Importance and Role of Radioisotopes to the Medical Community

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Radionuclides Used in Clinical Nuclear Medicine (Diagnostic)

- Single Photon

$^{99}Mo/^{99m}Tc$ generator, ^{201}Tl, ^{111}In, ^{67}Ga, *I

- Positron Emitting

^{18}F 2-fluoro-2-deoxy-glucose

Increase in Nuclear Medicine Procedures

Year	Procedures (millions)	Annual % + or -
1997	12.9	
1998	13.6	5.4%
1999	14.7	8.1%
2000	16.2	10.2%
2001	16.8	3.7%
2002	18.4	9.5%
2005	19.7	7.1%
2006	17.7	-10.2%

- From IMV 2007 Nuclear Medicine Market Summary Report

Types of Procedures

Type	2002	2005	2006
Cardiovascular	54%	57%	56%
Bone	23%	20%	17%
Liver/Hepatobiliary	6%	7%	7%
Respiratory	6%	4%	4%
Renal	3%	3%	3%
Infection/Abcesses	2%	2%	2%
Tumor	2%	2%	2%
Other	4%	2%	2%
Thyroid/Parathyroid		3%	3%

•From IMV 2007 Nuclear Medicine Market Summary Report

Nuclear Medicine Procedure Volume (Millions)

Type	1999	2001	2002	2005
Cardiovascular	7.1	8.4	9.9	9.8
Bone	3.7	4.2	4.2	3.4
Liver/Hepatobiliary	1.4	1.7	1.7	1.2
Respiratory	1.1	1.1	1	0.7
Thyroid/Parathyroid	0.4	0.5	0.5	0.5
Infection/Abcesses	0.4	0.4	0.4	0.4
Tumor	0.3	0.3	0.4	0.3
Other	0.2	0.2	0.3	0.4
Renal				0.5

•From IMV 2007 Nuclear Medicine Market Summary Report

Increase in Total PET Patient Studies

Year	Procedures (Thousands)	Annual Increase
2001	248.3	
2002	447.2	80%
2003	706.1	58%
2005	1129.9	60%

- From Bio-Tech Systems

Increase in PET and PET/CT Studies (Thousands)

Studies	2001	2002	Annual Increase	2003	Annual Increase	2005	Annual Increase
Oncology	182.6	385.7	111%	638.8	66%	1045.4	64%
Cardiac	18.9	16.7	-12%	22.3	34%	35.9	61%
Neurologic	10.1	15.5	53%	24.9	61%	39.8	60%

- From Bio-Tech Systems

Historic and Forecast PET Procedure Volume for Cardiology, Neurology and Oncology

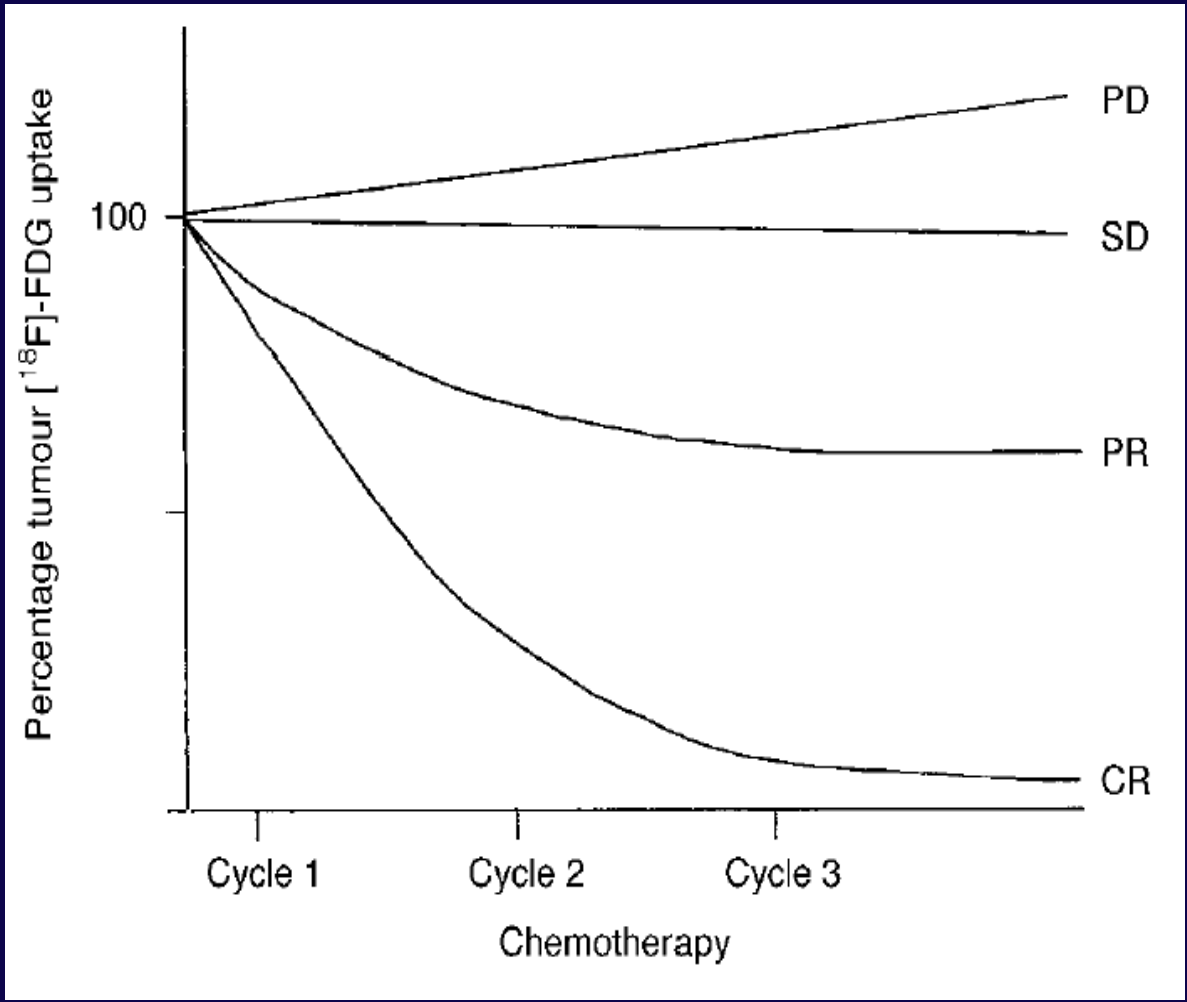
Year	Myocardial	% growth	% of total	Neurology	% growth	% of total	Oncology	% growth	% of total	Total PET Procedures	% growth
2000	8,000	60.0	7.3	6,000	20.0	5.5	38,000	126.2	71.7	52,000	109.6
2001	20,000	150.0	11.8	10,000	66.7	5.9	140,000	268.4	82.8	170,000	226.9
2002	36,000	80.0	14.1	18,000	80.0	7.0	206,000	47.1	80.5	260,000	52.9
2003	57,000	58.3	8.3	28,000	55.6	4.1	600,000	191.3	87.6	685,000	163.5
2004	85,000	49.1	8.5	42,000	50.0	4.2	875,000	45.8	87.3	1,002,000	46.3
2005	115,000	35.3	8.4	60,000	42.9	4.4	1,200,000	37.1	87.3	1,375,000	37.2
2006	145,000	26.1	8.4	85,000	41.7	4.9	1,500,000	25.0	86.7	1,730,000	25.8
2007	180,000	24.1	8.6	115,000	35.3	5.5	1,800,000	20.0	85.9	2,095,000	21.1
2008	215,000	19.4	8.7	145,000	26.1	5.9	2,100,000	16.7	85.4	2,460,000	17.4
2009	245,000	14.0	8.7	180,000	24.1	6.4	2,400,000	14.3	85.0	2,825,000	14.8
2010	270,000	10.2	8.5	210,000	16.7	6.6	2,700,000	12.5	84.9	3,180,000	12.6

- From Bio-Tech Systems

Treatment Assessment with FDG-PET

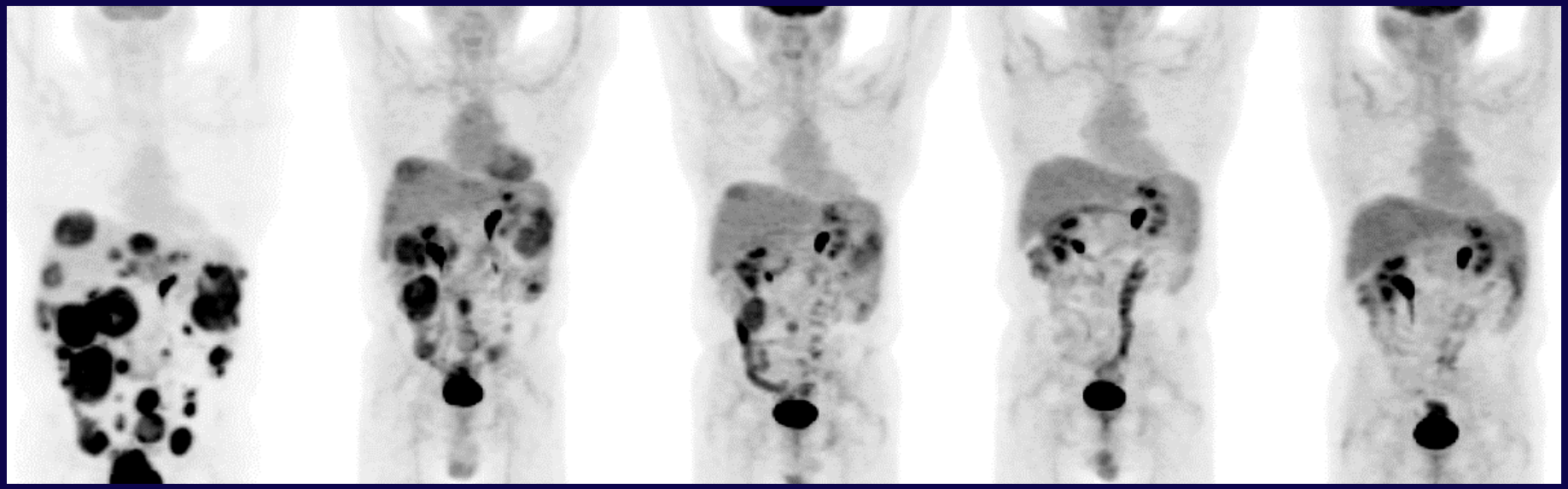
- Residual mass: post-treatment effect or tumor?
- Prediction and early monitoring of treatment effectiveness

Hypothetical Relationship of Tumor FDG Uptake to Clinical Outcome



Young H, et al. Eur J Cancer 1999; 35:1773

STI571 Trial in GIST
Dana-Farber Cancer Institute



Baseline | **24 hours** | 7 days | 2 months | 5.5 months

Major Areas of Research

Development of agents to image:

- Amyloid plaques in Alzheimer's Disease
- Cellular proliferation
- Tissue hypoxia in tumors, heart disease and stroke
- Receptors – Neurological, tumor and cardiac
- Cell trafficking
- Monitoring gene therapy

Standard Nuclides Produced at Washington University

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

Non Standard Nuclides Selected for Production

- Cu-60, Cu-61, Cu-64 - wide range of $t_{1/2}$

  Cu-64 has the potential for diagnosis and therapy

- I-124, Br-76, Br-77 - PET and therapeutic isotopes nuclides applicable to a

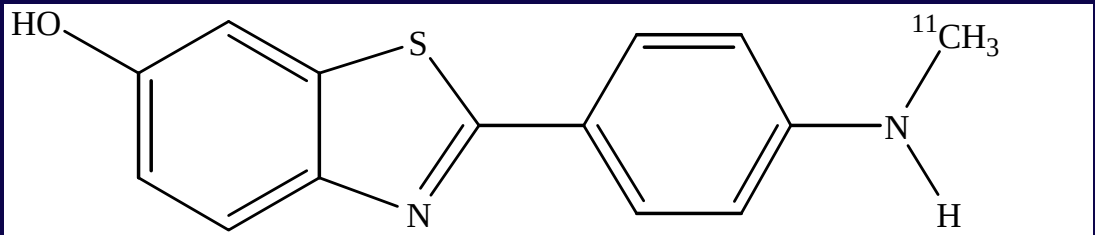
  wide range of compounds

- Tc-94m - PET Tc-nuclide

- Ga-66 - $t_{1/2}$ between Ga-68 and Ga-67

- Y-86 - potentially useful for dosimetry prior to Y-90 therapy

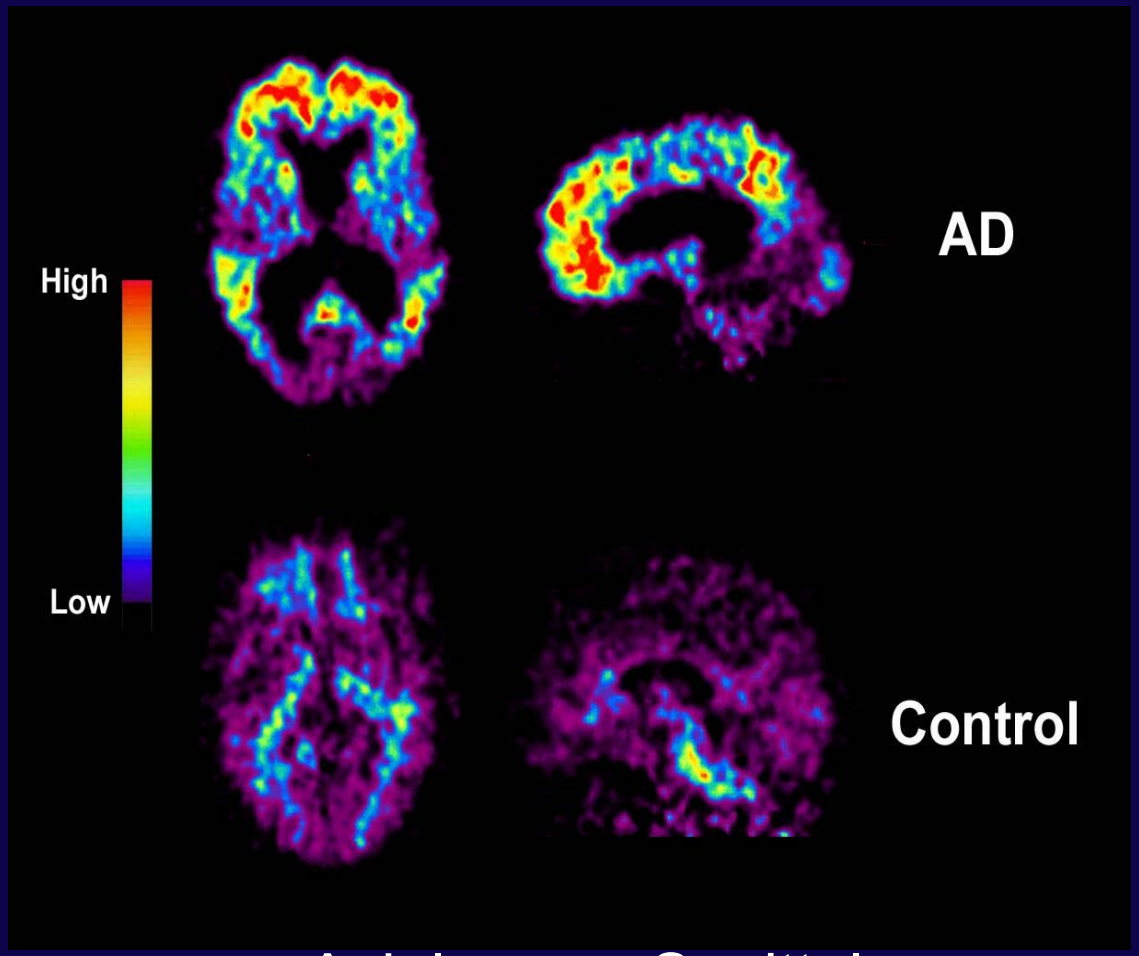
Benzothiazole Analog, [^{11}C]PIB, is a PET Tracer for *in vivo* Imaging of β-Amyloid Plaques



N-[^{11}C]methyl-6-OH-BTA-1

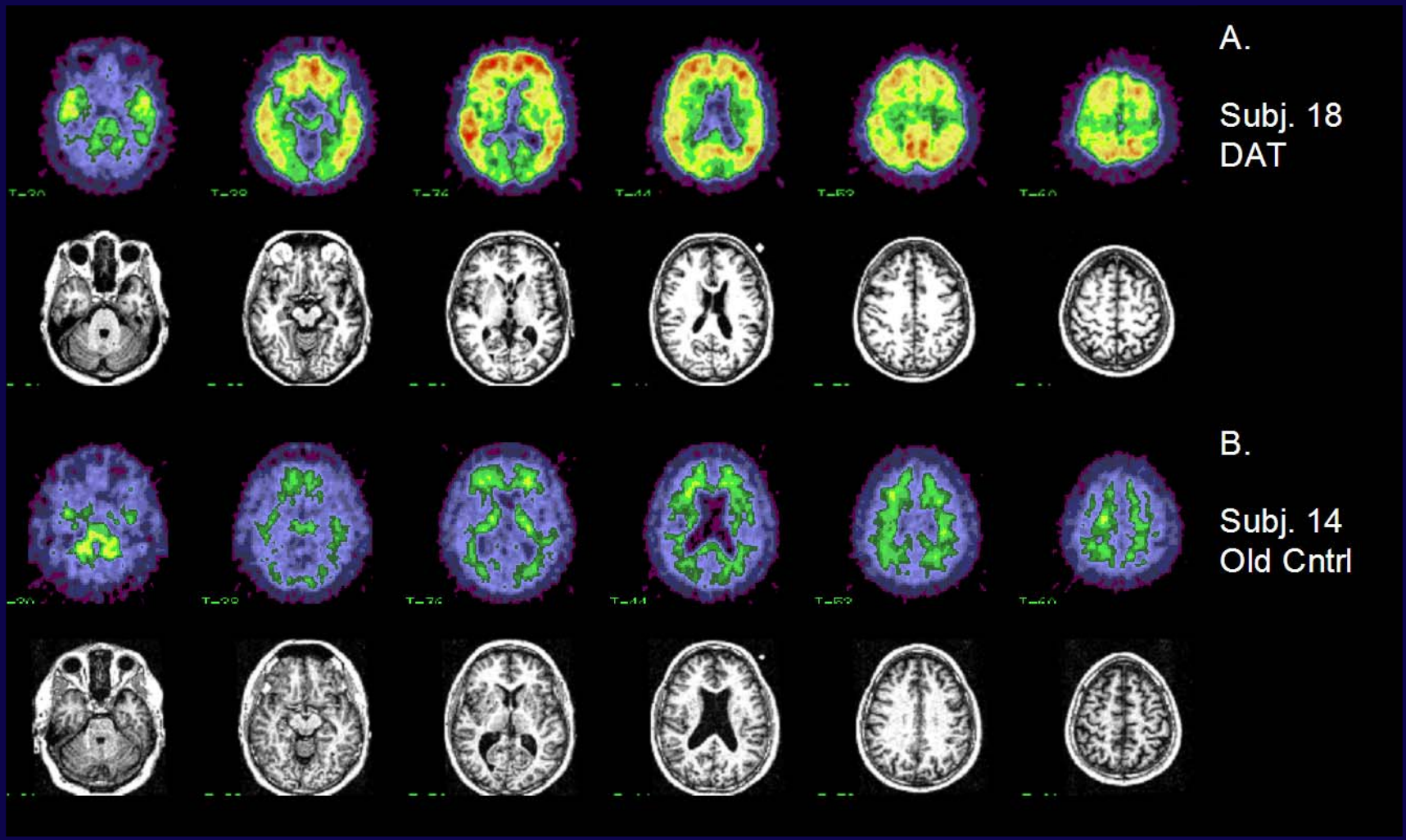
Courtesy of William E. Klunk, MD, PhD and Chet Mathis, PhD

In vivo Amyloid Binding of [^{11}C]PIB: Mild AD Patient vs. Normal Control



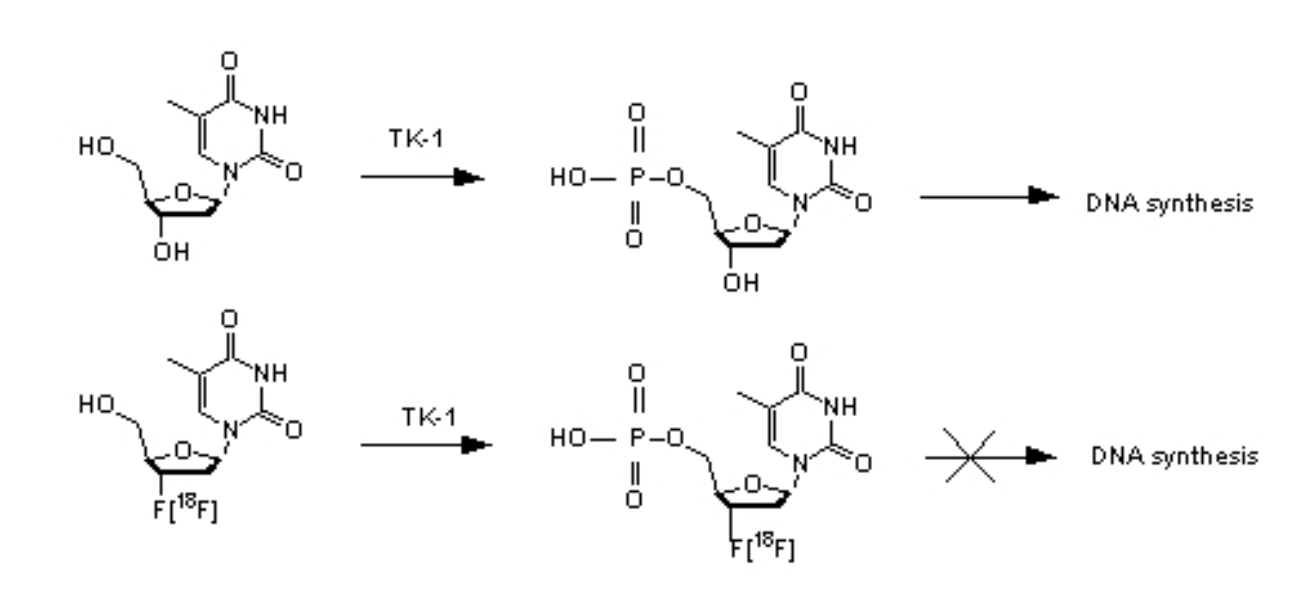
Courtesy of William E. Klunk, MD, PhD and Chet Mathis, PhD

PIB Uptake

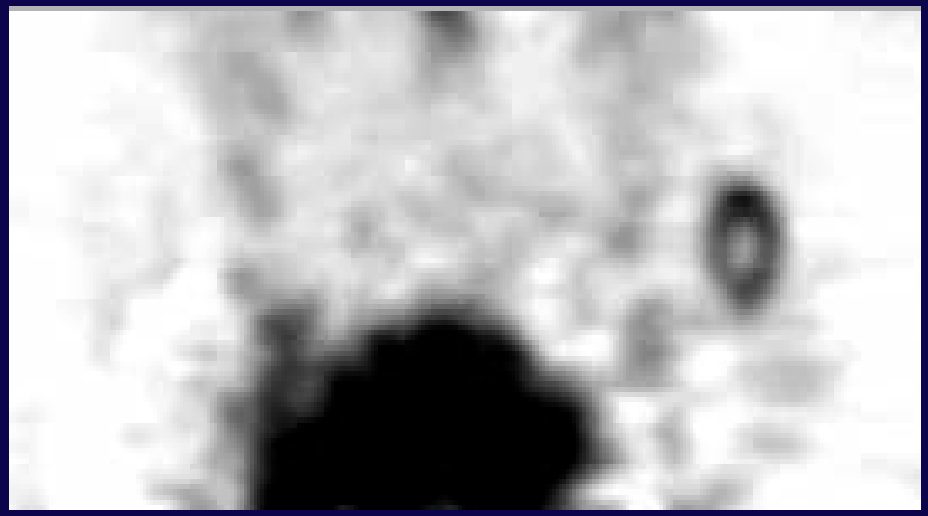


Imaging with FLT

- ^{18}F-FLT is taken up by cells and phosphorylated by TK1, which leads to intracellular trapping within the cell.
- The retention of FLT within the cell provides a measure of cellular TK activity, an enzyme which is closely tied to cellular proliferation.



Imaging Breast Cancer with FLT



Pre-Treatment

FLT Coronal Images

Post-Treatment

A. Shields et al.

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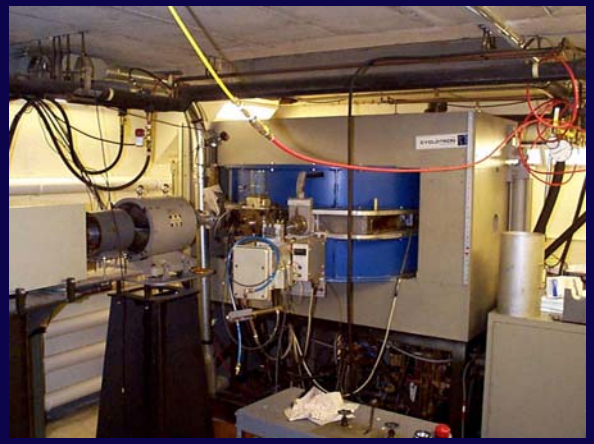
Imaging Hypoxia

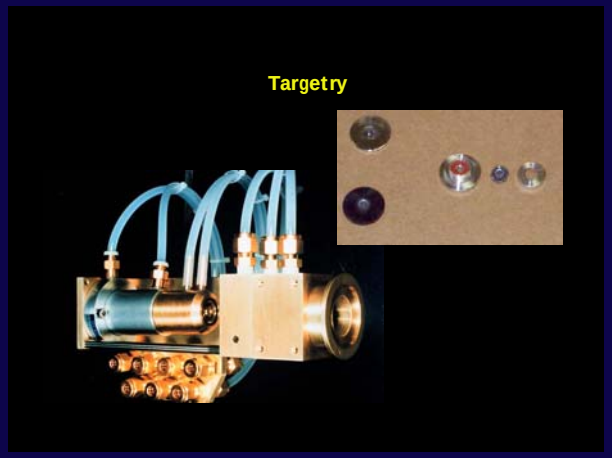
Copper Radionuclides

Isotope	Half-life	Decay modes /\%	Maximum β^+ energy (MeV)	Reaction	Natural abundance of target isotope
^{60}Cu	23.7 m	β^+/93.0 EC/7.0	3.92	^{60}Ni(p,n)	26.1%
^{61}Cu	3.32 h	β^+/60.0 EC/7.0	1.22	^{61}Ni(p,n)	1.25%
^{64}Cu	12.7 h	β^+/19.0 EC/43.0 β^-/38	0.66	^{64}Ni(p,n)	1.16%

^{60}Cu(ATSM) – Chemistry and Engineering



Cyclotron



Target Holder

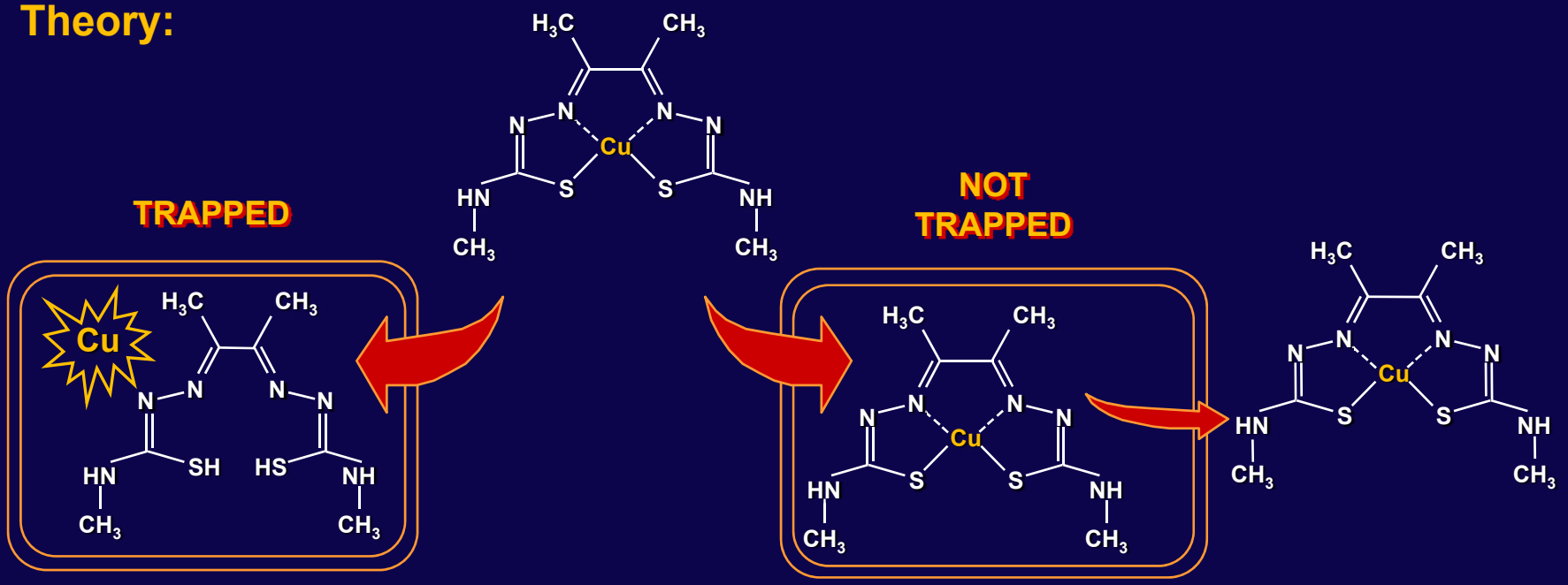
Production technology developed with Newton Scientific, Inc with NIH Small Business Grants

Chemical Purification and Drug Manufacture

DW McCarthy et al., Nucl Med Biol 1999;26:351-358

PET Imaging Agents – Cu(ATSM)

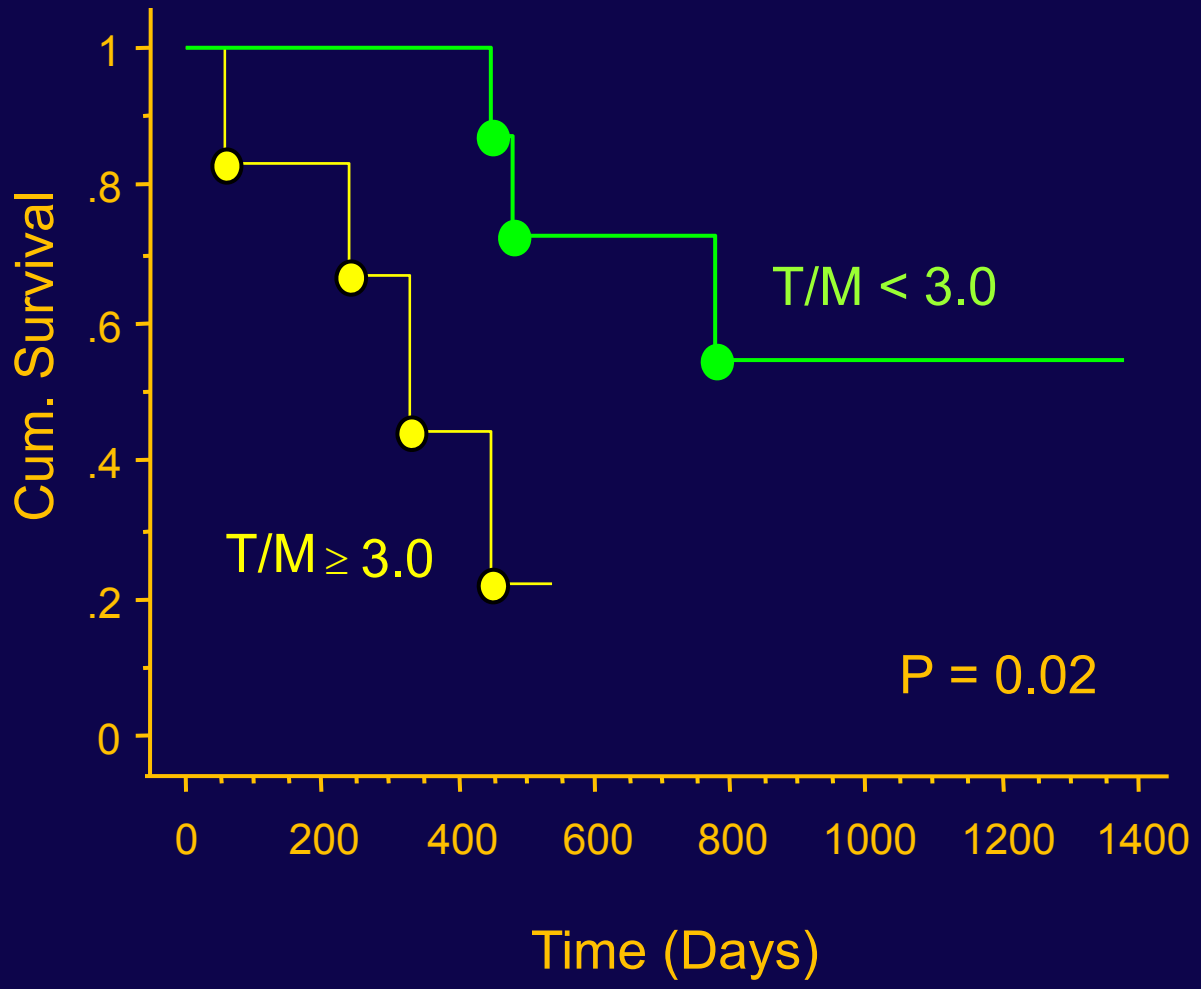
Theory:



Hypoxic cell ($-O_2$)

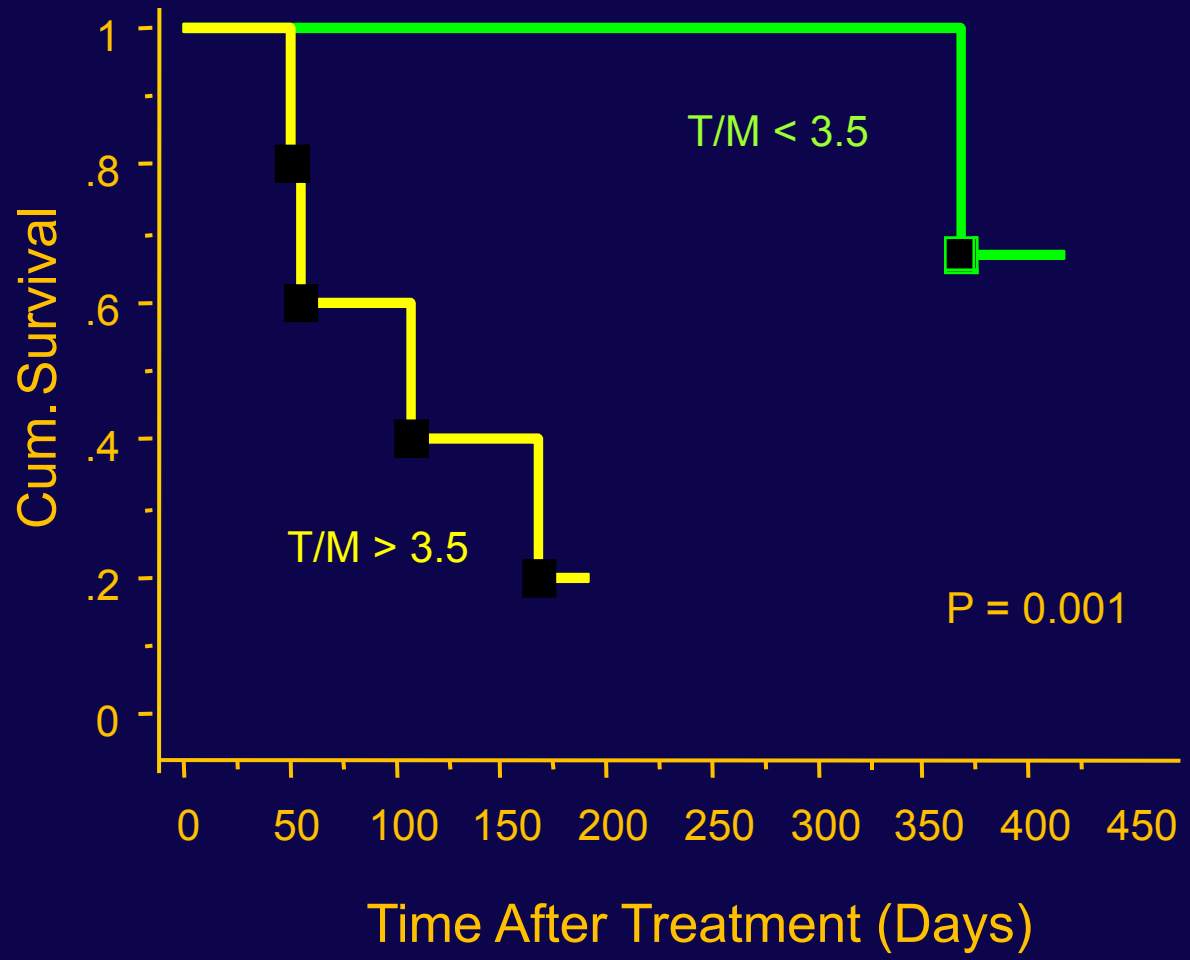
Normal cell ($+O_2$)

Overall Survival Based on ^{60}Cu-ATSM Uptake (T/M) in NSCLC (n=14)



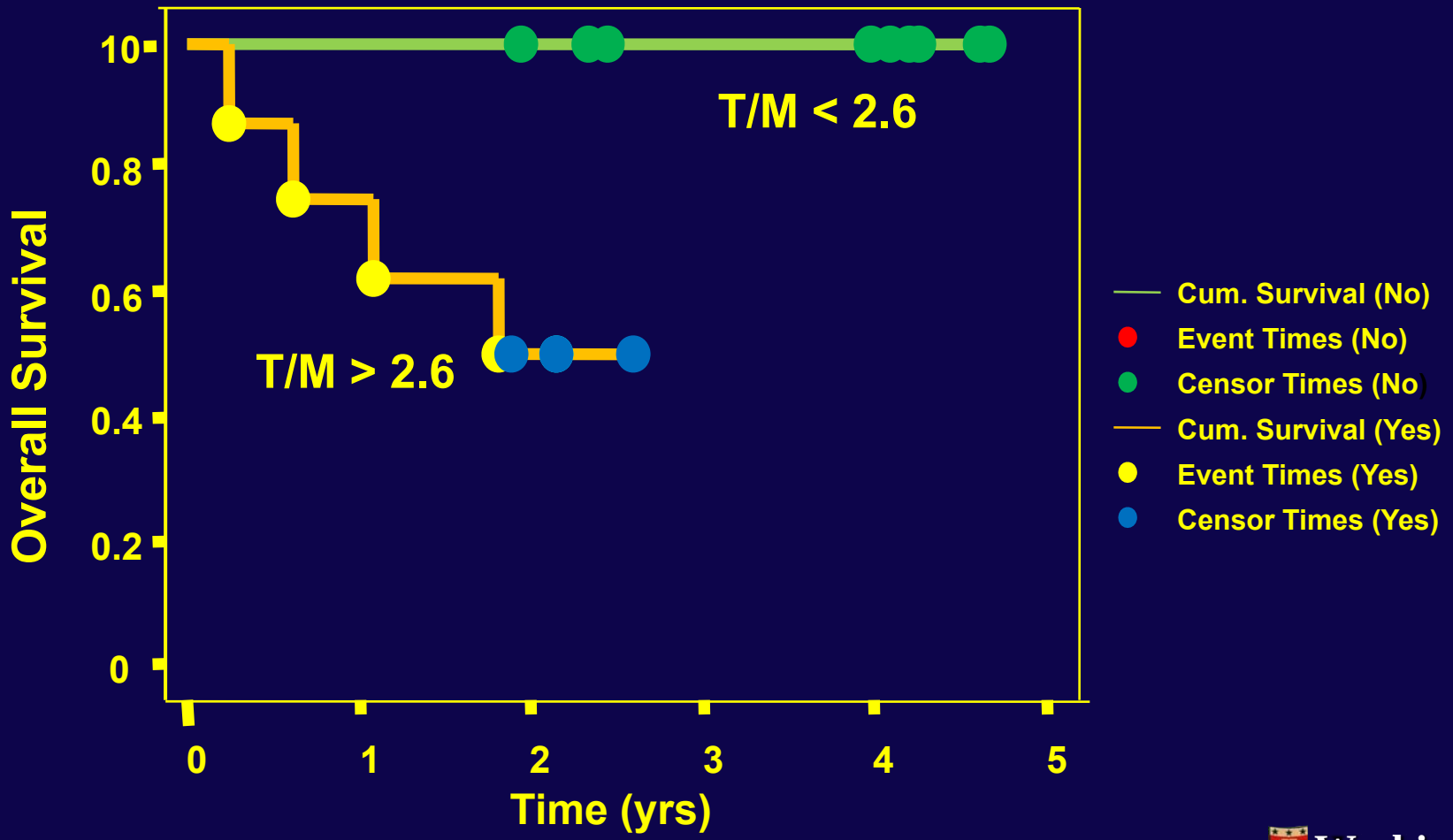
Dehdashti et al., Eur J Nucl Med Mol Imag 30:844-850, 2003

Disease-Free Survival Based on ^{60}Cu-ATSM Uptake in Cervical Cancer (n = 14)



Dehdashti et al., IJORBP 55(5):1233-1238, 2003

Survival Based on ^{60}Cu-ATSM Uptake in Rectal Cancer (n=17)

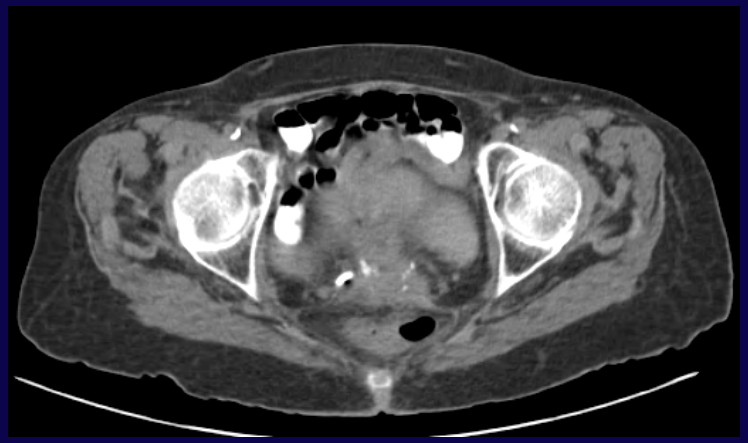


Unpublished data

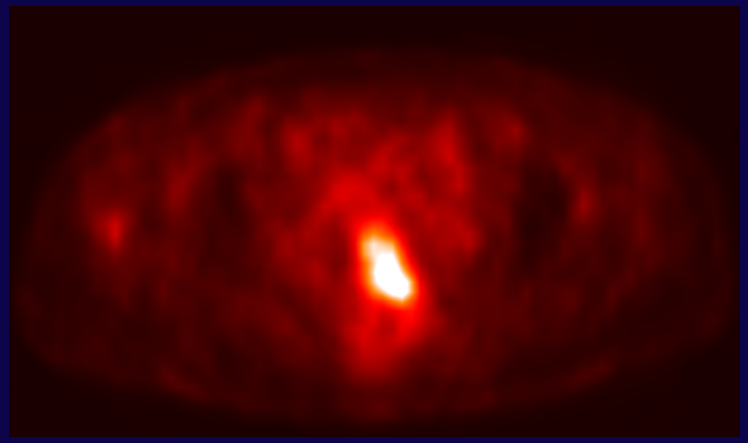
Comparison of ^{60}Cu-ATSM and ^{64}Cu-ATSM (IND 62,675)

- Assessed quality of ^{60}Cu- and ^{64}Cu-ATSM PET images
- Crossover study of 10 patients with Ib2-IVa cervical CA
  - Subjective – comparable; but, ^{64}Cu-ATSM images less noisy
    - Similar quality in 8 patients
    - ^{64}Cu-ATSM better than ^{60}Cu-ATSM in 2 patients
  - T/M evaluation
    - Generally better target to background ratio (tumors seen more clearly on ^{64}Cu-ATSM-PET in most cases)

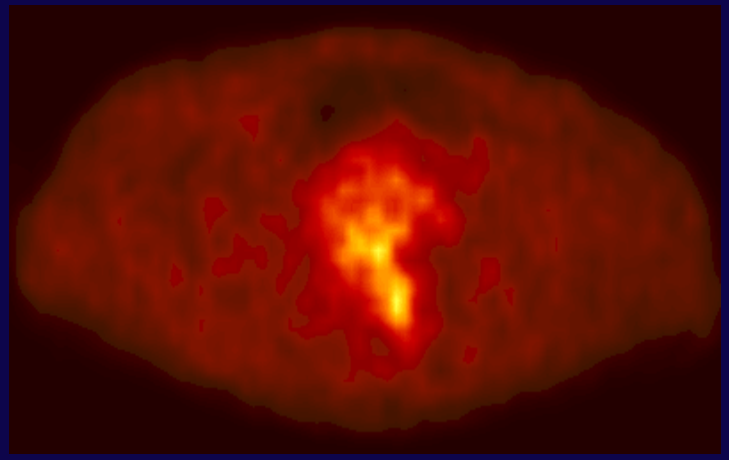
CT



FDG-PET

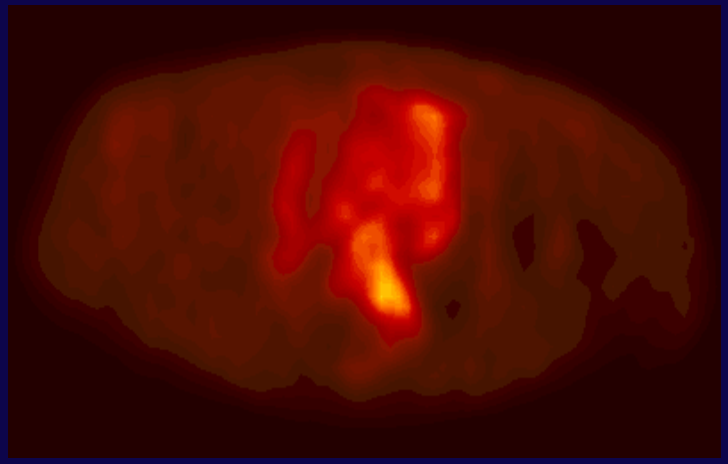


^{60}Cu-ATSM-PET



T/M = 5.0

^{64}Cu-ATSM-PET



T/M = 5.8

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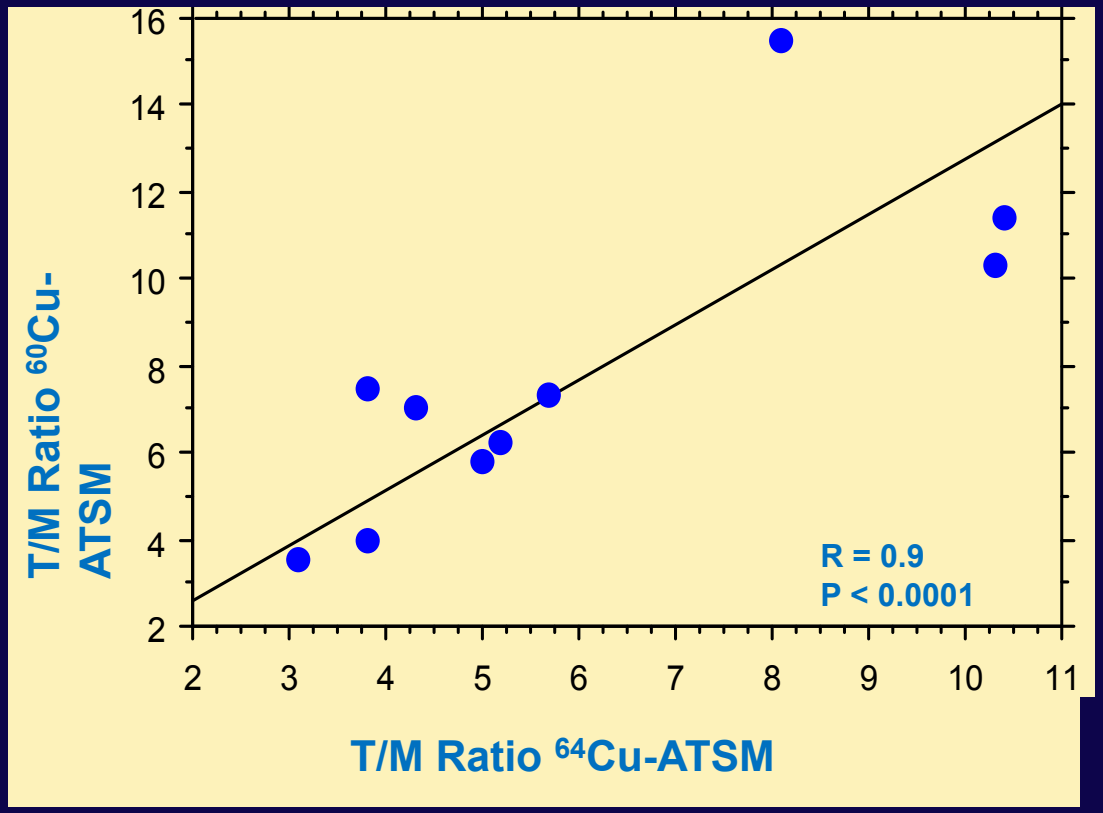
Comparison of ^{60}Cu-ATSM and ^{64}Cu-ATSM (IND 62,675)

- **Correlation of T/M for ^{60}Cu-ATSM and ^{64}Cu-ATSM**



Tumor Detection and Treatment Using Bavituximab Labeled with Arsenic Radionuclides

Guiyang Hao, Xiankai Sun, Philip E.Thorpe, and Ralph P. Mason

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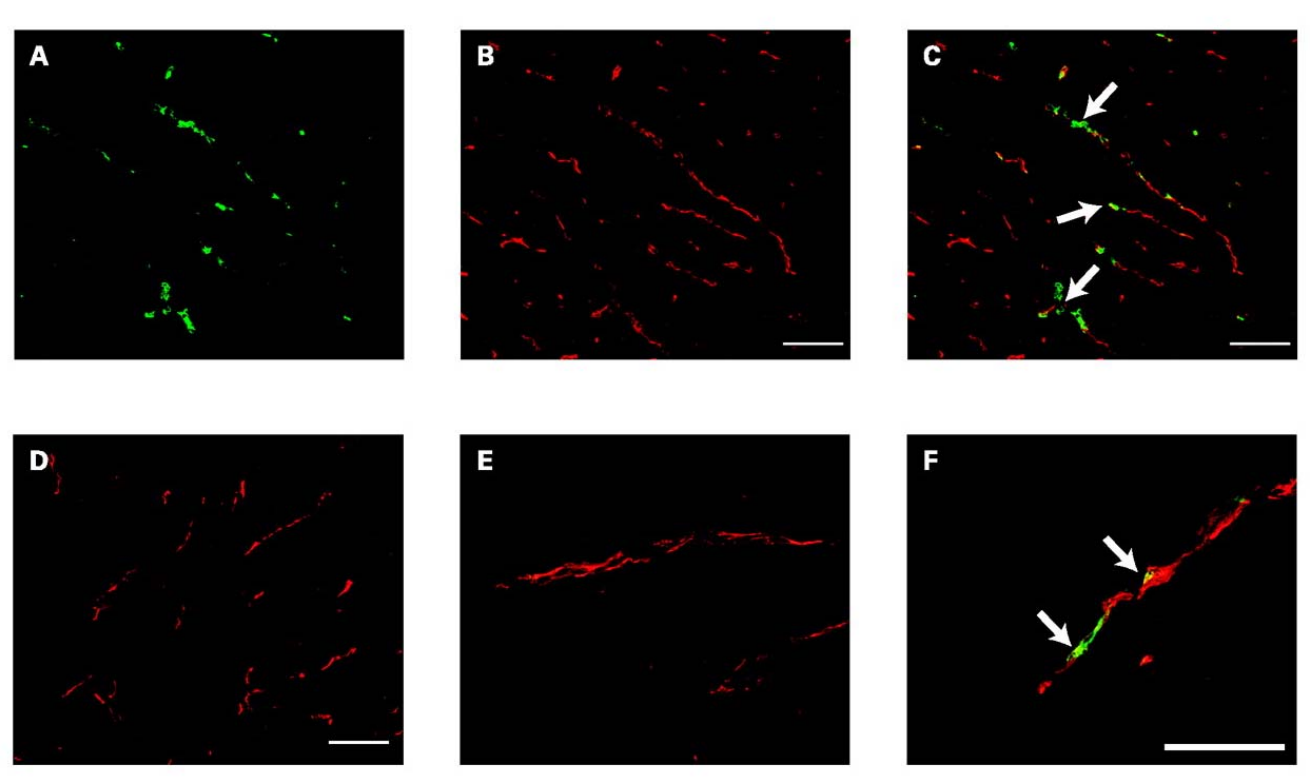
Bavituximab: A chimeric antibody targeting exposed vascular phosphatidylserine. It is composed of the Fv regions of the mouse antibody 3G4 and the constant regions of human IgG1.

Bavituximab binds to human β2-glycoprotein I with an affinity of 1.7×10^{-8} mol/L (monovalent interaction) and an avidity of ~10^{-10} mol/L.

Rituximab (monoclonal antibody Thera, CD20): a negative control in this project.

Ran et al. *Clin. Cancer Res.* 2005,11:1551

Localization of Bavituximab to Tumor Vessels



A: stained with biotinylated goat anti-human IgG followed by Cy2-streptavidin (green) to detect localized bavituximab; **B**: stained with mouse anti-rat CD31 followed by Cy3-labeled goat anti-mouse IgG (red) to detect vascular endothelium; **C**: a merged image of bavituximab localized on CD31-positive endothelium. **D**: a merged image of blood vessels in the tumor of a rat injected with rituximab (negative control). **E-F**, higher magnification merged images of blood vessels in tumors from rats injected with rituximab (**E**) or bavituximab (**F**). Bars, 100 μm. (Dunning prostate R3227-AT1 tumor)

Decay Data of Arsenic Radioisotopes

Property	^{71}As	^{72}As	^{73}As	^{74}As	^{76}As	^{77}As
$T_{1/2}$[d]	2.7	1.1	80.3	17.8	1.1	1.6
Mode of decay (%)	EC (70)	EC (12.2)	EC (100)	EC (66)	β^- (100)	β^- (100)
	β^+ (30)	β^+ (87.8)		β^+ (29)		
Most abundant γ-lines [kev]	175.0 (82.0%)	834.0 (79.5%) 629.9 (7.9%)	53.4 (10.0%)	595.8 (59.0%) 634.8 (15.4%)	559.1 (45.0%) 657.1 (6.2%)	239.0 (1.6%) 520.6 (0.5%)
Mean positron energy [kev]	350	1170		440		

Jennewein et al. *App. Rad. Isot.*, 2005, 63:343–351

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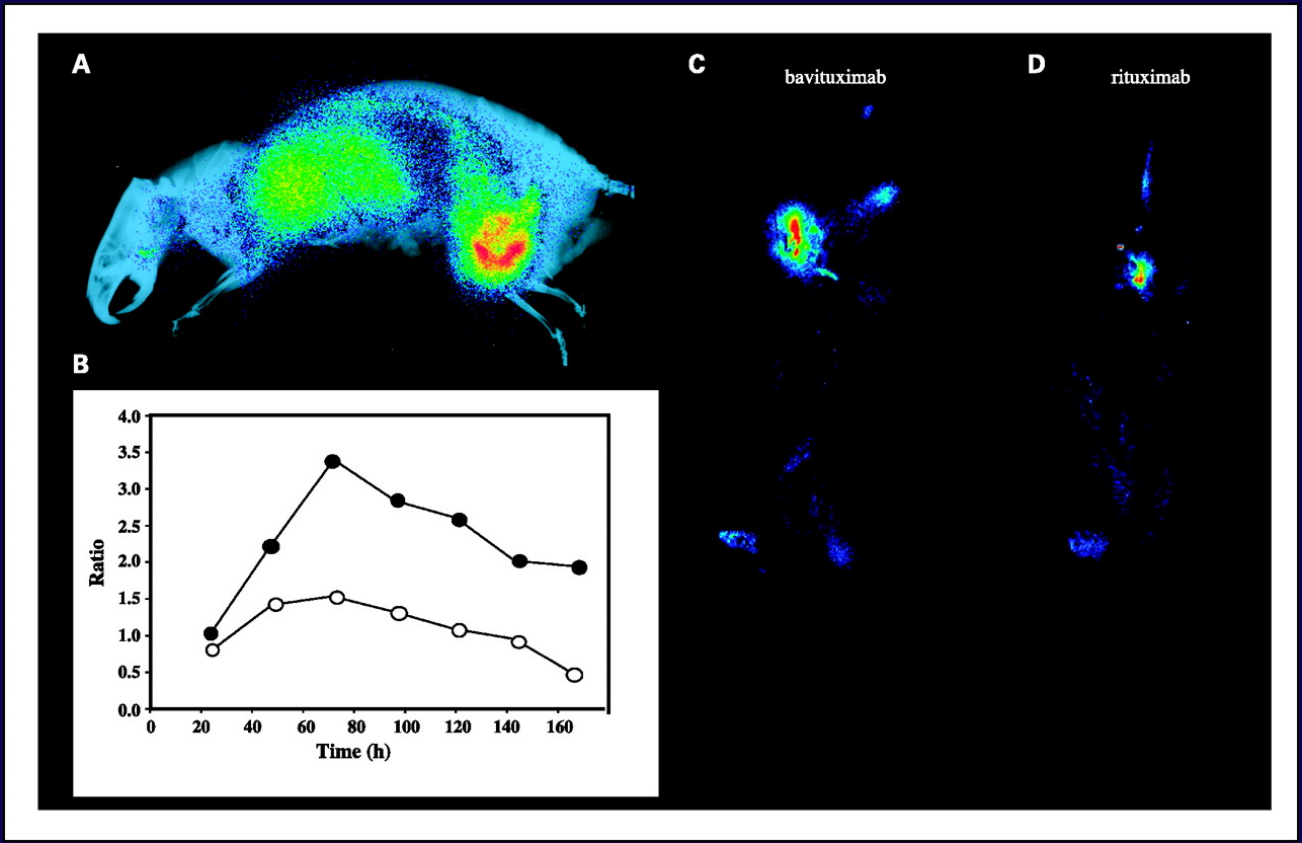
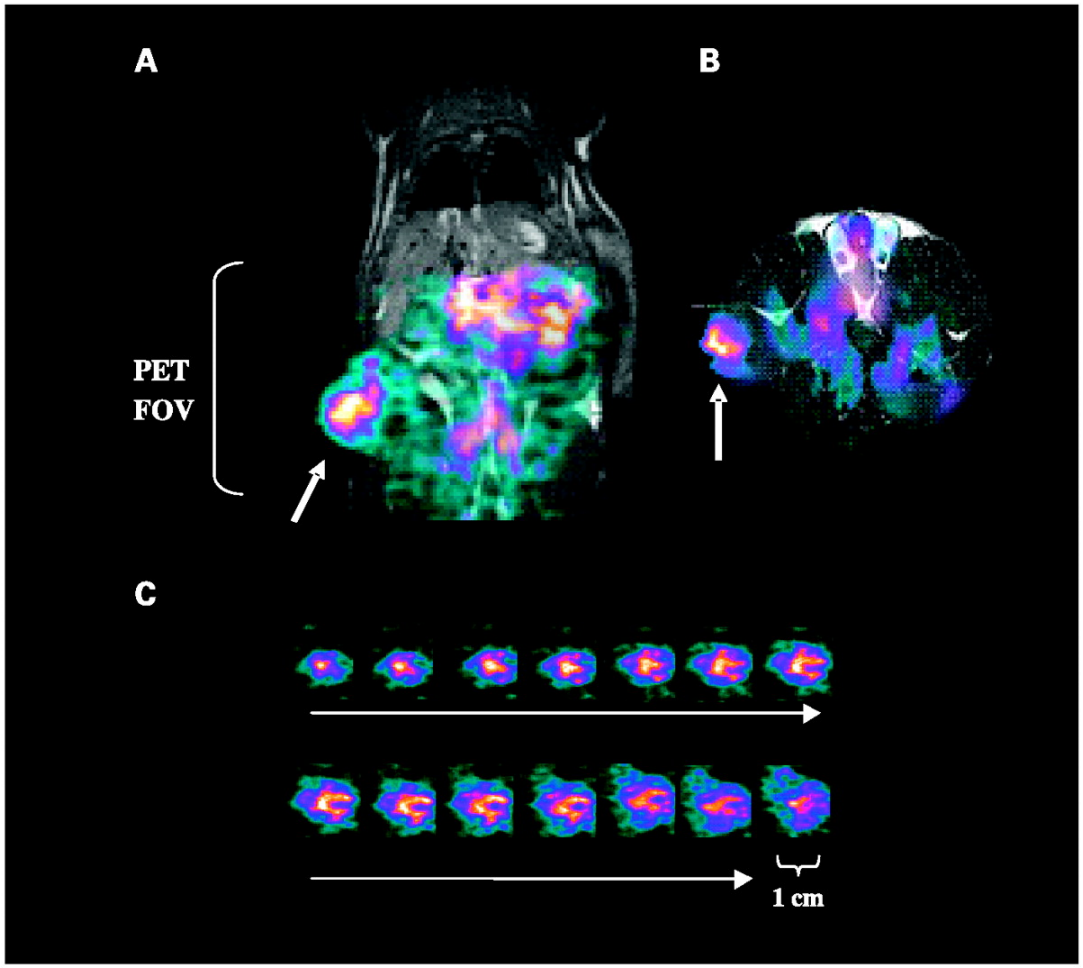
Whole-body Planar Scintigraphy



A: Image of rat injected with 5MBq [^{74}As]bavituximab 72h p.i.; **B**: uptake ratio of [^{74}As]bavituximab in tumor versus upper organs (liver, lung, heart) at various time points after injection (outer tumor regions; entire tumor); **C-D**: scintigraphy of rats injected with 3MBq [^{77}As]bavituximab or [^{77}As]rituximab (negative control).

Small Animal



A-B: small animal PET images obtained from a Dunning prostate R3227-AT1 tumor-bearing rat 48 h after injection of 10MBq of [^{74}As]bavituximab coronal (**A**) and transaxial (**B**). PET intensity is overlaid on slices obtained by 3-D MRI.

C: images of 1-mm sequential tumor slices from the 3-D data sets.

Jennewein et al. Clin Cancer Res 2008;14(3)

Conclusion

Radioarsenic-labeled bavituximab has shown potential as a new agent for imaging (^{74}As) the vasculature and radiotherapy (^{77}As) of solid tumors.

Acknowledgements

DOD IDEA awards
W81XWH-06-1-0149 and W81XWH-06-1-0050

National Cancer Institute Pre-ICMIC P20
CA086334 and SAIRP U24 CA126608

The first $^{68}Ge/^{68}Ga$ Generator

G.I Gleason, *Int J Appl Rad Isot*, 1960, 8, 90-94

International Journal of Applied Radiation and Isotopes, 1960, Vol. 8, pp. 90–94. Pergamon Press Ltd. Printed in Northern Ireland

A Positron Cow

G. L. GLEASON
Abbott Laboratories, Oak Ridge, Tennessee, U.S.A.

(*Received* 6 *January* 1960)

Short-lived Ga^{68} can be prepared from its long-lived parent, Ge^{68}, thus providing a convenient source of positron-emitting activity for medical or other applications. Solvent extraction is used for the rapid separation of the gallium daughter and a method for the production of the germanium parent is given. A review of the usable positron emitters serves to underscore the advantages of the Ge–Ga^{68} system.

UNE VACHE À POSITRONS

Le Ga^{68} de courte vie peut se préparer de son antécédent de longue vie, le Ge^{68}, fournissant ainsi une source d'activité lançant des positrons, convenable aux applications médicales parmi autres. L'extraction à solvents sert à la séparation rapide du gallium généré et on présente une méthode de produire le germanium antécédent. Une revision des émetteurs utilisables de positrons sert à souligner les avantages du système Ge–Ga^{68}.

ИСТОЧНИК ПОЗИТРОНОВ

Короткоживущий Ga^{68}, полученный из долгоживущего Ge^{68} может быть использован в качестве удобного источника позитронов для медицинских и других целей. Быстрое отделение галлия производится путем экстрагирования его из раствора. Описан метод получения исходного германия. Обзор применяемых источников позитронов показывает преимущества системы Ge–Ga^{68}.

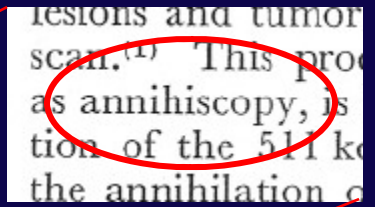
EINE POSITRONEN KUH

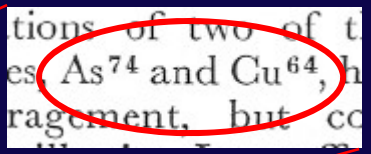
Kurzlebiges Ga^{68} kann aus der langlebigen Muttersubstanz Ge^{68} hergestellt werden, wodurch eine bequeme Positronen-Quelle für medizinische und andere Zwecke erhalten wird. Extraktion Aus der Lösung wird zur schnellen Abtrennung von Gallium verwendet und die Methode zur Herstellung der Muttersubstanz Germanium wird angegeben. Es wird ein Überblick über die verwendbaren Positronenstrahler gegeben aus welchem die Vorteile des Ge–Ga^{68} Systems deutlich hervorgehen.

INTRODUCTION

One of the more sophisticated techniques to emerge from the wide variety of medical applications of radioisotopes in recent years is the localization of certain intercranial lesions and tumors by the so-called positron scan.[1] This procedure, which we refer to as annihiscopy, is based on the 180° correlation of the 511 keV radiation arising from the annihilation of positrons with detection by means of two opposing counters recording only coincident events. Thus, concentrations of positron emitters offer a type of "beamed" signal to search out which may offer advantages over similar concentrations of isotopes emitting only isotropic γ-radiation.

The limited availability and/or expense of suitable positron-emitting isotopes has, unfortunately, proven a serious handicap to this otherwise promising technique. This, coupled with a high initial outlay for instrumentation has limited clinical evaluation to relatively few institutions. Commercial preparations of two of the more important isotopes, As^{74} and Cu^{64}, have been of some encouragement, but contingent supply problems still exist. In an effort to find some solution, the latest nuclear data have been searched for more ideal source material.





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JOURNAL NUCLEAR MEDICINE 4:326-330, 1963

PRELIMINARY PROGRESS NOTE[1]

Localization of Brain Tumors with the Positron Scintillation Camera[2,3]

Hal O. Anger, B.S., and Alexander Gottschalk, M.D.

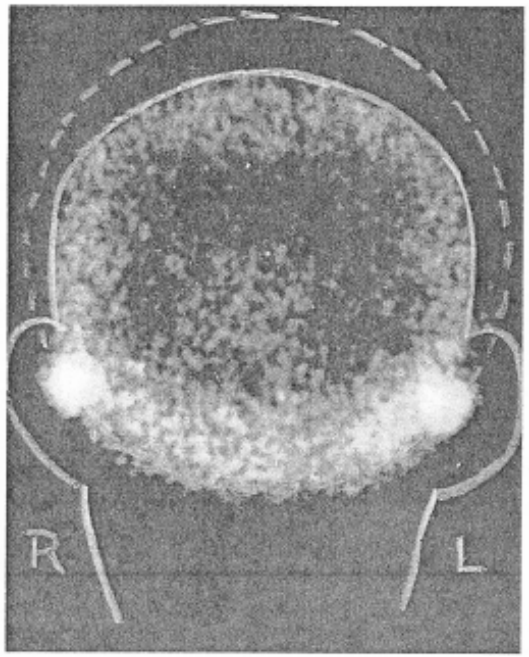


Fig. 1. A 10-minute positron scintiphoto taken with Ga^{68}-EDTA. This frontal view shows a large midline meningioma.

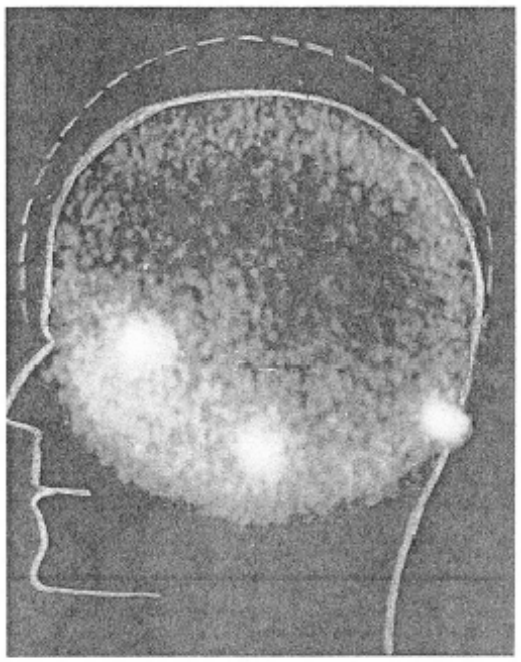
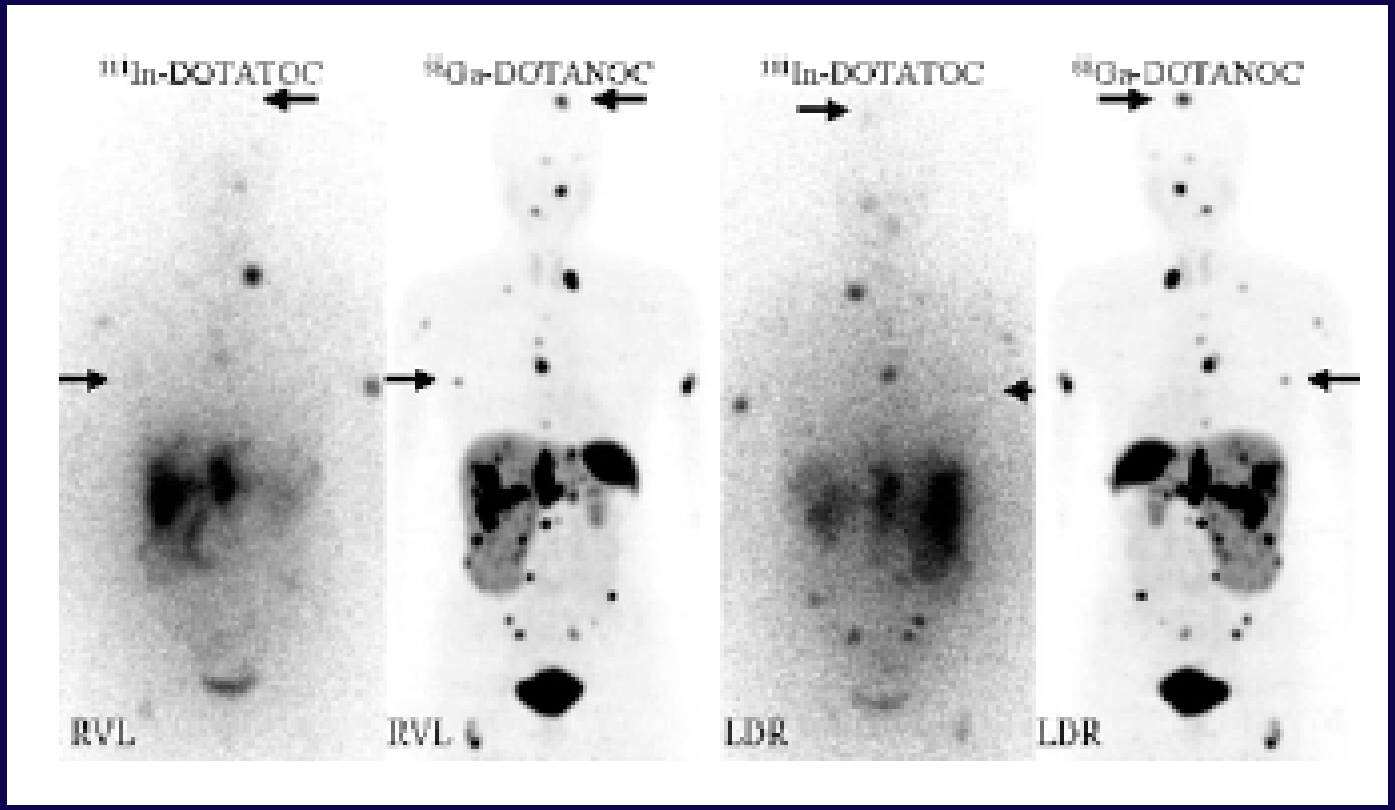


Fig. 2. A 10-minute lateral positron scintiphoto demonstrating an area of abnormal uptake posterior to the eye marker in a patient with a chromophobe adenoma of the pituitary.

^{68}Ga-DOTANOC: a first compound for PET imaging with high affinity for somatostatin receptor subtypes 2 and 5

Damian Wild[1], Helmut R. Mäcke[1], Beatrice Waser[2], Jean Claude Reubi[2], Mihaela Ginj[1], Helmut Rasch[1], Jan Müller-Brand[1], Michael Hofmann[3]

Eur J Nucl Med Mol Imaging (2005) :724



Translation of PET agents to the Clinic

95% of studies involve FDG

WHY?

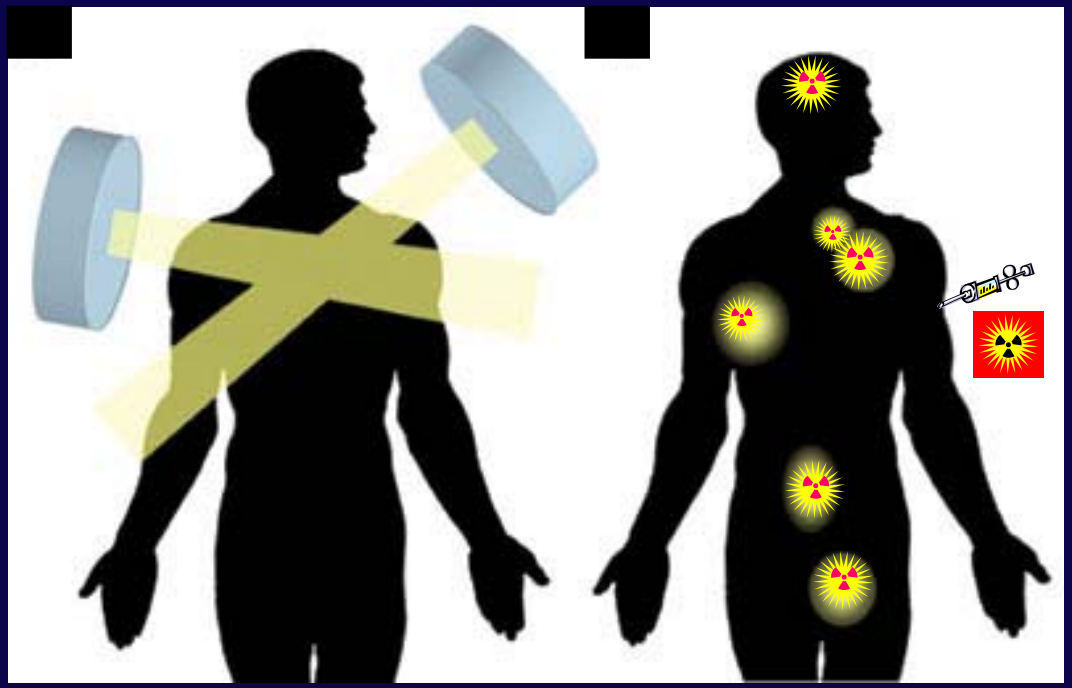
Barriers to Translation (PET agents)

- Nuclide Availability
- Intellectual property
- Radiochemical yields
- Variable Specific Activity
- Approval process

Emerging Trends in Radiotherapy

 # 1 Better match radiation field to tumor dimensions
#2 More potent radiation to increase effectiveness

External Beam Targeted Radionuclide



Advantages of Targeted Radiotherapy

- Potentially can be applied to:
  - Tumor sites not detectable by imaging
  - Multi-focal disease
  - Simultaneous application to primary and metastatic disease

Short range, high LET α-particles

Selected α-Particle Emitting Radionuclides

Radionuclide	Daughters	Half-life	α-particle Energy (MeV)	Yield per 100 decays
^{149}Tb		4.15 h	3.97	17
^{211}At		7.21 h	5.87	42
	^{211}Po	516 msec	7.44	58
^{212}Bi		61 min	6.05	36
	^{212}Po	298 nsec	8.78	64
^{213}Bi		45.6 min	5.84	36
	^{213}Po	4.2 μsec	8.38	64
^{225}Ac		10 days	5.75	100
	^{221}Fr	4.9 min	6.36	100
	^{217} At	32 msec	7.07	100
	^{213}Bi	45.6 min	5.84	2
	^{213}Po	4.2 μsec	8.38	98

Bismuth-213

^{225}Ac

10 d

α

^{221}Fr

4.8 m

α

^{217}At

0.032 s

α

^{213}Bi

46 m

α

^{213}Po

0.004 ms

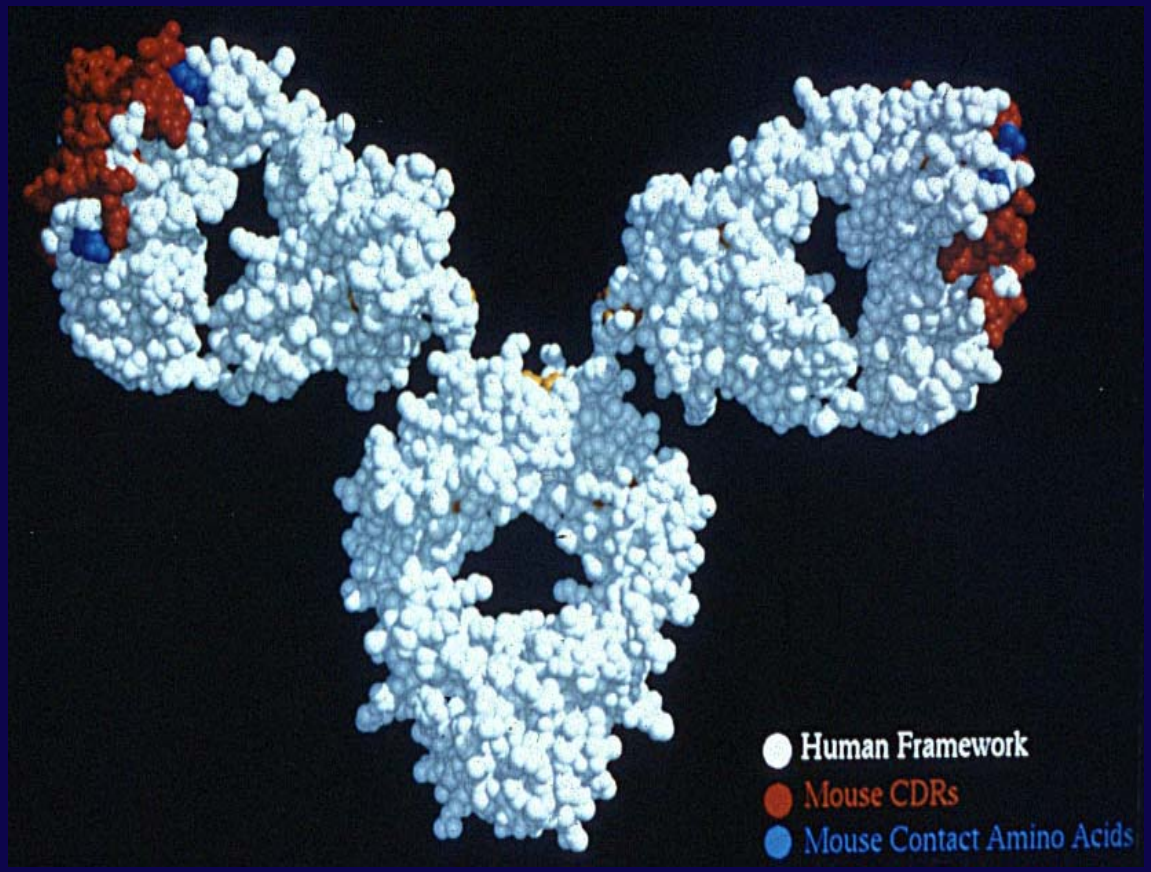
^{209}Pb

3.3 h

^{209}Bi

Bi-213-Labeled Hu195

- Reacts with CD33 antigen over expressed on acute myelogenous leukemia
- CHX-A-DTPA chelate



Jurcic and Scheinberg, MSKCC

Phase I Trial of ^{213}Bi-HuM195

^{213}Bi-HuM195
- *Level 1:* 0.28 mCi/kg
- *Level 2:* 0.42 mCi/kg
- *Level 3:* 0.56 mCi/kg
- *Level 4:* 0.7 mCi/kg
- *Level 5:* 1 mCi/kg

- Patients were treated with 16-95 mCi in 3-7 fractions.
- HuM195 doses were adjusted to a specific activity of 12-15 mCi/mg.

- Myelosuppression lasted 12-41 days (median, 22 days).
- Transient, low-grade liver function abnormalities were seen in 6 patients.
- Maximum tolerated dose was not reached.
- 14/18 patients had reductions in bone marrow blasts.

Jurcic JG *et al. Blood* 2002; 100:1233-1239.

Comparison of ^{131}I, ^{90}Y, and ^{213}Bi Dosimetry for HuM195

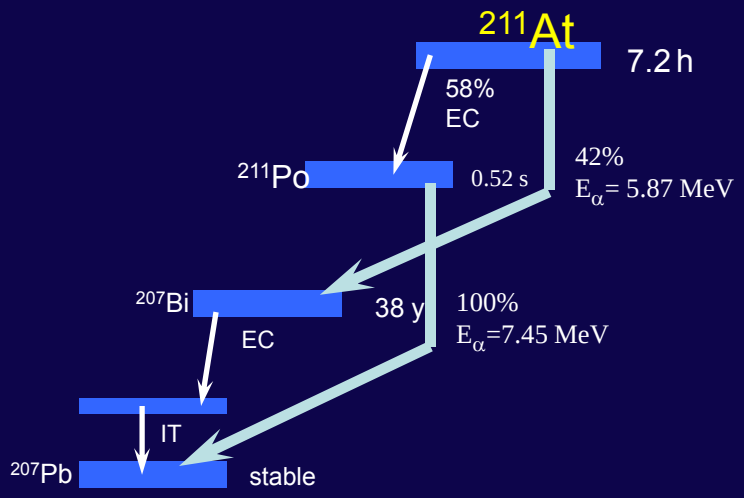
Isotope	Mean Absorbed Dose (mSv/MBq)			Marrow/ Whole Body Ratio
	Marrow	Liver	Whole Body	
^{131}I	2.7	0.8	0.16	14.4
^{90}Y	6.8	4.0	0.49	13.9
^{213}Bi	9.8	5.8	0.0004	27,300

Jurcic JG *et al. Blood* 2002; 100:1233-1239

Rationale for α-Particle Emitters in Cytoreduced Disease

- The short range and high LET of α-particles make them best-suited for treatment of small-volume disease.
- In patients with overt AML, there are 10^{16} CD33 binding sites, making it difficult to target 1-2 ^{213}Bi atoms to each leukemia cell.
- Hypothesis: Cytoreduction with cytarabine should decrease tumor burden by 1-2 logs and increase the ratio of ^{213}Bi atoms to target cells.

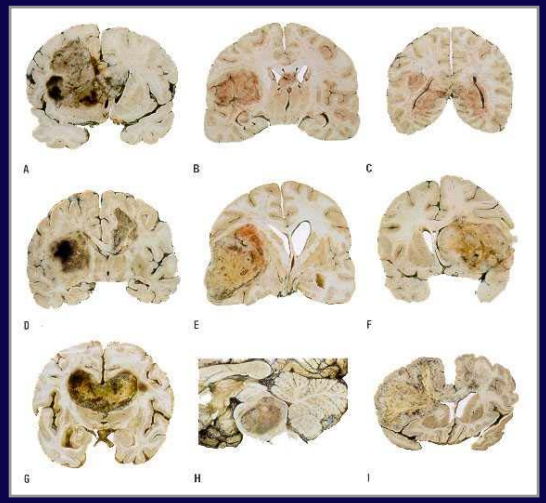
Astatine-211

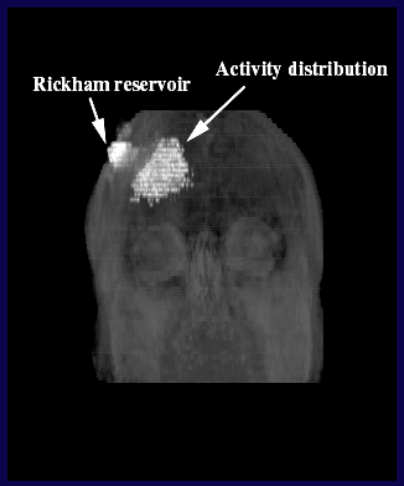


Rationale for Targeted Radiotherapy

- 7.2 hr half-life compatible with MRT pharmacokinetics
- α-emission with each decay
- No long-lived daughter radionuclides
- Cyclotron produced at reasonable cost
- Can be imaged providing safety margin

Rationale for Initiating Clinical Trials of ^{211}At Targeted α-Particle Therapy with ^{211}At-labeled Chimeric 81C6 in Glioma Patients

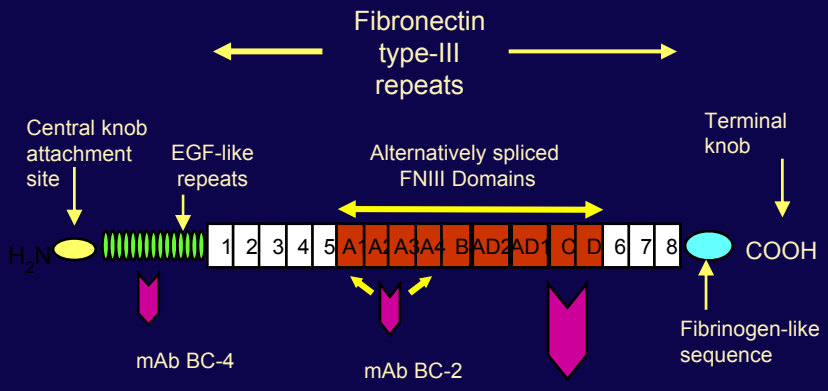




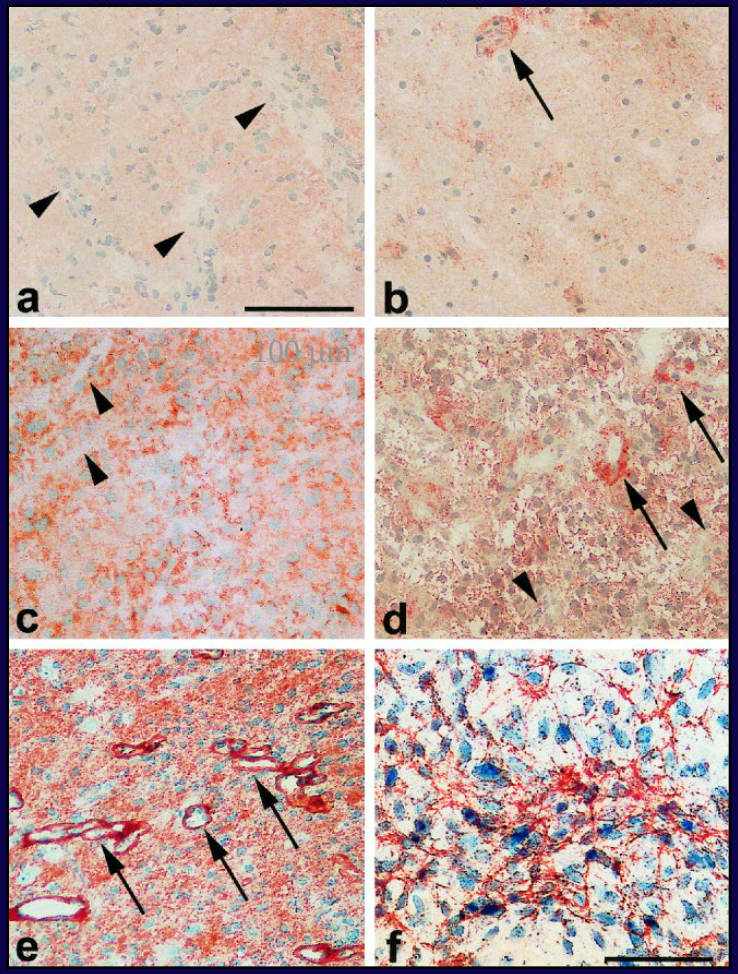
- Clinical need
  - Poor prognosis for conventional XRT even with TMZ
  - >90% local recurrence
- Non-intravenous setting minimizes risk and maximizes tumor delivery
- Wealth of experience in patients with ^{131}I-labeled mAb in this setting

Tenascin Expression in Brain Tumors

- Extracellular matrix glycoprotein
- Expressed on >95% of GBM
- Hexamer with 200-300 kDa arms



mAb 81C6



WHO Grade II

Perivascular
11/25

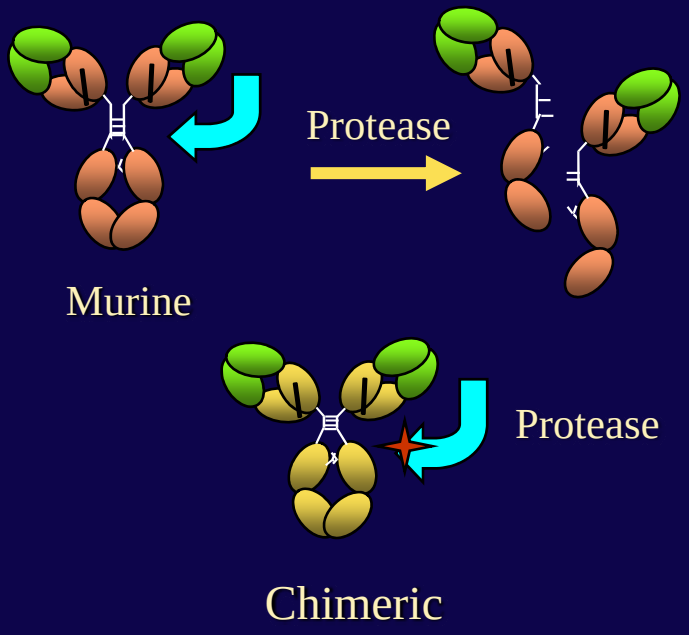
WHO Grade III
Perivascular
9/13

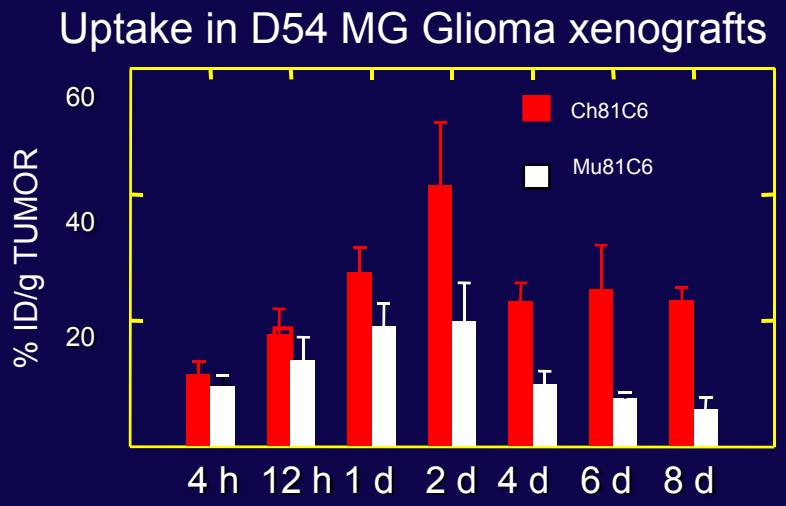
WHO Grade IV
Perivascular
48/48

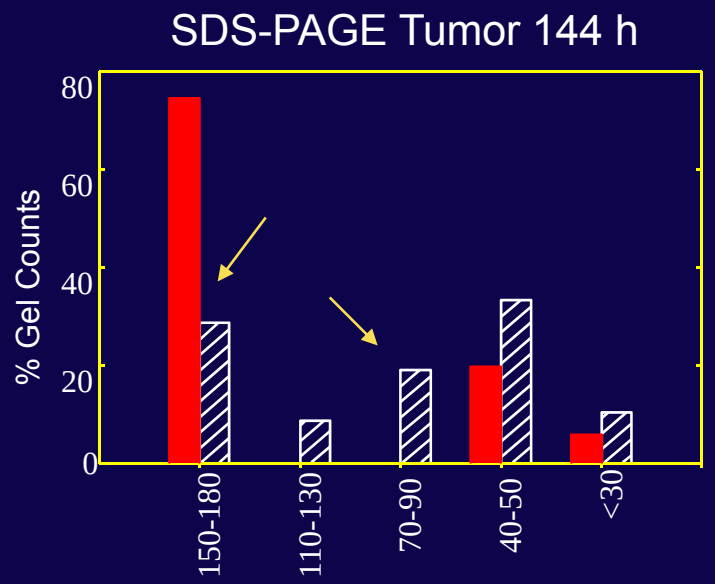
Herold-Mende, 2002

Chimeric 81C6 IgG_2

- Higher retention in tumor and many normal tissues
- Less generation of 75 kD metabolite in vivo
- Slower SCRC clearance in patients





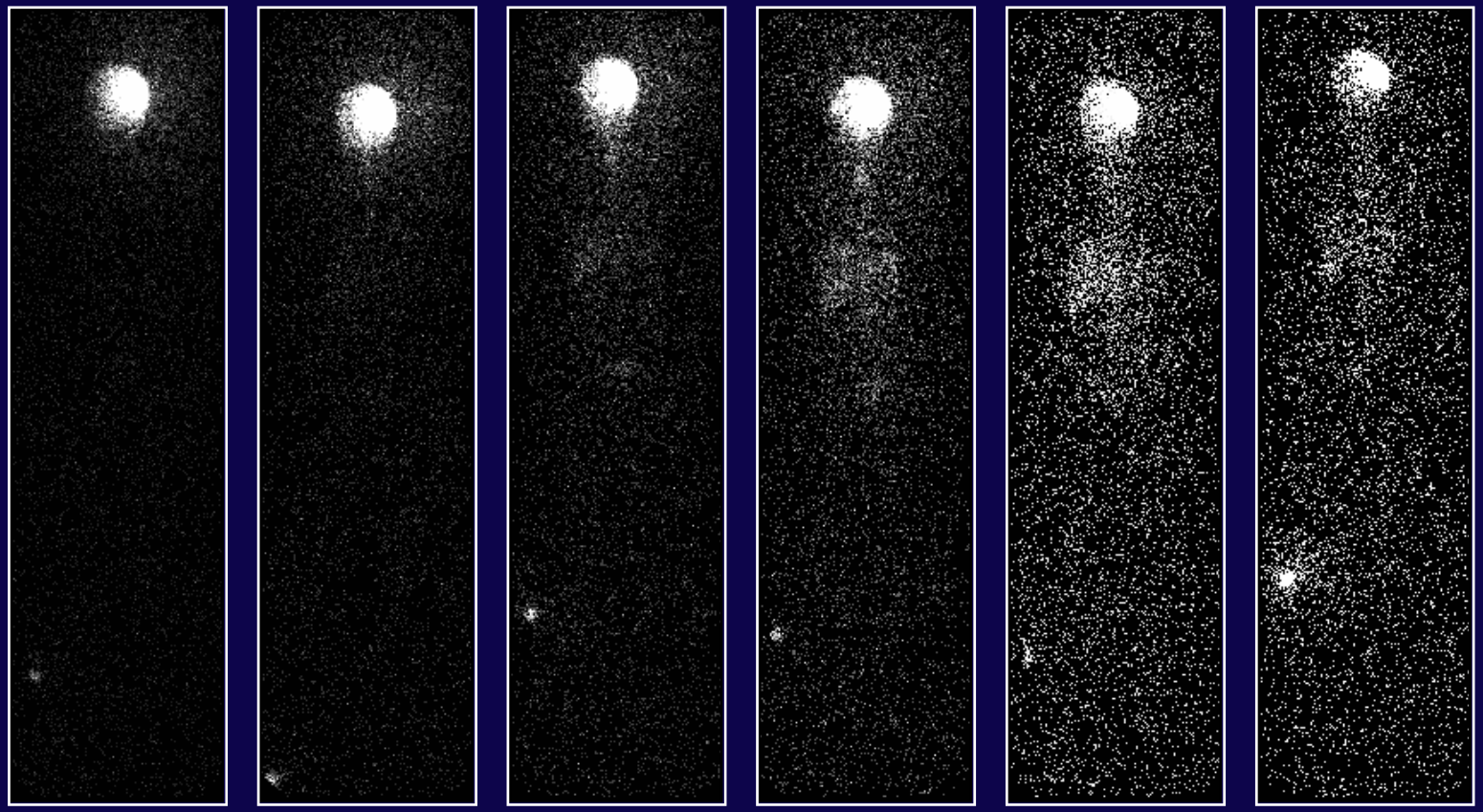


At-211 Labeled Chimeric 81C6: Clinical Protocol

- Thyroid blocking with SSKI and Cytomel beginning 48 hr prior to therapy
- Dose administration via indwelling catheter
- Patients injected via the SCRC with 10 mg of mAb labeled with 2 (n=5), 4 (n=7), 6.7 (n=5) or 10 mCi (n=1) mCi ^{211}At
- Blood sampling at 1, 2, 4, 8, 12, 18 and 24 hr
- SPECT of head and whole body imaging at 2, 4, 8, 18 and 24 hr

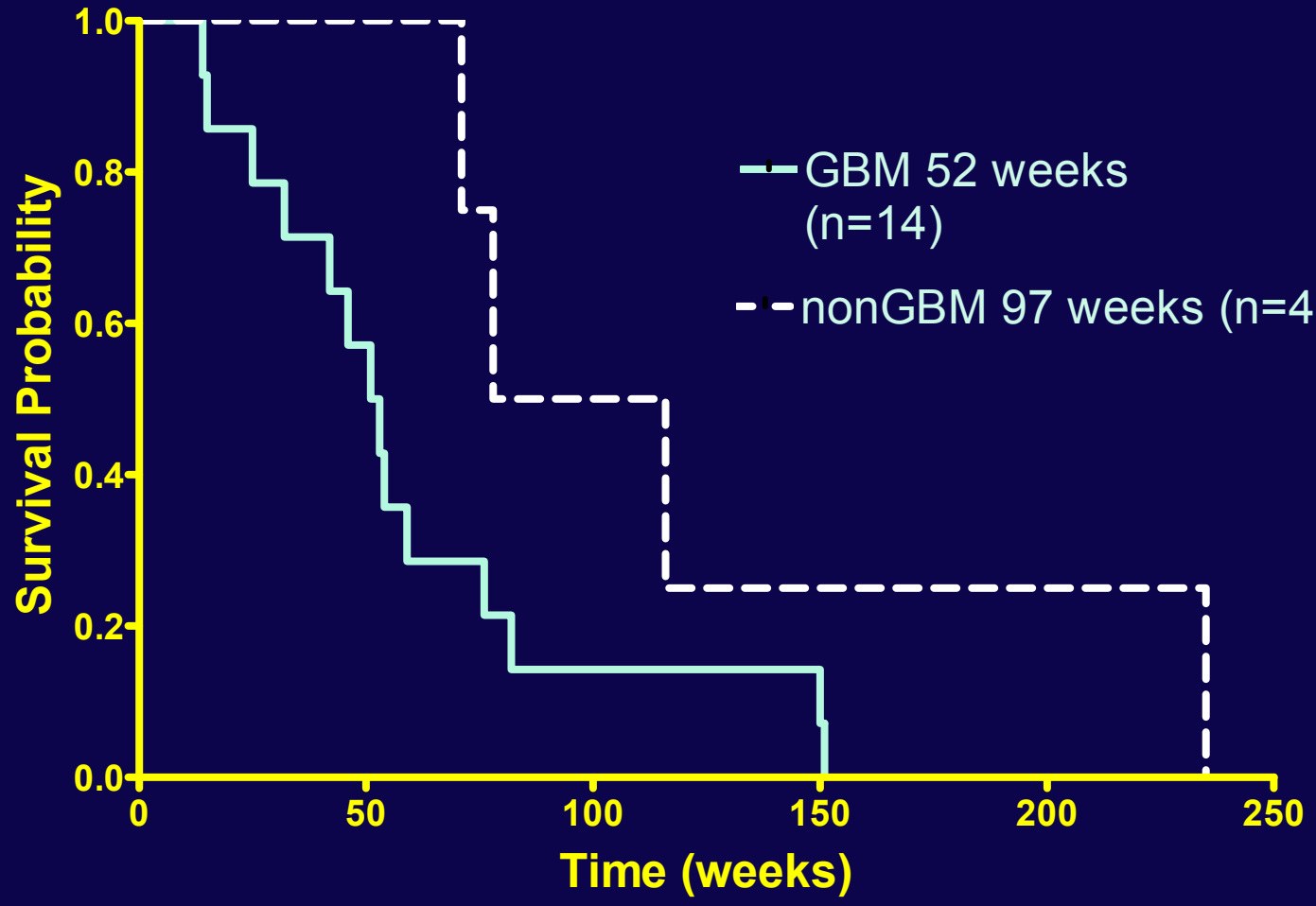
Whole Body Images after SCRC Injection of ^{211}At-Labeled 81C6

1% window; i.e. upper threshold set to 0.01X maximum pixel count



0.9 h 2.0 h 4.7 h 8.7 h 18.2 h 25.4 h

Phase 1 ^{211}At-Labeled Chimeric 81C6 in Recurrent Brain Tumor Patients: Outcome



Historical Control: GBM 31 weeks Brem et al. 1995

Survival: Recurrent Patients

- 8 of 14 GBM patients survived for 1 year
- Two GBM patients survived for nearly 3 years (151 and 152 weeks)
- All patients with lower grade tumors survived for more than 71 weeks (71, 78, 116, 235 weeks)

Radionuclide Availability

- Most crucial need for those emitting "short range" radiation:

short	Low energy β	^{67}Cu
shorter	α-emitter	^{225}Ac, ^{211}At
shortest	Auger	^{77}Br

Specific Activity

- Challenge is greater for therapy than imaging (acceptable contrast vs. homogeneous delivery of effective level of radionuclide)
- Competition of cold and hot molecule for receptor
  - Some molecular targets expressed at low levels (α-MSH receptor)
  - Many molecular targets expressed with high degree of heterogeneity within tumor
- Cross fire can compensate in part for this but at the expense of specificity

Regulatory Affairs

- Requirement for evaluating late radiation effects without adequate guidance (endpoints, species, time frame)
- Guidelines for radiotoxicity of high-LET emitters
- Handling of patient-specific treatment plans (cocktails of radionuclides and carriers, variations in dosing schemes)

Consequences of Heterogeneity for Radionuclide Needs

- Macro: Need to administer multiple radionuclides to compensate for range of tumor sizes in a particular patient
- Micro: Need to balance advantages of longer range radiation (cross fire of receptor negative populations) with disadvantages (irradiation of normal tissue)
- Normal tissue: Need to distribute uptake of labeled catabolites among organs through use of different radionuclides and labeling methods