GenScript ProBio Plasmid Platform

Accelerating Vaccine development against COVID-19

GenScript ProBio

Confidential and Privileged

Milestones: Expert in Plasmid Manufacturing

Plasmid in research grade

Started CDMO business

Business expansion and experience accumulation through collaborations

2002-2017 | **2017-2018** | **2019-2020**

- 1st plasmid Process development facility in CN
- 1st plasmid CMC case
- **Over 10** plasmid CMC orders
- **Over 30** batches of plasmid mfg.
- Provide GMP plasmid suitable **for DNA vaccine** from US *US partner*
- 1st plasmid mfg. **for clinical use**
- Plasmid for **mRNA vaccine** against COVID-19
- Plasmid for **mRNA vaccine** *Undisclosed partner*

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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.

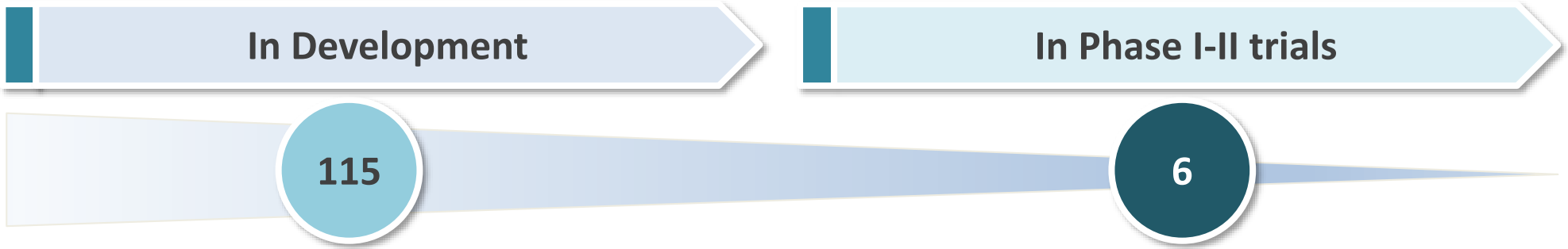
CanSinoBIO gsk

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

Worldwide R&D Progress of Nucleic Acid Vaccine



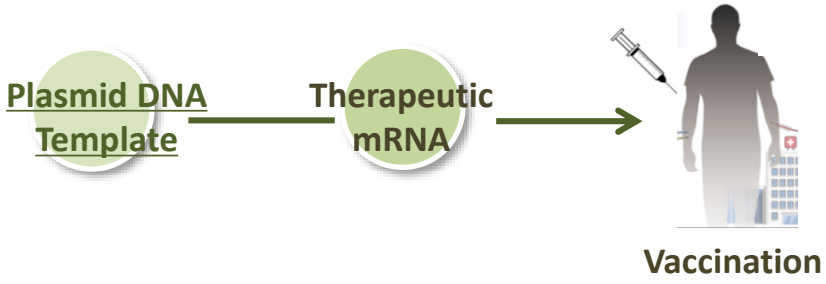
➢ **6 candidates in Phase I-II trials**

Vaccine candidate	Developer or sponsor	Technology	Phase of trial; participants	Location(s)
mRNA Vaccine				
mRNA-1273	Moderna, US National Institute of Allergy and Infectious Diseases	lipid nanoparticle dispersion containing messenger RNA	Phase I (45)	United States
Ad5-nCoV	CanSino Biologics	recombinant adenovirus type 5 vector	Phase II; 500	Wuhan, China
Covid-19/aAPC	Shenzhen Geno-Immune Medical Institute	lentiviral vector, pathogen-specific artificial antigen presenting dendritic cells	Phase I; 100	Shenzhen, China
LV-SMENP-DC	Shenzhen Geno-Immune Medical Institute	lentiviral minigene vaccine, dendritic cells modified with lentiviral vector	Phase I; 100	Shenzhen, China
DNA Vaccine				
INO-4800	Inovio Pharmaceuticals, CEPI	DNA plasmid delivered by electroporation	Phase I; 40	United States
Inactivated COVID-19 vaccine (Vero cells)	Sinovac Biotech, Wuhan Institute of Biological Products	Vero-cell-derived inactivated COVID-19 vaccine	Phase I	Henan, China

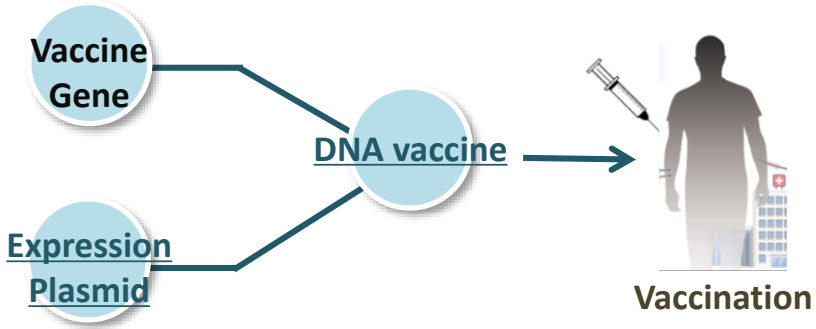
Source: WHO, As of April, 2020

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
GenScript ProBio's Offerings	• ProPlasmid	• Plasmid CMC	• GMPro Plasmid	• GMP plasmid	

Various levels of plasmid available

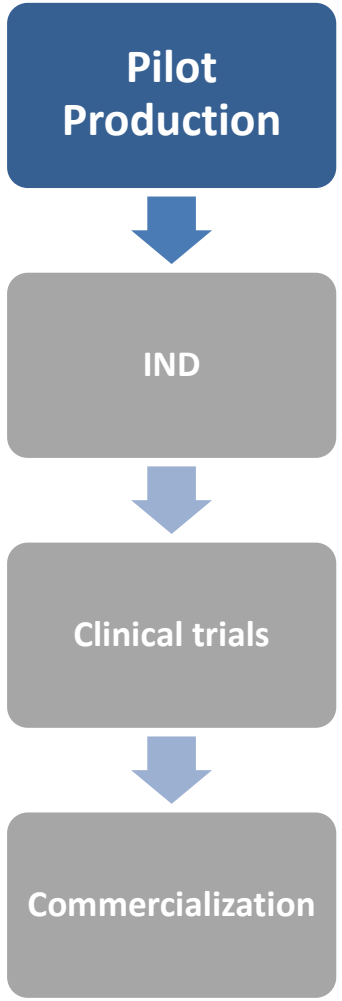
1. Plasmid as raw materials
2. Plasmid as DS/DP

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



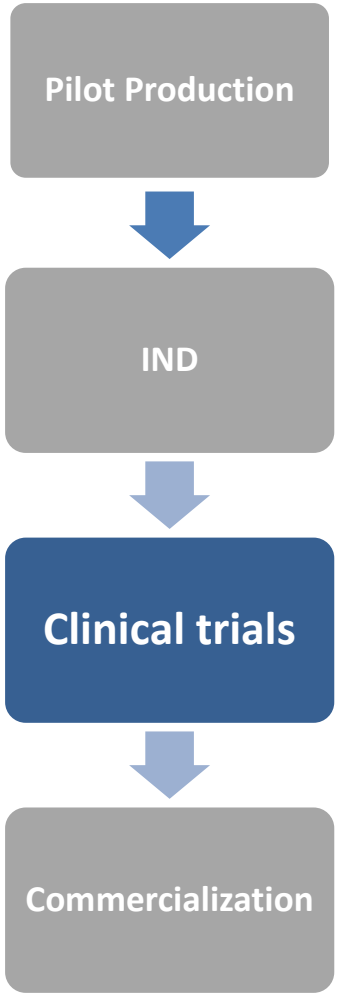
■ Non-clinical stage

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

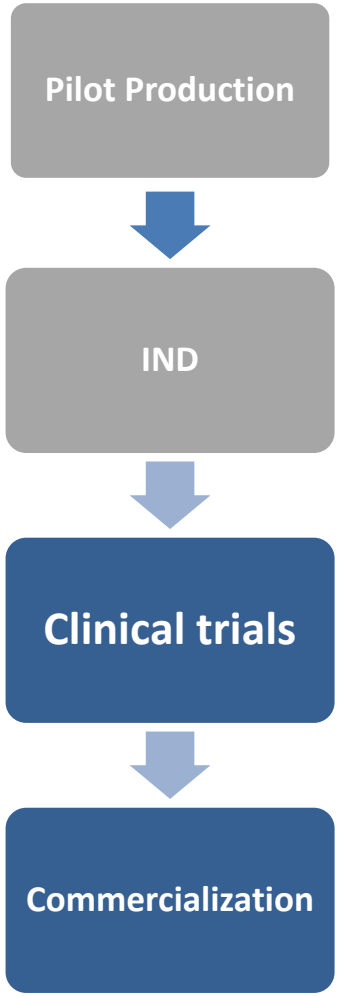


Early Stage Clinical

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.

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 • CMV vaccine as a prophylaxis • H5N1 pandemic influenza • H1N1 pandemic influenza • Anthrax (prophylaxis) • HSV-2 (therapeutic)	• 17 INDs Filed • 4 Master Files • Orphan (#4), Fast Track (#2), QIDP[4)] (#1)	• CaFDB[1)] for commercial-scale • Vaccine Research Center (VRC, NIH) • DAIDS, NIH • IPPOX & P5 (Gates Foundation) • Sanofi[3)] • Astellas[3)]

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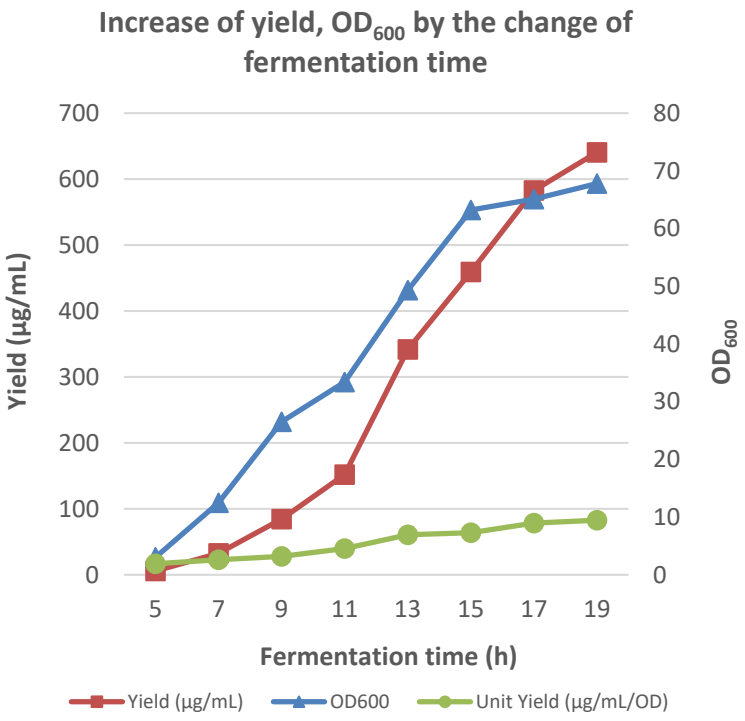
*** Experiences in manufacturing, regulatory applications and GMP inspections are based on Vical's experts, who are now employed by Genopis. Genopis acquired Vical's key professionals as well as manufacturing assets and supporting utilities in July 2018.**

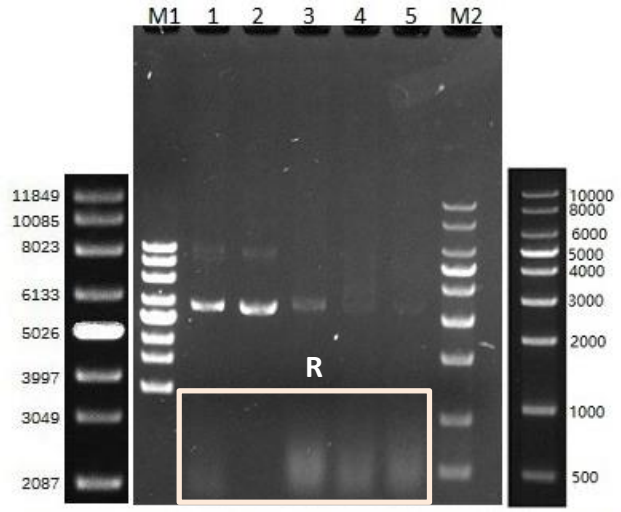
Case Studies – Plasmid Manufacturing Process

Fermentation Process



✓ High density fermentation ✓ High yield

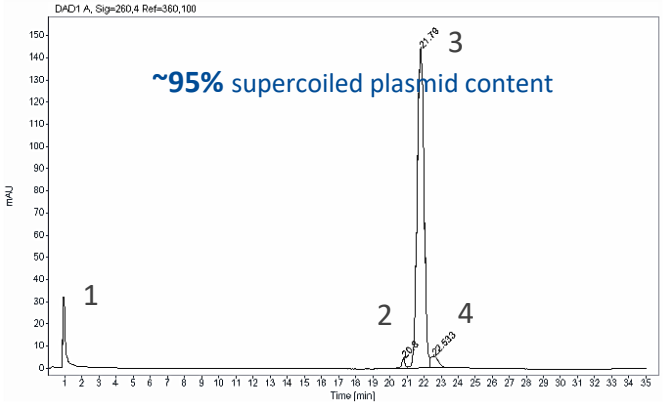
Purification Process



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

CONTENTS

GenScript ProBio: Excellent Vaccine Partner

Accelerate GCT Product Development

- **3 clinical plasmids mfg., 1 clinical lentivirus mfg.**
- **2 IND clearance from NMPA: CAR-T and TCR-T;**
- **Over 10 CMC projects** on going;
- Collaboration with **Merck** to construct GCT platform.

◆ Strategic Collaboration with various companies

- Collaboration on pre-clinical CMC, IND filing of GCT products;
- GenScript will be prepared for further large-scale production.
- Projects including CAR-T, TCR-T, UCAR-T, etc.;
- Accelerate the industrialization of GCT products;

Successful Collaborations in Various Projects

XLifeSc TCRT

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

GenScript ProBio

2019

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

2020

- Clinical P&V mfg.
- **Clinical trial initiated on 03.25.2020**

StemiRNA mRNA

StemiRNA

GenScript ProBio

02.2020

- mRNA project against COVID-19 set up

04.2020

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

GenScript ProBio

THANKS

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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.