# Combining Carbon-ions radiotherapy and Boron Neutron Capture Therapy

## in vitro and in silico preliminary studies

Alessandro Somenzi

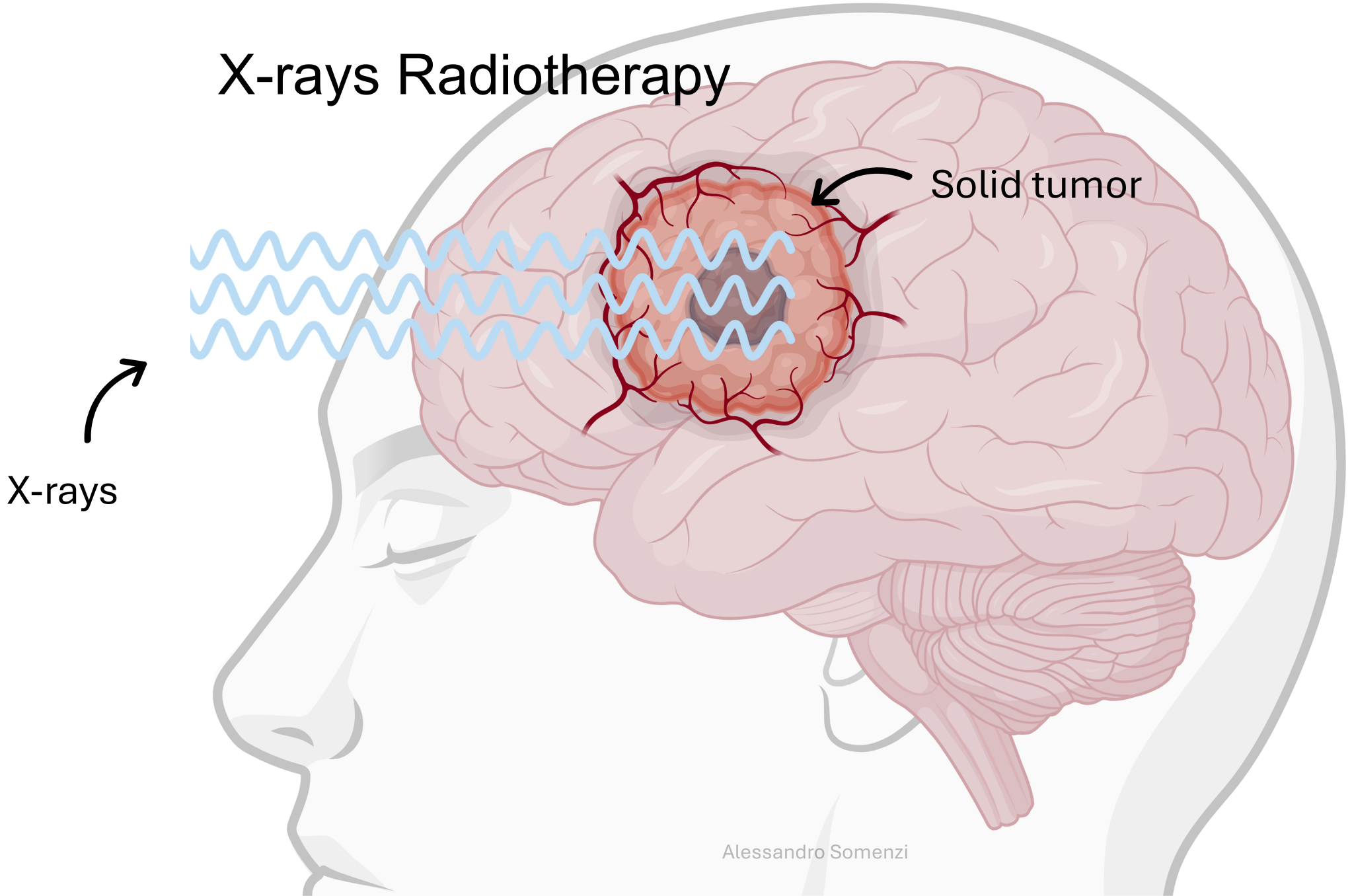
IRSN becomes ASNR Autorité de sûreté nucléaire et de radioprotection

UNIVERSITÀ DI PAVIA

CNAO Centro Nazionale di Adroterapia Oncologica

L.E.N.A.

# X-rays Radiotherapy

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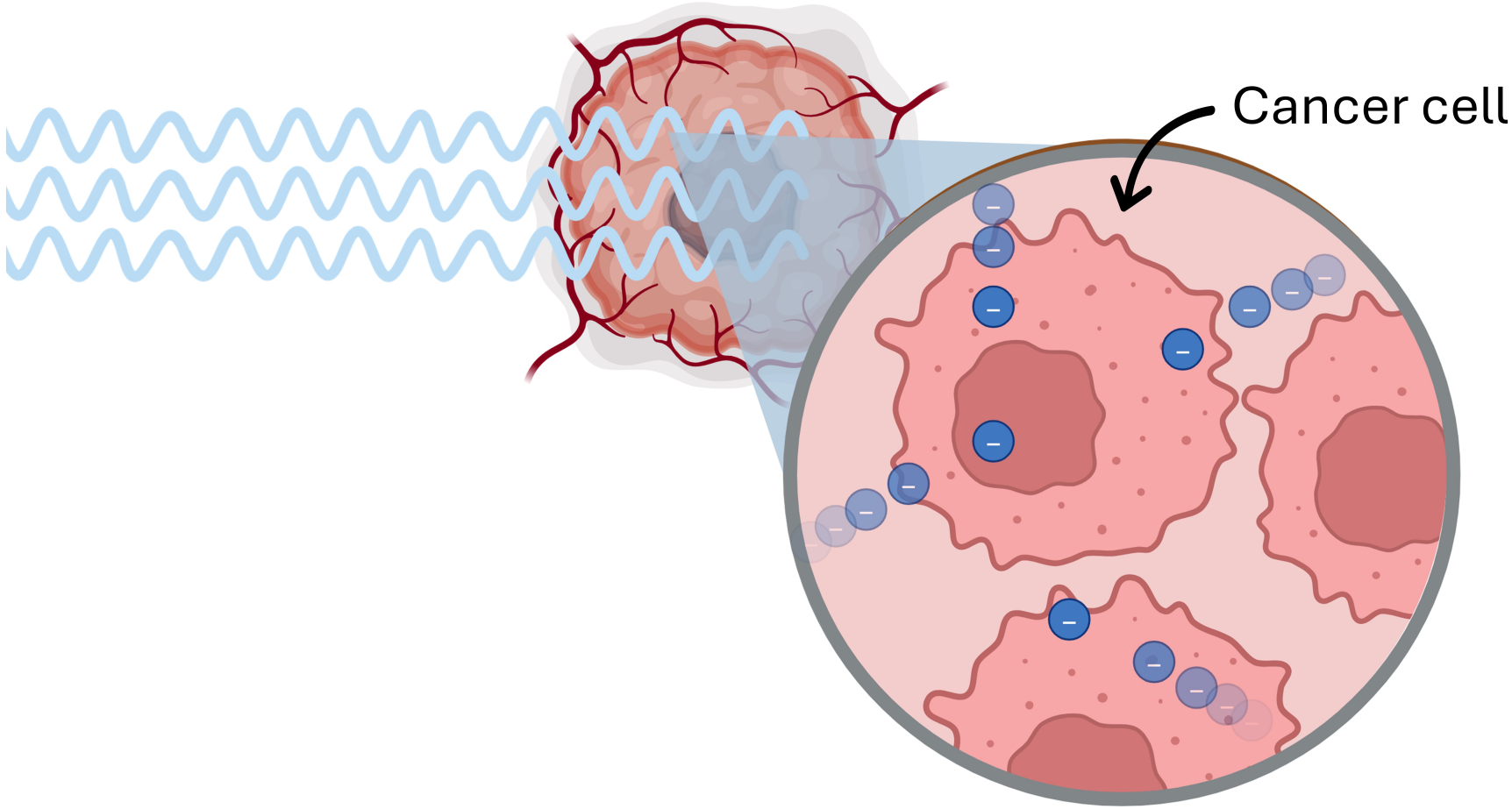

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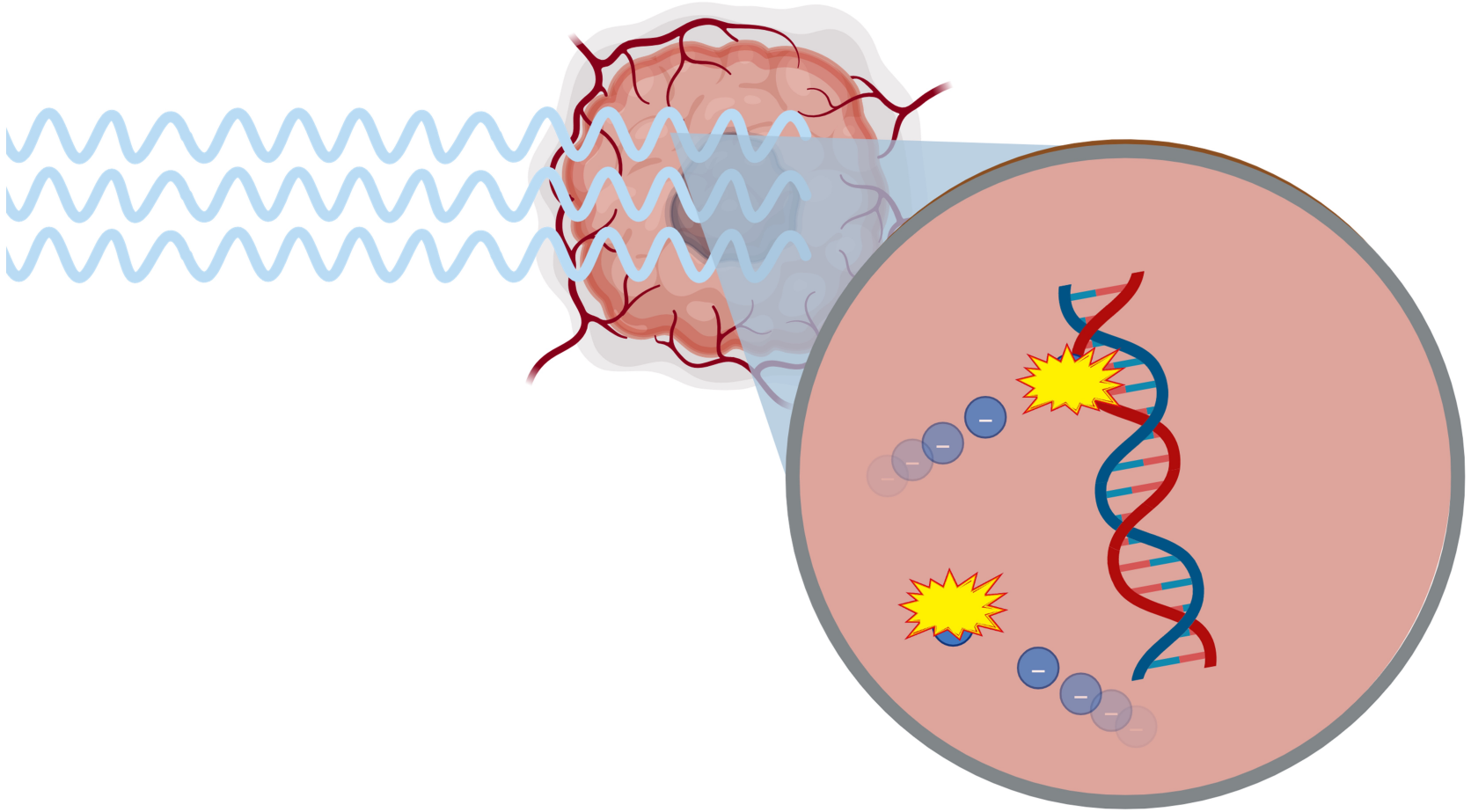

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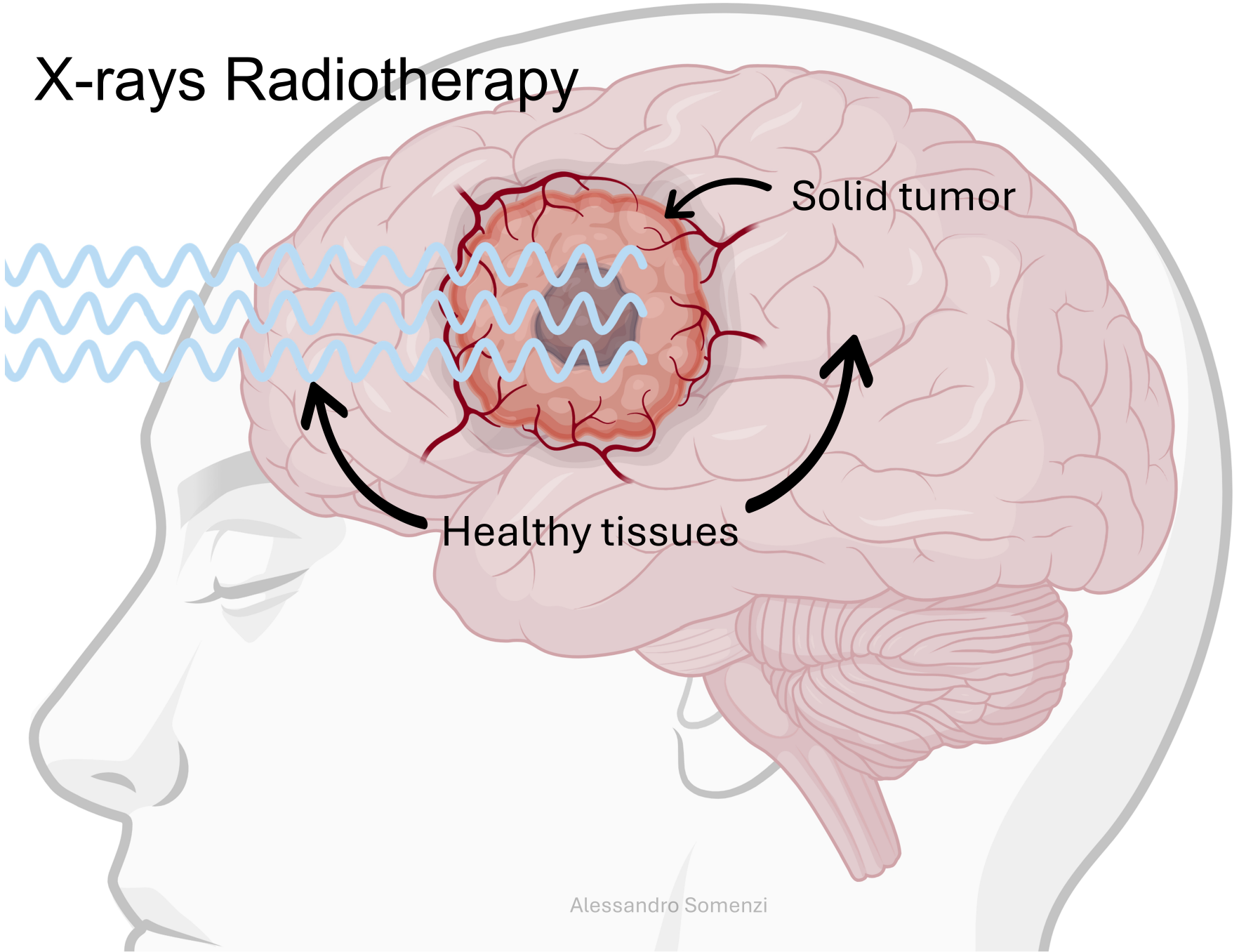


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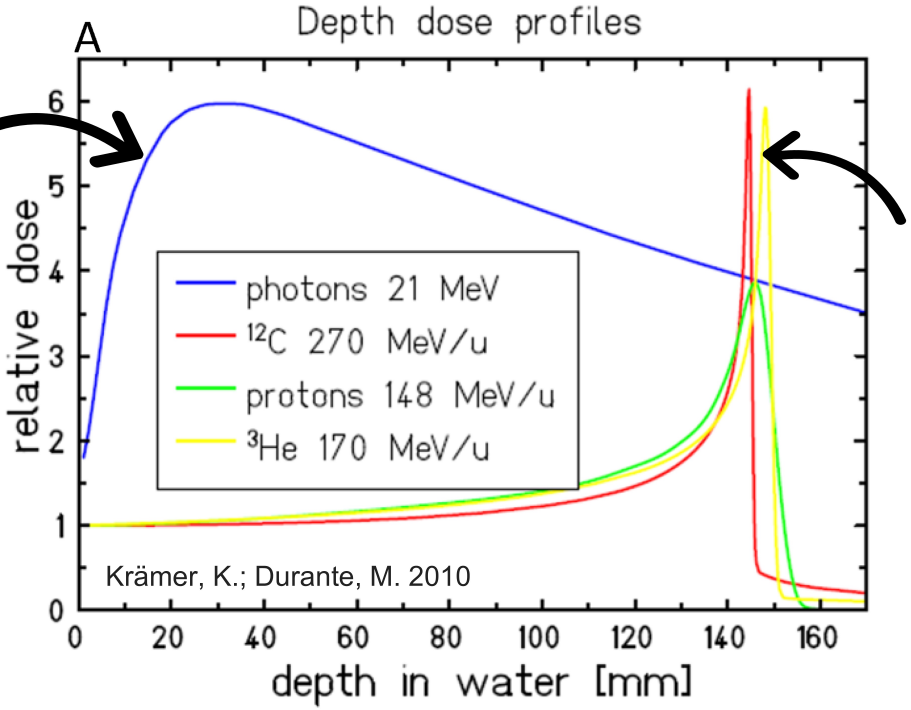


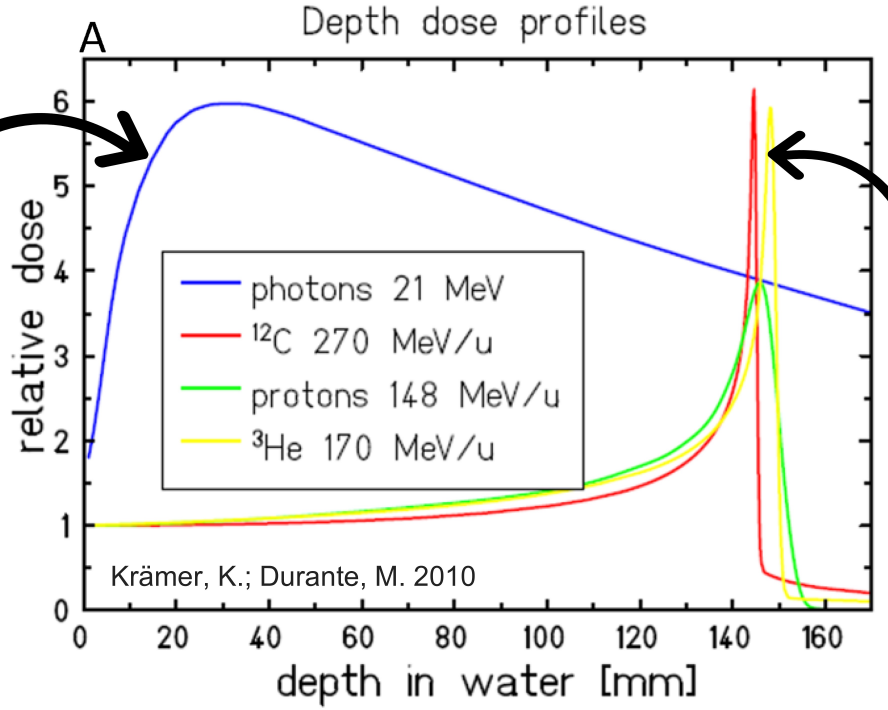

Photons

C-ions

Higher **precision** than X-rays

# Carbon-ions Radiotherapy

Photons

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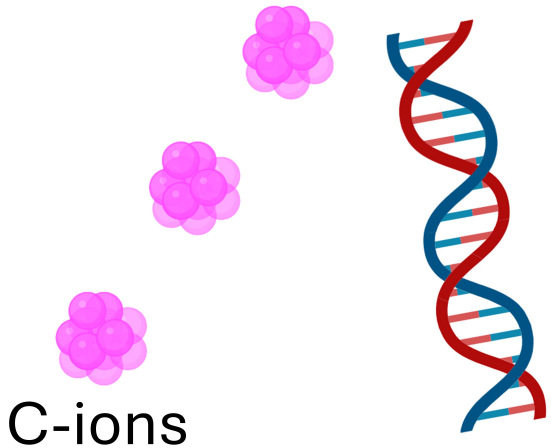
C-ions



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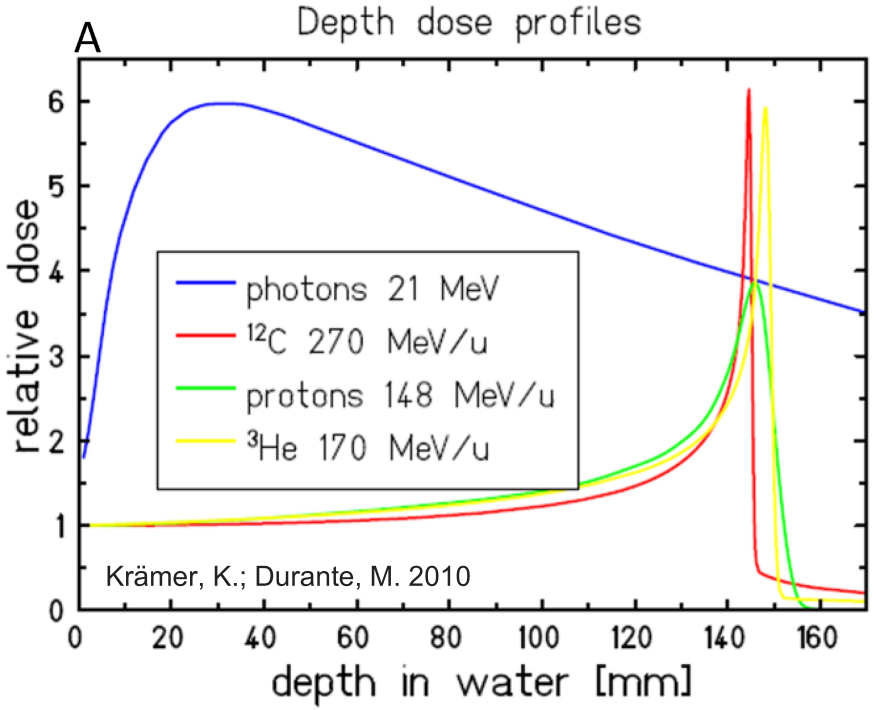
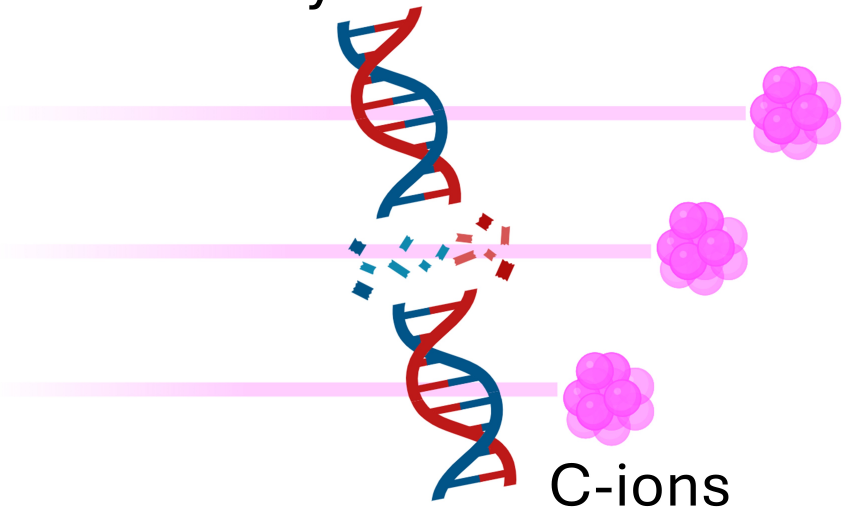
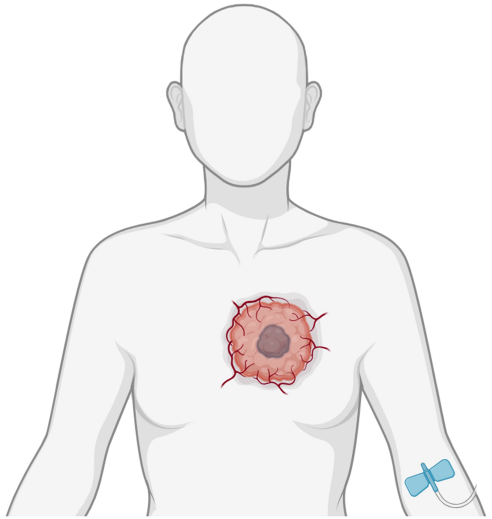



Higher **precision** than X-rays

Higher **biological effectiveness** than X-rays



# Boron Neutron Capture Therapy (BNCT)



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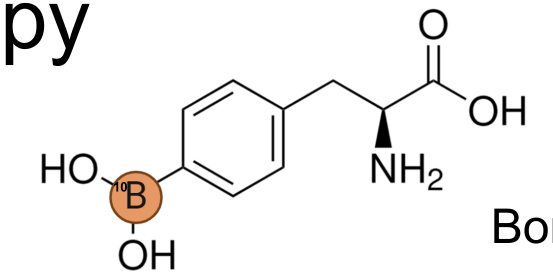
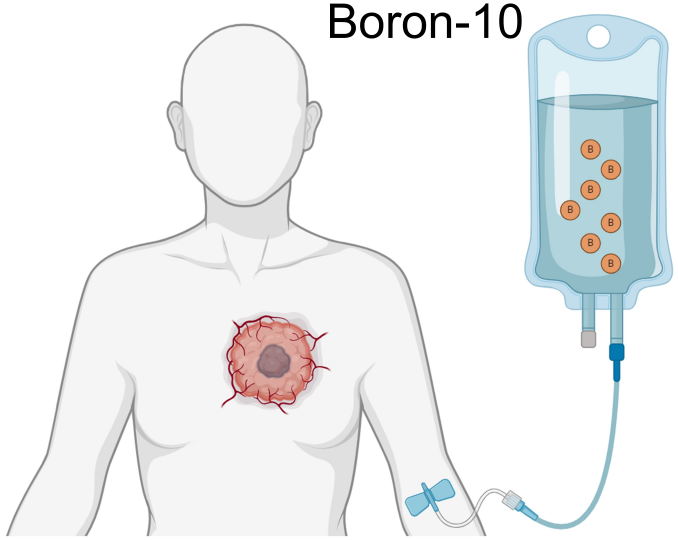



Boronated drug

Boron-10



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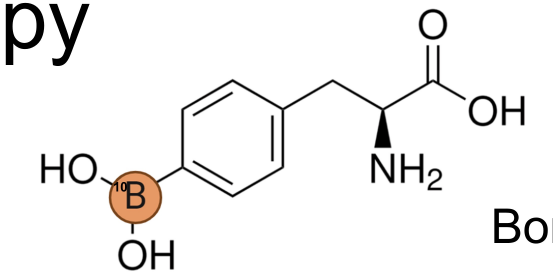


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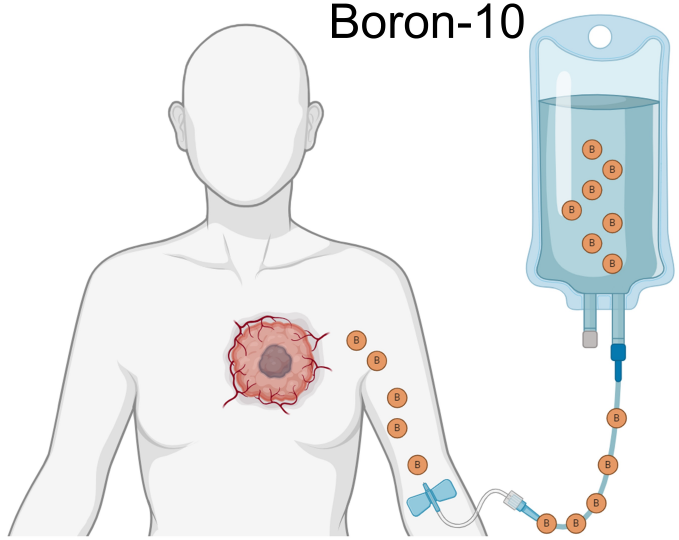

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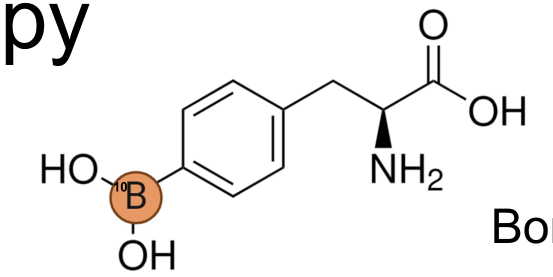


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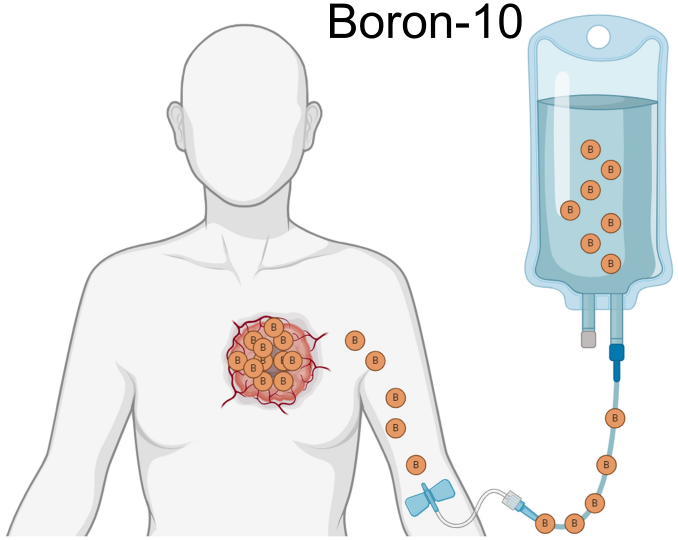

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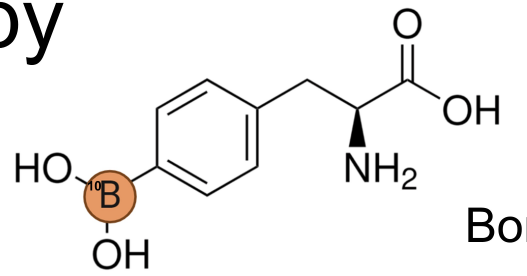


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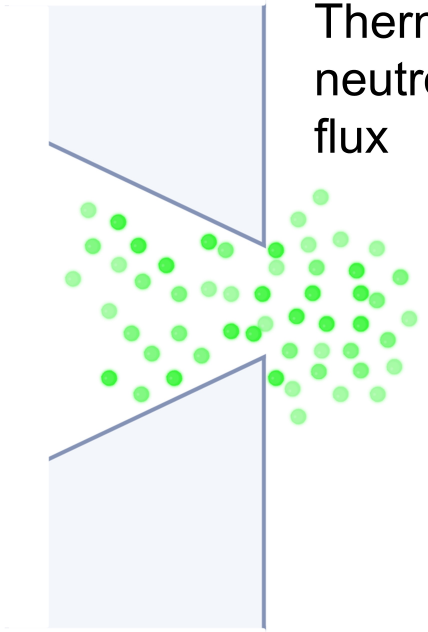
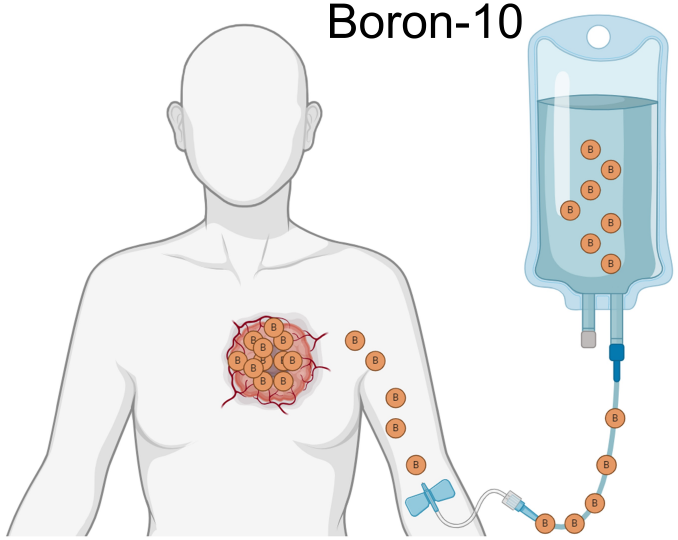


Thermal neutron flux



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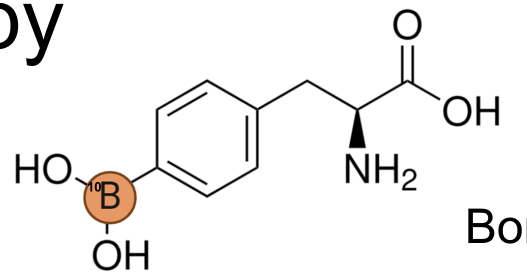
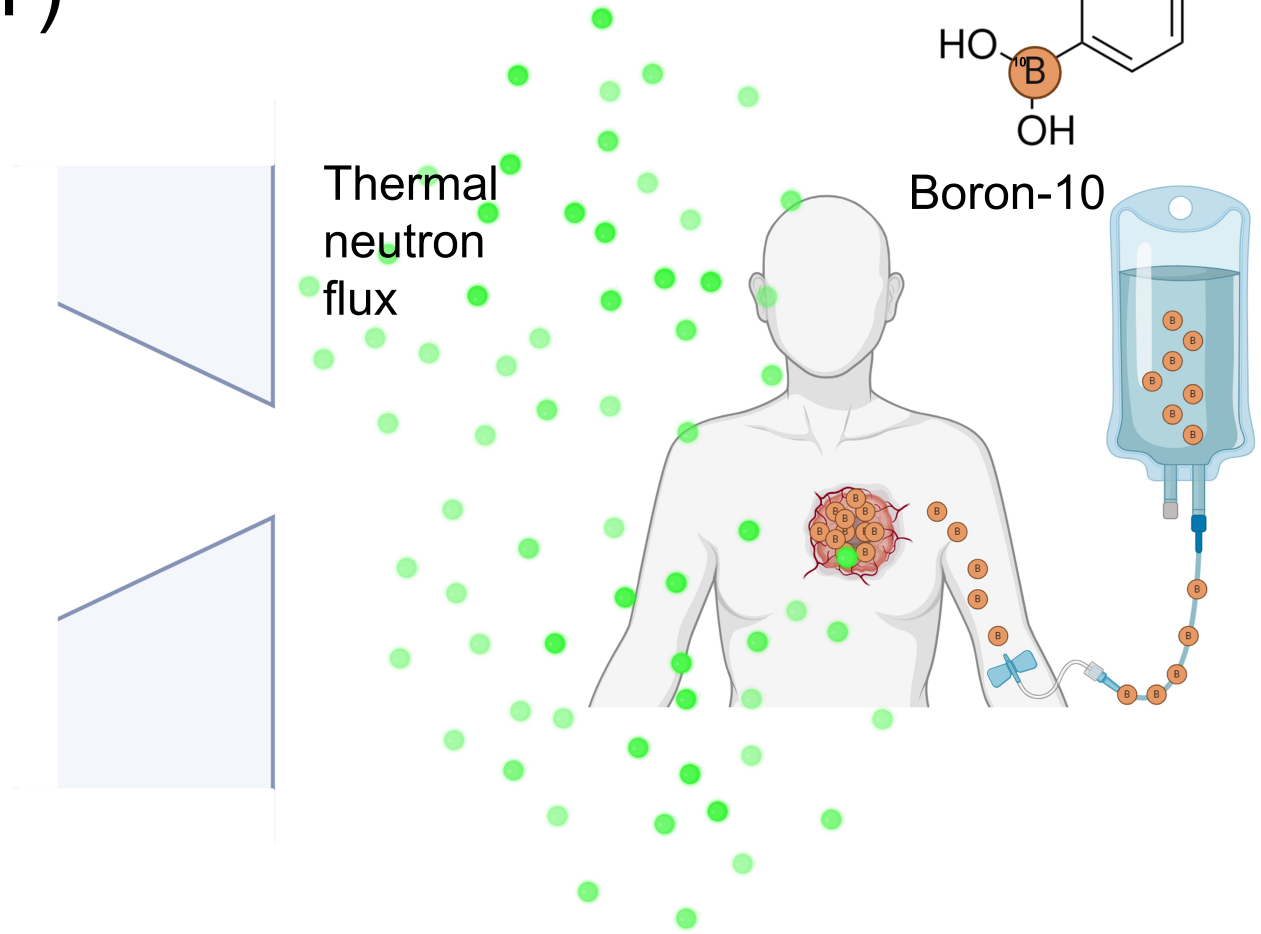



Boronated drug



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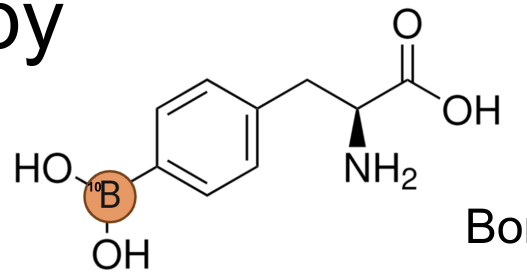


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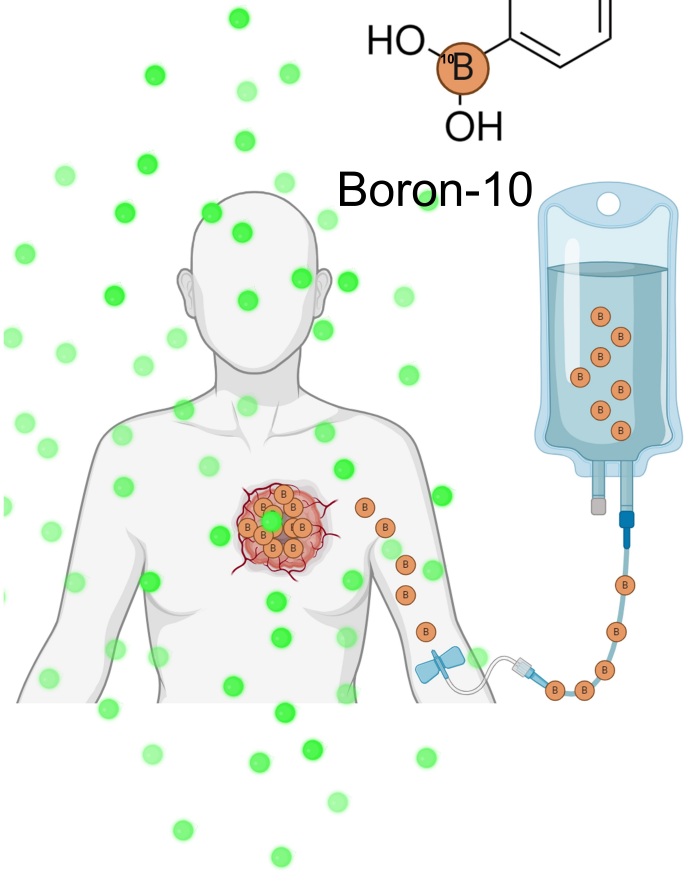

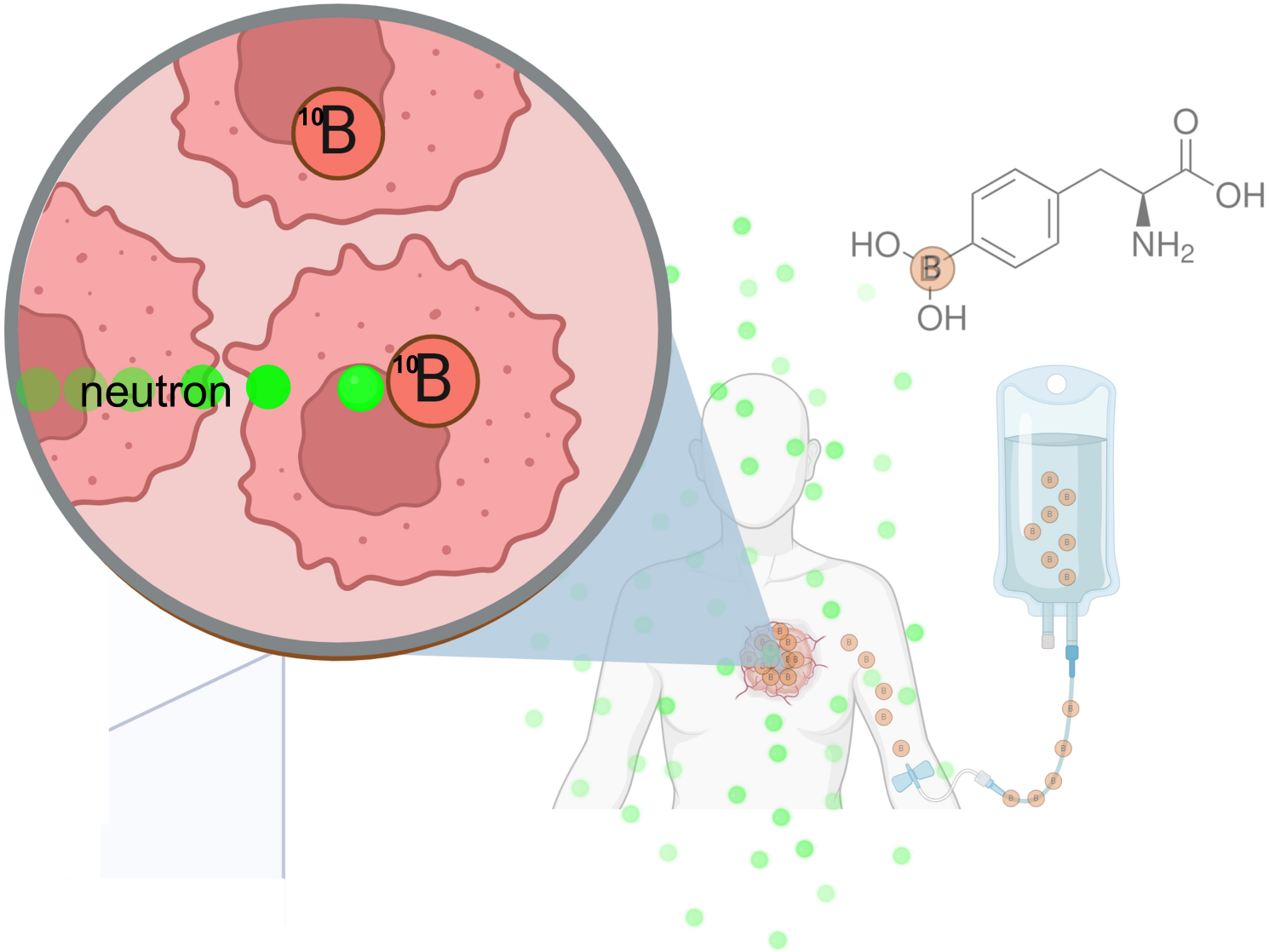


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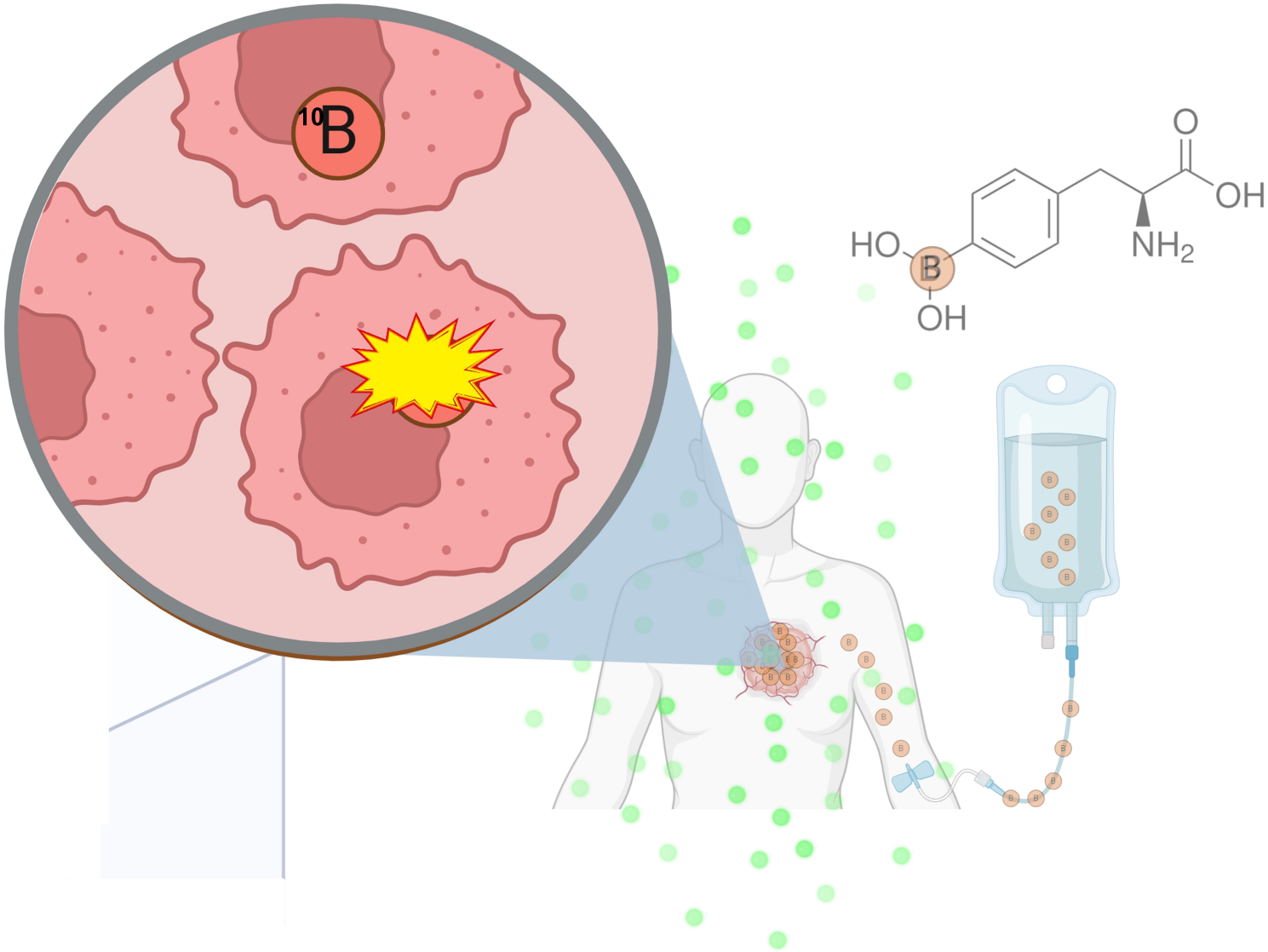


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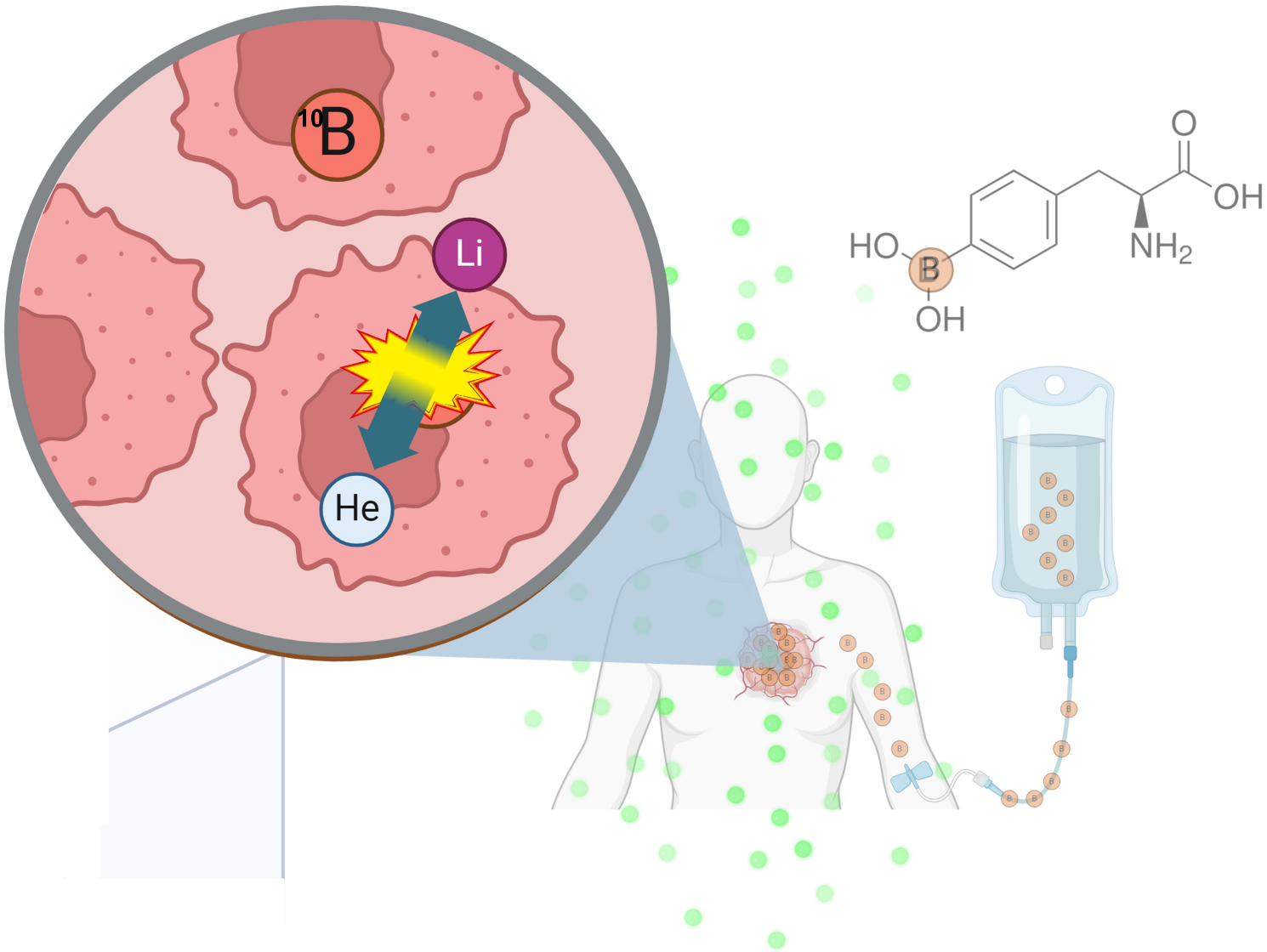


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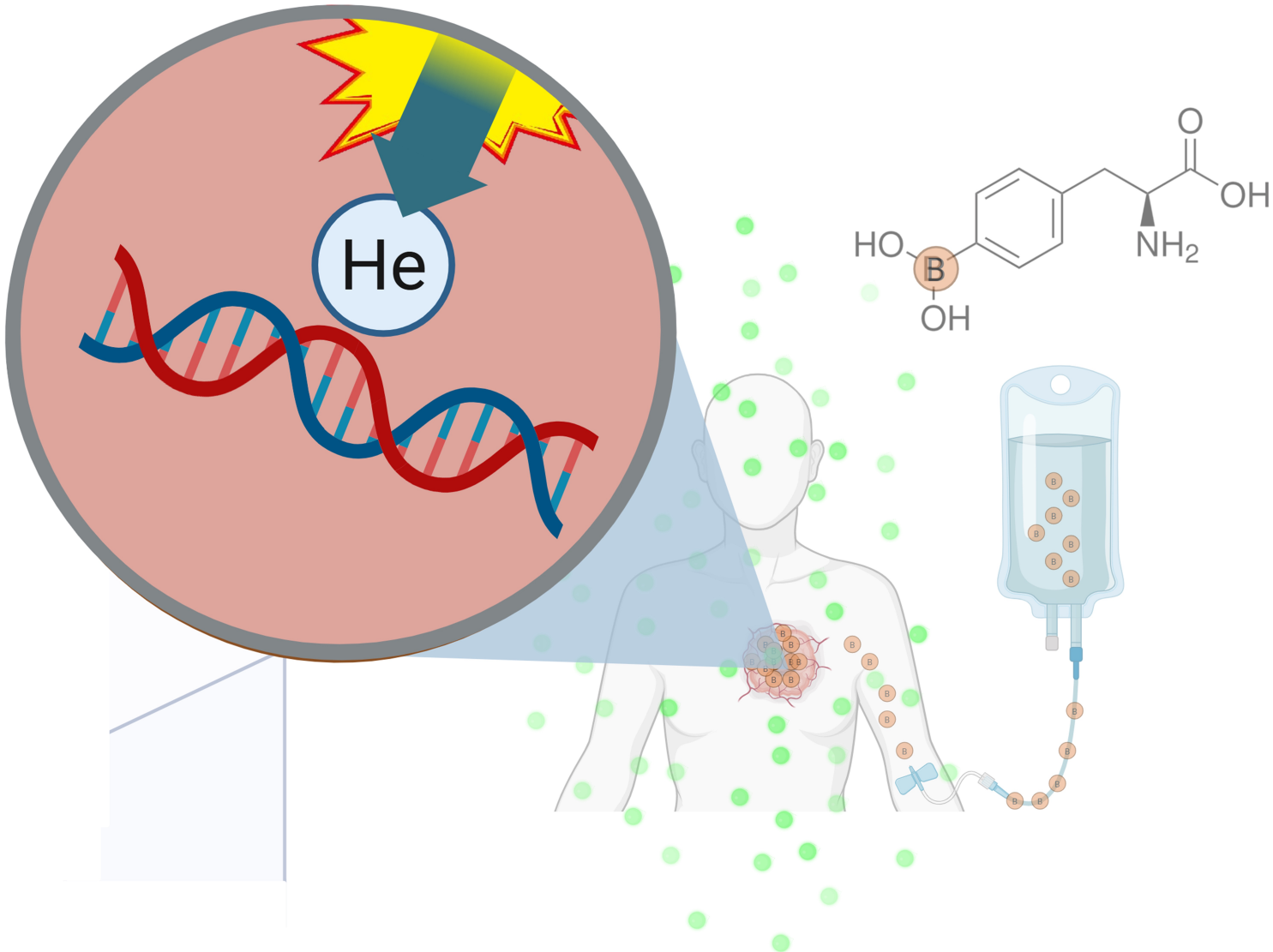


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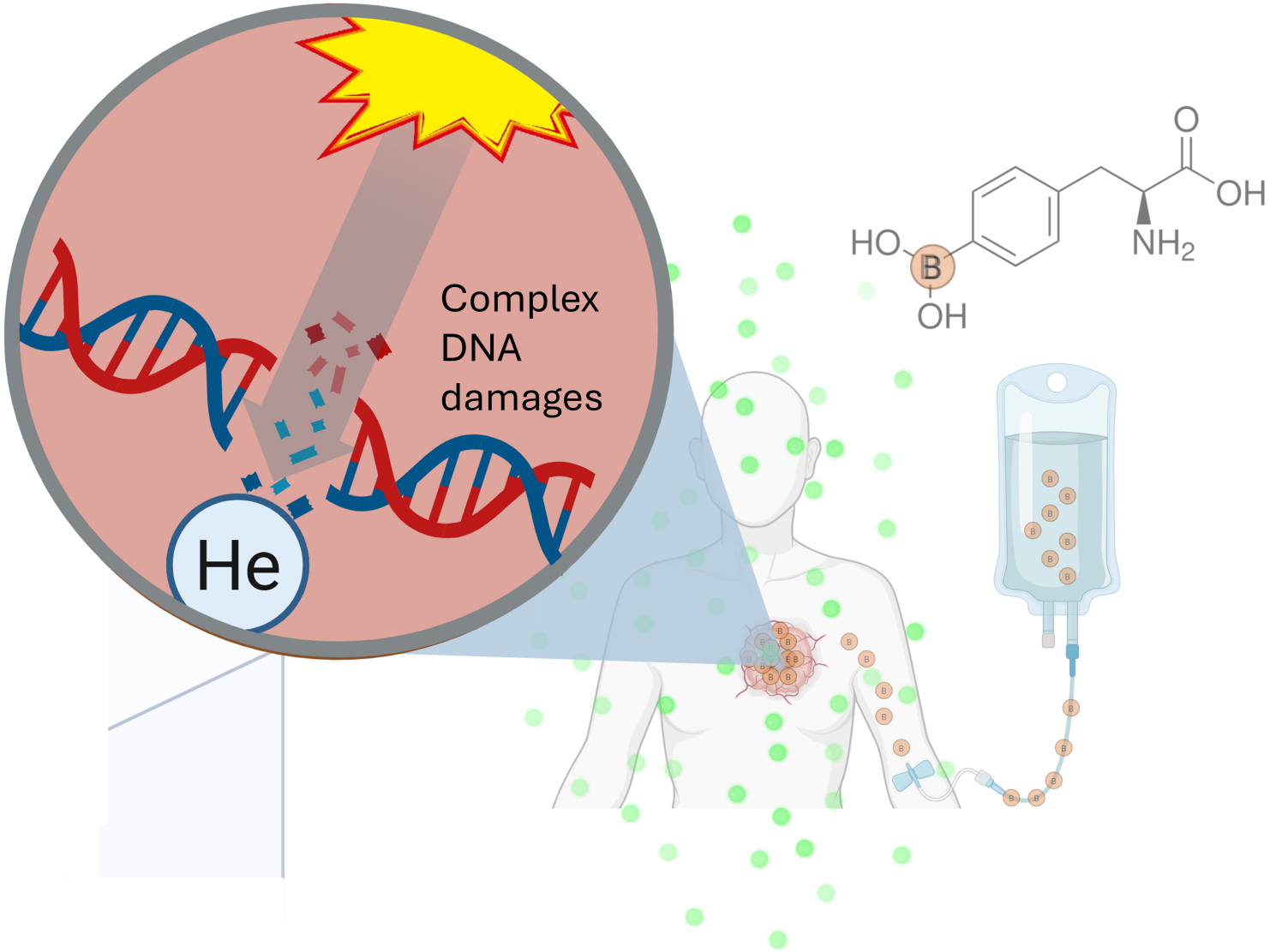
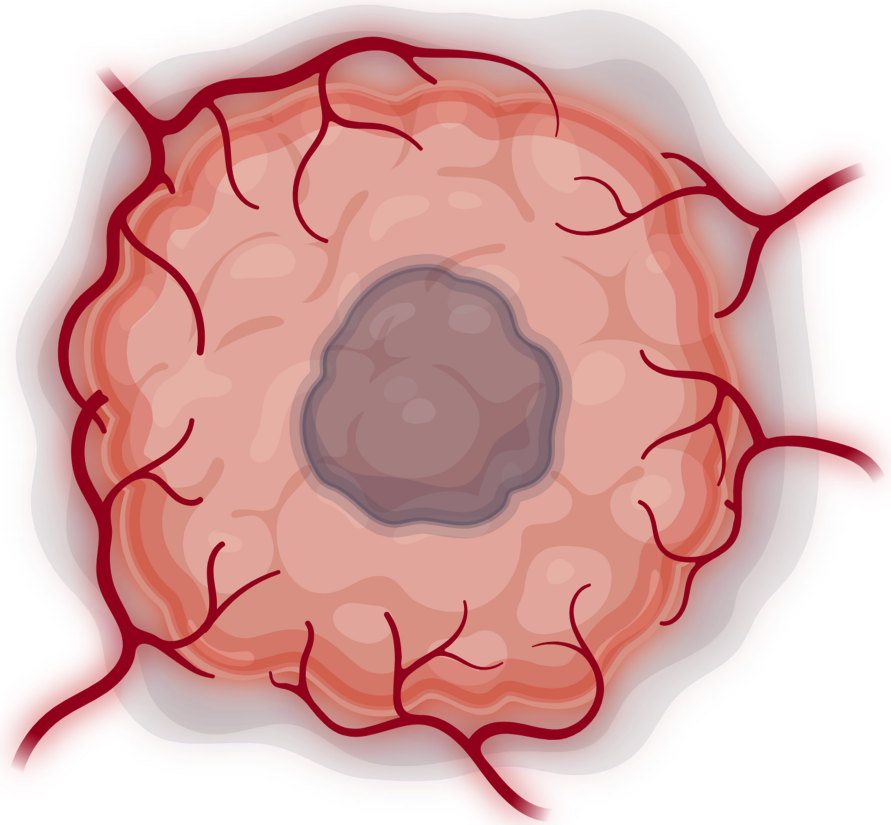
Higher **biological effectiveness** than X-rays



# Why should we combine them?



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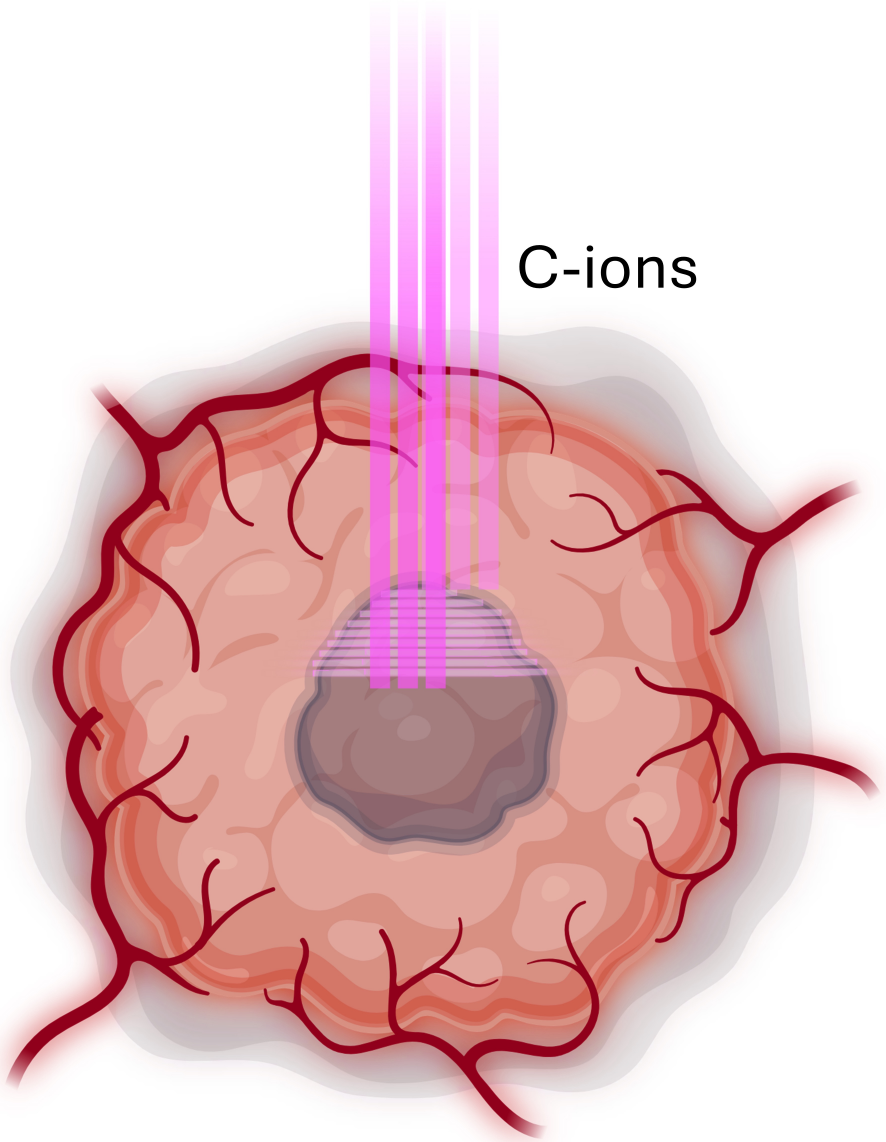
Inner region:
Sleeping cancer cells



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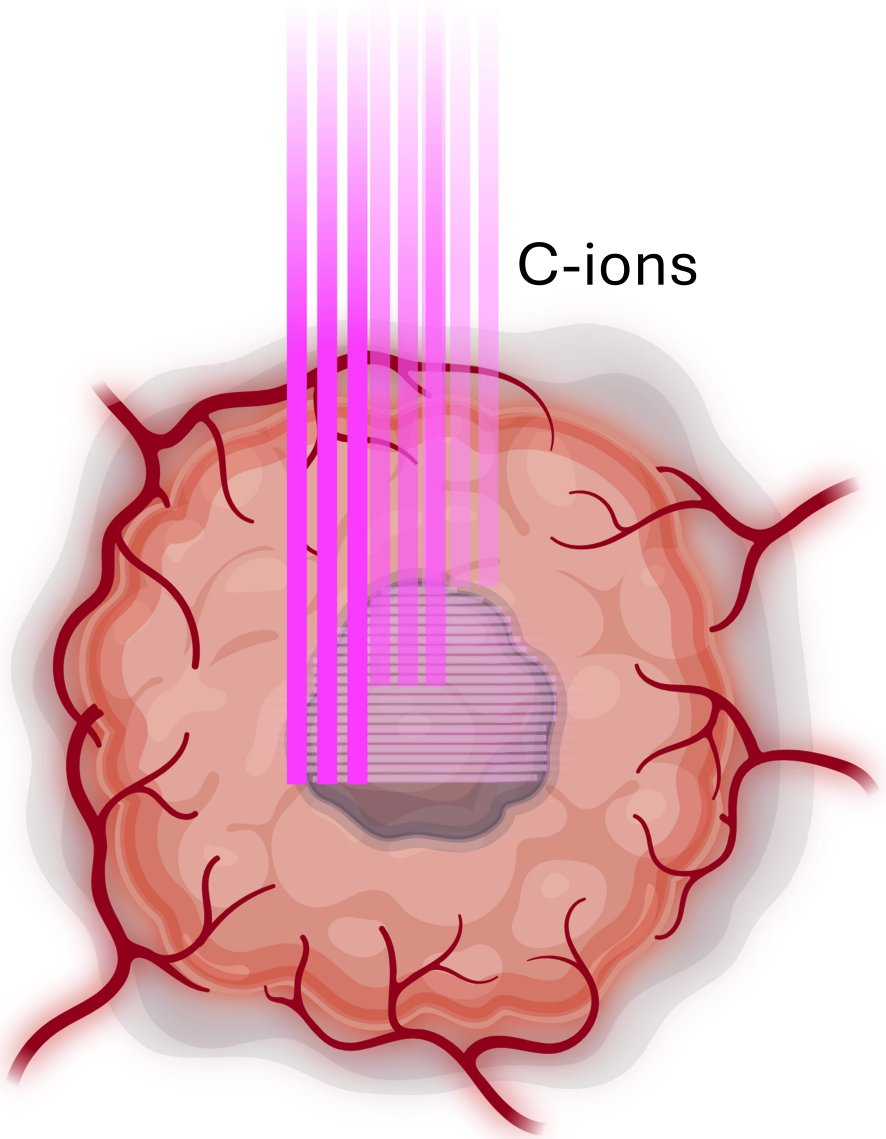

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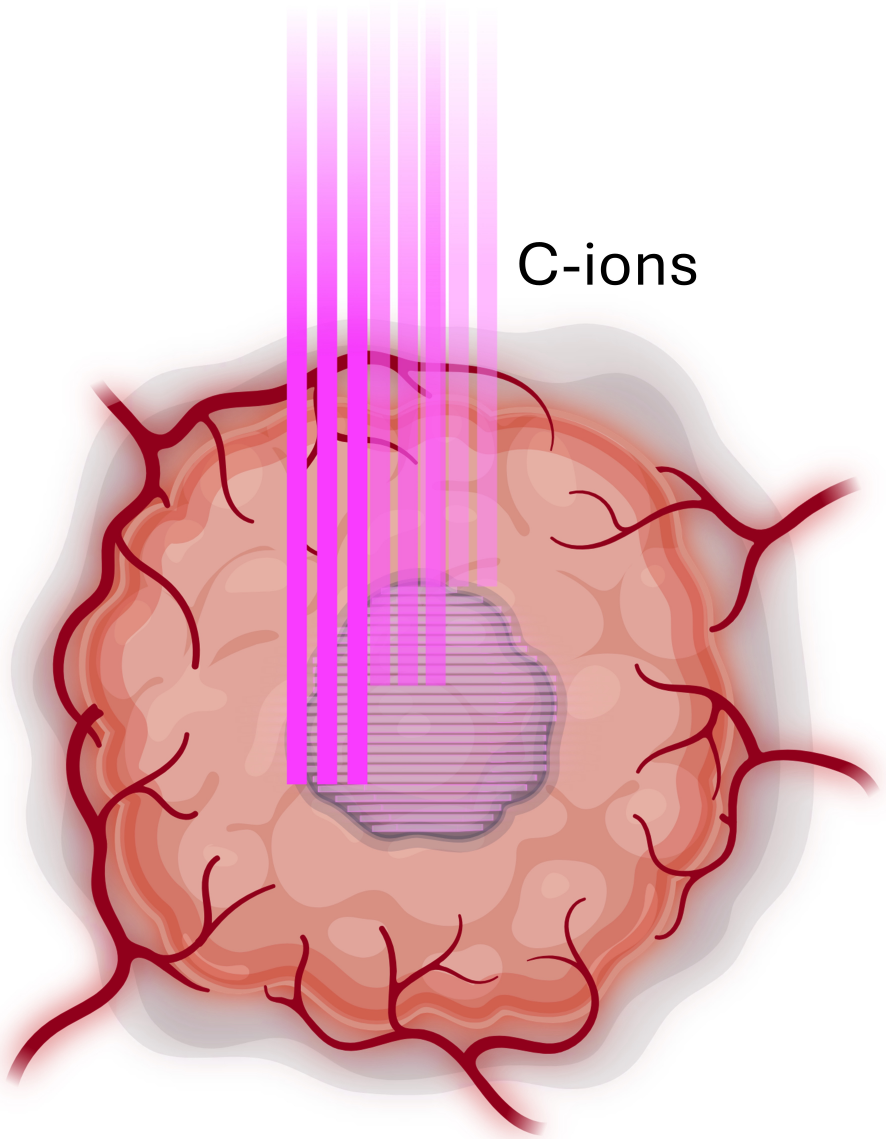

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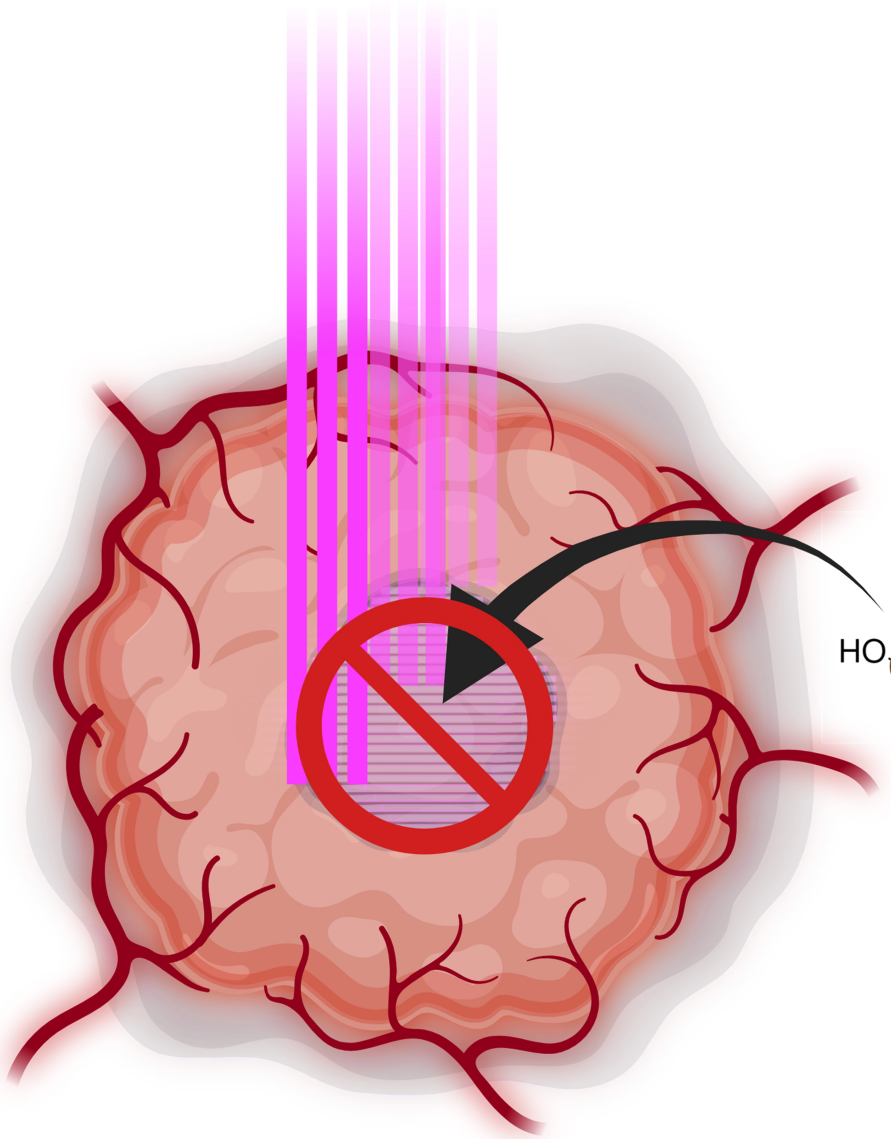
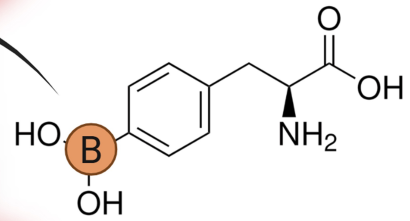
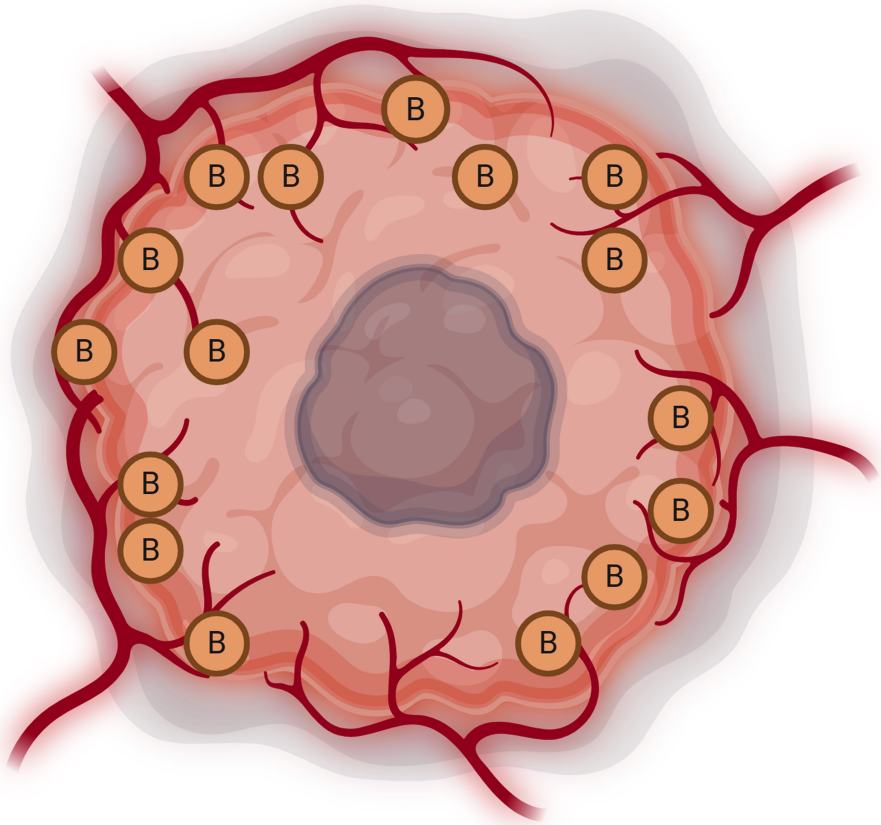




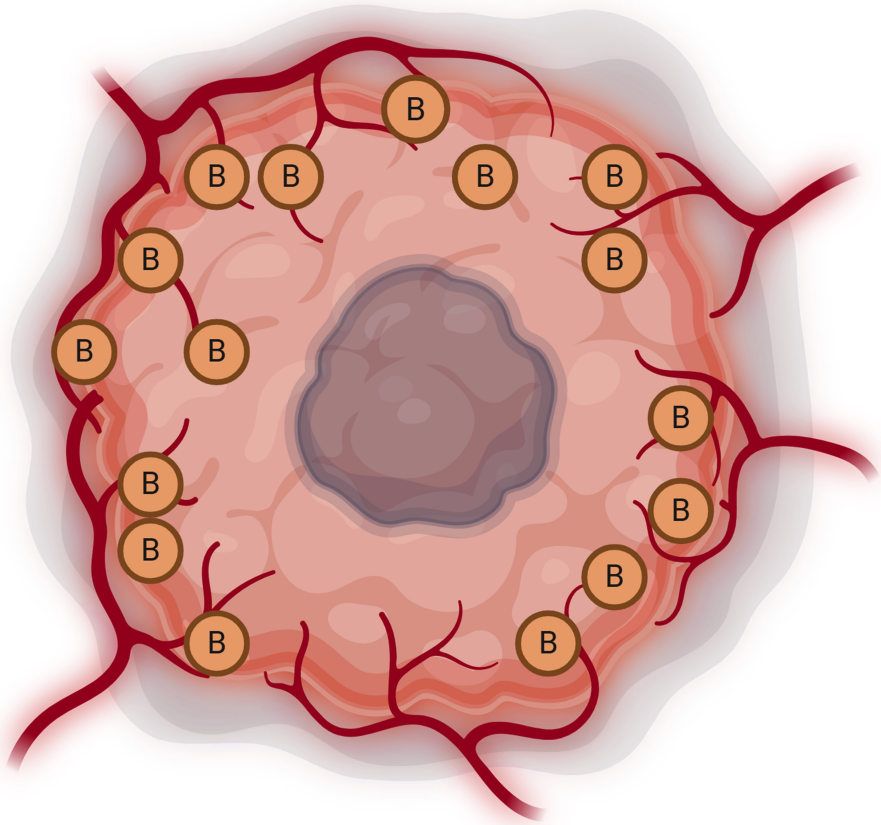

Boronated drugs need more active cells




External region: more vascularized and active cancer cells

Perfect for BNCT!

Thermal neutrons

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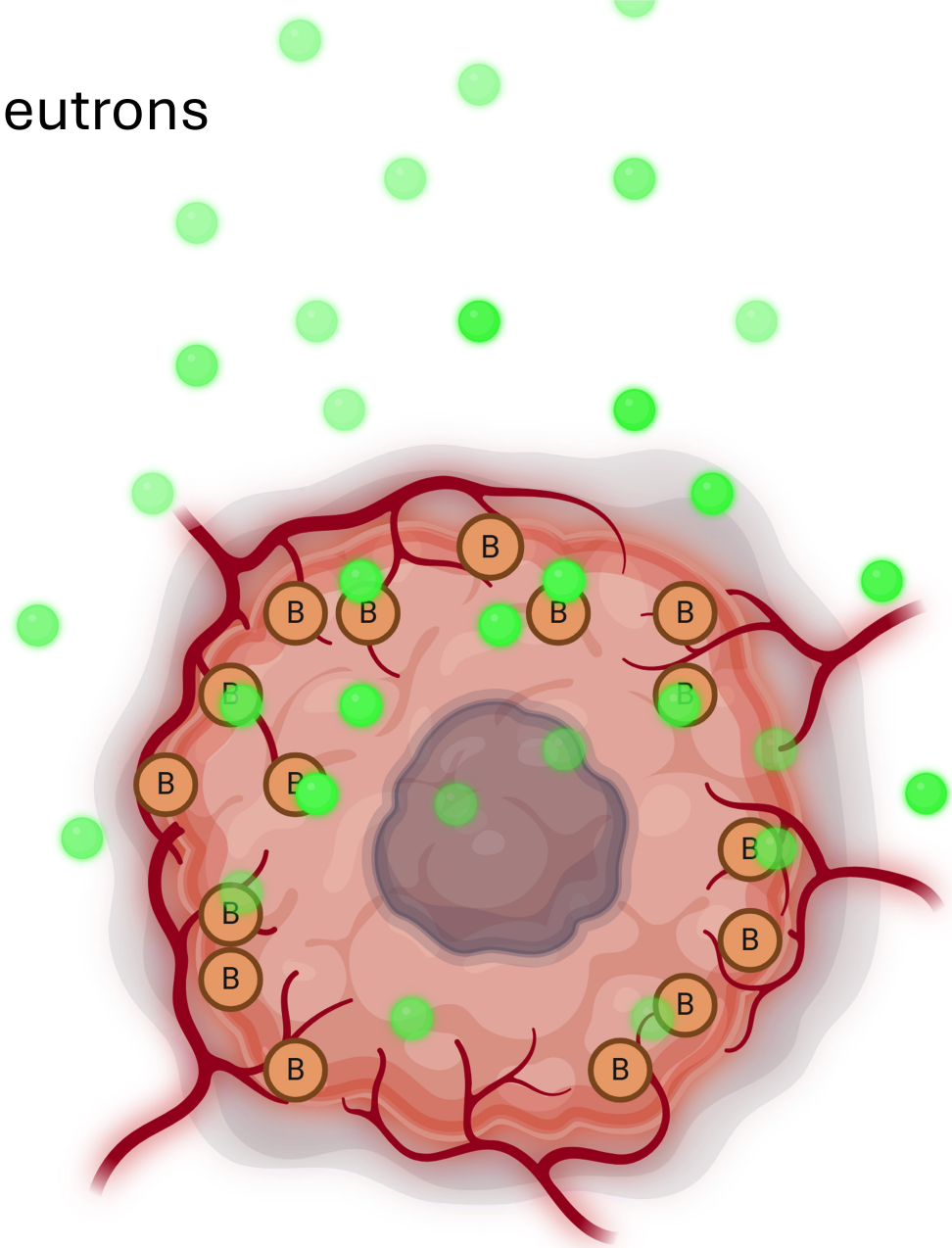


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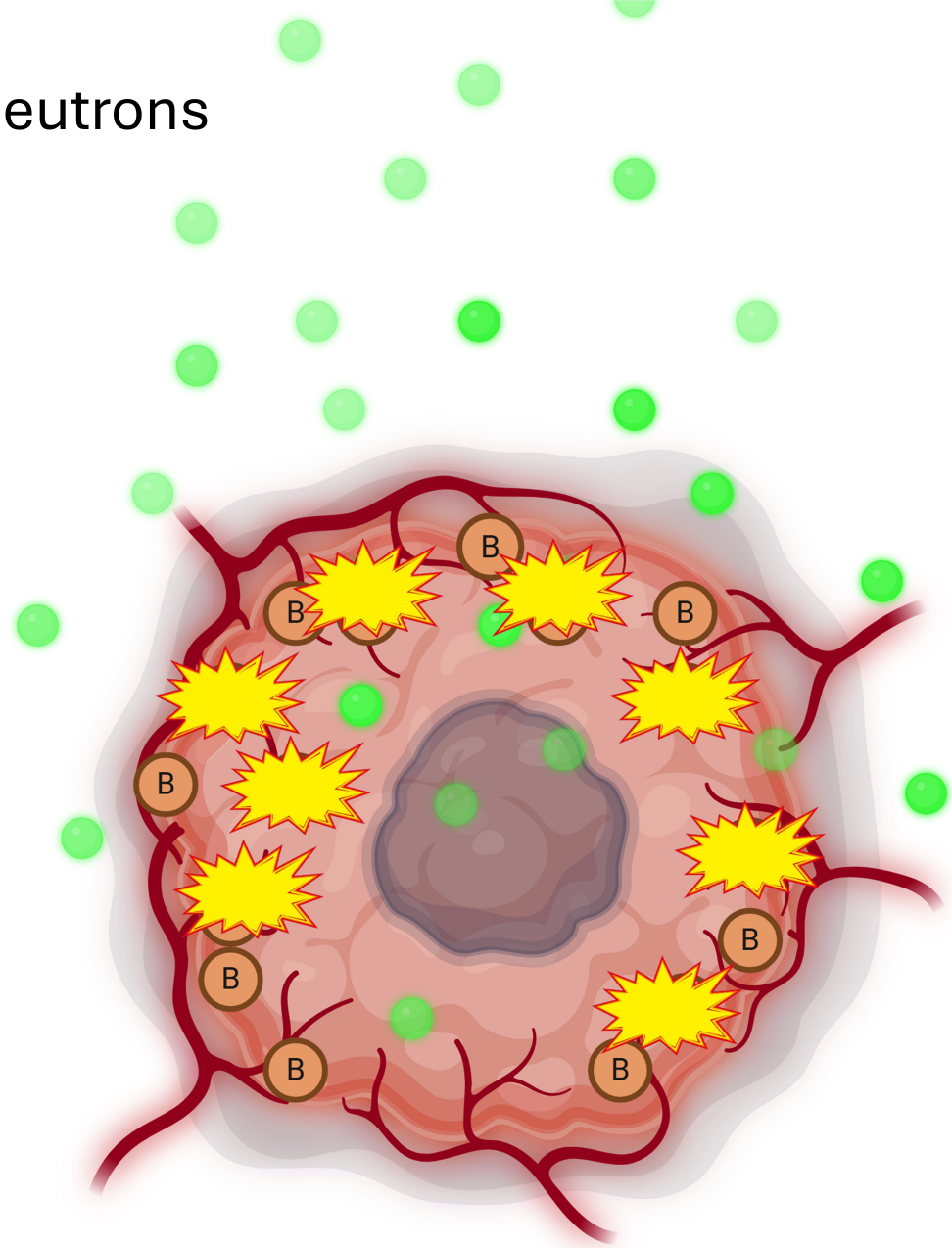


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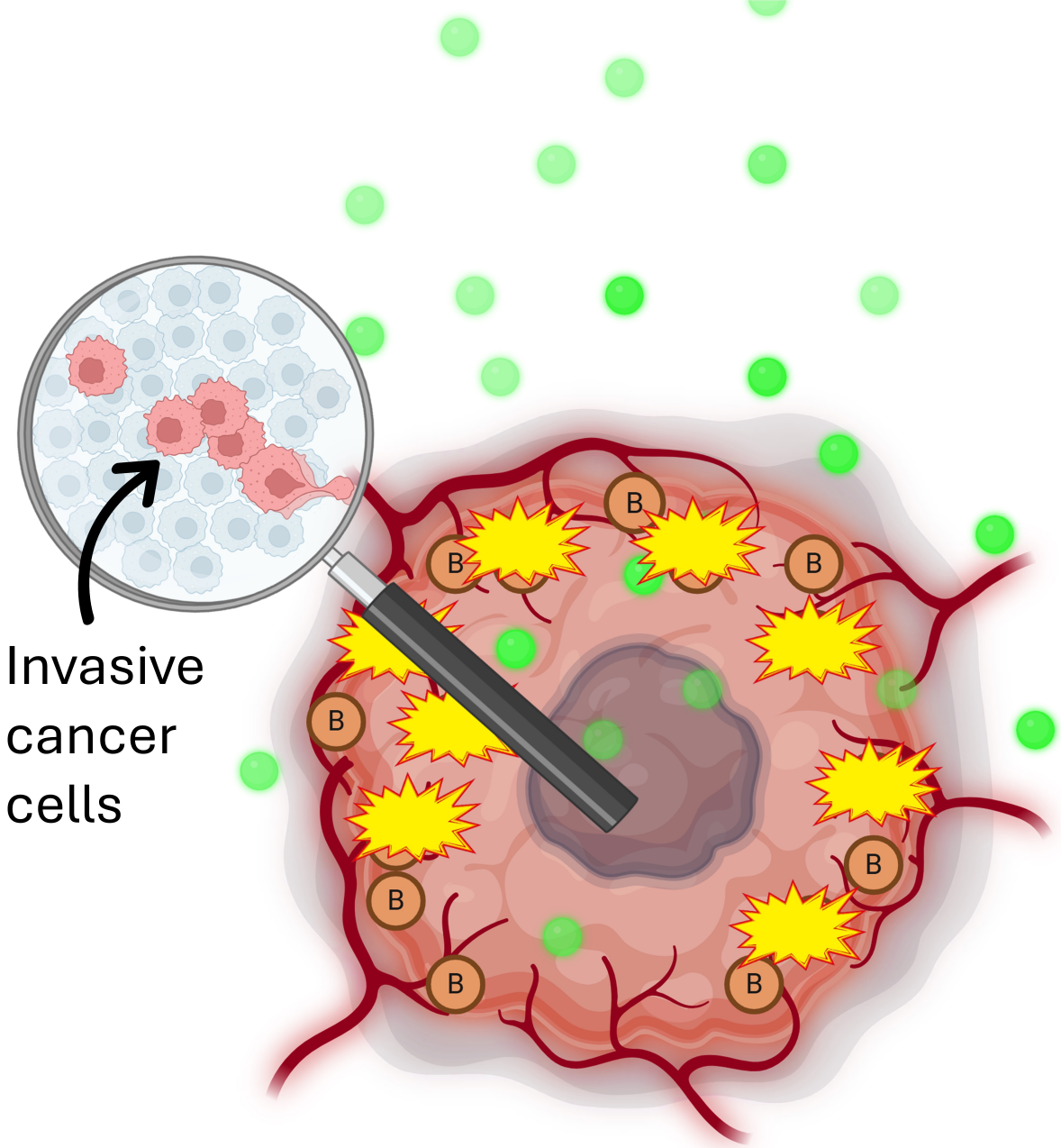


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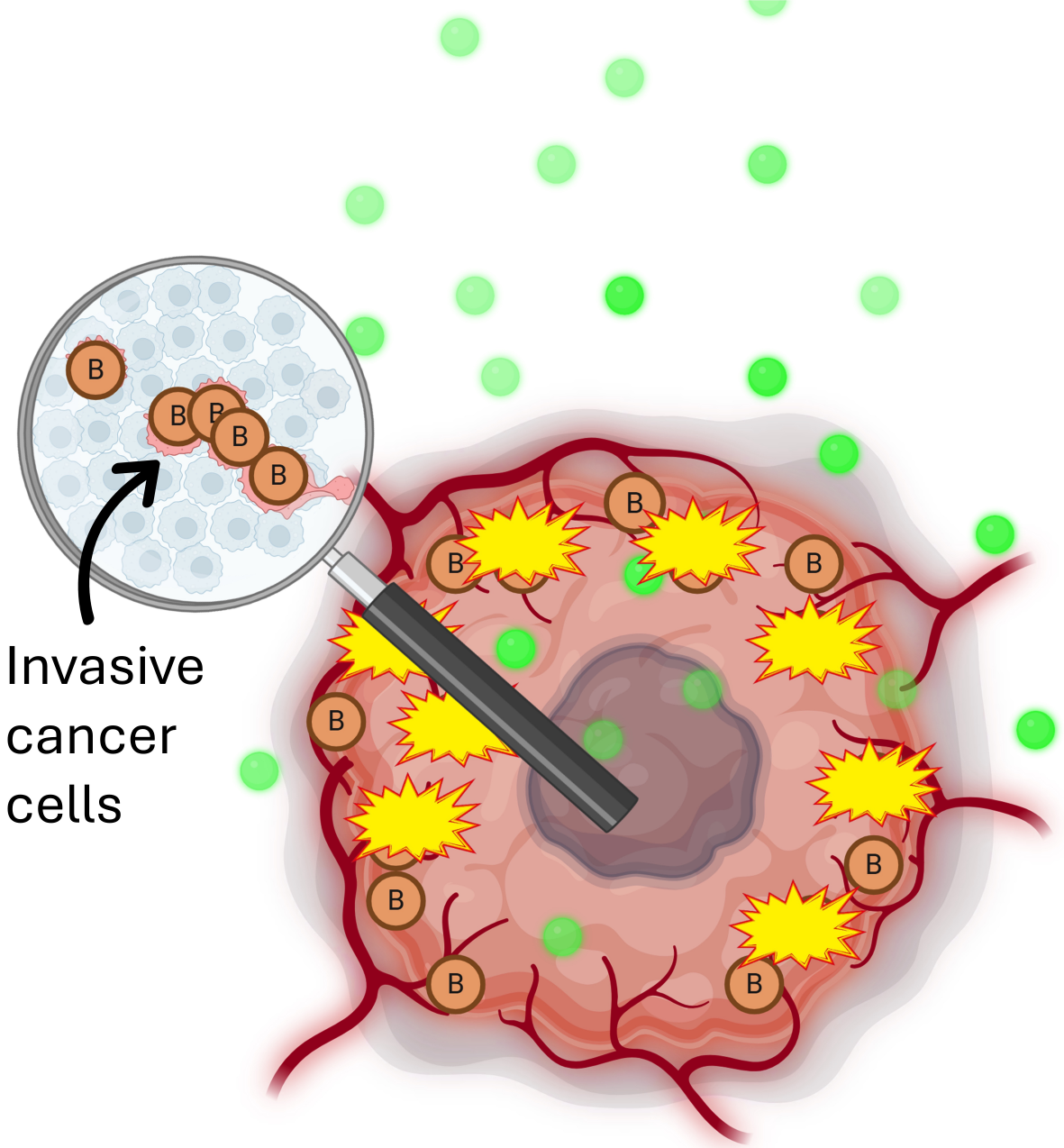


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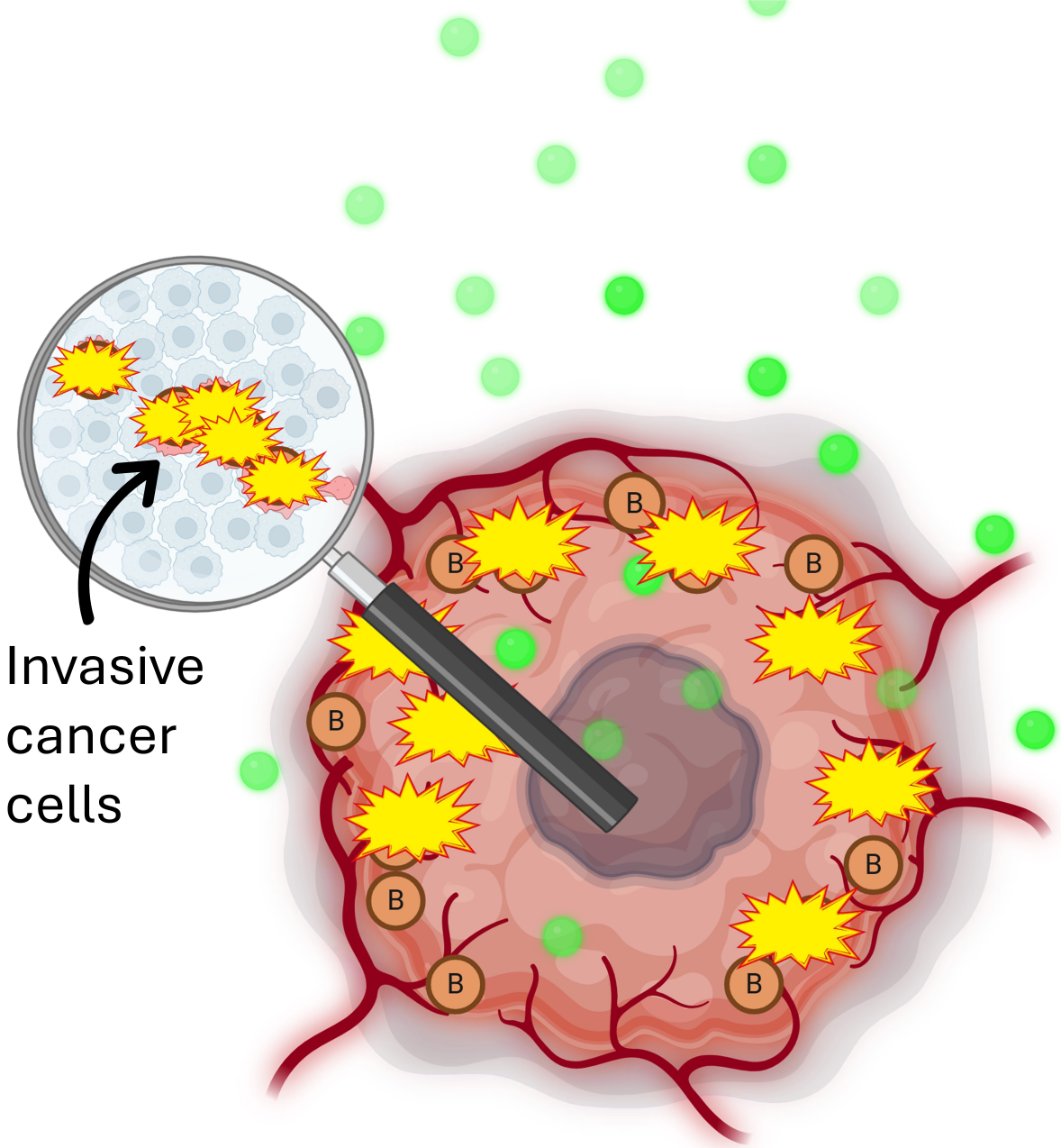


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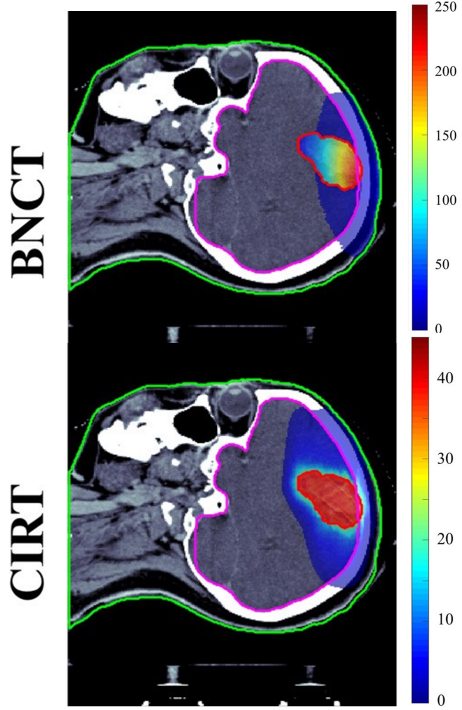


Physics in Medicine & Biology

IPEM
Institute of Physics and Engineering in Medicine

PAPER

# Combined BNCT-CIRT treatment planning for glioblastoma using the effect-based optimization

Yang Han[1,2], Changran Geng[1,*], Saverio Altieri[2,3], Silva Bortolussi[2,3], Yuanhao Liu[1,4], Niklas Wahl[5,6] and Xiaobin Tang[1,*]

[1] Department of Nuclear Science and Technology, Nanjing University of Aeronautics and Astronautics, Nanjing, People's Republic of China

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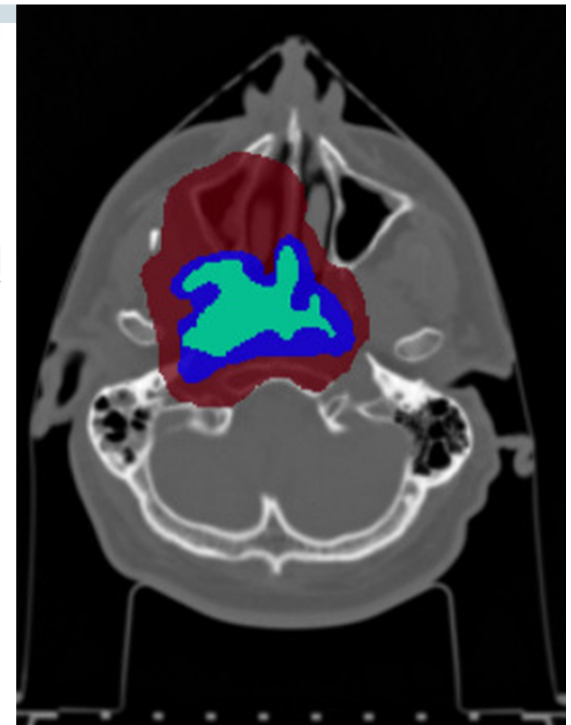
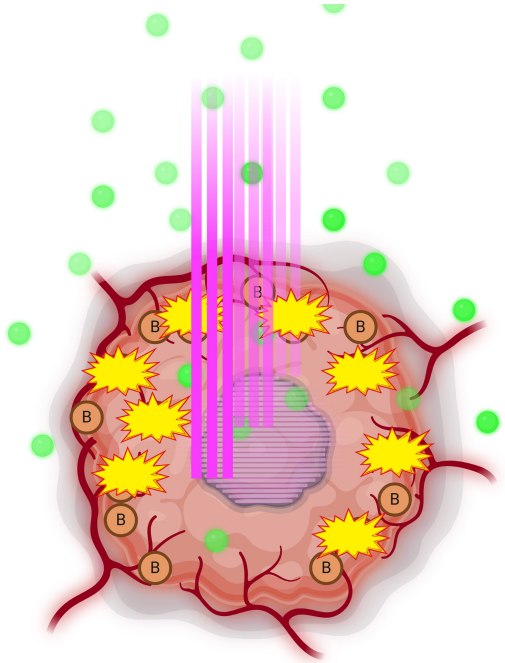


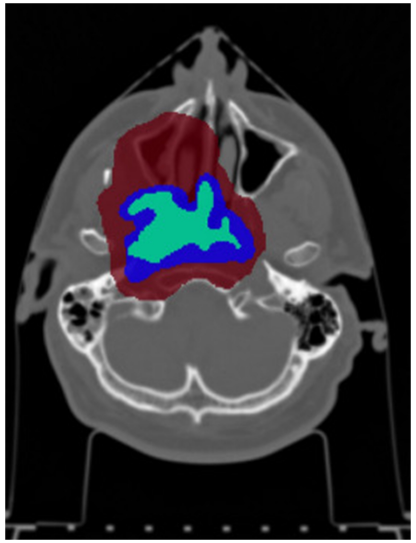
Check for updates

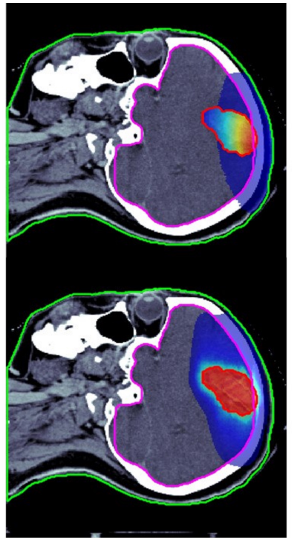
OPEN

# Using the photon isoeffective dose formalism to compare and combine BNCT and CIRT in a head and neck tumour

Ian Postuma[1], Chiara Magni[1,2], Barbara Marcaccio[1,2,3], Setareh Fatemi[1], Valerio Vercesi[1], Mario Ciocca[1,4], Giuseppe Magro[4], Ester Orlandi[4], Barbara Vischioni[4], Sara Ronchi[4], Yuan-Hao Liu[5,6], Yang Han[2,6], Changran Geng[6], Sara Josefina González[3,7,8,9] & Silva Bortolussi[1,2,9]✉





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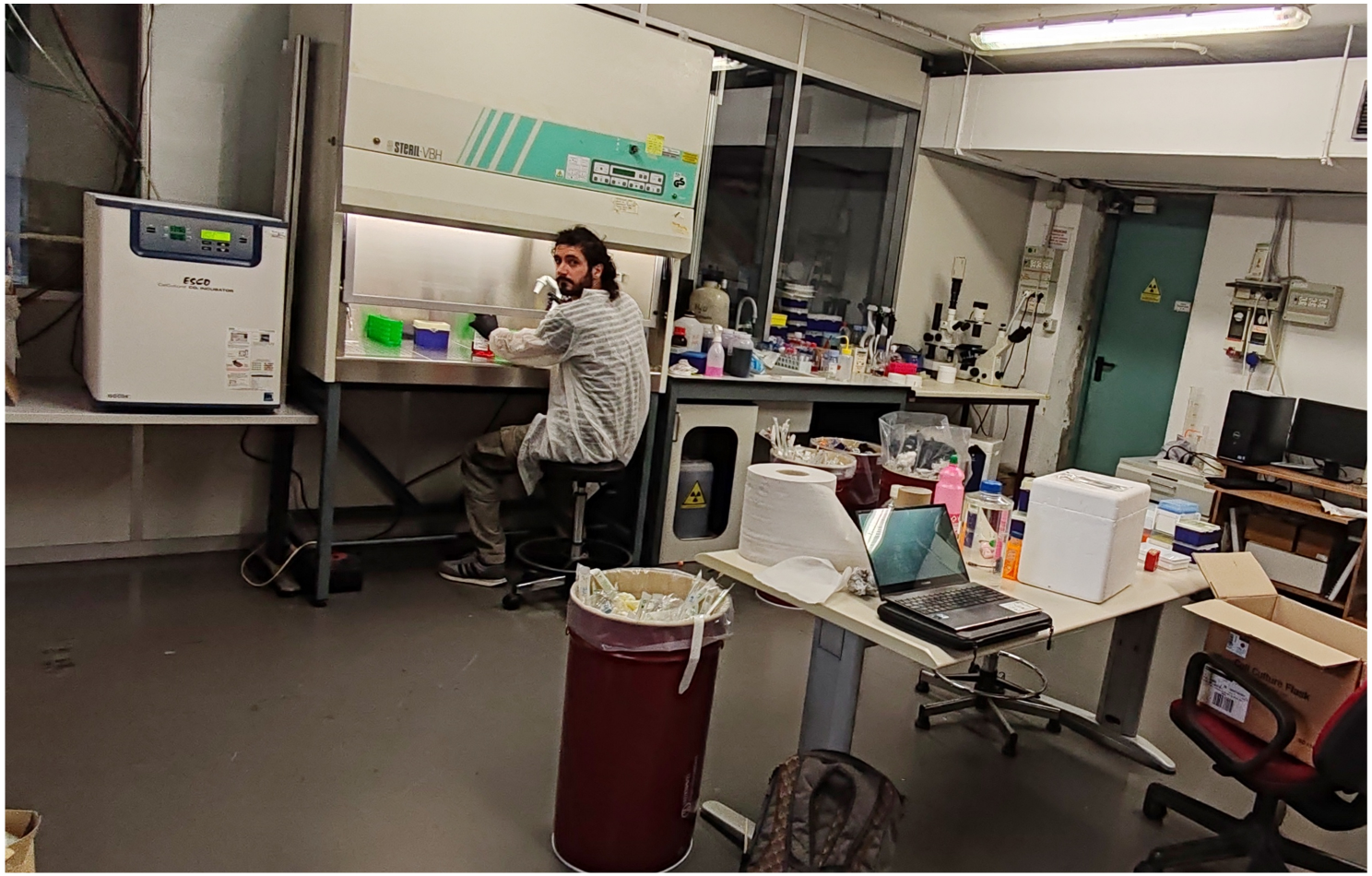
# in vitro



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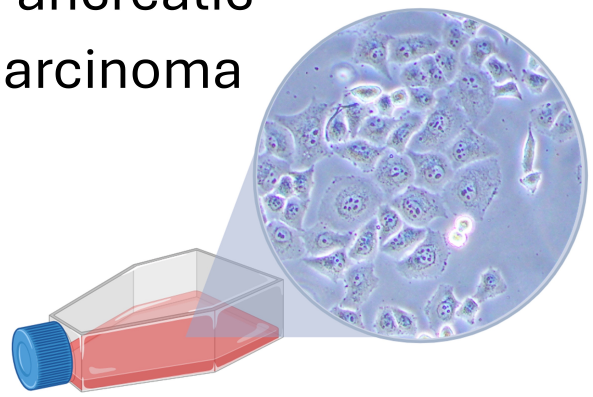
- PANC-1 cell line

  Ductal Pancreatic Adenocarcinoma



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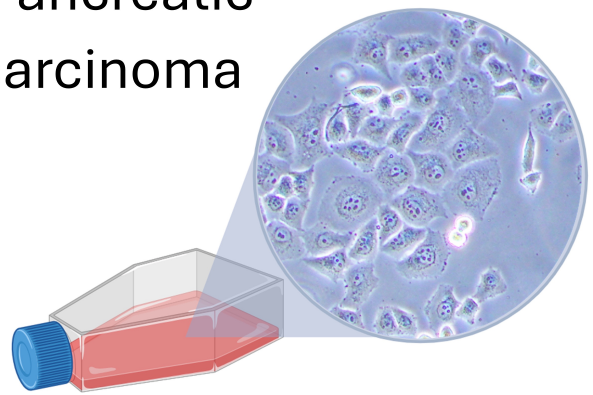
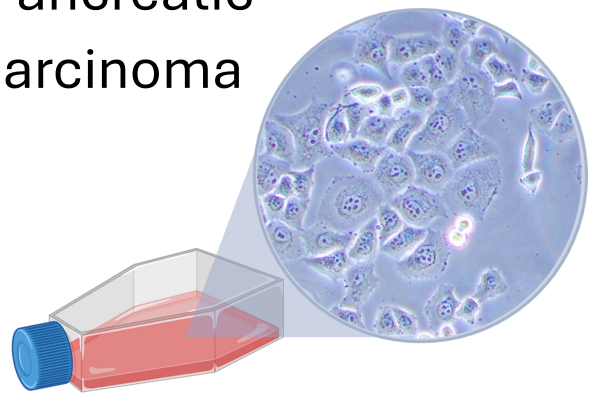


- Comparing single treatments
- Combined treatment

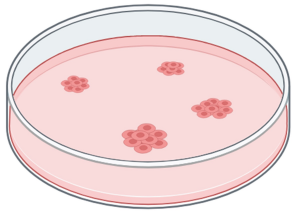
- PANC-1 cell line

  Ductal Pancreatic

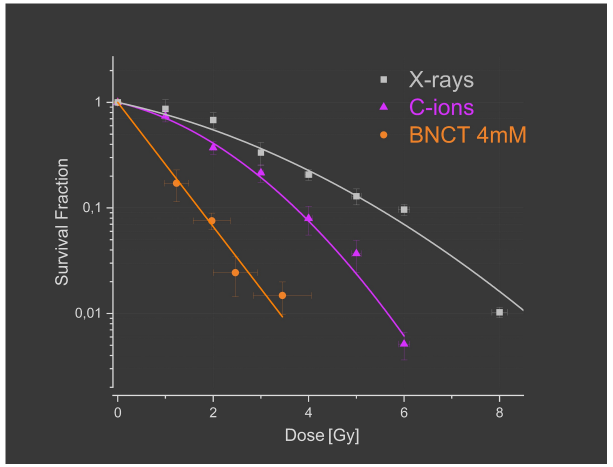
  Adenocarcinoma



Clonogenic assays



Dose-Survival curves

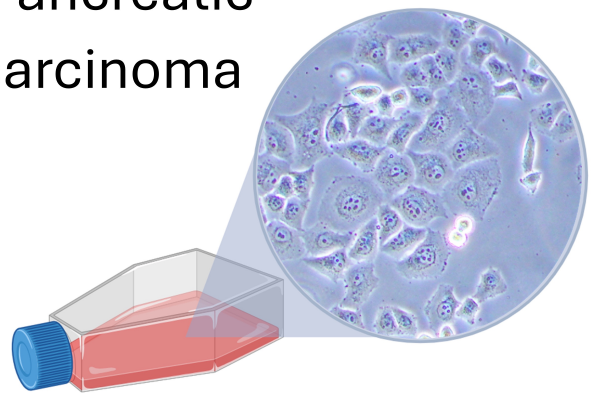



- Comparing single treatments
- Combined treatment

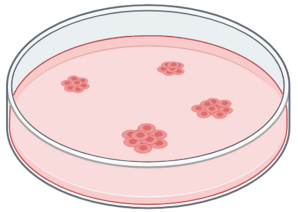
- PANC-1 cell line

  Ductal Pancreatic

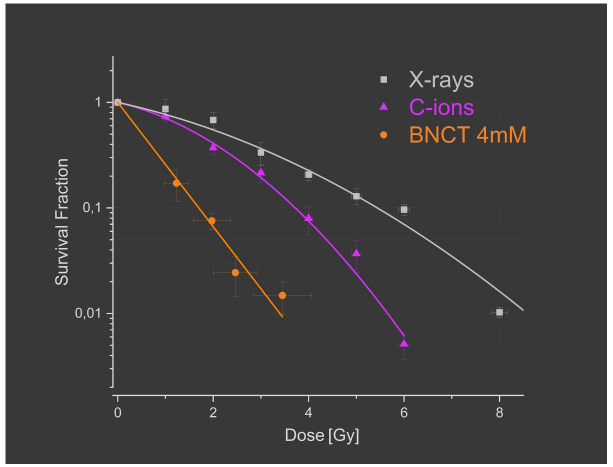
  Adenocarcinoma

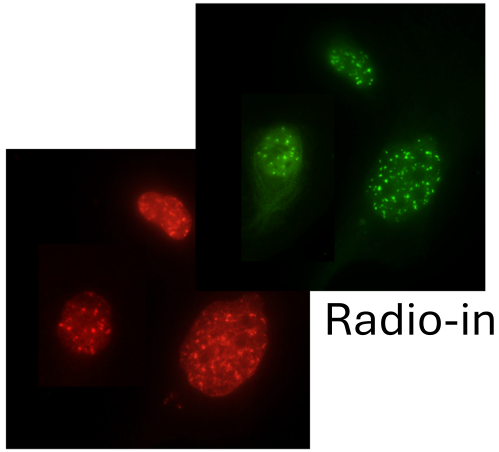


Clonogenic assays



Dose-Survival curves



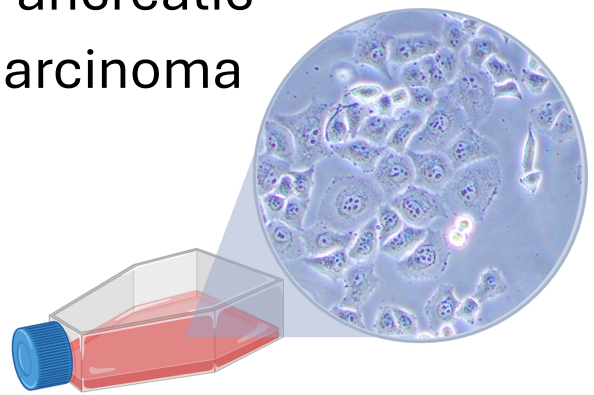



Radio-induced foci

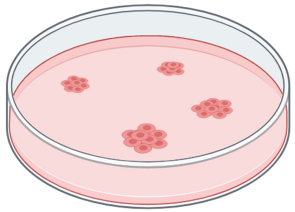
- Comparing single treatments
- Combined treatment

- PANC-1 cell line

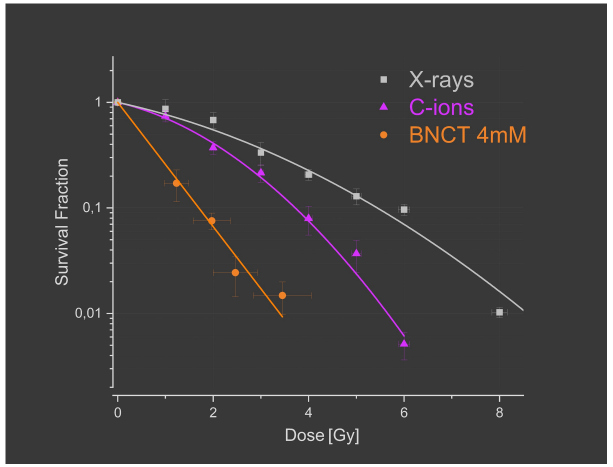
  Ductal Pancreatic Adenocarcinoma

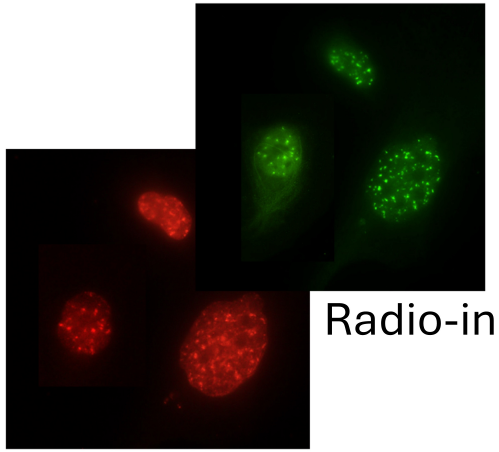


Clonogenic assays



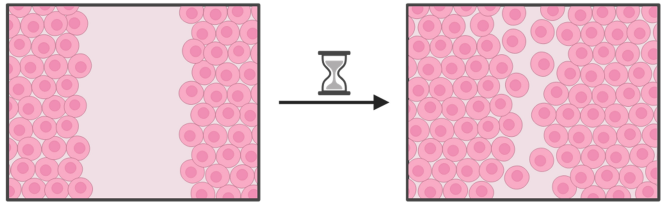
Dose-Survival curves



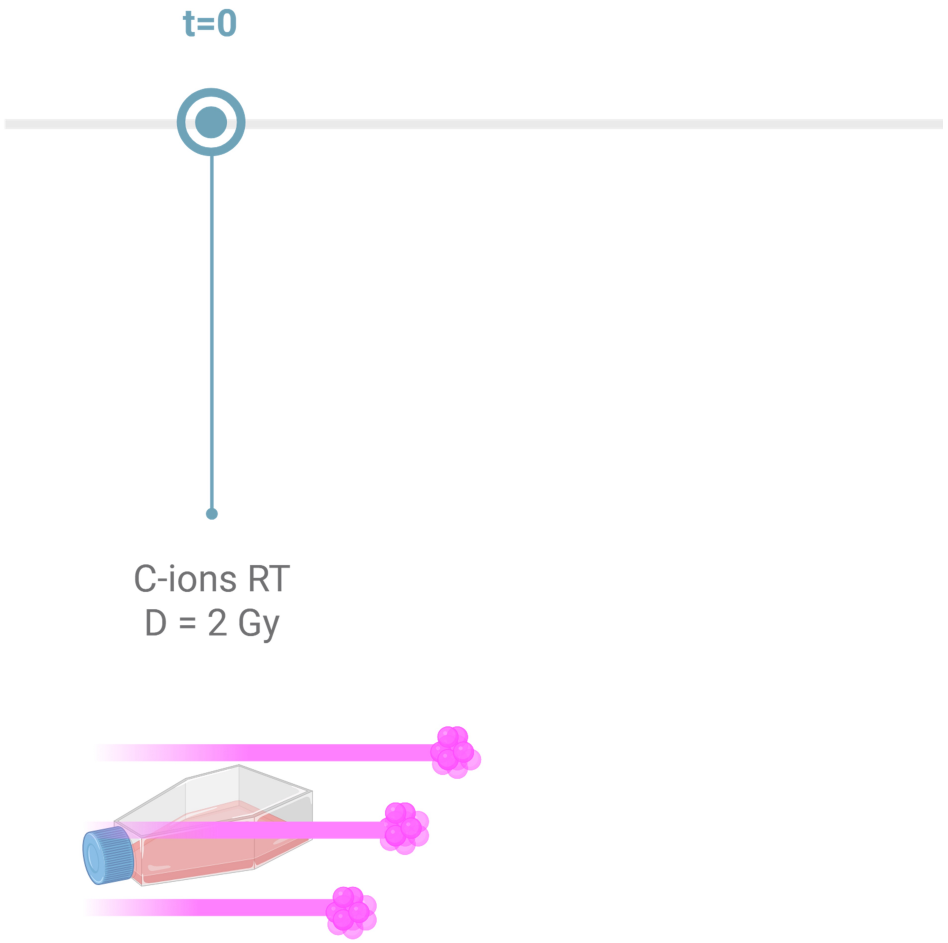
Radio-induced foci

- Comparing single treatments
- Combined treatment



Cell collective migration

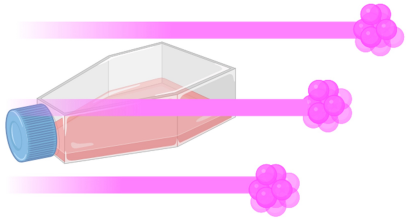
# C-ions



# C-ions

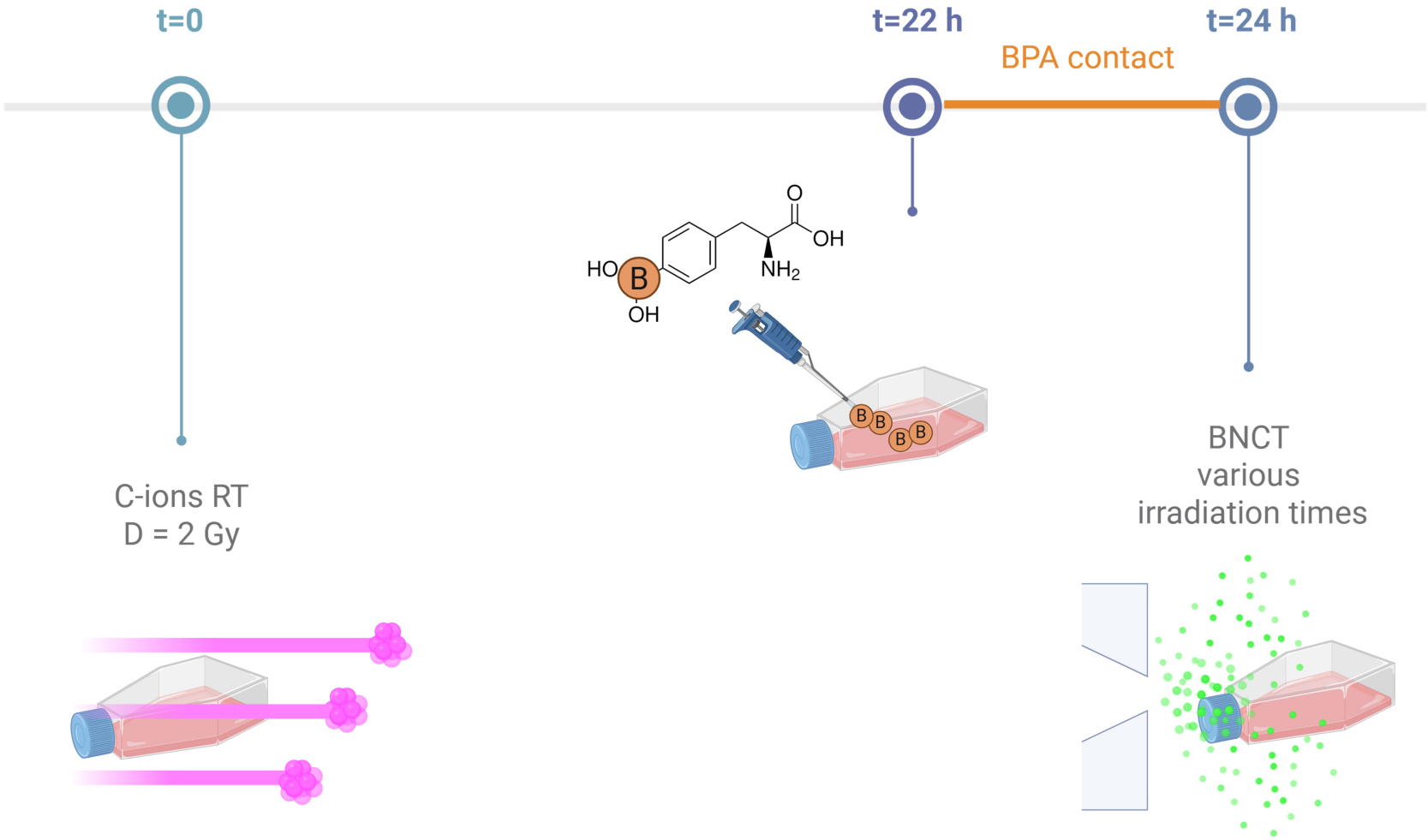
t=0

C-ions RT
D = 2 Gy

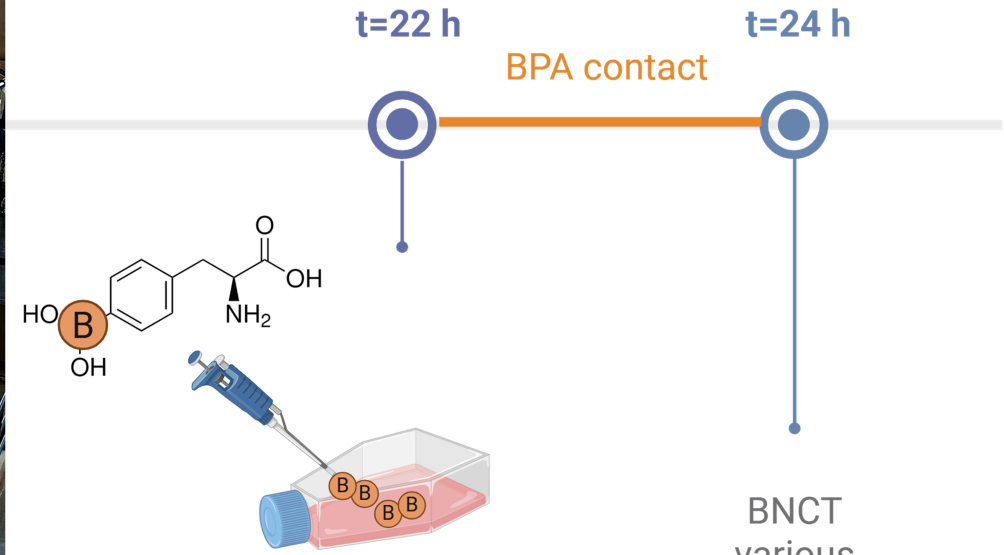


CNAO, Pavia

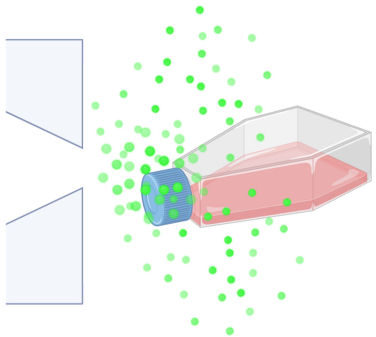
# C-ions + BNCT


t=0
t=22 h
t=24 h
BPA contact
HO
B
OH
O
OH
NH2
B
B
B
B
C-ions RT
D = 2 Gy
BNCT
various
irradiation times

L.E.N.A., Pavia

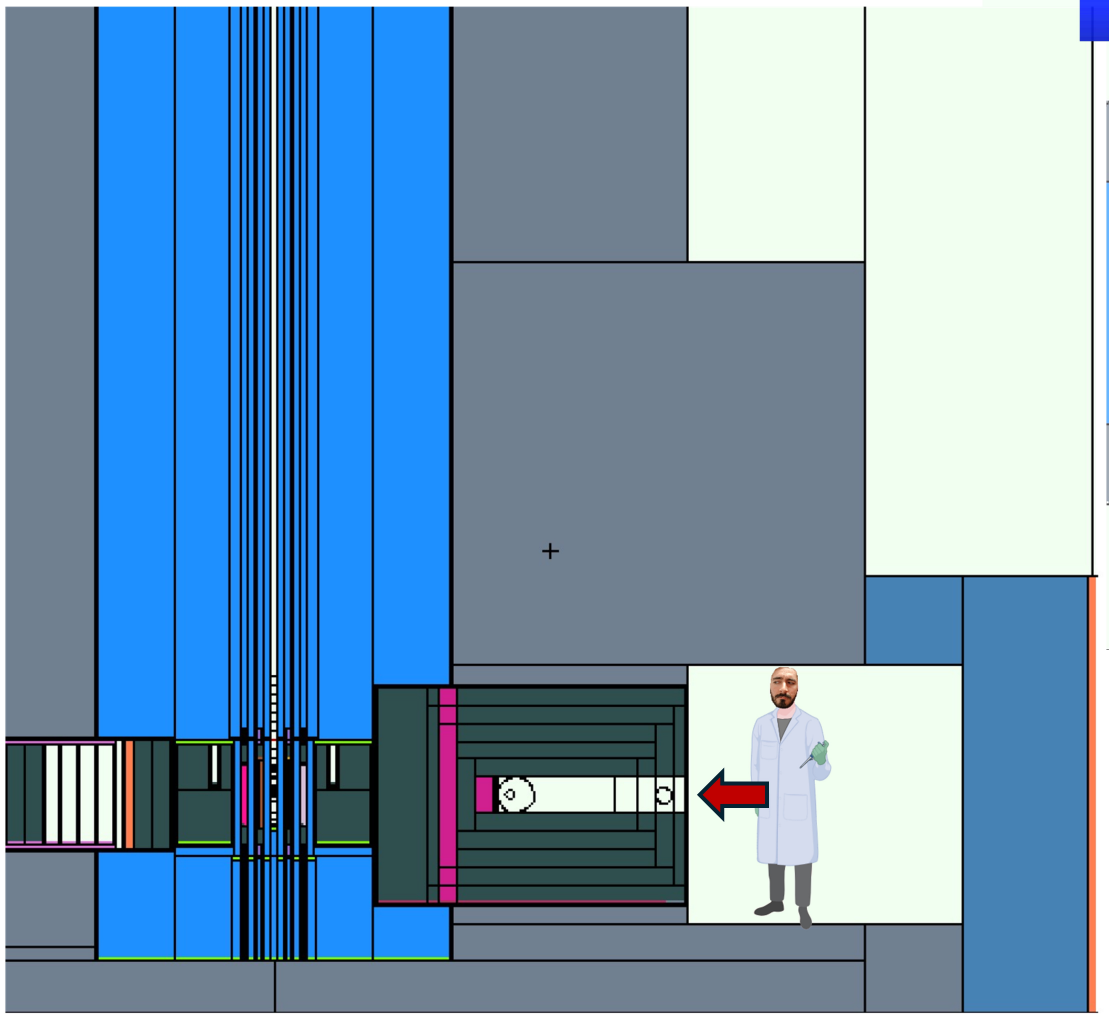


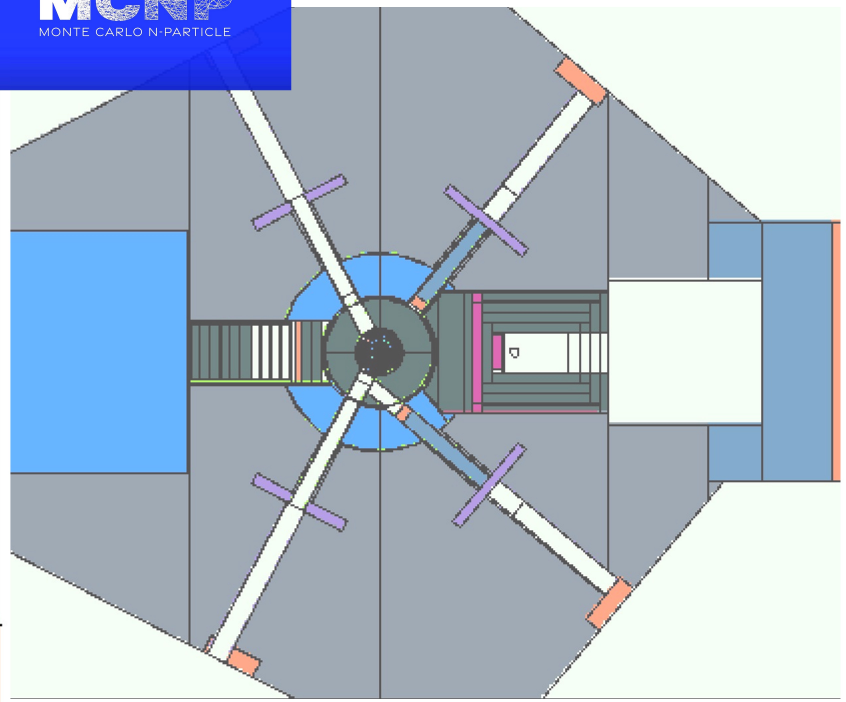

BNCT
various
irradiation times



Alessandro Somenzi

# Computational dosimetry with MCNP

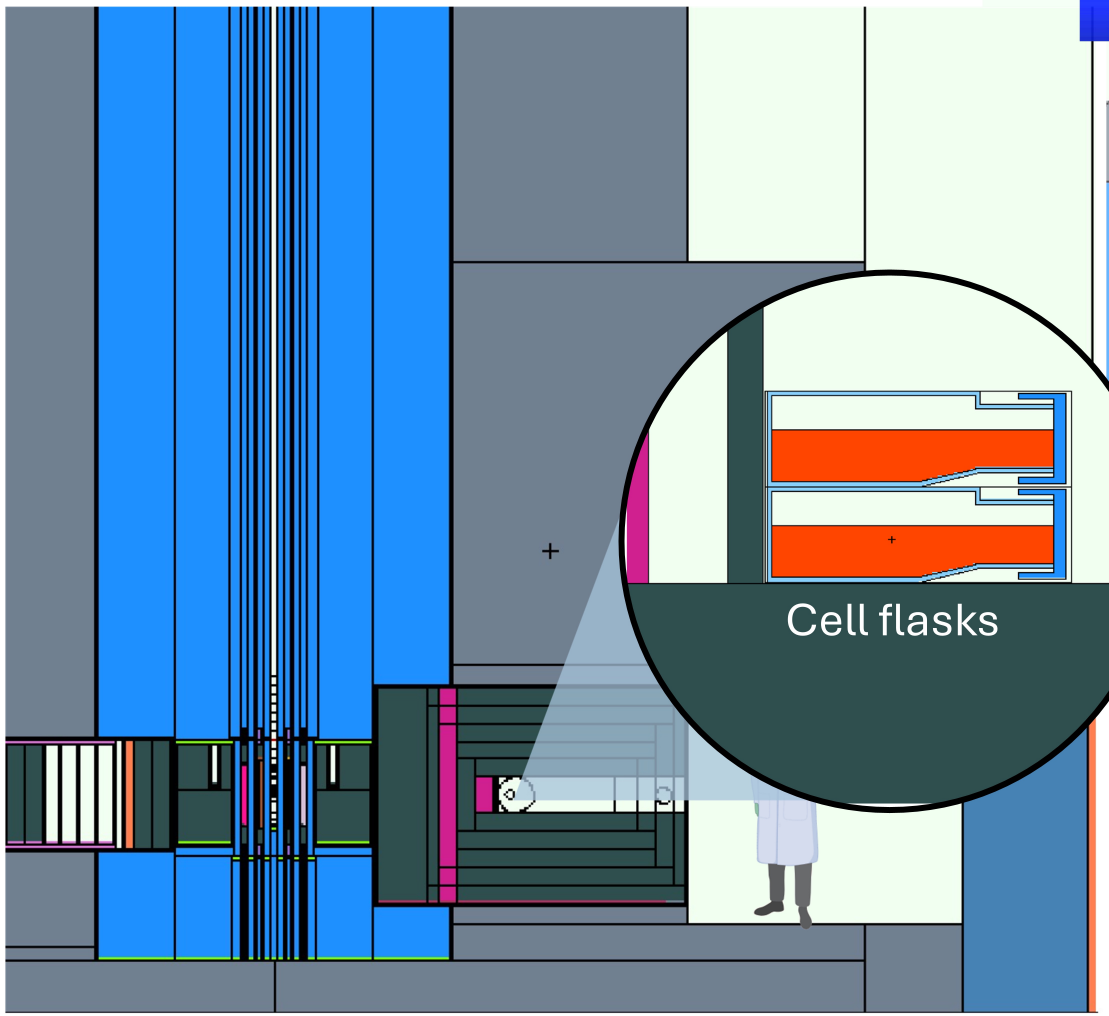


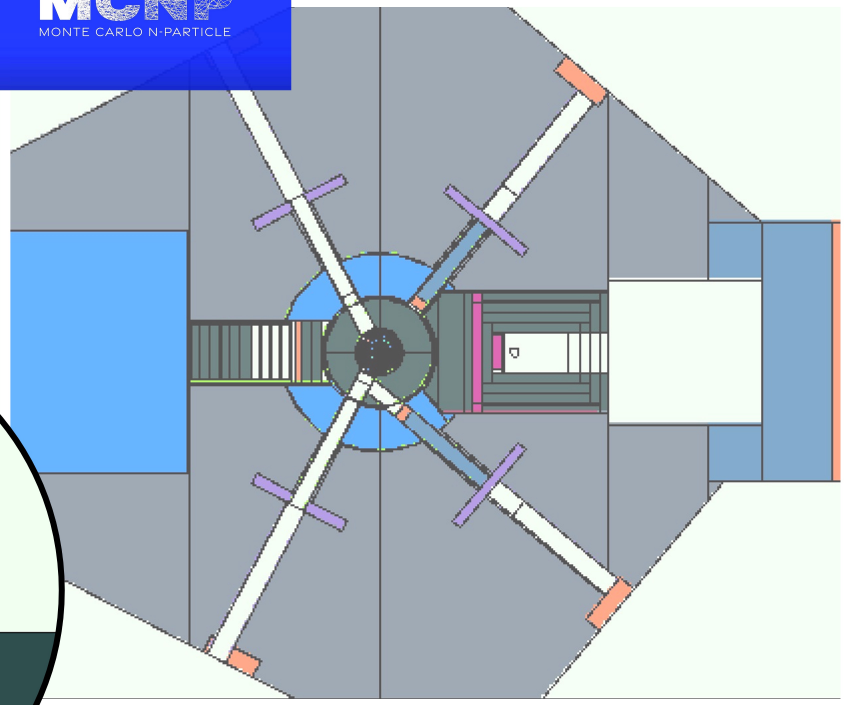


- Cells modelled as monolayer
- Transport of n & γ
- Capture reactions on $^{10}B$, $^{14}N$, $^{1}H$
- n scattering on $^{1}H$

# Computational dosimetry with MCNP

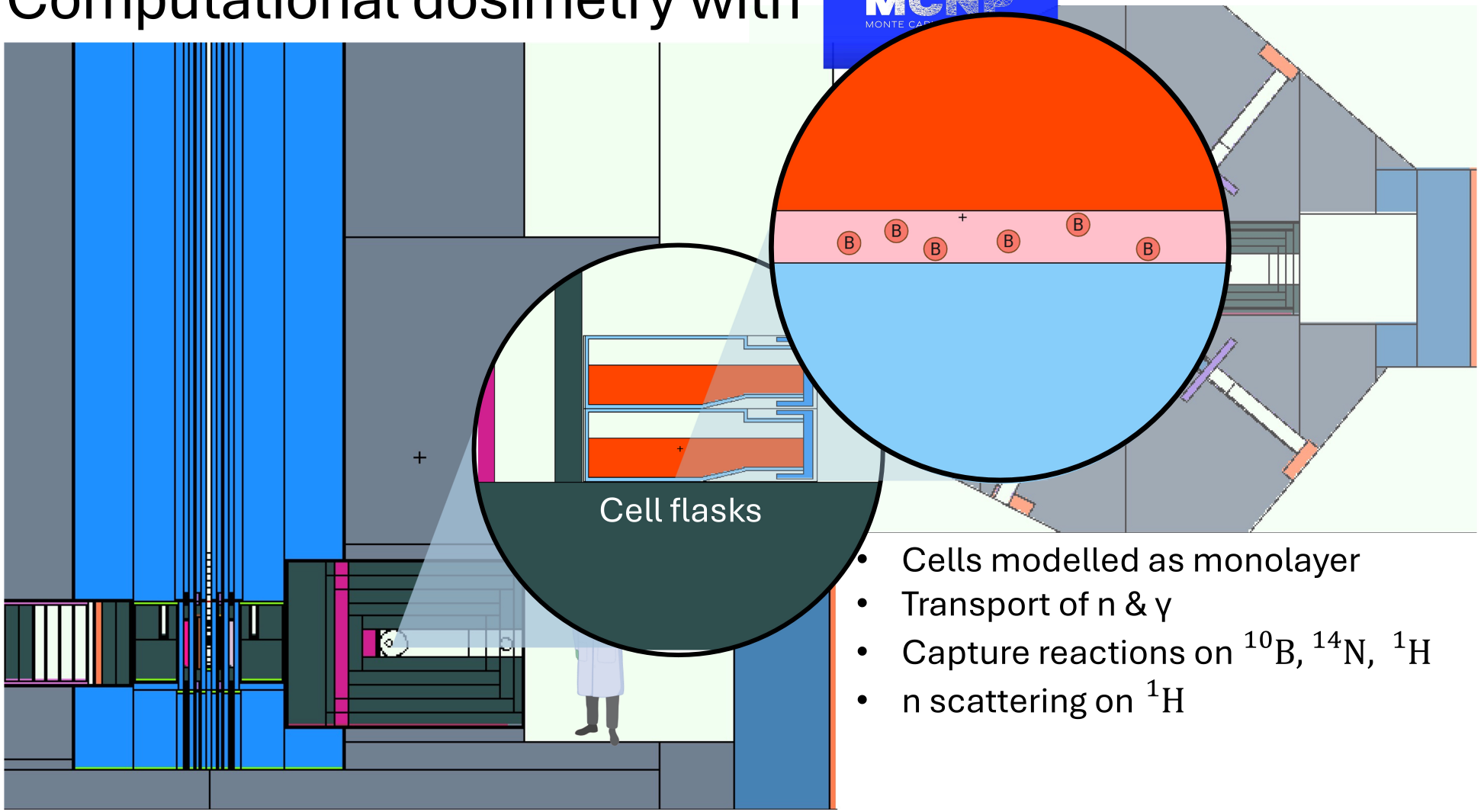
MONTE CARLO N-PARTICLE



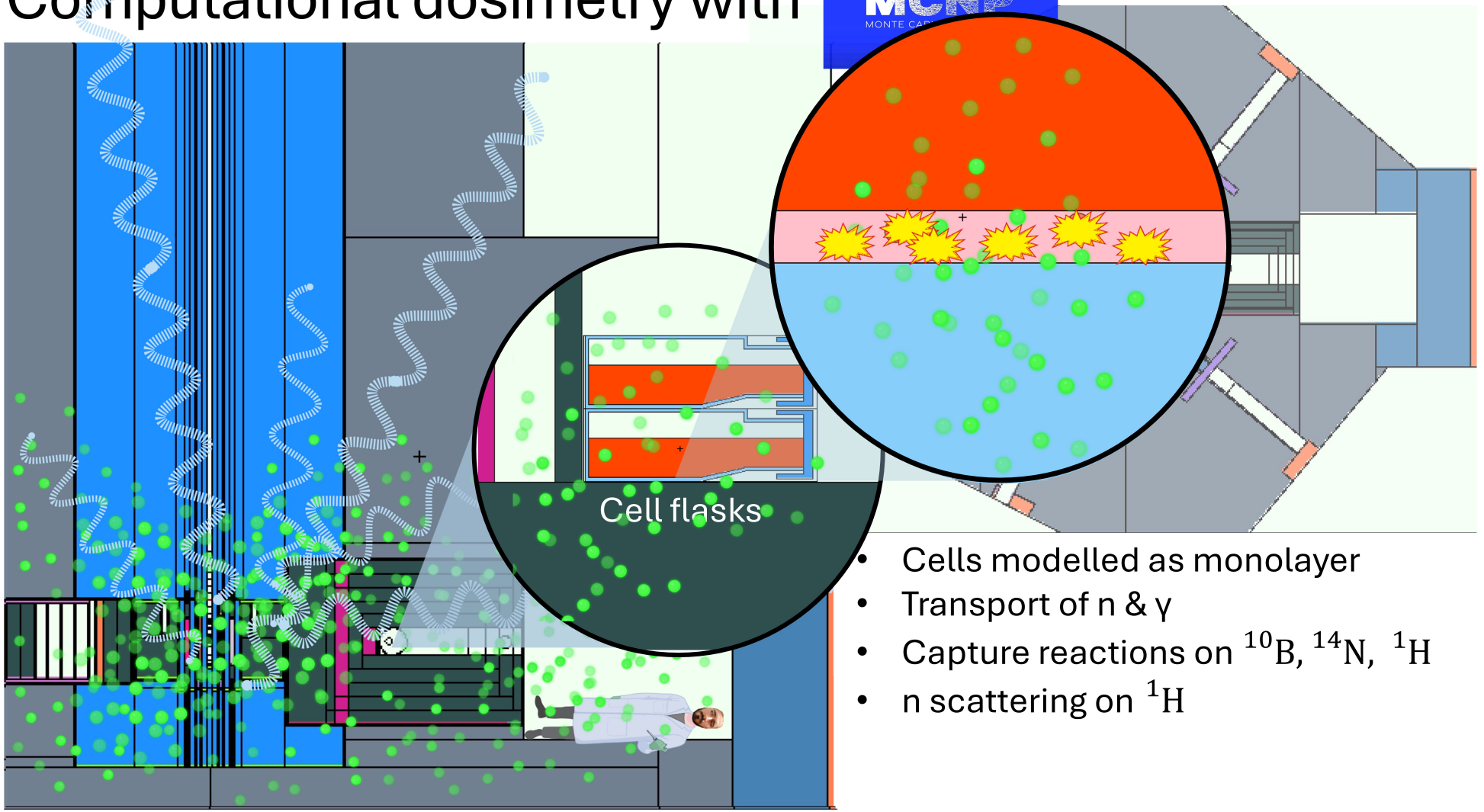
- Cells modelled as monolayer
- Transport of n & γ
- Capture reactions on $^{10}B$, $^{14}N$, $^{1}H$
- n scattering on $^{1}H$

# Computational dosimetry with MCNP

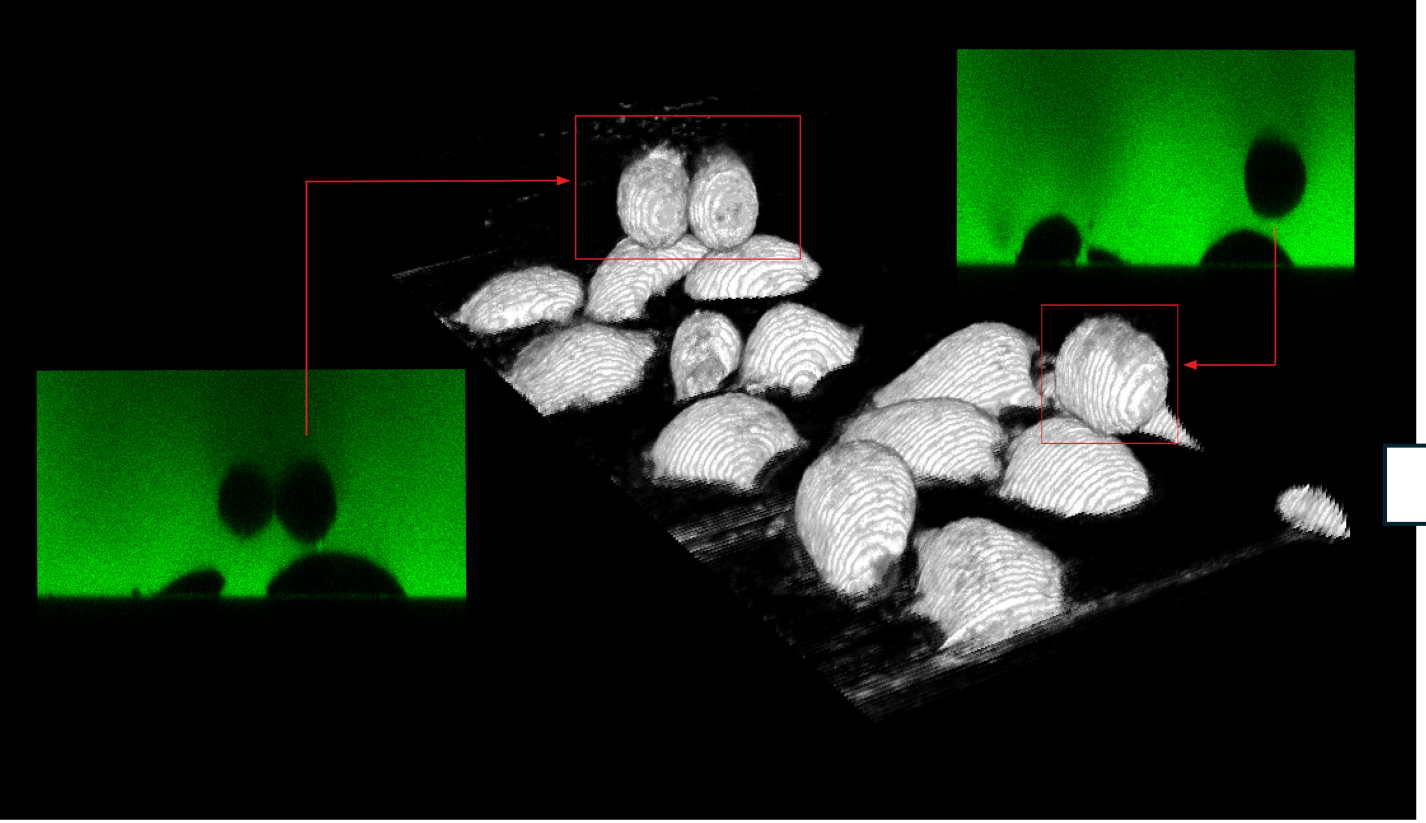



- Cells modelled as monolayer
- Transport of n & γ
- Capture reactions on $^{10}B$, $^{14}N$, $^{1}H$
- n scattering on $^{1}H$

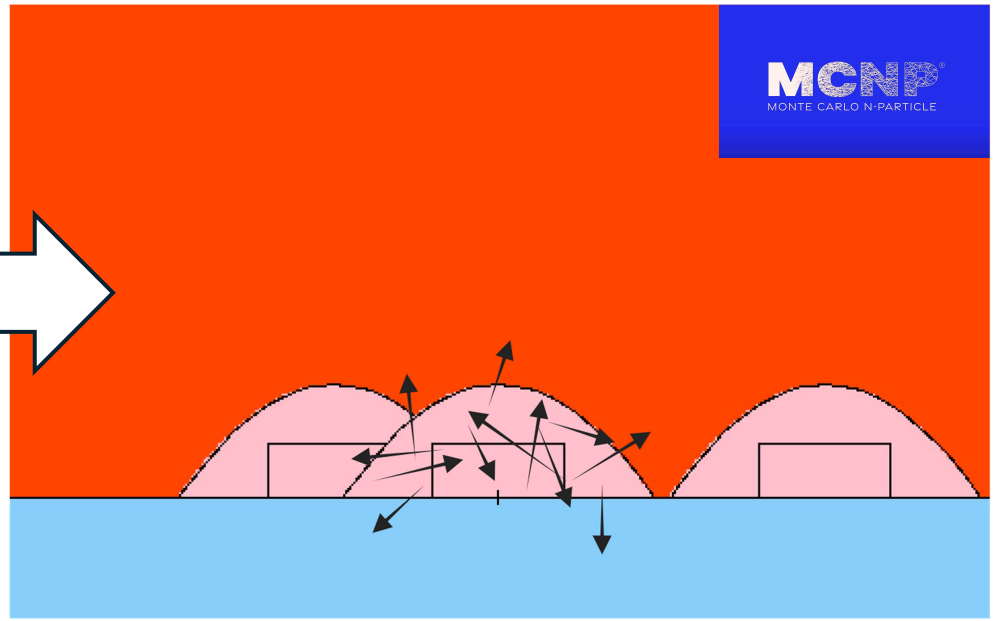
# Computational dosimetry with MCNP

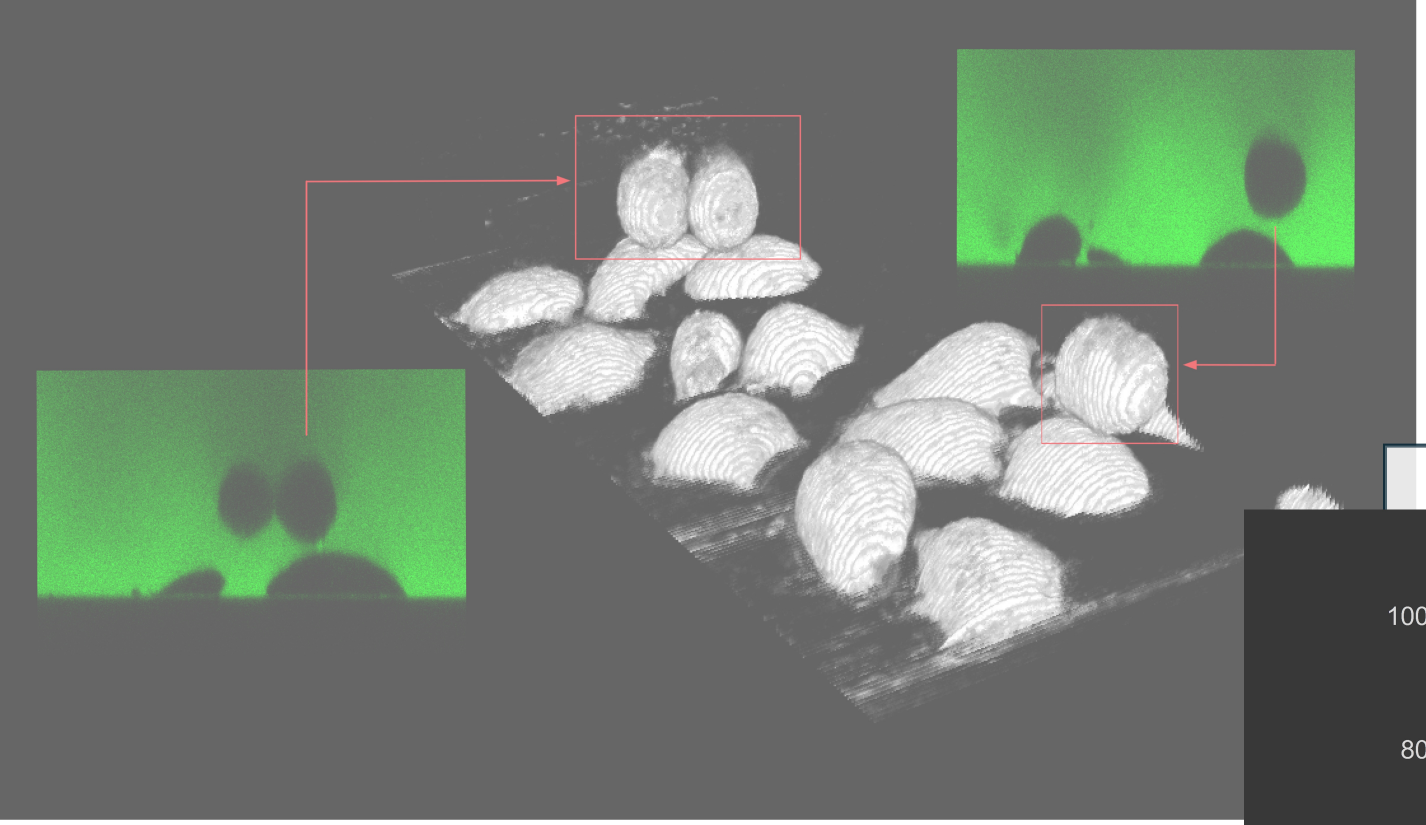



- Cells modelled as monolayer
- Transport of n & γ
- Capture reactions on $^{10}B$, $^{14}N$, $^{1}H$
- n scattering on $^{1}H$



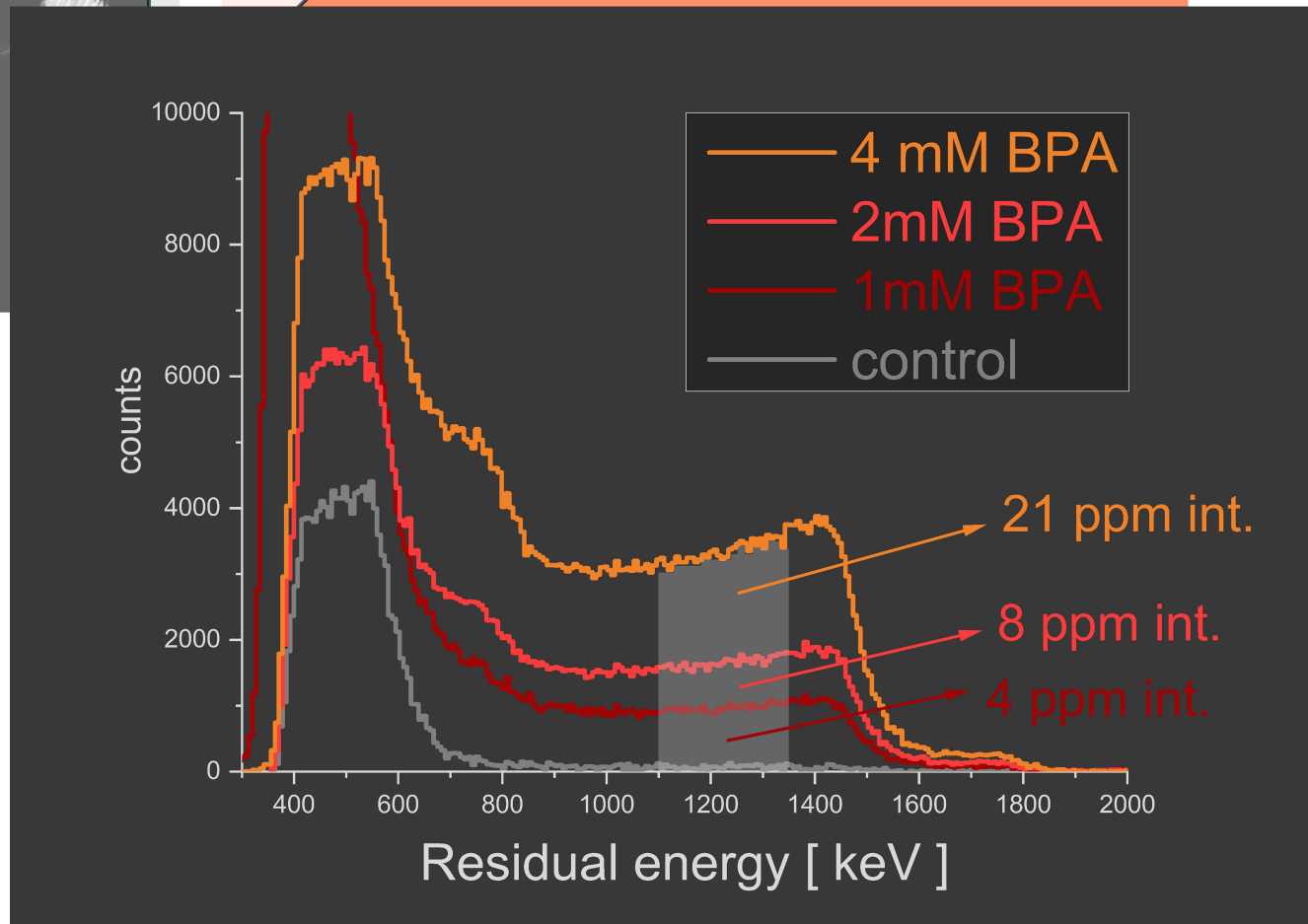
- Transport of Alpha and Lithium inside cells





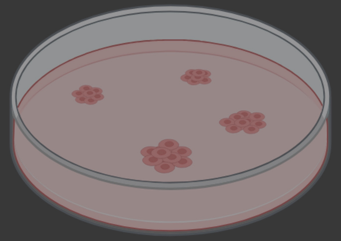
- Transport of Alpha and Lithium inside cells

MCNP
MONTE CARLO N-PARTICLE

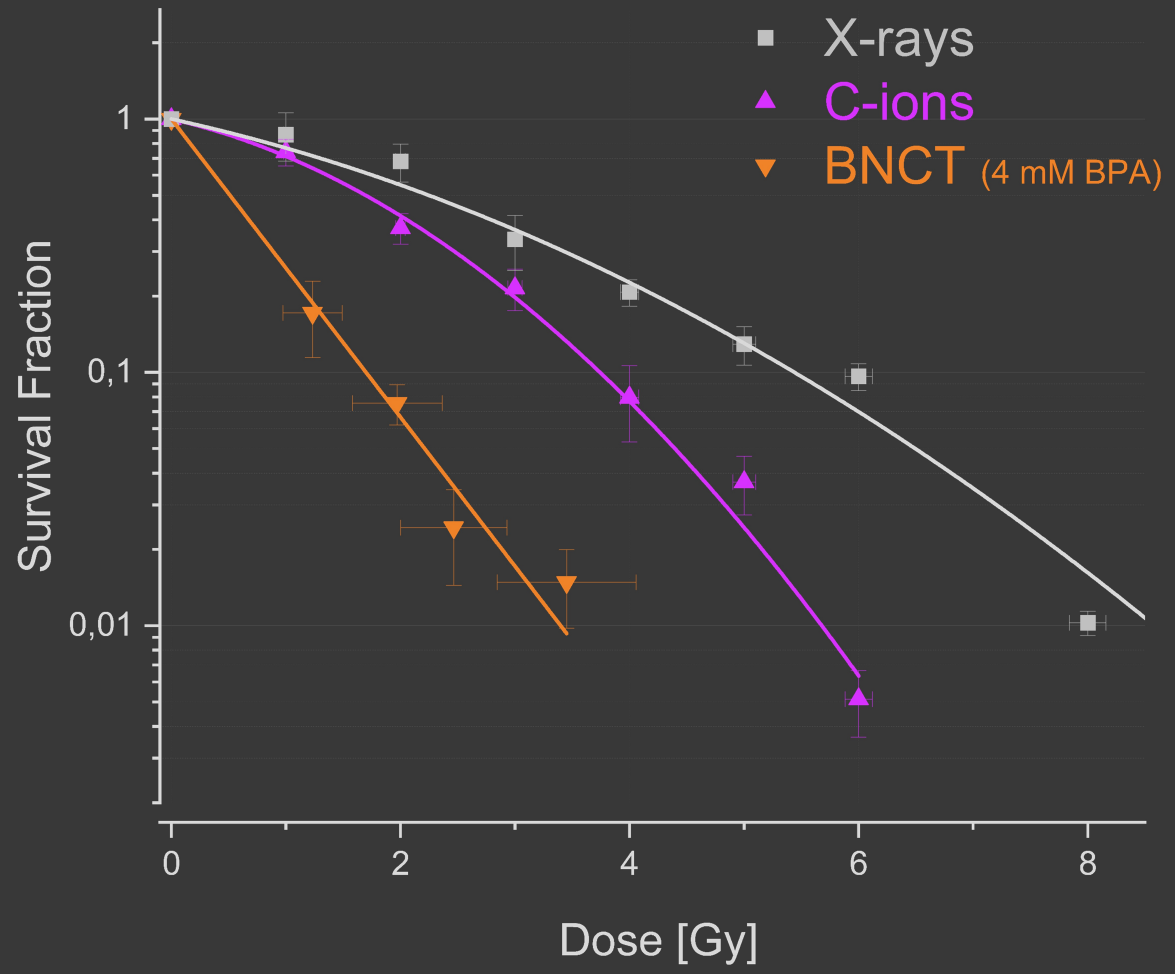


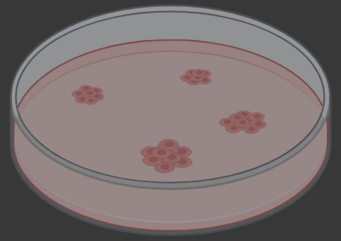

# Boron-10 internalization Measurements: alpha spectrometry

Confirmed with ICP-Mass spectrometry

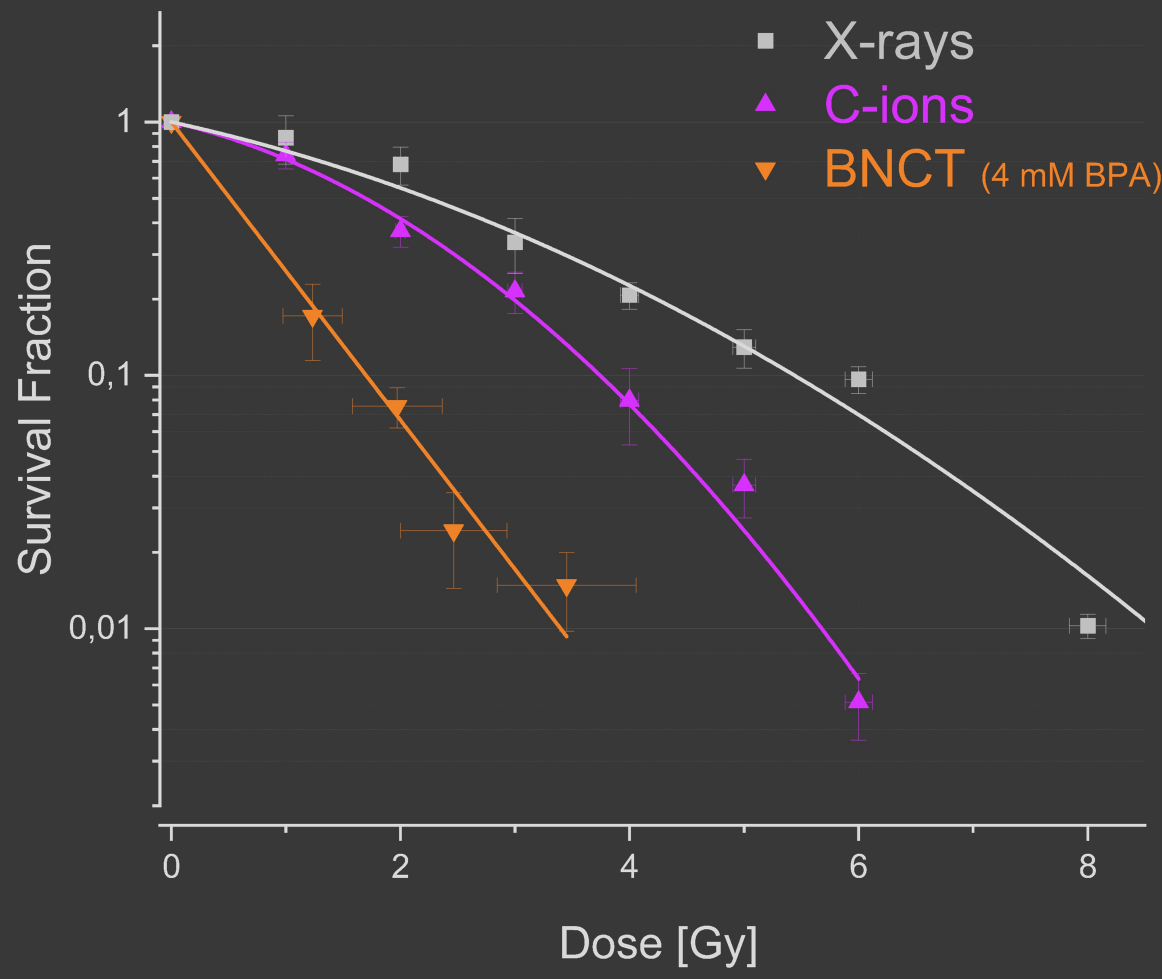


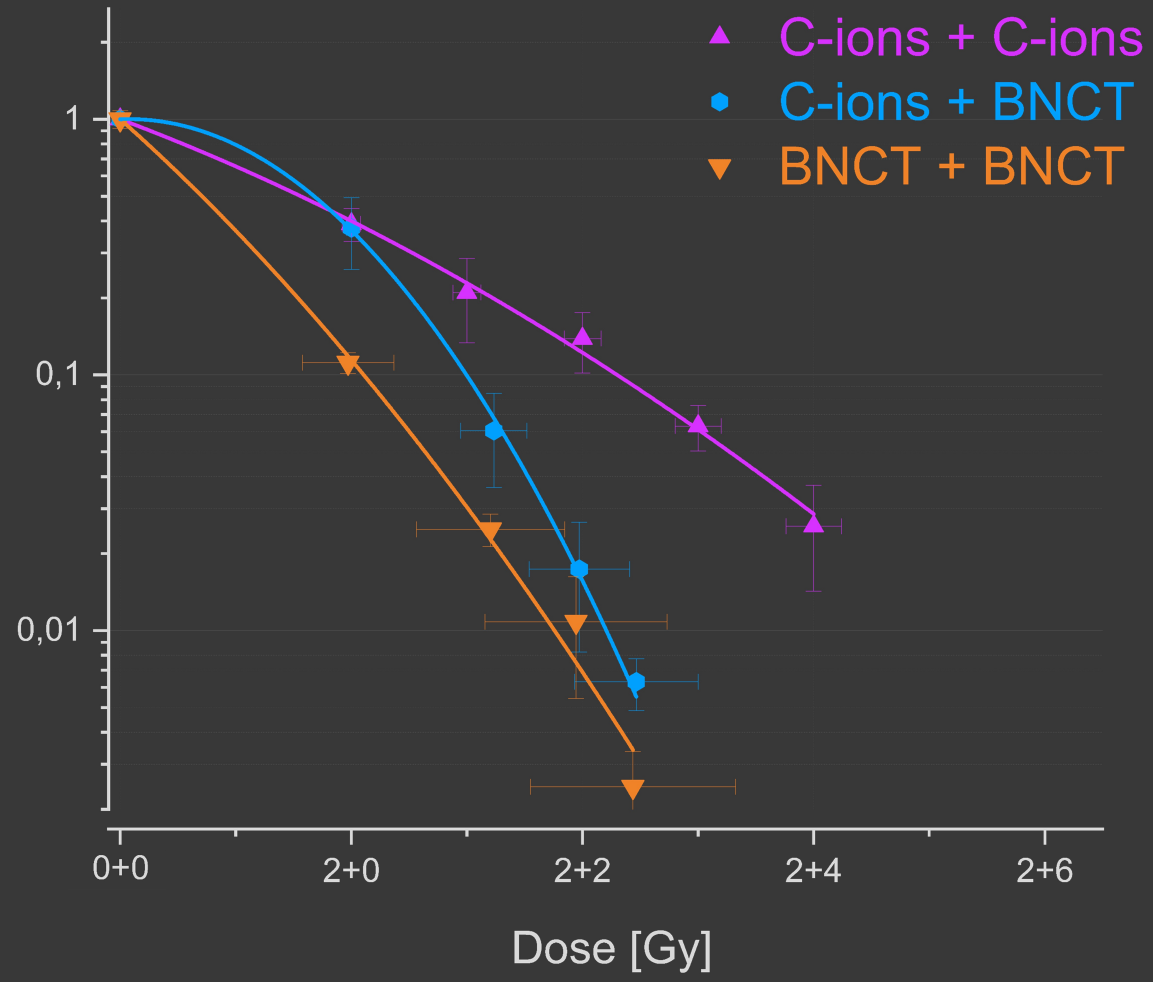
# Dose-Survival curves

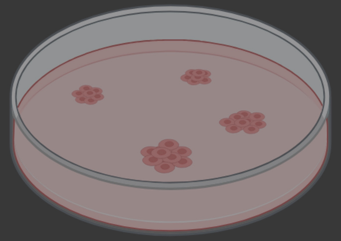




# Dose-Survival curves

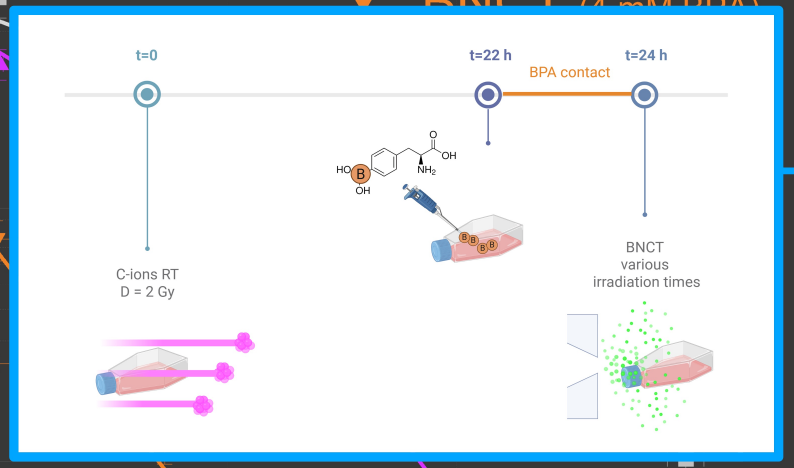




# Dose-Survival curves

X-rays
C-ions
BNCT (4 mM BPA)

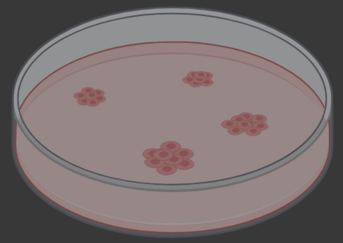


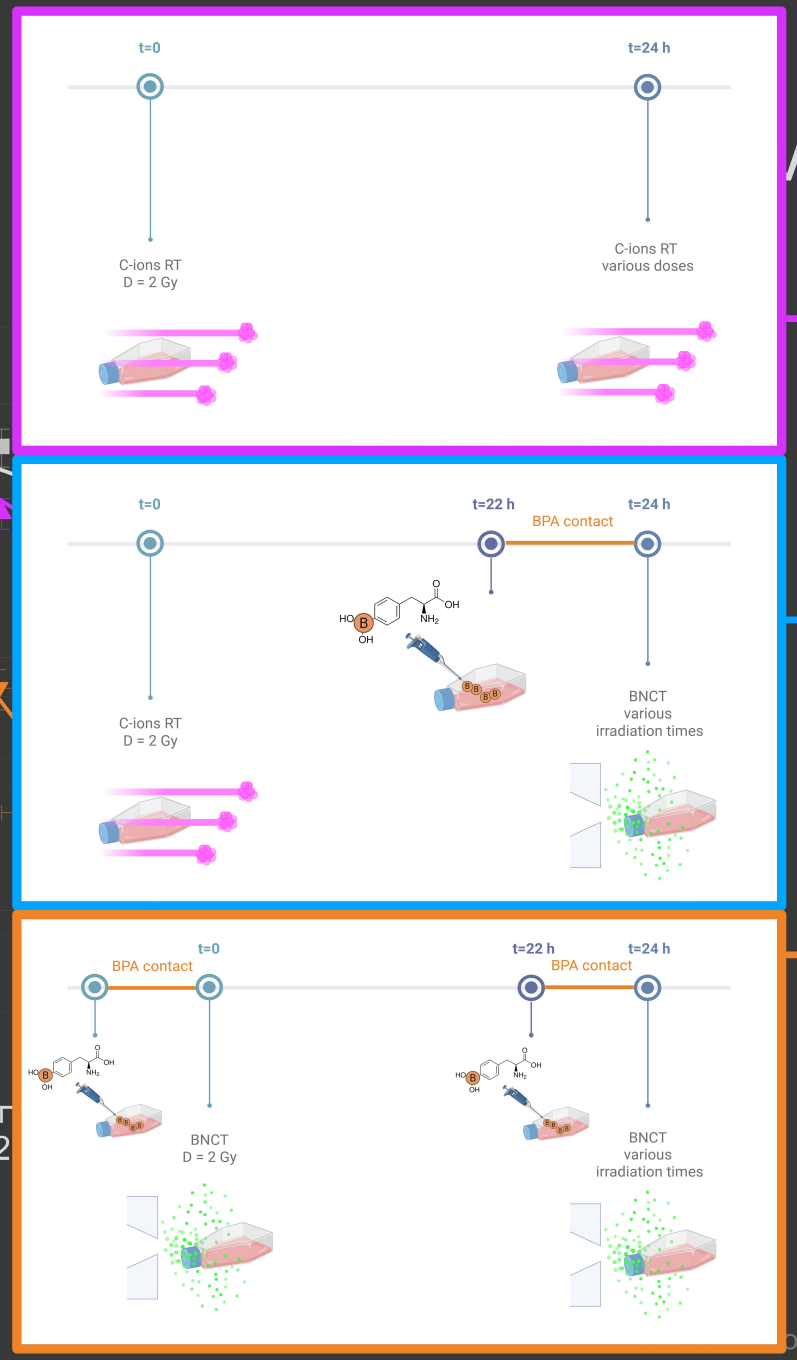

Survival Fraction
1
0,1
0,01
0
2
4
6
8
Dose [Gy]

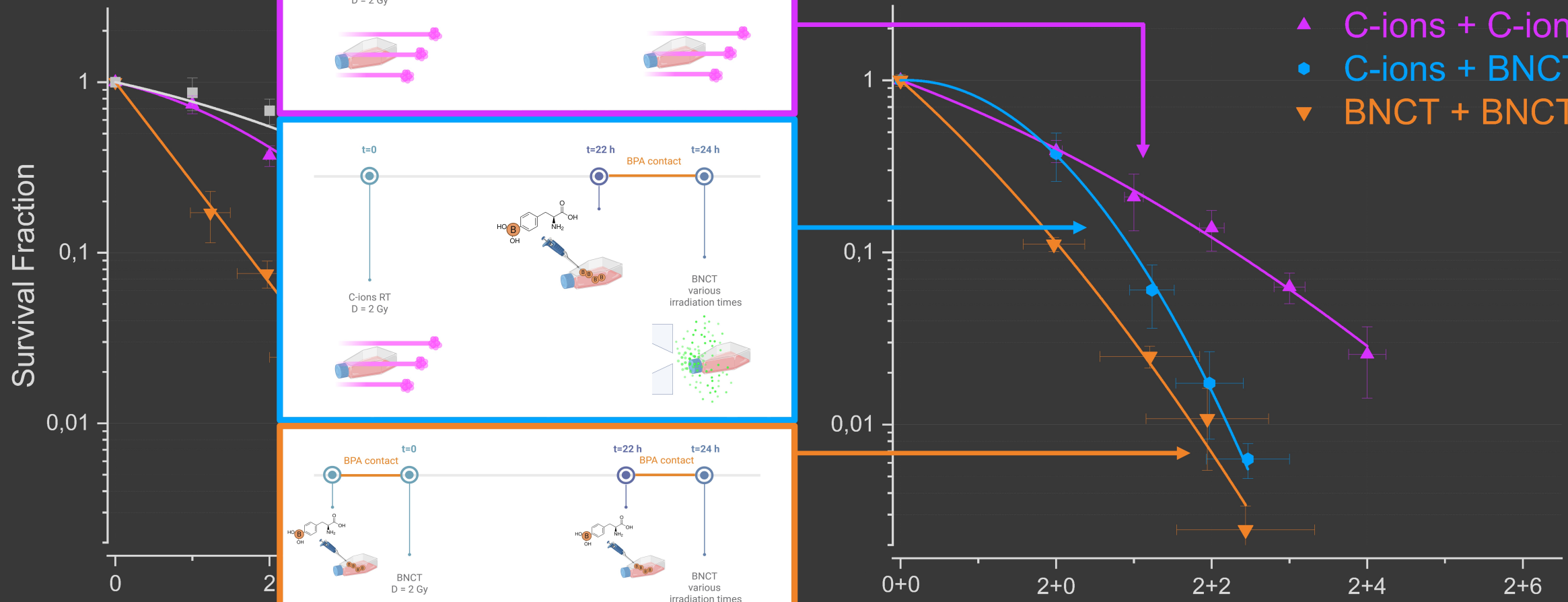
C-ions + C-ions
C-ions + BNCT
BNCT + BNCT

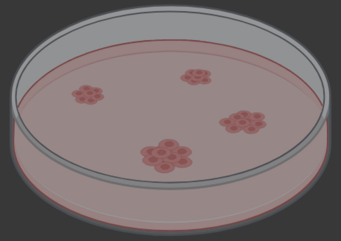
1
0,1
0,01
0+0
2+0
2+2
2+4
2+6
Dose [Gy]

# val curves

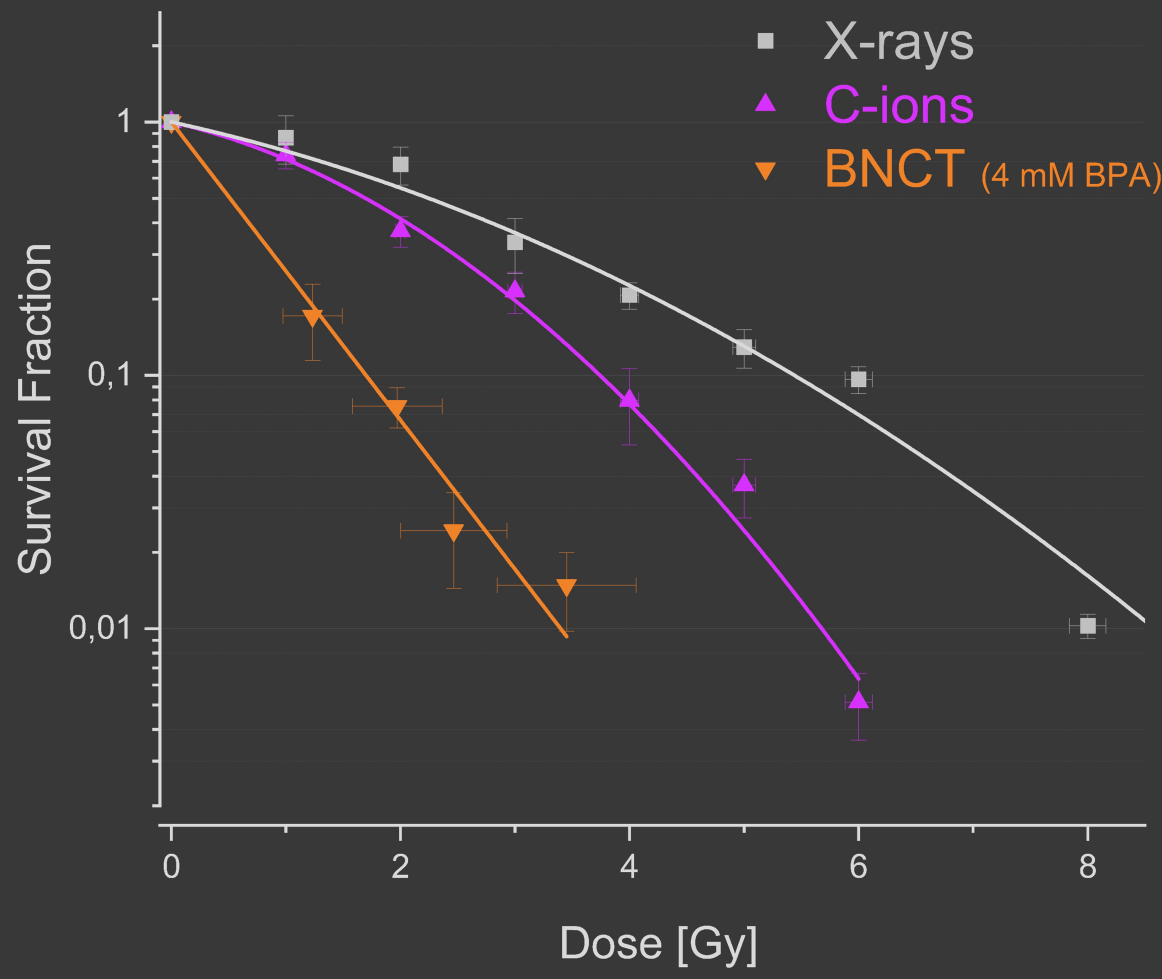


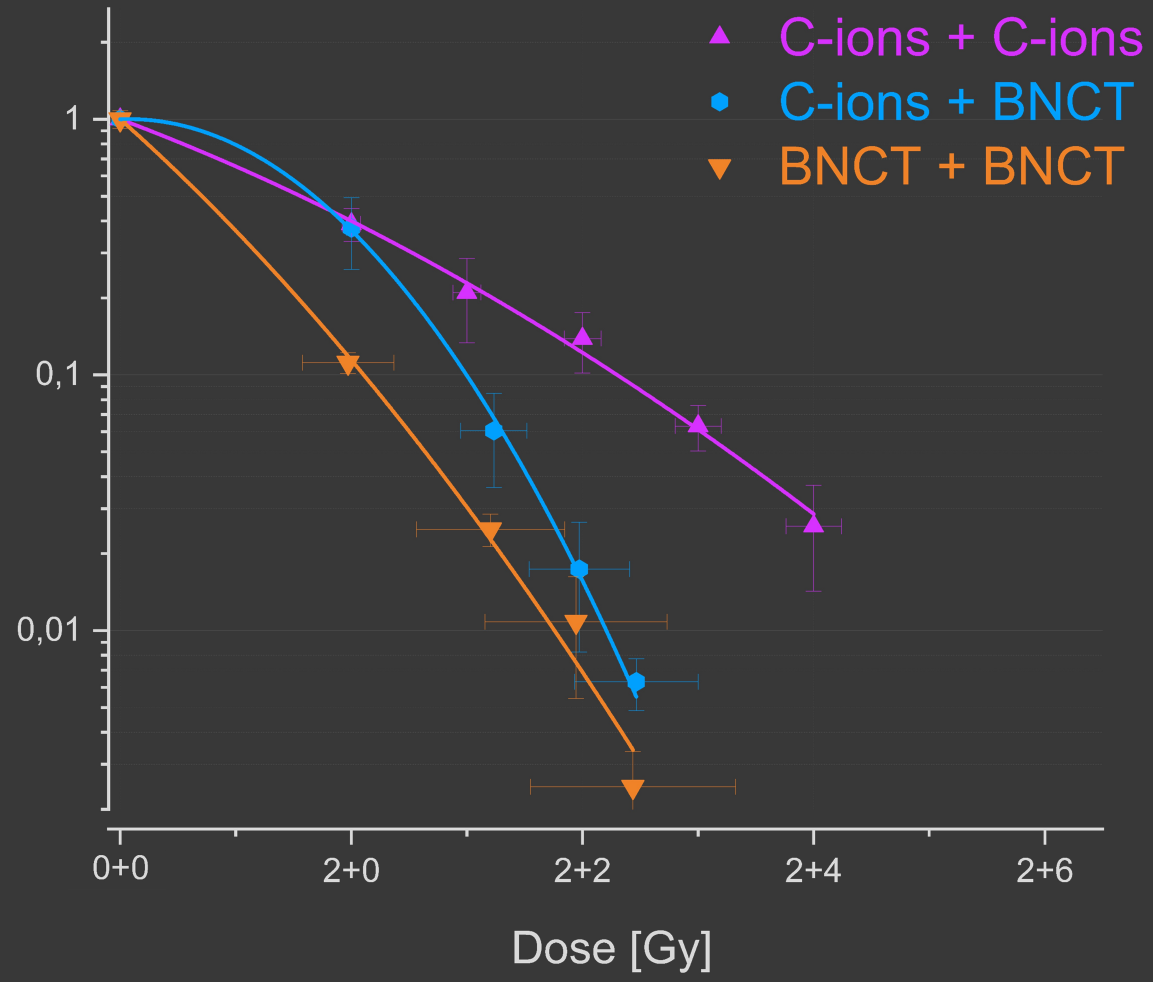

t=0
t=24 h
C-ions RT
D = 2 Gy
C-ions RT
various doses
t=0
t=22 h
BPA contact
t=24 h
C-ions RT
D = 2 Gy
BNCT
various
irradiation times
t=0
BPA contact
t=22 h
t=24 h
BPA contact
BNCT
D = 2 Gy
BNCT
various
irradiation times

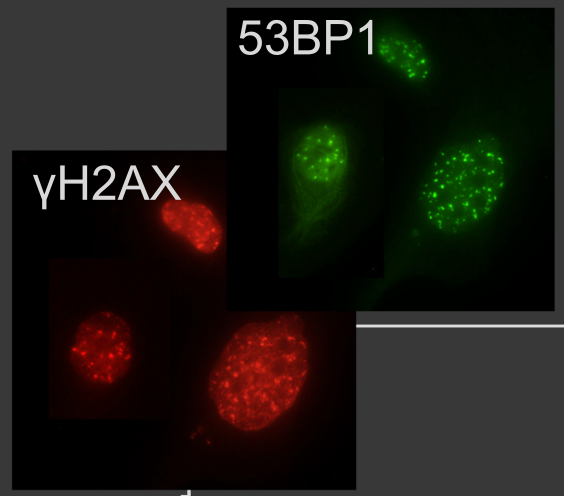

Survival Fraction
1
0,1
0,01
0
2
0+0
2+0
2+2
2+4
2+6
Dose [Gy]
C-ions + C-ions
C-ions + BNCT
BNCT + BNCT



# Dose-Survival curves






# Radio-Induced Foci per cell at 24 hours

single treatments (2 Gy)

fractionated treatments (2+2 Gy)

FOCI / cell at 24h

30

20

10

0

0 Gy

C-ions

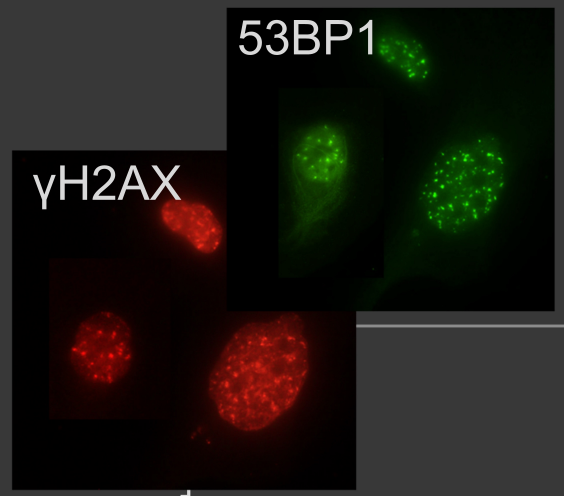
BNCT

0 Gy

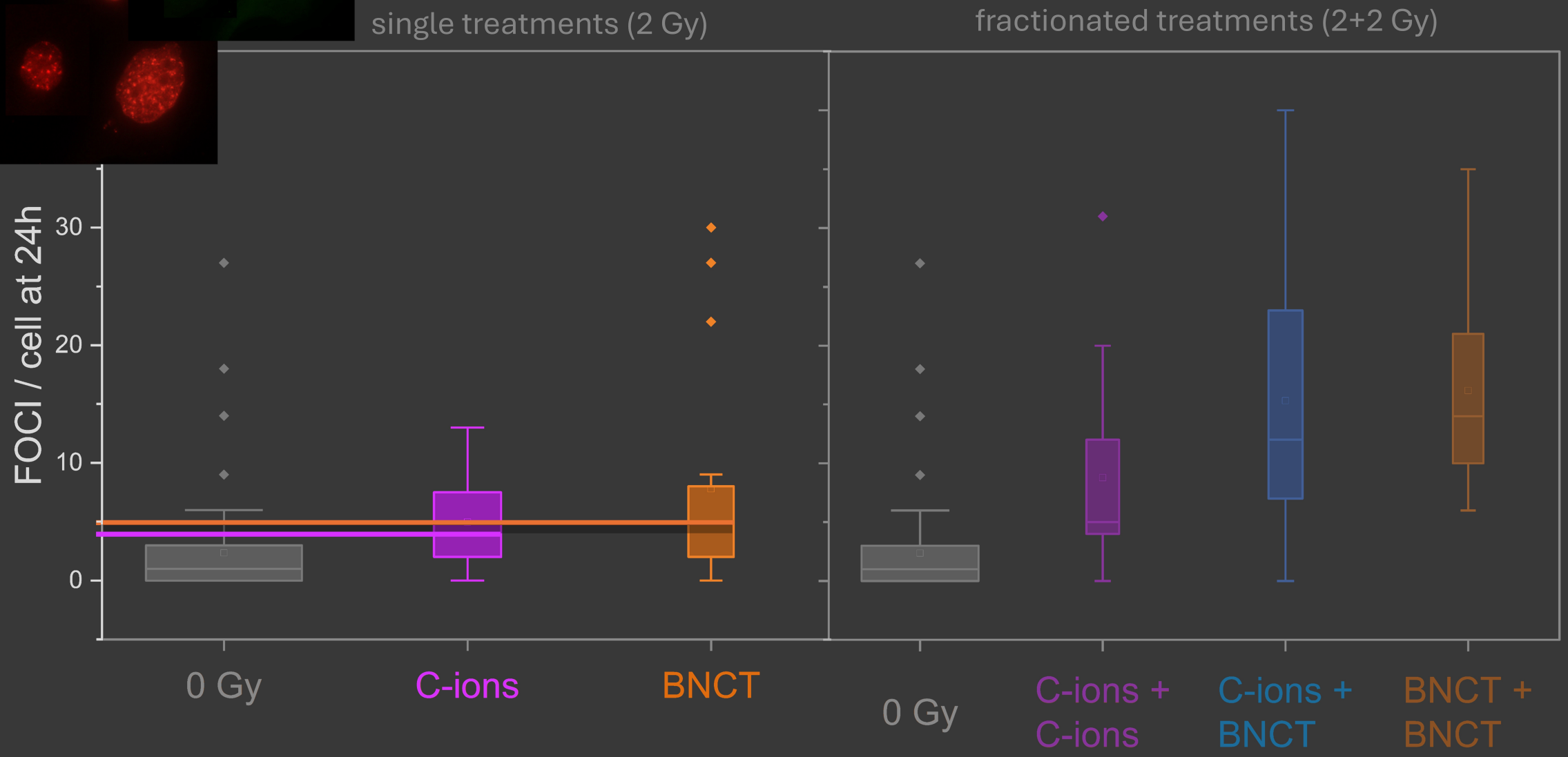
C-ions + C-ions

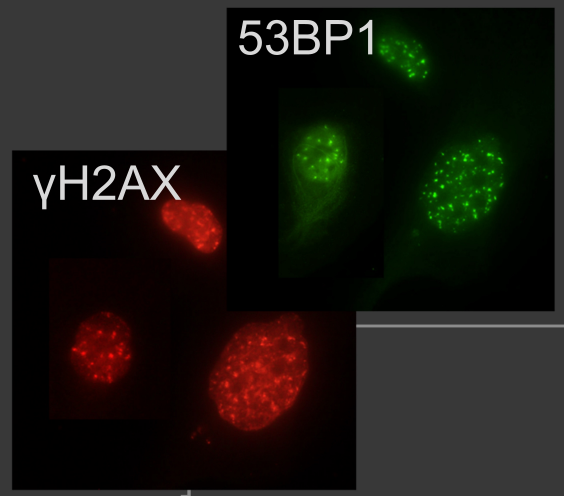
C-ions + BNCT

BNCT + BNCT

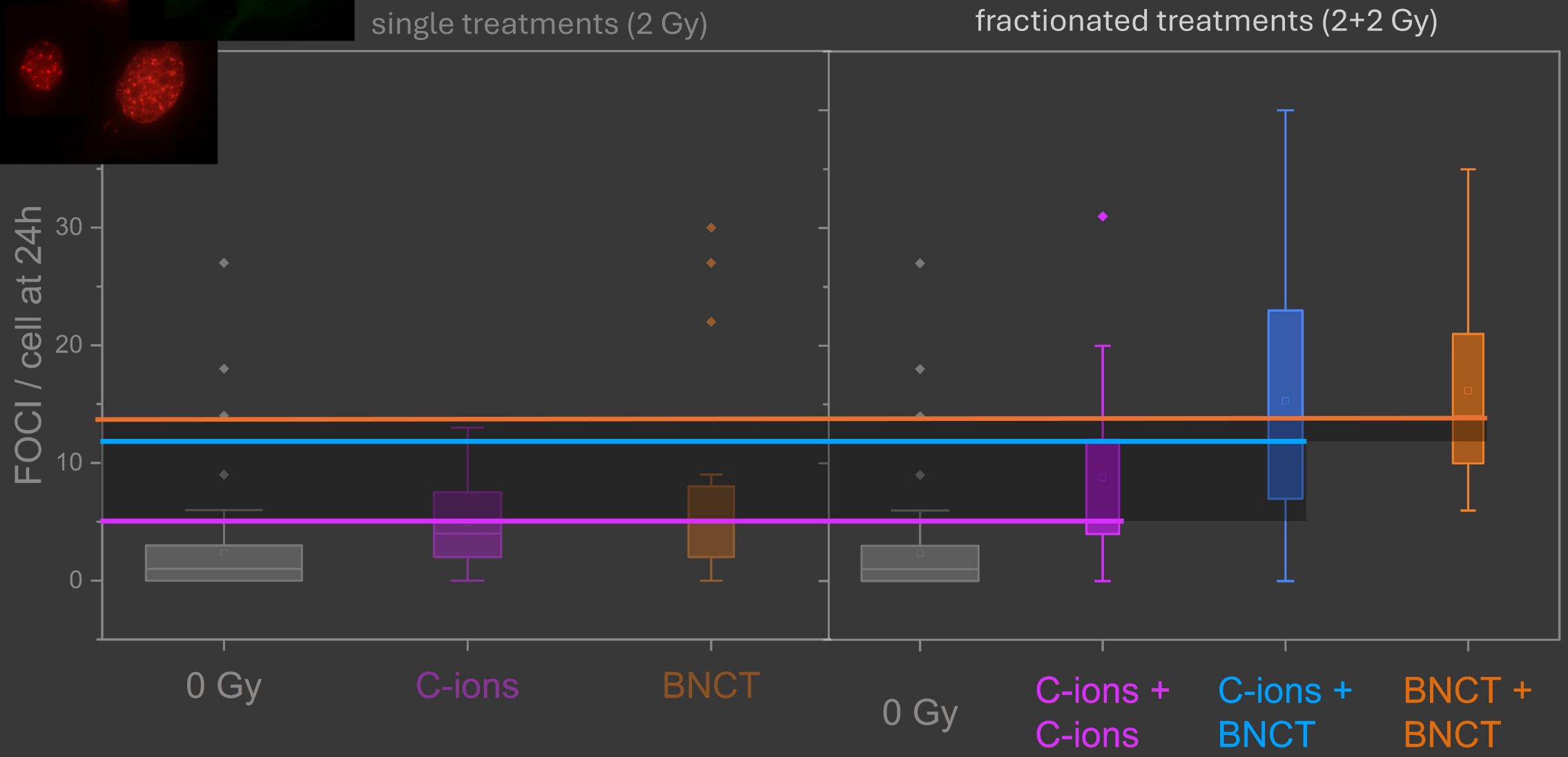


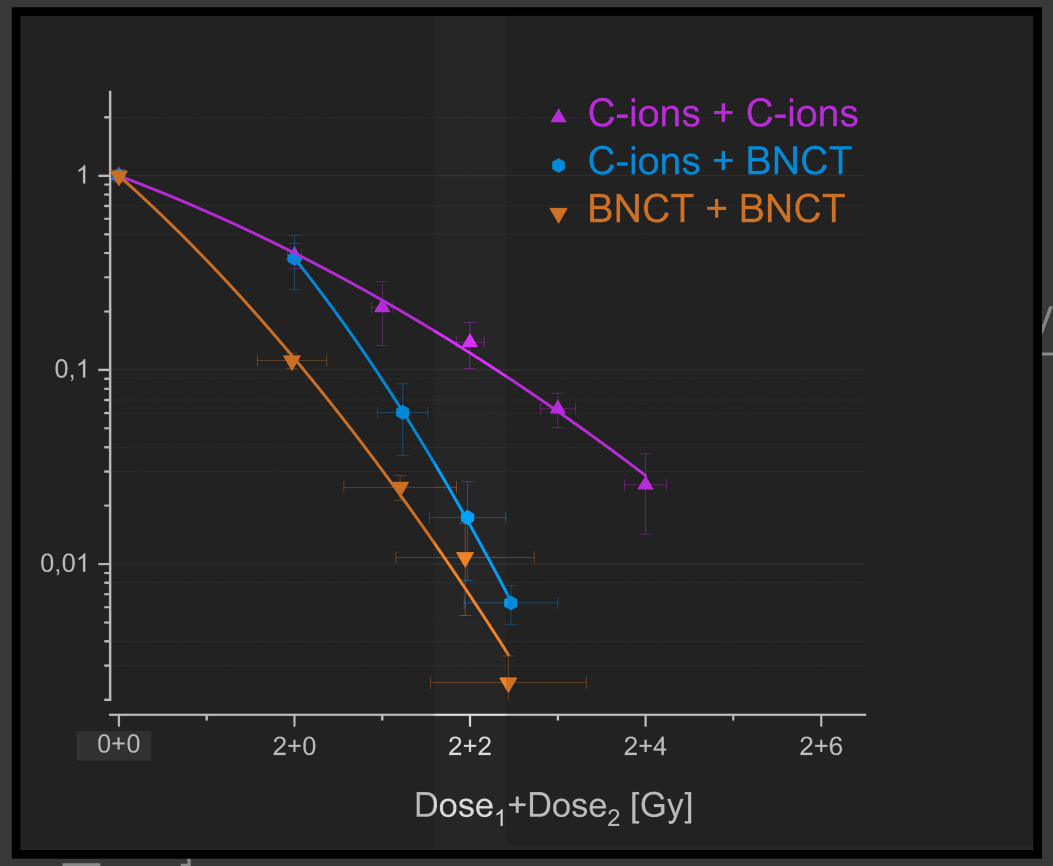

# Radio-Induced Foci per cell at 24 hours






# Radio-Induced Foci per cell at 24 hours






fractionated treatments (2+2 Gy)

FOCI

10

0

0 Gy

C-ions

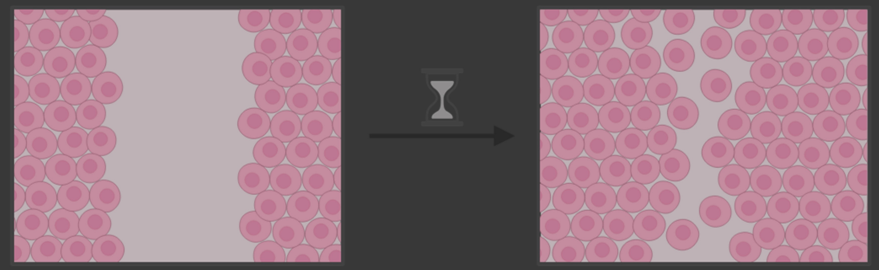
BNCT

0 Gy

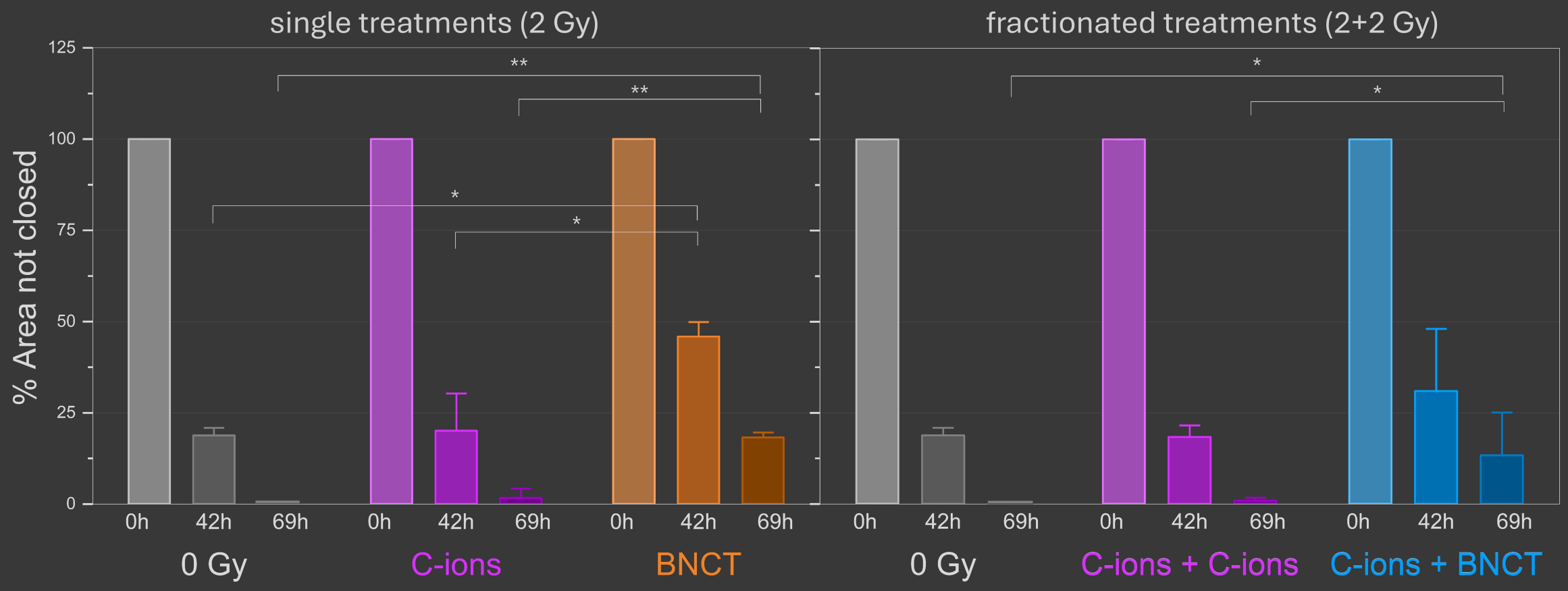
C-ions + C-ions

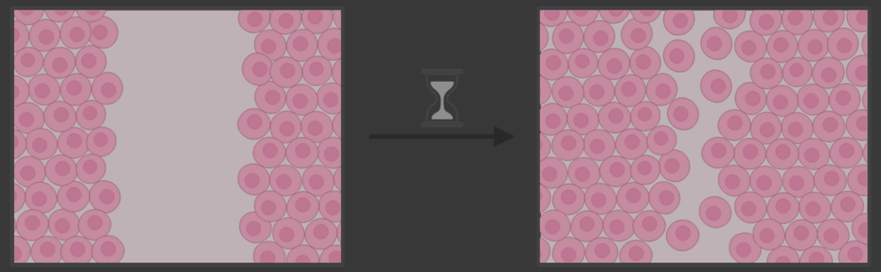
C-ions + BNCT

BNCT + BNCT

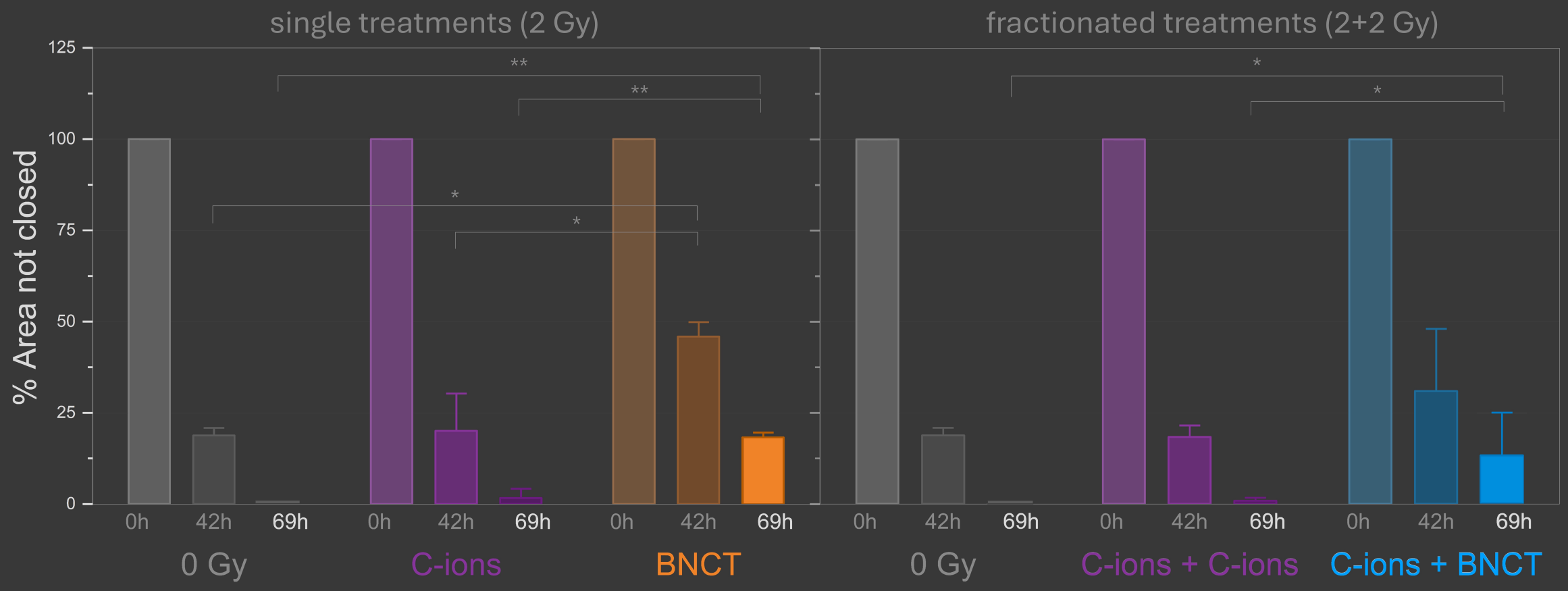


# Collective migration assay





# Collective migration assay



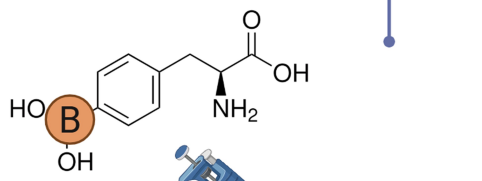
# Carbon-ions + BNCT

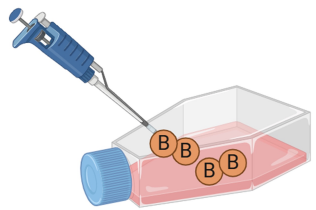
t=0

t=22 h

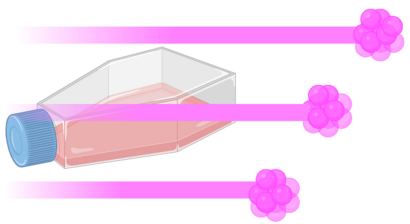
BPA contact

t=24 h

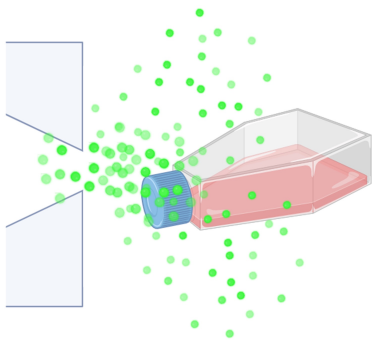



C-ions RT
D = 2 Gy



BNCT
various
irradiation times



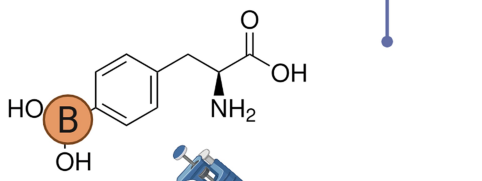
# Carbon-ions + BNCT

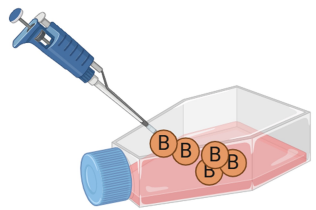
t=0

t=22 h

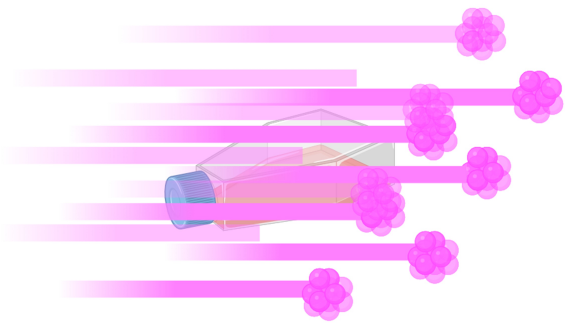
BPA contact

t=24 h

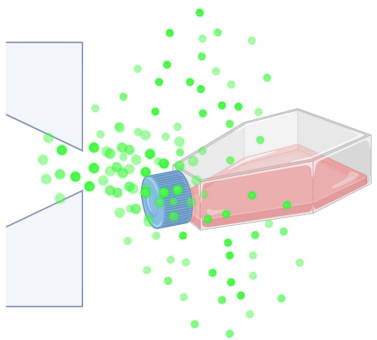



C-ions RT
various doses



BNCT
various
irradiation times



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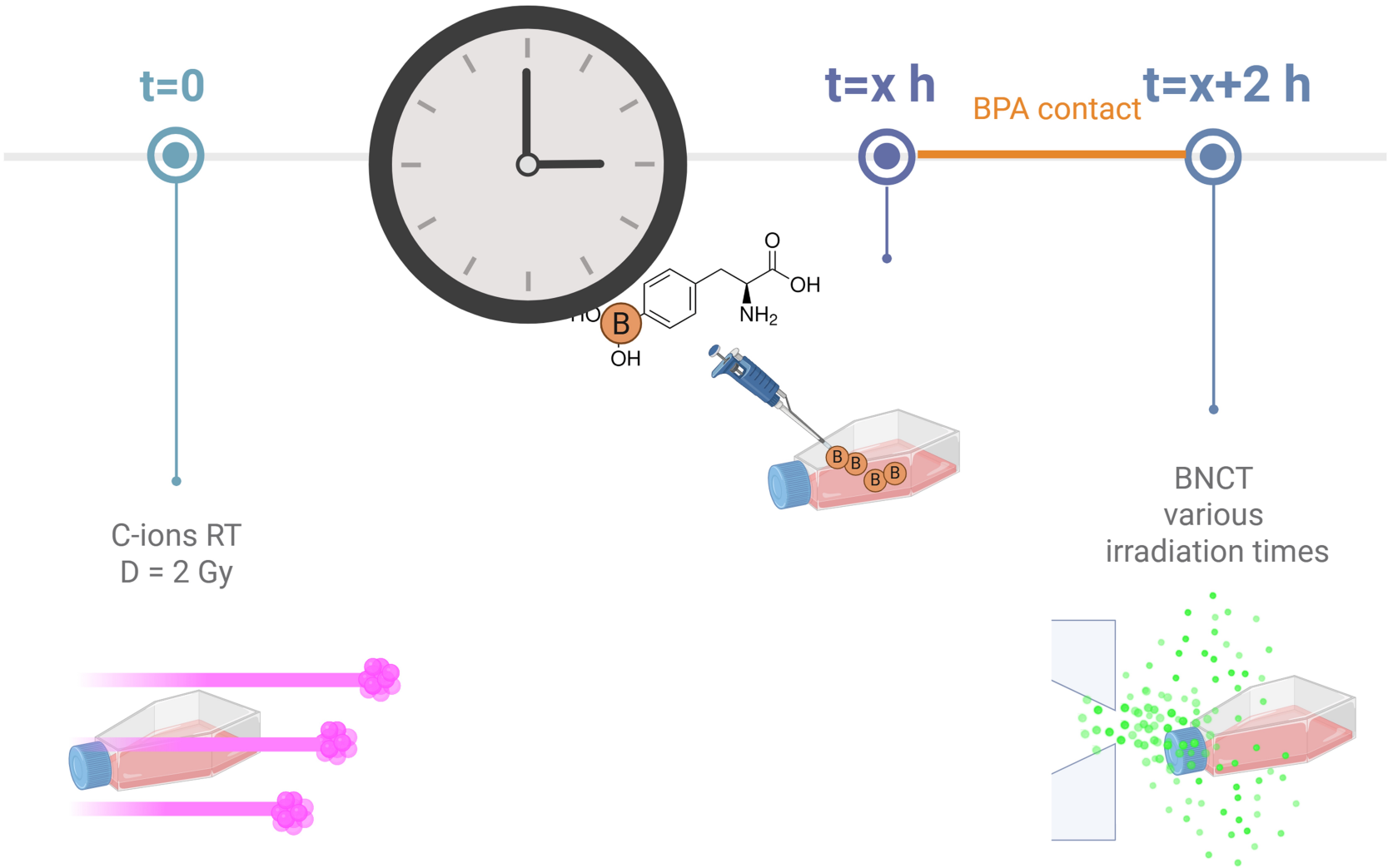
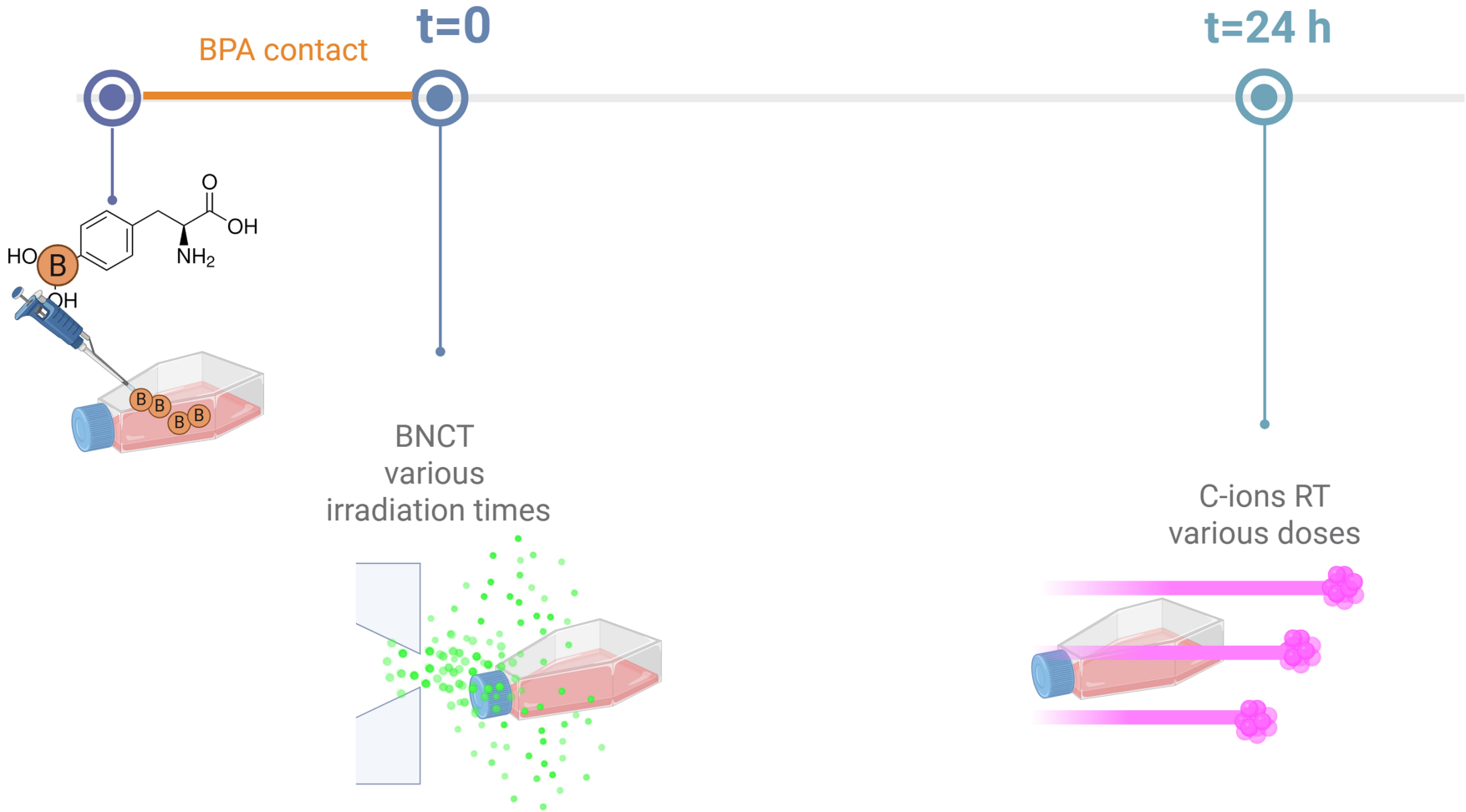
# Carbon-ions + BNCT



# BNCT + Carbon-ions

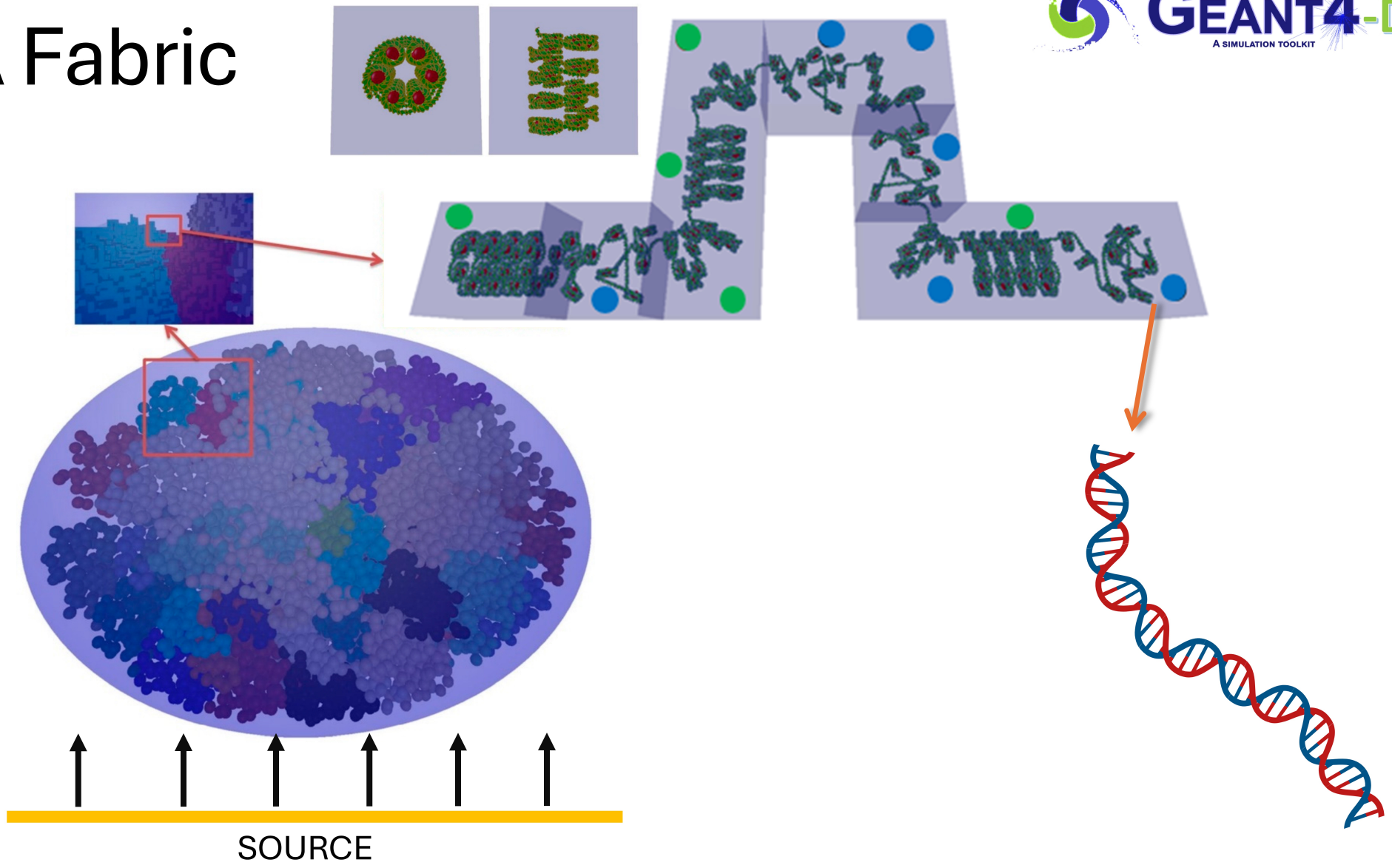


# In silico

IRSN becomes ASNR Autorité de sûreté nucléaire et de radioprotection

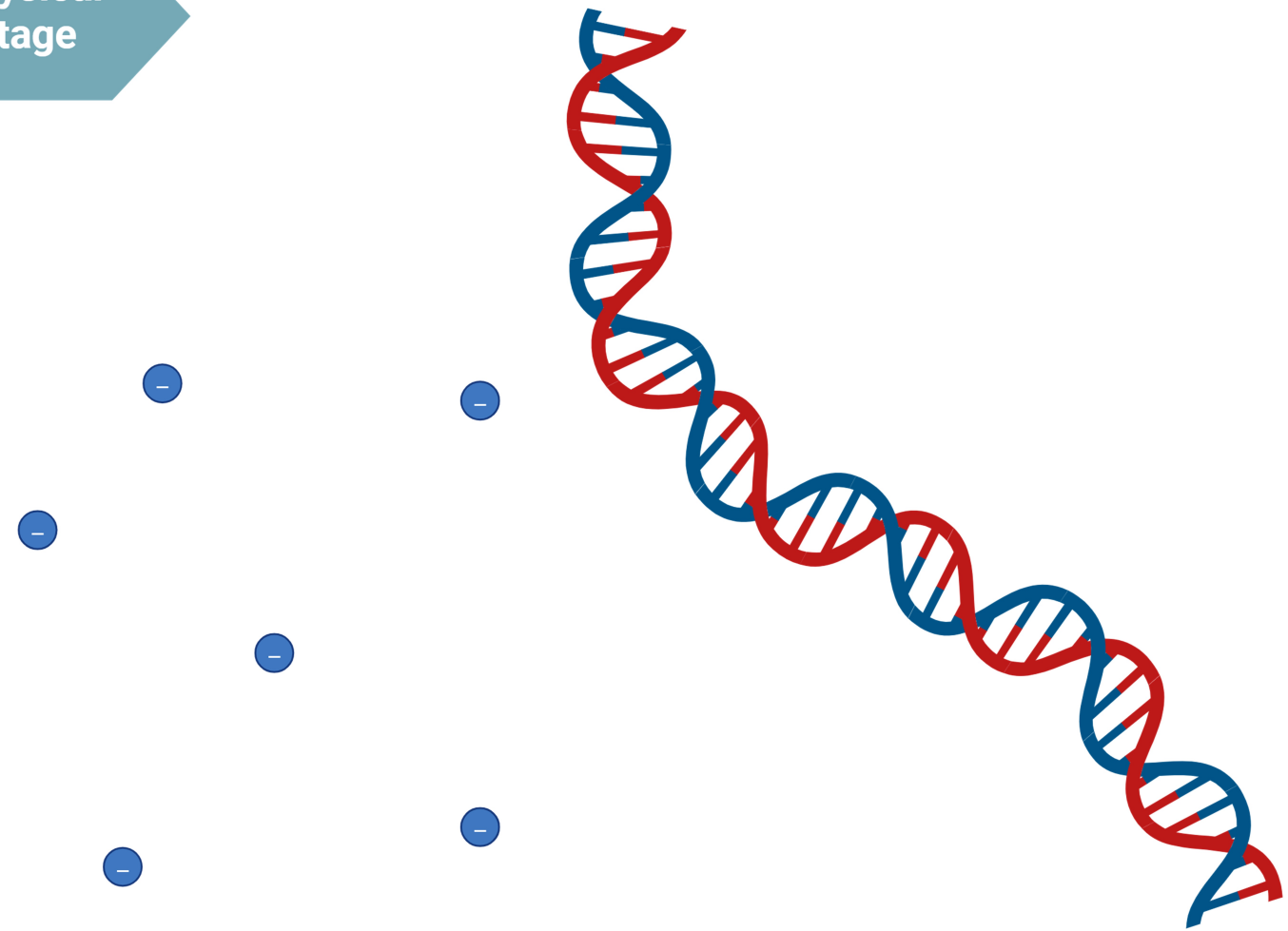
GEANT4-DNA A SIMULATION TOOLKIT

# DNA Fabric



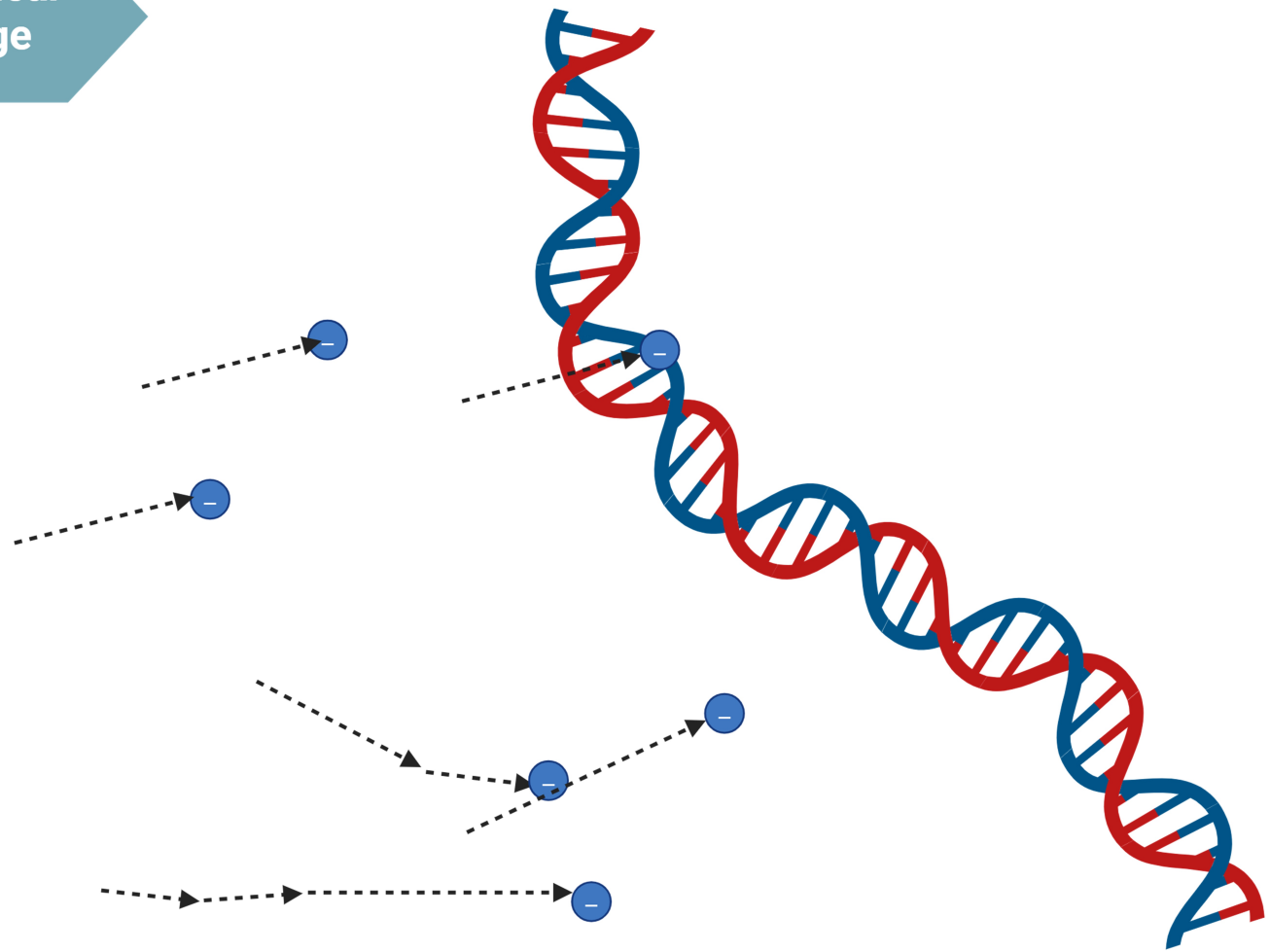
$10^{-17}$ - $10^{-12}$ s

**Physical stage**



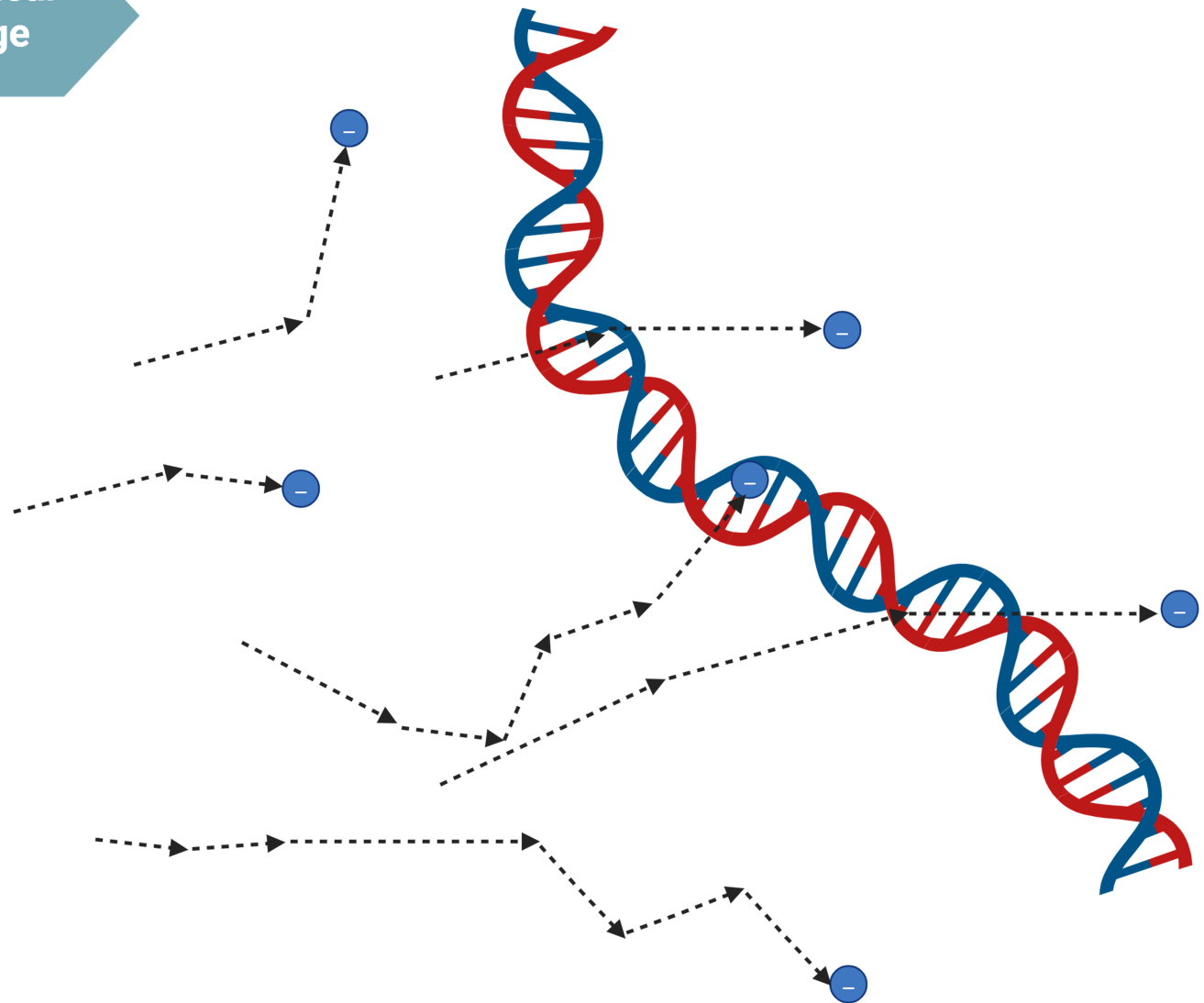
$10^{-17}$ - $10^{-12}$ s

**Physical stage**



$10^{-17}$ - $10^{-12}$ s

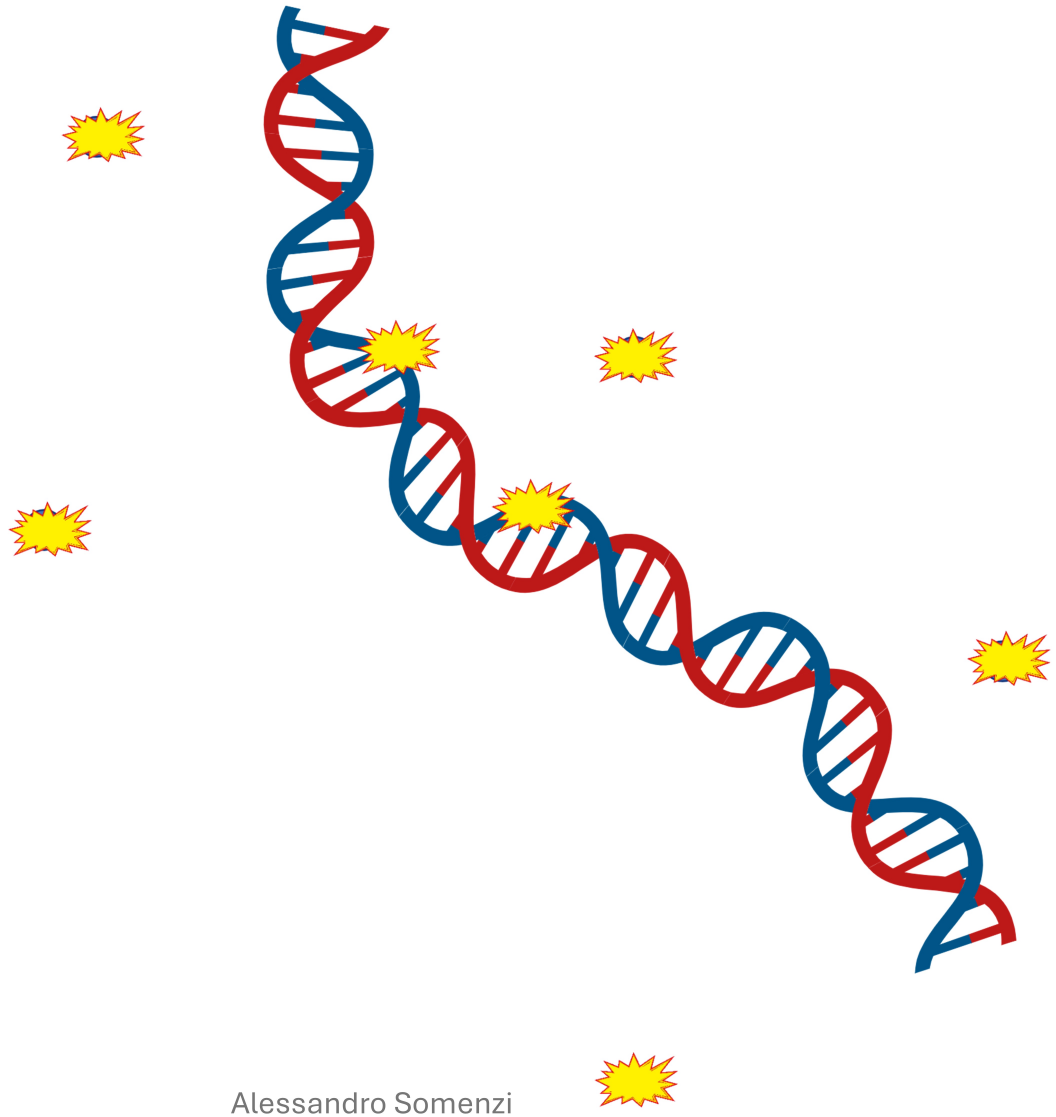
**Physical stage**

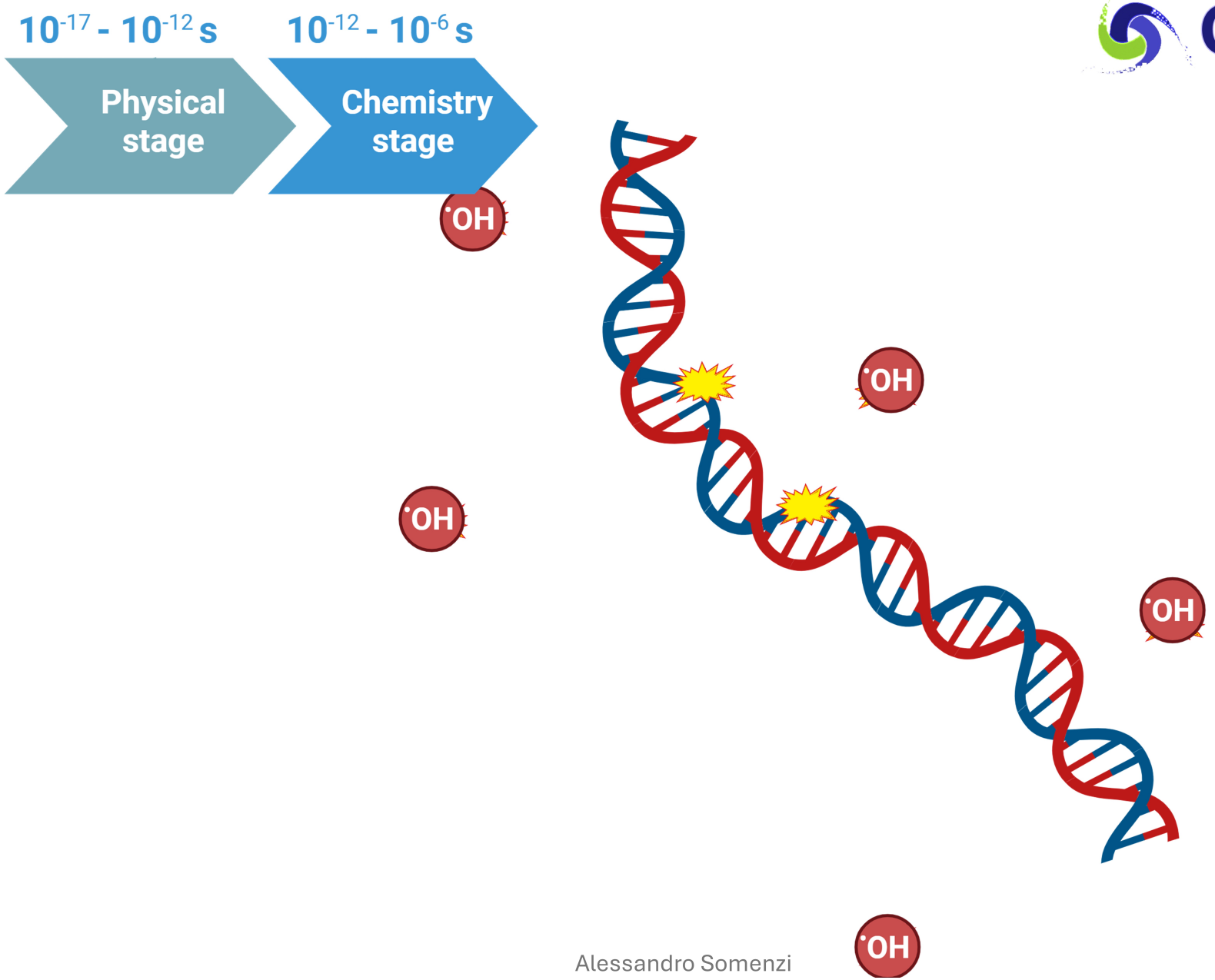


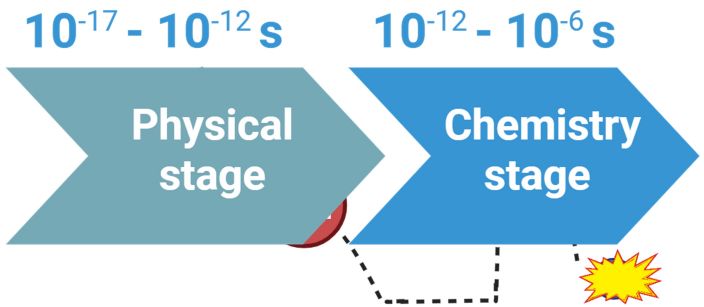
$10^{-17}$ - $10^{-12}$ s

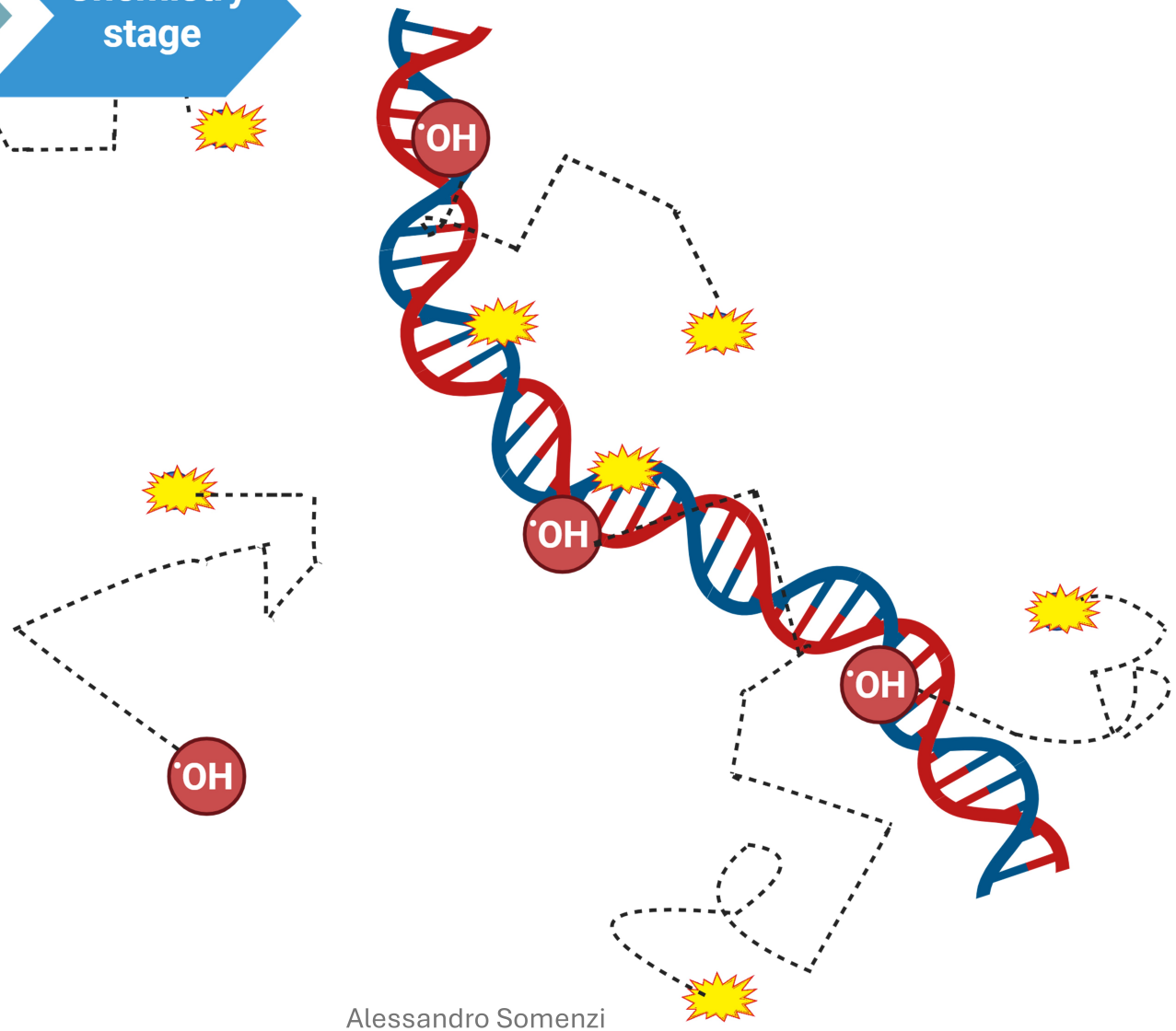
**Physical stage**

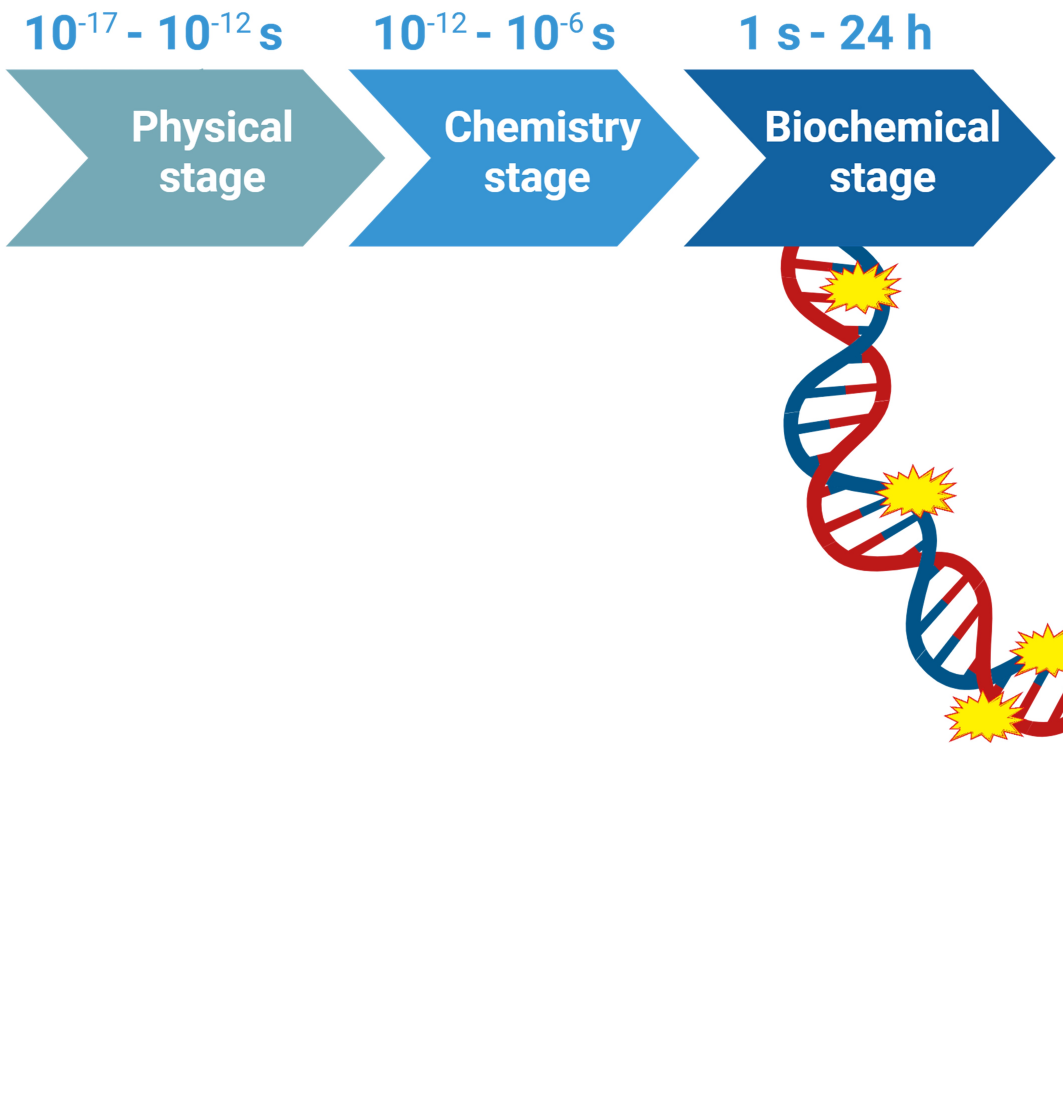
GEANT4-DNA
A SIMULATION TOOLKIT



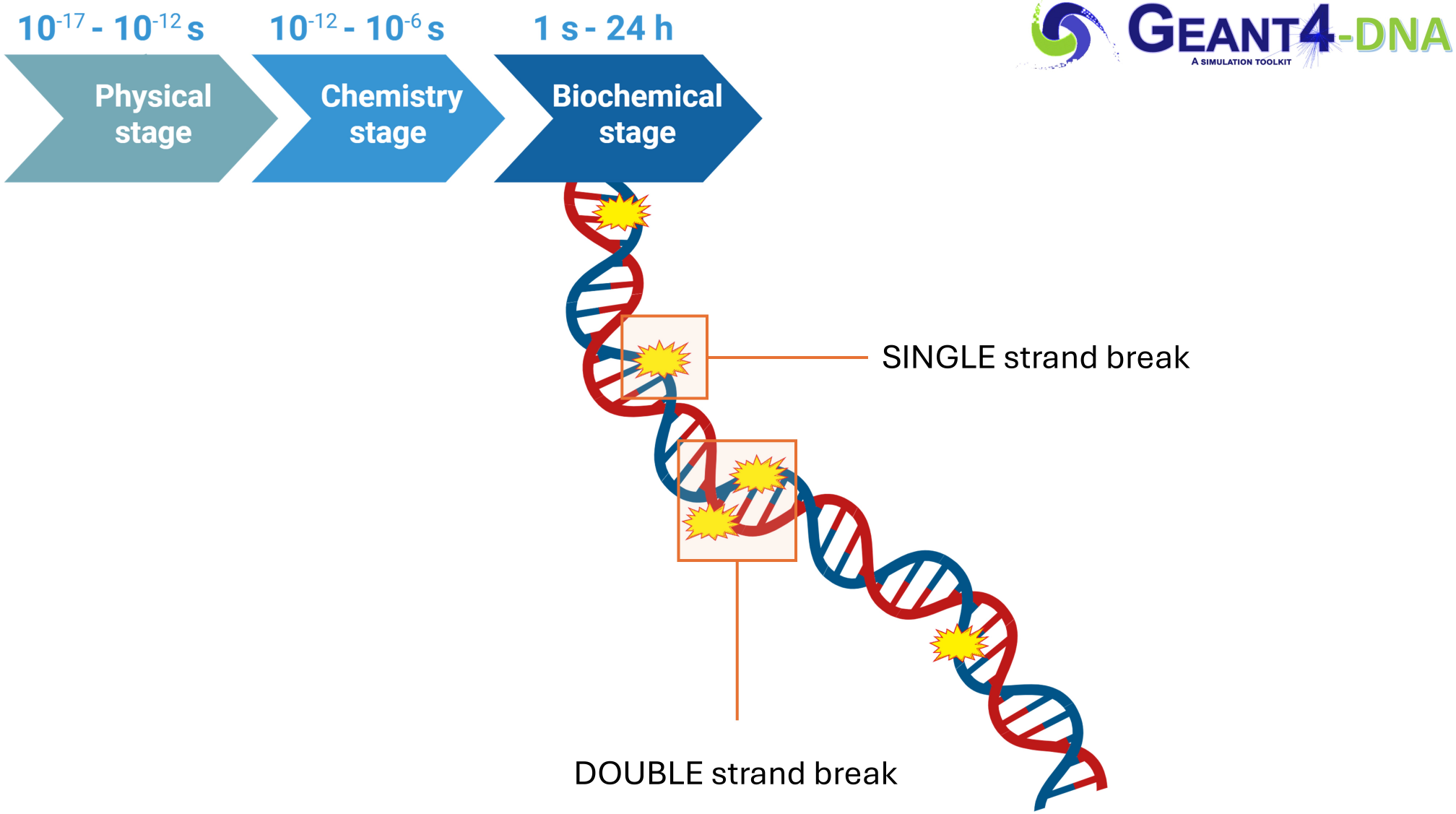

$10^{-17}$ - $10^{-12}$ s
$10^{-12}$ - $10^{-6}$ s
Physical stage
Chemistry stage
•OH
•OH
•OH
•OH
•OH


$10^{-17}$ - $10^{-12}$ s
$10^{-12}$ - $10^{-6}$ s
Physical stage
Chemistry stage


•OH
•OH
•OH
•OH

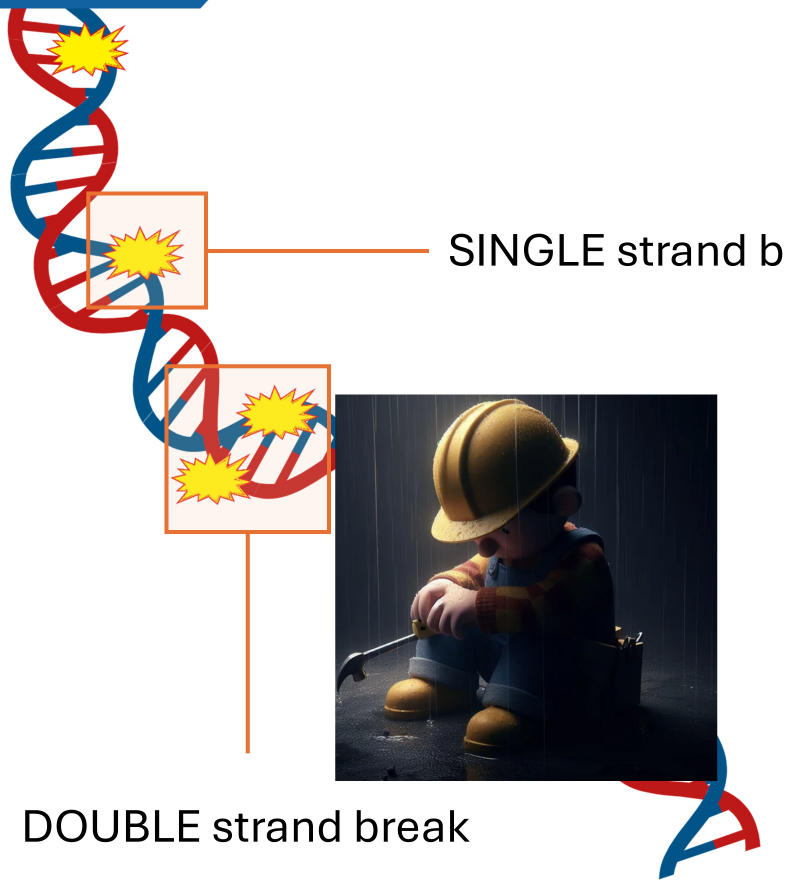



GEANT4-DNA
A SIMULATION TOOLKIT


$10^{-17}$ - $10^{-12}$ s
$10^{-12}$ - $10^{-6}$ s
1 s - 24 h
Physical stage
Chemistry stage
Biochemical stage
SINGLE strand break
DOUBLE strand break

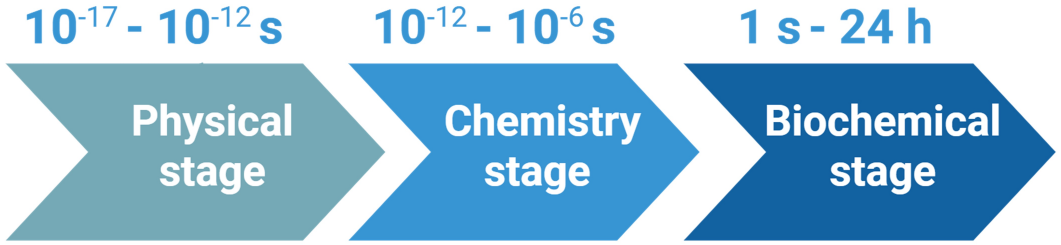
$10^{-17}$ - $10^{-12}$ s | $10^{-12}$ - $10^{-6}$ s | 1 s - 24 h

Physical stage → Chemistry stage → Biochemical stage



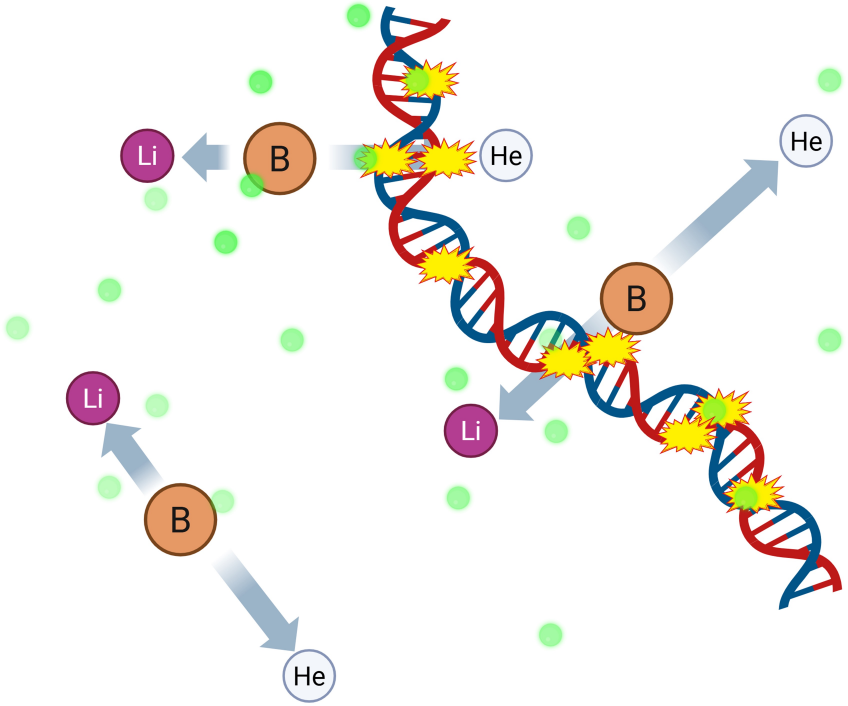
SINGLE strand break

DOUBLE strand break

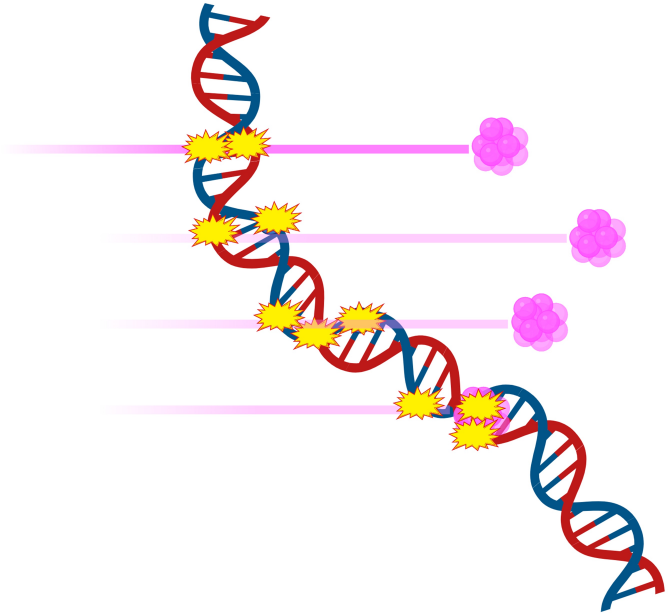



GEANT4-DNA
A SIMULATION TOOLKIT

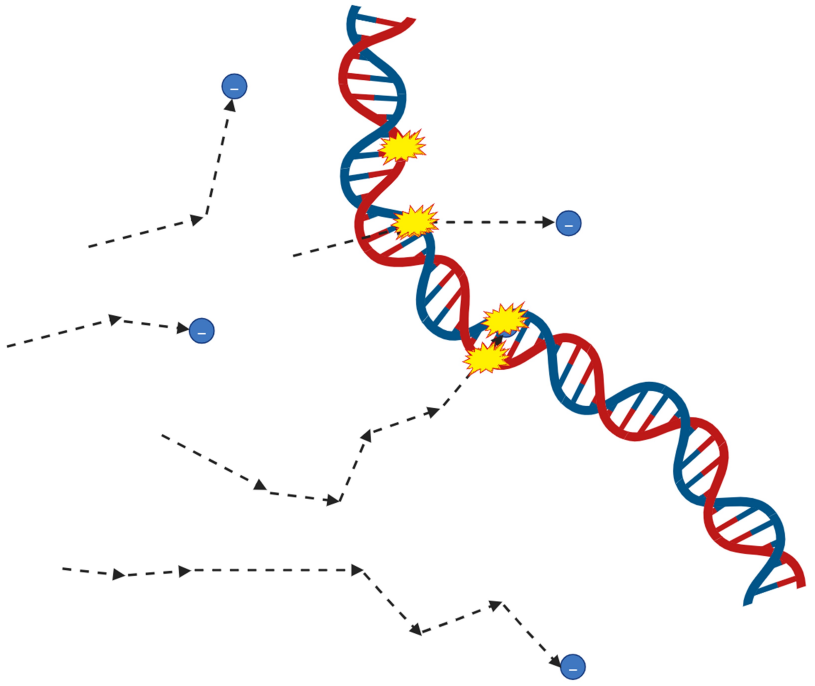
## BNCT

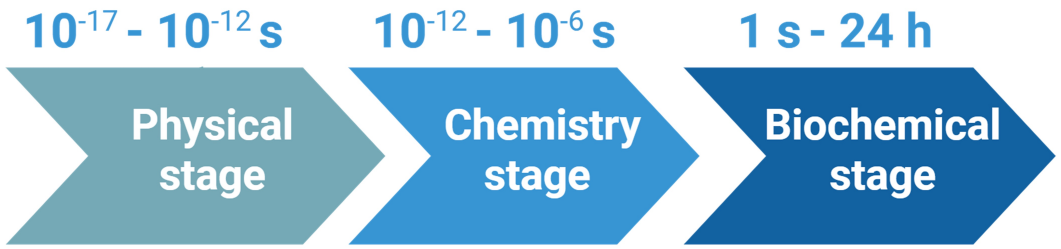



## C-ions



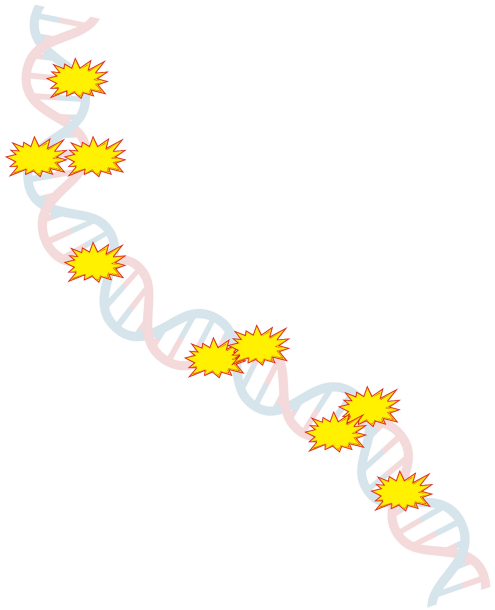
## X-rays



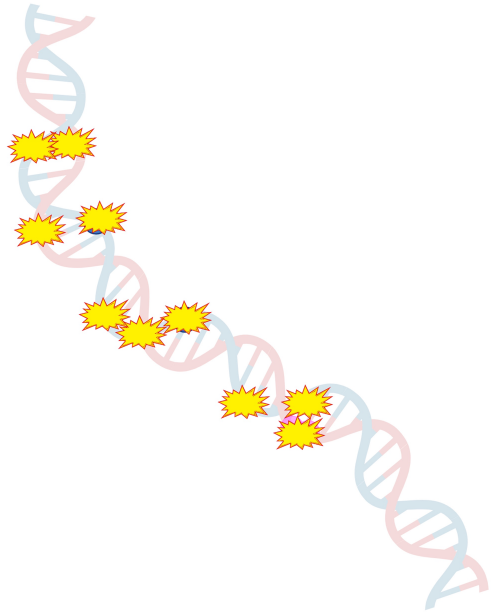



GEANT4-DNA
A SIMULATION TOOLKIT

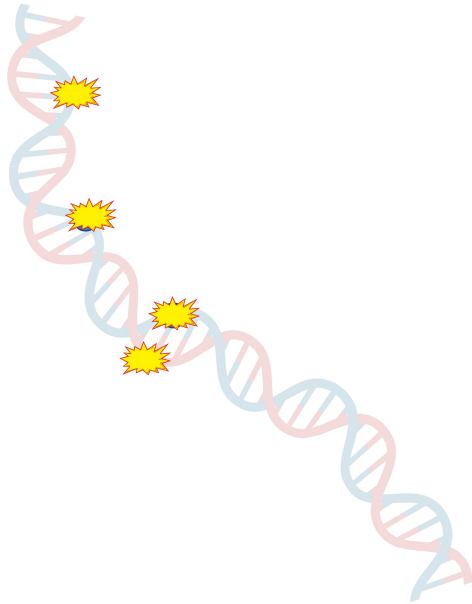
BNCT



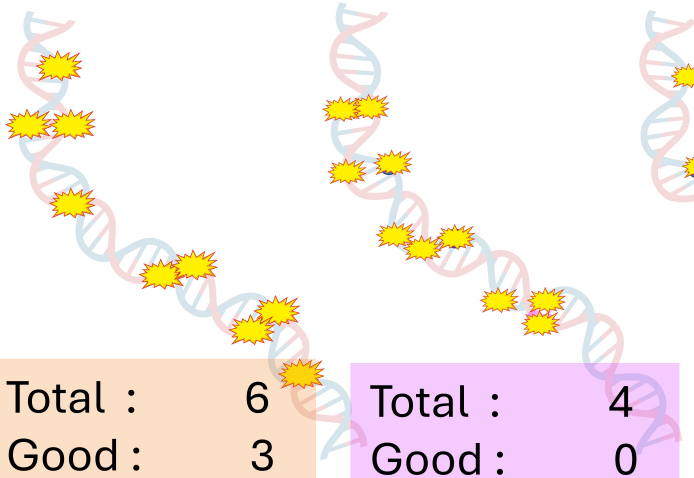
C-ions



X-rays



BNCT C-ions X-rays

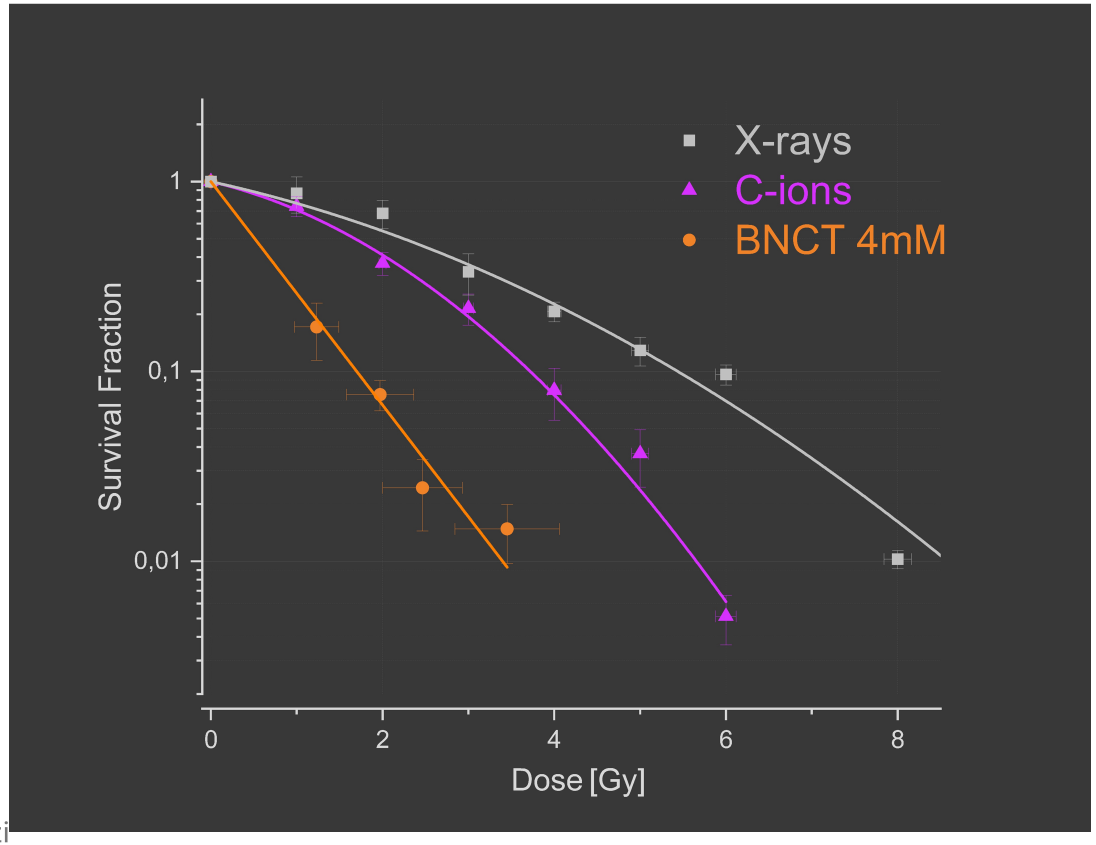


| BNCT | |
|---|---|
| Total : | 6 |
| Good : | 3 |
| Bad : | 3 |
| Very bad: | 0 |

| C-ions | |
|---|---|
| Total : | 4 |
| Good : | 0 |
| Bad : | 1 |
| Very bad: | 3 |

| X-rays | |
|---|---|
| Total : | 3 |
| Good : | 2 |
| Bad : | 1 |
| Very bad: | 0 |

Survival after 10 days

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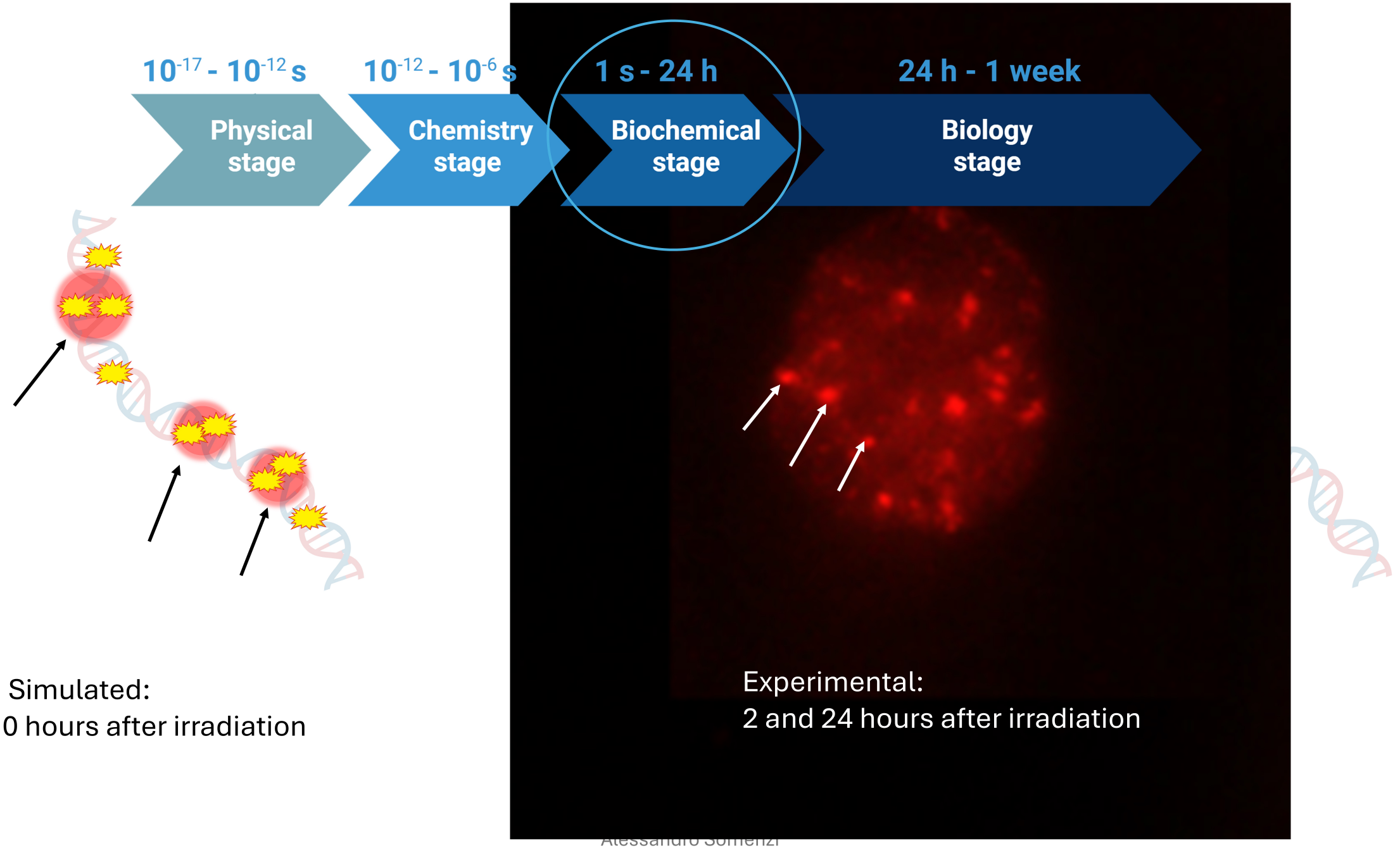
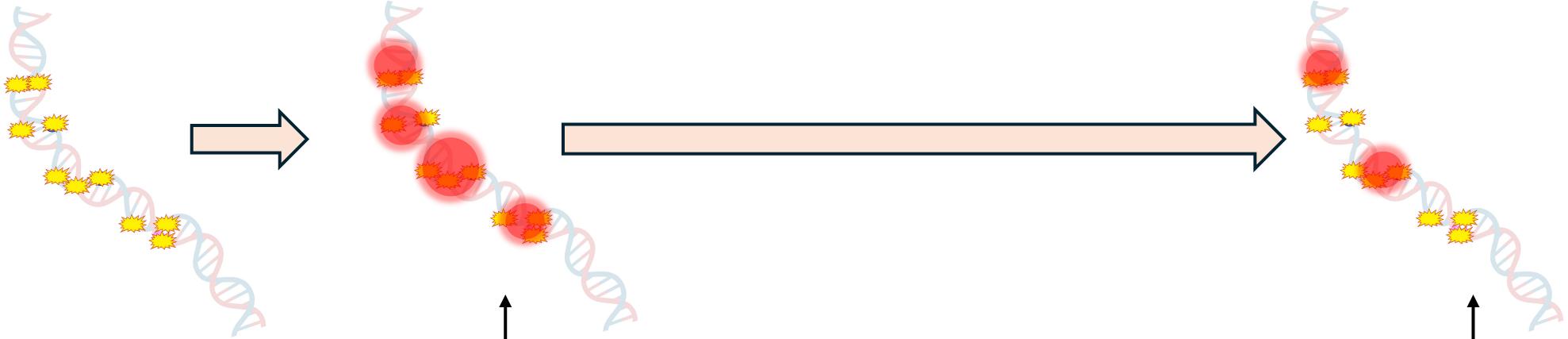
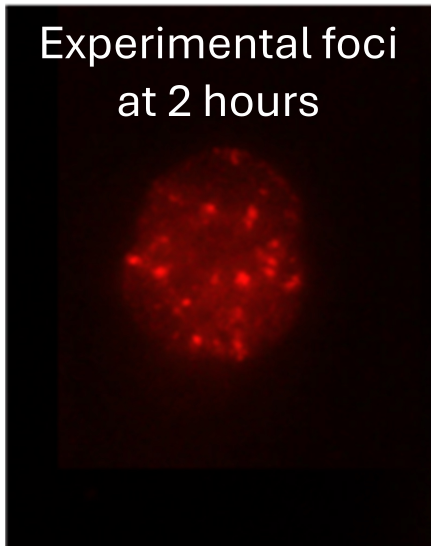

$10^{-17}$ - $10^{-12}$ s
$10^{-12}$ - $10^{-6}$ s
1 s - 24 h
24 h - 1 week
Physical stage
Chemistry stage
Biochemical stage
Biology stage
Simulated:
0 hours after irradiation
Experimental:
2 and 24 hours after irradiation

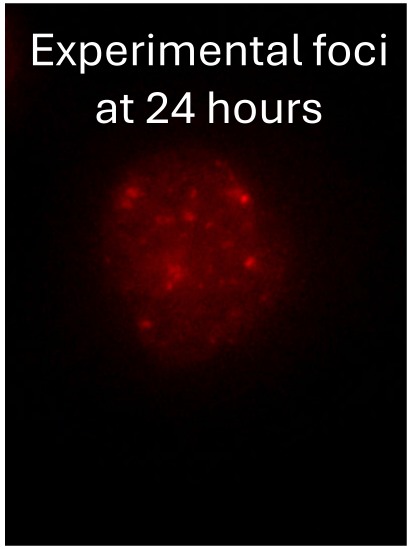
Initial damages yield

Foci 2 hours

Foci 24 hours

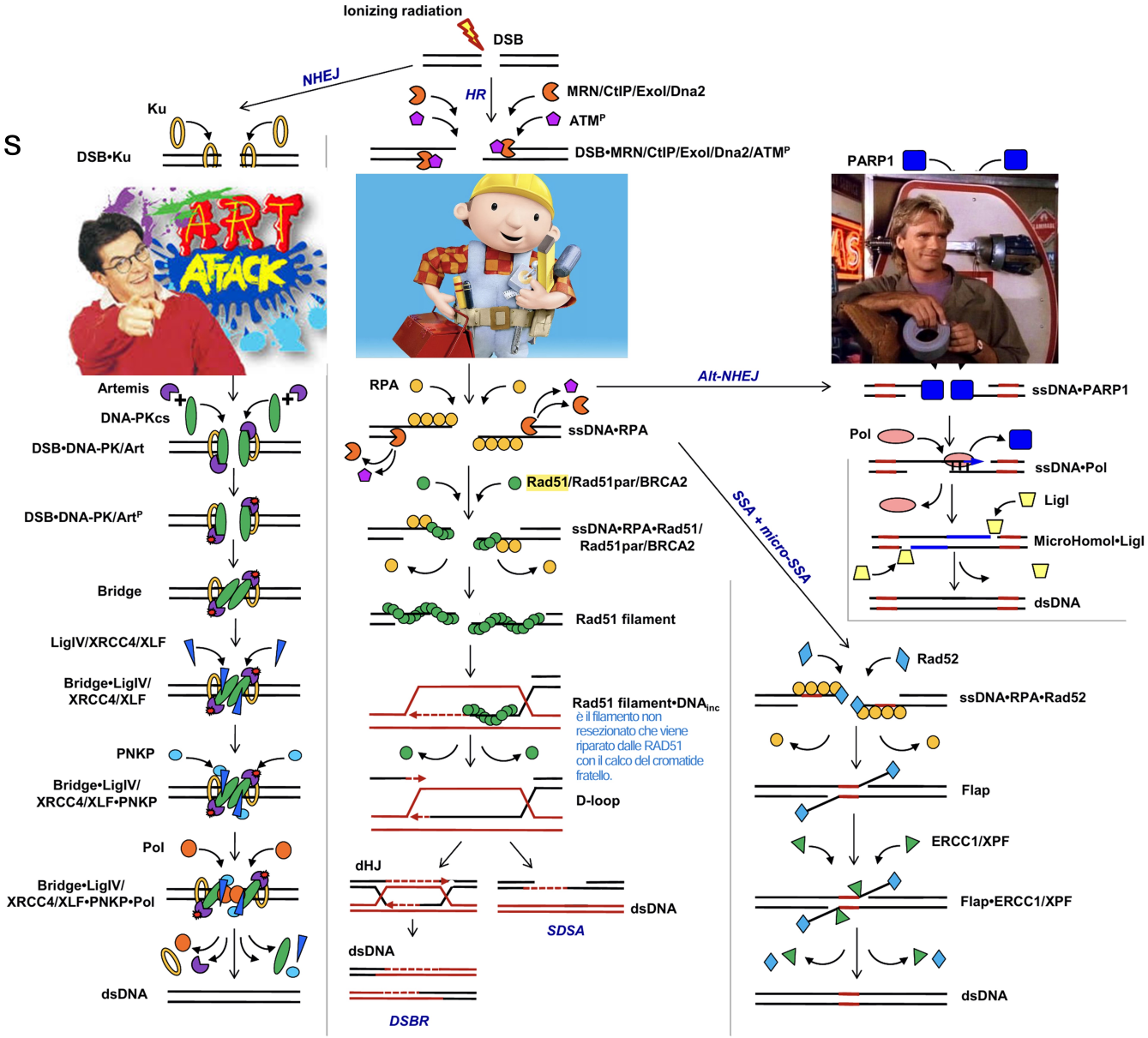




# Belov model

(of the cellular mechanisms
for radio-induced
DNA damage repair)



# repair mechanisms

Initial damages yield

Foci 2 hours

Foci 24 hours

## Belov model

$$\frac{dN_0}{dt} = \alpha(L)\frac{dD}{dt}N_{ir} - V$$ $$- V$$ $$- V$$

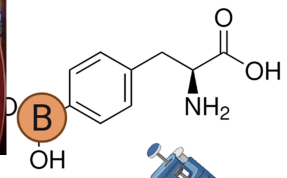
# Carbon-ions + BNCT

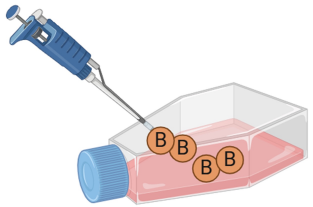
t=0

t=22 h

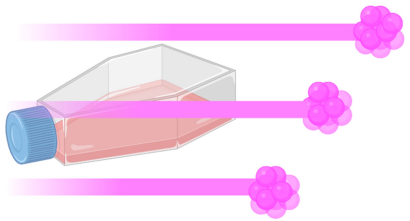
BPA contact

t=24 h

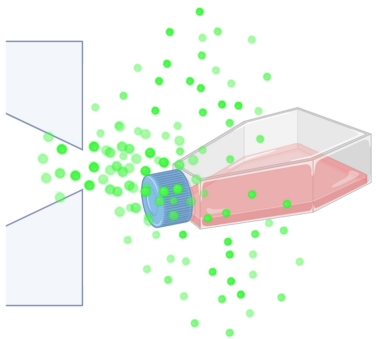


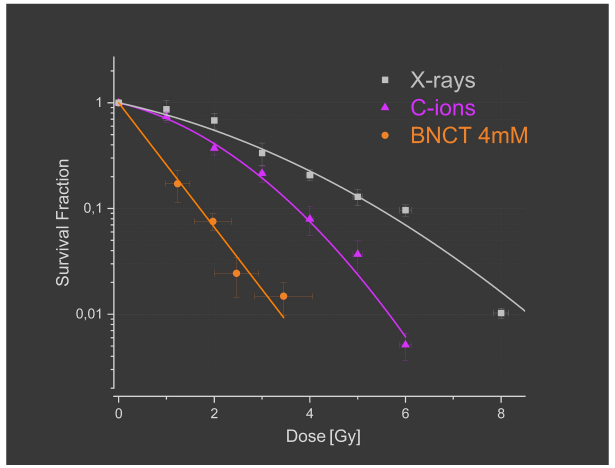

C-ions RT
D = 2 Gy



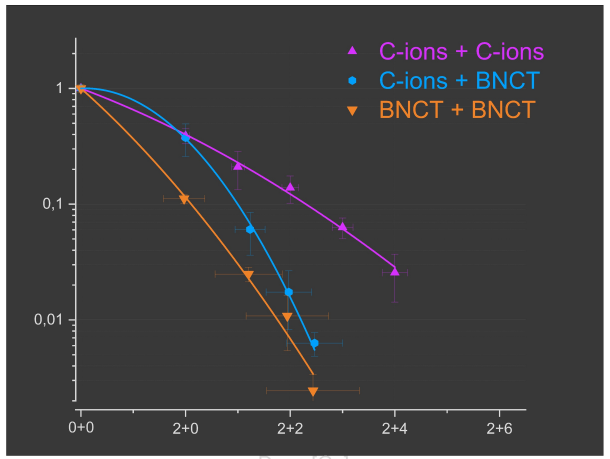
BNCT
various
irradiation times



# Conclusions...




BNCT (4 mM BPA) most effective treatment on PANC-1 cell line



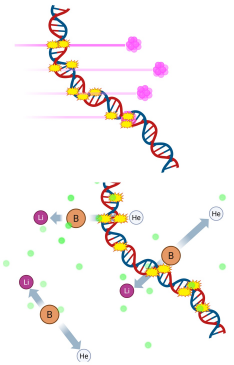

The Combined treatment C-ions RT + BNCT has a higher biological effectiveness than C-ions + C-ions

Intermediate effects between C-ions and BNCT

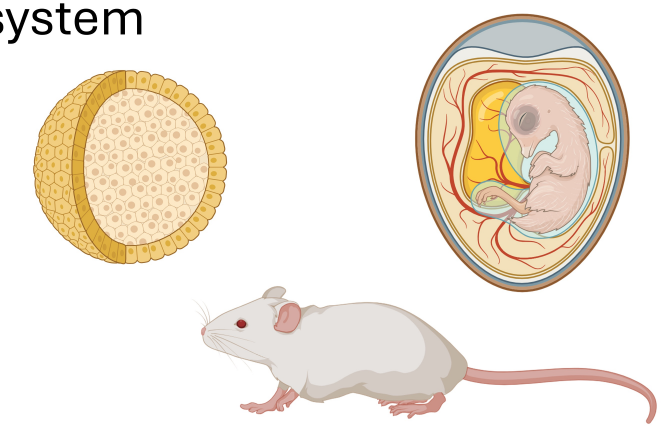
# ... and Next Steps

Match survival curves & simulations
Continue the investigation of the mechanisms involved in the combined treatment

GEANT4-DNA
A SIMULATION TOOLKIT



3D models with vascular system



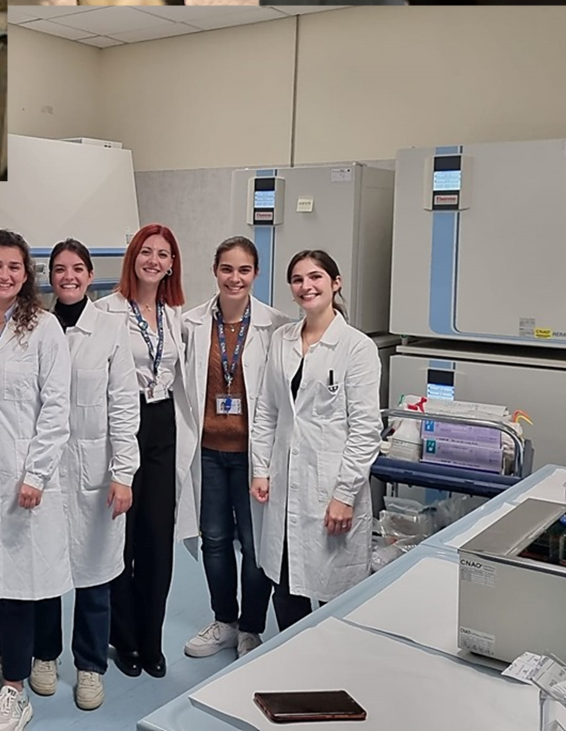
Thanks

CNAO
Centro Nazionale di Adroterapia Oncologica

IRSN becomes ASNR Autorité de sûreté nucléaire et de radioprotection

L.E.N.A.

Yann



Fondazione CNAO, Pavia
R&D department chief Dr. Marco Pullia and Radiobiology group

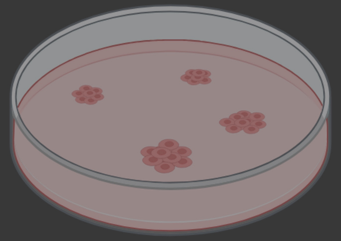
L.E.N.A., Pavia

ASNR, Fontanay aux Roses, France
Laboratoire de dosimétrie des rayonnements ionisants, Chief Dr. Carmen Villagrasa and Dr Yann Perrot

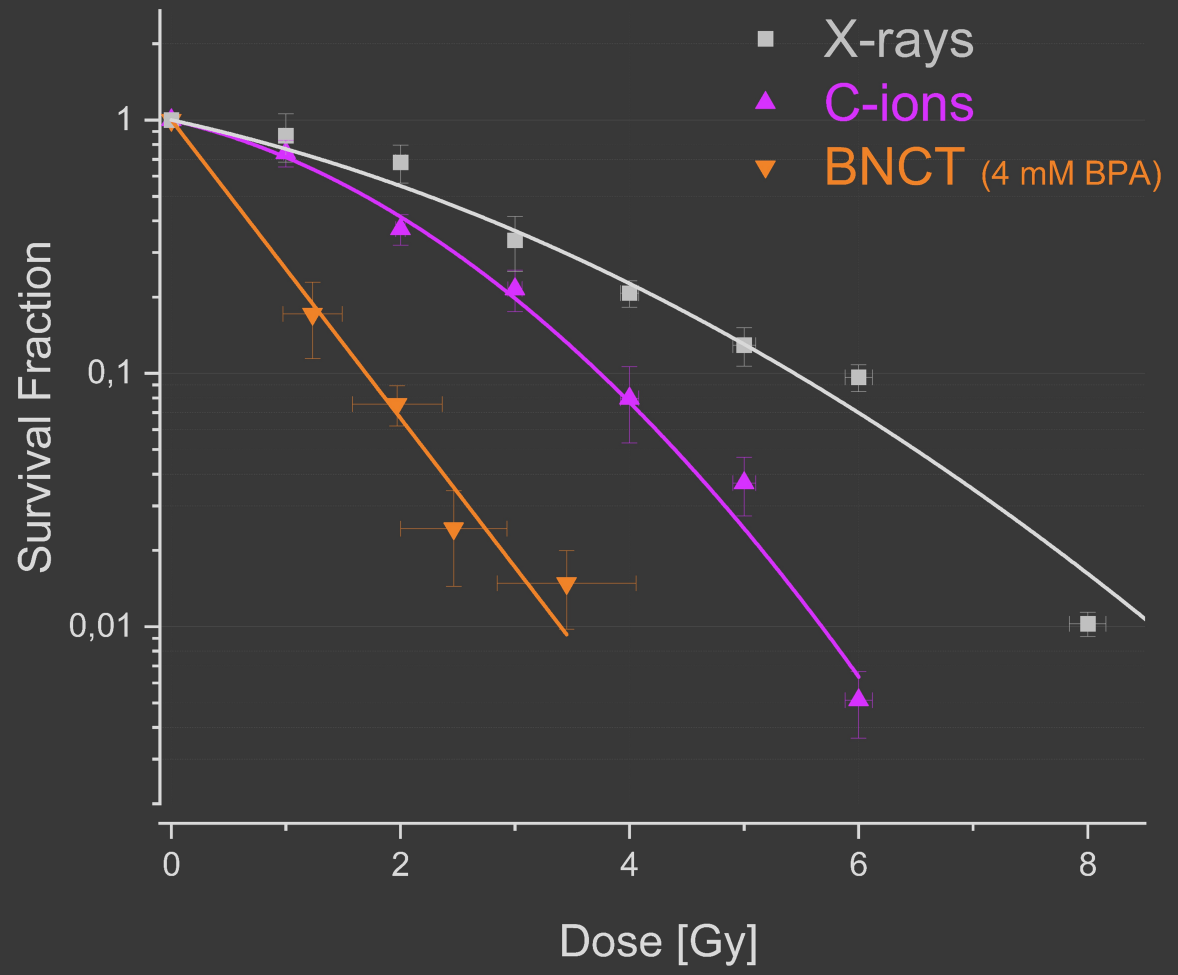
University of Torino
Simonetta Geninatti and Diego Alberti

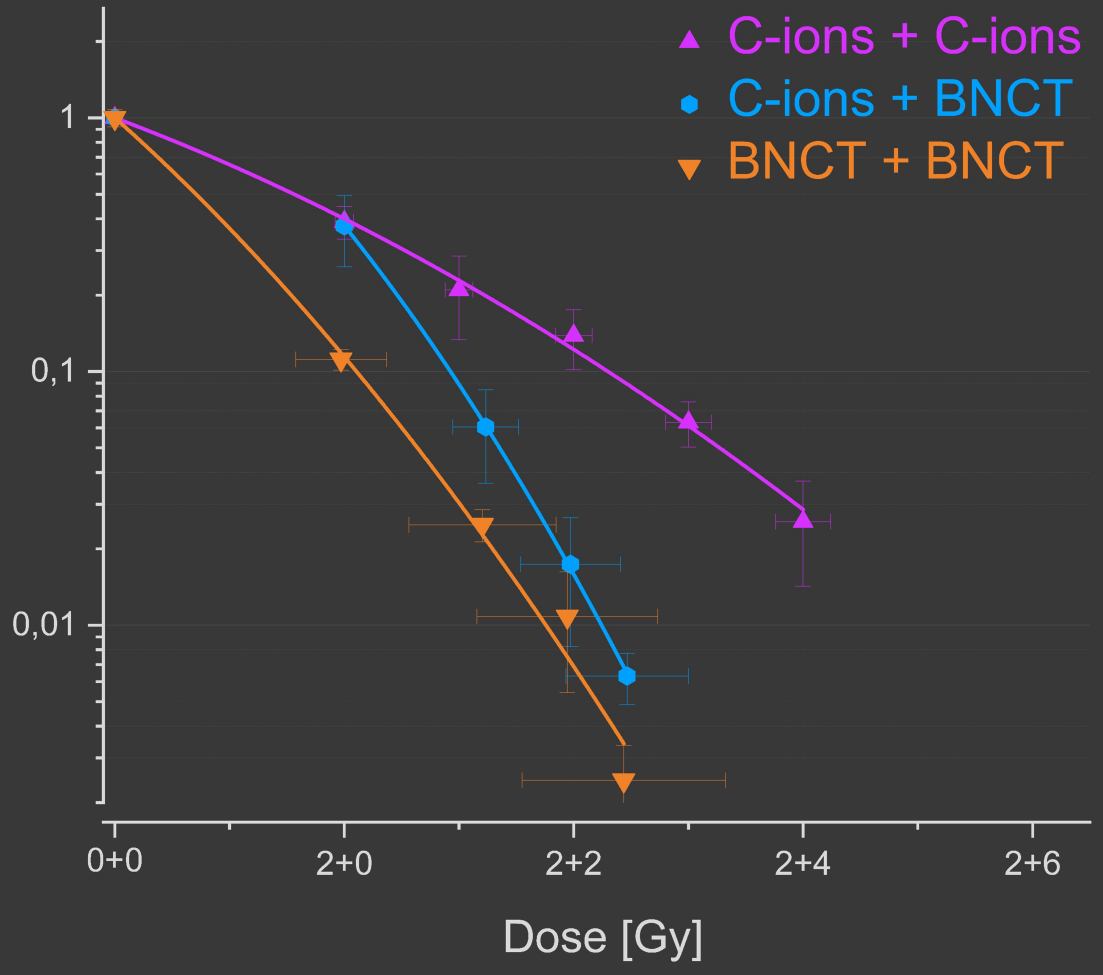
Centro Grandi Strumenti, UNIPV

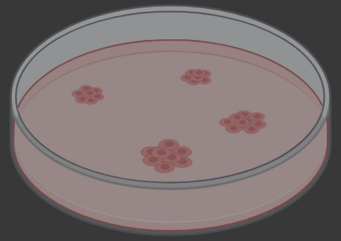
IRCCS Maugeri



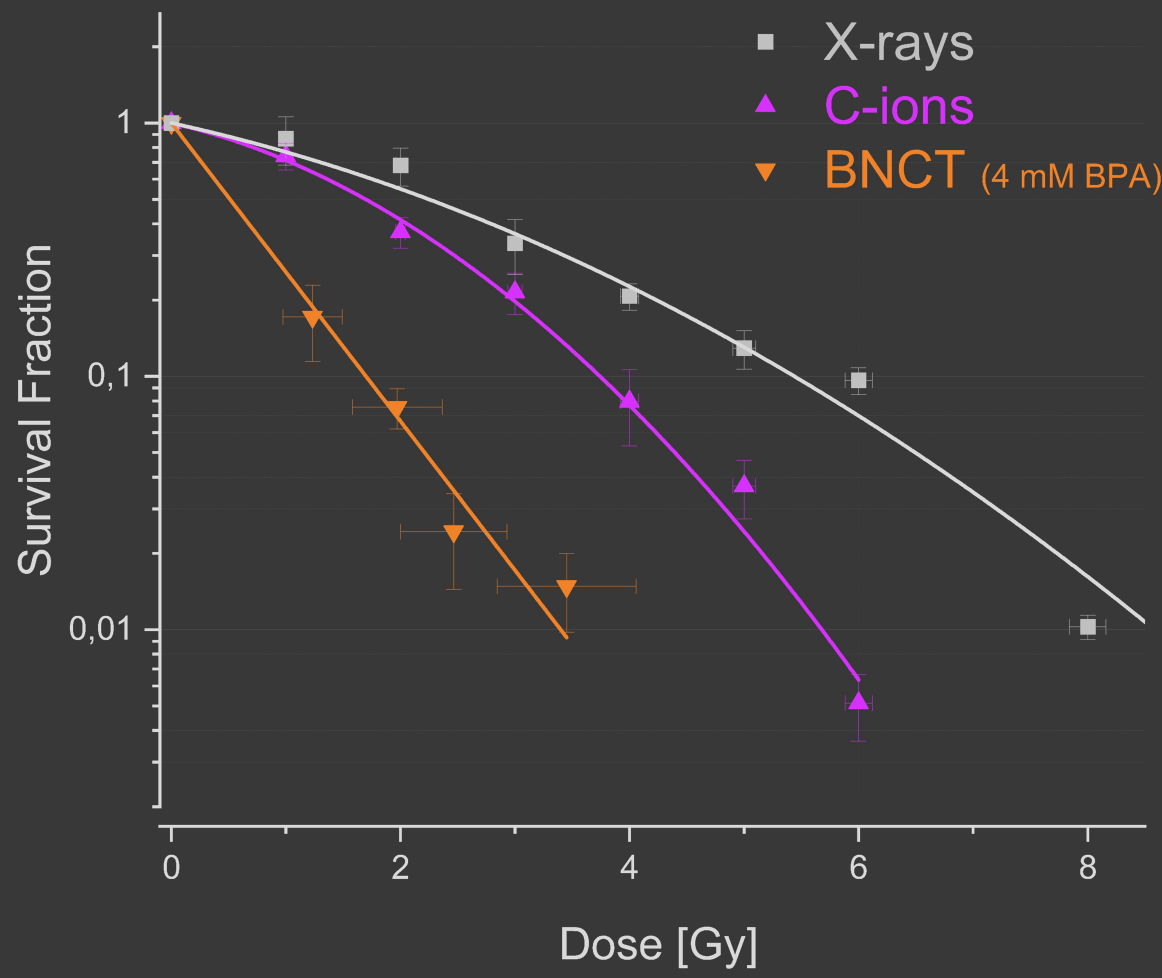
# Dose-Survival curves

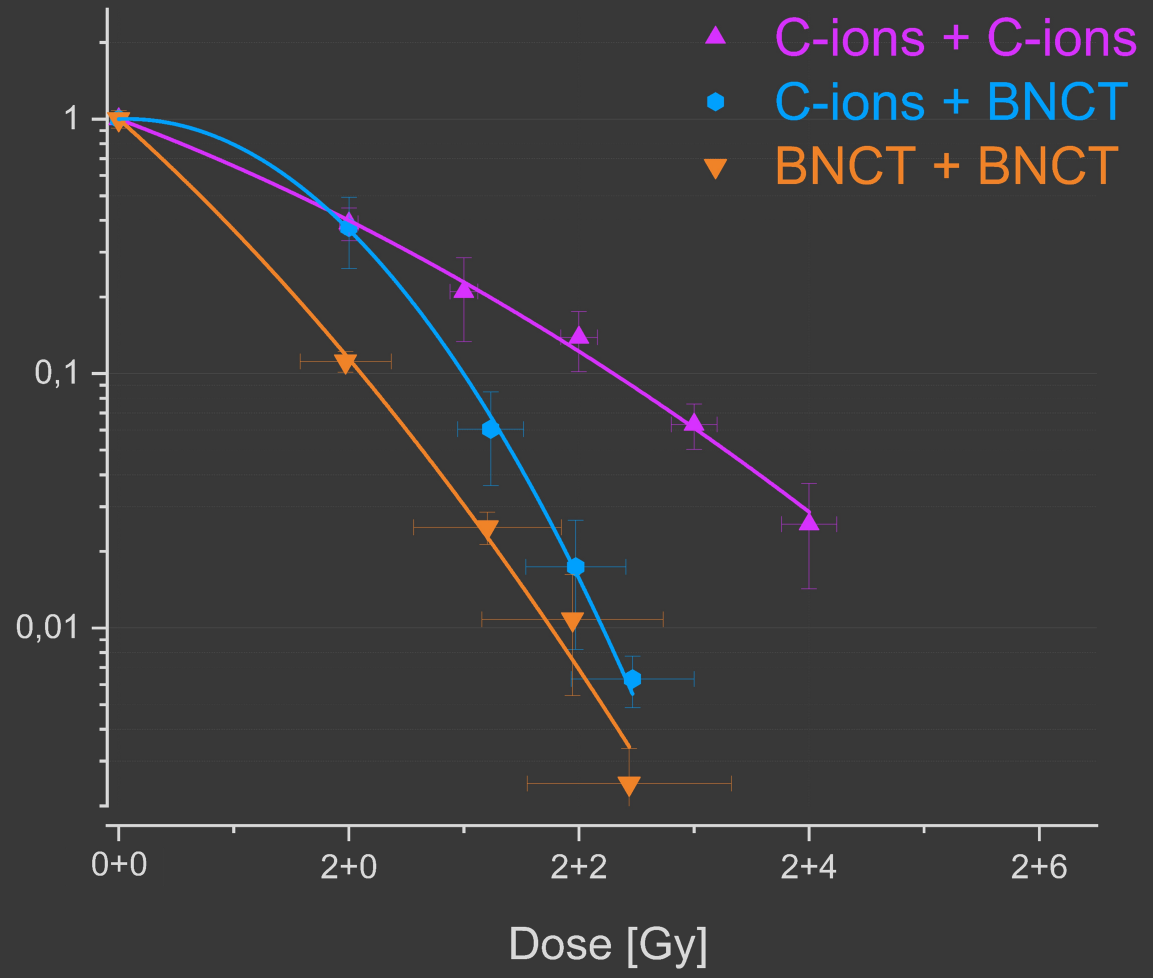


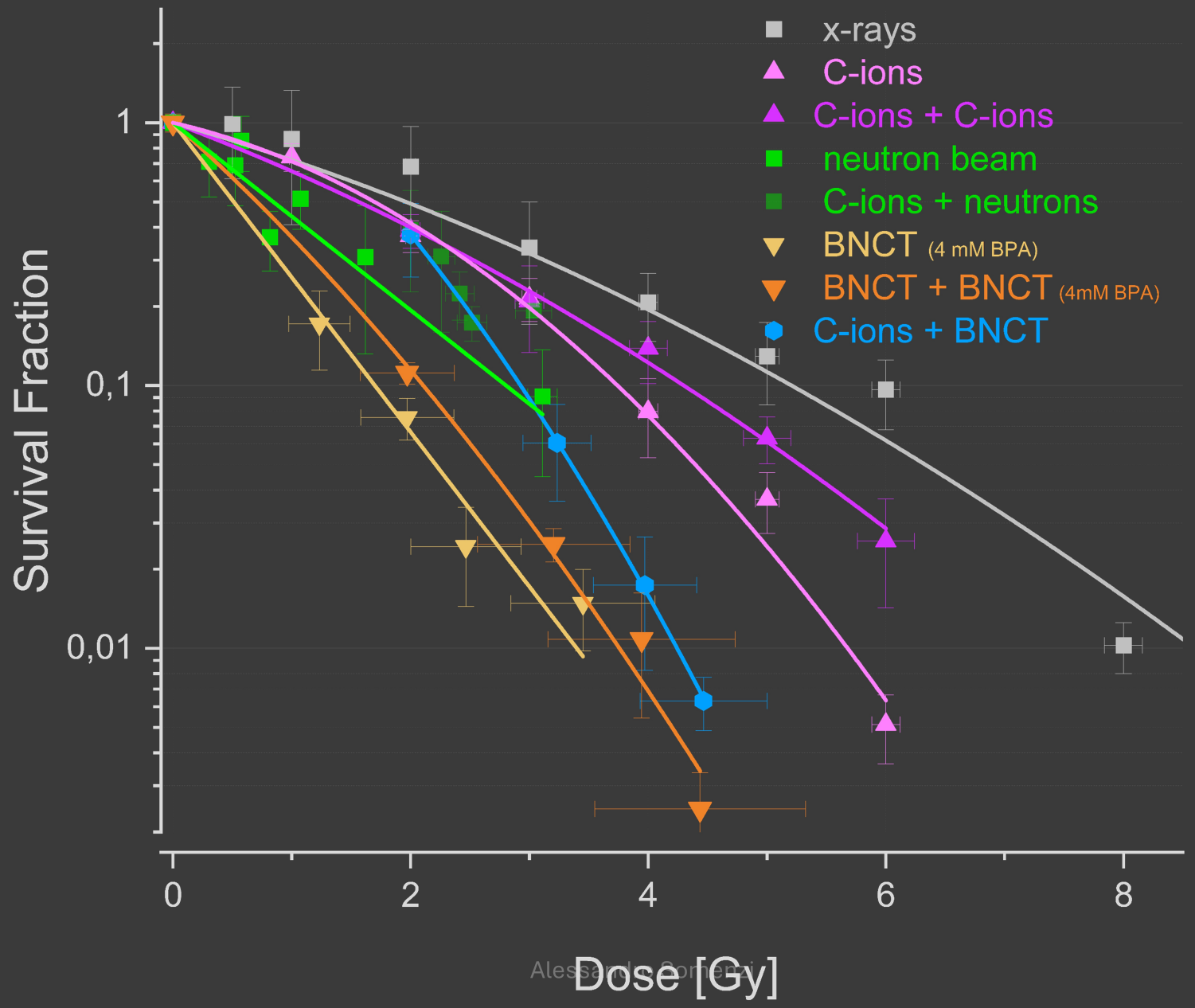





# Dose-Survival curves




x-rays
C-ions
C-ions + C-ions
neutron beam
C-ions + neutrons
BNCT (4 mM BPA)
BNCT + BNCT (4mM BPA)
C-ions + BNCT
Survival Fraction
1
0,1
0,01
0
2
4
6
8
Dose [Gy]