Nanoradiator therapy and synchrotron X-ray imaging of malignant brain tumor

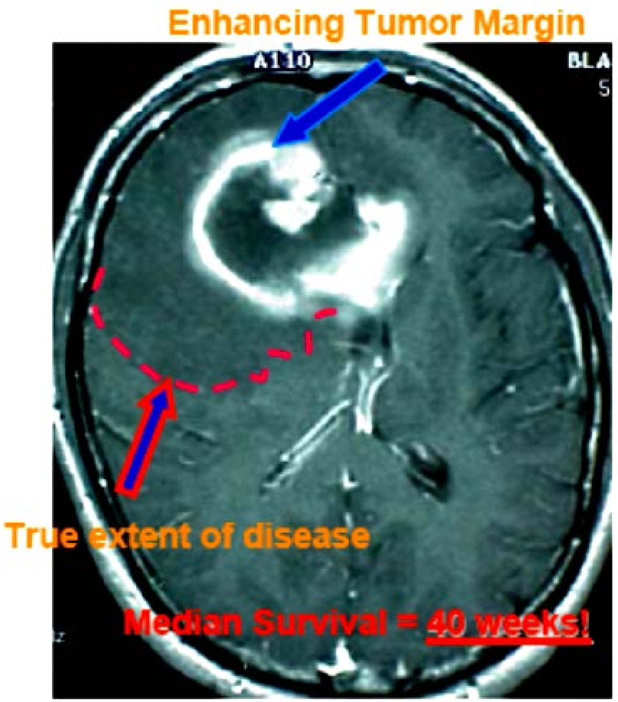
Jong-Ki Kim, Seung-Jun Seo, Sung-Mi Han, Jae-Kun Jeon, Won-Seok Jang,

Catholic University of Daegu, Korea

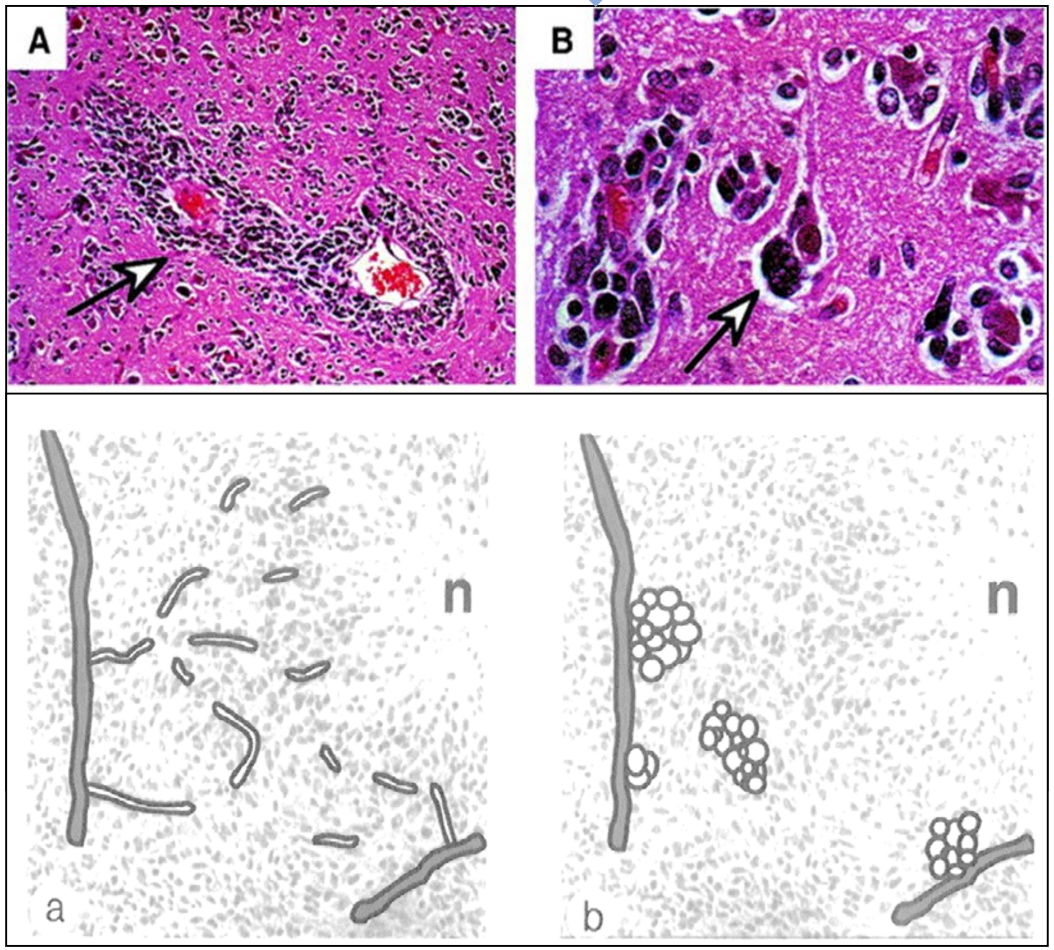
Ando Masami, Sunaguchi, Tetsuya Yuasa,

Tokyo University of Science, Gunma & Yamagata Universities

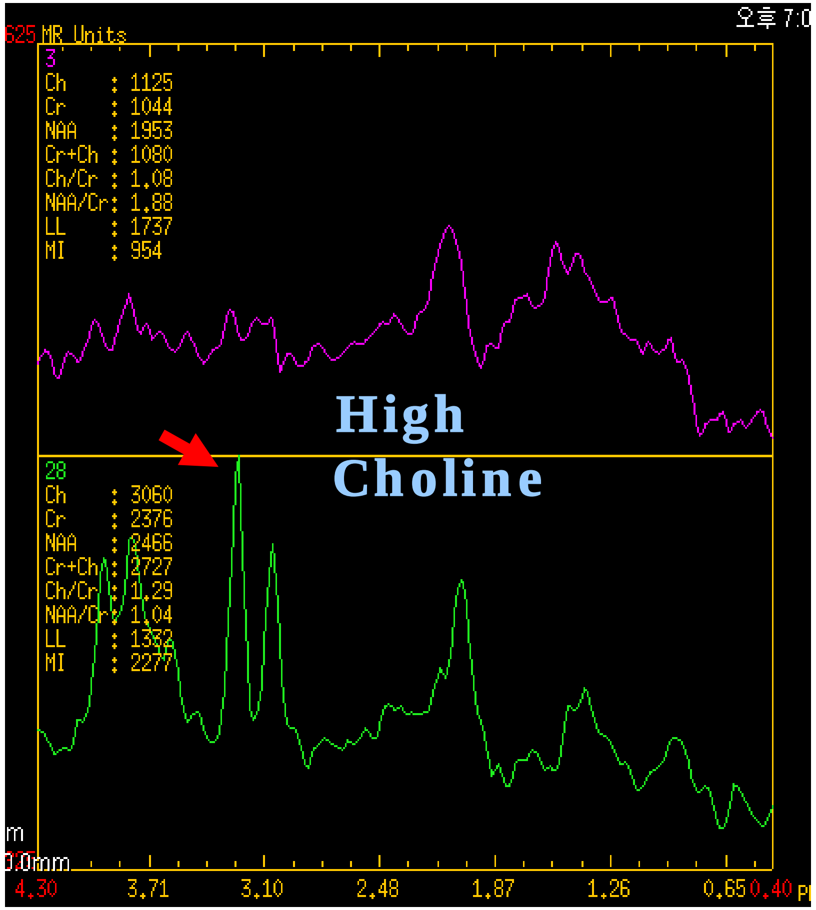
Infiltrative Malignant glioma
:Detecting microvessel proliferation



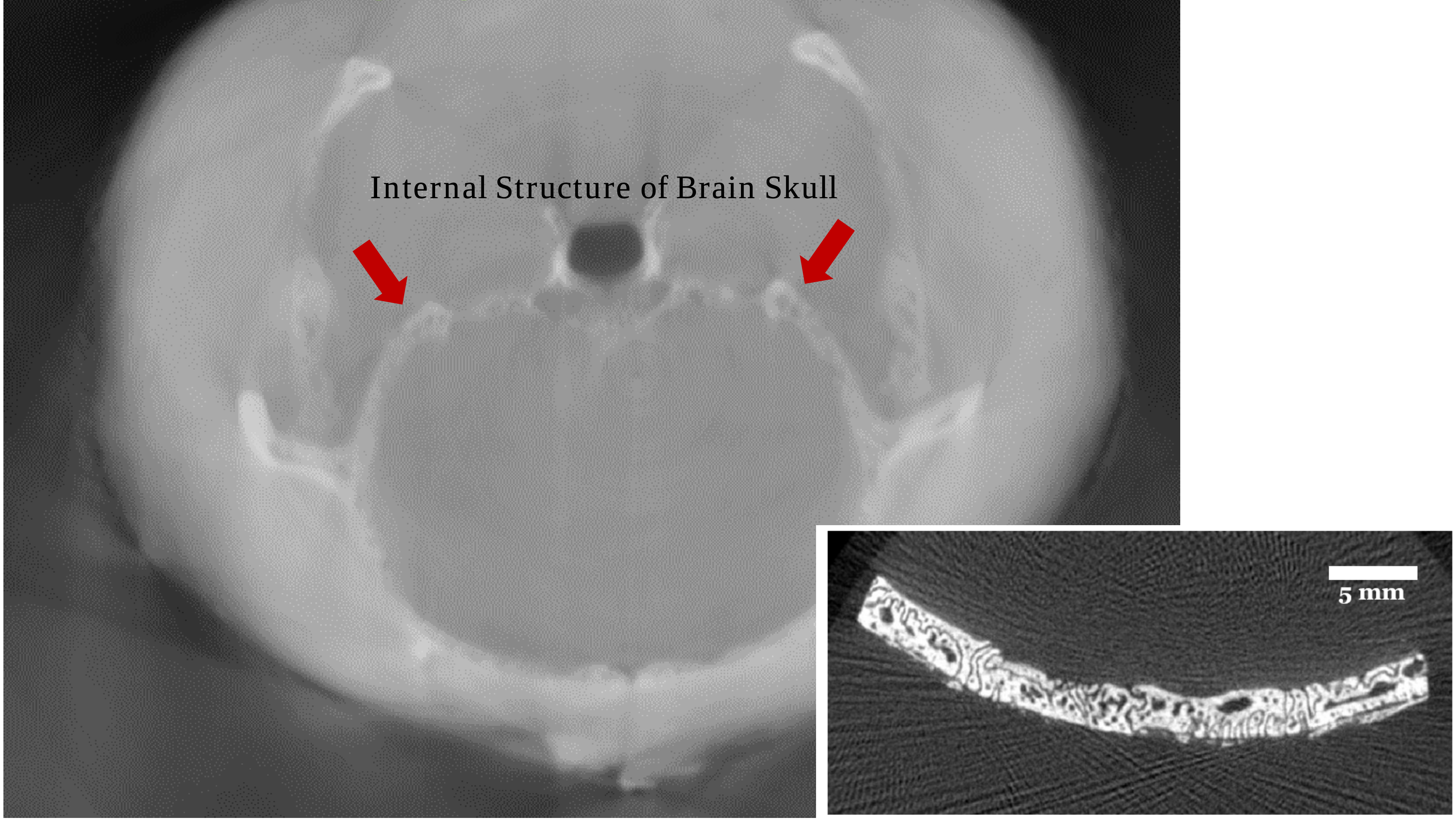
Gadolinium Enhanced MRI Scan:
Glioblastoma



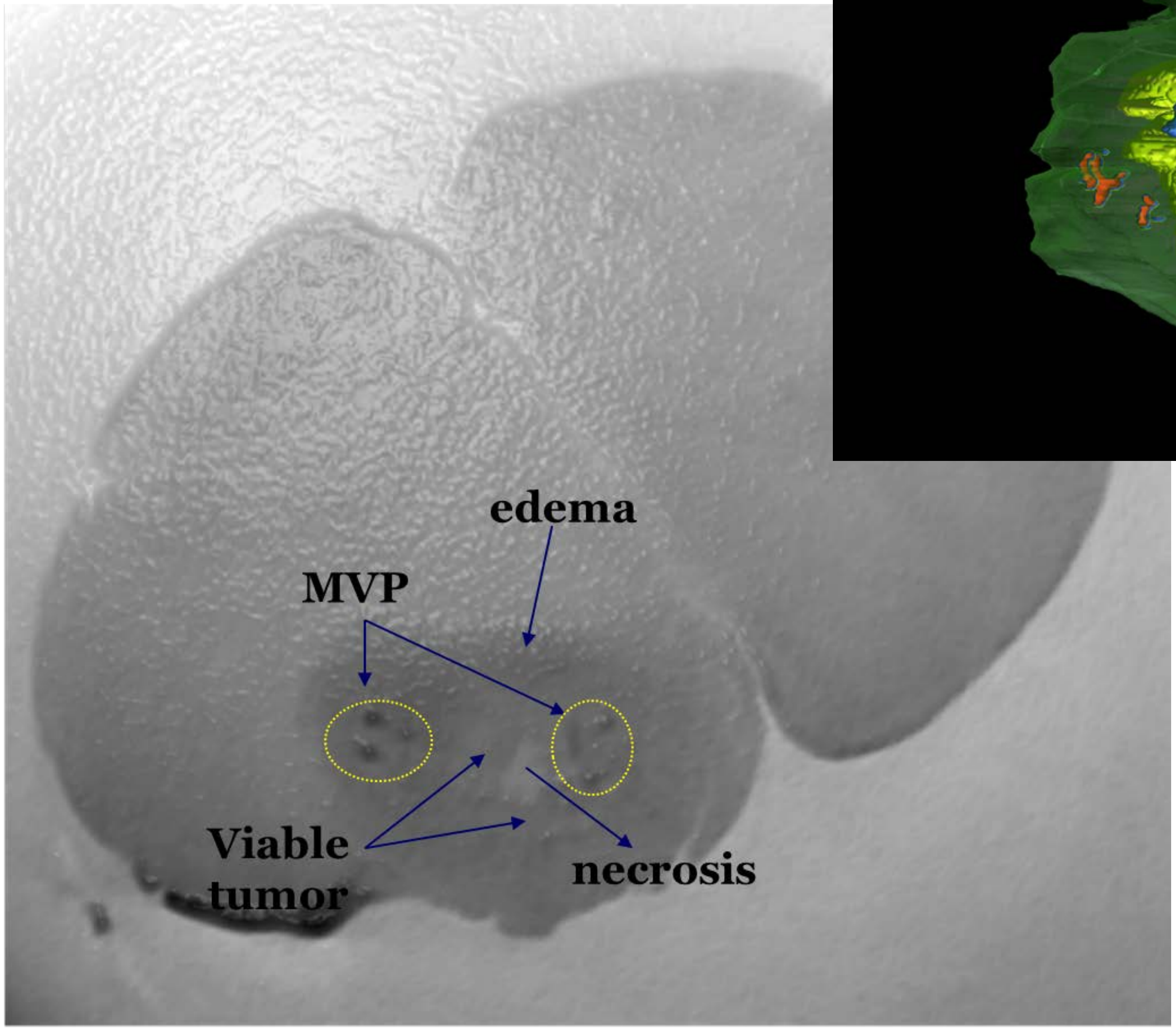
In vivo ^{1}H MR spectroscopy

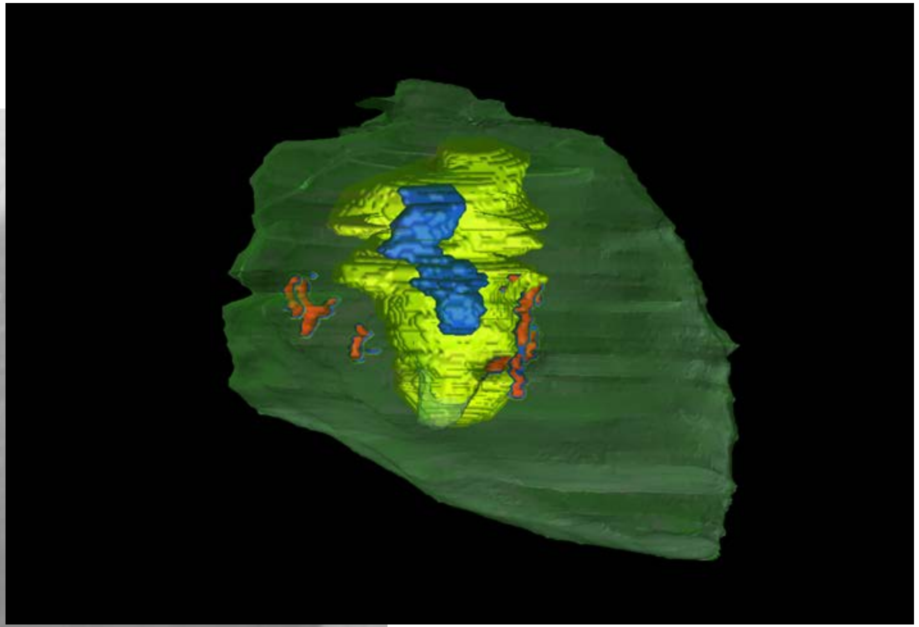


Contrast loss in Diffraction based in vivo SR-imaging of skull-based brain



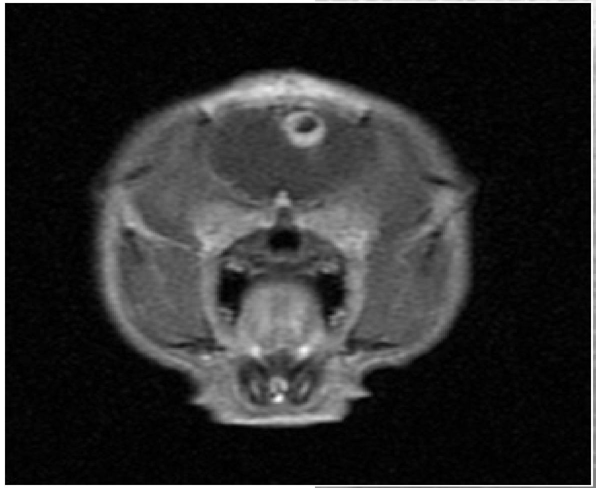
DEI-CT Imaging of MVP

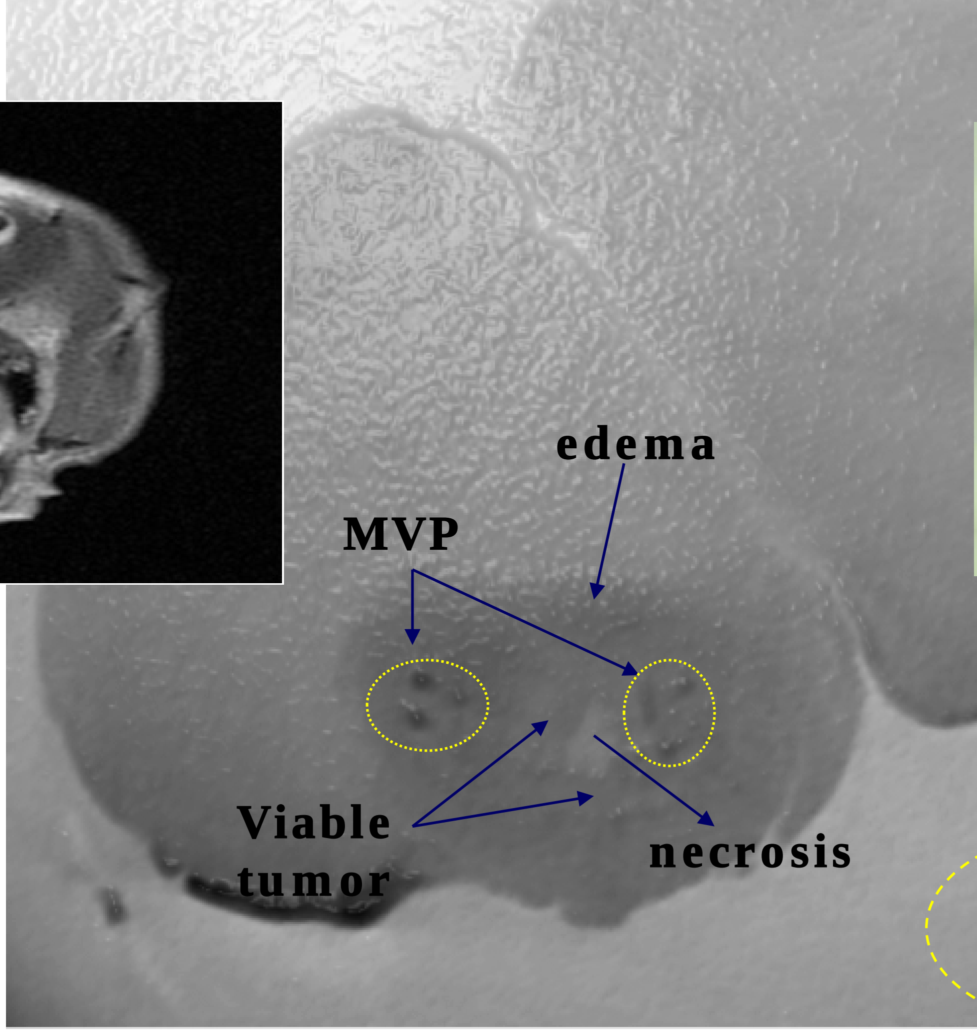


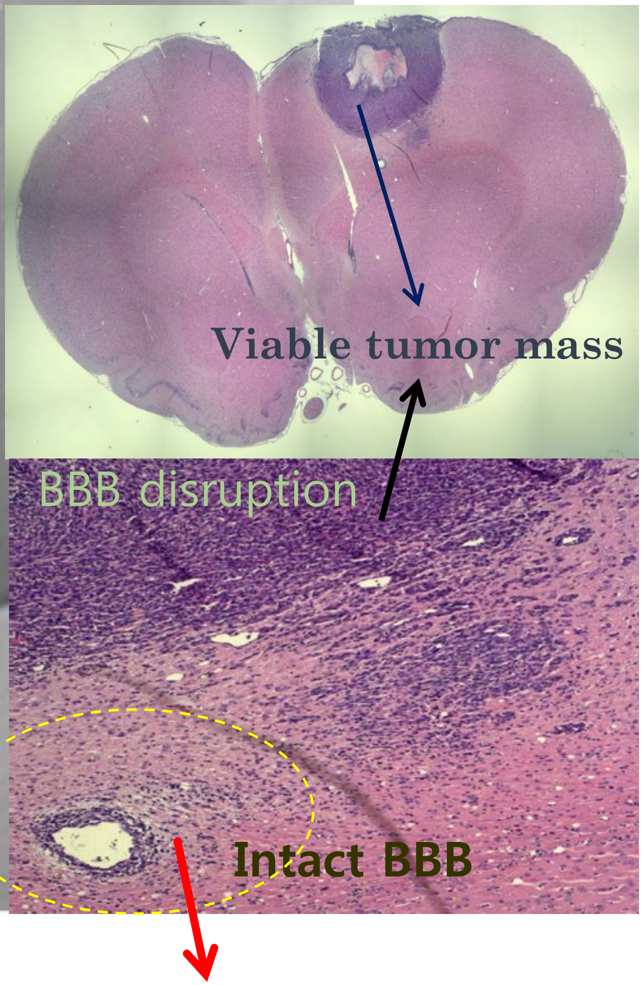


Kim et al 2012
Physics Med Biol

Therapeutic target:Infiltrative cancer cells

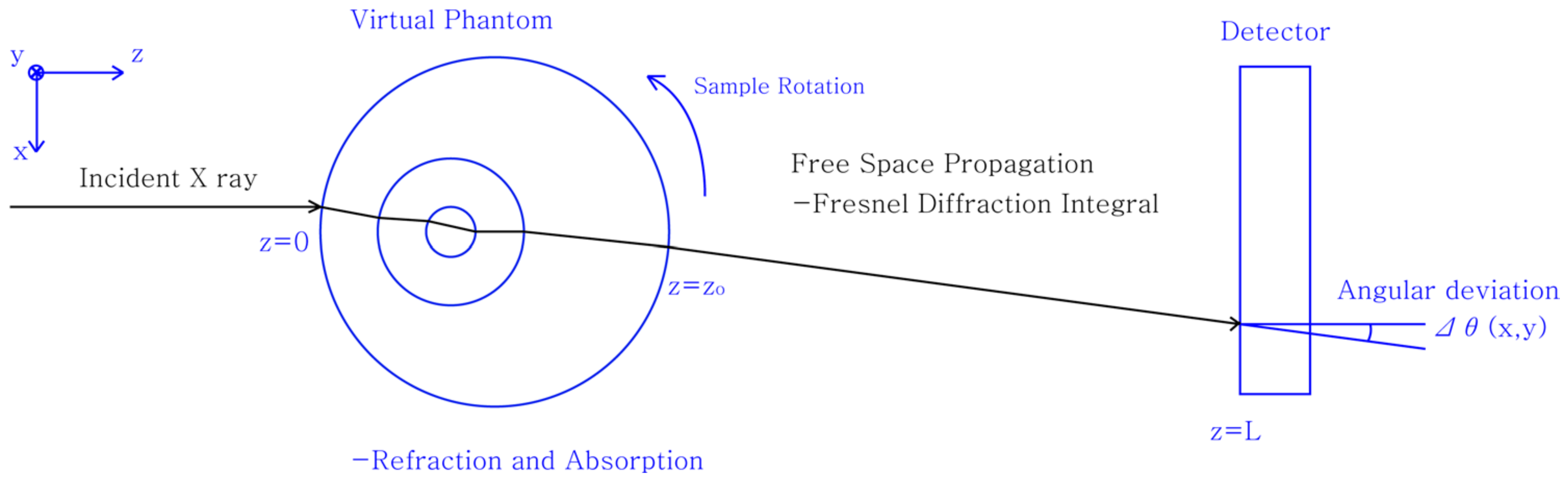


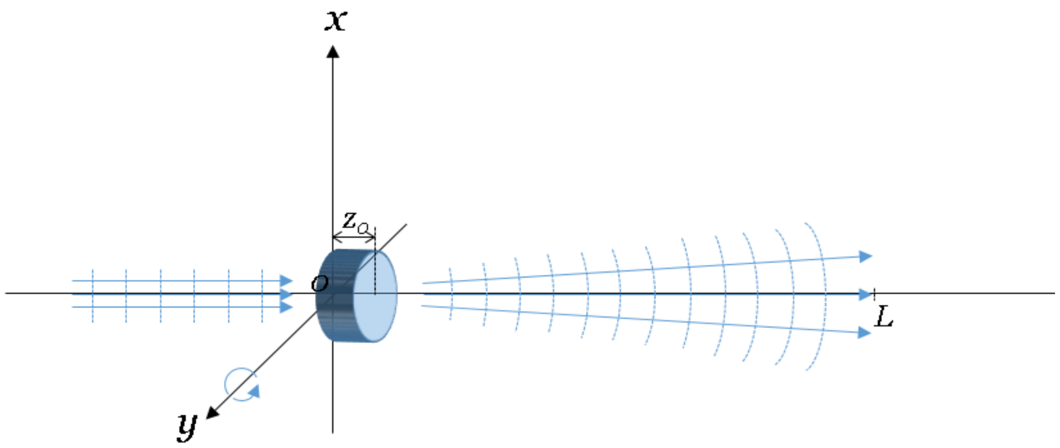




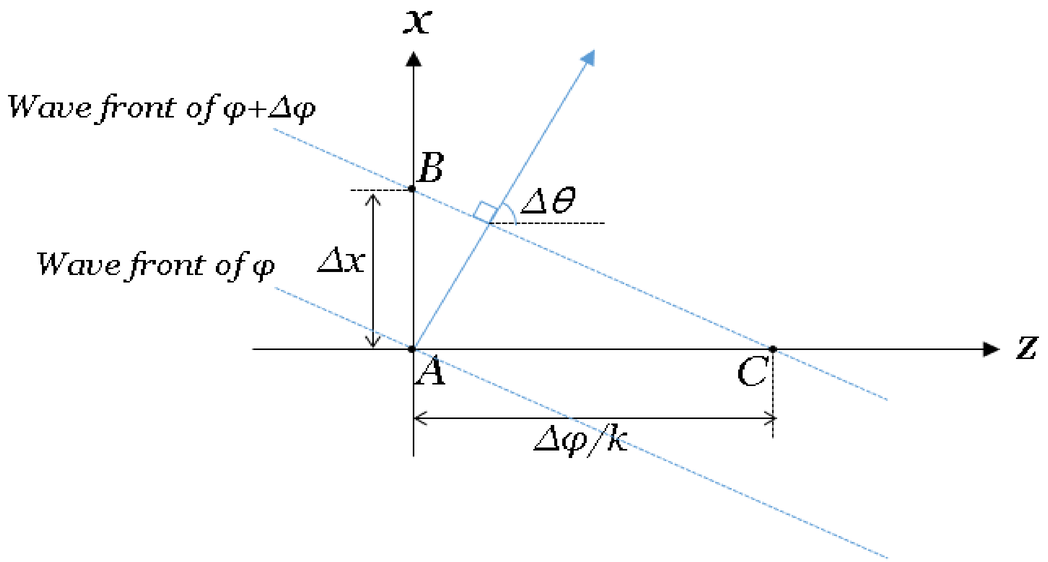
Infiltrative cancer cells: therapeutic target

Simulation of skull-brain phantom





Wave Simulation Diagram



$\Delta\vartheta$ *calculation from phase difference*

Wave Simulation Method

Exit wave after penetrating phantom

$$\psi_\omega(x,y,z=0+z_0) = exp\left\{-k\int_{z=0}^{z=0+z_0}\beta_\omega(x,y,z)dz\right\}exp\left\{-ik\int_{z=0}^{z=0+z_0}\delta_\omega(x,y,z)dz\right\}\Psi_{\omega,0}(x,y,z=0)$$

Free space propagation – Fresnel diffraction integral; sample-to-detector space

$$\Psi_\omega(x,y,z=L) = exp(ikL)\,\mathcal{F}^{-1}exp\left[\frac{-iL\left(k_x^2+k_y^2\right)}{2k}\right]\mathcal{F}\Psi_\omega(x,y,z=z_0)$$

Approximation using Fourier derivative theorem; X-ray photon at detector phase

$$\Psi_\omega(x,y,z=L) = exp(ikL)\left[1+\frac{iL\nabla_\perp^2}{2k}\right]\Psi_\omega(x,y,z=z_0)$$

, where $\nabla_\perp^2 = \frac{\partial^2}{\partial x^2}+\frac{\partial^2}{\partial y^2}$

Calculation of angular deviation from phase difference

$$\Delta\theta(x,y) = tan^{-1}\left(\frac{\Delta\varphi_\omega(x,y)}{k\Delta x}\right)$$, where $\Delta\varphi_\omega(x,y) = \varphi_\omega(x+\Delta x,y) - \varphi_\omega(x,y)$

X-ray Refraction Contrast Image Reconstruction Algorithm

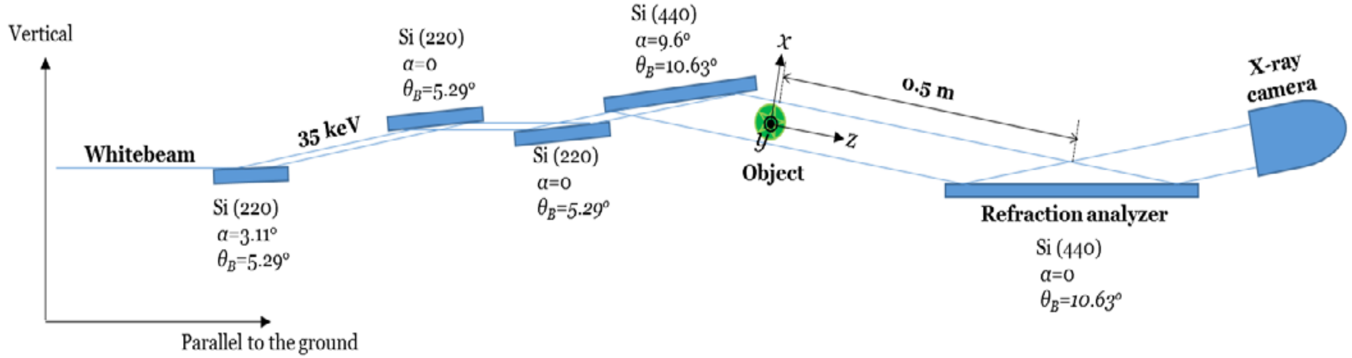
$\Delta\theta(x, y)$ map for each angle of object rotation was first convoluted with a sign function which is defined as

$sgn(x) = 0.5\ (x > 0), 0\ (x = 0), -0.5\ (x < 0)$.

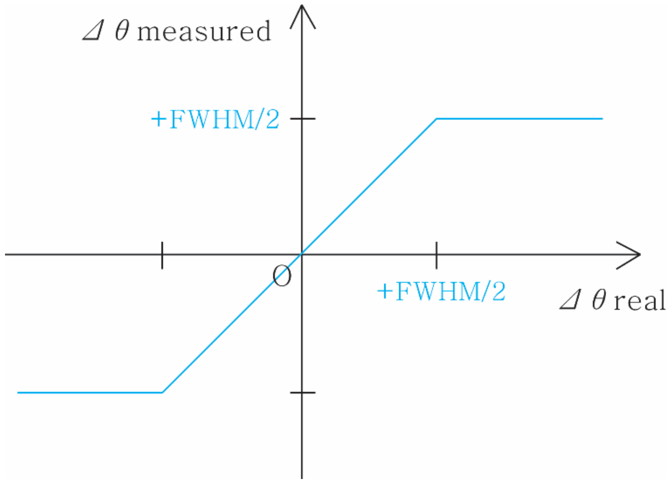
Then, the results were put into the inverse Radon transform. For filtered backprojection, linear interpolation and Hamming filter were used.

Virtual Phantom design

	water	skull	Gray/ White matter	Glioma edema	Glioma viable region	Glioma necrosis
δ	1.88×10^{-7}	3.36×10^{-7}	1.96×10^{-7}	2.00×10^{-7}	1.97×10^{-7}	1.95×10^{-7}
β	8.69×10^{-11}	4.90×10^{-10}	9.15×10^{-11}	9.38×10^{-11}	9.20×10^{-11}	9.09×10^{-11}

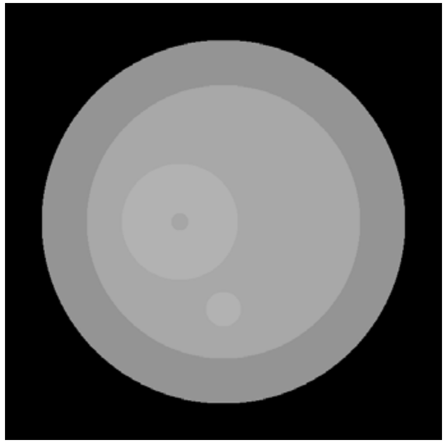


Response function of refraction analyzer

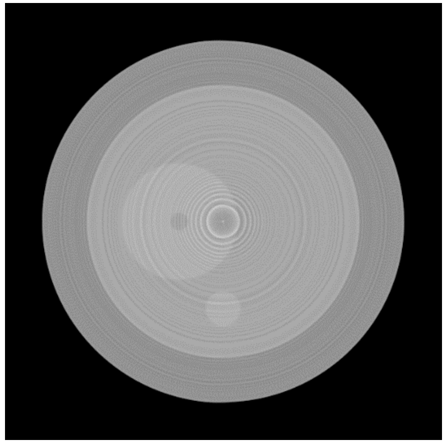


In Si 440 crystal FWHM is 0.35 arcsec

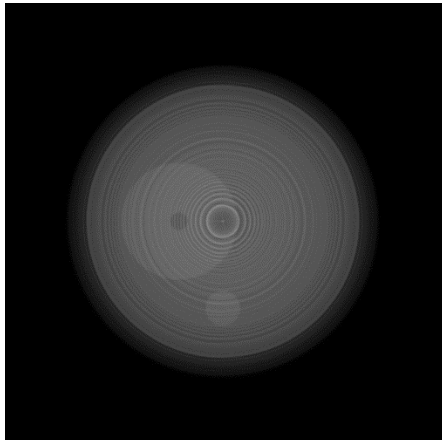
Result of simulation from the phantom without skull



Result 1 (a) Phantom without skull



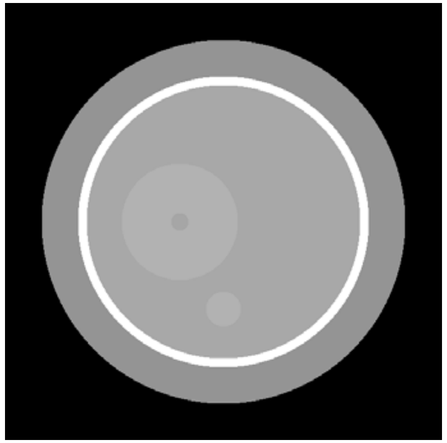
(b) Reconstructed image with wave simulation



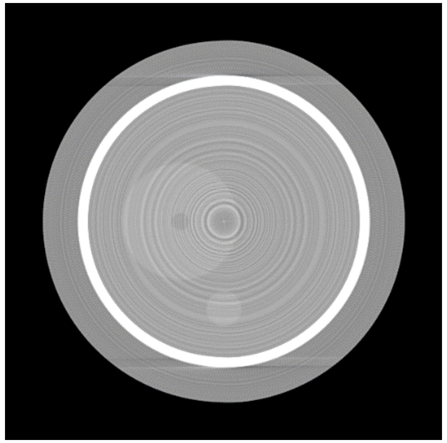
(c) Reconstructed image when response function of crystal was taken account

$\delta \times 10^7$	water	Gray/White matter	glioma edema	glioma necrosis
Result 1 (a)	1.88	1.96	2.00	1.95
Result 1 (b)	1.8682±0.1383 (0.628%)	1.9603±0.0166 (0.0153%)	1.9977±0.0206 (0.115%)	1.9527±0.0231 (0.138%)
Result 1 (c)	1.1228±0.3396 (40.3%)	1.6277±0.0433 (17.0%)	1.7136±0.0294 (14.3%)	1.6796±0.0234 (13.9%)

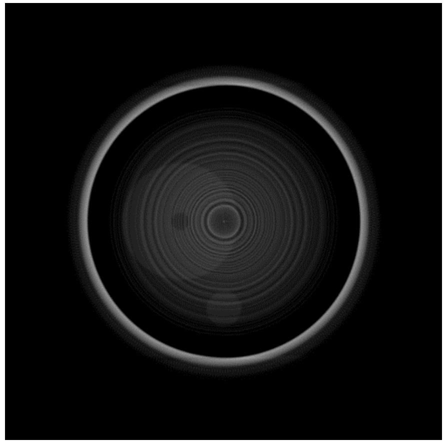
Result of simulation from the phantom with skull



Result 2 (a) Phantom with skull



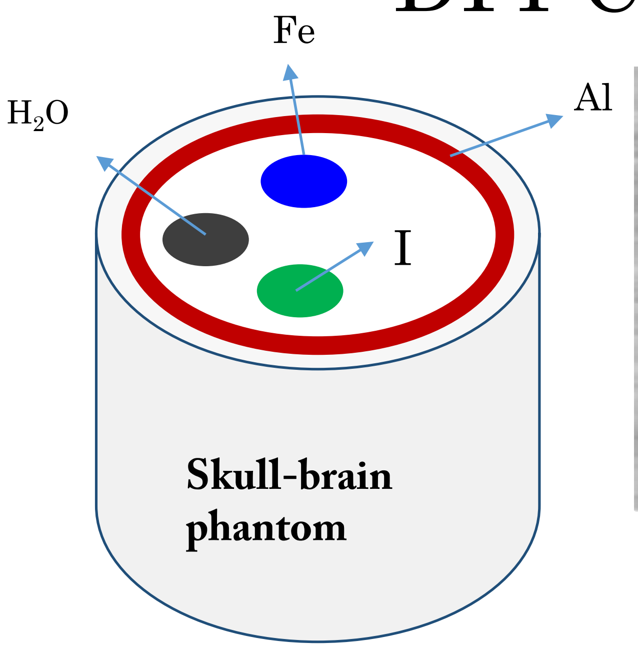
(b) Reconstructed image with wave simulation

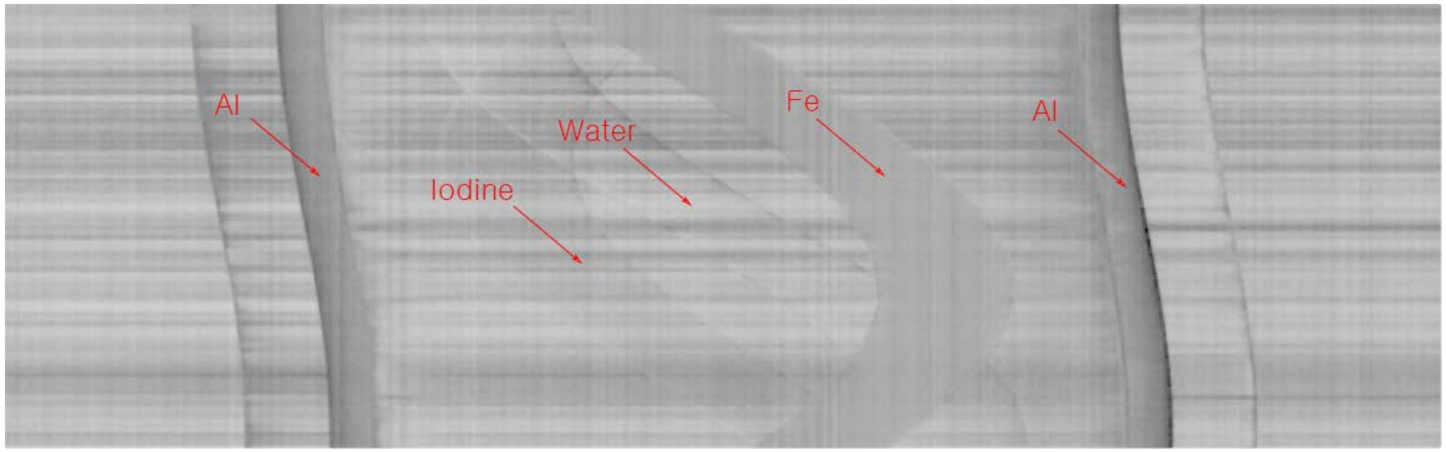


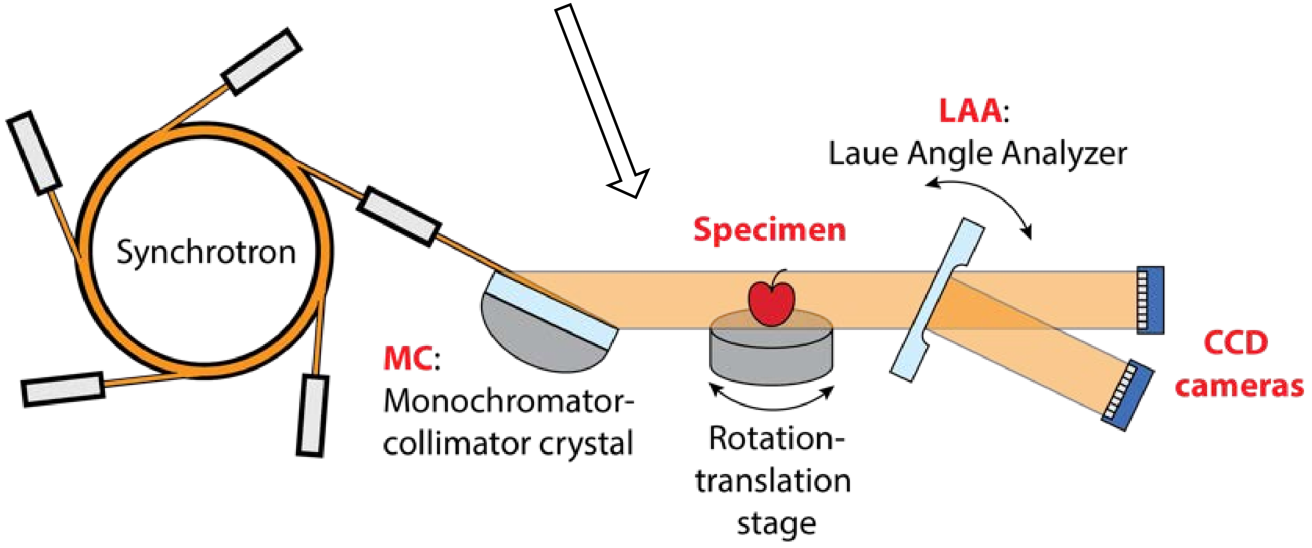
(c) Reconstructed image when response function of crystal was taken account

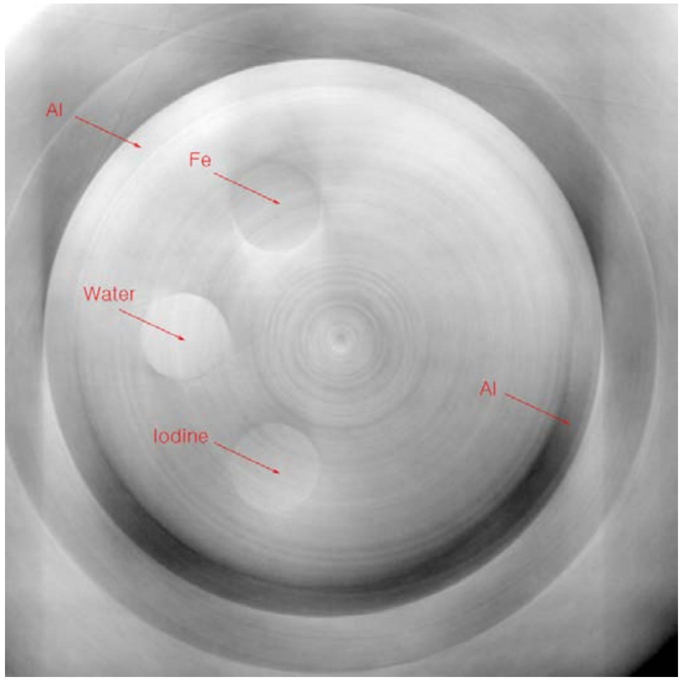
$\delta \times 10^7$	water	skull	Gray/White matter	glioma edema	glioma necrosis
Result 2 (a)	1.88	3.36	1.96	2.00	1.95
Result 2 (b)	1.8749±0.1383 (0.271%)	3.2789±0.0716 (2.41%)	1.9665±0.0716 (0.331%)	1.9978±0.0320 (0.110%)	1.9522±0.0269 (0.113%)
Result 2 (c)	1.0566±0.3360 (43.8%)	1.7130±0.1133 (49.0%)	1.3439±0.1142 (31.4%)	1.4992±0.0457 (25.0%)	1.4787±0.0269 (24.2%)

DFI-CT imaging of skull-brain phantom

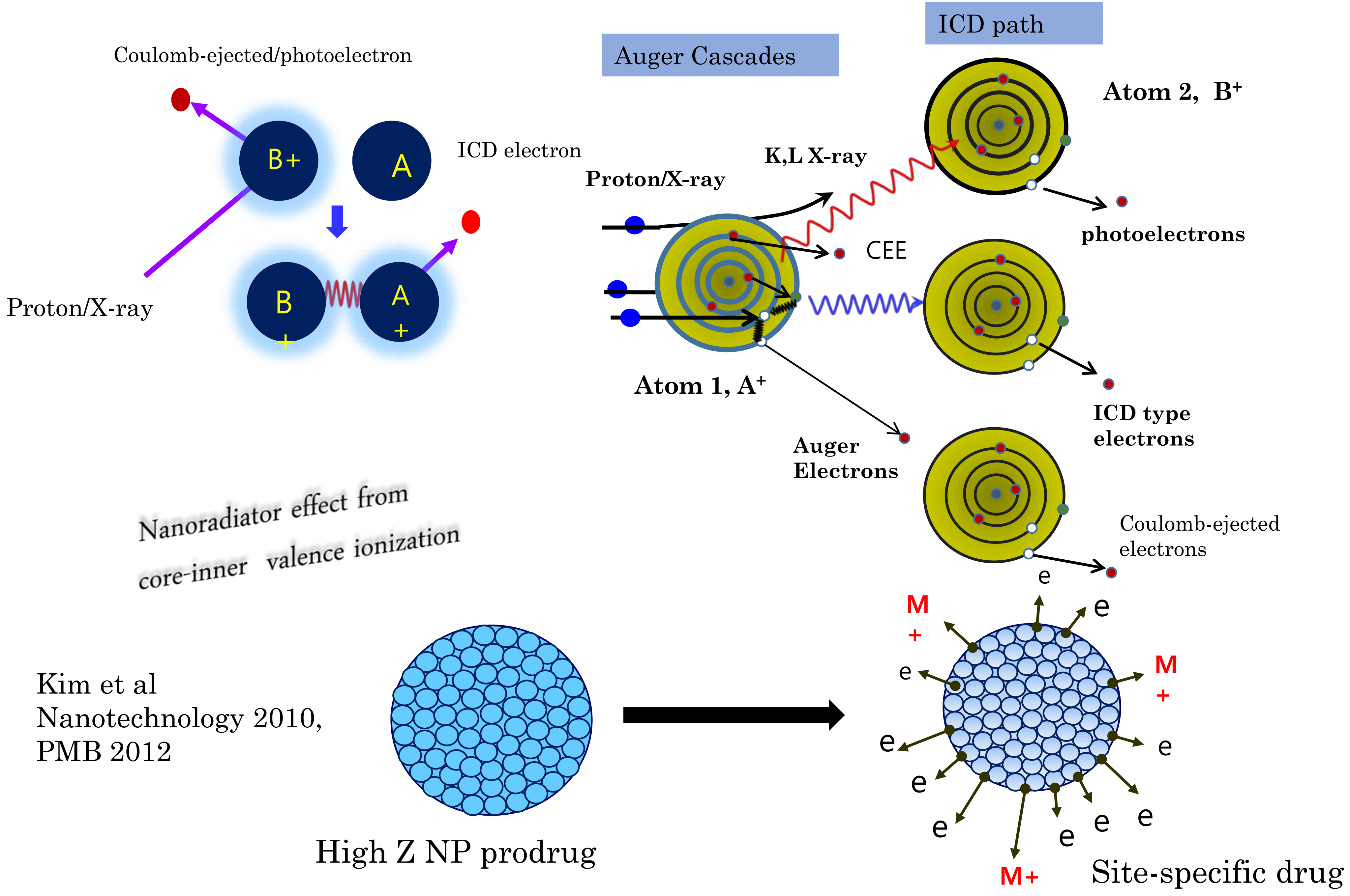






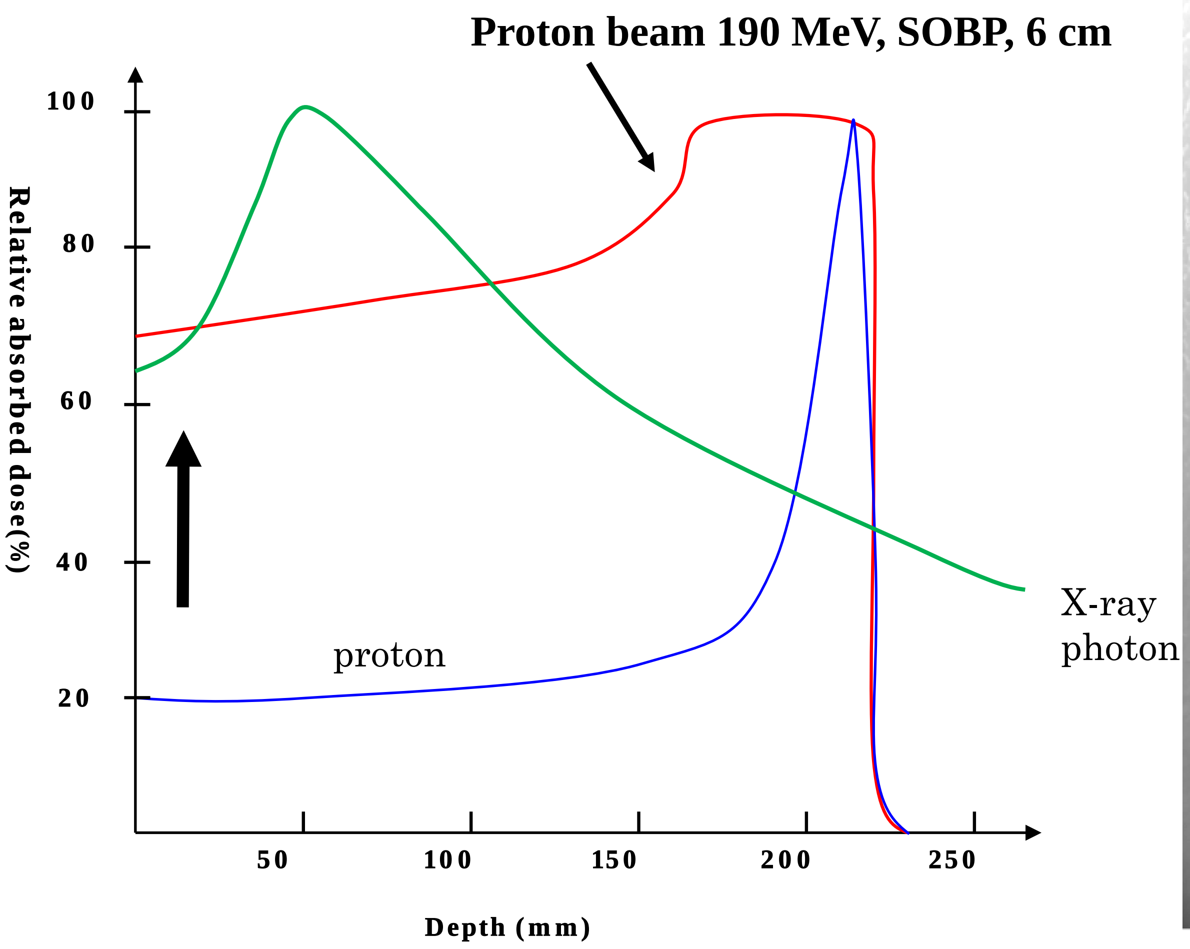


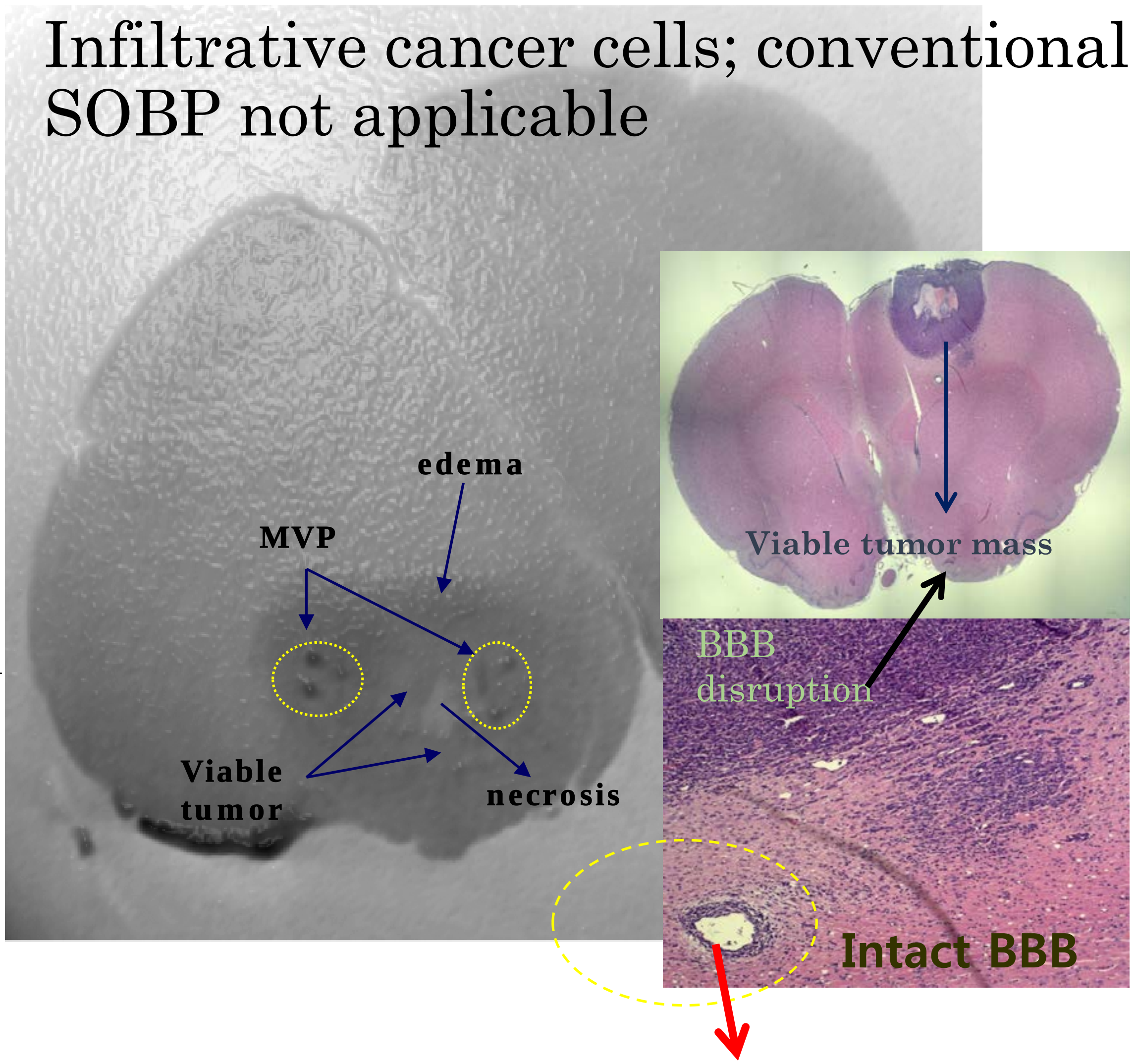
Site-specific Coulomb nanoradiator (CNR) Therapy



Coulomb-ejected/photoelectron
B+
A
ICD electron
B
+
A
+
Proton/X-ray
Auger Cascades
ICD path
Atom 2, B+
K,L X-ray
Proton/X-ray
photoelectrons
CEE
Atom 1, A+
ICD type
electrons
Auger
Electrons
Coulomb-ejected
electrons
Nanoradiator effect from
core-inner valence ionization
Kim et al
Nanotechnology 2010,
PMB 2012
High Z NP prodrug
M
+
M
+
M+
e
Site-specific drug

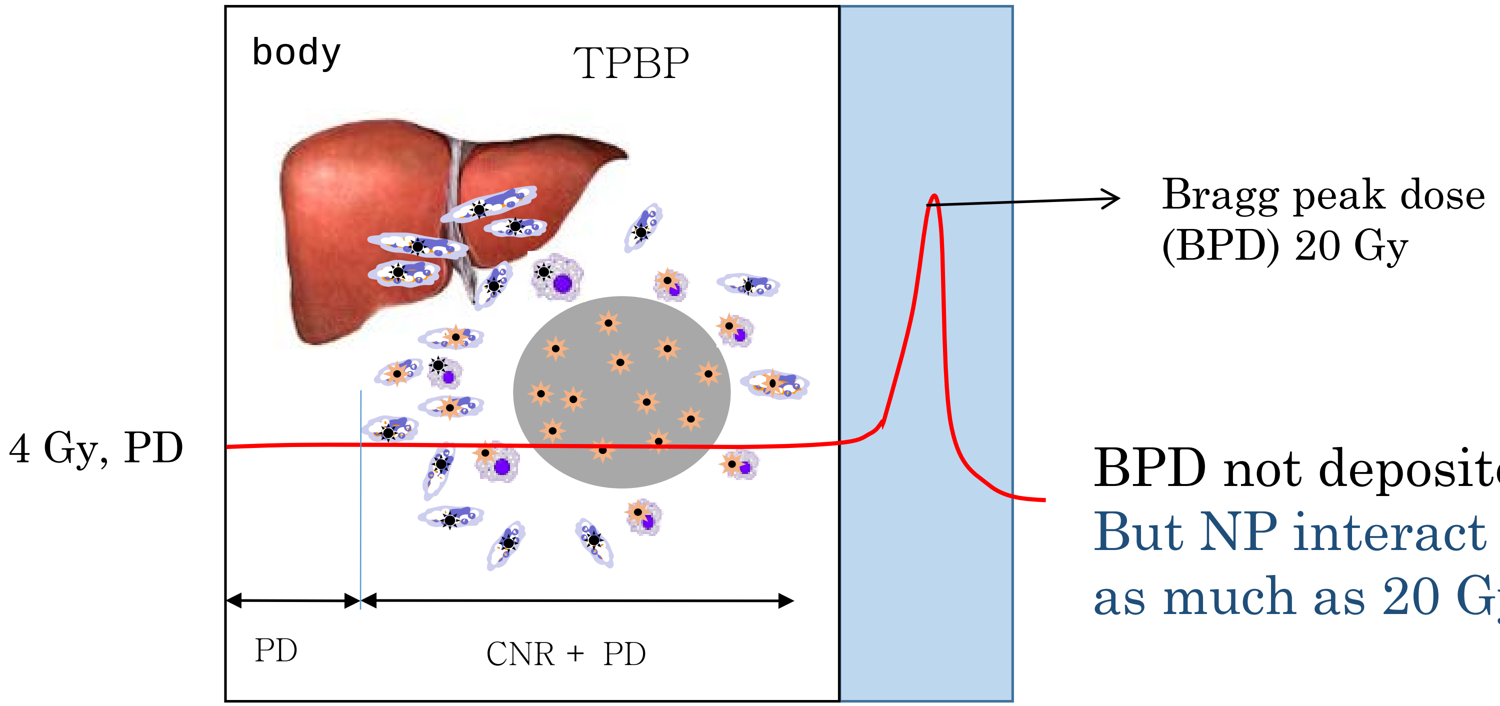
Site-specific Coulomb nanoradiator Therapy by Traversing Single pristine Bragg-peak





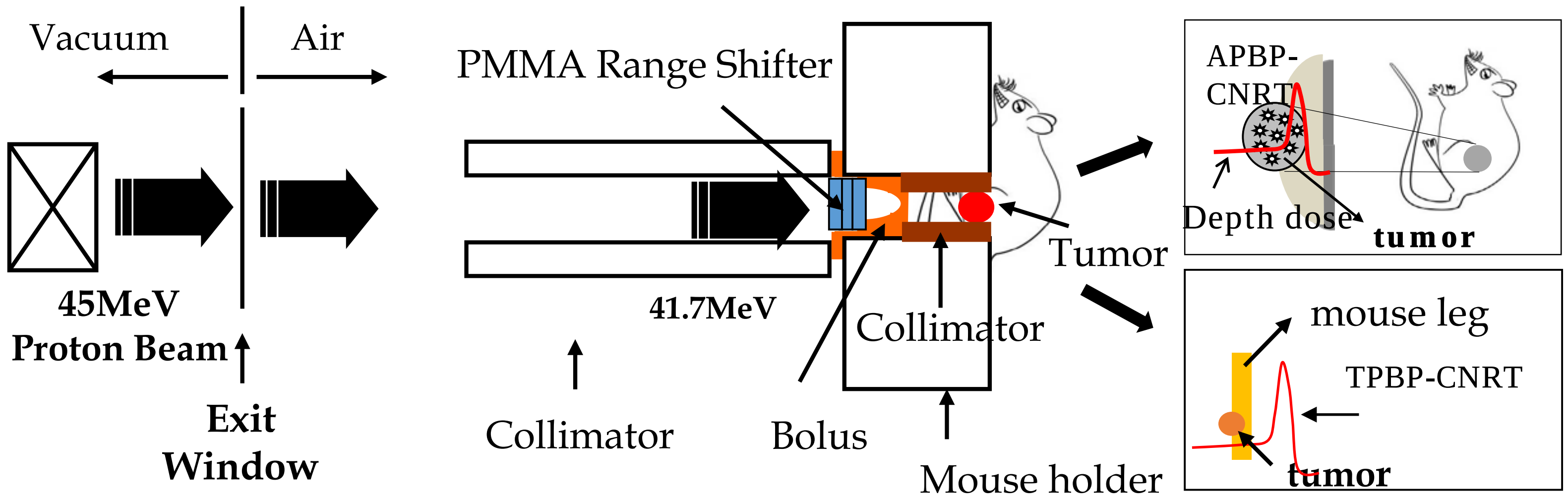
Infiltrative cancer cells: therapeutic target

Traversing Bragg-Peak induced CNR effect

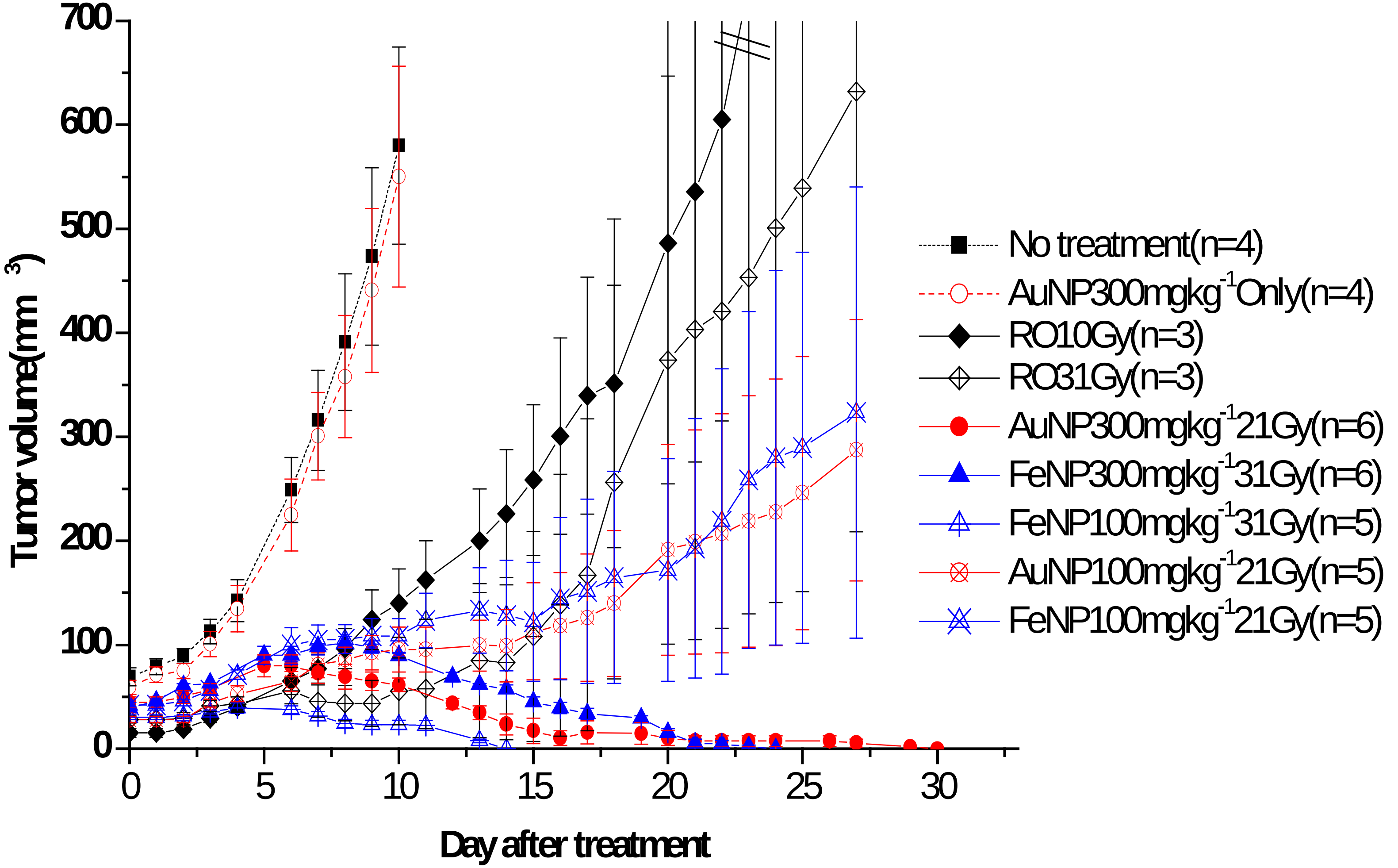


BPD not deposited inside
But NP interact with it
as much as 20 Gy, induce CNR

Test of therapeutic effect from TBP-CNR

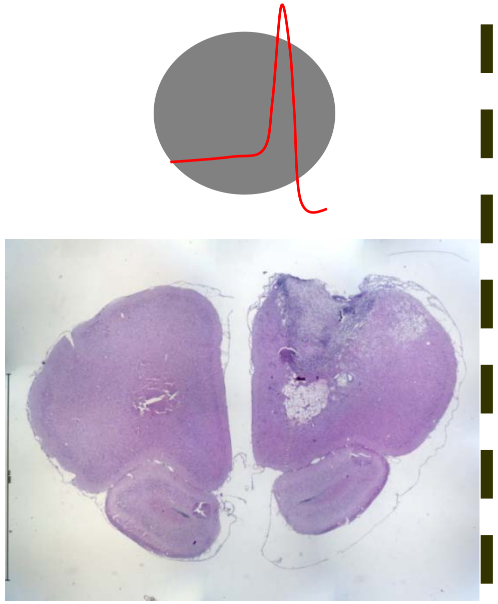


Therapeutic effect of TBP-CNR

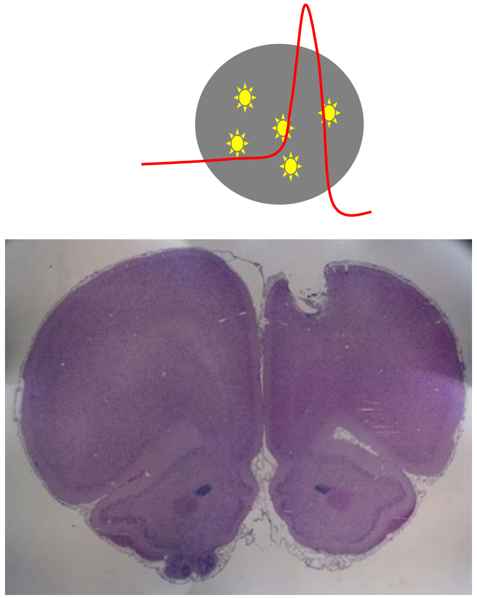


Kim et al 2102 PMB

CNR treatment on glioma by single BP 40 MeV

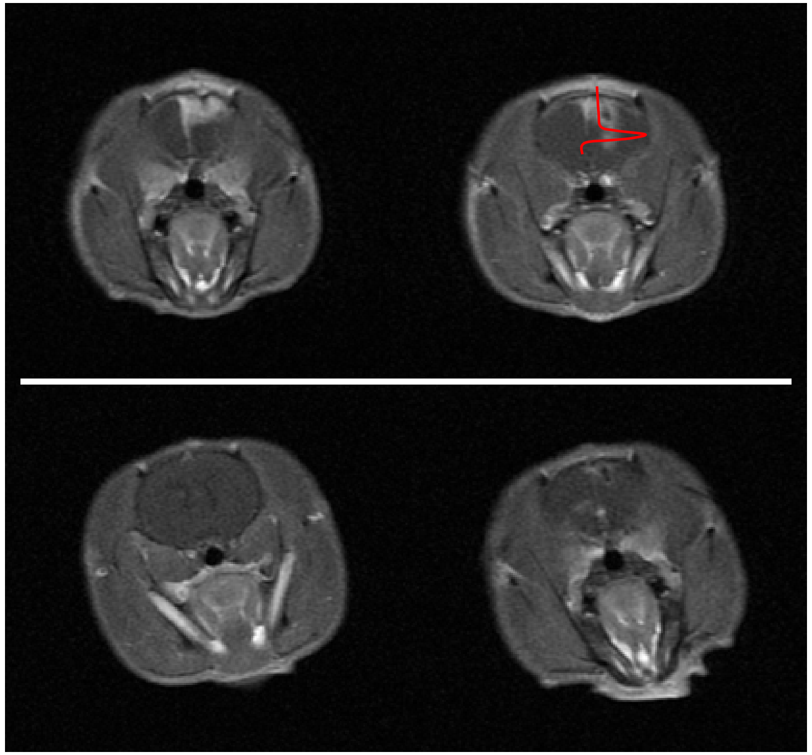


Proton alone
40 Gy



40 Gy CNR with
FeONP 300mg/kg

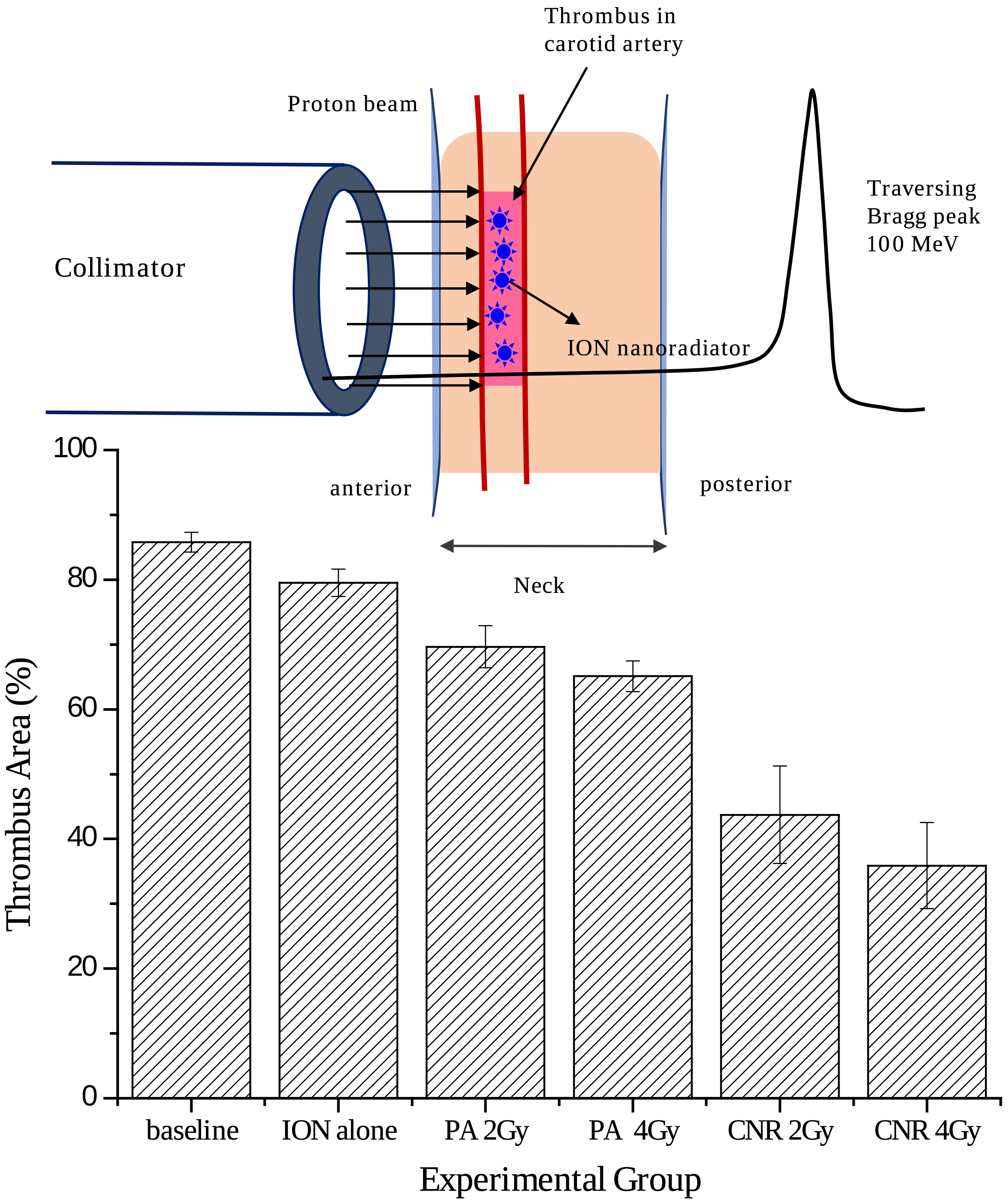
Pre-treatment

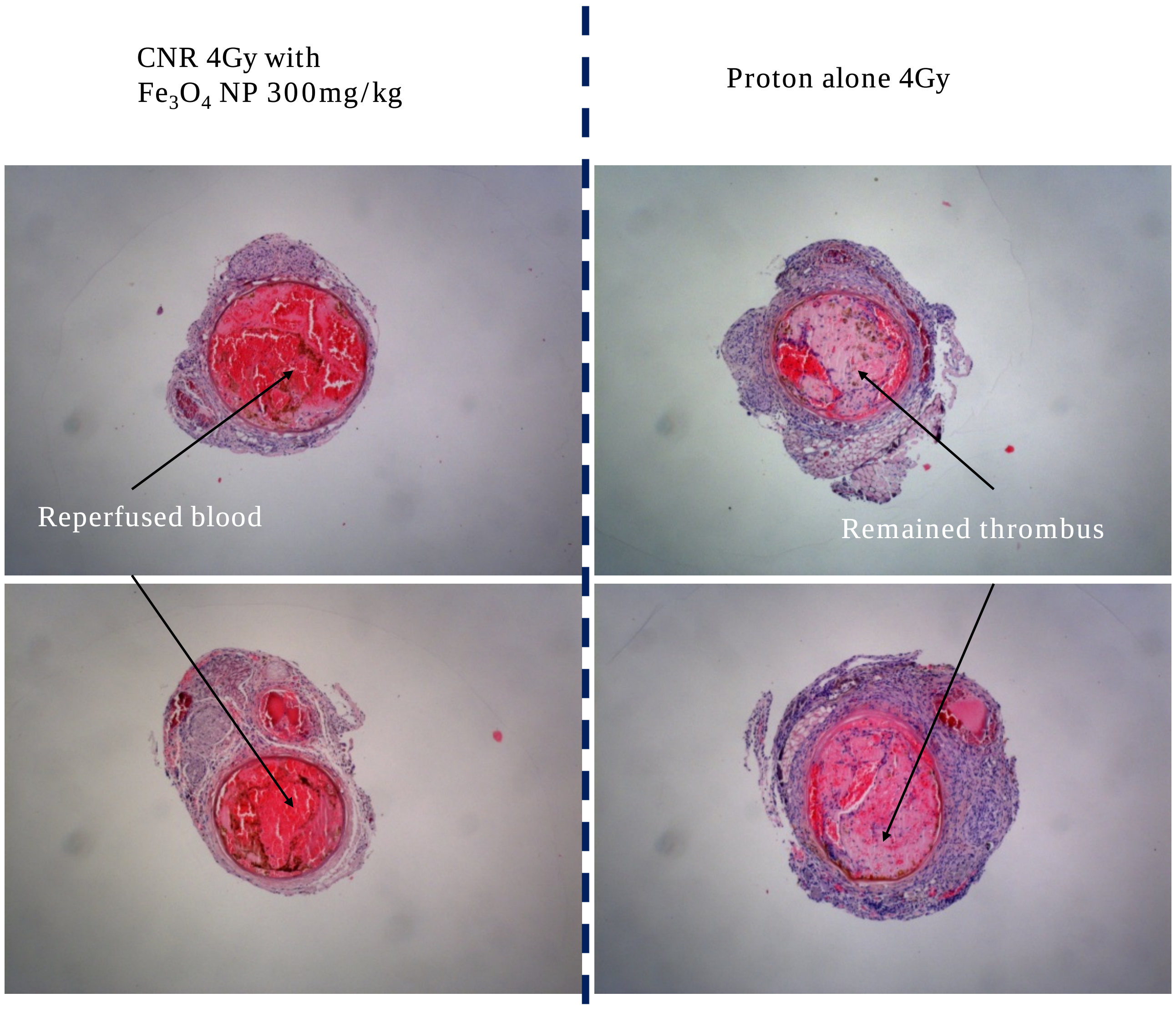


Post-treatment

Seo et al 2013
J Cancer Therapy

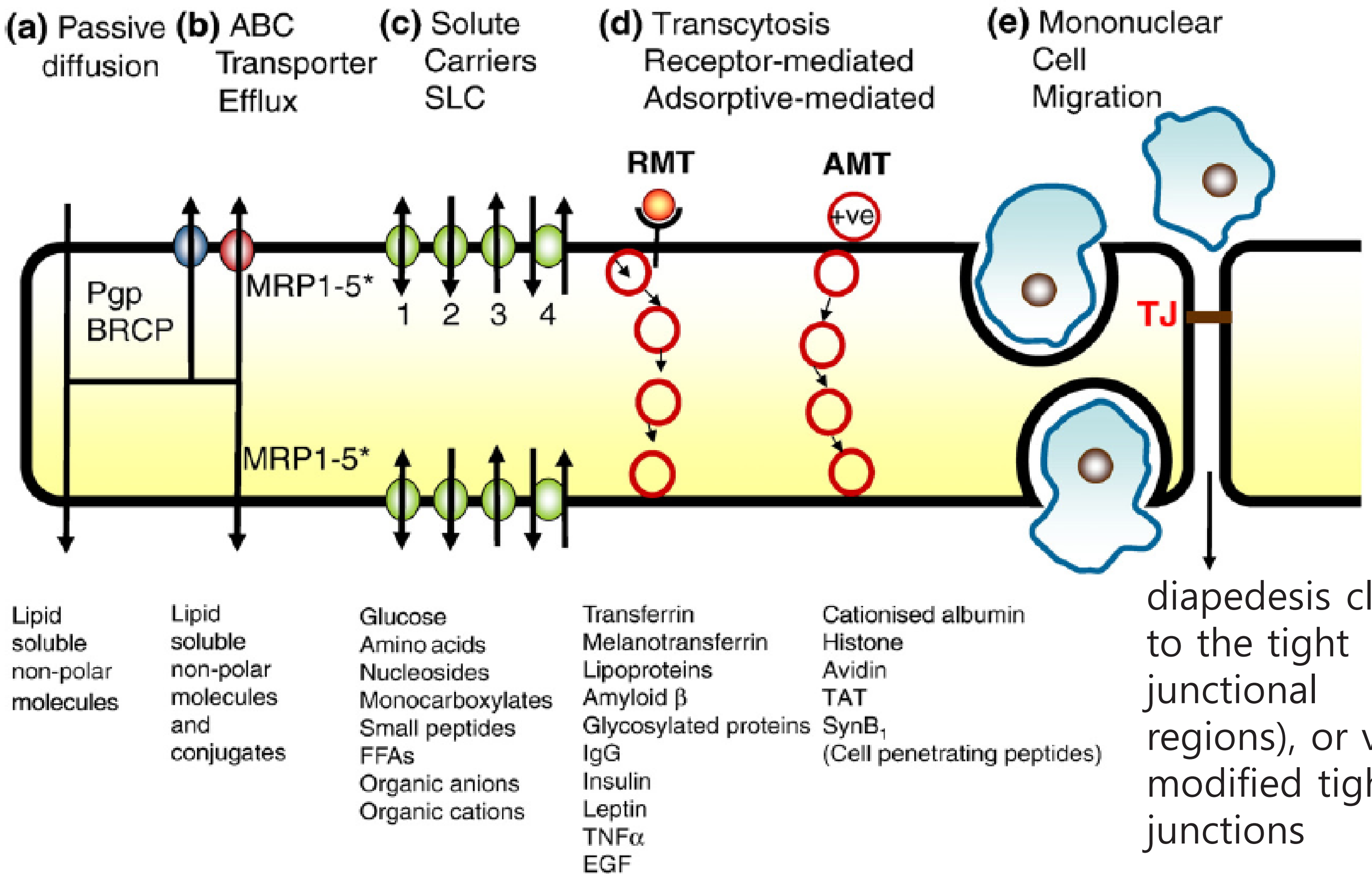
CNR-mediated thrombus reduction/flow recovery



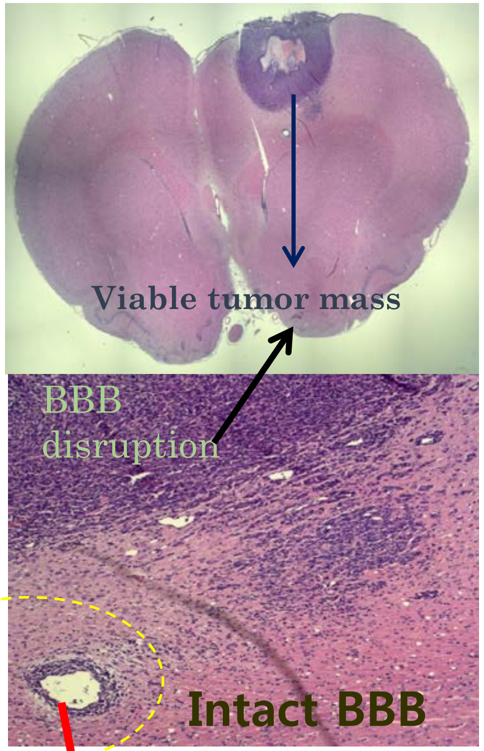


Submitted 2016

Routes of transport across the BBB

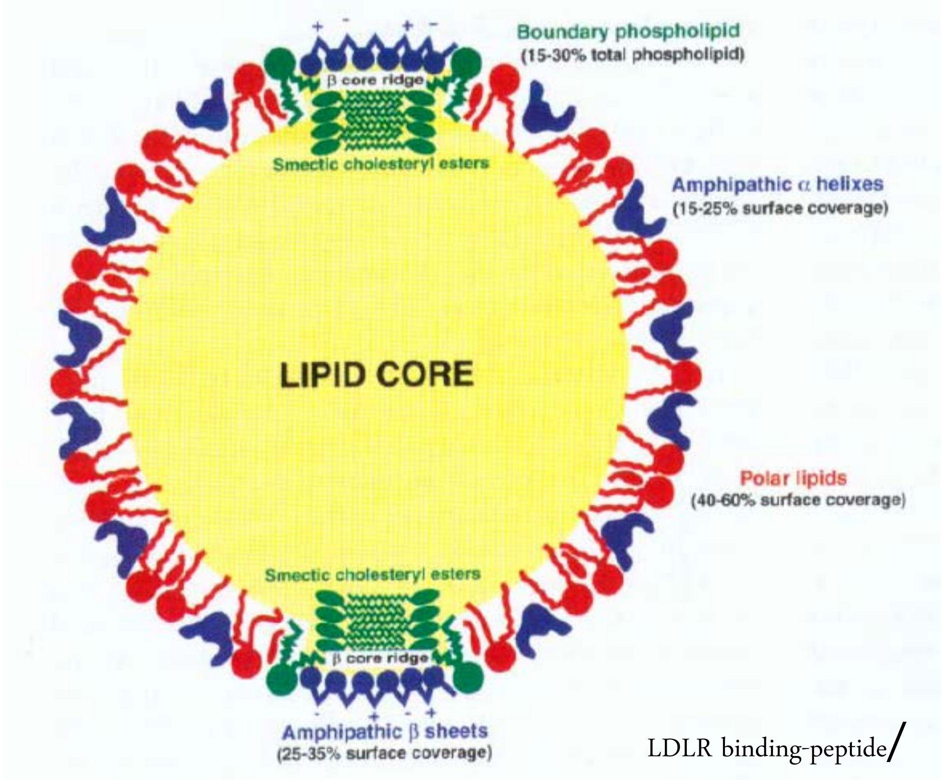


diapedesis close to the tight junctional regions), or via modified tight junctions

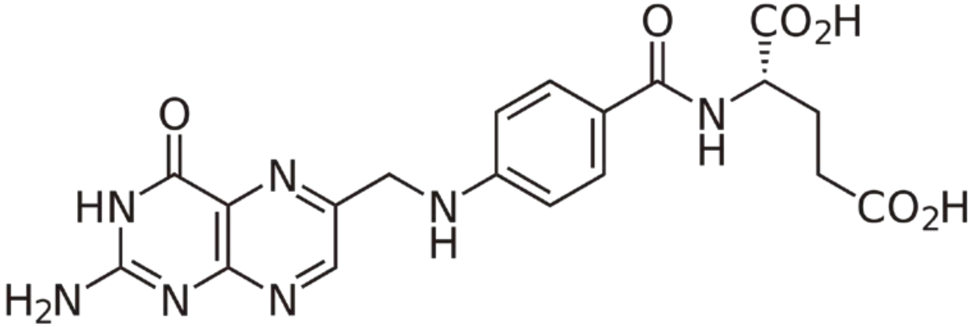


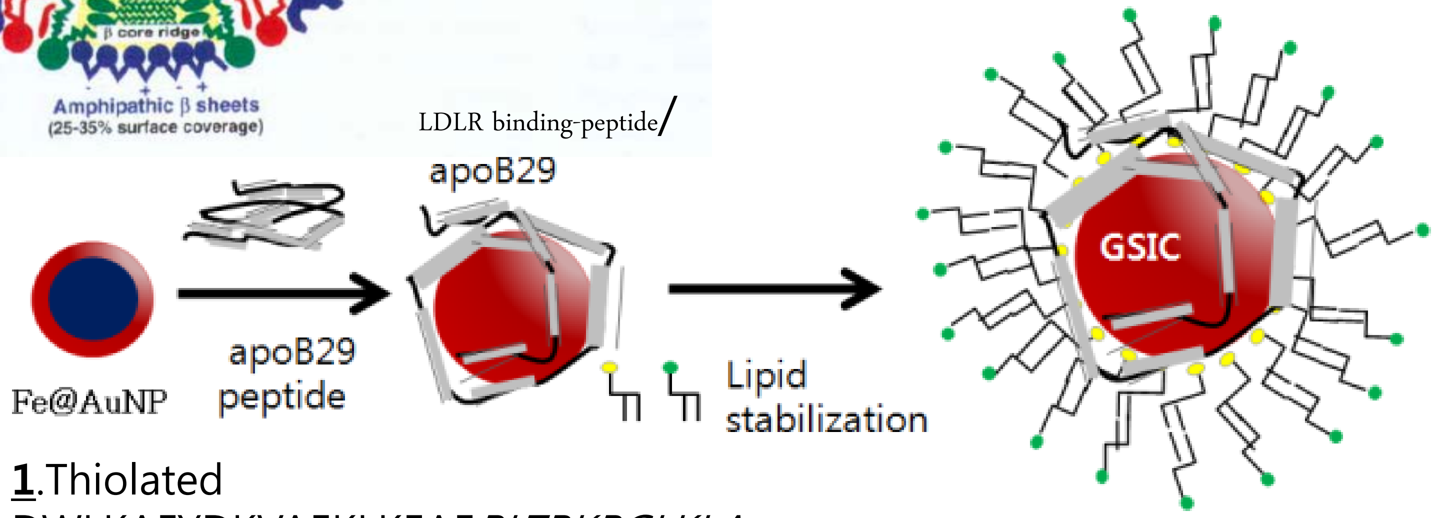
Infiltrative cancer cells: therapeutic target

Bioinspired-syntheitc LDL-Gold-core-shell NP targeting glioma LDLR



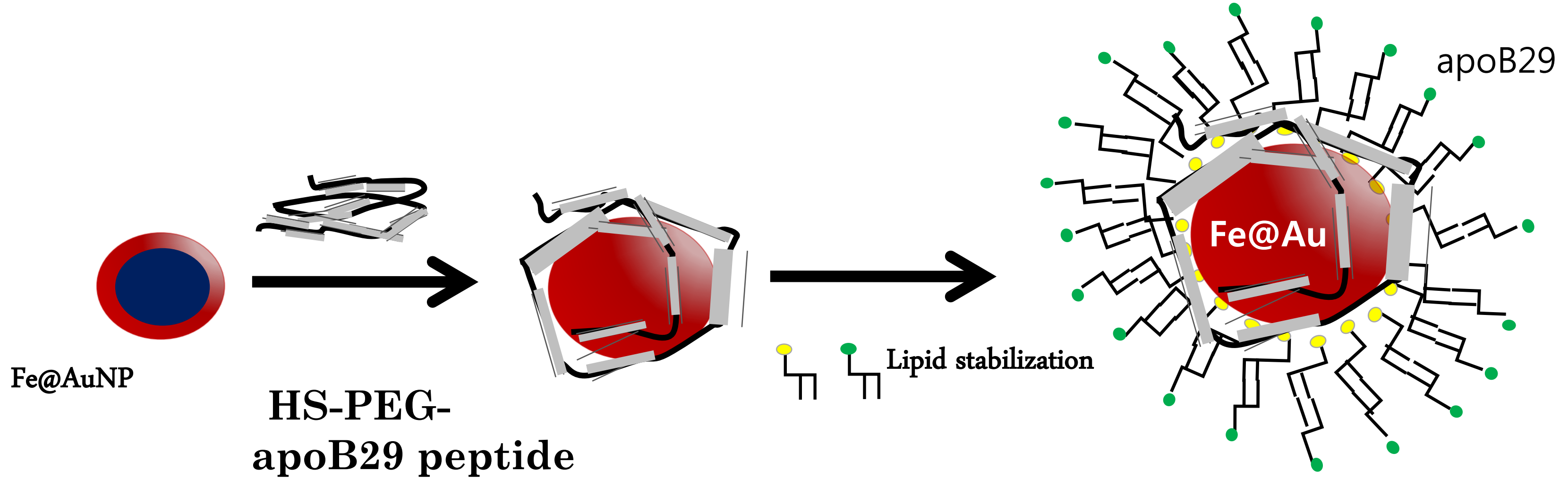
BBB crossing
Via LDR-mediated transcytosis
Plus targeting TAM-folateR in glioma

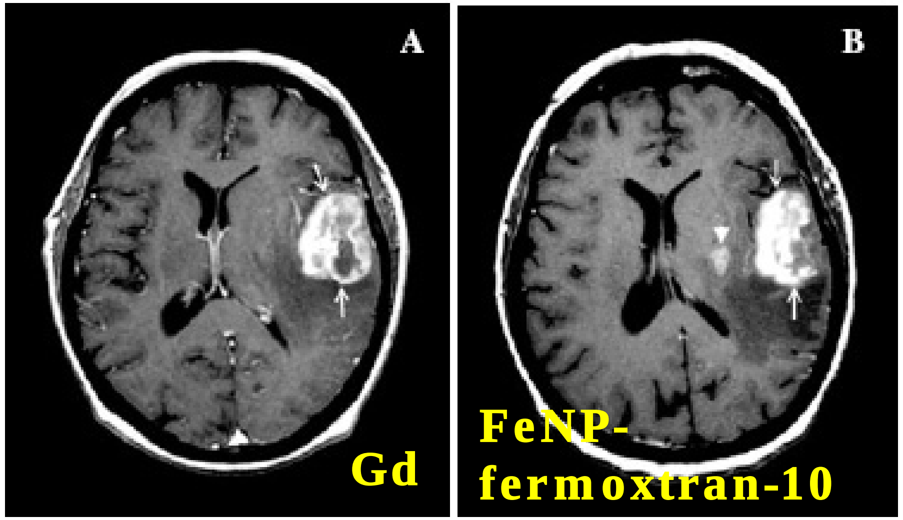




1.Thiolated
DWLKAFYDKVAEKLKEAF*RLTRKRGLKLA*

LDL-receptor in BBB
:delivery high-Z nanoparticles through intact BBB



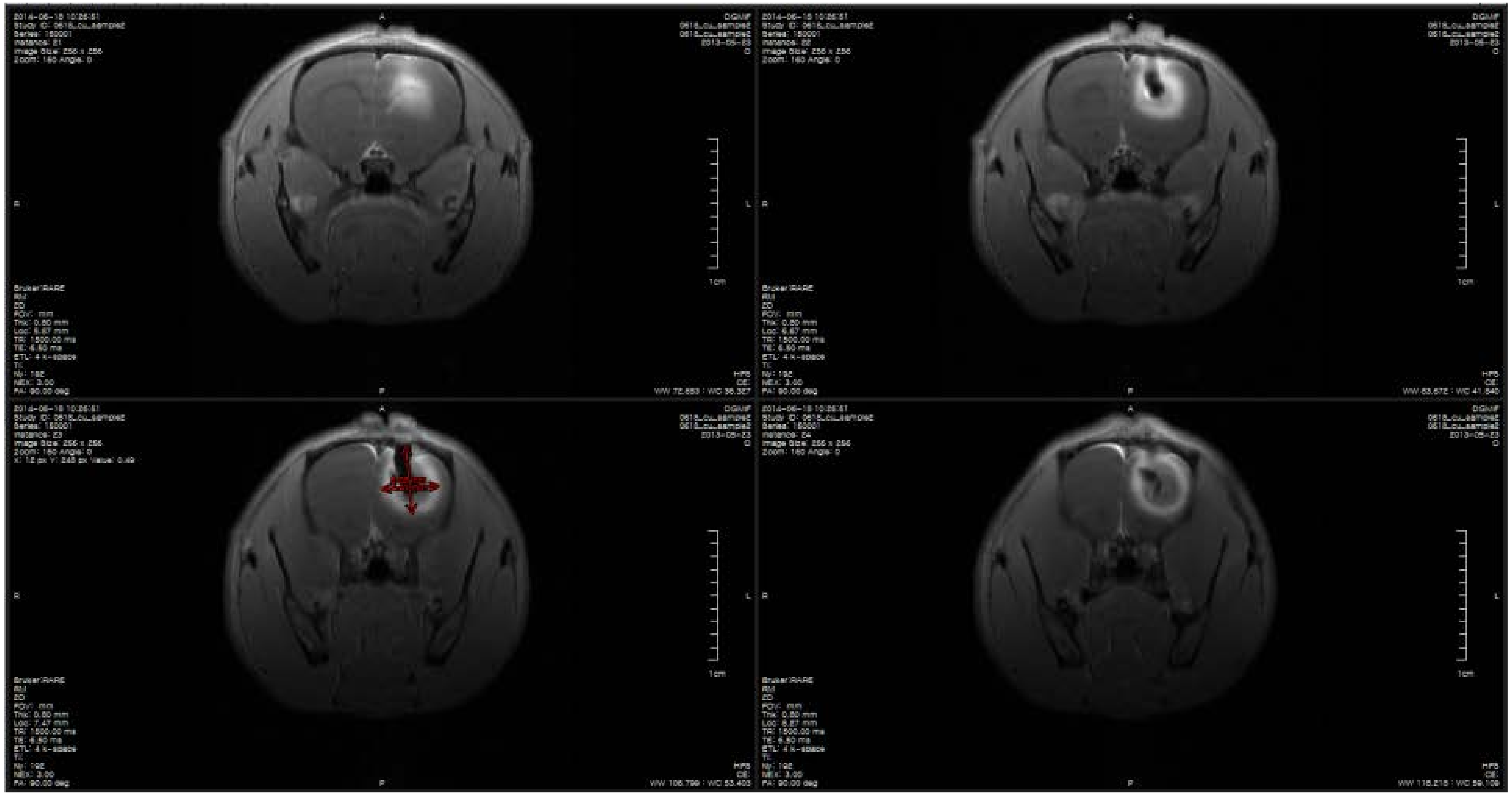


Nanomedicine 2010

Delivery thru intact and disrupted BBB

1. **Exploit LDLr/Macrophage in transcytosis-BBB Crossing over**
2. **Molecular Imaging of tumor infiltration**
3. **Site-specific CNR nanobeacon therapy**

F98 glioma model present tumor infiltration (MVP) and overexpression LDLR



BBB-transcytosis

•LDLR

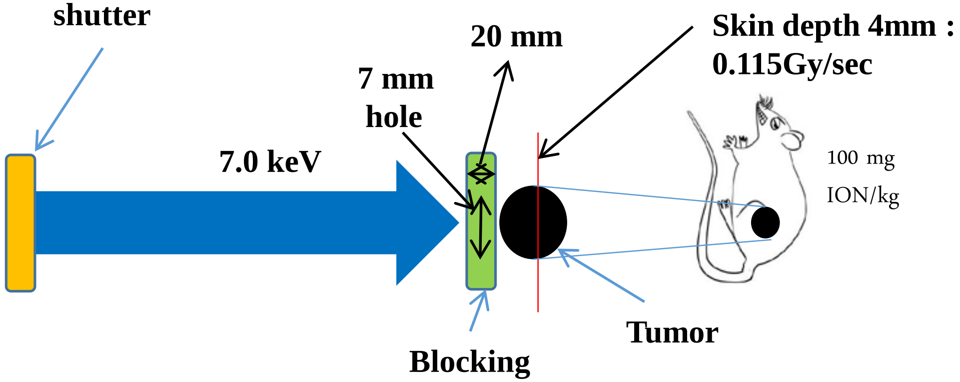
・Tumor infiltration

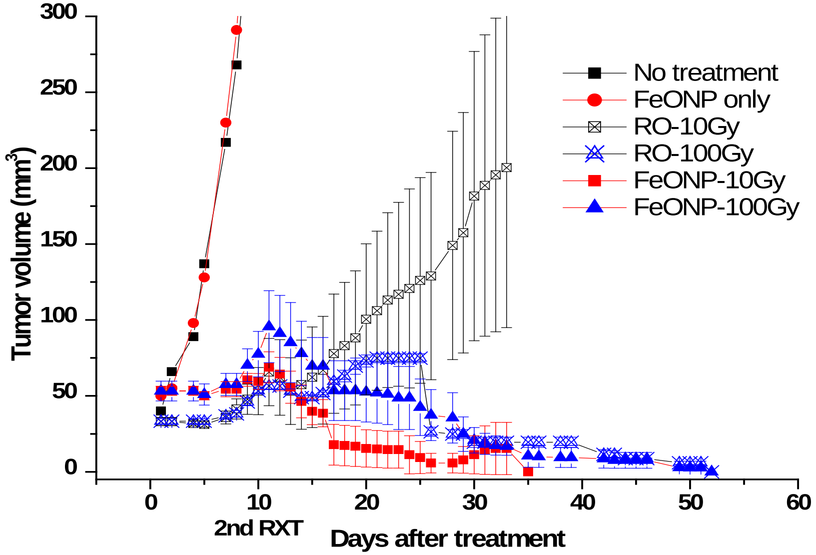
-TAM-Folate

Photoelectric Nanoradiator for glioma treatment

Monochromatic SR 50 KeV X-ray

KimJK, Korea



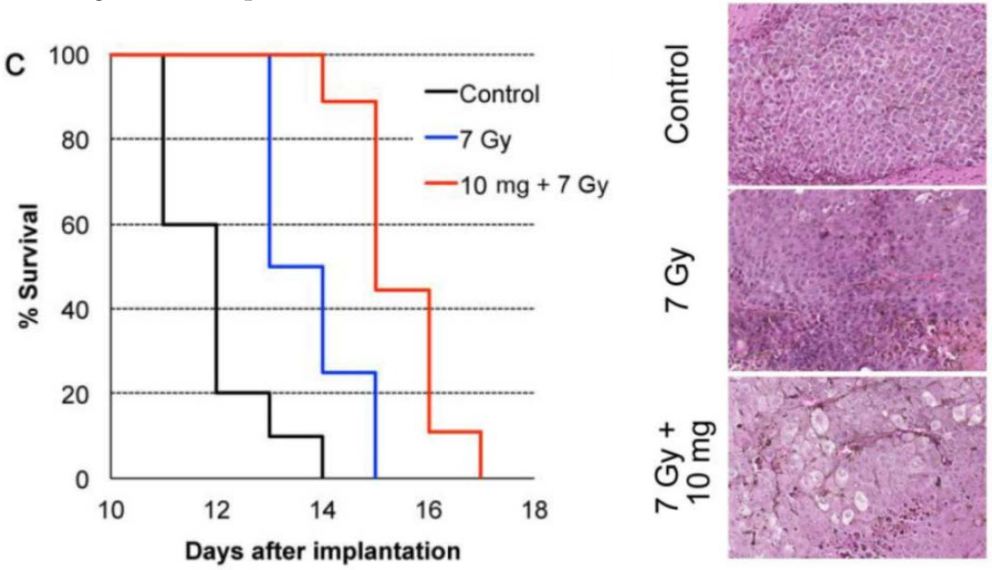


Radiation Oncology 2012

PLS BMI

French group
Hélène Elleaume, Lucie Sancey

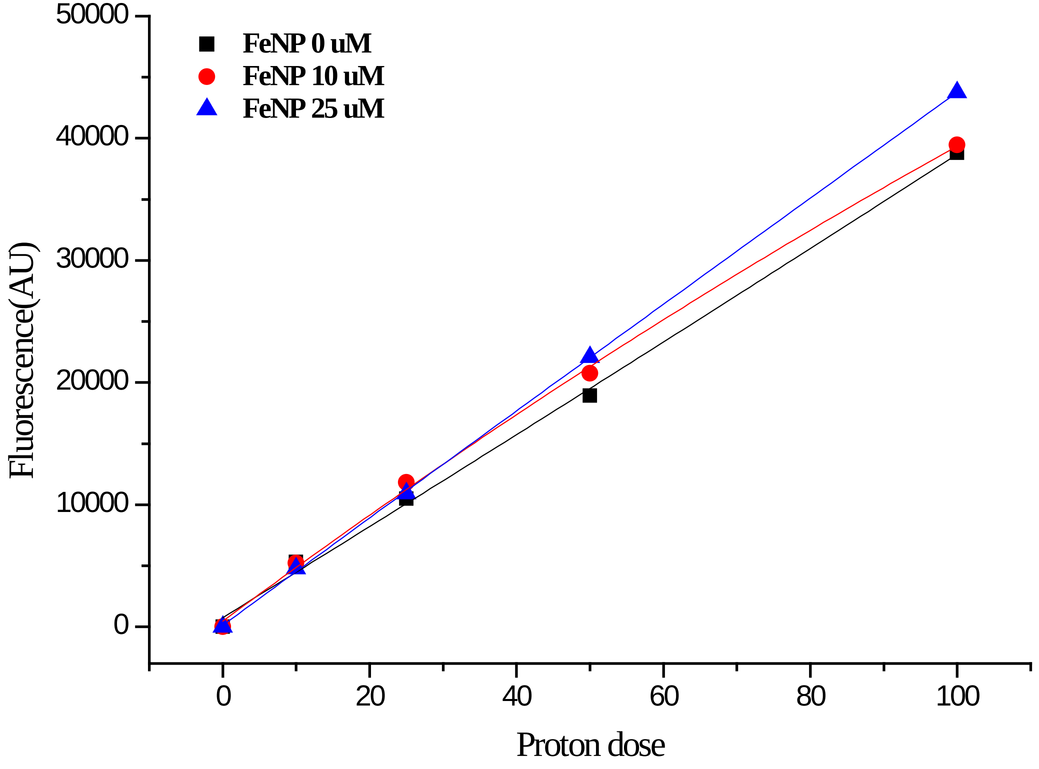
- Fe_3O_4 NP (ION)- 30-80 KeV monochromatic
  - Mössbauer effect +photoelectric effect leading to NR
- GdONP (AGuIX®)-320 kV, F98 model
  - 7 Gy at a dose rate of 2 Gy/min
  - 10 mg, IV, 3.5 h prior to irradiation

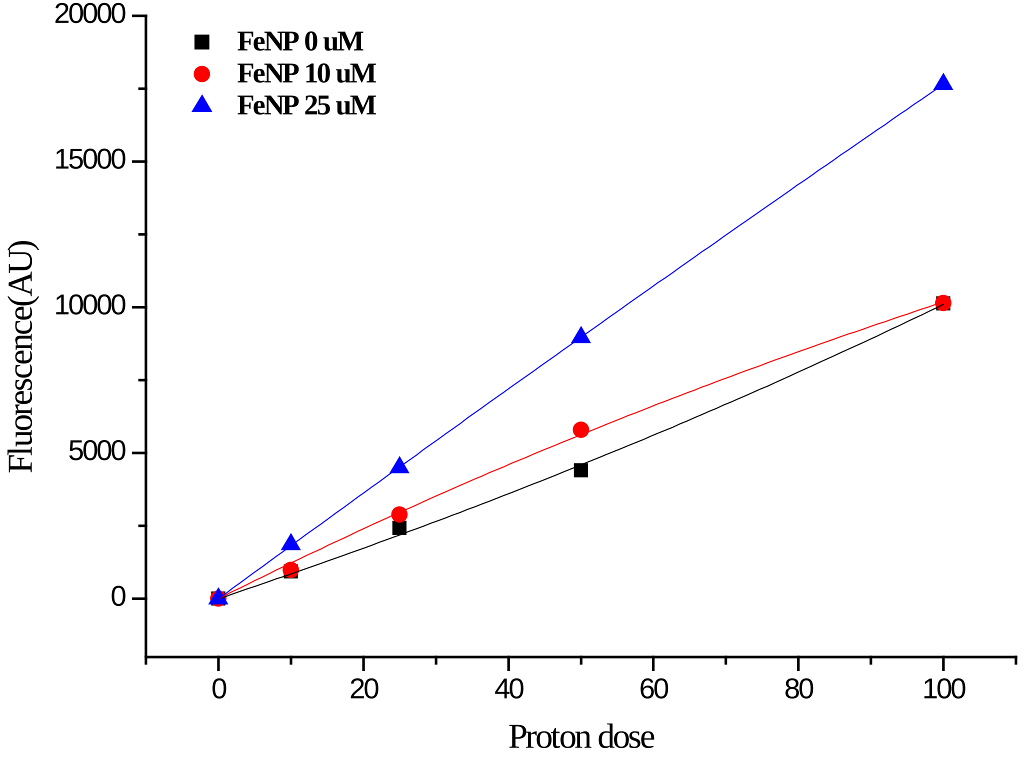


Theransotics 2016

Dosimetry of ION-nanoradiator

100 MeV traversing proton beam





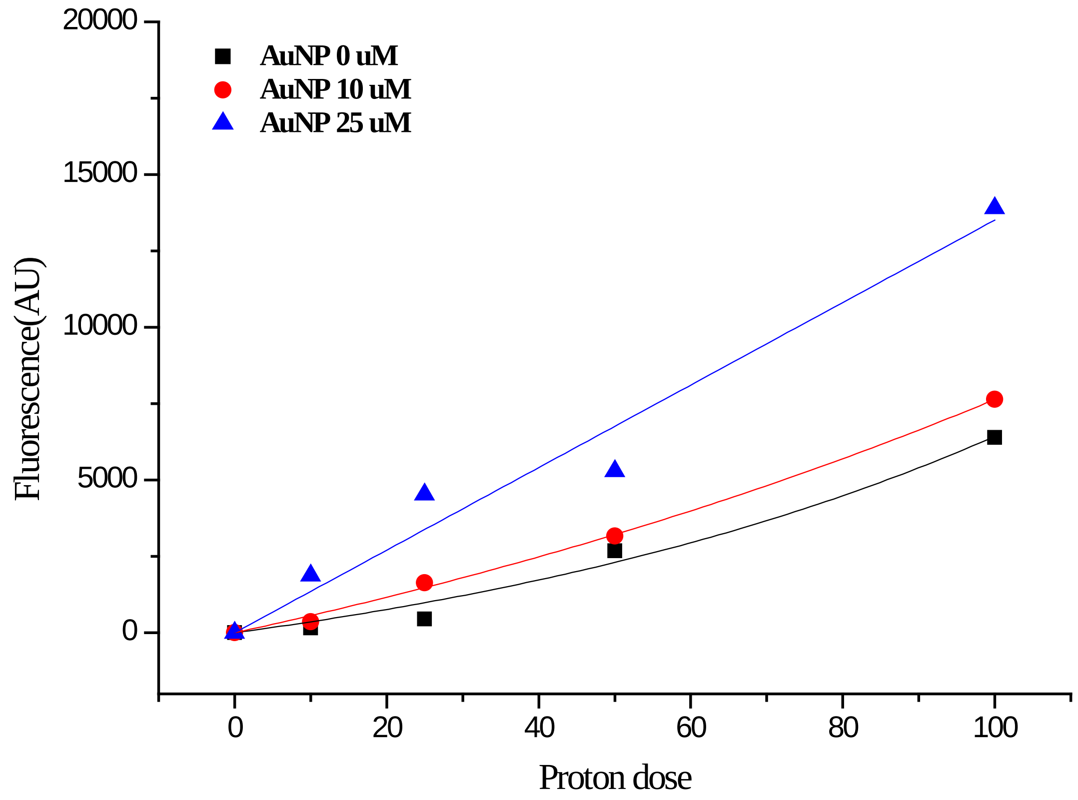
$$\frac{[OH^-]_{CNR}}{[OH^-]_{PA}} = 1.15$$

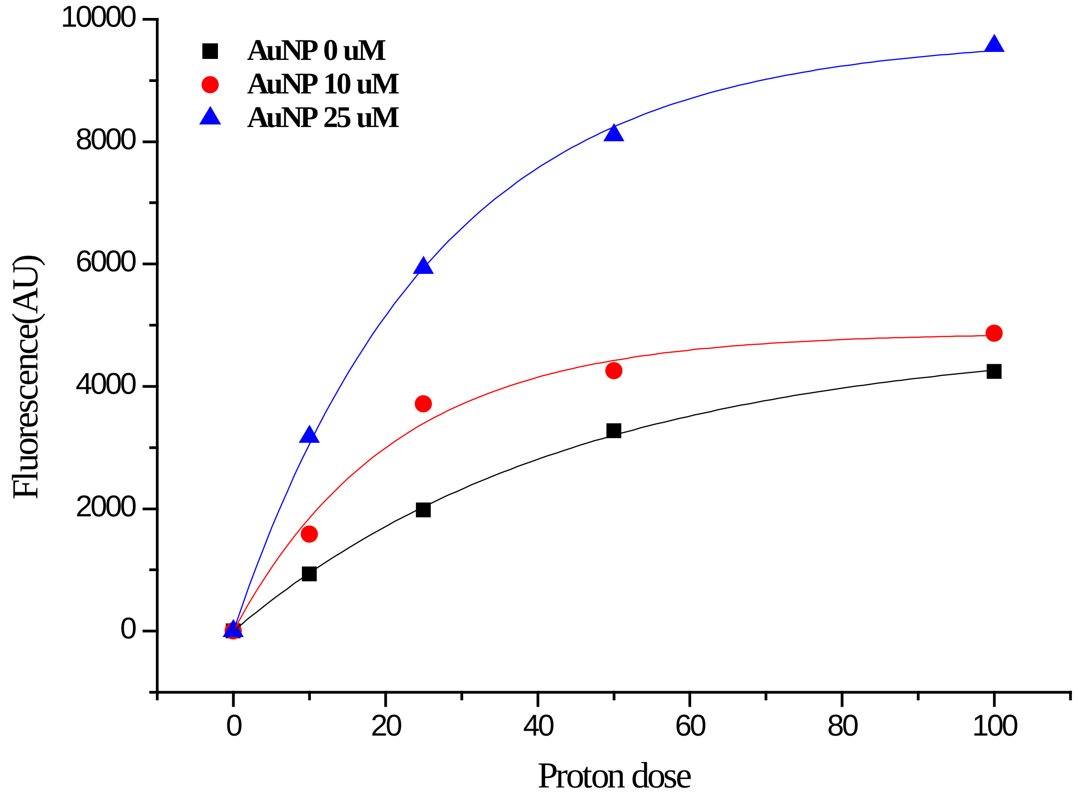
$$\frac{[O_2{}^-]_{CNR}}{[O_2{}^-]_{PA}} = 2.53$$

$Y_{[LEEs]/}Y_{[X\text{-}FL]}$ =2.53/1.15

Dosimetry of AuNP-nanoradiator

100 MeV traversing proton beam





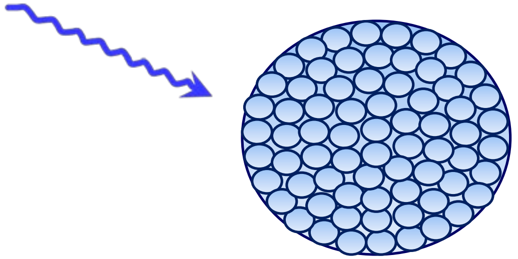
$$\frac{[OH^-]_{CNR}}{[OH^-]_{PA}} = 7.14$$

$$\frac{[O_2{}^-]_{CNR}}{[O_2{}^-]_{PA}} = 2.13$$

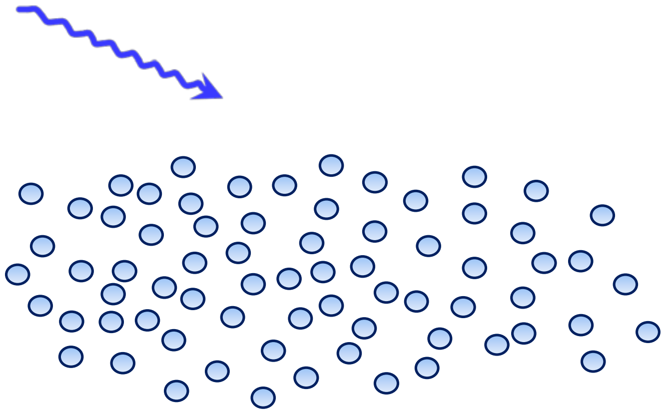
$Y_{[LEEs]/}Y_{[X\text{-}FL]}$ =2.13/7.14

NEXAF study to investigate ICD electron emission

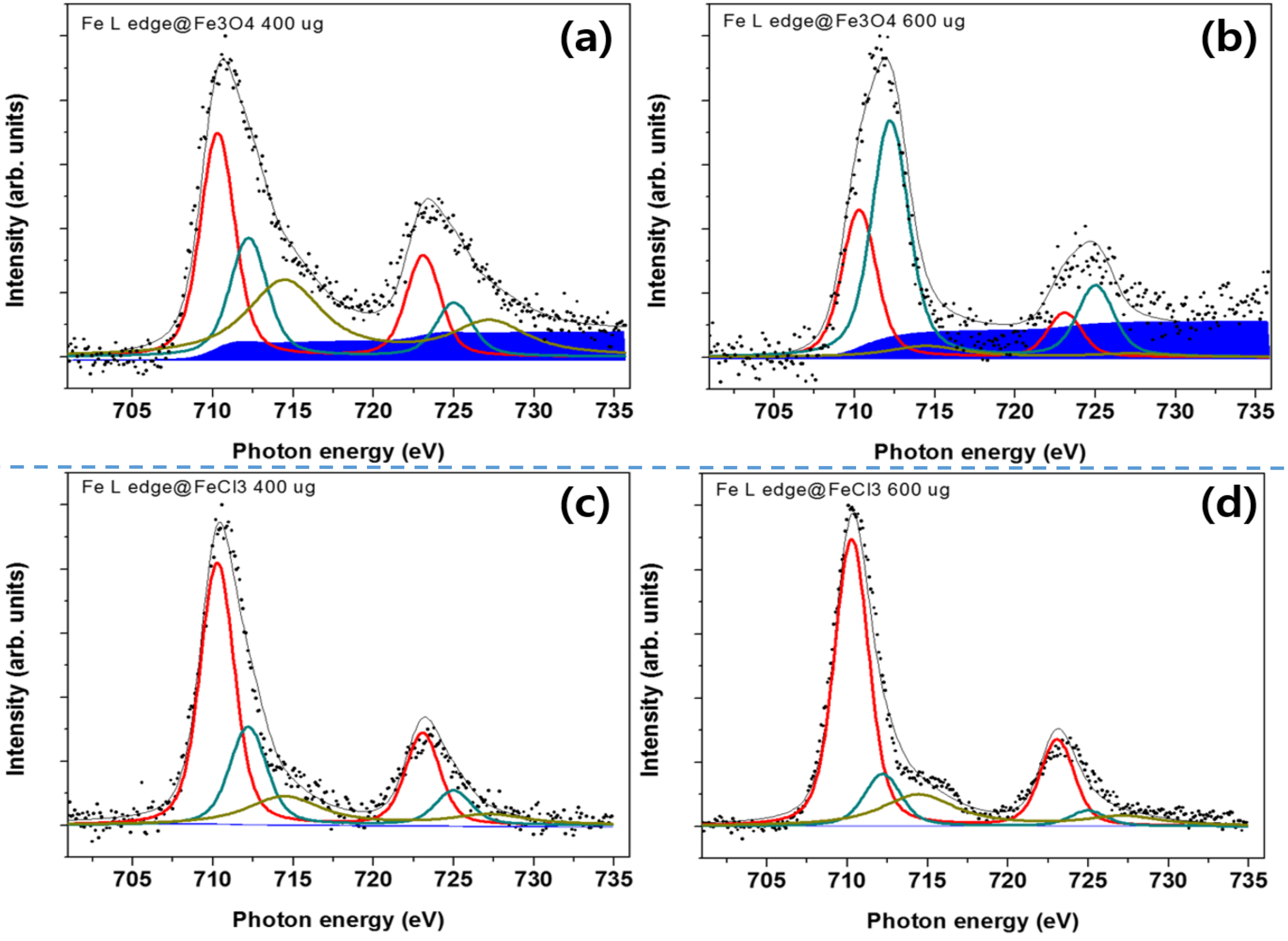
Fe L-edge X-ray



Fe_3O_4 NP Fe-Fe ICD (+)



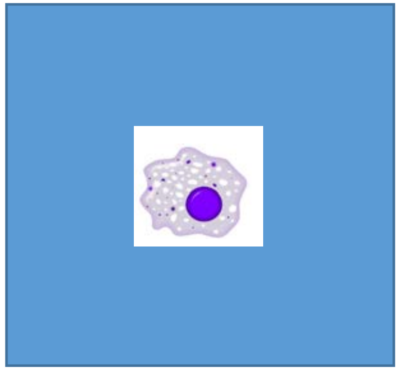
$FeCl_3$ Fe-Fe ICD (−)



PLS Photoemission beamline

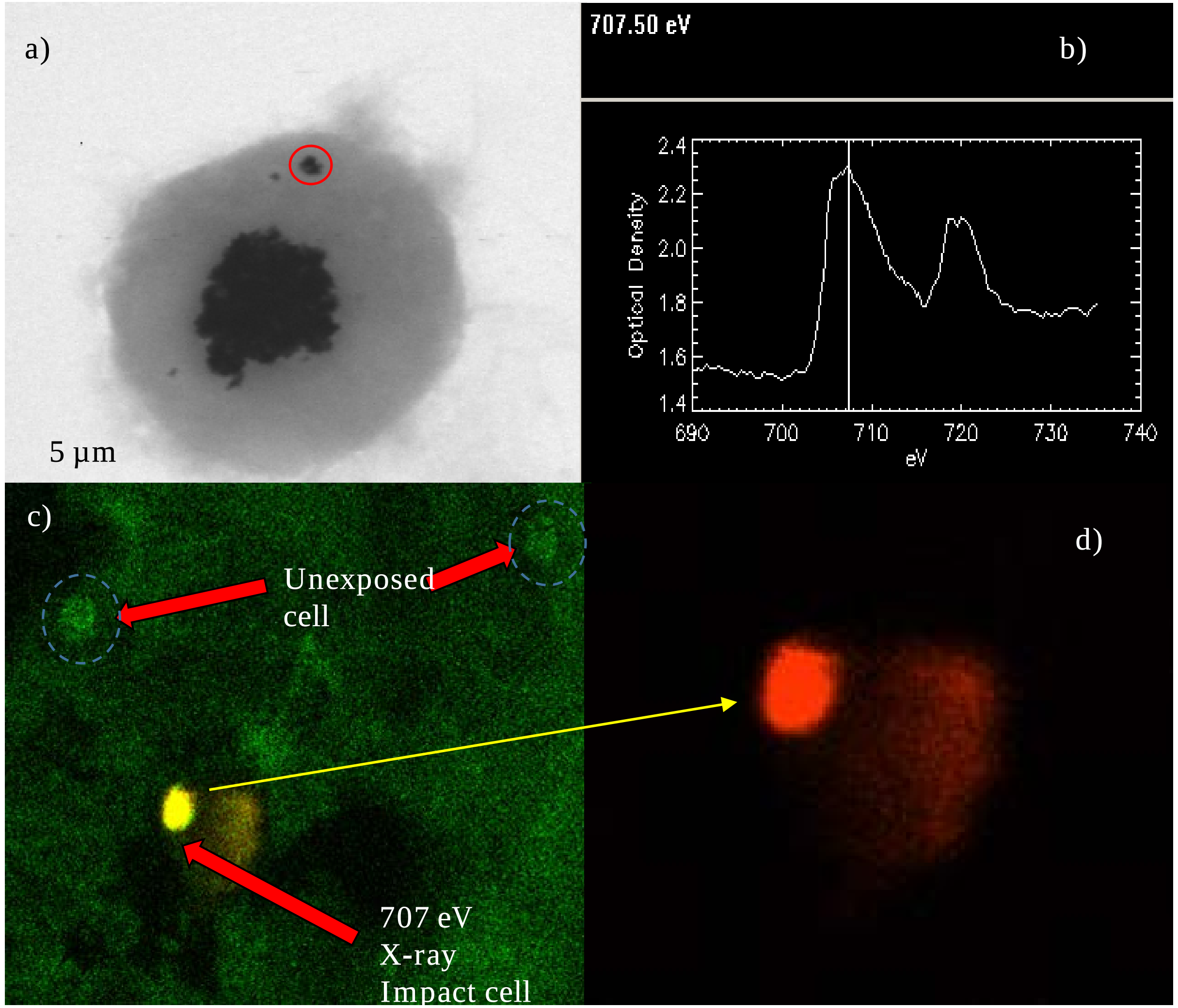
Nanoradiator energy transfer in cell

STXM-based X-ray Pump Optical Probe



Zone-plate focused
30 nm-x-ray beam
DHE:imaging $[O_2^-]$
by confocal FL MS

PLS STXM beamline



conclusion

- Internal structure of skull: source of diffraction anomaly
- Traversing Ion beam-induced Nanoradiator: site-specific therapeutic nanobeacon
- ICD path for nanoradiator dose-enhancement
- Transcytosis-mediated BBB crossing vs targeted high-Z NP for the treatment of infiltrative GBM