WELCOME

Free Educational Webinar

Critical Steps in PET Radiopharmaceutical Development and Updated FDA Regulations

Presenting Experts:

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PET in Drug Development

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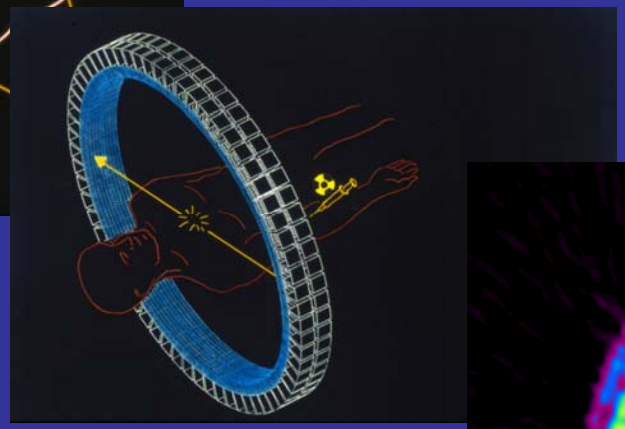
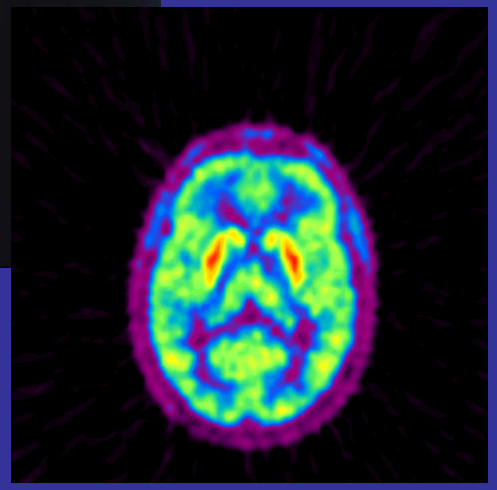
Positron Emission Tomography

Biological radionuclides: ^{15}O, ^{11}C, ^{18}F



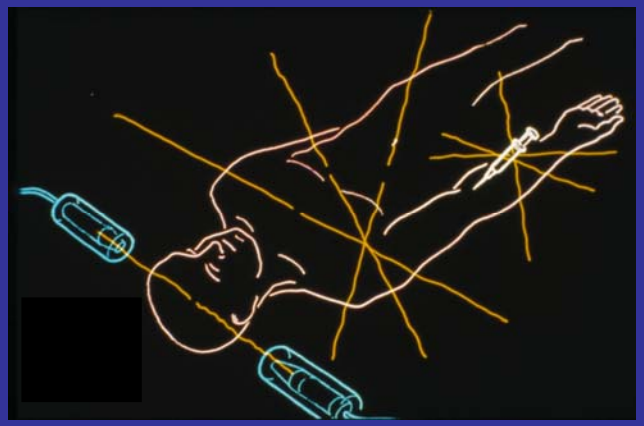


Quantitative

Picomolar sensitivity → tracer amounts

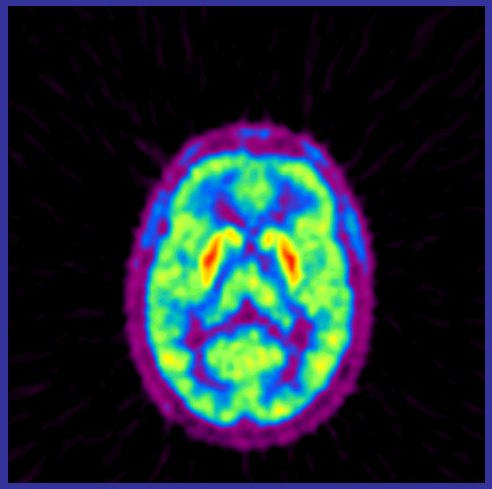
PET Diagnosis

Inject



Wait

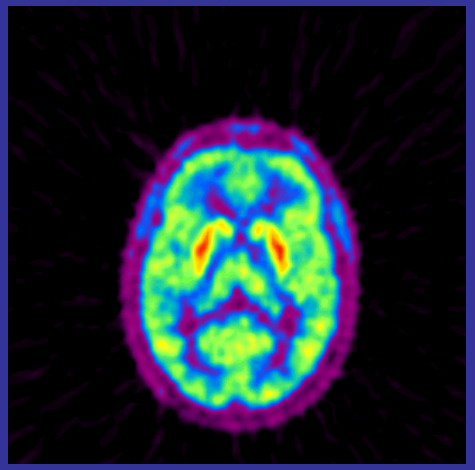
Scan



Increased uptake:

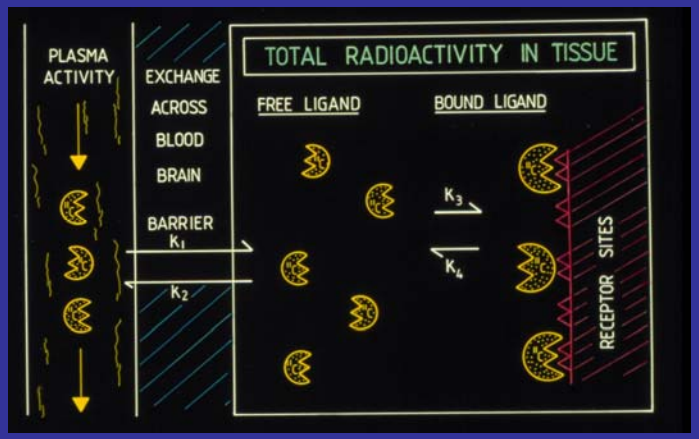
- Increased binding
- Increased flow and/or extraction
- Increased delivery

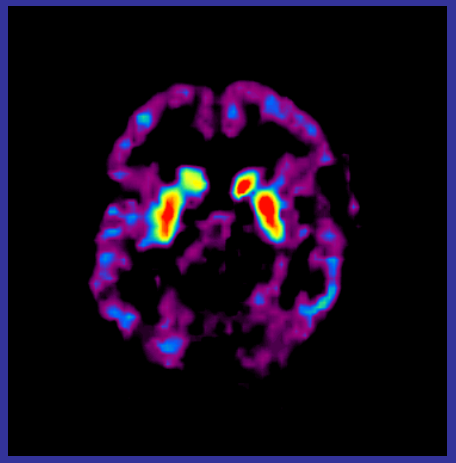
Need for Quantification

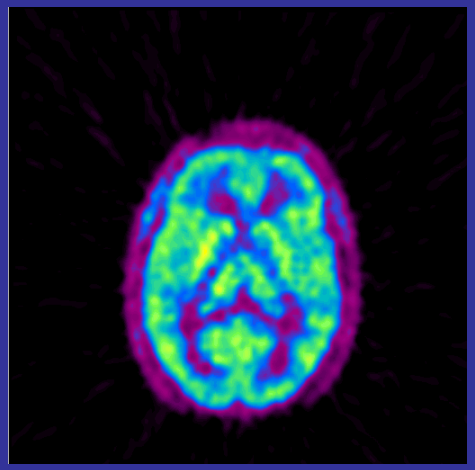


base-line

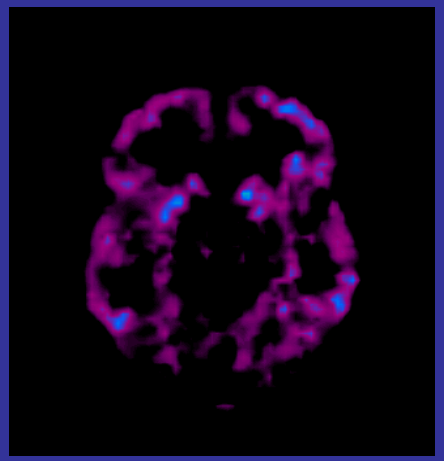
Tracer kinetic model







post-aprepitant



Uptake

Specific Binding

Optimal Dose Selection and Timing

Dose Selection: Ziprazidone

Purpose:

To establish the minimum dose of ziprasidone required to occupy striatal dopamine D_2 receptor by 65 to 85%

Methods:

8 healthy male volunteers

20 to 34 years of age

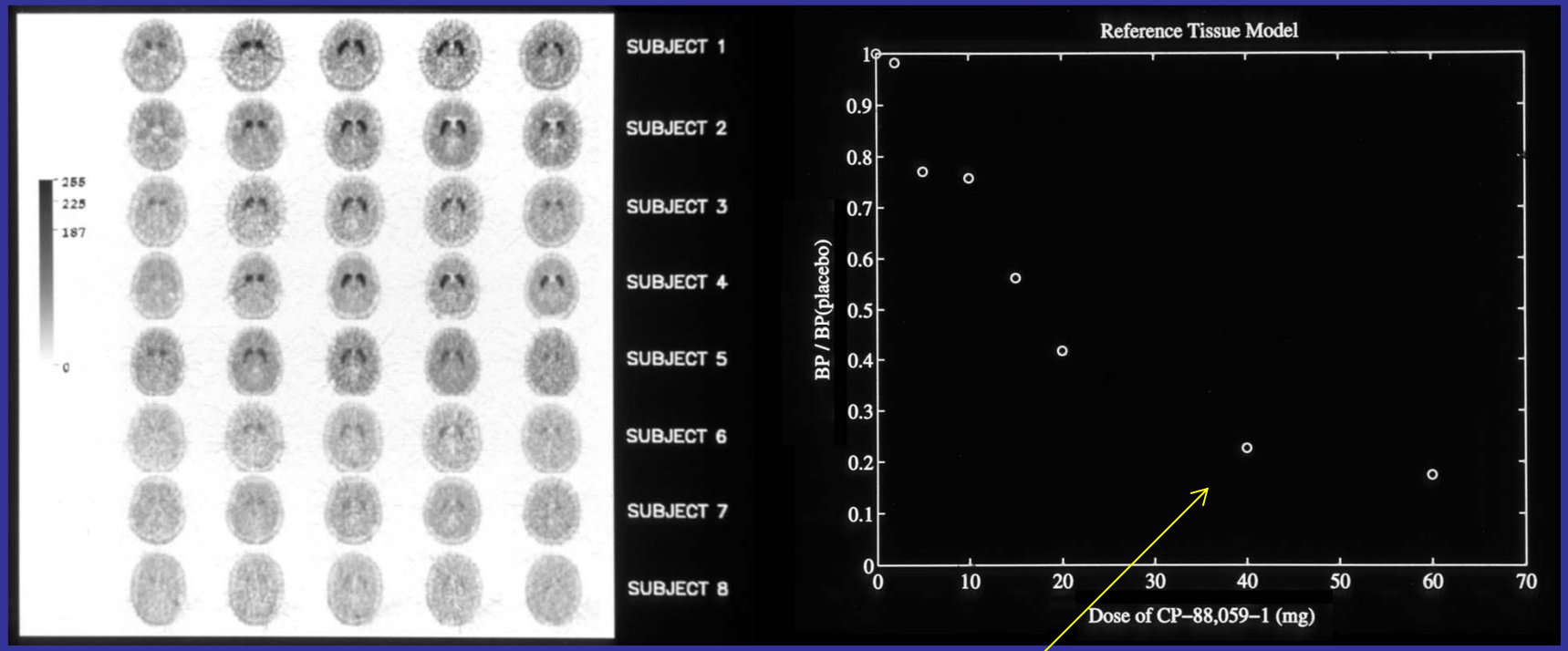
5 hours before PET scanning

- 1 subject placebo
- others: 2-60 mg ziprasidone

[^{11}C]raclopride: Simplified reference tissue model

Dose Selection: Ziprazidone

D_2 receptor occupancy



Selected dose

Bench et al., *Psychopharmacology* (1993) 112:308-314

Dosing Regime: Ziprazidone

Purpose:

To assess the time course of binding of ziprasidone to striatal dopamine D_2 receptors in order to determine the optimal dosage regimen

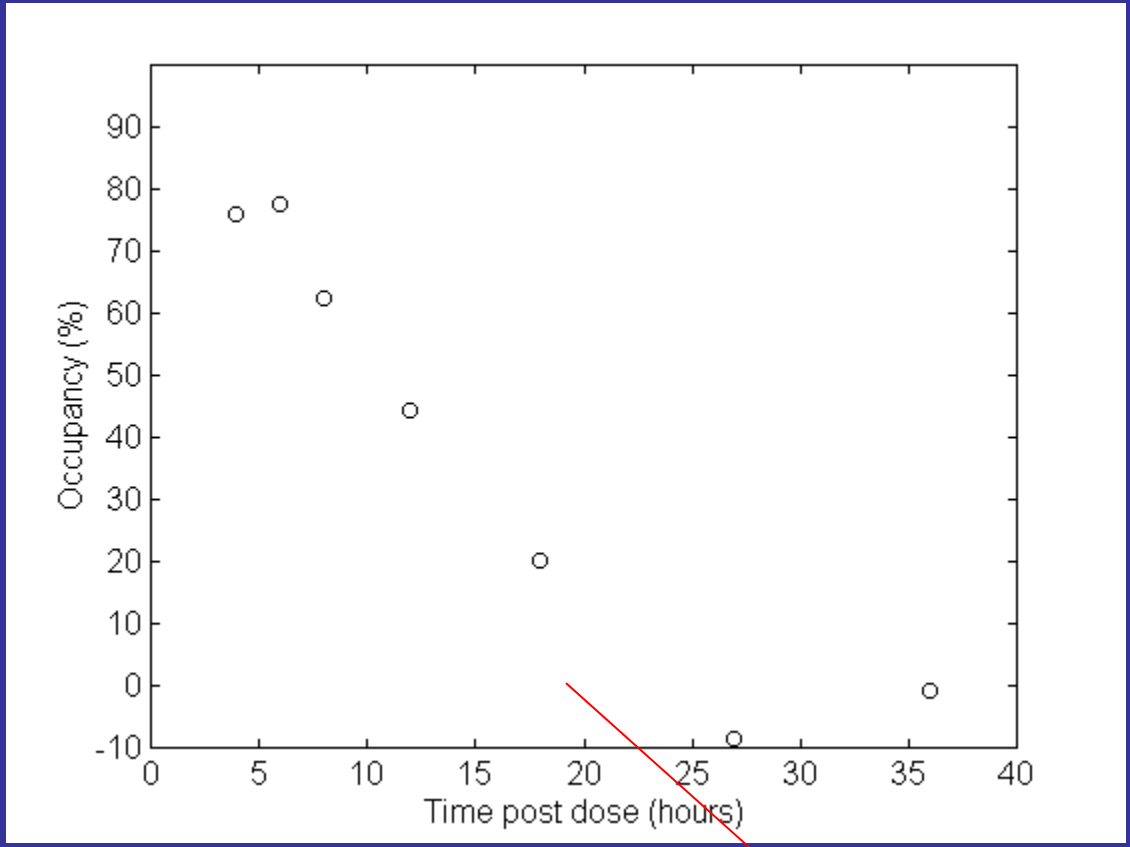
Methods:

7 healthy male volunteers

- 20 to 33 years of age
- 1 subject placebo, 4 hours before scanning
- others: 40 mg ziprasidone
  - 4-36 h before PET scanning

[^{11}C]raclopride: simplified reference tissue model

Dosing Regime: Ziprazidone



Twice daily

Data from Bench et al., *Psychopharmacology* (1996) 124:141-147

MAO-B Inhibition Study

Purpose:

To determine the minimum dose of the reversible inhibitor Ro 19-6327 needed to inhibit >90% of brain MAO-B

Methods:

8 healthy male volunteers

12 h before PET scanning

– 1 subject: 20 mg *(L)*-deprenyl

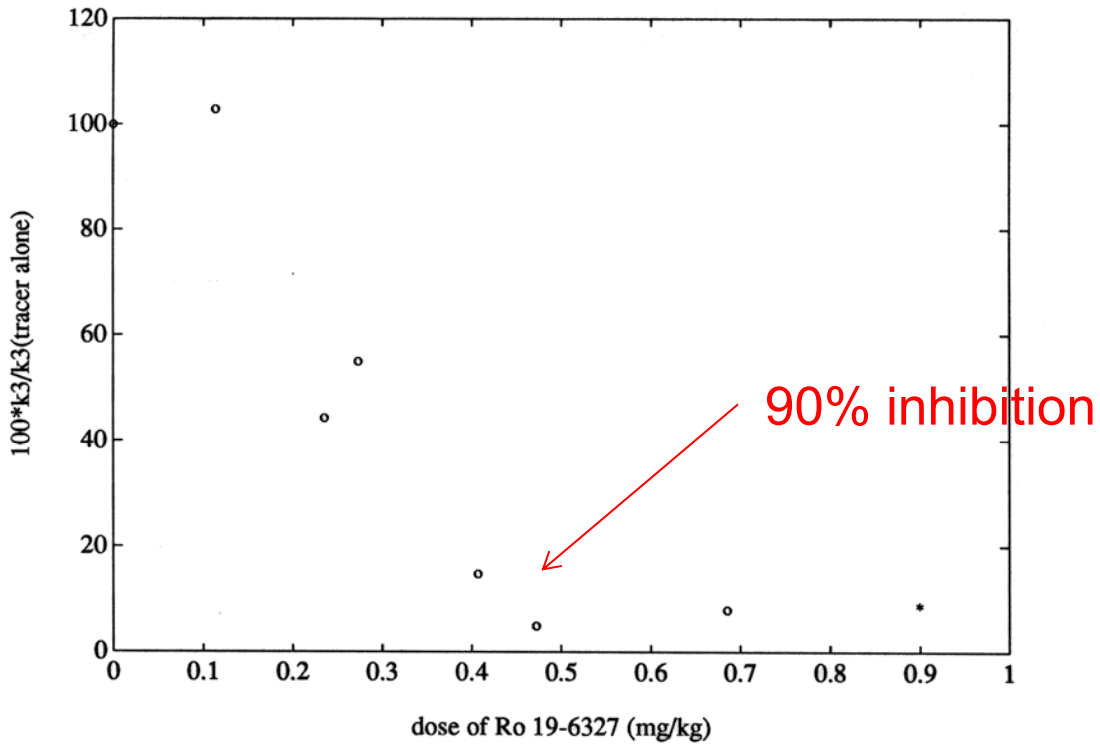
– 6 subjects: 10-50 mg Ro 19-6327

(L)-[^{11}C]deprenyl

Suicide inhibitor of MAO-B → Irreversible plasma input model

Uptake measure of MAO-B activity

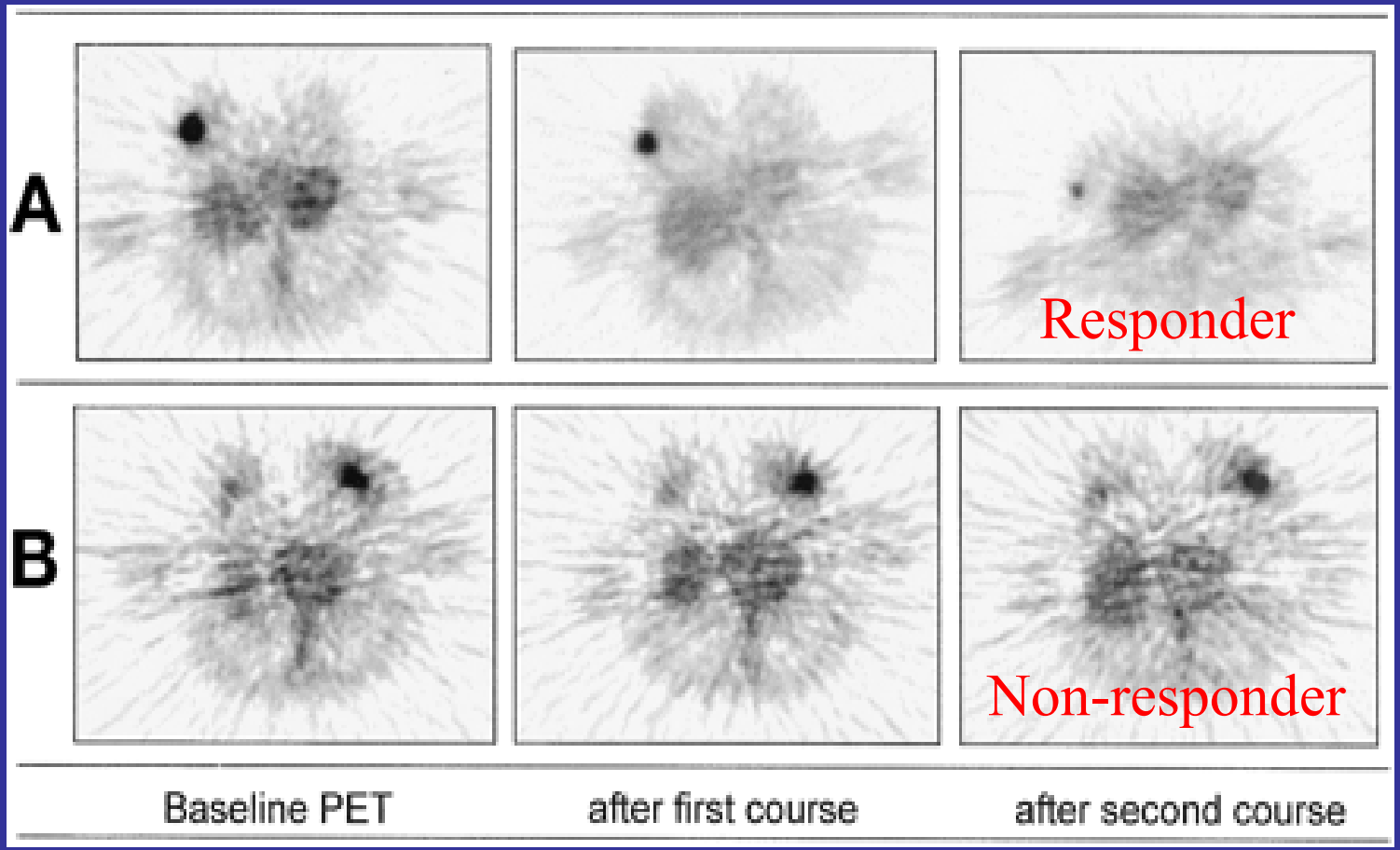
Deprenyl: Dose Response (k_3)



Lammertsma et al. (1991) *J Cereb Blood Flow Metab* **11**: 545-556.

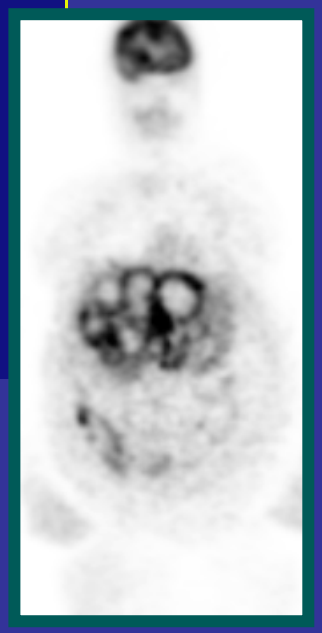
Response Monitoring

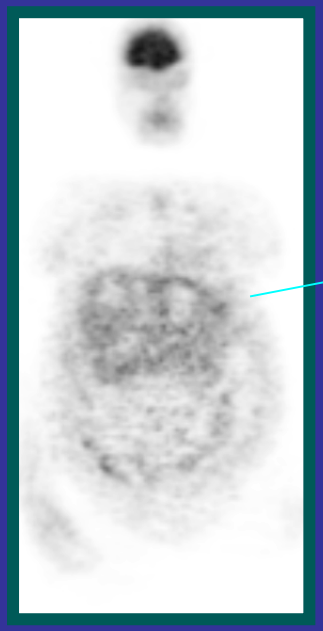
FDG Response Monitoring



Schelling et al. JCO 2000

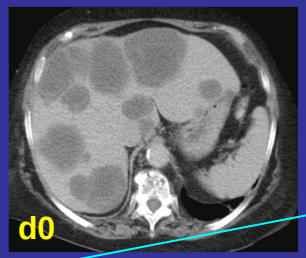
FDG Response Monitoring

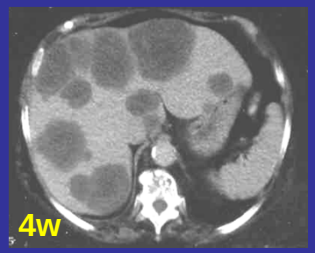




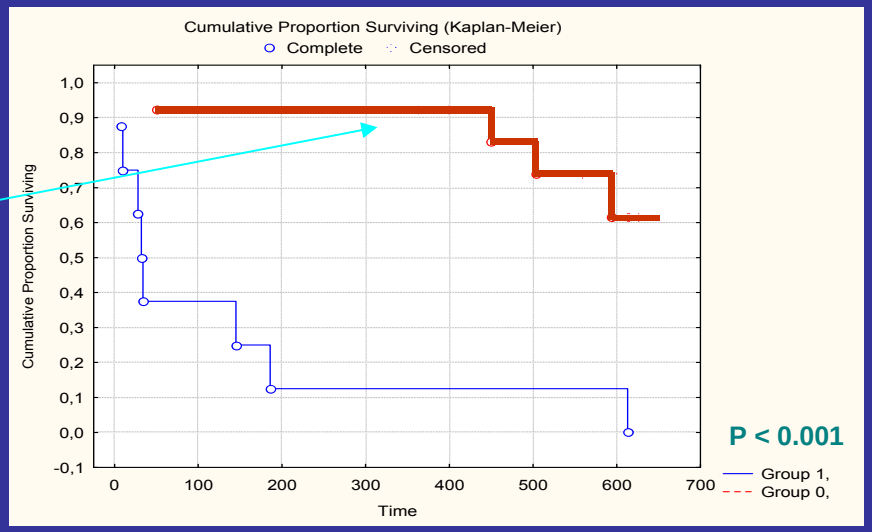
d0 d8

FDG





CT

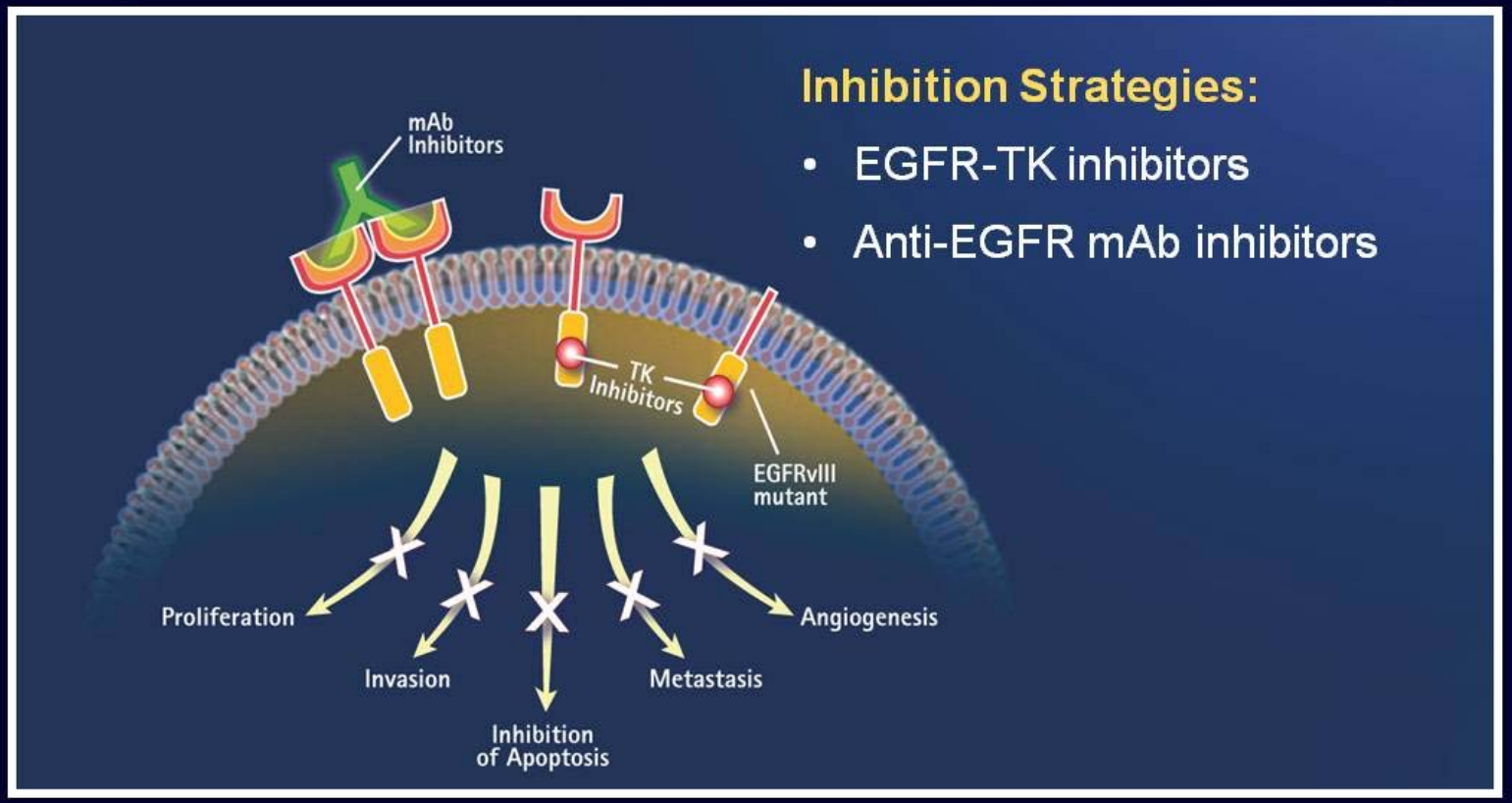


Assessment early during therapy

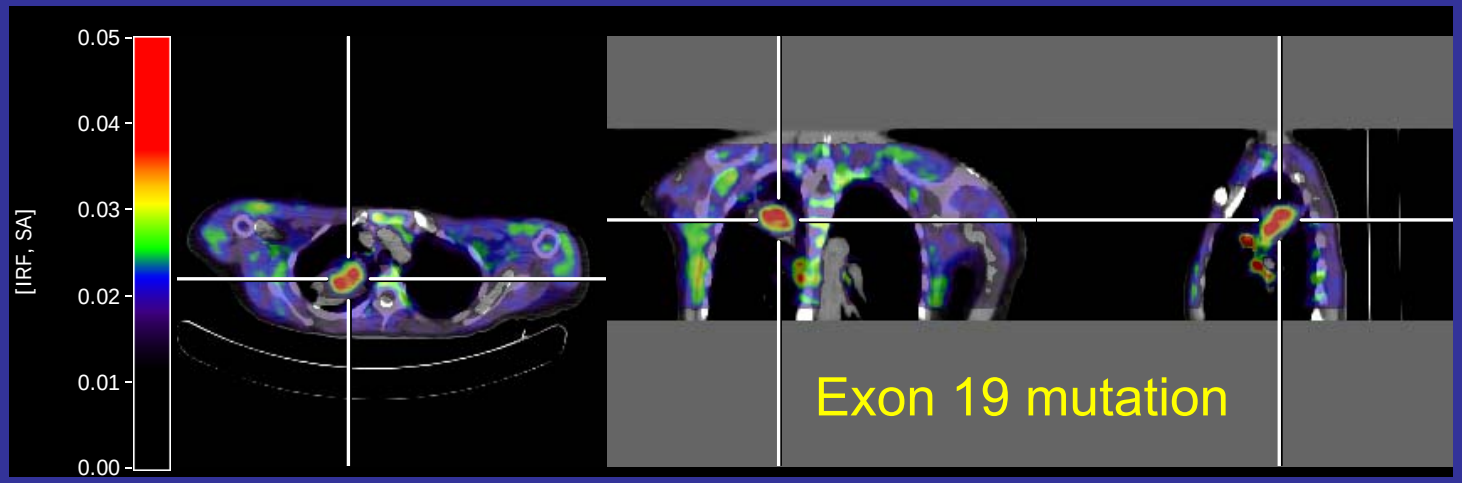
Response Prediction

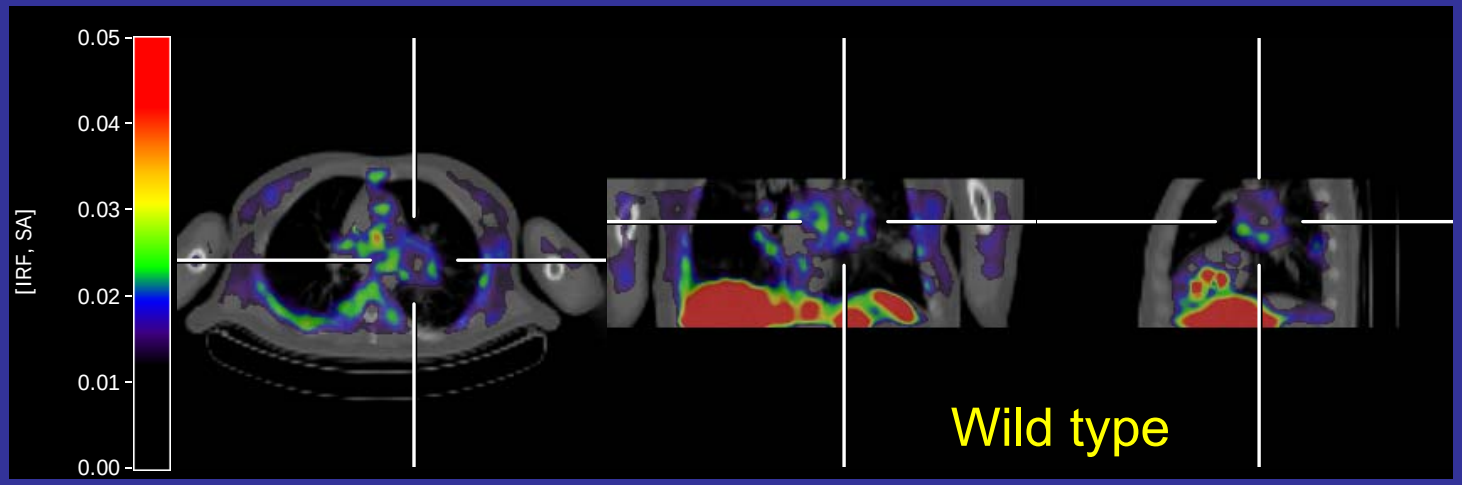
Erlotinib

The EGFR Axis



[^{11}C]*methyl*-erlotinib in NSCLC





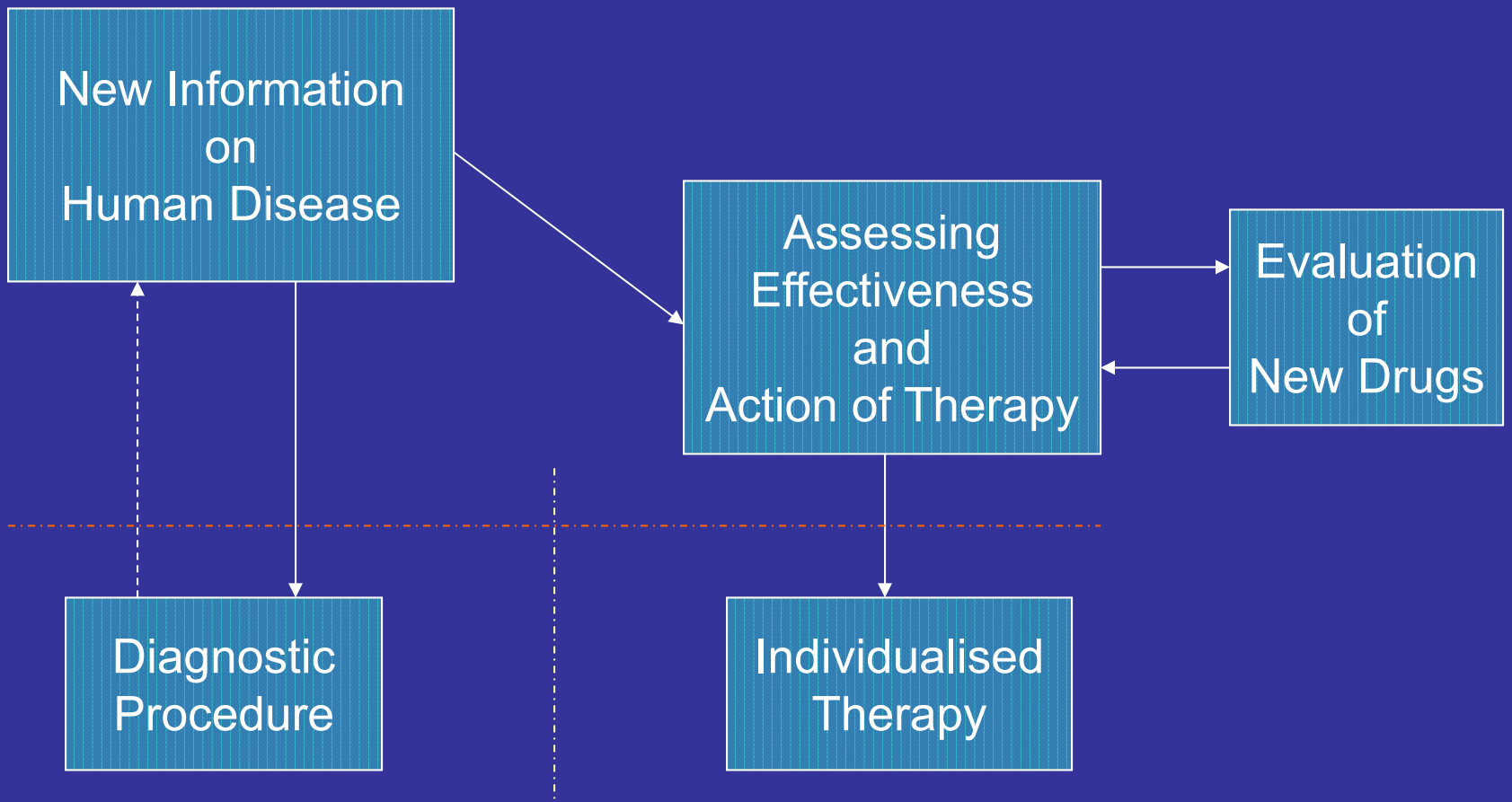
Data Bahce et al.

Summary

PET in Drug Development

- **Establishing optimal dose for larger trials**
  - Avoid a too low dose: no therapeutic effect
  - Avoid a too high dose: unnecessary side effects
- **Determining optimal dosing regimes**
  - Avoid trials with unsuitable drugs (kinetics too fast)
- **Monitoring response early during trial**
  - Earlier assessment of therapeutic effect
  - Read out of tumour biology (rather than anatomy)
- **Prediction of response**
  - Selection of target population for clinical trial

Positron Emission Tomography



Development of a PET tracer

Bert Windhorst
Radiopharmaceutical chemist

Outline

Route of PET tracer development

Process discussed as a case: [^{11}C]R116301

Critical steps - 1

Radiochemistry

- Selection and design and synthesis of lead compounds
- Optimization of pharmacokinetic properties
- Radiolabeling with suitable radionuclide

Preclinical evaluation

- Binding characteristics on cells and membranes or autoradiography
- Small animal: ex vivo biodistribution, (*in vitro*, *ex vivo*) autoradiography
- Distribution and metabolism studies in rats with preclinical PET imaging

Critical steps - 2

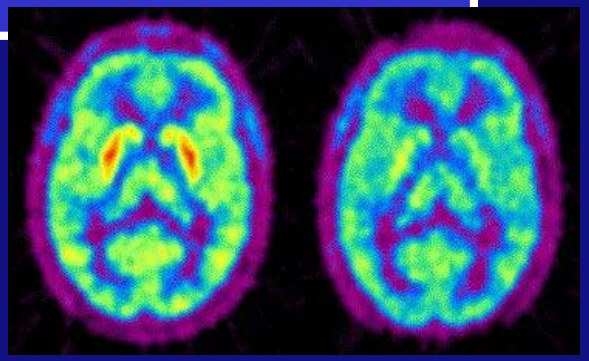
Clinical evaluation

Toxicological safety assessment. (microdosing concept)

Set up GMP production

Validation of PET tracer in human volunteers, including dosimetry studies, Typically N=6-12

Proof of concept: 10 patients vs 10 controls



Suited for clinical applications

Target compound : R116301

R116301 characteristics

Pharmacology

High affinity for human NK1 receptors : K_D = 0.08 nM
R116301 is a selective NK1 antagonist
Subnanomolar affinity for the guinea pig, gerbil
and ferret NK1 receptor
Anxiolytic activity in gerbils (0.1-2.5 mg/kg s.c.)

Toxicology

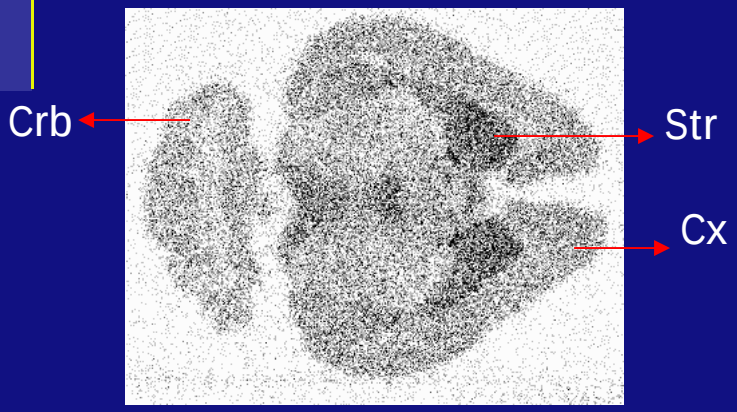
No toxicological effects found in several species

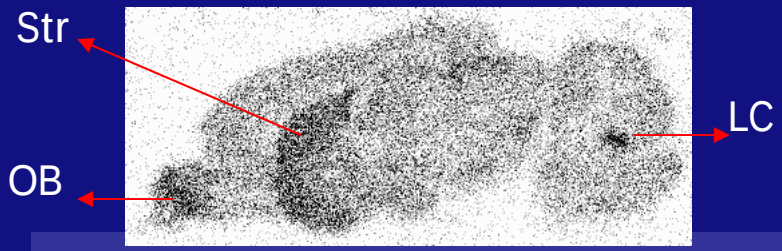
Phase I clinical data

Well tolerated (up to 600 mg) and has anxiolytic like properties

Pharmacology

Ex vivo autoradiography [^{3}H]R116301 (gerbil)

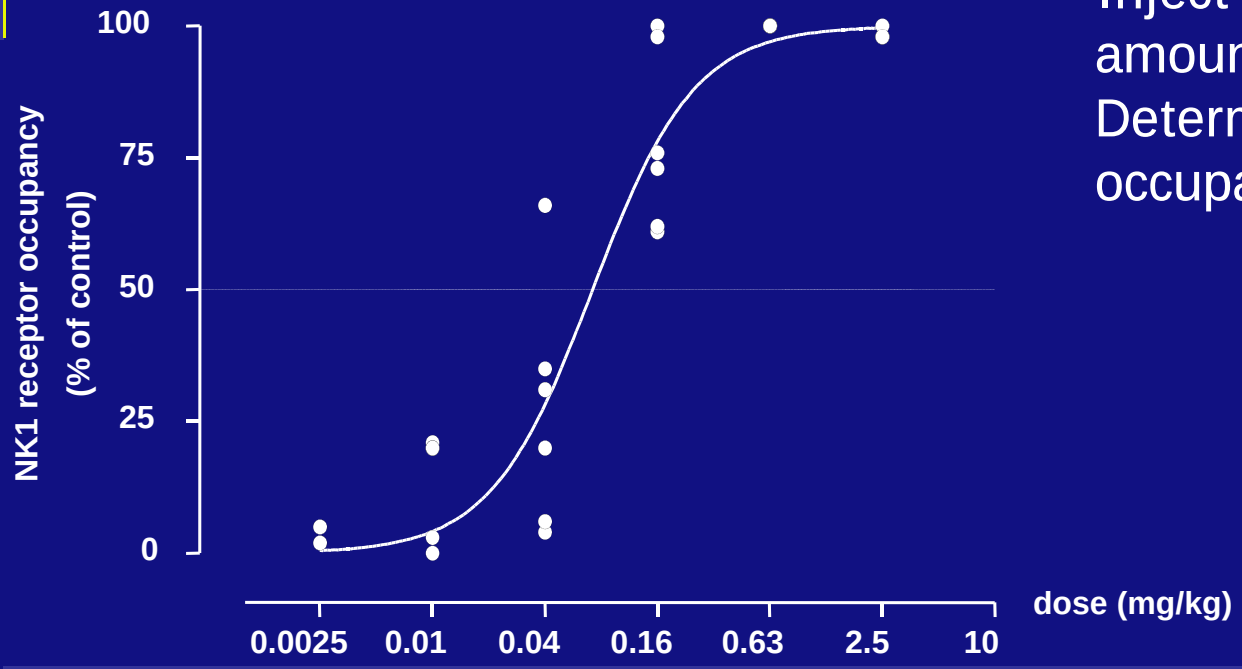




Inject gerbil with [^{3}H]R116301
Dissect brain after 1 hour
Slice brain in 20µm slices
Determine radioactivity
Measure of :
- Uptake in the brain
- Regional distribution

Pharmacology

Ex vivo receptor binding [^{3}H]subP (gerbil striatum)



Inject gerbils with different amounts of R116301
Determine receptor occupancy

Radiolabeling R116301

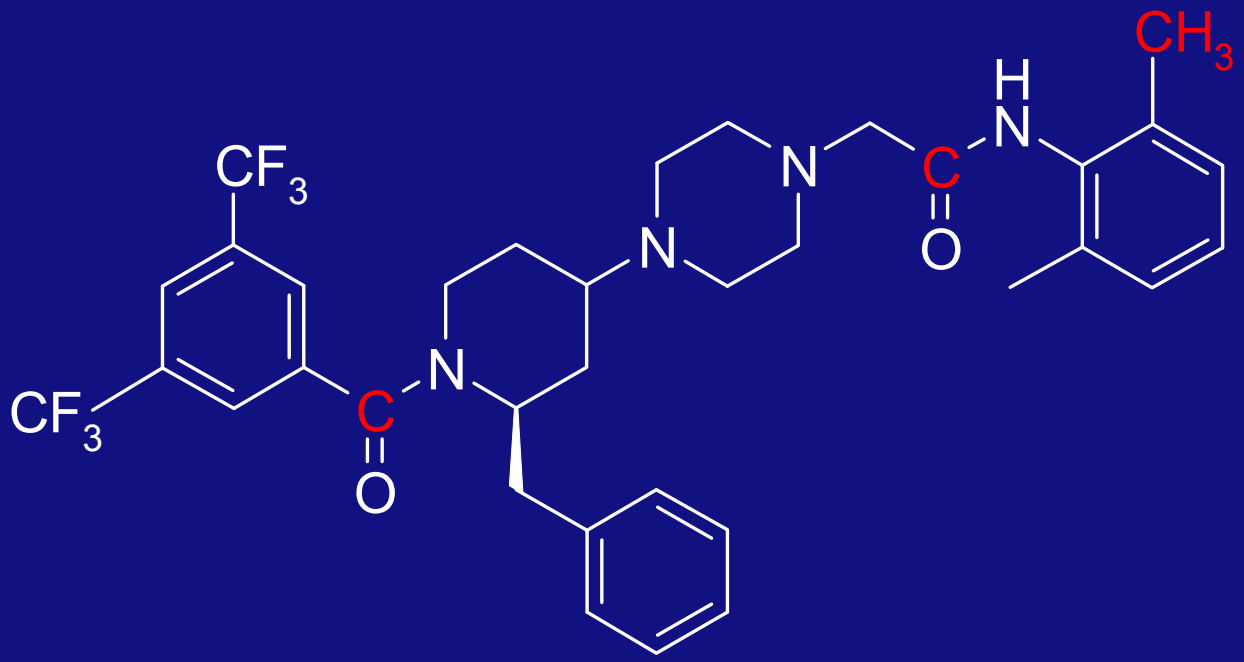
Strategy : labeling possibilities

Radiolabeling R116301

Strategy : labeling possibilities

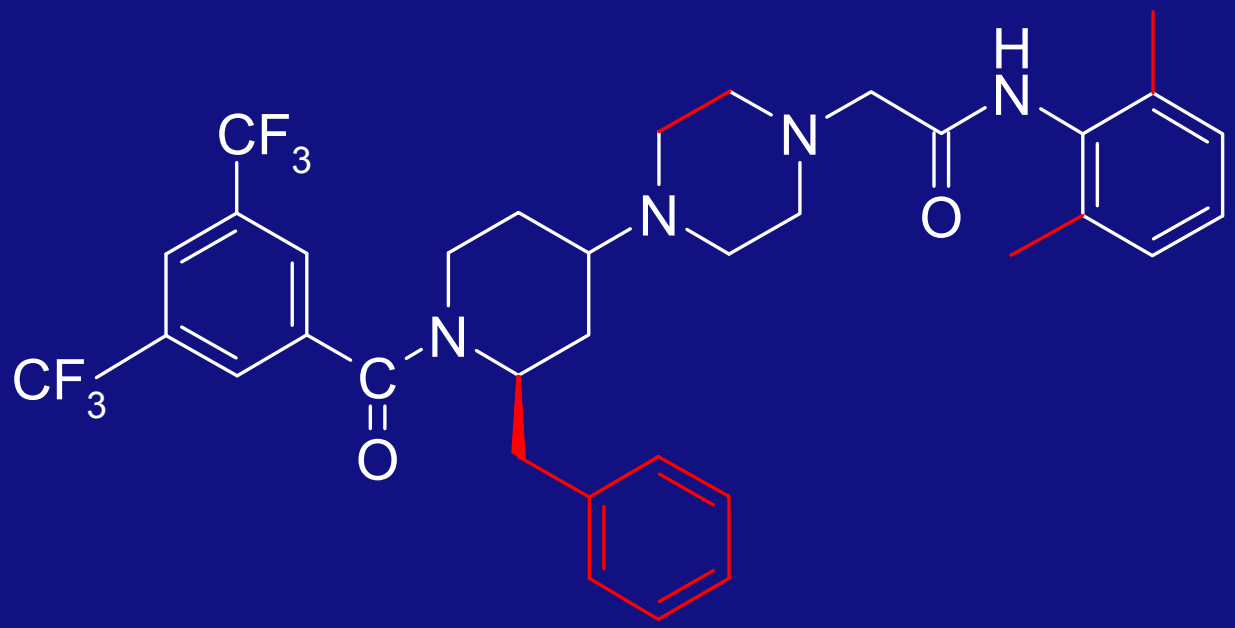
Radiolabeling R116301

Strategy : labeling possibilities



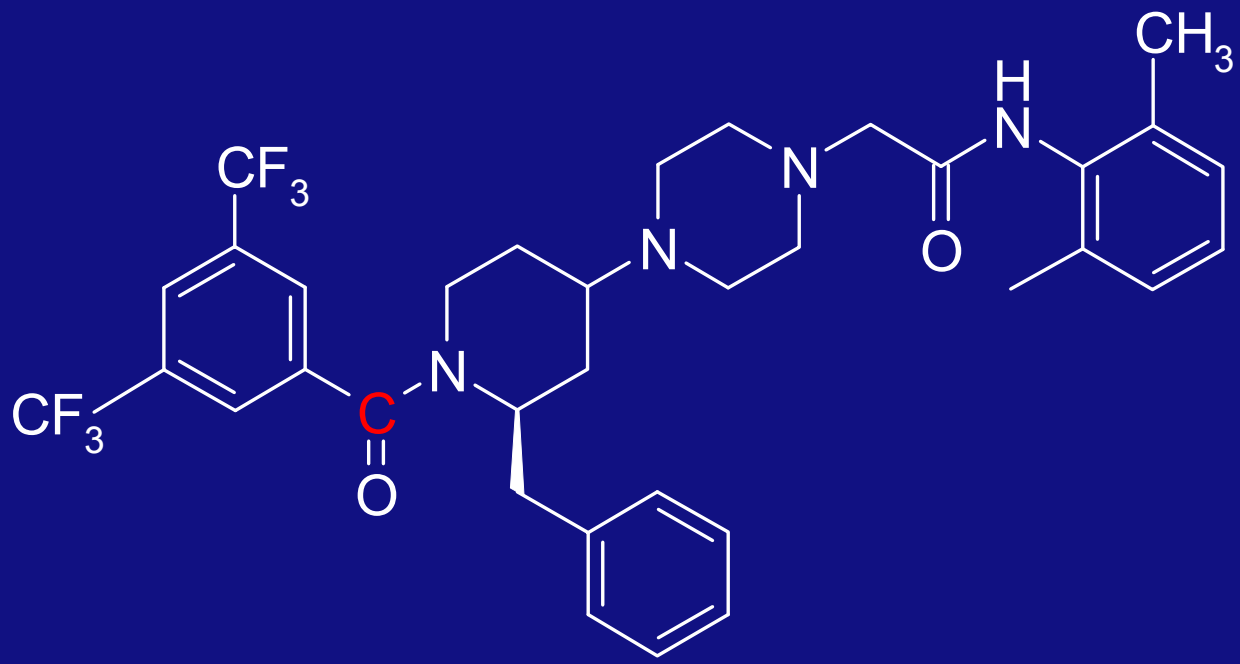
Radiolabeling R116301

Strategy : metabolism

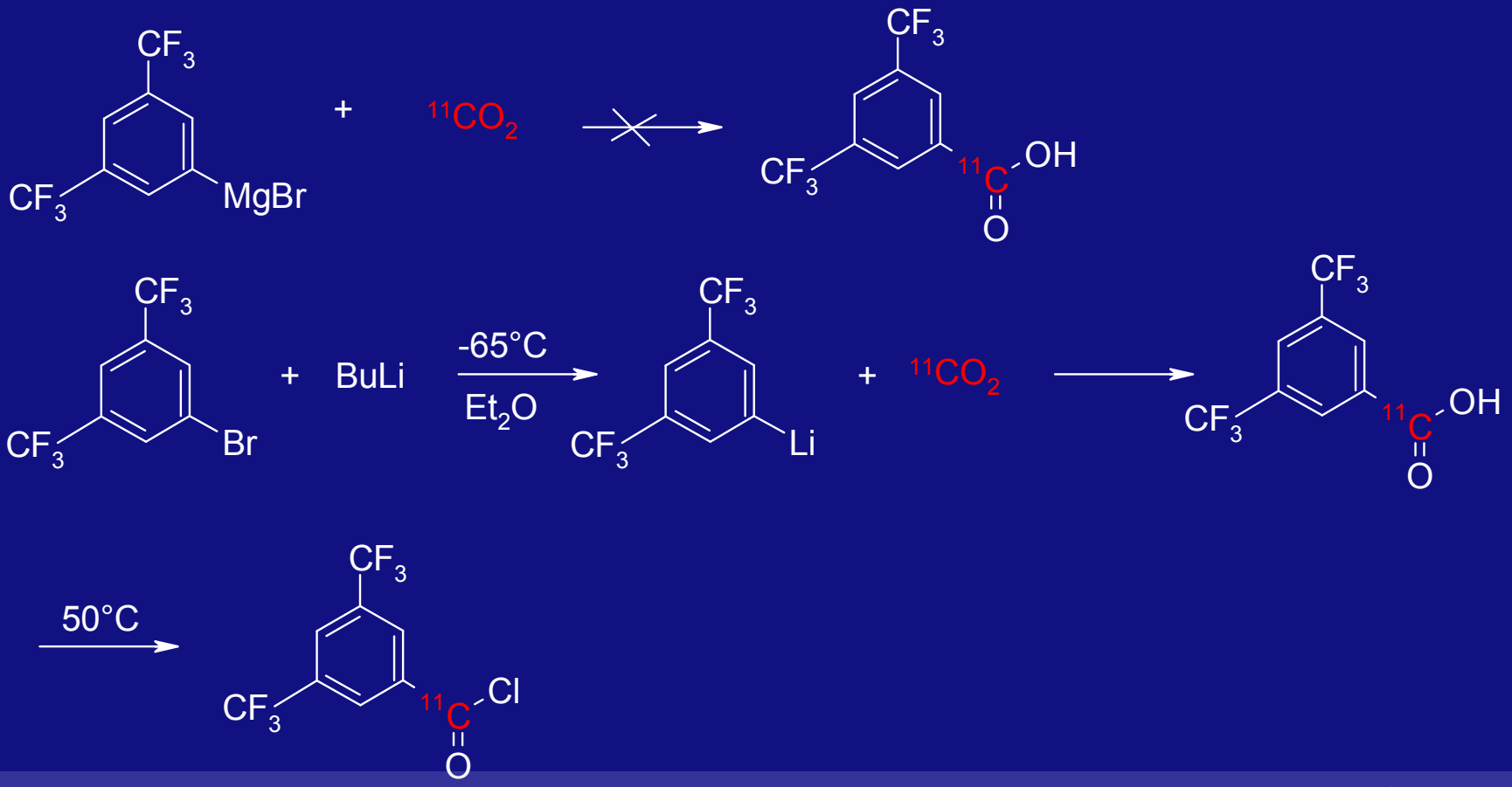


Radiolabeling R116301

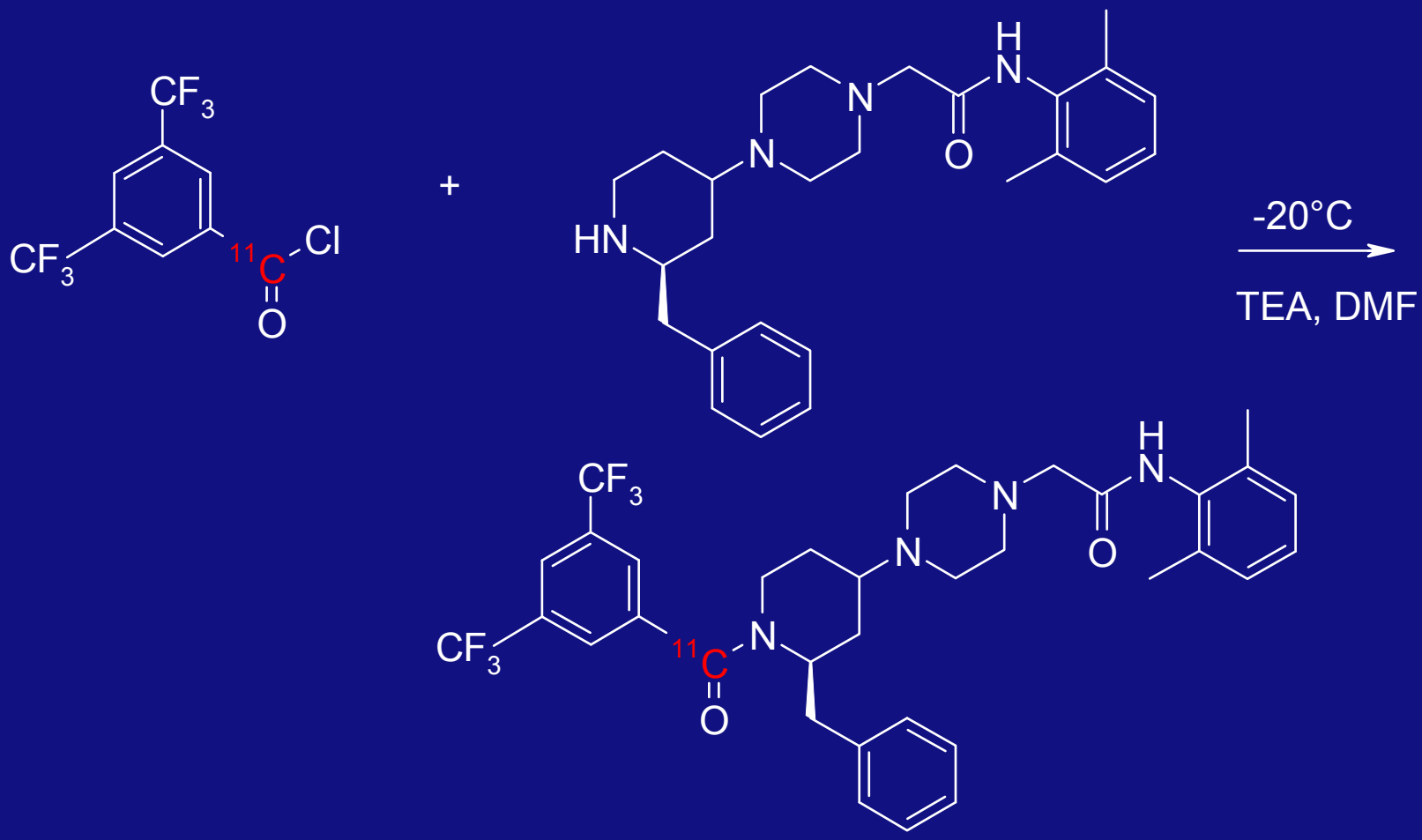
Selected position



Radiosynthesis



Radiosynthesis

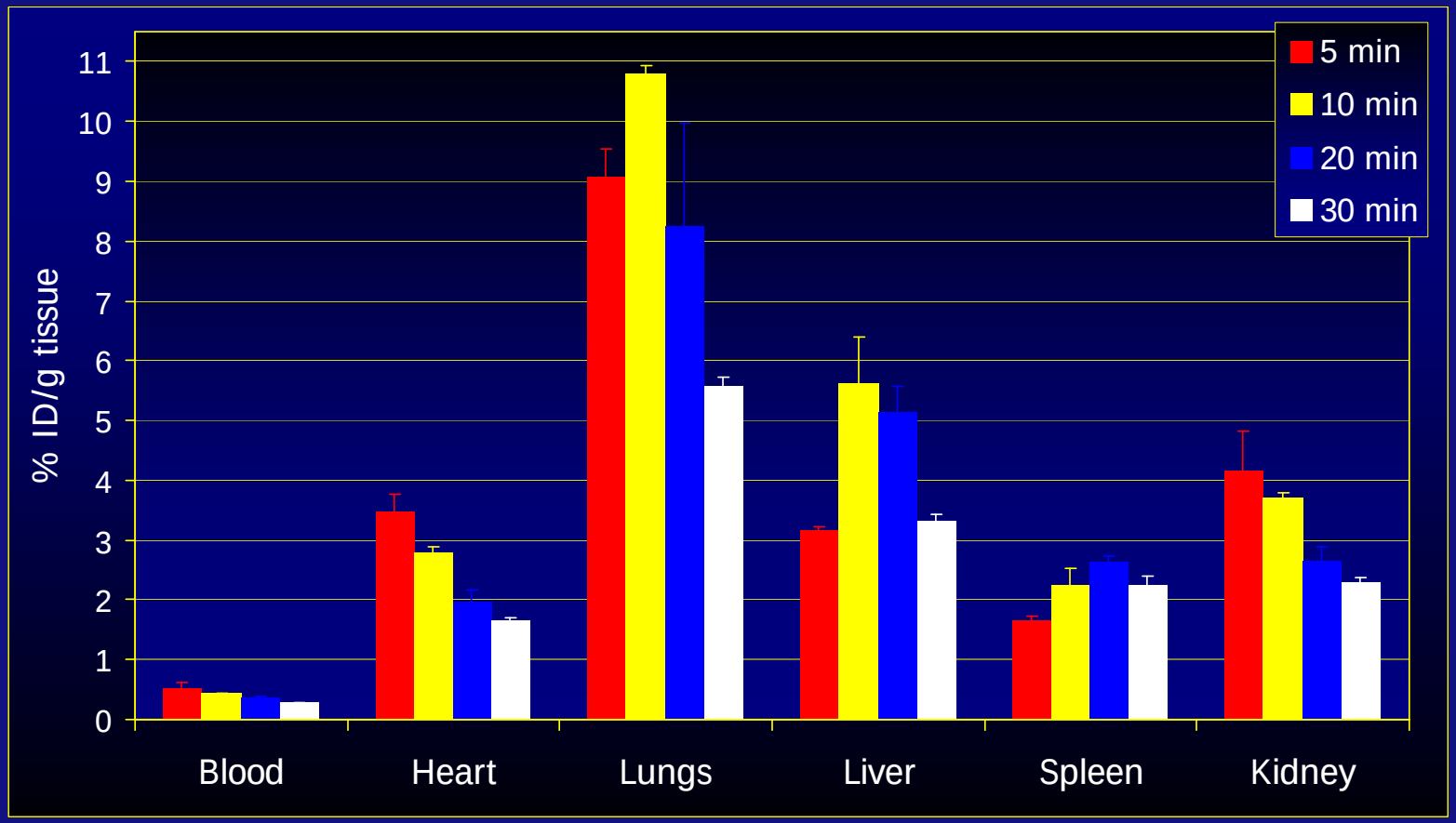


Ex vivo biodistribution

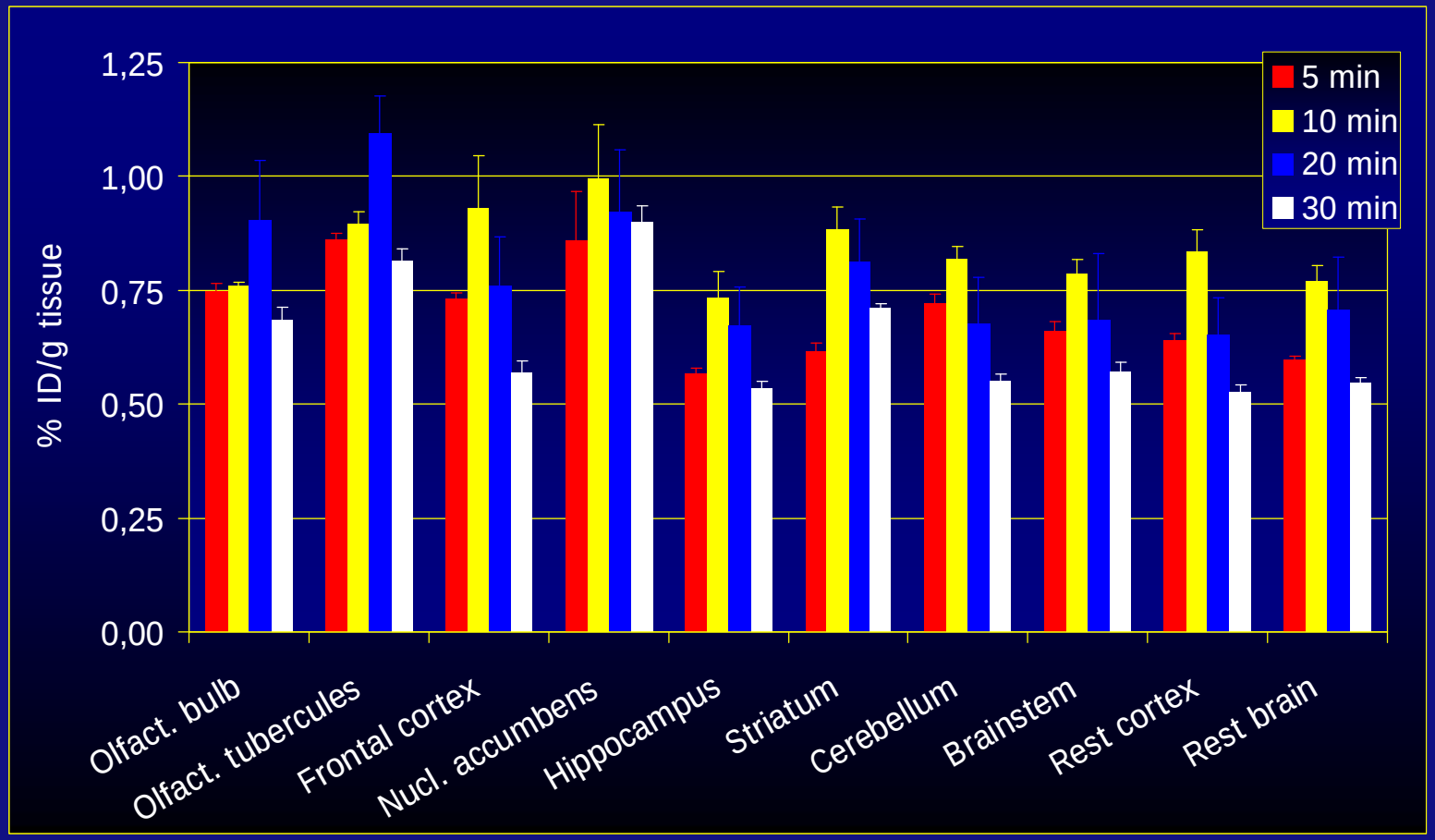
Inject gerbil with 40 MBq of [^{11}C]R116301
Dissect brain at selected timepoints
Determine amount of radioactivity
Correct for weight of organ

Results in % of the total injected dose per gram

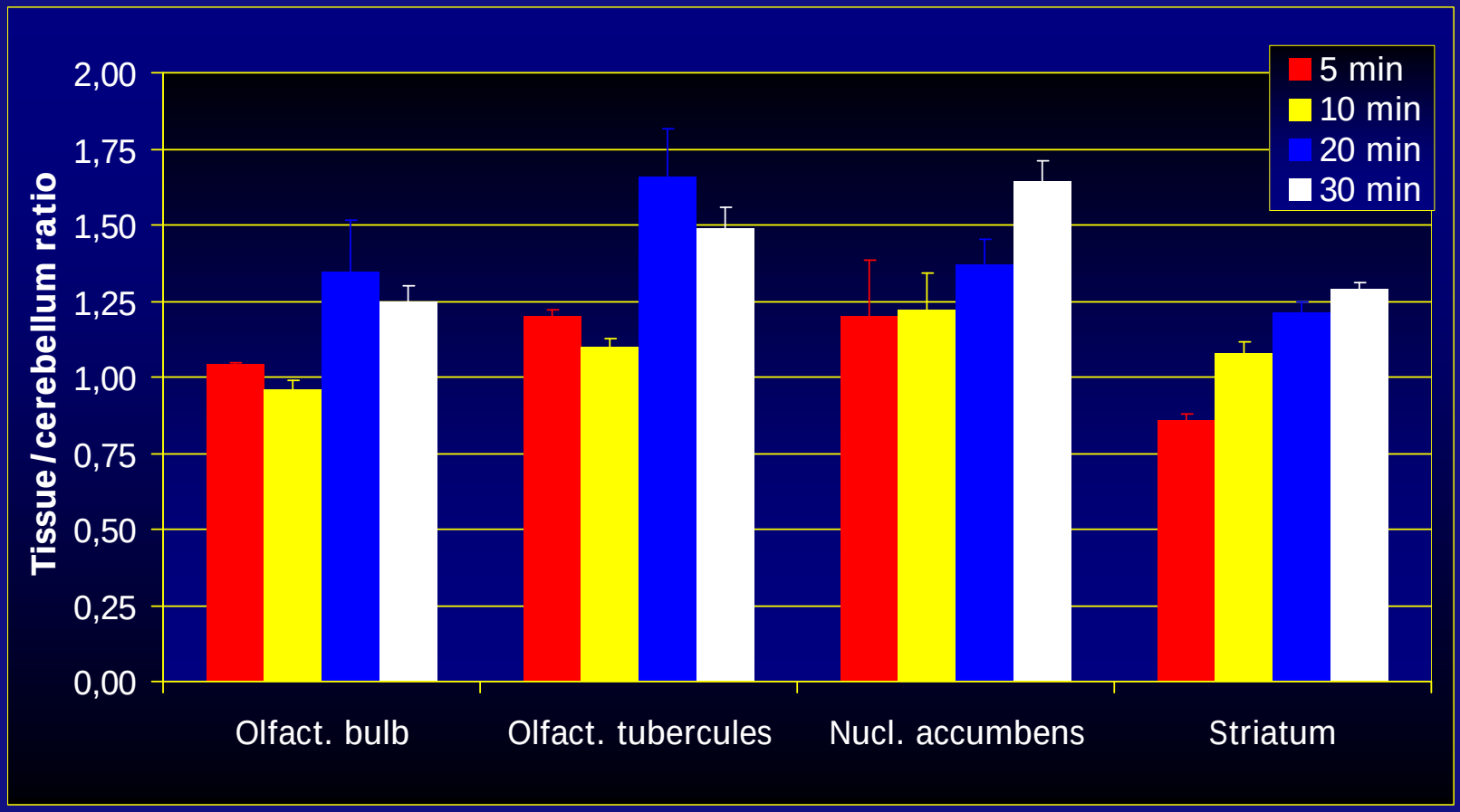
Peripheral distribution



Cerebral distribution



Target vs non target regions



Microdosing toxicity

According to EMA guideline 'microdosing' *(CPMP/ICH/286/95, June 2009)*

Table 3 Recommended Non-Clinical Studies to Support Exploratory Clinical Trials

Clinical:		Non clinical:		
Dose to be Administered	**Start and Maximum Doses**	**Pharmacology**	**General Toxicity Studies[a]**	**Genotoxicity[b] / Other**
Approach 1: Total dose ≤ 100 µg (no inter-dose interval limitations) AND Total dose ≤ 1/100th NOAEL and ≤1/100th pharmacologically active dose (scaled on mg/kg for i.v. and mg/m^2 for oral)	Maximal and starting doses can be the same but not exceed a total accumulated dose of 100 µg	*In vitro* target/ receptor profiling should be conducted Appropriate characterization of primary pharmacology (mode of action and/or effects) in a pharmacodynamically relevant model should be available to support human dose selection.	Extended single dose toxicity study (see footnotes c and d) in one species, usually rodent, by intended route of administration with toxicokinetic data, or via the i.v. route. A maximum dose of 1000-fold the clinical dose on a mg/kg basis for i.v. and mg/m^2 for oral administration can be used.	Genotoxicity studies are not recommended, but any studies or SAR assessments conducted should be included in the clinical trial application. For highly radioactive agents (e.g. PET imaging agents), appropriate PK and dosimetry estimates should be submitted.

Microdosing toxicity

Summary

2 week tox with 1000 x expected dose in rats

- 1 group sacrified after 24 hr (male and female)
- 1 group sacrified after 2 weeks (male and female)
- Assess: clinicial chemistry and pathology

To be performed in GLP certified lab

GMP

Good Manufacturing Practice

clinical trials directive: 2001/83

GMP directive: 2003/94

Requires full Quality Management, focus on

Clean room technology

Annex 3, radiopharmaceuticals

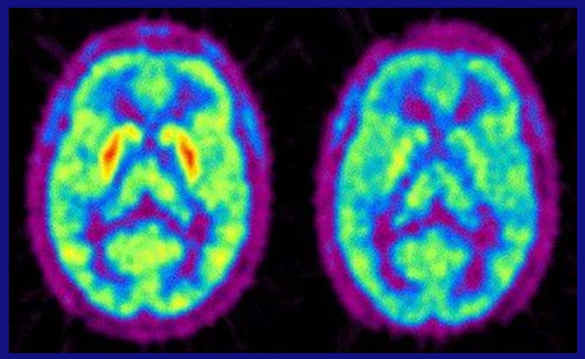
Validation

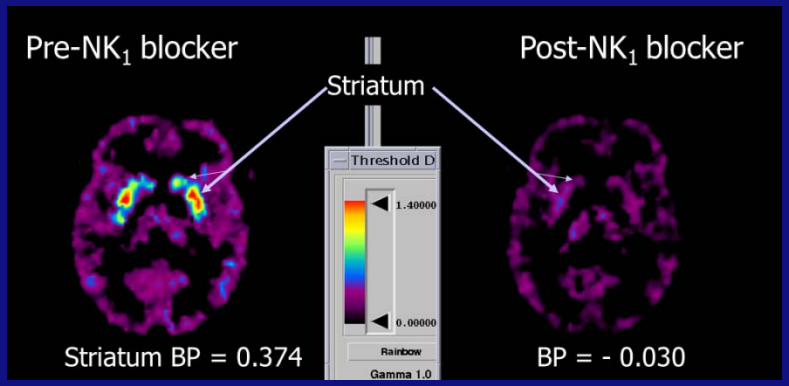
GMP cleanroom

Radiochemistry results

Yield : 600-2200 MBq (at time injection)
10-35 % (cfd)
SA : 28-69 GBq/µmol (at time injection)
Purity > 98%
Sterile, isotonic, pyrogen free

[^{11}C]R116301 PET:





Considerations

Selection of lead compound:

if required and possible: perform additional studies

Labeling position:

avoid radiolabelled metabolites acting at the same binding site

Animal research:

focus on final goal: human application. Distribution, metabolism, dosimetry.

Microdosing toxicity:

could be relatively costly

GMP compliancy:

certified lab is essential

Updated US FDA Regulation for PET Drugs

Will Lee
Vice President, Regulatory Affairs
Cato Research

Overview

- Recent History
- New Rule Effective
  - June 12, 2012
- Stakeholders
- Overview of PET Regulations

History (1)

- Food and Drug Modernization Act of 1997 provided that FDA establish regulations for PET drugs
  - Approval procedures
  - Current Good Manufacturing Practices (cGMP) requirements

History (2)

- FDA received numerous requests to extend the submission deadline of NDA and ANDAs
- In 2009, FDA finalized the procedures and requirements for PET drugs
  - Mandated that within 2 years, a facility must submit an NDA or ANDA for any PET drug marketed for clinical use

History (3)

- FDA was concerned about preventing access to PET drugs
  - On December 6, 2011 FDA provided a notice of FDA Exercise of Enforcement Discretion of PET Drugs
- FDA will NOT exercise enforcement discretion of PET drugs for clinical use after June 12, 2012

New Rule

- If a facility produces PET drugs for clinical use after June 12, 2012
  - By June 12, 2012 it must submit:
    - NDA
    - ANDA
    - IND (Expanded Access)
  - By December 12, 2015 all producers of PET drugs must be operating under an approved NDA or ANDA, or effective IND

Stakeholders

- Physicians using PET drugs in clinical practice
- Facilities that produce PET drugs
- Investigators using PET drug for basic science research
- Sponsors testing investigational new drugs with PET drugs

Clinical Use

Definition of Clinical Use

- Component of current clinical care
- No intent to systematically study safety or effectiveness of the drug

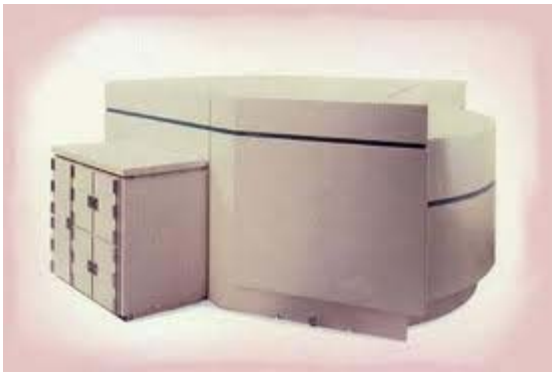
Clinical Use of PET Drugs

- PET scanning with fludeoxyglucose (FDG), called FDG-PET, is widely used in clinical oncology
  - Explore the possibility of cancer metastasis

Physician Obligation

- Physicians using PET drugs in clinical practice
  - Submit nothing to the Local or National Regulatory Bodies

Manufacturing Facility



Facilities that produce PET Drugs (1)

- For the following PET drugs
  - Fludeoxyglucose F18
  - Sodium Fluoride F18
  - Ammonia N13
  - Rubidium chloride Rb82
- Submit NDA or ANDA

Facilities that produce PET Drugs (2)

- For the following PET drugs
  - Carbon monoxide C11
  - Fluorodopa F18 inection
  - Flumazanil C11 injection
  - Mespiperione C11 injection
  - Methionine C11 injection
  - Raclopride C11 injection
  - Sodium acetate C11 injection
  - Water O15 injection
- Submit Expanded Access IND or NDA

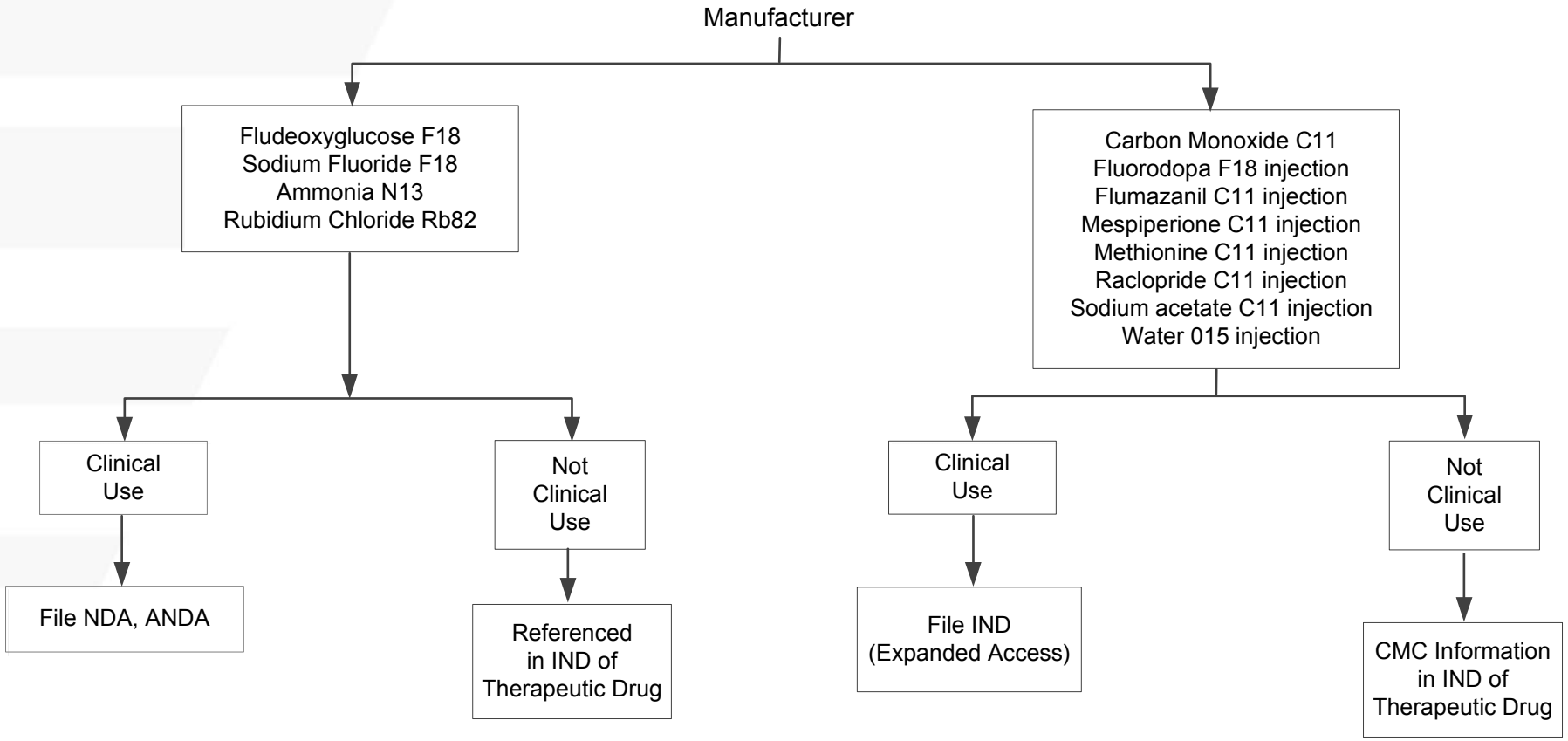
IND (Expanded Access)

- Expanded Access:
  - Certain PET drugs already in clinical use
  - Primary purpose is to diagnose or monitor serious disease/condition in patients without active disease manifestation
  - Rare usage makes it commercially unfeasible and does not justify submission of NDA/ANDA

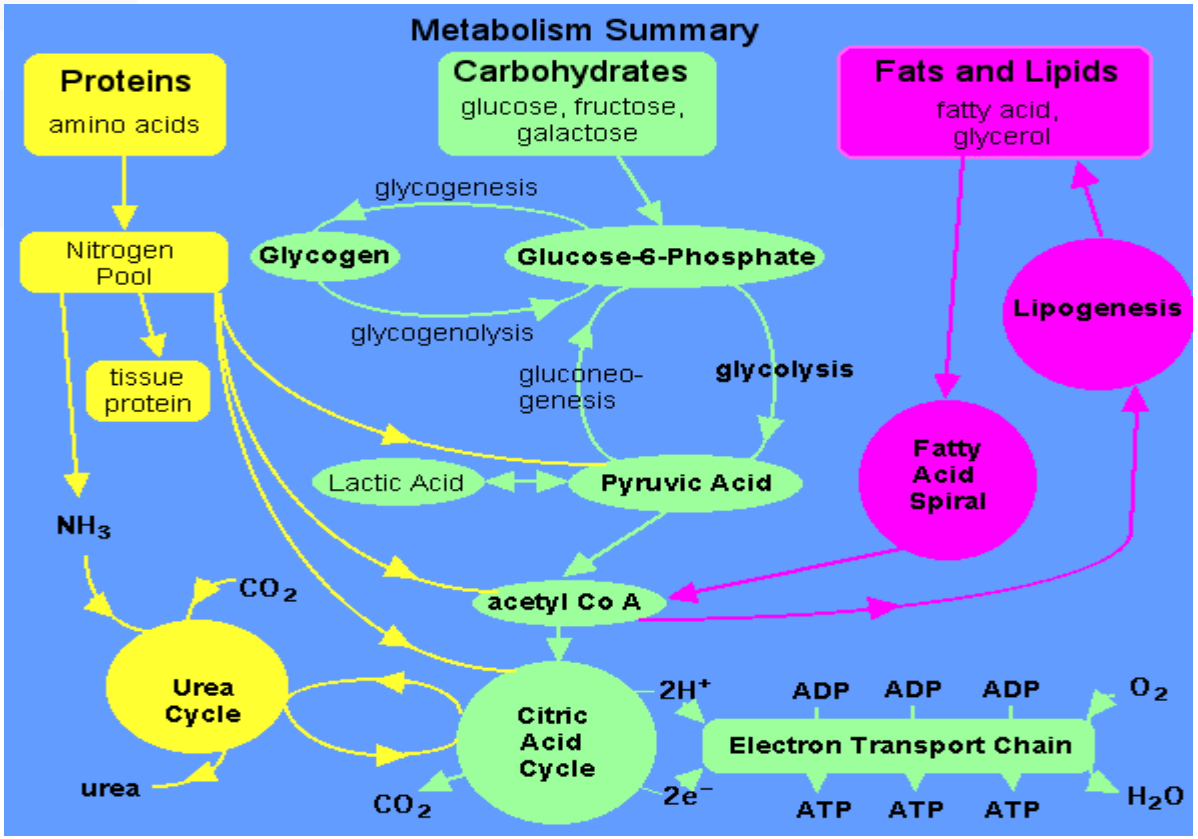
IND (Expanded Access)

- Use of the PET drug by the institution producing the PET drug is limited to use within that institution
- Very short half-life of the isotope and use in a small niche population of the PET drug
- Comply with USP Monograph or 21 CFR 212

Manufacturer Obligation



Basic Research



Definition of Research Use

- Basic science research
- Not using for immediate therapeutic, or diagnostic purpose
- No intent to determine safety or effectiveness for clinical use
- Dose not known to cause any pharmacologic effect
- Radiation dose within specific limits

Example of Basic Research

- Metabolism of a neuropeptide to investigate its role in physiology, pathophysiology and biochemistry
- Localization of the radioactive neuropeptide drug to a particular organ or fluid space and to determine the kinetics of localization

PET drug for Basic Science Research

- Obtain Radioactive Drug Research Committee (RDRC) approval
- IND is not required
- IRB approval is required

Biotech/Pharma

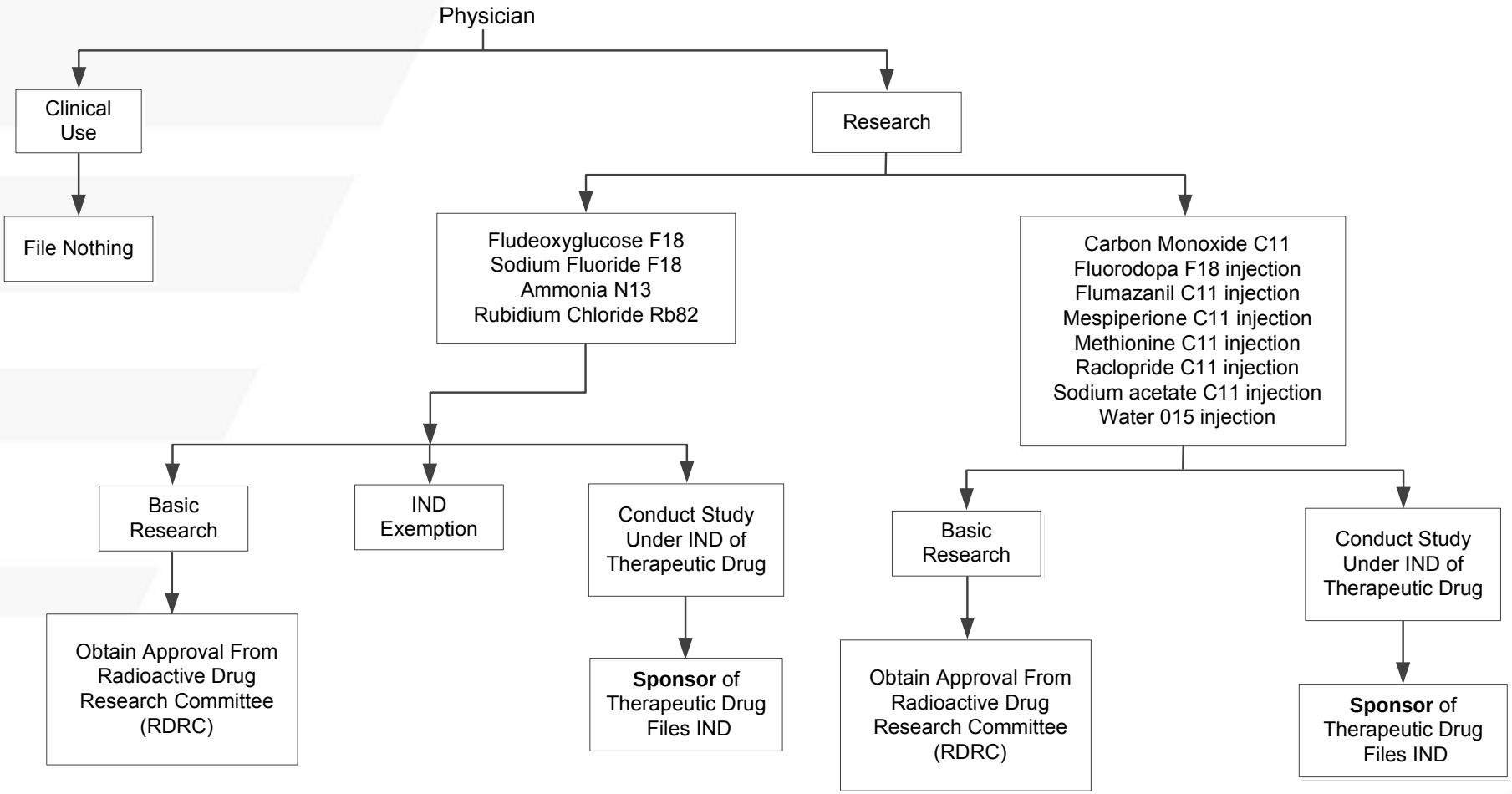
Sponsors testing Investigational New Drugs

- Conducting studies to determine the safety and effectiveness of a new PET imaging drug
  - Submit Traditional IND for the new PET Imaging drug
  - Submit Exploratory IND to test multiple candidate PET imaging drugs
    - Led to 2012 approval of F-18 Florbetapir for amyloid imaging

Sponsors testing Investigational New Drugs

- Monitoring progress of investigational new drug with PET imaging
  - PET drug is being made at a facility that has submitted an NDA or ANDA
  - IND Exemption - No requirement to submit IND until December 12, 2015

Physician/Researcher and Sponsor Obligation



Stakeholders (1)

- Facilities that produce PET drugs
  - Submit NDA, ANDA or Expanded Access IND
- Physicians using PET drugs in clinical practice
  - Submit Nothing
- Investigators using PET drug for basic science research
  - Submit to Radioactive Drug Research Committee

Stakeholders (2)

- Biotech/Pharma
  - Testing New PET Imaging Drugs
    - Submit Traditional IND or Exploratory IND
  - Testing investigational new drugs with PET imaging
    - Submit amendment to the IND for the investigational new drug
    - IND exemption for the PET drug with a submitted NDA or ANDA

Recap of Updated FDA Regulations

- After June 12, 2012
  - FDG, NaF, Ammonia, Rubidium chloride
    - Submit NDA/ANDA for Clinical Use
  - For all other PET drugs
    - Submit Expanded Access IND or NDA

QUESTIONS?

Free Educational Webinar

Critical Steps in PET Radiopharmaceutical Development and Updated FDA Regulations

THANK YOU

A copy of this presentation maybe downloaded at
Cato's Blog: www.ask-cato.com

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