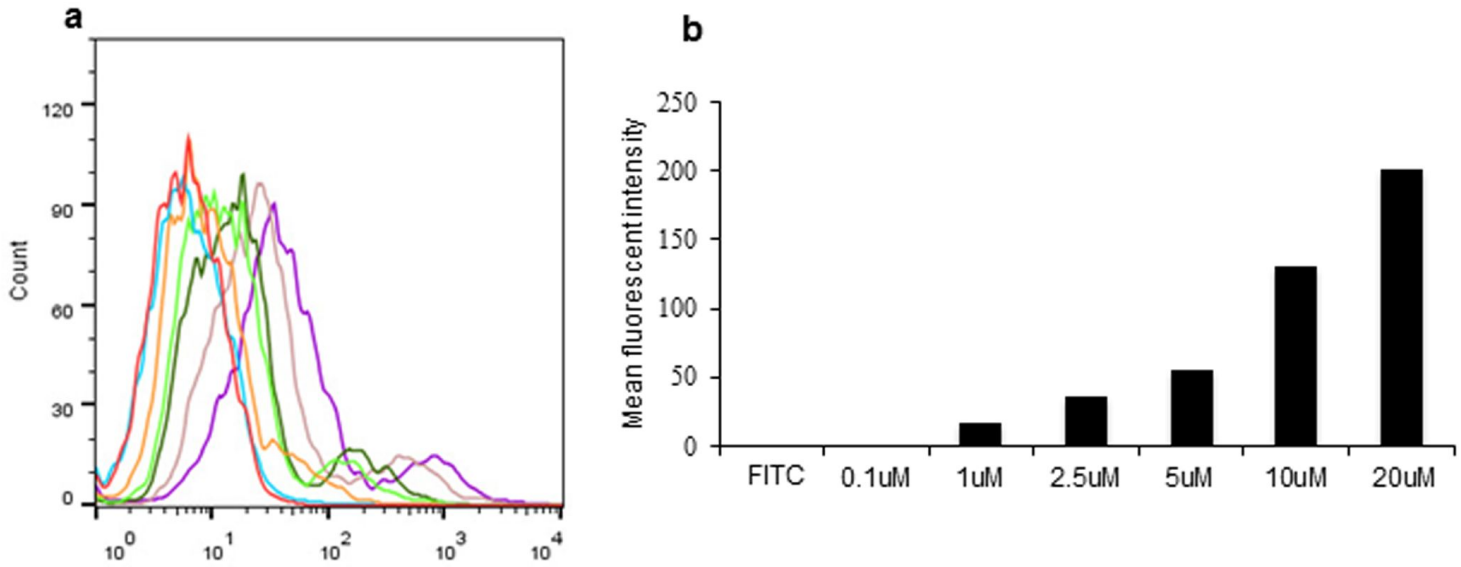
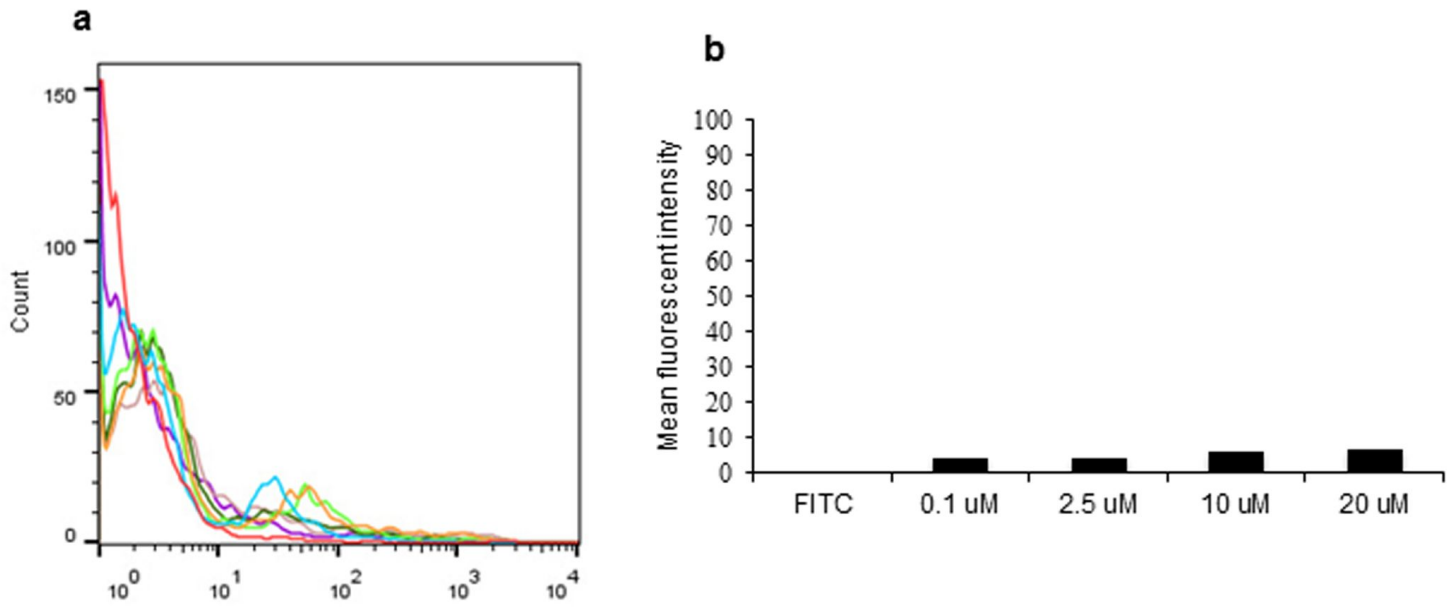
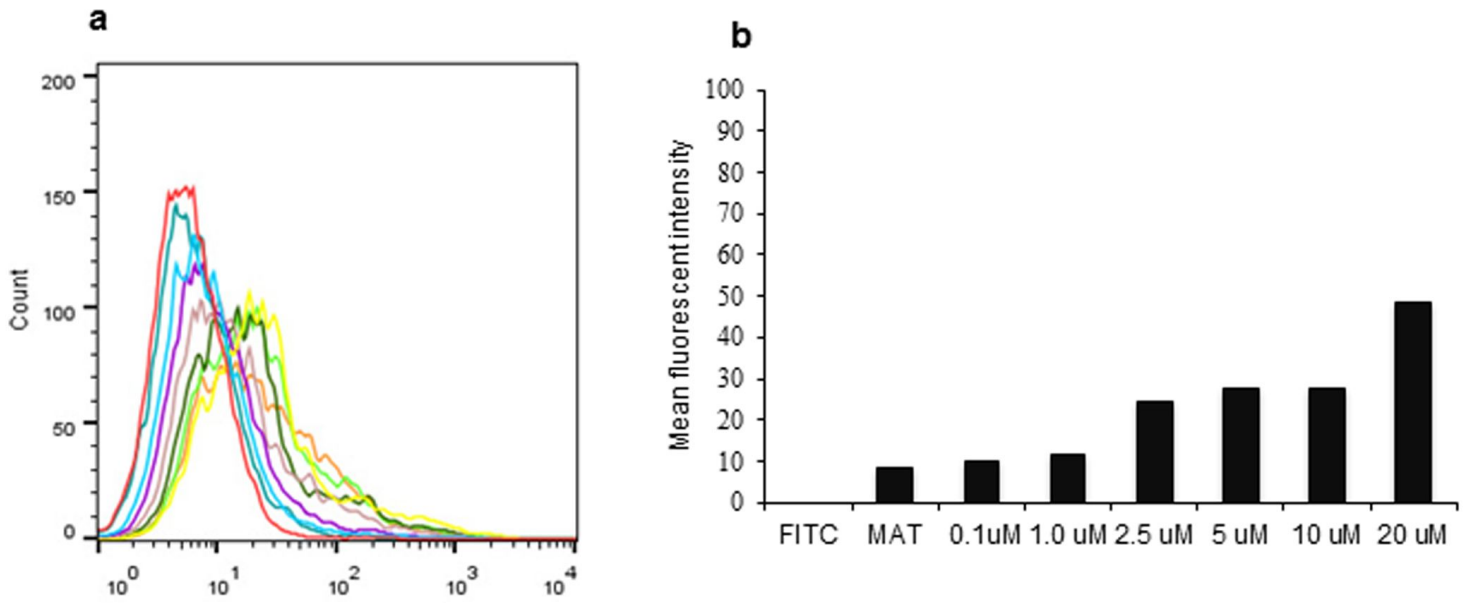


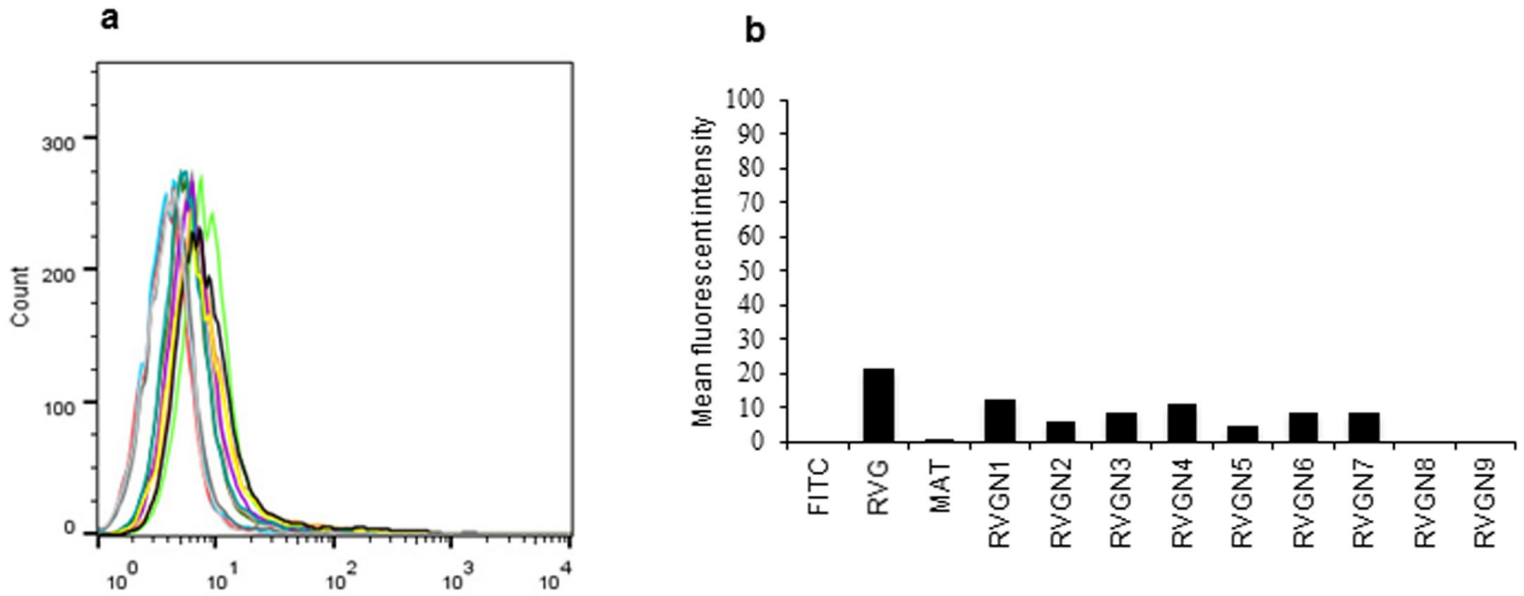
Supplementary Figure 1: **RVG-29 peptide binds to M17 cells.** (**a**) M17 cells were incubated with increasing concentrations of biotinylated-RVG-29 peptide: 0.1 µM (turquoise), 1 µM (orange), 2.5 µM (light green), 5 µM (dark green), 10 µM (pink) and 20 µM (purple) or FITC alone (red), and stained with avidin-FITC before analysis by flow cytometry. (**b**) Representative histogram with the mean fluorescence intensity of the peptides bound to M17 cells is shown.



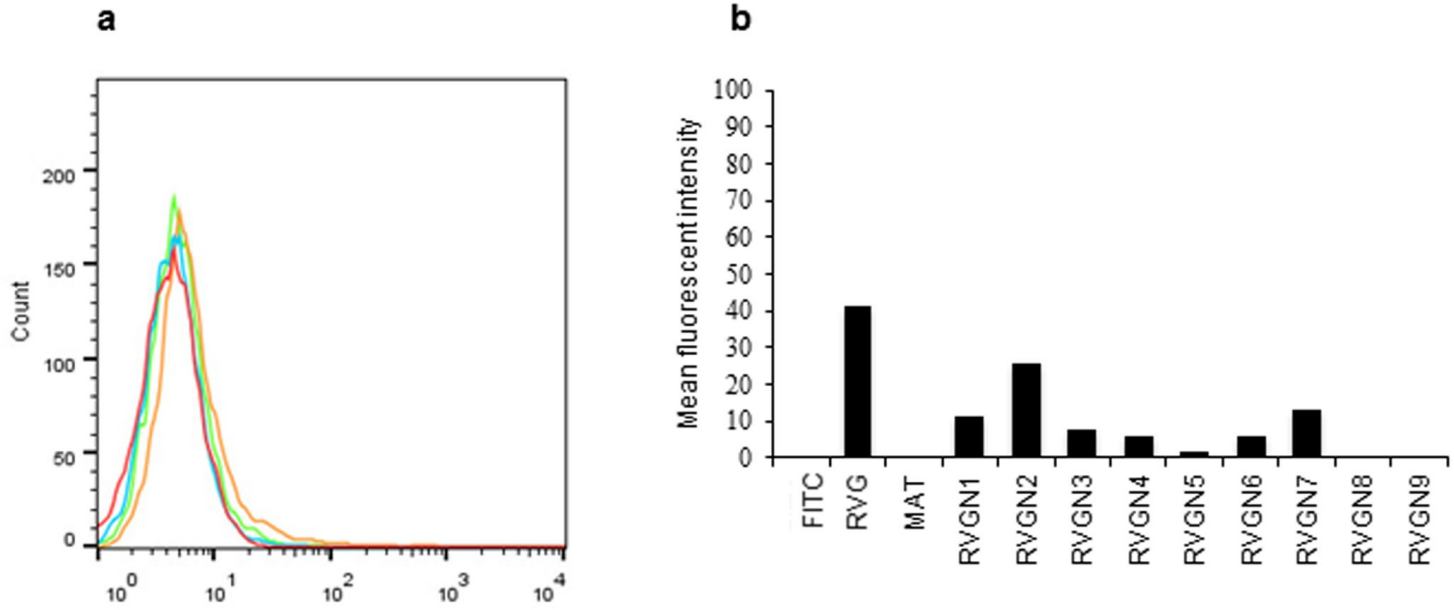
Supplementary Figure 2: **MAT peptide does not bind to M17 cells.** (**a**) M17 cells were incubated with increasing concentrations of biotinylated-MAT peptide: 0.1 µM (turquoise), 1 µM (orange), 2.5 µM (light green), 5 µM (dark green), 10 µM (mauve) and 20 µM (purple) or FITC alone (red), and stained with avidin-FITC before analysis by flow cytometry. (**b**) Representative histogram with the mean fluorescence intensity of the peptides bound to M17 cells is shown.



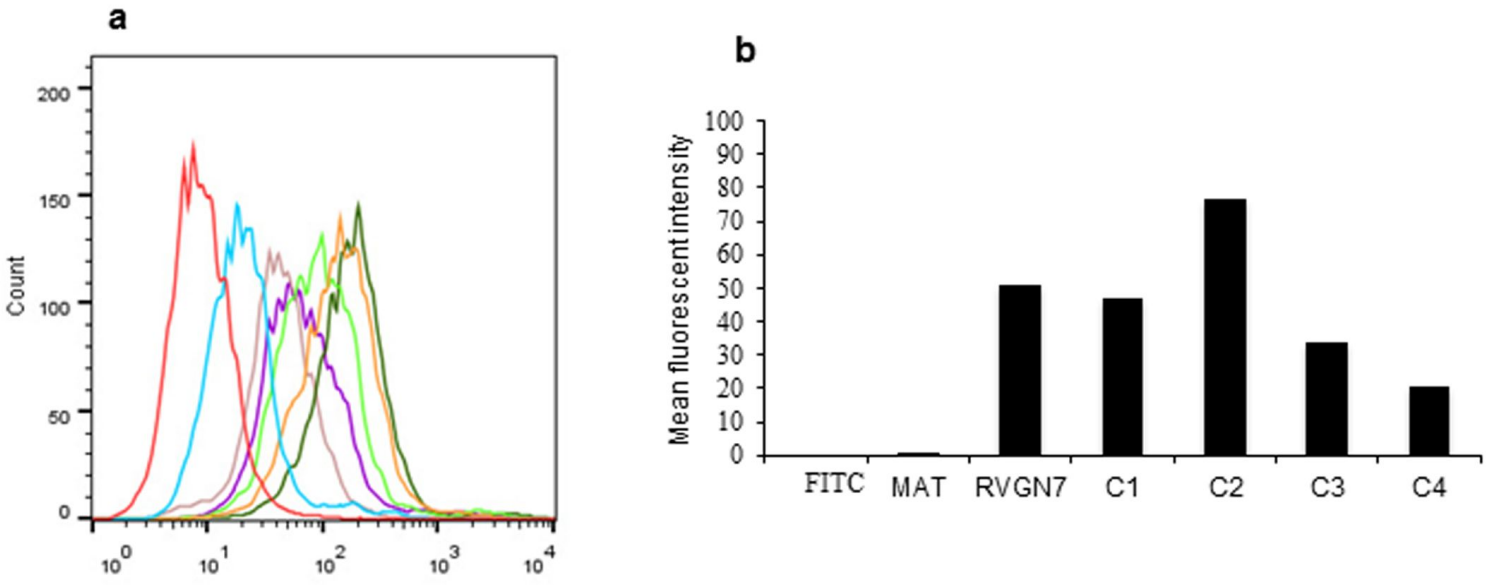
Supplementary Figure 3: **RVGN7 peptide binds to M17 cells in a dose-dependant manner.** (**a**) M17 cells were incubated increasing concentrations of biotinylated-RVGN7 peptide: 0.1 µM (turquoise), 1 µM (yellow), 2.5 µM (teal), 5 µM (purple), 10 µM (mauve), 20 µM (dark green), 10µM MAT (orange) or FITC alone (red), and stained with avidin-FITC before analysis by flow cytometry. (**b**) Histogram representing the mean fluorescence intensity of peptides bound to M17 cells is shown.



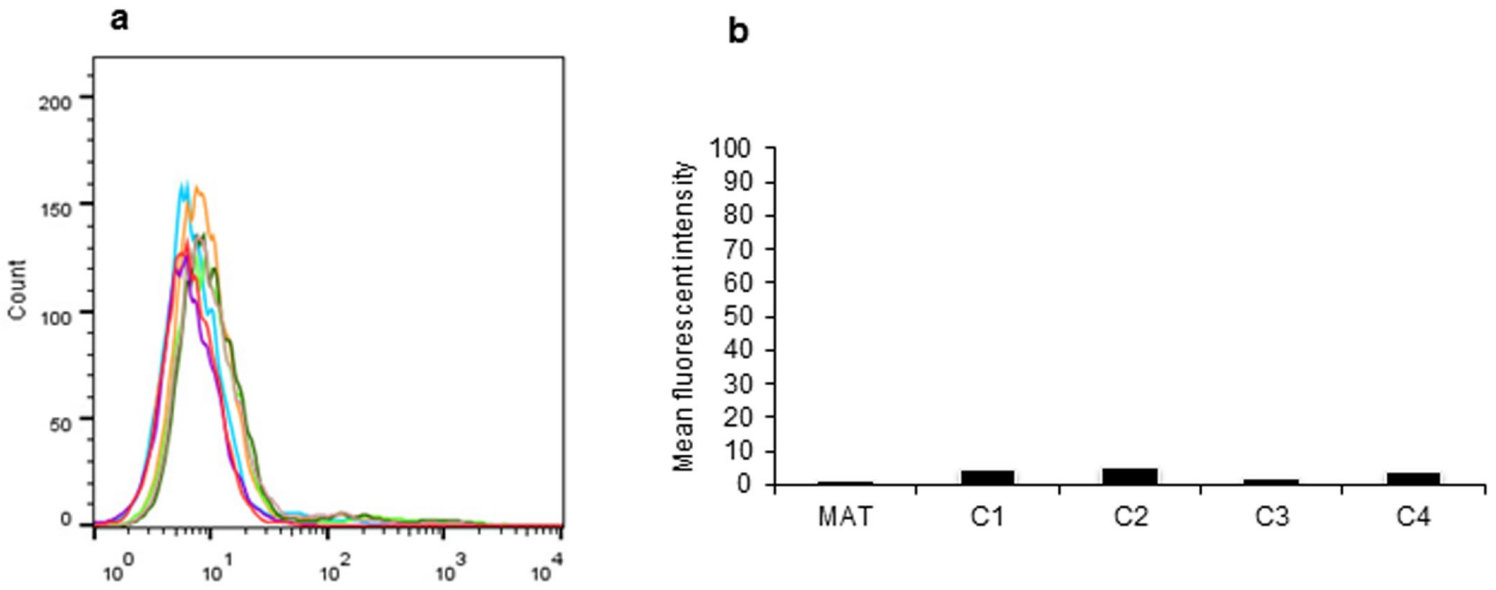
Supplementary Figure 4: RVG-29 derived peptides do not bind to S2103 cells. (**a**) S2103 cells were incubated with 10 µM of biotinylated-peptide solutions of RVG-29 (dark grey), MAT (black), RVGN1 (yellow), RVGN2 (teal), RVGN3 (purple), RVGN4 (mauve), RVGN5 (dark green), RVGN6 (light green), RVGN7 (orange), RVGN8 (turquoise), RVGN9 (red) or FITC alone (light grey), and stained with avidin-FITC before analysis by flow cytometry. (**b**) Histogram representing the mean fluorescence intensity of the peptides bound to S2103 cells is shown.



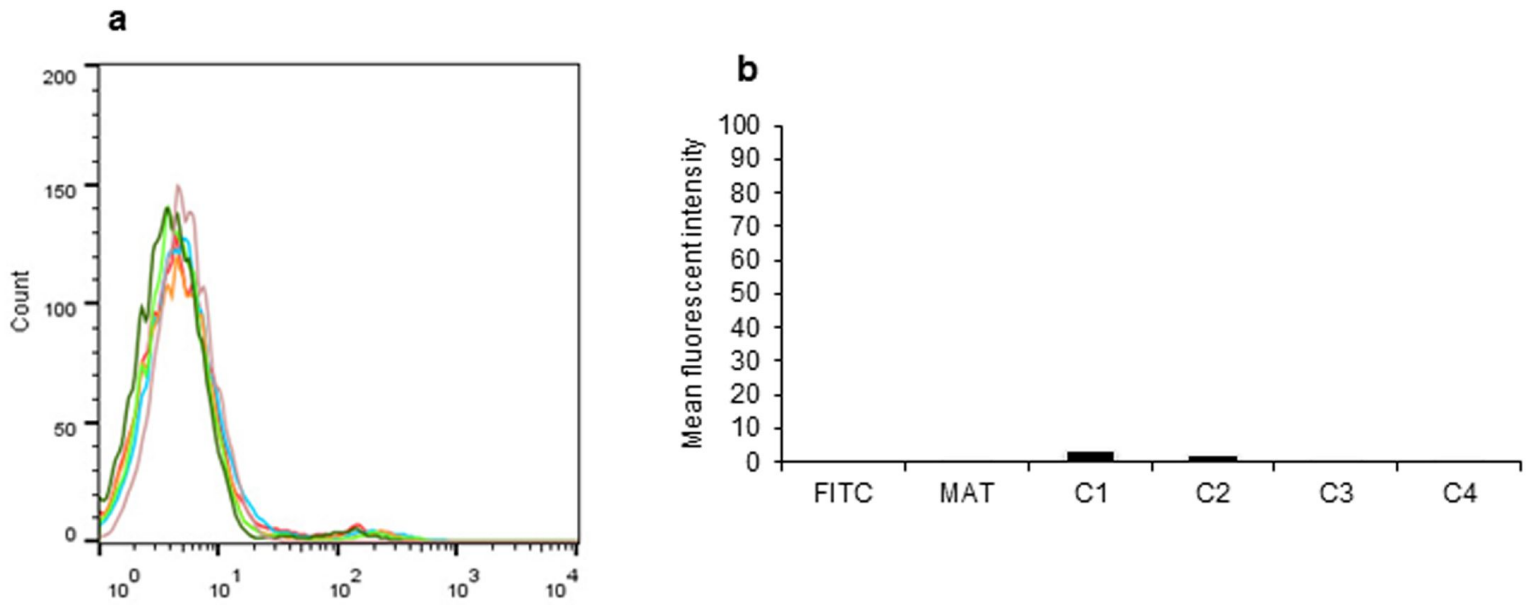
Supplementary Figure 5: RVG-29 derived peptides do not bind to L929 cell line. (**a**) L929 cells were incubated with 10 µM of biotinylated-peptide solutions of RVG-29 (orange), MAT (turquoise), RVGN7 (green) or FITC alone (red), and stained with avidin-FITC before analysis by flow cytometry. (**b**) Histogram representing the mean fluorescence intensity of the peptides bound to L929 cells is shown.



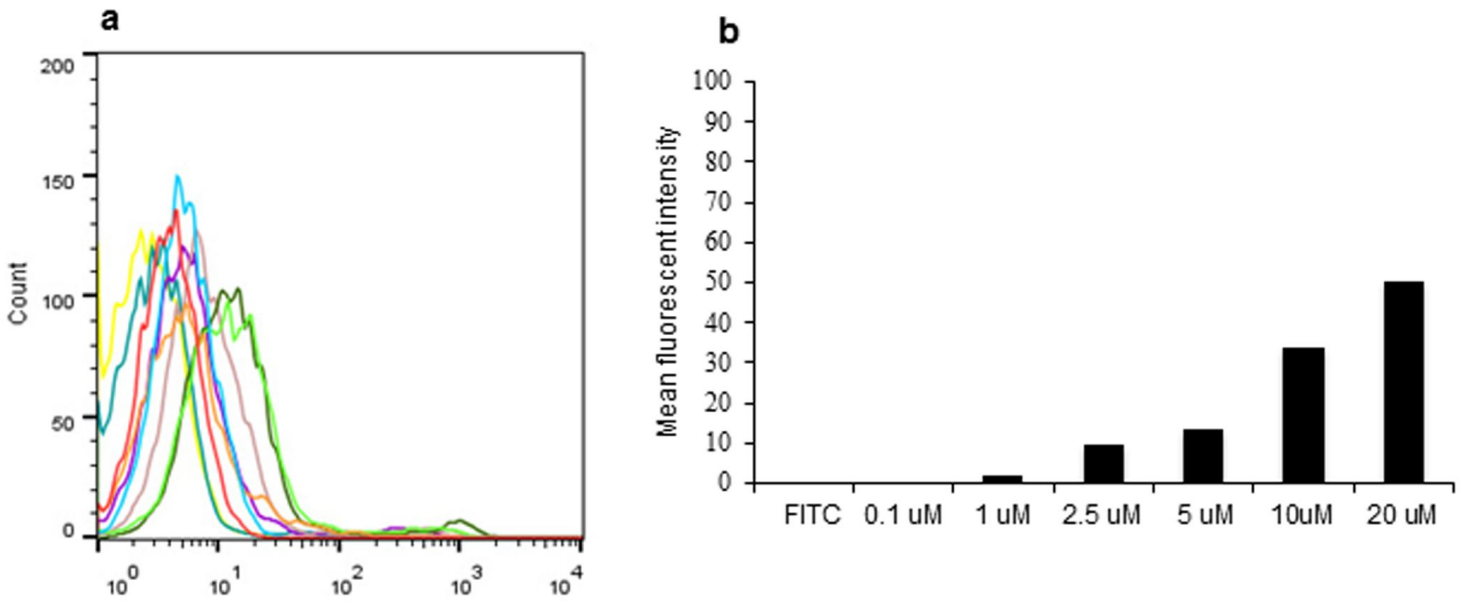
Supplementary Figure 6: C-terminal truncated, RVGN7 derived peptides bind to PC12 cell line. (**a**) PC12 cells were incubated with 10 µM of biotinylated-peptide solutions of RVGN7 (orange), MAT (turquoise), C1 (light green), C2 (dark green), C3 (mauve), C4 (purple) or FITC alone (red), and stained with avidin-FITC before analysis by flow cytometry. (**b**) Histogram representing the mean fluorescence intensity of the peptides bound to PC12 cells is shown.



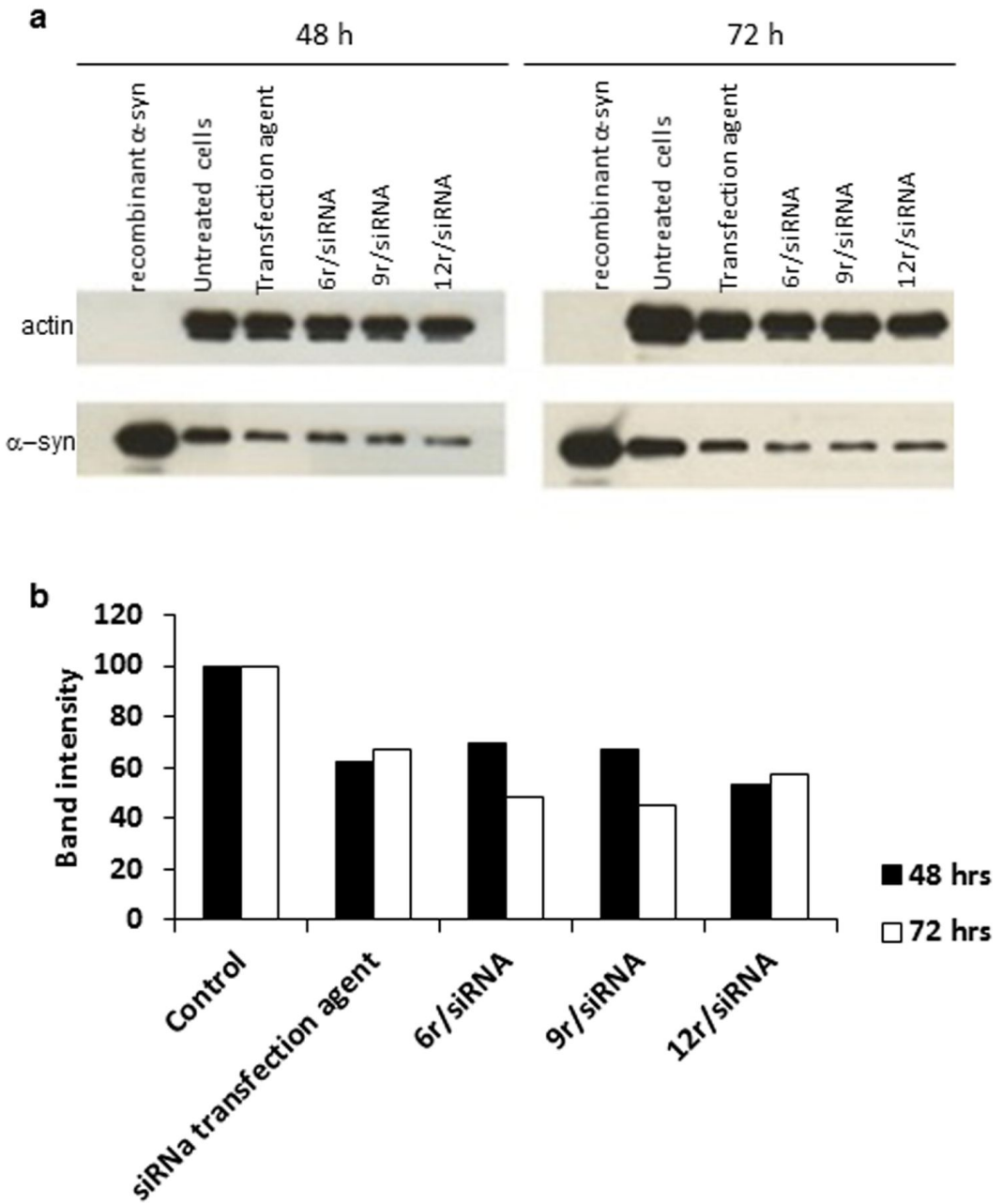
Supplementary Figure 7: **C-terminal truncated, RVGN7 derived peptides do not bind to L929 cell line.** (**a**) L929 cells were incubated with 10 µM of biotinylated-peptide solutions of MAT (purple), C1 (dark green), C2 (light green), C3 (orange), C4 (turquoise) or FITC (red), and stained with avidin-FITC before analysis by flow cytometry. (**b**) Histogram representing the mean fluorescence intensity of the peptides bound to L929 cells is shown.



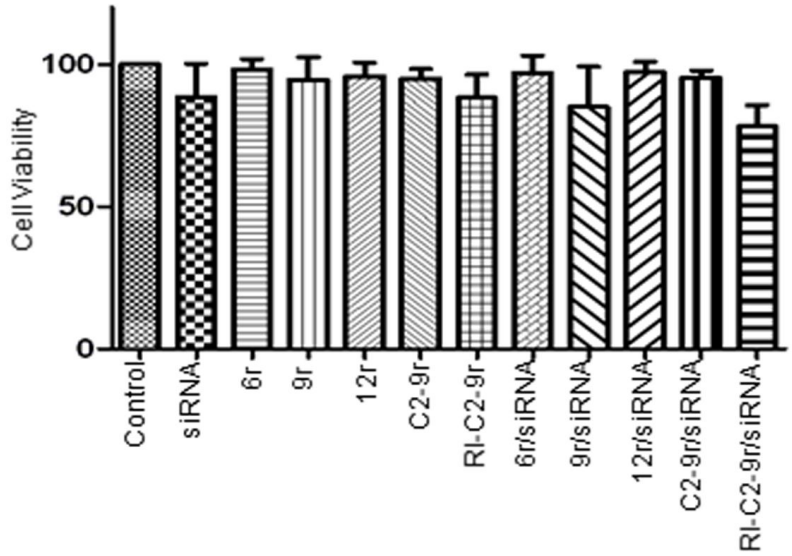
Supplementary Figure 8: **C-terminal truncated, RVGN7 derived peptides do not bind to S2103 cell line.** (**a**) S2103 cells were incubated with 10 µM of biotinylated-peptide solutions of MAT (dark green), C1 (light green), C2 (orange), C3 (turquoise), C4 (red) or FITC alone (mauve), and stained with avidin-FITC before analysis by flow cytometry. (**b**) Histogram representing the mean fluorescence intensity of the peptides bound to S2103 cells is shown.



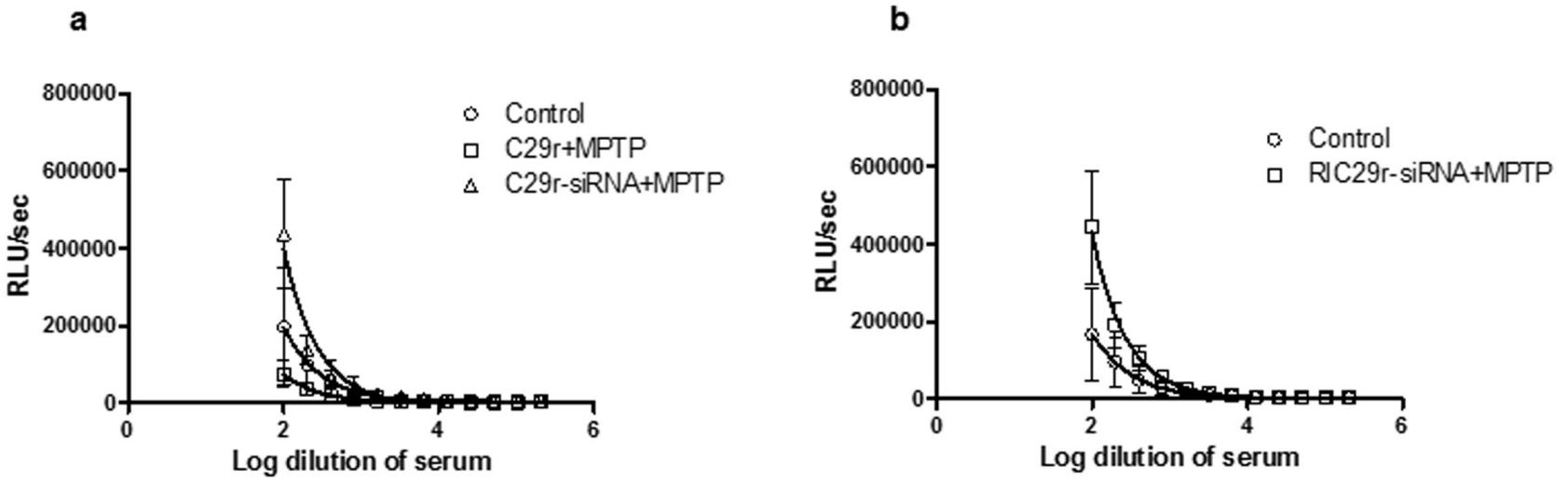
Supplementary Figure 9: **C2 peptide binds to M17 cells in a dose-dependent manner.** (**a**) M17 cells were incubated with with increasing concentrations of biotinylated-C2 peptide: 0.1 µM (light green), 1 µM (dark green), 2.5 µM (mauve), 5 µM (purple), 10 µM (teal), 20 µM (yellow) or FITC alone (turquoise), and stained with avidin-FITC before analysis by flow cytometry. (**b**) Histogram representing the mean fluorescence intensity of the peptides bound to M17 cells is shown.



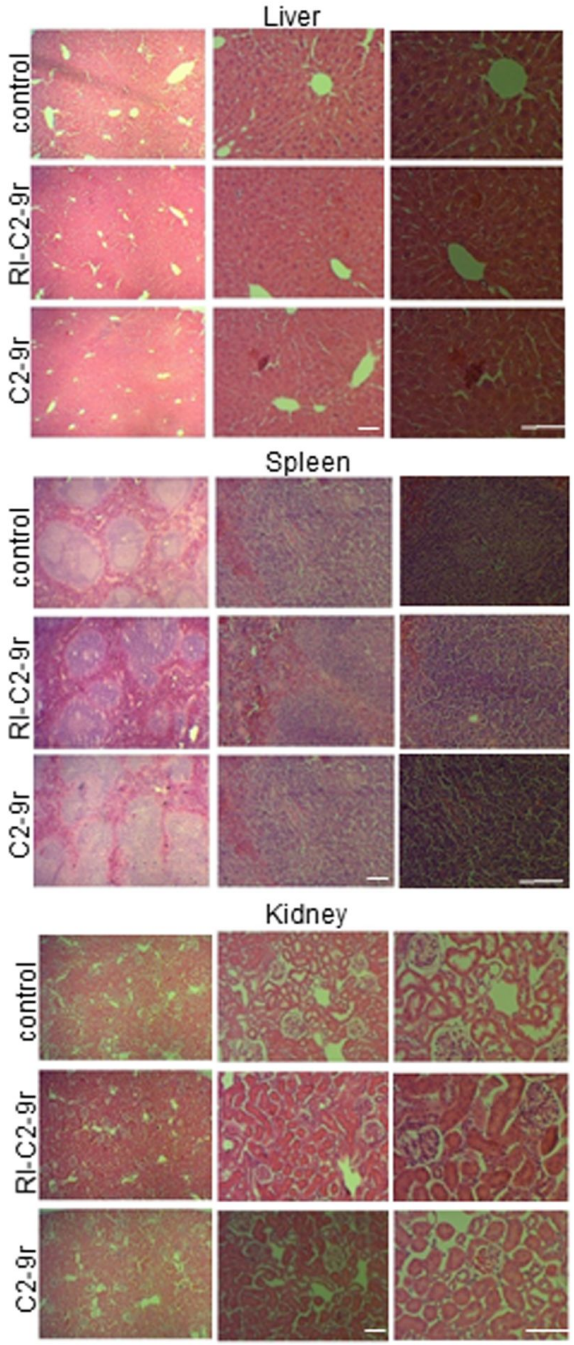
Supplementary Figure10: Silencing of α-syn by siRNA transfected by poly-arginines : Proteins were extracted from cells at 48 h and 72 hrs after transfection with siRNA complexed with polyarginine peptides (6r, 9r and 12r) or siRNA transfected with commercial media, as control. The α-syn expression was evaluated by western blotting (**a**) and the expression level was quantified and normalized to beta-actin (**b**).



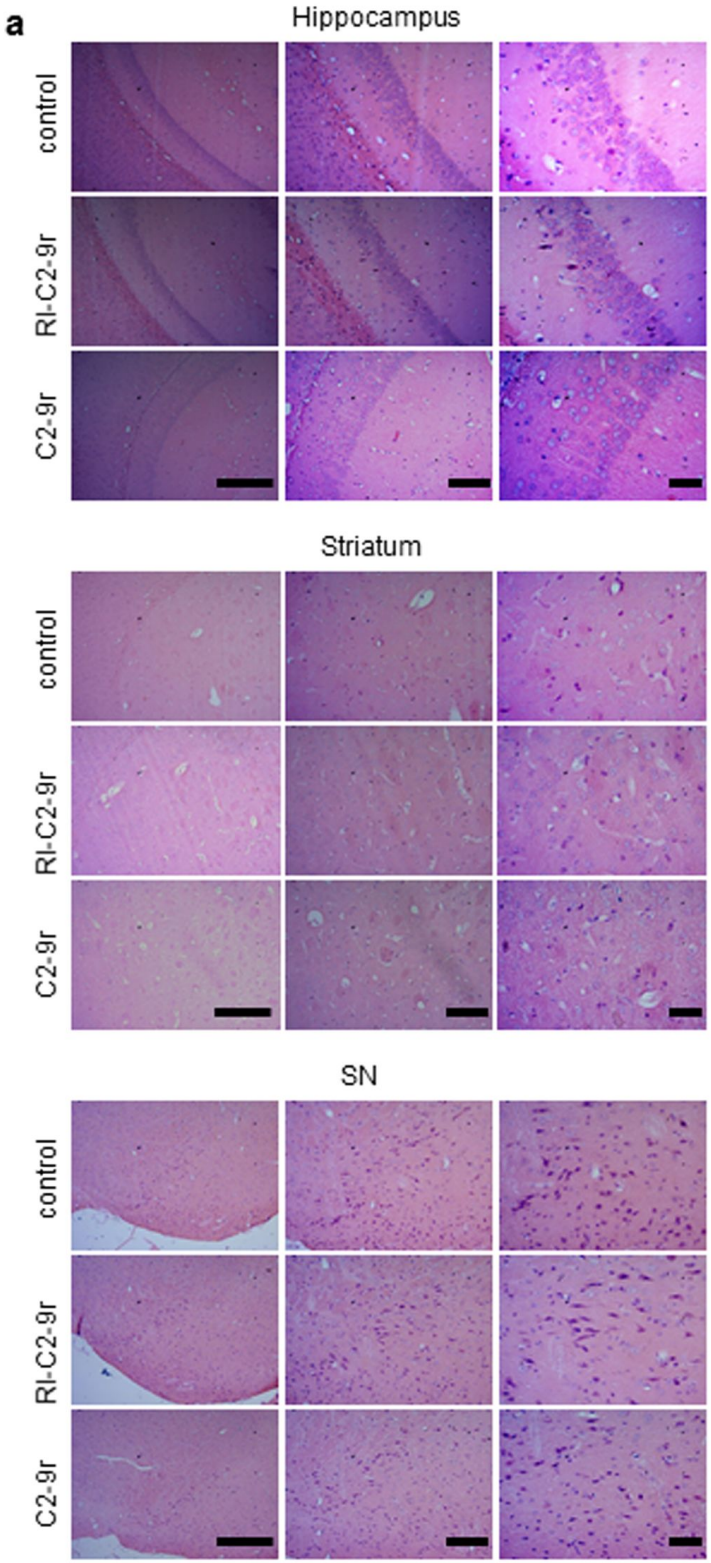
Supplementary Figure 11: **Knockdown of *SNCA* does not alter cell viability.** The viability of M17 cells was assessed using MTT assay after 72 h of incubation with siRNA/vector complexes or with the vectors alone or siRNA alone. There was no significant difference in cell viability between treated and untreated cells.

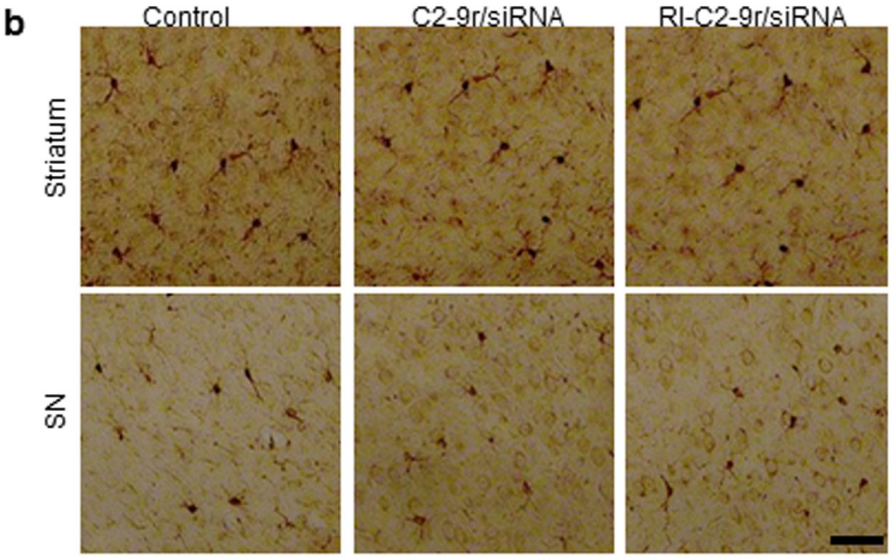


Supplementary Figure 12: **Vectors C2-9r and RI-C2-9r do not induce immune response.** Mice were injected intravenously with siRNA complexed with either C29r or RIC29r vectors or with PBS as negative control and serum samples collected after 21 days were tested for the presence of antibodies to C29r (**a**) or RIC29r (**b**) by ELISA. No significant differences were observed in the immune response between control and vector treated groups.

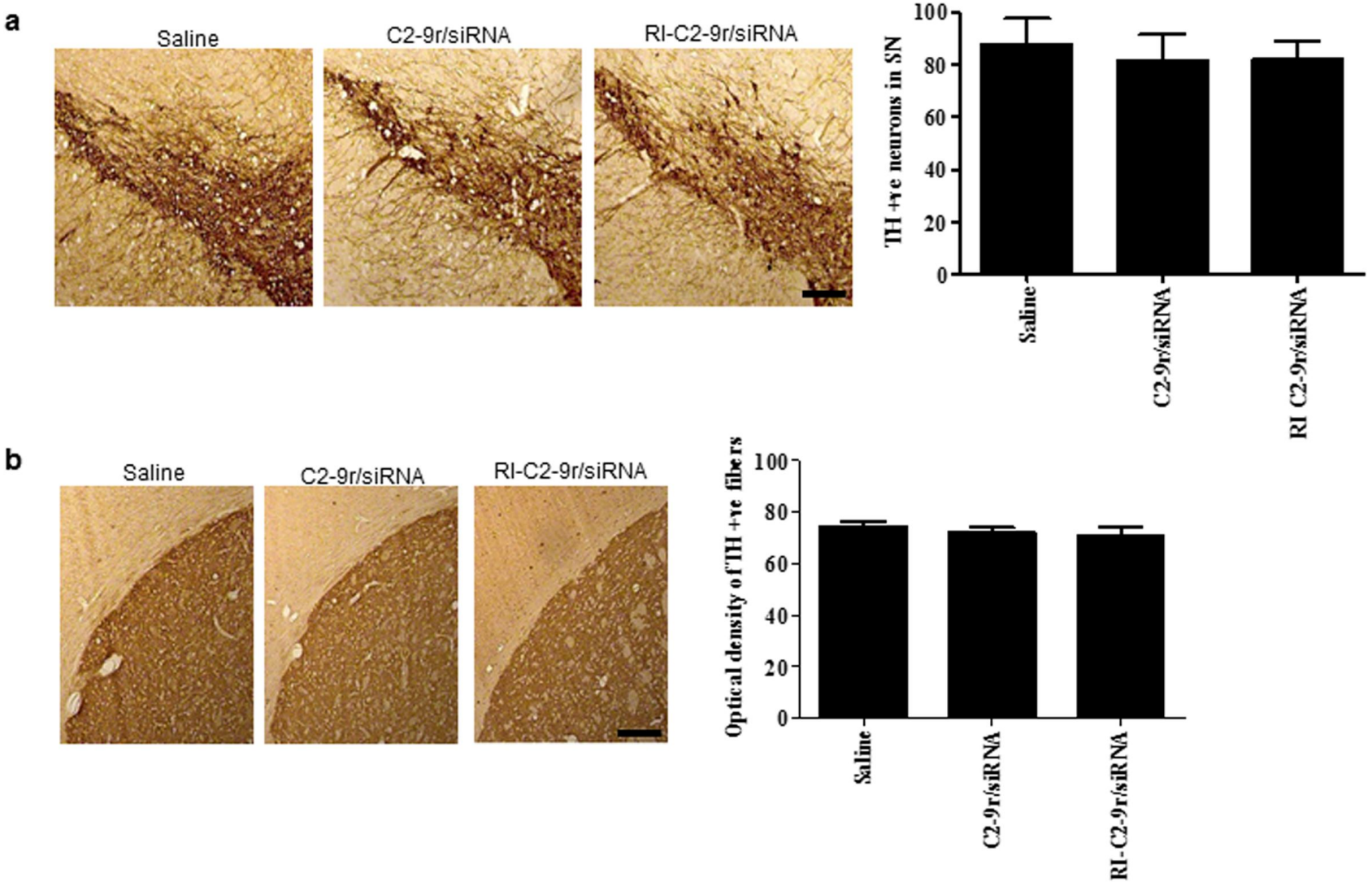


Supplementary Figure 13: **Vectors C2-9r and RI-C2-9r do not induce cytotoxicity.** Mice were injected intravenously with siRNA/vector complexes or saline (control) and sacrificed 48 h post-injection after which the liver, spleen and kidneys were collected and post-fixed. The tissues were processed for hematoxylin and eosin immunostaining. No pathological lesions were detected in the liver, spleen or kidney that could be suggestive of toxicity. Representative images at lower and higher magnifications are shown. Scale bars are 50 µm.





Supplementary Figure 14: **Vectors C2-9r and RI-C2-9r do not induce cytotoxicity within the brain.** (**a**) Mice were injected intravenously with siRNA/vector complexes or saline (control) and sections at the level of substantia nigra, striatum and hippocampus within the brain were processed for hematoxylin and eosin immunostaining. No abnormal neuronal morphology or pathological lesions were observed that is indicative of neurotoxicity. Representative images at lower and higher magnifications are shown. Scale bars are 50, 20 and 10 µm. (**b**) Immunohistochemistry of ionized calcium binding adaptor molecule-1 (Iba-1) was carried out in the substantia nigra (SN) and striatum of mice that had been intravenously injected withwith siRNA/vector complexes or saline (control) to observe microglial activation. No remarkably activated or hypertrophied microglia were observed in the SN and striatum of siRNA/vectors or control mice. Scale bar is 20 µm.



Supplementary Figure 15: **siRNA/vector complexes do not induce TH+ neuronal cell death.** TH immunohistochemistry was carried out in mice that had been intravenously injected with **siRNA/vectors or saline (control)** to observe the loss of TH positive (TH+ve) dopaminergic neurons in SN and dopaminergic axonal loss in the striatum. Profound expression of TH+ve neurons (**a**) and striatal fibers (**b**) were observed in siRNA/vectors and control group mice. Moreover, quantitative analysis of TH+ve neurons and fibers showed no significant difference between the siRNA/vectors and control mice. Scale bar is 500 μm.