

Additional Table 2 Summary of studies targeting complement activation after SCI							
Study	Species	Model detail	Intervention groups	Treatment time	Follow-up	Histological outcomes	Functional outcomes
A. Inhibitors of Ig-Complement Interaction/Activation (Figure 4.1)							
Ankeny et al., 2009	C57bl6 mice	Controlled impactor T9	WT B-cell Depletion WT SCI serum FcγR -/- C3 -/-	NA	7-63 days	- B-cell depletion reduced immunoglobulin and C1q deposition on neurons and glial cells after SCI - SCI leads to production of pathologic IgG and IgM autoantibodies	- B-cell depletion improved hindlimb-forelimb coordination starting 1 week post-injury - Serum (IgG and IgM) from SCI mice reconstituted injury in intact SC - Pathologic effect of IgM and IgG was mitigated with FcγR or C3 deficiency.
Narang et al., 2017	C57bl6 mice	Controlled impactor T10	WT Rag1-/- B-cell Depletion B4-Crry	30 min	21 days	Rag1-/- or B-cell depletion → Reduced lesion volume and demyelination B4IgM or C2-IgM → Reconstituted injury in Rag1-/- mice B4-Crry → Reduced lesion volume and demyelination → Reduced IgM and C3d deposition	- Motor recovery significantly improved in antibody deficient (Rag1-/-) or B cell depleted mice compared to WT - Administration of B4 or C2 IgM resulted in worsening of motor recovery in Rag1-/- mice - B4-Crry resulted in acute and chronic improvement in motor recovery compared to WT
B. Inhibition of Classical Complement Pathway (Figure 4.2)							
Galvan et al., 2008	BUB mice	Controlled impactor T9	WT C1q-/-	NA	28 days	C1q-/-: → reduced lesion volume and demyelination → No effect on astrocyte activation → No effect on immune cell infiltrate	C1q deficiency improved fine motor recovery
Tei et al., 2008	Wistar rats	Controlled impactor T12	WT+Vehicle WT+C1INH	0-30 min	7 days	C1-INH: → reduced lesion volume and demyelination → Decreased neutrophil infiltration	C1 INH improved motor recovery starting at day 7 post SCI
C. Inhibition of C3 Activation (Figure 4.3)							



Li et al., 2005	Sprague Dawley rats	Weight drop T10	WT WT+sCR1	Day 1	3-21 days	sCR1 → reduced C3 deposition → reduced neutrophil infiltration	Improved motor function days 3-21 with acute sCR1 treatment
Guo et al., 2023	C57bl6 mice	Weight drop T12	WT C3-/-	NA	21 days	C3-/-: → Improved nerve fiber regeneration → Suppressed astrocyte activation → Protected neurite formation in dorsal root ganglion neurons <i>in vitro</i> when co-cultured with astrocytes	C3-/- improved locomotor function on days 4-21
Qiao et al., 2006	C57bl6 mice	Weight drop T12	WT C3-/- CR2-Crry	1 hour	21 days	C3-/- or CR2Crry: → Reduced lesion volume & demyelination → Inhibited acute and chronic neutrophil infiltration	C3-/- or CR2-Crry administration improved locomotor function on days 4-21
D. Inhibition of Alternative and Terminal Pathways (Figure 4.4)							
Qiao et al., 2010	C57bl6 mice	Weight drop T12	WT fB-/- CD59-/- WT+anti-fB Ig	1 and 13 hours	21 days	fB -/- or anti-fB: → Reduced lesion volume & demyelination → Inhibited acute neutrophil and monocyte infiltrate → Reduced C3 and C9 deposition CD59-/-: → High deposition of C9 → Increased lesion volume and neutrophil infiltrate	Locomotor function improved in fB-/- and anti-fB treated mice and worsened with CD59-/-
Su et al. 2020	PVG rats	Controlled impactor T9	WT C6-/-	NA	42 days	No significant difference in lesion volume when C6-/- compared to WT littermates	Worse motor performance with C6-/-
E. Inhibition of C3a/C3aR Interaction (Figure 4.5)							



Brennan et al., 2019	C57bl6 mice	Controlled impactor T9	WT C3aR-/- C3aR-/- → WT BMC WT → C3aR-/- BMC	Day 1-7	35 days	<p>C3aR-/-:</p> <ul style="list-style-type: none"> → Exacerbate lesion volume and demyelination chronically, effect suppressed with neutrophil depletion → Increased neutrophil infiltration <p>C3aR-/- (CNS Chimera):</p> <ul style="list-style-type: none"> - no effect on lesion or neutrophil infiltration <p>C3aR-/- (BM Chimera):</p> <ul style="list-style-type: none"> - increased neutrophil infiltration 	C3aR-/- results in worsening of motor outcome after SCI via disinhibition of neutrophil mobilization
F. Inhibition of C5a/C5aR Interaction (Figure 4.6)							
Beck et al., 2010	Sprague Dawley rats	Controlled impactor T9	WT WT + C5aR1A	1-7 or 14-28 days	180 days	<p>PMX205 (C5aR1A):</p> <ul style="list-style-type: none"> → reduced macrophage infiltration on day 7 → Subacute (14-28) treatment reduced myelin regeneration 	Worse locomotor function and motor coordination with subacute PMX205 treatment
Li et al., 2014	C57bl6 mice	Forceps compression T11	WT WT + C5aR1A C5 -/-	Pre-injury & Day 1	28 days	<p>C5-/- or C5aR1A:</p> <ul style="list-style-type: none"> → Decreased SC atrophy & demyelination → Decreased astrocyte activation & macrophage infiltration 	Improved locomotor function and motor coordination with acute C5aR1A treatment or C5-/-
Brennan et al., 2015	C57bl6 mice	Controlled impactor T9	WT WT + C5aR1A C5aR1 -/- C5aR1-/- → WT BMC	Day 1-7	35 days	<p>C5aR1-/-:</p> <ul style="list-style-type: none"> → Exacerbate lesion volume and demyelination chronically → Reduce astrocyte activation and macrophage infiltration → C5aR1-/- only in peripheral immune cells had no effect on outcomes <p>C5aRA (PMX205): (Given first week):</p> <ul style="list-style-type: none"> → Reduced lesion volume and improved myelination chronically → No effect on astrocyte activation, reduced macrophage infiltration → Protective effects absent if treatment is given post-7 days 	<ul style="list-style-type: none"> - C5aR1-/- and prolonged (Post 7 Days) treatment with C5aR1A resulted in worse chronic locomotor function and motor coordination - C5aR1-/- restricted to peripheral immune cells (CM Chimera) did not have an effect on the outcome - Acute (within 7 days) treatment with C5aR1A resulted in improved locomotor function and motor coordination



Biggins et al., 2017	C57bl6 mice	Controlled impactor T9	WT	Pre-injury & for 7 Days	C5aR2^{-/-}:	→ Worse lesion volumes → Did not impact neutrophil/macrophage infiltration C5aR1A (PMX205): → Reduced lesion volume and demyelination → Reversed the effect of C5aR2 ^{-/-}
			C5aR2 ^{-/-}		- C5aR2 ^{-/-} worsens chronic motor recovery - C5aR1A improved motor recovery in WT and C5aR2 ^{-/-} mice	
			WT + C5aR1A			
			C5aR2 ^{-/-} + C5aR1A			

BMC: Bone-marrow chimera; C1-INH: C1 inhibitor; C5aR1A: C5aR1 antagonist; FcγR: Fc-gamma receptor; Ig: antibody; NA: not applicable; sCR1: soluble complement receptor 1; SCI: spinal cord injury; WT: wild-type.