

Spinal cord repair: releasing the neuron-intrinsic brake on axon regeneration, (AxonRepair)

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After SCI, the connections between nerve cells in the brain and in the spinal cord are lost and fail to grow back. In patients with SCI this results in permanent disability, including paralysis below the level of the injury, and loss of sensory, bladder and sexual function.

There are two major obstacles to the regeneration of nerve fibers (referred to as axons) of central nervous system (CNS) neurons. First, CNS nerve cells do not switch on the necessary machinery for vigorous regrowth of axons. Second, a nerve cell has to deliver the necessary components for growth to the tip of the nerve fibre, which may be quite far as the axon can extend a long way from the cell body. Many CNS nerve cells fail to transport growth proteins into their axons after injury. These proteins are essential for nerve fiber regeneration through the hostile terrain of a spinal lesion. In AxonRepair we aim to promote axon regeneration in the spinal cord by 1. Activating the gene program required for nerve fiber extension, and by 2. Overcoming the transport block of growth-promoting proteins into injured axons.

To achieve aim 1 our approach takes advantage of know-how collected by our consortium on the powerful regenerative abilities of peripheral nerve cells. Peripheral nerve cells do regenerate successfully because they have a kind of 'switch' which turns on a robust regenerative machinery, and because they do not exclude growth-related molecules from their axons. We have identified key molecular components of this switch and aim to use these to activate the regeneration program in neurons after a spinal cord lesion. Previous attempts to do this have focused on individual molecules, which can be considered individual parts of the switch. In AxonRepair we are attempting a novel strategy where we target multiple collaborating elements of the switch at the same time.

Many mature CNS neurons have a specialized structure at the transition zone between their cell body and their axon that acts as a molecular barrier for transport of pro-regenerative proteins. It has recently been recognized that this molecular barrier plays a major role in the failure of axon regeneration: following an injury certain proteins (e.g. integrins) required for axon regeneration are excluded from the nerve fibers. Aim 2 of AxonRepair is therefore to "dissolve" the transport barrier allowing transport of essential pro-regenerative proteins into injured axons.

At the completion of AxonRepair we expect to have developed an intervention strategy to promote robust axon regeneration and functional recovery after injury to long spinal cord axon tracts. The results obtained in the context of AxonRepair will provide the basis for a potential therapeutic strategy for SCI.