Istituto Nazionale di Fisica Nucleare
LABORATORI NAZIONALI DI LEGNARO

ADMIRAL
ISOLPHARM
SPES exotic beams for medicine

Laboratori Nazionali di Legnaro – INFN

Radiobiology of ^{111}Ag: calculation of the cellular S-values by mean of Geant4

Analysis of an uninvestigated but interesting cell line: the LNCaP.

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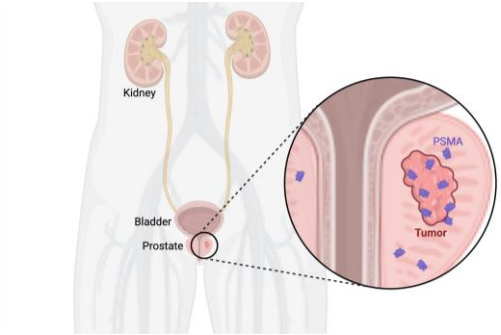
Outline

I. Study of the LNCaP cell line
II. Model of an adherent LNCaP cell
III. Results of the Geant4 simulation
IV. UMR-106 clonogenic assay
V. A new (ongoing) *in vitro* clonogenic assay
VI. Next purposes

Study of the LNCaP cell line

What is the LNCaP cell line?

The Lymph Node Carcinoma of the Prostate (LNCaP) cell line is derived from a metastatic lesion in a lymph node of a prostate cancer patient.

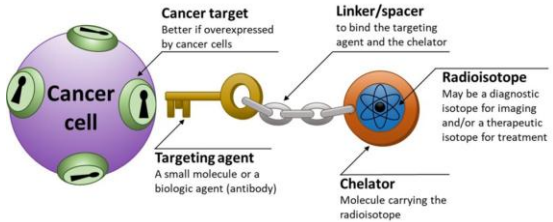


Why is it interesting?

It expresses the PSMA (Prostate Specific Membrane Antigen) overexpressed by cancer cells, like LNCaP. PSMA is already widely exploited in the prostate cancer-addressing radiopharmaceuticals, like the $^{177}\mathbf{Lu-PSMA-617}$, binding the lutetium radioactive nucleus to the PSMA ligand PSMA-617.

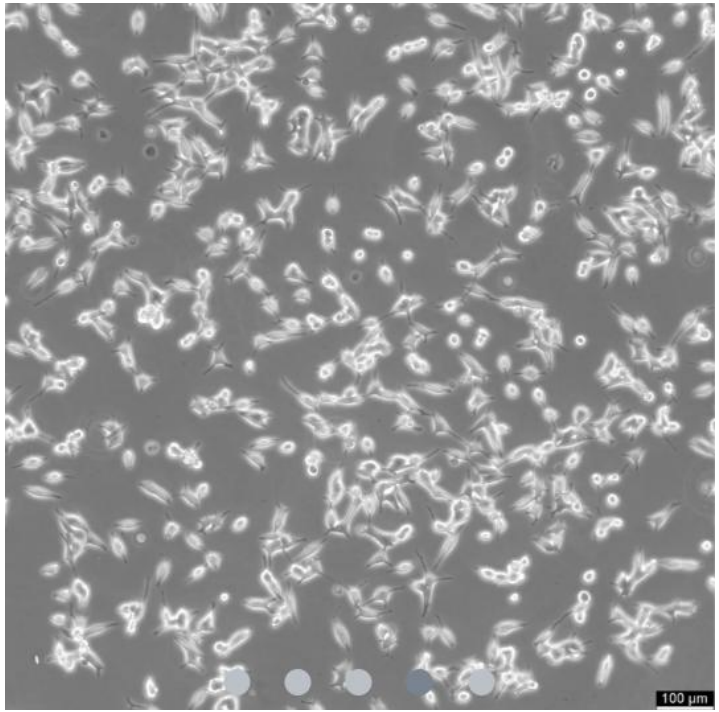
What will be done in ADMIRAL?

The ADMIRAL WP1 team will develop a PSMA-617 $^{111}\mathrm{Ag}$-bearing molecule to address LNCaP cells.



Study of the LNCaP cell line

Estimation of the LNCaP cells main dimensions



Using ImageJ, the main dimensions of the cells, needed to be known to model them, have been estimated:

$d_{cell} = 21.22\ \mu m$ (*)

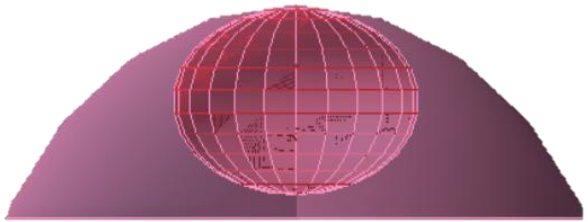
$d_{nucleus} = 8.95\ \mu m$

(*) The result shown during the last ISOLPHARM meeting has been corrected to consider very small cells that had been disregarded setting a too high threshold for the size.

Model of an adherent LNCaP cell

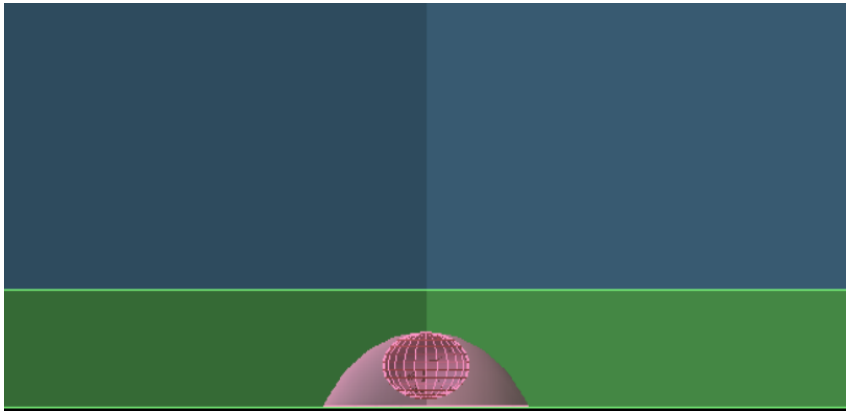
Adherent LNCaP cell

Cell = spherical segment of $21.22\ \mu m$ diameter section.
Nucleus = ellipsoid of radii $4.475\ \mu m$ in the *x* and *y* directions, $2.8\ \mu m$ in the *z* direction, to simulate adhesion.



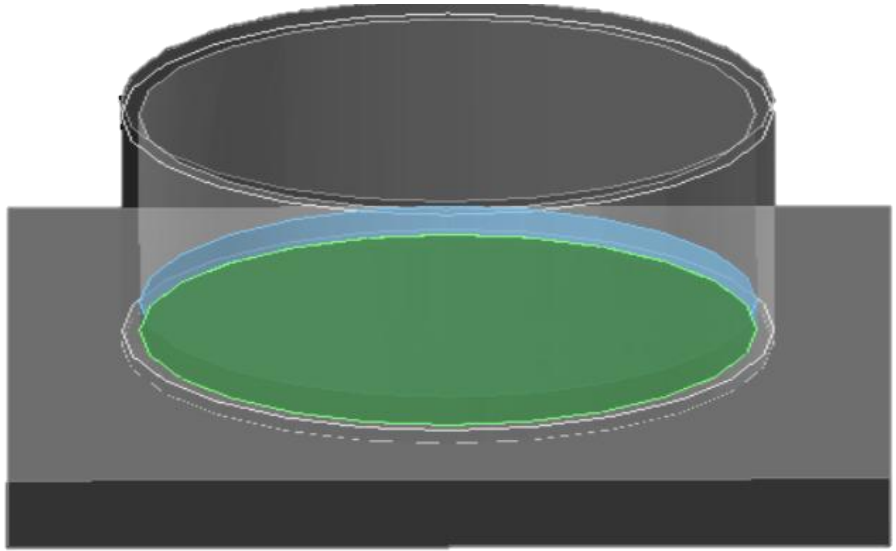
The cell culture medium

«Bottom» culture medium = culture medium populated by cells.
«Top» culture medium = culture medium supposed to host no cells.



Model of an adherent LNCaP cell

The whole experimental setup



For the P35 dish:

- $\text{diameter} = 35\ \text{mm}$
- $\text{thickness} = 1\ \text{mm}$
- $\text{height} = 16\ \text{mm}$
- material = polystyrene

For the support plane:

- $\text{height} = 5\ \text{mm}$
- material = stainless-steel

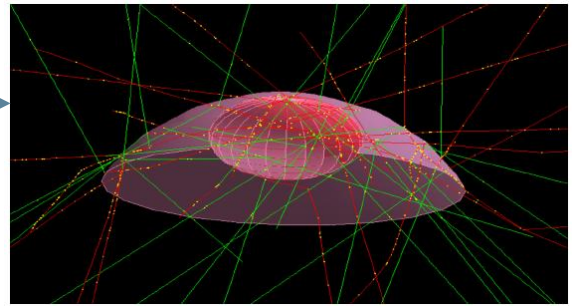
For the culture medium:

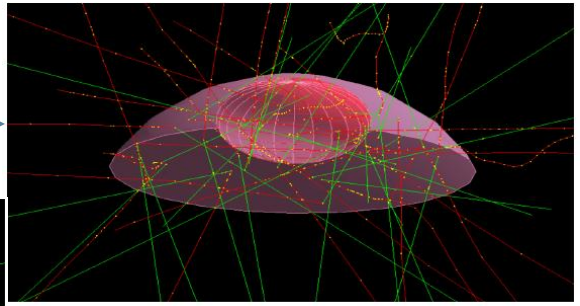
- $\text{height}_{\text{bottom}} = 10\ \mu\text{m}$
- $\text{height}_{\text{top}} = 2.09\ \text{mm}$
- material = water

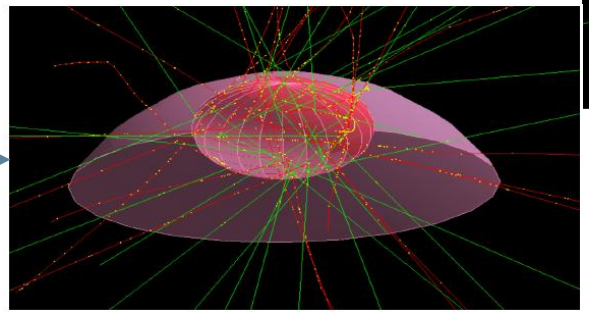
Results of the Geant4 Simulation

Self-absorbed dose

^{111}Ag decay site	Target region	S_{self} [μGy/(Bq·s)]
Membrane	Cytoplasm	117.4
	Nucleus	101.6
Cytoplasm	Cytoplasm	183.9
	Nucleus	129.9
Nucleus	Cytoplasm	129.3
	Nucleus	654



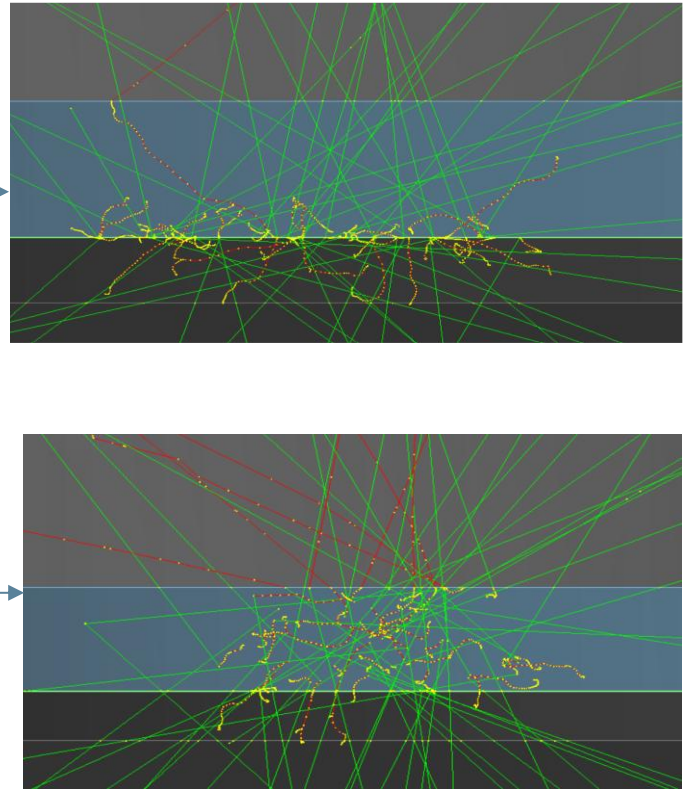




Results of the Geant4 Simulation

Environmental dose

^{111}Ag decay site	Radioactive volume [ml]	Target region	S_{env} [Gy·ml/(Bq·s)]
Bottom culture medium	2.827×10^{-4}	Cytoplasm	1.26×10^{-12}
		Nucleus	1.12×10^{-12}
Top culture medium	4.9395×10^{-2}	Cytoplasm	2.39×10^{-11}
		Nucleus	2.39×10^{-11}

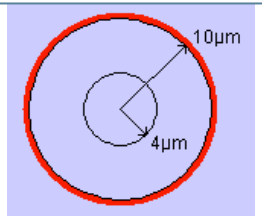


Results of the Geant4 Simulation

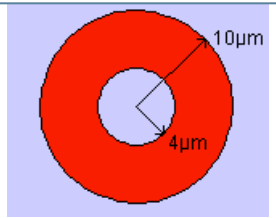
Benchmark with the MIRDcell software output

All the simulations performed up to now on cells irradiated by ^{111}Ag neglect the adhesion of the cells. Being highly depending on the geometry of the radionuclide distribution, the S-values calculated are different.

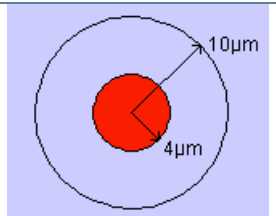
^{111}Ag *distributed over the cell membrane (CS)*



^{111}Ag *distributed in the cell cytoplasm*



^{111}Ag *distributed in the cell nucleus*

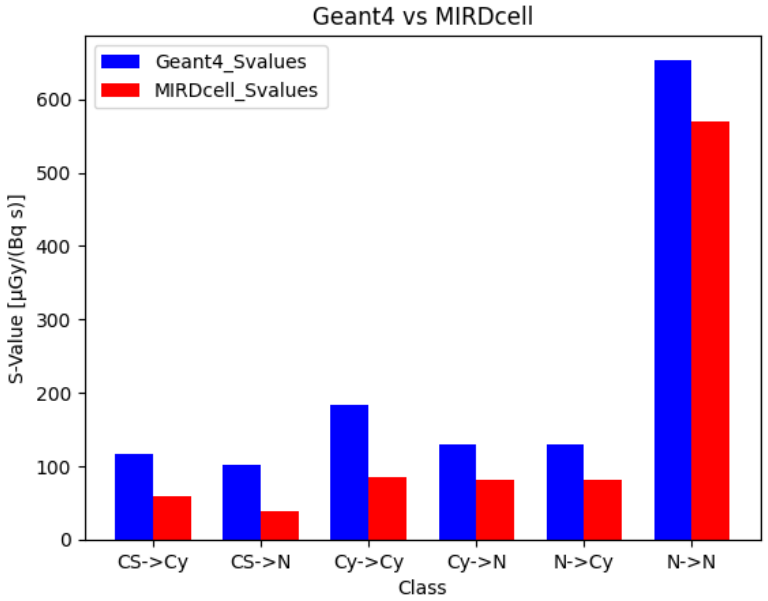


Results of the Geant4 Simulation

Benchmark with the MIRDcell software output

Here, the results obtained through the software MIRDcell for spherical LNCaP cells are reported.

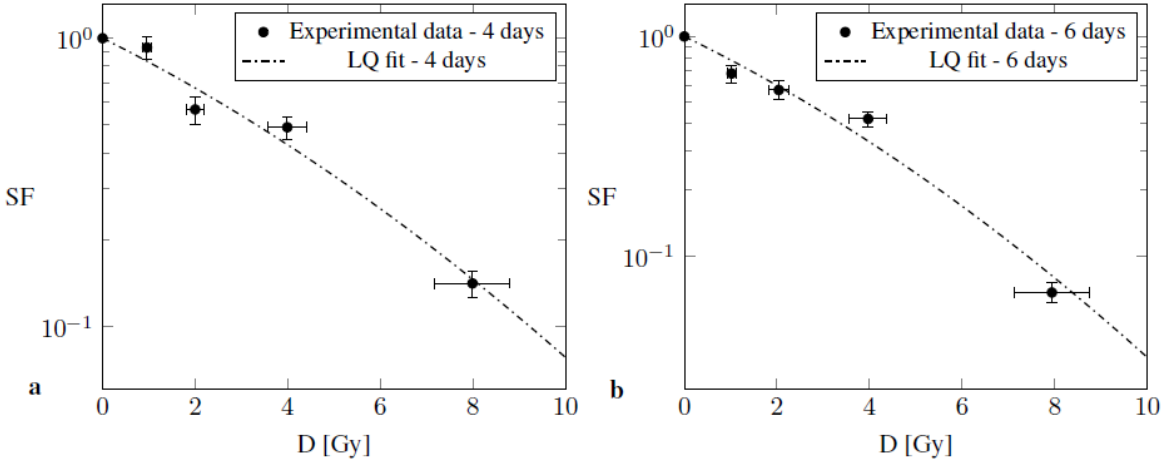
S(CS->Cy) [µGy/(Bq·s)]	58.7
S(CS->N) [µGy/(Bq·s)]	38.3
S(Cy->Cy) [µGy/(Bq·s)]	85.7
S(Cy->N) [µGy/(Bq·s)]	81.3
S(N->Cy) [µGy/(Bq·s)]	81.3
S(N->N) [µGy/(Bq·s)]	569



UMR-106 clonogenic assay

Data analysis and modelling - LQ

$$SF = e^{-\alpha D - \beta D^2}$$



α	β
0.19 ± 0.06	0.007 ± 0.010

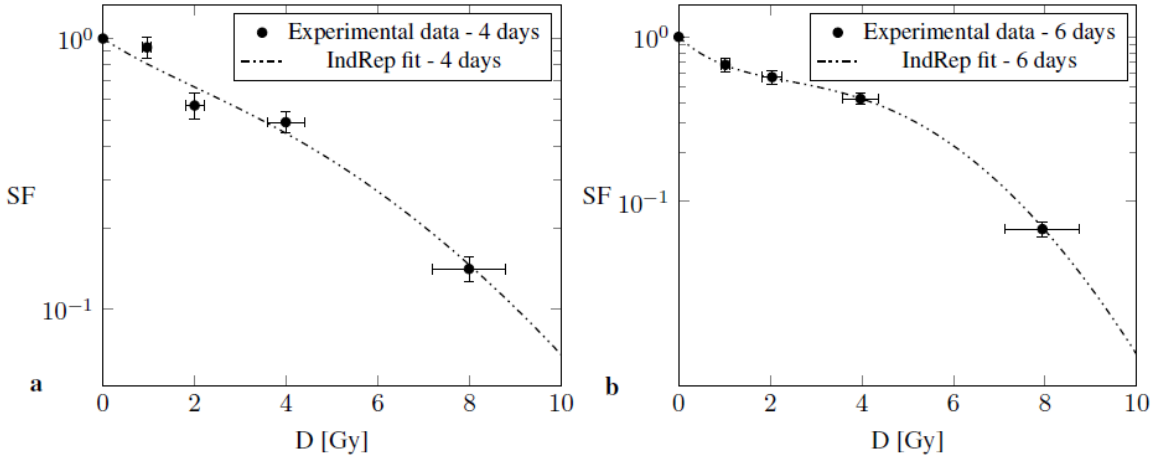
α	β
0.24 ± 0.06	0.010 ± 0.012

UMR-106 clonogenic assay

Data analysis and modelling - IndRep

$$SF = exp(-\alpha_r D(1 + (\alpha_s/\alpha_r - 1)exp(-D/D_C)) - \beta D^2)$$

$(D_C = 2.5\ \text{Gy})$



α_s	α_r	β
0.26 ± 0.26	0.11 ± 0.28	0.016 ± 0.035

α_s	α_r	β
0.59 ± 0.01	-0.19 ± 0.01	0.062 ± 0.002

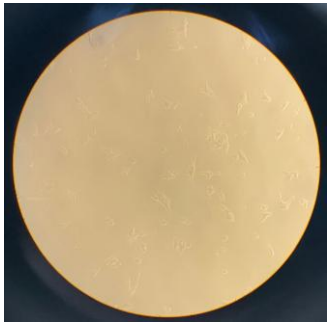
A new (ongoing) *in vitro* clonogenic assay

Weeks 12/05-16/05 and 19/05-23/05 updates:

New clonogenic assay performed on the LNCaP cell line.

- Cells, seminated on 13 May have been put in contact with ^{111}Ag on 15 May. Each Petri dish contains 50.000 cells, supposed to be a proper concentration for the experiment.

- On 15 May the ^{111}Ag solution has been introduced in the Petri dishes in different amounts to study the different conditions of interest.



A new (ongoing) *in vitro* clonogenic assay

Weeks 12/05-16/05 and 19/05-23/05 updates:

- Cells in half of the Petri dishes have been in contact with ^{111}Ag for 4 days, up to today. This morning, we have washed the cells, put a clean (non radioactive) culture medium and seeded them.

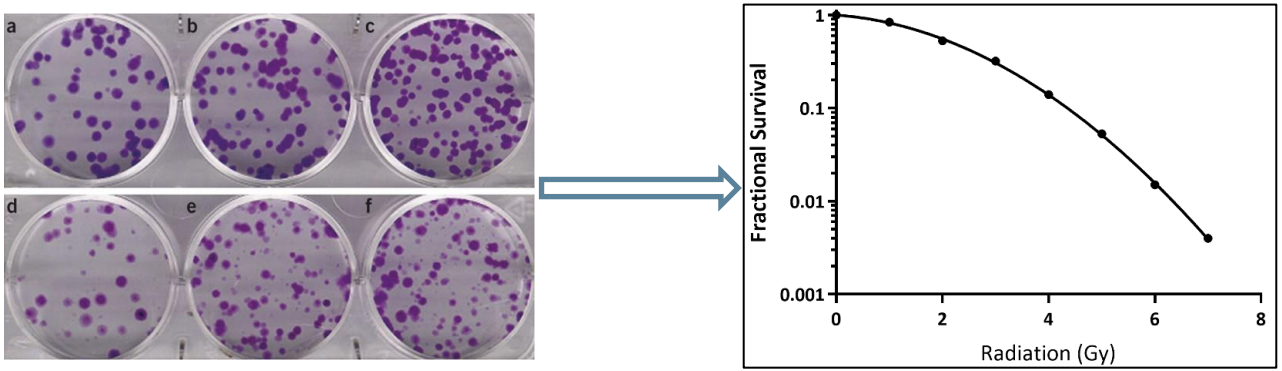
CONDITION	INITIAL CELL SEEDING
CTR	100, 250, 500
1 Gy	100, 250, 500
2 Gy	100, 250, 500
4 Gy	250, 500, 1000
8 Gy	250, 500, 1000, 5000

- In order to make the clonogenic test, these will be grown for two or three weeks (* this will be evaluated) before being fixed.

A new (ongoing) *in vitro* clonogenic assay

Weeks 12/05-16/05 and 19/05-23/05 updates:

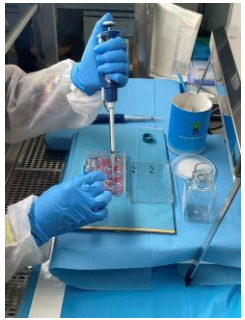
- The remaining cells will be kept in contact with ^{111}Ag until Wednesday 21 May, when they will be washed and seeded as described above.
- Finally, the clones will be counted and the cell survival curve will be obtained.

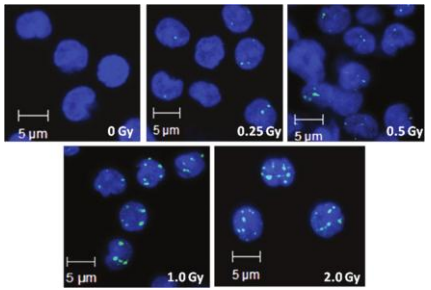


Next purposes

- From the Cell Survival Assay to the Nuclear Foci Assay:

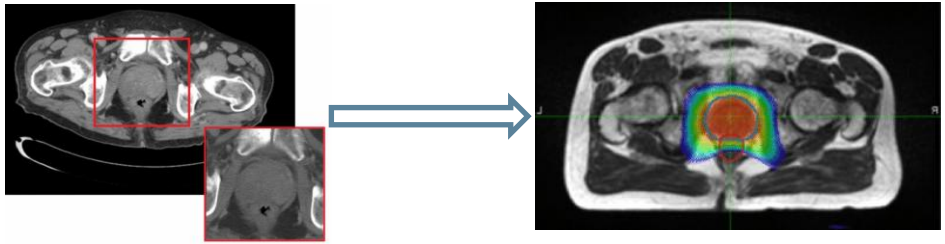
UMR-106 cells treated with ^{111}Ag on February 2025 will be soon analyzed using the fluorescence microscopy technique to count the *nuclear foci* induced by the ionizing radiations. The dedicated microscope is now under installation at the Biology Laboratory in Pavia.





- From the cell to the patient:

Treatment plan on a human prostate using a real CT scan on the software IT STARTS.



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Thank you!