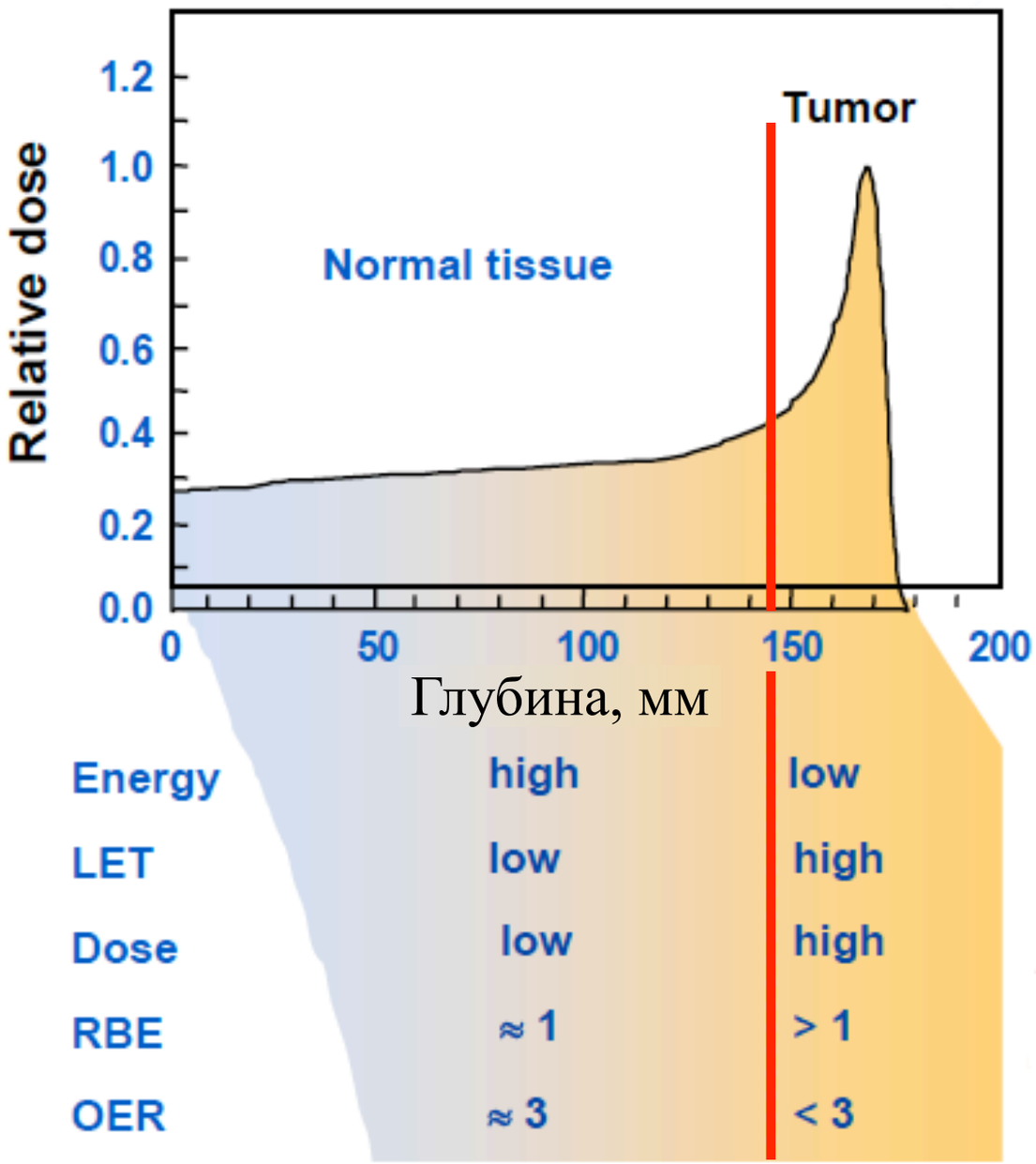
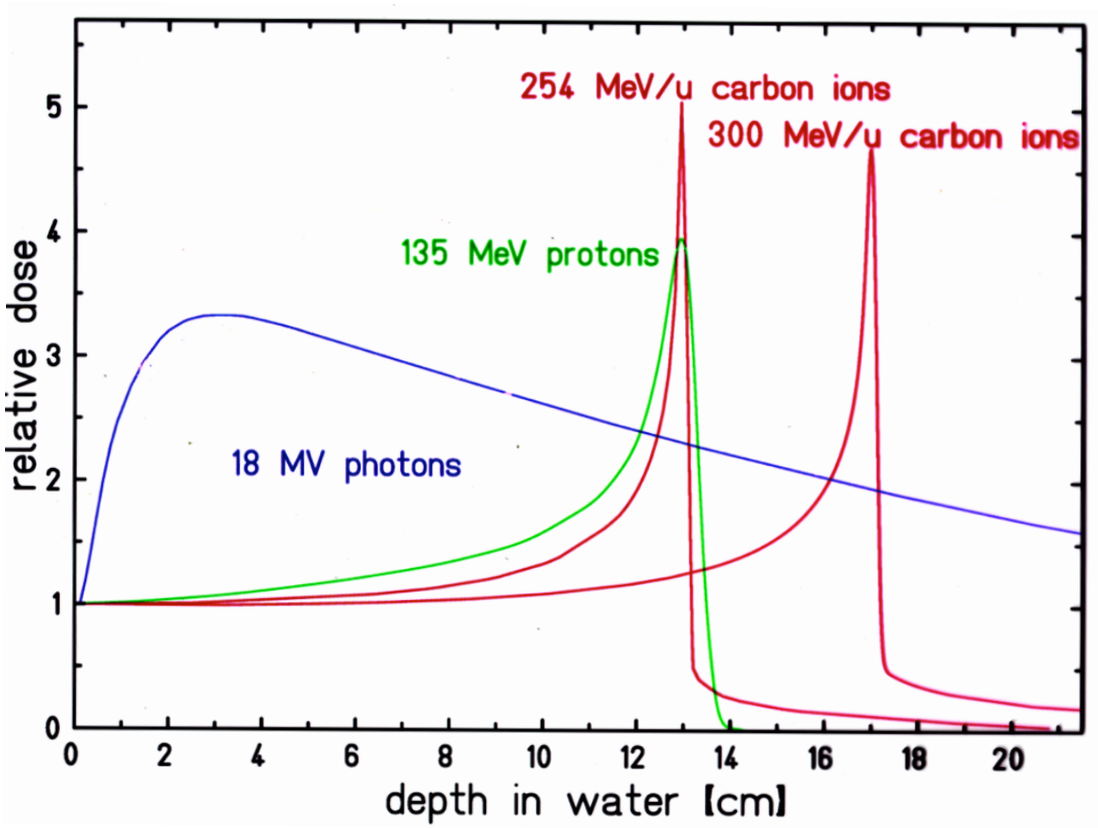
THE EXPERIENCE OF RADIOBIOLOGICAL RESEARCH WITH HEAVY ION BEAMS AT ITEP

Nikolay Markov
markov@itep.ru

Motivation: Heavy Ion Therapy



Durante & Loeffler, Nature Rev Clin Oncol 2010



Availability of Heavy Ion Therapy is increasing worldwide - 8 centers in operation, 3 under construction. Approx. 13000 patients were treated with C-ions since 1994 (http://www.ptcog.ch)

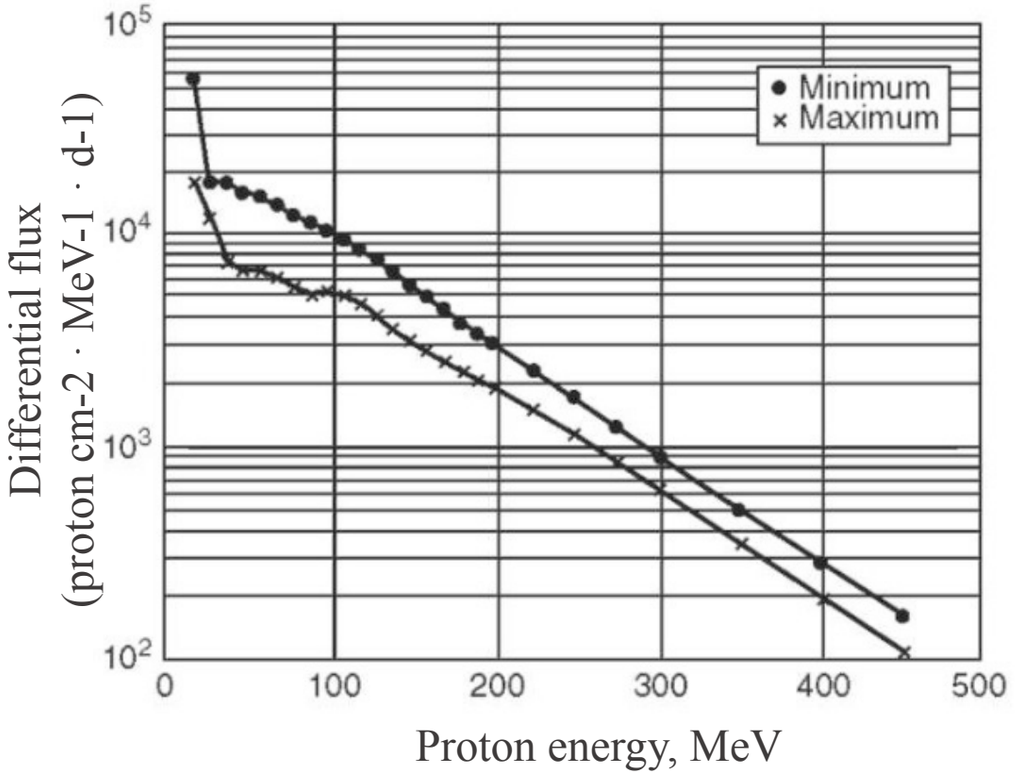
Key research areas in hadrontherapy

1. Moving targets
2. TPS: RBE modeling, reducing uncertainly
3. Secondary cancer risk
4. Individual radiosensityvity
5. Genetic background
6. Cancer stem cells
7. Hypofractionation

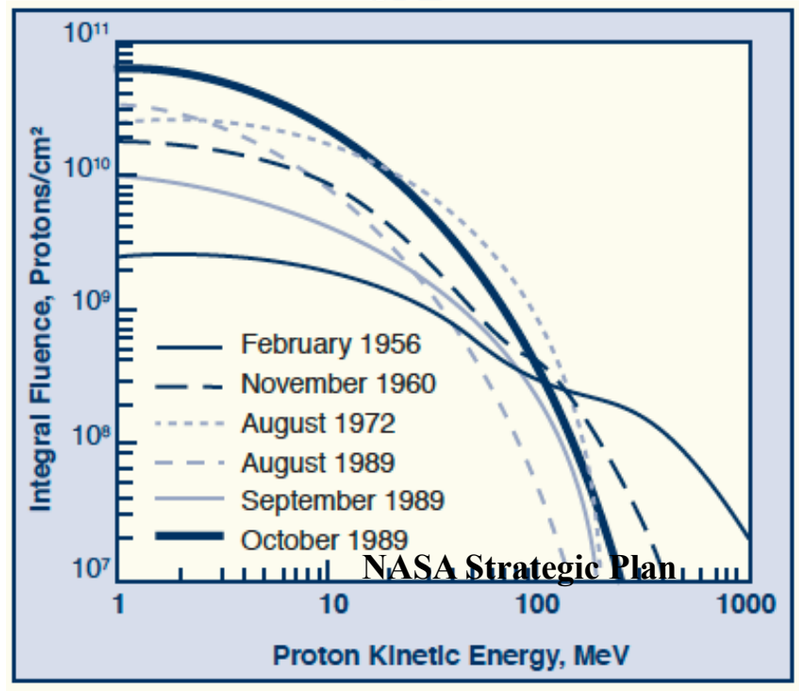
Motivation: Radiobiology for Space Research

1. Galactic Cosmic Rays (GCR) - high energy protons; highly charged, energetic atomic nuclei (HZE particles)
2. Solar Particles Events (SPE) - medium and high energy protons
3. Trapped Radiation - medium energy protons and electrons

Trapped Radiation

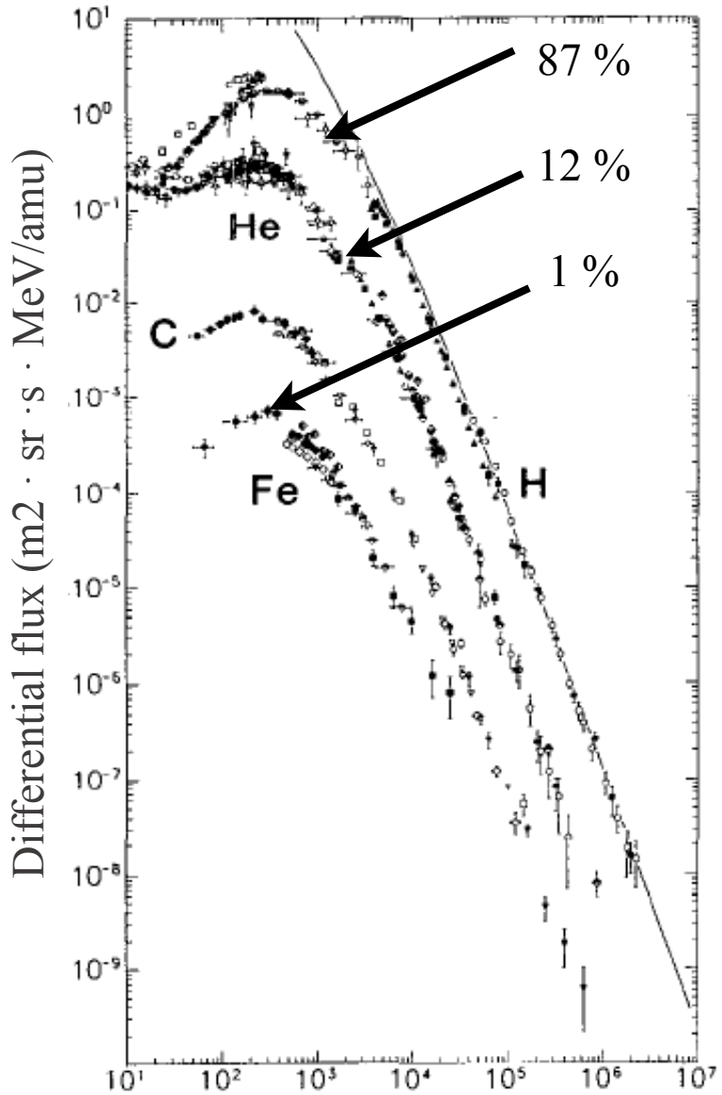


Distribution in Energy of Proton Fluxes in SPE



NASA Strategic Plan

Energy Spectra of GCR



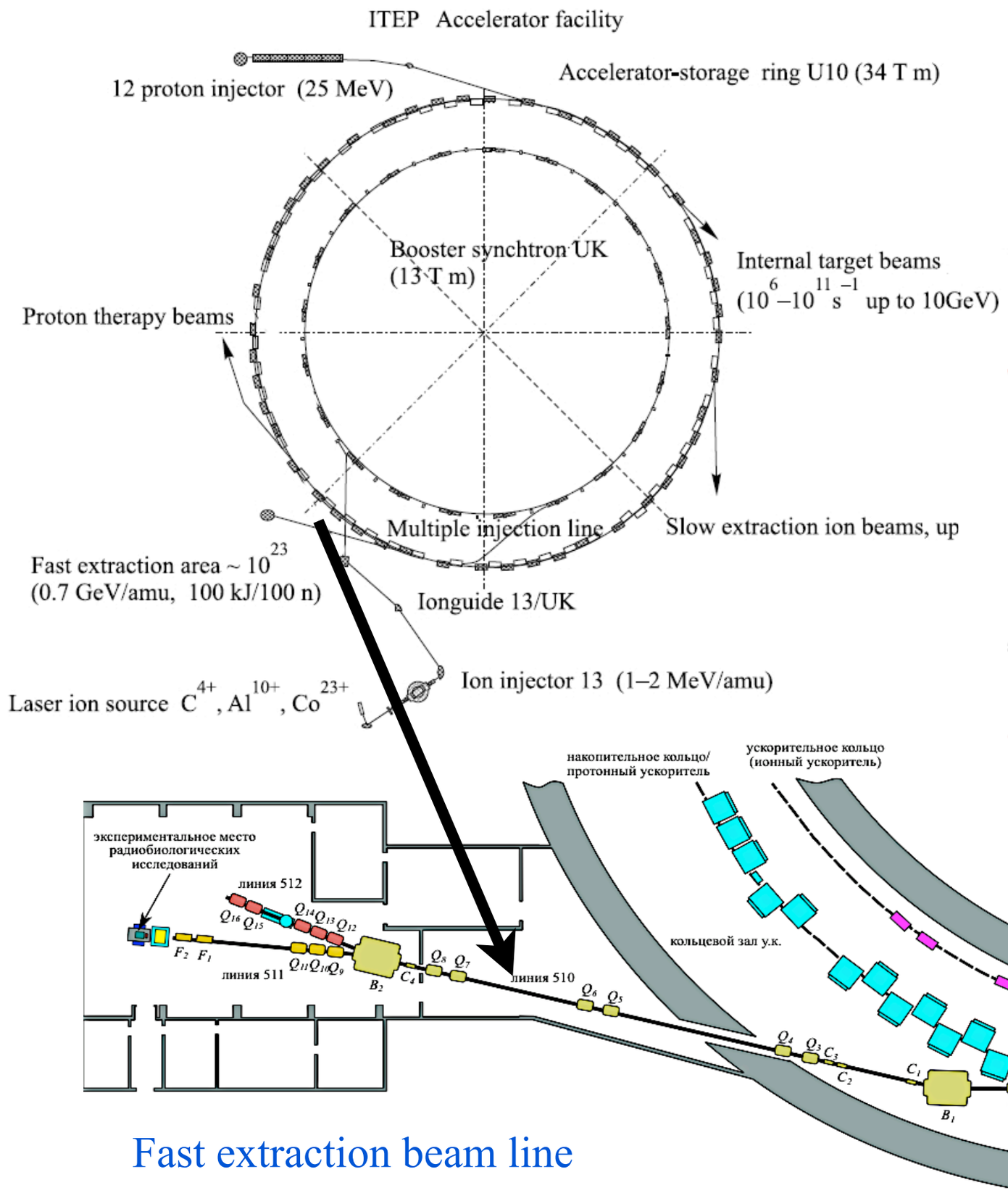
Relative Contribution of Different Components of GCR to Dose Equivalent

* behind aluminum of 5g/cm2

Main objectives of space radiobiology:

- Development of an effective shielding against space radiation;
- Reduction of biological uncertainty;
- Estimation of the risks of the harmful radiation effects (neurodegeneration, cancer induction);

Heavy ions for radiobiology in ITEP

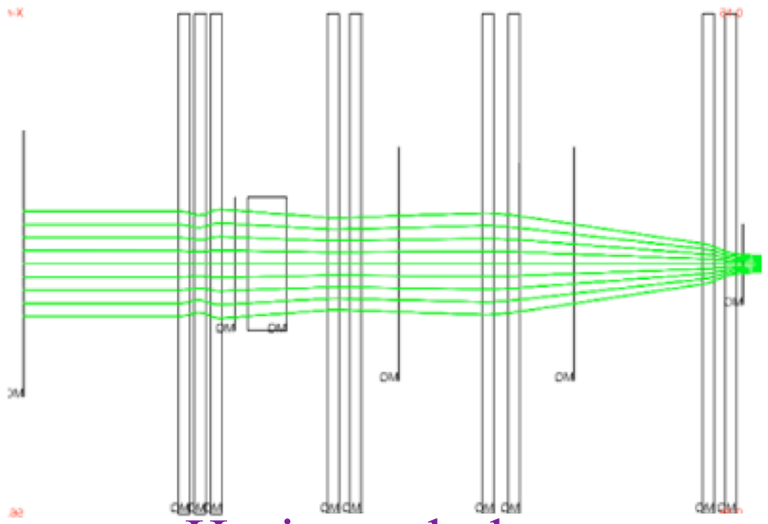


Fast extraction beam line

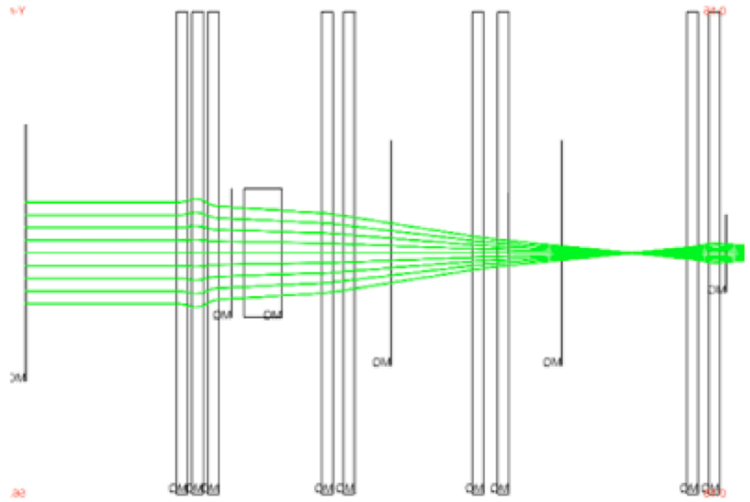
Beam parameters

Ion	$^{12}C^{6+}$	$^{56}Fe^{26+}$
Energy	215 MeV/amu	230 MeV/amu
Particles per pulse	10^6 - 10^9	10^6 - 10^8
Pulse width	800 ns	800 ns

Results of beam dynamic calculation with COSY Infinity

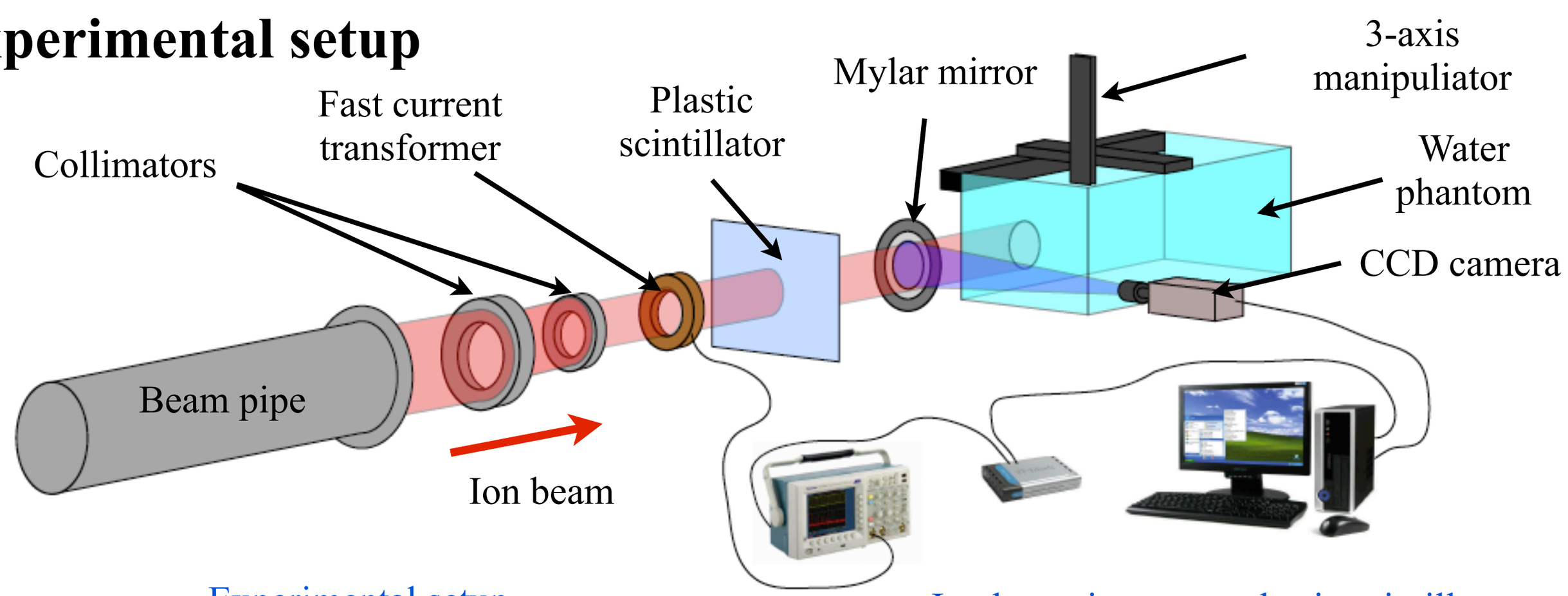


Horizontal plane

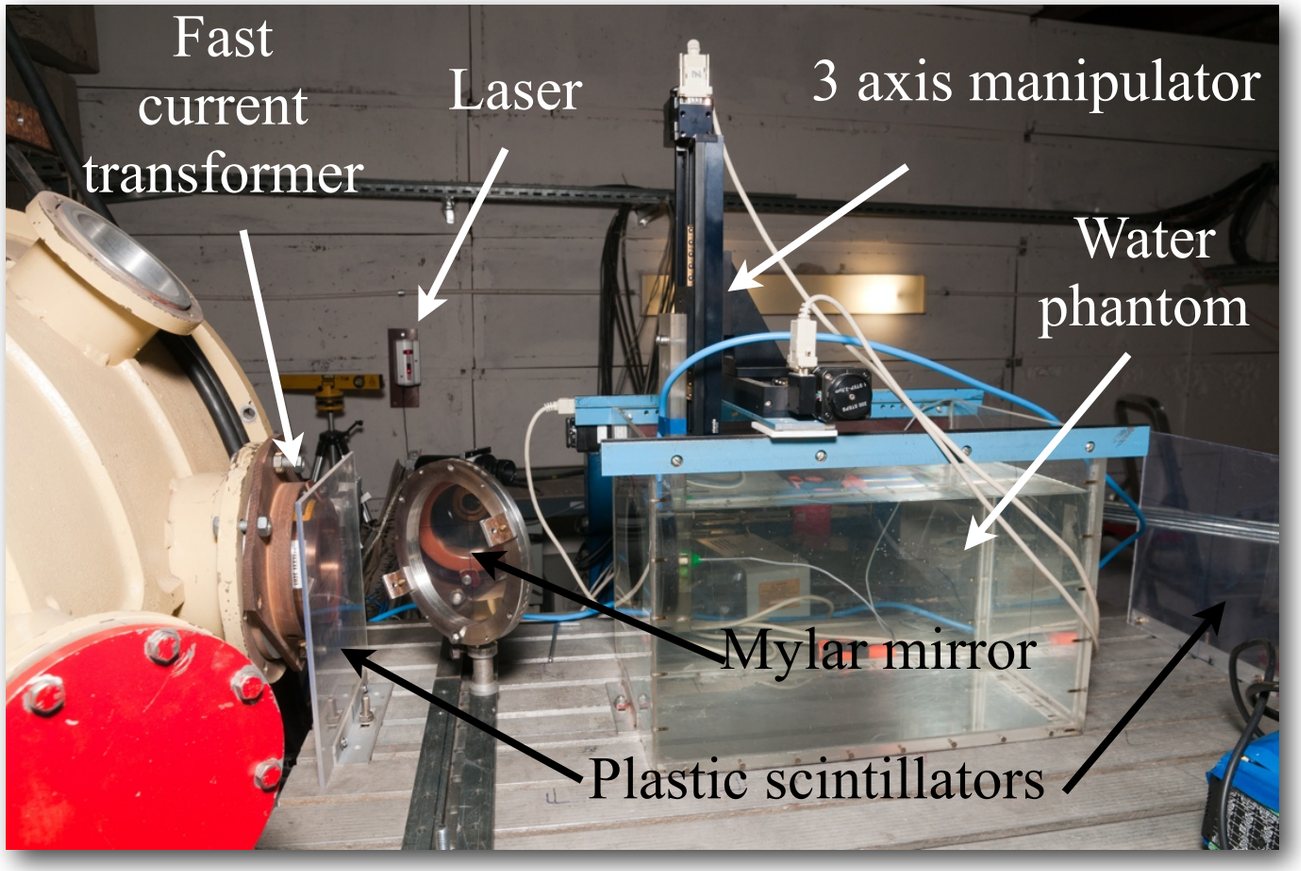


Vertical plane

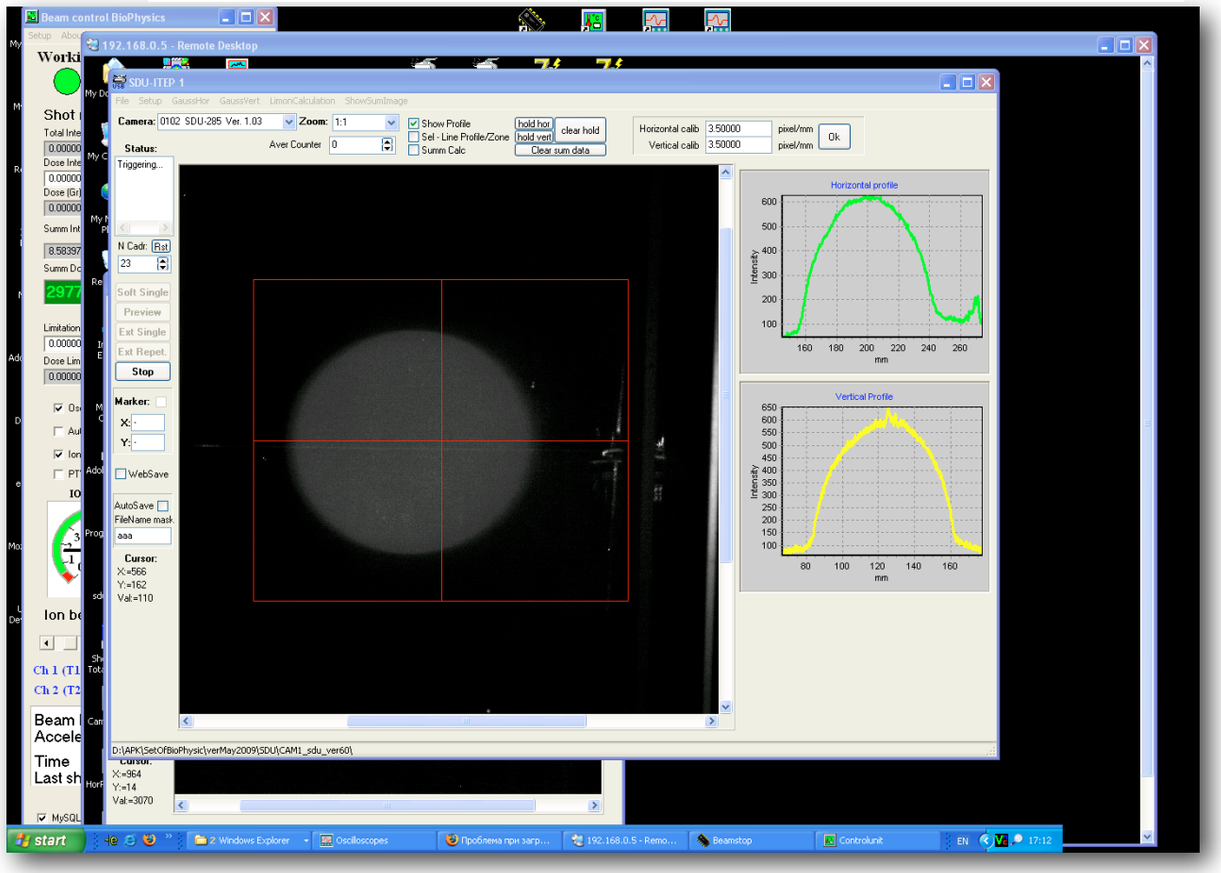
Experimental setup



Experimental setup

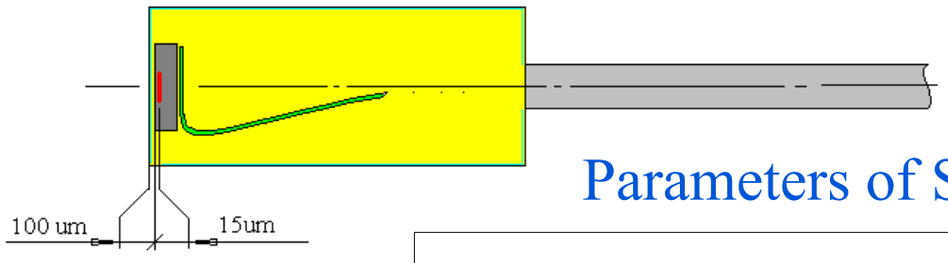


Ion beam image on plastic scintillator



Depth-dose curve measurements

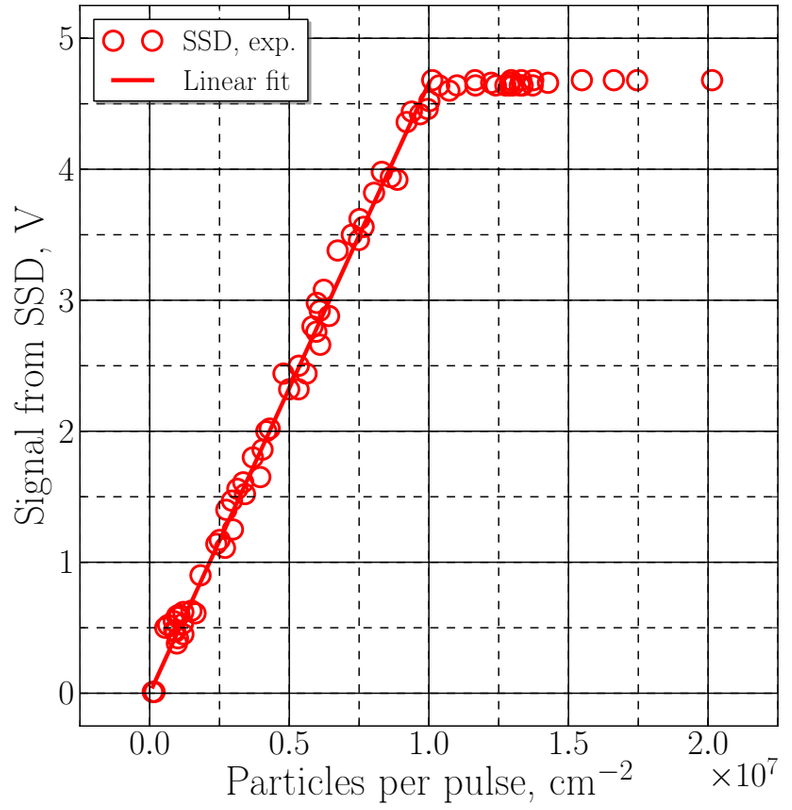
Silicon Semiconductor Detector (SSD)



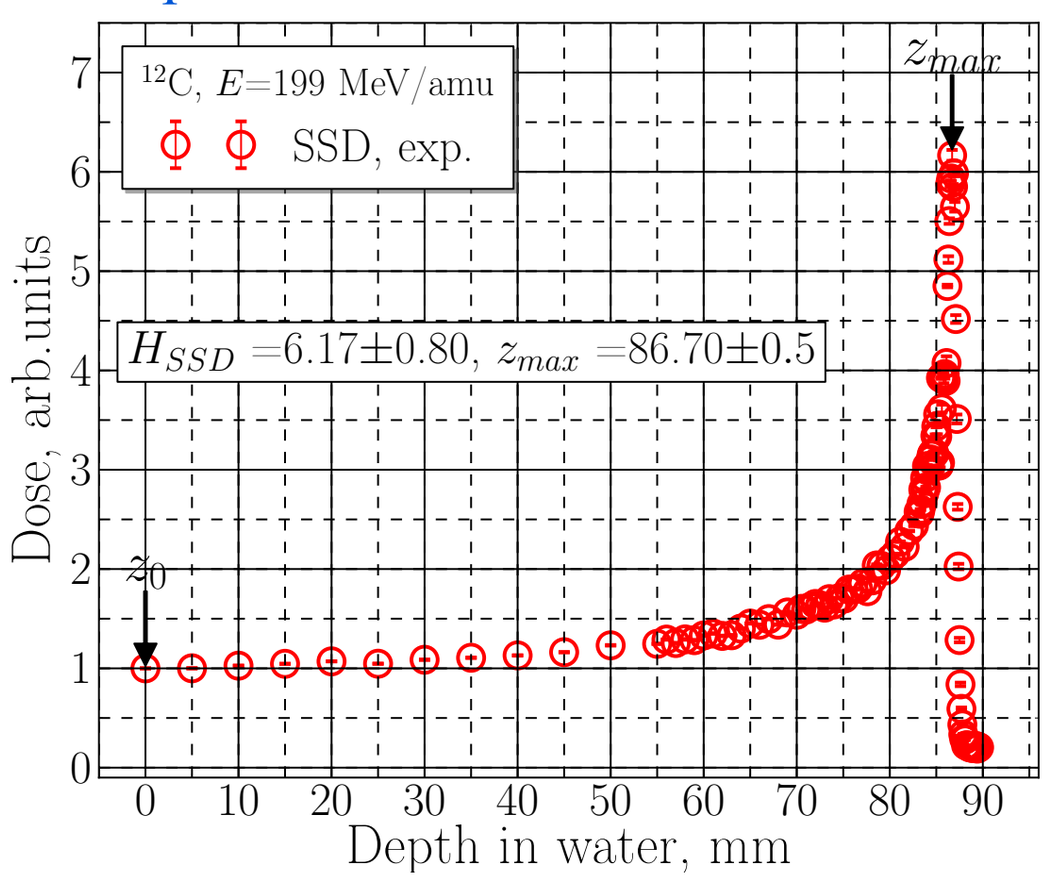
Parameters of SSD used in exp.

Detector type	Hi-p-type
Thickness of Si plate	0.2 mm
Thickness of sensitive layer	15 mkm
Sensitive area	1x1 mm^2

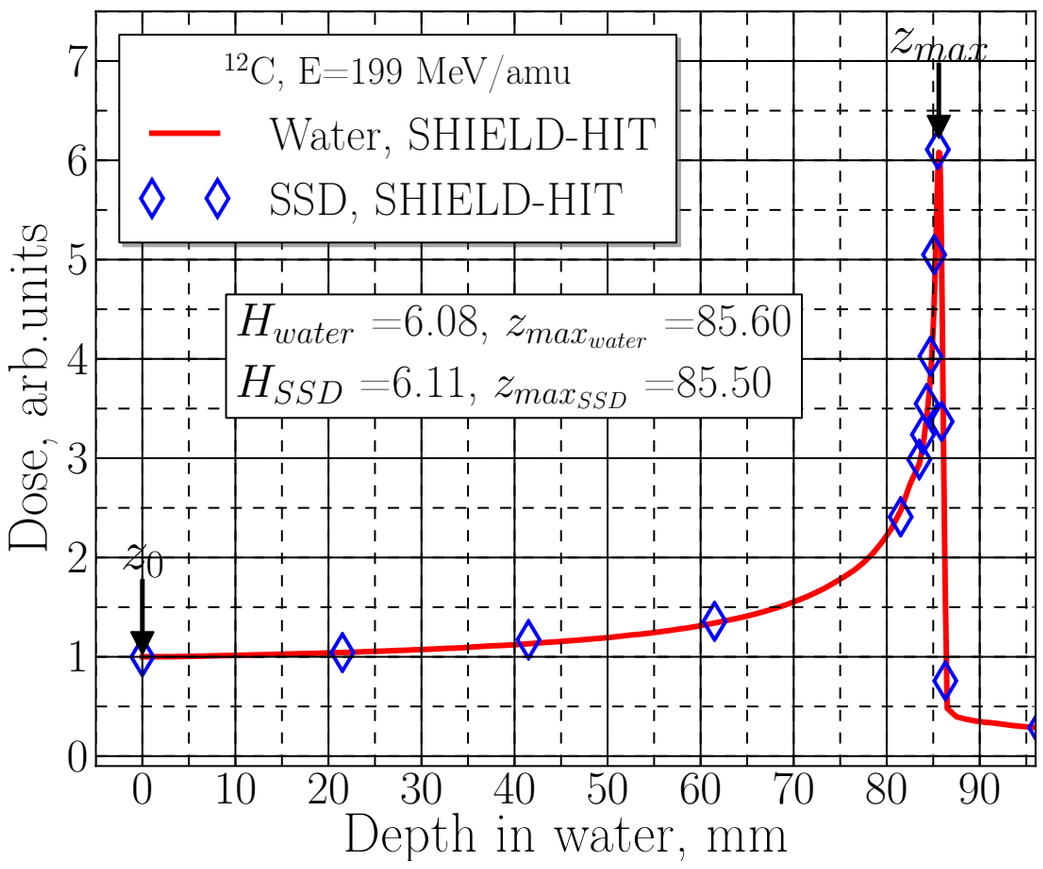
SSD dose rate linearity in entrance region



Depth-dose curve measured with SSD



Results of SHIELD - HIT calculation



Absorbed dose determination

1. Measurements of the depth-dose curve

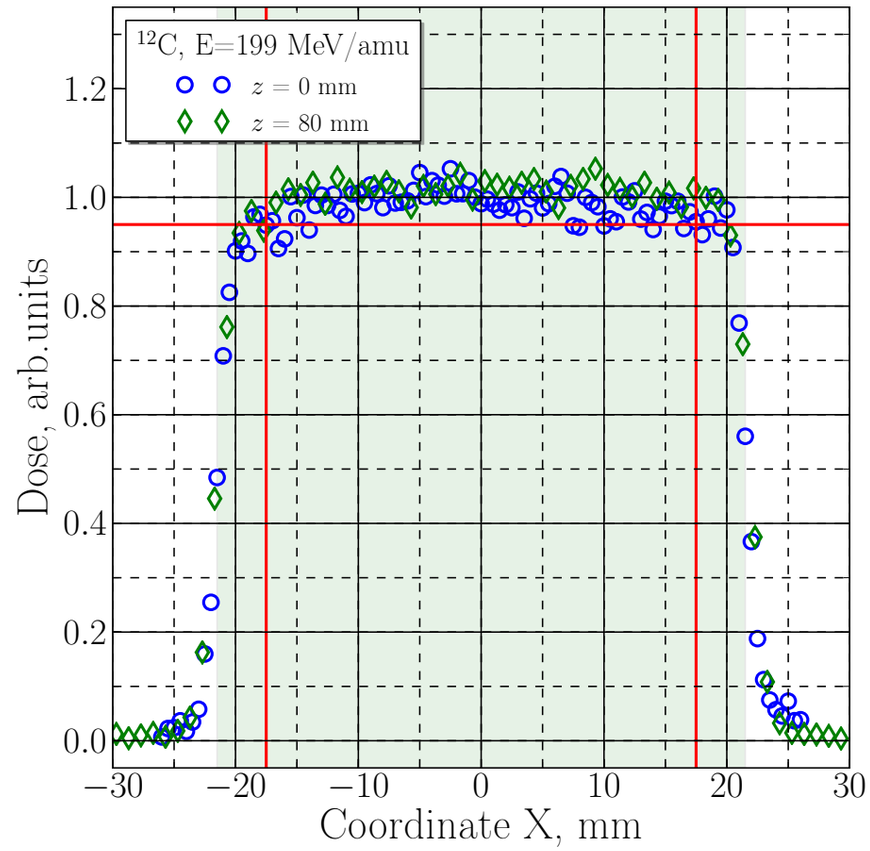
2. Position of the Bragg peak

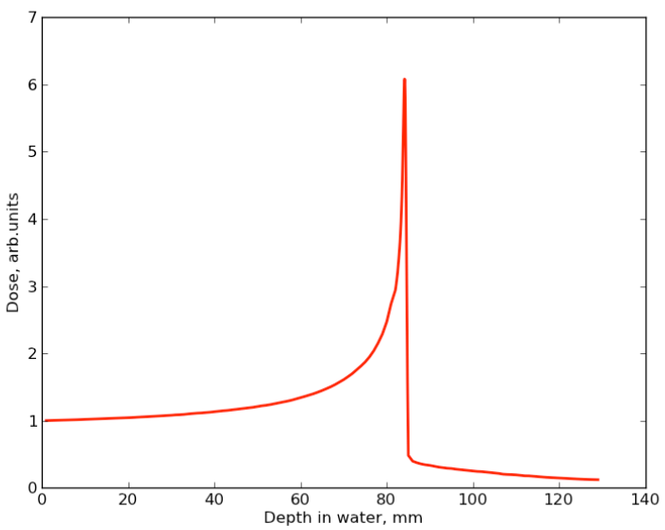
3. Calculation of the ion beam energy E at the point z0 (with TRIM code)

4. Absorbed dose for a thin layer at the point z0

$$D = 1.602 \cdot 10^{-9} \left(\frac{dE}{dx}\right)_E \times \frac{N}{S} \times \frac{1}{\rho}$$

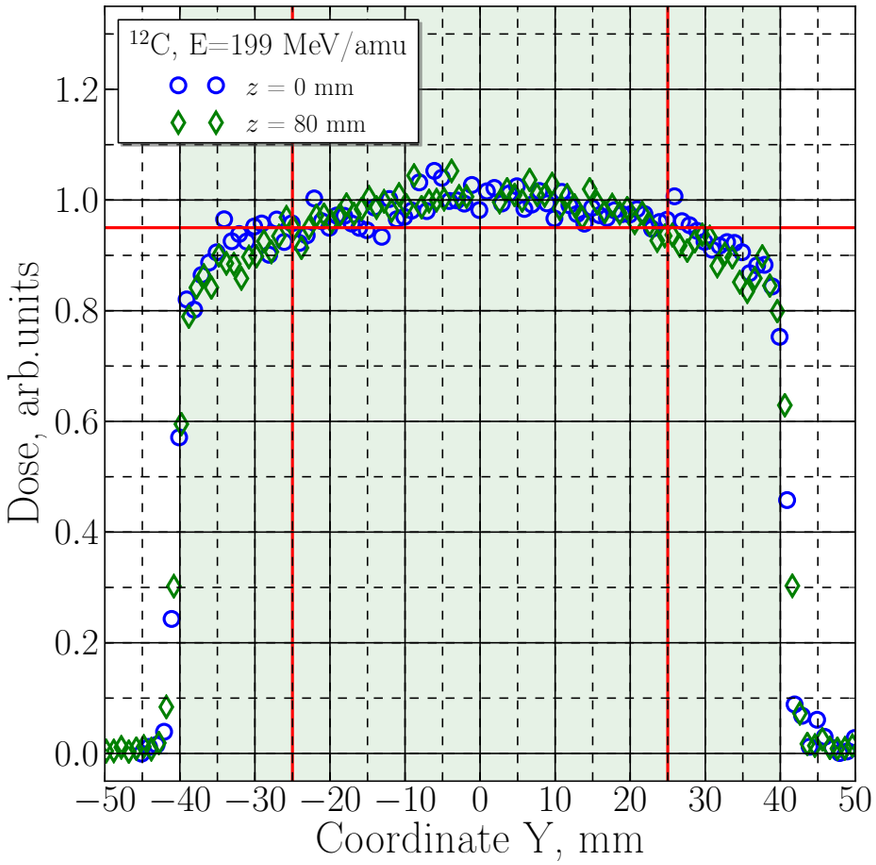
Transversal distributions





Uncertainty in absorbed dose

	Relative uncertainty, %
Number of particles	≤ 3.5
Field size	1
Ion energy	1
Stopping power	2 - 3
Total	< 5



Radiochromic Film Dosimetry

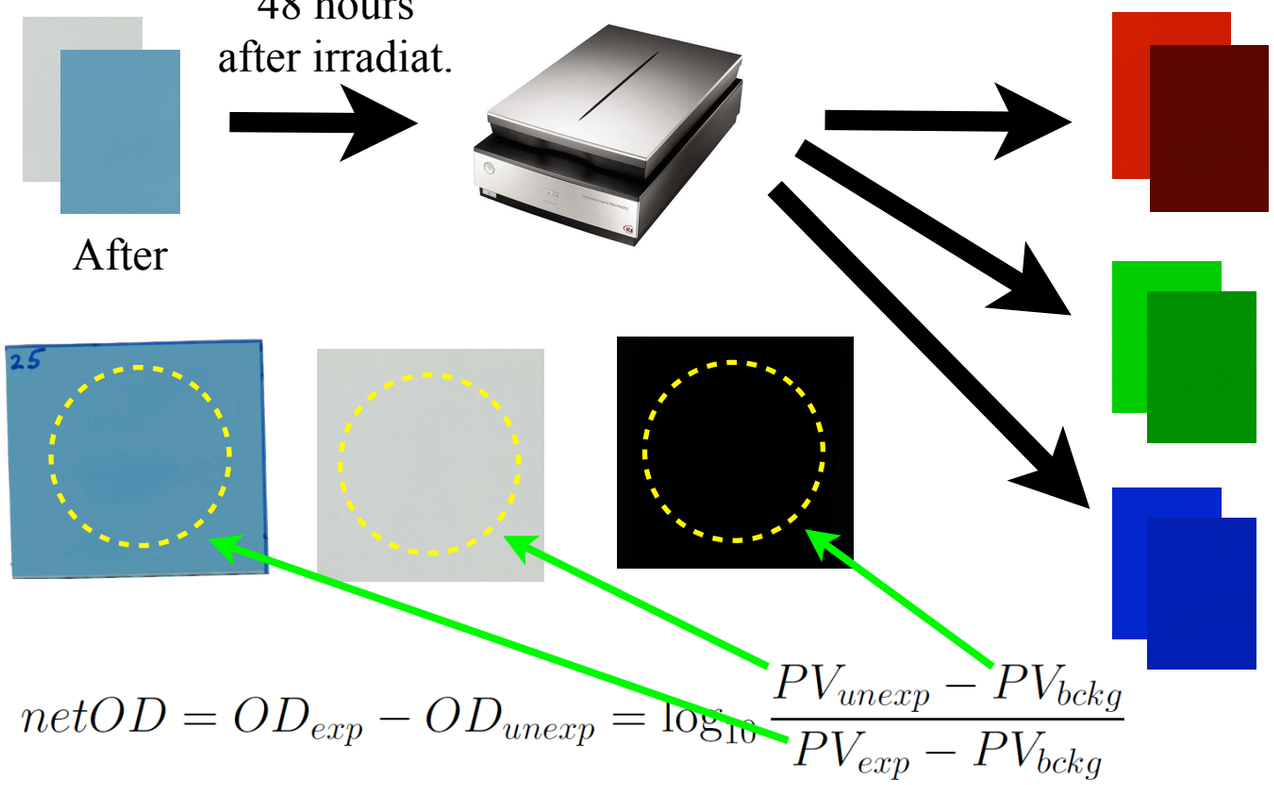
MD-V2-55: 1-100 Gy, thickness 317.5 mkm

1. Calibration with 6 MV photons in MRRC

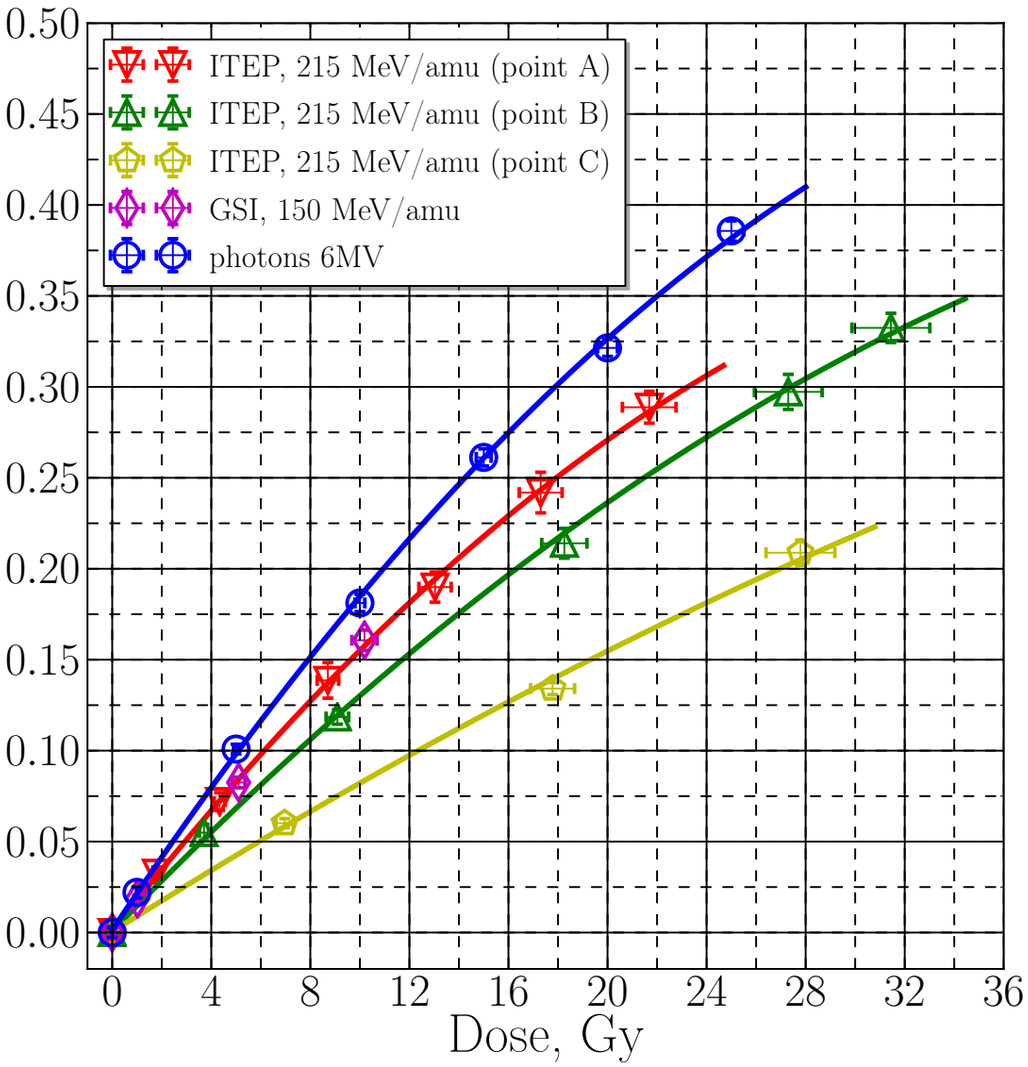
Before

After

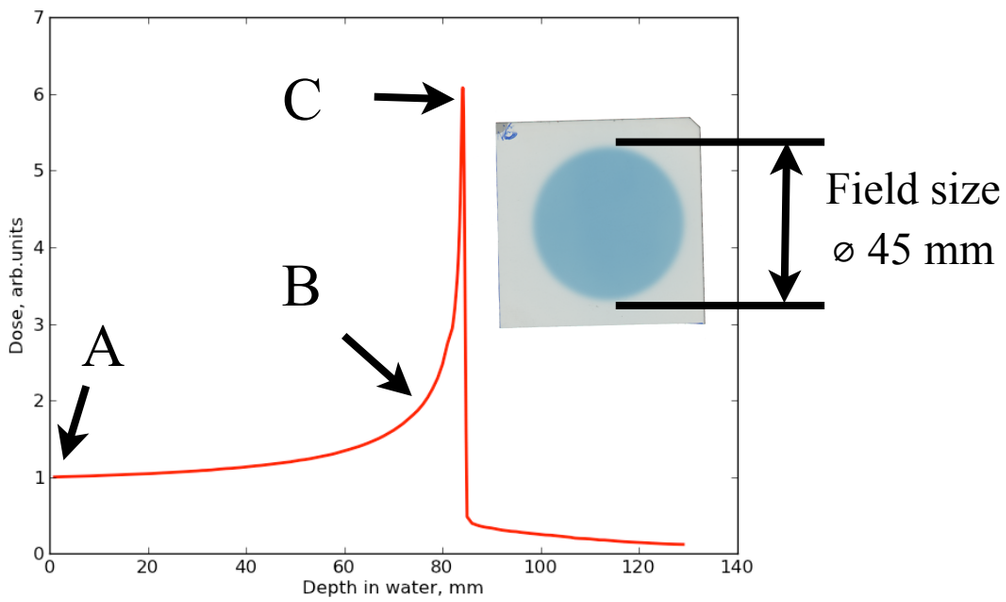
48 hours after irradiat.



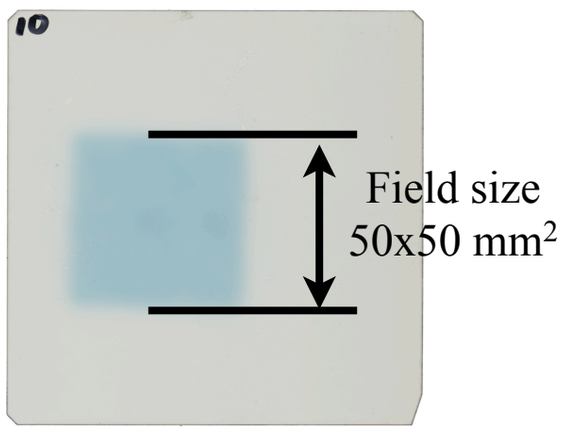
$$netOD = OD_{exp} - OD_{unexp} = \log_{10}\frac{PV_{unexp} - PV_{bckg}}{PV_{exp} - PV_{bckg}}$$



2. Calibration in ITEP (^{12}C, 215 MeV/amu)

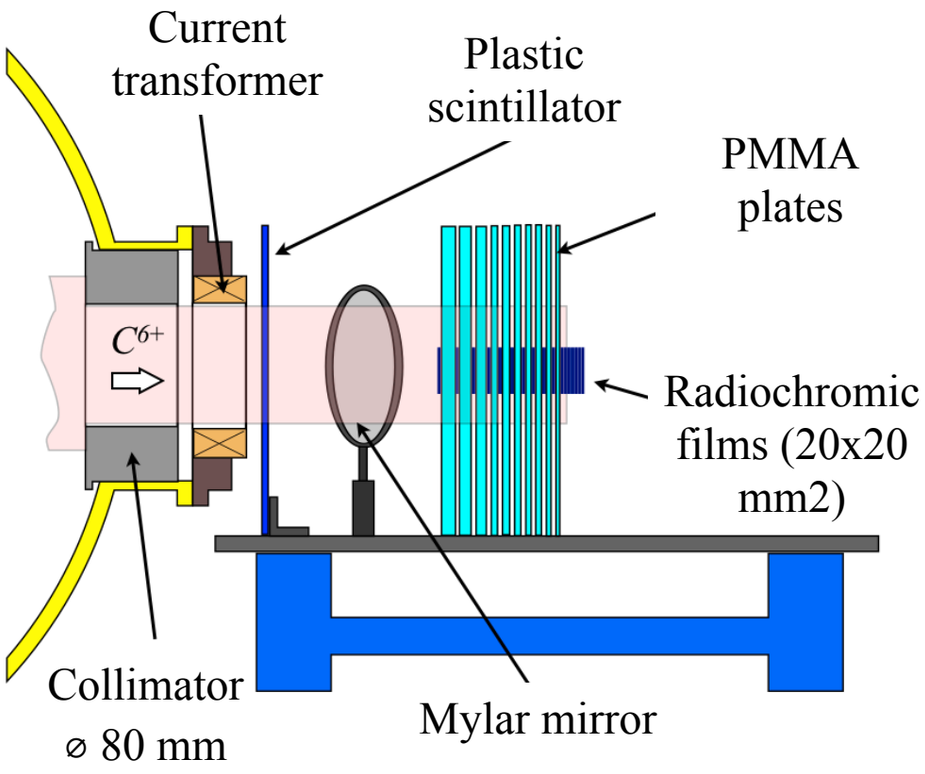


3. Calibration in GSI (^{12}C, 150 MeV/amu)

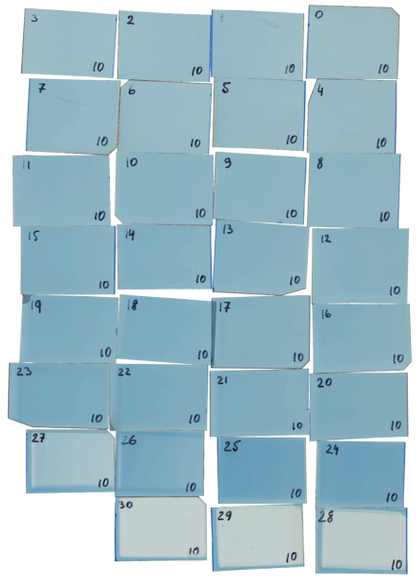


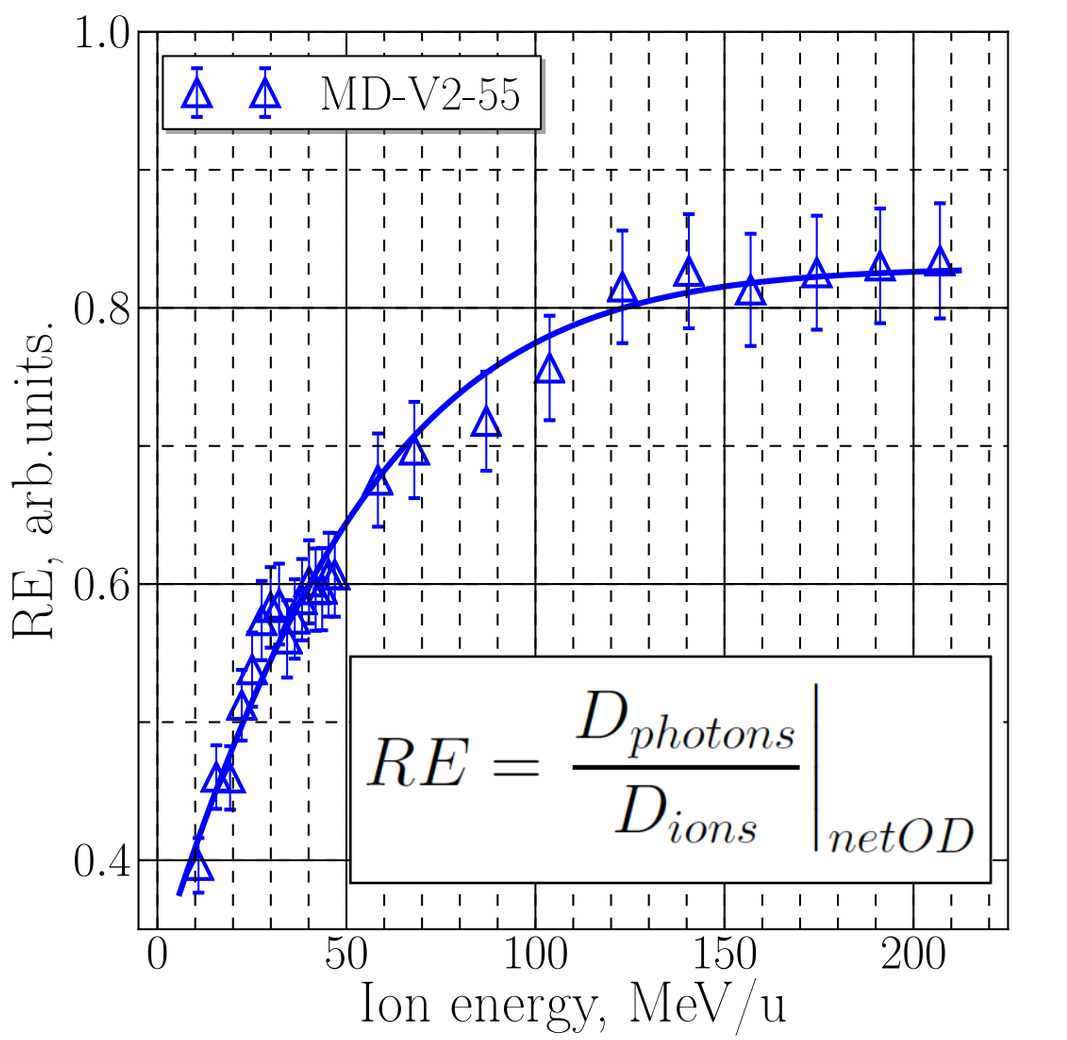
For uniform irradiation a raster scanning system with a “pencil” beam was used.
“Pencil” beam - Gaussian shape, with FWHM 2 mm

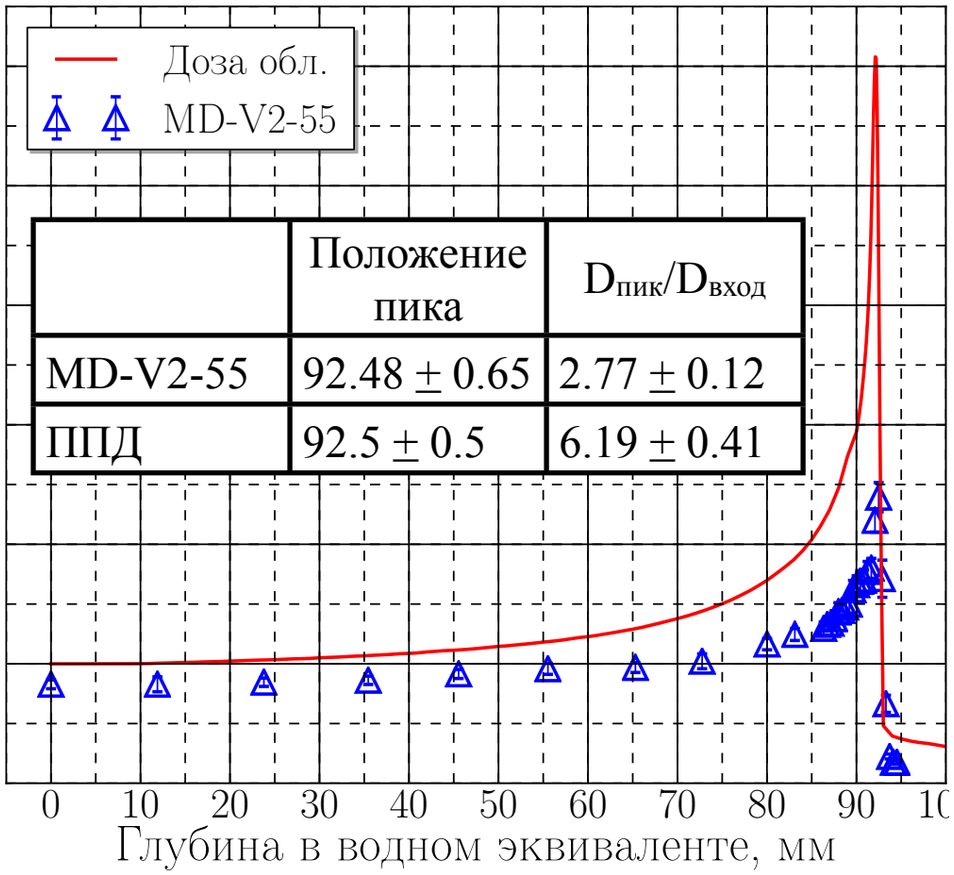
Relative effectiveness of RCF



Water Equivalent Path Length of PMMA 1.16



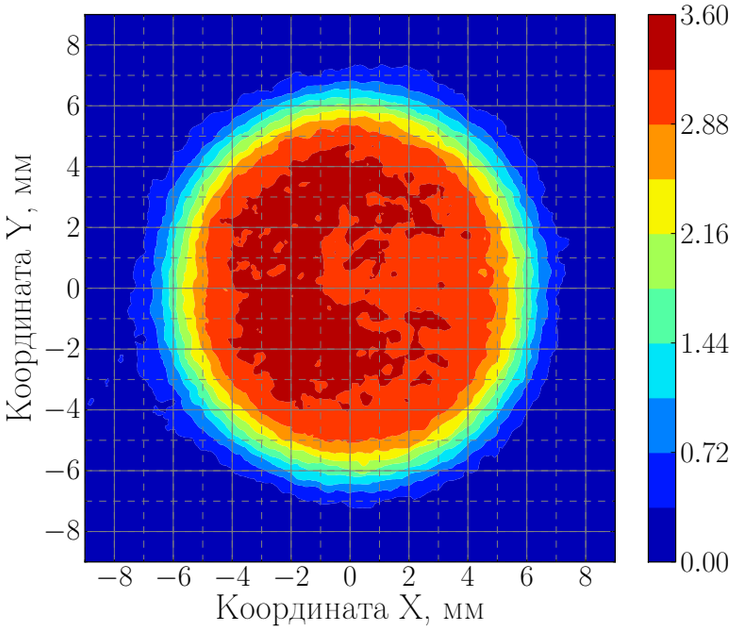




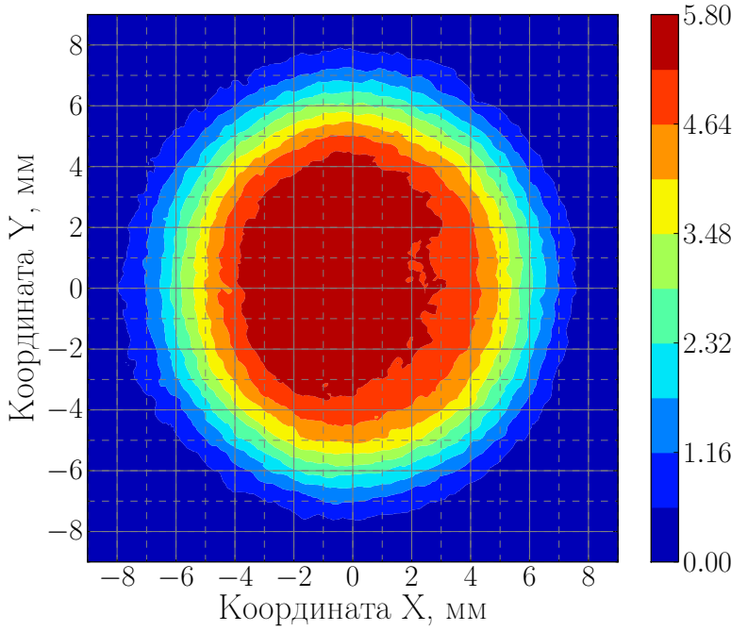
	Положение пика	$D_{пик}/D_{вход}$
MD-V2-55	92.48 ± 0.65	2.77 ± 0.12
ППД	92.5 ± 0.5	6.19 ± 0.41

Iso-dose distributions

z = 0 mm

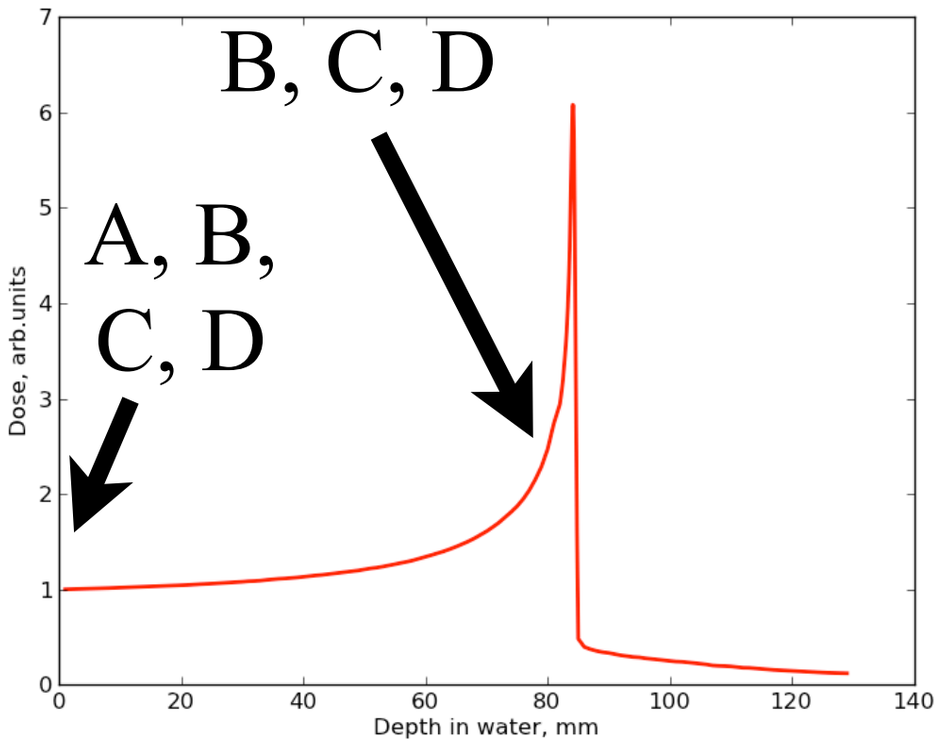


z = 80 mm



Radiobiological experiments “in vitro”

A	Human peripheral blood lymphocytes. For irradiation cells were placed in tubes (eppendorf 5 ml). Chromosome aberrations were analyzed in metaphases 48h after radiation exposure.
B	Breast cancer cell line Cal51 with normal karyotype. For irradiation cells were grown as monolayer and placed in 12.5 cm2 culture flasks. After irradiation chromosome aberration were analyzed
C	Chinese hamster ovary cells CHO-K1. For irradiation cells were grown as monolayer and placed in 12.5 and 25 cm2 culture flasks. After irradiation cell survival was measured with a colony assay.
D	Melanoma B16F10 cells. For irradiation cells were grown as monolayer and placed in 25 cm2 culture flasks. After irradiation cell survival was measured with a colony assay.

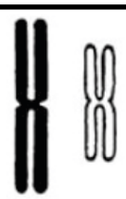
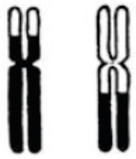


1. Eppendorf

2. Culture flasks

Methods of analysis

1. Analysis of chromosome aberration

Normal	Chromatid break	Chromosome fragment	Acentric ring	Centric ring with fragment	Translocation
					
Chromatid exchange		Dicentric with fragment		Reciprocal exchange	
					

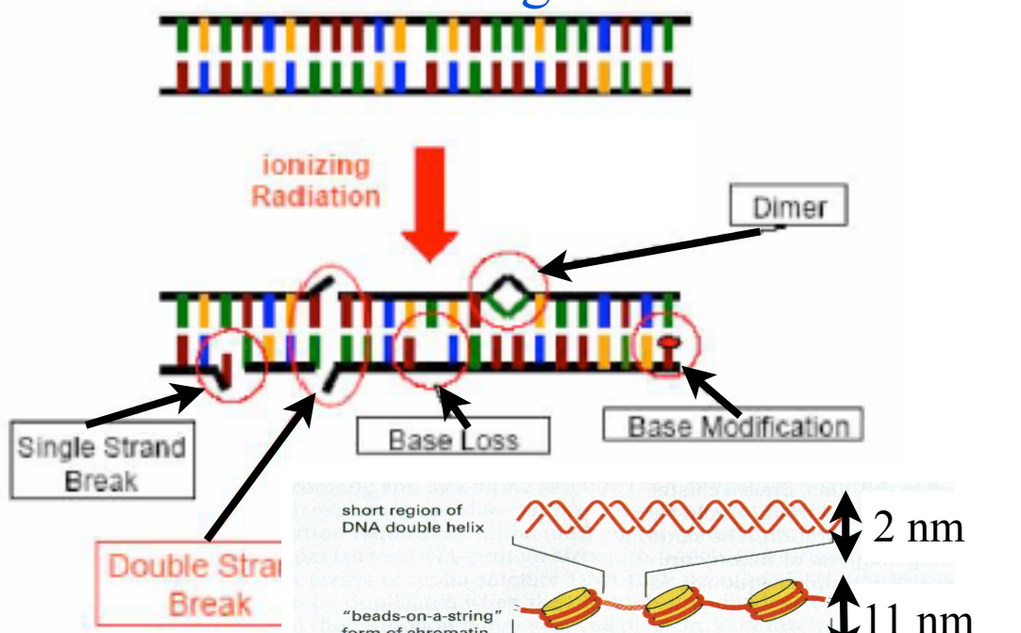
Not used

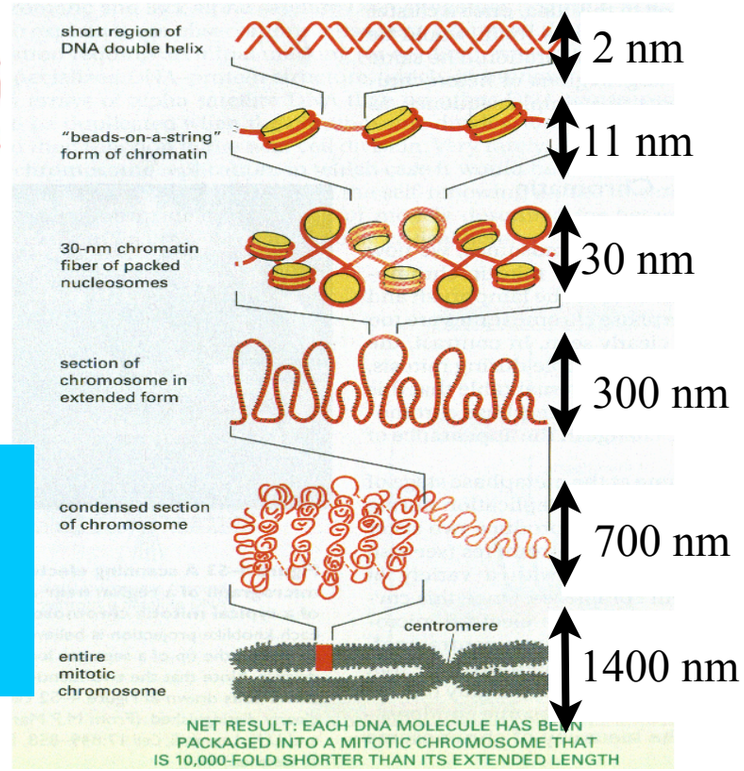
2. Cell survival based on a colony assay

A cell is considered surviving after exposure, if it forms a colony consisting of more than 50 cells. Cell survival was determined as follows:

$$S = \frac{N_{col}}{(N_{cells} \times (PE/100))}$$

DNA damages

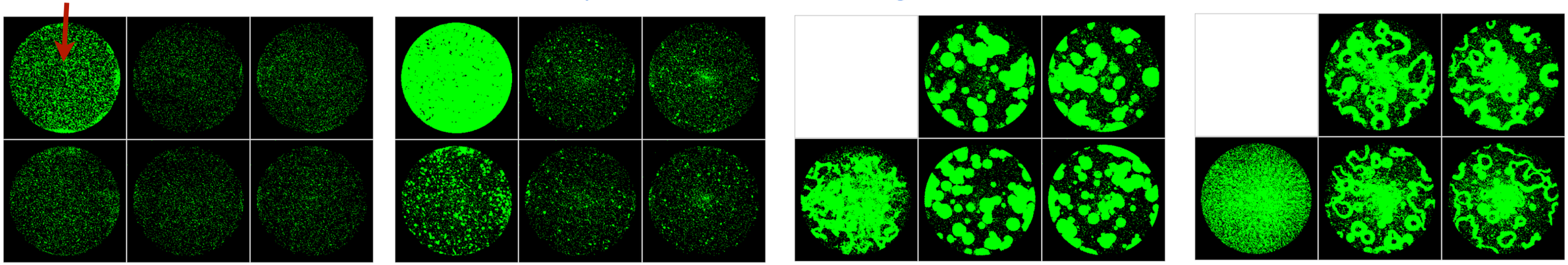




Alberts, 2002

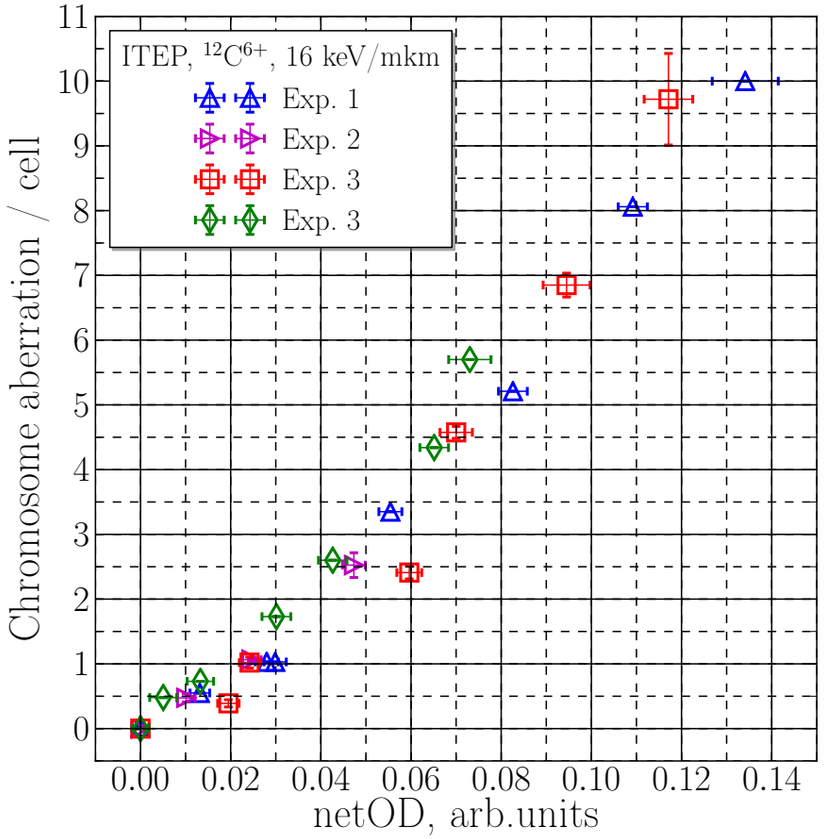
Dynamic of colonies grouth

Control



1-day | 3-day | 5-day | 7-day

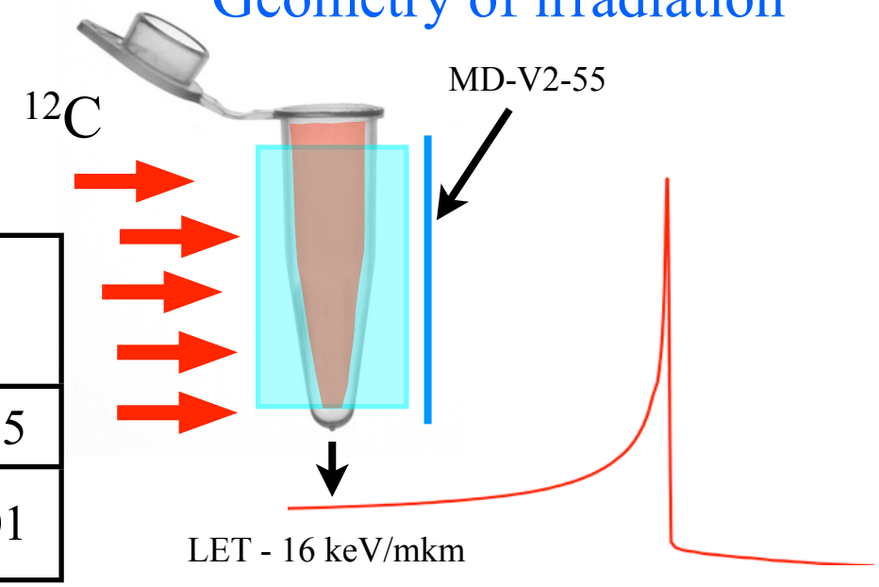
Results of lymphocyte irradiation

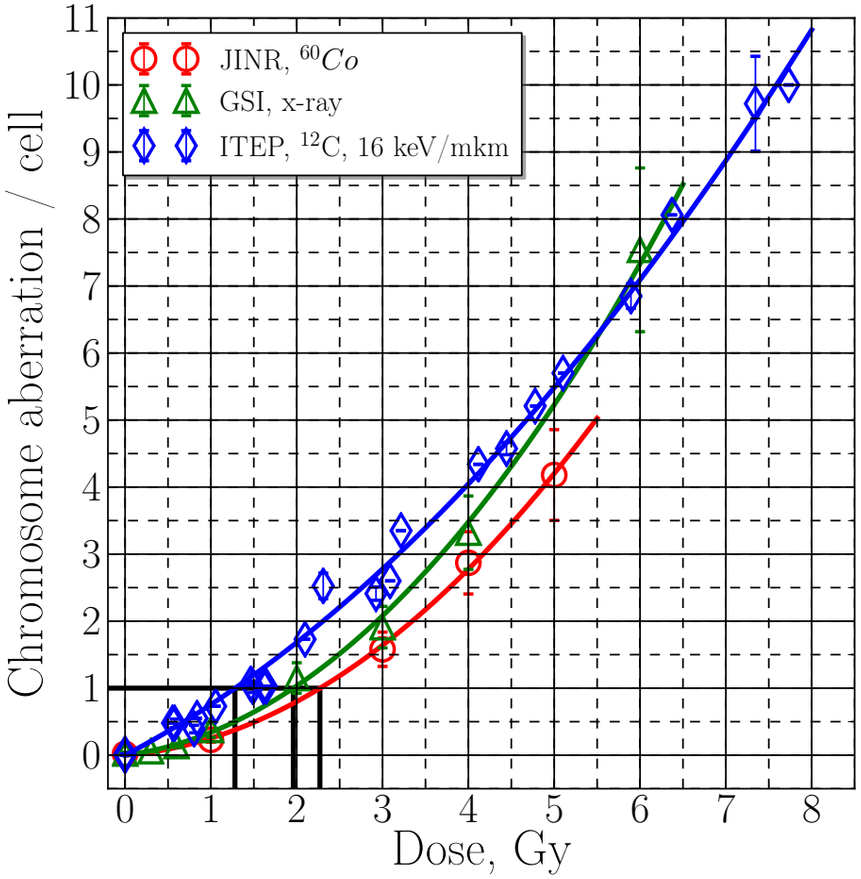


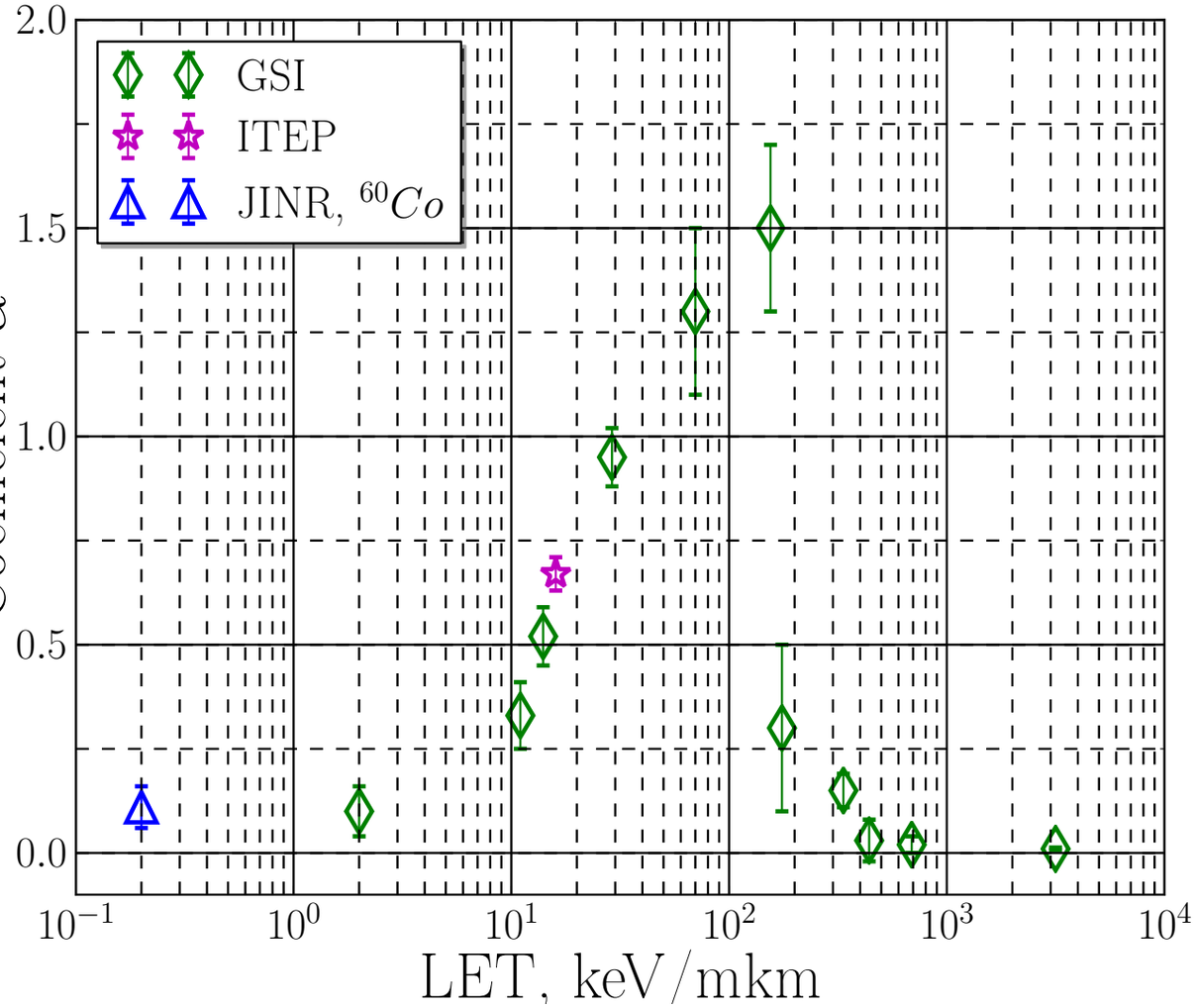
$$Y = \alpha \cdot D + \beta \cdot D^2$$

	^{12}C, 16 keV/ mkm	^{60}Co
α	0.67 ± 0.04	0.11 ± 0.05
β	0.09 ± 0.01	0.15 ± 0.01

Geometry of irradiation

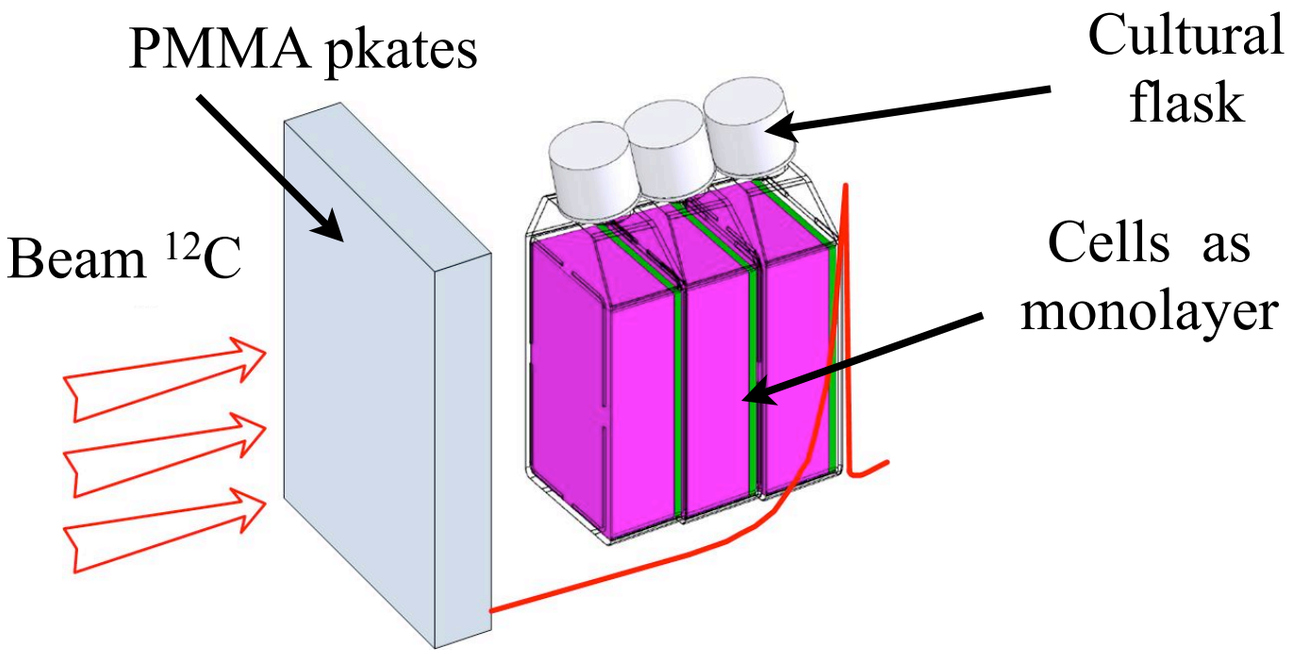




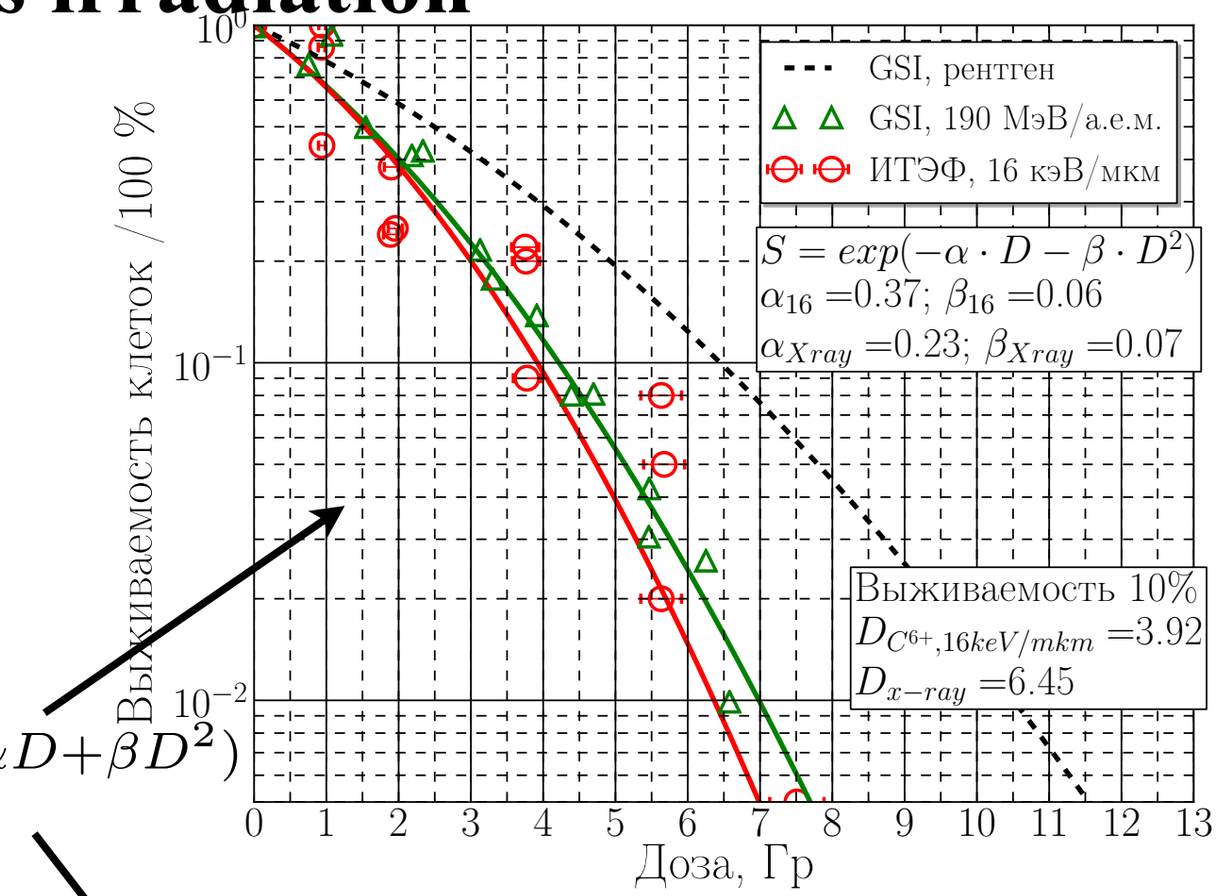


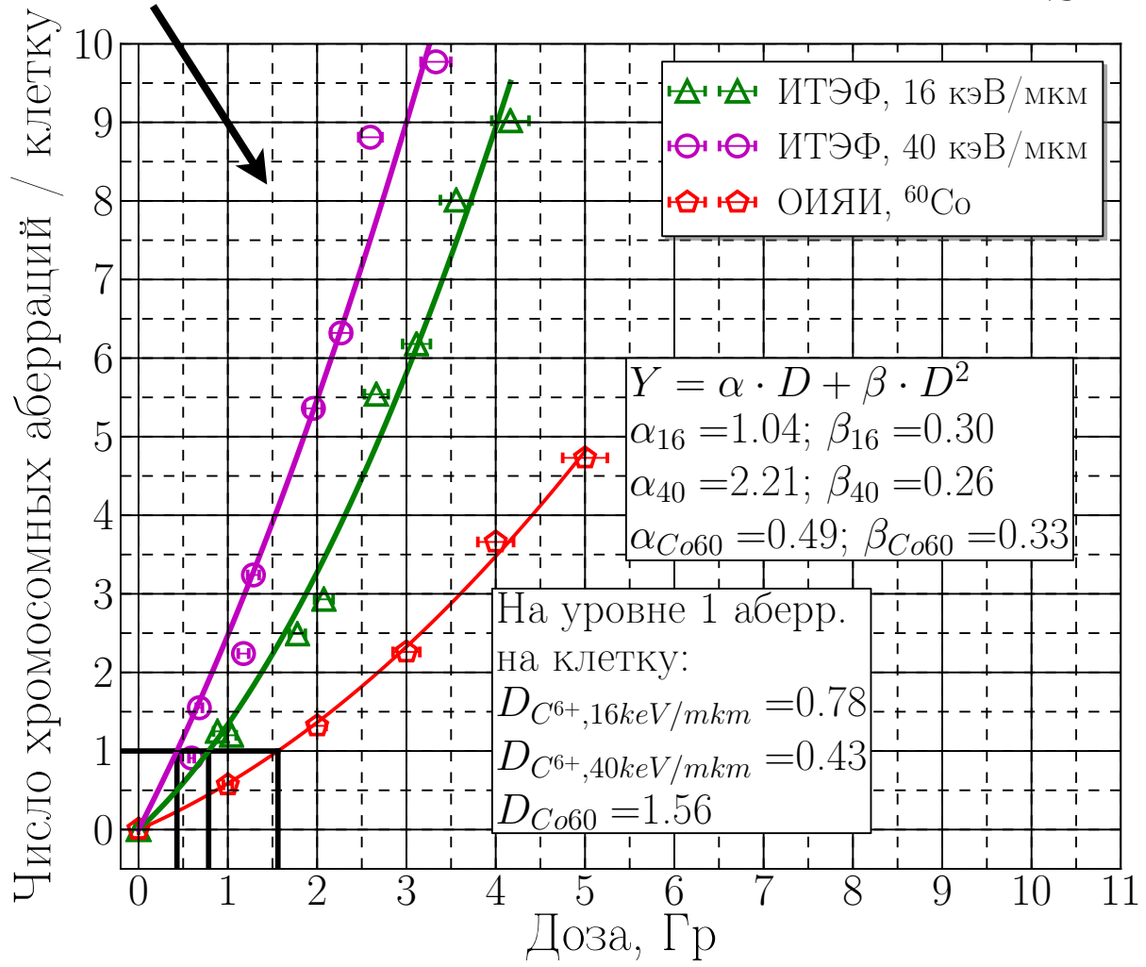
Ryonfa Lee, Elena Nasonova, et al, Radiat. Environ. Biophys (2011) 50(3) 371-81

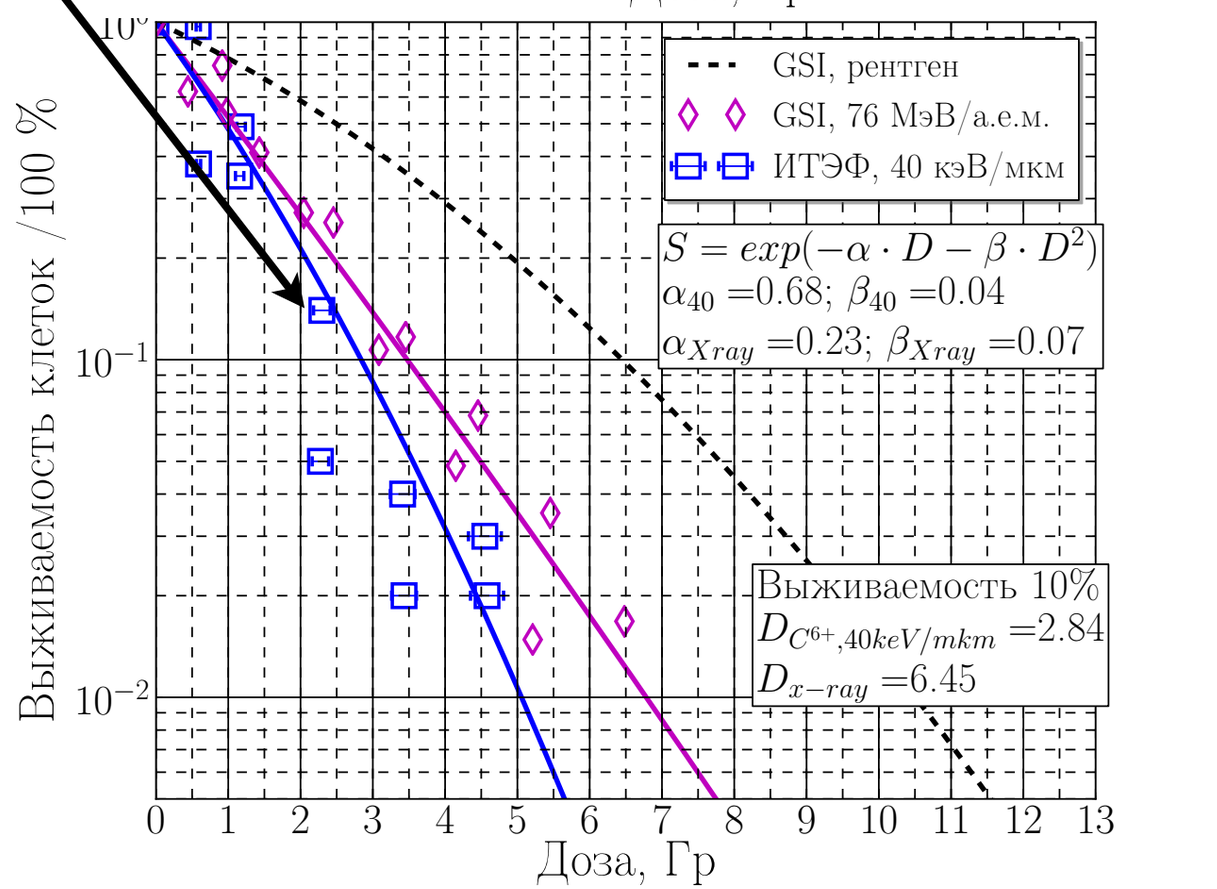
Results of CHO-K1 and Cal51 cells irradiation



Cal51: $Y = \alpha \cdot D + \beta \cdot D^2$ **CHO-K1:** $S = e^{-(\alpha D + \beta D^2)}$





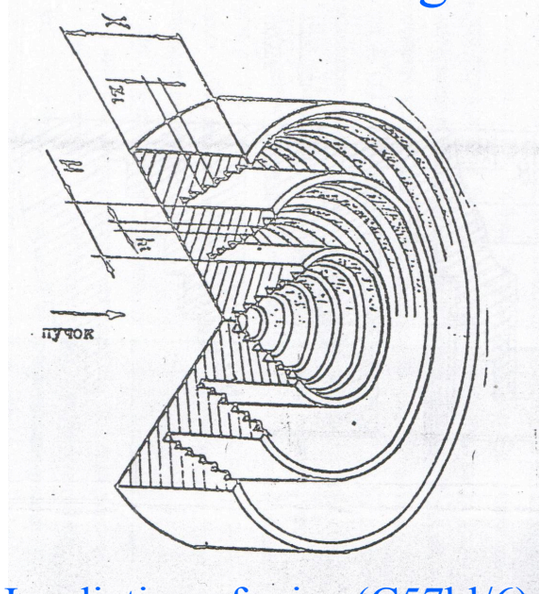


Summary of radiobiological experiments “in vitro”

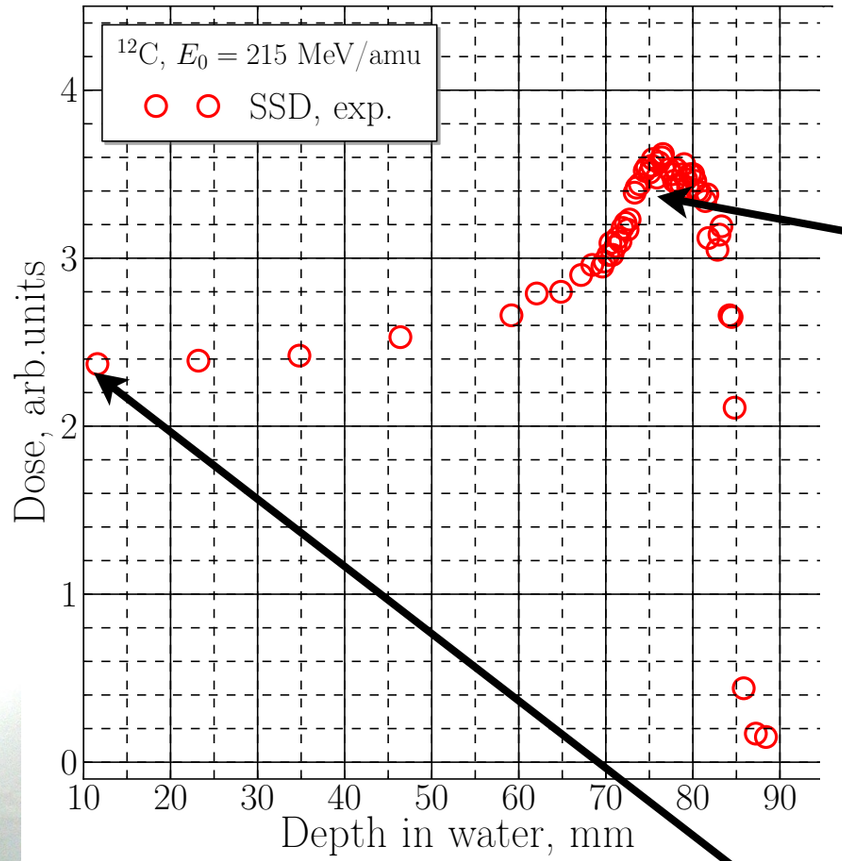
	Cell type	Depth in water eq., mm	LET, kev/mkm	Dose range, Gy	RBE (x-ray)	RBE (60Co)
1	Lymphocyte	0	16	0 - 8	1.53 ± 0.11	1.77 ± 0.13
2	Cal51	0	16	0 - 4	-	2.02 ± 0.11
		82	40	0 - 4	-	3.63 ± 0.16
3	B16F10	23	20	0 - 10	-	1.45 ± 0.12
		85	44	0 - 8	-	2.46 ± 0.15
4	CHO-K1	0	16	0 - 8	1.65 ± 0.11	-
		82	40	0 - 5	2.27 ± 0.13	-

Radiobiological experiments “in vivo”

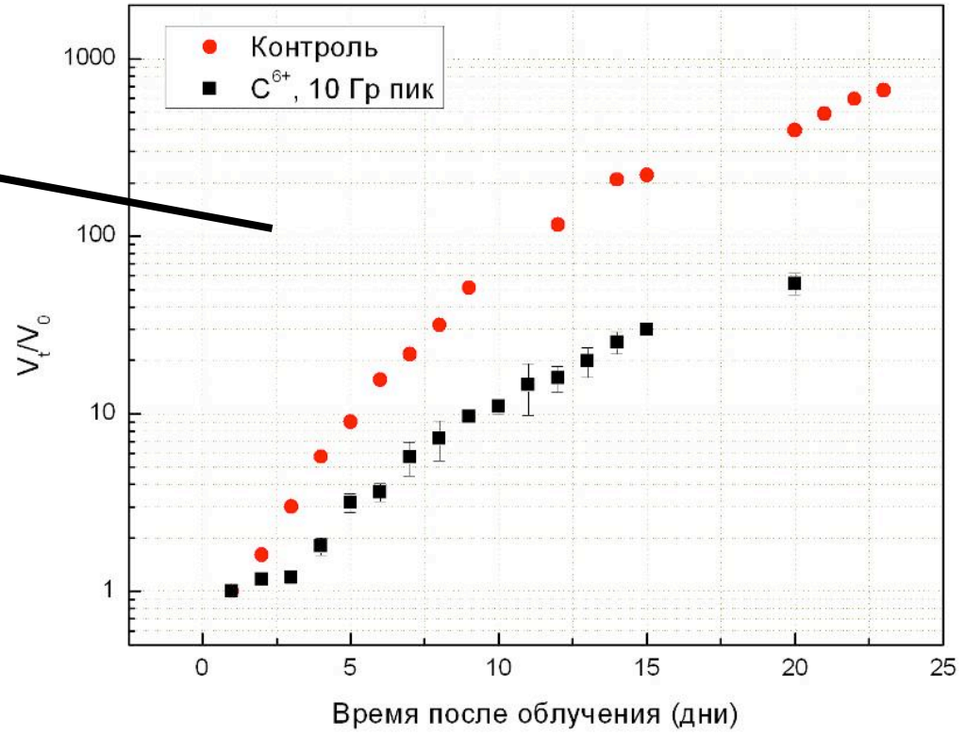
Structure of the ridge filter



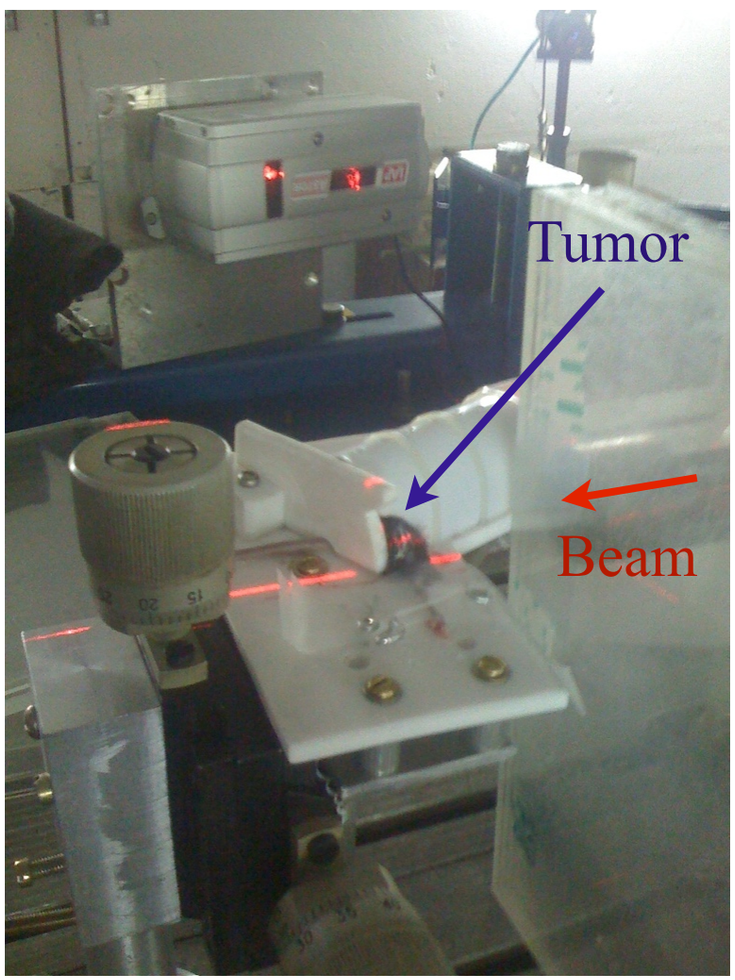
Spread-out Bragg Peak

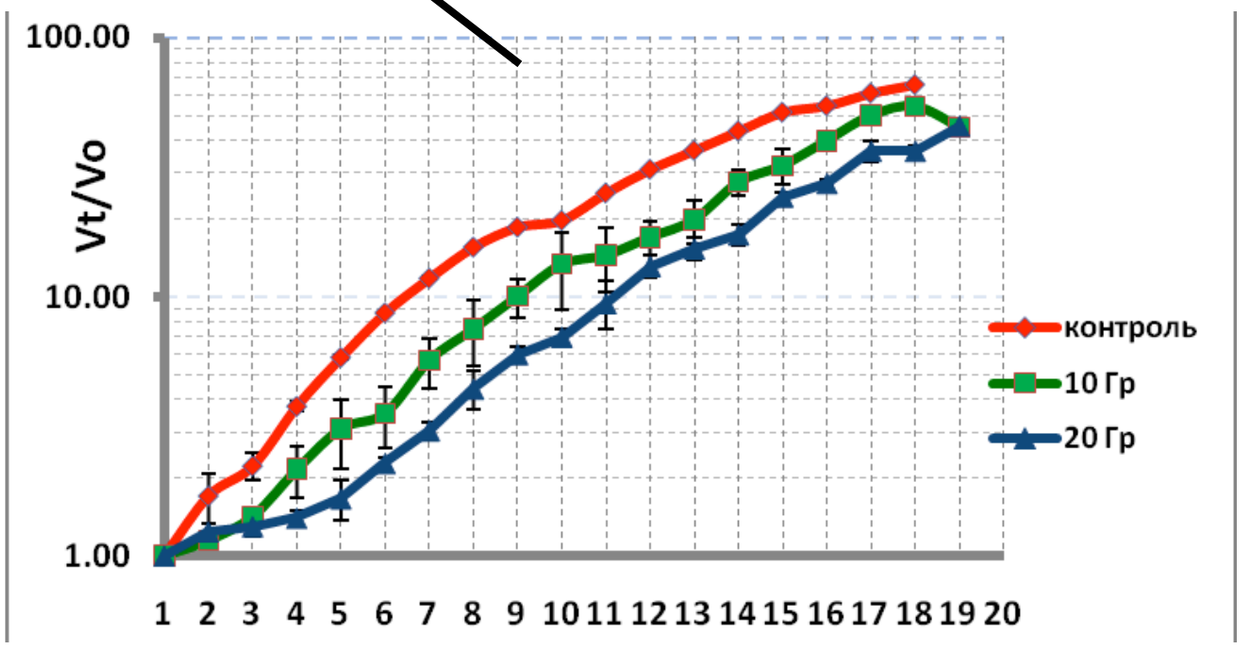


Results of mouse irradiation



Irradiation of mice (C57bl/6)with inoculated B16F10 cells

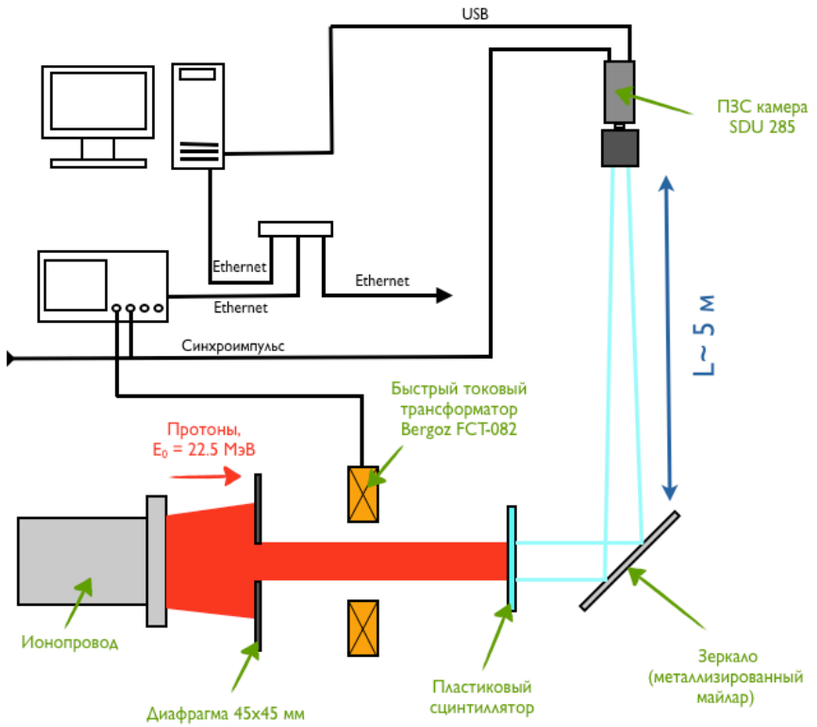




Further radiobiological research in ITEP

Proton linear accelerator I-2

Max. Energy, MeV	22.5
Pulse width, mks	2 - 30
Max. field size, mm	85
Particles per pulse, protons/cm^2	10^7 - 10^{11}
Range in water, mm	~ 5
Min. LET, keV/mkm	2.4



1. RBE of low energy protons
2. Bystander effect
3. Micro-beams (single cell - single particle)