

The background of the slide is a detailed, colorful illustration of a cell's internal structure. It features various organelles such as mitochondria with their characteristic folds, a nucleus with a nucleolus, and numerous small vesicles and granules. The color palette is primarily light blue, green, and yellow, giving it a scientific and biological feel. The overall image is slightly blurred, creating a sense of depth and focus on the text in the foreground.

Exosomes & exRNAs

Cristina Sisu

Journal Club

3rd October 2012

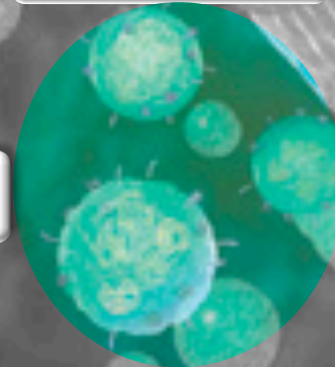
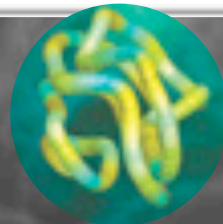
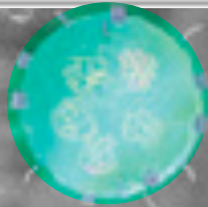
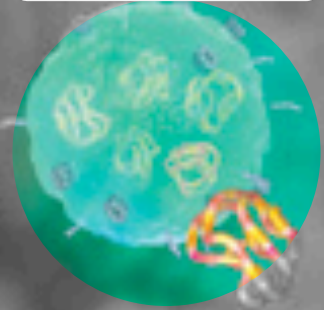
Exosomes

structure

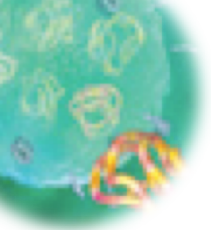
function

importance

exRNA



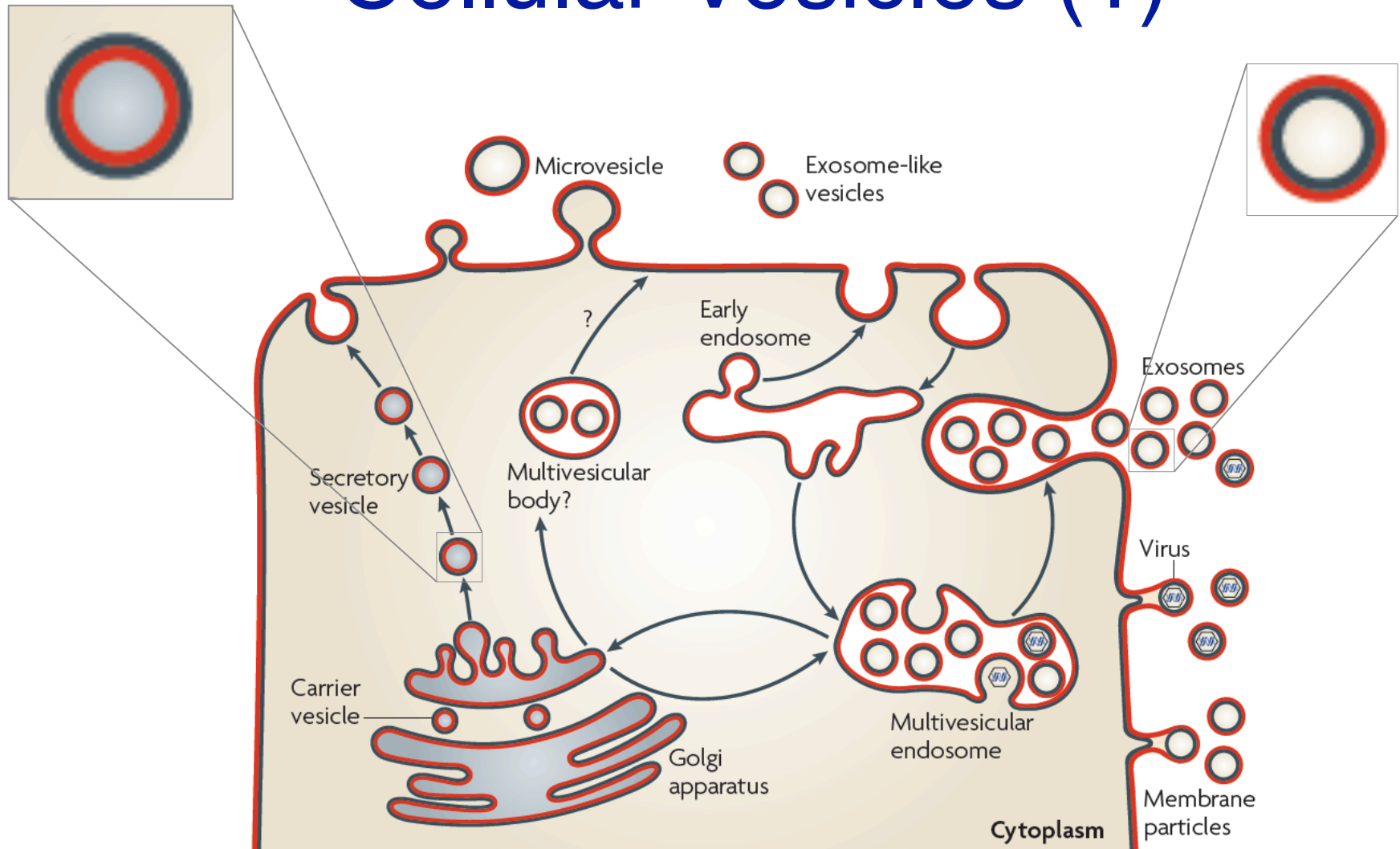
EXOSOMES



What Are Exosomes?

- Secreted membrane vesicles
- Diameter: 30-100nm
- Contain cytoplasmic components
- Have a lipid bilayer
- Originate from tumor cells, dendritic cells, lymphoid cells, mesothelial cells, epithelial cells, or cells from different tissues or organs
- Secreted only by living cells
- Located in various body fluids

Cellular Vesicles (1)



Cellular Vesicles (2)

- Spherical structures limited by a lipid bilayer
- 2 types:
 - Carrier vesicles
 - Strictly intracellular
 - Contain material from the originating compartment
 - Expose the cytoplasmic side of their parent at their outer surface
 - Membrane vesicles
 - Expelled into the extracellular space
 - Contain cytosol
 - Expose the luminal side of the membrane to their outer surface
 - *Miniature Cells*

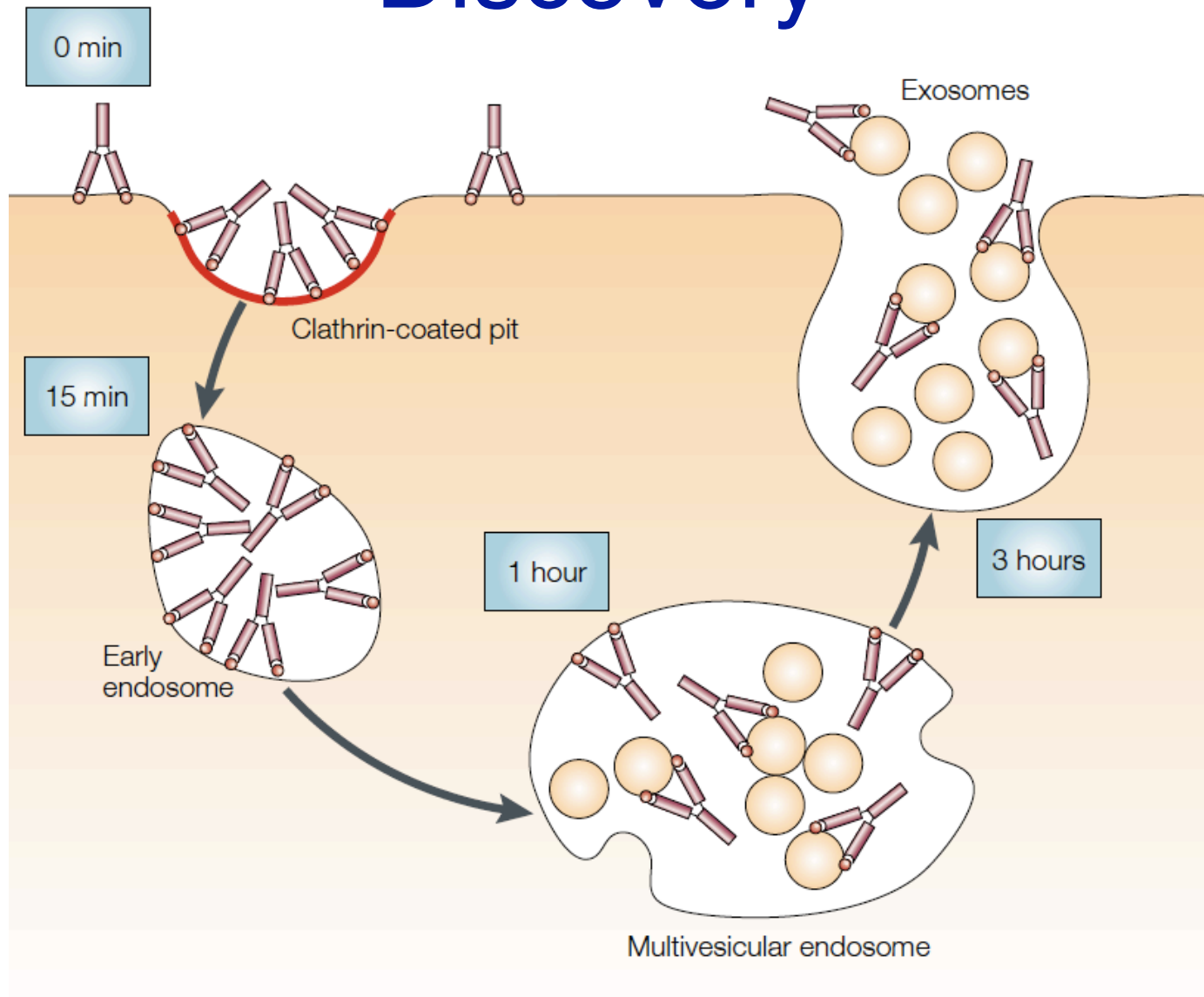
Membrane Vesicles

Feature*	Exosomes	Microvesicles	Ectosomes	Membrane particles	Exosome-like vesicles	Apoptotic vesicles
Size	50–100 nm	100–1,000 nm	50–200 nm	50–80 nm	20–50 nm	50–500 nm
Density in sucrose	1.13–1.19 g/ml	ND	ND	1.04–1.07 g/ml	1.1 g/ml	1.16–1.28 g/ml
Appearance by electron microscopy [†]	Cup shape	Irregular shape and electron-dense	Bilamellar round structures	Round	Irregular shape	Heterogeneous
Sedimentation	100,000 g	10,000 g	160,000–200,000 g	100,000–200,000 g	175,000 g	1,200g, 10,000 g or 100,000 g
Lipid composition	Enriched in cholesterol, sphingomyelin and ceramide; contain lipid rafts; expose phosphatidylserine	Expose phosphatidylserine	Enriched in cholesterol and diacylglycerol; expose phosphatidylserine	ND	Do not contain lipid rafts	ND
Main protein markers	Tetraspanins (CD63, CD9), Alix and TSG101	Integrins, selectins and CD40 ligand	CR1 and proteolytic enzymes; no CD63	CD133; no CD63	TNFRI	Histones
Intracellular origin	Internal compartments (endosomes)	Plasma membrane	Plasma membrane	Plasma membrane	Internal compartments?	ND

A Brief History of Exosome Discovery

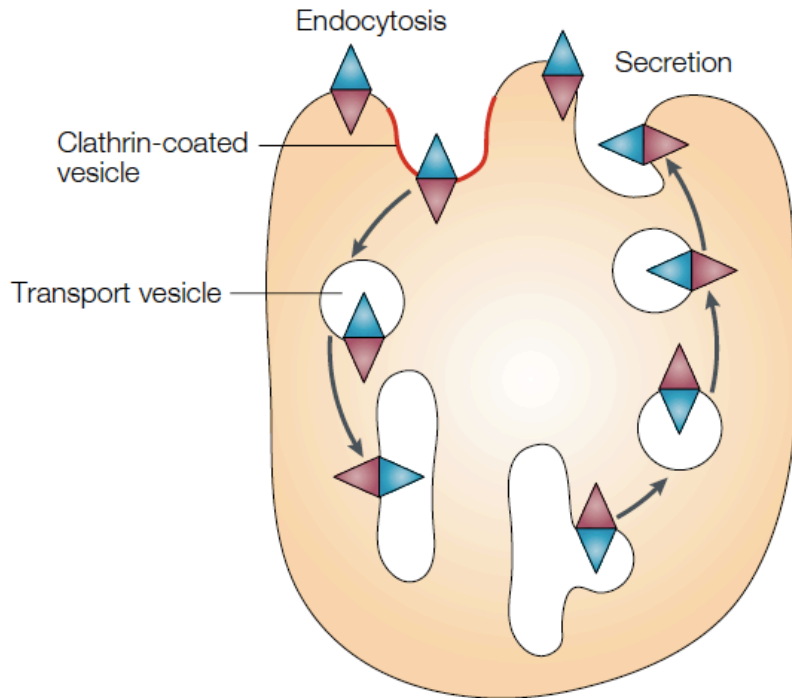


Discovery

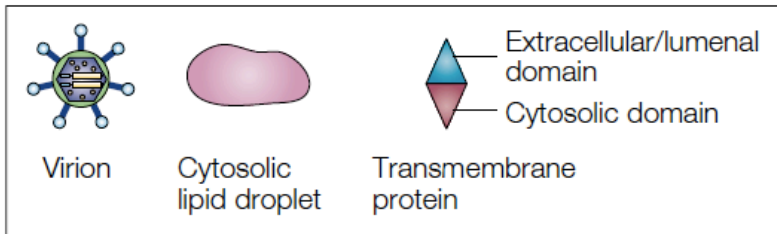
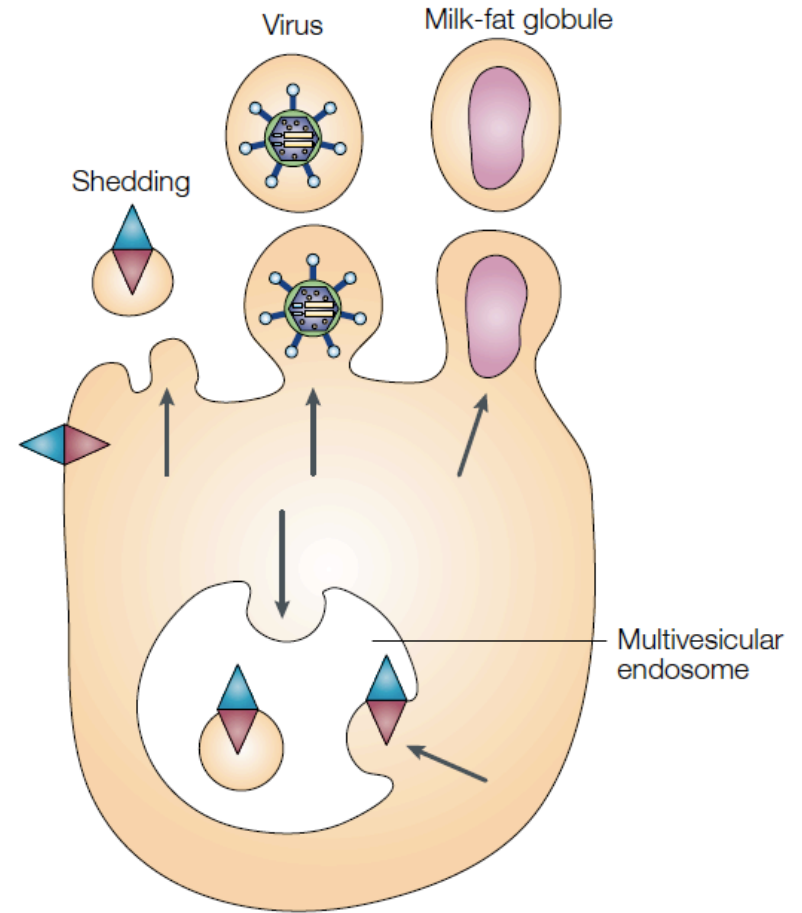


Biogenesis

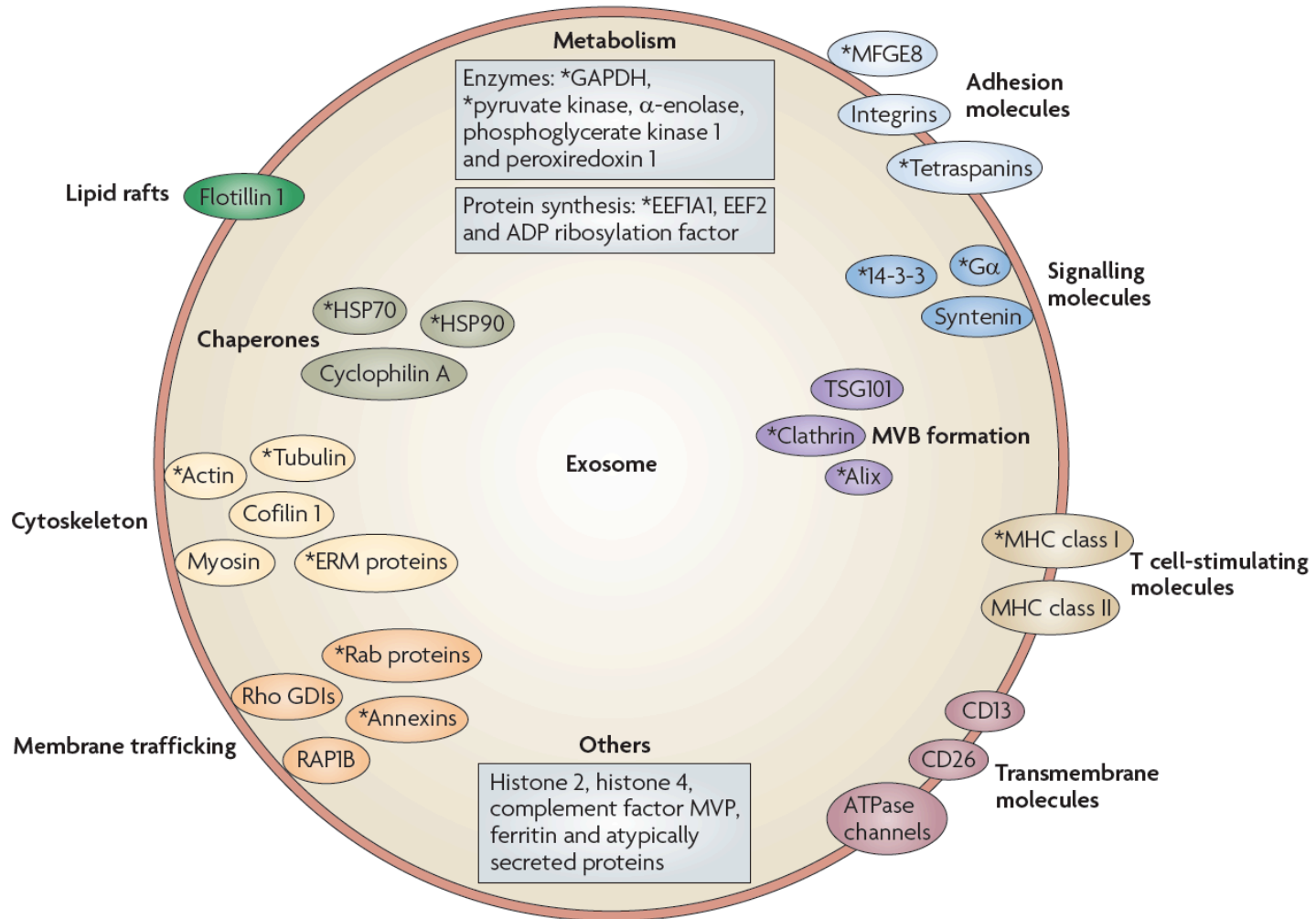
a Normal intracellular-budding events



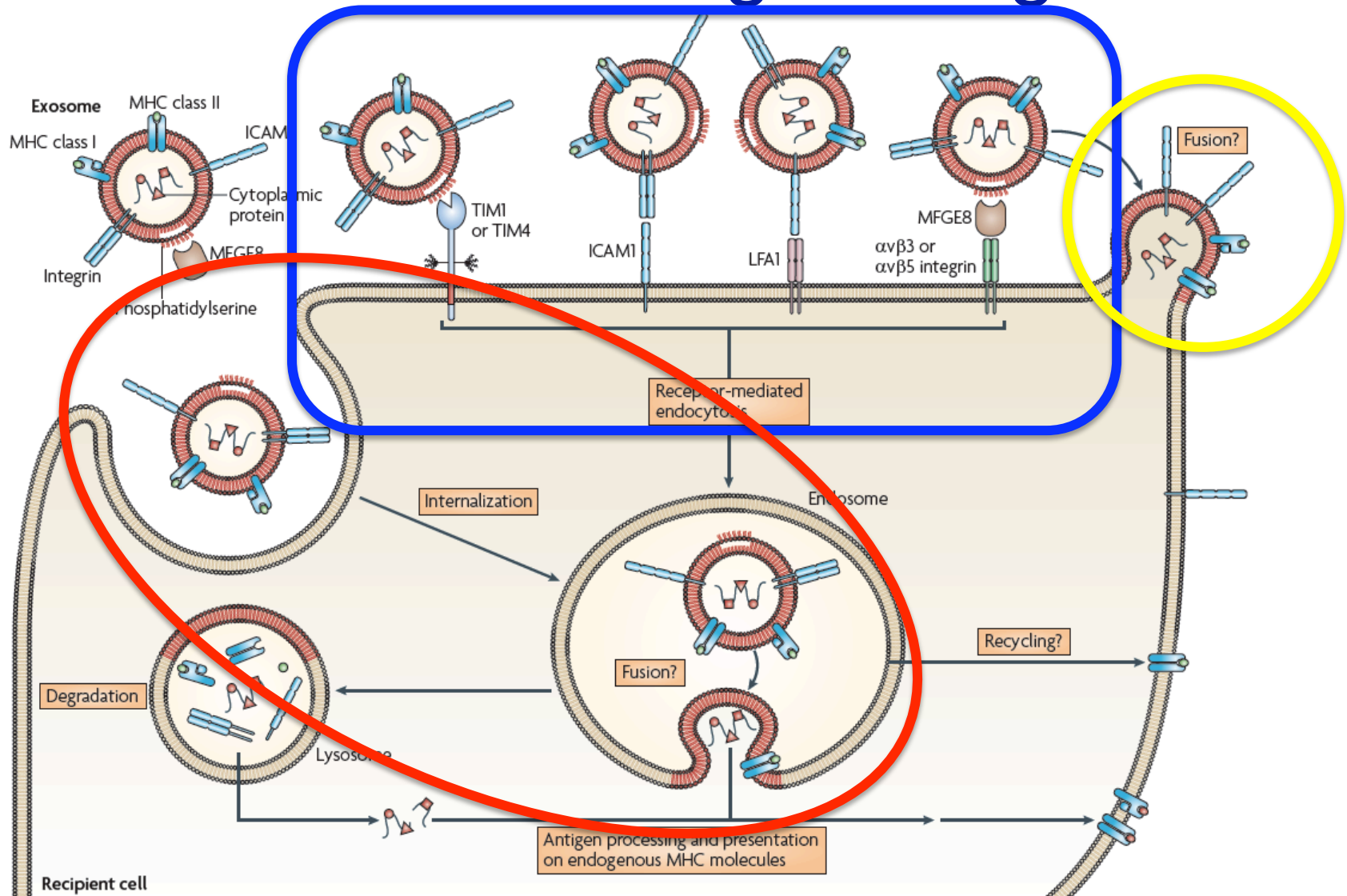
b Reverse intracellular-budding events



Structural Organization



Interaction With Neighboring Cells

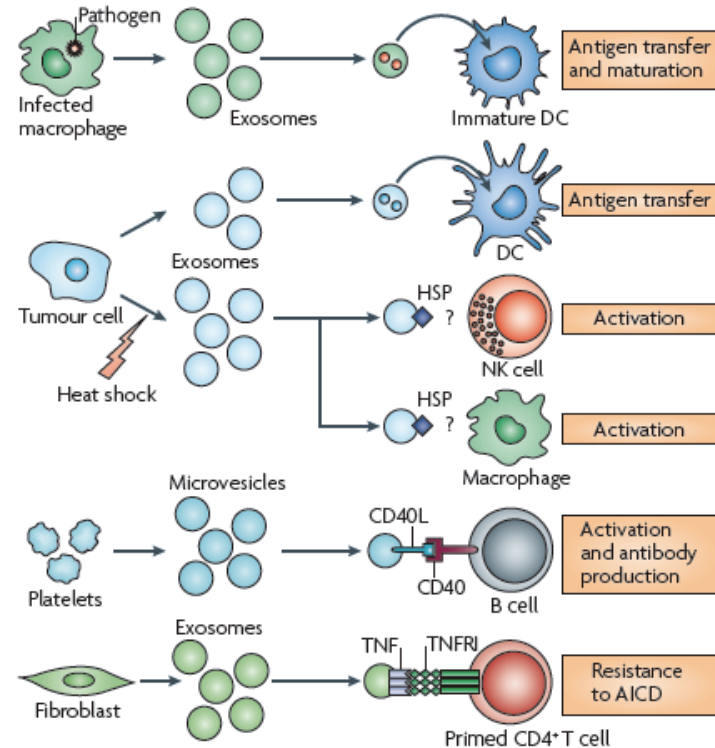
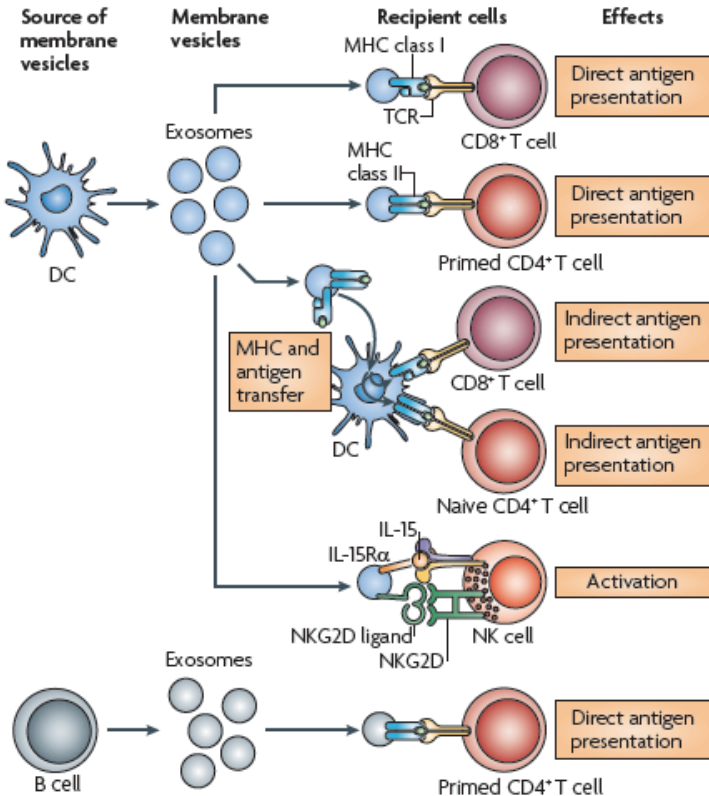


Biological Function

- Mediate intercellular communication
 - Facilitate interaction between two cells without a direct cell-cell contact
 - Develop new adhesion features through binding to target cells
 - Exchange membrane proteins and cytosol between cells
- Considered an alternative to lysosomal degradation
- Transfer of antigens from tumor cells to DCs

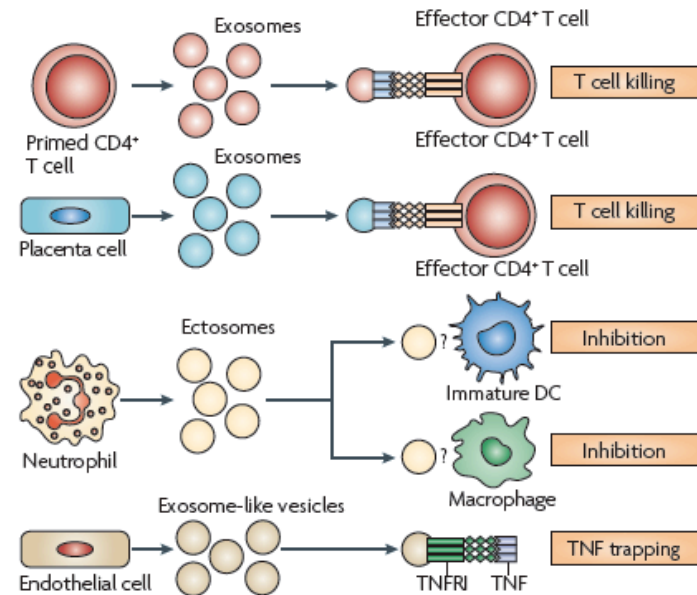
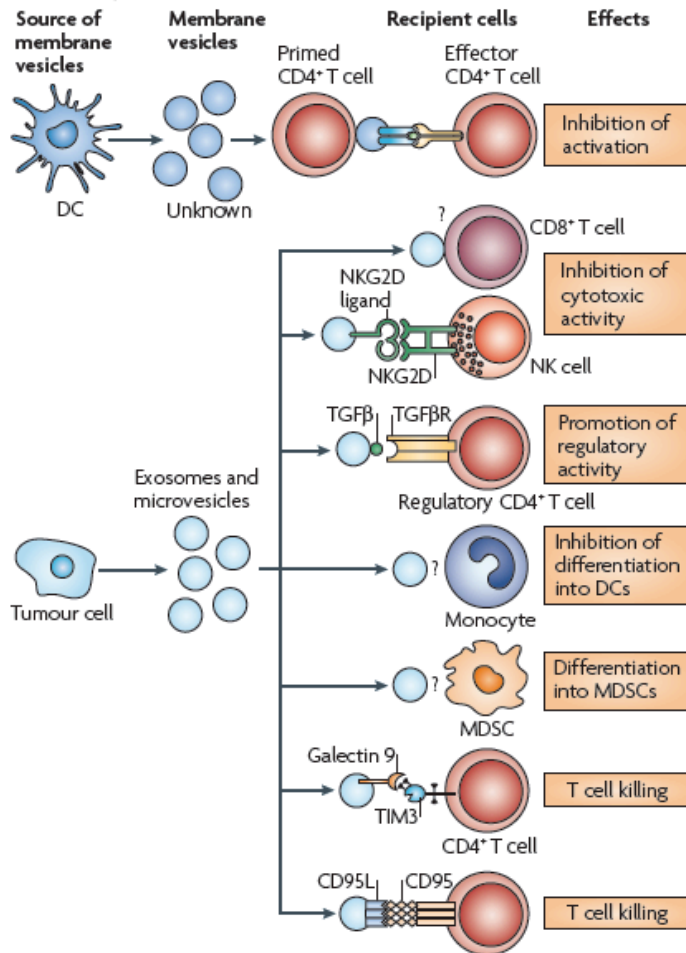
Physiological Roles (1)

a Activating effects of secreted vesicles on immune cells

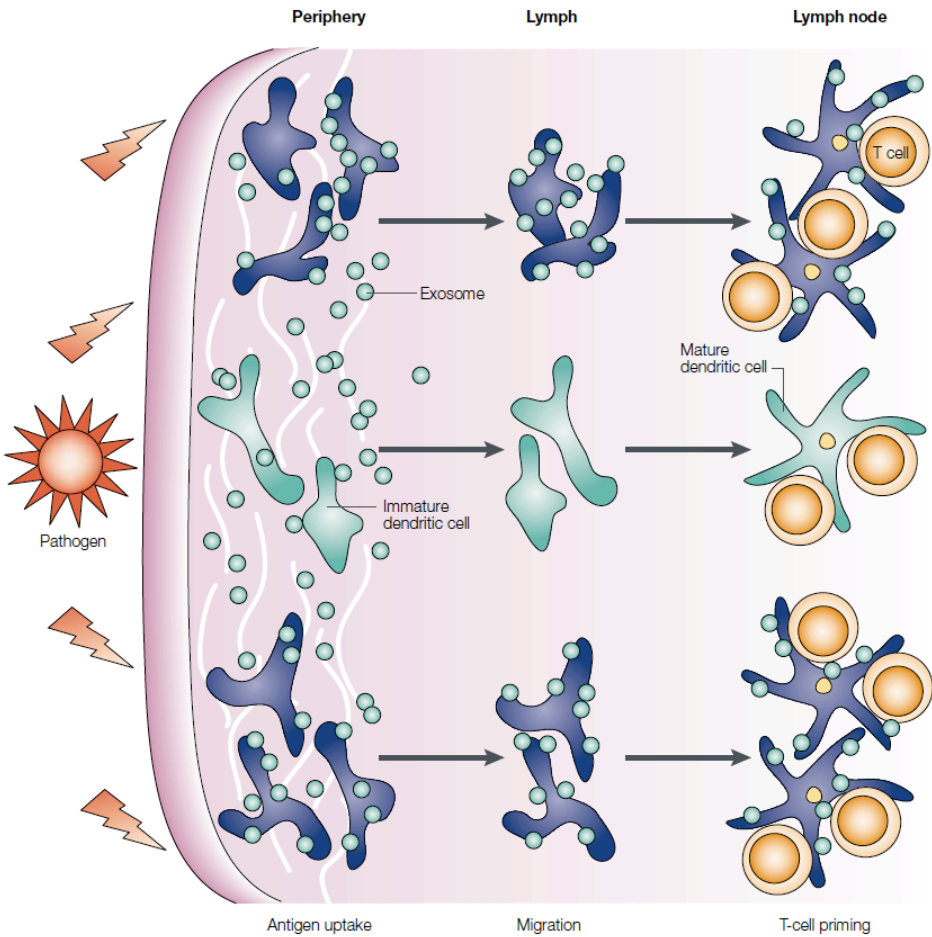


Physiological Roles (2)

b Inhibitory effects of secreted vesicles on immune cells



Exosomes in Immune Responses



Importance

- Functional roles: cellular communication, immune system modulation and tumor progression.
 - transfer RNAs including mRNA and microRNA as well as protein to neighboring cells
- Circulating exosome levels have also been found to be elevated in diseased states such as ovarian cancer, lung cancer, and melanoma
- Exosomal load assessment and exosomal molecular profiling may be used for disease detection and monitoring.

Literature

LETTERS

nature
cell biology

Multivesicular bodies associate with components of miRNA effector complexes and modulate miRNA activity

Derrick J. Gibbins¹, Constance Claudio¹, Mathieu Erhardt¹ and Olivier Voinnet^{1,2}

LETTERS

nature
cell biology

Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells

Hadi Valadi^{1,3}, Karin Ekström^{1,3}, Apostolos Bossios¹, Margareta Sjöstrand¹, James J. Lee² and Jan O. Lötvall^{1,4}

LETTERS

nature
cell biology

Silencing by small RNAs is linked to endosomal trafficking

Young Sik Lee^{1,2,6}, Sigal Pressman¹, Arlise P. Andress¹, Kevin Kim¹, Jamie L. White¹, Justin J. Cassidy¹, Xin Li^{1,4}, Kim Lubell¹, Do Hwan Lim², Ik Sang Cho², Kenji Nakahara^{1,3}, Jonathan B. Preall¹, Priya Bellare^{1,5}, Erik J. Sontheimer¹ and Richard W. Carthew^{1,6}

**EXOSOMES: COMPOSITION,
BIOGENESIS AND FUNCTION**

Clotilde Théry^{}, Laurence Zitvogel[‡] and Sebastian Amigorena^{*}*

exRNAs



exRNAs

- RNA molecules found in exosomes
- Some are specific to exosomes and not found in the parent cell

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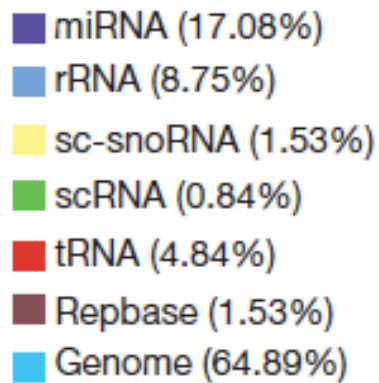
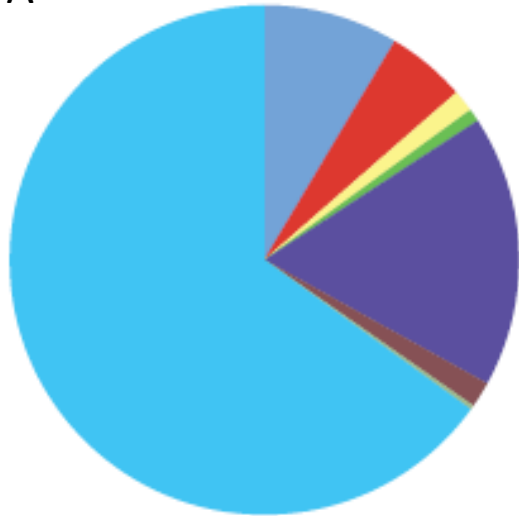
Hadi Valadi^{1,3}, Karin Ekström^{1,3}, Apostolos Bossios¹, Margareta Sjöstrand¹, James J. Lee² and Jan O. Lötvall^{1,4}



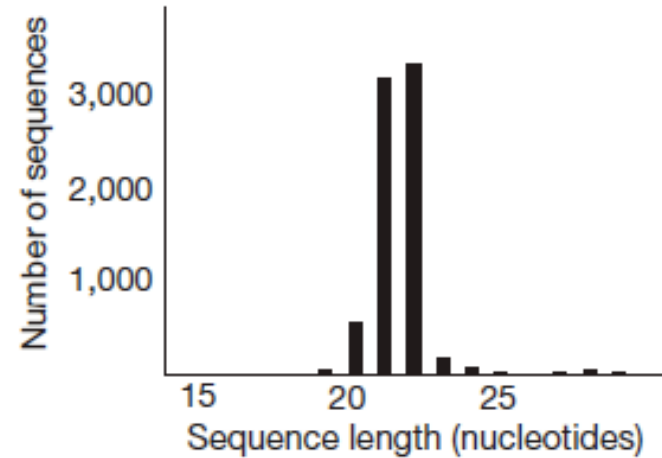
- Database of exosomal proteins, RNAs and lipids
 - 146 studies
 - 13333 protein entries – 4563 different proteins
 - 2375 mRNA entries – 1639 mRNAs
 - 764 miRNA
 - 194 lipid entries

Diversity

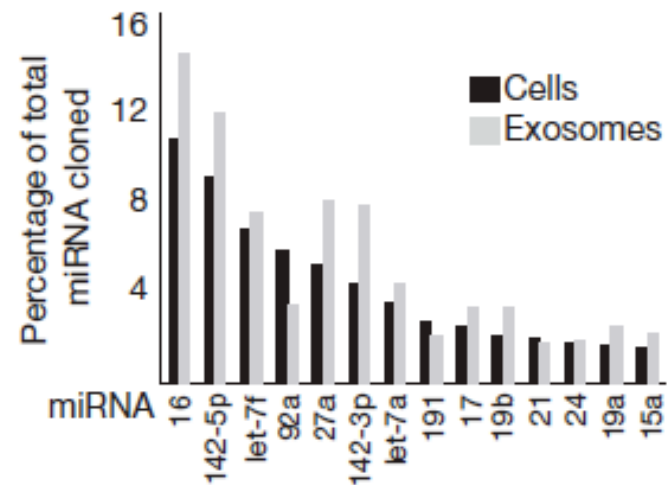
A



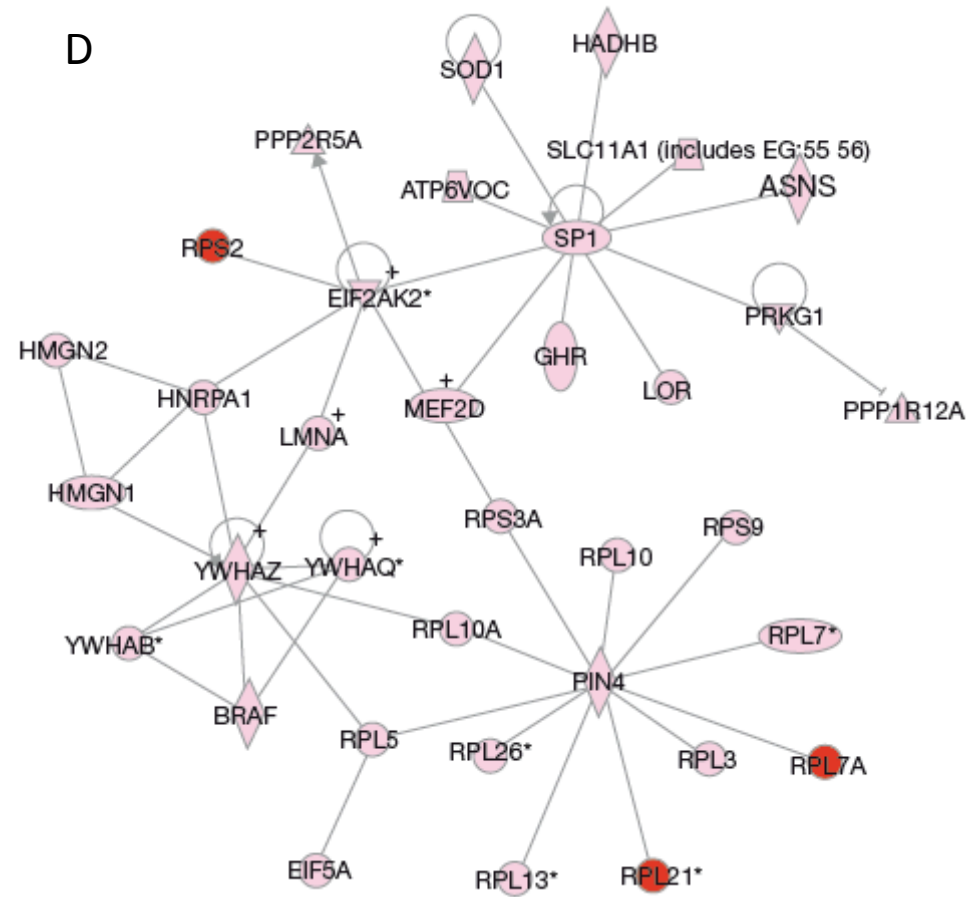
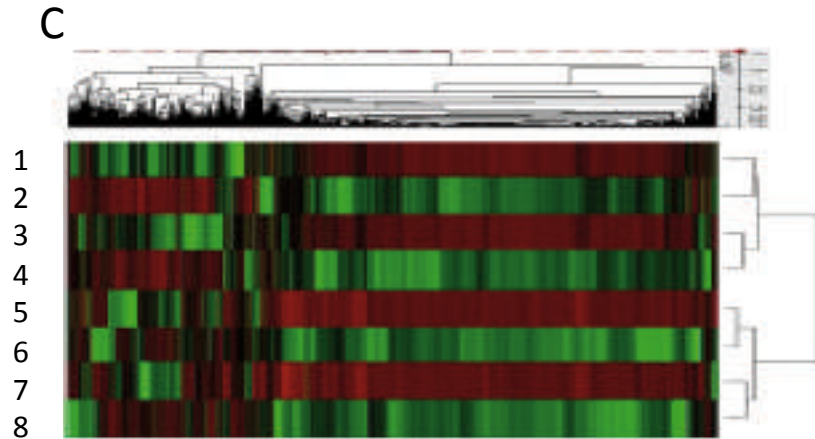
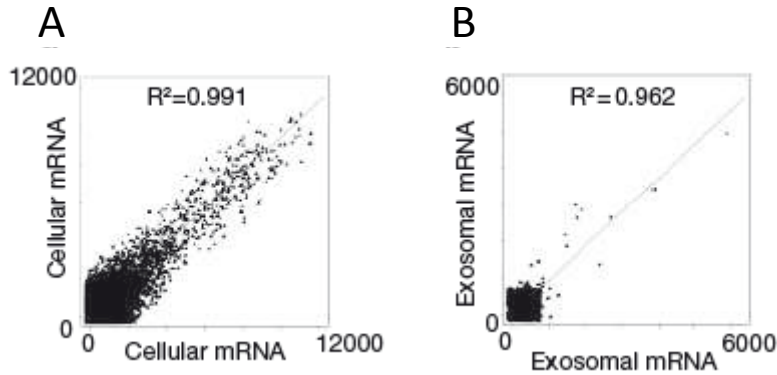
B



C



Interactions



Why Study Exosomes & exRNAs?

- Exosome release is exacerbated in tumor cells
- ex-miRNA from tumor exosomes are parent cell specific
- miRNA profiling of circulating tumor exosomes could potentially be used as surrogate diagnostic markers for biopsy profiling, extending its utility to screening asymptomatic populations

Exosomes, exRNAs & Cancer

Ovarian Cancer

- Malignant ascites-derived exosomes of ovarian carcinoma patients contain CD24 and EpCAM. *Gynecol Oncol.* 2007 Dec;107(3):563–71. Epub 2007 Sept 27.
- Claudin-containing exosomes in the peripheral circulation of women with ovarian cancer. *BMC Cancer.* 2009 Jul 20;9:244.

Breast Cancer

- Purification, characterization and biological significance of tumor-derived exosomes. *Anticancer Res.* 2005 Nov-Dec;25(6A):3703-3707.
- Proteomics of MUC1-containing lipid rafts from plasma membranes and exosomes of human breast carcinoma cells MCF-7.. *Proteomics* 2009 May;9(10):2820-35

Prostate Cancer

- Senescence-Associated Exosome Release from Human Prostate Cancer Cells. *Cancer Res* 2008;68(19):7864–71

Brain Cancer / Glioblastoma

- Intercellular transfer of the oncogenic receptor EGFRvIII by microvesicles derived from tumour cells. *Nat Cell Biol.* 2008 May;10(5):619-24.
- Proteomic and immunologic analyses of brain tumor exosomes. *Graner MW FASEB J.* 2009 May;23(5):1541-57. Epub 2008 Dec 24.

exRNAs

- Exosomal microRNA: a diagnostic marker for lung cancer. *Clin Lung Cancer.* 2009 Jan;10(1):42-6.
- MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. *Gynecol Oncol.* 2008 July;110(1):13–21



Special Thursday
Allergy & Immunology
Seminar at Immunobiology Time

**"Immune Cell - Derived Vesicles
(Exosomes Carrying RNA):
Tiny Messengers With Great Potential"**

Professor Marca Wauban, PhD
Intercellular Communication
Department of Biochemistry & Cell Biology
Faculty of Veterinary Medicine
Utrecht University
Utrecht, The Netherlands

Thursday, October 4, 2012, 10:30 a.m.
Yale Medical School TAC Auditorium

THANK YOU!