Pre-clinical Imaging in Co-clinical Trials

John D. Hazle, Ph.D., FAAPM, FACR

Professor and Chairman
Department of Imaging Physics
Bernard W. Biedenharn Chair in Cancer Research

THE UNIVERSITY OF TEXAS
MD Anderson ~~Cancer~~ Center

What's driving cancer research?

- GOOD NEWS
  - Death rates for the four most common cancers (prostate, breast, lung, colorectal), and all cancers combined, continue to decline.

Cancer treatment spending continues to rise along with total health care spending.

  - Incidence rates of some cancers are rising including melanoma of the skin, non-Hodgkin lymphoma, childhood cancer, kidney and renal, leukemia, thyroid, pancreas, liver, testis, and esophagus.
  - Death rates for pancreas, esophagus, thyroid, and liver are increasing.
  - Few *cures*.

Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2011

Five-year Relative Survival Rates* (%) by Stage at Diagnosis, US, 2004-2010

	All Stages	Local	Regional	Distant		All Stages	Local	Regional	Distant
Breast (female)	89	99	85	25	Ovary	45	92	72	27
Colon & rectum	65	90	71	13	Pancreas	7	26	10	2
Esophagus	18	40	21	4	Prostate	99	>99	>99	28
Kidney†	72	92	65	12	Stomach	28	64	29	4
Larynx	60	75	43	35	Testis	95	99	96	73
Liver‡	17	30	11	3	Thyroid	98	>99	98	55
Lung & bronchus	17	54	27	4	Urinary bladder§	77	69	34	6
Melanoma of the skin	91	98	63	16	Uterine cervix	68	91	57	16
Oral cavity & pharynx	63	83	61	37	Uterine corpus	82	95	68	18

*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2004-2010, all followed through 2011. †Includes renal pelvis. ‡Includes intrahepatic bile duct. §Rate for in situ cases is 96%.

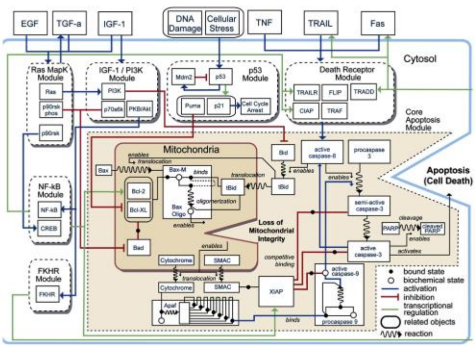
Local: an invasive malignant cancer confined entirely to the organ of origin. **Regional:** a malignant cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** a malignant cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

Source: Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute, Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission.

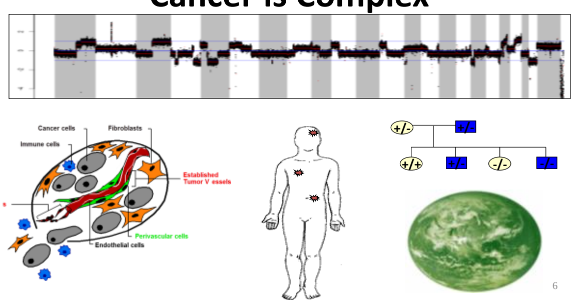
American Cancer Society, Inc., Surveillance Research, 2015

Barriers to progress

- Limited insights into factors driving cancer evolution and metastasis
- Elemental knowledge of the cancer genome
- Poor understanding of the target *biology*
  - In what context (genetic, micro-environmental, host and macro-environmental) is the target rate-limiting?
- Lack of insight on appropriate combination of therapies
  - Tumor will find a way to bypass a single-point intervention
  - Co-extinction is required to shut down a complex highly-redundant network
- Challenged cancer drug development ecosystem



Cancer is Complex

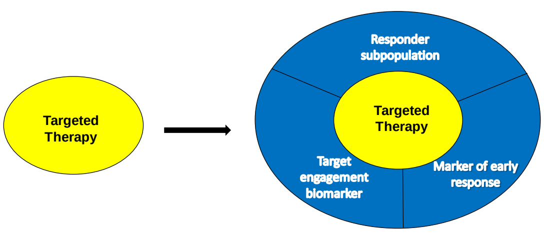


A Paradigm Shift in Clinical Trial Design

One size fits all | *Biomarker driven*

Mission of the Center for Co-Clinical Trials at MD Anderson
To accelerate the development and pre-clinical evaluation of drugs to inform the design and implementation of clinical trials.

Enhanced value through biological insights



The bridge to the MDACC clinic (and back)

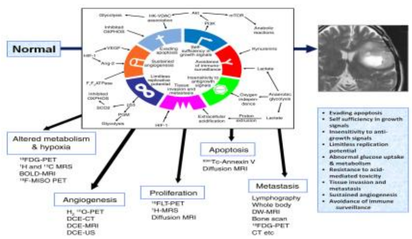
***Integration** of preclinical **and** clinical insights is the key to maximizing patient impact.*

Genomic evidence is not sufficient

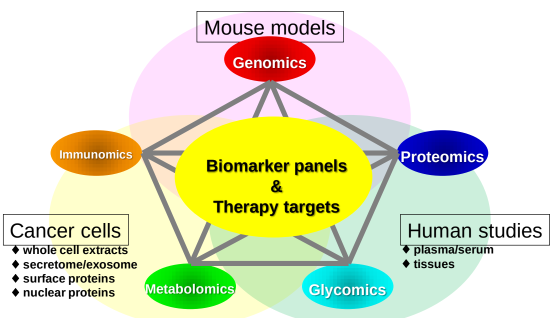
- Hundreds to thousands of candidates
- Few drivers and many bystander events
- All drivers are not of equal importance
- Drivers are highly context-specific

Prioritization must be based on <u>both</u> genomic **<u>and</u>** biological **evidence**

Imaging the hallmarks of cancer



Padhani A R , Miles K A Radiology 2010;256:348-364



Small Animal Imaging Facility

Advancing cancer science through pre-clinical imaging

John D. Hazle, Ph.D.
Director and Bernard W. Biedenharn Chair in Cancer Research

James A. Bankson, Ph.D.
Deputy Director

Charles Kingsley
Lab Manager

THE UNIVERSITY OF TEXAS MD Anderson ~~Cancer~~ Center
Making Cancer History®

Mission and vision

- The mission of the Small Animal Imaging Facility (SAIF) is to provide outstanding pre-clinical imaging to advance cancer research at MDACC.
- Our vision is to provide high-quality services using state-of-the-art equipment and dedicated personnel.
- Developing advanced technologies for small animal imaging is also a goal.

Financial support

The **Small Animal Imaging Facility (SAIF)** is a core institutional research resource partially funded by Cancer Center Support Grant (P30 CA16672, PI-DePinho)

- CCSG support (25%)
- Partial faculty and core staff salary support (25%)
- Remaining operating costs generated by user fees (50%)
- Institution provides capital equipment through Technology Task Force prioritization

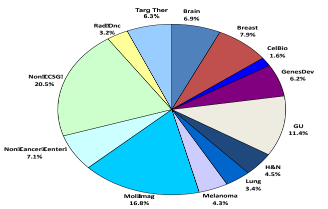
SAIF access prioritization

SAIF is an institutional core research resource that is partially supported by the CCSG.

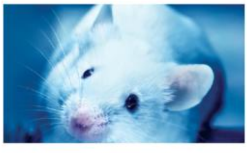
- Any cancer center member can request access
- Priority is given to NIH funded investigators
- Variable user fee schedule
  - Cancer Center members (subsidized by CCSG)
  - Other academic
  - Instrument access only or full experimental support

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

2014 utilization by CCSG program



THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®



Small animal imaging: Data that's more than skin deep

To minimize complexity, researchers often study cellular proteins or nucleic acids in isolation. But sometimes—when testing a drug's efficacy and safety, for instance, or monitoring tumor progression—ex vivo just won't do. The only way to know how a compound or cells will behave in the body is to put them into an animal and watch what happens live. The results are easily recognizable in the pages of your favorite journal: the ghostly outline of a mouse, with a telltale multicolored heat bloom indicating where the action is. **By Jeffrey M. Perkel**

The Small Animal Imaging Facility at **The University of Texas MD Anderson Cancer Center** sports three MRI scanners in its instrument stable, and they are "by far the most widely used" of the lab's hardware, says John Hazle, professor of imaging physics and the facility director. Among other reasons, he says, MRI provides "excellent soft-tissue imaging and the ability to image some physiology and continued>

SCIENCE sciencemag.org/products 1271

SAIF faculty and staff

Faculty
John D. Hazle, Ph.D., Director
Jim Bankson, Ph.D., Deputy Director, MR
Yiping Shao, Ph.D., Nuclear & PET
Mian Alauddin, Ph.D., Radiochemistry
Pratip Bhattacharya, Ph.D., MRS
Richard Bouchard, Ph.D., Ultrasound
Dianna D. Cody, Ph.D., X-ray and CT
Laurence Court, Ph.D., SARRP
Vikas Kundra, M.D., Ph.D., MI
Kostia Sokolov, Ph.D., Optical

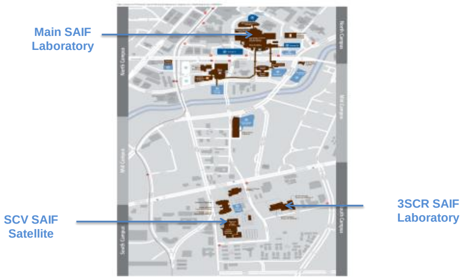
Staff
Charles Kingsley, Lab Manager
Jorge Delacerda, Techologist
Kristen Maldenado, Techologist
Keith Michel, Technologist
Vivien Tran, Technologist
Mai Dinh, M.B.A., Administrator
Jim Jacob, Administrative Assistant

SAIF services

- Consultation on planning the best imaging approach and experiment design.
- Preparation of animals before, management of animals during and recover after imaging experiments .
- Developing custom hardware and software.
- Analysis of image data.

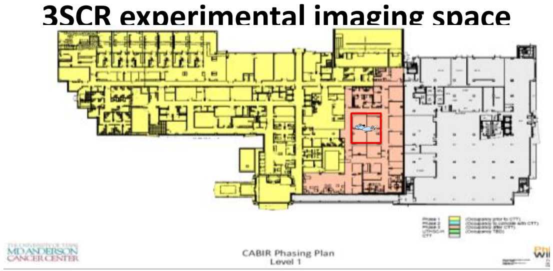
SAIF lab spaces

- Main Campus lab core of 2,500 NSF located adjacent to the SPF rodent housing facility in the BSRB basement
  - Another 800 NSF of office/dry lab space is assigned on Tan 2nd floor
  - 4.7 T MR has about 1,000 NSF of space ~75 yards away in Tan Zone basement
- SCV lab space of 1,250 NSF located in the vivarium
- 3SCR facility has 5,500 NSF of lab space and is contiguous with a 5-room vivarium



SAIF Main Lab configuration

3SCR experimental imaging space



SAIF instrumentation

- MR Core
  - 4.7 T, 40 cm Bruker Biospec — Main Campus
  - 7 T, 30 cm Bruker Biospec — Main Campus
  - 7 T, 30 cm Bruker Biospec — 3SCR
  - Hyperpolarizer(s) — Main Campus
- Magnetic relaxometer
  - Senior Scientific — 3SCR
- X-ray and CT Core
  - Specimen CT (9 μm resolution) — Main Campus
  - Micro-CT (up to 45 μm resolution) — Main Campus
  - Faxitron — Main Campus

SAIF instrumentation

- Ultrasound Core
  - Vevo 770 — SCV Satellite
  - iThera photo-acoustic Optical — 3SCR
  - Caliper *Lumina* (BLI, BFI, x-ray) — Main Campus
  - Caliper *Spectrum* (BLI, BFI) — SCV
- Photoacoustic
  - Vevo 2100 LAZR photo-acoustic — Main Campus
  - iThera PA system — 3SCR
- Radiation research platform
  - Precision Medical 225Cx — Main Campus

Managing small animals

The smallest patient

- Proper animal support is critical to imaging procedure
- Challenges
  - Size

    Mouse vs Human

    20-40 g 50-100 kg
  - Variable imaging time
  - Inaccessible location
  - Specific imaging requirements

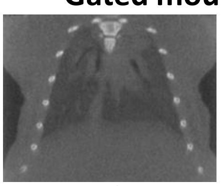
MD Anderson Cancer Center

Custom resources – Roger Price, D.V.M., Ph.D.

- Anesthesia
- IV catheters
- Endotracheal intubation and ventilation
- Body temperature

MD Anderson Cancer Center

Gated mouse lung *in vivo*



Non-gated mouse

Respiratory gated mouse

Differences in lung structure appearance primarily due to obtaining image data at near full inspiration which provides much better tissue contrast and reduces blurring.

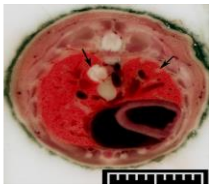
Cody et al, Murine lung tumor measurement using respiratory-gated micro-computed tomography, *Invest Radiol* 40(5):263-269, 2005

MD Anderson Cancer Center

Correlated block-faced imaging

- Animal frozen immediately after imaging procedure
- Sliced at levels as thin as 100µm along imaging planes
- Digital photograph of block face between each slice

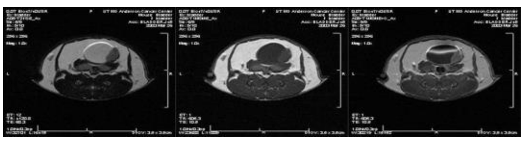
Jim Klostergaard, Ph.D.
Thoracic/Head & Neck Oncology



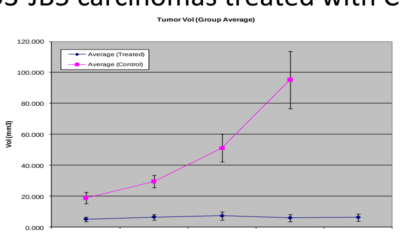
Jonathan Kurie, M.D.
Thoracic/Head & Neck Oncology

253-JB5 carcinomas treated with C225

T1-weighted | T2-weighted | T1-weighted + Gd-DTPA



253-JB5 carcinomas treated with C225



Black et al, BJU epub ahead of print, September 2010.

MR assessment of antiangiogenic therapy

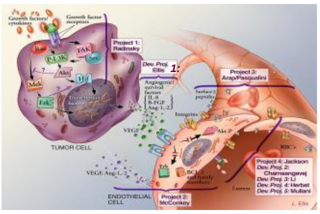


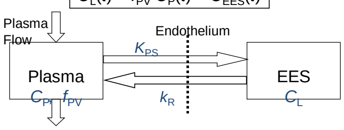
Image courtesy of Lee M. Ellis, M.D.

U54 Project 4 (MR):

- Pharmacokinetic analysis of single/dual tracer data with IHC & micro auto-radiography correlations.
- Longitudinal monitoring of antiangiogenic therapies in animals with IHC correlations.
- Longitudinal assessment of antiangiogenic therapies in patients with IHC correlations

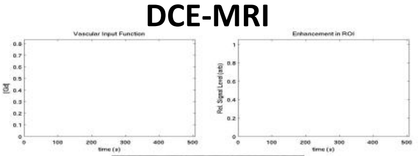
Two compartment kinetic model

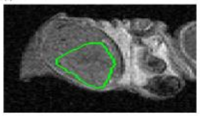
$$C_L(t) = f_{PV}\, C_P(t) + C_{EES}(t)$$



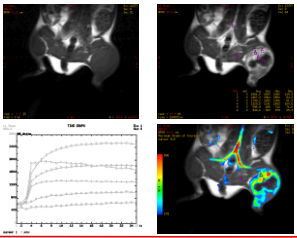
C_P = [Gd] in plasma (mM)
C_L = [Gd] in extravascular, extracellular space (mM)
K_{PS} = endothelial transfer coefficient (mM min^{-1} cc of $tissue^{-1}$)
k_R = reflux rate (min^{-1})
f_{PV} = fractional plasma volume
Modified Patlak two-compartment kinetic model (see Daldrup *et al.*, AJR 171:941, 1998)

DCE-MRI

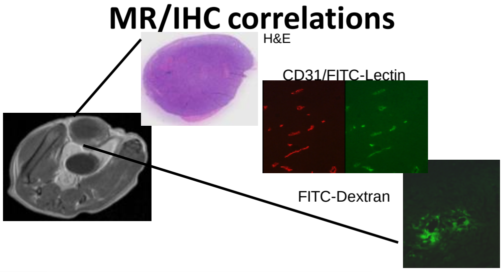




Parametric map analysis mode



MR/IHC correlations



Pharmacokinetic modeling

- Single-tracer
  - Modified Patlak model (two-compartment, separate rate constants).
- Dual-tracer
  - Sigmoidal-exponential function fit separately to MMCM data and (baseline corrected) low-MW uptake data.
  - vp from MMCM data fit, ve and Ktrans from low-MW data fit.
- All models implemented in the IDL programming environment in both ROI and pixel-by-pixel modes.

Magnetic Resonance in Medicine 58:705–716 (2007)

Comparison of Single- and Dual-Tracer Pharmacokinetic Modeling of Dynamic Contrast-Enhanced MRI Data Using Low, Medium, and High Molecular Weight Contrast Agents

Robert C. Orth,* James Bankson, Roger Price, and Edward F. Jackson

Table 1
Contrast Agent General Properties

Contrast agent	Molecular weight (Da)	First-pass extraction fraction	Elimination route
Magnevist	938	0.5[a]	Renal
Gadomer-17	35,000[b]	Minimal	Renal
PG-Gd-DTPA	228,000	Near zero	Mononuclear phagocyte system and biodegradation/elimination

[a]First-pass extraction fraction measurements for low molecular weight contrast agents range from 0.1-1.0.
[b]Actual molecular weight = 17 kDa; the globular shape of the molecule results in an apparent molecular weight of 35 kDa.

Multi-animal imaging to increase throughput

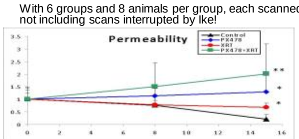
- Array of commercially available linear volume coils
- 2.75x increase in throughput
- No sacrifice in SNR, resolution
- No significant differences in DCE-MRI measurements made using single-animal vs 4x

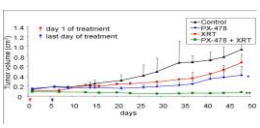
Ramirez et al. *J Magn Reson Imag* 26:1162-6, 2007.
Ramirez et al. *Magn Reson Med* 58:610-5, 2007.

Multi-animal PX/XRT for pancreas ca

In collaboration with Garth Powis and David Schwartz, multi-animal imaging strategies were applied to evaluate sequencing of PX-478 and XRT in a mouse model of pancreatic cancer:

With 6 groups and 8 animals per group, each scanned 3-4 times, we collected 160 dynamic datasets – not including scans interrupted by Ike!





Imaging biomarkers (V_{VF}) revealed statistically significant changes in responding group as early as 3 days after conclusion of therapy, preceding detectable differences in tumor size by > 1 wk.

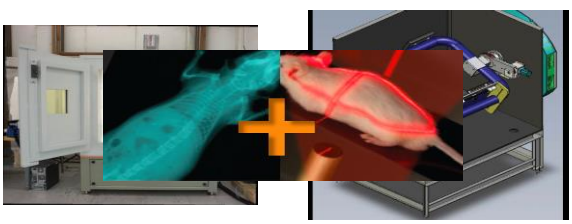
Schwartz, et al. *Mol Cancer Ther* 9(7):2057-67, 2010.

Micro-PET/CT

PET tracers (Mian Alauddin, Ph.D.)

- ^{18}F-FLT, ^{18}F-D-FMAU and ^{18}F-L-FMAU
  - cellular proliferation
- ^{18}F-Fluoroacetate
  - PET imaging of prostate cancer.
- ^{18}F-Lactose derivative
  - PET imaging of pancreatic cancer.
- ^{18}F-FHBG and ^{18}F-FEAU
  - PET imaging of HSV1-tk gene expression and Stem cell/T-cell trafficking.
- ^{18}F-FAHA and analogues
  - PET imaging of epigenetic (histone deacetylase).

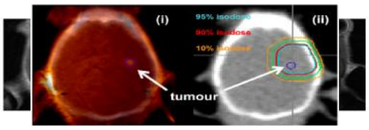
Precision Medical X-rad 225Cx



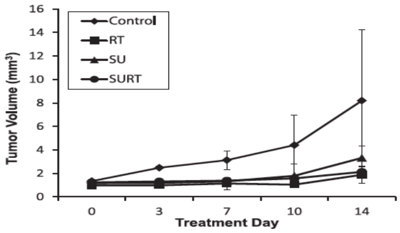
Imaging Biomarker Dynamics in an Intracranial Murine Glioma Study of Radiation and Antiangiogenic Therapy

Caroline Chung, MD,* Shahrzad Jalali, PhD,[†] Warren Foltz, PhD,[‡] Kelly Burrell, MSc,[§] Petra Wildgoose, BSc,[||] Patricia Lindsay, PhD,[¶] Christian Graves, BSc,** Kevin Camphausen, MD,[††] Michael Milosevic, MD,[‡‡] David Jaffray, PhD,[§§] Gelareh Zadeh, MD, PhD,[||||] and Cynthia Ménard, MD[¶¶]

4 Chung et al. Volume ■ • Number ■ • 2012
International Journal of Radiation Oncology • Biology • Physics
Imaging biomarkers for radiation and antiangiogenics 5

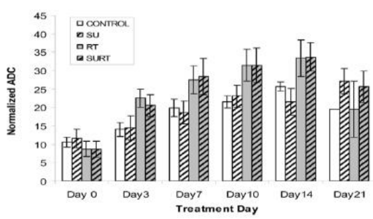


MR derived tumor volume



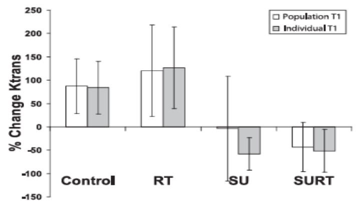
4 Chung et al. Volume ■ • Number ■ • 2012
International Journal of Radiation Oncology • Biology • Physics
Imaging biomarkers for radiation and antiangiogenics 5

MR anisotropic diffusion coefficient



4 Chung et al. Volume ■ • Number ■ • 2012
International Journal of Radiation Oncology • Biology • Physics
Imaging biomarkers for radiation and antiangiogenics 5

MR derived changes in perfusion



4 Chung et al.
Volume ■ • Number ■ • 2012

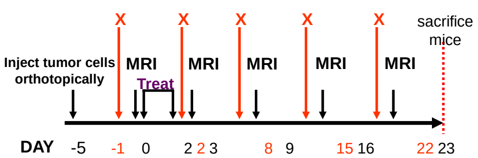
International Journal of Radiation Oncology • Biology • Physics
Imaging biomarkers for radiation and antiangiogenics 5

Preclinical Assessment of Therapeutic Agents for Thyroid Cancer Using Dynamic Contrast-Enhanced Magnetic Resonance Imaging

Stephen Y. Lai, M.D., Ph.D., FACS
Associate Professor
Head and Neck Surgery
Molecular and Cellular Oncology

14th International Thyroid Congress
September 11-16, 2010
Paris, France

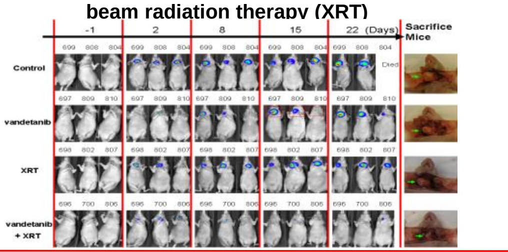
Schematic of Treatment and Imaging for Animals With Vandetanib and External Beam Radiation Therapy



X = Bioluminescence imaging (Xenogen)

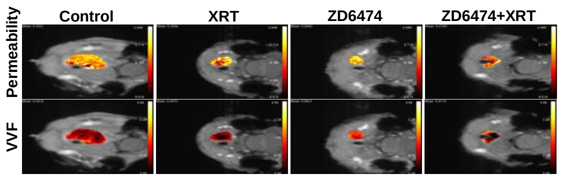
3 days of treatment
vandetanib 25 mg/kg
XRT 3 Gy/fraction

Combined treatment with Vandetanib and external beam radiation therapy (XRT)



MD Anderson Cancer Center

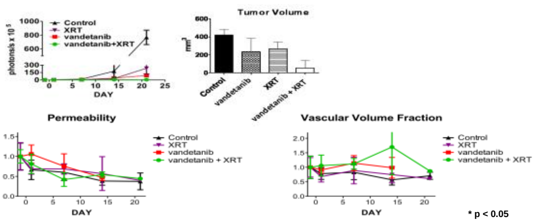
Parametric maps of permeability and vascular volume fraction (VVF) from DCE-MRI



7 days post-treatment

MD Anderson Cancer Center

Combined treatment with Vandetanib and XRT significantly decreases tumor volume and alters vascular characteristics



MD Anderson Cancer Center

Conclusions

- The orthotopic xenograft model is a valuable preclinical platform for the assessment of targeted therapeutic approaches for ATC.
- Imaging-based biomarkers from DCE-MRI quantified alterations in vascular permeability and vascular volume fraction due to treatment.
- The combination of vandetanib and radiation therapy significantly reduced tumor growth and altered tumor microenvironment characteristics.
- Combination therapy enhanced tumor necrosis and reduced micro vessel density in the ATC orthotopic xenograft model.
- These results suggest that the combination of vandetanib and radiation therapy may be a novel option in the treatment of ATC.

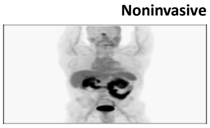
THE UNIVERSITY OF TEXAS MD Anderson ~~Cancer~~ Center Making Cancer History

Center for Advanced Biomedical Imaging Research

- MR750 3.0T MR
- Gem-Stone dual energy CT
- Discovery 690 PET/CT
- PETrace cyclotron
- Multiple hot cells
- Machine shop
- Image Processing and Visualization Laboratory

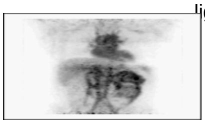
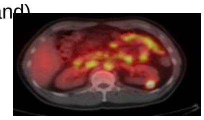
56

Center for Advanced Biomedical Imaging Research
Noninvasive Tissue Characterization




NSCLC

$\alpha_v\beta_3$ Integrin Receptor Imaging (^{18}F-AH111585) (Arg-Gly-Asp ligand)

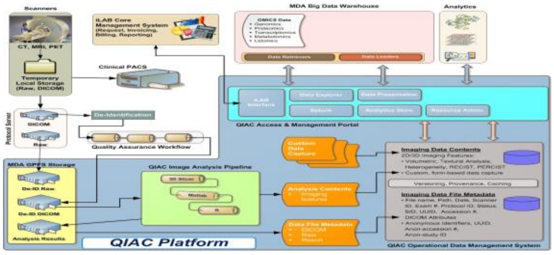
Renal CA

^{124}I-cG250 Antibody (binds carbonic

57

Courtesy Eric Roren

QIAC: Architecture & Workflow



58

Summary

- Co-clinical trials are viewed as acritical component of precision medicine therapy development
- Requires both clinical and pre-clinical (mouse) models and instrumentation
- Unified data platforms are desirable to harmonize analysis

MDAnderson Cancer Center

59