ImmunoTools *special* Award 2014

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Peripheral nerve injury induced neuropathy and neuropathic pain: role of a new player

Neuropathic pain, resulting from damage to or dysfunction of the nervous system, is a chronic pain largely resistant to treatment mainly because the underlying mechanisms are still poorly understood. It is now recognized that neuropathic pain is caused by a pathological interaction between neuronal, glial and immune cells, and chemokines play a key role in coordinating injury-associated nociceptive events, as they serve to regulate inflammatory responses, and can simultaneously act on elements of both the central and peripheral nervous system.

A new family of chemokines, the Bv8/Prokineticin family has recently emerged as a critical player in immune system and inflammatory diseases *(Giannini et al., 2009)*. Like chemokines, prokineticins activate two G protein-linked receptors named prokineticin receptor 1 (PKR1) and prokineticin receptor 2 (PKR2), localized in the brain, dorsal root ganglia (DRG), neurons, granulocytes, macrophages and endothelial cells. Bv8/PK2 is overexpressed in inflamed tissues and has a crucial role in neutrophil-dependent inflammatory hypernociception. In vitro Bv8 activates macrophages to migrate and to produce proinflammatory cytokines IL-1 and IL-12.

Considering that Bv8/PK2 is over-expressed in inflammatory granulocytes, both prokineticins and their receptors are expressed in neurons, glial cells, endothelial cells and in cells of the immune system and that the system is involved in nociception and immunoregulation, the Bv8/PK system appears as a pivotal candidate for mediating the neuroimmune interactions in neuropathic pain.

It has been shown previously in studies on rats that injury on peripheral nerves alters blood spinal cord barrier (BSCB) function and the administration of proinflammatory cytokine such as IL-1β or MCP-1 have the ability to open the BSCB and to stimulate immune cell trafficking across the BSCB (*Echeverry et al, 2011*).

Preliminary results from our laboratory, using a mouse model of traumatic neuropathy, the sciatic nerve chronic constriction injury (CCI), indicate that treatment of injured animals with a prokineticin receptor antagonist, PC1, which do not interfere with normal pain perception, significantly reduced or abolished the development of thermal hyperalgesia and allodynia.

The ImmunoTools *special* Award 2014 would be of great benefit to me as it would be used to investigate, in the animal model of neuropathic pain (Chronic constriction injury - CCI), if the intravenously or intrathecally administration of the different cytokine (such as rm G-CSF, rm

GM-CSF, rm IL-1alpha, rm IL-1beta, rm IL-2, rmIL-3, rm IL-4, rm IL-5, rm IL-6, rm IL-7, rm IL-9, rm IL-10, rm IL-11, rm IL-13, rm IL-15, rm IL-16, rm IL-17A, rm IL-17C, rm IL-17F, rm IL-19, rm IL-20, rm IL-21, rm IL-22, rm IL-25 / IL-17E, rm IL-27, rm IL-31, rm IL-33, rm M-CSF, rm NGF-beta, RANTES / CCL5, rm sCD40L / CD154, rm SCF, rm SDF-1α / CXCL12a, rm SDF-1β / CXCL12b, rm TNFα, rm TPO, rm VEGF) induces changes in Bv8/PK2, PKR1 or PKR2 expression levels in the lumbar spinal cord.

And I also want to evaluate which is the effect of PC1 treatment on the IL-1β and MCP-1 induced BSCB permeability.

Giannini E, Lattanzi R, Nicotra A, Campese AF, Grazioli P, Screpanti I, Balboni G, Salvadori S, Sacerdote P, Negri L. (2009) *"The chemokine Bv8/prokineticin 2 is up-regulated in inflammatory granulocytes and modulates inflammatory pain"* **Proc Natl Acad Sci U.S.A** 106:14646-14651.

Echeverry S, Shi XQ, Rivest S, Zhang J. (2011) *" Peripheral Nerve Injury Alters Blood-Spinal Cord Barrier Functional and Molecular Integrity through a Selective Inflammatory Pathway"* **The Journal of Neuroscience** 31:10819 -10828.