



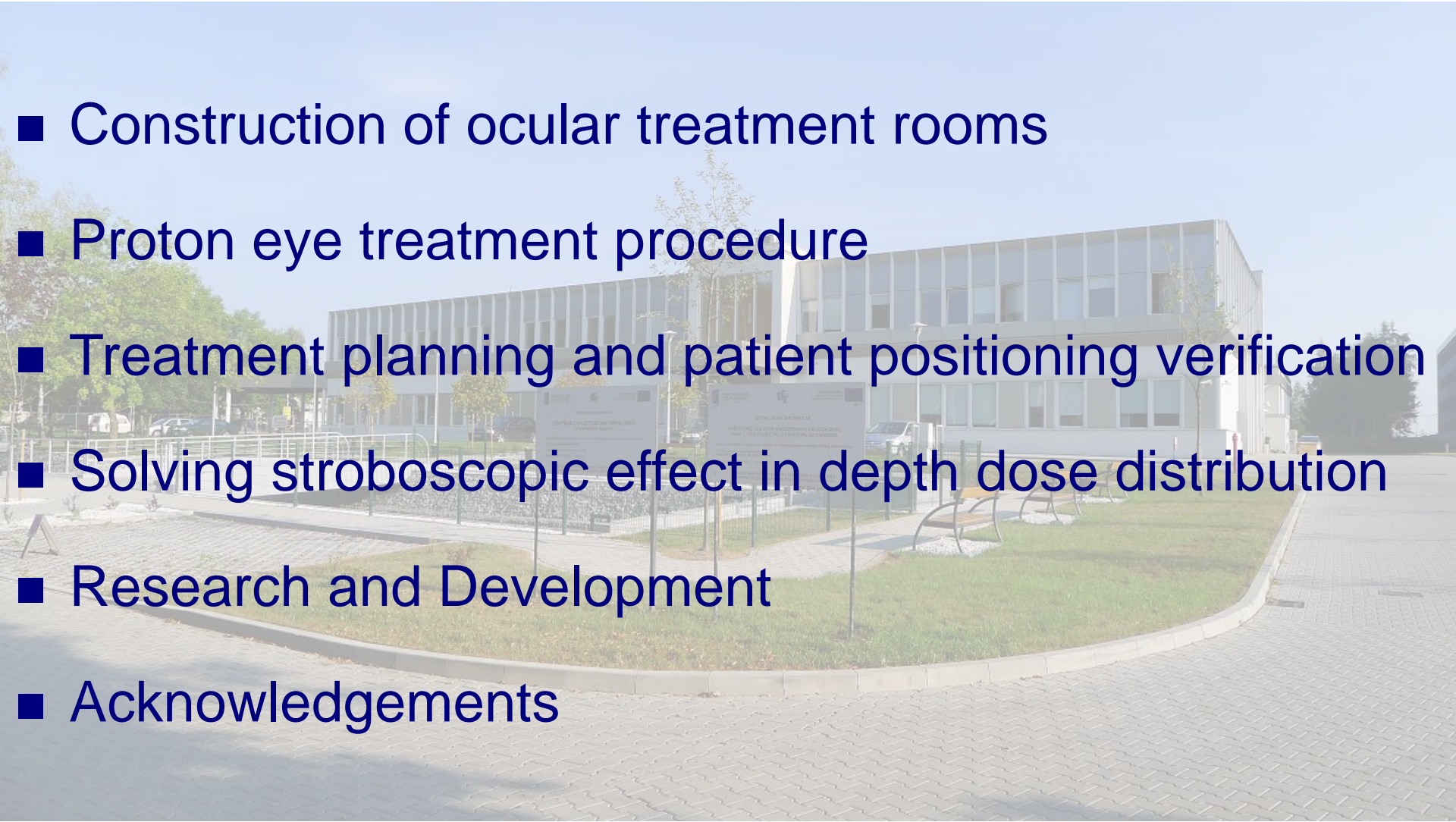
10 Years of Proton Radiotherapy of Ocular Melanoma at IFJ PAN

10 lat radioterapii protonowej oka w IFJ PAN

Tomasz Kajdrowicz

Cyclotron Center Bronowice, Institute of Nuclear Physics PAN, Kraków, Poland

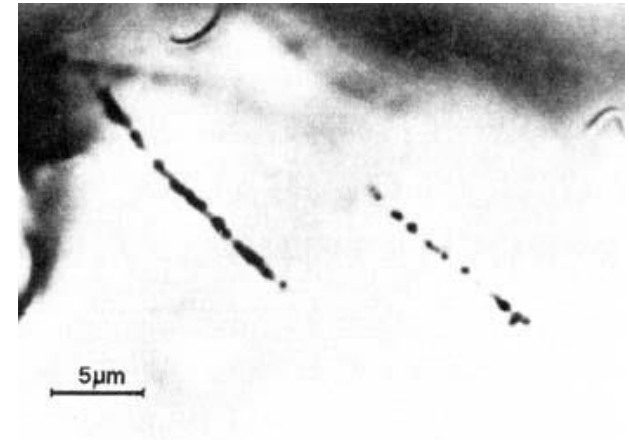
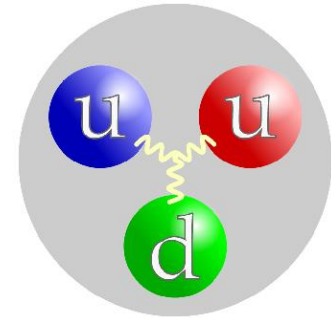
15 April 2021

- Construction of ocular treatment rooms
 - Proton eye treatment procedure
 - Treatment planning and patient positioning verification
 - Solving stroboscopic effect in depth dose distribution
 - Research and Development
 - Acknowledgements
- 
- The background image shows a modern, multi-story building with a glass facade, likely the IFJ PAN facility. The building is surrounded by a paved area and some greenery. In the foreground, there are several informational signs on a paved area, and a few benches are visible. The sky is clear and blue.

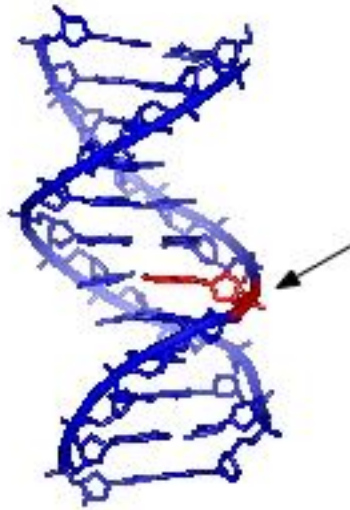
10^{-6} to 10^{-5} seconds after The Big Bang ...

... quarks started formation of Baryons like protons.

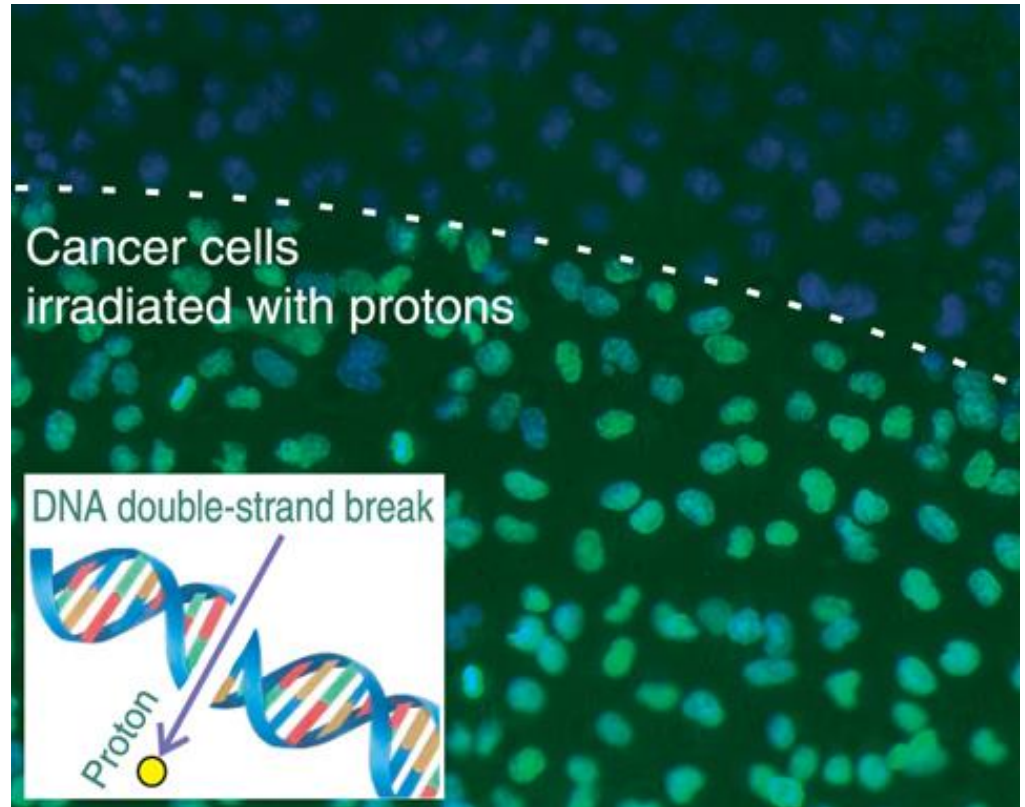
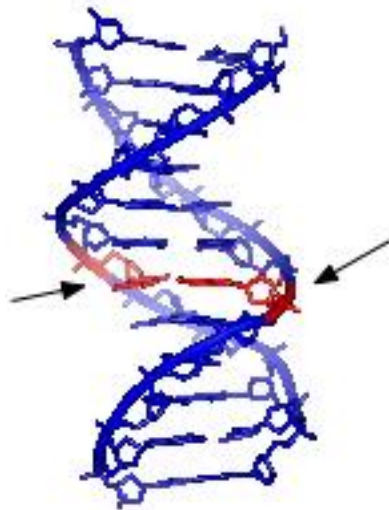
- Proton is forming nucleus of hydrogen
- Hydrogen is the most common chemical element in the universe
- Each proton consists of two up quarks and one down quark
- As a consequence it has a **positive electric charge** ...
- ... and as such it can be **accelerated by electric field**
- Accelerated protons slow down in matter losing energy mostly due to **multiple electromagnetic collisions** with atomic electrons and nuclei
- Atomic electrons gain energy leading to **ionization of atoms**
- Proton is **1840 times heavier than electron**
- It travels through tissue like matter on average in **straight lines**



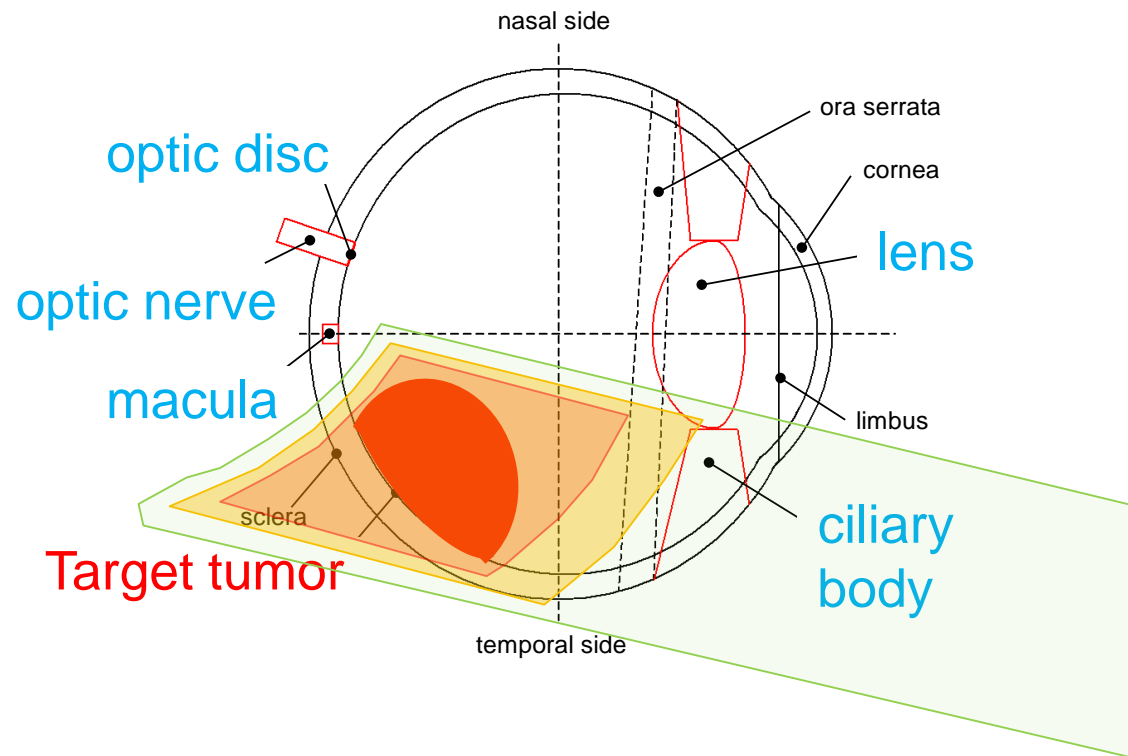
Single



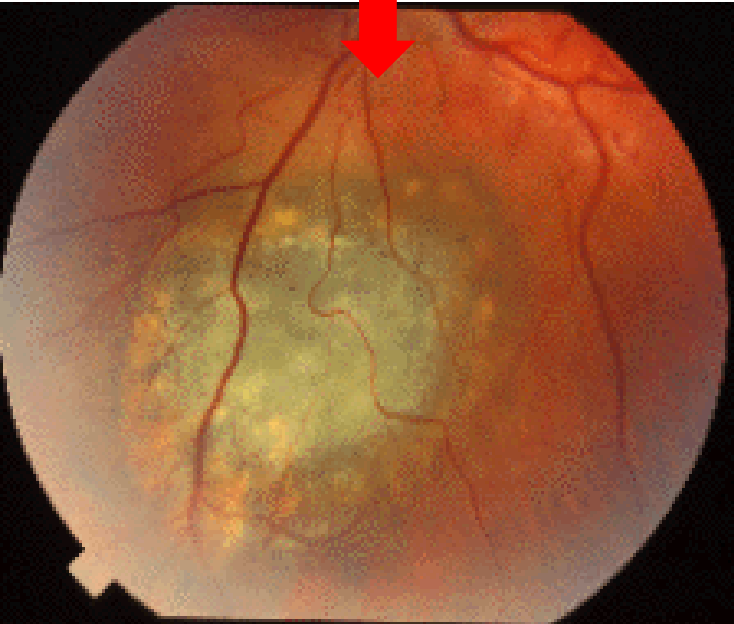
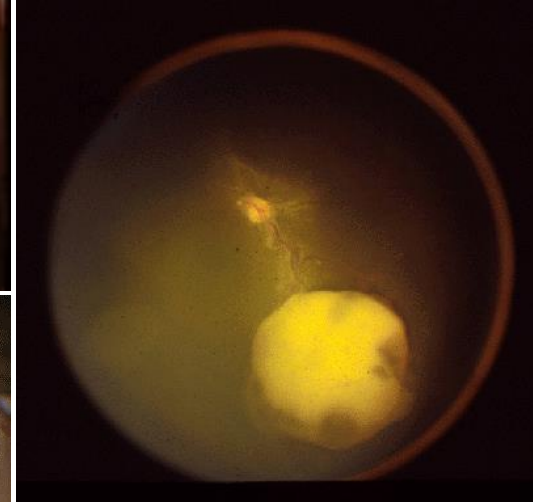
Double

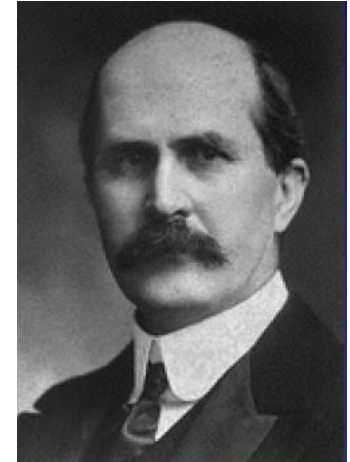
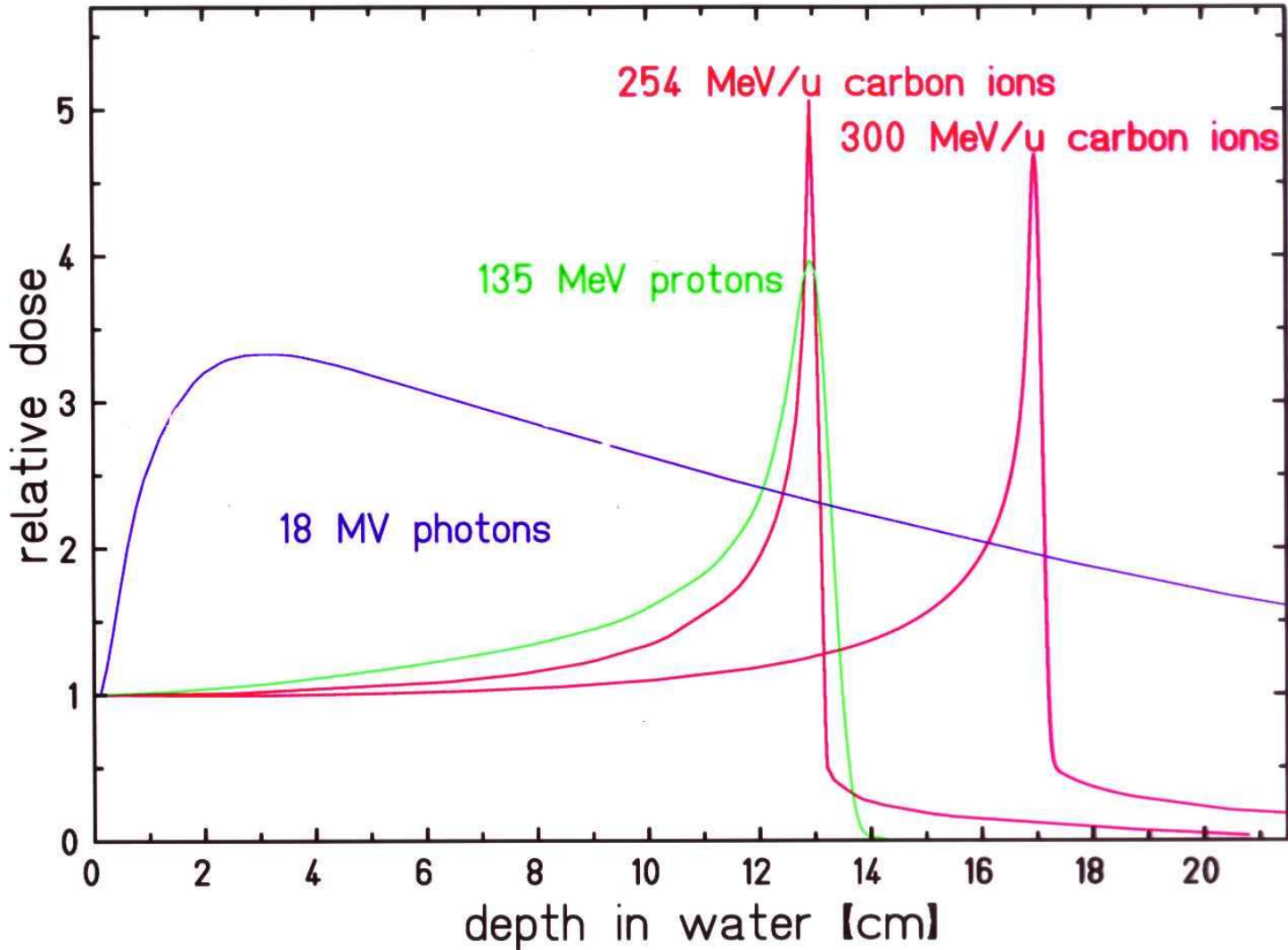


- Minimum dose to kill all tumor cells
- Limit of normal tissue complications
- Main organs at risk (OAR) of an eye
 - Optic disc and nerve
 - Macula
 - Ciliary body and lens



- Iris melanoma
- Conjunctival melanoma
- Malignant melanoma
- Retinoblastoma
- Melanocytoma
- **Choroidal melanoma**





William Henry Bragg
(1862 – 1942)

Centrum Radioterapii Protonowej przy IFJ w Krakowie

15th December, 1994

Prof. dr hab. Andrzej Budzanowski submits a project proposal to „Fundacja Współpracy Polsko-Niemieckiej” (Stiftung für deutsch-polnische Zusammenarbeit)

Partners on German side are:

- Institut fuer Medizin Forschungszentrum Juelich
- Hahn Meitner Institut, Berlin

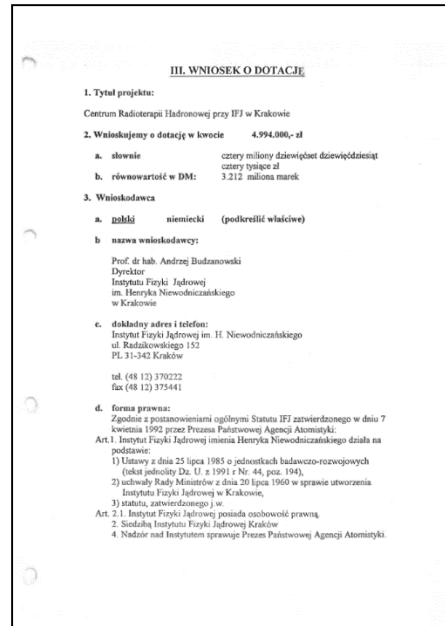


Tabela 1. Ogólny harmonogram realizacji projektu

Nazwa zadania	1995	1996	1997	1998
T-1 Zainstalowanie cyklotronu AIC-144 w hali eksploatacyjnej				
T-2 Adaptacja Cyklotronu AIC-144 dla potrzeb terapii protonowej				
T-3 Sterowanie i automatyzacja pracy AIC-144 w systemie komputerowym				
T-4 Opracowanie i wykonanie traktów transportu i formowania wiązek terapeutycznych				
T-5 Wyposażenie stanowisk radioterapii neutronowej oraz terapii protonowej oka				
K-1. Opracowanie metod i ocena skuteczności radioterapii neutronowej				
K-2 Opracowanie metod leczenia i ocena skuteczności radioterapii neutronowej; mięśniaków				
K-3 Próby kliniczne terapii protonowej u chorych z czerniakiem oka				
K-4. Monitorowanie aktywności makrocząstek metodą ERP od pacjentów leczonych neutronami				
Z-1 Opracowanie nowego modelu zwierzęcych czerniaków oka u chomików i gerbilla				
Z-2 Testowanie zestawu do terapii protonowej na zwierzęcych modelach czerniaka oka				
Z-3 Analiza możliwości wykorzystania spektroskopii ERP dla celów prognostycznych w leczeniu				
Z-4 Porównanie RBE w indukowaniu różnych efektów biologicznych przy użyciu wiązki neutronowej				
Z-5 Opracowanie biologicznej dozymetrii dawki pochłoniętej w limfocytach krwi ludzkiej				
Z-6 Wczesny i późny odczyn popromienny tkanki zdrowej po napromiennianiu neutronami i protonami.				
Z-7 Obliczenia transportu i depozycji energii promieniowania w nawiązaniu do adaptacji cyklotronu AIC-144				
Z-8 Przygotowanie kadry fizyków medycznych dla celów radioterapii hadronowej				
Z-9 Mikrodozymetryczna ocena jakości biologicznej wiązki neutronów i protonów				
R-1 Produkcja radioizotopów medycznych				

Summer 2-week-long Internship at IFJ PAN

Summer, 1997

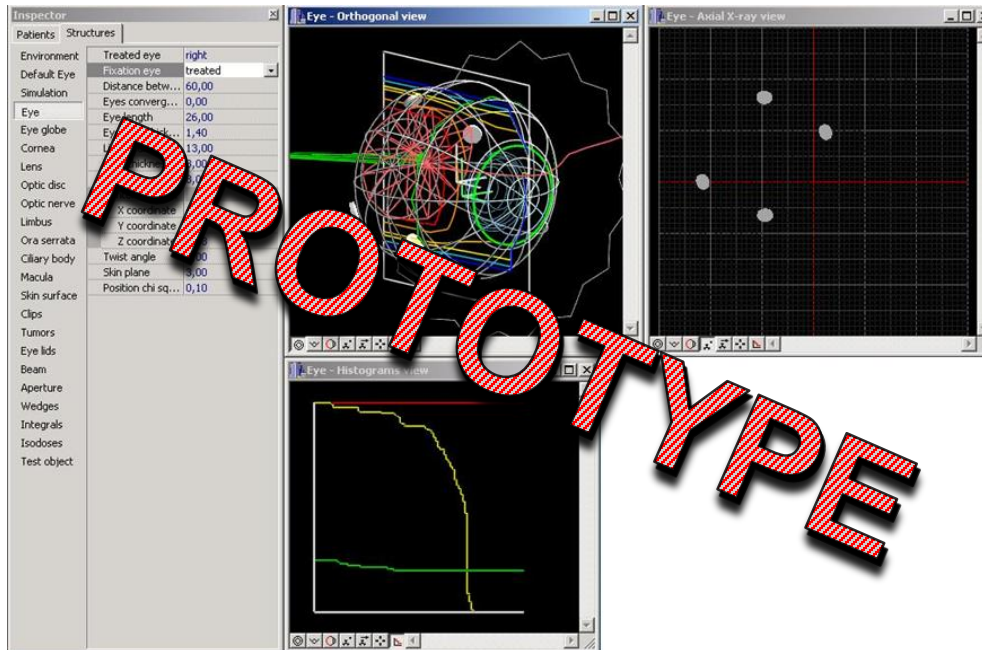
2-week-long internship organized by dr Paweł Olko to write a prototype of a treatment planning system (TPS) for proton therapy of ocular melanoma

Spring, 2000

TPS functional prototype as a part of Master Thesis

Autumn, 2005

FDA approved and CE marked commercial TPS (2 free-of-charge licenses for IFJ PAN)



Akademia Górniczo – Hutnicza
im. Stanisława Staszica w Krakowie

Wydział Fizyki i Techniki Jądrowej



Praca magisterska

Mateusz Bajer, Tomasz Kajdrowicz
kierunek fizyka techniczna
specjalność fizyka komputerowa

Eyeplan
Komputerowe planowanie i wspomaganie
protonowej terapii nowotworów oka

Opiekun dr Mariusz Kopeć

Kraków 2000

Starting cooperation with Clinical Partners

First cooperation agreement between Collegium Medicum UJ - Krakow University Hospital and IFJ PAN on development of proton eye therapy signed on 27.06.2005

Funding elements of the treatment room from the National Fund for Fighting Cancer (University Hospital) – 2006

Public tenders and installation of equipment at IFJ PAN – 2007-2008

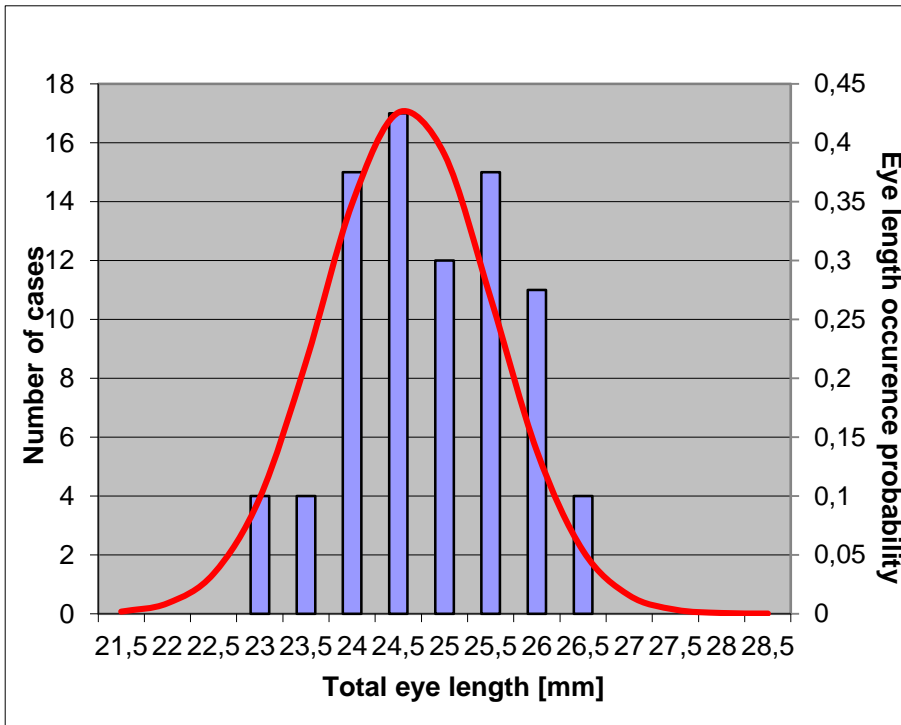


Proton beam range sufficient to treat ocular patients

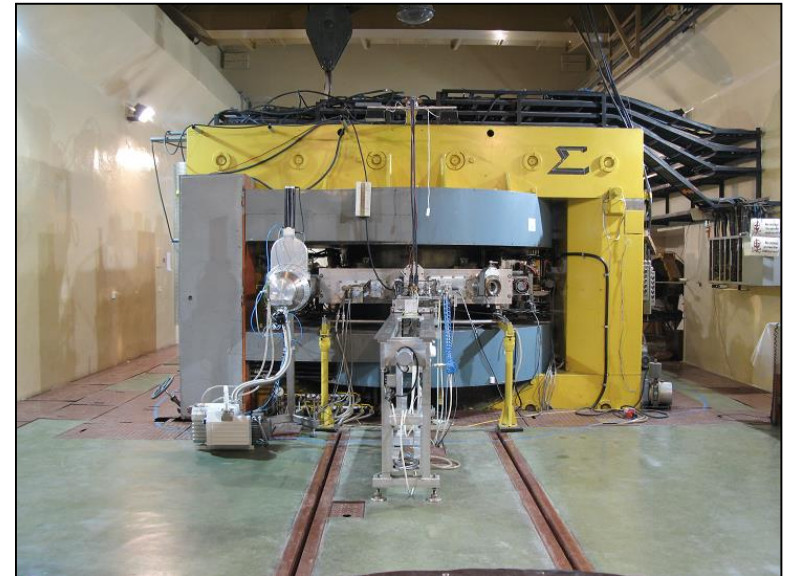
19th December, 2005

Working Meeting at Kopernika Street in Kraków

- prof. Bożena Romanowska-Dixon
- prof. Paweł Olko
- dr Jan Swakoń
- Tomasz Kajdrowicz



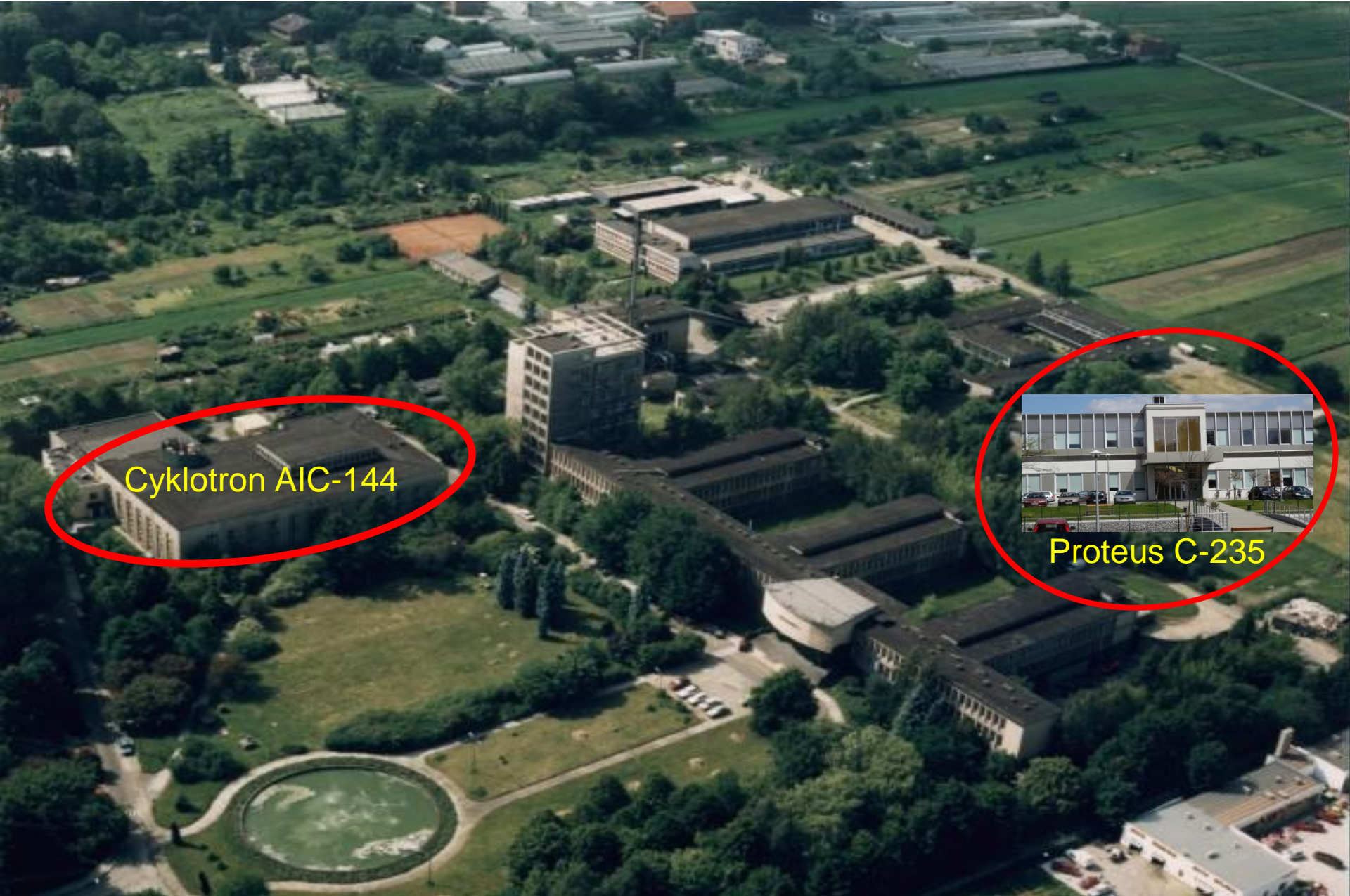
AIC-144 cyclotron produces 60 MeV protons resulting in range in water of 29 mm.



Discussing patient proton beam range requirements for sample Polish population.

Mean eye length with sclera is 24.6 mm.

More than 95% cases could be treated with 60 MeV proton beam from AIC-144 cyclotron.



Cyklotron AIC-144



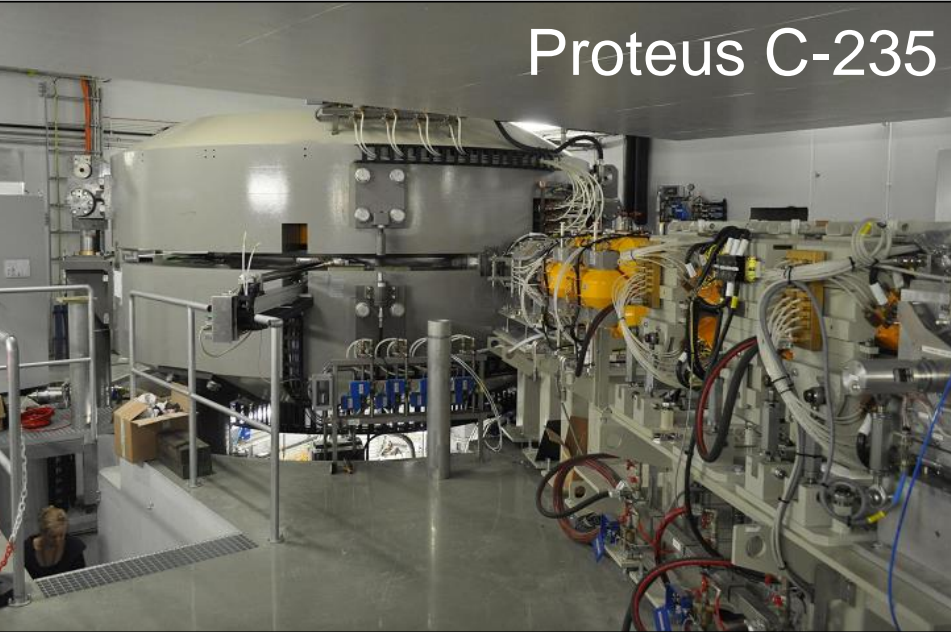
Proteus C-235

AIC-144:

- Weight 150 tons
- **60 MeV – 29 mm H₂O**
- Up to 100 nA
- **Pulsed beam at 50 Hz**



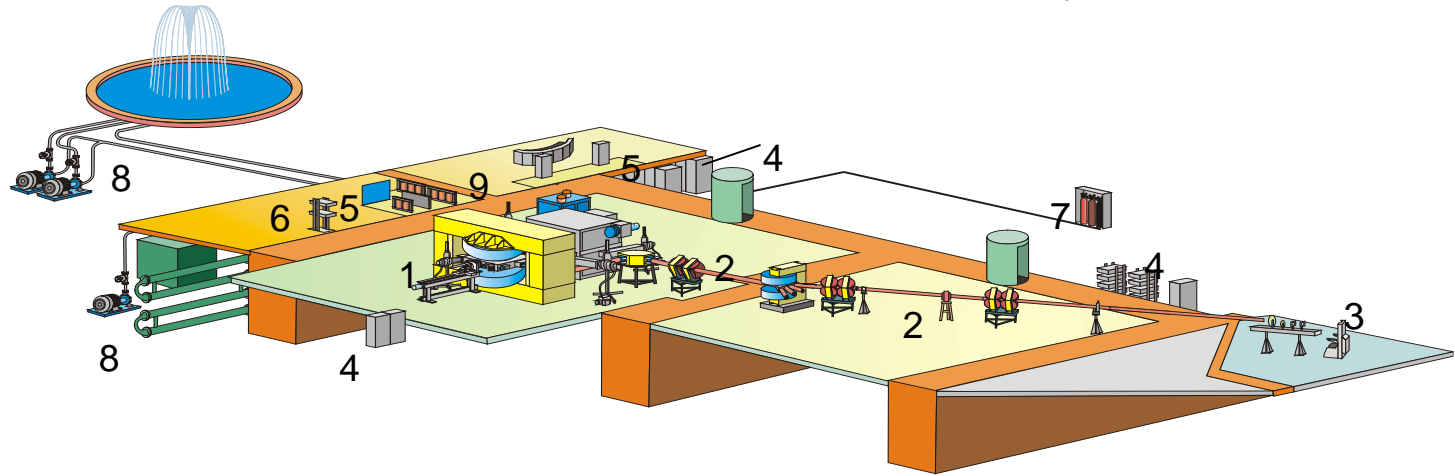
Proteus C-235



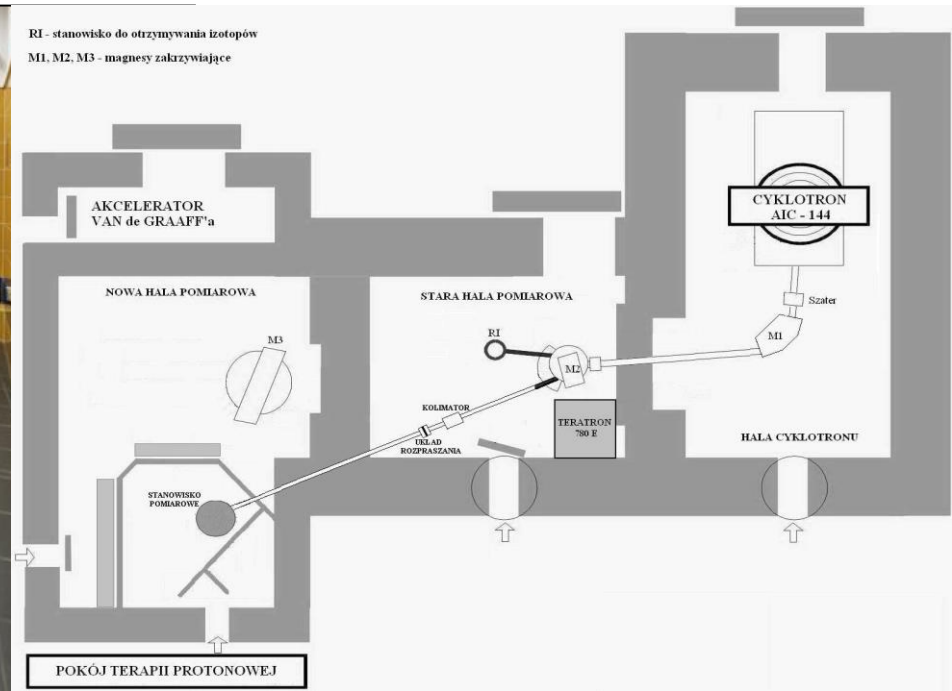
Proteus C-235:

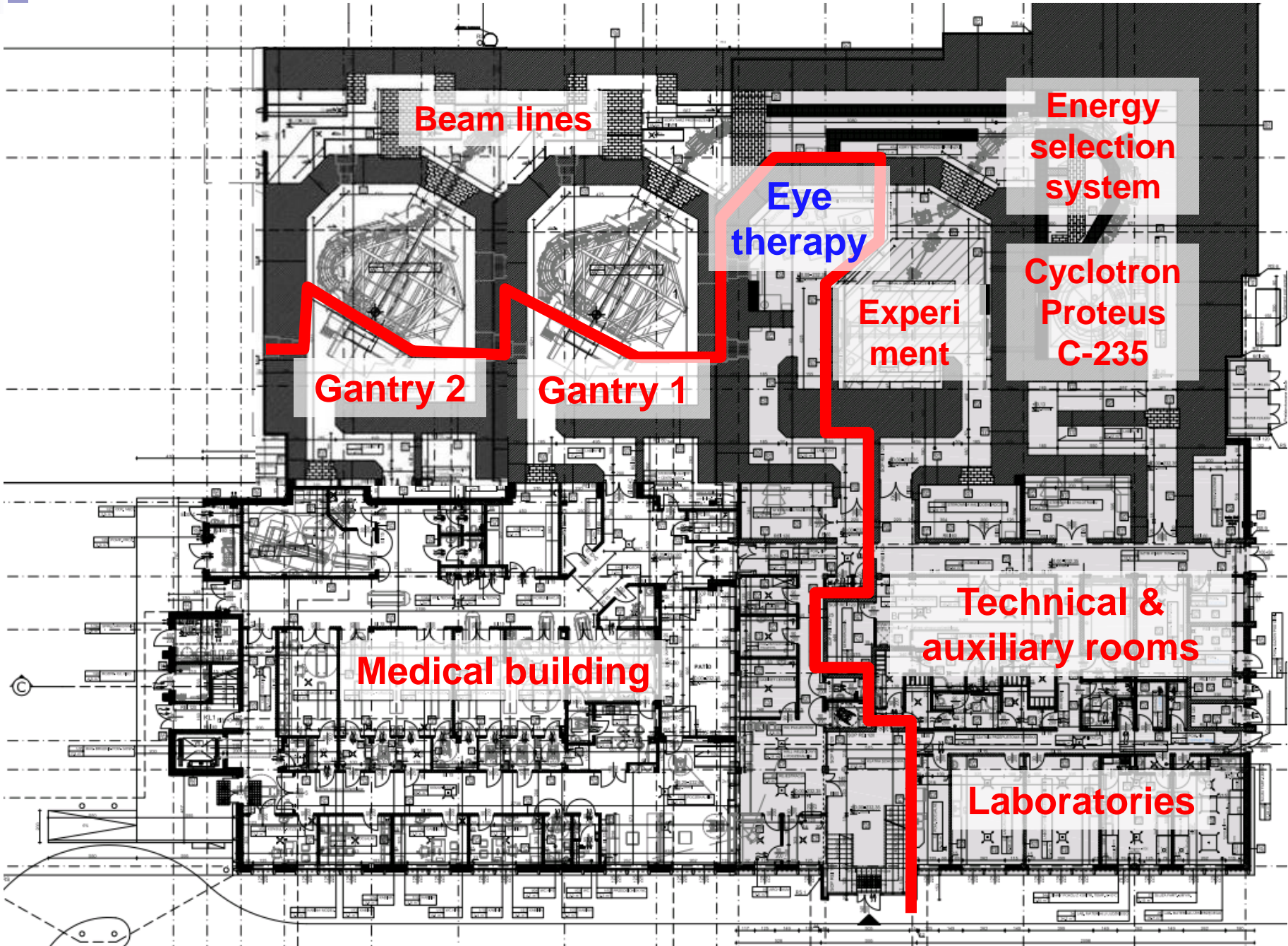
- Weight 220 tons
- **70 – 230 MeV 4 – 32 cm H₂O**
- Up to 600 nA
- **Quasi-continuous beam at 106 MHz**

Ocular treatment room at AIC-144 cyclotron



(Swakoń J., Sulikowski J., Olko P., technical departments and many others)





Beam lines

Energy selection system

Cyclotron Proteus C-235

Experiment

Eye therapy

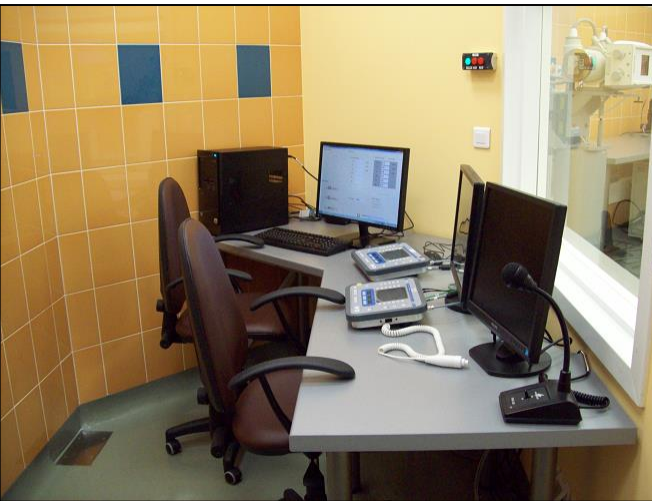
Gantry 2

Gantry 1

Medical building

Technical & auxiliary rooms

Laboratories



- ❑ **Developed at IFJ PAN**
 - ❑ **70 MeV at nozzle entrance**
 - ❑ **CE marking** in collaboration with IBA
 - ❑ **Treating patients since 2016**
- (Swakoń J., Horwacik T., Góra Ł. and many others)*

Advantages of the new eye treatment room

- bigger maximum beam range allowing for all treatment cases
- excellent beam stability
- robotic chair with isocentric rotation
- automatic digital imaging
- faster workflow
- patient waiting rooms

Who helped us?

- Hahn Meitner Institut (Helmholtz-Zentrum), Berlin, Germany
- Clatterbridge Cyclotron Centre, Liverpool, UK
- Centre de Protonthérapie (Curie Institut), Orsay, France
- Laboratori Nazionali del Sud, Catania, Italy
- Paul Scherrer Institute, Villingen, Switzerland
- University of Florida Health Proton Therapy Institute, Jacksonville, USA



Andreas Weber

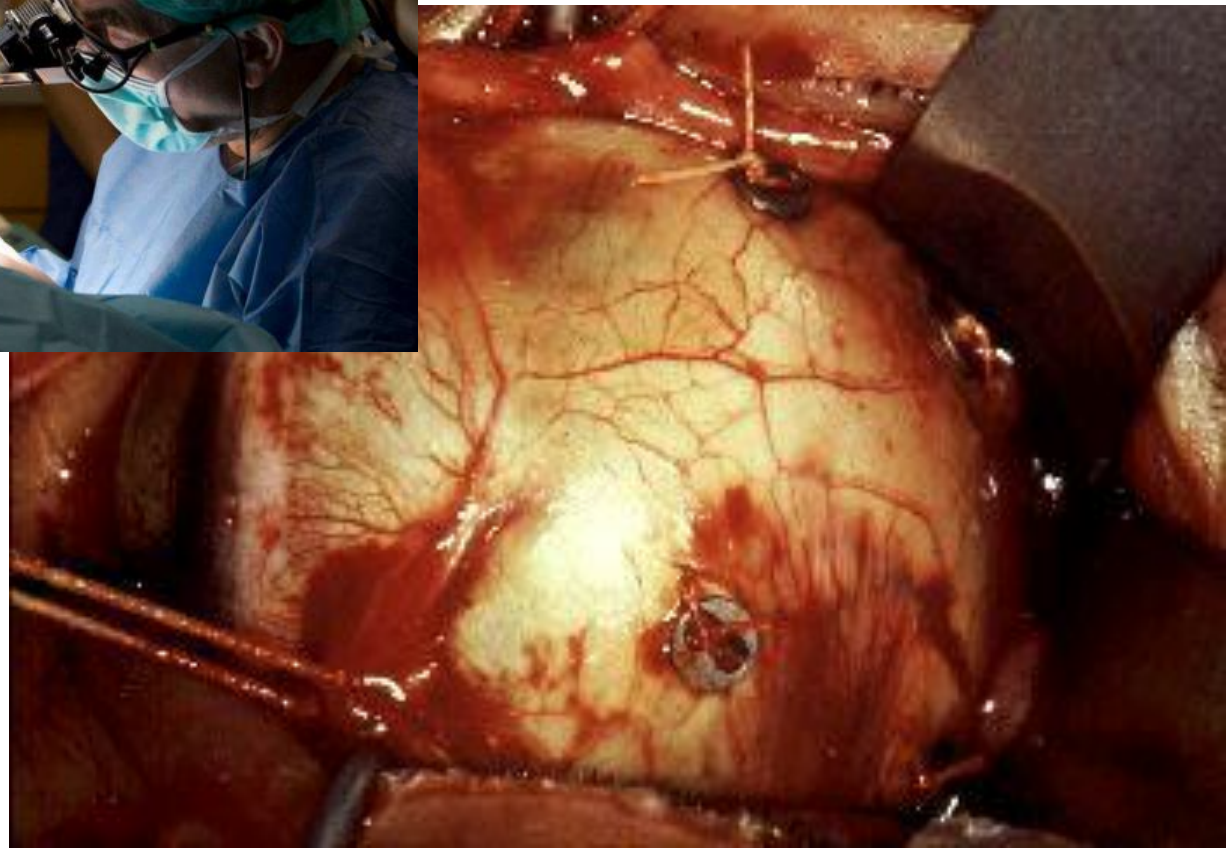
Whom we helped?

- Fondazione Centro Nazionale Adroterapia Oncologica, Pavia, Italy
- National Cancer Center, Seoul, Korea
- Holland PTC, Delft, Netherlands

Patient preparation – tantalum markers surgery



prof. M. H. Foerster
(Charité, Berlin)

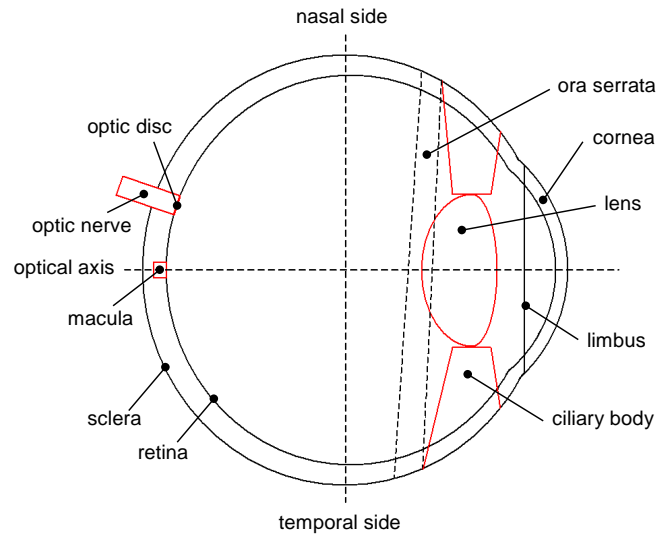


prof. B. Romanowska-Dixon
(CM UJ, Kraków)



Clinical data needed for treatment planning:

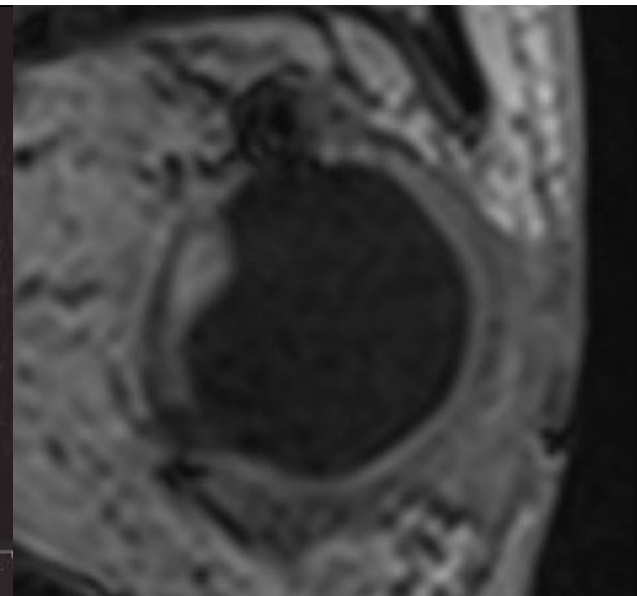
- Intraoperative measurements
- Ultrasound
- IOL Master
- Optical Coherent Tomography
- Fundus images
- MRI / CT



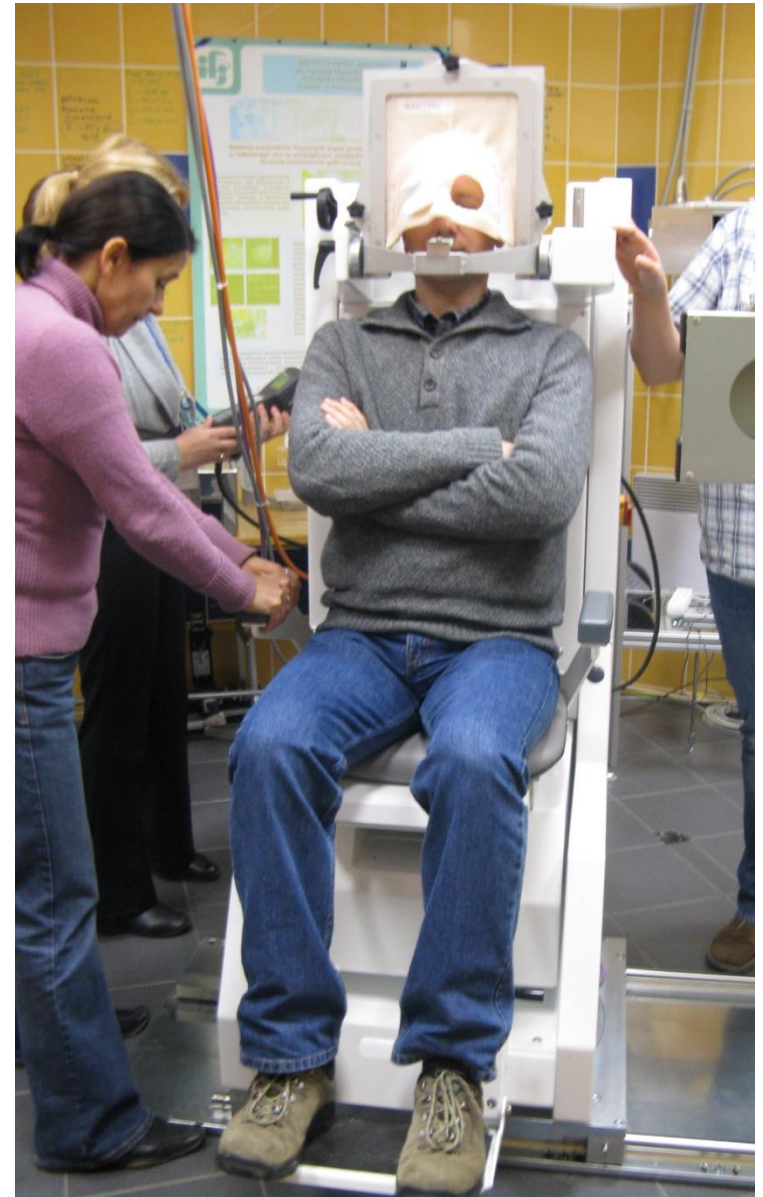
Centrum Onkologii
Instytut im. Marii Skłodowskiej-Curie
Oddział w Krakowie

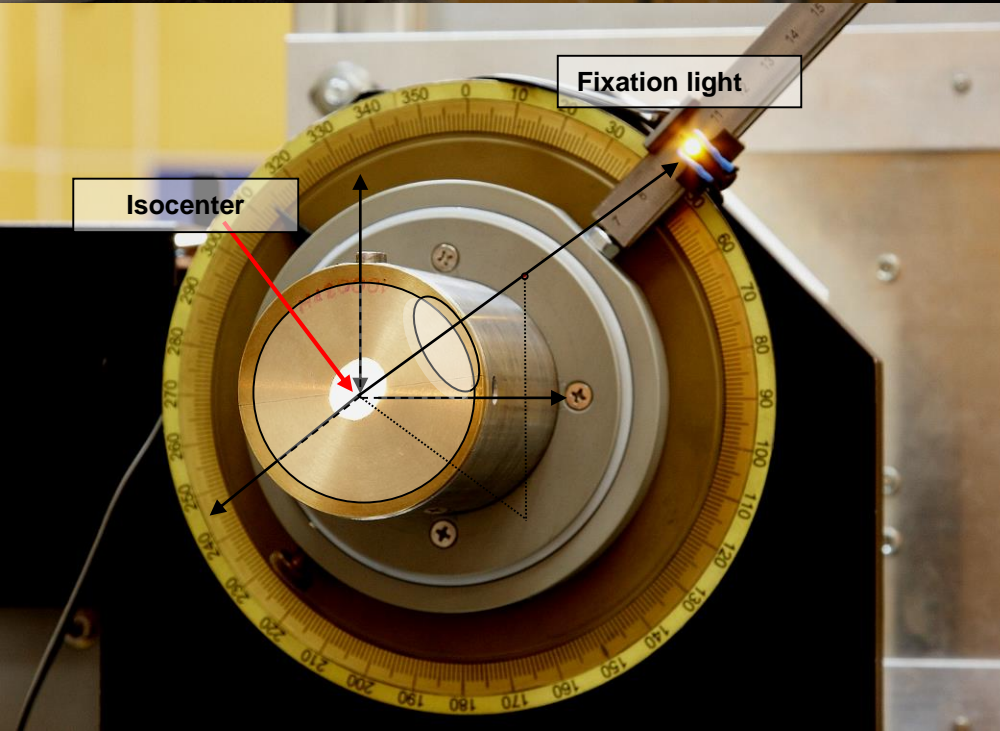
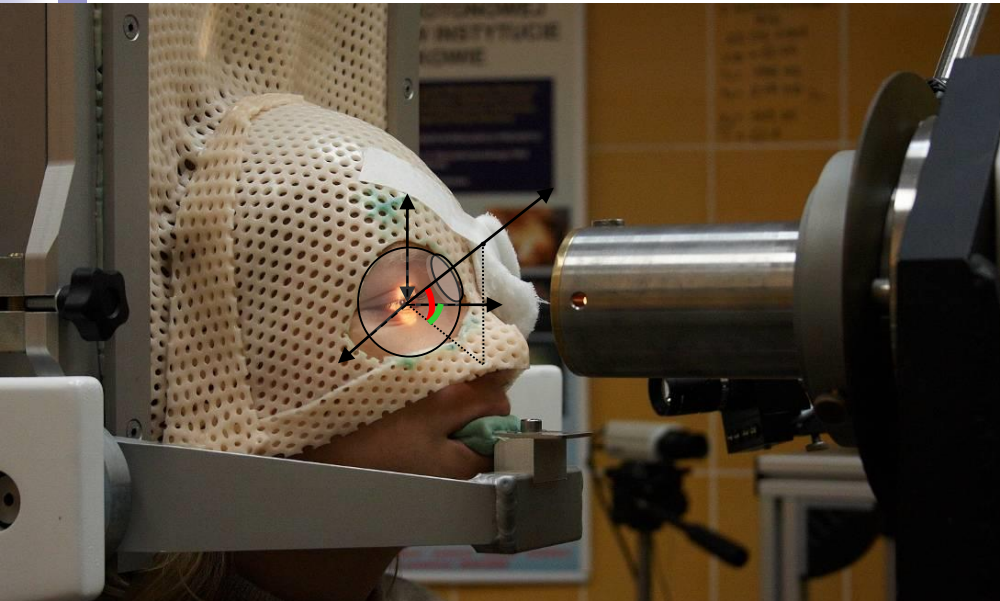


Szpital
Uniwersytecki
w Krakowie



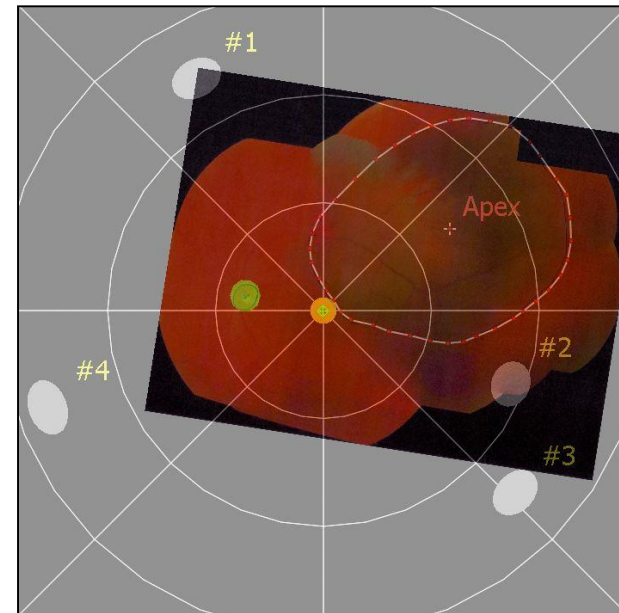
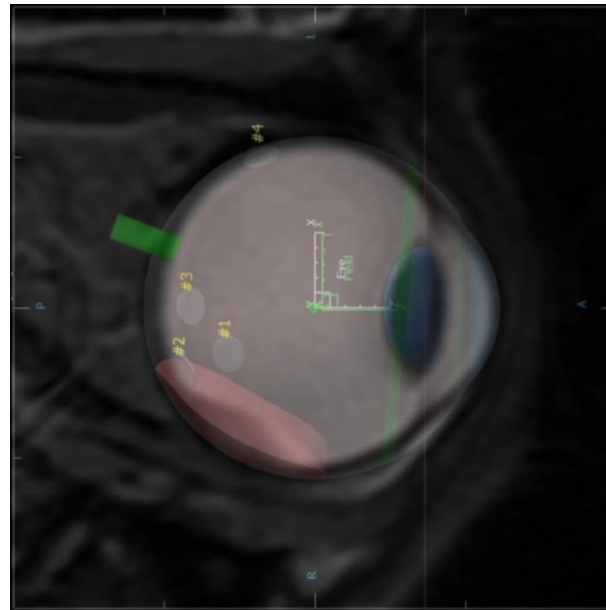
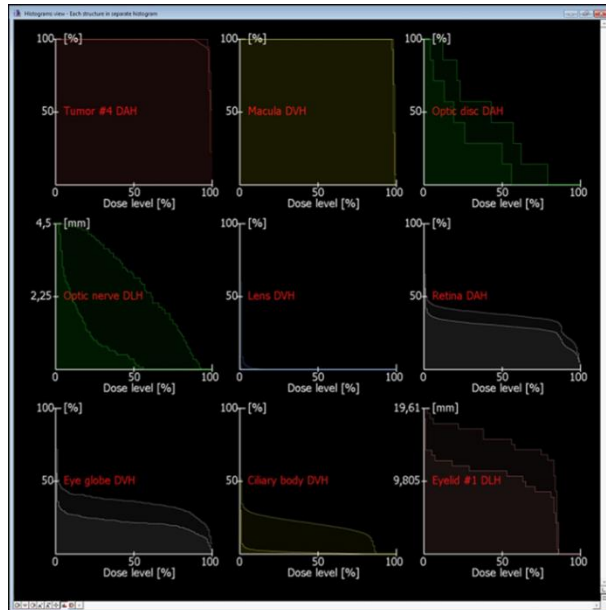
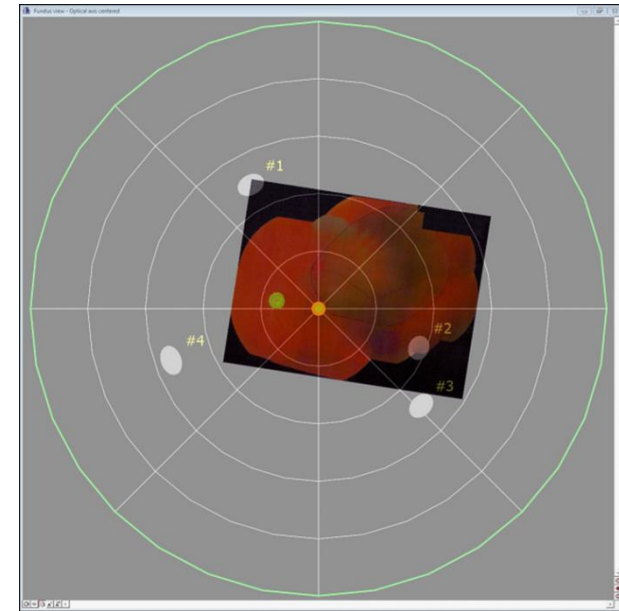
Patient immobilization – thermoplastic mask and bite block





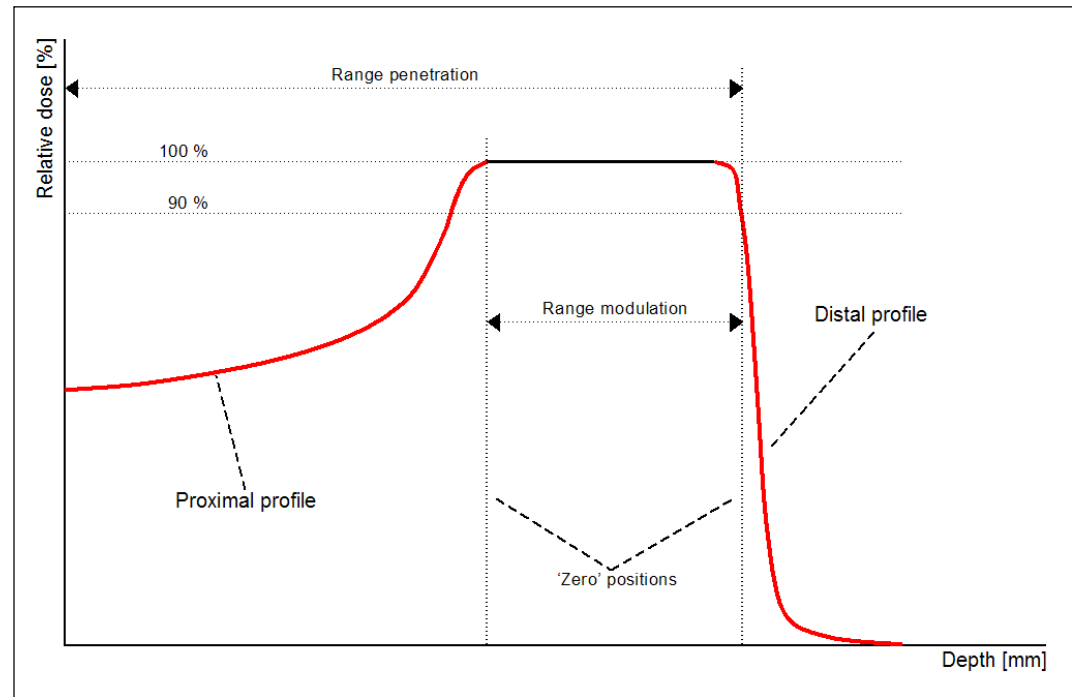
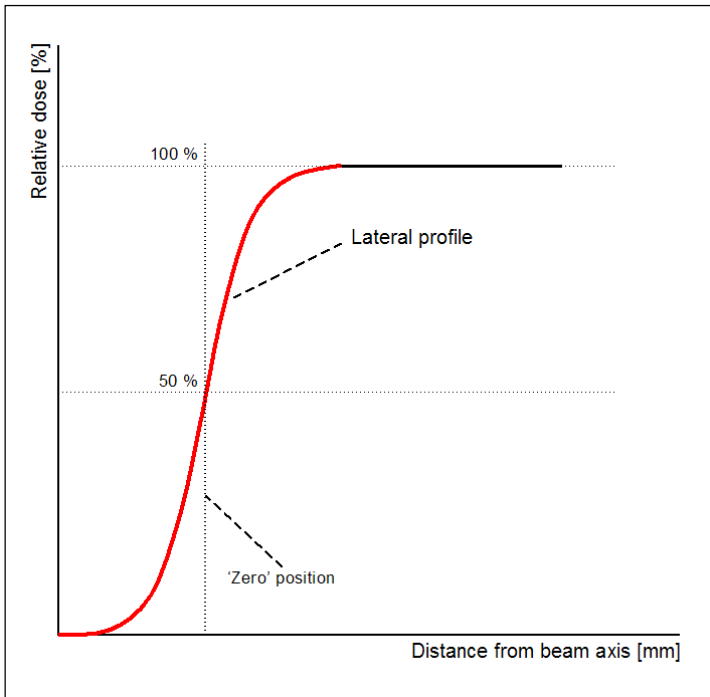
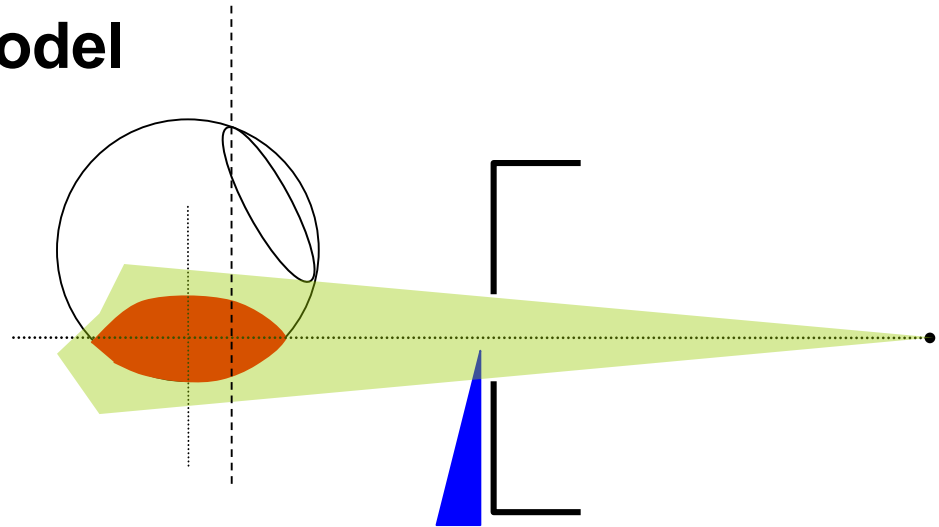
In-house developed software for supporting treatment planning

- Tumor base entrance
- MRI registration
- Plan evaluation

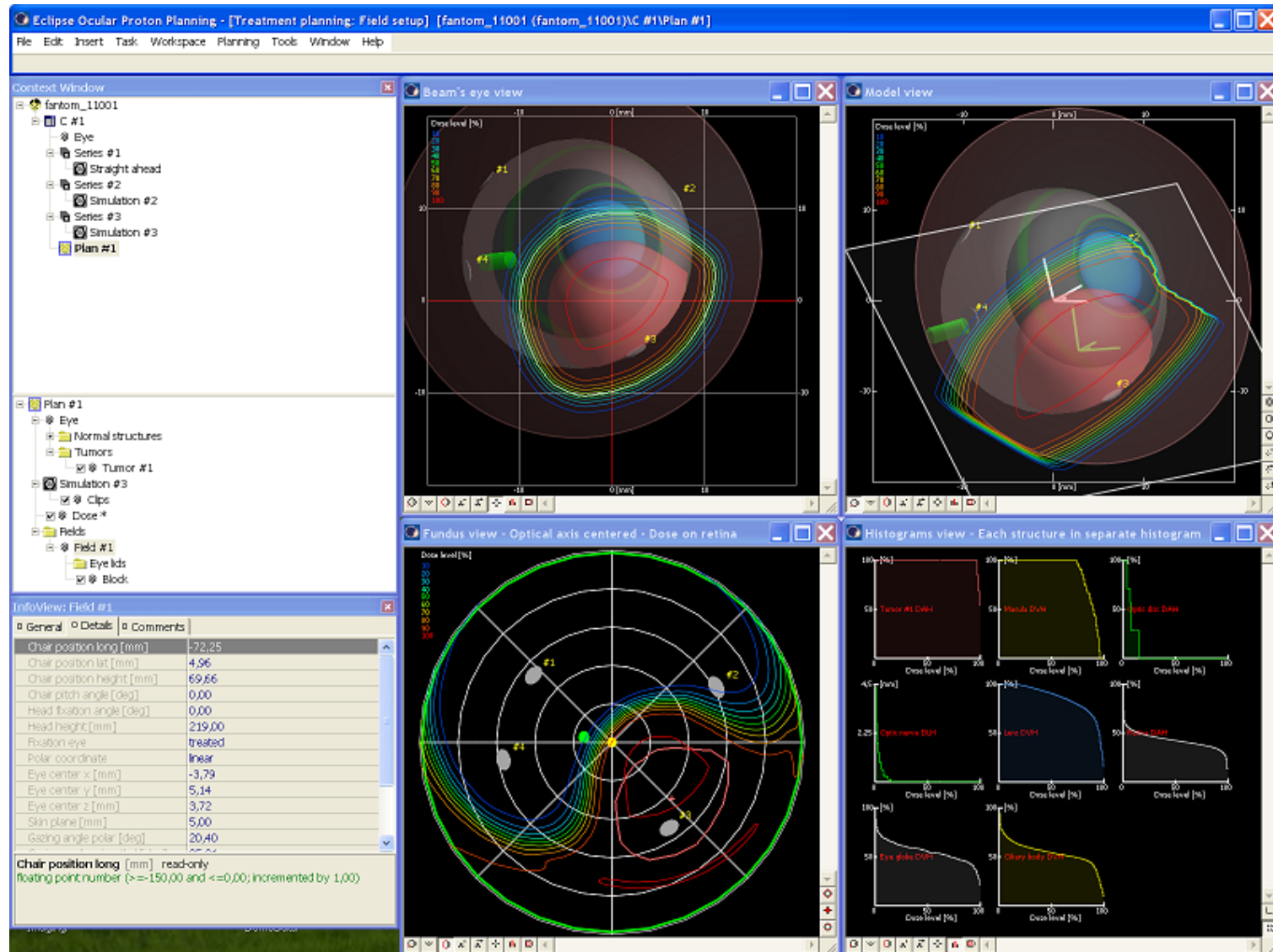


Development of Beam model

- Axial & lateral profiles
- Range
- Modulation
- Multiprofile algorithm
- Real time calculations

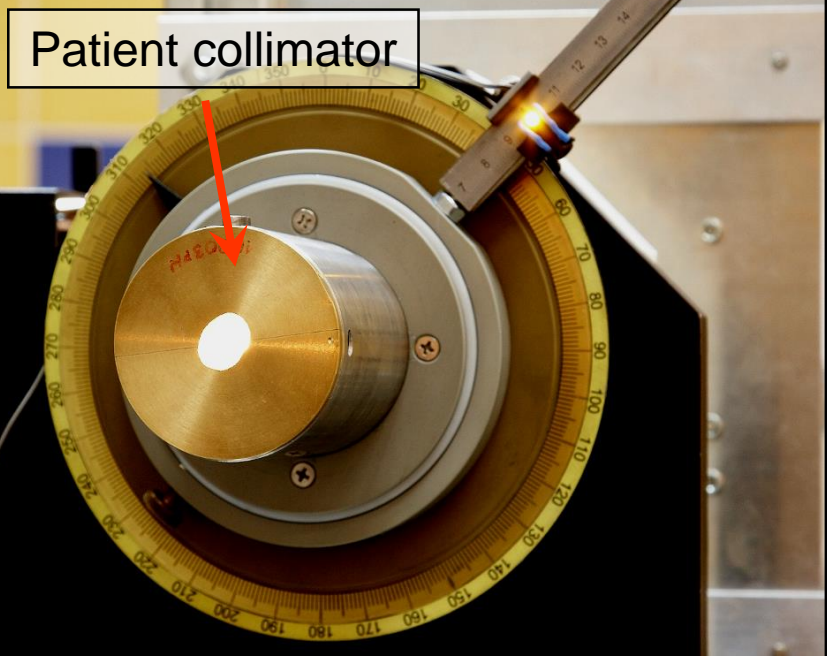
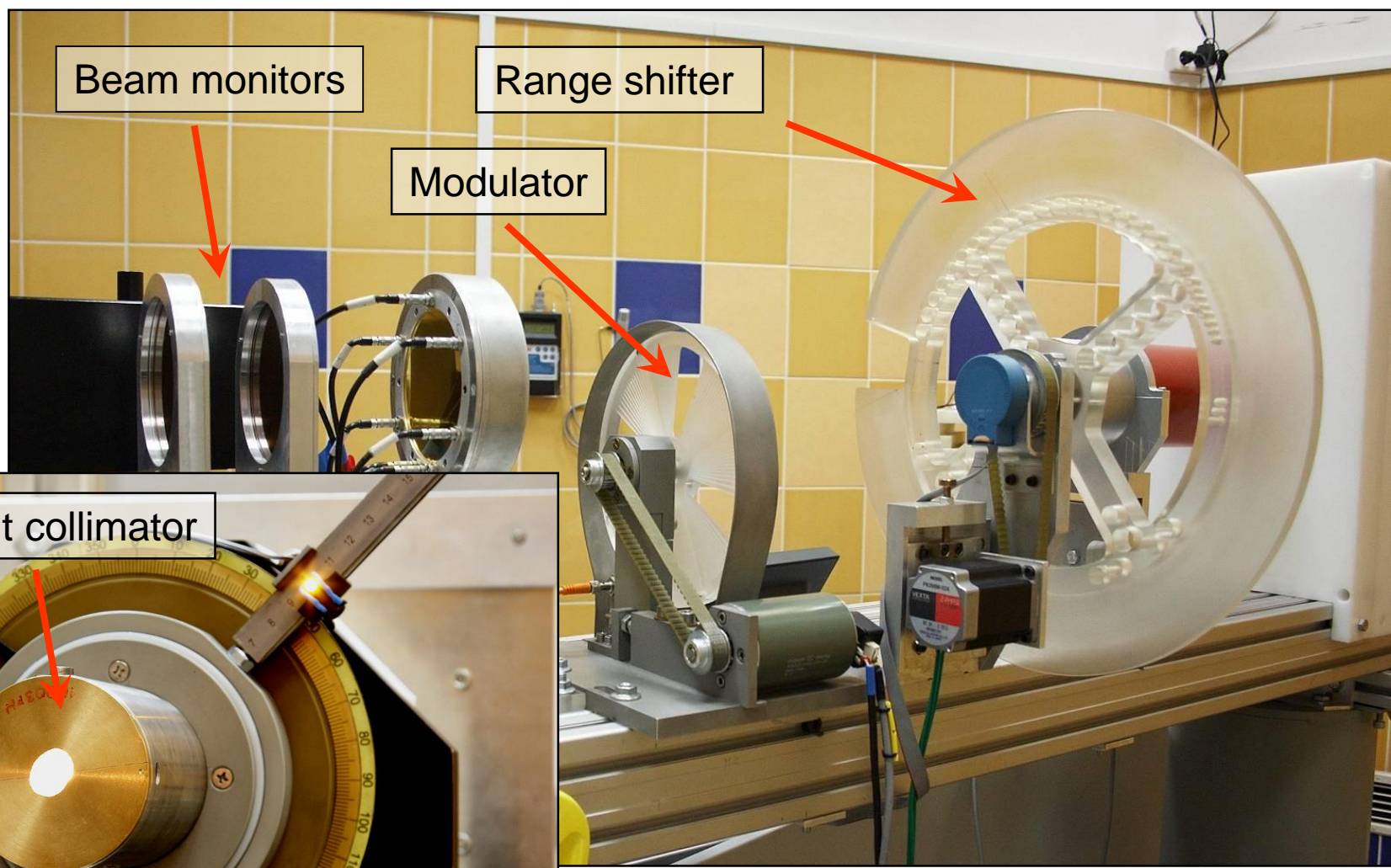


3D dose distribution in Eclipse Ocular Proton Planning



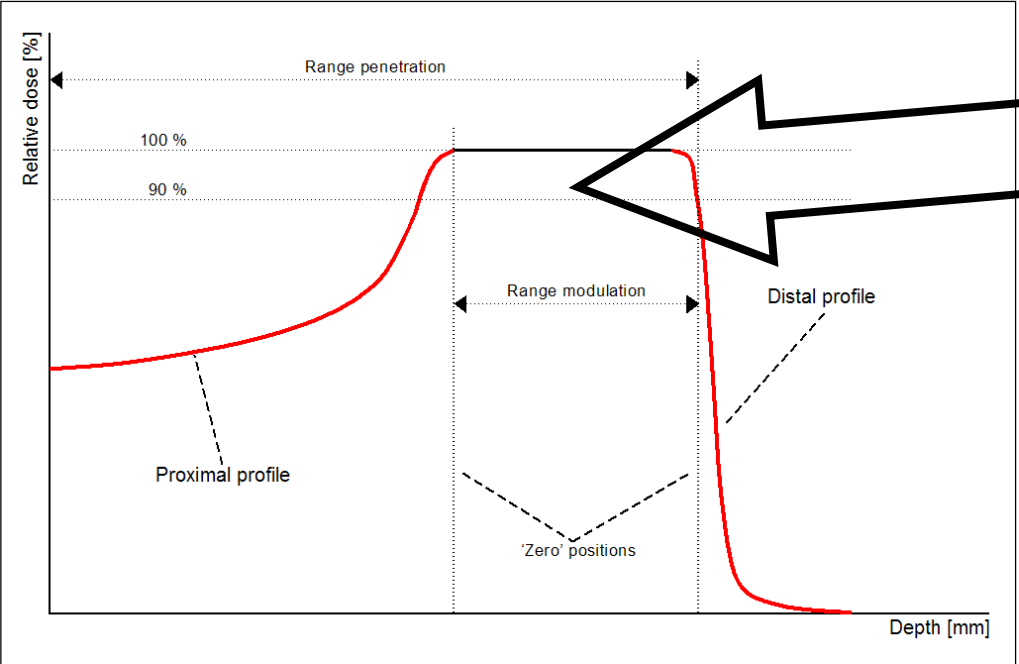
Kajdrowicz T., Bajer M. (Varian Medical Systems Inc.)

Passive scattering beam formation devices



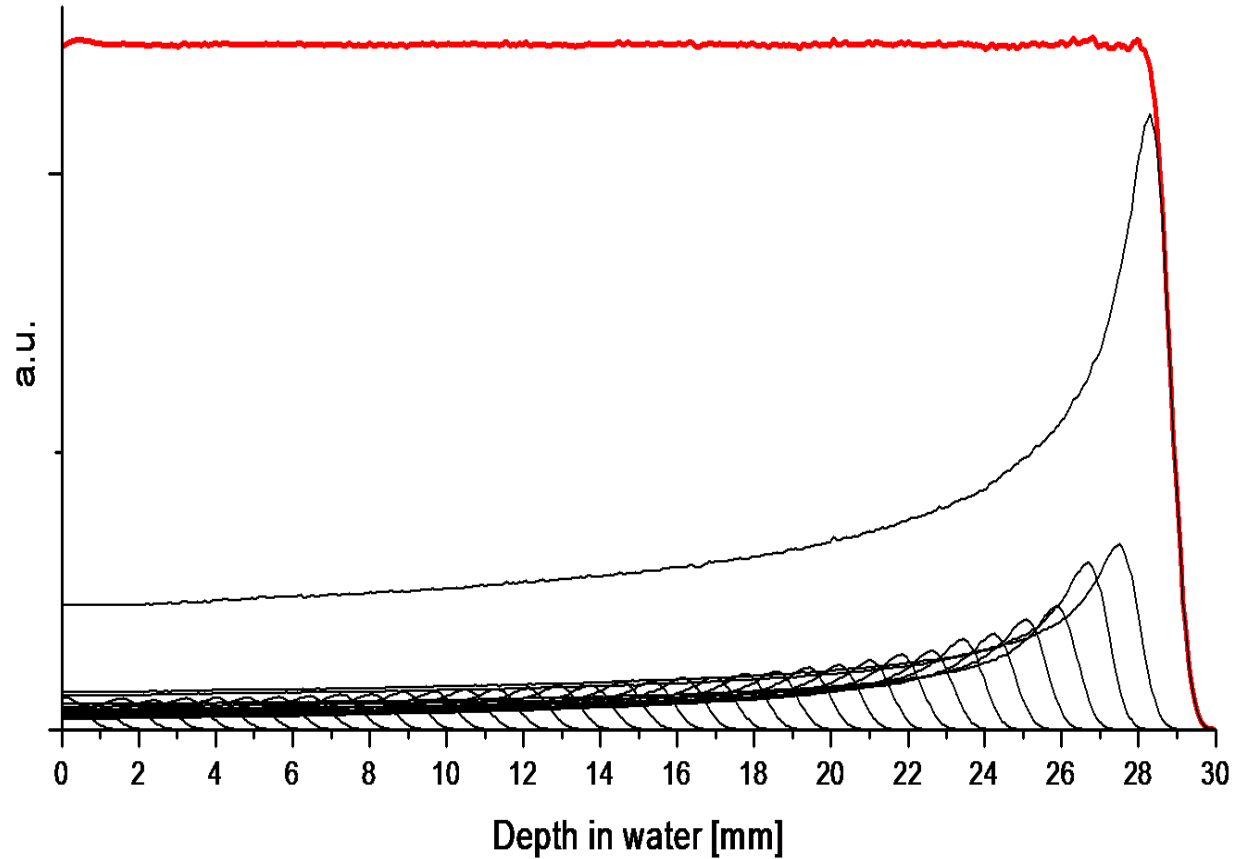
■ Range modulation – Spread Out Bragg Peak (SOBP)

- rotating wheel
- changing PMMA thickness



Varian Medical Systems, *Eclipse Ocular Proton Planning User Guide*, 2007

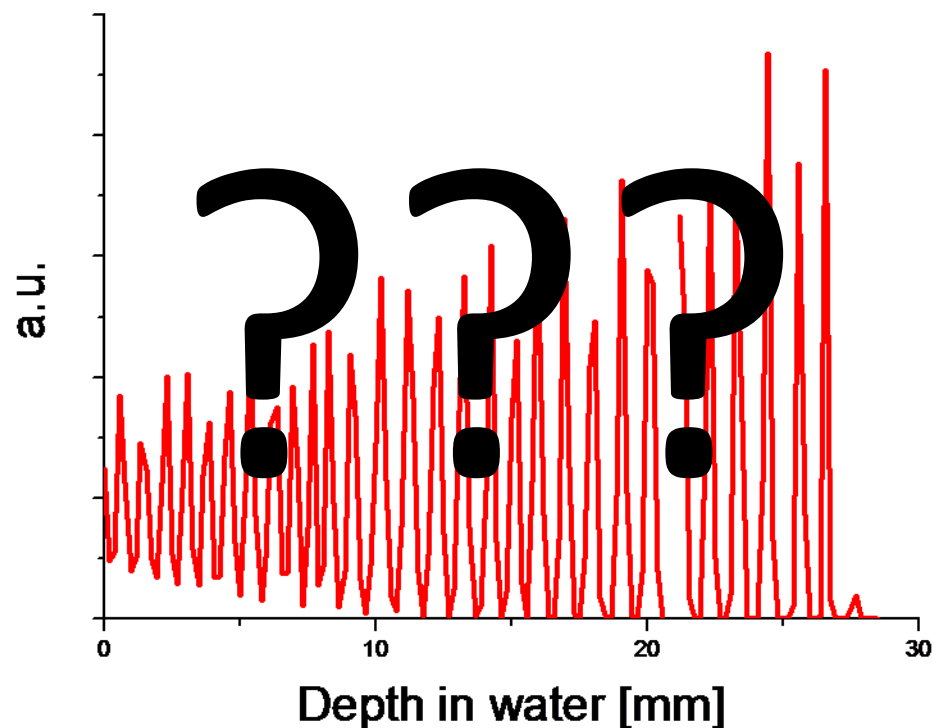
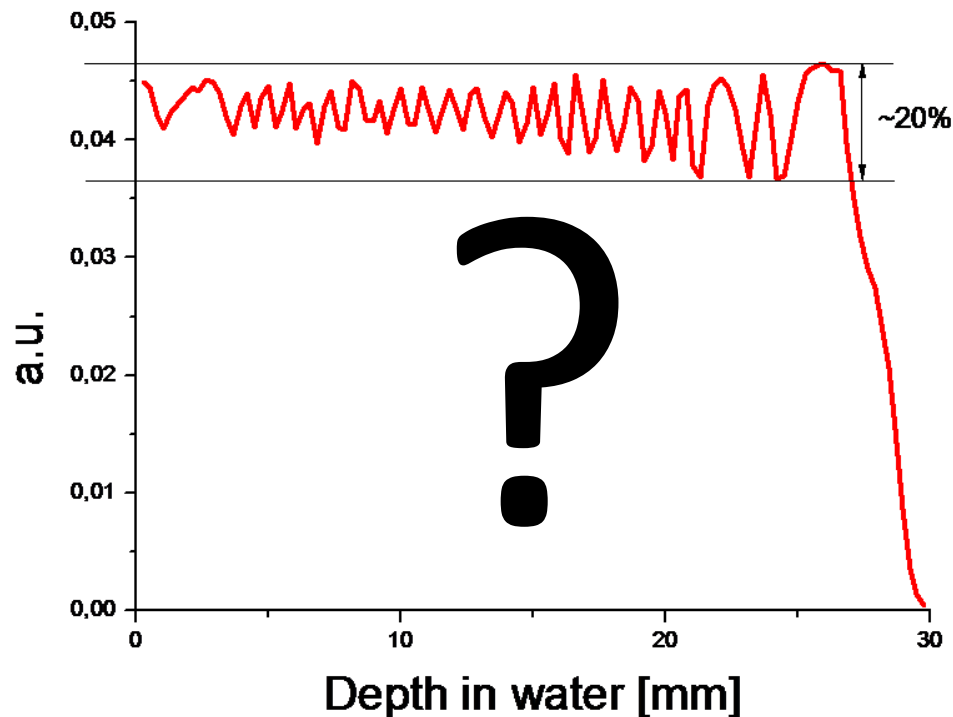
Spread Out Bragg Peak formation



Modulator

Experimental verification of modulators

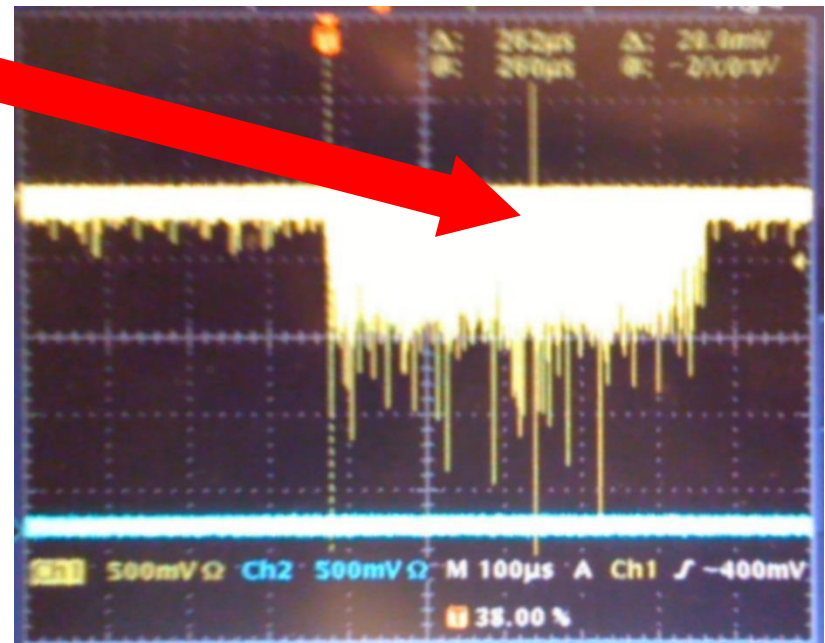
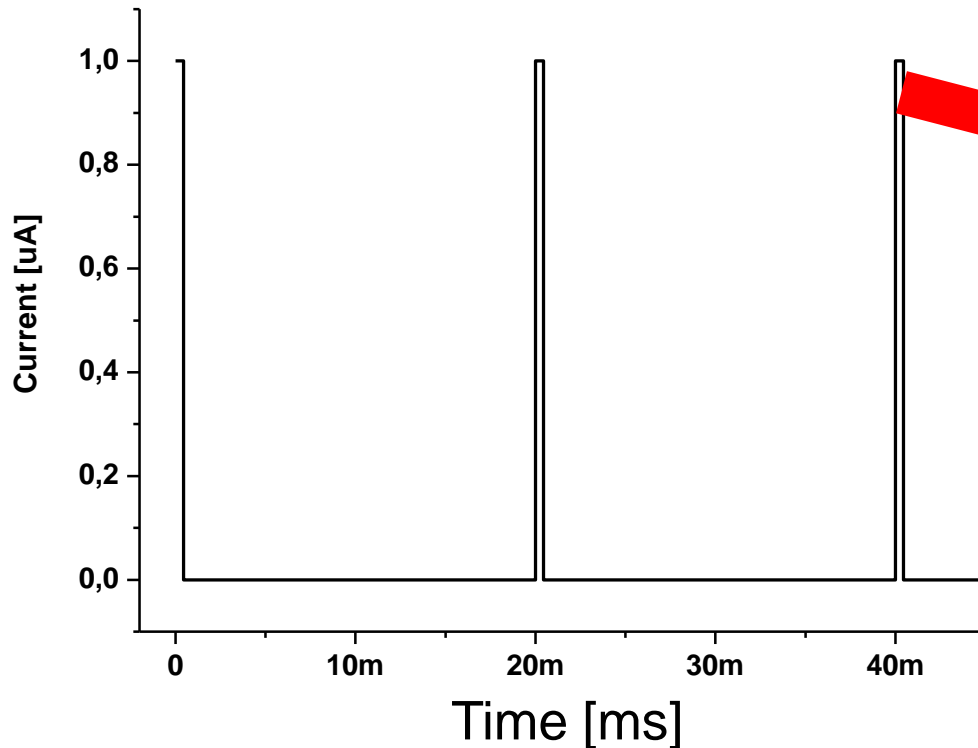
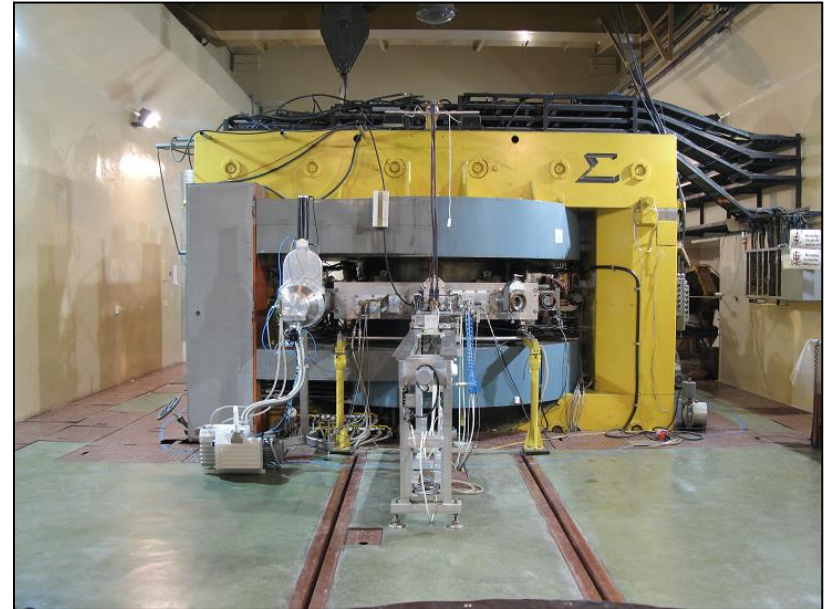
using 3D water phantom scanner and Markus ionization chamber



It did not look like SOBP 😞

Beam time structure of AIC-144 cyclotron

- Pulse repetition 50 [Hz]
- Pulse length 0.46 [ms]

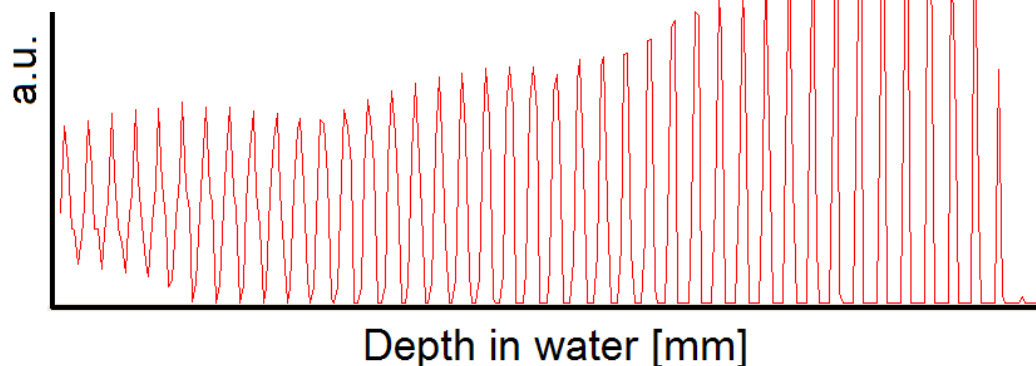
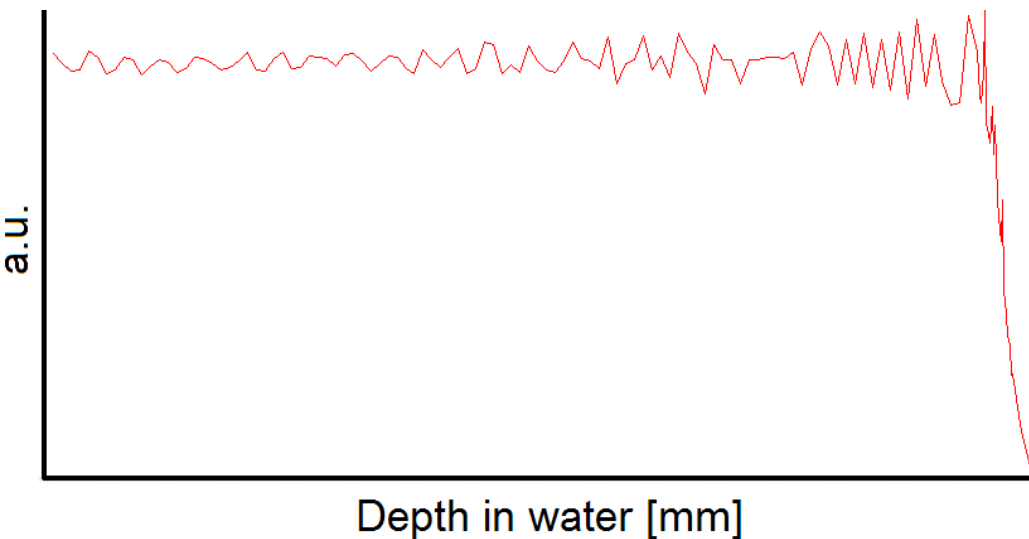


SOBP simulator software

- Beam parameters
- Modulator definition
- Measurement conditions

Beam Simulator

Modulator File name <input type="text" value="open modulator file"/> <input type="button" value="Open..."/>		Beam Properties Repetition Time [ms] Measurement Time [ms] 20,00 100		Calculation Type <input checked="" type="radio"/> Modulator shape verification <input type="radio"/> Multichannel detector <input type="radio"/> Scanner	
Rotation Speed [rps] Sections 30,00 4 <input checked="" type="checkbox"/> Sections Mirrored		Impuls Length [ms] No. of Measurements 0,35 3		Random parameters <input checked="" type="checkbox"/> Starting point <input type="checkbox"/> Rotation speed deviation	
Bragg Curve File name <input type="text" value="open bragg curve file name"/> <input type="button" value="Open..."/>		Irradiation time [s] Measurement Delay [ms] 3,000 100			



Conclusion from measurements and SOBP simulations

- problem is not a consequence of wrong measurement conditions
- it depends on:
 - pulsed beam structure
 - modulator rotational speed
- ... it is a sort of Wagon wheel effect.



Equation for stroboscopic effect

Methods

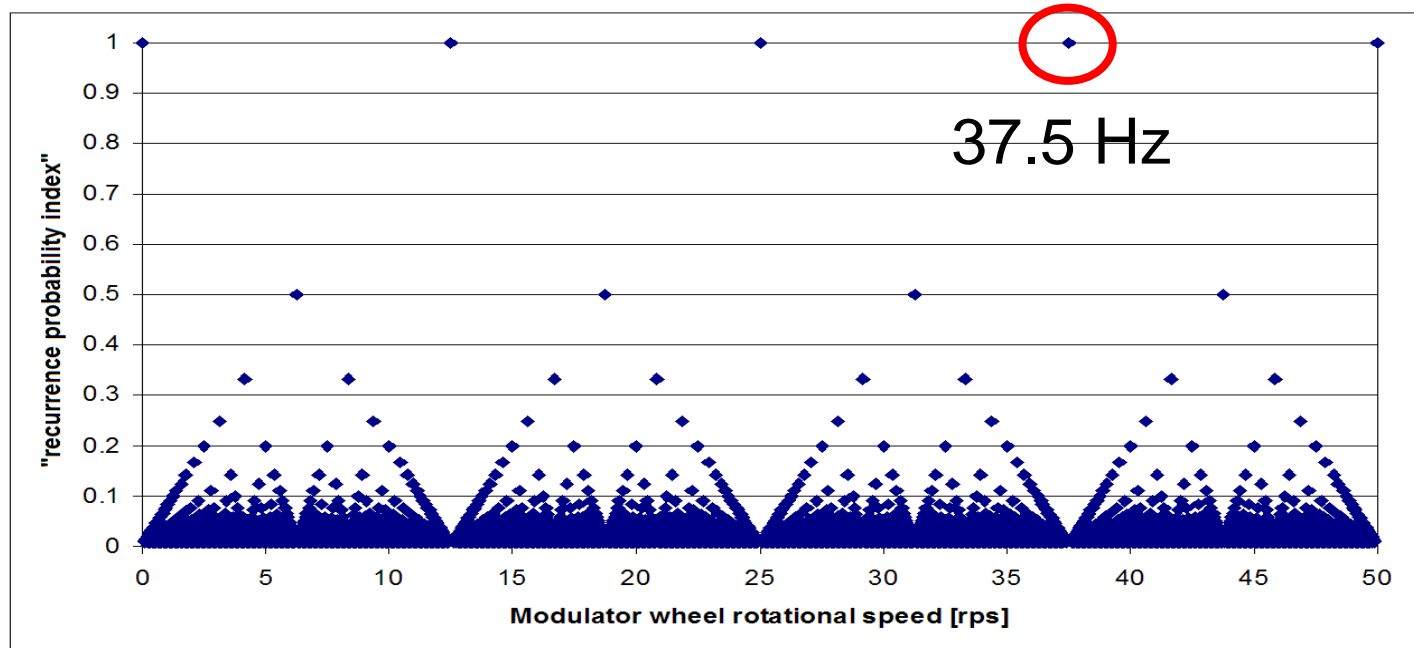
$$T_{modulator} = \frac{M}{n} \cdot T_{beam} \rightarrow T_{modulator} = \left(k + \frac{m}{n} \right) \cdot T_{beam}$$

where M, k, m, n are all integers and $m < n$

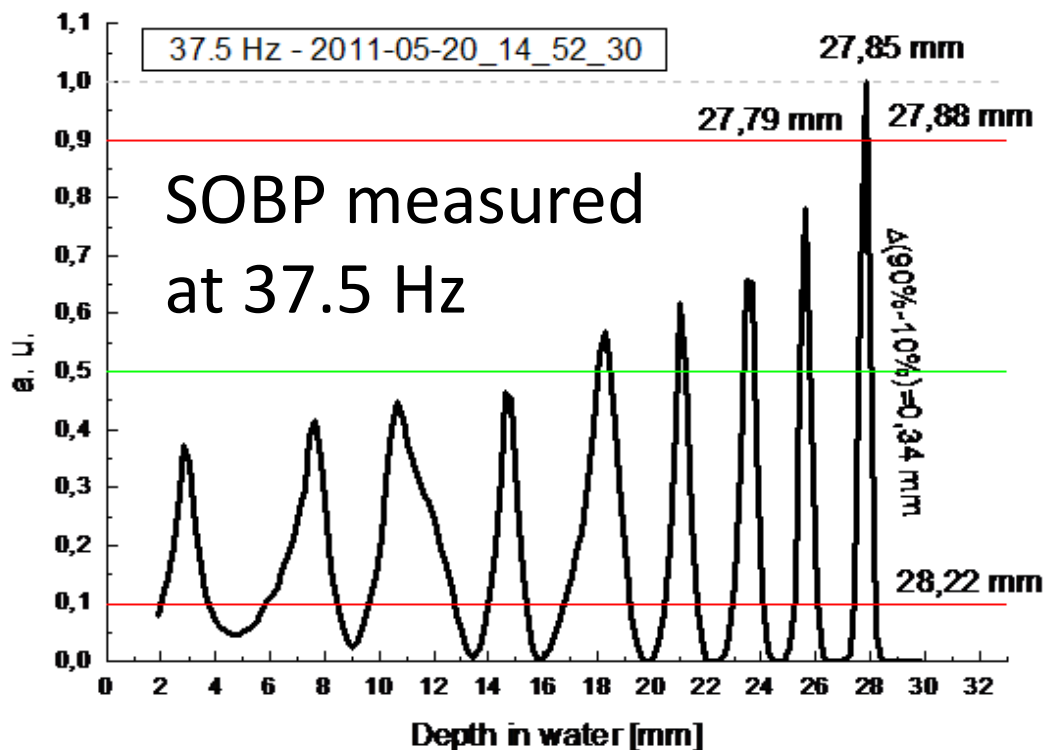
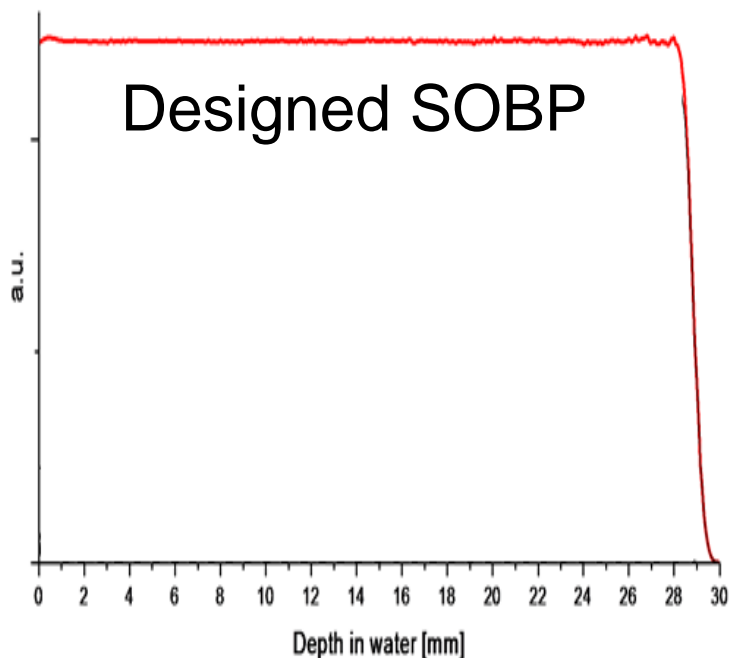
T_{beam} – beam pulse repetition time

$T_{modulator}$ – modulator wheel section recurrence time

Results



Experimental verification of calculations

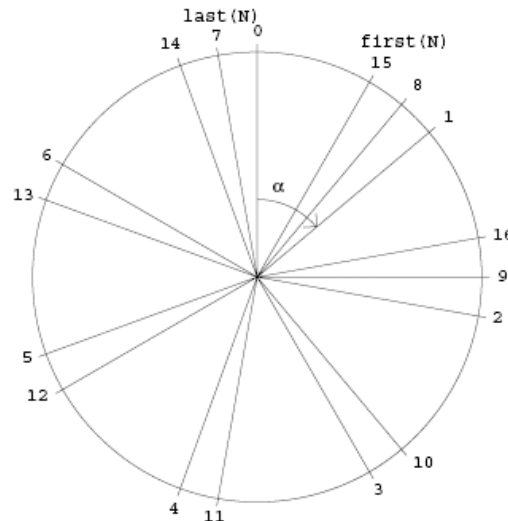


Theoretical model has been confirmed experimentally

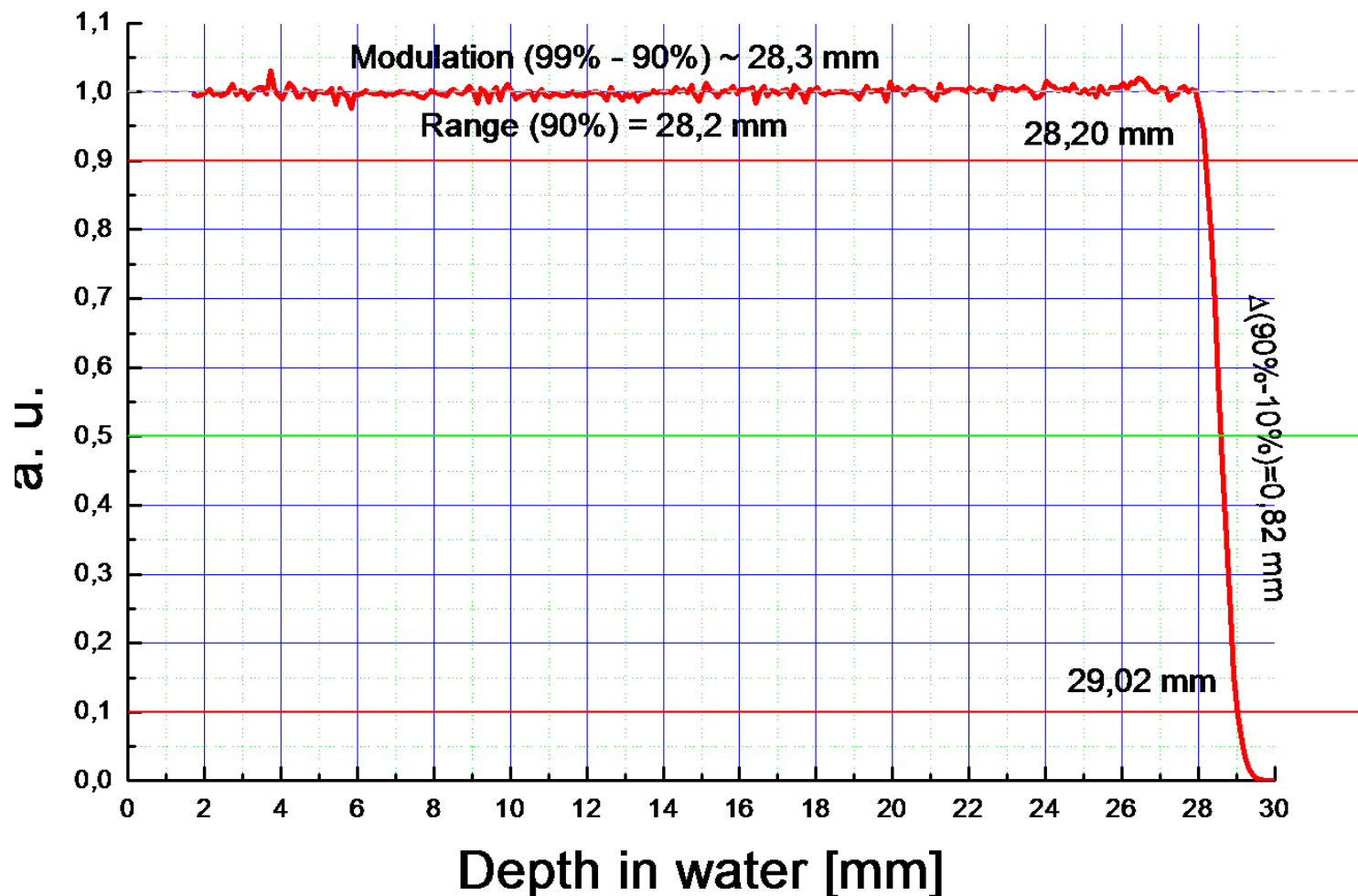
Searching for optimal asynchronous modulator rotational frequency

$$W_n(\alpha) = \{x_1, \dots, x_n\} \quad \text{for} \quad x_n = n\alpha \pmod{1}$$

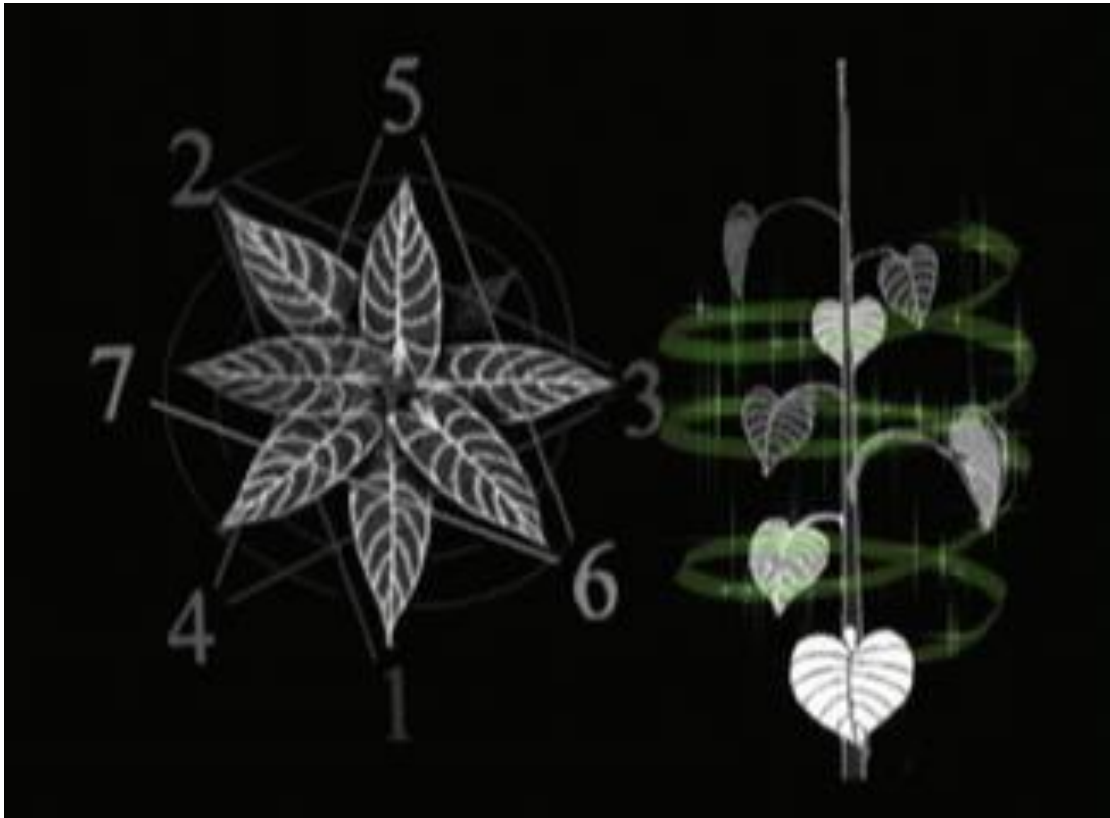
where $n = 1, 2, \dots$ and $\alpha \in [0, 1)$



FINAL RESULT – Perfect SOBP at 33.1 Hz



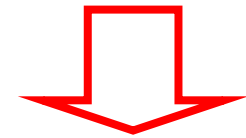
Nature solves the equidistribution equation



Phyllotaxis of a plant
equidistribution of sun light over leaves

Golden angle

$$\alpha = \tau = \frac{\sqrt{5} - 1}{2}$$



Rotational speed
of modulator:

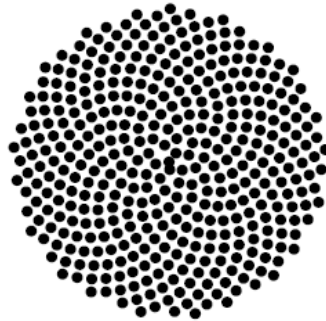
~ 32.725 Hz

■ Golden angle:

- Most uniform distribution of beam pulses (no recurrence)
- Very low dose discrepancy, but ...
- Mechanically unavailable frequency
- ~ 32.725 Hz is unfortunately very close to a high resonant frequency (32.8125 Hz) by less than 0.1 Hz



Golden Angle $- 0.1^\circ$



Golden Angle



Golden Angle $+ 0.1^\circ$





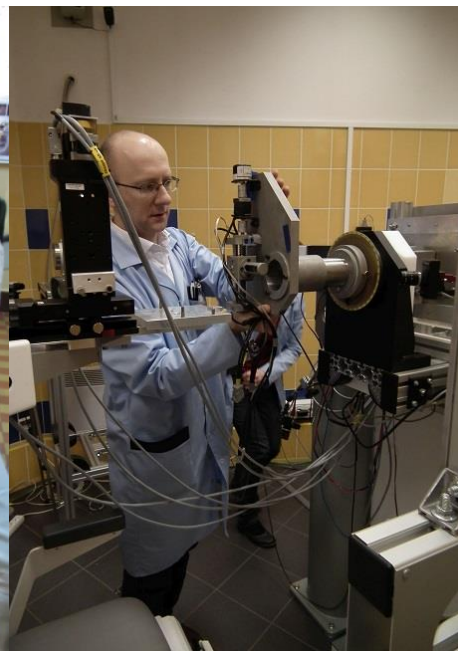
My name is A, QA – quality assurance



Centrum Onkologii
Instytut im. Marii Skłodowskiej-Curie
Oddział w Krakowie



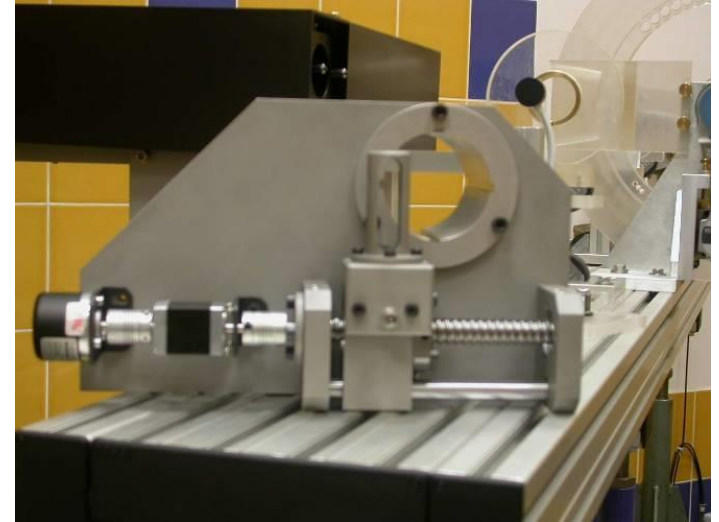
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Uniwersytecki
w Krakowie



In-house developed phantoms and scanners



PMMA range phantom



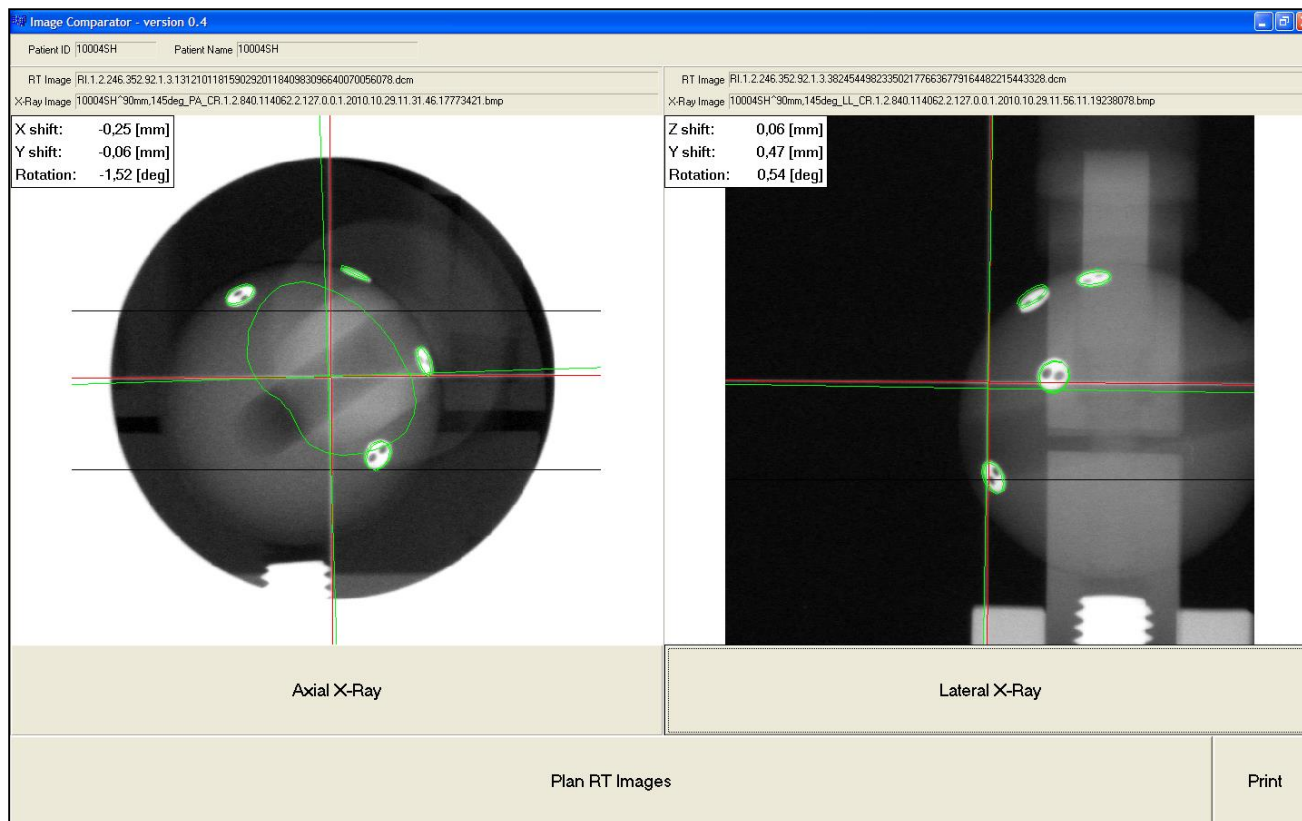
Lateral profile scanner



3D scanner and water phantom

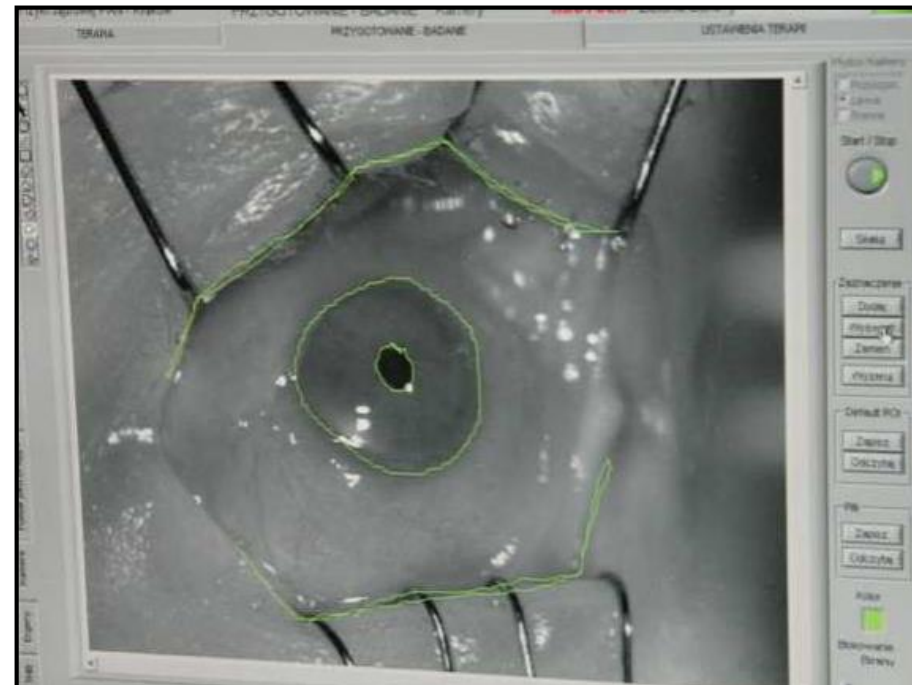
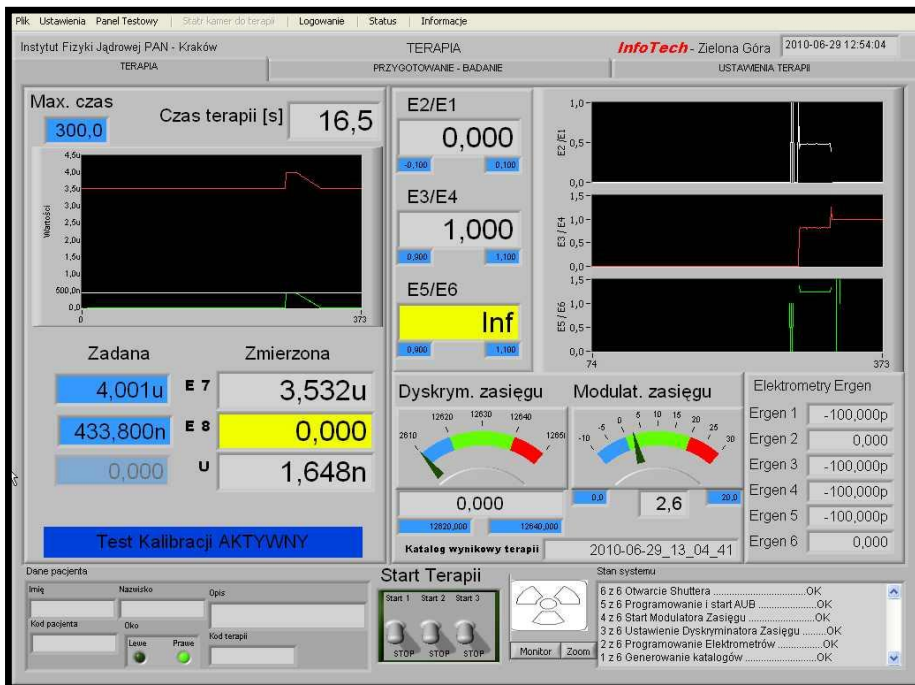


In-house developed Patient Positioning Verification System



It allows for quick patient positioning with submillimeter precision

Treatment delivery – 4 fractions, 15 Gy_{RBE} each



Number of fraction	Dose delivered (planned) [CGE]	Dose delivered [CGE]	Independent dose controle [CGE]	Total dose [CGE]	Time [s]
Fraction 1	15.00	15.001	15.068	15.001	51
Fraction 2	15.00	15.044	15.057	30.045	53.5
Fraction 3	15.00	15.020	15.043	45.065	60.5
Fraction 4	15.00	15.026	15.026	60.091	63.5

The team almost complete



prof. M. Jeżabek



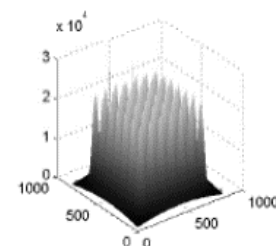
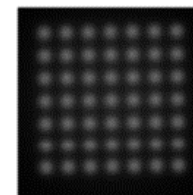
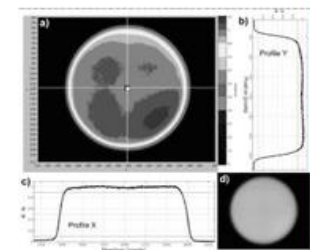
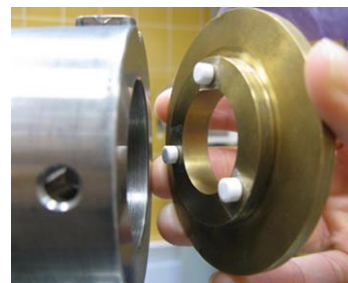
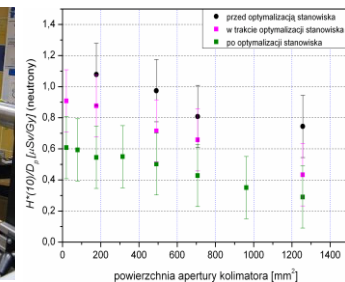
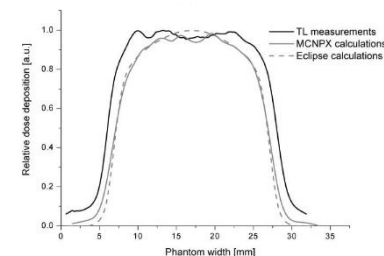
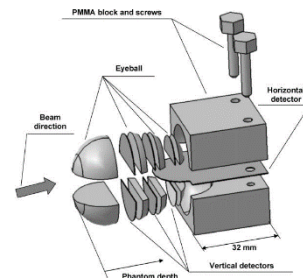
Movie by dr hab. Jerzy Grębosz
Terapia protonowa nowotworów oka
sekretariat.ccb@ifj.edu.pl

- **292 patients** of University Hospital in Krakow treated:
 - 128 patients at AIC-144
 - 164 patients at CCB ELTR
- *Age between 17 to 75 years
 - 52 years on average
 - 3% patients below < 22
- *Female 46%, Male 54%
- *Right eye 49%, left eye 51%
- *Tumor height
 - < 5mm 72 %
 - 5-10mm 24 %
 - > 10mm 4%
- *Follow up of 93% patients → **97% local control**

*Romanowska-Dixon B, Markiewicz A, Sas-Korczyńska B, Medoń D, Walasek T. Evaluation of intraocular proton beam irradiation complications after choroidal melanoma treatment. *Klinika Oczna / Acta Ophthalmologica Polonica*. 2016;118(4):289-292. doi:10.5114/ko.2016.71741.

*Romanowska-Dixon B Terapia protonowa czerniaka naczyniówki, Seminarium, 2016

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- Biological effects and inter-individual variability in peripheral blood lymphocytes of healthy donors exposed to 60 MeV proton radiotherapeutic beam, *Panek A, Miszczyk J, Swakoń J*, *Int. J. Radiat. Biol.*, 94 (2018) 1085-1094
- and more ...

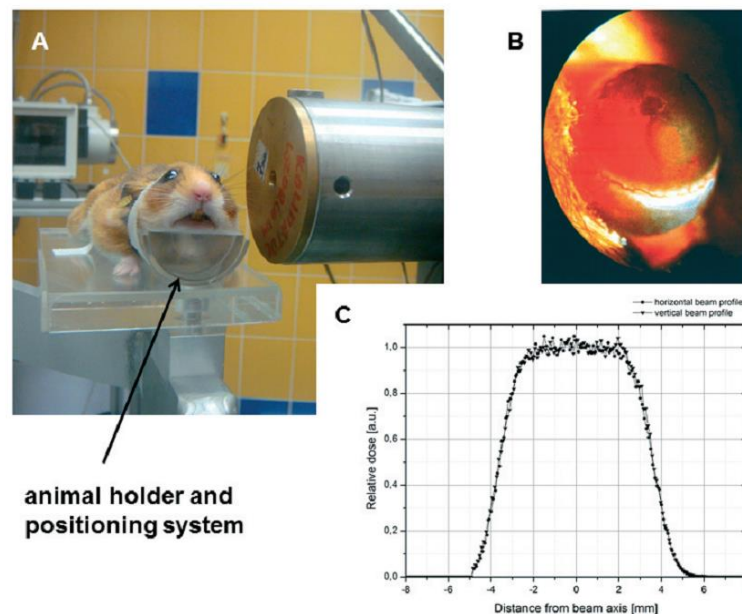


Figure 1. Hamster eye irradiation with proton beam. (A) Hamster in the animal positioning system, (B) hamster eye with the tumor, magnification 10x and (C) proton beam dose depth distribution and lateral profiles of the beam used for hamster eye irradiation.

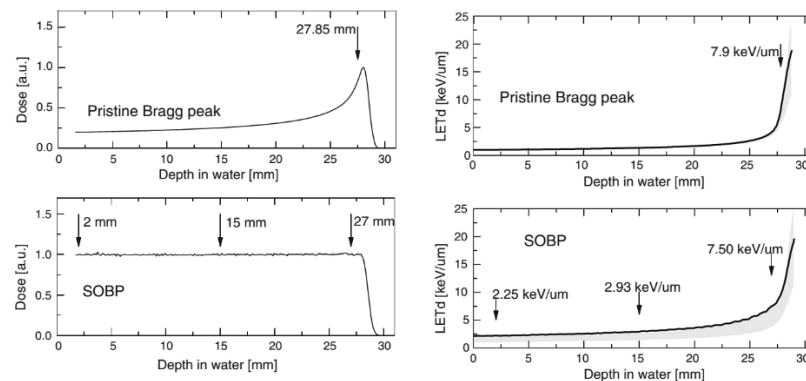
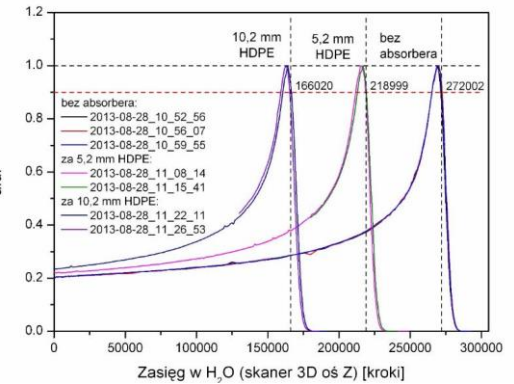


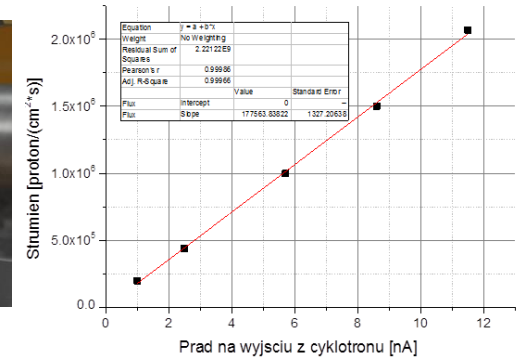
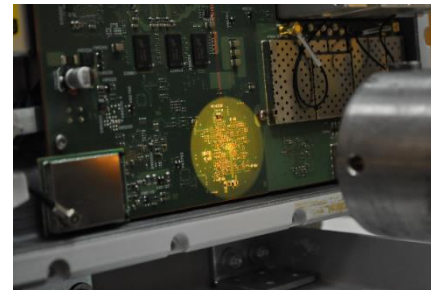
Fig. 1 Depth-dose distributions of the proton beam produced at the IFJ PAN Kraków (nominal energy 60 MeV) measured in a water phantom using a Marcus ion chamber. *Upper panel:* pristine beam; *lower panel:* SOBP. *Arrows* indicate positions at which cells (human fibroblasts) were irradiated: near (at 27.85 mm) the maximum of the Bragg peak in a pristine beam, and at three depths (2, 15, and 27 mm) of the SOBP of full width 28.4 mm

Fig. 2 Depth distributions of dose-averaged LET (LET_d) and of IQR of LET_d (shaded) of the proton beam produced at the IFJ PAN, simulated by Monte Carlo calculations. *Upper panel:* pristine beam; *lower panel:* SOBP. Calculated values of LET_d at irradiation positions are also shown

- Testing of electronics for first Polish satellite LEM



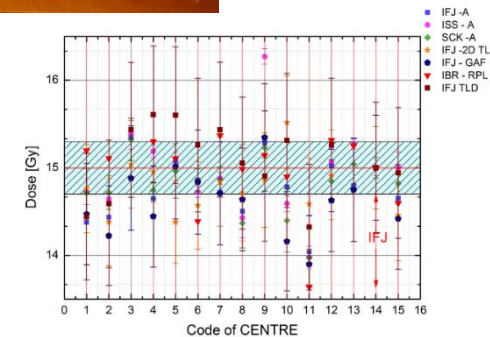
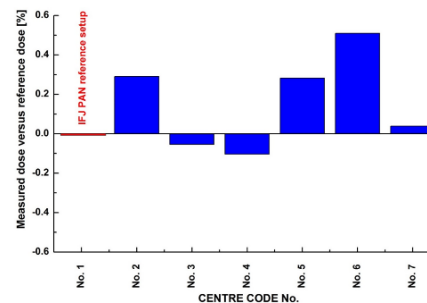
- Testing of electronics for GSM basestation of the manned flight to Moon



- PTCOG OPTIC group intercomparison using mailed dosimetry



- and more ...



The proton eye physics team (10 years compilation)



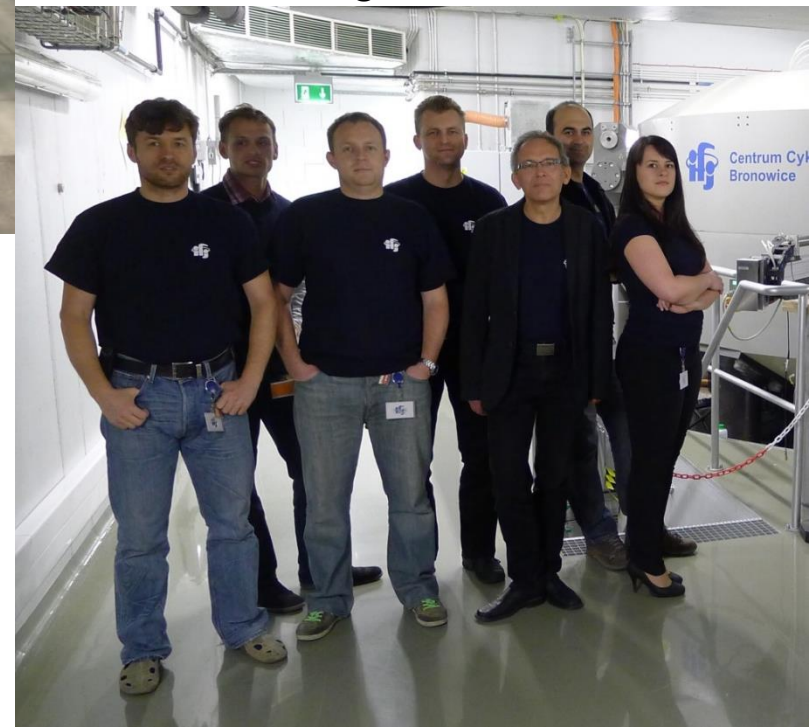


DCA Team after last patient irradiation on AIC-144

IT Team



DCP Team during commissioning of Proteus C-235



In developing and executing the clinical part of this project, the team of IFJ PAN **physicists** and **engineers** closely collaborated with

ophthalmologists, radiation oncologists, radiologists, medical physicists, radiation therapist and **nurses** from the Department of Ophthalmology and Ophthalmic Oncology (Collegium Medicum of the Jagiellonian University) and with

radiation oncologists from the Centre of Oncology – Institute in Krakow (currently National Institute of Oncology in Krakow).



Podziękowania dla

Obecnej i poprzednim Dyrekcji IFJ PAN

Kierownika Centrum Cyklotronowego Bronowice

Kolegów i Koleżanek z *Samodzielnej Pracowni Radioterapii Protonowej*

Kolegów i Koleżanek z *Działu Cyklotronu AIC-144*

Kolegów i Koleżanek z *Centrum Cyklotronowego Bronowice*

Kolegów i Koleżanek z *Działu Cyklotronu Proteus*

Kolegów i Koleżanek z *Zakładu Badań Radiacyjnych i Radioterapii Protonowej*

Kolegów i Koleżanek z *Zakładu Fizyki Radiacyjnej i Dozymetrii*

Kolegów i Koleżanek z *Działu Budowy Aparatury i Infrastruktury Naukowej*

Kolegów i Koleżanek z *Zakładów Naukowych*

Kolegów i Koleżanek ze *wszystkich laboratoriów badawczych i pomiarowych*

Kolegów i Koleżanek ze *wszystkich działów administracyjnych i ekonomicznych*

Kolegów i Koleżanek ze *wszystkich działów technicznych i pomocniczych*

Pracowników *Szpitala Uniwersyteckiego w Krakowie*

Pracowników *Narodowego Instytutu Onkologii Oddział w Krakowie*

Członków *Narodowego Konsorcjum Radioterapii Hadronowej*

Przyjaciół i Sympatyków projektu