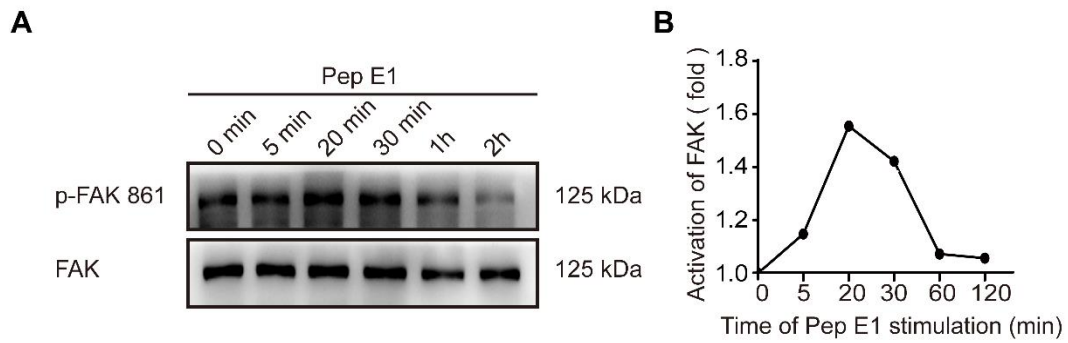
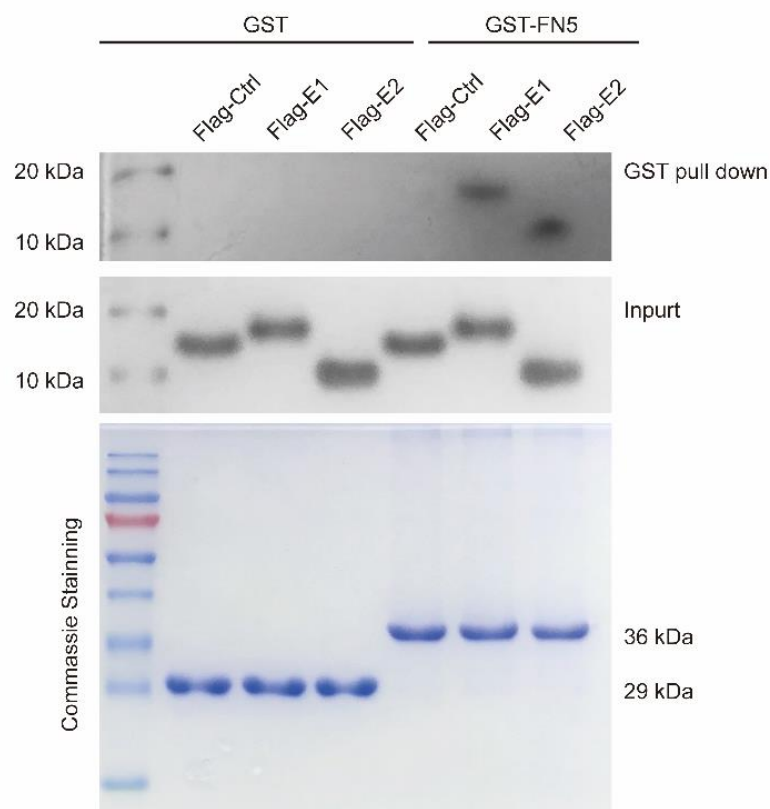


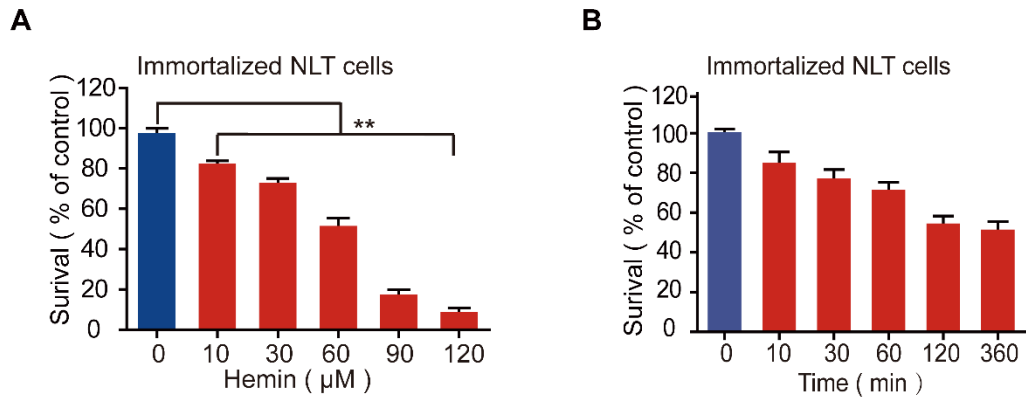
**Figure S1. Pep Ctrl does not activate downstream pathways of Netrin-1.** (A) Cortical neurons were stimulated with gradient concentration of Pep Ctrl. Cell lysates were incubated with the indicated antibodies to detect the phosphorylation of FAK, SFK and ERK. (B) Quantifications of peptide induced FAK PY861 in neurons.  $n = 3$ . (C) Quantifications of peptide induced SFK PY418 in neurons.  $n = 3$ . (D) Quantifications of peptide induced ERK PY202/204 in neurons.  $n = 3$ . Data are presented as the means  $\pm$  SEM. One-way ANOVA was used for all statistical analyses shown in this figure (ns, not significant).



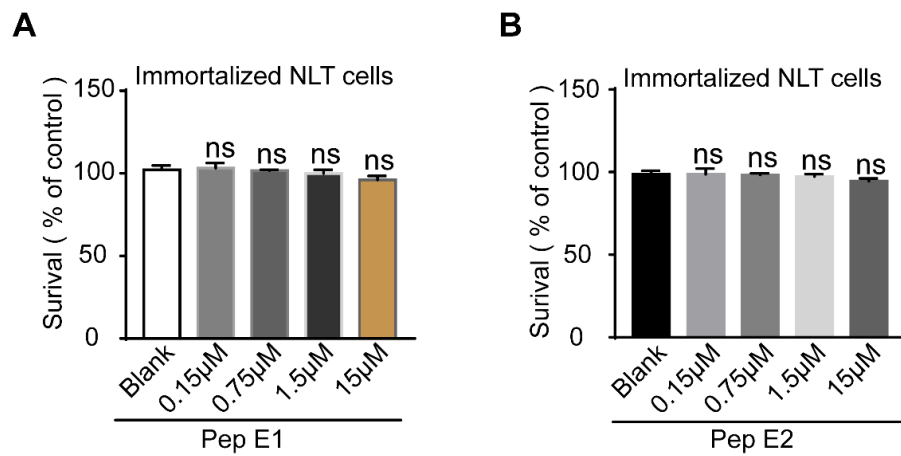
**Figure S2. Pep E1 increased FAK tyrosine phosphorylation in a time-dependent manner.**  
(A) Cortical neurons (DIV3) were stimulated with peptide E1 for the indicated time. Cell lysates were incubated with the specially antibody to detect the phosphorylation of FAK Y861. (B) Quantifications of peptide E1 induced FAK PY861 in neurons were shown in (A). n = 3.



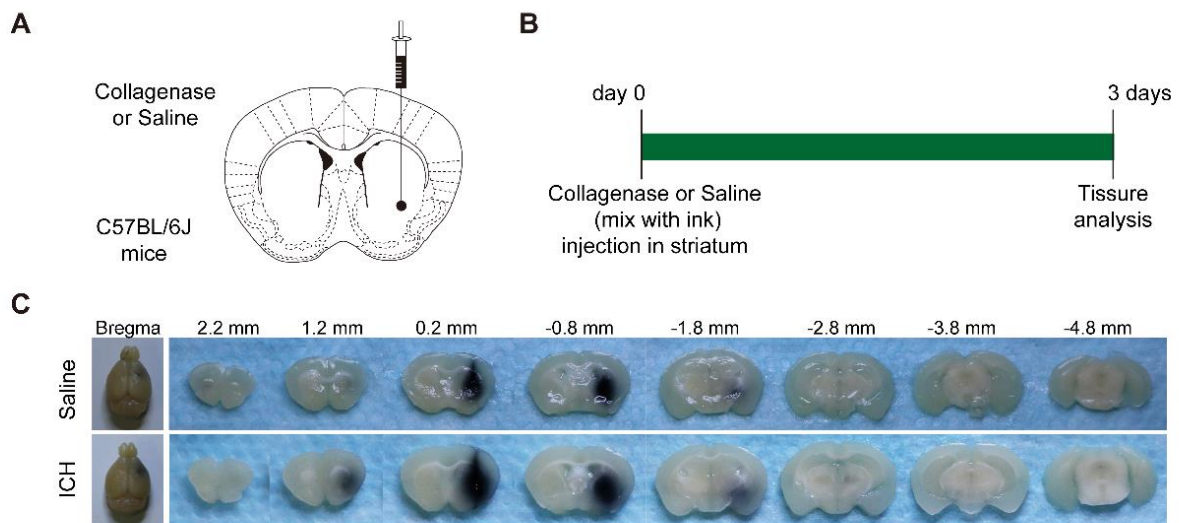
**Figure S3. Pep E1 and E2 direct binding with DCC's FN5 domain.** Synthesized N-terminal added Flag sequence peptides Flag-Ctrl, Flag-E1 and Flag-E2 were incubated with the GST-DCC-FN5 and GST proteins respectively, then evaluated by SDS-PAGE.



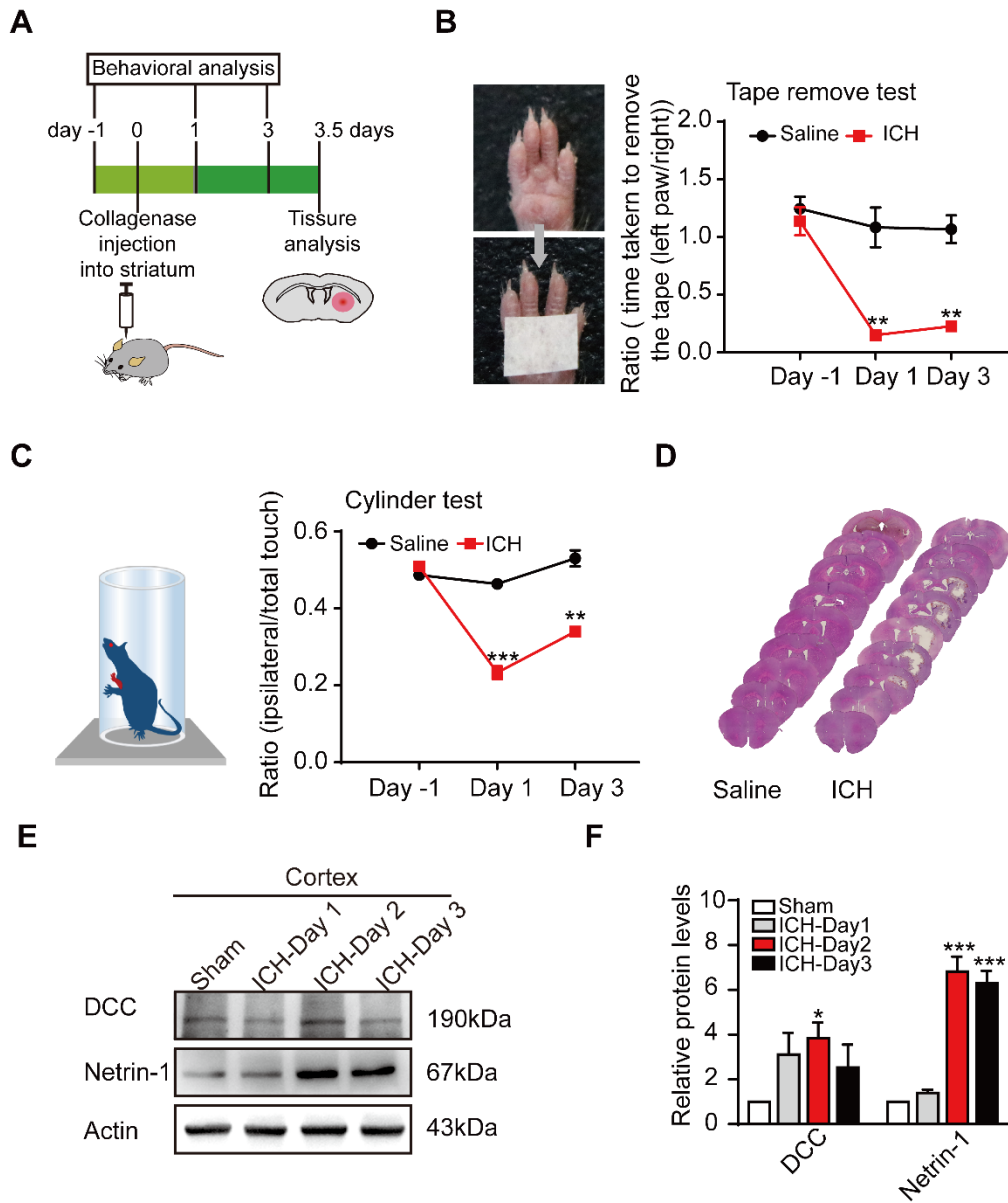
**Figure S4. Hemin induced a dose and time-dependent neurotoxicity in cultured NLT cells.** (A) CCK8 assays showed that hemin induces dose-dependent death of NLT cells.  $n = 4$ . (B) CCK8 assays showed that hemin induces time-dependent death of NLT cells.  $n = 4$ . Data are presented as the means  $\pm$  SEM. One-way ANOVA was used for all statistical analyses shown in this figure (\*\* $p < 0.001$ , ns, not significant).



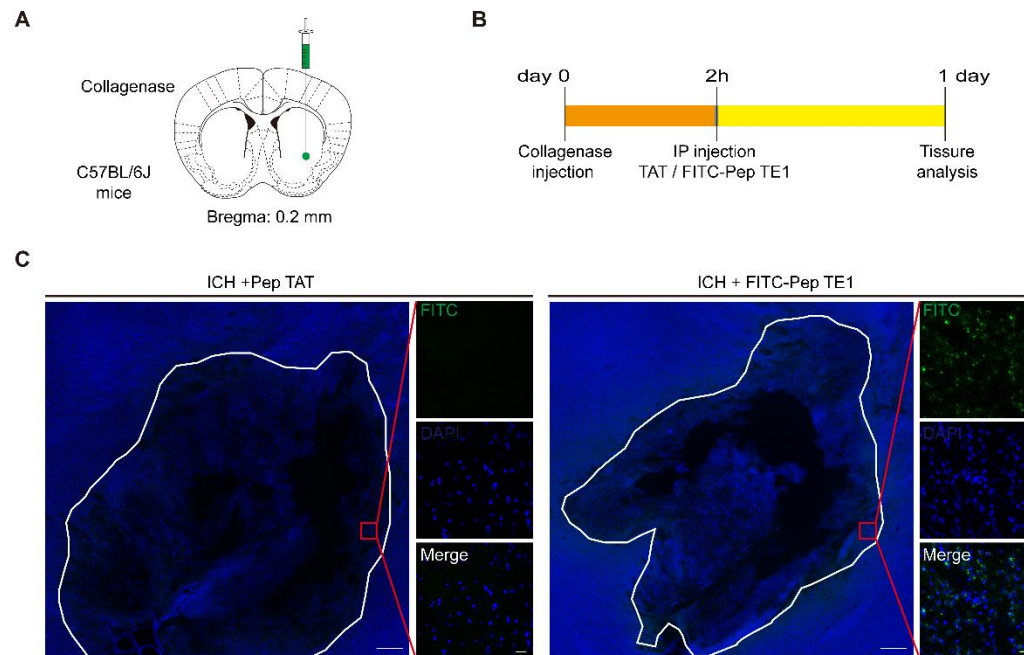
**Figure S5. The peptides don't affect cell viability in NLT cells.** (A) CCK8 assays showed that series dose of Pep E1 has not impact on cell viability.  $n = 4$ . (B) CCK8 assays showed that series dose of Pep E2 does not affect cell viability.  $n = 4$ . Data are presented as the means  $\pm$  SEM. One-way ANOVA was used for all statistical analyses shown in this figure (ns, not significant).



**Figure S6. Collagenase injection volume is measured in mouse model of ICH.** (A) Schematic of strategies used to inject Collagenase and Saline in C57 mice. (B) Experimental timeline. (C) Representative images showing ink area were similar in the Saline and ICH brain.

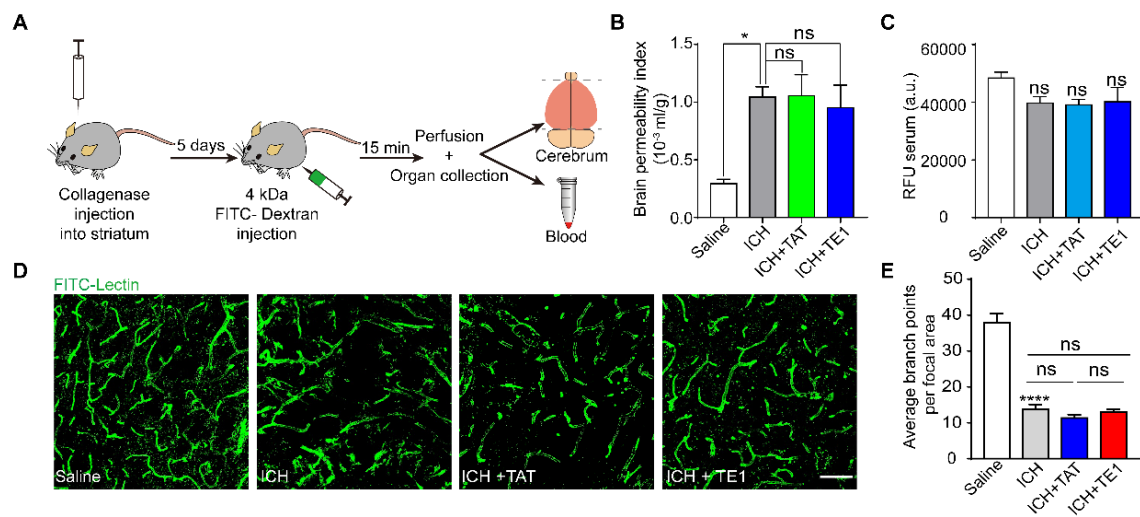


**Figure S7. The protein levels of Netrin-1 and DCC is increased following experimental ICH.** (A) Schematic of the experimental paradigm of modeling ICH in mice. (B-C) Intracerebral hemorrhage in mice were shown neurological deficit by an adhesive tape remove test (B) and cylinder test (C).  $n = 3$ . (D) Representative HE stained brain sections at 3 days after ICH built. Scale bar, 1 mm. (E) Immunoblot analysis of Netrin-1 and DCC in the ipsilateral cortex at different time points after ICH. (F) Quantitative analysis of the western blot results shown in (E), respectively ( $*p < 0.05$ ,  $**p < 0.01$ ,  $***p < 0.001$ ; ns, not significant).  $n = 3$ .



**Figure S8. The FITC signal of FITC labeled peptide TE1 was detectable in the hematoma region after ICH.** (A) Schematic of strategies used to inject Collagenase and Saline in C57 mice. (B) Experimental timeline. (C) Representative images detective FITC signals of hematoma region. Scale bars, 200 and 10  $\mu$ m respectively.





**Figure S9. Netrin-1 derived peptide E1 no effected on the disruption of the blood-brain barrier permeability and microvessel after ICH.** (A) Illustrations of in vivo BBB permeability assay using fluorescent tracers in an intracerebral hemorrhage model. (B) Homogenized ipsilateral hemisphere (free of the olfactory lobes, cerebellum and hindbrain) were utilized to obtain dextran permeability by measuring the raw fluorescence units (RFUs) on a microplate reader. Set the gain to optimal and use excitation/emission (nm) values of 490/520 for FITC dye and start the measurement to obtain the RFUs. Permeability Index (mL/g) = (Tissue RFUs/g tissue weight) / (Serum RFUs/mL serum). n = 3. (C) Serum fluorescence values (arbitrary units—a.u.) indicate equivalent tracer absorption between treat with/without TE1 mice. n = 3. (D) Representative confocal microscopy analysis of lectin-positive microvessels (green) in mice treat with/without TE1 at 5 days after ICH. Scale bar, 50  $\mu$ m. (E) Quantitative analyses for the total number of branch points in the focal area between with/without TE1 treatment groups of the perihematomal region. n = 4.

## Supplementary Table 1

| Figure     | Measure       | Value                       | Comparisons                 | Analysis | Statistic value | P value  |
|------------|---------------|-----------------------------|-----------------------------|----------|-----------------|--|
| Figure. 2C | protein level | Mock = 0.5027               | Mock (n = 3) VS             |          |                 | Mock vs. NTN1-WT: p = 0.0123                         |
|            |               | Netrin-1 = 0.9411           | Netrin-1 (n = 3)            | One-way  | F (2, 6) =      | Mock vs. NTN1- (Δ407-443): p                         |
|            |               | Netrin-1-(Δ407-443) = 0.627 | Netrin-1-(Δ407-443) (n = 3) | ANOVA    | 9.728           | = 0.0123<br>NTN1-WT vs. NTN1- (Δ407-443) : p= 0.0502 |
| Figure. 2E | protein level | GST = 0.2912                | GST (n = 3) VS              | One-way  | F (2, 6) =      | GST vs GST-EGF3: p = 0.022                           |
|            |               | GST-EGF3 = 0.6181           | GST-EGF3 (n = 3)            | ANOVA    | 47.77           | GST vs Netrin-1: p = 0.002                           |
|            |               | Netrin-1 = 0.8123           | Netrin-1 (n = 3)            |          |                 | GST-EGF3 vs Netrin-1: p = 0.0263                     |
| Figure. 2F | protein level | GST = 0.6445                | GST (n = 3) VS              | One-way  | F (2, 6) =      | GST vs GST-EGF3: p = 0.0249                          |
|            |               | GST-EGF3 = 0.8867           | GST-EGF3 (n = 3)            | ANOVA    | 16.42           | GST vs Netrin-1: p = 0.0032                          |
|            |               | Netrin-1 = 1.019            | Netrin-1 (n = 3)            |          |                 | GST-EGF3 vs Netrin-1: p = 0.1930                     |
| Figure. 2G | protein level | GST = 0.3535                | GST (n = 3) VS              | One-way  | F (2, 6) =      | GST vs GST-EGF3: p = 0.0269                          |
|            |               | GST-EGF3 = 0.7297           | GST-EGF3 (n = 3)            | ANOVA    | 16.25           | GST vs Netrin-1: p = 0.0032                          |
|            |               | Netrin-1 = 0.9449           | Netrin-1 (n = 3)            |          |                 | GST-EGF3 vs Netrin-1: p = 0.1813                     |
| Figure. 3D | protein level | Mock = 0.3546               | Mock (n = 3) VS             |          |                 | Mock vs 0.2 μM: p = 0.9999                           |
|            |               | 0.2 μM = 0.3569             | 0.2 μM (n = 3)              | One-way  | F (3, 8) =      | Mock vs 1.5 μM: p = 0.0309                           |
|            |               | 1.5 μM = 0.8771             | 1.5 μM (n = 3)              | ANOVA    | 4.704           | Mock vs 12 μM: p = 0.9126                            |
|            |               | 12 μM = 0.4401              | 12 μM (n = 3)               |          |                 |  |
| Figure. 3E | protein level | Mock = 0.3793               | Mock (n = 3) VS             |          |                 | Mock vs 0.2 μM: p = 0.9983                           |
|            |               | 0.2 μM = 0.3584             | 0.2 μM (n = 3)              | One-way  | F (3, 8) =      | Mock vs 1.5 μM: p = 0.0471                           |
|            |               | 1.5 μM = 0.8537             | 1.5 μM (n = 3)              | ANOVA    | 3.996           | Mock vs 12 μM: p = 0.8420                            |
|            |               | 12 μM = 0.4884              | 12 μM (n = 3)               |          |                 |  |
| Figure. 3F | protein level | Mock = 0.508                | Mock (n = 3) VS             |          |                 | Mock vs 0.2 μM: p = 0.9941                           |
|            |               | 0.2 μM = 0.533              | 0.2 μM (n = 3)              | One-way  | F (3, 8) =      | Mock vs 1.5 μM: p = 0.9942                           |
|            |               | 1.5 μM = 0.5329             | 1.5 μM (n = 3)              | ANOVA    | 0.0379          | Mock vs 12 μM: p = 0.9739                            |
|            |               | 12 μM = 0.5501              | 12 μM (n = 3)               |          |                 |  |
| Figure. 3G | protein level | Mock = 0.4042               | Mock (n = 3) VS             |          |                 | Mock vs 0.2 μM: p = 0.6529                           |
|            |               | 0.2 μM = 0.569              | 0.2 μM (n = 3)              | One-way  | F (3, 8) =      | Mock vs 1.5 μM: p = 0.0255                           |
|            |               | 1.5 μM = 0.9628             | 1.5 μM (n = 3)              | ANOVA    | 5.096           | Mock vs 12 μM: p = 0.0437                            |
|            |               | 12 μM = 0.9009              | 12 μM (n = 3)               |          |                 |  |
| Figure. 3H | protein level | Mock = 0.426                | Mock (n = 3) VS             | One-way  | F (3, 8) =      | Mock vs 0.2 μM: p = 0.7523                           |
|            |               | 0.2 μM = 0.518              | 0.2 μM (n = 3)              | ANOVA    | 8.01            | Mock vs 1.5 μM: p = 0.0104                           |

|                                  |                         |                      |                          |                  |  |                                  |
|----------------------------------|-------------------------|----------------------|--------------------------|------------------|--|----------------------------------|
| Figure. 3I                       | protein level           | 1.5 $\mu$ M = 0.8684 | 1.5 $\mu$ M (n = 3)      | One-way<br>ANOVA | F (3, 8) =<br>4.889  | Mock vs 12 $\mu$ M: p = 0.0158   |
|                                  |                         | 12 $\mu$ M = 0.8353  | 12 $\mu$ M (n = 3)       |                  |  |                                  |
|                                  |                         | Mock = 0.3051        | Mock (n = 3) VS          |                  |  | Mock vs 0.2 $\mu$ M: p = 0.3252  |
|                                  |                         | 0.2 $\mu$ M = 0.6627 | 0.2 $\mu$ M (n = 3)      |                  |  | Mock vs 1.5 $\mu$ M: p = 0.0190  |
|                                  |                         | 1.5 $\mu$ M = 1.105  | 1.5 $\mu$ M (n = 3)      |                  |  | Mock vs 12 $\mu$ M: p = 0.0499   |
| Figure. 3K<br>DCC <sup>+/-</sup> | protein level           | 12 $\mu$ M = 0.9556  | 12 $\mu$ M (n = 3)       | One-way<br>ANOVA | F(3, 8) =<br>5.586   |                                  |
|                                  |                         | Pep Ctrl = 0.2937    | Pep Ctrl (n = 3) VS      |                  |  | Pep ctrl vs Netrin-1: p = 0.0153 |
|                                  |                         | Netrin-1 = 0.9328    | Netrin-1 (n = 3)         |                  |  | Pep ctrl vs Pep E1: p = 0.0303   |
|                                  |                         | Pep E1 = 0.8503      | Pep E1 (n = 3)           |                  |  | Pep ctrl vs Pep E1: p = 0.0463   |
| Figure. 3K<br>DCC <sup>-/-</sup> | protein level           | Pep E2 = 0.8005      | Pep E2 (n = 3)           | One-way<br>ANOVA | F(3, 8) =<br>0.3429  |                                  |
|                                  |                         | Pep Ctrl = 0.2927    | Pep Ctrl (n = 3) VS      |                  |  | Pep ctrl vs Netrin-1: p = 0.6786 |
|                                  |                         | Netrin-1 = 0.5313    | Netrin-1 (n = 3)         |                  |  | Pep ctrl vs Pep E1: p = 0.7825   |
|                                  |                         | Pep E1 = 0.4887      | Pep E1 (n = 3)           |                  |  | Pep ctrl vs Pep E1: p = 0.8434   |
| Figure. 4B<br>DCC                | protein level           | Pep E2 = 0.4615      | Pep E2 (n = 3)           | One-way<br>ANOVA | F(4, 10) =<br>12.79  |                                  |
|                                  |                         | Sham = 1             | Sham (n = 3) VS          |                  |  | Sham vs Hemin-2h: p = 0.7397     |
|                                  |                         | Hemin-2h = 1.963     | Hemin-2h (n = 3)         |                  |  | Sham vs Hemin-6h: p = 0.0008     |
|                                  |                         | Hemin-6h = 6.563     | Hemin-6h (n = 3)         |                  |  | Sham vs Hemin-12h: p = 0.0028    |
|                                  |                         | Hemin-12h = 5.703    | Hemin-12h (n = 3)        |                  |  | Sham vs Hemin-24 h: p = 0.7842   |
| Figure. 4B<br>Netrin-1           | protein level           | Hemin-24h = 1.891    | Hemin-24h (n = 3)        | One-way<br>ANOVA | F(4, 10) =<br>2.873  |                                  |
|                                  |                         | Sham = 1             | Sham (n = 3) VS          |                  |  | Sham vs Hemin-2h: p = 0.9230     |
|                                  |                         | Hemin-2h = 1.976     | Hemin-2h (n = 3)         |                  |  | Sham vs Hemin-6h: p = 0.0419     |
|                                  |                         | Hemin-6h = 5.731     | Hemin-6h (n = 3)         |                  |  | Sham vs Hemin-12h: p = 0.1581    |
|                                  |                         | Hemin-12h = 4.426    | Hemin-12h (n = 3)        |                  |  | Sham vs Hemin-24 h: p = 0.3418   |
| Figure. 4C                       | Survival (% of control) | Hemin-24h = 3.597    | Hemin-24h (n = 3)        | One-way<br>ANOVA | F(3, 12) =<br>0.2046   |                                  |
|                                  |                         | Blank = 97.49        | Blank (n = 4) VS         |                  |  | Blank vs Pep Ctrl: p > 0.9999    |
|                                  |                         | Pep Ctrl = 97.64     | Pep Ctrl (n = 4)         |                  |  | Blank vs Pep E1: p = 0.9110      |
|                                  |                         | Pep E1 = 99.92       | Pep E1 (n = 4)           |                  |  | Blank vs Pep E2: p > 0.9999      |
| Figure. 4D                       | Survival (% of control) | Pep E2 = 97.54       | Pep E2 (n = 4)           | Two-way<br>ANOVA | F (9, 48) =<br>1.728<br>F (3, 48) =<br>2.143<br>F (3, 48) =<br>10.77 |                                  |
|                                  |                         |                      | Hemin+Pep Ctrl (n =4) VS |                  |  | P=0.1083                         |
|                                  |                         |                      | Hemin+Netrin-1 (n =4)    |                  |  | P=0.1071                         |
|                                  |                         |                      | Hemin+Pep E1 (n =4)      |                  |  | P<0.0001                         |
| Figure. 4F                       | % of Cell viability     |                      | Hemin+Pep E2 (n =4)      |                  |  |                                  |
|                                  |                         | Blank = 97.15        | Blank (n = 9)            |                  |  | Hemin vs blank: p = 0.0001       |

|            |                         |                            |                            |               |                    |  |
|------------|-------------------------|----------------------------|----------------------------|---------------|--------------------|--|
| Figure. 4G | % of Dead cells         | Hemin = 56.35              | Hemin (n = 9) VS           |               |                    | Hemin vs Hemin+Netrin-1: p = 0.036     |
|            |                         | Hemin+Netrin-1 = 57.81     | Hemin+Netrin-1 (n = 9)     | One-way ANOVA | F(5, 48) = 24.98   | Hemin vs Hemin+Ctrl: p = 0.3227        |
|            |                         | Hemin+ Ctrl = 57.81        | Hemin+Ctrl (n = 9)         |               |                    | Hemin vs Hemin+E1: p = 0.030           |
|            |                         | Hemin+ E1 = 72.91          | Hemin+E1 (n = 9)           |               |                    | Hemin vs Hemin+E2: p = 0.9997          |
|            |                         | Hemin+E2 = 55.49           | Hemin+E2 (n = 9)           |               |                    |  |
|            |                         | Blank = 2.855              | Blank (n = 9)              |               |                    | Hemin vs blank: p = 0.0001             |
|            |                         | Hemin = 43.85              | Hemin (n = 9)              |               |                    | Hemin vs Hemin+Netrin-1: p = 0.043     |
|            |                         | Hemin+Netrin-1 = 27.37     | Hemin+Netrin-1 (n = 9)     | One-way ANOVA | F(5, 48) = 23.34   | Hemin vs Hemin+Ctrl: p = 0.9961        |
|            |                         | Hemin+ Ctrl = 42.19        | Hemin+Ctrl (n = 9)         |               |                    | Hemin vs Hemin+E1: p = 0.036           |
|            |                         | Hemin+ E1 = 27.09          | Hemin+E1 (n = 9)           |               |                    | Hemin vs Hemin+E2: p = 0.9999          |
| Figure. 4H | Survival (% of control) | Hemin+E2 = 43.92           | Hemin+E2 (n = 9)           |               |                    |  |
|            |                         | Blank = 95                 | Blank (n = 8)              |               |                    | Hemin vs blank: p = 0.0001             |
|            |                         | Hemin = 52.5               | Hemin (n = 8) VS           |               |                    | Hemin vs Hemin+0.15 $\mu$ M: p = 0.048 |
|            |                         | Hemin+0.15 $\mu$ M = 63.01 | Hemin+0.15 $\mu$ M (n = 8) | One-way ANOVA | F(4, 35) = 16.02   | Hemin vs Hemin+ 5 $\mu$ M: p = 0.4669  |
|            |                         | Hemin+ 5 $\mu$ M = 60.69   | Hemin+ 5 $\mu$ M (n = 8)   |               |                    | Hemin vs Hemin+ 10 $\mu$ M: p = 0.9395 |
|            |                         | Hemin+ 10 $\mu$ M = 56     | Hemin+ 10 $\mu$ M (n = 8)  |               |                    |  |
|            |                         | Saline = 101.8             | Saline (n = 6) VS          |               |                    | Sham vs ICH: p = 0.008                 |
|            |                         | ICH = 92.19                | ICH (n = 6)                | One-way       | F(3, 20) =         | Sham vs ICH+TAT: p = 0.001             |
|            |                         | ICH+TAT = 90.4             | ICH+TAT (n = 6)            | ANOVA         | 11.78              | Sham vs. ICH+TE1: p = 0.3297           |
|            |                         | ICH+TE1 = 98.48            | ICH+te1 (n = 6)            |               |                    |  |
| Figure. 5E | Remove tape ratio       |                            | Saline (n = 10)            |               | F (9, 106) = 6.354 | P<0.0001                               |
|            |                         |                            | ICH (n = 6) VS             | Two-way ANOVA | F (3, 106) = 38.08 | P<0.0001                               |
|            |                         |                            | ICH+TAT (n = 6)            |               | F (3, 106) = 45.53 | P<0.0001                               |
|            |                         |                            | ICH+te1 (n = 8)            |               |                    |  |
|            |                         |                            | Saline (n = 10)            | Two-way ANOVA | F (9, 92) = 44.09  | P<0.0001                               |
| Figure. 5F | Touch ratio             |                            | ICH (n = 6) VS             |               | F (3, 92) = 263.3  | P<0.0001                               |

|             |                   |                  |                    |               |                    |                   |                                |
|-------------|-------------------|------------------|--------------------|---------------|--------------------|-------------------|--------------------------------|
| Figure. 5H  | Hemorrhage volume |                  | ICH+TAT (n = 6)    |               |                    | F (3, 92) = 260.9 | P<0.0001                       |
|             |                   |                  | ICH+te1 (n = 8)    |               |                    |                   |                                |
|             |                   | Saline = 0.012   | Saline (n = 10) VS |               |                    |                   | saline vs ICH: p < 0.0001      |
|             |                   | ICH = 7.605      | ICH (n = 6)        |               |                    |                   | saline vs ICH+TAT p < 0.0001   |
|             |                   | ICH+TAT = 7.6375 | ICH+TAT (n = 6)    | One-way ANOVA | F(3, 49) = 32.78   |                   | saline vs ICH+TE1: p < 0.0001  |
|             |                   | ICH+TE1 = 4.3875 | ICH+te1 (n = 8)    |               |                    |                   | ICH vs ICH+TAT: p > 0.9999     |
|             |                   |                  |                    |               |                    |                   | ICH vs ICH+TE1: p = 0.0031     |
|             |                   |                  |                    |               |                    |                   | ICH+TAT vs ICH+TE1: p = 0.0085 |
|             |                   |                  |                    |               |                    |                   |                                |
|             |                   |                  |                    |               |                    |                   |                                |
| Figure. 6B  | Cell number       |                  |                    |               |                    |                   |                                |
|             |                   | Saline = 3.083   | Saline (n =4) VS   |               |                    |                   | saline vs ICH: p < 0.0001      |
|             |                   | ICH = 78.38      | ICH (n = 4)        |               |                    |                   | saline vs ICH+TAT p < 0.0001   |
|             |                   | ICH+TAT = 77.49  | ICH+TAT (n = 4)    | One-way ANOVA | F(3, 158) = 54.53  |                   | saline vs ICH+TE1: p = 0.0023  |
|             |                   | ICH+TE1 = 30.02  | ICH+te1 (n = 4)    |               |                    |                   | ICH vs ICH+TAT: p = 0.9989     |
|             |                   |                  |                    |               |                    |                   | ICH vs ICH+TE1: p = 0.0041     |
|             |                   |                  |                    |               |                    |                   | ICH+TAT vs ICH+TE1: p = 0.0032 |
|             |                   |                  |                    |               |                    |                   |                                |
|             |                   |                  |                    |               |                    |                   |                                |
|             |                   |                  |                    |               |                    |                   |                                |
| Figure. 6D  | Cell number       |                  |                    |               |                    |                   |                                |
|             |                   | Saline = 11.53   | Saline (n =4) VS   |               |                    |                   | saline vs ICH: p < 0.0001      |
|             |                   | ICH = 52.22      | ICH (n = 4)        |               |                    |                   | saline vs ICH+TAT p < 0.0001   |
|             |                   | ICH+TAT = 54.22  | ICH+TAT (n = 4)    | One-way ANOVA | F(3, 99) = 36.52   |                   | saline vs ICH: p < 0.0001      |
|             |                   | ICH+TE1 = 42.86  | ICH+te1 (n = 4)    |               |                    |                   | ICH vs ICH+TAT: p = 0.9410     |
|             |                   |                  |                    |               |                    |                   | ICH vs ICH+TE1: p = 0.0328     |
|             |                   |                  |                    |               |                    |                   | ICH+TAT vs ICH+TE1: p = 0.0132 |
|             |                   |                  |                    |               |                    |                   |                                |
|             |                   |                  |                    |               |                    |                   |                                |
|             |                   |                  |                    |               |                    |                   |                                |
| Figure. 6F  | Cell number       |                  |                    |               |                    |                   |                                |
|             |                   | Saline = 7.585   | Saline (n =4) VS   |               |                    |                   | saline vs ICH: p = 0.6329      |
|             |                   | ICH = 9.731      | ICH (n = 4)        |               |                    |                   | saline vs ICH+TAT p = 0.2465   |
|             |                   | ICH+TAT = 11.1   | ICH+TAT (n = 4)    | One-way ANOVA | F(3, 84) = 1.2     |                   | saline vs ICH: p = 0.8343      |
|             |                   | ICH+TE1 = 9.458  | ICH+te1 (n = 4)    |               |                    |                   | ICH vs ICH+TAT: p = 0.7667     |
|             |                   |                  |                    |               |                    |                   | ICH vs ICH+TE1: p = 0.9989     |
|             |                   |                  |                    |               |                    |                   | ICH+TAT vs ICH+TE1: p = 0.8288 |
|             |                   |                  |                    |               |                    |                   |                                |
|             |                   |                  |                    |               |                    |                   |                                |
|             |                   |                  |                    |               |                    |                   |                                |
| Figure. S1B | protein level     |                  |                    |               |                    |                   |                                |
|             |                   | Mock = 0.2218    | Mock (n = 3) VS    |               |                    |                   | Mock vs 0.2 μM: p = 0.9937     |
|             |                   | 0.2 μM = 0.2363  | 0.2 μM (n = 3)     | One-way       | F (3, 8) = 0.03619 |                   | Mock vs 1.5 μM: p = 0.9991     |
|             |                   | 1.5 μM = 0.2143  | 1.5 μM (n = 3)     | ANOVA         |                    |                   | Mock vs 12 μM: p = 0.9999      |
|             |                   | 12 μM = 0.218    | 12 μM (n = 3)      |               |                    |                   |                                |
| Figure. S1C | protein level     |                  |                    |               |                    |                   |                                |
|             |                   | Mock = 0.5585    | Mock (n = 3) VS    |               |                    |                   | Mock vs 0.2 μM: p = 0.9050     |
|             |                   | 0.2 μM = 0.5885  | 0.2 μM (n = 3)     | One-way       | F (3, 8) = 0.3093  |                   | Mock vs 1.5 μM: p = 0.9827     |
|             |                   | 1.5 μM = 0.5425  | 1.5 μM (n = 3)     | ANOVA         |                    |                   | Mock vs 12 μM: p = 0.9817      |

|             |                         |                      |                      |         |             |   |
|-------------|-------------------------|----------------------|----------------------|---------|-------------|---|
|             |                         | 12 $\mu$ M = 0.5422  | 12 $\mu$ M (n = 3)   |         |             |   |
|             |                         | Mock = 0.5463        | Mock (n = 3) VS      |         |             | Mock vs 0.2 $\mu$ M: p = 0.9845                   |
| Figure. S1D | protein level           | 0.2 $\mu$ M = 0.507  | 0.2 $\mu$ M (n = 3)  | One-way | F (3, 8) =  | Mock vs 1.5 $\mu$ M: p = 0.9999                   |
|             |                         | 1.5 $\mu$ M = 0.552  | 1.5 $\mu$ M (n = 3)  | ANOVA   | 0.0974      | Mock vs 12 $\mu$ M: p = 0.9871                    |
|             |                         | 12 $\mu$ M = 0.5833  | 12 $\mu$ M (n = 3)   |         |             |   |
|             |                         | 0 $\mu$ M = 98.2     | 0 $\mu$ M (n = 4) VS |         |             | 0 $\mu$ M vs 10 $\mu$ M hemin: p < 0.0001         |
|             |                         | 10 $\mu$ M = 83.01   | 10 $\mu$ M (n = 4)   |         |             | 0 $\mu$ M vs 30 $\mu$ M hemin: p < 0.0001         |
|             |                         | 30 $\mu$ M = 73.67   | 30 $\mu$ M (n = 4)   | One-way | F (5, 18) = | 0 $\mu$ M vs 60 $\mu$ M hemin: p < 0.0001         |
| Figure. S4A | Survival (% of control) | 60 $\mu$ M = 52.23   | 60 $\mu$ M (n = 4)   | ANOVA   | 369.1       | 0 $\mu$ M vs 90 $\mu$ M hemin: p < 0.0001         |
|             |                         | 90 $\mu$ M = 18.32   | 90 $\mu$ M (n = 4)   |         |             | 0 $\mu$ M vs 120 $\mu$ M hemin: p < 0.0001        |
|             |                         | 120 $\mu$ M = 9.669  | 120 $\mu$ M (n = 4)  |         |             | 10 $\mu$ M hemin vs 120 $\mu$ M hemin: p = 0.0040 |
|             |                         | 0 min = 101.2        | 0 min (n = 4) VS     |         |             | blank vs 10min: p = 0.0159                        |
|             |                         | 10 min = 85.78       | 10 min (n = 4)       |         |             | blank vs 30min: p = 0.0004                        |
|             |                         | 30 min = 77.93       | 30 min (n = 4)       | One-way | F (5, 18) = | blank vs 60min: p = 0.0001                        |
| Figure. S4B | Survival (% of control) | 60 min = 72.35       | 60 min (n = 4)       | ANOVA   | 31.71       | blank vs 120min: p = 0.0001                       |
|             |                         | 120 min = 55.38      | 120 min (n = 4)      |         |             | blank vs 360min: p = 0.0001                       |
|             |                         | 360 min = 52.23      | 360 min (n = 4)      |         |             |   |
|             |                         | Blank = 102.2        | Blank (n = 4) VS     |         |             | Blank vs 0.15 $\mu$ M: p = 0.9928                 |
|             |                         | 0.15 $\mu$ M = 103.2 | 0.15 $\mu$ M (n = 4) | One-way | F (4, 15) = | Blank vs 0.75 $\mu$ M: p = 0.9992                 |
| Figure. S5A | Survival (% of control) | 0.75 $\mu$ M = 101.6 | 0.75 $\mu$ M (n = 4) | ANOVA   | 1.438       | Blank vs 1.5 $\mu$ M: p = 0.8963                  |
|             |                         | 1.5 $\mu$ M = 99.92  | 1.5 $\mu$ M (n = 4)  |         |             | Blank vs 12 $\mu$ M: p = 0.2382                   |
|             |                         | 15 $\mu$ M = 96.1    | 15 $\mu$ M (n = 4)   |         |             |   |
|             |                         | Blank = 98.63        | Blank (n = 4) VS     |         |             | Blank vs 0.15 $\mu$ M: p = 0.9999                 |
|             |                         | 0.15 $\mu$ M = 98.7  | 0.15 $\mu$ M (n = 4) | One-way | F (4, 15) = | Blank vs 0.75 $\mu$ M: p = 0.9974                 |
| Figure. S5B | Survival (% of control) | 0.75 $\mu$ M = 98.27 | 0.75 $\mu$ M (n = 4) | ANOVA   | 1.438       | Blank vs 1.5 $\mu$ M: p = 0.7885                  |
|             |                         | 1.5 $\mu$ M = 97.29  | 1.5 $\mu$ M (n = 4)  |         |             | Blank vs 12 $\mu$ M: p = 0.0559                   |
|             |                         | 15 $\mu$ M = 94.58   | 15 $\mu$ M (n = 4)   |         |             |   |
|             |                         |                      | Saline (n = 3) VS    |         | F (2, 12) = |   |
|             |                         |                      |                      |         | 6.64        | P=0.0114  |
|             |                         |                      | ICH (n = 3)          | Two-way | F (2, 12) = |   |
| Figure. S7B | Remove tape ratio       |                      |                      | ANOVA   | 11.97       | P=0.0014  |
|             |                         |                      |                      |         | F (1, 12) = |   |
|             |                         |                      |                      |         | 19.4        | P=0.0009  |
|             |                         |                      | Saline (n = 3) VS    | Two-way | F (2, 12) = |   |
| Figure. S7C | Touch ratio             |                      |                      | ANOVA   | 57.08       | P<0.0001  |

|                         |                    |                   |                   |         |                                  |                                |
|-------------------------|--------------------|-------------------|-------------------|---------|----------------------------------|--------------------------------|
|                         |                    |                   | ICH (n = 3)       |         | F (2, 12) =<br>69.26<br>P<0.0001 |                                |
|                         |                    |                   |                   |         | F (1, 12) =<br>162.8<br>P<0.0001 |                                |
| Figure. S7E<br>DCC      | protein level      | Sham = 1          | Sham (n = 3) VS   |         |                                  | Sham vs ICH-Day 1: p = 0.0993  |
|                         |                    | ICH-Day 1 = 3.449 | ICH-Day 1 (n = 3) | One-way | F(3, 8) =                        | Sham vs. ICH-Day 2: p = 0.0378 |
|                         |                    | ICH-Day 2 = 4.11  | ICH-Day 2 (n = 3) | ANOVA   | 3.539                            | Sham vs. ICH-Day 3: p = 0.3587 |
|                         |                    | ICH-Day 3 = 2.529 | ICH-Day 3 (n = 3) |         |                                  |                                |
| Figure. S7F<br>Netrin-1 | protein level      | Sham = 1          | Sham (n = 3) VS   |         |                                  | Sham vs ICH-Day 1: p = 0.8590  |
|                         |                    | ICH-Day 1 = 1.4   | ICH-Day 1 (n = 3) | One-way | F(3, 8) =                        | Sham vs. ICH-Day 2: p = 0.0002 |
|                         |                    | ICH-Day 2 = 5.821 | ICH-Day 2 (n = 3) | ANOVA   | 32.7                             | Sham vs. ICH-Day 3: p = 0.0004 |
|                         |                    | ICH-Day 3 = 5.293 | ICH-Day 3 (n = 3) |         |                                  |                                |
| Figure. S9B             | Permeability index | Saline = 0.2922   | Saline (n = 4) VS |         |                                  | saline vs ICH: p = 0.0193      |
|                         |                    | ICH = 1.044       | ICH (n = 3)       |         |                                  | saline vs ICH+TAT p = 0.0176   |
|                         |                    | ICH+TAT = 1.056   | ICH+TAT (n = 3)   | One-way | F(3, 10) =                       | saline vs ICH+TE1: p = 0.0261  |
|                         |                    | ICH+TE1 = 0.9519  | ICH+te1 (n = 4)   | ANOVA   | 6.9                              | ICH vs ICH+TAT: p > 0.9999     |
|                         |                    |                   |                   |         |                                  | ICH vs ICH+TE1: p = 0.9685     |
|                         |                    |                   |                   |         |                                  | ICH+TAT vs ICH+TE1: p = 0.9554 |
| Figure. S9C             | RFU serum          | Saline = 48444    | Saline (n = 4) VS |         |                                  | saline vs ICH: p = 0.3178      |
|                         |                    | ICH = 39655       | ICH (n = 3)       |         |                                  | saline vs ICH+TAT p = 0.2725   |
|                         |                    | ICH+TAT = 39101   | ICH+TAT (n = 3)   | One-way | F(3, 10) =                       | saline vs ICH+TE1: p = 0.3055  |
|                         |                    | ICH+TE1 = 40174   | ICH+te1 (n = 4)   | ANOVA   | 1.848                            | ICH vs ICH+TAT: p = 0.9995     |
|                         |                    |                   |                   |         |                                  | ICH vs ICH+TE1: p = 0.9995     |
|                         |                    |                   |                   |         |                                  | ICH+TAT vs ICH+TE1: p = 0.9958 |
| Figure. S9E             | Branch points      | Saline = 37.8     | Saline (n = 4) VS |         |                                  | saline vs ICH: p < 0.0001      |
|                         |                    | ICH = 13.75       | ICH (n = 4)       |         |                                  | saline vs ICH+TAT p < 0.0001   |
|                         |                    | ICH+TAT = 11.3    | ICH+TAT (n = 4)   | One-way | F(3, 10) =                       | saline vs ICH+TE1: p < 0.0001  |
|                         |                    | ICH+TE1 = 13      | ICH+te1 (n = 4)   | ANOVA   | 1.848                            | ICH vs ICH+TAT: p = 0.4987     |
|                         |                    |                   |                   |         |                                  | ICH vs ICH+TE1: p = 0.9769     |
|                         |                    |                   |                   |         |                                  | ICH+TAT vs ICH+TE1: p = 0.7635 |

## Supplementary Table 2

Netrin-1 ( $\Delta 407-443$ ) :

ATGATGCGCGCAGTGTGGGAGGCGCTGGCGGCGCTGGCGGCGGTGGCGTGCCTGG  
TGGGCGCGGTGCGCGGCGGGCCCGGGCTCAGCATGTTTCGCGGGCCAGGCGGCGCA  
GCCCCGATCCCTGCTCGGACGAGAACGGCCACCCGCGCCGCTGCATCCCCGGA CTTTG  
TCAATGCGGCCTTCGGCAAGGACGTGCGCGTGTCCAGCACCTGCGGCGCGCCCCC  
GGCGCGCTACTGCGTG GTGAGCGAGCGCGGCGAGGAGCGGCTGCGCTCGTGCCAC  
CTCTGCAACGCGTCCGACCCCAAGAAGGCGCACCCGCCCCGCTTCCTCACCGACCT  
CAACAACCCGCACAACCTGACGTGCTGGCAGTCCGAGAACTACCTGCAGTTCCCG  
CACAACGTACGCTCACACTGTCCCTCGGCAAGAAGTTCGAAGTGACCTACGTGA  
GCCTGCAGTTCTGCTCGCCGCGGCCCCGAGTCCATGGCCATCTACAAGTCCATGGAC  
TACGGGCGCACGTGGGTGCCCTTCCAGTTCTACTCCACGCAGTGCCGCAAGATGTA  
CAACCGGCCGCACCGCGCGCCCATCACCAAGCAGAACGAGCAGGAGGCCGTGTG  
CACCGACTCGCACACCGACATGCGCCCGCTCTCGGGCGGCCTCATCGCCTTCAGCA  
CGCTGGACGGGCGGCCCTCGGCGCACGACTTCGACAACCTCGCCCGTGCTGCAGGA  
CTGGGTACGGCCACAGACATCCGCGTGGCCTTCAGCCGCCTGCACACGTTTCGGCG  
ACGAGAACGAGGACGACTCGGAGCTGGCGCGCGACTCGTACTTCTACGCGGTGTC  
CGACCTGCAGGTGGGCGGCCCGGTGCAAGTGCAACGGCCACGCGGCCCGCTGCGTG  
CGCGACCGCGACGACAGCCTGGTGTGCGACTGCAGGCACAACACGGCCGGCCCCG  
AGTGCGACCGCTGCAAGCCCTTCCACTACGACCGGCCCTGGCAGCGCGCCACAGC  
CCGCGAAGCCAACGAGTGCGTGGCCTGTAAGTCAACCTGCATGCCCGGCGCTGC  
CGCTTCAACATGGAGCTCTACAAGCTTTCGGGGCGCAAGAGCGGAGGTGTCTGCCT  
CAACTGTCGCCACAACACCGCCGGCCGCCACTGCCATTACTGCAAGGAGGGCTAC  
TACCGCGACATGGGCAAGCCCATCACCCACCGGAAGGCCTGCAAAGCCTGTGATT  
GCAGCCGCTCTCCCATCGCCCCCTGCATAAAGATCCCTGTAGCGCCGCCGACGACT  
GCAGCCAGCAGCGTGGAGGAGCCTGAAGACTGCGATTCTACTGCAAGGCCTCCA  
AGGGGAAGCTGAAGATTAACATGAAAAAGTACTGCAAGAAGGACTATGCCGTCC  
AGATCCACATCCTGAAGGCGGACAAGGCGGGGACTGGTGGAAGTTCACGGTGAA  
CATCATCTCCGTGTATAAGCAGGGCACGAGCCGCATCCGCCGCGGTGACCAGAGC  
CTGTGGATCCGCTCGCGGGACATCGCCTGCAAGTGTCCCAAATCAAGCCCCTCAA  
GAAGTACCTGCTGCTGGGCAACGCGGAGGACTCTCCGGACCAGAGCGGCATCGTG  
GCCGATAAAAGCAGCCTGGTGATCCAGTGGCGGGACACGTGGGCGCGGCGGCTGC  
GCAAGTTCAGCAGCGTGAGAAGAAGGGCAAGTGCAAGAAGGCCTAG