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

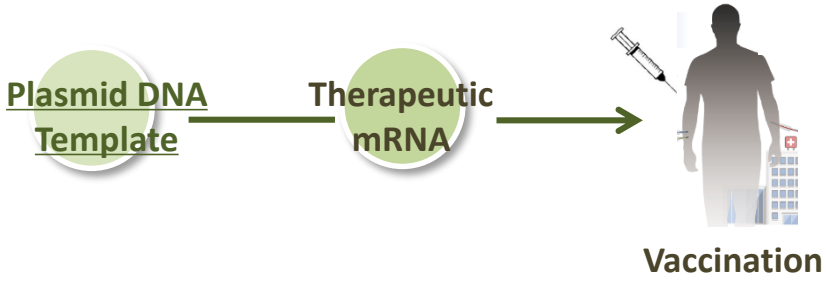
3 Whole virus vaccine (conventional)

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

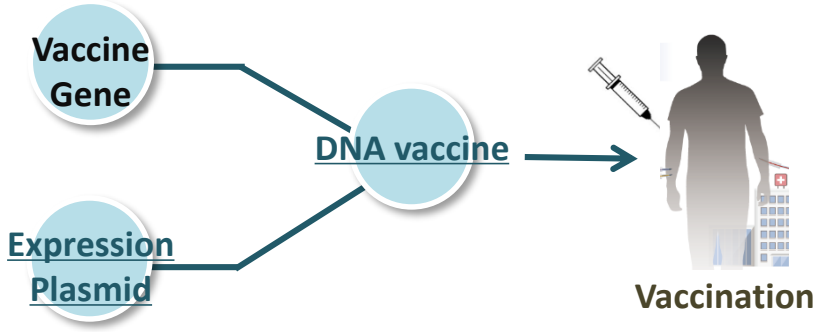
Source: WHO

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	4 Late stage Clinical trials	Commercialization
GenScript ProBio's Offerings	• ProPlasmid	• Plasmid CMC	• GMPro Plasmid	• GMP plasmid	

Various levels of plasmid available

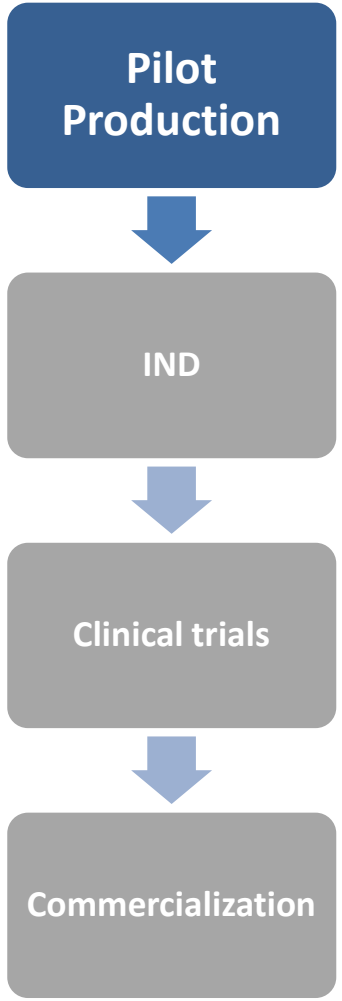
1. Plasmid as raw materials
2. Plasmid as DS/DP

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



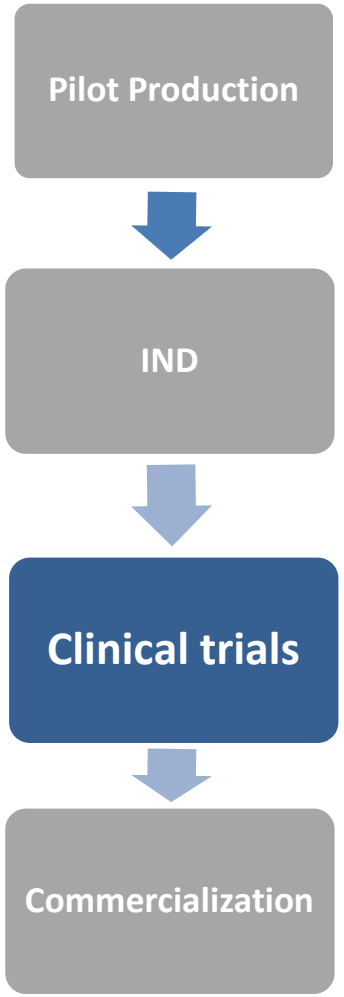
■ Non-clinical stage

Service	Quantity	Deliverables
ProPlasmid	1 mg 20 mg 100 mg 0.5 g 1 g 5 g	1. Plasmid 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



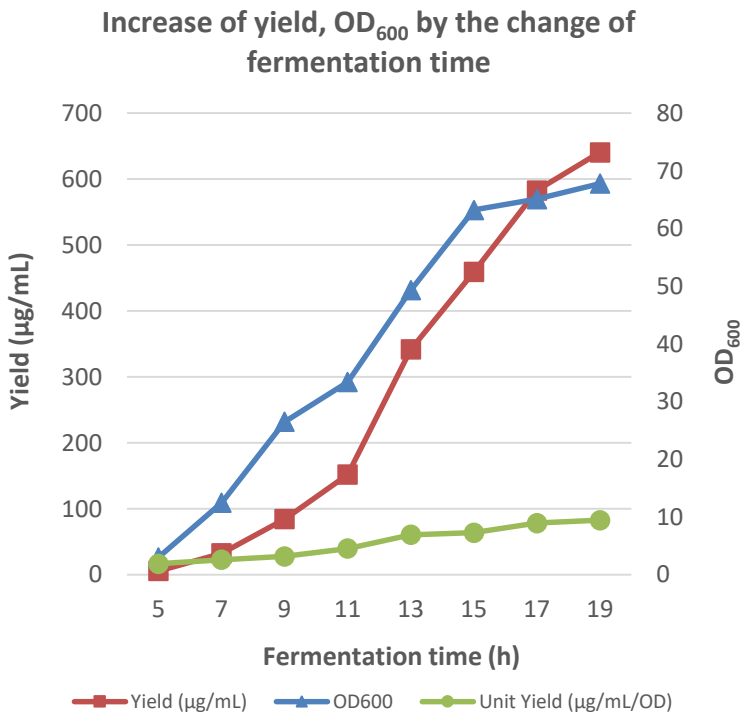
Early Stage Clinical

Service	Quantity	Deliverables
GMPro plasmid	1 mg 5mg 10mg 50mg 100 mg 0.5 g 1 g 2 g 5 g	1. COA 2. Plasmid 3. TSE/BSE statement 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.

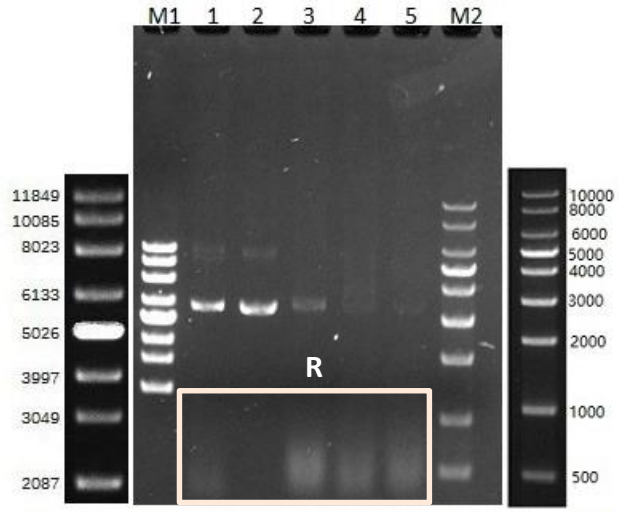
Case Studies – Plasmid Manufacturing Process

Fermentation Process



✓ High density fermentation ✓ High yield

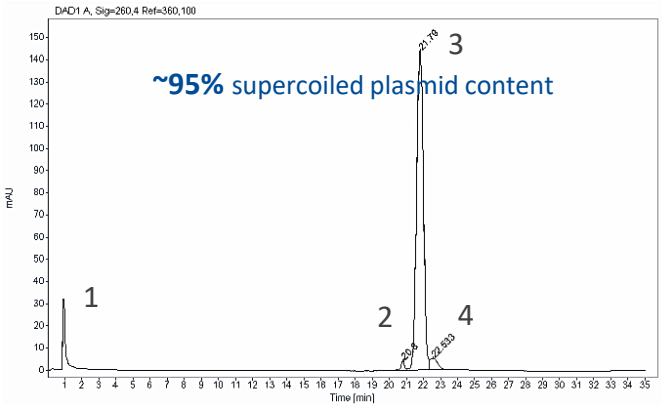
Purification Process



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

GenScript PROBIO

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

GMP Facility Expansion: For Commercial Manufacturing

	2018	2019	2021	2022	2023
FACILITY	**Plasmid Process Development Facility** Lot Area：**1,200m²** Accumulative Area：**1,200m²**	**GMP Virus Facility** Lot Area：**2,500m²** Accumulative Area：**3,700m²**	**GMP Plasmid Facility** Lot Area：**6,400m²** Accumulative Area：**10,100m²**	**GMP Facility (Clinical and Commercial mfg. Center)** Lot Area：**30,000m²** Accumulative Area：**40,100m²**	
APPLICATION	Preclinical plasmid preparation Plasmid process development Plasmid for early clinical phase	Preclinical virus preparation Virus process development Virus for early clinical phase	Capacity expansion Plasmid for CMC, clinical phase and commercialization	Plasmid and virus manufacturing for late clinical phase and Commercial use	

Global Partnerships and Solid Track Record

~60 Plasmid & Virus CMC & Clinical GMP Projects

- 7 IND approved from NMPA&FDA
- Over 20 P&V CMC projects
- Over 30 clinical plasmid mfg. batches
- Over 10 clinical lentiviral vector mfg. batches
- Plasmid CMC and mfg. for over 10 mRNA customers

Key Accounts:

- Provide plasmid and lentiviral vector for >30 big pharma and leading biotech
- Provide plasmid for 3 leading vaccine company

XLifeSc TCRT

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

02.2020
- mRNA project against COVID-19 set up

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

Abogen mRNA

2020
- 1st round 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.

GenScript PROBIO

THANK YOU !

www.genscriptprobio.com