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Chapter 7

On Overcoming Barriers to Application of Neuroinflammation Research

Edward L. Tobinick, Tracey A. Ignatowski and Robert N. Spengler

Additional information is available at the end of the chapter

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Abstract

Throughout history, new ideas in medicine or science have met initial resistance by entrenched medical or scientific communities. Barriers to medical innovation fall into six main categories as listed here in order of historical chronology: (1) Theological, (2) Academic, (3) Scientific, (4) Financial, (5) Governmental, and (6) Commercial. Researchers in the field of neuroinflammation often encounter such obstacles that may include denialism. Despite these barriers, recognition of the therapeutic potential of targeting neuroinflammation for treatment of stroke, traumatic brain injury, Alzheimer's disease, spinal pain, and a variety of additional brain disorders has accelerated in the past 10 years. Consequently, a paradigm shift in scientific thinking regarding neuroinflammation as a therapeutic target is now underway.

Keywords: denialism, perispinal, etanercept, stroke, traumatic brain injury, Alzheimer's, sciatica, neuroinflammation, spasticity, cognitive dysfunction, TNF

1. Introduction

> *I remember at an early period of my own life showing to a man of high reputation as a teacher some matters which I happened to have observed. And I was very much struck and grieved to find that, while all the facts lay equally clear before him, those only which squared with his previous theories seemed to affect his organs of vision.* (Lister [1]).

There is growing scientific evidence of the central involvement of neuroinflammation in the pathogenesis of a diverse group of neurological disorders [2–31]. This is particularly important since basic research fuels applied science's innovations. Despite this evidence,

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translation of neuroinflammation research findings by basic scientists into therapeutic methods that are widely employed has been hindered by the traditional barriers that are put into place by entrenched medical and scientific communities [32–40]. Of these barriers, denialism, the refusal to accept or even examine verifiable facts that conflict with one's philosophy, is particularly onerous and may undermine public health [40, 41]. Recognition of the existence of these barriers and careful consideration of their nature promise to facilitate the treatment of neuroinflammatory disorders [22, 38, 42, 43].

2. Barriers to translation of medical innovation

> *A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.* (Planck [33]).

Barriers to medical innovation fall into six main categories, in approximate order of chronology: (1) Theological, (2) Academic, (3) Scientific, (4) Financial, (5) Governmental, and (6) Commercial. Any one of these barriers by itself can present an insurmountable blockade to the translational practice of a new medical discovery. Within each of these categories, denialism often operates to obstruct the progress of a new scientific discovery.

Historically, *theological barriers* to the acceptance of new scientific concepts have been formidable [34]. Prominent historical examples include the resistance of the Church to the scientific ideas of Galileo and Darwin [32, 34, 35, 40]. While theological barriers have diminished, they remain to the present day, including theological barriers to stem-cell and contraception research and practice.

Academic barriers can also impede or prevent scientific progress [32, 34, 35, 38, 39]. Ever since scientists and physicians organized into special societies, these societies have wielded their political and economic power to influence the acceptance [or nonacceptance] of new scientific concepts relevant to their interests [32, 34, 35, 38–40].

Scientific barriers are complex and multifaceted [32, 34–37, 39]. Scientific communities organize around certain shared assumptions, termed "paradigms," that form the foundations of their scientific beliefs [35]. New scientific discoveries, at odds with existing scientific dogma, have historically been attacked and willfully ignored, often by the reigning scientific "authorities" of the time [32, 34–40].

Financial barriers have always created difficulties for scientists because hypothesis generation, scientific discovery, data confirmation, and publication of a new scientific concept necessitates the gathering of sufficient financial resources to support what is characteristically a lengthy and expensive endeavor [39, 44]. Particularly expensive is drug development, which typically requires hundreds of millions of dollars of investment to achieve a new FDA indication, with some recent Alzheimer clinical trials costing more than a billion dollars [44, 45].

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Governmental barriers have become increasingly complex over time, particularly so in recent decades. These barriers are justified by ethical, humanitarian, and public interest considerations as illustrated, for example, by the Tuskegee experiment. Nevertheless, as exemplified by the considerations that led to the passage of the recent twenty-first century Cures Act, governmental regulations have the potential to slow the pace of medical progress and may be subject to misuse.

Viewed in totality, the difficulty in achieving translation of any radically new or different medical innovation, particularly one that breaks new scientific ground, is readily appreciated [32, 34, 35, 38–40, 46]. Awareness of these barriers may help facilitate the process of successfully surmounting them [32, 34, 35, 38–40, 46–48].

3. Galileo: denialism during the dawning of the scientific method

> *What do you say to the leading philosophers of the university faculty here who, with the lazy obstinacy of a glutted adder, despite invitations a thousand times repeated, refuse even to glance either at the planets or the moon, or even at the telescope itself? Truly the eyes of these men are closed to the light of truth.* (Galileo [40]).

Galileo is considered by many to be the father of the scientific method. Despite his many pioneering scientific discoveries, it is well known that his scientific work was actively resisted by the Church. The denialism regarding Galileo's observational astronomical discoveries, including his discovery of the four largest moons of Jupiter, was, however, not limited to the *theological barrier* promulgated by Cardinal Bellarmine and the Roman Catholic Church, the dominant religion of Galileo's Italy. Rather it notably included an *academic barrier*: denialism by the university academics of the time, who joined the Church in refusing to even look through the telescope that Galileo had invented [32].

Galileo's letter communicates the single reason he was imprisoned and his ideas obstructed: denialism, due to willful ignorance or "willful blindness" by the academics and theologians of his time to the natural scientific truths regarding astronomical bodies that he had discovered [32]. It is tragic that willful blindness to life-saving medical discoveries, epitomized by the example of Semmelweis, may persist for decades before such denialism is overcome and still operates today [1, 22, 32, 36–39, 43, 47, 49].

4. Denialism in the nineteenth century: Semmelweis

> *The innate resistance of science to revolutionary change means that when truly major change is called for, the scientific community often and wrongly opposes it at first.*
>
> *Dogmatism in science and medicine: how dominant theories monopolize research and stifle the search for truth.*(Bauer [39]).

New medical discoveries need to overcome all of the enumerated barriers to achieve widespread acceptance and translation [32, 34, 38, 39]. A well-known historical example is illustrative of the existence of many such barriers. In mid-nineteenth century Vienna, Ignaz Semmelweis, through astute observation and careful study, deduced and then provided compelling scientific evidence that handwashing by obstetricians prior to assisting in childbirth dramatically reduced maternal mortality [36, 37]. His ground-breaking discovery, however, failed to achieve acceptance during his lifetime, due to academic denialism [36, 37]. The entrenched obstetrical community of his time simply refused to recognize his life-saving findings for decades [36, 37].

> *[Semmelweis] made the intriguing observation that obstetrical mortality within the conveniences of a hospital setting, and in the hands of sophisticated physicians, was far greater than that in the hands of simple midwives….He postulated that doctors coming from the autopsy room to the maternity ward brought with them the cause of childbed fever. His crude antiseptic measures, years before Lister, were sufficient to bring the mortality rate down from 25% to around 1%.*
>
> *Semmelweis's thinking was greeted with skepticism, and, at times, derision. His colleagues resented the constraints he had placed on them and the implications that they were the agents of death [49].*

It is not difficult to see how Semmelweis's findings threatened their specialty [36, 37, 49]. Semmelweis faced denialism by the leading obstetrical specialists of his time, a barrier he was unable to overcome [32, 34–39]. Additionally, Semmelweis's discovery that handwashing prevented life-threatening maternal infection conflicted with the scientific dogma followed by the obstetricians and general medical community of his time [32, 34–39].

A different and opposite historical example demonstrates the value of medical specialty support for the dissemination of medical innovation. In 1884 Sigmund Freud and his colleague Carl Koller were studying the medicinal effects of cocaine in Vienna [50, 51]. Koller discovered that topical eyedrops containing cocaine could be fashioned into an aqueous solution that produced effective local anesthesia of the cornea [50, 51]. On September 11, 1884, he performed the first ophthalmologic surgery using cocaine as a local anesthetic on a patient [50]. Koller's preliminary report was presented by his friend, opthalmologist Joseph Brettauer, at the conference of the German Opthalmologic Society in Heidelberg on September 15, 1884 [50]. Koller's discovery was rapidly embraced by the world-wide opthalmology community [50]. Within months cocaine was being used to achieve painless eye surgery around the world [50].

5. Commercial barriers to application of scientific discoveries

> *When the work was presented, my results were disputed and disbelieved, not on the basis of science but because they simply could not be true.* (Marshall [47]).

Neither Semmelweis nor Koller faced *commercial barriers* to application of their medical discoveries. In the twenty-first century, commercial barriers may be those most significant in preventing translation of a new scientific discovery [39]. This is particularly true with respect to translation of new discoveries regarding drugs and biologics [39, 44]. Marshall faced years

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of skepticism and resistance from gastroenterologists prior to his 2005 Nobel Prize for the discovery of *Helicobacter pylori* as a cause of peptic ulcers, recognition that led to the commercialization of his discoveries by Procter and Gamble [47]. Regulatory approval of new indications for existing drugs or biologics requires voluminous specialized regulatory filings and, traditionally, the completion of multiple, large, randomized, controlled clinical trials [44]. These requirements routinely necessitate not only the expenditure of hundreds of millions of dollars but also the explicit cooperation of the drug's manufacturer [44, 45]. Without such cooperation, regulatory approval is not possible.

There is a widespread misconception that drug manufacturers readily provide financial support for the implementation of randomized clinical trials (RCTs) of their drugs for any new indication supported by the peer-reviewed medical literature [52]. In fact, many novel uses of drugs are discovered by clinicians, rather than by drug manufacturers [44, 52]. In reality, companies consider the competitive landscape, market size, cost and difficulty of manufacturing, anticipated regulatory hurdles, patent structure (indications, patent life, etc.) covering their drug and its competitors and their projected earnings in their calculus [44]. Additional difficulties involved in successful RCT design include selection of indication, suitable patient population and inclusion criteria, exclusion criteria, drug dosing (amount and dosing interval), drug formulation (vehicle, pH, viscosity), and delivery method (particularly critical for central nervous system indications) [44, 51]. Independent drug discovery start-ups and academic research centers are, in many ways, more suited to performing such research, but have difficulty independently financing such costly undertakings. Alternative funding sources, such as government research grants, are extraordinarily competitive, particularly for researchers unaffiliated with leading research universities.

6. Medical dogma as a barrier to neuroinflammation research

> *The Semmelweis case shows in striking fashion that too much respect for the dominant paradigm can damage the interests of patients.* (Gillies [36]).

Today, more than 150 years after Semmelweis and 30 years after Marshall's discovery, medical dogma still operates to interfere with medical progress [32, 34, 35, 38, 39, 47, 53]. The example of most relevance to neuroinflammation research is the dogma surrounding the use of antiamyloid therapeutics for Alzheimer's disease [53, 54]. The continuing clinical trial failure of these drugs suggests that the underlying hypothesis is, in some way, faulty [45, 53, 54]. It is well known that investments in developing and testing antiamyloid drugs [all of which have failed] have dominated Alzheimer research funding for more than two decades, effectively funneling billions of dollars of research money away from competing drugs, such as therapeutics directly targeting neuroinflammation [45, 53, 54]. The recent announcement from the new UK Dementia Research Institute acknowledges these accumulated failures and indicates a resulting shift in research direction [53]. As Bart De Strooper, the new head of the institute, recently said, "The evidence suggests that inflammation is another key factor in killing brain cells and we should be targeting that" [53].

7. Perispinal injection as a novel method for delivery of CNS drugs

> *So how should scientists respond to denialism? The first step is to recognize when it is present. Denialism changes the rules of the game. Conventional approaches to scientific progress such as hypothesis generation and testing, and argument and counterargument which seek to elicit the underlying truth no longer apply.* (McKee and Diethelm [41]).

Rapid neurological improvement after perispinal etanercept challenges the dogma that etanercept, and other large molecules, cannot reach the brain in therapeutically effective amounts after perispinal delivery[1] [51]. In fact, the ability of perispinal injection to deliver a physiologically effective dose of a drug to the spinal cord was first demonstrated by Corning in 1885 [51]. The difficulty of delivering large molecules to the central nervous system (CNS) after peripheral delivery has long presented an obstacle to neuroinflammation research and translation of that research into viable commercial products in humans [10, 22, 51]. The unique anatomy of the cerebrospinal venous system (CSVS) (**Figure 1**), the anatomic route by which perispinal etanercept is delivered to the CNS, has been confirmed by independent authorities [51, 55–59]. Increasing awareness of the potential of perispinal injection as a method for effective delivery of large molecules to the CNS promises to dramatically alter the therapeutic possibilities for brain disorders [9, 10, 18, 21, 22, 25, 28, 30, 31, 42, 43, 55, 57, 59, 60].

8. Overcoming denialism in the twenty-first century: perispinal etanercept

> *Confronted with any illness of whatever type or severity, a doctor has two ethical imperatives. The first is to ensure that a specific patient receives the best available current medical care. The second is to develop new treatments so that the patient and others with the same problem can be treated completely, easily, and economically. The second ethical imperative will, if it leads to a successful outcome, have an enormous effect on the health and well-being of humankind. (*Horrobin [46*).*

Denialism remains a potent barrier to scientific progress, even in the twenty-first century, as evidenced by holocaust denialism, tobacco-cancer denialism, AIDS denialism, and other examples of incorrect beliefs promulgated in the face of undeniable facts. Perispinal etanercept, a novel off-label treatment for four neuroinflammatory indications (spinal neuropathic pain, including sciatica; Alzheimer's disease; and chronic neurological dysfunction after stroke or traumatic brain injury) has emerged as a new therapeutic modality with unique clinical effects documented in the peer-reviewed medical literature [7, 8, 10, 51, 62–68]. The scientific rationale for the use of perispinal etanercept for these indications is extensive and has been previously reviewed [10, 19, 51, 65, 66, 68]. As the National Academy of Medicine has recently stated, "*Complementing randomized clinical trials, the ability to collect data from actual clinical practice presents a great opportunity to gain new insights about the efficacy and safety of new drugs*… [69]." This is exactly what has been done with perispinal etanercept and demonstrates

[1]"Perispinal delivery" is used here to denote perispinal injection superficial to the ligamentum flavum, utilizing the vertebral venous plexuses as a route to penetrate the relevant physiological barriers (ligamentum flavum and meninges).

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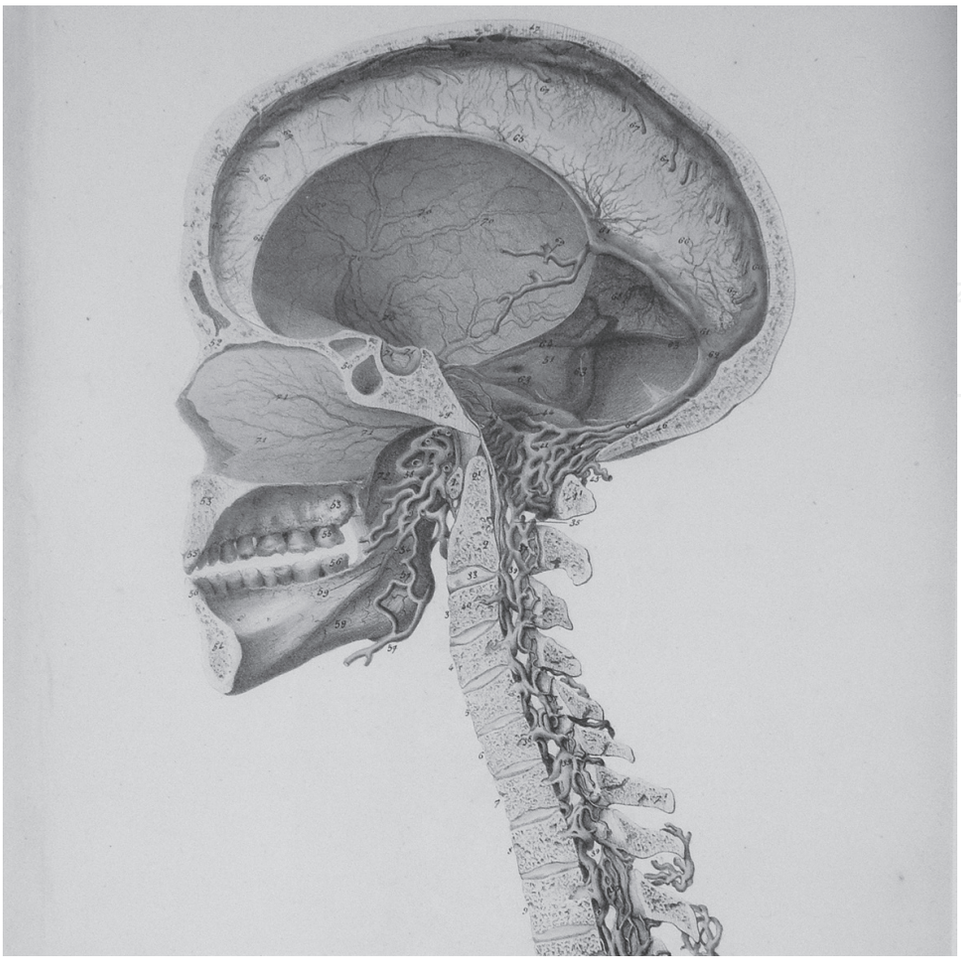


Figure 1. The cerebrospinal venous system, detail of Plate 5 from Breschet [61], Courtesy of the Sidney Tobinick Collection. ©2017 Edward Tobinick, used with permission.

the major role of clinicians in the discovery of new indications for existing drugs [7, 16, 51, 52, 62, 63, 67, 68].

Rapid neurological improvement is characteristic for each of the four off-label indications, often noticeable within minutes of the first dose [7, 8, 16, 51, 62, 64, 67, 68, 70, 71]. The spectrum of improvement as well as its rapidity are novel and may be attributed to the unique physiological effects of etanercept as well as the novel perispinal method of delivery enabled by the cerebrospinal venous system [8, 10, 16, 51, 55, 65, 68]. For example, in a series of 612 consecutive patients with chronic poststroke neurological dysfunction treated with perispinal etanercept, statistically significant improvements in motor impairment, spasticity, sensory impairment, cognition, psychological/behavioral function, aphasia, and pain, with evidence of a strong treatment effect even in the subgroup of patients treated more than 10 years after stroke, have been documented [16].

Significant neurological improvement of the degree documented after perispinal etanercept had not been previously noted with any therapeutic modality, but recently, the possibility of motor recovery years after stroke has been confirmed using modified bone marrow-derived

mesenchymal stem cells [72]. This stem cell trial involved 18 patients with stable, chronic stroke treated with surgical transplantation of specialized allogeneic stem cells by needle injection into the peri-infarct brain after burr-hole craniostomy [72]. The clinical results in this trial were not attributed to the conversion of these specialized cells into neuronal cells [72–74]. Rather, as one scientist not involved with the trial suggested in his letter to the lead author,

> *….injecting SB623 cells into the chronic poststroke brain can be predicted to generate, over time, an increasingly anti-tumor necrosis factor state in this compartment. This would be consistent with clinical observations (http://www.strokebreakthrough.com/videos-by-category/) that introducing a widely used specific antitumor necrosis factor agent, etanercept, into this same compartment through Batson's plexus, followed by a short period of head-down positioning, has led to safe and rapid onset of poststroke improvements similar to those reported to evolve slowly after intracranial introduction of SB623 cells* [73].

The lead author of the stem cell study responded,

> *Immunomodulation related to protein and molecular factors secreted by the SB623 cells could be one of the mechanisms underlying the observed neurological recovery in our patients and could suggest that there is ongoing chronic inflammation >6 months after stroke that is suppressing intact neural circuits and rendering them nonfunctional. This concept has some support in the recent preclinical and clinical literature. In addition, it is conceivable that the transplanted SB623-secreted factors are enhancing native neurogenesis or synaptogenesis, potentially through blocking excess tumor necrosis factor effects after stroke, although this is unproven* [74].

Furthermore, the favorable effects of etanercept on spinal neuropathic pain, first documented clinically after perispinal injection [7, 10, 62, 65, 75], have been confirmed in four subsequent randomized, double-blind, placebo-controlled clinical trials [76–79]. These studies and others have led "to the emergence of TNF inhibitors as available strategies for clinical treatment of pain associated with intervertebral disc herniation" [60] and foreshadowed the reduction in central pain reported after stroke and traumatic brain injury (TBI) in patients treated with perispinal etanercept [16, 67, 68].

Additional scientific support for the perispinal etanercept stroke and TBI results has come from basic science studies of etanercept in stroke and TBI models, all of which demonstrated favorable results [80–86]. Recent independent scientific publications have also been supportive of these results [15, 18, 20–26, 28–31, 42, 59, 60, 79, 87–105].

Our current thinking regarding the rapid and sustained neurological improvement documented after perispinal etanercept for neuroinflammatory indications involves the following mechanisms, each of which involves amelioration of neuroinflammatory pathophysiology by etanercept (**Table 1**).

8.1. Immediate neutralization of excess TNF

Rapid neutralization of TNF by binding to excess circulating TNF is a known physiological effect of etanercept and the main scientific rationale behind its use for its approved indications [10]. Excess TNF has been implicated in the pathogenesis of Alzheimer's disease, stroke, TBI and neuropathic pain [10, 18, 21, 60, 65, 66, 68].

Physiological effect
1. Immediate neutralization of excess TNF
2. Modulation of neurotransmission at the individual synapse
3. Modulation of neuronal network function (synaptic scaling)
4. Reduction of microglial activation
5. Reduction in neuropathic pain
6. Activation of neurogenesis

Table 1. Mechanisms of amelioration of neuroinflammatory pathophysiology by etanercept.

8.2. Modulation of neurotransmission at the individual synapse

TNF's role as a gliotransmitter that modulates synaptic transmission and synaptic strength supports this as a physiological mechanism underlying the clinical effects of perispinal etanercept [8, 10, 15, 16, 65, 66, 68, 71, 106]. When applied exogenously to superfused brain tissue, TNF inhibits the stimulation (stimulations 1 and 2, S1 and S2, at 2 Hz, 120 shocks) evoked release of norepinephrine from noradrenergic axon terminals in the isolated median eminence [107]. Similarly, when TNF is applied to slices of the hippocampus, it inhibits stimulated (S1 at 1 HZ and S2 at 4 Hz) norepinephrine release in a concentration- and frequency-dependent manner [108–110]. In both studies, the addition of TNF was 15–16 minutes prior to stimulation, indicating that TNF does not require a long exposure time to develop modulatory effects. Interestingly, TNF inhibition of stimulated norepinephrine release under physiological conditions is altered in pathophysiological conditions. For example, the inhibition of stimulated norepinephrine release by TNF is supersensitized, or increased, during conditions whereby TNF expression is enhanced in the brain (chronic pain) [111, 112]. Thus, it is proposed that descending monoaminergic pain pathways providing endogenous analgesia are no longer engaged [23]. The rapid alleviation of chronic pain experienced by patients receiving perispinal etanercept may be explained by disinhibition of norepinephrine release and descending pain modulation.

8.3. Modulation of neuronal network function by mediation of synaptic scaling

The central role of TNF in modulating synaptic scaling and synaptic strength and thereby modulating neuronal network function may help explain the rapid and widespread neurological effects of perispinal etanercept, including its rapid improvement of cognition in Alzheimer's disease, poststroke cognitive dysfunction, and cognitive dysfunction after traumatic brain injury [8, 15, 16, 62, 67, 68, 71, 106].

8.4. Reduction of microglial activation

Etanercept has been shown to reduce microglial activation in multiple experimental models [81, 113, 114]; reviews: [10, 19]. Activated microglia release excess TNF, contributing to the

neurotoxicity and perturbations in synaptic mechanisms seen in neuroinflammatory disorders [10, 19, 26, 63, 68, 81, 93, 114, 115]. Reduction of microglial activation may be a mechanism whereby perispinal etanercept reduces central homeostatic dysregulation of TNF levels induced by microglial activation after stroke or traumatic brain injury.

8.5. Reduction in neuropathic pain

Brain TNF is overexpressed during the development of neuropathic pain [4, 111, 116, 117]. Treatment using TNF inhibitors has been shown to reduce neuropathic pain in both basic science models and in the clinical setting [5, 10, 16, 19, 25, 60, 62, 68, 76–79, 99, 114]. Preclinical studies have shown that blockade of TNF synthesis in the brain is antinociceptive [99]. Also, clinical case studies report that targeting TNF centrally is analgesic [62, 71, 79]. This may be due to blockade of TNF that restores neurotransmission homeostasis along pain pathways.

8.6. Activation of neurogenesis

Although there is some conflicting data, a variety of experimental models suggest that TNF or other pro-inflammatory cytokines, if present in excess, may inhibit neurogenesis [118–122]. TNF and interleukin-1 are involved in the decrease of neurogenesis evidenced in pain and depression models [123–125]. Mice receiving sciatic nerve chronic constriction injury to induce neuropathic pain developed depressive-like behavior for 4 weeks following ligature placement that was associated with increased hippocampal TNF and impaired dentate gyrus neurogenesis dependent on TNF receptor-1 signaling [126]. There is data suggesting that inflammatory blockade may restore adult neurogenesis [122]. This, theoretically, might be a potential mechanism that could contribute to the increasing neurological improvement observed after perispinal etanercept treatment over the course of months in some patients [16, 63, 68, 120–122].

Perispinal etanercept has successfully traversed a variety of scientific, academic, and governmental barriers to achieve scientific acceptance and recognition [9, 11, 13, 15, 18, 20–26, 28–31, 42, 57, 59, 60, 79, 81, 82, 88–91, 93–98, 100–105, 114, 115, 123, 125, 127–133]. This was accomplished despite considerable misinformation published online by competing medical specialists, who refused the opportunity to observe, first-hand, the rapid neurological effects of perispinal etanercept, despite repeated invitations to do so [43, 48]. Such denialism is in the tradition of that faced by Galileo, Semmelweis, Lister and Marshall, but it has no place in science or medicine [1, 22, 32, 33, 35–39, 41–43, 47].

As Glaziou and colleagues have stated [134]:

> *Confident inferences about the effects of treatment are justified in several situations in which treatment effects are unlikely to be confused with the effects of biases. These include, in particular, … interventions … where there is a rapid response on a stable background [*134*].*

The rapid neurological improvement repeatedly observed in thousands of patients with chronic, intractable neurological dysfunction after treatment with perispinal etanercept,

combined with strong, independent, basic science support, constitutes compelling evidence that mandates the recognition of these clinical effects and the initiation of the necessary actions, including the funding of randomized clinical trials, by the relevant medical specialties and governmental agencies, for the benefit of the public.

9. Overcoming barriers to the application of neuroinflammation research

> *I by no means expect to convince experienced naturalists whose minds are shocked with a multitude of facts all viewed, during a long course of years, from a point of view directly opposite to mine….But I look with confidence to the future, to young and rising naturalists, who will be able to look at both sides of the question with impartiality.*
>
> Charles Darwin [135], *The Origin of Species,* 1845.

The key to overcoming barriers to application of neuroinflammation research is education. It is essential that medical students and neuroscientists receive training in basic immunology, the role of cytokines in physiology and pathophysiology and the essential concepts underlying neuroinflammation. Because neuroinflammation is not concrete and visible under the microscope in the same way that pathology such as amyloid plaques are, improved methods, access and utilization of new and emerging methods for imaging neuroinflammation are also essential. Today, fortunately, the initial promise of neuroinflammation research is bearing fruit, and a paradigm shift in scientific thinking in this regard is well underway. Recognition of the necessity of neuroinflammation research for the successful development of new treatments for neurological disease must be a key goal of society. The allocation of sufficient research and educational funding to this end is essential.

Conflict disclosures

Edward Tobinick has multiple issued and pending US and foreign patents, assigned to TACT IP, LLC, that claim perispinal methods of use of etanercept and other drugs for treatment of neurological disorders, including but not limited to US patents 6419944, 6537549, 6982089, 7214658, 7629311, 8119127, 8236306, 8349323, 8900583; and Australian patents 758523 and 2011323616 B2. Dr. Tobinick is the CEO of TACT IP, LLC and founder of the Institute of Neurological Recovery, a medical practice that utilizes perispinal etanercept and trains physicians in its use as a therapeutic modality. Tracey Ignatowski and Robert Spengler have been unpaid expert witnesses for the INR. Tracey Ignatowski and Robert Spengler's professional activities include their work as co-directors of neuroscience at NanoAxis, LLC, a company formed to foster the commercial development of products and applications in the field of nanomedicine that include novel methods of inhibiting TNF. The article represents the authors' own work in which NanoAxis, LLC was not involved.

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