BIOGRAPHICAL SKETCH

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NAME: Andre Obenaus

eRA COMMONS USER NAME (credential, e.g., agency login): aobenaus

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Loma Linda University, Riverside, CA	B.Sc.	05/1984	Biophysics
University of British Columbia, Vancouver, B.C.	Ph.D.	06/1989	Neurophysiology

I have a long-standing interest in the use of non-invasive imaging modalities to understand normal brain physiological functions and those that accompany pathophysiology. Probing white matter using neuroimaging methods is an area of published interest using diffusion tensor imaging (DTI) as a non-invasive readout. For example we have published several studies in altered white matter after mild TBI (Wendel 2018) and in our proposed limited bedding and nesting (LBN) model of fragmented maternal care (Bolton et al 2018). These approaches used tractography as well as quantitative indices of white matter alterations including dispersion. We also have experience in acquiring resting and evoked fMRI data using very light planes of anesthesia.

Historically my interests have been in cerebral pathophysiology of disease, including TBI, stroke and epilepsy. I have used standardized imaging tools (T2, DWI) to extensively describe the evolution of magnetic resonance imaging (MRI) signals to characterize status epilepticus models (Wall 2000, Eidt 2004). In collaboration with Dr. TZ Baram (also Conte Center PI), we have further examined whether very acute (<4hr) MR signals could be predictive of animals that become epileptic later in life following febrile seizures (Choy et al 2014). More recently we have extended these studies to report that unique inflammatory markers correlate with these predicative MR signals (Patterson et al 2015) as well as expand the time window over which we can observe these modified signals (Curran 2018, Epilepsia, in revision). We are now extending these studies to investigate how febrile seizures alters learning and memory circuits in the brain using DTI.

In addition, as a co-investigator in the NIMH funded “Conte Center on Brain Programing in Adolescent Vulnerabilities” we have been examining developing new methods including gray-matter DTI to assess local brain changes as well as long-range circuits in rodents exposed to early life adversity (Molet 2016, Bolton 2018). We have described altered hippocampal microstructure using DTI that reflected behavioral alterations including memory deficits and anhedonia. Our recent report in Biological Psychiatry reported increased tracts in adults experiencing fragmented early-life experiences (Bolton et al 2018). These novel and other emerging analytical approaches will be utilized in our proposed research efforts related to understanding modifications to brain circuitry.

As the former Director of the Non-Invasive Imaging Laboratory (NIL) at Loma Linda University, I was instrumental in purchase, installation and all imaging activities on our high field MRIs (4.7T, 11.7T), a micro-CT and a micro-PET which supported the research efforts of numerous NASA, DOD and NIH funded researchers as well as my own research. At the present time I am the Director of the Preclinical and Translational Imaging Center at UCI which houses a state of the art 9.4T MRI. I have extensive experience as well as significant resources for computational analysis of imaging data and examples of these efforts are reported in Ghosh et al 2012 and Donovan et al 2012, including national and international patents.

These experiences, coupled with my productive collaborations with the PI, TZ Baram for close to ten years, provide me with the skills and the passion to enable the success of our renewed Center.

B. Positions and Honors

1989-1993 Postdoctoral Fellow, University of California, Los Angeles
1995-1996 Research Associate, University of California, Los Angeles
1996-2000 Clinical Assistant Professor, University of Saskatchewan
1999-2004 Canadian Institutes for Health Research (CIHR) Scholarship
2000- 2007 Asst Professor, Radiation Medicine Dept, Loma Linda University
2005- 2012 Director, Non-Invasive Imaging Laboratory, Radiation Medicine Dept, Loma Linda University
2007- 2012 Associate Professor, Radiation Medicine Dept, Loma Linda University
2008 2012 Adjunct Professor, Biophysics and Bioengineering, Loma Linda University (Dept closed)
2008 - Adjunct Professor, Dept Cell Biology & Neuroscience, Univ. California, Riverside
2012 - Adjunct Professor, Div. of Interdisciplinary Studies, School of Behavioral Health, LLU
2012 - 2017 Adjunct Professor, Radiation Medicine Dept, Loma Linda University
2012 - 2015 Associate Professor, Pediatrics Dept, Loma Linda University
2014 - 2017 Adjunct Professor, Pediatrics Dept, Univ. of California, Irvine
2015 - 2017 Professor, Pediatrics Dept, Loma Linda University
2017- Professor, Pediatrics Dept., University of California, Irvine (UCI)
2017- Professor, Anatomy and Neurobiology Dept., UCI
2017- Director, Preclinical and Translational Imaging Center, School of Medicine, UCI
2018- Fellow, Center for Neurobiology of Learning and Memory, UCI

C. Contributions to Science

Neuroimaging identifies consequences of early life adversity:

In collaboration with Dr. TZ Baram, we have investigated novel MRI approaches to examine the consequences of adversity on neuronal circuits and their integrity as well as on brain tissue microstructure (Molet 2016). Specifically, we have shown that high resolution DTI of hippocampal subregions reports on the paucity of dendritic arborization seen on histology. We have extended these novel findings to enhanced imaging strategies to other brain nodes (ie. amygdala) (Obenaus 2018). Most recently, we reported enhanced numbers of tracts connecting amygdala and medial prefrontal cortex following early life adversity (Bolton et al 2018). Thus, informed investigations such as these could lead to emergence of biomarkers that might be predictive for adult pathology. We have been extending these studies to evaluate high resolution DTI and rsfMRI for structural and functional connectivity.

1. Baram, TZ, Davis, E, **Obenaus, A**, Sandman, C, Small, S, Solodkin, A, Stern, H. (2012) Fragmentation and unpredictability of early-life experience in mental disorders. *Am J Psychiatry* 169(9): 907-15. PMC3483144
2. Molet J, Maras PM, Kinney-Lang E, Harris NG, Rashid F, Ivy AS, Solodkin A, **Obenaus A**, Baram TZ. (2016) MRI uncovers disrupted hippocampal microstructure that underlies memory impairments after early-life adversity. *Hippocampus*. 2016;26:1618-1632. PMC5452614
3. **Obenaus A**, Kinney-Lang E, Jullienne A, Shereen D, Solodkin A, Dunn JF, Baram TZ. (2018) Seeking the Amygdala: Novel use of Diffusion Tensor Imaging to delineate the basolateral amygdala. *ASNeuro*. (submitted)
4. Bolton JL, Molet J, Regev L, Chen Y, Rismanchi N, Haddad E, Yang DZ, **Obenaus A**, Baram TZ (2018) Anhedonia following early-life adversity involves aberrant interaction of reward and anxiety circuits and is reversed by partial silencing of amygdala corticotropin-releasing hormone gene. *Biol Psychiatry*. 2018;15;83(2):137-147. PMC5723546

Advances in computational analysis of MR images: Our own research has led to the development of dedicated computer algorithms related to rapid and unbiased analysis of MR images. There have been three primary areas of focus: 1) determination of ischemic lesions, including rescuable penumbra and non-salvageable tissues (core), 2) identification of sites of TBI injury on MR images, including evolution of hemorrhage and 3) investigations of tract dispersion tracts within the brain following perturbations. Different approaches have been utilized; including Hierarchal Region Splitting (HRS) and multi-level contextual information along with probabilistic mapping can identify and predict regions of TBI and tissue that might be recoverable in stroke. These efforts have led to awarding of a US and International patent related to this work: US Patent: 8731261, European Patent: 11748009.5-1265. Currently in progress are nascent efforts to quantify dispersion of brain tracts following perturbations identified using DTI.

1. Bianchi A, Bhanu B, **Obenaus A.** (2015) Dynamic Low-Level Context for the Detection of Mild Traumatic Brain Injury. *IEEE Trans Biomed Eng*. 2014;62(1):145-53. Epub, PMID: 25073162
2. Ghosh N, Recker R, Shah A, Bhanu B, Ashwal S, **Obenaus A**. (2011) Automated ischemic lesion detection in a neonatal model of hypoxic ischemic injury. *J Mag Res Imaging.* 2011;33:772-81, PMID:21448940
3. Ghosh N, Yuan X, Turenius CI, Tone B, Ambadipudi K, Snyder EY, **Obenaus A**, Ashwal S. (2012) Automated core-penumbra quantification in neonatal ischemic brain injury. *J Cereb Blood Flow Metab*. 32(12):2161-70. PMC3520032
4. Ghosh N, Sun Y, Bhanu B, Ashwal S, **Obenaus A.** (2014) Automated detection of brain abnormalities in neonatal hypoxia ischemic injury from MR images. *Med Image Anal*. 2014;18:1059-1069. PMC4145020

Identification of an early MRI biomarker for epilepsy: Epilepsy and in particular, febrile seizures (FS) have been difficult to diagnosis from radiologic assessments on diagnostic imaging. My early work in animal models of epilepsy utilized magnetic resonance imaging (MRI) indices to be one of the first to describe the pathological progression along with correlative histopathology using a clinical scanner (Wall et al 2001). Subsequent studies have moved to increasing field strengths (4.7T, 9.4T, 11.7T) to enhance our ability to identify biomarkers of epileptogenesis. More recently in collaboration with Dr. TZ Baram (UC Irvine) we identified the emergence of a MRI biomarker at very acute (<4hr) time periods that was predictive of animals that become epileptic later in life following FS (Choy et al 2014). More recently we have extended these studies to report that unique inflammatory markers correlate with these predicative MR signals (Patterson et al 2015). While we have observed these MR signals at high field strengths we need to translate these findings to clinically relevant MR scanners (i.e. 3T) to ultimately determine if these signals can be observed in human FS (Curran 2018 Epilepsia, under revision). We are now extending these studies by using DTI to map modifications in the brain circuitry after FS, specifically those related to learning and memory. Such advances will profoundly alter our ability to clinically identify putative patients that may develop life-long epilepsy.

1. Wall, C., Kendall, E.J., **Obenaus, A.** (2000) Rapid alterations in apparent diffusion coefficients with anatomical correlates in a model of status epilepticus. *AJNR Am J Neurorad.* 2000;21:1841-1852. PMID:11110536
2. Choy M, Dubé CM, Patterson K, Barnes SR, Maras P, Blood AB, Hasso AN, **Obenaus A**, Baram TZ. (2014) A novel, noninvasive, predictive epilepsy biomarker with clinical potential. *J Neurosci*. 2014;34:8672-84. PMC4069350
3. Barry JM, Choy M, Dube C, Robbins A, **Obenaus A**, Lenck-Santini PP, Scott RC, Baram TZ, Holmes GL. (2015) T2 relaxation time post febrile status epilepticus predicts cognitive outcome. *Exp Neurol*. 2015; 269:242-252. PMC4446141
4. Patterson KP, Brennan GP, Curran M, Kinney-Lang E, Dubé C, Rashid F, Ly C, **Obenaus A**, Baram TZ. (2015) Rapid, Coordinate Inflammatory Responses after Experimental Febrile Status Epilepticus: Implications for Epileptogenesis. *eNeuro*. 2015; 2(5). PMC4699830

MRI imaging of novel neuroprotective compounds for stroke: Neuroprotective strategies for stroke have been difficult to translate to the clinic. In a long standing collaboration with Drs Ginsberg, Belayev and Bazan, I have been instrumental in providing non-invasive neuroimaging assessments of putative neuroprotective compounds. The goal of these ongoing studies is not only to identify potential compounds but also to use clinically relevant assessments such as magnetic resonance imaging (MRI) in tracking improved behavioral and pathophysiological outcomes. These collaborations extend back to 2005 when we published our first paper on neuroimaging of intracerebral hemorrhage (Belayev et al 2007). Since then we have had a very productive collaboration focusing on neuroprotective strategies in stroke. These collaborative efforts have yielded >10 papers. More recently we have undertaken neuroimaging analysis of the effects of DHA and various derivatives (Belayev et al 2011, 2012, 2013, 2017 etc). In many of these studies we found that DHA and in particular when complexed to albumin, is highly neuroprotective in an MCAO model of stroke. These efforts have now resulted in a provisional patent submission: Provisional US Patent: 62155016. In addition, I have been the first to utilize MR imaging to track stem cells for >1yr after implantation in an animal model of neonatal hypoxia ischemia (Obenaus et al 2011). We have since published extensively using MR imaging of stem cells including novel approaches such as susceptibility weighted imaging to enhance visualization of their anatomical localization (Baghchechi et al 2017).

1. Baghchechi M, Plaia A, Hamer M, Ghosh N, Ashwal A, **Obenaus A**. (2017) Susceptibility Weighted Imaging Identifies Iron-Oxide Labeled Human Neural Stem Cells: Automated Computational Detection. *Dev. Neurosci*. 2017; 38:445-457 [Epub ahead of print], PMID:28343216
2. Zhang JH, **Obenaus A**, Liebeskind DS, Tang J, Hartman R, Pearce WJ (2017) Recanalization, reperfusion, and recirculation in stroke. *J Cereb Blood Flow Metab*. 2017; 37:3818-3823. PMC5718333
3. Belayev L, Mukherjee PK, Balaszczuk V, Calandria JM, **Obenaus A**, Khoutorova L, Hong SH, Bazan NG. (2017) Neuroprotectin D1 upregulates Iduna expression and provides protection in cellular uncompensated oxidative stress and in experimental ischemic stroke. *Cell Death Differ*. 2017; 24:1091-1099. PMC5442474
4. Ashwal S., Ghosh N, Turenius CI, Dulcich, M, Denham, CM, Tone B, Hartman, R, Snyder EY, **Obenaus** A. (2013) The Reparative Effects of Neural Stem Cells in Neonatal Hypoxic Ischemic Injury are Not Influenced by Host Gender, *Pediatric Res.* 2014; 75:603-11. PMC4404035

MR imaging of traumatic brain injury reports ensuing hemorrhagic and white matter decrements: Mild TBI (mTBI) can lead to long-term neuropsychological deficits and neuroimaging of white matter is increasingly important. We have pursued several avenues of inquiry, specifically, 1) effect of repetitive mTBI on white matter, 2) development of hemorrhage after TBI, and 3) effects of mTBI on juvenile white matter. In a series of publications we have found that repetitive bilateral TBI induces hemorrhagic progression at the TBI injury site that results in an increased inflammatory response (Donovan et al 2012, Huang et al 2013). Further, these TBI cohorts also revealed dramatic changes in white matter as assessed by diffusion tensor imaging (DTI), consistent with altered behavioral functions (Donovan 2014, Wendel 2018). Similarly, I have used electrophysiology to assay both epilepsy and radiation induced alterations within the hippocampus (Vlkolinsky et al 2008, 2009). We have extended our electrophysiological investigations in juvenile TBI (Ajao et al 2012) to those observed in the adult (Koeppen 2018). We are now expanding many of these studies to evaluate the response of the vasculature in the brain following TBI (Zhang 2012, Obenaus 2016, Salehi 2017, 2018) including gender (Jullienne 2018).

1. Donovan VM, Kim C, Anugerah AK, Coats JS, Oyoyo U, Pardo A, **Obenaus A.** (2014) Repeated Mild Traumatic Brain Injury Results in Long-Term White Matter Disruption. *J Cereb Blood Flow Metab.* 2014; 34:715-23. PMC3982100
2. Rodriguez-Grande B*, **Obenaus A***, Ichkova A, Aussudre J, Bessy T, Barse E, Hiba B, Catheline G, Barrière G, Badaut J. (2018) Gliovascular changes precede white matter damage and long-term disorders in juvenile mild closed head injury. *Glia*. 2018; [Epub ahead of print] * joint first authors. PMID:29665077. PMC in process.
3. Jullienne A, Salehi A, Affeldt B, Baghchechi M, Haddad E, Avitua A, Walsworth M, Enjalric I, Hamer M, Bhakta S, Tang J, Zhang J, Pearce WJ, **Obenaus A**. (2018) Male and female mice exhibit divergent responses of the cortical vasculature to traumatic brain injury. J Neurotrauma. 2018 Mar 5. doi: 10.1089/neu.2017.5547. [Epub ahead of print]. PMID:29648973
4. Koeppen J, Nguyen AQ, Nikolakopoulou AM, Garcia M, Hanna S, Woodruff S, Figueroa Z, Obenaus A, Ethell IM. (2018) Functional consequences of synapse remodeling following astrocyte-specific regulation of ephrin-B1 in the adult hippocampus. *J. Neurosci*. 2018; pii: 3618-17. [Epub ahead of print] PMID: 29793972

Complete List of Published Work in PubMed.
http://www.ncbi.nlm.nih.gov/pubmed/?term=obenaus+a

D. Additional Information: Research Support and/or Scholastic Performance
ONGOING

NIH NHLB R01HL139685-01-05 2017 – 2021
Perinatal stroke: effects of bioactive lipids on immune-neurovascular axis and brain repair
PI: Vexler, Z (UC San Francisco), $39,487. Obenaus, A (co-investigator)
Goal: The goal is to examine the effects of n3-Polyunsaturated Fatty Acids (n3-PUFA) and Spingosine-1-phosphate signaling on brain repair after transient middle cerebral artery occlusion (tMCAO) in neonatal mice. Vascular assessments of therapy will be performed.

NIH/NIMH P50 MH 096889 2013-2019

Fragmented early life environment and cognitive and emotional vulnerabilities
PI: Baram, T.Z. (UC Irvine), $10,000,000 Conte Center award. Obenaus, A (co-investigator)
Goal: Use of novel neuroimaging methods to understand the effects of early life fragmentation on long-term behavioral alterations. Role: 15% support, Part of Projects 1, 4 and Imaging Core, undertake all animal imaging for Conte Center, data collection, analysis and imaging support, correlate to human imaging data.

NIH NINDS 1 P01 NS082184-01A1 2014-2019
Center for Hemorrhage Research.
PI: Zhang, J, $6,700,000, Obenaus, A (PI Project 3, Associate Center Director, also Imaging Core Director)
Goals: Identify common vascular elements and treatments in SAH, ICH and TBI. Role: 15% support, vascular analysis of TBI injury, development of novel microscopy methods for studying the vasculature, MR imaging support for functional quantitative assessment of brain perfusion and metabolism.

NIH NINDS, RO1 NS0335439, 2014–2019
Epileptogenesis following FSE: mechanisms, biomarkers, prevention
PI: Baram, TZ., $1,250,000, Co-I: Obenaus, A.
Goals: Identify biomarkers of febrile seizures and their underlying mechanisms. Role: Perform all neuroimaging related to febrile seizure biomarkers, imaging analysis, manuscript preparation, novel methods of analysis.

NIH NINDS R01NS103483-01A1 2018-2022
Childhood stroke: effects of infection-induced arteriopathies
PI: Vexler, Zinaida S., $1,021,833, Co-I: Obenaus, A.
Goals: Identify the neurovascular alterations following perinatal inflammation and susceptibility to stroke later in childhood. Neuroimaging of white matter is also investigated

COMPLETED (selected)
NIH/NINDS Centers without Walls (Epilepsy) 2012-2015
Prevention of temporal lobe epilepsy.
PI: J. McNamara (Duke University), Co-I Baram TZ (University of California, Irvine) $800,000, Obenaus, A (co-investigator)
Goals: Identify MRI based signatures of temporal lobe epilepsy to improve clinical diagnosis, Role: 10% support, acquire MRI data for multi-institutional neuroimaging program for epilepsy, provide data and analysis.

1R01NS078755-01A1 (Zhang), 9/1/2012 – 6/30/2015,
Harness Germinal Matrix Hemorrhage,
PI: John H. Zhang, NIH/NINDS, $1,218,750 Obenaus, A (co-investigator)
Goals: The major goal of this project is to establish the mechanisms of neonatal germinal matrix hemorrhage and potential treatment options; Role: 5% support, providing neuroimaging of injury.

NIH NICHD, 2010-2015
AQP4 and JNK inhibition together reduce edema and excitotoxic injury in jTBI.
PI. Jerome Badaut $1,227,809; Obenaus, A (co-investigator)
Goals: Assess combinatorial approaches to reducing injury after jTBI. Role: 20% support, manage data collection, prepare manuscripts

NIH NINDS 1R01NS078279-01A2 2011-2016
Cognitive Deficits After Experimental Febrile Seizures: Neurobiology & Biomarkers
MPI Holmes G. (Dartmouth College/Vermont), Baram TZ (University of California Irvine) $1, 565,461, Obenaus, A (co-investigator)
Goal: Evaluate brain tissue following febrile seizures for neuroimaging biomarkers. Role: 10% support, collect imaging data, assist with analysis, and prepare manuscripts