ADC Clinical Core Leaders meeting: Can we do more with biomarkers?

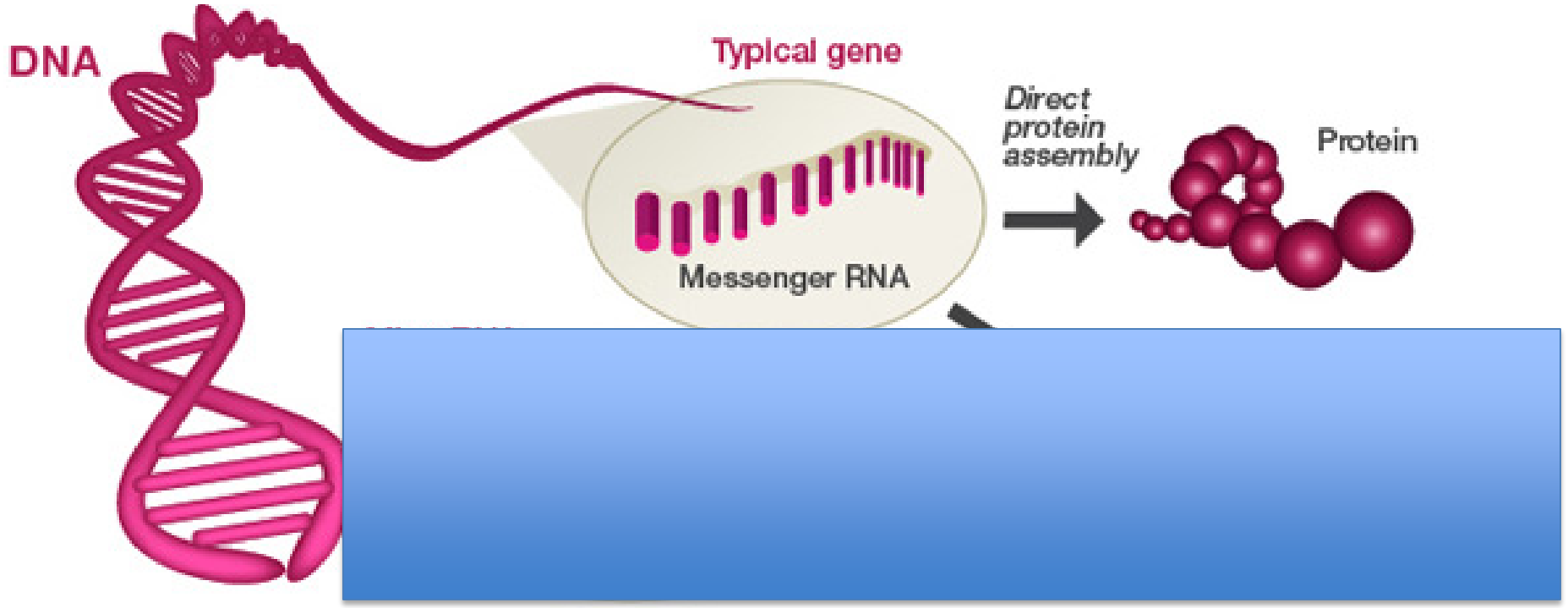
Joseph Quinn, MD

April 16, 2016

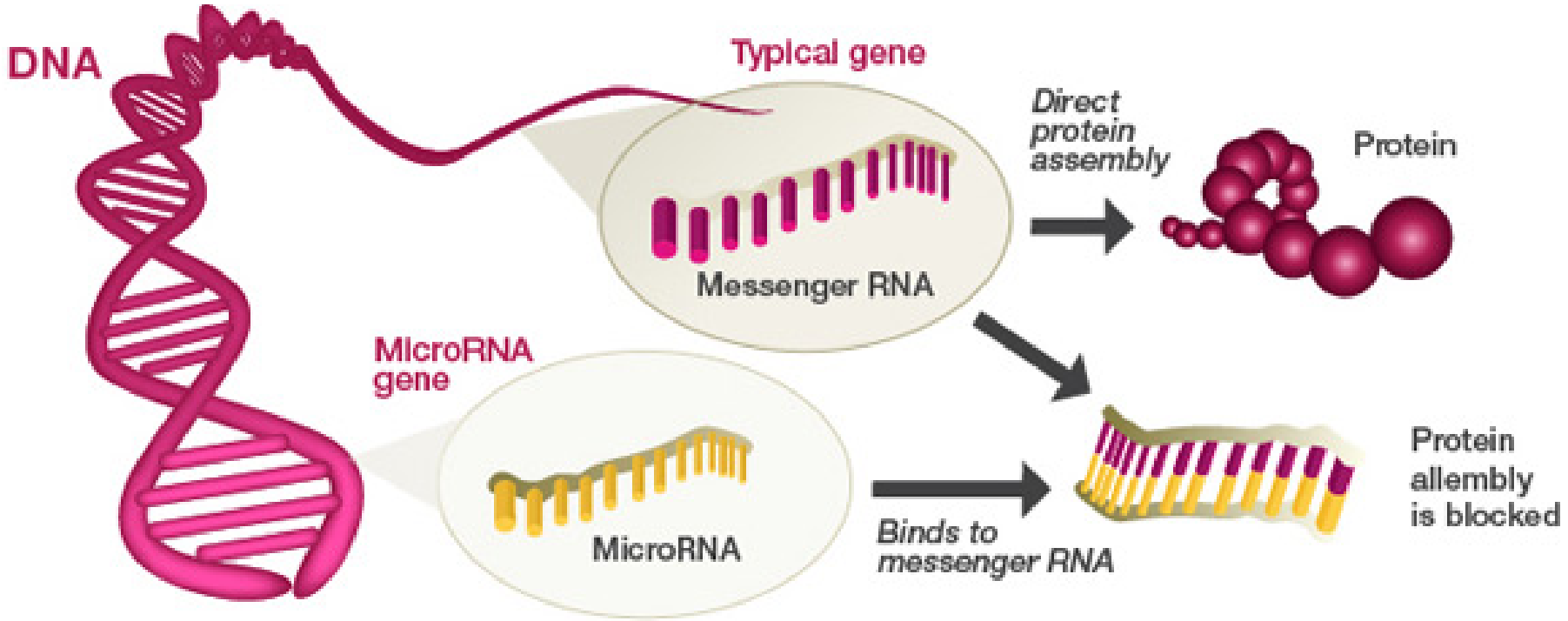
New initiatives with biomarkers of neurodegenerative disease:

- Extracellular microRNAs as biomarkers
- Isolation of CNS-derived exosomes from peripheral blood

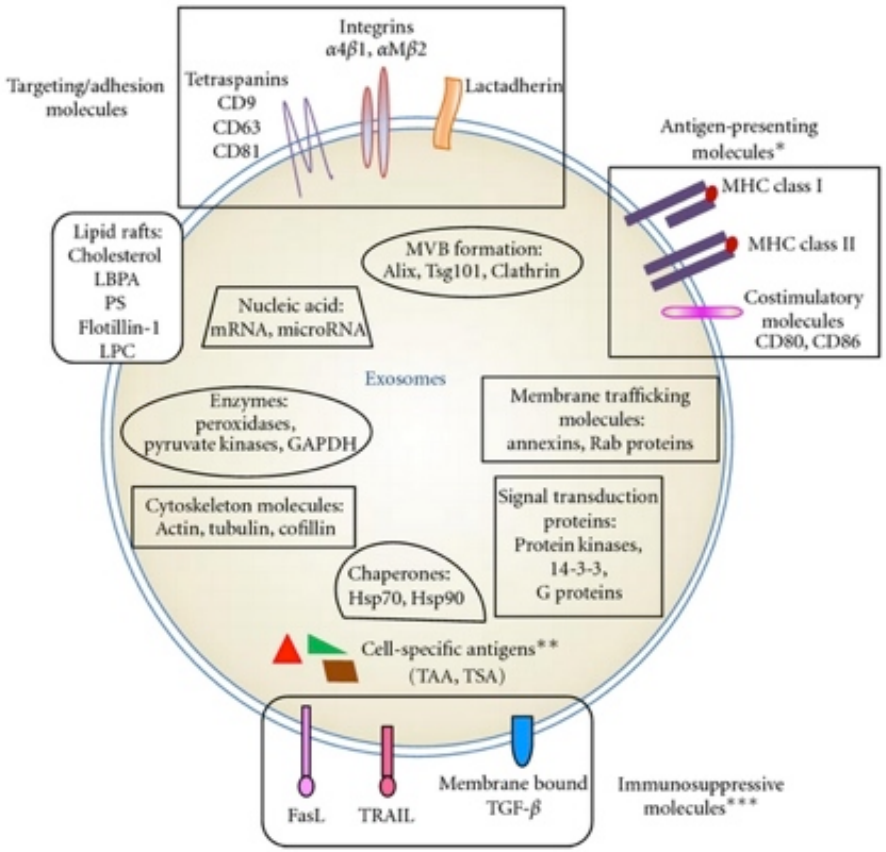
Central dogma of biology:

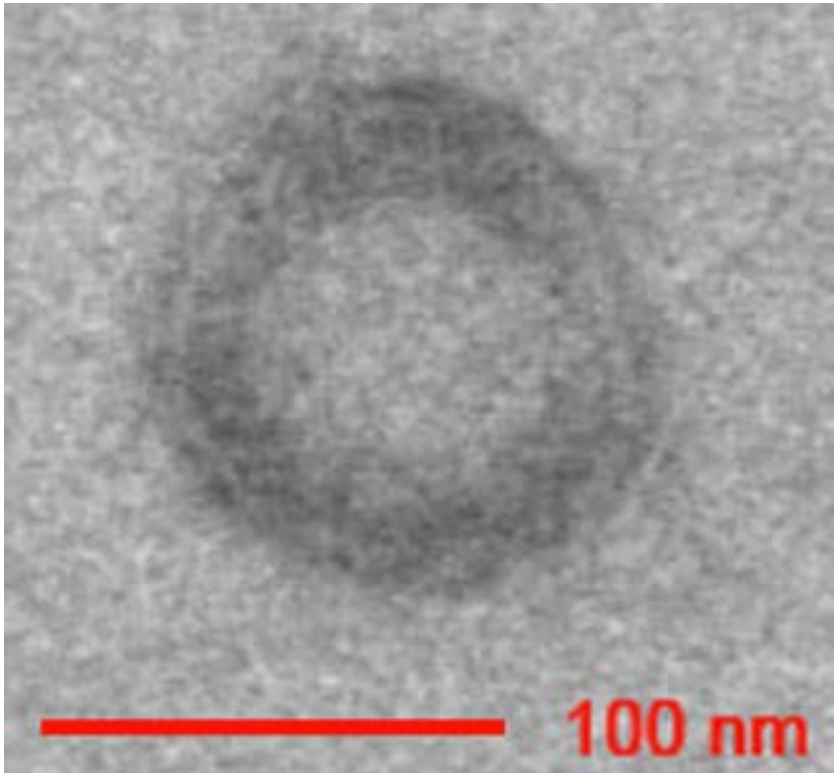


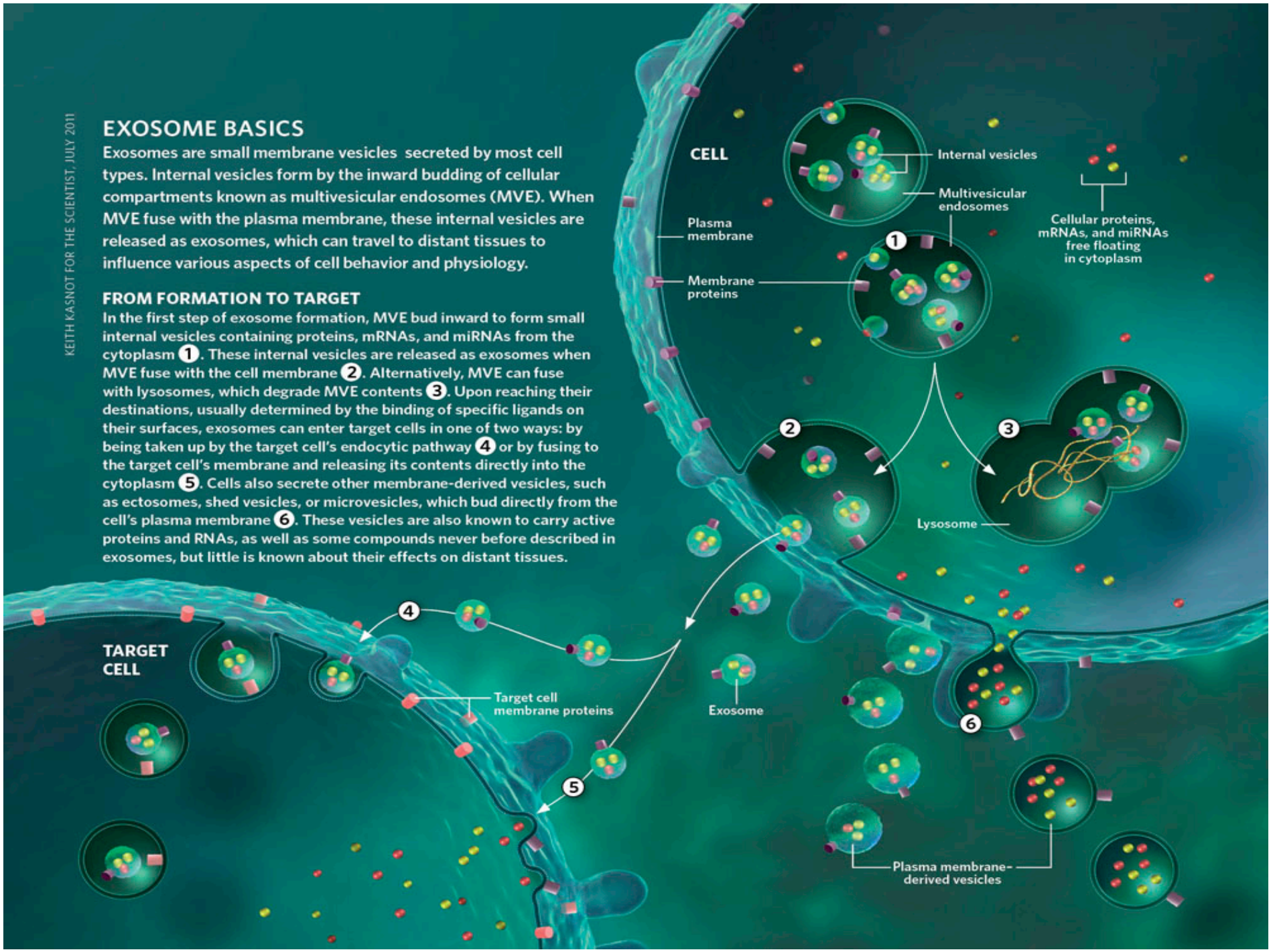
The new biology of microRNAs:

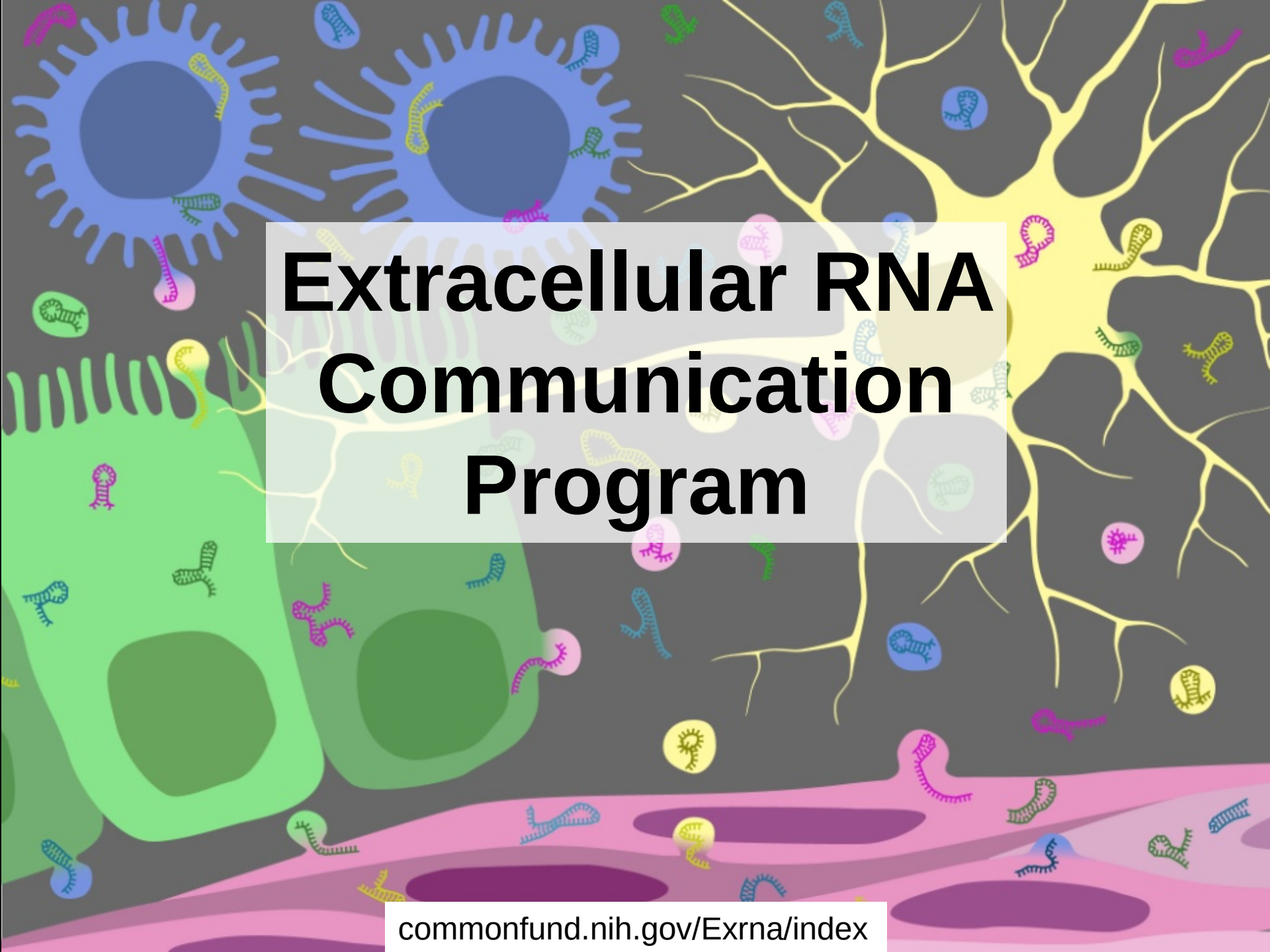


Extracellular RNA & Exosomes






KEITH KASNOT FOR THE SCIENTIST, JULY 2011
EXOSOME BASICS
Exosomes are small membrane vesicles secreted by most cell types. Internal vesicles form by the inward budding of cellular compartments known as multivesicular endosomes (MVE). When MVE fuse with the plasma membrane, these internal vesicles are released as exosomes, which can travel to distant tissues to influence various aspects of cell behavior and physiology.
FROM FORMATION TO TARGET
In the first step of exosome formation, MVE bud inward to form small internal vesicles containing proteins, mRNAs, and miRNAs from the cytoplasm 1. These internal vesicles are released as exosomes when MVE fuse with the cell membrane 2. Alternatively, MVE can fuse with lysosomes, which degrade MVE contents 3. Upon reaching their destinations, usually determined by the binding of specific ligands on their surfaces, exosomes can enter target cells in one of two ways: by being taken up by the target cell's endocytic pathway 4 or by fusing to the target cell's membrane and releasing its contents directly into the cytoplasm 5. Cells also secrete other membrane-derived vesicles, such as ectosomes, shed vesicles, or microvesicles, which bud directly from the cell's plasma membrane 6. These vesicles are also known to carry active proteins and RNAs, as well as some compounds never before described in exosomes, but little is known about their effects on distant tissues.
CELL
Internal vesicles
Multivesicular endosomes
Cellular proteins, mRNAs, and miRNAs free floating in cytoplasm
Plasma membrane
Membrane proteins
1
2
3
Lysosome
TARGET CELL
4
Target cell membrane proteins
Exosome
5
6
Plasma membrane-derived vesicles



Extracellular RNA Communication Program

commonfund.nih.gov/Exrna/index

National Institutes of Health (NIH)

27 Institutes and Centers (ICs)

NIH Institutes

National Cancer Institute (NCI)
National Eye Institute (NEI)
National Heart, Lung, and Blood Institute (NHLBI)
National Human Genome Research Institute (NHGRI)
National Institute on Aging (NIA)
National Institute on Alcohol Abuse and Alcoholism (NIAAA)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
National Institute of Biomedical Imaging and Bioengineering (NIBIB)
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
National Institute on Deafness and Other Communication Disorders (NIDCD)
National Institute of Dental and Craniofacial Research (NIDCR)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Institute on Drug Abuse (NIDA)
National Institute of Environmental Health Sciences (NIEHS)
National Institute of General Medical Sciences (NIGMS)
National Institute of Mental Health (NIMH)
National Institute on Minority Health and Health Disparities (NIMHD)
National Institute of Neurological Disorders and Stroke (NINDS)
National Institute of Nursing Research (NINR)
National Library of Medicine (NLM)

NIH Centers

Center for Information Technology (CIT)
Center for Scientific Review (CSR)
John E. Fogarty International Center (FIC)
National Center for Complementary and Alternative Medicine (NCCAM)
National Center for Advancing Translational Sciences (NCATS)
NIH Clinical Center (CC)

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Data Management and Resource Repository (DMRR) on Extracellular RNA (U54) RFA-RM-12-010

MILOSAVLJEVIC, ALEKSANDAR	BAYLOR COLLEGE OF MEDICINE	Data management and Resource Repository for the exRNA Atlas

Extracellular RNA Biogenesis, Biodistribution, Uptake, and Effector Function (U19) RFA-RM-12-012

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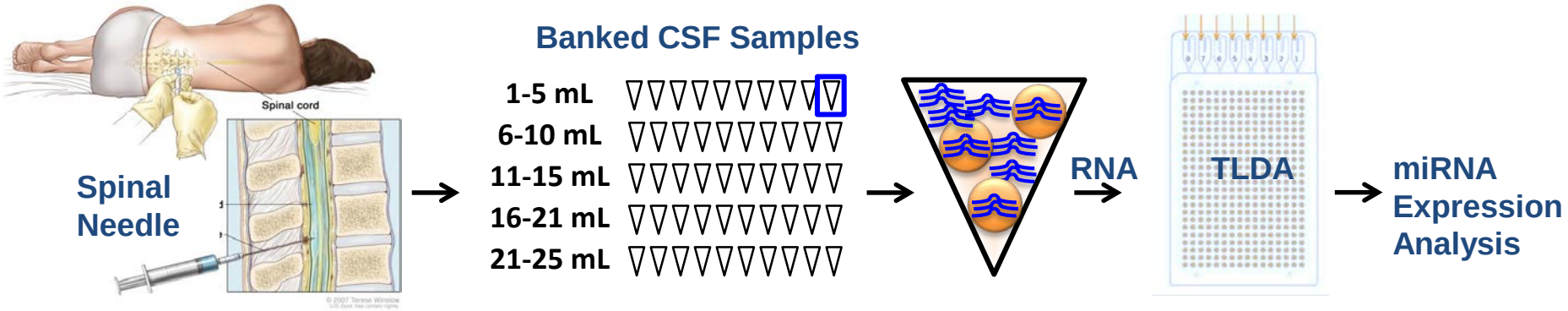
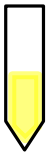


Final UH3 miRNA Donor Table – Complete

	Control	AD	All
Subjects			
Male	23	30	53
Female	26	20	46
Total	49	50	99
	Mean +/- SD	Mean +/- SD	Mean +/- SD
Age at LP			
Male	69.61 +/- 9.82	68.7 +/- 7.49	69.09 +/- 8.5
Female	66.15 +/- 8.94	70.75 +/- 6.94	68.15 +/- 8.37
Total	67.78 +/- 9.43	69.52 +/- 7.27	68.66 +/- 8.41
MMSE at LP			
Male	28.83 +/- 1.64	18.23 +/- 6.71	22.83 +/- 7.37
Female	29.58 +/- 0.7	18.35 +/- 6.08	24.7 +/- 6.9
Total	29.22 +/- 1.28	18.28 +/- 6.4	23.7 +/- 7.18

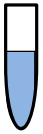
CSF to Array Data Process



500µL CSF

(Total) RNA Isolation

- mirVana Paris RNA Isolation kit
- 2 X 100µL elution (with H_2O)



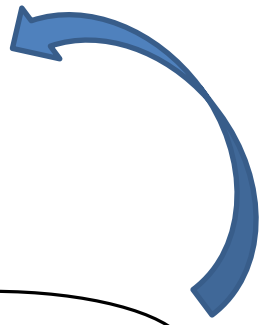
200µL Isolated RNA

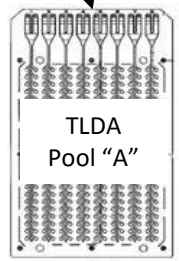
Concentration

- Zymo Research RNA Clean & Concentrator-5
- Eluted with 9µL H_2O

~8µL Concentrated RNA

Assay Results for 754 human microRNAs (384 assays per TLDA Card)





TLDA Pool "A"

800µL Loaded on TLDA Card

miRNA Pool "A"

Transfer 3.2µL

Transfer 2.5µL

+ 75µL H_2O =

Transfer 18µL

450µL 2X TaqMan PCR MasterMix + 432µL H_2O

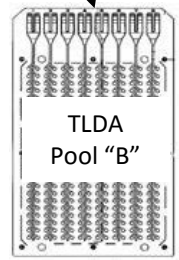
8µL **Reverse Transcription** Reaction Volume

25µL **Pre-Amplification** Reaction Volume

100µL **Diluted Pre-Amplification** Reaction Volume

900µL **PCR Detection Master Mix** Reaction Volume

800µL Loaded on TLDA Card



TLDA Pool "B"

miRNA Pool "B"

Transfer 3.2µL

Transfer 2.5µL

+ 75µL H_2O =

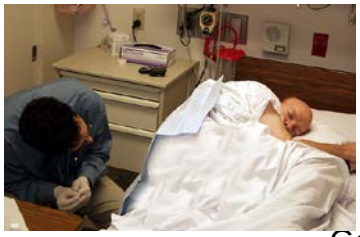
Transfer 18µL

450µL 2X TaqMan PCR MasterMix + 432µL H_2O

miRNA data generation:

- 99 CSF samples
- 756 miRNAs probed per sample
- 332 miRNAs with signal to include in analysis

UH2 Study Design and Flow



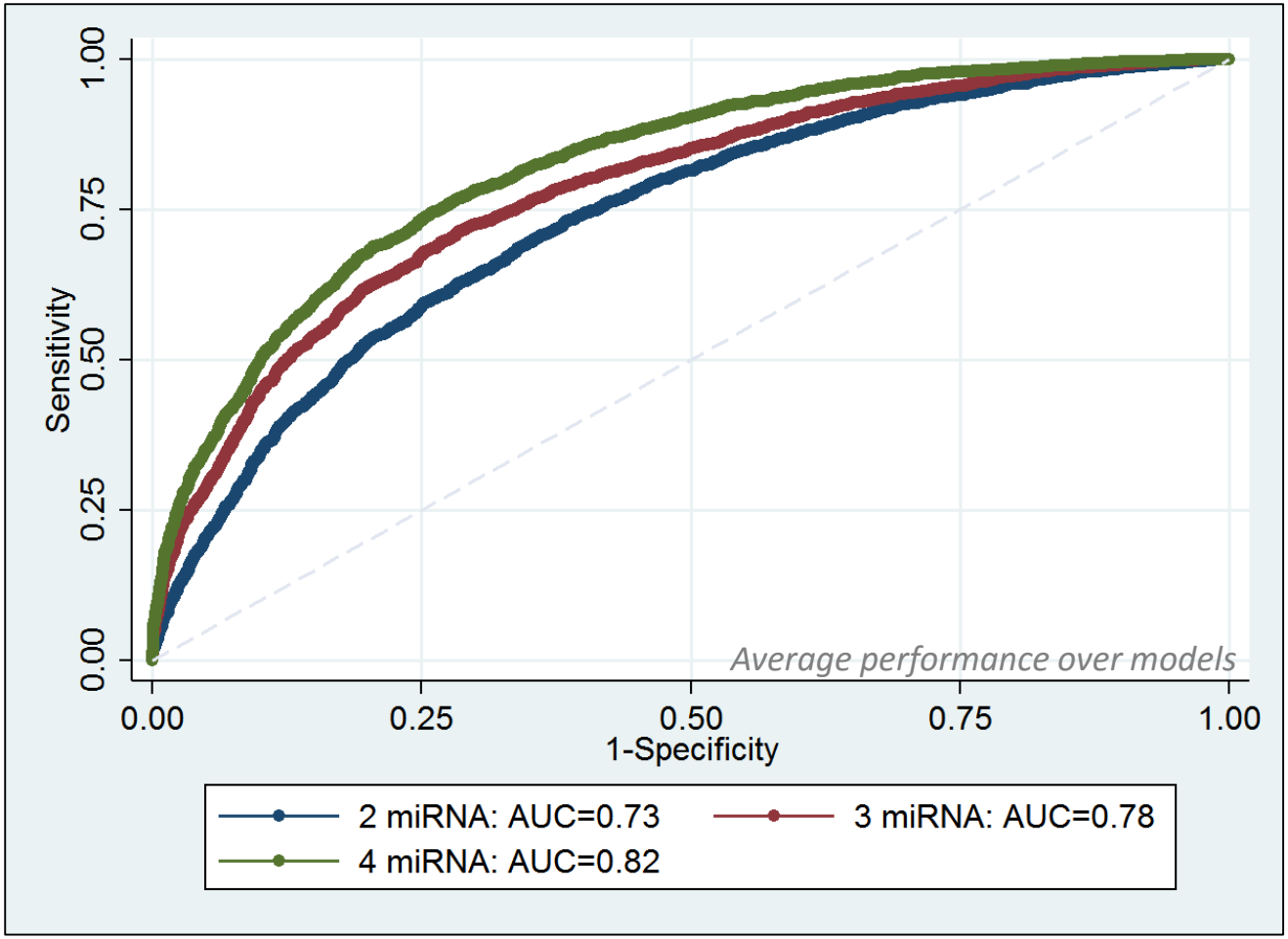
Joseph Quinn
Betty Lind
Genevieve Leineweber
Obtain Clinically Characterized Human CSF Samples from the Oregon Alzheimers Disease Center
Transfer Assigned CSF Samples to Jay Phillips

Jay Phillips
Chris Harrington
Isolate and Characterize Total RNA from CSF
Perform TaqMan Low-Density Array (TLDA) Analysis on CSF RNA
Transfer Data from QuantStudio to Theresa Lusardi

Theresa Lusardi
Perform Human miRNA Array Data Analysis for Ct and ΔCt

Jodi Lapidus
Theresa Lusardi
Perform Statistical Analysis of Human miRNA Array Data
Identify High-Priority miRNA Candidates
Correlate Candidate miRNAs with Clinical Characteristics

Combinations of CSF miRNA discriminate AD vs. Control



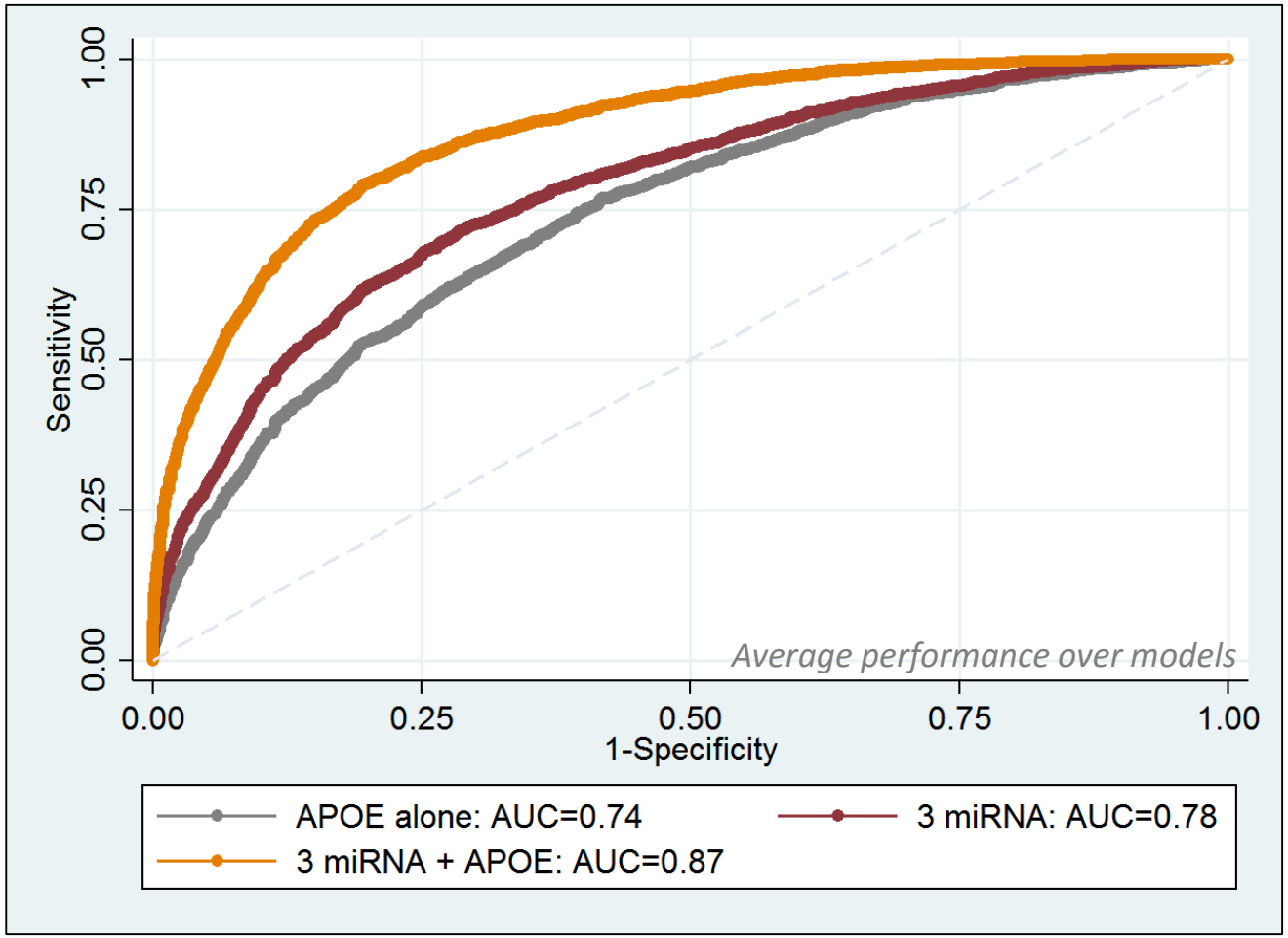
Combinations of best-performing 2 marker models had area under ROC curve (AUC) of 0.73, on average. (blue)

Best performing 3 marker models increased AUC to 0.78. (maroon)

Best performing 4 marker models raised AUC to 0.82. (green)

Classification performance of combinations of CSF miRNA reached our planned benchmarks

CSF miRNAs add incremental value to a current AD biomarker - ApoE4



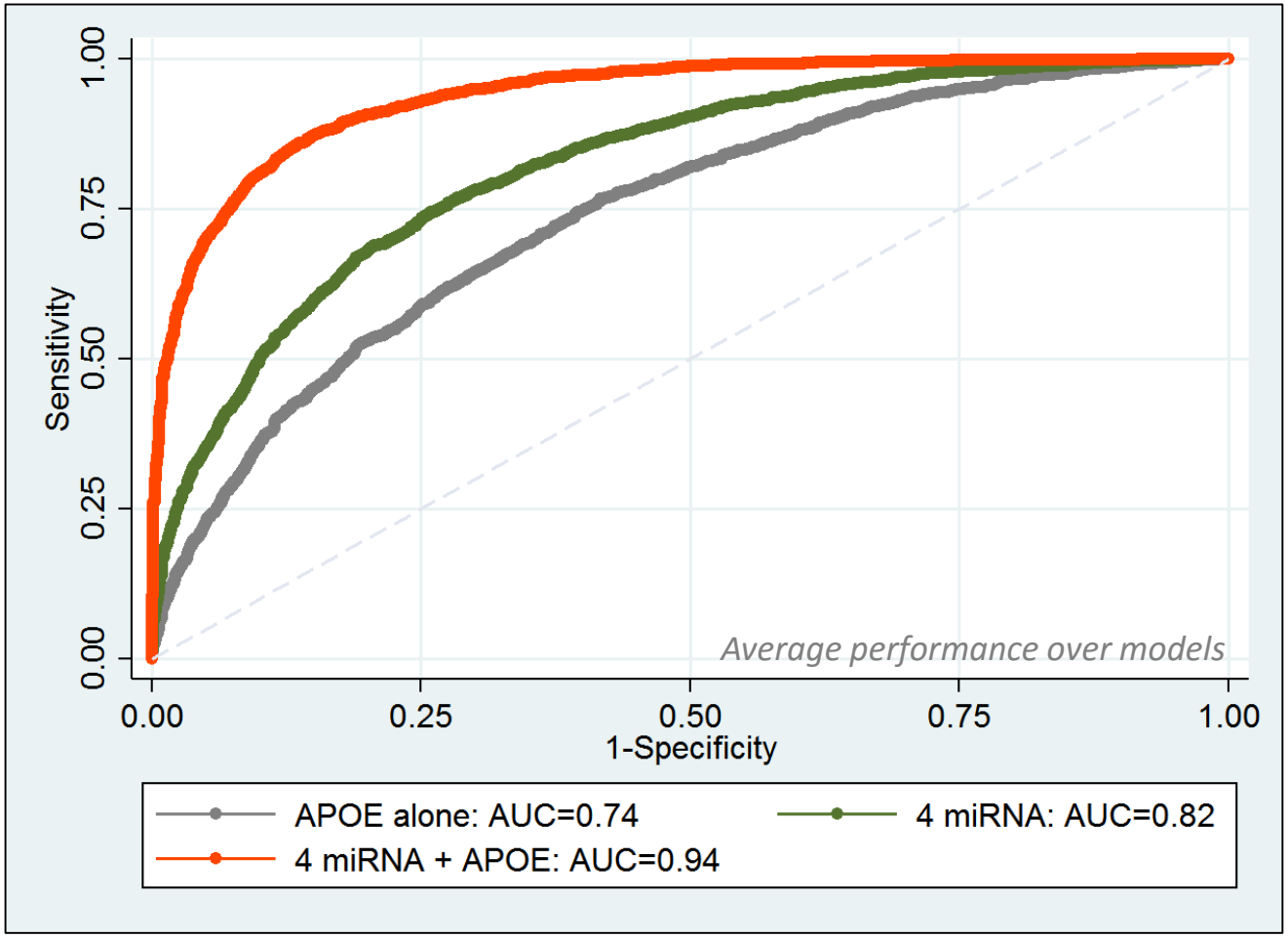
Performance of ApoE4 alone in our subjects has AUC of 0.74. (gray)

Best performing 3 marker models performed better than ApoE4 in our subjects. (maroon)

Combining ApoE4 with best performing 3 marker models yields AUC=0.87. **(orange)**

Combinations of 3 CSF miRNA perform better than tests used in current practice, combined with ApoE4 status contribute important information

CSF miRNAs add incremental value to a current AD biomarker - ApoE4



Performance of ApoE4 alone in our subjects has AUC of 0.74. (gray)

Best performing 4 marker models performed better than ApoE4 in our subjects. (green)

Combining ApoE4 with best performing 4 marker models yields AUC=0.94. (red)

Combinations of 4 CSF miRNA combined with ApoE4 status have excellent discriminative ability for AD

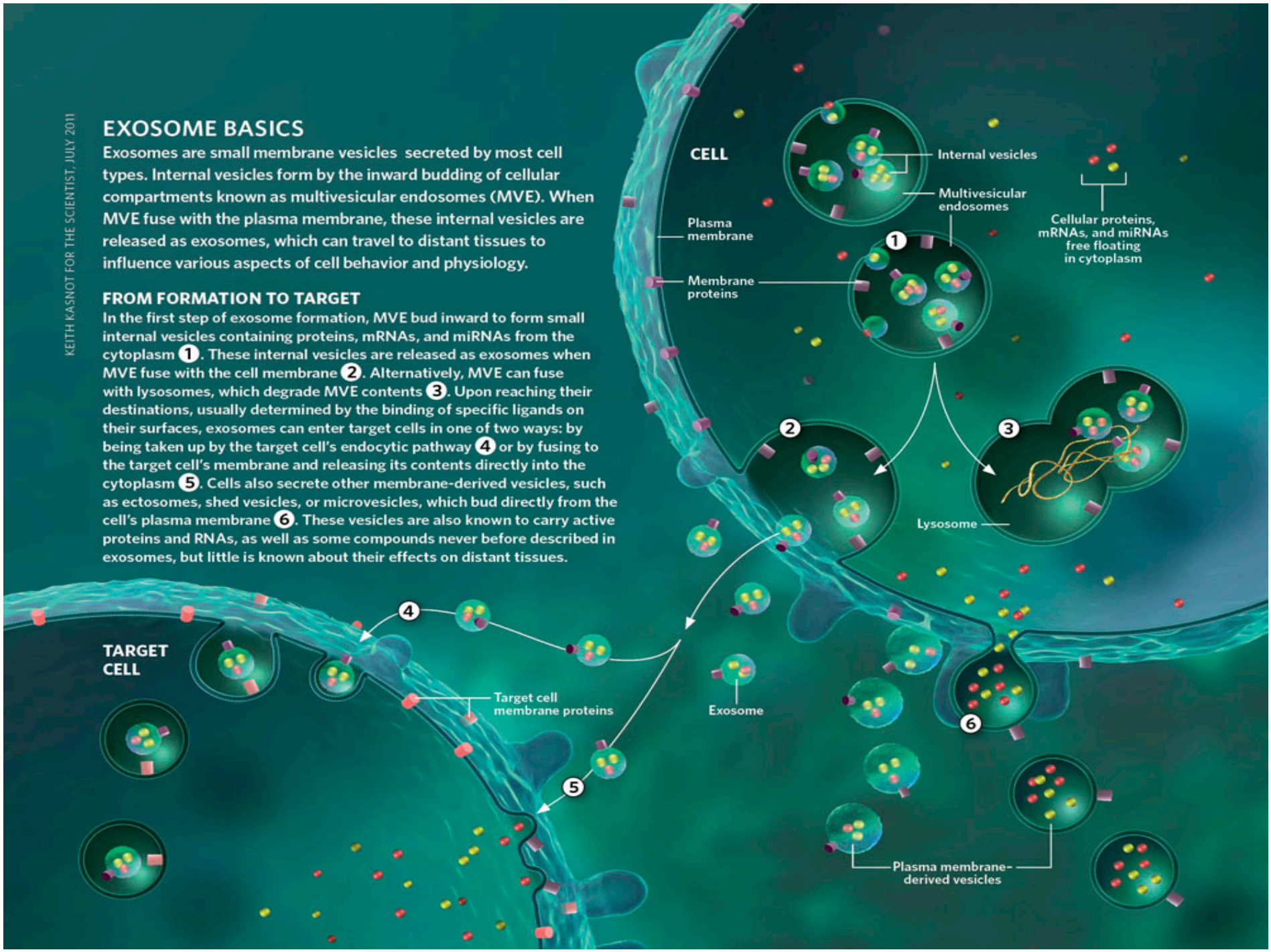
Conclusions:

- CSF miRNAs are promising as novel biomarkers in neurodegenerative disease

Pros and cons of CSF:

- **Pro:**
- in direct communication with CSF tissue
- CSF markers discriminate patients from controls.

- **Con:**
- Challenging to collect in many cases.
- Studies of plasma levels of protein biomarkers of AD and PD have not shown differences between patients and controls, with confounding factors including:
  - Blood brain barrier
  - Dilution of CNS markers by large volume of blood
  - Identical proteins produced in periphery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CELL
Internal vesicles
Multivesicular endosomes
Cellular proteins, mRNAs, and miRNAs free floating in cytoplasm
Plasma membrane
Membrane proteins
1
2
3
Lysosome
TARGET CELL
4
Target cell membrane proteins
Exosome
5
6
Plasma membrane-derived vesicles

Plasma exosomal α-synuclein is likely CNS-derived and increased in Parkinson's disease

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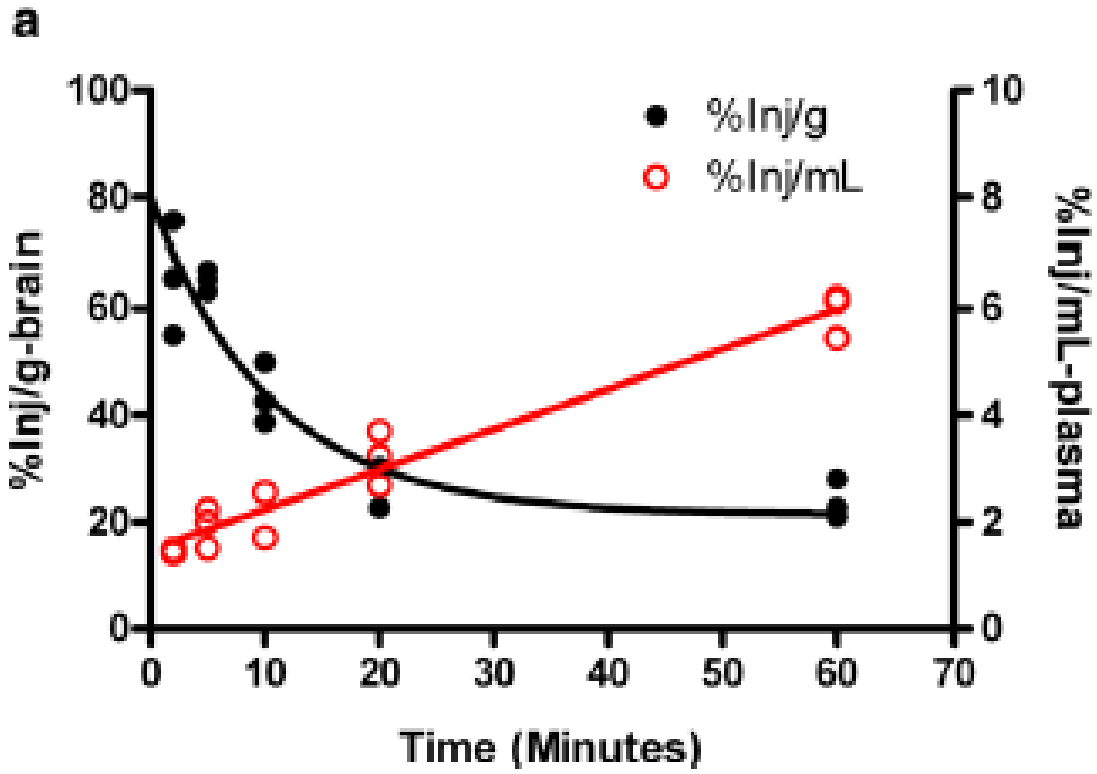
Acta Neuropathol (2014) 128:639–650



Plasma exosomal α-synuclein is likely CNS-derived and increased in Parkinson's disease

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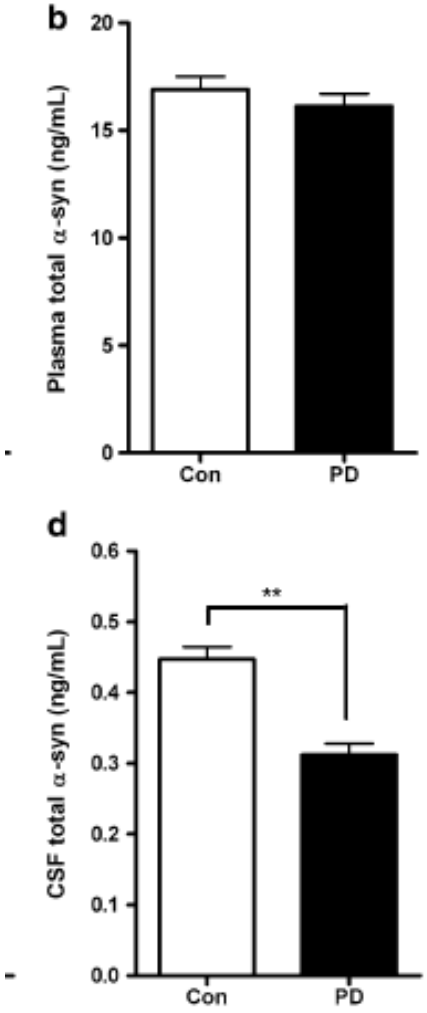

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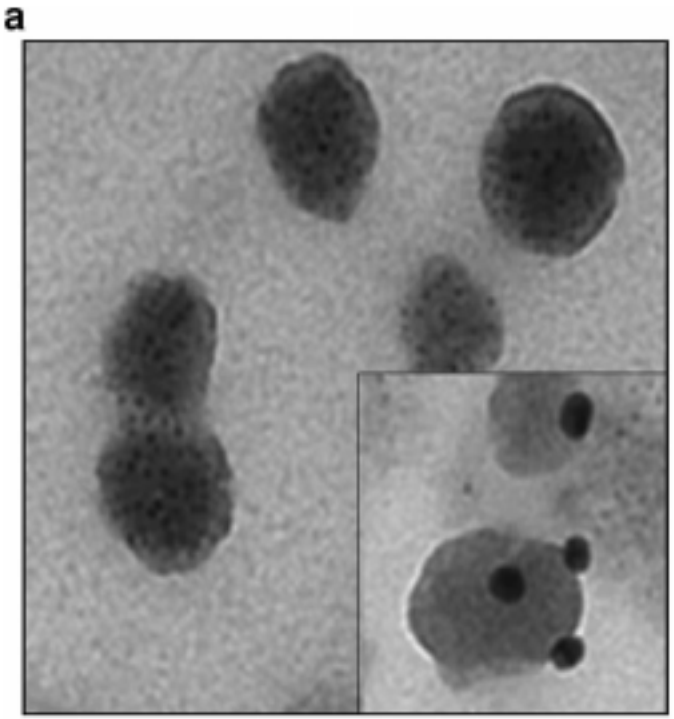

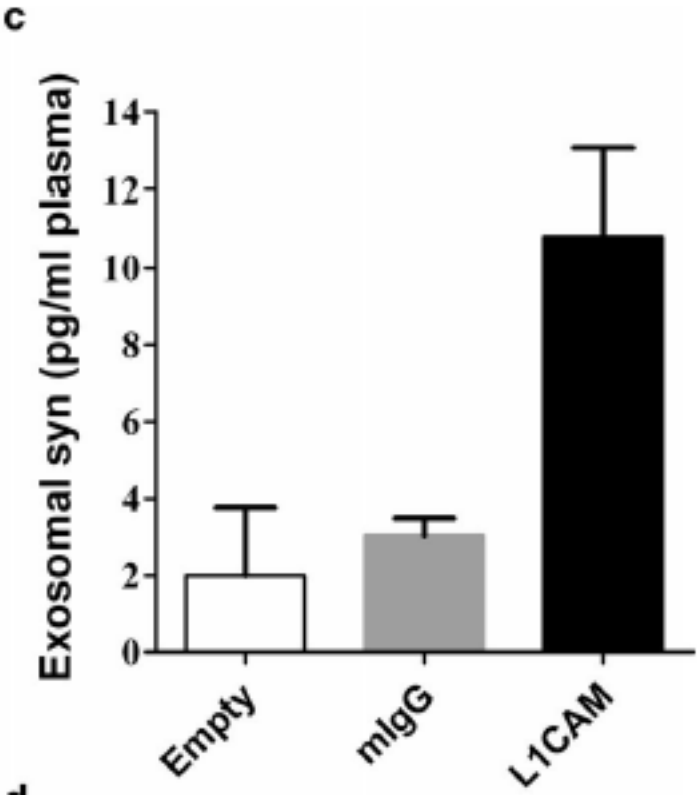

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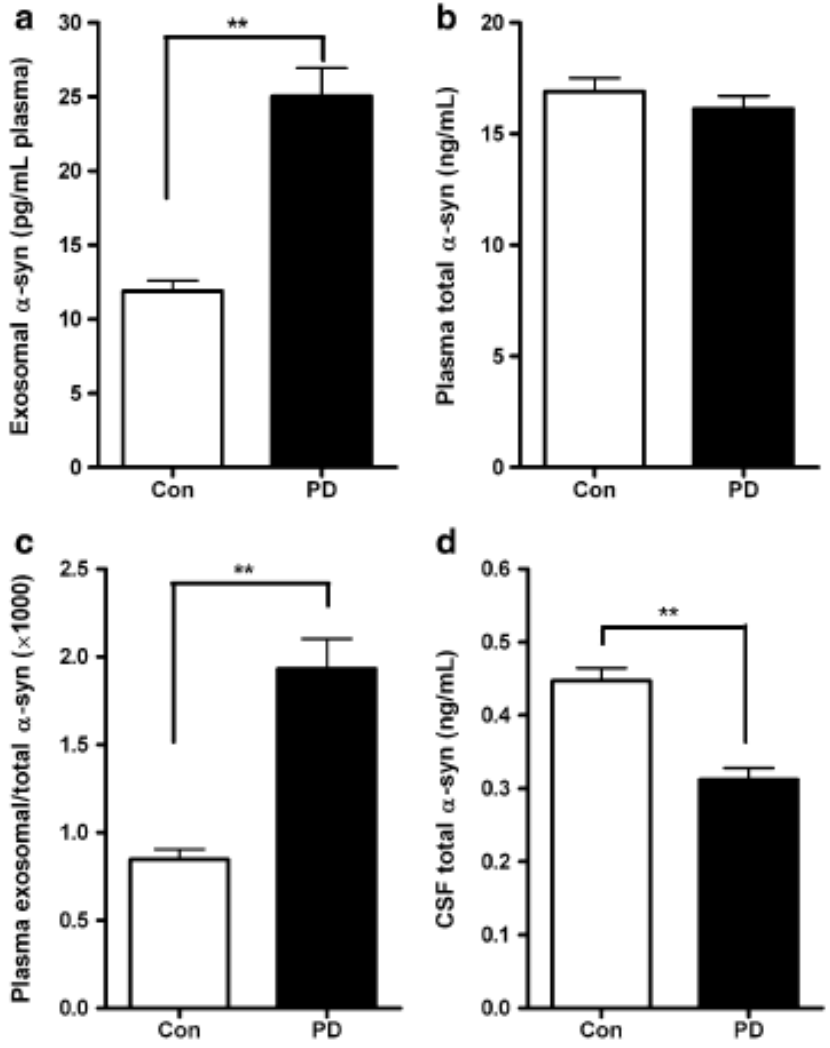

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- Should the ADCs begin banking plasma on UDS subjects in a uniform manner?