In the CNS, the axon distal to the injury dies, in the PNS the axon regenerates.

The regenerative ability depends on:

- Intrinsic ability of regeneration:
  - Growth mode: Developing axons have actin rich active growth cone, containing lamellipodia and filopodia
  - Tranmission mode: release of neurotransmittors
- Permissive environment:
  - Experimental evidence: injury were induced to four nerves, PNS environment allow regeneration.
    - Spinocortical neuron: CNS injury does not regenerate
    - Dorsal root ganglion: CNS injury does not regenerate, PNS does
    - Motor neurons: PNS injury regenerates
    - Autonomic neuron: PNS injury regenerates
  - Schwann cells in CNS: oligodendrocytes. Schwann cells in PNS: Remak cells and myelinating schwann cells. All have poor regenerative ability.
  - Schwann cells undergo phenotypic changes to become repair schwann cells, provide strong regenerative ability.
    - Elongation in shape, form repair column, guide growth of the nerve.
    - Neurotrophin release: GDNF NGF BDNF, promotes cell proliferation and neuronal growth.
    - Myelin breakdown: Myelin inhibit axon growth
    - Axon guidance: provide growth tract from the injury site to the growth target.

- Difficult nerve regeneration in larger organisms.
  - Slow growth of axon takes long to grow to target, however repair schwann cells degenerate.
  - Regenerative markers have decreased in denervated tissues (e.g. GDNF, BDNF, Shh), number of cells regenerated also decrease (Eggers et al., 2009)
  - The target tissue also deteriorates and undergoes atrophy over time

- CNS regeneration
  - CNS environment is inhibitory
  - Astrocyte becomes reactive astrocyte, proliferate around the injury site
  - Oligodendrocytes fails to break down myelin around the injury site
  - Microglia migrate towards the injury site, form blockage (glial scar cause physical impedance)
    - Experimental inhibition by downregulating STAT3 prevent astrocyte proliferation caused increased inflammation and cell death.
- During development, both CNS and PNS can regenerate, ability is lost in adults.

Regenerative approaches:

- Stimulation of pro-growth pathways e.g. EGF/mTOR pathway
- Grafting of repair mode schwann cells to provide growth environment, neurons does not tend to grow out of the environment.
- Grafting of embryonic stem cells, can achieve adequate effects, but have too great proliferative potentials.