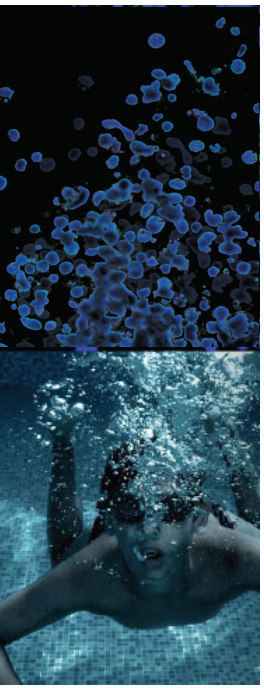
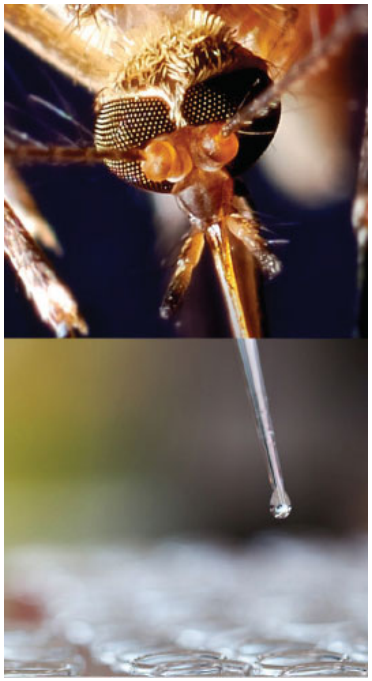
Extracellular Vesicles: For Better and for Worse

Heather Branscome, M.S.
Lead Biologist, ATCC

Fatah Kashanchi, Ph.D.
Professor, George Mason University

Credible Leads to Incredible™





About ATCC

- Founded in 1925, ATCC is a non-profit organization with HQ in Manassas, VA, and an R&D and Services center in Gaithersburg, MD
- World's largest, most diverse biological materials and information resource for cells and microbes – the "*gold standard*"
- Innovative R&D company featuring gene editing, NGS, advanced models such as exosomes
- cGMP biorepository
- Partner with government, industry, and academia
- Leading global supplier of authenticated cell lines, viral and microbial standards
- Sales and distribution in 150 countries, 19 international distributors
- Talented team of 450+ employees, over one-third with advanced degrees

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Overview

- Overview of Extracellular Vesicles (EVs)
- Characterization and Analysis of “Damaging EVs”
- Characterization and Analysis of “Reparative EVs”
- Summary and Future Directions

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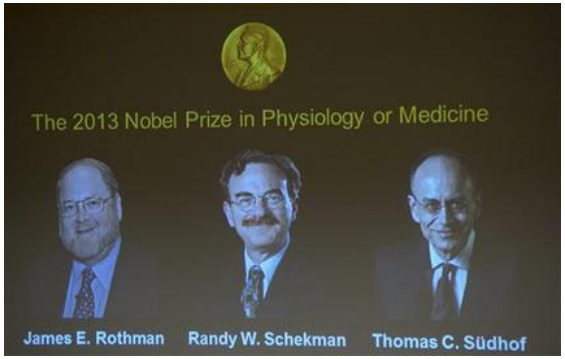
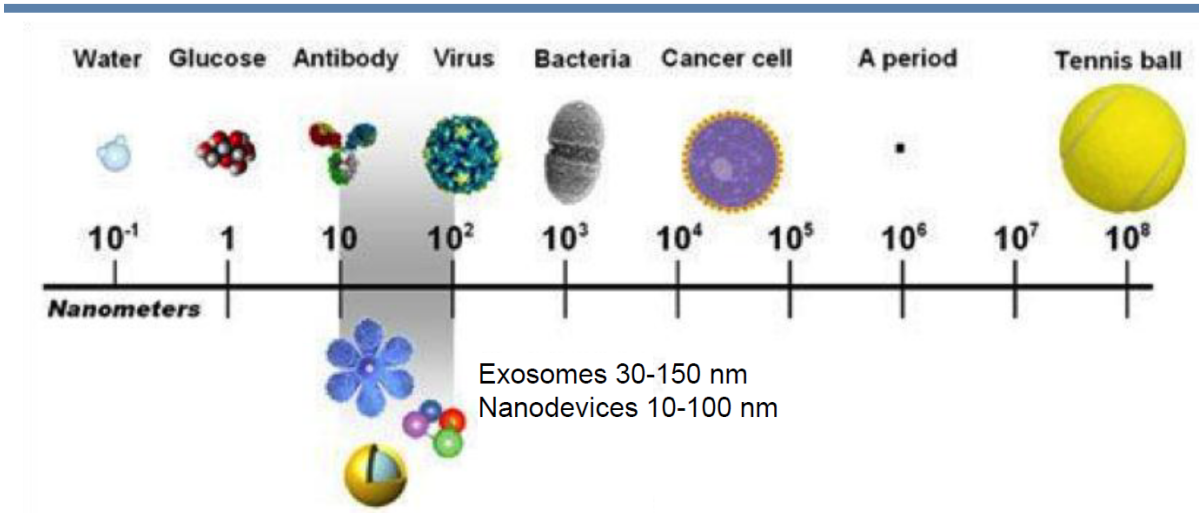
Overview





Internal volume of exosomes (diameter 30-150 nm) is ~4-1500 $x10^{-24}$ m^3

The volume of one average 50 kDa protein or 100 nt RNA molecule is ~6 $x10^{-26}$ m^3

->Exosome theoretically can hold up ~70-25,000 small proteins or short RNA

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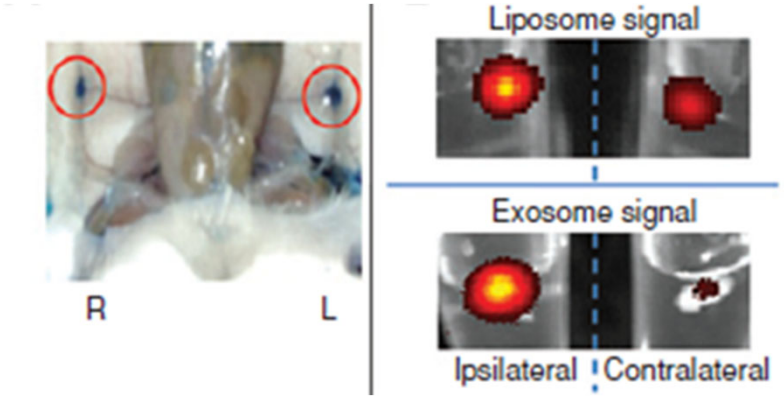
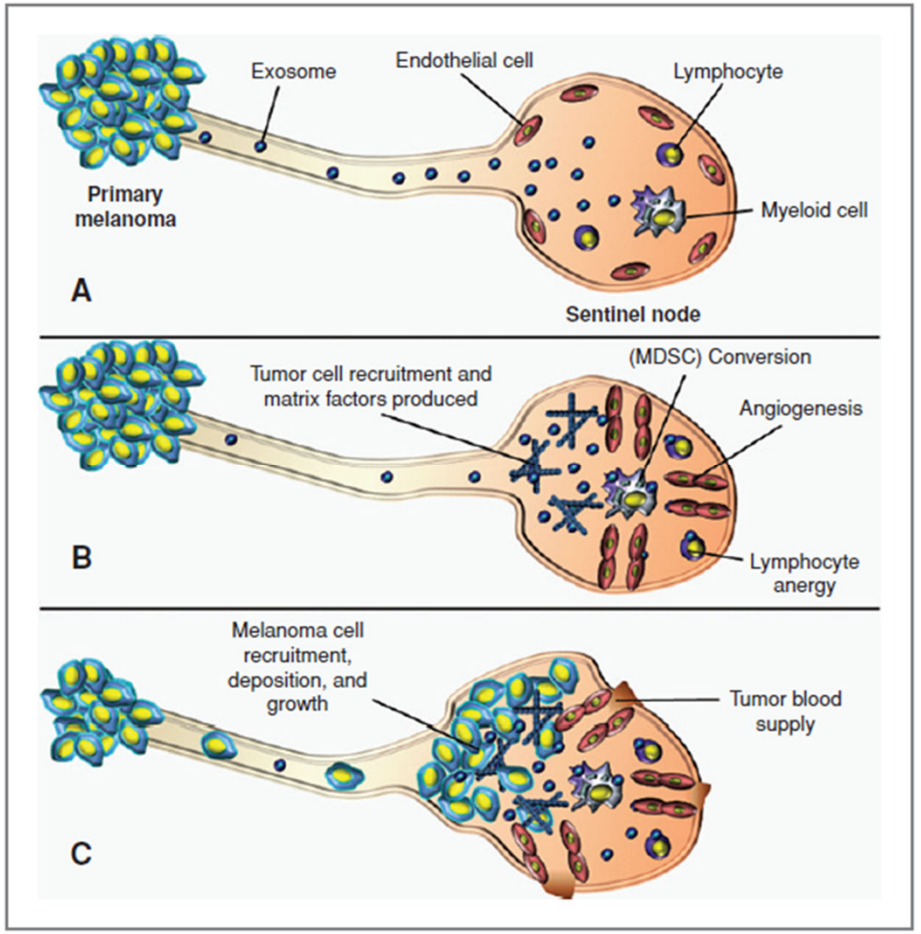
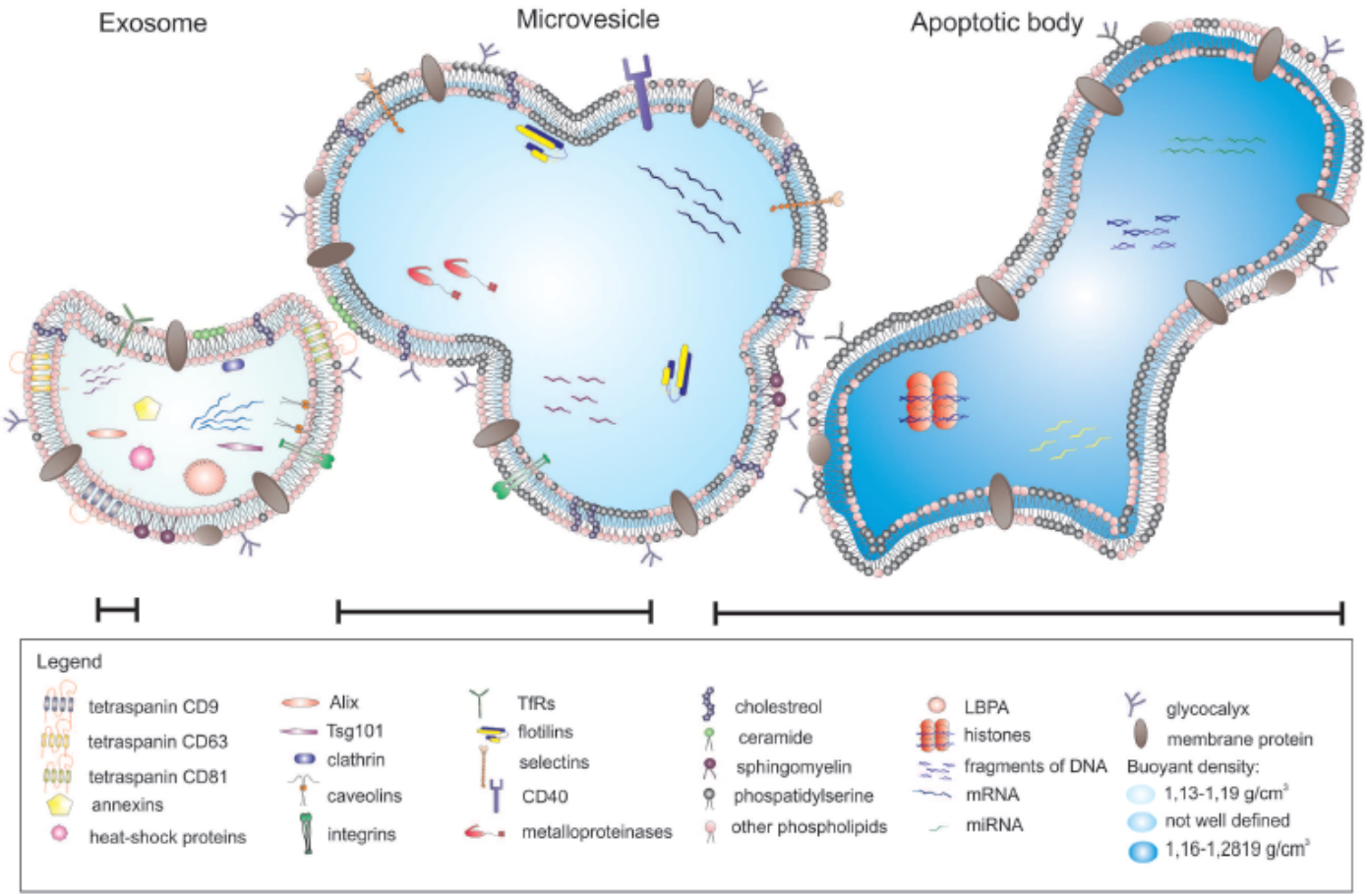
Clinical Significance of EVs





Hood et al. *Cancer Res*. 2011

Types of EVs



Koniusz et al. *Frontiers in Cellular Neuroscience.* 2016

EVs (from uninfected cells)

Exosomes

- •Well defined shape under EM
- •50 to 100 nm
- •Formed intracellularly
- •Contain tetraspanin proteins: CD63, CD81, CD9
- •Contain ESCRT-pathway proteins ALIX and TSG101

Exosome-like vesicles

- •20 to 50 nm
- •Originate from multivesicular bodies formed by other organelles (Golgi)
- •Lack ESCRT proteins ALIX and TSG101

Microvesicles (ectosomes)

- •100 to 1000 nm
- •Originate from outward budding/fission of plasma membrane (exocytosis)
- •Do not contain tetraspanin proteins
- •Similar lipid composition to plasma membrane

Apoptotic bodies

- •500 to 4000 nm
- •Formed only during programmed cell death
- •Contain DNA and histones

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EV Research and Infections: Tip of an Iceberg

Baltimore groups are:

- I: dsDNA type (examples: Adenovirus, Herpesvirus, Poxvirus)
- II: ssDNA type (+)sense DNA (example: Parvovirus)
- III: dsRNA type (example: Reovirus)
- IV: (+)ssRNA type (+)sense RNA (examples: Picornavirus, Togavirus)
- V: (−)ssRNA type (−)sense RNA (examples: Orthomyxovirus, Rhabdovirus)
- VI: ssRNA-RT type (+)sense RNA with DNA intermediate to life-cycle (example: Retrovirus)
- VII: dsDNA-RT type (example: Hepadnavirus)

PubMed Search:	# of Manuscripts:
Viruses	~10^6
Intracellular Pathogens & Viruses (all DNA and RNA)	1,749
Intracellular Pathogens & Fungi (Candida, Cryptococcus, Aspergillus)	6,049
Intracellular Pathogens & Parasites (Leishmania, Malaria, Chagas, Sleeping sickness)	1,300
Intracellular Pathogens & Bacteria (TB, Listeria, Salmonella)	7,703

PubMed Search:	# of Manuscripts:
Parasites	239,892
Bacteria	~2.1 x 10^6
Fungi	~1.6 x 10^6

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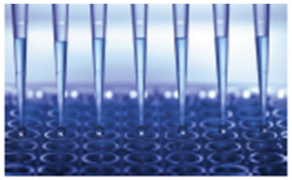
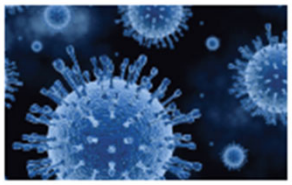
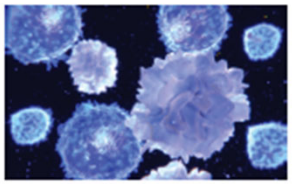
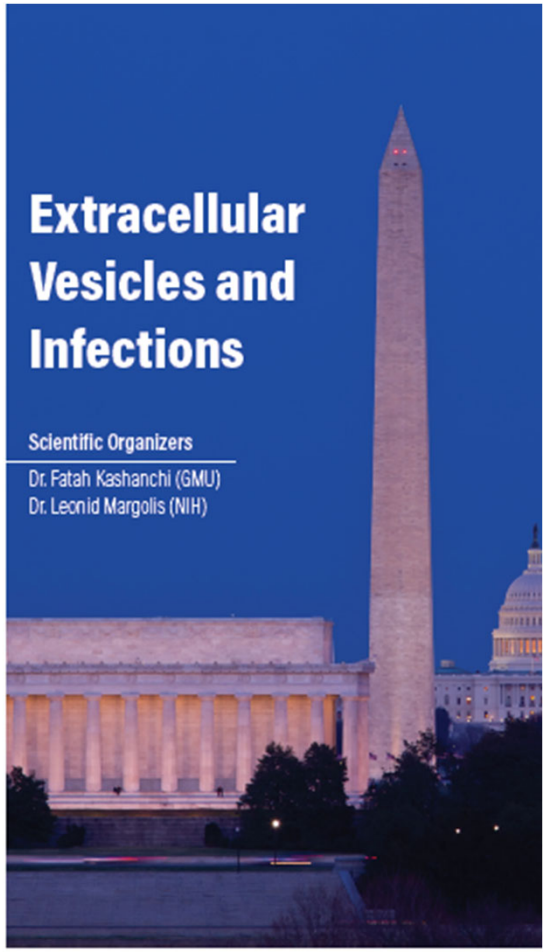






Extracellular Vesicles and Infections



Scientific Organizers

Dr. Fatah Kashanchi (GMU)
Dr. Leonid Margolis (NIH)

June 1 – 2, 2018
Bolger Center in Potomac, Maryland

Exosomes in Human Infectious Diseases Conference

05 Mar 2020 - 08 Mar 2020 | Nassau, Bahamas

Important Dates

Early Bird	19 Sep 2019
Talk Submission	26 Sep 2019
Poster Submission	09 Jan 2020
Registration Deadline	10 Jan 2020

Synopsis

Extracellular vesicles (EVs), which are generated by almost all living cells, are now considered to be an important system of cell-cell communication. A large volume of data has been published on EVs in different fields of biology and medicine, from immunology to marine biology. These data are discussed at large international meetings that gather thousands of researchers.

However, there is still a need for more-focused meetings at which the importance and reliability of the data should be evaluated by a narrow circle of experts. Here, we propose to organize a small conference that will focus on one of the most important aspects of EVs, their role in infectious human diseases. The aim of the proposed conference is to improve our understanding of the mechanisms of this involvement and to evaluate EVs as potential therapeutic targets.

Join us alongside chairs **Leonid Margolis** (NIH/NICHD), **Fatah Kashanchi** (George Mason University) and **Graça Raposo** (Institut Curie, CNRS)

Plenary Speakers

Randy Schekman
University of California, Berkeley
Philip Stahl
Washington University in St. Louis
Yoel Sadovsky Magee
Womens Research Institute
Andrew Hill
La Trobe University
Stephen Gould
Johns Hopkins University
Guillaume van Niel
INSERM
Genoveffa Franchini
NIH

- **50% registration support for selected young investigators**
- **Poster Prizes Available**

Registration rate includes 3 nights' fixed accommodation (05, 06 and 07 Mar 2020) and a 24hour all-inclusive food and beverage package for the conference period.

www.fusion-conferences.com

Overview

- Overview of Extracellular Vesicles (EVs)
- Characterization and Analysis of “Damaging EVs”
- Characterization and Analysis of “Reparative EVs”
- Summary and Future Directions

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Topics to Be Discussed

1. Background on viruses, autophagy and EVs (damaging EVs; diagnostics)

2. Isolation of EVs from latent HIV-1 and other virally infected cells (HTLV-1, RVFV, Ebola and Zika)

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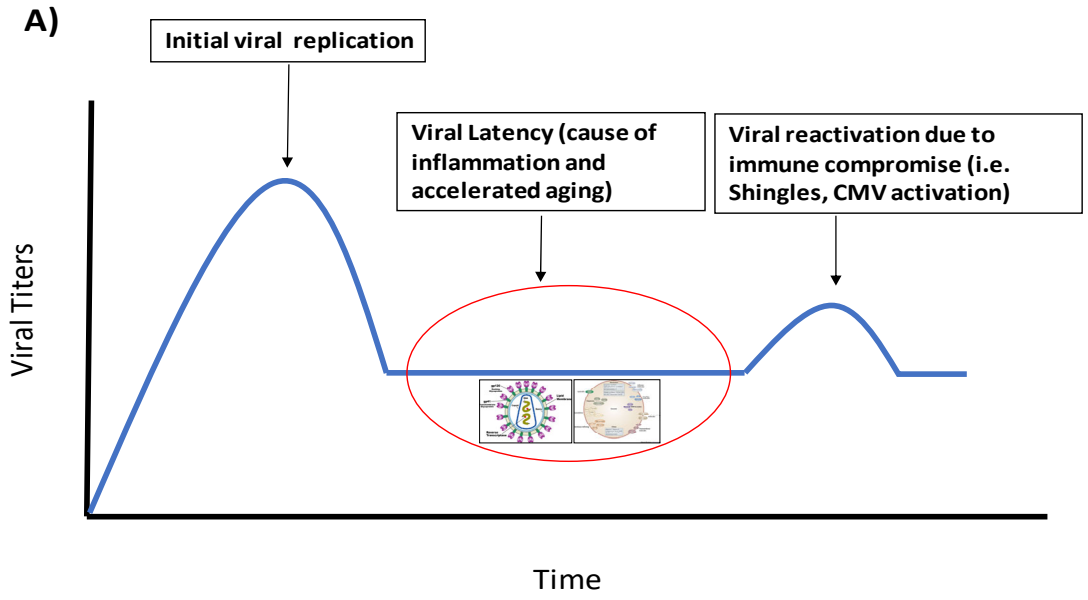
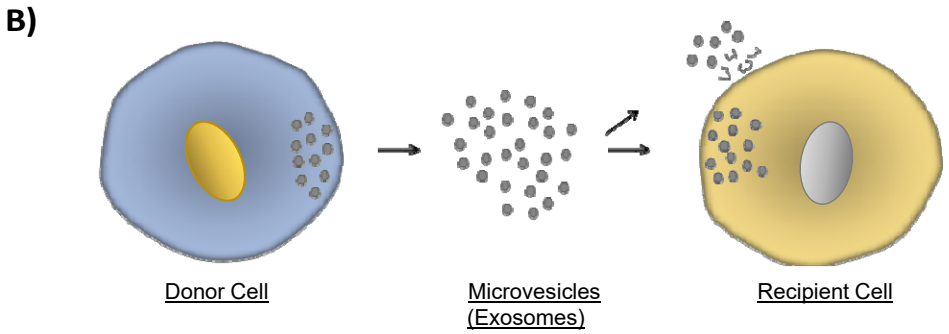
Characterization and Analysis of "Damaging EVs"





Epidemiology

A)

Table 1. Baseline Characteristics Among 190 Study Subjects

Characteristic	Value
Age, years	51 (44–57)
Male sex, % of patients	92
$CD4^+$ T-cell count, cells/mm^3	523 (249–728)
T cells expressing CD4, %	23 (16–32)
$CD8^+$ T-cell count, cells/mm^3	844 (606–1185)
T cells expressing CD8, %	48 (37–57)
Nadir $CD4^+$ T-cell count, cells/mm^3	113 (29–227)
Duration of HAART suppression, months	31 (14–66)
Agent included in HAART, no. of patients	
Protease inhibitor	124
NNRTI	73
Raltegravir	14
Maraviroc	1
Enfuvirtide	3

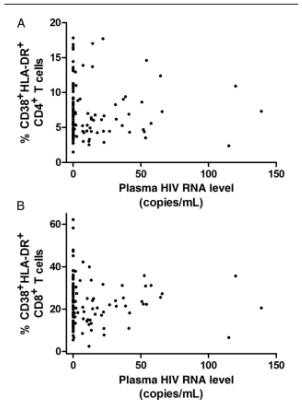


Figure 1. No associations between ultrasensitive plasma human immunodeficiency virus (HIV) RNA levels and T-cell activation. Ultrasensitive plasma HIV RNA levels were measured using the COBAS AmpliPrep/COBAS TaqMan HIV-1 test, version 2.0. All *P* values are >.40.

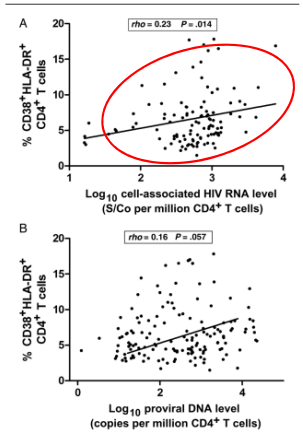


Figure 2. Cell-based measures of viral persistence are modestly associated with immune activation.

B)

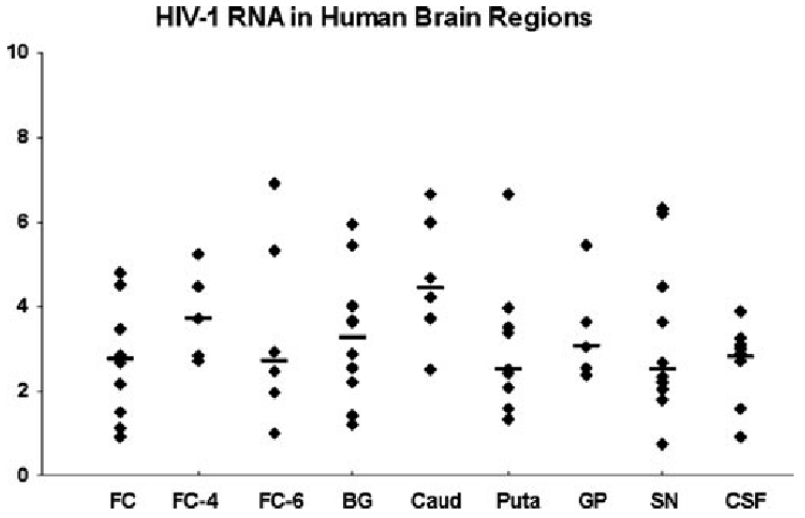
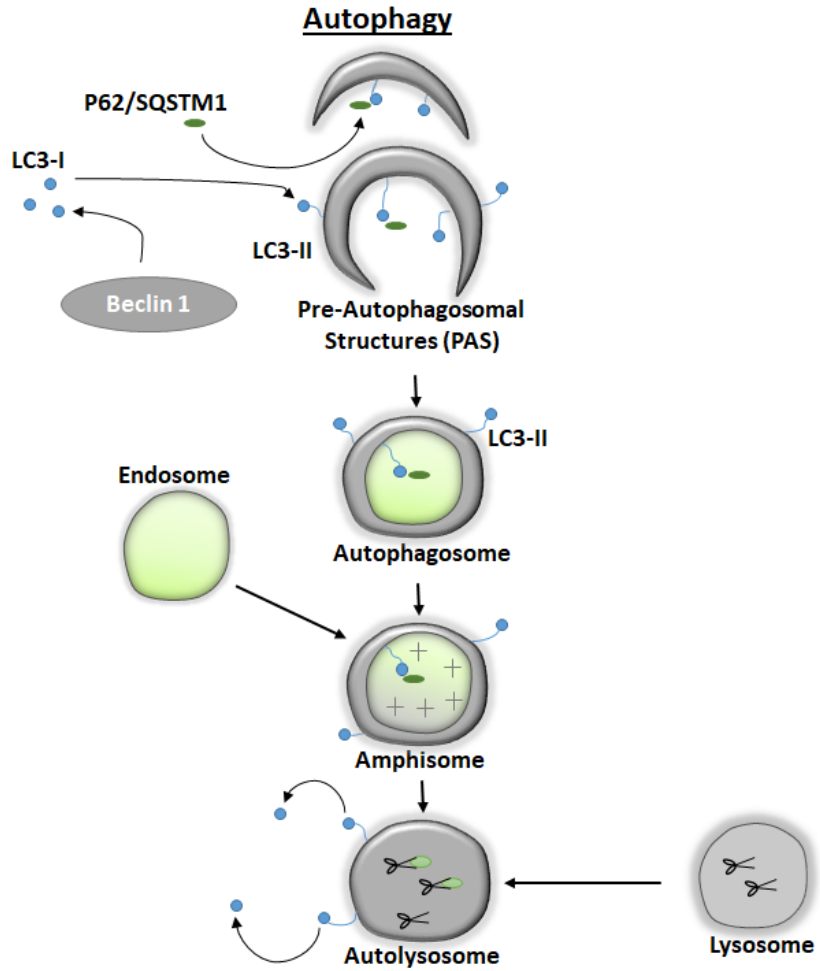


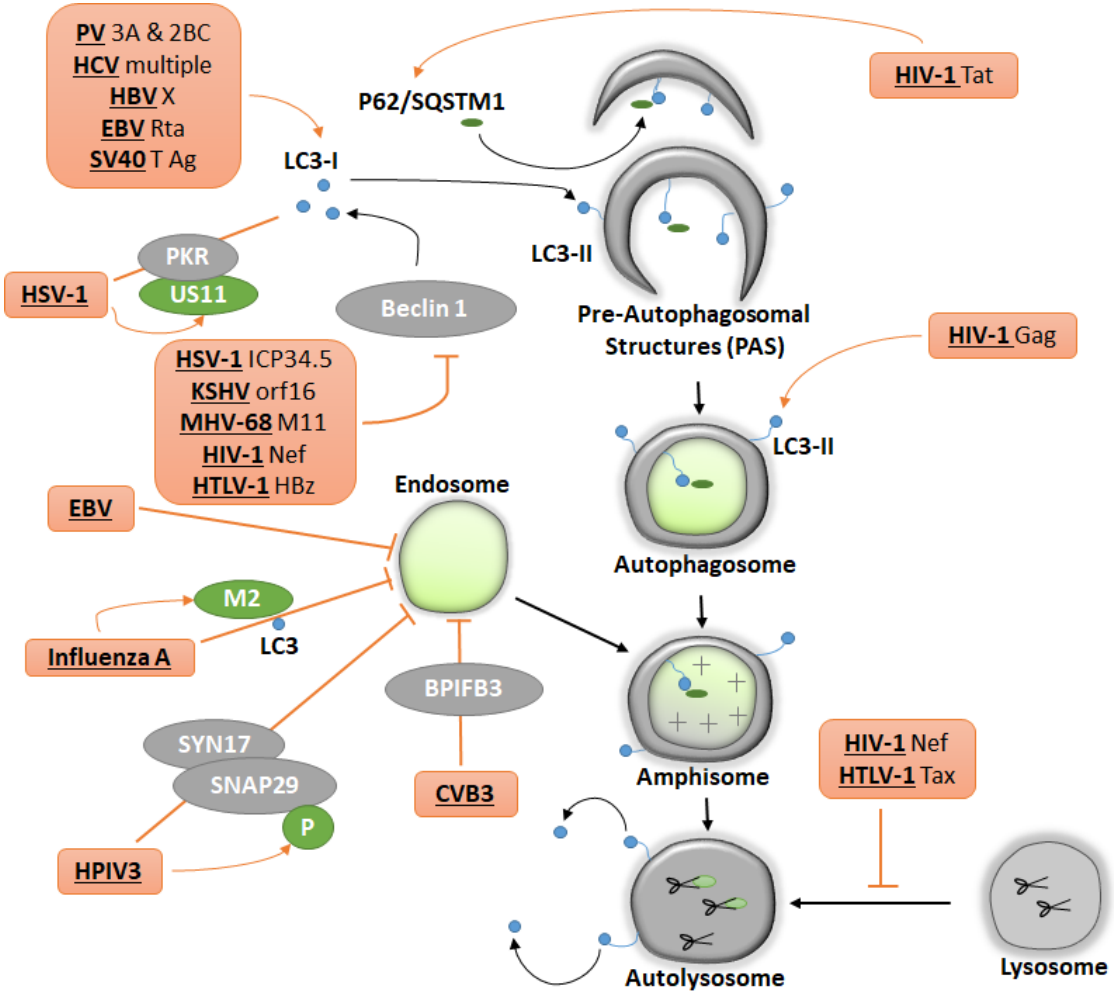
Figure 1 HIV-1 RNA load (log_{10} copies/g tissue) in each region of HIV-1+ individuals is presented in a scatter plot. The horizontal bars represent the median value in each region. Viral load values were higher in caudate nucleus compared to that in the other regions (FC-4, FC-6, BG, putamen, globus pallidus, SN), and the lowest values were found in FC and CSF.

A) Hatano et al. *JID*. 2013
B) Kumar et al. *J Neurovirol*. 2007

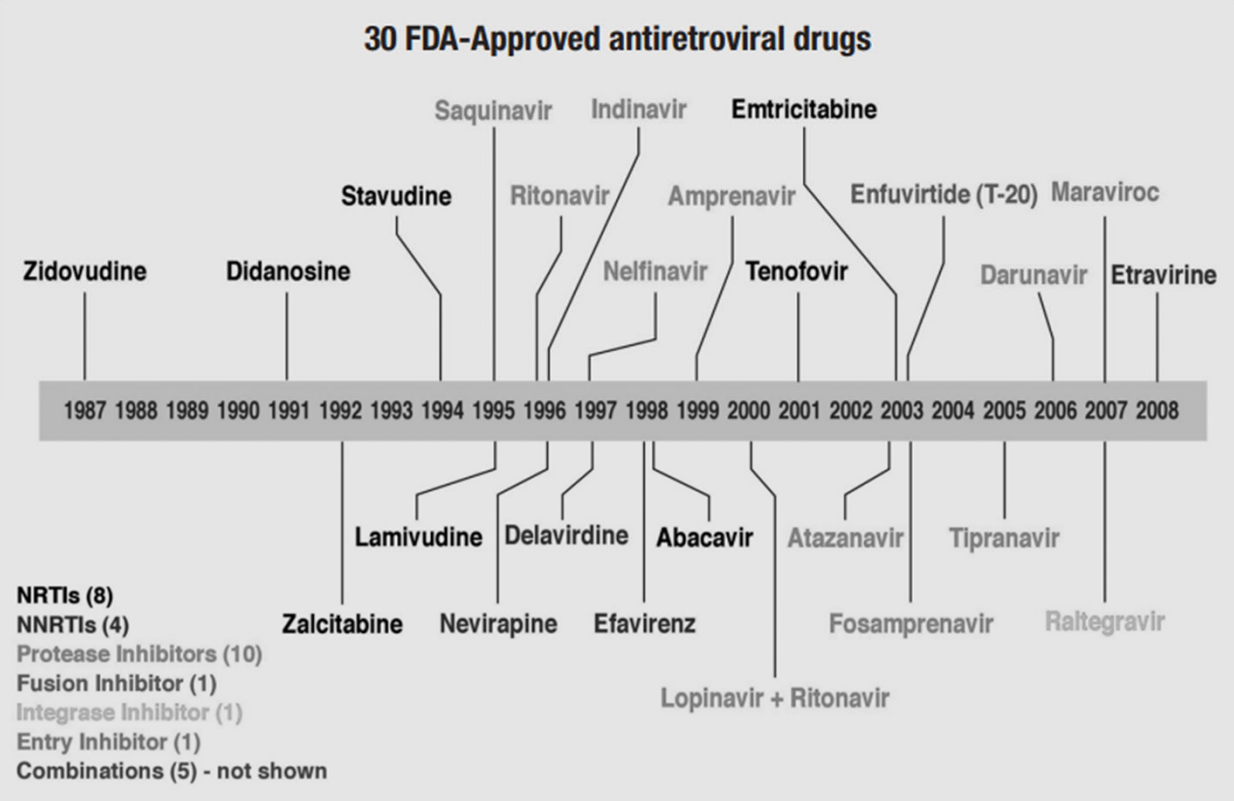
Mechanism


Autophagy
P62/SQSTM1
LC3-I
LC3-II
Beclin 1
Pre-Autophagosomal
Structures (PAS)
LC3-II
Endosome
Autophagosome
Amphisome
Autolysosome
Lysosome

Mechanism


PV 3A & 2BC
HCV multiple
HBV X
EBV Rta
SV40 T Ag
P62/SQSTM1
HIV-1 Tat
LC3-I
LC3-II
PKR
US11
HSV-1
Beclin 1
Pre-Autophagosomal Structures (PAS)
HIV-1 Gag
HSV-1 ICP34.5
KSHV orf16
MHV-68 M11
HIV-1 Nef
HTLV-1 HBz
LC3-II
Endosome
EBV
Autophagosome
M2
LC3
Influenza A
BPIFB3
SYN17
SNAP29
P
CVB3
Amphisome
HIV-1 Nef
HTLV-1 Tax
HPIV3
Autolysosome
Lysosome

Treatment

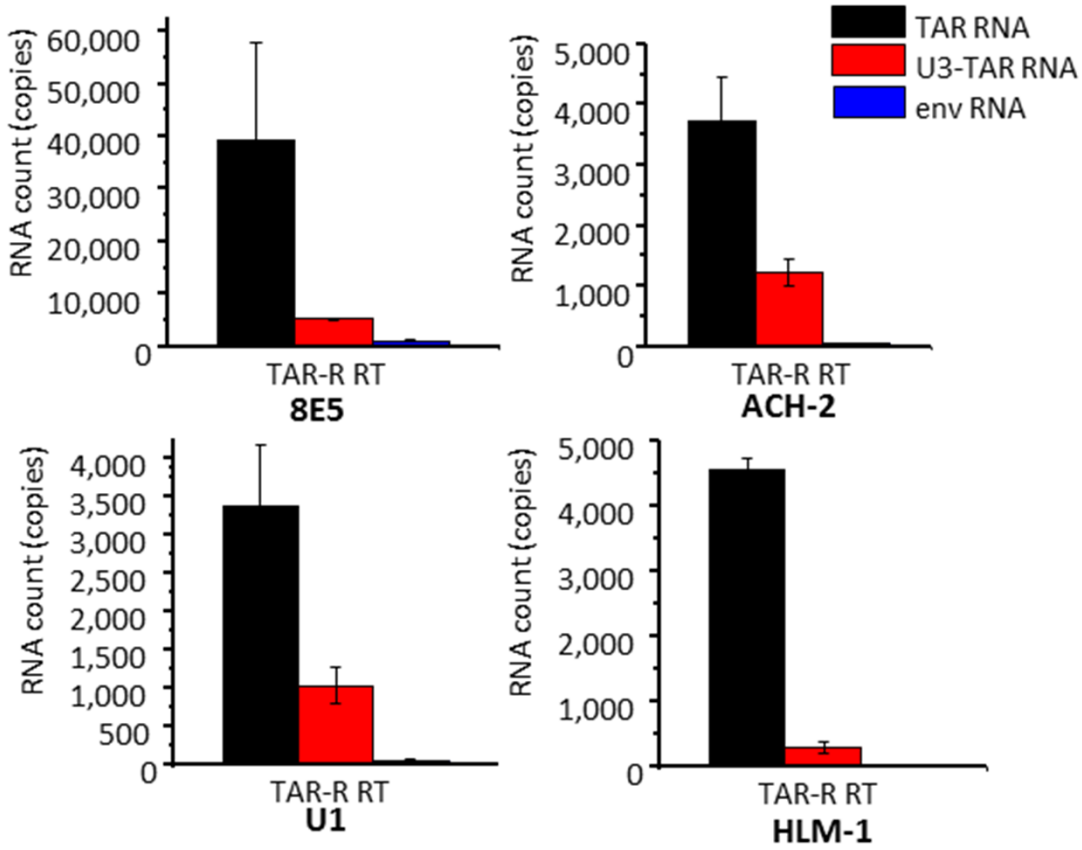


No FDA-Approved Transcription Inhibitors

Palmisano and Vella. *Ann Ist Super Sanita*. 2011

Characterization and Analysis of "Damaging EVs"

TAR RNA is present in culture supernatants of HIV-1 infected cells



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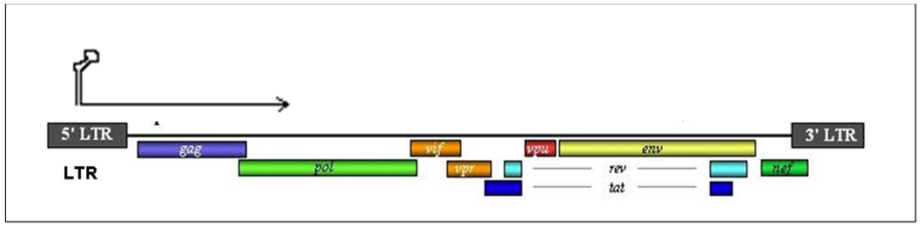
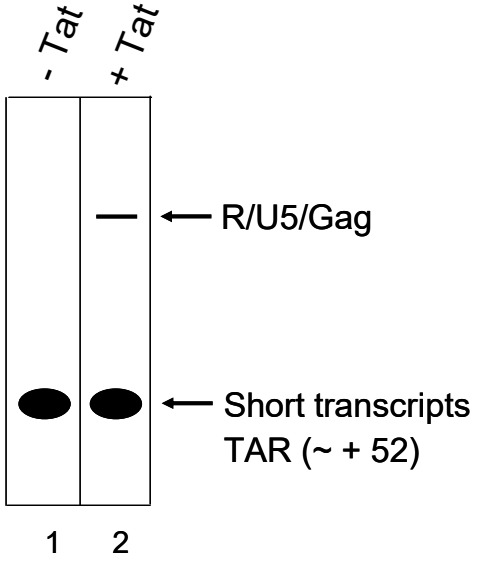
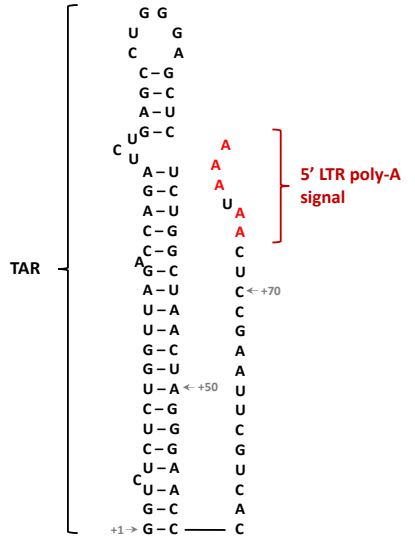
Characterization and Analysis of "Damaging EVs"

TAR RNA (short transcripts)







- More than 70 papers from late 80s to present
- Detected *in vitro*, *in vivo* and in latent patient cells

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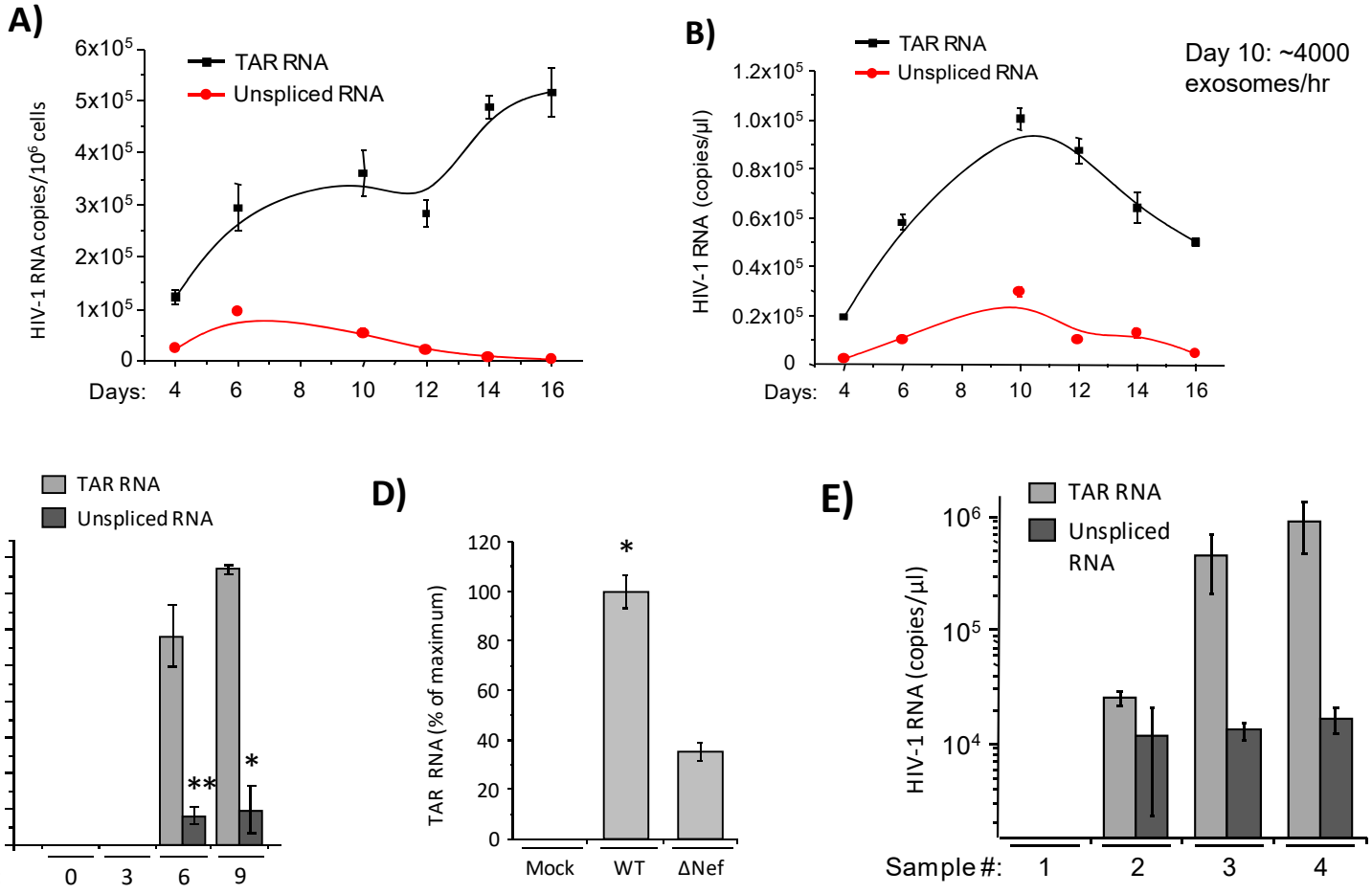
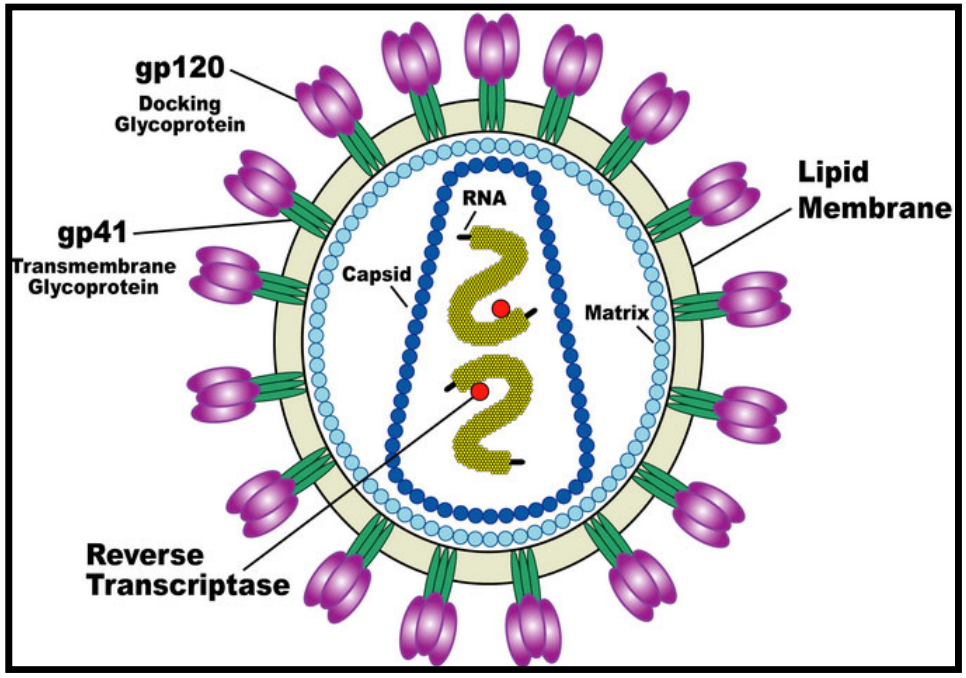
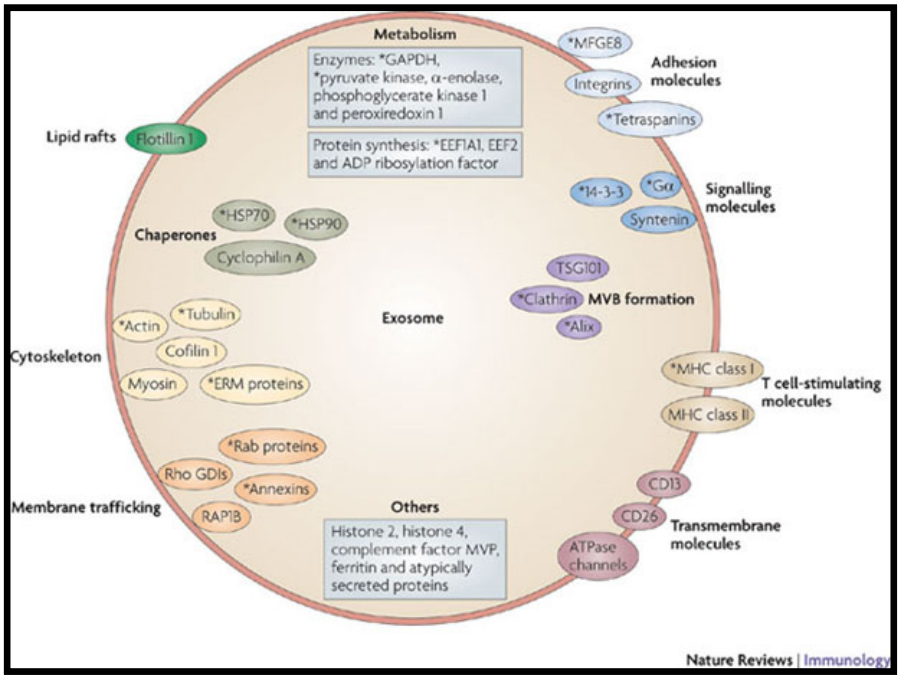
Characterization and Analysis of "Damaging EVs"



Sampey et al. *JBC*. 2016

Characterization and Analysis of "Damaging EVs"





Thery et al. *Nat Rev Immunol*. 2009

Characterization and Analysis of "Damaging EVs"

SCIENTIFIC REPORTS

Correction: Publisher Correction

OPEN

Antiretroviral Drugs Alter the Content of Extracellular Vesicles from HIV-1-Infected Cells

Received: 3 January 2018
Accepted: 1 May 2018
Published online: 16 May 2018

Catherine DeMarino[1], Michelle L. Pleet[1], Maria Cowen[1], Robert A. Barclay[1], Yao Akpamagbo[1], James Erickson[1], Nicaise Ndembi[2], Manhattan Charurat[2], Jibreel Jumare[2], Sunday Bwala[3], Peter Alabi[4], Max Hogan[5], Archana Gupta[5], Nicole Noren Hooten[6], Michele K. Evans[6], Benjamin Lepene[7], Weidong Zhou[8], Massimo Caputi[9], Fabio Romerio[2], Walter Royal 3rd[10], Nazira El-Hage[11], Lance A. Liotta[8] & Fatah Kashanchi[1]

To date, the most effective treatment of HIV-1 is a combination antiretroviral therapy (cART), which reduces viral replication and reverses pathology. We investigated the effect of cART (RT and protease inhibitors) on the content of extracellular vesicles (EVs) released from HIV-1-infected cells. We have previously shown that EVs contain non-coding HIV-1 RNA, which can elicit responses in recipient cells. In this manuscript, we show that TAR RNA levels demonstrate little change with the addition of cART treatment in cell lines, primary macrophages, and patient biofluids. We determined possible mechanisms involved in the selective packaging of HIV-1 RNA into EVs, specifically an increase in EV-associated hnRNP A2/B1. More recent experiments have shown that several other FDA-approved drugs have the ability to alter the content of exosomes released from HIV-1-infected cells. These findings on cART-altered EV content can also be applied to general viral inhibitors (interferons) which are used to treat other chronic infections. Additionally, we describe unique mechanisms of ESCRT pathway manipulation by antivirals, specifically the targeting of VPS4. Collectively, these data imply that, despite antiretroviral therapy, EVs containing viral products are continually released and may cause neurocognitive and immunological dysfunction.

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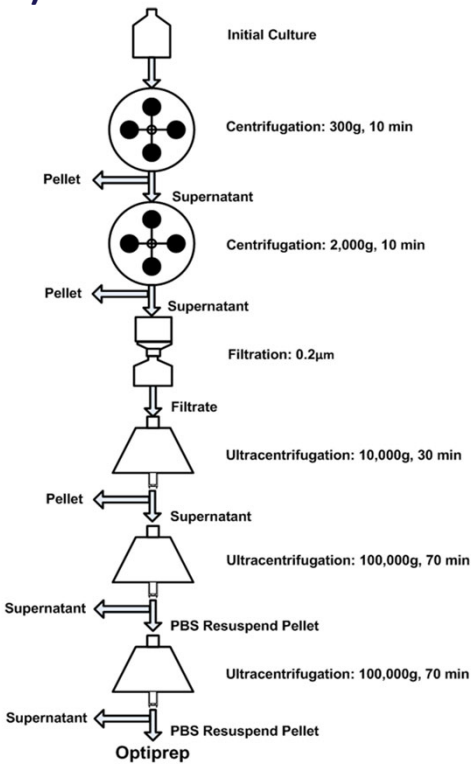
Isolation

A)



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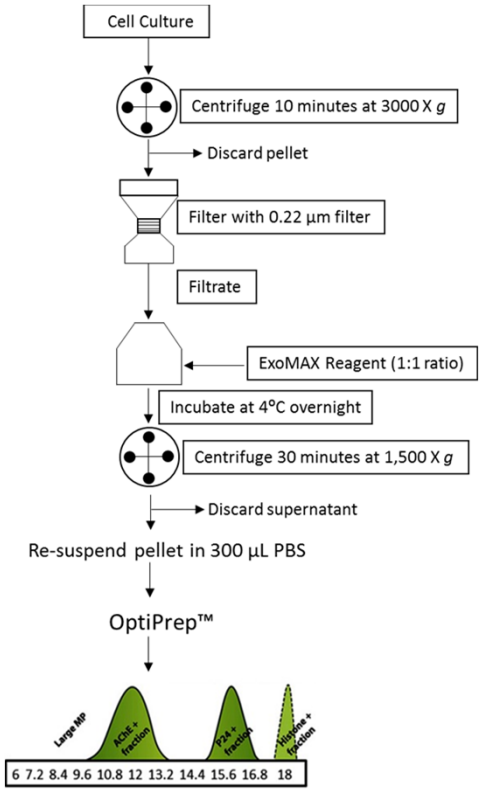

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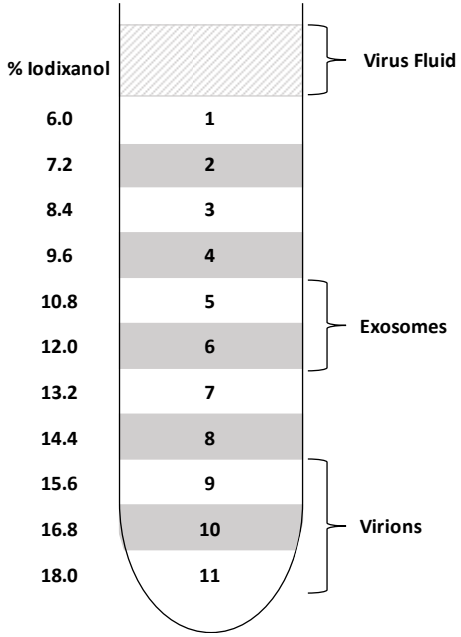

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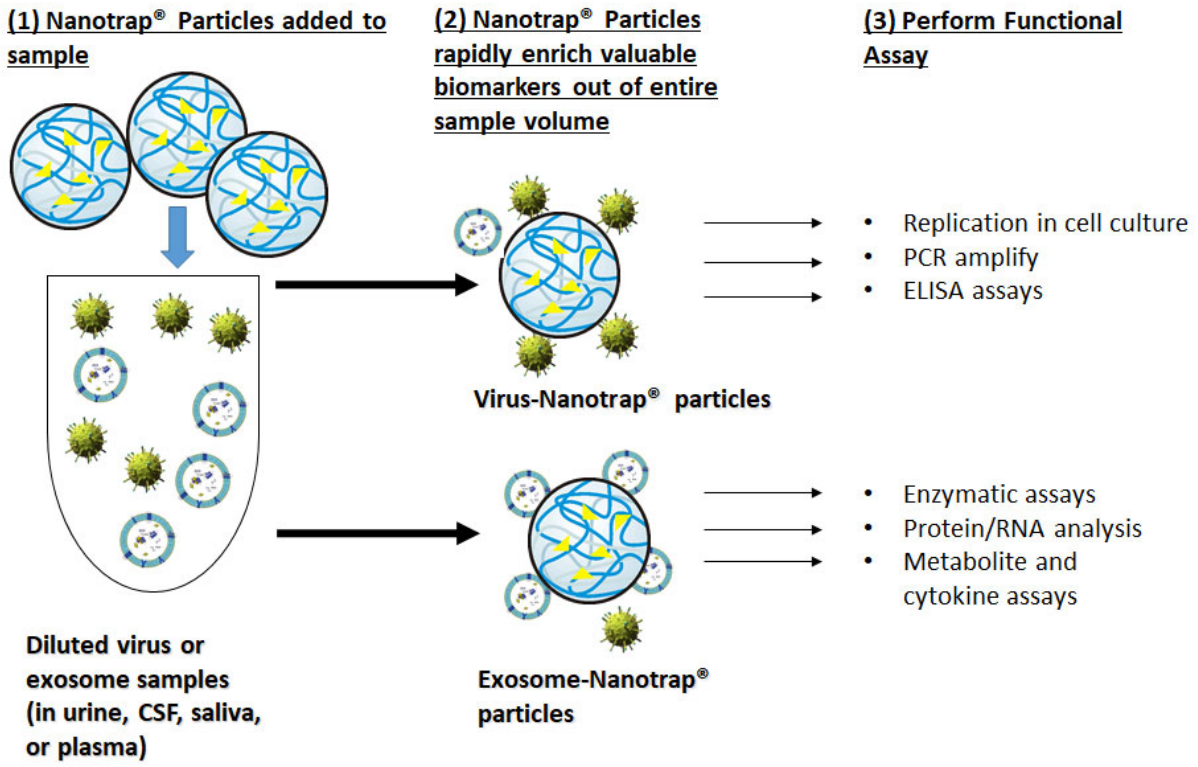
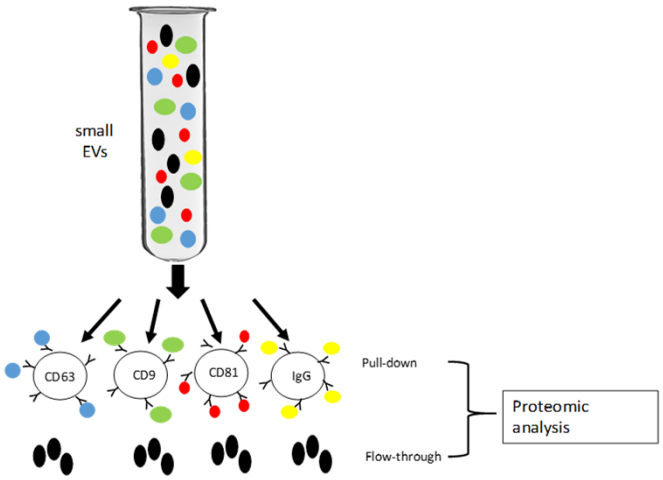
Characterization and Analysis of "Damaging EVs"

Using Nanotrap® particles to capture exosomes or viruses



Characterization and Analysis of "Damaging EVs"

A)



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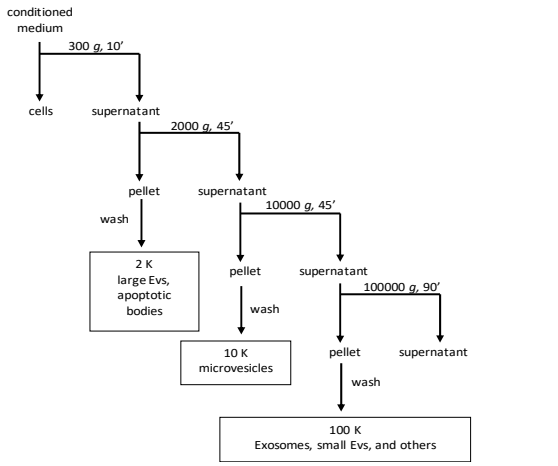

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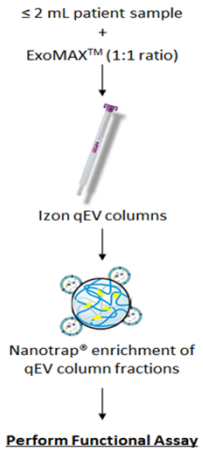
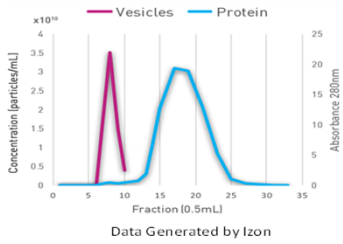
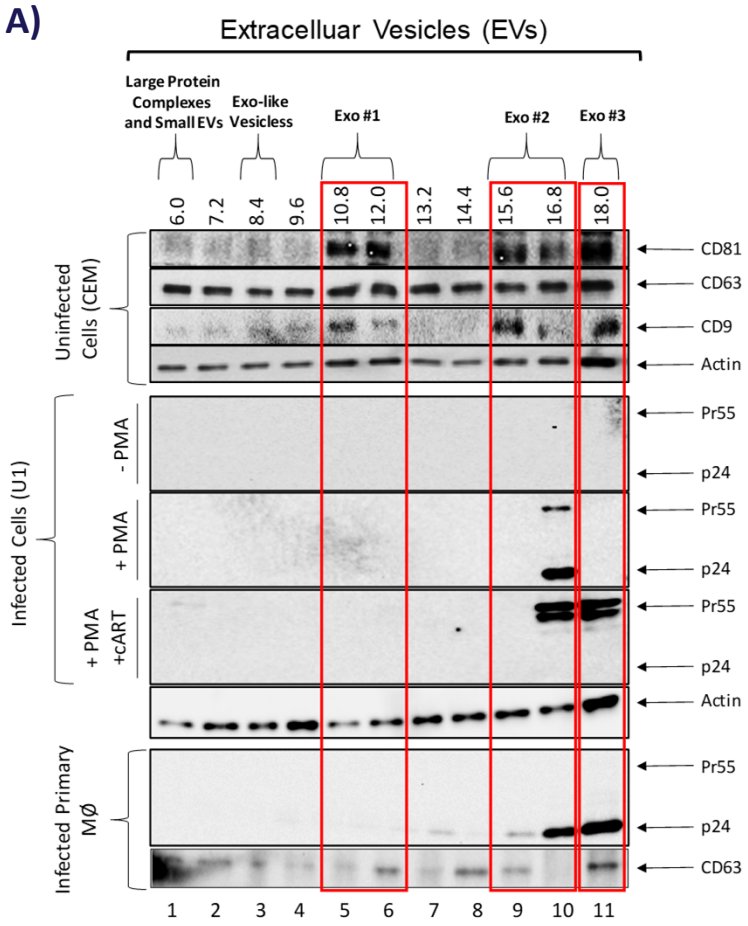
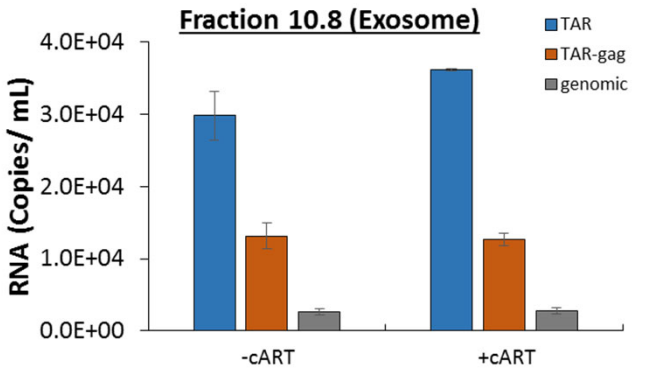


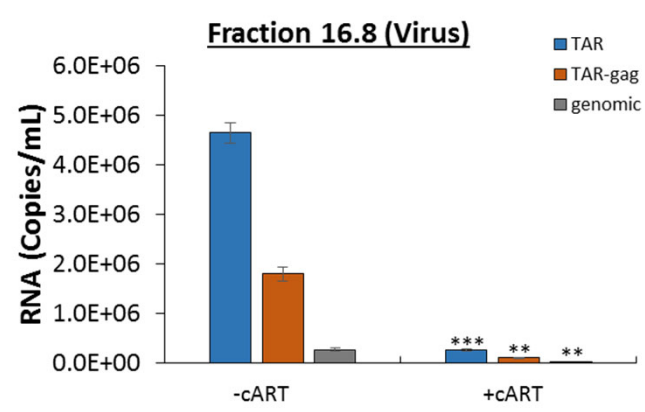


- qEV IZON column separation (size)

Characterization and Analysis of "Damaging EVs"

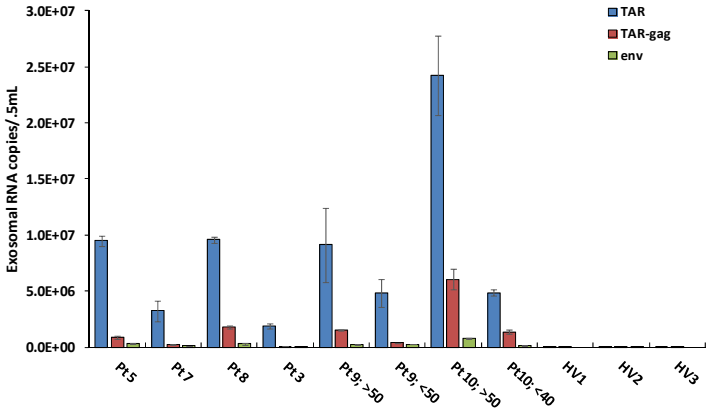






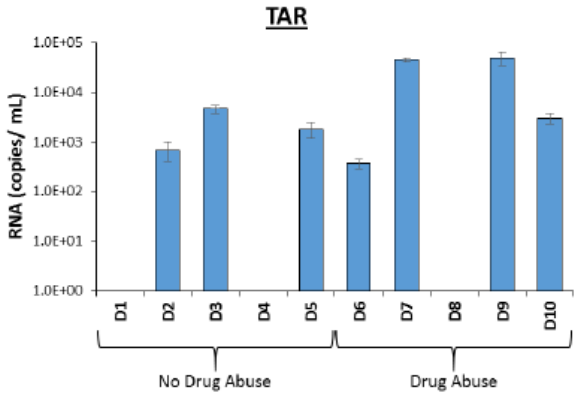
Characterization and Analysis of "Damaging EVs"

A)



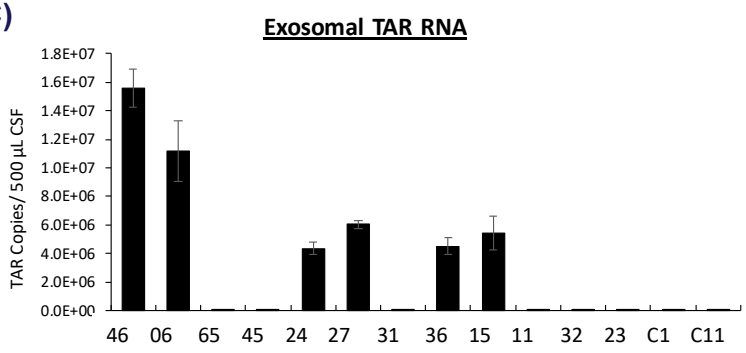
In collaboration with Dr. Cliff Lane's Lab, NIH

B)



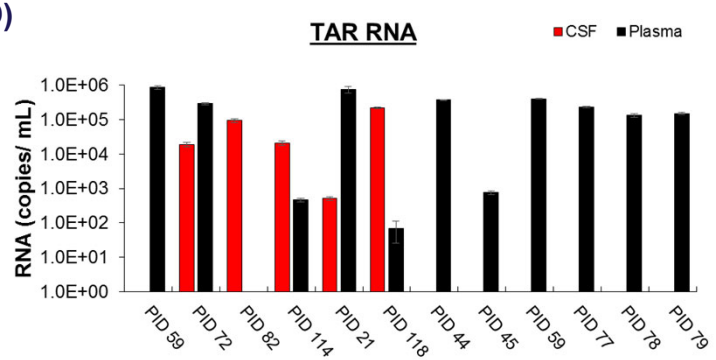
In collaboration with Dr. Nikki Noren Hooten, NIA

C)



In collaboration with Dr. Avi Nath's Lab, NIH

D)

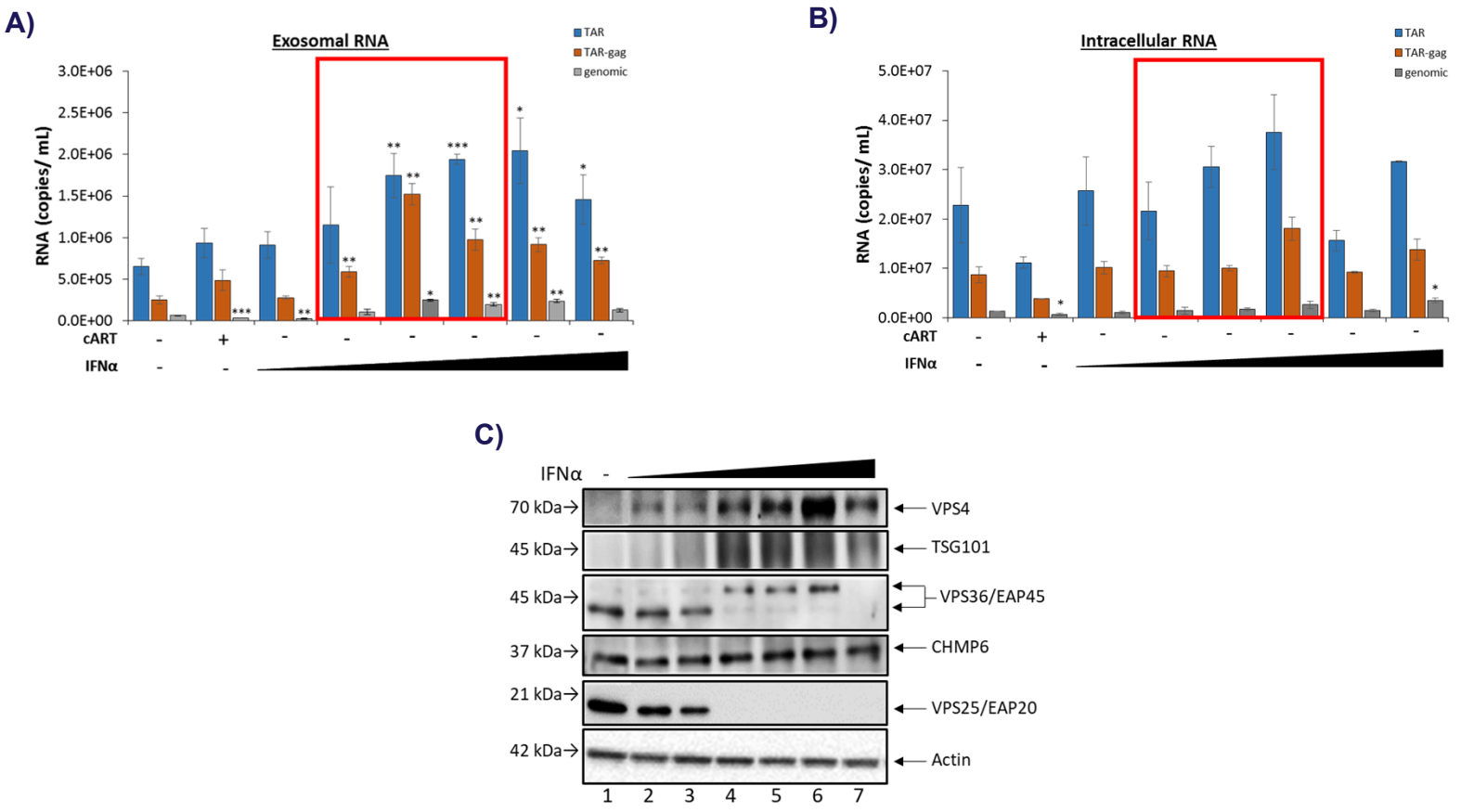


In collaboration with Dr. Walter Royal, U MD/Nigeria

ATCC

Characterization and Analysis of "Damaging EVs"

Interferon Alters EV Content Through the ESCRT Pathway



Characterization and Analysis of "Damaging EVs"

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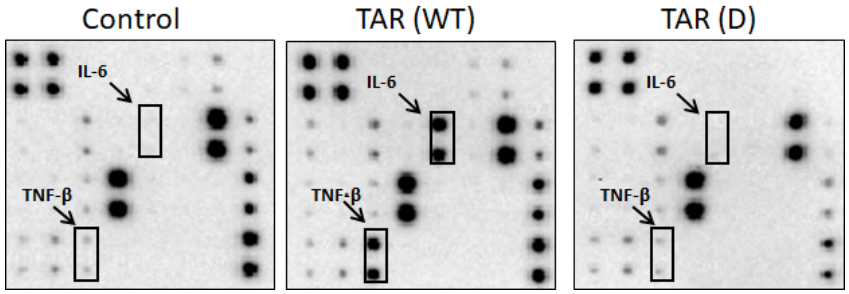

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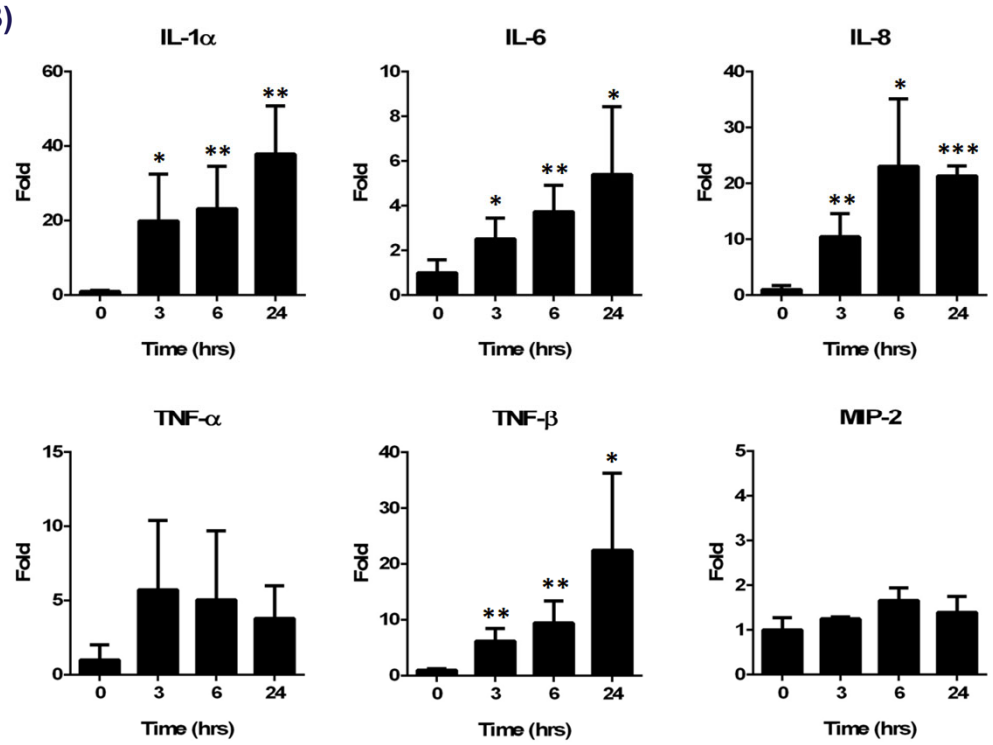
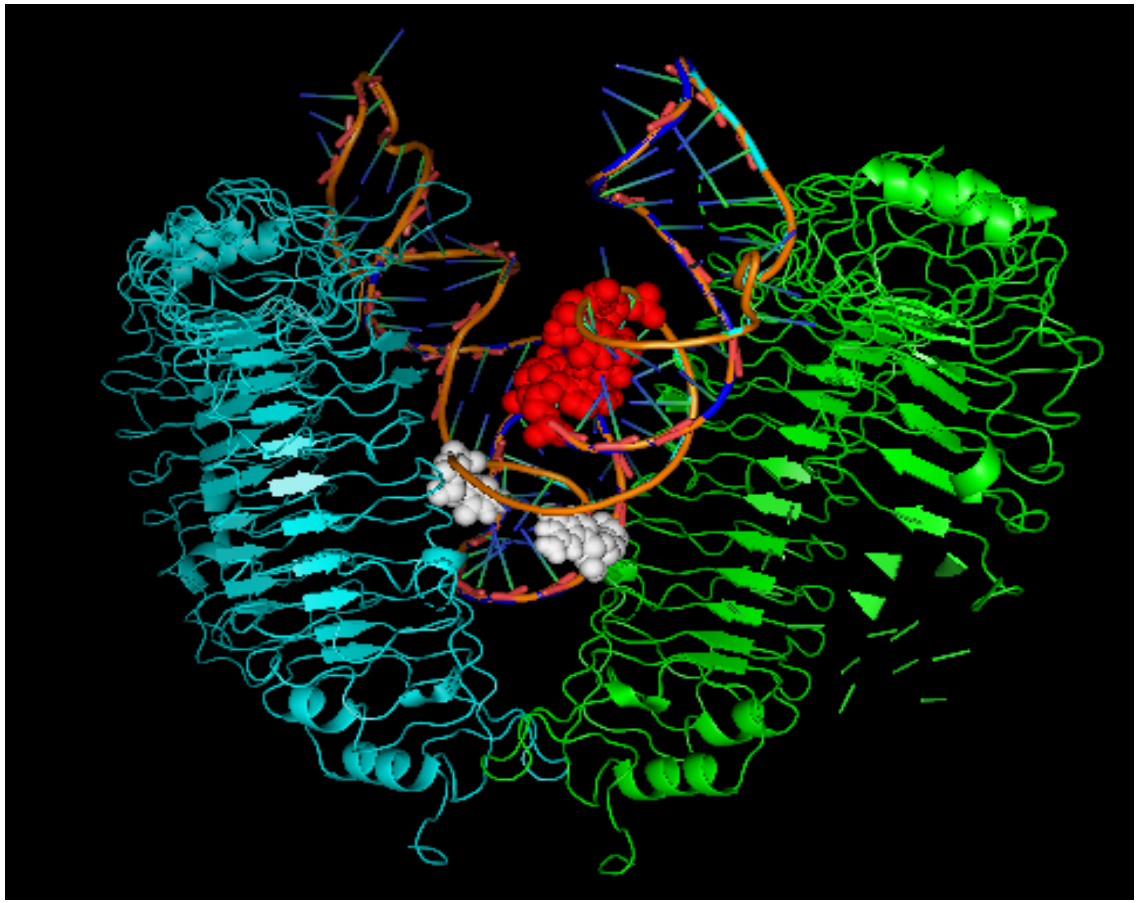


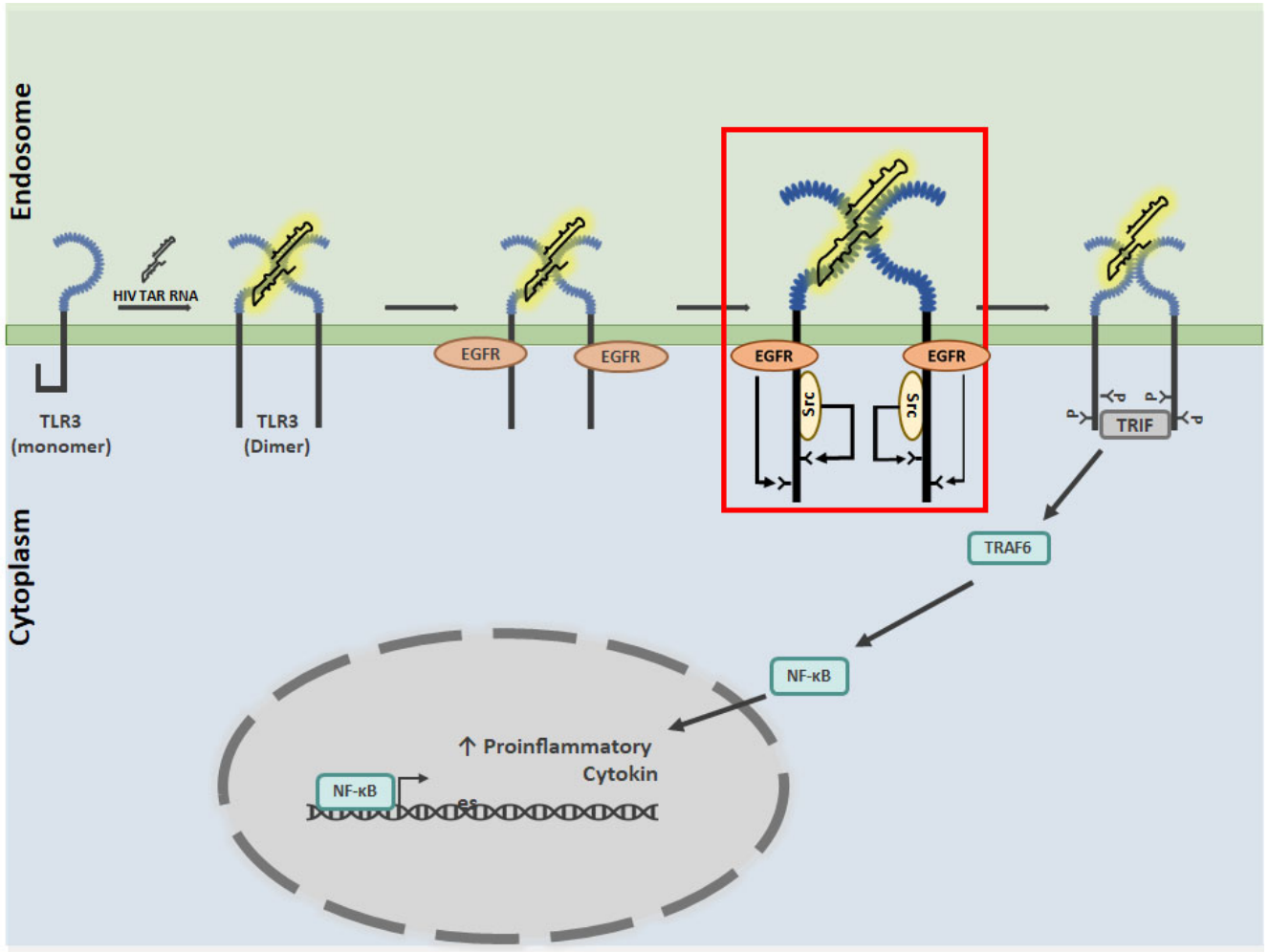
*P<0.05, **P<0.01, ***P<0.001 vs. 0 h control

Characterization and Analysis of "Damaging EVs"

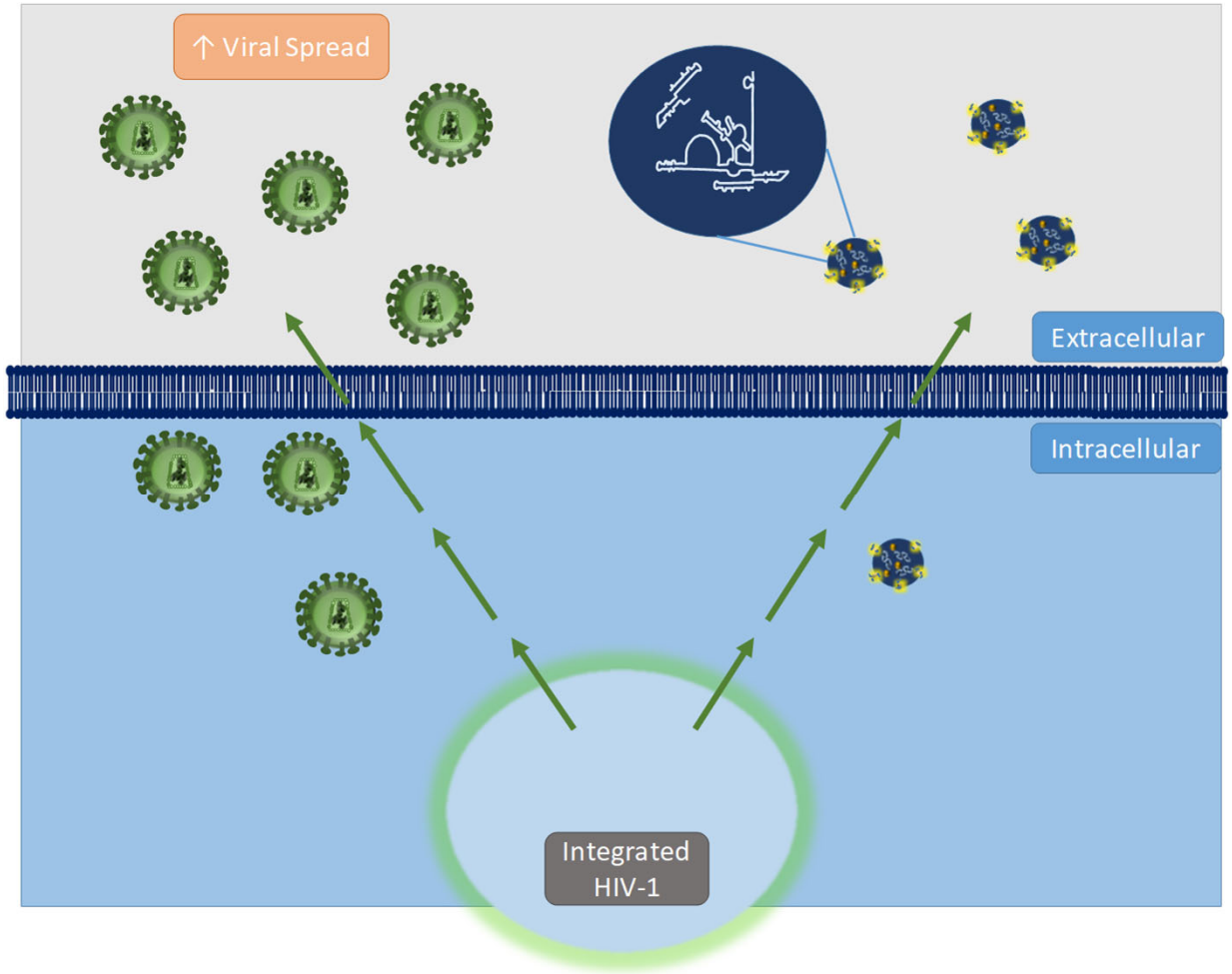


TAR RNA: TLR3 signaling complex.

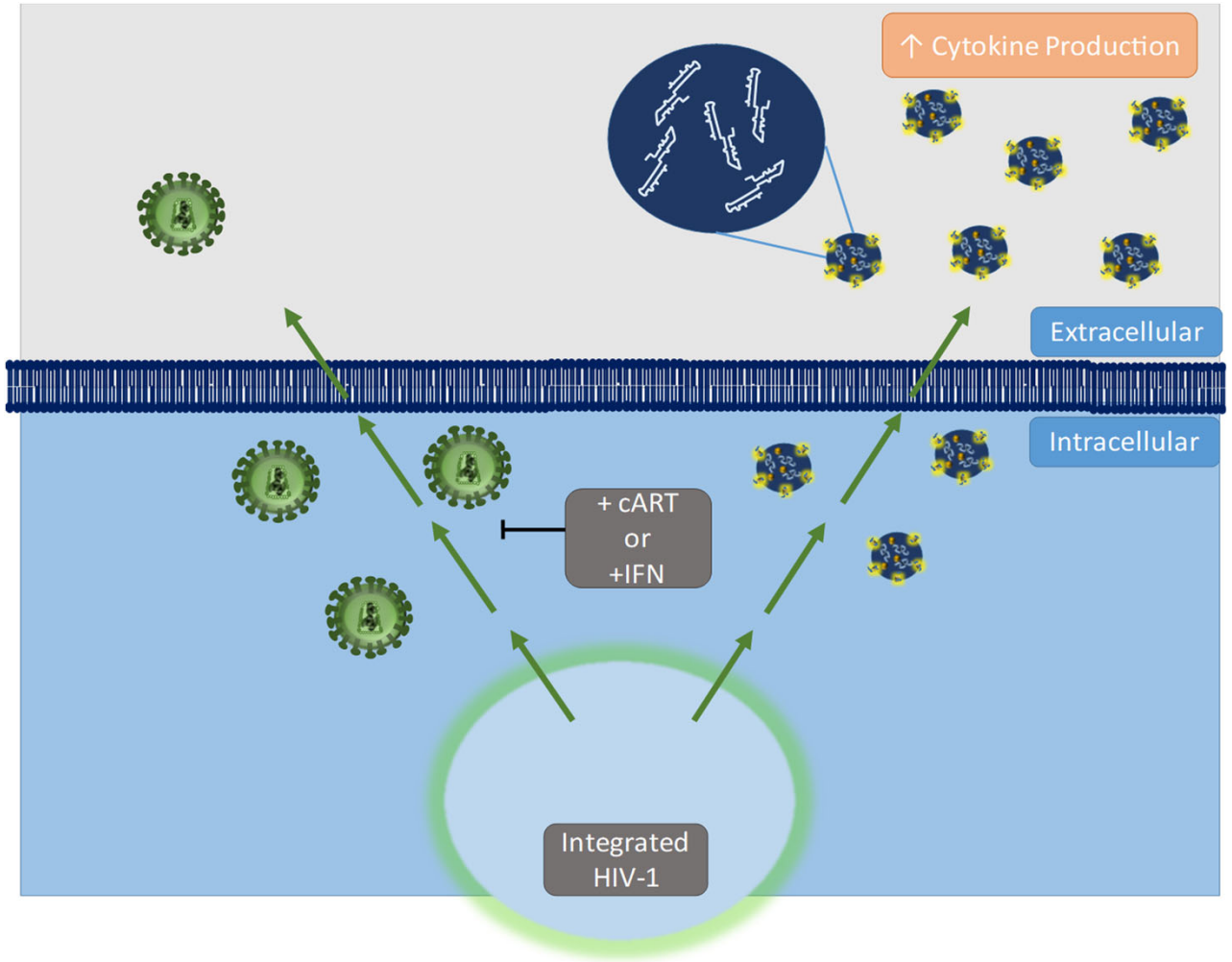
Mechanism


Endosome
HIV TAR RNA
TLR3
(monomer)
TLR3
(Dimer)
EGFR
EGFR
EGFR
EGFR
Src
Src
P
P
P
P
TRIF
TRAF6
Cytoplasm
NF-κB
↑ Proinflammatory
Cytokin
NF-κB

Mechanism


↑ Viral Spread
Extracellular
Intracellular
Integrated
HIV-1

Mechanism


↑ Cytokine Production
Extracellular
Intracellular
+ cART
or
+IFN
Integrated
HIV-1

Overview

- Overview of Extracellular Vesicles (EVs)
- Characterization and Analysis of “Damaging EVs”
- Characterization and Analysis of “Reparative EVs”
- Summary and Future Directions

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Topics to Be Discussed

1. Background on stem cells and stem cell EVs (reparative EVs)

2. Functional effects of stem cell EVs
   - Wound healing and skin repair
   - Cardiac, eye repair
   - CNS repair (stroke, TBI, SCI, neurodegenerative disorders)

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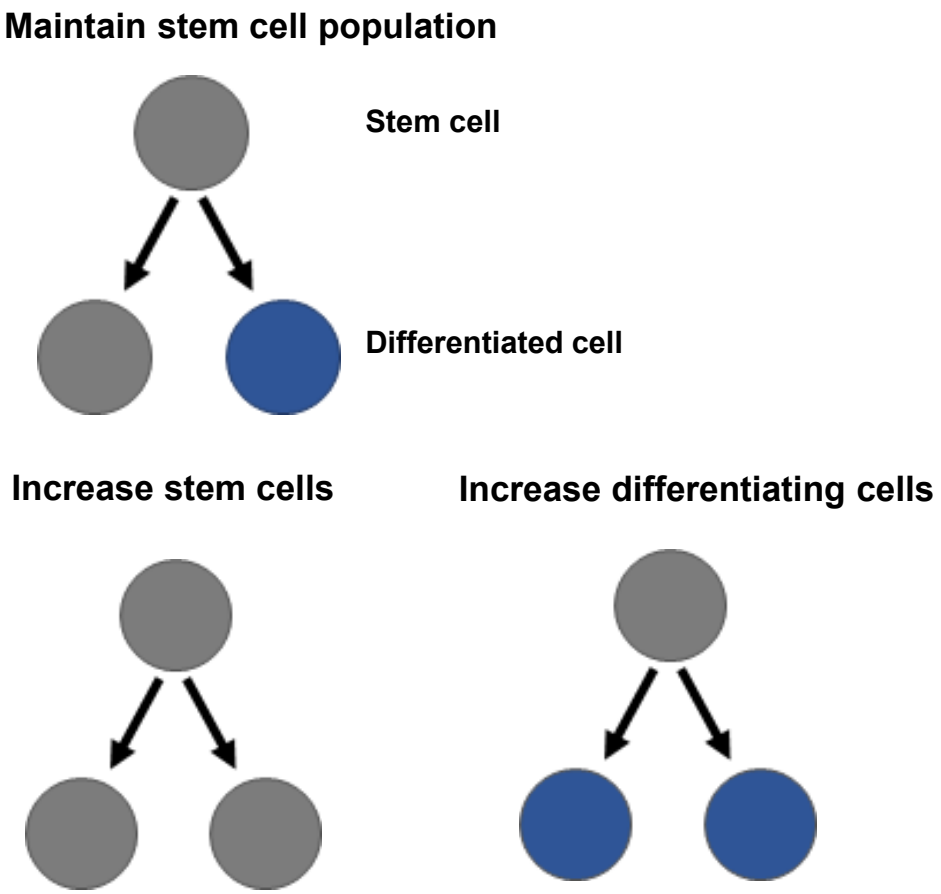
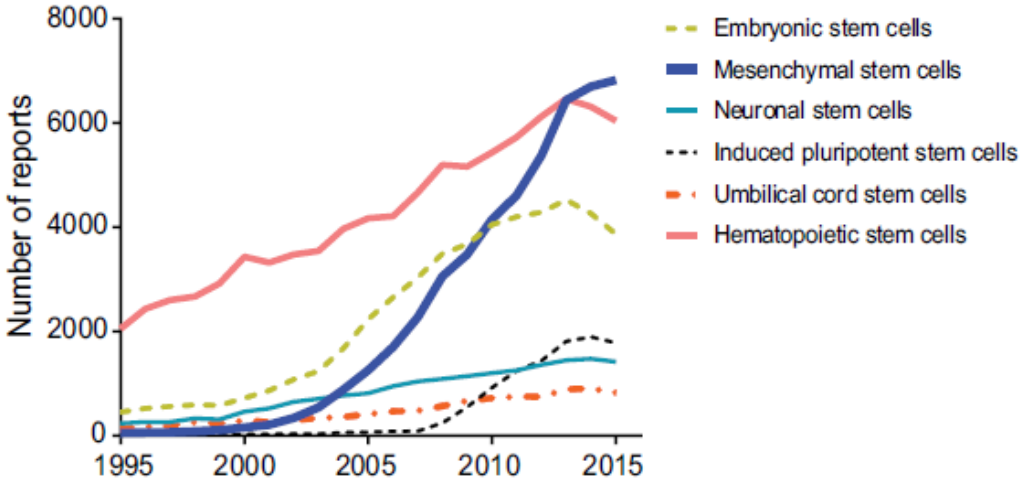
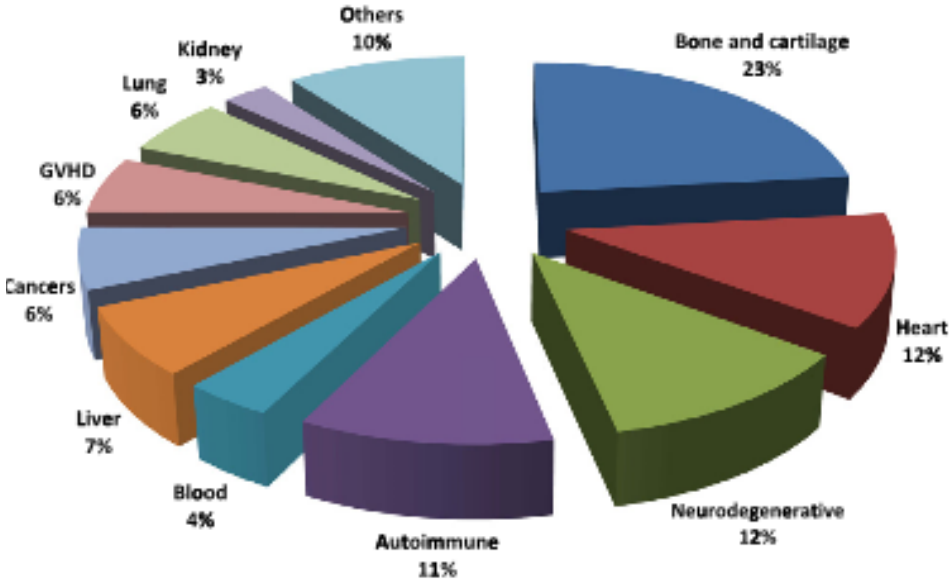
Stem Cells

- **Defining characteristics**
  - Self-renewal
  - Differentiation potential
- **Types of stem cells**
  - Embryonic stem cells
  - Adult (somatic) stem cells
  - Induced pluripotent stem cells



Stem Cell Therapy





Samsonraj et al. *Stem Cells Translational Medicine*. 2017
Marquez-Curtis et al. *Cryobiology.* 2015

Stem Cell EVs

- Contain various biological cargo (miRNAs, lncRNAs, proteins, cytokines) that can be transferred to recipient cells
- Proposed to play a role in homeostasis through tissue repair, regeneration, and immunomodulation
- **Potential alternative to stem cell therapy due to higher potency, increased stability/shelf life, and lower immunogenicity**
- Widely studied in the context of skin/wound healing, angiogenesis, cardiac repair, and CNS-related pathologies

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Stem Cell EVs

Stem Cell Research & Therapy

RESEARCH Open Access

Exosomes from acellular Wharton's jelly of the human umbilical cord promotes skin wound healing

Nazifah Bakhtyar[1], Marc G. Jeschke[1,2,3*], Elaine Herer[1,5], Mohammadali Sheikholeslam[1,3] and Saeid Amini-Nik[1,3,4*]

WJSC World Journal of Stem Cells

Submit a Manuscript: http://www.f6publishing.com World J Stem Cells 2018 August 26; 10(8): 106-115
DOI: 10.4252/wjsc.v10.i8.106 ISSN 1948-0210 (online)

REVIEW

Stem cell-derived exosomes - an emerging tool for myocardial regeneration

Erzsebet Lazar, Theodora Benedek, Szilamer Korodi, Nora Rat, Jocelyn Lo, Imre Benedek

Hindawi
Stem Cells International
Volume 2019, Article ID 5738510, 9 pages
https://doi.org/10.1155/2019/5738510

Research Article

Mesenchymal Stem Cell-Derived Extracellular Vesicles for Corneal Wound Repair

Hongyan Tao,[1,2] Xiaoniao Chen,[2] Hongmei Cao,[1] Lingyue Zheng,[3] Qian Li,[2] Kaiyue Zhang,[1] Zhibo Han,[4,5] Zhong-Chao Han,[4,5] Zhikun Guo,[6] Zongjin Li,[1,6,7] and Liqiang Wang[2]

J Trauma Acute Care Surg. 2019 Dec 5. doi: 10.1097/TA.0000000000002563. [Epub ahead of print]

Early Single-Dose Treatment with Exosomes Provides Neuroprotection and Improves Blood-Brain Barrier Integrity in Swine Model of Traumatic Brain Injury and Hemorrhagic Shock.

Williams AM[1], Bhatti UF[1], Brown JF[1], Biesterveld BE[1], Kathawate RG[1], Graham NJ[1], Chtraklin K[1], Siddiqui AZ[1], Dekker SE, Andjelkovic A[2], Higgins GA[3], Buller B[4], Alam HB[1].

Exosomes Derived From Bone Mesenchymal Stem Cells Ameliorate Early Inflammatory Responses Following Traumatic Brain Injury

Haoqi Ni[1,2], Su Yang[1,2], Felix Siaw-Debrah[1,2], Jiangnan Hu[3], Ke Wu[1,2], Zibin He[1,2], Jianjing Yang[1,2], Sishi Pan[1,2], Xiao Lin[1,2], Haotuo Ye[1,2], Zhu Xu[1,2], Fan Wang[1,2], Kunlin Jin[1,3], Qichuan Zhuge[1,2] and Lijie Huang[1,2]**

[1] Zhejiang Provincial Key Laboratory of Aging and Neurological Disorder Research, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, [2] Department of Neurosurgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, [3] Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, TX, United States

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Materials Science & Engineering C
journal homepage: www.elsevier.com/locate/msec

hucMSC derived exosomes promote functional recovery in spinal cord injury mice via attenuating inflammation

Guodong Sun[a,1], Guangqiang Li[a,1], Dehai Li[a], Wanjun Huang[a], Renwen Zhang[b], Hua Zhang[a], Yuanyuan Duan[a,*], Baocheng Wang[a,*]

Neural Regen Res. 2019 Sep; 14(9): 1626–1634. PMCID: PMC6557105
doi: 10.4103/1673-5374.255978 PMID: 31089063

Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease

Edwin E. Reza-Zaldivar,[1] Mercedes A. Hernández-Sapiéns,[1] Yanet K. Gutiérrez-Mercado,[1] Sergio Sandoval-Ávila,[1] Ulises Gomez-Pinedo,[2] Ana L. Márquez-Aquirre,[1] Estefanía Vázquez-Méndez,[1] Eduardo Padilla-Camberos,[1] and Alejandro A. Canales-Aquirre[1*]

Proc Natl Acad Sci U S A. 2017 Apr 25; 114(17): E3536–E3545. PMCID: PMC5410779
Published online 2017 Apr 10. doi: 10.1073/pnas.1703920114 PMID: 28396435
PNAS Plus
Neuroscience

Intranasal MSC-derived A1-exosomes ease inflammation, and prevent abnormal neurogenesis and memory dysfunction after status epilepticus

Qianfa Long,[a,1,2] Dinesh Upadhya,[a,b,c,2,3] Bharathi Hattiangady,[a,b,c] Dong-Ki Kim,[a] Su Yeon An,[a] Bing Shuai,[a,b,c] Darwin J. Prockop,[a,c,d,4,5] and Ashok K. Shetty[a,b,c,4,5]

Journal of Neuroimmune Pharmacology
https://doi.org/10.1007/s11481-019-09865-y

ORIGINAL ARTICLE

Check for updates

Stem Cell Extracellular Vesicles and their Potential to Contribute to the Repair of Damaged CNS Cells

Heather Branscome[1,2] · Siddhartha Paul[3] · Pooja Khatkar[1] · Yuriy Kim[1] · Robert A. Barday[1] · Daniel O. Pinto[1] · Dezhong Yin[3] · Weidong Zhou[4] · Lance A. Liotta[4] · Nazira El-Hage[5] · Fatah Kashanchi[1]

ATCC

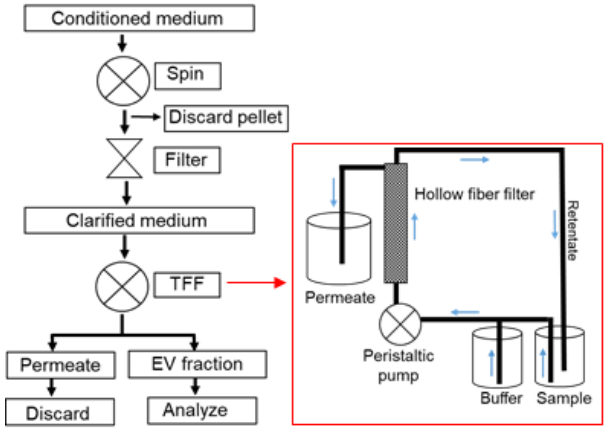
EVs and EV Donor Cells

- **Mesenchymal Stem Cells (MSCs; ATCC® PCS-500-012™)**
  - Human, normal
  - Bone-marrow derived
  - Authenticated for characteristic surface marker expression (CD90, CD73, CD105 positive; CD14, CD34, CD45 negative)
  - Multi-lineage differentiation potential (adipocyte, chondrocyte, osteocyte)
- **Induced Pluripotent Stem Cells (iPSCs; ATCC® ACS-1019™)**
  - Human, normal
  - Foreskin fibroblast-derived
  - Sendai virus reprogrammed
  - Authenticated for expression of stem cell markers (TRA-1-60, SSEA-4 positive; SSEA-1 negative)
  - Evaluated for pluripotency
- **A549 Lung Carcinoma (ATCC® CCL-185™)**
  - Control used for large-scale manufacturing and isolation
  - Equivalent to CCL-185-EXM™ (also: ATCC® SCRC-4000-EXM™, CRL-1435-EXM™, CCL-247-EXM™)

ATCC

EV Isolation and Characterization

A)



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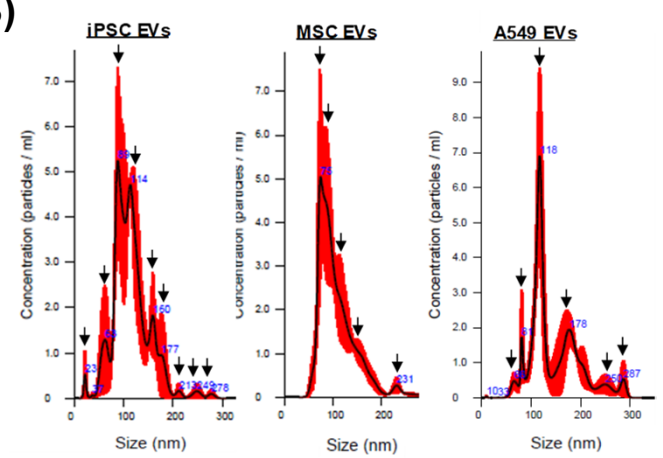

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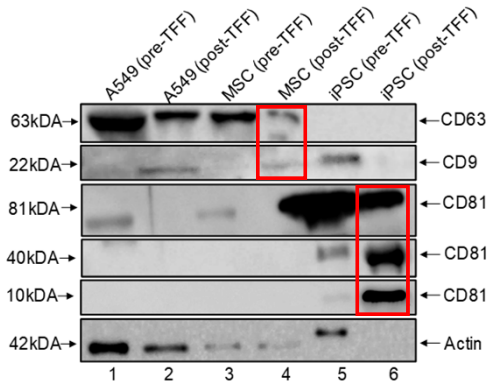
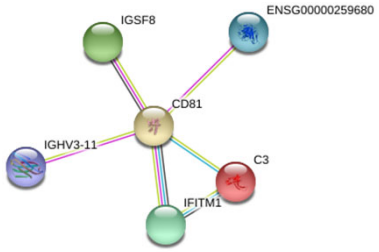
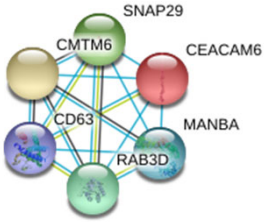


D)

CD81



CD63

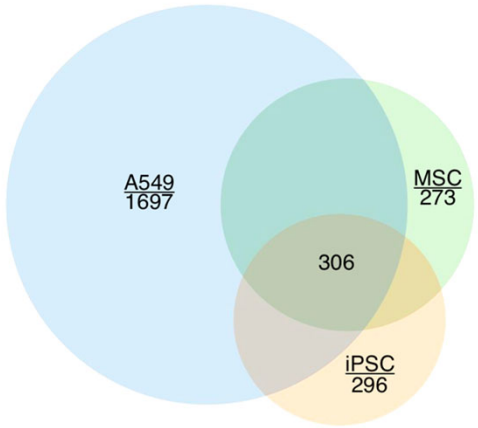


GeneCards.org

ATCC

EV Characterization

A)



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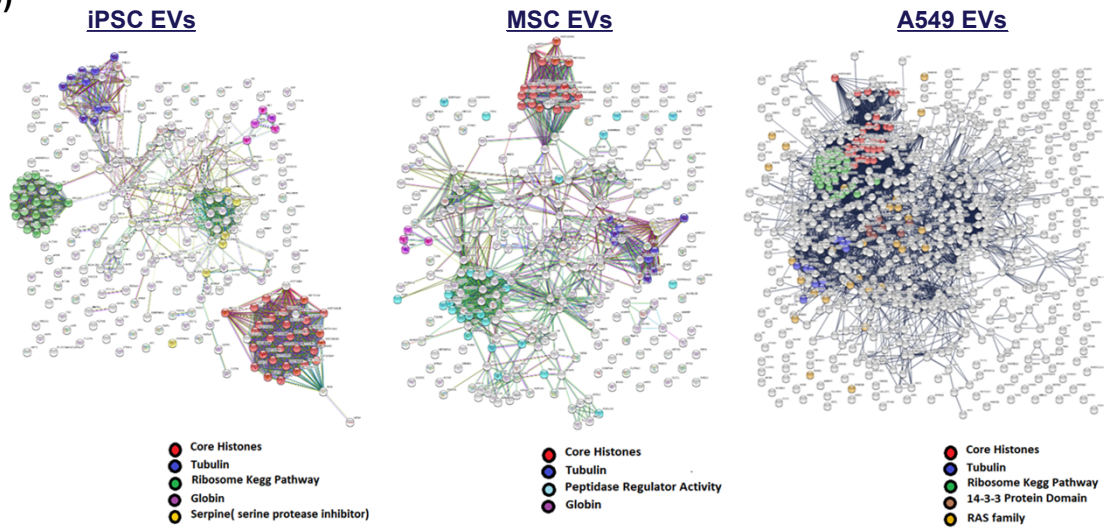

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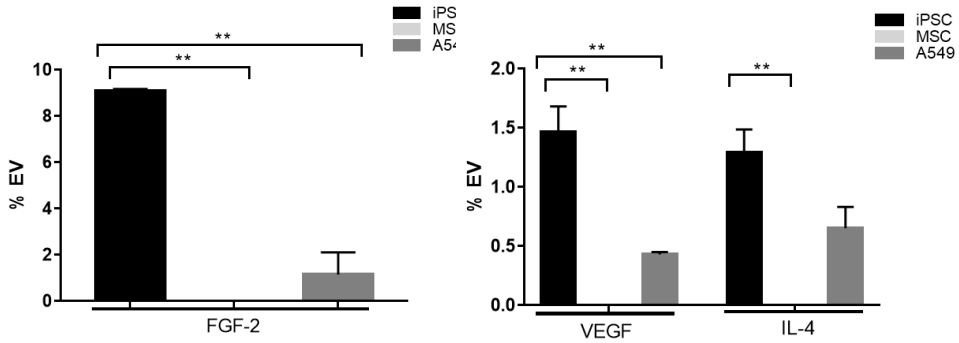

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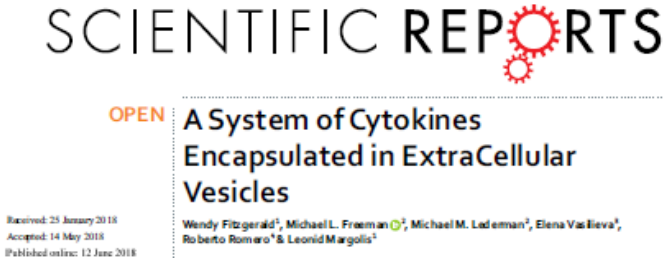

SCIENTIFIC REPORTS

OPEN

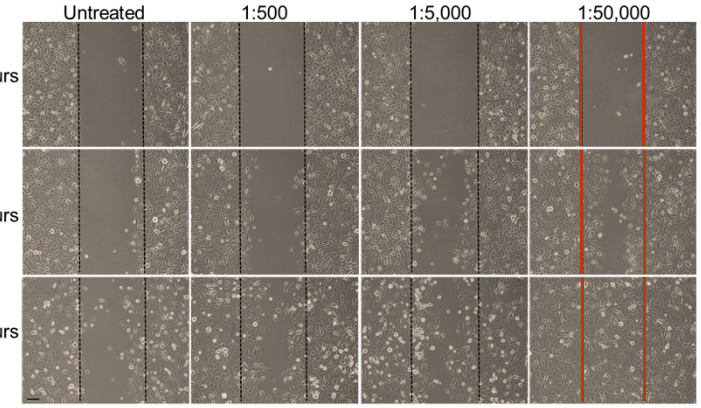
A System of Cytokines Encapsulated in ExtraCellular Vesicles

Wendy Fitzgerald[1], Michael L. Freeman[2], Michael M. Lederman[3], Elena Vasilieva[4], Roberto Romero[4] & Leonid Margolis[1]

Received: 25 January 2018
Accepted: 14 May 2018
Published online: 12 June 2018

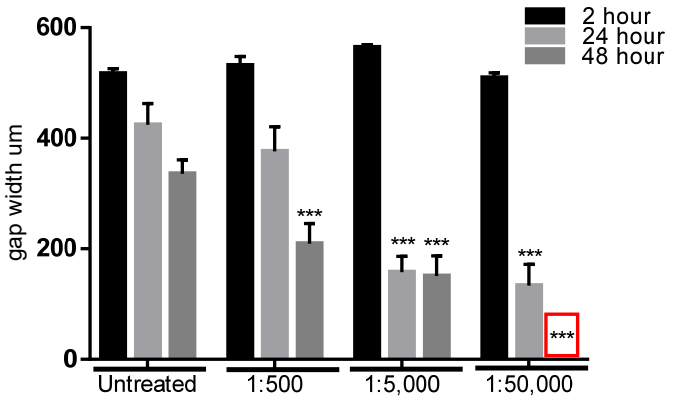
EV Functionality

A)



iPSC EVs

B)



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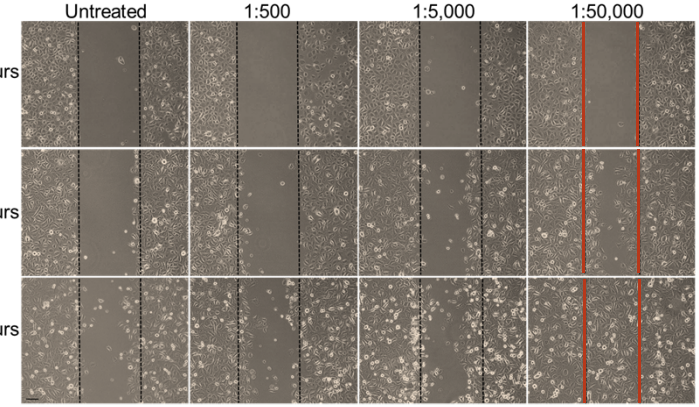
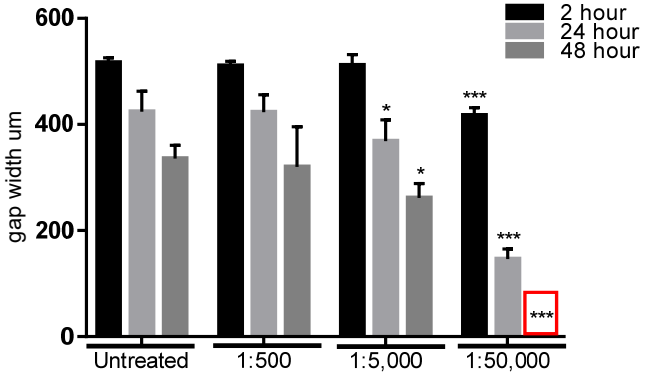


MSC EVs

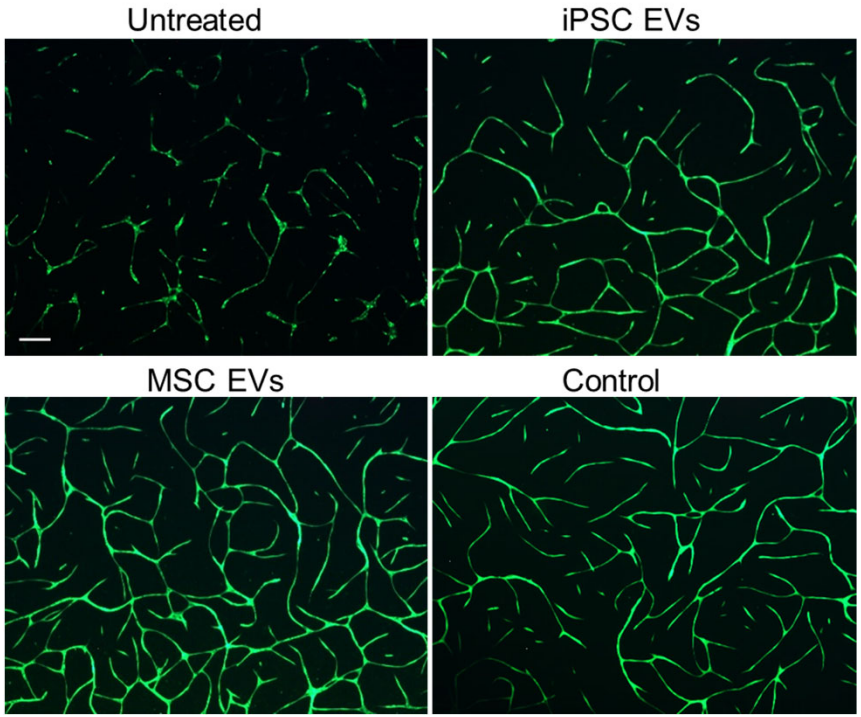
D)



EV Functionality

Angio-***Ready***™ Angiogenesis Assay System (ATCC® ACS-2001-2™)

A)



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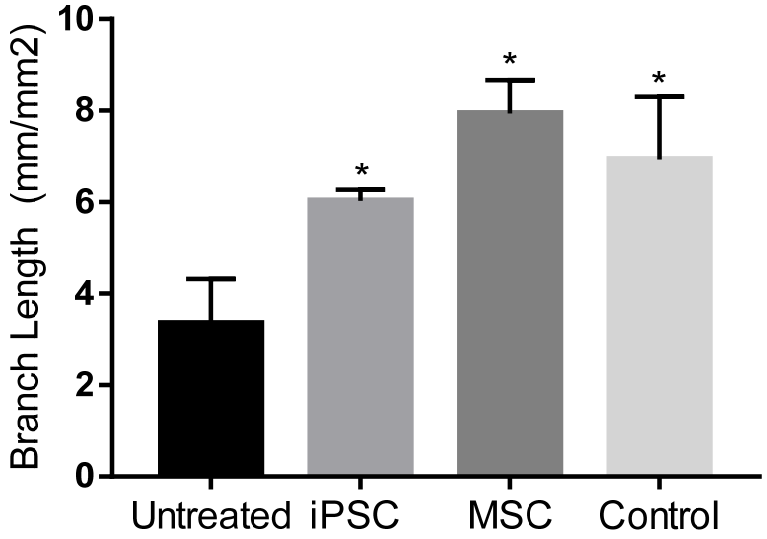
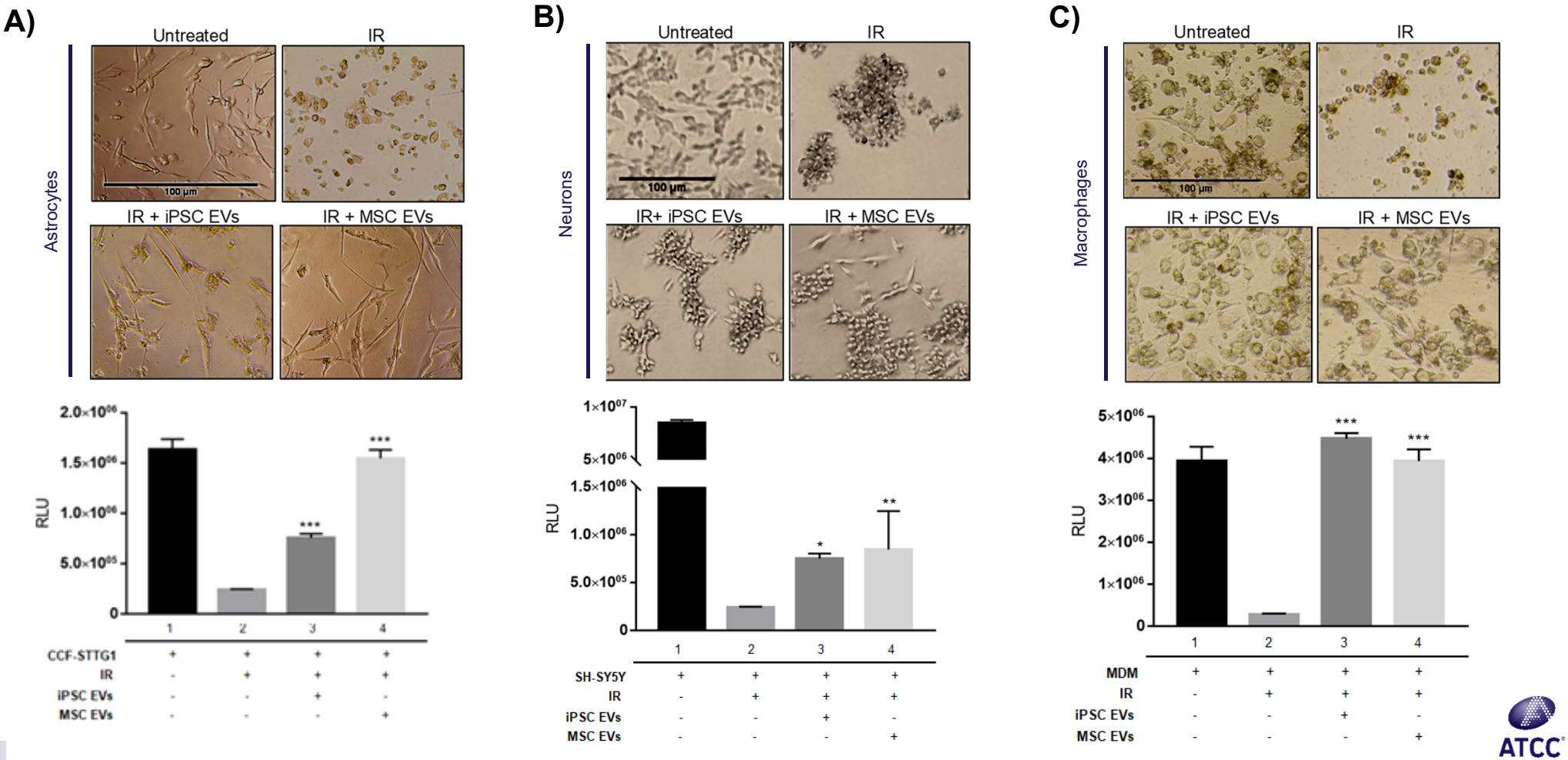
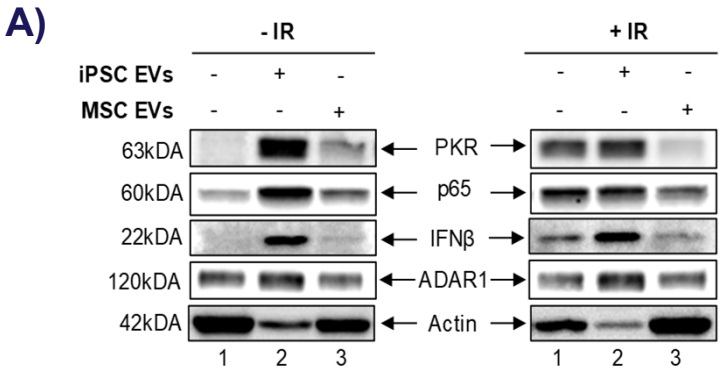
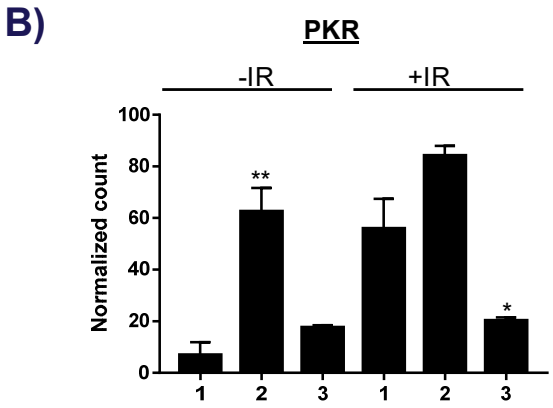


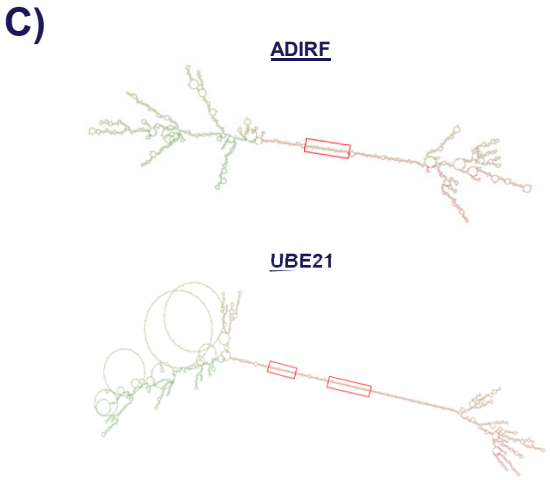
EV Functionality

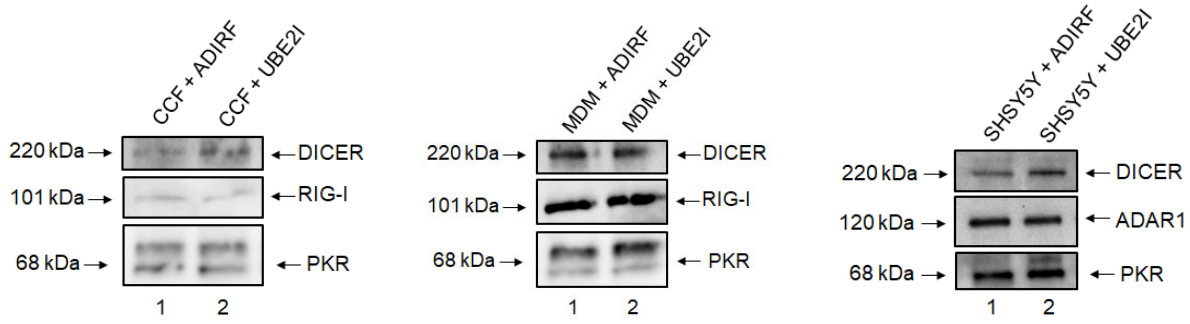


EV Functionality









Overview

- Overview of extracellular Vesicles (EVs)
- Characterization and Analysis of “Damaging EVs”
- Characterization and Analysis of “Reparative EVs”
- Summary and Future Directions

ATCC

Summary

- Extracellular vesicles (EVs) such as exosomes are critical mediators of intercellular communication. The diverse biological cargo that is associated with these vesicles is believed to mediate the pleiotropic effects of EVs.
- Infected cells secrete “Damaging EVs” which contain viral non-coding RNAs and other viral proteins and these EVs can be separated from infectious virions.
- Stem cells secrete “Reparative EVs” which contain both non-coding RNAs and cytokines that can contribute to processes relevant to cellular repair.

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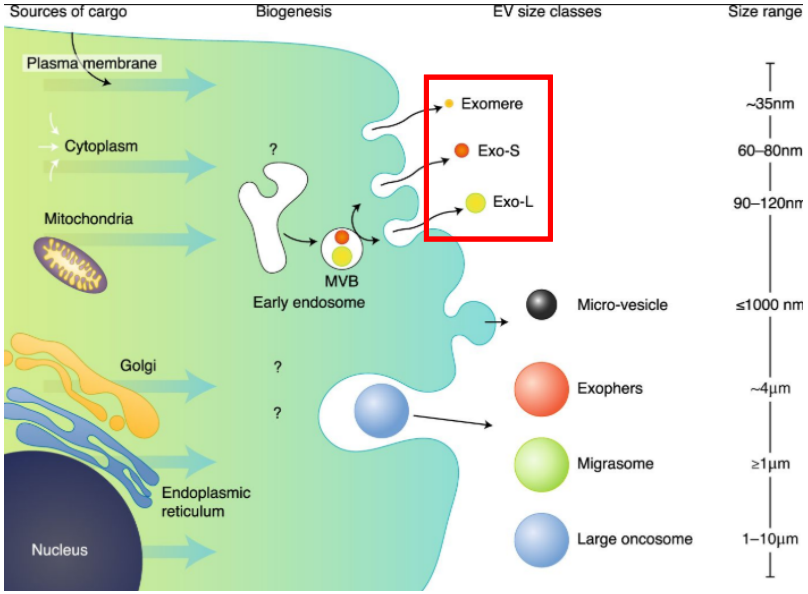
Future Directions

Further Purification of EV subpopulations

A)



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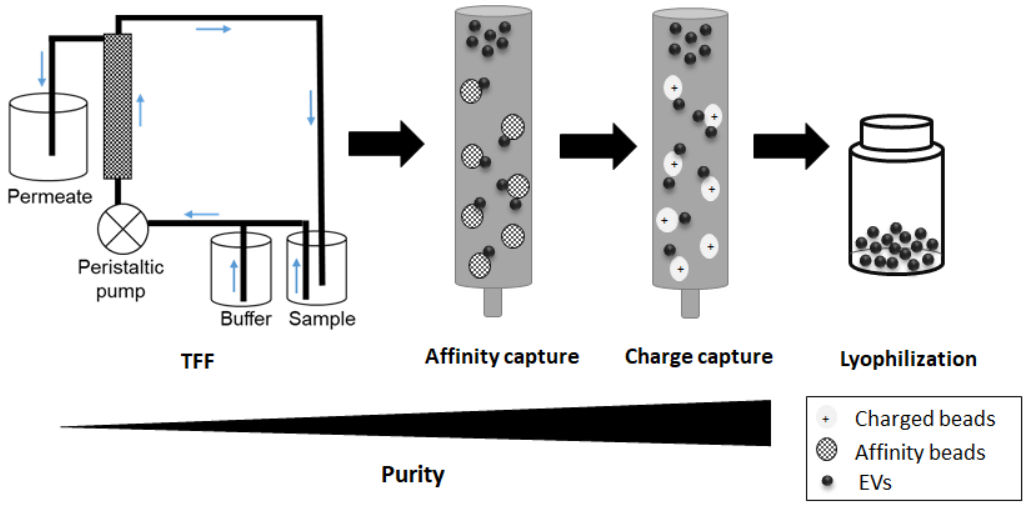
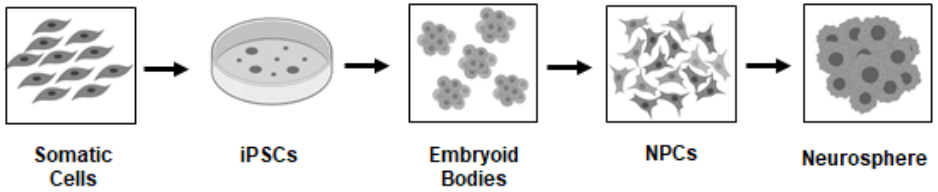


Zijlstra & Di Vizio. *Nature Cell Biology*. 2018

Future Directions

Advanced functionality assays using neurospheres derived from ATCC ACS-5003™ (unpublished data)

A)



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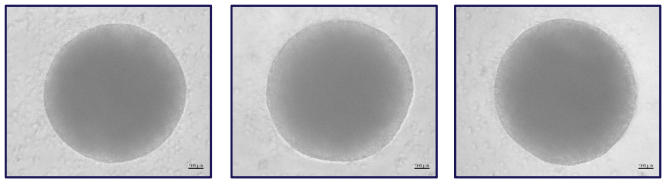

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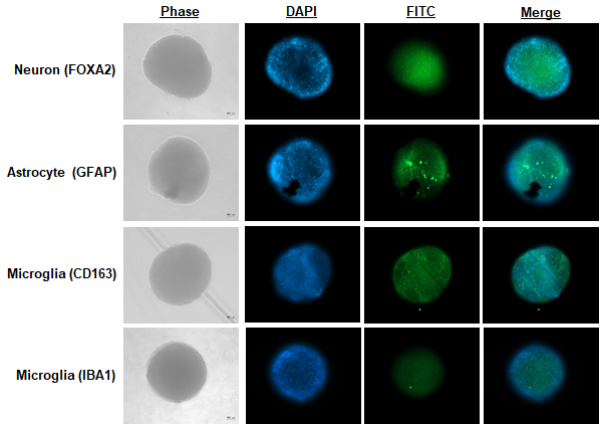

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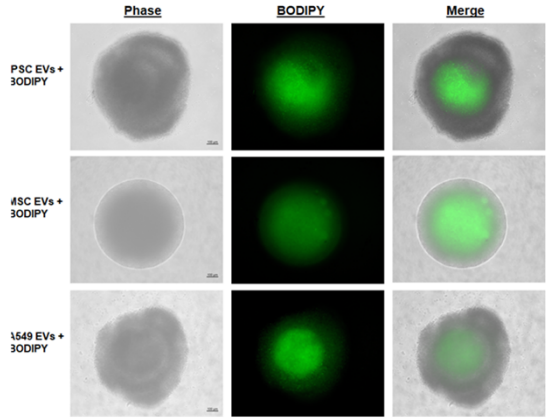
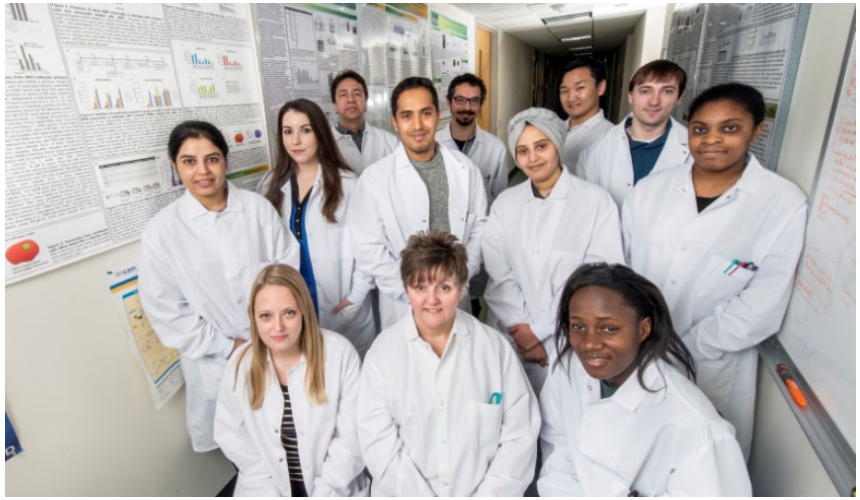
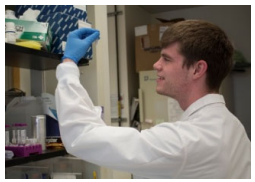
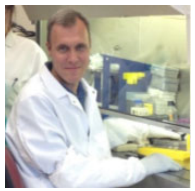


Acknowledgements







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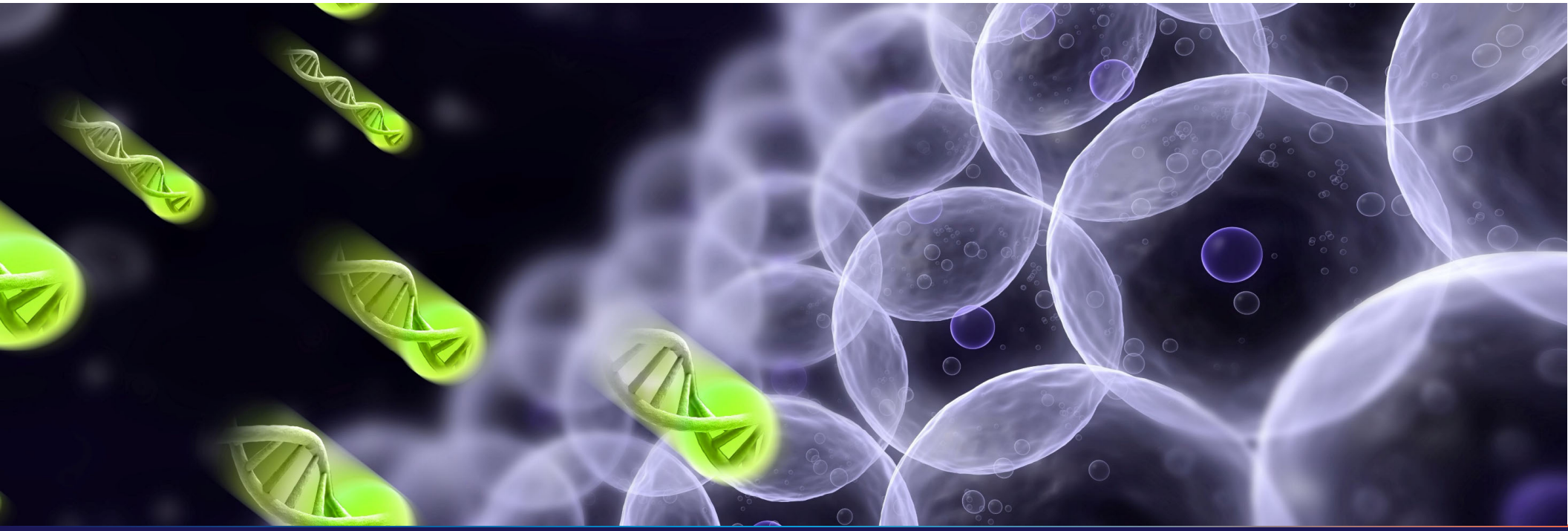

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