BIOGRAPHICAL SKETCH

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NAME: Chen, John W.

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

POSITION TITLE: Associate Professor of Radiology

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
Cornell University, Ithaca, NY	AB	06/1992	Chemistry, Genetics
University of Illinois at Urbana-Champaign, Urbana, IL	PHD	06/1997	Physical Chemistry
University of Illinois, Chicago, IL	MD	06/1999	Medicine
University of Illinois, Urbana, IL	Resident	05/2000	Medicine Internship
Massachusetts General Hospital, Boston, MA	Resident	06/2004	Radiology Residency
Massachusetts General Hospital, Boston, MA	Fellow	06/2005	Neuroradiology Fellowship

A. Personal Statement

As a physician-scientist, I have a broad background in chemistry as well as clinical and experimental and clinical imaging of neurological diseases. My laboratory performs basic and translational studies to better understand neuroinflammation. We investigate the roles of molecular pathways and innate immune processes related to myeloid cells in clinically important diseases such as stroke and multiple sclerosis. A key aspect of our research is in deciphering complex in vivo biology by using innovative molecular imaging technologies, targeted molecular treatments, advanced experimental models as well as human trials. Ultimately, we hope to advance the diagnosis and treatment of these diseases by developing novel imaging and treatment strategies.

I have established a research program investigating the highly damaging enzyme myeloperoxidase (MPO), secreted by pro-inflammatory myeloid cells such as activated macrophages, microglia, and neutrophils. We have established a class of activatable molecular imaging agents that can detect MPO activity with high sensitivity and specificity, and validated its use in mouse models of multiple sclerosis and stroke to track disease activity and treatment changes. We have also validated this class of molecular imaging agents in mouse models of gliomatosis, seizure vasculitis, myocardial infarction, transplant rejection, and rabbit model of atherosclerosis. Both MRI and nuclear imaging agents for myeloperoxidase imaging are available. I have over 20 years of experience in developing and validating imaging agents for MRI and nuclear imaging. I am an inventor of the MRI agents for myeloperoxidase (MPO) activity. Recently, my team invented and validated a new PET imaging agent (Wang et al., *PNAS* 2019) targeting MPO activity, upon which ^{18}F-EH301 is based upon. I also have over 15 years of experience investigating imaging in animal models and human inflammatory diseases, especially in neurological diseases, in both clinical and basic research settings. We have investigated how MPO can be used as both an imaging biomarker and a treatment target for multiple sclerosis using animal models. As co-Director of the i3, I have helped to secure the approval of IND applications for six PET probes and conducted early phase clinical trials.

Ongoing projects that I would like to highlight include:

RF1AG075055
Chen (PI)
8/1/22-7/31/27
Developing a PET tracer targeting myeloperoxidase activity for neurodegenerative diseases

R44AG079734
Larson (PI); Chen (consortium PI)
9/1/22-8/31/25
PET imaging of damaging neuroinflammation in Alzheimer's disease

R01 NS103998
Chen (PI)
5/1/18-2/28/23
Imaging macrophage and microglial functional diversity in stroke

R01 NS103998-04S1
Chen (PI)
5/15/21-2/28/23
Imaging macrophage and microglial functional diversity in stroke
(administrative supplement to also study Alzheimer's disease)

RG-1902-33633
Chen (PI)
10/1/2019-9/30/2022
Targeting the ubiquitous oxidative aldehyde acrolein in multiple sclerosis

B. Positions, Scientific Appointments, and Honors

2021 - 2022	Guest Editor, Special issue on myeloperoxidase, International Journal of Molecular Sciences
2018 -	Editorial Board Member, Scientific Reports
2014, 2015, 2017, 2018, 2020, 2021	Study section panel member, Congressionally Directed Medical Research Programs, Department of Defense
2014 -	Associate Professor, Harvard Medical School, Boston, MA
2014 -	Radiologist, Massachusetts General Hospital, Boston, MA
2014 -	Co-Director, Institute for Innovation in Imaging, Massachusetts General Hospital, Boston, MA
2013	Special Emphasis Panel (R03, R21) study section member, National Cancer Institute, NIH
2013 -	Associate Radiologist, Massachusetts General Hospital, Boston, MA
2011 -	Director of Neurological Imaging Clinical Trials, Massachusetts General Hospital, Boston, MA
2008 - 2014	Assistant Professor, Harvard Medical School, Boston, MA
2006	Certificate of Added Qualification, Neuroradiology, American Board of Radiology
2005 - 2013	Assistant Radiologist, Massachusetts General Hospital, Boston, MA
2005 - 2008	Instructor, Harvard Medical School, Boston, MA
2004	Diplomat, Diagnostic Radiology, American Board of Radiology

Honors

2016	Distinguished Investigator, Academy of Radiology Research
2013-2020	Editor's Recognition Awards for Reviewing with Distinction, *Radiology*
2011	Partners in Excellence Award in Leadership, Partners Healthcare
2008	Molecular Imaging Travel Award, Radiological Society of North America
2004	Stanley M. Wyman Award (most outstanding graduating radiology resident at Massachusetts General Hospital), Massachusetts General Hospital
2004	Top Basic Science Abstract Award, Academy of Molecular Imaging

2003 Resident Research Grant Award, Radiological Society of North America
2002 Outstanding Research Resident Award, Radiological Society of North America
2001 Introduction to Research Award, American Roentgen Ray Society

C. Contributions to Science

1. I have worked on noninvasive means to probe inflammation and the innate immune response. I conceived and designed a class of highly specific and sensitive activatable molecular imaging agents that targets myeloperoxidase (MPO), a highly damaging enzyme secreted in inflammation, and validated the agents in vitro and in vivo. I also provided evidence for its mechanism of action and applied the agent to study the innate immune response in models of multiple clinically important diseases. Due to the flexible design, the agents can be adopted for multiple imaging modalities, including MRI and nuclear imaging. To validate MPO imaging results, we have established a specific method for assaying tissue MPO activity. Recently, we have developed a new generation of highly efficacious MRI agent targeting MPO activity that is up to 3X more sensitive than prior generation, which is the subject of this grant application.

a. **Chen JW**, Querol Sans M, Bogdanov A Jr, Weissleder R. Imaging of myeloperoxidase in mice by using novel amplifiable paramagnetic substrates. Radiology. 2006 Aug;240(2):473-81.

b. Rodriguez E, Nilges M, Weissleder R, **Chen JW**. Activatable magnetic resonance imaging agents for myeloperoxidase sensing: mechanism of activation, stability, and toxicity. J Am Chem Soc, 2010, 132(1):168-77. PMCID: PMC2802665.

c. Wang C, Keliher E, Zeller MWG, Wojtkiewicz GR, Aguirre AD, Buckbinder L, Kim H-Y, Chen J, Maresca K, Ahmed MS, Jalali Motlagh N, Nahrendorf M**, Chen JW**. An activatable PET-imaging radioprobe is a dynamic reporter of myeloperoxidase activity in vivo. Proc Natl Acad Sci U S A, 2019, 116(24):11966-11971. PMCID: PMC6575581.

d. Wang C, Cheng D, Jalali Motlagh N, Kuellenberg EG, Wojtkiewicz GR, Schmidt SP, Stocker R, **Chen JW**. Highly efficient activatable MRI probe to sense myeloperoxidase activity. J Med Chem, 2021, 64(9), 5874-5885. PMCID: PMC8564765.

2. Multiple sclerosis (MS) is the most common neurological disease affecting young patients. Its diagnosis and treatment are challenging. I showed that MPO imaging sensitivity and specifically reports MPO activity to noninvasively identify inflammatory demyelinating lesions in the brain in mouse models of MS, even during the clinically quiescent stage. We further provided evidence that linked MPO imaging to the innate immune response in murine MS, demonstrating that longitudinal MPO imaging mirrored the temporal changes of myeloid immune cells in the inflamed brain and can be used to track therapeutic response. Using MPO imaging, we demonstrated that chronic cerebrospinal venous insufficiency did not cause neuroinflammation or demyelinating lesions, thus helping to settle this phenomenon as an etiology for MS. We also found MPO is a potential therapeutic target for MS. We recently discovered that D-mannose can suppress MPO activity and block phagocytosis in neuroinflammation.

a. **Chen JW**, Breckwoldt MO, Aikawa E, Chiang G, Weissleder R. Myeloperoxidase-targeted imaging of active inflammatory lesions in murine experimental autoimmune encephalomyelitis. Brain. 2008;131(Pt 4):1123-33. PMCID: PMC4044727.

b. Pulli B, Ali M, Wojtkiewicz GR, Iwamoto Y, Li A, **Chen JW**. Myeloperoxidase Immunoradiology Improves Detection of Acute and Chronic Experimental Multiple Sclerosis. Radiology, 2015, 275(2):480-9. PMCID: PMC4455671.

c. Zhang Y, Dong H, Seeburg DP, Wojtkiewicz GR, Waterman P, Pulli B, Forghani R, Ali M, Iwamoto Y, Swirski FK, Chen JW. Multimodal Molecular Imaging Demonstrates Myeloperoxidase Regulation of Matrix Metalloproteinase Activity in Neuroinflammation. Mol Neurobiol. 2019, 56(2):954-962. PMCID: PMC6261713.

d. Wang J, Jalali Motlagh N, Wang C, Wojtkiewicz GR, Schmidt S, Chau C, Narsimhan R, Kuellenberg EG, Zhu C, Linnoila J, Yao Z, **Chen JW**. D-mannose suppresses oxidative response and blocks phagocytosis in experimental neuroinflammation. P Natl Acad Sci U S A, 2021, 118(44), e2107663118.

3. Stroke is one of the most devastating and common causes of morbidity and mortality in the United States, and treatment is limited to the first few hours after stroke. I demonstrated that MPO imaging noninvasively tracks the inflammatory response as the stroke evolves. I found that MPO activity remains elevated up to 21 days post stroke in experimental murine stroke, and in vivo MPO activity correlates positively with infarct size. In mouse models of embolic stroke using thrombi or microbeads, we demonstrated that MPO activity is elevated even in these small infarcts. I found that by inhibiting MPO activity, we markedly decreased infarct size and substantially improved neurobehavioral and survival of stroke animals. MPO inhibition was effective even when given during the subacute stage of stroke, a time point few therapeutic options currently exist. We also demonstrated that MPO inhibition can provide neuroprotection and increase neurogenesis after stroke.

a. Breckwoldt MO*, **Chen, JW***, Stangenberg L, Aikawa E, Rodriguez E, Liu S, Moskowitz M, Weissleder R. Tracking the inflammatory response in stroke in vivo by sensing the enzyme myeloperoxidase. P Natl Acad Sci U S A. 2008;105:7387-7392. (*co-first authors). PMCID: PMC2587593.

b. Forgani R, Kim HJ, Wojtkiewicz GR, Bure L, Wu Y, Hayase M, Wei Y, Zheng Y, Moskowitz MA, **Chen JW**. Myeloperoxidase propagates damage and is a potential therapeutic target for subacute stroke. J Cereb Blood Flow Metab, 2015, 35(3):485-93. PMCID: PMC4348390.

c. Kim H, Wei Y, Lee JY, Wu Y, Zheng Y, Moskowitz MA, **Chen JW**. Myeloperoxidase inhibition increases neurogenesis after ischemic stroke. J Pharmacol Exp Ther. 2016, 359(2):262-72. PMCID: PMC5074486.

d. Kim HY, Wei Y, Wojtkiewicz G, Lee JY, Moskowitz MA, **Chen JW**. Reducing myeloperoxidase activity decreases inflammation and increases cellular protection in ischemic stroke. J Cereb Blood Flow & Metab, 2019, 39(9), 1864-1877. PMCID: PMC6727136.

4. Nonalcoholic fatty liver disease (NAFLD) is a major public health challenge because of increasing prevalence, difficulty in diagnosis, complex pathogenesis, and lack of approved therapies. My coworkers and I identified myeloperoxidase (MPO) is an important oxidative enzyme in NAFLD. In human liver biopsy samples, there is increased MPO activity in NASH samples compared with steatosis samples. In murine NASH models, MPO contributes to hepatocyte injury, activates transforming growth factor-β (TGF-β) and hepatic stellate cells (HSCs), and promotes fibrosis. Conversely, in MPO-deficient mice, we found reduced hepatocyte injury, decreased levels of TGF-β, fewer activated HSCs, and less severe fibrosis (4). In addition, MPO can activate matrix metalloproteinases (MMPs) (5) that can also cause hepatocyte apoptosis (6, 7). We also showed that MPO imaging can differentiate NASH from steatosis in animal models of NASH and in human biopsy samples.

a. Pulli B, Ali M, Iwamoto Y, Zeller MW, Schob S, Linnoila JJ, **Chen JW**. Myeloperoxidase-hepatocyte-stellate cell crosstalk promotes hepatocyte injury and fibrosis in experimental NASH. Antioxid Redox Signal. 2015, 23(16):1255-1269. PMCID: PMC4677570.

b. Puli B, Wojtkiewicz GR, Iwamoto Y, Ali M, Zeller MW, Bure L, Wang C, Choi Y, Masia R, Guimaraex AR, Corey KE, **Chen JW**. Molecular MR imaging of myeloperoxidase distinguishes steatosis from steatohepatitis in Non-Alcoholic Fatty Liver Disease, Radiology, 284(2):390-400. PMCID: PMC5548451.

Complete List of Published Work in my Bibliography (90 publications; 4 chemistry publications from 1994-1998 not indexed by pubmed):
http://www.ncbi.nlm.nih.gov/pubmed/?term=(chen%2Bjw+and+massachusetts)+OR+(chen%2Bjw+and+stanford)+OR+(chen%2Bjw+and+paramagnetic)+OR+(chen%2Bjw+and+myeloperoxidase+and+2009)+NOT+zebrafish+NOT+carbachol)+OR+(charest+EGFR+2009+not+dendriworms)