Jerry Collins, FDA/CDER ACPS/NCSS Meeting 9-March-00

At the initial NCSS meeting (14-Dec-99), I suggested that the drug development process could be improved by the application of imaging technology. In particular, I emphasized noninvasive functional imaging with Positron Emission Tomography (PET) for unique pharmacokinetic and pharmacodynamic studies.

The limiting feature for PET use is the availability of suitable radiolabeled probes. Thus, a broad issue in imaging which needs to be resolved is:

What are the characteristics of a good PET imaging probe?

To move the field forward, how can the NCSS concept of a consortium of Academia/Industry/Government facilitate nonclinical aspects of PET imaging probe development?

In my view, the most effective strategy is to pick an area that is sufficiently mature that successful probe development seems likely, and to proceed with a demonstration project.

My recommendation today is that NCSS endorse the formation of an Expert Working Group for PET Imaging to select, design, and conduct a demonstration project.

In order to demonstrate that this field is ripe for immediate action, I'm describing today two areas as examples. The Expert Working Group could pick one of them for moving ahead. Alternately, if the members feel that there is an even more attractive opportunity in another area, that could be their recommendation.

As I mentioned at the 14-Dec-99 meeting, the two general application areas are:

- drug delivery to target (pharmacokinetics, PK)
- drug impact on target (pharmacodynamics, PD)

One example for each area is presented on next few pages of this document.

For the PK area, the next page explores the potential of PET imaging to determine the impact of modulators of drug delivery (transport). The P-glycoprotein efflux pump (a.k.a., MDR, a member of the ABC cassette transport protein family) is the prototype.

For the PD area, the third and fourth pages illustrate the use of thymidine analogs as PET probes for DNA synthesis. A variety of analogs have been tested at one or more stages of probe development: cell culture, rodents, dogs, and humans.

Is Drug Transport Important?

The Human Genome
50,000 - 100,000 genes

140,000 genes (Incyte, Sept.'99)

20% are transport proteins
(Doug Ross, Sept.'99)

Issue: **Efflux pumps in tumors push out anticancer drugs at varying rates.**
Tumors in a "homogeneous" patient population are a mixture of "fast" and "slow" effluxers.

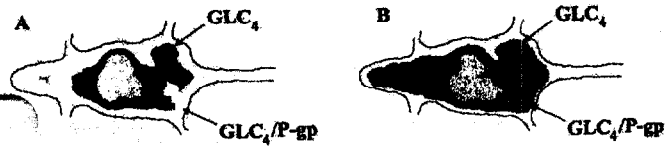
Impact: **Tumors with "fast" efflux fail to respond**

Potential Outcomes:

Can you pre-select potentially responsive tumors?

For potentially unresponsive tumors, can other maneuvers be tried?

Hendrikse, de Vries et al. Cancer Res (99)



Rat with 2 implanted tumors: one ("P-gp") resistant to due to P-gp overexpression.
Panel A: 11C-verapamil given by itself.
One hour later, a second dose of 11C-verapamil given with cyclosporin (Panel B).
Note effect on brain as well as tumor.

What Question Are We Asking?

Does an Adequate Amount of Drug Accumulate in the Tumor?

Caveat: **Accumulation of drug in the tumor is <u>essential</u>, but is <u>not</u> the sole determinant of chemosensitivity.**

Search for the "perfect probe" for efflux pumps *in vivo*

^{99m}Tc-sestamibi was the opening chapter, but need more sensitivity, better resolution, and more <u>relevance</u>

^{11}C-verapamil: better sensitivity, resolution

^{11}C-daunorubicin: *seems* more relevant

- **also, complicated by metabolism**

^{18}F-FDG: general utility, but *irrelevant* here

Analogy of efflux pump probes to CYP450:

- **goal: determine intersubject variability**
- **many substrates were known**
- **single probe sought**
- **single inhibitor sought**

Over the course of time, we realized that P-450 is a family of enzymes, characterized by:

- **different substrate specificities**
- **different inhibitor effects**

Current story for transport quite similar; we find a new pump almost every month...

Imaging Proliferation (DNA Synthesis)
Thymidine or Analogs

dTMP → → DNA
(TK) ↑
dThd

1. Direct use of circulating dThd for DNA synthesis provides a potential probe.
2. In the lab, when ^{3}H-dThd added, it's interpreted as "labeling-index" or "proliferation marker."
3. Can also use BUDR, IUDR, FIAU, FMAU.

Clinical Interest in ^{11}C-dThd for Imaging

1972 Christman	Initial Proposal
1988 Martiat	Tested in NHL
1992 van Eijkeren	Head & Neck
1994 Vander Borgt	Brain Tumors
1998 Shields	Lung Tumor

Thymidine as a Proliferation Marker

Drawback:

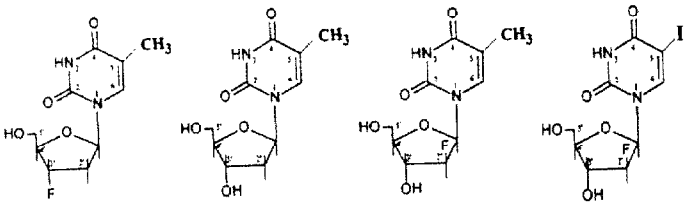
dThd →Thy → → bicarbonate; CO_2

Rapidly & extensively catabolized (radiolabeled products circulating as "background noise")

Practical Alternatives to dThd:

-- Must Block Catabolism
-- While Retaining Anabolism

PET Imaging: Proliferation Markers



FLT dThd (TdR) FMAU FIAU

CELL CULTURE DATA SHOWS:

dTMP → → DNA
(TK) ↑
dThd

FMAUMP → → DNA
(TK) ↑
FMAU

FMAU readily enters cells
FMAU phosphorylated by TK to FMAUMP
FMAUMP incorporated into DNA
Extract DNA,digest,measure FMAU by HPLC

Sample Images on Next Page:

^{11}C-dThd in human

^{124}I-FIAU in rat

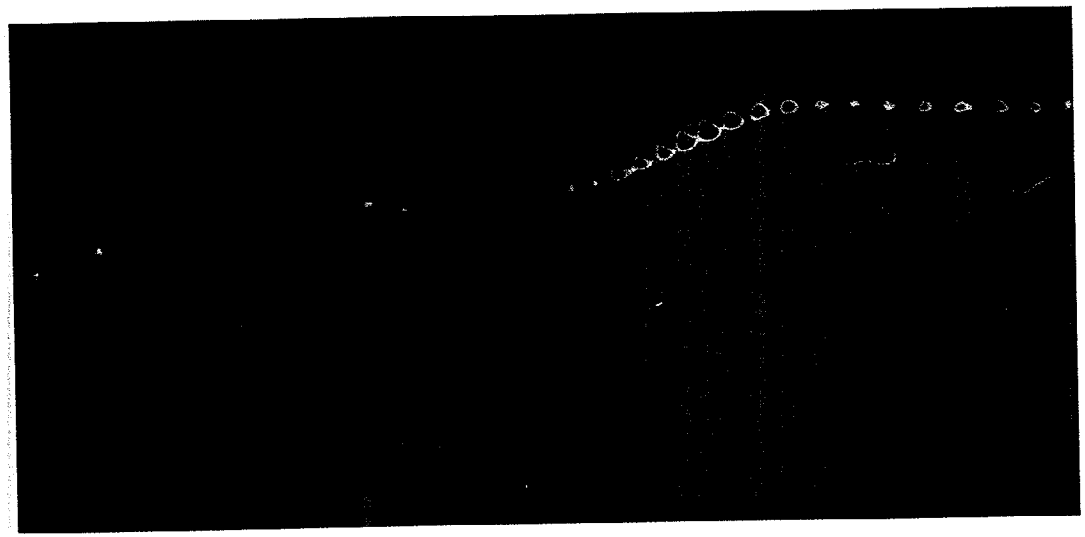
^{18}F-FLT in dog

Shields J.Nucl.Med (1998)

^{11}C-thymidine {TdR or dThd}

Patient with lung tumor (upper arrow)

Vertebral marrow (lower arrow)



Tjuvajev, Blasberg ('98)

Cancer Res HSV-tk+ tumors

^{124}I-FIAU as probe

rat in human PET imager

Shields (1999)

J.Clin.Pharmacol.

^{18}F-FLT {3'-F-dThd}

Healthy Dog