Marie-Laure.Beaud@unifr.ch

# BDNF interferes with a treatment neutralizing Nogo-A in adult macaques subjected to incomplete spinal cord injury.

M.-L. Beaud[1], E.M. Rouiller[1], J. Bloch[3], A. Mir[4], M.E. Schwab[2] and T. Wannier[1].

*1: Dept of Medicine, Uni Fribourg; 2: Brain Research Inst., Uni Zurich; 3: CHUV, Lausanne; 4: Novartis, Basel*

**Grant Sponsors:** Swiss National Science Foundation, grants No 31-43422.95, 4038-43918, 31-61857.00 (EMR); Novartis Foundation; NCCR 'Neural Plasticity and Repair'

## INTRODUCTION

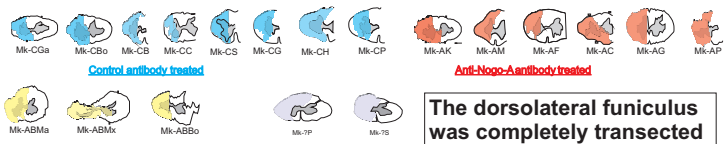
In rodents and monkeys with spinal cord injury (SCI), neutralizing the neurite growth inhibiting molecule Nogo-A with a specific antibody promotes both the regeneration of corticospinal (CS) fibers and functional recovery. However, the rostro-caudal extent covered by regenerating CS fibers remains limited and the soma of the CS neurons affected by such lesions shrinks independently of whether the animals are treated or not.
In parallel, a different line of studies has shown that neurotrophic factors such as BDNF (brain-derived neurotrophic factor) may induce neurite growth, in particular of CS fibers, and prevent atrophy of axotomized rubrospinal neurons.
This data raise the question as to whether the effects obtained by neutralizing Nogo-A can be strengthened by adding BDNF to the treatment.

## CONCLUSION

**Our preliminary data suggest that the association between BDNF and the anti-Nogo-A antibody reduces the positive impact of the antibody neutralizing Nogo-A alone. In fact, the animals treated with the combination of BDNF and of the anti-Nogo-A antibody present a level of functional recovery comparable to animals treated with a control antibody. Furthermore, ongoing analysis suggests that sprouting of CS fibers at the cervical (C3) level is comparable to that observed in control antibody treated monkeys, in line with the behavioural data. Pyramidal neurons in layer V of motor cortex shrink despite the presence of BDNF.**

## RESULTS

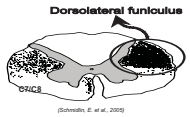
### 1) Localisation and extent of the cervical spinal cord lesion




The dorsolateral funiculus was completely transected by the cervical cord lesion in most animals.

### 2) Staining results

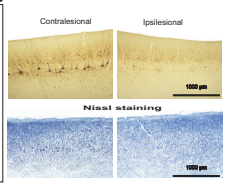
**A. BDA staining in the spinal cord**




CS fibers are mainly located in the dorsolateral funiculus.

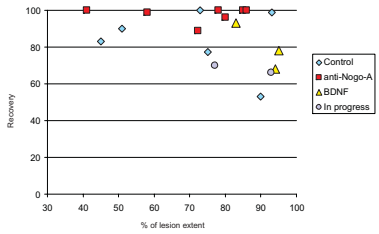
**B. SMI-32 staining in the motor cortex**

- SMI-32 stained the pyramidal neurons of cortical layers III and V.
- An inter-hemispheric difference of staining intensity of the layer V was observed.

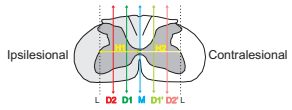


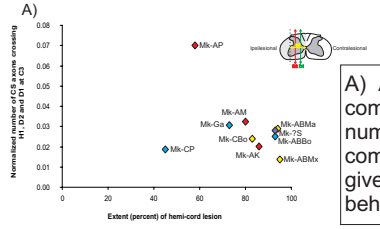

### 3) Functional recovery

The animals treated with the BDNF/anti-Nogo-A antibody combination reach levels of functional recovery similar to those observed in animals treated with a control antibody.

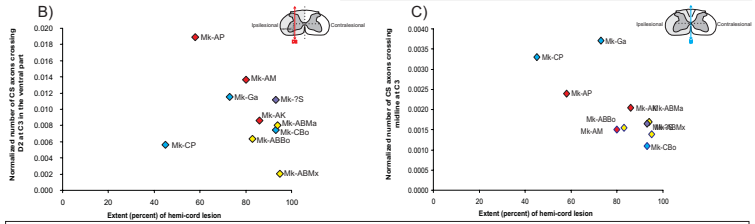



### 4) Sprouting at the cervical C3 level



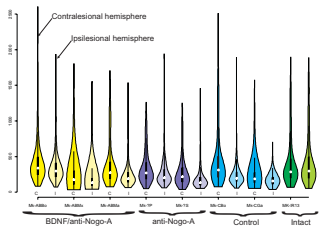




A) At C3 level, across animals with a comparable lesion extent, the normalized number of BDA-labelled CS fibers is comparable, irrespective of the treatment given. This is in agreement with the behavioural data.




At C3 level, the normalized number of CS fibers in the ipsilesional ventral grey matter (B) is not increased by the combination of BDNF with the anti-Nogo-A antibody. The same tendency is observed for the fibers crossing the midline (C).

### 5) Shrinkage of layer V pyramidal neurons




The presence of BDNF does not hinder the shrinkage of layer V pyramidal neurons in motor cortex caused by axotomy.

## METHODS

Lesion
A unilateral cervical spinal cord lesion was performed at C7-C8 level on 4 groups of monkeys:
- controls (using a control antibody; n=8)
- anti-Nogo-A (using an antibody neutralizing Nogo-A; n=6)
- BDNF/anti-Nogo-A (using BDNF with an antibody neutralizing Nogo-A; n=3).
- ongoing monkeys (n=2)

Behavioural assessment

Functional recovery was investigated using a modified version of the Brinkman-board task, which measures hand and finger dexterity.

Anatomical assessment
1) Biotinylated dextran amine (BDA) was injected into the motor cortex and the number of CS fibres was counted rostrally to the lesion at C3 level.
2) SMI-32 staining was used in M1 in order to measure the number and cross-sectional area of pyramidal neurons in the layer V.