



IS3R 2023 | Berlin/Germany | August 24–26, 2023



# Small-molecule Targeting of PSMA for Life

**Martin Pomper** *Johns Hopkins University*

# Relevant disclosures

- *Johns Hopkins University (employee); D&D Pharmatech (equity); Precision Molecular, Inc. (co-founder, research, royalties, consulting); z-alpha (co-founder, consulting); PlenaryAI, Inc. (co-founder); Progenics Pharmaceuticals (research, royalties); Advanced Accelerator Applications (research, licensing, consulting); Hoffman-LaRoche (research); RefleXion (SAB); Otsuka (consulting); Janssen (consulting); Sanofi (research); AstraZeneca (consulting); Jubilant (consulting); OrbiMed (consulting) CraniUS (SAB); Novartis (SAB); Muna Therapeutics (consulting); Pharmaron (SAB); Earli (SAB, equity)*

## The Role of Nuclear Medicine in the World of Modern Healthcare

Dec. 1, 4:30–5:20 PM



**Sanjiv Sam Gambhir**

*Professor & Chair, Department of Radiology  
Stanford University*

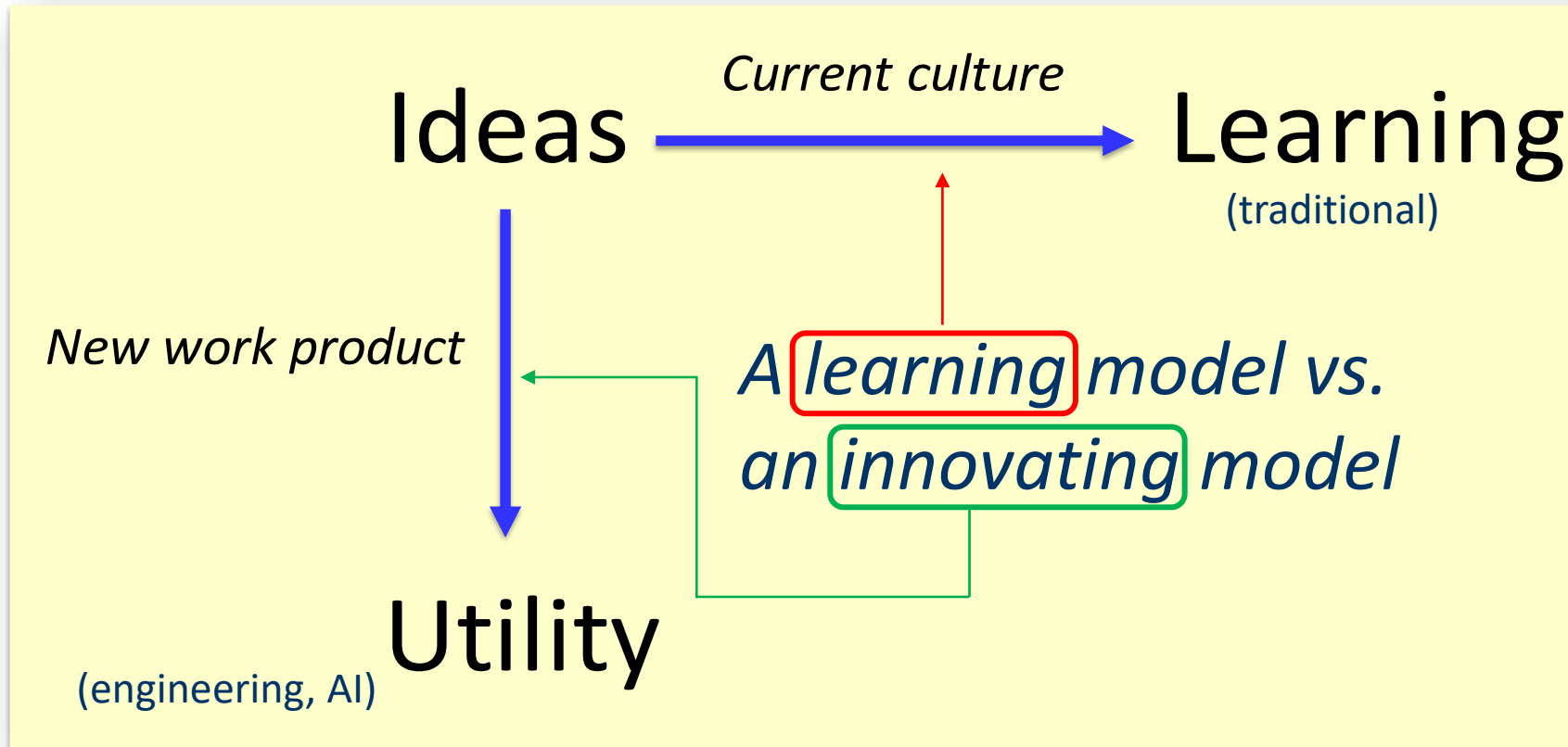
NUCLEAR  
REACTIONS  
1942: A Historic Breakthrough,  
an Uncertain Future

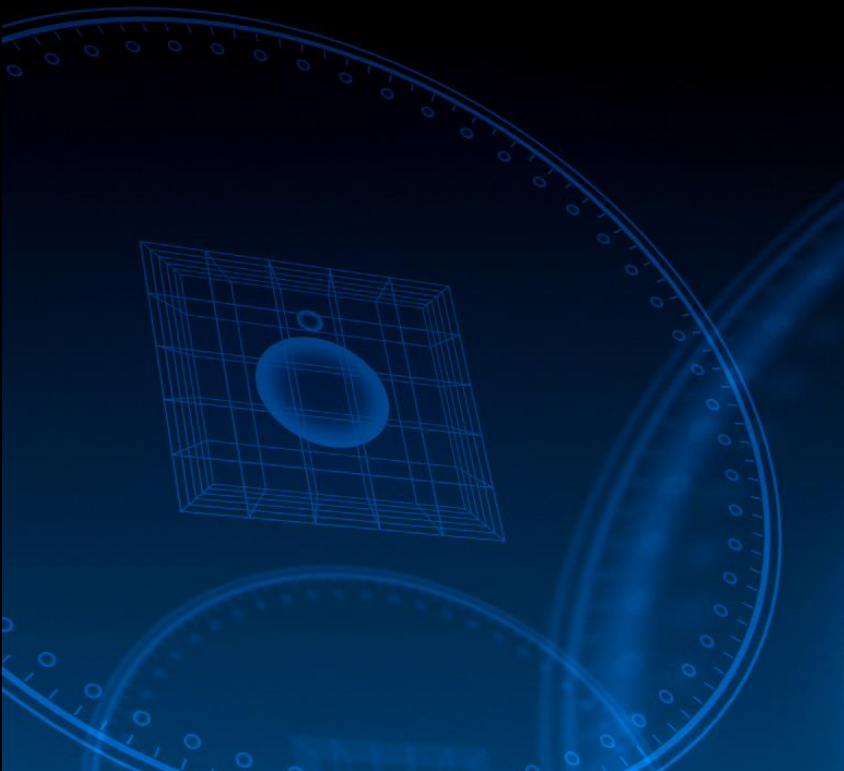


**Martin Pomper**

*Henry N. Wagner, Jr. Professor of Radiology, The Russell H.  
Morgan Department of Radiology and Radiological Science,  
Johns Hopkins Medical School*

# Innovation ~ transformation

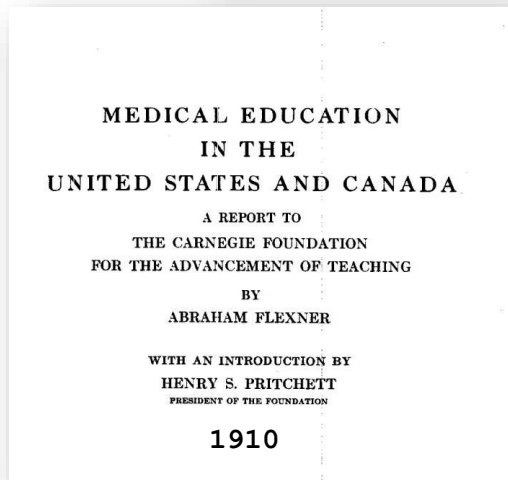
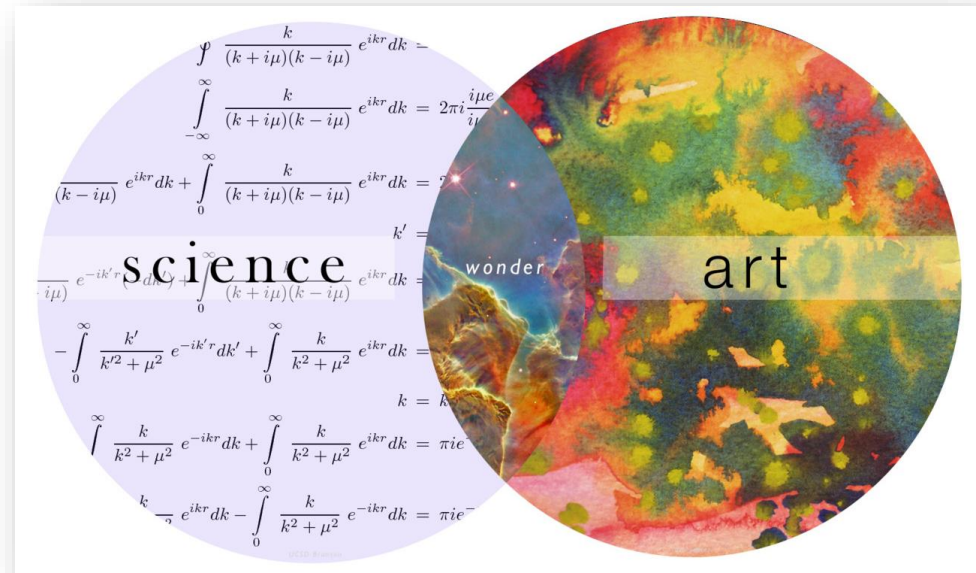


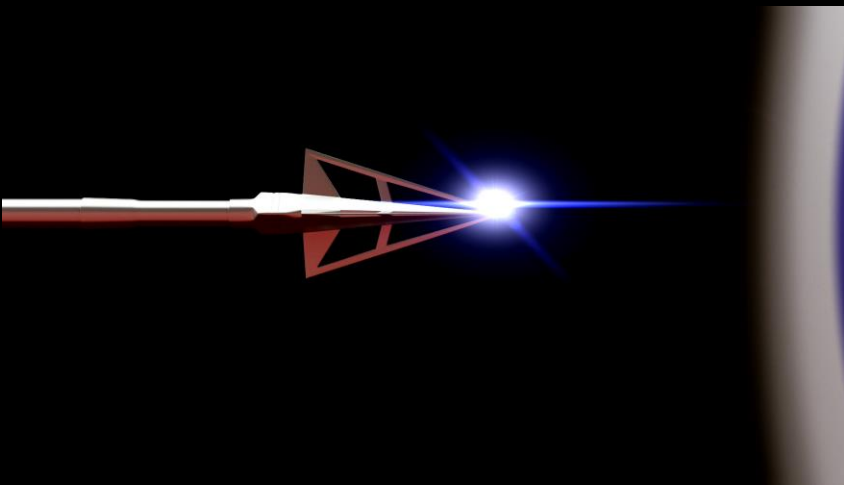


TIMES ARE CHANGING

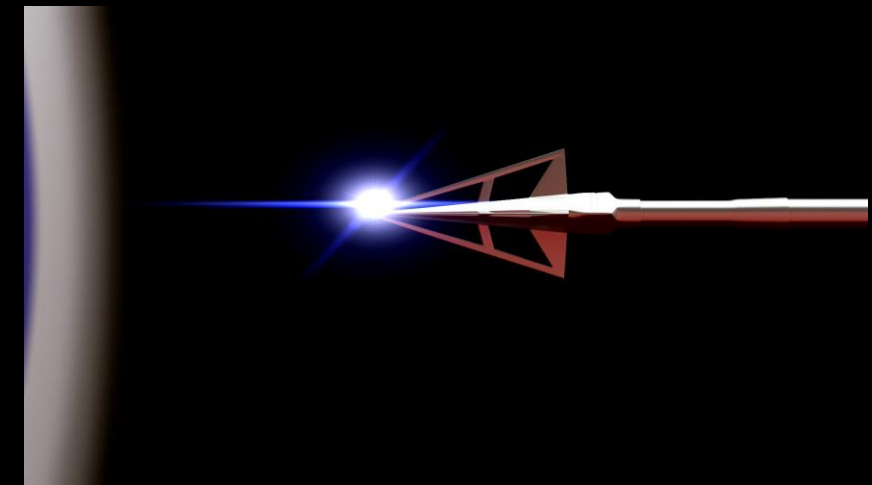


# Paradigm shifts

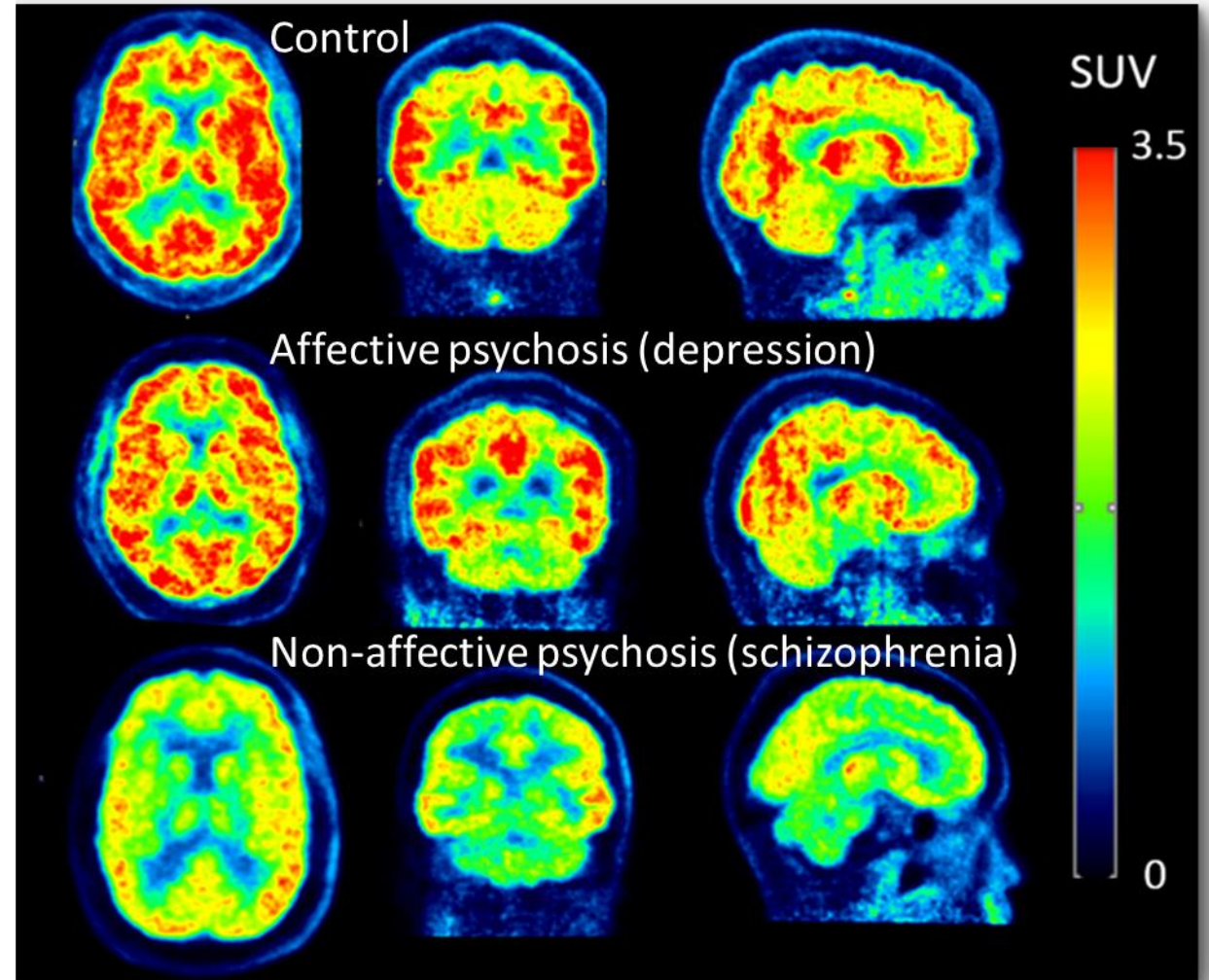
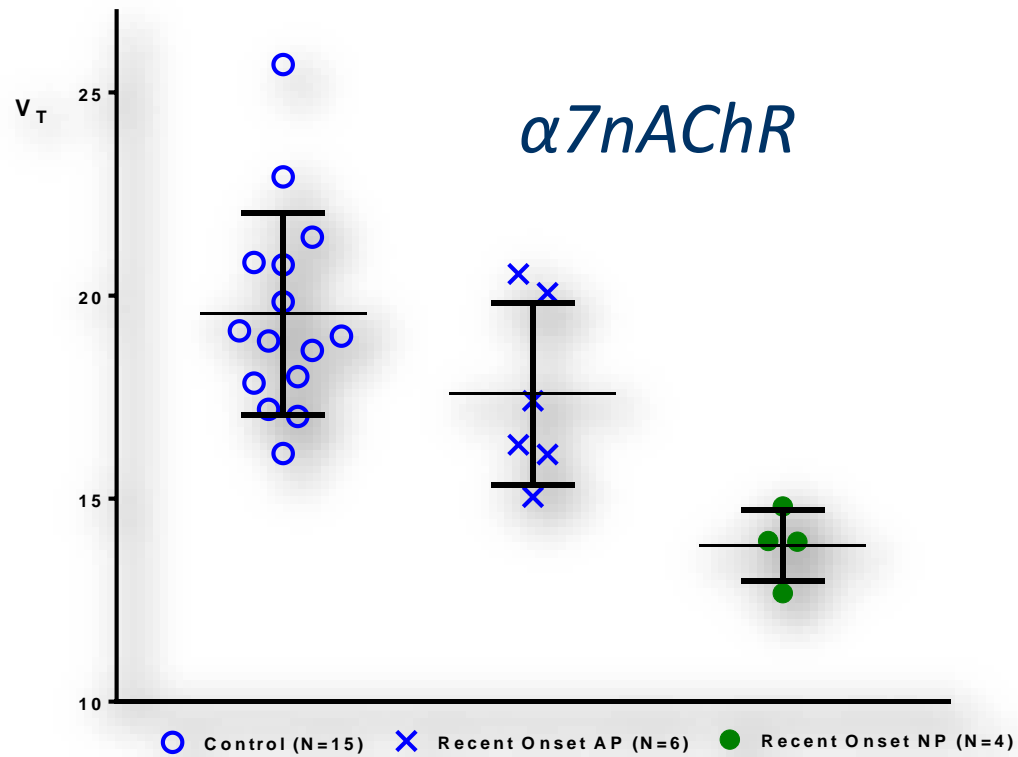




PRECISION



# Subtyping of disease with precision imaging





## CANCER ETIOLOGY

## RESEARCH ARTICLE

## CANCER

# Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies

Chetan Bettegowda,<sup>1,2\*</sup> Mark Sausen,<sup>1\*†</sup> Rebecca J. Leary,<sup>1\*‡</sup> Isaac Kinde,<sup>1\*</sup>  
 Yuxuan Wang,<sup>1</sup> Nishant Agrawal,<sup>1,2</sup> Bjarne R. Bartlett,<sup>1,3</sup> Hao Wang,<sup>1</sup> Brandon Lubber,<sup>1</sup>  
 Rhoda M. Alani,<sup>4</sup> Emmanuel S. Antonarakis,<sup>1</sup> Nilofer S. Azad,<sup>1</sup> Alberto Bardelli,<sup>5,6,7</sup>  
 Henry Brem,<sup>2</sup> John L. Cameron,<sup>2</sup> Clarence C. Lee,<sup>8</sup> Leslie A. Fecher,<sup>9,10</sup> Gary L. Gallia,<sup>2</sup>  
 Peter Gibbs,<sup>11,12</sup> Dung Le,<sup>1,3</sup> Robert L. Giuntoli,<sup>2</sup> Michael Goggins,<sup>2</sup> Michael D. Hogarty,<sup>13</sup>

Cells needed:  $50 \times 10^6$

risk among  
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at only a third of the variation  
 factors or inherited  
 om mutations arising during  
 portant not only for

onmental factors or inherited  
 predispositions. The majority is due to “bad luck,” that is, random mutations arising during  
 DNA replication in normal, noncancerous stem cells. This is important not only for  
 understanding the disease but also for designing strategies to limit the mortality it causes.

PROPOSED CHEMICAL APPROACHES TO THE IN VIVO DIAGNOSIS  
AND TREATMENT OF ALZHEIMER'S DEMENTIA

Reported by Marty Pomper

April 20, 1987

Clinically, Alzheimer's dementia (AD) presents as a progressive and inexorable loss of memory and cognitive function in elderly individuals.<sup>1</sup> Very recently, tremendous advances have been made toward understanding AD at the molecular and genetic levels.<sup>2</sup> Irrespective of these advances, the



UNIVERSITY OF  
**ILLINOIS**  
URBANA-CHAMPAIGN

*J. Med. Chem.* **1996**, *39*, 619–622

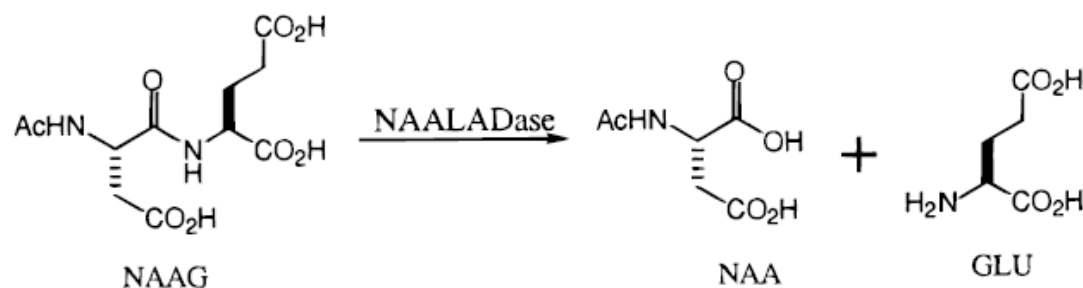
619

## Design, Synthesis, and Biological Activity of a Potent Inhibitor of the Neuropeptidase N-Acetylated $\alpha$ -Linked Acidic Dipeptidase

Paul F. Jackson,<sup>\*,†,§</sup> Derek C. Cole,<sup>†</sup> Barbara S. Slusher,<sup>‡,§</sup> Susan L. Stetz,<sup>‡</sup> Laurie E. Ross,<sup>‡</sup>  
Bruce A. Donzanti,<sup>‡</sup> and Diane Amy Trainor<sup>†</sup>

*Departments of Medicinal Chemistry and Pharmacology, ZENECA Pharmaceuticals, Wilmington, Delaware 19897*

*Received October 17, 1995*<sup>®</sup>



**Table 1.** *In Vitro* Activity of NAALADase Inhibitors

compd	$K_i$ ( $\mu$ M)
3	0.275 $\pm$ 0.08
4	700 $\pm$ 67.3
7	1.89 $\pm$ 0.19

*Proc. Natl. Acad. Sci. USA*  
Vol. 93, pp. 749–753, January 1996  
Neurobiology

## **Prostate-specific membrane antigen is a hydrolase with substrate and pharmacologic characteristics of a neuropeptidase**

(cancer/excitatory neurotransmission/*N*-acetylaspartylglutamate/*N*-acetylated  $\alpha$ -linked acidic dipeptidase/glutamate)

RUTH E. CARTER\*<sup>†‡</sup>, ALEXIS R. FELDMAN\*, AND JOSEPH T. COYLE\*<sup>†§</sup>

\*Department of Psychiatry, Massachusetts General Hospital–East, Charlestown, MA 02129; <sup>†</sup>The Consolidated Department of Psychiatry, Harvard Medical School, Boston, MA 02115; and <sup>‡</sup>Graduate Program in Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205

*Communicated by Seymour S. Kety, Department of Health and Human Services, Bethesda, MD, October 20, 1995 (received for review June 18, 1995)*



**DEPARTMENT OF THE ARMY**

U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND  
524 PALACKY STREET  
FORT DETRICK, MARYLAND 21702-5024

REPLY TO  
ATTENTION OF:

April 8, 1998

Congressionally Directed Medical Research Programs -  
PCRP C

Martin Pomper, MD, PhD  
Johns Hopkins University Medical School  
Department of Radiology/Neuroradiology  
600 North Wolfe Street  
Baltimore, MD 21287-2182

RE: PC970561 - "Radiolabeled NAALADase Inhibitors as  
Imaging Agents for Prostate Cancer"

STATUS: **NOT RECOMMENDED FOR FUNDING**

Dear Doctor Pomper:

Radiol

N GILBERT

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currently  
g reliance  
ased on a

PubMed.gov  
US National Library of Medicine  
National Institutes of Health

PubMed

Advanced

Format: Abstract

*Anticancer Res.* 1987 Sep-Oct;7(5B):927-35.

## Monoclonal antibodies to a new antigenic marker in epithelial prostatic cells and serum of prostatic cancer patients.

[Horoszewicz JS<sup>1</sup>](#), [Kawinski E](#), [Murphy GP](#).

1 State University of New York, Buffalo, Department of Urology 14214.

**Abstract**  
Stable clones of murine hybridomas 7E11-C5 and 9H10-A4 were obtained following immunization with LNCaP cells. The LNCaP cells were isolated from a human prostatic cancer (Ca). Both hybridomas secreted monoclonal antibodies (MoAb) of the IgG1 subclass which were reactive with the insoluble, cytoplasmic, **membrane** rich fractions of the immunogen. Neither MoAb reacted with the soluble cytosol of LNCaP cells nor with purified human prostatic acid phosphatase (PAP) nor **prostate specific** antigen (PSA). MoAb 9H10-A4 reactivity was very narrow and limited to the surfaces of LNCaP cells only. MoAb 7E11-C5 specificity was restricted to human prostatic epithelium, both



# Prostate-specific Membrane Antigen Expression in Normal and Malignant Human Tissues<sup>1</sup>

**David A. Silver, Inmaculada Pellicer,  
William R. Fair, Warren D. W. Heston, and  
Carlos Cordon-Cardo<sup>2</sup>**

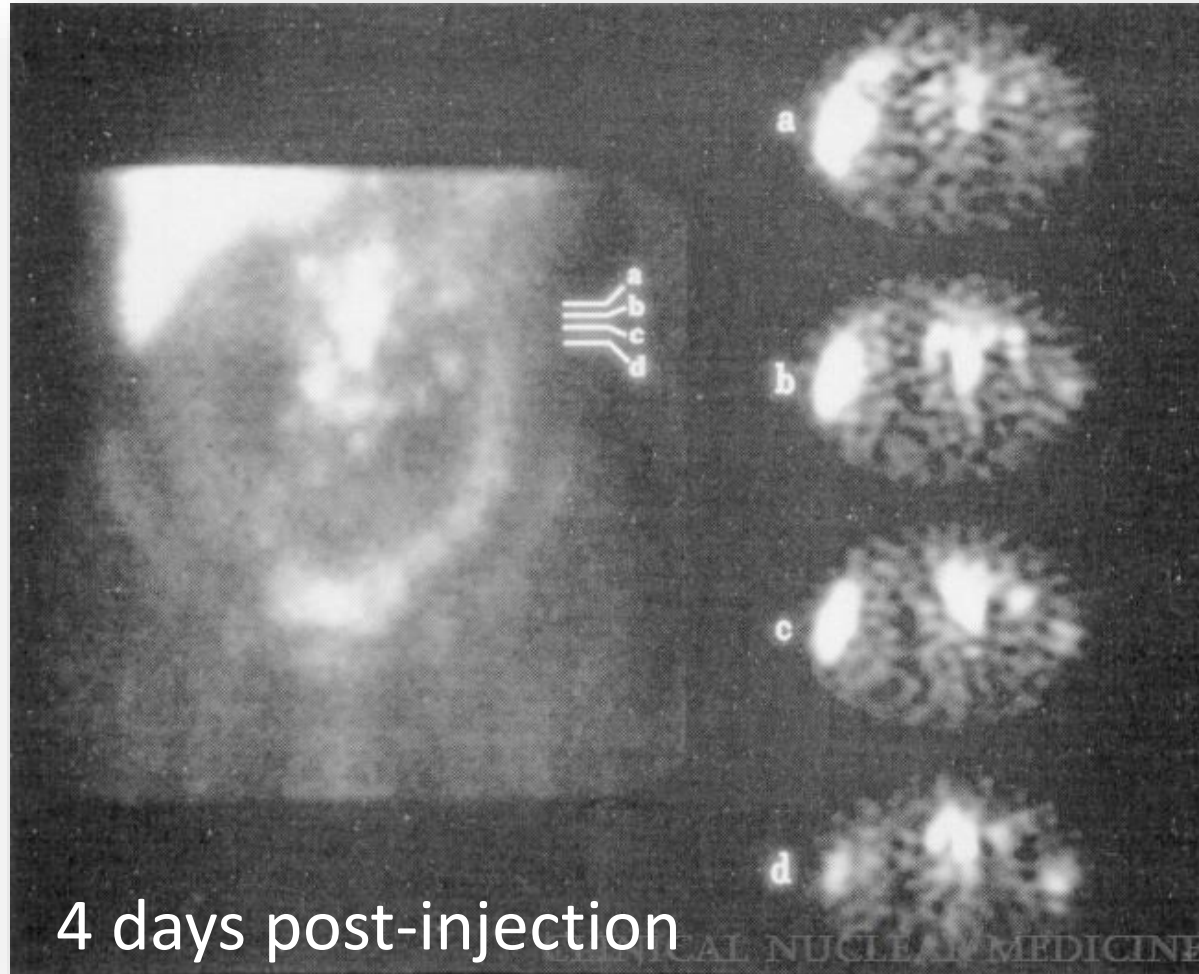
Urology Service, Department of Surgery [D. A., W. R. F.,  
W. D. W. H.] and Division of Molecular Pathology, Department of  
Pathology [I. P., C. C. C.], Memorial Sloan-Kettering Cancer Center,  
New York, New York 10021

tion. The neoexpression of PSMA in endothelial cells of capillary beds in certain tumors may be related to tumor angiogenesis and suggests a potential mechanism for specific targeting of tumor neovasculature.

## INTRODUCTION

PSMA<sup>3</sup> is a  $M_r$  100,000 type II membrane protein consist-

# PSMA antibodies for imaging





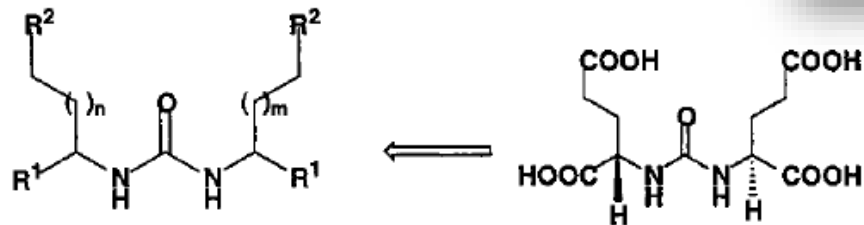


Alan Kozikowski, Ph.D.

## NAAG PEPTIDASE INHIBITORS AND THEIR POTENTIAL FOR DIAGNOSIS AND THERAPY

*Nat Rev Drug Disc* 2005

*Jia Zhou<sup>\*</sup>, Joseph H. Neale<sup>‡</sup>, Martin G. Pomper<sup>§</sup> and Alan P. Kozikowski<sup>\*||</sup>*

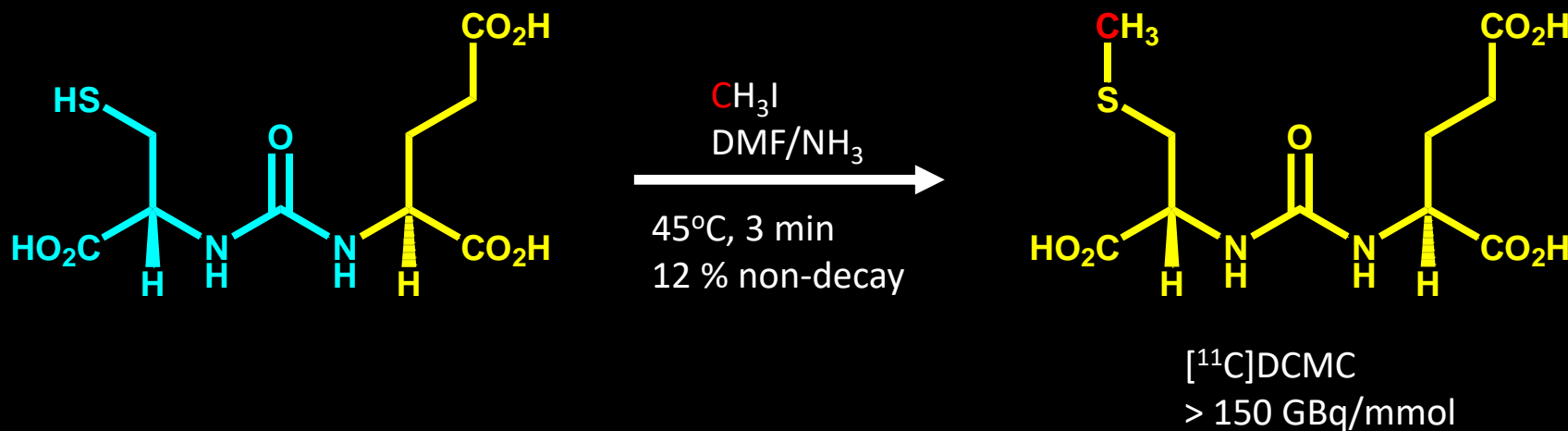


$R^1/R^2 = \text{COOH, SH, SBU}^t$ ;  $m, n = 0, 1$

Glu-C(O)-Glu

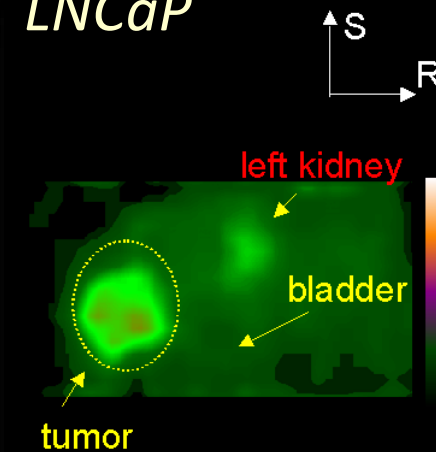
*J Med Chem* 2001

# Initial PSMA-targeted small molecule



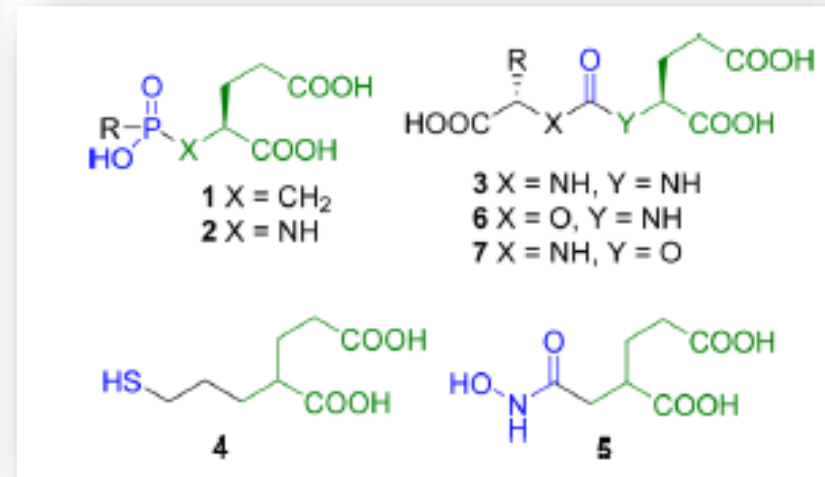
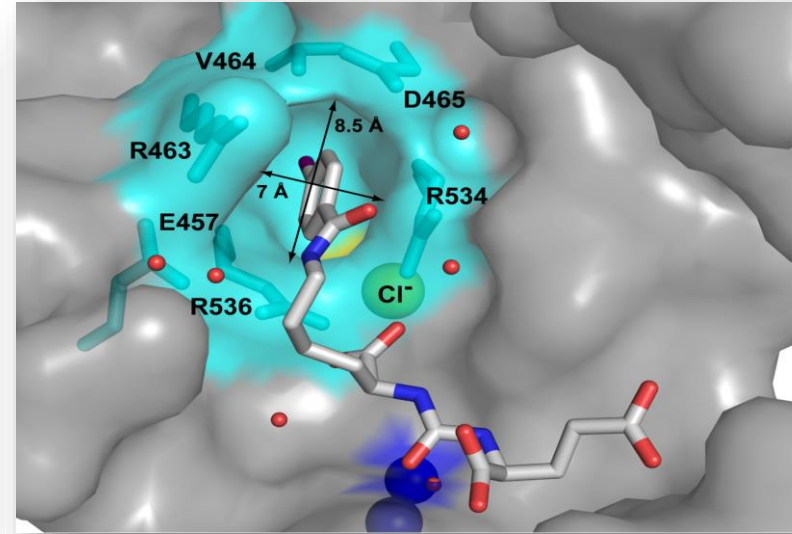
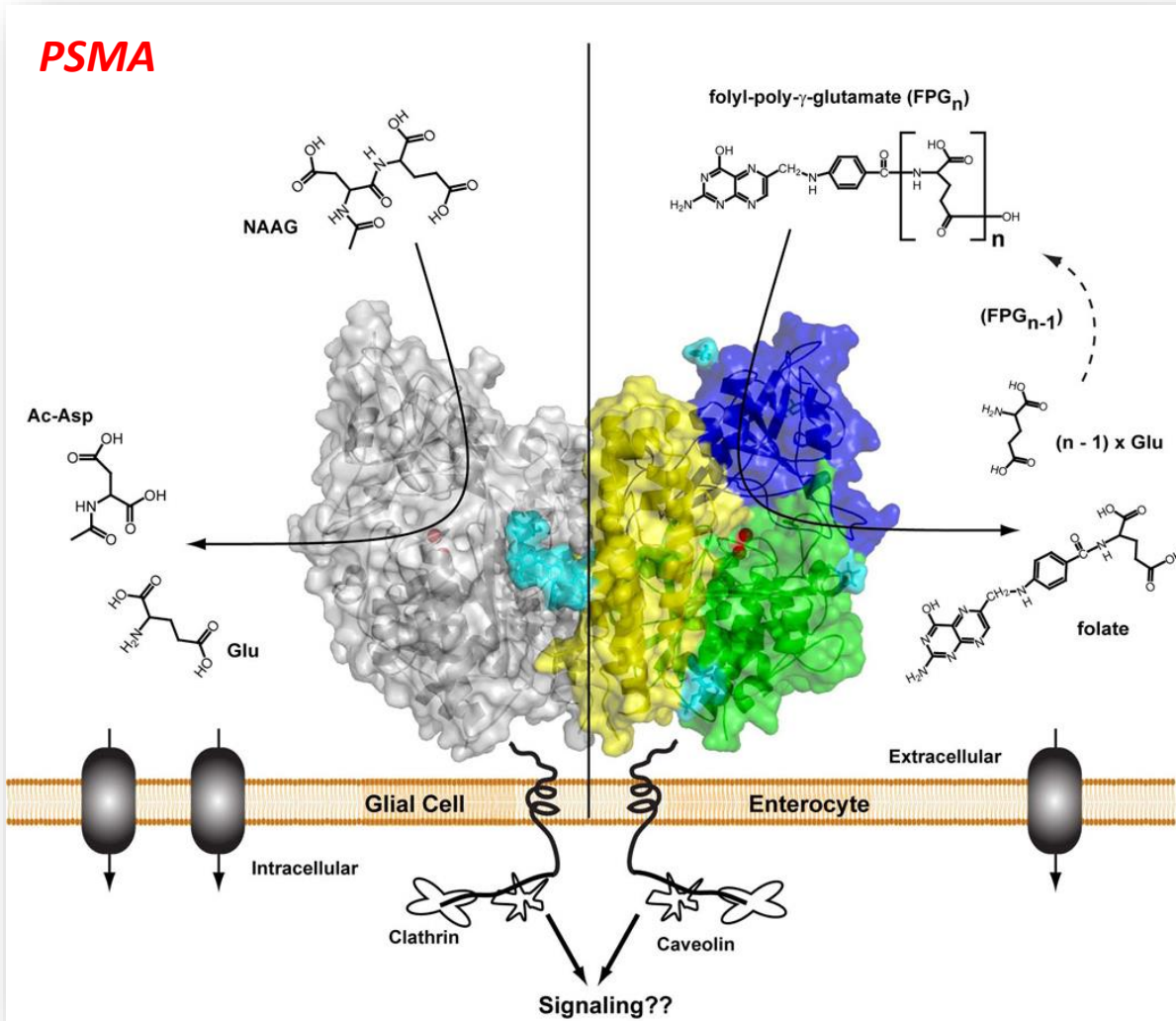
*Mol Imaging 2002*

*LNCaP*



*Clin Cancer Res 2005*

Analogs labeled with radionuclides amenable to SPECT, such as iodine-123, are currently being pursued, the precursors of which may also be modified to be used for therapy (with iodine-125/131).



1 **Imaging, Diagnosis, Prognosis***Clin Cancer Res* 2005

F

**Imaging, Diagnosis, Prognosis***Clin Cancer Res* 2008

Ra

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A

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*J. Med. Chem.* 2008, 51, 7933–7943

7933

Cy Radiohalogenated Prostate-Specific Membrane Antigen (PSMA)-Based Ureas as Imaging Agents  
 for Prostate Cancer

Published OnlineFirst October 31, 2011; DOI:10.1158/1078-0432.CCR-11-1357

Raf

Jurg

Alan Ying Chen,<sup>†</sup> Catherine A. Foss,<sup>†</sup>  
 Mark Castanares,<sup>‡</sup> Shawn E.

*Russell H. Morgan Department of  
 Johns Hopkins Medical Institution*

**Imaging, Diagnosis, Prognosis**

**2-(3-{1-Carboxy-5-[(6-[<sup>18</sup>F]Fluoro-Pyridine-3-Carbonyl)-Amino]-Pentyl}-Ureido)-Pentanedioic Acid, [<sup>18</sup>F]DCFPyL, a PSMA-Based PET Imaging Agent for Prostate Cancer**

Ying Chen<sup>1</sup>, Mrudula Pullambhatla<sup>1</sup>, Catherine A. Foss<sup>1</sup>, Youngjoo Byun<sup>1,2</sup>, Sridhar Nimmagadda<sup>1</sup>,  
 Srinivasan Senthambizchelvan<sup>1</sup>, George Sgouros<sup>1</sup>, Ronnie C. Mease<sup>1</sup>, and Martin G. Pomper<sup>1</sup>

**Clinical  
 Cancer  
 Research**

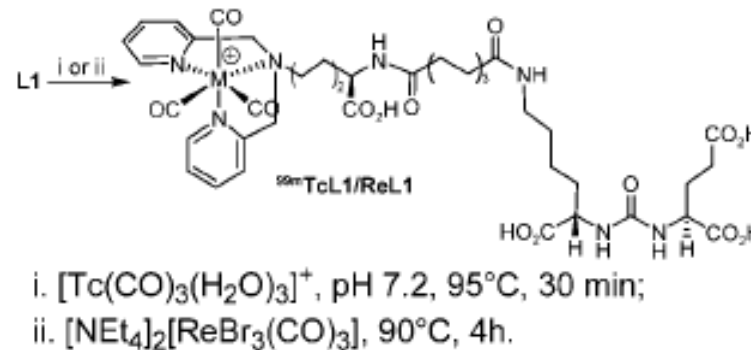
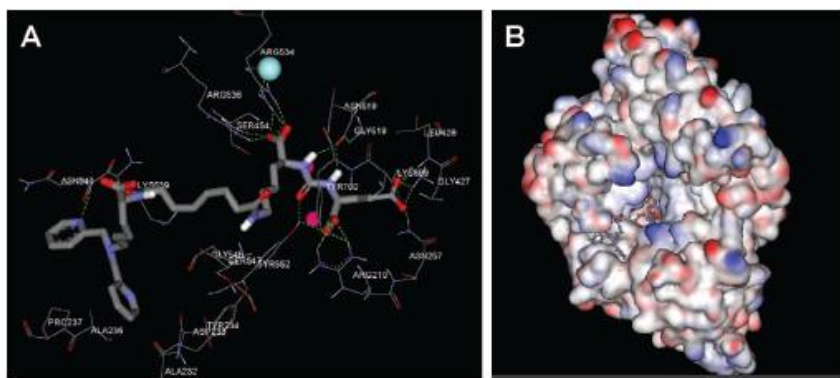
4504

*J. Med. Chem.* **2008**, *51*, 4504–4517

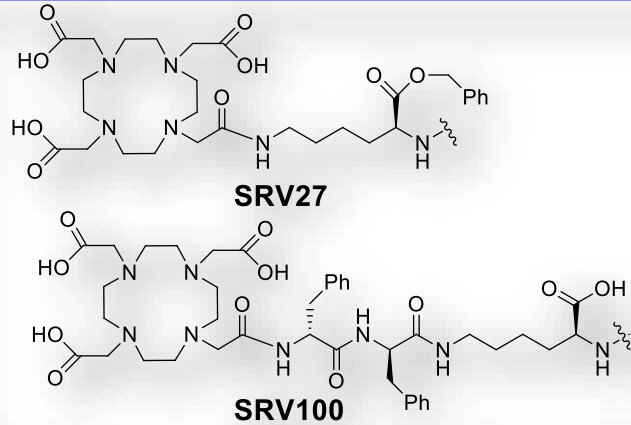
## Synthesis and Evaluation of Technetium-99m- and Rhenium-Labeled Inhibitors of the Prostate-Specific Membrane Antigen (PSMA)

Sangeeta R. Banerjee,<sup>†</sup> Catherine A. Foss,<sup>†</sup> Mark Castanares,<sup>‡</sup> Ronnie C. Mease,<sup>†</sup> Youngjoo Byun,<sup>†</sup> James J. Fox,<sup>†</sup> John Hilton,<sup>†</sup> Shawn E. Lupold,<sup>§</sup> Alan P. Kozikowski,<sup>||</sup> and Martin G. Pomper<sup>\*,†,‡</sup>

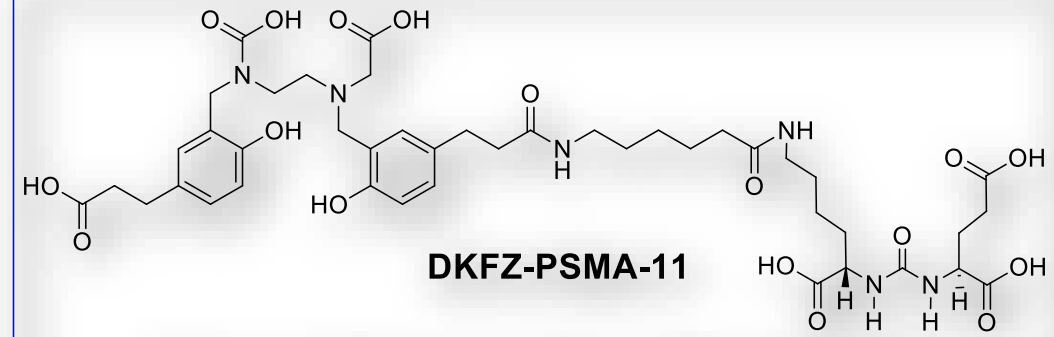
*Russell H. Morgan Department of Radiology and Radiological Sciences, Department of Pharmacology & Molecular Sciences, Department of Urology, Johns Hopkins Medical Institutions, Baltimore, Maryland 21231, and Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Illinois 60612*



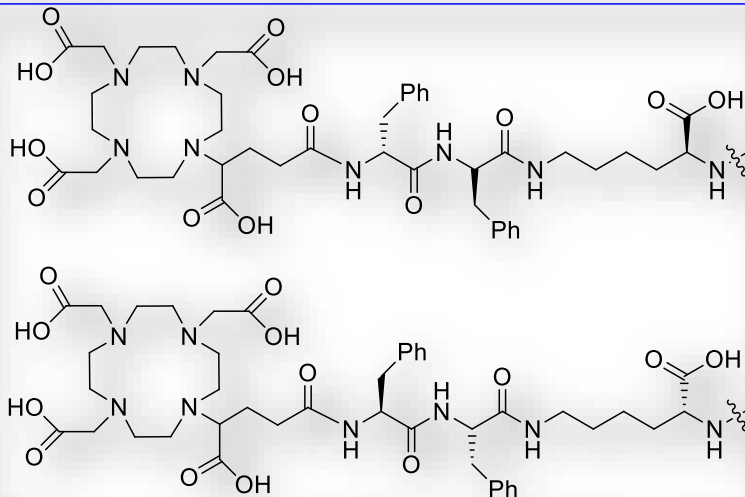
# <sup>68</sup>Ga-labeled agents for PET



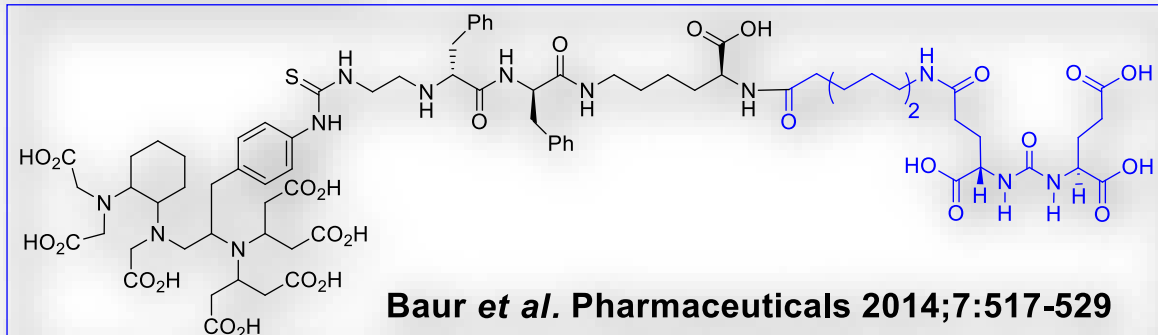
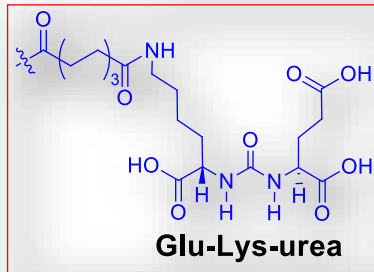
**Banerjee et al. J Med Chem. 2010; 53:5333-5341**



**Eder et al, Bioconjug Chem. 2012; 23:688-697**



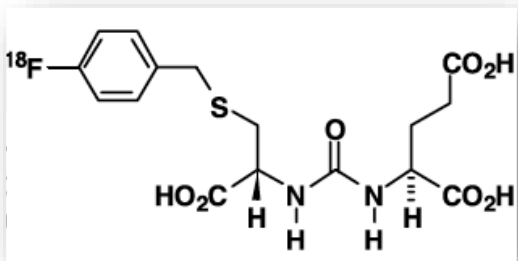
**Weineisen et al. EJNMMI Res. 2014;4:63**



**Baur et al. Pharmaceuticals 2014;7:517-529**

# First-generation $^{18}\text{F}$ compounds

$[^{18}\text{F}]\text{DCFBC}$

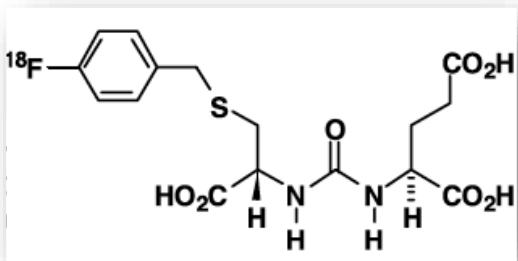


*Cho J Nucl Med 2012*



# First-generation $^{18}\text{F}$ compounds

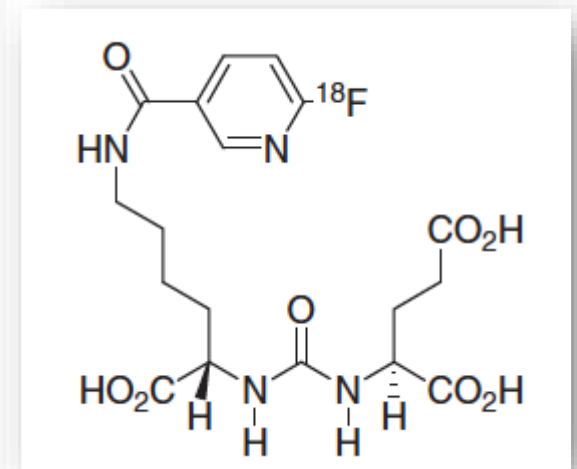
$[^{18}\text{F}]\text{DCFBC}$



*Cho J Nucl Med 2012*



$[^{18}\text{F}]\text{DCFPyL (PyL)}$



*Szabo Mol Imaging Biol 2015*



# Detecting Prostate Cancer with DCFPyL

**Martin G. Pomper**

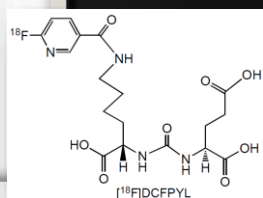
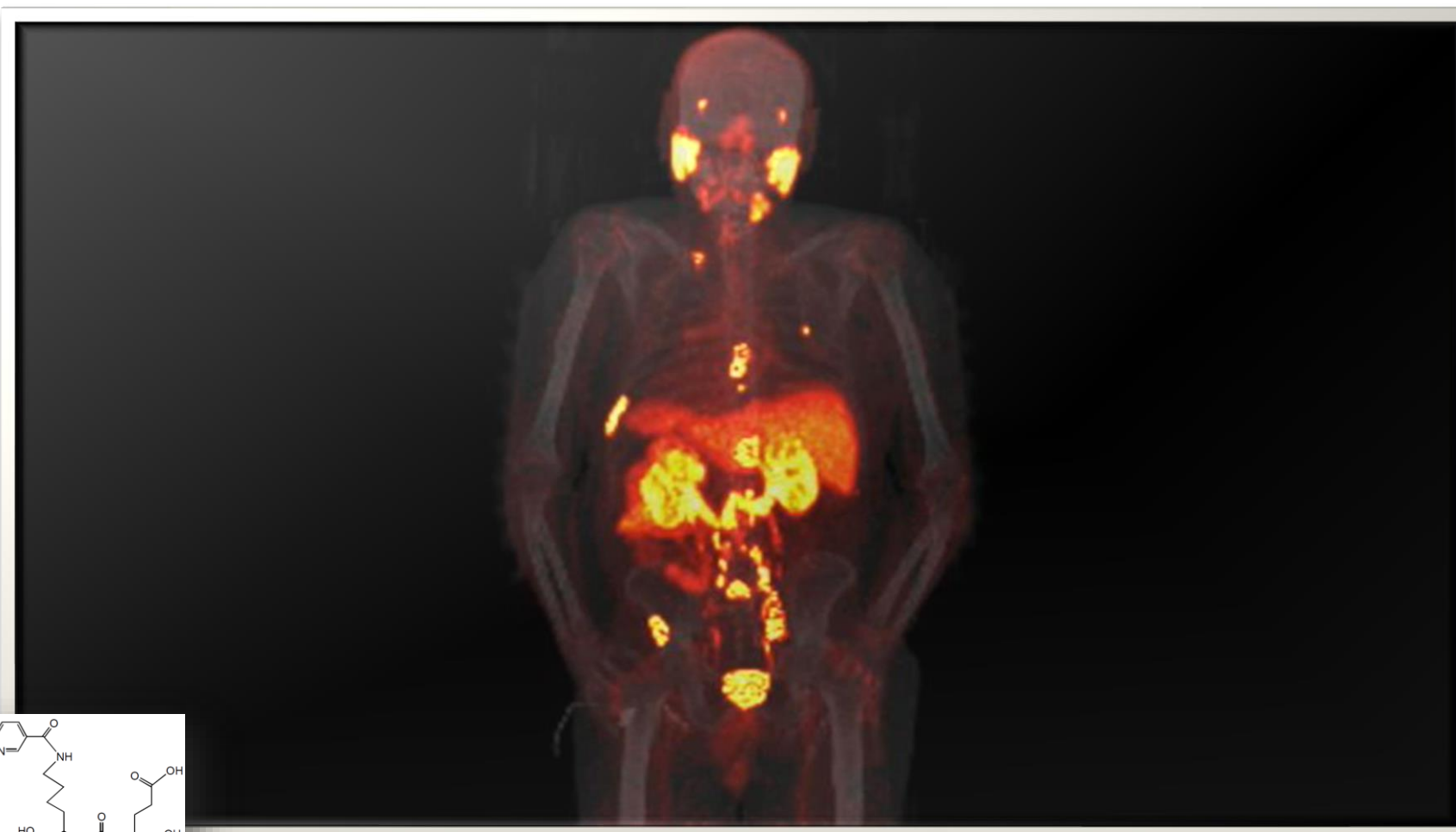
**The Russell H. Morgan Department of  
Radiology and Radiological Science**

*22<sup>nd</sup> Annual Prostate Cancer Foundation  
Scientific Retreat  
Washington, DC  
October 10, 2015*



**JOHNS HOPKINS**  
M E D I C I N E

# Earlier detection of prostate cancer



Ron Mease, Ph.D.

# Detect, see, treat



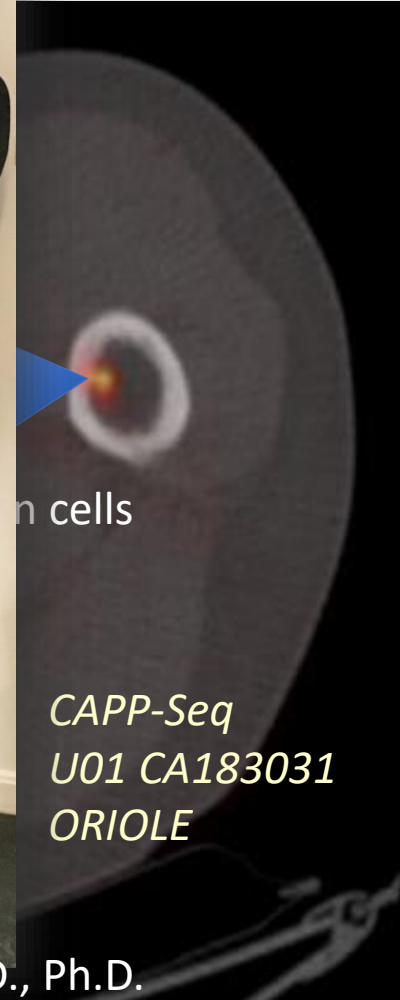
Steven Rowe, M.D., Ph.D.



50 million cells



Phuoc Tran, M.D., Ph.D.



CAPP-Seq  
U01 CA183031  
ORIOLE



Michael Gorin, M.D.

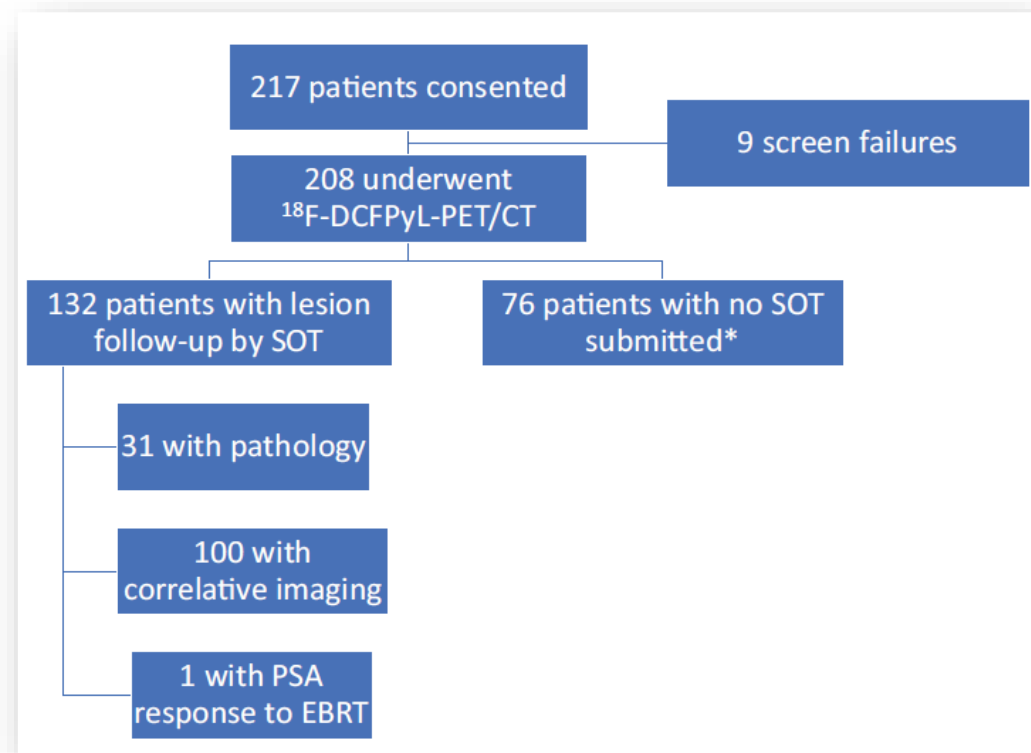
# CONDOR

Published OnlineFirst February 23, 2021; DOI: 10.1158/1078-0432.CCR-20-4573

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

## Diagnostic Performance of <sup>18</sup>F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study

Michael J. Morris<sup>1</sup>, Steven P. Rowe<sup>2</sup>, Michael A. Gorin<sup>3</sup>, Lawrence Saperstein<sup>4</sup>, Frédéric Pouliot<sup>5</sup>, David Josephson<sup>6</sup>, Jeffrey Y.C. Wong<sup>7</sup>, Austin R. Pantel<sup>8</sup>, Steve Y. Cho<sup>9</sup>, Kenneth L. Gage<sup>10</sup>, Morand Piert<sup>11</sup>, Andrei Iagaru<sup>12</sup>, Janet H. Pollard<sup>13</sup>, Vivien Wong<sup>14</sup>, Jessica Jensen<sup>14</sup>, Tess Lin<sup>14</sup>, Nancy Stambler<sup>14</sup>, Peter R. Carroll<sup>15</sup>, Barry A. Siegel<sup>16</sup>, and CONDOR Study Group



When assessing patients with suspected prostate cancer metastasis who are candidates for initial definitive therapy or suspected recurrence based on elevated PSA,

PYLARIFY<sup>®</sup> REVEALS **THE CLEARER PICTURE.**<sup>2-10</sup>



Piflufolastat F 18 Injection (PYLARIFY<sup>®</sup>)

**NCCN** Category 2A\*  
**RECOMMENDED**<sup>11</sup>

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Not actual patients.

NCCN=National Comprehensive Cancer Network.

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Prostate Cancer V.1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed September 20, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind

# Clinical spaces for imaging of PSMA

- Pre-surgical staging in high-risk patients
  - Detection of disease in early biochemical recurrence
  - Guide focal therapy in oligometastatic disease
  - Guide focal therapy in widespread metastatic disease
  - Selection of patients for radiopharmaceutical therapy
  - Therapeutic monitoring
- 
- Selection of candidates for active surveillance
  - Applications outside of prostate cancer

# PyL-avid lesions on BAT means early progression

*Bipolar  
Androgen  
Therapy*

Patient

#1

#2

#3

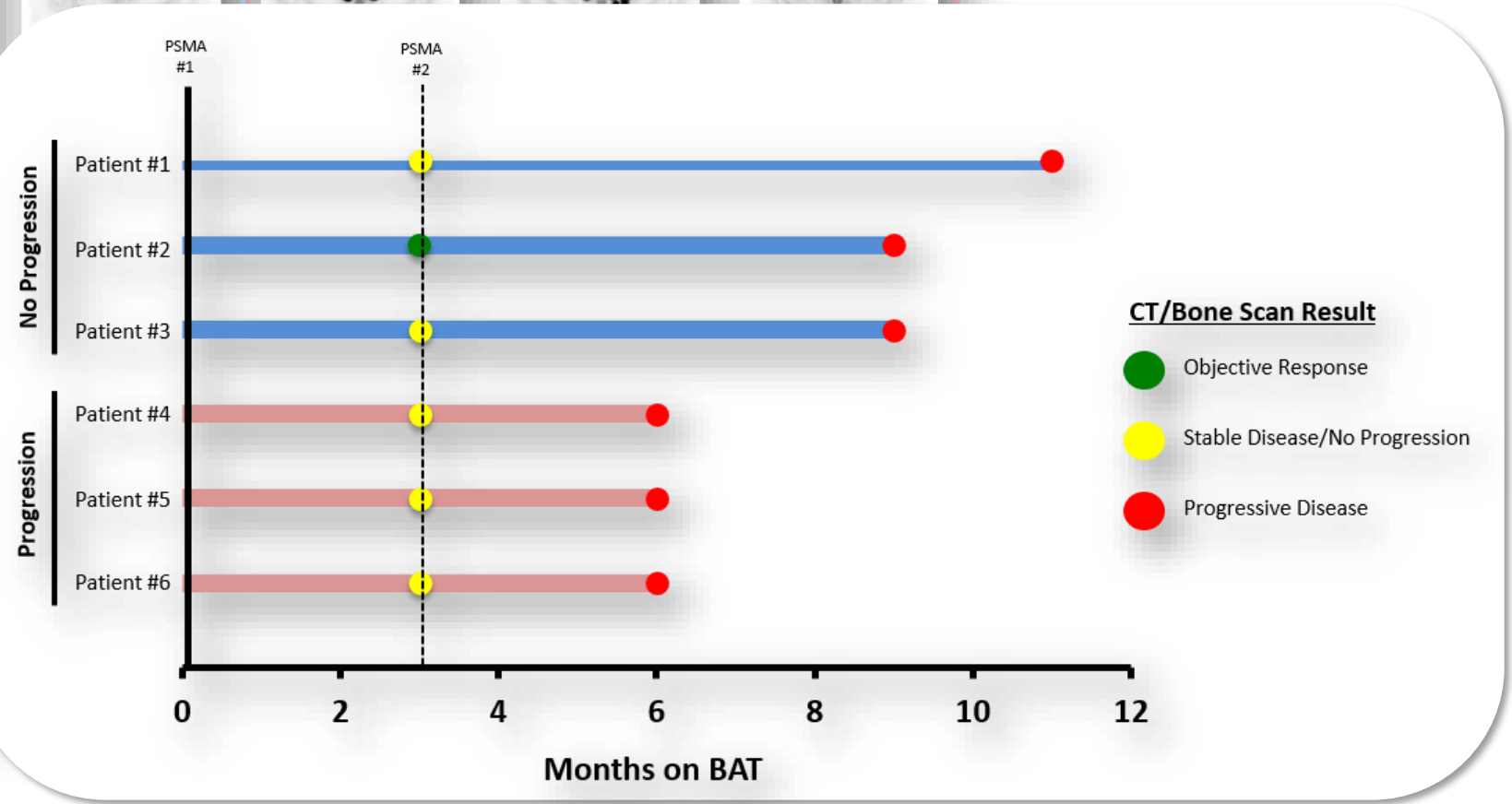
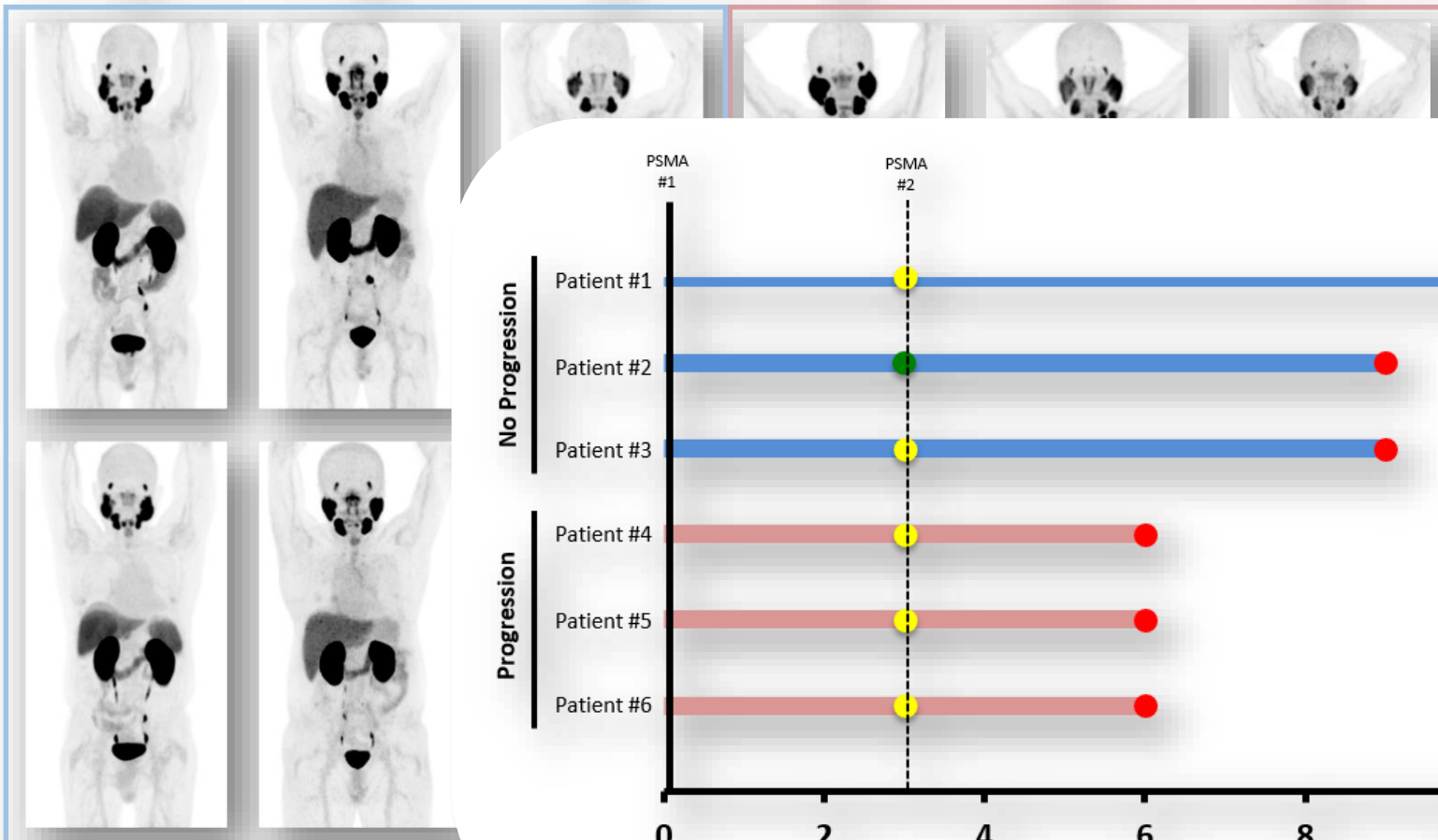
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#6

Baseline

Follow-Up

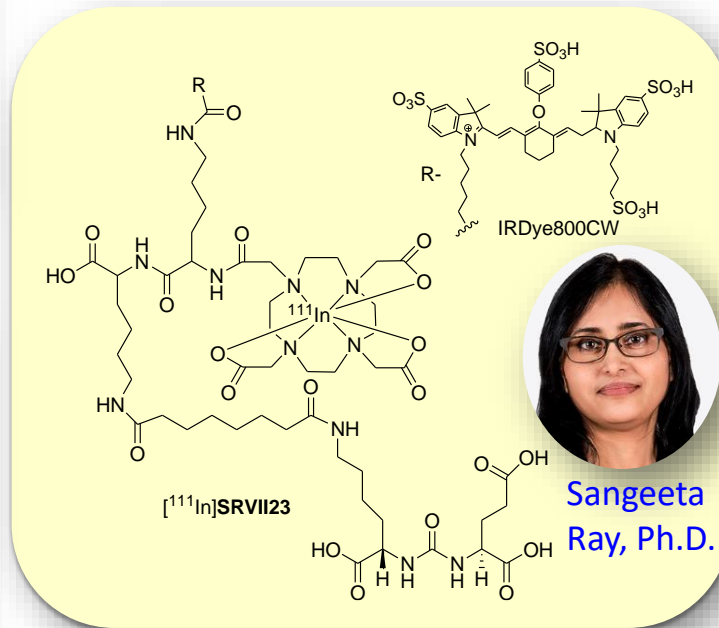
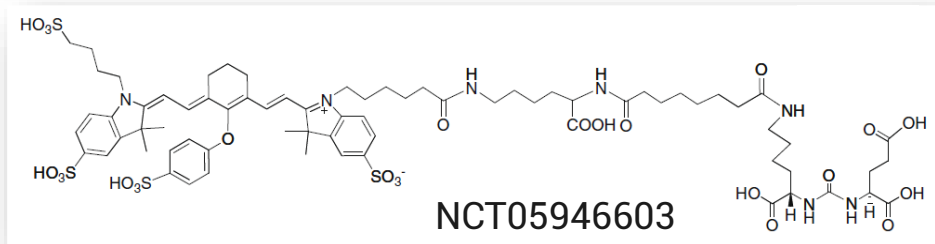


**CT/Bone Scan Result**

- Objective Response
- Stable Disease/No Progression
- Progressive Disease

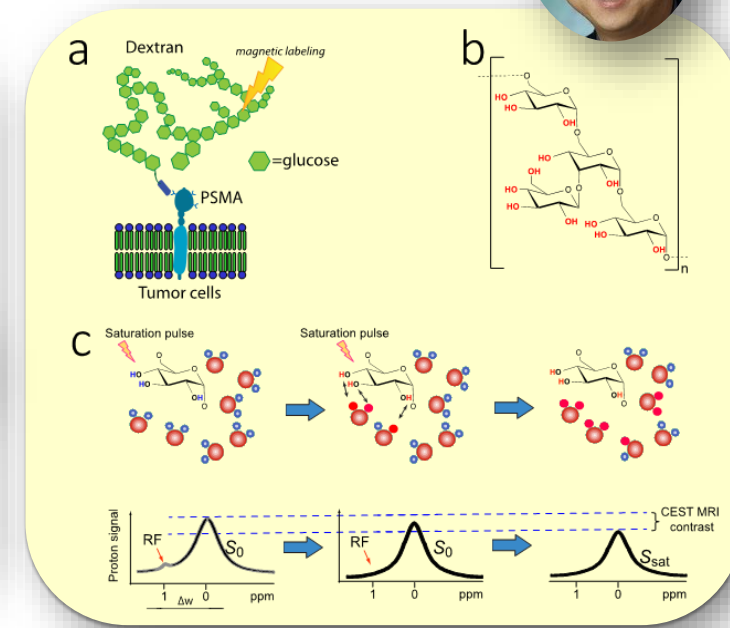
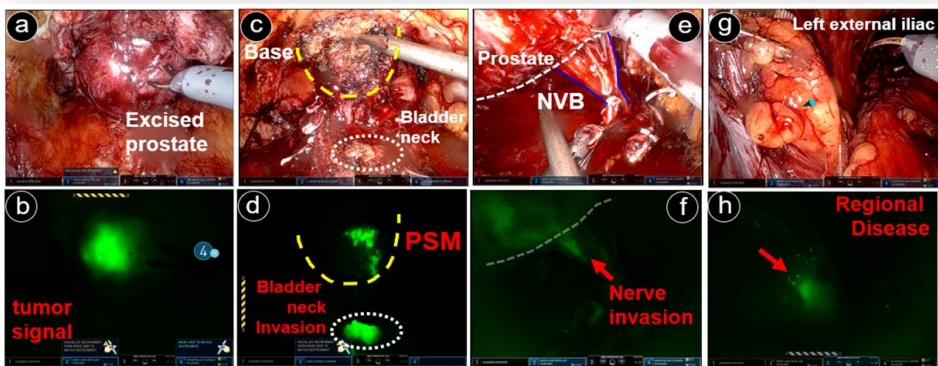
# Ureas targeting PSMA: multimodal

Guanshu Liu, Ph.D.

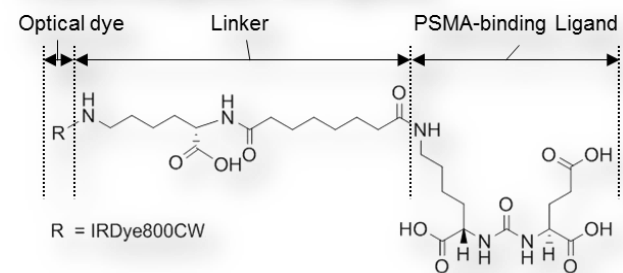


Sangeeta Ray, Ph.D.

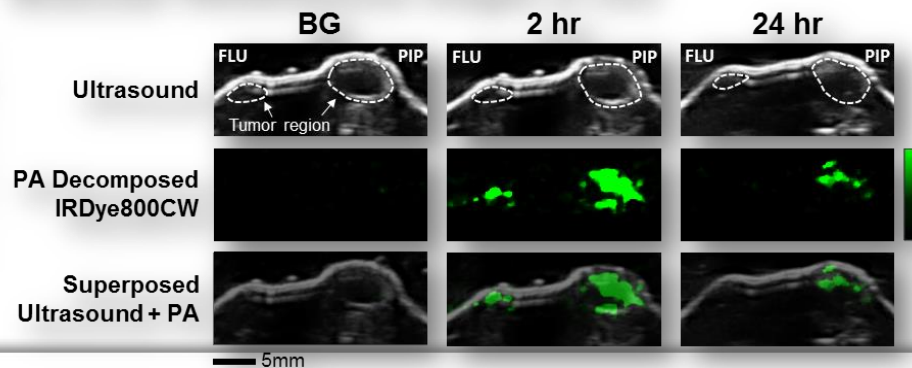
*Eur Urol Oncol in press*



## PSMA-targeted PA agents



## Molecular PA/Ultrasound Images *in vivo*



Chen *BBRC* 2009, *Biomolecules* 2022

Banerjee *Angew Chem* 2011

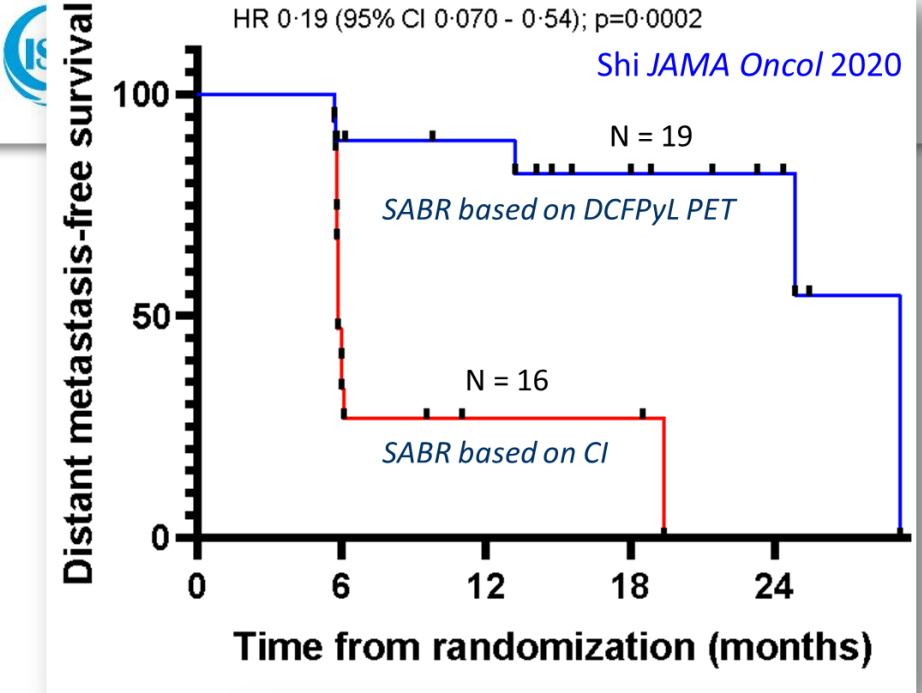
Liu *Nat Biomed Eng* 2017

Zhang *Biophotonics* 2018

Lesniak *Nanoscale* 2021

Wu *Photoacoustics* 2022





Boinapally *Sci Rep* 2021

Cytotoxic Drug (MMAE)

Cathepsin B Cleavable Linker

Targeting Ligand (PSMA)

PSMA+

FAP+

$^{64}\text{Cu}$ -FP-L1 targets FAP+ and PSMA+ tumors specifically

FP-L1

$^{64}\text{Cu}$

Boinapally *EJNMMI* 2022

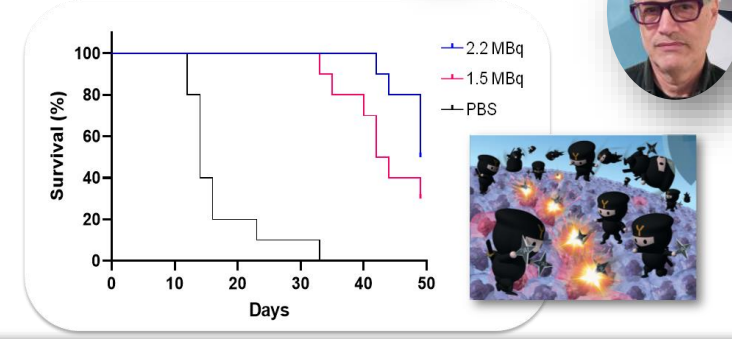
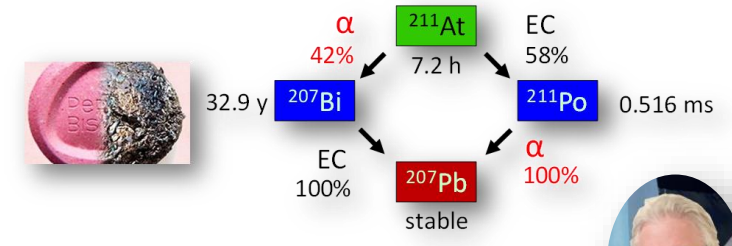
Srikanth Boinapally,  
Ph.D.

Table 1 – Overview of different PSMA-RADS scores (version 2.0)

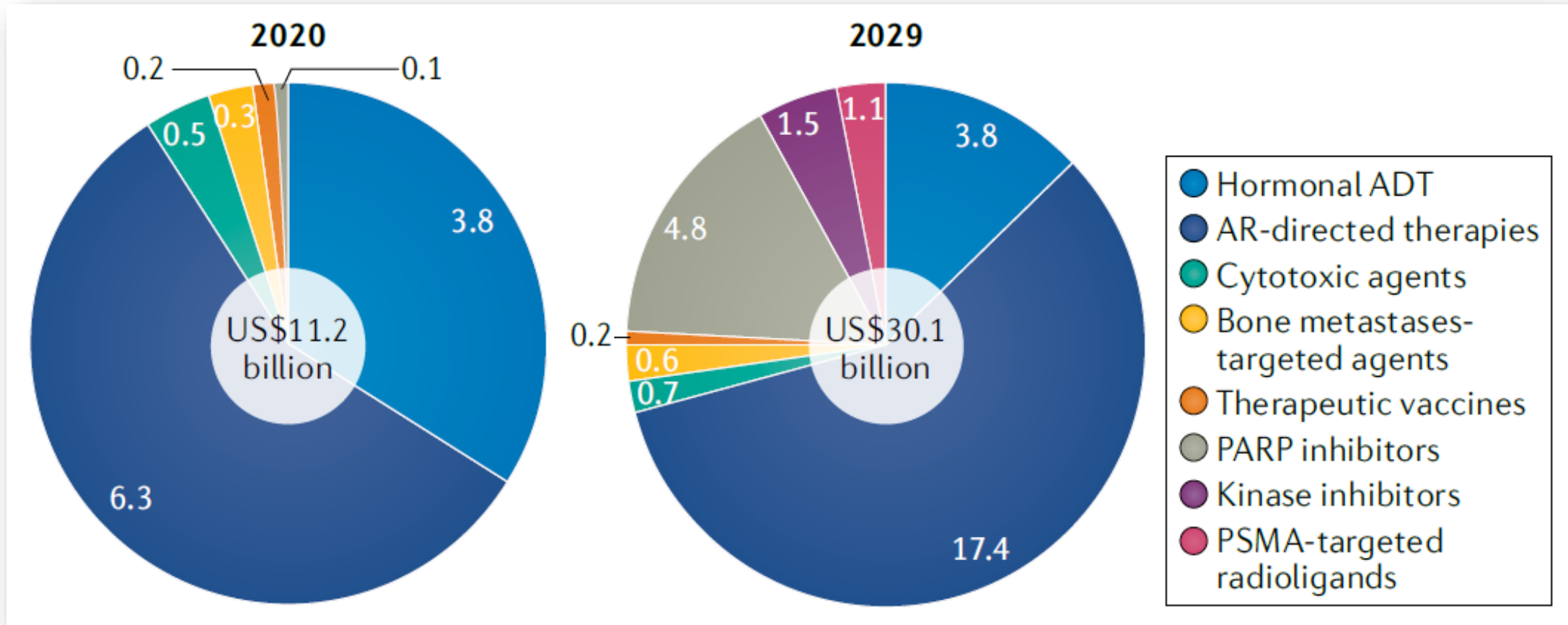
PSMA-RADS 1 (benign)	Benign lesion characterized by biopsy or pathognomonic features (1 and 2)
PSMA-RADS 2 (likely benign)	Equivocal (focal, but low level such as blood pool) uptake in soft-tissue site; equivocal uptake in bone lesion atypical of PC involvement; degenerative or another benign etiology; Fig. 3) Upon follow-up, stable lesions without treatment are likely benign
PSMA-RADS 3 (equivocal)	Equivocal uptake in soft-tissue site typical of PC involvement; equivocal uptake in bone lesion atypical of PC involvement; degenerative or another benign etiology; Fig. 3) Upon follow-up, stable lesions without treatment are likely benign
PSMA-RADS 3A	Equivocal uptake in soft-tissue site typical of PC involvement; equivocal uptake in bone lesion atypical of PC involvement; degenerative or another benign etiology; Fig. 3) Upon follow-up, stable lesions without treatment are likely benign
PSMA-RADS 3B	Equivocal uptake in bone lesion not definitive but also typical of PC involvement; degenerative or another benign etiology; Fig. 3) Upon follow-up, stable lesions without treatment are likely benign

Werner *Eur Urol* 2023

Steven Rowe,  
M.D., Ph.D.

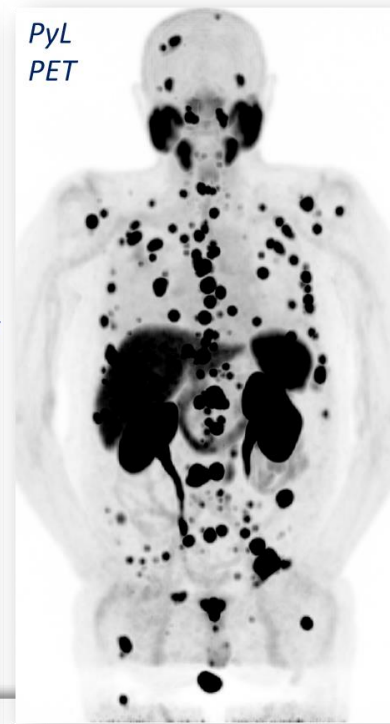
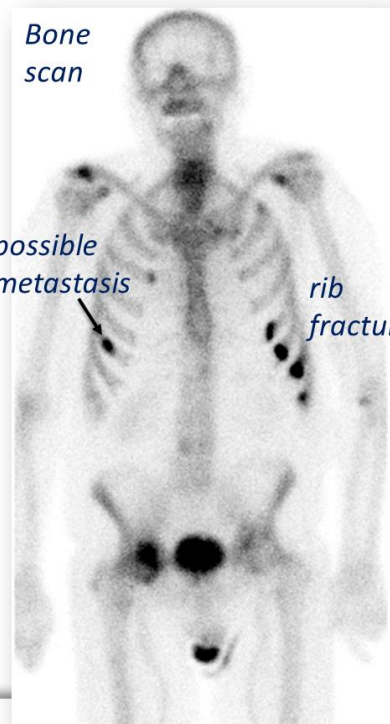
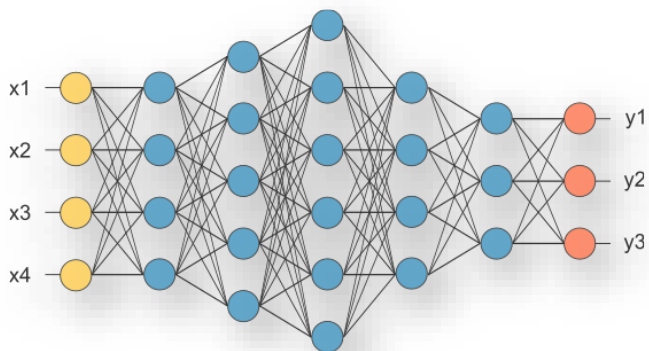
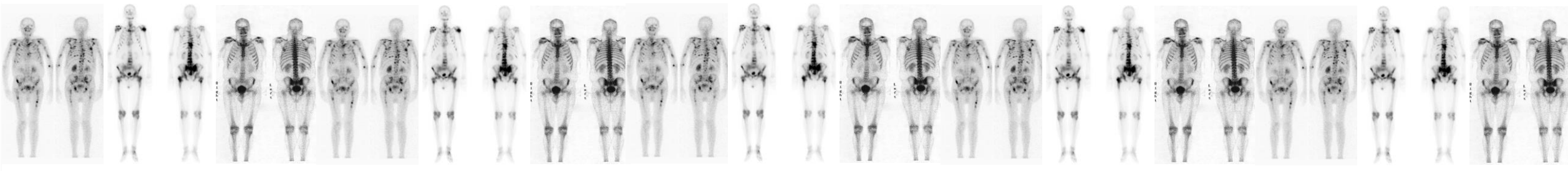


# The future of drugs to treat prostate cancer





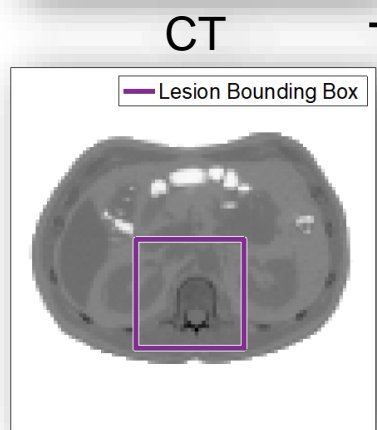
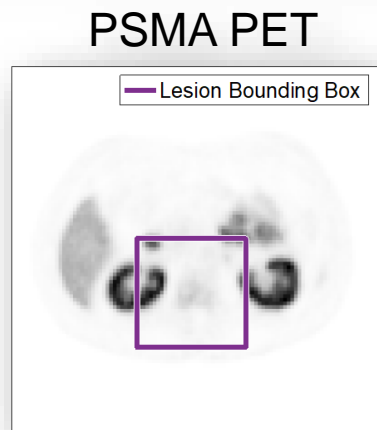
# A word on machine learning



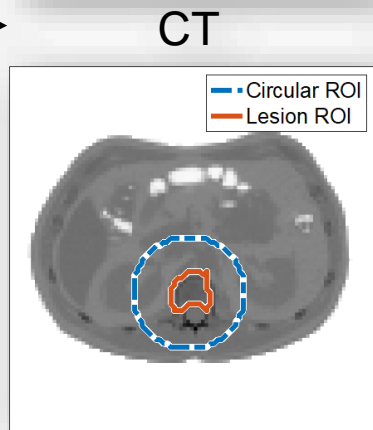
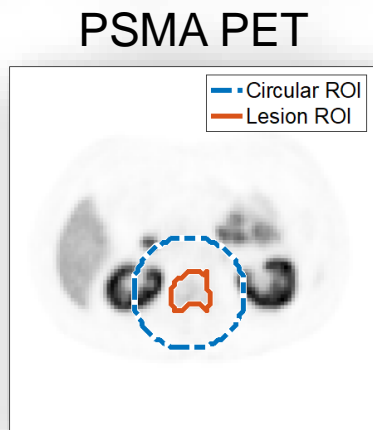
*Need discovery to understand fundamentals of disease for optimal care.*

# Assign patients to risk-stratified groups

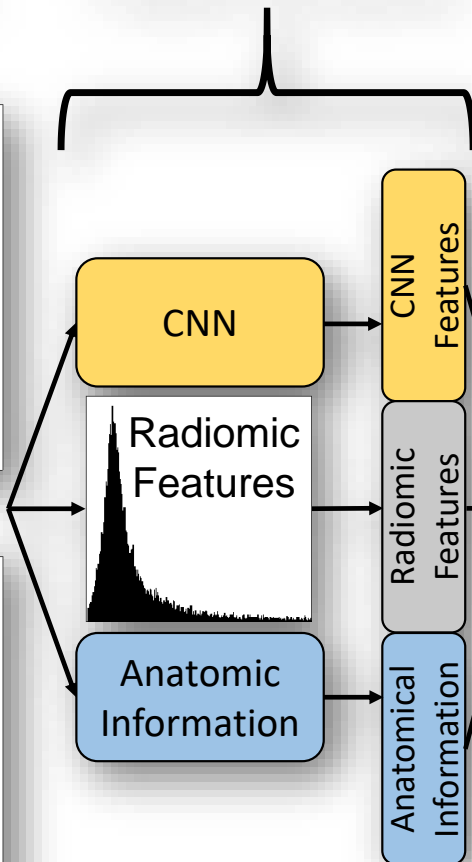
Step 1:  
Detection & Localization



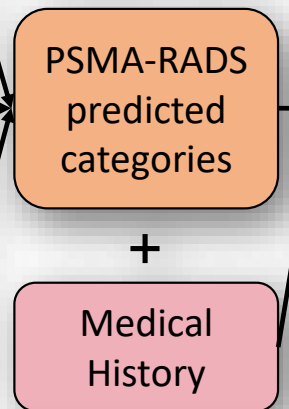
Step 2:  
Segmentation



Step 3:  
Feature Extraction



Step 4:  
Classification



Step 5:  
Decision



*“The lesion in the left 10<sup>th</sup> rib is PSMA-RADS 3B. Based on the courses of similar patients, advise <sup>177</sup>Lu PSMA 617 therapy”*



Kevin Leung, Ph.D.

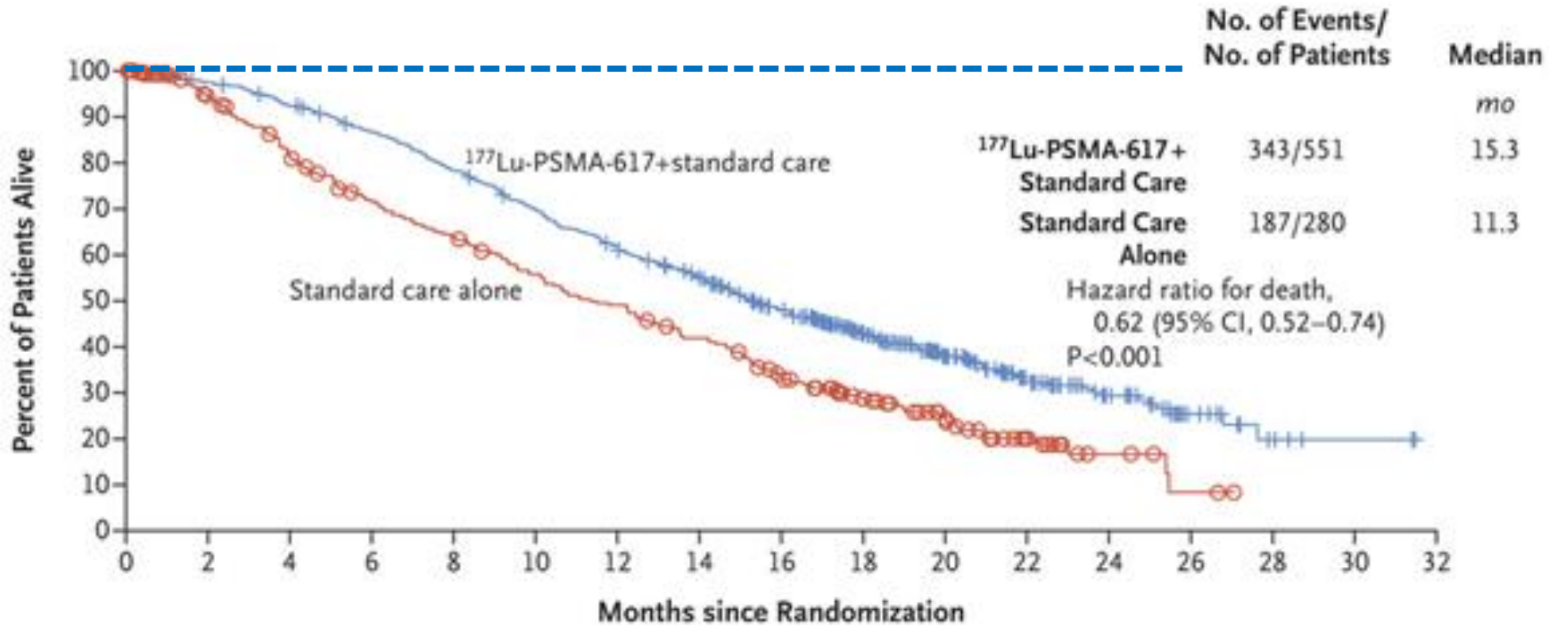
*Combining AI and MI*



SO MUCH  
FOR US TO DO



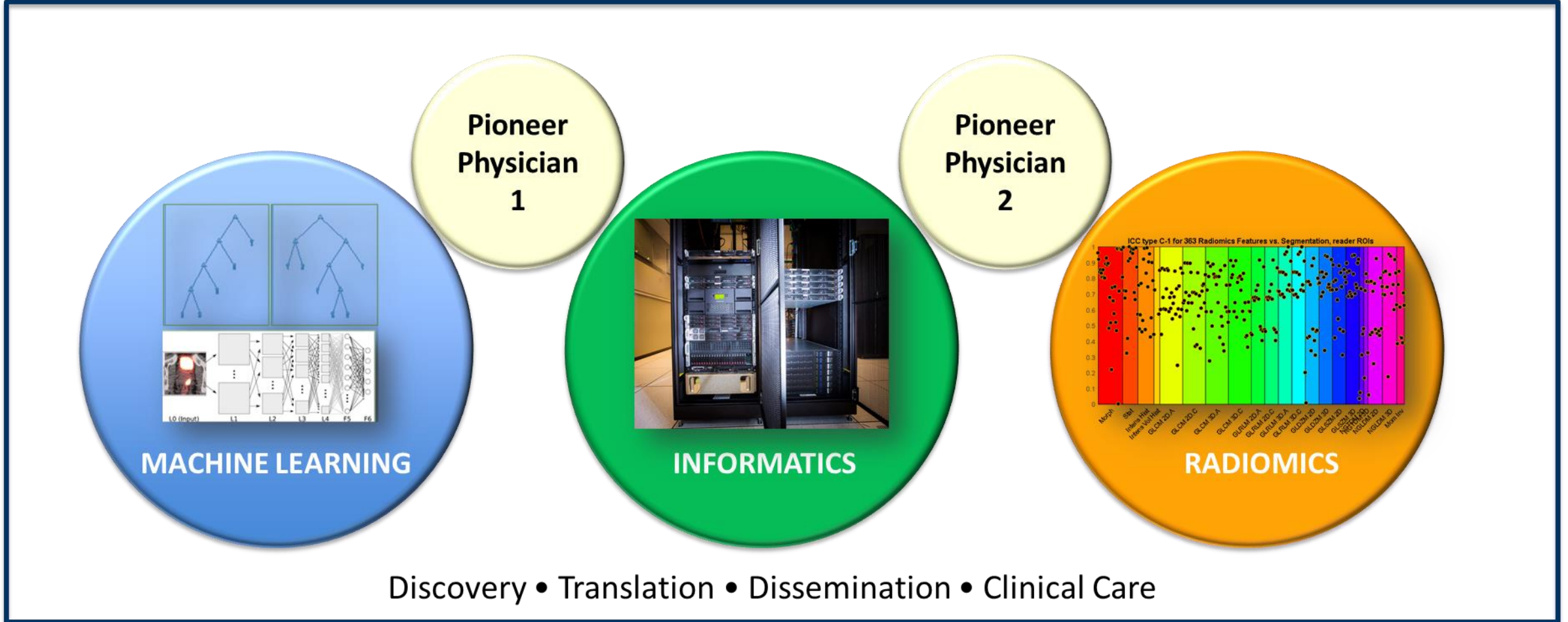
### Overall Survival



#### No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
<b>177Lu-PSMA-617+standard care</b>	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
<b>Standard care alone</b>	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

# A hybrid model advancing clinical care





# Small, smart and fully digital



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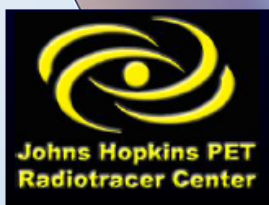
# Precision Molecular Imaging

• Cancer • Inflammation •

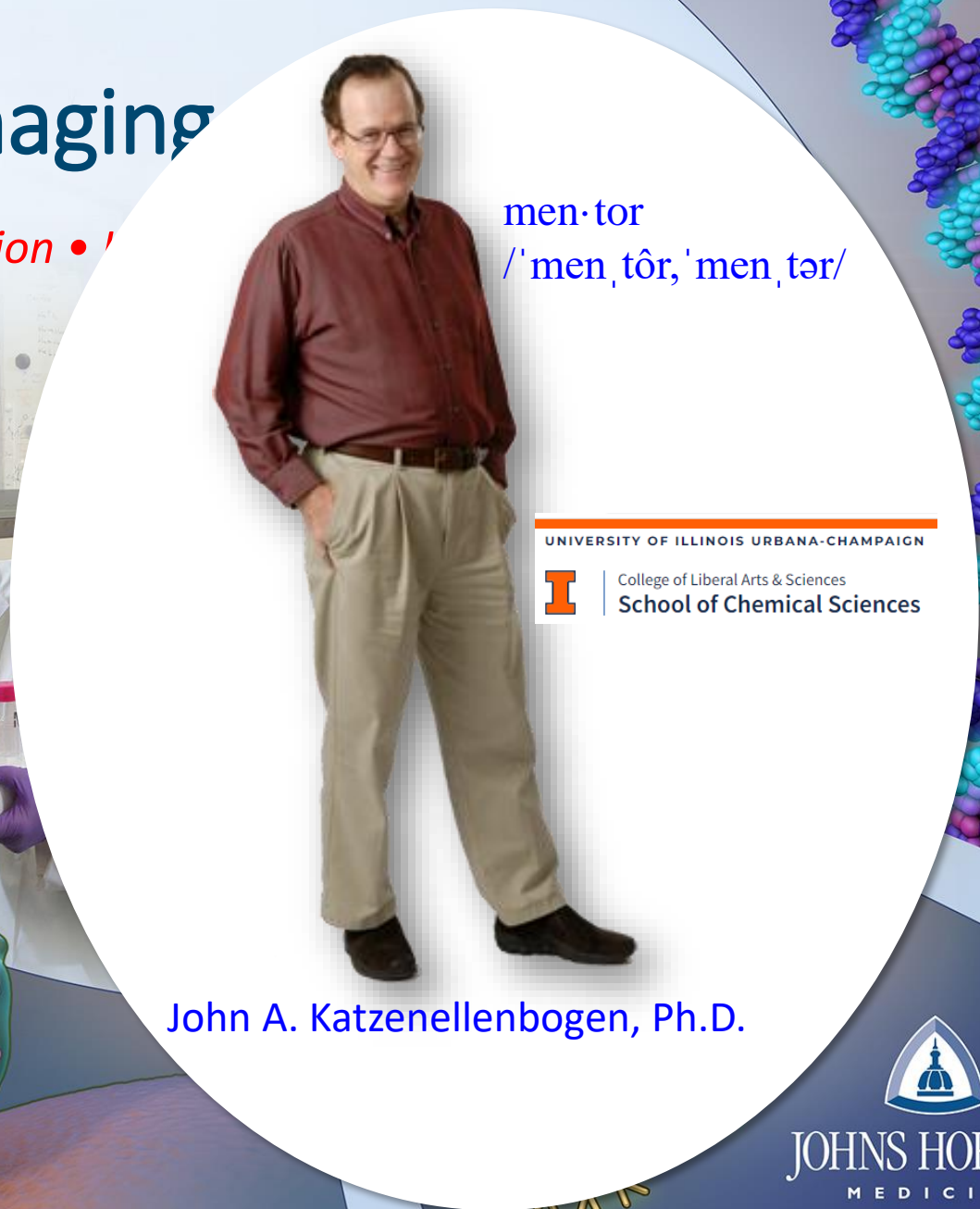
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Laurence Carroll	Bei Cheng

THE RUSSELL H. MORGAN DEPARTMENT OF  
RADIOLOGY AND RADIOLOGICAL SCIENCE



Johns Hopkins PET  
Radiotracer Center



men·tor  
/'men,tôr,'men,tər/

UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN



College of Liberal Arts & Sciences  
School of Chemical Sciences

John A. Katzenellenbogen, Ph.D.



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