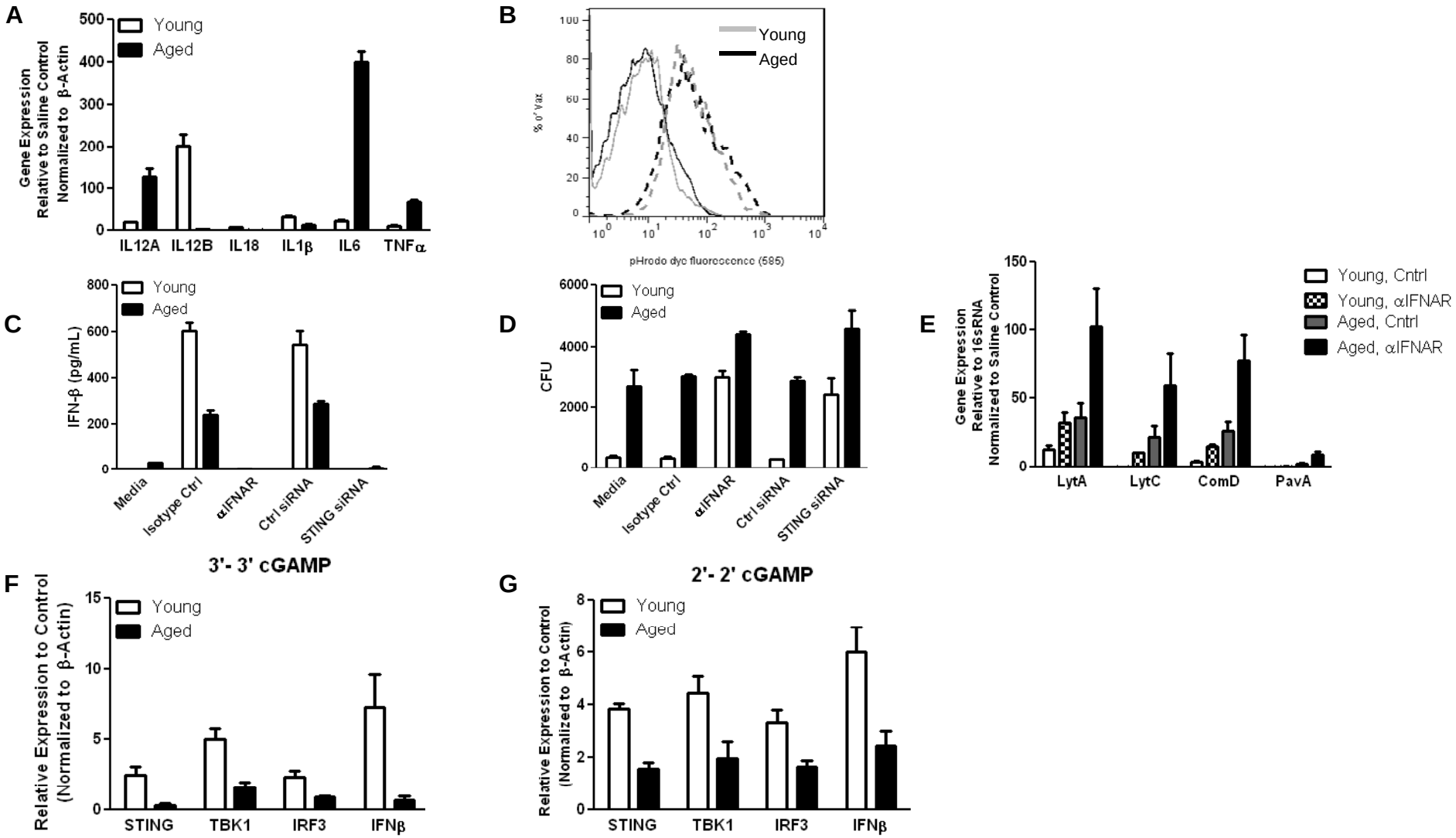
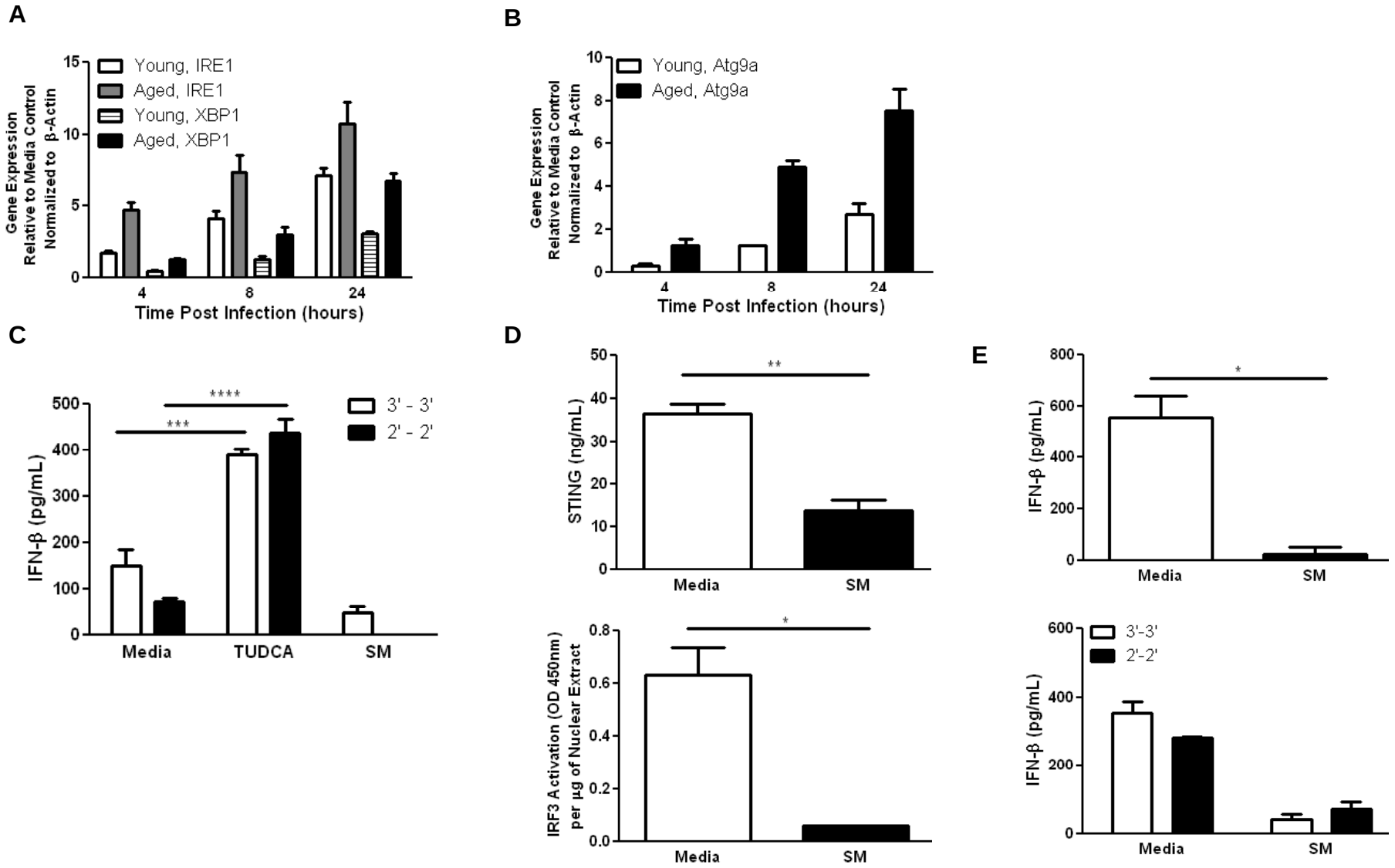
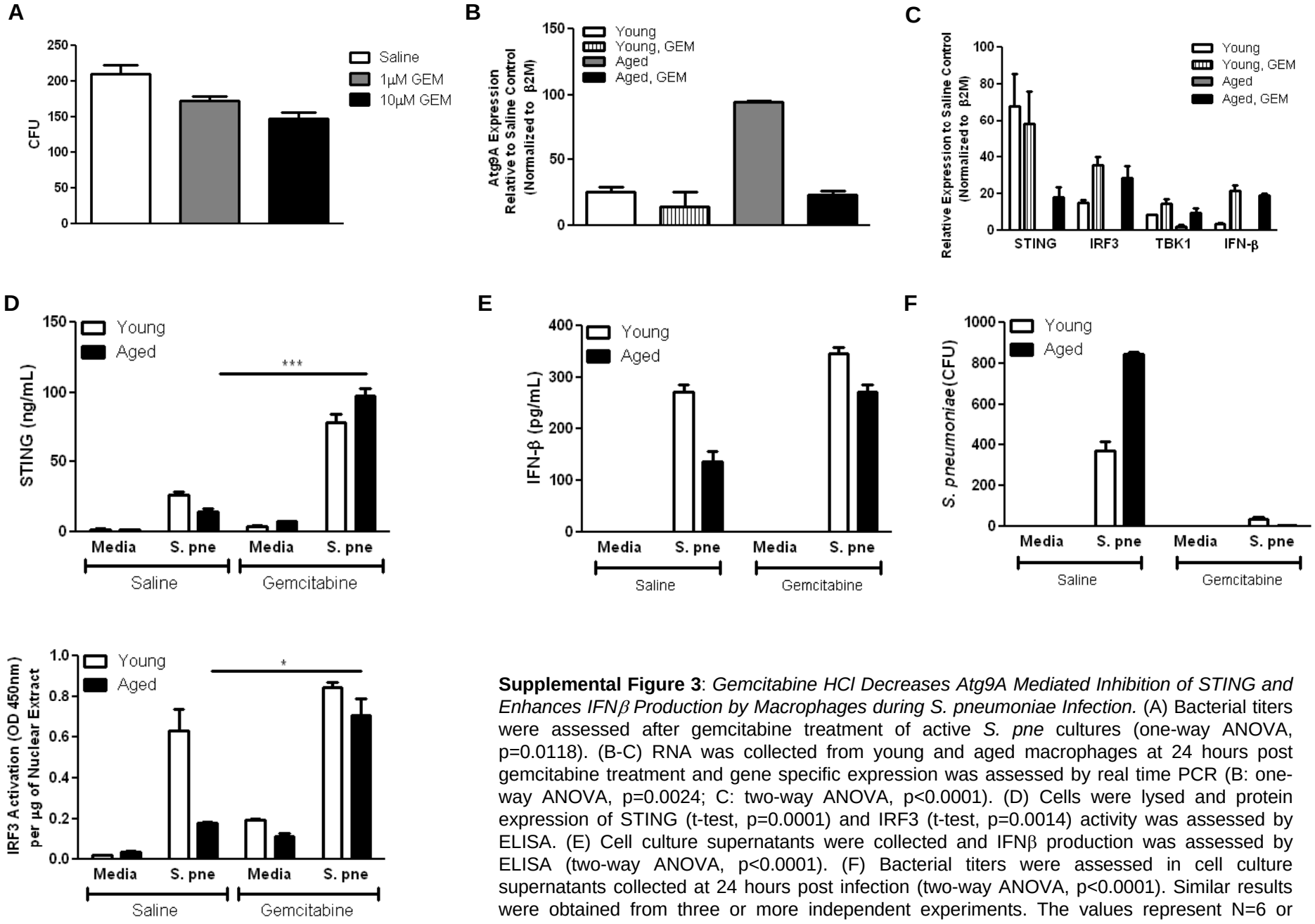


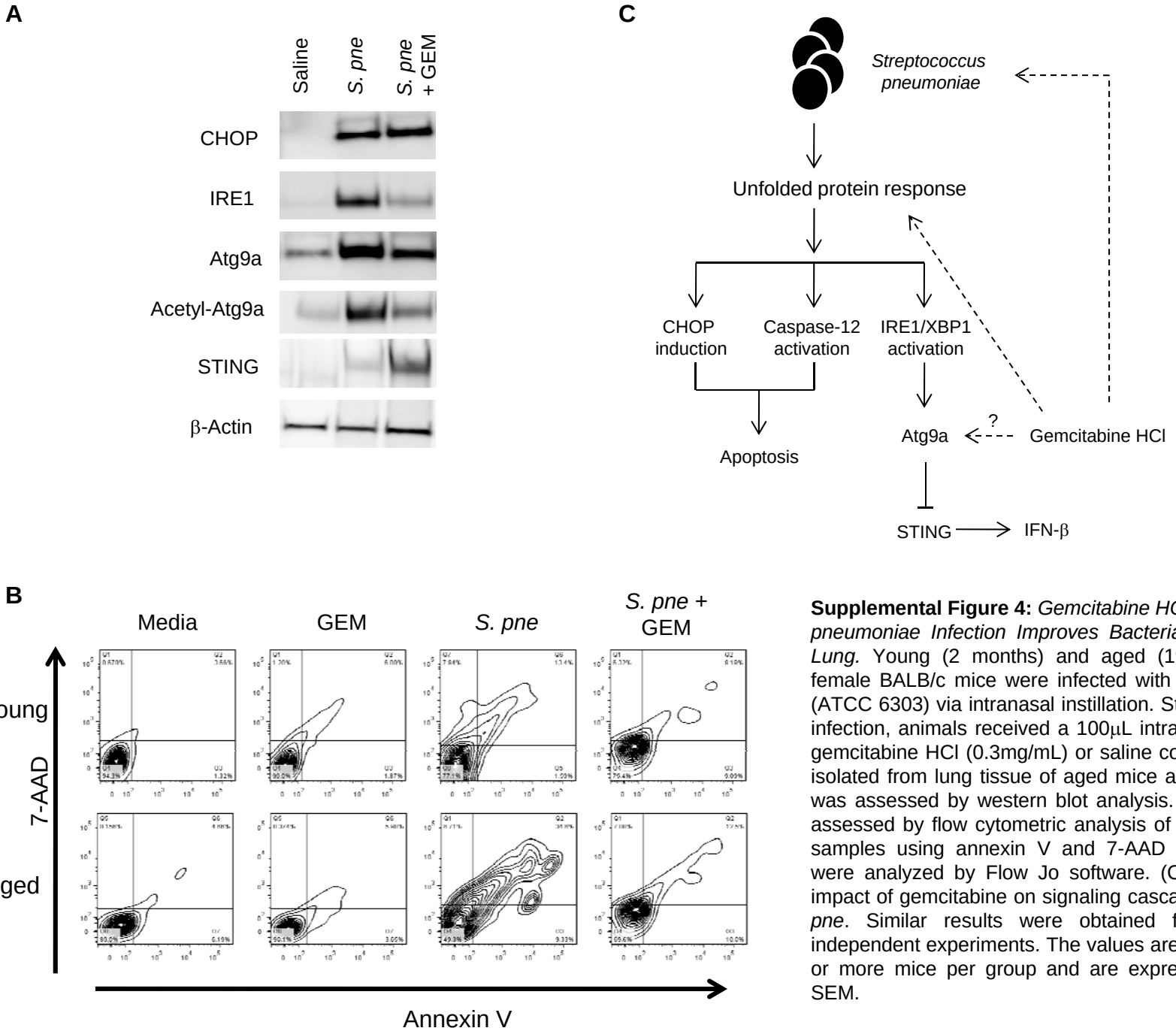
Supplemental Figure 1: *Enhanced S. pneumoniae titers and lytic gene expression in aged macrophages*. (A) RNA was isolated from young and aged lung 24 hours post *S. pne* infection and gene expression was assessed by real time PCR (two-way ANOVA, $p<0.0001$). (B) Young (grey line) and aged (black line) macrophages were cultured with pH Rodo labeled *S. pne* for 30 minutes for 37°C under sterile conditions prior to flow cytometric analysis. Solid lines: untreated cells and dashed lines: pHrodo *S. pne* treated macrophages. (C) IFNβ production by isotype, αIFNAR, or siRNA treated young and aged macrophages was assessed by ELISA (two-way ANOVA, $p<0.0001$). (D) Bacterial titers in cell culture supernatants were assessed at 24 hours post *S. pne* infection (t-test, $p=0.0493$). (E) RNA was isolated from isotype and anti-IFNAR antibody treated young and aged macrophages 24 hours post culture and bacterial lytic gene expression was assessed by real time PCR (two-way ANOVA, $p=0.003$). (F-G) RNA was isolated from young and aged macrophages 24 hours post culture with (F) 3'-3' and (G) 2'-2' cGAMPs and assessed by real time PCR (F: two-way ANOVA, $p<0.0001$; G: two-way ANOVA, $p<0.0001$). Similar results were obtained from three or more independent experiments. The values represent N=6 or greater per experiment and are expressed as the mean ± SEM.



Supplemental Figure 2: *ER stress mediated gene expression and production of IFNβ.* (A-B) RNA was isolated from macrophages at select time points post culture of *S. pne*. Gene expression was assessed by real time PCR (A: two-way ANOVA, $p<0.0001$; B: two-way ANOVA, $p=0.0002$). (C) IFNβ production by aged macrophages in response to TUDCA and SM treatment was assessed by ELISA (t-test, $p<0.05$). (D-F) STING expression, IRF3 activation, and IFNβ production by young macrophages in response to SM treatment during *S. pne* infection was assessed by ELISA (D-F: t-test, $p<0.05$). IFNβ production by young macrophages in response to SM treatment during stimulation with 3'-3' and 2'-2' cGAMPs was assessed by ELISA (two-way ANOVA, $p=0.0347$). Similar results were obtained from three or more independent experiments. The values represent N=6 or greater per experiment and are expressed as the mean ± SEM.



Supplemental Figure 3: *Gemcitabine HCl Decreases Atg9A Mediated Inhibition of STING and Enhances IFNβ Production by Macrophages during S. pneumoniae Infection.* (A) Bacterial titers were assessed after gemcitabine treatment of active *S. pne* cultures (one-way ANOVA, p=0.0118). (B-C) RNA was collected from young and aged macrophages at 24 hours post gemcitabine treatment and gene specific expression was assessed by real time PCR (B: one-way ANOVA, p=0.0024; C: two-way ANOVA, p<0.0001). (D) Cells were lysed and protein expression of STING (t-test, p=0.0001) and IRF3 (t-test, p=0.0014) activity was assessed by ELISA. (E) Cell culture supernatants were collected and IFNβ production was assessed by ELISA (two-way ANOVA, p<0.0001). (F) Bacterial titers were assessed in cell culture supernatants collected at 24 hours post infection (two-way ANOVA, p<0.0001). Similar results were obtained from three or more independent experiments. The values represent N=6 or greater per experiment and are expressed as the mean ± SEM.



Supplemental Figure 4: *Gemcitabine HCl Treatment during S. pneumoniae Infection Improves Bacterial Clearance in Aged Lung.* Young (2 months) and aged (19 months) male and female BALB/c mice were infected with $1x10^3$ CFU of *S. pne* (ATCC 6303) via intranasal instillation. Starting at 4 hours post infection, animals received a 100μL intraperitoneal injection of gemcitabine HCl (0.3mg/mL) or saline control. (A) Protein was isolated from lung tissue of aged mice and protein expression was assessed by western blot analysis. (B) Cell viability was assessed by flow cytometric analysis of young and aged lung samples using annexin V and 7-AAD staining. All samples were analyzed by Flow Jo software. (C) Summary figure of impact of gemcitabine on signaling cascades in response to *S. pne*. Similar results were obtained from three or more independent experiments. The values are representative of five or more mice per group and are expressed as the mean ± SEM.