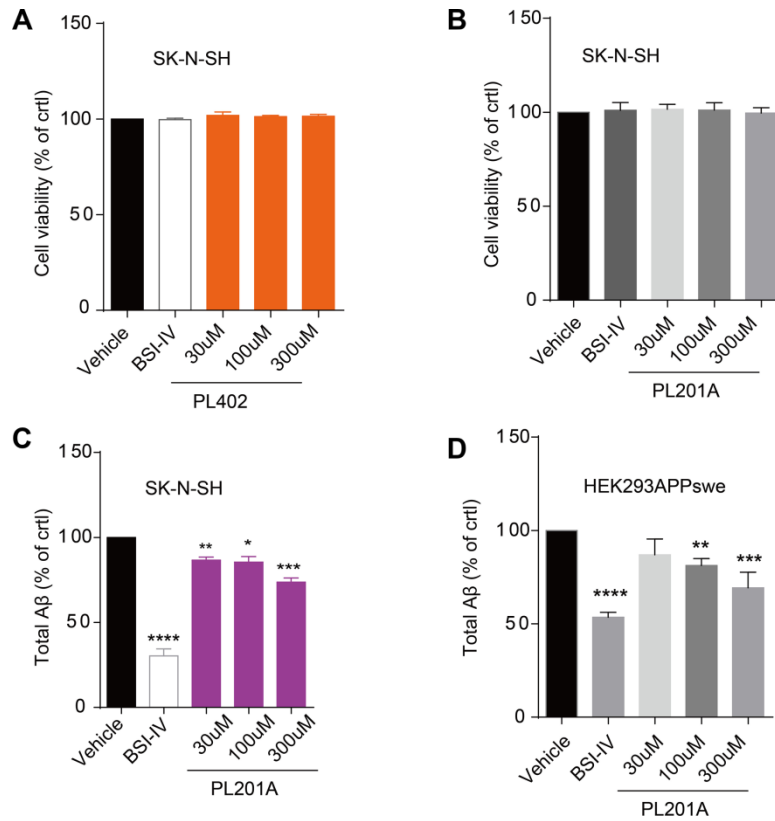
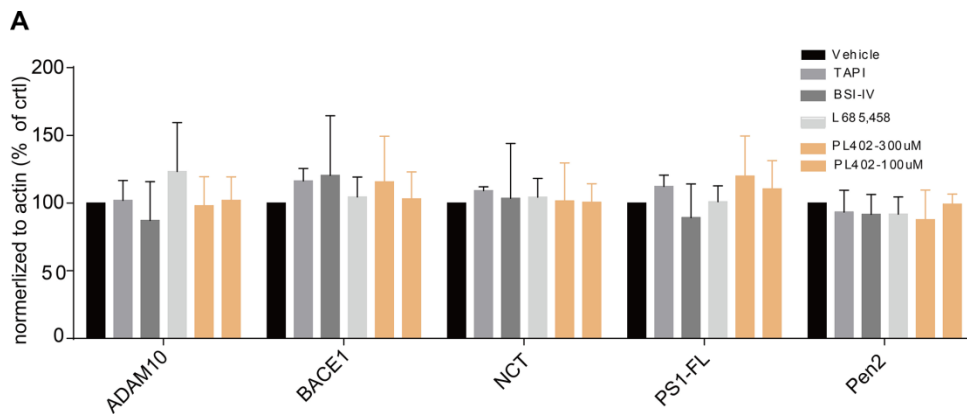


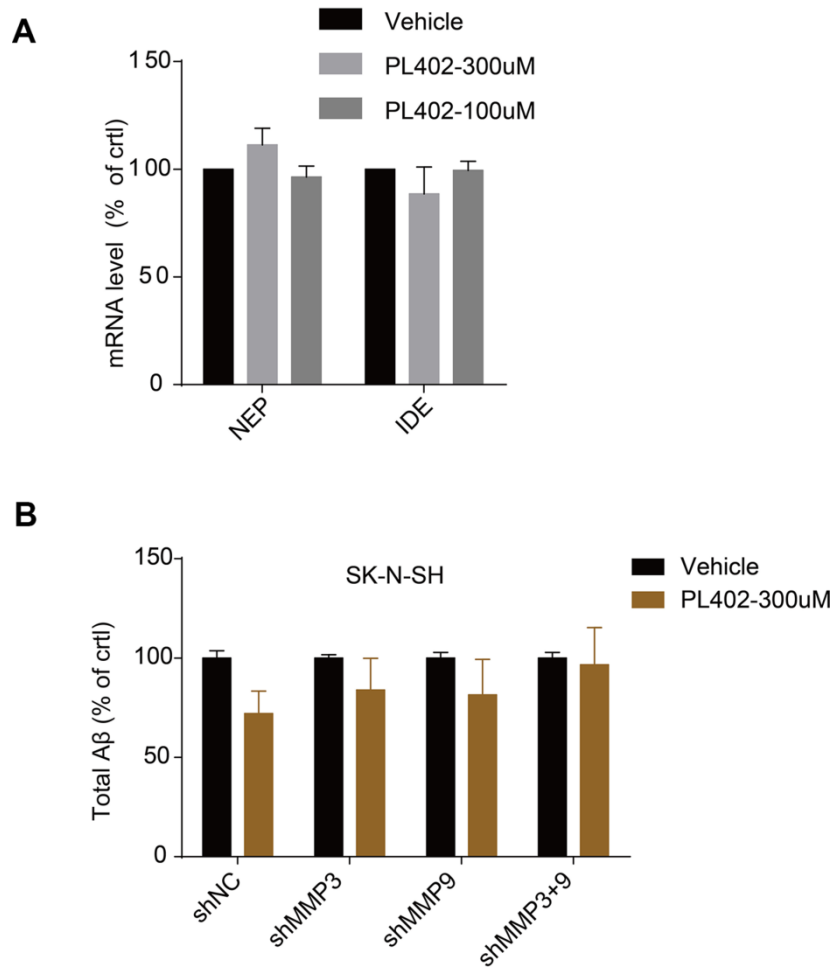
**SUPPLEMENTARY FIGURES**



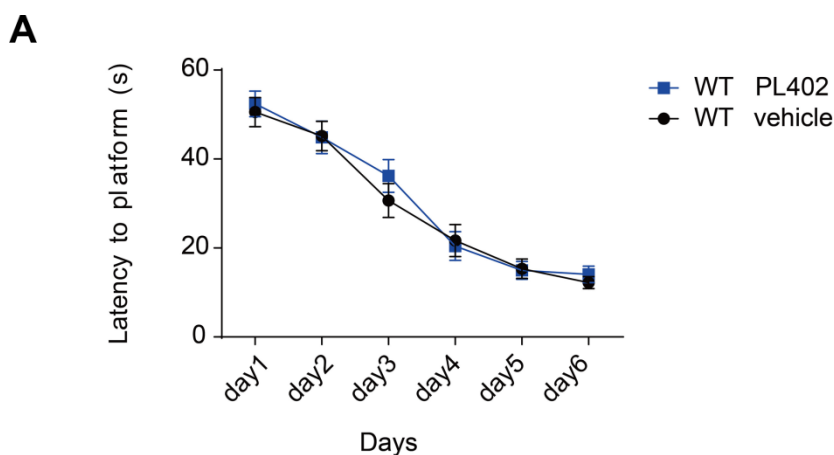
**Supplementary Figure 1. The cell viability or Aβ level in response to PL402 or PL201A treatment.** (A) The cell viability of SK-N-SH cells in response to vehicle (0.1% DMSO), 0.1μM. BACE inhibitor IV (BSI-IV), and the PL402 at 30μM, 100μM or 300μM for 24 hours measured by CellTiter-Glo Assay. (B) The cell viability of SK-N-SH cells in response to vehicle (0.1% DMSO), 0.1μM BACE inhibitor IV (BSI-IV), and the PL201A at 30μM, 100μM or 300μM for 24 hours measured by CellTiter-Glo Assay. (C) The levels of Aβ produced by SK-N-SH cells in response to vehicle (0.1% DMSO), 0.1μM BSI-IV, and the PL201A at 30μM, 100μM or 300μM for 24 hours. (D) The total Aβ level in HEK293/APPswe culture medium treated with vehicle (0.1% DMSO), 0.1μM BSI-IV, or the PL201A at 30μM, 100μM or 300μM for 24h measured by sandwich ELISA. The Data are presented as mean ± SEM, n ≥ 3 independent experiments, \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001 and \*\*\*\*p < 0.001 compared to the control of each group, analyzed by one-way ANOVA followed by Bonferroni test.



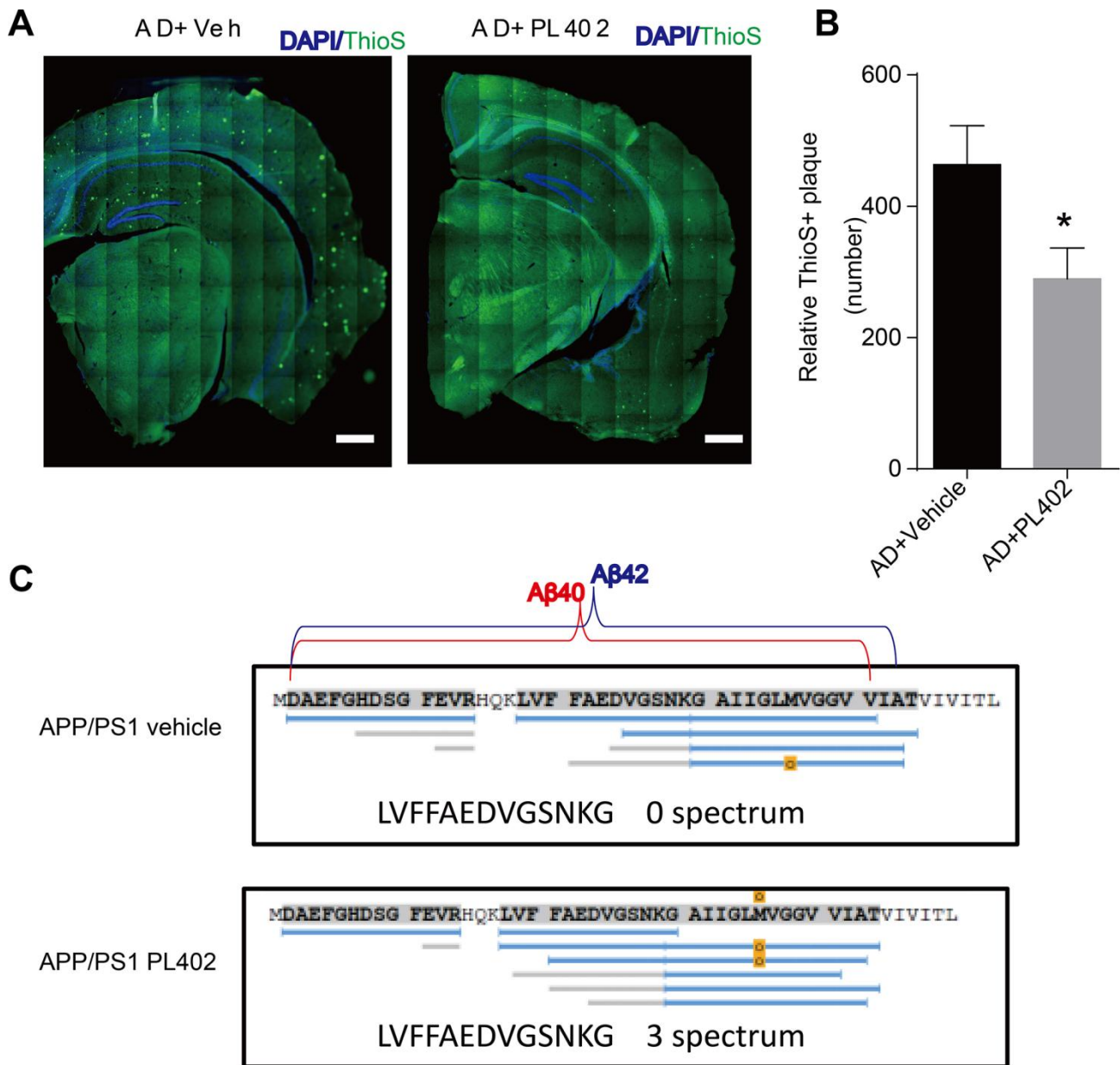
**Supplementary Figure 2. The quantification of the α/β/γ-secretase expression for Figure 2C.** The statistical analysis for Figure 2C using ImageJ analysis. Data were normalized to the actin.



**Supplementary Figure 3. The expression of ADEs and the knockdown of MMP3 or/and MMP9 in SK-N-SH cells. (A).** The mRNA level of A $\beta$  degradation enzymes (NEP and IDE) measured by RT-qPCR in SK-N-SH cells treated with vehicle (0.1% DMSO) or PL402 at 100 $\mu$ M and 300 $\mu$ M for 24h. **(B).** The levels of total A $\beta$  produced by SK-N-SH cells measured by ELISA after treatment with vehicle (0.1% DMSO) or PL402 at 300 $\mu$ M for 24h in the cells which was transfected with the shRNA targeting MMP3 or/and MMP9.



**Supplementary Figure 4. PL402 does not affect cognitive function and memory in WT mice.** Morris water maze (MWM) test of vehicle- or PL402 treated WT mice (n=8 mice per group).



**Supplementary Figure 5. PL402 alleviates amyloid plaque burden and promotes A $\beta$  degraded fragments in APP/PS1 mice.** (A, B). Representative images (A) of A $\beta$  plaques in APP/PS1 mice stained with the Thioflavin S (ThioS) in coronal mouse brain cryo-sections (n = 5 per group) and the number of A $\beta$  plaques (B), were quantified from entire brain sections using Image-Pro Plus 5.1 software (Media Cybernetics), scale bar =500  $\mu$ m. \*p < 0.05 compared to the control group, analyzed by one-way ANOVA followed by Bonferroni test. (C). Representatives of truncated A $\beta$  peptides in mouse brain tissues using the mass spectrometry (MS) approach, and the blue lane indicated the various A $\beta$  peptides.