

**Pre-clinical – Clinical Assessment
Practical Imaging Processes
to Demonstrate
the Organs & Tissues Biodistribution of
Nanoscale Elements**

**George Q. Mills, MD, MBA
Vice President, Medical Imaging Consulting
Perceptive Informatics, Inc**

Critical Path

Nanotechnology

Imaging 2004

To determine the biodistribution of nanoparticles of various sizes in order to determine:

- Fate in vivo**
- Potential toxicity organs & tissues**
- Routes excretion**
- Organs & tissues retention**

What is the effect of particle size on the distribution of a therapeutic agent?

- **Comparative biodistribution study**
- **non-targeted nanoparticle**
- **“non-nanoparticle size”**

Challenges - Current Knowledge

“Known” Physiologic Barriers to Entry

Blood-Brain Barrier

Cornea

Change???

**Exploratory IND Enable
First-in-Human Clinical Trials
Confirmation of Pre-clinical Assessment
Facilitate Human subjects confirmation of pre-
clinical findings
Utilize
“Diagnostic dose” (“Microdose”)
“Without therapeutic intent”**

Rapid development assessments/portfolio-protocol design

Plan future human trials

Safety schema

- **Non-target/unexpected organ localization**
- **Kidney, liver, gastrointestinal tract**
- **Routes/rates of clearance**
- **Radiation Dosimetry – diagnostic [PET]**

Efficacy schema – selection/localization/retention

- **Tumor**
- **Abscess**

“Not-so-promising”

Nanoparticles - Drugs/Biologics

“Close early”

Reduce development time

Reduces overall development costs

“Promising” Drugs/Biologics

Close the Exploratory IND

Proceed to standard Phase 1 study

Continue development

**“ FIH”/Early Experience/Portfolio Assessment
in the Exploratory IND**

**Comparative
Biodistribution Imaging Trials**

Well Established Available Techniques

Unsealed Source Radiation Dosimetry

BEXXAR/Zevalin

Technique

- 1. [Radio]label the investigational drug/biologic candidates**
- 2. Comparative whole body biodistribution imaging over time**

- 1. Pre-clinical PK - Select multiple imaging time points**
 - a) Baseline - 30 min – 60 min – 90 min**
 - b) Baseline - 24 hrs – 48 hrs – 72 hrs – 96 hrs**

2. Radiolabeling technique

- **Non-destructive to Biologic/Drug**
- **Linker technology - needed**
- **In-vivo stability of the radiolabel**

3. Potential PET radiolabel

- **stability**
- **half-life**

C-11	F-18	I-124
20 mins	110 mins	4.18 days

4. Potential

Gamma radiolabel

- **stability**
- **half-life**

I-123	In-111	I-131
13.6 hours	2.8 days	8.01 days

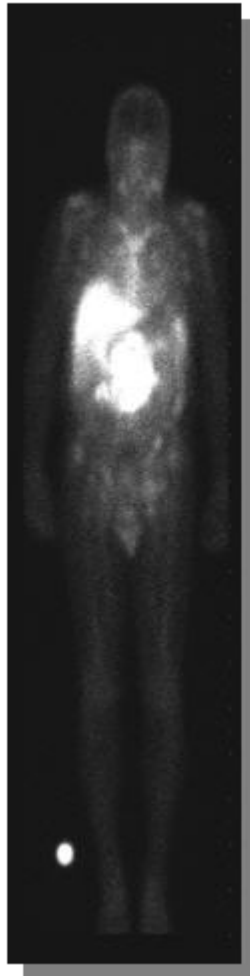
Whole Body Biodistribution Imaging

PAREXEL
clinical research

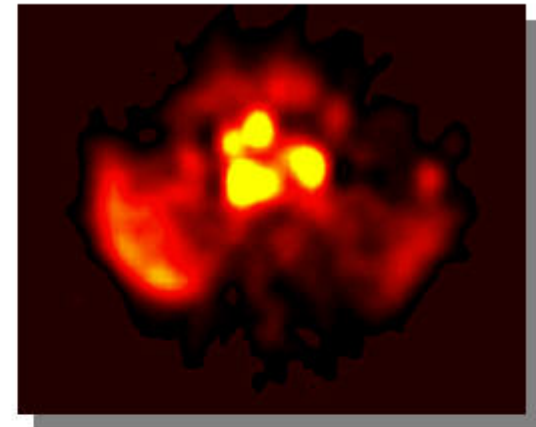
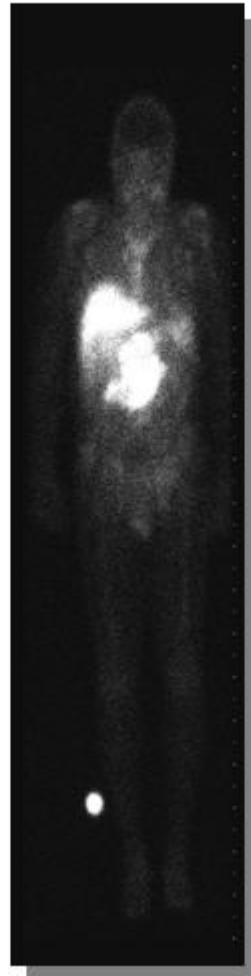
Time Point
1



Time Point
2



Time Point
3



SPECT



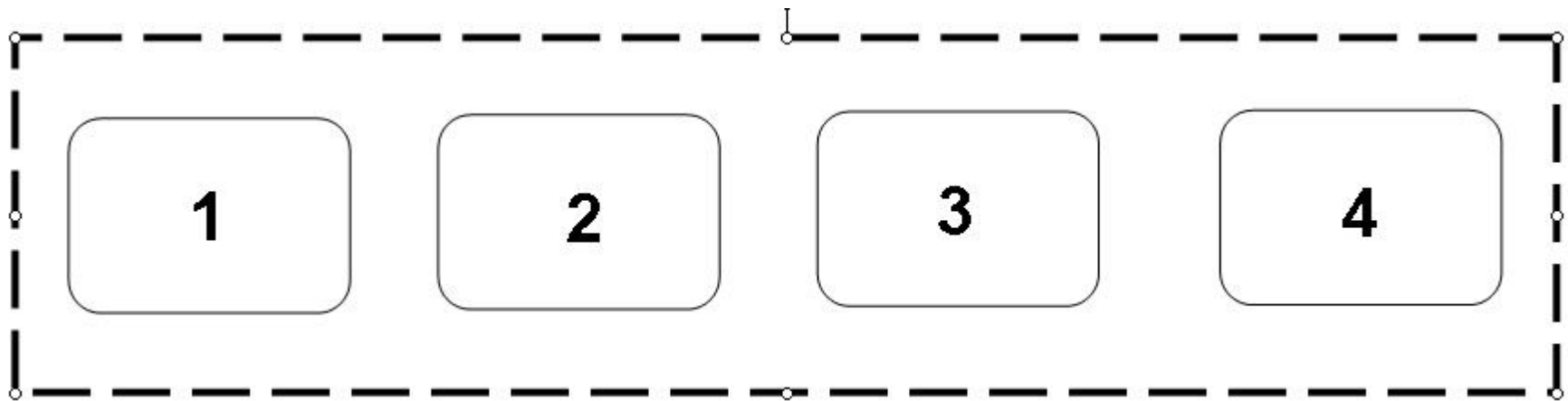
CT

**“Competitive - Comparative”
Biodistribution Portfolio Analysis
Whole Body Biodistribution Studies**

Size, Charge, Source

“Horizontal Portfolio Analysis”

Simultaneous assessment



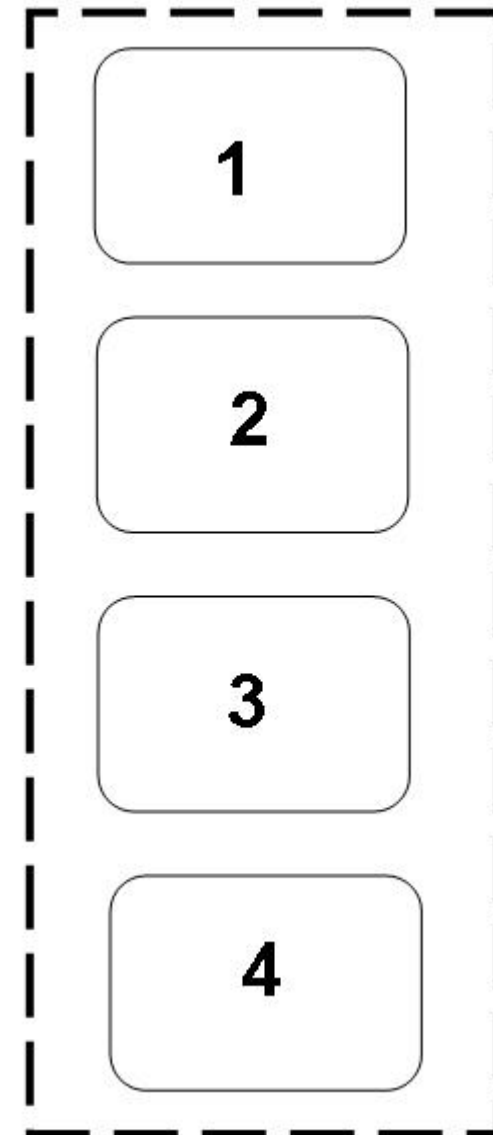
Dependent upon CMC

**“Vertical portfolio
analysis”**

**Sequential “Top-down”
assessment**

“First to perform - Wins”

Dependent upon CMC



Relate “imaging signals” to long term biologic/drug development

Expected imaging of

radiolabeled therapeutic -> tumor

Is that efficacy?

Unexpected radiolabeled therapeutic ->

organ localization

Is that a safety concern?

Radioactive Drugs Research Committees

Regulatory Options for Human Research Testing

Radioactive Drug Research Committees (RDRC) – Have been utilized for PET development

21 CFR 361 (a): RDRC approval is limited to research studies intended to obtain basic information regarding the metabolism...but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes.

- **Cannot conduct “clinical trial” of a diagnostic radioactive drug**
- **Outcome of radioactive drug study is not to be used for diagnosis and/or to guide subsequent therapeutic decisions**

Utilize

Exploratory IND and/or standard IND development, rather than RDRC development for a commercial product

Thank you!

George Q. Mills, MD, MBA

Vice President, Medical Imaging Consulting

Perceptive Informatics, Inc.

George.Mills@Perceptive.com

202-468-1986