Pre-clinical Imaging in Co-clinical Trials

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What’s driving cancer research?

- **GOOD NEWS**
  - Death rates for the four most common cancers (prostate, breast, lung, colorectal), and all cancer combined continue to decline.
  - The rate of cancer incidence has declined since the early 2000s.
  - Length of cancer survival has increased for all cancers combined.

- **BAD NEWS**
  - 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.

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.
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
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 both genomic and biological evidence

Imaging the hallmarks of cancer

Mouse models

Genomics

Immunomics

Cancer cells
- secretome/exosome
- surface proteins
- nuclear proteins

Proteomics

Biomarker panels & Therapy targets

Human studies
- plasma/serum
- tissues

Glycomics

Metabolomics
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

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

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**2014 utilization by CCSG program**

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**Small animal imaging: Data that’s more than skin deep**

*The Small Animal Imaging Facility at The University of Texas MD Anderson Cancer Center (2014) The SAI staffs in its instrument stable, and they are “by far the most widely used” of the core facilities says John Hopp, 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”.*
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
Kostya Sokolov, Ph.D., Optical

Staff
Charles Kingsley, Lab Manager
Jorge Delacerda, Technologist
Kristen Maldenado, Technologist
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
  - 7 T, 30 cm Bruker Biospec
  - 7 T, 30 cm Bruker Biospec
  - Hyperpolarizer(s)
- Magnetic relaxometer
  - Senior Scientific
- X-ray and CT Core
  - Specimen CT (9 µm resolution)
  - Micro-CT (up to 45 µm resolution)
  - Faxitron
- School of Audiology and Speech Science
  - Ultrasound Core
    - Vevo 770
    - iThera photo-acoustic Optical
    - Caliper Lumina (BLI, BFI, x-ray)
    - Caliper Spectrum (BLI, BFI)
- Photoacoustic
  - Vevo 2100 LAZR photo-acoustic
  - iThera PA system
- Radiation research platform
  - Precision Medical 225Cx

Managing small animals
The smallest patient

- Proper animal support is critical to imaging procedure
- Challenges
  - Size
    - Mouse vs Human
      - 20-40 g vs 50-100 kg
  - Variable imaging time
  - Inaccessible location
  - Specific imaging requirements

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

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

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.

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

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

253-JB5 carcinomas treated with C225

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

MR assessment of antiangiogenic therapy

U54 Project 4 (MR):
- Pharmacokinetic analysis of single/dual tracer data with IHC & microautoradiography correlations.
- Longitudinal monitoring of antiangiogenic therapies in animals with IHC correlations.
- Longitudinal assessment of antiangiogenic therapies in patients with IHC correlations

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

Two compartment kinetic model

\[ C(t) = f_{PV} C_{P}(t) + C_{EES}(t) \]

- \( C(t) \) = tracer concentration at time \( t \) (mM)
- \( f_{PV} \) = fractional plasma volume
- \( C_{P}(t) \) = tracer concentration in plasma (mM)
- \( C_{EES}(t) \) = tracer concentration in extravascular, extracellular space (mM)
- \( k_{PS} \) = endothelial transfer coefficient (mM min\(^{-1}\) cc of tissue\(^{-1}\))
- \( k_{R} \) = reflux rate (min\(^{-1}\))

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.
  - $v_p$ from MMCM data fit, $v_e$ and $K_{trans}$ from low-MW data fit.
- All models implemented in the IDL programming environment in both ROI and pixel-by-pixel modes.
**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


**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 ($V_F^*$) 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.

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-FAU
  - 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
MR derived tumor volume

MR anisotropic diffusion coefficient
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
Combined treatment with Vandetanib and external beam radiation therapy (XRT) significantly decreases tumor volume and alters vascular characteristics.

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

*VVF* = vascular volume fraction

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

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