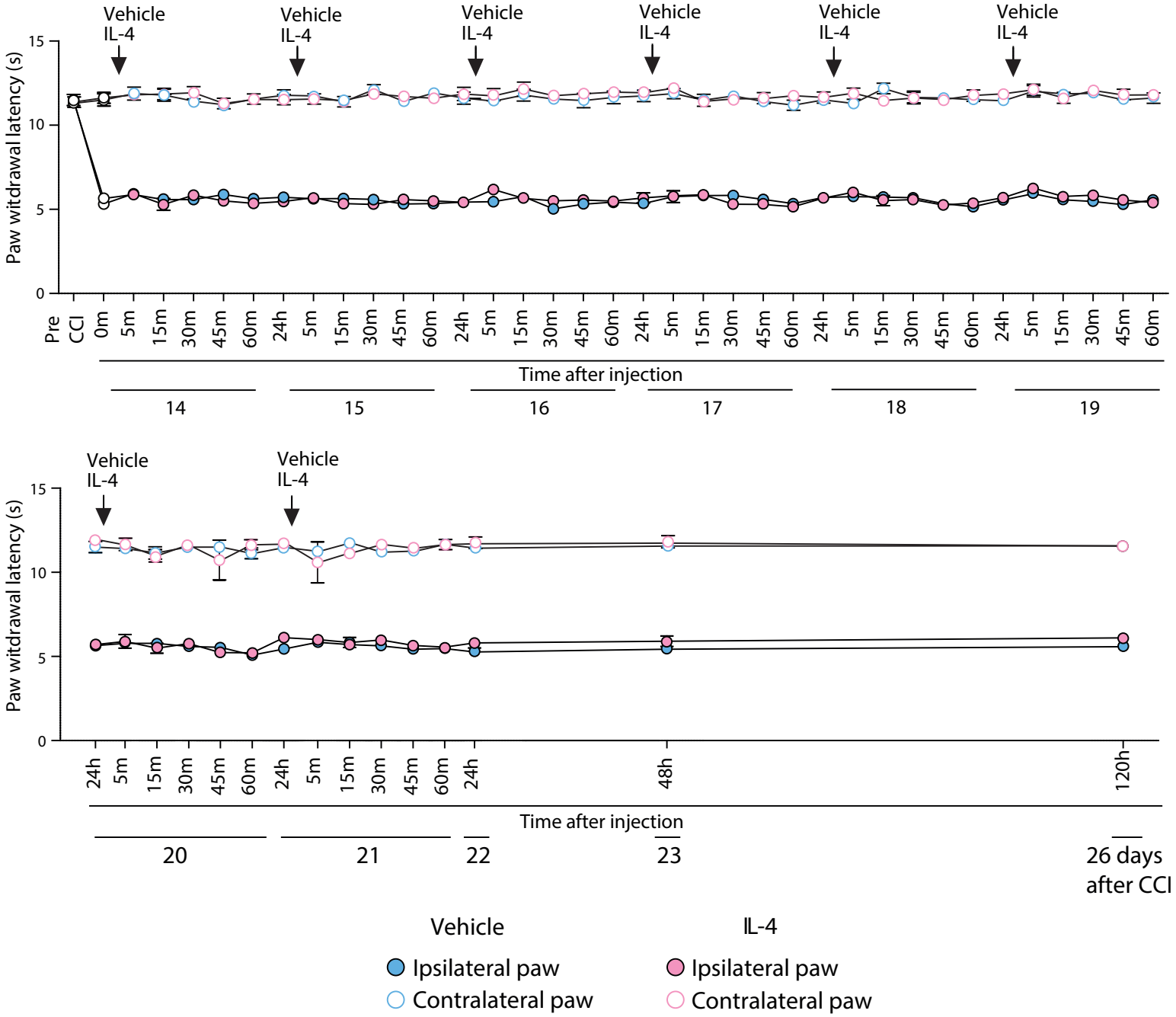
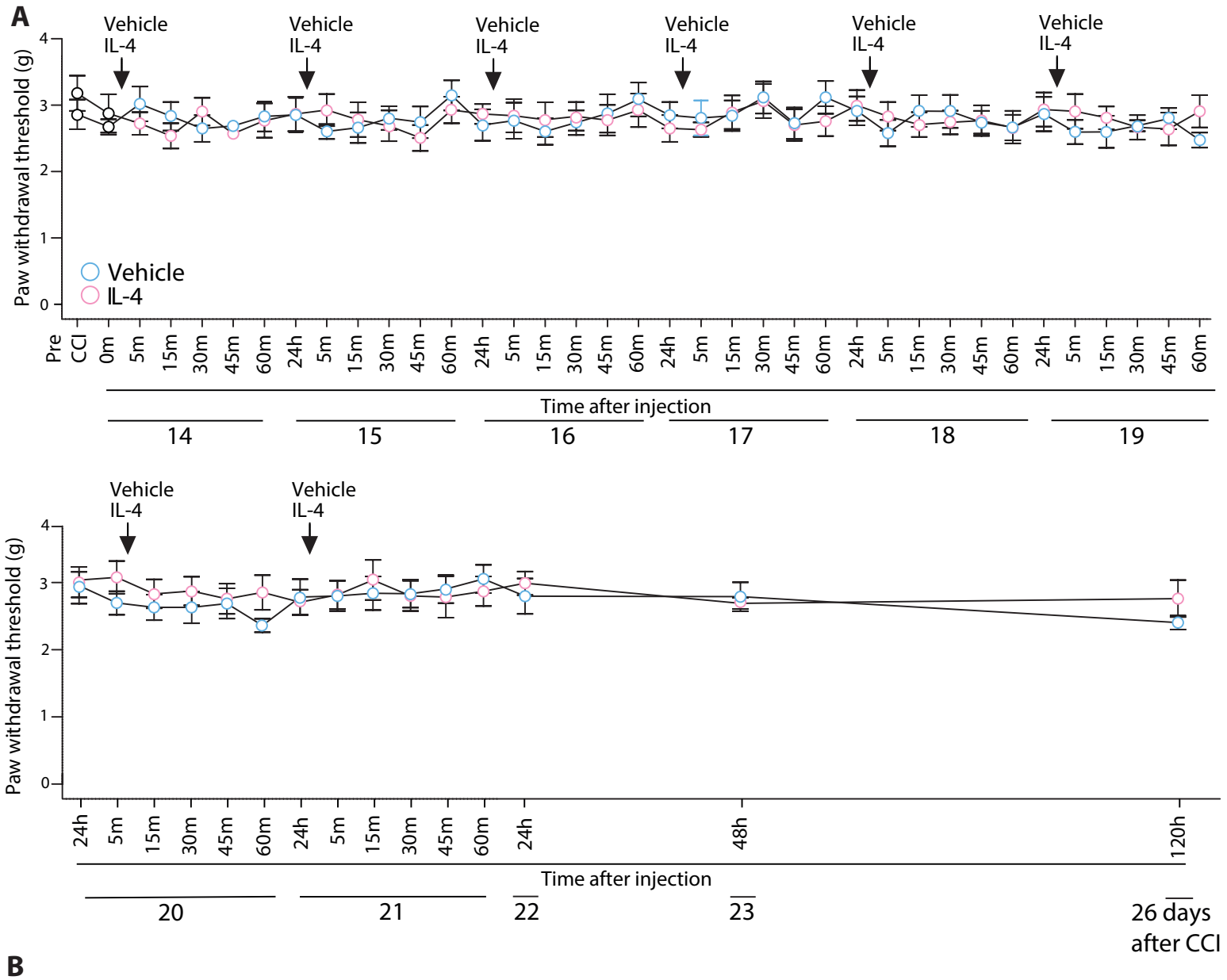
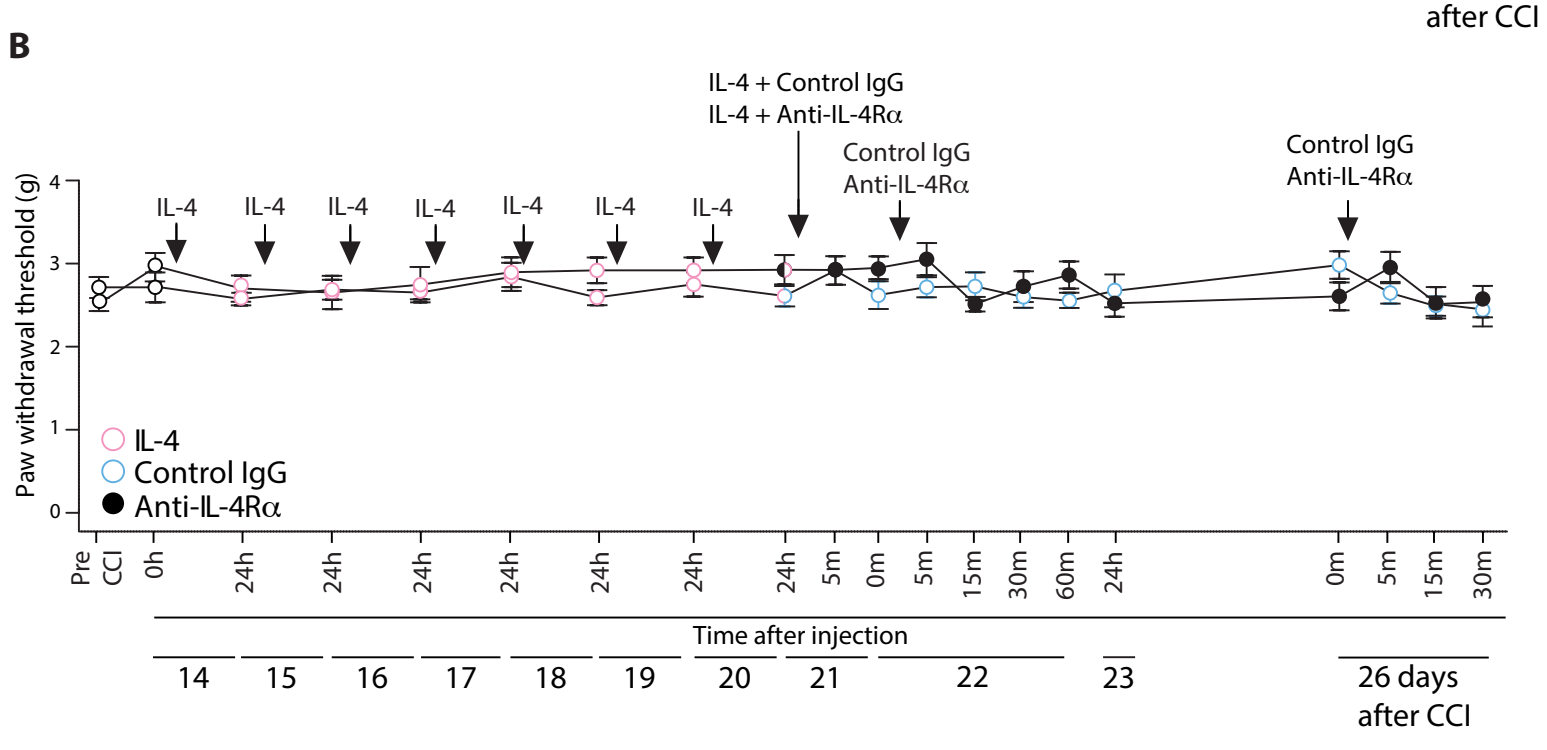
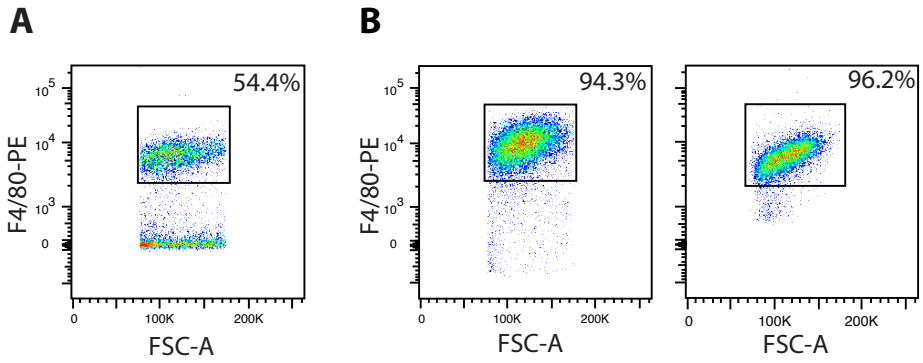


Supplemental Figure 1. IL-4 application at damaged nerves does not alleviate heat hypersensitivity. IL-4 (200 ng) was injected daily on days 14–21 after CCI at the CCI site. Heat paw withdrawal latencies were measured before, 5–60 min and 24 h after each injection until day 22, and then on day 23 (48 h after the last injection), and on day 26 after CCI (120 h after the last injection). The latencies were measured in hind paws ipsilateral and contralateral to CCI by the Hargreaves test. Control group was tested accordingly. Arrows indicate injections. $P > 0.05$ vs. vehicle; 2-way repeated-measures ANOVA. Data are represented as mean ± SEM. n = 9 animals per group.

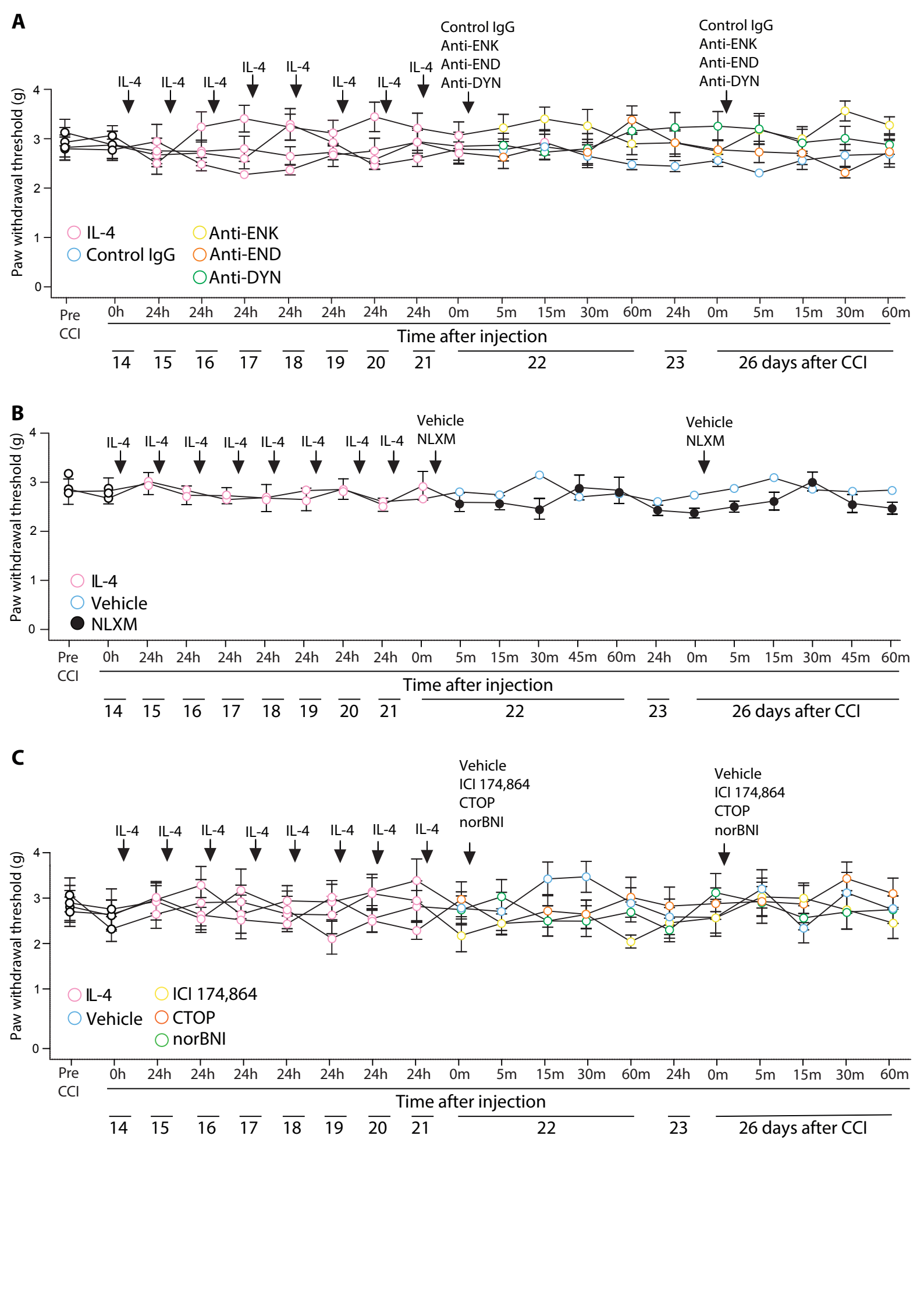

A
Vehicle
IL-4
Paw withdrawal threshold (g)
Vehicle
IL-4
Pre
CCI
Time after injection
14
15
16
17
18
19
20
21
22
23
26 days
after CCI


B
IL-4 + Control IgG
IL-4 + Anti-IL-4Rα
Control IgG
Anti-IL-4Rα
IL-4
Paw withdrawal threshold (g)
Control IgG
Anti-IL-4Rα
Pre
CCI
Time after injection
14
15
16
17
18
19
20
21
22
23
26 days
after CCI

Supplemental Figure 2. No changes in mechanical sensitivity in paws contralateral to CCI following IL-4 and anti-IL-4Rα applied at damaged nerves. This Figure refers to Figure 1. (**A**) Time-course following IL-4 injection. IL-4 (200 ng) was injected daily on days 14–21 after CCI at the CCI site. Mechanical von Frey thresholds were measured before, 5–60 min and 24 h after each injection until day 22, and then on day 23 (48 h after the last injection), and on day 26 after CCI (120 h after the last injection). (**B**) Time-course following IL-4 and anti-IL-4Rα injection. Anti-IL-4Rα (6 μg) was injected with IL-4 (200 ng) on day 21 after CCI (when IL-4 was applied last time), and again alone (without IL-4) on days 22 and 26 after CCI. Von Frey thresholds were measured before and 24 h after each IL-4 injection (on days 14–21), 5 min after IL-4 and anti-IL-4Rα co-injection (on day 21), before and 5–60 min (on day 22) and 24 h (on day 23) after the second anti-IL-4Rα injection, and before and 5–30 min after the third anti-IL-4Rα injection (on day 26). Control groups were tested accordingly. Arrows indicate injections. $P > 0.05$ vs. control (vehicle or control IgG); 2-way repeated-measures ANOVA. Data are represented as mean ± SEM. $n = 9$ animals per group.



Supplemental Figure 3. Flow cytometric verification of purity of macrophages isolated by F4/80+ IMS from damaged nerves. (**A** and **B**) Representative dot blot plots showing that F4/80+ macrophages constituted 54% of all cells isolated from damaged nerves (on day 22 after CCI) before IMS (**A**), but they represented 94% (left blot) to 96% (right blot) of all cells after IMS (**B**). F4/80+ macrophages are shown inside the rectangular gates. The data were analyzed using FlowJo software.


A
Control IgG
Anti-ENK
Anti-END
Anti-DYN
Control IgG
Anti-ENK
Anti-END
Anti-DYN
IL-4
IL-4
IL-4
IL-4
IL-4
IL-4
IL-4
IL-4
Paw withdrawal threshold (g)
IL-4
Control IgG
Anti-ENK
Anti-END
Anti-DYN
Pre CCI
0h
24h
24h
24h
24h
24h
24h
24h
0m
5m
15m
30m
60m
24h
0m
5m
15m
30m
60m
Time after injection
14
15
16
17
18
19
20
21
22
23
26 days after CCI
B
Vehicle
NLXM
Vehicle
NLXM
IL-4
IL-4
IL-4
IL-4
IL-4
IL-4
IL-4
IL-4
Paw withdrawal threshold (g)
IL-4
Vehicle
NLXM
Pre CCI
0h
24h
24h
24h
24h
24h
24h
24h
0m
5m
15m
30m
45m
60m
24h
0m
5m
15m
30m
45m
60m
Time after injection
14
15
16
17
18
19
20
21
22
23
26 days after CCI
C
Vehicle
ICI 174,864
CTOP
norBNI
Vehicle
ICI 174,864
CTOP
norBNI
IL-4
IL-4
IL-4
IL-4
IL-4
IL-4
IL-4
IL-4
Paw withdrawal threshold (g)
IL-4
Vehicle
ICI 174,864
CTOP
norBNI
Pre CCI
0h
24h
24h
24h
24h
24h
24h
24h
0m
5m
15m
30m
60m
24h
0m
5m
15m
30m
60m
Time after injection
14
15
16
17
18
19
20
21
22
23
26 days after CCI

Supplemental Figure 4. No changes in mechanical sensitivity in paws contralateral to CCI following application of IL-4 with opioid peptide antibodies or opioid receptor antagonists at damaged nerves. This Figure refers to Figure 8. (**A)** Time-course following application of IL-4 (200 ng) with antibodies to opioid peptides, anti-ENK (2 μg), anti-END (2 μg), or anti-DYN (4 μg). (**B**) Time-course following application of IL-4 (200 ng) with peripherally restricted opioid receptor antagonist NLXM (10 μg). (**C**) Time-course following application of IL-4 (200 ng) with antagonists selective at δ- (ICI 174,864; 8 μg), μ- (CTOP; 2 μg), and κ-receptors (norBNI; 20 μg). Antibodies and antagonists were injected 24 h after the last IL-4 injection (on day 22 after CCI) and again 5 days after IL-4 injection (on day 26 after CCI). Von Frey thresholds were determined before and 24 h after each IL-4 injection (on days 14–21), before and 5–60 min after the first injection of antibodies and antagonists (on day 22), once on day 23 (24 h after the first injection of antibodies and antagonists), and on day 26, before and 5–60 min after the second injection of antibodies and antagonists. Control groups were tested accordingly. Arrows indicate injections. $P > 0.05$ vs. control (control IgG or vehicle); 2-way repeated-measures ANOVA. Data are represented as mean ± SEM. $n = 9$ animals per group.