ST PHARM

# 에스티팜 mRNA Platform 연구개발 현황

2023. 03. 08

에스티팜

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:D
WE BELIEVE VISION 2025

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# Evolution of STP's mRNA Platform Technology

| Stage 1 | Stage 2 | Stage 3 |
|---|---|---|
| **Developing core mRNA technology and COVID-19 mRNA vaccine** | **Establishing mRNA GMP manufacturing and One-stop CDMO service** | **Preparing the emerging infectious disease and Expanding to the next round** |
| ▪ **Initiated mRNA platform in 2018**<br>▪ **5' Cap analog**<br>- SmartCap®<br>- Capping Library Screening (>30)<br>▪ **Lipid nanoparticle (LNP) DDS**<br>- SMARTLNP®, STLNP®<br>- Genevant LNP<br>▪ **In-house COVID-19 mRNA vaccine**<br>- STP2104: Ancestral strain vaccine<br>- STP2152: Omicron strain vaccine<br>- STP2250 & 2260: Pan-coronavirus vaccine | ▪ **mRNA GMP manufacturing facility**<br>- Completed mid-scale (May 2021)<br>- Large-scale under construction (1Q 2023)<br>▪ **GMP production of key raw materials**<br>- 5' Caps (kg/yr)<br>- Ionizable & PEG-lipids in LNP (MT/yr)<br>▪ **One-stop mRNA CDMO service**<br>- From R&D: Asset development<br>- To IND-enabling package: AMD, CMC, etc. | ▪ **Expedite-100 Days Strategy**<br>- Rapid development of mRNA vaccine against diverse infectious disease within 100 days<br>- Collaborations with Vernagen<br>▪ **Beyond COVID-19 pandemic world**<br>- Expanding to new indications (cancer, autoimmune disease)<br>- Planting new modality (circRNA, CAR-NKT)<br>- Collaborations with Levatio Therapeutics |

# 5’-Capping Technology: SmartCap

# SmartCap® and Capping Library Screening

## SmartCap® and Capping Library Screening

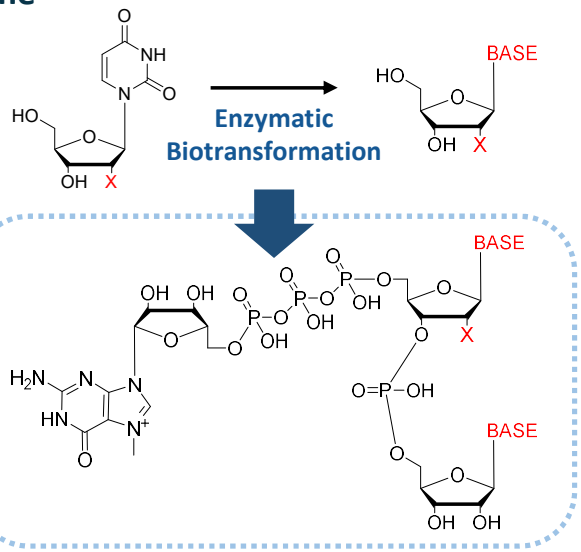
### SmartCap®

- Patented novel 5’-capping reagent
- Library of 30 different 5’-capping analogs
- Utilizing the know-hows & experience from oligonucleotide RSM synthesis
- **Updating stability data**
  - ✓ Both powder and solution form are stable at room temperature (>12 months)

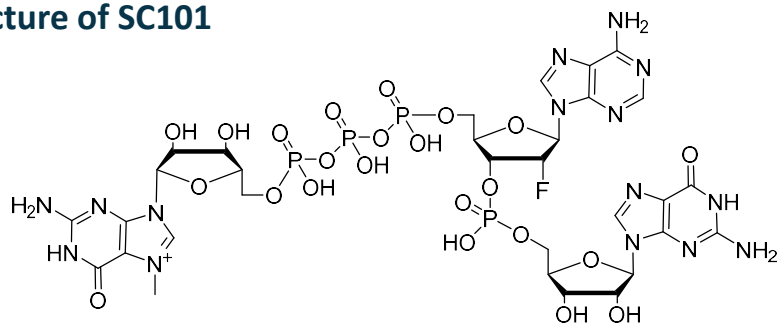
### Capping Library Screening (CLS)

- Screening capping library to identify the most suitable 5’-capping analog with highest efficiency
- **ORF and/or target-specific screening and selection**

➢ **General Scheme**



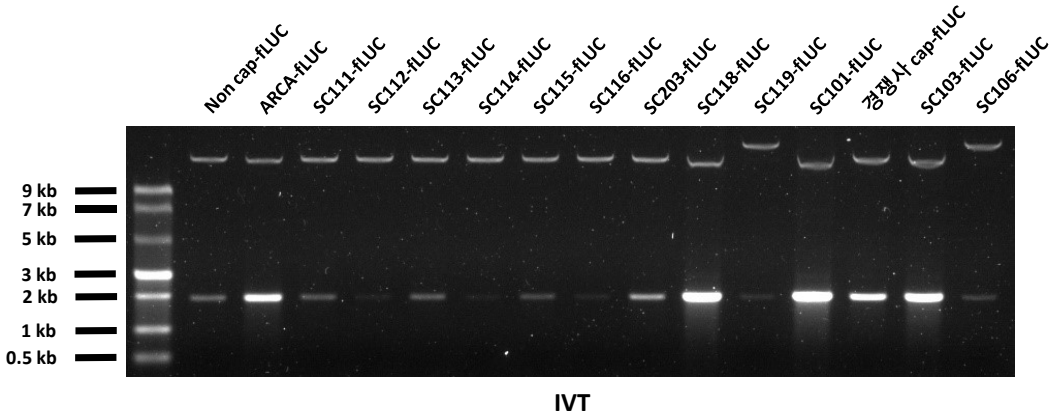

➢ **Structure of SC101**

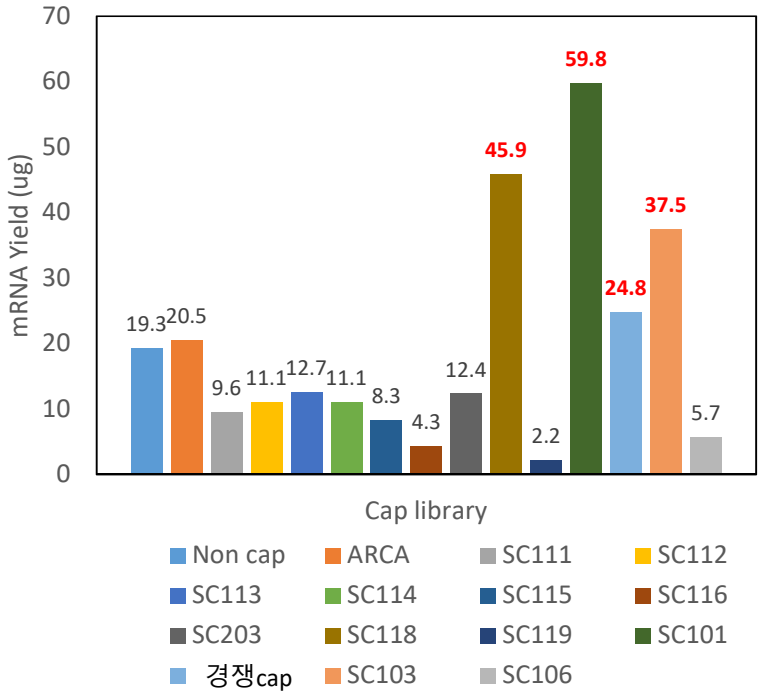


# SmartCap® and Capping Library Screening

**1. fLUC naked mRNA**

**- *in vitro* transcription**



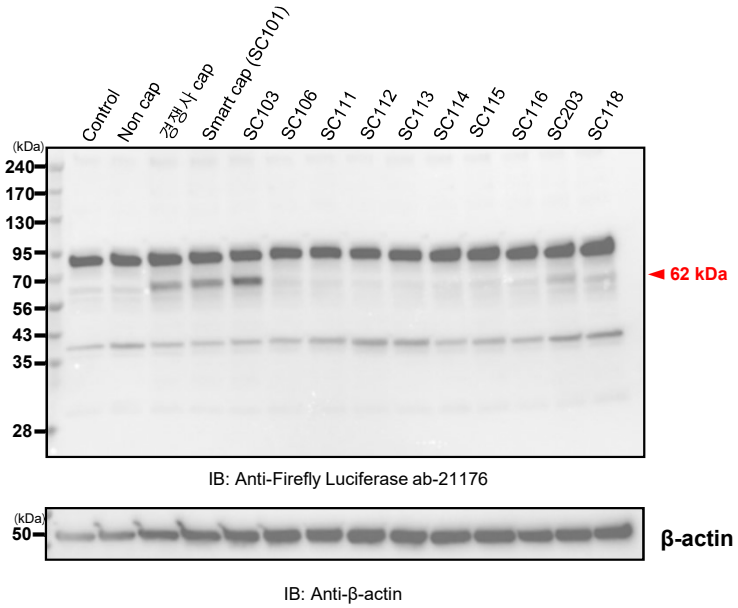




SC101 > SC118 > SC103 > C.C

# SmartCap® and Capping Library Screening

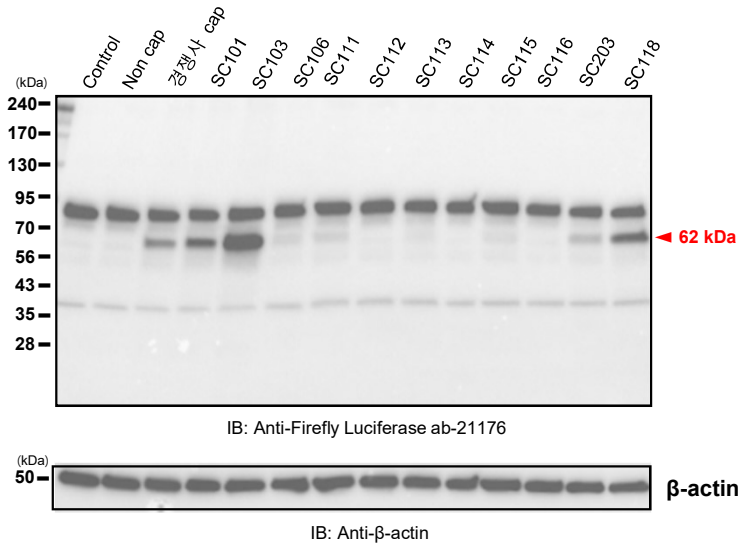
**1. fLUC Western Blot**

**- HEK293T cell**




SC101 > SC103 > C.C > SC203 > SC118

**- Huh7 cell**



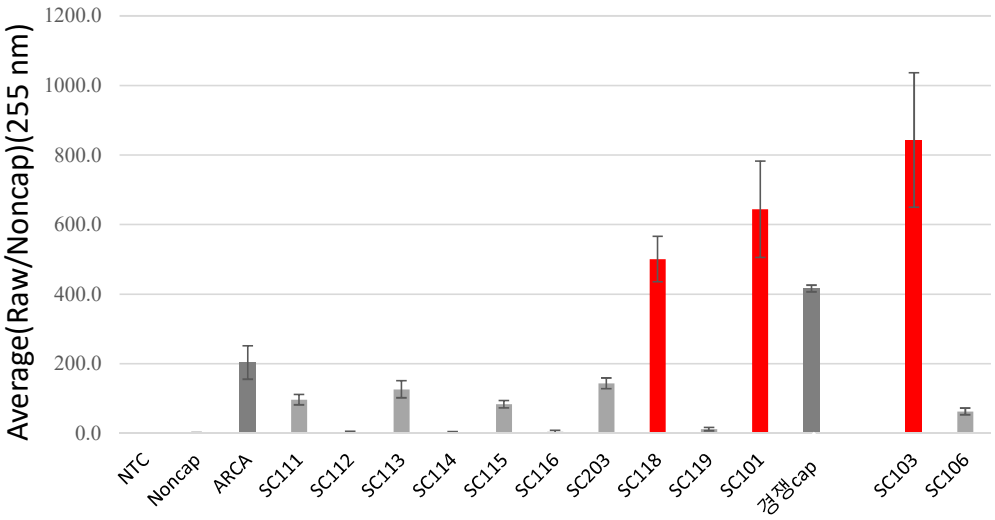

SC103 > SC118 > SC101 > C.C > SC203

# SmartCap® and Capping Library Screening

**1. fLUC Luciferase assay**

**- HEK293T cell**

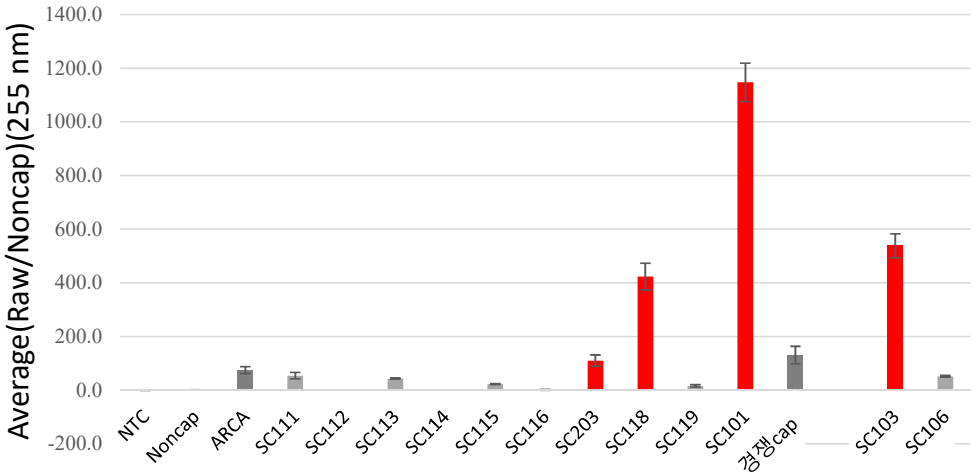
**Cap-analog: Luciferase assay**




SC103 > SC101 > SC118 > C.C

**- Huh7 cell**

**Cap-analog: Luciferase assay**
**1006- Huh-7 4*104 cell/well Transfection 24 hr**

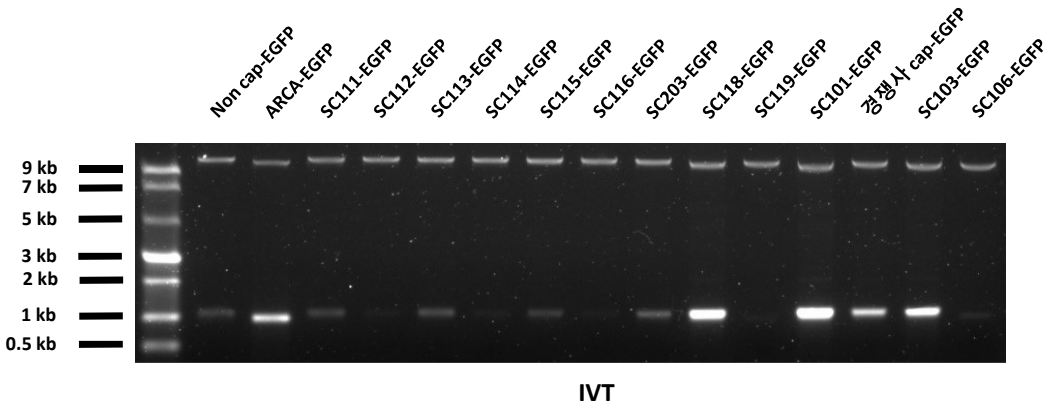


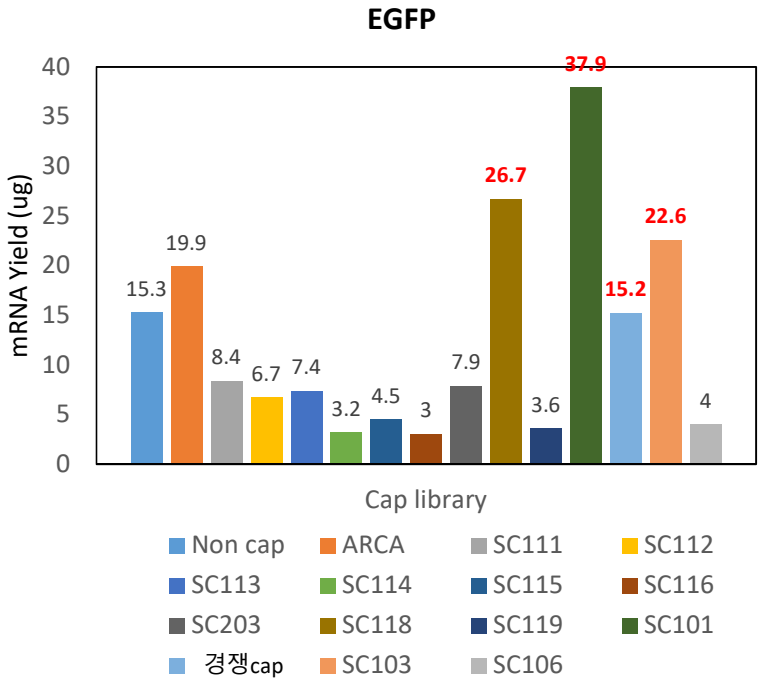

SC101 > SC103 > SC118 > C.C

# SmartCap® and Capping Library Screening

**2. eGFP naked mRNA**

**- *in vitro* transcription**



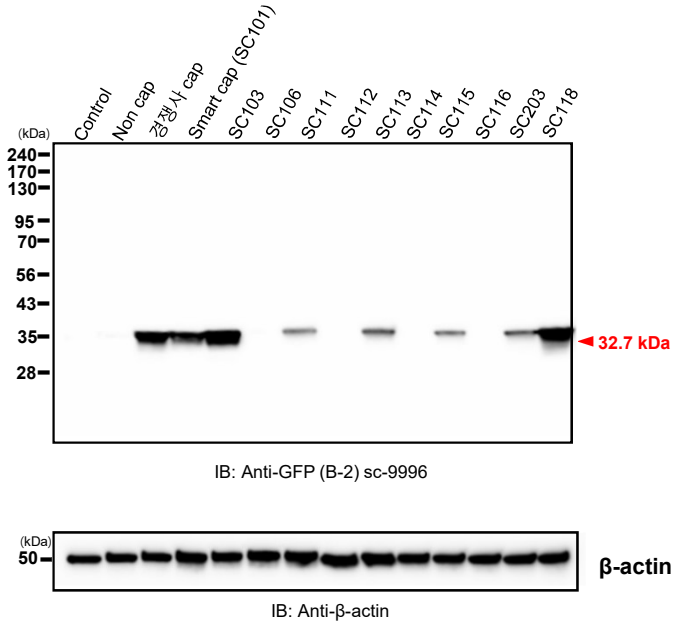




SC101 > SC118 > SC103 > C.C

# SmartCap® and Capping Library Screening

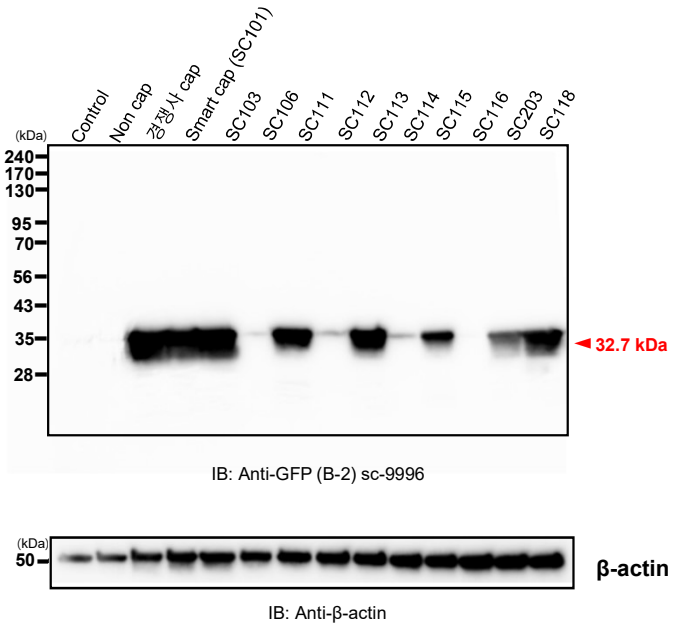
## 2. eGFP Western Blot

### - HEK293T cell




SC118 > SC103 > C.C > SC101 > SC203

### - Huh7 cell



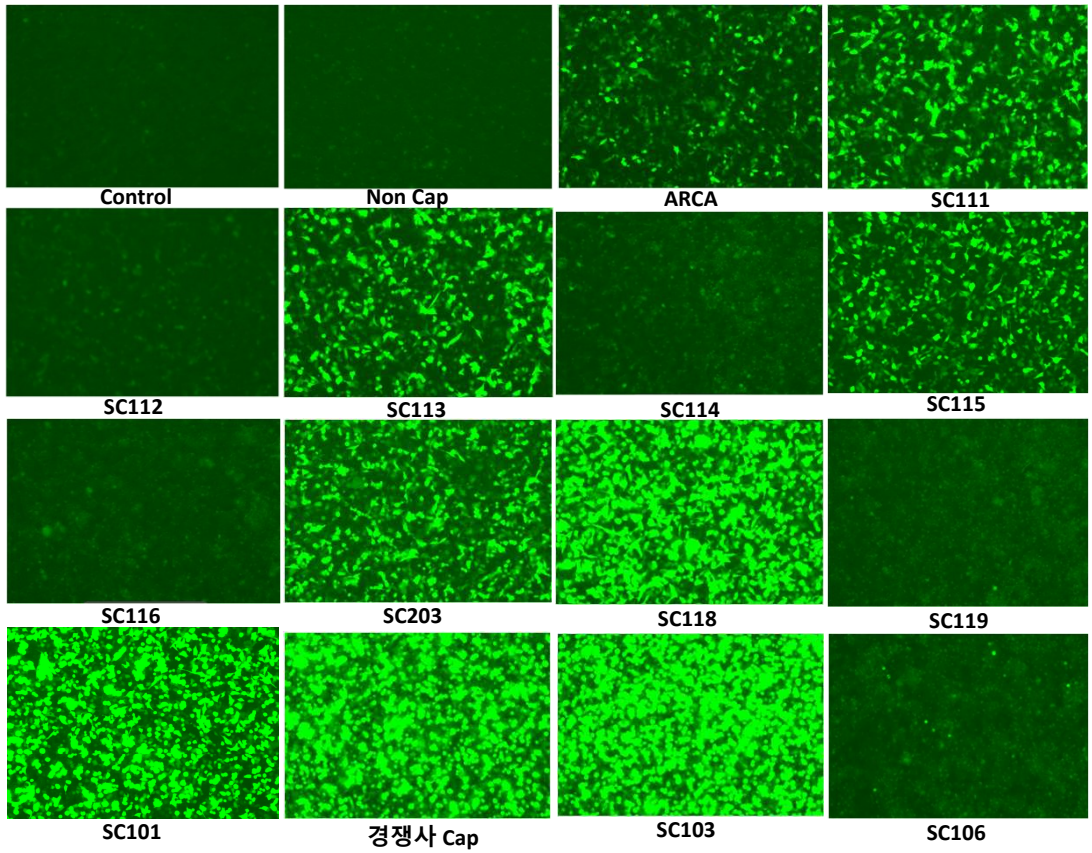

SC118 > C.C > SC101 > SC203 > SC103

# SmartCap® and Capping Library Screening

## 2. eGFP 형광현미경

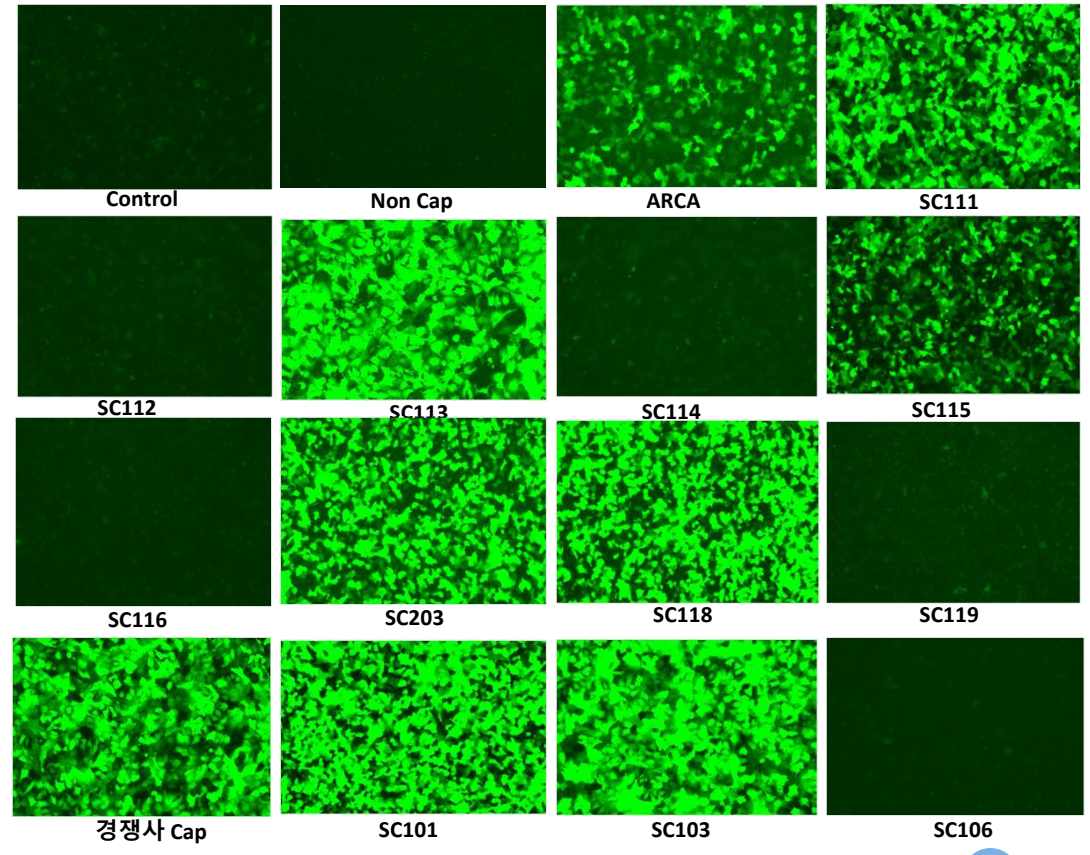
### - HEK293T cell

10X




### - Huh7 cell

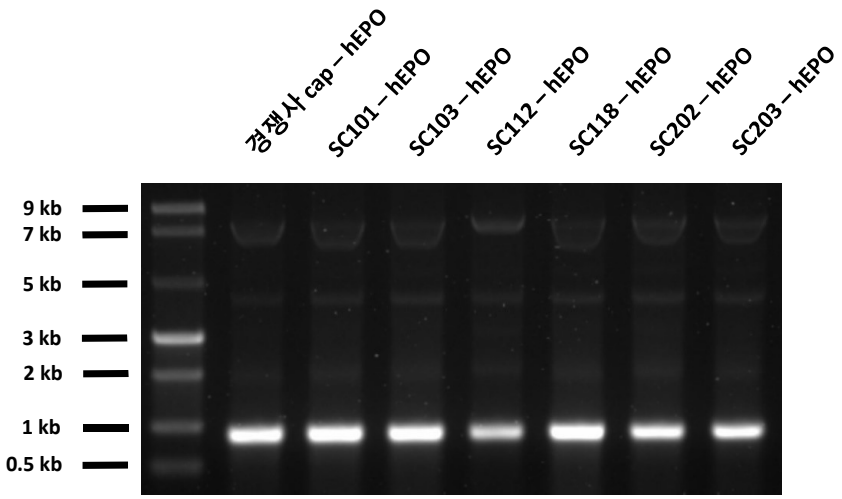
10X

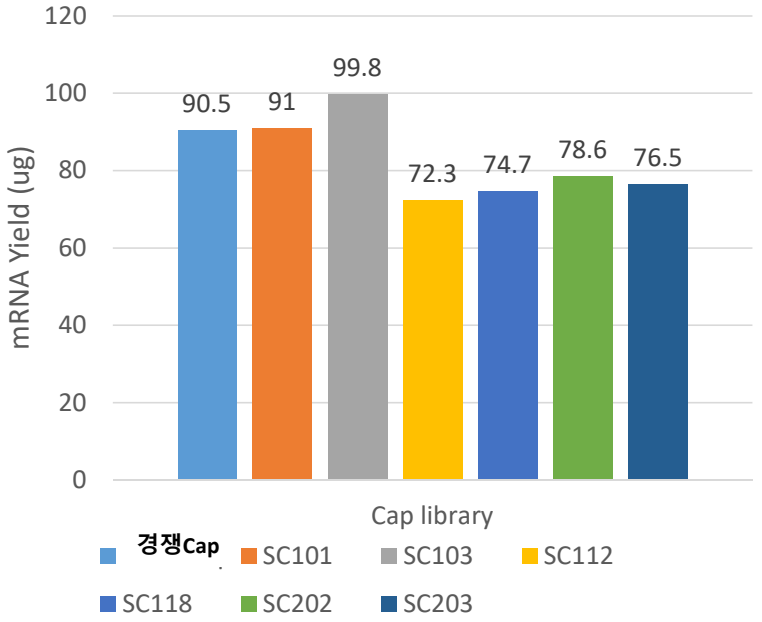


# SmartCap® and Capping Library Screening

**3. hEPO**

**- *in vitro* transcription**



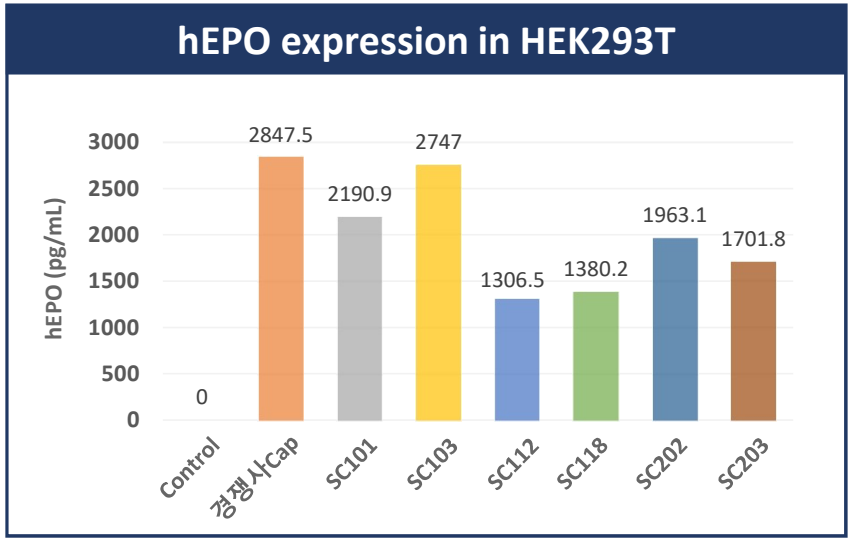



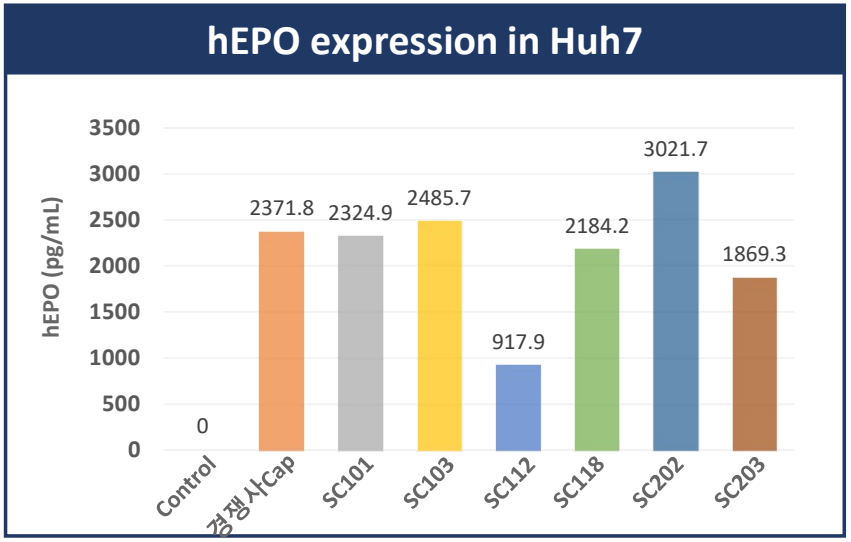

SC103 > SC101 > 경쟁사 cap > SC202

# Cell-dependent transfection efficiency

- SmartCap analogs and 경쟁사Cap were tested to observe in vitro hEPO transfection efficiency in two different cell lines
- Different protein expression levels observed from SmartCap analogs depending on the cell line (HEK293T/Huh7) and the payload
- In general, SC101 and SC103 showed comparable expression level to 경쟁사Cap, and SC118 and SC202 varied greatly depending on the cell line

**3. hEPO**



# Capping Libray Screening System : Summary

- **Trinucleotide SmartCAP Potecy**

| 1. fLUC | | | |
|---|---|---|---|
| **Cell line** | **IVT** | **Western blot** | **Luciferase assay** |
| **HEK293T** | SC101 > SC118 > SC103 > 경쟁사Cap | SC101 > SC103 > 경쟁사 Cap > SC203 > SC118 | SC103 > SC101 > SC118 > 경쟁사Cap |
| **Huh 7** | | SC103 > SC118 > SC101 > 경쟁사Cap > SC203 | SC101 > SC103 > SC118 > 경쟁사Cap |

| 2. eGFP | | |
|---|---|---|
| **Cell line** | **IVT** | **Western blot** |
| **HEK293T** | SC101 > SC118 > SC103 > 경쟁사Cap | SC118 > SC103 > 경쟁사Cap > SC101 > SC203 |
| **Huh 7** | | SC118 > 경쟁사Cap > SC101 > SC203 > SC103 |

| 3. hEPO | | | |
|---|---|---|---|
| **Cell line** | **IVT** | **ELISA** | **Reference** |
| **HEK293T** | SC103 > SC101 > 경쟁사Cap > SC202 | SC202 > SC203 > SC103 > SC101 = SC118 | SC202 > 경쟁사Cap > SC101 |
| **Huh 7** | | SC202 > SC103 > 경쟁사Cap > SC101 > SC118 | SC202 > SC101 > 경쟁사Cap |

❖ Coding sequence and/or cell-specific SmartCAP available by Capping Libray Screening System

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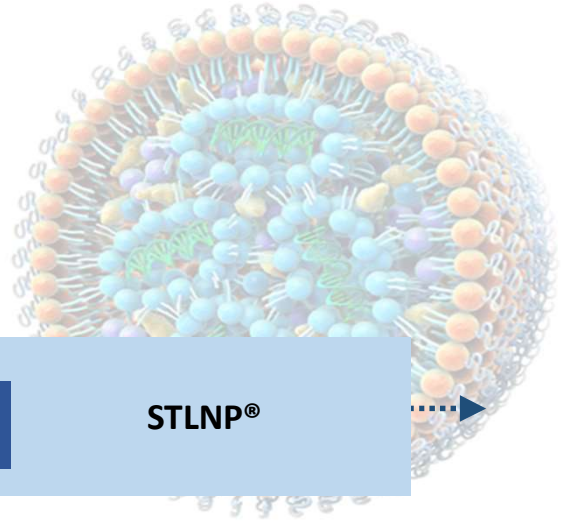
# LNP Technology

# ST PHARM's LNP technology – STLNP® & SmartLNP®

***From Conventional to Next Generation LNP***



## ✓ LNP development and application at ST PHARM

**1 In-licensed LNP Technology**

- Genevant LNP technology to expedite the development of COVID-19 mRNA vaccine
- **Proven, unsurpassed** and currently in clinical

**2 SmartLNP®**

- Developed in collaborations with academy in Korea
- With **novel ionizable lipid**, focused in improving potency and immune responses

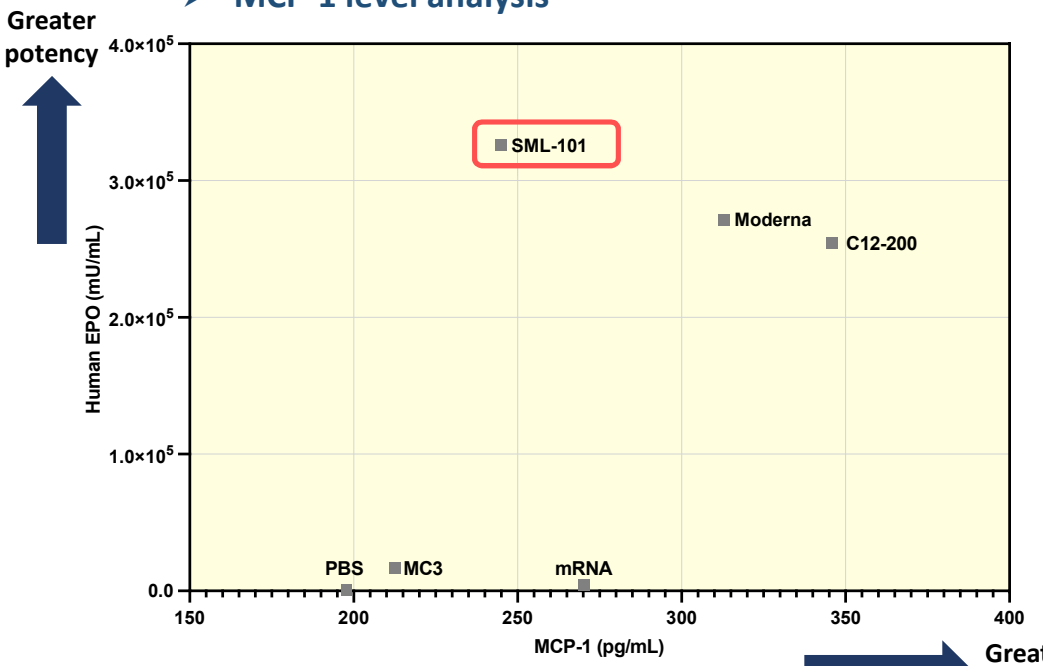
**3 STLNP®**

- Series of novel ionizable lipids for STLNP®
- To be applied for **mRNA CDMO**
- Further application to cancer and autoimmune disease vaccines is under evaluation

# Influence of ionizable lipid on LNP potency

- SmartLNP (SML-101) showed the greatest potency and lower immune stimulation compare to other LNP formulations, indicating the importance of ionizable lipids for formulation and its potency

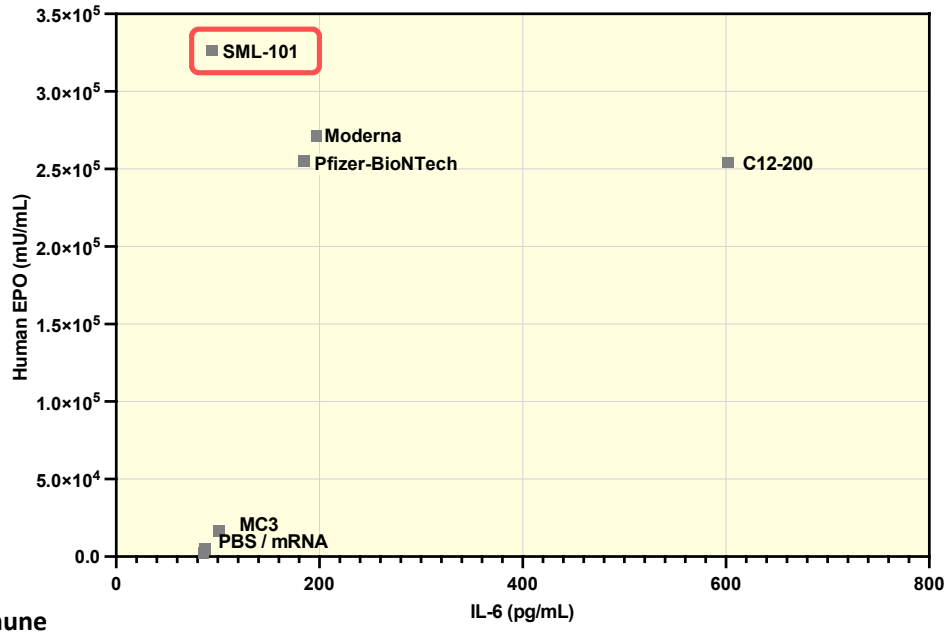
## ➢ MCP-1 level analysis




- hEPO @ 6h (0.5 mg/kg; Balb/C mice; IV injection )

Greater immune stimulation

## ➢ IL-6 level analysis

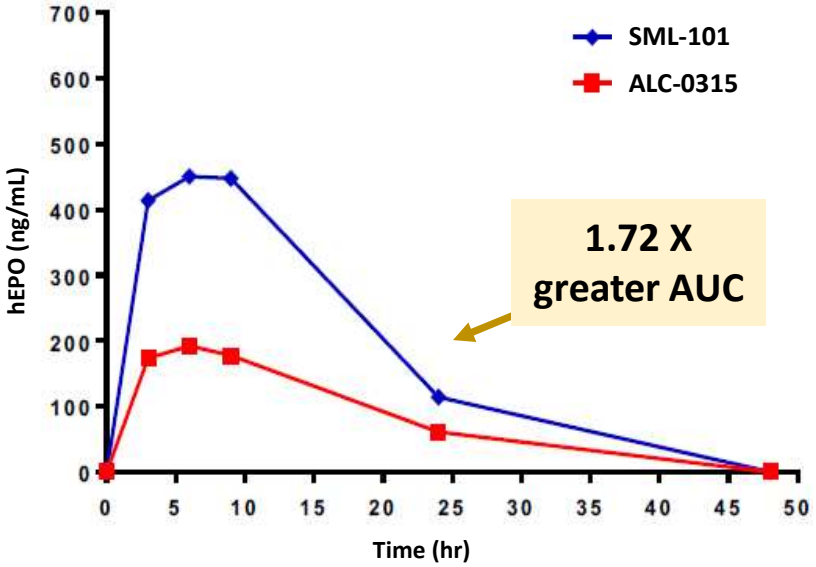



- hEPO @ 6h (0.5 mg/kg; Balb/C mice; IV injection )

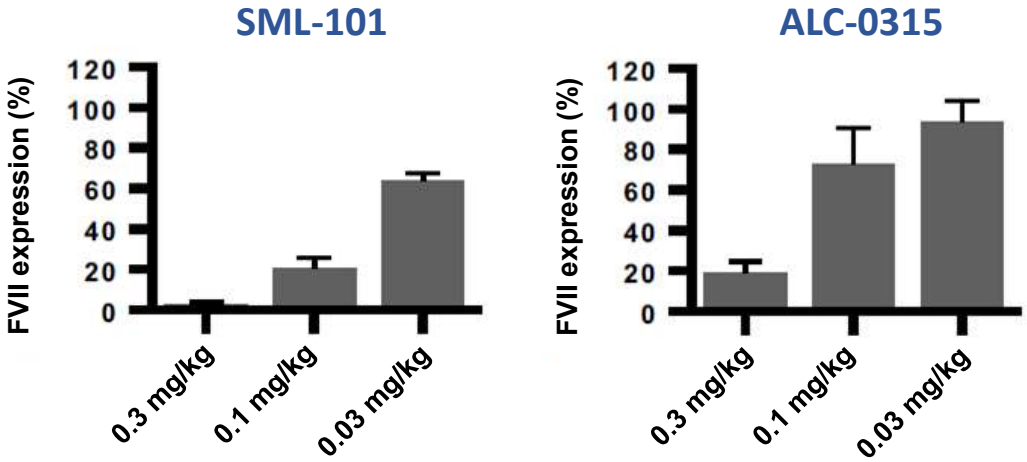
# *In vivo* transfection efficacy of SML-101

- *In* vivo expression level of hEPO **mRNA** encapsulated in SML-101 showed 1.72 times higher AUC than Pfizer-BioNTech LNP (ALC-0315) in blood for 48 hours after IV injection (0.1 mg/kg)
- *In vivo* delivery of **target-specific siRNA** encapsulated in SML-101 and ALC-0315 LNP confirmed through FVII knock-down efficiency study, and SML-101 had greater inhibition effect than ALC-0315 at all dose levels

## ➢ *In vivo* delivery of hEPO mRNA



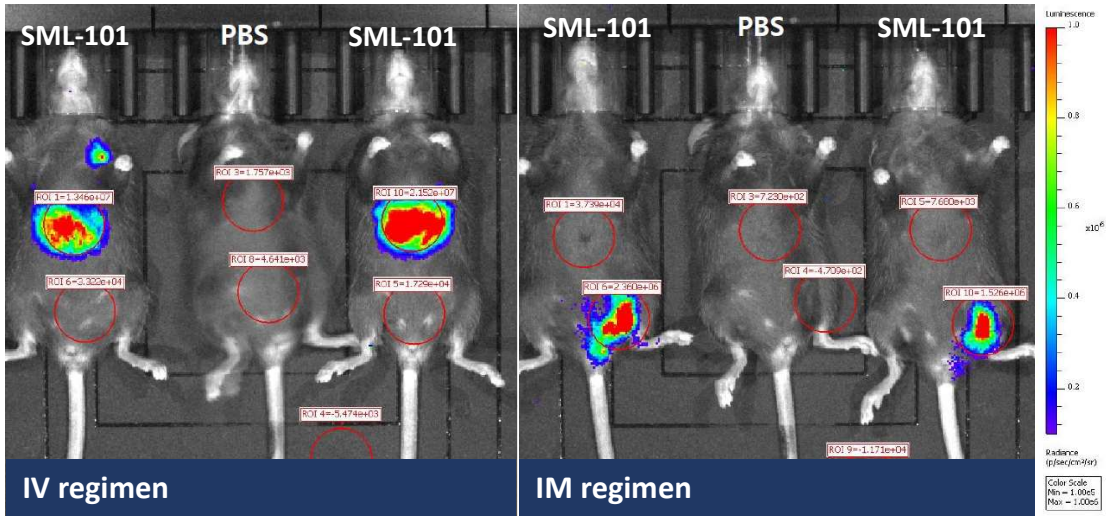

## ➢ *In vivo* delivery of target-specific siRNA



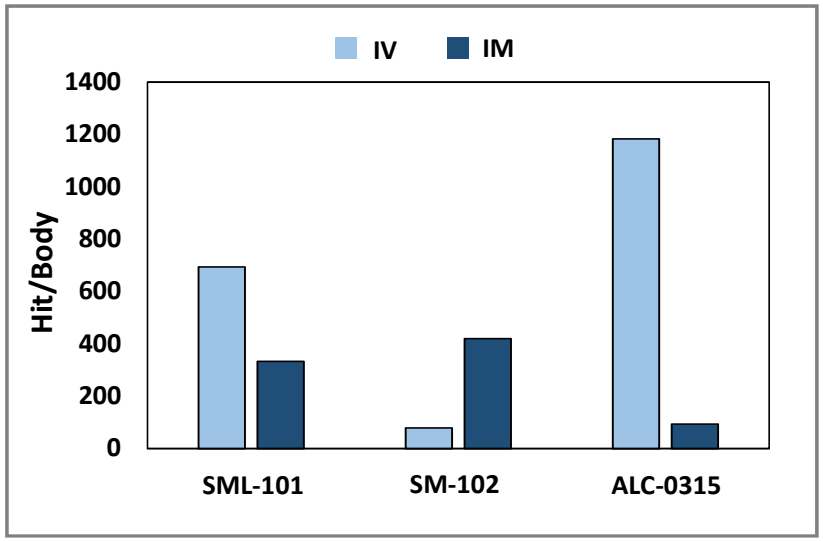
# *In vivo* biodistribution of SML-101 – IV & IM

- Both IV and IM injection of LNP formulated with SML-101 showed a good biodistribution data
- **IV injection fLuc expression profile:** ALC-0315 > **SML-101** > SM-102 (Moderna)
- **IM injection fLuc expression profile:** SM-102 ≥ **SML-101** > ALC-0315

## ➢ SML-101 fLuc expression profile – IV/IM injection

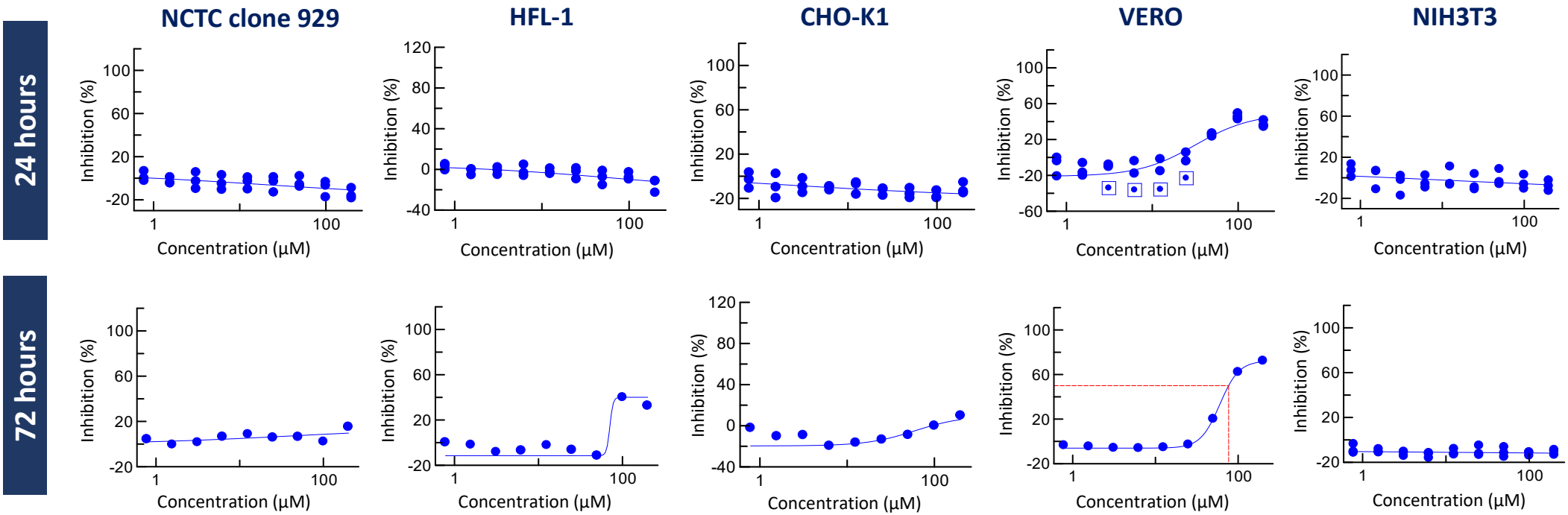



## ➢ Comparison data of fLuc expression profile



# Toxicity of LNP (1): Cytotoxicity of STP1244

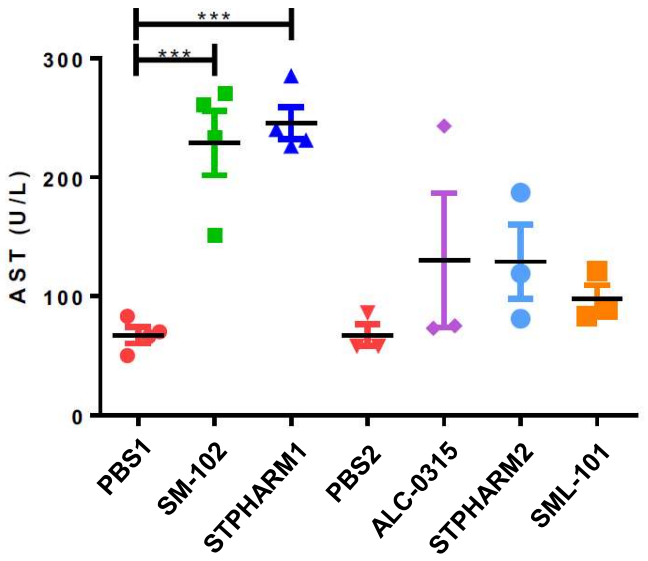
- Cytotoxicity of ionizable lipid (STP1244) used in SML-101 LNP formulation was evaluated, and overall it showed high $IC_{50}$ profile meaning that it shows low cell viability
- Cytotoxicity of STP1244 was measured by treating the cell lines for 24/72 hrs and its $IC_{50}$ values were >200, except in VERO cell at 72 hrs (76.72)



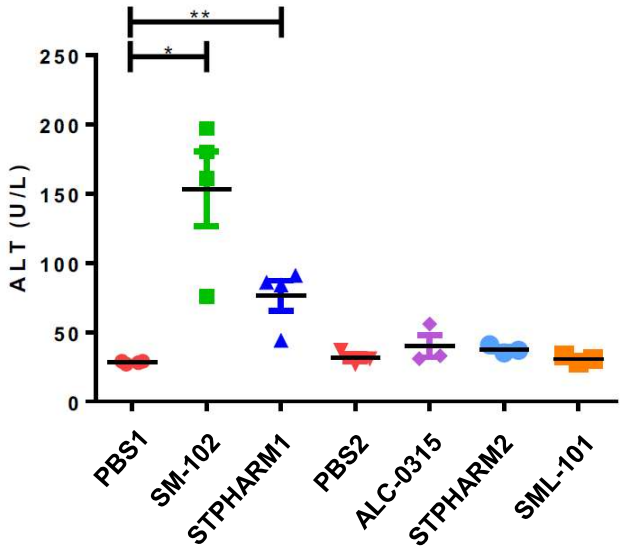
# Toxicity of LNP (2): Hepatotoxicity of SML-101

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured after 24 hours IV injection of fLuc mRNA encapsulated in SML-101 at 2.0 mg/kg dose into C57BL/6 mice
- SML-101 showed comparable AST & ALT level with

➢ **AST comparison study**




➢ **ALT comparison study**

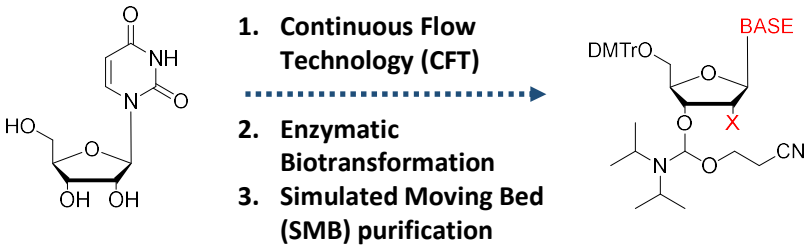


# Manufacturing Capacity

# Mass production capability of RSM

## SmartCap® and raw materials of capping reagent

- Incorporating **oligonucleotide CFT and SMB technology** for mass production of 5'-capping
- Mass production of **diverse capping reagents**, including SmartCap, BioNTech-Pfizer and Moderna's capping reagent, is available from key raw materials **(> multi-kg/year)**
- Both **non-GMP and GMP-grade** intermediate and product available




## Ionizable/PEG lipids in LNP

- Production under tightly **controlled GMP-like or GMP condition**
- Raw materials are supplied by strategic domestic partners that are reliable, qualified and cost-effective
- ST PHARM is manufacturing both **ionizable and PEG-lipids**, required for LNP formulation
- **Current capacity**

| LNP Components | Production Capacity |
|---|---|
| **Ionizable lipids** | > 3MT/year |
| **PEG lipids** | > 1MT/year |

***Production of key lipids will be available upon client's request***

# ST PHARM mRNA plant capacity

- Mid-scale to commercial-scale production operates in GMP condition, meeting FDA GMP guidance
- **Facility area:** Total 9,237 $ft^2$

| Production Scale | Naked mRNA | LNP-encapsulated mRNA |
|---|---|---|
| **R&D** | Up to non-clinical animal study | |
| **Mid-scale** | 291 g/year (1.2 g/batch) | 182 g/year (1 g/batch) |
| **Commercial-scale** *single-use for LNP | 2,912 g/year (12 g/batch) | 1,456 g/year (10 g/batch) |

** Customized or dedicated facility available as per client's request*


## ➢ Milestone and Timeline

**2020**

**August** — Completion of R&D and small-scale

**2021**

**May** — Completion of mid-scale facility

**2022**

**February** — GMP certified by MFDS

**2023**

**March** — Completion of commercial-scale facility (EXPECTED)

# ST PHARM' Role in Global Vaccine Hub

***ST PHARM provides seamless GMP manufacturing service from LNP-encapsulated mRNA to key materials of caps & lipids in LNP***

## *mRNA Vaccine Manufacturing*

- Technology-transfer is **NOT** necessary
- Only permission of mRNA vaccine production needed from Moderna or Pfizer
- Available expanded territory to global markets upon clients' or CEPI's request

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## *Capping Reagent & Lipids in LNP Production*

- Technology-transfer is **NOT** necessary
- **[5'-Cap]** Mass production of key intermediates in both non- and GMP-grade key intermediates (>multi-kg/year)
- **[LNP lipids]** Mass production of two essential lipids in both non- and GMP-grade (ionizable >3 MT/yr; PEG-lipid >1 MT/yr)

# Acknowledgements


## *Special thanks to*

- Genevant
- Korea of Health and welfare, KDCA
- Korea Drug Development Fund (KDDF)
- KPBMA
- Dong A ST
- GC and Mogam
- Hanmi
- Ajou University
- Ewha Women University
- Sogang University
- Catholic University of Korea
- Korea University
- Chungbuk University

## *ST PHARM family members*











감사합니다
Natick
Dankon
Taing
Grazie
Danke
Ευχαριστώ
Dalu
唔該
Obrigado
شكرا
Thank You
köszönöm
Takk
Tack
Спасибо
Dank
Gracias
धन्यवाद
Tak
谢谢
Merci
ありがとう
Toda
Дякую
Tesekkür ederim
khop kun
Asante
Gratias
Shokran
cám ơn