Masitinib for the treatment of amyotrophic lateral sclerosis (ALS)

Preclinical overview

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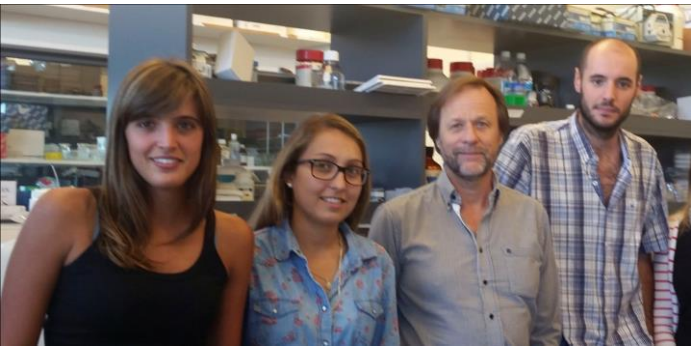
ENCALS Annual Meeting 2017

Ljubljana, Slovenia (18-20 May 2017)

Acknowledgments:



Emiliano Trias

Sofia Ibarburu

Romina Barreto

Olivier Hermine et al.

Patrice Dubreuil et al.

Joe Beckman et al.

Patricia Cassina et al.

Main Funding:

Disclaimer:
Partially funded by Ab Science since Dec 2016

Summary of recent clinical findings for masitinib in ALS

The phase 3 study of masitinib as an add-on therapy to riluzole in ALS was a success, with masitinib demonstrating a clinically meaningful retardation of disease progression

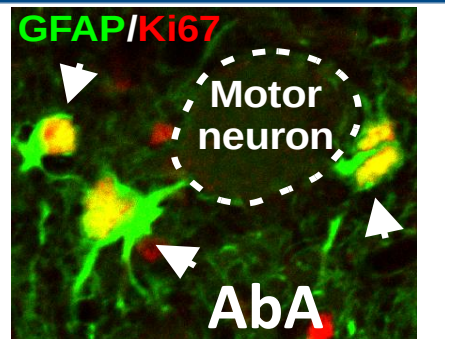
- Masitinib orally administered at 4.5 mg/kg/day in ALS patients with a baseline ALSFRS-R progression rate of <1.1 points/month showed significant disease retardation in terms of:
  - ΔALSFRS-R and ALSFRS-R slope
  - Time elapsed between treatment initiation and decline in ALSFRS-R of nine points (PFS)
  - ALSAQ-40 score
  - FVC

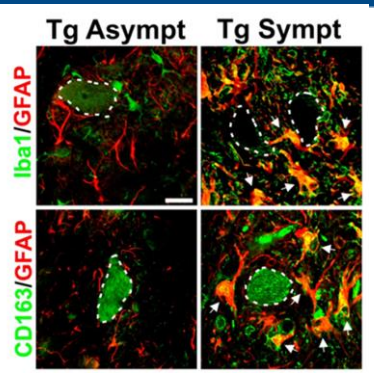
AB SCIENCE

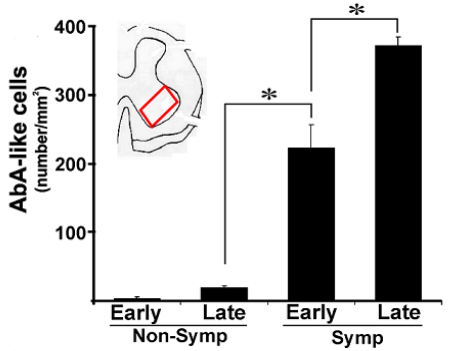
These positive clinical findings are supported by equally compelling preclinical data

Why post-paralysis tyrosine kinase inhibition in ALS?

Identification of aberrant glial cells that proliferate after paralysis onset in SOD1^{G93A} rats







Tyrosine kinase inhibitors target aberrant glial cells via CSF1R

Post-paralysis treatment with masitinib slows paralysis progression in SOD1^{G93A} rats

AB Science launches phase 2/3 clinical trial with masitinib
- **Double blind**
- **394 patients, 3 arms**
- **48 weeks**

Positive therapeutic effects

2011 — **2014** — **2016**

PNAS

Phenotypically aberrant astrocytes that promote motoneuron damage in a model of inherited amyotrophic lateral sclerosis

Pablo Díaz-Amarilla[a], Silvia Olivera-Bravo[a], Emiliano Trias[a], Andrea Cragnolini[b], Laura Martínez-Palma[c], Patricia Cassina[c], Joseph Beckman[d,e], and Luis Barbeito[a,b,1]

Phenotypic transition of microglia into astrocyte-like cells associated with disease onset in a model of inherited ALS

*Emiliano Trias[1], Pablo Díaz-Amarilla[1], Silvia Olivera-Bravo[1], Eugenia Isasi[1], Derek A. Drechsel[2,3], Nathan Lopez[2,3], C. Samuel Bradford[2,3], Kyle E. Ireton[2,3,5], Joseph S. Beckman[2,3,4] and Luis Barbeito[5]**

Trias *et al. Journal of Neuroinflammation* (2016)

RESEARCH

Post-paralysis tyrosine kinase inhibition with masitinib abrogates neuroinflammation and slows disease progression in inherited amyotrophic lateral sclerosis

Significance of aberrant glial cell phenotypes in pathophysiology of amyotrophic lateral sclerosis

Emiliano Trias, Sofia Ibarburu, Romina Barreto-Núñez, Luis Barbeito*

Isolation and characterization of aberrant glial cells (AbAs)

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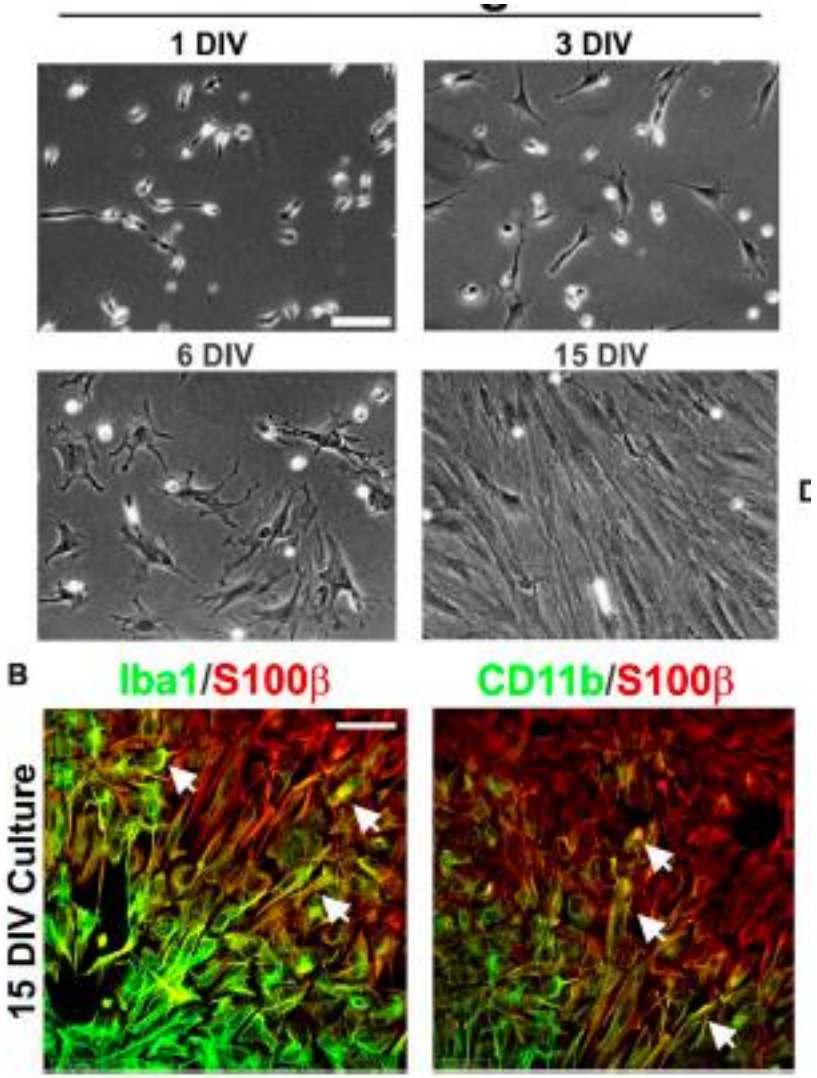
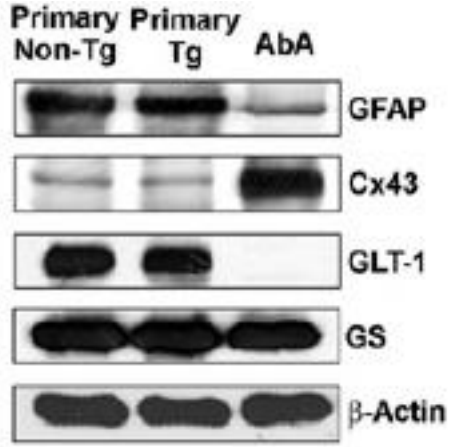
Symptomatic SOD1^{G93A} rat

Spinal Cord culture





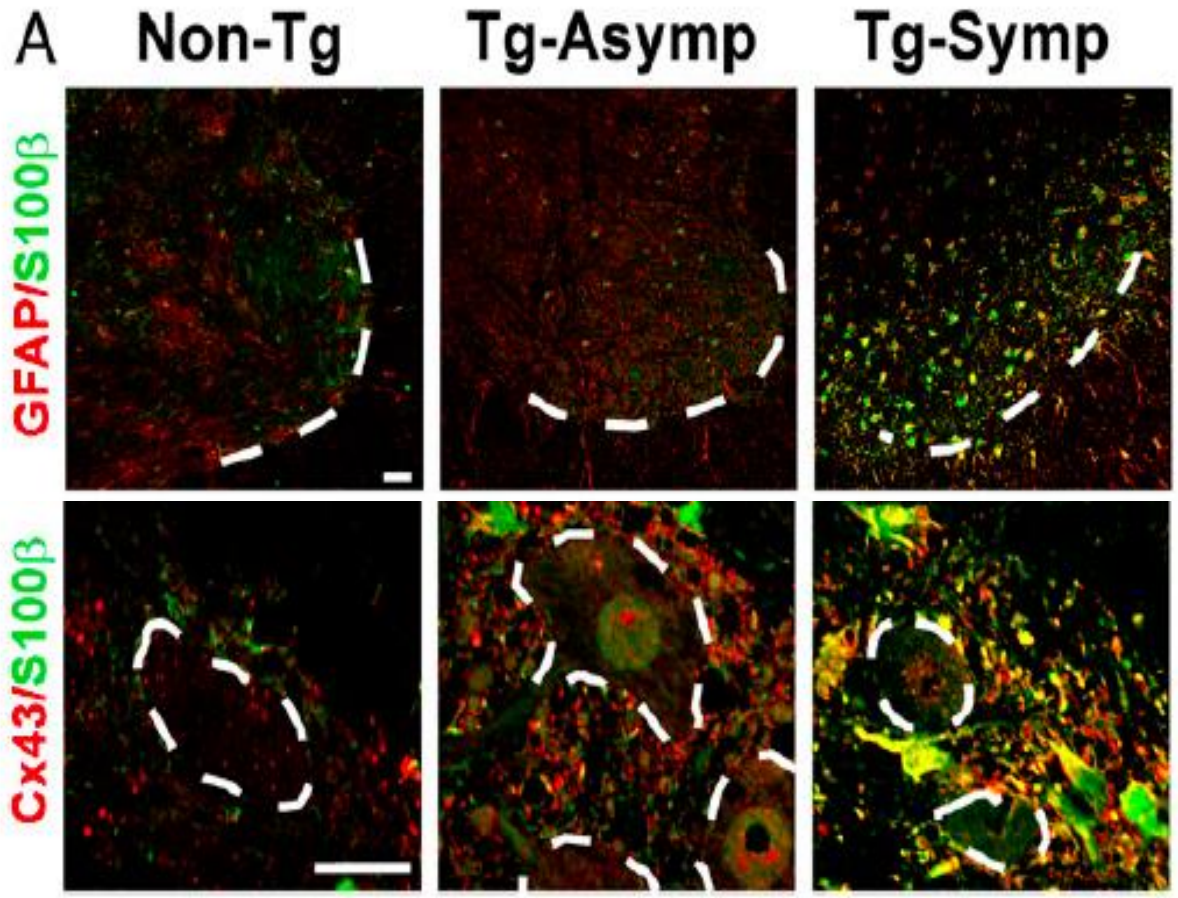
Relevant:

AbAs are the most toxic cells yet identified to embryonic motor neurons in cell culture

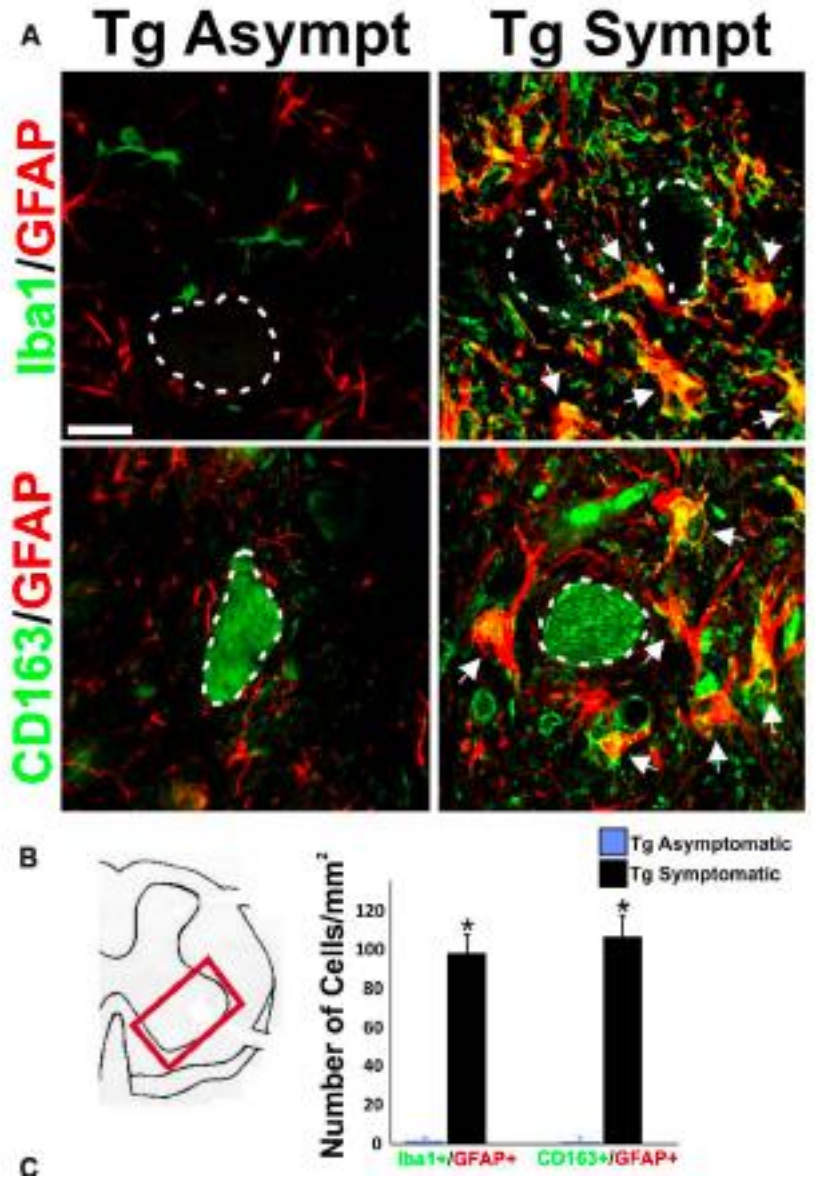
Díaz-Amarilla et al, 2011

Trias et al, 2013

Identification of aberant glial cells in the degenerating spinal cord



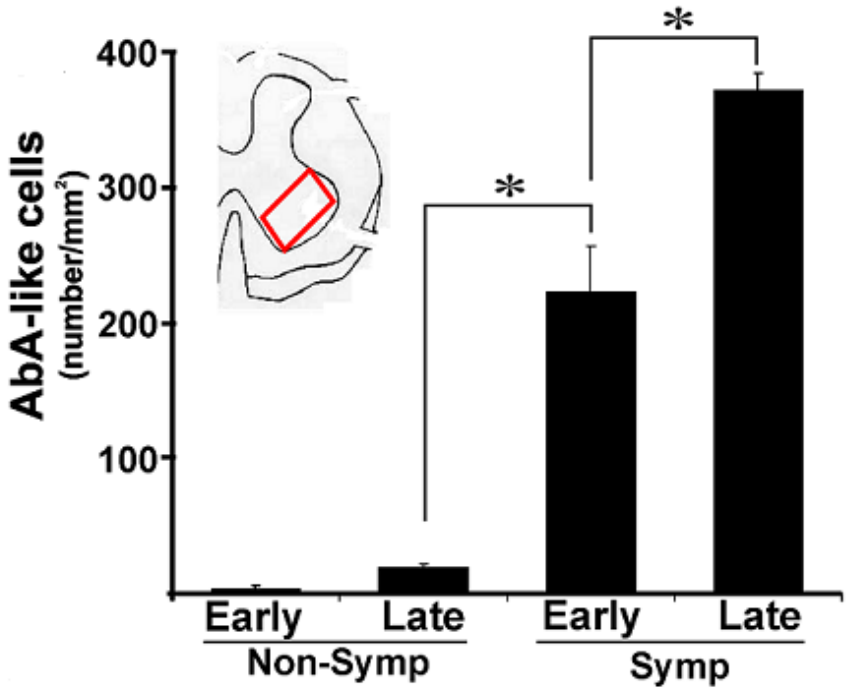
- Appear around damaged motor neurons
- Express mixed astrocytic/microglial markers

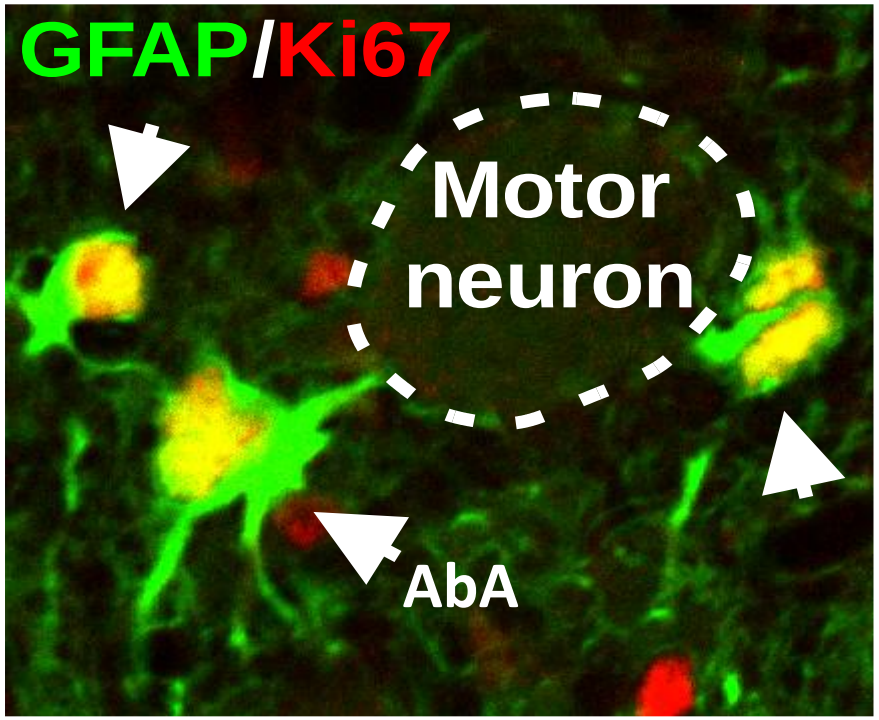


Díaz-Amarilla et al, 2011

Trias et al, 2013

AbA proliferation after paralysis onset





- **Emerge only after paralysis onset (mediate rapid paralysis progression in SOD1G93A rats?)**
- **Active proliferation (targeted by antineoplasic drugs?)**
- **Lack of replicative senescence in vitro**

Díaz-Amarilla et al, 2011

Trias et al, 2013

Masitinib as a prototypic inhibitor of type III growth factor receptors

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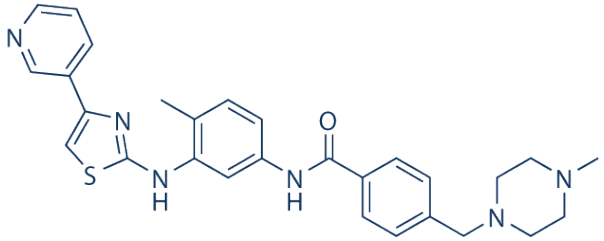
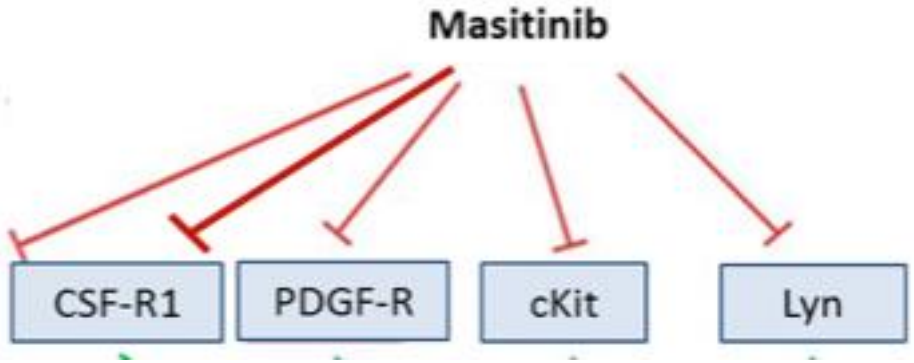
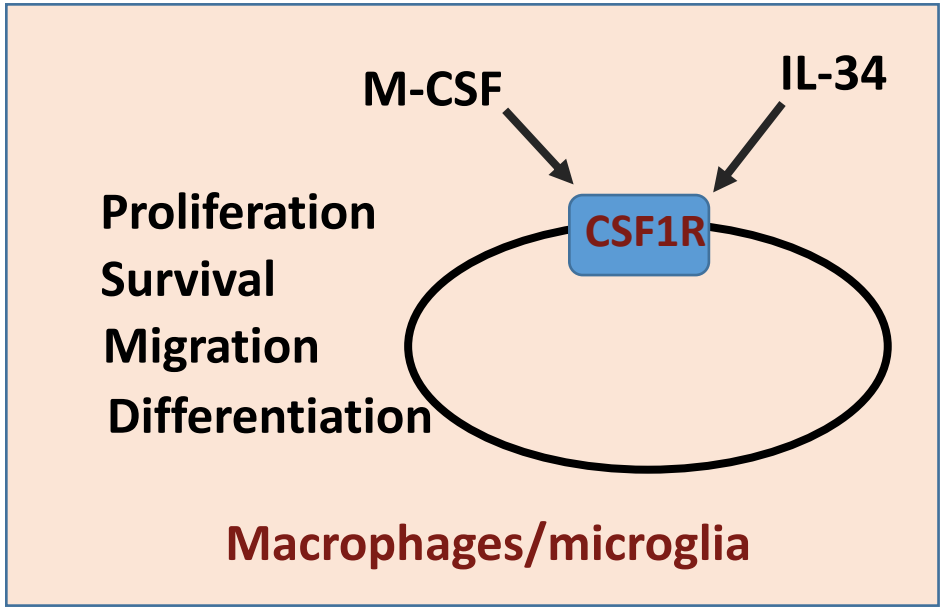
Masitinib (AB1010)

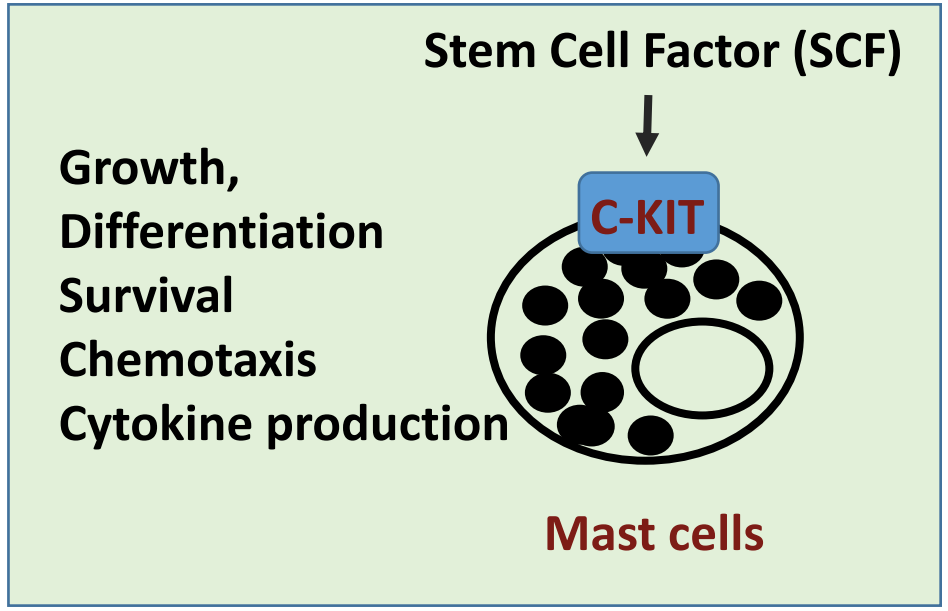


Olivier Hermine



- **Anti-neoplasic drug (mast cell tumors & others)**
- **Currently in clinical trials for ALS, Alzheimer's disease, MS, severe indolent mastocytosis and severe asthma.**





Masitinib treatment after paralysis onset increases survival of SOD1^{G93A} rats

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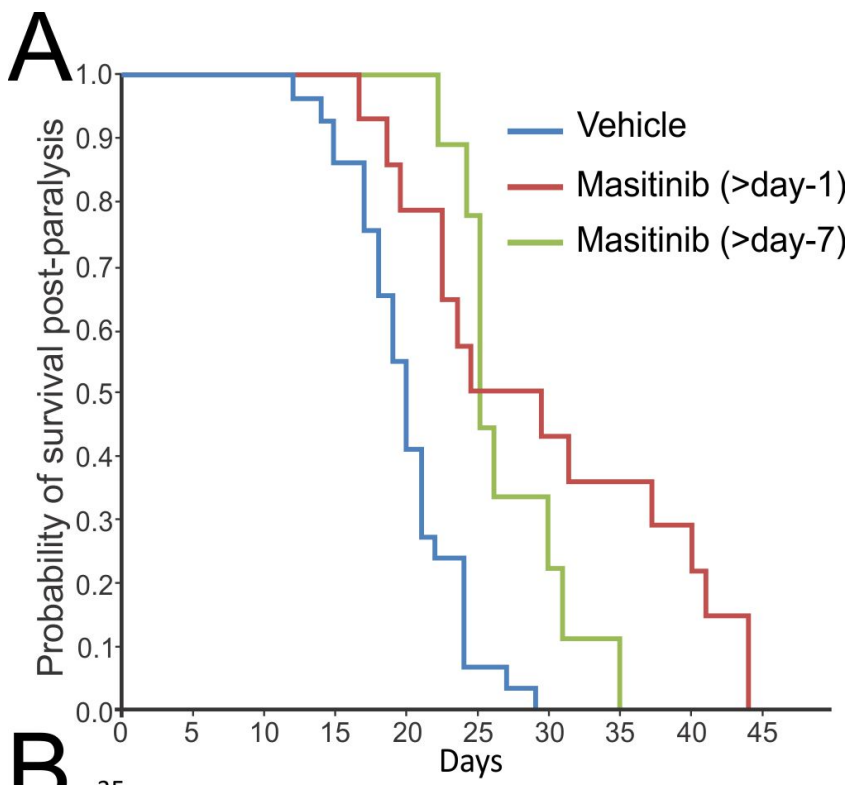
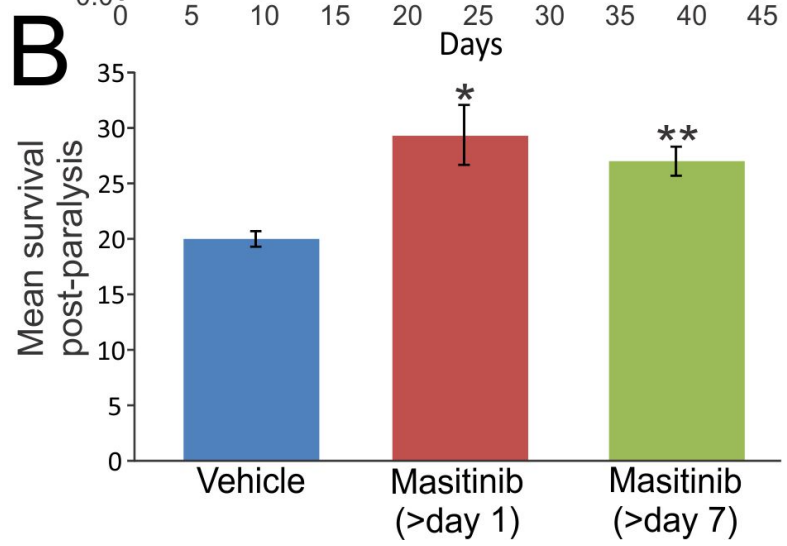
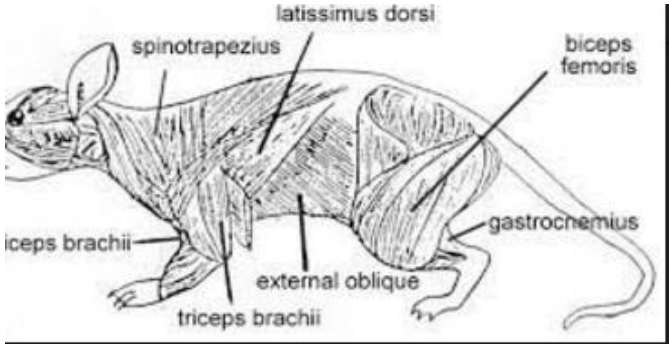




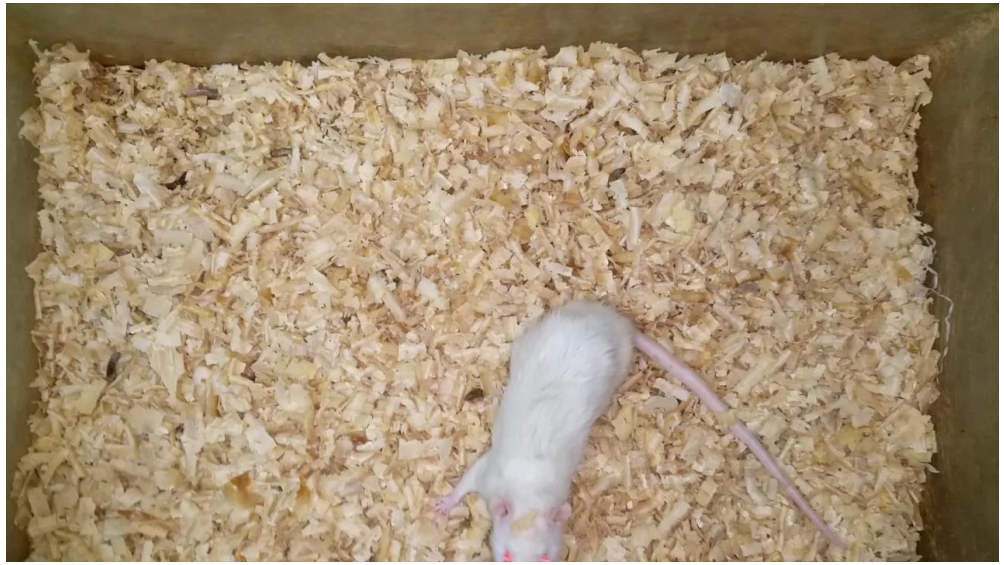
- Daily oral Masitinib (30mg/k) or vehicle administration, starting after paralysis onset
- Survival was increased even when treatment was started 7 days after paralysis onset.
- Masitinb prolongs post-paralysis survival with minor effects on overall survival.
- Well adapted to ALS clinical setting

Trias et al, JNI 2016

Hindlimb paralysis onset (day 1)
(5-6 months old)



Vehicle (20d after onset)

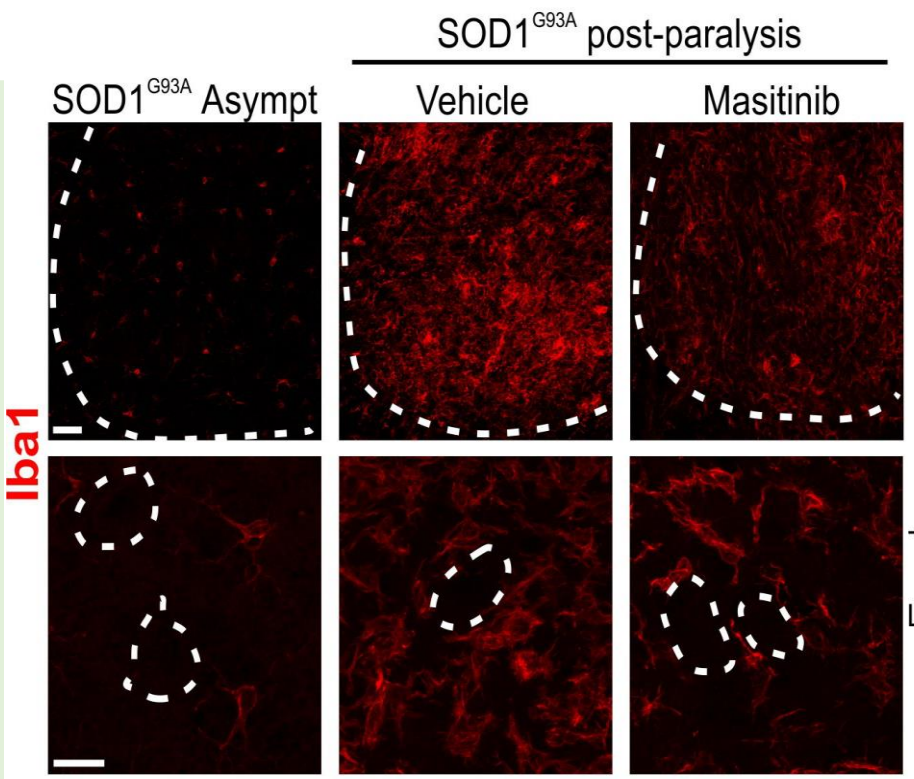


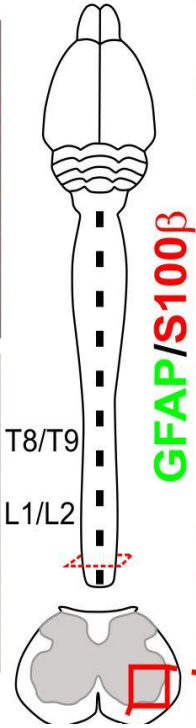
Masitinib (30 mg/kg)

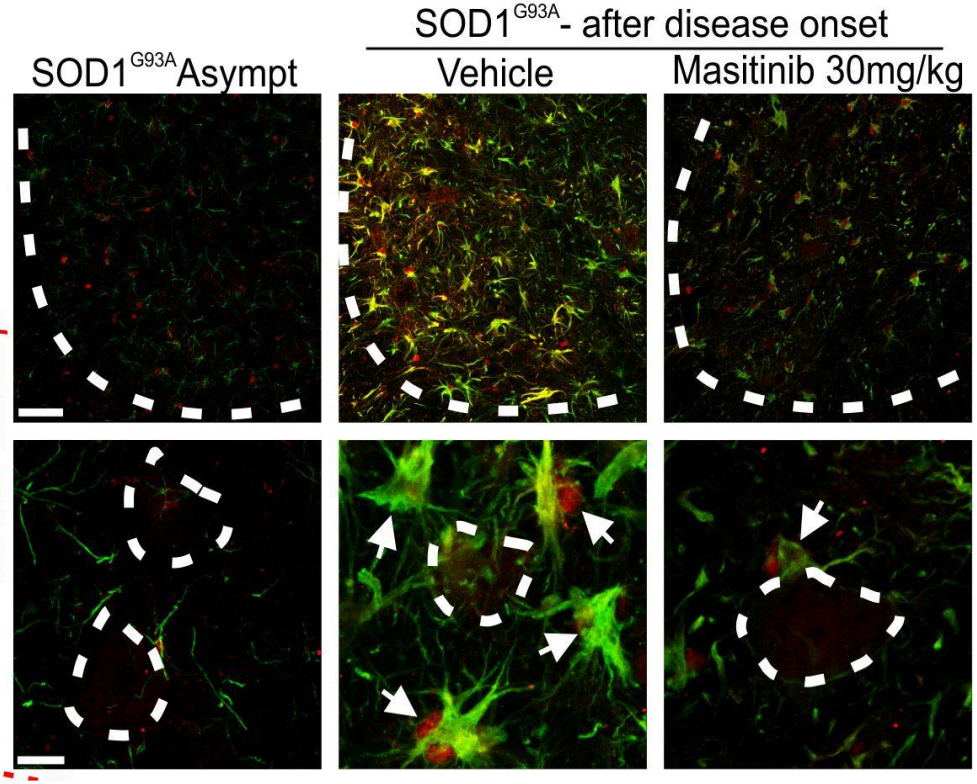
MOA-1:
Reduction of microgliosis and aberrant glial cells through CSF-1R inhibition

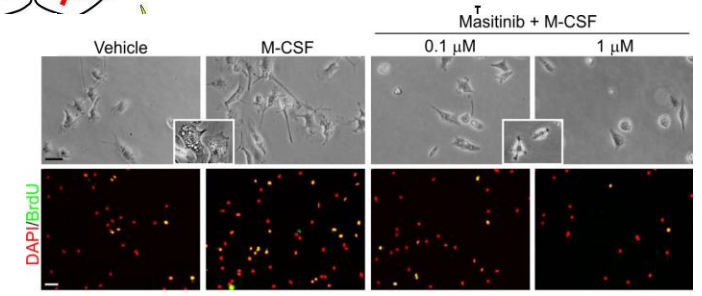
Method:

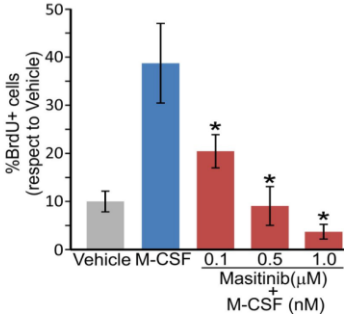
- Treatment starting day 1 post-paralysis lasting 20 days.
- Masitinib 30mg/kg vs vehicle orally, 7/7 d
- Hindlimb onset only







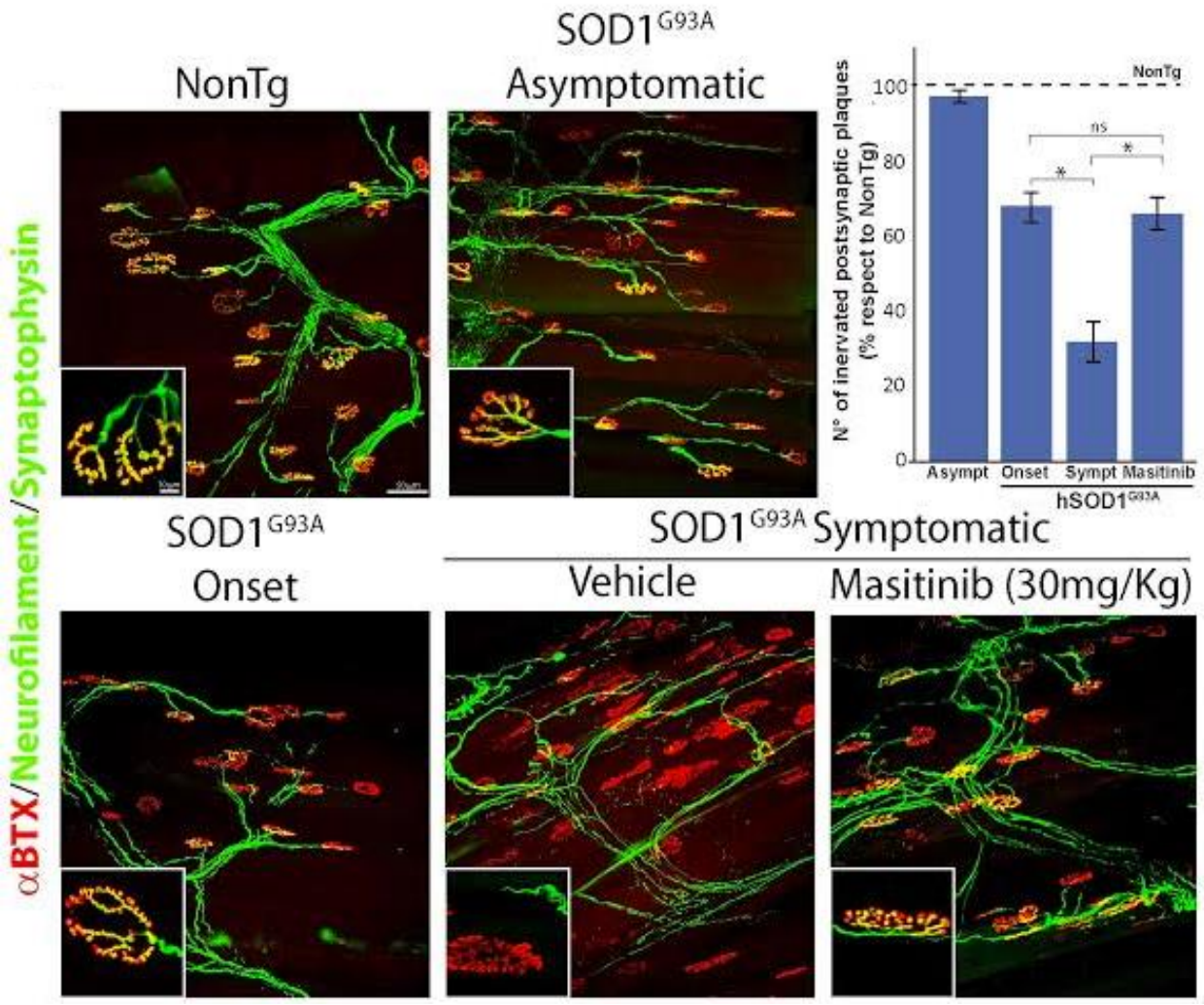




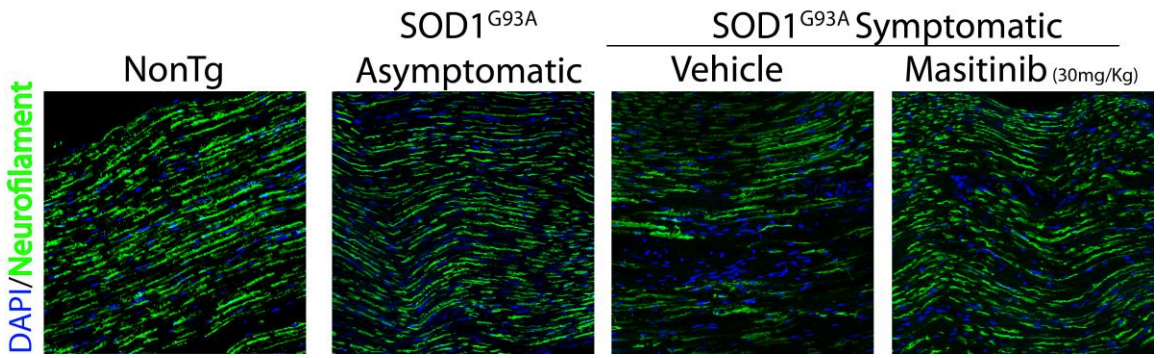
Trias et al, JNI 2016

Masitinib prevents motor neuron degeneration

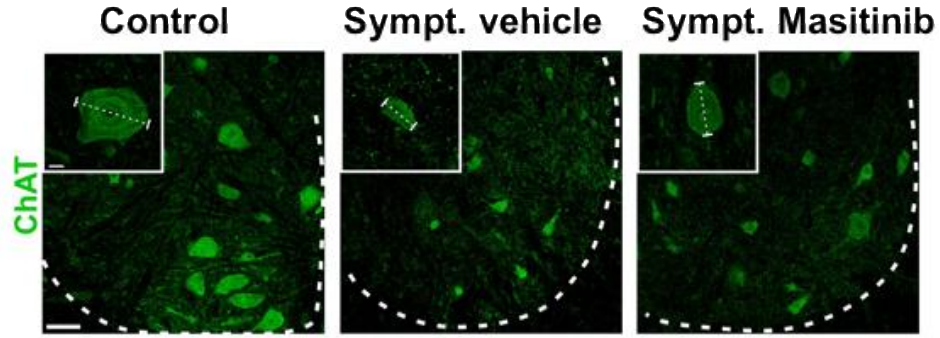
Institut Pasteur de Montevideo



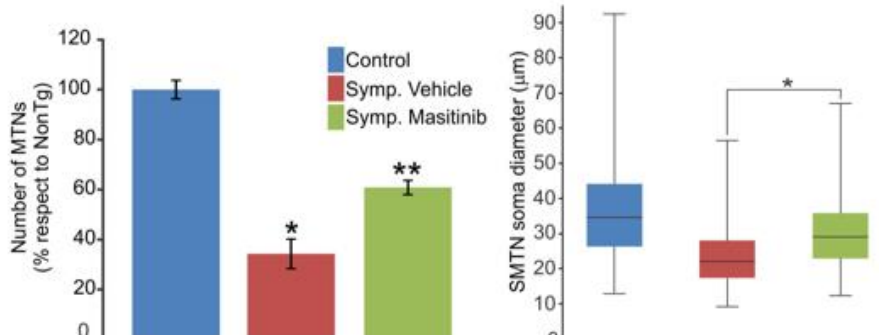
NMJs (EDL muscle)



Sciatic nerve

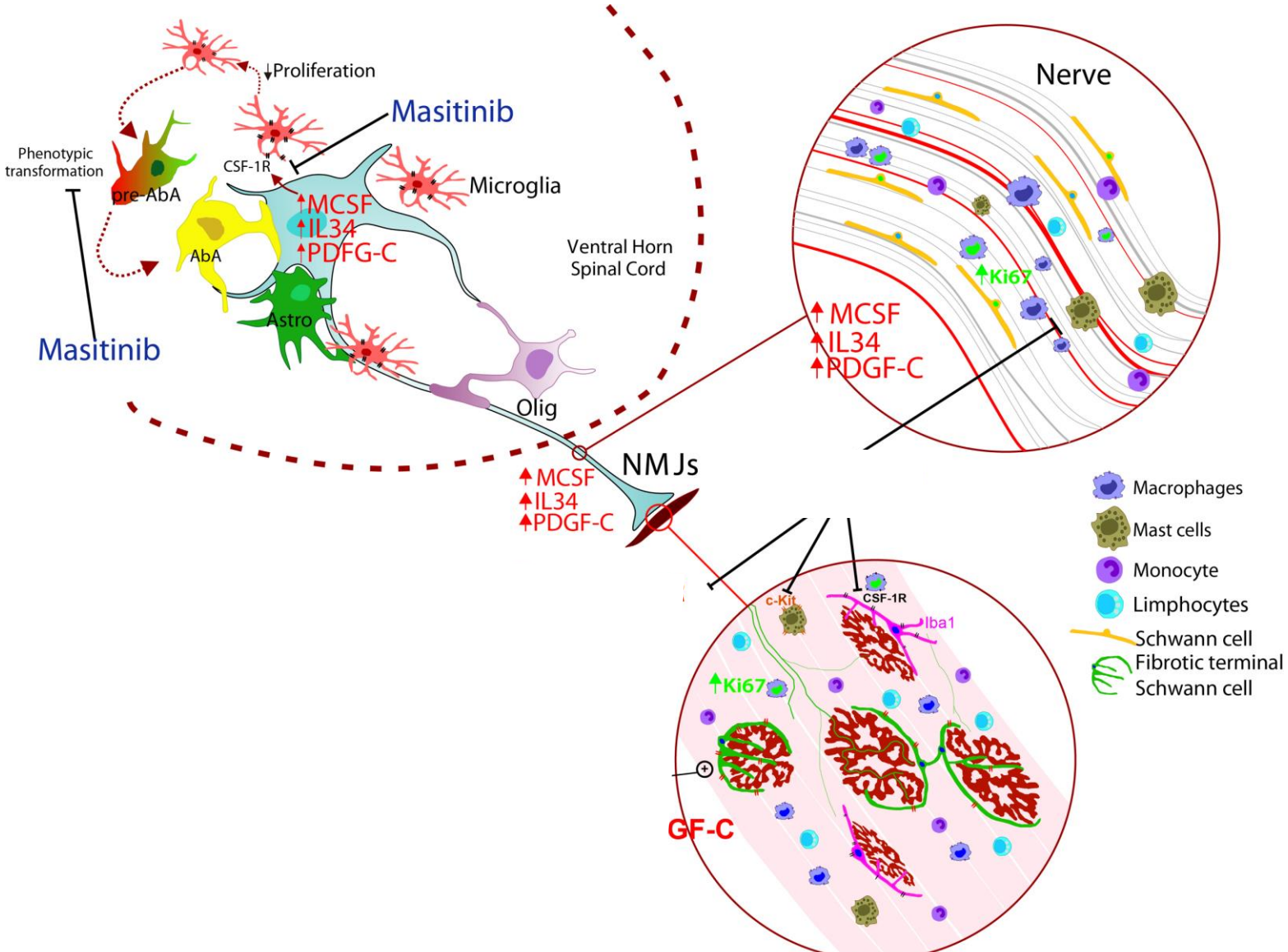


Spinal cord



Trias et al, JNI 2016

Alternative cellular targets for masitinib in the PNS



Mast cells cluster together with motor nerve endings and macrophages in EDL muscle

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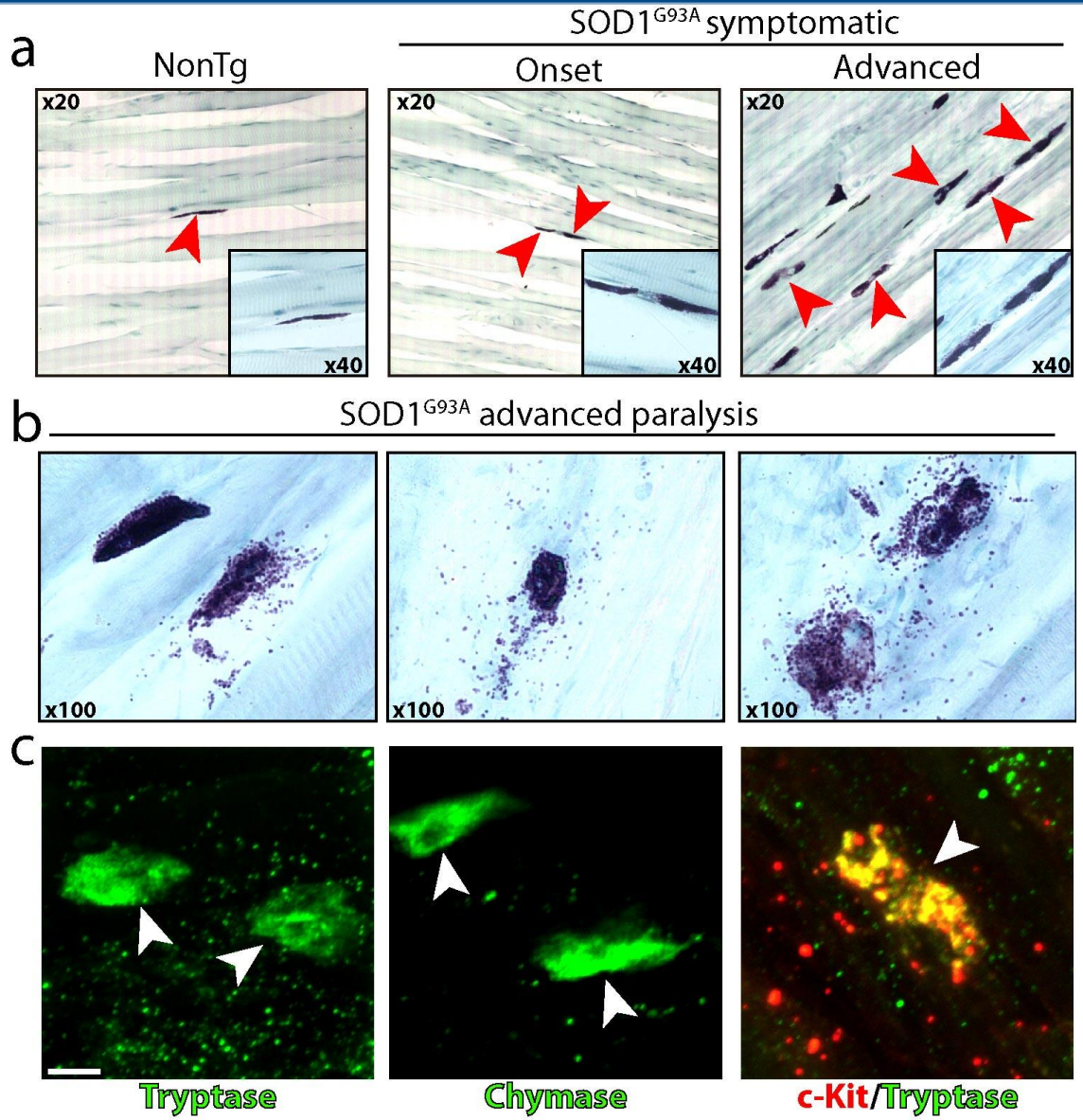

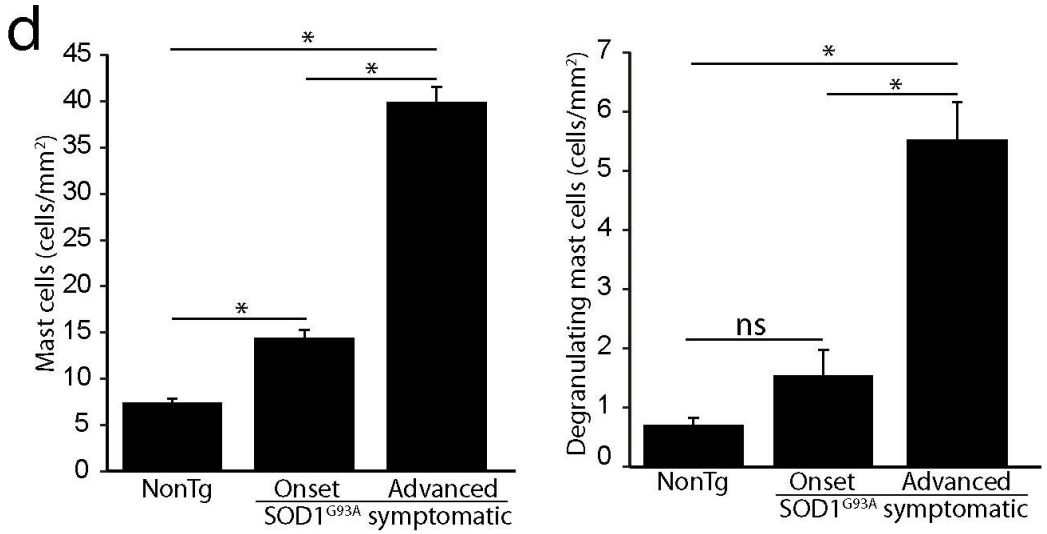

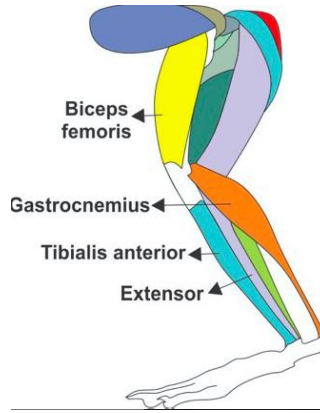

Trias et al, Unpublished data

Mast cells cluster together with motor nerve endings and macrophages in EDL muscle

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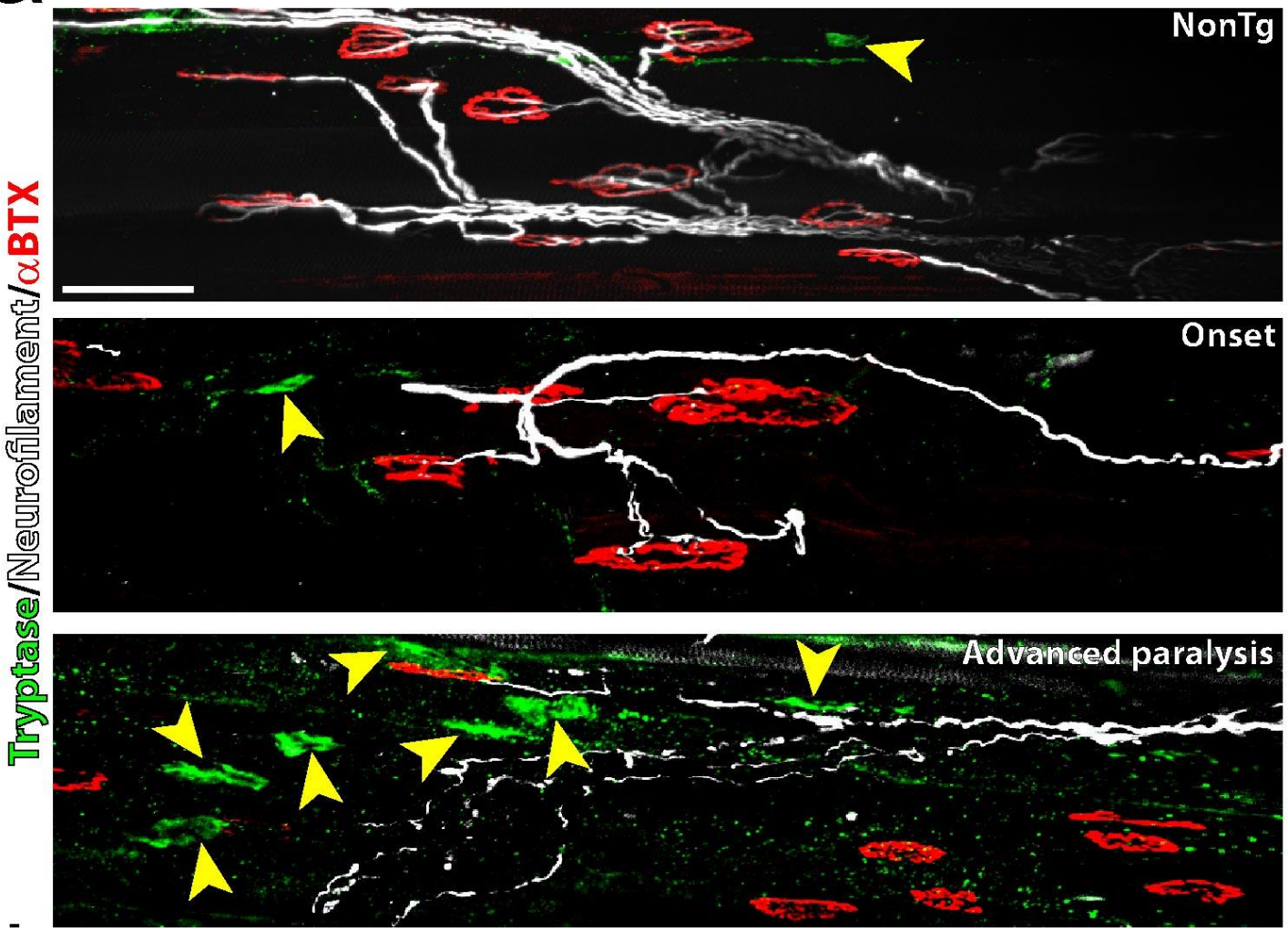

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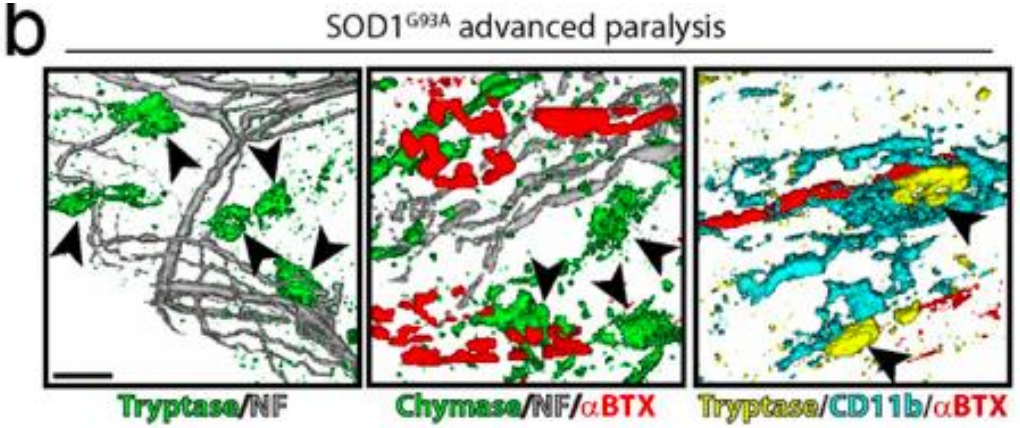
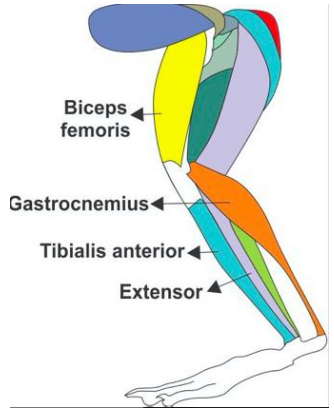
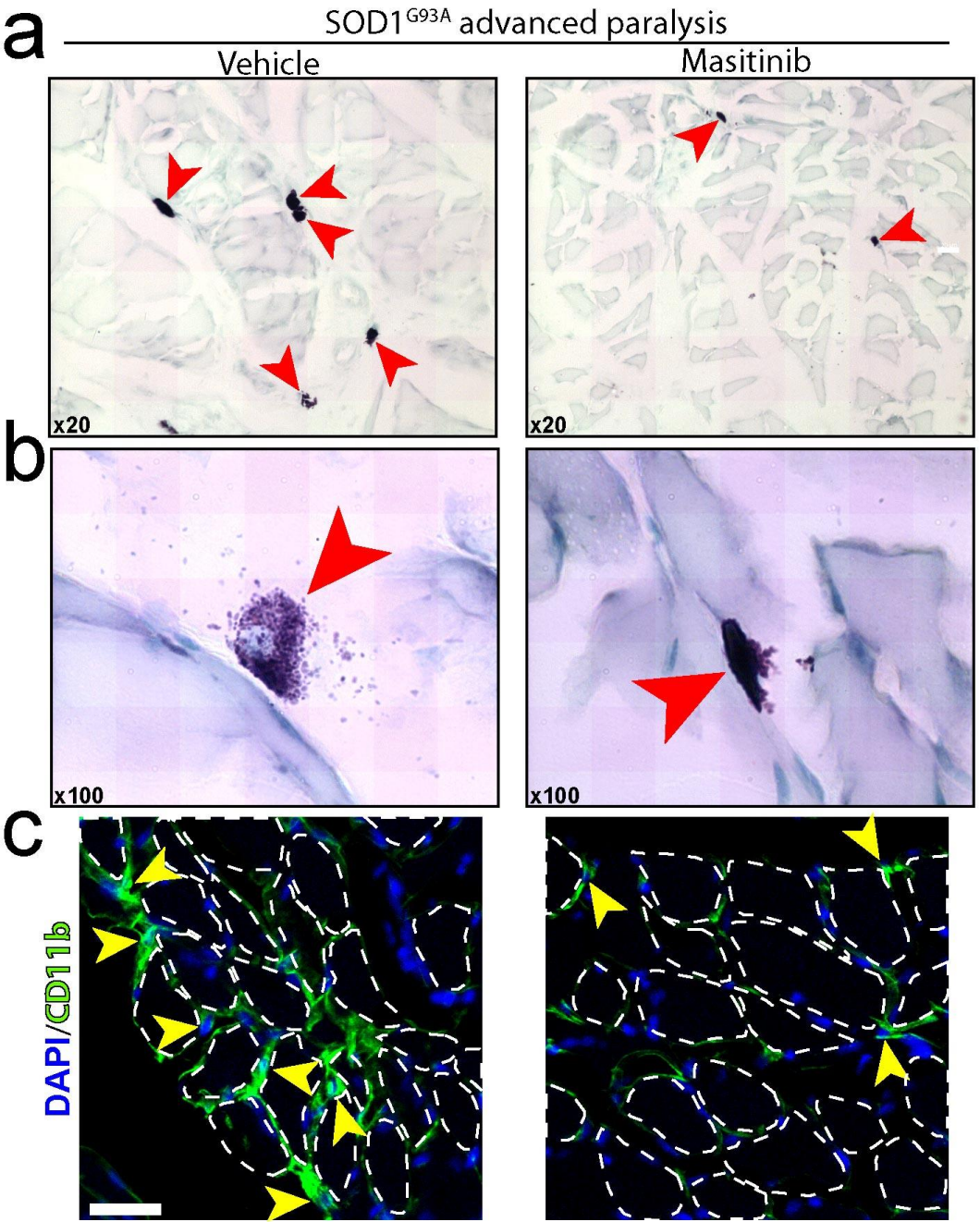
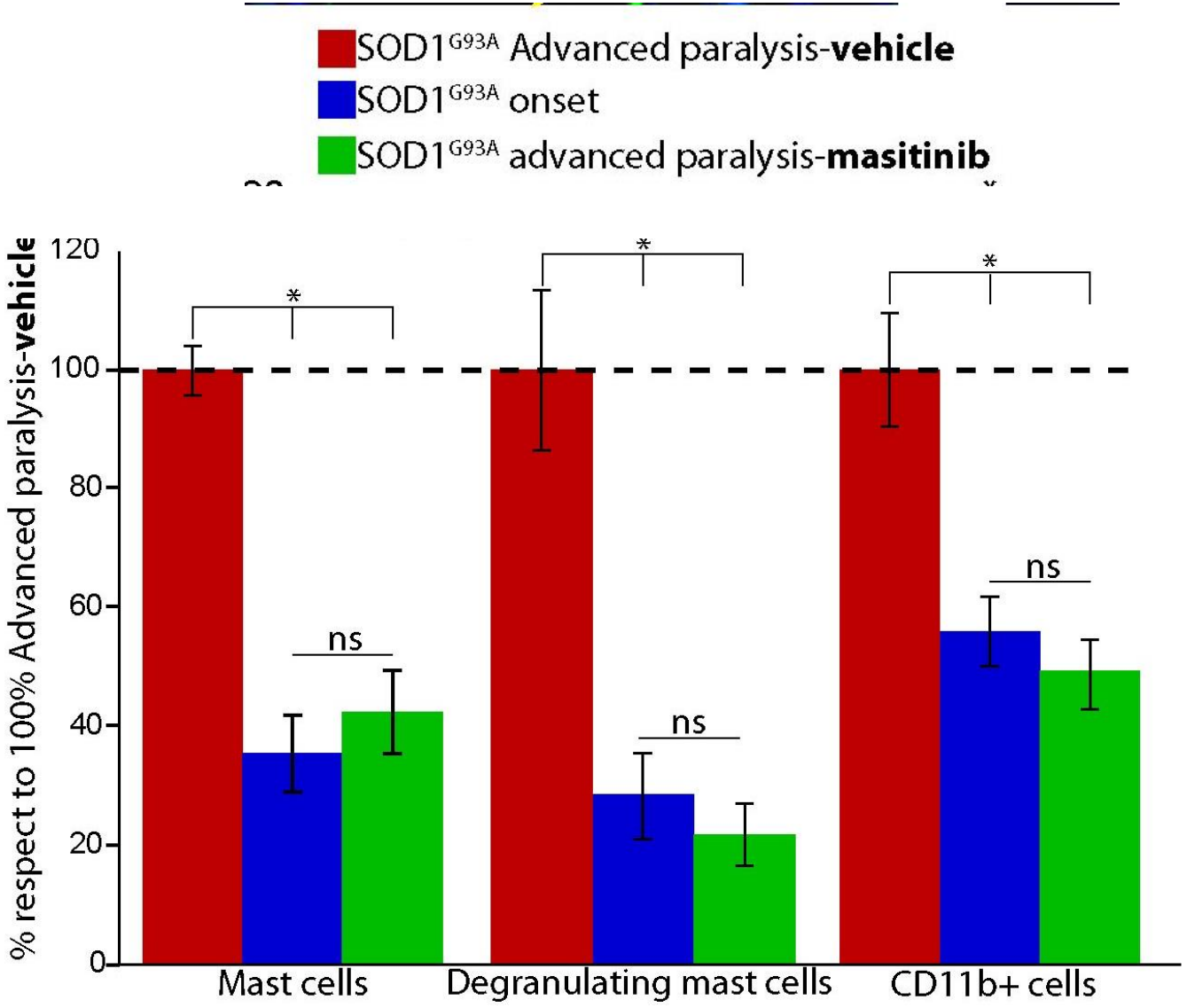




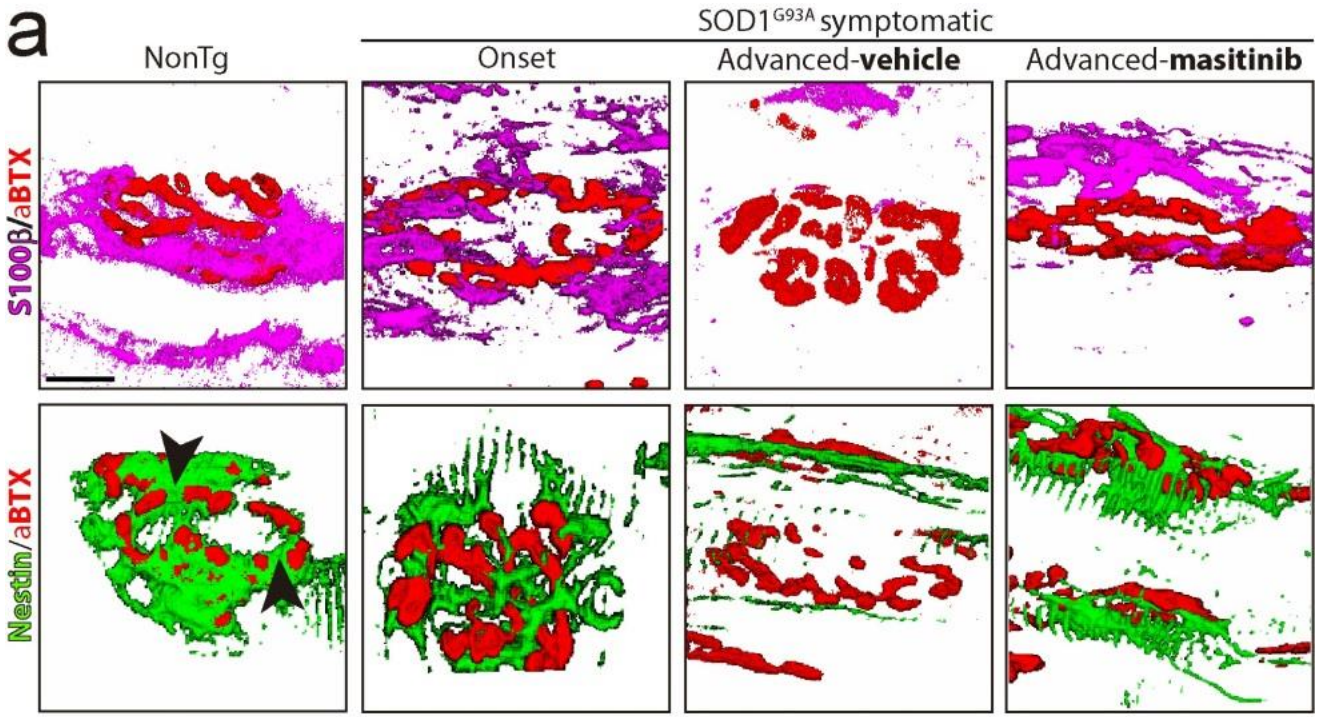
Trias et al, Unpublished data

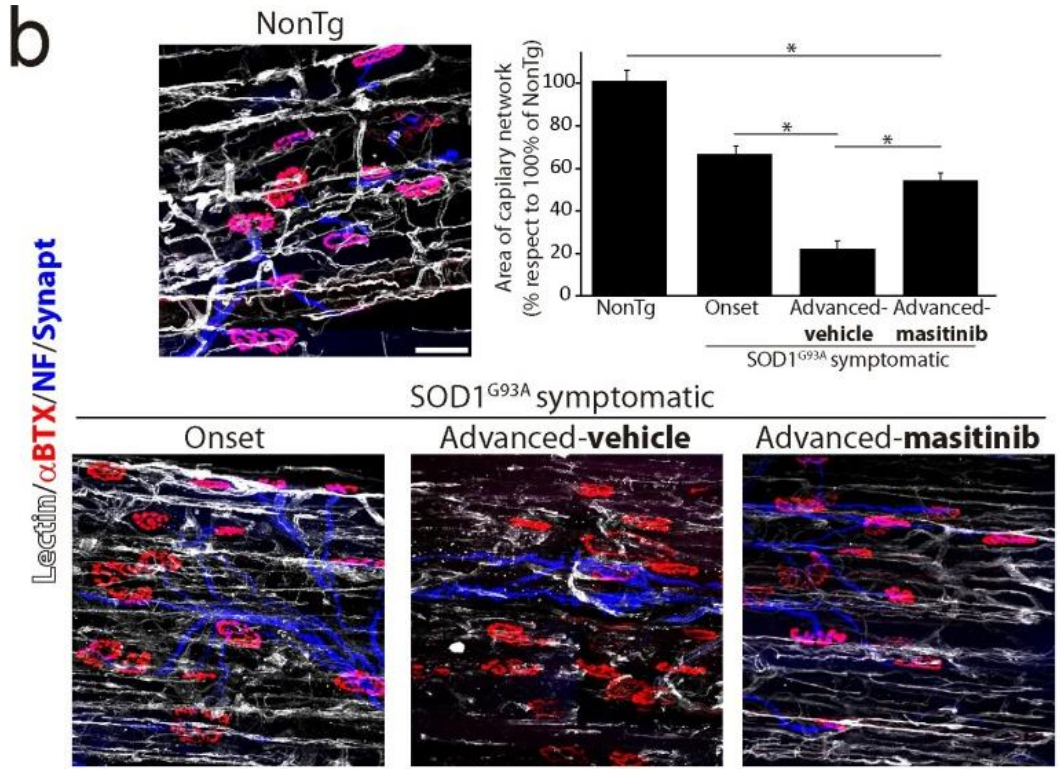
MOA 2: Masitinib prevents mast cell and macrophage infiltration in the PNS





Masitinib prevents Schwann cells and vascular remodeling





Masitinib reduces mast cells accumulation in the sciatic nerve

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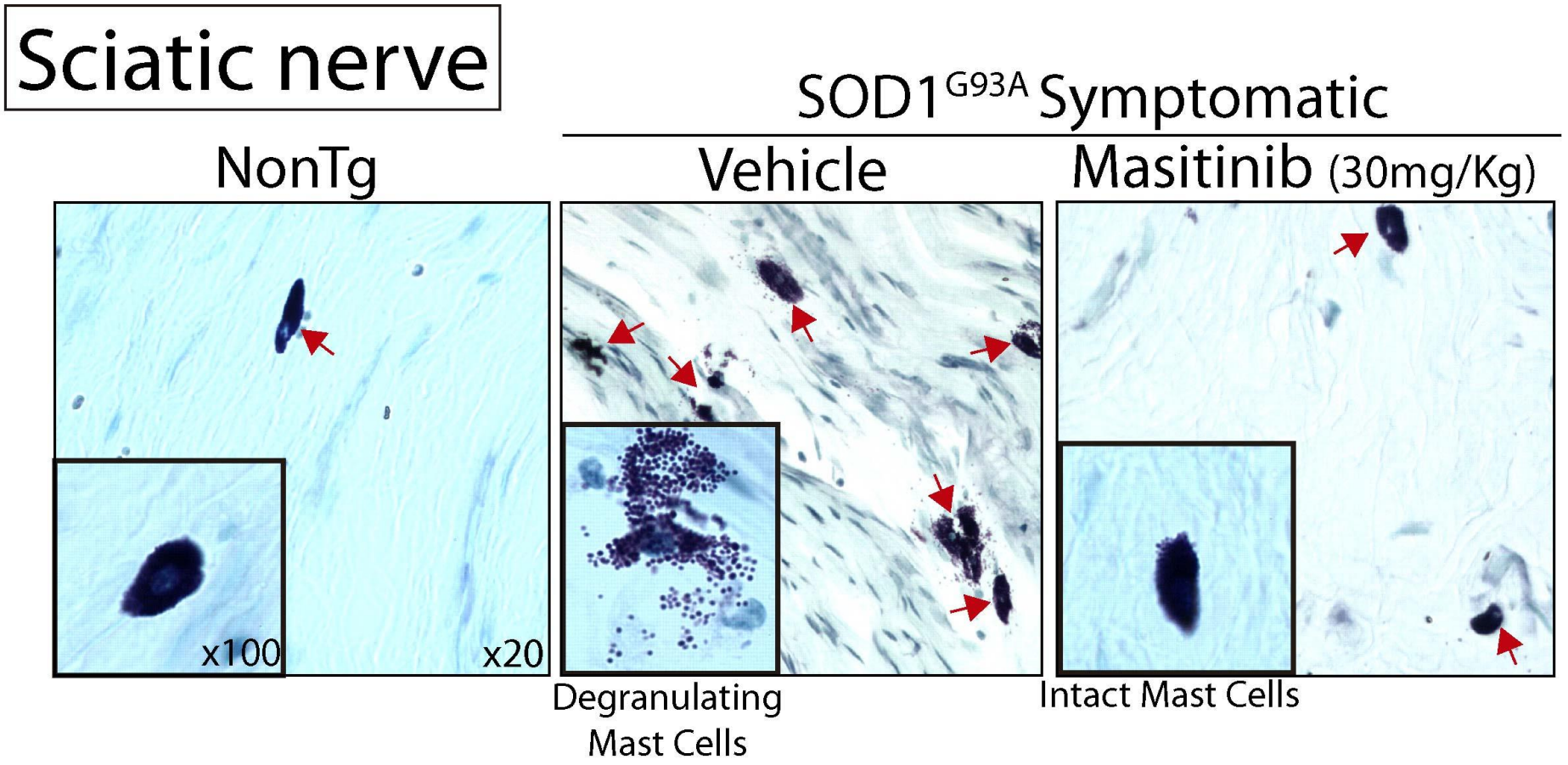
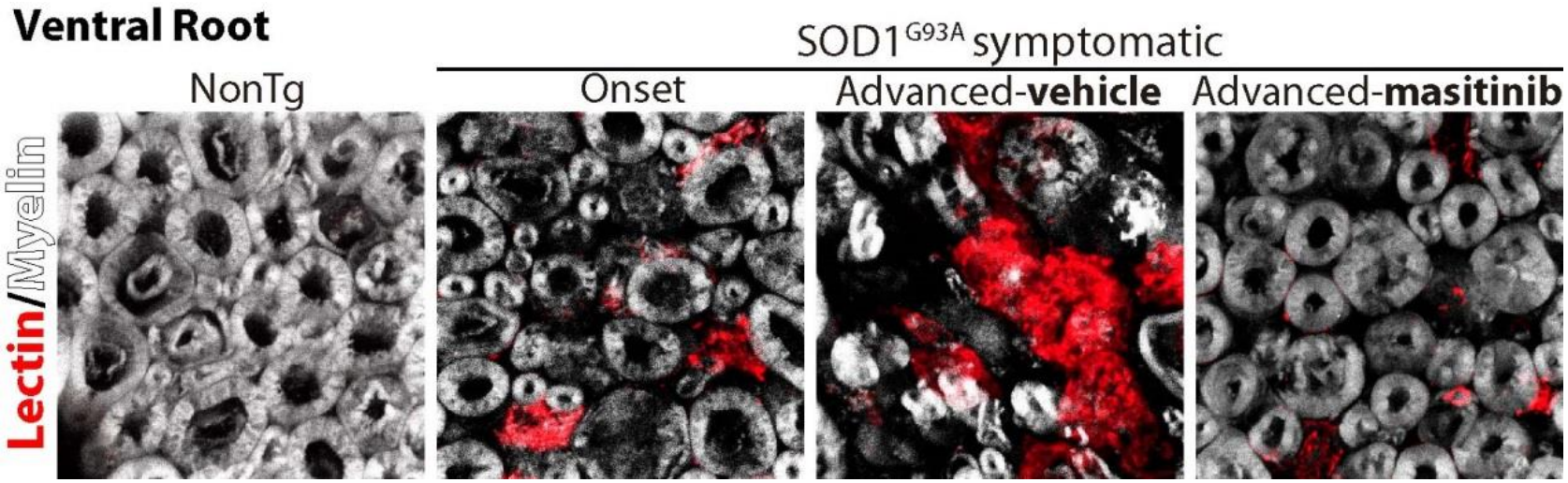
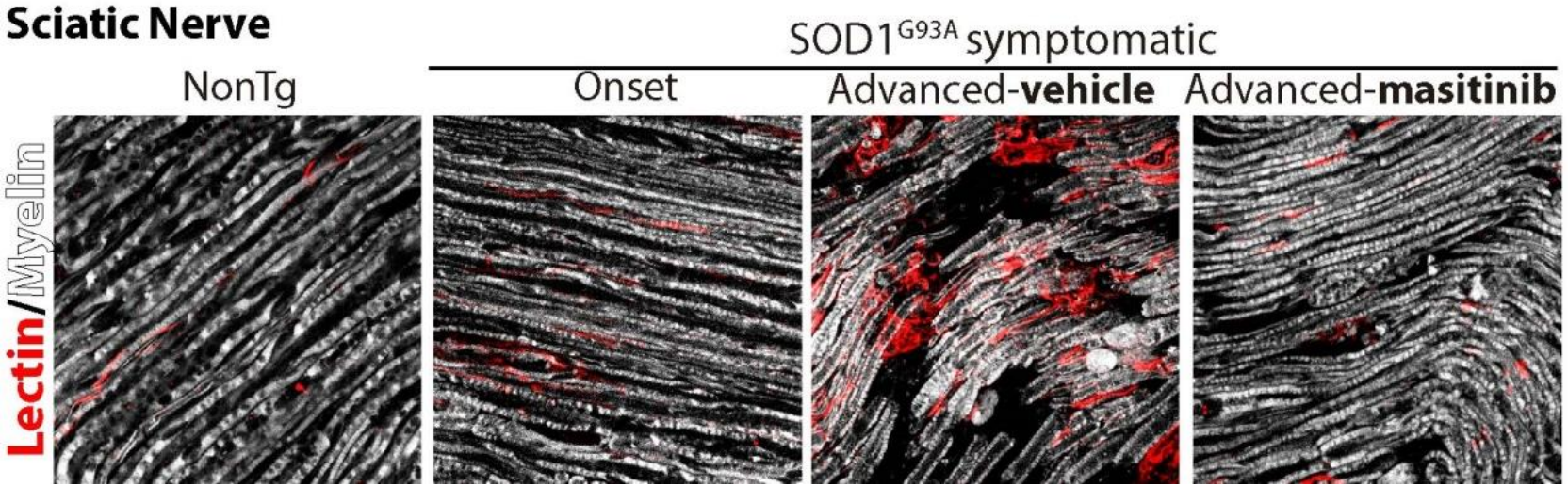


Trias et al, Unpublished data

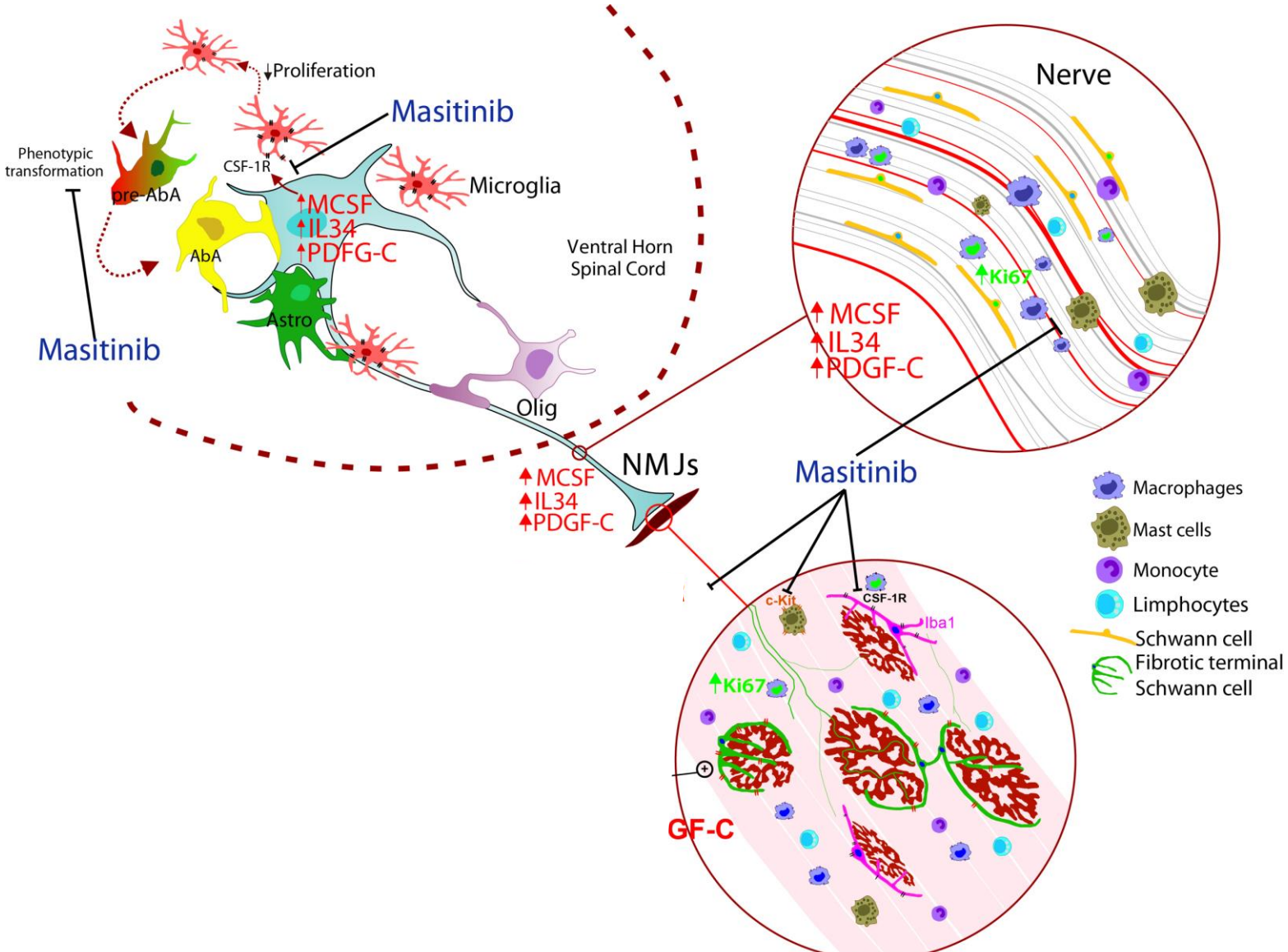
Masitinib reduces macrophages infiltration





Trias et al, Unpublished data

Conclusions 1



Multi-target

Multi-faceted

Further research needed

Conclusions

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- **Masitinib reduces anomalous inflammatory response (neurotoxic environment) associated to rapid paralysis progression in both CNS and PNS.**
- **Targets microglial cells, macrophages and mast cells expressing CSFR1 or C-Kit.**
- **Masitinib could delay the dying-back of motor nerve endings and preserve NMJ innervation.**

Tyrosine Kinase inhibitors: a hope for slowing paralysis progression in ALS patients?

THANKS !!

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