



# Perispinal etanercept for neuroinflammatory disorders

**Edward Tobinick**

Institute for Neurological Research, a private medical group, inc. 100 UCLA Medical Plaza, Suites 205-210, Los Angeles, CA 90095, United States

**Excess TNF is centrally involved in the pathogenesis of a variety of neuroinflammatory disorders, including Alzheimer's disease, other forms of dementia, intervertebral disc-related pain, and related disorders. TNF causes neuronal dysfunction, regulates synaptic mechanisms, and mediates amyloid-induced disruption of molecular mechanisms involved in memory. Perispinal administration of etanercept, a potent anti-TNF fusion protein, is a treatment modality whose rapid clinical effects may be related to modulation of these TNF-related mechanisms, particularly the role of TNF as a gliotransmitter capable of regulating synaptic transmission. This approach utilizes therapeutic delivery of etanercept across the dura via the cerebrospinal venous system, a confluence of the venous plexuses of the spine and the brain, in which flow is bi-directional owing to the absence of venous valves.**

Recent advances in the basic scientific understanding of the role of the immune system in the regulation of neuronal function have provided new insight into the central role played by an excess of the cytokine, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), in neuroinflammatory disorders [1–3]. The pro-inflammatory effects of TNF are widely recognized to contribute to the pathogenesis of a variety of diseases [4]. It is now recognized that, in addition to its role as a pro-inflammatory cytokine, TNF is one of a handful of identified gliotransmitters [5,6]. As a gliotransmitter, TNF functions to modulate synaptic transmission [7,8]. TNF plays a central role in the glial–neuronal interactions that influence both memory mechanisms and neuropathic pain [1,9–12]. These insights now help to explain, in selected neuroinflammatory disorders, the rapid positive clinical effects of etanercept, a recombinant dimeric fusion protein consisting of the extracellular ligand-binding portions of two human p75 TNF- $\alpha$  receptors linked to the Fc fragment of human IgG1 [13]. By binding to TNF and blocking its interaction with cell surface TNF receptors, etanercept reduces the biologic effect of excess TNF [14]. Optimal therapeutic efficacy, however, requires that etanercept be able to reach the therapeutic target in adequate concentration [15]. For neuroinflammatory disorders involving the central nervous system this requires novel

methods of anatomically targeted delivery because large molecules, such as etanercept, cannot cross the blood–brain barrier when delivered systemically [16]. The anatomic and functional continuity of the spinal and cerebral venous systems, such that their combination may be referred to as the cerebrospinal venous system, provides an anatomic route whereby perispinal etanercept may cross the dura and reach the neuraxis [17–20]. An understanding of the use of perispinal etanercept for the treatment of neuroinflammatory disorders, such as Alzheimer's disease (AD), sciatica, and related disorders, requires a more detailed knowledge of the cerebrospinal venous system and the effects of TNF on glial–neuronal interactions.

## **TNF and glial–neuronal interactions**

*TNF, a gliotransmitter, regulates synaptic communication between neurons*

Neuroinflammation involves activation of both microglia and astrocytes [1,2,11,20,21]. Activated microglia may produce a variety of signaling molecules, including TNF [1,11,20,22–27]. Glial activation is operative in disorders of both the brain and spinal cord, including Alzheimer's disease, neuropathic pain, and spinal radiculopathy [1,2,11,20–27]. In Alzheimer's disease neuroinflammation may accelerate amyloid deposition, and amyloid deposition may activate microglia, producing a deleterious positive feedback loop [2,25–30]. Modulation of glial activation has been

Corresponding author: Tobinick, E. (etmd@ucla.edu)