

Pôle Physique



Environnement

Santé

Geant 4 GATE Labex PRIMES

Physique, Radiobiologie, Imagerie Médicale et Simulation



# RACE

## RA**d**iation resistance of cancer **C**ells using Geant4 **D**N**A**

Sept2013 – Sept2015



Plan cancer 2009  
2013

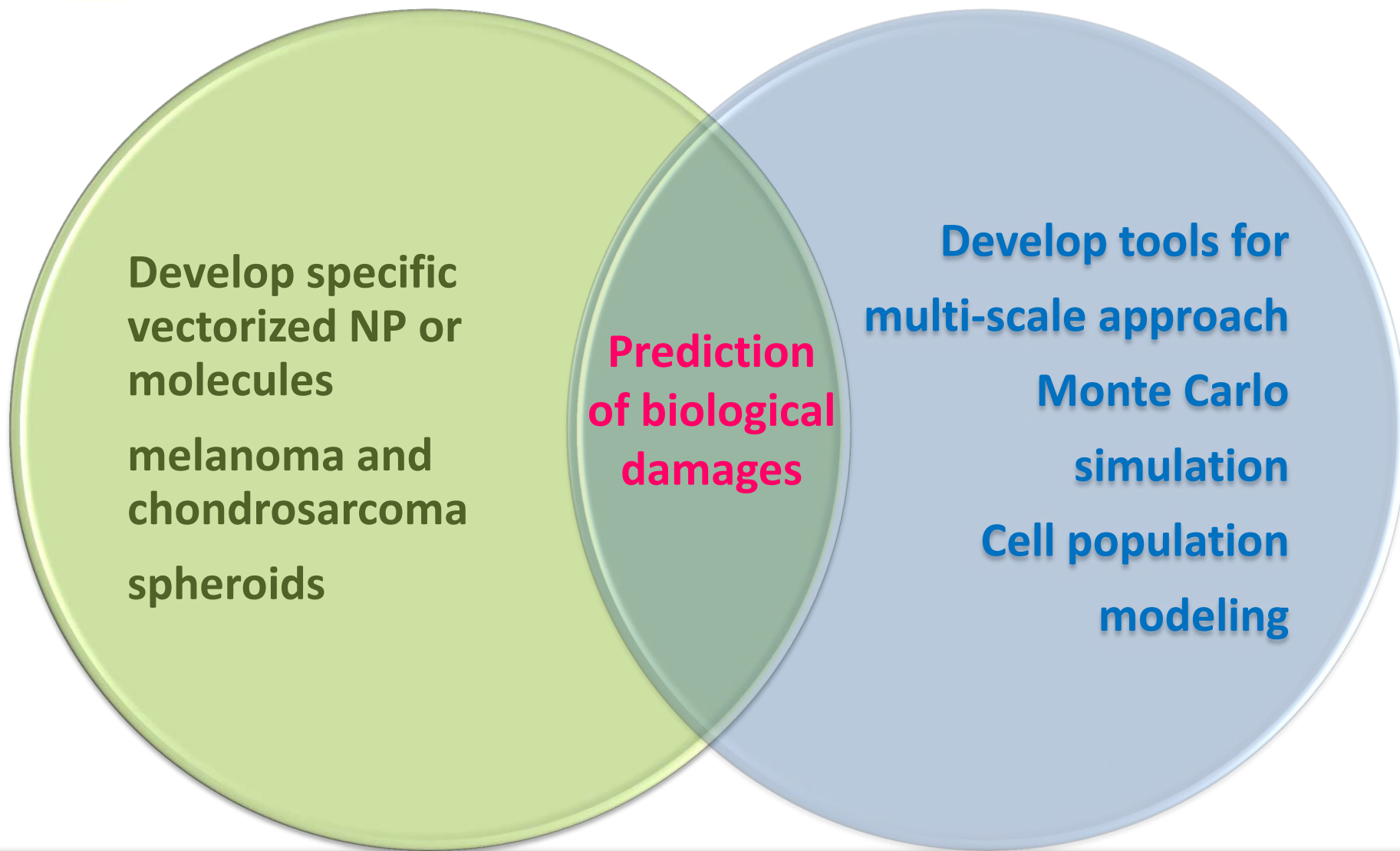
**Coordinators:** L. Maigne, E. Miot-Noirault

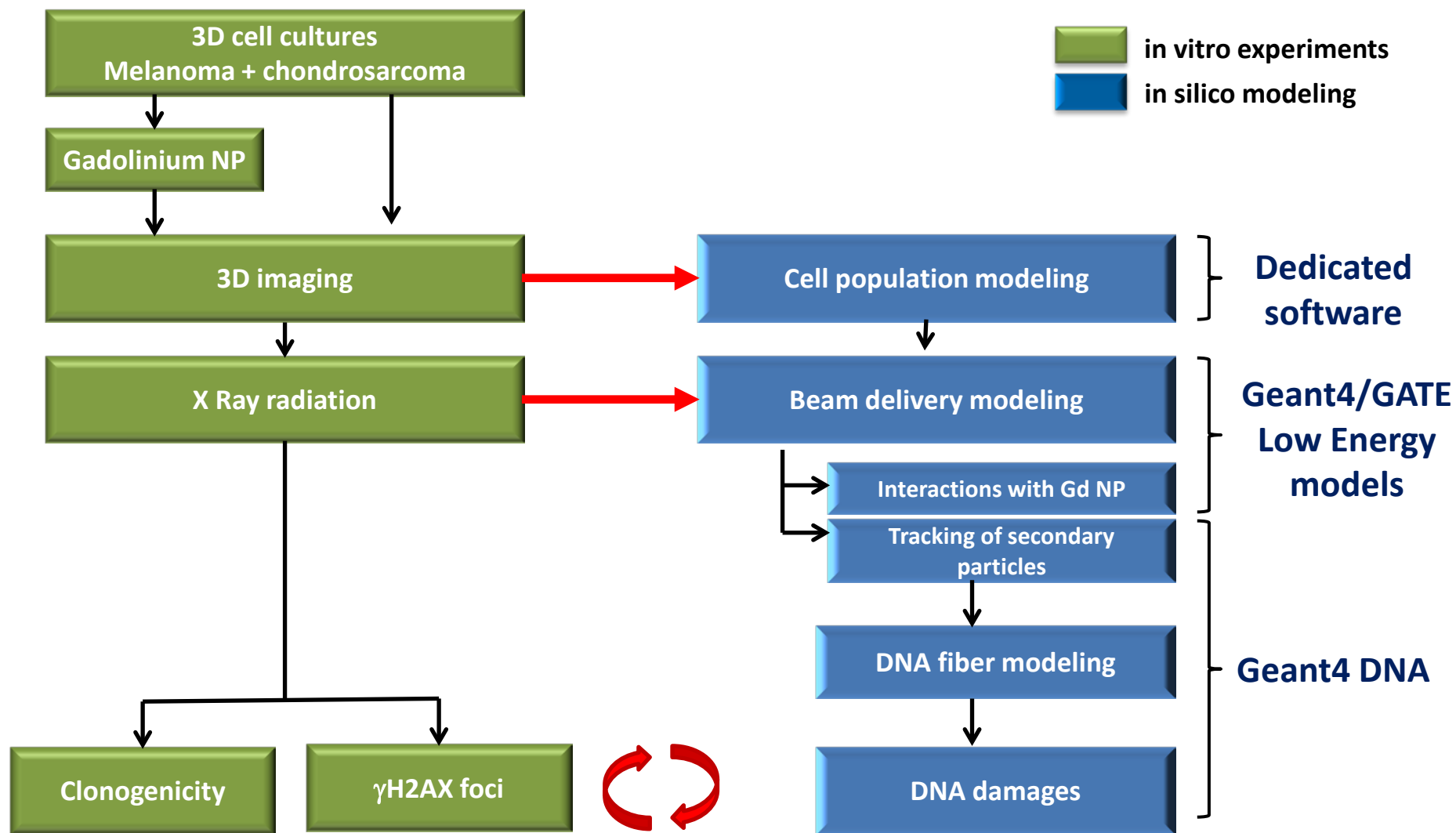
**Members:** F. Degoul, E. Débiton, H. Payno, Y. Perrot, C. Peyrode, E. Roche





# How to improve resistant cancer treatments ?

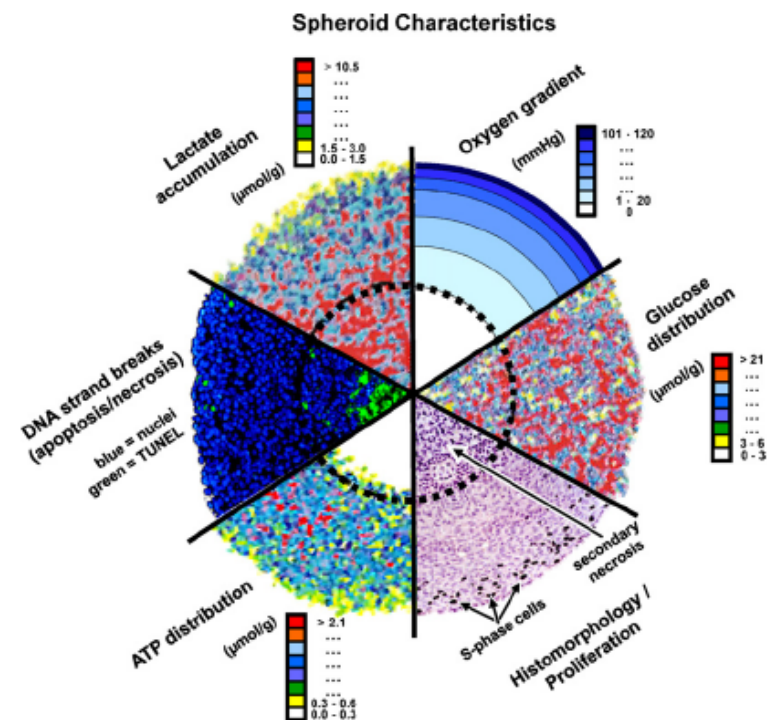
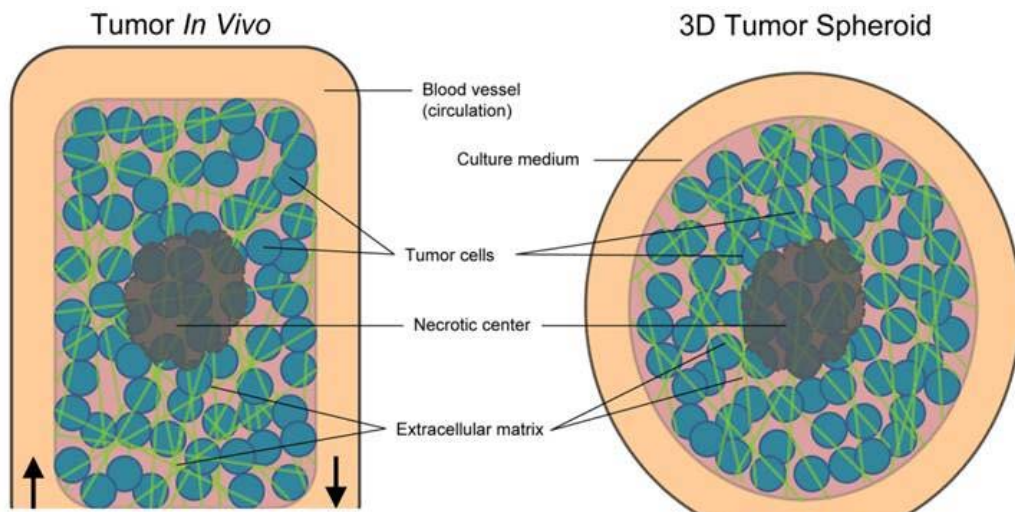




# CELL POPULATION

# Why 3D cell models?

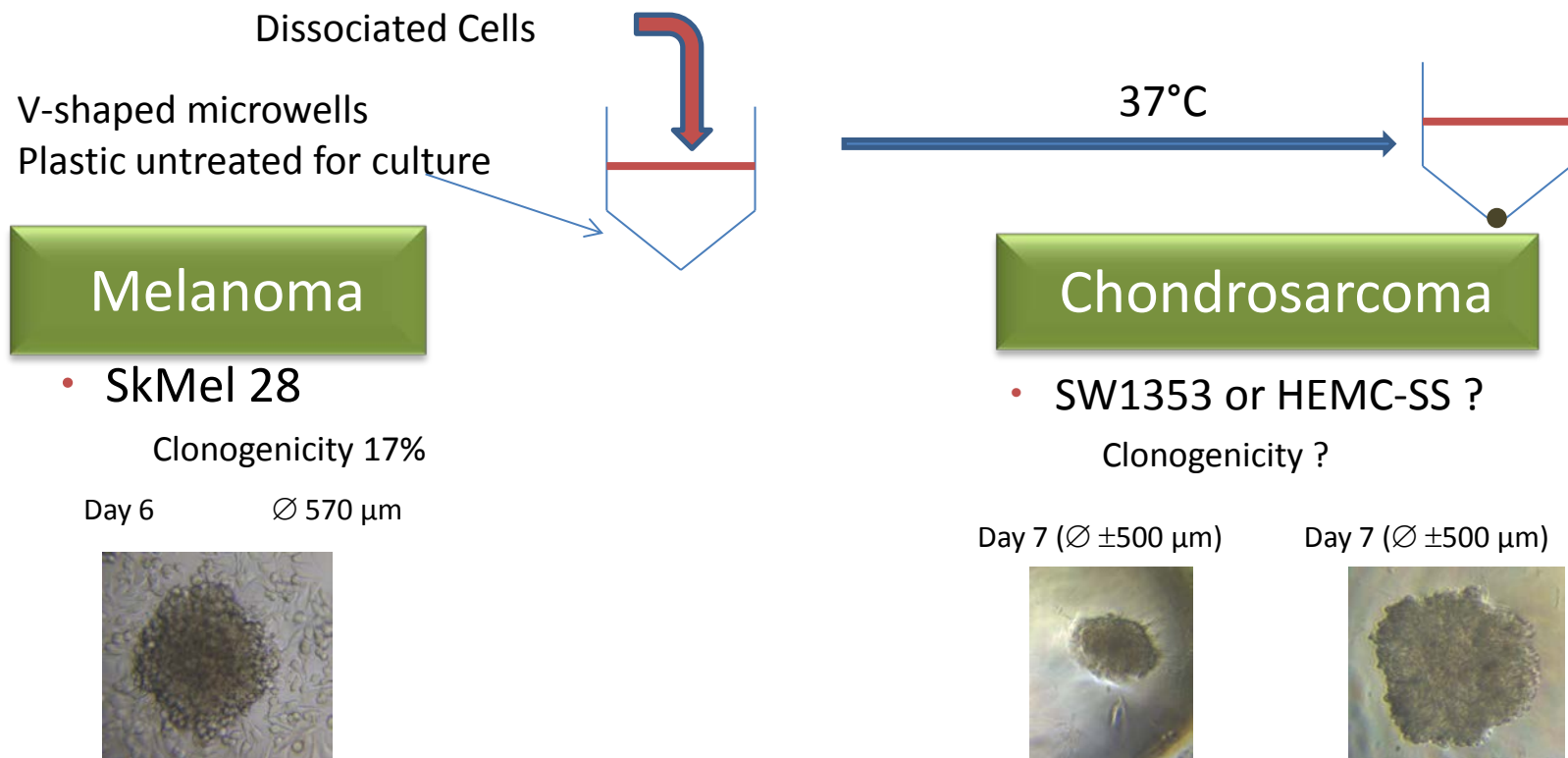
- ▶ Human model
- ▶ Low sensitivity to ionizing radiation
- ▶ Ability to vectorized NP *in vivo* to increase DNA damages



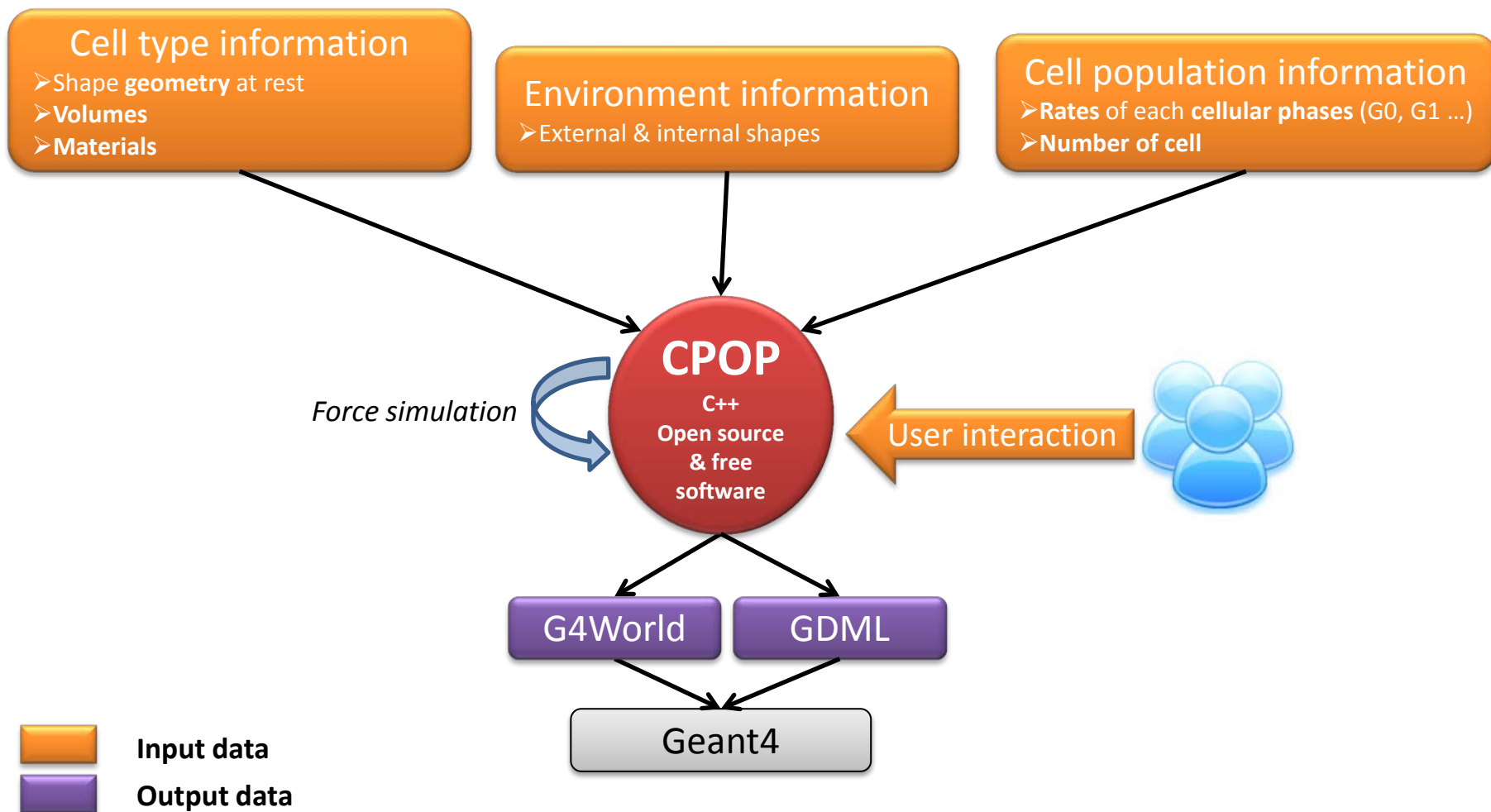
From Hirschhaeuser et al., 2010, J Biotech

# 3D cell culture

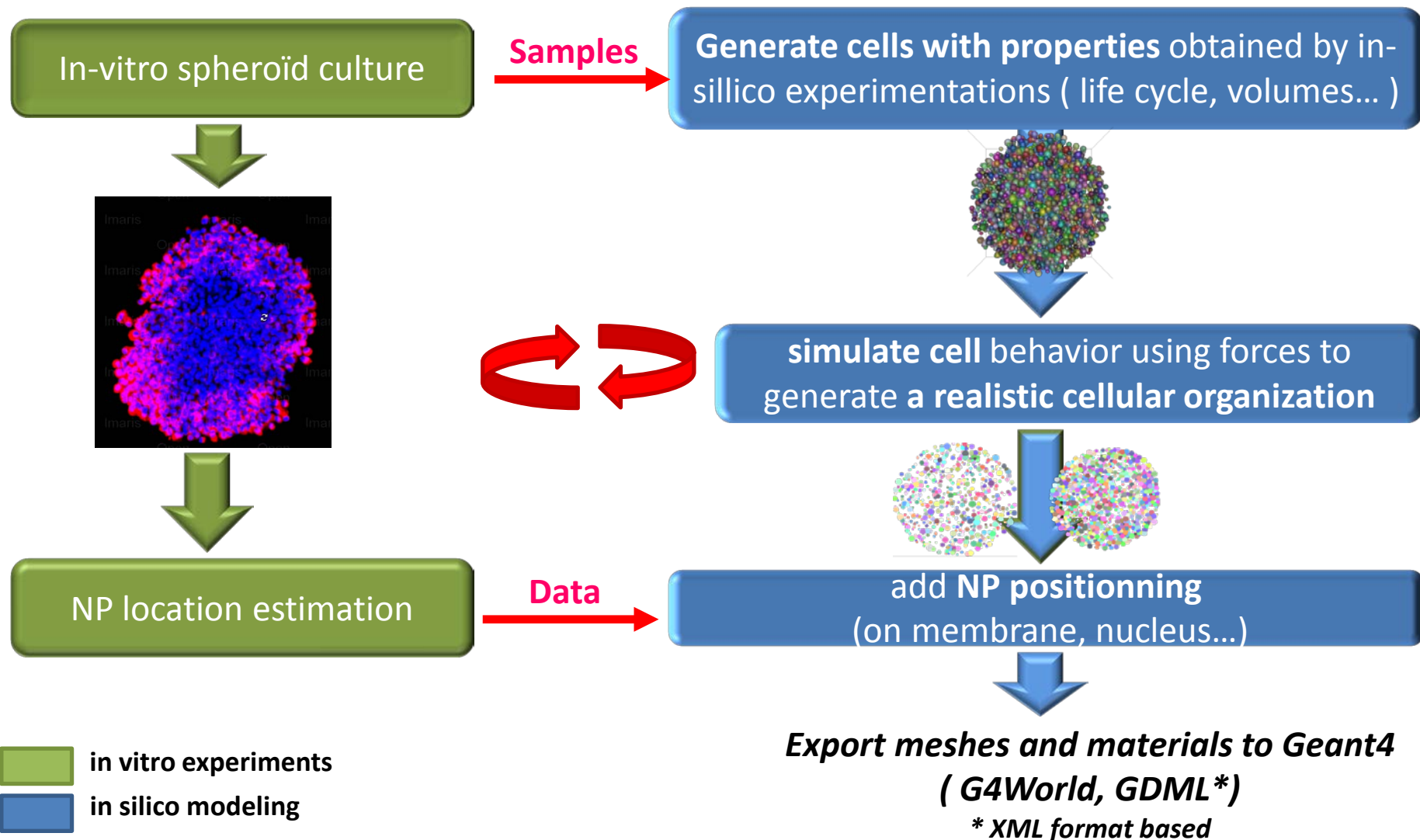
- ▶ Selection criteria
  - ▶ Clonogenic ability
  - ▶ Ability to form multicellular spheroids in methyl-cellulose containing medium



# Cell POPulation modeler

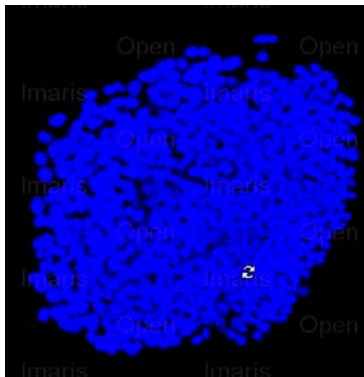


# The Cell POPulation modeler

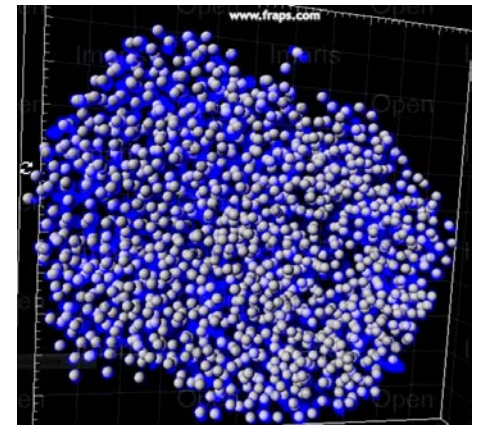


# Spheroid & cell characterization

- ▶ Cell shape *in situ* (confocal microscopy or SPIM)
  - ▶ Nuclear shape and dimension (DAPI)
  - ▶ Cell shape and dimension by cytoplasmic membrane staining (lipophilic fluorochrome)
  - ▶ Hypoxia evaluation *in situ* (Anh. Carb. IX activity)
- ▶ Growth characterization
  - ▶ Spheroid growth kinetic ( $\emptyset$  or volume)
  - ▶ Doubling time of cells (DNA or protein content)
  - ▶ Cell cycle analysis after dissociation (FCM)



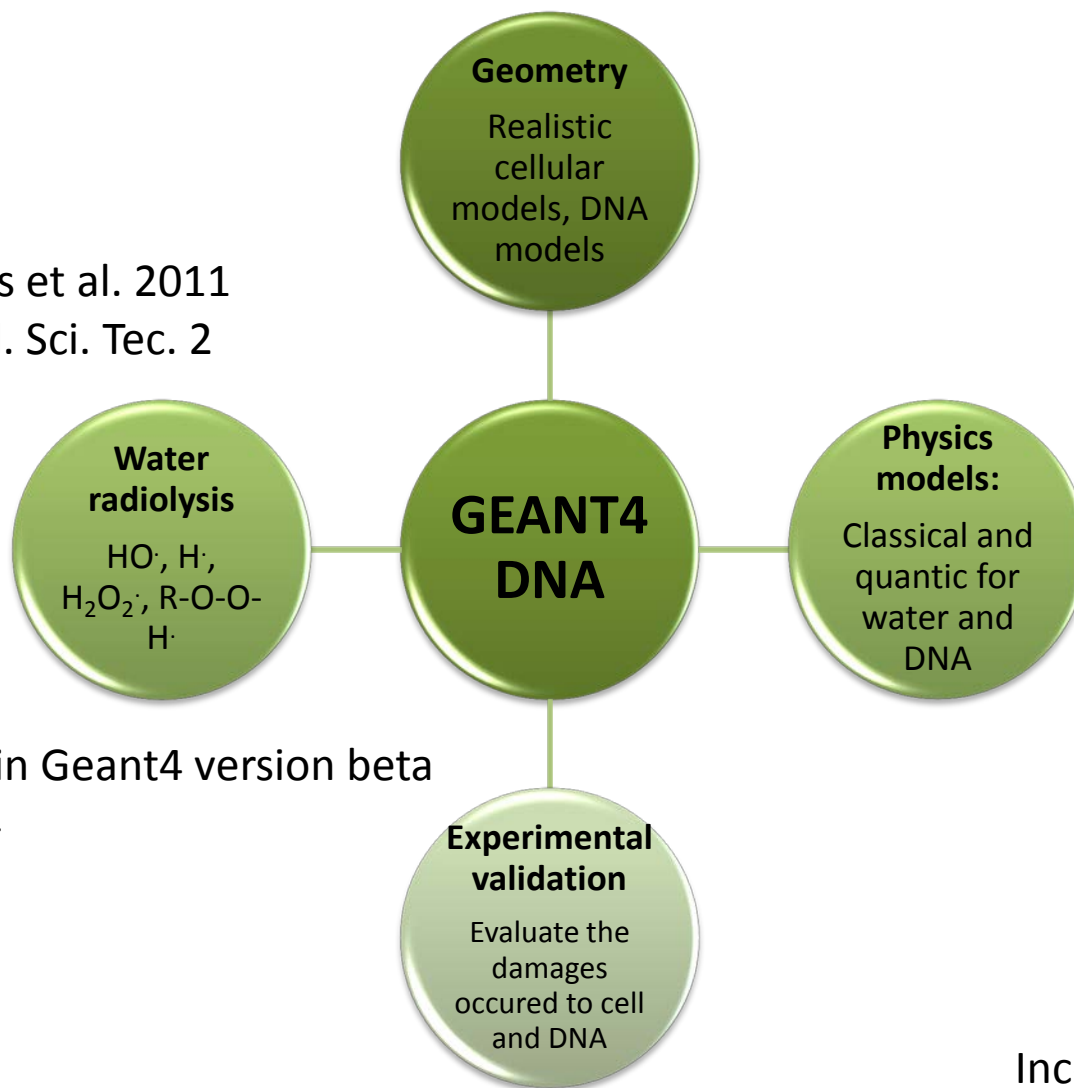
Data from *in-vitro* experimentations.



IMARIS data analysis

# MULTI-SCALE GEANT4 MONTE CARLO SIMULATION

Karamitros et al. 2011  
Prog. Nucl. Sci. Tec. 2

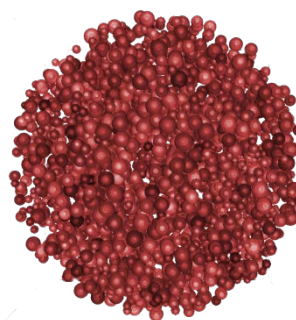
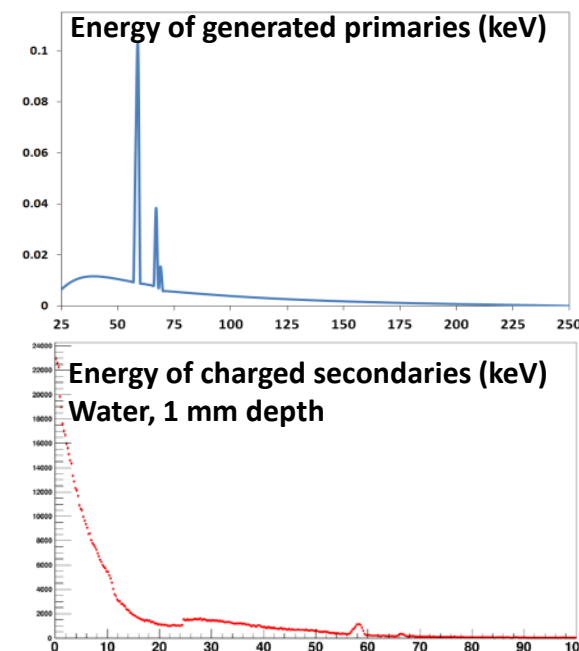


Expected in Geant4 version beta  
June 2014

Incerti et al. Med. Phys. 2010

# Spheroid irradiation

- X-RAD 320 system @ PAVIRMA
  - Voltage: 5 to 320 kV
  - Intensity: 0.1 to 45 mA
  - Circular field: radius 14 to 50 cm
  - Dose rate up to 13 Gy / min (5kGy max)
- Calibration
  - 250 kV RX beam
- Monte Carlo modeling
  - GATE/Geant4: Livermore models
  - $4 \times 10^9$  primaries (<1% uncertainty)
  - Metrics: production of secondaries



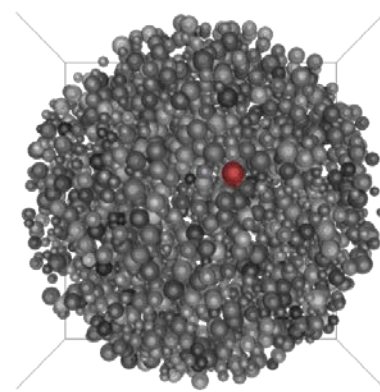
# Energy deposition per cell

- PAVIRMA beam characteristics

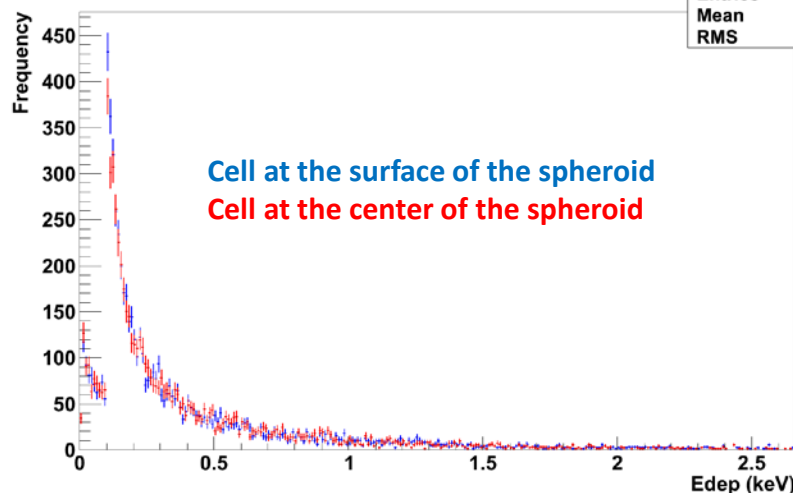
- Emax 250 keV : photoelectric effect
- 2mm Al filter
- Field size: 14.15 cm
- SSD = 50 cm
- Beam quality constant over 1 mm

- Energy deposition

- Geant4 10.0.p01, Livermore models
- Energy deposition in 10  $\mu\text{m}$  diameter cell
- Need to add NPposition

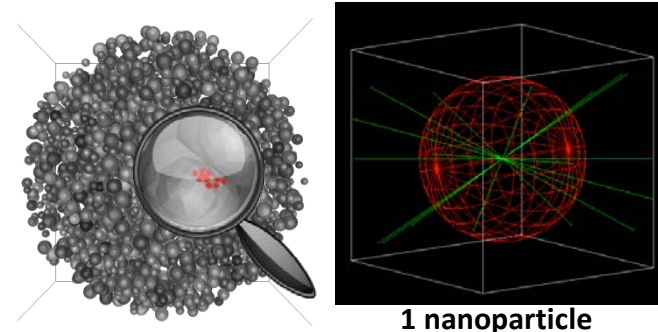
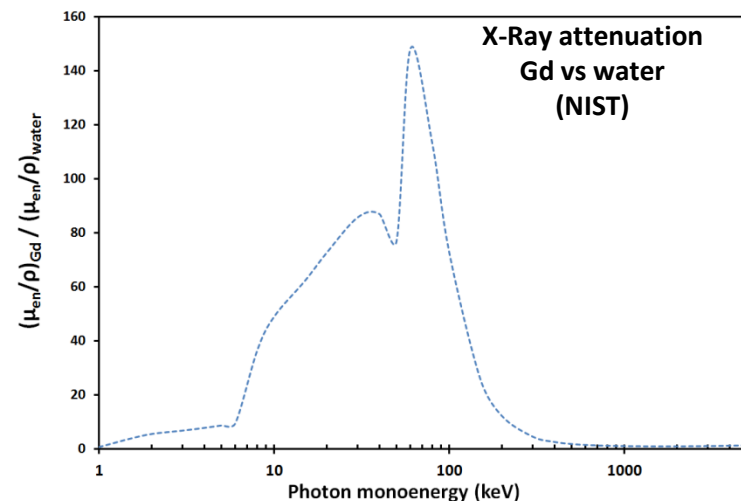


Energy deposited by secondaries



# Gadolinium NP simulation

- AGuIX AC13 nanoparticles
  - 4Si-DTPA
    - ~3.5 nm diam .at pH = 7.4
    - 8.5 kDa
    - 21 TEOS, 18 APTES, 10 DTPA, 10 Gd, fraction in mass of Gd = 12%
  - Optimal energy to get differential effect ~50 keV
- Monte Carlo modeling
  - Geant4.10.00.p01, Livermore + fluo + auger
  - Metrics for preliminary study:
    - Production of charged secondaries
    - Number of photoelectric events in the nanoparticle



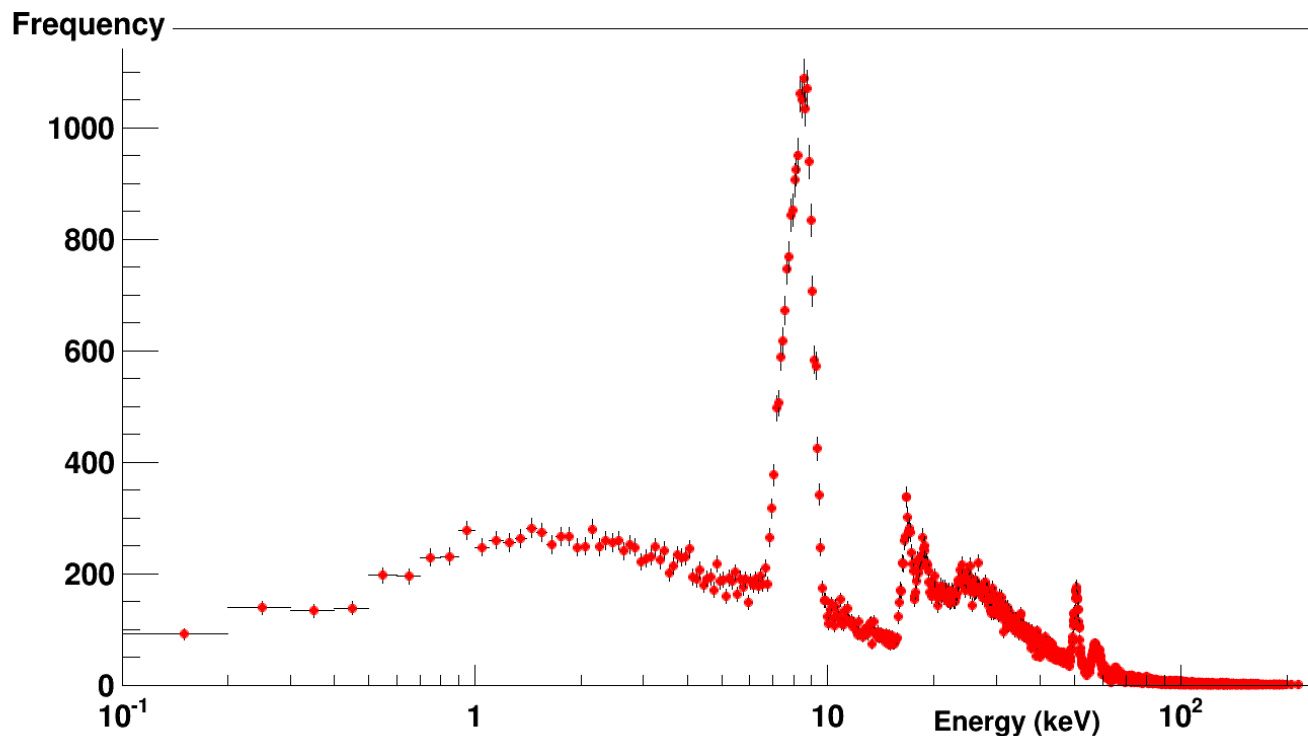
# Secondaries produced by NP

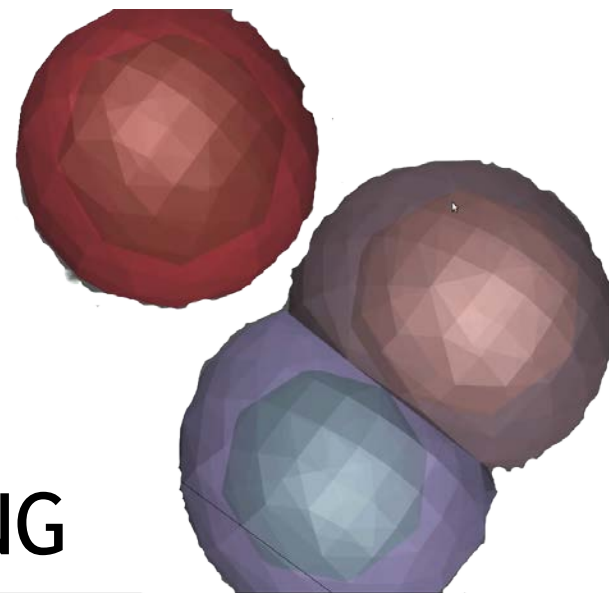
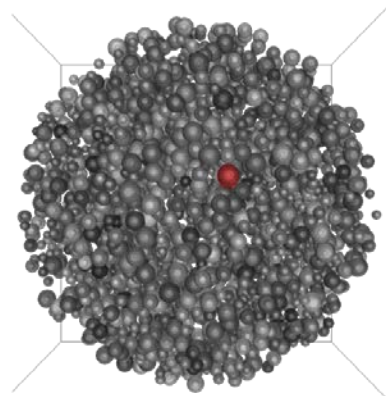
## Photoelectric event per primary

Primary	NP Si-DTPA
Gamma 52 keV	$1.8 \times 10^{-5}$
PAVIRMA	$1.3 \times 10^{-6}$

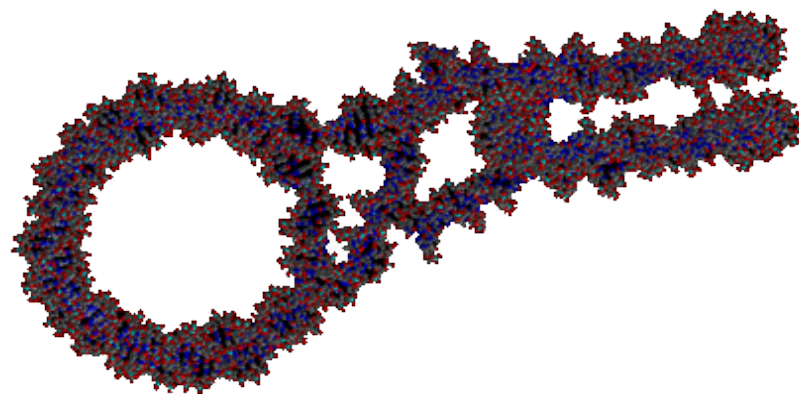


Energy of charged secondaries (keV)





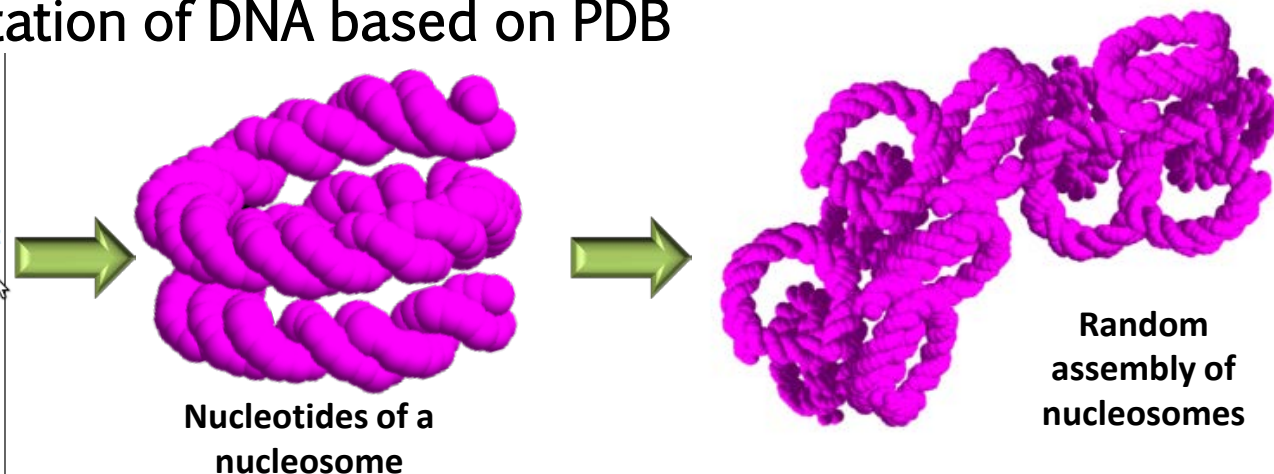
# DNA DAMAGE PREDICTION USING GEANT4-DNA



# DNA geometry and direct damages

- Atomic representation of DNA based on PDB

HEADER	DNA	Element	Chain/Strand ID	Residue/Nucleotide number	Atoms coordinates
...	MODEL	1			04-OCT-00 1FZX
...	ATOM	1	05'	1	9.256 -9.769 4.573
...	ATOM	2	C5'	1	10.679 -9.579 4.526
...	...	...	...	...	...
...	ATOM	31	H05'	1	8.851 -8.927 4.348
...	ATOM	32	P	2	11.658 -7.780 9.003
...	...	...	...	...	...
...	ATOM	64	H22	2	9.859 2.240 7.805
...	ATOM	65	P	3	13.850 -2.418 12.300
...	...	...	...	...	...
...	ATOM	382	H22	12	-4.024 2.925 36.606
...	TER	383		12	
...	ATOM	384	05'	13	-9.356 10.980 33.794
...	...	...	...	...	...
...	ATOM	759	H6	24	7.443 4.634 2.491
...	TER	760		24	
...	ENDMDL				



- At the moment

- Direct damages in a dinucleosome using X-ray irradiator

$$\text{SSB} = 85 \pm 1 \text{ /Gy/Gbp}$$

$$\text{DSB} = 3 \pm 1 \text{ /Gy/Gbp}$$

- To do

- Expand the nucleosome geometry

- Include indirect damages

- Geant4 advanced example to be provided

in the next release (december 2014)

# PERSPECTIVES

- Production of biological data for radioresistant cells
  - Using or not Gd nanoparticles
  - Morphology of spheroids, survival rates, production of foci
- Develop tools / methodology for a multi-scale modeling
  - Simulation of realistic Gd distribution
  - Calculation of direct DNA damages
  - Tools provided to the scientific community via the Geant4-DNA collaboration
- Correlation of experiments with simulations