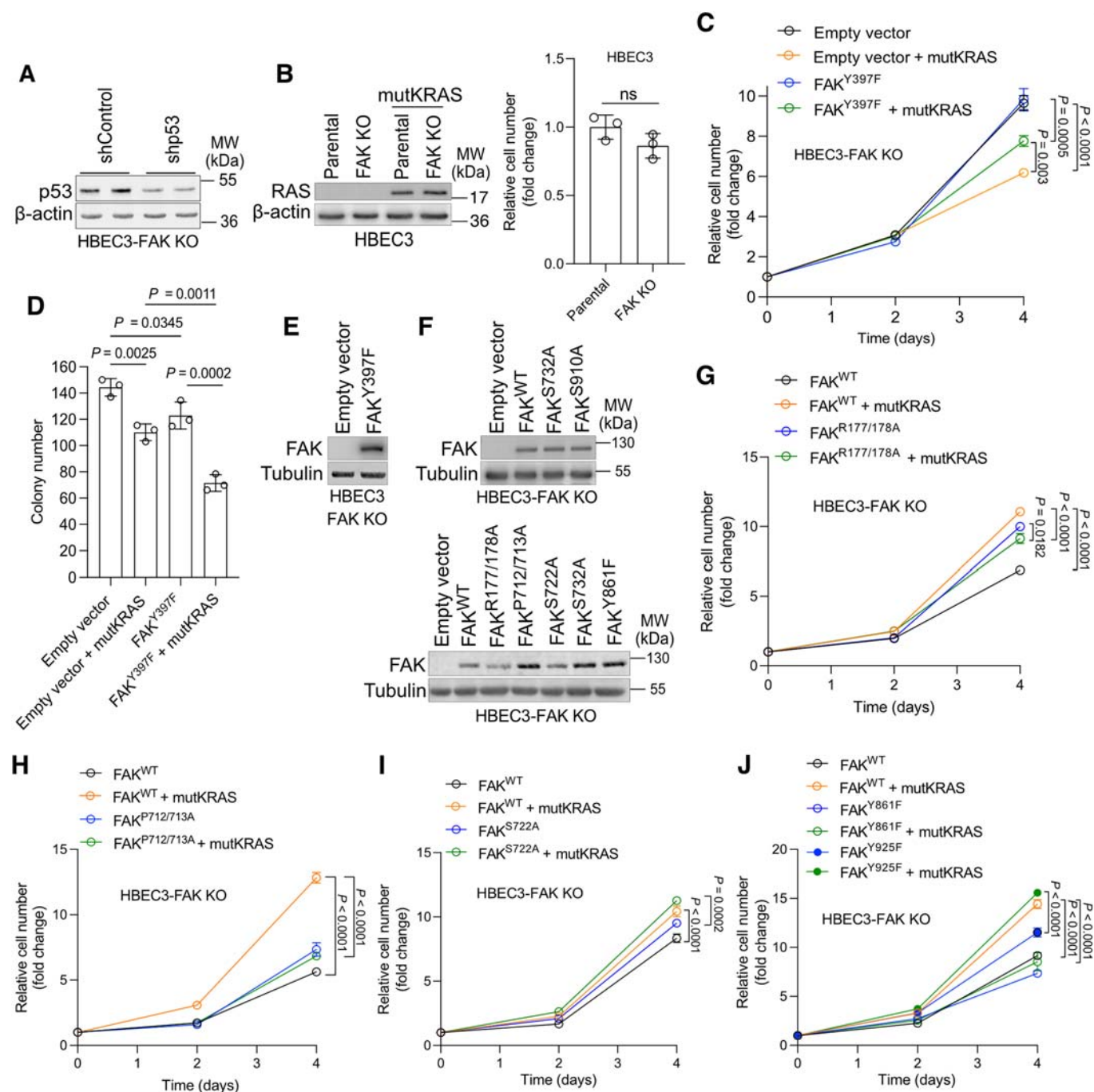


Expanded View Figures

Figure EV1. Functional characterization of the different human FAK phospho-mutants.

(A) Immunoblot analysis of the indicated targets of HBEC3-FAK KO cell line transduced with a lentiviral plasmid carrying either a control shRNA (scramble) or a shRNA against human p53. (B) Immunoblot analysis of the indicated targets in parental and FAK knockout HBEC3 cell line transduced with either an empty vector or a plasmid encoding mutant KRAS (left) and relative cell number of the indicated groups calculated at day 4 (right); $n = 3$. MutKRAS: mutant KRAS; ns: not significant. (C) Relative cell number of HBEC3-FAK KO cell line transduced either with empty vector (pWZL-Hygro) or with the FAK phospho-mutant Y397F (pWZL-Hygro-FAK Y397F) in the absence or presence of mutKRAS (pBABE-zeo or pBABE-zeo-KRAS^{G12D}). MutKRAS: mutant KRAS; $n = 3$. Note that the Empty vector and Empty vector + mutKRAS group plots are the same as in main Fig. 1E because these experiments were performed at the same time for direct comparison. (D) Relative quantification of colony forming capacity of HBEC3-FAK KO cells previously transduced as indicated; $n = 3$. (E) Immunoblot analysis of the indicated targets in HBEC3-FAK KO cells transduced either with empty vector (pWZL-Hygro) or with the FAK phospho-mutant Y397F (pWZL-Hygro-FAK Y397F). (F) Immunoblot analysis of the indicated targets in HBEC3-FAK KO transduced either with empty vector (pWZL-Hygro) or wild-type FAK (pWZL Hygro-FAK WT) or with the indicated human FAK phospho-mutants. (G–J) Relative cell number of HBEC3-FAK KO cell line transduced either with wild-type FAK (pWZL Hygro-FAK WT) or the indicated human FAK phospho-mutants in the absence or presence of mutKRAS^{G12D} (pBABE-zeo or pBABE-zeo-KRAS^{G12D}). MutKRAS: mutant KRAS; $n = 3$. Graphical data are mean $\pm$ SD. Statistical analyses were done using two-tailed unpaired Student's *t* test or one-way ANOVA; *n*, number of biologically independent samples.



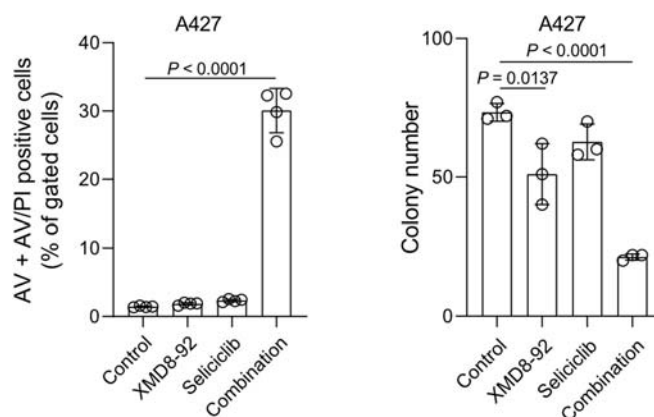


Figure EV2. Co-inhibition of ERK5 and CDK5 increases apoptosis and suppresses colony forming capacity of KRAS mutant NSCLC cells.

Relative quantification of cell death by flow cytometry analysis of Annexin V-Atto 633 (AV) + Annexin V/PI (AV/PI)-positive (left) and colony number (right) of A427 cells treated with XMD8-92 or Seliciclib (10 μ M for apoptosis assay and 2.5 μ M for colony formation each, respectively) alone or in combination; $n = 3$. Graphical data are mean $\pm$ SD. Statistical analyses were done using one-way ANOVA; n , number of biologically independent samples.

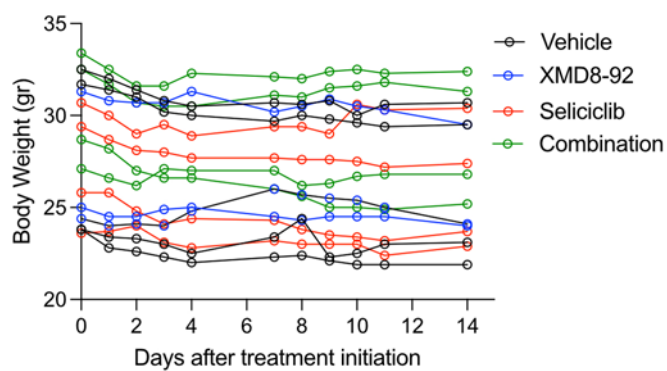


Figure EV3. The treatment of *LSL-Kras^{G12D/WT},p53^{flax/flax}* mice with XMD8-92 and/or Seliciclib is well tolerated.

Body weight of *Kras^{G12D/WT},p53^{flax/flax}* mice treated with vehicle or XMD8-92 or Seliciclib or combination of XMD8-92 and Seliciclib for 2 weeks.

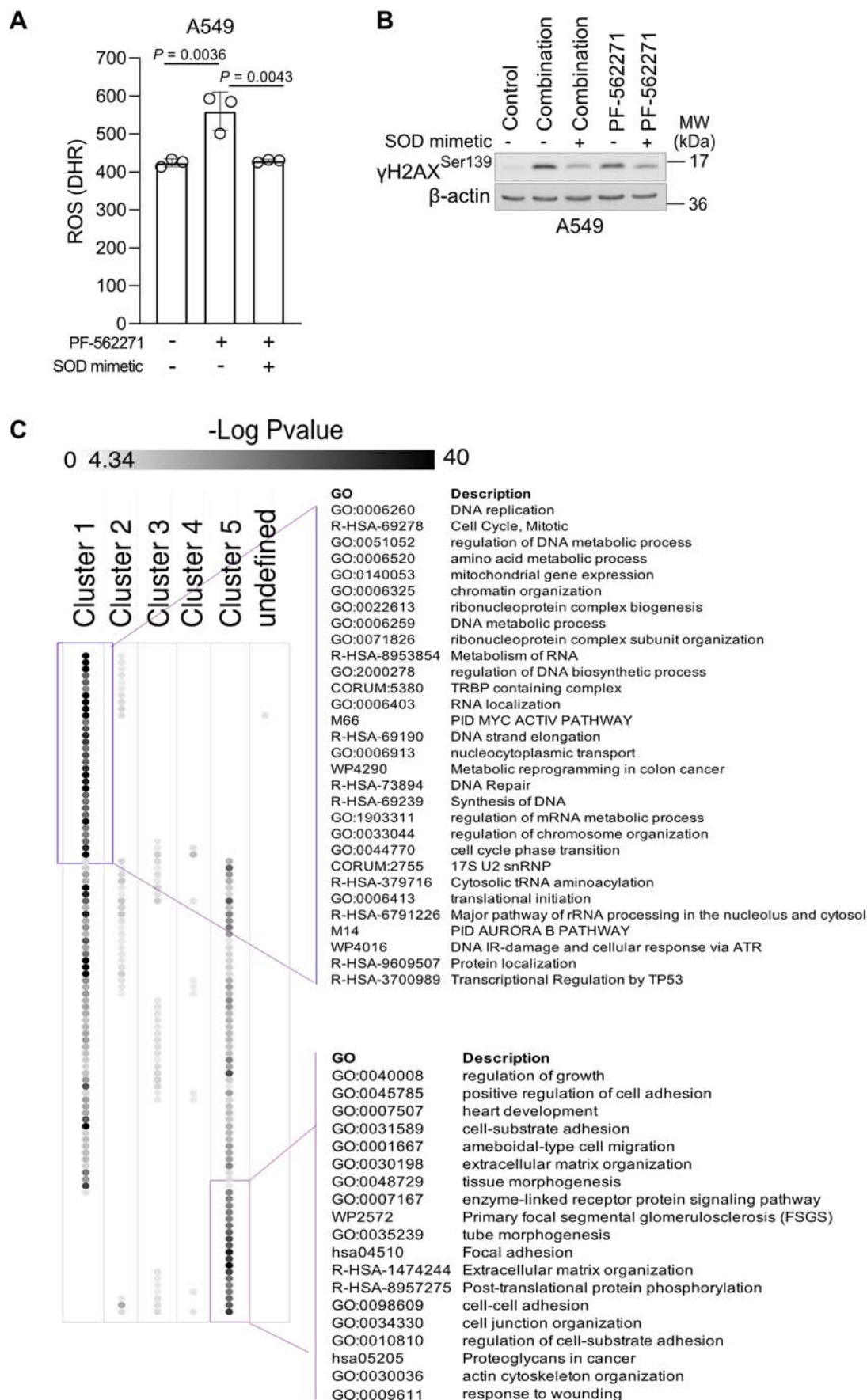


Figure EV4. SOD mimetics rescue ROS-induced DNA damage in mutant KRAS NSCLC.

(A) Quantification of DHR (ROS marker, green) in A549 cells treated with PF-562271 (10 μ M) in the presence or absence of the SOD mimetic, MnTMPyp (25 μ M); $n = 3$. Graphical data are mean $\pm$ SD. Statistical analyses were done using one-way ANOVA; n , number of biologically independent samples. (B) Immunoblot analysis for the indicated targets in A549 cells line, treated with DMSO (control) or with a combination of XMD8-92 and Seliciclib (10 μ M) or PF-562271 (5 μ M) in the presence or absence of the SOD mimetic, MnTMPyp (25 μ M). (C) Metascape-derived analysis of the functional categories associated to the 5 clusters from main Fig. 5C. Enriched terms were filtered based on the enrichment score and accumulative hypergeometric P values ($P < 0.05$). Remaining significant terms were then hierarchically clustered into a tree based on Kappa-statistical similarities among their gene memberships. Then 0.3 kappa score was applied as the threshold to cast the tree into term clusters.

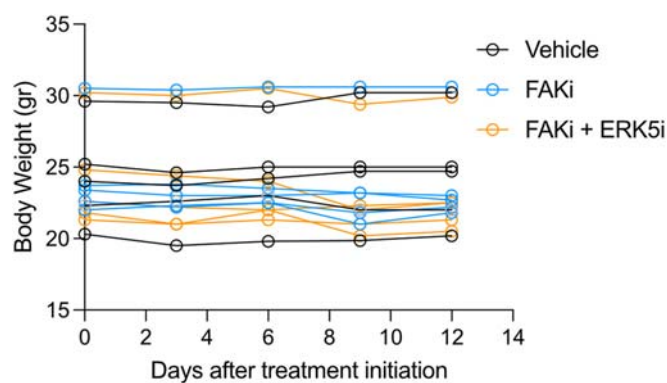


Figure EV5. The treatment of *LSL-Kras^{G12D/WT};p53^{flax/flax}* mice with VS4718 (FAKi) or VS4718 (FAKi) + XMD8-92 (ERK5i) is well tolerated.

Body weight of *Kras^{G12D/WT};p53^{flax/flax}* mice treated with vehicle or VS-4718 (FAKi) or a combination of VS-4718 and XMD8-92 (FAKi + ERK5i) for 2 weeks.