

IR Book | Feb. 2023

ST PHARM

Technology Driven Gene therapy CDMO
From Oligonucleotide to xRNA





PART 01

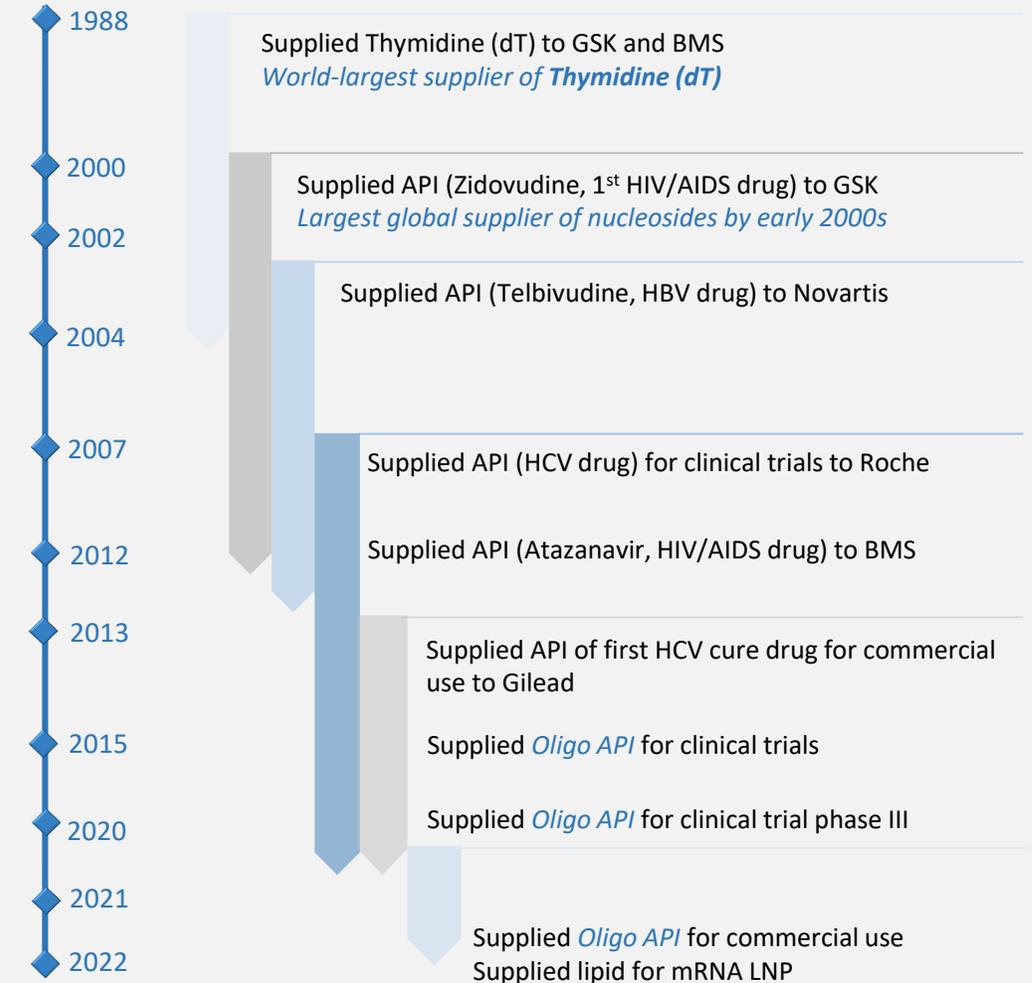
Introduction



ST PHARM HISTORY

- 1983 Foundation of Samchully Pharm
- 2010 Joined Dong-A Socio Group and the corporate name changed to ST PHARM (Science and Technology)
- 2015 Completed 2nd Campus (Banwol)
FDA(USA) and PMDA (Japan) cGMP Inspection
- 2016 EU cGMP Inspection/ Established a subsidiary (STAR, USA)
Listed (IPO) as a public company (KOSDAQ: 237690)
- 2018 Commence Oligo GMP Manufacturing at Oligo Banwol Plant (1.8mol)
Awarded 2018 Global API Manufacturing (Oligonucleotide) Growth Excellence Leadership by Frost & Sullivan
- 2019 Acquired two CRO(AnaPath R&S) in Europe
STP1002(Colorectal cancer) IND approval (Phase1)
- 2020 Received 2019 Roche CDMO Award
STP0404 (AIDS) IMPD approval (Phase1)
- 2021 Established LEVATIO and VERNAGEN (USA, RNA biotech)
Initiated Mid-scale mRNA GMP facility set up (Banwol Campus)
Started development of COVID-19 vaccine (mRNA)
Disclosed Oligonucleotide 2nd plant plan (Banwol Campus)
- 2022 STP2104 (COVID19, mRNA Vaccine) IND approval (Phase1)
Awarded 2022 Global API Manufacturing(Oligonucleotide) Growth Excellence by Frost & Sullivan
Completed 1st & 2nd Oligo plant expansion (6.4 Mole)
Banwol campus, FDA cGMP Inspection, NAI
STP0404 (AIDS, small molecule) Phase2a

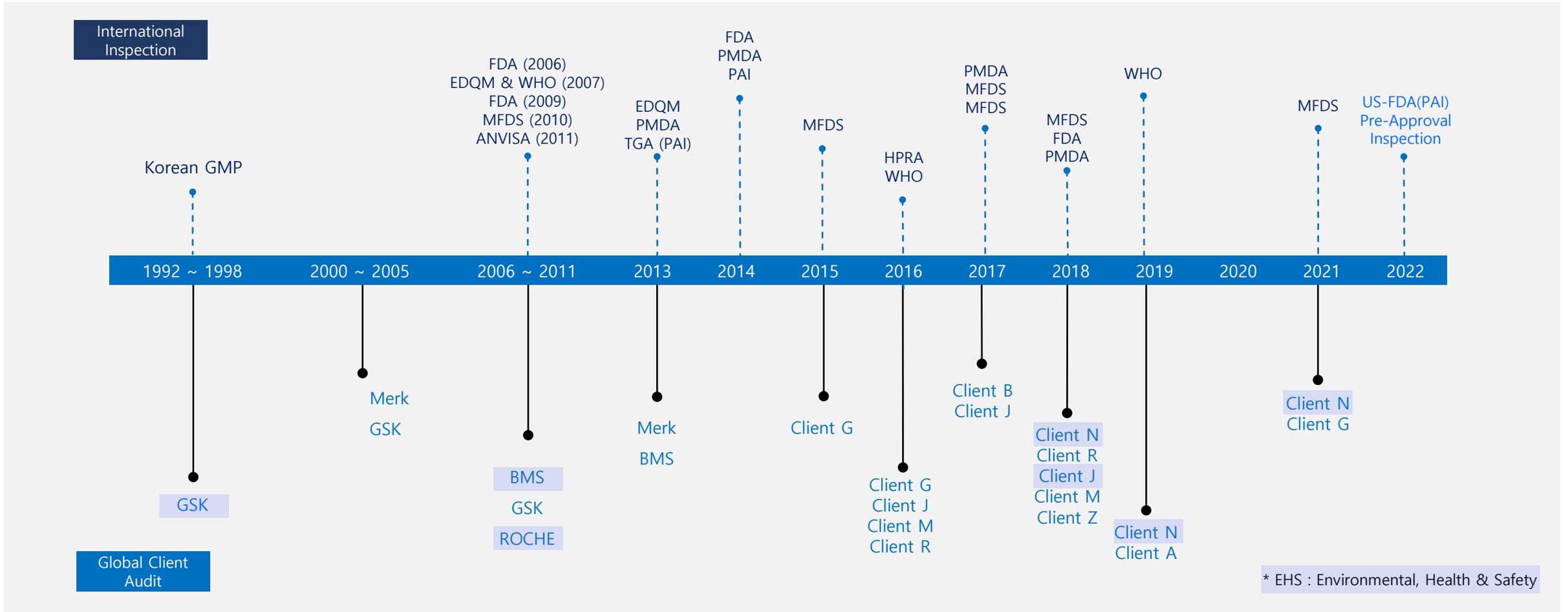
SUPPLY RECORD



Introduction



Approval history



Successfully Inspected by





Gene therapy CDMO business from oligonucleotide to xRNA
Seamless Development from Manufacturing to Non-clinical animal safety service

ANAPATH SERVICES
BASEL, SWITZERLAND
(HISTOPATHOLOGY SERVICE)

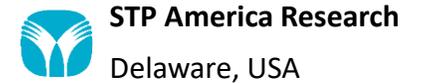
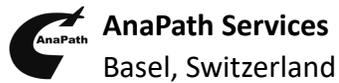
ANAPATH RESEARCH
BARCELONA, SPAIN
(PRE-CLINICAL RESEARCH)

ST PHARM
(HQ)
SOUTH KOREA

STP AMERICA RESEARCH
DELAWARE, USA

VERNAGEN
ATLANTA, USA
(BIOTECH, MRNA R&D)

LEVATIO
SAN DIEGO, USA
(BIOTECH, CAR-NKT R&D)





ST PHARM CDMO strategy



1983. Nucleoside/tide

- Monomer (PNS / PA)
- Zidovudine (AIDS)
- Sofosbuvir (HCV)



2008. Oligonucleotide

- Antisense (ASO)
- siRNA / miRNA
- Aptamer
- Decoys
- Others



2018. Polynucleotide

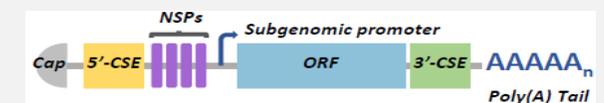
- mRNA



- circRNA



- samRNA





PART 02

Market Overview



Overview

RNA-based therapeutics, fundamentally controlling gene expression (disease-relevant gene), 3rd generation therapy

RNA based drugs

- mechanism: interfere or control the expression of protein that causes disease
- type: Anti-sense (ASO), siRNA, miRNA, etc.
- Approved drugs: 1. Spinraza (Biogen) SMA (Sales USD 2.1Billion/year)
2. Leqvio (Novartis) Hyperlipidemia, LDL-C

Advantages and Challenges

- Advantages

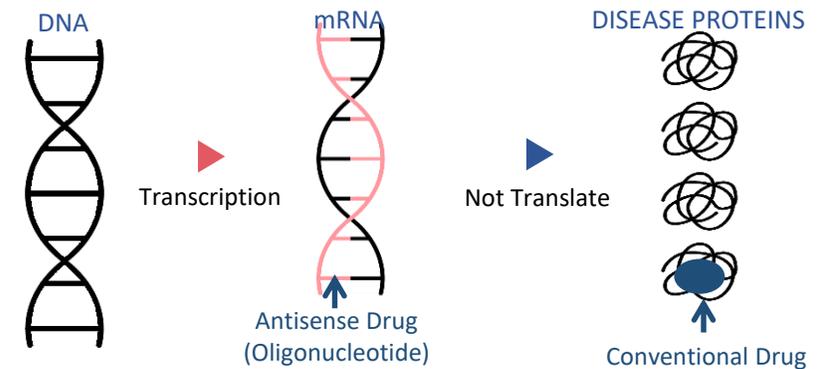
- Targeting undruggable pathways
- Rapid and cost effective development ► **under 2 years Pre-clinical stage**
- Low tolerance (no Protein-Protein interaction) ► **better than existing therapy**
- Long term effect (Leqvio 2T/annum VS Repatha 1-2T/monthly)
- Price (Leqvio below \$4000/annum VS Repatha about \$5850/annum)

- Challenges

- Delivery issues (to penetrate specific cell) cf. Liver, Spinal cord, etc.
- **new delivery method: LNP, Avidity's AOC (Antibody Oligonucleotide Conjugates)**
- Mass production (Few CDMO in global market, shortage issue)

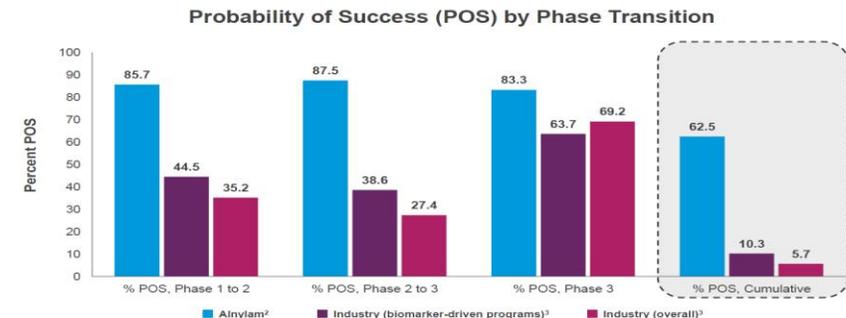
Central Dogma

Mechanism of RNA based drug (ASO)



62.5% Success by Phase transition

High-Yield Productivity of Alnylam RNAi Therapeutics Platform
Comparison of Historical Industry Metrics to Alnylam Portfolio¹



¹ Analysis as of December 2020. Past rates of Alnylam and industry respectively may not be predictive of the future
² Alnylam programs biomarker-driven at all stages of development (100%). Figures include ALNY-originated molecules now being developed by partners.
³ Wong et al., *BioStatistics* (2019) 20, 2, pp. 273-286

[ref. : Alnylam]



■ Geron, Imetelstat, new Oligonucleotides drug in blood cancer

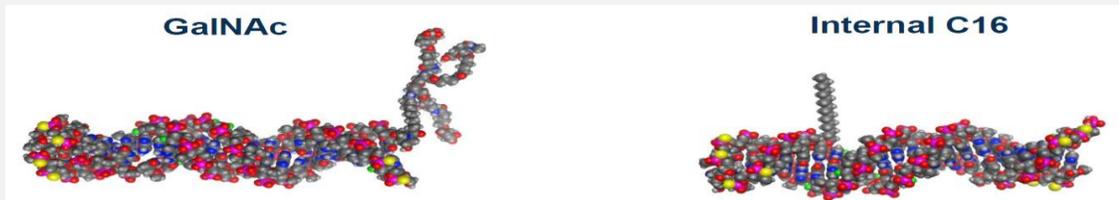
MDS(myelodysplastic syndrome), Forecasting sales 1.2B/year
 2023 plans on target for regulatory submission in US and EU, commercial launch in 1H. 24
 MF(myelofibrosis) in Phase 3, AML(acute myeloid leukemia) in Phase 1
 required Oligo amounts are 137kg, considering 20k patients are treated(total patients in US and EU are approximately 40k)

■ Avidity, direct delivery through IM(IntraMuscular)

AOC(Antibody Oligonucleotide Conjugates)
 Possibility of various cancer cures, beyond rare and chronic diseases

■ Alnylam, C16 conjugated platform

deliver siRNA to the CNS
 Alzheimer's, Parkinson's, ALS(Amyotrophic lateral sclerosis) disease



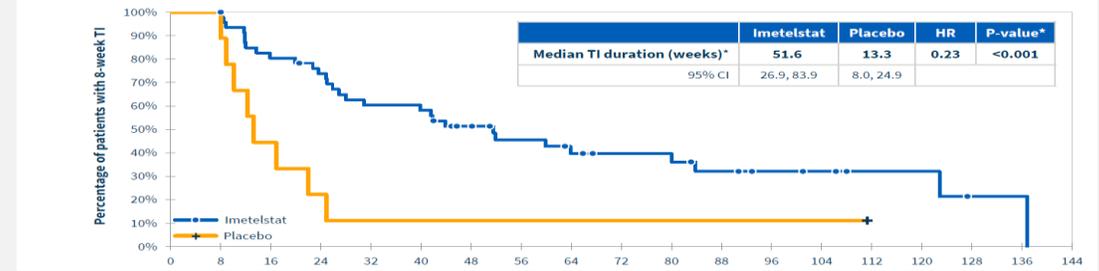
Met primary endpoint (8-week TI)

Highly statistically significant and clinically meaningful improvement in 8-week TI

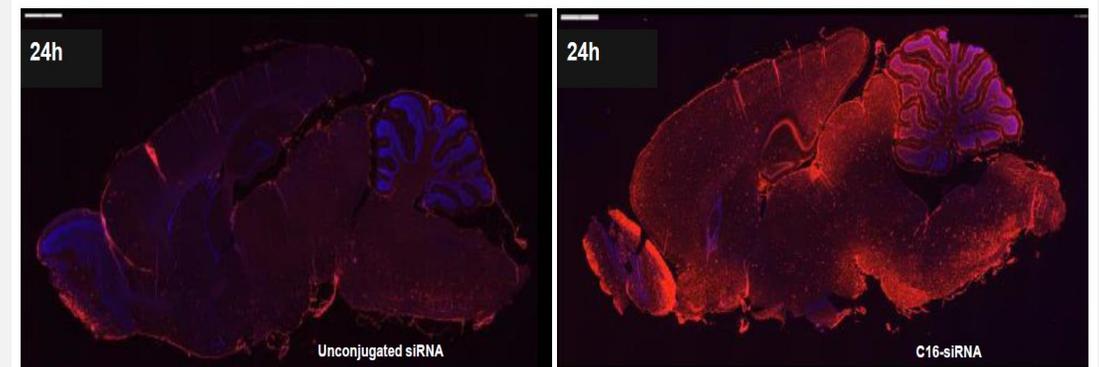
	Imetelstat (n=118)	Placebo (n=60)	P-value*
8-week TI, n (%)	47 (39.8)	9 (15.0)	<0.001
95% CI	(30.9, 49.3)	(7.1, 26.6)	

Median duration of 8-week TI*

Highly statistically significant and clinically meaningful durability of TI



[Geron]



[Alnylam]

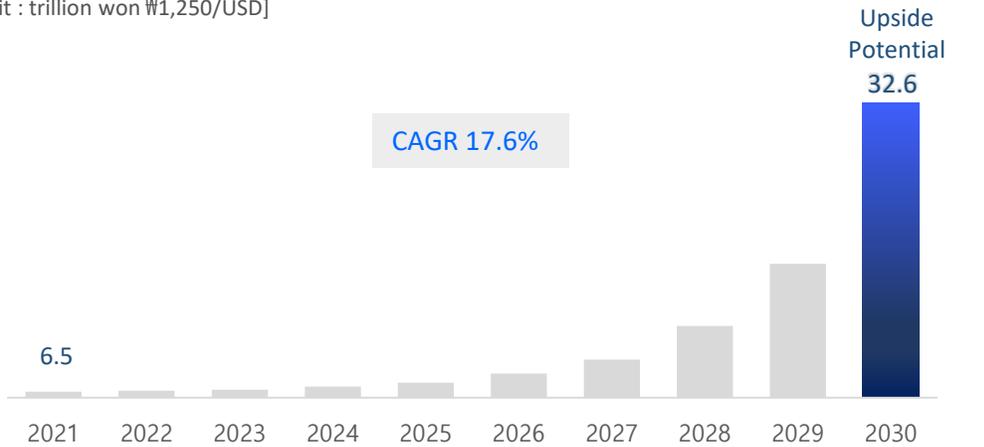


▪ Dawn of RNA-based Therapeutics

- '18 development of Gal-NaC has enabled an expansion to chronic liver-related diseases, Big pharma's investment on RNA pipeline hikes
- Starting '24, blockbuster RNA drugs will be commercialized, such as Leqvio (Inclisiran)
- Demand for Oligonucleotides will rise
- Global RNA-based drugs market '21 6.5 trillion to '30 32.6 trillion won
- Big pharma's movement: License-in (IONIS, ALNYLAM, ARROWHEAD)
Self-development

▪ Global RNA Therapeutics market (excl. mRNA)

[unit : trillion won ₩1,250/USD]



[Research & Market July. 2021]

▪ Oligonucleotides demand forecast ▶ 12 tons per year (when commercialized)

만성 질환 관련 올리고뉴클레오타이드 개발 현황 및 필요한 연간 생산량 산출

기업	치료제	질환	타겟	개발 단계	한번 투약 (g)	투약 간격 (1년)	1인 연간 투약량 (g)	환자 수 (1년)*	연간 필요 생산량 (kg)	비고
Ionis	Pelacarsen	심혈관 질환	Apo(a)	P3	80	12번	960	1,000,000	960	Novartis
	Vupanorsen	고지혈증 치료제	ANGPTL3	P2	80	12번	960	1,380,000	1,325	Pfizer
	Olezarsen	심혈관 질환	ApoCIII	P3	50	12번	600	1,000,300	600	
	IONIS-AGT-Lrx	저항성 고혈압	AGT	P2	80	8번	640	540,675	346	
	ION449 (AZD8233)	이상지질혈증	PCSK9	P2	120	2번	360	1,380,000	497	AstraZeneca
	ION224	비알콜성지방간염	DGAT2	P2	80	12번	960	640,000	614	
	IONIS-MAPTlx	알츠하이머, 치매	TAU	P2	100	4번	400	1,500,000	600	Biogen
	Bepirovirsen	B형 간염 치료제	HBV	P2	300	6번	1,800	1,000,000	1,800	GSK
Alnylam	Leqvio (inclisiran)	이상지질혈증	PCSK9	판매	300	2번	600	1,380,000	828	
	Zilebesiran (ALN-AGT)	고혈압 치료제	AGT	P2	600	2번	1,200	1,000,000	1,200	
	ALN-HBV02 (MR-2218)	B형 간염 치료제	HBV	P2	200	2번	400	500,000	200	
Dicerna	DCR-HBV5 (RG6346)	B형 간염 치료제	HBV	P2	360	4번	1,440	500,000	720	Roche
	ARO-ANG3	이상지질혈증	ANGPTL3	P2	200	2번	400	1,380,000	552	
Arrowhead	ARO-HSD	비알콜성지방간염	HSD17β13	P2	200	2번	400	1,000,000	400	GSK
	JNJ-3989	B형 간염 바이러스	HBV	P2	400	3번	1,200	500,000	600	Janssen
	AMG890 (olpasiran)	심혈관 질환	LP(a)	P2	200	4번	800	1,000,000	800	Amgen

참조: 임상 2상 단계의 물질은 투약 용량 및 투약 간격 변동 가능; 미국, 유럽, 일본, 중국 등 선진국 내 타겟 환자 수의 10~20%로 가정

[Samsung Securities]



Overview

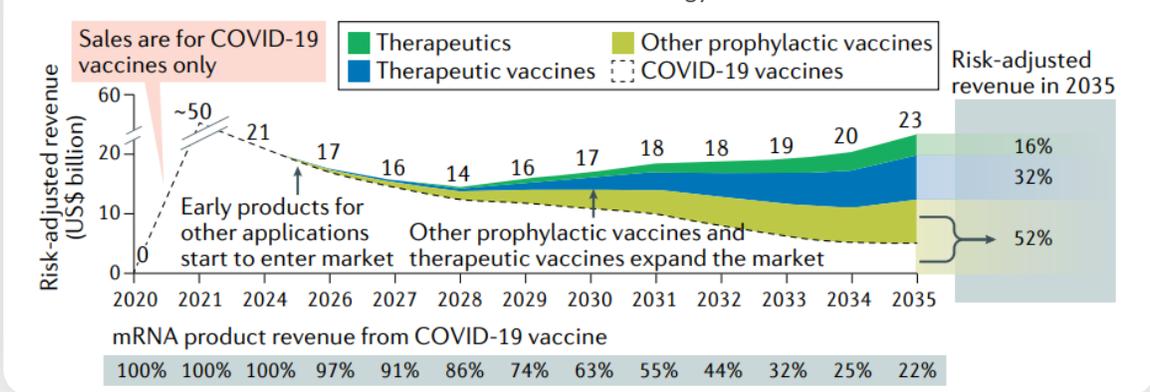
- widespread use of mRNA vaccines for COVID 19.
- Market grows from \$46.7 billion in 2021 to **\$101.3 billion by 2026** (CAGR 16.8%)

mRNA therapeutics

- **Safety/ Specificity** (binding to target disease)
 - No risk of genomic integration /
 - Inducing protein coding and inhibiting translation
- Capacity for rapid development and potential for low-cost manufacture
- **Essential roles** in protein expression

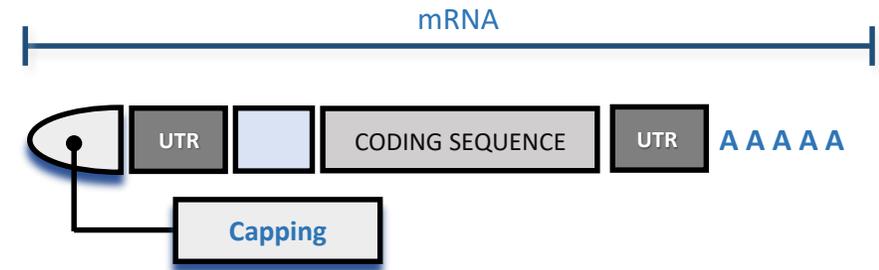
Broad applicability in the treatment or prevention of disease

A forecast for the evolution of the market for mRNA technology

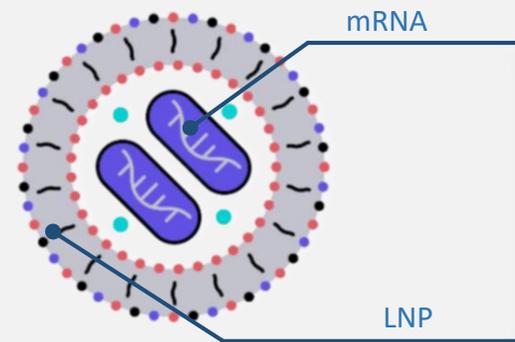


mRNA Platform

1) 5' Capping



2) LNP (Lipid Nano Particle)

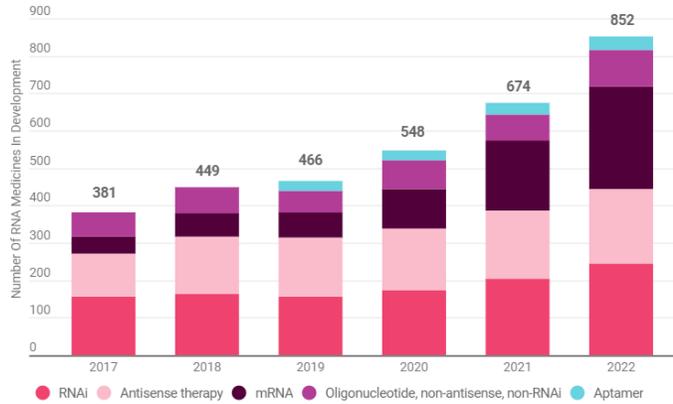


LNP component

- ✓ Lipid
- ✓ Ionizable lipid
- ✓ Cholesterol
- ✓ PEG, Polyethylene glycol



Exhibit 1: Growth In RNA Pipeline Has Doubled Since 2017



Notes: Chart includes candidates in development from preclinical through pre-registration. Annual snapshots taken in May.

Exhibit 2: RNA Technologies: Source Of Increasing Venture Capital Investment

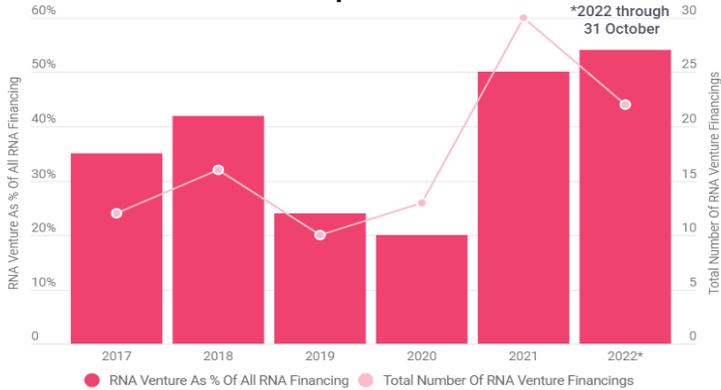
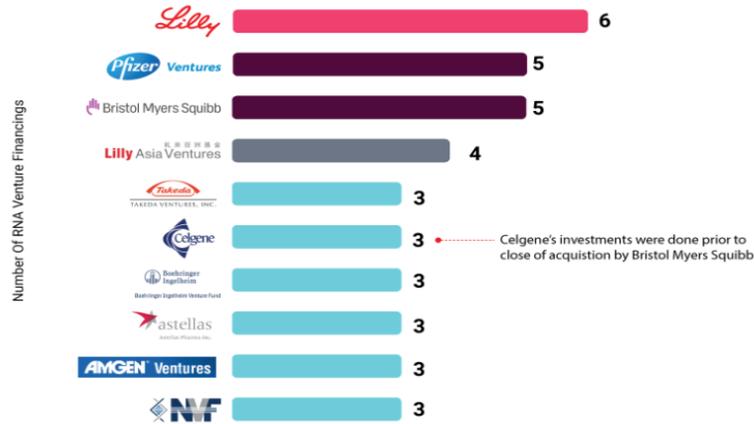
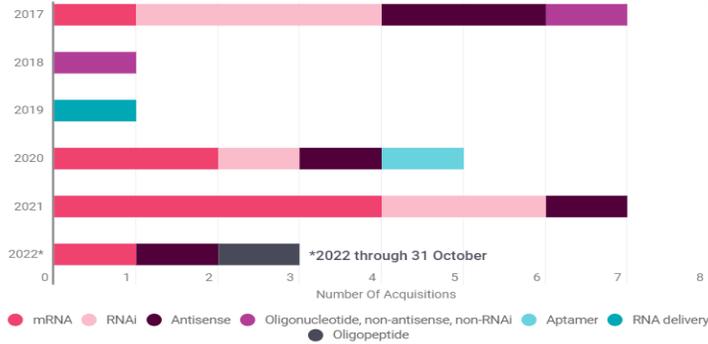


Exhibit 4: Most Active Corporate/Pharma Investors In RNA Venture Rounds Since 2017



Data through 31 October 2022

Exhibit 6: Shift From RNAi To mRNA: RNA Acquisitions By Modality



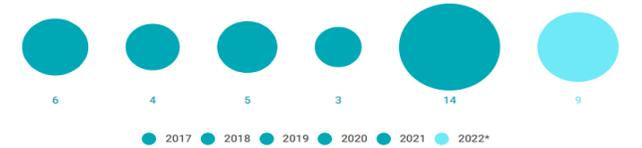
Notes: mRNA category includes vaccines, therapeutics, or cell therapies. Deals that include >1 RNA modality were counted more than once.

Exhibit 5: RNA Partnerships Are Growing With Average Values >\$500M

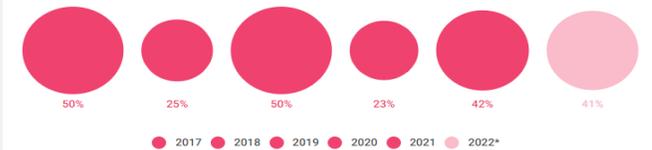


Note: Size of bubble represents average deal value for that year
* 2022 through 31 October

Number Of RNA Venture Rounds With Corporate Investors



Corporate-Backed RNA Venture Rounds As Percentage Of All RNA Venture Rounds

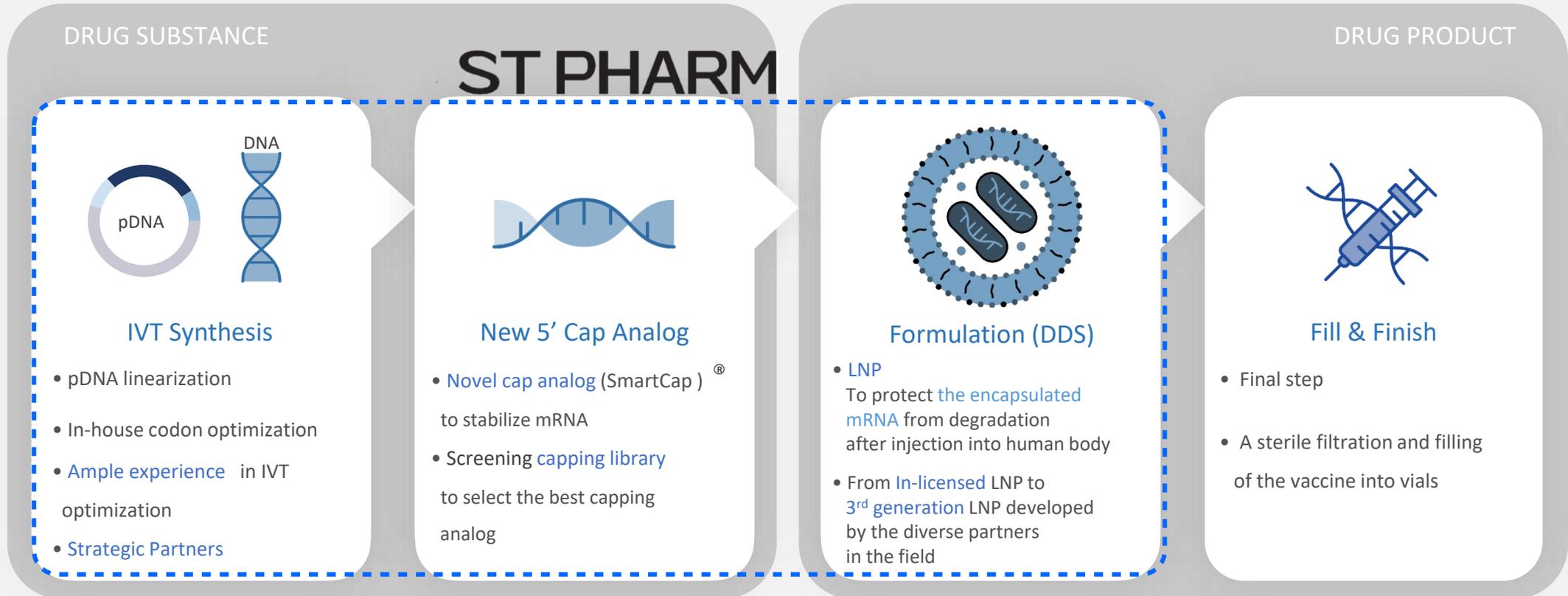


*2022 through 31 October

[출처 : Biomedtracker]



▪ mRNA manufacturing process



STPHARM connects all aspects of mRNA drug development to clinical and commercialized production



PART 03

Business Overview



ST PHARM's Core Strength (Oligonucleotide CDMO)

- Global top-3 positioned service
- The only integrated In-House production capability in the global market (From monomer to oligonucleotide)
- Innovative manufacturing system (ex. Biotransformation technology)
- **Strong track record** in new drug API manufacture proven in **US & Europe** (+ 15 years)

Manufacturing Capacity Expansion (disclosed)

- 1st & 2nd expansion : *Completed in 2022 2Q*
Installing additional manufacturing trains in Banwol plant
(Initiate by Apr & June of 2022) * financial support from a global client (2nd)
- 3rd expansion : Additional building (Banwol campus) planned

Strong Track Record

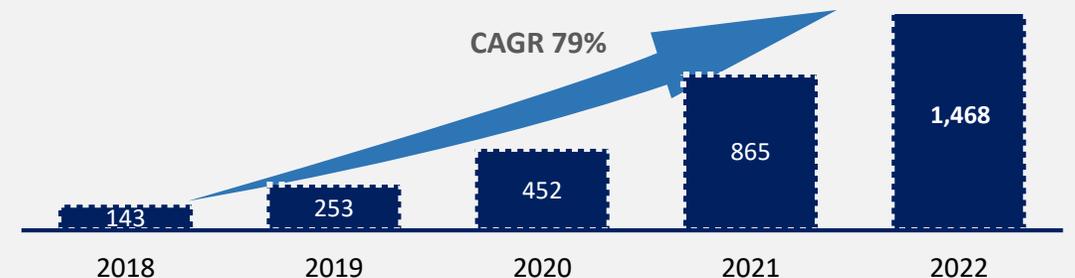
- Awarded 2018 Global API Manufacturing Growth Excellence Leadership Award (Frost & Sullivan)
- Awarded 2022 Asia-Pacific Oligonucleotide CDMO Company (Frost & Sullivan)
- Roche CDMO Award 2019
Oligo New Drug (First in global), Small Molecule New Drug (First in Asia)

ST PHARM's Oligo CDMO projects

Clients	Indication	Stage			
		Phase1	Phase2	Phase3	Commercial
Company A	Hyperlipidemia	Progress bar from Phase 1 to Commercial			
Company B	SMA	Progress bar from Phase 1 to Commercial			
Company A	Arteriosclerosis	Progress bar from Phase 1 to Phase 3			
Biotech C	MDS / MF	Progress bar from Phase 1 to Phase 3			
Biotech D	CVD	Progress bar from Phase 1 to Phase 3			
Company E	Hepatitis B	Progress bar from Phase 1 to Phase 3			
Company F	Hepatitis B	Progress bar from Phase 1 to Phase 2			
Company G	Thrombophilia	Progress bar from Phase 1 to Phase 2			
Biotech D	HAE	Progress bar from Phase 1 to Phase 2			
Company F	NASH	Progress bar from Phase 1 to Phase 2			
Company H	Hepatitis B	Progress bar from Phase 1 to Phase 2			

ST PHARM's Oligo CDMO sales

[Unit: 100 Million KRW]



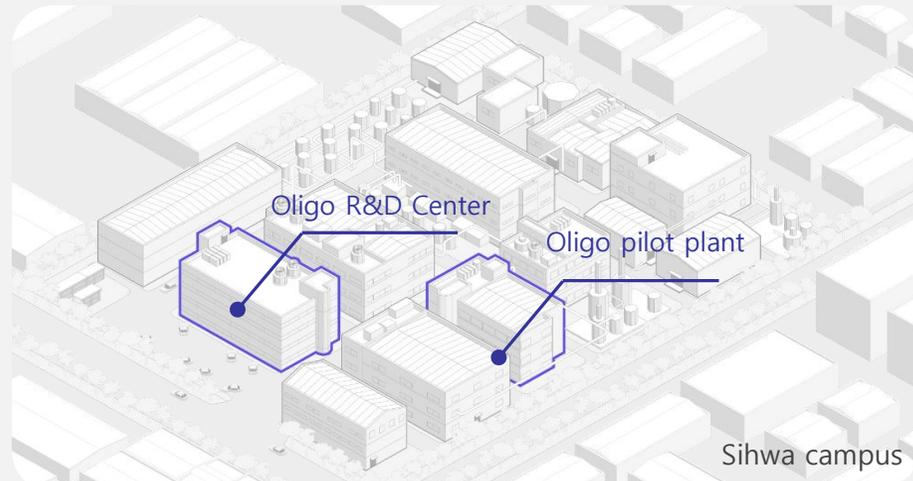


Capacity (Oligonucleotide)

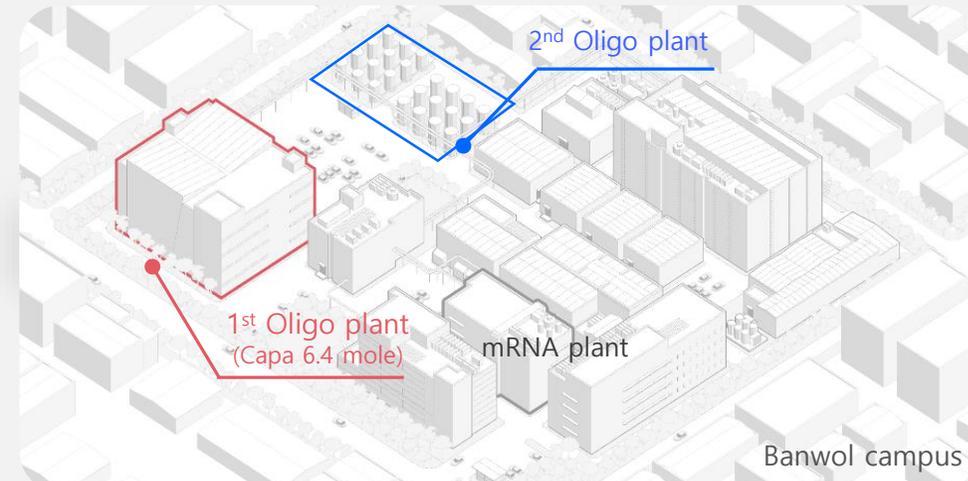
ST PHARM plans to invest in total \$126 million USD to build a 2nd oligonucleotide manufacturing plant.

[1 mole ≙ 167kg~500kg]

Oligo production	Current	2022, 3Q	2024, 3Q	2026, 1Q
	1 st Plant	1 st Plant (1 st & 2 nd expansion)	2 nd Plant (1 st stage)	2 nd Plant (2 nd stage)
Total CAPA (Facility / Line)	2.0 mole (about 500kg)	6.4 mole (1t-3.2t)	10.2 mole (1.7t-5.1t)	14.0 mole (2.3t-7t)
	1	4	7	10
	1.0 time	3.2 times	5.1 times	7.0 times



2021



2022

Production amount

43kg/n batch

52kg/n batch (21% ▲)

yield rate increase due to process improvement

Production time
(Synthesis and Purification)

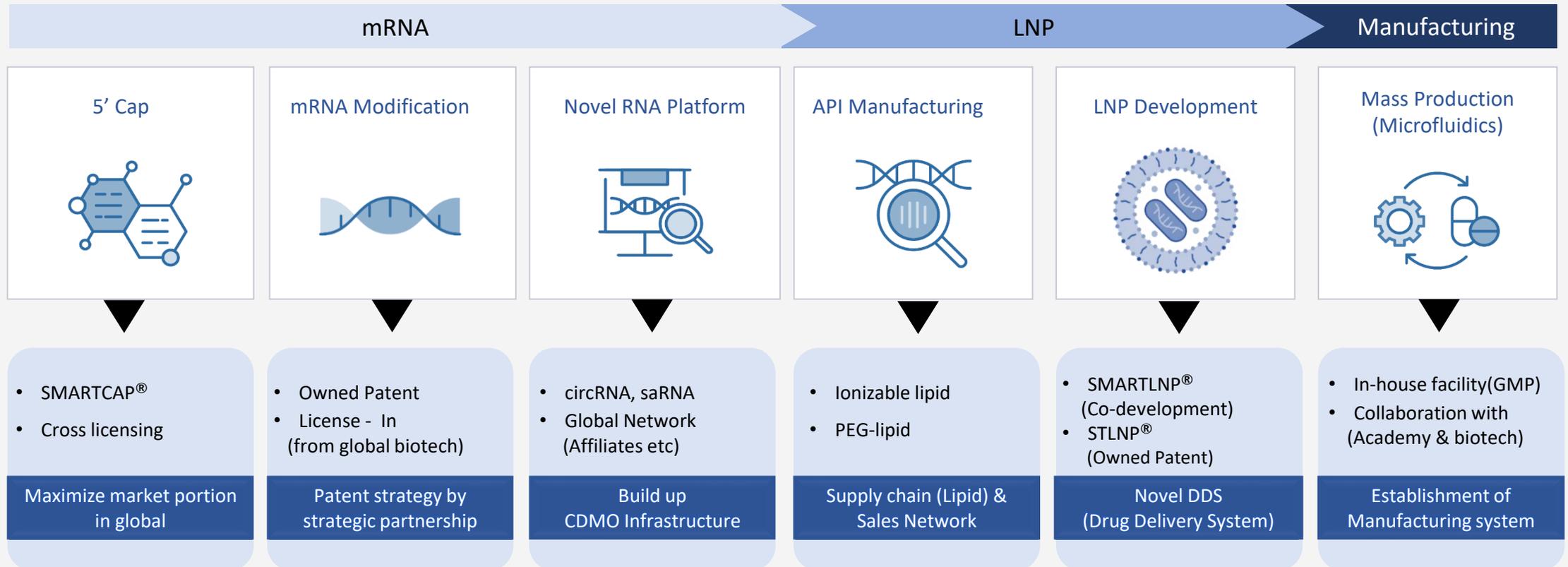
27 days/n batch

19 days/n batch (28% ▼)

period decrease due to continuous production, trained manpower



■ mRNA Business Strategy



Establishment of mRNA CDMO Infrastructure by Technology Internalization (DDS) & Raw material production (Lipid)



Core Technology

The only company have

1) 5'capping 2) LNP Platform Technology

ST PHARM's own patented Capping technology (SMARTCAP®)

ST PHARM's own patented LNP (STLNP™, SMARTLNP™)1



▶ SMARTCAP®

- Stabilizing synthetic technology of mRNA
- Patented in Korea / USA (on going)
- Diverse cap analogues (over 30 types)
- Cost - effectiveness

▶ CAP Library Screening System

- Customized cap analogues ▶ customized client service
- Higher gene expression ▶ flexibly able to control target gene

▶ STPHARM LNP Strategies

1. In-Licensing LNP

- Proven, unsurpassed technology (applied to Covid19 vaccine)

2. ST Pharm LNP (STLNP™)

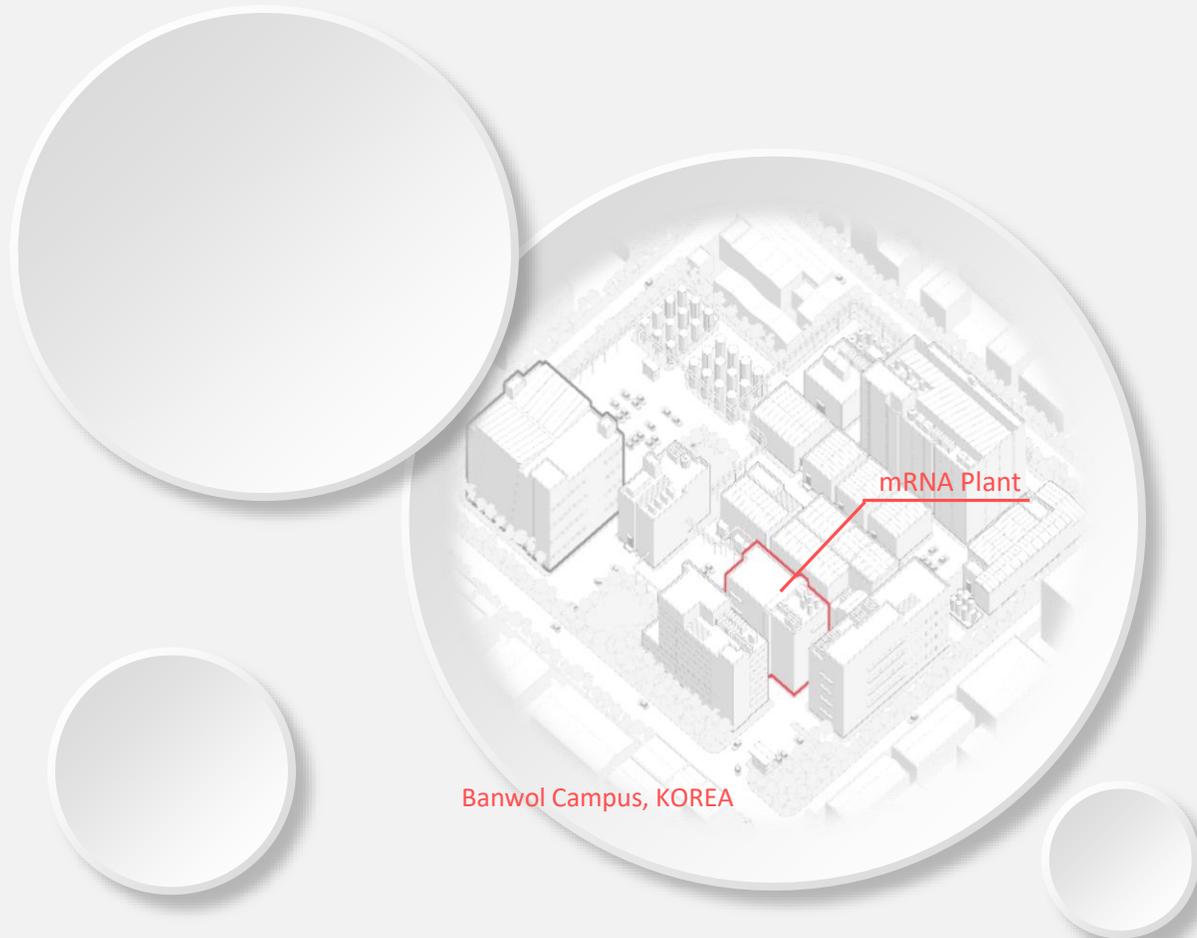
- ST PHARM's own patented LNP ('2020)
- Platform for mRNA CDMO

3. Next generation LNP (SMARTLNP™)

- Collaborations with E-HWA Women's Univ. in KOREA
- Improving stability and immune response



“From milligram to kilogram scale production”



➤ 1. R&D / Small scale production

mRNA plant ,1F (Banwol)
Completion: 2020.08
Capacity : gram / month (for pre-clinical)

➤ 2. Mid-scale production (GMP)

mRNA plant ,1F (Banwol)
Completion: 2021.05
Capacity: mg to multi-gram /month
1,000 mil. dose/year

➤ 3. Large / Commercial scale production (GMP)

mRNA plant, 3/5F (Banwol)
Capacity: 100-120g/month
3,500 mil.~0.1bil. dose/year

* Customized facility available as per client's request



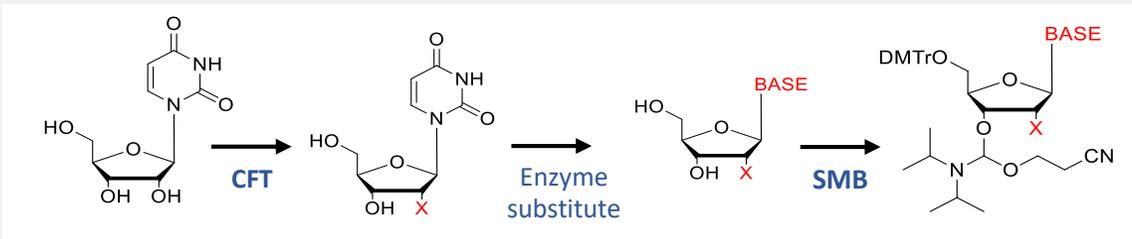
SmartCap®

- Own novel capping analogues with 30 types(competitor 3 types)
- Oct. '20, registered patent in Korea, processing the global patent(expecting 1H. 23)
- Data announcement at global conference in Nov. '22
- ▶ 12 months reliability data both solid and liquid phase

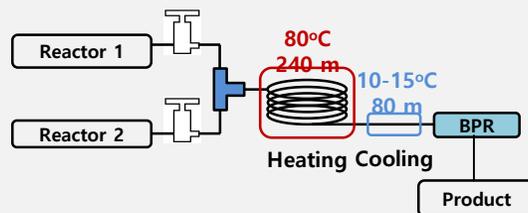
Capping Library Screening(CLS)

Optimized capping selection matched with target tissues or diseases

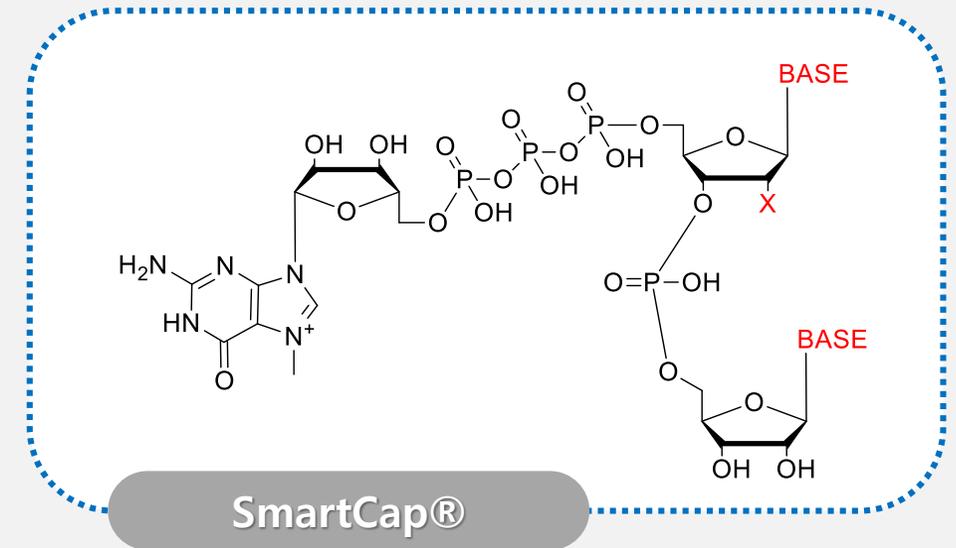
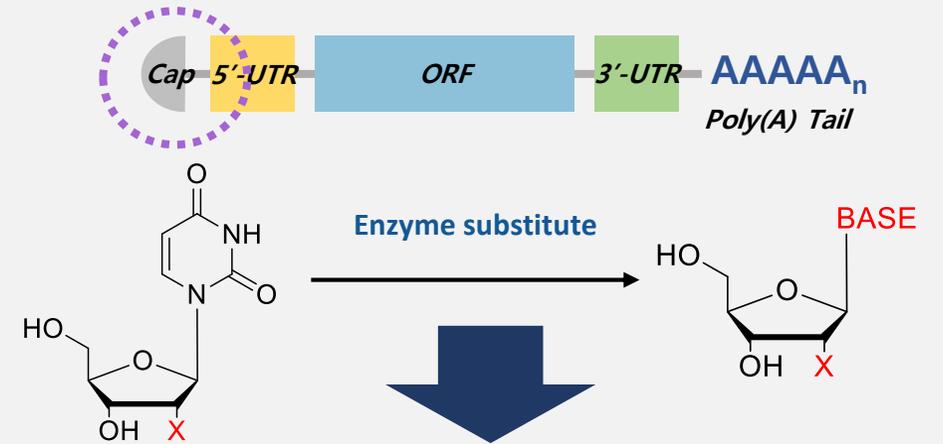
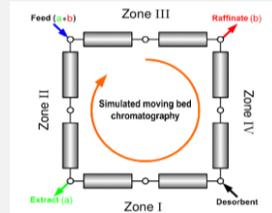
Mass production with innovation: kg size production per year



Continuous Flow Technology (CFT)



Simulated Moving Bed (SMB) Technology





▪ LNP platform

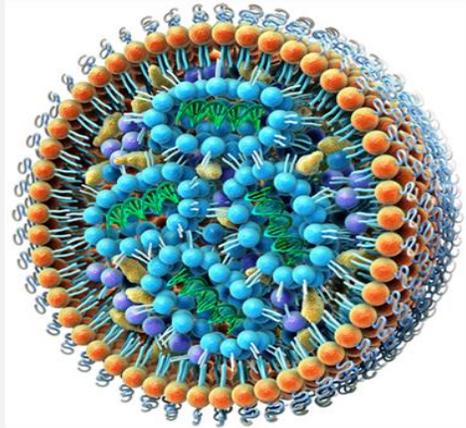


Image Source from Precision Nanosystems

In-licensing LNP

- Genevant LNP
- Only available to COVID-19 mRNA vaccine

STLNP®

- Own developed LNP
- for mRNA CDMO(neoantigen, autoantigen vaccine etc.)

SmartLNP®

- Next generation LNP
- 2 types candidates in pre-clinical stage(co-develop with EWHA university)
- More protein expression (33% EPO, erythropoietin expression increase)

▪ Lipid, GMP mass production capability

	BioNTech-Pfizer		Moderna	
Ionizable lipid	ALC-0315	More than 3 tons/year	SM-102	More than 3 tons/year
PEG, Polyethylene glycol	ALC-0159	More than 1 tons/year	PEG2000-DMG	More than 1 tons/year

[at Sihwa campus]



▪ Vernagen(Atlanta, USA)

mRNA based vaccine for infectious disease

Indication	partnership
Shingles virus	Emory university, US
RSV(respiratory syncytial virus)	
SFTSV(Severe Fever with Thrombocytopenia Syndrome)	ChonBuk university, Korea
Nipah Virus	Duke university, Singapore
Langya Virus	
Heartland Virus	CDC, US

[at discovery the candidates stage]

▪ Levatio(San-Diego, USA)

Gene/Cell therapeutics with mRNA, circRNA, CAR-NKT

	2021	2022	2023	2024
Platform		circRNA Platform development	Engineering & validation	
Autoantigen		Finding drug candidates	MOA/PoC	IND filing
Neoantigen		Finding drug candidates	MOA/PoC	IND filing
CAR-NKT		Finding drug candidates		MOA/PoC
CAR-NKT		Finding drug candidates		MOA/PoC

*MOA: Mechanism of Action, PoC: Proof of Concept]



In 2019, Acquired Global CRO company in Europe (Client-dependent CMO ⇒ Client-leading CDMO)
After completion of restructuring in 2020, achieved of turnaround.

▪ AnaPath Research (Barcelona, Spain)

- Established in 1986 (Envigo, Spain)
- AnaPath acquired in Nov. 2019
- Building, 10 thousands sqm, Land, 20 thousands sqm
- More than 800 animals (e.g. monkey, rabbit, dog)

▪ AnaPath Service (Basel, Switzerland)

- CSO : Klaus Weber (Specialized in histopathology)
- The biggest non-clinical CRO in Europe
- GLP Approval (In 2006), Joined EU Safety Alliance
- Up to 1000 experiments (chronic toxicity, carcinogen)



Project Mgmt



Sub-Contract



Thank You

ST PHARM

Technology-Driven Gene therapy CDMO
From Oligonucleotide to mRNA

