GenScript PROBIO

# Accelerating Vaccine development against COVID-19

## GenScript ProBio Plasmid Platform

Confidential and Privileged

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# Therapies in development against COVID-19

## Three main groups of therapies

**Vaccine**
*(for prevention)*

Training the immune system to recognize and combat pathogens by introducing antigens into the body to trigger an immune response for prevention.

**Antibody**
*(for treatment)*

Passive immunity by blocking parts of the surface of a virion to render its attack ineffective.

**Antiviral agent**
*(for treatment)*

Block the viruses from entering the cell or inhibit the replication of viruses in cells.

## Subtypes of vaccine:

### 1 Nucleic acid vaccine (Novel)

Administration of nucleic acid vaccines results in the endogenous generation of viral proteins that mimic antigen produced during natural viral infection.

moderna BIONTECH inovio CUREVAC

### 2 Subunit vaccine (conventional)

Presents an antigen to the immune system without viral particles, using a specific, isolated protein of the pathogen, and to stimulate long-lasting protective/therapeutic immune responses.

CanSinoBIO gsk

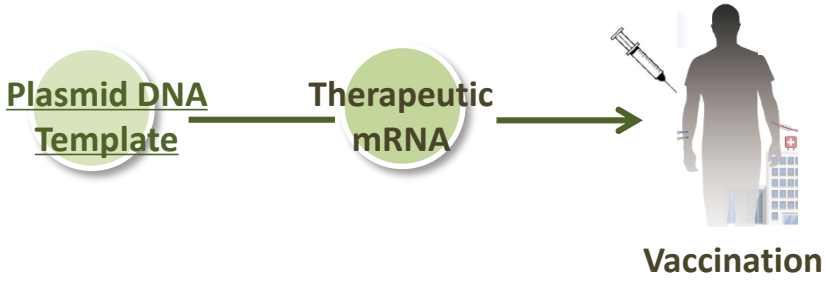
### 3 Whole virus vaccine (conventional)

Uses the entire virus particle, fully destroyed, and can be recognized by the immune system and evoke an adaptive immune response.

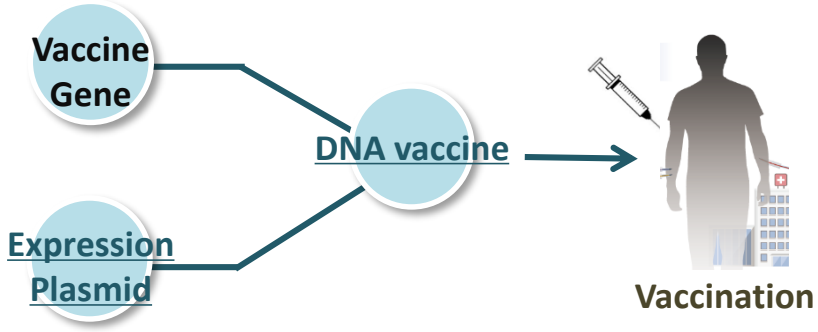
*Source: WHO*

# Plasmid in DNA Vaccine and mRNA Vaccine

## mRNA Vaccine




## DNA Vaccine




## *GenScript ProBio supporting plasmid for vaccines*

| Development Cycle | 1 Pilot Production | 2 IND | 3 Early stage Clinical trials | Late stage Clinical trials | 4 Commercialization |
|---|---|---|---|---|---|
| GenScript ProBio's Offerings | • ProPlasmid | • Plasmid CMC | • GMPro Plasmid | • GMP plasmid | |

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# Plasmid Platform at GenScript ProBio

| Development Cycle | 1 Pilot Production | 2 IND | 3 Early stage Clinical trials | Late stage Clinical trials | 4 Commercialization |
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## Various levels of plasmid available

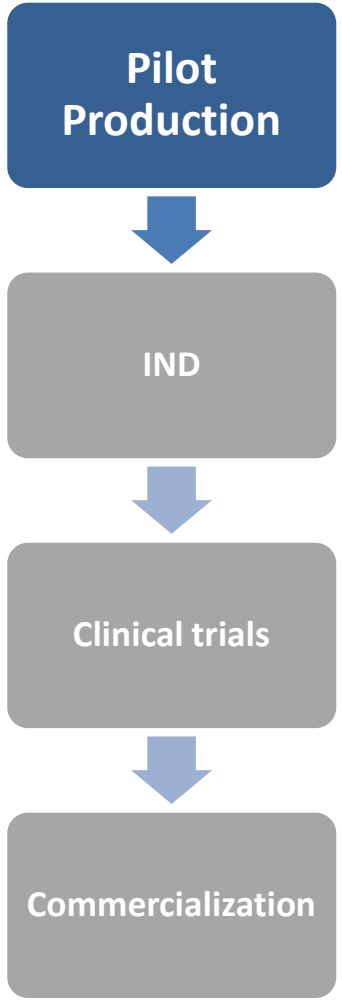
1. Plasmid as raw materials
2. Plasmid as DS/DP

## Plasmid Applications

- For production of viral vectors: AAV, Lentivirus, Adenovirus, HSV, Retrovirus
- **For production of mRNA vaccine: IVT-mRNA**

- Complexed Plasmid DNA;
- Minicricle plasmid DNA;
- **DNA vaccine**

# Non-clinical Stage： ProPlasmid Manufacturing



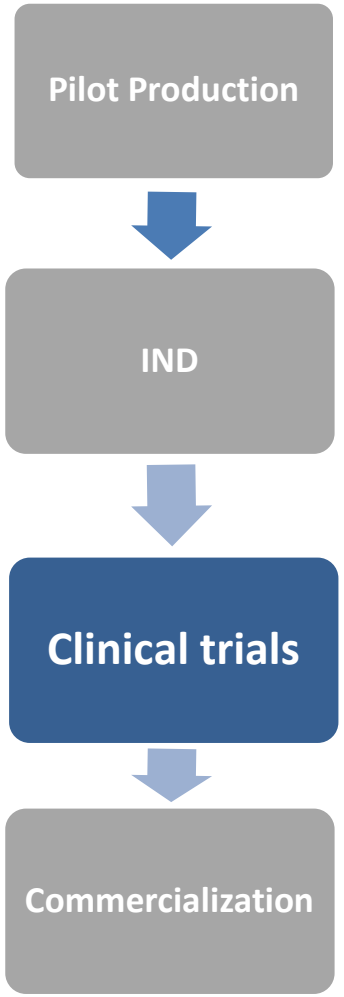

■ Non-clinical stage

| Service | Quantity | Deliverables |
|---|---|---|
| ProPlasmid | 1 mg<br>20 mg<br>100 mg<br>0.5 g<br>1 g<br>5 g | 1. Plasmid<br>2. CoA |
| *Non-clinical stage with critical QA control* | | |

**GenScript Advantages:**

- ✓ **Highest QA control** in non-clinical stage
- ✓ **Detailed records and documents** ensure traceability
- ✓ **Animal free, antibiotic free**, reduce the harm to animal and human body.
- ✓ High Density Fermentation → High Yield： **600—800 mg/L.**

# Early Stage Clinical: GMPro Plasmid Manufacturing

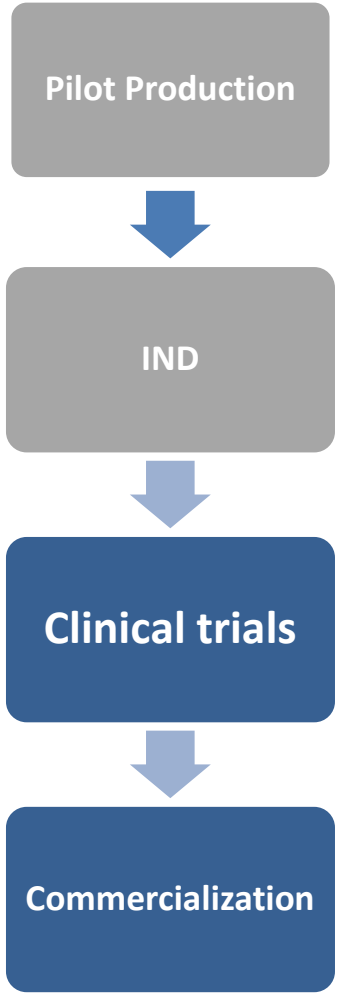



## Early Stage Clinical

| Service | Quantity | Deliverables |
|---|---|---|
| GMPro plasmid | 1 mg<br>5mg<br>10mg<br>50mg<br>100 mg<br>0.5 g<br>1 g<br>2 g<br>5 g | 1. COA<br>2. Plasmid<br>3. TSE/BSE statement<br>4. Mfg. summary report |
| ***Applicable for plasmid manufacturing in clinical phase I with full QA control*** | | |

- ✓ **Animal free, antibiotic free**, reduce the harm to animal and human body.
- ✓ High Density Fermentation → High Yield： **600—800 mg/L.**
- ✓ Manufacturing process compliant to GMP, **full record** guarantee traceability.

# Clinical and Commercial: GMP Plasmid Manufacturing




■ Clinical and commercial supply

| | |
|---|---|
| **Facility** | GMP facility in US |
| **Manufacturing** | Starting from WCB |
| | High density fermentation |
| | Multiple-step purification |
| **QC** | 11 assays |
| **QA** | Full QA |
| **Application** | Clinical phase and commercial supply |

**Experience in manufacturing**

Accumulated experience in manufacturing pDNA as DS and DP for late-phase clinical trials

**Regulatory Applications**

- 17 INDs Filed
- 4 Master Files
- Orphan (#4), Fast Track (#2), QIDP[4)] (#1)

**GMP Inspections**

- CaFDB[1)] for commercial-scale
- Vaccine Research Center (VRC, NIH)
- DAIDS, NIH
- IPPOX & P5 (Gates Foundation)
- Sanofi[3)]
- Astellas[3)]

Note: 1) CaFDB: California Food and Drug Branch; 2) VRC: Vaccine Research Center; 3) including QP inspection for EU; 4) QIDP: Qualified Infectious Disease Product.

# Advantages in GMP Plasmid Manufacturing

1. **Accumulated experience in manufacturing pDNA as DS and DP for late-phase clinical trials**

2. **Extensive knowledge and expertise in fermentation and purification processes**

3. **Guaranteed GMP quality via expertise and best practices acquired from Vical**

4. **Active investment for reinforcing in-house capabilities and ensuring cutting-edge systems**

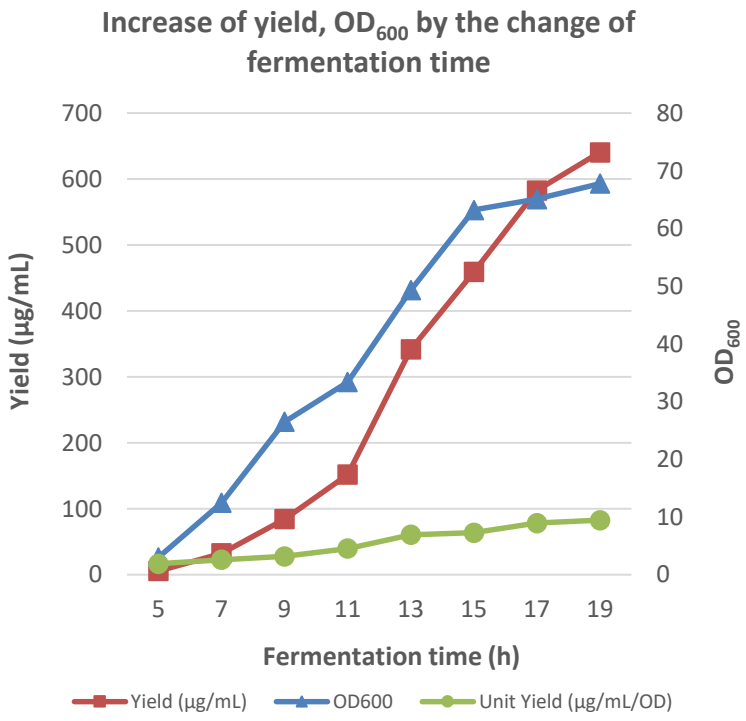
| Experience in manufacturing DNA Vaccines* | Regulatory Applications* | GMP Inspections* |
|---|---|---|
| • CMV vaccine for transplant recipients<br>• CMV vaccine as a prophylaxis<br>• H5N1 pandemic influenza<br>• H1N1 pandemic influenza<br>• Anthrax (prophylaxis)<br>• HSV-2 (therapeutic) | • 17 INDs Filed<br>• 4 Master Files<br>• Orphan (#4), Fast Track (#2), QIDP[4)] (#1) | • CaFDB[1)] for commercial-scale<br>• Vaccine Research Center (VRC, NIH)<br>• DAIDS, NIH<br>• IPPOX & P5 (Gates Foundation)<br>• Sanofi[3)]<br>• Astellas[3)] |

Note: 1) CaFDB: California Food and Drug Branch; 2) VRC: Vaccine Research Center; 3) including QP inspection for EU; 4) QIDP: Qualified Infectious Disease Product

*** Experiences in manufacturing, regulatory applications and GMP inspections are based on Vical's experts, who are now employed by Genopis. Genopis acquired Vical's key professionals as well as manufacturing assets and supporting utilities in July 2018.**

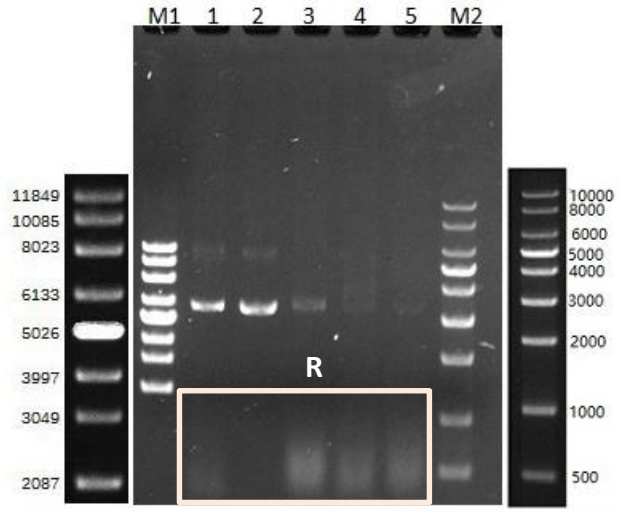
# Case Studies – Plasmid Manufacturing Process

## Fermentation Process




✓ High density fermentation ✓ High yield

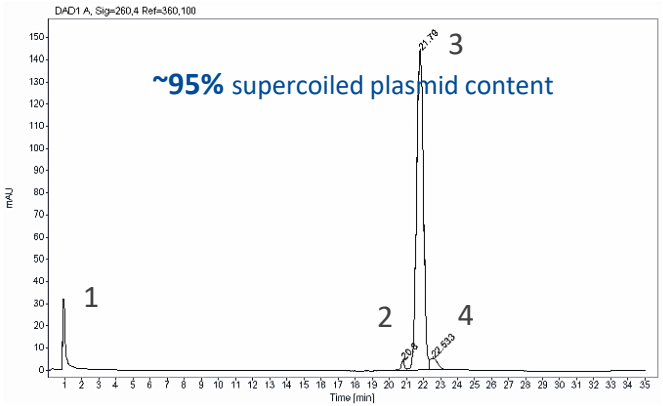
## Purification Process




**Agarose gel electrophoresis (AGE): obvious decrease of RNA content through 1st purification step.**

M1: Supercoiled DNA Ladder Marker
M2: 1 kb DNA Ladder Marker
1: Lysate
2: Sample after 1st step
3: Waste of salt elution
4: Waste of salt elution
5: Waste of water elution
R: RNA bands

## QC Release




| Sample | Time | Area (%) |
|---|---|---|
| OC-Plasmid | 20.800 | 1.62 |
| SC-Plasmid | 21.790 | 94.07 |
| dimer-Plasmid | 22.533 | 4.31 |

**HPCL: After the 2nd purification step, the content of supercoiled plasmid has already reached 95%**

1: Solvent; 2: Open circular plasmid;
3: Supercoiled plasmid; 4: Dimer plasmid

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- mRNA vaccine against COVID-19
- GenScript ProBio Plasmid Platform
- **Excellent Partner for Vaccines**

# Facility Construction Plan for Consistent Support: from Early Research to Commercial



| | 2020 | 2021 | 2022 | 2023 |
|---|---|---|---|---|
| FACILITY | Plasmid Process Development Facility | GMP Virus Facility | **GMP Plasmid Facility In US** | GMP Plasmid Facility | GMP Facility (Clinical and Commercial mfg. Center) |
| APPLICATION | Preclinical plasmid preparation<br>Plasmid process development<br>Plasmid for early clinical phase | Preclinical virus preparation<br>Virus process development<br>Virus for early clinical phase | GMP plasmid manufacturing for clinical and commercial supply | Capacity expansion<br>Plasmid for early clinical phase | Plasmid and virus manufacturing for late clinical phase and Commercial use |

# Global Partnerships and Solid Track Record

## ~60 Plasmid & Virus CMC & Clinical GMP Projects

- Over **10** P&V CMC projects
- Over **30** plasmid mfg. batches
- Over **20** lentivirus mfg. batches
- Plasmid CMC and mfg. for **4** mRNA vaccine

## Key Accounts:

- Provide plasmid and lentiviral vector for **>30** big pharma and leading biotech

Kite A GILEAD Company · PTC THERAPEUTICS · 주식회사 유틸렉스 · LifeSc 香雪生命科学

- Provide plasmid for 3 leading vaccine company

VBI VACCINES · StemRNA · ABOGEN

## Milestones: from IND to GMP mfg., from China to globe, from NMPA to FDA, from drug product to vaccine

**2002-2017**

- 1st plasmid process development facility in CN

**2017-2018**

- 1st plasmid **IND** for **CAR-T** got approval from **NMPA**

**2019-2020**

- 1st P&LVV **IND** for **TCR-T** got approval from **NMPA**
- 1st P&LVV **IND** for **TCR-T** got approval from **FDA**
- 1st P&LVV mfg. for **clinical use** for **TCR-T**
- 1st Plasmid **CMC** for **mRNA Vaccine** got approval from NMPA
- 1st P&V CMC project from **Korea**
- >20 P&LVV mfg. for **US** customer

# Successful Collaborations in Various Projects

## XLifeSc TCRT

XLifeSc 香雪生命科学 Improving Lives By Innovation In Immunology

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**2019**
- CMC
- IND submission in NMPA
- **Successful IND from NMPA**

**2020**
- Clinical P&V mfg.
- **Clinical trial initiated in CN**
- IND clearance in **FDA (Sep.)**

## StemiRNA mRNA

StemiRNA

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**02.2020**
- mRNA project against COVID-19 set up

**04.2020**
- Clinical plasmid mfg.
- **Clinical trials initiate**

## Abogen mRNA

ABOGEN

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**2020**
- 1st batch of COVID-19 projects set up by CN government

**06.2020**
- Clinical plasmid mfg.
- **Clinical trials initiate**

# Appendix

# The Basics of mRNA Vaccine

## Mechanism of mRNA vaccine

Induce the production of antibodies which will bind to potential pathogens.

Delivery of the vaccine into the body.

Encoded sequence is translated by the host cells to produce the antigens.

The antigens stimulate the body's adaptive immune system to produce antibodies against the pathogen.

## Production of mRNA vaccine

Produced by *in vitro* reactions with recombinant enzymes, ribonucleotide triphosphates (NTPs) and a **plasmid DNA template**.

**mRNA Synthesis**

- **Template plasmid DNA** produced in *Escherichia coli,* and is linearized using a restriction enzyme;
- mRNA is synthesized from NTPs by a DNA-dependent RNA polymerase from bacteriophage;
- Template plasmid DNA is degraded by incubation with DNase;
- mRNA is enzymatically or chemically capped to enable efficient translation *in vivo*.

**Purification**

- Processed though several purification steps to remove reaction components, including enzymes, free nucleotides, residual DNA and truncated RNA fragments;
- purification at the clinical scale utilizes derivatized microbeads in batch or column formats (easier to utilize at large scale)

**Storage**

- Exchanged into a final storage buffer and sterile-filtered for subsequent filling into vials for clinical use.

# mRNA Vaccine Showing Satisfying Performance

- The use of mRNA has several beneficial features over subunit, killed and live attenuated virus, as well as DNA-based vaccines.

**Higher delivery rate than DNA vaccine**

DNA is supposed to penetrate nucleus to allow transcription to happen, while translation happens in cytoplasm, where is easier to penetrate.

**Faster to manufacture, easier to manufacture in large quantities**

Produced by high yields of *in vitro* transcription reactions, potential for rapid, inexpensive and scalable manufacturing.

**Higher Safety and efficacy**

1. Manufacturing process does not involve toxic chemicals or cell culture, avoid adventitious viruses;
2. Short manufacturing time presents few opportunities to introduce contaminating microorganisms.

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# THANK YOU !

www.genscriptprobio.com