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"Temporal Lobe Epilepsy: One Neurosurgeon's Journey"
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Introduction

I wish to thank Dr. Michael LeMole for his gracious and entertaining introduction.

I want to speak today about my personal professional journey in neurosurgery. In 1980, the past Chairman of the Department of Biochemistry at the St. Louis University School of Medicine, Dr. Robert Olson, advised each member of the incoming medical school class to adopt a "personal theme" which would guide us through our medical education. I accepted this advice. My theme was and continues to be the creative pursuit of new knowledge, to uncover the truths of nature, with an personal emphasis on discovering heretofore undiscovered truths about normal and abnormal brain function. I have since learned that this theme conforms to the definition of "science" coined by the late quantum physicist, David Bohm (1). My perspective on professional life was further informed by the late Morgan Maxfield, the graduation speaker at Central High School of St. Joseph, Missouri in 1976 who observed that "you will define your life by what you choose to do in your free time". What we naturally choose to do and take pleasure in and from which we receive internal reinforcement and inner strength will most noticeably be the source of our happiness, success and sustained intellectual and personal growth. And so today, this WNS Presidential Address will focus on my personal passion in science, "Temporal Lobe Epilepsy: One Neurosurgeon's Journey".

My disclosures are all relevant to today's talk. I thank the National Institutes of Health for financial support of our laboratory, The Medical Device (Visualase) Division of the Medtronic Corporation for clinical trial support and recognize the University of Arizona Technology Transfer Office for developing intellectual property based on the subject of today's address.

Contemporary Temporal Lobe Epilepsy Surgery

In the Second Century, there lived the Roman emperor and stoic philosopher, Marcus Aurelius, who wrote in his autobiography, "To Myself", known today by the title, "Meditations", that all things are related and turn in upon themselves; there is nothing in nature which is not inter-related to any other thing. This philosophy provides the basis for understanding the perspective of the academic mission. This mission, in the context of epilepsy surgery, illustrates the fact that the clinician's laboratories are multifaceted and include the medical record, a clinical electronic database; the intensive care unit; the epilepsy monitoring unit; the neurosurgery tissue bank and, in the 21st century, the genetics core laboratory.

Kwan and Brodie determined that success with anti-epileptic medications rapidly diminishes after the second anticonvulsant is administered (2). Overall today, approximately 20% of patients with epilepsy are medically refractory. For patients in whom medical therapy fails to control seizures, an alternative method of therapy is neuromodulation, illustrated by vagus nerve stimulation (VNS) and responsive neurostimulation (RNS). Wiebe *et al.* in 2001 published a random-

ized, controlled trial of medical versus surgical therapy in intractable temporal lobe epilepsy demonstrating that, at one year, 58% of the surgical group and 8% of the medical group were seizure free ($p<0.001$) (3). In 2012, Engel *et al.* performed the second, and probably the last ever, randomized controlled trial of medical versus surgical therapy in intractable temporal lobe epilepsy demonstrating a 2 year seizure-free rate of 73% in the surgical and 0% in the medical groups (4).

Despite the unequivocal evidence for efficacy of surgical treatment of intractable temporal lobe epilepsy, epilepsy surgery is underutilized. The prevalence of epilepsy in the United States is approximately 1% (3,300,000), 20% of whom are medically intractable (660,000), representing surgical treatment as an option in approximately one-fourth of patients (165,000) with all epilepsy centers combined evaluating only approximately 5,000 patients annually. There are approximately 150,000 new cases of epilepsy diagnosed each year costing $15.5 billion including that due to lost employment and measurable quality of life costs. There is an average 20 year delay in referral for epilepsy surgery with an estimated 1% of temporal lobe epilepsy surgery candidates being operated upon (5,6).

The epilepsy surgeon's armamentarium includes depth electrodes and subdural strip and grid electrodes to survey the depths of the cerebrum and cortical surfaces for characterization and localization of epileptic foci. Beginning in the early 1990s, we investigated the prognostic value of the neurosurgeon's armamentarium during long-term subdural EEG recording for selection of epilepsy surgery candidates (7,8). Among patients treated with anterior temporal lobectomy with amygdalohippocampectomy, we found unilateral onset, electrical onset pattern beginning as fast spike trains, absence of frontal lobe background desynchronization at onset, an interhemispheric propagation time of greater than 8 seconds, and increased duration from ictal subdural EEG seizure onset to clinical seizure onset to be predictive of post-operative seizure-free outcome (7,8). In addition, it is well known that unilateral medial temporal sclerosis is prognostic for improved post-operative seizure freedom. The temporal lobe seizure focus may also be localized with MR spectroscopy detection of unilateral temporal lobe reduction in NAA (n-acetylaspartate). Unilateral temporal lobe hypometabolism on FDG-PET (Fluorodeoxyglucose-Positron Emission Computed Tomography) is also valuable in localizing the temporal lobe seizure focus. In 1997, we published the results of long-term subdural thermal diffusion flowwmetry, developed by our late 2009 WNS President, Dr. Phil Carter, in temporal lobe epilepsy (9). We discovered that beginning approximately 20 minutes pre-ictal, temporal cortical cerebral blood flow (CBF) begins to significantly increase from its interictal hypoperfused state approximating normal CBF at electrocorticographic seizure onset (9). Thus, the EEG seizure onset seems to be an epiphenomenon, preceded by cerebral perfusion changes. These results are reminiscent of the metabolic redox changes shown to occur more than 20 minutes prior to seizure onset in the intact cat hippocampus (10). Building upon the cerebral perfusion abnormalities present in temporal lobe epilepsy, difficult to localize seizure foci may be detected using subtraction ictal single photon emission computed tomography (SPECT) coregistered to MRI (SISCOM).

The economic benefits of surgical treatment of intractable temporal lobe epilepsy are clearly documented. In 1995, Barbara Warren, the Director of the Arizona Medicaid program, analyzed the cost benefit for epilepsy surgery at the University of Arizona (11). Within such an analysis, quality of life improvements are most important variables. It was concluded that from a purely economic perspective, the reduction in costs of admissions, medications, and Emergency Department visits eventually justifies up-front cost of temporal lobe epilepsy surgery (11). With re-

gard to neuropsychological functioning after temporal lobe epilepsy surgery, seizure-free patients (but not those who are only significantly improved in seizure frequency) have significant improvement in multiple neuropsychological indices, including Mental Health Index and Depression scales (12). Towards this end of achieving a post-operative seizure-free outcome, we described in 2002 the value of multiply concordant seizure focus localizing factors in predicting seizure freedom (13). Once quadruple concordance of seizure focus localizing data are achieved there is an approximately 80% likelihood of post-operative seizure-free outcome (13).

The neurosurgical operative approach to anterior temporal lobectomy with amygdalohippocampectomy (ATL/AH) begins with supine positioning with ipsilateral shoulder elevation and the side of the head to be operated upon rotated contralaterally by approximately 90 degrees. Positioning the head in maximum extension facilitates the approach to the medial temporal lobe. A frontal-temporal scalp incision is performed and a pterional craniotomy is elevated. The dura over the temporal and inferior frontal lobes is opened in a cruciate fashion, exposing the Sylvian fissure. A temporal corticectomy is performed with the posterior margin determined by the language dominance of the temporal lobe involved (4.5 cm and at least 5.5 cm posterior to the anterior middle fossa in the dominant and non-dominant temporal lobes, respectively). The corticectomy is continued along the inferior margin of the Sylvian fissure. After elevating and removing the lateral temporal cortex, the amygdala is resected during which the third cranial nerve is visualized. Then, the hippocampus is resected en bloc during which the posterior cerebral artery and cerebral peduncle are visualized. Several years ago, we analyzed our first 133 cases of ATL/AH and determined that our 2-year post-operative seizure-free rate was 66%, in line with most comprehensive epilepsy center results (14). An additional 29% of patients had significant (> 90% seizure frequency) reduction in seizure frequency. There has been considerable discussion regarding the relative merits of performing amygdalohippocampectomy with or without anterior temporal lobectomy (14). Some authors have documented improved seizure outcome with ATL/AH while others have shown no difference when compared to selective AH alone. Similarly, cognitive outcome reports for ATL/AH versus AH have ranged from no difference between the two procedures to some favoring selective AH based on improved memory, particularly verbal memory, and possibly attention function (14).

We are presently in a golden era for epilepsy therapy. Continuously emerging new medications, epilepsy surgical techniques, and neuromodulation therapies must be individualized in a physician-patient partnership with the goal of producing seizure freedom without undesirable side effects.

Stereotactic Laser Amygdalohippocampotomy (SLAH)

The current trend in epilepsy surgery is towards increasingly minimally invasive therapeutic solutions. In accordance with this trend, thermal destruction of epileptic foci using laser ablation has emerged as a promising neurosurgical treatment strategy. The essential range of temperatures desired for time-dependent thermal ablation is between 44 to 59 degrees Centigrade. Epilepsy surgeons have recognized that the trajectory along the long axis of much of the amygdala and hippocampus is a straight line. This anatomic conformation is amenable to linear stereotactic ablation strategies. The technique of stereotactic laser amygdalohippocampotomy (SLAH) involves a small occipital scalp incision, placement of an occipital burr hole, and insertion of the stereotactic probe along the long axis of the amygdala and hippocampus. The intraoperative work flow is conducive to interactive neurosurgical resident education and assignment of increasingly graded responsibility as the resident's technical operative neurosurgical skills

develop. The laser ablation work station displays near real time thermal MRI images providing the epilepsy surgeon with near instantaneous feedback on the extent of permanent thermal medial temporal lobe tissue ablation. After laser ablation, a damage model is created and associated blood-brain barrier disruption documented on T2-FLAIR MRI brain scanning to confirm the medial temporal lobe ablation. We participated in the original clinical trial of stereotactic laser amygdalohippocampotomy (SLAH) among 10 original participating epilepsy surgery centers. The average length of stay for SLAH was 1.6 days, initially in the intensive care unit but now patients are admitted to the regular neurosurgical floor for post-operative recovery. Soon, I predict we will perform these procedures on an outpatient basis in otherwise healthy individuals. One year post-SLAH seizure freedom was obtained in 57% of patients (15).

Whether the surgical procedure is ATL/AH or SLAH, there are multiple reasons for under-utilization of temporal lobe epilepsy surgery. There may be referral bias or lack of referral, patient fear of even minimally invasive surgery, a preference for a less invasive albeit less effective procedure (i.e. VNS, RNS), the continued use of anticonvulsant medications despite likely failure, and the fact that neuromodulation is technically less challenging than definitive respective or ablative surgery. In accord with the interest in minimally invasive surgery, SLAH represents a new surgical option which, while minimally invasive, is also effective and associated with low morbidity. Medial temporal sclerosis is the hallmark neuropathological change in temporal lobe epilepsy. Classically, the CA4 hippocampal field is affected (16). Anatomic considerations for SLAH include optimization of ablation of both the amygdala and hippocampus. Three-dimensional reconstruction of medial temporal lobe structures assists in developing prognostic value for technical parameters employed in the SLAH procedure. For instance, there is a trend towards improved 6-month seizure-free outcome when the volume difference between the ablated and contralateral hippocampus exceeds 25% (17,18). When the volume of ablation exceeds 70% of either the amygdala or the hippocampus with an additional 50% ablation of the remaining medial temporal lobe structure there is a one-year post-operative Engel I seizure-free rate of 80% (17,18). In summary, SLAH is a promising minimally invasive approach to amygdalohippocampotomy (57% seizure free at 12 months). Larger series and long term seizure outcomes need to be examined. Long term adverse effects on visual fields (quadrantanopia) remain to be determined and potentially improved neurocognitive impacts need further study. Optimization of SLAH ablation volume and more personalized patient selection may improve outcome in the future.

New Frontiers in Temporal Lobe Epilepsy Surgery Candidate Selection

The pathophysiology of temporal lobe epilepsy involves inflammatory change and blood-brain barrier (BBB) disruption (19). From 1997 to 2013, we published evidence of BBB disruption and leukocyte transit across the blood-brain barrier in temporal lobe epilepsy (19,20). The cerebral vessels showed fibrin leakage, perivascular macrophages and expression of IL-6 on endothelial cells (19). In 1997, we described an artificial human blood-brain barrier constructed from human epileptic temporal cortical endothelial cells and demonstrated that immune mediators, such as TNF-alpha, opened a paracellular route for leukocyte migration from the systemic circulation into the brain (20). The gaps in BBB endothelial cells permitting leukocyte passage could be created by immune-mediated stimulants such as LPS (lipopolysaccharide) and, by implication, immune cell-mediated pathologies such as temporal lobe epilepsy (21). Furthermore, we demonstrated in 1997, with our collaborators at Temple University and the University of Nebraska, that leukocyte activation was the central event affecting monocyte BBB migration and that among these activating pathologies were widespread astrogliosis, apoptosis of neurons, den-

dritic damage, and macrophage/microglial activation (22). Ultrastructurally, leukocytes traversed the BBB from the luminal to the abluminal surface in the course of leukocyte trafficking in the brain. In addition to the paracellular route, transendothelial diapedesis has been demonstrated as a mechanism for leukocyte brain entry creating what are known as 'invadosome-like protrusions' (ILPs) (23).

Leukocyte trafficking within the brain originates through paracellular and transcellular endothelial routes as well as choroid plexus endothelial migration. Having studied the inflammatory nature of temporal lobe epilepsy (TLE) pathophysiology, we began to develop a translational hypothesis designed to study leukocyte transformation in TLE (19). Given the bidirectional cellular and molecular interactions between leukocytes and the epileptic brain, systemic (peripheral) leukocytes were thought potentially to offer a relatively noninvasive means to assess differences in gene expression that are induced under conditions recapitulating or reflecting temporal lobe epilepsy pathophysiology (25).

In 2012, a novel sample preparation method produced transmission electron microscopy (TEM) direct imaging of double stranded (ds) λ-DNA in the A conformation (24). This new visualization of the molecular library of life and the knowledge of leukocyte trafficking within the epileptic brain motivated our team to ask the question: Does leukocyte gene expression differ between epilepsy surgery patients rendered seizure-free and non-seizure-free? (25).

We recognized the need to enhance selection criteria for surgical candidates with improved prognostic value for post-operative seizure-free outcome. We performed RNA sequencing (RNA-Seq) on whole blood leukocyte samples taken from 16 patients with intractable TLE prior to SLAH to test the hypothesis that pre-operative leukocyte RNA expression profiles are prognostic for postoperative seizure outcome (25). Multidimensional scaling analysis of leukocyte RNA expression data detected distinct clustering of patients with seizure free (SF) and non-seizure-free (NSF) outcomes (24). Differential expression (DE) analyses performed on SF versus NSF groups identified 24 significantly dysregulated genes (≥ 2.0-fold change, p-value < 0.05, and False Discovery Rate, FDR < 0.05) (25). Network and pathway analyses discovered differential activation of pathways involved in morphology of oligodendrocytes, lipid metabolism, development of astrocytes, and the inflammatory response (25).

Among the 24 differentially expressed leukocyte RNAs from TLE patients with SF versus NSF outcomes, four are associated with long-chain fatty acid metabolism: ALOX15B (Fold Change, FC: -3.1), PLP1 (FC: +3.2), HGB1 (FC: -2.7), and FADS2 (FC: +2.6) (25). Upregulated genes predictive of seizure-free outcome included ABCA4 (ATP Binding Cassette Subfamily A Member 4) (involved in cell lipid transport), PLP1 (Proteolipid Protein 1) (encoding oligodendroglia myelination), and FADS2 (Fatty Acid Desaturase 2) (involved in DHA Synthesis) (25). Among genes involved in lipid Metabolism, Transport and Inflammation pathways, ALOX15B (Arachidonate 15-Lipoxygenase Type B), which Oxidizes fatty acids and mediates inflammation through IL-12, IL-1B and TNF-α, was downregulated in seizure-free patients (25). Regarding pathways involved in Cell Morphology and Nervous System Development/Function, leukocyte GFAP (Glial Fibrillary Acidic Protein) RNA was upregulated in post-operative seizure-free patients (25). Hippocampal sclerosis and cortical gliosis correlate with seizure-free outcome. Anticonvulsant effects of astrocytosis include astrocytic gap junctions which facilitate potassium buffering, calcium wave spreading, and adenosine synthesis, adenosine being the most powerful endogenous anticonvulsant. The results of the leukocyte RNA analyses suggest that pre-operative leukocyte RNA expression profiles have prognostic value for seizure outcome following SLAH (25).

Currently, our research efforts have focused on *neurosurgical genomics*, using leukocyte RNA expression to predict the outcome of neurosurgical operative intervention. In the future, it may be possible to develop *genomic neurosurgery*, in which leukocyte and/or brain RNA expression may be engineered to produce the genomic signature prognostic of post-operative seizure freedom, obviating the need for neurosurgical operative intervention.

In conclusion, traditional approaches of anterior temporal lobectomy and amygdalohippocampectomy continue to produce excellent seizure outcome results. Minimally invasive stereotactic laser amygdalohippocampotomy is a promising new technique producing seizure freedom with low morbidity. Genomic neurosurgery is on the horizon of our knowledge and may one day permit genetic engineering of seizure freedom without operative neurosurgical intervention.

I wish to thank my closest collaborators in these research efforts, Drs. Michael Hammer and Ryan Sprissler of the University of Arizona Core Genetics Laboratory, Dr. Milan Fiala, our immunology colleague at UCLA, Dr. Marlys Witte who established and maintains our Lymphology Laboratory at the University of Arizona, where diagnostic specimens are processed and our current Chief Resident in Neurosurgery, Dr. Robert Bina, who aspires to a functional neurosurgical career. I thank my late wife Mary Ann and our First Lady Shauna Weinand who is with us today and my children Mike, Jamie and Lauren for their continuous support of what to me seems like an avocation of neurosurgical research.

I thank you, the Western Neurosurgical Society members, for your confidence and support in electing me to serve as your President this year. It has been the greatest privilege of my professional career to serve as your President.

Thank you.

References

1. Bohm D. Wholeness and the implicate order. London: Rutledge Classics.1980.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000 Feb 3;342(5):314-9. DOI: 10.1056/NEJM200002033420503
3. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001 Aug 2;345(5):311-8. DOI: 10.1056/NEJM200108023450501
4. Engel J Jr, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, Sperling MR, Gardiner I, Erba G, Fried I, Jacobs M, Vinters HV, Mintzer S, Kieburtz K; Early Randomized Surgical Epilepsy Trial (ERSET) Study Group. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA. 2012 Mar 7;307(9):922-30. doi: 10.1001/jama.2012.220.
5. Berg AT. Understanding the delay before epilepsy surgery: who develops intractable focal epilepsy and when? CNS Spectr. 2004 Feb;9(2):136-44.
6. Engel J Jr. Why is there still doubt to cut it out? Epilepsy Curr. 2013 Sep;13(5):198-204. doi: 10.5698/1535-7597-13.5.198.

7. Weinand ME, Wyler AR, Richey ET, Phillips BB, Somes GW. Long-term ictal monitoring with subdural strip electrodes: prognostic factors for selecting temporal lobectomy candidates. J Neurosurg. 1992 Jul;77(1):20-8. DOI: 10.3171/jns.1992.77.1.0020
8. Weinand ME, Kester MM, Labiner DM, Ahern GL. Time from ictal subdural EEG seizure onset to clinical seizure onset: prognostic value for selecting temporal lobectomy candidates. Neurol Res. 2001 Sep;23(6):599-604. DOI: 10.1179/016164101101199072
9. Weinand ME, Carter LP, el-Saadany WF, Sioutos PJ, Labiner DM, Oommen KJ. Cerebral blood flow and temporal lobe epileptogenicity. J Neurosurg. 1997 Feb;86(2):226-32. DOI: 10.3171/jns.1997.86.2.0226
10. O'Connor MJ, Herman CJ, Rosenthal M, Jöbsis FF. Intracellular redox changes preceding onset of epileptiform activity in intact cat hippocampus. J Neurophysiol. 1972 Jul;35(4):471-83. DOI: 10.1152/jn.1972.35.4.471
11. Warren BH. Cost and quality outcomes of comprehensive epilepsy monitoring review of referrals in a managed Medicaid program. Physician Exec. 1995 Nov;21(11):16-8.
12. Hermann BP, Wyler AR, Ackerman B, Rosenthal T. Short-term psychological outcome of anterior temporal lobectomy. J Neurosurg. 1989 Sep;71(3):327-34. DOI: 10.3171/jns.1989.71.3.0327
13. Labiner DM, Weinand ME, Brainerd CJ, Ahern GL, Herring AM, Melgar MA. Prognostic value of concordant seizure focus localizing data in the selection of temporal lobectomy candidates. Neurol Res. 2002 Dec;24(8):747-55. DOI: 10.1179/016164102101200843
14. Ramey WL, Martirosyan NL, Lieu CM, Hasham HA, Lemole GM Jr, Weinand ME. Current management and surgical outcomes of medically intractable epilepsy. Clin Neurol Neurosurg. 2013 Dec;115(12):2411-8. doi: 10.1016/j.clineuro.2013.09.035. Epub 2013 Oct 11. Review.
15. Robert Gross, Jon Willie, Sandra Helmers, Kimford Meador, Suzette Laroche, R. Edward Faught, Evan Gedzelman, Ashwini Sharan, Michael Sperling, Richard Marsh, Gregory Cascino, Gregory Worrell, Jerry Shih, R. Wharen, William Tatum, Gautam Popli, A. Laxton, Daniel Couture, Martin Weinand , David Labiner, Ashesh Mehta, Cynthia Harden, David Woodrum, Robert Watson and Ravish Patwardhan. STEREOTACTIC LASER AMYGDALOHIPPOCAMPOTOMY FOR MESIAL TEMPORAL LOBE EPILEPSY: COLLECTIVE EXPERIENCE FROM SEVEN SINGLE-CENTER, PROSPECTIVE, INVESTIGATOR-INITIATED STUDIES. Abstract 2.339. American Epilepsy Society 68th Annual Meeting, Seattle, WA, December 5-9, 2014.
16. Na M, Liu Y, Shi C, Gao W, Ge H, Wang Y, Wang H, Long Y, Shen H, Shi C, Lin Z. Prognostic value of CA4/DG volumetry with 3T magnetic resonance imaging on postoperative outcome of epilepsy patients with dentate gyrus pathology. Epilepsy Res. 2014 Oct;108(8):1315-25. doi: 10.1016/j.eplepsyres.2014.06.005. Epub 2014 Jul 7.
17. Gautam Popli, Daniel Couture, A. Laxton, Robert Gross, Jon Willie, Ashwini Sharan, Michael Sperling, David Labiner, Martin Weinand , Richard Marsh, Gregory Worrell,Gregory Cascino, Jerry Shih, R. Wharen, William Tatum, Ravish Patwardhan, Brad Fernald and A. Shetty. STEREOTACTIC LASER ABLATION: HOW MUCH HIPPOCAMPAL ATROPHY OPTIMIZES SEIZURE FREEDOM? Abstract 2.337. American Epilepsy Society 68th Annual Meeting, Seattle, WA, December 5-9, 2014.
18. Ashwini Sharan, Chengyuan Wu, Michael Sperling, Robert Gross, Jon Willie, David Labiner, Martin Weinand , Richard Marsh, Gregory Worrell, Gregory Cascino, Gautam Popli, Daniel Couture, Jerry Shih, William Tatum, Ashesh Mehta, Cynthia Harden, Ravish Patwardhan, Brad Fernald, Anil Shetty and Ashok Gowda. STEREOTACTIC LASER ABLATION: HOW MUCH HIPPOCAMPUS AND AMYGDALA ABLATION VOLUME OPTIMIZES SEIZURE

FREEDOM? Abstract 2.256. American Epilepsy Society 68th Annual Meeting, Seattle, WA, December 5-9, 2014.
19. Fiala M, Avagyan H, Merino JJ, Bernas M, Valdivia J, Espinosa-Jeffrey A, Witte M, Weinand M. Chemotactic and mitogenic stimuli of neuronal apoptosis in patients with medically intractable temporal lobe epilepsy. Pathophysiology. 2013 Feb;20(1):59-69. doi: 10.1016/j.pathophys.2012.02.003. Epub 2012 Mar 22.
20. Fiala M, Looney DJ, Stins M, Way DD, Zhang L, Gan X, Chiappelli F, Schweitzer ES, Shapshak P, Weinand M, Graves MC, Witte M, Kim KS. TNF-alpha opens a paracellular route for HIV-1 invasion across the blood-brain barrier. Mol Med. 1997 Aug;3(8):553-64.
21. Persidsky Y, Stins M, Way D, Witte MH, Weinand M, Kim KS, Bock P, Gendelman HE, Fiala M. A model for monocyte migration through the blood-brain barrier during HIV-1 encephalitis. J Immunol. 1997 Apr 1;158(7):3499-510.
22. Persidsky Y, Gendelman HE. Development of laboratory and animal model systems for HIV-1 encephalitis and its associated dementia. J Leukoc Biol. 1997 Jul;62(1):100-6.
23. Carman CV. Mechanisms for transcellular diapedesis: probing and pathfinding by 'invadosome-like protrusions'. J Cell Sci. 2009 Sep 1;122(Pt 17):3025-35. doi: 10.1242/jcs.047522.
24. Gentile F, Moretti M, Limongi T, Falqui A, Bertoni G, Scarpellini A, Santoriello S, Maragliano L, Proietti Zaccaria R, di Fabrizio E. Direct imaging of DNA fibers: the visage of double helix. Nano Lett. 2012 Dec 12;12(12):6453-8. doi: 10.1021/nl3039162. Epub 2012 Nov 28.
25. Bina R, Weinand M. Leukocyte RNA Expression Correlates with Seizure-Free Outcome Following Stereotactic Laser Amygdalohippocampotomy. Abstract 140. Congress of Neurological Surgeons Annual Meeting, Houston, TX, October 8, 2018. (Ryan Sprissler, Robert Bina, Willard Kasoff, Marlys Witte, Michael Bernas, Christina Walter, David Labiner, Branden Lau, Michael Hammer, Martin Weinand. Leukocyte RNA Expression: Prognostic Value for Seizure-Free Outcome following Stereotactic Laser Amygdalohippocampotomy. *Nature Scientific Reports*, submitted 2018).