INR Scientific Bibliography and Background

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Disclaimer: The treatment methods discussed herein are off-label and are not yet supported by randomized, double-blind, placebo-controlled clinical trials. These methods are neither sponsored nor endorsed by UCLA; rather they are original concepts which were invented and patented at the Institute, and all rights to these patents are retained exclusively by the Institute for Neurological Research, a private medical group, inc. Please see the Legal Notice at http://www.nrimed.com/legal.htm.

Section I: Overview

Edward Tobinick MD, the Medical Director of the Institute for Neurological Research® (INR®), a private medical group, inc., is actively involved in research, teaching, and the private practice of medicine. He is an Assistant Clinical Professor of Medicine at the David Geffen School of Medicine at UCLA and has been a member of the UCLA Clinical Faculty for more than 20 years.

Dr. Tobinick's research interests have been wide-ranging in medicine, and have resulted in publications in the fields of neurology, oncology, virology, and immunology, among others. His first scientific publication was in the field of cardiovascular nuclear medicine. His most recent publications have all been in the field of neurology. Dr. Tobinick is certified by the American Board of Internal Medicine and the American Board of Dermatology. He graduated from Brandeis University Phi Beta Kappa with honors in biology, attended medical school at the University of California San Diego School of Medicine in La Jolla, and completed internship and both residencies at UCLA Hospital in Los Angeles.

Dr. Tobinick has long-standing interests in mechanisms of disease, immunology, immunotherapeutics, and neurology. In the late 1990's he began to concentrate on developing new therapeutic uses for cytokine antagonists, particularly antagonists of tumor necrosis factor(TNF), a class of medications newly available for therapeutic use in humans.

In a series of patent applications, filed beginning in 1999, Dr. Tobinick detailed new methods of use of TNF antagonists for consideration in the treatment of patients with a variety of clinical disorders involving inflammation. Through January 2006 he has been awarded 11 U.S. patents for these treatment methods which he invented, with multiple additional patent applications pending. These patents described methods of use of TNF antagonists for treating neurological disorders, including sciatica and other forms of disc-

related pain[see Section II and also references 1-9,16-19,21,22,23,26,27]; other forms of neuropathic pain [see Section II and references 1-9,16-19,21,22,23,26,27]; pain due to cancer metastasis to bone[see Section IV and references 14, 23, 27, 28]; Alzheimer's disease[see Section III]; spinal cord injury[10, 11]; myasthenia gravis[12, 13]; and a variety of other clinical disorders for which there existed a widespread unmet medical need.

For more than a decade, Dr. Tobinick has been teaching and providing voluntary medical services at the Venice Family Clinic, the largest free clinic in the U.S. The Clinic has recently added Dr. Tobinick to its prestigious Rossman/Davidson Wall of Honor, which bears the names of "distinguished volunteer clinicians who have provided direct health services to the Clinic's patients in an exemplary manner for more than a decade." The Venice Family Clinic is affiliated with the UCLA School of Medicine, and has received multiple awards honoring its delivery of quality healthcare to the poor and homeless.

Dr. Tobinick's published papers have been cited by more than 150 scientific publications from around the world. His early inventions have now been supported by an increasing number of scientific studies from academic centers around the globe, including those following:

1. Igarashi, T., et al., *2000 Volvo Award winner in basic science studies: Exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathology*. Molecular, histologic, and behavioral comparisons in rats. Spine, 2000. 25(23): p. 2975-80.
2. Sommer, C., et al., *Etanercept reduces hyperalgesia in experimental painful neuropathy*. J Peripher Nerv Syst, 2001. 6(2): p. 67-72.
3. Genevay, S., S. Stingelin, and C. Gabay, *Efficacy of etanercept in the treatment of acute, severe sciatica: a pilot study*. Ann Rheum Dis, 2004. 63(9): p. 1120-3.
4. Atcheson, S.G. and T. Dymeck, *Rapid resolution of chronic sciatica with intravenous infliximab after failed epidural steroid injections*. Spine, 2004. 29(12): p. E248-50.
5. Murata, Y., et al., *Selective inhibition of tumor necrosis factor-alpha prevents nucleus pulposus-induced histologic changes in the dorsal root ganglion*. Spine, 2004. 29(22): p. 2477-84.
6. Onda, A., S. Yabuki, and S. Kikuchi, *Effects of neutralizing antibodies to tumor necrosis factor-alpha on nucleus pulposus-induced abnormal nociresponses in rat dorsal horn neurons*. Spine, 2003. 28(10): p. 967-72.
7. Murata, Y., et al., *Nucleus pulposus-induced apoptosis in dorsal root ganglion following experimental disc herniation in rats.* Spine, 2006. **31**(4): p. 382-90.
8. Takahashi, N., et al., *TNF-alpha and phosphorylation of ERK in DRG and spinal cord: insights into mechanisms of sciatica.* Spine, 2006. **31**(5): p. 523-9.
9. Ohtori, S., et al., *Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back Pain and Modic Type 1 or Type 2 changes on MRI.* Spine, 2006. **31**(9): p. 1026-31.
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*14. Anderson, G.M., M.T. Nakada, and M. DeWitte, *Tumor necrosis factor-alpha in the pathogenesis and treatment of cancer*. Curr Opin Pharmacol, 2004. 4(4): p. 314-20.
*15. Irving, G., et al., *Novel pharmacologic options in the treatment of neuropathic pain*. CME Accredited Roundtable Monograph through Mt. Sinai School of Medicine, 2004.
*16. Korhonen, T., Karppinen, J., Malmivaara, A., et. al., *Efficacy of infliximab for disc herniation-induced sciatica:one-year follow-up*. Spine, 2004. 29(19): p. 2115-9.
*17. Sommer, C. and M. Schafers, *Mechanisms of neuropathic pain: the role of cytokines*. Drug Discovery Today: Disease Mechanisms, 2004. 1(4): p. 441-448.
*18. *Appropriatezza della diagnosi e del trattamento chirurgico dellÕernia del disco lombare sintomatica* LINEA GUIDA October 2005. 2005.
*19. Guia De Practica Clinica *Lumbalgia Inespecifica* version espanola de la Guia de Practica Clinica del Programma Europeo Cost B13. European Commission Directorate General Research, 2005.
*20. Kinch JW, Ryan TJ, *Right Ventricular Infarction*. New England Journal of Medicine 1994 Apr 28;330(17):1211-7.
*21. Bhargava, A., et al., *Injection Therapy for Lumbar Radiculopathy*. Current Opinion in Orthopedics, 2005. 16: p. 152-157.
*22. Cohen, S.P., et al., *Lumbar discography: a comprehensive review of outcome studies, diagnostic accuracy, and principles*. Reg Anesth Pain Med, 2005. 30(2): p. 163-83.
*23. Wacnik, P.W., et al., *Nociceptive characteristics of tumor necrosis factor-alpha in naive and tumor-bearing mice*. Neuroscience, 2005. 132(2): p. 479-91.
* 24. Aoki Y., Takahashi, K., Ohtori, S., Moriya, H., *Neuropathology of Discogenic Low Back Pain: A Review*. The Internet Journal of Spine Surgery. 2005. 2(1).
*25. Lai ST. *Treatment of Severe Acute Respiratory Syndrome*. Eur J Clin Microbiology Infectious Diseases, 2005. 24(9): 583-591.
* 26. Yaksh T, Sorkin L. *Mechanisms of Neuropathic Pain*. Current Medicinal Chemistry - Central Nervous System Agents, 5(2), June 2005, p. 129-140.
*27. Myers, R.R., W.M. Campana, and V.I. Shubayev, *The role of neuroinflammation in neuropathic pain: mechanisms and therapeutic targets*. Drug Discov Today, 2006. 11(1-2): p. 8-20.
*28. Yan L., Anderson, G.M., M. DeWitte G, M.T. Nakada, *Therapeutic potential of cytokine and chemokine antagonists in cancer therapy*. European Journal of Cancer, Volume 42, Issue 6, April 2006, p. 793-802.

*citations to published articles written by Edward Tobinick, MD.

Section II: TNF and Disc-related Pain

> *"The domain of sciatica is at the edge of a mini revolution. For ten years evidence have been accumulating in favour of a local inflammation rather than a pathology resulling only from a nerve compression. This hypothesis has first been strengthened by the discovery of inflammatory mediators in human herniated discs and then by animal models. These models have demonstrated the impossibility for nerve root compression to produce sciatica in the absence of inflammation and the importance of proinflammatory cytokines in this pathology. TNF-alpha have been proved to be the most important inflammatory cytokine and TNF-alpha modulators has*

been most effective in the treatment of these models"
Abstract from: Genevay, S., P. A. Guerne, et al. (2004). "[Efficacy of tumor necrosis factor-alpha blockade for severe sciatica?]." Rev Med Suisse Romande 124(9): 543-5.

Editor's note: The INR® pioneered the use of TNF-alpha modulators for the treatment of patients with intractable disc-related pain. *See the following articles:*

1. Tobinick, E.L. and S. Britschgi-Davoodifar, *Perispinal TNF-alpha inhibition for discogenic pain*. Swiss Med Wkly, 2003. 133(11-12): p. 170-7.
2. Tobinick, E.L., *Targeted etanercept for discogenic neck pain: uncontrolled, open-label results in two adults*. Clin Ther, 2003. 25(4): p. 1211-8.
3. 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.
4. Tobinick E. *The Cerebrospinal Venous System: Anatomy, Physiology, and Clinical Implications.* Medscape General Medicine, 2006. 8(1): 53f.

Because of the known role of inflammatory pathways in the generation of severe, intervertebral disc-related pain and nerve root dysfunction (manifesting, for example, as sciatica after disc herniation), corticosteroids (either systemically or, preferably, by perispinal (epidural) injection) are a standard treatment modality[1-3].

Inflammation plays a key role in the generation of pain associated with intervertebral disc herniation or annular tear of the disc capsule. A portion of the disc, the nucleus pulposus, is inherently inflammatory, releasing inflammatory mediators when the disc capsule is disrupted or torn. This inflammatory pain is common and often refractory to treatment utilizing conventional treatment modalities, including epidural steroid injections and/or spinal surgery[4-9].

Although perispinal injection of corticosteroids is routinely performed for treatment of disc-related pain this method is invasive and the efficacy of this approach is limited. Perispinal injection of corticosteroids is performed because perispinal delivery of anti-inflammatories in the vicinity of the affected nerve routes is thought to provide additional efficacy compared with systemic administration. Perispinal administration may facilitate entry of anti-inflammatories into the vertebral venous system and thereby facilitate delivery of therapeutic medication into the nerve roots, dorsal root ganglia, and spinal cord[10-25].

A key role in the generation of disc-related pain has been established for the inflammatory cytokine tumor necrosis factor-alpha (TNF). Excess TNF is generated when a disc is damaged, and TNF has been found to be the central cause of pain, nerve root damage, and nerve dysfunction in experimental models of disc herniation[26-38].

In 2001 there were multiple, reliable, published, peer-reviewed scientific medical articles which provided a scientific basis for consideration of the use of anti-TNF medications for selected patients with intractable disc-related pain[1-12, 14-38].

Since 2001 multiple, reliable, peer-reviewed, scientific articles have been published in the medical literature which provide additional scientific support for consideration of this new treatment approach for selected patients with intractable pain[13, 39-72].

Dr. Tobinick's multiple, peer-reviewed, published scientific studies documenting the results of this innovative treatment modality have been cited by multiple authoritative, peer-reviewed, published scientific sources from around the world[47, 52, 56, 59, 60, 62, 63, 68, 71].

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*****Indicates a publication which cites one of Dr. Tobinick's published articles.

Section III: TNF and Alzheimer's disease

Editor's note: Dr. Tobinick and his co-authors were the first to report the successful use of TNF-alpha modulators for Alzheimer's disease. *See:*

1. 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.

Increasing scientific evidence implicates the inflammatory molecule TNF-alpha in the development of Alzheimer's Disease

In 2005 and the first four months of 2006 there were no less than 21 significant, peer-reviewed scientific articles which suggest a role for TNF in the development of Alzheimer's disease(AD) [12,14-16,18-20,22-25,30,33,36,38,39,42,60-63]. Excess TNF has been demonstrated in both the serum, plasma and the cerebrospinal fluid in patients with AD, and to correlate with progression of Mild Cognitive Impairment to AD [27,29,42,60]. Certain variations in genes encoding TNF have been found to be associated with AD [19, 63]. Several recent review articles have discussed the central role of inflammation in the development of AD [16,24,62]. Specific methods of use of specific anti-TNF biological molecules for consideration in AD were invented at the INR® [64-68].

1. ***Inflammation is centrally involved in the pathogenesis of Alzheimer's Disease***[1-42].
2. ***TNF-alpha is involved in AD mechanisms***[7, 9-12, 14, 15, 17, 19, 20, 22-30, 33, 35-47, 60-63].

3. ***TNF is involved in neuronal inflammation***[7, 9-11, 14, 15, 17, 19, 20, 22-30, 33, 35, 36, 43-59].

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Section IV. TNF-alpha and painful solid tumor metastasis to bone

In 2001 the INR® pioneered consideration of the use of biological TNF antagonists for the treatment of selected patients with intractable pain due to solid tumor metastasis to bone. In the scientific article Dr. Tobinick subsequently wrote discussing this new approach to treatment, he explained:

> "*…by interfering with tumor-induced osteoclast function, etanercept may interrupt a self-amplifying osteoclast-mediated cycle of bone invasion leading to bone resorption leading to release of tumor growth factors leading to further bone invasion…Targeted delivery of etanercept may allow achievement of higher local concentrations of TNF-alpha antagonist at the pathologic site, which may produce a greater therapeutic effect*."[1].

His pioneering concepts have been supported by articles from multiple academic centers, including those below[2-4], all of which cited Dr. Tobinick's article[1]. The abstract from a 2006 review of this new approach follows:

> *A new paradigm is becoming widely accepted, that chronic inflammation, driven in part by chemokines and cytokines at the site of a tumour, may facilitate tumour progression instead of promoting anti-tumour immunity. Tumours and activated stromal cells secrete pro-inflammatory chemokines and cytokines that act either directly or indirectly through stimulation of the vascular endothelium to recruit leukocytes to the tumour. After activation, these tumour-associated leukocytes release angiogenic factors, mitogens, proteolytic enzymes, and chemotactic factors, recruiting more inflammatory cells and stimulating angiogenesis to sustain tumour growth and facilitate tumour metastasis. Breaking this cycle by inhibiting targets such as cytokines, chemokines and other inflammatory mediators, either alone, or more realistically, in combination with other therapies, such as anti-angiogenic or cytotoxic agents, may provide highly efficacious therapeutic regimens for the treatment of malignancies. This article reviews anti-cytokine and anti-chemokine therapies being pursued in cancer, and discusses in more detail anti-tumour necrosis factor-alpha (TNF) approaches.*
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> Abstract from: Yan L., Anderson, G.M., M. DeWitte G, M.T. Nakada, *Therapeutic potential of cytokine and chemokine*

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