UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

EDWARD LEWIS TOBINICK M.D., A MEDICAL CORPORATION d/b/a THE INSTITUTE OF NEUROLOGICAL RECOVERY, a California Medical Corporation; INR PLLC d/b/a INSTITUTE OF NEUROLOGICAL RECOVERY, a Florida professional limited liability company; and EDWARD TOBINICK, M.D., an individual,

Plaintiffs,

v.

CASE NO.

STEVEN NOVELLA, M.D., an individual; YALE UNIVERSITY, a Connecticut corporation; SGU PRODUCTIONS, LLC, a Connecticut limited liability company; and SOCIETY FOR SCIENCE-BASED MEDICINE, INC., a Florida corporation,

Defendants.
_____/

COMPLAINT

Plaintiffs, EDWARD LEWIS TOBINICK M.D, A MEDICAL CORPORATION d/b/a THE INSTITUTE OF NEUROLOGICAL RECOVERY, a California Medical Corporation ("the Institute"); INR PLLC d/b/a INSTITUTE OF NEUROLOGICAL RECOVERY, a Florida professional limited liability company (collectively with the Institute, "the INR Plaintiffs"); and EDWARD TOBINICK, M.D. ("Tobinick"), through undersigned counsel, hereby sue Defendants, STEVEN NOVELLA, M.D. an individual ("Novella"); YALE UNIVERSITY, a Connecticut corporation ("YALE"); SGU PRODUCTIONS, LLC, a Connecticut limited liability company ("SGU"); and SOCIETY FOR SCIENCE-BASED MEDICINE, INC., a Florida corporation ("SBM") (collectively with Novella, Yale and SGU, "Defendants"), and in support, state as follows:

NATURE OF ACTION

1. This is a civil action for, among other things, injunctive relief and damages in excess of $75,000.00, exclusive of interest and costs. This civil action concerns violations of Section 43(a) of the Lanham Act, 15 U.S.C. §1125(a);

THE PARTIES

2. Plaintiff EDWARD LEWIS TOBINICK M.D, A MEDICAL CORPORATION d/b/a THE INSTITUTE OF NEUROLOGICAL RECOVERY is a medical corporation organized under the laws of the State of California, with its principal place of business in Los Angeles County, California.

3. Plaintiff INR PLLC is a corporation organized under the laws of the State of Florida, with its principal place of business in Palm Beach County, Florida.

4. Plaintiff TOBINICK resides in Palm Beach County, Florida, is over the age of eighteen, and is otherwise *sui juris*.

5. Defendant NOVELLA resides in the State of Connecticut, is over the age of eighteen, and is otherwise *sui juris*.

6. Defendant YALE is a corporation organized under the laws of the State of Connecticut, with its principal place of business in Connecticut.

7. Defendant SGU is a corporation organized under the laws of the State of Connecticut, with its principal place of business in Connecticut.

8. Defendant SBM is a corporation organized under the laws of the State of Florida, with its principal place of business in Leon County, Florida.

JURISDICTION AND VENUE

9. This Court has subject matter jurisdiction of the action pursuant to 28 U.S.C. §§ 1331 and 1338 and 15 U.S.C. § 1121 because this action arises under the trademark laws of the United States (15 U.S.C. §1051 et. seq.)

10. Defendants are doing business in this district and is transacting business in this district by committing the complained of tortious acts within this district. By reason of the foregoing acts of Defendants, in personam jurisdiction exists over the Defendants.

11. Defendants have committed the complained of tortious acts in commerce which may lawfully be regulated by Congress. Defendants' complained of activities have affected and damaged Plaintiffs' interstate business which is located within this District. Venue is proper in this District as to Defendants pursuant to 28 U.S.C. §1391 (b)(2) and (c)(2).

GENERAL ALLEGATIONS

12. The INR Plaintiffs provide medical services to selected patients with unmet medical needs.

13. In pertinent part to the relief requested in this action, the INR Plaintiffs provide commercial medical treatment for patients after stroke.

14. In direct competition with the INR Plaintiffs, NOVELLA and YALE also provide commercial medical treatment for patients after stroke.

15. The treatment methods provided by the INR Plaintiffs differ from the treatments methods provided by NOVELLA and YALE.

16. More specifically, the INR Plaintiffs utilize etanercept delivered by perispinal administration for treatment of patients after stroke, including for treatment of post-stroke spasticity.

17. NOVELLA and YALE use Botox® for treatment of post-stroke spasticity.

18. In violation of the Lanham Act, NOVELLA has and continues to publish a false advertisement disparaging Plaintiffs entitled "Enbrel for Stroke and Alzheimer's", (the "Advertisement") and implying that the INR Plaintiffs' use of etanercept is ineffective and useless. A copy of the Advertisement is attached hereto as Exhibit 1.

19. Likewise, YALE, SGU and SBM have directly made and continue to publish the Advertisement by linking to the website www.sciencebasedmedicine.org on which the advertisement resides, or publishing it on their own websites or otherwise promoting it.

20. In addition to constituting a false advertisement, the Advertisement also tarnishes the federally registered trademarks of the INR Plaintiffs. "Institute of Neurological Recovery" is a registered trademark owned by INR PLLC, and "INR" is a registered trademark owned by the Institute.

21. Despite the assertions in the Advertisement, however, the fact is that the INR Plaintiffs have had great success in treating their patients with etancercept after stroke.

22. Further, substantial scientific evidence suggests that etanercept has utility for a variety of neuroinflammatory conditions, including for medical treatment after stroke.

23. Etanercept works by blocking the effects of excess amounts of a protein called TNF.

24. TNF is an immune signaling molecule that is centrally involved in the initiation and amplification of the inflammatory response.

25. Blocking TNF reduces inflammation.

26. TNF-mediated inflammation is not limited to the joints.

27. TNF-mediated inflammation also occurs in the skin, the gastrointestinal tract, the eyes, and the brain, spinal cord, and spinal nerve roots.

28. TNF-mediated inflammation is a generalized phenomenon that may occur in every organ system.

29. Etanercept has been established to be useful for a wide variety of inflammatory disorders in multiple organ systems.

30. The evidence-based use of etanercept for selected neuroinflammatory indications is supported by current best evidence, including not only the peer-reviewed Scientific Publications of the INR Plaintiffs' physicians and their colleagues, but also the peer-reviewed publications of independent academic scientists.

31. In fact, as of May 2014, there is substantial scientific evidence in both the basic science and clinical medical literature that suggests the potential utility of etanercept for a variety of neurological disorders.

32. There are multiple scientific studies that have specifically tested etanercept in animals and humans.

33. Over the course of more than a decade, the INR Plaintiffs' physicians and their colleagues have published a series of peer-reviewed publications that have helped illuminate the role of immune mechanisms in the pathogenesis of a variety of neuroinflammatory disorders. In particular, these publications have provided new insight into the role of excess TNF in brain disorders and neuropathic pain.

34. The INR Plaintiffs' scientific findings have been published in multiple, peer-reviewed medical articles, including articles published in the journals Expert Review of Neurotherapeutics, CNS Drugs, BMC Neurology, Current Alzheimer Research, Clinical Therapeutics, Drug Discovery Today, and Current Medical Research and Opinion.

35. There have been citations to the INR Plaintiffs' publications by hundreds of academic scientists from around the world, including in *Nature Clinical Practice Neurology* and *F1000 Biology*.

36. TOBINICK is one of the physicians at, and is the founder of, the INR Plaintiffs. He graduated Phi Beta Kappa and Magna Cum Laude with honors in biology from Brandeis University in Waltham, Massachusetts, received his M.D. from the University of California San Diego School of Medicine in La Jolla, California, and completed post-graduate residencies at UCLA. He has been an invited ad hoc expert reviewer for the journals *Brain Research*, *CNS Drugs*, *Current Alzheimer Research*, *Experimental Neurology*, *Future Neurology*, *Journal of Neurochemistry*, *Journal of Neuroimmunology, Neuroscience, and Pharmaceutical Medicine,* and was a member of the Editorial Board of the *Journal of Neuroinflammation*.

37. TOBINICK has presented his scientific findings regarding the effects of etanercept for neurological disorders at multiple U.S. and international medical and scientific conferences, including the Days of Molecular Medicine Conference at the Karolinska Institute in Sweden in 2006; the 2008 Drug Repositioning Summit in Boston; the International Conference on Alzheimer's Disease in Chicago in 2008; the 7th Annual Alzheimer's Drug Discovery Conference in New York in 2006; the 2008 Best Practices in the Continuum of Care: Advances in Alzheimer's Disease Management conference at the University of Arkansas Medical Sciences in Little Rock, Arkansas; and, in 2009, the 3rd International Restauracion

Neurologica Conference in Havana, Cuba, the World Pharmaceutical Congress in Philadelphia and the 5th Modern Drug Discovery Conference in San Diego.

38. TOBINICK has performed collaborative research with scientists from multiple academic centers, including with scientists from Stanford University School of Medicine.

39. The Advertisement is extremely inflammatory and defamatory in nature as it contains multiple false and misleading statements of fact regarding Plaintiffs.

40. Advertisement's claims regarding the effectiveness of the INR Plaintiff's treatments are not supported by the evidence and are literally false.

41. Specifically, the Advertisement states that "*Tobinick...is claiming that a wide range of neurological conditions not known to be immune mediated are treated by a specific immunosuppressant*."

42. This implies not only that etanercept should not be used for neurological conditions such as stroke and Alzheimer's disease as the INR Plaintiffs do, but also that stroke and Alzheimer's disease are not known to be immune mediated.

43. Both propositions are false.

44. Indeed, the pathophysiology of both stroke and Alzheimer's disease are well known to be immune-mediated.

45. For example, Richard Ransohoff MD, Editor of the new journal Neurology: Neuroimmunology and Neuroinflammation, has stated:

> Neuroinflammation has been studied for decades almost exclusively as a cardinal feature of explicitly inflammatory processes such as MS, NMO, inflammatory neuropathy, acute infection, stroke, and trauma. With recent genetic findings it is now clear that inflammation plays a central (but not exclusive) part in Alzheimer disease, Parkinson disease, tauopathy, and other neurodegenerations. Inflammation is also strongly suspected as having a role in neurodevelopmental disease, including autism and schizophrenia.

Ransohoff, R., *Call for papers: Neurology: Neuroimmunology & Neuroinflammation, a new Neurology journal.* Neurology, 2014. **82**: p. 648-649.

46. Furthermore, in 2013 and 2014 alone there were no fewer than 10 separate publications reporting favorable effects of etanercept for neuroinflammatory indications.

47. The Advertisement further states that "*Tobinick has also started to publish case series – little more than retrospective case series reporting on his own patients.... all but worthless coming from a clinic like Tobinick's*."

48. This statement is false.

49. The publications of TOBINICK include multiple, invited review articles in prominent journals. And, the observational studies published by TOBINICK and his colleagues include patients treated by multiple physicians, not simply TOBINICK's own patients. Further, the scientific publications of TOBINICK and his colleagues have been cited by hundreds of researchers from academic centers around the world and in neuroscience journals such as Nature Clinical Practice Neurology. And, TOBINICK has been an invited *ad hoc* reviewer for the journals *Brain Research, CNS Drugs, Current Alzheimer Research, Experimental Neurology, Future Neurology, Journal of Neurochemistry, Journal of Neuroimmunology, Neuroscience, and Pharmaceutical Medicine,* and was a member of the Editorial Board of the *Journal of Neuroinflammation.*

50. The Advertisement further falsely implies that the INR Plaintiffs have committed a health fraud insomuch as the Advertisement was placed into a category identified as "Health Fraud."

51. Not only is this defamatory and outrageous as it implies that the Plaintiffs have intended to willfully deceive patients, but it also implies Plaintiff have violated Federal Law.

52. Specifically, 18 U.S.C. 1347 defines Health care fraud as a crime wherein one attempts to defraud Medicare or Medicaid.

53. For the reasons identified herein, any suggestion that Plaintiffs are committing a health fraud are false.

54. Likewise any assertion that Plaintiffs are violating Federal Law in this or any other manner are false as they do not bill Medicare or Medicaid.

55. In addition to the false claims relating to the substantive aspects of the Plaintiffs' practice, the Advertisement also contains numerous false, inflammatory and defamatory statements which are objectively disproved.

56. The Advertisement falsely asserts that the INR Plaintiffs are "*a one-man institute*".

57. The fact is, however, that the INR Plaintiffs employ multiple physicians.

58. The Advertisement falsely states that "*Tobinick has since moved his clinic to Florida, which is a very quack-friendly state.*"

59. However, the California offices of the Institute were open at the time the Advertisement was published, and remain in operation today.

60. Florida is not a "quack-friendly state."

61. Further, The Advertisement has deceived consumers.

62. The Plaintiffs were recently featured favorably on the Australian and New Zealand versions of 60 Minutes for their etanercept treatments for stroke patients.

63. As a result of the publicity, there was an initial high level of interest amongst consumers for the treatments.

64. However, that interest has been materially eroded as result of the Advertisement.

65. Plaintiffs have specifically identified a customer who has made an appointment for consultation, but cancelled that appointment after viewing the Advertisement.

66. At all times material hereto, YALE has directly made and continues to make the false and malicious statements itself by providing links to Novella's website (www.sciencebasedmedicine.org) on which the Advertisement resides, on Yale's own website.

67. YALE has also contributorily infringed on Plaintiffs' trade names by continuing to support and to promote NOVELLA's conduct in making the false and malicious statements contained within the Advertisement. Such support and promotion has enabled NOVELLA to infringe on Plaintiffs' trade names with YALE's full knowledge of the conduct. All the while, YALE has failed to take reasonable remedial measures.

68. Further, YALE has profited from the false and malicious statements contained within the Advertisement, as YALE provides services which directly compete with the services provided by Plaintiffs.

69. At all times material hereto SGU has directly made and continues to make the false and malicious statements itself by publishing the Advertisement on a website it owns, www.sciencebasedmedicine.org.

70. According to the website, www.sciencebasedmedicine.org was expressly "created to promote and discuss the views" of its editors.

71. SGU has also contributorily infringed on Plaintiffs' trade names by publishing the Advertisement on its website. Such publication has enabled NOVELLA to infringe on Plaintiffs' trade names with SGU's full knowledge of the conduct. All the while, SGU has failed to take reasonable remedial measures.

72. Further, SGU has profited from the false and malicious statements contained within the Advertisement, as viewers visit SGU's website to read the Advertisement.

73. As stated on the website www.sciencebasedmedicine.org, SBM is an organization that was created as, "the next step toward educating consumers" about the views found on the website.

74. As such, SBM has directly made and continues to make the false and malicious statements itself by "educating consumers" about the Advertisement.

75. SBM has also contributorily infringed on Plaintiffs' trade names by "educating consumers" about the Advertisement. Such action has enabled NOVELLA to infringe on Plaintiffs' trade names with SBM's full knowledge of the conduct. All the while, SBM has failed to take reasonable remedial measures.

76. On or about May 17, 2013, Plaintiffs notified NOVELLA, via written correspondence, that the Advertisement was false and defamatory. A true and correct copy of the correspondence is attached as Exhibit "2".

77. At that time, Plaintiffs also demanded that NOVELLA retract the Advertisement, and immediately cease and desist from disseminating the falsehoods any further.

78. As of this date, NOVELLA has ignored or refused to comply with Plaintiffs' demand to cease and desist using the false and deceptive Advertisement.

79. On or about May 5, 2014, Plaintiffs notified Yale, via written correspondence, that the Advertisement was false and defamatory. A true and correct copy of the correspondence is attached as Exhibit "3".

80. At that time, Plaintiffs also demanded that YALE cease and desist from promoting the falsehoods any further.

81. As of this date, YALE has ignored or refused to comply with Plaintiffs' demand to cease and desist from promoting the falsehoods.

82. On or about May 21, 2014, Plaintiffs notified SGU, via written correspondence to it and its website's editors, that the Advertisement was false and defamatory. A true and correct copy of the correspondence is attached as Exhibit "4".

83. At that time, Plaintiffs also demanded that SGU retract the Advertisement, and immediately cease and desist from publishing the Advertisement any further.

84. As of this date, SGU has ignored or refused to comply with Plaintiffs' demand to cease and desist using the false and deceptive Advertisement.

85. On May 23, 2014, shortly after Exhibits 3 and 4 were received by YALE and SGU, respectively, NOVELLA edited the Advertisement to correct some of the falsehoods contained therein.

86. The changes to the Advertisement were published on SGU's website for a few hours. However, by the end of the day, the edits had been removed and the Advertisement was returned to its original form.

87. The temporary changes to the Advertisement on May 23, 2014 show that Defendants knew of and were readily able to correct the falsehoods contained within the Advertisement, but maliciously and intentionally choose to libel Plaintiffs instead.

88. As a direct, natural and proximate result of Defendants' actions, Plaintiffs have suffered damages including, lost profits, lost customers, lost goodwill and damage to their business and professional reputation.

89. As a further direct, natural and proximate result of Defendants' actions, Plaintiffs have been compelled to retain the law firm of Tripp Scott, P.A. and have become obligated to pay all costs and attorney's fees associated with this action.

COUNT I - VIOLATION OF 15 U.S.C.A. §1125(a)

90. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 89 of this Complaint as if fully set forth herein.

91. Section 43 of the Lanham Act, 15 USC 1125(a) provides as follows:

> (a) Civil Action
> (1) Any person who, ...in connection with any goods or services, ...uses in commerce any word, term, name, ...or any combination thereof, or any false designation of origin, false or misleading description of fact, or false or misleading representation of fact, which --
>
> * * * *
>
> (B) in commercial advertising or promotion, misrepresents the nature, characteristics, qualities or geographic origin of his or her or another person's goods, services, or commercial activities,
>
> shall be liable in a civil action by any person who believes that he or she is or is likely to be damaged by such act.

92. The acts complained of above constitute a clear violation of 15 U.S.C.A. §1125(a) in that the Advertisement falsely describes Plaintiffs' services.

93. Pursuant to 15 U.S.C.A. 1116(a), Plaintiffs are entitled to an injunction to prevent the continued violation of 15 U.S.C.A. §1125(a).

94. Furthermore, as the conduct of the Defendants was and is willful and intentional, Plaintiffs are entitled to relief under 15 U.S.C.A. 1117(a) which provides that:

> When ... a violation under section 1125(a) ... of this title ... shall have been established in any civil action arising under this chapter, the plaintiff shall be entitled, subject to the provisions of 1111 and 1114 of this title [inapplicable], and

> subject to the provisions of equity, to recover (1) the defendant's profits, (2) any damages sustained by the plaintiff, and (3) the cost of the action. .... In assessing damages the court may enter judgment, according to the circumstances of the case, for any sum above the amount of actual damages, not exceeding three times such amount. If the court shall find that the amount of the recovery based on profits is either inadequate or excessive the court may in its discretion enter judgment for such sum as the court shall find to be just, according to the circumstances of the case. Such sum in either of the above circumstances shall constitute compensation and not a penalty. The court in exceptional circumstances may award reasonable attorneys fees to the prevailing party.

95. As a direct and proximate result of Defendants' conduct, Plaintiffs have retained the law firm of Tripp Scott, P.A. to represent them in this matter and they are obligated to pay the law firm all costs and its attorney's fees associated with this action. Pursuant to 15 U.S.C.A. 1117(a) Plaintiffs are entitled to recoup such costs and attorney's fees as Defendants' conduct was a willful and intentional violation of 15 U.S.C.A. 1125(a), and constituted a flagrant disregard for Plaintiffs' previous demands.

WHEREFORE, Plaintiffs demand:

I. That Defendants, their officers, agents, employees, servants, privies, successors and assigns, and all persons and organizations in active concert, participation and combination with them, be enjoined and restrained from directly or indirectly disseminating false statements concerning Plaintiffs or otherwise engaging in deceptive acts and practices in the conduct of its business;

II. That Defendants be required to account to Plaintiffs for any and all profits derived by Defendants, and to compensate Plaintiffs for all damages sustained by Plaintiffs by reason of the acts complained of herein, and that the Court:

(a) award Plaintiffs compensatory damages in an amount to be proven at trial for the injuries Plaintiffs sustained as a result of Defendants' acts complained of herein,

(b) award punitive and exemplary damages sufficient to deter Defendants from similar conduct in the future;

(c) require Defendants to pay Plaintiffs the costs of this action, including Plaintiffs' attorneys' fees; and

(d) require Defendants to pay Plaintiffs' prejudgment and post-judgment interest at the applicable rates on all amounts awarded;

III. That Defendants be required to disseminate corrective advertising, at Defendants' expense and upon Plaintiffs' approval, that informs the trade and the purchasing public at large of Defendants' unlawful conduct as complained of herein and of the judgment requiring Defendants to cease such unlawful conduct, and/or require Defendants to pay Plaintiffs costs in producing and disseminating such corrective advertising;

IV. That Defendants, within 30 days after service upon them of the judgment, file with the Court and serve upon Plaintiffs a written report, under oath, setting forth in detail the manner and form in which Defendants have complied with the injunction provisions of said judgment; and,

V. That Plaintiffs have such other and further relief as the court may deem just and proper.

COUNT II - UNFAIR COMPETITION

96. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 89 of this Complaint as if fully set forth herein.

97. This cause of action arises under the common law of unfair competition. Jurisdiction of this court is by virtue of 28 U.S.C. §1338(b) and by the principles of supplemental jurisdiction, 28 U.S.C. §1367. Venue lies under 28 U.S.C. §1391.

98. Defendants' wrongful acts of unfair competition have proximately caused and will continue to cause Plaintiffs substantial injury to their goodwill and reputation.

99. Defendants' wrongful acts have caused and will continue to cause Plaintiffs irreparable harm.

100. Plaintiffs have no adequate remedy at law for Defendants continued acts of unfair competition.

101. Plaintiffs are entitled to a judgment restraining Defendants from engaging in further unfair competition and infringement and for all resulting damages.

WHEREFORE, Plaintiffs demand:

I. That Defendants, their officers, agents, employees, servants, privies, successors and assigns, and all persons and organizations in active concert, participation and combination with them, be enjoined and restrained from directly or indirectly disseminating false statements concerning Plaintiffs or otherwise engaging in deceptive acts and practices in the conduct of its business;

II. That Defendants be required to account to Plaintiffs for any and all profits derived by Defendants, and to compensate Plaintiffs for all damages sustained by Plaintiffs by reason of the acts complained of herein, and that the Court:

(a) award Plaintiffs compensatory damages in an amount to be proven at trial for the injuries Plaintiffs sustained as a result of Defendants' acts complained of herein, that said damages be trebled pursuant to 15 U.S.C. §1117;

(b) award punitive and exemplary damages sufficient to deter Defendants from similar conduct in the future;

(c) require Defendants to pay Plaintiffs the costs of this action, including Plaintiffs' attorneys' fees pursuant to 15 U.S.C. §1117; and

(d) require Defendants to pay Plaintiffs prejudgment and post-judgment interest at the applicable rates on all amounts awarded;

III. That Defendants be required to disseminate corrective advertising, at Defendants' expense and upon Plaintiffs' approval, that informs the trade and the purchasing public at large of Defendants' unlawful conduct as complained of herein and of the judgment requiring Defendants to cease such unlawful conduct, and/or require Defendants to pay Plaintiffs' costs in producing and disseminating such corrective advertising;

IV. That Defendants, within 30 days after service upon them of the judgment, file with the Court and serve upon Plaintiffs a written report, under oath, setting forth in detail the manner and form in which Defendants have complied with the injunction provisions of said judgment; and,

V. That Plaintiffs have such other and further relief as the court may deem just and proper.

COUNT III - TRADE LIBEL

102. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 89 of this Complaint as if fully set forth herein.

103. Defendants maliciously publicized false, deceptive or misleading statements affecting the reputation and business interests of Plaintiffs.

104. As a direct result of Defendants' actions, Plaintiffs have suffered damages including the loss of profits, customers, goodwill, and damage to its reputation.

105. But for Defendants' false, deceptive or misleading statements, Plaintiffs would not have suffered damage to their reputation and had clients believing that Plaintiffs' services are a sham.

WHEREFORE, Plaintiffs demand judgment against Defendants for damages, both compensatory and punitive, together with prejudgment interest, costs and attorney's fees pursuant to Section 57.105, Florida Statutes, and for such other additional relief as this Court deems just, necessary, reasonable and proper.

COUNT IV – LIBEL PER SE

106. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 89 of this Complaint as if fully set forth herein.

107. Defendants maliciously publicized false, deceptive or misleading statements affecting the reputation of TOBINICK.

108. As a direct result of Defendants' actions, TOBINICK has suffered damages including the loss of profits, customers, goodwill, and damage to his reputation.

109. But for Defendants' false, deceptive or misleading statements, TOBINICK would not have suffered damage to his reputation.

WHEREFORE, TOBINICK demands judgment against Defendants for damages, both compensatory and punitive, together with prejudgment interest, costs and attorney's fees

pursuant to Section 57.105, Florida Statutes, and for such other additional relief as this Court deems just, necessary, reasonable and proper.

COUNT V - TORTIOUS INTERFERENCE WITH BUSINESS RELATIONSHIPS

110. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 89 of this Complaint as if fully set forth herein.

111. Plaintiffs had advantageous business relationships with its customers and clients.

112. Defendants knew of those relationships.

113. Defendants have intentionally and without justification tortiously interfered with Plaintiffs' business relationships by making false statements about Plaintiffs.

114. As a result of Defendants' tortious interference, Plaintiffs have incurred damages.

WHEREFORE, Plaintiffs demand judgment against Defendants for damages, both compensatory and punitive, together with prejudgment interest, costs and attorney's fees pursuant to Section 57.105, Florida Statutes, and for such other additional relief as this Court deems just, necessary, reasonable and proper.

/s/Alexander D. Brown ,

Respectfully submitted this 9th day of June 2014.

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Enbrel for Stroke and Alzheimer's

Posted by Steven Novella on May 8, 2013 (30 Comments)

A recent article in the LA times tells of a husband's quest to find a treatment for his wife's Alzheimer's disease. This is a narrative that journalists know and love – the brave patient or loved-one who won't accept the nihilism of the medical establishment, who finds a maverick doctor willing to buck the system.

The article itself at least was not gushing, it tended toward a neutral tone, but such articles do tend to instill in the public a very counterproductive attitude toward science and medicine. I would have preferred an exposé of a dubious clinic exploiting desperate patients by peddling false hope. That is a narrative in which journalists rarely engage.

The story revolves around Dr. Edward Tobinick and his practice of perispinal etanercept (Enbrel) for a long and apparently growing list of conditions. Enbrel is an FDA-approved drug for the treatment of severe rheumatoid arthritis. It works by inhibiting tumor necrosis factor (TNF), which is a group of cytokines that are part of the immune system and cause cell death. Enbrel, therefore, can be a powerful anti-inflammatory drug. Tobinick is using Enbrel for many off-label indications, one of which is Alzheimer's disease (the focus of the LA Times story).

The Dubious Health Clinic

Before I go into the details of Tobinick's claims, let's review the typical features of what we commonly call the "quack clinic" or the dubious health clinic. I wrote about this in 2009, and listed the following features:

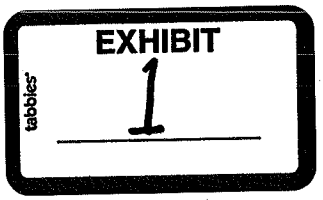
- The clinic often has an impressive name, such as "The Institute Of," but lacks any formal affiliation with an established institution, like a university or hospital, and was founded and may even continue to be operated by one person.

- The clinic claims to treat or cure one or more diseases that is currently believed to be incurable. Their claims sound too good to be true.

- There is only one clinic in the world that can perform their special procedure or that uses their proprietary treatment. Sometimes the treatment offered is new and experimental.

- The clinic claims to cure a variety of diseases, all with different causes and pathophysiology, with a single treatment – the "one cure for all diseases" approach.

- The clinic is often located in a country with little or no regulation.



- The clinic claims that it is the victim of repression. Typically they will say that either Big Pharma, the medical establishment, the insurance industry – or some other convenient villain – is trying to suppress their revolutionary treatment. Alternatively, the "medical establishment" is simply closed-minded to their paradigm-shifting ideas.

- Testimonials are used to promote the treatments offered by the clinic, but they have not published appropriate research in legitimate peer-reviewed journals.

- When challenged by professional organizations, the clinic defends itself by appealing to politicians, using the testimonies of previous patients who believe they have been helped by the clinic and the accusation of a conspiracy of those trying to protect their monopoly.

The Institute of Neurological Recovery

Now let's take a look at Tobinick's clinic. It has an impressive name – a one-man institute. The website proclaims:

> The Institute of Neurological Recovery (INR®) is pleased to provide this introduction to its pioneering medical concepts, research, and treatment programs. INR designates a group of separate medical practices that utilize innovative, patented, off-label medical treatments developed by Edward Tobinick M.D. These treatment methods are designed to target a number of neuroinflammatory conditions with unmet medical need.

Many of the features of a dubious clinic are right there – the impressive name, claim to treat many conditions with one treatment, emphasis on how innovative the treatments are. The website also claims that his treatments are patented.

This is an interesting side issue, worthy of it's own post. There has been a surge in the US in recent years in medical procedure patents. However, the first (and I think only) infringement lawsuit lost its case. Medical procedure patents are generally opposed by medical organizations as counterproductive profiteering and are banned in 80 countries. They are still legal in the US but there has been a number of legislative efforts recently to limit or ban them.

The patented procedure (even if not enforced) seems like just another way to market the uniqueness of the treatments offered by the dubious clinic.

The list of conditions for which Tobinick claims or even has patented use of Enbrel include Alzheimer's, stroke, traumatic brain injury, Parkinson's disease, carpal tunnel syndrome, brain tumor, spinal cord injury, and back pain. That quite impressive for a doctor who isn't even a neurologist. Tobinick is an internist who, prior to curing a long list of neurological diseases, specialized in laser hair removal.

The LA Times reports:

> But his claims about the back treatment led to an investigation by the California Medical Board, which placed him on probation for unprofessional conduct and made him take classes in prescribing practices and ethics.

Tobinick has since moved his clinic to Florida, which is a very quack-friendly state. Its "health care freedom" law effectively shields dubious practitioners from pesky medical boards.

Plausibility and Evidence

When considering just the notion that Enbrel, a TNF inhibitor, might have a broad range of applications, this is entirely plausible. It is common for immunosuppressive drugs to gain an FDA approved indication for one specific condition, such as transplant rejection or rheumatoid arthritis, and then to be used off-label for many other autoimmune conditions.

This is very tricky, however, as the immune system is complex. There are different components to the immune system, and different aspects of immunity are involved in different auto-immune conditions. Therefore there is no one immunosuppressant drug or treatment for all auto-immune conditions.

When a new immune suppressing drug comes on the market it is common for it to be tried in a variety of conditions – but practice then follows evidence. Initially we might see some case reports, followed by a case series. If the drug shows promise, then a double-blind placebo-controlled trial would ultimately determine its effectiveness.

This is definitely a gray area of off-label use. How much evidence is necessary to justify an off-label use of a drug – and how far off label? Sometimes the popularity of a new off-label use of a drug gets ahead of the evidence. In most cases, however, eventually the research is done and practice conforms to the evidence.

The claims of Tobinick, however, are not in the gray area – they are leaps and bounds ahead of the evidence. Further, the conditions he claims to treat are not clearly immune-mediated diseases. It's one thing to use an immune-suppressing drug to treat a disease that is known to be caused by immune activity, and probably the kind of immune activity suppressed by the drug.

Tobinick, however, is claiming that a wide range of neurological conditions not known to be immune mediated are treated by a specific immunosuppressant.

On his website he cites many studies, but none of them establish the effectiveness of Enbrel for any of the conditions he is treating. Most of them are simply identifying that TNF is increased in the condition. This is very weak evidence, however, as markers of

immune activity are frequently increased in diseases that are not caused by immune activity. The immune system is very reactive – it reacts to disease with inflammation (often what we refer to as the cleanup crew). The inflammation is not causing the disease, it is simply the body's reaction to it.

Tobinick has also started to publish case series – little more than retrospective case series reporting on his own patients. This is weak evidence even when coming from an established researcher within their own area of expertise. It is all but worthless coming from clinic like Tobinick's.

This is where his lack of expertise is especially relevant. Such arguments are often portrayed as elitist, as if a mere internist cannot have a valuable insight into how to treat neurological disease. But medicine and research are complex and there are many pitfalls. Unless you have expertise dealing with strokes or dementia, including how to properly research these conditions, you are likely to fall for these pitfalls.

For example, in his recent case series he writes:

> Significant improvement was noted irrespective of the length of time before treatment was initiated; there was evidence of a strong treatment effect even in the subgroup of patients treated more than 10 years after stroke and TBI.

This, if anything, is evidence that the observed treatment effect is mere placebo. It is very implausible that stroke or TBI deficits will be equally responsive to an anti-inflammatory treatment (or any treatment) regardless of time since the stroke or trauma.

Stroke researchers are also very familiar with what is known as the "cheerleader effect." Take any patient with chronic deficits, give them any intervention and then encourage them to function better, and they will function better. This can result simply from trying harder, or even just the incidental physical therapy benefit of engaging in a treatment and being evaluated.

Unless all these factors are controlled for with proper blinding, no conclusions about the treatment effect are possible. Tobinick is providing the kind of evidence that is guaranteed to be positive, but not the kind of evidence that would determine if his treatments are effective or not.

Conclusion

If you strip away the gratuitous narrative in the LA Times story and just look at the facts presented, a very different narrative emerges. Ken Chiate brought his wife to Tobinick's clinic for 165 injections of Enbrel over four years, at a cost of $800 each (that's $132,000). During that time there were questionable subjective effects from the

treatment, typical of placebo-only effects. Meanwhile his wife continued to relentlessly progress, as is typical of the disease, until she finally died in 2011.

According to the article, the treatments gave Chiate a sense of purpose and of hope – a false hope, it turned out. He still clings to the idea that Enbrel may be an effective treatment for Alzheimer's disease – even though Tobinick himself has apparently moved on to treating stroke.

In my opinion, the story documents exploitation of a well-meaning and desperate husband at the hands of a dubious practitioner, practicing at the fringes of medical ethics and evidence, making bold claims without adequate justification. The story also documents the utter failure of the regulatory system to prevent (or even properly react to) such exploitation. Florida in particular appears to be a haven for such activity.

Posted in: Health Fraud, Medical Ethics, Politics and Regulation

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May 17, 2013

RE: "Enbrel for Stroke and Alzheimer's", retrieved from

http://www.sciencebasedmedicine.org/index.php/enbrel-for-stroke-and-alzheimers/ on

Friday, May 17, 2013

Steven P. Novella, M.D.

64 Cobblestone Dr

Hamden, CT 06518

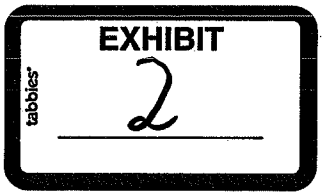
(203) 281-6277

via E-mail on May 17, 2013 to SNovella@theskepticsguide.org

via Certified Mail Return Receipt on May 17, 2013

Dear Dr. Novella,

I write to you directly as a result of the article, "Enbrel for Stroke and Alzheimer's", you wrote and posted on your website, sciencebasedmedicine.org, on May 8, 2013, an article that is still visible to the public. I note that your website seems to be widely read, as one of the commentors regarding the article hailed from Australia (the commentor had been previously aware of the work of my colleagues and I with perispinal etanercept). As you are aware, we have never met, nor corresponded, nor spoken, and I really was not aware



of your work until your post. I note that you are "the president and co-founder of the New England Skeptical Society, the host and producer of the popular weekly science podcast, The Skeptics' Guide to the Universe, and the author of the NeuroLogicaBlog, a daily blog that covers news and issues in neuroscience, but also general science, scientific skepticism, philosophy of science, critical thinking, and the intersection of science with the media and society." I also note that you are a board-certified Neurologist, a member of the American Academy of Neurology, and an academic clinical neurologist at the Yale University School of Medicine.

In view of the fact that we have never met or corresponded, and the content of your article, I think it may be helpful if I provide some additional scientific background regarding perispinal etanercept. Much of this information, and most of these scientific references are available on our websites, such as nrimed.com, but I include some of this information to help provide this background information for you in a convenient place.

Scientific Background

These articles provide a cogent discussion of the scientific rationale or data or discussion relevant to the use of perispinal etanercept for the treatment of selected neuroinflammatory disorders[1-69].

Pertinent scientific evidence has been accumulating in the scientific, peer-reviewed, published medical literature for more than a decade:

Etanercept, a recombinant tumor necrosis factor receptor (p75)-Fc fusion protein competitively inhibits tumor necrosis factor-alpha (TNF). Etanercept has been successfully used in patients with rheumatoid arthritis, where it reduces pain and inflammation. Because locally produced proinflammatory cytokines play a role in pain after nerve injury, we investigated whether etanercept can reduce pain and hyperalgesia in an animal model of painful neuropathy, the chronic constriction injury of the sciatic nerve. C57BL/6 mice received etanercept or sham treatment by local near-nerve injection to the injured nerve or by systemic application. Treatment with etanercept reduced thermal hyperalgesia and mechanical allodynia significantly in both modes of application. The effect of etanercept was present in animals that were treated from the time of surgery and in those that were treated from day 6, when hyperalgesia was already present. These results suggest the potential of etanercept as a treatment option for patients with neuropathic pain. *From* Sommer C, Schafers M, Marziniak M, Toyka KV: **Etanercept reduces hyperalgesia in experimental painful neuropathy.** *J Peripher Nerv Syst* 2001, **6**:67-72.

STUDY DESIGN: The possibility to prevent nucleus pulposus-induced functional and structural nerve root injury by selective tumor necrosis factor-alpha inhibition was assessed in an experimental model in the pig spine. OBJECTIVE: The objective of the study was to evaluate the role of tumor necrosis factor-alpha in the mediation of nucleus pulposus-induced nerve injury by using selective inhibition. SUMMARY OF BACKGROUND DATA: The cytokine tumor necrosis factor-alpha has been suggested to play a key role in the nerve root injury induced by local application of nucleus pulposus. However, previous studies have not been able to distinguish the effects between tumor necrosis factor-alpha and other disc-related cytokines because of the use of nonspecific cytokine inhibition. METHODS: Autologous nucleus pulposus was harvested from a lumbar disc and applied to the porcine sacrococcygeal cauda equina. The pigs were simultaneously treated with two selective tumor necrosis factor-alpha inhibitors (etanercept n = 8 and infliximab n = 5), a heparin analogue (enoxaparin n = 5) or saline for control (n = 5). After 7 days the nerve conduction velocity over the application zone was determined and samples of the exposed nerve roots were collected for light microscopic evaluation. RESULTS: The two tumor necrosis factor-alpha inhibitors prevented the reduction of nerve conduction velocity and also seemed to limit the nerve fiber injury, the intracapillary thrombus formation, and the intraneural edema formation. However, treatment with enoxaparin did not seem to be different from control regarding reduction of nerve conduction velocity or histologic changes. CONCLUSIONS: The data clearly indicate that tumor necrosis factor-alpha is involved in the basic pathophysiologic events leading to nerve root structural and functional changes after local application of nucleus pulposus. The study therefore provides a basic

scientific platform with potential clinical implications regarding the use of anti-tumor necrosis factor-alpha medication as treatment in patients with disc herniation and sciatica. *From* Olmarker K, Rydevik B: **Selective inhibition of tumor necrosis factor-alpha prevents nucleus pulposus-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity: possible implications for future pharmacologic treatment strategies of sciatica.** *Spine (Phila Pa 1976)* 2001, **26**:863-869. [68]

OBJECTIVES: To analyse the cerebrospinal fluid (CSF) values of the proinflammatory cytokines, interleukin 1beta (IL1beta), tumour necrosis factor alpha (TNFalpha), GM-CSF, of the anti-inflammatory cytokine TGFbeta, of tau protein, a marker for neurodegeneration, and of beta amyloid (Abeta), a protein involved in the formation of senile plaques, in prospectively followed up patients with mild cognitive impairment (MCI). METHODS: Analyses of CSF levels of TNFalpha, IL1beta, GM-CSF, TGFbeta, betaa, and tau protein were performed using ELISA in 56 patients with MCI who were followed up prospectively and in 25 age matched, healthy controls. RESULTS: Patients with MCI displayed significantly higher levels of TNFalpha and tau protein and significantly lower levels of TGFbeta and Abeta compared with the healthy controls. After nine months of follow up, 25 patients still displayed MCI while the remaining 31 patients had progressed to Alzheimer's disease (AD). Only MCI patients who progressed to AD at follow up, showed significantly higher CSF levels of TNFalpha than controls. In addition, reduced CSF-Abeta42 levels were only found in MCI patients that progressed to AD, further supporting the notion that disturbed metabolism of Abeta is an early finding in AD. CONCLUSIONS: These results demonstrate increased production of the proinflammatory cytokine, TNFalpha and decreased production of the anti-inflammatory cytokine TGFbeta in patients with MCI at risk to develop AD, suggesting a propensity towards inflammation in this patient group and indicating that CNS inflammation is a early hallmark in the pathogenesis of AD. *From* Tarkowski E, Andreasen N, Tarkowski A, Blennow K: **Intrathecal inflammation precedes development of Alzheimer's disease.** *J Neurol Neurosurg Psychiatry* 2003, **74**:1200-1205.[32]

OBJECTIVE: To examine the potential of etanercept, a biological inhibitor of tumour necrosis factor-alpha (TNF), delivered by perispinal administration, for the treatment of pain associated with intervertebral disc disease. METHODS: Charts from 20 selected patients treated at our private clinic by perispinal delivery of etanercept 25 mg for severe, chronic, treatment-resistant discogenic pain were reviewed. Therapeutic benefit was assessed clinically and was documented by changes in a validated pain instrument, the Oswestry Disability Index. The patients

were treated off-label with etanercept as part of our usual practice of medicine. Five detailed case reports are presented, including three additional patients. RESULTS: Rapid, substantial and sustained clinical pain reduction was documented in this selected group of patients. The cohort of 20 patients had a mean age of 56.5 and mean duration of pain of 116 months. Nine of the patients had undergone previous spinal surgery; 17 had received an epidural steroid injection or injections (mean 3.2). This group of patients received a mean of 1.8 doses (range 1-5, median 1.0) of etanercept during the observation period. The mean length of follow-up was 230 days. Clinical improvement was confirmed by a decrease in the calculated Oswestry Disability Index from a mean of 54.85 +/- 12.5 at baseline, improving to 17.2 +/- 15.3 ($p < 0.003$) at 24 days and ending at 9.8 +/- 13 ($p < 0.003$) at 230 days. CONCLUSIONS: TNF inhibition by etanercept delivered by perispinal administration may offer clinical benefit for patients with chronic, treatment-resistant discogenic pain. Further study of this new treatment modality is warranted. *From* Tobinick EL, Britschgi-Davoodifar S: **Perispinal TNF-alpha inhibition for discogenic pain.** *Swiss Med Wkly* 2003, **133**:170-177. [35]

Sommer C, Schäfers M: **Mechanisms of neuropathic pain: the role of cytokines.** *Drug Discovery Today: Disease Mechanisms* 2004, **1**:441-448.

Inflammatory immune mechanisms play a central role in the causation of Alzheimer's disease (AD). Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, the "master regulator" of the immune response, is the key initiator of immune-mediated inflammation in multiple organ systems, including the brain. Scientific evidence identifying TNF-alpha involvement in the pathogenesis of AD began accumulating a decade ago in experimental models. In vitro, with use of a human monocytic cell line, beta amyloid was found to stimulate secretion of TNF-alpha. TNF-alpha plus gamma-interferon was found to induce beta-amyloid production. Beta amyloid was shown to stimulate microglial inflammatory pathways, resulting in neurotoxicity mediated by TNF-alpha generated by reactive microglia and monocytes. Clinical evidence followed, with a central place for TNF-alpha in AD pathogenesis suggested by demonstration of 25-fold elevated levels of TNF-alpha in the cerebrospinal fluid of patients with AD, and the finding that increased cerebrospinal fluid TNF-alpha levels correlated with clinical deterioration. In 2005, the evidence supporting TNF-alpha involvement in AD accelerated, including identification of a greater risk for AD in an Australian population associated with a polymorphism in the promoter region of the TNF gene.

Increasing amounts of laboratory evidence implicate TNF-alpha in inflammatory molecular mechanisms producing neurotoxicity, neuronal death, or neuronal dysfunction involving both TNF-glutamate or TNF-amyloid interactions. In a brain slice culture model, TNF-alpha was found to potentiate glutamate neurotoxicity, with TNF-alpha and glutamate acting synergistically to induce neuronal cell death. Stimulation of microglial metabotropic glutamate-2 receptors on rat primary microglia was found to induce TNF-alpha release, and contribute to microglial neurotoxicity. In cultured hypothalamic cells, glutamate was found to induce the expression and release of TNF-alpha, which was postulated to be potentially related to physiologic regulation of sleep and wakefulness. TNF-alpha both directly affects glutamatergic synaptic transmission, increasing AMPA receptors on synapses, and modulates synaptic plasticity. Of particular relevance to memory impairment in AD, beta-amyloid inhibition of long-term potentiation appears to be mediated by TNF-alpha.

Substantial laboratory evidence implicates beta-amyloid-induced neuroinflammation with neurotoxicity, and this appears to be an early event in neurodegeneration. Experimental models using beta-amyloid-stimulated murine microglia suggest that beta-amyloid-induced neuronal death may be mediated by synergy between TNF-alpha and glutamate-induced neurotoxicity. In addition to TNF-alpha, beta amyloid upregulates other inflammatory mediators in the brain, including interleukin (IL)-1 beta, IL-6, nitric oxide, and inducible nitric oxide synthase. Increasing evidence suggests that microscopic inflammation resulting from the release of inflammatory cytokines, including TNF-alpha, by amyloid-beta-activated microglia plays a central role in the neurotoxicity that occurs in AD. This hypothesis suggests that specific anti-inflammatory agents that downregulate this inflammatory process could potentially be of therapeutic benefit in AD.

Therapeutic agents that selectively inhibit the biologic activity of TNF-alpha have recently become available for human use. One of these is etanercept, a dimeric fusion protein that is produced with recombinant DNA technology and composed of 934 amino acids with a total molecular weight of 150,000 d. It consists of a fragment of the human 75-kd (p75) TNF receptor linked to the Fc portion of human immunoglobulin (Ig)G1. Etanercept binds specifically to TNF and blocks its interaction with cell-surface TNF receptors. By avidly binding excess TNF, etanercept functions as an extraordinarily potent TNF antagonist. Because of the known role of inflammation in AD pathogenesis, etanercept has been suggested as a possible therapeutic agent for AD. It is approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis, with pilot

studies and basic science investigations suggesting possible utility for a variety of neurologic disorders.

Pilot studies ("proof-of-concept" studies) in small numbers of patients are a common starting point for new therapeutic approaches. While not providing the same degree of robust scientific evidence offered by randomized, double-blind, placebo-controlled trials, pilot studies are nevertheless useful for helping to define the feasibility of a new scientific approach, and may yield valid statistical data if carefully designed, even with a minimum number of subjects. Indeed, the era of biologic anti-TNF-alpha therapy for the treatment of rheumatoid arthritis was ushered in by an open-label, uncontrolled, nonrandomized pilot study published in The Lancet in 1994 involving only 7 patients.

To investigate the feasibility of using etanercept for the treatment of AD, we initiated a 6-month, open-label pilot study.CONTEXT: Current pharmacologic treatments for Alzheimer's disease (AD) do not prevent long-term clinical deterioration. Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, has been implicated in the pathogenesis of AD. CONTEXT: Current pharmacologic treatments for Alzheimer's disease (AD) do not prevent long-term clinical deterioration. Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, has been implicated in the pathogenesis of AD....

Abstract
OBJECTIVE: To investigate the use of a biologic TNF-alpha inhibitor, etanercept was given by perispinal extrathecal administration for the treatment of AD. METHODS: This was a prospective, single-center, open-label, pilot (proof-of-concept) study, in which 15 patients with mild-to-severe AD were treated for 6 months. We administered etanercept, 25-50 mg, once weekly by perispinal administration. Main outcome measures included the Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), and the Severe Impairment Battery (SIB). RESULTS: The average age of our patient population was 76.7. The mean baseline MMSE was 18.2 (n = 15); the mean baseline ADAS-Cog was 20.8 (n = 11); and the mean baseline SIB was 62.5 (n = 5). There was significant improvement with treatment, as measured by all of the primary efficacy variables, through 6 months: MMSE increased by 2.13 -/+ 2.23, ADAS-Cog improved (decreased) by 5.48 -/+ 5.08, and SIB increased by 16.6 -/+ 14.52. CONCLUSION: An increasing amount of basic science and clinical evidence implicates inflammatory processes and resulting glial activation in the pathogenesis of AD. This small, open-label pilot study suggests that inhibition of the inflammatory cytokine TNF-alpha may hold promise as a potential approach to AD treatment. Further study in randomized, placebo-controlled clinical trials is merited. *From* Tobinick E, Gross H,

Weinberger A, Cohen H: **TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study.** *MedGenMed* 2006, **8:25.** (citations omitted). [43]

OBJECTIVE: Documentation of the clinical results obtained utilizing perispinal etanercept off-label for treatment-refractory back and neck pain in a clinical practice setting. RESEARCH DESIGN AND METHODS: The medical charts of all patients who were treated with etanercept for back or neck pain at a single private medical clinic in 2003 were reviewed retrospectively. Patients were treated if they had disc-related pain which was chronic, treatment-refractory, present every day for at least 8 h, and of moderate or severe intensity. Patients with active infection, demyelinating disease, uncontrolled diabetes, lymphoma or immunosuppression were excluded from treatment with etanercept. Etanercept 25 mg was administered by subcutaneous injection directly overlying the spine. Visual Analogue Scales (VAS, 0-10 cm) for intensity of pain, sensory disturbance, and weakness prior to and 20 min, 1 day, 1 week, 2 weeks, and 1 month after treatment were completed. Inclusion criteria for analysis required baseline and treatment VAS data. MAIN OUTCOME MEASURES: Before and after treatment VAS comparisons for intensity of pain, sensory disturbance, and weakness. RESULTS: 143 charts out of 204 met the inclusion VAS criteria. The 143 patients had a mean age of 55.8 +/- 14, duration of pain of 9.8 +/- 11 years, and an initial Oswestry Disability Index of 42.8 +/- 18, with 83% having back pain, 61% sciatica, and 33% neck pain. 30% had previous spinal surgery, and 69% had previously received epidural steroid injections (mean 3.0 +/- 3). The patients received a mean of 2.3 +/- 0.7 doses of perispinal etanercept separated by a mean interval of 13.6 +/- 16.3 days. The mean VAS intensity of pain, sensory disturbance, and weakness were significantly reduced after perispinal etanercept at 20 min, 1 day, 1 week, 2 weeks, and 1 month with a $p < 0.0001$ at each time interval for the first dose in this patient population. CONCLUSIONS: Perispinal etanercept is a new treatment modality which can lead to significant clinical improvement in selected patients with chronic, treatment-refractory disc-related pain. Generalizability of the present study results is limited by the open-label, uncontrolled methodology employed. Based on this and other accumulating recent studies, etanercept may be useful for both acute and chronic disc-related pain. Further study of this new treatment modality utilizing double-blind placebo controlled methodology is indicated. *From* Tobinick E, Davoodifar S: **Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: a study of clinical observations in 143 patients.** *Curr Med Res Opin* 2004, **20:**1075-1085. [38]

After an ischemic stroke, neurons in the core are rapidly committed to die, whereas neuron death in the slowly developing penumbra is more amenable to therapeutic intervention. Microglia activation contributes to delayed inflammation, but because neurotoxic mechanisms in the penumbra are not well understood, we developed an in vitro model of microglia activation and propagated neuron killing. To recapitulate inflammatory triggers in the core, microglia were exposed to oxygen glucose-deprived neurons and astrocytes. To model the developing penumbra, the microglia were washed and allowed to interact with healthy naive neurons and astrocytes. We found that oxygen-glucose deprivation (OGD)-stressed neurons released glutamate, which activated microglia through their group II metabotropic glutamate receptors (mGluRs). Microglia activation involved nuclear factor kappaB (NF-kappaB), a transcription factor that promotes their proinflammatory functions. The activated microglia became neurotoxic, killing naive neurons through an apoptotic mechanism that was mediated by tumor necrosis factor-alpha (TNF-alpha), and involved activation of both caspase-8 and caspase-3. In contrast to some earlier models (e.g., microglia activation by lipopolysaccharide), neurotoxicity was not decreased by an inducible nitric oxide synthase (iNOS) inhibitor (S-methylisothiourea) or a peroxynitrite scavenger [5,10,15,20-tetrakis(N-methyl-4'-pyridyl)porphinato iron (III) chloride], and did not require p38 mitogen-activated protein kinase (MAPK) activation. The same microglia neurotoxic behavior was evoked without exposure to OGD-stressed neurons, by directly activating microglial group II mGluRs with (2S,2'R,3'R)-2-(2'3'-dicarboxycyclopropyl) glycine or glutamate, which stimulated production of TNF-alpha (not nitric oxide) and mediated TNF-alpha-dependent neurotoxicity through activation of NF-kappaB (not p38 MAPK). Together, these results support potential therapeutic strategies that target microglial group II mGluRs, TNFalpha overproduction, and NF-kappaB activation to reduce neuron death in the ischemic penumbra. *From* Kaushal V, Schlichter LC: **Mechanisms of microglia-mediated neurotoxicity in a new model of the stroke penumbra.** *J Neurosci* 2008, **28:**2221-2230. [51]

BACKGROUND: Recent clinical studies point to rapid and sustained clinical, cognitive, and behavioral improvement in both Alzheimer's disease and primary progressive aphasia following weekly perispinal administration of etanercept, a TNF-alpha inhibitor that acts by blocking the binding of this cytokine to its receptors. This outcome is concordant with recent basic science studies suggesting that TNF-alpha functions in vivo as a gliotransmitter that regulates synaptic function in the brain. We hypothesized that perispinal etanercept had the potential to improve verbal function in Alzheimer's disease, so we included several standarized measures of verbal ability to evaluate language skills in a clinical trial of

perispinal etanercept for Alzheimer's disease. METHODS: This was a prospective, single-center, open-label, pilot study, in which 12 patients with mild-to-severe Alzheimer's disease were administered etanercept, 25-50 mg, weekly by perispinal administration for six months. Two additional case studies are presented. RESULTS: Two-tailed, paired t-tests were conducted comparing baseline performance to 6-month performance on all neuropsychological measures. Test batteries included the California Verbal Learning Test-Second Edition, Adult Version; Logical Memory I and II(WMS-LM-II) from the Wechsler Memory Scale-Abbreviated; the Comprehensive Trail Making Test (TMT); Boston Naming Test; and letter(FAS) and category verbal fluency. All measures revealed a significant effect except for the Boston Naming Test and the TMT-4, with WMS-LM-II being marginally significant at $p = .05$. The FAS test for letter fluency was most highly significant with a $p < 0.0007$. In addition, rapid improvement in verbal fluency and aphasia in two patients with dementia, beginning minutes after perispinal etanercept administration, is documented. CONCLUSION: In combination with the previously reported results of perispinal etanercept in Alzheimer's disease and primary progressive aphasia, these results further argue that larger scale studies of this therapeutic intervention, including Phase 3 trials, are warranted in dementias. In addition, these results may provide insight into the basic pathophysiologic mechanisms underlying Alzheimer's disease and related forms of dementia, and suggest the existence of novel, rapidly reversible, TNF-mediated pathophysiologic mechanisms in Alzheimer's disease which are worthy of further investigation. *From* Tobinick EL, Gross H: **Rapid improvement in verbal fluency and aphasia following perispinal etanercept in Alzheimer's disease.** *BMC Neurol* 2008, **8:27. [70]**

Tumour necrosis factor (TNF), a key regulator of varied physiological mechanisms in multiple organ systems, is an immune signalling molecule produced by glia, neurons, macrophages and other immune cells. In the brain, among other functions, TNF serves as a gliotransmitter, secreted by glial cells that envelope and surround synapses, which regulates synaptic communication between neurons. The role of TNF as a gliotransmitter may help explain the profound synaptic effects of TNF that have been demonstrated in the hippocampus, in the spinal cord and in a variety of experimental models. Excess TNF is present in the CSF of individuals with Alzheimer's disease (AD), and has been implicated as a mediator of the synaptic dysfunction that is hypothesized to play a central role in the pathogenesis of AD. TNF may also play a role in endothelial and microvascular dysfunction in AD, and in amyloidogenesis and amyloid-induced memory dysfunction in AD. Genetic and epidemiological evidence has implicated increased TNF production as a risk factor for AD.

Perispinal administration of etanercept, a potent anti-TNF fusion protein, produced sustained clinical improvement in a 6-month, open-label pilot study in patients with AD ranging from mild to severe. Subsequent case studies have documented rapid clinical improvement following perispinal etanercept in both AD and primary progressive aphasia, providing evidence of rapidly reversible, TNF-dependent, pathophysiological mechanisms in AD and related disorders. Perispinal etanercept for AD merits further study in randomized clinical trials. *From* Tobinick E: **Tumour necrosis factor modulation for treatment of Alzheimer's disease: rationale and current evidence.** *CNS Drugs* 2009, **23:**713-725. [4]

Tumor necrosis factor-alpha (TNF-alpha) is a central regulator of inflammation, and TNF-alpha antagonists may be effective in treating inflammatory disorders in which TNF-alpha plays an important pathogenetic role. Recombinant or modified proteins are an emerging class of therapeutic agents. To date, several recombinant or modified proteins which acts as TNF antagonists have been disclosed. In particular, antibodies that bind to and neutralise TNF have been sought as a means to inhibit TNF activity. Inhibition of TNF has proven to be an effective therapy for patients with rheumatoid arthritis and other forms of inflammatory disease including psoriasis, psoriatic arthritis, and ankylosing spondylitis, inflammatory bowel disease. Additionally, the efficacy of preventing septic shock and AIDS has been questioned as a result of recent research. The currently available therapies include a soluble p75 TNF receptor:Fc construct, etanercept, a chimeric monoclonal antibody, infliximab, and a fully human monoclonal antibody, adalimumab. Certolizumab pegol is a novel TNF inhibitor which is an antigen-binding domain of a humanized TNF antibody coupled to polyethylene glycol (PEG) to increase half-life, and thus is Fc-domain-free. In this review, we discuss briefly the present understanding of TNF-alpha-mediated biology and the current therapies in clinical use, and focus on some of the new therapeutic approaches with small-molecule inhibitors. Moreover, we examine recent reports providing important insights into the understanding of efficacy of thalidomide and its analogs, as TNF-alpha activity inhibitories, especially in therapies of several inflammatory diseases within the nervous system. *From* Esposito E, Cuzzocrea S: **TNF-alpha as a therapeutic target in inflammatory diseases, ischemia-reperfusion injury and trauma.** *Curr Med Chem* 2009, **16:**3152-3167. [13]

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. *From* Tobinick E: **Perispinal etanercept for neuroinflammatory disorders.** *Drug Discov Today* 2009, **14:**168-177. [5]

Since anti-TNF agents are administered parenterally in the noncerebral diseases discussed above, they unsurprisingly encounter no particular anatomical barrier preventing access to the site of pathology. Clearly, a drawback with testing these agents against putative TNF-driven encephalopathies is that they are about as large as albumin and globulin, so cannot be expected to pass the bloodbrain barrier efficiently, where, as discussed in various Sections of this review, much evidence is consistent with excess TNF being harmful. One group has addressed the challenge of brain access through adapting a lesson from the basic aviation medicine literature, in which the effects of 5 min of head-down positioning allows appreciable albumin and globulin to enter the CSF, probably though the choroid plexus (Wen et al., 1994). Indeed, these authors suggested this manoeuvre as a way to get large molecules in to the brain for therapeutic purposes. Combined with an injection route for etanercept that drains into Batson's plexus, this has been used with the intention of accessing the CSF via the choroid plexus. In 2006 an open trial with etanercept injected by this route, in which 15 Alzheimer's patients were treated for 6 months, was published (Tobinick et al., 2006), as have case reports since (Tobinick & Gross, 2008). Etanercept administered in this way has recently been shown to reach the cerebral ventricles in the rat (Tobinick et al., 2009). This argues that this route is much less invasive but functionally equivalent to i.c.v., which is routinely used for anti-TNF biological agents of this size to access the CSF in basic animal studies on roles of TNF in brain function (Medeiros et al., 2007; Galic et al., 2008; Riazi et al., 2008; Liesz et al., 2009). We note that a similar challenge is addressed when treating brain-sited lymphoma with rituximab, a monoclonal antibody effective against non-Hodgkin lymphoma, which expresses CD20, the target of the antibody. Unfortunately its normal intravenous route for non-cerebral lymphomas is ineffective (Rubenstein et al., 2003), so intraventricular administration was seen as the logical alternative. It was successful in a Phase I trial (Rubenstein et al., 2007), but it would be of practical interest to establish whether the less invasive Batson's

plexus route, above, will prove to be equally efficacious. Arguments in favour of this route in neutralizing brain TNF have recently been reviewed (Tobinick, 2010).

Despite the direction of the literature, calls for a double-blind human Alzheimer's trial using etanercept by this route (Tobinick et al., 2006) have not yet attracted industry or government funding. This is in marked contrast to the readiness, in 1993 (see Section 6.2.2), of the manufacturers of another of the above anti-TNF agents to expand a very similar open trial on rheumatoid arthritis (Elliott et al., 1993) into a double-blind study (Elliott et al., 1994). We note, however, that an essentially identical trial except it is to employ etanercept subcutaneously, is soon to begin (see http://www.clinicaltrials.gov/ct2/show/NCT01068353). In view of the albumin-like size of this biomolecular construct, and a previous blinded trial (fewer subjects, but over 24 weeks) employing this route having a negative outcome (Bohac et al., 2002), giving funding precedence to a trial using this route is surprising. The challenge in getting etanercept to where it matters in Alzheimer's disease is, in addition to the rituximab example (previous paragraph), also addressed by studies in which intravenous infliximab, a similar sized molecule, can be presumed not to have entered the CSF because TNF levels in this compartment remained unchanged (Andersson et al., 2006; Kikuchi et al., 2008).

In 2003 a promising high-affinity inhibitor of human TNF was discovered to be secreted by Tanapox virus (Brunetti et al., 2003). From its molecular weight (Rahman et al., 2006), its inability to pass the blood brain barrier will still be a concern for using this protein to treat cerebral conditions, but its extraordinarily high activity compared to neutralizing specific antibodies against TNF has encouraged commercial development as VT-346, with Alzheimer's disease as well as rheumatoid arthritis and Crohn's disease the stated targets (March 16 2010 press release at www.vironinc.com). Others (see http://www.bionity.com/news/e/107293) are developing TNF neutralizing antibodies, of a type (Harmsen & De Haard, 2007) small enough to pass the blood brain barrier, for systemic use in human disease. These nanobodies are an attractive second generation drug, but like VT-346 are some years away from clinical trials. In contrast, infliximab, etanercept and adalimumab, already administered to millions of people annually in relative safety, have an immediate attraction for dealing with the large-scale clinical challenge already present, particularly in Alzheimer's disease, provided it actually gets into the CSF. *From* Clark IA, Alleva LM, Vissel B: **The roles of TNF in brain dysfunction and disease.** *Pharmacol Ther* 2010, **128:**519-548. [16]

Abstract: Until recently, the central nervous system (CNS) has been thought to be an immune privileged organ. However, it is now understood that neuroinflammation is linked with the development of several CNS diseases including late-onset Alzheimer's disease (LOAD). The development of inflammation is a complex process involving a wide array of molecular interactions which in the CNS remains to be further characterized. The development of neuroinflammation may represent an important link between the early stages of LOAD and its pathological outcome. It is proposed that risks for LOAD, which include genetic, biological and environmental factors can each contribute to impairment of normal CNS regulation and function. The links between risk factors and the development of neuroinflammation are numerous and involve many complex interactions which contribute to vascular compromise, oxidative stress and ultimately neuroinflammation. Once this cascade of events is initiated, the process of neuroinflammation can become overactivated resulting in further cellular damage and loss of neuronal function. Additionally, neuroinflammation has been associated with the formation of amyloid plaques and neurofibrillary tangles, the pathological hallmarks of LOAD. Increased levels of inflammatory markers have been correlated with an advanced cognitive impairment. Based on this knowledge, new therapies aimed at limiting onset of neuroinflammation could arrest or even reverse the development of the disease. *From* McNaull BB, Todd S, McGuinness B, Passmore AP: **Inflammation and anti-inflammatory strategies for Alzheimer's disease--a mini-review.** *Gerontology* 2010, **56**:3-14. [17]

TNF-alpha is thought to be the main regulator of the pro-inflammatory response in the brain. Evidence suggests that TNF-alpha overproduction is likely one of the key events leading to LOAD pathogenesis. TNF-alpha is pro-duced by microglia and overproduction has been linked with neuronal cell death. Cultured brain slices in vitro show TNF-alpha increases neuronal glutamate neurotoxicity and leads to cellular damage and death. Animal models of LOAD have indicated that TNF-alpha upregulation can lead to increased beta-Amyloid and NFT formation. It is therefore interesting that spinal levels of TNF-alpha in AD patients are increased up to 25-fold and that levels of spinal TNF-alpha correlate with clinical deterioration of LOAD. Recently, therapeutic agents that inhibit TNF-alpha activity were shown to improve and reverse cognitive decline in some patients . This exciting finding provides solid evidence for the role of TNF-alpha in the development of LOAD and strongly suggests that onset of neuroinflammation is central to LOAD onset. *From* McNaull BB, Todd S, McGuinness B, Passmore AP: **Inflammation and anti-inflammatory strategies for Alzheimer's disease--a mini-review.** *Gerontology* 2010, **56**:3-14. [17]

Etanercept is a potent antagonist of TNF, a pleotropic immune signaling molecule that is also a pivotal regulator of synaptic function. Excess TNF is centrally involved in the pathogenesis of a variety of inflammatory neurological disorders, including Alzheimer's disease, sciatica, traumatic brain injury and spinal cord injury. Perispinal etanercept produces rapid improvement in both Alzheimer's disease and sciatica and in other forms of disc-related pain. Basic research and the observed clinical effects suggest that etanercept has the surprising ability to penetrate into the cerebrospinal fluid after perispinal administration. Perispinal administration is a novel method of delivery designed to introduce this anti-TNF molecule into the bidirectional cerebrospinal venous system and the cerebrospinal fluid to facilitate its selective delivery to either spinal structures or the brain. The scientific rationale, physiologic mechanisms, clinical effects and potential clinical indications of this therapeutic approach are the subject of this article. *From* Tobinick E: **Perispinal etanercept: a new therapeutic paradigm in neurology.** *Expert Rev Neurother* 2010, **10**:985-1002. [3]

At the time of approval of etanercept by the FDA, the role of TNF in neurological disorders was incompletely understood. Novel methods of drug delivery were needed because of the high molecular weight of etanercept and the problems faced by large molecules in traversing the blood-brain barrier(BBB). Perispinal methods were designed for selective delivery of etanercept. Perispinal administration results in rapid local delivery of etanercept to the vertebral venous system and the cerebrospinal fluid (CSF), with rapid local delivery to sites of TNF excess. Rapid response suggests immediate neutralization of excess TNF, resulting in normalization of synaptic mechanisms. *From* Esposito E, Cuzzocrea S: **Anti-TNF therapy in the injured spinal cord.** *Trends Pharmacol Sci* 2011, **32**:107-115. [6]

Inflammation plays an important role in the pathogenesis of Alzheimer's disease (AD). Overexpression of tumor necrosis factor-alpha (TNF-alpha) occurs in the AD brain. Recent clinical studies have shown that the anti-TNF-alpha therapy improves cognition function of AD patients rapidly. However, the underlying mechanism remains elusive. The present study investigates the effects of intracerebroventricular injection of the monoclonal TNF-alpha antibody, Infliximab, on the pathological features of AD in the APP/PS1 double transgenic mice. We found that Infliximab administration reduced the levels of TNF-alpha, amyloid plaques, and tau phosphorylation as early as three days after daily injection of 150 mug Infliximab for three days. The number of CD11c-positive dendritic-like cells and the expression of CD11c were found to be increased concurrently after Infliximab injection. These data suggested that the

CD11c-positive dendritic-like cells might contribute to the Infliximab-induced reduction of AD-like pathology. Furthermore, our results support the use of anti-TNF-alpha for the treatment of AD. *From* Shi JQ, Shen W, Chen J, Wang BR, Zhong LL, Zhu YW, Zhu HQ, Zhang QQ, Zhang YD, Xu J: **Anti-TNF-alpha reduces amyloid plaques and tau phosphorylation and induces CD11c-positive dendritic-like cell in the APP/PS1 transgenic mouse brains.** *Brain Res* 2011, **1368:**239-247.[57]

PURPOSE: TNFalpha is an inflammatory mediator related to neuropathic pain including sciatica. Much basic research suggests that anti-TNFalpha therapy may be useful for the treatment of sciatica. The purpose of this study was to clarify the effects of etanercept in a dorsal root ganglion (DRG) compression model. METHODS: Adult male Sprague-Dawley rats (200-250 g, n = 60) were used. An L-shaped stainless rod was used to compress the left L5 DRG in the saline and etanercept groups. No rod was used in the sham group. In the etanercept group, 1 mg of etanercept was applied locally onto the DRG at the end of surgery. Saline was applied in the saline and sham groups. On day 3 and day 7 after surgery, the number of ED1-immunoreactive (IR) cells (macrophages) in the DRG was calculated by immunohistochemical methods (n = 6). In addition, double-immunofluorescence labeling for ED1 and TNFalpha was performed. Behavioral testing with von Frey filaments and a heat stimulator was performed (n = 12). RESULTS: ED1-IR cells in the DRG significantly increased in the control group compared with the sham group ($p < 0.05$). Some ED1-IR cells were co-labeled for TNFalpha. In the etanercept group, decrease in mechanical threshold was significantly inhibited compared with the saline group ($p < 0.05$). Thermal hyperalgesia was observed in the control group, but in neither the sham nor etanercept group ($p < 0.05$). CONCLUSION: Etanercept attenuated the pain-related behavior induced by DRG compression. These findings suggest that mechanical effects on the DRG might be reduced by etanercept in addition to the effects on nucleus pulposus in lumbar disc herniation. *From* Watanabe K, Yabuki S, Sekiguchi M, Kikuchi SI, Konno SI: **Etanercept attenuates pain-related behavior following compression of the dorsal root ganglion in the rat.** *Eur Spine J* 2011.

BACKGROUND: Thrombolytic therapy reduces stroke size and disability by reperfusion and salvage of ischaemic penumbra. Emerging evidence suggests that retrieved penumbra may be the site of ongoing inflammatory pathology that includes extensive microglial activation. Microglial activation may be associated with excessive levels of tumour necrosis factor (TNF) and resultant neurotoxicity. Etanercept, a potent biologic

TNF antagonist, reduces microglial activation in experimental models and has been therapeutically effective in models of brain and neuronal injury. Perispinal administration of etanercept, previously reported to be beneficial for the treatment of Alzheimer's disease, may facilitate delivery of etanercept into the brain. OBJECTIVE: The objective of this report is to document the initial clinical response to perispinal etanercept in the first chronic stroke cohort so treated. METHODS: Three consecutive patients with stable and persistent chronic neurological deficits due to strokes that had failed to resolve despite previous treatment and rehabilitation were evaluated at an outpatient clinic. They were treated off-label with perispinal etanercept as part of the clinic's practice of medicine. RESULTS: All three patients had chronic hemiparesis, in addition to other stroke deficits. Their stroke distributions were right middle cerebral artery (MCA), brainstem (medulla) and left MCA. The two patients with MCA strokes had both received acute thrombolytic therapy. Each of the three patients was treated with an initial dose of perispinal etanercept 13, 35 and 36 months following their acute stroke, respectively. Significant clinical improvement following perispinal etanercept administration was observed in all patients. Onset of clinical response was evident within 10 minutes of perispinal injection in all patients. Improvements in hemiparesis, gait, hand function, hemi-sensory deficits, spatial perception, speech, cognition and behaviour were noted among the patients treated. Each patient received a second perispinal etanercept dose at 22-26 days after the first dose that was followed by additional clinical improvement. CONCLUSIONS: Open-label administration of perispinal etanercept resulted in rapid neurological improvement in three consecutive patients with chronic neurological dysfunction due to strokes occurring 13-36 months earlier. These results suggest that stroke may result in chronic TNF-mediated pathophysiology that may be amenable to therapeutic intervention long after the acute event. Randomized clinical trials of perispinal etanercept for selected patients with chronic neurological dysfunction following stroke are indicated. *From* Tobinick E: **Rapid improvement of chronic stroke deficits after perispinal etanercept: three consecutive cases.** *CNS Drugs* 2011, **25**:145-155. [24]

STUDY DESIGN: Prospective randomized trial. OBJECTIVE: To examine the effect of the tumor necrosis factor alpha (TNF-alpha) inhibitor, etanercept, on radicular pain by its epidural administration onto spinal nerves in patients with lumbar spinal stenosis. SUMMARY OF BACKGROUND DATA: TNF-alpha is thought to play a crucial role in the radicular pain caused by lumbar disc herniation and spinal stenosis. Intravenous infusion of infliximab for sciatica has been examined in 2 studies; however, the results were equivocal. METHODS: Eighty patients with low back and radicular leg pain were investigated. We diagnosed the

patients by physical examination, and X-ray and magnetic resonance imaging. In 40 patients, we epidurally administered 2.0 mL of lidocaine and 10 mg of etanercept onto the affected spinal nerve, and 2.0 mL of lidocaine and 3.3 mg of dexamethasone was used in 40 patients. Low back pain, leg pain, and leg numbness were evaluated using a visual analogue scale (VAS) and Oswestry Disability Index (ODI) score before and for 1 month after epidural administration. RESULTS: Low back pain, leg pain, and leg numbness in the 2 groups were not significantly different before epidural administration. Epidural administration of etanercept was more effective than dexamethasone for leg pain (3 days, and 1, 2, and 4 weeks: $P < 0.05$), low back pain (3 days, and 1 and 2 weeks: $P < 0.05$), and leg numbness (3 days, and 1 and 2 weeks: $P < 0.05$). No adverse event was observed in either group. CONCLUSION: Our results indicate that epidural administration of a TNF-alpha inhibitor onto the spinal nerve produced pain relief, but no adverse event. TNF-alpha inhibitors may be useful tools for the treatment of radicular pain caused by spinal stenosis. *From* Ohtori S, Miyagi M, Eguchi Y, Inoue G, Orita S, Ochiai N, Kishida S, Kuniyoshi K, Nakamura J, Aoki Y, et al: **Epidural administration of spinal nerves with the tumor necrosis factor-alpha inhibitor, etanercept, compared with dexamethasone for treatment of sciatica in patients with lumbar spinal stenosis: a prospective randomized study.** *Spine (Phila Pa 1976)* 2012, **37**:439-444. [30]

Excess tumor necrosis factor (TNF) plays a pivotal role in the pathogenesis of Alzheimer's disease(AD). Clinical improvement following perispinal administration of etanercept in patients with Alzheimer's disease and other forms of dementia and brain dysfunction is characteristically evident within minutes. The rapidity and constellation of the clinical effects across multiple domains (cognition, mood, memory, motor function, and attention) suggest they are mediated by non-synaptic signaling mechanisms previously unrecognized for etanercept. These mechanisms likely extend beyond the known roles of TNF as a gliotransmitter that modulates synaptic strength, synaptic scaling, and AMPA receptor trafficking. Preliminary basic science and clinical investigation suggests that perispinal administration of etanercept may lead to its rapid penetration into the cerebrospinal fluid (CSF) within the cerebral ventricles. Diffusion of large molecules into the periventricular brain parenchyma is known to occur, but this process may not be sufficient to explain the rapidity of the clinical effects. There exist populations of cells, including CSF-contacting neurons and modified ependymal cells called tanycytes, that have receptive surfaces in direct contact with the CSF. It is hypothesized that the rapid clinical effects of perispinal etanercept involve non-synaptic signal transduction across the ependymal barrier and into neuronal networks via these CSF-contacting cells. This hypothesis challenges the dogma that penetration of a

therapeutic into the cerebral parenchyma through the endothelium of the cerebral vasculature (the so-called blood- brain barrier) is necessary to produce rapid clinical effects in AD. CSF-contacting cells may constitute a therapeutic target for a diverse group of brain, psychiatric and spinal disorders. *From* Tobinick E: **Deciphering the physiology underlying the rapid clinical effects of perispinal etanercept in Alzheimer's disease.** *Curr Alzheimer Res* 2012, **9**:99-109.[1]

It is well known that the inflammatory response plays an important role in AD and other tauopathies, and that a chronic inflammatory state, including diabetes mellitus, hypertension and periodontitis, is a risk factor for AD. Beta-amyloid deposition is considered to be an important inducer of the chronic inflammatory response. A relationship between NFT burden and microglial activation has also been demonstrated....Interestingly, microglial activation precedes NFT formation, and administration of an immunosuppressant, FK506, ameliorates microgliosis and tau pathology in a P301S mutant tau Tg mouse model. Several clinical trials targeting inflamation have been conducted....A single centre, open label, small group study indicated that prespinal injection of etanercept, a tumour necrosis factor inhibitor used for treatment of rheumatoid arthritis, improved cognition in AD patients. A phase II, double blind, placebo controlled study of etanercept in AD patients is ongoing (http://clinicaltrials.gov/ct2/show/NCT01068353). *From* Yoshiyama Y, Lee VM, Trojanowski JQ: **Therapeutic strategies for tau mediated neurodegeneration.** *J Neurol Neurosurg Psychiatry* 2012. [62]

Alzheimer disease has also been linked to increase expression of inflammatory cytokines, and microglial activation has been observed in AD post mortem and in vivo....An increase in TNF-alpha is associated with cognitive decline in AD. In mouse models of AD, TNF-alpha is implicated in enhanced amyloid production, tau hyperphosphorylation, and cell death, and countering TNF-alpha improves both symptoms and pathology. Beta-amyloid aggregation in mouse hippocampus and cortex has also been induced by inflammation. *From* Perry DC, Lehmann M, Yokoyama JS, Karydas A, Lee JJ, Coppola G, Grinberg LT, Geschwind D, Seeley WW, Miller BL, et al: **Progranulin Mutations as Risk Factors for Alzheimer Disease.** *JAMA Neurol* 2013:1-5.[61]

Abstract

Background

Tumor necrosis factor-alpha (TNF-α) is elevated early in injured brain after traumatic brain injury (TBI), in humans and in animals. Etanercept (a TNF-α antagonist with anti-inflammatory effects) attenuates TBI in rats by reducing both microglial and astrocytic activation and increased serum levels of TNF-α. However, it is not known whether etanercept improves outcomes of TBI by attenuating microglia-associated, astrocytes-associated, and/or neurons-associated TNF-α expression in ischemic brain. A well clinically relevant rat model, where a lateral fluid percussion is combined with systemic administration of etanercept immediately after TBI, was used. The neurological severity score and motor function was measured on all rats preinjury and on day 3 after etanercept administration. At the same time, the neuronal and glial production of TNF-α was measured by Immunofluorescence staining. In addition, TNFα contents of ischemic cerebral homogenates was measured using commercial enzyme-linked immunosorbent assay kits.

Results

In addition to inducing brain ischemia as well as neurological and motor deficits, TBI caused significantly higher numbers of microglia-TNF-α double positive cells, but not neurons-TNF-α or astrocytes-TNF-α double positive cells in the injured brain areas than did the sham operated controls, when evaluated 3 days after TBI. The TBI-induced cerebral ischemia, neurological motor deficits, and increased numbers of microglia-TNF-α double positive cells and increased TNF-α levels in the injured brain were all significantly attenuated by etanercept therapy.

Conclusion

This finding indicates that early microglia overproduction of TNF-α in the injured brain region after TBI contributes to cerebral ischemia and neurological motor deficits, which can be attenuated by etanercept therapy. Studies in this model could provide insight into the mechanisms underlying neurological motor disturbance in brain-injured patients. *From* Chio CC, Chang CH, Wang CC, Cheong CU, Chao CM, Cheng BC, Yang CZ, Chang CP: **Etanercept attenuates traumatic brain injury in rats by reducing early microglial expression of tumor necrosis factor-alpha.** *BMC Neurosci* 2013, **14**:33. [67]

Inhibiting tumor necrosis factor-alpha (TNF-α) with etanercept is effective for attenuating TBI-induced cerebral contusion, motor and cognitive dysfunction, astrocytic and microglial activation, and activated inflammation [11, 12]. *From* Cheong CU, Chang CP, Chao CM, Cheng BC, Yang CZ, Chio CC: **Etanercept attentuates traumatic brain injury in rats by reducing brain TNF-alpha contents and**

by stimulating newly formed neurogenesis. *Mediators of Inflammation* 2013, **2013 Article ID 620837, 9 pages.** [66]

5. Conclusion
The current study demonstrates that TBI, in addition to inducing cerebral contusion and neurological motor deficits, induces the overproduction of TNF-α as well as the increased numbers of the colocalizations of BrdU and DCX specific markers in the contused bran tissues. Levels of etanercept can be detected in brain following systemic delivery of etanercept to TBI animals. In addition, cerebral contusion, neurological motor deficits, and increased brain contents of TNF-α can be attenuated, whereas the increased numbers of colocalizations of BrdU and DCX specific markers in the contused brain tissue can be enhanced by etanercept therapy during TBI. Thus, it appears that etanercept attenuates TBI in rats by reducing TNF-α contents and by enhancing newly formed neurogenesis in the contused brain tissues. *From* Cheong CU, Chang CP, Chao CM, Cheng BC, Yang CZ, Chio CC: **Etanercept attentuates traumatic brain injury in rats by reducing brain TNF-alpha contents and by stimulating newly formed neurogenesis.** *Mediators of Inflammation* 2013, **2013 Article ID 620837, 9 pages.** [66]

Kumar A, Stoica BA, Sabirzhanov B, Burns MP, Faden AI, Loane DJ: **Traumatic brain injury in aged animals increases lesion size and chronically alters microglial/macrophage classical and alternative activation states.** *Neurobiol Aging* 2013, **34:**1397-1411. **[65]**

King MD, Alleyne CH, Jr., Dhandapani KM: **TNF-alpha receptor antagonist, R-7050, improves neurological outcomes following intracerebral hemorrhage in mice.** *Neurosci Lett* 2013. **[11]**

Abstract
A single traumatic brain injury is associated with an increased risk of dementia and, in a proportion of patients surviving a year or more from injury, the development of hallmark Alzheimer's disease-like pathologies. However, the pathological processes linking traumatic brain injury and neurodegenerative disease remain poorly understood. Growing evidence supports a role for neuroinflammation in the development of Alzheimer's disease. In contrast, little is known about the neuroinflammatory response to brain injury and, in particular, its temporal dynamics and any potential role in neurodegeneration. Cases of traumatic brain injury with survivals ranging from 10 h to 47 years post injury (n = 52) and age-matched, uninjured control subjects (n = 44) were selected from the Glasgow

> Traumatic Brain Injury archive. From these, sections of the corpus callosum and adjacent parasaggital cortex were examined for microglial density and morphology, and for indices of white matter pathology and integrity. With survival of >/=3 months from injury, cases with traumatic brain injury frequently displayed extensive, densely packed, reactive microglia (CR3/43- and/or CD68-immunoreactive), a pathology not seen in control subjects or acutely injured cases. Of particular note, these reactive microglia were present in 28% of cases with survival of >1 year and up to 18 years post-trauma. In cases displaying this inflammatory pathology, evidence of ongoing white matter degradation could also be observed. Moreover, there was a 25% reduction in the corpus callosum thickness with survival >1 year post-injury. These data present striking evidence of persistent inflammation and ongoing white matter degeneration for many years after just a single traumatic brain injury in humans. Future studies to determine whether inflammation occurs in response to or, conversely, promotes white matter degeneration will be important. These findings may provide parallels for studying neurodegenerative disease, with traumatic brain injury patients serving as a model for longitudinal investigations, in particular with a view to identifying potential therapeutic interventions. *From* Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W: **Inflammation and white matter degeneration persist for years after a single traumatic brain injury.** *Brain* 2013, **136**:28-42. [10]

Dr. Novella, it takes a long time for new ideas in medicine and science to disseminate. Perispinal etanercept, despite the fact that it remains an emerging treatment option that is unfamiliar to many, has received scientific recognition from independent academic scientists and physicians, as one may ascertain by examining the list of scientific publications that have cited our perispinal etanercept publications, now numbering in the hundreds. I list just a sample of the recent publications and textbooks[6-9, 16-18, 20-23, 26, 28, 29, 31, 39, 50, 53-55, 57, 59, 60, 62, 71-127]. You may not be aware of the international interest in this area of work. Just a single example is the international symposium that took place in Basel, Switzerland in May 2012 entitled "*Meeting on the*

roles of TNF in brain dysfunction and disease." This international conference included presentations by internationals scientists, including pioneers in the field.

There is additional evidence, some of which has been presented at recent international conferences. For example, in 2012, at the world's largest Alzheimer conference, the Alzheimer's Association International Conference, the following presentation was made, published as P2-374 in Alzheimer's and Dementia, Volume 8, Issue 4, Supplement, July 2012:

> EFFECTS OF ANTI-TNF THERAPY ON AMYLOID PATHOLOGY AND NEUROINFLAMMATION IN 12- MONTH-OLD ARCAß TRANSGENIC MICE
>
> Jordan McAfoose, Luka Kulic, Tobias Welt, Claudia Sp€ani, Rebecca Derungs, Armanda Pfister, Roger Nitsch, Division of Psychiatry Research, University of Zurich, Zurich, Switzerland.
>
> Background: In 2008, Tobinick and colleagues demonstrated that Etanercept anti-TNF therapy could be used for the treatment of AD. Although this treatment approach has advanced to Phase II clinical trial the underlying therapeutic mechanisms remain unknown.
>
> Methods: To identify the mechanisms we launched an AD mouse model study, in which we infused Etanercept or vehicle control into the ventricles of arcAb mice over 28 days using ALZET osmotic minipumps; with an additional 15 non-treated transgenic and wildtype mice as a further controls. All mice underwent general health and neurological examination, as well as, cognitive assessment before they were sacrificed for further biochemical and histological analyses.
>
> Results: Our findings demonstrated a treatment dependent improvement in cognitive performance in two hippocampus-dependent cognitive tests. Biochemical analyses suggested that the improvement in cognition was not associated with changes in soluble brain Abeta levels but rather a decrease in Formic acid insoluble Abeta levels. Histological analysis demonstrated a treatment-induced lowering of Abeta plaques and an increased clearance of Abeta plaques towards the vasculature.Stainings against GFAP and Iba1 further demonstrated a reduction in astrocytosis with parallel elevations in microglia activation.

> Conclusions: These findings suggest a neuroinflammatory and amyloid-lowering mechanism of anti-TNF therapy, in which Abeta is solubilized and cleared towards the vasculature.

These favorable basic science findings provide a mechanistic explanation for the favorable clinical results that have been published. Professor Sue Griffin, Co-Editor of the Journal of Neuroinflammation, discussed her experience when she flew out to visit our office and observe perispinal etanercept treatment firsthand. in her published Commentary, based upon her own eyewitness account[50]:

> In this section, my comments reflect my own thoughts on this treatment strategy and my own experiences in viewing it, and are accompanied by a few of my own remarks directed toward the necessity of giving attention to this novel treatment. I first became aware of this treatment when a reporter from *The Los Angeles Times* contacted me in 2006 for a comment on an article he was writing on a novel and successful Alzheimer treatment trial. Although my interest was piqued by this, it was only more recently when Dr. Tobinick contacted me and sent a preprint of the findings discussed in the *Times* [3] that I decided to go and see for myself the treatment and talk to the patients and family members. I called the day before, and was invited to visit the next day, November 7, 2007. Each of the three patients I saw treated had been tested and diagnosed with probable Alzheimer's disease by a neurologist before perispinal etanercept treatment had begun. They and their families invited me to be present during the treatment and in the interviews before and after. I noticed clinical improvement in each of the three patients within minutes following treatment. My first impression was that there was a clear, easily discernible, difference in each. They were more cheerful, more at ease, and more attentive. My impressions were the same as those shared by each of the families (please see the movie for example). This rapid turn around brought to mind the first time, now almost two decades ago[17], that I was the original witness to the remarkable overexpression of immune cytokines in activated glia in Alzheimer patients and even in fetuses and neonates with Down's syndrome – I was amazed!

There are additional scientific references on our websites; you allude to our websites in your article. In fact, you state "*On his website he cites many studies, but none of them establish the effectiveness of Enbrel for any of the conditions he is treating.*" Your statement is simply false. For example, as you are aware, my colleagues and I do continue to use perispinal etanercept for sciatica associated with disc herniation or spinal stenosis in selected patients. Our first peer-reviewed articles published in 2003 and 2004 (my colleagues and I were the first to report the clinical effects of etanercept for disc-related pain and sciatica[33, 35, 38]), and there are now published, peer-reviewed randomized, double-blind, controlled studies that are positive (e.g. [30]). As our published articles have documented, my colleagues and I have more than a decade of favorable clinical experience using etanercept for sciatica and related conditions. Considering the published clinical evidence, including the published, randomized double-blind evidence, and multiple positive basic science studies, it is clear that your statement is misguided and not in the best interests of science, medicine, or the public[3, 23, 25, 30, 37-39, 52, 55, 69, 97, 127, 128].

Thus, in view of the published, peer-reviewed scientific literature, including randomized, controlled studies; the eyewitness accounts from prominent experts and journalists; and the fact that you never met me, I was shocked at the content and tone and conclusions of your article. You use words like "dubious", "quack" and "fraud", and "exploitation" and overall paint a false and highly defamatory picture, seemingly based mainly upon a newspaper article written about a single patient by a newspaper reporter who never even visited our medical office, and never met the patient in question. You have never even

called me to ask about our results. Rather than advance medical science, your defamatory attack on my work and that of my colleagues could well have a chilling effect on the science-based and rationale use of existing therapeutics for off-label indications, uses that may be of significant benefit for patients with intractable medical conditions[129-131]. Moreover, I do not believe that your public defamatory attack on me, particularly in view of the evidence elaborated herein and present in the medical literature, is consistent with the ethical guidelines of our profession and the American Academy of Neurology.

In view of the above, I request that you immediately retract your article; it is not in the public interest, and it is both false and defamatory. I request that you also retract any related defamatory postings, and refrain from such activity in the future. At this time, I also invite you to visit our medical office, and learn about what we do, and find out for yourself about the potential of perispinal etanercept in Neurology.

Sincerely,

Edward Tobinick M.D.

Attachment: Tobinick E: **Perispinal etanercept: a new therapeutic paradigm in neurology.** *Expert Rev Neurother* 2010, **10**:985-1002.

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VIA EMAIL AND FEDEX DELIVERY
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Re: Institute of Neurological Recovery and Dr. Tobinick adv. Dr. Steven Novella & Yale

Dear Ms. Robinson:

Please be advised that the undersigned law firm has been retained by the Institute of Neurological Recovery, INR PLLC and Dr. Edward Tobinick MD (collectively "our clients"). We write to you in connection with the above referenced matter involving one of your employees, Steven Novella MD, a neurologist who provides commercial services for patients after stroke at the Yale Neurology Clinic ("YNC") and at the Yale Botulinum Program ("YBP"). As you are likely aware, one of the common commercial services provided at the YBP is the use of Botox® for treatment of post-stroke spasticity, an FDA-approved use of Botox® that directly competes with the medical services provided by our clients. Dr. Novella is promoted as a Yale Neurologist "Deflating Scientific Fallacies" and as a Skeptic on various Yale associated web-links, accompanied by descriptions of his work at the YNC and the YBP, and links directly to his Skeptic websites, including Science-based Medicine ("SBM"). Please refer to the attached **"Exhibit A"** for a list of some of these web-links.

Although it is expected that an institution such as yours would promote its employed professionals, such as Dr. Novella, it is unorthodox to anticipate an institution – *especially* one as highly-regarded as Yale – to support and promote a professional engaging in unethical and illegal behavior. In this case, for the reasons more thoroughly explained below, Yale is engaging in such behavior through its support and promotion of the conduct of Dr. Novella. As described

EXHIBIT
tabbies
3

below, Dr. Novella has engaged in an unwarranted, unprovoked, unfair and unjustifiable public smear campaign and attack against our clients that has resulted in our clients sustaining irreparable injury and significant loss of business, not to mention the more troubling detrimental effect it has had on patients suffering from an illness that could otherwise be treated by our clients. Dr. Novella's actions are in derogation of Section 6.3 of the American Academy of Neurology's Code of Conduct, amount to unfair competition under common law and under Section 43(a) of the federal Lanham Act, and also amount to defamation and libel *per se*. Yale's acquiescence, endorsement (regardless of tacit or direct) and failure to control the illegal conduct of its employee – Dr. Novella – equally exposes Yale under the law.

As you may be aware, Dr. Novella has published an article entitled "Enbrel for Stroke and Alzheimer's", which can be found at http://www.sciencebasedmedicine.org/enbrel-for-stroke-and-alzheimers/. A simple Google® search of our client, Dr. Tobinick, locates the article within the first couple of hits. This reality is problematic as the article is extremely inflammatory and defamatory in nature as it contains multiple false and misleading statements of fact regarding our clients. For example, the Dr. Novella's article falsely asserts that our client, the Institute of Neurological Recovery is, "*a one-man institute*". The fact is that the Institute employs multiple physicians, a fact that is plainly apparent from even casual perusal of our client's publications, such as Tobinick, E., N.M. Kim, G. Reyzin, H. Rodriguez-Romanacce, and V. Depuy, *Selective TNF Inhibition for Chronic Stroke and Traumatic Brain Injury : An Observational Study Involving 629 Consecutive Patients Treated with Perispinal Etanercept.* CNS Drugs, 2012. **26**(12): p. 1051-70. In fact, the website on which Dr. Novella's article is published actually links to this particular publication, yet it is recklessly ignored by him.

Another false and malicious statement within Dr. Novell's article is the suggestion that "*Tobinick has since moved his clinic to Florida, which is a very quack-friendly state.*" Again, this statement by Dr. Novella is false and misleading. A response is not necessary to the outrageous suggestion that "Florida…is a quack friendly state", and its negative implications against our clients, but had Dr. Novella conducted even a hint of research he would have learned that our clients' California offices were open at the time he published his article, and the California office remains in operation today.

Yet another example of a false and misleading statement by Dr. Novella is the suggestion in his published article that "*Tobinick…is claiming that a wide range of neurological conditions not known to be immune mediated are treated by a specific immunosuppressant.*" Like the others, this statement of fact is false and misleading. Indeed, in 2013 and 2014 alone there were no fewer than 10 separate publications reporting favorable effects of etanercept for neuroinflammatory indications, a list of which can be reviewed on the attached **Exhibit "B"** hereto. Furthermore, the pathophysiology of both stroke and Alzheimer's are well known to be immune-mediated. For example, Richard Ransohoff MD, Editor of the new journal Neurology: Neuroimmunology and Neuroinflammation, has stated:

> "There has been an explosion of new knowledge about how inflammation affects the diseases of aging, such as Alzheimer's .... and stroke" (Neurology: Neuroimmunology & Neuroinflammation launch!), and
>
> Neuroinflammation has been studied for decades almost exclusively as a cardinal feature of explicitly inflammatory processes such as MS, NMO, inflammatory neuropathy, acute infection, stroke, and trauma. With recent genetic findings it is now clear that inflammation plays a central (but not exclusive) part in Alzheimer disease, Parkinson disease, tauopathy, and other neurodegenerations. Inflammation is also strongly suspected as having a role in neurodevelopmental disease, including autism and schizophrenia.

Ransohoff, R., *Call for papers: Neurology: Neuroimmunology & Neuroinflammation, a new Neurology journal.* Neurology, 2014. **82**: p. 648-649.

Bottom line, the scientific basis underlying the use of etanercept for post-stroke neurological dysfunction and Alzheimer's disease is supported by a wealth of published, peer-reviewed scientific literature. The collection of scientific evidence supporting the use of selective TNF inhibitors for treatment of neuroinflammatory disorders has continued to increase in the recent past, including a new study demonstrating favorable effects of etanercept in an Alzheimer's model. Some of these published studies are noted in the attached **Exhibit "C"** hereto for your reference. Clearly, based on the foregoing, Dr. Novella is stating a falsity when he states that "*Tobinick...is claiming that a wide range of neurological conditions not known to be immune mediated are treated by a specific immunosuppressant.*"

As a final non-exhaustive example of the malicious falsehoods within Dr. Novella's published article, he states that "*Tobinick has also started to publish case series – little more than retrospective case series reporting on his own patients.... all but worthless coming from a clinic like Tobinick's.*" Not unlike the others, this statement is false and intentionally misleading. The publications of Dr. Tobinick include multiple, invited review articles in prominent journals. And, the observational studies published by Dr. Tobinick and his colleagues include patients treated by multiple physicians, not simply Dr. Tobinick's own patients. A short exemplary list of these published, peer-reviewed scientific articles can be reviewed on **Exhibit "D"** attached hereto for your reference. Further, the scientific publications of Dr. Tobinick and his colleagues have been cited by hundreds of researchers from academic centers around the world and in neuroscience journals such as Nature Clinical Practice Neurology, and Dr. Tobinick has been an invited *ad hoc* reviewer for the journals *Brain Research, CNS Drugs, Current Alzheimer Research, Experimental Neurology, Future Neurology, Journal of Neurochemistry, Journal of Neuroimmunology, Neuroscience, and Pharmaceutical Medicine* and a member of the Editorial

Board of the *Journal of Neuroinflammation.* Suffice it to say, these are not the scientific credentials of a "quack" physician as suggested by Dr. Novella.

In light of the foregoing, it is unequivocally clear that Dr. Novella, a Neurologist employed and publicly promoted by Yale, has engaged in a concerted and malicious effort to unfairly compete against and disparage the amazing work of our clients. As a promoted Yale Neurologist, Dr. Novella's repeated usage of falsely disparaging phrases such as "quack", "dubious", "lack of expertise", "worthless coming from a clinic like Tobinick's", "Tobinick is providing the kind of evidence that is guaranteed to be positive," and "exploitation of a well-meaning and desperate husband at the hands of a dubious practitioner" on his webpage, becomes that much more problematic and troubling. And, to add insult to injury, Dr. Novella placed his article about our clients in the category of "Health Fraud", implying that our clients and its physicians are involved in and committing health fraud. Clearly this malicious behavior, supported by Yale, is actionable under the law and will not be tolerated.

Etanercept for neuroinflammatory indications, such as stroke, Alzheimer's disease and sciatica is not a "scientific fallacy", but rather represents evidence-based, emerging off-label uses of this therapeutic molecule for intractable medical conditions that are supported by peer-reviewed, published scientific literature, clinical data, and basic science studies with a firm, scientific rationale. These uses may help fulfill important unmet medical needs of thousands of patients that your doctor is deterring for his own envious reasons.

As previously stated, Dr. Novella's false and misleading published statements on a website promoted by Yale have caused irreversible injury to the Institute and the Institute's physicians, including Dr. Tobinick. **The force and effect of Dr. Novella's disparaging remarks and unjustified attacks on our clients are amplified and supported by Novella's close association to Yale, the Yale University School of Medicine, and Yale Neurology and by Yale's characterization of Dr. Novella as a Yale academic clinical neurologist who is "Deflating Scientific Fallacies."** In this regard, demand is hereby made that Yale immediately and publicly dissociate itself from Dr. Novella's article and the false allegations contained therein. In addition, inasmuch as we are hopeful that Yale would not condone such reckless behavior by one of its own professionals, we urge Yale to immediately initiate an investigation of these facts to determine if Dr. Novella's actions constitute academic misconduct under the rules governing faculty conduct at Yale. Mischaracterizations of the scientific evidence are not in the public interest, nor in the interest of Yale, medicine, or science.

As a final aside, you should note that the information contained herein was carefully detailed in a cease and desist letter sent to Dr. Novella on May 17, 2013 by Dr. Tobinick, a copy of which is attached hereto as **Exhibit "E".** Unfortunately, much like his attitude in publishing

his article, Dr. Novella notably assumed a careless attitude and did not respond; hence, necessitating this correspondence to you.

We look forward to your immediate compliance with the demands set forth herein, and expect notification of such action within seven (7) business days of your receipt of this letter. Under the circumstances that your doctor's article is causing grave harm to our clients, and thwarting the care of thousands of patients in need, we believe that such a short time frame is both appropriate and necessary. Of course, in the meantime, please feel free to contact me *via* email (pgh@trippscott.com) or via my direct dial phone number (954.760.4913).

Very truly yours,

PETER G. HERMAN
For the Firm

Exhibit "A"
Yale Web-Links

a. Yale:

http://news.yale.edu/2011/04/05/deflating-scientific-fallacies
http://bbs.yale.edu/about/article.aspx?id=2500
http://www.yale.edu/opa/arc-ybc/v34.n6/story10.html

b. Yale School of Medicine:

http://medicine.yale.edu/neurology/patients/neuromuscular/steven_novella.profile
http://yalemedicalgroup.org/services/steven_novella-2.profile?source=news
http://medicine.yale.edu/neurology/patients/generalneurology/steven_novella-1.profile
http://medicine.yale.edu/neurology/patients/generalneurology/steven_novella-2.profile
http://people.yale.edu/about/article.aspx?id=2500
http://medicine.yale.edu/news/news.aspx?id=2500
http://medicine.yale.edu/neurology/article.aspx?id=2500
http://medicine.yale.edu/neurology/people/steven_novella.profile
http://medicine.yale.edu/neurology/people/steven_novella-2.profile
http://medicine.yale.edu/intranet/facultybydept/steven_novella.profile
http://medicine.yale.edu/about/profiles/steven_novella.profile

d. Yale Neurology:

http://medicine.yale.edu/neurology/patients/neuromuscular/steven_novella.profile
http://medicine.yale.edu/neurology/patients/generalneurology/steven_novella-1.profile
http://medicine.yale.edu/neurology/patients/generalneurology/steven_novella-2.profile
http://medicine.yale.edu/neurology/people/steven_novella.profile
http://medicine.yale.edu/neurology/people/steven_novella-2.profile
http://medicine.yale.edu/neurology/article.aspx?id=2500

Exhibit "B"
2013-2014 Publications reporting favorable effects of
etanercept for neuroinflammatory indications

1. Ye, J., et al., *Etanercept reduces neuroinflammation and lethality in mouse model of Japanese encephalitis.* J Infect Dis, 2014.

2. Tobinick, E., et al., *Immediate neurological recovery following perispinal etanercept years after brain injury.* Clin Drug Investig, 2014. **34**(5): p. 361-6.

3. Ekici, M.A., et al., *Effect of etanercept and lithium chloride on preventing secondary tissue damage in rats with experimental diffuse severe brain injury.* Eur Rev Med Pharmacol Sci, 2014. **18**(1): p. 10-27.

4. Detrait, E.R., et al., *Peripheral administration of an anti-TNF-alpha receptor fusion protein counteracts the amyloid induced elevation of hippocampal TNF-alpha levels and memory deficits in mice.* Neurochem Int, 2014.

5. Coelho, S.C., et al., *Etanercept reduces thermal and mechanical orofacial hyperalgesia following inflammation and neuropathic injury.* Eur J Pain, 2014.

6. Sainoh, T., et al., *Intradiscal Administration of Tumor Necrosis Factor-Alpha Inhibitor, Etanercept, Clinically Improves Intractable Discogenic Low Back Pain: A Prospective Randomized Study*, in *International Society for the Study of the Lumbar Spine 40th Annual Meeting*. 2013: Scottsdale, Arizona.

7. Freeman, B.J., et al., *Randomized, Double-blind, Placebo-Controlled, Trial of Transforaminal Epidural Etanercept for the Treatment of Symptomatic Lumbar Disc Herniation.* Spine (Phila Pa 1976), 2013. **38**(23): p. 1986-94.

8. Chio, C.C., et al., *Etanercept attenuates traumatic brain injury in rats by reducing early microglial expression of tumor necrosis factor-alpha.* BMC Neurosci, 2013. **14**(1): p. 33.

9. Cheong, C.U., et al., *Etanercept attenuates traumatic brain injury in rats by reducing brain TNF- alpha contents and by stimulating newly formed neurogenesis.* Mediators Inflamm, 2013. **2013**: p. 620837.

10. Boivin, N., et al., *The combination of valacyclovir with an anti-TNF alpha antibody [etanercept] increases survival rate compared to antiviral therapy alone in a murine model of herpes simplex virus encephalitis.* Antiviral Res, 2013. **100**(3): p. 649-53.

Exhibit "C"
Scientific publications reporting favorable effects of etanercept for neuroinflammatory indications

1. Tobinick E, Rodriguez-Romanacce H, Levine A, Ignatowski TA, Spengler RN. Immediate neurological recovery following perispinal etanercept years after brain injury. Clinical drug investigation. 2014;34(5):361-6.
2. Detrait ER, Danis B, Lamberty Y, Foerch P. Peripheral administration of an anti-TNF-alpha receptor fusion protein counteracts the amyloid induced elevation of hippocampal TNF-alpha levels and memory deficits in mice. Neurochemistry international. 2014.
3. Iwatsuki K, Arai T, Ota H, Kato S, Natsume T, Kurimoto S, et al. Targeting anti-inflammatory treatment can ameliorate injury-induced neuropathic pain. PLoS One. 2013;8(2):e57721.
4. Freeman BJC, Ludbrook GL, Hall S, Cousins M, Mitchell B, Jaros M, et al. A Randomized, Double-blind, Placebo-controlled Trial of Transforaminal Epidural Etanercept for the Treatment of Symptomatic Lumbar Disc Herniation. Spine. 2013;ahead of print, 10.1097/01.brs.0000435140.61593.4c.
5. Chio CC, Chang CH, Wang CC, Cheong CU, Chao CM, Cheng BC, et al. Etanercept attenuates traumatic brain injury in rats by reducing early microglial expression of tumor necrosis factor-alpha. BMC Neurosci. 2013;14(1):33.
6. Cheong CU, Chang CP, Chao CM, Cheng BC, Yang CZ, Chio CC. Etanercept attentuates traumatic brain injury in rats by reducing brain TNF-alpha contents and by stimulating newly formed neurogenesis. Mediators of Inflammation. 2013;2013 Article ID 620837, 9 pages.
7. Tobinick E, Kim NM, Reyzin G, Rodriguez-Romanacce H, DePuy V. Selective TNF inhibition for chronic stroke and traumatic brain injury: an observational study involving 629 consecutive patients treated with perispinal etanercept. CNS Drugs. 2012;26(12):1051-70.
8. Tobinick E. Deciphering the physiology underlying the rapid clinical effects of perispinal etanercept in Alzheimer's disease. Curr Alzheimer Res. 2012;9(1):99-109.
9. Roh M, Zhang Y, Murakami Y, Thanos A, Lee SC, Vavvas DG, et al. Etanercept, a widely used inhibitor of tumor necrosis factor-alpha (TNF-alpha), prevents retinal ganglion cell loss in a rat model of glaucoma. PLoS One. 2012;7(7):e40065.
10. Ohtori S, Miyagi M, Eguchi Y, Inoue G, Orita S, Ochiai N, et al. Epidural administration of spinal nerves with the tumor necrosis factor-alpha inhibitor, etanercept, compared with dexamethasone for treatment of sciatica in patients with lumbar spinal stenosis: a prospective randomized study. Spine (Phila Pa 1976). 2012;37(6):439-44.
11. Maudsley S, Chadwick W. Progressive and unconventional pharmacotherapeutic approaches to Alzheimer's disease therapy. Curr Alzheimer Res. 2012;9(1):1-4.
12. Watanabe K, Yabuki S, Sekiguchi M, Kikuchi SI, Konno SI. Etanercept attenuates pain-related behavior following compression of the dorsal root ganglion in the rat. Eur Spine J. 2011.
13. Tobinick E. Rapid improvement of chronic stroke deficits after perispinal etanercept: three consecutive cases. CNS Drugs. 2011;25(2):145-55.
14. Shen CH, Tsai RY, Tai YH, Lin SL, Chien CC, Wong CS. Intrathecal Etanercept Partially

Restores Morphine's Antinociception in Morphine-Tolerant Rats via Attenuation of the Glutamatergic Transmission. Anesth Analg. 2011;113(1):184-90.
15. Shen CH, Tsai RY, Shih MS, Lin SL, Tai YH, Chien CC, et al. Etanercept restores the antinociceptive effect of morphine and suppresses spinal neuroinflammation in morphine-tolerant rats. Anesth Analg. 2011;112(2):454-9.
16. Kowall NW. Rational Therapeutics for Alzheimer's Disease and Other Dementias. The Handbook of Alzheimer's Disease and Other Dementias. 2011:301-11.
17. Esposito E, Cuzzocrea S. Anti-TNF therapy in the injured spinal cord. Trends Pharmacol Sci. 2011;32(2):107-15.
18. Dogrul A, Gul H, Yesilyurt O, Ulas UH, Yildiz O. Systemic and spinal administration of etanercept, a tumor necrosis factor alpha inhibitor, blocks tactile allodynia in diabetic mice. Acta diabetologica. 2011;48(2):135-42.
19. Tobinick E. Perispinal etanercept: a new therapeutic paradigm in neurology. Expert Rev Neurother. 2010;10(6):985-1002.
20. McNaull BB, Todd S, McGuinness B, Passmore AP. Inflammation and anti-inflammatory strategies for Alzheimer's disease--a mini-review. Gerontology. 2010;56(1):3-14.
21. Labbate LA. Drugs for the Treatment of Dementia. In: Labbate LA, editor. Handbook of Psychiatric Drug Therapy, 6th Edition. 6th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010. p. 254-64.
22. Kato K, Liu H, Kikuchi S, Myers RR, Shubayev VI. Immediate anti-tumor necrosis factor-alpha (etanercept) therapy enhances axonal regeneration after sciatic nerve crush. J Neurosci Res. 2010;88(2):360-8.
23. Clark IA, Alleva LM, Vissel B. The roles of TNF in brain dysfunction and disease. Pharmacol Ther. 2010;128(3):519-48.
24. Chio CC, Lin JW, Chang MW, Wang CC, Yang CZ, Chang CP. Therapeutic evaluation of etanercept in a model of traumatic brain injury. J Neurochem. 2010;115(4):921-9.
25. Alamin TF, Agarwal V. Chapter 5: The Mechanisms of Pain from Intervertebral Discs. In: Phillips FM, Lauryssen C, editors. The Lumbar Intervertebral Disc: Thieme Medical Publishers, Inc.; 2010.
26. Tobinick EL, Chen K, Chen X. Rapid intracerebroventricular delivery of Cu-DOTA-etanercept after peripheral administration demonstrated by PET imaging. BMC Res Notes. 2009;2:28.
27. Tobinick E. Perispinal etanercept for neuroinflammatory disorders. Drug Discov Today. 2009;14(3-4):168-77.
28. Tobinick E. Tumour necrosis factor modulation for treatment of Alzheimer's disease: rationale and current evidence. CNS Drugs. 2009;23(9):713-25.
29. Marchand F, Tsantoulas C, Singh D, Grist J, Clark AK, Bradbury EJ, et al. Effects of Etanercept and Minocycline in a rat model of spinal cord injury. Eur J Pain. 2009;13(7):673-81.
30. Kato K, Kikuchi S, Shubayev VI, Myers RR. Distribution and tumor necrosis factor-alpha isoform binding specificity of locally administered etanercept into injured and uninjured rat sciatic nerve. Neuroscience. 2009;160(2):492-500.
31. Cohen SP, Bogduk N, Dragovich A, Buckenmaier CC, 3rd, Griffith S, Kurihara C, et al. Randomized, double-blind, placebo-controlled, dose-response, and preclinical safety study of transforaminal epidural etanercept for the treatment of sciatica. Anesthesiology.

2009;110(5):1116-26.
32. Zanella JM, Burright EN, Hildebrand K, Hobot C, Cox M, Christoferson L, et al. Effect of etanercept, a tumor necrosis factor-alpha inhibitor, on neuropathic pain in the rat chronic constriction injury model. Spine (Phila Pa 1976). 2008;33(3):227-34.
33. Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. J Neuroinflammation. 2008;5:2.
34. Tobinick EL, Gross H. Rapid improvement in verbal fluency and aphasia following perispinal etanercept in Alzheimer's disease. BMC Neurol. 2008;8:27.
35. Tobinick E. Perispinal etanercept produces rapid improvement in primary progressive aphasia: identification of a novel, rapidly reversible TNF-mediated pathophysiologic mechanism. Medscape J Med. 2008;10(6):135.
36. Rowin J. Etanercept treatment in myasthenia gravis. Ann N Y Acad Sci. 2008;1132:300-4.
37. Griffin WS. Perispinal etanercept: potential as an Alzheimer therapeutic. J Neuroinflammation. 2008;5:3.
38. Goldberg RJ. International conference on Alzheimer's disease 2008: Summary of new research: perispinal etanercept improves primary progressive aphasia. Brown University Geriatric Psychopharmacology Update. 2008;12(10):4.
39. Dahl E, Cohen SP. Perineural injection of etanercept as a treatment for postamputation pain. Clin J Pain. 2008;24(2):172-5.
40. Tobinick E. Perispinal etanercept for treatment of Alzheimer's disease. Curr Alzheimer Res. 2007;4(5):550-2.
41. Tobinick E, Gross H, Weinberger A, Cohen H. TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study. MedGenMed. 2006;8(2):25.
42. Tuzun E, Meriggioli MN, Rowin J, Yang H, Christadoss P. Myasthenia gravis patients with low plasma IL-6 and IFN-gamma benefit from etanercept treatment. J Autoimmun. 2005;24(3):261-8.
43. Tobinick E, Davoodifar S. Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: a study of clinical observations in 143 patients. Curr Med Res Opin. 2004;20(7):1075-85.
44. Sommer C, Schäfers M. Mechanisms of neuropathic pain: the role of cytokines. Drug Discovery Today: Disease Mechanisms. 2004;1(4):441-8.
45. Rowin J, Meriggioli MN, Tuzun E, Leurgans S, Christadoss P. Etanercept treatment in corticosteroid-dependent myasthenia gravis. Neurology. 2004;63(12):2390-2.
46. Genevay S, Stingelin S, Gabay C. Efficacy of etanercept in the treatment of acute, severe sciatica: a pilot study. Ann Rheum Dis. 2004;63(9):1120-3.
47. Tobinick EL, Britschgi-Davoodifar S. Perispinal TNF-alpha inhibition for discogenic pain. Swiss Med Wkly. 2003;133(11-12):170-7.
48. Chin RL, Sherman WH, Sander HW, Hays AP, Latov N. Etanercept (Enbrel) therapy for chronic inflammatory demyelinating polyneuropathy. J Neurol Sci. 2003;210(1-2):19-21.
49. Sommer C, Schafers M, Marziniak M, Toyka KV. Etanercept reduces hyperalgesia in experimental painful neuropathy. J Peripher Nerv Syst. 2001;6(2):67-72.
50. Olmarker K, Rydevik B. Selective inhibition of tumor necrosis factor-alpha prevents nucleus pulposus-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity: possible implications for future pharmacologic treatment strategies of

sciatica. Spine (Phila Pa 1976). 2001;26(8):863-9.
51. Knoblach SM, Fan L, Faden AI. Early neuronal expression of tumor necrosis factor-alpha after experimental brain injury contributes to neurological impairment. J Neuroimmunol. 1999;95(1-2):115-25.

Exhibit "D"
Selected Publications by Dr. Tobinick and his Colleagues

1. Tobinick E, Rodriguez-Romanacce H, Levine A, Ignatowski TA, Spengler RN. Immediate neurological recovery following perispinal etanercept years after brain injury. Clinical drug investigation. 2014;34(5):361-6.
2. Tobinick E, Kim NM, Reyzin G, Rodriguez-Romanacce H, DePuy V. Selective TNF inhibition for chronic stroke and traumatic brain injury: an observational study involving 629 consecutive patients treated with perispinal etanercept. CNS Drugs. 2012;26(12):1051-70.
3. Tobinick E. Deciphering the Physiology Underlying the Rapid Clinical Effects of Perispinal Etanercept in Alzheimer's Disease. Curr Alzheimer Res. 2012;9(1):99-109.
4. Tobinick E. Rapid improvement of chronic stroke deficits after perispinal etanercept: three consecutive cases. CNS Drugs. 2011;25(2):145-55.
5. Tobinick E. Perispinal etanercept: a new therapeutic paradigm in neurology. Expert Rev Neurother. 2010;10(6):985-1002.
6. Tobinick EL, Chen K, Chen X. Rapid intracerebroventricular delivery of Cu-DOTA-etanercept after peripheral administration demonstrated by PET imaging. BMC Res Notes. 2009;2:28.
7. Tobinick E. Perispinal etanercept for neuroinflammatory disorders. Drug Discov Today. 2009;14(3-4):168-77.
8. Tobinick E. Tumour necrosis factor modulation for treatment of Alzheimer's disease: rationale and current evidence. CNS Drugs. 2009;23(9):713-25.
9. Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. J Neuroinflammation. 2008;5:2.
10. Tobinick EL, Gross H. Rapid improvement in verbal fluency and aphasia following perispinal etanercept in Alzheimer's disease. BMC Neurol. 2008;8:27.
11. Tobinick E. Perispinal etanercept produces rapid improvement in primary progressive aphasia: identification of a novel, rapidly reversible TNF-mediated pathophysiologic mechanism. Medscape J Med. 2008;10(6):135.
12. Tobinick E. Perispinal etanercept for treatment of Alzheimer's disease. Curr Alzheimer Res. 2007;4(5):550-2.
13. Tobinick E, Vega CP. The cerebrospinal venous system: anatomy, physiology, and clinical implications. MedGenMed. 2006;8(1):53.
14. Tobinick E, Gross H, Weinberger A, Cohen H. TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study. MedGenMed. 2006;8(2):25.
15. Tobinick E, Davoodifar S. Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: a study of clinical observations in 143 patients. Curr Med Res Opin. 2004;20(7):1075-85.
16. Tobinick EL, Britschgi-Davoodifar S. Perispinal TNF-alpha inhibition for discogenic pain. Swiss Med Wkly. 2003;133(11-12):170-7.

INR PLLC
2300 Glades Road, Suite 305E
Boca Raton, Florida 33431
(561) 353-9707

May 17, 2013

RE: "Enbrel for Stroke and Alzheimer's", retrieved from

http://www.sciencebasedmedicine.org/index.php/enbrel-for-stroke-and-alzheimers/ on

Friday, May 17, 2013

Steven P. Novella, M.D.

64 Cobblestone Dr

Hamden, CT 06518

(203) 281-6277

via E-mail on May 17, 2013 to SNovella@theskepticsguide.org

via Certified Mail Return Receipt on May 17, 2013

Dear Dr. Novella,

I write to you directly as a result of the article, "Enbrel for Stroke and Alzheimer's", you wrote and posted on your website, sciencebasedmedicine.org, on May 8, 2013, an article that is still visible to the public. I note that your website seems to be widely read, as one of the commentors regarding the article hailed from Australia (the commentor had been previously aware of the work of my colleagues and I with perispinal etanercept). As you are aware, we have never met, nor corresponded, nor spoken, and I really was not aware

of your work until your post. I note that you are "the president and co-founder of the New England Skeptical Society, the host and producer of the popular weekly science podcast, The Skeptics' Guide to the Universe, and the author of the NeuroLogicaBlog, a daily blog that covers news and issues in neuroscience, but also general science, scientific skepticism, philosophy of science, critical thinking, and the intersection of science with the media and society." I also note that you are a board-certified Neurologist, a member of the American Academy of Neurology, and an academic clinical neurologist at the Yale University School of Medicine.

In view of the fact that we have never met or corresponded, and the content of your article, I think it may be helpful if I provide some additional scientific background regarding perispinal etanercept. Much of this information, and most of these scientific references are available on our websites, such as nrimed.com, but I include some of this information to help provide this background information for you in a convenient place.

Scientific Background

These articles provide a cogent discussion of the scientific rationale or data or discussion relevant to the use of perispinal etanercept for the treatment of selected neuroinflammatory disorders[1-69].

Pertinent scientific evidence has been accumulating in the scientific, peer-reviewed, published medical literature for more than a decade:

Etanercept, a recombinant tumor necrosis factor receptor (p75)-Fc fusion protein competitively inhibits tumor necrosis factor-alpha (TNF). Etanercept has been successfully used in patients with rheumatoid arthritis, where it reduces pain and inflammation. Because locally produced proinflammatory cytokines play a role in pain after nerve injury, we investigated whether etanercept can reduce pain and hyperalgesia in an animal model of painful neuropathy, the chronic constriction injury of the sciatic nerve. C57BL/6 mice received etanercept or sham treatment by local near-nerve injection to the injured nerve or by systemic application. Treatment with etanercept reduced thermal hyperalgesia and mechanical allodynia significantly in both modes of application. The effect of etanercept was present in animals that were treated from the time of surgery and in those that were treated from day 6, when hyperalgesia was already present. These results suggest the potential of etanercept as a treatment option for patients with neuropathic pain. *From* Sommer C, Schafers M, Marziniak M, Toyka KV: **Etanercept reduces hyperalgesia in experimental painful neuropathy.** *J Peripher Nerv Syst* 2001, 6:67-72.

STUDY DESIGN: The possibility to prevent nucleus pulposus-induced functional and structural nerve root injury by selective tumor necrosis factor-alpha inhibition was assessed in an experimental model in the pig spine. OBJECTIVE: The objective of the study was to evaluate the role of tumor necrosis factor-alpha in the mediation of nucleus pulposus-induced nerve injury by using selective inhibition. SUMMARY OF BACKGROUND DATA: The cytokine tumor necrosis factor-alpha has been suggested to play a key role in the nerve root injury induced by local application of nucleus pulposus. However, previous studies have not been able to distinguish the effects between tumor necrosis factor-alpha and other disc-related cytokines because of the use of nonspecific cytokine inhibition. METHODS: Autologous nucleus pulposus was harvested from a lumbar disc and applied to the porcine sacrococcygeal cauda equina. The pigs were simultaneously treated with two selective tumor necrosis factor-alpha inhibitors (etanercept n = 8 and infliximab n = 5), a heparin analogue (enoxaparin n = 5) or saline for control (n = 5). After 7 days the nerve conduction velocity over the application zone was determined and samples of the exposed nerve roots were collected for light microscopic evaluation. RESULTS: The two tumor necrosis factor-alpha inhibitors prevented the reduction of nerve conduction velocity and also seemed to limit the nerve fiber injury, the intracapillary thrombus formation, and the intraneural edema formation. However, treatment with enoxaparin did not seem to be different from control regarding reduction of nerve conduction velocity or histologic changes. CONCLUSIONS: The data clearly indicate that tumor necrosis factor-alpha is involved in the basic pathophysiologic events leading to nerve root structural and functional changes after local application of nucleus pulposus. The study therefore provides a basic

scientific platform with potential clinical implications regarding the use of anti-tumor necrosis factor-alpha medication as treatment in patients with disc herniation and sciatica. *From* Olmarker K, Rydevik B: **Selective inhibition of tumor necrosis factor-alpha prevents nucleus pulposus-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity: possible implications for future pharmacologic treatment strategies of sciatica.** *Spine (Phila Pa 1976)* 2001, **26**:863-869. [68]

OBJECTIVES: To analyse the cerebrospinal fluid (CSF) values of the proinflammatory cytokines, interleukin 1beta (IL1beta), tumour necrosis factor alpha (TNFalpha), GM-CSF, of the anti-inflammatory cytokine TGFbeta, of tau protein, a marker for neurodegeneration, and of beta amyloid (Abeta), a protein involved in the formation of senile plaques, in prospectively followed up patients with mild cognitive impairment (MCI). METHODS: Analyses of CSF levels of TNFalpha, IL1beta, GM-CSF, TGFbeta, betaa, and tau protein were performed using ELISA in 56 patients with MCI who were followed up prospectively and in 25 age matched, healthy controls. RESULTS: Patients with MCI displayed significantly higher levels of TNFalpha and tau protein and significantly lower levels of TGFbeta and Abeta compared with the healthy controls. After nine months of follow up, 25 patients still displayed MCI while the remaining 31 patients had progressed to Alzheimer's disease (AD). Only MCI patients who progressed to AD at follow up, showed significantly higher CSF levels of TNFalpha than controls. In addition, reduced CSF-Abeta42 levels were only found in MCI patients that progressed to AD, further supporting the notion that disturbed metabolism of Abeta is an early finding in AD. CONCLUSIONS: These results demonstrate increased production of the proinflammatory cytokine, TNFalpha and decreased production of the anti-inflammatory cytokine TGFbeta in patients with MCI at risk to develop AD, suggesting a propensity towards inflammation in this patient group and indicating that CNS inflammation is a early hallmark in the pathogenesis of AD. *From* Tarkowski E, Andreasen N, Tarkowski A, Blennow K: **Intrathecal inflammation precedes development of Alzheimer's disease.** *J Neurol Neurosurg Psychiatry* 2003, **74**:1200-1205.[32]

OBJECTIVE: To examine the potential of etanercept, a biological inhibitor of tumour necrosis factor-alpha (TNF), delivered by perispinal administration, for the treatment of pain associated with intervertebral disc disease. METHODS: Charts from 20 selected patients treated at our private clinic by perispinal delivery of etanercept 25 mg for severe, chronic, treatment-resistant discogenic pain were reviewed. Therapeutic benefit was assessed clinically and was documented by changes in a validated pain instrument, the Oswestry Disability Index. The patients

were treated off-label with etanercept as part of our usual practice of medicine. Five detailed case reports are presented, including three additional patients. RESULTS: Rapid, substantial and sustained clinical pain reduction was documented in this selected group of patients. The cohort of 20 patients had a mean age of 56.5 and mean duration of pain of 116 months. Nine of the patients had undergone previous spinal surgery; 17 had received an epidural steroid injection or injections (mean 3.2). This group of patients received a mean of 1.8 doses (range 1-5, median 1.0) of etanercept during the observation period. The mean length of follow-up was 230 days. Clinical improvement was confirmed by a decrease in the calculated Oswestry Disability Index from a mean of 54.85 +/- 12.5 at baseline, improving to 17.2 +/- 15.3 ($p < 0.003$) at 24 days and ending at 9.8 +/- 13 ($p < 0.003$) at 230 days. CONCLUSIONS: TNF inhibition by etanercept delivered by perispinal administration may offer clinical benefit for patients with chronic, treatment-resistant discogenic pain. Further study of this new treatment modality is warranted. *From* Tobinick EL, Britschgi-Davoodifar S: **Perispinal TNF-alpha inhibition for discogenic pain.** *Swiss Med Wkly* 2003, **133**:170-177. [35]

Sommer C, Schäfers M: **Mechanisms of neuropathic pain: the role of cytokines.** *Drug Discovery Today: Disease Mechanisms* 2004, **1**:441-448.

Inflammatory immune mechanisms play a central role in the causation of Alzheimer's disease (AD). Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, the "master regulator" of the immune response, is the key initiator of immune-mediated inflammation in multiple organ systems, including the brain. Scientific evidence identifying TNF-alpha involvement in the pathogenesis of AD began accumulating a decade ago in experimental models. In vitro, with use of a human monocytic cell line, beta amyloid was found to stimulate secretion of TNF-alpha. TNF-alpha plus gamma-interferon was found to induce beta-amyloid production. Beta amyloid was shown to stimulate microglial inflammatory pathways, resulting in neurotoxicity mediated by TNF-alpha generated by reactive microglia and monocytes. Clinical evidence followed, with a central place for TNF-alpha in AD pathogenesis suggested by demonstration of 25-fold elevated levels of TNF-alpha in the cerebrospinal fluid of patients with AD, and the finding that increased cerebrospinal fluid TNF-alpha levels correlated with clinical deterioration. In 2005, the evidence supporting TNF-alpha involvement in AD accelerated, including identification of a greater risk for AD in an Australian population associated with a polymorphism in the promoter region of the TNF gene.

Increasing amounts of laboratory evidence implicate TNF-alpha in inflammatory molecular mechanisms producing neurotoxicity, neuronal death, or neuronal dysfunction involving both TNF-glutamate or TNF-amyloid interactions. In a brain slice culture model, TNF-alpha was found to potentiate glutamate neurotoxicity, with TNF-alpha and glutamate acting synergistically to induce neuronal cell death. Stimulation of microglial metabotropic glutamate-2 receptors on rat primary microglia was found to induce TNF-alpha release, and contribute to microglial neurotoxicity. In cultured hypothalamic cells, glutamate was found to induce the expression and release of TNF-alpha, which was postulated to be potentially related to physiologic regulation of sleep and wakefulness. TNF-alpha both directly affects glutamatergic synaptic transmission, increasing AMPA receptors on synapses, and modulates synaptic plasticity. Of particular relevance to memory impairment in AD, beta-amyloid inhibition of long-term potentiation appears to be mediated by TNF-alpha.

Substantial laboratory evidence implicates beta-amyloid-induced neuroinflammation with neurotoxicity, and this appears to be an early event in neurodegeneration. Experimental models using beta-amyloid-stimulated murine microglia suggest that beta-amyloid-induced neuronal death may be mediated by synergy between TNF-alpha and glutamate-induced neurotoxicity. In addition to TNF-alpha, beta amyloid upregulates other inflammatory mediators in the brain, including interleukin (IL)-1 beta, IL-6, nitric oxide, and inducible nitric oxide synthase. Increasing evidence suggests that microscopic inflammation resulting from the release of inflammatory cytokines, including TNF-alpha, by amyloid-beta-activated microglia plays a central role in the neurotoxicity that occurs in AD. This hypothesis suggests that specific anti-inflammatory agents that downregulate this inflammatory process could potentially be of therapeutic benefit in AD.

Therapeutic agents that selectively inhibit the biologic activity of TNF-alpha have recently become available for human use. One of these is etanercept, a dimeric fusion protein that is produced with recombinant DNA technology and composed of 934 amino acids with a total molecular weight of 150,000 d. It consists of a fragment of the human 75-kd (p75) TNF receptor linked to the Fc portion of human immunoglobulin (Ig)G1. Etanercept binds specifically to TNF and blocks its interaction with cell-surface TNF receptors. By avidly binding excess TNF, etanercept functions as an extraordinarily potent TNF antagonist. Because of the known role of inflammation in AD pathogenesis, etanercept has been suggested as a possible therapeutic agent for AD. It is approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis, with pilot

studies and basic science investigations suggesting possible utility for a variety of neurologic disorders.

Pilot studies ("proof-of-concept" studies) in small numbers of patients are a common starting point for new therapeutic approaches. While not providing the same degree of robust scientific evidence offered by randomized, double-blind, placebo-controlled trials, pilot studies are nevertheless useful for helping to define the feasibility of a new scientific approach, and may yield valid statistical data if carefully designed, even with a minimum number of subjects. Indeed, the era of biologic anti-TNF-alpha therapy for the treatment of rheumatoid arthritis was ushered in by an open-label, uncontrolled, nonrandomized pilot study published in The Lancet in 1994 involving only 7 patients.

To investigate the feasibility of using etanercept for the treatment of AD, we initiated a 6-month, open-label pilot study.CONTEXT: Current pharmacologic treatments for Alzheimer's disease (AD) do not prevent long-term clinical deterioration. Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, has been implicated in the pathogenesis of AD. CONTEXT: Current pharmacologic treatments for Alzheimer's disease (AD) do not prevent long-term clinical deterioration. Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, has been implicated in the pathogenesis of AD....

Abstract
OBJECTIVE: To investigate the use of a biologic TNF-alpha inhibitor, etanercept was given by perispinal extrathecal administration for the treatment of AD. METHODS: This was a prospective, single-center, open-label, pilot (proof-of-concept) study, in which 15 patients with mild-to-severe AD were treated for 6 months. We administered etanercept, 25-50 mg, once weekly by perispinal administration. Main outcome measures included the Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), and the Severe Impairment Battery (SIB). RESULTS: The average age of our patient population was 76.7. The mean baseline MMSE was 18.2 (n = 15); the mean baseline ADAS-Cog was 20.8 (n = 11); and the mean baseline SIB was 62.5 (n = 5). There was significant improvement with treatment, as measured by all of the primary efficacy variables, through 6 months: MMSE increased by 2.13 -/+ 2.23, ADAS-Cog improved (decreased) by 5.48 -/+ 5.08, and SIB increased by 16.6 -/+ 14.52. CONCLUSION: An increasing amount of basic science and clinical evidence implicates inflammatory processes and resulting glial activation in the pathogenesis of AD. This small, open-label pilot study suggests that inhibition of the inflammatory cytokine TNF-alpha may hold promise as a potential approach to AD treatment. Further study in randomized, placebo-controlled clinical trials is merited. *From* Tobinick E, Gross H,

Weinberger A, Cohen H: **TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study.** *MedGenMed* 2006, **8:25.** (citations omitted). [43]

OBJECTIVE: Documentation of the clinical results obtained utilizing perispinal etanercept off-label for treatment-refractory back and neck pain in a clinical practice setting. RESEARCH DESIGN AND METHODS: The medical charts of all patients who were treated with etanercept for back or neck pain at a single private medical clinic in 2003 were reviewed retrospectively. Patients were treated if they had disc-related pain which was chronic, treatment-refractory, present every day for at least 8 h, and of moderate or severe intensity. Patients with active infection, demyelinating disease, uncontrolled diabetes, lymphoma or immunosuppression were excluded from treatment with etanercept. Etanercept 25 mg was administered by subcutaneous injection directly overlying the spine. Visual Analogue Scales (VAS, 0-10 cm) for intensity of pain, sensory disturbance, and weakness prior to and 20 min, 1 day, 1 week, 2 weeks, and 1 month after treatment were completed. Inclusion criteria for analysis required baseline and treatment VAS data. MAIN OUTCOME MEASURES: Before and after treatment VAS comparisons for intensity of pain, sensory disturbance, and weakness. RESULTS: 143 charts out of 204 met the inclusion VAS criteria. The 143 patients had a mean age of 55.8 +/- 14, duration of pain of 9.8 +/- 11 years, and an initial Oswestry Disability Index of 42.8 +/- 18, with 83% having back pain, 61% sciatica, and 33% neck pain. 30% had previous spinal surgery, and 69% had previously received epidural steroid injections (mean 3.0 +/- 3). The patients received a mean of 2.3 +/- 0.7 doses of perispinal etanercept separated by a mean interval of 13.6 +/- 16.3 days. The mean VAS intensity of pain, sensory disturbance, and weakness were significantly reduced after perispinal etanercept at 20 min, 1 day, 1 week, 2 weeks, and 1 month with a $p < 0.0001$ at each time interval for the first dose in this patient population. CONCLUSIONS: Perispinal etanercept is a new treatment modality which can lead to significant clinical improvement in selected patients with chronic, treatment-refractory disc-related pain. Generalizability of the present study results is limited by the open-label, uncontrolled methodology employed. Based on this and other accumulating recent studies, etanercept may be useful for both acute and chronic disc-related pain. Further study of this new treatment modality utilizing double-blind placebo controlled methodology is indicated. *From* Tobinick E, Davoodifar S: **Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: a study of clinical observations in 143 patients.** *Curr Med Res Opin* 2004, **20:**1075-1085. [38]

After an ischemic stroke, neurons in the core are rapidly committed to die, whereas neuron death in the slowly developing penumbra is more amenable to therapeutic intervention. Microglia activation contributes to delayed inflammation, but because neurotoxic mechanisms in the penumbra are not well understood, we developed an in vitro model of microglia activation and propagated neuron killing. To recapitulate inflammatory triggers in the core, microglia were exposed to oxygen glucose-deprived neurons and astrocytes. To model the developing penumbra, the microglia were washed and allowed to interact with healthy naive neurons and astrocytes. We found that oxygen-glucose deprivation (OGD)-stressed neurons released glutamate, which activated microglia through their group II metabotropic glutamate receptors (mGluRs). Microglia activation involved nuclear factor kappaB (NF-kappaB), a transcription factor that promotes their proinflammatory functions. The activated microglia became neurotoxic, killing naive neurons through an apoptotic mechanism that was mediated by tumor necrosis factor-alpha (TNF-alpha), and involved activation of both caspase-8 and caspase-3. In contrast to some earlier models (e.g., microglia activation by lipopolysaccharide), neurotoxicity was not decreased by an inducible nitric oxide synthase (iNOS) inhibitor (S-methylisothiourea) or a peroxynitrite scavenger [5,10,15,20-tetrakis(N-methyl-4'-pyridyl)porphinato iron (III) chloride], and did not require p38 mitogen-activated protein kinase (MAPK) activation. The same microglia neurotoxic behavior was evoked without exposure to OGD-stressed neurons, by directly activating microglial group II mGluRs with (2S,2'R,3'R)-2-(2'3'-dicarboxycyclopropyl) glycine or glutamate, which stimulated production of TNF-alpha (not nitric oxide) and mediated TNF-alpha-dependent neurotoxicity through activation of NF-kappaB (not p38 MAPK). Together, these results support potential therapeutic strategies that target microglial group II mGluRs, TNFalpha overproduction, and NF-kappaB activation to reduce neuron death in the ischemic penumbra. *From* Kaushal V, Schlichter LC: **Mechanisms of microglia-mediated neurotoxicity in a new model of the stroke penumbra.** *J Neurosci* 2008, **28**:2221-2230. [51]

BACKGROUND: Recent clinical studies point to rapid and sustained clinical, cognitive, and behavioral improvement in both Alzheimer's disease and primary progressive aphasia following weekly perispinal administration of etanercept, a TNF-alpha inhibitor that acts by blocking the binding of this cytokine to its receptors. This outcome is concordant with recent basic science studies suggesting that TNF-alpha functions in vivo as a gliotransmitter that regulates synaptic function in the brain. We hypothesized that perispinal etanercept had the potential to improve verbal function in Alzheimer's disease, so we included several standarized measures of verbal ability to evaluate language skills in a clinical trial of

perispinal etanercept for Alzheimer's disease. METHODS: This was a prospective, single-center, open-label, pilot study, in which 12 patients with mild-to-severe Alzheimer's disease were administered etanercept, 25-50 mg, weekly by perispinal administration for six months. Two additional case studies are presented. RESULTS: Two-tailed, paired t-tests were conducted comparing baseline performance to 6-month performance on all neuropsychological measures. Test batteries included the California Verbal Learning Test-Second Edition, Adult Version; Logical Memory I and II(WMS-LM-II) from the Wechsler Memory Scale-Abbreviated; the Comprehensive Trail Making Test (TMT); Boston Naming Test; and letter(FAS) and category verbal fluency. All measures revealed a significant effect except for the Boston Naming Test and the TMT-4, with WMS-LM-II being marginally significant at $p = .05$. The FAS test for letter fluency was most highly significant with a $p < 0.0007$. In addition, rapid improvement in verbal fluency and aphasia in two patients with dementia, beginning minutes after perispinal etanercept administration, is documented. CONCLUSION: In combination with the previously reported results of perispinal etanercept in Alzheimer's disease and primary progressive aphasia, these results further argue that larger scale studies of this therapeutic intervention, including Phase 3 trials, are warranted in dementias. In addition, these results may provide insight into the basic pathophysiologic mechanisms underlying Alzheimer's disease and related forms of dementia, and suggest the existence of novel, rapidly reversible, TNF-mediated pathophysiologic mechanisms in Alzheimer's disease which are worthy of further investigation. *From* Tobinick EL, Gross H: **Rapid improvement in verbal fluency and aphasia following perispinal etanercept in Alzheimer's disease.** *BMC Neurol* 2008, **8**:27. [70]

Tumour necrosis factor (TNF), a key regulator of varied physiological mechanisms in multiple organ systems, is an immune signalling molecule produced by glia, neurons, macrophages and other immune cells. In the brain, among other functions, TNF serves as a gliotransmitter, secreted by glial cells that envelope and surround synapses, which regulates synaptic communication between neurons. The role of TNF as a gliotransmitter may help explain the profound synaptic effects of TNF that have been demonstrated in the hippocampus, in the spinal cord and in a variety of experimental models. Excess TNF is present in the CSF of individuals with Alzheimer's disease (AD), and has been implicated as a mediator of the synaptic dysfunction that is hypothesized to play a central role in the pathogenesis of AD. TNF may also play a role in endothelial and microvascular dysfunction in AD, and in amyloidogenesis and amyloid-induced memory dysfunction in AD. Genetic and epidemiological evidence has implicated increased TNF production as a risk factor for AD.

Perispinal administration of etanercept, a potent anti-TNF fusion protein, produced sustained clinical improvement in a 6-month, open-label pilot study in patients with AD ranging from mild to severe. Subsequent case studies have documented rapid clinical improvement following perispinal etanercept in both AD and primary progressive aphasia, providing evidence of rapidly reversible, TNF-dependent, pathophysiological mechanisms in AD and related disorders. Perispinal etanercept for AD merits further study in randomized clinical trials. *From* Tobinick E: **Tumour necrosis factor modulation for treatment of Alzheimer's disease: rationale and current evidence.** *CNS Drugs* 2009, **23:**713-725. [4]

Tumor necrosis factor-alpha (TNF-alpha) is a central regulator of inflammation, and TNF-alpha antagonists may be effective in treating inflammatory disorders in which TNF-alpha plays an important pathogenetic role. Recombinant or modified proteins are an emerging class of therapeutic agents. To date, several recombinant or modified proteins which acts as TNF antagonists have been disclosed. In particular, antibodies that bind to and neutralise TNF have been sought as a means to inhibit TNF activity. Inhibition of TNF has proven to be an effective therapy for patients with rheumatoid arthritis and other forms of inflammatory disease including psoriasis, psoriatic arthritis, and ankylosing spondylitis, inflammatory bowel disease. Additionally, the efficacy of preventing septic shock and AIDS has been questioned as a result of recent research. The currently available therapies include a soluble p75 TNF receptor:Fc construct, etanercept, a chimeric monoclonal antibody, infliximab, and a fully human monoclonal antibody, adalimumab. Certolizumab pegol is a novel TNF inhibitor which is an antigen-binding domain of a humanized TNF antibody coupled to polyethylene glycol (PEG) to increase half-life, and thus is Fc-domain-free. In this review, we discuss briefly the present understanding of TNF-alpha-mediated biology and the current therapies in clinical use, and focus on some of the new therapeutic approaches with small-molecule inhibitors. Moreover, we examine recent reports providing important insights into the understanding of efficacy of thalidomide and its analogs, as TNF-alpha activity inhibitories, especially in therapies of several inflammatory diseases within the nervous system. *From* Esposito E, Cuzzocrea S: **TNF-alpha as a therapeutic target in inflammatory diseases, ischemia-reperfusion injury and trauma.** *Curr Med Chem* 2009, **16:**3152-3167. [13]

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. *From* Tobinick E: **Perispinal etanercept for neuroinflammatory disorders.** *Drug Discov Today* 2009, **14:**168-177. [5]

Since anti-TNF agents are administered parenterally in the noncerebral diseases discussed above, they unsurprisingly encounter no particular anatomical barrier preventing access to the site of pathology. Clearly, a drawback with testing these agents against putative TNF-driven encephalopathies is that they are about as large as albumin and globulin, so cannot be expected to pass the bloodbrain barrier efficiently, where, as discussed in various Sections of this review, much evidence is consistent with excess TNF being harmful. One group has addressed the challenge of brain access through adapting a lesson from the basic aviation medicine literature, in which the effects of 5 min of head-down positioning allows appreciable albumin and globulin to enter the CSF, probably though the choroid plexus (Wen et al., 1994). Indeed, these authors suggested this manoeuvre as a way to get large molecules in to the brain for therapeutic purposes. Combined with an injection route for etanercept that drains into Batson's plexus, this has been used with the intention of accessing the CSF via the choroid plexus. In 2006 an open trial with etanercept injected by this route, in which 15 Alzheimer's patients were treated for 6 months, was published (Tobinick et al., 2006), as have case reports since (Tobinick & Gross, 2008). Etanercept administered in this way has recently been shown to reach the cerebral ventricles in the rat (Tobinick et al., 2009). This argues that this route is much less invasive but functionally equivalent to i.c.v., which is routinely used for anti-TNF biological agents of this size to access the CSF in basic animal studies on roles of TNF in brain function (Medeiros et al., 2007; Galic et al., 2008; Riazi et al., 2008; Liesz et al., 2009). We note that a similar challenge is addressed when treating brain-sited lymphoma with rituximab, a monoclonal antibody effective against non-Hodgkin lymphoma, which expresses CD20, the target of the antibody. Unfortunately its normal intravenous route for non-cerebral lymphomas is ineffective (Rubenstein et al., 2003), so intraventricular administration was seen as the logical alternative. It was successful in a Phase I trial (Rubenstein et al., 2007), but it would be of practical interest to establish whether the less invasive Batson's

plexus route, above, will prove to be equally efficacious. Arguments in favour of this route in neutralizing brain TNF have recently been reviewed (Tobinick, 2010).

Despite the direction of the literature, calls for a double-blind human Alzheimer's trial using etanercept by this route (Tobinick et al., 2006) have not yet attracted industry or government funding. This is in marked contrast to the readiness, in 1993 (see Section 6.2.2), of the manufacturers of another of the above anti-TNF agents to expand a very similar open trial on rheumatoid arthritis (Elliott et al., 1993) into a double-blind study (Elliott et al., 1994). We note, however, that an essentially identical trial except it is to employ etanercept subcutaneously, is soon to begin (see http://www.clinicaltrials.gov/ct2/show/NCT01068353). In view of the albumin-like size of this biomolecular construct, and a previous blinded trial (fewer subjects, but over 24 weeks) employing this route having a negative outcome (Bohac et al., 2002), giving funding precedence to a trial using this route is surprising. The challenge in getting etanercept to where it matters in Alzheimer's disease is, in addition to the rituximab example (previous paragraph), also addressed by studies in which intravenous infliximab, a similar sized molecule, can be presumed not to have entered the CSF because TNF levels in this compartment remained unchanged (Andersson et al., 2006; Kikuchi et al., 2008).

In 2003 a promising high-affinity inhibitor of human TNF was discovered to be secreted by Tanapox virus (Brunetti et al., 2003). From its molecular weight (Rahman et al., 2006), its inability to pass the blood brain barrier will still be a concern for using this protein to treat cerebral conditions, but its extraordinarily high activity compared to neutralizing specific antibodies against TNF has encouraged commercial development as VT-346, with Alzheimer's disease as well as rheumatoid arthritis and Crohn's disease the stated targets (March 16 2010 press release at www.vironinc.com). Others (see http://www.bionity.com/news/e/107293) are developing TNF neutralizing antibodies, of a type (Harmsen & De Haard, 2007) small enough to pass the blood brain barrier, for systemic use in human disease. These nanobodies are an attractive second generation drug, but like VT-346 are some years away from clinical trials. In contrast, infliximab, etanercept and adalimumab, already administered to millions of people annually in relative safety, have an immediate attraction for dealing with the large-scale clinical challenge already present, particularly in Alzheimer's disease, provided it actually gets into the CSF. *From* Clark IA, Alleva LM, Vissel B: **The roles of TNF in brain dysfunction and disease.** *Pharmacol Ther* 2010, **128**:519-548. [16]

Abstract: Until recently, the central nervous system (CNS) has been thought to be an immune privileged organ. However, it is now understood that neuroinflammation is linked with the development of several CNS diseases including late-onset Alzheimer's disease (LOAD). The development of inflammation is a complex process involving a wide array of molecular interactions which in the CNS remains to be further characterized. The development of neuroinflammation may represent an important link between the early stages of LOAD and its pathological outcome. It is proposed that risks for LOAD, which include genetic, biological and environmental factors can each contribute to impairment of normal CNS regulation and function. The links between risk factors and the development of neuroinflammation are numerous and involve many complex interactions which contribute to vascular compromise, oxidative stress and ultimately neuroinflammation. Once this cascade of events is initiated, the process of neuroinflammation can become overactivated resulting in further cellular damage and loss of neuronal function. Additionally, neuroinflammation has been associated with the formation of amyloid plaques and neurofibrillary tangles, the pathological hallmarks of LOAD. Increased levels of inflammatory markers have been correlated with an advanced cognitive impairment. Based on this knowledge, new therapies aimed at limiting onset of neuroinflammation could arrest or even reverse the development of the disease. *From* McNaull BB, Todd S, McGuinness B, Passmore AP: **Inflammation and anti-inflammatory strategies for Alzheimer's disease--a mini-review.** *Gerontology* 2010, **56**:3-14. [17]

TNF-alpha is thought to be the main regulator of the pro-inflammatory response in the brain. Evidence suggests that TNF-alpha overproduction is likely one of the key events leading to LOAD pathogenesis. TNF-alpha is pro-duced by microglia and overproduction has been linked with neuronal cell death. Cultured brain slices in vitro show TNF-alpha increases neuronal glutamate neurotoxicity and leads to cellular damage and death. Animal models of LOAD have indicated that TNF-alpha upregulation can lead to increased beta-Amyloid and NFT formation. It is therefore interesting that spinal levels of TNF-alpha in AD patients are increased up to 25-fold and that levels of spinal TNF-alpha correlate with clinical deterioration of LOAD. Recently, therapeutic agents that inhibit TNF-alpha activity were shown to improve and reverse cognitive decline in some patients . This exciting finding provides solid evidence for the role of TNF-alpha in the development of LOAD and strongly suggests that onset of neuroinflammation is central to LOAD onset. *From* McNaull BB, Todd S, McGuinness B, Passmore AP: **Inflammation and anti-inflammatory strategies for Alzheimer's disease--a mini-review.** *Gerontology* 2010, **56**:3-14. [17]

Etanercept is a potent antagonist of TNF, a pleotropic immune signaling molecule that is also a pivotal regulator of synaptic function. Excess TNF is centrally involved in the pathogenesis of a variety of inflammatory neurological disorders, including Alzheimer's disease, sciatica, traumatic brain injury and spinal cord injury. Perispinal etanercept produces rapid improvement in both Alzheimer's disease and sciatica and in other forms of disc-related pain. Basic research and the observed clinical effects suggest that etanercept has the surprising ability to penetrate into the cerebrospinal fluid after perispinal administration. Perispinal administration is a novel method of delivery designed to introduce this anti-TNF molecule into the bidirectional cerebrospinal venous system and the cerebrospinal fluid to facilitate its selective delivery to either spinal structures or the brain. The scientific rationale, physiologic mechanisms, clinical effects and potential clinical indications of this therapeutic approach are the subject of this article. *From* Tobinick E: **Perispinal etanercept: a new therapeutic paradigm in neurology.** *Expert Rev Neurother* 2010, **10**:985-1002. [3]

At the time of approval of etanercept by the FDA, the role of TNF in neurological disorders was incompletely understood. Novel methods of drug delivery were needed because of the high molecular weight of etanercept and the problems faced by large molecules in traversing the blood-brain barrier(BBB). Perispinal methods were designed for selective delivery of etanercept. Perispinal administration results in rapid local delivery of etanercept to the vertebral venous system and the cerebrospinal fluid (CSF), with rapid local delivery to sites of TNF excess. Rapid response suggests immediate neutralization of excess TNF, resulting in normalization of synaptic mechanisms. *From* Esposito E, Cuzzocrea S: **Anti-TNF therapy in the injured spinal cord.** *Trends Pharmacol Sci* 2011, **32**:107-115. [6]

Inflammation plays an important role in the pathogenesis of Alzheimer's disease (AD). Overexpression of tumor necrosis factor-alpha (TNF-alpha) occurs in the AD brain. Recent clinical studies have shown that the anti-TNF-alpha therapy improves cognition function of AD patients rapidly. However, the underlying mechanism remains elusive. The present study investigates the effects of intracerebroventricular injection of the monoclonal TNF-alpha antibody, Infliximab, on the pathological features of AD in the APP/PS1 double transgenic mice. We found that Infliximab administration reduced the levels of TNF-alpha, amyloid plaques, and tau phosphorylation as early as three days after daily injection of 150 mug Infliximab for three days. The number of CD11c-positive dendritic-like cells and the expression of CD11c were found to be increased concurrently after Infliximab injection. These data suggested that the

CD11c-positive dendritic-like cells might contribute to the Infliximab-induced reduction of AD-like pathology. Furthermore, our results support the use of anti-TNF-alpha for the treatment of AD. *From* Shi JQ, Shen W, Chen J, Wang BR, Zhong LL, Zhu YW, Zhu HQ, Zhang QQ, Zhang YD, Xu J: **Anti-TNF-alpha reduces amyloid plaques and tau phosphorylation and induces CD11c-positive dendritic-like cell in the APP/PS1 transgenic mouse brains.** *Brain Res* 2011, **1368:**239-247.[57]

PURPOSE: TNFalpha is an inflammatory mediator related to neuropathic pain including sciatica. Much basic research suggests that anti-TNFalpha therapy may be useful for the treatment of sciatica. The purpose of this study was to clarify the effects of etanercept in a dorsal root ganglion (DRG) compression model. METHODS: Adult male Sprague-Dawley rats (200-250 g, n = 60) were used. An L-shaped stainless rod was used to compress the left L5 DRG in the saline and etanercept groups. No rod was used in the sham group. In the etanercept group, 1 mg of etanercept was applied locally onto the DRG at the end of surgery. Saline was applied in the saline and sham groups. On day 3 and day 7 after surgery, the number of ED1-immunoreactive (IR) cells (macrophages) in the DRG was calculated by immunohistochemical methods (n = 6). In addition, double-immunofluorescence labeling for ED1 and TNFalpha was performed. Behavioral testing with von Frey filaments and a heat stimulator was performed (n = 12). RESULTS: ED1-IR cells in the DRG significantly increased in the control group compared with the sham group ($p < 0.05$). Some ED1-IR cells were co-labeled for TNFalpha. In the etanercept group, decrease in mechanical threshold was significantly inhibited compared with the saline group ($p < 0.05$). Thermal hyperalgesia was observed in the control group, but in neither the sham nor etanercept group ($p < 0.05$). CONCLUSION: Etanercept attenuated the pain-related behavior induced by DRG compression. These findings suggest that mechanical effects on the DRG might be reduced by etanercept in addition to the effects on nucleus pulposus in lumbar disc herniation. *From* Watanabe K, Yabuki S, Sekiguchi M, Kikuchi SI, Konno SI: **Etanercept attenuates pain-related behavior following compression of the dorsal root ganglion in the rat.** *Eur Spine J* 2011.

BACKGROUND: Thrombolytic therapy reduces stroke size and disability by reperfusion and salvage of ischaemic penumbra. Emerging evidence suggests that retrieved penumbra may be the site of ongoing inflammatory pathology that includes extensive microglial activation. Microglial activation may be associated with excessive levels of tumour necrosis factor (TNF) and resultant neurotoxicity. Etanercept, a potent biologic

TNF antagonist, reduces microglial activation in experimental models and has been therapeutically effective in models of brain and neuronal injury. Perispinal administration of etanercept, previously reported to be beneficial for the treatment of Alzheimer's disease, may facilitate delivery of etanercept into the brain. OBJECTIVE: The objective of this report is to document the initial clinical response to perispinal etanercept in the first chronic stroke cohort so treated. METHODS: Three consecutive patients with stable and persistent chronic neurological deficits due to strokes that had failed to resolve despite previous treatment and rehabilitation were evaluated at an outpatient clinic. They were treated off-label with perispinal etanercept as part of the clinic's practice of medicine. RESULTS: All three patients had chronic hemiparesis, in addition to other stroke deficits. Their stroke distributions were right middle cerebral artery (MCA), brainstem (medulla) and left MCA. The two patients with MCA strokes had both received acute thrombolytic therapy. Each of the three patients was treated with an initial dose of perispinal etanercept 13, 35 and 36 months following their acute stroke, respectively. Significant clinical improvement following perispinal etanercept administration was observed in all patients. Onset of clinical response was evident within 10 minutes of perispinal injection in all patients. Improvements in hemiparesis, gait, hand function, hemi-sensory deficits, spatial perception, speech, cognition and behaviour were noted among the patients treated. Each patient received a second perispinal etanercept dose at 22-26 days after the first dose that was followed by additional clinical improvement. CONCLUSIONS: Open-label administration of perispinal etanercept resulted in rapid neurological improvement in three consecutive patients with chronic neurological dysfunction due to strokes occurring 13-36 months earlier. These results suggest that stroke may result in chronic TNF-mediated pathophysiology that may be amenable to therapeutic intervention long after the acute event. Randomized clinical trials of perispinal etanercept for selected patients with chronic neurological dysfunction following stroke are indicated. *From* Tobinick E: **Rapid improvement of chronic stroke deficits after perispinal etanercept: three consecutive cases.** *CNS Drugs* 2011, **25**:145-155. [24]

STUDY DESIGN: Prospective randomized trial. OBJECTIVE: To examine the effect of the tumor necrosis factor alpha (TNF-alpha) inhibitor, etanercept, on radicular pain by its epidural administration onto spinal nerves in patients with lumbar spinal stenosis. SUMMARY OF BACKGROUND DATA: TNF-alpha is thought to play a crucial role in the radicular pain caused by lumbar disc herniation and spinal stenosis. Intravenous infusion of infliximab for sciatica has been examined in 2 studies; however, the results were equivocal. METHODS: Eighty patients with low back and radicular leg pain were investigated. We diagnosed the

patients by physical examination, and X-ray and magnetic resonance imaging. In 40 patients, we epidurally administered 2.0 mL of lidocaine and 10 mg of etanercept onto the affected spinal nerve, and 2.0 mL of lidocaine and 3.3 mg of dexamethasone was used in 40 patients. Low back pain, leg pain, and leg numbness were evaluated using a visual analogue scale (VAS) and Oswestry Disability Index (ODI) score before and for 1 month after epidural administration. RESULTS: Low back pain, leg pain, and leg numbness in the 2 groups were not significantly different before epidural administration. Epidural administration of etanercept was more effective than dexamethasone for leg pain (3 days, and 1, 2, and 4 weeks: $P < 0.05$), low back pain (3 days, and 1 and 2 weeks: $P < 0.05$), and leg numbness (3 days, and 1 and 2 weeks: $P < 0.05$). No adverse event was observed in either group. CONCLUSION: Our results indicate that epidural administration of a TNF-alpha inhibitor onto the spinal nerve produced pain relief, but no adverse event. TNF-alpha inhibitors may be useful tools for the treatment of radicular pain caused by spinal stenosis. *From* Ohtori S, Miyagi M, Eguchi Y, Inoue G, Orita S, Ochiai N, Kishida S, Kuniyoshi K, Nakamura J, Aoki Y, et al: **Epidural administration of spinal nerves with the tumor necrosis factor-alpha inhibitor, etanercept, compared with dexamethasone for treatment of sciatica in patients with lumbar spinal stenosis: a prospective randomized study.** *Spine (Phila Pa 1976)* 2012, **37**:439-444. [30]

Excess tumor necrosis factor (TNF) plays a pivotal role in the pathogenesis of Alzheimer's disease(AD). Clinical improvement following perispinal administration of etanercept in patients with Alzheimer's disease and other forms of dementia and brain dysfunction is characteristically evident within minutes. The rapidity and constellation of the clinical effects across multiple domains (cognition, mood, memory, motor function, and attention) suggest they are mediated by non-synaptic signaling mechanisms previously unrecognized for etanercept. These mechanisms likely extend beyond the known roles of TNF as a gliotransmitter that modulates synaptic strength, synaptic scaling, and AMPA receptor trafficking. Preliminary basic science and clinical investigation suggests that perispinal administration of etanercept may lead to its rapid penetration into the cerebrospinal fluid (CSF) within the cerebral ventricles. Diffusion of large molecules into the periventricular brain parenchyma is known to occur, but this process may not be sufficient to explain the rapidity of the clinical effects. There exist populations of cells, including CSF-contacting neurons and modified ependymal cells called tanycytes, that have receptive surfaces in direct contact with the CSF. It is hypothesized that the rapid clinical effects of perispinal etanercept involve non-synaptic signal transduction across the ependymal barrier and into neuronal networks via these CSF-contacting cells. This hypothesis challenges the dogma that penetration of a

therapeutic into the cerebral parenchyma through the endothelium of the cerebral vasculature (the so-called blood- brain barrier) is necessary to produce rapid clinical effects in AD. CSF-contacting cells may constitute a therapeutic target for a diverse group of brain, psychiatric and spinal disorders. *From* Tobinick E: **Deciphering the physiology underlying the rapid clinical effects of perispinal etanercept in Alzheimer's disease.** *Curr Alzheimer Res* 2012, 9:99-109.[1]

It is well known that the inflammatory response plays an important role in AD and other tauopathies, and that a chronic inflammatory state, including diabetes mellitus, hypertension and periodontitis, is a risk factor for AD. Beta-amyloid deposition is considered to be an important inducer of the chronic inflammatory response. A relationship between NFT burden and microglial activation has also been demonstrated....Interestingly, microglial activation precedes NFT formation, and administration of an immunosuppressant, FK506, ameliorates microgliosis and tau pathology in a P301S mutant tau Tg mouse model. Several clinical trials targeting inflamation have been conducted....A single centre, open label, small group study indicated that prespinal injection of etanercept, a tumour necrosis factor inhibitor used for treatment of rheumatoid arthritis, improved cognition in AD patients. A phase II, double blind, placebo controlled study of etanercept in AD patients is ongoing (http://clinicaltrials.gov/ct2/show/NCT01068353). *From* Yoshiyama Y, Lee VM, Trojanowski JQ: **Therapeutic strategies for tau mediated neurodegeneration.** *J Neurol Neurosurg Psychiatry* 2012. [62]

Alzheimer disease has also been linked to increase expression of inflammatory cytokines, and microglial activation has been observed in AD post mortem and in vivo....An increase in TNF-alpha is associated with cognitive decline in AD. In mouse models of AD, TNF-alpha is implicated in enhanced amyloid production, tau hyperphosphorylation, and cell death, and countering TNF-alpha improves both symptoms and pathology. Beta-amyloid aggregation in mouse hippocampus and cortex has also been induced by inflammation. *From* Perry DC, Lehmann M, Yokoyama JS, Karydas A, Lee JJ, Coppola G, Grinberg LT, Geschwind D, Seeley WW, Miller BL, et al: **Progranulin Mutations as Risk Factors for Alzheimer Disease.** *JAMA Neurol* 2013:1-5.[61]

Abstract

Background

Tumor necrosis factor-alpha (TNF-α) is elevated early in injured brain after traumatic brain injury (TBI), in humans and in animals. Etanercept (a TNF-α antagonist with anti-inflammatory effects) attenuates TBI in rats by reducing both microglial and astrocytic activation and increased serum levels of TNF-α. However, it is not known whether etanercept improves outcomes of TBI by attenuating microglia-associated, astrocytes-associated, and/or neurons-associated TNF-α expression in ischemic brain. A well clinically relevant rat model, where a lateral fluid percussion is combined with systemic administration of etanercept immediately after TBI, was used. The neurological severity score and motor function was measured on all rats preinjury and on day 3 after etanercept administration. At the same time, the neuronal and glial production of TNF-α was measured by Immunofluorescence staining. In addition, TNFα contents of ischemic cerebral homogenates was measured using commercial enzyme-linked immunosorbent assay kits.

Results

In addition to inducing brain ischemia as well as neurological and motor deficits, TBI caused significantly higher numbers of microglia-TNF-α double positive cells, but not neurons-TNF-α or astrocytes-TNF-α double positive cells in the injured brain areas than did the sham operated controls, when evaluated 3 days after TBI. The TBI-induced cerebral ischemia, neurological motor deficits, and increased numbers of microglia-TNF-α double positive cells and increased TNF-α levels in the injured brain were all significantly attenuated by etanercept therapy.

Conclusion

This finding indicates that early microglia overproduction of TNF-α in the injured brain region after TBI contributes to cerebral ischemia and neurological motor deficits, which can be attenuated by etanercept therapy. Studies in this model could provide insight into the mechanisms underlying neurological motor disturbance in brain-injured patients. *From* Chio CC, Chang CH, Wang CC, Cheong CU, Chao CM, Cheng BC, Yang CZ, Chang CP: **Etanercept attenuates traumatic brain injury in rats by reducing early microglial expression of tumor necrosis factor-alpha.** *BMC Neurosci* 2013, **14**:33. [67]

Inhibiting tumor necrosis factor-alpha (TNF-α) with etanercept is effective for attenuating TBI-induced cerebral contusion, motor and cognitive dysfunction, astrocytic and microglial activation, and activated inflammation [11, 12]. *From* Cheong CU, Chang CP, Chao CM, Cheng BC, Yang CZ, Chio CC: **Etanercept attentuates traumatic brain injury in rats by reducing brain TNF-alpha contents and**

by stimulating newly formed neurogenesis. *Mediators of Inflammation* 2013, **2013 Article ID 620837, 9 pages.** [66]

5. Conclusion
The current study demonstrates that TBI, in addition to inducing cerebral contusion and neurological motor deficits, induces the overproduction of TNF-α as well as the increased numbers of the colocalizations of BrdU and DCX specific markers in the contused bran tissues. Levels of etanercept can be detected in brain following systemic delivery of etanercept to TBI animals. In addition, cerebral contusion, neurological motor deficits, and increased brain contents of TNF-α can be attenuated, whereas the increased numbers of colocalizations of BrdU and DCX specific markers in the contused brain tissue can be enhanced by etanercept therapy during TBI. Thus, it appears that etanercept attenuates TBI in rats by reducing TNF-α contents and by enhancing newly formed neurogenesis in the contused brain tissues. *From* Cheong CU, Chang CP, Chao CM, Cheng BC, Yang CZ, Chio CC: **Etanercept attentuates traumatic brain injury in rats by reducing brain TNF-alpha contents and by stimulating newly formed neurogenesis.** *Mediators of Inflammation* 2013, **2013 Article ID 620837, 9 pages.** [66]

Kumar A, Stoica BA, Sabirzhanov B, Burns MP, Faden AI, Loane DJ: **Traumatic brain injury in aged animals increases lesion size and chronically alters microglial/macrophage classical and alternative activation states.** *Neurobiol Aging* 2013, **34:**1397-1411. [65]

King MD, Alleyne CH, Jr., Dhandapani KM: **TNF-alpha receptor antagonist, R-7050, improves neurological outcomes following intracerebral hemorrhage in mice.** *Neurosci Lett* 2013. [11]

Abstract
A single traumatic brain injury is associated with an increased risk of dementia and, in a proportion of patients surviving a year or more from injury, the development of hallmark Alzheimer's disease-like pathologies. However, the pathological processes linking traumatic brain injury and neurodegenerative disease remain poorly understood. Growing evidence supports a role for neuroinflammation in the development of Alzheimer's disease. In contrast, little is known about the neuroinflammatory response to brain injury and, in particular, its temporal dynamics and any potential role in neurodegeneration. Cases of traumatic brain injury with survivals ranging from 10 h to 47 years post injury (n = 52) and age-matched, uninjured control subjects (n = 44) were selected from the Glasgow

> Traumatic Brain Injury archive. From these, sections of the corpus callosum and adjacent parasaggital cortex were examined for microglial density and morphology, and for indices of white matter pathology and integrity. With survival of >/=3 months from injury, cases with traumatic brain injury frequently displayed extensive, densely packed, reactive microglia (CR3/43- and/or CD68-immunoreactive), a pathology not seen in control subjects or acutely injured cases. Of particular note, these reactive microglia were present in 28% of cases with survival of >1 year and up to 18 years post-trauma. In cases displaying this inflammatory pathology, evidence of ongoing white matter degradation could also be observed. Moreover, there was a 25% reduction in the corpus callosum thickness with survival >1 year post-injury. These data present striking evidence of persistent inflammation and ongoing white matter degeneration for many years after just a single traumatic brain injury in humans. Future studies to determine whether inflammation occurs in response to or, conversely, promotes white matter degeneration will be important. These findings may provide parallels for studying neurodegenerative disease, with traumatic brain injury patients serving as a model for longitudinal investigations, in particular with a view to identifying potential therapeutic interventions. *From* Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W: **Inflammation and white matter degeneration persist for years after a single traumatic brain injury.** *Brain* 2013, **136**:28-42. [10]

Dr. Novella, it takes a long time for new ideas in medicine and science to disseminate. Perispinal etanercept, despite the fact that it remains an emerging treatment option that is unfamiliar to many, has received scientific recognition from independent academic scientists and physicians, as one may ascertain by examining the list of scientific publications that have cited our perispinal etanercept publications, now numbering in the hundreds. I list just a sample of the recent publications and textbooks[6-9, 16-18, 20-23, 26, 28, 29, 31, 39, 50, 53-55, 57, 59, 60, 62, 71-127]. You may not be aware of the international interest in this area of work. Just a single example is the international symposium that took place in Basel, Switzerland in May 2012 entitled "*Meeting on the*

roles of TNF in brain dysfunction and disease." This international conference included presentations by internationals scientists, including pioneers in the field.

There is additional evidence, some of which has been presented at recent international conferences. For example, in 2012, at the world's largest Alzheimer conference, the Alzheimer's Association International Conference, the following presentation was made, published as P2-374 in Alzheimer's and Dementia, Volume 8, Issue 4, Supplement, July 2012:

> EFFECTS OF ANTI-TNF THERAPY ON AMYLOID PATHOLOGY AND NEUROINFLAMMATION IN 12- MONTH-OLD ARCAß TRANSGENIC MICE
>
> Jordan McAfoose, Luka Kulic, Tobias Welt, Claudia Spɛani, Rebecca Derungs, Armanda Pfister, Roger Nitsch, Division of Psychiatry Research, University of Zurich, Zurich, Switzerland.
>
> Background: In 2008, Tobinick and colleagues demonstrated that Etanercept anti-TNF therapy could be used for the treatment of AD. Although this treatment approach has advanced to Phase II clinical trial the underlying therapeutic mechanisms remain unknown.
>
> Methods: To identify the mechanisms we launched an AD mouse model study, in which we infused Etanercept or vehicle control into the ventricles of arcAb mice over 28 days using ALZET osmotic minipumps; with an additional 15 non-treated transgenic and wildtype mice as a further controls. All mice underwent general health and neurological examination, as well as, cognitive assessment before they were sacrificed for further biochemical and histological analyses.
>
> Results: Our findings demonstrated a treatment dependent improvement in cognitive performance in two hippocampus-dependent cognitive tests. Biochemical analyses suggested that the improvement in cognition was not associated with changes in soluble brain Abeta levels but rather a decrease in Formic acid insoluble Abeta levels. Histological analysis demonstrated a treatment-induced lowering of Abeta plaques and an increased clearance of Abeta plaques towards the vasculature.Stainings against GFAP and Iba1 further demonstrated a reduction in astrocytosis with parallel elevations in microglia activation.

> Conclusions: These findings suggest a neuroinflammatory and amyloid-lowering mechanism of anti-TNF therapy, in which Abeta is solubilized and cleared towards the vasculature.

These favorable basic science findings provide a mechanistic explanation for the favorable clinical results that have been published. Professor Sue Griffin, Co-Editor of the Journal of Neuroinflammation, discussed her experience when she flew out to visit our office and observe perispinal etanercept treatment firsthand. in her published Commentary, based upon her own eyewitness account[50]:

> In this section, my comments reflect my own thoughts on this treatment strategy and my own experiences in viewing it, and are accompanied by a few of my own remarks directed toward the necessity of giving attention to this novel treatment. I first became aware of this treatment when a reporter from *The Los Angeles Times* contacted me in 2006 for a comment on an article he was writing on a novel and successful Alzheimer treatment trial. Although my interest was piqued by this, it was only more recently when Dr. Tobinick contacted me and sent a preprint of the findings discussed in the *Times* [3] that I decided to go and see for myself the treatment and talk to the patients and family members. I called the day before, and was invited to visit the next day, November 7, 2007. Each of the three patients I saw treated had been tested and diagnosed with probable Alzheimer's disease by a neurologist before perispinal etanercept treatment had begun. They and their families invited me to be present during the treatment and in the interviews before and after. I noticed clinical improvement in each of the three patients within minutes following treatment. My first impression was that there was a clear, easily discernible, difference in each. They were more cheerful, more at ease, and more attentive. My impressions were the same as those shared by each of the families (please see the movie for example). This rapid turn around brought to mind the first time, now almost two decades ago[17], that I was the original witness to the remarkable overexpression of immune cytokines in activated glia in Alzheimer patients and even in fetuses and neonates with Down's syndrome – I was amazed!

There are additional scientific references on our websites; you allude to our websites in your article. In fact, you state "*On his website he cites many studies, but none of them establish the effectiveness of Enbrel for any of the conditions he is treating.*" Your statement is simply false. For example, as you are aware, my colleagues and I do continue to use perispinal etanercept for sciatica associated with disc herniation or spinal stenosis in selected patients. Our first peer-reviewed articles published in 2003 and 2004 (my colleagues and I were the first to report the clinical effects of etanercept for disc-related pain and sciatica[33, 35, 38]), and there are now published, peer-reviewed randomized, double-blind, controlled studies that are positive (e.g. [30]). As our published articles have documented, my colleagues and I have more than a decade of favorable clinical experience using etanercept for sciatica and related conditions. Considering the published clinical evidence, including the published, randomized double-blind evidence, and multiple positive basic science studies, it is clear that your statement is misguided and not in the best interests of science, medicine, or the public[3, 23, 25, 30, 37-39, 52, 55, 69, 97, 127, 128].

Thus, in view of the published, peer-reviewed scientific literature, including randomized, controlled studies; the eyewitness accounts from prominent experts and journalists; and the fact that you never met me, I was shocked at the content and tone and conclusions of your article. You use words like "dubious", "quack" and "fraud", and "exploitation" and overall paint a false and highly defamatory picture, seemingly based mainly upon a newspaper article written about a single patient by a newspaper reporter who never even visited our medical office, and never met the patient in question. You have never even

called me to ask about our results. Rather than advance medical science, your defamatory attack on my work and that of my colleagues could well have a chilling effect on the science-based and rationale use of existing therapeutics for off-label indications, uses that may be of significant benefit for patients with intractable medical conditions[129-131]. Moreover, I do not believe that your public defamatory attack on me, particularly in view of the evidence elaborated herein and present in the medical literature, is consistent with the ethical guidelines of our profession and the American Academy of Neurology.

In view of the above, I request that you immediately retract your article; it is not in the public interest, and it is both false and defamatory. I request that you also retract any related defamatory postings, and refrain from such activity in the future. At this time, I also invite you to visit our medical office, and learn about what we do, and find out for yourself about the potential of perispinal etanercept in Neurology.

Sincerely,

Edward Tobinick M.D.

Attachment: Tobinick E: **Perispinal etanercept: a new therapeutic paradigm in neurology.** *Expert Rev Neurother* 2010, 10:985-1002.

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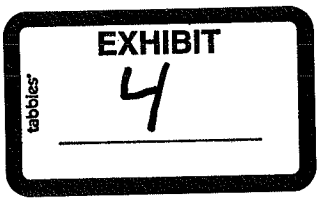
Re: Institute of Neurological Recovery and Dr. Tobinick adv. Dr. Steven Novella, Yale and Science-Based Medicine, Inc.

Dear Sirs:

Please be advised that the undersigned law firm has been retained by the Institute of Neurological Recovery, INR PLLC and Dr. Edward Tobinick MD (collectively "our clients"). We write to you in furtherance of the above referenced matter in connection with an article written by Steven Novella, MD, Founder and Executive Director, and published by Science-based Medicine ("SBM") on its Science-Based Medicine website, registered to SGU Productions, LLC, and entitled "Enbrel for Stroke and Alzheimer's". The article can be found at http://www.sciencebasedmedicine.org/enbrel-for-stroke-and-alzheimers/ (the "Article"). As you know, Dr. Novella is the founder of SBM, and a neurologist who provides commercial services for patients after stroke at the Yale Neurology Clinic ("YNC") and at the Yale Botulinum Program ("YBP"). One of the common commercial services provided at the YBP is the use of Botox® for treatment of post-stroke spasticity, an FDA-approved use of Botox® that directly competes with the medical services provided by our clients.



A simple Google® search of our client, Dr. Tobinick, locates the Article within the first couple of hits. This reality is problematic as the Article is extremely inflammatory and defamatory in nature as it contains multiple false and misleading statements of fact regarding our clients. For example, Dr. Novella's Article falsely asserts that our client, the Institute of Neurological Recovery is, "*a one-man institute*". The fact is that the Institute employs multiple physicians, a fact that is plainly apparent from even casual perusal of our client's publications, such as Tobinick, E., N.M. Kim, G. Reyzin, H. Rodriguez-Romanacce, and V. Depuy, *Selective TNF Inhibition for Chronic Stroke and Traumatic Brain Injury : An Observational Study Involving 629 Consecutive Patients Treated with Perispinal Etanercept.* CNS Drugs, 2012. **26**(12): p. 1051-70.

Another false and malicious statement within the Article is the suggestion that "*Tobinick has since moved his clinic to Florida, which is a very quack-friendly state*." Again, this statement is false and misleading. A response is not necessary to the outrageous suggestion that "Florida…is a quack friendly state", and its negative implications against our clients, but had your organization and/or Dr. Novella conducted even a hint of research, it and he would have been learned that our clients' California offices were open at the time the article published, and the California office remains in operation today.

Yet another example of a false and misleading statement is the suggestion in the Article that "*Tobinick... is claiming that a wide range of neurological conditions not known to be immune mediated are treated by a specific immunosuppressant*." Like the others, this statement of fact is false and misleading. Indeed, in 2013 and 2014 alone there were no fewer than 10 separate publications reporting favorable effects of etanercept for neuroinflammatory indications, a list of which can be reviewed on the attached **Exhibit "A"** hereto. Furthermore, the pathophysiology of both stroke and Alzheimer's are well known to be immune-mediated. For example, Richard Ransohoff MD, Editor of the new journal Neurology: Neuroimmunology and Neuroinflammation, has stated:

> "There has been an explosion of new knowledge about how inflammation affects the diseases of aging, such as Alzheimer's …. and stroke" (Neurology: Neuroimmunology & Neuroinflammation launch!), and
>
> Neuroinflammation has been studied for decades almost exclusively as a cardinal feature of explicitly inflammatory processes such as MS, NMO, inflammatory neuropathy, acute infection, stroke, and trauma. With recent genetic findings it is now clear that inflammation plays a central (but not exclusive) part in Alzheimer disease, Parkinson disease, tauopathy, and other neurodegenerations. Inflammation is also strongly suspected as having a role in neurodevelopmental disease, including autism and schizophrenia.

Ransohoff, R., *Call for papers: Neurology: Neuroimmunology & Neuroinflammation, a new Neurology journal.* Neurology, 2014. **82**: p. 648-649.

Bottom line, the scientific basis underlying the use of etanercept for post-stroke neurological dysfunction and Alzheimer's disease is supported by a wealth of published, peer-reviewed scientific literature. The collection of scientific evidence supporting the use of selective TNF inhibitors for treatment of neuroinflammatory disorders has continued to increase in the recent past, including a new study demonstrating favorable effects of etanercept in an Alzheimer's model. Some of these published studies are noted in the attached **Exhibit "B"** hereto for your reference. Clearly, based on the foregoing, the Article states a falsity where it states that "*Tobinick... is claiming that a wide range of neurological conditions not known to be immune mediated are treated by a specific immunosuppressant.*"

As a final non-exhaustive example of the malicious falsehoods within Dr. Novella's Article, it states that "*Tobinick has also started to publish case series – little more than retrospective case series reporting on his own patients.... all but worthless coming from a clinic like Tobinick's.*" Not unlike the others, this statement is false and intentionally misleading. The publications of Dr. Tobinick include multiple, invited review articles in prominent journals. And, the observational studies published by Dr. Tobinick and his colleagues include patients treated by multiple physicians, not simply Dr. Tobinick's own patients. A short exemplary list of these published, peer-reviewed scientific articles can be reviewed on **Exhibit "C"** attached hereto for your reference. Further, the scientific publications of Dr. Tobinick and his colleagues have been cited by hundreds of researchers from academic centers around the world and in neuroscience journals such as Nature Clinical Practice Neurology, and Dr. Tobinick has been an invited *ad hoc* reviewer for the journals *Brain Research, CNS Drugs, Current Alzheimer Research, Experimental Neurology, Future Neurology, Journal of Neurochemistry, Journal of Neuroimmunology, Neuroscience, and Pharmaceutical Medicine* and a member of the Editorial Board of the *Journal of Neuroinflammation.* Suffice it to say, these are not the scientific credentials of a "quack" physician as suggested by Dr. Novella's Article.

In light of the foregoing, it is unequivocally clear that Dr. Novella has engaged in a concerted and malicious effort to unfairly compete against and disparage the amazing work of our clients. The Article's repeated usage of falsely disparaging phrases such as "quack", "dubious", "lack of expertise", "worthless coming from a clinic like Tobinick's", "Tobinick is providing the kind of evidence that is guaranteed to be positive," and "exploitation of a well-meaning and desperate husband at the hands of a dubious practitioner", is that much more problematic and troubling. And, to add insult to injury, SBM placed Dr. Novella's Article in the category of "Health Fraud", implying that our clients and its physicians are involved in and committing health fraud. Clearly this malicious behavior is actionable under the law and will not be tolerated.

Etanercept for neuroinflammatory indications, such as stroke, Alzheimer's disease and sciatica is not a "scientific fallacy", but rather represents evidence-based, emerging off-label uses of this therapeutic molecule for intractable medical conditions that are supported by peer-reviewed, published scientific literature, clinical data, and basic science studies with a firm, scientific rationale. These uses may help fulfill important unmet medical needs of thousands of patients that you and Dr. Novella are deterring for Dr. Novella's own envious reasons.

As previously stated, the false and misleading statements published by SBM in the Article have caused irreversible injury to the Institute and the Institute's physicians, including Dr. Tobinick. In this regard, demand is hereby made that SBM immediately and publicly retract Dr. Novella's Article, remove the Article from its website and cease and desist from any further publishing of the Article.

We look forward to your immediate compliance with the demands set forth herein, and expect notification of such action within seven (7) days of your receipt of this letter. Under the circumstances that Dr. Novella's Article is causing grave harm to our clients, and thwarting the care of thousands of patients in need, we believe that such a short time frame is both appropriate and necessary. Of course, in the meantime, please feel free to contact me *via* email (pgh@trippscott.com) or via my direct dial phone number (954.760.4913).

Very truly yours,

/s/Peter G. Herman

PETER G. HERMAN
For the Firm

Exhibit "A"
2013-2014 Publications reporting favorable effects of
etanercept for neuroinflammatory indications

1. Ye, J., et al., *Etanercept reduces neuroinflammation and lethality in mouse model of Japanese encephalitis*. J Infect Dis, 2014.

2. Tobinick, E., et al., *Immediate neurological recovery following perispinal etanercept years after brain injury*. Clin Drug Investig, 2014. **34**(5): p. 361-6.

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Exhibit "B"
Scientific publications reporting favorable effects of
etanerept for neuroinflanimatory indications

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Exhibit "C"
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