Title: Resolving the events and roles in neurogeneration – an ontological basis for species-dependent immunological and neurological processes (NeuroGenO)

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Background: Neuro-regeneration is an important process which is influenced by neurodegenerative and immunological-inflammatory processes (IIPs) at the same time. Collecting and analyzing the known processes between the different agents – from the neurological system and the body overall - is an important domain to understand the competing functions between the involved parts. As an outcome, novel approaches can be identified and tested to improve the very limited neuro-regenerative capacity of neurons in the central nervous system after trauma, as traumatic brain injury (TBI), cerebral ischemia [1] and spinal cord injury (SCI[2], for review see [3]).

The blood-brain barrier plays an important role to separate the central nervous system (CNS) from the agents in the regular blood stream including the immunological cells and cytokines. Once the blood-brain barrier is interrupted, the immunological and inflammatory agents interact with the CNS tissue and at the same time, the CNS trauma induces changes in the overall immunological state of the body. Understanding the interplay between the immunological-inflammatory system and the neurological structures is essential for important research in both domains, including the development of new drugs. In particular the macrophages play the major role setting the balance between both processes.

More in detail, the inflammation following the CNS injury induces secondary damage and tissue degeneration. For example, pro-inflammatory macrophages induce axonal dieback by, e.g., the release of the matrix metalloprotease (MMP), which then disrupts the spinal cord-blood barrier, causing leucocyte influx and cytokine up-regulation (see also [6]). On the other hand, immune cells may also expose beneficial effects for neuroprotection and regeneration, depending on multiple factors [4]. For example, macrophages show a continuum of phenotypic transitions between a tissue damaging, pro-inflammatory type (M1) and the contrary reparatory type (M2)[5]. As a result, a treatment approach could target the positive or the negative regulation of the immune response alike, and it is necessary to detangle the parameters (including the neuronal factors) that lead to benefits or to disadvantages from the immune system.

Last but not least, the observed findings stem from experiments in different species: they have to be consolidated and should help to select the appropriate experimental setup for the evaluation of targets for future treatments (e.g. MMP inhibitor infusion, immune suppression) [7, 8]. For example, the infusion of an MMP-9 inhibitor in rats has been effective. However it has been ineffective in dogs [2], and, similarly, monocyte depletion is beneficial in rats in contrast to mice [7]. The implantation of activated autologous macrophages into the lesion site demonstrated to be beneficial in rodents [9], but failed in dogs [10] as well as in humans (phase 2 clinical trial) [11]. As a consequence, these
controversies have to be resolved to choose the right animal model (or models) for testing and for efficient use of resources (Fig. 1).

**Fig. 1: Species-specific interplay of neuronal regeneration, CNS trauma and immune response**

**Problem:** Resolve the activities and roles of cells and molecular factors of the immune system that modulate neuronal regeneration considering the importance of the specific animal model and the dependencies between the involved agents. Identify processes (in a given animal model) that enable experimental testing of the interplay between the bodily immune system and the neuronal system tissues.

**Work program:** We aim to define an ontological model representing the domain knowledge on neuroregeneration and the immune-inflammatory response induced by a CNS trauma. The model will be species independent, but will also make reference to species-specific differences. Ideally all differences will be resolved to the same model.

The core information is collected from domain experts and from the published pre-clinical data, for example from the scientific literature. With a focus on the interplay between immune response and neuronal regeneration, we can currently identify around 158,000 PubMed listed publications (querying the MeSH terms “spinal cord injury” (SCI) or “brain injury” (TBI)). Both CNS trauma types serve as experimental setting in animal models to explore the described phenomena (see Fig. 2).

The established ontology will be describing the published evidence and involved mechanisms for beneficial or detrimental immune effects on neuronal regeneration in SCI and TBI. We then use the biological process ontology to categorize the information from the available 4,000 publications concerned with immunological effects (MeSH terms “immune system” and “spinal cord injury” or “brain injury”) into a structured database (year 1&2). Moreover, in the second year, we want to generate new knowledge by using the ontology to extract species-specific differences in neuronal regeneration after trauma and therapeutic immunomodulation.
Fig. 2: Overview on work program.

**Outcome/Aim:** The resulting ontology and database will represent the state-of-the-art knowledge on the species-specific inflammatory and immune response in neuronal regeneration. It denominates alternatives in the therapy based on the findings, improves the selection of experiments and animal models for preclinical CNS trauma research and branches out to existing reference data resources, e.g. ontologies, biological fact resources (UniProtKb), and the scientific literature. The results will be made available as an open access ontology.

**References**


