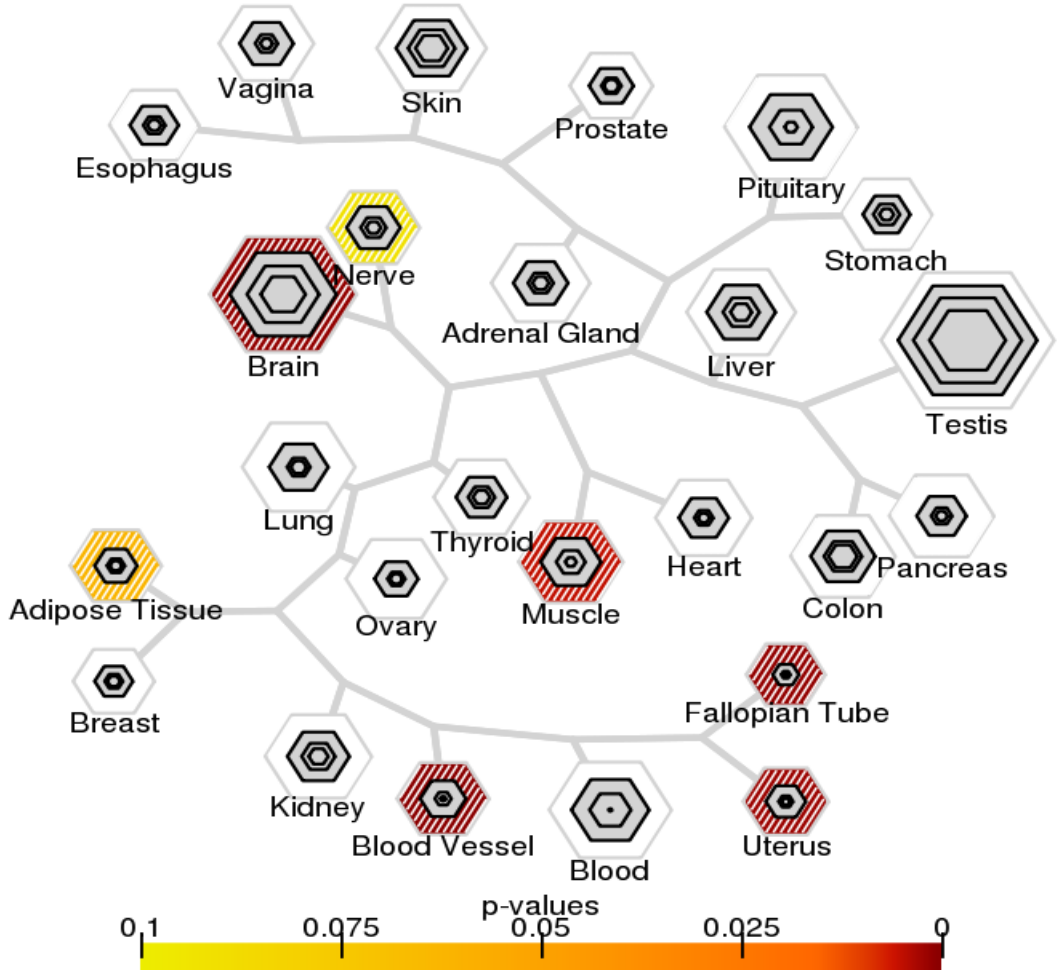
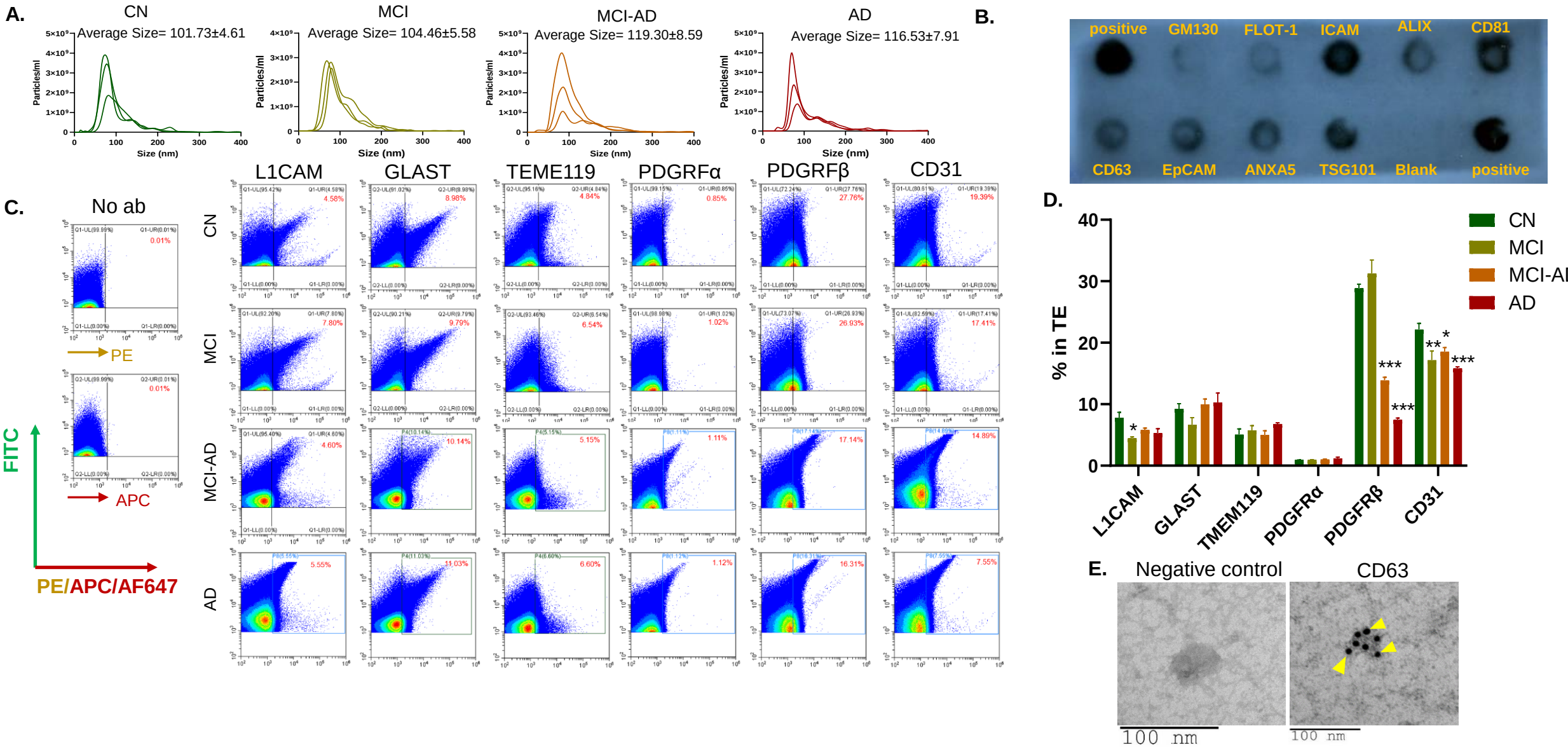
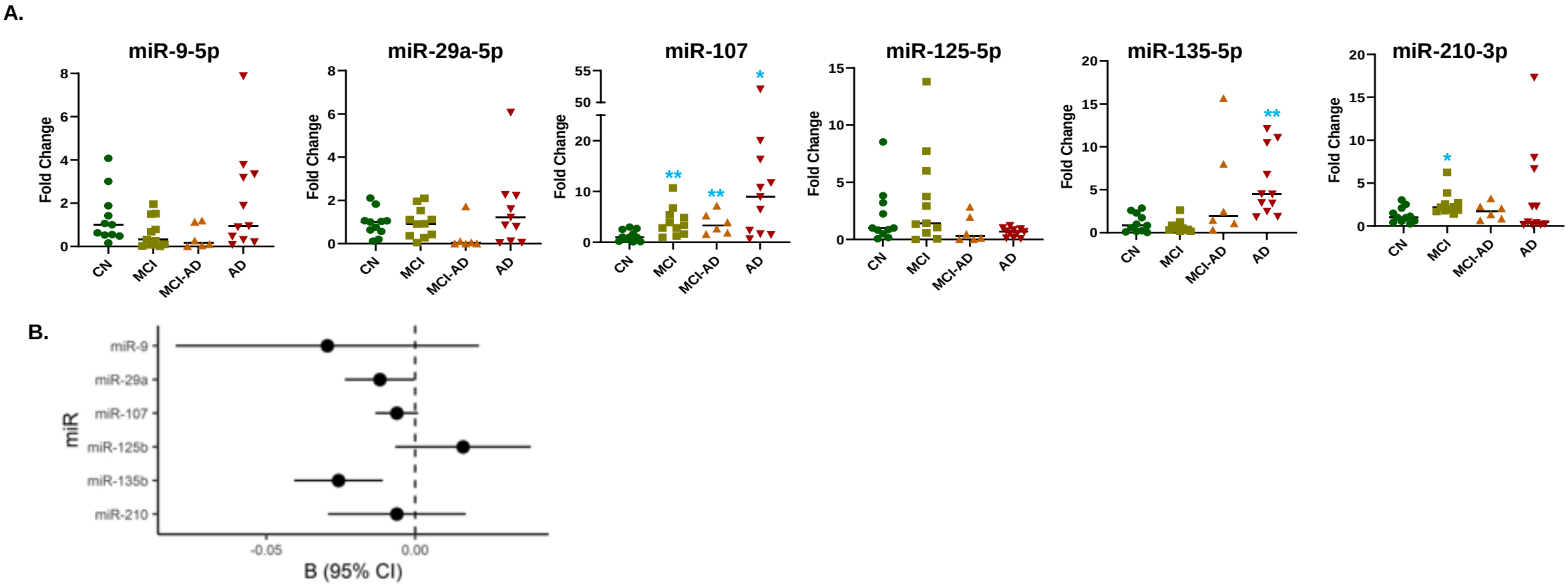


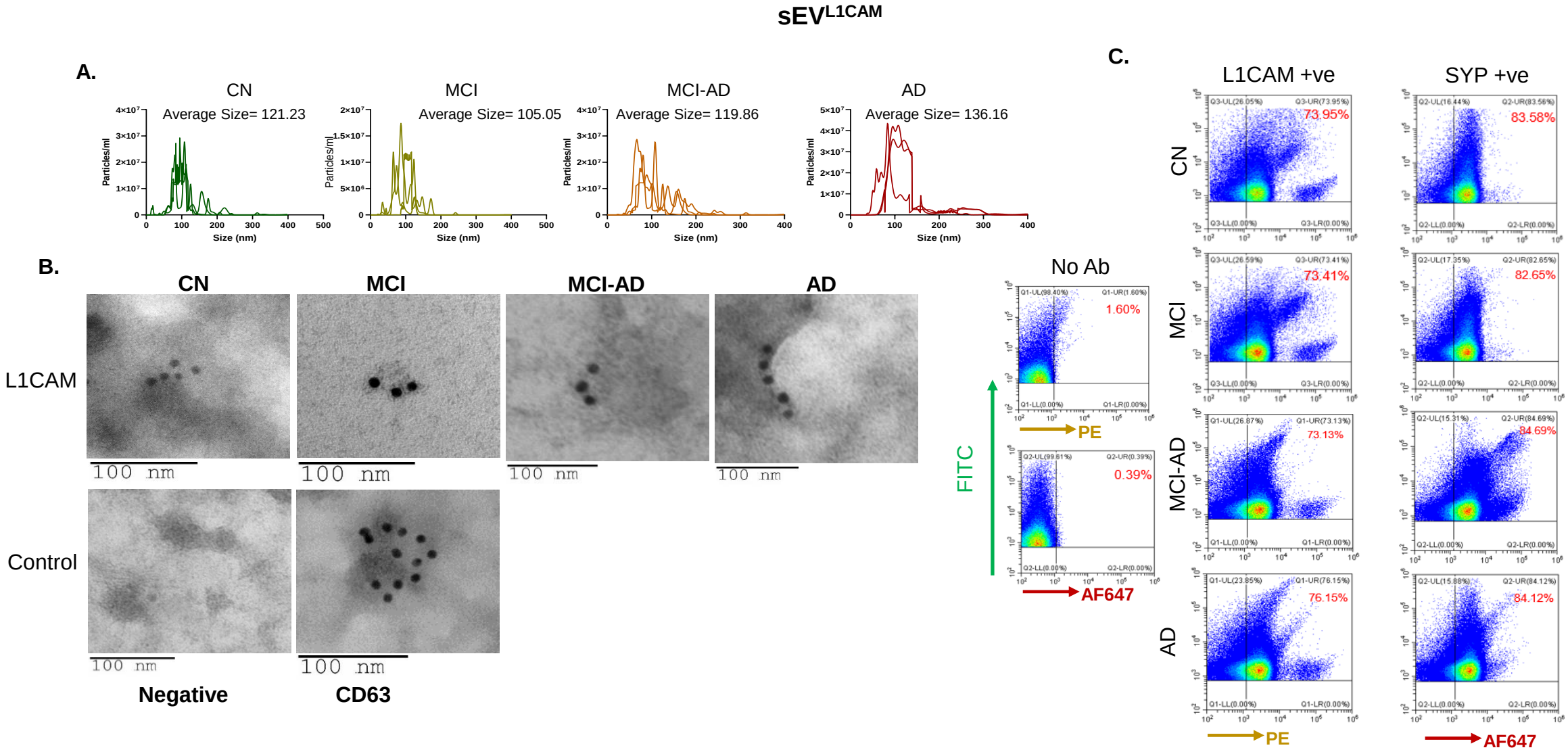
Supplementary Figure 1. Tissue enrichment analysis of the key 8 miRNAs targets (top 1% targets) was performed using Tissue Specific Expression Analysis (TSEA) online platform.



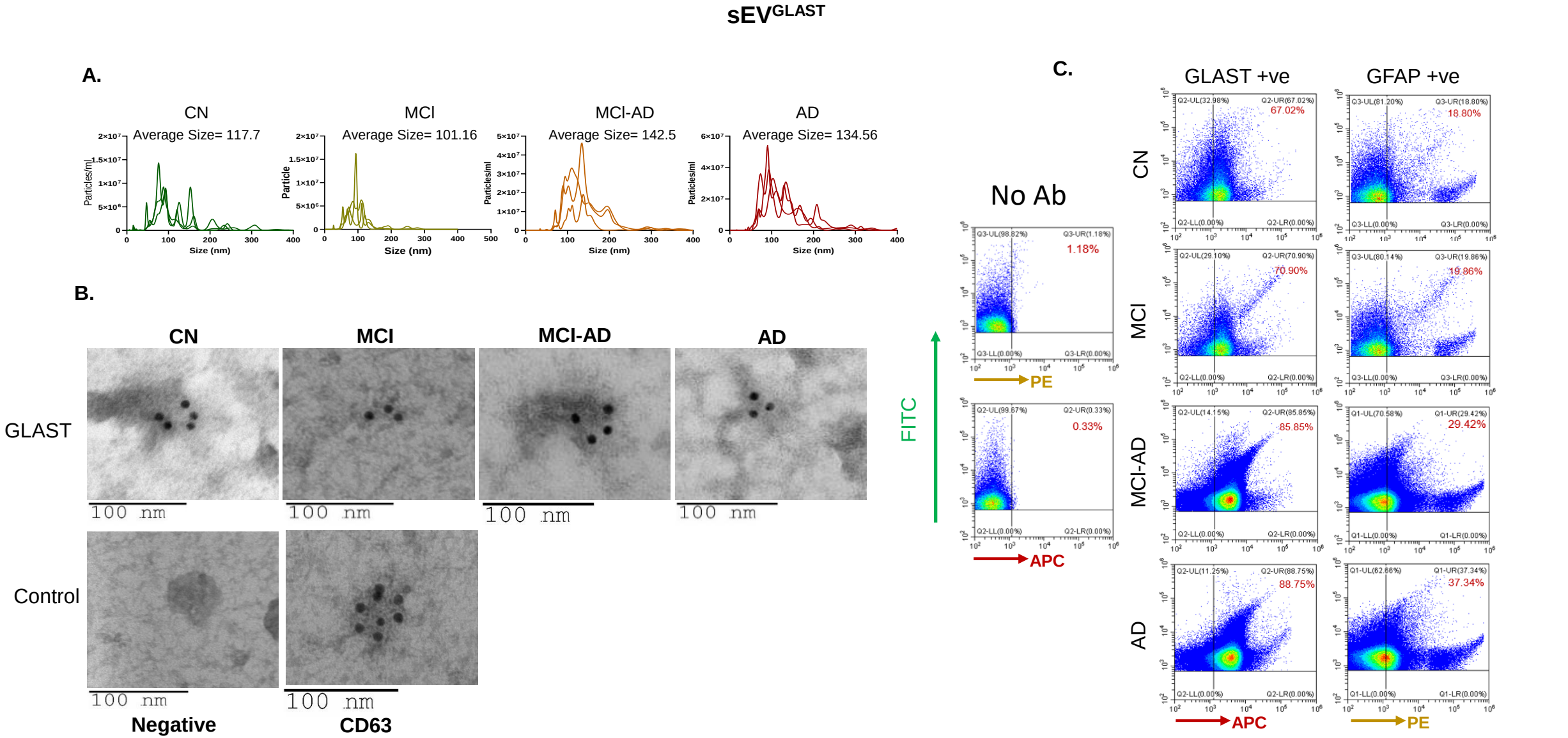
Supplementary Figure 2. Characterization of total sEV (TE). (**A)** Size and concentration of total sEV, isolated from the plasma of all the subjects by a modified precipitation method, were measured by nanoparticle tracking analysis (NTA). For each group 3 TE samples were analyzed by NTA by taking 5 videos of 30 sec each. Each line represents the average of 5 videos. Average size is represented as ±SEM. **(B)** TE were characterized by Exo-Check array, and a representative blot is shown. **(C)** Flow cytometry analysis was performed for TE to identify the L1CAM, GLAST, TMEM119, PDGFRα, PDGFRβ and CD31 +ve sEV after labeling TE with membrane labeling dye CellBrite steady 488 and specific fluorescent antibody. Left panel shows the TE labeled only with membrane labeling dye without any antibody. **(D)** Percentage of L1CAM, GLAST, TMEM119, PDGFRα, PDGFRβ and CD31 +ve TE was analyzed by flow cytometry and plotted (± SEM) using GraphPad Prism 9.1.2. *p<0.05, **p<0.005, ***p<0.0005. **(E)** Representative TEM image of TE showed the presence of CD63 on sEV surface (right panel, yellow arrowhead), TE without the primary antibody was used as negative control (left panel).



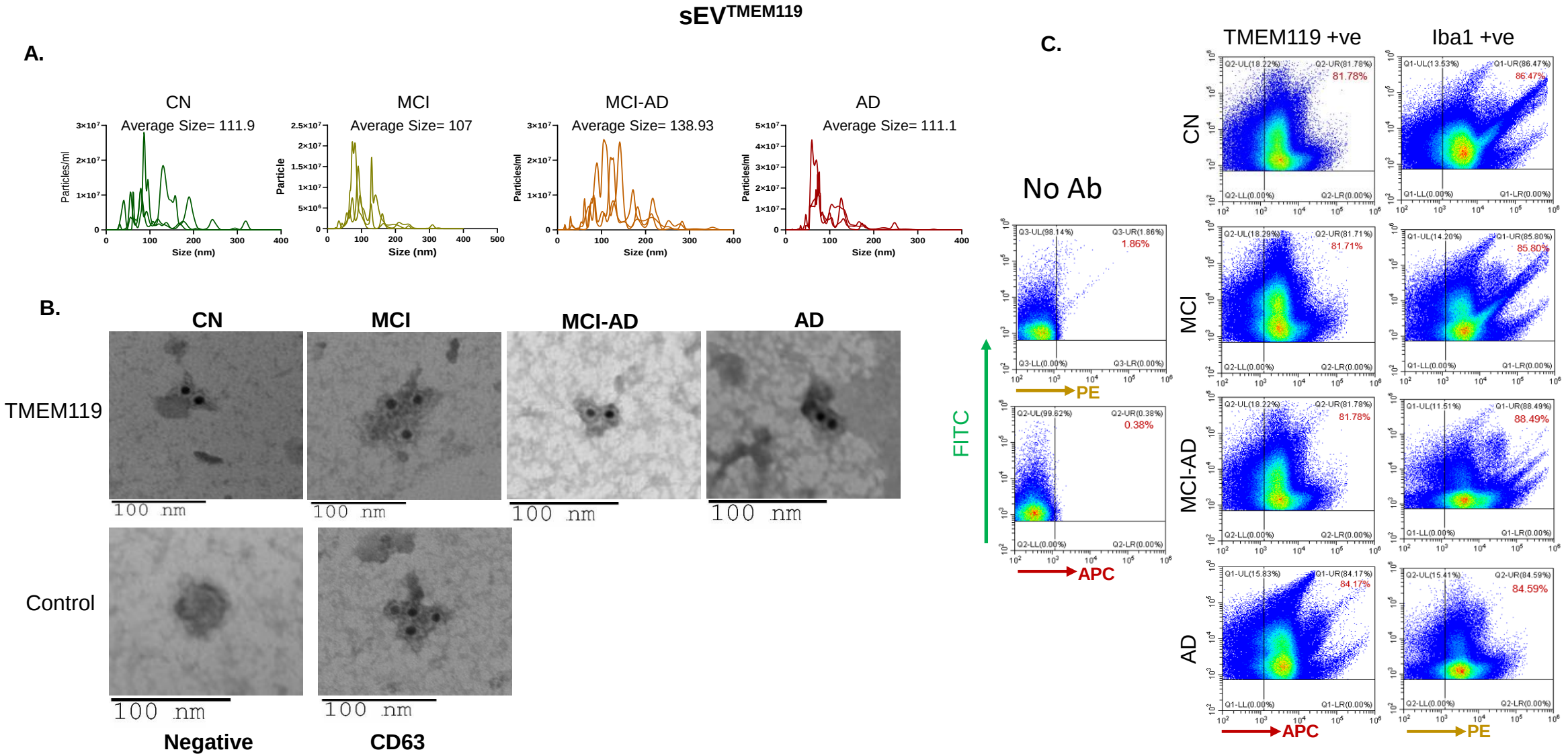
Supplementary Figure 3. miRNA expression analysis in TE. **(A)** The expression of various miRNAs in TE was analyzed by real time PCR method. The expression of miRNAs is presented as fold change with respect to control group (CN). *p<0.05, **p<0.005. **(B)** Correlation of miRNAs expression in TE with the temporal cortical thickness measured by MRI.



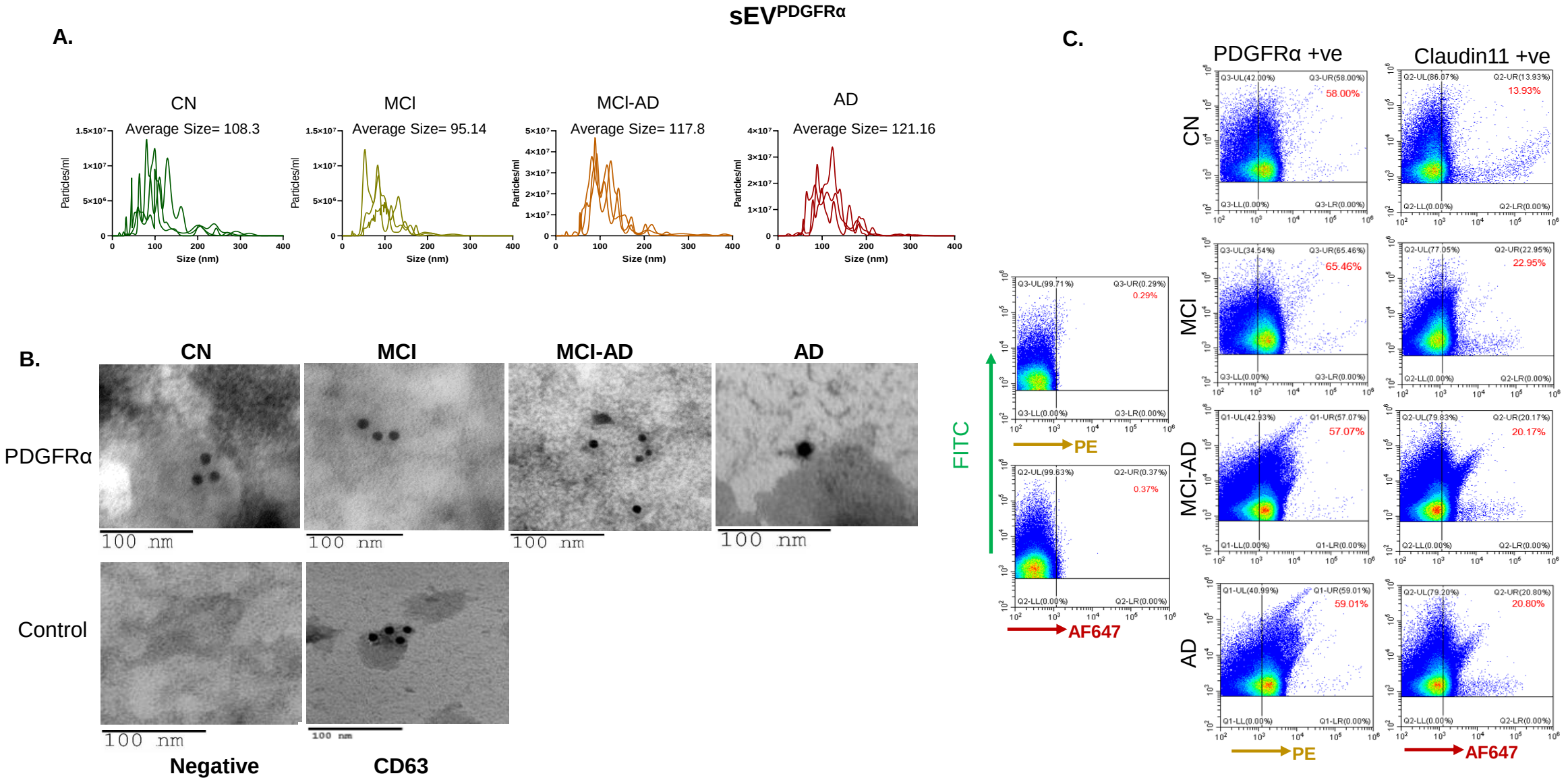
Supplementary Figure 4. Characterization of sEV^{L1CAM}. (**A)** Size and concentration of sEV^{L1CAM}, isolated from the TE using L1CAM-biotin antibody and streptavidin tagged magnetic beads, were measured by nanoparticle tracking analysis (NTA). For each group, 3 sEV^{L1CAM} samples were analyzed by NTA by capturing 5 videos of 30 sec each. Each line represents the average of 5 videos. **(B)** Surface expression of biomarkers on sEV^{L1CAM} was assessed using a specific primary antibody (L1CAM and CD63 as positive control) and gold-labeled secondary antibodies on sEV^{L1CAM} isolated from each group. Representative TEM images are shown at 98,000x, and a scale bar is presented below each image. **(C)** Flow cytometry analysis was performed to confirm the purity of sEV^{L1CAM}. sEV^{L1CAM} with only CellBrite steady 488 membrane dye (FITC) but without any other fluorescent antibody (unlabeled) were used as control (Left panel) to set the gate for L1CAM(PE)+ and synaptophysin(APC)+ve populations.



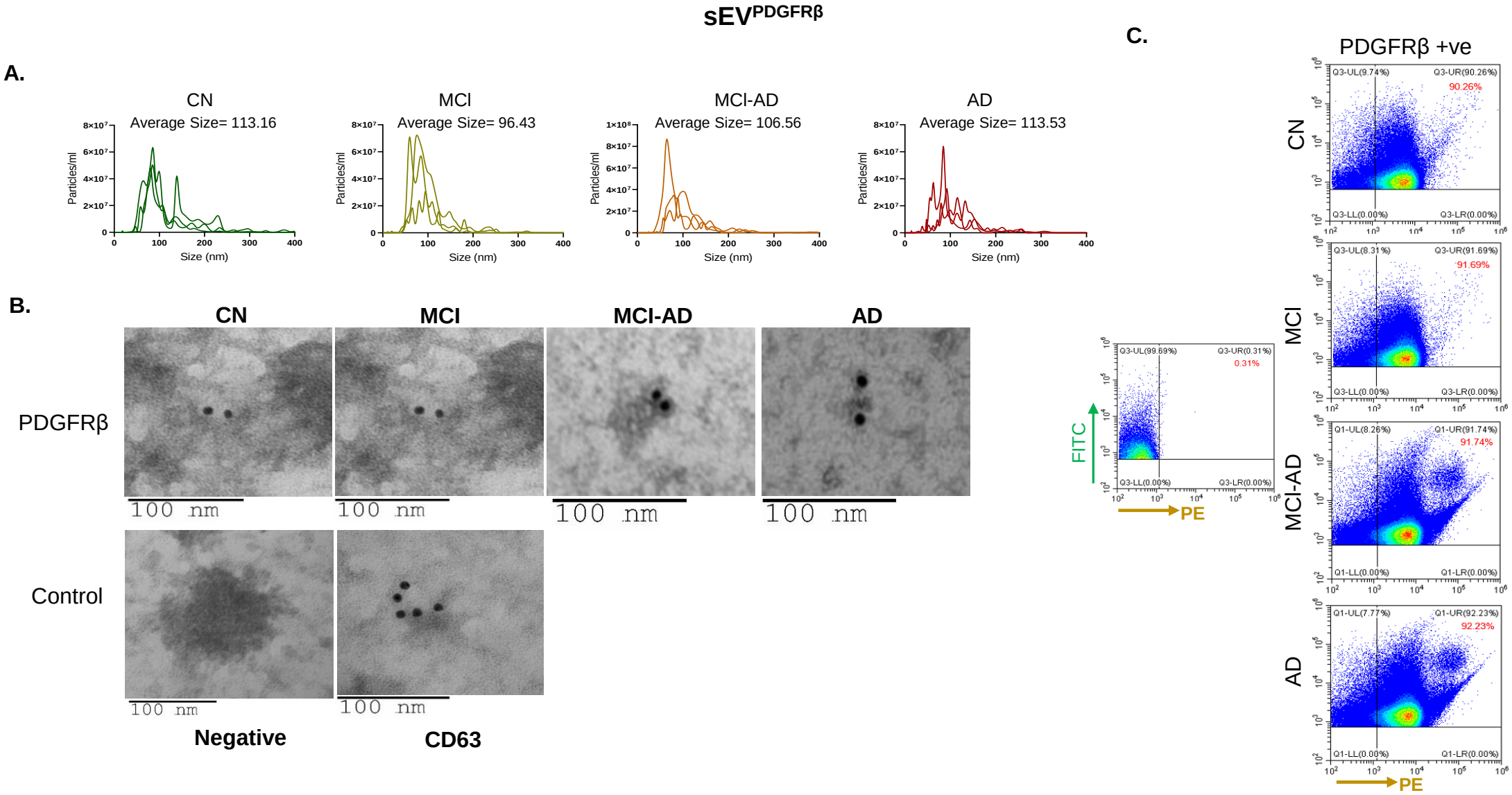
Supplementary Figure 5. Characterization of sEV^{GLAST}. **(A)** Size and concentration of sEV^{GLAST}, isolated from the TE using GLAST-biotin antibody and streptavidin tagged magnetic beads, were measured by nanoparticle tracking analysis (NTA). For each group 3 sEV^{GLAST} samples were analyzed by NTA by taking 5 videos of 30 sec each. Each line represents the average of 5 videos. **(B)** Surface expression of biomarkers on sEV^{GLAST} was assessed using a specific primary antibody (GLAST and CD63 as positive control) and gold-labeled secondary antibodies on sEV^{GLAST} isolated from each group. Representative TEM images are shown at 98,000x, and a scale bar is presented below each image. **(C)** Flow cytometry analysis was performed to confirm the purity of sEV^{GLAST}. sEV^{GLAST} with only CellBrite steady 488 membrane dye (FITC) but without any other fluorescent antibody (unlabeled) were used as control (Left panel) to set the gate for GLAST(APC)+ and GFAP(PE)+ve populations.



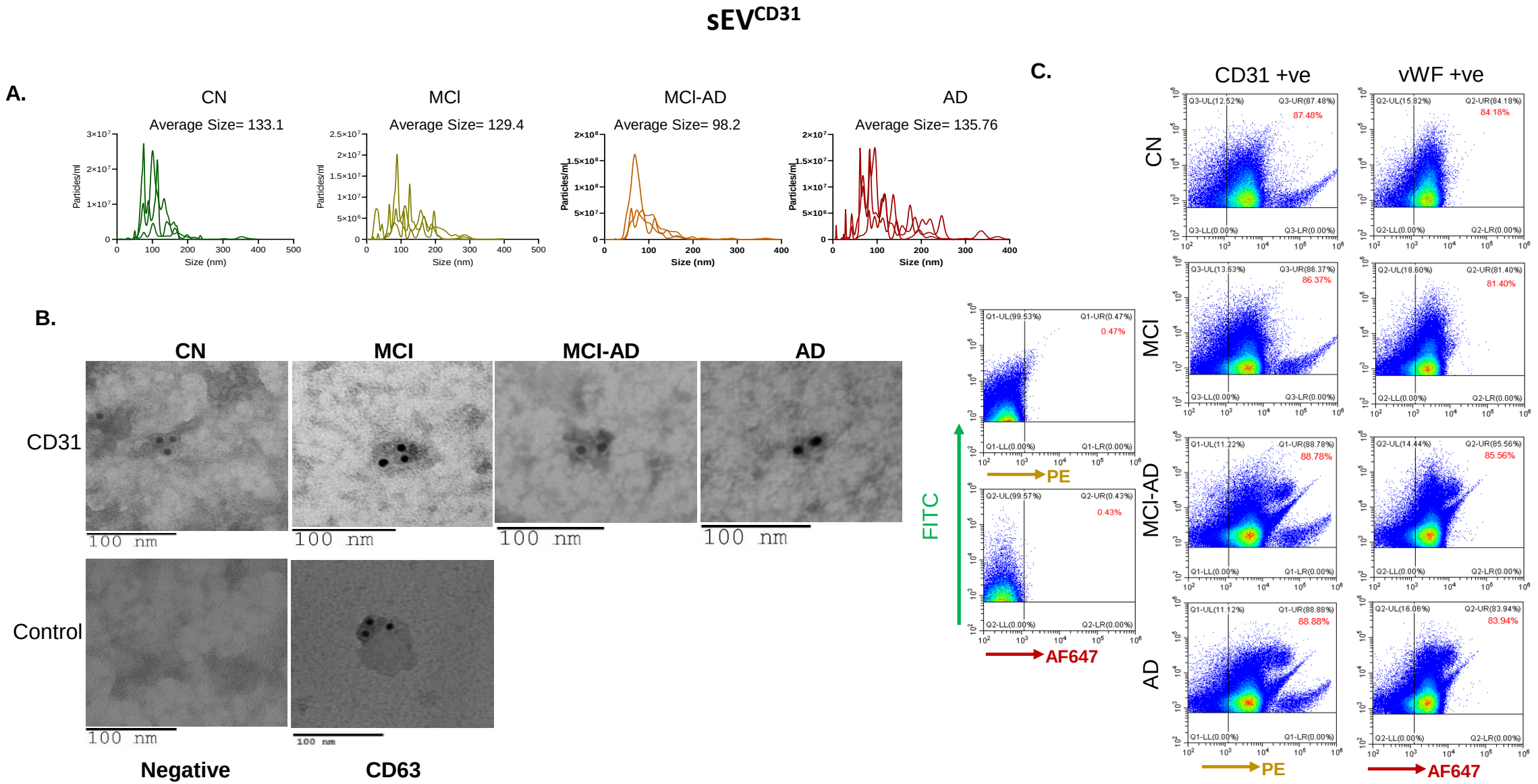
Supplementary Figure 6. Characterization of sEV^{TMEM}. **(A)** Size and concentration of sEV^{TMEM119}, isolated from the TE using TMEM119-biotin antibody and streptavidin tagged magnetic beads, were measured by nano particle tracking analysis (NTA). For each group 3 sEV^{TMEM119} samples were analyzed by NTA by taking 5 videos of 30 sec each. Each line represents the average of 5 videos. **(B)** Surface expression of biomarkers on sEV^{TMEM119} was assessed using a specific primary antibody (TMEM119 and CD63 as positive control) and gold-labeled secondary antibodies on sEV^{TMEM} isolated from each group. Representative TEM images are shown at 98,000x, and a scale bar is presented below each image. **(C)** Flow cytometry analysis was performed to confirm the purity of sEV^{TMEM119}. sEV^{TMEM119} with only CellBrite steady 488 membrane dye (FITC) but without any other fluorescent antibody (unlabeled) were used as control (Left panel) to set the gate for TMEM119 (APC)+ and Iba1 (PE)+ve populations.



Supplementary Figure 7. Characterization of sEV^{PDGFRα}. **(A)** Size and concentration of sEV^{PDGFRα}, isolated from the TE using PDGFRα-biotin antibody and streptavidin tagged magnetic beads, were measured by nanoparticle tracking analysis (NTA). For each group 3 sEV^{PDGFRα} samples were analyzed by NTA by taking 5 videos of 30 sec each. Each line represents the average of 5 videos. **(B)** Surface expression of biomarkers on sEV^{PDGFRα} was assessed using a specific primary antibody (PDGFRα and CD63 as positive control) and gold-labeled secondary antibodies on sEV^{PDGFRα} isolated from each group. Representative TEM images are shown at 98,000x, and a scale bar is presented below each image. **(C)** Flow cytometry analysis was performed to confirm the purity of sEV^{PDGFRα}. sEV^{PDGFRα} with only CellBrite steady 488 membrane dye (FITC) but without any other fluorescent antibody (unlabeled) were used as control (Left panel) to set the gate for PDGFRα (PE)+ and claudin11 (AF647)+ve populations.

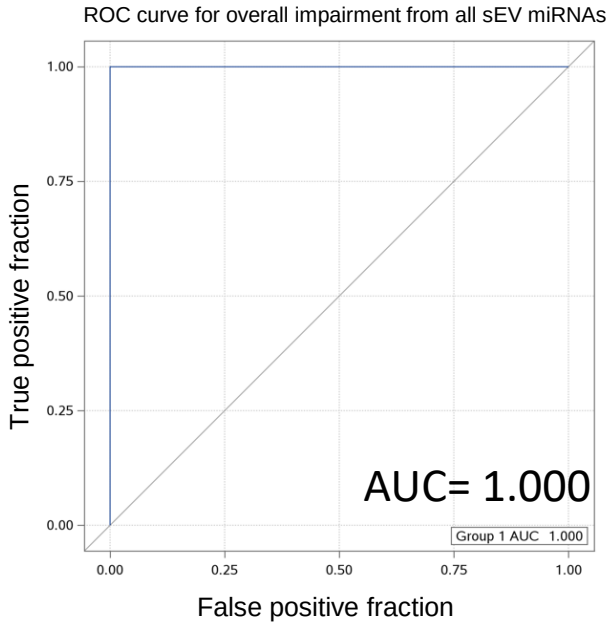


Supplementary Figure 8. Characterization of sEV^{PDGFRβ}. (**A)** Size and concentration of sEV^{PDGFRβ}, isolated from the TE using PDGFRβ-biotin antibody and streptavidin tagged magnetic beads, were measured by nanoparticle tracking analysis (NTA). For each group, 3 sEV^{PDGFRβ} samples were analyzed by NTA by taking 5 videos of 30 sec each. Each line represents the average of 5 videos. **(B)** Surface expression of biomarkers on sEV^{PDGFRβ} was assessed using a specific primary antibody (PDGFRβ and CD63 as positive control) and gold-labeled secondary antibodies on sEV^{PDGFRβ} isolated from each group. Representative TEM images are shown at 98,000x, and a scale bar is presented below each image. **(C)** Flow cytometry analysis was performed to confirm the purity of sEV^{PDGFRβ}. sEV^{PDGFRβ} with only CellBrite steady 488 membrane dye (FITC) but without any other fluorescent antibody (unlabeled) were used as control (Left panel) to set the gate for PDGFRβ (PE)+ ve populations.

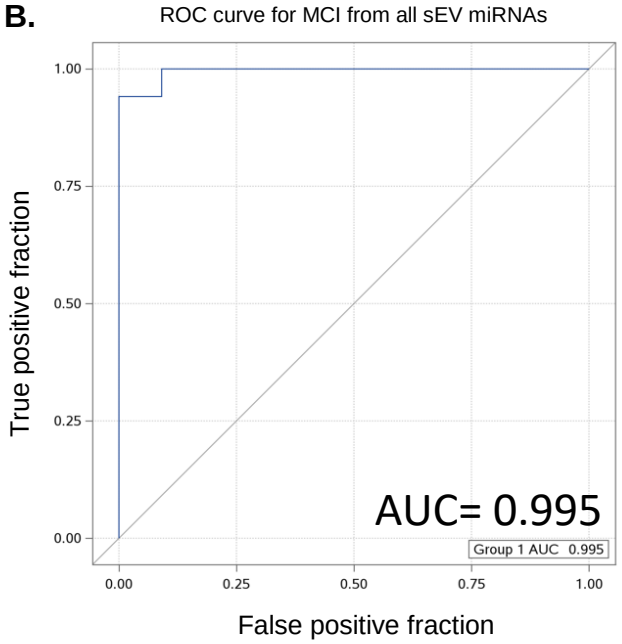


Supplementary Figure 9. Characterization of sEV^{CD31}. (**A)** Size and concentration of sEV^{CD31}, isolated from the TE using CD31-biotin antibody and streptavidin tagged magnetic beads, were measured by nanoparticle tracking analysis (NTA). For each group 3 sEV^{CD31} samples were analyzed by NTA by taking 5 videos of 30 sec each. Each line represents the average of 5 videos. **(B)** Surface expression of biomarkers on sEV^{CD31} was assessed using a specific primary antibody (CD31 and CD63 as positive control) and gold-labeled secondary antibodies on sEV^{CD31} isolated from each group. Representative TEM images are shown at 98,000x, and a scale bar is presented below each image. **(C)** Flow cytometry analysis was performed to confirm the purity of sEV^{CD31}. sEV^{CD31} with only CellBrite steady 488 membrane dye (FITC) but without any other fluorescent antibody (unlabeled) were used as control (Left panel) to set the gate for CD31 (PE)+ and vWF (APC)+ve populations.

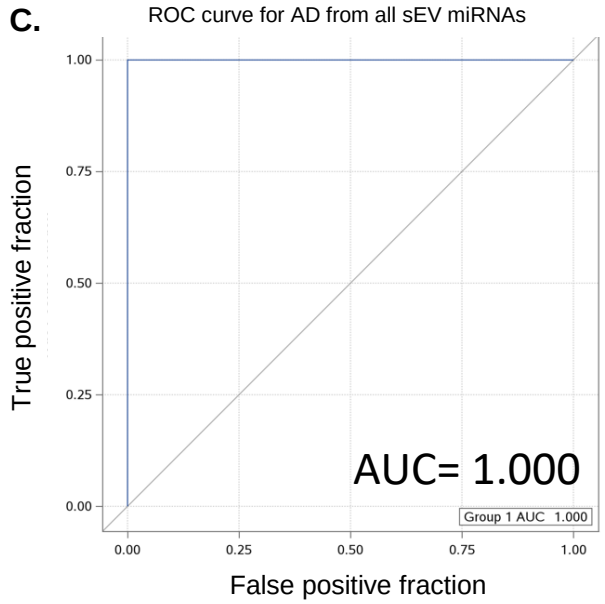
A.



B.



C.



Summary of Forward Selection			
Step	Effect Entered	Score Chi-Square	Pr > ChiSq
1	sEV$^{PDGR\beta}$_miR9a-5p	17.0634	<.0001
2	sEV^{CD31}_miR132-5p	9.0485	0.0026

Summary of Forward Selection			
Step	Effect Entered	Score Chi-Square	Pr > ChiSq
1	sEV^{CD31}_miR132-5p	13.8289	0.0002

Summary of Forward Selection			
Step	Effect Entered	Score Chi-Square	Pr > ChiSq
1	sEV^{CD31}_miR135b-5p	13.8407	0.0002

Supplementary Figure 10. Receiver operating characteristic (ROC) curves generated from forward selection, logistic regression classifiers selecting from all EV subtypes to model overall impairment **(A)**, MCI **(B)**, and AD dementia **(C)** with alpha=0.05. All models were adjusted for age and sex. Summary of forward selection shown under each ROC curve.