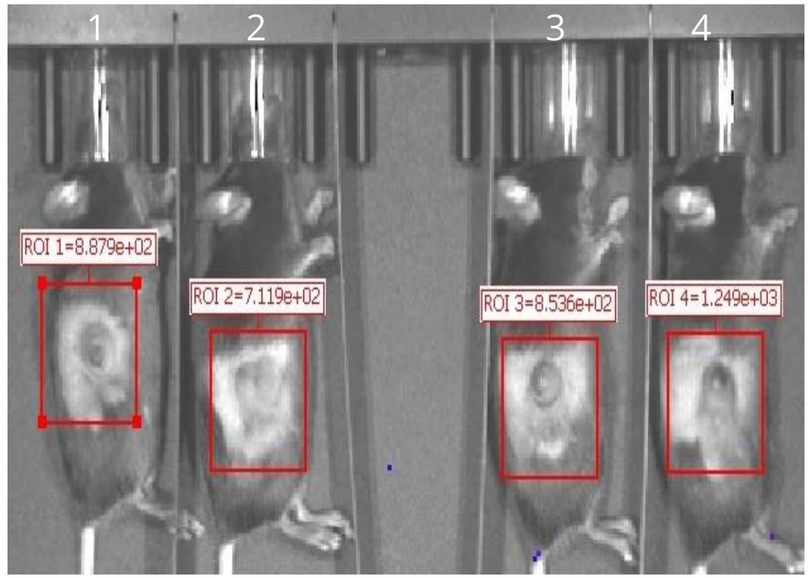
43K PEG-63 PAsp (DET) + Luc mRNA



24H

54H

PBS control



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Corporate Overview

- Collaboration Scope
- Business Model
- Quick Facts

Collaboration scope with Pharmaceutical Companies

Short Chain nucleic acid medicines

- Delivery of siRNA, ASO, miRNA using uPIC
- Main focus on cancer indication but other diseases upon request

MTA	Small scale testing of your siRNA, ASO, miRNA
Collaborative Research	Support for pre-clinical testing. Scale up synthesis of uPIC, pre-formulation until GLP toxicology etc.
Collaborative Development	GMP production support for uPIC

Long chain nucleic acid medicines

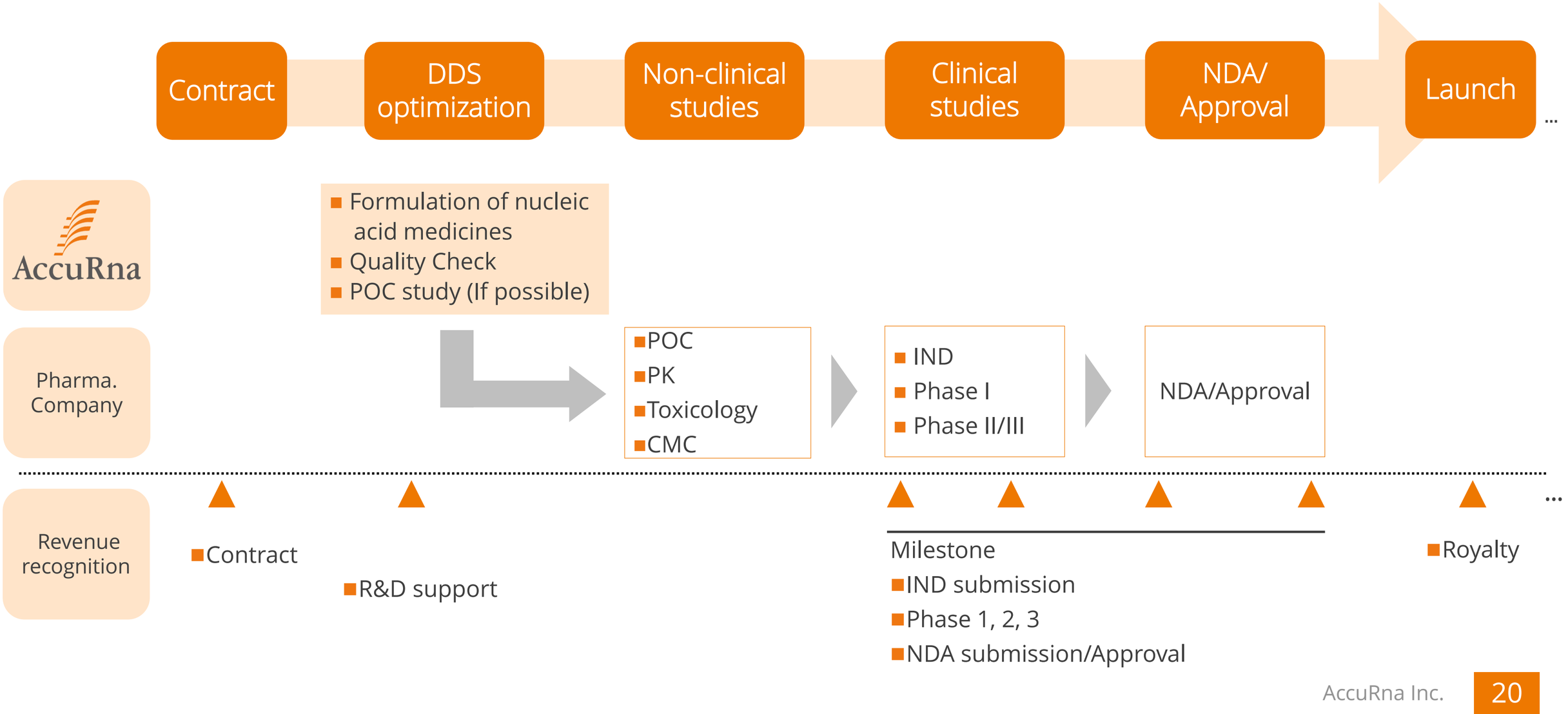
Two possible indication as;

- Enzyme replacement
- Vaccine therapy

MTA	Small scale testing of your own mRNA and possibly CRISP
Collaborative Research	Order made preparation of micelle, length of amino acid polymer matters
Collaborative Development	TBD Further discussion needed for GMP production at least at this moment

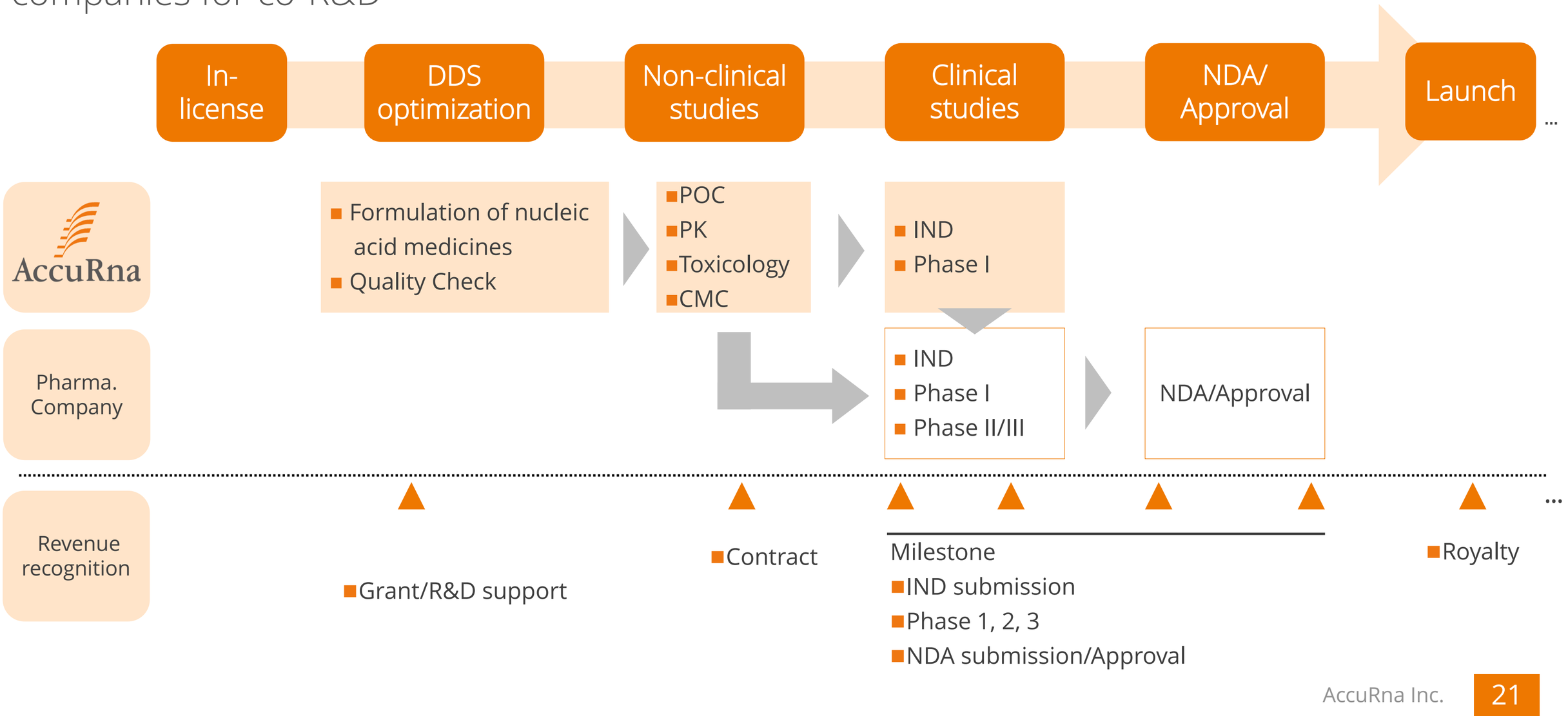
Business model : Platform Business

The alliance with Pharmaceutical companies for co-R&D with their own assets



Business model : Pipeline Business

The incubation of in-licensed academic seeds towards the alliance with Pharmaceutical companies for co-R&D



Quick Facts

Founding Year:

2015

Headquarters:

Tokyo, Japan

Management:

Keiko Hattori
Shiro Akinaga
Yusuke Ishikawa

Core Technologies:

- Drug Delivery System for RNA
- mRNA vaccines

Capitalization:

Paid-In Capital: ¥338 million
(As of Apr, 2018)

Investors:

Fast Track Initiative, Inc.
UTokyo Innovation Platform Co., Ltd.
SMBC Venture Capital Co., Ltd.
NanoCarrier Co., Ltd

Locations:

- Bunkyo-ku, Tokyo, Japan
- Kawasaki, Kanagawa, Japan

Academic Partners:

iCONM Innovation Center of NanoMedicine
COINS Center of Open Innovation Network for Smart Health
Nagoya University
Tokyo Medical and Dental University TMDU
The Institute of Medical Science The University of Tokyo 125TH IMSUT Anniversary