MSRV envelope protein is a highly potent agonist of human TLR4: relevance of GNbAC1 in Chronic Inflammatory Demyelinating Diseases treatment

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Multiple Sclerosis associated retrovirus (MSRV) encodes a pro-inflammatory and gliotoxic envelope protein named MSRV-Env. Though not detected in various neurological controls, MSRV-Env was detected in blood, brain lesions or peripheral nerves in patients with multiple sclerosis (MS) or with chronic inflammatory demyelinating polyradiculoneuropathies (CIDP). We performed the first pharmacological characterization of MSRV-Env pathogenic interaction with human TLR4 (hTLR4) and assessed GNbAC1 potential benefit in various relevant models mimicking some of MS or CIDP hallmarks.

Complete pharmacological characterisations of MSRV-Env and GNbAC1, a therapeutic antibody that targets MSRV-Env, were assessed on recombinant hTLR4 expressed in HEK-Blue™ cells. We showed that MSRV-Env is a highly potent full agonist of recombinant hTLR4. MSRV-Env is concentration-dependently inhibited by GNbAC1 and selective TLR4 antagonists. Furthermore, we demonstrated that MSRV-Env effect is mediated by its direct binding to hTLR4.

MSRV-Env expression in MS and CIDP patients' blood is clinically relevant as MSRV-Env induced a potent and concentration-dependent release of the pro-inflammatory cytokines IL-6 and TNF-α by cultured human peripheral blood mononuclear cells. This effect is specifically inhibited by GNbAC1 and selective TLR4 antagonists, which demonstrates that MSRV-Env is a potent direct agonist of native hTLR4 expressed by blood cells.

MSRV-Env is specifically expressed in MS brain lesions and we confirmed its pathogenic potential in cultured human oligodendrocytes precursor cells (hOPC). MSRV-Env impaired hOPC differentiation to mature myelinating cells through a direct interaction with native cerebral hTLR4, and this effect is potently, concentration-dependently and fully inhibited by GNbAC1.

MSRV-Env protein is detected in macrophages and Schwann cells in peripheral nerve biopsies from CIDP patients. Human Schwann cells in culture transfected or stimulated by MSRV-Env produced high levels of IL-6 and CXCL10, two key immune mediators involved in CIDP pathology. These effects are mediated by native hTLR4 expressed by human Schwann cells and inhibited by GNbAC1.

Taken together, our studies demonstrate that MSRV-Env is a highly potent and pathogenic agonist of hTLR4. MSRV-Env expression in the blood of MS and CIDP patients is potentially involved in the chronic inflammation associated with these conditions. Furthermore, MSRV-Env expressed in MS plaques may impair remyelination of brain lesions, and its parallel expression in CIDP nerve biopsies may trigger the release of critical immune mediators consistently

proposed as key factors involved in the causative pathways of CIDP. GNbAC1 inhibited MSRV-Env pathogenic properties in all investigated models and may offer a new therapeutic approach to these two chronic inflammatory demyelinating disorders which preserves innate immunity.