EURADOS
European Radiation Dosimetry Group e. V.

Microdosimetry of Auger emitters in radioimmunotherapy

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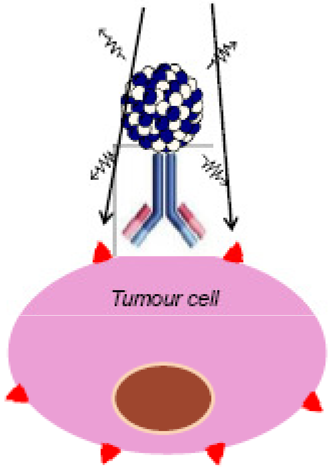
General context: RadioImmunoTherapy

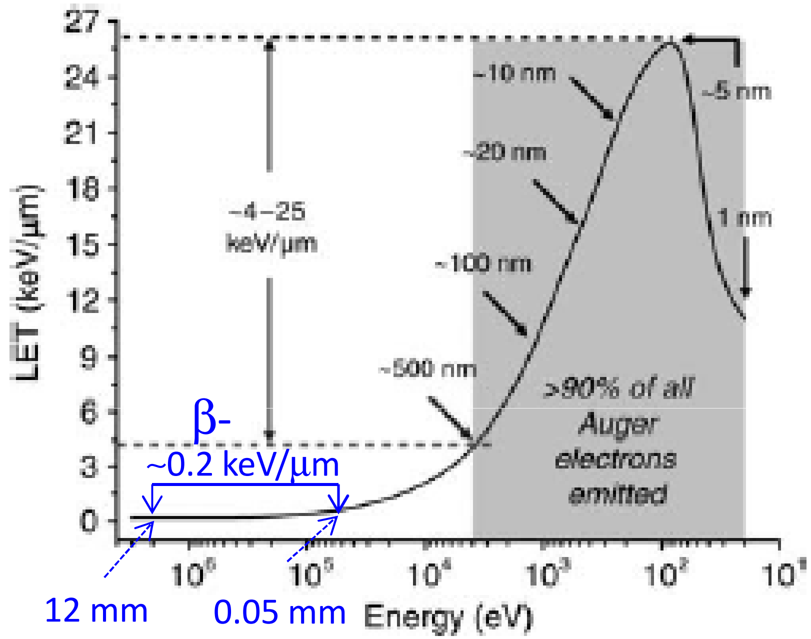
Tumour associated antigen

Monoclonal antibody



Radioactive source

- Particles(β-, α, …)
- Energy
- Half-life
- LET



↘ Toxicity of surrounded non-targeted cells

↗ Ionization density

Auger Electrons

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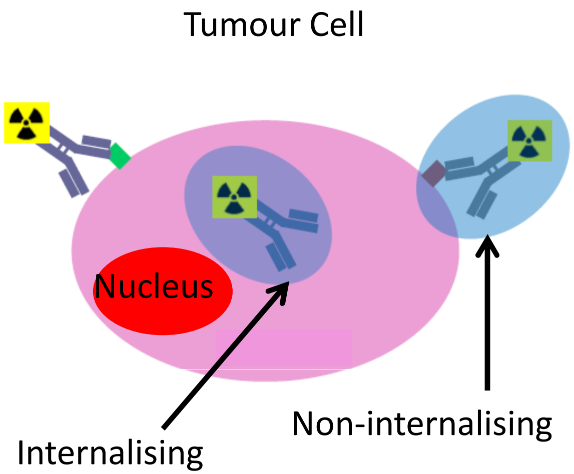
Treatment of solid tumors and single small cells or disseminated residuals tumors

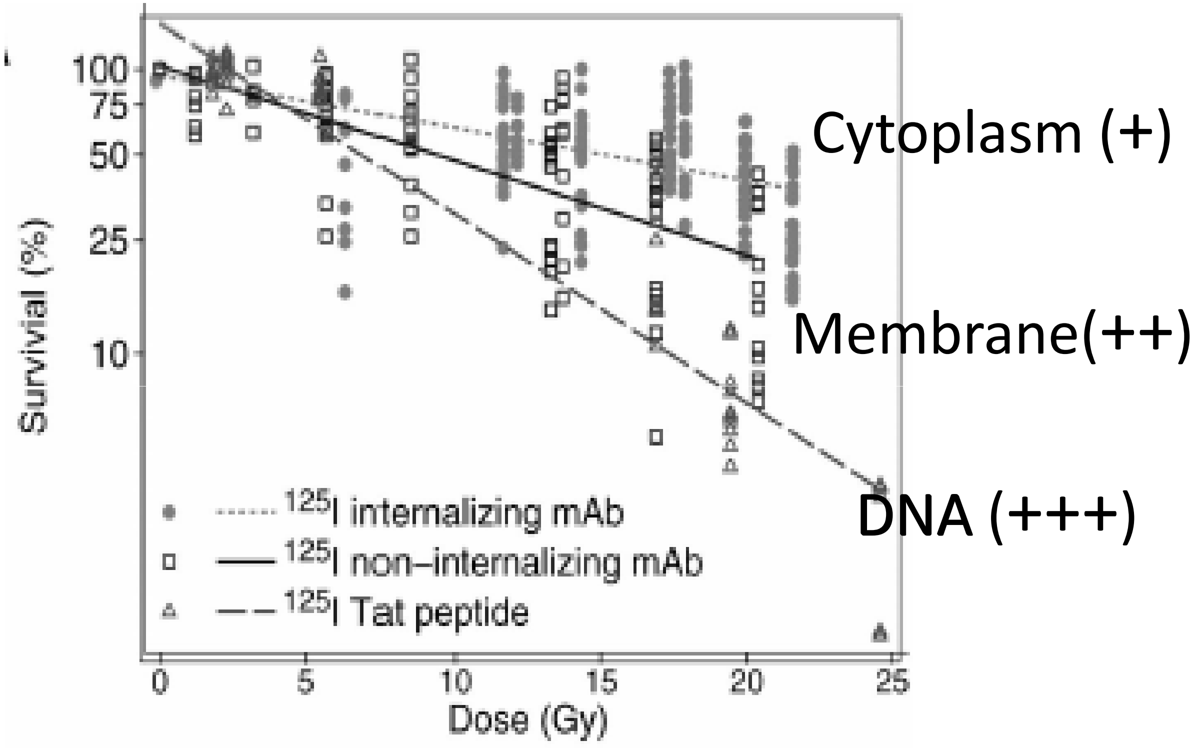
Kassis AI, Rad .Prot. Dos. 143(2-4), 241 (2011)

Radiobiological context

Study with ^{125}I

(A431 vulvar squamous carcinoma cells)
(SKOV3: ovarian carcinoma cells)





^{125}I
Energy: [0.03-34]keV
Half-life: 60 days

Clonogenic survival as a function
of the mean nuclear absorbed dose
(obtained using MIRD cellular S factors)

Pouget JP *et al.*, Radiat. Res., 170(2), 192 (2008)

Problematic

Is-it possible to develop realistic cell models

based on biological data

to have a better estimation of dose distribution?

'In vitro' studies

- Geometry
- Source Distribution

+

Monte Carlo simulation

?

N<-CS

Energy	S_{sphere}/ $S_{ellipsoid}$
5keV	0.085
10keV	0.713

Goddu *et al.* (1997)

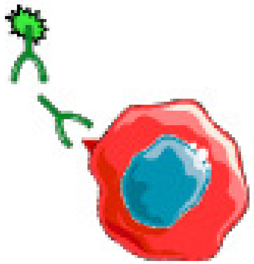
Method

1

2

3

Biological Experiments



Cell Labelling

+

Confocal fluorescence microscopy

Incerti S *et al.*, Rad. Prot. Dos., Vol. 133(1), 2 (2009)

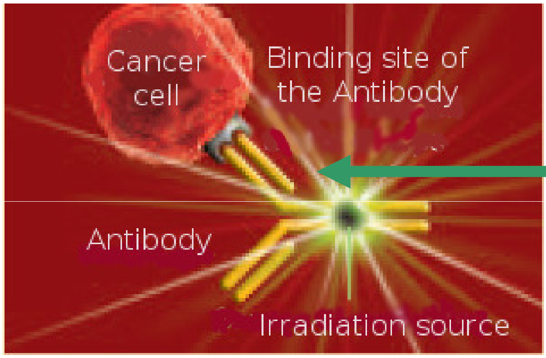
Human keratinocyte (HaCaT) line cell (3MeV alpha particles)

Triple cell labelling

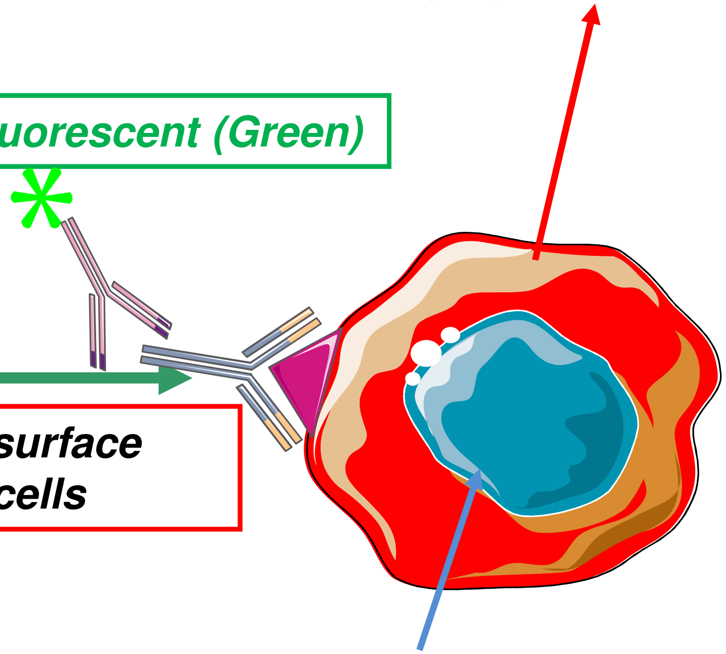
Tumoral cell line : A431CEA (*vulvar squamous carcinoma*)

Cytoplasm (Red)

Secondary antibody fluorescent (Green)



Primary antibody: cell surface SPECIFIC of TUMOUR cells



Nucleus (Blue)

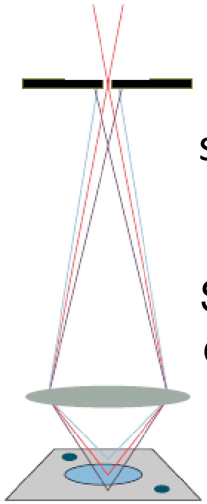
- **Labelling in 14 steps:**
  - Incubation with antibodies
  - Cells are washed between each step
  - Uptake
  - Permeabilization of cell membrane
  - …

35A7 : non-internalising antibody
m225 : internalising antibody

(Transfected with Carcino-Embryonic Antigen CEA)

From : ***http://www.ozh.ch/?pgR=antikoerper***

Confocal Imaging

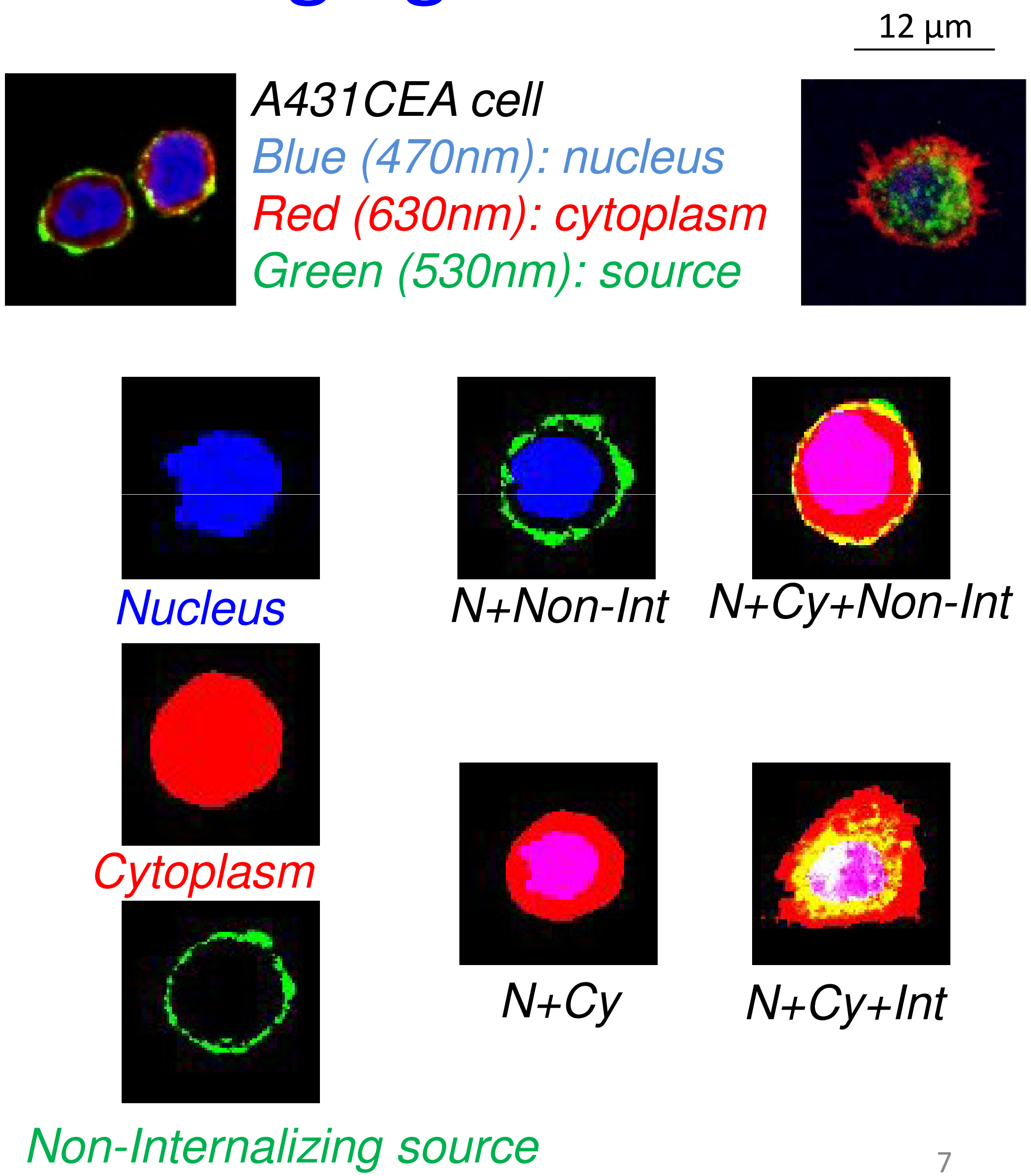


A pinhole (between sample and detector)

Selection of information coming from a SINGLE focal plane

ADVANTAGES / wildfield

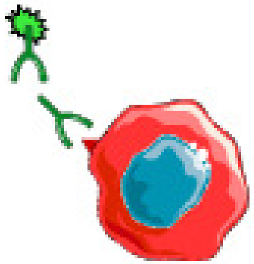
- ↗Lateral resolution
- To see signals from 1 or several probes
- To built 3D images



Method

1

Biological Experiments



Cell labelling

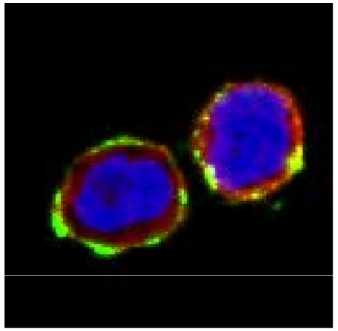
+

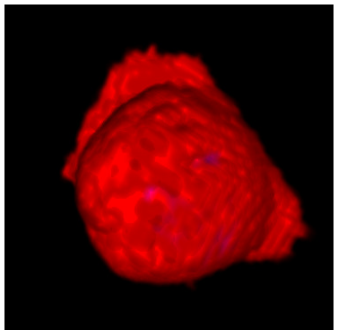
Confocal fluorescence microscopy

2

Image treatment

Geant4 reconstruction





3

Image processing

Geometry

- Noise substraction
- Suppress isolated pixels
- Fill holes for lack of labelling areas
- Suppress ‘overlap’

```
55000 24173 25937
0.369 0.369 0.186
0 0 0
-34 12 0 1
-33 12 0 1
-32 12 0 1
-31 12 0 1
-30 12 0 1
-29 12 0 2
-28 12 0 2
-27 12 0 2
-26 12 0 2
```

Voxel coordinates

Source

- Noise substraction

```
10566
12	-13	-6	2
-17	-12	-6	1
-16	-12	-6	3
-15	-12	-6	3
0	-12	-6	2
1	-12	-6	5
2	-12	-6	9
3	-12	-6	10
4	-12	-6	6
5	-12	-6	1
7	-12	-6	4
8	-12	-6	9
9	-12	-6	11
10	-12	-6	9
11	-12	-6	5
```

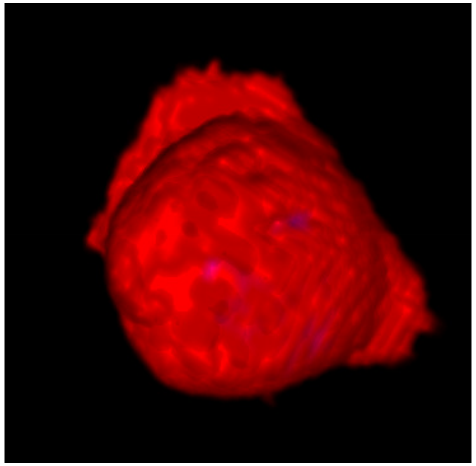
Voxel coordinates

GreenSignal intensity $\propto$ Relative quantity of primary antibody

+ Position shift

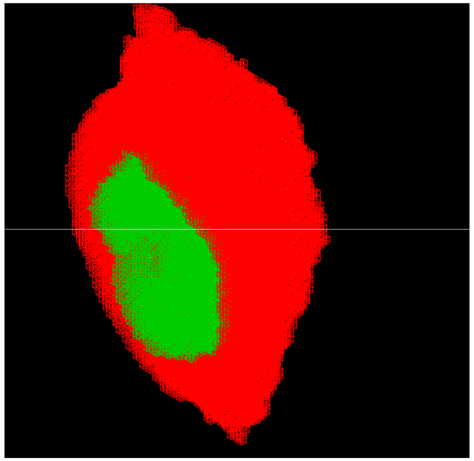
ImageJ software
http://rsbweb.nih.gov/ij

Image treatment and G4 reconstruction



3D cell represention (ImageJ)

GEANT4



view

Green : nucleus

Red : cytoplasm

1 voxel =

$0.3*0.3*0.2\ \mu m^3$

Incerti S *et al.,* Rad. Prot. Dos., 133(1), 2 (2009)

Method

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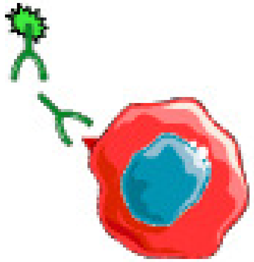
Biological Experiments



Cell Labelling

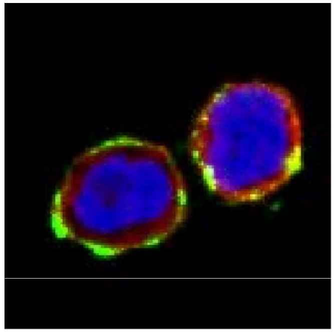
+

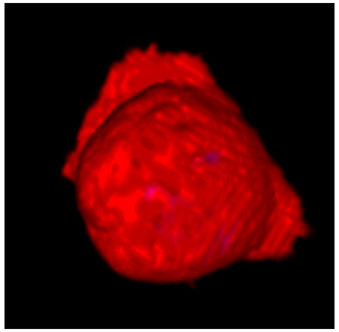
Confocal fluorescence microscopy

2

Image treatment

Geant4 reconstruction





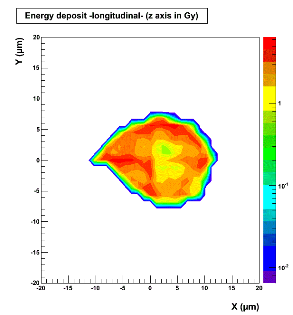
3

Calculations

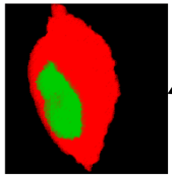
- Source position
- Monte Carlo Simulation

Example: monoenergetic e- source E=30keV

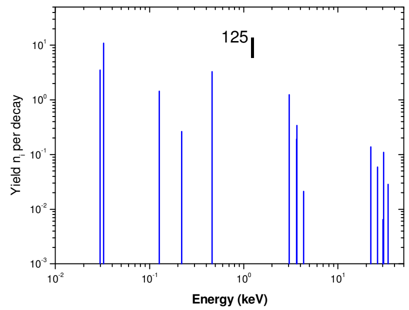
Absorbed dose (given z)



Calculations



- Reconstruction of the geometry
- One isolated cell: A431CEA
- Location of the source ^{125}I (AAPM Spectrum)
- Medium: Liquid water (ρ =1g/cm^3)



Monte Carlo simulation (Geant4 code)

Low energy Physics List
Livermore

Energy deposition in each voxel

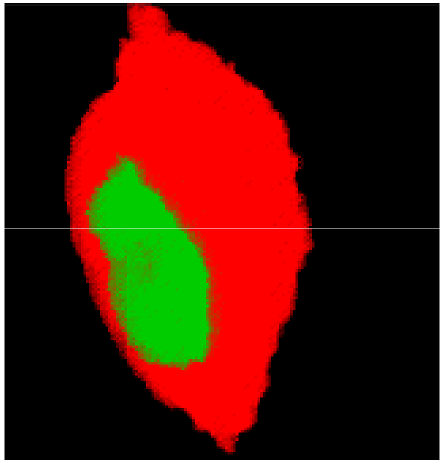
For nucleus and whole cell, comparisons based on :

- Absorbed Fraction
- S Factor
- Spectrum of deposited energy
- Energy/Volume Histogram

Geometry effect : Conditions

Single isolated A431CEA Cell

• Complex cell geometry



Cell volume: 1776 *µm³*

Nucleus volume: 437 *µm³*

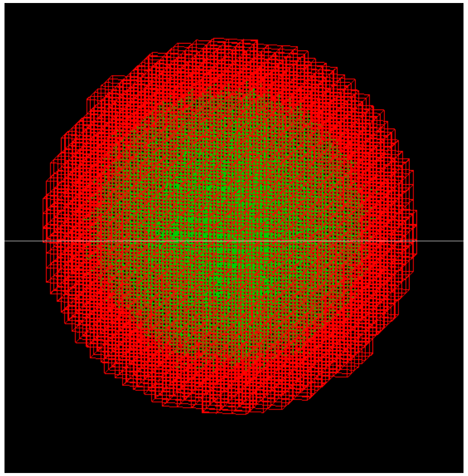
• *Equivalent volumes: nucleus and cell (error <1%)*

•*~ 80000 voxels in a cell of $0.3*0.3*0.2\ \mu m^3$*

• *Homogeneous source distribution at the cell surface*

• *10 000 000 primary electrons*

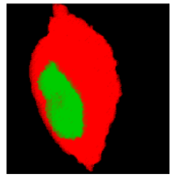
• Spherical cell geometry



Cell radius: 7.49 *µm*

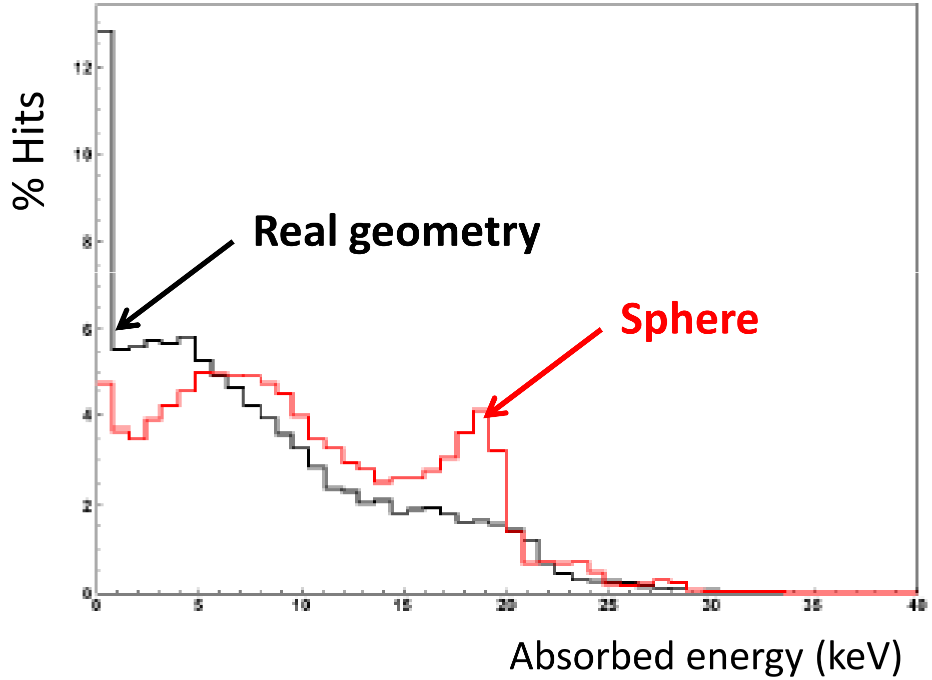
Nucleus radius: 4.70 *µm*

Geometry effect : Results



Homogeneous cell surface radioiodine

Geometry effect	Deposited Energy	
	Nucleus	Cell
Complex / sphere	0.88	0.96



Absorbed Energy Spectrum
In the nucleus

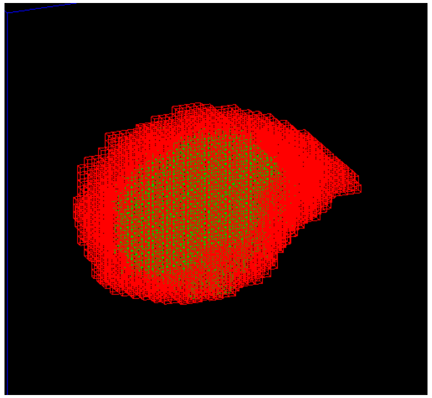
Source distribution: Conditions

Single isolated A431CEA Cell

- Heterogeneous source distribution

- Homogeous source distribution

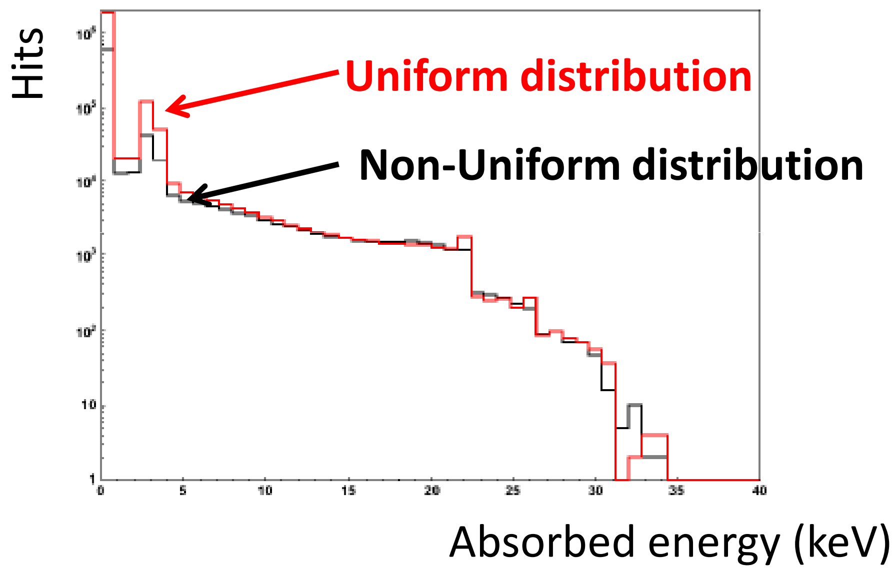
- Same complex geometry
- Same voxel size
- For non-internalising and internalising antibody configurations



Source distribution : Results

Non internalising primay antibody distribution

Source distribution	Deposit Energy	
	Nucleus	Cell
Non uniform/ uniform	0.63	1.10

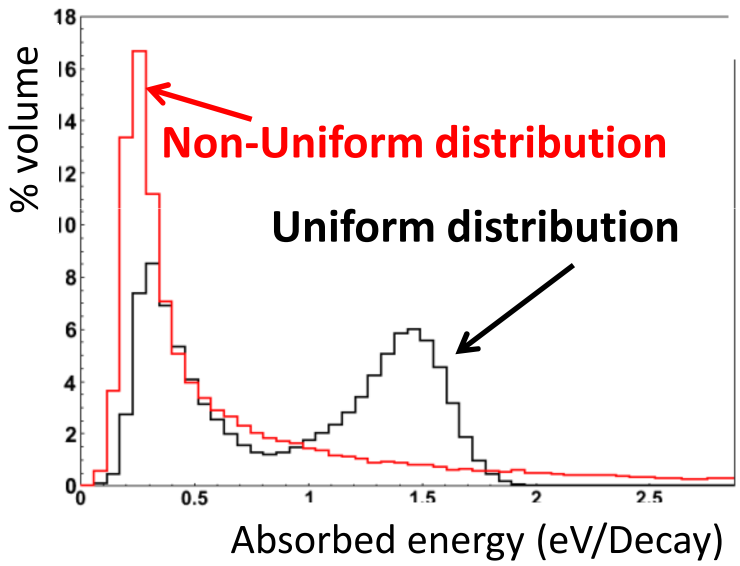


Absorbed Energy Spectrum in the nucleus

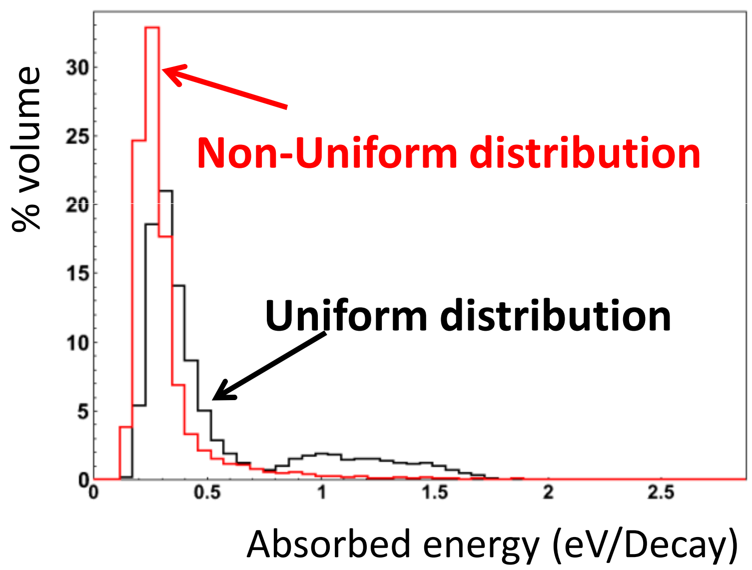
Source distribution : Results

Non internalising primay antibody distribution

Energy-Volume Histogram



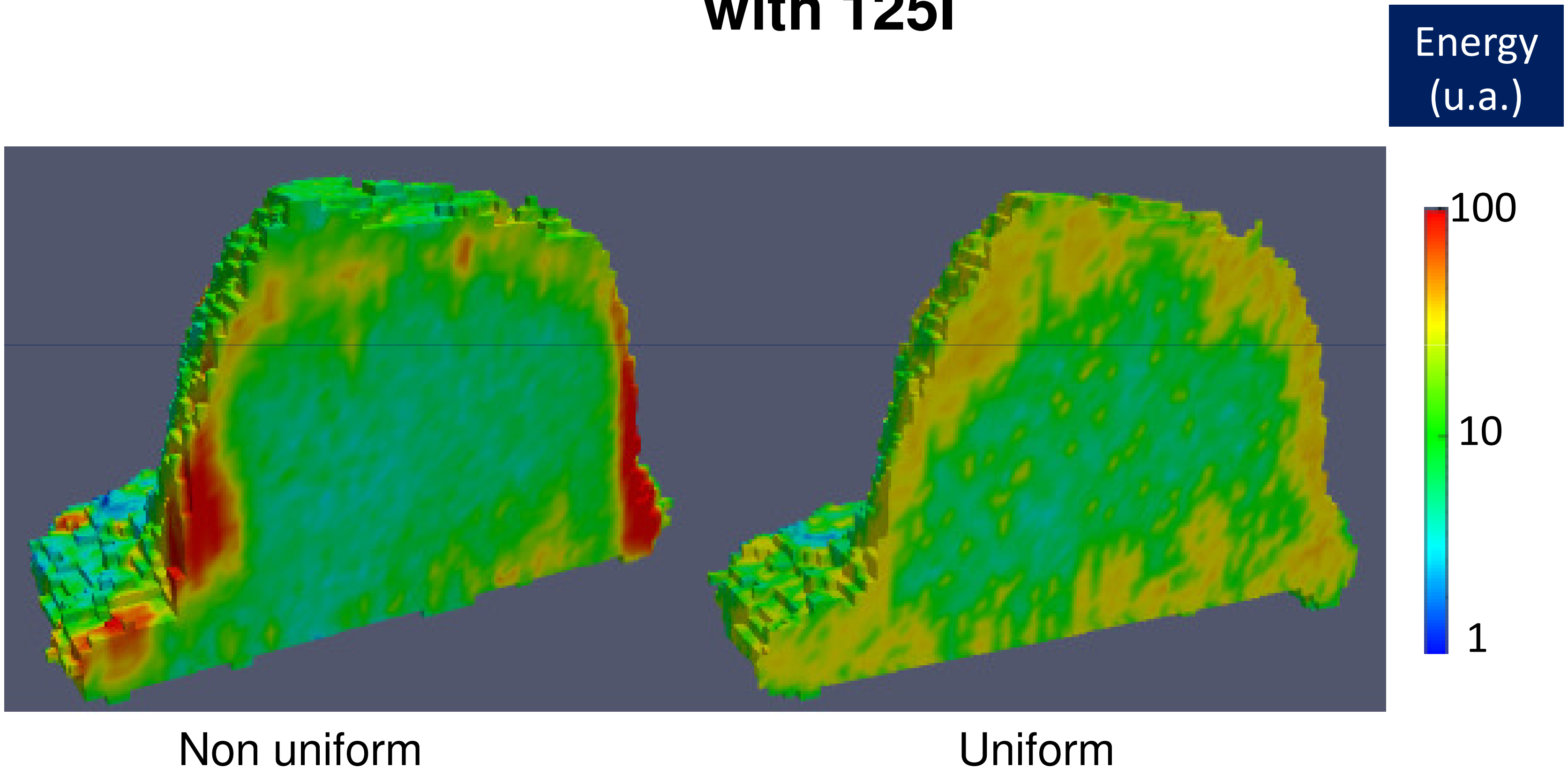
In the whole cell



In the nucleus

Source distribution : Results

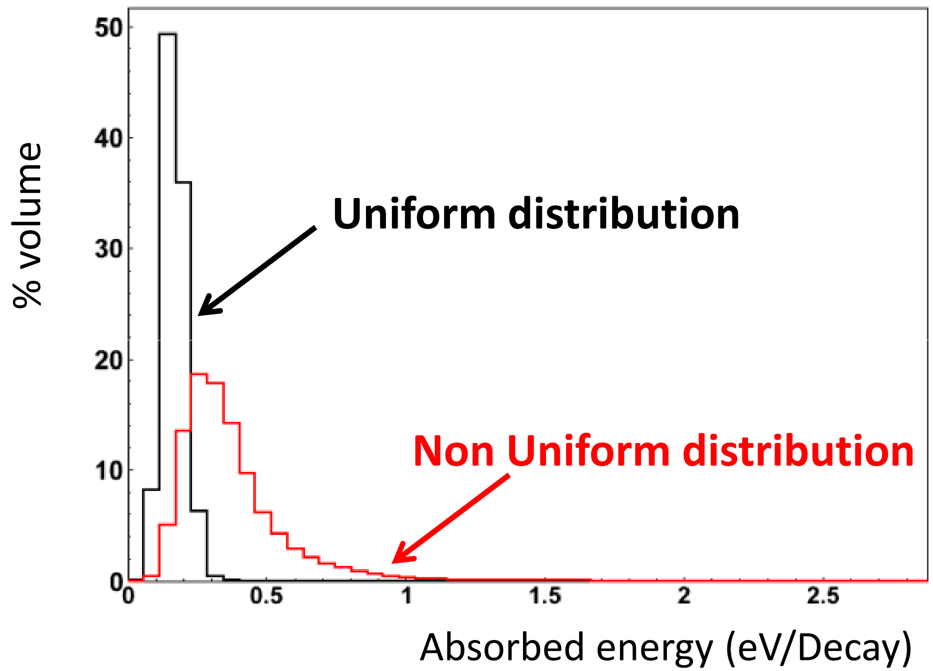
Non internalising primay antibody distribution labelled with 125I



Source distribution : Results

Internalising primary antibody distribution

Source distribution	Deposit Energy	
	Nucleus	Cell
Non uniform / uniform	2.32	2.29



Energy-Volume Histogram
in the cell

Conclusions

- First study:
  - Biological data
    - Realistic geometry +
    - Heterogeous distribution (internalising/non-internalising antibodies)
  - Introduced in Monte Carlo simulation
- Tumoral isolated cell
- These first results: differences

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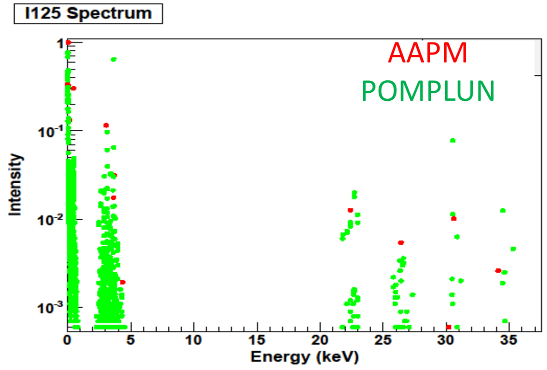
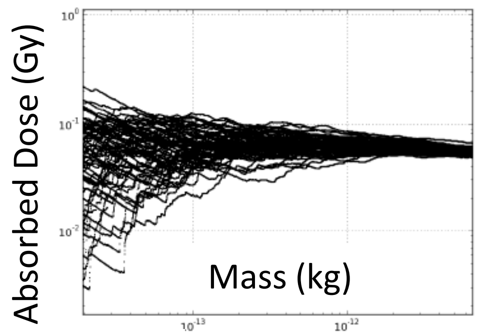
More cells in the cell line

Perspectives



- Spectrum
- Other Auger emitters
  - Like ^{67}Ga, ^{111}In, ^{123}I, ^{99}mTc, ^{201} Ta …
- Other cell lines (SKOV3, …)
- Time dependant biodistribution of the radionuclide in the cell
- Correlation with biological effect:
  - More cells in the same line to obtain the survival as a function of absorbed dose in the nucleus

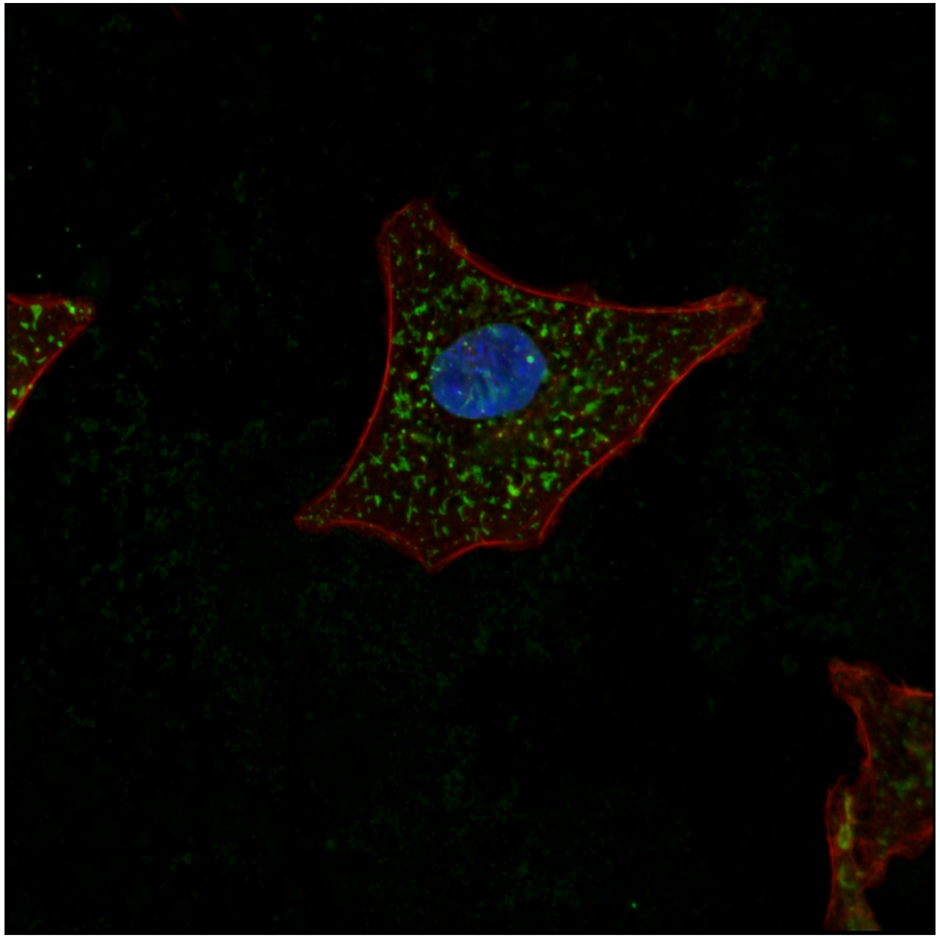
- Microdosimetry data

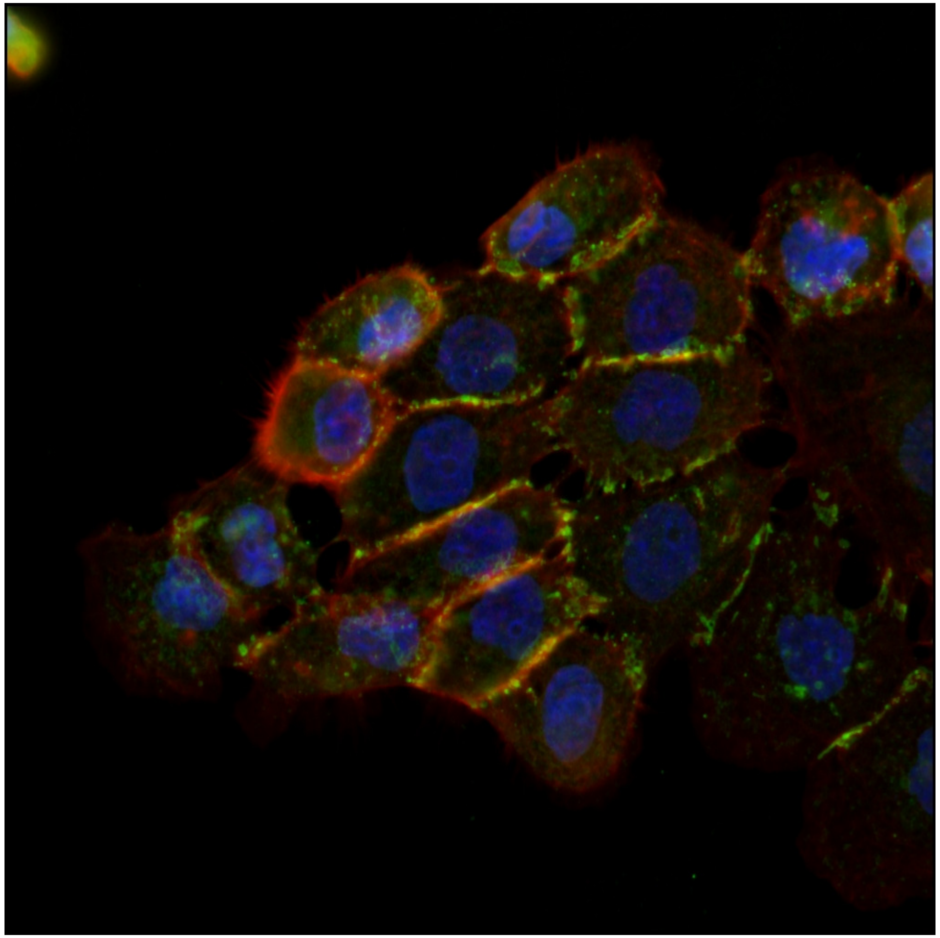


Sphere r=12μm,
Liquid water
125I
4000 electrons

Pomplun E. *et al.*, Rad. Res., 111(3), 533 (1987)

Exemples of 'beautiful' cells

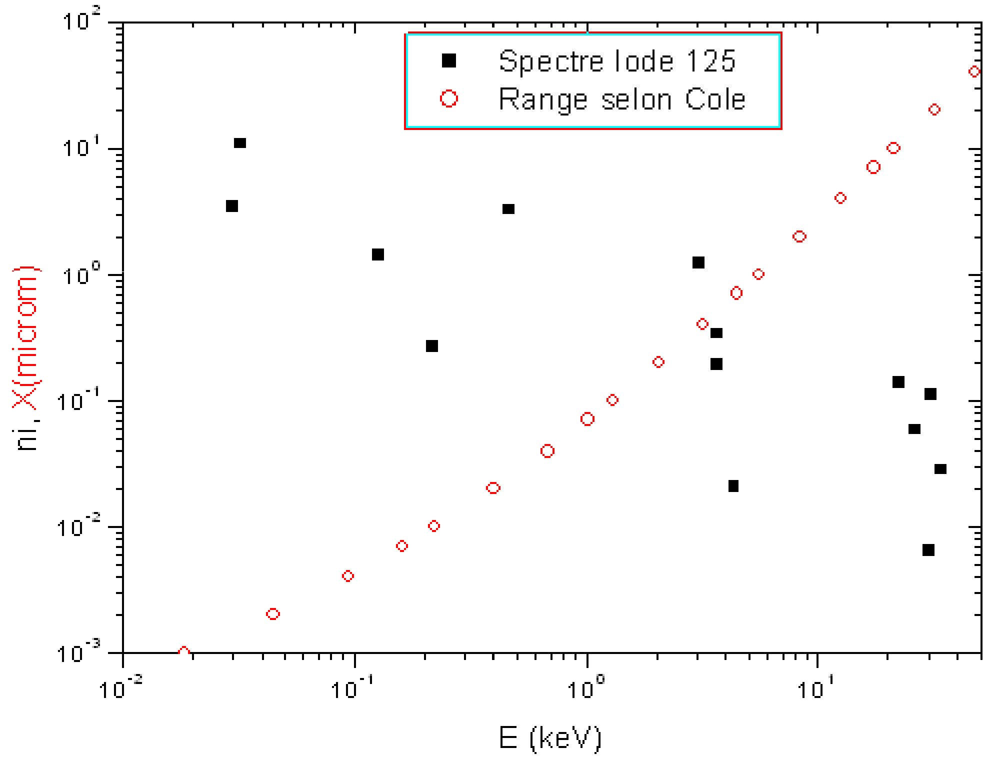




Thank you to Salome Paillas (IRCM)

Iodine 125

^{125}I		
Process	E_i	n_i
CK NNX	0.0299	3.51
Auger NXY	0.0324	10.9
CK MMX	0.127	1.44
CK LLX	0.219	0.264
Auger MXY	0.461	3.28
Auger LMM	3.05	1.25
IC 1 K	3.65	0.191
Auger LMX	3.67	0.340
Auger LXY	4.34	0.0211
Auger KLL	22.4	0.138
Auger KLX	26.4	0.059
Auger KXY	30.2	0.0065
IC 1 L	30.6	0.110
IC 1 M,N . . .	34.1	0.0284



Radionuclide: I-125 **Half-Life: 60.14 d** **Decay Mode: EC**

R_C (μm)	R_N (μm)	S(C←C) (Gy/Bq s)	S(C←CS) (Gy/Bq s)	S(N←N) (Gy/Bq s)	S(N←Cy) (Gy/Bq s)	S(N←CS) (Gy/Bq s)
3	2	1.52E-02	7.93E-03	4.83E-02	2.79E-03	6.08E-04
3	1	1.52E-02	7.93E-03	3.42E-01	3.91E-03	5.64E-04
4	3	6.67E-03	3.50E-03	1.52E-02	1.15E-03	3.68E-04
4	2	6.67E-03	3.50E-03	4.83E-02	1.24E-03	3.41E-04
5	4	3.54E-03	1.87E-03	6.67E-03	6.18E-04	2.53E-04
5	3	3.54E-03	1.87E-03	1.52E-02	6.12E-04	2.34E-04
5	2	3.54E-03	1.87E-03	4.83E-02	7.35E-04	2.25E-04
6	5	2.12E-03	1.14E-03	3.54E-03	3.90E-04	1.91E-04
6	4	2.12E-03	1.14E-03	6.67E-03	3.72E-04	1.77E-04
6	3	2.12E-03	1.14E-03	1.52E-02	4.12E-04	1.69E-04
7	6	1.38E-03	7.47E-04	2.12E-03	2.73E-04	1.51E-04
7	5	1.38E-03	7.47E-04	3.54E-03	2.58E-04	1.44E-04
7	4	1.38E-03	7.47E-04	6.67E-03	2.73E-04	1.38E-04
7	3	1.38E-03	7.47E-04	1.52E-02	3.06E-04	1.32E-04
8	7	9.58E-04	5.20E-04	1.38E-03	2.00E-04	1.19E-04
8	6	9.58E-04	5.20E-04	2.12E-03	1.92E-04	1.15E-04
8	5	9.58E-04	5.20E-04	3.54E-03	2.01E-04	1.14E-04
8	4	9.58E-04	5.20E-04	6.67E-03	2.17E-04	1.14E-04
9	8	6.94E-04	3.77E-04	9.58E-04	1.52E-04	9.50E-05
9	7	6.94E-04	3.77E-04	1.38E-03	1.46E-04	9.20E-05
9	6	6.94E-04	3.77E-04	2.12E-03	1.54E-04	9.13E-05
9	5	6.94E-04	3.77E-04	3.54E-03	1.65E-04	9.17E-05
10	9	5.20E-04	2.84E-04	6.94E-04	1.18E-04	7.72E-05
10	8	5.20E-04	2.84E-04	9.58E-04	1.14E-04	7.43E-05
10	7	5.20E-04	2.84E-04	1.38E-03	1.20E-04	7.34E-05
10	6	5.20E-04	2.84E-04	2.12E-03	1.29E-04	7.38E-05
10	5	5.20E-04	2.84E-04	3.54E-03	1.40E-04	7.50E-05