

Séminaire de Radiothérapie Interne Vectorisé
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Evaluation of uncertainties in pre-clinical cellular dosimetry of ^{111}In -labeled radiopharmaceuticals

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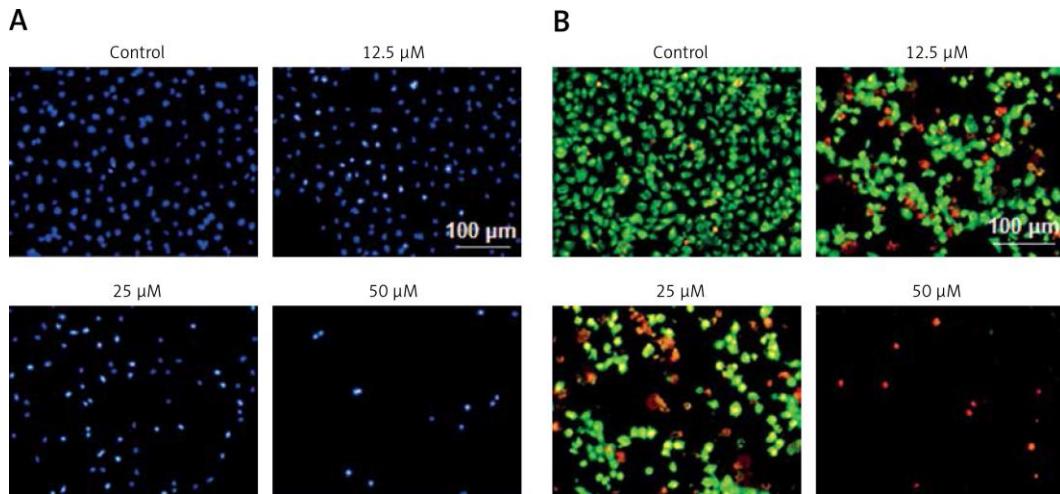
Preclinical Trials for radiopharmaceuticals

- Safety
- Effectiveness

In Vivo → Animal subjects



In Vitro → Human derived Cell lines

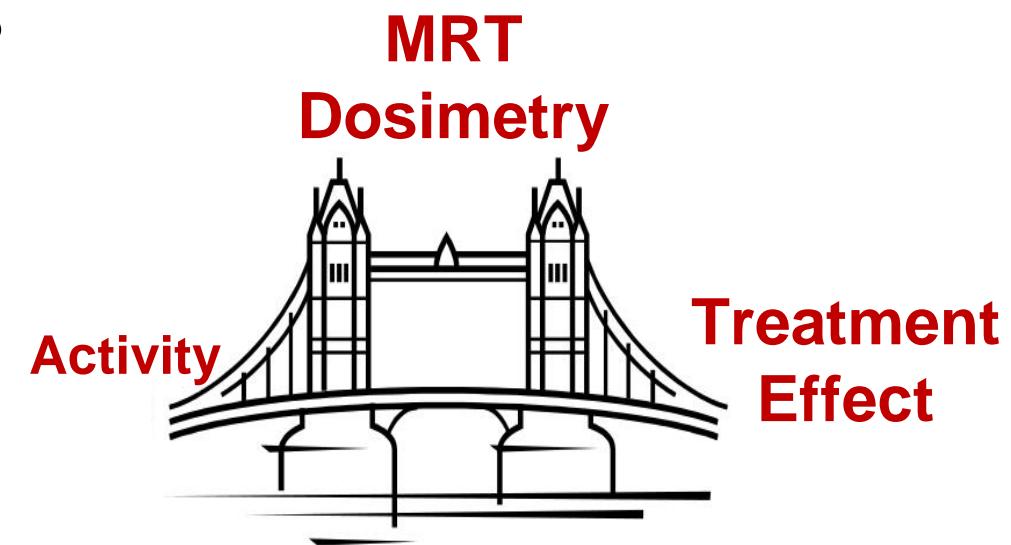


MRT Dosimetry

- ❑ **Absorbed Dose Distribution :**
 - ❖ RP accumulate over time
 - ❖ Varied between different cases

Activity should
be measured

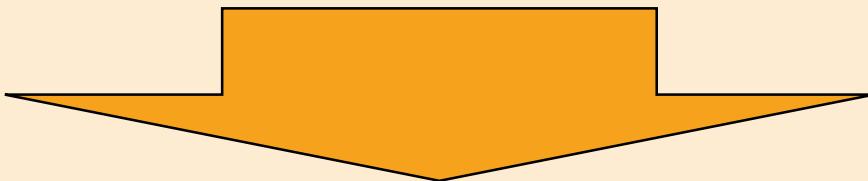
Dosimetry is more complex



Uncertainty

EBRT-----> 2% - 4%

**MRT----> different
sources of uncertainty**



challenging to assess

Random or Statistic

- From measurements

Systematic

- From formalism



Statistical Uncertainty

Random error associated to repeated experiments:

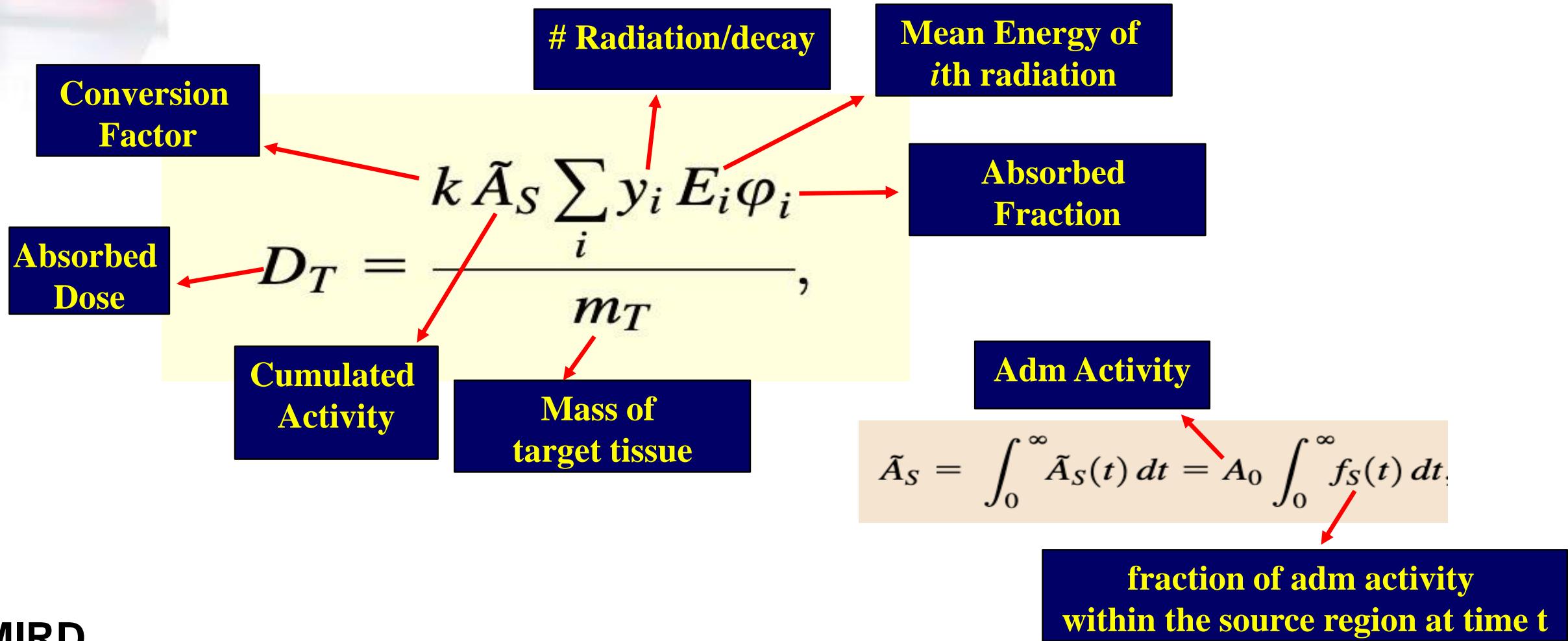
Standard Deviation



Main Sources

- ✓ **Cell Size measurement**
- ✓ **Cell Counting**
- ✓ **Activity measurements in Cell regions**
- ❖ **Gamma counter Calibration Factor**

Systematic Uncertainty





y_i, E_i

φ_i, m_T

Negligible

Not important
in final uncertainty

Based on
standard models

Vary in
cell size, shape
and energy spectrum

Results should be scaled to
real situation



Parameters affecting φ_i , m_T :

- ❖ Particle Stopping power → analytical calculations
 - ✓ Source of particle Stopping Power
- ❖ Beta Energy
 - ✓ Mean or Spectrum
- ❖ Cell Geometry
 - ✓ Shape and Size

$$S = \frac{k \sum_i y_i E_i \varphi_i}{m_T}$$



$$D_T = \tilde{A}_s \times S$$

Radionuclide	RC (μm)	RN (μm)	Ratio Spectrum/Mean	
			S($\text{N} \rightarrow \text{N}$)	S($\text{CS} \rightarrow \text{N}$)
^{90}Y	3	2	1.21	1.19
^{131}I	3	2	1.38	1.45
^{35}S	3	2	1.47	1.24
^3H	3	2	0.75	500
^{90}Y	10	5	1.20	1.6
^{131}I	10	5	1.40	1.30
^{35}S	10	5	1.30	0.9
^3H	10	5	0.91	-

**Dependence
of S-value on
use of beta
spectrum vs
mean energy**

* Howell R.W et al; MIRD Cellular S.Values: Self-Absorbed Dose Per Unit Cumulated Activity for Selected Radionuclides and Monoenergetic Electron and Alpha Particle Emitters, Society of Nuclear Medicine, 1997

Energy(MeV)	S(N→N) Ratio Monte Carlo/Stopping Power(by Cole)
0.001	0.99
0.005	1.0
0.01	1.01
0.03	1.02
0.05	0.99
0.10	0.92
0.5	0.87
1.0	0.82
2.0	0.79
2.5	0.76
Radionuclide	
³² P	0.88

The effect of
delta rays on
Cell Nucleus
S-Value*

* Howell R.W et al; MIRD Cellular S.Values: Self-Absorbed Dose Per Unit Cumulated Activity for Selected Radionuclides and Monoenergetic Electron and Alpha Particle Emitters, Society of Nuclear Medicine, 1997

Electron Energy (MeV)	Ratio $S_{\text{Sphere}}/S_{\text{Ellipsoid}}$		
	$S(N \rightarrow N)$	$S(Cy \rightarrow N)$	$S(CS \rightarrow N)$
0.005	1.03	0.816	0.085
0.01	1.10	1.02	0.713
0.100	1.14	1.13	0.945
2.5	1.13	1.13	0.992

**Dependence of
Electron S-value
on cellular
geometry
**Spheroid vs
Ellipsoid****

* Howell R.W et al; MIRD Cellular S.Values: Self-Absorbed Dose Per Unit Cumulated Activity for Selected Radionuclides and Monoenergetic Electron and Alpha Particle Emitters, Society of Nuclear Medicine, 1997



Uncertainty related to biokinetic fitting parameters

\tilde{A}_S

$$\tilde{A}_S = \int_0^\infty \tilde{A}_S(t) dt = A_0 \int_0^\infty f_S(t) dt.$$

$$f_S(t) = f_1 e^{-(\lambda_1 + \lambda_p)t} + f_2 e^{-(\lambda_2 + \lambda_p)t}$$

- ❖ Fractional uptake of the administered activity (f_1, f_2)
 - **Derived from fitting parameters**
- ❖ Biologic elimination parameters (λ_1, λ_2)
 - **Derived from fitting parameters**
- ❖ Physical decay constant (λ_P)
 - **Negligible**



Experimental Preclinical Dosimetry

- Radionuclide

^{111}In → auger electron emitter

- mAb

- Trastuzumab - IgG

- Peptide

- NLS - TAT - X(15, 30)

- In Vitro → Human derived Cell lines:

- A431CEA-LUC (Vulvar Squamous Carcinoma)



Method

- ✓ **1-3 M Cells seeded**
- ✓ **48 Hr Treatment**
 - **0.3 MBq of labelled Vectors**
- **Activity Measurement (Cell, Nucleus, ExtraNucleus)**
 - **24, 48, 72, 144 Hr**

→ → → **TAC** → **Cumulated Activity**
(Bq.s/Cell)



Method

- Absorbed Dose Calculation:
- S-Factor*(mGy/Bq.s):

$N \rightarrow N$, $Cy \rightarrow N$, $CS \rightarrow N$

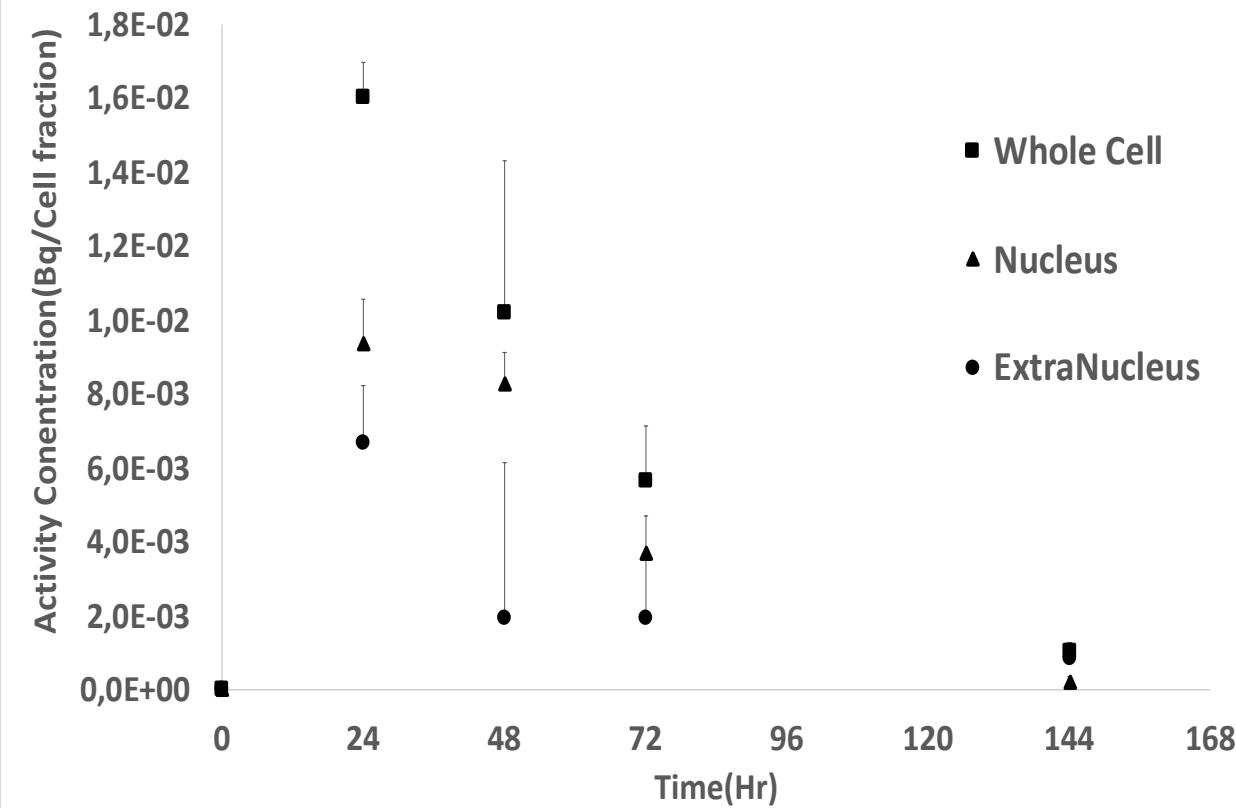
Single Cell, Cell Cluster, Monolayer

100%Cy
75%Cy-25%CS
50%Cy-50%CS
25%Cy-75%CS
100%CS

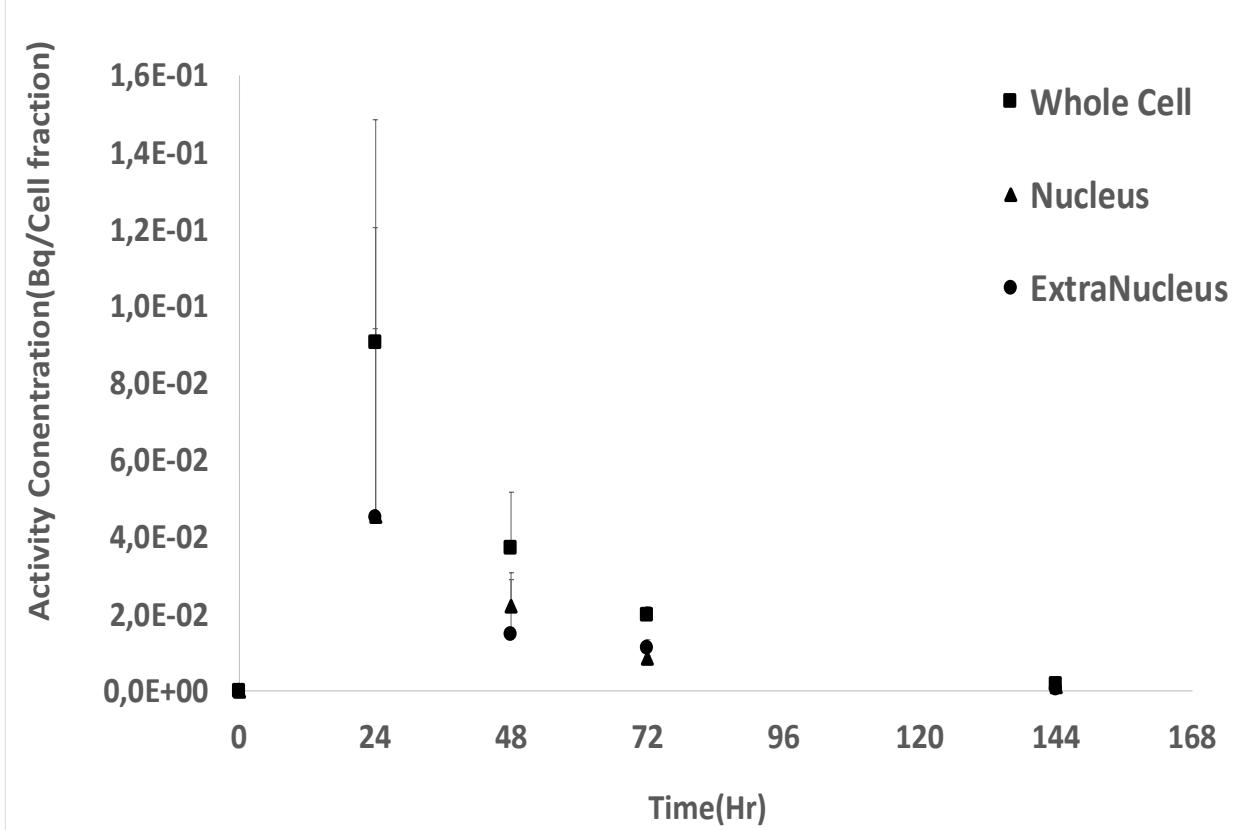
* Zhongli Cai et al, J Nucl Med 2010; 51:462–470

Results and Discussion

Time Activity Concentration for ^{111}In -trastuzumab-X15 in
A431CEA-LUC Cells



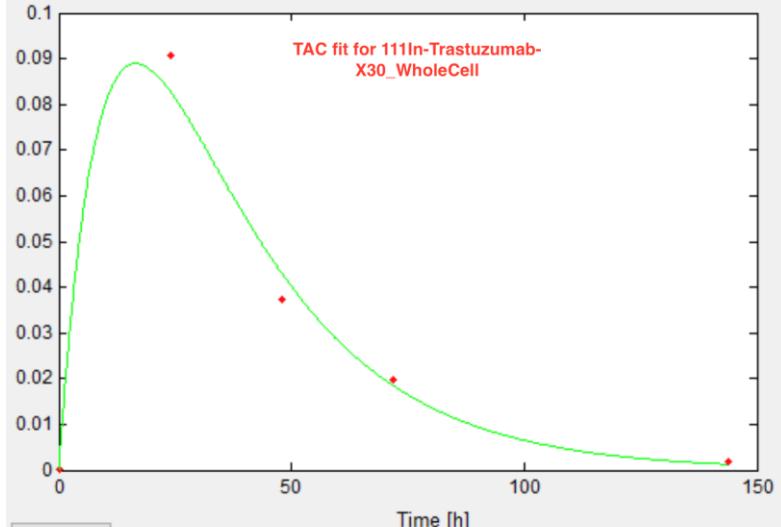
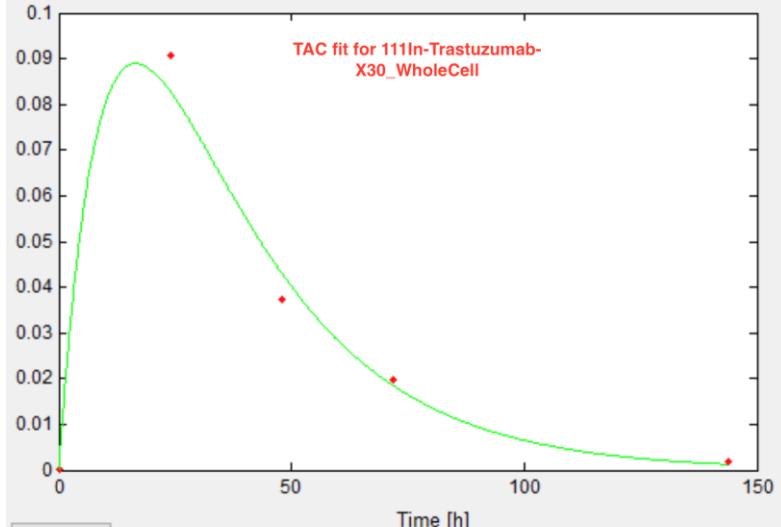
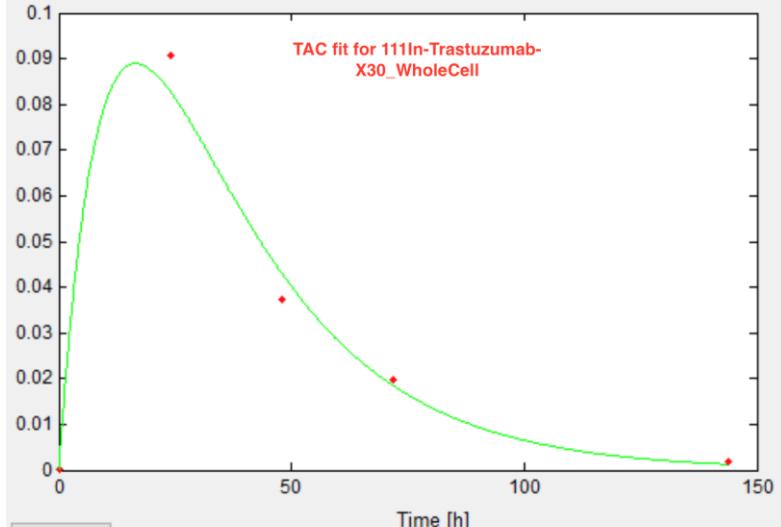
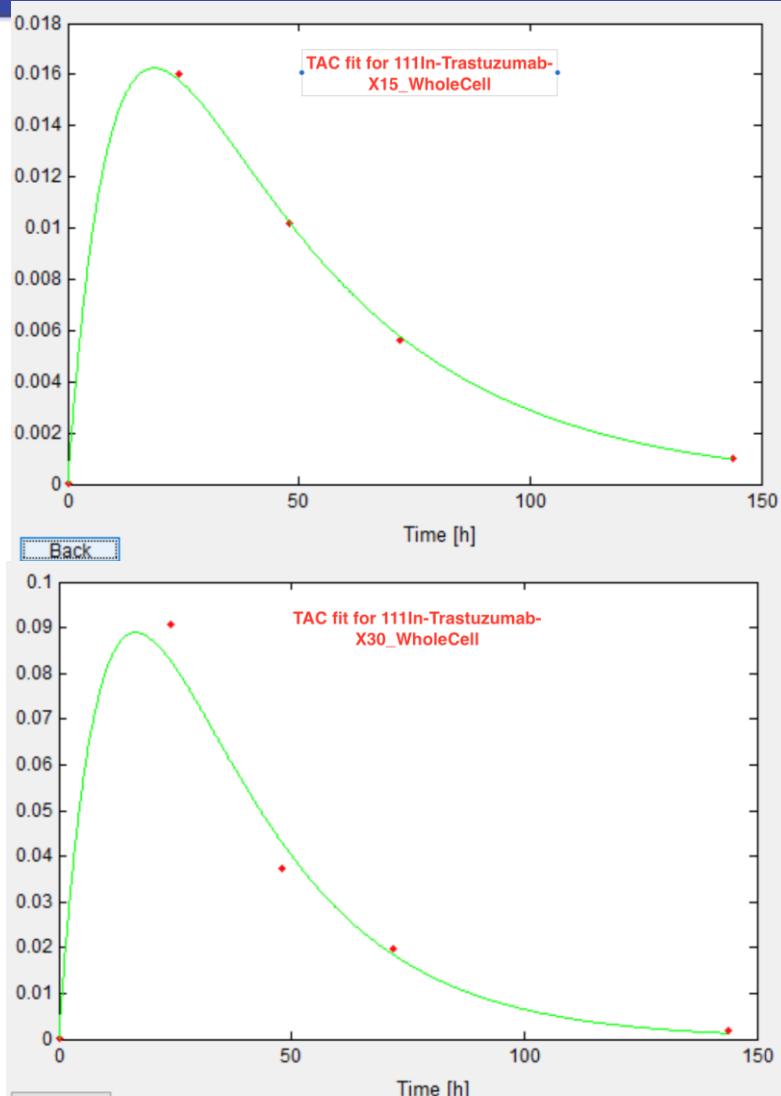
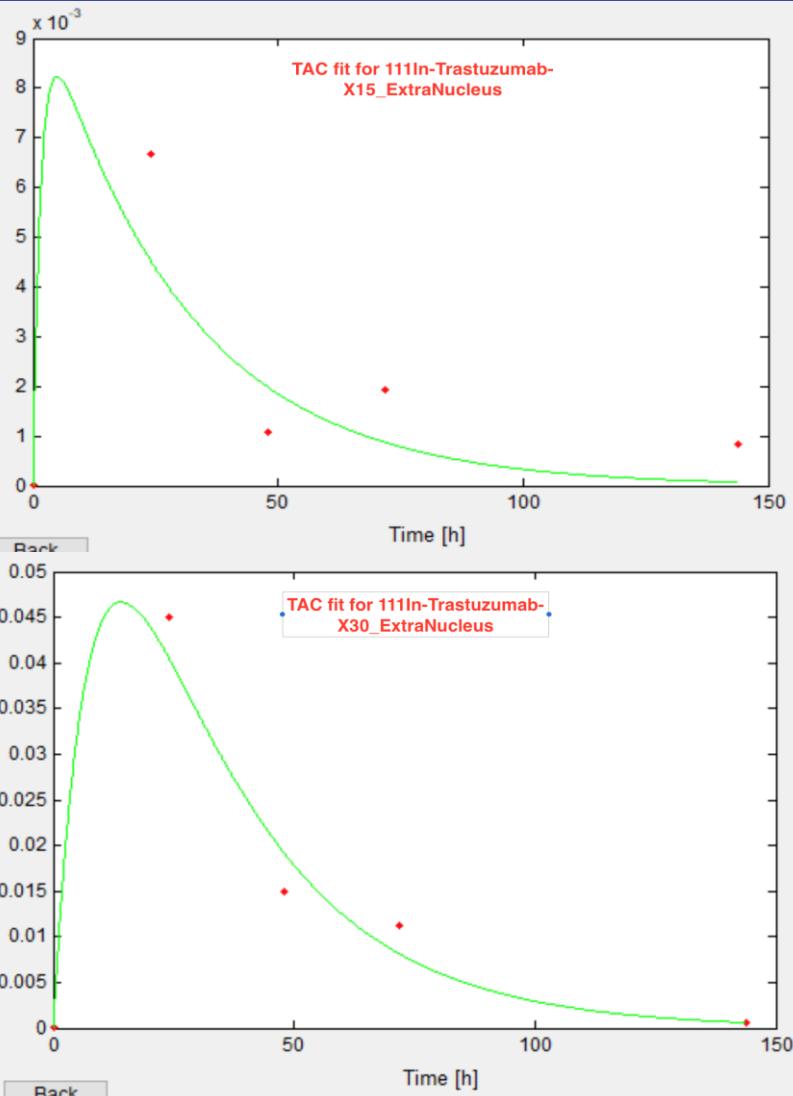
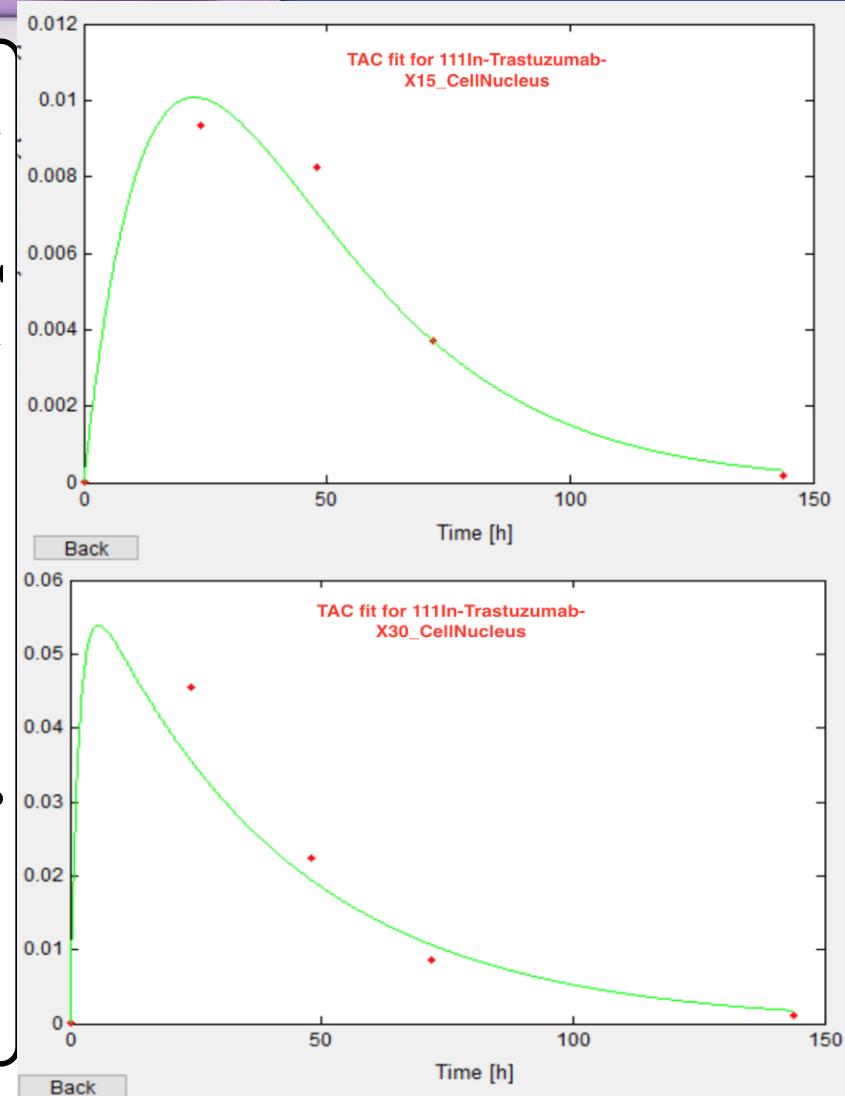
Time Activity Concentration for ^{111}In -trastuzumab-X30 in
A431CEA-LUC Cells



Bi-exponential fitting to TAC

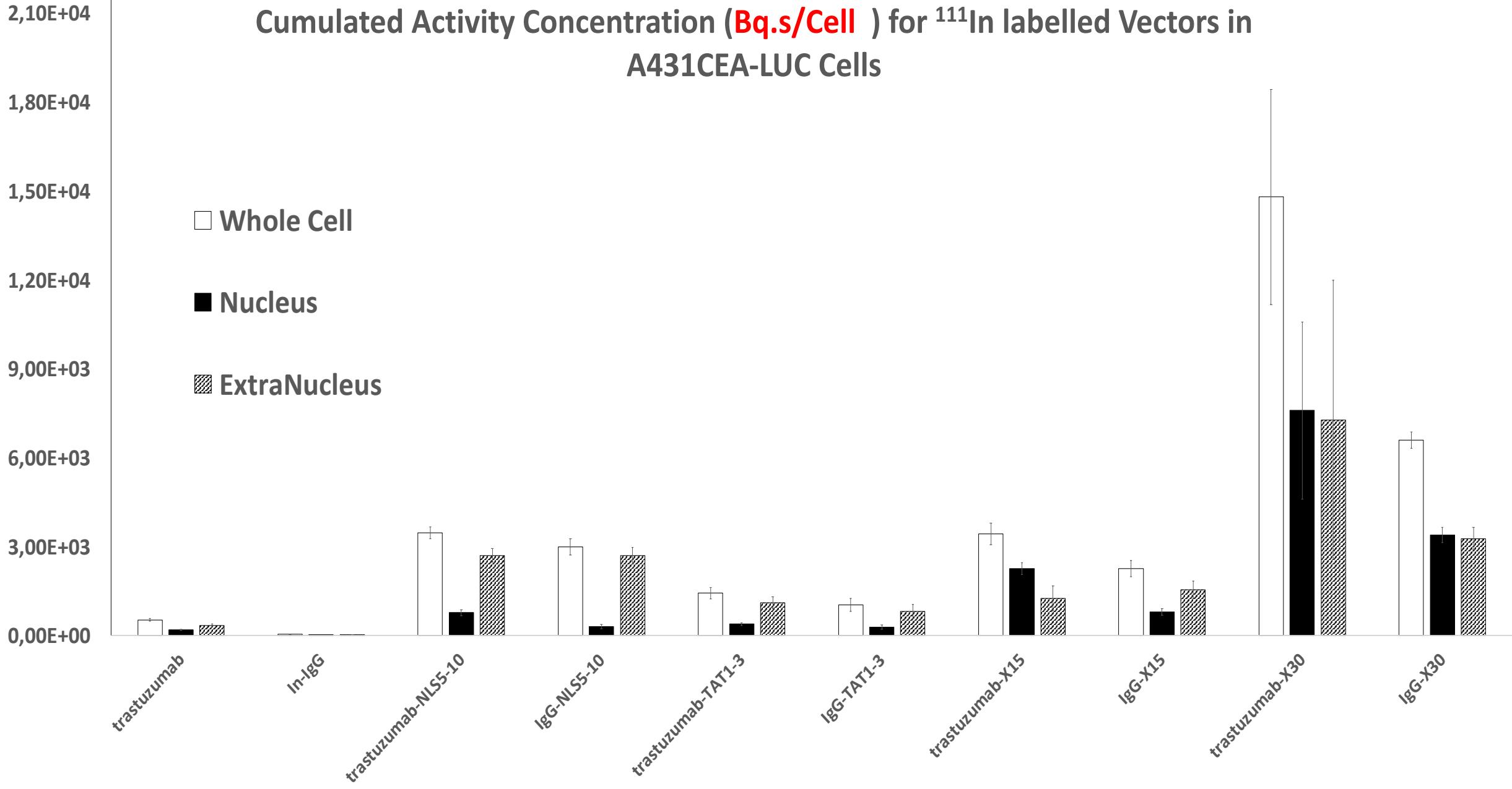


Activity Concentration(Bq/Cell)



Cumulated Activity Concentration (**Bq.s/Cell**) for ^{111}In labelled Vectors in A431CEA-LUC Cells

Cumulated Activity Concentration(Bq.s/Cell Fraction)

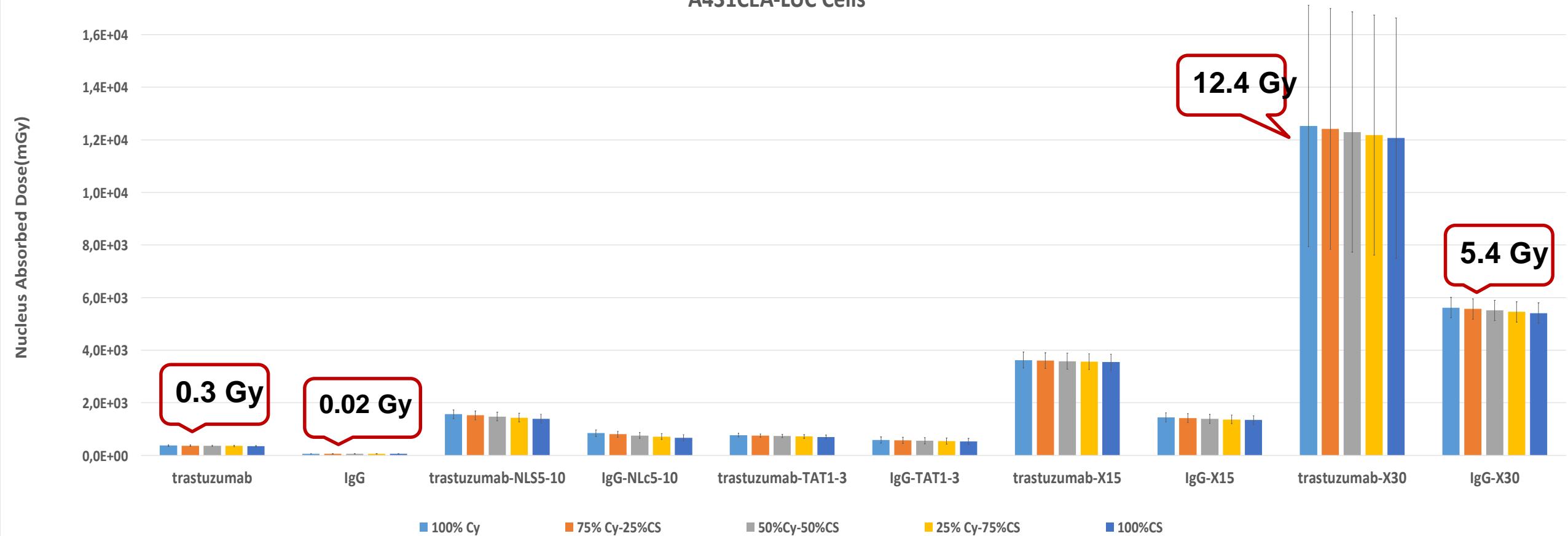


Uncertainties for Cumulated activity

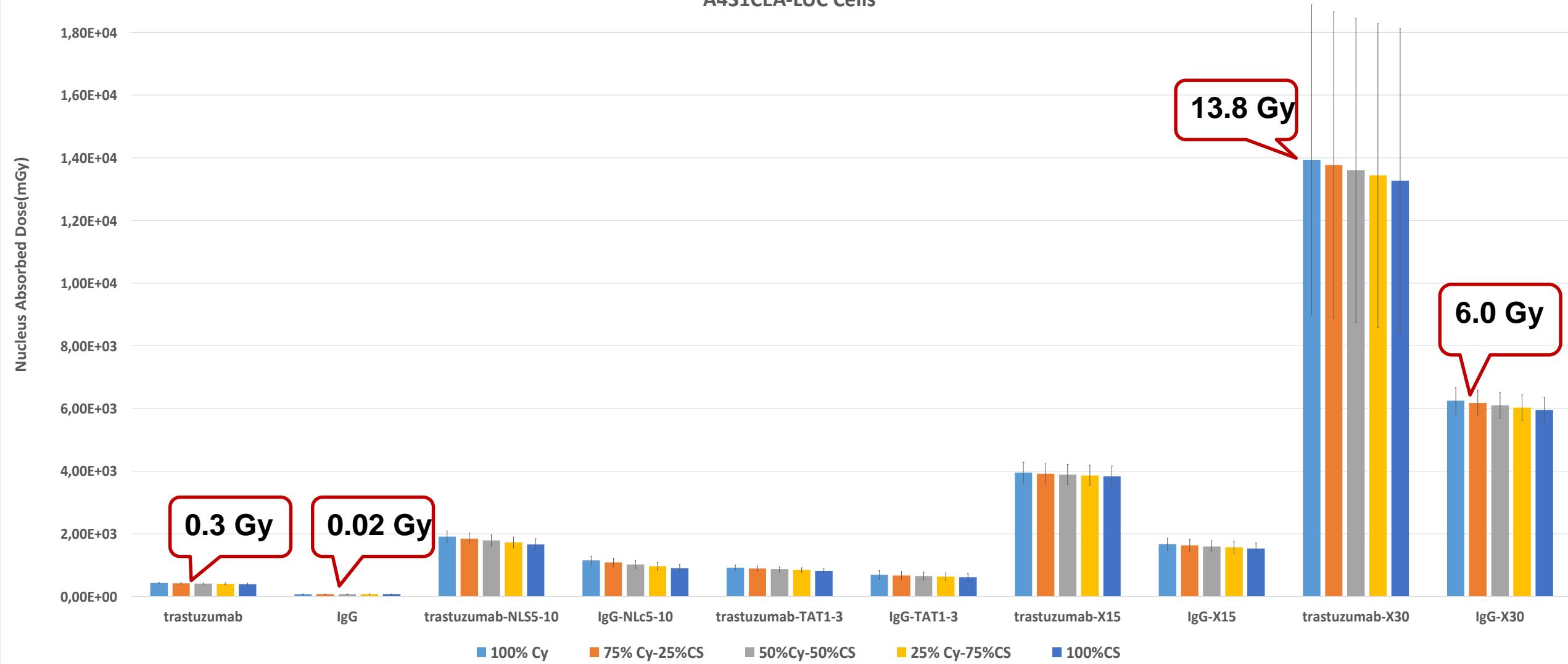
Mostly by calculation

	% Uncertainty		
Radiopharmaceuticals labelled with ^{111}In	Whole Cell (Bq.s/Cell)	Nucleus (Bq.s/ Cell)	ExtraNucleus (Bq.s/ Cell)
Trastuzumab	9	8	14
IgG	11	13	19
Trastuzumab-NLS ₅₋₁₀	6	14	8
IgG-NLS5-10	9	25	11
Trastuzumab-TAT1-3	13	11	18
IgG-TAT ₁₋₃	22	26	29
Trastuzumab-X15	11	9	33
IgG-X15	12	14	19
Trastuzumab-X30	25	39	65
IgG-X30	4	8	12

Nucleus Absorbed Dose(mGy) with different extranucleus activity distribution of ^{111}In -labeled vectors for Single Cell Model of A431CEA-LUC Cells

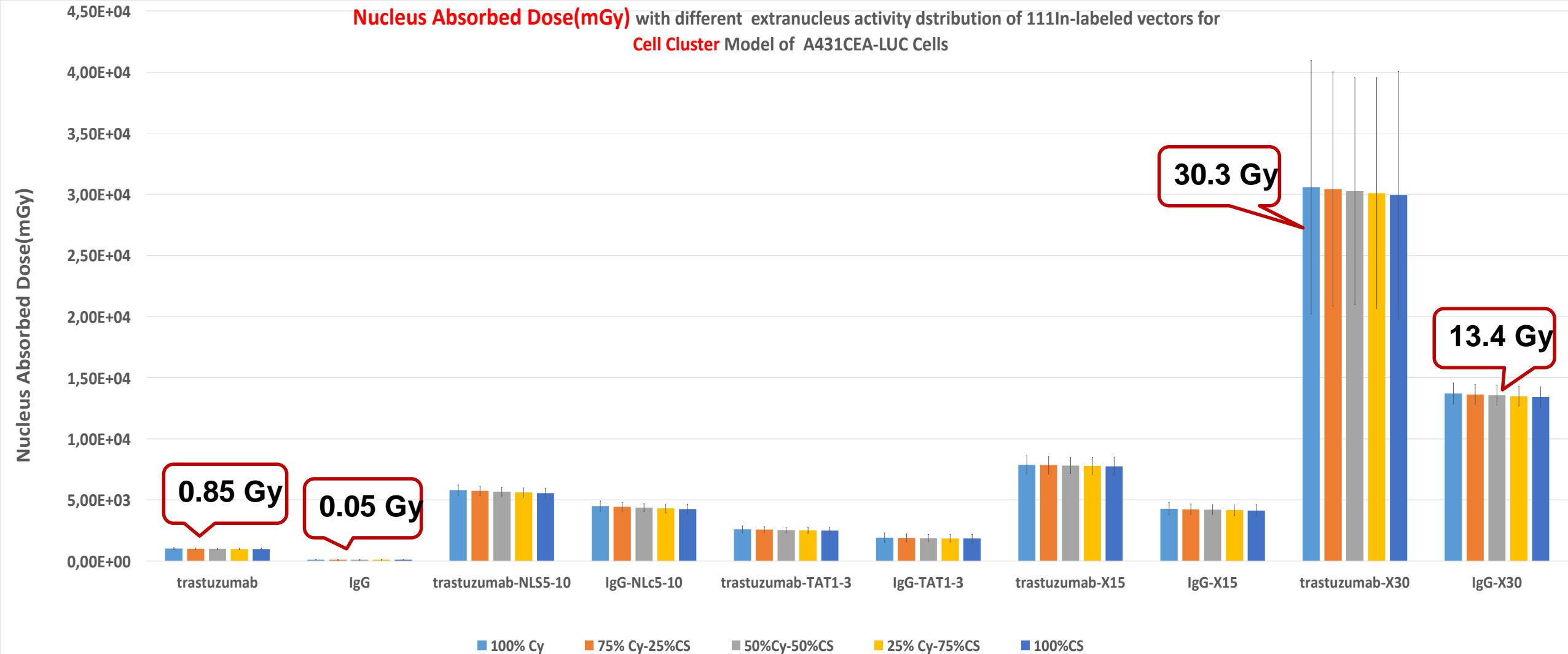


Nucleus Absorbed Dose(mGy) with different extranucleus activity distribution of ^{111}In -labeled vectors for Monolayer Model of A431CEA-LUC Cells





Nucleus Absorbed Dose(mGy) with different extranucleus activity distribution of ^{111}In -labeled vectors for
Cell Cluster Model of A431CEA-LUC Cells



Total Uncertainty for Nucleus Absorbed Dose

	% Uncertainty		
Radiopharmaceuticals labelled with ^{111}In	Single Cell model	Monolayer model	Cell Cluster Model
Trastuzumab	7	7	6
IgG	6	6	6
Trastuzumab-NLS ₅₋₁₀	11	11	6
IgG-NLS5-10	15	15	8
Trastuzumab-TAT1-3	9	9	8
IgG-TAT ₁₋₃	21	21	16
Trastuzumab-X15	8	8	8
IgG-X15	12	12	10
Trastuzumab-X30	37	37	31
IgG-X30	7	7	6

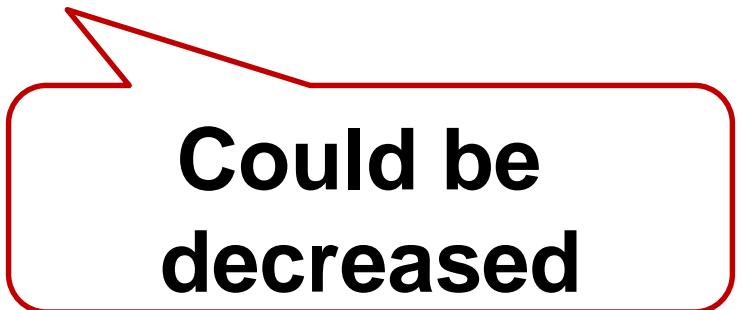
(>>4 Gy) (>>4Gy) (>>9Gy)



Summary and Conclusion

Systematic

Biokinetic parameters, Physical models terms, Decay
data, activity measurement,
energy spectrum, Cell shape, Stopping power



Could be
decreased



Uncertainty Sources

Random

Related to SD of the measurements

The major contributor
in this study

Max Uncertainty in this study for nucleus absorbed dose:

37%(>4 Gy), 37%(>4Gy) and 31%(>9Gy)
for

Single Cell, Monolayer and Cell Cluster Models

QUESTIONS?





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