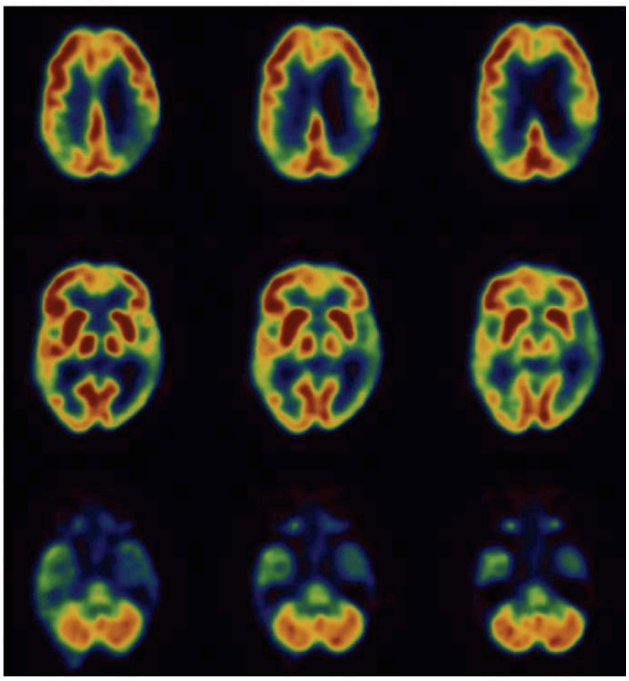
Institute for Neurological Research

a private medical group, inc

100 UCLA Medical Plaza
Suites 205-210
Los Angeles, California 90095
(310) 824-6191



Memory Disorders Program

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Introduction

The Institute for Neurological Research®, a private medical group, inc. (**INR**) is pleased to provide this detailed introduction to its pioneering medical concepts, research, and treatment programs.

Cascading basic science, genetic, and clinical evidence now supports a key role of the inflammatory cytokine, **TNF-alpha**, in the pathogenesis of Alzheimer's Disease. This is perhaps not surprising, in view of the fact that inflammation of the brain has long been established to be present in Alzheimer's Disease. Alzheimer's Disease therefore joins a long list of conditions, including rheumatoid arthritis, Crohn's Disease, psoriasis, and ankylosing spondylitis, which affect tens of millions of people across the globe, in which there is evidence that inflammation is initiated, maintained, or amplified by TNF-alpha.

The **INR** is unique in that it has pioneered, refined, and developed new methods of anti-TNF treatment for patients with a variety of conditions involving neurologic inflammation. The INR has active and on-going **anti-TNF treatment programs** for selected patients with Alzheimer's Disease and related disorders in which excess TNF-alpha has been implicated as a causative factor.

The INR is available to evaluate patients with memory impairment who have failed to adequately respond to medical treatment:

Memory Disorders Program:

Alzheimer's Disease
Fronto-temporal dementia
Primary progressive aphasia
Dementia

The INR welcomes telephone inquiries from physicians, patients, or family members with questions regarding its treatment programs or research.

In addition, the INR welcomes inquiries from academic medical centers, and biotechnology or pharmaceutical companies which have interest in anti-TNF research related to the causation and treatment of Alzheimer's Disease, frontotemporal dementia, traumatic brain injury, stroke, and primary progressive aphasia. The INR is currently conducting collaborative research with academic medical centers both in the U.S. and abroad.

The INR may be contacted directly by calling (310) 824-6199, by facsimile to (310) 824-6196, or by e-mail to info@nrimed.com. The website of the INR® is www.nrimed.com.

Appointments at the INR

Consultation and treatment with an INR physician is by appointment only. Appointments can be scheduled by calling the INR at (310) 824-6199, Monday through Friday, 8 AM to 5 PM.

The Institute for Neurological Research, a private medical group, inc., is located at 100 UCLA Medical Plaza, Suites 205-210, Los Angeles, California 90095. Convenient, in-building, underground parking is available.

For map and directions, please see page 22.

Referrals to the INR

The INR welcomes referrals from neurologists, geriatricians, internists, family physicians, other health care providers, or family members of patients with conditions associated with neurologic inflammation, such as Alzheimer's Disease, frontotemporal dementia, primary progressive aphasia, traumatic brain injury, and other forms of dementia. Individual treatment recommendations are only made following physician evaluation, including history, physical examination, and review of imaging studies.

The INR welcomes telephone inquiries from physicians and family members. In particular, the INR encourages telephone inquiry and discussion with an INR physician for those patients referred from locations at a geographic distance from Los Angeles prior to appointment scheduling. This is recommended especially for those patients who will be flying across country or from overseas for treatment at the INR, due to the special nature of the services provided at the INR, and the unique experience which the INR has performing anti-TNF treatment for Alzheimer's Disease.

The INR encourages referrals of patients with the following diagnoses who have failed to respond adequately to medical treatment:

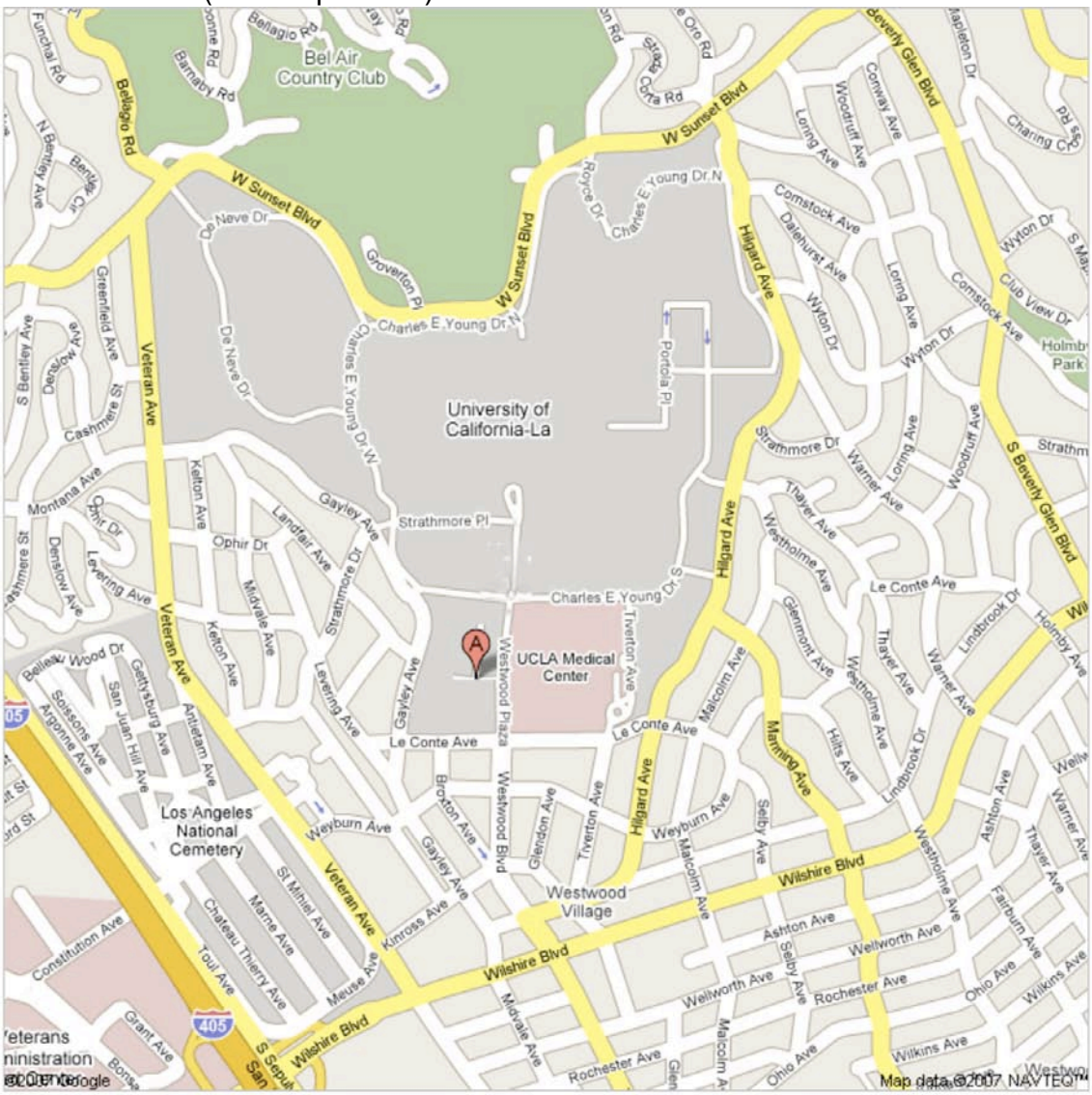
Memory Disorders Program:

Alzheimer's Disease
Fronto-temporal dementia
Primary progressive aphasia
Dementia

Map and Directions to the Institute for Neurological Research, a private medical group, inc.

The INR is located at 100 UCLA Medical Plaza, Suites 205-210, Los Angeles, California 90095. Appointments can be made by calling (310) 824-6199 Monday through Friday 8 AM to 5 PM. The Medical Plaza is on the southern edge of the campus, adjacent to the Medical Center and the Jules Stein Eye Center.

From the San Diego Freeway (Interstate 405) take the Wilshire Boulevard exit going east. Travel east on Wilshire about 3 blocks to Westwood Boulevard. Make a left onto Westwood Boulevard, traveling north thru the village of Westwood about 6 blocks. Cross over Le Conte Boulevard, onto the campus. The Medical Plaza is on your left, just north of Le Conte. Make a left turn onto Medical Plaza Drive. Park underneath the 100 Building, take the elevator to the second floor, then proceed to Suite 210 at the end of the hall. (See map below).



A. **Institute-Neurological Research**
100 Ucla Medical Plz, Los Angeles, CA
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Scientific Background: Excess TNF-alpha and neurologic inflammation

Inflammation is centrally involved in the causation of many neurologic disorders, including disc-related pain and Alzheimer's Disease. Inflammation is produced, amplified, and maintained by certain substances, called cytokines, which are released by cells of the immune system. One of these cytokines, called tumor necrosis factor-alpha, has been named the "master regulator" of the inflammatory response because of the key role it plays in initiating and increasing inflammation, in all of the organ systems of the human body, including the brain, the spinal cord, and the nerve roots.

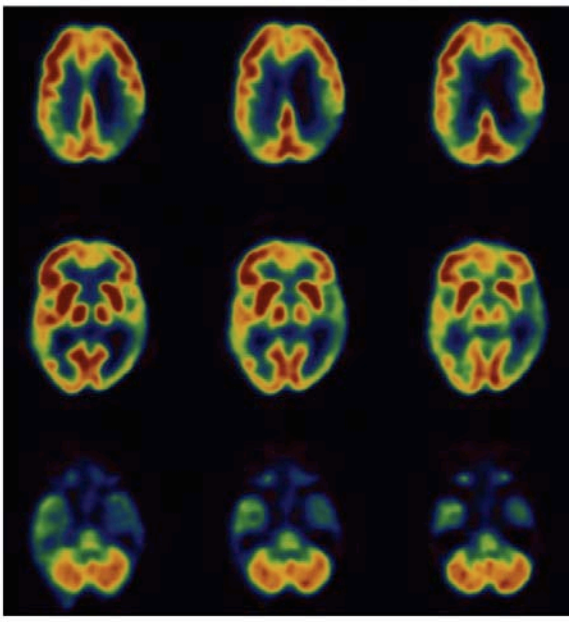

Figure 1. PET Scan demonstrating decreased cortical activity in a patient with mild Alzheimer's Disease.

Excess TNF-alpha is present in the cerebrospinal fluid in patients with Alzheimer's Disease, and has been implicated in the development of severe back, neck, and leg pain (sciatica) which may occur following disc herniation. In Alzheimer's excess TNF-alpha may interfere with brain function, and may negatively influence fundamental brain mechanisms involving amyloid and memory.

In 1998 specific biologic inhibitors of excess TNF-alpha became available for human use in the U.S. One of these TNF-alpha inhibitors, etanercept, has become the largest selling biologic in the world, with worldwide 2006 sales in excess of $4 billion.

The INR has invented, refined, and pioneered new methods of use of etanercept for the treatment of a variety of neurologic disorders, including disc-related back and neck pain, sciatica, and Alzheimer's Disease. These methods of use of etanercept are patented inventions of the INR, and are neither sponsored nor endorsed by UCLA; rather all rights to these methods are retained exclusively by the INR. U.S. patents 6015557, 6177077, 6419934, 6419944, 6471961, 6537549, 6982089, and 7214658; with additional issued and pending U.S. and foreign patents.

Selected references

Tobinick, E., H. Gross, A. Weinberger, H. Cohen, *TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study.* MedGenMed, 2006. **8**(2): p. 25.

Tobinick, E. and S. Davoodifar, *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): p. 1075-85.

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INR Memory Disorders Program

The INR has developed a new method of anti-inflammatory treatment for patients with disorders, such as Alzheimer's Disease, which are associated with memory impairment.

This new treatment method is available for selected patients following evaluation by an INR physician, and is particularly designed for those patients whose memory impairments have continued to progress despite previous treatment.

INR's anti-inflammatory approach is supported by basic science, genetic, and clinical evidence which suggests that inflammation is centrally involved in the development of Alzheimer's Disease. INR's anti-inflammatory approach utilizes a specific biologic inhibitor of a substance in the body, called TNF-alpha, which has been termed the "master regulator" of the immune response. This anti-TNF approach is compatible with, but completely different from, existing treatments for Alzheimer's or dementia, such as Aricept® or Namenda®.

For scientists and physicians:

New TNF data from the reknowned Framingham Study is the most recent robust scientific evidence supporting a key role of excess TNF-alpha in Alzheimer's. By negatively influencing synaptic regulation and amyloid, glutamate, NMDA, and inflammatory pathways, excess TNF, along with amyloid/tau, may constitute the "perfect storm" which attacks the brain and results in Alzheimer's progression. (see references 1-38 below).

The INR was the first to report the successful use of anti-TNF treatment for Alzheimer's disease in a pilot study. *See:*

Edward Tobinick MD, Assistant Clinical Professor of Medicine; Hyman Gross MD, Clinical Professor of Neurology, USC; Alan Weinberger MD, Associate Clinical Professor of Medicine/Rheumatology; Hart Cohen MD, FRCPC, Associate Clinical Professor of Medicine/Neurology. *TNF Modulation for Treatment of Alzheimer's Disease: A 6-Month Pilot Study.* Medscape General Medicine, 2006. 8(2):25.

Anti-TNF treatment is available for selected patients with dementia at the INR.

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INR U.S. issued patents

The following U.S. patents have issued to Edward Tobinick, MD, Medical Director of the INR (multiple additional patents, both foreign and domestic, are pending) (listed in reverse chronological order based upon issue date):

7,214,658 Method of delivering a TNF antagonist to the brain of a human by perispinal administration without direct intrathecal injection

6,982,089 Cytokine antagonists for neurological and neuropsychiatric disorders

6,623,736 Interleukin antagonists for the treatment of neurological, retinal and muscular disorders

6,537,549 Cytokine antagonists for the treatment of localized disorders

6,471,961 Interleukin antagonists for the treatment of neurological, retinal and muscular disorders

6,428,787 TNF inhibitors for the treatment of retinal disorders

6,423,321 Cytokine antagonists for the treatment of sensorineural hearing loss

6,419,944 Cytokine antagonists for the treatment of localized disorders

6,419,934 TNF modulators for treating neurological disorders associated with viral infection

6,379,666 TNF inhibitors for the treatment of neurological, retinal and muscular disorders

6,177,077 TNF inhibitors for the treatment of neurological disorders

6,015,557 Tumor necrosis factor antagonists for the treatment of neurological disorders

Scientific publications of the INR

The following are selected peer-reviewed, scientific publications (selected abstracts are included) that were authored by Edward Tobinick, MD, Medical Director of the INR:

1. Tobinick, E., H. Gross, A. Weinberger, H. Cohen, *TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study.* MedGenMed, 2006. **8**(2): p. 25.

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. 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: Increasing 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.

2. Tobinick, E.L. and S. Britschgi-Davoodifar, *Perispinal TNF-alpha inhibition for discogenic pain.* Swiss Med Wkly, 2003. **133**(11-12): p. 170-7.

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.

3. Tobinick, E.L., *Targeted etanercept for treatment-refractory pain due to bone metastasis: two case reports.* Clin Ther, 2003. **25**(8): p. 2279-88.

BACKGROUND: Parallel bodies of research suggest both a central role for osteoclasts in tumor-induced destruction of bone and the ability of biologic tumor necrosis factor-alpha (TNF-alpha) antagonists to attenuate the osteoclast-mediated bone destruction that accompanies a variety of nonmalignant disorders. Additional studies have implicated TNF-alpha in the promotion of osteoclast-mediated malignant osteolysis and the pathogenesis of neuropathic pain. TNF-alpha antagonists have the potential to interfere in both processes. OBJECTIVE: This article reviews the cases of 2 patients with treatment-refractory pain due to cancer metastases to bone who were given targeted injections of the biologic anti-TNF agent etanercept based on its potential to interfere directly with both malignant activation of osteoclasts and neuropathic pain. METHODS: One patient had a diagnosis of non-small cell lung cancer and the other had a diagnosis of breast cancer. Both presented with treatment-refractory pain due to bone metastases. The 2 patients received etanercept 25 mg by targeted SC injection in anatomic proximity to the site of spinal metastasis for relief of their treatment-refractory pain. RESULTS: Both patients experienced rapid, substantial, and sustained relief of chronic refractory pain at the treatment site after targeted administration of etanercept. Symptomatic improvement was correlated with objective measures of improvement, including weight gain in 1 patient and decreased uptake of radioactive tracer at the targeted site on positron emission tomography in the other. CONCLUSIONS: Etanercept delivered by targeted SC injection may be of clinical benefit in selected patients with treatment-refractory pain caused by bone metastases. Clinical trials are needed to define the potential benefit of biologic TNF-alpha antagonists in the treatment and prevention of malignant osteolysis.

4. Tobinick, E.L., *Targeted etanercept for discogenic neck pain: uncontrolled, open-label results in two adults.* Clin Ther, 2003. **25**(4): p. 1211-8.

BACKGROUND: Etanercept, a recombinant biologic anti-tumor necrosis factor (TNF)-alpha therapeutic, is approved for the treatment of certain autoimmune arthritides by subcutaneous (SC) injection. TNF-alpha has been suggested to play a central role in neuropathic pain and neuronal damage associated with intervertebral disc herniation. Directed local administration of etanercept, in anatomic proximity to the site of disc and neuronal abnormality, may result in an enhanced therapeutic response. OBJECTIVE: This study reviews findings from 2 patients with chronic, severe, discogenic cervical pain who were treated with a targeted cervical injection of etanercept with the objective of obtaining relief from their treatment-resistant pain. METHODS: In this uncontrolled, open-label study, the case histories of 2 patients (1 woman and 1 man) presenting with a history of chronic neck pain refractory to various treatments are reviewed. Both patients were treated with etanercept 25 mg by SC injection to the cervical region (case 1) or the posterior neck

overlying the spine (case 2). RESULTS: Both patients experienced almost complete pain relief as assessed subjectively. In case 1, the Oswestry score decreased from 58 before treatment to 6 one day following treatment. In addition, 1 day after treatment the patient reported a subjective assessment of 98% pain improvement, 100% sensory improvement, and 100% weakness improvement. She has remained asymptomatic for >1 year. In case 2, the Oswestry score decreased from 44 before treatment to 4 two months after treatment. The patient reported 100% pain relief and 90% sensory improvement 1 day after treatment. At 8-month follow-up, pain improvement continued to be 100% and sensory improvements was 75%. CONCLUSIONS: Etanercept, delivered by targeted SC injection, may be of benefit for selected patients with resistant pain associated with cervical disc disease. Further study of this new treatment modality is warranted.

5. Tobinick, E. and S. Davoodifar, *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): p. 1075-85.

6. Tobinick, E., *The cerebrospinal venous system: anatomy, physiology, and clinical implications.* MedGenMed, 2006. **8**(1): p. 53.
ABSTRACT: There is substantial anatomical and functional continuity between the veins, venous sinuses, and venous plexuses of the brain and the spine. The term "cerebrospinal venous system" (CSVS) is proposed to emphasize this continuity, which is further enhanced by the general lack of venous valves in this network. The first of the two main divisions of this system, the intracranial veins, includes the cortical veins, the dural sinuses, the cavernous sinuses, and the ophthalmic veins. The second main division, the vertebral venous system (VVS), includes the vertebral venous plexuses which course along the entire length of the spine. The intracranial veins richly anastomose with the VVS in the suboccipital region. Caudally, the CSVS freely communicates with the sacral and pelvic veins and the prostatic venous plexus. The CSVS constitutes a unique, large-capacity, valveless venous network in which flow is bidirectional. The CSVS plays important roles in the regulation of intracranial pressure with changes in posture, and in venous outflow from the brain. In addition, the CSVS provides a direct vascular route for the spread of tumor, infection, or emboli among its different components in either direction.

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The INR has invented, refined, and pioneered new methods of use of etanercept for the treatment of a variety of neurologic disorders, including disc-related back and neck pain, sciatica, and Alzheimer's Disease. These methods of use of etanercept are patented inventions of the INR, and are neither sponsored nor endorsed by UCLA; rather all rights to these methods are retained exclusively by the INR. U.S. patents 6015557, 6177077, 6419934, 6419944, 6471961, 6537549, 6982089, and 7214658; with additional issued and pending U.S. and foreign patents.

Citations to the scientific publications of the INR

The following peer-reviewed, scientific publications have cited one or more of the published studies of Edward Tobinick, MD, Medical Director of the INR:

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EDWARD TOBINICK MD

Edward Tobinick is a U.S. physician who has invented novel treatment approaches for a variety of medical conditions with widespread unmet medical need[1,2,3]. These conditions include several forms of severe back and neck pain (including sciatica and cervical radiculopathy); Alzheimer's Disease and other forms of dementia; a variety of additional neurological disorders; and pain due to cancer metastasis to the spine. Common to all of these conditions is the central involvement of inflammatory processes. Through May 2007 Dr. Tobinick has been awarded twelve U.S. patents for these new methods of treatment. His published papers have been cited in more than 150 scientific articles from leading academic centers around the world. His scientific work has been presented at medical conferences both in the U.S. and abroad. Major academic medical centers are currently involved in collaborative research with him to investigate his unique methods designed to deliver large molecules across the blood-brain barrier. In 2007 the anti-TNF pilot study for Alzheimer's Disease[1] conducted by Dr. Tobinick and his colleagues was recognized and cited by the prestigious Dana Alliance for Brain Initiatives in their Progress Report on Brain Research[4].

Dr. Tobinick graduated 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 is currently the Medical Director of the Institute for Neurological Research, a private medical group, inc. at 100 UCLA Medical Plaza in Los Angeles and Assistant Clinical Professor of Medicine at UCLA.

[1] Edward Tobinick MD; Hyman Gross MD, Clinical Professor of Neurology, USC; Alan Weinberger MD, Associate Clinical Professor of Medicine/Rheumatology; Hart Cohen MD, FRCPC, Associate Clinical Professor of Medicine/Neurology. *TNF Modulation for Treatment of Alzheimer's Disease: A 6-Month Pilot Study*. Medscape General Medicine, 2006. 8(2):25.
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[4]ABOUT THE DANA ALLIANCE FOR BRAIN INITIATIVES

More than 260 neuroscientists comprise the Alliance membership, joined by the common interest in advancing public awareness about brain research. Recognized as leaders in their respective fields, they are among the world's foremost authorities on neuroscientific research and clinical neurology topics. Each has made a personal commitment to support the mission of the Dana Alliance through active participation in outreach and educational activities. Among the current members, 10 have received the Nobel Prize. The 2007 Progress Report on Brain Research is available online on the website of the Dana Foundation, at www.dana.org.

Disclaimer: The off-label treatment methods discussed herein have been detailed in reliable, peer-reviewed, scientific publications. These methods of off-label use and administration of certain TNF-alpha antagonists, including etanercept, for selected clinical disorders, including disc-related back and neck pain, sciatica, and Alzheimer's Disease, are patented inventions of the INR; all rights to these patented methods of treatment are retained exclusively by the INR. The INR conducts a private medical practice. U.S. patents 6015557, 6177077, 6419934, 6419944, 6471961, 6537549, 6982089, 7214658 and additional issued and pending U.S. and foreign patents.

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Medical opinions differ, and no representation is made that the information in this brochure represents current general medical opinion or the standard of medical care. See ***California B&P 2234.1(4c)***: "Since the National Institute of Medicine has reported that it can take up to 17 years for a new best practice to reach the average physician and surgeon, it is prudent to give attention to new developments not only in general medical care but in the actual treatment of specific diseases, particularly those that are not yet broadly recognized in California". The information in this brochure respresents the opinion of a pioneering medical practice, which is presented here following the publication of scientific, peer-reviewed, published, pilot studies, and multiple published peer-reviewed basic science studies, but prior to the performance of double-blind, placebo-controlled, clinical trials for the off-label indications discussed herein.

All medications have potential adverse effects. These side effects must be weighed against the possibility of beneficial therapeutic effects with regard to treatment of the underlying illnesses in question. The class of therapeutics known as biologic TNF inhibitors, which includes etanercept, have been associated with serious adverse reactions. Off-label status of a drug or biologic means, by definition, that this medication has not been established by the FDA to be either safe or effective for this off-label use, even if the medication has been FDA-approved for other medical uses. We cannot guarantee, nor do we mean to imply, by any of the information in this brochure, that any single medication will necessarily lead to clinical improvement if administered for any given new patient. Screening or physician evaluation at the INR does not guarantee that treatment will be recommended or undertaken by the INR physician. Treatment decisions are made individually. Contraindications to medical treatment at the INR may be determined at any stage in the evaluation process, even prior to physician physical examination. The information in this brochure should not be interpreted as a treatment recommendation for any given patient; treatment recommendations cannot be given by an INR® physician without patient consultation and examination.

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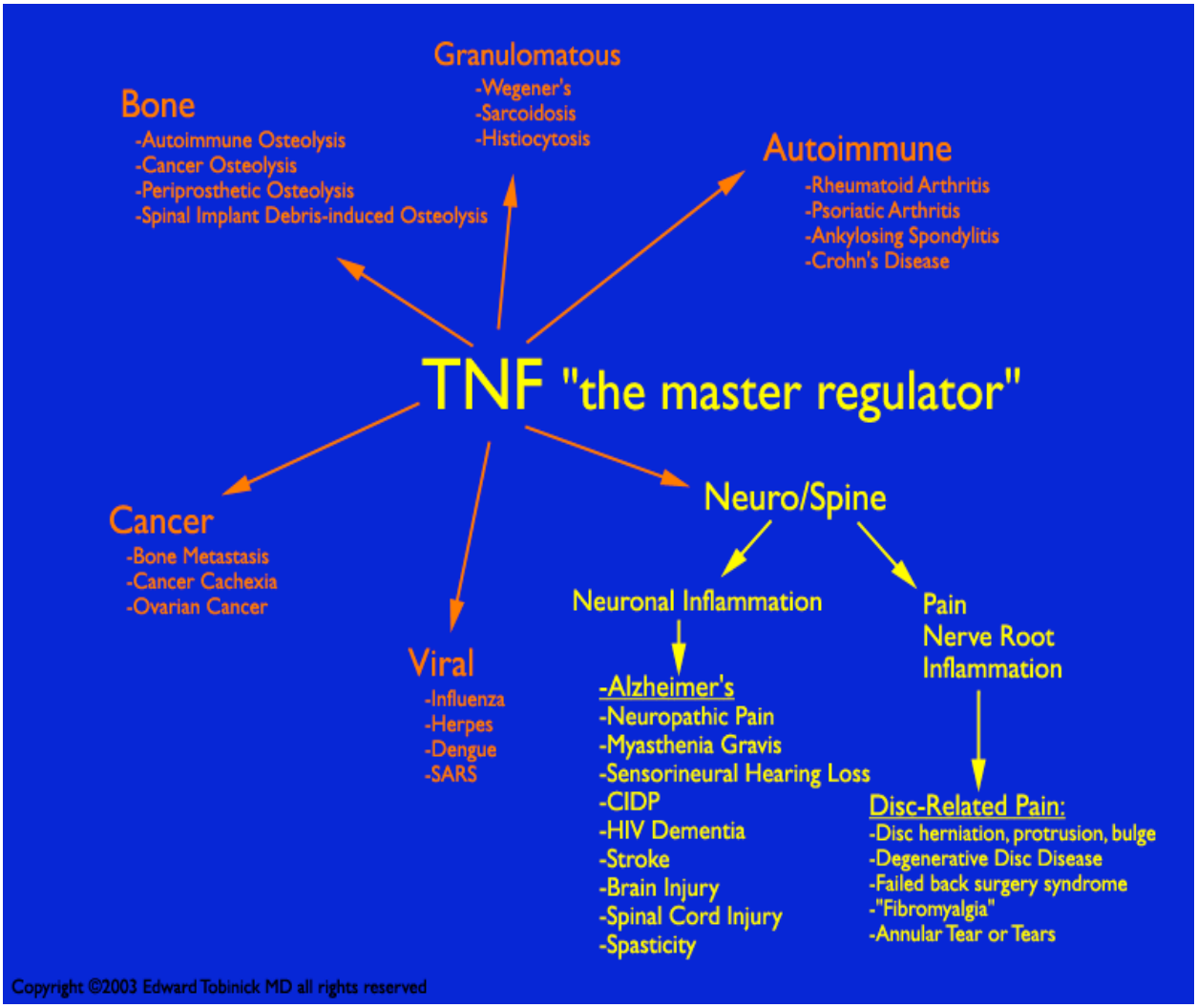

Figure 1. TNF-alpha, the master regulator of the inflammatory response. The INR has invented, refined, and pioneered unique therapeutic approaches which inhibit the inflammatory pathways mediated by the cytokine TNF-alpha.