POSTER SESSION
Thursday, October 28th
4:30 - 6:00 PM

LIST OF POSTERS

1. **Ivy Rosales, *et al***. Precision MR Imaging of Reactive Oxygen Species in a Mouse Model of Ischemia Reperfusion Injury.

2. **Negin Jalali Motlagh, *et al***. Molecular MRI targeting myeloperoxidase activity reveals effects of D-mannose on host response and glioma progression.

3. **Cuihua Wang, *et al***. A new generation of activatable MRI probe to detect myeloperoxidase activity and inflammation.

4. **Zeyneb Alshelh, *et al***. Neuro-immune signatures in chronic low back pain subtypes.

5. **Jessica Wang, *et al***. In vivo evaluation of COX-2 PET radiotracer [11C]BRD1158 in the Thy-1-COX-2 transgenic mouse model of human-COX-2 overexpression.

6. **Homan Kang, *et al***. Tumor-Associated Immune Cell Mediated Tumor Targeting Mechanism with NIR-II Fluorescence Imaging.

7. **Ludovica Brusaferri, *et al***. The Pandemic Brain: neuroinflammation in healthy, non-infected individuals during the COVID-19 pandemic.

8. **Hannah Bues, *et al***. A pilot study showing increased dorsal anterior cingulate cortex neuroinflammation in both long-term infectious onset chronic fatigue syndrome and recent onset ‘Long-COVID’.

9. **Vishal Birar, *et al***. Development of brain penetrant P2ry12 ligands towards microglia specific PET radiotracers.

10. **Christin Sander, *et al***. [11C]PBR28 radiotracer kinetics are not driven by alterations in cerebral blood flow.

Authors: Ivy Rosales,1 Mozhdeh Sojoodi,2 Ilknur Ay,3 Iris Yuwen Zhou,3 Huan Wang,3 Kenneth K. Tanabe,2 Peter Caravan,3 Eric M. Gale3*

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Title: Precision MR Imaging of Reactive Oxygen Species in a Mouse Model of Ischemia Reperfusion Injury

Abstract:
Objective: Imaging of extracellular reactive oxygen species (ROS) has been proposed as a non-invasive biomarker of inflammation. The goal of this work is to evaluate the capability of the oxidatively activated MR imaging probe Fe-PyC3A which upon oxidation changes from the virtually MR silent Fe2+ state to the strongly MR visible Fe3+ state, to image kidney inflammation in a unilateral mouse model of kidney ischemia reperfusion (IR) injury.

Methods: IR injury was generated via 26 min ligation of the left renal artery. MR Imaging was performed 1 day after IR injury. Wild type C57BL6 mice were imaged with a 3D T1-weighted sequence prior to and out to 20 minutes after injection of Fe-PyC3A, and then again following injection of gadoterate meglumine as non-oxidatively activated negative control probe. To confirm the link between Fe-PyC3A generated kidney MR signal increase and inflammation, IR injury and MR imaging were performed on gp91phox knockout mice in which myeloid leukocytes are incapable of respiratory burst. Ischemic damages and inflammation were confirmed ex vivo by H&E and IHC for myeloperoxidase positive cells. (Post-pre)injection change in kidney vs. muscle contrast-to-noise ratio (dCNR) in IR and normal contralateral kidney following Fe-PyC3A injection to both WT and gp91phox knockout mice were compared by two-way ANOVA followed by Tukey's post-test for multiple comparisons.

Results: Fe-PyC3A generates virtually no signal in normal kidney but strong signal in the outer medulla and cortex of the IR kidney within seconds of injection. Gadoterate generates strong signal in both kidneys. IR kidney vs muscle dCNR is significantly lower in gp91phox knockout mice compared to WT mice.

Conclusion: ROS imaging with Fe-PyC3A represents a potentially powerful technology to non-invasively diagnose, map, and monitor kidney inflammation.

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Title: Molecular MRI targeting myeloperoxidase activity reveals effects of D-mannose on host response and glioma progression

Abstract:
Purpose: Host immune response in the tumor microenvironment plays key roles in tumorigenesis. We aimed to determine the effect D-mannose, a drug with anti-inflammatory properties, has on oxidative stress and glioma progression using molecular MRI targeting myeloperoxidase (MPO), a highly oxidizing enzyme secreted in host defense, in a mouse glioma model.

Methods and Materials: Twenty-three immunocompetent C57BL/6J mice were intracranially implanted with CT-2A-luc mouse glioma stem cells. Three days after tumor implantation, mice were randomly divided into two groups (n= 11-12 per group) and treated intraperitoneally daily with 450mg/kg either D-mannose or with PBS as control. To evaluate MPO activity in vivo, mice were imaged on a 4.7T MRI scanner with 0.3mmol/kg of bis-5HT-DTPA-Gd (MPO-Gd) administered intravenously at 4 weeks after implantation. MPO activity assay and flowcytometry of brain leukocytes were also performed after MRI. Tumor size was tracked by bioluminescence (BLI) and MRI. In vitro MPO activity experiments were performed using activated leukocytes incubated with D-mannose (1 mg/ml, 2 mg/ml, 4 mg/ml). $P<0.05$ was considered statistically significance.

Results: D-mannose treatment decreased the size of gliomas compared to those that were PBS-treated (mean ± SEM, $p=0.0042$ for BLI and $p=0.0014$ for MRI). Surprisingly, D-mannose increased MPO-Gd enhancement in the peritumoral brain parenchyma ($p=0.015$) a result corroborated by ex vivo MPO activity assays (mean ± SEM, $p<0.0001$ for MPO protein, $p=0.0485$ for MPO activity). On flowcytometry, D-mannose-treated glioma mice contained fewer MPO-containing cells compared to PBS-treated glioma mice (mean ± SEM, $p<0.0001$), revealing that D-mannose increased MPO secretion. In vitro experiments further confirmed that D-mannose increased MPO activity.

Conclusions: Our results revealed that D-mannose unexpectedly increased secretion of active MPO from inflammatory leukocytes into the glioma microenvironment and this increased host immune response acted to reduce tumor size. Our study suggests that increasing MPO activity such as D-mannose administration may be potential new therapeutic direction for glioma treatment

Authors: Cuihua Wang, David Cheng, Negin Jalali Motlagh, Enrico G. Kuellenberg, John W. Chen#

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Title: A new generation of activatable MRI probe to detect myeloperoxidase activity and inflammation*

Abstract
Objective: Myeloperoxidase (MPO) is a highly oxidative and pro-inflammatory enzyme that can generate reactive oxygen/nitrogen species and cause tissue damage if overexpressed. MPO is implicated in multiple inflammatory diseases, and its activity can be noninvasively detected by MPO-Gd, an activatable MRI probe. However, the linear chelate used in MPO-Gd raised safety concerns and its relatively small increase in relaxivity after activation limited its translational potential. In this study, we aimed to develop a more stable and efficient MRI probe to detect MPO activity.

Methods: We designed and synthesized a highly efficient myeloperoxidase activatable MRI probe (heMAMP) that contains the macrocyclic DOTA as chelating moiety and two MPO-activatable 5-hydroxyindole moieties linked through a rigid amide bond. We validated the specificity and efficacy of heMAMP both in vitro and in vivo in rodent models of subcutaneous inflammation with wildtype and MPO-KO mice and unstable carotid atherosclerosis (tandem stenosis) with and without MPO inhibition (AZM198). We compared heMAMP with MPO-Gd and the conventional MRI agent DOTA-Gd.

Results: heMAMP demonstrated markedly higher Gd stability and greater relaxivity change after activation by MPO. In a mouse model of subcutaneous inflammation, heMAMP demonstrated a 2-3-fold increased contrast-to-noise ratio (CNR) compared to MPO-Gd, and 4-10 times higher CNR compared to conventional DOTA-Gd. The signal increase at the dose of 0.1 mmol/kg was comparable to that of MPO-Gd at 0.3 mmol/kg while little CNR increase was observed in MPO-KO mice, confirming the in vivo specificity of heMAMP. The increased efficacy of heMAMP was further confirmed in vivo in a model of unstable atherosclerotic plaque where heMAMP showed a comparable signal change and responsiveness to MPO inhibition at 3-fold lower dosage compared to MPO-Gd.

Conclusion: heMAMP is a potential translational candidate with superior stability and efficacy compared to MPO-Gd and other activatable analogues to detect MPO activity and inflammation.

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Title: Neuro-immune signatures in chronic low back pain subtypes

Abstract:
We recently showed that patients with different chronic pain conditions demonstrated elevated brain and/or spinal cord levels of the glial marker 18kDa translocator protein, which suggests that neuroinflammation might be a pervasive phenomenon observable across multiple etiologically heterogeneous pain disorders. Interestingly, the spatial distribution of this neuroinflammatory signal appears to exhibit a degree of disease specificity, suggesting that different pain conditions may exhibit distinct "neuroinflammatory signatures". To explore this hypothesis, we tested whether neuroinflammatory signal can characterize putative etiological subtypes of chronic low back pain patients based on clinical presentation. Specifically, we explored neuroinflammation in patients whose chronic low back pain either did or did not radiate to the leg (i.e., "radicular" vs. "axial" back pain).

Fifty-four chronic low back pain patients, twenty-six with axial back pain (43.7±16.6 y.o. [mean±SD]) and twenty-eight with radicular back pain (48.3±13.2 y.o.), underwent PET/MRI with [11C]PBR28, a second-generation radioligand for the 18kDa translocator protein. [11C]PBR28 signal was quantified using standardized uptake values ratio. Functional MRI data were collected simultaneously to the [11C]PBR28 data 1) to functionally localize the primary somatosensory cortex back and leg subregions and 2) to perform functional connectivity analyses. PET and functional MRI measures were compared across groups, cross-correlated with one another and with the severity of "fibromyalgianess". Furthermore, statistical mediation models were employed to explore possible causal relationships between these three variables.

For the primary somatosensory cortex representation of back/leg, [11C]PBR28 PET signal and functional connectivity to the thalamus were: 1) higher in radicular compared to axial back pain patients, 2) positively correlated with each other and 3) positively correlated with fibromyalgianess scores, across groups. Finally, 4) fibromyalgianess mediated the association between [11C]PBR28 PET signal and primary somatosensory cortex-thalamus connectivity across groups.

Our findings support the existence of "neuroinflammatory signatures" that are accompanied by neurophysiological changes, and correlate with clinical presentation in chronic pain patients. These signatures may contribute to the subtyping of distinct pain syndromes and provide information about inter-individual variability in neuro-immune brain signals, within diagnostic groups, that could eventually serve as targets for mechanism-based precision medicine approaches.

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Title: In vivo evaluation of COX-2 PET radiotracer [11C]BRD1158 in the Thy-1-COX-2 transgenic mouse model of human-COX-2 overexpression

Abstract:
Cyclooxygenase-2 (COX-2) is a prostaglandin-generating enzyme that exhibits low basal expression levels and is specifically upregulated in the brain in response to inflammatory challenges. COX-2 has been implicated in neurodegenerative and neuroinflammatory disease pathogenesis and is the major target of non-steroidal anti-inflammatory drugs (NSAIDs). We previously reported that BRD1158 is a selective COX-2 inhibitor with improved COX-2 affinity, plasma free fraction (fu,p) and faster on-rate (kon) compared to existing COX-2 ligands including rofecoxib, celecoxib, and MC1. [11C]BRD1158 demonstrated saturable and COX-2-specific binding in vivo with PET in a localized overexpression rat model (intrastriatal AAV-COX-2).

Objective: To further validate the performance of this radiotracer in vivo, we imaged Thy-1-COX-2 transgenic mice that constitutively overexpress human-COX-2 in neurons of the amygdala, striatum, cerebral cortex and hippocampus. We hypothesize that [11C]BRD1158 uptake correlates positively with COX-2 expression.

Methods: BRD1158 was radiolabeled at the methylsulfone by treating the corresponding thioester precursor with [11C]CH3I. Brain uptake of this radiotracer was evaluated by measuring whole-brain SUV in mice with PET-MR. Regional brain time activity curves were generated with PMOD using M. Mirrione mouse atlas.

Results: In vivo PET studies showed [11C]BRD1158 has high brain uptake and favorable wash out kinetics in both transgenic (whole-brain SUV Cmax = 1.9; t1/2 = 43.2 min) and wild type mice (whole-brain SUV Cmax = 1.5; t1/2 = 3.08 min). Our data show significantly higher radiotracer uptake in Thy-1-COX-2 transgenic mice (SUV30-50min = 0.869) compared to wild type control (SUV30-50min = 0.140). We report a 515% increase in [11C]BRD1158 whole-brain binding in Thy-1-COX-2 mice compared to WT.

Conclusion: In vivo PET-MR imaging studies with [11C]BRD1158 show significantly higher brain uptake in Thy-1-COX-2 transgenic mice in specific brain regions that overexpress human-COX-2 compared to wild type mice. We demonstrate that [11C]BRD1158 is a COX-2-specific radiotracer with favorable pharmacokinetic properties that enable in vivo evaluation of COX-2 activity. Future work will prepare for first in-human [11C]BRD1158 PET neuroimaging of COX-2.

Authors: Homan Kang, Hak Soo Choi

Institution: Massachusetts General Hospital

Title: Tumor-Associated Immune Cell Mediated Tumor Targeting Mechanism with NIR-II Fluorescence Imaging

Abstract:
Objective: The strategy of structure-inherent tumor targeting (SITT) with cyanine-based fluorophores is getting more attention because no chemical conjugation of targeting moieties is required. However, the targeting mechanism behind SITT has not yet been well explained. Here, we demonstrate that heptamethine cyanine-based fluorophores possess not only targetability of tumor microenvironments without the need for additional targeting ligands but also NIR-II imaging capabilities.

Methods: The TAIC-mediated tumor targeting mechanism was confirmed by flow cytometry and histological studies, in vivo NIR-II fluorescence imaging, and 3D tomographic imaging.

Results: Among the tested, the NIR-II capability of SH1 allows for deep tissue imaging in vivo such as bone marrow, cerebral vasculature, and blood vessels in tumors with improved resolution. With TAIC-mediated tumor-targeting, SH1 provided diverse tumor targetability with a high tumor-to-background ratio (TBR) ranging from 9.5 to 47 in pancreatic, breast, and lung cancer mouse models upon a single bolus intravenous injection. Using the state-of-the-art TriFoil InSyTe FLECT/CT imaging device, the fate of SH1 could be followed in real-time in full 3D in tumor-bearing animal models.

Conclusion: In this study, inspired by our recent success in the development of organ- or disease-specific fluorophores, we designed and synthesized TAIC-targeted fluorophore SH1 as a SITT agent for intraoperative NIR-II fluorescence imaging. The NIR-II capability of SH1 along with the InGaAs camera built-in NIR-II imaging system greatly facilitated image quality permitting the observation of signals in deep tissues and significantly improved the sensitivity in intraoperative cancer surgery. The SH1 fluorophore can reach a high TBR (9 to 47 in various cancer types) in tumor sites in comparison with healthy tissue. Furthermore, SH1 can also be used to detect small lesions such as metastatic tumors. Thus, SH1 presents itself as a promising cancer-targeting agent which will have a bright future in intraoperative optical imaging.

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Title: The Pandemic Brain: neuroinflammation in healthy, non-infected individuals during the COVID-19 pandemic

Abstract:
Objective: To determine whether neuroinflammation is an underlying mechanism for the variety of "sickness behavior"-like symptoms experienced by many during the pandemic, including among the non-infected.

Methods: Retrospective case-control study conducted on PET/MR imaging and serum data from healthy individuals' data acquired either before or after the COVID-19 pandemic onset. We compared fifty-seven 'Pre-Pandemic' and fifteen 'Pandemic' datasets from individuals originally enrolled as control subjects for various completed or ongoing, research studies available in our records. Because the focus of this study was on "sterile", and not virally-mediated, neuroimmune activation, only individuals with a confirmed negative test for SARS-CoV-2 antibodies at the time of the scan were included in the 'Pandemic' group. Main outcomes and measures were: Glial imaging markers (the 18 kDa translocator protein, TSPO, and myoinositol), serum inflammatory markers (interleukin-16, monocyte chemoattractant protein-1), PLS1 component for gene enrichment, clinical variables (physical and mental fatigue, dyscognition and mood alterations).

Results: Healthy individuals examined after the pandemic onset demonstrated elevated brain levels of (neuro)inflammatory markers, compared to those evaluated pre-pandemic. Subjects endorsing higher symptom burden showed higher TSPO signal in the hippocampus (mood alteration, mental fatigue), intraparietal sulcus and precuneus (physical fatigue), compared to those reporting little/no symptoms. Finally, TSPO signal elevations observed after the pandemic onset were spatially aligned with the patterns of constitutive expression of several genes involved in immune/neuroimmune functions.

Conclusion: This study is responsive to the increasing calls for studies promoting a better understanding of the effects of the pandemic on brain and mental health. The results of our analyses support a possible link between sterile-neuroinflammation and pandemic-related psychological distress and highlight the impact of the pandemic, which extends beyond the morbidity and mortality directly caused by the SARS-CoV-2 virus itself.

Authors: Hannah Bues, Minhae Kim, Ludovica Brusaferri PhD, Zeynab Alshelh PhD, Donna Felsenstein MD, Darin Dougherty MD, Marco Loggia PhD, Michael VanElzakker PhD

Institution: Massachusetts General Hospital/Harvard Medical School

Title: A pilot study showing increased dorsal anterior cingulate cortex neuroinflammation in both long-term infectious onset chronic fatigue syndrome and recent onset ‘Long-COVID’

Abstract:
Objective: The COVID-19 pandemic has caused an epidemic of “Long-COVID” or PASC (post-acute sequelae of COVID-19). People who fail to fully recover from acute COVID-19 report symptoms of fatigue, cognitive problems, light and noise sensitivities, and difficulty recovering from exertion. These symptoms strongly overlap with the existing symptom-based diagnostic label of chronic fatigue syndrome or myalgic encephalomyelitis (ME/CFS). While preliminary evidence suggests that ME/CFS symptoms may be driven by inflammatory processes in the central nervous system, little is known about the mechanisms of Long-COVID. Thus, the goal of the current study is to use positron emission tomography (PET) to study neuroinflammation in ME/CFS and Long-COVID patients.

Methods: In this ongoing study, neuroinflammation is quantified with the PET radioligand [11C]PBR28 which binds to a microglial activation-associated protein called TSPO. After injection with [11C]PBR28, participants’ brains are scanned by a dual PET-MR (magnetic resonance) scanner. The current pilot data show PET scans from one 29-year-old male with recent-onset ‘Long-COVID’ and one 66-year-old female with ME/CFS for 18 years. Healthy control scans are age, sex, and genotype matched. In this analysis, the occipital lobe was used as a reference region.

Results: In this preliminary analysis, the Long-COVID and the ME/CFS cases show similar patterns of increased PBR28 uptake in the dorsal anterior cingulate cortex (dACC), relative to control scans.

Conclusion: The dACC is a key structure in the maintenance of cognitive control, and is also known to be particularly sensitive to neuroinflammation. Thus, increased uptake in the dACC may explain the subjective “brain fog” symptoms that these patients experience. We hypothesize that analyses following further recruitment will show increased [11C]PBR28 uptake in the dACC, caudate nucleus, insular cortex, and dorsal brainstem. Future analyses will include fMRI of a dACC-activating task and MRS (magnetic resonance spectroscopy).

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Title: Development of brain penetrant P2ry12 ligands towards microglia specific PET radiotracers

Abstract:
Objective: There is emerging evidence that microglia play an important role in some of the earliest pathological events, including synaptic loss [1]. Currently, there is no way to study how these distinctive molecular signatures evolve throughout disease in the living human brain. One specific receptor, P2ry12, which is only expressed on microglia in the brain, appears to signify (and be mechanistically involved in) the change of microglia from homeostasis to other ‘active’ phenotypic states [2]. P2ry12 expression is lost in microglia during disease progression in mouse models and human multiple sclerosis, amyotrophic lateral sclerosis and Alzheimer’s disease. We have designed, synthesized, and characterized brain penetrant P2ry12 ligands as potential brain PET radiotracers.

Materials and Methods: Five novel P2ry12 radiotracers were synthesized and evaluated for brain uptake in vivo with PET in Sprague-Dawley rats. [11C]MP3-21 and [11C]MP3-30 were synthesized from their corresponding aryl bromides and radiolabeled via Pd-catalyzed cyanation with [11C]HCN. [11C]MP4-28, [11C]NS-21, and [11C]NS-14 were radiolabeled by 11CO2-fixation from their decoupled amines to form the corresponding [11C]urea.

Results: [11C]MP3-21 displayed low brain uptake (SUV = 1.1 at peak) and rapid washout kinetics in the rat brain (likely attributed to the acidic acyl sulfonamide linker). [11C]MP3-30 exhibited increased brain uptake (SUV = 1.5 at peak) with slower wash out kinetics, but failed to demonstrate saturable binding when blocked with its C-12 isotopologue, indicating high nonspecific binding. [11C]MP4-28 exhibited low brain uptake (SUV = 0.85 at peak), possibly due to its high molecular weight (416.9 g/mol) and lipophilicity (cLogP 4.24). [11C]NS-21, exhibited increased brain uptake (SUV = 1.5 at peak), but allyl [11C]NS-14 had high brain uptake (SUV = 4.2 at peak) and good kinetics likely attributed to its favorable physicochemical properties (Mol. Wt. 366.85 g/mol, cLogP 3.3, tPSA 74).

Discussion/Conclusion: [11C]NS-14 displayed high uptake in rat brain, and is the first reported brain penetrant p2ry12 ligand. Unfortunately, binding results indicated a decrease in affinity warranting further development. We are currently designing a larger chemical library of novel ligands optimized for high binding affinity and brain uptake as P2ry12 PET radiotracers.

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Title:
[11C]PBR28 radiotracer kinetics are not driven by alterations in cerebral blood flow

Abstract:
Objective: The positron emission tomography (PET) radiotracer [11C]PBR28 has been increasingly used to image the translocator protein (TSPO) as a marker of neuroinflammation in a variety of brain disorders. Interrelatedly, similar clinical populations can also exhibit altered brain perfusion, as has been shown using arterial spin labelling (ASL) in magnetic resonance imaging (MRI) studies. Hence, an unsolved debate has revolved around whether changes in perfusion could alter delivery, uptake, or washout of the radiotracer [11C]PBR28, and thereby influence outcome measures that affect interpretation of TSPO upregulation. The goal of this study was to experimentally test whether [11C]PBR28 pharmacokinetics and outcome measures are driven by alterations in cerebral blood flow (CBF).

Methods: Simultaneous PET/MRI with a bolus injection of the radiotracer [11C]PBR28 was acquired for 90 min, together with pseudo-continuous ASL, in two experimental designs: In human subjects, [11C]PBR28-SUV ratios and ASL-derived CBF from 15 low back pain patients was compared to 19 controls. In non-human primates, increases in CBF were induced with a hypercapnia intervention, while [11C]PBR28 outcome parameters were determined using a 2-tissue compartmental model.

Results: We demonstrate that [11C]PBR28 signal elevations in low back pain patients are not accompanied, in the same regions, by increases in CBF compared to healthy controls, and that areas of marginal hypoperfusion are not accompanied by decreases in [11C]PBR28 signal. In non-human primates, we show that hypercapnia-induced increases in CBF during radiotracer delivery or washout do not alter [11C]PBR28 outcome measures.

Conclusion: The combined results from two methodologically distinct experiments provide support from human data and direct experimental evidence from non-human primates that changes in CBF do not influence outcome measures reported by [11C]PBR28 PET imaging studies and corresponding interpretations of the biological meaning of TSPO upregulation.