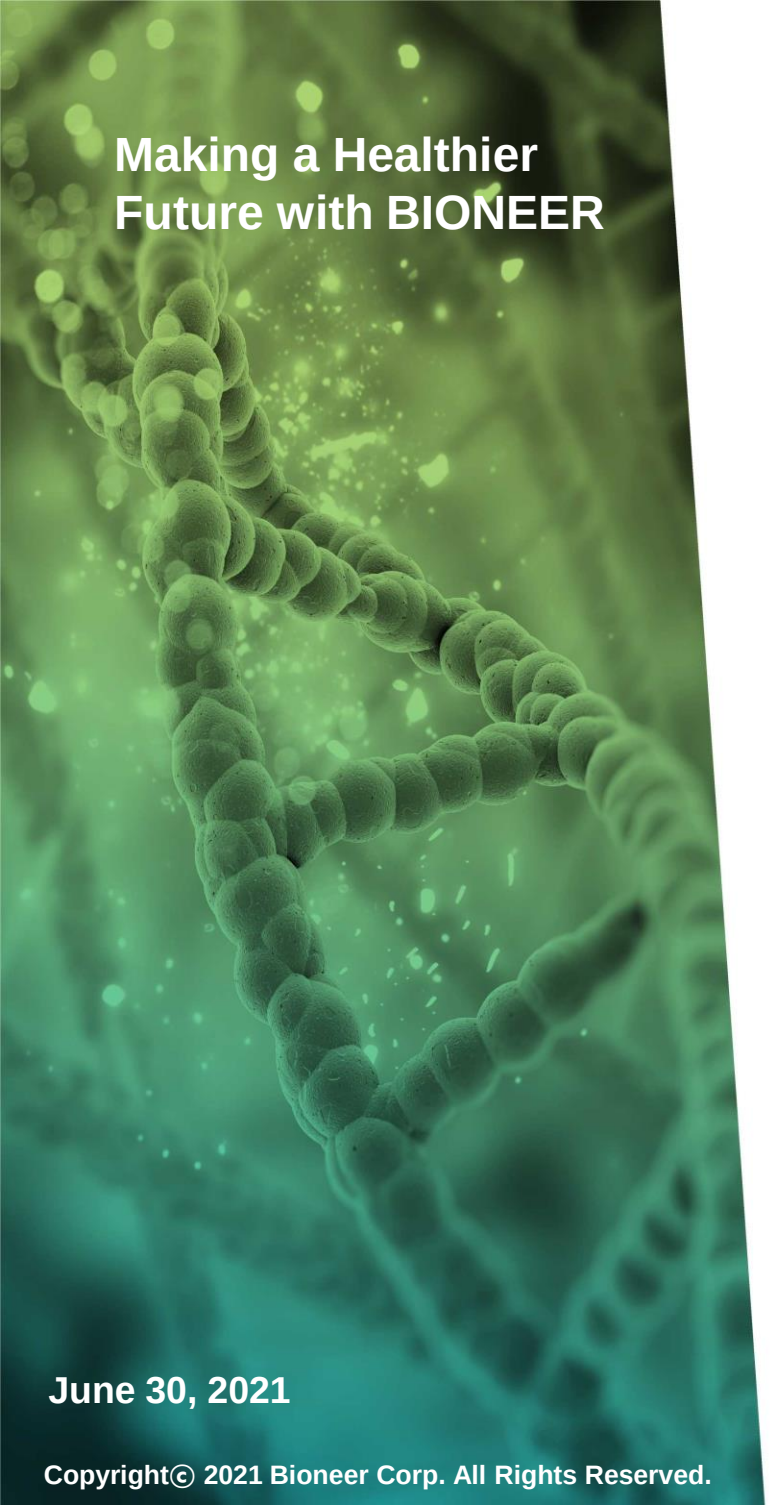

Making a Healthier Future with BIONEER

June 30, 2021

Introduction to SAMiRNA™

BIONEER Innovation • Value • Discovery

siRNAgen THERAPEUTICS

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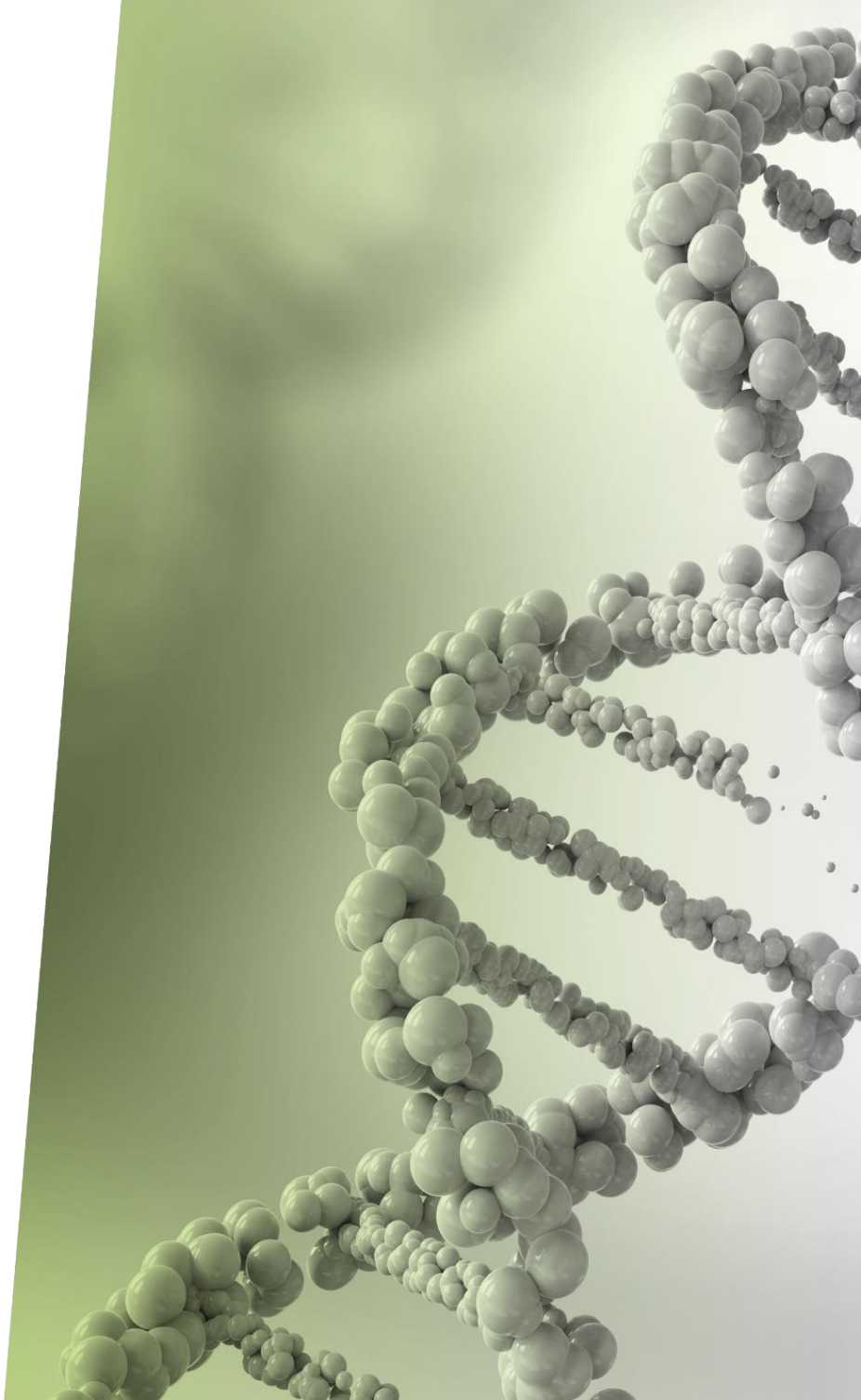

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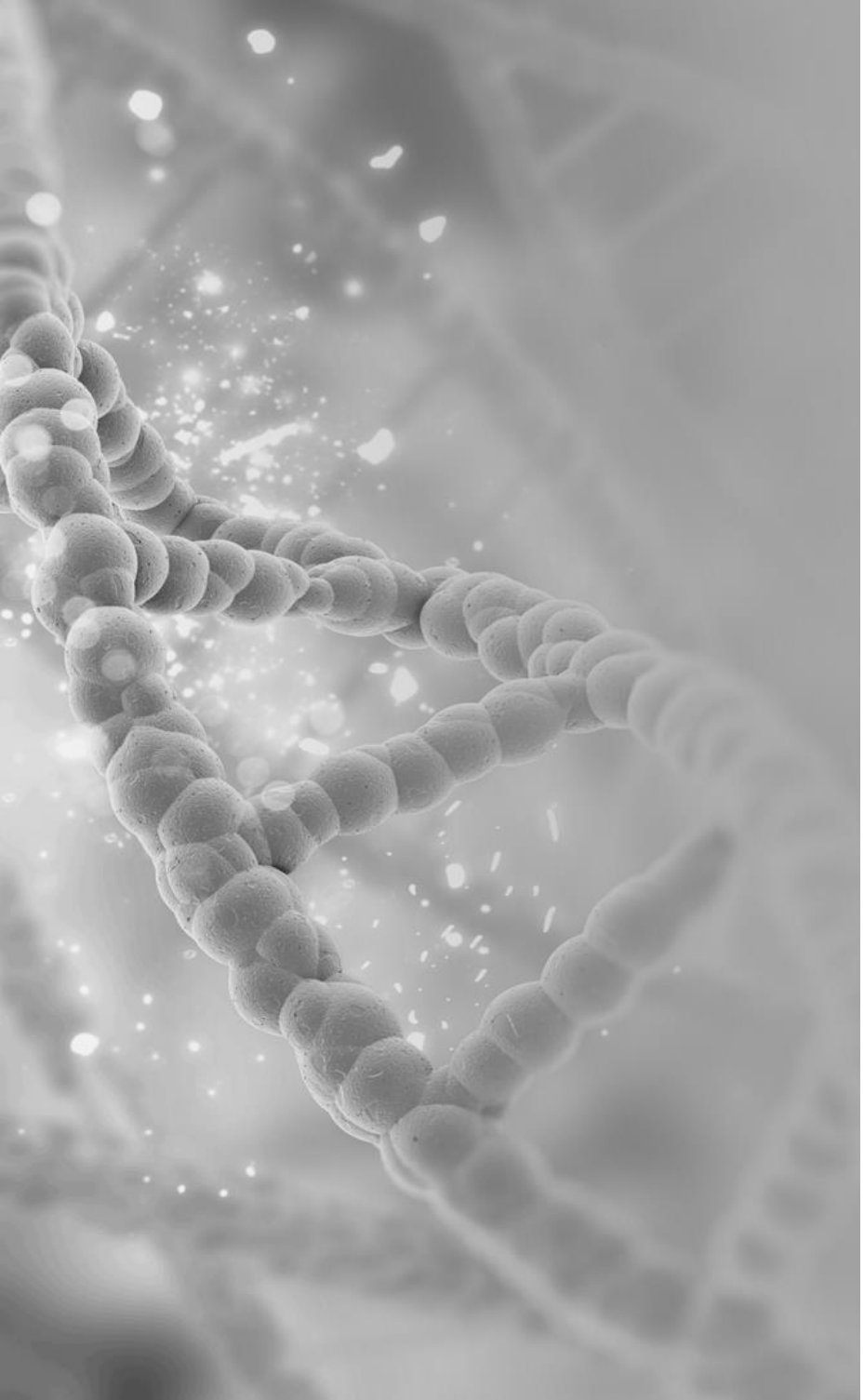


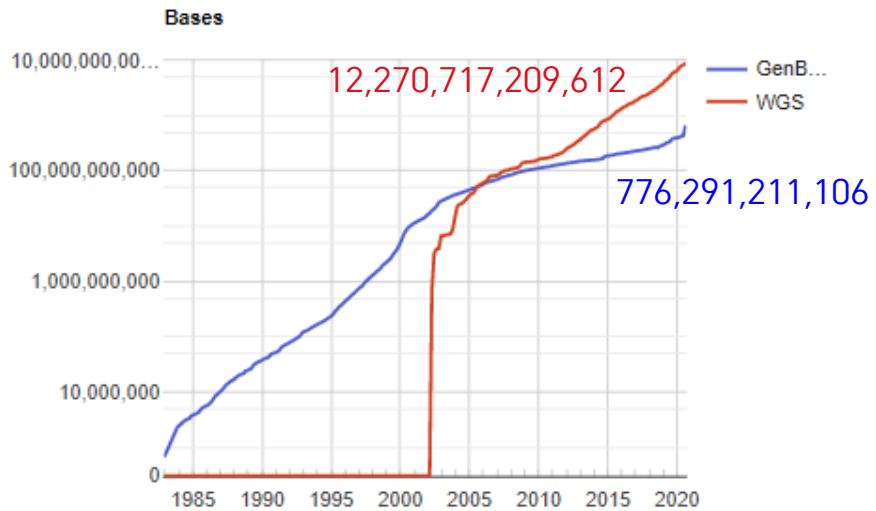
Prologue

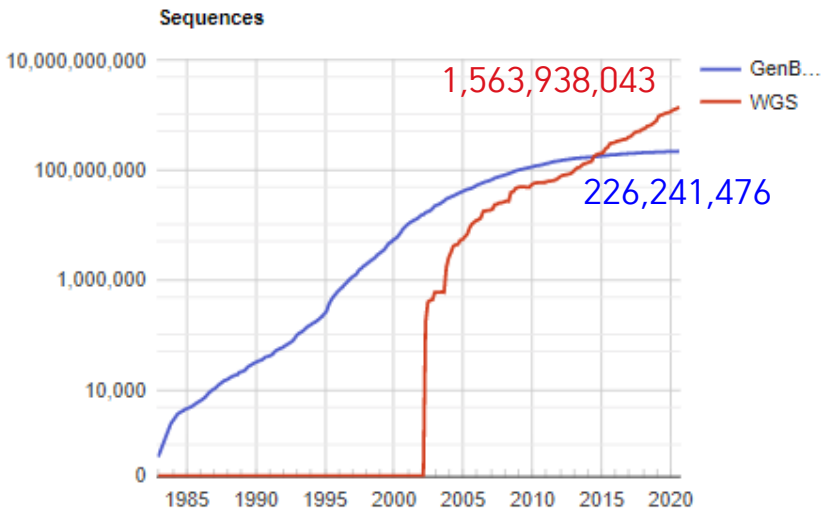
유전자기반 헬스케어 시대의 도래

유전자 분석기술은 매년 2배씩 발전하여 생물학의 디지털 시대 개막

질병관련 유전자 정보가 기하급수적으로 축적되어 신약개발의 새로운 시대 개막

GenBank and WGS Statistics (2021년 2월)





https://www.ncbi.nlm.nih.gov/genbank/statistics/

RNAi 치료제 시대의 도래

FDA approves first-of-its kind targeted RNA-based therapy to treat a rare disease

The U.S. Food and Drug Administration today approved Onpattro (patisiran) infusion for the treatment of peripheral nerve disease (polyneuropathy) caused by hereditary transthyretin-mediated amyloidosis (hATTR) in adult patients. This is the first FDA-approved treatment for patients with polyneuropathy caused by hATTR, a rare, debilitating and often fatal genetic disease characterized by

FDA approves givosiran for acute hepatic porphyria

On November 20, 2019, the Food and Drug Administration approved givosiran (GIVLAARI, Alnylam Pharmaceuticals, Inc.) for adults with acute hepatic porphyria (AHP).

Efficacy was evaluated in ENVISION (NCT03338816), a randomized, double-blind, placebo-controlled, multinational trial enrolling 94 patients with AHP. Patients were randomized (1:1) to receive once monthly

Novartis receives EU approval for Leqvio®* (inclisiran), a first-in-class siRNA to lower cholesterol with two doses a year**

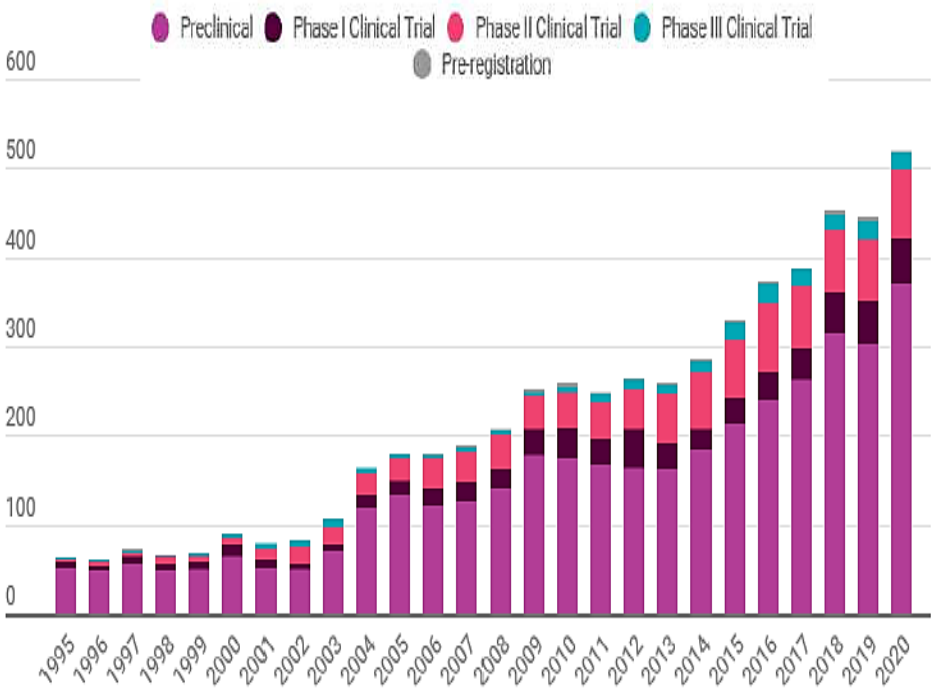
Basel, December 11, 2020 — Novartis announced today that the European Commission (EC) has approved Leqvio®* (inclisiran) for the treatment of adults with hypercholesterolemia or mixed dyslipidemia. This approval is based on the results of the robust ORION clinical development program, where Leqvio provided an effective and sustained low-density lipoprotein cholesterol (LDL-C) reduction of up to 52% in patients with elevated LDL-C, despite maximally tolerated statin therapy. With two doses a year, after an initial dose and one at 3 months, Leqvio is expected to support long-term adherence[1-3].

RNA 치료제 파이프라인 개발 현황

파이프라인 2004년 이후 지속 증가해 2020년 500개 이상

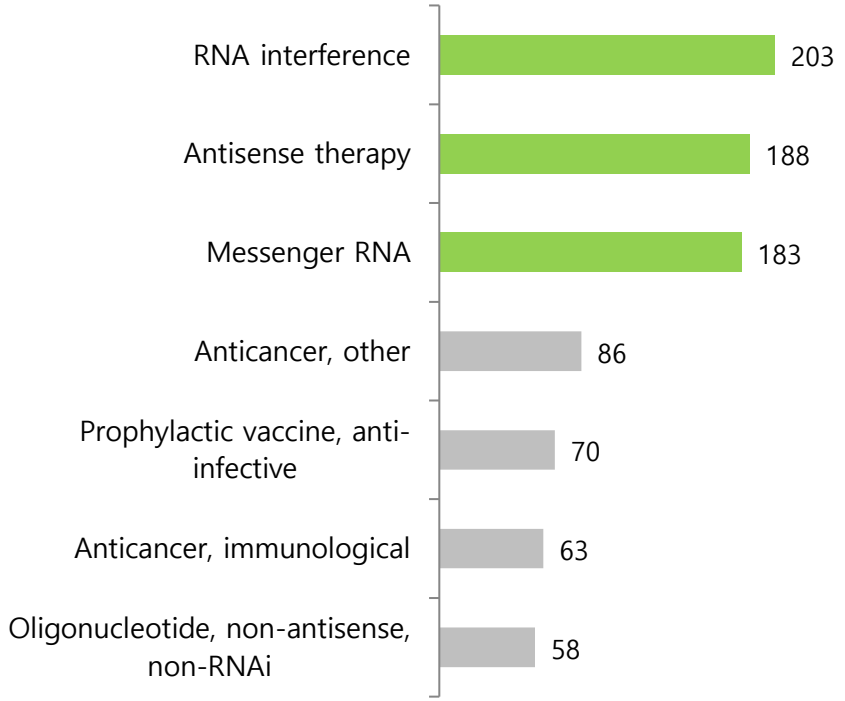
RNA 치료제 연도별 파이프라인 현황

- 371개(71%)가 전임상 단계, 19개가 임상 3단계



RNA 치료제 모달리티별 현황

- RNAi, Antisense oligonucleotide, mRNA 형태로 주로 개발



출처 : ASGCT, Gene, Cell, & RNA Therapy Landscape – Q1 2021 Quarterly Data Report, 2021.04

RNAi 치료제 허가 현황

RNAi Therapy Approved

Product	API	Approved	Indication	Developer
Onpattro	Patisiran	2018. 08.	Polyneuropathy (다발성 신경병증)	Alnylam
Givlaari	Givosiran	2019. 11.	Hepatic porphyria (간 포르피린증)	Alnylam
Oxlumo	Lumasiran	2020. 11.	Primary hyperoxaluria (원발성 과옥살산뇨증)	Alnylam
Leqvio	Inclisiran	2020. 12.	Hypercholesterolemia (고콜레스테롤 혈증)	Medicines*/ Novartis

* The Medicines Company

RNAi Therapy Phase III

API	Indication	Developer
Vutrisiran	Polyneuropathy (다발성 신경병증)	Alnylam
Nedosiran	Primary hyperoxaluria (원발성 과옥살산뇨증)	Dicerna
Fitusiran	Hemophilia A/B (A/B 혈우병)	Alnylam / Sanofi
Teprasiran	Acute kidney injury (급성 신장 손상)	Quark / Novartis
Cosdosiran	Primary angle glaucoma (원발성 개방 녹내장)	Quark
Tivanisiran	Dry eye disease (안구건조증)	Sylentis S.A

RNAi 기술의 미충족 수요 (Unmet Needs)

FDA approves first-of-its kind targeted RNA-based therapy to treat a rare disease

The most common adverse reactions reported by patients treated with Onpattro are infusion-related reactions including flushing, back pain, nausea, abdominal pain, dyspnea (difficulty breathing) and headache. All patients who participated in the clinical trials received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the

FDA approves givosiran for acute hepatic porphyria

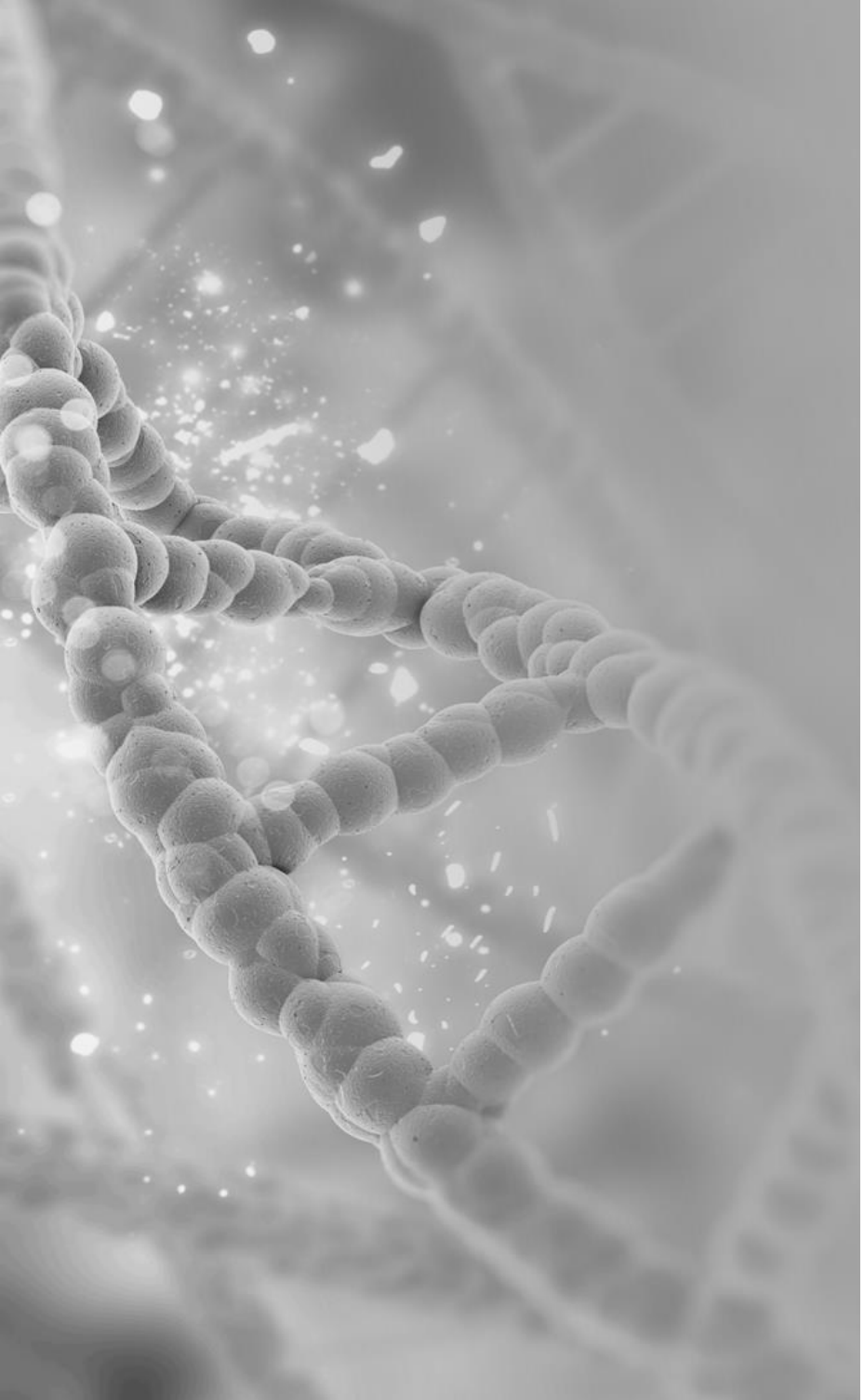
The most common adverse reactions (>20% of patients) included nausea and injection site reactions. The label contains warnings for anaphylactic reactions, hepatic and renal toxicities, and injection site reactions. Hepatic toxicity was mostly transaminase elevation. Renal toxicity was mostly serum creatinine elevation and decreases in estimated glomerular filtration rate.

상용화 시대 개막했으나
아직 해결해야 할 과제들 남아

부작용
(선천면역반응)

세포 내 전달
(표적장기에 전달)

생산 비용 절감
& 품질 관리



Chapter

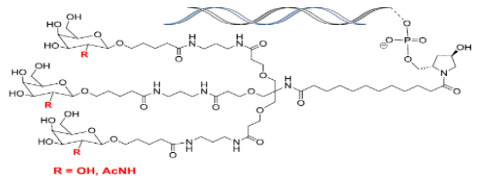
01

SAMiRNA™ Platform

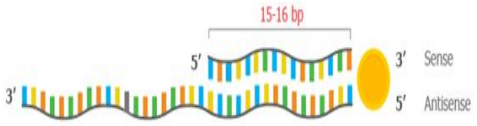
SAMiRNA™ is an Unique Single-molecular Nanoparticle siRNA

Naked Oligo

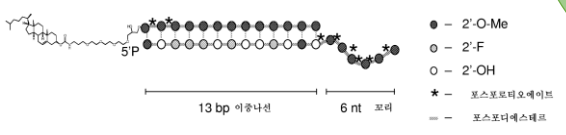
Alnylam
GalNAc-siRNA Conjugates

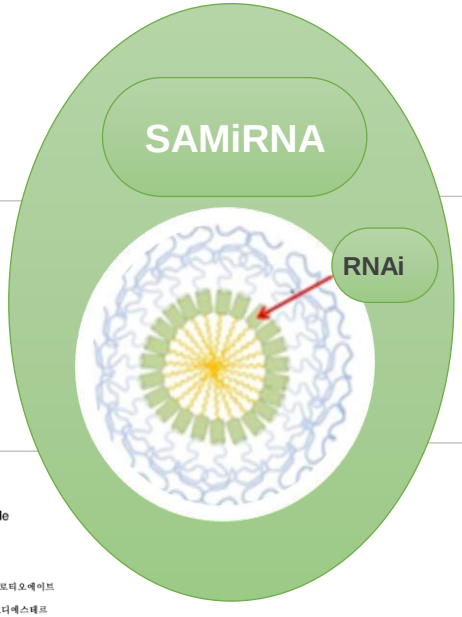


Olix
Cell penetrating-long asymmetric siRNA (Cp-lasiRNA)

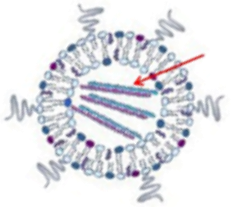


RXi
self-delivering RNAi (sd-rxRNA®)
: RNAi + Antisense

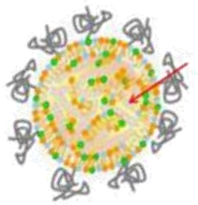




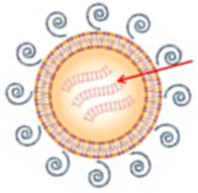
Nanoparticle



Alnylam



Dicerna

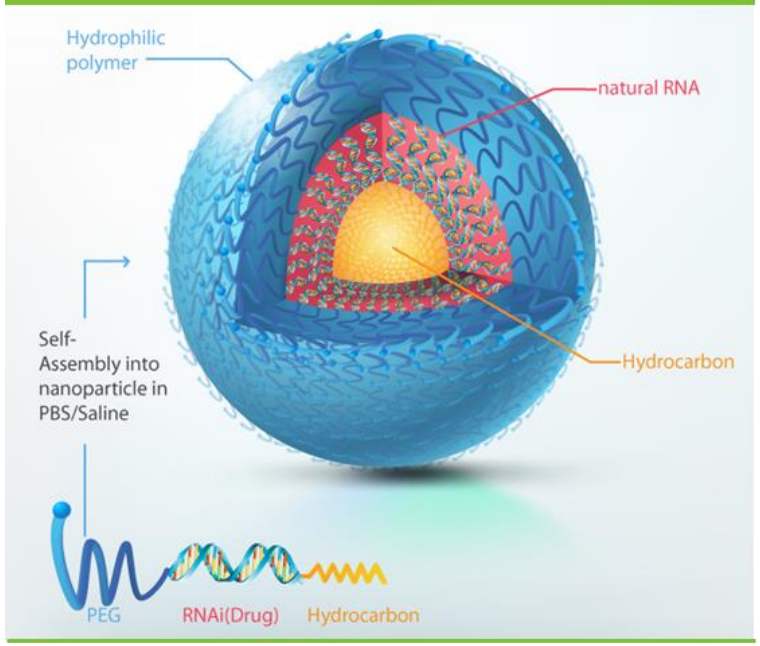


Tekmira

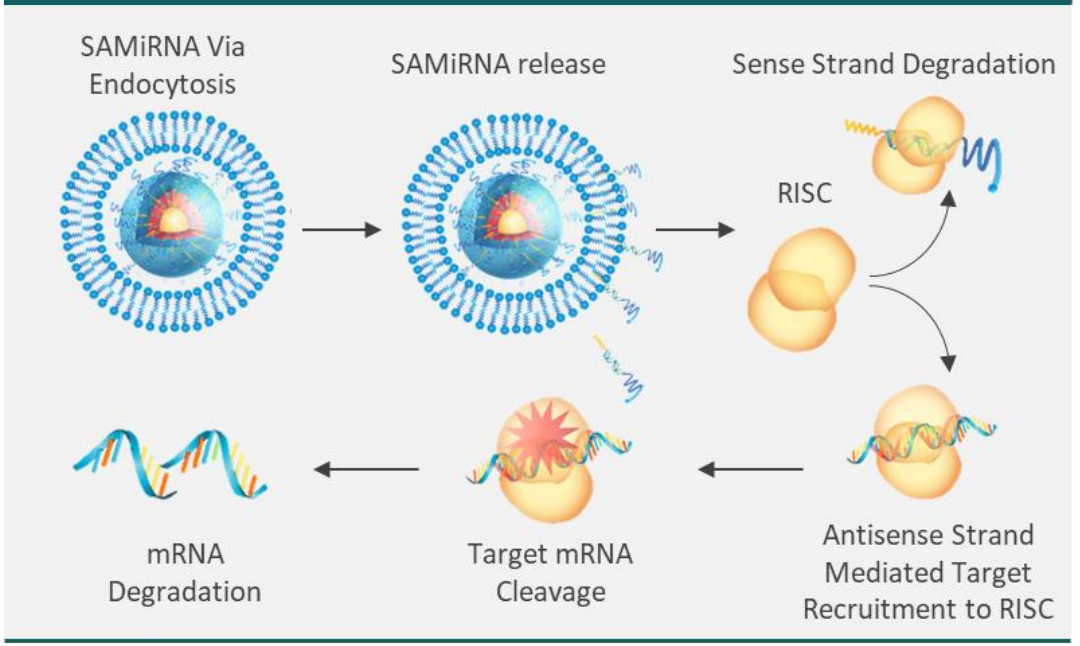
SAMiRNA™ (Self-Assembled-Micelle Inhibitory RNA)

SAMiRNA™ enables delivery of miRNA / siRNA without modification

Structure



Mechanism

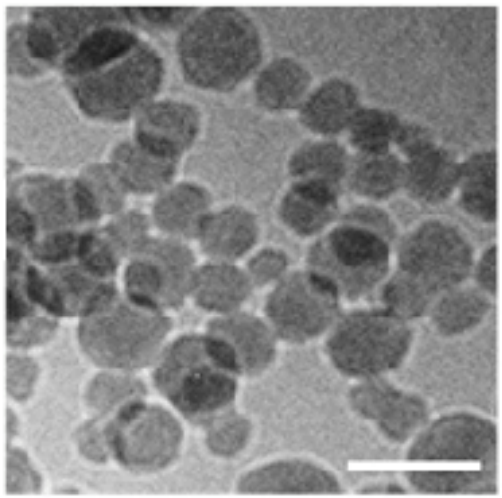


Protected by USP 8779114 and family patents

Physical Characteristics of SAMiRNA™

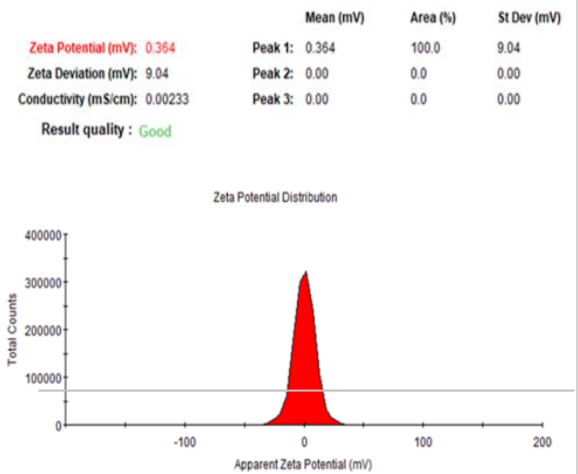
SAMiRNA™ spontaneously forms a neutral siRNA nanoparticle (size :~90 nm)

Cryo-TEM images of SAMiRNA™



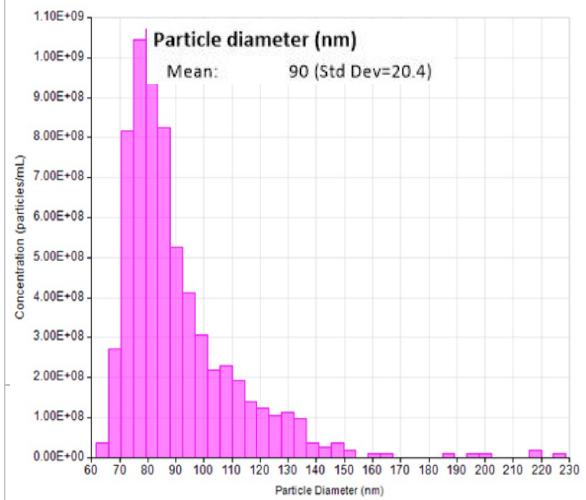
scale bar = 100 nm

Surface charge of SAMiRNA



zeta potential of SAMiRNA™ measured by Nano-ZS (Malvern).

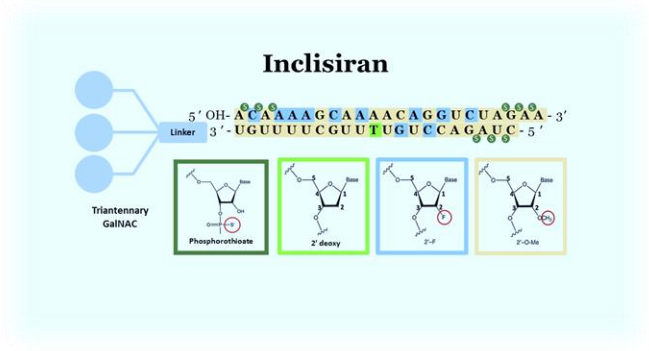
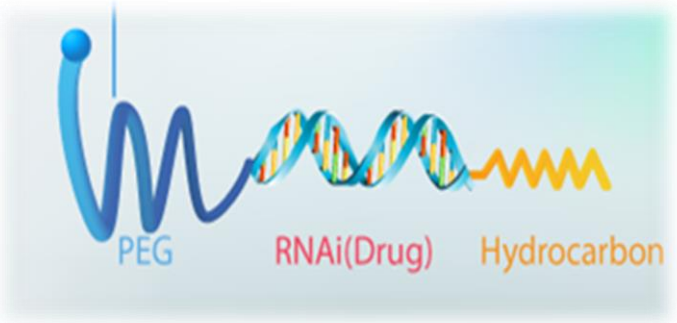
SAMiRNA size analysis by qNano platform



SAMiRNA™ titrated using a qNano particle analyzer (IZON Science, Oxford, UK)

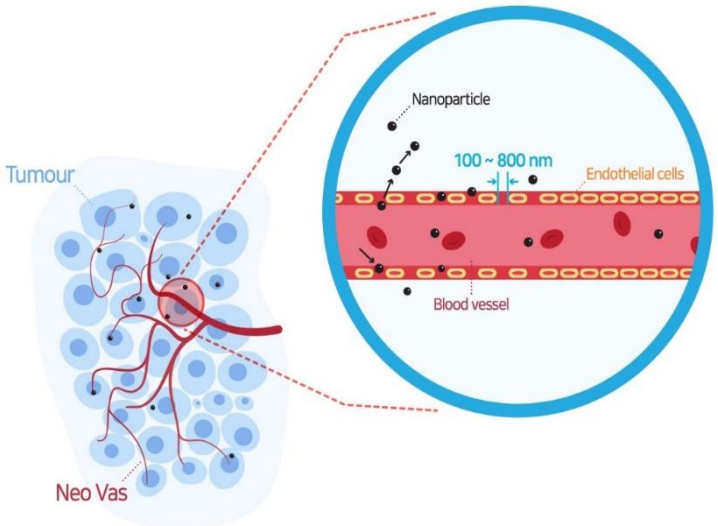
Protected by USP 8779114 and family patents

SAMiRNA™ vs Inclisiran

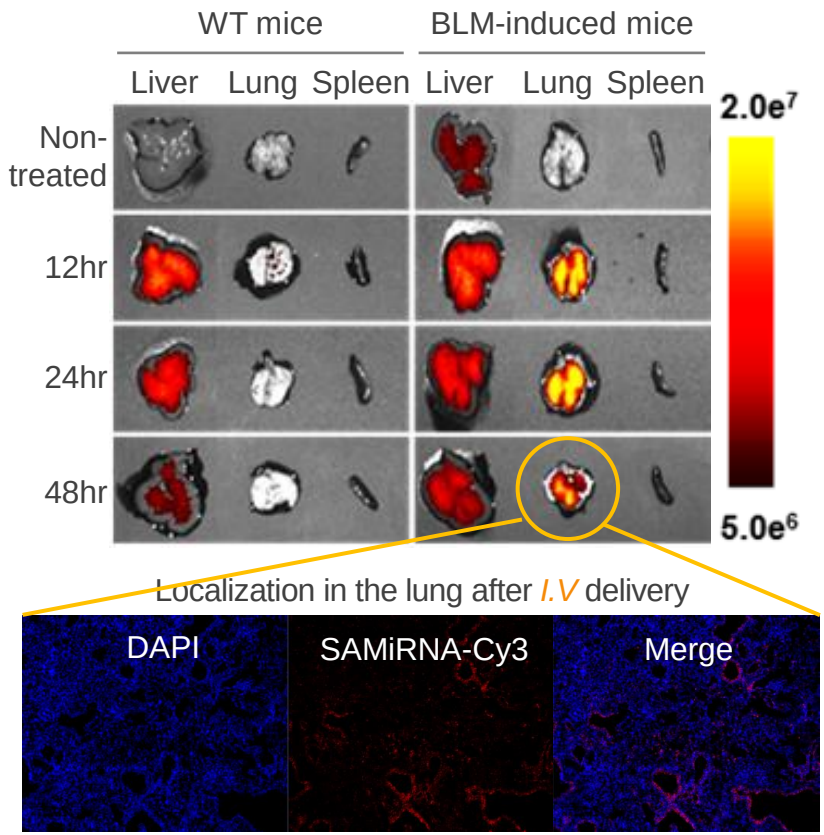
	Inclisiran (16 KDa)	SAMiRNA-AREG (13KDa)
API	Heavily modified siRNA	Native siRNA
Conjugates	Tri-GalNAC	HEG & Hydrocarbon
Molar mass	16,248.27 g/mol	13,739.28 g/mol
		

SAMiRNA™ is Selectively Delivered to Tumor and Inflamed Tissues

EPR (Enhanced Permeability & Retention) Effect of SAMiRNA



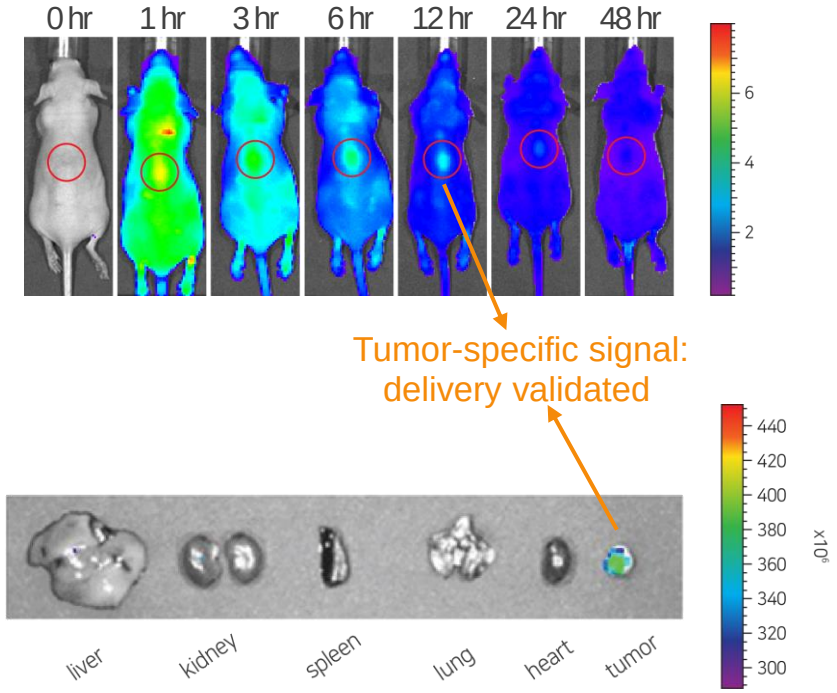
SAMiRNA™ is selectively delivered to inflamed (fibrosis) tissues.



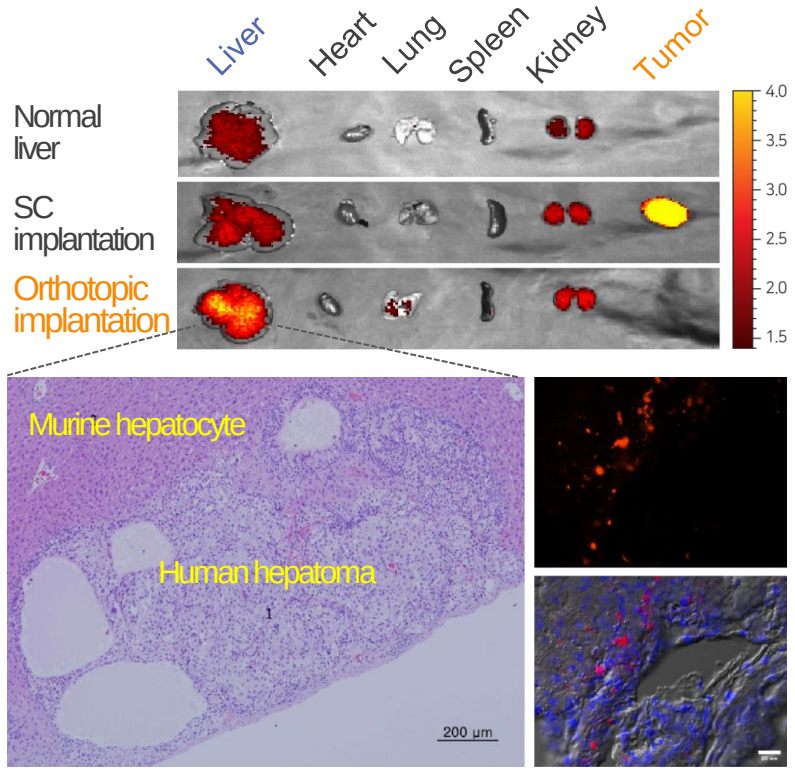
In-vivo real-time NIR fluorescence imaging of SAMiRNA™ in fibrosis models

SAMiRNA™ is mainly Delivered to Tumor Tissues by EPR

S.C. grafted HCC model

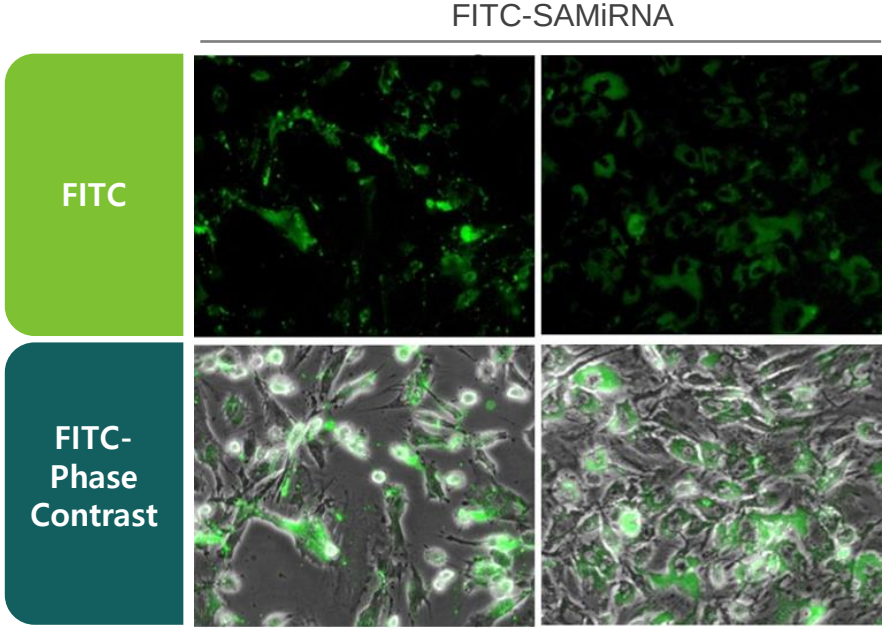


Orthotopic HCC model



SAMiRNA™ is Delivered to Other Cell by Direct Treatment

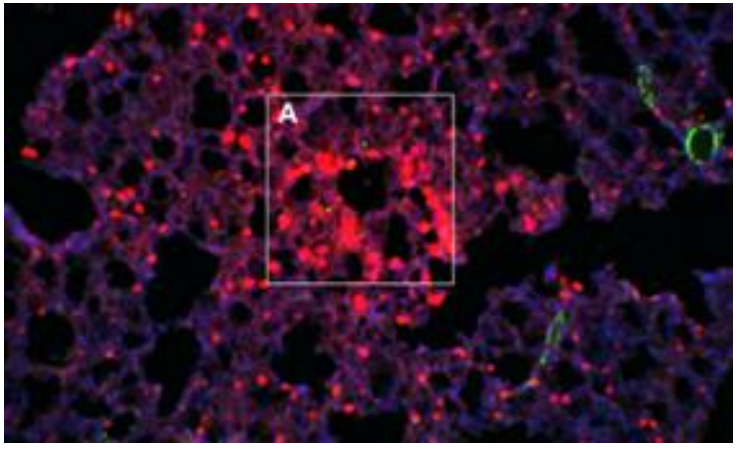
SAMiRNA-FITC is efficiently delivered to human synoviocytes (Rheumatoid Arthritis)



FITC-labeled SAMiRNA-Cont nanoparticle (Green) was treated for 48hrs and the cell was fixed with 2% PFA and analyzed with phase contrast fluorescence microscope at 200X.

SNU Hospital, Depart of Int Med

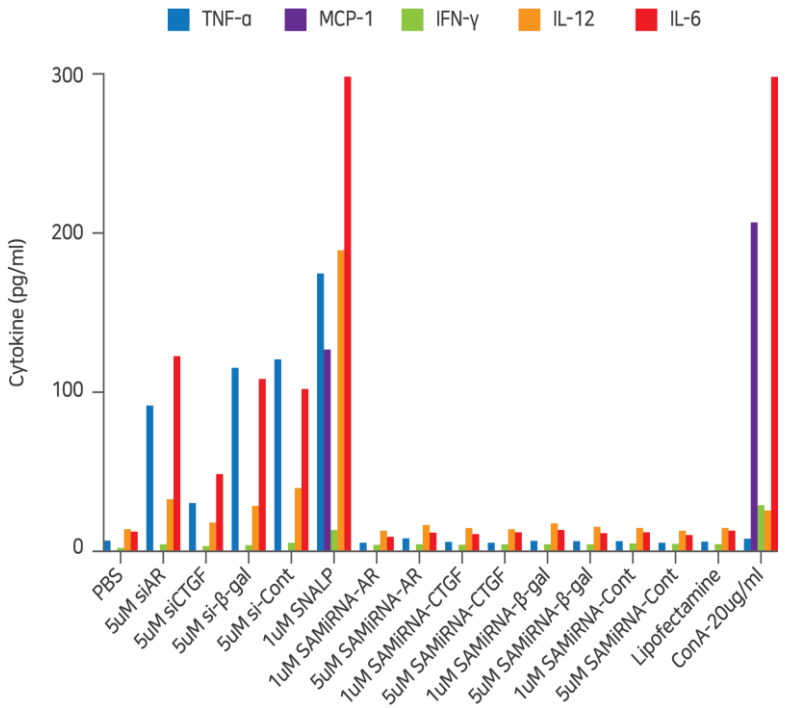
SAMiRNA-Cy5 is efficiently delivered to mouse lung tissue by inhalation



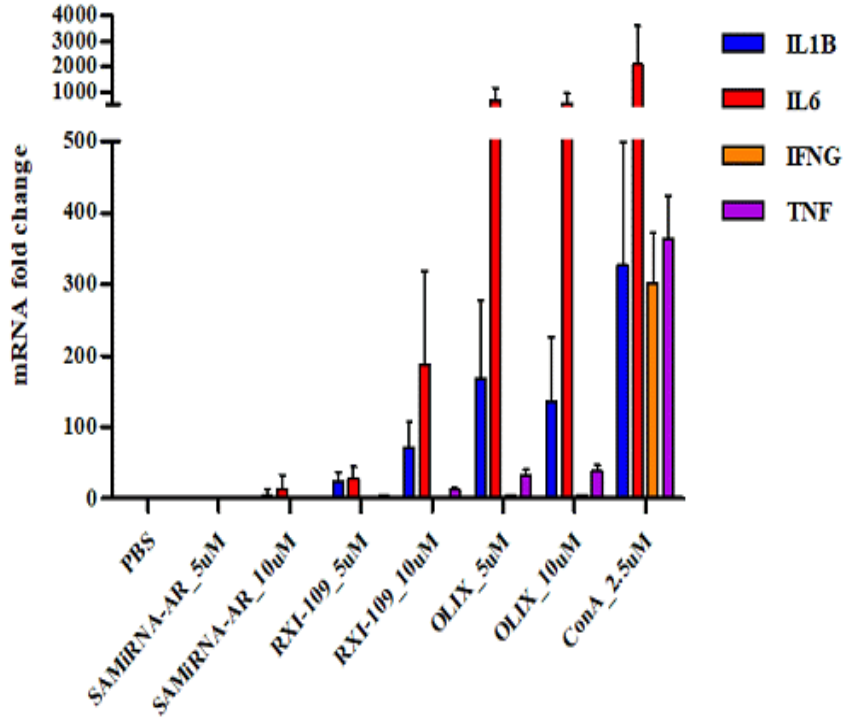
Cy5-labeled SAMiRNA nanoparticle (Red) was treated for 5 mins by portable ultrasonic nebulizer and the lung tissue was fixed and analyzed with confocal microscope at 200X.

SAMiRNA™ Overcomes Innate Immune Toxicity

SAMiRNA™ treatment at 1- 5 uM on human PBMCs shows no innate immune stimulation.(ELISA data)



SAMiRNA™ treatment up to 10 uM onto human PBMC shows no innate immune stimulation.(qPCR data)

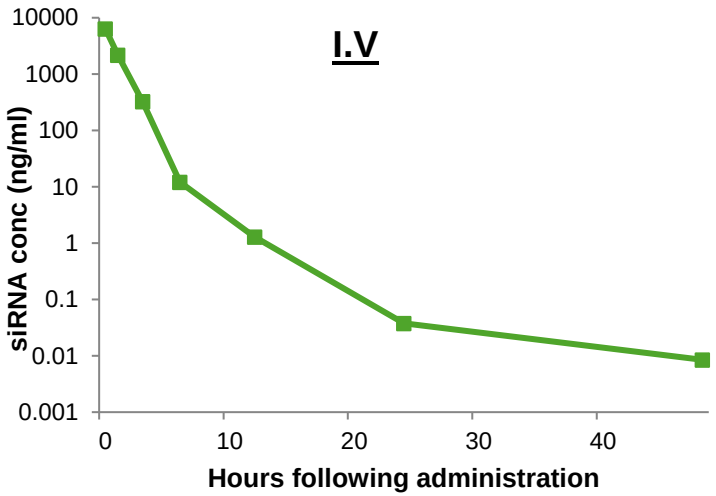


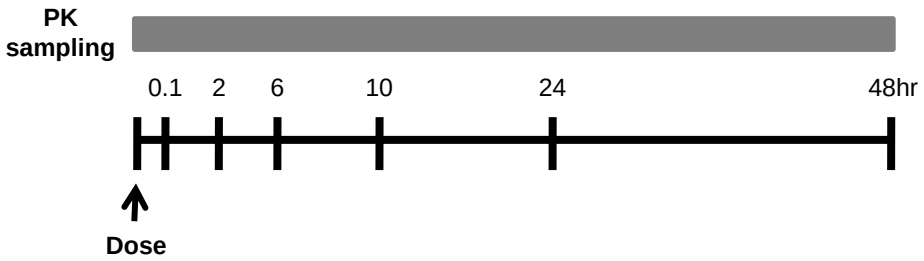
Measured by Magnetic Luminex Screening Assay (R&D systems, LXSAMSM) serviced by Woongbe meditech Korea)

J. Biol. Chem. *2016 Yoon et. al.*

PK Profile of SAMiRNA™ in Mouse Blood

- In vivo quantification of SAMiRNA administered through I.V in BLM-fibrosis model
- A time course PK in serum by qPCR-based measurement





SAMiRNA-AREG	I.V
Dose (mg/kg)	5
$AUC_{0\rightarrow t}$ (hr*ng/ml)	6076.164
Cmax (ng/ml)	6341.65
Tmax (hr)	0.1
T1/2 (hr)	4.318

J. Biol. Chem. *2016 Yoon et. al.*

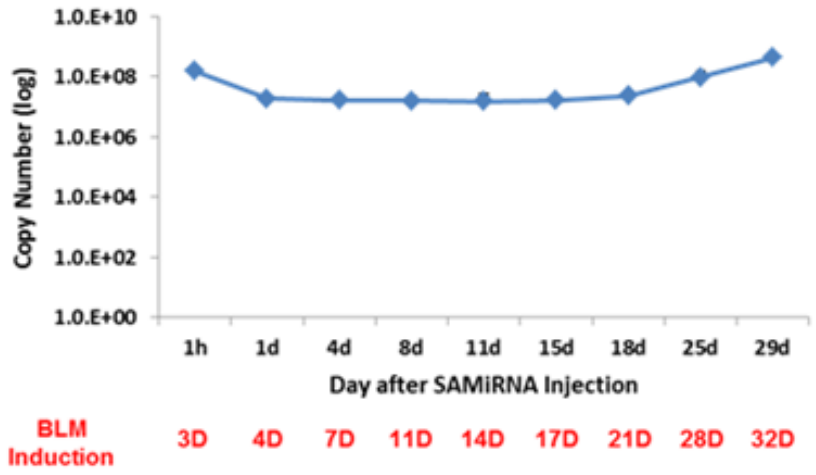
PK/PD of SAMiRNA™ in Lung Tissue of BLM Induced IPF

One dose of SAMiRNA sustains Efficacy up to 1 month

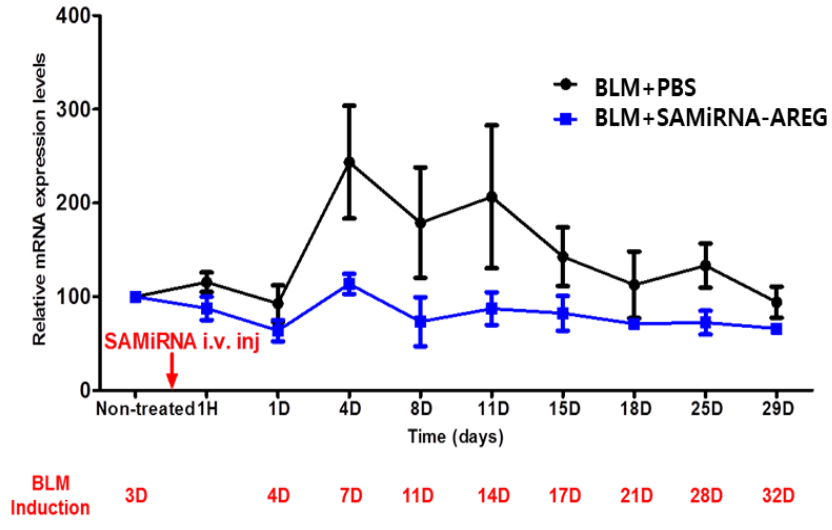
PK/PD of SAMiRNA(antisense strand) administered through IV in BLM-fibrosis model

- A time course PK of lung tissue by Ago2-IP & HiT(Heat in Triton)-qPCR measurement
- PD of lung tissue by qRT-PCR measurement shows that SAMiRNA is effective for a month.

PK profile (5mpk, I.V)



PD study (5mpk, I.V)



Pre-clinical Toxicology Studies of SAMiRNA-AREG

KIT(Korea Institute of Toxicology), Charles River Laboratories

General Toxicology Study

- Mouse (NOAEL in mouse > 300mpk)
- Acute toxicity, 2 Weeks Dose Range Finding(DRF), Repeated Dose 4-Week Toxicity and Toxicokineitc Study with a 2-Week Recovery Period

▶ I.V single administration of SAMiRNA was well-tolerated with no overt toxicity

- Monkey (NOAEL in monkey > 100mpk)
- Stepwise dose-escalating study, 2-Week Dose Range Finding, Repeated Dose 4-Week Toxicity and Toxicokineitc Study with a 2-Week Recovery Period

▶ No clinically significant or dose-dependent changes were observed

▶ SAMiRNA-AREG did not induce test item-related adverse effect

▶ SAMiRNA-AREG-related toxicological changes were not seen in all parameters

Genetic Toxicology Study

- Mammalian Micronucleus Assay, *In Vitro* Chromosome aberration assay, Bacterial Reverse Mutation Assay

▶ SAMiRNA did not induce genetic toxicity

Safety Pharmacology Study

- Irwin test, Respiratory test (Respiratory Function Study), hERG test : hERG Potassium Channel Preliminary Study

▶ SAMiRNA-AREG did not produce any significant effects

Cardiovascular monkey telemetry Study

charles river

▶ No effects in cynomolgus monkeys at doses of 25, 50, and 100 mg/kg

▶ NOAEL of SAMiRNA was 100mg/kg in monkey

*NOAEL : No Observed Adverse Effect Level

Toxicology Reports (2021)

Comparisons of Preclinical Tox with Other RNAi Drugs

SAMiRNA™ is much less toxic than other modalities in mouse and NHP

*NOAEL : No Observed Adverse Effect Level

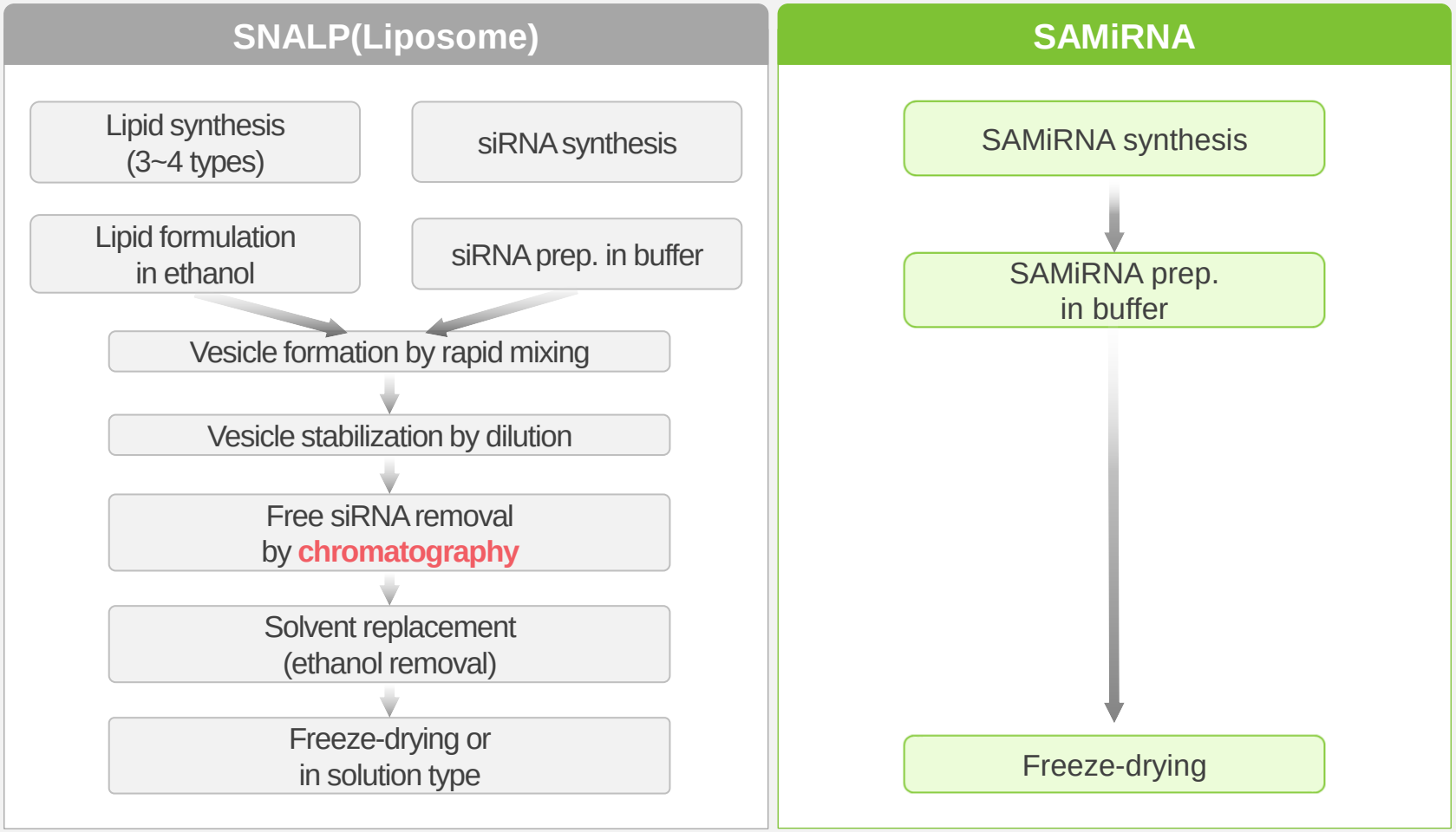
Developer	Drug	NOAEL 4 or 7 weeks (mg/kg/wk)	Safety margins
Alnylam[1]	ALN-TTR02 (Patisiran-LNP)	Rat ≥ 1 & NHP ≥ 1-3	Rat & NHP > 5X
	ALN-TTRsc (Revusiran-GalNAc)	Rat ≥ 30* & NHP ≥ 300	Rat > 6X & NHP > 60X
	ALN-AS1 (Givosiran-GalNAc)	Rat ≥ 30* & NHP ≥ 150	Rat > 300X & NHP > 1500X
	ALN-AAT (GalNAc)	Rat ≥ 50* & NHP ≥ 150	Rat > 160X & NHP > 500X
IONIS[2]	Kynamro (Mipomersen-ASO)	Mouse ≥ 10 & NHP ≥ 30	Mouse > 3.3X & NHP > 10X
	Spinraza (Nusinersen-ASO)	NHP: 0.3 mg/dose / 39 mg/yr	Similar human dose
Arrowhead[3]	ARC-521 (DPC siRNA)	Monkey deaths at high dose	All DPSs clinical trial hold
	ARO-AAT (TRiM™ siRNA)	Rat & NHP ≥ 300	*N/A*
Rxi[4]	Rxi-109 (Modified siRNA)	Rat ≥ 18.8 & NHP ≥ 12.8	NHP > 400X
SAMiRNA	**Bioneer (Natural RNAi)**	**Mouse > 300 & NHP > 100**	***TBD***

* GalNAc conjugated siRNA shows Basophilic granules in renal tubule epithelium at high does only Rats

1. Presented by Alnylam Corp presentation
2. FDA Pharmacology Reviews Appl # 203568Orig1s000
3. Presented by Arrowhead Corp presentation
4. Presented by Rxi Corp presentation

Advantages of Manufacturing

One-step automated solid-phase synthesis, No formulation/encapsulation.
Simple manufacturing process enables a large-scale production at much lower cost.



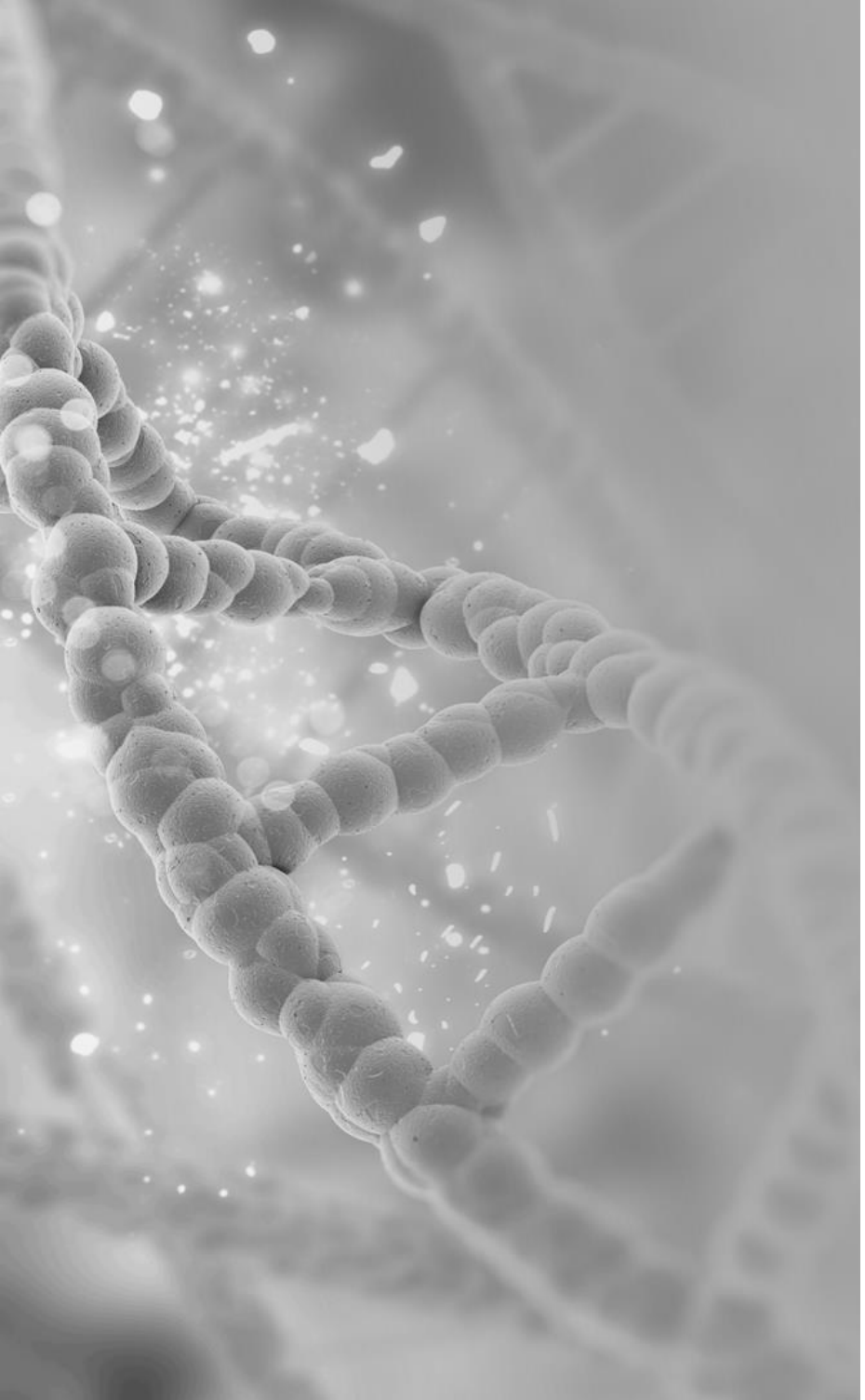
SAMiRNA™ is the Next Generation siRNA Therapeutics

- **No Adverse Events or Innate Immune stimulation** by Unmodified RNA conjugated with hydrophilic polymer and hydrocarbon

- **Delivery to various tissues** (inflamed tissues, tumors) by IV, ID, SC injection, and (lung) by inhalation
- **Cost Advantages** in large scale production & QC

  Single Molecule, One-step automated solid-phase synthesis, No formulation/encapsulation

- **Strong intellectual property** SAMiRNA™ core technology and drug pipeline are protected by more than 190 patents approved and pending in major market.

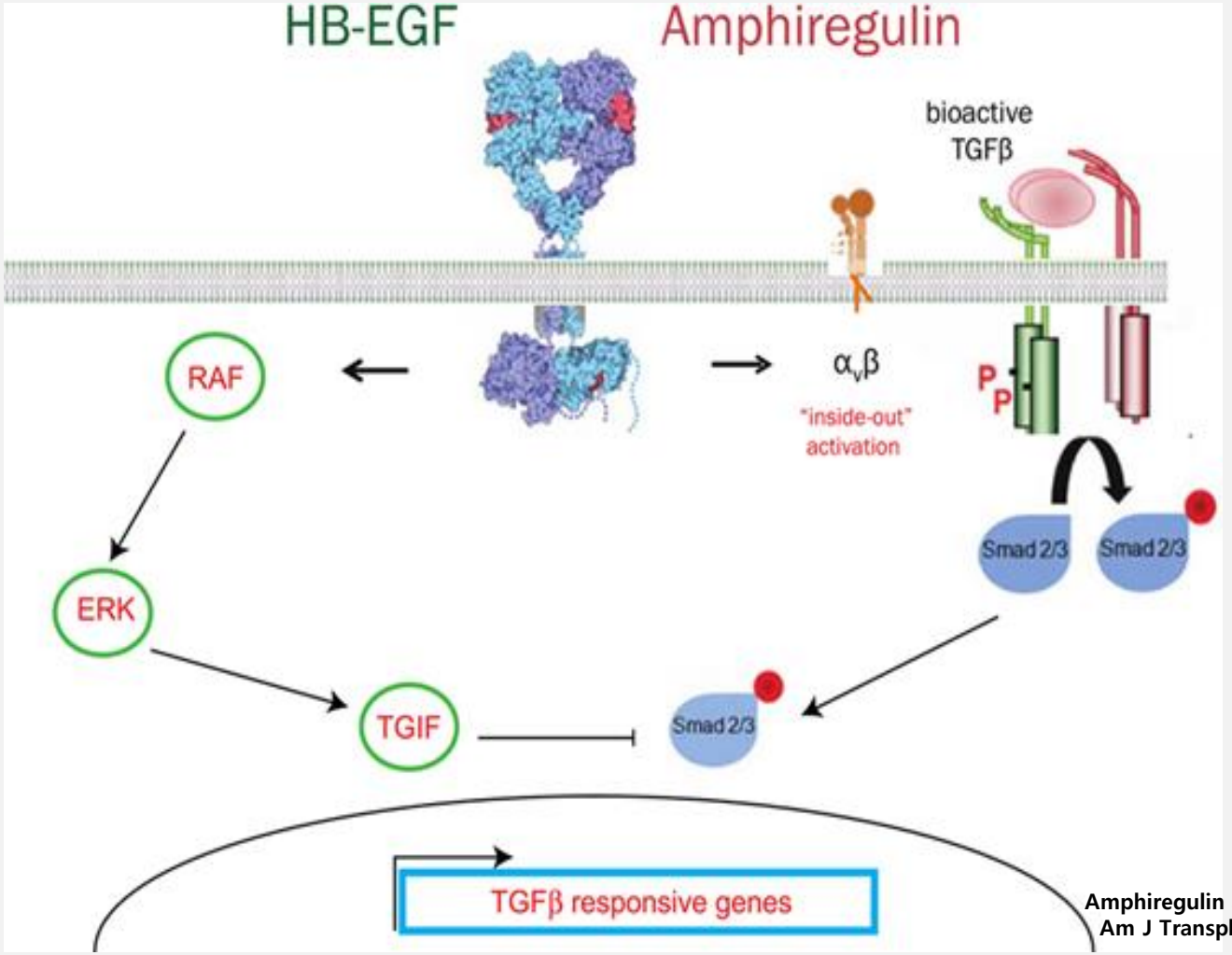


Chapter

02

Amphiregulin

Amphiregulin as a Key Driver of Tissue Fibrosis

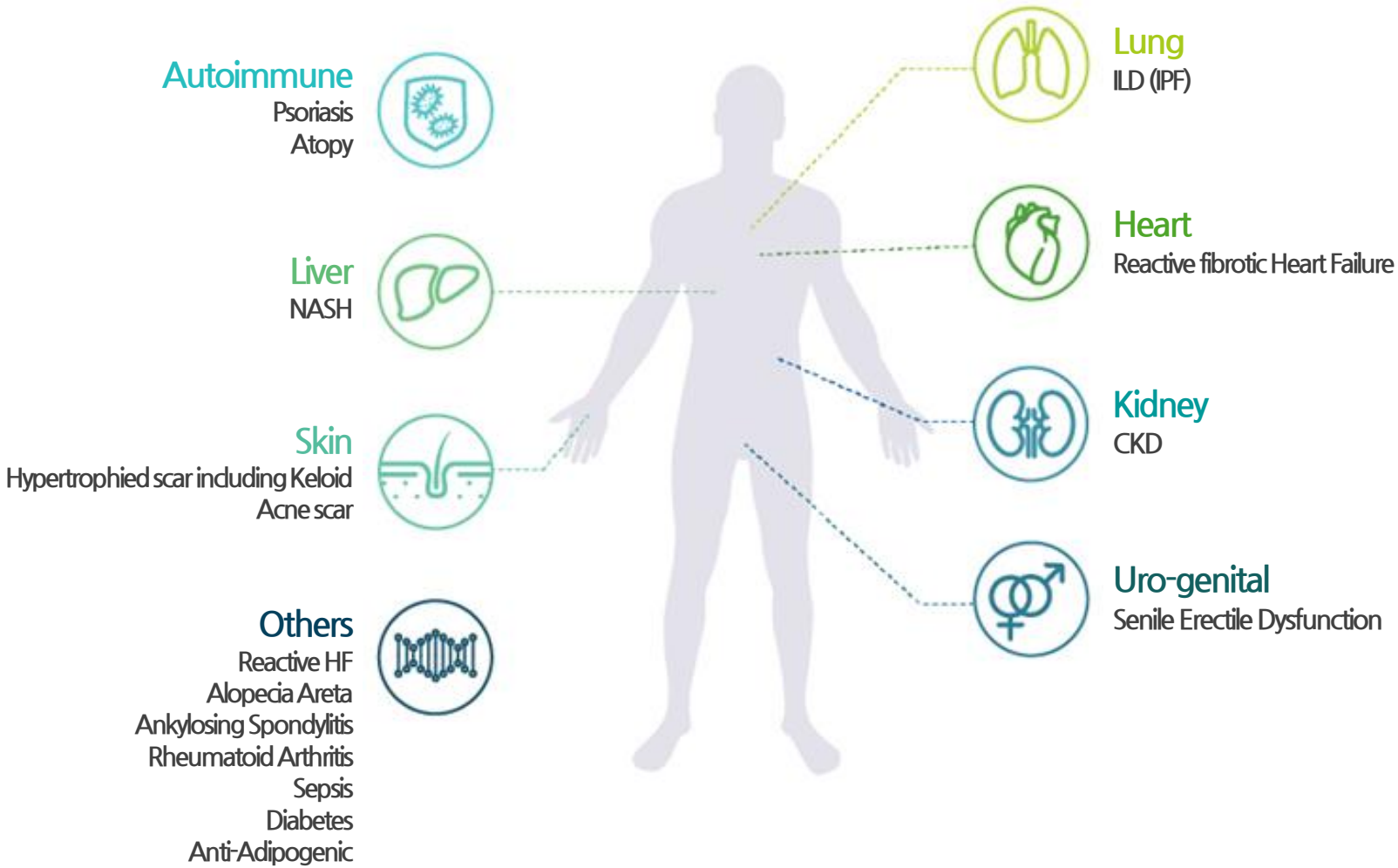


Amphiregulin as a driver of tissue fibrosis
Am J Transplant. 2020;20:631–632

- EGFR shows a so-called ″agonistic bias″ : ligands with different affinities induce the activation of different downstream signaling pathways.
- **low affinity**-ligand **amphiregulin** induces the activation of **TGFβ**
- **high-affinity** ligand **HB-EGF** activates **TGIF**(intracellular inhibitor of TGFβ-signaling) : **preventing the differentiation of pericytes into myofibroblasts**
- HB-EGF -/- mice develop more severe forms of tissue fibrosis.
- EGFR inhibitor-treated cancer patients → **block** this HB-EGF-mediated physiological counterbalance to **TGFβ signaling** → progression of **tissue fibrosis**

SAMiRNA™ has Potential for Anti-Fibrotic Diseases

Focusing on the discovery and development of RNAi therapeutics through its own innovative SAMiRNA™ technology to maximize efficacy and minimize adverse events.



Review Summary of AREG & Cancer

Anti-proliferative

- **Amphiregulin Exosomes Increase Cancer Cell Invasion**
  CellPress, James N Higginbotham, Michelle Demory Beckler, Jonathan D.Gephart
  https://doi.org/10.1016/j.cub.2011.03.043
- **Amphiregulin regulates proliferation and migration of HER2-positive breast cancer cells.**
  Cell Oncol (Dordr). 2018 Apr;41(2):159-168. doi: 10.1007/s13402-017-0363-3. Epub 2017 Nov 27
- **Amphiregulin Is a Critical Downstream Effector of Estrogen Signaling in ERα-Positive Breast Cancer.**
  Cancer Res. 2015 Nov 15;75(22):4830-8. doi: 10.1158/0008-5472.CAN-15-0709. Epub 2015 Nov 2.
  Peterson EA1, Jenkins EC1, Lofgren KA2, Chandiramani N1, Liu H1, Aranda E1, Barnett M1, Kenny PA3
- **Amphiregulin induces human ovarian cancer cell invasion by down-regulating E-cadherin expression.**
  FEBS Lett. 2014 Nov 3;588(21):3998-4007. doi: 10.1016/j.febslet.2014.09.017. Epub 2014 Sep 23.
  So WK1, Fan Q1, Lau MT1, Qiu X1, Cheng JC1, Leung PC2.
- **An antibody to amphiregulin, an abundant growth factor in patients' fluids, inhibits ovarian tumors.**
  Oncogene. 2016 Jan 28;35(4):438-47. doi: 10.1038/onc.2015.93. Epub 2015 Apr 27.
  Carvalho S1, Lindzen M1, Lauriola M1, Shirazi N1, Sinha S1, Abdul-Hai A2, Levanon K

TME

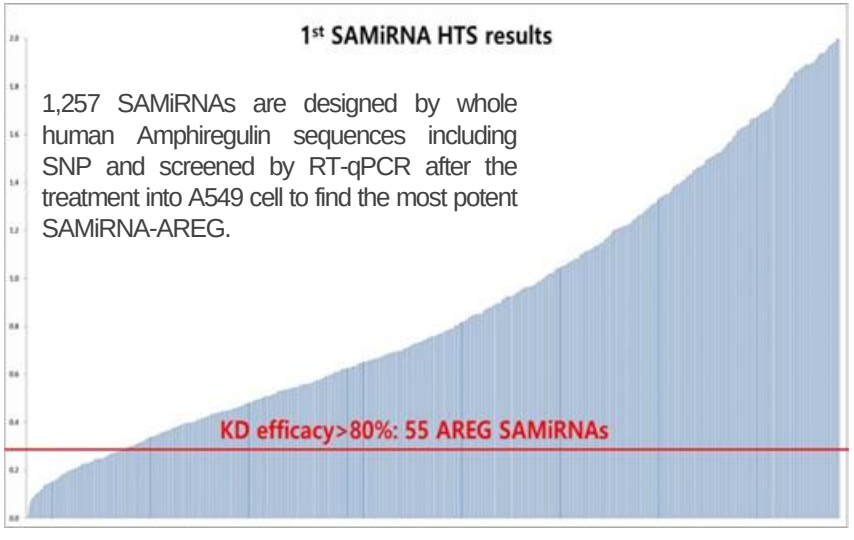
- **Recent studies revealed that AREG is also present in the tumor microenvironment (TME) and contributes to therapeutic resistance.**
  Amphiregulin in Cancer: New Insights for Translational Medicine.
  Trends Cancer. 2016 Mar;2(3):111-113. Xu Q1, Chiao P2, Sun Y3.

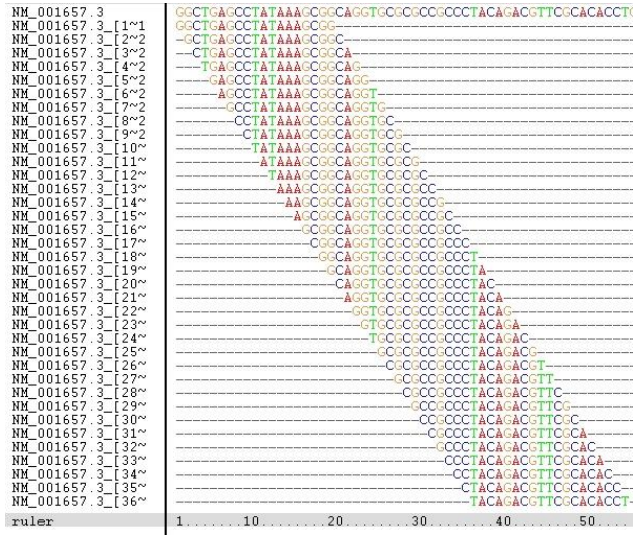
Acquired Resist

- **Amphiregulin as a Novel Resistance Factor for Amrubicin in Lung Cancer Cells.**
  Anticancer Res. 2017 May;37(5):2225-2231.Tokunaga S1, Nagano T2, Kobayashi K1, Katsurada M1, Nakata K1, Yamamoto M1
- **Amphiregulin confers trastuzumab resistance via AKT and ERK activation in HER2-positive breast cancer.**
  Kim JW, Kim DK, Min A, Lee KH, Nam HJ, Kim JH, Kim JS, Kim TY, Im SA, Park IA.
  J Cancer Res Clin Oncol. 2016 Jan;142(1):157-65. doi: 10.1007/s00432-015-2012-4. Epub 2015 Jul 21

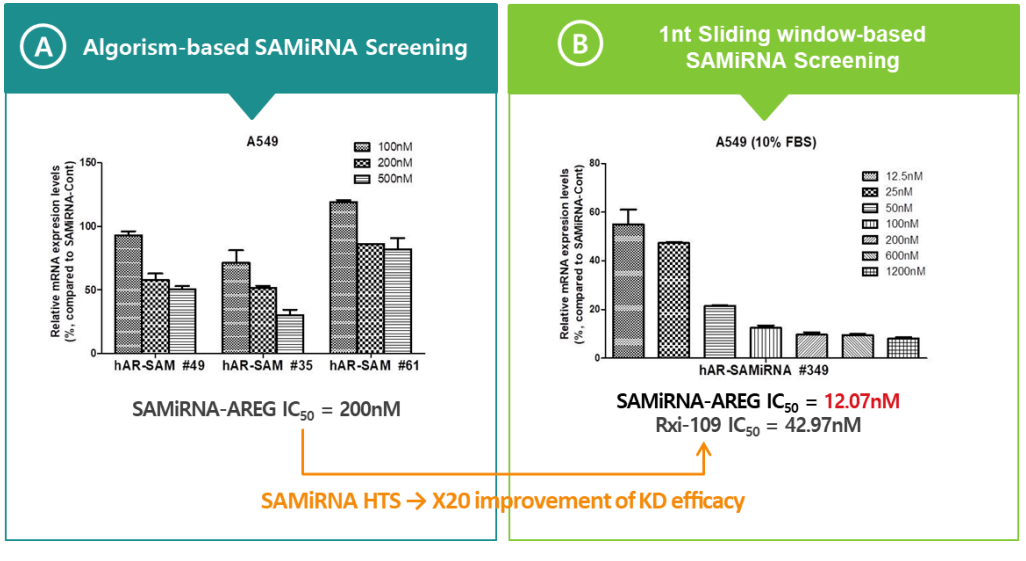
Complete Screening of SAMiRNA-AREG Drug Candidate

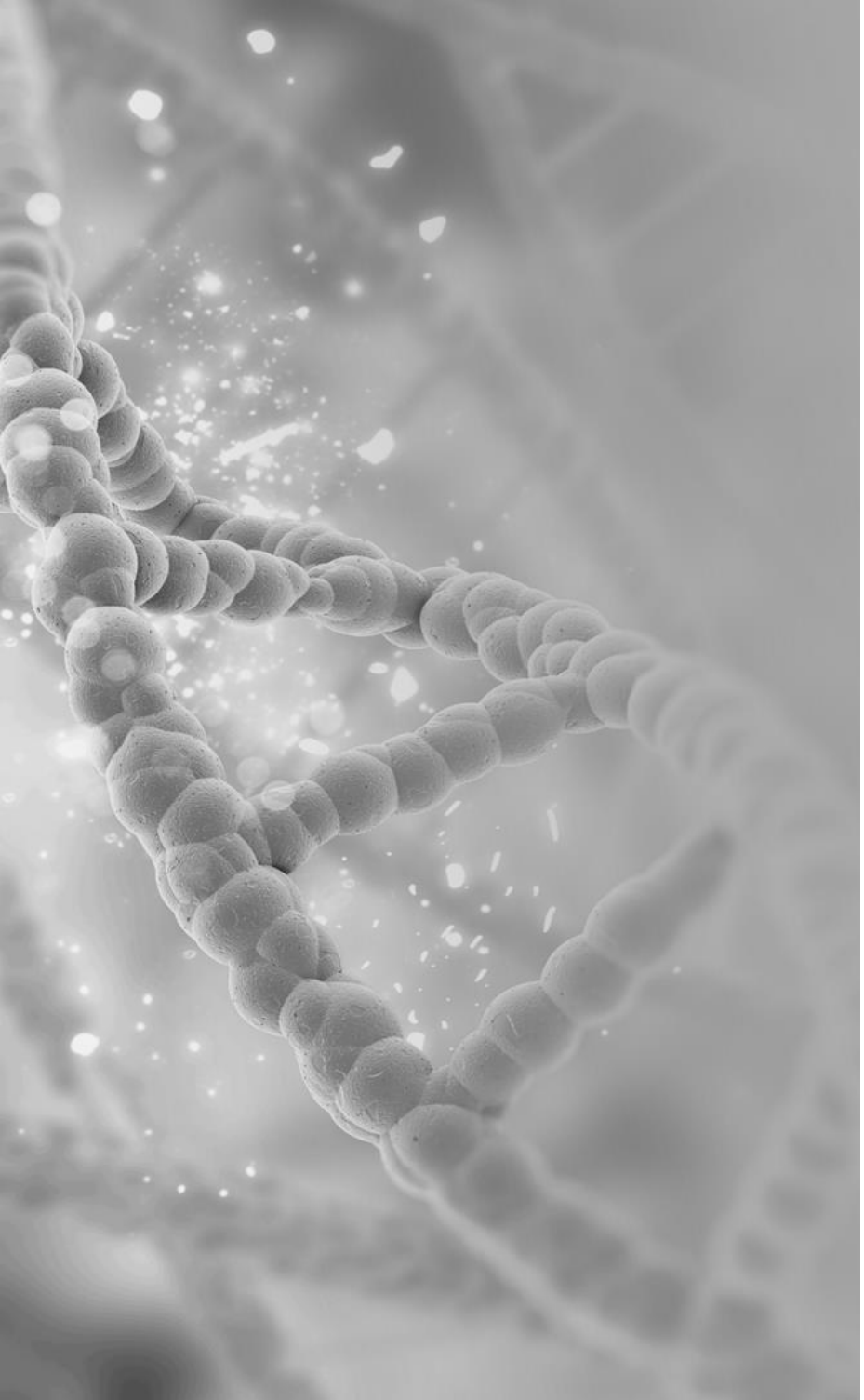
All possible sequences were screened by sliding window HTS





Comparison of SAMiRNA-AREG IC_{50} between kinetics algorithm and sliding widow





Chapter

03

IPF

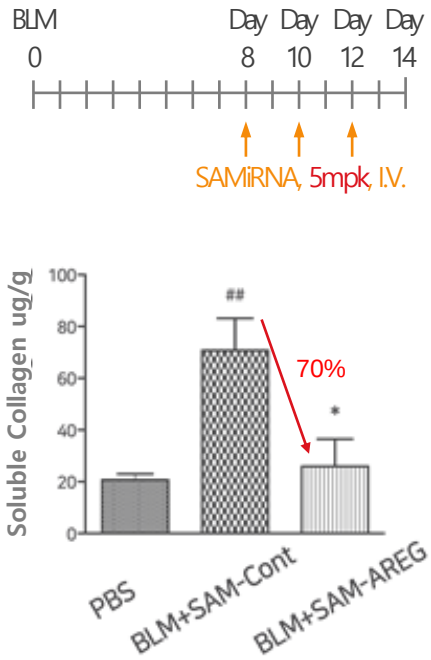
Summary of Pre-clinical PF Mouse Study

Amphisiran on	BLM ILD model	TGF-β tg model	Silica ILD model
Fibrosis Markers: All decreased	AREG a-SMA Collagen 1 & 3A1 Fibronectin Soluble collagen H&E(inflammatory cell infiltration) M's T(collagen)	AREG Soluble collagen Collagen 1 & 3A1 Fibronectin M's T(collagen)	AREG a-SMA Collagen1& 3A1 Fibronectin TGF-β1 H&E(inflammatory cell infiltration) M's T(collagen)
Inflammatory Markers: All decreased	F4/80(macrophage marker) TNF-α MCP-1 VCAM-1 ICAM-1 BALF cell staining		F4/80(macrophage marker) TNF-α MCP-1 VCAM-1 ICAM-1
Pulmonary Function Test: All Improved		Rn ↓ G ↓ H ↓ Rrs ↓ Ers ↓ Crs ↑	Rn (airway resistance) unit: (ml/s) G (air-flow resistance in lung tissue) unit:(ml/s) H (tissue elasticity) unit:(ml) Rrs (respiratory system (airway, lungs, thorax) resistance) unit:(ml/s/cmH2O) Ers (respiratory system elasticity) unit:(ml/cmH2O) Crs (respiratory system compliance, the reciprocal of elasticity) unit:(ml/cmH2O)

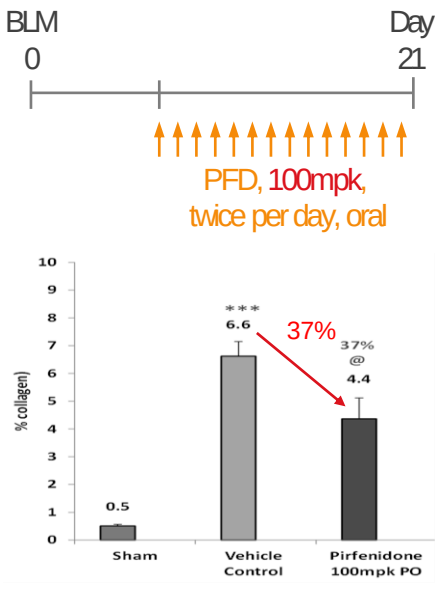
Comparison of Pre-clinical Efficacy

Improved collagen clearance at lower dosage and frequency

SAMiRNA-AREG

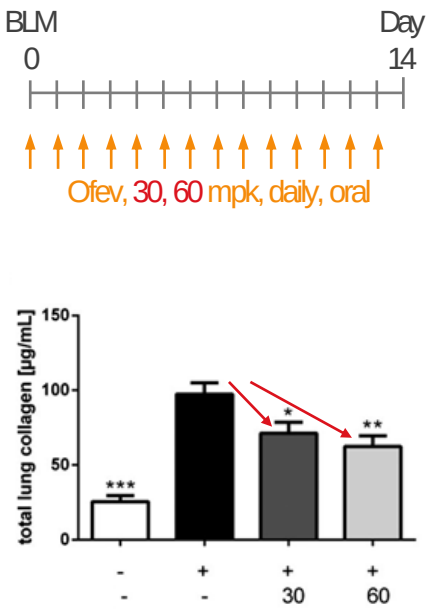


Pirfenidone (Roche)



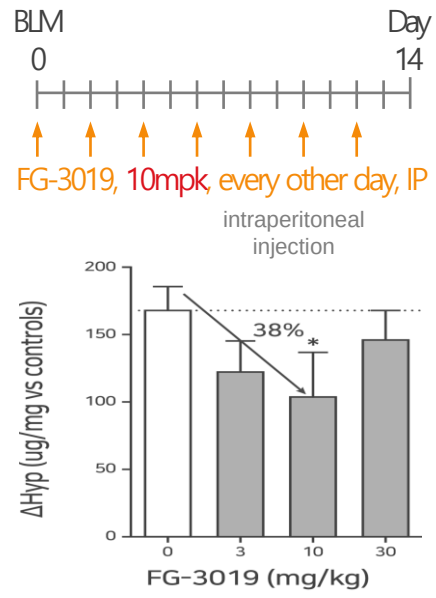
Pirfenidone in vivo data adopted by bioRxiv 2018 Han-Soo Kim et al.

Nintedanib (Boehringer Ingelheim)



Nintedanib in vivo data adopted by J Pharmacol Exp Ther. 2014 May;349(2):209-20

FG-3019 (Fibrogen)

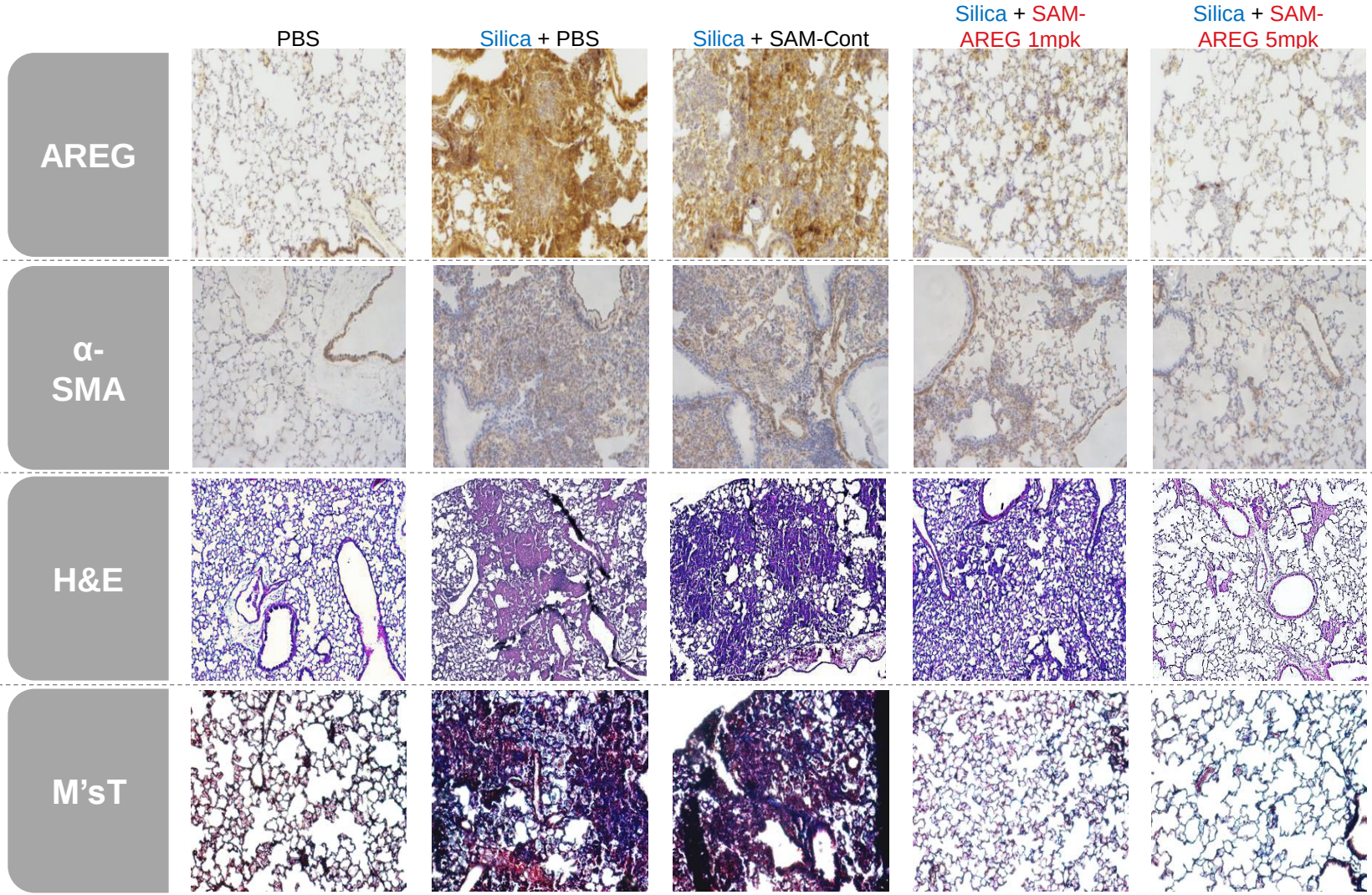


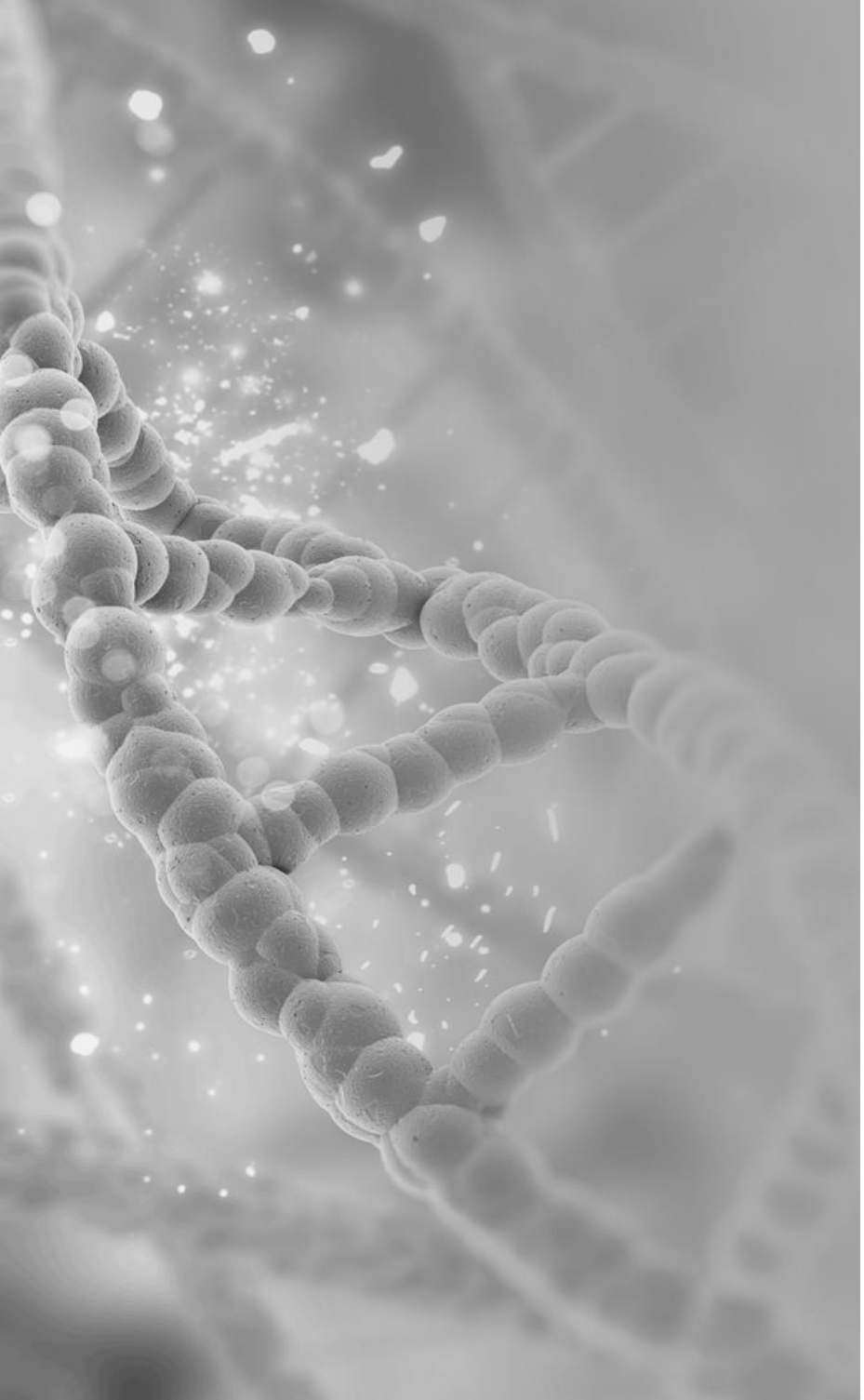
Fibrogenesis & Tissue Repair. 2011 Wang et. al

Collagen contents measured by Sircol assay kit

In-vivo Efficacy in Silica-induced PF Model

SAMiRNA-AREG by IV administration is mainly delivered to lung and efficiently suppresses myofibroblast proliferation (IHC) and decreases the immune cell infiltration



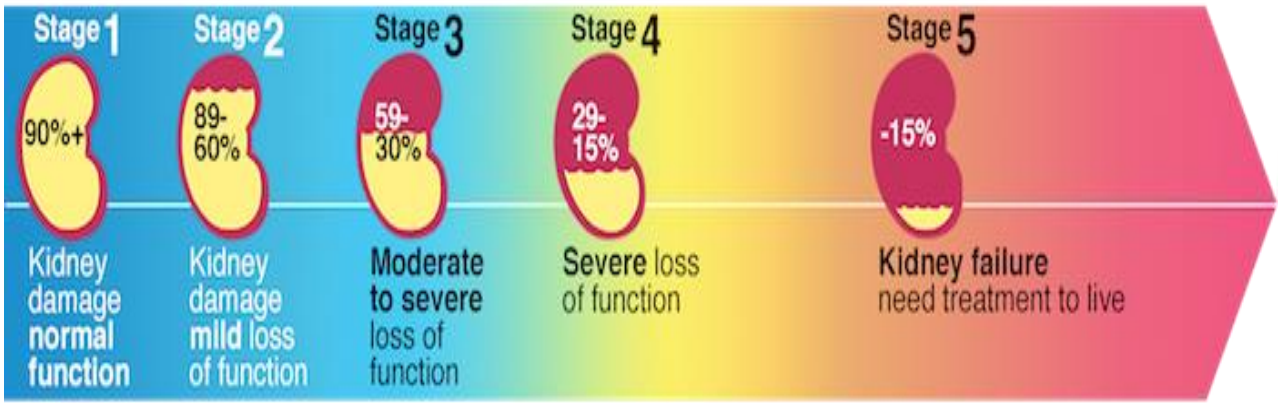


Chapter

04

CKD

Disease Overview



Renal fibrosis, an ultimate result of CKD, leads to kidney failure.

Patients with kidney failure eventually require treatment with dialysis or kidney transplant.

Currently, there is no efficient treatment for renal fibrosis.

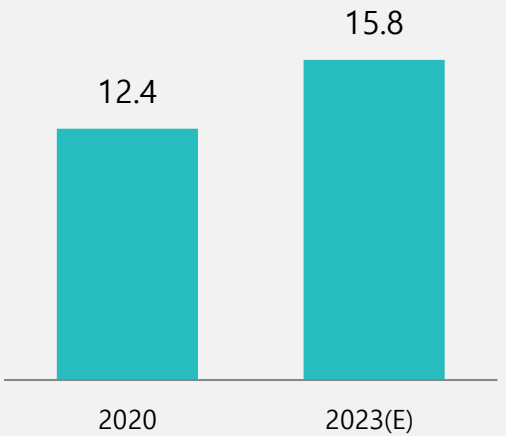
Prevalence [1]

Total Prevalent cases of

756 million

worldwide in 2020

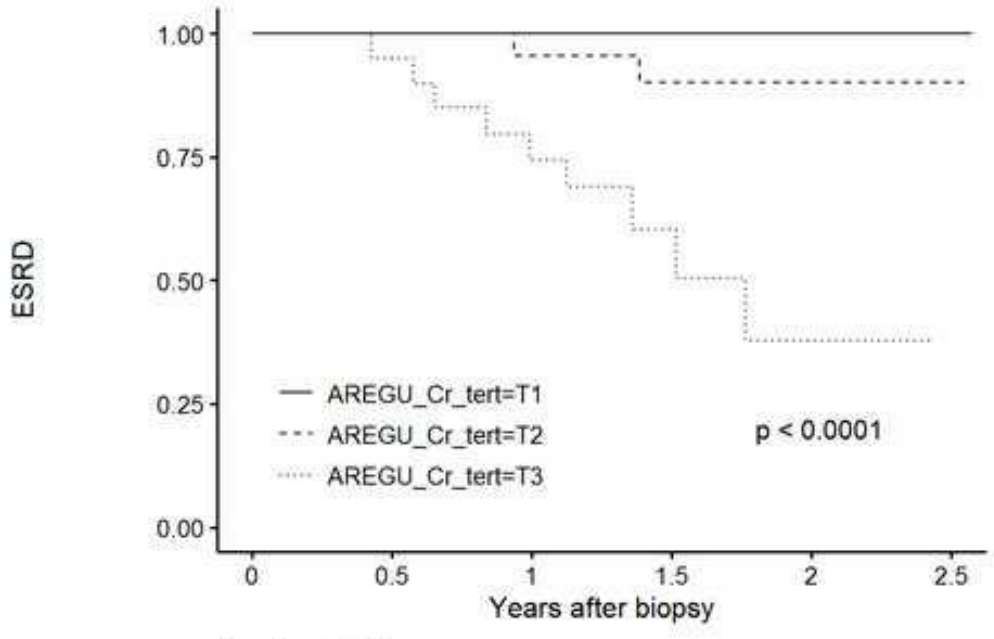
Market Size (USD Billion) [2]



1. Source: Datamonitor healthcare, Market spotlight: renal disease (2020)
2. Source: Marketwatch (2020)

Amphiregulin is the Evil Signal of CKD

Kaplan-Meier survival curves by tertiles of urine AREG for ESRD



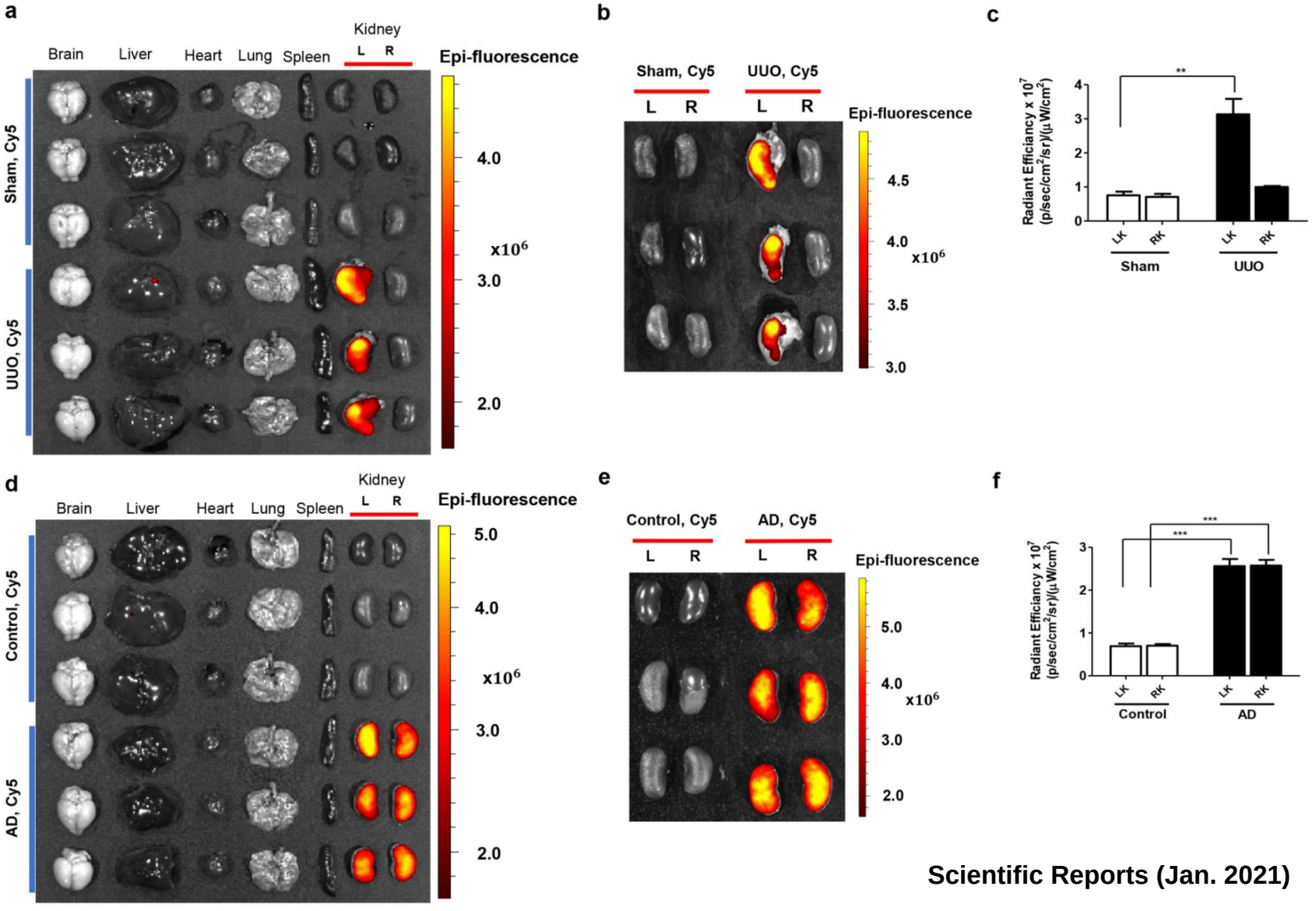
Check the amount of Amphiregulin in urine according to the stage of chronic kidney disease. Kaplan-Meier survival curve graph comparing the progression of end-stage renal disease(ESRD) according to the Amphiregulin concentration in the patient group who underwent renal biopsy. Urine Amphiregulin concentration is divided into three groups through the third quartile, and the lowest concentration is named T1(0.598 - 9.472 pg/mgCr), T2(9.473 - 39.904 pg/mgCr), T3(39.905 - 597.252 pg/mgCr).

Selective Delivery to the Inflamed Kidney Model

*** *Ex-vivo* fluorescence imaging of Cy5-SAMiRNA-AREG**

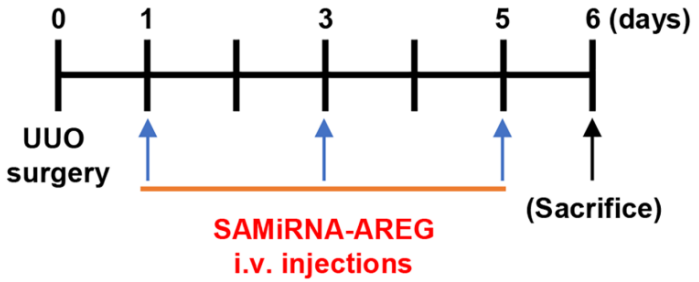
UUO

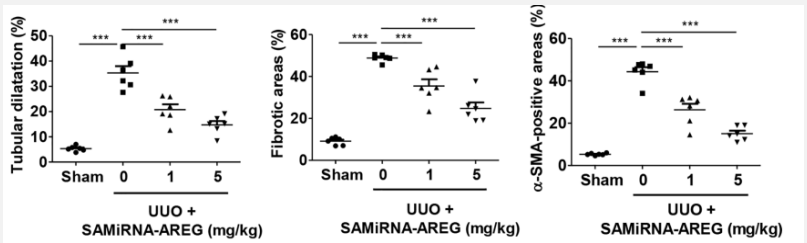
AD

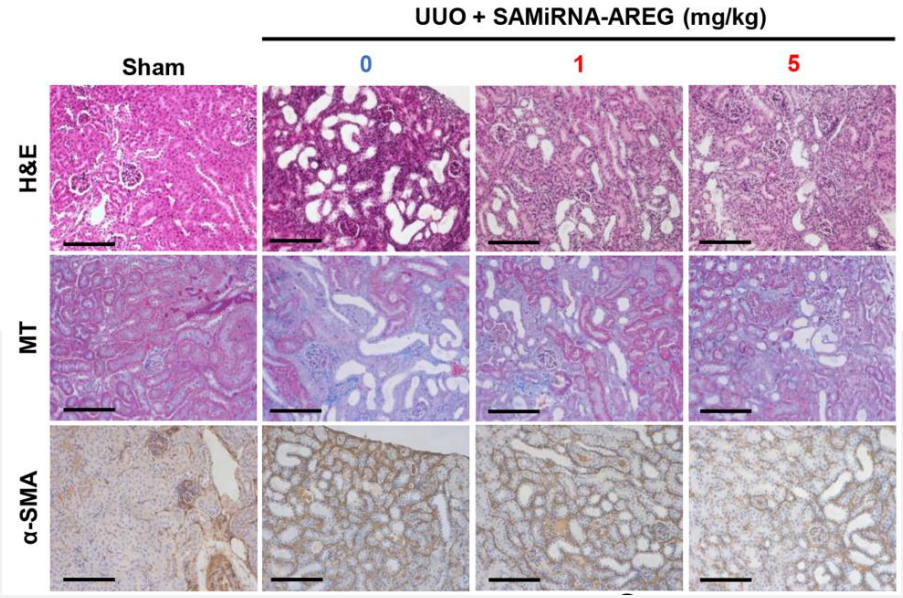


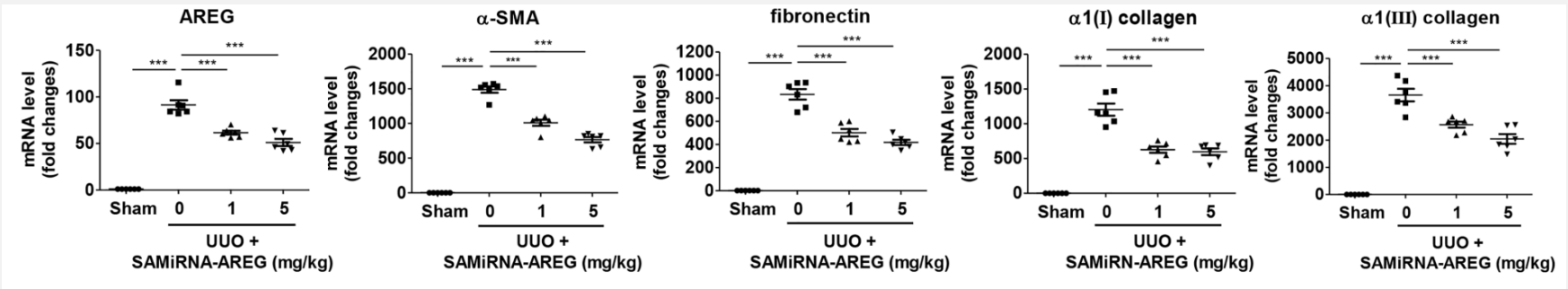
Scientific Reports (Jan. 2021)

In-vivo Efficacy of SAMiRNA-AREG in UUO Model





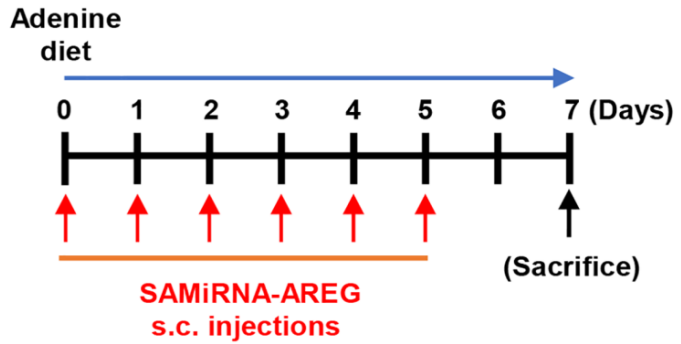


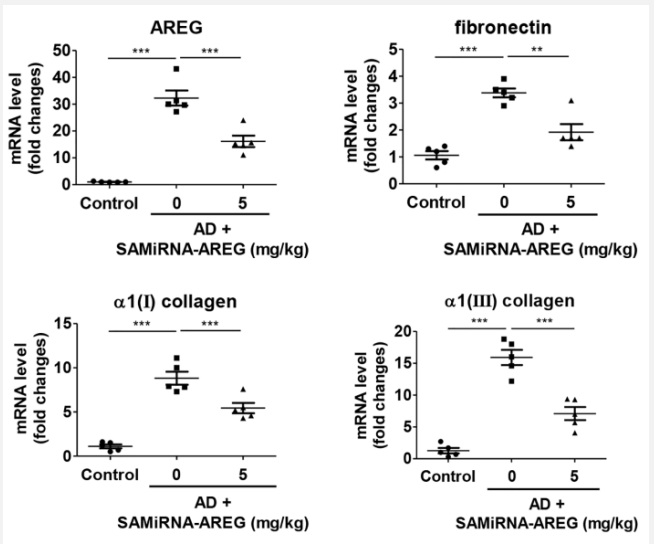


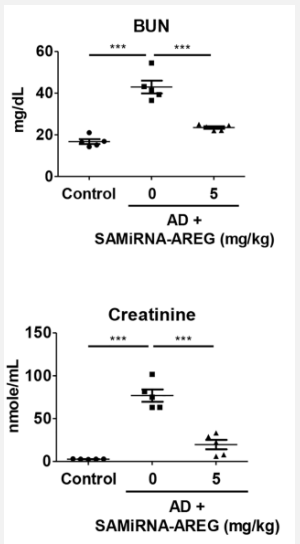
Individual groups were compared using ANOVA with Newman-Keuls post-hoc test. *P < 0.05 (compared to all other study groups and as indicated). Normal control diet (n = 5), UUO + PBS (n = 5), UUO + SAMiRNA-AREG 1mpk (n = 5), UUO + SAMiRNA-AREG 5mpk (n = 5)

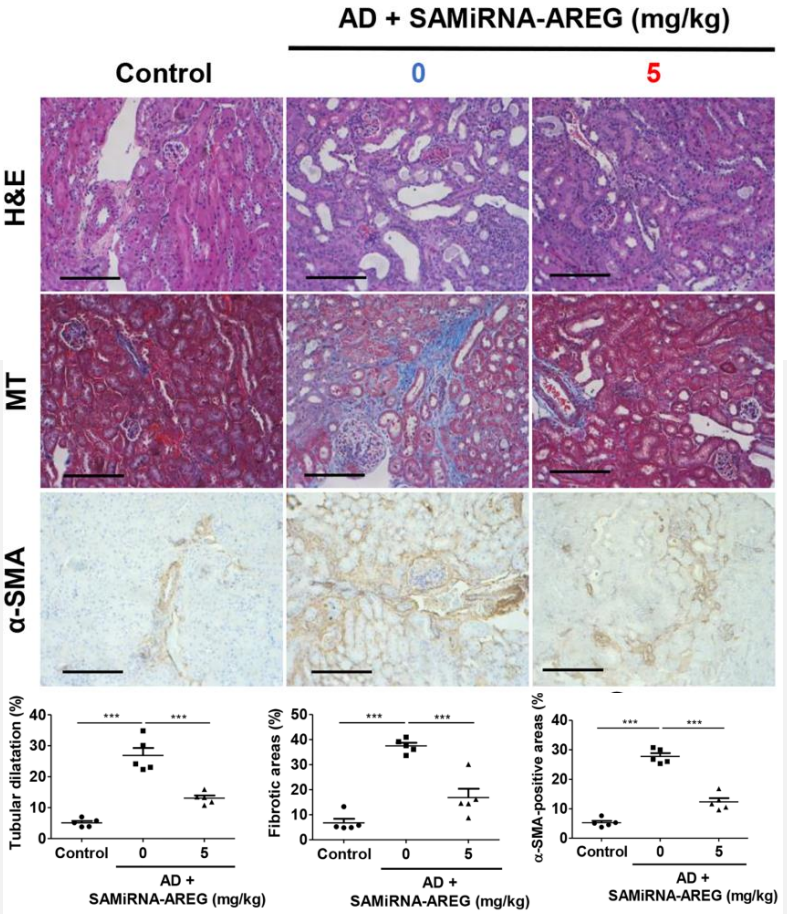
Scientific Reports (Jan. 2021)

In-vivo Efficacy in Adenine-Induced CKD Model



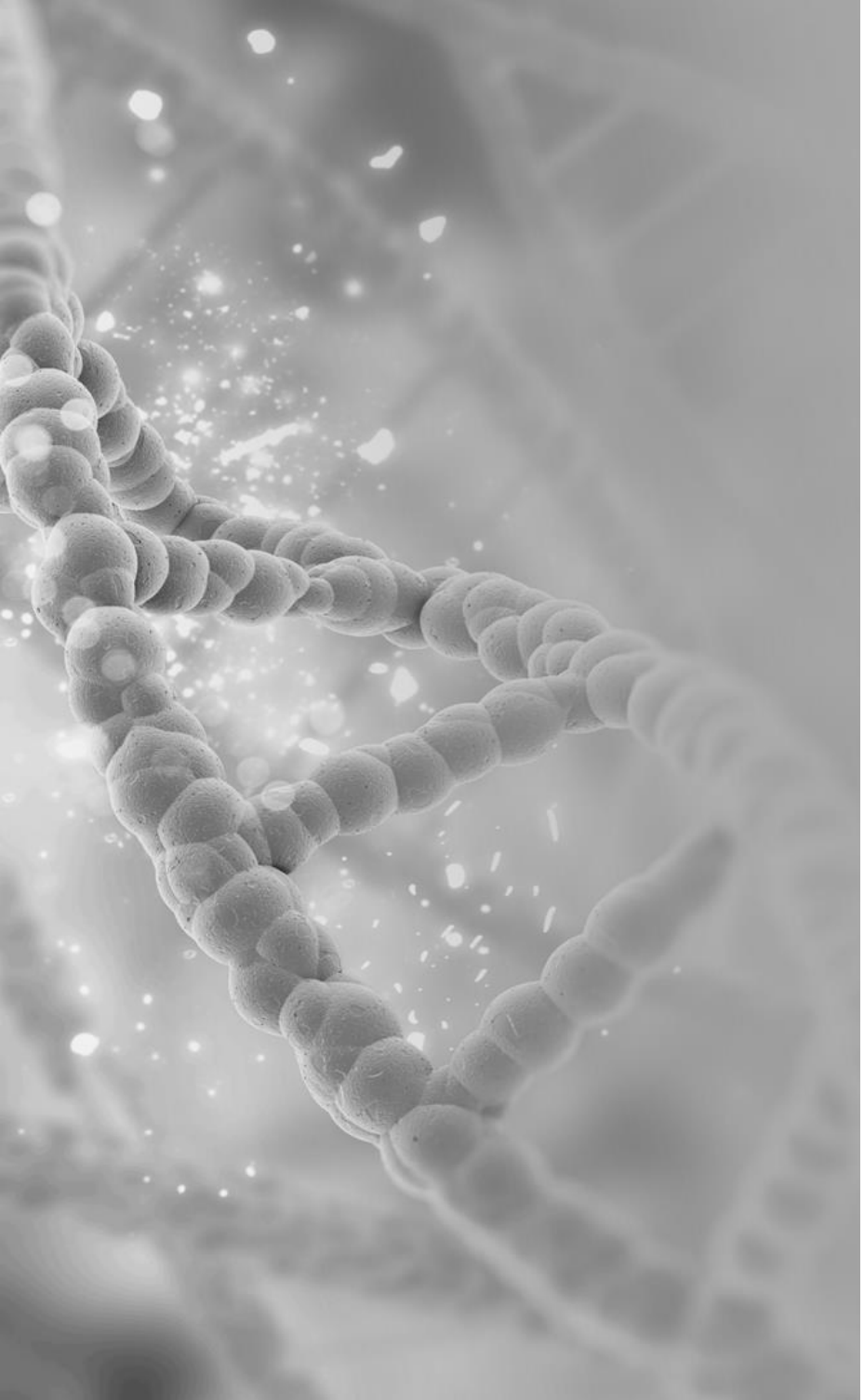






Individual groups were compared using ANOVA with Newman-Keuls post-hoc test. *P < 0.05 (compared to all other study groups and as indicated). Normal control diet (n = 5), AD + PBS (n = 5), AD + SAMiRNA™ S.C 6 times (n = 5), AD + SAMiRNA™ I.V 6 times (n = 5).

Scientific Reports (Jan. 2021)

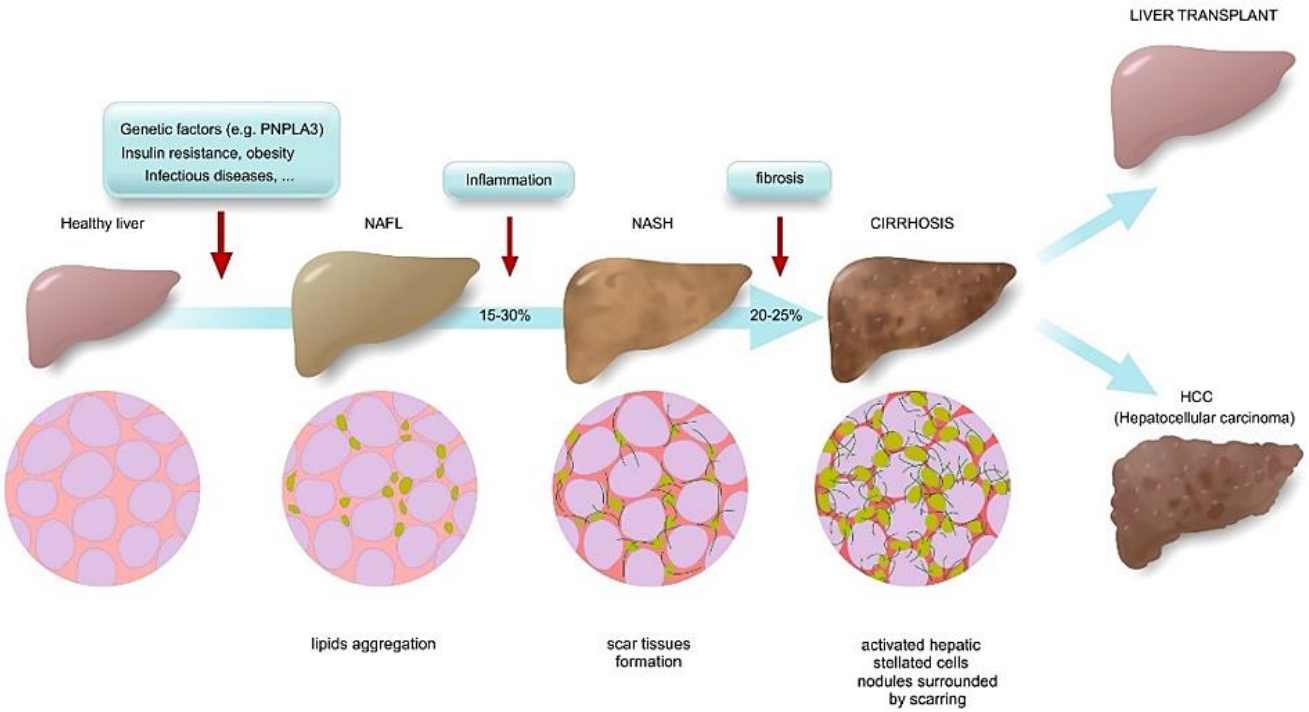


Chapter

05

NASH

Disease Overview



NASH and NAFLD are “silent” disease, until symptoms of advanced stage of liver damage, such as jaundice, confusion, and buildup of fluid in abdomen occur. Currently there are many compounds are under investigation.

1. Source: Datamonitor healthcare, Market spotlight: renal disease (2020)
2. Source: Marketwatch (2020)

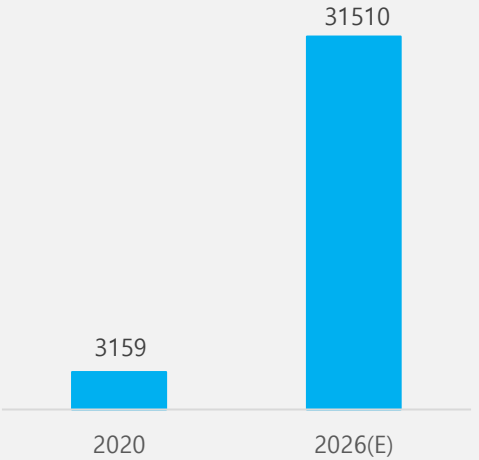
Prevalence [1]

Total Prevalent cases of

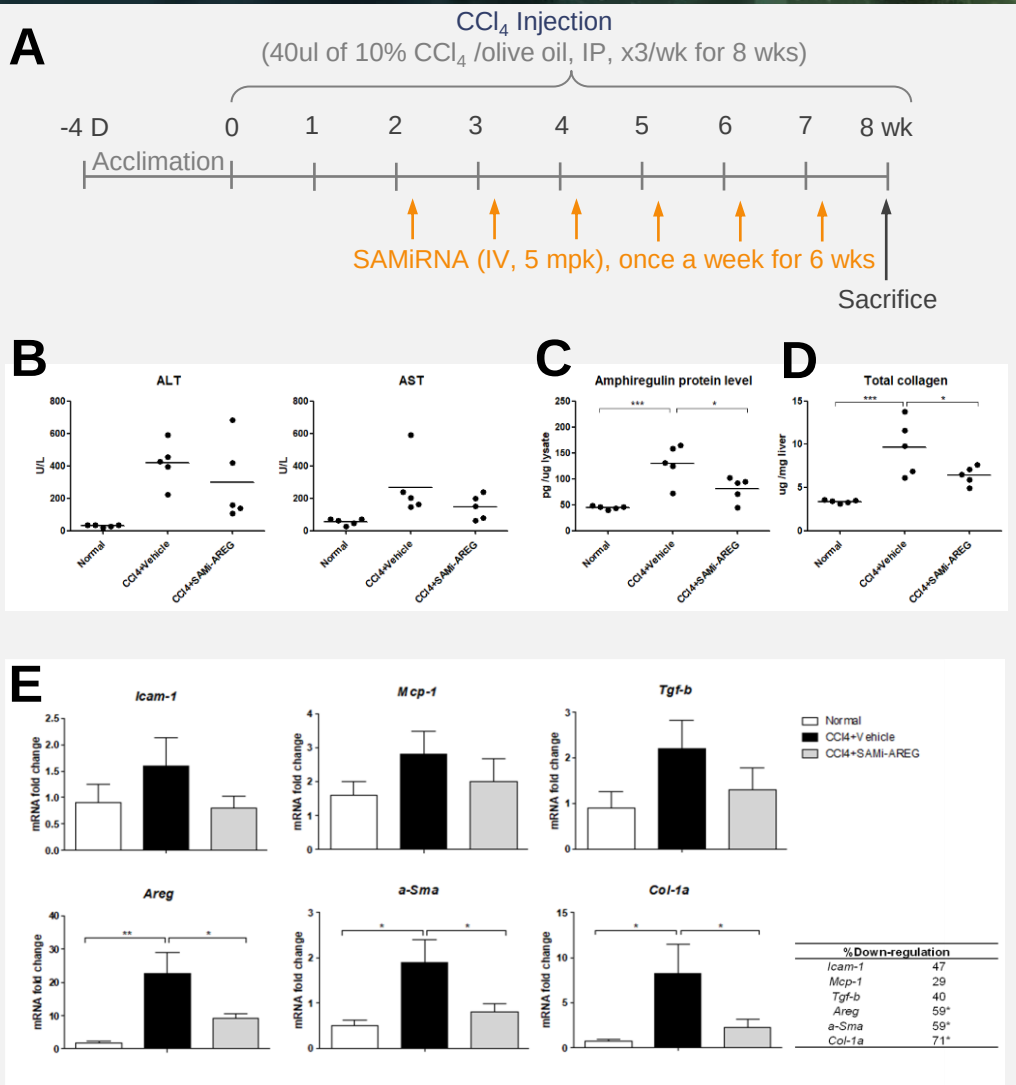
891 million

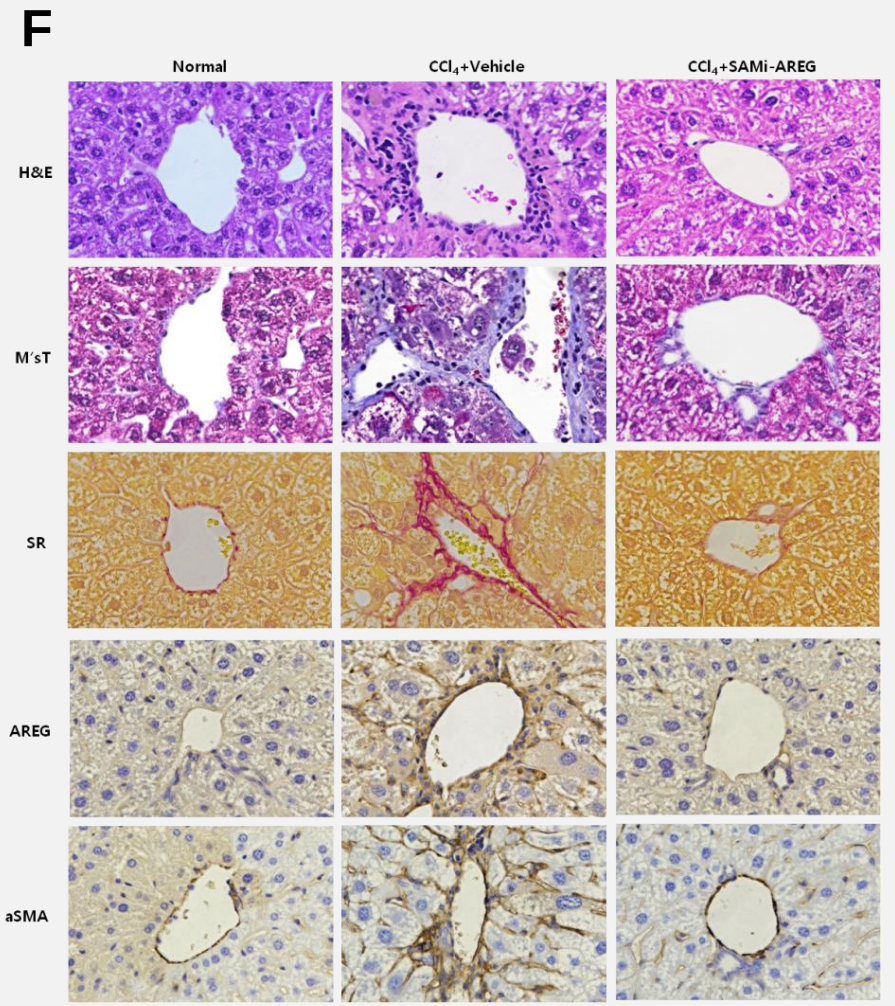
worldwide in 2020

Market Size (USD Million) [2]



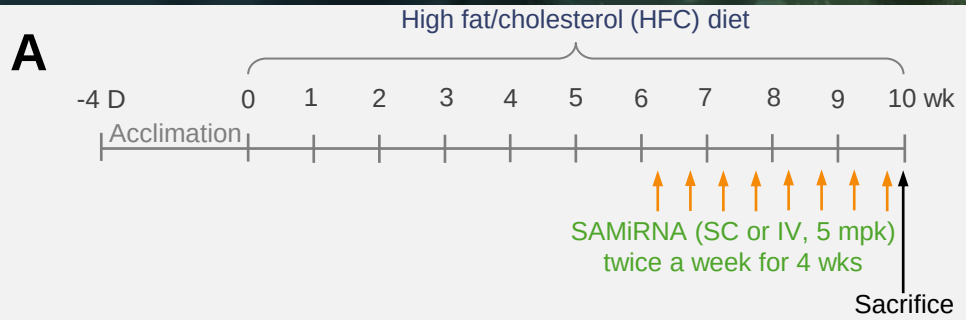
In-vivo Efficacy Study in CCl_4 Mouse Fibrosis Model

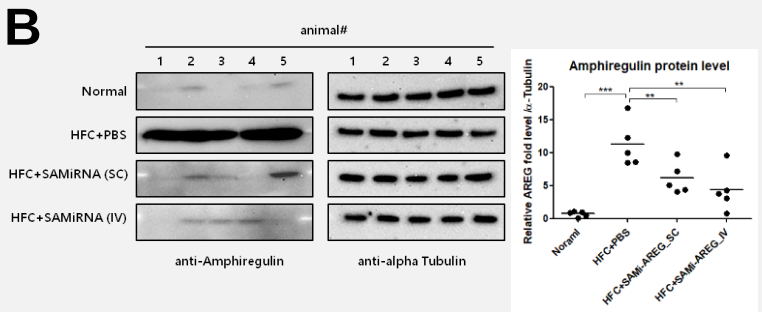


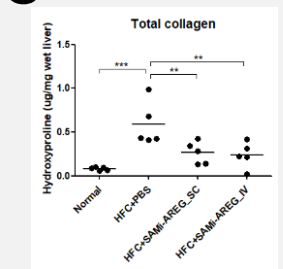


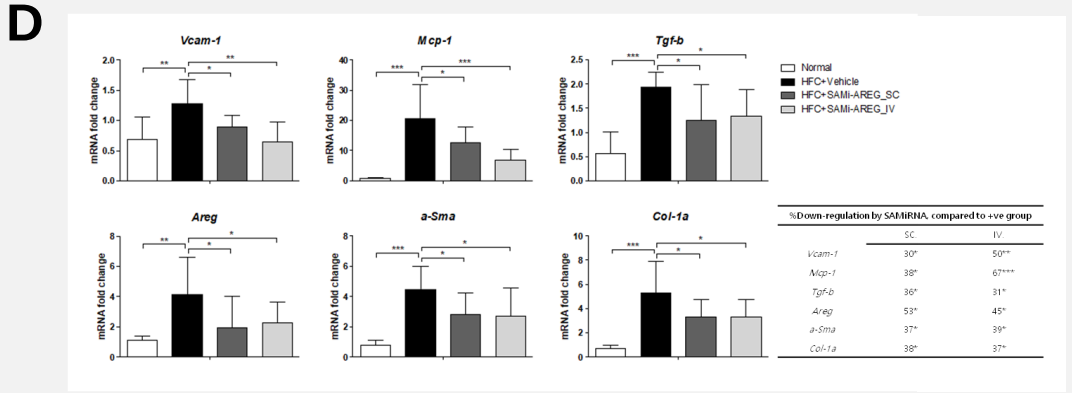
Schematic diagram of study (A). Liver fibrosis was induced by ip. injection of CCl_4 for 2 weeks post-drug administration. SAMiRNA was treated by iv. once a week for 6 weeks with prolonged CCl_4 induction. Liver and blood samples were analyzed as follows. Blood-biochemistry (B), target protein level (C, ELISA), total collagen (D, sircol assay), related mRNA expression level (E, qPCR) and tissue staining (F; HE, MT, SR, AREG and aSMA in order from the top; magnification, x400). Statistical significance was examined with one-way analysis of variance (ANOVA) followed by the Newman-Keuls Multiple Comparison Test. *p<0.05, **p<0.01, ***p<0.005.

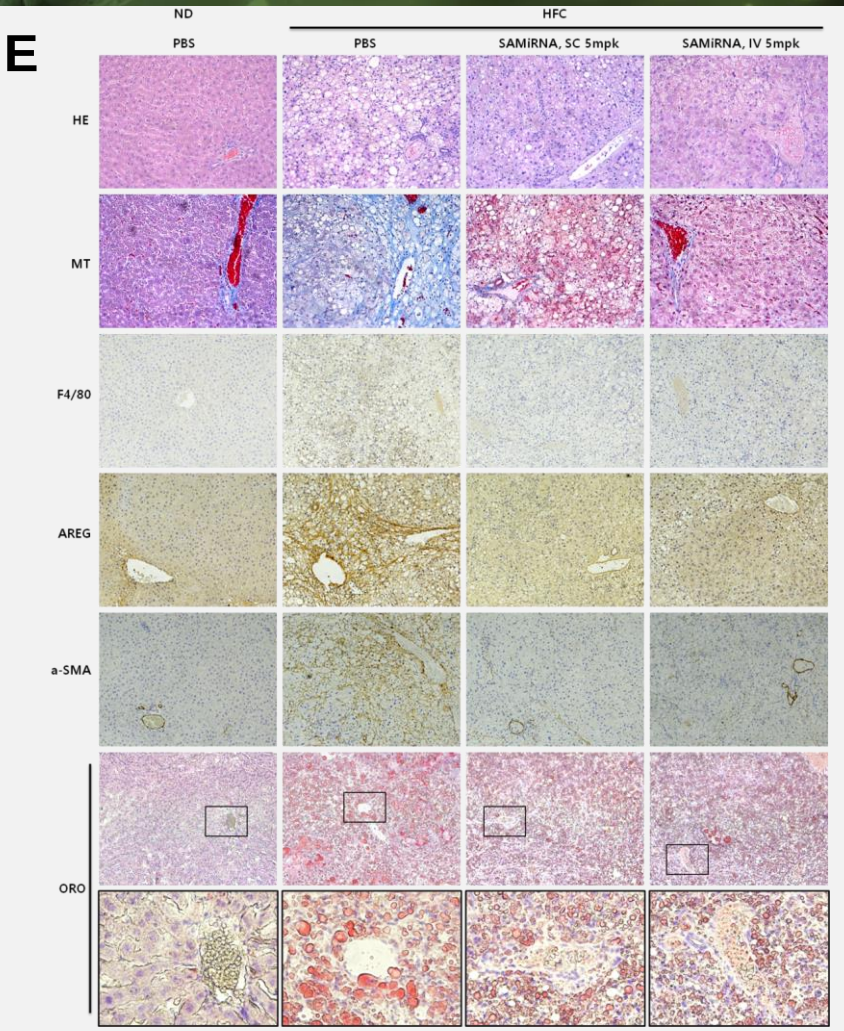
In-vivo Efficacy Study in HFC Diet-Induced NASH Rat Model



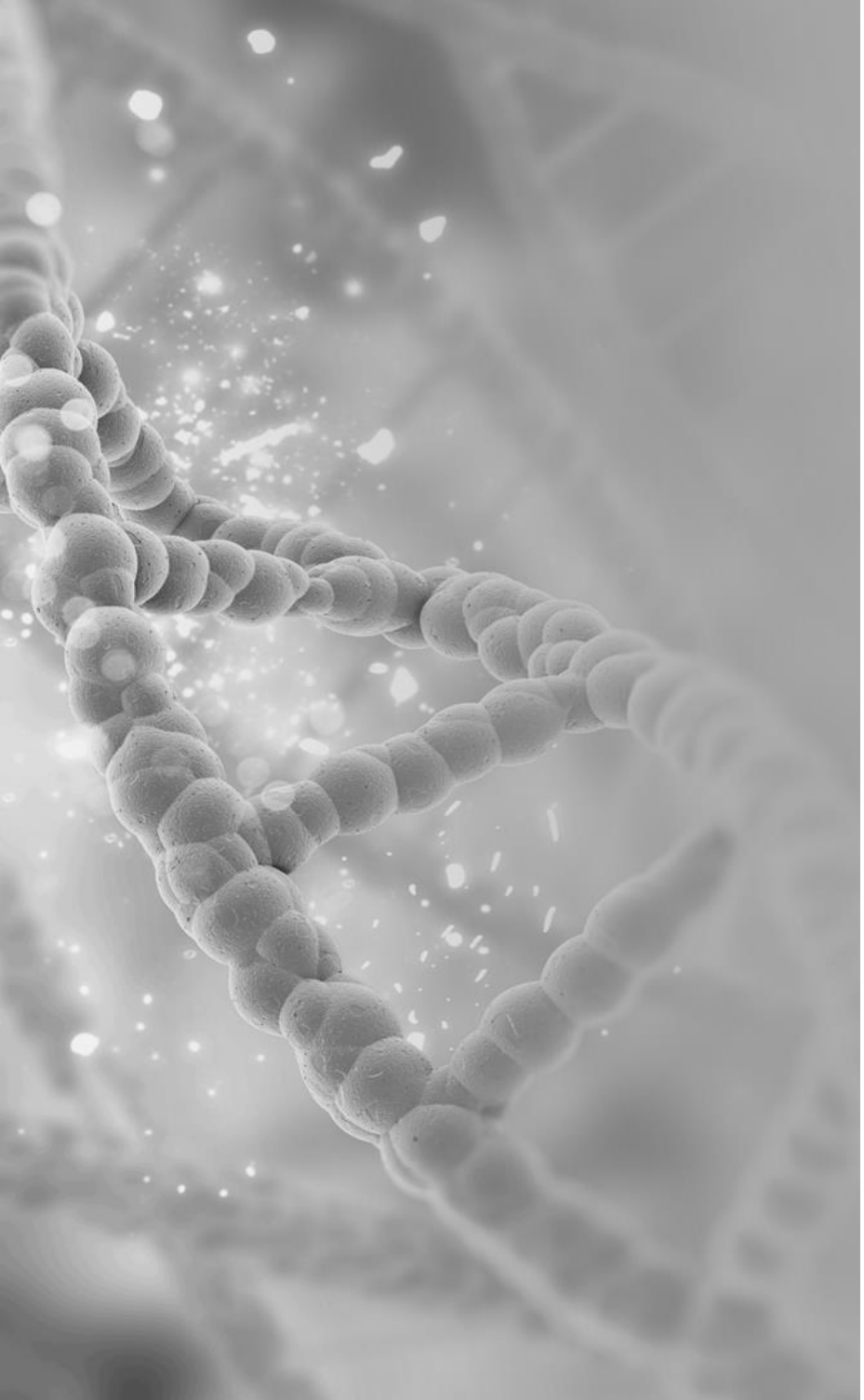








Schematic diagram of study(A). NASH dietary model was established by free feeding of HFC for 6 weeks pre-drug administration. SAMiRNA was treated by sc. or iv. twice a week for 4 weeks with prolonged HFC diet. Liver samples were analyzed as follows. amphiregulin protein level(B, western blot), total collagen(C, hydroxyproline assay), related mRNA expression level(D, qPCR) and tissue staining(E; HE, MT, F4/80, AREG, aSMA and Oil Red O in order from the top; magnification, x100, x600 in zoom). Statistical significance was examined with one-way analysis of variance (ANOVA) followed by the Newman-Keuls Multiple Comparison Test. *p<0.05, **p<0.01, ***p<0.005.



Chapter

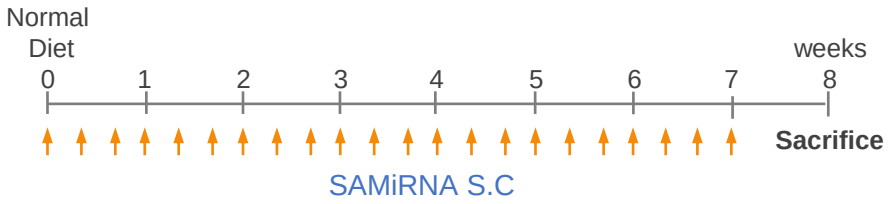
06

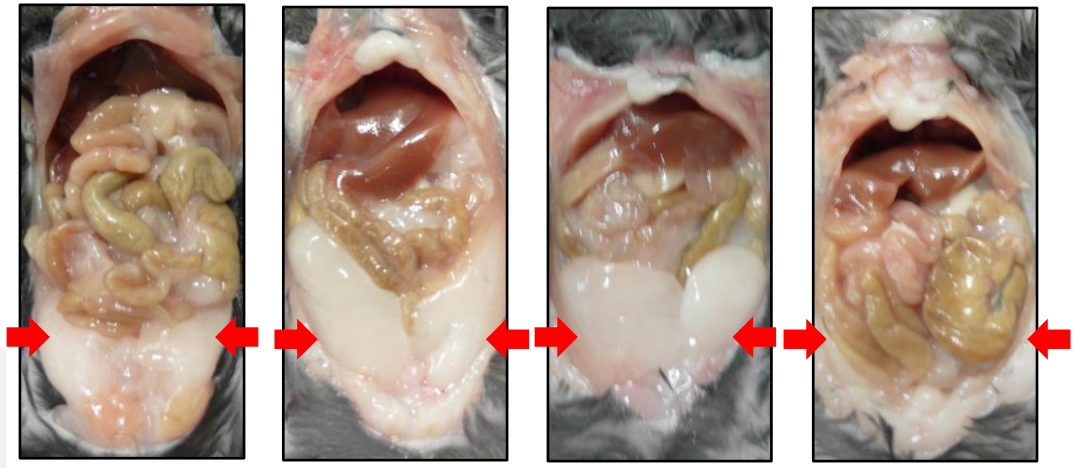
Other Programs

SAMiRNA : Anti-Obesity

SAMiRNA™ by S.C SAMiRNA-AREG Reduced ~70% of WAT in db/db Mouse

db/db mouse obesity model





db/m | db/db + PBS | db/db + SAMi-Cont | db/db + SAMi-AREG

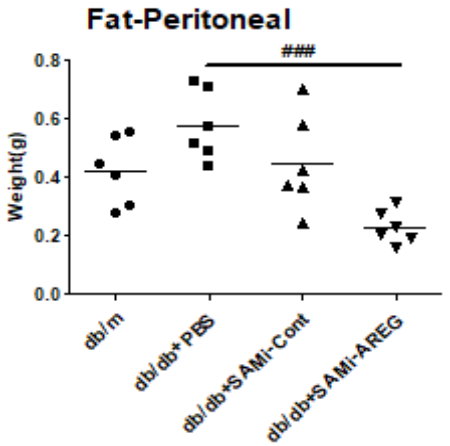
American Diabetes Association. | DiabetesPro®

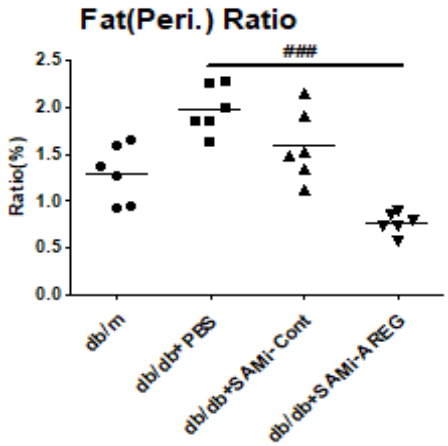
Amphiregulin, a New Adipogenic Growth Factor

Year: 2006
Abstract Number: 1353-P

- **Amphiregulin, a new adipogenic growth factor can promote both proliferation and differentiation of adipocyte.**
- Amphiregulin, autocrine/paracrine growth factors within the adipose tissue itself could play a role in its expansion.
- AREG expression in human adipocytes correlates with BMI and its expression is induced in a mouse model of diet-induced obesity.
- In vitro, the expression of AREG is rapidly increased during preadipocyte to adipocyte conversion.

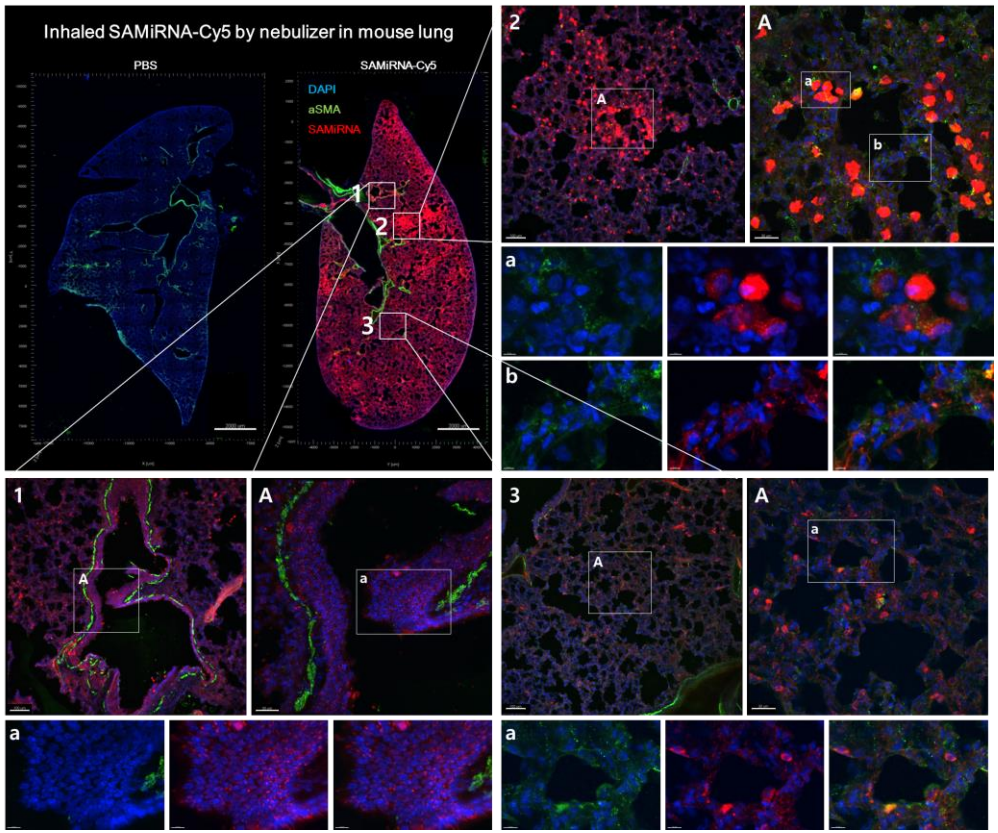
Author: JACQUES ROBIDOUX
Congress: 66th Scientific Sessions (2006)
Category: Integrated Physiology - Adipocyte Biology



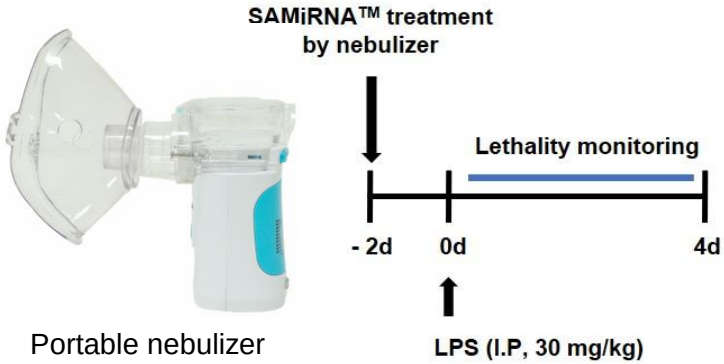


In-vivo Efficacy of SAMiRNA-xxx in Sepsis Model

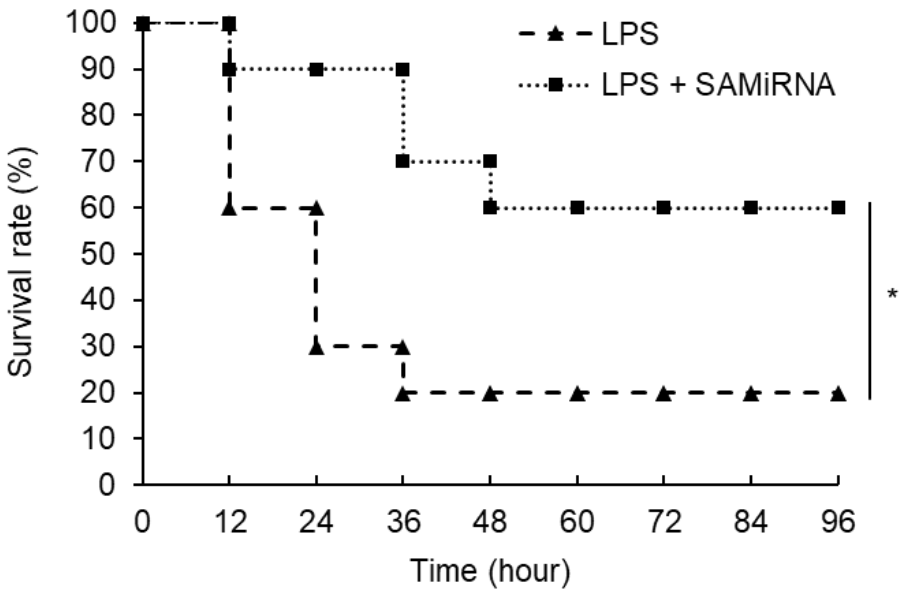
Inhaled SAMiRNA-Cy5 by nebulizer is efficiently delivered to lung tissues



Inhaled SAMiRNA-xxx by nebulizer efficiently improves survival rate of LPS-induced sepsis mice



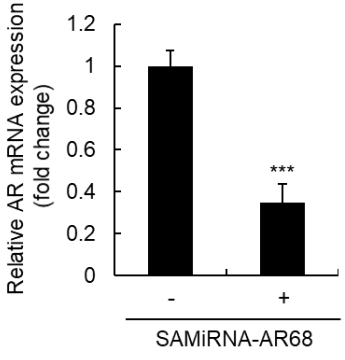
Portable nebulizer

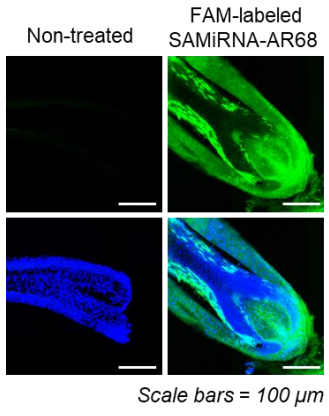


Efficacy of SAMiRNA-AR in Androgenetic Alopecia

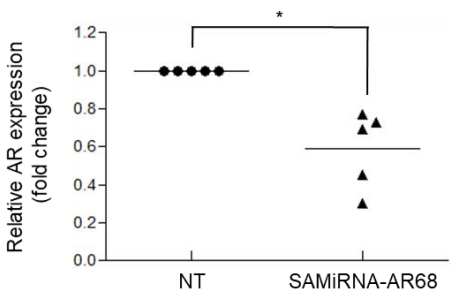
탈모환자를 대상으로 SAMiRNA-AR의 농도 및 도포방법을 다르게 디자인한 독립적인 3번의 인체적용시험을 각 6개월씩 진행하여 SAMiRNA-AR의 안전성과 탈모개선 효능을 입증

Androgen receptor silencing efficacy of SAMiRNA-AR in human DPCs and hair follicles

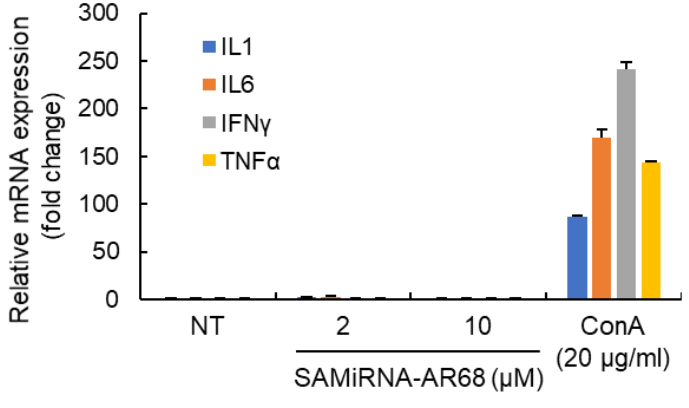




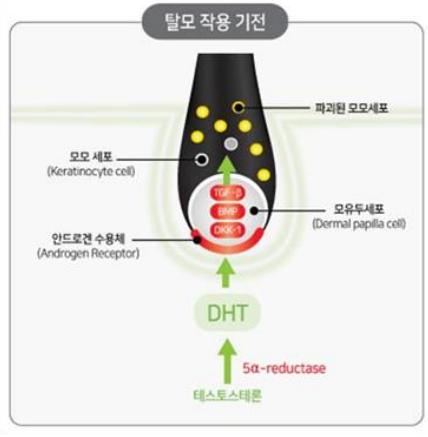
Scale bars = 100 μm

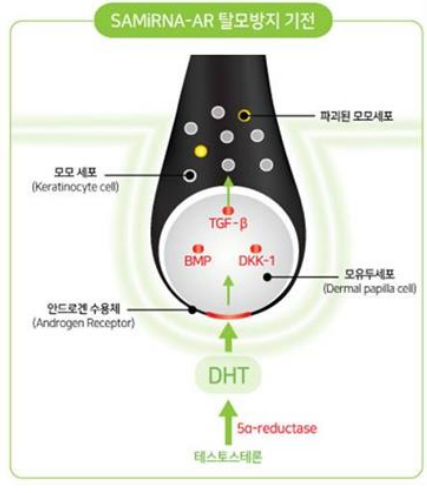


SAMiRNA-AR treatment shows no innate immune stimulation in human PBMC



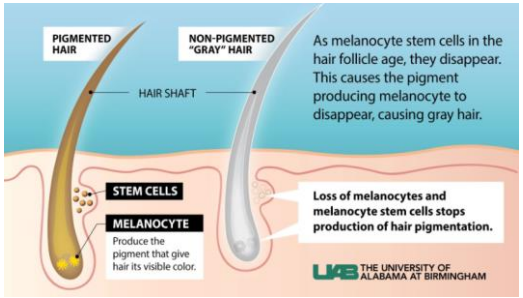
Schematic representation of alleviating hair loss by SAMiRNA-AR

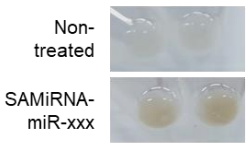


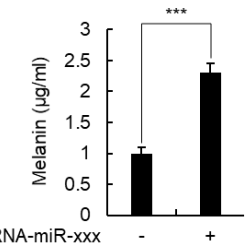


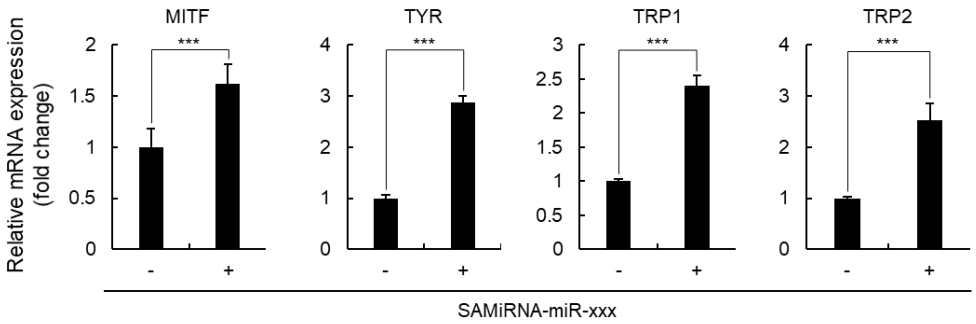
Ex-vivo Efficacy of SAMiRNA-miR-xxx in Human Grey Hair

SAMiRNA-miR-xxx induces melanogenesis in human melanocytes (*in vitro*)

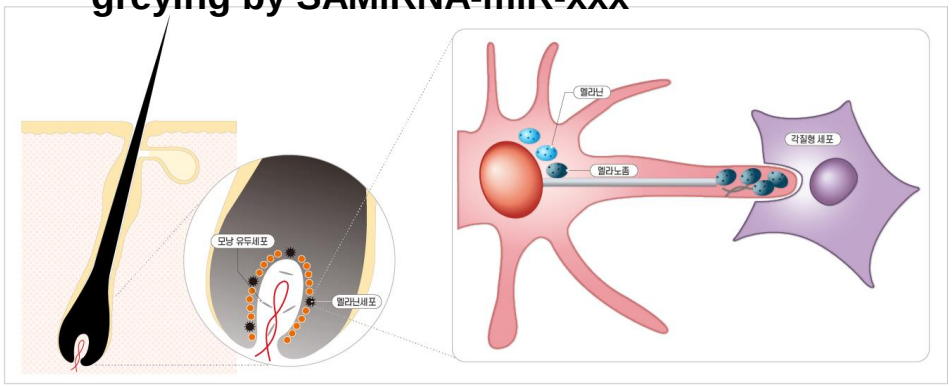




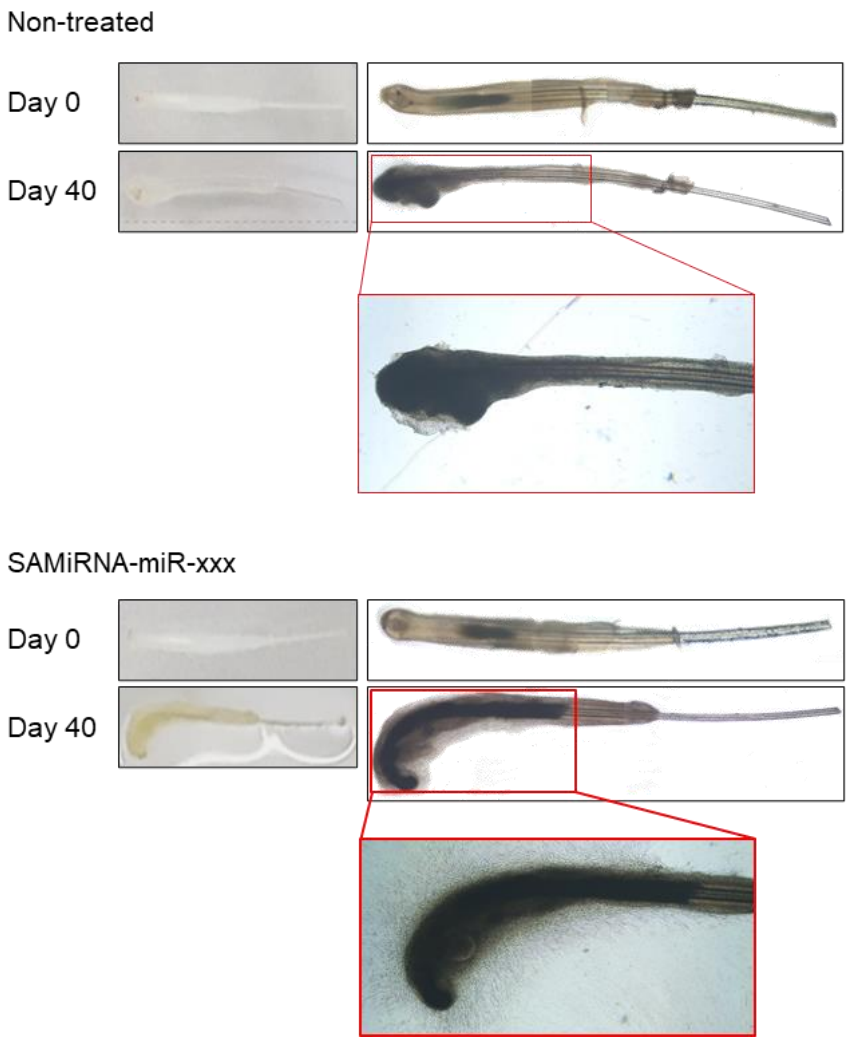




Schematic representation of alleviating hair greying by SAMiRNA-miR-xxx



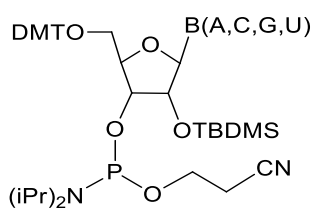
SAMiRNA-miR-xxx induces melanogenesis in human grey hair (*ex vivo*)

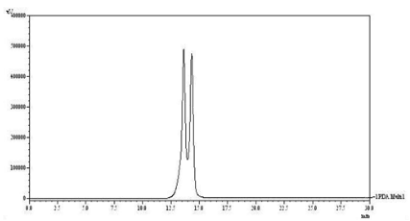


Bioneer has Manuf. Plant for Raw Materials of SAMiRNA

Over 100 kinds of raw materials has been developed in production scale

RNA-Phosphoramidites

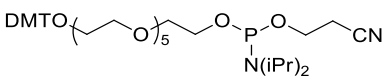




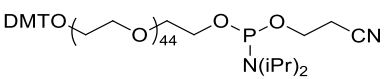
RP- HPLC: ≥ 99%, 31P-NMR: ≥ 99%

Modification Phosphoramidites

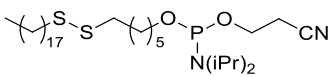
Atom 18 Spacer phosphoramidite



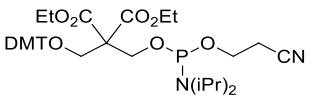
PEG 2000 phosphoramidite



C18-6 Disulfide phosphoramidite



Phosphorylation reagent II



Plant Facilities

Overview of Plant Reactor

6000L Reactor

Overview of Pilot Reactor

300L Reactor

Filter Dryer

Solvent Drying System

Bioneer's High-throughput SAMiRNA Synthesis

30,000 RNA oligos synthesis capacity per day


Pipeline : raw materials


HT-Oligo Synthesizer : 20 systems

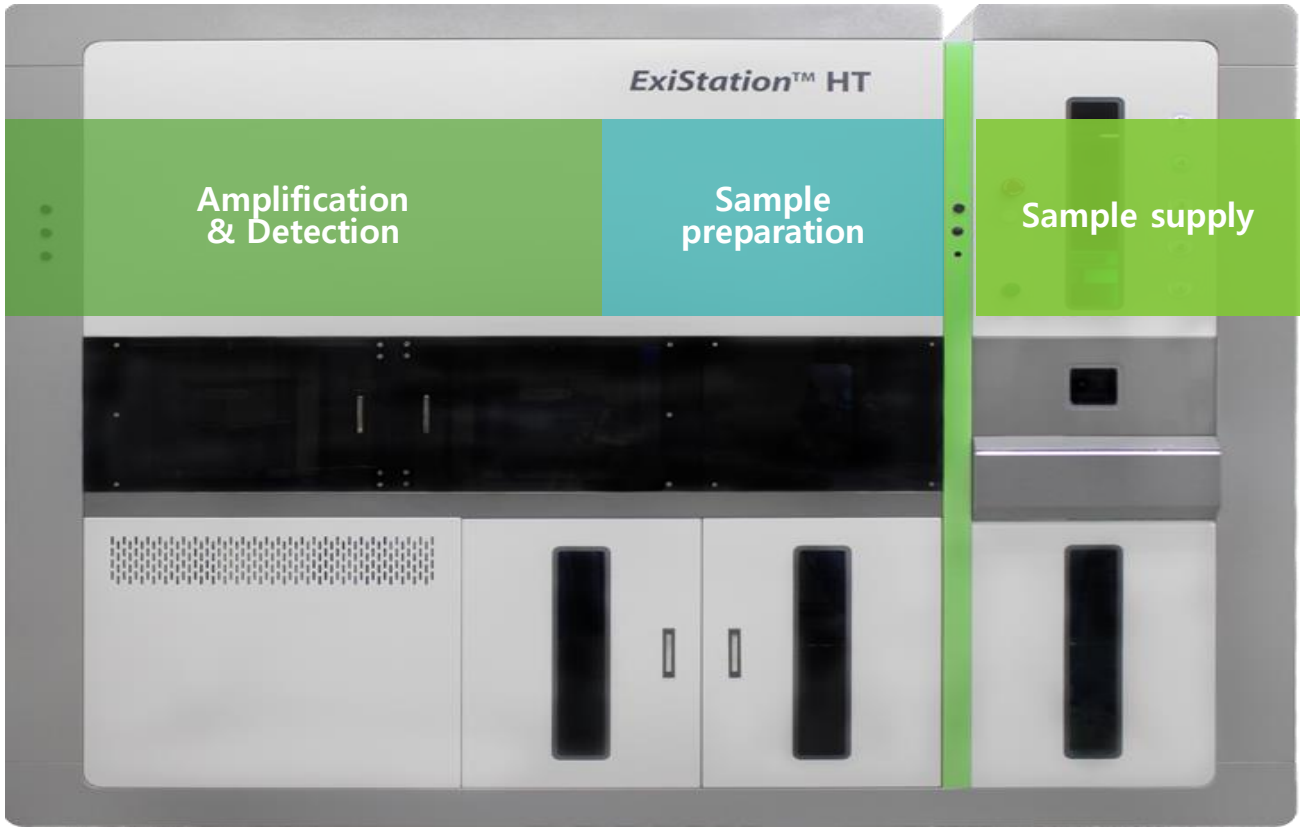

HT-Oligo Purifier : 10 systems

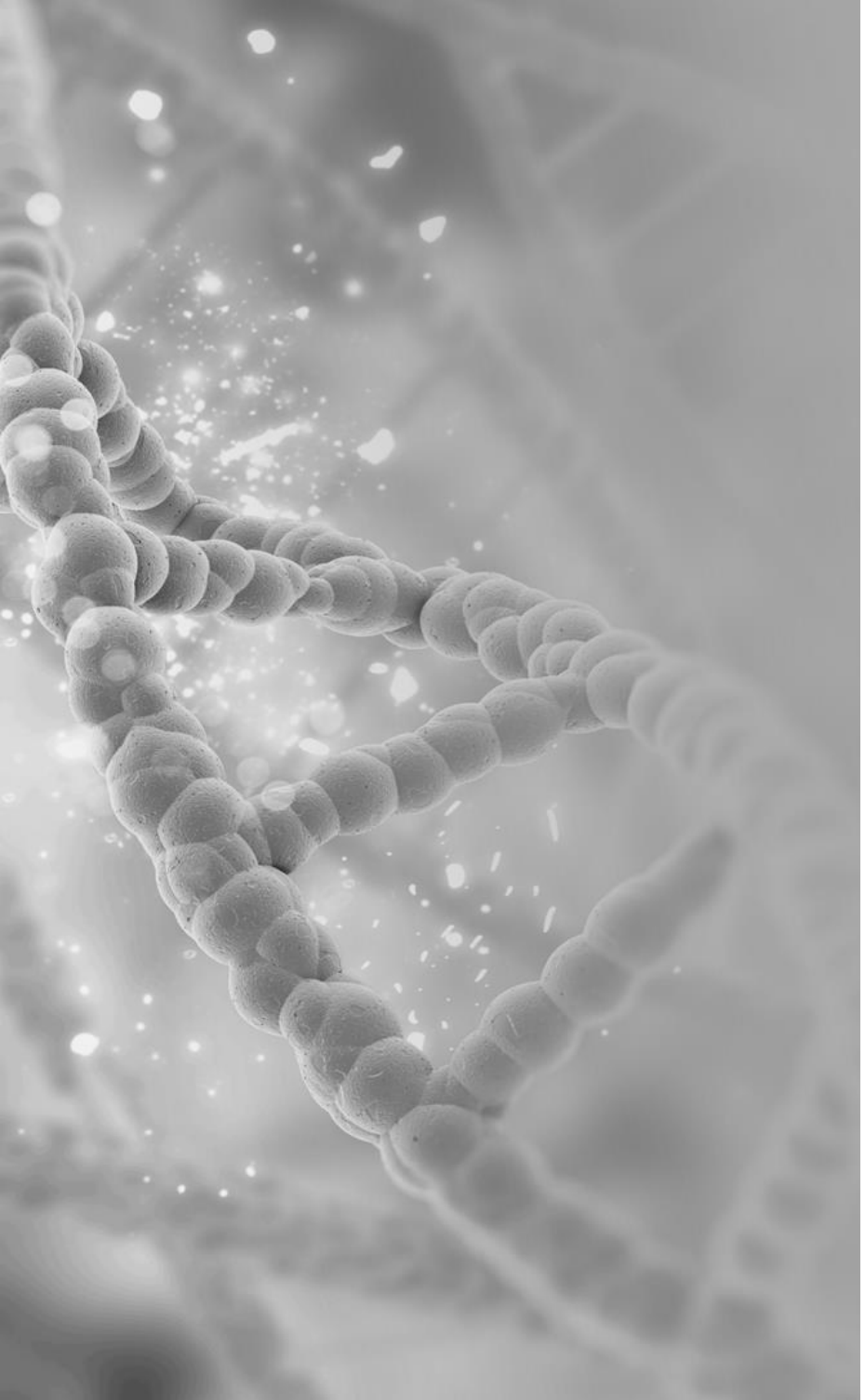

HT-Oligo Dispenser : 20 systems

High-throughput Screening: *ExiStation*™ HT

ExiStation™ HT enables a high-throughput SAMiRNA screening

- Fully automated “Sample-in and Data-out” operation
- 5 X 96 well plates can be screened without human intervention
- 5 colors fluorescence assay is possible for multiplex-assay





Chapter

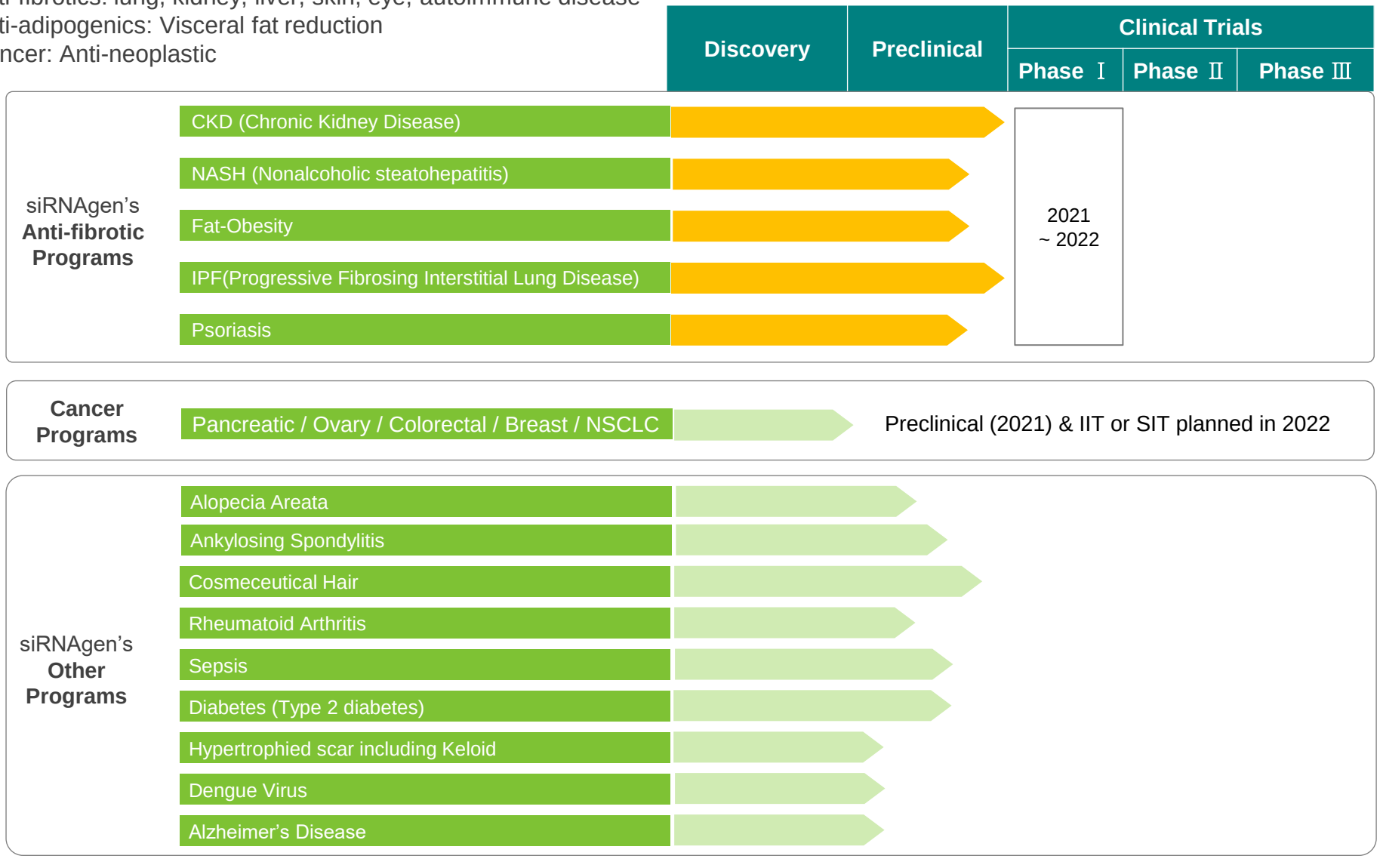
07

Clinical Plans

SAMiRNA™ Development Pipelines

Major fields of development

- Anti-fibrotics: lung, kidney, liver, skin, eye, autoimmune disease
- Anti-adipogenics: Visceral fat reduction
- Cancer: Anti-neoplastic



SAMiRNA™ Development Pipelines

COVID-19 Therapeutics & New target therapeutics

- Startup focusing RNAi-drug development with unparalleled SAMiRNA™ platform tech.
- Spin-off from Bioneer, which has strong gene research infra & 30 yrs. experience.

Pipeline	Target Indications
SAMiRNA-AREG	• Anti-fibrotic : CKD, DNP, ARDS, Scar/Keloid, Psoriasis, IPF, NASH, RIF, Systemic Sclerosis, Anti-obesity(Body-fat management) • Anti-proliferative: Pancreatic/Colorectal/Breast/Ovarian Cancer with AREG↑) • Hair-loss treatment • Rheumatoid Arthritis • Alopecia Areata • Sepsis • Ankylosing Spondylitis • Diabetes Mellitus • Anti-viral (COVID-19/SARS' Dengue Virus) drug
RNAi-OOOO, FIC	
RNAi-OOO & OOOO, FIC	
RNAi-OOOO, FIC	
RNAi-OOOOO, FIC	

SAMiRNA™ Development Pipelines in Post COVID19 Era

> Nephrol Dial Transplant. 2021 Jan 1;36(1):87-94. doi: 10.1093/ndt/gfaa314.

Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA

ERA-EDTA Council; ERACODA Working Group

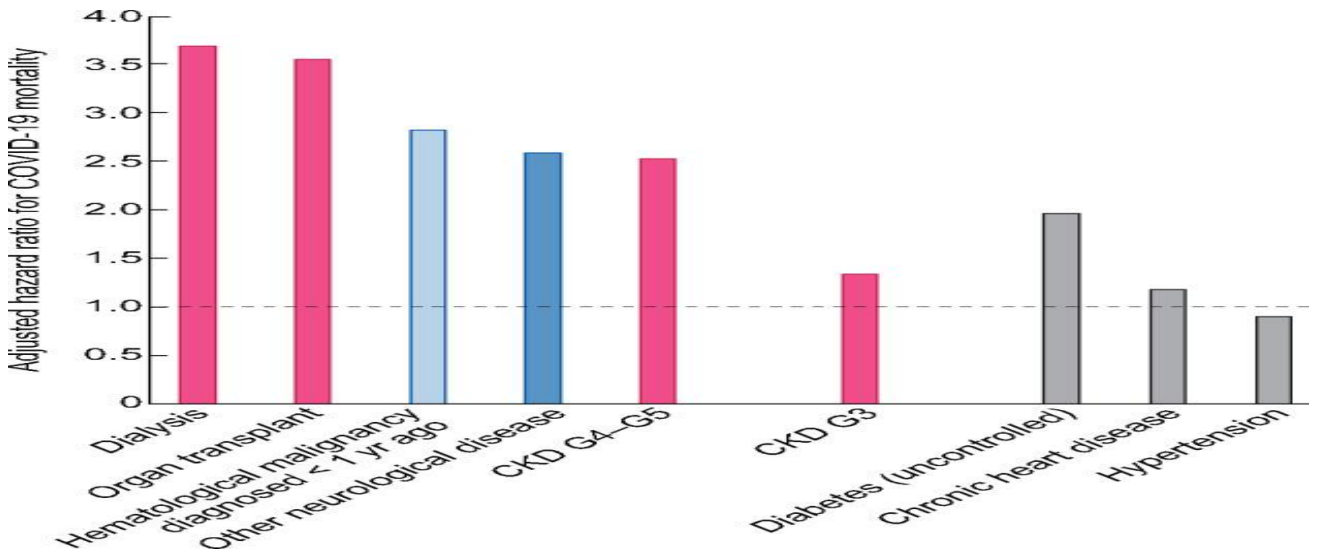
Collaborators + expand

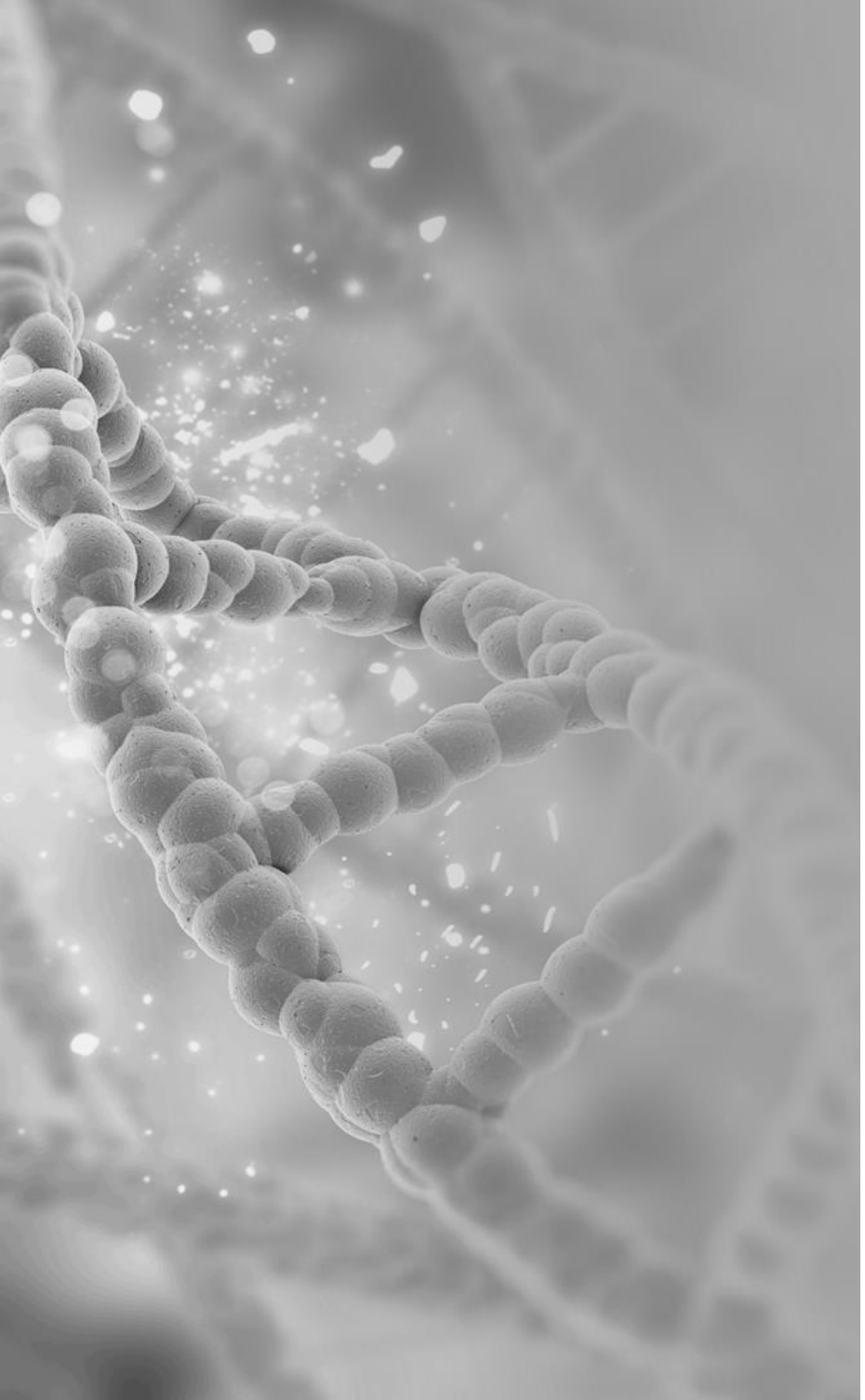
PMID: 33340043 PMCID: PMC7771976 DOI: 10.1093/ndt/gfaa314

Free PMC article

Abstract

Diabetes, hypertension and cardiovascular disease have been listed as risk factors for severe coronavirus disease 2019 (COVID-19) since the first report of the disease in January 2020. However, this report did not mention chronic kidney disease (CKD) nor did it provide information on the relevance of estimated glomerular filtration rate (eGFR) or albuminuria. As the disease spread across the globe, information on larger populations with greater granularity on risk factors emerged. The recently published OpenSAFELY project analysed factors associated with COVID-19 death in 17 million patients. The picture that arose differs significantly from initial reports. For example, hypertension is





Chapter

08

IP Portfolio

SAMiRNA IP 확보 전략

연도	지원기관	사업명칭	내 용
2011	특허청	IP-R&D 전략지원사업	치료용 siRNA 및 siRNA 전달체 개발 특허분석으로 선행기술 분석 및 강한 IP 포트폴리오 확보
2012	특허청	IP 활용전략 지원사업	섬유증 타겟 SAMiRNA 치료제 개발 특허분석 및 IP 전략구축
2013	특허청	IP-R&D 전략지원사업	암 핵산마커 DB를 이용한 백혈병을 포함하는 난치암 RNAi 치료제 개발 및 타깃 발굴전략 구축
2016	특허청	IP-R&D 전략지원사업	siRNA 기반 SAMiRNA를 적용한 면역항암치료제 개발을 위한 IP-R&D 전략구축

SAMiRNA FTO Analysis

Patent Holder (inventor)	Patent No. (filing date/priority)	Title	Main claim	Overhang	siRNA Length	Infringe-ment
Alnylam Europe AG (Limmer)	EP1550719B 2008-12-24 1999-1-30	Double stranded RNA (dsRNA) for inhibition the expression of a defined gene	Oligoribonucleotide with double-stranded structure (dsRNA) for inhibiting the expression of a given target gene in mammalian cells, wherein the dsRNA consists of 15 to 21 base pairs is and one strand of the dsRNA one to the target gene complementary to from 15 to 21 consecutive nucleotide pairs existing region I and in the double-stranded structure complementary region II is formed by two separate RNA single strands, wherein the double-stranded structure is stabilized by chemical linkage of the individual strands.	No limitation	15~21	매우 낮음
	EP1214945B 2005-06-08 1999-01-30	Method and medicament for inhibiting the expression of a defined gene	A method for inhibiting the expression of a given target gene in a mammalian cell in vitro, wherein a 15-49 base pairs exhibiting oligoribonucleotide with double-stranded structure (dsRNA) is introduced into the mammalian cell, wherein one strand of the dsRNA having one to the target gene is at least partially complementary to a maximum of 49 successive nucleotide pairs region I and has a complementary double-stranded structure in the region II is formed by two separate RNA single strands.	No limitation	15~49 (15~21)	매우 낮음
Carnegie Institute Of Washington	US6506559 2003-01-14 1997-12-23	Genetic inhibition by double-stranded RNA	A method to inhibit expression of a target gene in a cell in vitro comprising introduction of a ribonucleic acid (RNA) into the cell in an amount sufficient to inhibit expression of the target gene, wherein the RNA is a double-stranded molecule with a first strand consisting essentially of a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and a second strand consisting essentially of a ribonucleotide sequence which is complementary to the nucleotide sequence of the target gene, wherein the first and the second ribonucleotide strands are separate complementary strands that hybridize to each other to form said double-stranded molecule, and the double-stranded molecule inhibits expression of the target gene.	No limitation	No limitation	매우 낮음
Univ Massachusetts (Fire/Mello)	US7538095 2009-5-26 1997-12-23	Genetic inhibition by double-stranded RNA	A method to inhibit expression of a target gene in a cell in vitro comprising synthesizing at least two ribonucleic acids (RNAs) in the cell in an amount sufficient to inhibit the expression of a target gene, wherein the at least two RNAs form a double-stranded structure containing separate complementary strands, wherein the first RNA consists essentially of a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and the second RNA consists essentially of a ribonucleotide sequence which is complementary to the nucleotide sequence of the target gene, wherein the first and the second ribonucleotide sequences are complementary sequences that hybridize to each other to form said double-stranded structure, and wherein the target gene is an endogenous gene.	No limitation	No limitation	매우 낮음

IP Portfolio for SAMiRNA Drug Development

Strong IPs over 190 patents

SAMiRNA Platform	• over 85 patents
RNAi Candidates	• over 100 patents
Others	• Companion Diagnosis, Nebulizer formulation

IP Portfolio for SAMiRNA Drug Development

Strong IPs over 190 patents

KR 1,224,828B	▪ 2009. 5. 14. 출원, 2013. 1. 16. 등록 ▪ SAMiRNA 원천 기술 특허 ▪ 주요국 특허 보유
KR 1,722,948B	▪ 2012. 1. 5. 출원, 2017. 3. 29. 등록 ▪ 리간드가 결합된 SAMiRNA 기술 특허 ▪ 주요국 특허 보유
KR 1,862,349B	▪ 2014. 7. 4. 출원, 2018. 5. 23 등록 ▪ New SAMiRNA 원천 특허 ▪ 친수성 그룹의 개량 ▪ 주요국 특허 보유
KR 2,208,588B	▪ 2015. 4. 6. 출원, 2021년 1월 22일 등록 ▪ SAMiRNA-AREG 특허 ▪ 이중나선 올리고 RNA 및 이를 포함하는 섬유증 치료용 약학 조성물 ▪ 주요국 특허 출원

IP Portfolio for SAMiRNA Drug Development

Strong IPs over 190 patents

- Platform Technology

US 8,779,114B

– 2014/07 Patented, siRNA conjugate and preparing method thereof

US 9,326,941B

– 2016/05 Patented, Nanoparticular double-stranded oligo RNA molecule with high efficacy and method of preparing the same

US 10,030,243B

– 2018/07 Patented, Improved nanoparticular oligonucleotide conjugates with high efficacy and method of preparing the same

- RNAi Candidates

US 10,208,309B

– 2019/02 Patented, Novel double strand oligo RNA and pharmaceutical compositions for preventing or treating fibrosis or respiratory diseases containing the same

IP Portfolio for SAMiRNA Drug Development

Strong IPs over 190 patents

- 동반진단 특허

PCT/KR2021/004557

- 동반진단 특허
- Composition for diagnosing kidney disease using urine sample

- 흡입제형 특허

KR 10-2021-0029927

- Nebulizer 흡입 제형
- Composition for administration of double-stranded oligonucleotide structures using an ultrasonic nebulizer for prevention or treatment of respiratory viral infection including COVID-19, pulmonary fibrosis caused by viral infection, or respiratory diseases

SAMiRNA Publication

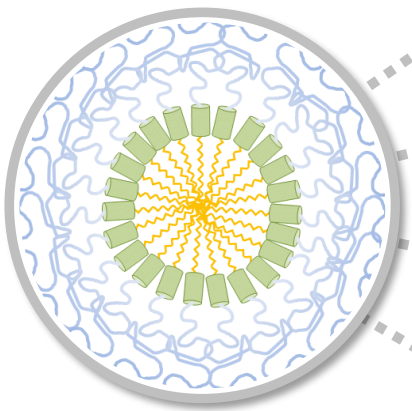
Title	Journal
Safety pharmacology of self-assembled-micelle inhibitory RNA-targeting amphiregulin (SAMiRNA-AREG), a novel siRNA nanoparticle platform	Toxicology Reports 8 (2021) 839–845
In vivo silencing of amphiregulin by a novel effective Self-Assembled-Micelle inhibitory RNA ameliorates renal fibrosis via inhibition of EGFR signals	Scientific Reports. (2021) 11:2191
Self-assembled Micelle Interfering RNA for Effective and Safe Targeting of Dysregulated Genes in Pulmonary Fibrosis	Journal of Biological Chemistry. Vol. 291, No. 12, pp. 6433–6446, March 2016
Modifiers of TGF-b1 effector function as novel therapeutic targets of pulmonary fibrosis	Korean J Intern Med 2014;29:281-290
Amphiregulin, an Epidermal Growth Factor Receptor Ligand, Plays an Essential Role in the Pathogenesis of Transforming Growth Factor--induced Pulmonary Fibrosis	The Journal of Biological Chemistry Vol. 287, No. 50, pp. 41991–42000, December 2012

SAMiRNA Collaboration

공동 연구 기관	분야	내용
Prof Chun Geun Lee, MD., Ph.D. Department of Molecular Microbiology and Immunology, Department of Medicine, Alpert Medical School, Brown University	PF	Pulmonary fibrosis drug development program
Prof Choon Sik Park, MD., Ph.D. Genome Research Center and Division of Allergy and Respiratory Medicine, Soonchunhyang University Bucheon Hospital	PF	In-vivo efficacy study in silica-induced PF mouse model
Prof Eun Young Lee, MD., Ph.D. Department of Internal Medicine, Soonchunhyang University Cheonan Hospital	CKD	CKD drug development program
Prof Jaeho Cho, MD., Ph.D. Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine	RIF	방사선 유발 섬유화증
㈜유한양행	3개 타겟	Collaboration and Licensee
KIT (Korea Institute of Toxicology) & Charles River Laboratories	GLP-tox	전임상 독성 시험
Seoul National University Medical Center	CKD	Ph1 Clinical Study Partner
LSK	CRO	Domestic CRO
COVANCE	CRO	Global CRO
Syngene	CMO	Drug Substance
Integrity Bio	CMO	Drug Product
서원대학교 글로벌피부임상센터	Hair loss treatment	Clinical Study Partner
㈜엘리드	CRO	Hair Loss Treatment clinical study

IP Portfolio Strategy

SAMiRNA 치료제 원천기술 확보 및 라이센싱-아웃을 위한 강력한 특허 포트폴리오 구축

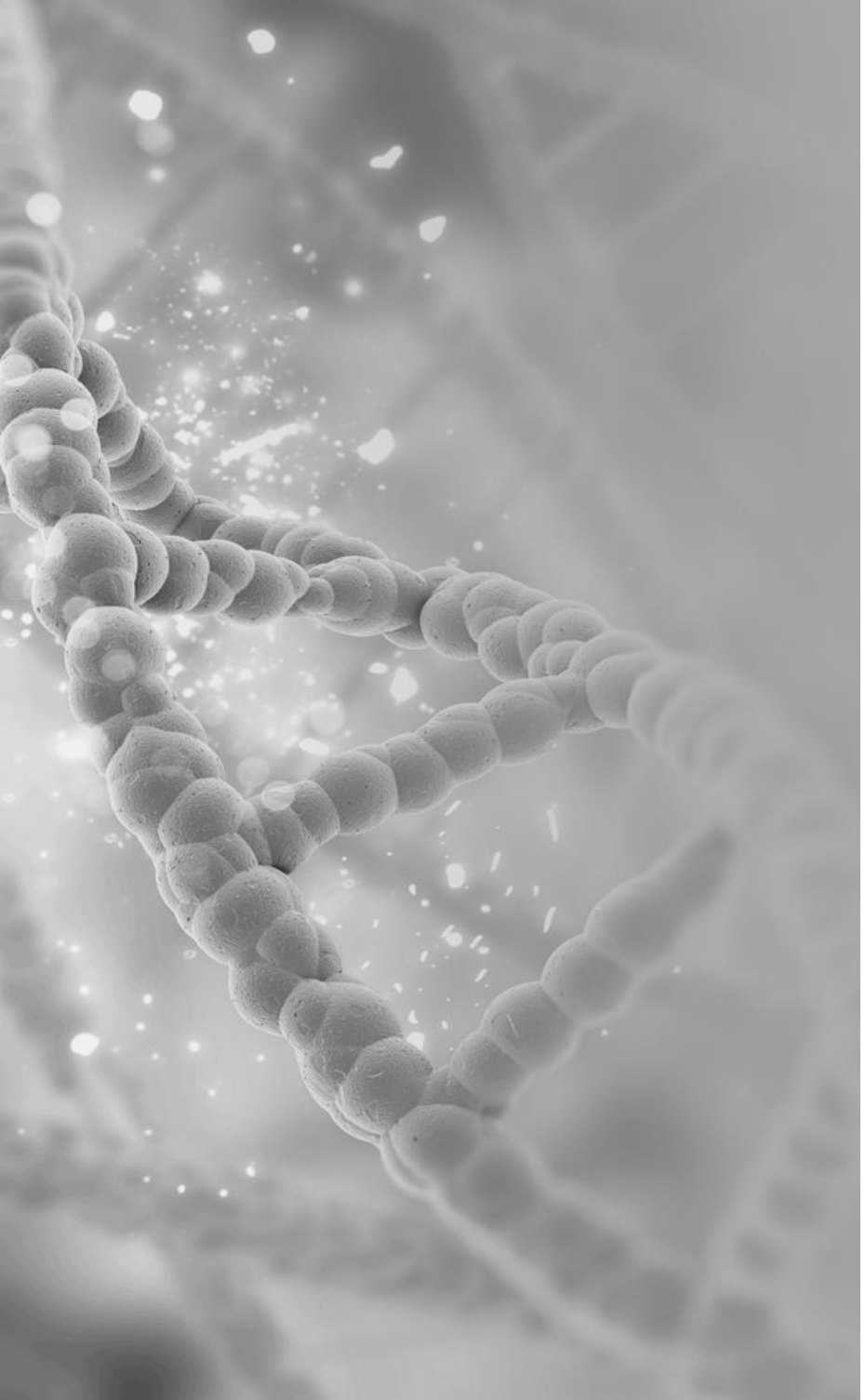


1. 정부 IP R&D 사업을 이용하여 선행기술조사, 특허침해분석, 시장분석, 보완특허 출원전략, 해외진입 전략, 라이센싱 전략 등 심도 있는 컨설팅 수행

2. SAMiRNA 원천특허를 포함하여 190여건의 특허를 보유함으로써, RNAi 기반의 난치병 신약개발 위한 원천기술의 전세계 독점적 지위 확보

3. SAMiRNA 플랫폼에 기반한 섬유화증, 켈로이드, 고형암, 패혈증 등 각종 난치병 치료 신약 개발 진행 및 지속적인 IP 확보

4. 강력한 SAMiRNA IP 포트폴리오를 기반으로 글로벌 제약사 및 연구그룹과 타깃 특이적 공동연구, 사업개발 및 라이센싱-아웃 진행



Chapter

09

Market Potentials

Amphisiran Global Market Size & Positioning

	Market Size (in USD)	Prevalence	Positioning
IPF & Covid-PF	**4 B**	20/100,000 persons for males and 13/100,000 persons for females	Better efficacy than Pirfenidone™/Ab to CTGF with much less A/E & dosage. Confirmed Anti-ECM/Inflammation/EMT. “orphan”
CKD	**15 B**	more than 1 in 7 adults	Confirmed AREG is excellent prognostic marker for ESRD on human/working on podocyte, GBM, distal Tubular cells & improving GFR, inflammation, EMT, fibrosis & HbA1C on animal.
NASH	**20 B**	20~50/1,000	Anti- Adipogenic/Inflammation/Fibrosis
Visceral Obesity	**>600 B**	1/3 Adult	Inhibiting differentiation to adipocyte & TG
Breast Cancer	**29 B**	~40/100,000	Anti-TME >-Tumorigenic>-Mets “first in market”
NSCLC	**22 B**	2.1M in 2018 (11.6% all cancer)	Inhibiting Bony mets (exosomal AREG) & Anti-TME
Pancreatic Cancer	**4 B**	5.5/100,000 for men 4.0/100,000 for women	Inhibiting ductal invasion of cancer cell “Breakthrough”

siRNAgen Market Positioning

	Roche Pirfenidone™	siRNAgen Therapeutics SAMiRNA-AREG	Dicerna GalXC-siRNA
Indication	IPF (Marketed)	IPF/NASH/CKD/Cancer	NASH (Phase 2a)
Deal	8.3 B (Roche)	At least 600M (up-front+ milestone)	0.2 B up-front + milestone
Differences	Small molecule With many troublesome A/E (obscure MOA). Less efficacy than SAMiRNA.	Precisely targeting siRNA-AREG (less A/E). Bio-degradable simple PEG & lipid conjugates, which cause no innate immune reaction. Much less manufacturing cost and simple QC process. Selectively targeting inflamed/cancer tissue tailored for chronic inflammatory disease and cancer.	GalXC-carrier Induces innate immune reaction. High manufacturing cost and complex QC
X-factor		1 IV injection/Month with low dose will be enough for achieving target therapeutic goal (IPF, CKD, Cancer) with little A/E.	

Licensing-out Status

siRNAgen Therapeutics
SAMiRNA-AREG

Phase	Preclinical
Company	Global Big Pharmaceutical (Non-disclosure)
Status	L/O contract negotiating & under discussion with other company
Deal	Negotiating
Asset	Targeting SAMiRNA-AREG

Licensing Deals of RNAi

Licensor	Licensee	Deal date	Deal size (US$)	License Target	Indication	Stage
Arrowhead	**Horizon**	2021 Jun	40M upfront + 660M milestone	ARO-XDH	Gout	**Pre-clinical**
Arrowhead	**Takeda**	2020 Oct	300M upfront + 740M milestone	ARO-AAT	Alpha-1 Antitrypsin-Associated Liver Disease	**Phase II**
Evox	**Eli lilly**	2020 Jun	30M upfront + 1.2B milestone	DeliverEX platform (5 target)	Neurological disorders	**Discovery**
Silence	**AstraZeneca**	2020 Mar	80M upfront + 2B milestone (400M/target)	GalNAc-siRNA platform	Cardiovascular, Renal, Metabolic and Respiratory Diseases	**Discovery**
Dicerna	**Novo Nordisk**	2019 Nov	225M upfront + 357.5M milestone/target	RNAi technology platform GalXC	metabolic and liver-related diseases (NASH, Diabetes, Obesity)	**Discovery**
Dicerna	**Roche**	2019 Nov	200M upfront + 1.47B milestone	DCR-HBVS	HBV	**Phase I**
Silence	**Mallinckrodt**	2019 Jul	20M upfront + 703M milestone	SLN500 & two additional complement-targeted assets (option)	Autoimmune diseases.	**Pre-clinical**
Alnylam	**Regeneron**	2019 Apr	800M upfront + 200M milestone	preclinical disease programs	Ocular and CNS Diseases	**Pre-clinical**
Dicerna	**Eli lilly**	2018 Oct	200M upfront + 3.5B milestone (350M/target)	RNAi technology platform GalXC	cardio-metabolic, neurodegeneration and pain	**Discovery**
Arrowhead	**Janssen (J&J)**	2018 Oct	250M upfront + 3.5B milestone	ARO-HBV & three new targets (option)	HBV	**Phase I/II**
Dicerna	**Boehringer Ingelheim**	2017 Nov	10M upfront + 191M milestone	RNAi technology platform GalXC	NASH	**Discovery**
Nitto Denko	**BMS**	2016 Nov	100M upfront	ND-L02-s0201 (HSP47 siRNA)	NASH	**Phase I**
Arrowhead	**Amgen**	2016 Sep	56.5M upfront + 617M milestone	ARC-LPA program	cardiovascular disease	**Pre-clinical**


We invite you to explore the new clinical development
with our next generation siRNA platform.
Join us today.
Thank You !