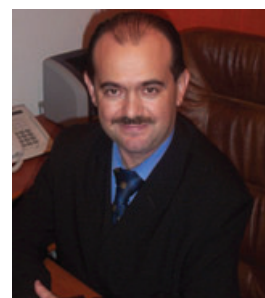


## Brain recovery – towards an unified theory

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Despite the large body of evidence we have today, for reorganization, repair and functional recovery after injury, the underline mechanisms for these combined processes are still unclear. This “blind spot” has negative impact on development of treatment strategies in the near future. To solve this issue, it is not easy to reconcile divergent opinions, despite all new available research technologies: some scientists would argue for a precise localization of brain functions in specific areas, others would hypothesize that different functions are more widely distributed throughout the brain. Some critical points of view regarding this general concept stated that recovery of function in neurological diseases in fact does not exist. These suggest that only one type of compensation exists [1]. In this context, plasticity is defined by the extent to which such alleviation is possible. Taking into consideration the data from many fMRI and PET scanning studies, as well as from studies showing discrepancy between functional consequences of acute *versus* chronic lesions [2] and the classic example of “serial lesion effect” [3], it appears that more arguments favour the theory that brain functions are widely distributed and in constant dynamic change [4–6].

It seems also that CNS has an equipotentiality of vicarious functions. Nowadays, we generally accept the idea that dynamic neuronal networks reorganization is permanently active and not only a characteristic of the damaged brain. After constant negative results in translating data from basic to clinical trials for neuroprotection, in stroke, traumatic brain injury and other neurological conditions, we acknowledge that a shift of strategy in development of pharmacological treatments is needed [7]. A deeper understanding of brain functioning and pathophysiological processes is mandatory in this respect.

Regarding brain biology today, we have learned that neurotrophicity, neuroprotection, neuroplasticity and neurogenesis are the key endogenous neurobiological processes that act together under genetic control to generate *endogenous defence activity* (EDA), which attempts to counteract pathophysiological processes [8]. These fundamental neurobiological processes lack

absolute boundaries; they overlap and share common mechanisms in such a way that they cannot be separated within the continuum of EDA [9]. EDA can be endogenously or pharmacologically activated. Furthermore, neurobiological processes of EDA share common mechanisms with pathophysiological processes. For example, excitotoxicity, neurotrophicity and neuroplasticity all have NMDAR stimulation as their common important driver [10, 11]. Inflammation is another important contributor to neuroregeneration, stimulating neuroplasticity *via* trophic factors [12–16]. Regulation disturbances in each of the four major players of EDA are themselves causes of some pathological conditions. A deficit of endogenous neurotrophicity and neuroprotection will always increase the susceptibility for a lesion. So far, no pathologies have been described to involve an excess of neurotrophicity or neuroprotection.

For neuroplasticity, both up-regulation and down-regulation can generate pathological processes. Down-regulation generates a deficit of recovery, whereas up-regulation generates different neuropathological patterns of plasticity, such as neuropathic pain, multiple sclerosis, movement disorders, tinnitus, and more.

With regard to neurogenesis, both up-regulation and down-regulation might generate pathological conditions (*e.g.* down-regulation associates with Alzheimer's disease). Up-regulation of oligodendrogenesis and astrogenesis beyond normal regeneration is responsible for neuroproliferative disorders (cerebral tumours).

These processes are regulated *via* key endogenous players, such as neurotrophic factors and neurotrophic like molecules. In order to successfully compete with pathological processes and support neurorecovery, EDA might be therapeutically enhanced by pharmacological intervention, physical means, electromagnetic stimulation, psychological support, environmental stimulation, stem cell transplantation or any demonstrated combinations of these factors capable of improving a patient's condition. The brain is able to use the same neurotrophic factors for both neuroprotection and neuroplasticity, although in different combinations. They are activated during altered gene expression induced by lesioning.

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Brain ischaemia regulates the expression of more genes than any other condition. However, many activated genes are not translated into proteins after injury [17, 18]. For example, in stroke, endogenous neuroprotection is maximally effective in the ischaemic area, at 72 hrs following an insult. Any further positive clinical outcome is driven by processes of neuroplasticity and neurogenesis.

Considering all these developments, the *Journal of Cellular and Molecular Medicine* decided to initiate a Brain Recovery Review Series. In the spirit of translational medicine, the aim is to integrate new concepts like EDA, with the results of genomic, transcriptomic and proteomic studies in post-injury responses. Another important purpose of the series will be to recapitulate the advances in better

understanding of excitotoxicity, inflammation, apoptotic-like processes, and the role of neurotrophic factors. We will also review the current status and perspectives in “neuroprotection” and thrombolysis in stroke and traumatic brain injury emerging therapies.

In this issue, Silvia Lanfranconi, University of Milano, Department of Neurological Sciences, reviews new data on growth factors in ischaemic stroke. In the same spirit, Kurt Jellinger, Institute of Clinical Neurobiology, Austria, highlights some updates on basic mechanisms of neurodegeneration.

In the future issues, important updates regarding stroke and traumatic brain injury recovery will be discussed. We are finally aiming to create a stimulating platform of discussions regarding the re-approach of translational paradigm in neurorecovery.

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