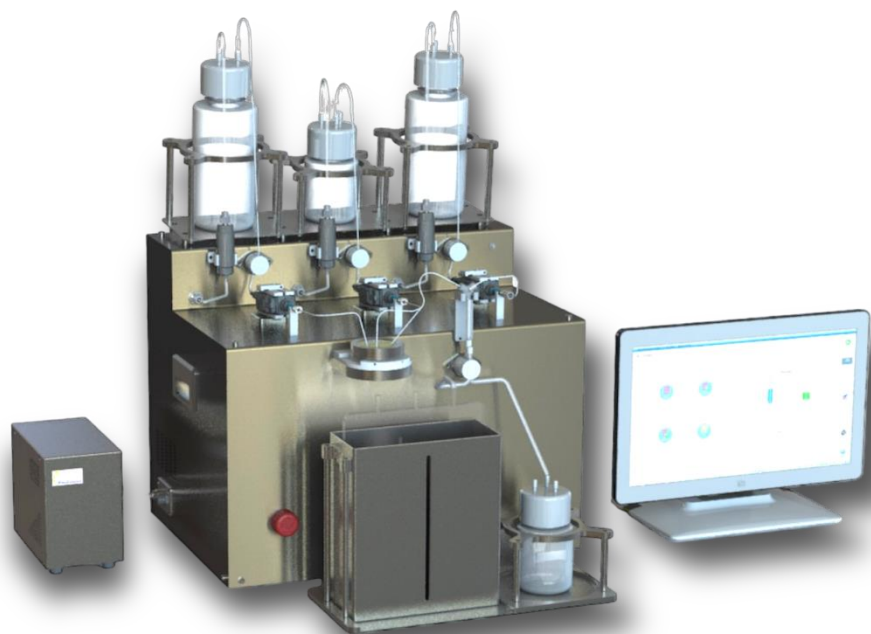


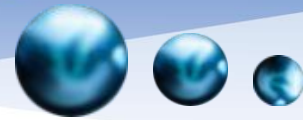
NanoGenerator[®] MAX Nanoparticle Synthesis System



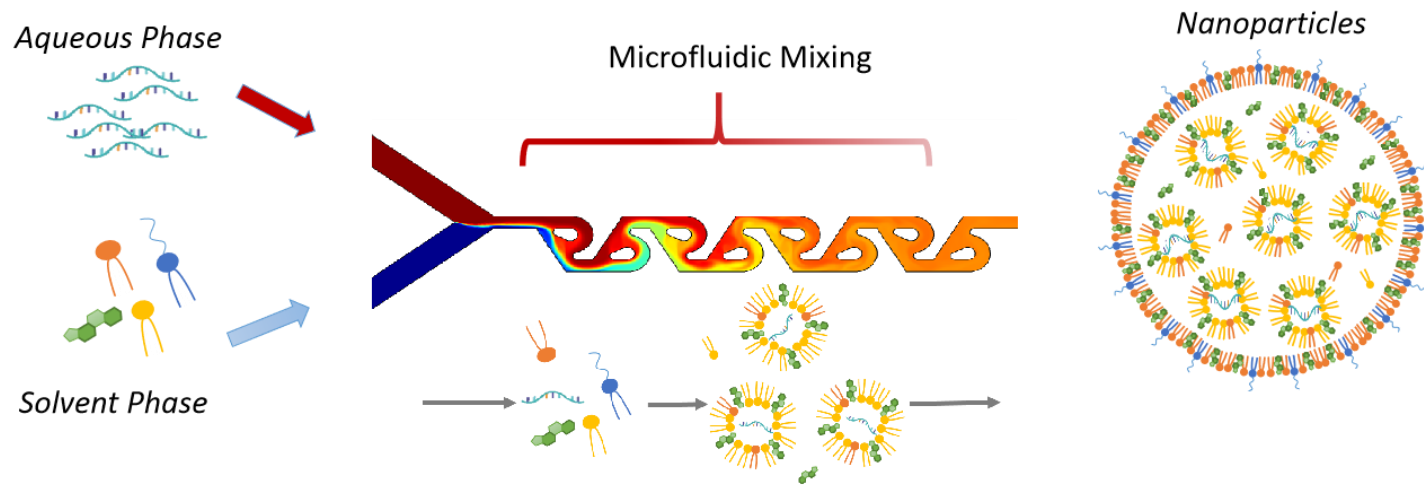
PreciGenome






Mar 2024

What are Lipid Nanoparticles?

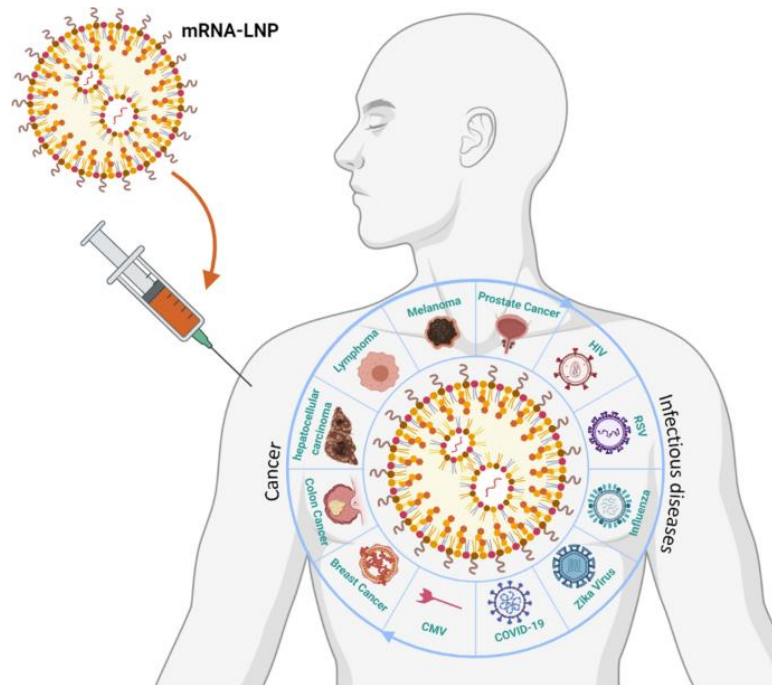
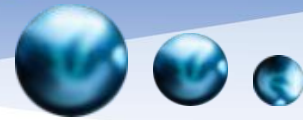


Lipid nanoparticles (LNPs) are self-assembling structures of natural or synthetic lipids in an aqueous environment.



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

RNA-LNP Therapeutics and Vaccines

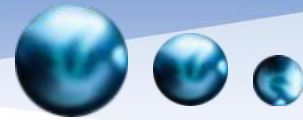


Name	Disease	Encoded antigen	Administration route	ClinicalTrials.gov identifier	Phase
Infections					
mRNA-1273	SARS-CoV-2	Spike	i.m.	NCT04470427	III (EUA and CMA)
BNT162b2	SARS-CoV-2	Spike	i.m.	NCT04368728	III (EUA and CMA)
CVnCoV	SARS-CoV-2	Spike	i.m.	NCT04652102	III
mRNA-1647	Cytomegalovirus	Pentameric 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).

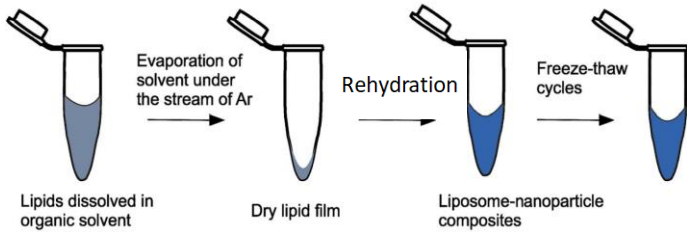
[Nature Reviews Materials](#) volume 6, pages1078–1094 (2021)

Lipid Nanoparticle Synthesis Methods



Conventional Methods

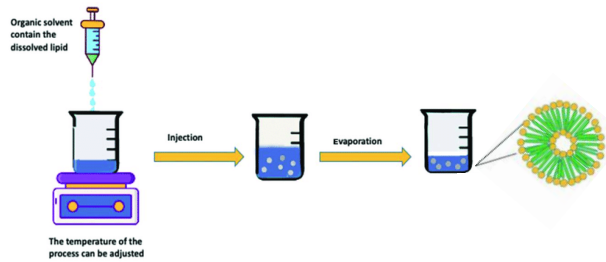
A Film hydration



- Established method
- Versatile method

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

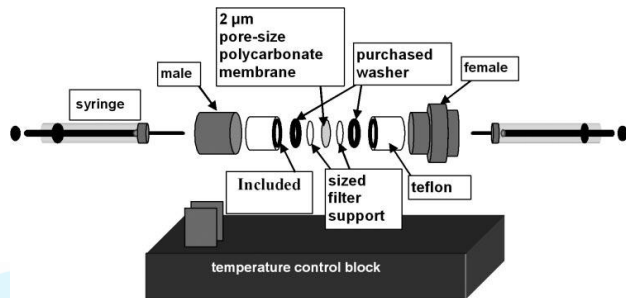
B Solvent injection



- Simple and fast
- Scaling-up possibility
- Controllable

- Exposing to organic solvent
- High PDI
- Stability problem

C Extrusion

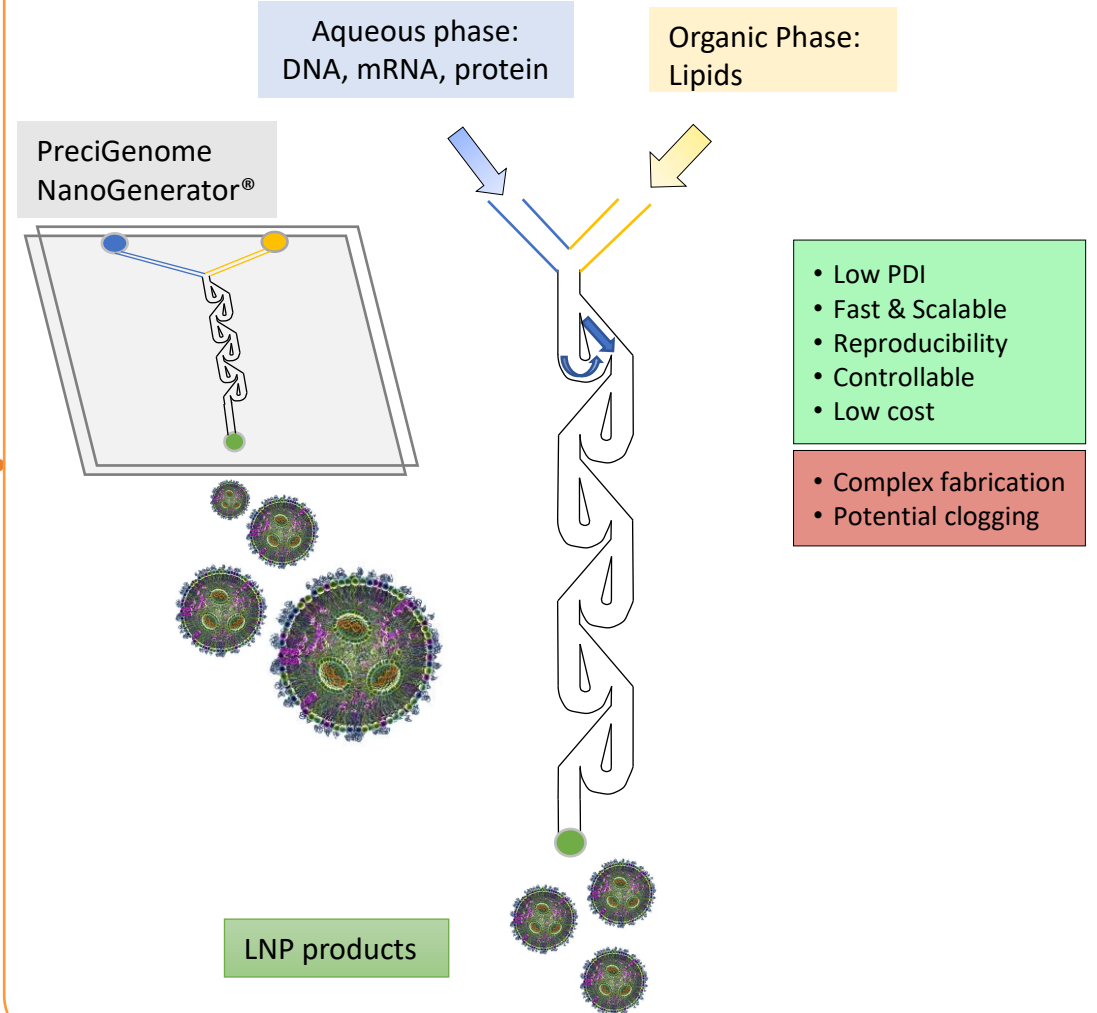


- Established method
- Uniform and homogenous formulation

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

Nanomaterials, Volume 11, 2021, 3440

Microfluidic Mixing

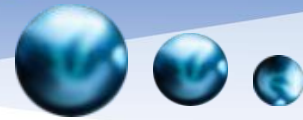


- Low PDI
- Fast & Scalable
- Reproducibility
- Controllable
- Low cost

- Complex fabrication
- Potential clogging

VS.

NanoGenerator[®] - Nanoparticle Synthesis System



FLEX-S



FLEX-S PLUS



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

FLEX-M



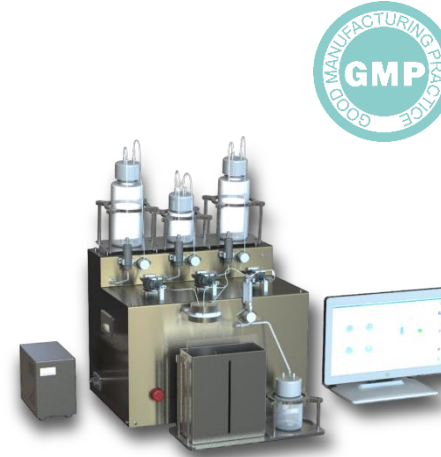
- Flex-M: 1 – 12 ml

PRO



- Pro: 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



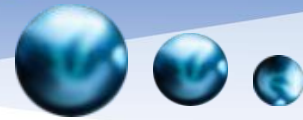
DISCOVERY & SCREEN

PRE-CLINICAL DEVELOPMENT

CLINICAL
DEVELOPMENT

CUSTOM SOLUTION

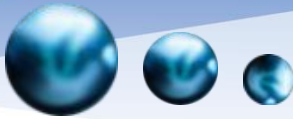
NanoGenerator® MAX — Intro



- 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

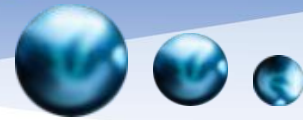


NanoGenerator® MAX — Spec



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:

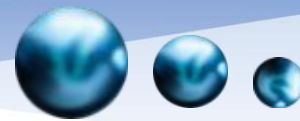
(Sterilized, Nuclease free, pre-assembled)



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



NanoGenerator® MAX — Software

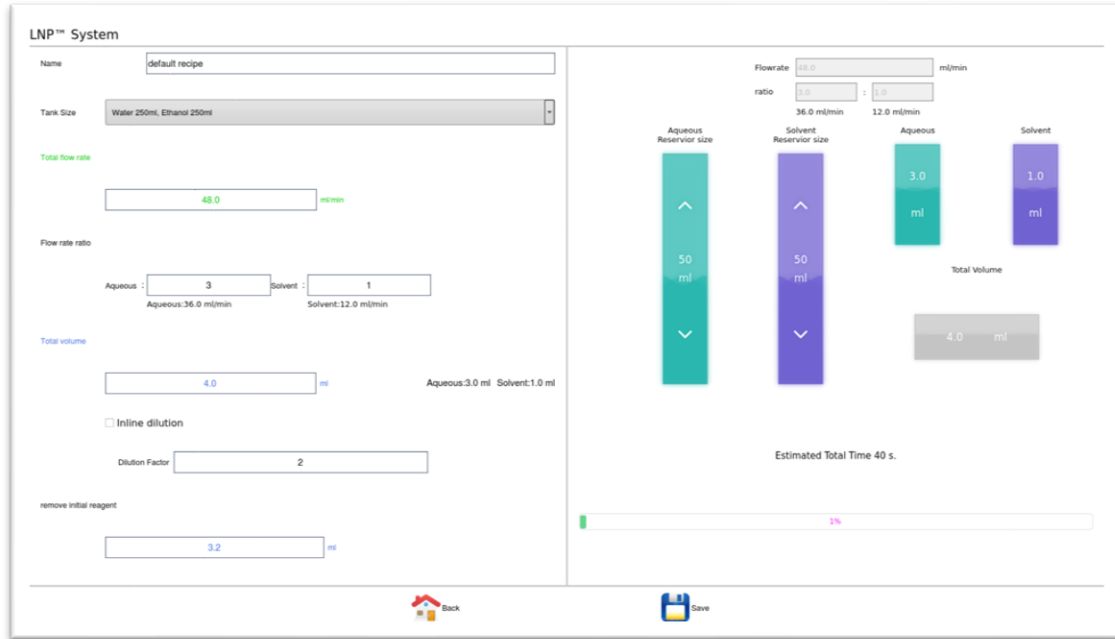
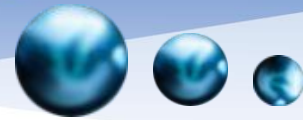


Software (21 CFR Part 11) Features:

- 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)

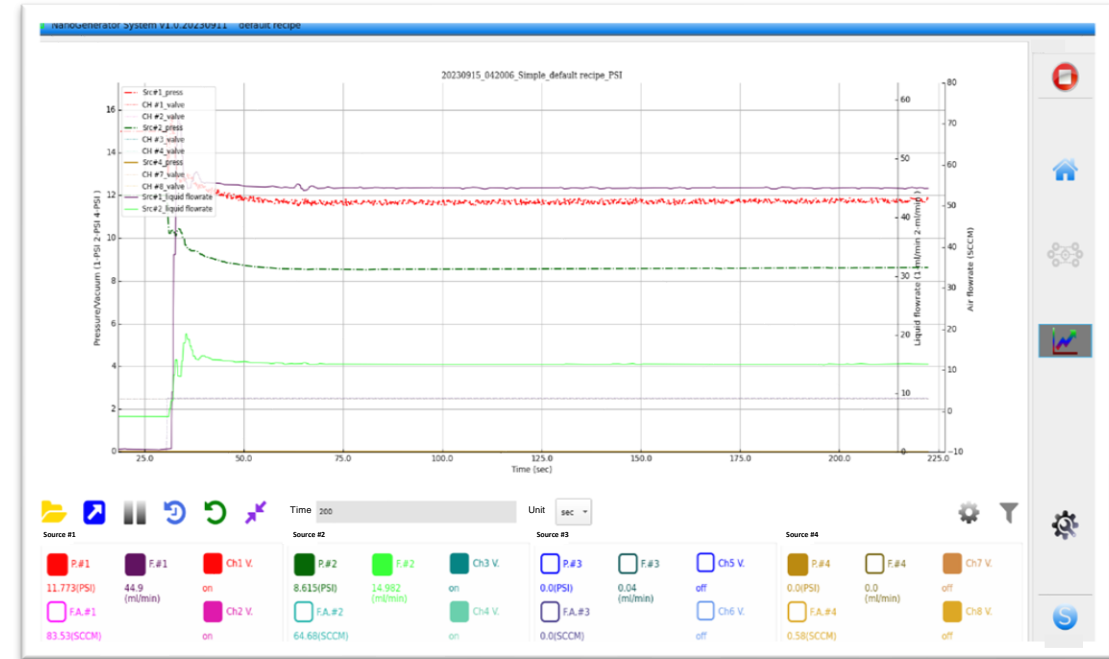
The screenshot displays the NanoGenerator System v1.0.20230524 software interface. The top window, titled 'LNP™ System', shows a control panel with a progress bar and 'Estimated Total Time 40 s.'. The bottom window, titled 'Settings List' and 'Current Settings (Advanced Mode)', shows a table with columns for Mode, Configuration, and Last Modify. The table contains one entry: 'default.recipe.advanced' with a last modify date of '2023/05/29 13:16:37'. Below the table are buttons for 'Load', 'Save', 'Set as Default', 'Import', 'Export', and 'Delete'. The 'Others' section includes a 'Pressure Unit' dropdown set to 'psi' and a grid of buttons: 'Data Export', 'Software Update', 'Import Data', 'Firmware Update', 'Flow Sensor Calibrating', 'System Time', 'Self-Check', and 'About'. A 'Functions' menu at the bottom includes 'History Data', 'User Management', 'Zero', and 'Audit Trail'.

NanoGenerator® MAX — Software



Easy-to-use UI to set parameters including:

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

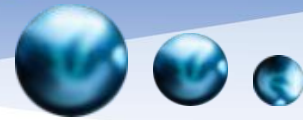


Easy-to-use real-time flow rate /pressure chart including:

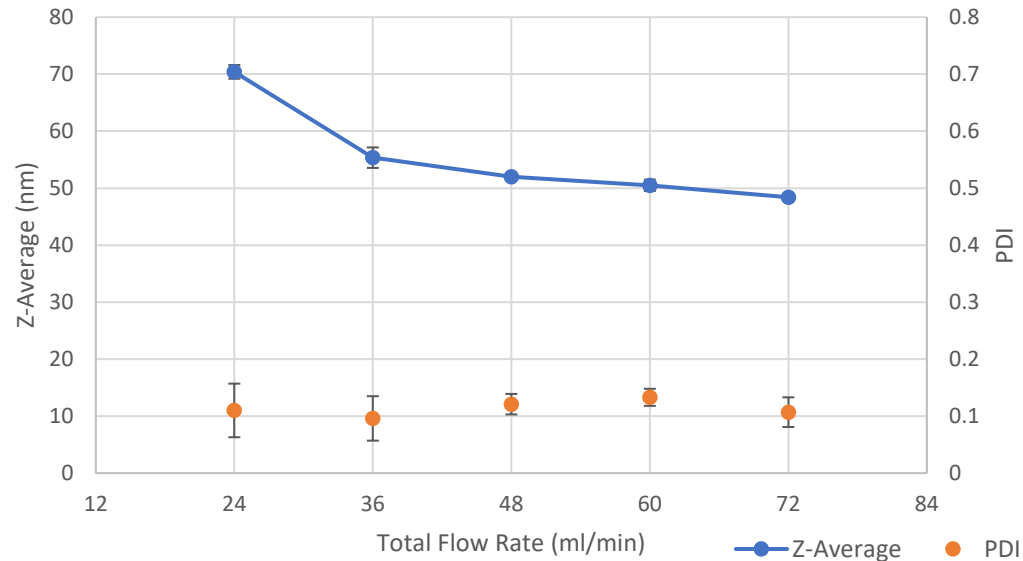
- Flow rate
- Pressure
- Air flow rate

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

NanoGenerator® MAX — Performance



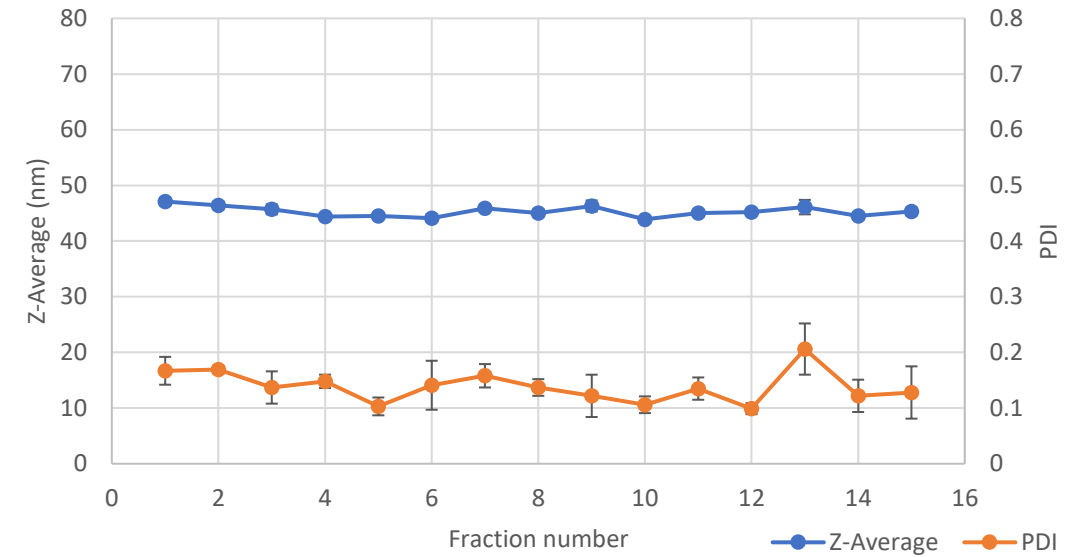
Nanoparticle Size vs. Total Flow Rate



- 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

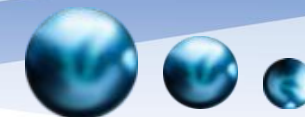
Nanoparticle Size uniformity (50 ml/fraction)



- 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

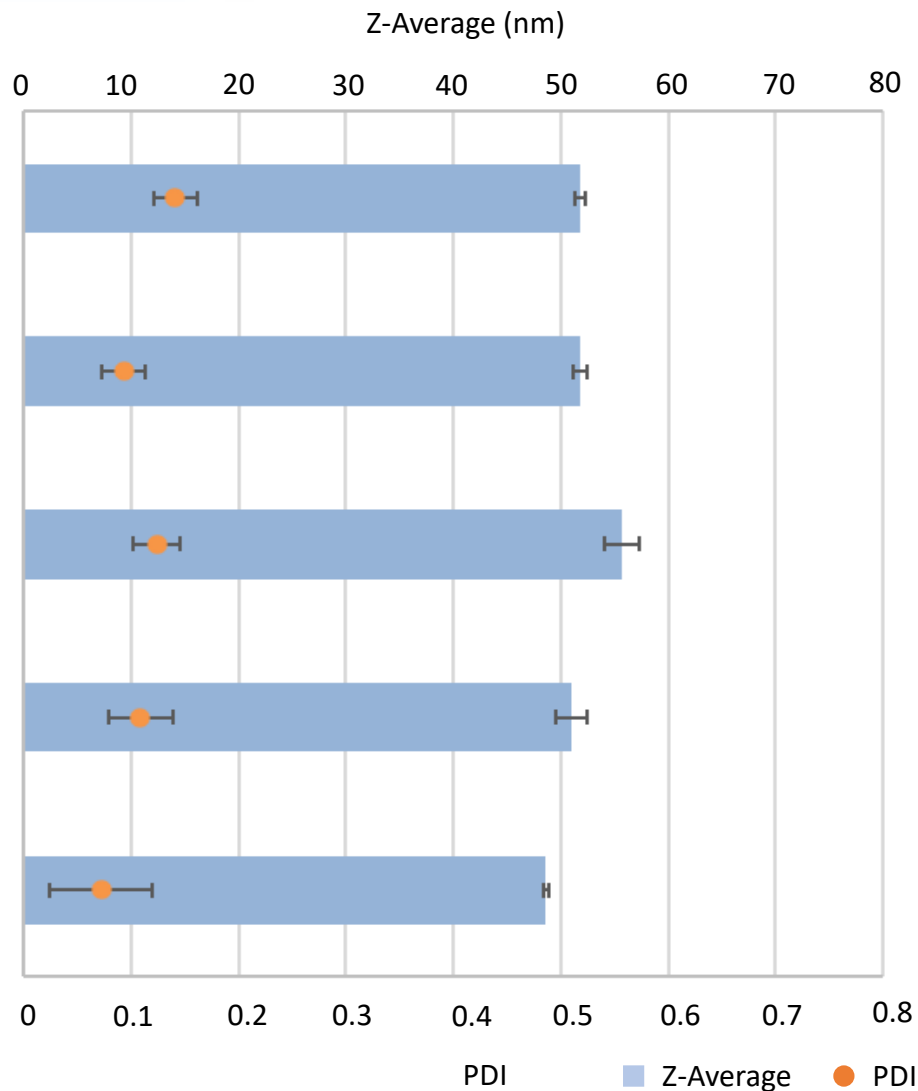
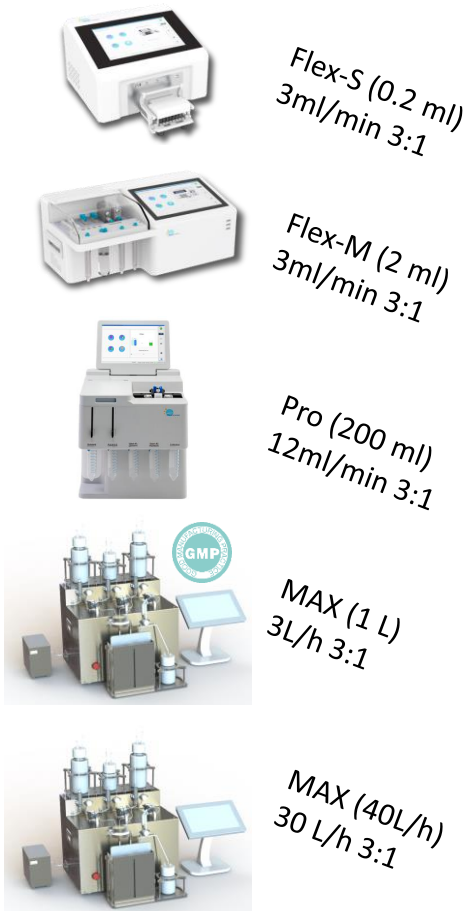
NanoGenerator® — Scale Up



DISCOVERY &
SCREEN

PRE-CLINICAL
DEVELOPMENT

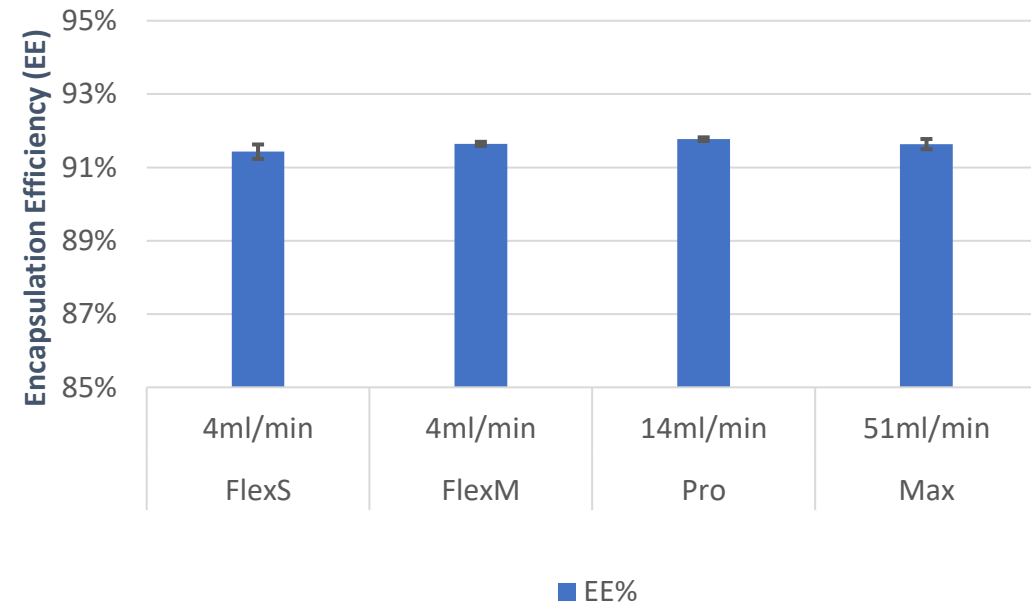
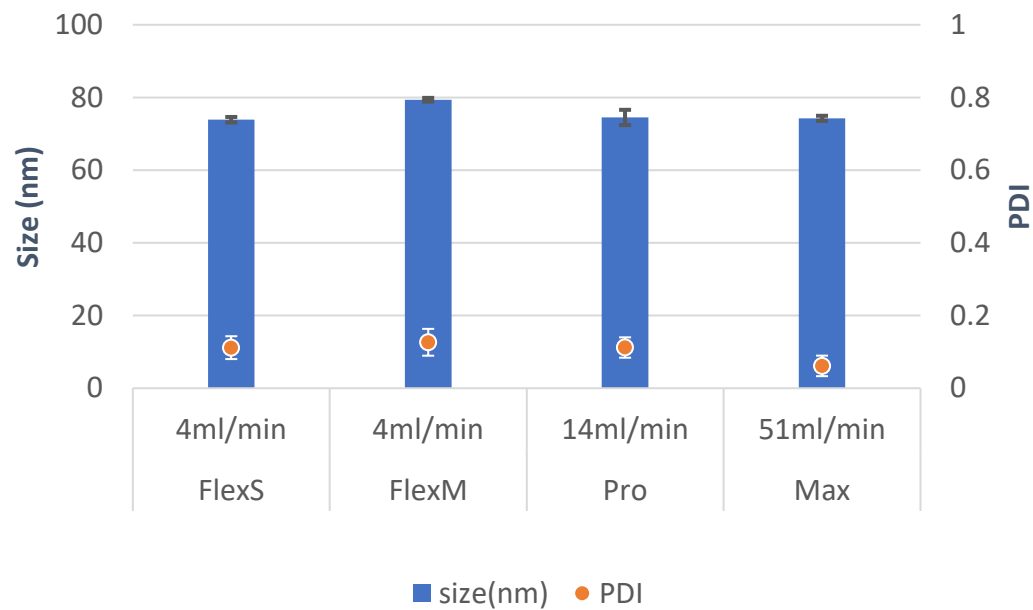
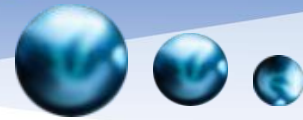
CLINICAL
DEVELOPMENT



- 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

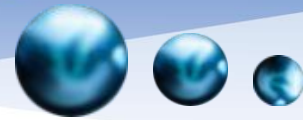
Reagents	
Aqueous phase	Sodium acetate buffer (100mM, pH5.2)
Solvent phase	LipidFlex, 15mM in ethanol

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

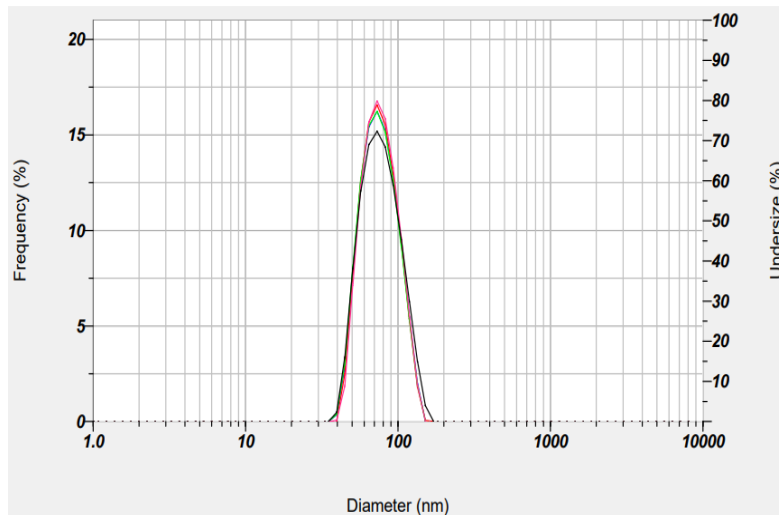


Figure 1. mRNA(eGFP)-LNP Synthesized by NanoGenerator. Average diameter is 67.3 nm. PDI is 0.106. Encapsulation efficiency is 94.5% (Ribo Green RNA Quantification Kit).

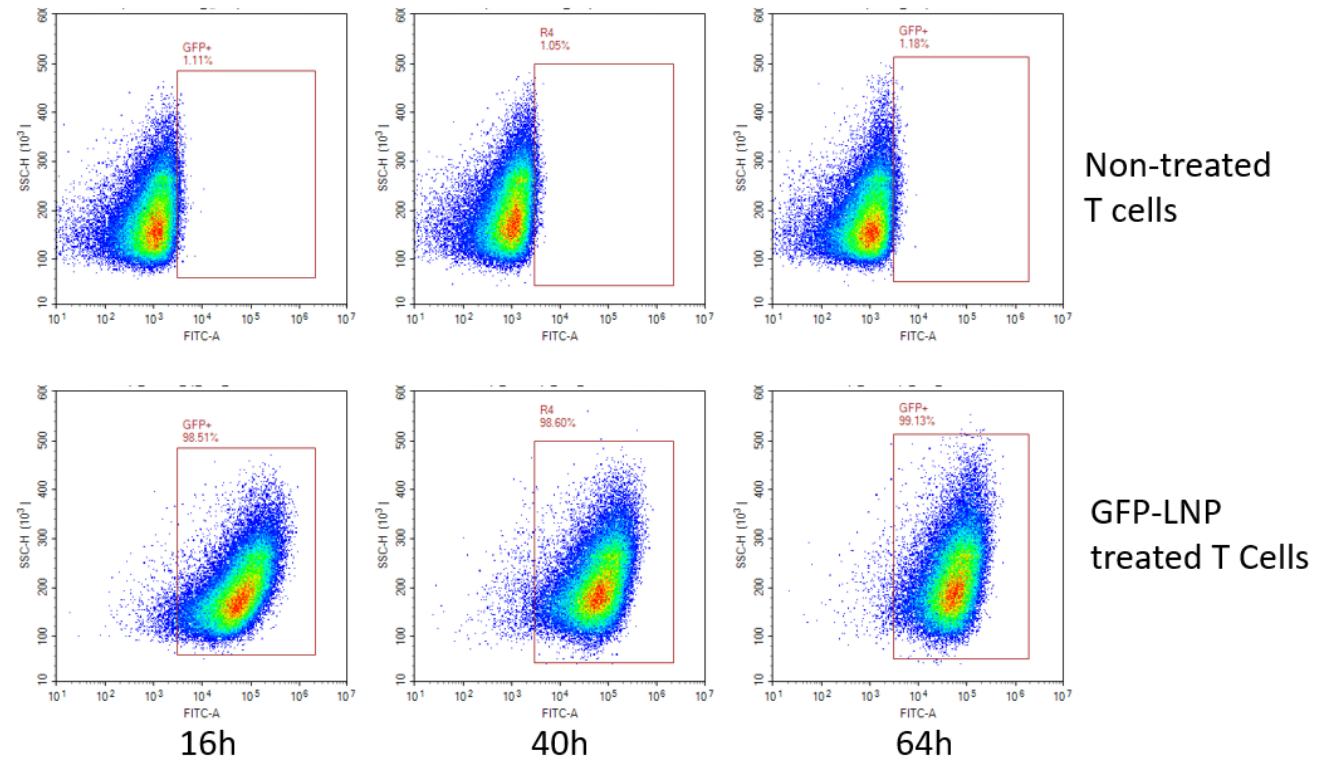
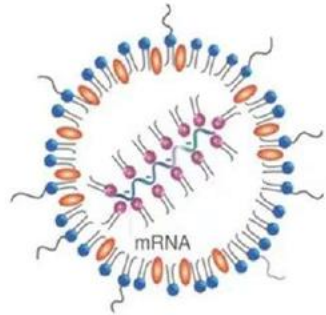
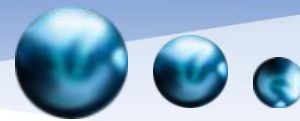


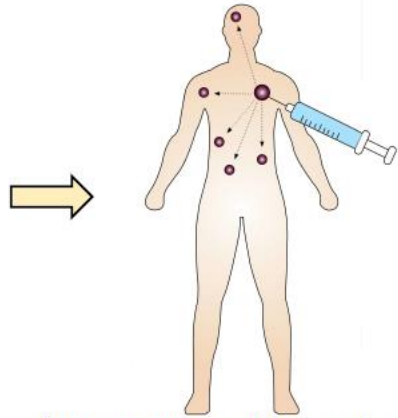
Figure 2. GFP(+) positive population of control (non-treat) and EGFP mRNA LNP treated primary T cells at 16, 40 and 64 hours. Cells were stained (1:50) using Biolegend 7-AAD Viability Staining for 10 minutes. Gating: First select for individual cells (excluding doublets). Then select for the healthy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



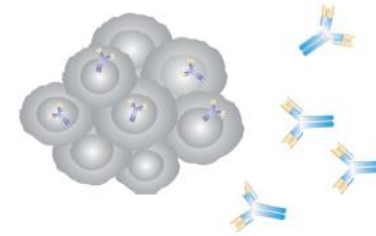
mRNA Encapsulation

In Vitro Transcription of mRNA encoding bispecific antibody & others.



Intra-tumoral injection

What happens post-injection?

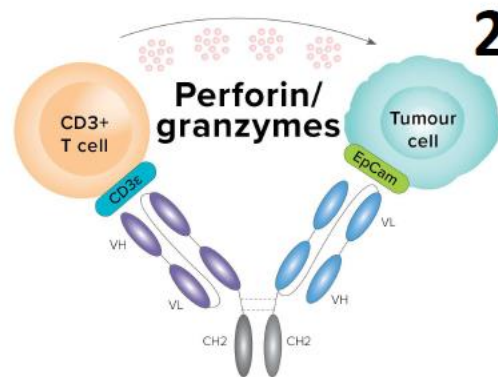


1

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

Co-encapsulation or Co-injection with:

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



2

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



1 Tumor antigens

- TAA
- TSA
- Whole tumor cell antigens

2 Adjuvants

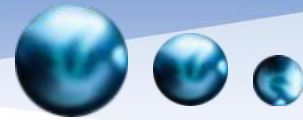
- Immune stimulation
- Enhance antigen availability
- Regulate immune phenotype

3 Delivery

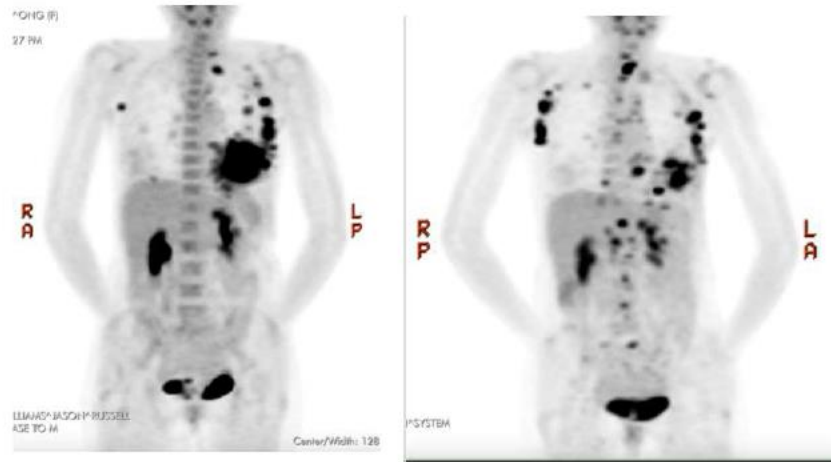
- Peripheral delivery
- Lymph node delivery
- Cytosolic delivery

3

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



Treatment of Two Late-Stage Breast Cancer Cases



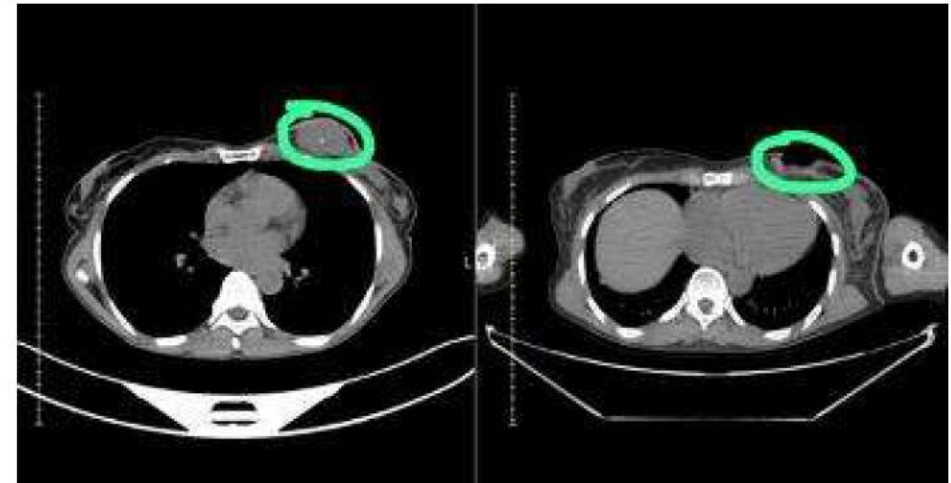
PET-CT 12/14/2023
Pre-treatment

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

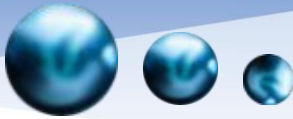
4/22/2024 After one Injection

Triple negative breast cancer

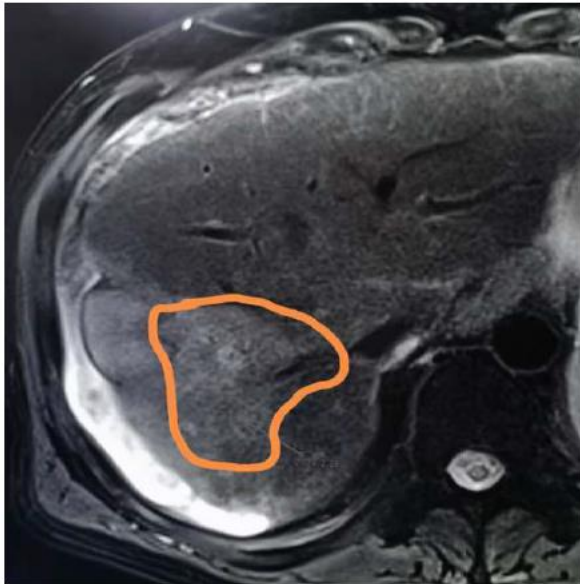
Case 2

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.



Cholangiocarcinoma with Liver Metastasis



02/28/2024 after one injection

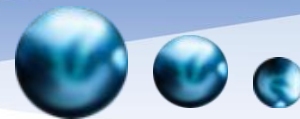


07/24/2024, after four injections

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

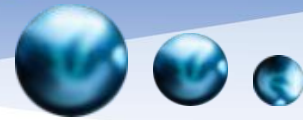


56.0 x 43.0 mm

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

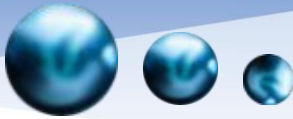


- Affordable configuration
- Lower cost per run

Custom Support

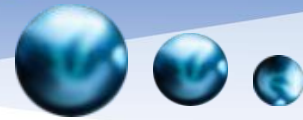


- Demo, Training and Support
- Extended Warranty
- Hot swap option
- Local US company



- **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 No. 020230724-01

Product Name	GMP Consumable Bag	Type	Sample	Lot No.	Sample
Sample ID	1, 2, 3, 4	Sterilization Lot No.	202307220101	Test Date	2023-07-24
Inoculation Method	<input type="checkbox"/> Membrane Filter <input checked="" type="checkbox"/> Direct Inj.				
FTM Lot No.	FTM-230724				
TSB Lot No.	TSB-230724				
Positive Strain	Staphylococcus aureus				

Test Result:

Culture Medium	Sample ID	1	2
FTM 30 - 35°C	1	-	-
	2	-	-
	3	-	-
	4	+	+
TSB 20 - 25°C	1	-	-
	2	-	-
	3	-	-
	4	-	-

Incubation Temperature (°C): 33

Dish No.: 1

Incubation Time: 24h, 48h

Average: ✓

Conclusion: ✓/Com

Remark: ✓

Notice: Put the "P" in the "I", in the "Re"

Tested by/Date: Yu Yanwei 2023

PurePower Medical Suzhou Purepower Medical Technology Co.,Ltd

EO Residual Test Report

No.: QT/QG/Q04-02 No. 020230724-01

Sample Name	GMP Consumable	Type	Sample
Lot No.	Sample		
Sample No.			
Test Date	2023		

Test Reference: JL-QG/Q04 EO Residual Test

Item	Sample1	Sample2	Sample3	Conclusion	Remark
					✓

Tested by/Date: Yu Yanwei

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 LLC

Manufacturer: Same as Applicant

Manufacturing Facility(ies): Suzhou Precige Unit 202, Building

Report No.: E526160-D1003

Report (Re) Issue Date: 2023-12-06

Base Standard(s): EN 61010-1:2011

Additional Standards: N/A

Report Types: This report consists of Information

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, control and protection parts

Report Number: E

Date of issue: 2

Total number of pages: 1

Name of Testing Laboratory preparing the Report: N

Applicant's name: P

Address: 2

Test specification:

Standard: I

Test procedure: I

Non-standard test method: N

TRF template used: I

Test Report Form No.: I

Test Report Form Originator: V

Master TRF: 2

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This report is not valid as a CB Test Report and appended to a CB Test Certificate if applicable.

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Statement of Compliance

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No. 4790895205-2.1-51
Issue Date: 2023-08-26

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

CE

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