INTRO	3D CT	Bone CT	Lung Met uCT
Small Int CT	BBB	Onco PET	CNS
Liver 4D	Kidney	Platelets	Tumor Markers
BLI	Cardiac	Vascular	Radio Chem
iTox			

BIOLAURUS®

Imaging the Future of Therapeutics®

WHO WE ARE

We are In Vivo **Preclinical Molecular Imaging** Contract Research Specialists.

We **Collaboratively Partner with YOU** to design and implement successful scientific studies and imaging assays, speeding your timelines and reaching your goals. Using our "Hybrid Integration Model", integrating with your processes, as determined by YOU. A new kind of contract research company.

You Benefit from our "Distributed Business Model" (DBM) – a BioLaurus Core Team, plus a network of dynamic providers who we hand-select to conduct in-life studies much like a Clinical Research Organization partners with hospitals and clinics. Strength in the power of networks.

BioLaurus – the Center of our Research Affiliates:

Client / Sponsor

BioLaurus
Study Director
Research Team
Instrumentation
Imaging
Analytics

Vivariums

Analytics Labs

Imaging Resource Partners

Scientists

BioLaurus relationship with Client / Sponsor:

- BioLaurus is Primary Study Director through entire study
- BioLaurus is Primary Repository of all Study Data
- BioLaurus is Primary Partner in MSA, SOW, and all contracts with Sponsor
- BioLaurus is Primary conduit to Sponsor

BioLaurus relationship with our Pharmaceutical Contract Research Affiliates:

- BioLaurus is Primary Study Director through entire study
- BioLaurus is Coordinator of Activities
- BioLaurus is Liaison with all involved

BioLaurus is Seamlessly Translational

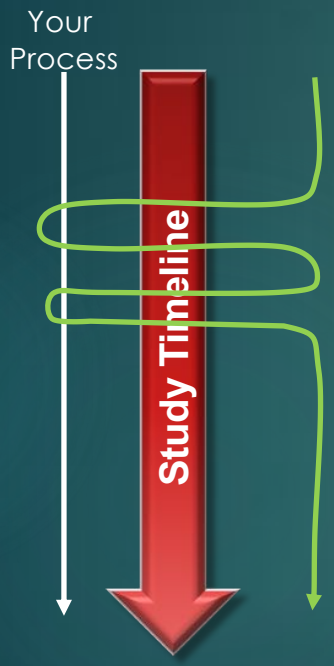
Another benefit of our Business Model

BioLaurus PreClinical Studies can easily transition to our DBM Network of Partners for seamless Phase 0 and Phase I studies

BioLaurus **Integrates with Your Process** based on Your Needs:

CONTRACTED

Think of us as a "Contractor"



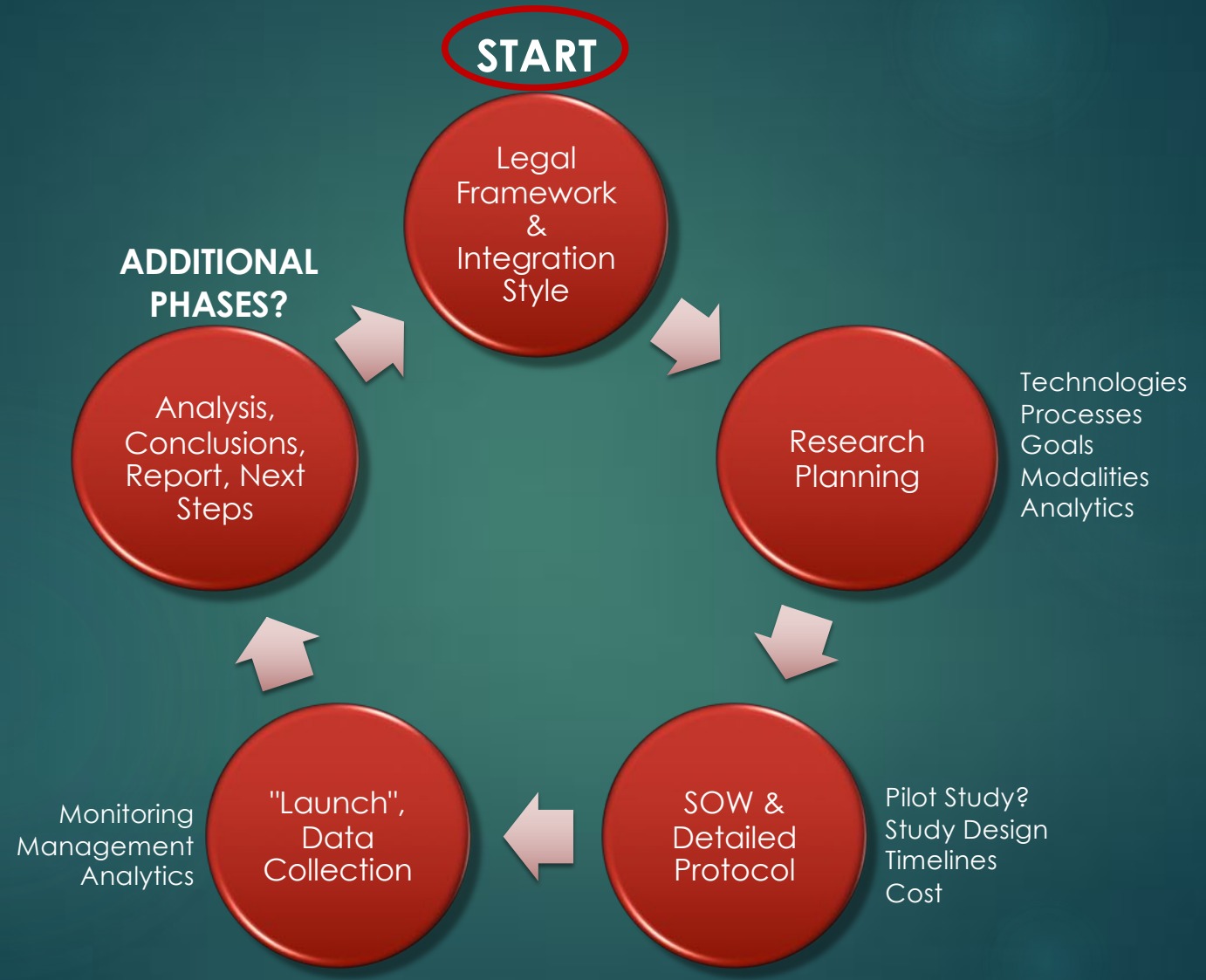
We CUSTOM-DESIGN our Approach with You:

Joint Goal & Desired Outcomes Setting
Joint Protocol Design
Established Governance Structures
Efficient Decision Mapping
Open Communication Channels
Weekly Joint Team Meetings
Integration with Your Processes
Acclimate to Your Management Style

Think of us as part of your "Team"

INTEGRATED

BioLaurus Working Blueprint

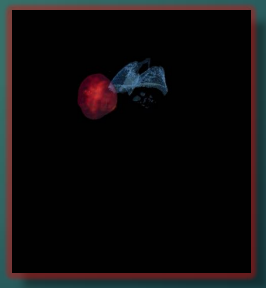


BioLaurus Is Your **Complete** Molecular Imaging Specialist

- **Strong Strategic Design** – our executive leadership works with you at a strategic level to design venerable outcomes for your needs.
- **Strong Tactical Execution** – our specialized experts conduct all aspects of a research study from study design, to the specialized techniques, technology, imaging analytics, and reporting you need to succeed

STRATEGIC

TACTICAL



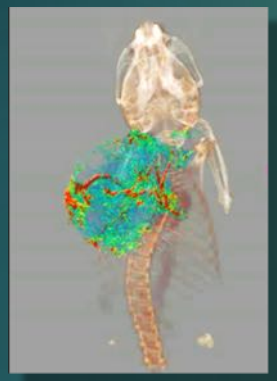
INTRO | 3D CT | Bone CT | Lung Met uCT | Small Int CT | BBB | Onco PET | CNS | Liver 4D | Kidney | Platelets | Tumor Markers | BLI | Cardiac | Vascular | Radio Chem | iTox

BioLaurus Integrated Solutions

Study Design
- Efficacy
- Assay Development
- Safety Tox

Study Monitor
- In-Life Study Conduct/monitoring
- Select CRO/vivarium
- Select Imaging Instrumentation
- On site monitoring during study

Multi-modality Imaging
- Conduct Study Imaging
  - PET/SPECT ….
  - CT/Ultrasound/Optical
  - MRI
  - Flow Cytometry



Tumor CT Angiography

Analytics
- 4D visualization
- Real Time
- Quantitative
- Kinetics
- Multi-compartment
- Dosimetry

Drug and Function Biomarkers
- Drug and biomarker labeling chemistry (FLI and BLI) and radiochemistry (C-11, F18, Tc-99m,In-111,Zr-89….)
- Contrast tracers

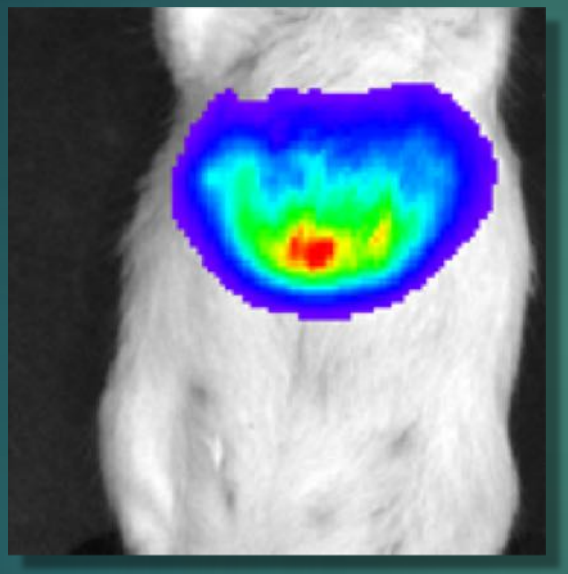
Report

Image Informatics

Digital Replica
Re-interrogate

INTRO | 3D CT | Bone CT | Lung Met uCT | Small Int CT | BBB | Onco PET | CNS | Liver 4D | Kidney | Platelets | Tumor Markers | BLI | Cardiac | Vascular | Radio Chem | iTox

BioLaurus' Comprehensive Imaging Capabilities



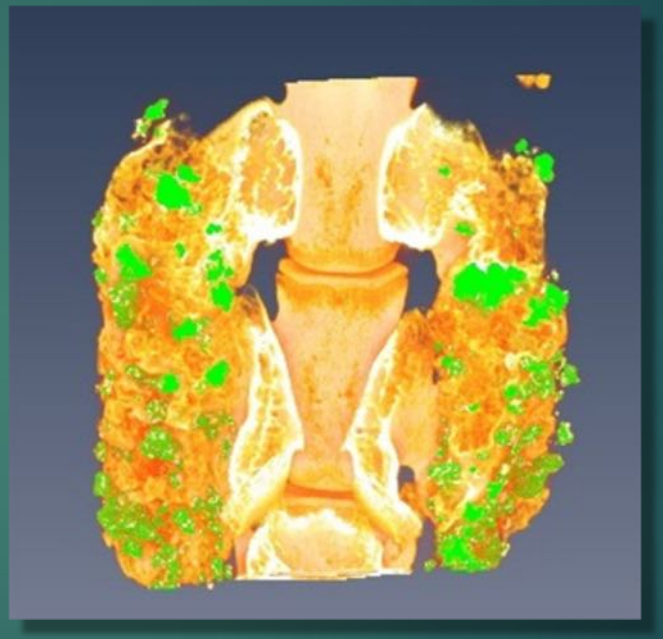
Therapeutic Indication

- Oncology
- Central Nervous System
- Cardiomyopathy
- NASH
- Platelet Activation/Survival
- Immune Therapeutics
- Stem Cell Therapeutics
- Cardiovascular
- Pulmonary
- Bone Regeneration
- Gastro-intestinal

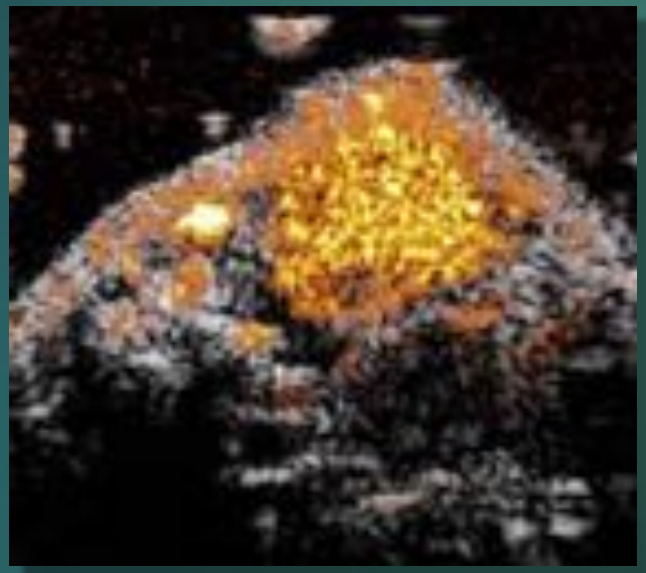
BioLaurus' Comprehensive Imaging Capabilities (con't)

Service

- Study Design
- Imaging Assay Development
- Safety Pharmacology
- Imaging PK/PD
- Imaging Toxicology (iTox™)
- In Vivo Efficacy
- Mechanism of Action
- Disease Staging
- Biodistribution



BioLaurus' Comprehensive Imaging Capabilities (con't)



Imaging Modality

- SPECT
- PET
- CT
- Micro-CT
- MRI
- Ultrasound Microbubble
- Optical Imaging
  - BLI
  - FLI
  - FLT (fluorescence lifetime)

Our Imaging Capabilities Span Rodents to **NHP**

BioLaurus ***breaks the mold and offers imaging of larger animals***

Integration Across Technology Platforms

Consultation Study Design

Identify the solution
Match the technology with the solution
Multi-modality
Flexibility; in vivo +/- histology
Chemistry / radiopharmacy

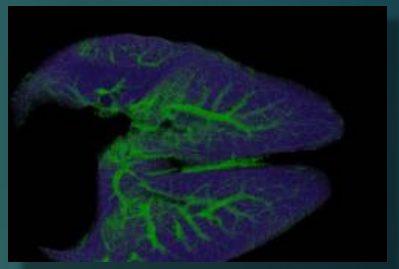
Drug or Biomarker

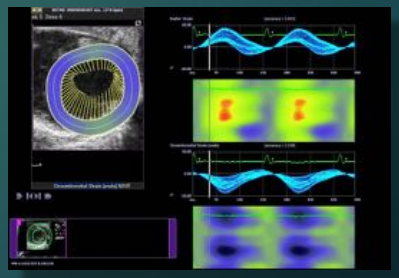
In-Life Imaging

Blood Sample
Tissue Sample

Histology
Analytics (LC-MS)
Clin Chem/Hematology

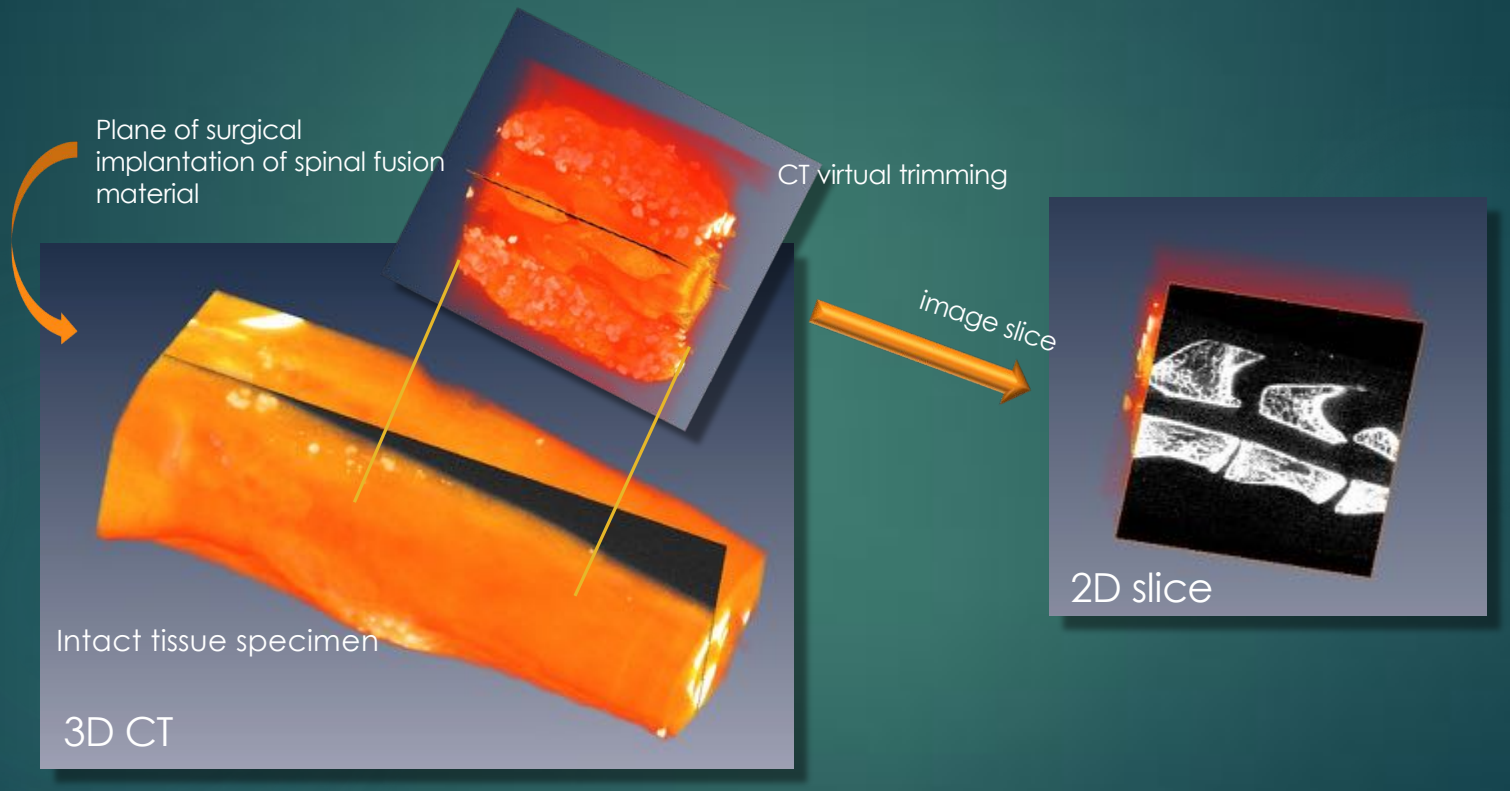
Image Analysis - data PACS and computational analysis





Research Capabilities – An Overview

CT Non-Destructive Histology …
Like Superman, seeing the unseen

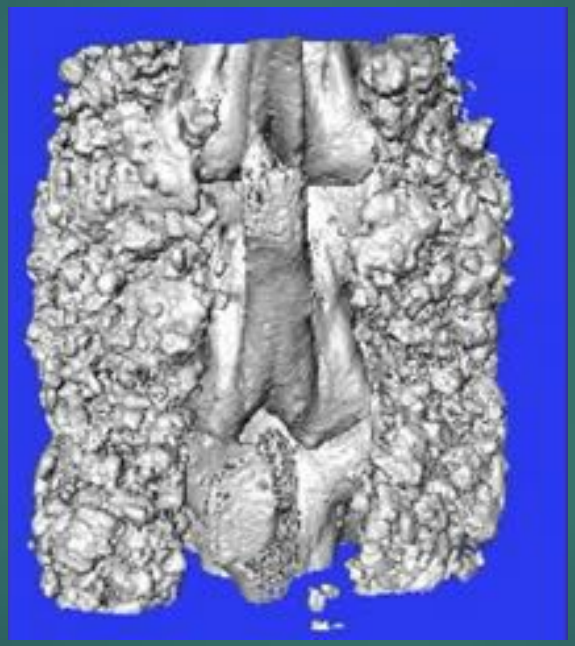


CT Imaging – New Bone Analytics Gold Standard

Bone regeneration – degeneration
Materials induced spinal fusion

Bone Analysis

- Bone cortical thickness
- Bone cortical perimeter
- Bone volume
- Bone mineral content (mg)
- BMD(mg/cc)
- Tissue mineral content (mg)
- Tissue mineral density (mg/cc)
- BVF



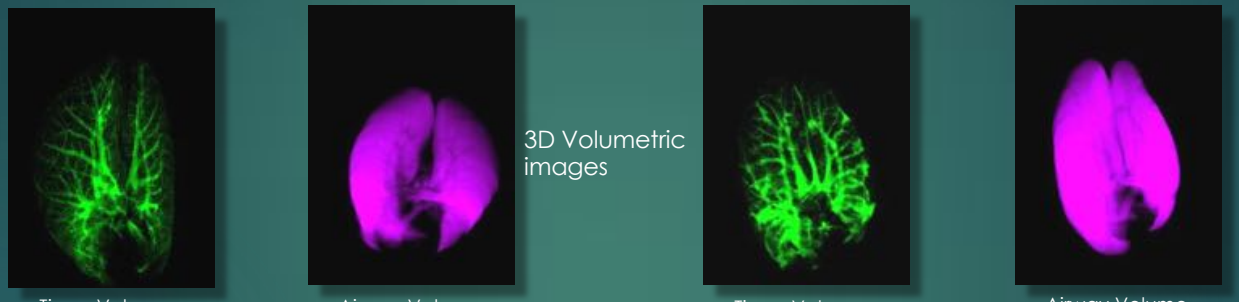
µCT MORPHOMETRY (3D)

- BV/TV
- BS/BV
- Tb.Th
- Tb.N
- Tb.Sp
- Ct.Th
- Tb.Pf
- SMI
- Euler #
- Euler # / volume
- DA

Lung Metastasis Imaged By microCT Validated by Histopath

Normal Mouse Lung

EBC-1 Bearing Mouse Lung



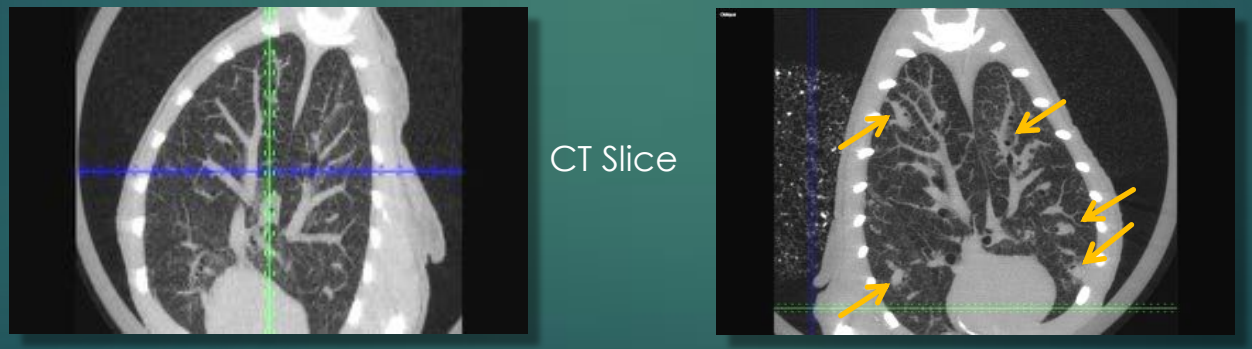
Tissue Volume

Airway Volume

3D Volumetric images

Tissue Volume

Airway Volume



CT Slice

CT Assay of Small Intestine FFA Lipid Absorption

BioLaurus has developed a CT assay tracking and quantitating enterocyte absorption / excretion of iodinated free fatty acids (FFA) in the small intestine.

A triglyceride is introduced into the duodenum and rapidly broken down into iodinated - FFA and 2-MG. The FFA is rapidly absorbed by the mucosa (see "donut" hole profiles in figure).

Shown is an overlay of two time points as tracer moves through the small intestine at 15 minute time point intervals.

Drug Blood Brain Barrier (BBB) Permeability and PK

H-3, C-14 Tracer Radioscintigraphy

Radiotracer Injected

30 sec to 3 min

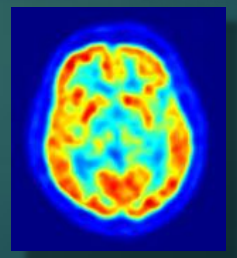
Arterial blood sample - $\int_{t=n}^{t=0} DPM$

Brain Tissue Processing

Cryo-cut sectioning

Radioscintigraphy

cpm/g brain
cpm/ml plasma
EF, P values



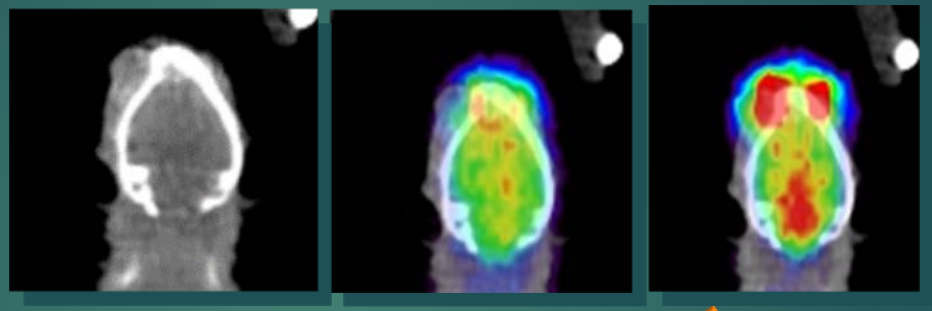
Autoradiography

Drug Blood Brain Barrier (BBB) Permeability and PK

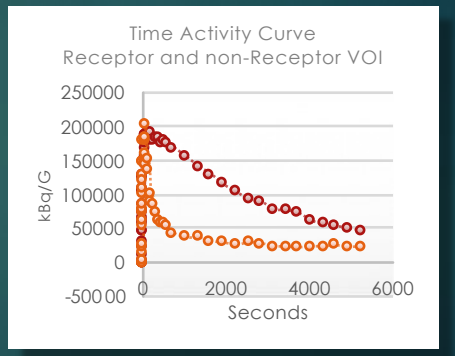
Dynamic PET Imaging

Group 1 (n=5) ,
^{11}C-Drug,^{18}F-Drug, ^{124}I-Drug, or ^{89}Zr-Drug

1 sec to 1 hour

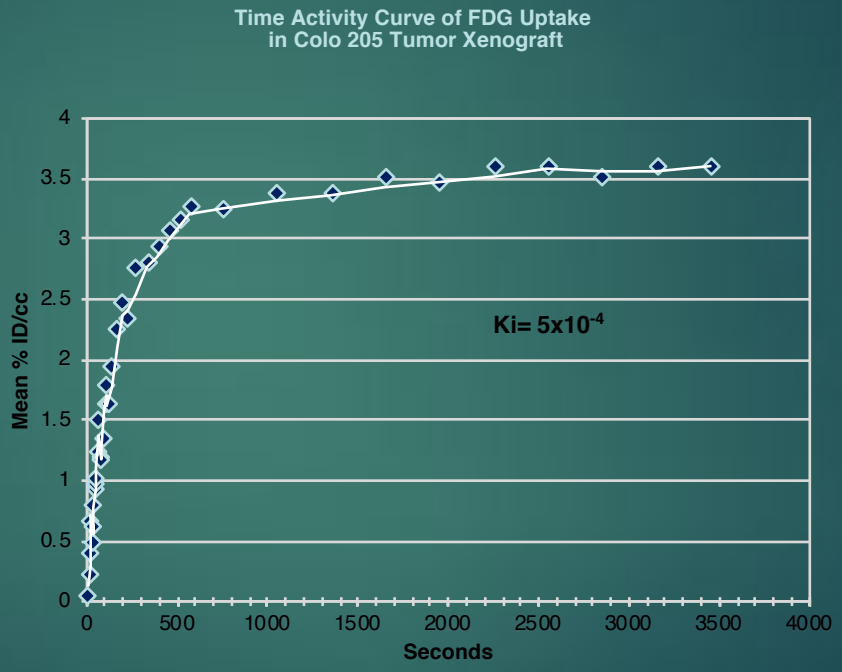


Arterial blood sample - $\int_{t=n}^{t=0} DPM$

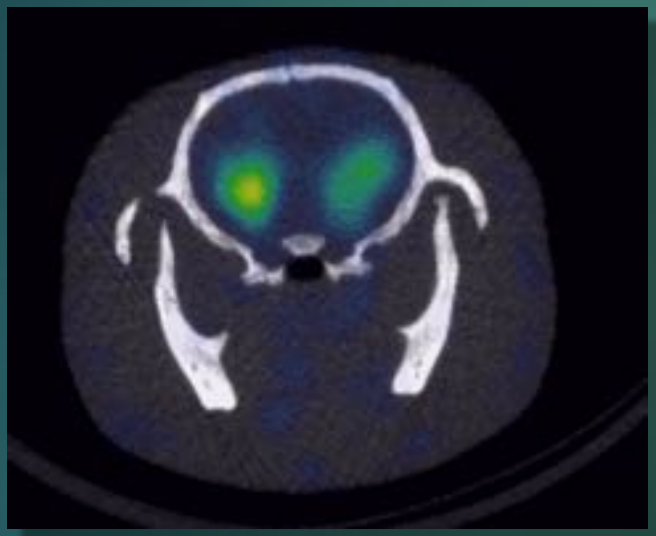


P values (1-90 sec data)
PK values (1-6000 sec data)

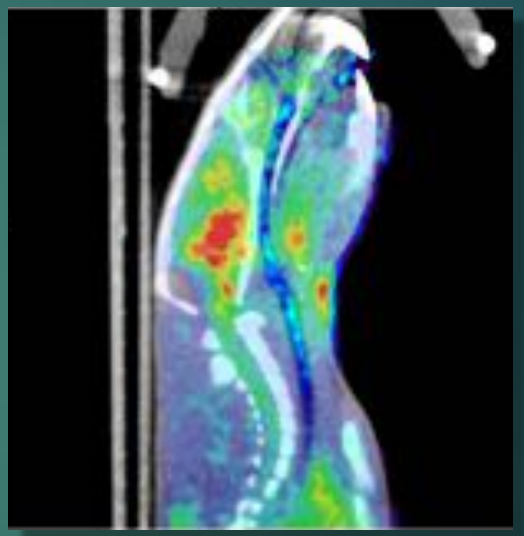
PET PK (Dynamic Imaging) in cancer tissue not possible by conventional PK (blood)



CNS Receptor Imaging - Quantitation

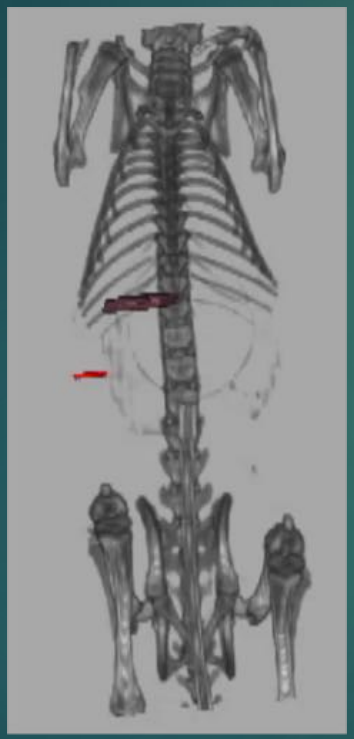


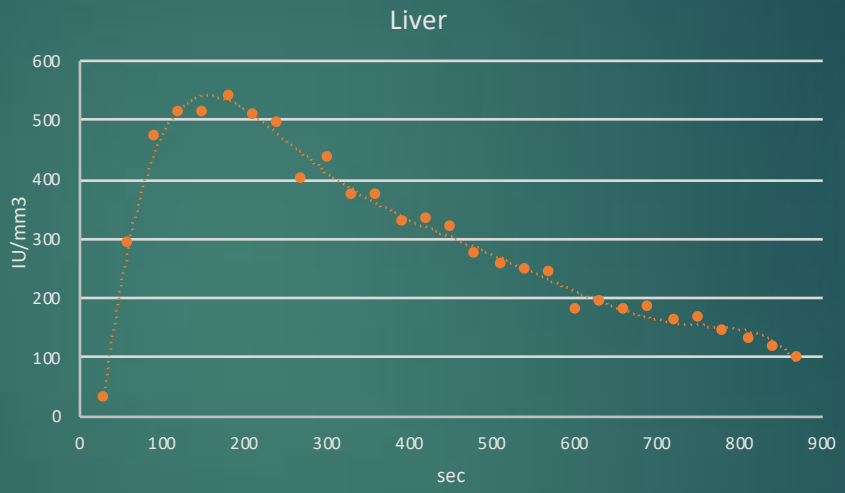
DAT Imaging Rat Striatum



Mu-opiod Receptor

SPECT PK Multi-Compartmental Dynamic Imaging(4D) - Liver Hepatobiliary Function

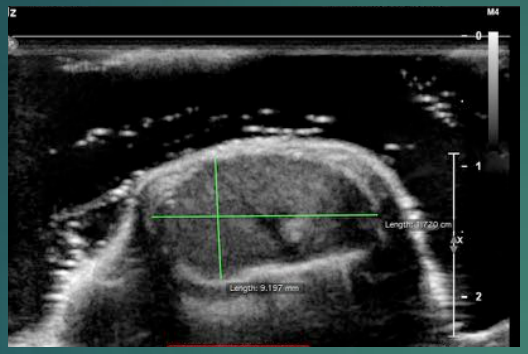




Rat injected iv with Tc-99m mebrofenin, a hepatobiliary function marker. Mebrofenin along with CT contrast imaging is used in multiple liver disease indications including oncology, NASH, and other hepatobiliary conditions. Drug tracked in real time. Graph of liver uptake and excretion..

Murine NASH Model – Liver Fibrosis

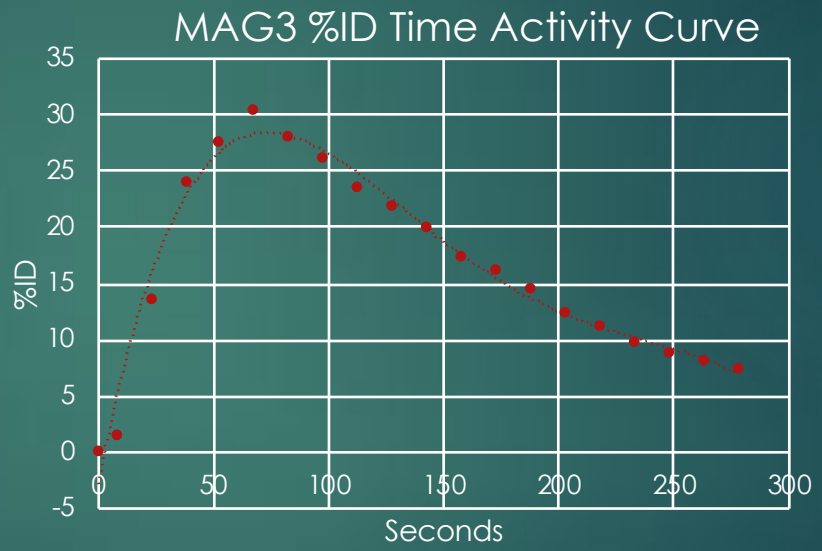
Control



NASH

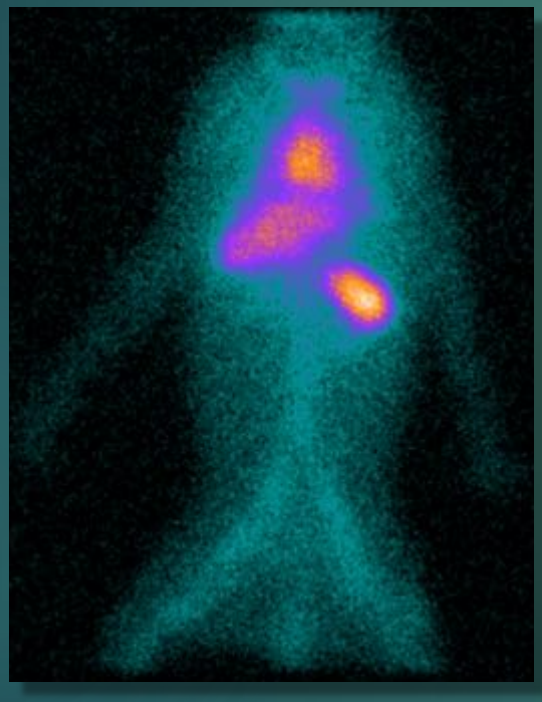
Nonalcoholic steatohepatitis (NASH) is a progressive inflammatory liver disease associated with the build up of fat in the liver . The disease begins with increasing fat in the liver and ends in extensive liver fibrosis (shown above). Ultrasound imaging is capable of quantifying liver fibrosis as shown above in ultrasound images of age matched mice after 12 weeks on a normal diet (Control) or a CD-HFD diet (NASH).

Renogram – Dynamic Kidney Function Imaging



Right kidney

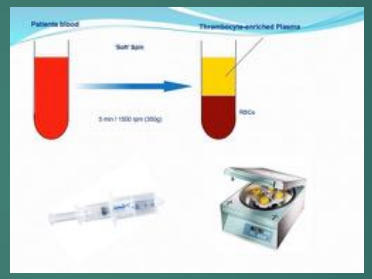
NHP Platelet Survival and Sequestration SPECT Imaging In-111 Labeled Autologous PLT



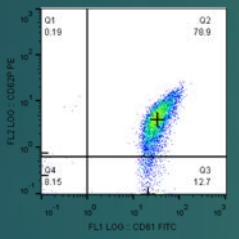
- In Vivo Autologous PLT Sequestration Imaging is the clinical Gold Standard for examining the pathologic mechanisms by which PLT thrombocytopenia occurs.
  - HIT (heparin induced thrombocytopenia)
  - ITP (idiopathic thrombocytopenia, autoimmune)
  - Drug induced IT (drug-PLT interaction triggers immune response and thrombocytopenia)
- Sequestration to the spleen or liver is determined by quantifying the levels of ^{111}Indium labeled PLT in each organ before and following drug dosing

Autologous Platelet Sequestration Procedures

Cynomolgus Monkey
Rabbit
Pig



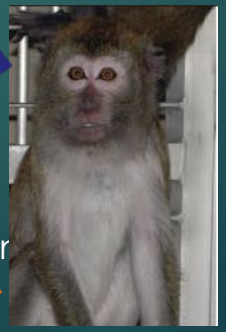
Gamma Camera Image



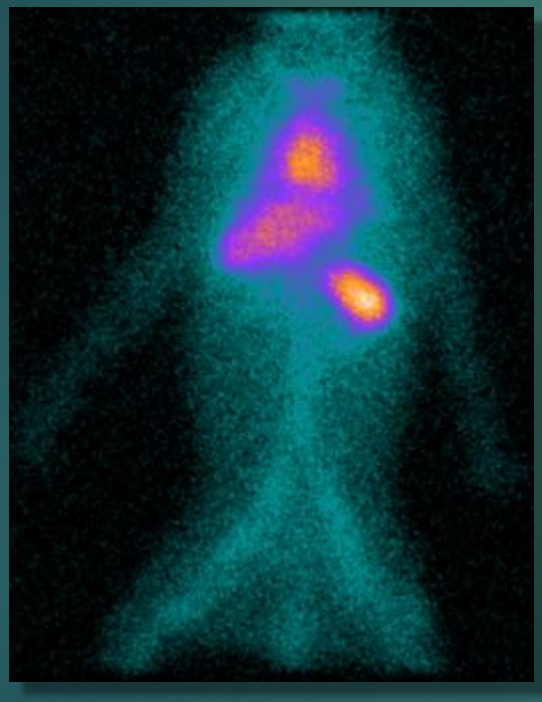
FCM QC (CD62P-)

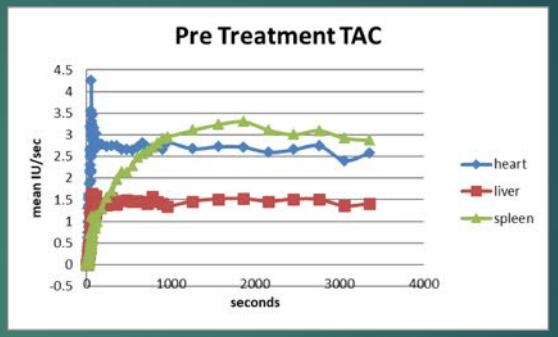
^{111}In labeling

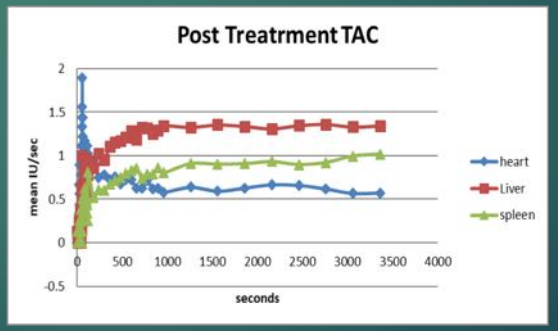
Autologous PLT reinjection



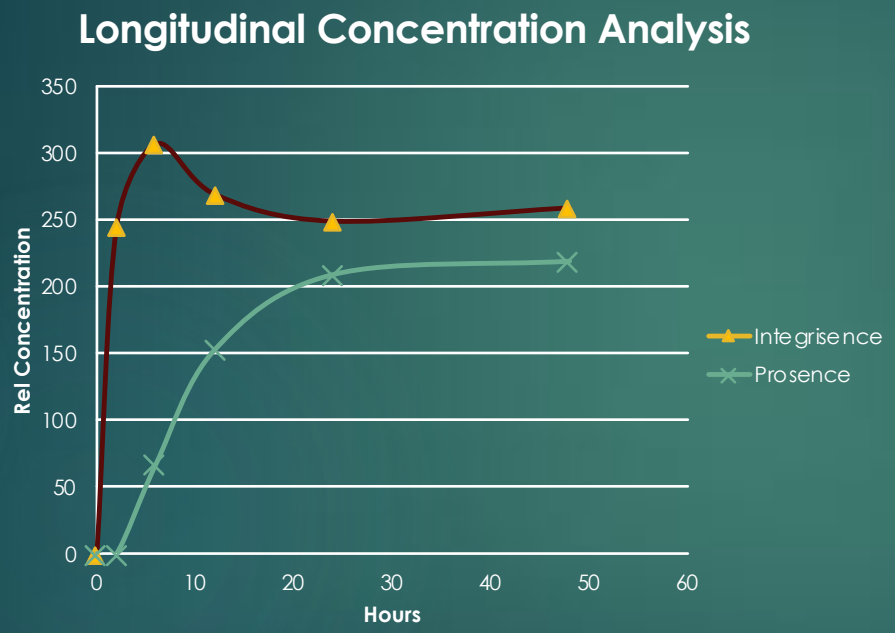
NHP Platelet Survival and Sequestration SPECT Imaging In-111 Labeled Autologous PLT Dynamic (TAC) Imaging



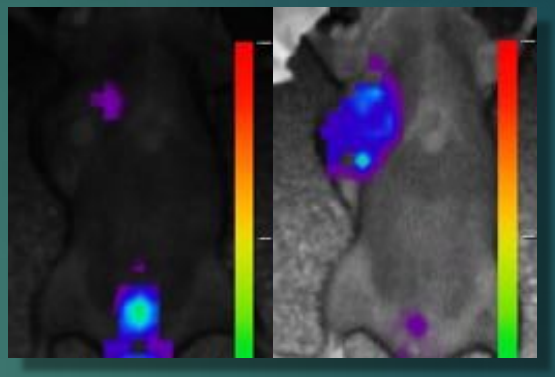




Fluorescence Imaging (FLI) of Tumor Markers



HCT-116 xenograft tumor.



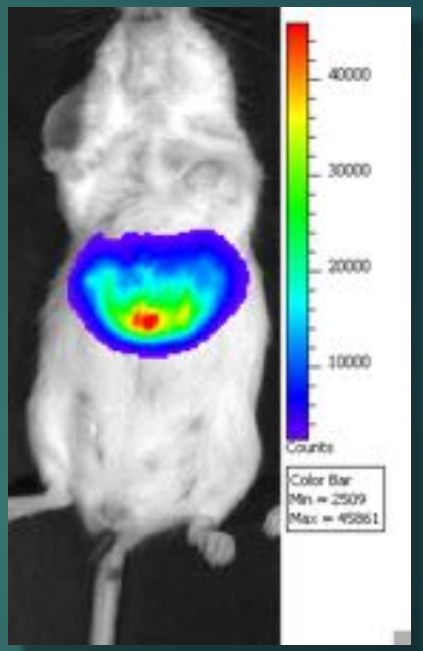
5 min 24 hour
Integrisence

Integrisence is a vascular integrin receptor marker
Prosence is a cathepsin D (tumor marker) activated fluorophore

Bioluminescence Imaging (BLI)

- Bioluminescence imaging is widely used to track cells in mice. Results are typically expressed as counts or p/sec/cm^2/sr

- Two test systems are available at BioLaurus
  - Cells (stem cells, T-cells, tumor cells) transduced with Luc reporter gene for tracking in vivo
  - Gene therapy delivery – whole body HDTV transduction with gene constructs that include Luc reporter gene. Track organs transfected, level of gene transduction, and gene persistence.

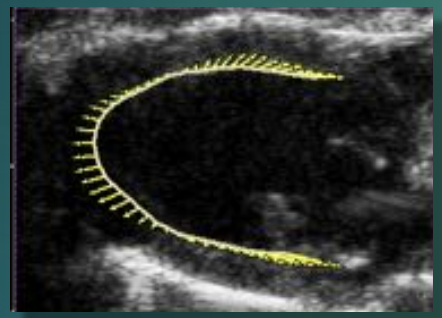


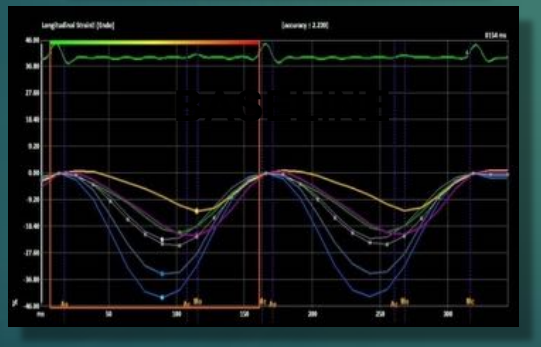
HDTV with Luc-albumin promoter plasmid

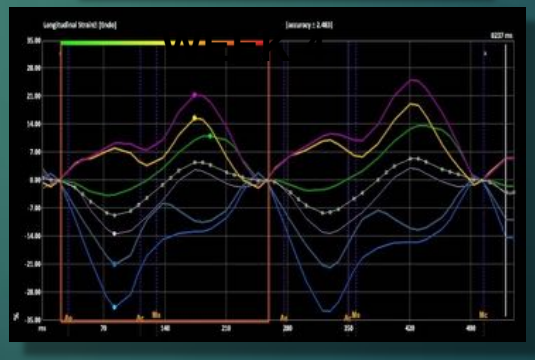
Ultrasound Cardiac Tox Imaging:

Longitudinal Strain Velocity Vector Imaging

Cardiac strain can be analyzed in one of three directions: radial, circumferential, and longitudinal. With each heart beat the myocardium in six segments is tracked and analyzed. The same data set includes, standard EF, T2P, and Peak% . Shown here; longitudinal strain in rat treated with doxorubicin.



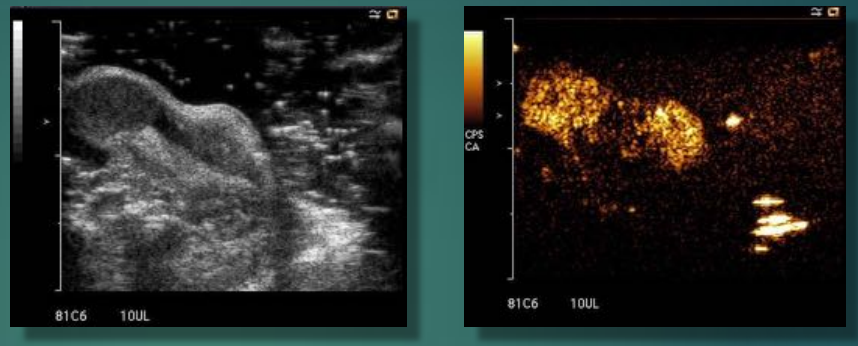




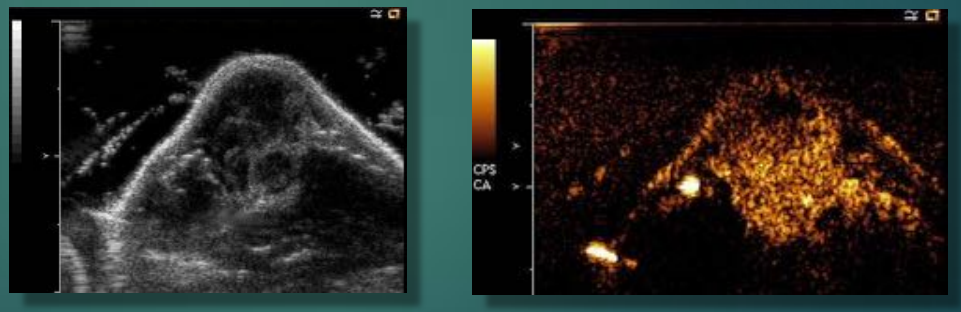
Ultrasound Microbubble Tumor Biomarkers

Targeted microbubbles to vascular associated tumor markers can be used to rapidly assess angiogenesis and drug induced vascular normalization.

Multiple biomarkers can be assessed serially in the same tumor.



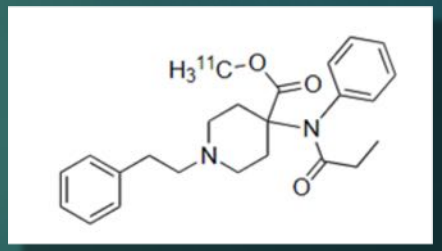
Renal Carcinoma -Tenascin Mab microbubbles – B mode (left) – Contrast mode (right)



Renal Carcinoma - VEGFR2 Peptide microbubble – B mode (left) – Contrast mode (right)

Full Range Chemistry Capabilities

- Radio-Chemistry
  - Cyclotron generation of wide range of radio tracers, in particular C-11 and F18
  - Radiochemical synthesis of radiotracers – example C-11 carfentanil, FDG
  - Chelator chemistry from small molecules to monoclonal antibodies to peptides and anti –sense oligos
  - Radiotracer Tc-99m to Zr-89 for PET and SPECT imaging
- Flourophore chemistry for fluorescence imaging
- CT tracer development
- Cell labeling including In-111, fluorescence, reporter gene (luciferase, TK)



Toxicology
Added Value of iTOX

14D Acute Tox → Inject Drug D1-D14
150 rats → D14 → D21

D14 → Animal weight
Clin Chem
Hematology
+/- urinalysis

D21 → Recovery Groups

Choice of PET/SPECT
label Drug/Biomarker →

→ In Vivo Image
D1, D7, D14

→ Recovery Imaging
D21, D28,…

→ Necropsy

→ Histology

→ Necropsy

→ Histology

Imaging: longitudinal – multi organ
Functional toxicity in vivo
Dose Accumulation
Recovery

Tumor Efficacy
Comparison of Conventional and Imaging Study

Assay Dev -Drug → Inject Drug/Biomarker
96 mice/rats → 6 timepoints over 28 days
Measure tumor size
Harvest Blood and tumor tissue

Choice of PET/SPECT
label Drug/Biomarker →

→ In Vivo Image
6 time points
28 days

Analysis:
Tumor size 1◦
Metastasis
FDG
Apoptosis
Angiogenesis

Tissue weighed

Tissue Extracts → Assay → Analysis

Tissue Prep → Histology → Pathology

Examples of BioLaurus Pharmaceutical Partners:

THANK YOU

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