Clinical Evaluation of Glibenclamide in Patients with Acute Cervical Spinal Cord Injuries

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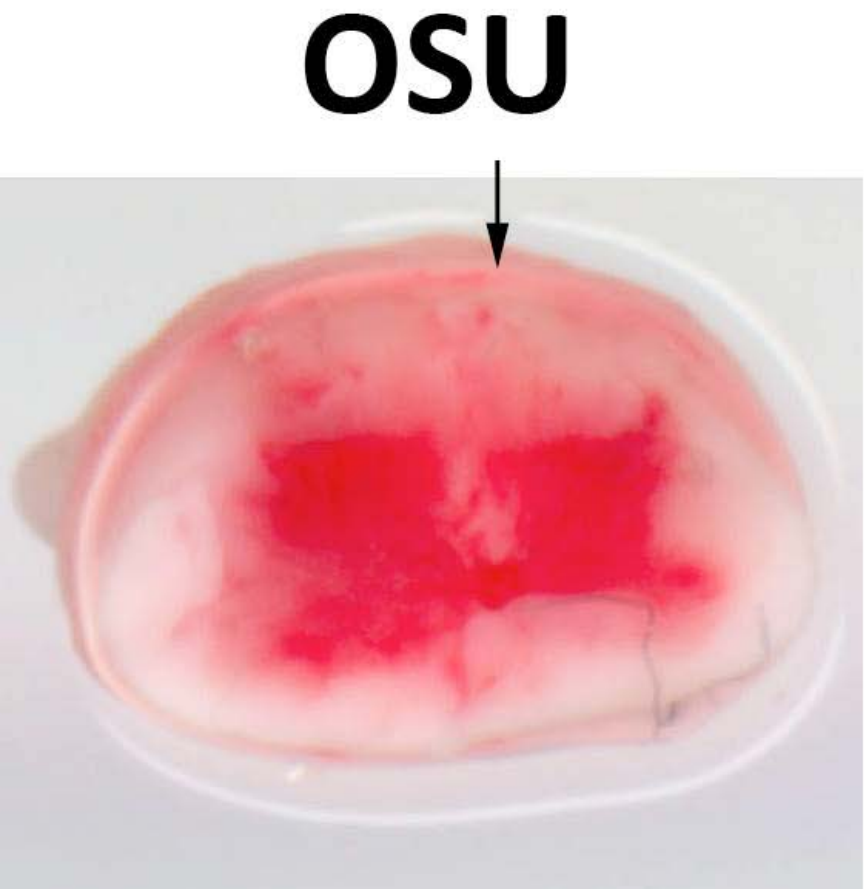
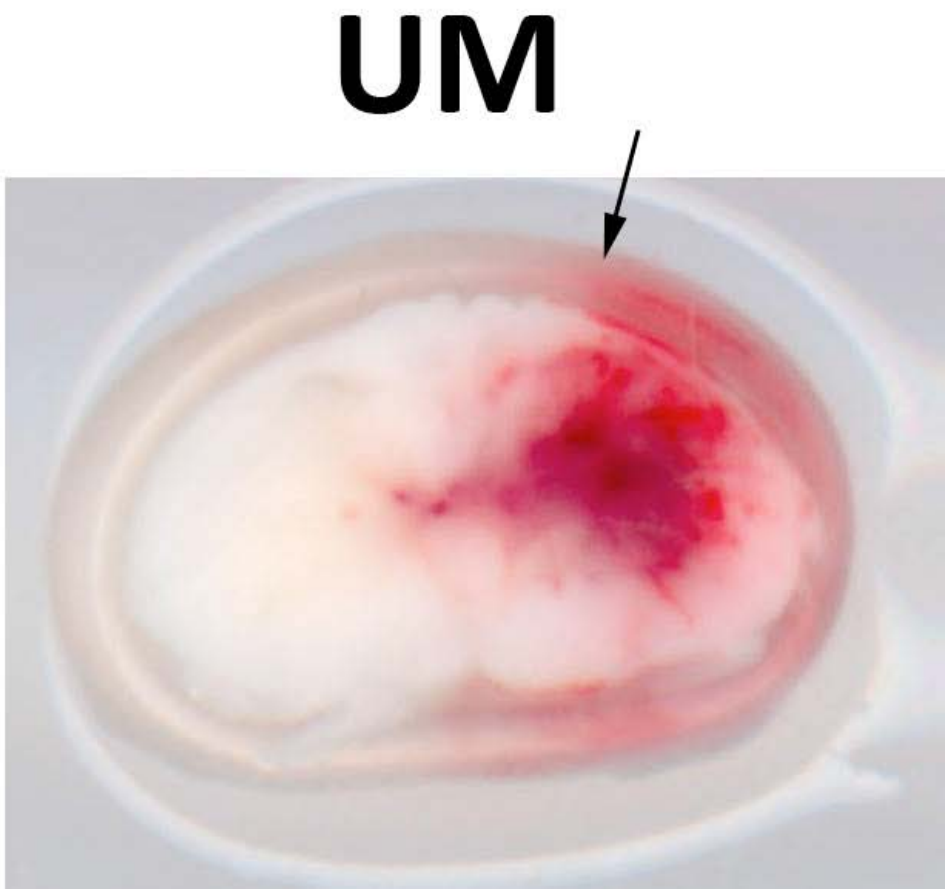
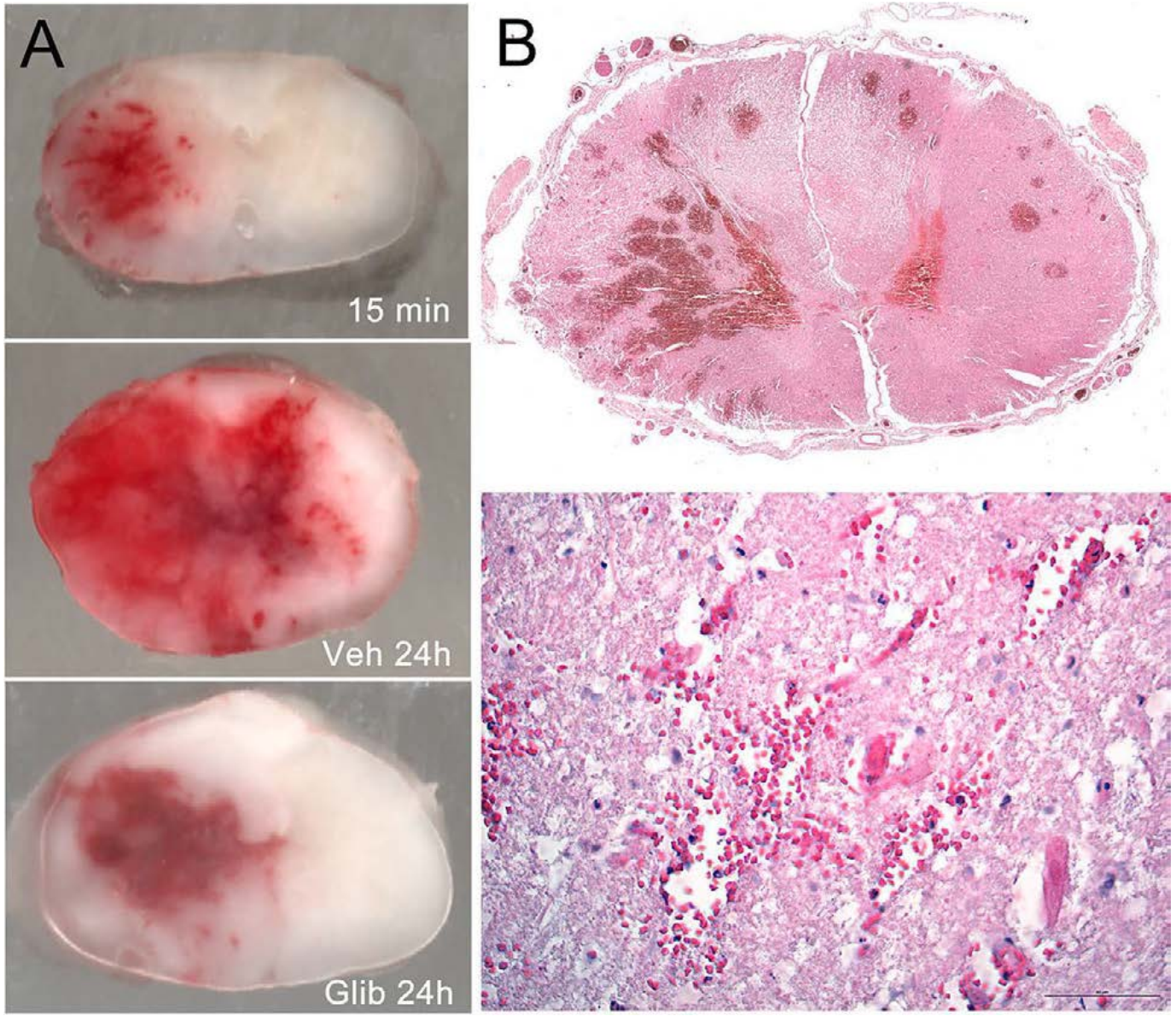
No Disclosures

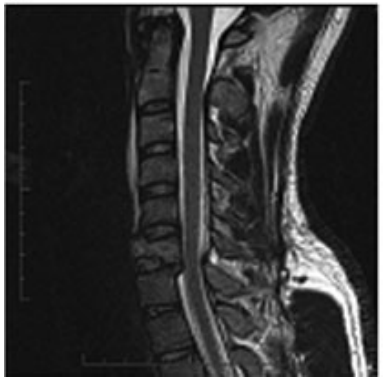
- Progressive hemorrhagic necrosis is a clinically significant 2° injury process

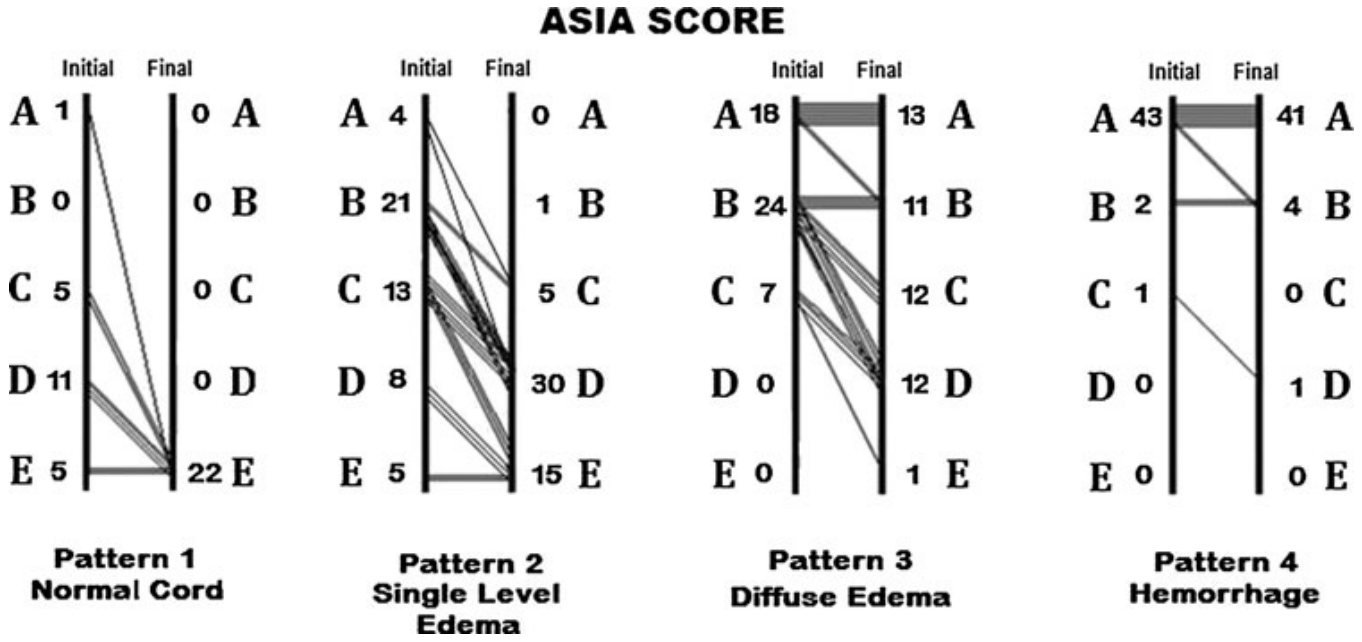






Simard et al 2012





Goulet et al, 2011

Lesion Expansion

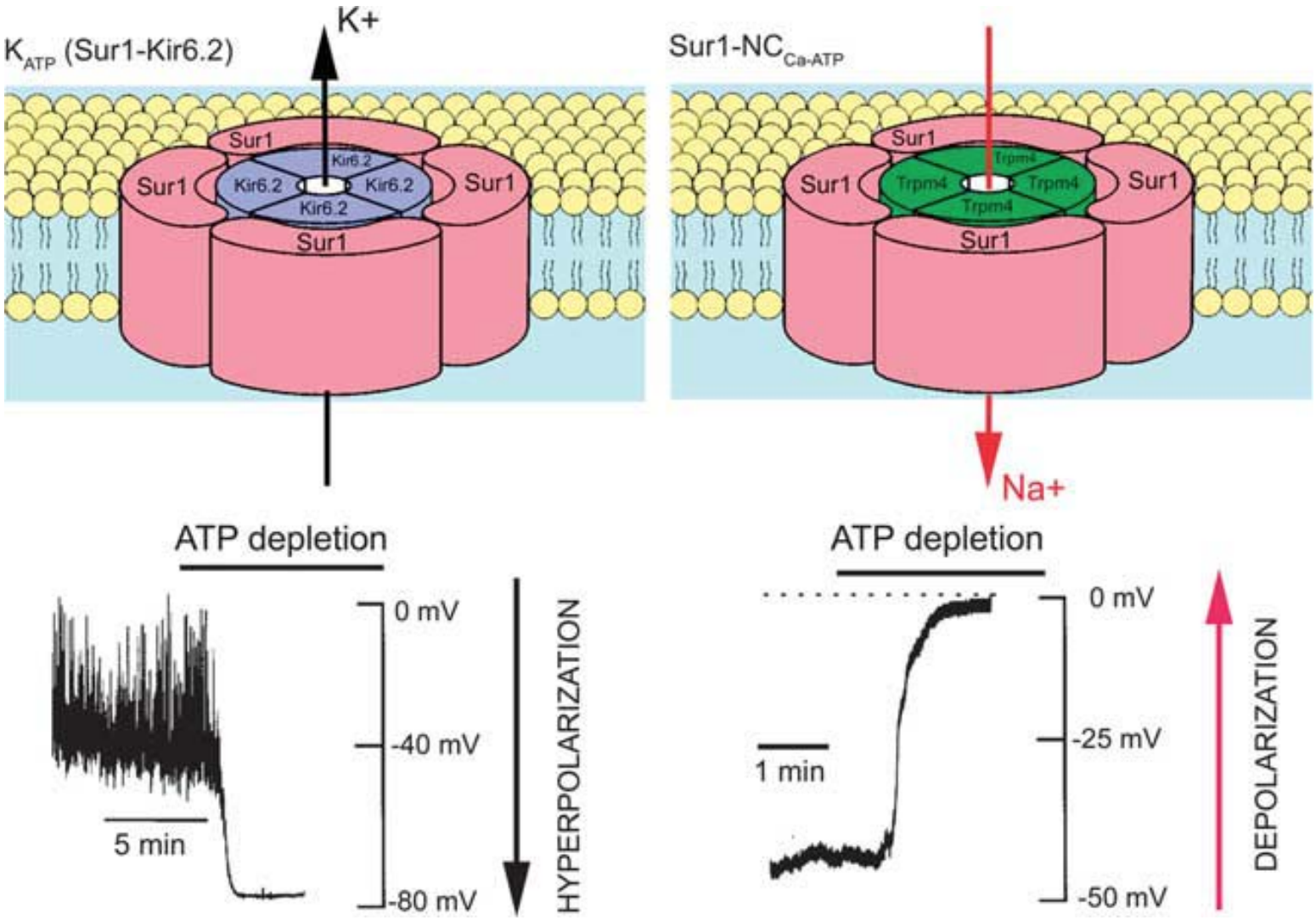
Effective doubling of primary hemorrhage

Capillary dysfunction

Coalescing of petechial hemorrhages

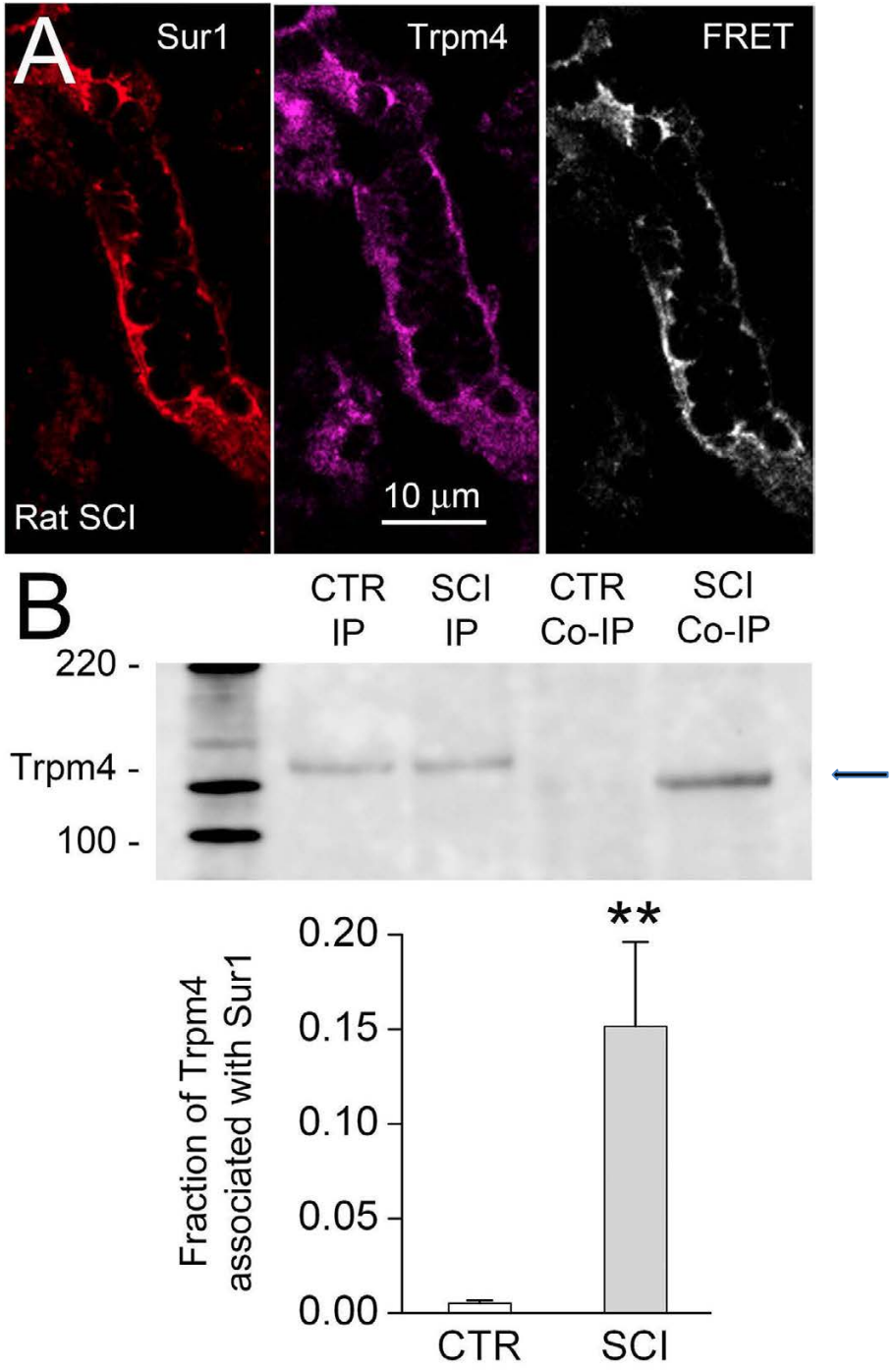
Autodestruction of spinal cord tissues

Interplay with other 2° injury processes



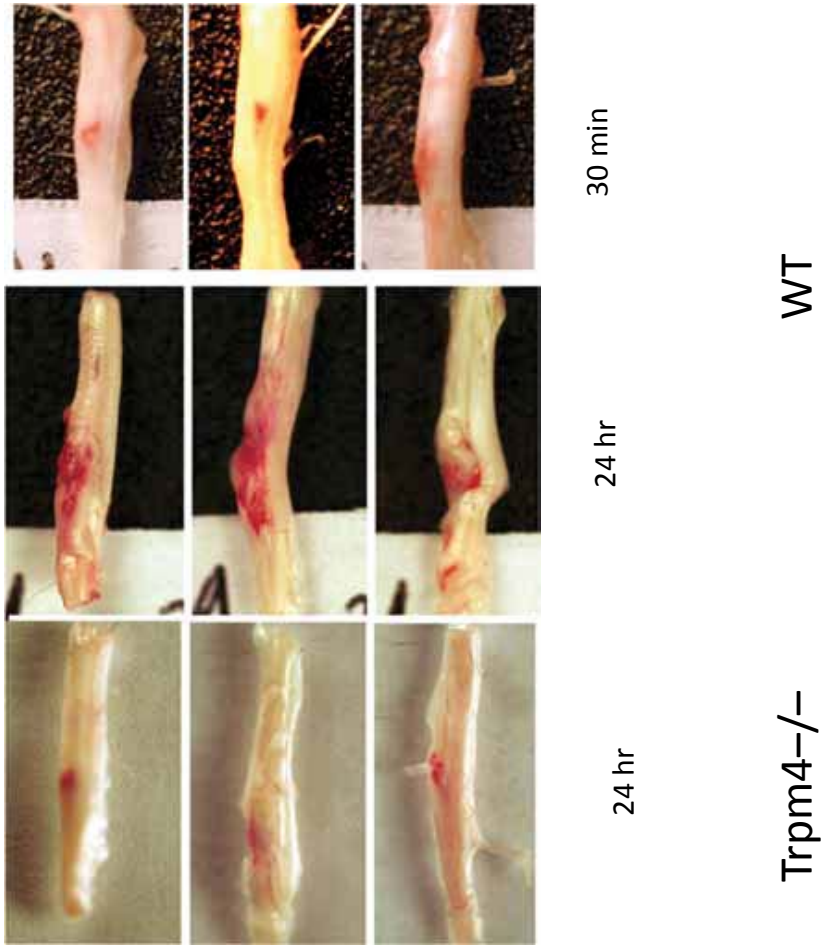
Simard et al 2012

Sur1-Trpm4 channels expressed and activated early following SCI



Identical phenotype of *Abcc8-/-* and *Trpm4-/-* mice

Identical phenotype of rats administered *Abcc8* and *Trpm4* antisense

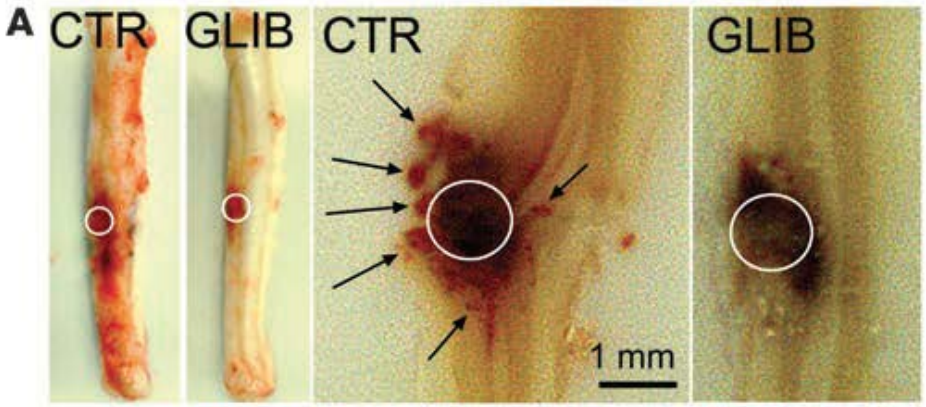


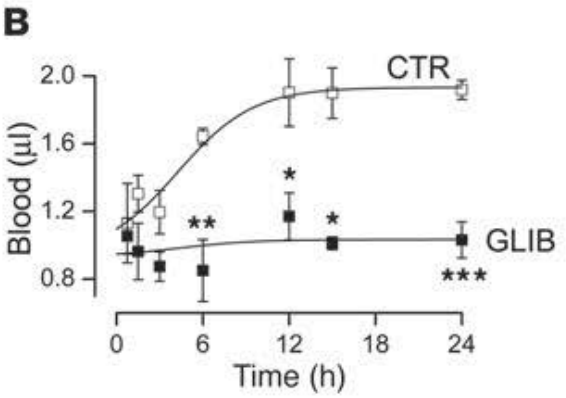
Gerzanich et al, 2009
Simard et al, 2010

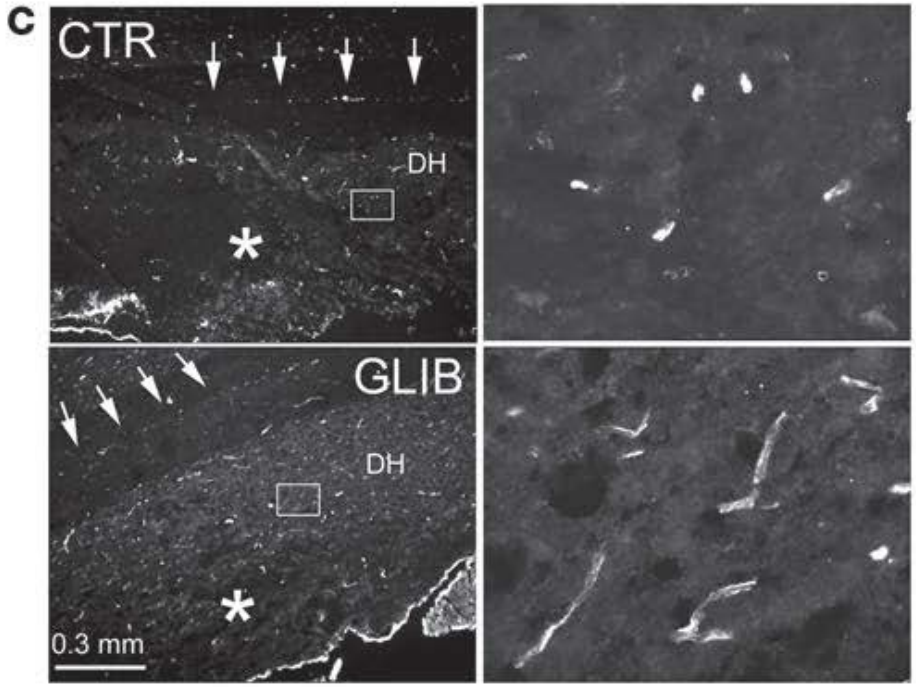
Glibenclamide potently inhibits channel (EC_{50} = 48 nM)

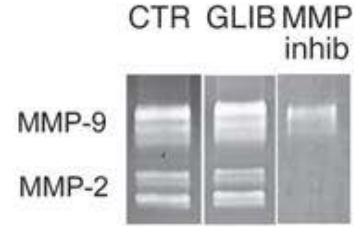
- Independent replication of outcome assessments has been achieved

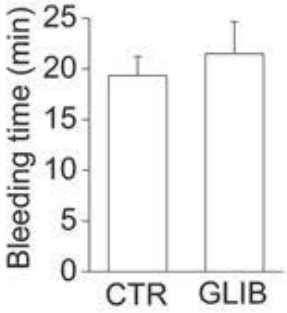
- These provide evidence of efficacy in relevant animal models



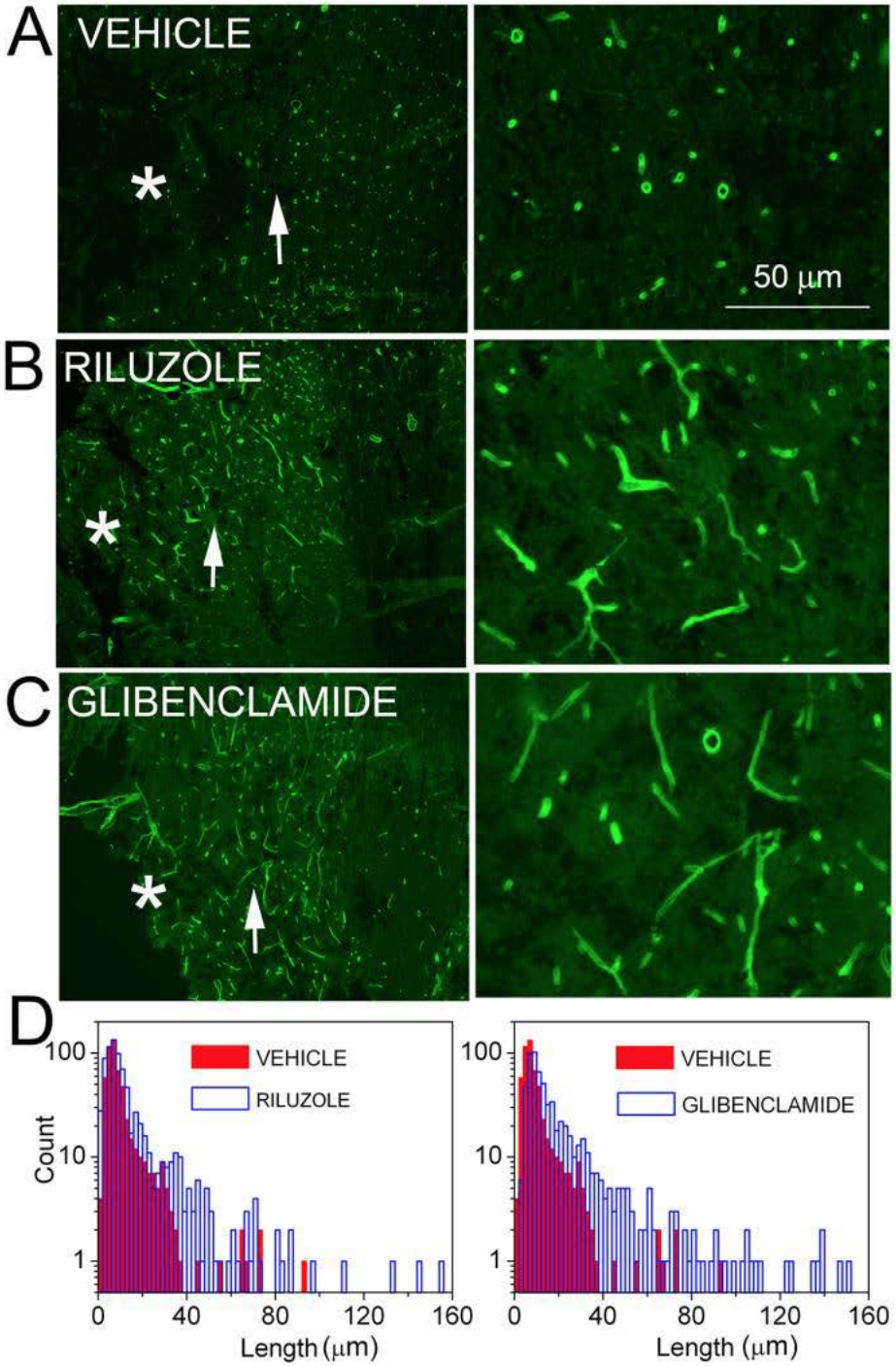








Simard et al 2007



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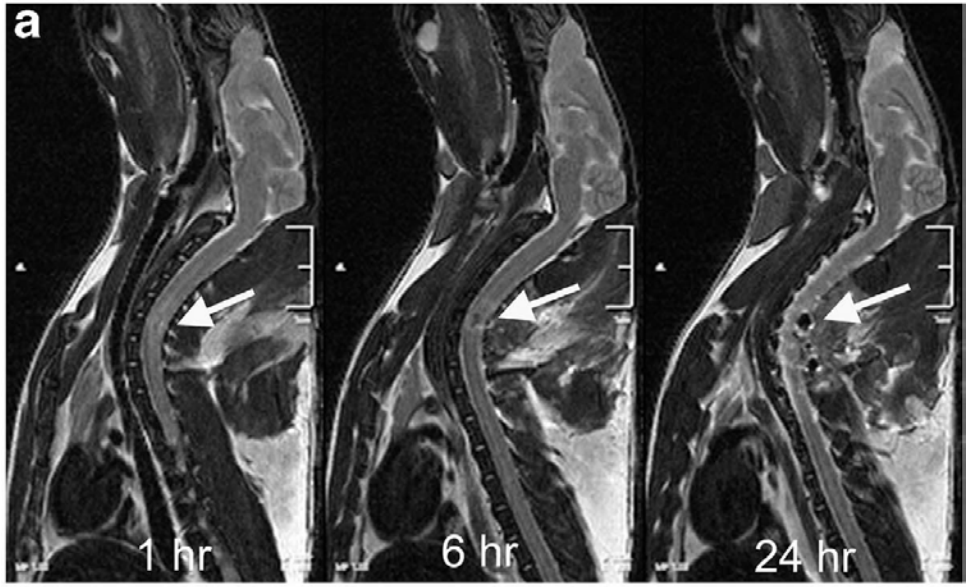
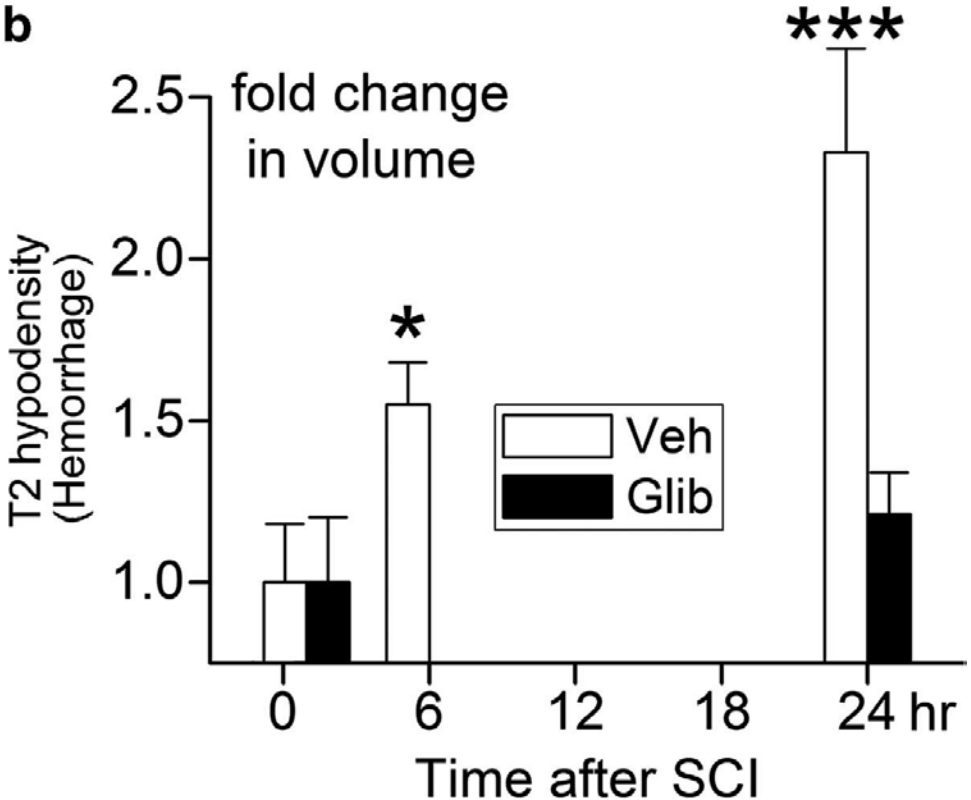
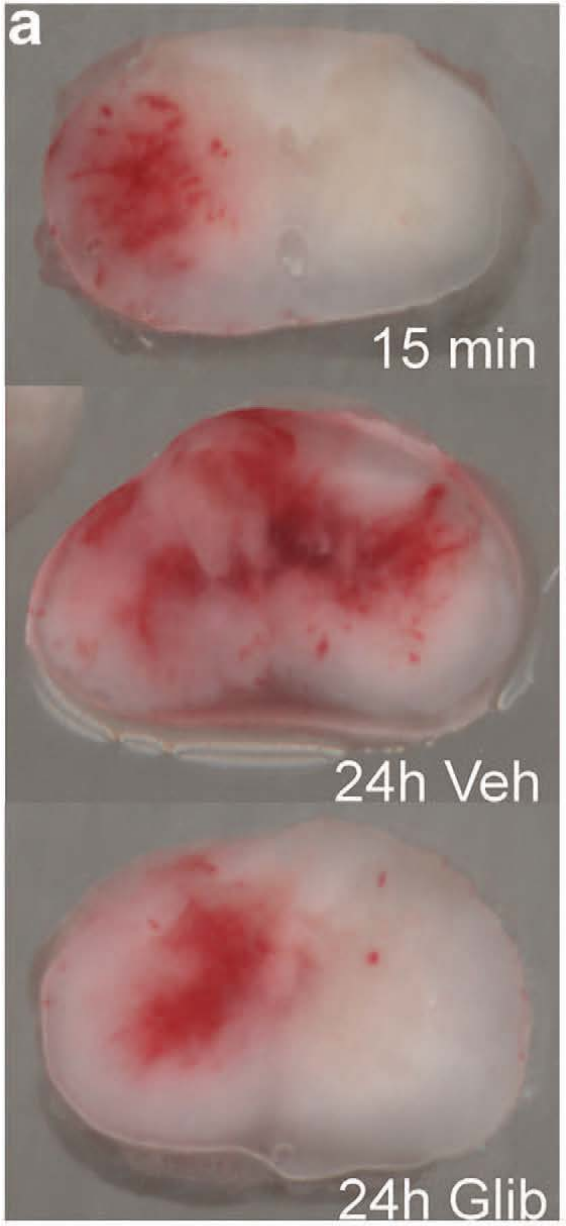
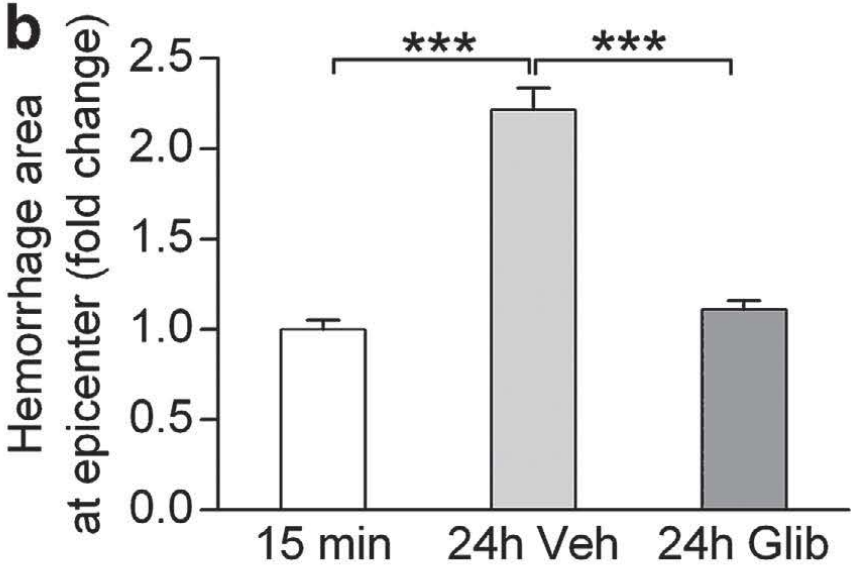
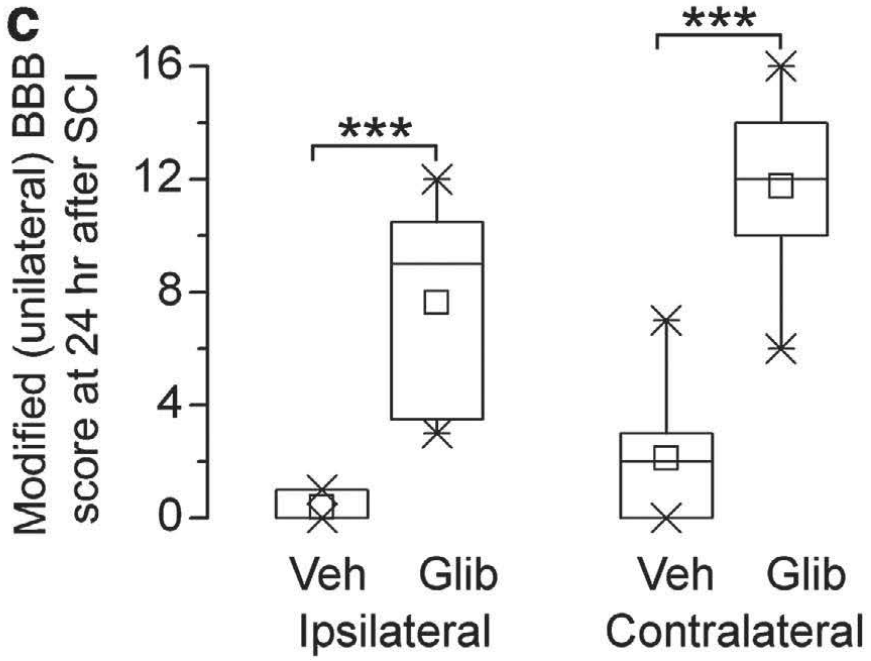




Simard et al 2013







Simard et al 2013

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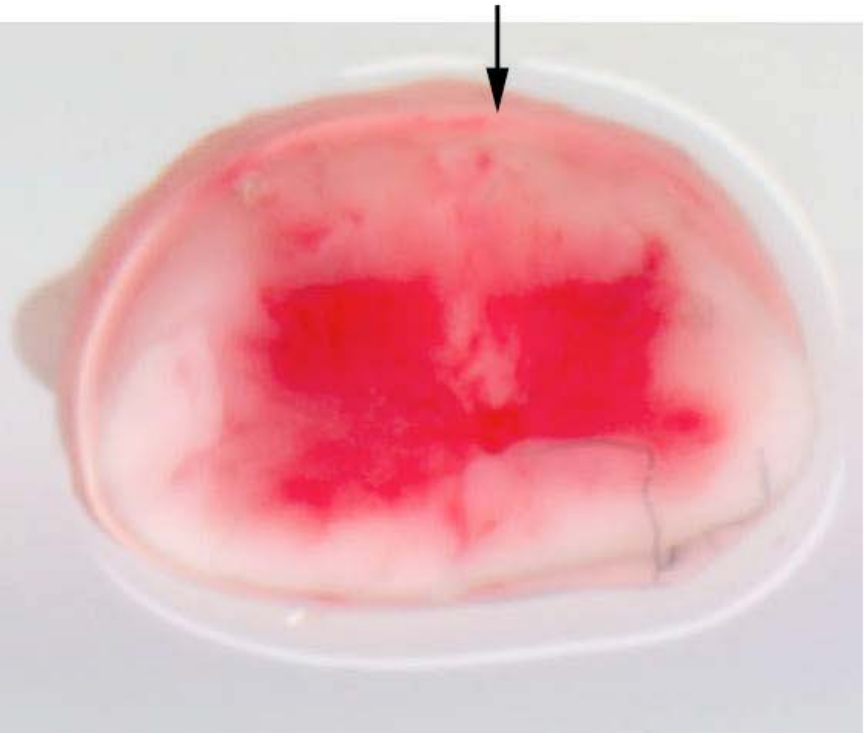

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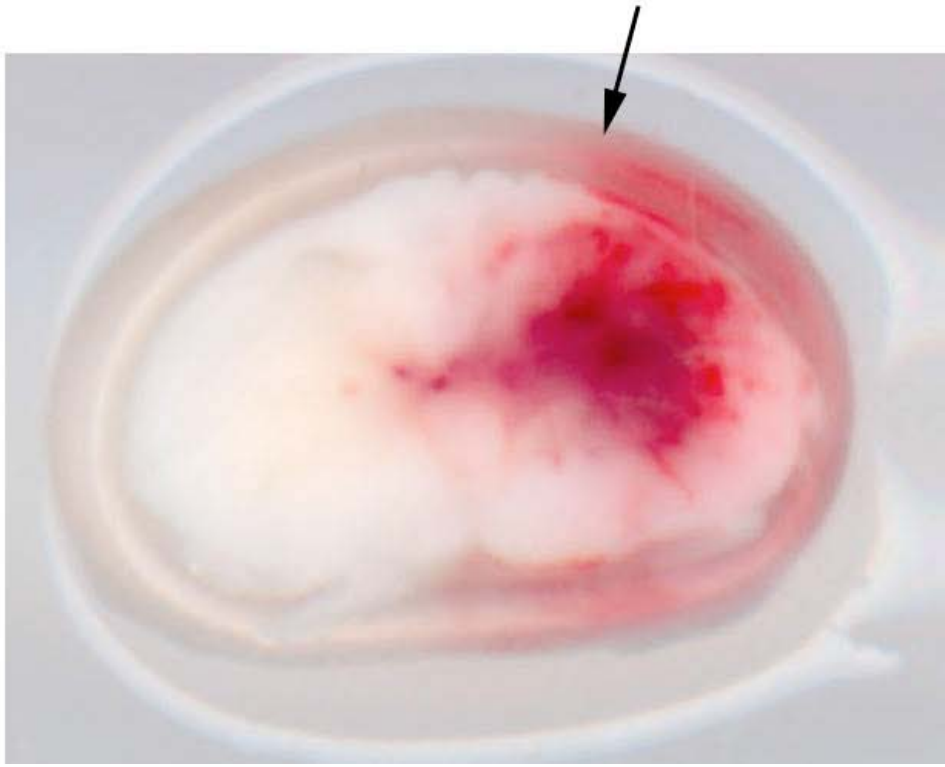
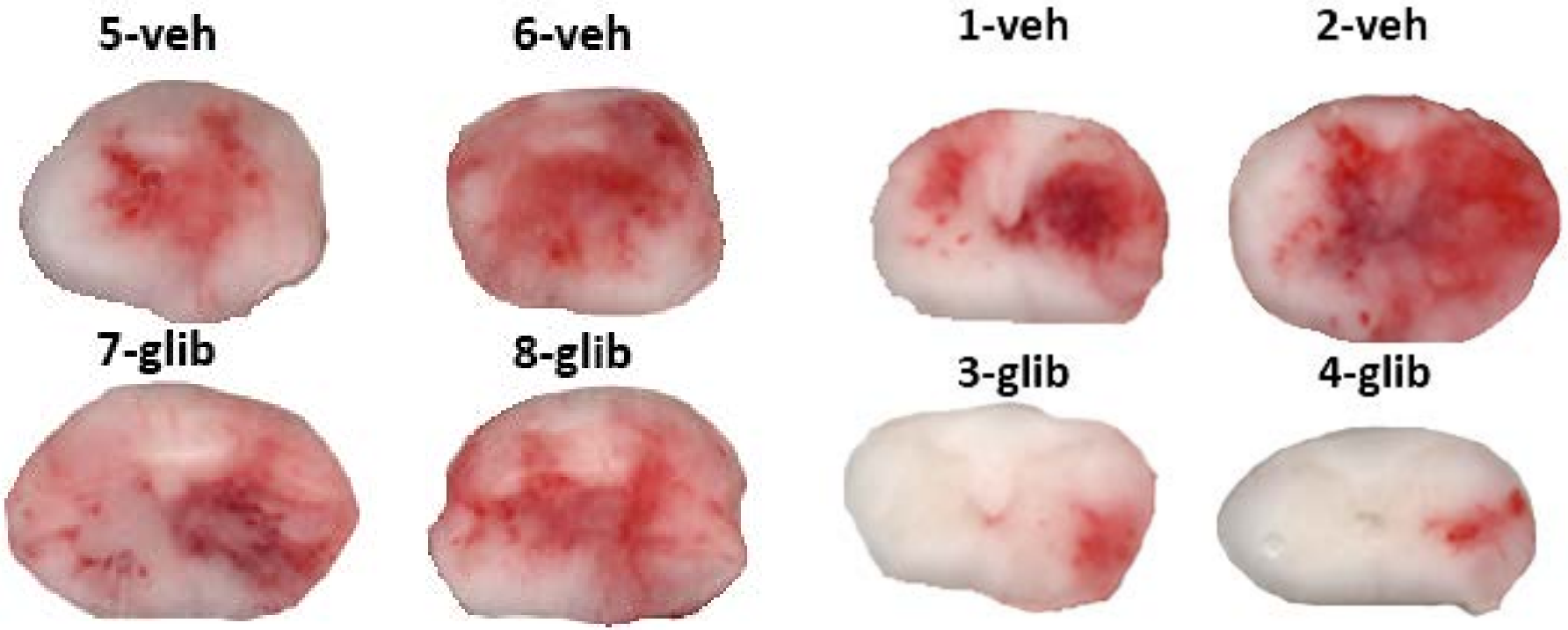


Popovich et al, 2012



Medial

Standard

Phase 1 – Injectable Glibenclamide (RP-1127)

- IV formulation
  - Maintain constant receptor occupancy
  - Avoid unpredictable GI absorption
- Evaluation of safety and tolerability of bolus dose followed by a 72 hr infusion
- Assess pharmacokinetics and glucose/insulin pharmacodynamic responses

No serious AEs including no ECG changes

3 mg/day not associated with hypoglycemia

Steady state plasma levels 27.3 ± 8.4 ng/mL

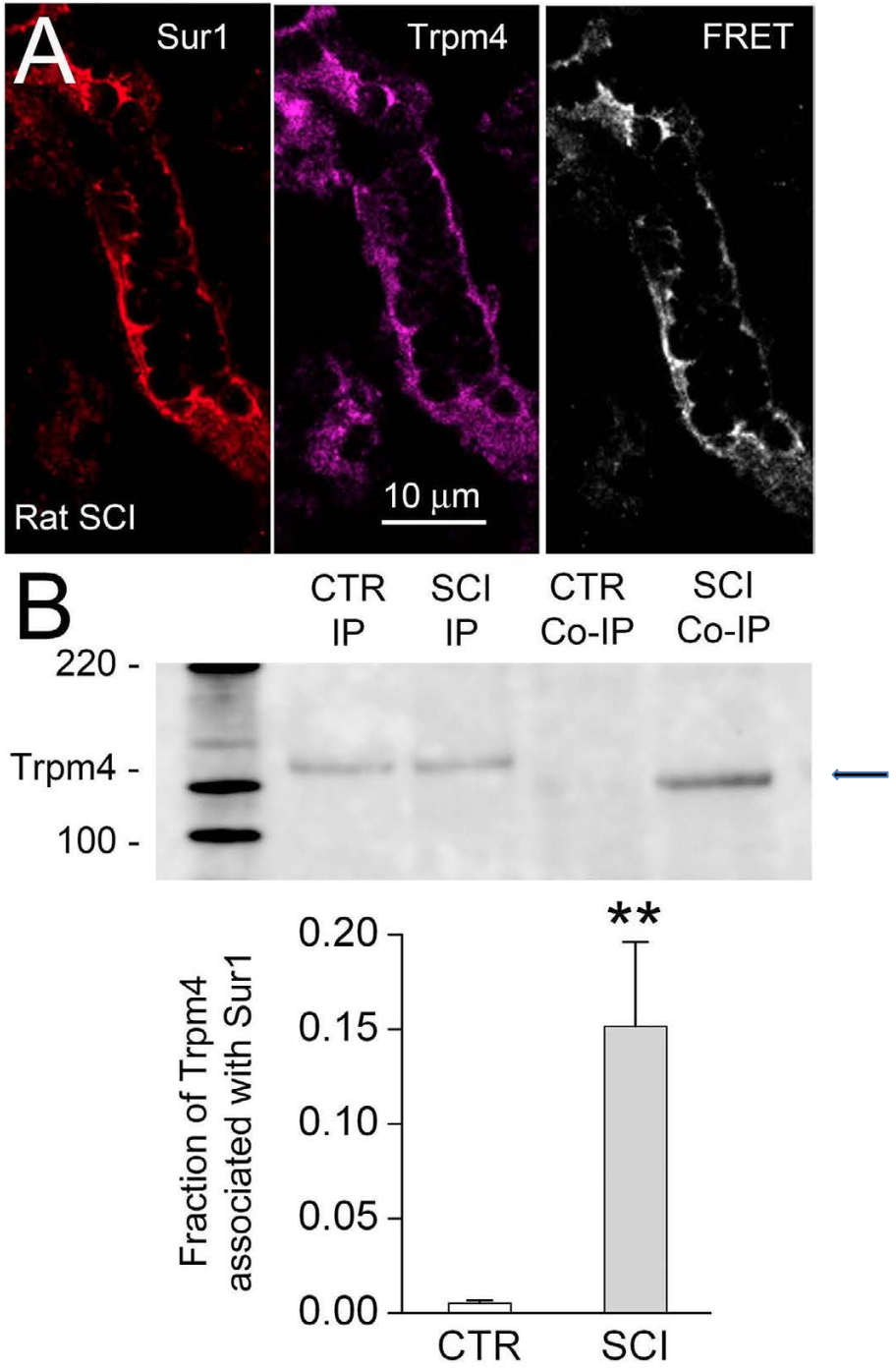
Dose	Number of Patients		
	RP-1127	Placebo	Total
0.02 mg bolus + 0.40 mg/day	8	2	10
0.13 mg bolus + 3.00 mg/day	16	4	20
0.26 mg bolus + 6.00 mg/day	1	1	2
0.43 mg bolus + 10.00 mg/day	1	1	2
Total	26	8	34

GAMES-RP Pilot and Phase II

- 10 patient open-label, 2 institutions
- Multicenter RCT, double-blind, 2-stage adaptive design
- Time from symptom onset to drug infusion ≤ 10 hrs

- Clinically feasible delivery method
- Degree of invasiveness and risk
- Suitability for multicenter study
- Cost – Industry partner ✔
- Optimization of dose, duration of therapy, and therapeutic window

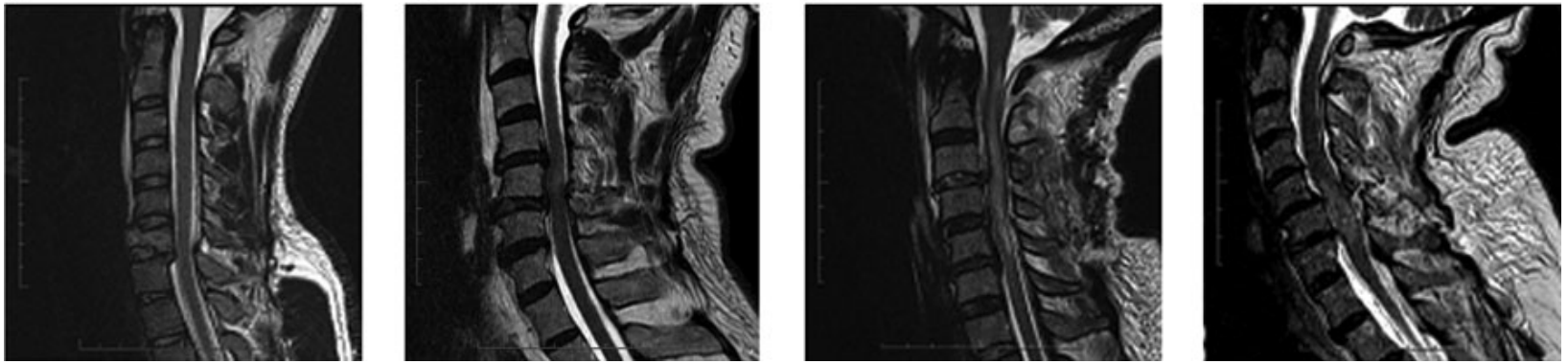
Sur1-Trpm4 channels expressed and activated *early* following SCI



Pilot phase open-label evaluation

- Under EFIC requirements for emergency research
- Administer drug as soon as IV established (on site, ED)
- Assess feasibility and safety (AEs)
- Compare to historical controls
- Include imaging arm

Sequence of drug administration vs imaging



Phase 2 Study

- **Primary Efficacy Outcome:** Determine if glibenclamide treatment versus placebo control results in neurological improvement in treated patients as measured by the ASIA motor score at 12 months

- **Primary Safety Outcomes:** Compare frequency and severity of AEs/SAEs (BG-related and cardiac-related safety)

- **Secondary Outcomes:** SCIM III, SF-36v2, SCI-QoL, change in T2 hyperintensity volume (need to stratify)

Inclusion Criteria

- Age ≥ 16 and ≤ 65,
- ASIA grades A, B, C
- C4-C8 injury levels

Exclusion Criteria

- Co-incident traumatic brain injury with GCS < 13
- EtOH threshold level
- Penetrating SCI
- Prisoner
- Pregnancy

Positives

- Glibenclamide is a long-standing FDA-approved anti-diabetic drug
- Independent pre-clinical replication
- Pre-clinical efficacy depends on injury model

Acknowledgements

- Marc Simard
- Kevin Sheth
- Michel Torbey