IOWA HEALTH CARE | Holden Comprehensive Cancer Center

Program 3: Free Radical Metabolism and Imaging (FRMI)

April 2, 2025

NCI Designated Comprehensive Cancer Center

CHANGING MEDICINE.
CHANGING LIVES.®

Our Program

Theme 1

Free radical biology and redox-based therapeutics

Theme 2

Monitoring patient outcomes with molecular imaging

Theme 3

Novel approaches to improving theranostics

Program Co-Leader
Douglas Spitz, PhD

Program Co-Leader
Yusuf Menda, MD

Program Snapshot

Program Overview
37 Full Members
7 Associate Members

New Members
- **Sarah Short, PhD**
- **Calvin Carter, PhD**
- **Michael Petronek, PhD**
- **Andrean Simons-Burnett, PhD**
- **Sanjana Dayal, PhD**
- **Kailin Yang , MD, PhD**

FRMI Publications	
Total Publications	65
High Impact	7 (11%)
Intra-Programmatic	22(34%)
Inter-Programmatic	12(18%)
Multi-Institutional	32(50%)

High Impact Collaborative NCI Grants
NCI SPORE (Quelle, Howe, Menda, MPI)
A0 - Score 20
NCI P01 CA217797 (Cullen, Spitz, MPIs)
NCI T32 CA078586-25 (Spitz, PI); Competitive Renewal Burnett/Spitz (MPIs) Score - 20
NCI P01 CA244091 (Spitz Project 4 Co-leader)

Specific Funding Source	Direct Costs 2/1/2025
NCI Peer-Review Projects	$1,925,500
Other NIH Peer-Review Projects	$2,001,227
Other Peer-Review Projects	$46,450
Total Peer Reviewed	$3,973,177

New Grants 2024

London, Barry and Allen, Bryan (MPIs):
NIH/NIAID U01 AI184289 6/2024-5/2027

Sex-dependent Impairment of Nitric Oxide Signaling and Mitochondrial Metabolism in Radiation-Induced Cardio-Pulmonary Dysfunction

Goal: Identify mechanisms using redox biochemistry for inhibiting cardiac injury during radiation exposure.

Burnett, Andrean (PI):
NIH/NIDCR R01DE033695 9/2024-8/2029

Inflammation and EGFR crosstalk in HNSCC Therapy

Goal: To elucidate mechanisms by which EGFR and inflammation can be manipulated to improve head and neck cancer therapies outcomes.

VA Merit I01BX004829-05A2 1/2025-12/2028

IL-1-based immunotherapy in HNSCC

Goal: To study mechanisms for enhancing IL-1-based immunotherapy in HNSCC.

FRMI – 2020 Excellent to Outstanding

Strengths:
- Led by investigators with complementary expertise
- FRMI program is a cornerstone program of the HCCC
- Free radical component under the exceptional leadership of Dr. Spitz
- There is evidence of moving preclinical hypothesis to clinical studies
- The work on ascorbate demonstrates the impact of the interaction between basic and clinical investigators

Weaknesses Identified	Response
Imaging component, it is not as strong as the free radical component due to lack of innovation and clearly articulated vision beyond its role in complementing the redox metabolism aspect of this program	• Moving forward with strong new investment in a 203/212Pb theranostic program for combining high LET targeted CXCR4 therapy with redox biology manipulations in preclinical and clinical work resulting in an impact score of 20 on the A0 NET SPORE submission reviewed in Feb 2025. • Strong MRI and PET imaging projects providing biomarkers for predicting responses imbedded in the pharmacological ascorbate P01 resulting in new grant submissions and papers.
The program has not fully realized the potential of tumor genomics and epigenetics in complementing the research done in this program.	Moving forward with studies in collaboration with CGP for targeted genomics to interface with redox biology program around Keap1 mutations, redox biology, development of resistance, and therapy responses. Completed a retreat with CGP that supported joint Oberley awards.

EAB Comments 2023

Strengths:

• Unique and impactful program. History of pioneering new understanding of radiation biology and translational research.
• Focus on redox biochemistry, novel discovery in the area of metabolic imaging, and development of new cancer therapeutics based on metabolic changes.
• High impact examples of using MRI imaging to predict therapeutic response in glioblastoma, development of novel combinations for head and neck cancer, and studies which identified mechanisms to protect normal tissue in models of colon cancer radiotherapy.
• Impressive program leadership with a well-articulated vision as well as strategies to address the needs of the catchment area through discovery and translation.
• The development of a prudent succession plan for leadership changes. New leadership as DEO of Radiation Oncology (Dr. Allen) and the Division of Free Radical and Radiation Biology (Dr. Simons-Burnett) provides a good opportunity to bring new resources to recruit a nationally recognized investigator to lead the science in this program.
• Recent acquisition of an MR-Linac will further increase the opportunity for translation and novel trial design in the radiation oncology space.
• The program is pioneering strategies to advance understanding of new, promising theranostics.

Weakness:

• There remains a lack of programmatic focus for some of the imaging scientists in the program. The program was involved in the NET SPORE submission and further opportunities exist to consider acceleration of translational imaging studies.

Program Integration with Training and Education

FRMI Related Research Activities

Journal clubs weekly
Seminars weekly
Translational Research Meeting with all programs presenting weekly
Normal tissue PPG working group
Redox regulation of immunology working group
P3 Award for Redox Regulation of Immunology in lung cancer therapy
P3 FLASH Program and summer fellowship program

With Office of Cancer Career Enhancement and Training (OCCET)

FRMI has initiated an integration of the Free Radical and Radiation Biology T32 with the Cancer Biology program with 3 pre-doc and 3-post trainees shared among 28 faculty mentors. Competitive Renewal Reviewed 2-2025; **Impact score - 20**

Pre-Doc	Post-Doc
Kyle Current (FRRB) – Dr. London	2 Positions Open
Akshaya Warrier (CBIO) – Dr. Dodd	Dr. Sunny Huang – Drs. Carter/Spitz
Amanda Pope (CBIO) - Drs. Henry/Cullen	Dr. Michael Schrodt – Dr. Short
Ellen Voigt (CBIO) – Dr. Quelle	

- Mentoring: 2 CBIO grad, 2 summer undergrads, 2 ICARE Postbacs
- Emerging Leaders Council: 4 members 2024-2025

FRMI Integration with COE

Program Liaison

Jessica Sieren, PhD
Associate Professor
Department of Radiology

Iowa Cancer Consortium Members

# Joined	# Active
4	2

Researcher Videos on COE Website

- Jessica Sieren, PhD: Using AI to improve lung cancer detection & treatment
- Claudia Mello-Thoms, PhD: Reducing diagnostic error in radiology

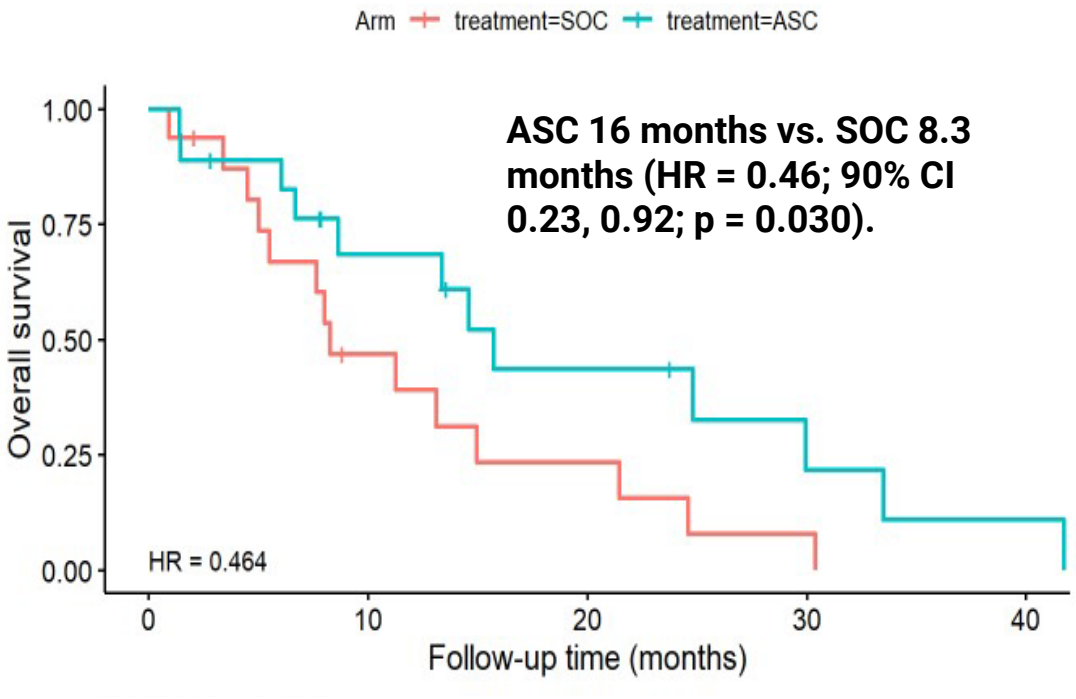
COE Collaborative Webinar Series

- 1 researcher presented during one session and engaged as a participant in several other sessions

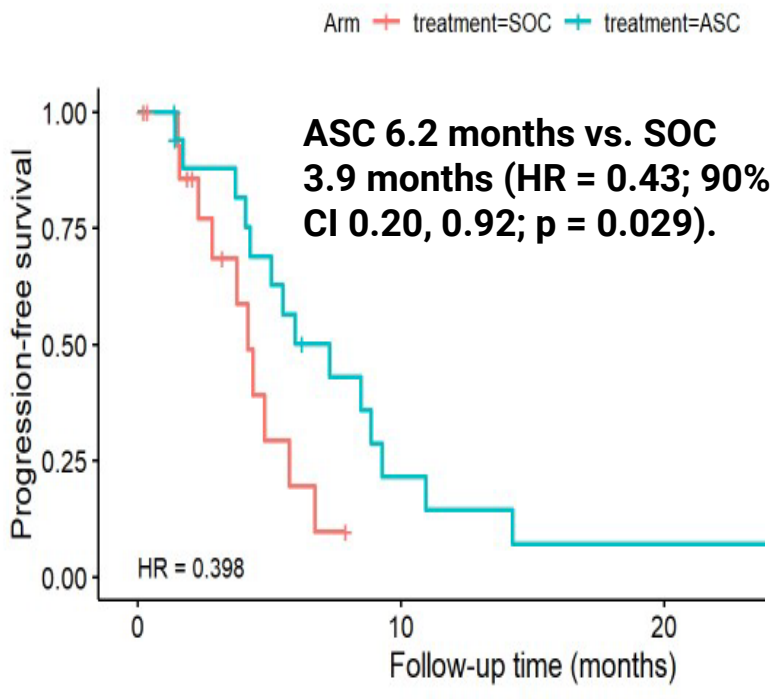
Iowa Cancer Registry 99 Counties Project

- Project aims to enhance community engagement and education around cancer prevention and control across all 99 counties
- 2 researchers are participating in the 99 Counties Project

Scientific Highlight – Collaboration: ET & FRMI & CEPS Pharmacological Ascorbate and Pancreatic Cancer Therapy



ASC 16 months vs. SOC 8.3 months (HR = 0.46; 90% CI 0.23, 0.92; p = 0.030).



ASC 6.2 months vs. SOC 3.9 months (HR = 0.43; 90% CI 0.20, 0.92; p = 0.029).

Safety

- **Median treatment time/subject (ASC:179 days *vs.* SOC 94 days)**
- **Median total dose of nab-paclitaxel/subject (ASC: 3,123 mg *vs.* SOC: 1,398 mg)**
- **Median total dose of gemcitabine/subject (ASC: 32,713 mg *vs.* SOC: 14,100 mg)**

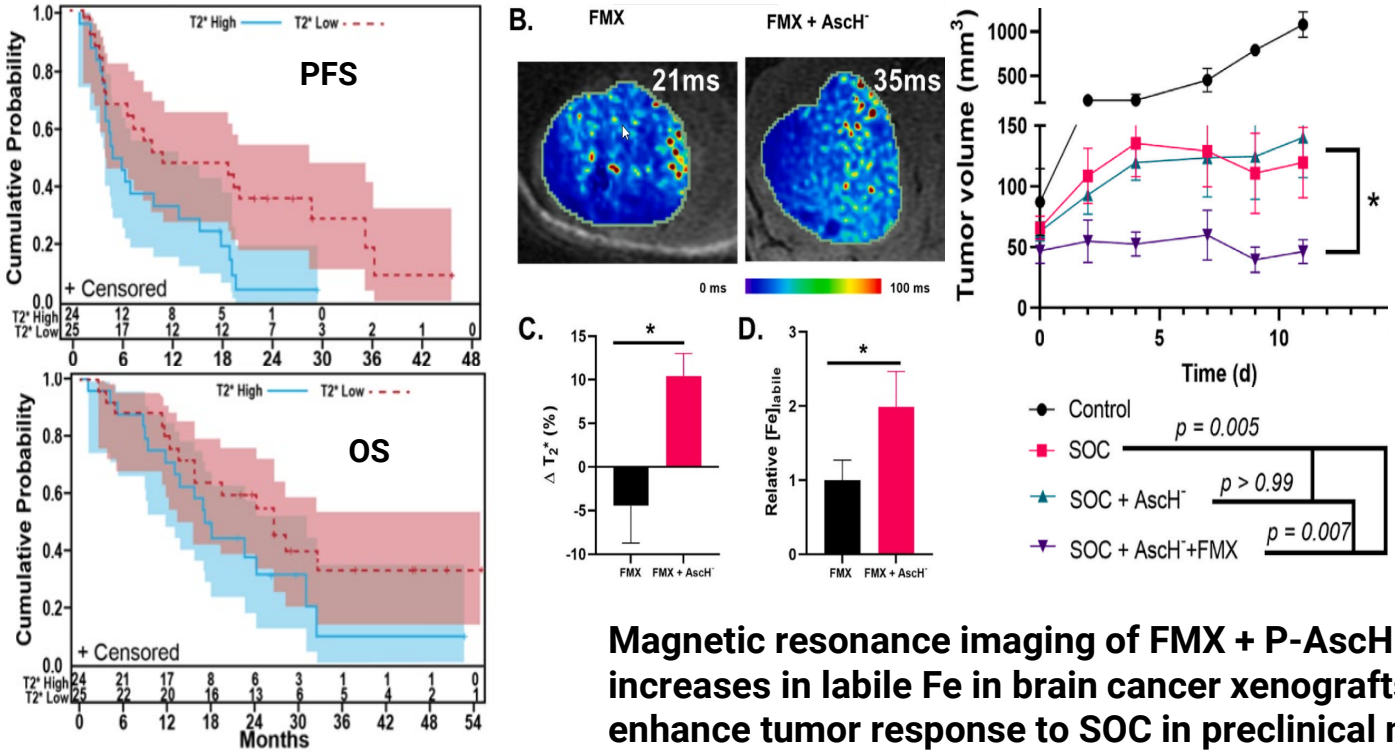
Bodeker KL, **Smith BJ**, **Berg DJ**, **Chandrasekharan C**, **Sharif S**, **Fei N**, Vollstedt S, Brown H, Chandler M, Lorack A, McMichael S, Wulfekuhle J, Wagner BA, **Buettner GR**, **Allen BG**, **Caster JM**, Dion B, Kamgar M, **Buatti JM**, **Cullen JJ**: A randomized trial of pharmacological ascorbate, gemcitabine, and nab-paclitaxel for metastatic pancreatic cancer. ***Redox Biol***. 2024; 77:103375. PMID: 39369582

Scientific Highlight – Collaboration: ET & FRMI & CEPS Pharmacological Ascorbate and GBM Therapy (P01CA217797A1 and R21CA270742)

Magnetic resonance imaging of iron metabolism with T2* predicts an enhanced responses to pharmacological ascorbate + SOC in patients with GBM that can be further manipulated with treatment with Ferumoxytol (FMX) iron nanoparticles

Results: P-AscH- was increased median overall survival in 55 subjects to 19.6 months (90% CI: 15.7 – 26.5 months) that was a statistically significant increase compared to historic control patients (14.6 months).

Subjects with initial T2* relaxation < 50 ms were associated with a significant increase in PFS compared to T2*high subjects (11.2 months vs. 5.7 months, p < 0.05) and a trend towards increased OS (26.5 months vs. 17.5 months).

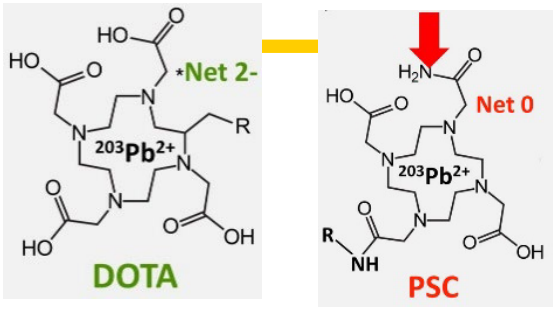


Magnetic resonance imaging of FMX + P-AscH- can detect increases in labile Fe in brain cancer xenografts that can also enhance tumor response to SOC in preclinical models.

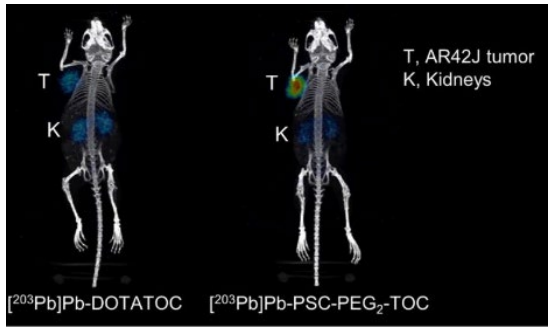
Petronek MS, Monga V, Bodeker KL, Kwofie M, Lee CY, **Mapuskar KA**, Stolwijk JM, Zaher A, Wagner BA, **Smith MC**, Vollstedt S, Brown H, Chandler ML, Lorack AC, Wulfekuhle JS, Sarkaria JN, **Flynn RT**, Greenlee JDW, Howard MA, **Smith BJ**, Jones KA, **Buettner GR**, **Cullen JJ**, St-Aubin J, **Buatti JM**, **Magnotta VA**, **Spitz DR**, **Allen BG**: Magnetic resonance imaging of iron metabolism with T2* mapping predicts an enhanced clinical response to pharmacological ascorbate in patients with GBM. ***Clin Cancer Res***. ***Clin Cancer Res***. 2024; 30(2):283-293. doi: 10.1158/1078-0432.CCR-22-3952. PMID: 37773633

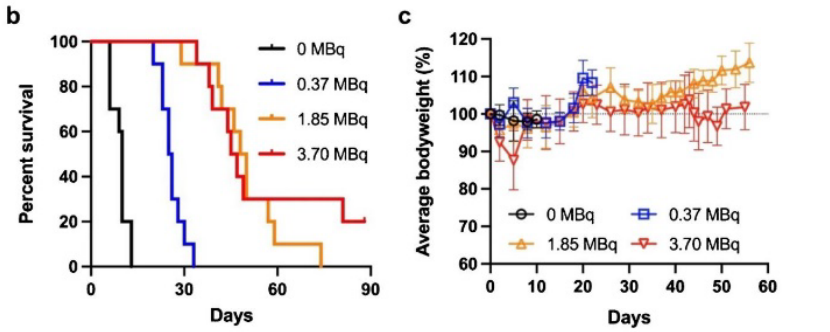
Radiotheranostics

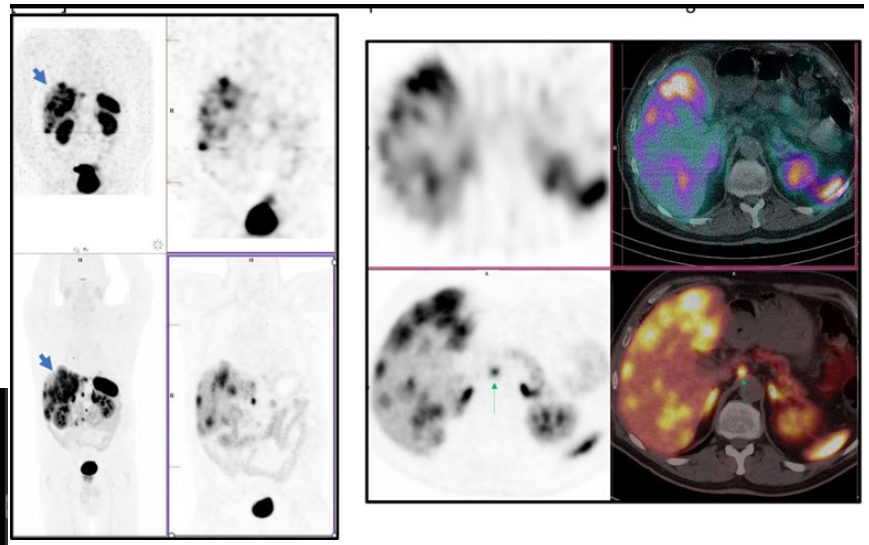
Pb-212 PSC-TOC Alpha Particle Therapy of NETs

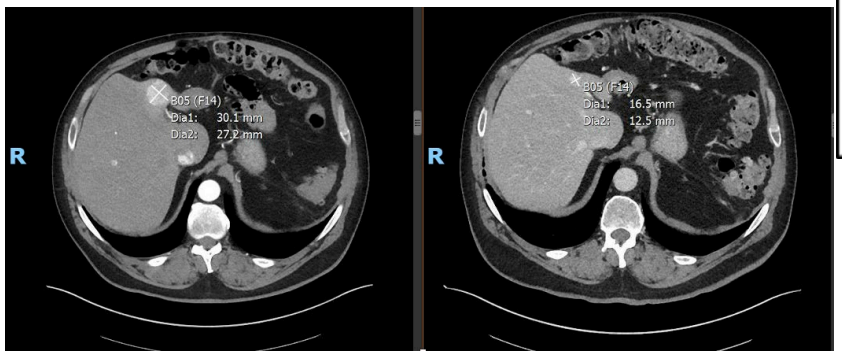


Improved radiolabeling
Improved renal clearance
Improved receptor binding
Improved internalization









- Imaged 10 patients and established radiation dosimetry
- Treated the 2 dose cohorts in dose escalation Phase 1 study

Industry Sponsored Clinical Trials- Active

- Lu-177 FAPI; pancreatic, NSCLC, breast- Phase 1/2
- ACTION-1- Ac-225 DOTATATE; NET- Phase 1b/3
- Pb-212 VMT101; melanoma- Phase 1
- Ac-225 PSMA; prostate cancer- Phase 1
- Ac-225 DOTATATE; SCLC- Phase 1
- Dosimetry-based PRRT IIT- NETs

Lee D, Li M, Liu D, Baumhover NJ, Sagastume EA, Marks BM, Rastogi P, Pigge FC, **Menda Y**, Johnson FL, **Schultz MK**. Structural modifications toward improved lead-203/lead-212 peptide-based image-guided alpha-particle radiopharmaceutical therapies for neuroendocrine tumors. ***Eur J Nucl Med Mol Imaging***. 2024; 51(4):1147-1162. PMID: 37955792

FRMI Strengths and Challenges

Strengths

- Highly collaborative translational program well-integrated into both Redox Biology and Therapy, Theranostic, and MRI/PET imaging modalities
- New funding initiatives in redox regulation of immunological responses, normal tissue injury, FLASH radiotherapy, and theranostics involving members of all 4 HCCC programs.

Challenges and Opportunities

- Recruitment of new leaders and transitioning the FRMI program leadership
- New P01 development
- New targeted redox genomics studies (ie.,targeting Keap1/STK11 mutants)
- New FLASH irradiator being commissioned at Iowa in 2025

Future Direction & Goals

- **Expand basic and translational research on redox metabolism/imaging**
  - Theranostic approaches with High LET $Pb^{212/203}$ targeting CXCR4 combined with redox modifiers of hydroperoxide metabolism in lung NETs and NECs leading to new funding opportunities including NET SPORE and SCLC R01
  - Normal tissue response modifiers that also sensitize to traditional cancer therapy based on fundamental differences in cancer cell redox metabolism (SOD mimetics and pharmacological ascorbate), Ascorbate P01 renewal
- **Leverage new equipment for evaluation of novel approaches to tumor imaging with a focus on imaging of free radical metabolism and predicting therapy responses**
  - T2* studies with ascorbate on the MR LINAC
  - New FLASH P01 development and multi-institutional P01 renewal with UCI

FRMI Discussion