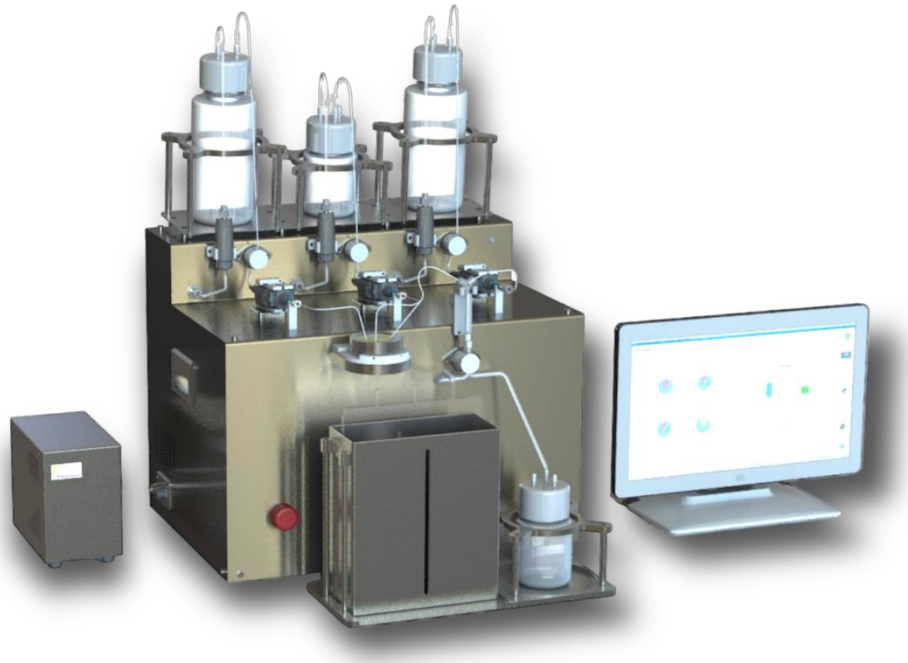
NanoGenerator® MAX Nanoparticle Synthesis System

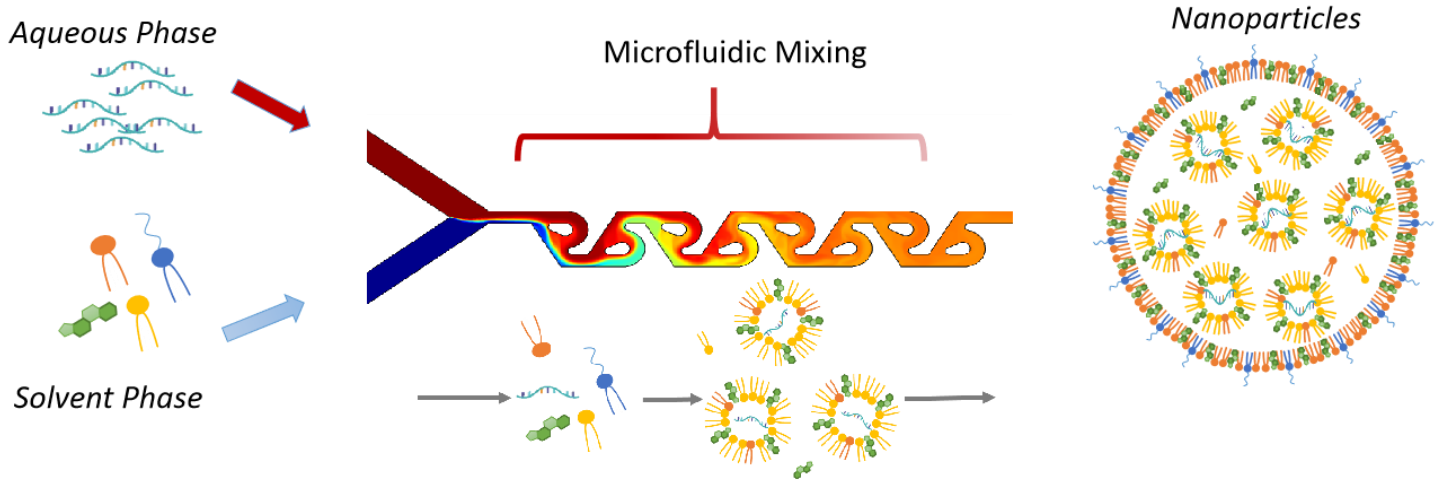


PreciGenome

Jan 2025

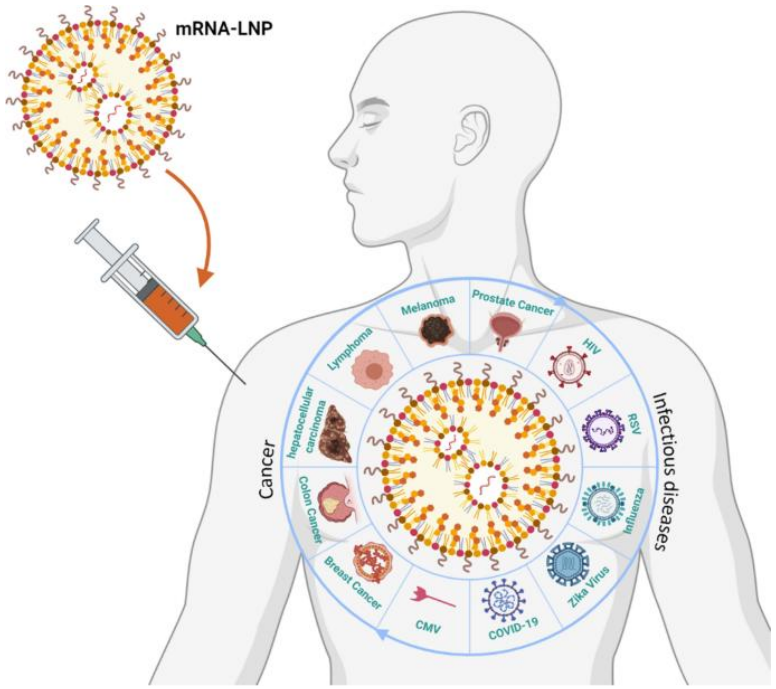
What are Lipid Nanoparticles?

Lipid nanoparticles (LNPs) are self-assembling structures of natural or synthetic lipids in an aqueous environment.



- Cationic/ionizable lipid
- Structural lipid
- Cholesterol
- PEGylated lipid
- Nucleic acid payload

RNA-LNP Therapeutics and Vaccines



Name	Disease	Encoded antigen	Administration route	ClinicalTrials.gov identifier	Phase
Infections					
mRNA-1273	SARS-CoV-2	Spike	i.m.	NCT04470427	III (EUA and CMA)
BNT162b2	SARS-CoV-2	Spike	i.m.	NCT04368728	III (EUA and CMA)
CVnCoV	SARS-CoV-2	Spike	i.m.	NCT04652102	III
mRNA-1647	Cytomegalovirus	Pentameric complex and B glycoprotein	i.m.	NCT04232280	II
mRNA-1388	Chikungunya virus	Chikungunya virus antigens	i.m.	NCT03325075	I
CV7202	Rabies virus	G glycoprotein	i.m.	NCT03713086	I
Cancer					
mRNA-5671/ V941	Non-small-cell lung cancer, colorectal cancer, pancreatic adenocarcinoma	KRAS antigens	i.m.	NCT03948763	I
mRNA-4157	Melanoma	Personalized neoantigens	i.m.	NCT03897881	II
mRNA-4650	Gastrointestinal cancer	Personalized neoantigens	i.m.	NCT03480152	I/II
HARE-40	HPV-positive cancers	HPV oncoproteins E6 and E7	i.d.	NCT03418480	I/II

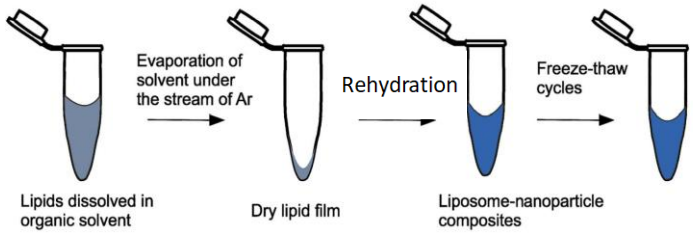
Kiaie, S.H., Majidi Zolbanin, N., Ahmadi, A. *et al.* Recent advances in mRNA-LNP therapeutics: immunological and pharmacological aspects. *J Nanobiotechnol* **20,** 276 (2022).

Nature Reviews Materials **volume 6**, pages1078–1094 (2021)

Lipid Nanoparticle Synthesis Methods

Conventional Methods

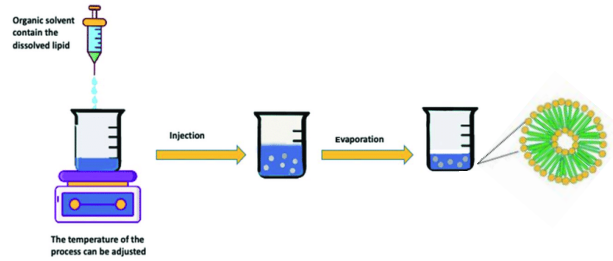
A Film hydration



- Established method
- Versatile method

- High consumption of the organic solvent
- High PDI
- Lack of reproducibility
- Need for additional downsizing step
- Difficulties in scaling-up

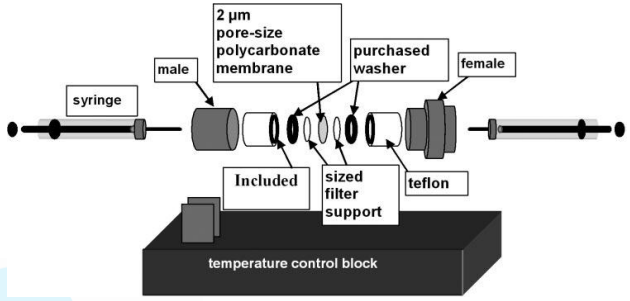
B Solvent injection



- Simple and fast
- Scaling-up possibility
- Controllable

- Exposing to organic solvent
- High PDI
- Stability problem

C Extrusion



- Established method
- Uniform and homogenous formulation

- Possible clogging of the membrane pores
- Difficulties in scaling up

Nanomaterials, Volume 11, 2021, 3440

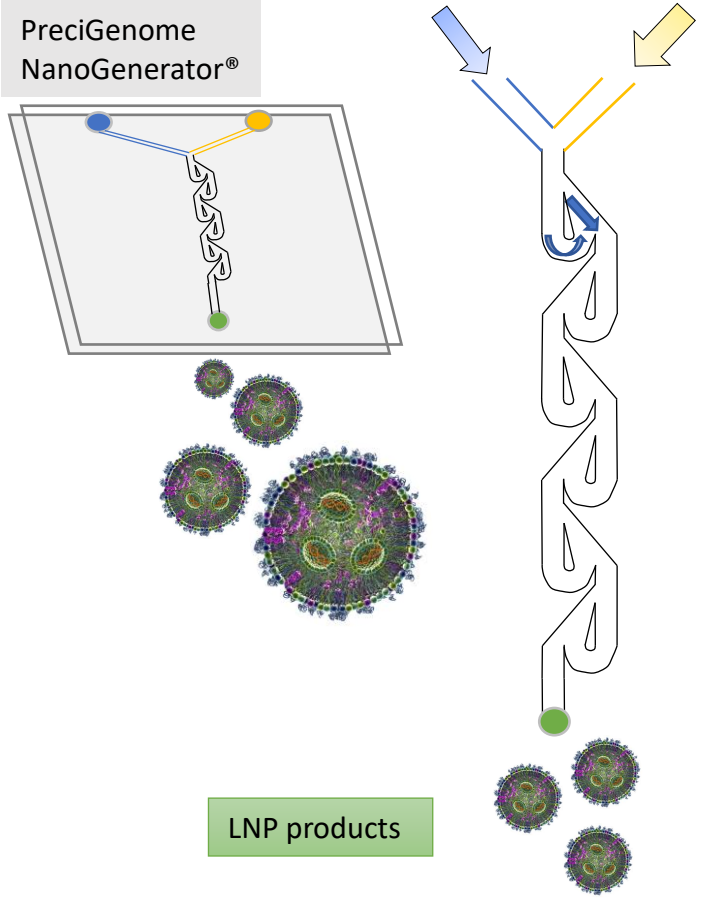
VS.

Microfluidic Mixing

Aqueous phase: DNA, mRNA, protein

Organic Phase: Lipids

PreciGenome NanoGenerator®



- Low PDI
- Fast & Scalable
- Reproducibility
- Controllable
- Low cost

- Complex fabrication
- Potential clogging

NanoGenerator® - Nanoparticle Synthesis System

Flex-S

Flex-S Plus

- Flex-S: 0.1 – 2 ml
- Flex-S Plus: High-throughput discovery & screening

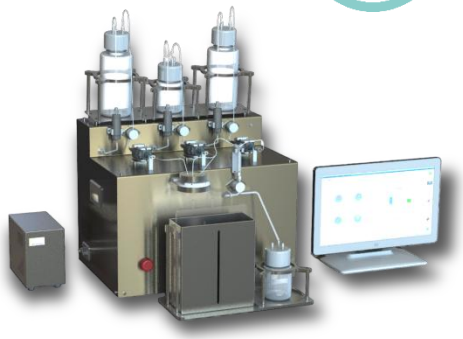
Flex-M

- Flex-M: 1 – 12 ml

Flex-M Premium

- Flex-M Premium: 2– 200 ml

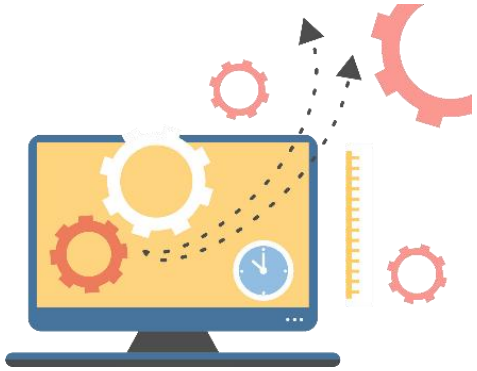
Max



Clinical development
GMP certified manufacturing

- MAX: 50ml – 1L
- MAX (40L/h): >20L

OEM



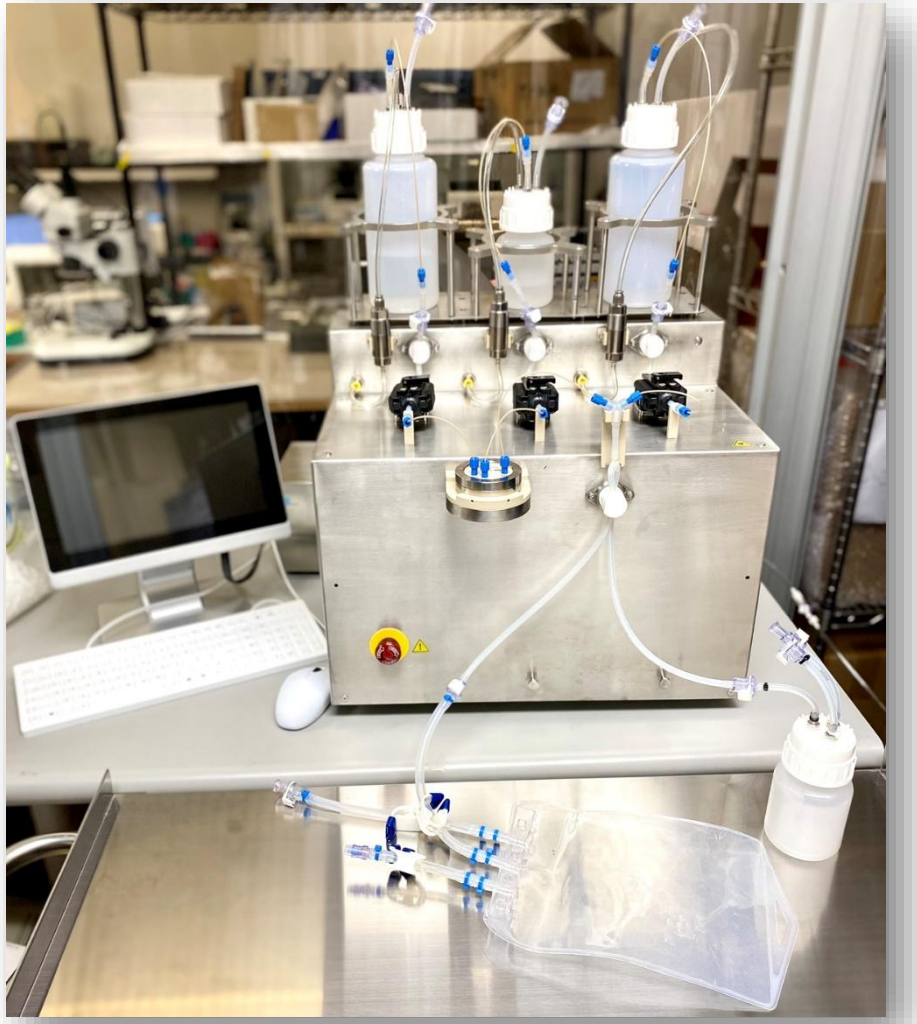
Custom design and OEM solutions
GMP certified manufacturing

- >400 L throughput

Discovery & Screen — **Pre-clinical development** — **Clinical development** — **Custom solution**

NanoGenerator® MAX — Intro

- The NanoGenerator® Max is designed for clinical and commercial production. Two versions are available:
  - RUO: Preclinical applications
  - cGMP: Clinical and commercial production
- Two flow kits are available with different supported throughput:
  - 4.8 L/h flow kit: 50 mL – 1 L
  - 40 L/h flow kit: >20 L



NanoGenerator® MAX — Spec

Model	NanoGenerator® MAX			
	RUO flow kit 4.8 L/h	GMP flow kit 4.8 L/h	RUO flow kit 40 L/h	GMP flow kit 40 L/h
cGMP compliance	N/A	Yes	N/A	Yes
Software (21 CFR Part 11 compliant)	Optional	Yes	Optional	Yes
Throughput	50 ml – 1 L		> 20 L	
Total flow rate	1.2 – 4.8 L/h		Up to 40 L/h	
Flow rate ratio	1:1 – 9:1		1:1 – 5:1	
Inline dilution	1:1 – 5:1			
Size range	40 – 200 nm			
PDI	0.05 – 0.2			
Encapsulation efficiency	Up to 99%			
Payload	DNA, mRNA, siRNA, protein, small molecules, etc.			
Dimension (L × W × H)	620 × 380 × 430 mm			
Weight	50 Kg		65 Kg	

NanoGenerator® MAX — Contents

Instrument:

- Pneumatic system
- Valves
- Flow rate sensors
- Consumable kit
- Monitor (optional)
- Pumps (optional)

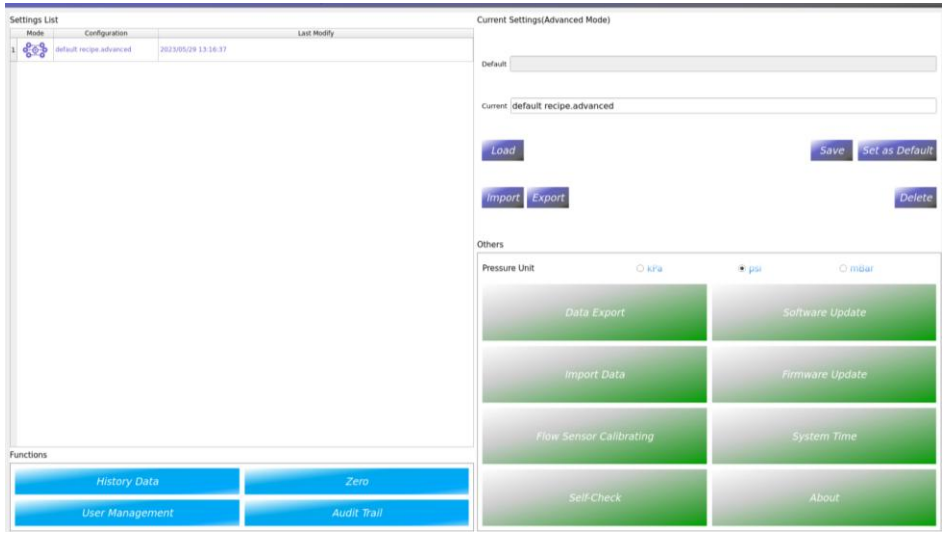
Consumable Kit:
(Sterilized, Nuclease free, pre-assembled)

- Sample bottle (aqueous)
- Sample bottle (solvent)
- Sample bottle (dilution)
- Waste bottle
- Bioprocessing bag (collection)
- Tubing & connectors
- Mixing chip

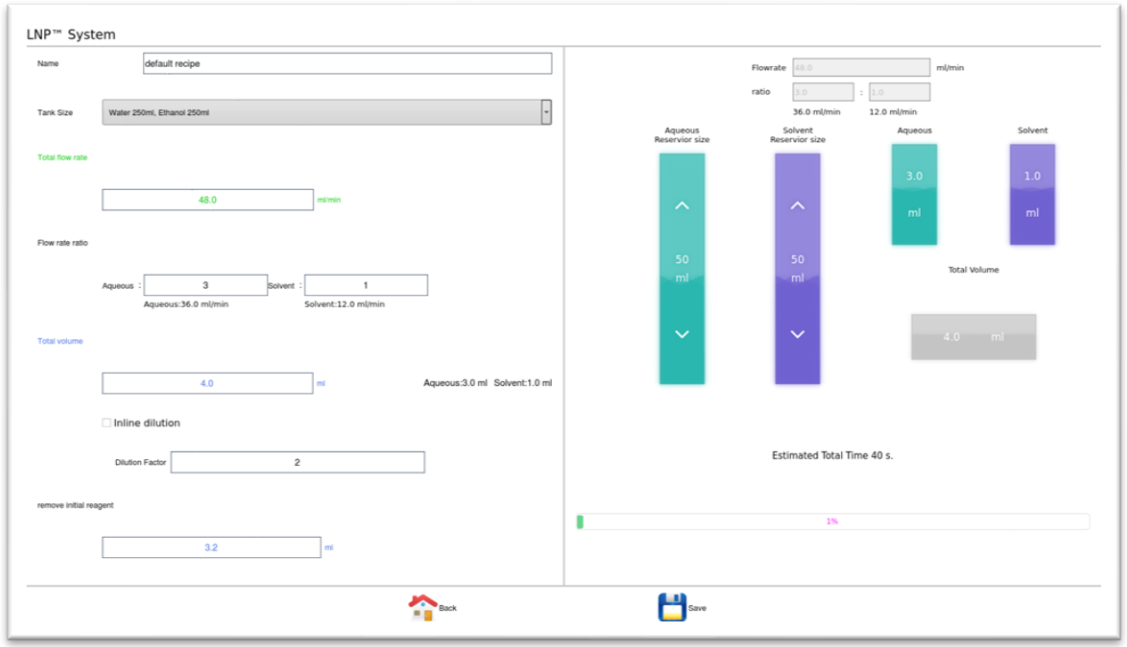
NanoGenerator® MAX — Software

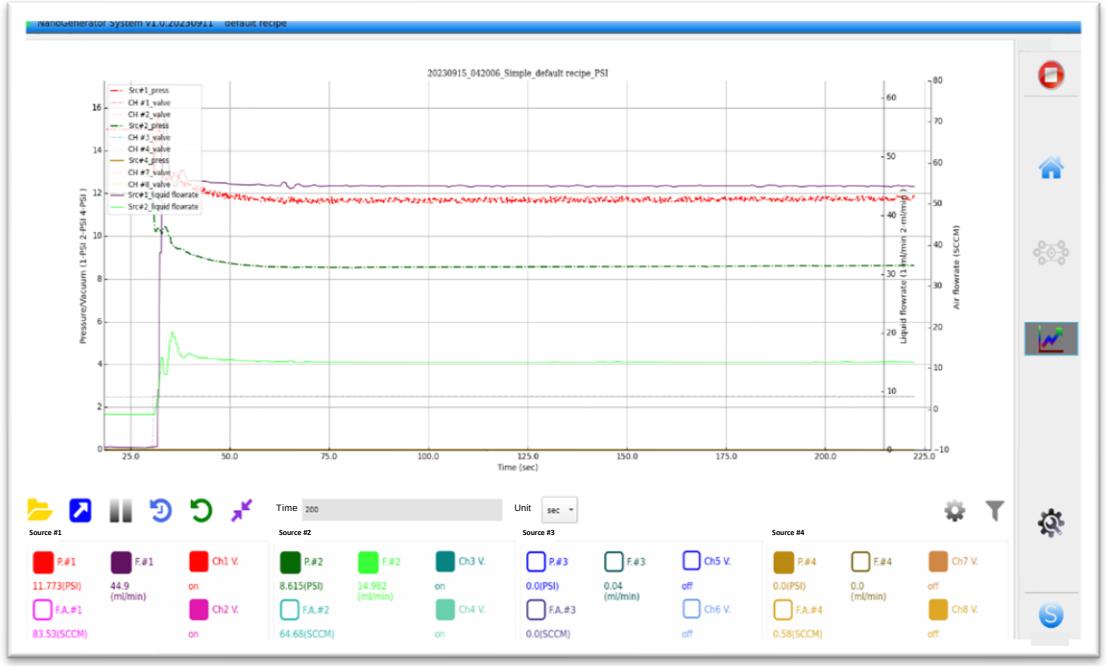
Software (21 CFR Part 11) Features:

- Experimental parameter setting
- Experimental recipe save/load
- Real-time pressure/flow rate chart
- Historic experimental parameter tracking
- Historic pressure/flow rate tracking
- System self-diagnostic system
- Real-time flow rate diagnostic system
- Warning system
- Manual & automatic emergency stop system
- User management
- Audit trail
- Zero flow calibration
- Flow sensor maintenance & re-calibration (Service)



NanoGenerator® MAX — Software





Easy-to-use UI to set parameters including:

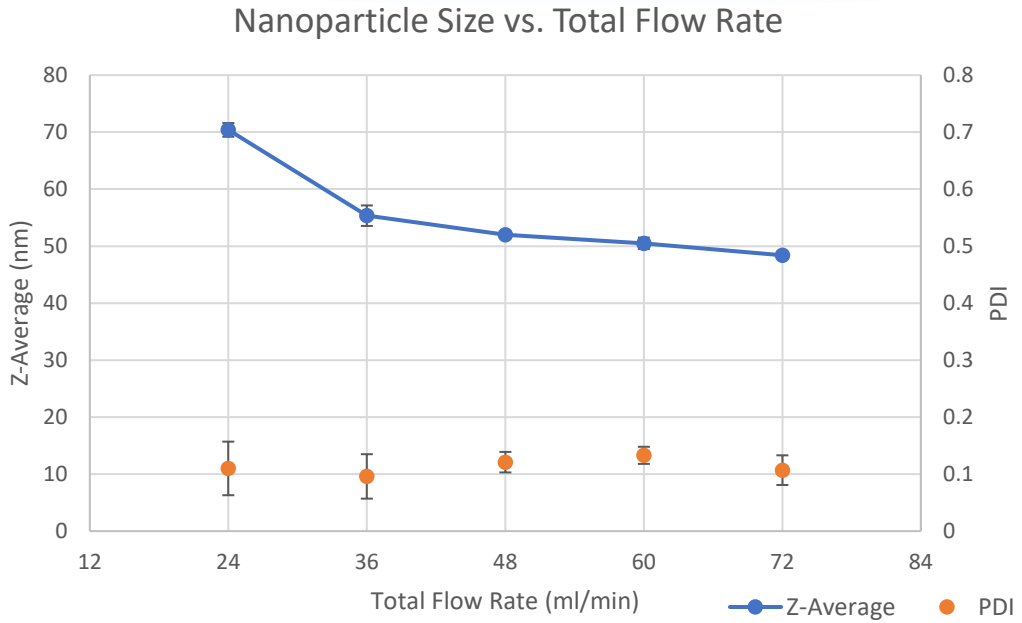
- Total flow rate
- Flow rate ratio
- Production volume
- Inline dilution factor
- Waste volume

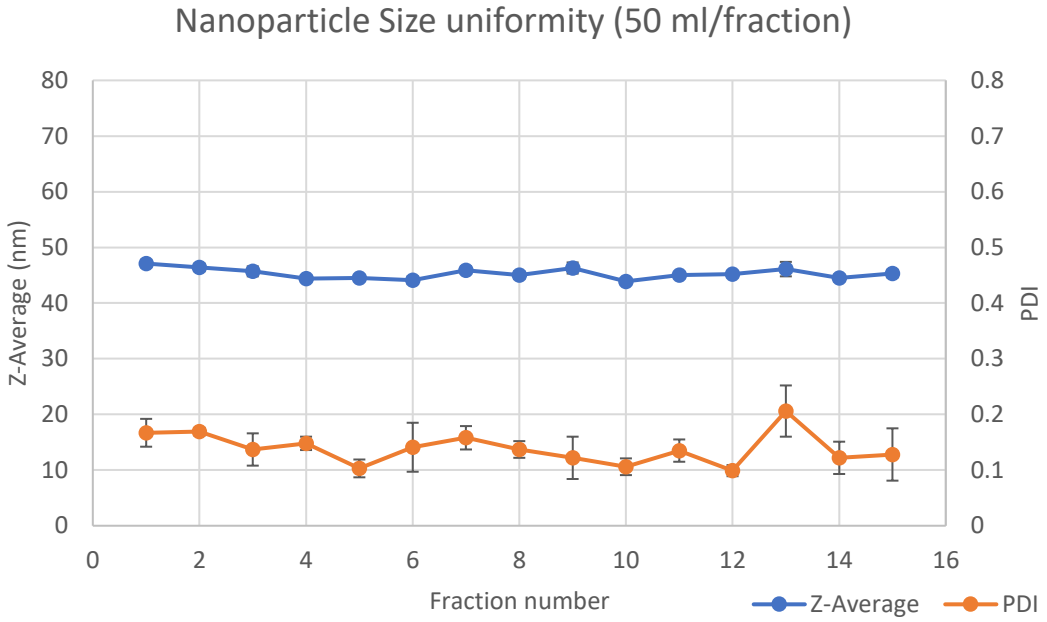
Easy-to-use real-time flow rate /pressure chart including:

- Flow rate
- Pressure
- Air flow rate

All parameters are tracked for aqueous, solvent, and inline dilution lines

NanoGenerator® MAX — Performance





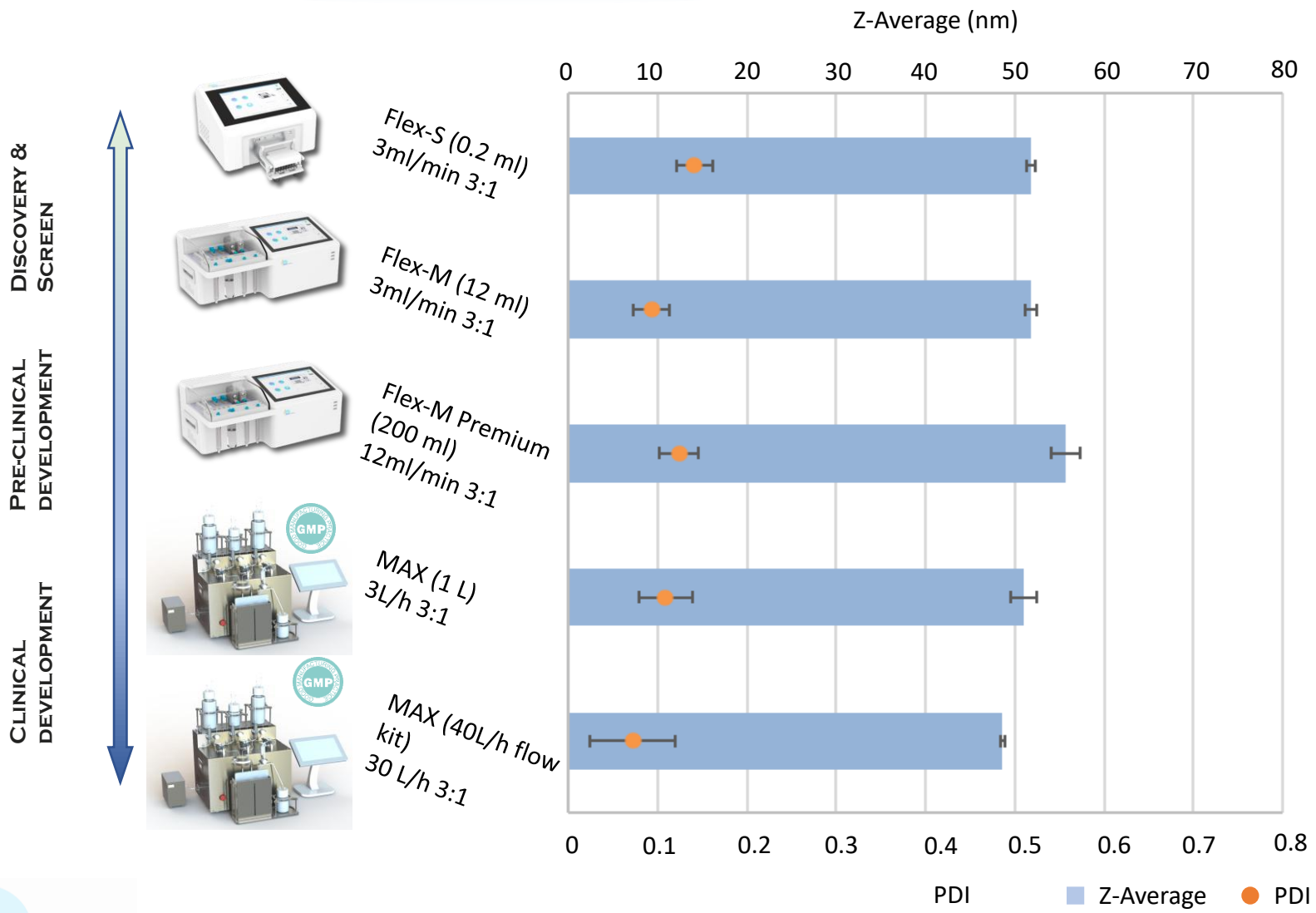
- Nanoparticle size decreases as total flow rate increases
- Size decrease experiences diminishing returns when the flow rate reaches 48 ml/min

	Reagents
Aqueous phase	Sodium acetate buffer (100mM, pH5.2)
Solvent phase	LipidFlex, 15mM in ethanol

- Throughout the entire production run, there is no significant difference in the nanoparticle size and PDI

	Reagents
Aqueous phase	Phosphate-Buffered Saline (1X, pH7.4)
Solvent phase	LipidDemo, 15mM in ethanol

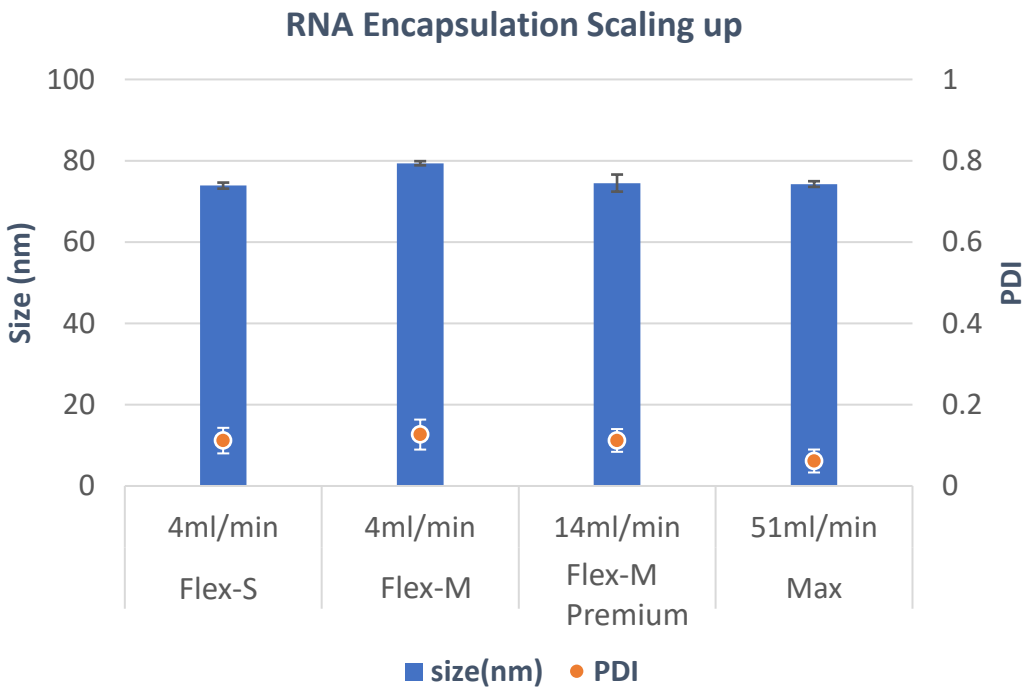
NanoGenerator® — Scale Up

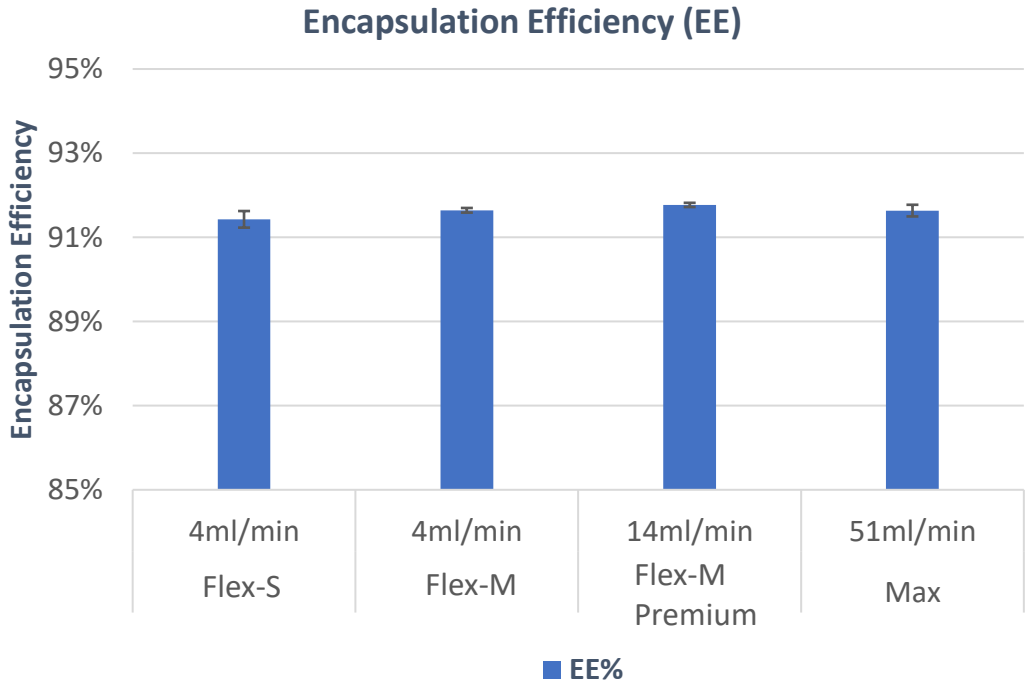


- Nanoparticle size is consistent across different production volumes if using optimal flow rates
- Mixing mechanism is the same for all PreciGenome instruments
- Production can be scaled up from discovery & screening to preclinical & clinical trial production

Reagents	
Aqueous phase	Sodium acetate buffer (100mM, pH5.2)
Solvent phase	LipidFlex, 15mM in ethanol

NanoGenerator® — Scale Up





	Reagents
Aqueous phase	Sodium acetate buffer (100mM, pH5.2)
Payload	RNA (~600 nt)
Solvent phase	LipidFlex RNA-LNP kit

Case Study: mRNA LNPs for T cell Transfection

eGFP mRNA Lipid Nanoparticles

Z-Average Diameter: 67.3 nm

PDI: 0.106

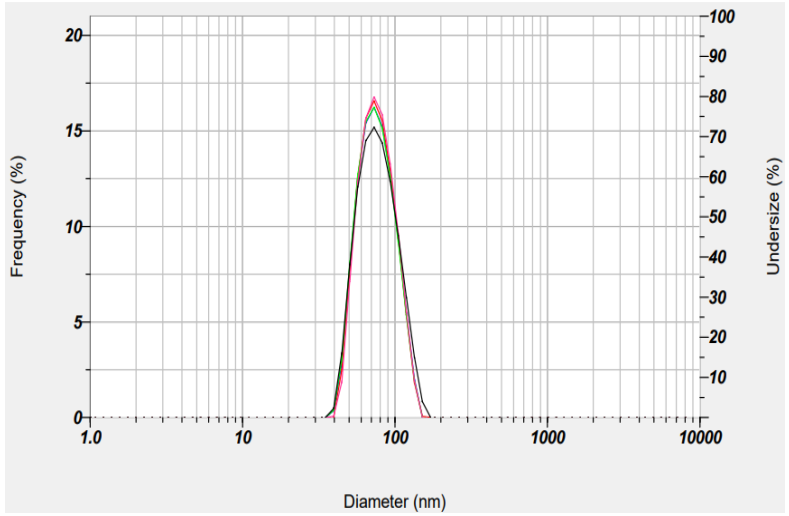


Figure 1. mRNA(eGFP)-LNP Synthesized by NanoGenerator. Average diameter is 67.3 nm. PDI is 0.106. Encapsulation efficiency is 94.5% (Ribo Green RNA Quantification Kit).

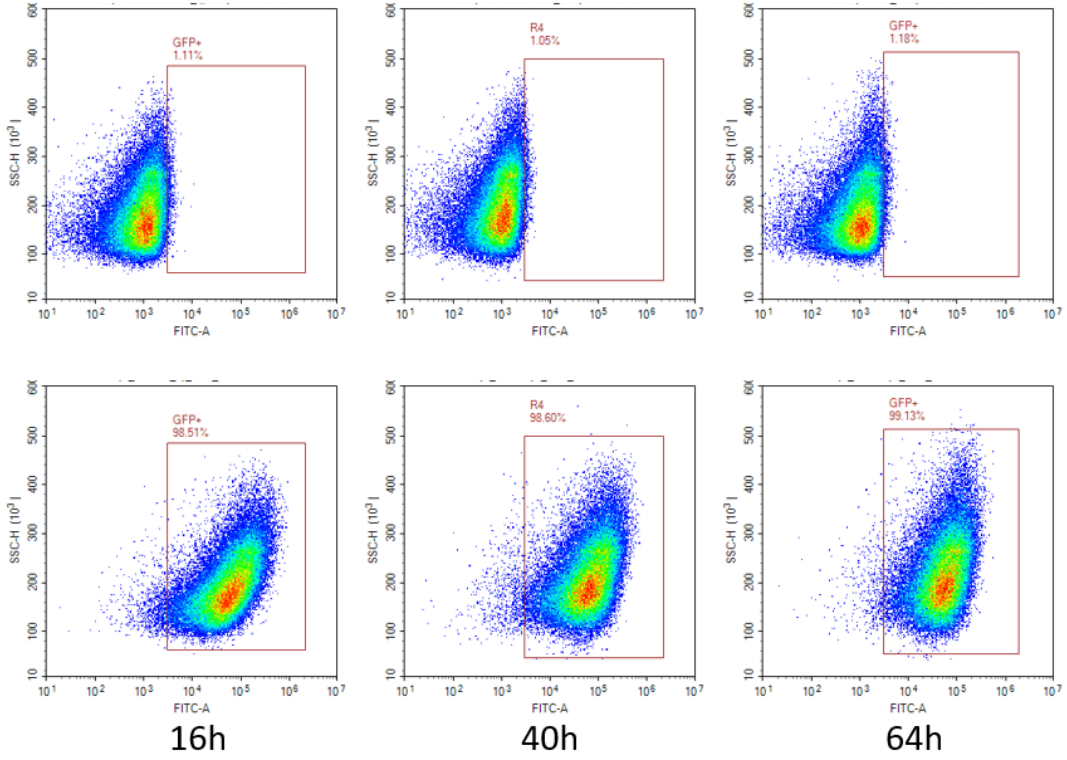
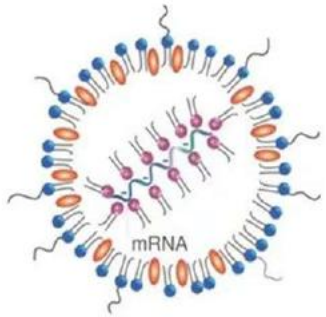


Figure 2. GFP(+) positive population of control (non-treat) and EGFP mRNA LNP treated primary T cells at 16, 40 and 64 hours. Cells were stained (1:50) using Biolegend 7-AAD Viability Staining for 10 minutes. Gating: First select for individual cells (excluding doublets). Then select for the healthy cell population. Then select for viable cells by excluding cells which are positive for 7-AAD. Gate for FitC-A channel (GFP)

Case Study: Bi-specific Antibody Delivered by mRNA-LNP

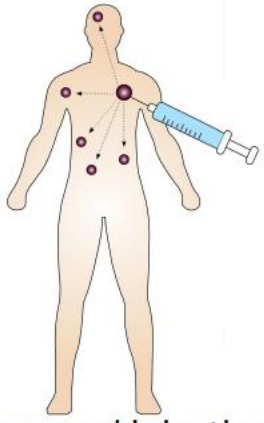


mRNA Encapsulation

In Vitro Transcription of mRNA encoding bispecific antibody & others.

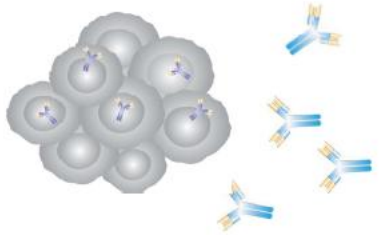
Co-encapsulation or Co-injection with:

Checkpoint Inhibitor: PD-1 ab, PD-L1 ab...
Immunomodulator: CD40, OX40L, CD70...
Chemokine: CXCL2, CXCR1, CXCL9...



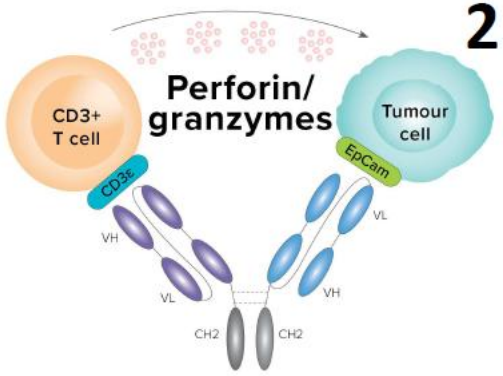
Intra-tumoral injection

What happens post-injection?



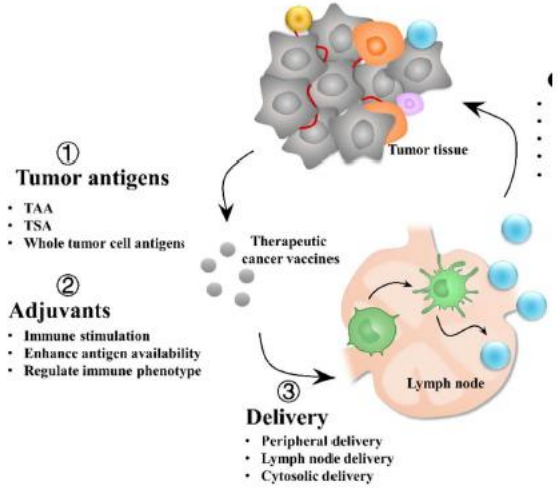
1

Tumor cells translate mRNAs into bispecific antibody and Immuno-mediator (Tumor factory)



2

Antibody + T cell infiltration = Tumor cell lysis (T cell Therapy)

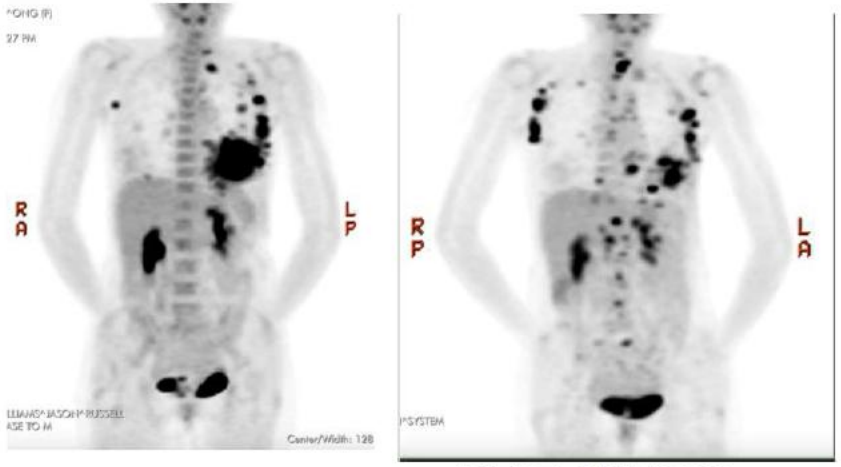


3

Released TAA & Neoantigen from lysate + Immuno-mediator (adjuvant)
= Innate Immune system activation (Tumor vaccine)

Case Study: Bi-specific Antibody Delivered by mRNA-LNP

Treatment of Two Late-Stage Breast Cancer Cases



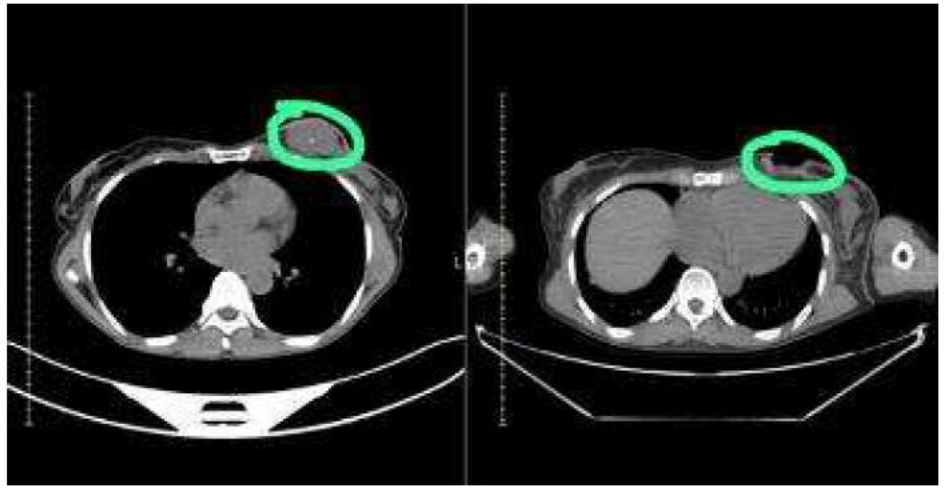
PET-CT 12/14/2023
Pre-treatment

PET-CT 6/18/2024
Post-treatment

Unresectable breast cancer with skin lesion

Case 1 Three photos

1. Appearance before treatment
2. Considerable change in appearance on skin lesions after first treatment
3. Continued improvement on skin lesions after two treatments



4/1/2024 Baseline

4/22/2024 After one Injection

Triple negative breast cancer

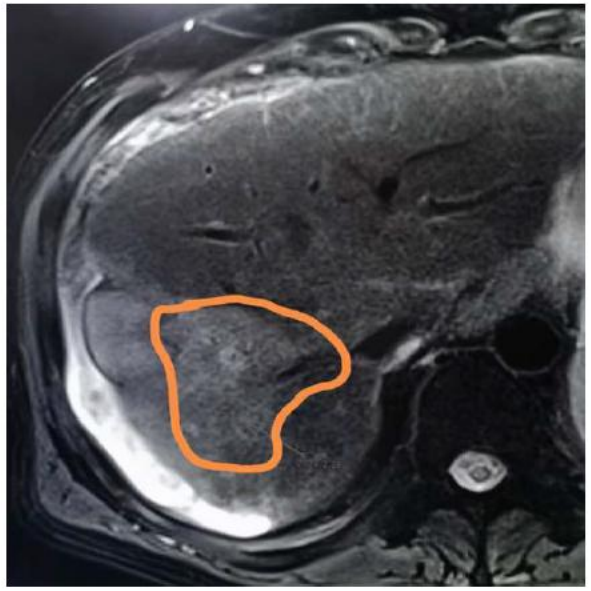
Case 2

Left: CT scan showing a stage 3 invasive ductal carcinoma that did not respond to prior immunotherapy

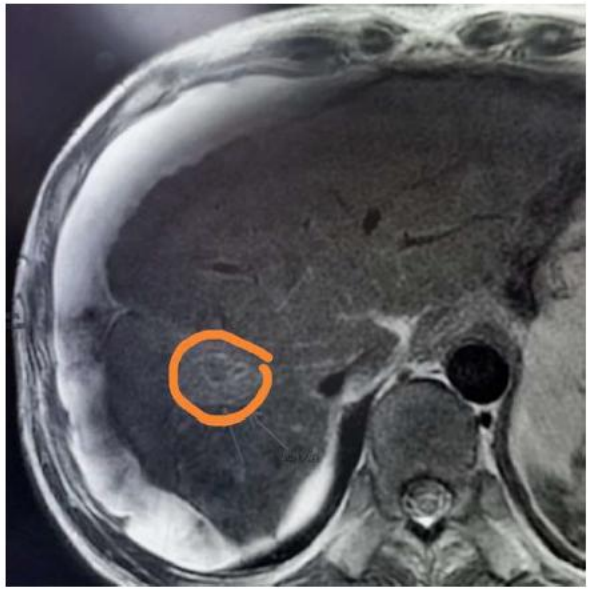
Right: After one treatment, the tumor has dramatically resolved.

Case Study: Bi-specific Antibody Delivered by mRNA-LNP

Cholangiocarcinoma with Liver Metastasis



02/28/2024 after one injection



07/24/2024, after four injections

Case Information: A 45-year-old male patient, HBsAg positive for over 2 years, presented with intrahepatic lesions and abdominal distension. A recent CT scan revealed a large abnormal density in the liver's right lobe, enlarged abdominal lymph nodes, and a portal vein defect, indicating hepatocellular carcinoma with lymph node metastasis and portal vein cancer thrombosis. The patient's liver function was Child-Pugh grade A with some blood count abnormalities.

The posttreatment CT scan showed dramatic shrink of the intrahepatic cholangiocarcinoma after four intratumoral injections of the EpCAM-CD3-Fc+IM-1+IM-2 cocktail mRNA-LNP. The Patient requested more injections on 9/12/2024

Case Study: Bi-specific Antibody Delivered by mRNA-LNP

Liver Metastases from Colorectal Cancer

Lesion 1

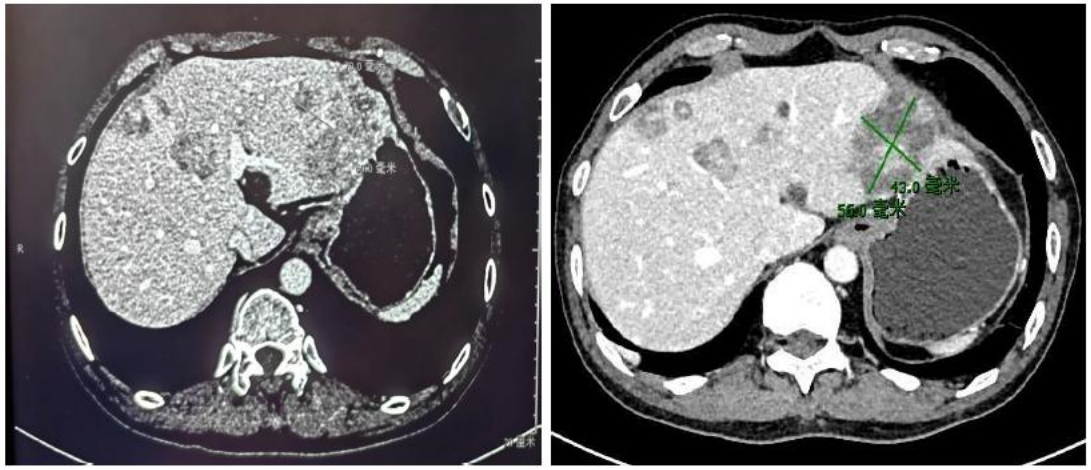
37.0 x 28.0 mm

3/25/2024

27.0 x 24.0 mm

4/27/2024

Lesion 2



70.0 x 60.0 mm

3/25/2024

56.0 x 43.0 mm

4/27/2024

The enhanced CT scan of the upper abdomen showed that the intrahepatic tumor had shrunk

Why PreciGenome?

High Performance & Efficiency

- Tunable size (40-200 nm)
- Low PDI (0.05-0.2)
- High encapsulation efficiency

Open Platform

- Upgradable system
- Transferable microfluidic chips

Scalable Throughput

- Low volume for screening (Flex-S)
- Medium volume production (Flex-M)
- High volume production (Pro, MAX-GMP)

Simple Operation

- Simple setup
- Compact size
- Intuitive UI w/ touchscreen

Cost Effective

- Affordable configuration
- Lower cost per run

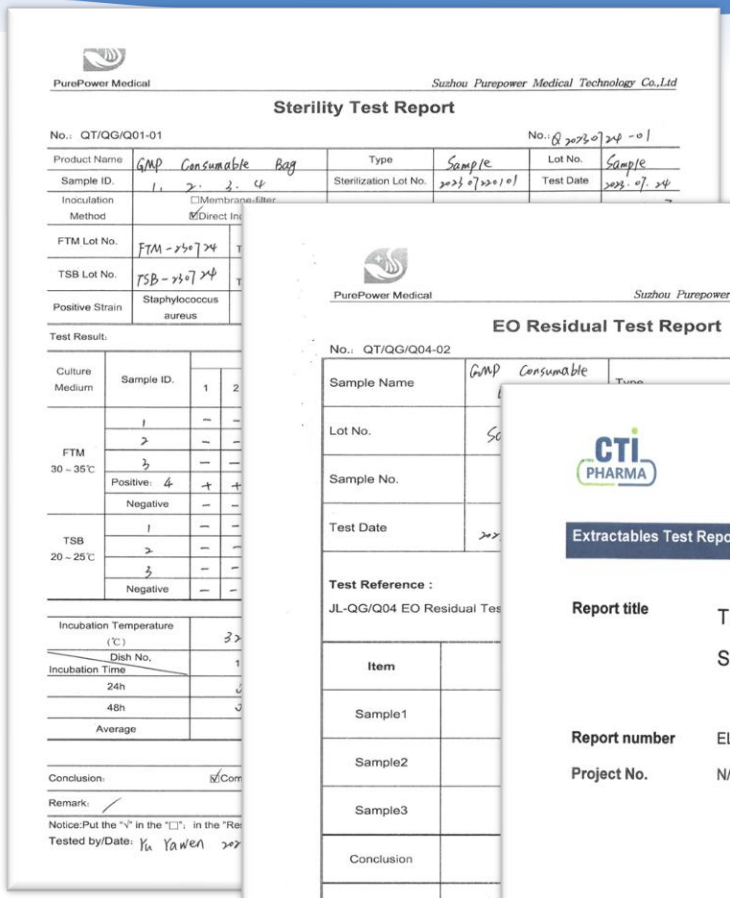
Custom Support

- Demo, Training and Support
- Extended Warranty
- Hot swap option
- Local US company

Appendix I

- **Manual**
- **Standard Operation Procedure (SOP)**
- **Warranty (1 year)**
- **Documentation related to cGMP compliance (cGMP version)**
  - ✓ Installation qualification, operational qualification, performance qualification
  - ✓ Report of consumable items
  - ✓ Chemical compatibility report of consumable items
  - ✓ Report of endotoxin test
  - ✓ Report of RNase/DNase free test
  - ✓ Report of sterilization test
  - ✓ Report of ethylene oxide residue test
  - ✓ 21 CFR Part 11 report
  - ✓ Electromagnetic compatibility report
  - ✓ Report of safety regulations
  - ✓ Other reports by requesting

Appendix II



PurePower Medical — Suzhou Purepower Medical Technology Co.,Ltd

Sterility Test Report

No.: QT/QG/Q01-01

Product Name	GMP Consumable Bag	Type	Sample	Lot No.	Sample
Sample ID.	1. 2. 3. 4	Sterilization Lot No.	20230720101	Test Date	2023.07.24
Inoculation Method	☐Membrane filter ☑Direct In				
FTM Lot No.	FTM-230724				
TSB Lot No.	TSB-230724				
Positive Strain	Staphylococcus aureus				

Test Result:

	Sample ID.	1	2
FTM 30~35℃	1	–	–
	2	–	–
	3	–	–
	Positive: 4	+	+
	Negative	–	–
TSB 20~25℃	1	–	–
	2	–	–
	3	–	–
	Negative	–	–

Incubation Temperature (℃)	32
Dish No. / Incubation Time	1
24h	
48h	
Average	

Conclusion: ☑Com

Remark: /

Notice:Put the "√" in the "□"; in the "Re

Tested by/Date: Yu Yawen 202

PurePower Medical — Suzhou Purepower Medical Technology Co.,Ltd

EO Residual Test Report

No.: QT/QG/Q04-02

Sample Name	GMP Consumable
Lot No.	
Sample No.	
Test Date	

Test Reference :

JL-QG/Q04 EO Residual Tes

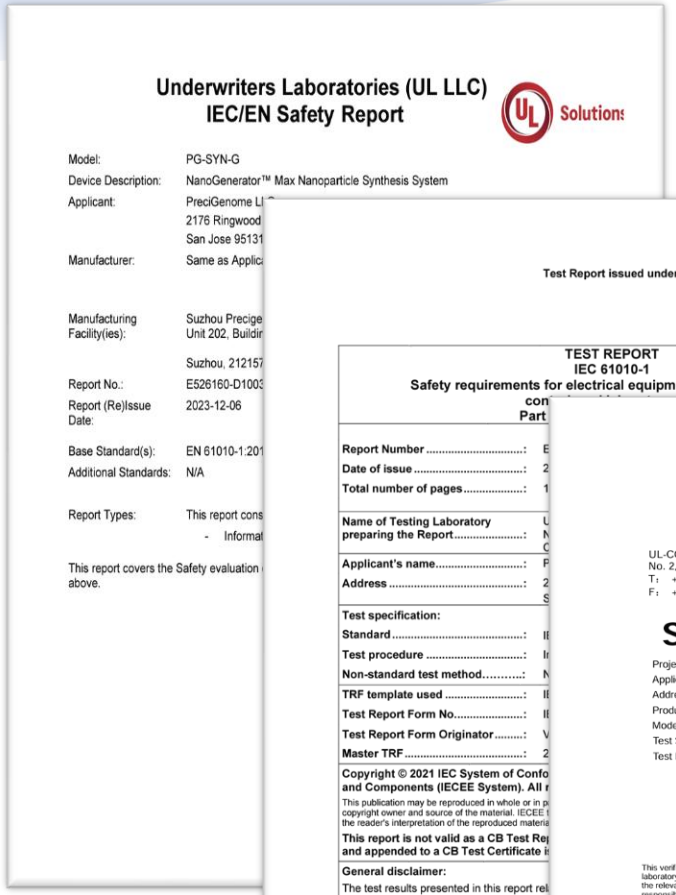
Item	
Sample1	
Sample2	
Sample3	
Conclusion	
Remark	/

Tested by/Date: Yu Yawe

CTI PHARMA

Extractables Test Report

Report title	The Extractables Study Report of Nanoparticle Synthesis System Consumables Kit
Report number	EL-REP-23-019.01-E
Project No.	N/A
Customer	PreciGenome LLC
Address	2176 Ringwood Ave. San Jose, CA, 95131, USA
Testing laboratory	Centre Testing International Pinchuang (Shanghai) Co., Ltd.
Testing laboratory address	1351 Wanfang Road, Minhang District, Shanghai

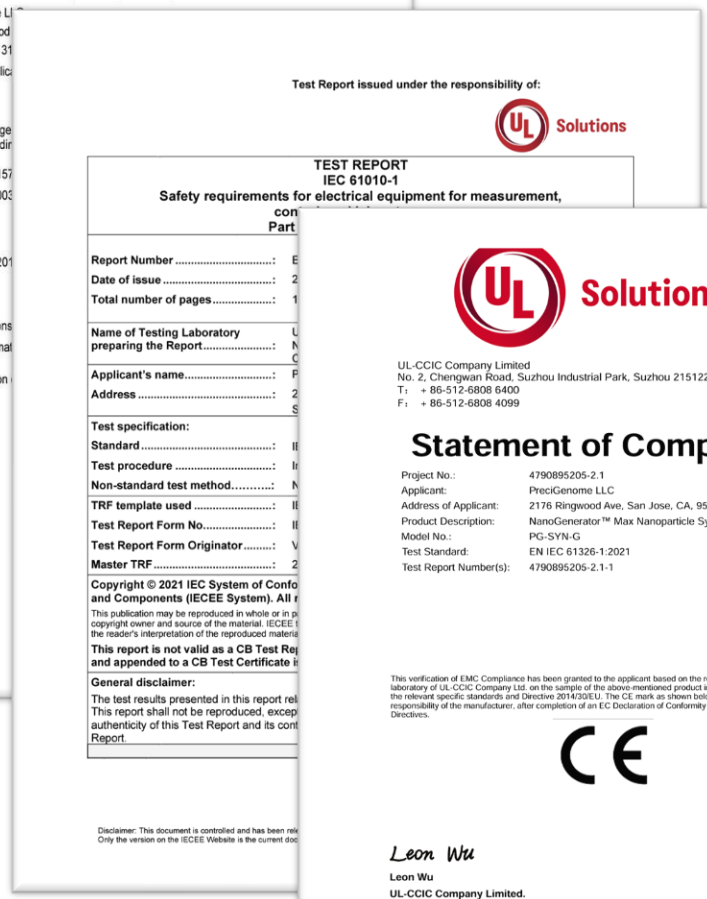


Underwriters Laboratories (UL LLC)
IEC/EN Safety Report

UL Solutions

Model:	PG-SYN-G
Device Description:	NanoGenerator™ Max Nanoparticle Synthesis System
Applicant:	PreciGenome LL 2176 Ringwood San Jose 95131
Manufacturer:	Same as Applic
Manufacturing Facility(ies):	Suzhou Precige Unit 202, Buildir Suzhou, 212157
Report No.:	E526160-D100
Report (Re)Issue Date:	2023-12-06
Base Standard(s):	EN 61010-1:201
Additional Standards:	N/A
Report Types:	This report cons - Informal

This report covers the Safety evaluation above.



Test Report issued under the responsibility of:

UL Solutions

TEST REPORT
IEC 61010-1
Safety requirements for electrical equipment for measurement, con Part

Report Number	E
Date of issue	2
Total number of pages	1
Name of Testing Laboratory preparing the Report	L N C
Applicant's name	P
Address	2 S
Test specification:	
Standard	II
Test procedure	Ir
Non-standard test method	N
TRF template used	II
Test Report Form No.	II
Test Report Form Originator	V
Master TRF	2

Copyright © 2021 IEC System of Confo and Components (IECEE System). All r

This publication may be reproduced in whole or in p copyright owner and source of the material. IECEE the reader's interpretation of the reproduced materia

This report is not valid as a CB Test Re and appended to a CB Test Certificate i

General disclaimer:

The test results presented in this report rel This report shall not be reproduced, excep authenticity of this Test Report and its cont Report.

Disclaimer: This document is controlled and has been rel Only the version on the IECEE Website is the current doc

UL Solutions

UL-CCIC Company Limited
No. 2, Chengwan Road, Suzhou Industrial Park, Suzhou 215122, China
T: + 86-512-6808 6400
F: + 86-512-6808 4099

No: 4790895205-2.1-S1
Issue Date:2023-08-26

Statement of Compliance

Project No.:	4790895205-2.1
Applicant:	PreciGenome LLC
Address of Applicant:	2176 Ringwood Ave, San Jose, CA, 95131, USA
Product Description:	NanoGenerator™ Max Nanoparticle Synthesis System
Model No.:	PG-SYN-G
Test Standard:	EN IEC 61326-1:2021
Test Report Number(s):	4790895205-2.1-1

This verification of EMC Compliance has been granted to the applicant based on the results of the tests, performed by laboratory of UL-CCIC Company Ltd. on the sample of the above-mentioned product in accordance with the provisions of the relevant specific standards and Directive 2014/30/EU. The CE mark as shown below can be used, under the responsibility of the manufacturer, after completion of an EC Declaration of Conformity and compliance with all relevant EC Directives.

CE

Leon Wu

Leon Wu
UL-CCIC Company Limited.

Copyright of this verification is owned by UL-CCIC Company Ltd. and may not be reproduced other than in full and with the prior approval of the General Manager. This verification is subjected to the governance of the General Conditions of Services, printed overleaf.