Masitinib significantly slows disease progression in post-paralysis SOD1^{G93A} rats and reduces inflammation in both CNS and PNS

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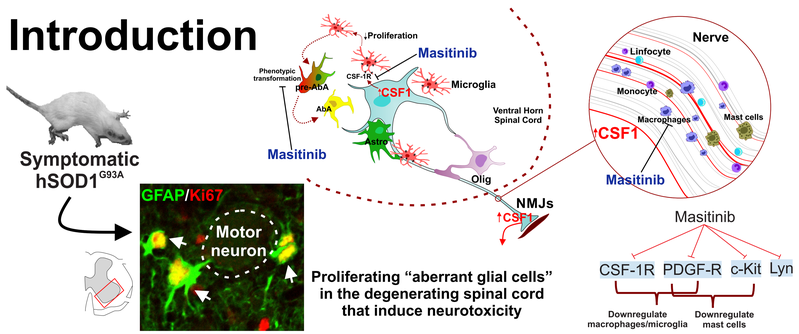
Introduction



Proliferating "aberrant glial cells" in the degenerating spinal cord that induce neurotoxicity

Hypothesis. **Tyrosine kinase inhibition with masitinib might prevent the appearance of aberrant glial cells, regulate inflammation in both central and peripheral nervous systems, and slow paralysis progression.**

Why masitinib?

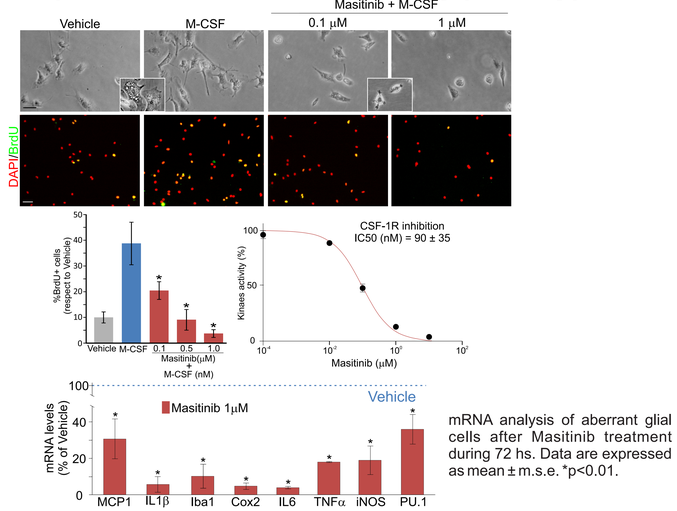
AB1010 is highly selective kinase inhibitor shown to prevent neuroinflammation in multiple sclerosis, stroke and Alzheimer's disease. Is presently being evaluated in clinical trials for oncologic and neurologic diseases.

Why post-paralysis?

Masitinib targets aberrant glial cells that emerge only after paralysis onset in the SOD1G93A rat model, which is characterized rapidly progressing disease progression.

Results

1 Masitinib inhibits M-CSF induced aberrant glial cell proliferation and inflammatory phenotype



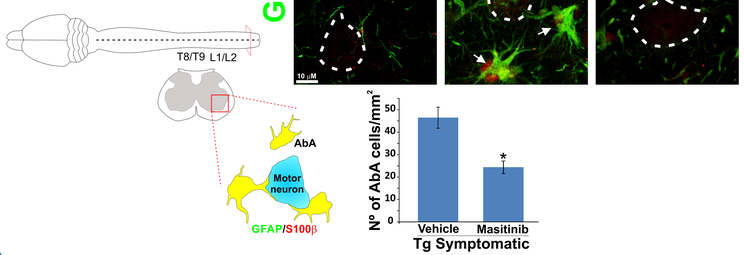
mRNA analysis of aberrant glial cells after Masitinib treatment during 72 hs. Data are expressed as mean ± m.s.e. *p<0.01.

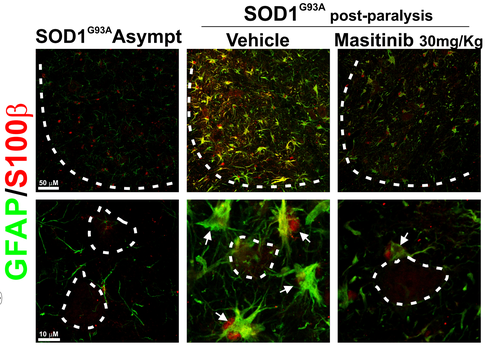
2 Masitinib reduces aberrant glial cells in the degenerating spinal cord

Methods. Daily masitinib 30 mg/kg vs Vehicle, orally.

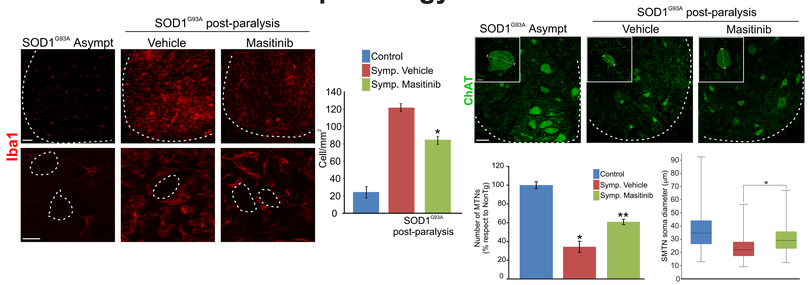
Treatment starting day 1 post-paralysis and lasting 20 days.

Hindlimb onset only

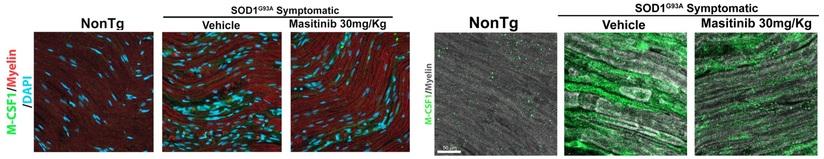




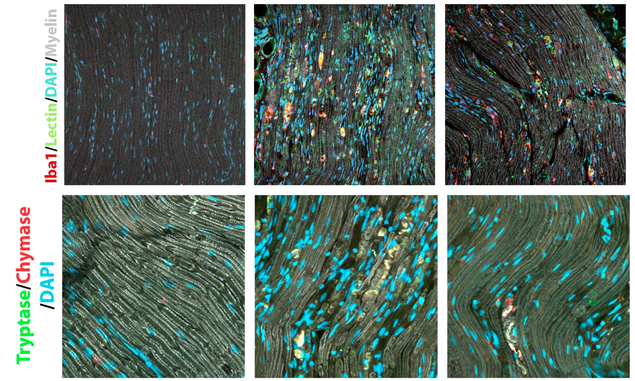
3 Masitinib prevents microglia activation and motor neuron pathology in ALS rats



4 M-CSF expression in the degenerating sciatic nerve



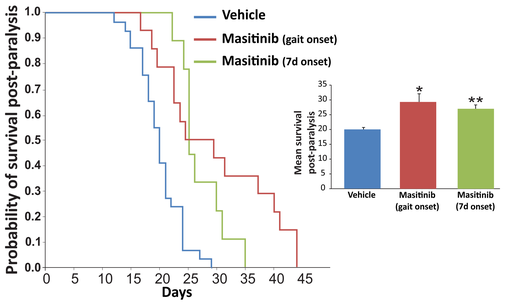
5 Masitinib reduces macrophages and mast cell cell inflitration in sciatic nerve



6 Masitinib increases post-paralysis survival

Methods. Daily oral masitinib (30mg/kg) or vehicle administration, starting after paralysis onset.

Survival was increased even when treatment was started 7 days after paralysis onset (7d onset).



Conclusions

- Masitinib **can slow paralysis progression** by targeting CNS aberrant glial cells and inflammatory cell infiltration in the PNS.
- Protective effect would be at least in part mediated by **masitinib inhibition of CSF-1R (microglia/macrophages) and c-Kit (mast cells)**
- Remarkably the protection can be obtained **when masitinib is administered post-paralysis.**
- Masitinib represents a new drug candidate for the treatment of ALS.

References

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