Corporate Overview

December 2018

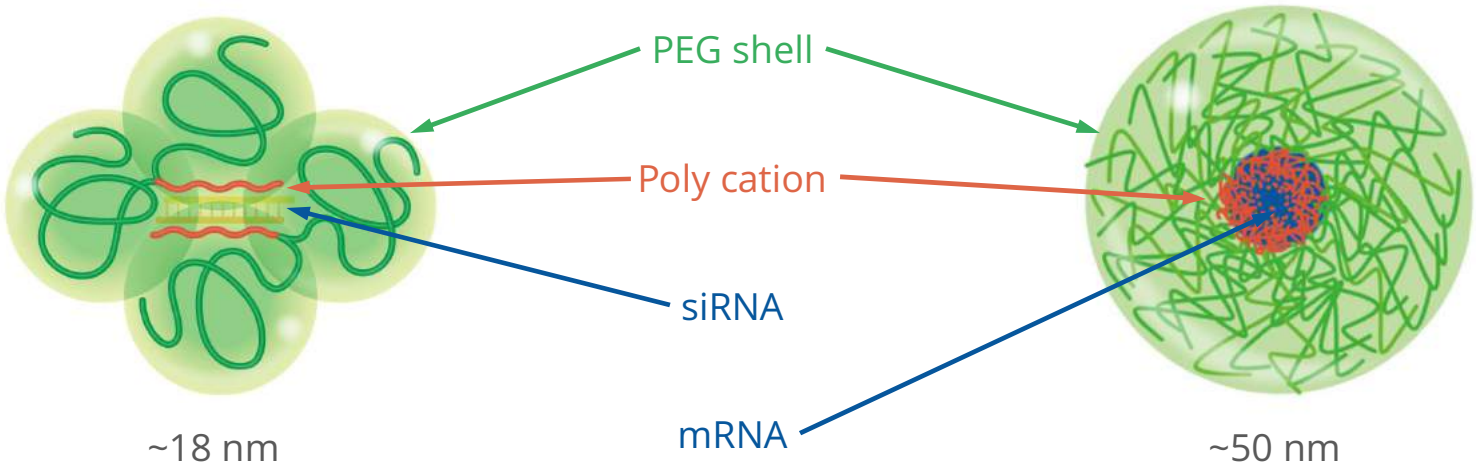
AccuRna

Mission

- A biotech company dedicated to drug discovery for nucleic acid therapeutics based on novel drug delivery platforms in disease areas of unmet medical need

Solution: Two DDS platforms of AccuRna

AccuRna's two DDS can contribute to the market expansion of nucleic acid therapeutics 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 such as siRNA, ASO and possibly miRNA

Polyplex micelle for long chain

AccuRna's polyplex micelle enables development of mRNA therapeutics as well as CRISPR-Cas

Nucleic Acid therapeutics

	Small molecule	Antibody	Oligonucleotide
			
Molecular weight	Small (< 500 Da)	Large (< 100,000 Da)	Medium (7,000-14,000Da)
Site of action	Extra- and intra- cellular	Extracellular	Extra- and intra- cellular
Oral availability	Yes	No	No
Cell permeability	Usually good	Not good	Not good
Mode of administration	Primarily oral	Primarily IV or SC	IV, SC, IT, IV

IV: intravenous, SC: subcutaneous, IT: intrathecal, IVT: intravitreal

Overview of the market

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

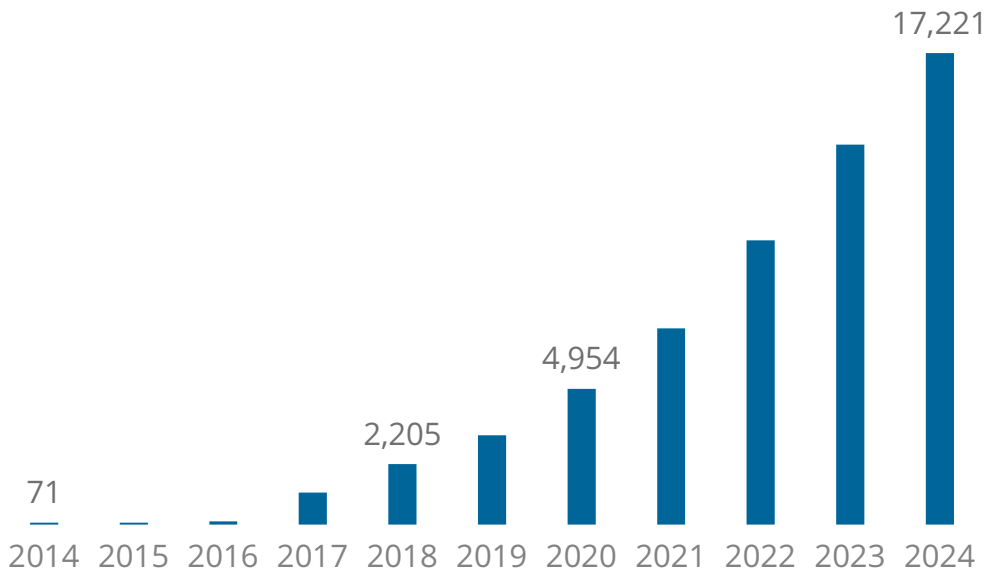
Merits

- 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.
- Target and mechanism of action are clear
- Specificity is high and side effects are limited

Market forecast at 2020

- The application has been expanded to cancer, infectious and genetic disease
- Some of the products are becoming successful
- The market is expected to become bigger after 2020 through the development of DDS technologies

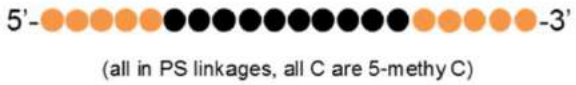
Unit: $1M



Source: Global Data

Advances in development of oligonucleotide-based therapeutics

Six major products have been approved as of December 2018 (1 Aptamer, 4 ASOs, 1 siRNA)

Name	Chemistry	Disease (target)	Year of approval
Pegaptanib (Macugen)		AMD of the retina (VEGF165 protein)	2004/12/17 (FDA)
Mipomersen (Kynamro)	 (all in PS linkages, all C are 5-methy C)	Hypercholesterolemia (ApoB100 mRNA)	2013/1/29 (FDA)
Eteplirsen (Exondys 51)		Duchenne muscular dystrophy (Dystrophin pre-mRNA)	2016/9/6 (FDA)
Nusinersen (Spinraza)	 (all in PS linkages, all C are 5-methy C)	spinal muscular atrophy (SMN2 pre-mRNA)	2016/12/23 (FDA)
Inotersen (Tegsedi)	 (all in PS linkages, all C are 5-methy C)	TTR Amyloidosis (ATTR) (Transthyretin mRNA)	2018/7/11 (EU)
Patisiran (Onppattro)	 (all in PO linkages, complexed with lipid nanoparticles)	TTR Amyloidosis (ATTR) (Transthyretin mRNA)	2018/8/10 (FDA)

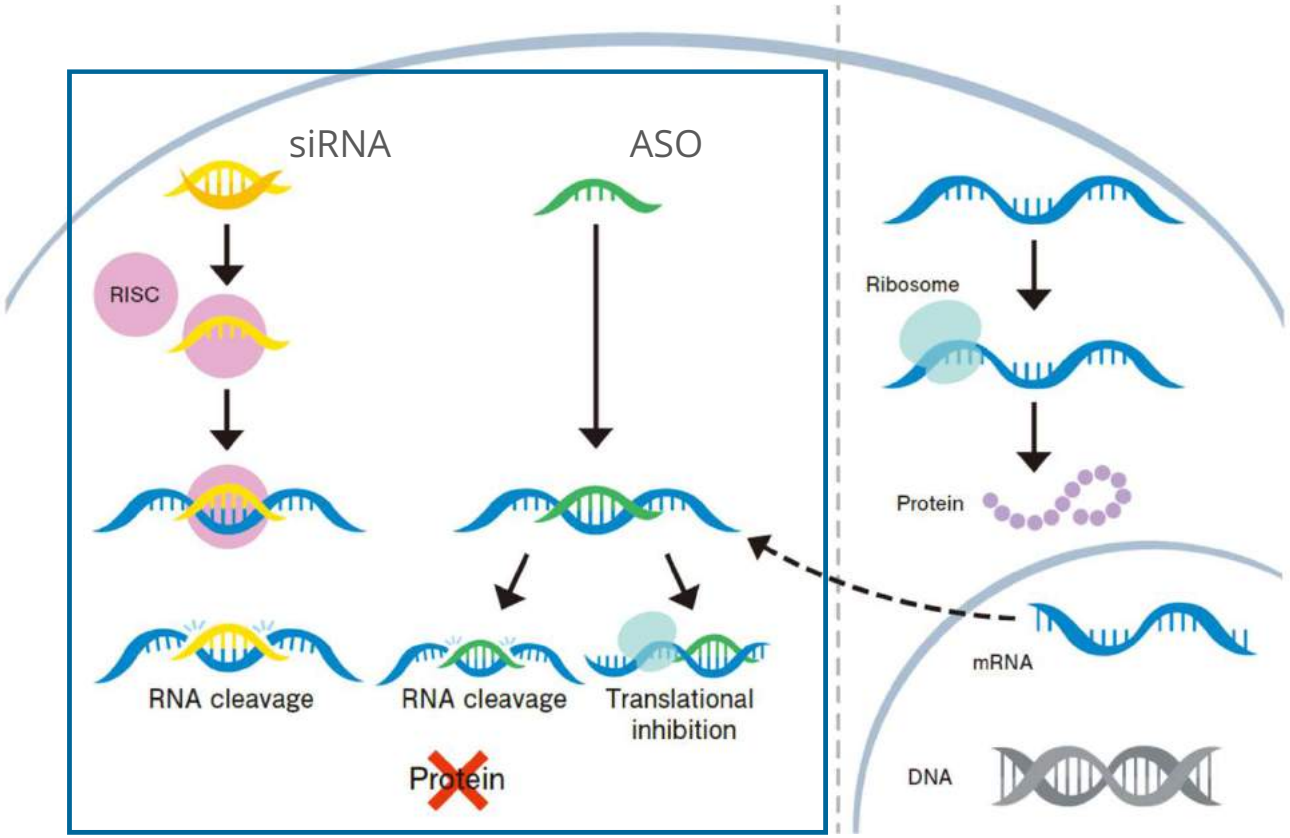
● 2'-H (deoxyribose); ● 2'-OH (ribose); ▲ 5'-[40kD]-[HN-$(CH_2)_5$O]-p-, [40kD] represents the two 20 kD PEG chains; ● 2'-O-Me RNA; ● 2'-F RNA; ● Thio-phosphoramidate; ● 2'-O-MOE RNA; ▲ 5'-[HO-$(CH_2O)_3$CO-piperazine]-; ● PMO linkage; ▲ 5'- palmitoyl-; ● LNA, PS linkages; GalNAc (see Figure 3). References/sources of the information are listed in Supplementary data.

Source: X. Shen et al, Nucleic Acids Research, 2018, Vol. 46, No. 4

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

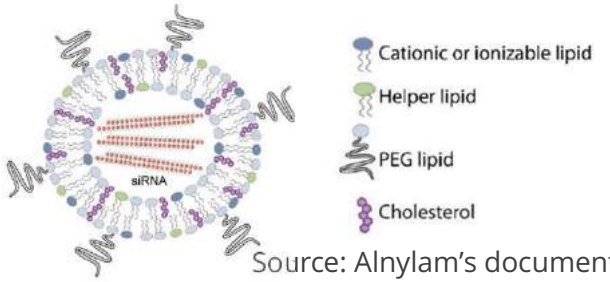
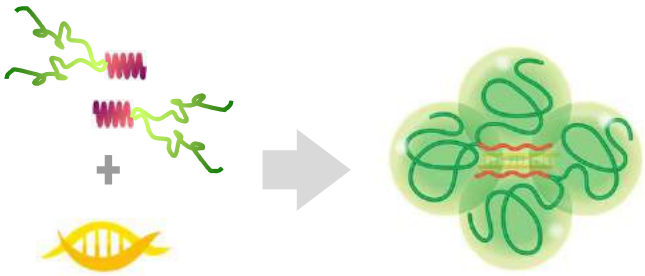
- Sequence-specific suppression of gene expression
- No genome damage
- Broad target selection
- Applicable to ncRNA

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)

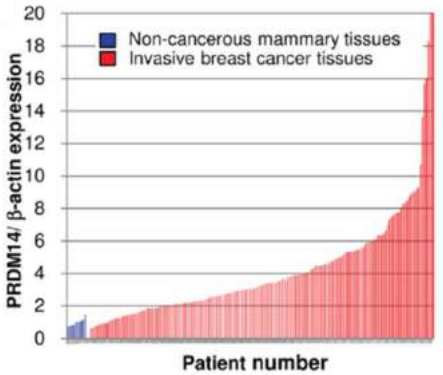
uPIC is a simple solution for DDS of short chain nucleic acid therapeutics as siRNA, ASO and miRNA

	LNP	AccuRna's technology (uPIC)
Diagram	 Source: Alnylam's document	
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	Several trials have been in progress Patisiran was approved in Aug. 2018	Nu human experience so far GLP toxicology studies were conducted with a given siRNA towards P1 in 2019

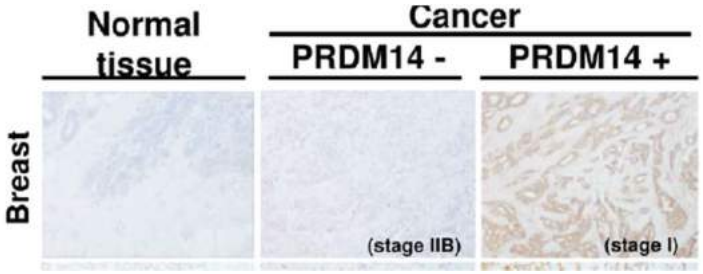
Development of PRDM14 siRNA/uPIC in MBC (1)

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

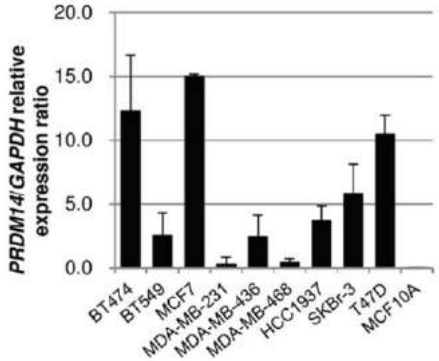
mRNA expression in MBC tissues



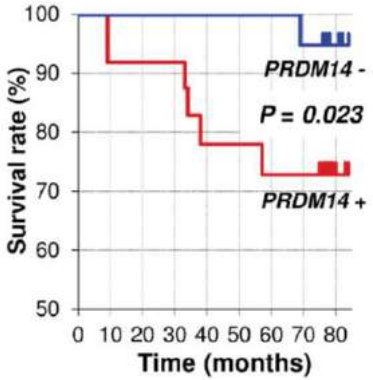
IHC analysis in MBC



mRNA expression in MBC cell lines



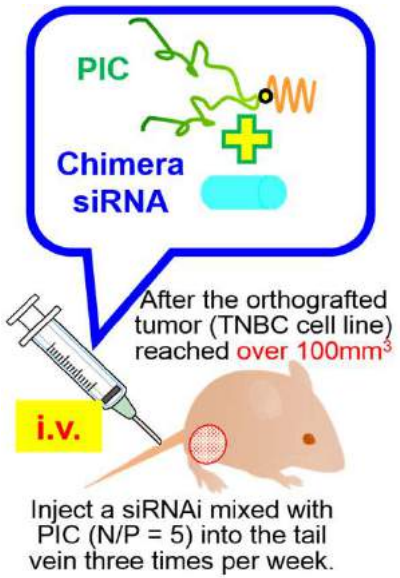
PRDM14 is a worse prognosis factor

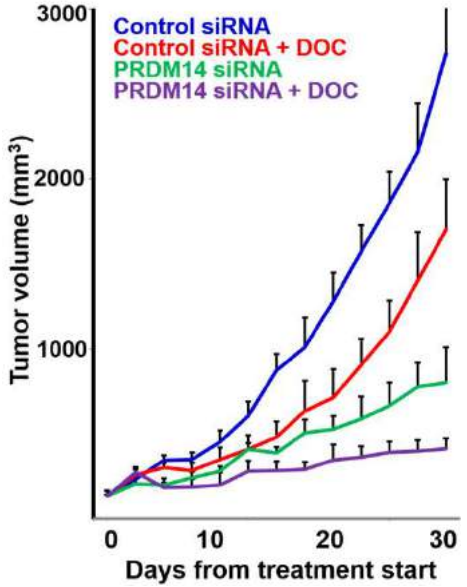


Source: H Taniguchi et al, Oncotarget 2017 8(29) 46856-46874

Development of PRDM14 siRNA/uPIC in MBC (2)

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





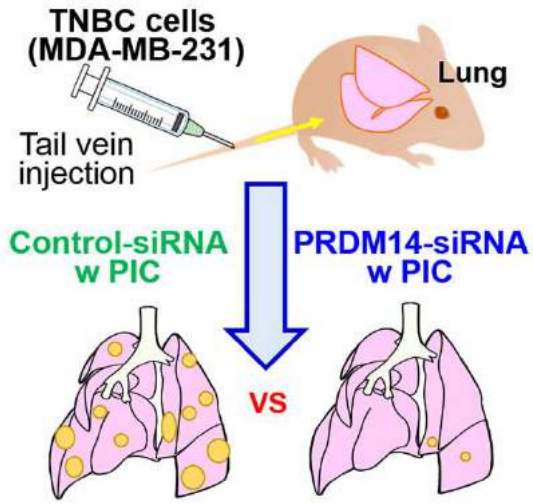
I. PRDM14-specific chimera siRNA (1mg/kg) mixed with a PIC nanocarrier (N/P ratio = 5) was injected into mice tail vain 3 times a week for a month, after the HCC1937 tumor reached over 100mm^3

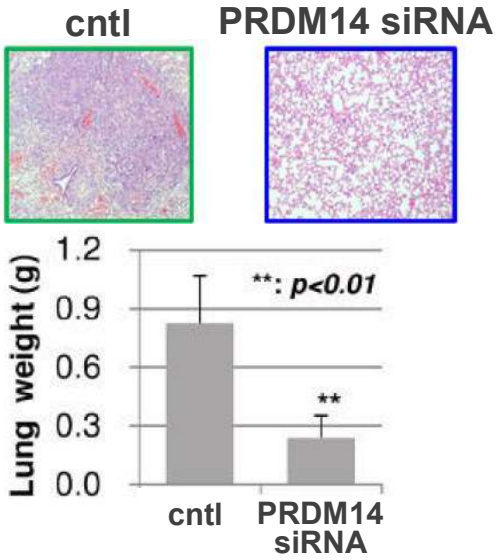
II. This treatment caused 50.3% reduction of mean relative tumor volume, 98% reduction by synergistic effect with docetaxel (3.0mg/kg).

Source: H Taniguchi et al., AACR 2018 #3959

Development of PRDM14 siRNA/uPIC in MBC (3)

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.

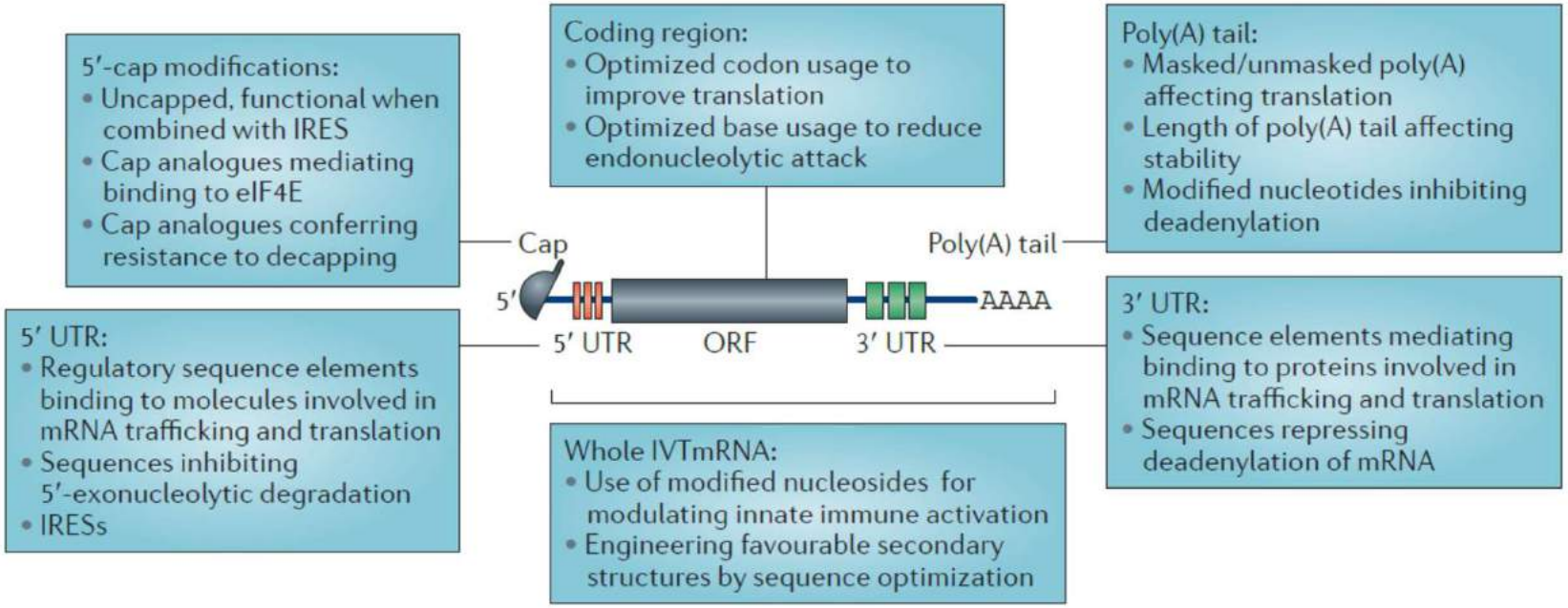
Source: H Taniguchi et al., AACR 2018 #3959

AccuRna's unique DDS for Long 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

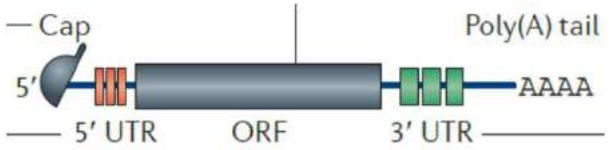
Prof . Sahin (Mainz Univ. and BioNTech) has wrote a “Bible paper” for mRNA Therapeutics in Nature Drug Discovery 2014



Source: U Sahin et al., Nature Reviews Drug Discovery volume 13, pages 759–780 (2014)

mRNA therapeutics: An Emerging Therapeutics of new era

Usage of mRNA as a drug: Synthesis of mRNA by IVT



Protein replacement

Alternative to Gene Therapy

moderna

AstraZeneca

ARCTURUS

Translate

etc.

VEGF mRNA (AstraZeneca)

Vaccine

Alternative to live attenuated vaccine or DNA/peptide vaccine

moderna

BIONTECH

CUREVAC the RNA people®

gsk

etc.

mRNA cancer vaccine (BioNTech)
mRNA Rabies vaccine (CureVac)

Genome Editing

CRISPR/Cas Therapy

CRISPR THERAPEUTICS

CASEBIA THERAPEUTICS

Intellia THERAPEUTICS

etc.

Issues for development of mRNA therapeutics

CMC	CMC for mRNA construct for efficient translation towards GMP production
Drug Delivery System	Mostly LNP but accumulation in liver
Regulatory environment	No clear guideline for mRNA therapy (No harmonization)
Selection	Selection of right diseases for mRNA therapeutics
Lack of understanding	Lack of understanding in medical and pharmaceutical society especially in Japan

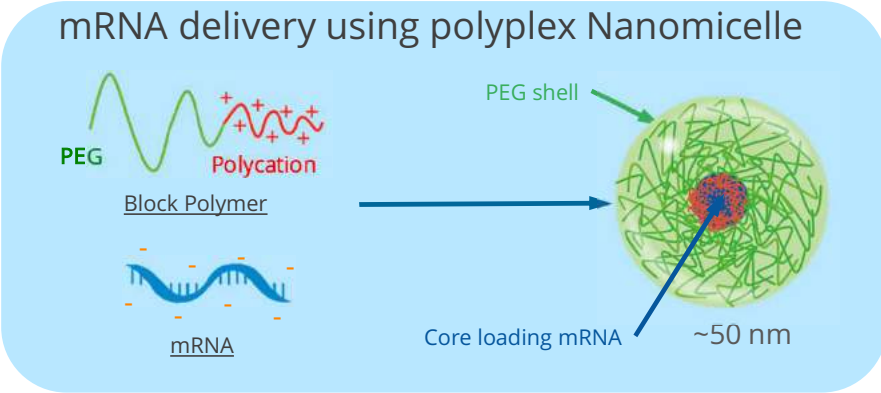
Novel DDS technology: Polyplex micellar nanosystems

Our polyplex micelle may provide solutions for the issues of mRNA

Issues in mRNA delivery

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

Solution

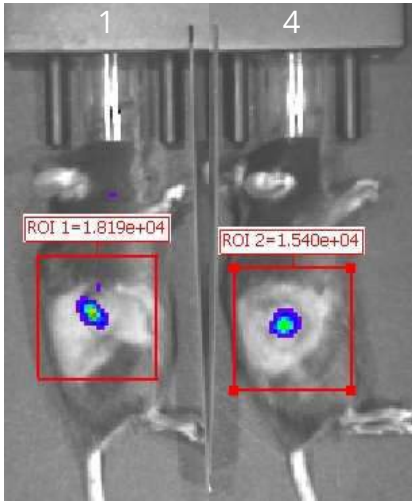


- Increased tolerability of mRNA
  against RNase attack
- Bypassing immune recognition
  by stealth PEG shell

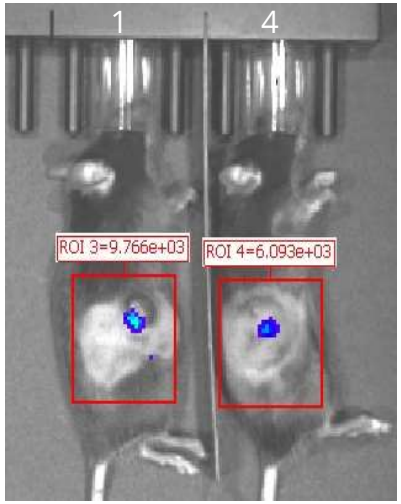
Polyplex micelle with a Luc mRNA

SC injection into tumor

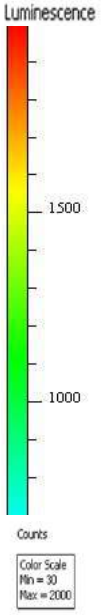
Polyplex micelle + Luc mRNA



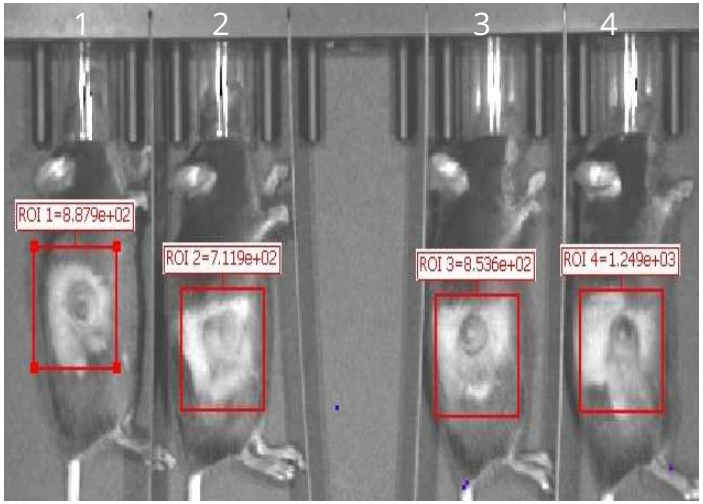
24H



54H



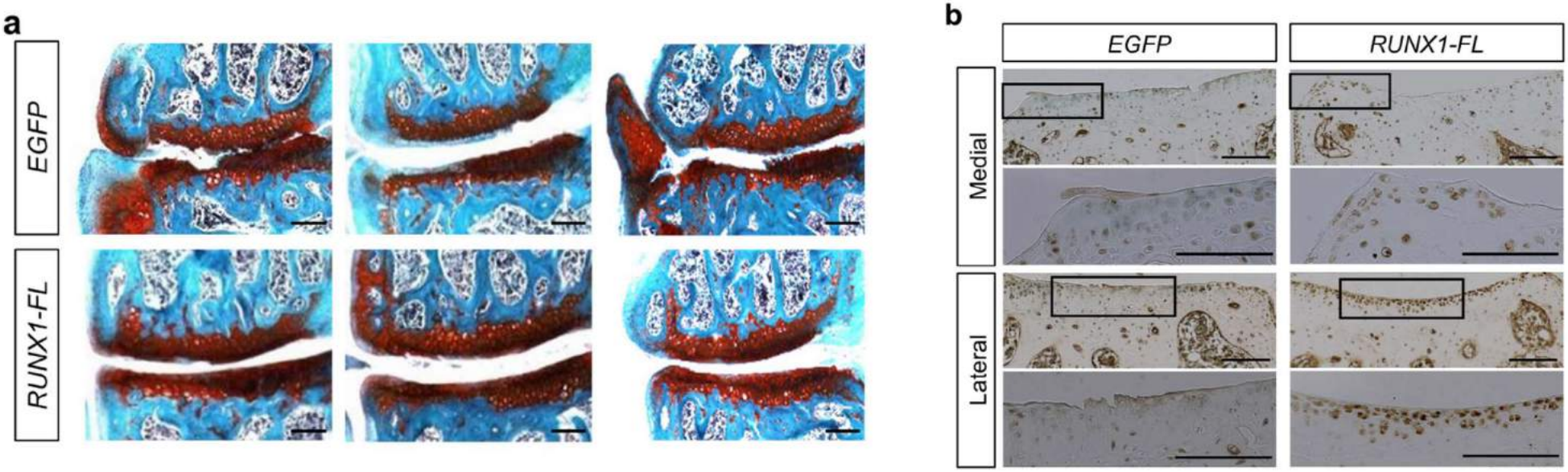
PBS + Luc mRNA



6 H

Application to OA model

RUNX 1 mRNA with PEG polyplex polymer were injected into mouse OA knee joints, OA progression was significantly suppressed compared with the non-treatment control.



Histological analyses with safranin-O staining revealed that OA progression was suppressed in the RUNX1-injected group compared with the control group, in terms of both cartilage degradation and osteophyte formation (Fig. 3a). No obvious inflammatory symptoms, such as outgrowth of the synovial membrane or infiltration of inflammatory cells, were observed on the histological sections (Fig. 3a). As was the case in the earlier study, overall RUNX1 protein expression in the articular cartilage was enhanced in the RUNX1-injected group (Fig. 3b).

Source: Aini et al., Sci Rep 6:18743, 2016

Application of PAsp (DET) to CRISPR-Cas system

nature biomedical engineering

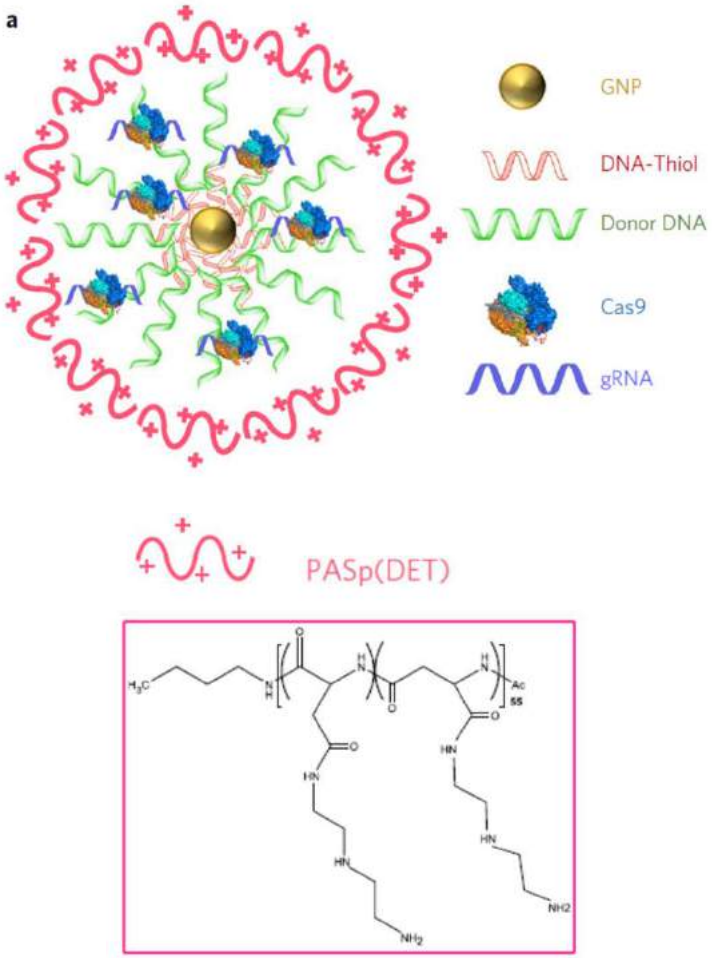
ARTICLES

DOI: 10.1038/s41551-017-0137-2

Nanoparticle delivery of Cas9 ribonucleoprotein and donor DNA in vivo induces homology-directed DNA repair

Kunwoo Lee[1], Michael Conboy[2], Hyo Min Park[1], Fuguo Jiang[3], Hyun Jin Kim[2,4,5], Mark A. Dewitt[3,6], Vanessa A. Mackley[1,2], Kevin Chang[3], Anirudh Rao[3], Colin Skinner[2], Tamanna Shobha[2], Melod Mehdipour[2], Hui Liu[1], Wen-chin Huang[2], Freeman Lan[2], Nicolas L. Bray[3,6], Song Li[2], Jacob E. Corn[3,6], Kazunori Kataoka[4,5,7], Jennifer A. Doudna[3,6,8,9,10], Irina Conboy[2*] and Niren Murthy[2*]

we demonstrate that a delivery vehicle composed of gold nanoparticles conjugated to DNA and complexed with cationic endosomal disruptive polymers can deliver Cas9 ribonucleoprotein and donor DNA into a wide variety of cell types and efficiently correct the DNA mutation that causes Duchenne muscular dystrophy in mice via local injection, with minimal off-target DNA damage.

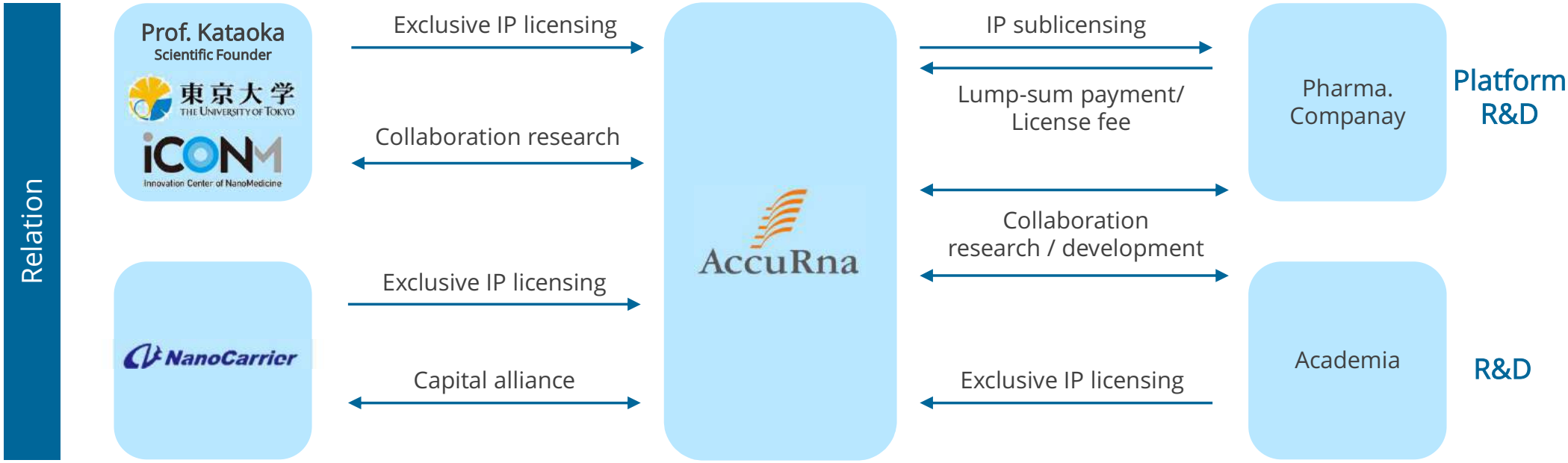


Corporate Overview

- Collaboration Scope
- Business Model
- Quick Facts

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 advoce

- Commercialization of technology
- Project management
- IP management

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

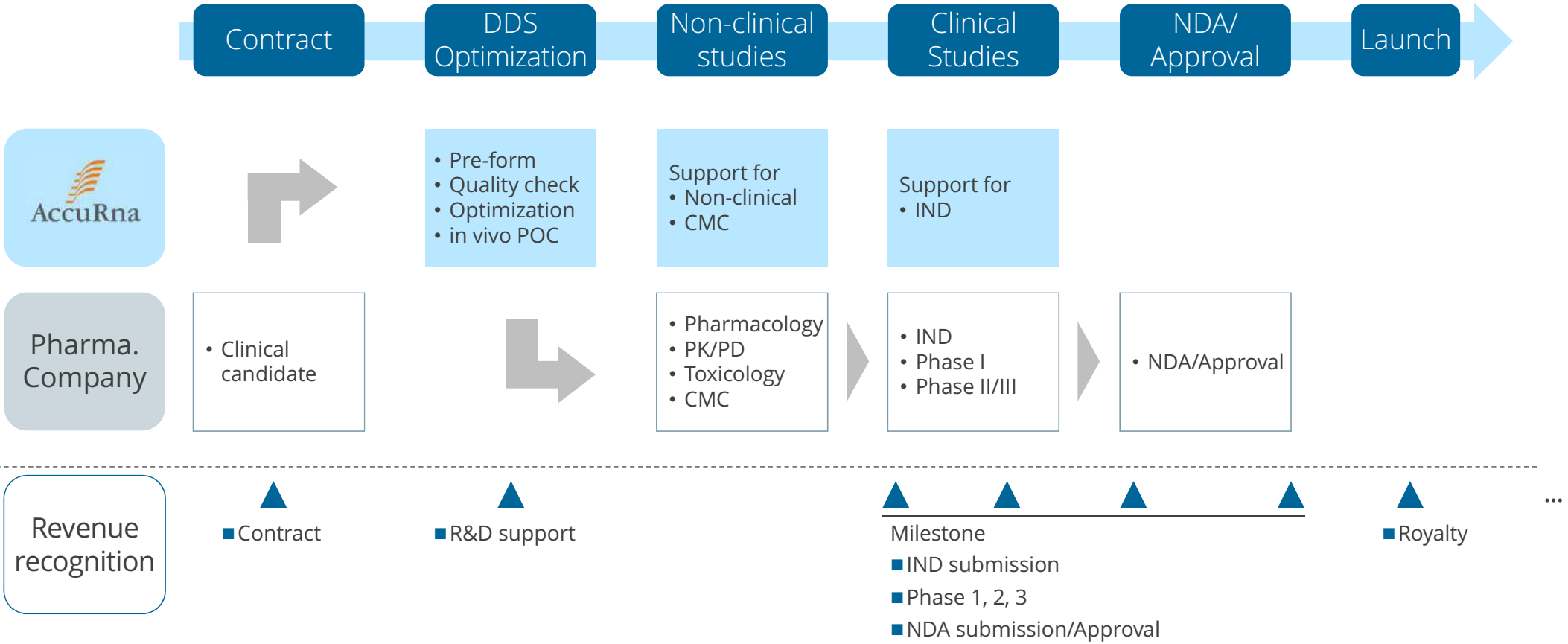
Two possible indication as;

- 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

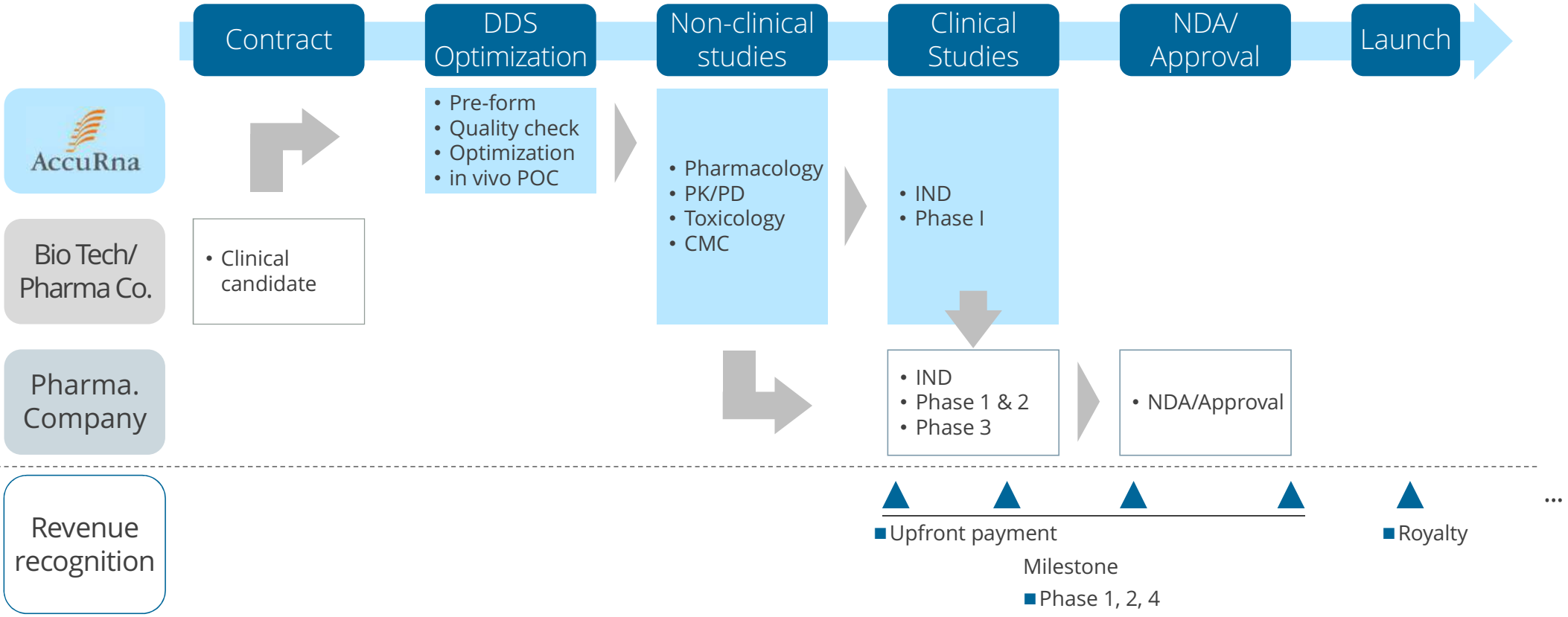
Business model – Platform Business

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



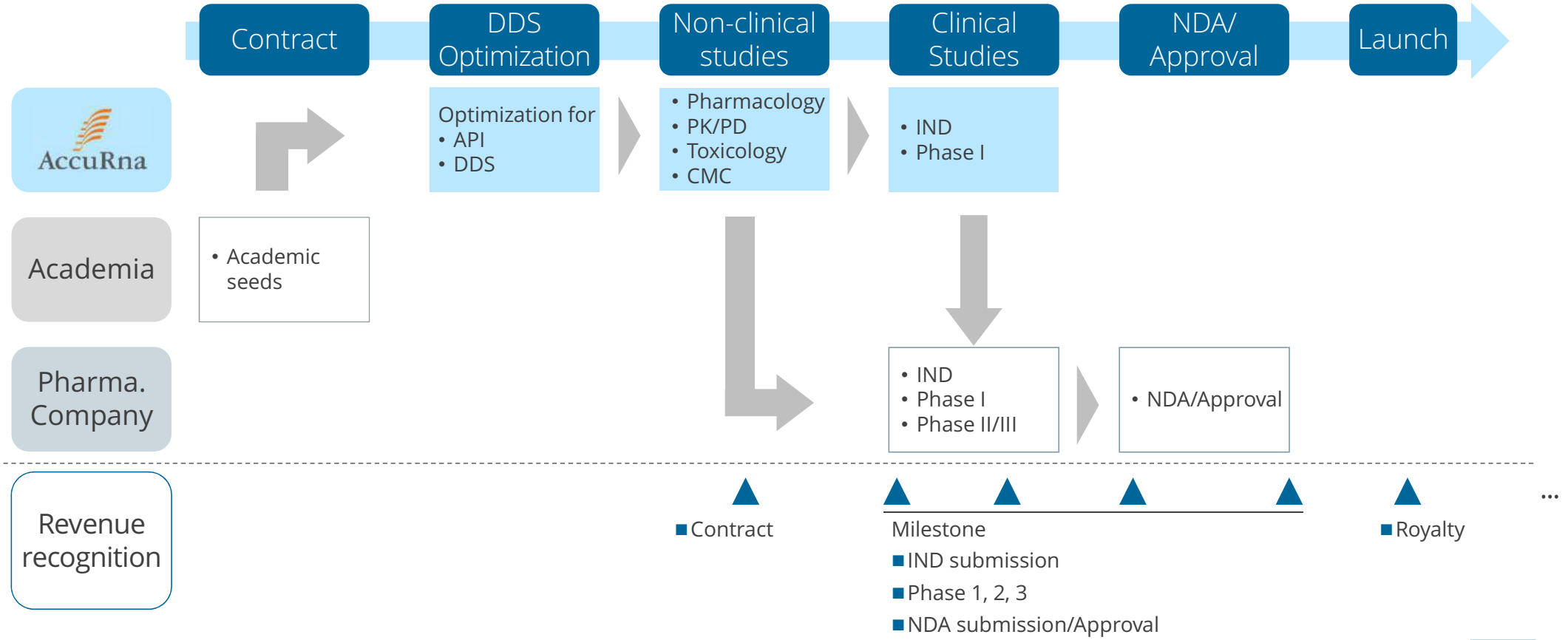
Business model – Co-development business

Collaborative development with Bio Tech (or Pharma Co) who has clinical candidate nucleic acid medicine (AccuRna to provide DDS technology)



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:	Headquarters:	Management:
Dec. 2015	Tokyo, Japan	Shiro Akinaga, CEO Keiko Hattori, Director
Core Technologies:	**Capitalization:**	**Investors:**
■ DDS platforms for nucleic acid medicines ■ Nucleic Acid Medicine Drug Discovery	Paid-In Capital: ¥338 M (As of Apr, 2018)	■ Fast Track Initiative, Inc. ■ UTokyo Innovation Platform Co., Ltd. ■ SMBC Venture Capital Co., Ltd. ■ NanoCarrier Co., Ltd
Locations:	**Partners:**	
■ Bunkyo-ku, Tokyo, Japan ■ Kawasaki, Kanagawa, Japan	iCONM Innovation Center of NanoMedicine COINS Center of Open Innovation Network for Smart Health NAGOYA UNIVERSITY TMDU 125TH IMSUT ANNIVERSARY	

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Contact：　info@accurna.com