

**Novel molecule based on aPC/EPCR PAR1 for the Treatment of Neuroinflammatory Diseases (Tel Hashomer)**

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**Novel molecule based on aPC/EPCR PAR1 for the Treatment of Neuroinflammatory Diseases**

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<b>Development Stage</b>	Preclinical Efficacy studies
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**Abstract**

Many neurological diseases are known to be associated with increased inflammation and over activation of protease activated receptors (PAR) by protein factors of the coagulation cascade. Activated protein C (aPC) via its receptor endothelial protein C receptor (EPCR) binding and signaling was found to modulate PAR1 activation.

We suggest novel molecules aimed at activating the aPC-EPCR cascade and counteract the effects of thrombin in neuroinflammation.

Thrombin is a protease well known for its role in coagulation. In addition to its role in the coagulation cascade, thrombin affects many cellular events by a group of receptors named protease activated receptors (PARs) PAR1 to PAR . PAR1 has been found in many tissues including the brain where it is found on several cell types including neurons, astrocytes and microglia. Activation of PARs can recruit multiple intracellular signaling pathways depending on the activating ligand.

aPC has a wide range of functions in the body. Through its direct interaction with thrombin it has known anticoagulant properties, however through the activation of the EPCR-PAR1 pathway it provides multiple important functions to maintain a regulated balance between hemostasis and host defense systems in response to vascular and inflammatory injury.

We recently have shown that in animal models of minimal traumatic brain injury (mTBI), PAR1 is upregulated with its activation being linked to the cognitive impairment resulting from the injury. In Parkinson's disease, a significant increase in the number of astrocytes expressing PAR1 has been reported in the substantia nigra pars compacta. In addition, upregulation of PAR1 in astrocytes has been observed in HIV encephalitis, implicating this receptor in neuroinflammatory responses. This idea is supported by the evidence of elevated levels of thrombin in

an experimental model of multiple sclerosis and other inflammatory brain diseases. Stimulation of PAR1 by thrombin causes proliferation of glia and produces reactive gliosis, infiltration of inflammatory cells, and angiogenesis. Finally, expression of PAR1 is increased in experimental models of Alzheimer's disease and brain ischemia.

We have published that thrombin regulates the threshold for synaptic plasticity in a concentration-dependent manner. We demonstrated that aPC induces metaplasticity and thereby enhances the ability to induce LTP. This effect of aPC is mediated by EPCR-dependent PAR1-activation. Hence, high concentrations of thrombin saturate the ability of neurons to express further LTP (memory and learning function) via direct PAR1-activation, while at low concentration thrombin mediates metaplasticity by enhancing LTP via aPC-EPCR mediated PAR1-signaling.

Besides its role in regulating synaptic transmission and plasticity, in the brain the aPC-EPCR-PAR1 pathway has also been shown to inhibit the proinflammatory effects of thrombin by stabilizing the BBB, counteract the activation of inflammatory cells such as microglia and prevent the formation of proinflammatory cytokines.

Therefore, the activation of this pathway in settings of neuroinflammation may both counteract the negative, proinflammatory effects of thrombin as well as restore proper neuronal transmission and function.

## **The Need**

Even though the interaction between the thrombin pathway and the inflammatory pathway seem to be playing a pivotal role in the pathogenesis of neuroinflammation and consequently mTBI, to date no therapeutic approach targeting this system is available. Steroids and NSAIDs (which in some cases are used in the acute therapeutically settings) may relieve the immediate physical symptoms, but they do not prevent nor cure the long term outcomes of the disease. Therefore, novel therapies that will interfere with the thromboinflammatory pathway are in desperate need in order to change the course of the disease

## **The Technology**

We have successfully synthesized a novel molecule which was found to interfere in the aPC/EPCR pathway, improved neurological function following neuroinflammatory processes and hold beneficial effects on target proteins and genes modification following neuroinflammation. Thus, we have a solid base to hypothesize that this novel molecule will improve neurological functions following chronic neuroinflammatory processes in human.

## Applications

Treatment for chronic based neurological diseases:

Neurodegenerative disease (Parkinson, Alzheimer, Chronic Traumatic Encephalopathy - CTE, etc.)

Neuroinflammatory diseases (Multiple Sclerosis, Neuromyelitis Optica, etc.).

## Advantages

We propose the aPC/EPCR pathway as a target of pharmacological intervention for the first time ever. We found that aPC/EPCR holds a major role in the pathogenesis of neuroinflammation processes. Pharmacological intervention in this pathway won't possibly cause bleeding complications which is the major side-effects of the available drugs acting on targets along the traditional coagulation cascade.

## The Market

Among neurodegenerative conditions, CTE caused by Traumatic Brain Injury (TBI) is a serious public health problem. Among TBI survivors, an estimated prevalence of 3.2-5.3 million Americans with TBI suffer long-term complications, including chronic disability. The economic burden is approximately \$4.5 billion from direct treatment at hospitals and long-term care, \$20.6 billion lost as a result of work absence or disability, and \$12.7 billion in lost income from premature death, all adding up to more than \$37.8 billion.

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