Hitachi Chemical

ExoComplete™ Strip 800

For fast and easy extracellular vesicle derived poly(A)$^+$ RNA isolation

INSTRUCTION MANUAL

For Research Use Only

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Intended Use

ExoComplete™ System is intended for research use of molecular biology applications. This product is neither intended for the diagnosis, prevention, or treatment of a disease, nor has it been validated for such use either alone or in combination with other products.

Product Description and Principle

ExoComplete™ System can isolate extracellular vesicle (EV)-derived poly(A)$^+$ RNA including messenger RNA (mRNA) in a microplate format by a simple and seamless procedure. Up to 96 samples can be easily processed at once.

EV from body fluids such as plasma, serum and urine can be captured by EV Capture device with a proprietary filter material. Depending on the sample volume and quantity, 3 types of devices are available: 1) EV Capture 8-well Strip for small volumes and small number of samples, 2) EV Capture 96-well Plate for small volumes and large number of samples, and 3) EV Capture Tube for large volumes of samples.

High EV affinity and porosity of the filter material allow high yield and reproducible isolation of EVs without the use of conventional ultracentrifugation. Undesirable substances larger than EV such as cells, cell debris and apoptotic bodies can be removed by centrifugation before applying to the EV Capture device.

The isolated EVs can be lysed directly on the EV Capture device by adding a lysis buffer. Guanidine thiocyanate and other components in the lysis buffer immediately and effectively inactivate ribonucleases to ensure isolation of intact RNA.

After transferring the EV lysates to the mRNA Capture Plate or mRNA Capture 8-well Strip, poly(A)$^+$ RNA is isolated through hybridization with single stranded oligo(dT) immobilized on the surface of the wells. The advantage of this method over conventional magnetic beads and spin column methods is better sample-to-sample reproducibility and ease of handling.

Once poly(A)$^+$ RNA is hybridized onto the mRNA Capture Plate or mRNA Capture 8-well Strip, a wide variety of downstream applications become available including:

- Real time quantitative RT-PCR (qPCR)
- Next-generation sequencing (NGS)
- Single- and double-stranded cDNA synthesis

Key Benefits

Easy to use

- Seamless process from EVs to mRNA isolation
- Minimal liquid transfer, fewer centrifugation steps
- Less hands-on time

High throughput

- Up to 96 samples can be processed at once

Excellent reproducibility

- Outstanding intra- and inter-assay precision

Kit Contents

ExoComplete™ Strip 800 Number of samples	**Part No. 88013** 24
EV Capture 8-well Strip (800µL/well)	3 X 8 well
mRNA Capture 8-well Strip	3 X 8 well
Lysis Buffer A	1 X 2 mL
Lysis Buffer B (Lyophilized)	1 x 60 µL
Lysis Buffer C	1x 120 µL
DNase RNase Free Water	1 x 300 µL
Wash Buffer A	1 x 35 mL
Wash Buffer B	1 x 65 mL
Sample Treatment Buffer	1 x 20 mL
Deep Well Plate	1
Aluminum seal	3

After mRNA isolation, cDNA can be synthesized directly in the well, using **Reverse Transcription Reagent (Part No 88017),** which was optimized especially for the mRNA Capture Plate and the mRNA Capture Strip.

Reverse Transcription Reagent Number of samples (30µL/reaction)	**Part No. 88017** 48
RT Buffer A	1 x 1,700 µL
RT Enzyme Mix B	1X 30 µL

Kit Storage

The ExoComplete™ products are shipped at ambient temperature.
Store all components at 0°C -30°C.
Prior to experiment, store Wash Buffer A and Wash Buffer B at 0°C-10°C.
If there is crystallization in the Lysis Buffer A and Wash Buffer A, warm up at 37°C until crystallization is dissolved, then store at 0°C -10°C.

Reverse Transcription Reagent is shipped with dry ice. Store at -20°C ± 5°C.

Equipment and Supplies Not Included in the Kit:

Supplies

- Ice pan or bucket
- Microcentrifuge tubes or centrifuge tubes
- 8-channel aspirator (recommended)
- 8-channel pipettor (recommended)
- Reservoirs for 8-channel pipettor (recommended)

Equipment

- Incubator (37°C)
- Centrifuge with microplate holders
- Vortexer
- Vacuum pump or vacuum line and dessicator (recommended)

Important Notes Before Use:

- First-time users should read through the entire manual prior to commencing an experiment.
- Do not allow mRNA Capture Plate or mRNA Capture 8-well Strip to sit for prolonged periods in between steps. Once the protocol has been initiated, proceed continuously to completion.
- The use of gloves and good laboratory technique are recommended to prevent RNase contamination causing RNA degradation.

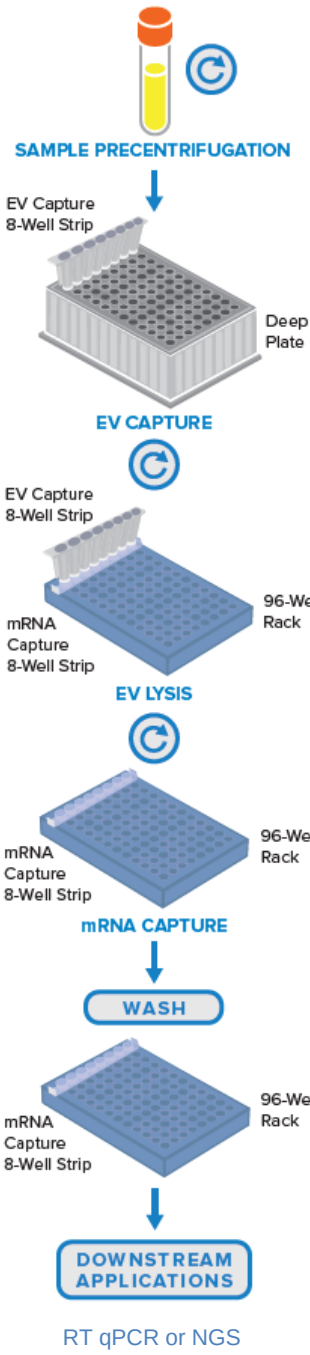
Safety Information

- Wear protective clothing, goggles and gloves when handling chemicals. For further information, please consult the appropriate safety data sheets (SDSs).
- Lysis Buffer A and Wash Buffer A contain guanidine thiocyanate, a known hazardous chemical that causes skin irritation.

- CAUTION: DO NOT add bleach or acidic solution directly to sample-preparation waste. Lysis Buffer A and Wash Buffer A contain guanidine thiocyanate, which can form highly reactive compounds when combined with bleach. If liquid containing these buffers is spilled, clean with a suitable laboratory detergent and water. If the spilled liquid contains potentially infectious agents, clean the affected area first with laboratory detergent and water, and then with 1 % (v/v) sodium hypochlorite.

Protocol Overview

ExoComplete™ Strip 800



STEP 1.

Centrifuge plasma sample at 3,500 xg for 15 min.

Transfer supernatant to a new tube and add 1/3 volume of Sample Treatment Buffer.

STEP 2.

Add Sample Mixture to EV Capture 8-well Strip.

Centrifuge strip at 2,500 xg for 5 min.

STEP 3.

Add Lysis Buffer.

Incubate at 37°C for 10 min.

Centrifuge at 2,500 xg for 5 min.

STEP 4.

Incubate at 4°C overnight.

STEP 5.

Wash with Wash Buffer A, then Wash Buffer B on ice.

STEP 6.

Add reverse transcription solution.*

Incubate at 37°C for 2 hrs.

OR

Elute mRNA

Incubate at 65°C for 5 min.

Protocol

Prior to Experiment

1. If Lysis Buffer A and/or Wash Buffer A have crystallization, warm up at 37°C to dissolve. It should then be stored at 4°C.
2. Keep Wash Buffer A and Wash Buffer B at 4°C prior to use.

Experimental Procedure

Step 1

1. Centrifuge sample to remove cells and cellular debris.

   Note: We recommend the following centrifugation conditions. These conditions may be modified.

   Plasma: centrifuge at 3,500 xg for 15 min at 4°C
   Urine: centrifuge at 800 xg for 15 min at 4°C

2. Transfer supernatants to a microcentrifuge tube and add 1/3 volume of Sample Treatment Buffer. For example, if plasma sample (supernatant) is 600 µL, add 200 µL of Sample Treatment Buffer. Mix well by briefly vortexing.
3. Place the EV Capture 8-well Strip on the top of the Deep Well Plate.

Step 2

4. Transfer up to 800 µL of the sample and Sample Treatment Buffer mixture to the EV Capture 8-well Strip.
5. Cover the top of the strips with the Aluminum seal to avoid any contamination.
6. Centrifuge at 2,500 xg for 5 min at 4ºC.

   Note: If sample volume is more than the capacity of the well, repeat steps 4 - 6.

7. Reconstitute Lysis Buffer B (lyophilized) by adding 60 µL of DNase RNase free water.

   Note: Reconstituted Lysis Buffer B can be stored at -20°C. Do not repeat freeze – thaw cycles.

Step 3

8. Prepare working lysis buffer at the ratio as described below.

   Note: The working lysis buffer volume corresponds to the number of wells.
   Do not alter the ratio of each buffer. Each well requires 60 µL of working lysis buffer. Make enough solution with at least approximately 10-20% more. The buffer should be prepared fresh for each new procedure.

working lysis buffer	per well
Lysis Buffer A	55.5 µL
Lysis Buffer B	1.5 µL
Lysis Buffer C	3.0 µL
Total volume	60 µL/well

9. Remove the mRNA Capture Strip from the storage pouch and place on the 96-well Rack. Mark the wells to be used.
10. Place the EV Capture 8-well Strip on top of the mRNA Capture Strip.
11. Add 60 µL of the working lysis buffer to the respective wells of the EV Capture 8-well Strip and place the Aluminum seal on top of the strip.
12. Incubate at 37ºC for 10 min.
13. Centrifuge at 2,500 xg for 5 min at 4°C.

Step 4

14. Discard EV Capture 8-well Strip and place the Aluminum seal on top of the mRNA Capture 8-well Strip.
15. Incubate the mRNA Capture 8-well Strip at 2-8ºC overnight (>16 hours).

    Note: Overnight incubation is recommended to ensure capturing low abundant genes that take longer hybridization.

    Note: Do not reuse EV Capture 8-well Strip and mRNA Capture 8-well Strip

Step 5

16. Fill pan or a bucket with ice.
17. Place the mRNA Capture 8-well Strip (with Rack) and reservoirs for Wash Buffers on ice.
18. Take out Wash Buffer A and Wash Buffer B from the refrigerator and pour into the reservoir on ice (the volumes of Wash Buffers are dependent on the number of sample wells).

    *Note: Keep the strips and wash buffers **ICE COLD**.*

19. Aspirate lysates in the mRNA Capture 8-well Strip.
20. Dispense 100 µL of Wash Buffer A into each well and aspirate. Repeat two more times (total of 3 times).
21. Dispense 150 µL of Wash Buffer B into each well, cover with the lid and incubate 3 min then aspirate. Repeat two more times (total of 3 times).

22. Take out the mRNA Capture 8-well Strip from ice pan. Remove any remaining liquid in the wells.

    Note: It is highly recommended to tap strips face down several times on lint-free cloth followed by vacuum drying in the vacuum desiccator for 10 min.

Step 6

23. The mRNA hybridized to the strip can be used directly as a template for cDNA synthesis or eluted as mRNA for downstream applications such as NGS.
    a. For cDNA synthesis:
        1) Directly add reverse transcription solution (Reverse Transcription Reagent, Part No 88017, or other desired solution) to well and follow manufacturer's protocol.

    b. For mRNA elution:
        1) Add 60 µL of DNase and RNase free water and cover wells tightly with clear or aluminum seal.
        2) Incubate at 65°C for 5 min, then cool to 4°C for 5 min.
        3) Centrifuge at 1500 xg for 1 min at 4°C.
        4) Transfer eluted mRNA to microfuge tube and store at -80°C or proceed to downstream application.

Appendix

References

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Limitations of Procedure

a) The ExoComplete™ System is designed, manufactured, and sold for research purposes only. This product is NOT intended for use in diagnostic or clinical procedures.

b) Information in this document is subject to change without notice. Hitachi Chemical Diagnostics, Inc. assumes no responsibility

c) Great care should be exercised in handling the products. Each component of the ExoComplete™ System should be stored at recommended storage conditions. Exercise care when handling kit components to prevent inadvertent nuclease contamination. (Hands and dust particles are the most common sources of nuclease contamination)

d) Accurate and reproducible results are dependent upon properly functioning instruments and reagents and good laboratory technique.

Trademarks

Real-time PCR or qPCR (quantitative PCR) is covered by patents owned by Life Technologies Corporation, Applied Biosystems Inc. or its subsidiaries as applicable. All other trademarks are the sole property of their respective owners.

Literature Citation

When describing a procedure for publication using this product, please refer to it as the ExoComplete™ System.

Patents and Licensing Notifications

The ExoComplete™System is covered by patents: US Patent Nos.6638428, 6844158 and foreign equivalents, 7258976, 7214781 and foreign equivalent, 7374881 and foreign equivalent, 7741023 and foreign equivalents, 7745180 and foreign equivalents, 7939300, 7981608, 7968288, 8076105, 8101344, 7816081, 7838239 and foreign equivalent, 8268982, 8268566, 9150920, 9012615 and foreign equivalent, 9458496, 9662649, 9719129 and foreign equivalent; ZL03809293.X, JP4772055, JP5706913, EP2513336, JP5767336, JP5837691, EP2635189, ZL201180052766.9, DE212013000295.5, EU003433440-0001_0009, JP6059350 JP1576471, JP1576472, JP1576473, JP1576474, JP1576593, JP1576594, JP1576595, JP1576596, JP1576475, JP6106277, and US and foreign patent applications currently pending.

Terms and Conditions of Sale

With respect to sales and use of ExoComplete™ System, please refer to the entire Terms and Conditions of Sale set forth herein.

These Terms and Conditions of Sale ("Terms and Conditions") shall govern all orders for and purchases of products from Hitachi Chemical Diagnostics, Inc. (HCD) and constitute a binding contract between HCD and the customer identified on the face of the Quotation and/or Sales Acknowledgement, as applicable. Customer accepts these Terms and Conditions by making a purchase from or placing an order with HCD unless customer and HCD have signed a separate agreement, in which case the separate agreement will govern to the extent there is any conflict with these Terms and Conditions.

These Terms and Conditions contain the entire understanding of the parties with regard to the matters contained herein and supersede and replace in their entirely and any all prior communications and contemporaneous agreements and understandings, whether oral, written, electronic or implied, if any, and any subsequent purchase order(s) terms from customer, between the parties with regard to the subject matter hereof.

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The price for any products provided by HCD ("Product") shall be the price stated in HCD's quotation to customer for the Product ("Quotation") or, for repeat sales based upon an original Quotation without the issuance of a new Quotation, the price stated in HCD's Sales Acknowledgement to customer for the Product ("Sales Acknowledgement"). Quotations are valid for thirty (30) days from the quotation date unless otherwise stated in the Quotation. All taxes (such as any applicable sales, use, transaction, excise or similar taxes), fees, duties, levies or federal, state, local, provincial or other governmental assessments or charges ("Taxes"), shipping and handling charges, freight and insurance are excluded from Product prices but payable by customer and may be billed as separate items on the invoice of HCD. Customer shall pay all Taxes related to Product (other than income taxes assessed against HCD's net income). In order to claim any exemption from such Taxes, customer shall provide HCD with a tax exemption certificate acceptable to the relevant taxing authorities. HCD reserves the right to make adjustments to pricing and Product for reasons including, but not limited to, changing market conditions, Product discontinuation, Product unavailability, and supplier price changes. All orders are subject to Product availability.

2. PAYMENT
Invoiced amounts are due and payable within the time period specified on the invoice measured from the invoice date. Customer agrees to pay interest on all past-due sums at the lower of one and one-half percent (1.5%) per month or the highest rate allowed by law. Customer will pay for, and will indemnify and hold HCD and its parent and affiliates harmless from, any applicable Taxes imposed on the Products. If customer intends to claim any exemption from such taxes, fees or charges, customer must do so at the time of purchase and provide HCD with the necessary supporting documentation. In the event of a payment default, customer will be responsible for all of HCD's costs of collection, including, but not limited to, court costs, filing fees and attorneys' fees.

3. ACCEPTANCE OF ORDERS, TITLE AND RISK OF LOSS OR DAMAGE
HCD may accept or reject any customer purchase order for Product in whole or in part. If HCD accepts a purchase order, it will use reasonable efforts to ship the Product ordered under the purchase order within a reasonable time after ordered, or, if a shipment date is stated in HCD's Quotation or Sales Acknowledgement, on or before such date. Unless otherwise stated in HCD's Quotation or Sales Acknowledgement, as applicable, title and risk of loss or damage with respect to all Products shall pass from HCD to customer upon transfer of possession of the Product to a carrier at HCD's or its manufacturer's facility (freight prepaid and added).

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Customer may cancel an order of ten (10) units or less if such request is sent to HCD thirty (30) or more days prior to shipment. An order of more than ten (10) units cannot be cancelled.

6. TECHNICAL SUPPORT
HCD will provide technical support to customer with respect to Product during HCD's business hours at a level that is customary in the industry in responding to customer's questions regarding Product.

7. REJECTION OF GOODS AND WARRANTY
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fifteen (15) days from the date of customer's receipt of the Product containing (i) a detailed description of the Rejected Product and the reason for rejection, (ii) the lot number corresponding to the Rejected Product, if applicable, and (iii) the "best use by" date of the Rejected Product, if applicable. In certain circumstances HCD may require additional information or have additional instructions in support of a claim for Rejected Product. For any valid claim timely made and agreed to by HCD, HCD will replace the Product or component(s), or refund the purchase price paid, at HCD's option. Shipping and insurance charges for the replacement will be covered by HCD. The replacement is made only to the customer purchasing the Product directly from HCD, is not transferable and does not extend to the benefit of any other person or entity, unless otherwise expressly stated in writing by HCD. The foregoing is customer's sole remedy with respect to any warranty of Rejected Product, provided however, such warranty shall not apply to any Product that (i) has been modified or altered, (ii) is not maintained or is used in a manner other than specified in the protocols, instruction manuals and other written materials, as applicable, created by HCD, relating to the use, operation, support or maintenance of the Product(s) ("Documentation"), or (iii) is mishandled or treated with abuse or negligence.

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