Advancing Nuclear Medicine Through Innovation

National Academies of Science 2007 Report

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EVOLUTION IN IMAGING

- **Anatomical** (Plain films, CT, MRI, US, Optical)
- **Functional** (Angiography, Doppler, NM, DCE-MRI)
- **Molecular** (PET, SPECT, MRS, Fluorescence, Smart-contrast enhanced MRI)

Goals of Molecular Imaging

Facilitate the understanding of the molecular basis of disease

Provide a mechanism for rapid translation of developments in cellular and molecular biology and other basic sciences into improvements in patient care

Applications of Molecular Imaging

- Visualization of tissue metabolism, biochemistry and molecular targets/receptors using labeled or tagged biologically active compounds
- Adjunct to diagnosis and staging of disease in the absence of anatomic findings
- Determination of biological response to specific therapeutic agents
- Understanding the pharmacology of new drugs using labeled analogues

Existing and Emerging Clinical Molecular Imaging

- PET/CT
- SPECT/CT
- MR Spectroscopy
- Contrast enhanced US/Doppler
- Bio-active MR contrast agents
- PET/MRI

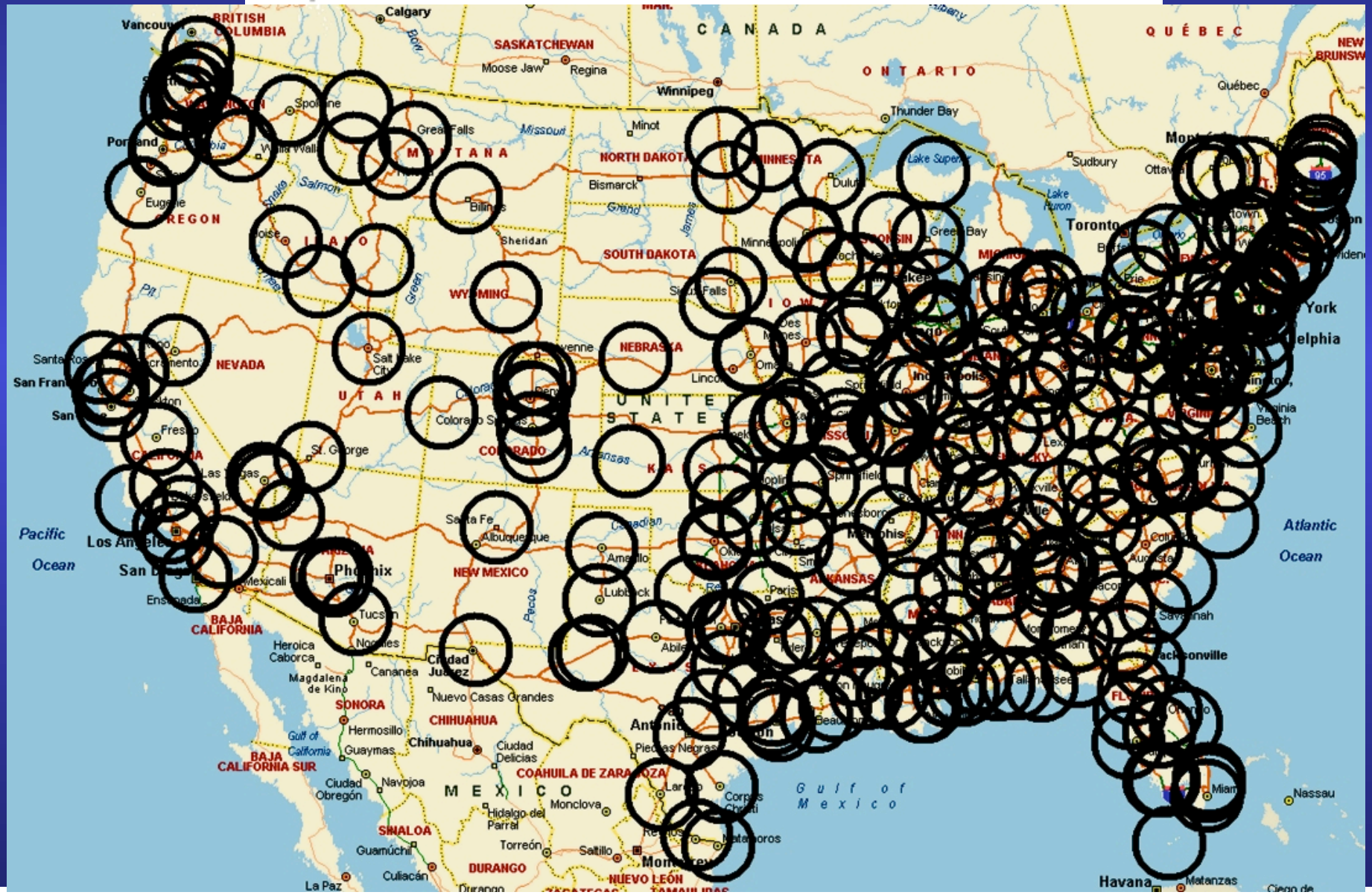
Positron Emission Tomography

A clinical molecular imaging modality that enables visualization and quantification of biochemical processes *in vivo*

How Available is Positron Emission Tomography in the United States?

James C. Patterson II, MD, PhD, Michael L. Mosley

Biomedical Research Foundation of Northwest Louisiana, Louisiana State University Health Science Center, 1501 Kings Highway, Shreveport, LA 71103, USA

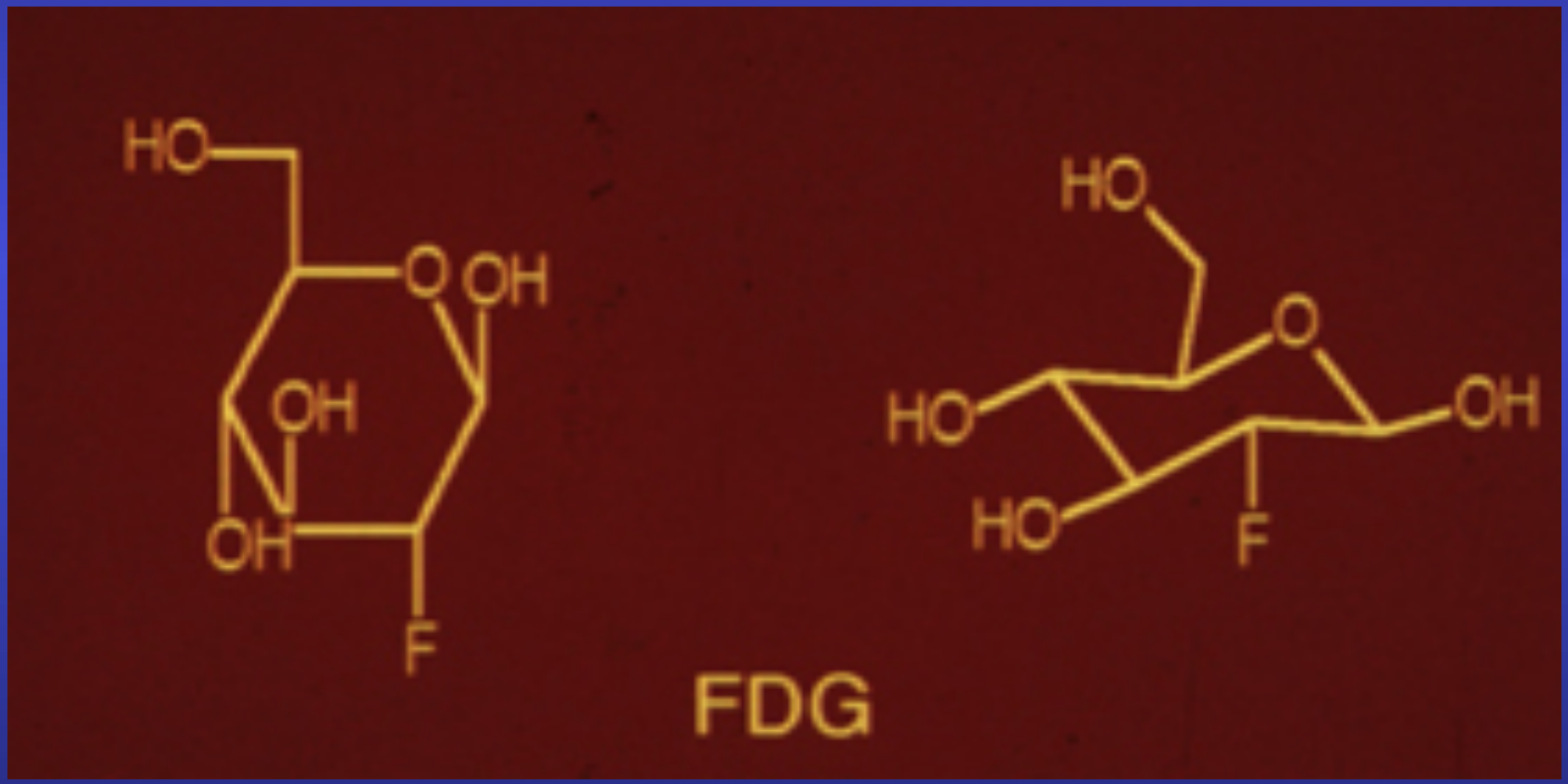


Increase in PET Imaging Sites

Year	Sites	Annual Increase
2001	690	
2002	1080	36%
2003	1500	39%

Bio-Tech Systems Radiopharmaceutical Report 2004

PRIMARY PET RADIOTRACER: FDG



FDG Sales

Year	Sales ($million)	Annual Increase
2003	$202	
2004	$270	34%
2010	$795	

Bio-Tech Systems Radiopharmaceutical Report 2004

Increase in PET Procedures

Year	Procedures (million)	Annual Increase
2003	1.0	
2004	1.4	37%
2010	3.2	

Bio-Tech Systems Radiopharmaceutical Report 2004

PET/CT Hybrid Technology

The benefits of both PET and CT can be used to improve diagnostic accuracy and optimize patient care

Paradigm Shift

Data from concurrent studies becomes *essential* for timely diagnosis and management decisions

Percent of dedicated PET and PET/CT scanners in the U.S.

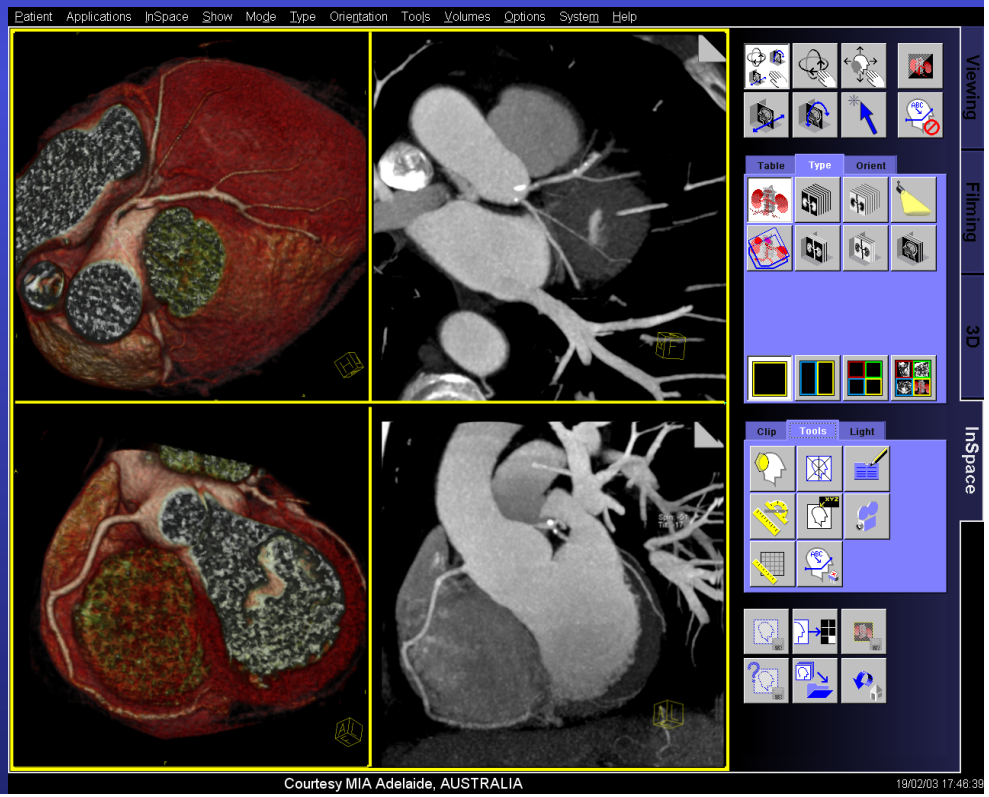
Year	PET	PET/CT
2001	91%	9%
2002	67%	33%
2003	46%	54%
2004 (early)	33%	67%

Bio-Tech Systems Radiopharmaceutical Report 2004

Multi-slice CT Applications

CT:

- The Power of Multi-slice CT
  - 70 cm whole body in 25 sec
- Breath-hold studies
  - High resolution lung <10 s
- Arterial studies
  - cerebral angiography <4 s
- Cardiac exams
  - scan time < 20 sec



Clinical Applications of FDG/PET: *Oncology*

Diagnosis and Staging

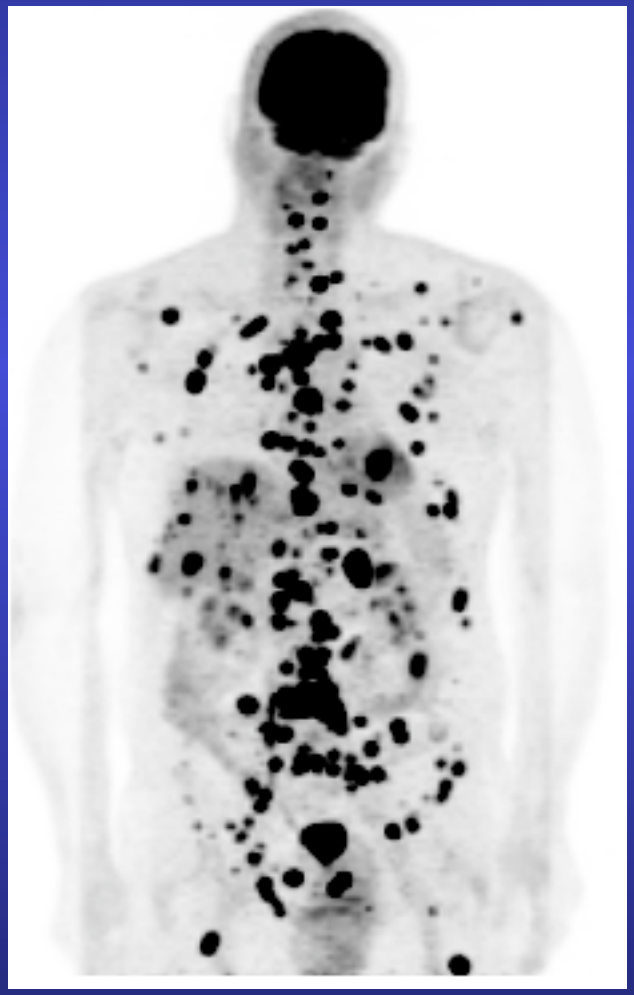
Treatment Planning

Treatment Response

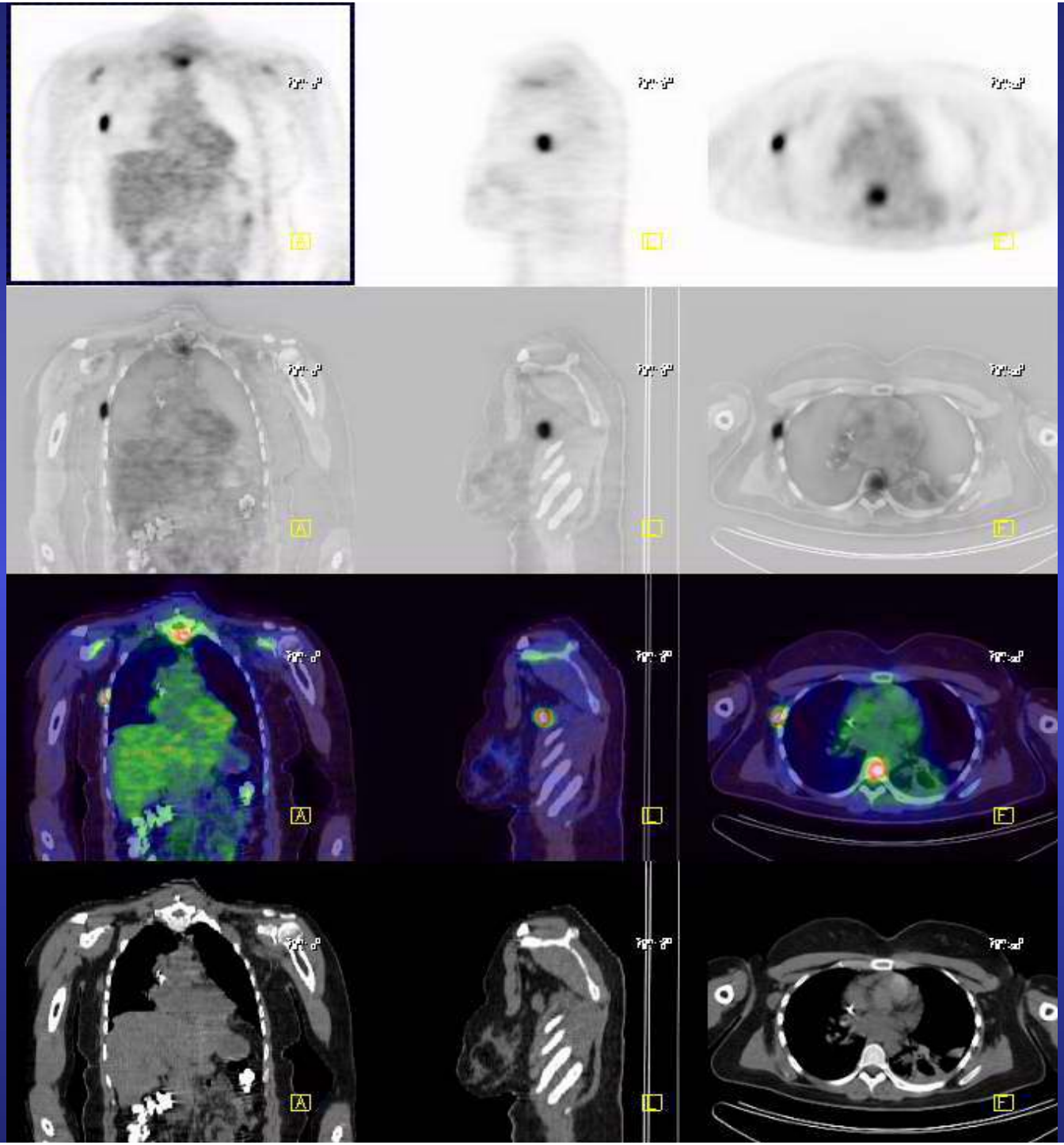
Detection of Recurrent or Residual Disease

Re-staging

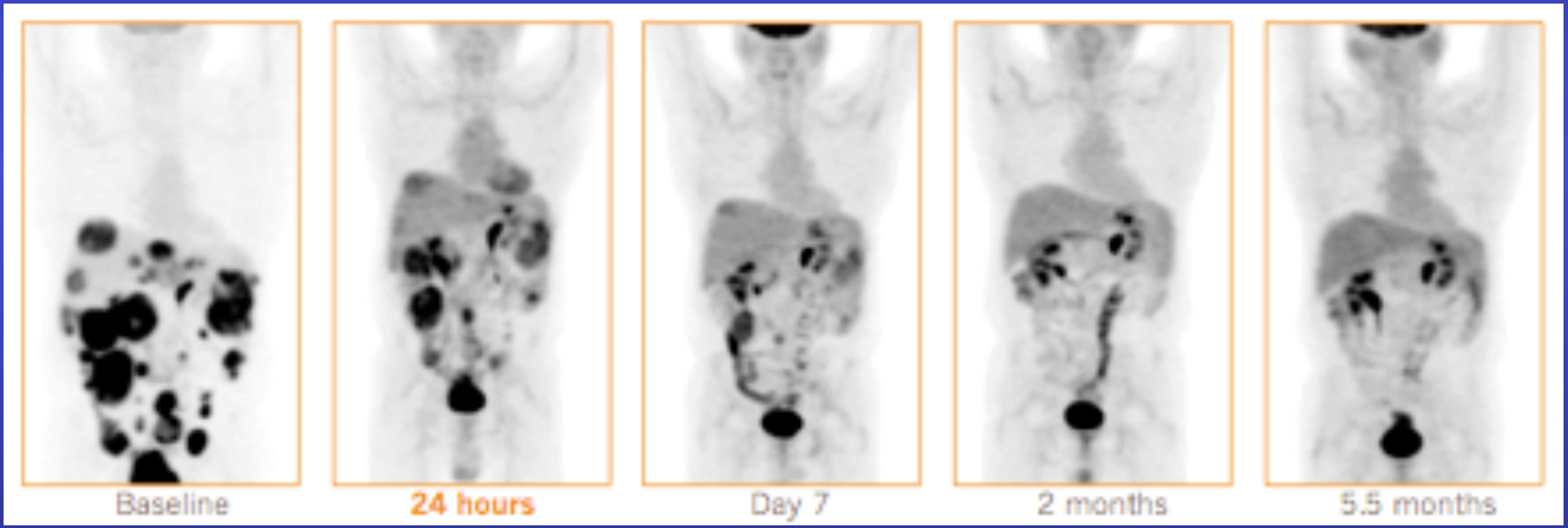
Melanoma



Breast CA



Early Treatment Response: GIST

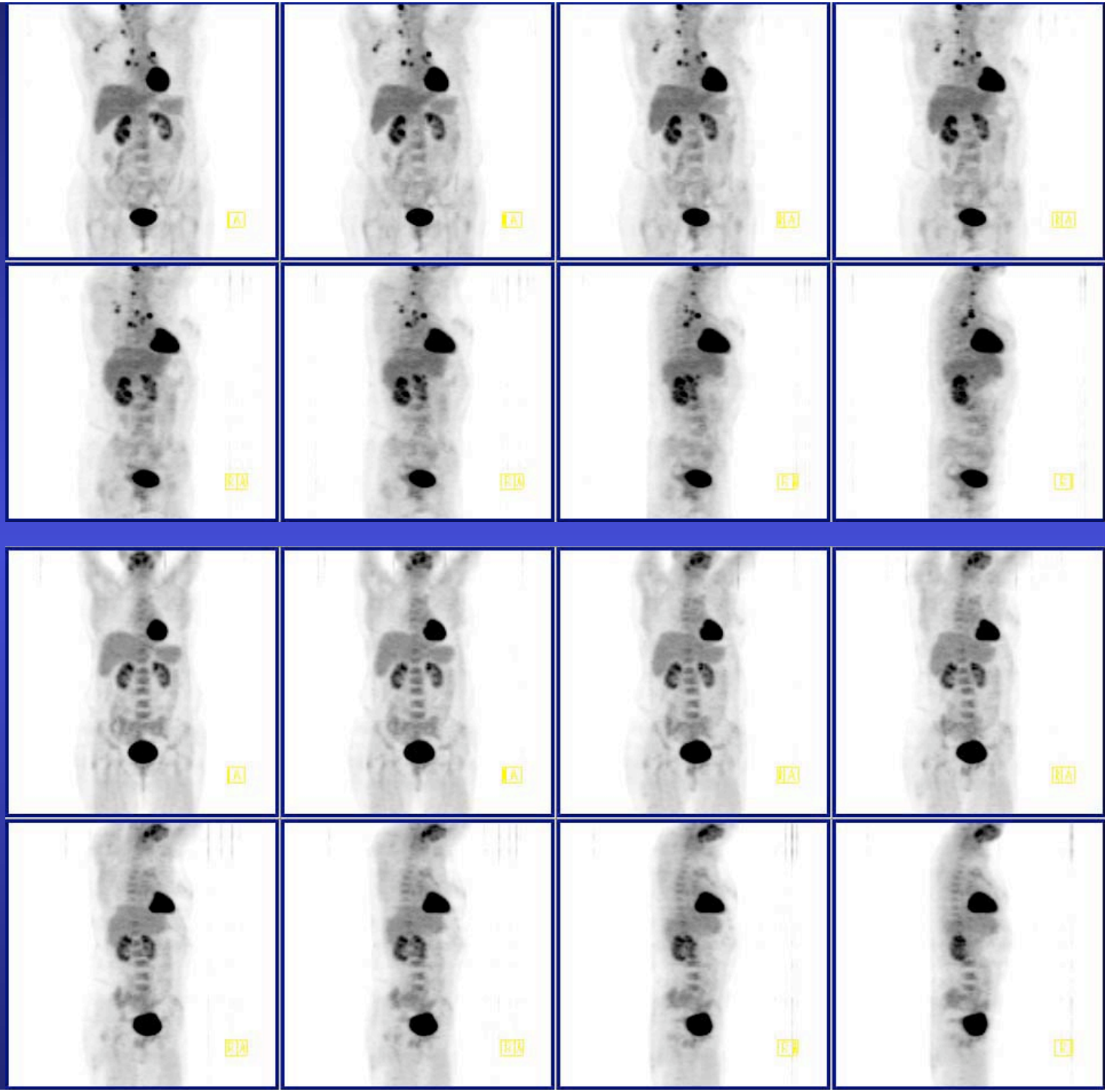


Van den Abbeele et al. Dana-Faber/Novartis ST1571

Pre-Tx

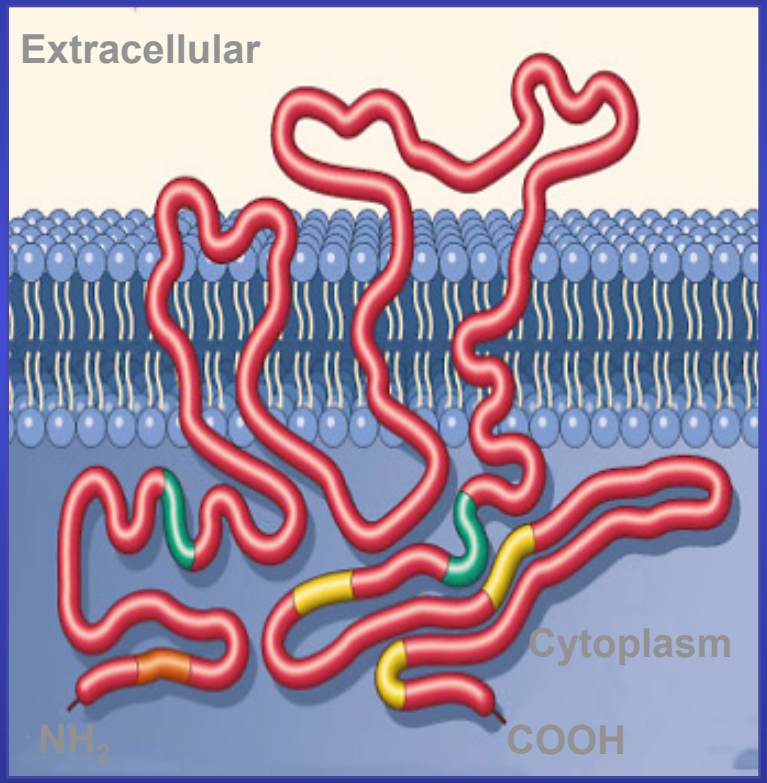
Breast Cancer

Post-Tx Day 14



Combining Molecular Medicine with Molecular Imaging

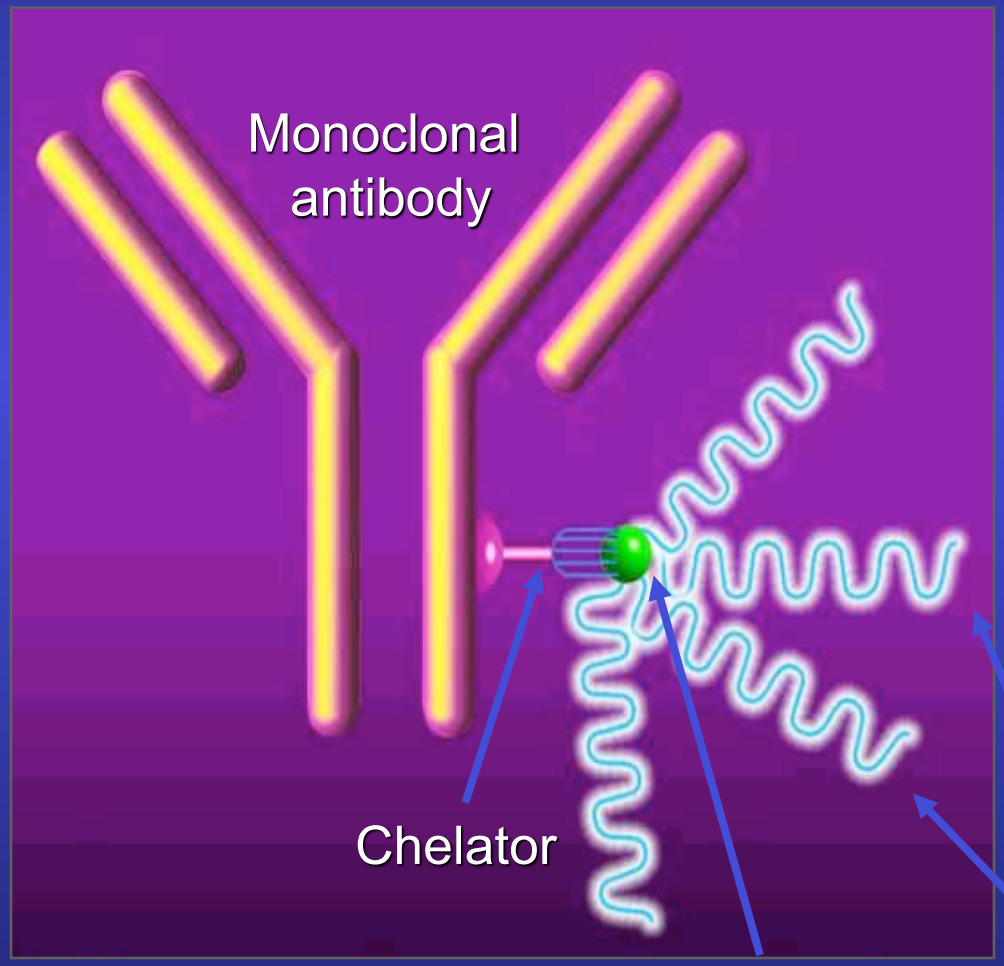
CD20 Structure



- 297 amino acids
- 4 transmembrane domains
- Intracellular phosphorylation consensus sequences for serine/threonine kinases
  - Protein kinase C (orange)
  - Calmodulin/calcium (green)
  - Casein kinase II (yellow)

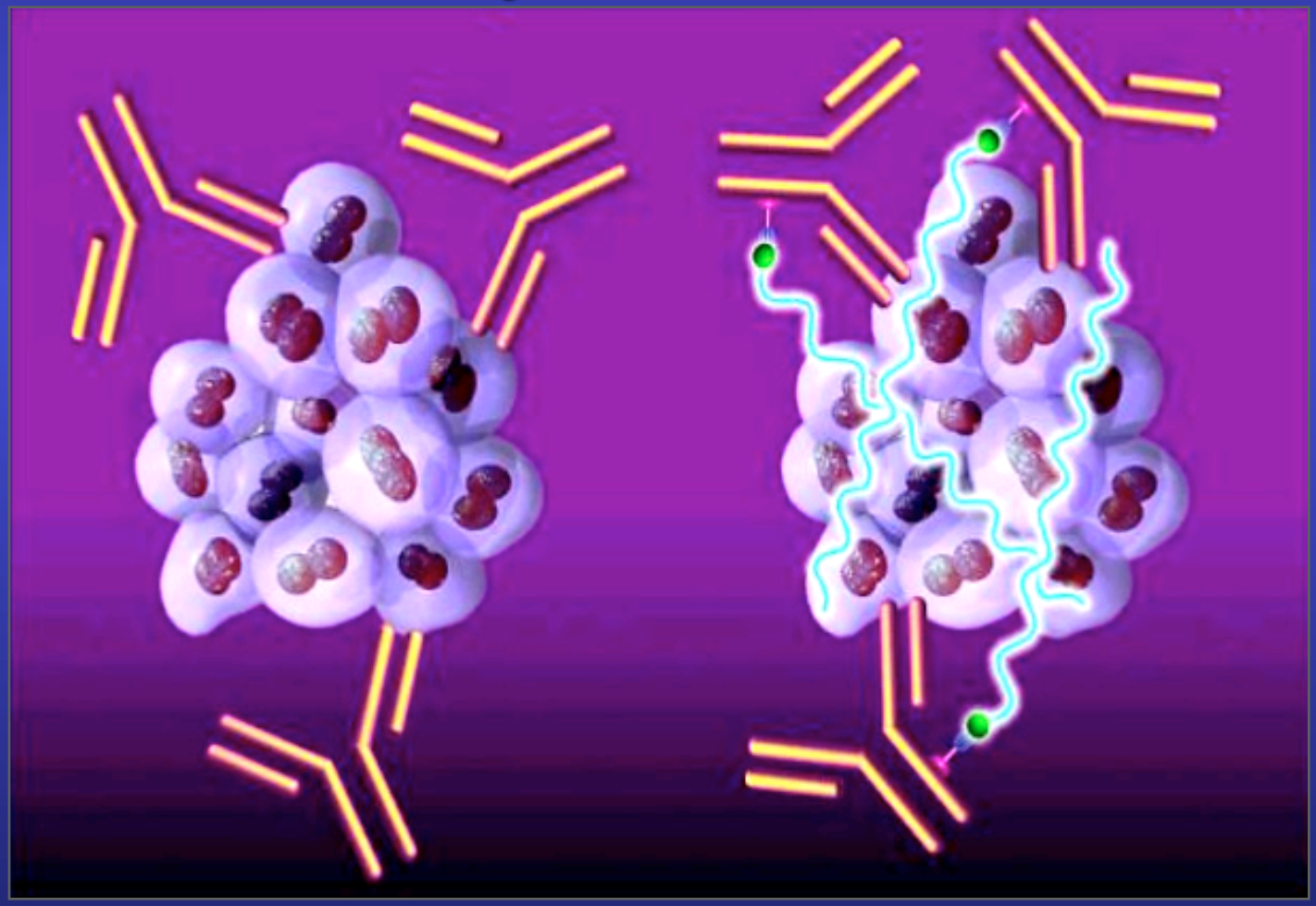
Riley and Sliwkowski. *Semin Oncol.* 2000;27(suppl 12):17-24.

^{90}Y Zevalin™ Radioimmunotherapy Delivers Increased Cytotoxicity by Antibodies

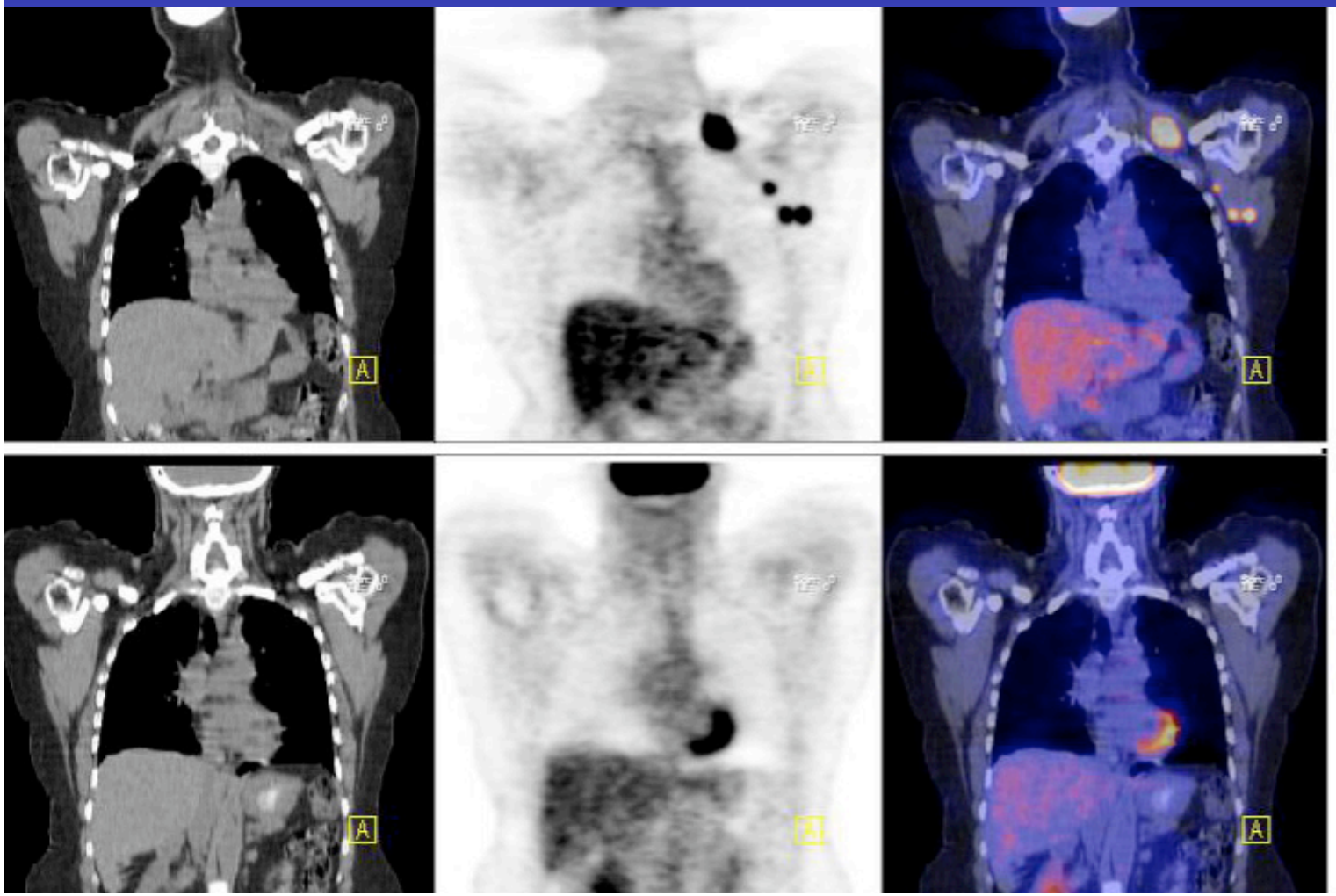


- Ibritumomab
  - Murine monoclonal antibody parent of Rituxan® (rituximab)
- Tiuxetan
  - Conjugated to antibody, forming strong urea-type bond
  - Stable retention of ^{90}Y

^{90}Y Zevalin™ Produces a Crossfire Effect



Non-Hodgkin's Lymphoma: Pre- and Post-Zevalin



Before Zevalin

After Zevalin

Cyclotron Produced Positron Emitters

Conventional Isotopes

	Reaction	$T_{1/2}$ (min)
^{15}O	$^{14}N(d,n)^{15}O$	2.04
^{13}N	$^{16}O(p,n)^{13}N$	9.97
^{11}C	$^{14}N(p,n)^{11}C$	20.3
^{18}F	$^{18}O(p,n)^{18}F$	109.7

Non-Conventional Isotopes

	Reaction	$T_{1/2}$ (min)
^{60}Cu	$^{60}Ni(p,n)^{60}Cu$	23.7 min
^{94m}Tc	$^{94}Mo(p,n)^{94m}Tc$	52 min
^{66}Ga	$^{66}Zn(p,n)^{66}Ga$	9.5 h
^{64}Cu	$^{64}Ni(p,n)^{64}Cu$	12.8 h
^{86}Y	$^{86}Sr(p,n)^{86}Y$	14.7 h
^{76}Br	$^{76}Se(p,n)^{76}Br$	16.2 h

PET National Coverage Determination
CMS Transmittal 31 Change Request 3741

- Diagnosis, staging and re-staging
  - NSCLC, lymphoma, melanoma, esophageal cancer, colorectal cancer, head & neck cancer
- Solitary pulmonary nodule
- Staging and re-staging metastatic breast cancer; *monitoring response to therapy*
- Re-staging thyroid cancer
- Myocardial viability – FDG
- Myocardial perfusion – Rubidium; ^{13}N Ammonia
- Brain – pre-surgical evaluation of refractory seizures
- Brain – dementia for differential diagnosis of FTD vs. AD
- Initial staging newly diagnosed cervical cancer

(See Section III.1 Covered indications for PET scans and limitations / requirements for usage of CIM, 50-36 for exact verbiage.)

Future Coverage for FDG PET
"Coverage with Evidence Development" (CED)

For oncology procedures which have not yet been evaluated completely for positive or negative coverage determinations by CMS.

CMS and ACRIN (American College of Radiology Imaging Network) will establish a PET "Registry"

Participating PET sites are enrolling patients in this registry which will collect pre-and post-PET clinical data from referring physicians to assess PET's ability to assist in patient management on non-covered tumors and indications.

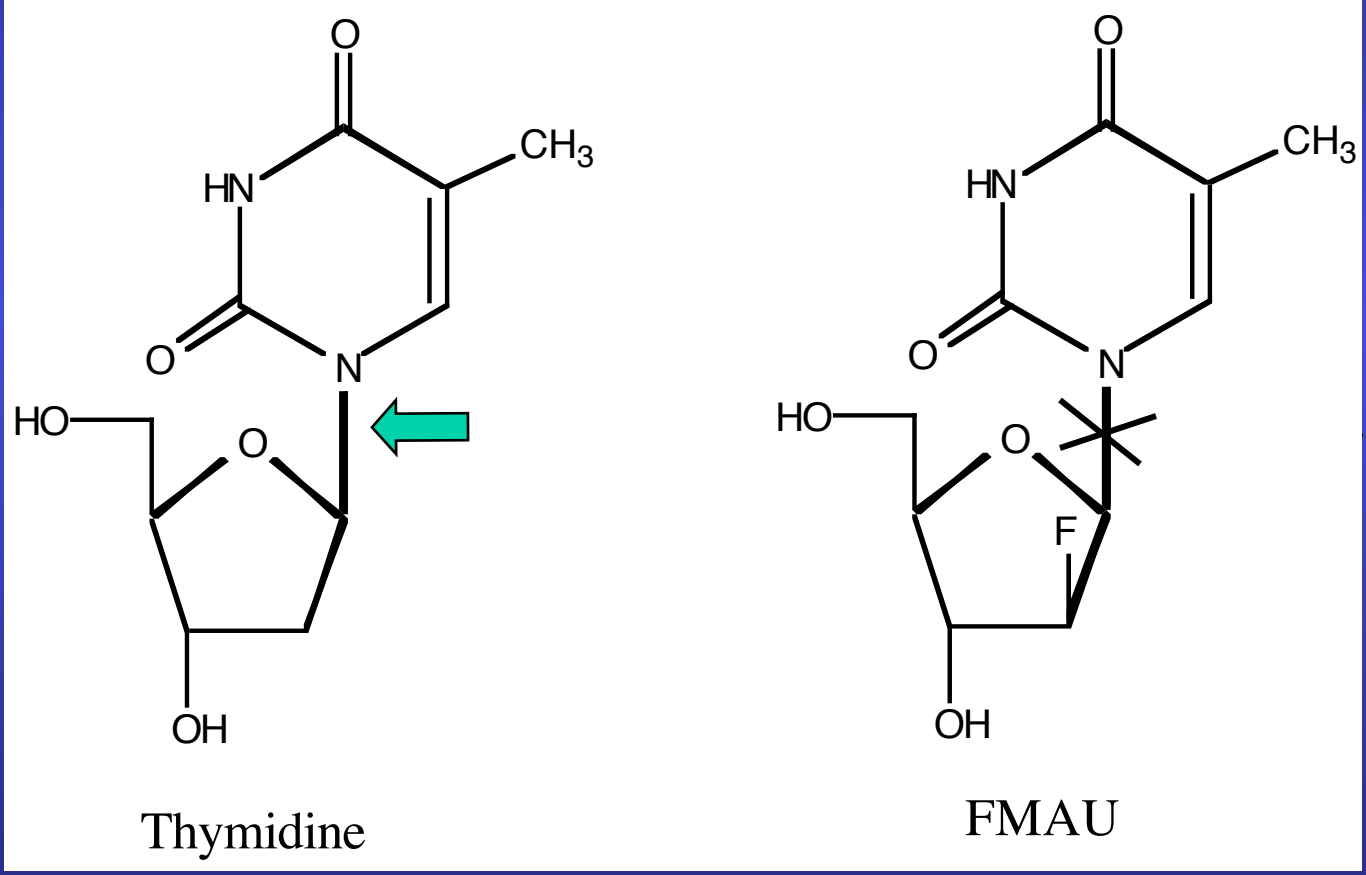
Potential Agents for Imaging Cellular Proliferation

- SPECT/Planar Imaging
  - [$^{131,\ 123}$ I] IUDR
  - [^{123} I] FIAU
- PET Imaging
  - [^{11}C] Thymidine
  - [^{11}C] or [^{18}F]-FMAU
  - [^{18}F] FLT
  - [^{124}I] or [^{18}F]-FIAU
  - [^{76}Br] BrUdR

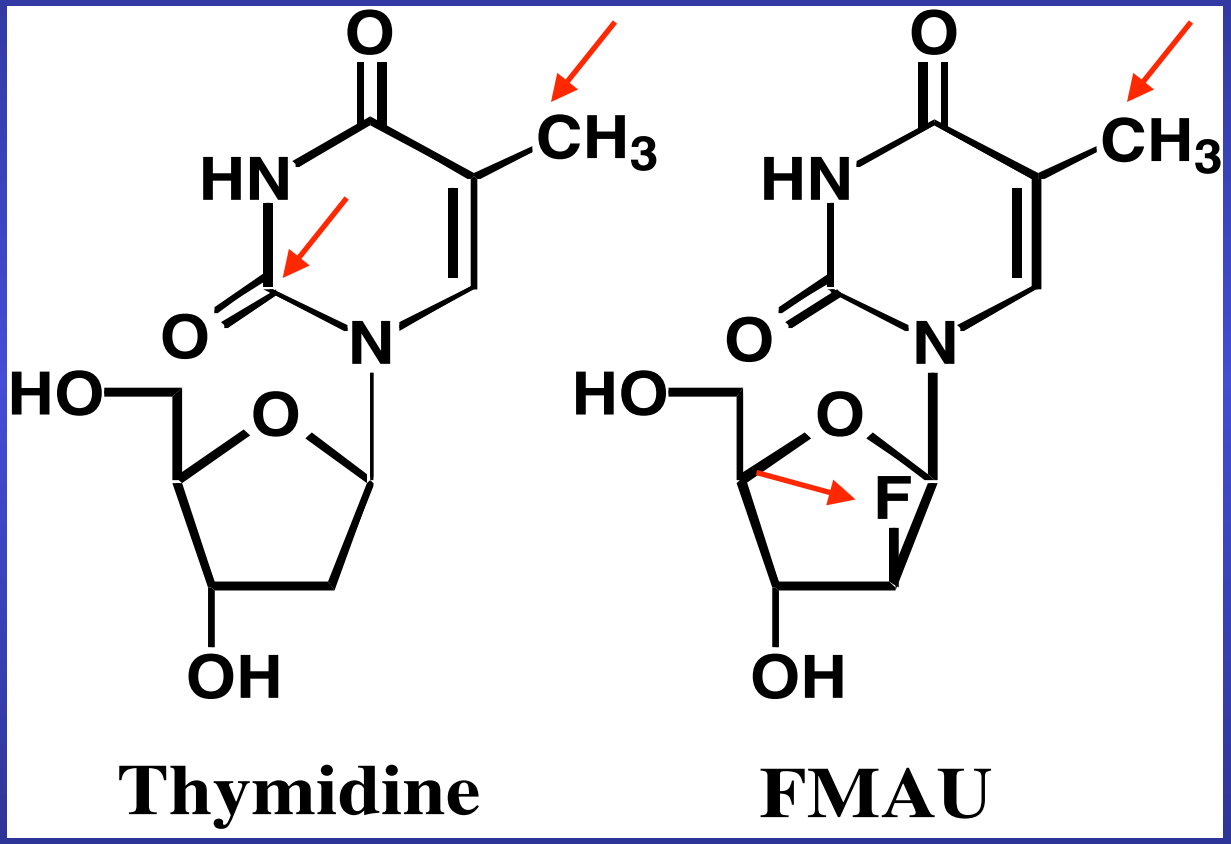
Ideal Cell Proliferation Marker

- A radiotracer which has similar *in vivo* properties to thymidine, including cellular transport, phosphorylation, and DNA incorporation, but limited catabolism
- Potential Development
  - FMAU shares many of these *in vivo* characteristics of thymidine, yet is not significantly catabolized *in vivo*.
  - [^{11}C/^{18}F]-FMAU should be a potential compound for PET imaging studies of cellular proliferation

FMAU:
A Novel PET Marker of Cell Proliferation



RADIOLABELING OF THYMIDINE AND FMAU

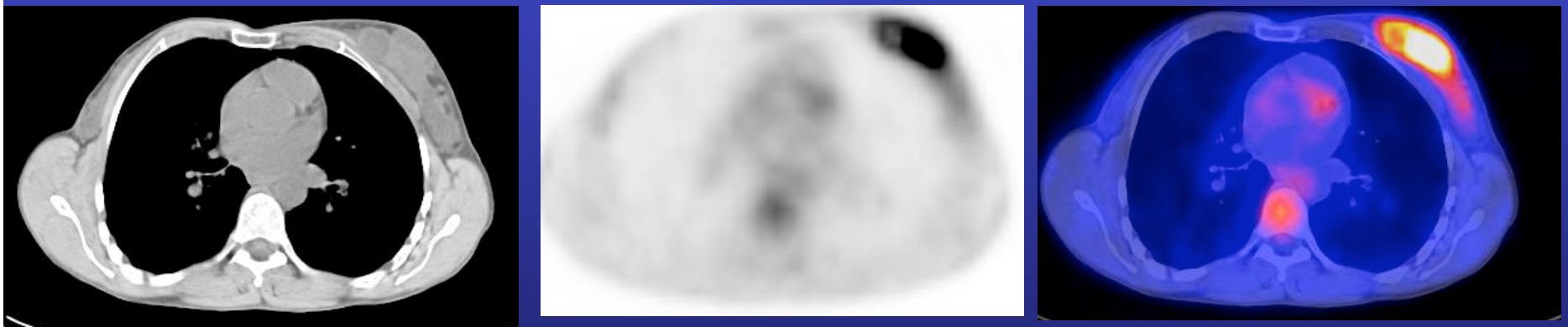


=Sites of labeling

FMAU: Breast Cancer

FMAU

FDG



FMAU for Oncologic Imaging

- Alternative to FLT for cell proliferation marker
- Properties most reflective of natural substrate except non-catabolized
- In clinical trials with physician-sponsored IND
- Lack of bone uptake and bladder activity may have clinical advantages over other agents
- Prepared with C-11 or F-18
- Protected IP
- Interest by FDA and industry for multi-center expansion

Translation to Clinical Studies

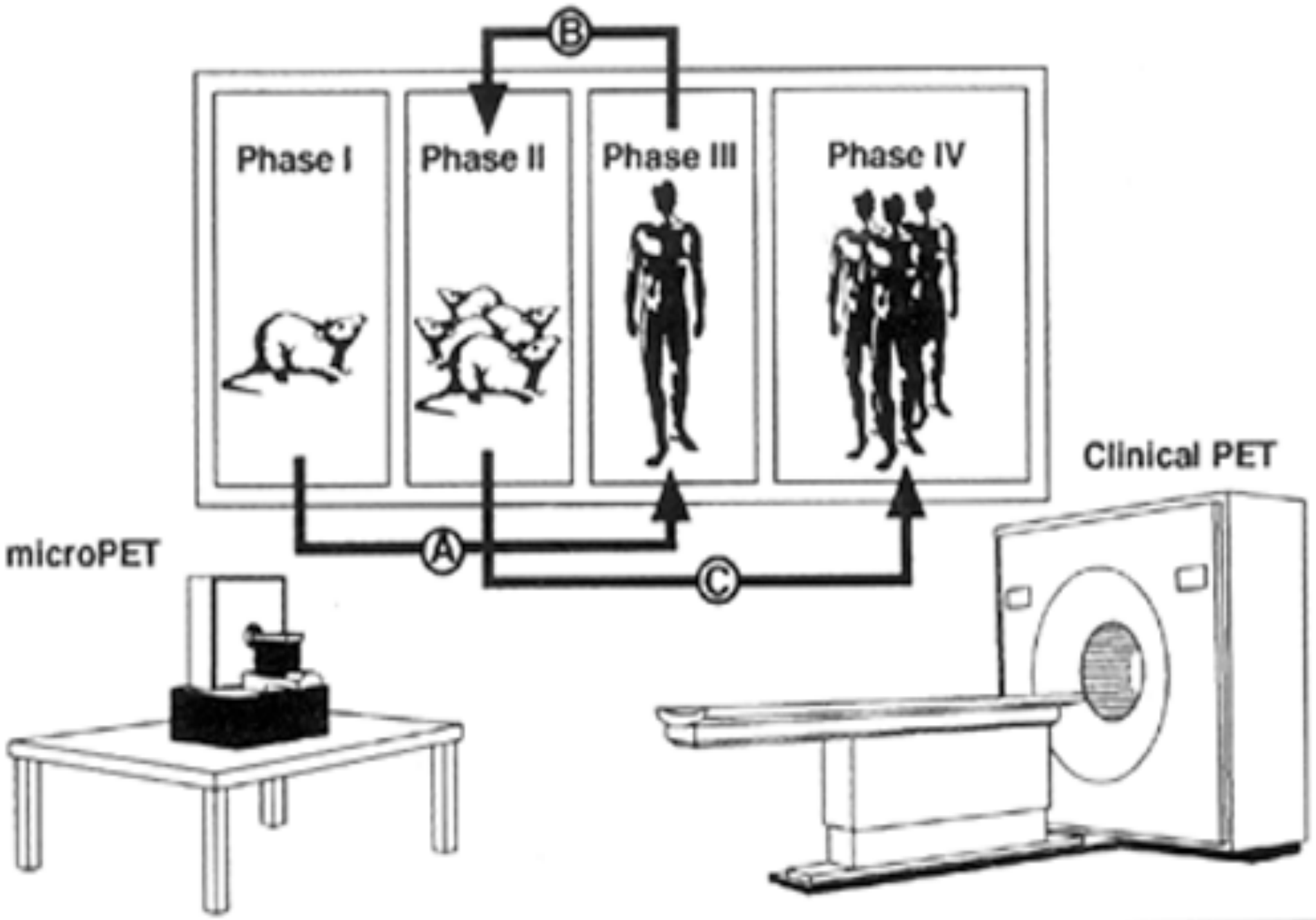
- IND or RDRC (dosimetry, toxicology)
- eIND
- Radiation Safety
- IRB

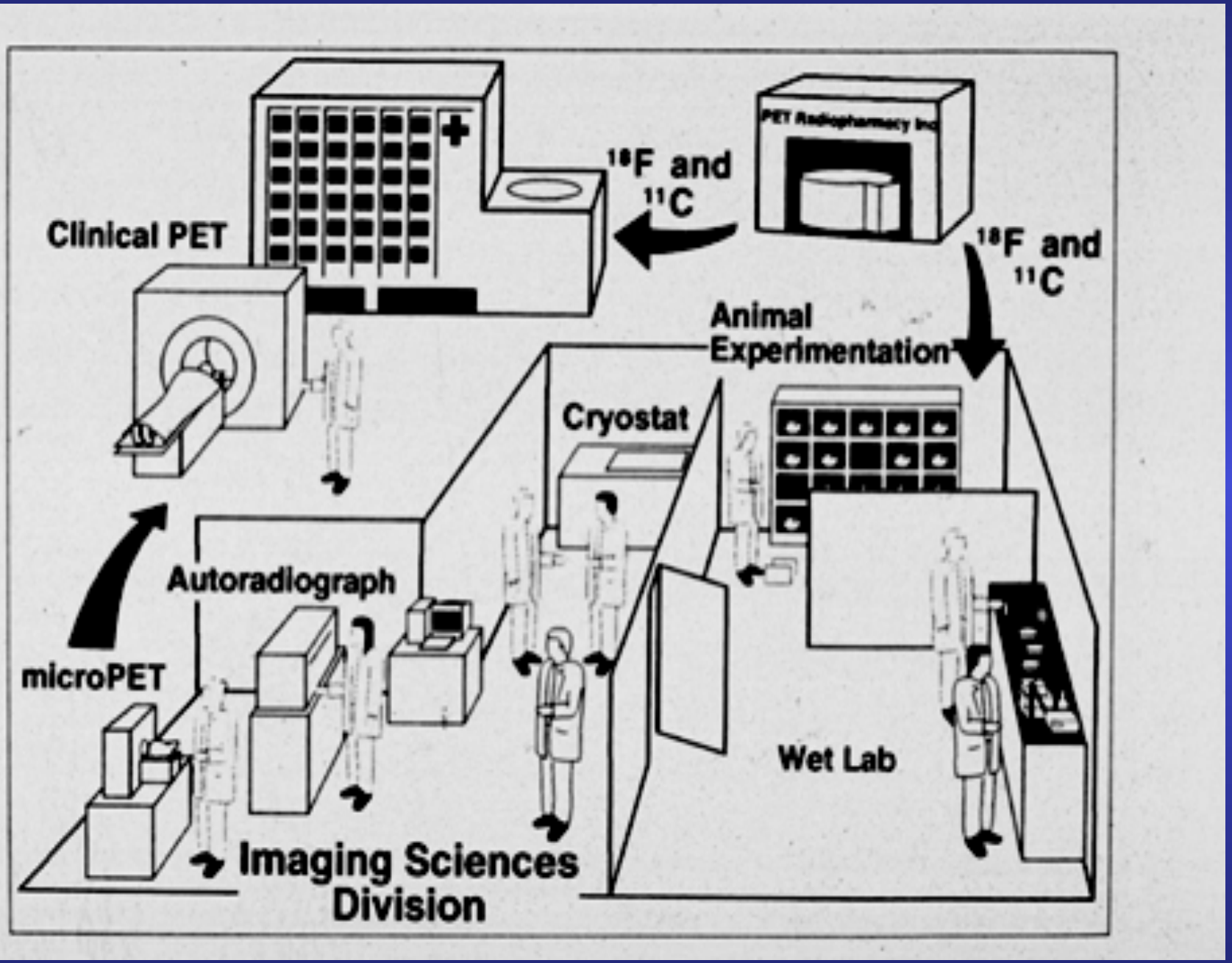
Small Animal and Cellular Imaging Instrumentation

- microPET
- microCT
- Fluorescence/Bioluminescence Scanners
- Confocal Microscopy
- Quantitative Autoradiography
- micro/high field MR
- microSPECT

In most cases augmented by innovation in design and utilization of novel radiotracers and contrast agents

A Clinical Trials Demonstration Project




Clinical PET
^{18}F and ^{11}C
^{18}F and ^{11}C
Animal Experimentation
Cryostat
Autoradiograph
microPET
Wet Lab
Imaging Sciences Division

"Targeted Imaging"
Drive Towards Personalized Medicine

- **Streamlining drug discovery: finding the right drug against the right target to treat the right disease *in the right patient*.**
- **For targeted imaging: finding the right molecular probe for the right target to monitor the right disease *in the right patient.***

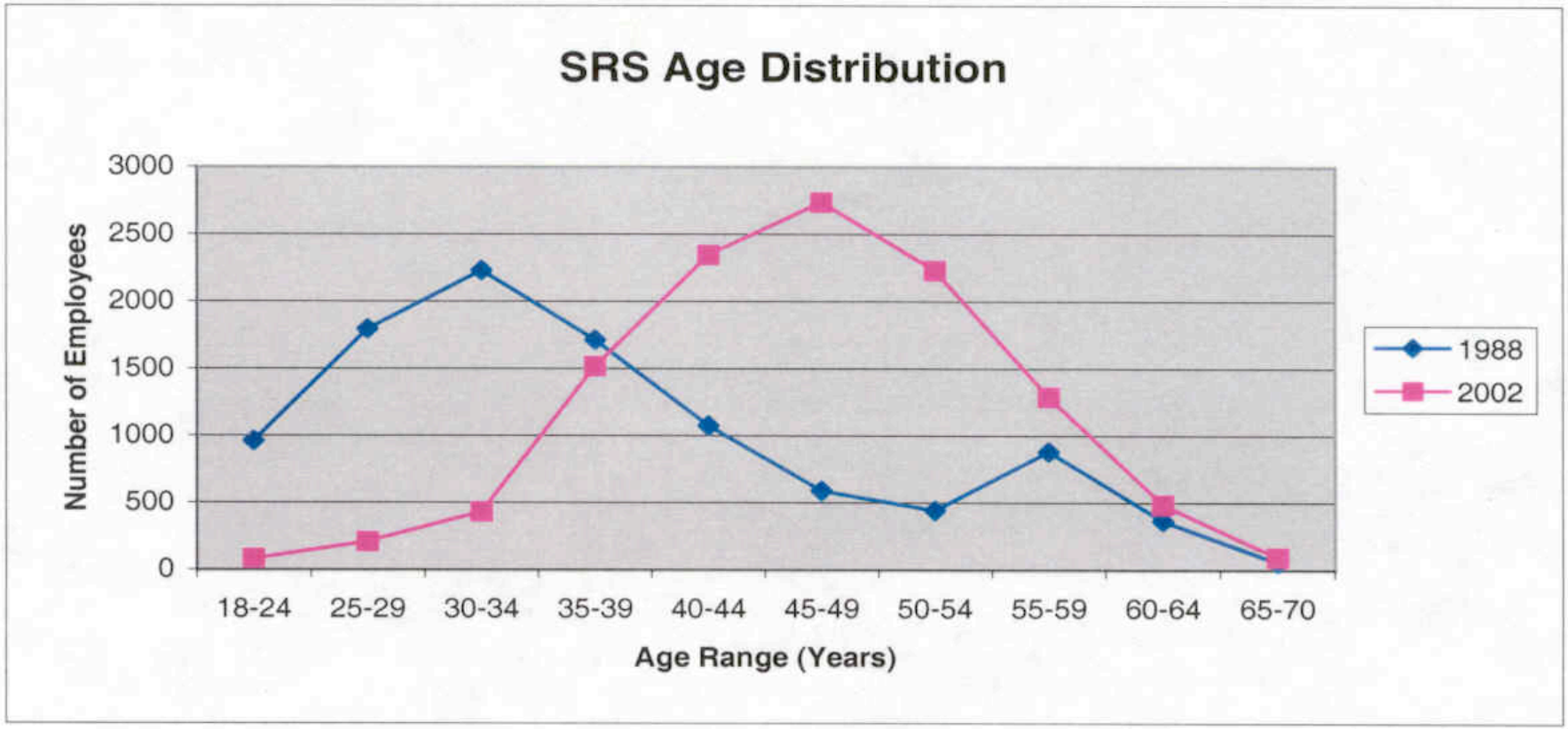
Uniform Protocols for Imaging in Clinical Trials

Initiated by NCI and FDA

Oversight Committee:
NCI, FDA, ACR, SNM, ASCO, NEMA, PhRMA, et al

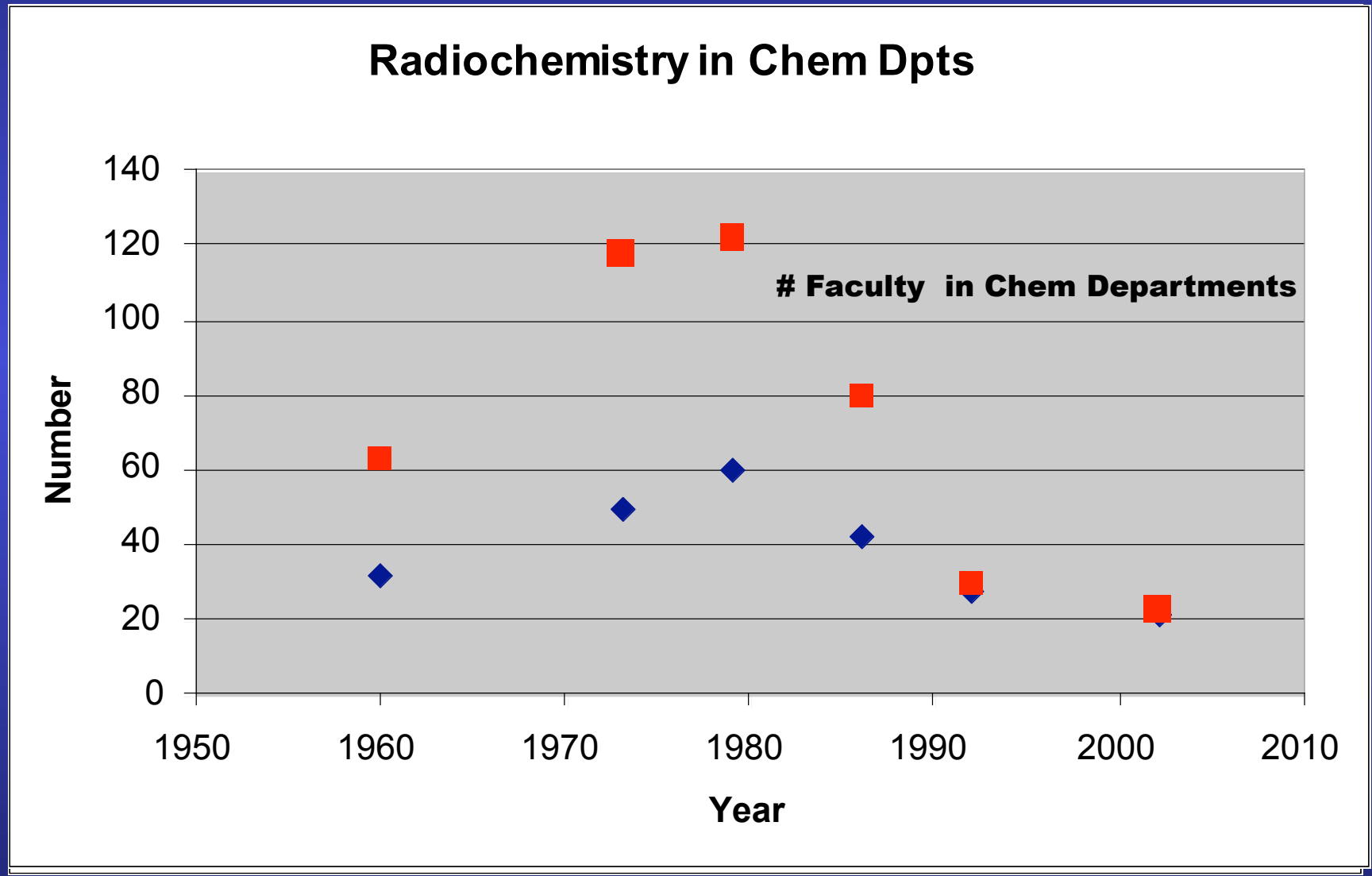
- Standardization of imaging technology platforms and protocols used in clinical trials is essential
- RECIST to be revisited
- Incorporation of Molecular Imaging technologies; surrogate markers

The DOE Nuclear Workforce

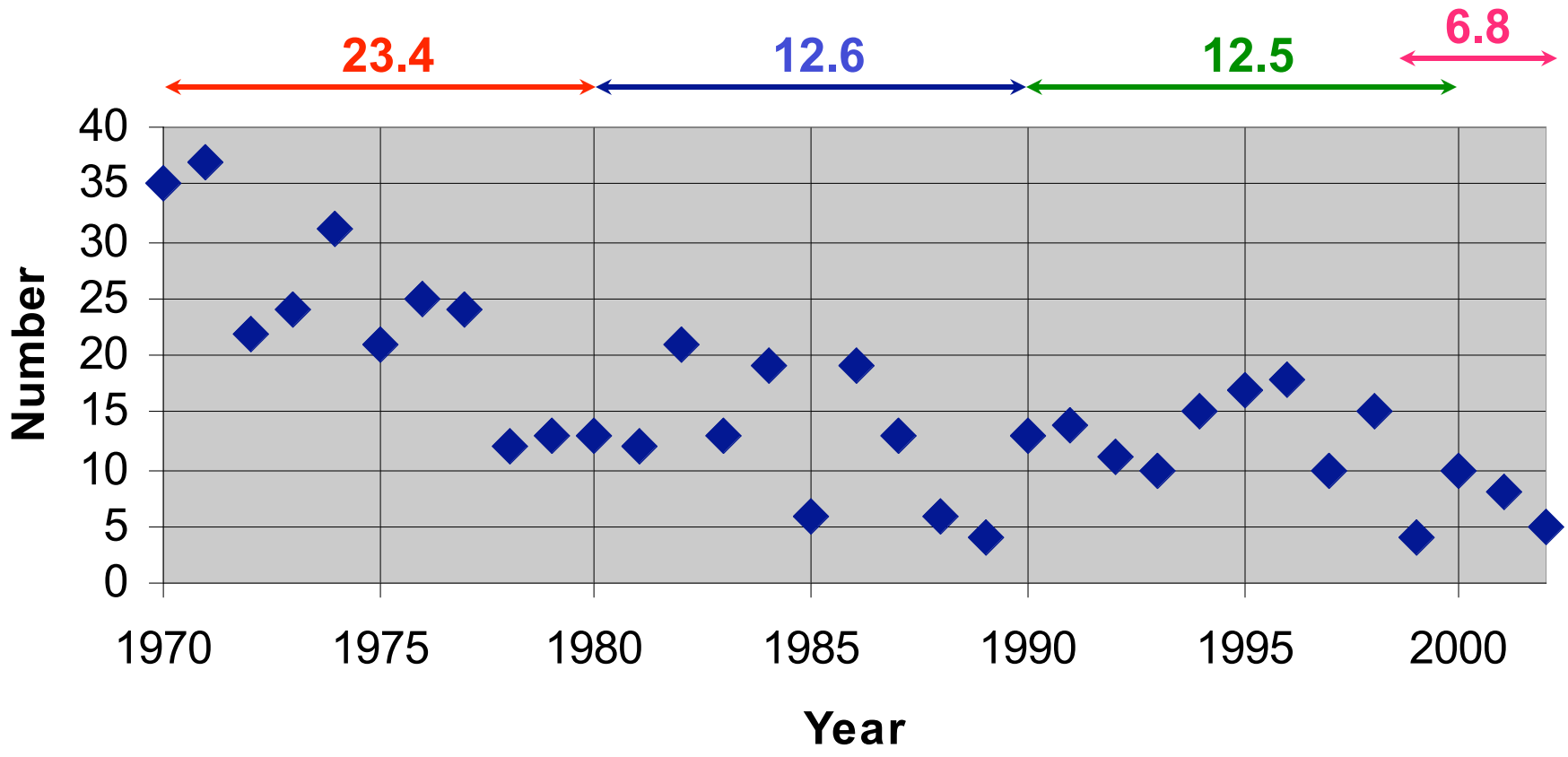


Courtesy of Prof. Sue B. Clark

Trends in Chemistry Faculty



Ph.D.s in Nuclear and Radiochemistry Awarded in the U.S.



Nuclear Physics vs. Nuclear/ Radiochemistry Ph.D. Graduates

- Number of chemistry & physics PhD's decreasing since early 1990's
- ~ 82 PhD's in nuclear physics per year (2000, 2001), out of ~1,400 PhD's in physics
- < 10 PhD's in radiochemistry per year (2000, 2001), out of ~ 1,800 PhD's in chemistry

STATUS REPORT

- Several sophisticated molecular imaging technologies are currently available for use in clinical trials at academic institutions throughout the US
- The need for use of radio-, optical and other forms of biologically active tracers or contrast agents to diagnose disease and assess efficacy of novel therapeutics is growing, particularly with the use of cytostatic drugs
- Hybrid imaging is becoming increasingly important as more biologically-targeted tracers are introduced
- Translational research and drug discovery/development will depend increasingly on targeted imaging for success

HOWEVER…

- The combined effects of increasing regulatory burden, work-force shortages and lack of protocol standardization have the potential to create the "perfect storm" in imaging research
- Reduction in Federal funding at NIH threatens success of the success of the Critical Path and the movement towards Personalized Healthcare
- Elimination of DOE funding in nuclear medicine will have a long-lasting negative impact on development of the next generation of imaging devices and radiopharmaceuticals
- DRA cuts and Part B reductions will significantly reduce or eliminate the ability of centers to fund research from practice revenue

National Academy of Sciences

"State of the Science in Nuclear Medicine"

Funded by DOE and NIH

15 Experts (National and International):
nuclear medicine and radiation oncology;
physics and chemistry;
engineering and instrumentation

- *Future needs of radiopharmaceutical development for the diagnosis and treatment of human disease*
- *Future needs for computational and instrument development for more precise localization of radiotracers in normal and aberrant cell physiologies*
- *National impediments to the efficient entry of promising new radiopharmaceutical compounds into clinical feasibility studies and strategies to overcome them*
- *Impacts of shortages of isotopes and highly trained radiopharmaceutical chemists and other scientists on nuclear medicine research, and short- and long-term strategies to alleviate these shortages*

Advancing Nuclear Medicine Through Innovation

Committee on State of the Science of Nuclear Medicine

Nuclear and Radiation Studies Board
Division of Earth and Life Sciences
Board on Health Sciences Policy
Institute of Medicine

National Research Council and Institute of Medicine
of the National Academies
National Academies Press 2007
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NAS FINDINGS

- Loss of Federal Commitment for NM Research
- Cumbersome Regulatory Requirements
- Inadequate Domestic Supply of Medical Radionuclides for Research
- Shortage of Trained Nuclear Medicine Scientists
- Need for Technology Development and Transfer

IMPEDIMENTS

- There is no short- or long-term programmatic commitment by any agency to funding chemistry, physics and engineering research and associated high-technology infrastructure (accelerators, instrumentation, and imaging physics) which are at the heart of NM technology research and development
- There is no domestic supplier for most of the radionuclides used in day to day NM practice in the US and no accelerator dedicated to research on medical radionuclides needed to advance targeted molecular therapy in the future
- Training for NM scientists, particularly for radiopharmaceutical chemists, has not kept up with current demands in universities and industry, a problem that is exacerbated by a shortage of university faculty in nuclear and radiochemistry

1. Loss of Federal Commitment for Nuclear Medicine Research

- Medical Applications and Sciences Program under DOE-OBER now grossly underfunded after decades of support for field, with products including FDG, PET, Tc-99m.
- DOE-Nuclear Energy (NE) Isotope Program not meeting needs of community; activities not adequately coordinated with DOE-OBER and NIH.
- Public Law 101-101, requiring full-cost recovery for DOE-produced isotopes, has restricted research isotope production and radiopharmaceutical research.

RECOMMENDATION 1:
ENHANCE THE FEDERAL COMMITMENT TO NM

- Support for the DOE-OBER NM research program should be re-instated
- National NM research program should be coordinated by the DOE and NIH, with the former emphasizing the general development of technology and the latter disease-specific applications
- Strategic planning should include academia, national labs and other sources of expertise.

2. Cumbersome Regulatory Requirements

- Complex US FDA toxicologic and other regulatory requirements that do not take into account differences in diagnostic and therapeutics agents
- Lack of specific guidelines from FDA
- Lack of consensus for standardized imaging protocols for clinical trials.

RECOMMENDATION 2:
Clarify and simplify regulatory requirements

- FDA should clarify and issue final guidelines for performing pre-investigational new drug evaluations
- FDA should issue final cGMPs for radiopharmacueticals, graded commensurate with the properties, applications and potential risks of the agents
- Develop prototypes of standardized imaging protocols for multi-institutional clinical trials

3. Inadequate Domestic Supply of Medical Radionuclides for Research

- No domestic source for most medical radionuclides used in day-to-day NM practice
- Lack of a dedicated domestic accelerator and reactor for production of isotope for NM research
- Parasitic use of high-energy physics machines has failed to meet the needs of the medical research community with regard to radionuclide type, quantity, timeliness of production and affordability

RECOMMENDATION 3:
Improve domestic medical radionuclide production

- Dedicated accelerator
- Appropriate upgrade to an existing research nuclear reactor

4. Shortage of Trained NM Scientists

- Critical shortage of clinical and research personnel in all nuclear medicine disciplines – impending "generation gap"
- Fewer US students with careers in chemistry - restriction of training grants to US citizens and permanent residents as required by the Public Service Act is a substantial impediment to recruitment of chemists

RECOMMENDATION 4:
Train NM scientists and provide additional innovative training grants

- NIH, DOE and professional societies should organize expert panels to discuss shortages and remedies, including curriculum development and funds for training grants
- Create innovative programs to engage overseas recruits perhaps by linking training to research

5. Need for Technology Development and Transfer

- Need for development of high specific imaging technology and targeted radiopharmaceuticals for disease diagnosis and treatment
- Improvements in detector technology, image reconstruction algorithms, and advanced data processing, as well as lower cost radionuclide production technologies are needed
- Transfer of technology discoveries from the laboratory to clinic is critical for future success
- Federally funded research and development has driven the field of NM practice world-wide

RECOMMENDATION 5:
Encourage interdisciplinary collaboration

- DOE-OBER should continue to encourage collaborations between physics, chemistry, computer sciences and imaging laboratories
- Consider multi-disciplinary centers to stimulate flow of new ideas and next generation radiopharmacueticals and imaging instrumentation
- Role of industry should be considered along with mechanisms to hasten technology transfer

Conclusions

- Growing need for radiopharmaceutical and other tracer development for the diagnosis and treatment of human disease in clinical practice and research trials.
- Regulatory and reimbursement impediments to the efficient entry of promising new diagnostic agents into clinical feasibility studies must overcome to ensure access.

Conclusions

- Impact of reduced DOE/NIH funding in nuclear medicine will have devastating long-term effects on the field of molecular imaging as well as the success multiple additional NIH initiatives unless reversed.
- Short and long-term strategies to alleviate the deficiencies in the basic and physician scientists in molecular imaging related fields must be identified soon to offset attrition.