Alpha and Auger-Emitting Radionuclides for Therapy

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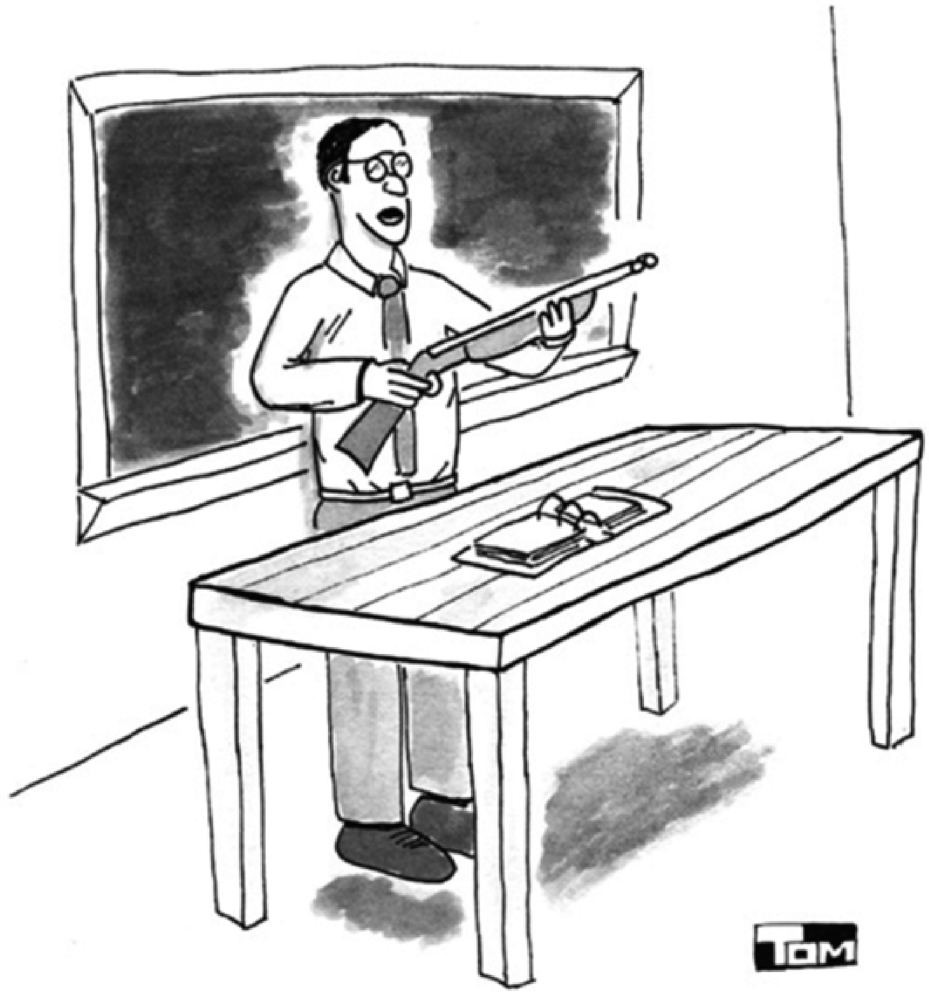
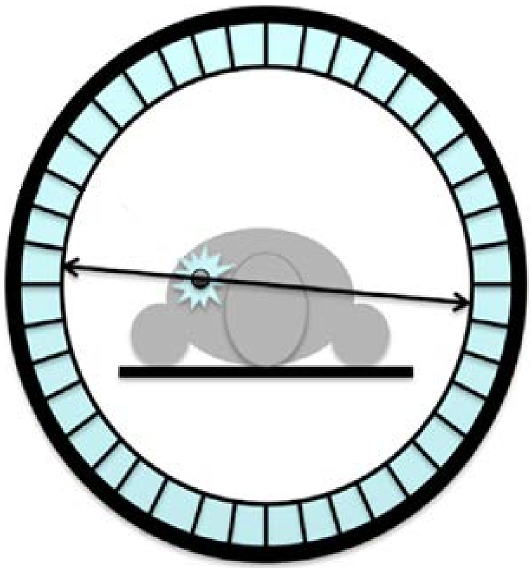
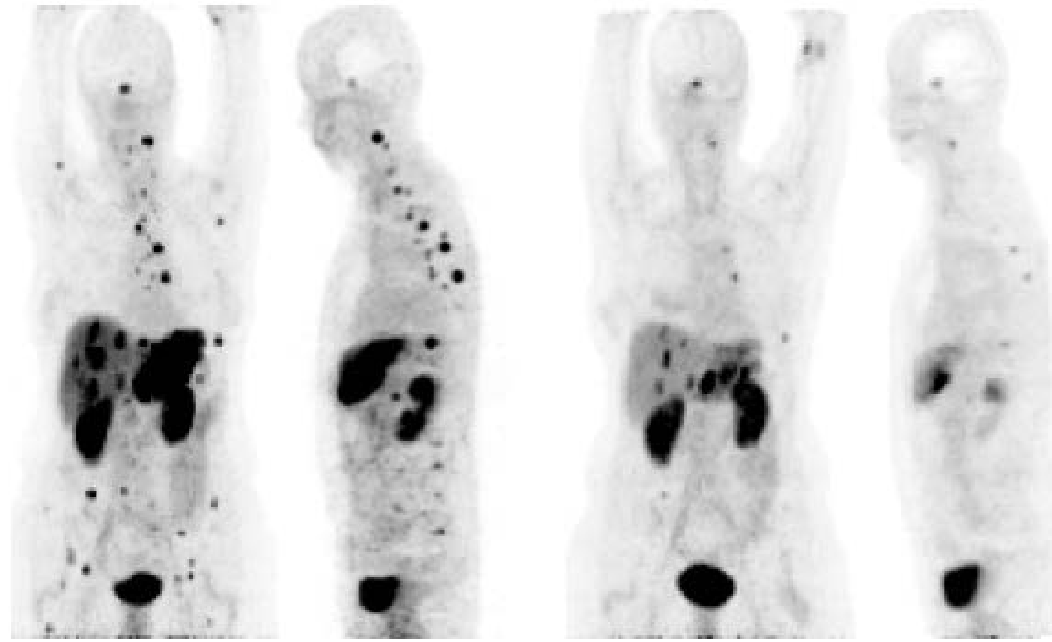
"PLEASE FEEL FREE TO INTERRUPT IF YOU HAVE A QUESTION."



Positron Emission Tomography



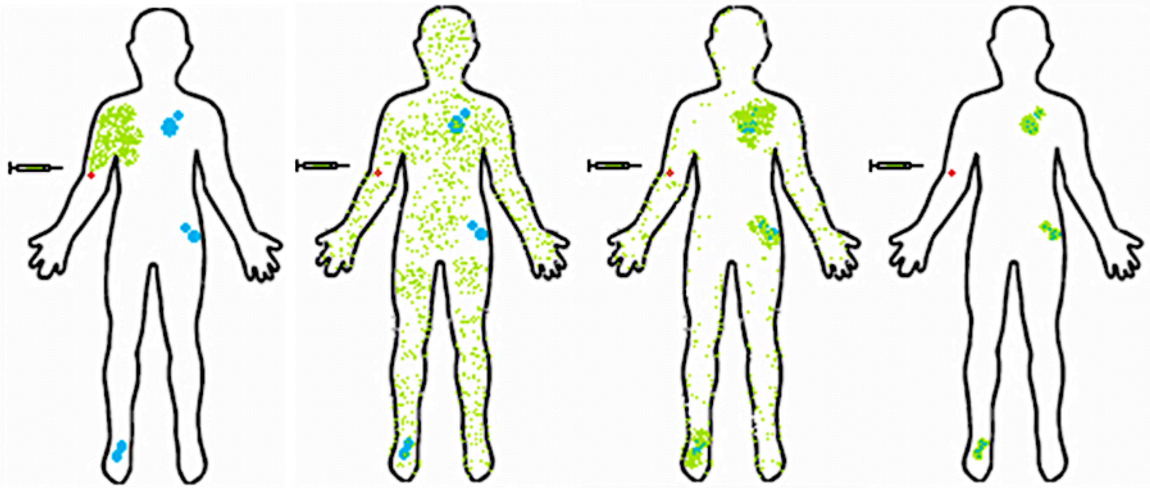
Van der Velt, et. al., Front. Oncol., 2013.



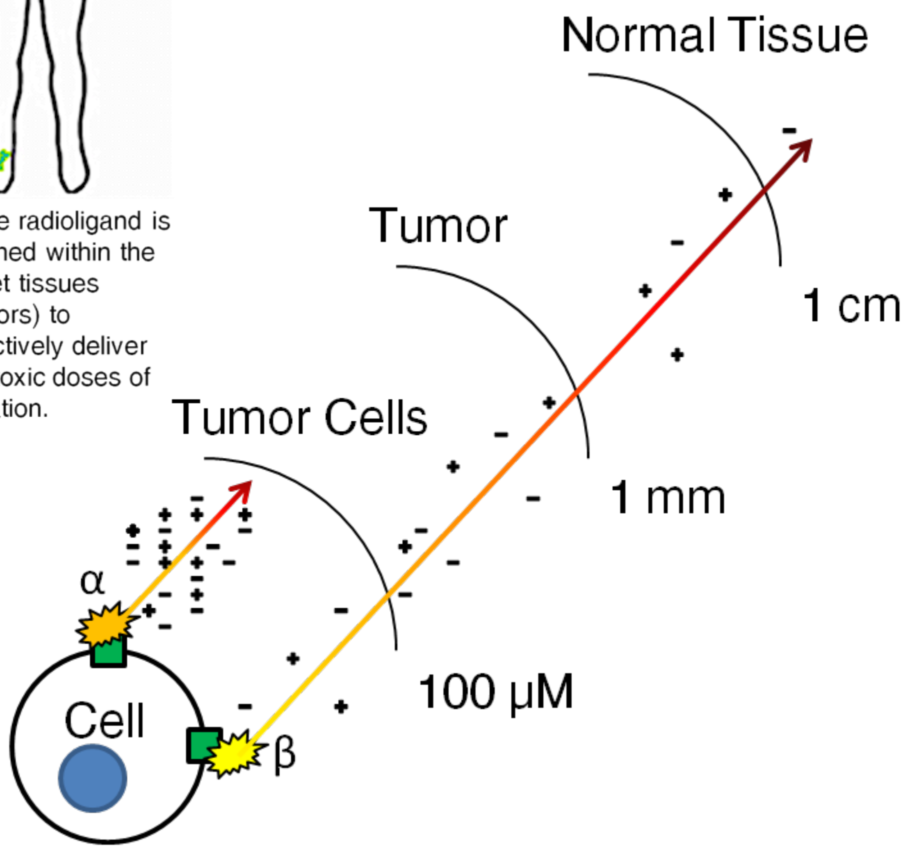
SNMMI Image of the Year, 2014. Molecular Imaging.

Isotope	Half-life ($t_{1/2}$)	β^+ Branch	β^+ Max Energy	Tracer examples
^{11}C	20.4 min	99.76%	0.96 MeV	PIB, Methionine, Choline
^{13}N	9.97 min	100%	1.19 MeV	Ammonia ($^{13}NH_3$)
^{15}O	2.04 min	99.89%	1.72 MeV	Water ($^{15}OH_2$)
^{18}F	109 min	96.9%	0.64 MeV	FDG, Fluoride ($^{18}F^-$)
^{82}Rb	1.27 min	96%	3.35 MeV	$^{82}RbCl$

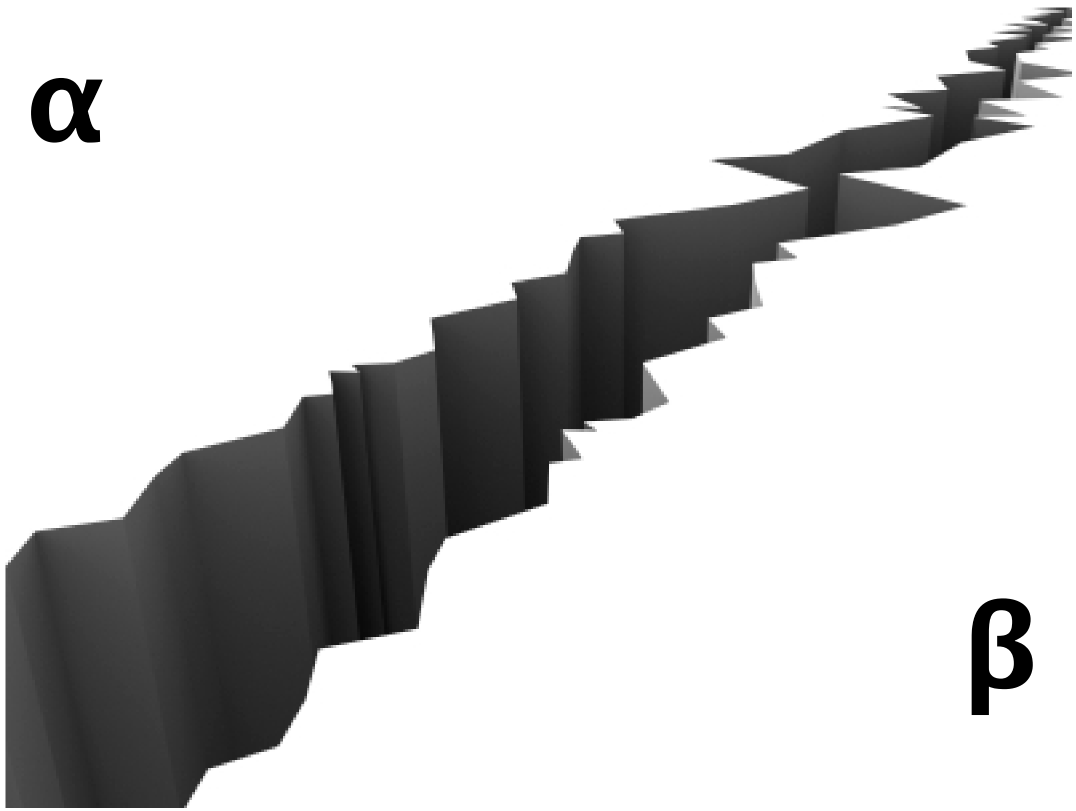
One Future for Radionuclide Production



1. The targeted radioligand is administered systemically to the patient.
2. The radioligand distributes throughout the patient.
3. The radioligand localizes and concentrates in target tissues (e.g. tumors) reducing radiation dose to non-target normal tissues.
4. The radioligand is retained within the target tissues (tumors) to selectively deliver cytotoxic doses of radiation.



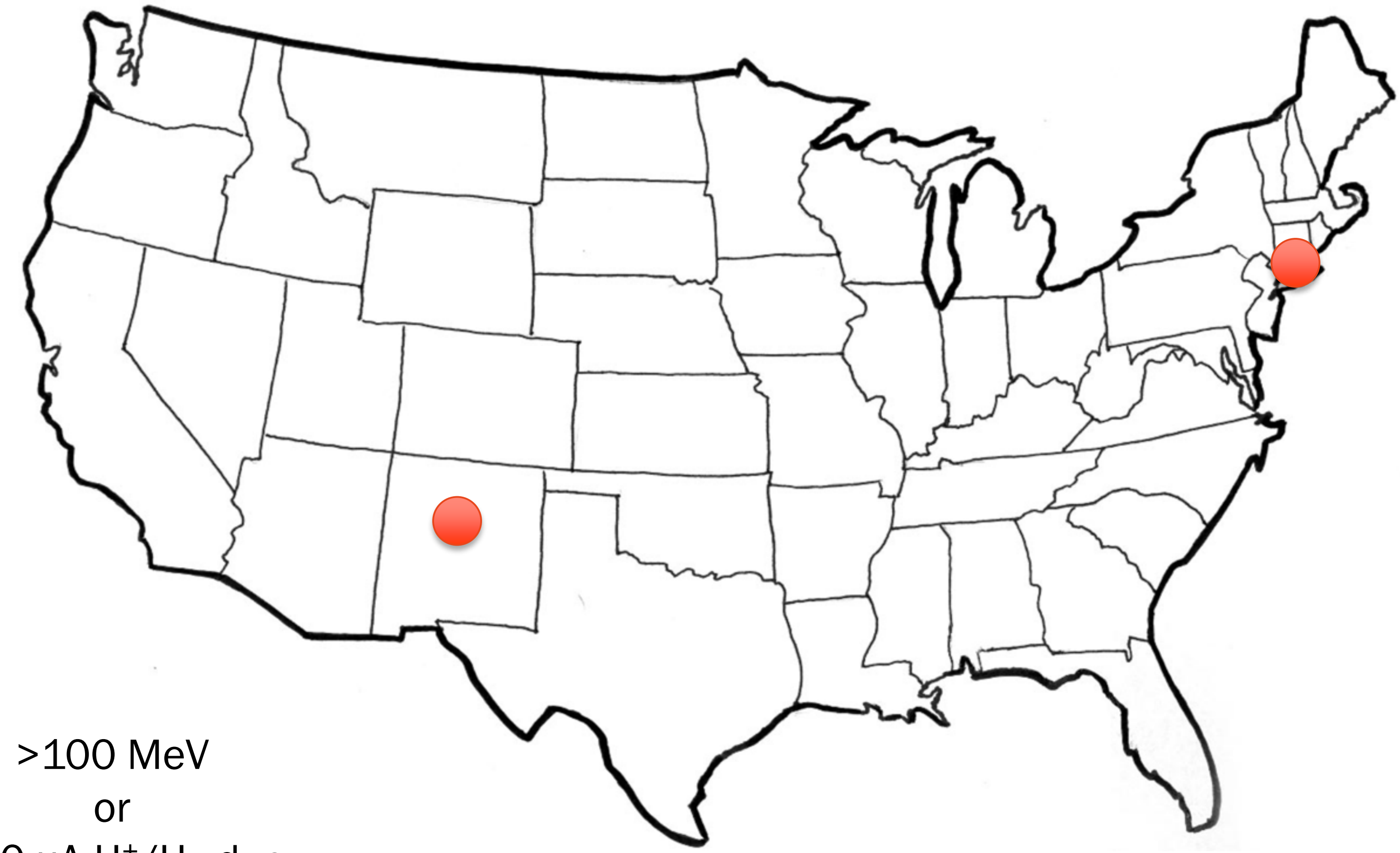
α



β

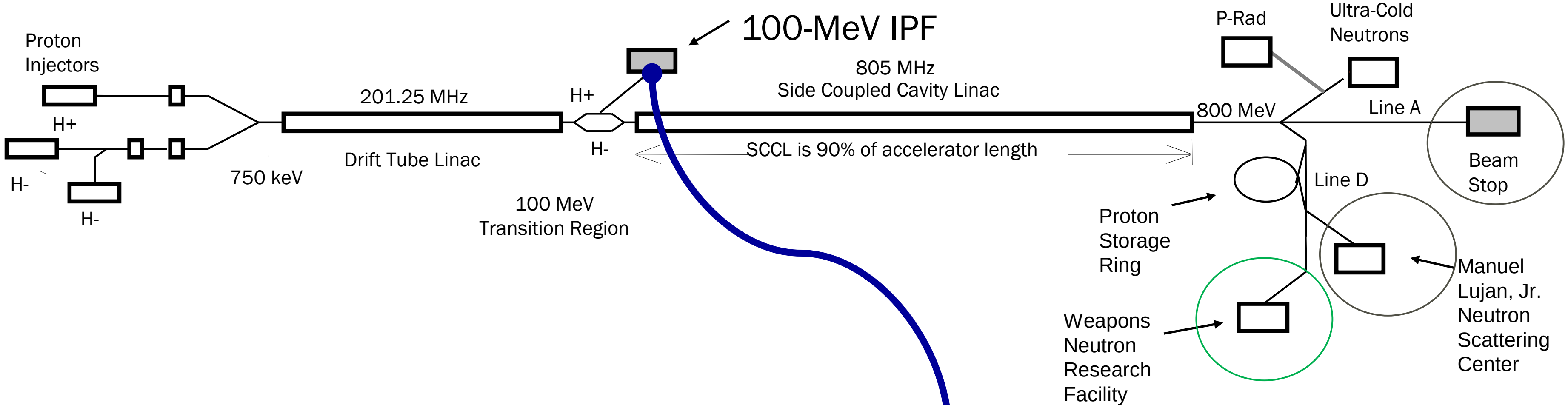
How you take your coffee

National-Scale Facilities for Charged-Particle Irradiations and Radionuclide Production



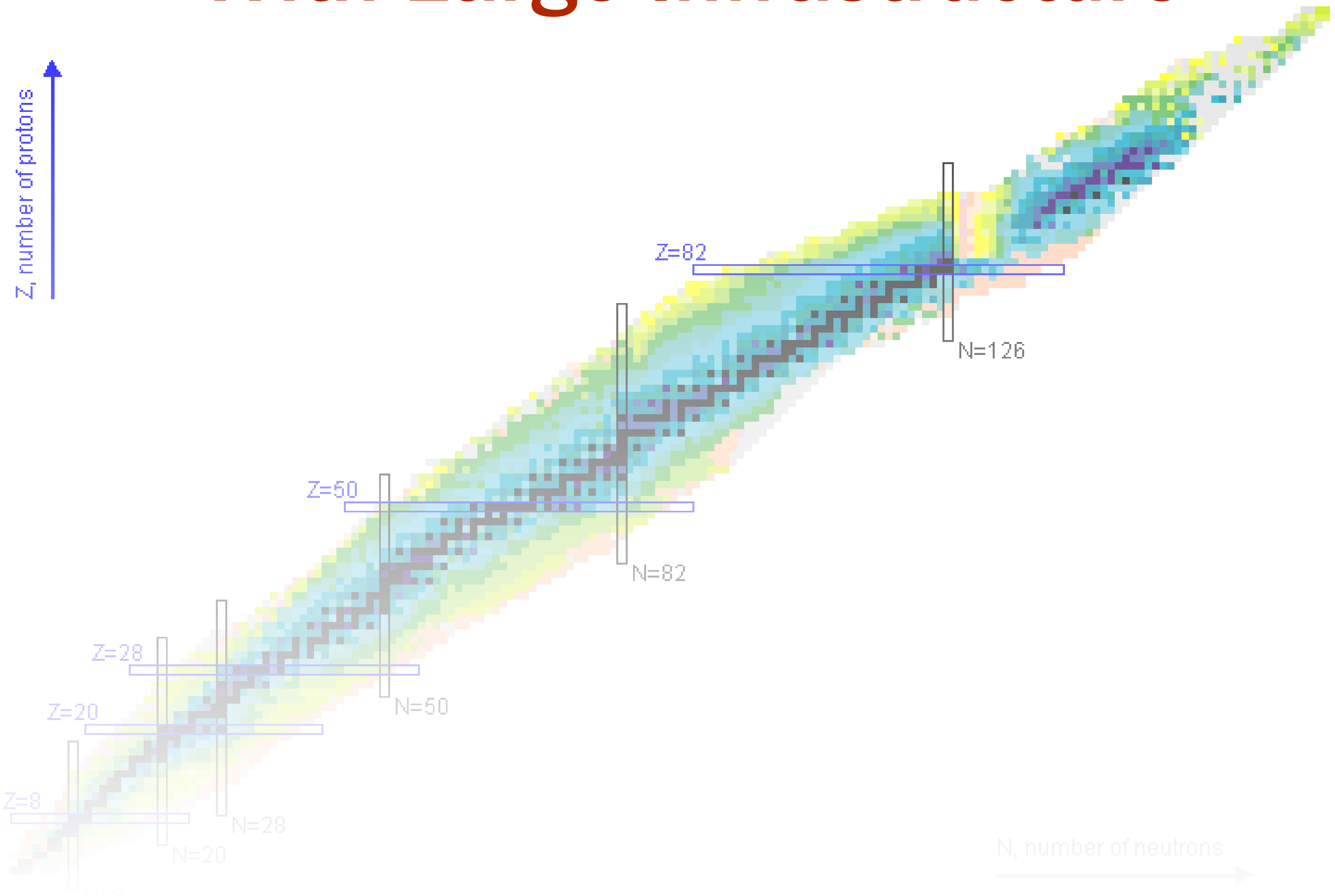
>100 MeV
or
>200 μA H^+/H^-, d, **α**

National Scale, Multi-User Infrastructure

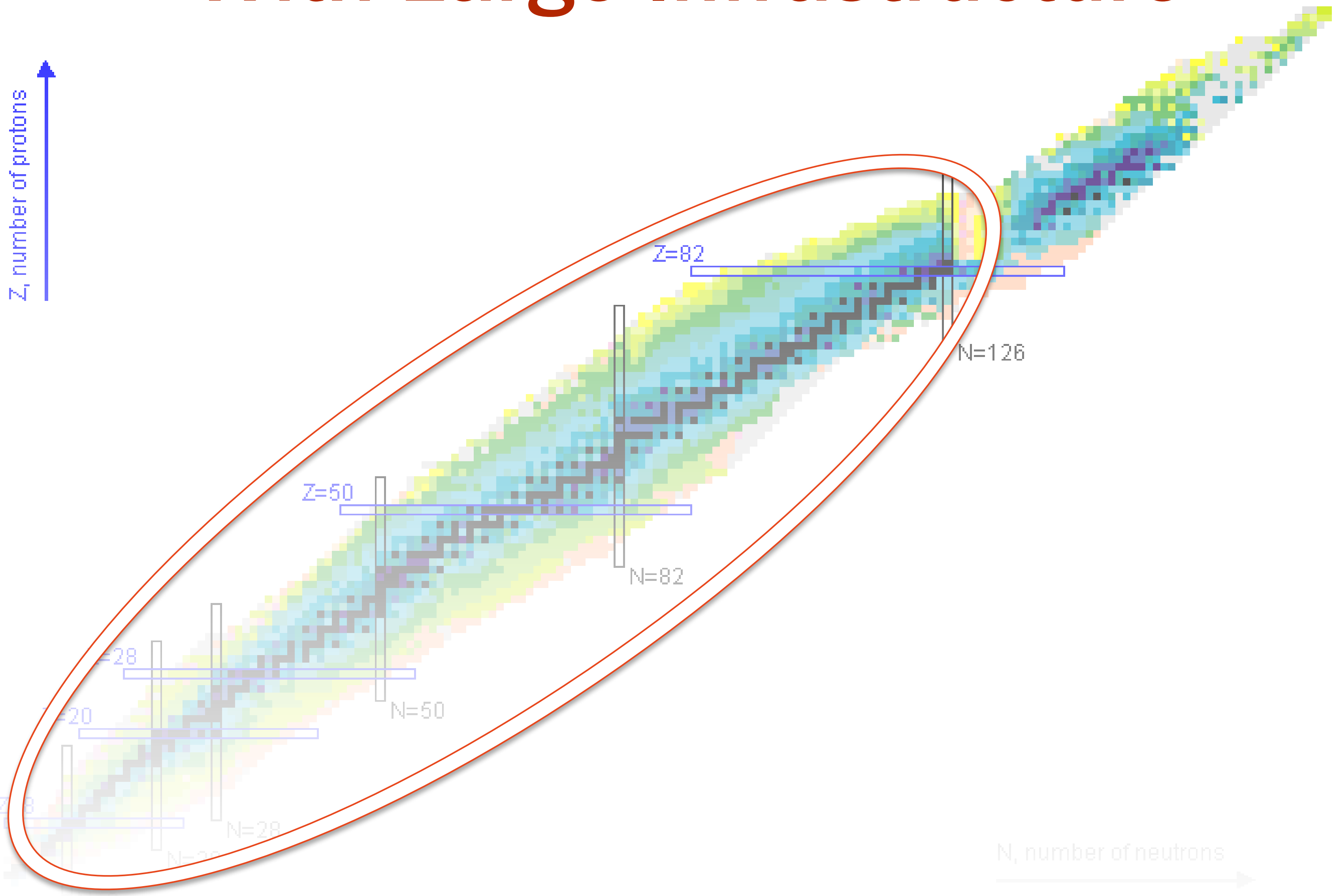


IPF at LANSCE

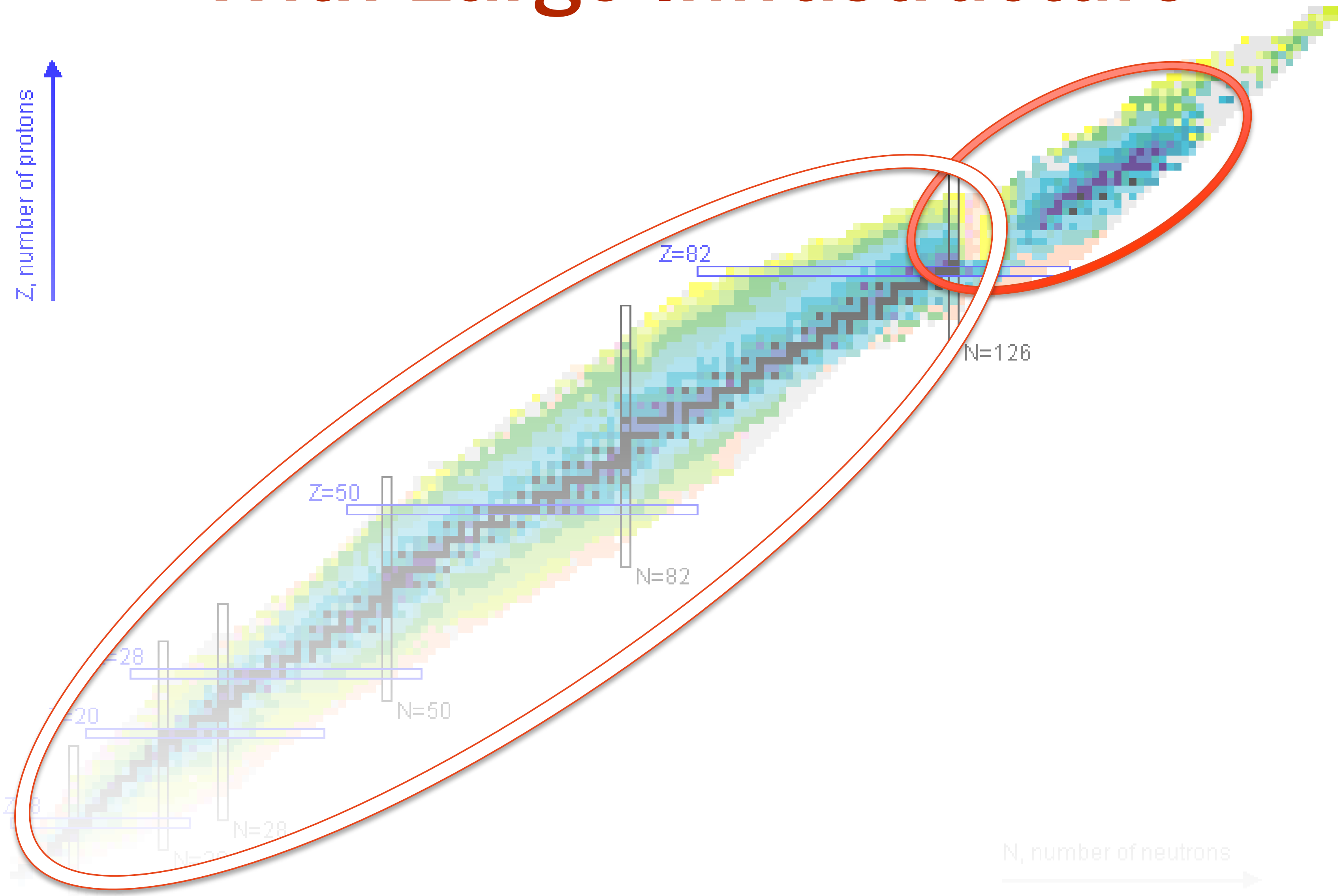
With Large Infrastructure



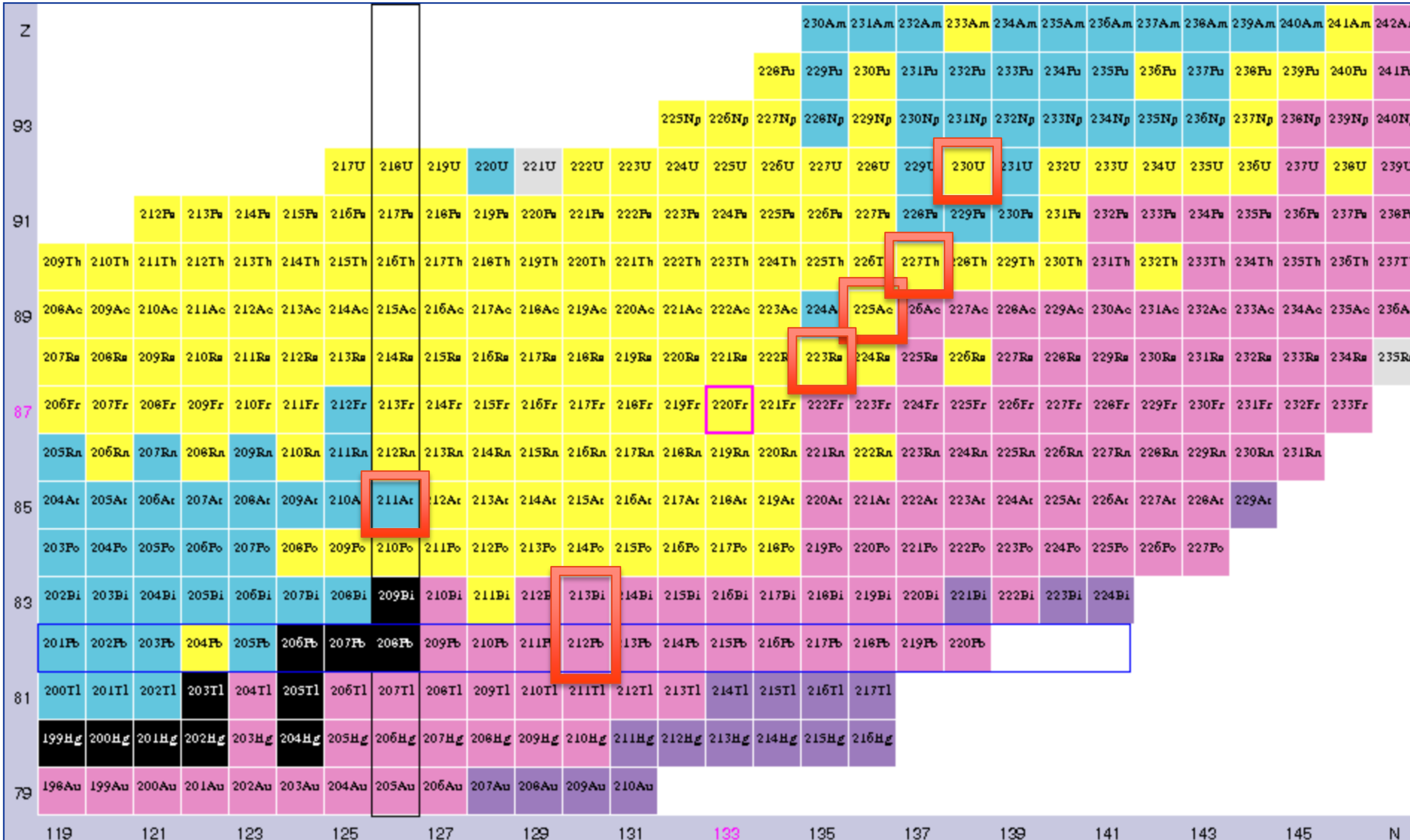
With Large Infrastructure



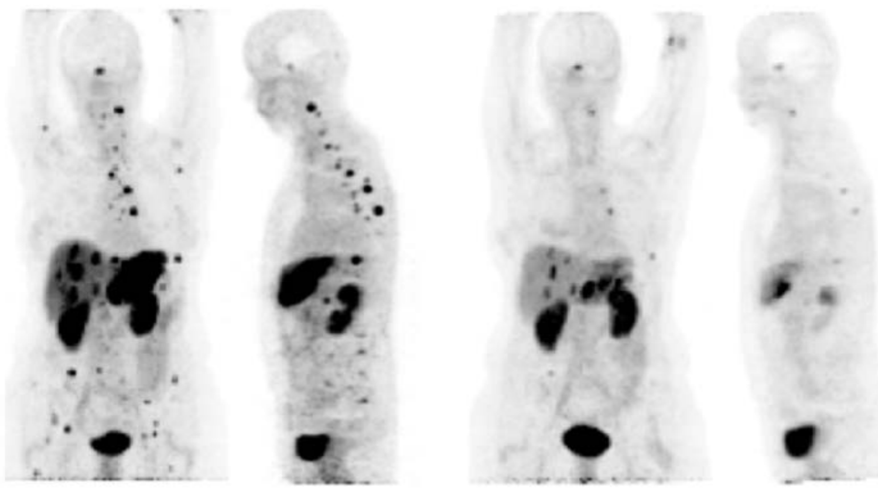
With Large Infrastructure



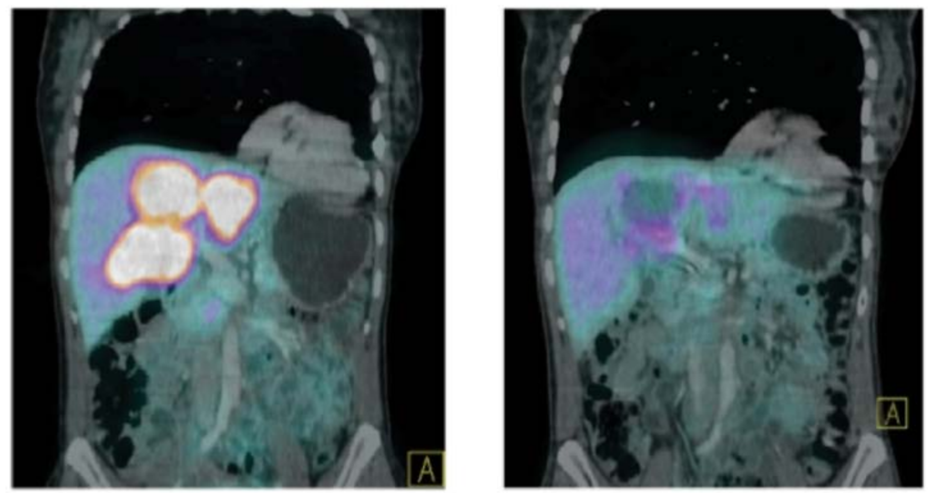
The Appealing Landscape



Curative Appeal in People

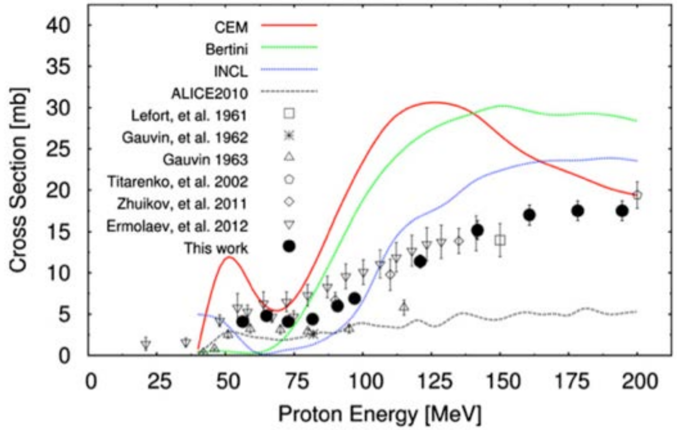


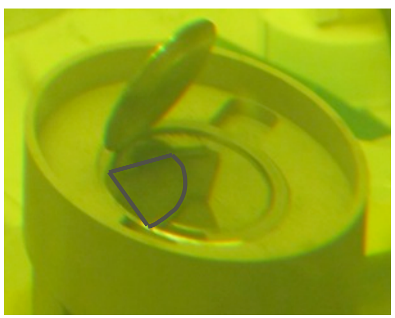
Case I: Shrinkage of liver lesions and bone metastases after i.a. therapy with 11 GBq Bi-213-DOTATOC

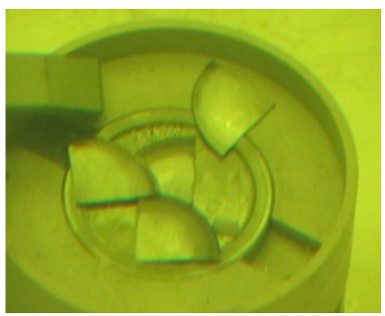


Case II: Response of multiple liver lesions after i.a. therapy with 14 GBq Bi-213-DOTATOC

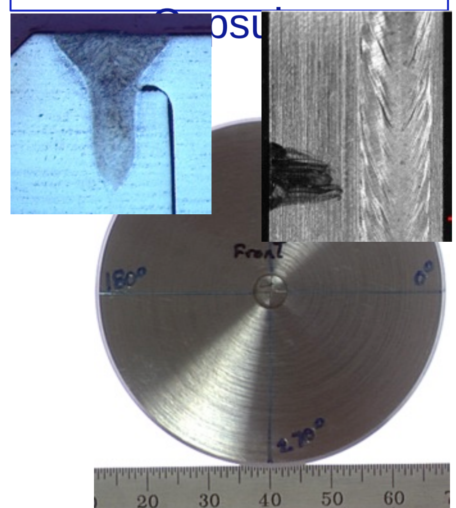
Th-232(p,x)Ac-225 for Alpha Radiotherapy

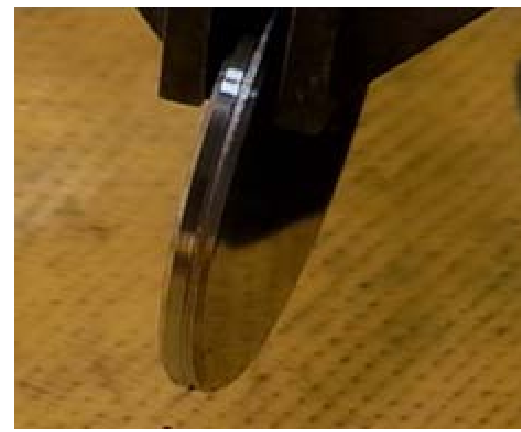


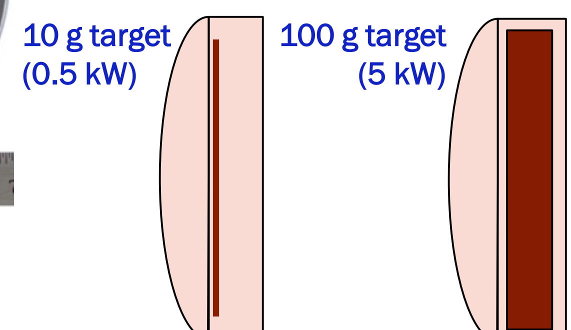




Electron Beam Welded Inconel







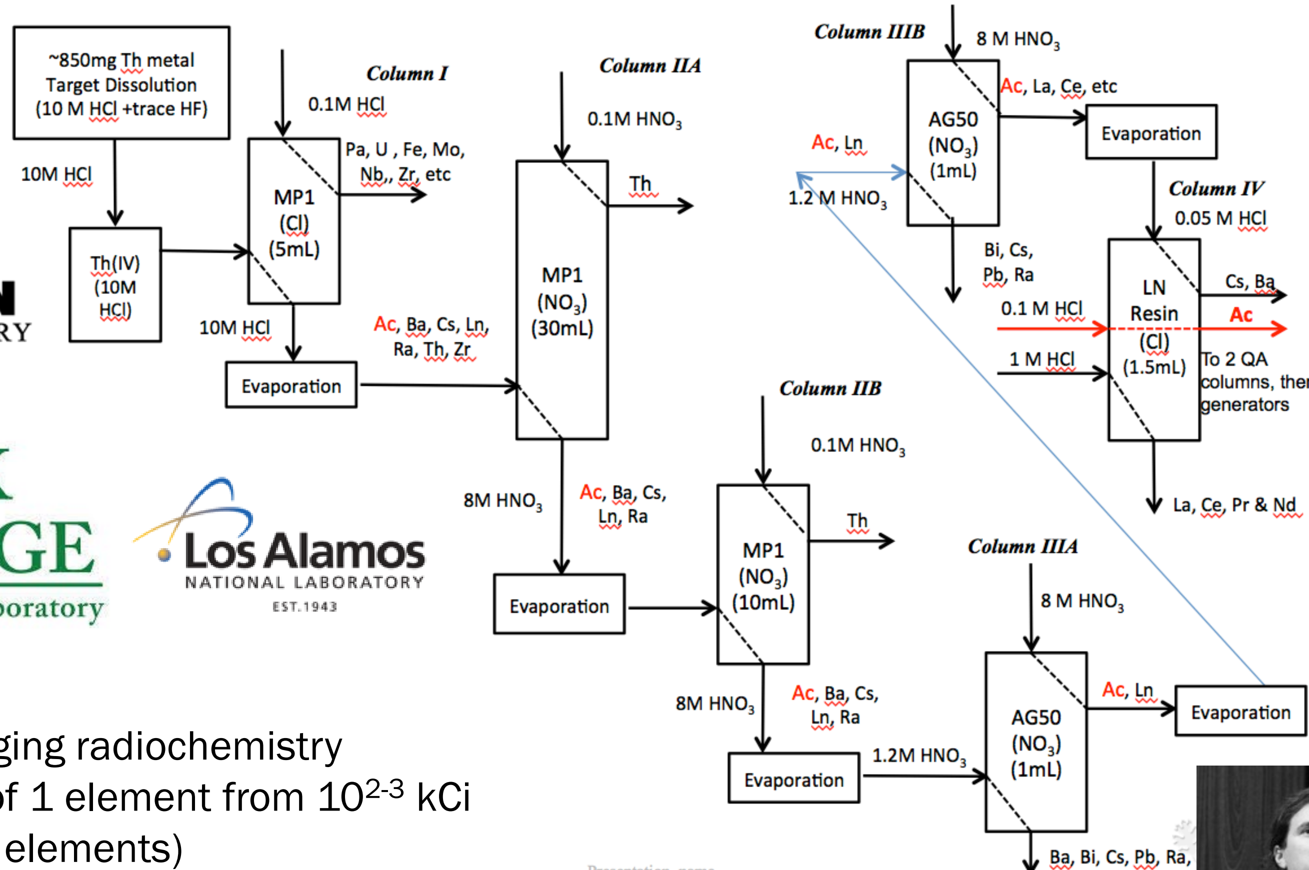
- Up to 7 day Irradiations at 230 μA
- Ci-scale yields of ^{225}Ac
- 20x the Current Global Annual Supply

BROOKHAVEN NATIONAL LABORATORY

Los Alamos NATIONAL LABORATORY EST.1943

Weidner et al., *App Rad Isotop*, 2012; Engle et al., *Rad Chim Acta*, 2014

Isolating ^{225}Ac from Irradiated Thorium



BROOKHAVEN NATIONAL LABORATORY

OAK RIDGE National Laboratory

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- Very Challenging radiochemistry (separation of 1 element from $10^{2\text{-}3}$ kCi of 70+ other elements)
- Light lanthanidies were a significant challenge (require 2 additional columns in the process)

Radchenko et al., *J Chrom A*, 2014

Dr. Valery Radchenko

The Appealing Landscape

- ^{225}Ac (^{213}Bi)
  - $^{232}Th(p,x)^{225}Ac$
  - $^{226}Ra(p,2n)^{225}Ac$
  - $^{226}Ra(n,\gamma)(n,\gamma)(n,\gamma)^{229}Th \rightarrow {}^{225}Ra \rightarrow {}^{225}Ac$
  - $^{226}Ra(\gamma,p)$ or $(\gamma,2n)^{225}Ra \rightarrow {}^{225}Ac$
- ^{212}Bi
  - Reactor production of ^{228}Th, multiple routes
- ^{227}Th (^{223}Ra)
  - Reactor production of ^{227}Ac, multiple routes from ^{226}Ra
  - The sole FDA-approved alpha-emitting radiopharmaceutical = $^{223}RaCl_2$
- $^{230}Pa/^{230}U$ (^{226}Th)
  - $^{232}Th(p,3n)^{230}Pa$
- ^{149}Tb
  - Multiple high energy charged particle spallation routes, ALL followed by online mass separation.
- ^{211}At
  - $^{209}Bi(\alpha,2n)^{211}At$
  - $^{209}Bi(^{7}Li,5n)$ or $^{209}Bi(^{6}Li,4n)^{211}Rn \rightarrow {}^{211}At$

Untenable (?) Cost

- National Radionuclide Providers operate under full-cost recovery models.
- Historically, industry takes over when a radionuclide becomes commercially viable.
- Commercial viability is harder to achieve when industry has to duplicate infrastructure at National Scales

Gedankenexperiment

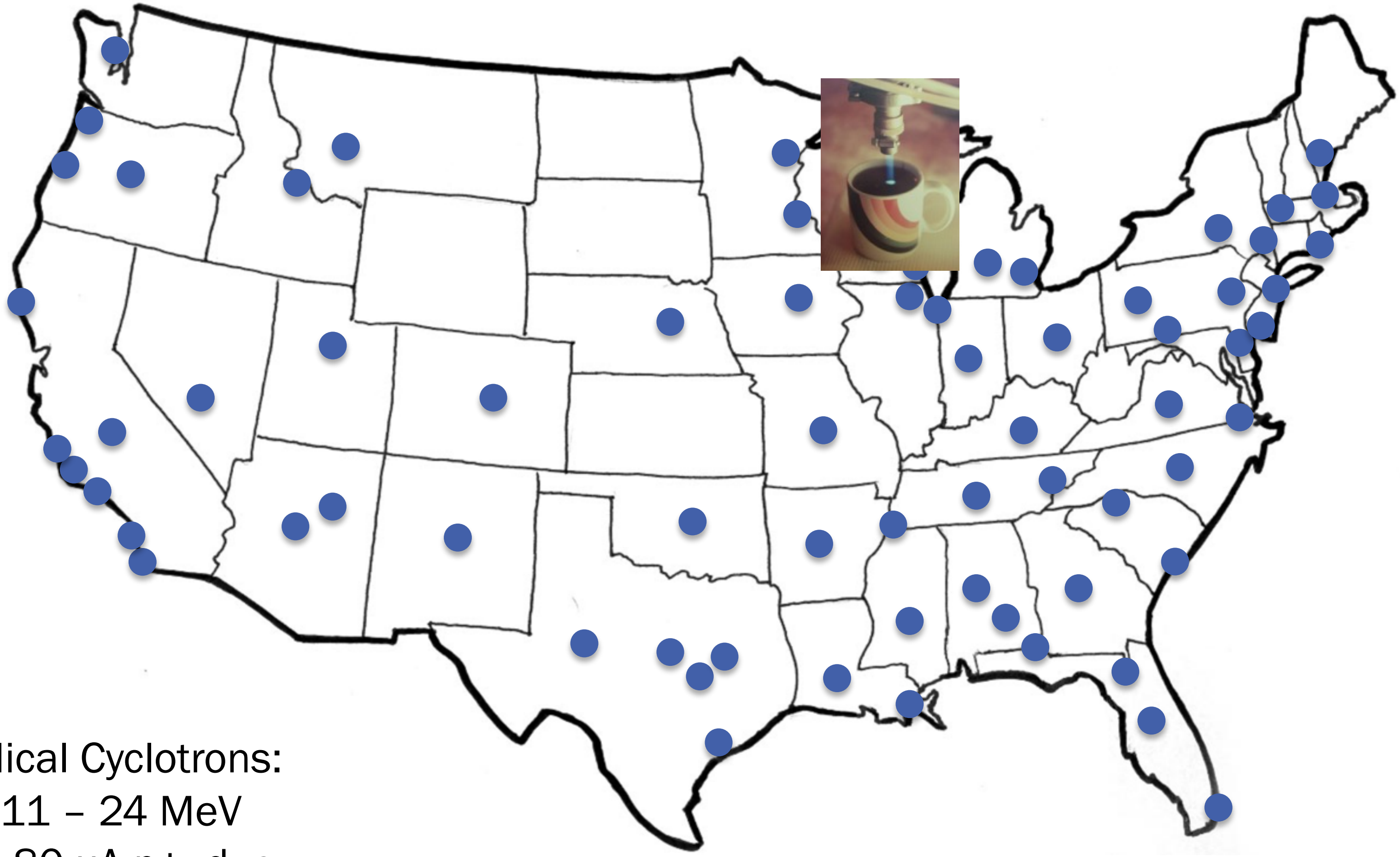
- Current Annual Supply of ^{225}Ac ~ 1 Ci
  (140 mCi every 6-8 weeks from ORNL ^{229}Th cow)
- Supply Increase from IPF + BLIP at Full Capacity ~ x50
  … or about 50 Ci

- 1 Treatment of ^{225}Ac-derived ^{213}Bi (the clinically-demonstrated agents) ~ 80 mCi → 10^2 patients/yr
  (3 rounds of therapy each)
- 3 Treatments of ^{225}Ac-labeled targeting vector per patient at ~ 1 mCi each → 10^4 patients/yr

- 14M Cancer Patients exist in the US at any one time.

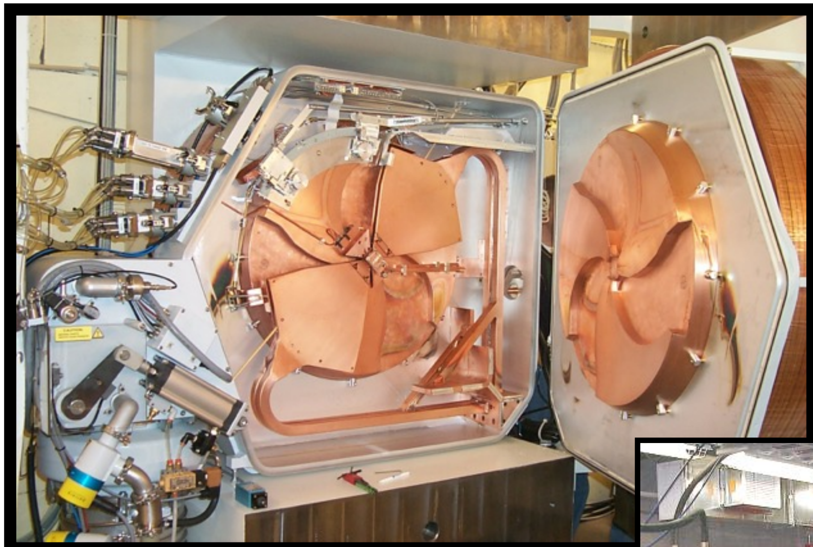
  - So…. What to do…

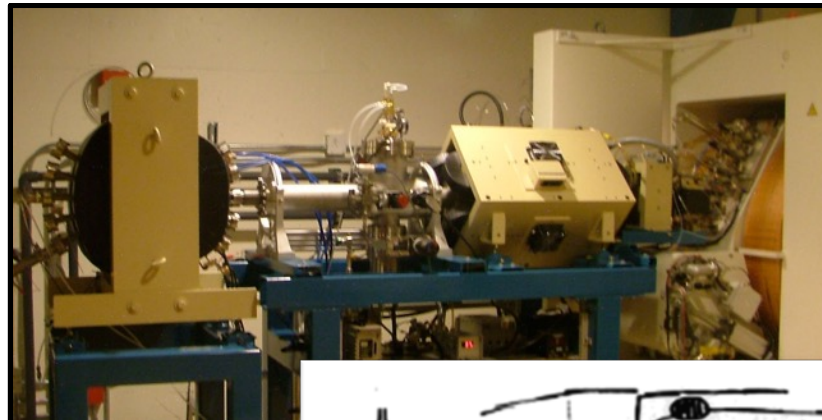
The Distributed Small-Cyclotron Network of Radionuclide-Producing Facilities

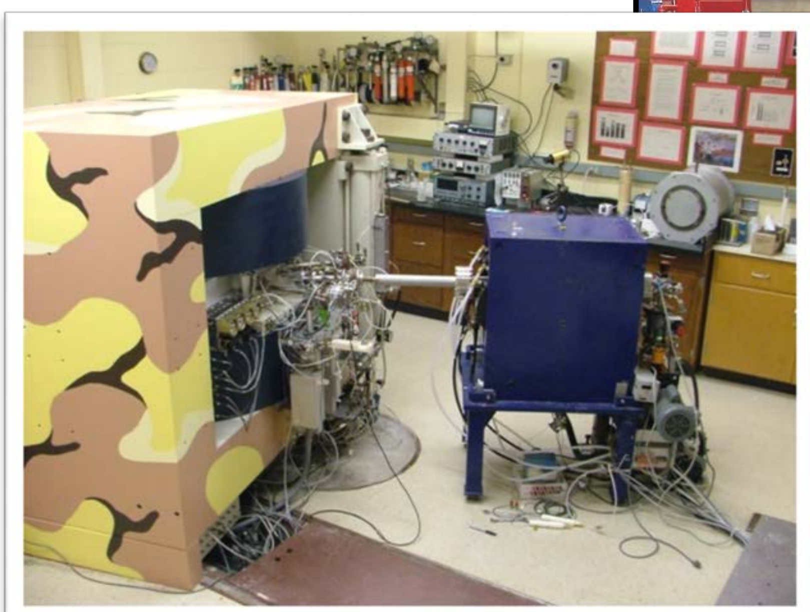


Medical Cyclotrons:
~ 11 – 24 MeV
10 – 80 μA p+, d, α

Shoot

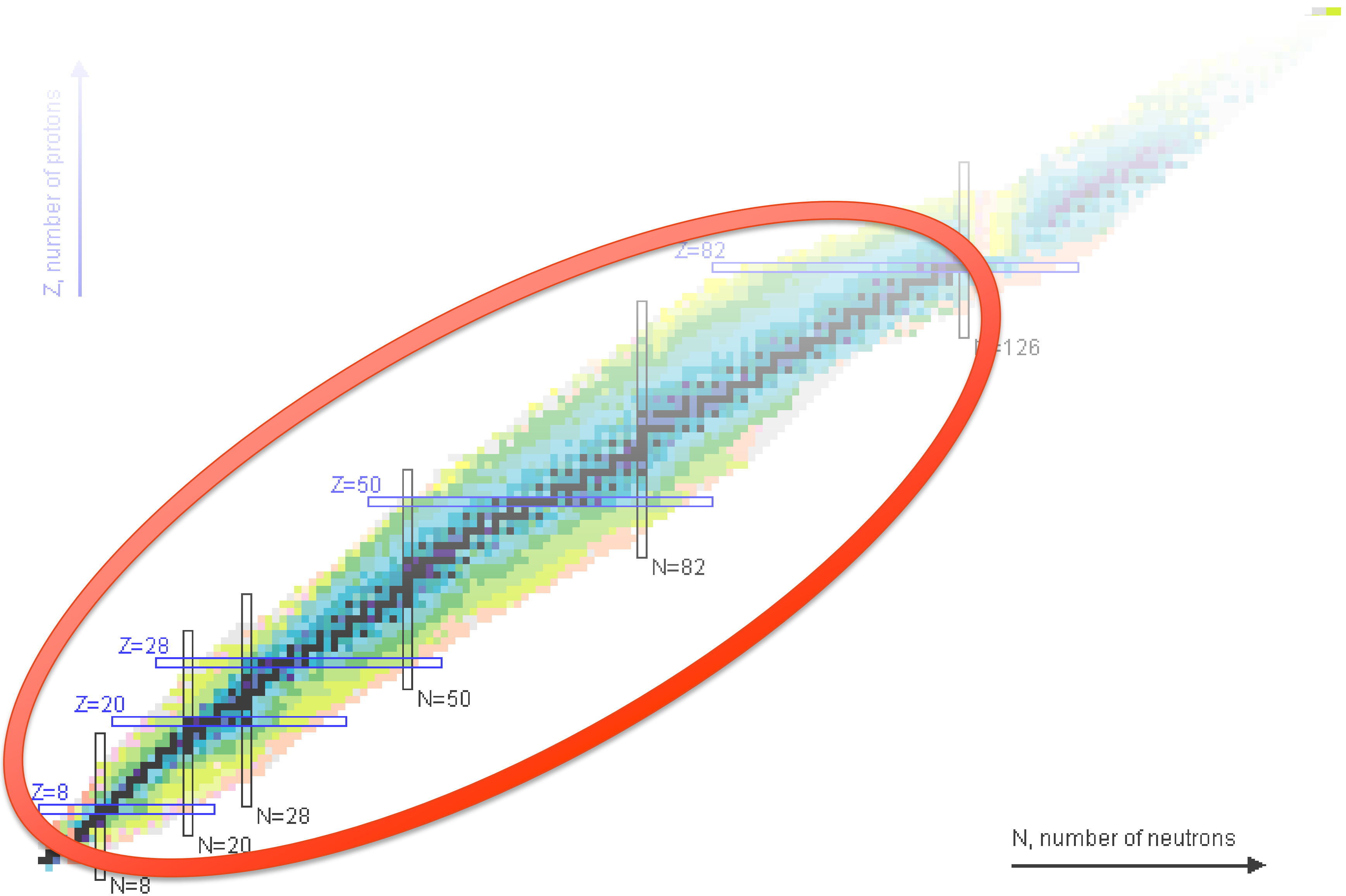






"Particles, particles, particles."

With Small Cyclotrons



The Menu du Jour

Nuclide	$t_{1/2}$	Reaction	%	Yield (EoSB)	SA	Synthon	Status
^{34m}Cl	32 m	^{36}Ar(d,α)	0.3	4.6 mCi/μA	-	Cl^-, ClF	animal imaging
^{44}Sc	3.9 h	^{44}Ca(p,n)	2	5.8	1	Sc^{3+}	animal imaging
^{45}Ti	3.1 h	^{45}Sc(p,n)	100	47	1	$TiCl_4$	animal imaging
^{51}Mn	46 m.	^{54}Fe(p, α)	5.8	26	1	Mn^{2+}	animal imaging
^{52g}Mn	5.6 d	^{52}Cr(p,x)	82	0.3	1	Mn^{2+}	animal imaging
^{61}Cu	3.4 h	^{60}Ni(d,n)	26	20	0.1	ATSM	patients
^{64}Cu	12.7 h	^{64}Ni(p,n)	0.9	170	25	Cu^{2+}	animals, distribution
^{66}Ga	9.6 h	^{66}Zn(p,n)	28	31	20	Ga-NOTA	animal imaging
^{68}Ga	68 m	^{68}Zn(p,n)	19	35	20	"	animal imaging
^{72}As	26 h	^{72}Ge(p,n)	27	102	-	As^{3+}	chem separation
^{86}Y	15 h	^{86}Sr(p,n)	10	26	1.5	Y-DOTA	animal imaging
^{89}Zr	78 h	^{nat}Y(p,n)	100	100	20	Zr-DFO	animals, distribution
^{95m}Tc	65 d	^{95}Mo(p,n)	16	21	-	Tc-in-Mo	chemistry

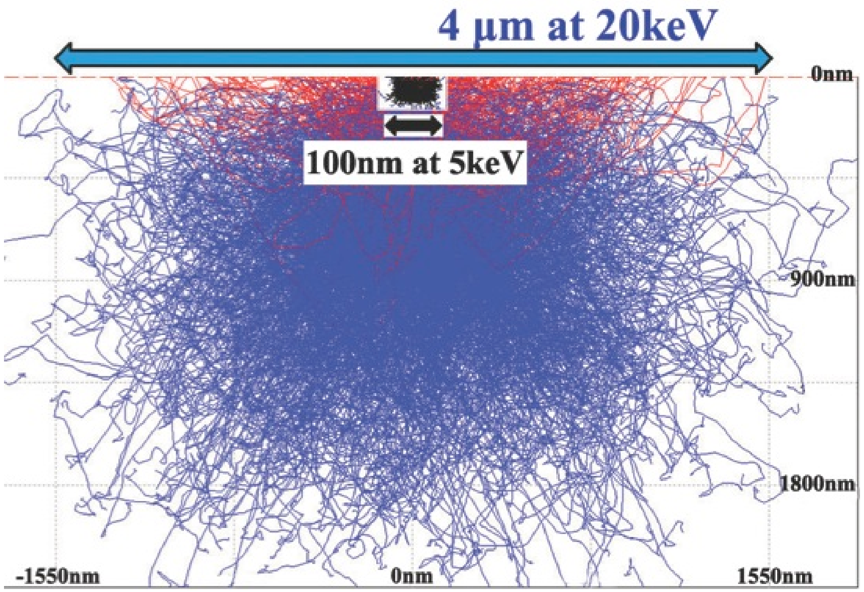
inception → acceptance

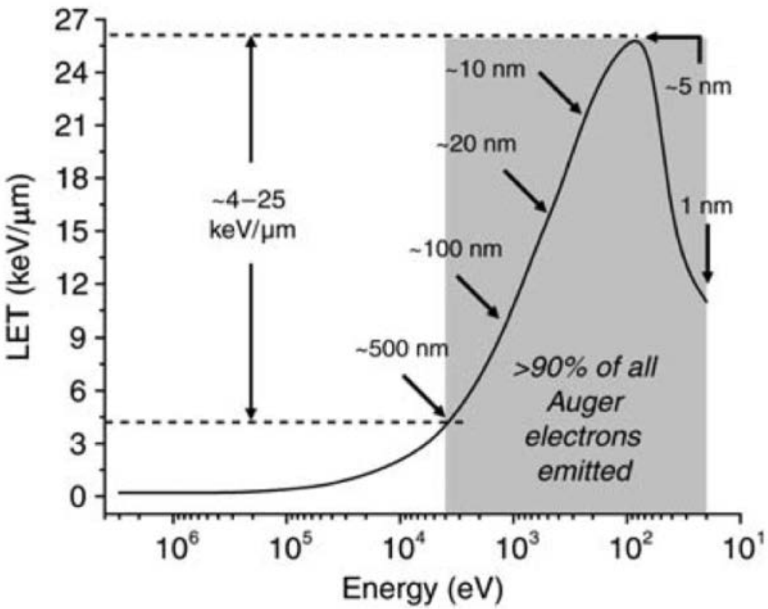
In-house few users distribution

Interesting Auger/Conversion Electron Emitters

- ^{111}In, ^{114m}In
- ^{125}I
- ^{94}Tc, ^{99m}Tc
- ^{117m}Sn
- ^{193m}Pt, ^{195m}Pt
- ^{119}Sb
- ^{58m}Co
- ^{71}Ge
- ^{77}Br, ^{80m}Br
- ^{67}Ga
- ^{103}Ru
- $^{140}Nd/^{140}Pr$
- ^{161}Tb
- ^{165}Er
- ^{55}Fe, ^{57}Fe, ^{59}Fe
- ^{197}Hg
- ^{201}Tl
- ^{158}Gd (from n,γ), ^{159}Gd
- ^{131}Cs
- ^{51}Cr
- ^{103}Pd
- ^{167}Tm
- ^{178}Ta

High-LET Augers?





A.I. Kassis, Rad. Prot. Dosimetry 143 (2011) 241.

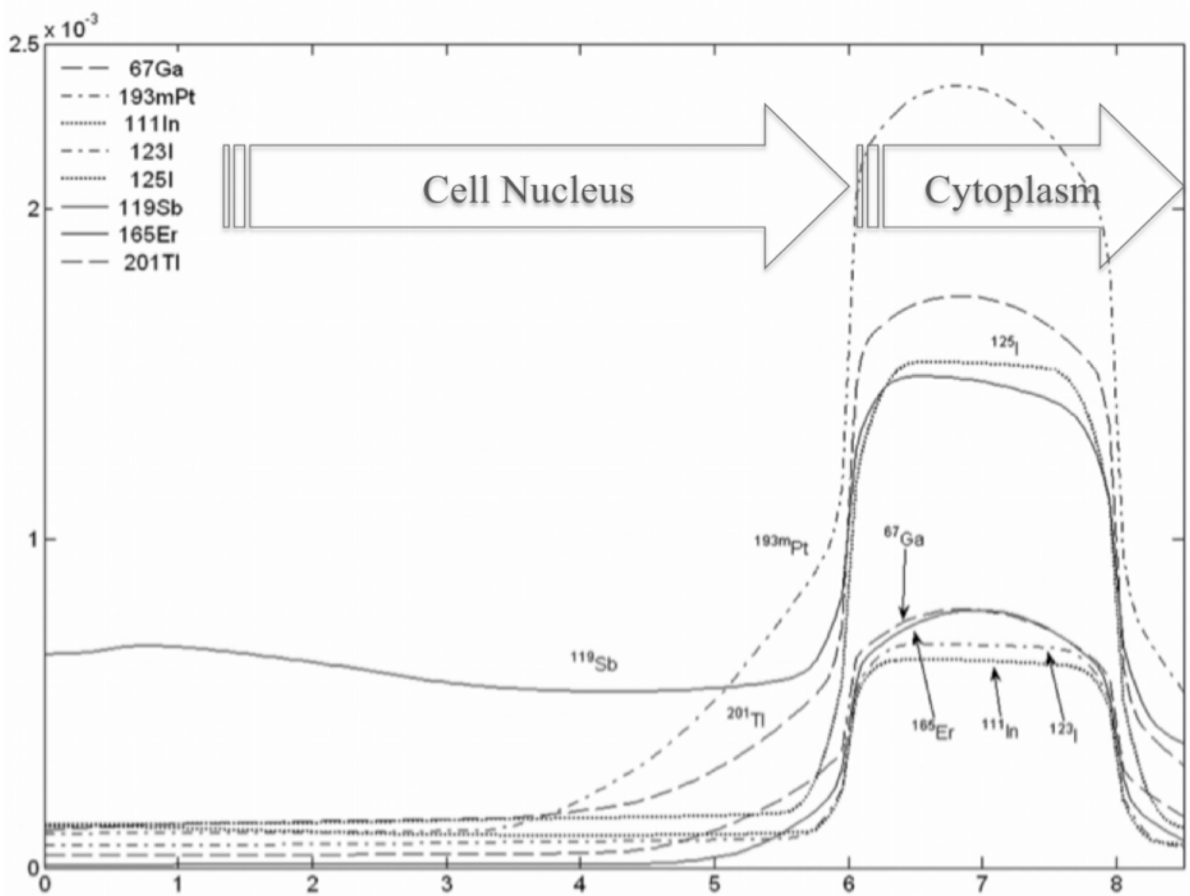
ICRP publication 92:

Relative Biological Effectiveness (RBE), QualityFactor (Q), and Radiation Weighting Factor (wR)

"….For Auger emitters bound to DNA, high RBE values have been reported and a wR of 20 or more appears to be appropriate. For those Auger electron emitters that enter the cell but are not bound to DNA, RBE values between 1.5 and 8 have been found for different endpoints in cell studies (Kassis et al., 1987; Makrigiorgios et al., 1990). Even the less critical case of more uniformly distributed Auger emitters should, therefore, be included in future considerations on a convention for wR values for Auger electron emitters."

Variable electron emission spectra → Variable cellular dosimetry

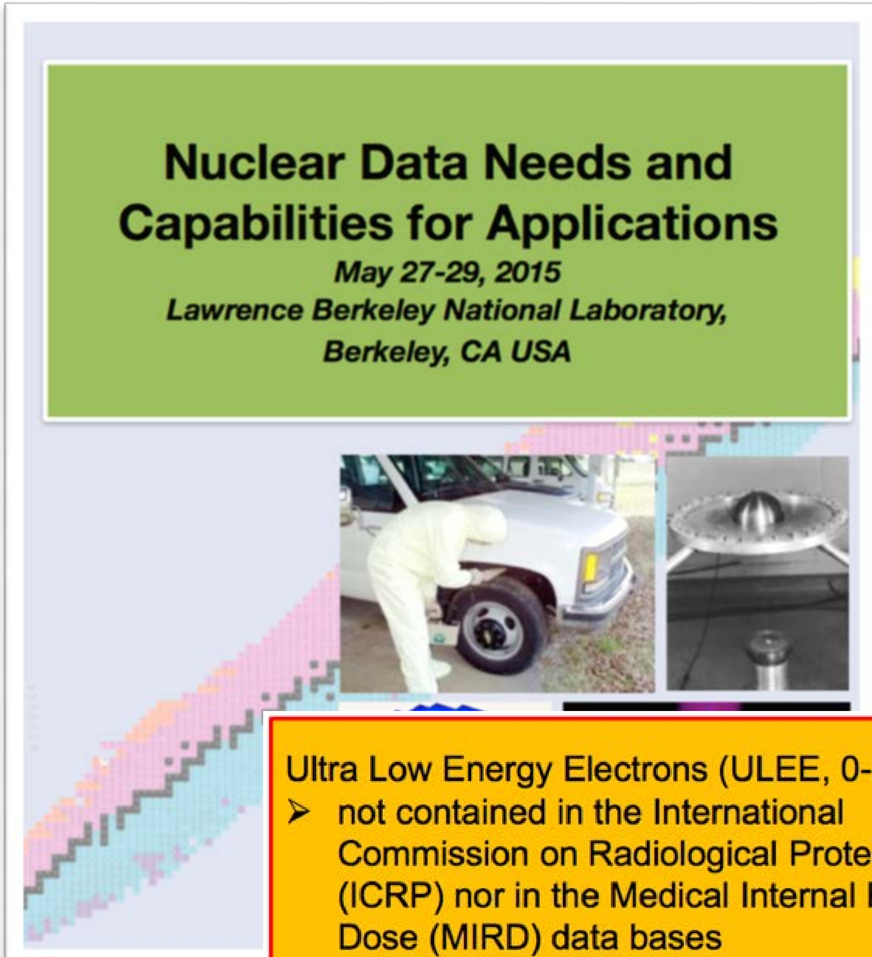
Dose (Gy s^{-1} Bq^{-1})



Cell Center (μm) Cell Outer Radius

Thisgaard (2008)

Nuclear Formation Reaction Data

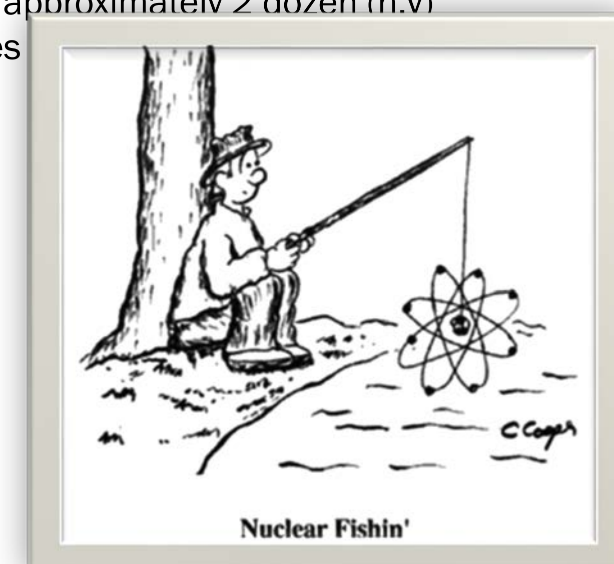


For medical radionuclides:

^{191}Ir(n,γ), ^{192}Os(d,n)^{192}Ir, ^{130}Te(n,γ)^{131}Te→^{131}I, ^{130}Te(d,p)^{131}Te→^{131}I, ^{130}Te(d,n)^{131}I, ^{187}Re(d,p)^{188}Re, ^{152}Sm(n,γ)^{153}Sm, ^{150}Nd(α,n)^{153}Sm, ^{185}Re(n,g)^{186}Re, ^{186}W(p,n)^{186}Re, ^{89}Y(n,γ)^{90}Y, many reactions to produce ^{125}I, ^{89}Sr(n,γ)^{90}Sr, ^{32}S(d,2p)^{32}P, multiple reactions esp. fast neutrons to produce ^{99}Mo, ^{226}Ra(γ,n)^{225}Fr→^{225}Ra→^{225}Ac, ^{226}Ra(n,x)^{225}Ac, ^{226}Ra(n,x)^{227}Ac, ^{131}Xe(p,n)^{131}Cs, ^{154}Sm(n,x)^{155}Eu (fast), ^{130}Te(α,np)^{132}I, ^{176}Yb(d,n)^{177}Lu, ^{53}Cr(d,n)^{54}Mn, ^{nat}Fe(p,x)^{52}Mn, ^{94}Zr(n,γ)^{95}Zr→^{95}Nb, ^{nat}Br(p,x)^{75}Se, ^{nat}I(p,x)^{127}Xe, ^{nat}Tm(p,x)^{169}Yb, ^{91}Zr(n,p)^{91}Y, approximately 2 dozen (n,γ) radionuclides

Ultra Low Energy Electrons (ULEE, 0-20 eV)

- not contained in the International Commission on Radiological Protection (ICRP) nor in the Medical Internal Radiation Dose (MIRD) data bases
- Substantial contribution to the overall absorbed dose and to molecular damage
- Strong correlation between stopping cross section and biological damage (double strand Breaks)



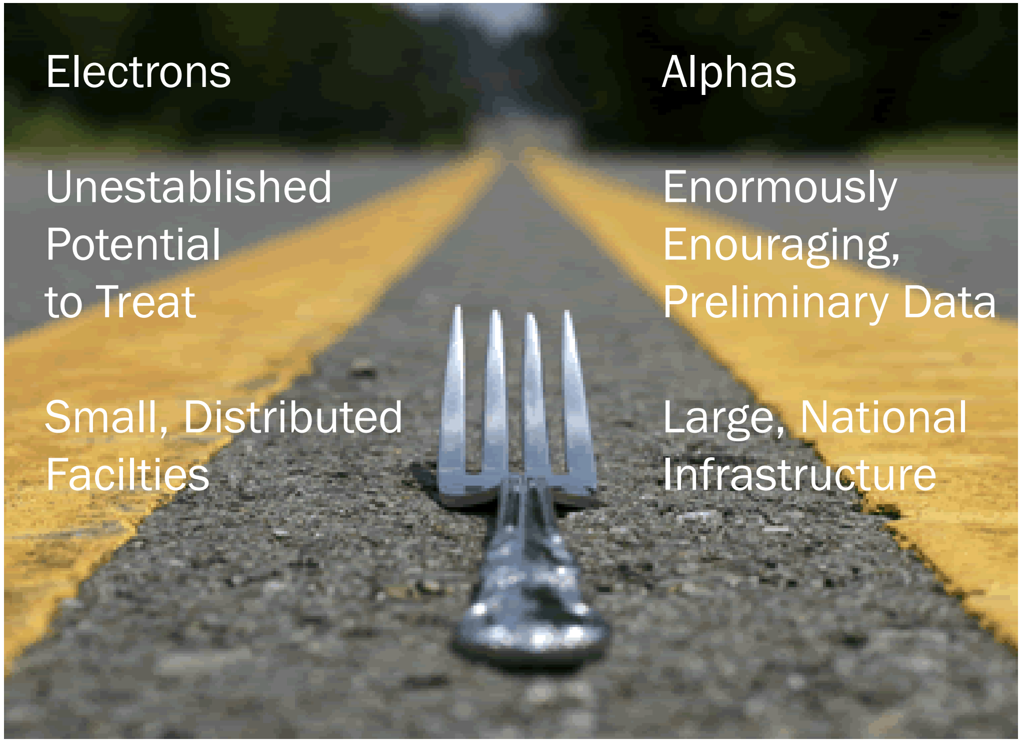
Gaps in Nuclear Structure Data, Weakness in Current Calculation Models

Table 1. Calculated Auger electron yield per nuclear decay for selected medical radioisotopes.

	RADAR[a] [13, 14]	DDEP[a] [15]	Eckerman & Endo[a] [16]	Howell[b] [17]	Stepanek[b] [18]	Pomplun[b] [19, 20]	Nikjoo[b] [6]
^{99m}Tc (6.007 h)	0.122	0.13	4.363	4.0		2.5	
^{111}In (2.805 d)	1.136	1.16	7.215	14.7	6.05		
^{123}I (13.22 h)	1.064	1.08	13.71	14.9		6.4	
^{125}I (59.4 d)	1.77	1.78	23.0	24.9	15.3	12.2	20.2
^{131}Cs (9.689 d)	0.4745		10.7				
^{201}Tl (3.04 d)	0.773	0.614	20.9	36.9			

Tibor Kibèdi, Dep. of Nuclear Physics, Australian National University *8-Dec-2014, IAEA CRP*

Summary


Electrons
Alphas
Unestablished Potential to Treat
Enormously Enouraging, Preliminary Data
Small, Distributed Facilties
Large, National Infrastructure

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Mike Connors
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Dave Thorn
Michael Fassbender
Maryline Ferrier
Justin Wilson
Benjamin Stein
Veronika Mocko… and many others

Thank you for your kind attention.

JOURNAL DE PHYSIQUE

Rayons X

Les points blancs aux origines des rayons β secondaires manifestent l'existence d'un rayonnement mou.

(*Tous ces clichés sont grossis environ 2 fois*).

Cliché 1.
Atmosphère d'argon.
Rayons X de 30 kilovolts.

P. Auger
Journal de Physique et le Radium, **6** (1925) 205.