Ref: OT-34

Title: A new therapy for the treatment of myeloproliferative diseases

Abstract:

The present invention describes the neural mechanisms regulating the haematopoietic niche, regulatory mechanisms that are impaired in myeloproliferative neoplasms (MPN) and that contribute to the disease´s pathogenesis, thereby emerging as new therapeutic targets. We demonstrate that production of interleukin 1 beta by mutant progenitors can damage the Schwann cells that protect sympathetic nerve endings in the bone marrow. This neuro-glial damage enhances the susceptibility of mesenchymal stem cell (MSC) in the haematopoietic niche to cell death caused by mutant haematopoietic cells. We show that CXCL12, a chemokine produced by nestin+ MSCs, can partially control the expansion of the mutant haematopoietic progenitors. The decrease in MSCs in the bone marrow and the concomitant decrease in CXCL12 levels in MPN accelerates disease progression. The use of neurotrophic agents that prevent or rescue neuro-glial damage, together with beta3 adrenergic agonists, which make up for the deficit of sympathetic stimulation of nestin+ MSCs, can control the expansion of leukemic stem cells and arrest disease progression. Therefore, we prove the existence of a sympathetic neuropathy in MPN affecting the haematopoietic niche in the bone marrow, which plays an essential role in MPN pathogenesis and has consequently emerges as a new therapeutic target.

Innovative aspects:

With the present invention we show that in MPNs, which were up till now considered as diseases caused autonomously by mutant haematopoietic progenitors, these progenitors damage their niche in manner that is necessary for the manifestation and progress of the disease. We identified new therapeutic targets based on alterations in the regulation of MSC in the hematopoietic niche by sympathetic nerves. We have also defined an in vitro method for prognosis/diagnosis of MPNs and/or to define the disease´s stage, and a method to screen for therapeutic compounds useful to treat MPNs.

Competitive advantages:

This development could lead to the design of more efficient therapies for MPN treatment using currently available drugs, alone or in combination with other available treatments. We define a new MPN treatment that can arrest disease progression. This treatment could be extended to other haematological disorders that involve the degeneration of sympathetic fibres innervating the bone marrow.

Key Words: myeloproliferative neoplasms, haematopoietic niche, bone marrow neuropathy, sympathetic fibres.

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