inside Therapeutics

PROTOCOL

TAMARA Extensive Cleaning: RNase Decontamination

Step-by-step cleaning of the TAMARA reservoir and fluidic path before a demonstration, after extensive use, or optionally ahead of any RNase-sensitive work.

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Author: Sezen Gul, PhD
Experimental work: Yannick Mousli, PhD; Jade Giraud, MSc
Illustrations & design: Julien Ridouard



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Introduction

This protocol describes an extensive cleaning workflow for the TAMARA nanoparticle formulation system, complementing the routine cleaning instructions provided in our RNA-LNP Formulation Protocols [1,2]. It is intended for situations requiring a more thorough cleaning than the routine between-run procedure, including preparation for demonstrations and periodic deep cleaning. It can also be performed ahead of any RNase-sensitive work when additional assurance is desired.

This extensive cleaning workflow combines standard TAMARA wash cycles with manual reservoir decontamination using an RNase-removal solution. It consists of four main stages: (1) pre-clean wash cycles, (2) manual RNase decontamination of the reservoir, (3) thorough rinsing with RNase-free water, and (4) final wash cycles (Fig. 1).

Notation. Throughout this document, H_2O refers to RNase-free water, and EtOH to pure ethanol. Wash solutions are listed in the order of aqueous tank/solvent tank (e.g., H_2O/EtOH). The symbol × indicates the number of consecutive wash cycles. Washes are performed sequentially in the order shown.

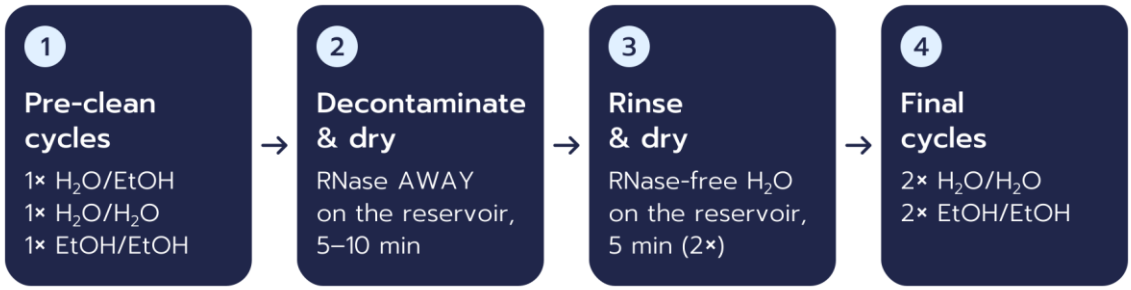


***Figure 1**. TAMARA extensive cleaning workflow for RNase decontamination.*

Which cleaning level do you need?

Routine cleaning is generally appropriate between experimental runs. The wash solutions and sequence can be adapted according to the formulation and experimental requirements. When more thorough cleaning is needed, the extensive cleaning workflow described here incorporates manual reservoir decontamination using an RNase-removal solution.

Table 1 summarizes routine between-run cleaning procedures detailed in our RNA-LNP Formulation Protocol: SM-102 or ALC-0315 [1,2], alongside the extensive cleaning workflow described in the following sections.

__Table 1__. Recommended cleaning procedures according to the experimental context.

Cleaning level	Situation	Recommended cleaning procedure
Routine between-run	Consecutive runs with the **same** lipid mix and RNA solution	≥1× H_2O/EtOH
Routine between-run — Broader	Consecutive runs with a **different** lipid mix or RNA solution	1× H_2O/EtOH 1× H_2O/H_2O 1× EtOH/EtOH
Extensive cleaning — RNase decontamination	Deeper cleaning before demonstrations or as part of periodic cleaning; optionally ahead of any RNase-sensitive work	**Pre-clean:** 1× H_2O/EtOH 1× H_2O/H_2O 1× EtOH/EtOH **Decontamination:** RNase AWAY on the reservoir, 5–10 min; then dry **Rinse:** H_2O on the reservoir, 5 min (2×); then dry **Final wash:** 2× H_2O/H_2O 2× EtOH/EtOH

Materials

__Table 2__. Materials required for TAMARA extensive cleaning with RNase decontamination.

Category	Materials
Equipment	• TAMARA system with its reservoir (S or L) • Pipette for loading the tanks (e.g., P5000)
Reagents	• RNase-free water • RNase-removal solution (e.g., RNase AWAY) • Pure ethanol • 70% ethanol for work-surface cleaning
Consumables	• Microfluidic chips • Low-lint laboratory wipes (e.g., Kimtech) • RNase-free pipette tips • Falcon tubes

Reminder: The standard wash cycle

The pre-clean and final wash steps in this protocol use the standard TAMARA wash cycle. The key steps are summarized below; detailed screen-by-screen instructions are available in the TAMARA User Manual [3].

1. On the Controller home screen, press Clean.
2. Install a gasket and a chip, close the Synthesis module, and place a collection tube at the chip outlet.
3. Purge any remaining liquid from the system, then press Next.
4. Open the Synthesis module and load the wash solutions into the aqueous and solvent tanks at the recommended volumes.
5. Close the Synthesis module, start the wash cycle, and allow the wash solutions to pass completely through the system. The cycle automatically ends with a purge to remove residual liquid from the system and chip.

TAMARA extensive cleaning protocol using an RNase-removal solution

This four-step procedure combines automated TAMARA wash cycles with manual reservoir decontamination using an RNase-removal solution. Follow the steps below to perform the extensive cleaning procedure.

Before you start

Setup checks

- **Power and connections:** Ensure that the power and pressure supplies are connected, the Controller is connected to the Synthesis module, and the Controller is switched on.
- **Inlet pressure:** TAMARA is specified for 8–10 bar (120–150 psi) using a dry, non-corrosive, non-explosive gas. Lower inlet pressures may reduce the maximum achievable total flow rate and cleaning performance.
- **Mixer selection:** For extensive cleaning, the baffle mixer can be used even if the staggered herringbone mixer (SHM) is used for experimental runs, or vice versa. This minimizes unnecessary exposure of the formulation mixer to cleaning solutions.
- **Controller settings:** Select the micromixer geometry installed for cleaning, the reservoir size, and the cleaning solvent, then enter the current laboratory temperature.
- **Waste collection:** Place a collection tube at the chip outlet to collect waste.

Handling

- **Gloves and wipes:** Wear RNase-free gloves throughout the procedure. Use Kimtech or equivalent low-lint wipes for wiping and drying.
- **Compatible liquids:** Use only liquids compatible with the wetted materials: PEEK (reservoir), TOPAS® COC (chip) and silicone (gasket). The TOPAS® COC chip is compatible with aqueous solutions and polar organic solvents but not with non-polar solvents (see TAMARA User Manual [3], Appendix B).
- **Reservoir filling:** Do not exceed the maximum reservoir volume. Maintain at least 1 cm of headspace between the liquid surface and the top of the reservoir.
- **Controller protection:** Do not use or spill liquid on the Controller module.
- **Chip reuse:** Chip reusability depends on the formulation, concentration, and processed volume. If the same mixer geometry will be used for extensive cleaning and subsequent experimental runs, a blank run is recommended to verify fluidic performance (see "Optional: Verify with a blank run" below).

Step 1: Pre-clean the system

1. On the Controller home screen, select Clean to access the wash-cycle workflow.
2. Run the following three wash cycles consecutively to flush the fluidic path:
   - 1× H_2O/EtOH
   - 1× H_2O/H_2O
   - 1× EtOH/EtOH

Step 2: Decontaminate the reservoir with RNase-removal solution

1. Prepare a clean work surface: apply 70% ethanol, then an RNase-removal solution (e.g., RNase AWAY), to a glass or ceramic surface, wiping the surface after each application with low-lint wipes.
2. Open the Synthesis module and remove the chip and the gasket. Remove the reservoir from the Synthesis module and place it on the cleaned work surface, away from the Controller module.
3. Spray the RNase-removal solution evenly over the reservoir surfaces. Thoroughly wet all inlet and outlet openings, ensuring that the solution also reaches the inside of both tanks. The tanks do not need to be filled, but all accessible surfaces and openings should be wetted.
4. Leave the RNase-removal solution in contact with the reservoir for 5–10 min.
5. Turn the reservoir upside down and drain any remaining solution.
6. Dab the reservoir dry with low-lint wipes and clean the benchtop.

Step 3: Rinse the reservoir with RNase-free water

1. Place the reservoir back on the cleaned work surface.
2. Thoroughly wet all tanks, channels and chip inlets with RNase-free water. A P5000 pipette can be used to dispense water.
3. Allow the water to overflow through the different compartments to help remove residual RNase-removal solution. Slight bubbling during rinsing is normal.
4. Leave the water in contact with the reservoir for approximately 5 min.
5. Empty the reservoir.
6. Repeat actions 2–5 once more (two rinses in total) to ensure thorough removal of residual RNase-removal solution.
7. Dab the reservoir dry with low-lint wipes.

Step 4: Run the final wash cycles

1. Once the reservoir is dry, reinstall it in the Synthesis module, together with the gasket and chip, ensuring that the chip is oriented in the desired direction.
2. Run the following TAMARA wash cycles sequentially:
   - 2× H_2O/H_2O
   - 2× EtOH/EtOH

Completing Steps 1–4 provides a thorough cleaning of the system in preparation for subsequent RNase-sensitive experiments.

Optional: Verify with a blank run

If the mixer geometry used for extensive cleaning will also be used in subsequent experimental runs, a blank run is recommended to verify fluidic performance before processing valuable samples.

1. Perform a blank run with your aqueous phase and solvent under the selected formulation conditions.
2. Compare the collected volume with the expected volume. A volume error of up to 10% is acceptable.
3. If the volume error exceeds 10%, use a new chip. If it is within the range, ensure the chip is dry and proceed with the experimental run.

After cleaning: System storage

- Ensure that no liquid remains in the system during storage. If liquid is present in the drain at the back of the Synthesis module, empty it.
- Lower the Synthesis module lid without locking the handle and leave the pressure connection tube connected to minimize the entry of contaminants.
- Turn off the pressure supply when the system is not in use.

References

1. Inside Therapeutics. RNA-LNP Formulation Protocol (SM-102). Section 3.8, “System cleaning” (p. 6).
2. Inside Therapeutics. RNA-LNP Formulation Protocol (ALC-0315). Section 3.8, “Clean the system” (p. 9).
3. Inside Therapeutics. TAMARA User Manual, document version T-UM.09.25-1. Chapter VI, “Cleaning protocol” (pp. 36–38), and Chapter VII, “Going further” (p. 44).