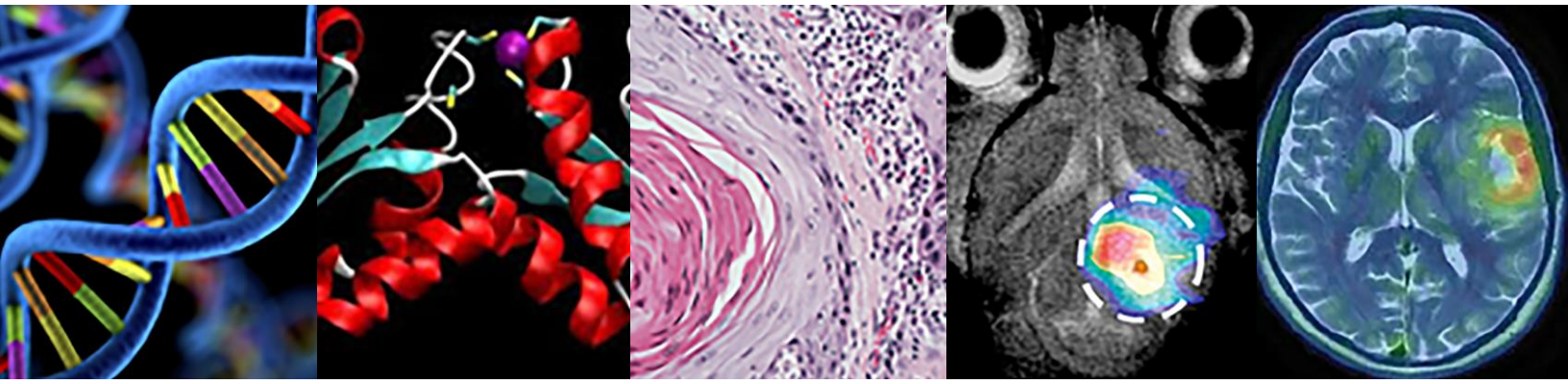
NIH NATIONAL CANCER INSTITUTE

Co-Clinical Imaging Research Resources Program



CIRP Annual Meeting

NCI Shady Grove Campus

May 20-21, 2024

https://wiki.nci.nih.gov/display/NCICRIP

Animal Models

Co-Clinical Trials

Quantitative Imaging

Informatics

2024 CIRP Annual Hybrid Meeting

May 20 - 21, 2024

Agenda

Day 1: May 20, 2024, EDT

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9:30 am **Introduction**

Huiming Zhang, PhD, DCTD, NCI

9:40 am **Welcome**

Janet Eary, MD, Associate Director, DCTD, NCI

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Part I CIRP program

Moderators: Huiming Zhang, PhD, NCI

Yantian Zhang, PhD, NCI

9:45 am **Session I CIRP Teams Progress**

Washington University Co-Clinical Imaging Research Resource

Kooresh Shoghi, PhD, Washington University in St Louis

10:05 am **A Quantitative PET/CT Research Resource for Co-Clinical Imaging of Lung Cancer Therapies**

Paul Kinahan, PhD, University of Washington

10:25 am **Co-Clinical Research Resource for Imaging Tumor Associated Macrophages**

Heike Daldrup-Link, MD, Stanford University

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10:45 am **Break (15 min)**

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11:00 am **Co-Clinical Quantitative Imaging of Small Cell Neuroendocrine Prostate Cancer Using Hyperpolarized 13C MRI**

John Kurhanewicz, PhD, University of California San Francisco

11:20 am **Development of an Open-Source Preclinical Imaging Informatics Platform for Cancer Research**

Kooresh Shoghi, PhD, Washington University in St Louis

11:40 am **University of Michigan Quantitative Co-Clinical Imaging Research Resource**

Brian Ross, PhD, University of Michigan

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12:00pm **Lunch Break (80 min)**

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1:20 pm **Integrating Omics and Quantitative Imaging Data in Co-Clinical Trials to Predict Treatment Response in Triple Negative Breast Cancer**

Mike Lewis, PhD, Baylor College of Medicine

1:40 pm **MDACC Predict**

Charles Manning, PhD, MD Anderson Cancer Center

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2:00 pm **Break (15 min)**

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2:15 pm **Session II Poster Power Pitch**

Advances in Animal Models, Co-Clinical Trials, and Co-Clinical Imaging Applications

Moderators: Cynthia Ma**,** PhD, Washington University in St Louis
Rong Zhou, PhD, University of Pennsylvania

2:50 pm **Advances in Imaging Acquisition, Data Processing, and Method Development**

Moderators: Robia Pautler, PhD, Baylor College of Medicine

Robert Miyaoka, PhD, University of Washington

3:25 pm **Advances in Informatics, Web Resources, and Method Development**

Moderators: James Gee, PhD, University of Pennsylvania

Jason Crane, PhD, University of California San Francisco

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4:00 pm **Session III Posters and Demonstrations**

5:30pm **End of Day 1**

Day 2, May 21, 2024, EDT

Part II Workshop on Co-Clinical Imaging Roadmap

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9:30 am **Session IV Co-Clinical Imaging in Advancing Precision Oncology**

Moderators: Brian Ross, University of Michigan
John Kurhanewicz, PhD, University of California San Francisco

9:30 am **Introduction**

Brian Ross, PhD, University of Michigan

John Kurhanewicz, PhD, University of California San Francisco

10:00 am **Animal models to enable co-clinical imaging trials**

Donna Peehl, PhD, University of California San Francisco

10:30 am **Image acquisition and data processing considerations to harmonize co-clinical imaging trials**

Cristian Badea, PhD, Duke University

11:00 am **Informatics needs to support integration of co-clinical imaging datasets, data mining, and advanced computing**

Kooresh Shoghi, PhD, Washington University in St Louis

11:30 am **Summary and Further Discussions**

Brian Ross, PhD, University of Michigan

John Kurhanewicz, PhD, University of California San Francisco

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12:00 pm **Lunch Break (60 min)**

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Part III CIRP Working Groups

1:00 pm **Session V Imaging Acquisition & Data Process (IADP) WG**

Moderators: Robia Pautler, PhD, Baylor College of Medicine

Robert Miyaoka, PhD, University of Washington

Presentations:

1:00 pm **Small Animal PET Imaging and Instrumentation**

Robert Miyaoka, PhD, University of Washington

1:30 pm **The International Photoacoustic Standardization Consortium: Prospects, challenges, and future directions on the path towards standardization in photoacoustic imaging**

Lina Hacker, PhD, University of Oxford

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2:00 pm **Break (10 min)**

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2:10 pm **Session VI Informatics & Outreach (IMOR) WG**

Moderators: James Gee, PhD, University of Pennsylvania

Jason Crane, PhD, University of California San Francisco

2:10 pm **WG Updates**

Jame Gee, PhD, University of Pennsylvania

2:15 pm **Data Archival and Resource Management Infrastructure for Preclinical Imaging**

Keynote: Federated Preclinical Imaging XNAT-Enabled Informatics (PIXI): PIXI interoperability environment demo to enable co-clinical imaging research in precision oncology

Andy Lassiter, Washington University in St Louis

2:31 pm **BiRAT: Platform for Biomedical Image Data Registry and Processing**

Frezghi Habte, PhD, Stanford University

2:39 pm **NCI Imaging Data Commons: Towards transparency, reproducibility, and scalability in imaging AI**

Andrey Fedorov, PhD, Brigham and Women's Hospital

2:47 pm **The MIRACCL Portal for Comparing Patient and PDX Response Using Cancer Image Features and Genomics in Co-Clinical Trials**

Heidi Dowst, Baylor College of Medicine

2:55 pm **Discussions**

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Part IV CIRP Management and Business

3:10 pm **Session VII Business Meeting: SC Committee Only**

Brian Ross, PhD, University of Michigan

John Kurhanewicz, PhD, University of California San Francisco

Huiming Zhang, PhD, NCI

3:30 pm **End of Day 2**

List of Posters for Power Pitch

Advances in Animal Models, Co-Clinical Trials, and Co-Clinical Imaging Applications

1. **Novel B cell gene signature to predict clinical response to combined EGFR and glutaminolysis inhibition in *KRAS* wild-type colorectal cancer**
   S-W Bae, KK Ciombor, et al., University of Texas MD Anderson Cancer Center
2. **Assessing response to chemotherapy in PDX models of small cell neuroendocrine prostate cancer using hyperpolarized ^{13}C Pyruvate MRI**
   I Mali, S Sahin, et al., University of California San Francisco
3. **Evaluating ΔFFNP-PET as an imaging biomarker of estrogen receptor α (ERα) functional status in preclinical models of ERα+ breast cancer with *ESR1* mutations**
   C Shyam, T Whitehead, et al., Washington University in St Louis
4. **A Quantitative PET/CT Research Resource for Co-Clinical Imaging of Lung Cancer Therapies**
   P Kinahan, R Miyaoka, et al., University of Washington
5. **Preliminary Analyses of single cell transcriptome reveal effects of stroma-directed drug and chemotherapy in a GEM model of pancreatic cancer**
   H Choi, M Gupta, et al., University of Pennsylvania School of Medicine
6. **MRI Assessment of Bone Marrow Metrics in Myelofibrosis**
   TH Robison, A Levinson, et al., University of Michigan School of Medicine

Advances in Imaging Acquisition, Data Processing, and Method Development

7. **Repeatability of a quantitative multiparametric MRI protocol measuring perfusion, cellularity, and hypoxia in a murine model of glioma: Preliminary results**
   A Das, DA Hormuth II, et al., University of Texas at Austin
8. **Reproducibility and Repeatability of T2*- and T2-Mapping in Osteosarcomas**
   R Roudi, LJ Pisani, et al., Stanford University
9. **Exploring VivoVist™ and Spectral Photon-Counting CT in Preclinical Cancer Studies**
   CT Badea, A Richard, et al., Duke University
10. **Predicting the response of combination chemotherapy and targeted therapy *via* mathematical modeling in a murine model of pancreatic cancer**
    K Vishwanath, R Zhou, et al., University of Texas at Austin
11. **Prediction of pCR by molecular subtype using robust lesion segmentation and radiomics/AI in the I-SPY 2 breast cancer clinical trial**
    HM Whitney, A Frantzen, et al., University of Chicago

12. **Modulating specific activity to determine optimal injected mass in reproducibility of ^{18}FFNP-PET imaging of low progesterone receptor expression in ERα+ breast cancer**

    T Whitehead, C Shyam, et al., Washington University in St Louis

Advances in Informatics, Web Resources, and Method Development

13. **FAST (Fast Analytical Simulator of Tracer)-PET: an accurate and efficient PET analytical simulation tool**

    Suya Li, M Hamdi, et al., Washington University in St Louis

14. **The ePAD platform for extracting and analyzing imaging features in Cancer Co-Clinical Trials**

    E Alkim, O Yurtsever, et al., Stanford University

15. **Hybridizing CT Tumor Volume Measurements with Standard of Care Clinical Measures for Immunotherapy Response Prediction using Mechanistic Modeling and Machine Learning**

    G Prakash, Z Wang, et al., Texas A&M University

16. **Developing CT radiomics based Surrogates for mIF based Angiogenesis Biomarkers in Clear Cell Renal Cell Carcinoma**

    A Setayesh, E Yi, et al., University of Southern California

17. **Image imputation with conditional generative adversarial networks captures clinically relevant imaging features on computed tomography**

    J Rich, J Le, et al., University of Southern California

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CIRP

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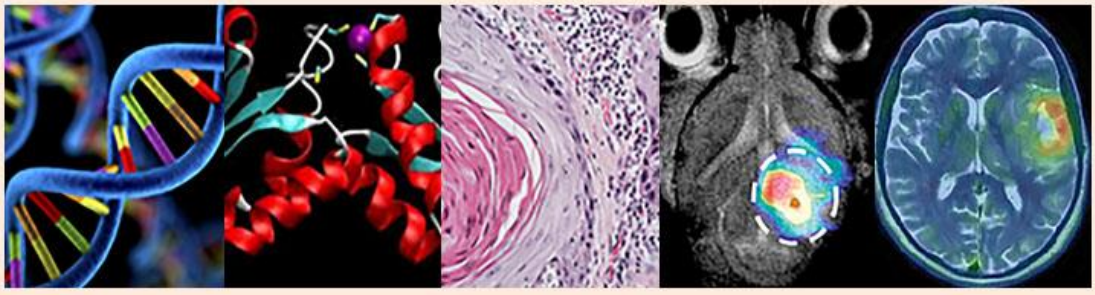

Presentation Abstracts

CIRP Program

Team Reports

Washington University Co-Clinical Imaging Research Resource (WU-C2IR2)

Kooresh Shoghi[1]*, Cynthia X. Ma[2], Shunqiang Li[2], Li Ding[2], Dong Zhou[1],
Amy Fowler[3], John A. Katzenellenbogen4, Farrokh Dehdashti[1]

Department of [1]Radiology and [2]Medicine, Washington University School of Medicine, St. Louis, MO; [3]Department of Radiology, University of Wisconsin-Madison; [4]Department of Chemistry, University of Illinois at Urbana-Champaign, Champaign, IL
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Breast cancer (BC) is the most common cancer diagnosed in women. Approximately 70% of BCs are estrogen receptor (ER) positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-). Endocrine therapy (ET) reduces recurrence risk and improves survival for many in this group. However, despite standard of care and adjuvant ET, over 20% patients with ER+/HER2- BC experience metastatic recurrence in the years to come, and virtually all patients with metastatic disease eventually experience disease progression on ET due to intrinsic or acquired resistance mechanisms. There are currently no biomarkers that reliably identify which of these advanced breast cancer patients will benefit from ET-based approaches so that chemotherapy could be avoided or delayed. The progesterone receptor (PgR) gene is highly regulated by ER at the mRNA and protein level. Previous clinical studies have demonstrated that changes in 18F-fluorofuranylnorprogsterone (FFNP) uptake after 17β-estradiol (E2) challenge (ΔFFNP-PET) are predictive of outcome. However, the impact of ESR1 mutations and clonality on ΔFFNP is not fully understood. To address this unmet need, the objective of this proposal is to develop co-clinical quantitative PET/CT imaging strategies integrated genoproteomic discovery to predict response to ET in patients with ER+/HER2- metastatic breast cancer (MBC). To that end, we will interface with a recently awarded phase II multicenter Translational Breast Cancer Research Consortium (TBCRC) trial to assess the functional status of estrogen receptor in patients with ER+/HER2- MBC. The U24 will have three specific aims: in Aim 1 we will optimize animal modeling and the quantitative accuracy of PET imaging agents of response to ET in ER+/HER2- BC patient-derived tumor xenografts (PDX). In Aim 2 we will implement optimal quantitative methods to predict response to ET in ER+/HER2- and integrate with multi-scale genoproteomic data across the co-clinical trial. In Aim 3, we will populate content from the co-clinical investigation on a web-accessible research resource and expand capabilities of co-clinical database (CCDB). In addition, high value multi-scale analytic data will be generated, including whole exome sequencing (WES), RNASeq, pathology, and CODetection by indEXing (CODEX) to characterize tumor heterogeneity. All data will be uploaded to an informatics resource available to the co-clinical community to test new algorithms and mine for novel leads integrating imaging and multi-scale analytic data to predict therapeutic response. We will present our efforts in the 2nd year of the award to characterize and optimize ΔFFNP-PET imaging using both in vitro assessment of cross-talk between ER and PgR as well as in vivo studies to optimize metrics of FFNP-PET. Overall, this proposal aims to have a far-reaching and high impact on the implementation of precision medicine in identifying, stratifying, and predicting response to ET+CDK4/6i in patients with ER+/HER2- MBC, integrating quantitative imaging with genoproteomic discovery.

Development of Quantitative Imaging Methods for Monitoring Tumor Associated Macrophages

Heike E. Daldrup-Link[1,2], Raheleh Roudi[1], Laura Pisani[1], Frezghi Habte[1], Tie Liang[1], Allison Pribnow[2], Sheri Spunt[2], Daniel Rubin[1,3,4]

[1]Department of Radiology, [2]Department of Pediatrics, Hematology/Oncology, [3]Department of Biomedical Data Science,[4]Department of Rad/Integrative Biomedical Imaging Informatics, Stanford University, CA.

Introduction: CD47, a well-characterized immune checkpoint, plays a pivotal role in osteosarcoma progression by engaging signal-regulatory protein alpha (SIRPα), an inhibitory receptor on tumor associated macrophages (TAM). This interaction establishes a pro-tumorigenic microenvironment by inhibiting TAM phagocytosis of cancer cells. CD47 blockade via mAbs has shown promise, but its clinical translation in pediatrics is hampered by the absence of robust TAM activity biomarkers. We propose a novel strategy utilizing ferumoxytol, an FDA-approved iron oxide nanoparticle readily phagocytosed by TAMs. By leveraging ferumoxytol's MRI detectability, we aim to develop a quantitative imaging approach for non-invasive detection and quantification of TAM infiltration within osteosarcomas. This approach has the potential to serve as a valuable tool for patient stratification and therapeutic monitoring of CD47mAb immunotherapy.

Purpose: To optimize and validate preclinical and clinical quantitative imaging techniques for *in vivo* quantification of TAM in osteosarcomas. We accomplish this goal with the following specific aims:

Aim 1. Optimize and validate pre-clinical quantitative imaging methods for TAM imaging
Aim 2. Implement the optimized methods in a co-clinical trial
Aim 3. Populate a web-accessible research resource

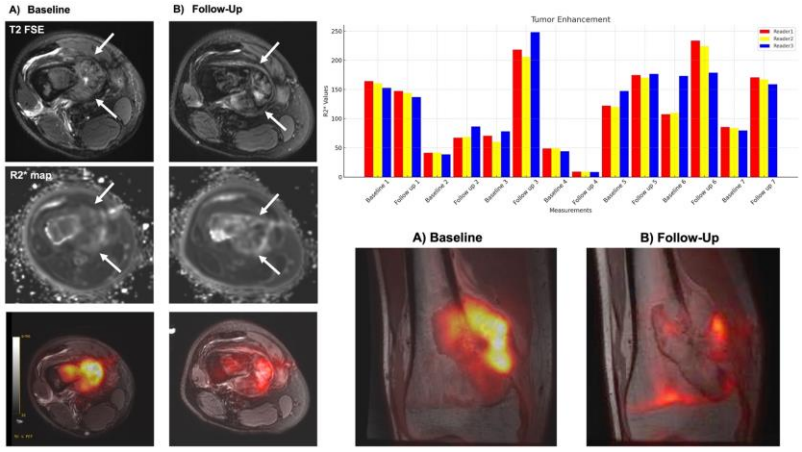

Figure 1: Ferumoxytol-enhanced MRI of macrophage activation in a human osteosarcoma: Representative T2-weighted fast spinecho MRI, corresponding R2* map and integrated ^{18}F-FDG PET/MRI of an osteosarcoma of the distal femur in a teenage patient at (A) baseline and (B) follow up after induction chemotherapy. After chemotherapy, an increased nanoparticle retention is apparent, as indicated by decreased T2-signal of the tumor (arrows) and increased R2* relaxation rates. (C) Repeated measurements of R2* values of 7 tumors at baseline and after induction chemotherapy (follow up).

Methods and Results: The approach and exemplary results of our TAM imaging studies are shown in Figure 1. A large part of our efforts in year 3 of our project focused on establishing the repeatability and reproducibility of tumor R2* measurements (Aim 1). We conducted repeated MRI scans of fifteen osteosarcomas in BALB/c mice on 3T and 7T scanners before and after intravenous iron oxide nanoparticle infusion, using T2-weighted fast spin echo, T2*-weighted multi-gradient echo and T2-weighted multi-slice multi-echo sequences. We found excellent agreement between duplicate acquisitions for both T2* and T2 measurements at either magnetic field strength, by the same individual (repeatability), and between individuals (reproducibility). Our team member Dr. Raheleh Roudi prepared a scientific manuscript with the results of these investigations, which is currently in press.

Next, we applied imaging protocols and image data analyses from our preclinical investigations in seven pediatric patients with osteosarcomas who underwent a ferumoxytol-enhanced MRI and T2* mapping (Aim 2). Three human readers measured R2* values of the tumor tissue at baseline and after induction chemotherapy. We found no significant difference between repeated tumor R2* measurements by the three readers. These investigations are ongoing and will be completed over the next months.
Finally, we populated a web-accessible research resource with methods and results collected from our co-clinical investigations (Aim 3) such that investigators at other centers can learn about quantitative imaging approaches for TAM imaging. Our team member Dr. Frezghi Habte will provide a presentation about our web-accessible research resource at the upcoming CIRP symposium.

Impact: Non-invasive quantitative imaging of TAM infiltration holds immense potential for guiding clinical decision-making in TAM-targeted therapies. This approach could serve as a powerful tool for patient stratification, enabling selection of those most likely to benefit, and potentially establish a new gold standard for monitoring response to novel immunotherapies. To facilitate collaboration and scientific transparency, we established a website about our program, which features all data, methods and protocols for our project: https://radweb.su.domains/cirp/.

A Quantitative PET/CT Research Resource for Co-Clinical Imaging of Lung Cancer Therapies

Paul Kinahan, Robert Miyaoka, Adrienne Lehnert, Mark Muzi, Delphine Chen, Christina Baik, Andrey Fedorov, A. McGarry Houghton

University of Washington, Harvard Medical School, and Fred Hutchinson Cancer Center

Although immune checkpoint inhibitor (ICI) therapy has been a tremendous clinical benefit for some non-small cell lung cancer (NSCLC) patients, only ~20% of NSCLC patients respond to anti-PD1/PDL1 therapy. We are developing methods for quantitative pre-clinical PET (positron emission tomography) imaging for ICI therapies in NSCLC. We are leveraging an existing co-clinical trial using our genetically engineered mouse models (GEMM) of lung adenocarcinoma and squamous cell carcinoma to develop, test and implement the methods and populate a web-accessible research resource. This web-accessible research resource will in turn leverage recent developments in quantitative cancer imaging informatics using the industry-standard DICOM format.

Our co-clinical trial is evaluating the hypothesis that neutrophils located within the tumor stroma retard the infiltration of tumor-reactive lymphocytes into the malignant portion of tumor and that neutrophil depletion will improve ICI response rates by removing this barrier. We are utilizing a CXCR2 antagonist that inhibits the recruitment of monocytes and neutrophils into the tumor microenvironment. Studies are underway in both the mouse models described above and in a phase 2 trial using SX-682 and pembrolizumab in patients with treatment naive stage IV or recurrent NSCLC.

In parallel we are developing informatics methods to capture and track the necessary meta-information along with appropriate response criteria for preclinical imaging. In addition, we are a evaluating quantitative pre-clinical PET imaging methods that are linked to quantitative clinical PET imaging methods

We are addressing these tasks with three Specific Aims:

1, Develop and optimize quantitative preclinical quantitative imaging methods and protocols. These methods will involve novel long-lived phantoms that can cross-calibrate multiple preclinical and clinical PET scanners. This are being tested with partner members of the Co-Clinical Imaging Research Resources Program.

2. Implement the optimized methods in our co-clinical trial of ICI treatment of NSCLC with a GEMM lung adenocarcinoma model and a GEMM model lung squamous cell carcinoma. From this we will evaluate how the information gleaned from the pre-clinical and clinical studies can be used to inform future pre-clinical studies in terms of imaging protocols and response criteria.

3. Share data and resources on co-clinical trials using quantitative PET imaging using a web-accessible open science approach (open source + open data) by extending the DICOM standard for pre-clinical small animal imaging with DICOM-compliant structures that provide necessary quantitative meta-data.

The methods and resources developed during this project will be distributed to accelerate the development of needed effective cancer therapies by improving the utility of early-phase oncology trials using co-clinical studies with PET imaging. In addition, we will determine, and potentially improve, the utility of PET imaging as a biomarker for early assessment of response in co-clinical immunotherapy studies by using an appropriate mouse model.

Co-Clinical Quantitative Imaging of Small Cell Neuroendocrine Prostate Cancer Using Hyperpolarized ^{13}C MRI – 2024 CIRP Meeting Update

Renuka Sriram, Shubhangi Agarwal, Ernesto Diaz, Sule Sahin, Ivina Mali, Romelyn DeLos Santos, Jenny Lewis, Avantika Sinha, Robert Bok, Jason Crane, Peder Larson, Donna Peehl and John Kurhanewicz*

Department of Radiology and Biomedical Imaging, University of California San Francisco

A subset of patients with metastatic castration resistant prostate cancer (mCRPC) develop a more aggressive small cell neuroendocrine (SCNC) prostate cancer phenotype. SCNC is characterized by its poor prognosis, and patients with liver metastases respond differently to therapy and have a particularly poor clinical outcome compared to those with bone metastases. This co-clinical study is aimed at developing optimal murine hyperpolarized (HP) ^{13}C MRI and multiparametric (mp) ^{1}H MRI protocols in realistic PDX models of SCNC bone and liver metastases to inform on therapeutic response using quantitative imaging metrics to populate an online website. HP ^{13}C pyruvate MRI is a new, safe, non-radioactive, stable-isotope imaging approach that can measure down-stream metabolism, specifically the metabolic flux of pyruvate to lactate (k_{PL}), which in preliminary metabolomic, murine and patient studies has shown the potential to metabolically detect metastatic SCNC and monitor its response to treatment. The co-clinical murine imaging study is being conducted in parallel with a phase 1 trial of HP ^{13}C MRI/mp ^{1}H MRI for assessing early response of SCNC to carboplatin treatment in prostate cancer patients with metastatic SCNC. To date, 20 HP [1-^{13}C]pyruvate/mp ^{1}H 3T MRI scans of patients (out of 33 patients proposed) with SCNC metastases to the bone (N=11) and liver (N=9) have been performed and used to define the ^{1}HP ^{13}C MRI/mp ^{1}H MRI protocol and inputless k_{PL} modeling approach being utilized and optimized in parallel preclinical studies.

Great progress has been made in improving the robustness of pre-clinical studies and in harmonizing them with the patient studies. As described in a recent publication liver and bone metastatic SCNC PDX models have been optimized for co-clinical metabolic imaging studies of therapeutic response. Optimizations focused on developing protocols that provided good tumor take rates, doubling times and reproducible tumor baseline morphologic, physiologic, and imaging characteristics of the metastatic SCNC liver and bone PDXs. A more sensitive preclinical echo planar imaging (EPI) dynamic pulse sequence was also implemented with a focus on harmonizing HP ^{13}C MRI data acquisition with patient studies. Pre-clinical imaging sensitivity of ^{13}C pyruvate metabolism was also made more consistent with patient studies through doubling the polarization of ^{13}C pyruvate ($\approx$ 40%) provided by using a new preclinical SpinAligner DNP Polarizer. Additionally, quantitative k_{PL} modeling and DICOM data storage pipelines have been developed for both pre-clinical and patient imaging data and the co-clinical data is viewable on an open-source data display platform (SIVIC) enabling integration of preclinical and clinical imaging data to better detect SCNC metastases and its response to treatment.

An initial preclinical study assessing one SCNC bone PDX (LTL610) prior to and after carboplatin treatment demonstrated that, like patient studies, there was a significant reduction in

k_{PL} that preceded changes in tumor volume and correlated with effective treatment - reduced cellularity and proliferation (Ki-67) on IHC and reduced ADC on DWI MRI and increased perfusion (^{13}C Urea AUC) after treatment. Based on this preliminary treatment study we optimized the dose of carboplatin, used a consistent and smaller baseline PDX tumor volume, extended the time of imaging follow-up from 1 to 2 cycles of carboplatin for a larger study of 3 SCNC PDX (LuCaP 93, LTL352 and LTL610) implanted in both the liver and bone. Through a collaboration with Washington University, a deep learning algorithm-based pipeline for automatically assessing changes in tumor volume with treatment was also implemented. SCNC liver tumor data from this larger optimized carboplatin treatment study demonstrated an earlier reduction in k_{PL} in tumor volume like what was observed the prior bone tumor study. Additionally, in initial studies of same PDX implanted in the liver and bone there was a differential response to chemotherapy like observed in the literature. Next steps include completing the pre-clinical carboplatin HP ^{13}C pyruvate MRI/mp ^{1}H MRI imaging study of metastatic SCNC and integrating co-clinical murine and patient data to assess the value of k_{PL} as an early predictor of therapeutic response. Additionally, the ability to co-polarize and inject ^{13}C urea and ^{13}C pyruvate using HP ^{13}C MRI to simultaneously measure both metabolism and perfusion in a single imaging acquisition will be exploited in future co-clinical studies to improve the modeling of kPL and provide an improved understanding of how changes in perfusion and drug delivery impact therapeutic response.

We continue making our U24 CIRP resources (Code & Tools, Image Datasets, Phantoms and SOPs) available on our frequently updated website, coclinicalimaging.ucsf.edu/resources, publications in protocols.io, as well as traditional peer reviewed manuscripts and presentations at scientific meeting.

Development of an Open-Source Preclinical Imaging Informatics Platform to support Co-Clinical Cancer Research

Kooresh Shoghi*, Andrew Lassiter, Steve Moore, James Quirk, Richard Laforest, Daniel Marcus

Department of Radiology Washington University School of Medicine, St. Louis, MO
*Contact info: Email, shoghik@wustl.edu; Tel: 314-362-8990.

Preclinical imaging is widely used in cancer research to devise novel tumor detection strategies, assess tumor burden and physiology/biology, as well as to validate novel therapeutic strategies and predictive and biomarkers of response to therapy. More recently, the use of co-clinical animal models, such as patient-derived tumor xenografts (PDX) and genetically engineered mouse models (GEMMs), has ushered an era of co-clinical trials where preclinical studies can inform clinical trials, thus potentially bridging the translational gap in cancer research. However, differences in the deployment of the instruments, differences in imaging formats and protocols, differences in animal models, and variability in analytic pipelines among other factors result in non-tractable data and poor reproducibility. Importantly, current databases are not compatible with complexity and growing demands in preclinical cancer imaging which include big data needs and collection of metadata/annotation to support NCI's precision medicine initiative. Thus, there is an unmet need to develop a unifying imaging informatics and workflow management platform to support co-clinical cancer research, which will ultimately support the premise of translational precision medicine. We are developing an open-source preclinical imaging informatics platform—Preclinical Imaging XNAT-enabled Informatics (PIXI)—to manage the workflow of preclinical imaging laboratories, harmonize imaging databases, and enable deployment of analytic and computational pipelines in preclinical imaging. PIXI is based on XNAT as the underlying informatics architecture. XNAT is used by over 200 academic institutions and industry entities as the backbone for data management across a wide range of imaging applications in clinical research, and thus offers a robust platform for the development and deployment of a co-clinical informatics platform. The Aims of the award are: 1) develop the PIXI database and server to capture preclinical imaging associated data, metadata, and preclinical imaging workflow and experiments; 2) develop the PIXI "point-of-service" interface, notebook capabilities, and software development kit (SDK); and 3) develop the PIXI container-based application ("App") environment to implement portable analytic pipelines. PIXI has been recently released publicly and is available at the PIXI website, https://www.pixi.org/, to download for local install as well through direct interface with the PIXI Center at Washington University in St. Louis.

University of Michigan Quantitative Co-Clinical Imaging Research Resource

Brian D. Ross, Moshe Talpaz, Thomas L. Chenevert, & Gary D. Luker

University of Michigan School of Medicine, Ann Arbor, MI 48109

The University of Michigan CIRP establishes a magnetic resonance imaging (MRI) resource for detection and quantitative assessment of myelofibrosis (MF) disease phenotypes within the bone marrow. MF is a progressive myeloproliferative cancer characterized by clonal proliferation of malignant hematopoietic stem cells. MF causes progressive bone marrow fibrosis, hepatosplenomegaly from accumulation of blood-forming cells, severe symptoms of inflammation, pathologic alterations in numbers of blood cells. Invasive assessment of MF patients currently utilize bone marrow biopsy as the clinical approach to stage patients. This biopsy is a painful, invasive test which samples bone marrow from a single site in the iliac crest. As MF presents with spatially varying pathologic changes in bone marrow, analyzing a single bone marrow site provides limited information about overall disease status which also complicates assessing therapy response over time. Quantification of therapy response is a cornerstone of pre-clinical drug development, clinical trials, and patient care. A currently open quantitative imaging co-clinical trial (NCT01973881) allows for the use of MRI to obtain scans from MF patients for development and validation of analytical protocols to develop robust reproducible methods critical for drug development to support patient care.

This effort focuses on development of a resource for quantitative MRI of bone marrow composition and architecture in MF, a hematologic cancer understudied and underserved by imaging. Key metrics of bone marrow disease using FDA-approved MRI sequences included in standard software packages for pre-clinical 7T and clinical 3T scanners: 1) bone marrow composition and cellularity (quantitative Dixon technique for fat/water); 2) replacement of normal bone marrow cells (mobility of water (diffusion, DWI)); and 3) extent and severity of fibrosis with associated changes in extracellular macromolecular components (magnetization transfer (MT)).

We will present standardization procedures for both mouse and human imaging developed for repeatability assessment of image data using MRI phantoms along with test/retest imaging procedures for mouse and human subjects to establish confidence intervals. Standardized workflow for quantifying changes in the bone marrow MRI data to capture spatial and temporal heterogeneity of imaging changes during progression and treatment response will be presented. Application of developed methods to co-clinical trials with standard-of-care and investigational therapies for MF will also be presented.

In summary, this CIRP resource will reduce variability in quantitative bone marrow MRI in both mouse studies and clinical trials, improve the ability to reliably implement these imaging biomarkers to advance co-clinical trials and drug development in MF and other hematologic malignancies.

Toward Practical Integration of Omic and Imaging Data in Co-Clinical Trials using MIRACCL, a web-based tool

Emel Alkim [1,†], Heidi Dowst [2†], Julie DiCarlo [3,4], Lacey E. Dobrolecki [5,6], Anadulce Hernández-Hererra [5], David A. Hormuth II [3,4], Yuxing Liao [5], Apollo McOwiti [2], Robia Pautler [7], Mothaffar Rimawi [5,8], Ashley Roark [5,8], Ramakrishnan Rajaram Srinivasan [5], Jack Virostko [3,4,9,10], Bing Zhang [2,5], Fei Zheng [2], Daniel L. Rubin [1,11,12,], Thomas E. Yankeelov [3,4,9,10,13,14,15] and Michael T. Lewis [2,5,6]*

[1]Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, CA; [2]Dan L Duncan Cancer Center, Baylor College of Medicine, Houston, TX; [3]Oden Institute for Computational Engineering and Sciences, [4]Livestrong Cancer Institutes, Austin, TX; [5]Lester and Sue Smith Breast Center, [6]Department of Molecular and Cellular Biology and Radiology, [7]Department of Physiology, [8]Department of Medicine, Baylor College of Medicine, Houston, TX; [9]Department of Oncology, [10]Department of Diagnostic Medicine, The University of Texas at Austin, Austin, TX; [11]Department of Radiology, [12]Department of Medicine, Stanford University School of Medicine, Stanford, CA; [13] Oden Institute for Computational Engineering and Sciences, [14]Department of Biomedical Engineering, The University of Texas at Austin, Austin, TX; [15]Department of Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, TX

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Co-clinical trials are the concurrent or sequential evaluation of therapeutics in both patients clinically and patient-derived xenografts (PDX) pre-clinically, in a manner designed to match the pharmacokinetics and pharmacodynamics of the agent(s) used. The primary goal is to determine the degree to which PDX cohort responses recapitulate patient cohort responses at the phenotypic and molecular levels, such that pre-clinical and clinical trials can inform one another. A major issue is how to manage, integrate, and analyze the abundance of data generated across both spatial and temporal scales, as well as across species. To address this issue, we are developing MIRACCL (molecular and imaging response analysis of co-clinical trials), a web-based analytical tool. For prototyping, we simulated data for a co-clinical trial in “triple-negative” breast cancer (TNBC) by pairing pre- (T0) and on-treatment (T1) magnetic resonance imaging (MRI) from the I-SPY2 trial, as well as PDX-based T0 and T1 MRI. Baseline (T0) and on-treatment (T1) RNA expression data were also simulated for TNBC and PDX. Image features derived from both datasets were cross-referenced to omic data to evaluate MIRACCL functionality for correlating and displaying MRI-based changes in tumor size, vascularity, and cellularity with changes in mRNA expression as a function of treatment.

MDACC-PREDICT

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This project represents a U24 Oncology Co-Clinical Imaging Resource entitled **MDACC-PREDICT** (MD Anderson Cancer Center-PET imaging Resource to Enhance Delivery of Individualized Cancer Therapeutics). Precision cancer medicine, which seeks to exploit unique cellular, molecular, and genetic characteristics of individual tumors to optimize treatment, remains a critically unmet need. Despite advances in biomarker technologies that yield high-quality cellular and genomic data, critical gaps remain to consistently match patients with cancer and ideal therapies. While 'predictive' genomic assays based on RNA and DNA are now commonplace, current methods largely ignore tumor phenotypes differentiable by quantitative imaging. The overarching vision for **MDACC-PREDICT** is a suite of quantitative imaging tools that facilitate the discovery of novel, predictive imaging-derived gene expression signatures; such signatures can be deployed by the greater oncology community to improve the personalization of cancer treatment. The linchpin of **MDACC-PREDICT** is positron emission tomography (PET) imaging. The sensitive and quantitative nature of PET, coupled with the ability to produce biologically active PET tracers, renders PET uniquely capable of both detecting tumors and profiling their specific features. Complementary to genomic approaches, PET imaging provides a quantitative, functional measure of tumor phenotype, and when coupled with biopsy approaches, can provide a significantly greater breadth of biological characterization.

We are utilizing PET tracers of glutamine metabolism in a co-clinical trial of patients with colorectal cancer (CRC) and patient-derived xenograft (PDX) mouse models of CRC. ^{11}C-glutamine/^{18}F-4-fluoro-glutamine and (4S)-4-(3-^{18}F-Fluoropropyl)-L-glutamic acid (^{18}F-FSPG) report on unique aspects of glutamine metabolism, glutamine influx and glutamate efflux respectively. We are evaluating these imaging agents as both predictive and prognostic biomarkers of response to treatment. In addition, we are implementing quantitative PET to discover predictive, imaging-derived gene expression signatures.

Our initial Aims include optimization of quantitative PET imaging protocols. We are developing protocols for standardization of ^{18}F-4-fluoro-glutamine PET in preclinical imaging studies. To analyze the reproducibility of PET imaging data, we have performed test-retest analyses with ^{18}F-4-fluoro glutamine using CRC subcutaneous xenograft models. We are currently performing agreement and reproducibility analyses comparing paired data on the same scanner across time (different days), data analyzed by multiple users, and data processed using different reconstruction algorithms. The effect of fasting on uptake of ^{18}F-4-fluoro-glutamine has also been analyzed.

We have opened a trial evaluating baseline PET with ^{11}C-glutamine and ^{18}F-FSPG prior to anti-EGFR antibody rechallenge (NCT03275974). To further elucidate the mechanisms behind drug treatment, we are studying ^{18}F-4-fluoro-glutamine and ^{18}F-FSPG preclinically using well-annotated PDX mouse models of CRC. PDX-bearing mice have undergone treatment studies using an anti-EGFR antibody in combination with CB-839. PET imaging was performed pre- and post-treatment. We are correlating the imaging data to treatment response. In addition, we are using RNA-Seq data from the PDXs to develop gene signatures associated with treatment response.

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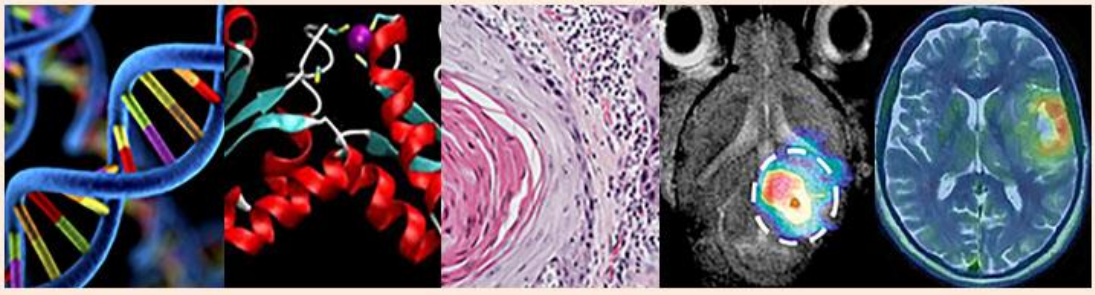

Roadmap Workshop Abstract

Co-Clinical Imaging in Advancing Precision Oncology

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Brian D. Ross,[4] and David A. Mankoff [5]

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Co-clinical trials are therapeutic investigations in which subtype-matched co-clinical animal models, such as patient-derived tumor xenografts (PDX) or genetically engineered mouse models (GEMM), are employed to inform a corresponding therapeutic clinical trial, either retrospectively or prospectively. A co-clinical imaging trial is a co-clinical trial in which a given translational imaging method is employed to assess/predict therapeutic outcome in both the preclinical and clinical arms of the co-clinical trial. The Co-clinical Imaging Research Resource Program (CIRP) of the National Cancer Institute (NCI) focuses on optimization of quantitative imaging methods to harmonize co-clinical imaging trials as well as dissemination of knowledgebase to support co-clinical imaging trials. The role of co-clinical imaging in precision oncology, however, is not well defined in NCI's recent publication of the new precision oncology initiative. As we approach the 10-year milestone of the CIRP, we would like to formulate a clear vision which outlines the role co-clinical imaging will play in advancing precision oncology. To that end, the CIRP aims to publish a White Paper highlighting the intersection points of co-clinical imaging in advancing precision oncology in the continuum of clinical trial design. In this segment of the CIRP annual meeting, we will define precision oncology in the context of the NCI's prior precision oncology initiative, NCI-MATCH, and the NCI's new initiatives, ComboMatch, MyeloMATCH, and iMATCH. We will provide the rationale for co-clinical imaging trial design to advance the NCI's precision oncology initiative through examples derived from the CIRP network and elsewhere. These examples will set the foundation for discussion topics as they relate to: animal models to enable co-clinical imaging trials, image acquisition and data processing considerations to harmonize co-clinical imaging trials, and finally informatics needs to support integration of co-clinical imaging datasets, data mining, and advanced computing. Leaders in respective fields will provide a summary of the current state, opportunities, and challenges in a given domain which will be followed by engaging discussions. Participants at the meeting are encouraged to share their thoughts and relevant experiences before, during or after the discussion. The goal of the discussion is to gather information and feedback to support the development of the White Paper.

Presentation Abstracts

CIRP WGs

IADP WG
IMOR WG

Small Animal PET Imaging and Instrumentation

Robert Miyaoka, University of Washington

Small animal imaging is an essential tool supporting research of precision medicine to improve outcomes and advance cures for cancer. Small animal PET offers special strengths including translatability to the clinic; quantitative imaging; dynamic whole-body imaging; the ability to image using nano- to pico- molar concentrations of administered compounds; and the ability to study animals serially over time. Genetically engineered mouse models (GEMM) and patient derived xenograft (PDX) models combined with small animal PET imaging offers wide-ranging possibilities for co-clinical trials. This presentation provides an overview of the development and evolution of small animal PET imaging. In addition, it offers a synopsis of detector and system configurations; multimodality PET imaging systems; image reconstruction and analysis tools; and devices to support multi-animal and multi-modal imaging. It concludes with a look toward technologies/methodologies that will further enhance the impact of small animal PET imaging, especially in the context of co-clinical trials.

The International Photoacoustic Standardization Consortium: Prospects, challenges, and future directions on the path towards standardization in photoacoustic imaging

Lina Hacker[1], James Joseph[2], Sarah E. Bohndiek[3,4] William C. Vogt[5] and Members of IPASC

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Photoacoustic Imaging (PAI) is an emerging modality offering high-resolution visualization of optical absorption contrast across various length scales, from organelles to human tissues. While extensively utilized in preclinical studies for mapping endogenous chromophores like haemoglobin and melanin, PAI has now transitioned into clinical applications. Research demonstrates its efficacy in studying cancer in early-stage human trials, highlighting its capacity to enhance tumour diagnosis, treatment monitoring, and surgical planning with precise insights into, notably, tumour vasculature and oxygenation. Clinically approved instruments (including one FDA-approved device for breast imaging) are now available commercially in many countries, but there is an urgent need for standardized methodologies to ensure precise and reproducible comparisons between different devices. The International Photoacoustic Standardisation Consortium (IPASC) was established to address this gap, bringing together academia, industry, and government stakeholders with the overall goal to reach an international consensus on PAI standardization to improve the quality of preclinical studies and to accelerate efforts in clinical translation. IPASC aims to: (1) define widely accepted test objects (‘phantoms’) and methods for use with preclinical and clinical PAI systems; (2) provide publicly available, reference datasets for testing of data reconstruction and spectral processing algorithms in an open standard data format; (3) to engage the clinical community to maximize the future patient benefit from PAI; and (4) agree upon a standardized and validated test methods for new PAI instruments to help with comparison of published results. Here, the progress made toward these efforts is outlined, highlighting prospects, challenges, and future trajectories.

Disclaimer: This presentation reflects the views of the authors and should not be construed to represent FDA’s views or policies.

Informatics & Outreach (IMOR) Working Group Updates

James Gee[1], Jason Crane[2]

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The mission of the IMOR WG is to facilitate the creation of a web-accessible co-clinical research resource that includes the imaging and omics data, acquisition, and processing methods, workflow documentation and meta-data standardization, and results collected from the CIRP investigations. This annual update will highlight the accomplishments of the WG from the past year, outline this year's IMOR-wide project, and introduce the overall theme of the session's featured presentations.

Federated Preclinical Imaging XNAT-Enabled Informatics (PIXI): PIXI interoperability environment demo to enable co-clinical imaging research in precision oncology

Andrew W. Lassiter, Stephen M. Moore, William Horton, James D. Quirk, Richard Laforest, Daniel S. Marcus, Kooresh I. Shoghi

Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO

Preclinical imaging workflows have been growing in complexity resulting in generation of large datasets. In this work, we report on efforts to develop an open-source preclinical imaging XNAT-enabled informatics (PIXI) platform to manage the workflows of preclinical image data acquisition, capture imaging-associated experiments including metadata and annotations, and to implement analytic pipelines in a unified environment. Our vision for PIXI extends beyond the initial implementation to support a federated network of PIXI instances to enable data sharing and collaboration across institutions.

PIXI is based on the widely used Extensible Neuroimaging Archive Toolkit (XNAT) as the underlying informatics architecture and offers a robust platform for the development and deployment of PIXI. The PIXI platform includes: the PIXI Server, which provides core database, user management, visualization, and workflow functionality; PIXI Point-of-Service (PoS) interface for data entry and PIXI Notebooks for data exploration and analysis; and PIXI Apps to enable automated image processing pipelines through Docker container environment.

With the recent release of PIXI, PET, CT and MR DICOM images are pushed to the PIXI server for workflow management with metadata captured through the DICOM image files for search and reporting as well as through the PoS. Multi-mouse images are supported by a custom RESTful API and Docker pipeline facilitating the splitting of images into individual datasets. Imaging workflow information can be entered or edited through the PoS interface including animal modeling information/metadata, descriptive data, and drug therapies. Newly developed workflows support uploading and managing native Inveon PET and CT images and IVIS bioluminescence (BLI) images. XNAT's search and reporting capabilities have also been extended to support PIXI's new data types and metadata. To enable open science, PIXI instances will interconnect through a federated model to allow site-to-site data and application sharing with configurable access control. Importantly, PIXI will also support interfaces to The Cancer Image Archive (TCIA) and the planned NCI Imaging Data Commons (IDC) to enable import and export of data to facilitate open science research. Through this federated model, data sharing and collaborations across institutions will be facilitated by PIXI, enhancing the efficiency and effectiveness of co-clinical imaging research to link spatial biology and multi-omics with imaging and therapeutic outcome.

Overall, the development of the PIXI platform is expected to have a profound impact on the management of preclinical imaging datasets and co-clinical imaging which will ultimately support translational precision oncology. Additional information, including the free download of PIXI, instructional videos, documentation, and mailing list sign-up, is available at https://www.PIXI.org/.

BiRAT: Platform for Biomedical Image Data Registry and Processing

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Purpose: Imaging tools for both preclinical and clinical research are invaluable for their ability to non-invasively detect and monitor disease and assess treatment response. The continuous generation of biomedical images and associated metadata at an increased rate makes image data management and sharing challenging. Especially, for pre-clinical images stored in vendor specific proprietary file formats, the routine image data handling and analysis methods become very cumbersome. Despite the availability of several image management tools, which are mostly tailored for clinical DICOM-based images, there is still a need for robust data handling tools. A web-based platform, BiRAT (Biomedical Imaging Registry, Analysis and Translation) is being developed to facilitate the pre-clinical image data registry and processing through early data capture, storage, processing, and analysis.

Methods: The application uses a data-driven bottom-up approach to early capture and store image and associated experimental data in their native formats. Through web and desktop clients, the original unstructured image data are annotated and uploaded in a structured hierarchical database to a cluster-based distributed data storage system. Various frontend and backend web-applications are being developed to manage, access, and share data for better data security and accessibility. The application also includes a robust 3D image viewer. Future development will also include modular processing software tools for computationally intensive tasks and AI implementation for various image data processing such as image segmentation, analysis, and quantification applications.

Results: The framework for containerized server architecture is deployed incorporating advanced technologies to provided distributed and scalable data storage. The server is configured to manage containerized workloads through latest Kubernetes distribution system. A web-application suite is also being implemented replacing the initial prototype development that has been built using only Django framework. The new implementation incorporates JavaScript programing for implementing robust dynamic data-driven web-applications. This implementation also enables modularization, making it easier to develop specific new applications as needed and incorporate various third-party web-applications. The focus on the current development is to develop robust web-based database capable of performing fast data upload with extended image data annotation and data retrieval system.

Conclusion: Robust web application and cluster based scalable server are being developed transforming the traditional approaches into a centralized data storage management system allowing more advanced data archiving and processing pipelines.

NCI Imaging Data Commons: Towards transparency, reproducibility, and scalability in imaging AI

Andrey Fedorov

Department of Radiology, Harvard Medical School

The remarkable advances of artificial intelligence (AI) technology are revolutionizing established approaches to the acquisition, interpretation, and analysis of biomedical imaging data. Development, validation, and continuous refinement of AI tools requires easy access to large high-quality annotated datasets, which are both representative and diverse. The National Cancer Institute (NCI) Imaging Data Commons (IDC) hosts over 60 TB of diverse publicly available cancer image data spanning radiology and microscopy domains. By harmonizing all data based on industry standards and colocalizing it with analysis and exploration resources, IDC aims to facilitate the development, validation, and clinical translation of AI tools and address the well-documented challenges of establishing reproducible and transparent AI processing pipelines. Balanced use of established commercial products with open-source solutions, interconnected by standard interfaces, provides value and performance, while preserving sufficient agility to address the evolving needs of the research community. Emphasis on the development of tools, use cases to demonstrate the utility of uniform data representation, and cloud-based analysis aim to ease adoption and help define best practices. Integration with other data in the broader NCI Cancer Research Data Commons infrastructure opens opportunities for multiomics studies incorporating imaging data to further empower the research community to accelerate breakthroughs in cancer detection, diagnosis, and treatment. The presentation will discuss the recent developments in IDC, highlighting resources, demonstrations, and examples that we hope can help you improve your everyday imaging research practices - both those that use public and internal datasets.

The MIRACCL Portal for Comparing Patient and PDX Response Using Cancer Image Features and Genomics in Co-Clinical Trials

Dowst, H.[1], Zheng, F[1]., Alkim, E.[2], McOwiti, A.[1], Rajaram Srinivasan, R.[1], Hormuth, D.[3], Yankeelov, T.[3], Rubin, D.[3], Lewis, M.T[1].

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INTRODUCTION: The Molecular and Imaging Response Analysis of Co-Clinical Trials (MIRACCL) platform was developed beginning three years ago to support the co-clinical RESPONSE trial at Baylor College of Medicine. The goal of MIRACCL is to enable comparison of treatment response within parallel studies between the patient and patient derived xenograft (PDX) cohorts. The response assessments include the measurement of multiple imagine features at pre-treatment and various points during a study along with samples taken for assessment of the genomic changes.

METHODS: To achieve this goal, we employee the use of web-technologies to enable visual and quantitative comparison of the imaging and genomics. Investigators at Baylor College of Medicine leveraged their expertise in patient derived xenograft development and model study implementation to generate the PDX imaging dataset and collect the model samples for sequencing. The University of Texas at Austin provided centralized patient and PDX image normalization, segmentation, and analysis while the Biomedical Informatics team at Stanford University provided the image visualization tool and imaging response assessment. Due to the difference in data modalities, data sources, and temporal collection of data it was necessary to place the data within the context of the study design and provide visual and quantitative comparisons of the study outcomes for various time points. The MIRACCL features created to achieve this goal include tabular cohort annotations, a side-by-side visualization of imaging response distributions, and a comparison of the upregulated and down regulated gene expression between cohorts. One of the imaging methods deployed in MIRACCL to assess treatment response measured response by longest diameter tumor which is then categorized by RECIST. Additional imaging comparison methods include signal enhancement ratio (SER), apparent diffusion coefficient (ADC), and tumor volume. Samples for sequencing taken at pre-treatment and throughout the design of the study are used to identify gene expression changes brought about by treatment. In the Omics module of MIRACCL, the 500 most frequently upregulated and 500 down regulated genes for each cohort are displayed based on user selected time points and imaging feature of interest. A Venn diagram is generated to identify the genes which are commonly regulated in both cohorts.

RESULTS & CONCLUSION: While these features have provided multiple methods of comparing the outcome of co-clinical trials, the research team desired to know the significance of these correlations and differences between the two cohorts. Consequently, the Analytic module was implemented in MIRACCL this past year. The analytics module focuses on two hypotheses: 1) PDX models of similar subtyping will respond in a similar manner to the patients enrolled in the trial and 2) Response can be predicted while on-treatment to determine if changes to treatment are warranted. The change in tumor quantifications from on-treatment to baseline were statistically correlated to changes in tumor quantifications from post-treatment to baseline to determine if response could be determined while currently on-treatment. The p value and r value of the spearman correlation are provided to determine the significance and clustering of the cohort. The enhancements afforded by MIRACCL's Analytics module summarize the treatment response of the patient and PDX cohorts and effectively address the hypothesis of the REPONSE trial. MIRACCL is now available for expansion as a tool for other trials co-clinical trials.

CIRP Poster Abstracts

Advances in Animal Models, Co-Clinical Trials, and Co-Clinical Imaging Applications

Novel B cell gene signature to predict clinical response to combined EGFR and glutaminolysis inhibition in *KRAS* wild-type colorectal cancer

Seong-Woo Bae[1], Kristen K. Ciombor[2], Jennifer G. Whisenant[2], M. Noor Tantawy[3, 4], Gary T. Smith[4, 5], John Paul Shen[6], Scott Kopetz[6], Jordan Berlin[2], H. Charles Manning[1]

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Within the scope of *KRAS* wild-type (WT) colorectal cancer (CRC) management, the utilization of monoclonal antibodies (mAbs) targeting the epidermal growth factor receptor (EGFR), specifically Cetuximab and Panitumumab, has been a pivotal strategy. Despite their adoption, the durability of response to these anti-EGFR mAbs is markedly sparse across CRC patient populations, highlighting an urgent need for deeper understanding of CRC biology and an expansion of research efforts. Positron Emission Tomography (PET) imaging, renowned for its sensitive and quantitative assessment capabilities, offers a non-invasive avenue to probe tumor metabolic activities. A critical observation in the oncogenic process is the alteration of glutaminolysis, a mechanism that facilitates the coupling of signal transduction to nutrient uptake and might promote mitogen-activated protein kinase (MAPK)-dependent proliferation, irrespective of *EGFR* mutational status. This alteration poses a potential barrier to the effectiveness of anti-EGFR therapies, underscoring the strategic importance of targeting glutaminolysis in the therapeutic regimen. Our research hypothesizes that an integrative methodology combining PET imaging with genomic insights could significantly unravel the complexities of *KRAS* WT CRC, enhancing the specificity and efficacy of targeted treatments. Our investigative efforts were directed towards identifying genomic and imaging biomarkers that predict responses to the simultaneous inhibition of EGFR and glutamine metabolism in *KRAS* WT CRC patients.

As a co-clinical trial, we assessed the efficacy of a combined treatment regimen targeting EGFR and glutaminolysis blockade in *KRAS* WT CRC patients and patient-derived xenografts (PDX). Reflecting on the treatment outcomes (RECIST1.1) observed in the clinical trial (NCT03263429), participants were categorized into two groups: those who responded to the treatment were designated as having "clinical benefit Yes," whereas those who did not respond were classified under the "clinical benefit No" group. The treatment demonstrated a clinical benefit in 7 out of 16 patients (43.8%) and in 3 out of 6 PDX models (50%). Our combined treatment approach has been clinically verified to confer significant benefits on patient survival metrics, specifically overall

survival (OS) and progression-free survival (PFS). The statistical analysis yielded a log-rank p-value of 0.0099 for OS, indicating a substantial improvement in survival rates, and an even more remarkable log-rank p-value of 0.00034 for PFS, underscoring the treatment's efficacy in delaying disease progression. The "Yes" group's median OS reached 13.1 months, compared to just 4.4 months for the "No" group. Similarly, the "Yes" group's median PFS was 5.91 months, greatly exceeding the 1.69 months median survival of the "No" group. Through bioinformatics analysis of bulk RNA sequencing data from the 16 patients, we delineated a gene signature associated with treatment response, which upon further validation across multiple public databases, revealed a significant correlation with B cell activation. Moreover, we explored the potential of deploying 18F-4-Fluoro-glutamine (^{18}F-Gln) or l-[5-11C]-glutamine (^{11}C-Gln) and (4S)-4-(3-[18F]fluoropropyl)-L-glutamate (^{18}F-FSPG) as markers for evaluating metabolic shifts in PDX and patient tumors before and after treatment with CB-839 and anti-EGFR therapy. In our observations within PDX and patient-derived tumors, we noted trends towards a reduction in FSPG-PET uptake post-treatment when there is a response. Regarding glutamine PET, across both trials, we were unable to identify clear trends, indicating the necessity for further investigation.

In conclusion, our findings suggest a profound linkage between B cell immunology and the enhanced therapeutic outcomes stemming from the concurrent inhibition of glutaminolysis and EGFR in *KRAS* WT CRC patients. The integration of these novel preliminary signatures with non-invasive monitoring of glutaminolysis activity via PET imaging represents a significant unresolved challenge. Larger prospective clinical trials are imperative to validate our preliminary findings and could significantly contribute to refined patient selection strategies for tailored treatment approaches.

Acknowledgments: This work was supported by grants from the NIH (P50 CA236733, U24 CA220325, S10 OD019963, and S10 OD016245). H. Charles Manning is a Cancer Prevention Research Institute of Texas (CPRIT) Scholar in Cancer Research and is supported by CPRIT RR200046.

Assessing response to chemotherapy in PDX models of small cell neuroendocrine prostate cancer using hyperpolarized ^{13}C Pyruvate MRI

Ivina Mali[1], Sule Sahin[1], Xiao Ji[1], Will Bryne[1], Avantika Sinha[1], Rosalie Nolley[1], Robert Bok[1], Peder Larson[1], Rahul Aggarwal[2], Donna Peehl[1], John Kurhanewicz[1], and Renuka Sriram[1]

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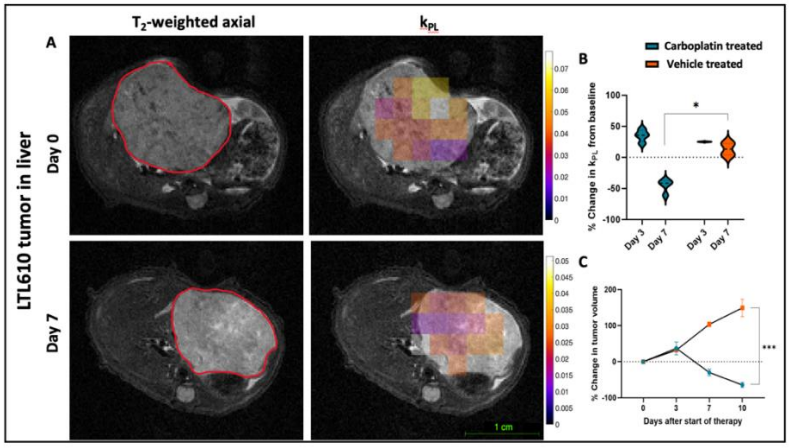
Small cell neuroendocrine (SCNC) prostate cancer (PCa) has risen as a consequence of second line anti-androgen therapy. This trans-differentiation commonly found in metastatic castration resistant prostate cancer (mCRPC) is very aggressive and associated with poor prognosis. SCNC tumors respond differently to therapy compared to the adenocarcinoma counterpart and has limited treatment options. Patients with metastases in the liver have a particularly poor prognosis relative to those with bone metastases alone. New clinical trial findings revealed that patients with mCRPC and liver metastases benefited from certain therapies such as androgen receptor signaling inhibitors and docetaxel, whereas those with bone metastasis did not. These findings underscore the need to be able to assess the response to therapy in a timely manner in metastatic sites which are generally considered unevaluable by RECIST criteria.

In this study, we use hyperpolarized (HP) [1-^{13}C] pyruvate MRI to non-invasively detect response to platinum-based chemotherapy in preclinical models of SCNC using patient-derived xenografts (PDX). LTL610 PDX of SCNC was implanted in the liver of NSG mice, and k_{PL}, the apparent rate of enzymatic conversion of HP [1-^{13}C] pyruvate to [1-^{13}C] lactate, was calculated. In the liver, a significant change in k_{PL} was observed on day 7 following treatment, before a significant decrease in tumor volume, which was observed on day 10. Preliminary studies in a mouse showed an earlier therapeutic response for the same dose of the drug in the bone. Decrease in LTL610 tumor metabolism in the liver post-treatment prior to a significant reduction in tumor volume might be indicative of the ability of k_{PL} in depicting an early response to therapy.



Representative T2-weighted axial MR images of LTL610 PDX in liver at baseline and 7 days after carboplatin treatment (A). T2 images with tumor boundaries in red (left) and overlaid with k_{PL} maps (right). Change in k_{PL} post chemotherapy (B). Percent change in tumor volume in response to therapy (C). *P<0.05; ***P<0.001.

Evaluating ΔFFNP-PET as an imaging biomarker of estrogen receptor α (ERα) functional status in preclinical models of ERα+ breast cancer with *ESR1* mutations

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Background: The progesterone receptor (PgR) gene is highly regulated by ER at the mRNA and protein level. Previous clinical studies have demonstrated that changes in ^{18}F-fluorofuranylnorprogsterone (FFNP) uptake after 17β-estradiol (E2) challenge (ΔFFNP-PET) are predictive of endocrine therapy response. However, the impact of *ESR1* mutations on ΔFFNP is not fully understood. In this work, we evaluate the utility of ΔFFNP as an imaging biomarker for assessing fER in preclinical models with and without mutations in *ESR1*.

Methods: MCF7 and T47D breast cancer cells expressing wild type (WT-ER) or ESR1 mutation, Y53S-ER, were used to generate tumor xenografts. $3x10^6$ tumor cells of either MCF7 or T47D were implanted in the second mammary fat pad of ovariectomized immunodeficient mice maintained on E2 water (8 µg/ml). For baseline assessment of PgR, E2 was withdrawn from drinking water 4 days prior to imaging. The ΔFFNP protocol consisted of 20 min static imaging 50 min post injection of FFNP at baseline and 24hr or 48hrs following E2 challenge with subcutaneous injection of either 20 µg/day or 30 µg/day. FFNP uptake in tumor was quantified by measuring SUV_{25} normalized to muscle uptake (T/M ratio). ER and PgR expression levels were determined by western blotting and immunohistochemistry in tissues collected at different time points. Student *t-test* and two- way ANOVA were performed to compare differences in FFNP-PET uptake between baseline and post-E2 challenge and biodistribution assay, respectively.

Results: In WT-ER MCF7 xenograft, there was a significant ($P<0.05$) increase (≈ 2 fold) in FFNP uptake at 48hrs following 30 µg/day E2 challenge, but not at 20 µg/day. Further, post-PET biodistribution assay demonstrated statistically significant increase in tumor uptake ($P<0.01$) from 0.32±0.02 %ID/gram at baseline to 2.02±0.76 % ID/gram at 48 hrs. Since optimal ΔFFNP was observed with 30 µg/day E2 challenge at 48 hrs, we selected this time point for further evaluation of ΔFFNP. In T47D implanted tumors, E2 challenge induced significant ($P\leq0.05$) elevation of FFNP uptake post-E2 ($SUV_{T/M}$=2.0) compared to the baseline imaging ($SUV_{T/M}$=1.4). In contrast, ERα mutant MCF-Y537S tumors were impervious to E2 challenge as there was no significant difference between FFNP uptake at baseline ($SUV_{T/M}$=1.806) and Post-E2 ($SUV_{T/M}$=1.874). IHC analysis for PgR expression concur with ΔFFNP imaging results with increased staining in WT-ER tumors following E2 challenge but not in Y537S-ER.

Conclusion: These findings confirm that the PgR is regulated by ER and thus PgR expression can serve as an imaging biomarker of fER. As an imaging biomarker of PgR expression,

ΔFFNP can provide an effective strategy for assessing fER as a potential predictive biomarker of clinical response to therapy. The crosstalk of ER and PgR with other pathways and impact of these interactions on ΔFFNP needs to be further evaluated.

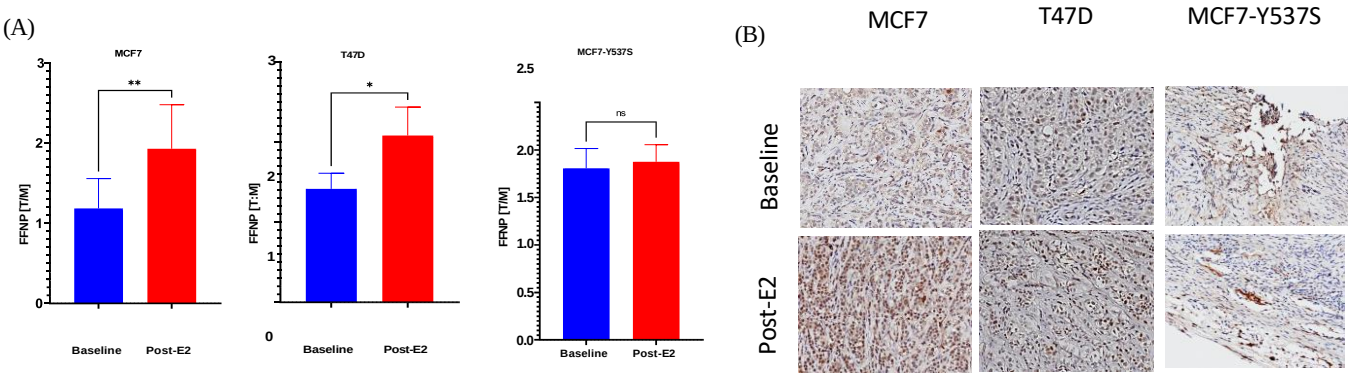

Figure 1. (A) ΔFFNP uptake in MCF7, T47D and MCF7- Y537S tumors bearing mice injected with 30 ug of estradiol once daily for 2 days. (B) Representative images of IHC stating for PgR expression in tissue showing increased expression of PgR levels in WT-ER tumor models (MCF7 and T47D) and in MC7-Y537S PgR expression remained unchanged.

A Quantitative PET/CT Research Resource for Co-Clinical Imaging of Lung Cancer Therapies

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Although immune checkpoint inhibitor (ICI) therapy has been a tremendous clinical benefit for some non-small cell lung cancer (NSCLC) patients, only ~20% of NSCLC patients respond to anti-PD1/PDL1 therapy. We are developing methods for quantitative pre-clinical PET (positron emission tomography) imaging for ICI therapies in NSCLC. We are leveraging an existing co-clinical trial using our genetically engineered mouse models (GEMM) of lung adenocarcinoma and squamous cell carcinoma to develop, test and implement the methods and populate a web-accessible research resource. This web-accessible research resource will in turn leverage recent developments in quantitative cancer imaging informatics using the industry-standard DICOM format.

Our co-clinical trial is evaluating the hypothesis that neutrophils located within the tumor stroma retard the infiltration of tumor-reactive lymphocytes into the malignant portion of tumor and that neutrophil depletion will improve ICI response rates by removing this barrier. We are utilizing a CXCR2 antagonist that inhibits the recruitment of monocytes and neutrophils into the tumor microenvironment. Studies are underway in both the mouse models described above and in a phase 2 trial using SX-682 and pembrolizumab in patients with treatment naive stage IV or recurrent NSCLC.

In parallel we are developing informatics methods to capture and track the necessary meta-information along with appropriate response criteria for preclinical imaging. In addition, we are a evaluating quantitative pre-clinical PET imaging methods that are linked to quantitative clinical PET imaging methods

We are addressing these tasks with three Specific Aims:

1, Develop and optimize quantitative preclinical quantitative imaging methods and protocols. These methods will involve novel long-lived phantoms that can cross-calibrate multiple preclinical and clinical PET scanners. This are being tested with partner members of the Co-Clinical Imaging Research Resources Program.

2. Implement the optimized methods in our co-clinical trial of ICI treatment of NSCLC with a GEMM lung adenocarcinoma model and a GEMM model lung squamous cell carcinoma. From this we will evaluate how the information gleaned from the pre-clinical and clinical studies can be used to inform future pre-clinical studies in terms of imaging protocols and response criteria.

3. Share data and resources on co-clinical trials using quantitative PET imaging using a web-accessible open science approach (open source + open data) by extending the DICOM standard for pre-clinical small animal imaging with DICOM-compliant structures that provide necessary quantitative meta-data.

The methods and resources developed during this project will be distributed to accelerate the development of needed effective cancer therapies by improving the utility of early-phase oncology trials using co-clinical studies with PET imaging. In addition, we will determine, and potentially improve, the utility of PET imaging as a biomarker for early assessment of response in co-clinical immunotherapy studies by using an appropriate mouse model.

Preliminary Analyses of single cell transcriptome reveal effects of stroma-directed drug and chemotherapy in a GEM model of pancreatic cancer

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Hypothesis: The dense stroma present in pancreatic ductal adenocarcinoma (PDA) harbors a unique tumor microenvironment (TME) that is immune suppressive and underlies the chemo-resistance of PDA. We have evaluated synthetic vitamin D combined with chemoimmunotherapy in a pilot clinical study (NCT03519308). To elucidate the underlying mechanisms of this treatment, we designed a matched study in a genetically engineered mouse model of PDA (KPC mice) to test the hypothesis that synthetic vitamin D enhances the effect of chemotherapy. Employing single-cell RNA sequencing (scRNAseq) analysis, we investigated changes in the TME and characterized cell types and gene expressions.

Methods: KPC mice were randomly assigned to one of four groups: 1) **Control** (untreated); 2) Nab-paclitaxel + gemcitabine + cisplatin (**Chemo**); 3) **Chemo +** synthetic vitamin D (calcipotriol, **Cal**); 4) **Chemo + Cal + PD-L1;** 5) **Chemo +** antifibrotic agent (losartan, **Losa**). The treatment lasted for 14 days followed by euthanasia and tumor collection for scRNAseq. The treatment lasted for 14 days as same as above treatment schedule, followed by scRNAseq. Utilizing the 10x Genomics protocol, cells were harvested from the tumor. Using the Cell Ranger (10X Genomics) output of filtered matrices supplied by the sequencing core, the Seurat package (v4) is used to integrate the data for each sample. Cirrocumulus was used for interactive exploration and visualization of datasets. Target genes were extracted from literature [1-4].

Results: Analysis of single-cell RNA sequencing(scRNAseq) data unveiled notable findings regarding the impact of different treatments on tumor growth and gene expression profiles. Specifically, Chemo treatment exhibited a significant delay in tumor growth compared to the Control group. However, it was observed to elevate the proportion of mesenchymal cells within the tumor and promote the upregulation of epithelial-to-mesenchymal transition (EMT) genes known to confer resistance to chemotherapy [1,2]. In contrast, the combination treatment of Chemo+Cal demonstrated a contrasting effect by increasing the fraction of epithelial cells while concurrently downregulating EMT genes when compared to Chemo alone. Transcriptomic analysis of tumor cells further elucidated the molecular mechanisms underlying these observations. Chemo treatment was associated with an elevation in the expression of Fibronectin 1 (FN1), a gene implicated in tumor invasiveness, EMT, and metastasis. Conversely, it was found to suppress the expression of Trefoil Factor Family 1 (Tff1), a gene known for its tumor-suppressive properties and sensitivity to chemotherapy. Chemo treatment reduced FAP expression in fibroblast cells. Furthermore, Chemo+Losa resulted in a significant accumulation of immune cells within the tumor, leading to the eradication of cancer cells.

Conclusion: Single cell transcriptome analysis provided valuable insights into treatment-induced molecular subtype changes, which may predict future resistance and invasiveness. Our study revealed important mechanisms of calcipotriol and losartan that enhance the efficacy of chemotherapy by downregulating chemo-resistant genes and upregulating the tumor suppression genes in PDA tumors.

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MRI Assessment of Bone Marrow Metrics in Myelofibrosis

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While biopsy remains the clinical standard for evaluating bone marrow in patients with the hematologic cancer, myelofibrosis (MF), its limited tissue sampling fails to capture heterogeneity of disease throughout the bone marrow space. Moreover, the painful nature of the procedure limits patient acceptance of repeated biopsies for assessment of disease evolution or treatment response. The UM CIRP team is investigating non-invasive, large-volume MRI survey of bone marrow alteration in MF and other myeloproliferative neoplasms.

In the clinical arm of our CIRP effort we evaluated bone marrow of 66 study participants (45 with MF; 15 with non-MF MPNs; and 6 healthy controls). We assessed patient bone marrow across three anatomic sites (lumbar vertebral bodies, ilium, and femoral heads), using three quantitative MRI metrics: proton density fat fraction (PDFF); apparent diffusion coefficient (ADC) and magnetization transfer ratio (MTR). We correlated these MRI metrics with a standard indicator if clinical patient prognosis (dynamic international prognostic scoring system; DIPSS) and cellularity and fibrosis score (MF grade) from the iliac crest biopsy. All MRI examinations were performed on a single 3T clinical scanner.

Participants with MF had elevated MT ratio (MTR) and ADC and lower PDFF compared to healthy participants. Non-MF MPN participants demonstrated the same trends, though to a lesser extent. Individual bone marrow metrics correlated strongly across anatomic sites (r-pearson from 0.57 to 0.89), though participants did demonstrate heterogeneity both within and among different regions. DIPSS risk groups had limited correlation with MRI metrics. To probe which quantitative MRI data are associated with marrow fibrosis, we developed a multivariate logistic regression model to stratify the 45 participants with MF by early fibrosis (MF grades “0-1”) and overt fibrosis (MF grades “2-3”). Out of seven MRI-anatomy metric combinations, PDFF in the vertebral bodies and ilium along with ADC in the ilium contributed most significantly to the model (accuracy = 84.6%, sensitivity to predict overt fibrosis = 88.9%, specificity = 75%, area under the receiver operator curve = 0.94). However, with the relatively limited number of participants, training and test sets were small, suggest model generalizability and robustness are limited. To simplify toward more clinically relevant terms, we evaluated early and overt fibrosis using ADC. We identified a significant association between ADC and bone marrow fibrosis. Participants with two or more abnormal ADC values (across the anatomic sites) had much greater odds of also having a fibrosis grade of MF-2 or higher (p value = 0.0007, odds ratio = 12.65 using Fisher’s exact test).

In summary, the selected quantitative bone marrow MRI metrics show promise to reflect relevant clinical indicators of MF bone marrow status, including cellularity and fibrosis, and may be useful in clinical drug trials and patient management of MF.

CIRP Poster Abstracts

Advances in Imaging Acquisition, Data Processing, and Method Development

Repeatability of a quantitative multiparametric MRI protocol measuring perfusion, cellularity, and hypoxia in a murine model of glioma: Preliminary results

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Introduction. We have developed a multiparametric MRI exam that combines dynamic contrast-enhanced MRI (DCE)-MRI to report on perfusion, diffusion weighted (DW)-MRI to evaluate tissue microstructure, and oxygen-enhanced (OE)-MRI to measure hypoxia. Here we present preliminary results on the repeatability of these techniques in a murine model of glioma.

Methods. A Bruker 7.0 T MRI system was used to collect: a high-resolution T_2-weighted images for segmentation, T_1-map *via* a variable flip angle approach, DCE-MRI data, DW-MRI data, and OE-MRI data in five rats with orthotopically placed C6 gliomas. A set of retest scans with an identical acquisition protocol were obtained after at least five half-lives of the contrast agent had passed. The following quantitative parameters were obtained from the MRI data: the volume transfer constant (K^{trans}) to estimate perfusion; extravascular, extracellular volume fraction (v_e); the apparent diffusion coefficient (ADC) to estimate tumor cellularity; the longitudinal relaxation rate (T_1); and the OE-derived change in T_1 to differentiate hypoxic from normoxic tissue.

Results. Figure 1 displays test/retest parameter maps on 1 rat tumor. Bland-Altman plots for all the parameters across all the animals suggest no systemic biases in our measurements. Wilcoxon signed rank tests between test and retest scans show no significant differences for all quantitative parameters ($p(ADC) = 1$, $p(T_1) = 0.63$, p(OE-derived ΔT_1) $= 0.81$, $p(K^{trans}) = 0.13$, $p(v_e) = 0.31$).

Discussion. We have demonstrated that we have developed a repeatable quantitative and multiparametric MRI protocol. Ongoing studies are collecting these data before and during radiation therapy for incorporation into a biology-based mathematical model designed to predict the response of tumors to treatment and, ultimately, optimize the delivery of radiation.

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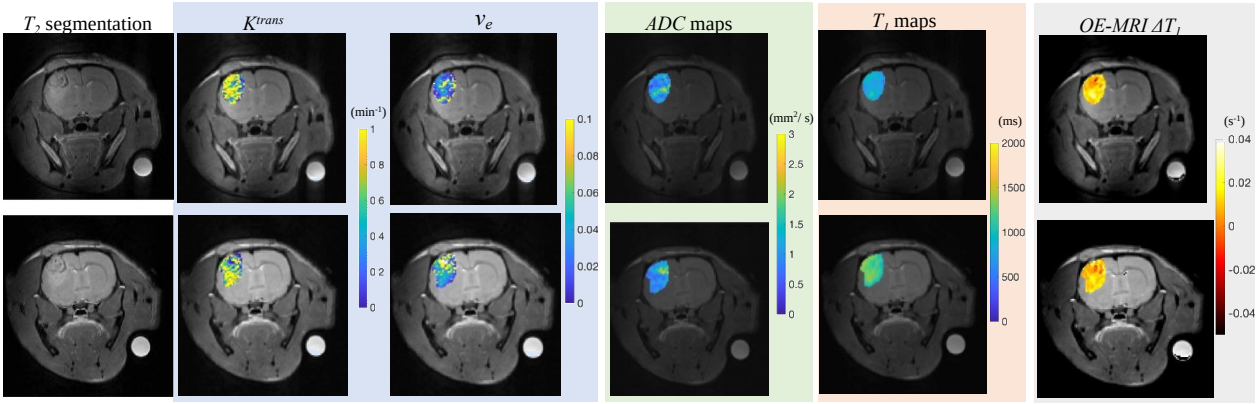

Figure 1. Representative test and retest images are shown for a single animal at the central tumor slice. The top row are images collected from the test protocol, and the bottom row are collected from the retest protocol. The distribution for each parameter is visually similar, as seen in this data.

Reproducibility and Repeatability of T2*- and T2-Mapping in Osteosarcomas

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Objectives: The five-year survival rate for pediatric metastatic osteosarcoma is 30%, emphasizing the need for new treatment options. CD47-targeted immunotherapies activate tumor-associated macrophages (TAM) in the osteosarcoma microenvironment. Since the tumor does not change in size in response to immunotherapy, at least not in the immediate post-treatment phase, an imaging technology that can visualize TAM activation would greatly help to identify responders to these new therapies. Iron oxide nanoparticles (IOP) are phagocytosed by TAMs and, therefore, enable TAM detection on T2- and T2*-weighted magnetic resonance images. The goal of our study was to assess the repeatability and reproducibility of T2*- and T2-mapping of osteosarcomas in a mouse model.

Methods: Fifteen BALB/c mice bearing-murine osteosarcomas underwent MRI on 3T and 7T scanners before and after intravenous IOP infusion, using T2-weighted fast spin echo, T2*-weighted multi-gradient echo and T2-weighted multi-slice multi-echo sequences. Each sequence was repeated twice. Tumor T2- and T2*-relaxation times were measured twice by two independent investigators. The agreement between T2* and T2 measurements on first and second acquisitions by each reader (intra-observer) refers to the repeatability, and agreement between the two readers (inter-observer) refers to the reproducibility. Repeatability and reproducibility were examined using concordance correlation coefficient (CCC) and Bland–Altman analysis and the mean difference is presented with 95% limits of agreement . In addition, we used coefficients of variation (CoV) to evaluate the distribution of the data relative to their average.

Results: Pre-contrast T2* relaxation times of osteosarcomas were significantly shorter at 7T (first acquisition 14.2 ms ± 2.35 ms, second acquisition 14.28 ms ± 2.08 ms) than at 3T (first acquisition 26.75 ms ± 5.56 ms, second acquisition 26.71 ms +- 6.09 ms, $p<0.001$)(Figure 1). At 24 hours after IOP infusion, all tumors demonstrated significant shortening of T2* relaxation times at 7T (first acquisition 10.21 ms ± 3 ms, second acquisition = 10.64 ms ± 2.97 ms) and at 3T (first acquisition 16.63 ms ± 5.67 ms, second acquisition 16.70 ms ± 5.73 ms, $p<0.001$). Similarly, pre-contrast T2 relaxation times of osteosarcomas were significantly shorter at 7T (first acquisition 41.24 ms ± 6.58 ms, second acquisition 41.60 ms ± 5.68 ms) than at 3T (first acquisition 65.06 ms ± 2.64 ms, second acquisition 65.11 ms ± 3.01 ms, $p<0.001$). At 24 hours after IOP infusion, all tumors demonstrated significant shortening of T2 relaxation times at 7T (first acquisition 34.44 ms ± 6.26 ms, second acquisition 34.42 ms ± 6.13 ms,) and at 3T (first acquisition 47.46 ms ± 7.89 ms, second acquisition 48.18 ms ± 7.70 ms, $p<0.001$).

We found excellent agreement between duplicate acquisitions for both T2* and T2 measurements at either magnetic field strength, by the same individual (repeatability), and between individuals (reproducibility). The repeatability CCC for T2* values were 0.99 (CoV 4.43%) for reader 1 and 0.98 (CoV 5.82%) for reader 2. The reproducibility of T2* values

between 2 readers was 0.99 (CoV 3.32%) for the first acquisitions and 0.99 (CoV 6.30%) for the second acquisitions. Regarding T2 values, the repeatability of CCC was similar for both readers, 0.98 (CoV for reader 1 = 3.64% and reader 2 = 4.45%). The CCC of the reproducibility of T2 was 0.99 (CoV 3.1%) for the first acquisition and 0.98 (CoV 4.38%) for the second acquisition. **Conclusion** Our results demonstrated high repeatability and reproducibility of quantitative T2*- and T2-mapping for monitoring the presence of TAMs in osteosarcomas.

Acknowledgment: This work was in part supported by a grant from the National Cancer Institute (NIH/NCI); grant number U24CA264298

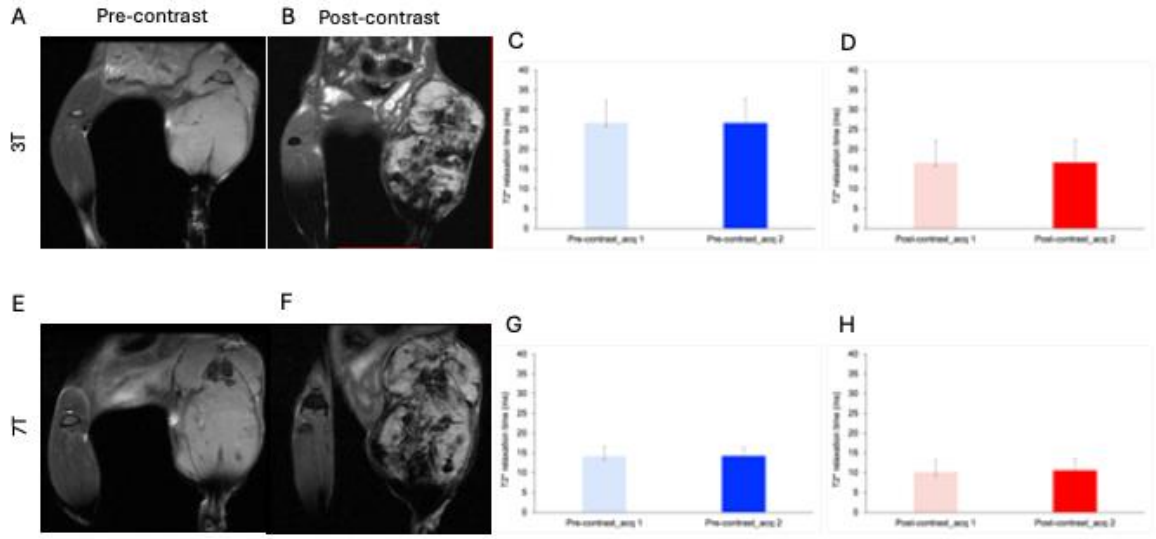

Figure 1. Representative repeated T2*-weighted acquisitions (Acq) of osteosarcomas at (A and B) 3 Tesla (3T) and (C and D) Quantitative tumor T2* relaxation times at 3T before IOP injection. Representative repeated T2*-weighted acquisitions (Acq) of osteosarcomas at (E and F) 7 Tesla (7T) and (G and H) Quantitative tumor T2* relaxation times at 3T before IOP injection.

Exploring VivoVist™ and Spectral Photon-Counting CT in Preclinical Cancer Studies

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In the evolving landscape of preclinical imaging, the pursuit of enhancing the diagnostic and therapeutic efficacy of computed tomography (CT) imaging has led to the exploration of advanced contrast agents and imaging technologies. Among these, spectral photon-counting (PC) micro-CT imaging emerges as a revolutionary technique, offering superior contrast resolution and material specificity. This study focuses on evaluating VivoVist™ (Nanoprobes, Inc), a barium (Ba)-based nanoparticle contrast agent, within this advanced imaging modality. VivoVist™ is distinguished by its prolonged circulation time, high contrast enhancement, and low toxicity, positioning it as an invaluable tool for improving CT imaging outcomes. Using a custom-built spectral micro-CT system with a photon-counting detector, we investigated the application of VivoVist™ through retro-orbital injections in both non-tumor-bearing and tumor-bearing C57BL/6 mice models. The efficacy of VivoVist™ was assessed through scans at various post-injection time intervals and using a multi-channel iterative reconstruction algorithm for multi-energy tomographic imaging with voxel sizes of 125 microns for standard resolution and 75 microns for enhanced resolution scan. Spectral decomposition had minimal cross-contamination. Our findings demonstrated significant contrast enhancements with VivoVist™, particularly at the 39 keV energy threshold, where enhancements exceeded 2000 Hounsfield Units (HU) in blood vessels. VivoVist™ provided an effective delineation of brain vasculature. There was a progressive decrease in blood concentration and increased uptake in the liver and spleen over time. In parallel, we explored the concurrent use of VivoVist™ with liposomal iodinated nanoparticles in a radiation therapy context for cancer treatment, revealing that VivoVist™, when used in combination with radiation therapy, did not significantly enhance the accumulation of liposomal iodine within head and neck squamous cell carcinoma (HNSCC) tumors. The average tumor volume in the test group (treated with VivoVist™ and radiation therapy) was significantly larger compared to the control group, with no statistically significant difference in iodine accumulation observed.

In conclusion, VivoVist™ has the ability to improve imaging precision in spectral PC micro-CT scans. Although combining it with radiation therapy didn't significantly change liposomal iodine levels in tumors, VivoVist™ effectively differentiated barium from iodine contrasts and significantly enhanced imaging at certain energy levels. These results underscore the importance of further investigating VivoVist™ for diagnostic and therapeutic uses, especially its role in cancer treatments and its potential to enhance the effects of radiation therapy.

Predicting the response of combination chemotherapy and targeted therapy *via* mathematical modeling in a murine model of pancreatic cancer

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Introduction. We aim to develop a parsimonious mathematical framework to characterize the response of pancreatic cancer to a range of chemotherapies (cisplatin, paclitaxel, and gemcitabine) +/- the influence of stromal-targeting drugs (calcipotriol and losartan) and an immune checkpoint inhibitor (anti-PDL1). The model is then used to differentiate non-responders from responders for each treatment scenario. Understanding tumor interactions through a mathematical lens is critical for advancing cancer treatment strategies and can motivate treatment optimization.

Methods. Longitudinal tumor volume measurements for five distinct combinations of chemotherapies, stromal targeting drugs, and immunotherapy (anti-PDL1) were acquired in mice (N = 49). We employ a set of ordinary differential equations aimed to capture key physiological features such as tumor proliferation, drug efficacy, and drug decay to emulate the progression and regression of pancreatic tumors to predict variation in tumor growth. Bayesian calibration of model parameters is derived on data from *in vivo* experiments conducted on mice with a genetically engineered model (GEM) of pancreatic cancer (KrasLSLG12D-Trp53LSLR172H-Pdx1-Cre).

Results. The model successfully mimics tumor growth in both control and treatment cases, displaying an average concordance correlation coefficient (CCC) of 0.992 ± 0.008 when comparing observed and predicted changes in tumor volumes. We extend our mathematical analysis by conducting leave-one-out predictions (average CCC = 0.736 ± 0.140), mouse-specific predictions (average CCC = 0.746 ± 0.045), and group-informed, mouse-specific predictions (CCC = 0.850 ± 0.093). In particular, the group-informed, mouse-specific predictions display an 81.26 ± 19.04% accuracy in discerning responders from non-responders across all treatment scenarios.

Conclusion. Our constructed mathematical framework reliably fits experimental tumor data and showcases a robust capability to predict response of pancreatic tumors to a variety of treatments. Future directions include adapting this model to identify optimal treatment schedules to optimize tumor control.

Prediction of pCR by molecular subtype using robust lesion segmentation and radiomics/AI in the I-SPY 2 breast cancer clinical trial

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Introduction: Radiomic features and AI extracted from dynamic contrast-enhanced magnetic resonance images (DCE-MRI) of the breast can be used to predict the diagnosis of lesions as malignant or benign.[1] We recently demonstrated that a fuzzy c-means lesion segmentation method[2] resulted in more successful feature extraction in the I-SPY 2 breast cancer clinical trial cohort available at TCIA[3] compared to other reports.[4] We now aim to evaluate the performance of automatically-extracted radiomic features[5–7] from this larger group of patients in the clinical trial in the task of predicting pathological complete response (pCR) in a subgroup receiving experimental neoadjuvant chemotherapy (NAC), for all lesions in the subgroup and by molecular subtype of lesions.

Methods: We calculated derived features for these patients as the ratio of the difference in radiomic feature value at mid-NAC and pre-NAC to the value at pre-NAC. Prognosis performance in the prediction of pCR was conducted for lesions in each molecular subtype and for all lesions using 10-fold cross validation. Stepwise feature selection followed by prognostication via a linear discriminant analysis classifier was conducted within each fold for each group of lesions by subtype. The area under the receiver operating characteristic curve in each scenario was evaluated using *a posteriori* bootstrapping of the likelihood of malignancy for the lesions (2000 iterations) and reported as the median and 95% confidence interval. Feature selection by feature category was reported for each molecular subtype and for all lesions.

Results: Pre-NAC and mid-NAC DCE-MR imaging series were available for a total of 676 lesions. When using the derived features, AUC performance in the prediction of pCR varied by molecular subtype (Table 1) and for all lesions it was comparable to other reports of radiomic features for this task.[8,9] The number of times derived features by category were selected in 10-fold cross validation varied across molecular subtypes. For example, while the percent difference in size features between mid-NAC and pre-NAC was not chosen frequently for HR+HER2- lesions, it was for all other subtypes. Conversely, the percent differences in shape and contrast enhancement kinetics features between mid-NAC and pre-NAC were prominent for HR+HER2- lesions, while being chosen less frequently for the other molecular subtypes.

Conclusion: Feature selection and prognosis performance in a large cohort of patients in the I-SPY 2 clinical trial differed by molecular subtype for derived features calculated between mid-NAC and pre-NAC. These results point to the relevance of customized prognosis models by lesion molecular subtype and the importance of future studies in optimizing imaging-based prognostic models in clinical trials

Table 1: Description of the lesions in the dataset, including number of patients with and without pCR across the I-SPY2 trial, AUC in the task of prediction of pCR, and the number of times a derived feature in each category was selected in 10-fold cross validation.

	Molecular subtype				All lesions
	HR+HER2+	**HR+HER2-**	**HR-HER2+**	**Triple negative**	
Number of patients with pCR (%)	70 (61%)	210 (83%)	20 (34%)	140 (56%)	440 (65%)
Number of patients without pCR (%)	44 (39%)	45 (17%)	38 (66%)	109 (44%)	236 (35%)
AUC (median, [95% CI]) in task of predicting pCR	0.66 [0.56,0.76]	0.61 [0.52,0.7]	0.57 [0.4,0.73]	0.58 [0.51,0.65]	0.68 [0.64,0.72]
Using derived radiomic features from mid-NAC compared to pre-NAC	**Number of times a derived radiomics feature in each category was selected in 10-fold cross validation**				
Size features	10	1	11	14	31
Shape features	3	10	0	0	3
Morphology features	0	0	0	2	2
Texture features	1	2	6	3	2
Contrast enhancement kinetic features	7	19	1	12	17

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Modulating specific activity to determine optimal injected mass in reproducibility of ^{18}FFNP-PET imaging of low progesterone receptor expression in ERα+ breast cancer

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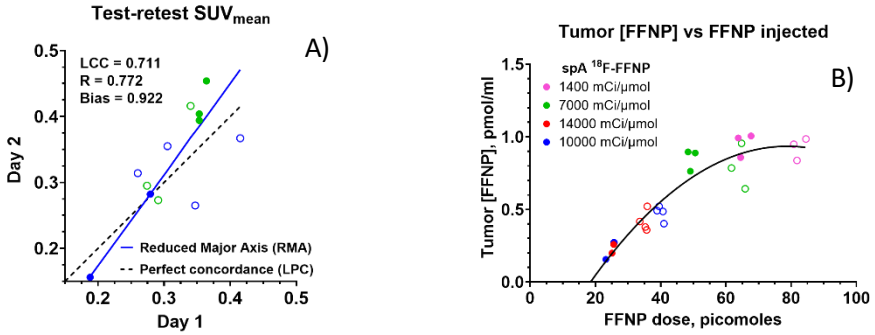
INTRODUCTION: The progesterone receptor (PgR) gene is highly regulated by ER at the mRNA and protein level. Previous clinical studies have demonstrated that changes in ^{18}F-fluorofuranylnorprogsterone (FFNP) uptake after 17β-estradiol (E2) challenge (ΔFFNP-PET) is a predictive biomarker of response to therapy in estrogen receptor α (ERα+) cancer. PgR expression in preclinical breast cancer models is generally low and varies widely across tumor models. Variability in Specific activity, **spA**, mCi/μmol, complicates reproducibility studies in low to medium PgR expressing models because the injected dose must have both sufficiently high signal-to- background to obtain a proper signal and a concentration of FFNP, [FFNP], sufficiently below saturation of PgR. Hence, PgR density, spA and injected mass of radiotracer are important considerations for ^{18}F-FFNP PET imaging. Here we present the results of a test-retest study in isogenic ERα+ T47D breast cancer model (low PgR expressing) using the standard SUV metrics combined with a FFNP binding analysis.

METHOD: Immunodeficient, ovariectomized mice were implanted with isogenic T47D cells in the 2nd mammary fat pad and maintained on E2 water (8 μg/ml). When the tumors reached sufficient volume, a 20 min static PET/CT scan was acquired 50 min post injection of FFNP. The same protocol was followed the next day. Total tumor [FFNP] was calculated from the tumor uptake (mCi/ml) and spA_{scan} (mCi/μmol). Repeatability in tumor SUV_{mean}, SUV_{muscle}, and their ratio, **T/M,** were analyzed. Concordance plots were used to assess and quantify reproducibility with the Pearson **R** (goodness of fit), the **bias**, and the Lin correlation coefficient (**LCC**=R x bias).

RESULTS: Repeatability of SUV_{muscle} and T/M was poor with LCC=0.274 and LCC=0.545, respectively. The LCC for SUV_{mean} was slightly above the acceptable threshold of 0.7 (Fig1A). The tumor [FFNP] vs injected pmol FFNP is displayed in Fig1B and suggests that the PgR receptors are saturated at high FFNP dose. The pink and green points in Fig 1B are near saturation and correspond to the green points on Fig 1A. Here they are more tightly distributed about the reduced major axis (RMA) (Fig1A) than the blue points and appear to be mostly responsible for bias. The red and blue points in Fig1B are in the more linear portion and correspond to the blue points in Fig 1A. In contrast to the green points these points are loosely distributed about the RMA, but evenly distributed about line of perfect concordance (LPC)

(Fig1A). Furthermore, the data suggests that keeping the pmol dose in the linear range and as constant as possible throughout the study should improve both goodness-of- fit and bias. The differences between the FFNP doses for the solid red and blue points in Fig1B is small. These points correspond to the two solid blue points in Fig1A. The data are too few to be definitive, but these two data are more tightly distributed around the LPC than the other data.



CONCLUSION: To maximize reproducibility the FFNP pmol dose should be kept as constant as possible in the lower, most linear part of the saturation plot to reduce bias.

CIRP Poster Abstracts

Advances in Informatics, Web Resources, and Method Development

FAST (Fast Analytical Simulator of Tracer)-PET: an accurate and efficient PET analytical simulation tool

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Introduction: Simulation of Positron Emission Tomography (PET) images is an essential tool in the development and validation of quantitative imaging workflows and advanced image processing pipelines. The most widely used Monte Carlo simulation tool, Geant4 Application for Tomographic Emission (GATE), suffers from high computational demands. Alternative analytical simulators either omit time of flight (TOF) implementations or still require long processing times. In this study, we develop and validate the quantitative accuracy of FAST-PET, a novel analytical framework to simulate PET images, as well as compare its performance against GATE as the gold standard.

Methods: An overview of the workflow is shown in Figure 1a. FAST-PET simulates PET images by performing precise forward projection, scatter, random estimation, and reconstruction that match the Siemens Vision-600 PET/CT scanner geometry and statistics using the Siemens reconstruction software e7 tools. Although the same process should be applicable to other scanner models, we focus on the simulation of the Biograph Vision-600 here. FAST-PET is calibrated according to a National Electrical Manufacturers Association (NEMA) Image Quality (IQ) phantom scan, so it only requires attenuation and activity maps with user-specified acquisition time and reconstruction settings as inputs to simulate PET images. In the first part of the validation, a physical NEMA IQ phantom was scanned for 10 minutes on the Biograph Vision-600, and the same phantom was simulated with both FAST-PET and GATE. In all cases, five 120-second frames and five 5- second frames were reconstructed using ordinary Poisson OSEM algorithm, with 8 iterations and 5 subsets, PSF correction, TOF, and no post-reconstruction filter. The activity mean maps were generated by taking the voxel- wise mean activity across the five noise realizations. For each acquisition time, its intensity distributions within regions of interest (ROIs) in the background and within 6 spheres were plotted in histograms to compare the three methods. To validate performance against clinical images, we simulated FAST-PET and GATE images of a 5-minute scan for 7 patients given their FDG-PET/CT images as ground truth. The reconstruction settings followed the previous description except with 4 iterations, 5 subsets, and 4 mm FWHM Gaussian post- reconstruction filter. Several normal organs (spleen, liver, stomach, pancreas, left and right lung) were segmented by MOOSE (Sundar, 2022), whereas tumors were segmented manually. The concordance correlation coefficient (CCC) of the mean intensities and coefficients of variation within normal organs and tumors was calculated to show their agreement.

Results: Figure 1b depicts representative slices of experimental and simulated (FAST-PET and GATE) 5-second and 120-second scans of the NEMA phantom. The distributions of mean

activity shown in Figure 1c exhibit notable similarity among all three methods for both long (120s) and short (5s) acquisition times, indicating that images produced by both simulation methods closely resemble real scan images in quantitative characteristics under both low and high noise conditions. Figure 1d depicts representative FAST-PET and GATE slices of clinical patient simulations with diagonal and opposite diagonal profiles. Their agreement indicates similarity between both simulated images. Scatter plots and CCC values in Figure 1e confirm the agreement between GATE and FAST-PET in terms of both mean activity and variability within ROIs. Critical to this effort, FAST- PET significantly outperforms GATE in efficiency, simulating a PET image in about 2.5 minutes compared to GATE's 56 hours on a 24-core, 3 GHz Intel computer, underscoring its speed and user-friendliness in simulating PET images.

Conclusion: FAST-PET has been developed and validated as an analytical simulation tool, designed to produce PET images that mirror those acquired from actual scanners and GATE simulations, while markedly reducing the processing time.

The ePAD platform for extracting and analyzing imaging features in Cancer Co-Clinical Trials

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The Molecular and Imaging Response Analysis of Co-Clinical Trials (MIRACCL [1]) framework is a web based analytical tool that integrates imaging and omics data to enable displaying image-based changes in cancer lesion characteristics with changes in omics data in response to treatment and correlating these changes between PDX animal models and patients. MIRACCL uses ePAD [2] for the image analysis and visualization. ePAD is a web-based system for medical image viewing, annotation, and quantitative analysis. It provides image management, feature calculation, and report generation for MIRACCL. ePAD analyses image annotations of tumors and computes their size changes over multiple image timepoints (e.g., pre-, on- and post-treatment) to generate response measures (by RECIST criteria), as well as waterfall plots of human subjects and PDX animals to show treatment response in study cohorts. ePAD extracts 932 quantitative radiomics image features from annotated regions using pyradiomics [3]. These features can be used by MIRACCL to produce cohort analysis treatment response on other quantitative image biomarkers such as lesion volume. Other image features include energy, entropy, skewness; shape features; and gray level co-occurrence matrix. Users can download the image features for additional analyses and to discover novel imaging biomarkers that predict treatment response.

We have recently enhanced the ePAD integration with MIRACCL to organize the data into multiple projects. We have also expanded our data by analyzing the whole dataset of the Breast Multiparametric MRI for prediction of NAC Response Challenge (BMMR2 Challenge) from the I-SPY trial and started adding PET data from another CIRP project into ePAD/MIRACCL. Currently, we have four projects in ePAD: simulation, prototype, I-SPY, and external CIRP project. Users can access the ePAD interface from MIRACCL to browse the patients and/or PDXs in these projects, generate waterfall reports showing treatment response for the project, and tumor burden reports for a patient or PDX. Users can also view images in a study, adjust the image display, and assess the adequacy of lesion outlines.

To demonstrate the capabilities of MIRACCL, the *Prototype* project with a simulated co-clinical study of triple negative breast cancer patients receiving treatment was used. We loaded images from 18 PDX animals at pre-, on- and post-treatment time points. We also loaded images from 191 patients from the I-SPY trial. At present, MIRACCL displays only 21 representative patients. The longest diameter was used to generate waterfall plots and categorization of cancer treatment response by the RECIST criteria. Waterfall plots (without RECIST categorization) were also produced based on volume and perfusion parameters (signal-enhancement ratio (SER) median and max, ADC median and max). Future work will add the patient data from another CIRP project and comparable PDX data for the whole I-SPY dataset and adding these projects in MIRACCL.

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Hybridizing CT Tumor Volume Measurements with Standard of Care Clinical Measures for Immunotherapy Response Prediction using Mechanistic Modeling and Machine Learning

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Introduction: Immune checkpoint inhibitor (ICI) immunotherapy is an effective cancer treatment, but only some patients receive therapeutic benefit, and often only some tumors respond to ICIs [1]. There is an unmet clinical need to identify which tumors will respond to ICI in a timely manner to facilitate personalized treatment decisions.

Objective: Our hypothesis is that predictive accuracy may be maximized when based on both mechanistic modeling and additional information that is likely associated with lesion response but not easily incorporated into a mechanistic model. We will test this hypothesis by hybridizing predictive mathematical modeling, a powerful tool demonstrated to predict immunotherapy outcomes [2], with machine learning (ML) methods that are also emerging as powerful predictive platforms, and which can include data not easily described mechanistically [3].

Methods: First, an existing mathematical model [4] was applied to predict per-lesion response to immune checkpoint inhibitor immunotherapy in n = 235 lesions from n = 93 patients by applying it retrospectively to time-course CT imaging of all individual lesion burdens. This model describes the change in tumor volume (ρ, cm^3) over time (t, $days$) after start of ICI immunotherapy treatment (on day t=0) as $d\rho/dt = (a_0 - \mu + \mu \cdot \Lambda) \cdot \rho - \mu \cdot \Lambda \cdot \rho^2$ (Eq. 1). a_0 (day^{-1}) is the tumor growth rate prior to initiation of immunotherapy, and a_1 (day^{-1}; not in Eq. 1) is tumor growth rate at the first restaging after start of ICI delivery, μ (day^{-1}) is the kill rate of tumor cells by activated T cells, and Λ is a measure of the anti-tumor immune state. After confirming the model parameters are distinct ($p < 0.001$ by Mann-Whitney U test) for lesions that respond (are smaller at last CT scan) vs. non-responder lesions (larger at last CT scan), the ML platform XGBoost was trained on a hybrid feature set consisting of both mechanistic model parameters calculated from CT imaging and relevant baseline clinical measures. First, we fit the XGBoost model to the full data set (μ, a_0, a_1, Λ, neutrophil count at baseline, neutrophil to lymphocyte ratio at baseline, age, and race), where the mechanistic model (Eq. 1) was fit to the complete time-series of retrospective tumor measurements to establish a baseline for 'best case' predictive accuracy. We then challenged the model by restricting the data to only that which is available by the time of first restaging to evaluate how the model might be used prospectively in the early stages of treatment by removing model parameters μ and Λ (calculated from all retrospective data) and retraining the ML model.

Results: The preliminary predictive accuracy using the hybrid mechanistic + ML model was found to be 87%. The data restricted model was found to have 72% accuracy, demonstrating

some loss of accuracy (to be expected) that comes with predictions made earlier in time that are based on less information.

Conclusion: These results support the feasibility of hybridizing mechanistic modeling with machine learning to predict lesion response to ICI based on both CT imaging and other clinical data. Notably, our model can be utilized by physicians in conjunction with the current standard of care to better identify which patients/tumors will respond to ICI without the need for any additional data collection. This could provide a way to make informed decisions about continuing ICI, changing treatment plans, or providing ancillary treatment to individual lesions.

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Developing CT radiomics based Surrogates for mIF based Angiogenesis Biomarkers in Clear Cell Renal Cell Carcinoma

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Introduction

Clear cell renal cell carcinoma (ccRCC) is the most common subtype of kidney cancer and known to be highly angiogenic. Important components of management include antiangiogenic treatments such as VEGF inhibitors and tyrosine kinase inhibitors. Currently, evaluation of patients' angiogenesis biomarkers is tissue-based, which is invasive and not suitable for frequent assessment. This study investigated the radiomics representation of histopathology-grounded angiogenesis biomarkers using contrast-enhanced CT clinical images. We focused on two markers associated with poor clinical outcomes in previous ccRCC studies: (1) HIF2a[1] and (2) CD31[2]. We demonstrate the feasibility of predicting these markers with our radiomics pipeline.

Methods

Segmented volumes of 171 primary ccRCC tumors from contrast-enhanced CT were analyzed using our radiomics pipeline, which generated 2863 features for each CT volume. Tumor specimens obtained via nephrectomy were stained with PanCK, HIF2a, and CD31 using multiplex immunofluorescence (mIF) technique. A single area of viable tumor epithelium per patient was selected for subsequent automated tissue and cell segmentation using the inForm Image Analysis software (Akoya Biosciences) to distinguish tumor and stroma and identify specific cell phenotypes. Random forest was used to train machine learning for a radiological representation of histopathological features. A 10-fold cross-validation procedure was used to assess model performance. The model was evaluated separately by tumor grade dichotomized into two categories: Low grade (Grades 1 and 2) and High grade (Grades 3 and 4). ElasticNet and Multivariate Adaptive Regression Splines (MARS) were used as the sensitivity analyses. The association between model predicted radiological representation vs. observed histopathological features was reported as a correlation coefficient (r).

Results

A total of 1,476 regions of interest were selected from the mIF samples. After cell segmentation, 6,731,412 cells were identified. Our results indicate that radiomics predicted the density of HIF2a+ cells at a statistically significant association, with the r of 0.22 (95% CI:[0.03, 0.4], $p<0.05$) in low grade samples after a 10 fold cross validation. This finding is consistent when using cell count and cell percentage with r of 0.19 (95% CI[0, 0.38]) and 0.28 (95% CI[0.1, 0.47]) respectively. However, no statistically significant associations were found in high grade samples. Also, no statistically significant associations were observed with CD31.

Conclusion

We demonstrate the feasibility of using radiomics to represent angiogenesis biomarkers . However, the performance is weaker when using histopathology features derived from a single region of interest in the tumor epithelium to train a radiomics-based model which is derived from the entire tumor lesion. Multiple regions of viable tumor epithelium should be sampled to

represent the heterogeneity of the tumor, but ideally whole slide quantification should be used to train radiological representation of the tumor microenvironment.

Grant Support: Wright Foundation and USC BUGS Program

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Image imputation with conditional generative adversarial networks captures clinically relevant imaging features on computed tomography

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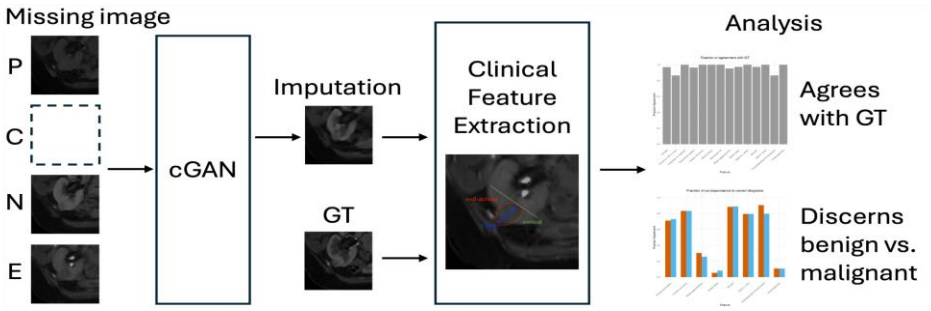
Introduction: Kidney cancer is among the top 10 most common malignancies in adults. Evaluation is commonly performed with four-phase computed tomography (CT) imaging, which images the mass at four points based on the point of contrast enhancement - precontrast, corticomedullary, nephrographic, and excretory. Missing or technically suboptimal phases is a frequent occurrence, and imputation of a missing image using data from the other three phases would help radiologists in more accurately characterizing renal masses. Deep learning approaches through conditional generative adversarial networks (cGANs) have recently shown promise in this image imputation task, although the clinical utility of these images has not been assessed. The purpose of this project is to determine the clinical utility of imputed CT scans from cGANs.

Materials and Methods: The study population consisted of 37 patients diagnosed with a renal mass on a multiphase CT scan. The cGAN was trained and validated with an additional complete 333 patient series from the same cohort. The tumor was annotated by an experienced radiologist. A list of 21 clinically relevant imaging features was created in consultation with radiologists and literature. These features were manually extracted from all ground truth (GT) and imputed images. Data analysis was performed in R. Statistical significance was assessed with a combination of binomial test, two proportion z test, and Wilcoxon rank-sum test.

Results: All 14 categorical clinical features had greater than 85% agreement rate between true images and their imputed counterparts. This high accuracy is maintained when stratifying across imaging phases. Imputed images also show good agreement with true images in clinically relevant radiomic features including mean intensity and enhancement. Imputed images possess the features specific to benign or malignant diagnosis at an equivalent rate to true images.

Conclusion: Imputed images from cGANs have large potential for clinical use due to their ability to retain clinically relevant features (Funding support by Ming Hsieh Institute).

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