Supplemental Figure 1. ADAM10 protein expression and ADAM10sa do not correlate in lung normal and cancer cells. Lysates of normal and cancer cells were prepared and ADAM10 and ADAM17 proteins and sheddase activities tested as described in *Fig. 1*. *(A)* ADAM10 and *(B)* ADAM17 protein concentrations were determined by ELISAs. *(C)* ADAM10sa and *(D)* ADAM17sa were quantified using PrAMA Syntherror/Sigmathreshold 0.5/1.55 parameters. H441A, H441B and H441C indicate 50-70%, 95-100% and 25% confluency of H441 cell cultures, respectively.
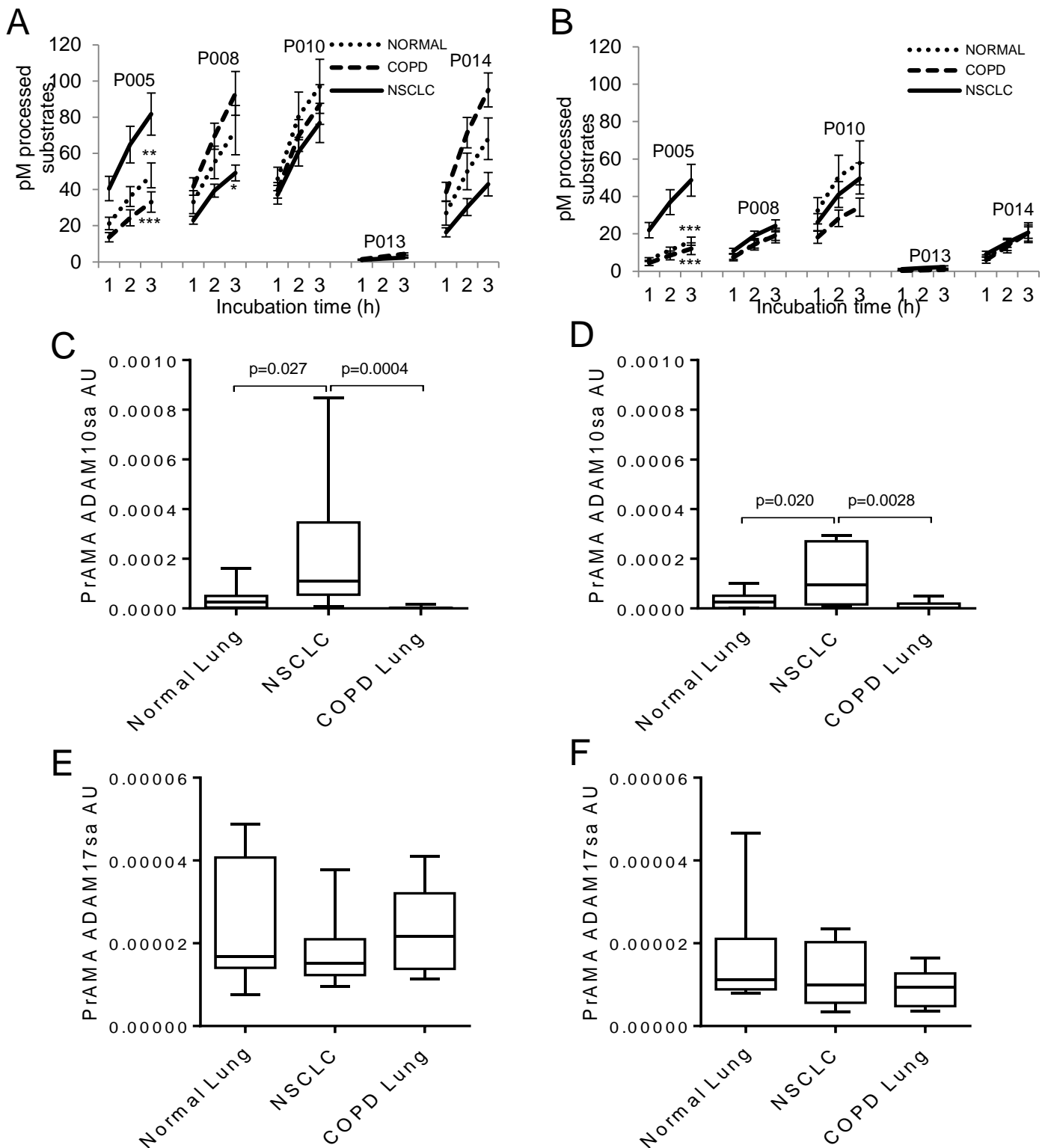
Supplemental Figure 2. Cryopreserved tissues either dry or in RNAlater consistently contain ADAM10sa and ADAM17sa. Ten pairs of tumor tissues and cancer-free lung tissue specimens obtained from the same stage IA-IIB NSCLC patients, and 10 lung tissue specimens obtained from COPD patients were stored for 1 to 5 years cryopreserved either dry *(A, C, E)* or in RNAlater *(B, D, F)*. Tissues were thawed, washed in cold PBS, lysed and their lysates tested for the ability to process PEPDAB substrates from 1 h to 3 h of incubation *(A, B)*. ADAM10sa *(C, D)* and ADAM17sa *(E, F)* of the 3 h substrate processing data were inferred using PrAMA Syntherror/Sigmathreshold 0.5/1.33 parameters. Data are presented as means $\pm$ STE of pM processed substrates *(A, B)*, and boxplots with medians, quartiles and ranges of PrAMA ADAM10sa AU *(C, D)* and PrAMA ADAM17sa AU *(E, F)*. *p=0.014-0.038; **p=0.0017-0.0079; ***p<0.0001
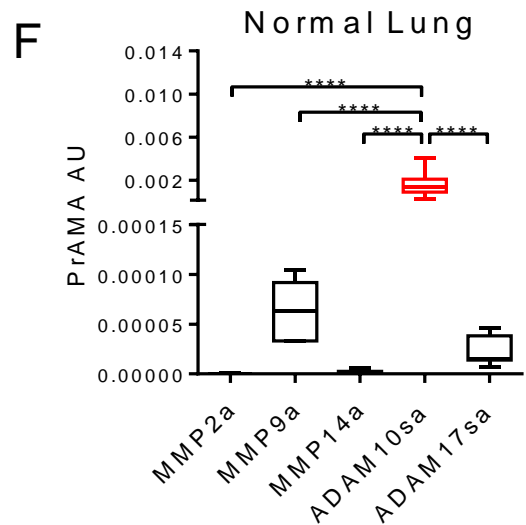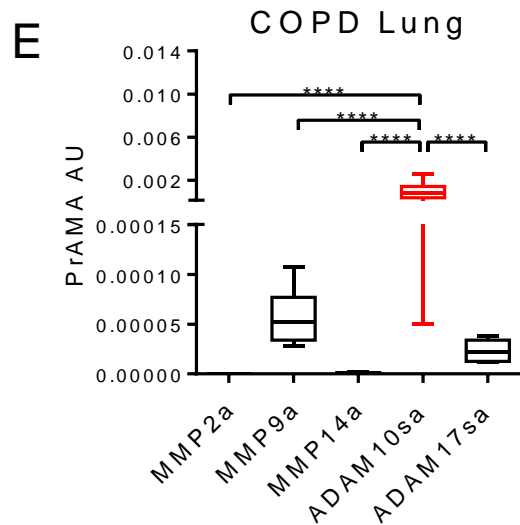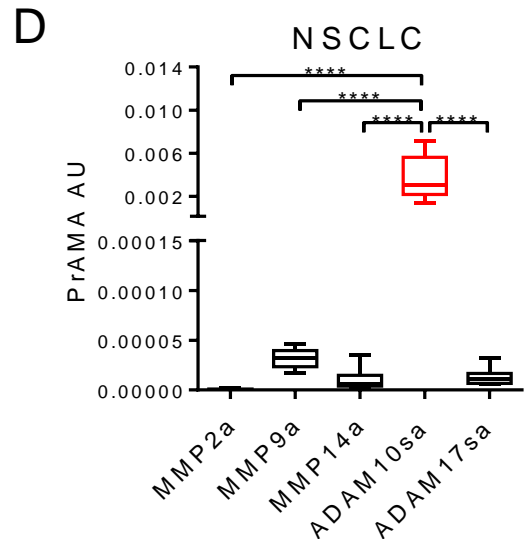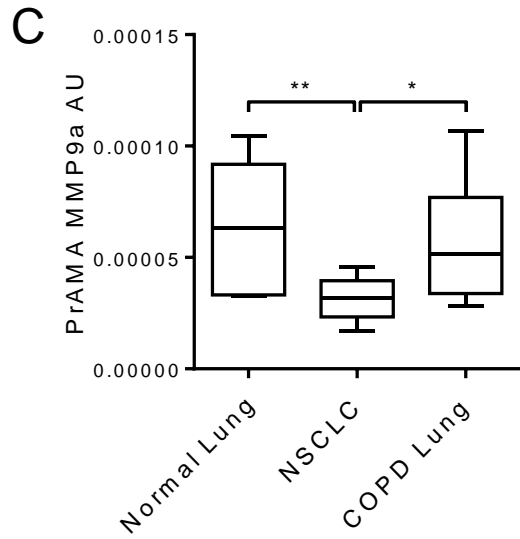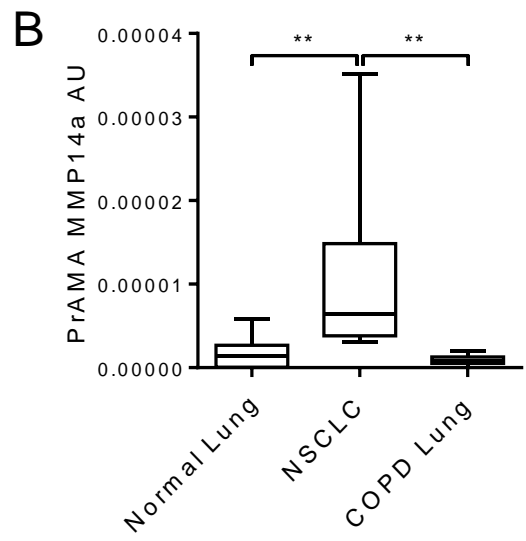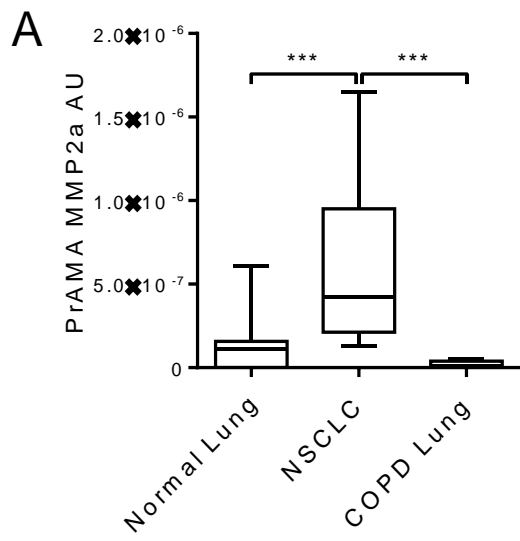
Supplemental Figure 3. ADAM10sa is a highly dominant enzyme activity in NSCLC tumor, COPD lung and normal lung tissues. A detailed PrAMA, including MMP2a, MMP9a, MMP14a, ADAM10sa and ADAM17sa, was performed in the same tissue lysates tested in the experiments presented in Suppl. Figs. 2A, 2C, 2E. The 3 h substrate processing data were inferred using PrAMA Syntherror/Sigmathreshold 0.6/1.00 parameters. Data are presented as boxplots with medians, quartiles and ranges of PrAMA AU. *p=0.02; **p=0.002-0.008; ***p<0.001; ****p<0.0001.
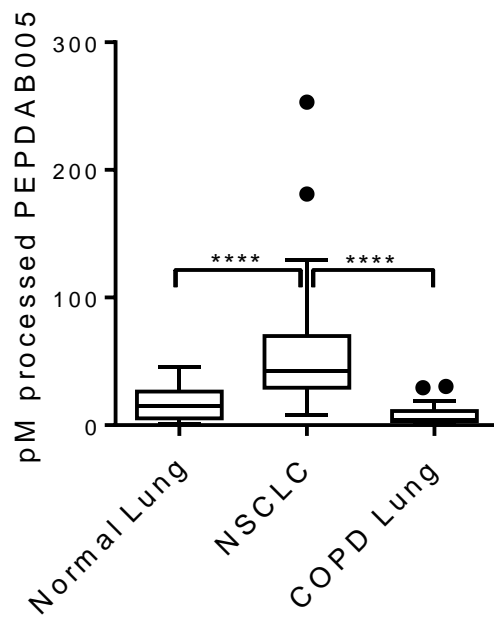
Supplemental Figure 4. Lysates of NSCLC tumors processed highly significantly better PEPDAB005 than lysates of normal or COPD lungs. Presented data are boxplots, medians, quartiles and ranges of processed PEPDAB005 pM at 3 h of incubation as shown in *Fig. 2C*.
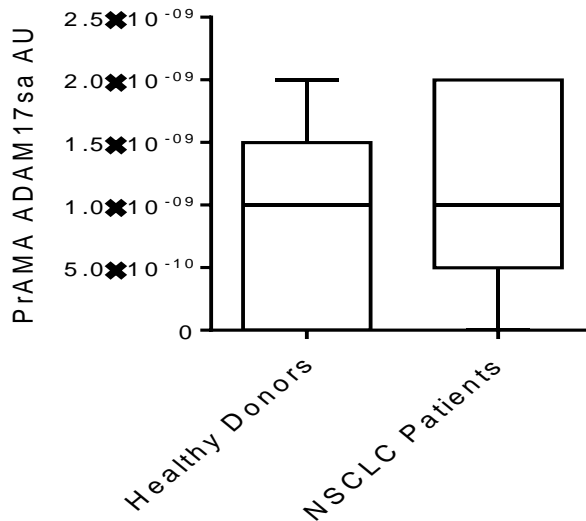
Supplemental Figure 5. Peripheral blood plasma exosomes of NSCLC tumor-bearing patients contain similar amounts of ADAM17sa as those of healthy individuals. PEPDAB processing data presented in *Fig. 4A* were analyzed by PrAMA ADAM17sa and presented as boxplots, medians, quartiles and ranges of ADAM17sa AU.