XPEP Exosome Mass Spec Kit

Cat# XPEP100A-1

User Manual

Store Kits at -20°C upon receipt

Contents

I. Introduction

A. Exosome Overview

Exosomes are 60 - 180 nm membrane vesicles secreted by most cell types in vivo and in vitro. These microvesicles are produced by the inward budding of multivesicular bodies (MVBs) and are released from the cell into the microenvironment following the fusion of MVBs with the plasma membrane. Exosomes are extracellular, nanoshuttle organelles that facilitate communication between cells and organs. Exosomes are found in blood, urine, amniotic fluid, breast milk, malignant ascites fluids and contain distinct subsets of RNAs and proteins depending upon the cell type from which they are secreted, making them useful for biomarker discovery. SBI has engineered tools and provides

services for exosome proteomic Mass spec analysis and next-generation sequencing of exosome RNA to accelerate the study of exosomes, exosome protein and exosome biomarkers.

B. The XPEP kits for exosome proteomic analysis

The XPEP kits allow researchers to routinely generate high quality exosome peptide libraries for Mass spec analysis. The kits work with exosomes isolated using ultracentrifugation as well as using ExoQuick (serum, plasma, ascites samples) or ExoQuick-TC (cell media, urine, spinal fluid) or immunopurify specific exosome subpopulations using SBI's Exo-Flow IP kits. The kit comes complete to create either exosome surface protein "shaving" peptide libraries or complete exosome peptide library preparations.

C. XPEP Procedures

Materials provided:

1. Complete exosome Lysis buffer: (5 ml)
2. Shaving buffer with exosome stabilization solution (5 ml)
3. Washing Buffer: (3 ml)
4. Reduction Buffer 1a: (20 ul)
5. Reduction Buffer 1b: (add 1 ml water to stock tube before use, stable for 2 weeks)
6. Digestion Buffer: (5 ml)
7. Trypsin digestion mixture (25 ul)
8. 10 kD spin columns (25 columns)
9. Collection tubes (50 tubes**)**

The protocol begins with either exosomes in a pellet form or in a concentrated solution. The minimum input amount of exosomes as measured by protein concentration is 500 ng to 1 ug. This equates to about 2 x 10^9 exosomes as starting input material. All spins take place in a standard 1.5 ml rotor in a microfuge and high speed can be at 13,000 or 10,000 rpm.

Serum exosomes tip: Use ExoQuick precipitation twice on a serum sample to remove some co-purifying serum proteins. To do this, take 250 ul serum, add 60 ul ExoQuick and incubate at 5°C

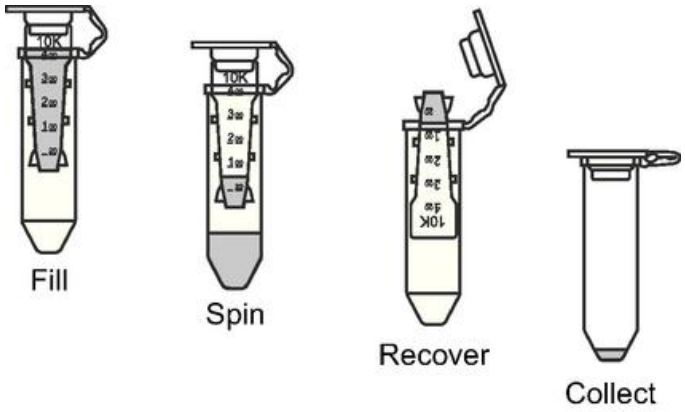
for 30 minutes. Spin the tube for 3 minutes at highest speed. Discard supernatant. Resuspend the exosome pellet in 250 ul 1x PBS and add 60 ul ExoQuick. Incubate at 5°C for 30 minutes and spin for 3 minutes at high speed to pellet the exosomes. These are now ready for MS analysis. If you have plasma samples, please defibrinate using SBI's cat# TMEXO-1 kit.

Media/Urine/CSF exosomes tip: For studying exosomes in media from cells in culture, you should grow your cells in the absence of bovine FBS. SBI offers bovine exosome-depleted FBS for this purpose (cat# EXO-FBS-50A-1). Urine and CSF samples should be pre-spun at 3,000 xg to pellet cellular debris prior to exosome isolation with SBI's ExoQuick-TC (cat# EXOTC10A-1).

NOTE:

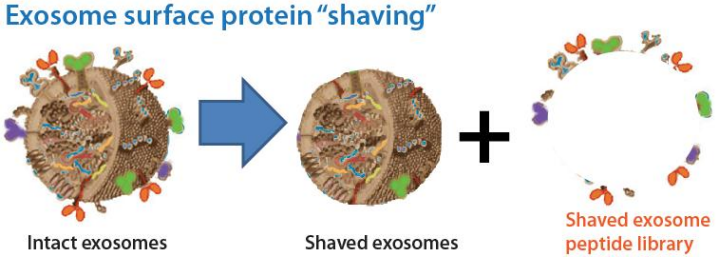
ExoQuick and ExoQuick-TC for exosome isolation purposes are not provided in the XPEP kits and can be purchased separately. The following ExoQuick products are recommended for exosome concentration prior to Exo-Flow purification.

The XPEP kits come complete with 10 kD cut-off spin columns for Mass Spec sample preparation. The typical column and collection tube use is outlined in the figure below.



XPEP-Shave surface protein analysis protocol

a. To the exosome pellet or liquid suspension, add 400 ul of Shaving buffer and mix gently by inversion 3 times. Exosome are now ready for trypsin shaving of surface proteins, proceed to Reduction, Alkylation and Digestion steps.



XPEP-Complete protein analysis protocol

a. To the exosome pellet or liquid suspension and add 0.5 ml of RIPA lysis buffer and vortex for vigorously for 10 seconds.
b. The sample is then heated for 15 minutes at 100°C.
c. Allow the sample cool down to room-temperature for 5 minutes.
d. Transfer the sample (Fill) into a 10 kD spin column and centrifuge it for 10 minutes at highest speed.
e. Discard the flow-through lysis solution, keep the spin column. (Spin)
f. Recover the solubilized exosome protein mixture by inverting the 10 kD column and inserting it into a fresh collection tube. Spin the inverted column for 2 minutes at high speed. The recovered volume should be about 100-200 ul, retain the spin column and collection tube for the next steps. (Recover)
g. Place the 10 kD column in the collection tube upright and transfer the 200 ul protein mixture to the spin column on top and add 100 ul of washing buffer. Pipet up and down a few times to mix.
h. Centrifuge the spin column at high speed for 5 minutes, discard flow through.
i. Buffer exchange the exosome protein mixture by adding 100 ul Digestion buffer to the spin column, pipet up and down 3 times to mix. This removes the urea from the mixture.

j. Centrifuge the column for 10 minutes at highest speed. Discard the flow through.
k. Repeat steps j-k one more time for a total of 2 exchanges.
l. Recover the exosome protein mixture by inverting the 10 kD column and inserting it into a fresh collection tube. Spin the inverted column for 2 minutes at high speed. The recovered volume should be about 200 ul.

Reduction, Alkylation and Digestion

a. To the 200 ul exosome protein solution in the collection tube, add 1.5 ul the Reduction buffer 1a .
b. Reduce the protein solution for 15 minutes at 60°C.
c. Allow the solution to cool down at room temperature for 5 minutes.
d. Add 100 ul of Reduction buffer 1b to the solution and store the solution in dark (cover with foil or place in a drawer) at room temperature for 30 minutes. Pre-warm the Trypsin solution at room temperature during this step for 15 minutes.
e. Add 2.5 ul of the pre-warmed Trypsin solution to the protein mixture and incubate at 37°C for 4 hours.
f. After 4 hours, immediately store the reaction at -20°C to stop the reaction. This is a convenient stopping point overnight**.**

Peptide library recovery

a. Thaw exosome protein peptide mixture at room temperature for 5 minutes.
b. Transfer the solution to a fresh 10 kD spin column with a fresh collection tube and centrifuge the solution for 10 minutes at high speed. (Collect)
c. The exosome peptide library in now in the collection tube, should be about 50-100 ul in volume with approximately 1-5 ug protein concentration (XPEP-Complete) or 0.2-1 ug protein concentration (XPEP-Shave).
d. This peptide mixture is ready to load on most Mass spectrometers directly.

Example Mass Spec analysis conditions

Each exosome peptide library sample can be analyzed by Nano LC/MS/MS with a Waters NanoAcquity HPLC system interfaced to a ThermoFisher Q Exactive. Peptide mixtures are loaded on a trapping column and eluted over a 75 um analytical column at 350 nL/min using a 2 hour reverse phase gradient; both columns are packed with Jupiter Proteo resin (Phenomenex). The injection volume is 30 uL. The Mass spectrometer is operated in data dependent mode, with the Orbitrap operating at 60,000 FWHM and 17,500 FWHM for MS and MS/MS respectively. The fifteen most abundant ions were selected for MS/MS.

Example data processing protocol

1. Data are searched using a local copy of Mascot with the following parameters:
2. Enzyme: Trypsin/P
3. Database: Swissprot Human (concatenated forward and reverse plus common contaminants.
4. Fixed modifications: Carbamidomethyl (C)
5. Variable modifications: Oxidation (M), Acetyl (N-term), Pyro-Glu (N-term Q), Deamidation (N,Q)
6. Mass values: Monoisotopic
7. Peptide Mass Tolerance: 10 ppm
8. Fragment Mass Tolerance: 0.02 Da
9. Max Missed Cleavages: 2
10. Mascot DAT files were parsed into the Scaffold software for validation, filtering and to create a nonredundant list per sample. Data are filtered using at 1% protein and peptide FDR and requiring at least two unique peptides per protein. A Scaffold file is generated for the study and contains all search results, coverage maps, peptide lists and product ion data.

Viewing XPEP mass spec data results

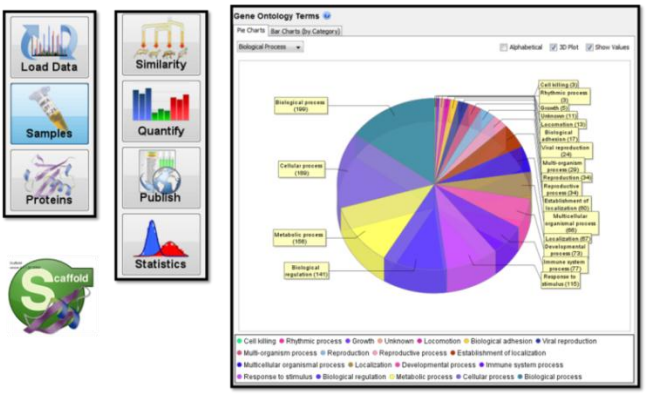
We recommend using the free Scaffold software to open, view and analyze the Scaffold file produced from the Mass spec instrument. Scaffold allows you to visualize and validate complex MS/MS proteomics experiments.

- Compare samples to identify biological relevance.
- Identify regulated isoforms and protein PTMs.
- Drill down into spectrum details and counts.
- Identify proteins intuitively and confidently.

- Create comprehensive lists of target proteins.
- Classify proteins by molecular function or organelle.
- Harness high through-put batch processing.

Scaffold software download link:
http://www.proteomesoftware.com/products/free-viewer

Scaffold software tutorials:
http://www.proteomesoftware.com/products/tutorial-videos/



Isolating Exosome using ExoQuick, ExoQuick-TC and Exo-Flow Immunocapture kits.

Description	Size	Catalog #
ExoQuick Serum exosomes	75 rxns	**EXOQ5A-1**
ExoQuick Plasma Exosome prep	75 rxns	**EXOQ5TM-1**
Thrombin Plasma Exosome prep	100 rxns	**TMEXO-1**
ExoQuick Serum exosomes	300 rxns	**EXOQ20A-1**
ExoQuick-TC for Tissue Culture Media	10 rxns	**EXOTC10A-1**
ExoQuick-TC for Tissue Culture Media	50 rxn	**EXOTC50A-1**

Exosome isolation protocols using ExoQuick reagents

Combine your biofluid sample containing exosomes with ExoQuick or ExoQuick-TC using the guidelines shown in the Table below. Mix the ExoQuick precipitation reagent with the biofluid sample by inversion and place at 4°C for 30 minutes to overnight, then recover the exosomes in a pellet with a low speed spin. Please refer to the ExoQuick or ExoQuick-TC User manuals for more details. Recommended amounts of exosomes provided in Table.

Biofluid	Sample volume	ExoQuick-TC volume	Resuspend exosome pellet	Volume to use in Exo-Flow
Urine	10 ml	2 ml	500 µL PBS	100 µL/rxn
Spinal fluid	10 ml	2 ml	500 µL PBS	100 µL/rxn
Culture media	10 ml	2 ml	500 µL PBS	100 µL/rxn

Biofluid	Sample volume	ExoQuick	Resuspend exosome pellet	Volume to use in Exo-Flow
Serum	**250 µL**	**63 µL**	**500 µL PBS**	**100 µL/rxn**
Plasma	**250 µL**	**63 µL**	**500 µL PBS**	**100 µL/rxn**
Ascites fluid	**500 µL**	**120 µL**	**250 µL PBS**	**100 µL/rxn**

Amount of exosomes to use

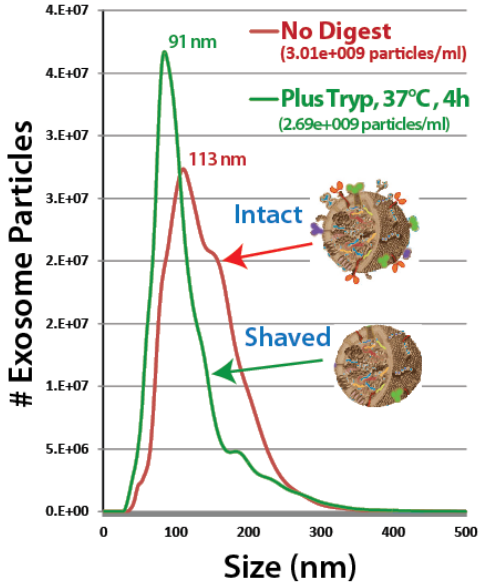
The number of exosomes in a given biofluid will vary depending upon the sample itself. There are abundant levels of exosome in serum, less in cell culture medium and urine. Use the guidelines in the Tables above as a starting point.

D. Sample XPEP exosome data

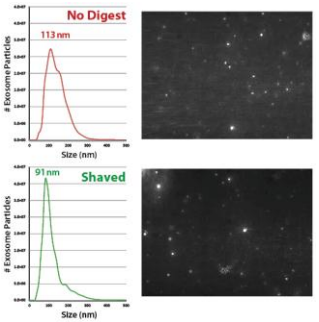
Exosomes were first isolated from the tissue culture medium from HEK293 cells grown in Exo-FBS exosome-depleted media supplement with standard DMEM. The cells were grown to 80-90% confluency in a 10 cm cell culture dish. The secreted

exosomes were isolated as stated in the protocol for ExoQuick-TC above. The exosome pellet was processed using the XPEP complete or XPEP Shaving procedures.

Sample XPEP-Shaved exosome NanoSight data

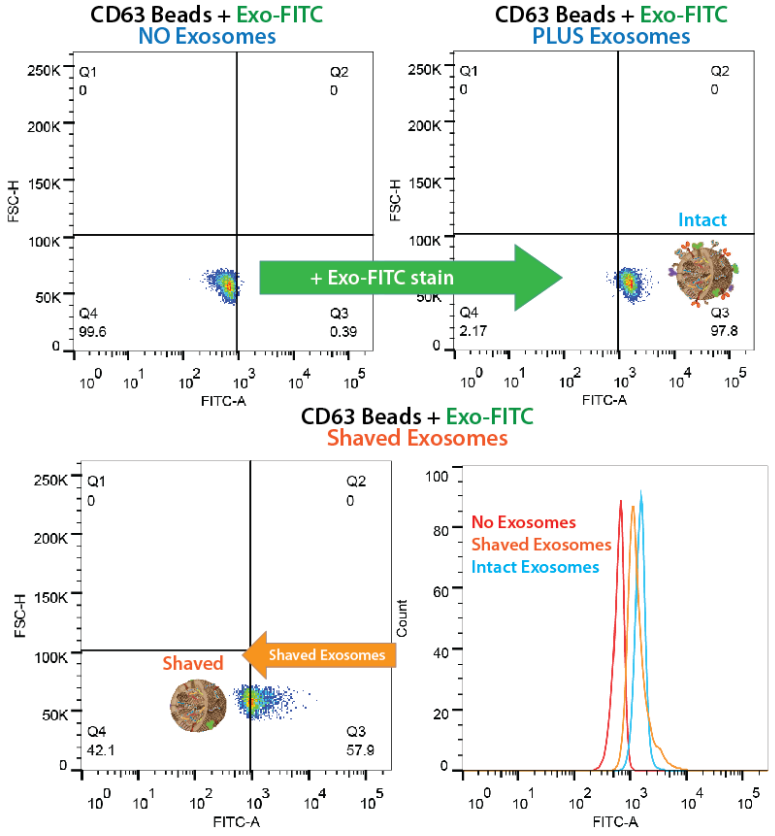


The shaved exosomes remain intact, but lose their surface protein “coats” and diameters condense into a more homogeneous population.



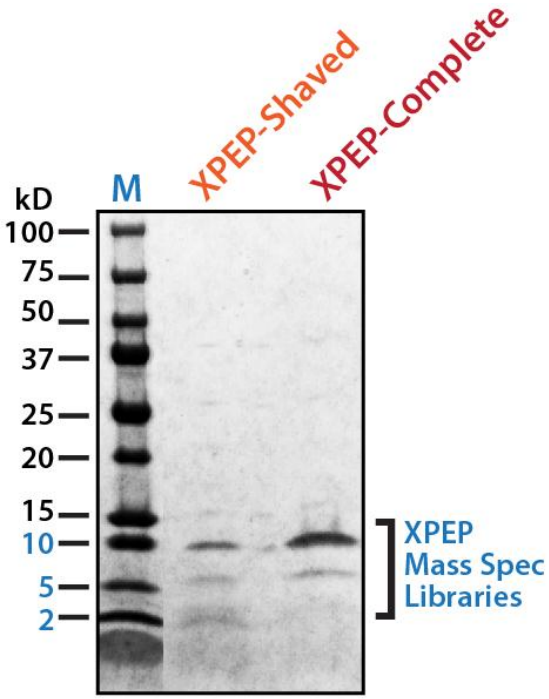
The XPEP-Shaved exosomes are intact, but lose their surface CD63 protein marker as measured by CD63 antibody bead capture and Exo-Flow FACs analysis (SBI cat# EXOFLOW300A-1 kit).

Sample XPEP-Shaved exosome FACs data



Sample XPEP SDS-PAGE data

XPEP Mass Spec protein libraries prepared by either the Shave or Complete protocols. Approximately 10 ug of the peptide libraries were separated on a 4-20% gradient SDS PAGE gel and stained with Imperial blue (Thermo Fisher) to visualize the library peptide size distributions. The peptide library fragments generated are of the expected 2-10kD fragment range and optimal for Mass Spec analysis. The XPEP-Shaved peptide libraries are typically 5-fold less than the libraries made using the XPEP-Complete protocol. The molecular weight marker is from Bio-Rad (Precision Plus Protein™ Dual Xtra Standards catalog #161-0377).



What to expect?

The protein content of exosomes can vary greatly depending upon the cell source from which it originated. Some common surface and internal proteins can be observed in typical exosomes and are identified in Mass Spec data.

Some common proteins to look for include: HSP (Heat Shock) proteins, GAPDH, Keratins, Tubulin, Actin, Vimentin, Fibulin, Fibronectin, Annexins, Flotillins, Galectin and α-Enolase.

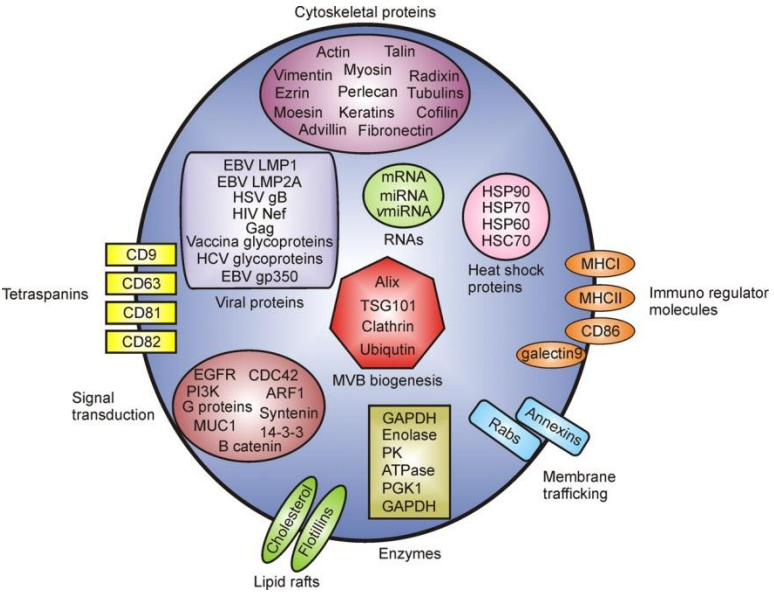


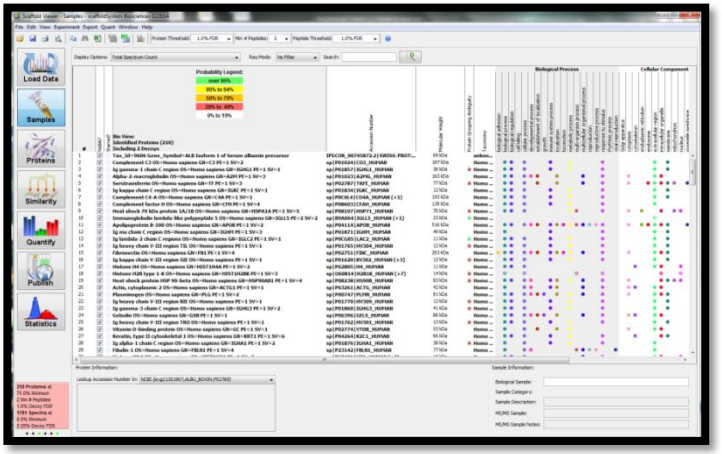
Image adapted from: David G. Meckes Jr. and Nancy Raab-Traub, "Microvesicles and Viral Infection". J. Virol. December 2011 vol. 85 no. 24 12844-12854.

Sample serum exosome MS/MS data

Exosomes were isolated from 500ul control human serum using ExoQuick. The exosome pellet was processed using the XPEP complete procedure. The peptide libraries were then analyzed by nano LC/MS/MS with a Waters NanoAcquity HPLC system interfaced to a ThermoFisher Q Exactive. Peptides were loaded on a trapping column and eluted over a 75um analytical column at 350nL/min using a 2hr reverse phase gradient; both columns were packed with Jupiter Proteo resin (Phenomenex). The injection volume was 30µL. The mass spectrometer was operated in datadependent mode, with the Orbitrap operating at 60,000 FWHM and 17,500 FWHM for MS and MS/MS respectively. The fifteen most abundant ions were selected for MS/MS and data analyzed using

MASCOT databases and Scaffold software

The software screenshot below and excel table below that image shows some example serum exosome protein MS/MS data with common exosome proteins highlighted in yellow.



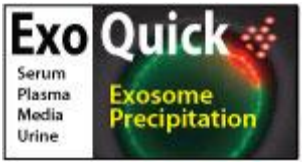
Identified Proteins	Accession Number	MW (kD)	Complete
Keratin, type II cytoskeletal 1 OS=Homo sapiens GN=KRT1 PE=1 SV	sp|P04264|K2C1_HUMAN	66 kDa	32
Tax_Id=9606 Gene_Symbol=KRT10 Keratin, type I cytoskeletal 10	IPI:CON_00009865.2|SWISS-PROT:	60 kDa	27
Tax_Id=9606 Gene_Symbol=KRT6A Keratin, type II cytoskeletal 6A	IPI:CON_00300725.7|SWISS-PROT:	60 kDa	8
Tax_Id=9606 Gene_Symbol=KRT5 Keratin, type II cytoskeletal 5	IPI:CON_00009867.3|SWISS-PROT:	62 kDa	8
Prohibitin-2 OS=Homo sapiens GN=PHB2 PE=1 SV=2	sp|Q99623|PHB2_HUMAN	33 kDa	11
Keratin, type II cytoskeletal 2 epidermal OS=Homo sapiens GN=KR	sp|P35908|K22E_HUMAN	65 kDa	21
Voltage-dependent anion-selective channel protein 1 OS=Homo s	sp|P21796|VDAC1_HUMAN	31 kDa	6
Actin, cytoplasmic 2 OS=Homo sapiens GN=ACTG1 PE=1 SV=1	sp|P63261|ACTG_HUMAN	42 kDa	61
Tax_Id=9606 Gene_Symbol=KRT14 Keratin, type I cytoskeletal 14	IPI:CON_00384444.5|SWISS-PROT:	52 kDa	7
Sideroflexin-1 OS=Homo sapiens GN=SFXN1 PE=1 SV=4	sp|Q9H9B4|SFXN1_HUMAN	36 kDa	3
Prohibitin OS=Homo sapiens GN=PHB PE=1 SV=1	sp|P35232|PHB_HUMAN	30 kDa	9
Heat shock 70 kDa protein 1A/1B OS=Homo sapiens GN=HSPA1A P	sp|P08107|HSP71_HUMAN	70 kDa	82
Glyceraldehyde-3-phosphate dehydrogenase OS=Homo sapiens G	sp|P04406|G3P_HUMAN	36 kDa	38
ADP/ATP translocase 2 OS=Homo sapiens GN=SLC25A5 PE=1 SV=7	sp|P05141|ADT2_HUMAN	33 kDa	11
Heat shock protein HSP 90-beta OS=Homo sapiens GN=HSP90AB1	sp|P08238|HS90B_HUMAN	83 kDa	61
60 kDa heat shock protein, mitochondrial OS=Homo sapiens GN=H	sp|P10809|CH60_HUMAN	61 kDa	28
Tax_Id=9606 Gene_Symbol=KRT9 Keratin, type I cytoskeletal 9	IPI:CON_00019359.3|SWISS-PROT:	62 kDa	7
Annexin A5 OS=Homo sapiens GN=ANXA5 PE=1 SV=2	sp|P08758|ANXA5_HUMAN	36 kDa	17
CD81 antigen OS=Homo sapiens GN=CD81 PE=1 SV=1	sp|P60033|CD81_HUMAN	26 kDa	9
Lysosome-associated membrane glycoprotein 1 OS=Homo sapiens	sp|P11279|LAMP1_HUMAN	45 kDa	2
CD9 antigen OS=Homo sapiens GN=CD9 PE=1 SV=4	sp|P21926|CD9_HUMAN	25 kDa	5
Heat shock protein HSP 90-alpha OS=Homo sapiens GN=HSP90AA1	sp|P07900|HS90A_HUMAN	85 kDa	58
Alpha-2-macroglobulin OS=Homo sapiens GN=A2M PE=1 SV=3	sp|P01023|A2MG_HUMAN	163 kDa	34
Voltage-dependent anion-selective channel protein 3 OS=Homo s	sp|Q9Y277|VDAC3_HUMAN	31 kDa	4
ADP/ATP translocase 3 OS=Homo sapiens GN=SLC25A6 PE=1 SV=4	sp|P12236|ADT3_HUMAN	33 kDa	11
Poly(rC)-binding protein 2 OS=Homo sapiens GN=PCBP2 PE=1 SV=	sp|Q15366|PCBP2_HUMAN	39 kDa	4
Complement C3 OS=Homo sapiens GN=C3 PE=1 SV=2	sp|P01024|CO3_HUMAN	187 kDa	31
Dolichyl-diphosphooligosaccharide--protein glycosyltransferase s	sp|P04843|RPN1_HUMAN	69 kDa	9
Phosphate carrier protein, mitochondrial OS=Homo sapiens GN=S	sp|Q00325|MPCP_HUMAN	40 kDa	3
Tubulin beta chain OS=Homo sapiens GN=TUBB PE=1 SV=2	sp|P07437|TBB5_HUMAN	50 kDa	50
Heat shock cognate 71 kDa protein OS=Homo sapiens GN=HSPA8 P	sp|P11142|HSP7C_HUMAN	71 kDa	42
Histone H2B type 1-K OS=Homo sapiens GN=HIST1H2BK PE=1 SV=3	sp|O60814|H2B1K_HUMAN (+7)	14 kDa	27
Annexin A2 OS=Homo sapiens GN=ANXA2 PE=1 SV=2	sp|P07355|ANXA2_HUMAN	39 kDa	9
Sodium/potassium-transporting ATPase subunit alpha-1 OS=Hom	sp|P05023|AT1A1_HUMAN	113 kDa	7
Tubulin alpha-1B chain OS=Homo sapiens GN=TUBA1B PE=1 SV=1	sp|P68363|TBA1B_HUMAN	50 kDa	40

E. Related Products and Services

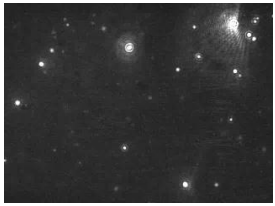
SBI offers a number of exosome research products. Review them here: http://www.systembio.com/exosomes

Isolate Exosomes with ExoQuick and ExoQuick-TC

One-step Exosome Isolation for Serum and Plasma, Tumor Ascites Fluid, Follicular fluid, Tissue Culture Media, Urine, Spinal fluid.



Purified human cancer exosomes and and mouse dexosomes

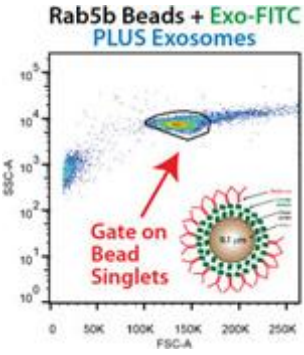


Use for RNA, Protein analysis, calibration standards and engineering cargo for delivery to target cells. All exosomes are characterized by NanoSight for size, intactness and concentration as well as tested to be CD63 positive by Western blot analysis. The purified exosomes are provided frozen with >1x10^6 exosomes (50 ug protein).

Fluorescently label exosome cargo

Label endogenous exosome RNAs Red and internal exosome Proteins Green to monitor exosome cargo delivery to cells in real-time.

Immunopurify Exosomes and use with FACS



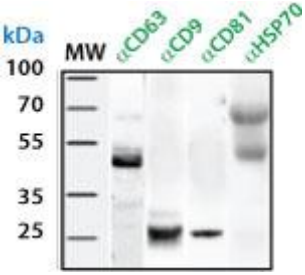
Selectively capture distinct subpopulations of intact exosomes based on a particular surface marker and sort by FACS - **"Flow Exometry"**. Choose from the following tetraspanin, annexin, adhesion, fusion and immune presentation targets or customize your own capture system.
• CD9 • CD31 • CD63 • CD81 • Rab5b • HLA-G

Culture Cells in Exosome-depleted FBS

Study exosomes from cultured cells and not from bovine exosomes in FBS itself. Exo-FBS has been stripped of bovine exosomes yet supports robust growth of cells in culture.

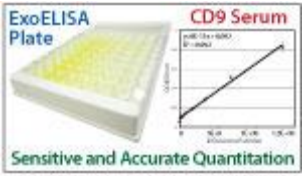
Verify Exosome Recovery with Antibodies and Antibody Arrays

Track exosomes by Western blots and Antibody Arrays using well-characterized exosome protein markers. Verify exosome recoveries after isolation with ExoQuick or ultracentrifugation using validated antibodies and arrays.



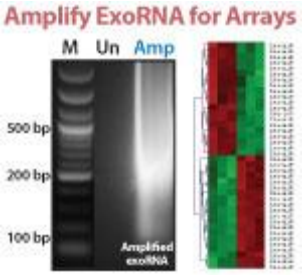
Quantitate Exosomes with ELISAs

Exo-ELISAs measure the levels of exosome particles with antibodies to detect CD9, CD63 or CD81. Highly sensitive and quantitative assays in a convenient 96-well format with validated exosome standards.



Amplify Exosome MicroRNAs with SeraMir for qPCR and microarrays

Purify exoRNAs with SeraMir columns and covert to cDNA for microRNA qPCR arrays or amplify exoRNAs for microarrays analysis.



Discover Novel Exosome RNA Biomarkers with Next-Gen Sequencing

Complete exosome RNA Next-Gen sequence analytics solution for researchers interested in identifying novel exosome-associated RNA biomarkers. Abundance, RNA type, expression heatmaps and genomic mapping all included in service.

F. Additional Materials Required

1) ExoQuick and/or ExoQuick-TC to isolate exosomes prior to making peptide libraries.
2) Standard 1x PBS
3) Sterile, 1.5 mL sample tubes
4) Standard bench top microfuge

G. Shipping and Storage Conditions for Kits

The XPEP kits are shipped on dry ice and should be stored at -20°C. Avoid freeze-thawing the reagents. Shelf life of the product is 1 year after receipt if stored in -20°C.

II. References

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