



Acceleration Strategies for mRNA-LNP Drug Development Focus on Shortening Early-Stage Process Development Timelines

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Contents

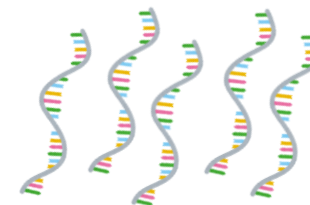
- 1 | Our IVT platform and process development technology
- 2 | High-Purity mRNA Manufacturing Technology Focused on dsRNA Reduction

Overview of mRNA Manufacturing Flow and Process Development Challenges

■ Schematic Diagram of mRNA API Manufacturing Process



Linear DNA



mRNA

■ Challenges in mRNA API Manufacturing

- mRNA quality, defined by factors such as full-length RNA percentage and residual dsRNA levels, is known to significantly impact target protein expression. Therefore, quality control of mRNA drug substance is critically important.
- *in vitro* transcription (IVT) is a multi-component system. Achieving high-quality mRNA and designing a robust manufacturing process requires considerable time.
- Downstream processes to enhance mRNA purity are also required.

➤ **Rapid Optimization of IVT process and Purification Process are Key to accelerating mRNA drug development**

Our mRNA Manufacturing and Process Development Framework

**Small scale
(for research use)**

mRNA synthesis
and QC

Release

- within one month

Sequence
determination
DNA procurement

Selecting
Initial IVT condition

**Middle to large scale
(for GLP-Tox, Phase1 CTM)**



mRNA synthesis
and QC

Release

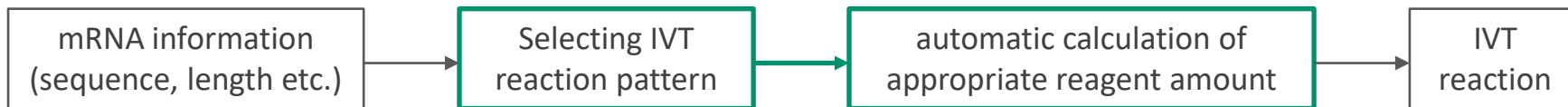
- Release four months
after development started

Optimization cycle using DOE

Development for purification process

Selecting a pre-determined IVT condition based on target mRNA information

- Based on sequence information and our experience, IVT reactions are classified into three patterns, and reagents amounts are automatically set.
- Applicable to various types of mRNA
- **Without experimental trial and error**



RNA No.	mRNA length (nt)	Condition	Yield (mg/mL IVT)	RNA Integrity (%)
RNA-1	860	B	4.5	76
RNA-2	900	A	5.3	96
RNA-3	3000	A	4.5	88
RNA-4	4300	B	4.6	91
RNA-5	11500	C	4.4	65

- **Our initial IVT condition enables rapid, medium-to-high quality mRNA synthesis for early-stage research. (no need for initial IVT reaction condition screening)**

Examples: Optimization flow of IVT process using Design of Experiment (DoE)

mRNA-5 (need to improve, previous slide)

RNA No.	mRNA length (nt)	Condition	Yield (mg/mL IVT)	RNA Integrity (%)
RNA-5	11500	C	4.4	65



Optimization by using DoE

Target value: yield 5mg/mL IVT, RNA Integrity >70%

Experiment 1

- 13 reactions
- Factor: [Mg], [T7 RNA pol.], [DNA]
- Analysis: main effect, interaction

Experiment 2

- 16 reactions
- Factor: [Mg], [T7 RNA pol.], [DNA], Temperature
- Analysis: main effect, interaction

Experiment 3

- **Select IVT condition in the design space**
- Compare the predicted values and measured values of the quality profile under the selected conditions.

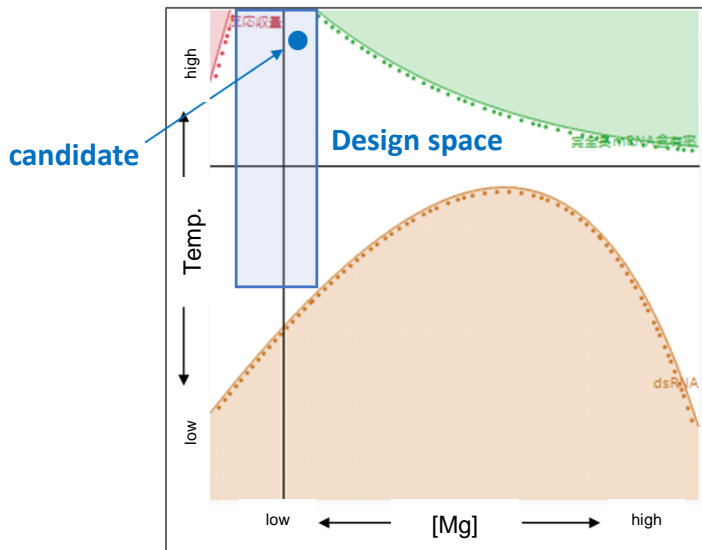
Defining the design space by Experiment 1 and 2

Examples: Comparison of mRNA Quality Predictions and Actual Measurements

condition	Prediction in design space				Actual measured value			
	Yield (mg/mL IVT)	Integrity (%)	Capping efficiency (%)	dsRNA (%)	Yield (mg/mL IVT)	Integrity (%)	Capping efficiency (%)	dsRNA (%)
original	-	-	-	-	4.4	64.8	-	0.73
candidate	5.2	74.4	99	0.19	5.4	74.3	98	0.26

Target value: yield 5mg/mL IVT, RNA Integrity >70%

Contour Profiler



【DOE conditions】

- Output: RNA yield [mg/mL], Integrity [%], dsRNA [%], Capping efficiency [%]
- Input: Mg [mM], Temperature [°C], T7 RNA polymerase [U], template DNA [mg/mL IVT]
- Plan: response surface model (central composite design (CCD))
- Model fitting: Least squares method

【IVT condition】

- NTPs: 5mM each, Capping reagent: 4mM
- Target mRNA length: 11500 nt



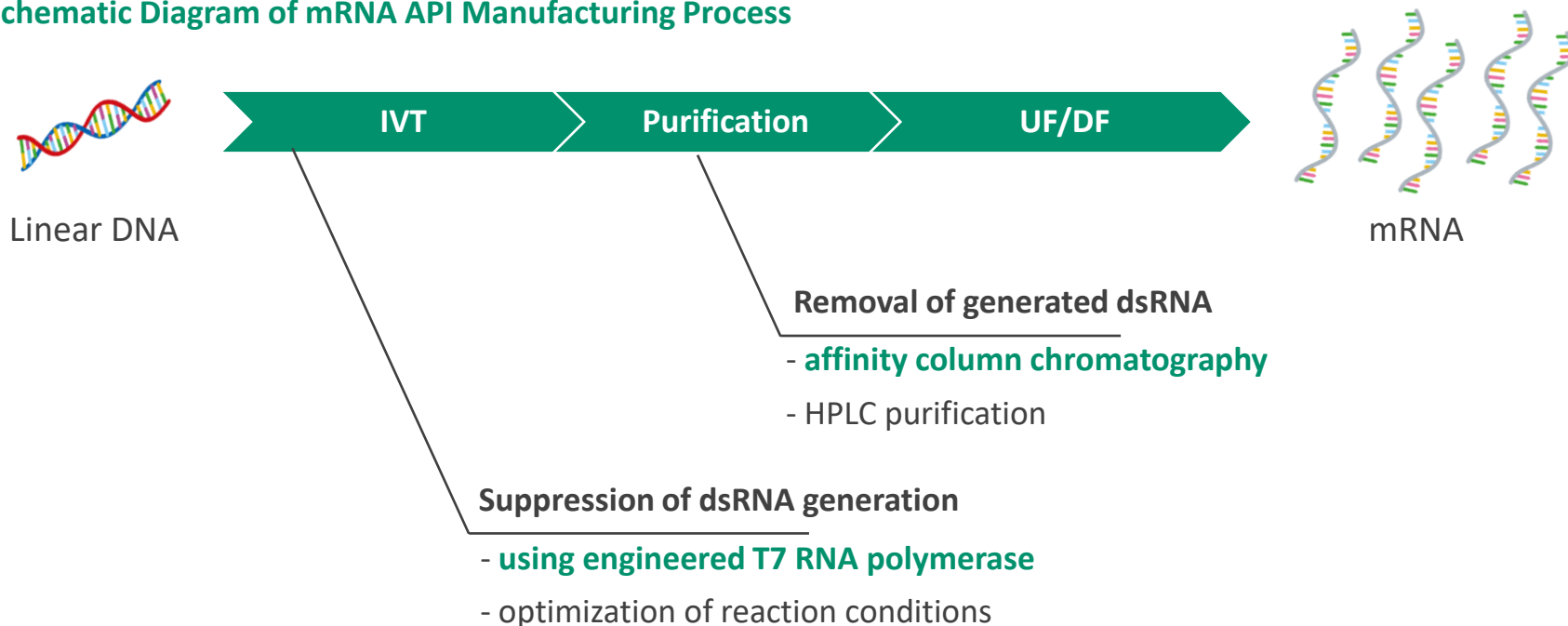
➤ **Optimal condition was determined in just three experimental cycles, allowing IVT optimization to be completed within one month.**

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Possible methods for reducing dsRNA

■ Schematic Diagram of mRNA API Manufacturing Process



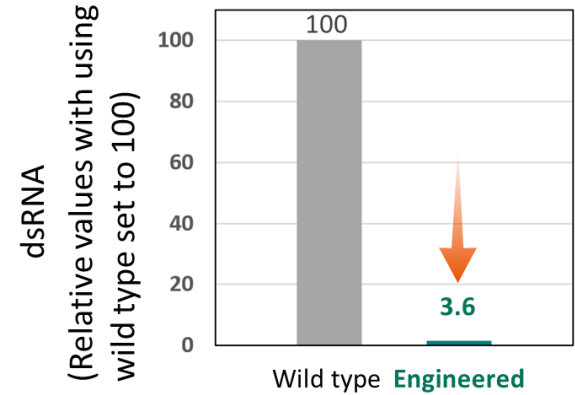
- We screened commercially available engineered T7 RNA polymerase that match our IVT platform.
- Furthermore, we implemented a column purification process to remove dsRNA in the downstream process.

Development of mRNA manufacturing technology for at dsRNA reduction

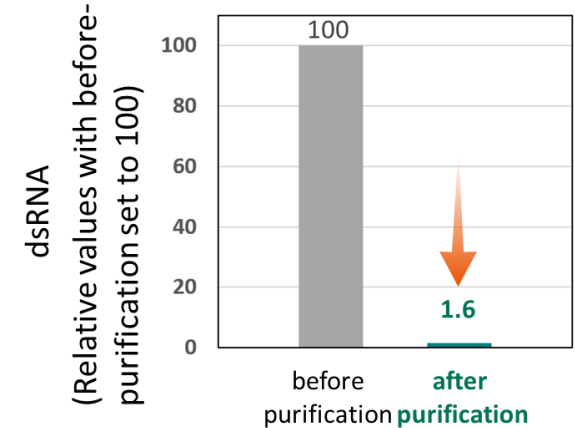
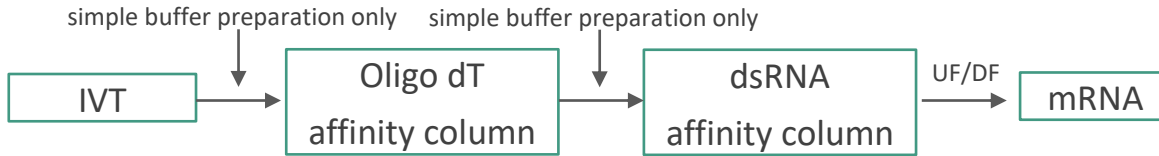
Suppression of dsRNA generation using engineered T7 RNA polymerase



- Engineered T7 RNA polymerase was made by Japanese company

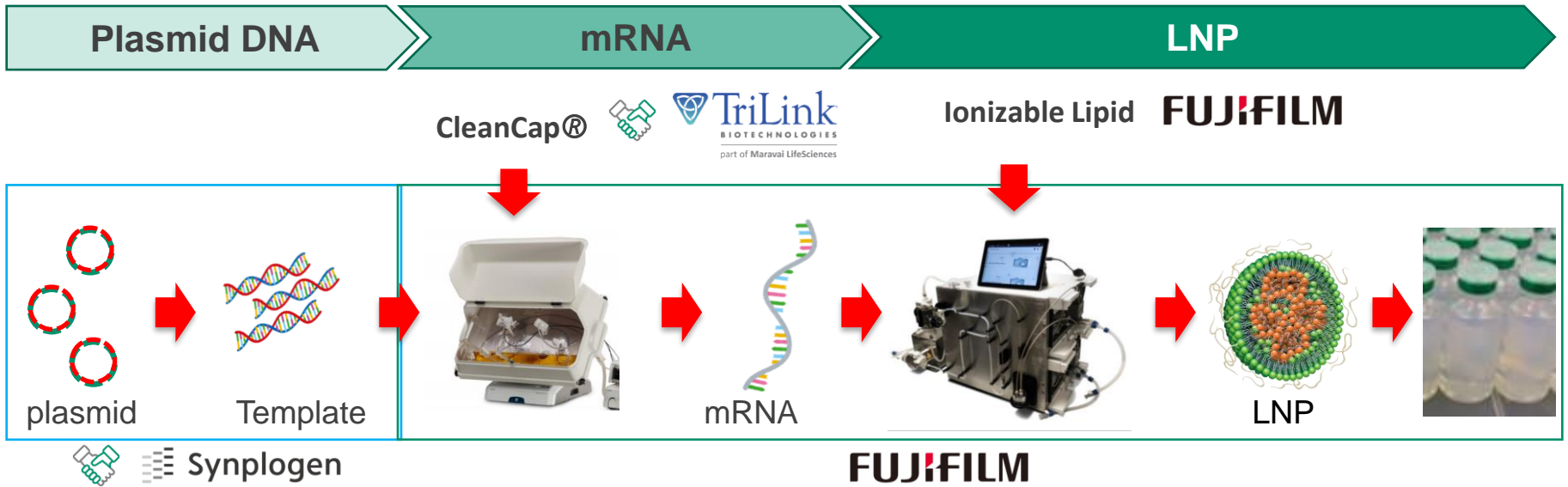


dsRNA removal by column purification



- **These technologies have been implemented in our laboratory.**
- **We have a proven track record of manufacturing mRNA.**
(2g scale, dsRNA <0.02%)

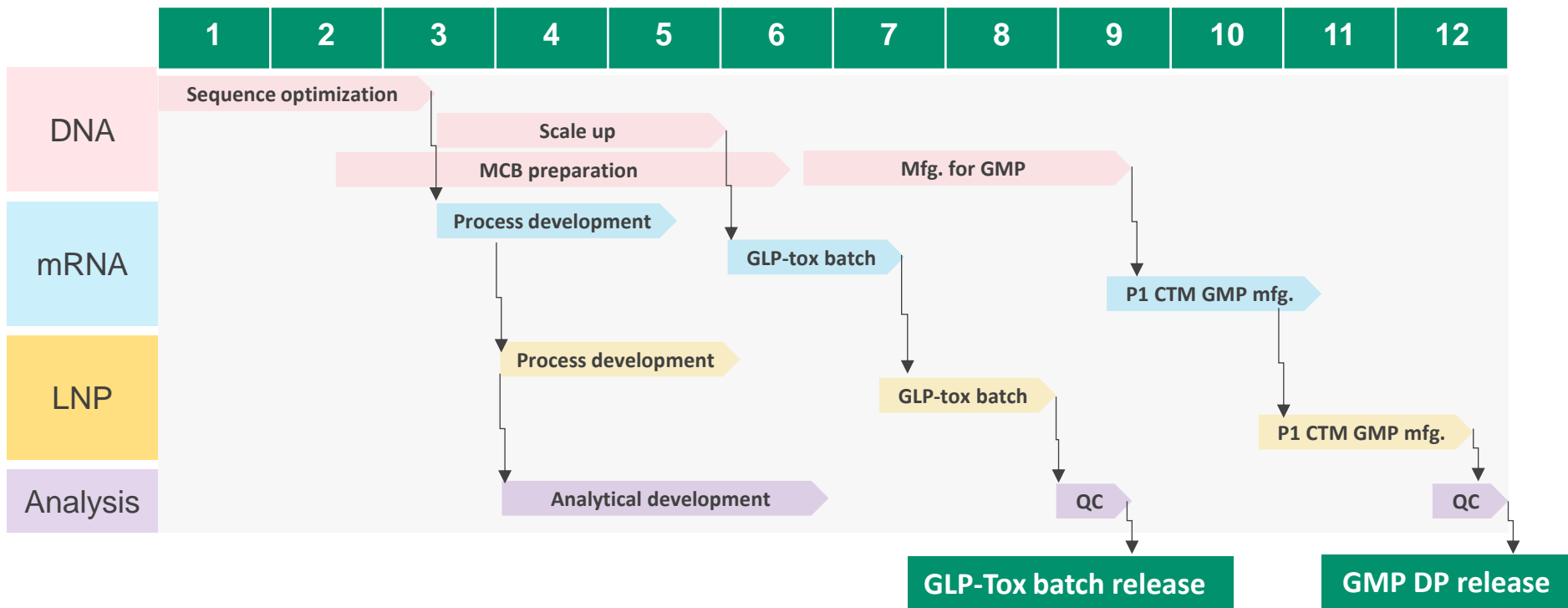
Our mRNA-LNP end-to-end CDMO service



- **For customers at research phase**
 - Designing mRNAs and LNPs and manufacturing prototypes
 - Optimizing mRNA-LNP formulations
- **For customers at development phase**
 - Developing process and analytical methods
 - Manufacturing mRNA-LNPs under GMP









Integrated manufacturing from mRNA sequence design to LNP formulation

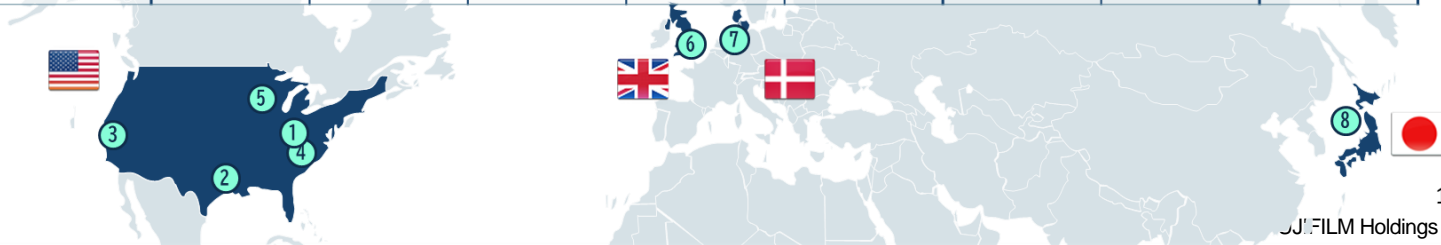
- Collaboration with partner companies for mRNA sequence design to template DNA manufacturing
- Acceleration achieved by performing all processes in-house: from mRNA process development to LNP investigational drug manufacturing, including analytical development




Bio CDMO business portfolio of FUJIFILM group

Reinforcing the global service offering for a wide range of modalities including the advanced therapeutics

		North America				Europe		Asia	
		RTP NC, US	College Station TX, US	Thousand Oaks CA, US	Holly Springs NCC, US	Madison Wisconsin, US	Billingham UK	Hillerod Denmark	Toyama Japan
Investment projects already announced as of Jun. 2024 *Without small molecules									
Figures in parentheses are the operation period of facilities under expansion.									
Antibody Drug	Large-Scale (=20,000L)				● (2025)		● (1st : 2024) (2nd : 2026)		
	Small-Medium Scale	●	●				● (2026)	● (2026)	
Recombinant Protein		●					● (2028)		
Gene Therapy			●				● (2027)		
Cell Therapy				● (2025)		● (2026)			
Vaccine		●	●			●		● (2027)	
ADC								● (2027)	
mRNA/LNP/Liposome								●	
Formulation			●	●	● (2025)		● (2024)	●	
Assembly, Labeling & Packaging					● (2025)		● (2024)	●	





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We bring diverse ideas, unique capabilities,
and extraordinary people together to change the world.

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