Co-Clinical Imaging Research Resources Program Network (CIRP)

Posters: #32-#37

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NIH NATIONAL CANCER INSTITUTE

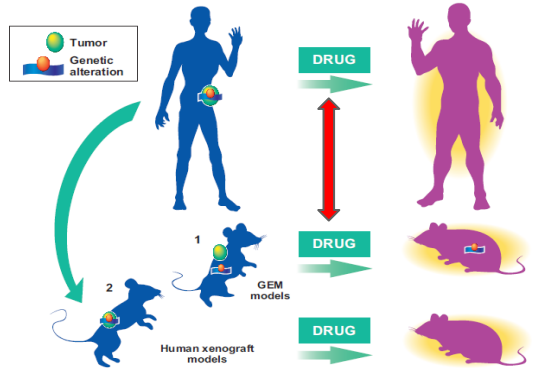
May 17, 2018

Scope of presentation

- ❑ Why Need Co-clinical Imaging?
- ❑ About PAR-16-385
- ❑ How to Apply to CIRP
- ❑ Awarded Teams

Why need Co-Clinical Imaging?

Co-clinical trials: investigations in patients and in parallel (or sequentially) in mouse or human-in-mouse models (GEMMs or PDXs) of cancer that mirror the genetic and biology of the patients malignancies or precancerous lesions.



Nardella et al, Cancer Discovery 2011:1:108

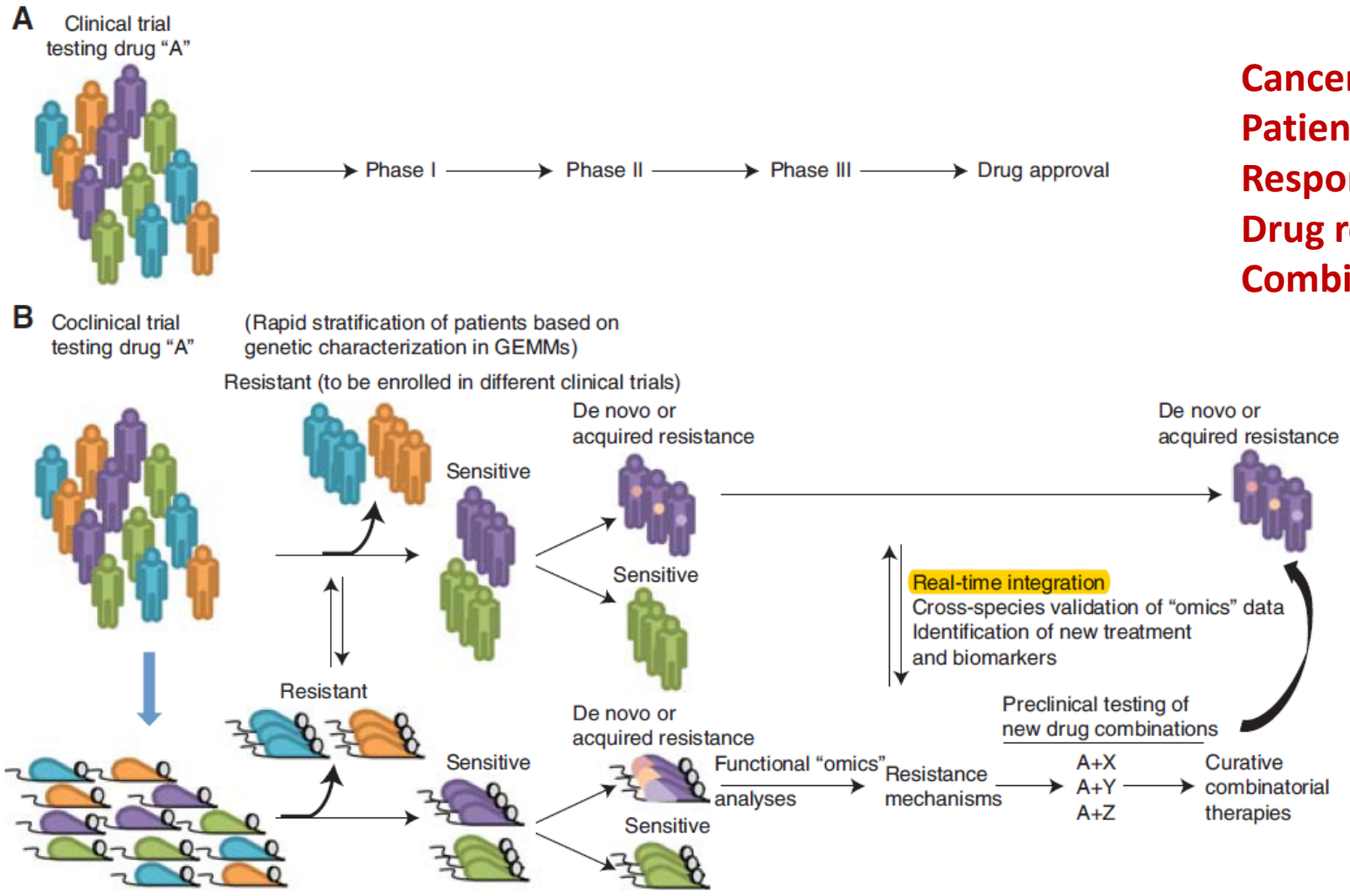
Progress:

2009: *NCI U01s: Integration of Mouse Models into Human Cancer Research,*
2012: first co-clinical trial report on NSCLC,
2015: NCI U24s: Co-clinical Imaging research resources, PAR-16-385,
2018: NCI U24s reissued: Co-clinical Imaging research resources.

Related resources: NCI patient-Derived Models Repository, EurOPDX consortium, Co-clinical trials centers & mouse hospitals in US.

NCI initiatives: PDXnet (2017), Biological comparison of PDXs (2016),

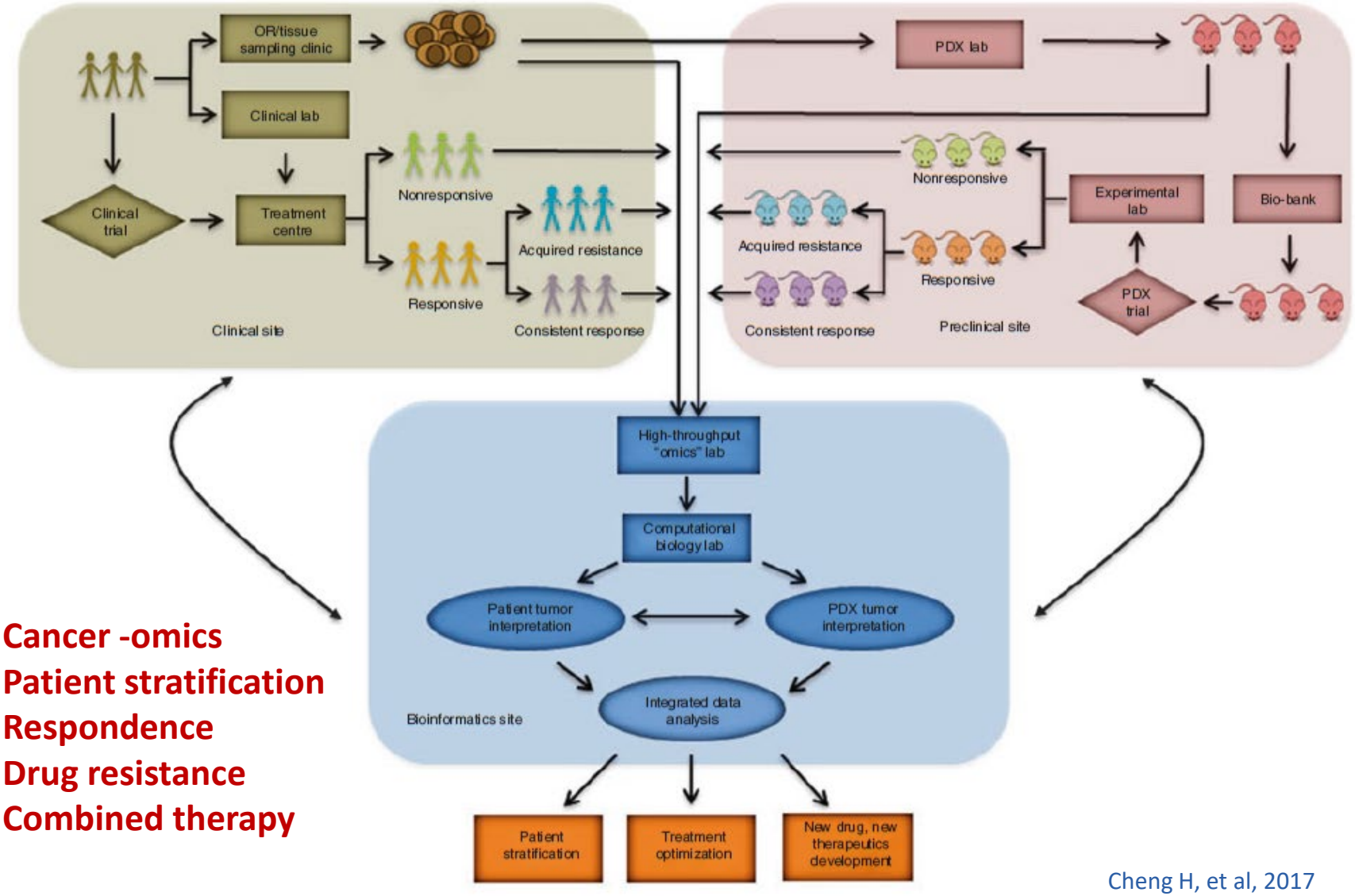
GEMMs-based co-clinical trial platform



Cancer -omics
Patient stratification
Respondence
Drug resistance
Combined therapy

Chen M, et al, Code Spring Harb Perspect Med, 2017

PDX-based co-clinical trial platform



Cancer -omics
Patient stratification
Respondence
Drug resistance
Combined therapy

Cheng H, et al, 2017

Problem and opportunity

- **Pre-clinical imaging methods are definitely non-standardized**
  - Methods (time, modality, animal issues)
  - Output data file formats, image processing
  - Comparison/conversion to clinical methods
- **Quality studies now need dedicated physicists**
  - Few biological laboratories have one
  - “Physicist-free” but reliable/reproducible methods needed
- **Sophisticated mouse models of human tumors can best help develop targeted therapeutics**
- **Resources needed to develop this area**

About PAR-16-385

Direction: develop co-clinical imaging research resources that will encourage a consensus on how quantitative imaging methods are optimized to improve the quality of the imaging results for co-clinical trials.

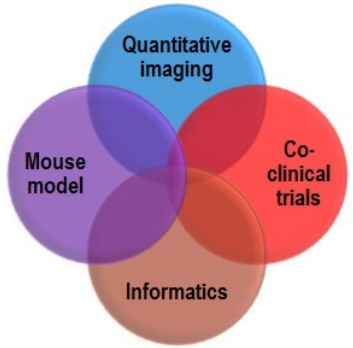
Four essential elements:

- **Co-clinical trials**: therapeutic or prevention, prospective or retrospective,
- **GEMMs or PDXs models**: mice, available, credentialed, validated,
- **Quantitative imaging**: preclinical identical to clinic, new methods require IND or IDE, user developed software tools allowed,
- **State-of-art informatics**: encourage data integration, use TCIA, NCIP Hub, contribute to OMF, QIN, EDRN, etc.

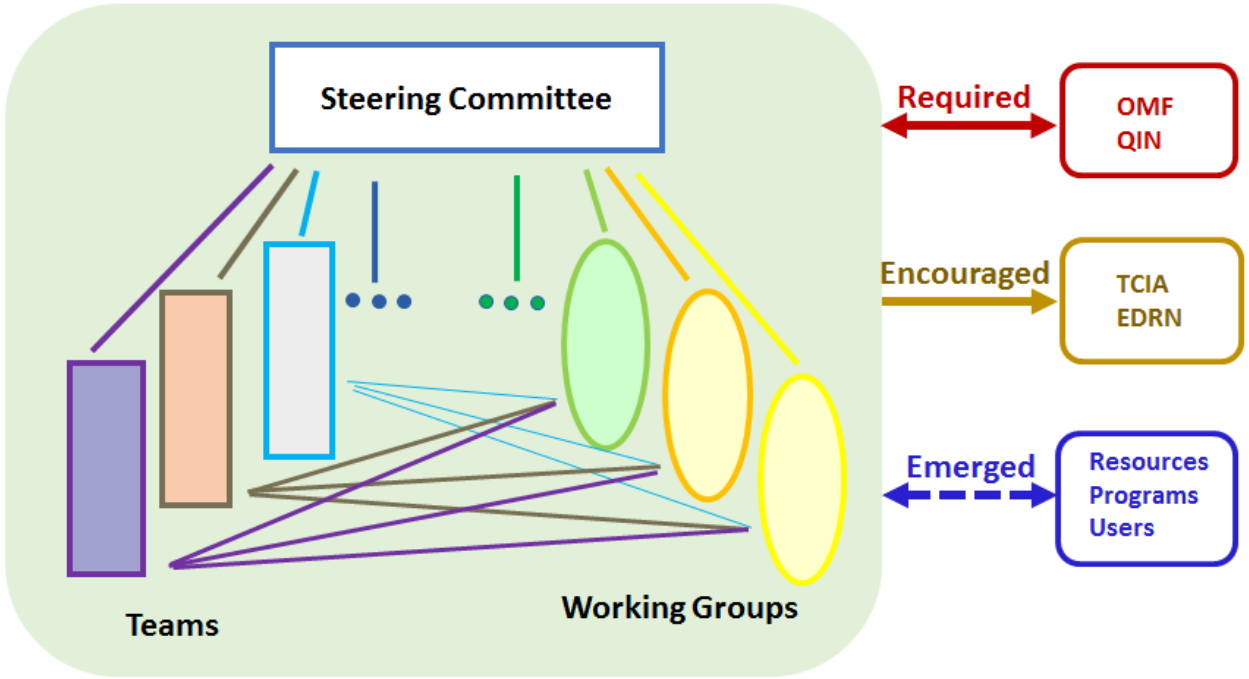
Deliverable: web-accessible resource, data, protocols, tools, etc.

CIRP Structure: steering committee & working groups,

CIRP Communication: CIRP Hub, T-cons, meetings,



CIRP organization



To reaffirm:

- ❑ Best practices are applied to every CIRP element,
- ❑ Emerging unmet needs in cancer community are addressed,
- ❑ Better supports are provided to co-clinical trials community.

CIRP Hub

Co-Clinical Imaging Research Resources Program Network (CIRP) [cirphub]

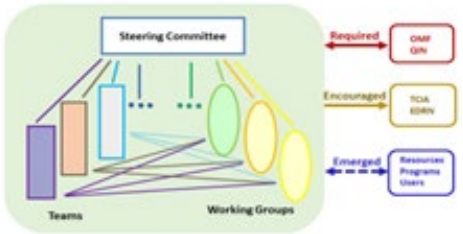
Overview | Members | Resources | Forum | Projects | Calendar | Announcements | Activity

About CIRP

The Co-Clinical Imaging Research Resources Program network (CIRP) is based on a trans-NCI initiative (PAR-16-385), which invites Cooperative Agreement applications to develop research resources that will encourage a consensus on how quantitative imaging methods are optimized to improve the quality of imaging results for co-clinical trials. Projects include optimization of pre-clinical quantitative imaging methods, implementation in co-clinical trials, and creating a web-accessible research resource that contains all the data, methods, workflow documentation, and results collected from cancer therapeutic or prevention co-clinical investigations. To achieve the goals of the CIRP, applicants are encouraged to organize multi-disciplinary teams with experience in mouse models research, human investigations, imaging platforms, quantitative imaging methods, decision support software and informatics to populate the research resource. Each resource contains four essential elements: animal models, co-clinical trials, quantitative imaging, and informatics.

Four essential elements

Network Structure



Teams

Washington University at St Louis, Kooresh Shoghi (shoghik@mir.wustl.edu)

Duke University, Cristian Badea (Cristian.Badea@duke.edu)

Team websites

Washington University at St Louis: https://c2i2.wustl.edu/

Duke University: https://sites.duke.edu/pcrgbe/

Application info

1. Pre-submission consultation template
2. FAQ

How to apply to CIRP

Pre-submission consultation:

- Contact us to get a pre-submission consultation template, it also can be download from cirphub: https://nciphub.org/groups/cirphub,
- Fill out the template with your team together,
- Send us your filled template,
- We will have a t-con with your team,
- Complete your application and submit.

Preparing an Application for Oncology Co-clinical Imaging Research Resources Program (CIRP) (U24)
PAR 16-385, https://grants.nih.gov/grants/guide/pa-files/PAR-16-385.html

Goal: This correspondence is a request that potential CIRP applicants send us an early, 1-2 pages high level description of their project. We will then arrange to discuss it by telephone conference call. The purpose of the T Con is to provide high level advice to ensure that the purpose of the CIRP PAR is understood, and that the proposed project is consistent with its goals. The purpose of this call is not to judge the quality of research or provide research advice.

1. **Program:** Cancer Imaging Program (CIP) staff will arrange a doodle to determine the time and date of the T Con. Participants will include interested program directors (CIP, DCB and DCP Program), all key investigators from the proposed OCIRR. The duration of the call will usually be ~45 minutes.

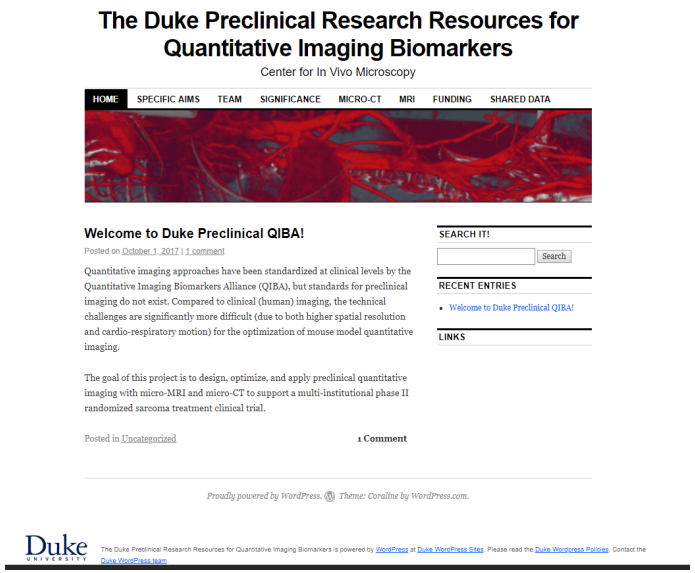
2. **Applicants** should prepare their written description after reading the PAR in detail. Pay particular attention to the sections on Purpose, Background, Research objective, Research strategy, and Review Criteria. Identify key PAR elements that are consistent with your planned translational research effort. Cover the following topics:

    a. Specify the selected co-clinical investigation, either therapy or prevention, and the important cancer problem(s) targeted by these investigations.

CIRP teams: to be growing

WUSTL: Kooresh Shoghi

Multi-parametric MRI & FDG-PET
Hybrid PET/MRI
TNBC co-clinical trial neoadjuvant treatment
PDXs Models



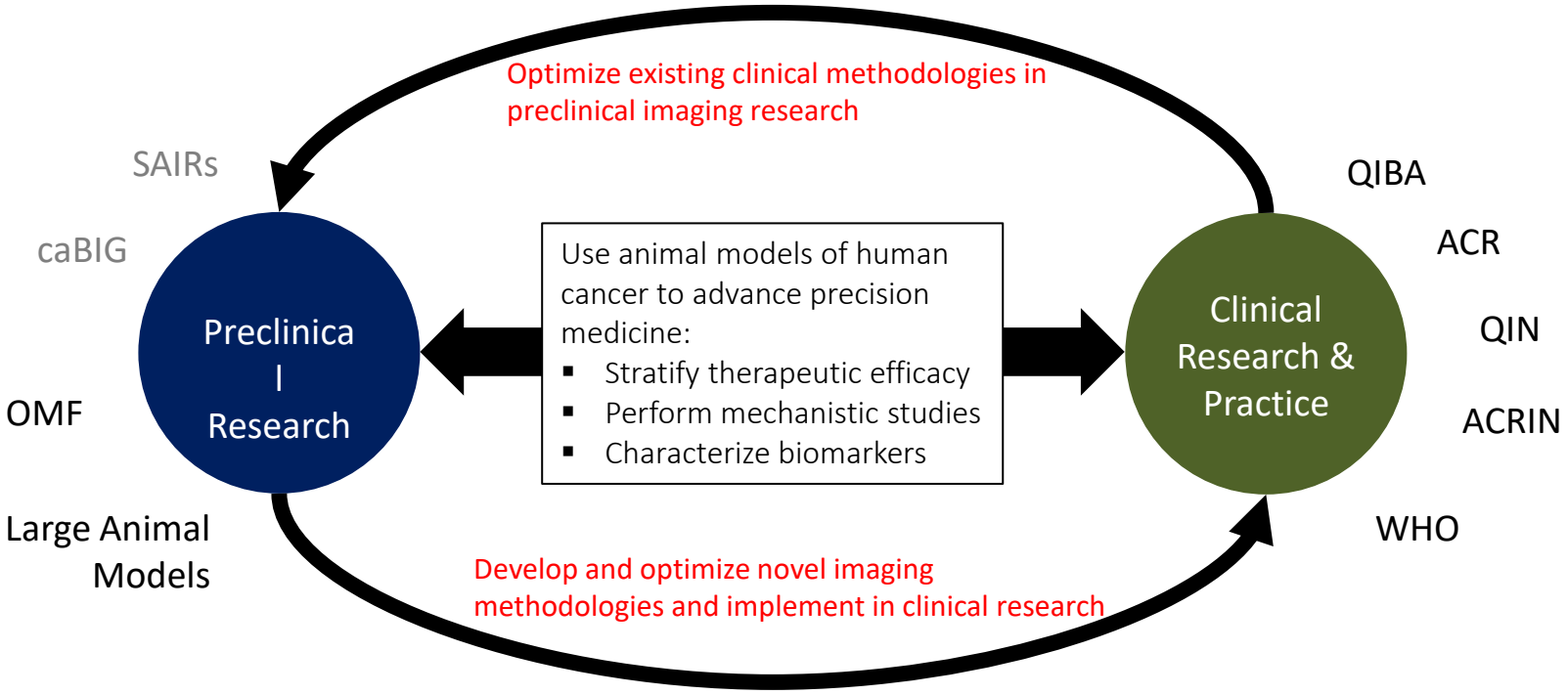
Duke: Cristian Badea

Micro-MRI & micro-CT
Stand-alone micro-MRI, micro-CT
Soft tissue sarcoma co-clinical trials
Immune checkpoint inhibitors & RT
GEMMs model

WU-C2IR2

Kooresh Shoghi*, Ph.D.
Joseph Ackerman, Ph.D.
Shunqiang Li, Ph.D.
Richard Wahl, M.D.

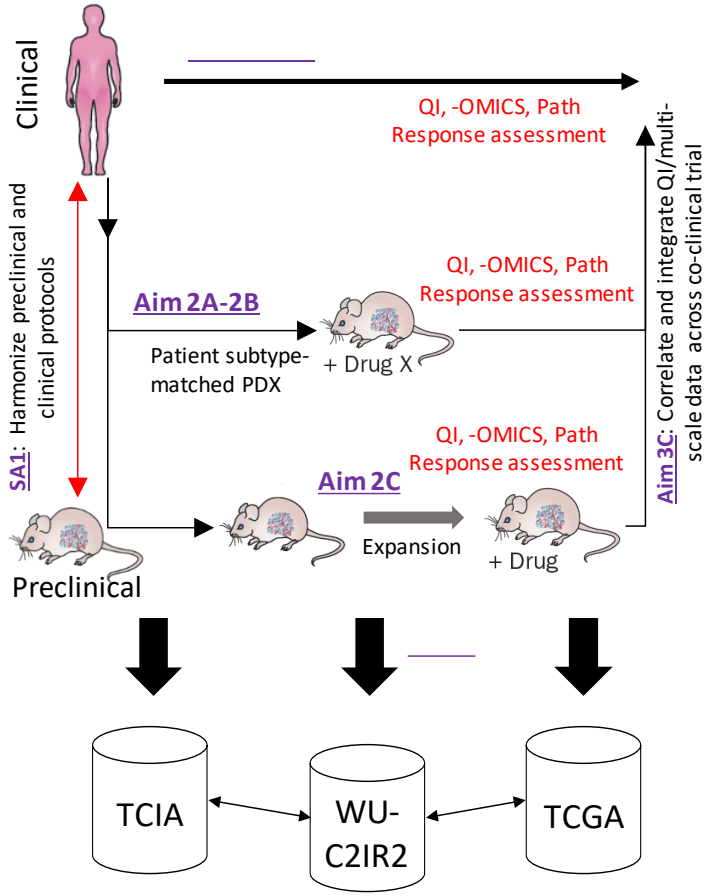
WU-C2IR2: Bi-Directional Translation



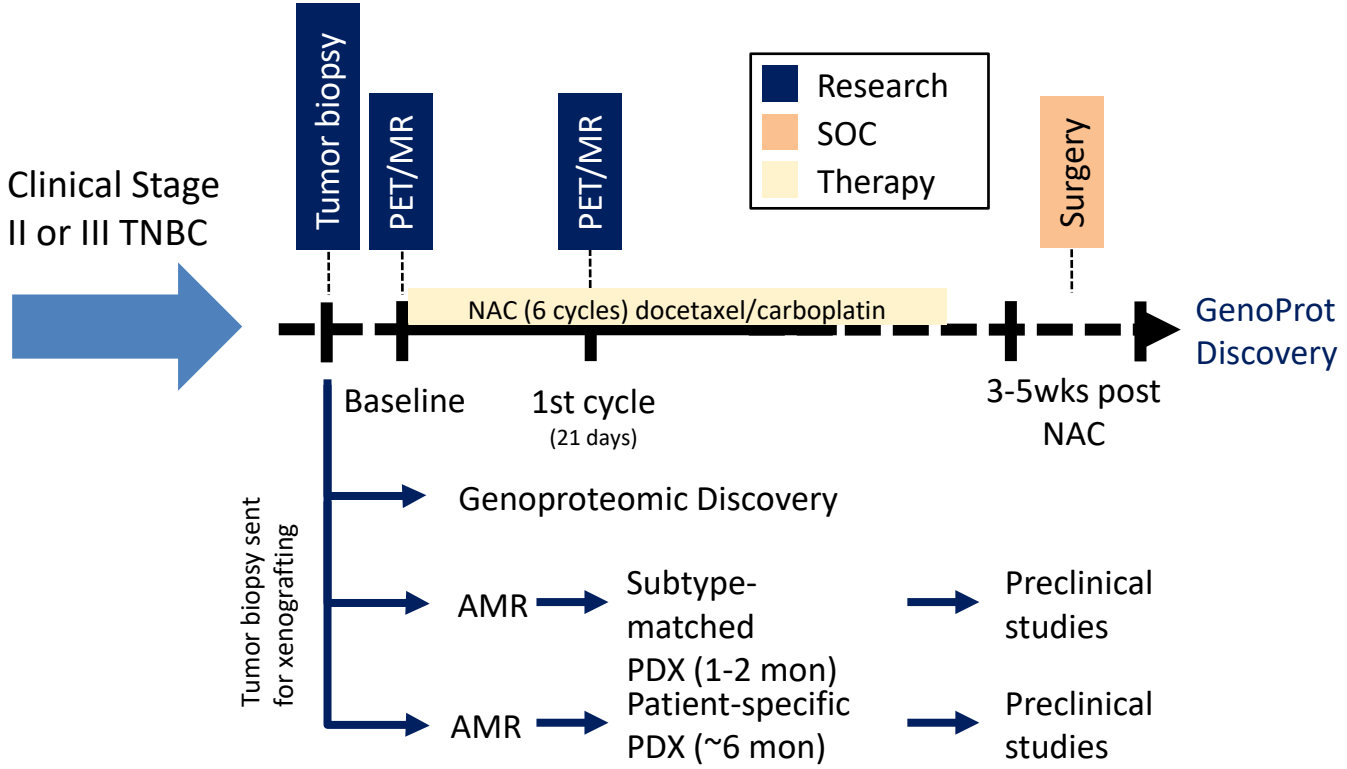
WU Co-Clinical Paradigm

Mission Statement: The objective of the WU-C2IR2 is to develop, optimize, and implement quantitative imaging (QI) methodologies to advance the science and clinical practice of precision medicine:

- Optimize the use of animal models of cancer (e.g., PDX) in oncologic imaging, in particular TNBC PDX.
- Develop and implement QI/radiomic pipelines to predict response to NAC therapy in TNBC.
- Integrate QI/radiomic image features with multi-scale analytic data (-OMICS, path) to enhance prediction.



Co-Clinical Trial Imaging Protocol



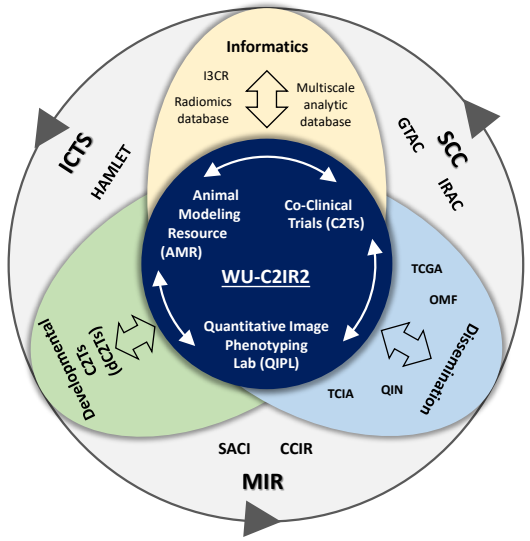
PET/MR Protocol

- Dynamic PET
- T1-weighted
- T2-weighted
- T1-map
- T2-map
- DTI/ADC
- DCE
  (temporal vs. spatial resolution)

Progress to date

- Performed gene expression analyses to identify 6 TNBC subtypes, generated PDX of 6 TNBC subtypes
- Optimized protocols for preclinical PET imaging, effects of temperature, tumor volume
- Characterized reproducibility of SUV-centric PET imaging metrics at baseline
- Performed initial co-clinical phantom studies for harmonization of preclinical-clinical protocols
- Optimized T1- and T2-weighted images with 2D spin echo multislice (SEMS) and fast spin echo (FSEMS) sequences before and after contrast-agent injection for PDX
- Optimized T2 mapping with 2D multi-echo multislice (MEMS) and validated using both phantoms and PDX mice.
- Optimized tumor volume measurements by MR and performed time course characterization in PDX
- Optimized apparent diffusion coefficient (ADC) measurements using a 2D spin echo multislice (SEMS) sequence with respiratory gating
- Optimized location of tumor implantation in PDX in support of simultaneous PET/MR imaging
- Developing preclinical imaging metrics of tumor heterogeneity for validation

https://c2ir2.wustl.edu/



NIH/NCI U24-CA209837
Mallinckrodt Institute of Radiology
Siteman Cancer Center

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Timothy Whitehead, Ph.D.
Madhusudan Savaikar, Ph.D.
Xia Ge, Ph.D.
John Engelbach
Nicole Fettig
Lori Strong
Margaret Morton
Amanda Klaas
Cyclotron Facility

SITEMAN CANCER CENTER
A NATIONAL CANCER INSTITUTE COMPREHENSIVE CANCER CENTER

Washington University in St. Louis
MIR Mallinckrodt Institute of Radiology

Duke pre-clinical QIBA

Cristian Badea*, Ph.D.
Allan G Johnson, Ph.D.

The Duke Preclinical Research Resources for Quantitative Imaging Biomarkers

(PIs: Badea CT, Johnson GA, NIH U24CA220245)

Clinical Trial

SU2C-SARC032 (NCT03092323)

Patient Selection
- Eligibility
- Consent

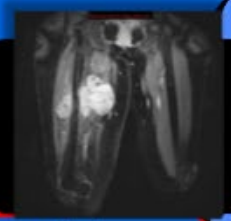
Tumor Classification
- Grade
- Histology

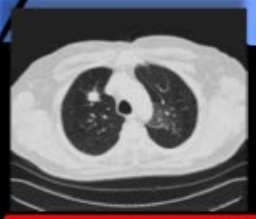
Objective:
- Investigate if neoadjuvant XRT + anti-PD-1 Tx (pembrolizumab) followed by surgical resection and adjuvant pembrolizumab improves disease-free survival for patients with high risk soft tissue sarcoma

Arm 1: Standard of Care
Image-guided XRT
- 50 Gy over 25 fractions
- MR imaging

SURGICAL RESECTION

Follow Up
- Chest CT





Arm 2: Experimental
Image-guided XRT + Pembro
- 50 Gy over 25 fractions
- Pembro 200mg q3w
- MR imaging

SURGICAL RESECTION

Follow Up
- Adj. Pembro
- Chest CT

Pre-Clinical Trial

Duke UNIVERSITY

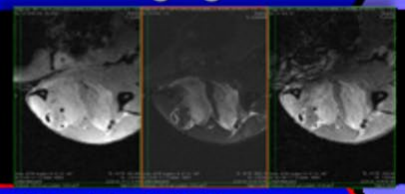
Tumor Initiation → Tumor Growth

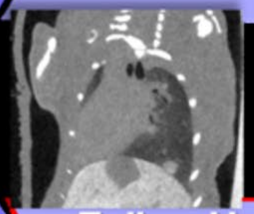
Objectives:
- Optimize preclinical imaging with MR and CT
- Apply preclinical imaging in the co-clinical trial to study of combination (XRT) and anti-PD-1 Tx in a GEMM of sarcoma.

Arm 1: Vehicle Controls
Short-term radiation therapy
- 20 Gy dose
- Isotope Ab, 10 mg/kg 3qw
- microMR imaging

SURGICAL RESECTION

Follow Up
- Chest microCT





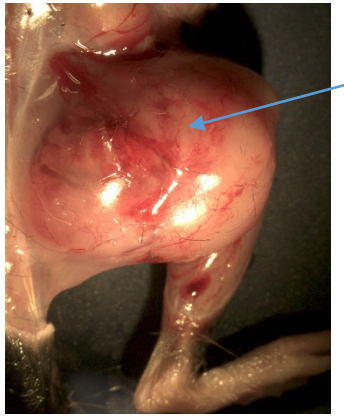
Arm 2: PD-1 Inhibitor T_x
Short-term radiation therapy
- 20 Gy dose
- PD-1 Ab, 10 mg/kg 3qw
- microMR imaging

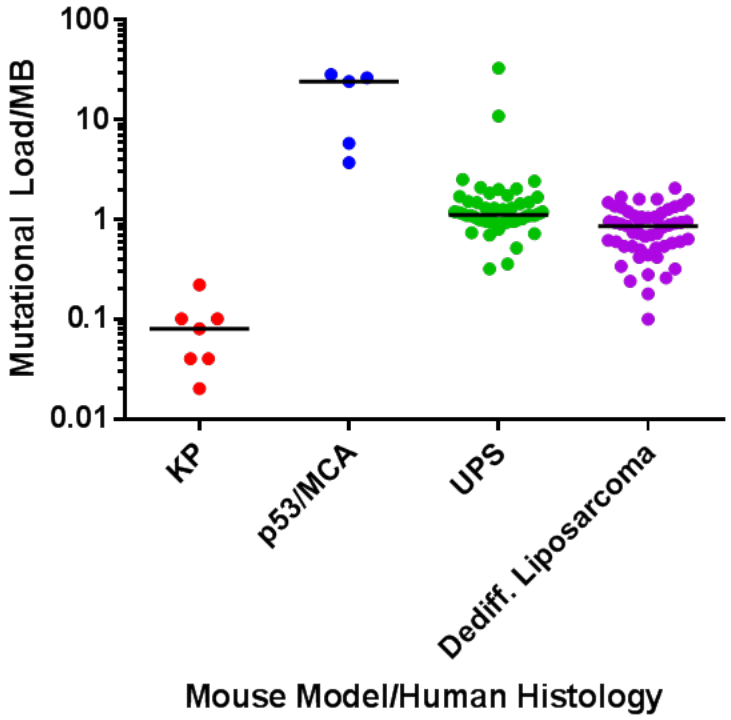
SURGICAL RESECTION

Follow Up
- Adj. Pembro
- Chest microCT

Genetically Engineered Mouse Models of Sarcoma

	KP Model	p53/MCA Model
Genotype	LSL-Kras; p53 fl/fl	p53 fl/fl
Tumor initiation	Adeno-Cre	Adeno-Cre + MCA
Time to tumor	8 – 12 weeks	8 – 12 weeks
Histology	High-grade sarcoma	High-grade sarcoma
Site of metastasis	Lungs	Lungs
Mutational load	Low	High

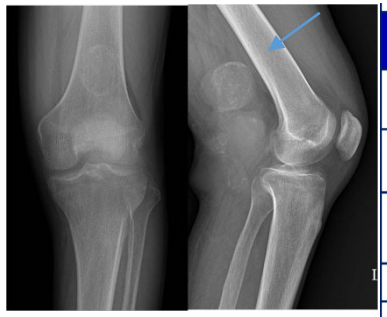


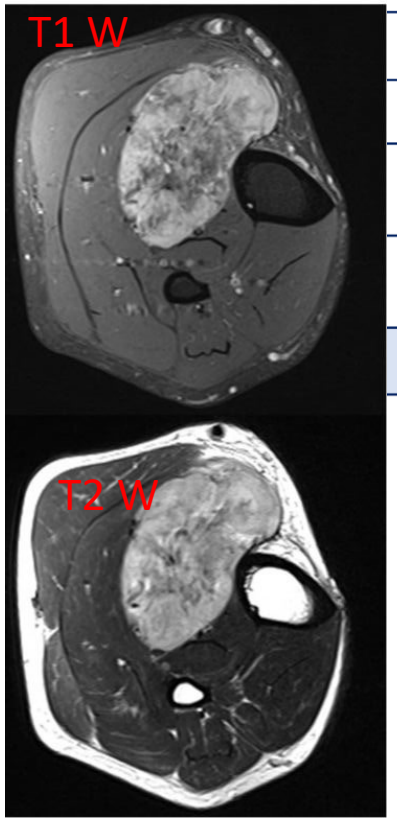


unpublished

Kirsch et al, *Nature Medicine* 2007

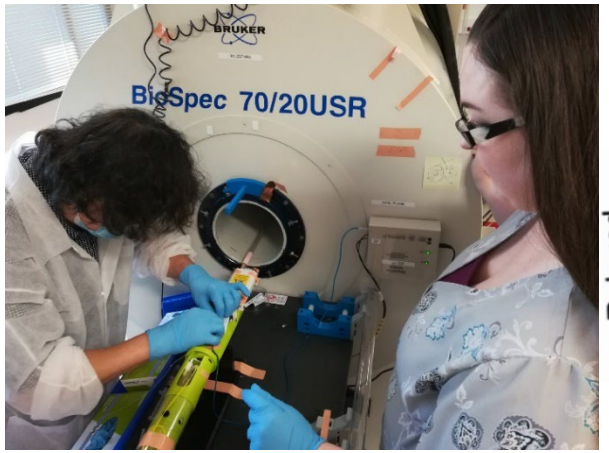
Clinically modeled micro-MR imaging of sarcomas

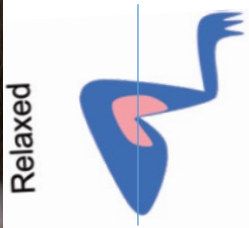


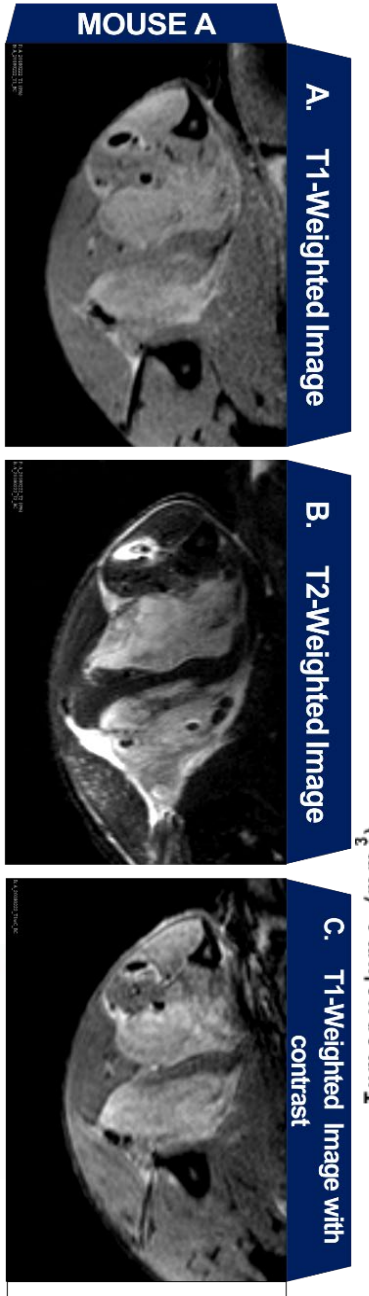


Parameter	ACR Practice Parameter Recommendation for body trunk (non-cardiac, non-brain)	Preclinical Selection/Goal
Coil Selection	Phased array surface coil	2X2 surface array coil
FOV	Selected to improve resolution and signal; case-by-case	28 mm X 28 mm (axial) 18 mm (sagittal)
Resolution	Highest reasonably achievable value	0.1 mm X 0.1 mm (axial) X 0.3 mm (sagittal)
SNR	Highest reasonably achievable value	~20
Sequence Selection	Inclusion of T1- and T2-weighted scans recommended	T1-weighted, T2-weighted, and T1-weighted + contrast
T1 sequence	TSE, FSE, or gradient-echo	Fast Low Angle SHot (FLASH) gradient-echo
T2 Sequence	TSE, FSE, or GRASE (gradient + spin-echo)	TurboRARE (Rapid Acquisition with Refocused Echoes)
Intravenous contrast	Delayed post-contrast T1-weighted imaging for enhanced neoplasm detection	T1-weighted image acquisition initiated 3 min post-injection (peak contrast ~3-8 min)
Fat suppression	Recommended; use of short tau inversion recovery (STIR), spectral presaturation inversion recovery (SPIR), or other	Fat suppression included in T1 and T2 sequences (selected inversion recovery)
Scan Time	As short as reasonably achievable **Typically ~ 1 hour**	**<1 hour**

-Bruker BioSpin 70/20
-72 mm volume coil coupled with a 2X2 surface coil array.

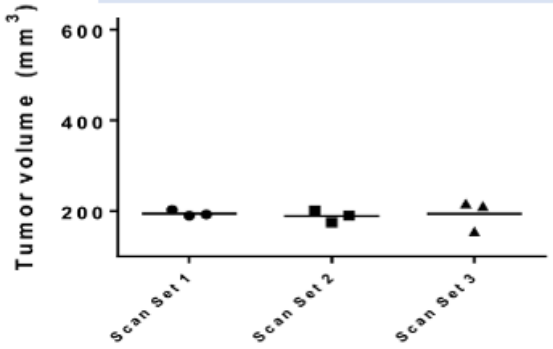




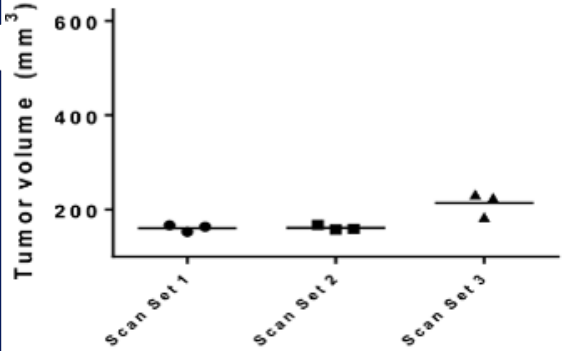


Repeatability and Precision

Hand-drawn Volume Measurement



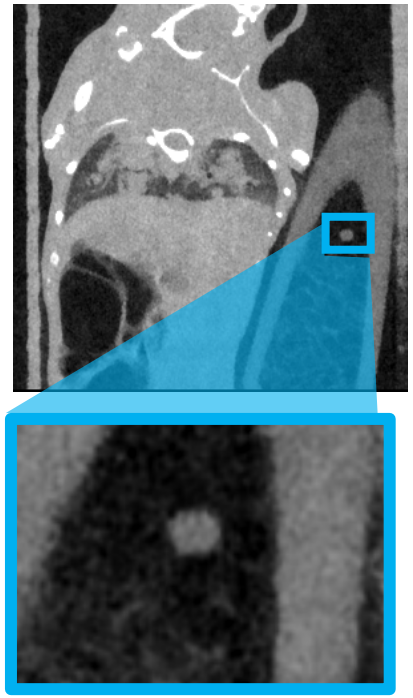
Semi-automated Volume Measurement

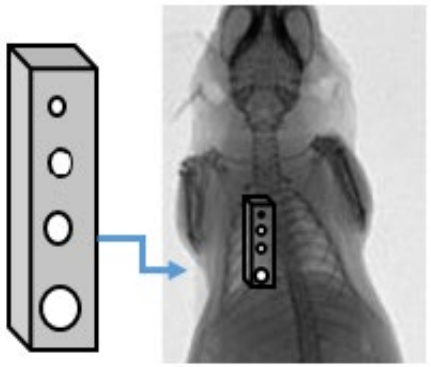


Park et al, World Journal of Surgical Oncology, 2010

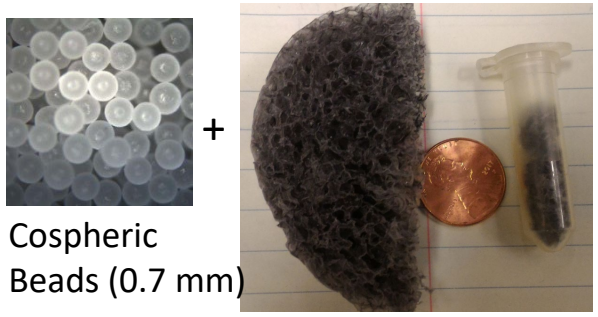
Micro-CT imaging of lung metastases

www.simutec.com

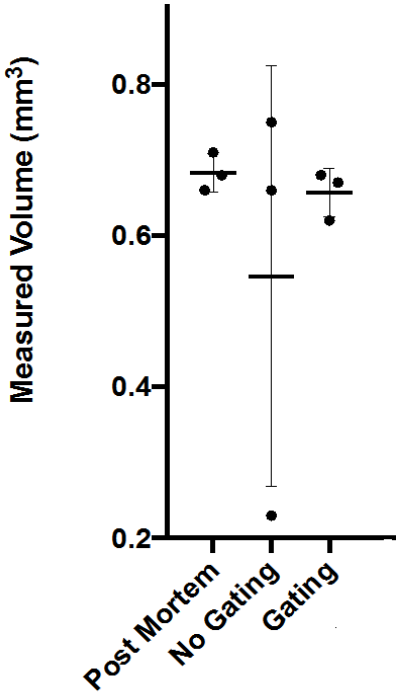




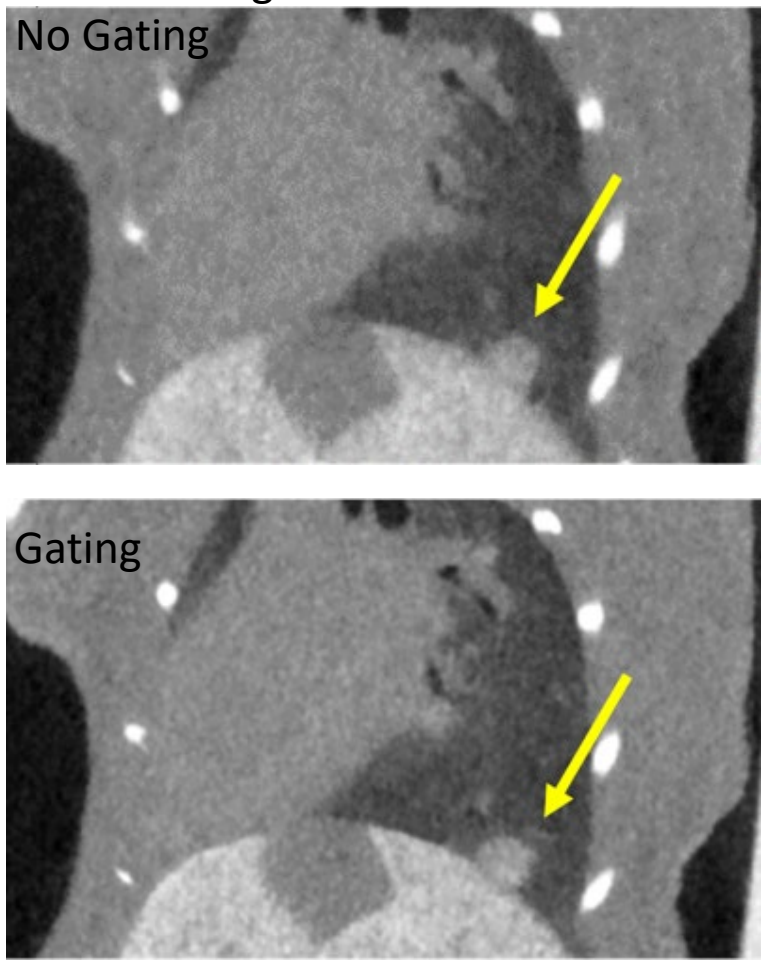
Pocket Phantom



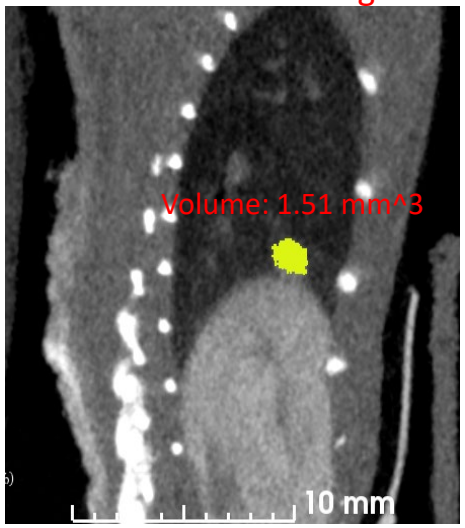
Cospheric Beads (0.7 mm)

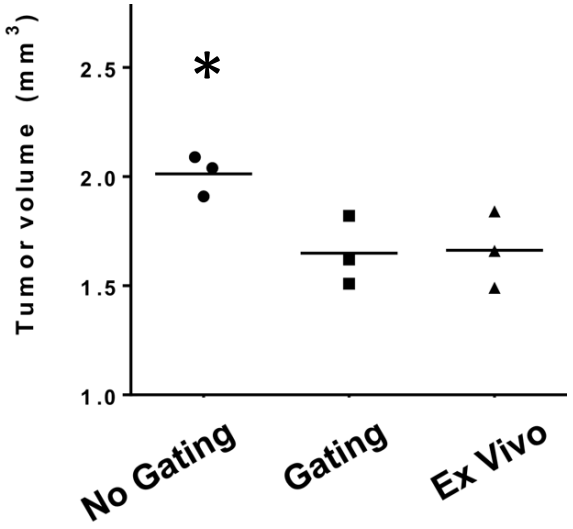


Imaged at 63 microns



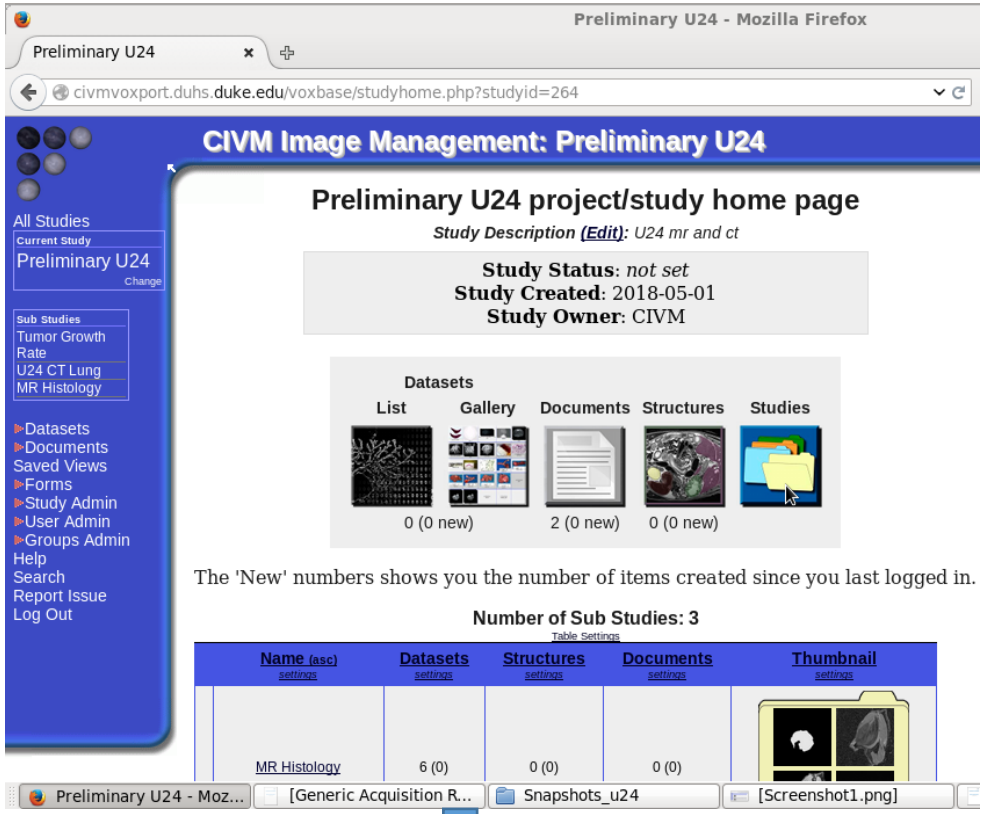
3D Slicer: semi-automatic segmentation



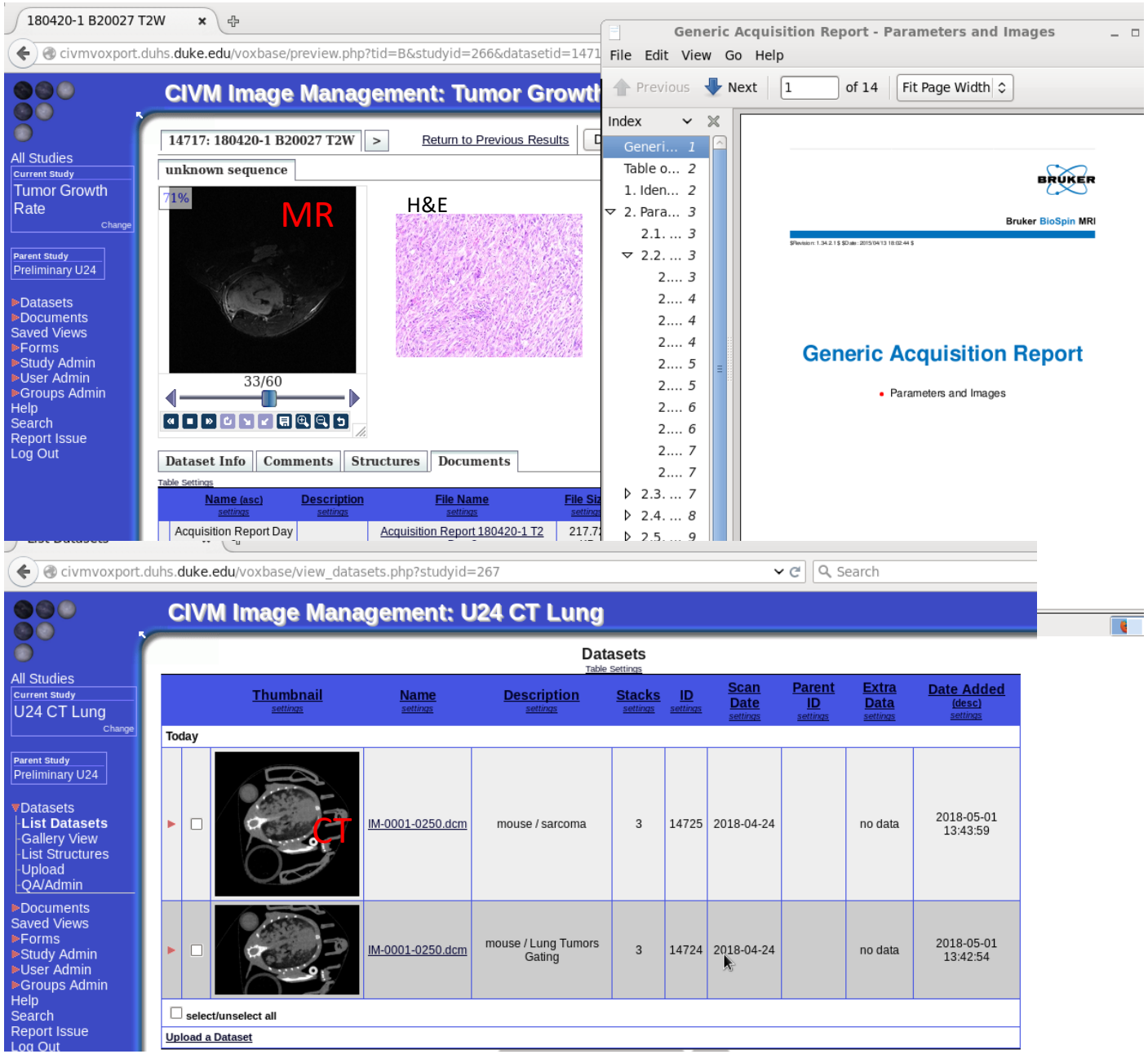


VoxPort/Voxstation for Data Sharing

- VoxPort is a MYSQL database
- VoxStation, the companion software provides external users interactive access



TCIA



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