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REVIEW

Neurodegenerative disease treatments by direct TNF reduction, SB623 cells, maraviroc and irisin and MCC950, from an inflammatory perspective – a Commentary

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ABSTRACT

Introduction: The importance of excessive cerebral tumor necrosis factor (TNF) concentrations as one of the central tenets of the pathogenesis of the neurodegenerative diseases is now widely known, but variably accepted.

Areas covered: Here we update the field by including material that is freely available on the large databases, particularly PubMed. We include the therapeutic outcomes with etanercept (a widely used specific anti-TNF biological), XPro1595 (a new double negative TNF inhibitor), 3,6[1]-dithiothalidomide, implanted SB623 stem cells, maraviroc (a CCR5 inhibitor used to treat AIDS), MCC950 (an NLRP3 inhibitor), and changes in the hormone irisin.

Expert opinion: Remarkably, considering the ample literature that links SB623 cells, maraviroc, MCC950 and irisin to TNF, these publications do not mention this cytokine, and therefore not their implicit involvement with controlling its cerebral levels. With regard to developments demonstrated by MCC950, we note that DAMPs and PAMPs recognize and activate both TLRs and inflammasomes in these disease states. Here, as in other illnesses, data suggests that preventing a pathogenic interaction could be achieved through shutting down either of these arms of innate immunity.

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Neurodegenerative disease; TNF; SB623 cells; maraviroc; irisin; MCC950

1. Background

A research perspective of neurodegenerative diseases that regards proteinaceous markers in brain sections to be disease-specific, and therefore useful as diagnostic tools that can also define mechanisms for the various clinical entities, has now almost gone. With it has largely gone the perception of fundamental differences in mechanisms, as distinct from emphasis and anatomical locations of events in each of these entities. Often this enlightenment was not so much through new knowledge, but an awareness that one could cast the net much wider and glean information that had been available for some time. The 'traditional' neurodegenerative diseases provide good examples of this. Amyloid beta (Aβ) deposits and tau tangles are found not only in Alzheimer's disease (AD) brains but across the neurodegenerative disease spectrum. Tauopathy, for example, has recently been noted to have been documented in 28 different neurodegenerative states [1], a far cry from its original, at the time implying specific, role in AD. Others have recently considered the pathways common to various neurodegenerative diseases in terms of phenotypic networks rather than clinical syndromes [2].

As well as tauopathy, cerebral Aβ and α-synuclein (αSyn) deposition are remarkably widespread, including being histologically evident in the changes brought on by a stroke, traumatic brain injury (TBI), cardiac arrest, and lead (Pb) poisoning, as we have discussed previously [3]. While Parkinson's disease (PD) has been the archetypal focus for α-Syn research, this protein has also been closely correlated with severity in AD, correlating better, indeed, than Aβ or tau when all are in their soluble forms [4]. Likewise, the transactive response (TAR) DNA-binding protein with a molecular weight of 43 kDa (TDP-43), originally identified as an intracellular ubiquitin-positive inclusion, is now the newest member of the growing list of neurodegenerative proteinopathies [5]. It was initially regarded as an important link between one form of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Subsequently, TDP-43 has been accepted to be present in most AD brains [6], as well as in many aged brains that do not meet the criteria defining FTLD [7]. In addition, other markers first described in other neurodegenerative states, and once regarded as unique to them, can be present in FTLD and ALS [8–10].

We and others have previously written about neurodegenerative diseases in general from an inflammatory perspective, in particular, the harmfulness of chronically increased cerebral levels of signaling cytokines that distort signaling pathways, thus harming neurotransmission, mitochondrial function, and cell viability [11–17]. In this Commentary, we note that the literature on therapeutic approaches directly addressing TNF reduction in neurodegenerative diseases now has a twelve-year history, with use of a specific anti-TNF biological [18] soon spreading to patients and models of both stroke and TBI. Five years later literature employing 3,6-dithiothalidamide, an inhibitor of TNF RNA, appeared in a TBI model [19] and soon after in AD and stroke models, as we discuss later. A further three years later an engineered double-negative form of TNF, XPro1595 [20], was

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Article highlights box

- Excess cerebral levels of the signaling cytokine TNF provide an important target for therapy against neurodegenerative diseases.
- Ample evidence in a number of models across the field, including human open trials, and inadvertent effects of anti-TNF agents chronically administered for approved treatments, are consistent with this.
- Emerging reports that a number of novel approaches are useful in neurodegenerative diseases are, although not mentioning TNF, can readily be argued to be conceptually anti-TNF-based.
- These functional similarities allow the case to be made for the efficacy, cost, and practical advantage of all these approaches, including those that constitute repurposing of agents already in use, should be assessed as part of the approvals process.

used in a Parkinson's disease (PD) model. Four more recent papers discussed here are best categorized as indirect TNF reduction, some authors surprisingly not mentioning this well-known cytokine and others perhaps not being aware of how it is linked to their work. This series of texts begins, in the present text, with a report of surgically implanting SB623 cells directly in the brain of stroke patients [21], which we have previously discussed at length [3]. Next, parenteral maraviroc [22] in stroke and TBI mouse models, manipulated gene levels of irisin [23] in mouse AD models, and oral MCC950 [24] for mouse PD models are discussed. We largely restrict our comments on these four recently emerged texts by summarising how they are linked through their integration with the TNF literature.

2. TNF and IL-1 generation – DAMPs, PAMPs, TLRs, NLRP3

The field of innate immunity, with which inflammation has become closely affiliated, became much more comprehensible through the advent of the concepts of pathogen-associated molecular patterns (PAMPs) [25], danger-associated molecular patterns (DAMPs) [26], and the transmembrane proteins referred to as Toll-like receptors (TLRs) [27]. TLRs are a member of one of the families of pattern recognition receptors (PRRs) that evolved before much of the rest of the immune system. Introducing these novel overarching terms and concepts has succeeded in casting a new light on the origins and consequences of the chronic generation of cytokines such as TNF, with its profound effects on disease pathogenesis as well as innate immunity. In practice, PAMPs and DAMPs perform identical tasks – indeed the case has been made to name them collectively as alarmins [28,29]. Having been extremely useful in understanding pathogenesis overlaps between systemic infectious and non-infectious states, these concepts are also proving their worth in comprehending neurodegenerative disease.

Much evidence exists that the various disease markers discussed here activate TLRs on or in cerebral cellular components, thereby chronically enhancing local levels of TNF and associated cytokines. Being of host origin, these markers are termed DAMPs. They can include hypomethylated host DNA (e.g. mtDNA released after trauma [30]), normal host DNA hypomethylated by lead (Pb) poisoning [31]), and High Mobility Group Box 1 (HMGB1). HMGB1 often arises from hypoxia, which enhances its release in many cell types [32]). Non-infectious material such as air pollutants [33], including diesel exhaust particles [34], are also referred to as DAMPs. As noted above, other non-host material, such as molecular patterns on pathogens that can enter the brain and cause chronic infections [35,36] are termed PAMPs. Intriguingly, the allergy literature regards biological allergens, while not technically pathogens, are referred to as possessing PAMP activity [37].

As a preamble to a text we later discuss on MCC950 [24], we comment briefly here on there being two parallel worlds of PRRs, Toll-like receptors (TLRs), and the NOD-like receptors (NLRs), both being as important in neurodegenerative diseases as elsewhere [38,39]. One of these NLRs, NLRP3, is particularly relevant here. TLRs, present across intra- or extracellular membranes, which trigger TNF release, and NLRs, located within the cytosol, are both activated by PAMPs and DAMPs. Activation of certain NLRs leads to the formation of cytosolic protein complexes termed inflammasomes, which regulate activation of caspase-1, an enzyme that, through cleavage of their precursor forms, generates active interleukin-1β (IL-1β) and IL-18.

3. The apparently central role of TNF in the neurodegenerative diseases

3.1. Treatment with anti-TNF agents

Whenever, for brevity, TNF is discussed alone in this text, it often implies the sense of other pro-inflammatory and anti-inflammatory cytokines that are usually generated soon afterward, such as IL-1β and IL-18, when inflammasome activitation has come into play. A primary driver function of TNF in these cytokine families can be inferred from the massively successful therapeutic use of anti-TNF biological agents in important systemic clinical conditions, beginning with rheumatoid arthritis in 1994 [40]. Indeed, in 2013 Schett and co-authors made what we see as a convincing case rationalizing why TNF should be expected to be more central than other cytokines to inflammatory disease pathogenesis [41].

As reviewed [42], for some years before interest in roles for cerebral-origin TNF in neurodegenerative states arose, this cytokine had been appreciated to be central to the pathogenesis of systemic infectious and certain non-infectious diseases. Experience with *in vivo* responses to specific anti-TNF biologicals over the last 12 years has generated a strong case for this being true for the important neurodegenerative diseases as well. Unfortunately, the first direct evidence emerged at the height of massive Pharma financial commitment to anti-Aβ trials in human AD, and this drew most funding and therefore intellectual effort in the field in this direction. Hence, the central role of excess cerebral TNF was extremely slow in attracting a following. Continuing failure of anti-Aβ trials, conceivably aided by over a decade's peer-reviewed criticism of their scientific implausibility [43,44], eventually played a part in overcoming this reticence [45]. Nowadays much literature points to the harmfulness of excess TNF in the central nervous system through a combination of loss of homeostasis, and therefore potentially reversible function loss, as well as cell death. Initially this was through outcomes of administering etanercept, a specific anti-TNF biological to AD patients in a 2006 uncontrolled trial [18], and since then in AD model mice [46], stroke model mice [47–49], further AD patients [50–54], post-stroke patients [55,56], mouse PD models [20,57], TBI patients [56], and a rat TBI model [58]. The routes of administration varied in ways described by these authors and do not affect the general

principle. Notably, the Tobinick reports quoted here utilize a novel perispinal method of getting large molecules through the blood-brain barrier (BBB) [59,60]. Although an apparent Holy Grail, this procedure remains unwelcome and unwitnessed by potential Pharma collaborators or by neurologists, despite being used and published in open trials and many clinical reports for 12 years. This seems irrational, and not in patients' interests since this perispinal approach is the conceptual genesis of all the post-2006 publications quoted in this paragraph. In addition etanercept, and most like other of the same class plus their biosimilars, constitute drug repurposing Clearly, much is at stake commercially.

3.2. XPro1595 cf. etanercept

XPro1595 is an exciting, impressively engineered, variant of TNF [61] that rapidly forms heterotrimers with native TNF to give a complex termed a dominant negative inhibitor of TNF because it can no longer bind and signal via TNFR1 or TNFR2. Importantly, transmembrane TNF signaling remains functional. This gives XPro1595 a practical advantage over the anti-TNF biologicals such as etanercept, in that latent infections by *Listeria monocytogenes, Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) and *M. tuberculosis* can still be suppressed normally. Administered subcutaneously, it is reported to reduce harmful effects in 6-OHDA Parkinson's model [20]. Clearly, sufficient reached the CSF to have a therapeutic effect, but this was only about one-thousandth of the plasma level. Another publication with the same senior author [62] used the same route of administration for XPro1595 to achieve a series of positive outcomes in a mouse AD model. From its molecular weight, it is likely to benefit from the same perispinal route as is employed with etanercept.

Notably, and despite its large size, administering subcutaneous etanercept long term has had detectable positive outcomes in AD and PD. A single-controlled AD patient trial was conducted in Southampton with subcutaneous etanercept [51]. In this tightly edited version of events, this trial can appear to have had a negative outcome. However, positive outcomes of this trial have been presented at international conferences (e.g. abstract 04–00-12, Alzheimer's Association International Conference Copenhagen, Denmark, 16 July 2014), and discussed in the first author's PhD thesis [53]. This covers the trial more extensively and is compatible with enough subcutaneously administered etanercept having entered the brain to have had worthwhile clinical effects. These data are consistent with a report, drawn from a particularly large database over a long period, of subcutaneous chronic use of etanercept to treat rheumatoid arthritis significantly reducing AD incidence [52]. A similar pattern, in this case, 78% lower incidence of PD, was recorded in a large number of patients who received peripherally administered anti-TNF biologicals to treat inflammatory bowel disease, compared with those not receiving this medication [54]. In our view, therefore, it seems premature to refer to etanercept as a non-BBB crossing TNF inhibitor [62], which could be taken to imply that only etanercept, and not XPro1595, would benefit from perispinal administration [60]. Only when XPro1595 and etanercept are compared directly, such as done in a mouse stroke model [48], can such judgments be made. In these studies intravenously administered XPro1595 and etanercept equally improved functional outcomes within the brain. Given their high molecular weights, both are likely to demonstrate much more rapid and effective outcomes, with a considerably lower total dose, when eventually compared on perispinal administration [60]. We note the accumulated years of exceptionally wide experience with anti-TNF biologicals such as etanercept, beginning in the early 1990s, whereas patients have not yet been exposed to XPro1595. Even so, given its ability to allow immunity to latent tuberculosis and similar infectious states to remain intact, eventual therapeutic advantages for this double negative TNF are highly plausible, and we regard this development as very positive for the field.

3.3. 3,6^1-dithiothalidomide

Another different approach to reducing excess cerebral TNF activity has arisen through using 3,6^1-dithiothalidomide, a synthetised agent that this group have shown readily enters the brain and decreases TNF RNA stability [63]. This has led to a series of closely related and well-reasoned papers [19,64–71]. These convincingly come to the same conclusion as the studies using anti-TNF biologicals, namely that experimental models of TBI, AD, post-stroke, and lipopolysaccharide-induced inflammation all operate through excessive TNF generation. There seems to be no reason, apart from the name reminding people of the parent compound, which has harmful properties it does not share, for this approach not yet to have blossomed.

3.4. Injecting SB623 stem cells into the brain

An additional line of evidence incriminating excess TNF as being central to the pathogenesis of these conditions arises from a 2016 uncontrolled trial of surgically implanted SB623 cells into brains of patients suffering from post-stroke syndromes [21]. These are modified stem cells from adult bone-marrow-derived cells that are transiently transfected with a plasmid construct encoding the intracellular domain of human Notch-1. Positive outcomes occurred, albeit much slower and less dramatic in onset, and requiring a more indirect and expensive delivery system entailing a team of neurosurgeons. Even so, these outcomes echoed aspects of those achieved in other uncontrolled trials with a specific anti-TNF biological given by the novel perispinal route in similar patients some years earlier [55,56]. The logic of these two approaches is clearly the same – how to get an anti-TNF effect to where it matters.

The groundwork for this 2016 stem cell study was laid in 2009, when mesenchymal stem cells introduced into a cerebral ventricle in a rat stroke model, significantly improved function while enhancing the production of the anti-inflammatory cytokine IL-10 and, crucially, decreasing TNF levels [72]. Thus, the capacity of these stem cells to improve post-stroke disabilities is most likely through creating a strong anti-inflammatory milieu, generated in this case by fibroblast growth factor 2 (FGF2) [73]. Among other activities, this cytokine counters TNF [74]. The Pharma that owns SB623 cells is rapidly expanding this work by funding large-controlled trials across the neurological disease spectrum (e.g. ClinicalTrial.gov Identifiers NCT02448641 and NCT02416492). In contrast, the perispinal etanercept procedure for countering excess TNF [55,56], the outcome of which

SB623 cells evidently mimics, yet does not quote [75] has still not raised any official curiosity within the American Academy of Neurology [76] despite years of requests, spanning the period during which the SB623 open trial was done [77], for members of this Academy to witness it. The numbers treated off-label by this method and witnessed by experienced people have mushroomed since a Californian legal judgment (California Case No. 04–2012-222,007, 22 May 2015) declared that there were sufficient data and research about the drug's safety and potential effectiveness to support this treatment continuing. There seems no scientifically or morally defensible reason why this novel post-stroke and post-TBI treatment route of administration [60], its outcomes readily viewable on the internet, and employing an agent in wide clinical use for decades, has not been disinterestedly witnessed and evaluated by neurologists over the past eight years.

3.5. CCR5 inhibition and its implications for TNF in neurodegenerative disease

More evidence pointing to the significance of excess cerebral TNF in neurodegenerative diseases comes from a recent study in which a large-dose daily of maraviroc (Selzentry), an AIDS medication, was administered intraperitoneally for 8–11 weeks in mouse post-stroke and post-TBI models [22]. This agent inhibits CCR5, a chemokine receptor expressed on T cells, macrophages, microglia, and neurons, and recently associated with learning and memory [78]. Maraviroc also enhances motor recovery and reduced cognitive decline in these mice, along with stabilization of dendritic spines [22], and its protective activity in the nigrostratum of hemiparkinson monkeys includes attenuating neuroinflammation [79]. Moreover, within a large cohort of stroke patients, carriers of a naturally occurring loss-of-function mutation in CCR5 (CCR5-Δ32) were reported to exhibit greater recovery of neurological impairment and neurological function.

This remarkable document [22] can perhaps be best characterized as being as fulsome in praise of excess TNF being a central mechanism for stroke and TBI as is possible without actually mentioning TNF, or the links their work has with this cytokine. For example, these human CCR5-Δ32 carriers would have been predicted, from experience since 2011 of anti-TNF improving stroke outcomes [47–49,55,56], to recover better from this condition by virtue of their documented innate poor capacity to generate TNF [80]. Maraviroc, an effective anti-TNF agent [81–84] is shown by these authors [22] to provide useful outcomes in post-stroke and post-TBI mice. Unaccountably, earlier reports of other anti-TNF agents operating thus in mice, rats, and people [47,55,56,58,85] have not been quoted, or compared with their findings. Moreover, since TNF is known to underlie the loss of dendritic spines in the experimental cardiac arrest brain [86], maraviroc can be expected, as shown [22], to preserve them. We also note that part of the logic discussed for performing these experiments is associated with shared principles in brain injury recovery and mechanisms of learning and memory. Prior work in Carmichael's laboratory on gamma-aminobutyric acid (GABA) [87], which reported that reducing extrasynaptic GABA promotes functional recovery after stroke, is also invoked. Since then, however, the virology world has reported that excessive TNF upregulates glutaminase [88], and this enzyme has been shown to catalyze the conversion of glutamate to GABA [89], as well as glutamine to glutamate. We would, therefore, expect the specific anti-TNF biological, etanercept, to reduce excess extrasynaptic GABA and improve learning ability in stroke, since its close relative, infliximab, causes both of these changes in hepatic encephalopathy [90]. Finally, we recall that a decade ago parasitologists showed that TNF up-regulates CCR5 expression by CD8 + T lymphocytes and promotes heart tissue damage during *Trypanosoma cruzi* infection and that both anti-TNF treatment [91] and a CCR5 antagonist [92] were beneficial.

3.6. Irisin and its implications for TNF in neurodegenerative disease

A still further line of evidence incriminating excess cerebral TNF levels chronically harming brain function arises from recent comprehensive publications about the exercise hormone irisin [23,93]. As with the MCC950 study below, neither text measures or discusses TNF. Nevertheless, it is crucial for the clinical application of this body of knowledge that we understand the place of irisin in the pathophysiological interplay that surrounds the role of TNF in neurodegenerative diseases. Lourenco and co-workers [23] report irisin, a hormone mainly released from a myokine when skeletal muscle is strongly exercised, as well as being expressed in the hippocampus at this time [94], as possessing striking novel activity in various experimental AD mouse models. In contrast, Young et al. [93] discuss the principle across the spectrum of neurodegenerative disease. However, the key to both of these texts could well lie in TNF. Albeit discovered for its role in changing white fat to brown [95], irisin had, in systemic inflammatory diseases [96–98] and acquired cerebral injury [99], and well before references 23 or 93 appeared, become appreciated to strongly inhibit TNF and functionally related cytokines.

Among the many cerebral functions that can be expected when cerebral TNF is chronically increased, and therefore be reversed by increasing irisin, are reduced synaptic plasticity [100] and poor memory [101]. Ample evidence exists that the Aβ these authors also employed to bring about these changes operates through enhancing TNF levels [102,103]. It should, therefore, come as no surprise that Lourenco and co-workers could, respectively, reverse or exacerbate synaptic failure, and memory impairment by either overexpressing or blocking what is effectively another endogenous anti-TNF agent, irisin. Specifically, increasing brain levels of irisin by using the adenoviral vector technique improved synaptic plasticity and memory defects in mouse models of AD, while reducing irisin levels via a lentiviral vector impaired synaptic plasticity and memory. Moreover, irisin was low in cerebrospinal fluid, but not plasma, from AD patients. This opens the prospect of therapeutically employing recombinant irisin so it reaches the hippocampus. Given the marked pleiotropic activity of TNF, and the width of its cerebral influence [13], its link to irisin invites a re-interpretation of much literature on its effects on brain function. Even so, the relevance of this work to patients would be enhanced if a report of the gene encoding FNDC5, the precursor of irisin, showing, in humans, a mutation argued to limit its relevance to human disease [104] had been discussed. Direct comparisons between specific anti-TNF biologicals on one hand, and their biosimilars, both of which are in present clinical use, and maraviroc,

MCC950, and irisin on the other, are warranted from scientific, government health funding and patient-need perspectives.

3.7. MCC950 and its implications for TNF in neurodegenerative disease

An additional line of evidence pointing to the significance of excess cerebral TNF in neurodegenerative diseases concerns the uses to which MCC950, a selective NLRP3-inflammasome inhibitor, has been put to in mouse PD models [24]. This synthetic compound MCC950, administered orally every day, reportedly blocks inflammasome activation and protects against nigrostriatal dopaminergic degeneration. While the authors do not discuss TNF, ample evidence exists that MCC950, a synthetic compound originally developed to inhibit interleukin-1β post-translational processing, also has strong anti-TNF properties [105–109]. NLRP3s are reported, as least in adipocytes [110], to be induced by TNF. We note that propofol and mangiferin, which the authors of this new work [24] have recently reported elsewhere [111] inhibit NLPR3 activity, also suppress TNF production [112,113]. In addition, XPro1595 (see above), a recombinant double-negative form of TNF with specific neutralizing activity against native TNF, produced a very similar outcome [20] in the same 6-hydroxydopamine (6-OHDA) PD model as achieved by Gordon and coworkers with MCC950 [24].

A comparison between details of outcomes with anti-TNF biologicals and MCC950, already suggested in a rat stroke model [108], seems warranted in this and other neurodegenerative states. Importantly, anti-TNF biologicals have been clinically successful, on a large scale, for decades. In contrast, under an alternative name, CP-456,773, MCC950 was tested in phase II human clinical trials for rheumatoid arthritis, but not developed further because it elevated serum liver enzyme levels in the clinic. The cause of this liver toxicity signal is not clear, although combined effects of its metabolically reactive furan moiety and a very high clinical dose of 1,200 mg per day, two well-known causes of drug-induced liver injury, might underlie the observed toxicity [114]. Table 1 of this recent review also lists a number of conditions (AD, inflammatory bowel disease, stroke, and TBI) against which specific anti-TNF biologicals have shown activity to also be improved by MCC950. There is not space here to discuss the potential for complexity between TNF and IL-1, but an impression of it may be gained by considering the capacity for TNF to induce IL-1 [115], and IL-1 to induce TNF [116,117]. Moreover, they synergise [118,119]. These observations imply a synergistically harmful cycling between these cytokines, and therefore between TLRs and NLRP3, the receptors that trigger there release, and are consistent with arguments put in place six years ago [38]. From this, we infer that MCC950, specific anti-TNF biologicals, and XPro1595 are equally valid ways to seek to halt this pathological synergy across a range of inflammatory diseases. The same can be said of the SB623 cell, maraviroc, irisin, and MCC590 approaches. They would reinforce not just each other, but also the other, acknowledged, anti-TNF approaches.

In summary, an intriguing recent series of highly positioned publications may be seen as efforts to put a distinctive, patentable stamp on alternative ways to understanding and treating the neurodegenerative diseases, by indirectly reducing chronically excessive cerebral levels of TNF. This fundamental approach has been extant for over a decade, and appears, in ways that include these SB623 cell, maraviroc, irisin, and MCC590 publications, to be coming in out of the cold.

4. Expert opinion

The ultimate goal of this research is to generate for neurodegenerative diseases a therapeutic principle that parallels what has previously been established for certain chronic systemic diseases. Persistently high levels of TNF have been known for many years as worthy targets in treating chronic disease states. The importance of this target for diseases such as rheumatoid arthritis, psoriasis, and Crohn's disease may be gauged from the massive income specific anti-TNF biologicals have provided to the pharmaceutical industry over recent years (Humira (adalimumab), Enbrel (etanercept) and Remicade (infliximab)) in the graph at https://www.forbes.com/sites/matthewherper/2015/07/29/the-top-drug-launches-of-all-time/#46db4cdf6512.). Researchers and industry have had their sights set, for over a decade, on the potential of this same approach to generate a similar usefulness, and income from the neurodegenerative diseases. It has been evident from the literature over these years that agents directed at essentially the same target on the other side of the blood-brain barrier are very likely to help patients. They will also generate a market for this industry, and therefore a cost for governments and the public likely to be at least as massive as those shown on the above graph.

The potential of treating these disease states by neutralizing excessive cerebral levels of TNF is undoubtedly enormous. In this commercial age, however, conflict arises. Those with an ultimate research goal of helping as many patients as possible look benignly on an example of drug re-purposing provided by injecting etanercept, an anti-TNF biological with many FDA-approved clinical applications by a novel route of administration. This appears to have stopped, in numerous patients, many post-stroke and post-TBI sequelae in their tracks but has never attracted backers willing to fund a controlled trial, except recently the Australian Government. This research direction has continued for almost a decade, and includes, in principle, the thalidomide analogues and XPro1595, a double negative rTNF. It has to be said that the pharmaceutical companies selling etanercept, which is financially threatened by biosimilars, refused engagement very early on. Clearly, times are very less patient-orientated than a couple of decades ago. In 1993, on being advised of success with infliximab, the first of anti-TNF biologicals, in open studies for rheumatoid arthritis, the company that owns this agent funded a controlled trial, run in conjunction with the originators of the concept. This reported a positive Phase III outcome within a year. Nowadays, times are such that the parent body of the US medical specialists who collaborate with pharmaceutical companies to research neurodegenerative disease have never to date, 13 years after the first open trial, even consented to witness the perispinal injection procedure or its clinical outcome. Evidently, they see drug repurposing as an anathema to novel patent-driven research funding and financial success. Thus, they have put themselves in a position, presumably rational from their perspective, of actively trying to stop

something they have never seen, and indeed very rarely acknowledge exists. Indeed, the court case they initiated to stop it being used off-label not only failed to do so, but actually gave its use legal encouragement. In contrast to neurologists, independent neuroscientists, often following their own leads, observe and quote this work while building on it. Already perispinal etanercept outcomes are raising interesting and useful scientific questions, such as how it acts so quickly, how it can be useful so long after the stroke or TBI episode, and how its effects last for so long. These are real outcomes seen in thousands of cases, and measurable by any witness with a timepiece.

Clearly, the perispinal etanercept deniers have ambitions to emulate or better this clinical outcome. There is little doubt that some will eventually be very successful in this, albeit at a much higher financial cost to governments and individuals than could have been the case, and at least a decade later than any agent already in widespread use in the clinic. Thus, it is important for science and the community that new treatments are compared in efficacy and price to the repurposing approach outlined above.

Looking ahead, once these post-stroke and post-TBI questions have practical answers in place, in our view a key question, already in many minds, is how well might these advances make the survival of stroke and TBI more likely. In other words, will any of the treatments that come out of post-stroke and post-TBI clinical trials with good reputations prove useful adjuncts soon after the stroke or traumatic event? The first week does not lend itself to distinguishing between inevitable and treatment-induced improvements unless the agent under consideration is well established to function later, when the clinical status is stable. Another key question is whether AD and PD treatment will gain from advances in stroke and TBI treatment. Their insidious onset and remorseless advance presents additional problems, but even a temporary respite through these tools would be instructive scientifically. These issues merit careful consideration by the neurodegenerative research community.

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