Cancer Radiotherapy Introduction

Prof Dr. Joao Seco, DKFZ Heidelberg

Dr. Hans-Peter Wieser, LMU München

Dr. Niklas Wahl, DKFZ Heidelberg

 j.seco@dkfz.de

Questions are welcome at any time

How to Treat Cancer ....
With minimal side-effects

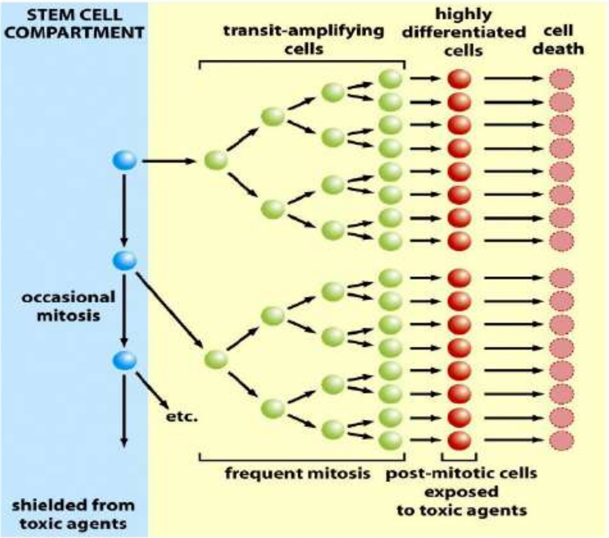
- Holy grail of oncology
- Identify characteristics that distinguish tumor cells from normal cells
- Design a <u>Monotherapy</u> that selectively ablates tumor cells

Some Biology…

Tissue organization and protection of the stem cell genome

stem cells can renew themselves through mitotic cell division and can differentiate into a diverse range of specialized cell types

the two broad categories of mammalian stem cells are embryonic stem cells & adult stem cells

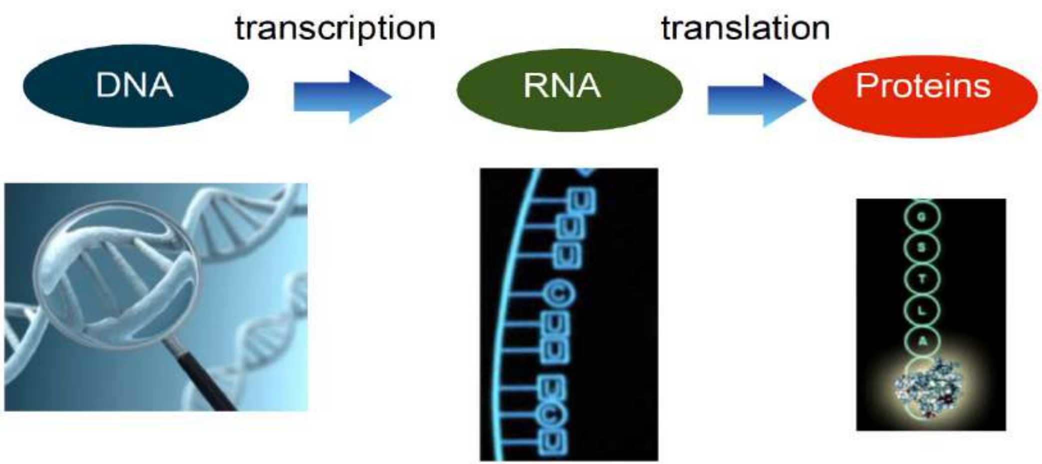


The Biology of Cancer (© Garland Science 2007)

dkfz.

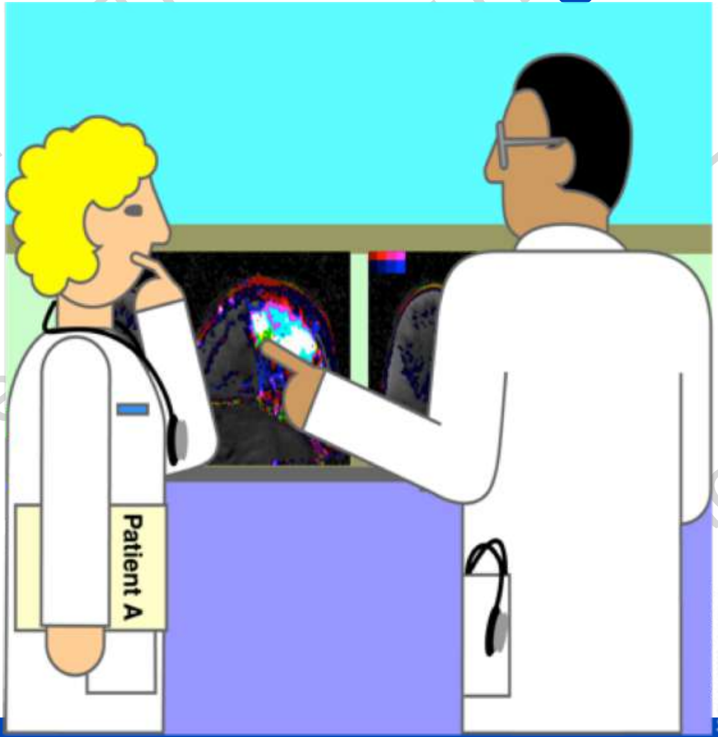
Some Biology…

The flow of genetic information

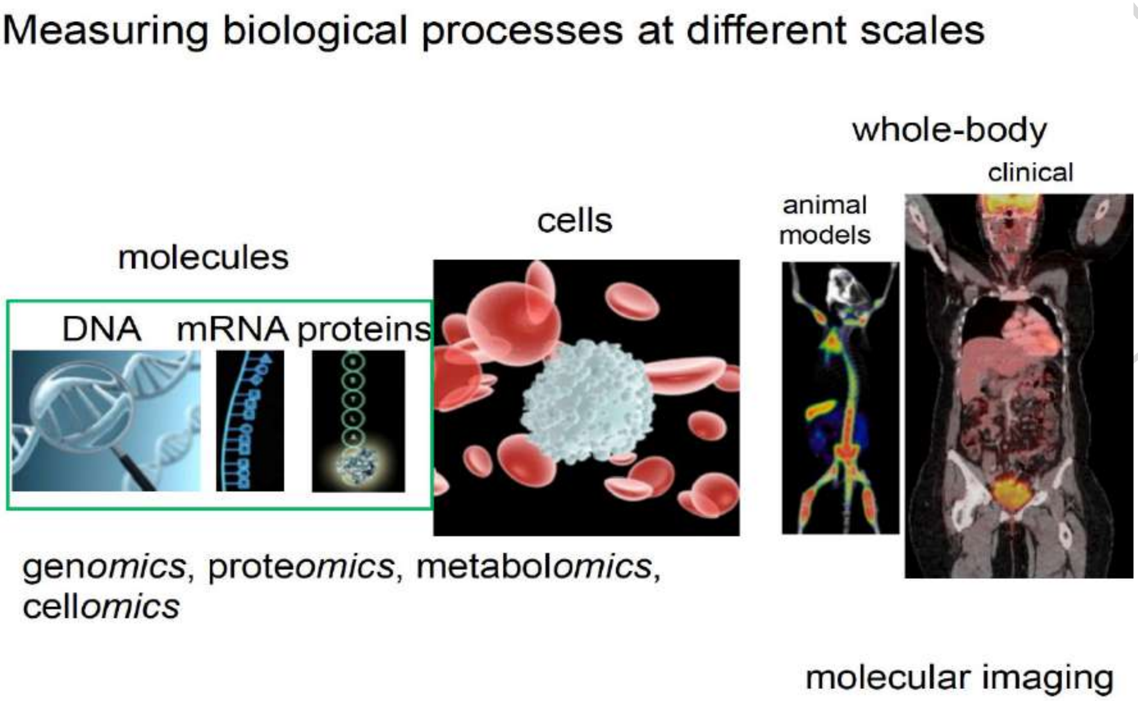


Some Biology…

How is cancer diagnosed?

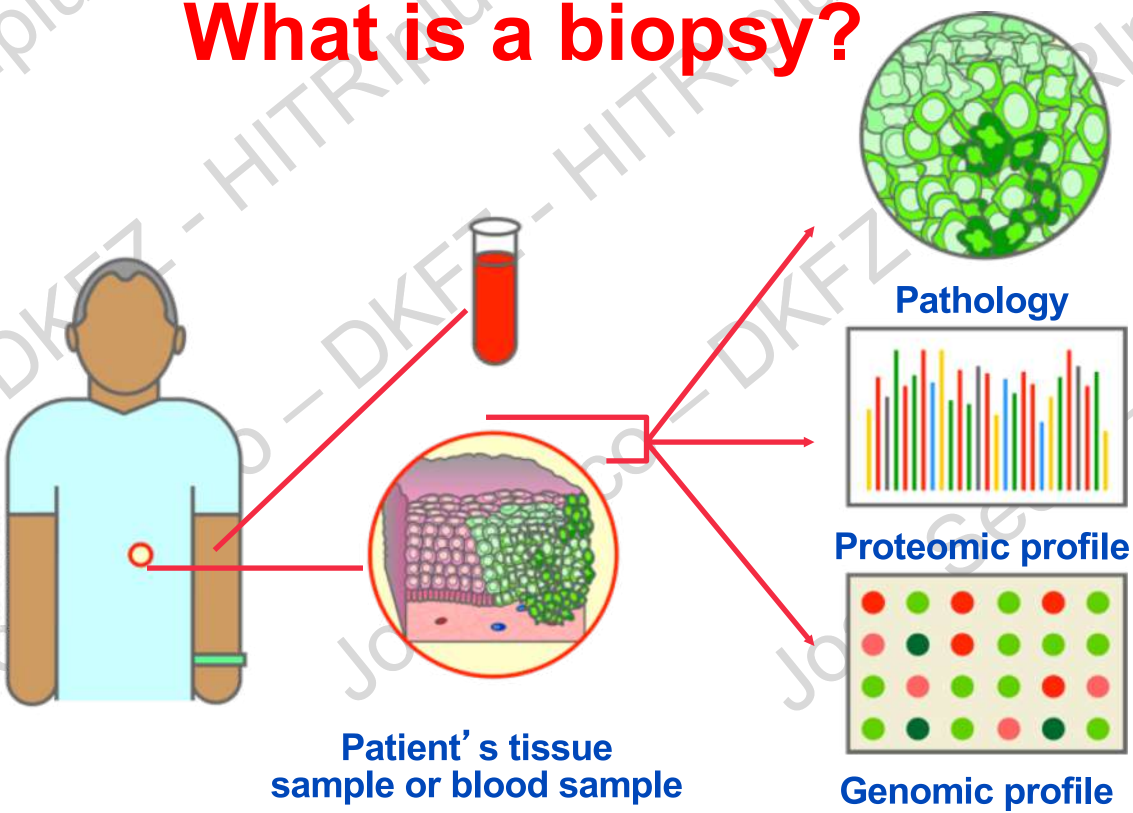


Patient Diagnostic Evaluation

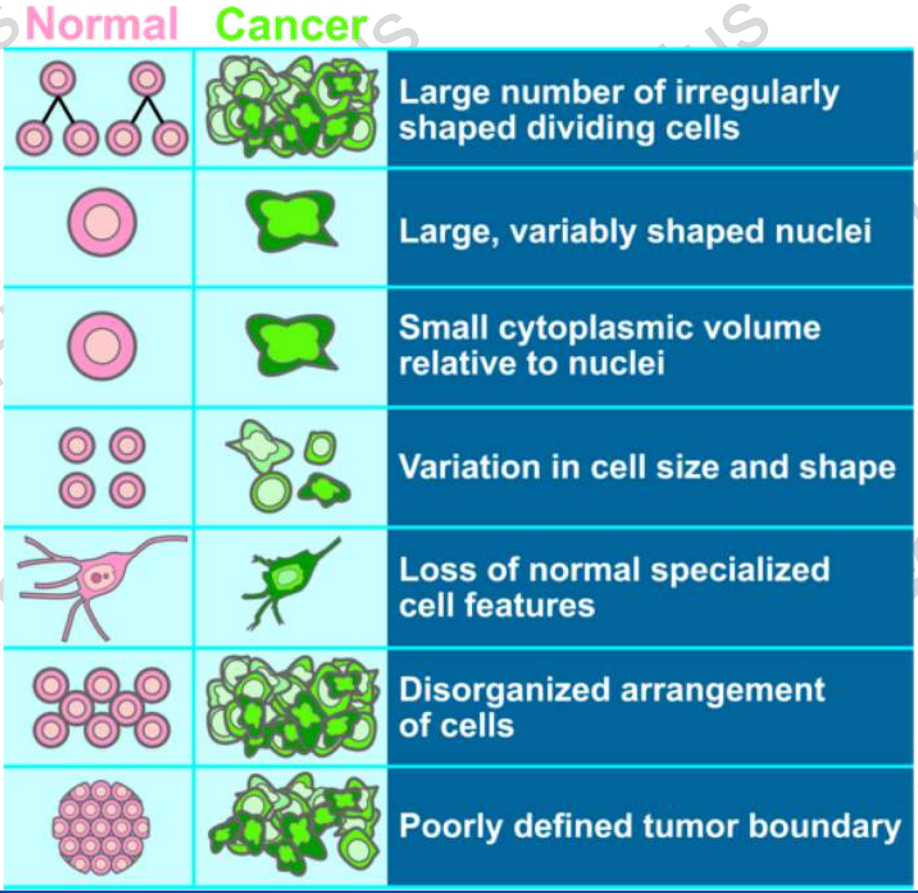


Let‘s start with Biology …

What is a biopsy?



What does a pathologist look for in biopsy tissue?



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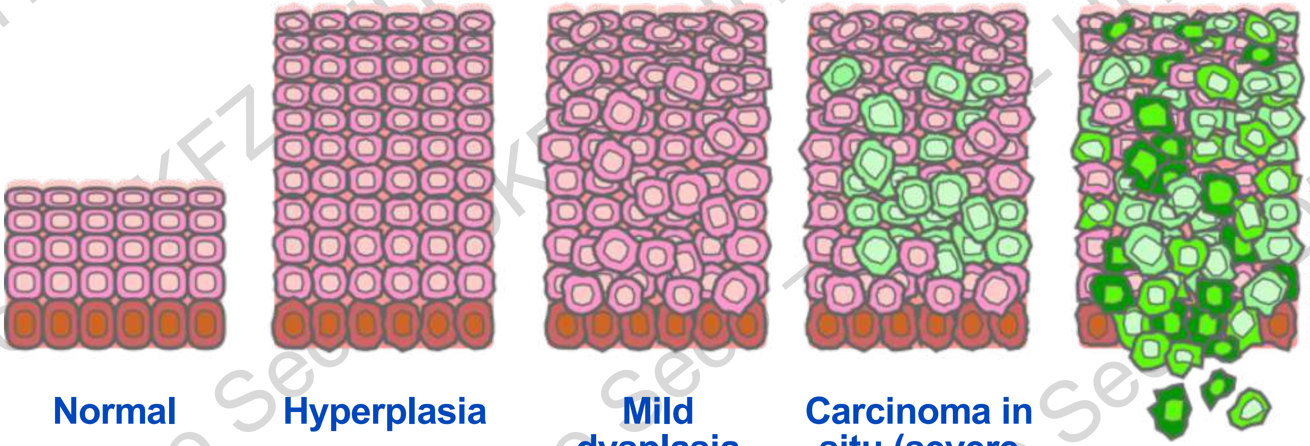
Some more Biology…

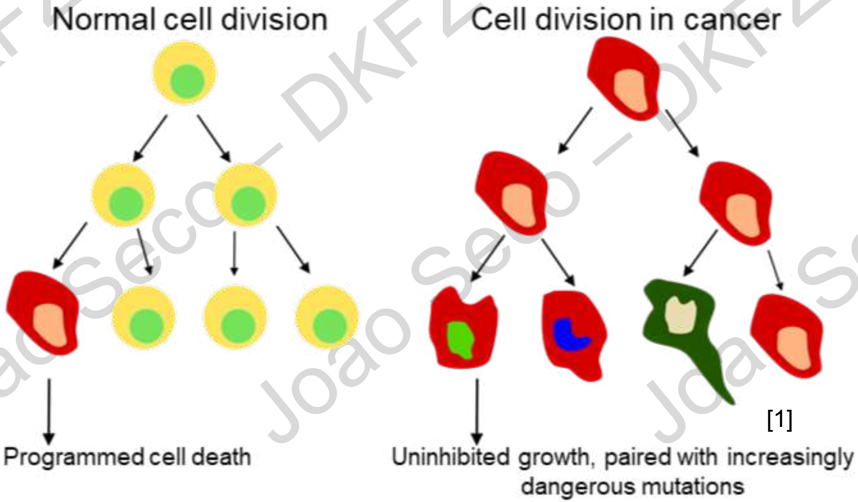
How does Cancer look like under the microscope?



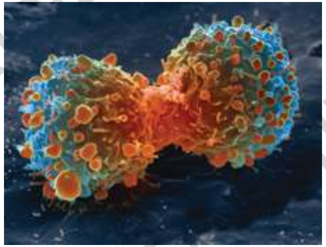
What is Cancer ?

- is uncontrolled cell proliferation and cell rampant growth
- cancer may spread to other parts of the body
- over 100 different types, individual

healthy cells vs. cancer cells



Cancer cell of a lung tumor during cell proliferation



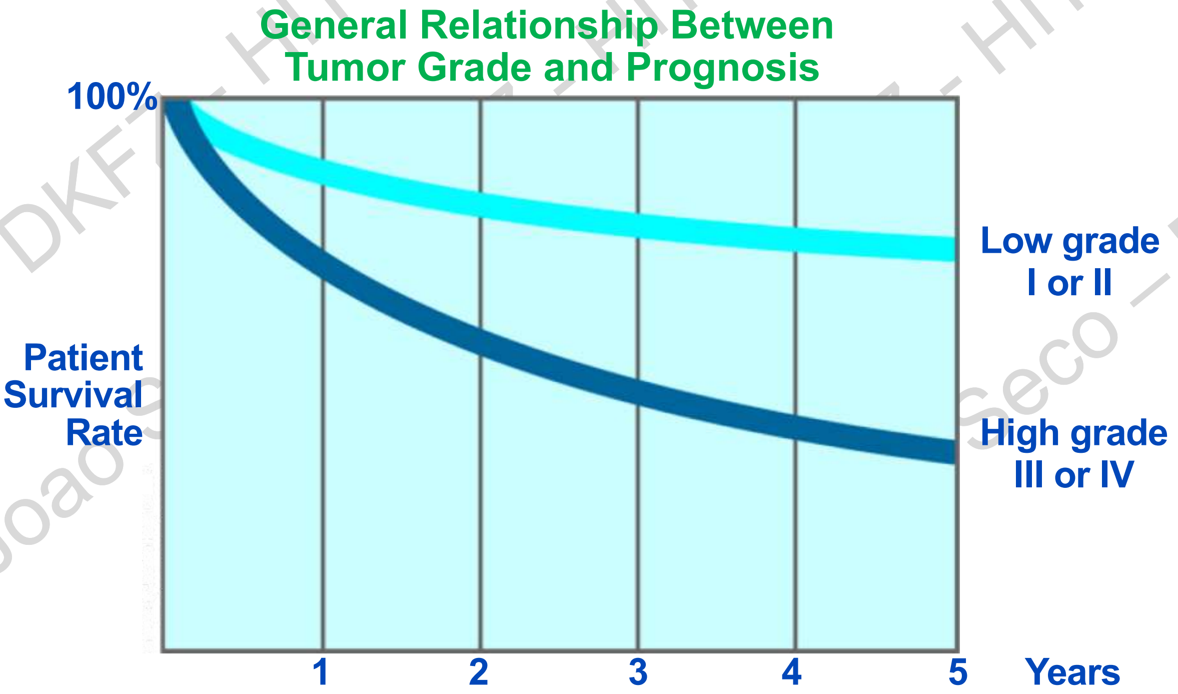
[2]

Theory of cancer formation:

(random) mutation levers out i.a. programmed cell death
→ cells need to be removed / killed "manually" for treatment

[1] Garak76, Suhadi Jorhaa'ir (https://commons.wikimedia.org/wiki/File:Zellteilung_normal_im_Gegensatz_zu_Krebs.svg), „Zellteilung normal im Gegensatz zu Krebs"
[2] fineartamerica - Lung Cancer Cell Division. - Accessed from https://fineartamerica.com/featured/lung-cancer-cell-division-sem-steve-gschmeissner.html?product=metal-print on 12.02.2021. Lettering was adapted.

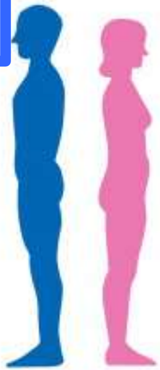
What is the relationship between tumor grade and patient survival?



2017 New Cancer Sites

Estimated New Cases

	Males			Females	
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**	**All Sites**	**852,630**	**100%**



j.seco@dkfz.de

2017 Cancer Deaths

Estimated New Cases

Males			Females		
Prostate	161,360	19%	Breast	252,710	30%
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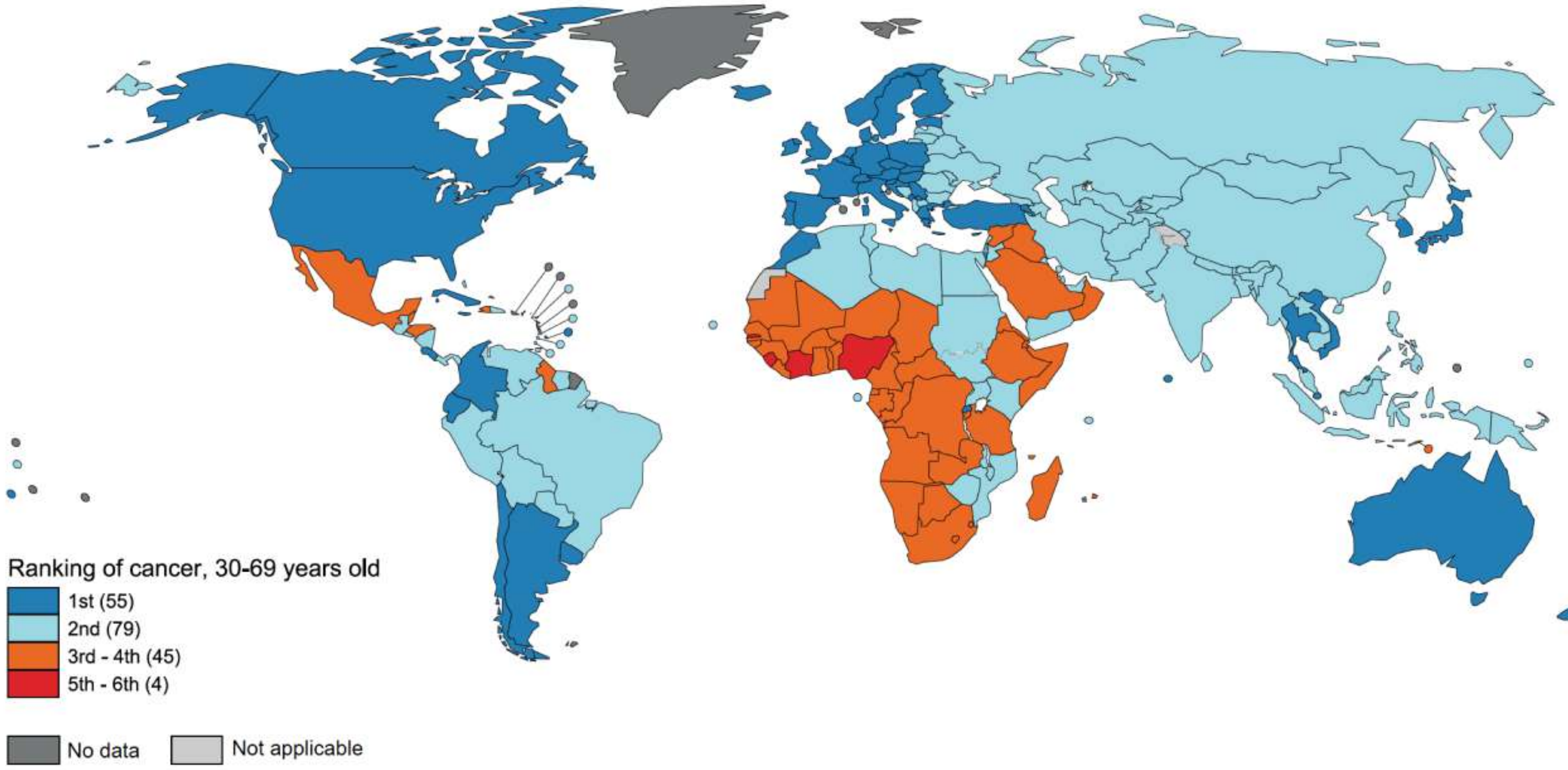
Estimated Deaths

Males			Females		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**	**All Sites**	**282,500**	**100%**

j.seco@dkfz.de

Cancer - incidence



[1] Stewart, B. W. K. P., and Christopher P. Wild. "World cancer report 2014." (2014).
[2] Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries
[3] RKI, Report on cancer in Germany for 2013/2014, cancer registry data
[4] RKI, Report on cancer in Germany for 2015/2016, cancer registry data

Hallmark of Cancer

“Warburg Effect”

Adequate oxygen

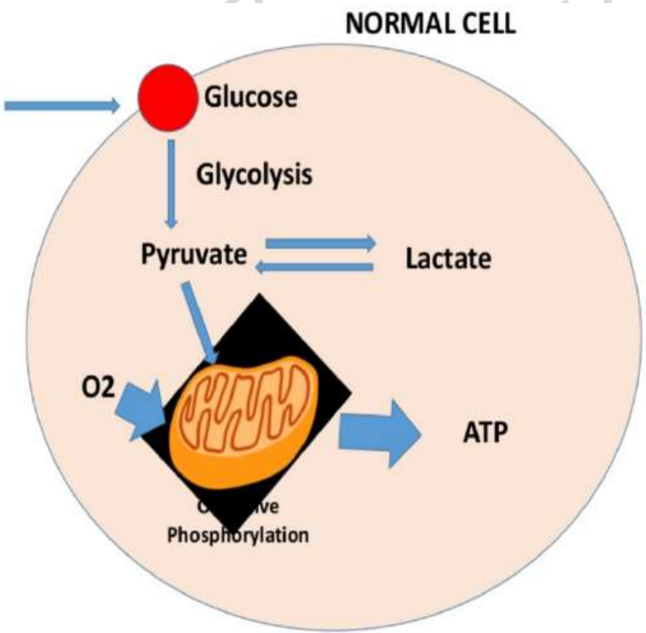
ATP is generated by Oxidative Phosphoryation

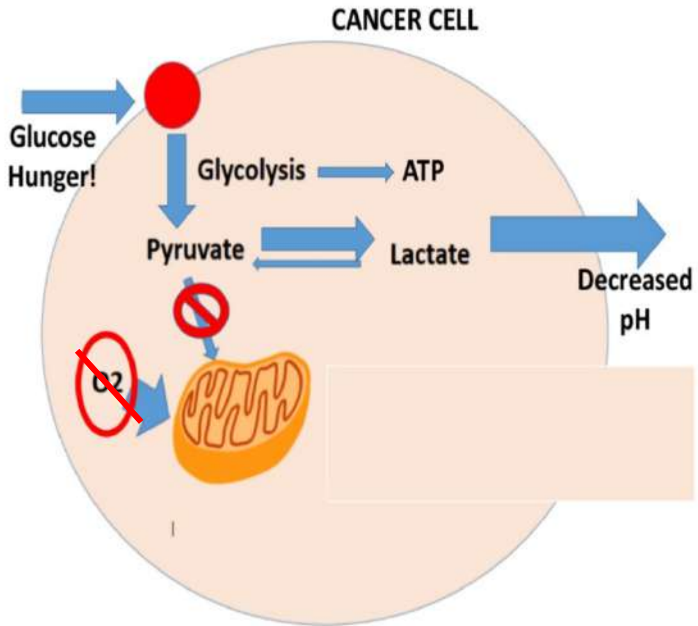
As Oxygen Decreases

Shift from Oxidative phosphorylation to **Glycolysis**

Anaerobic glycolysis

PASTEUR EFFECT





Glycolysis with O2 present

Otto Heinrich Warburg

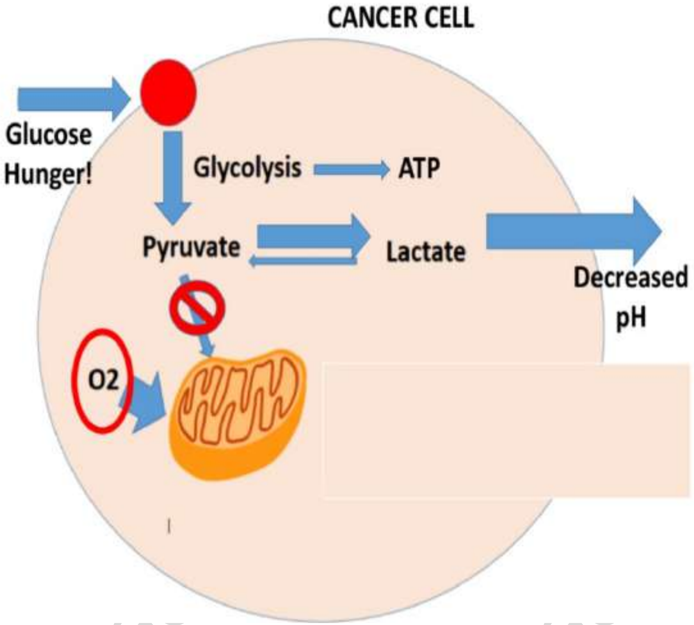
German Physiologist

Observed that cancer cells had increased rates of glycolysis

Despite the availability of adequate oxygen levels

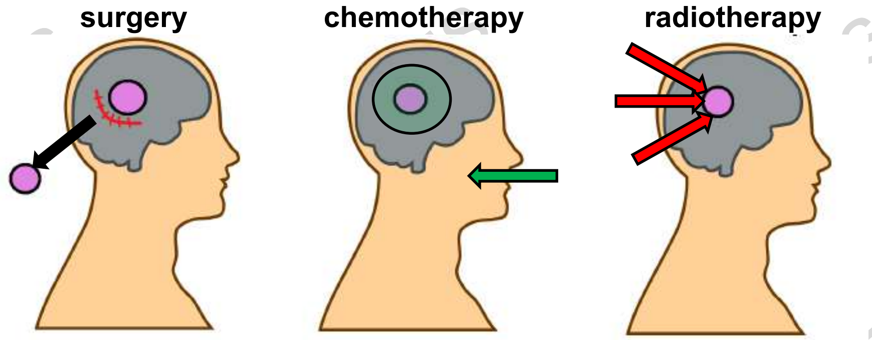
Aerobic glycolysis

WARBURG EFFECT



Why do cancer cells activate glycolysis despite the presence of oxygen?

Treatment options



cancer cells are removed	administration of drugs	ionizing radiation

External radiotherapy

Internal radiotherapy

electromagnetic radiation

particle radiation

brachytherapy

Goal:

1. CURE leads survival
2. PALLIATIVE leads better quality of life

Chances of survival:

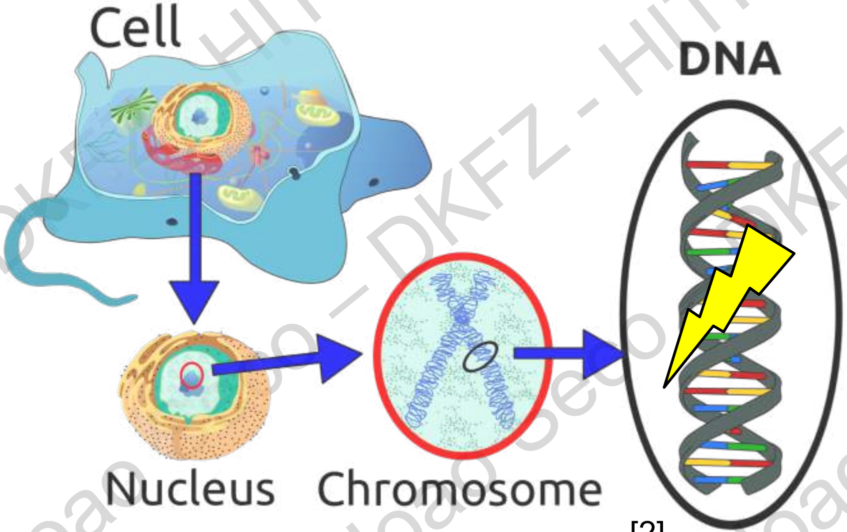
60% of all cancer patients survive more than 5 years [1]

- 10-year prognosis <1% pancreatic cancer
- 10-year prognosis ~84% prostate cancer

[1] A joint publication of the Robert Koch Institute and the German Cancer Associations (Gesellschaft der epidemiologischen Krebsregister in Deutschland e. V.), 11th issue, 2017, accessed on 20.11.2018

Radiotherapy - Biology

> 50% of all cancer patients receive radiotherapy [1]



[2]

Physical phase: 10^{-18} to 10^{-14} s

Elementary physical interactions between ionizing radiation and atom

Chemical phase: 1ms to ~ min

Reactive radicals react with molecules of the cell and change their chemical composition

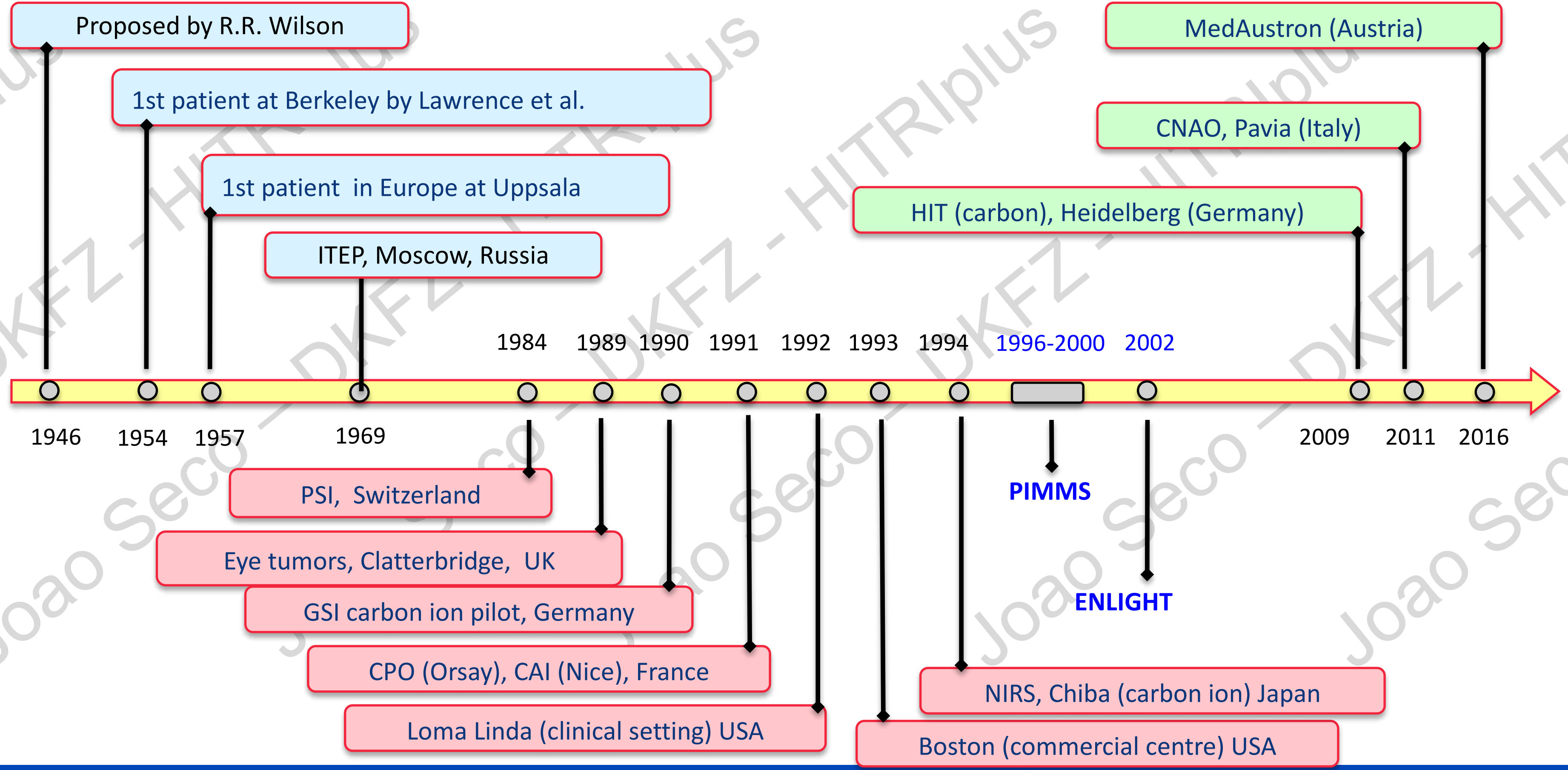
Biological phase: after 1s to years

Cell death, loss of function of the organism

Serial organs: e.g. spinal cord
Parallel organs: e.g. lung

[1] Atun R. Jaffray et. al, Expanding global access to radiotherapy. Lancet Oncol., 2015
[2] Sponk, Tryphon, Magnus Manske, User:Dietzel65, LadyofHats (Mariana Ruiz), Radio89 (https://commons.wikimedia.org/wiki/File:Eukaryote_DNA-en.svg), „Eukaryote DNA-en“, https://creativecommons.org/licenses/by-sa/3.0/legalcode

History of particle therapy



j.seco@dkfz.de

First idea by Robert Wilson in 1946

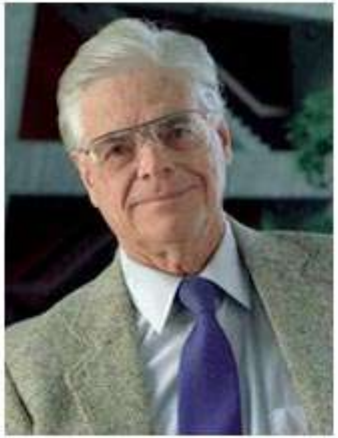
Radiological Use of Fast Protons

ROBERT R WILSON
Research Laboratory of Physics, Harvard University Cambridge, Massachusetts
Accepted for publication in July 1946.

Except for electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in large part, been due to the very short penetration in tissue of protons, deuterons, and alpha particles from present accelerators.

Higher-energy machines are now under construction, however, and the ions from them will in general be energetic enough to have a range in tissue comparable to body dimensions. It must have occurred to many people that the particles themselves now become of considerable therapeutic interest. The object of this paper is to acquaint medical and biological workers with some of the physical properties and possibilities of such rays.

To be as simple as possible, let us consider only high-energy protons: later we can generalize to other particles. The accelerators now being constructed or planned will yield protons of energies above 125 MeV (million electron volts) and perhaps as high as 400 MeV. The range of a 125 MeV proton in tissue is 12 cm., while that of a 200 MeV proton is 27 cm. It is clear that such protons can penetrate to any part of the body.



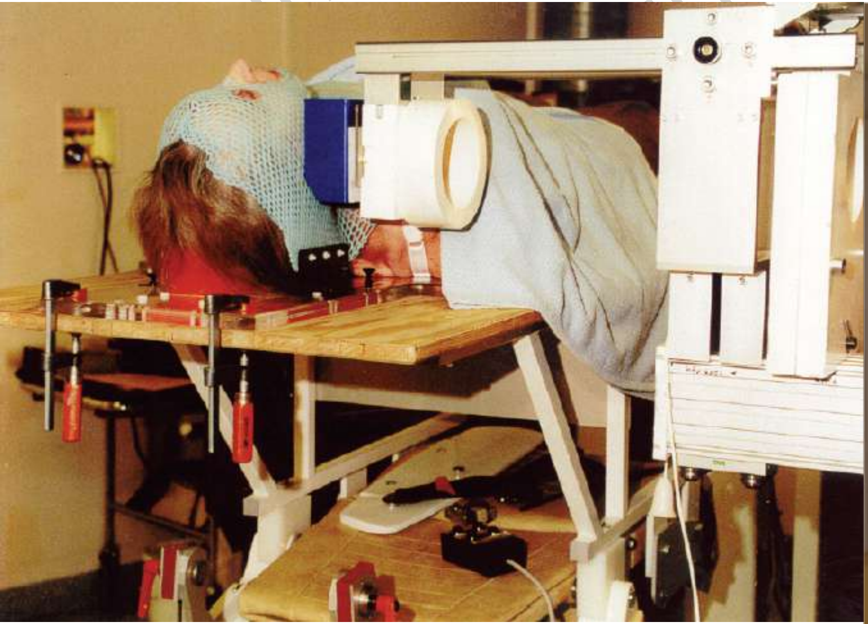
Robert Wilson

- **<u>In 1946 Harvard physicist Robert Wilson suggested</u>:**
  - **Protons can be used clinically**
  - **Accelerators are available**
  - **Maximum radiation dose can be placed within the tumor**
  - **Proton therapy provides sparing of normal tissues**
  - **Modulator wheels can spread narrow Bragg peak**

<u>"The Visionary"</u>

Patient Treatment

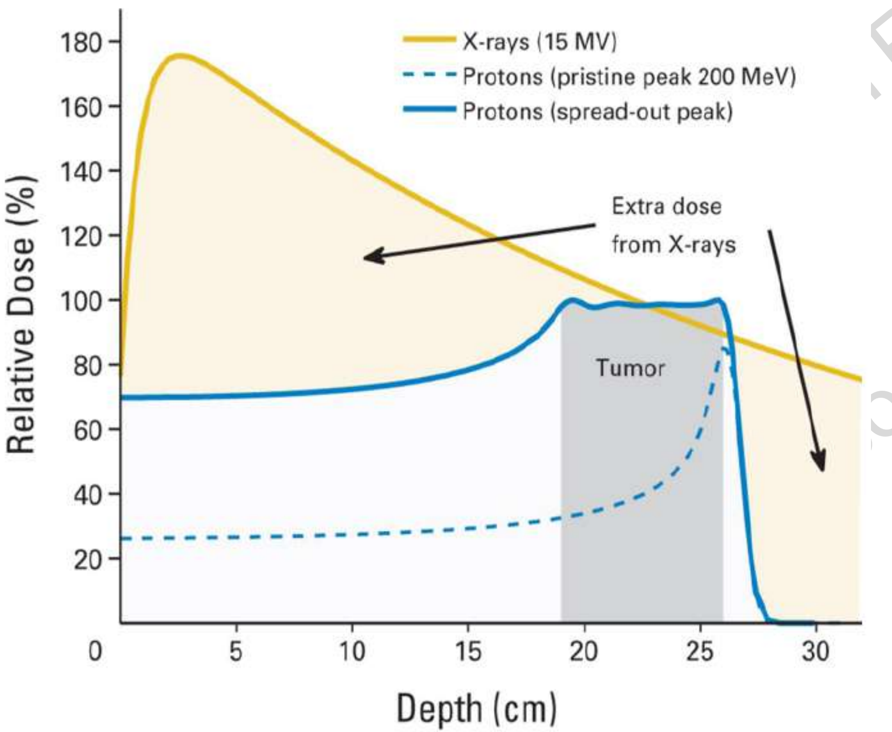
in Labs | **in Hospital**



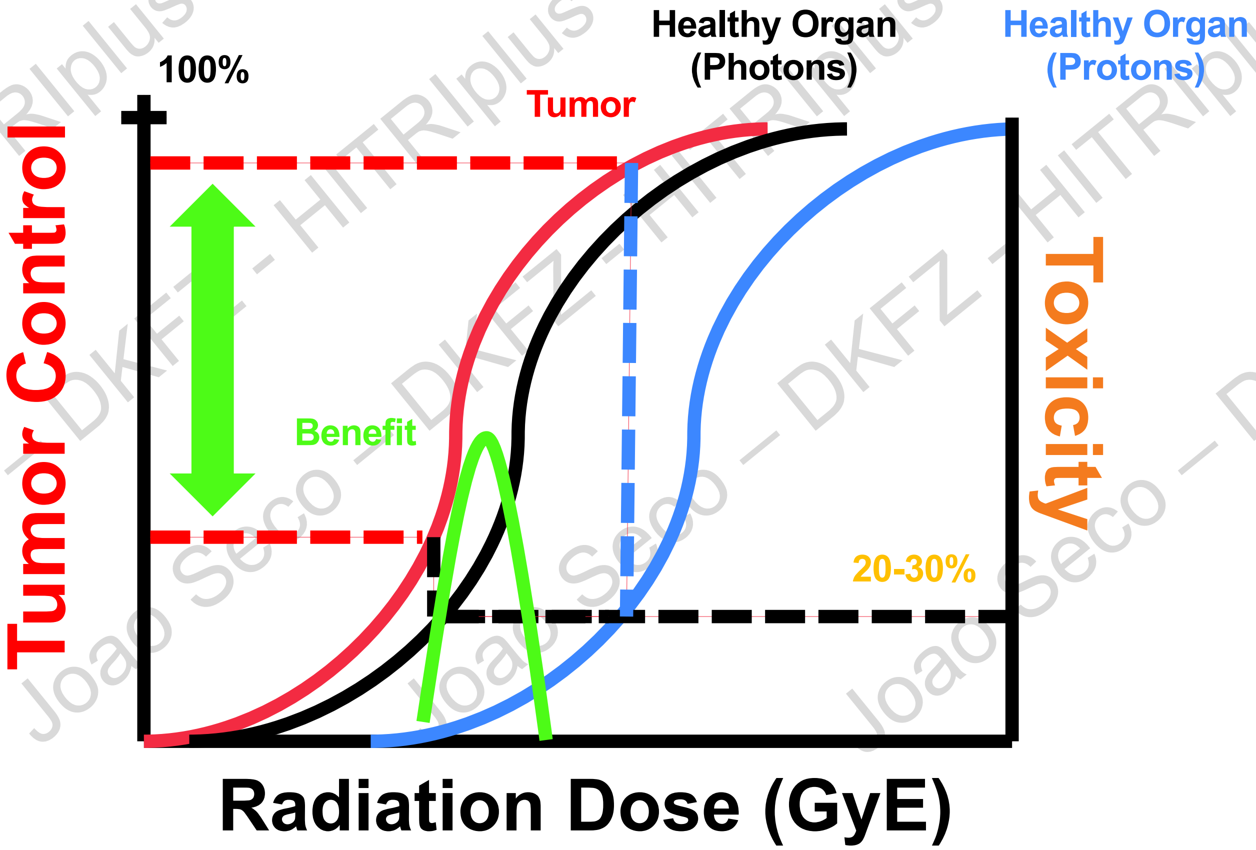
The Advantage of Protons Relative Photons

Proton Depth Dose Properties

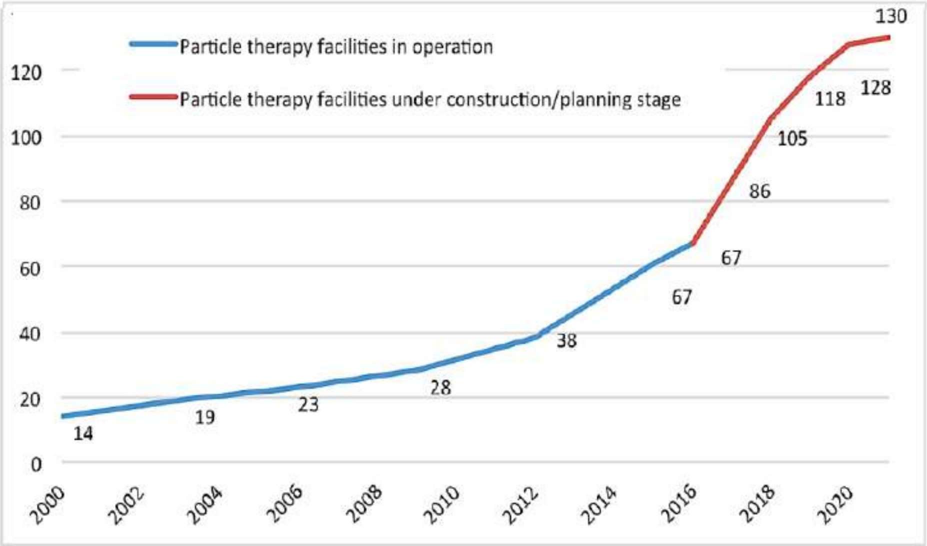
- **Relatively low entrance dose (plateau)**
- **Maximum dose at depth (Bragg peak)**
- **Rapid distal dose fall-off**
- **Energy modulation (Spread-out Bragg peak)**
- **RBE 1.1 close to unity**



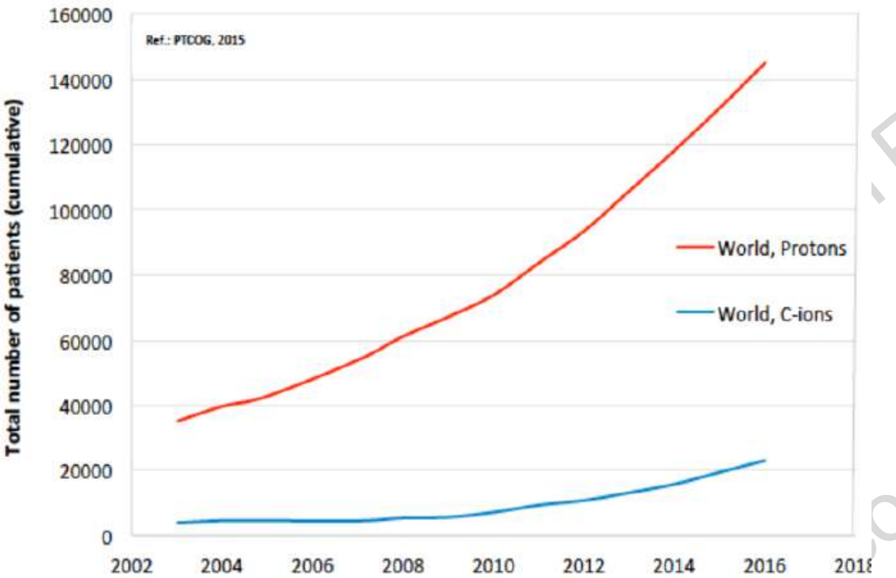
Quantifying the Advantage of Proton Therapy



Increase of ion therapy facilites



[1]



[2]

Currently: 112 facilities in operation worldwide
37 facilities under construction
29 facilities in planning stage

>200 000 patients were treated
<1% compared to radiotherapy with photons

[1] PTCOG – Facilities in Operation. Accessed from https://www.ptcog.ch/index.php/facilities-in-operation
[2] PTCOG – Patient statistics. Accessed from https://www.ptcog.ch/index.php/patient-statistics

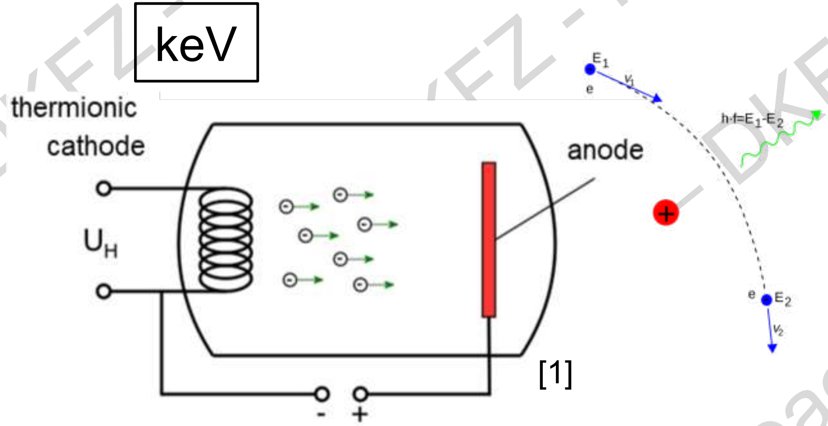
Generation of Photons or Particle Beams

j.seco@dkfz.de

Generation of high-energy photons

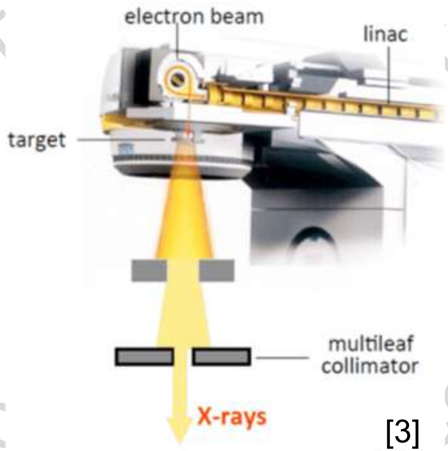
- photons are massless, have no electric charge and travel always at the speed of light
- No “acceleration, but frequency dependent energy”

- But: We can accelerate electrons!



[1]

[2]



[3]

tungsten target
→ bremsstrahlung

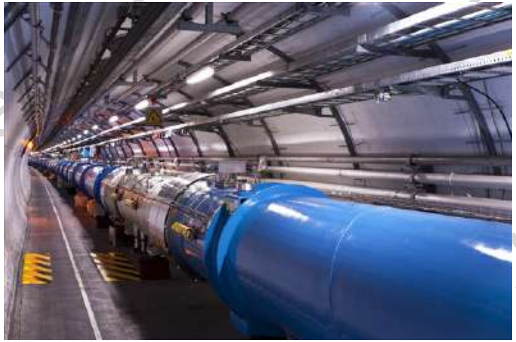
→ electrons loose energy due to bremsstrahlung → **high-energy photons**

[1] Physikunterricht-Online.de – Elektronen im elektrischen Feld. Accessed from https://physikunterricht-online.de/jahrgang-11/elektronen-im-elektrischen-feld/ on 12.02.2021, lettering was adapted
[2] Mouzi (https://commons.wikimedia.org/wiki/File:Linac.jpg), „Linac“, https://creativecommons.org/licenses/by-sa/3.0/legalcode
[3] ResearchGate – Figure – The linac (a), the magnets that deflect the electron beam by 270°. Accessed from https://www.researchgate.net/figure/The-linac-a-the-magnets-that-deflect-the-electron-beam-by-270-the-target-and-the_fig3_335972529 on 12.02.2021

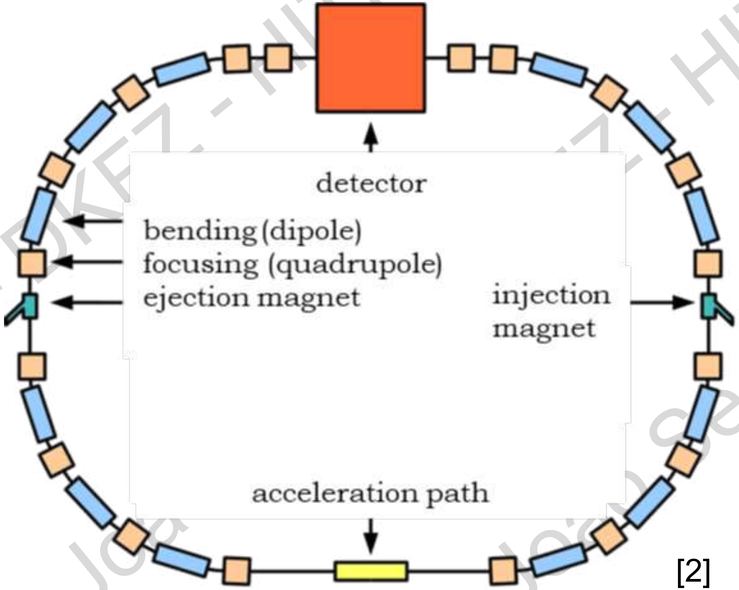
Particle accelerator

How do we generate high energy protons or ions?

- acceleration due to electric fields
- linear or circular accelerator (depending on the required energy)
- e.g. Large Hadron Collider LHC (CERN)



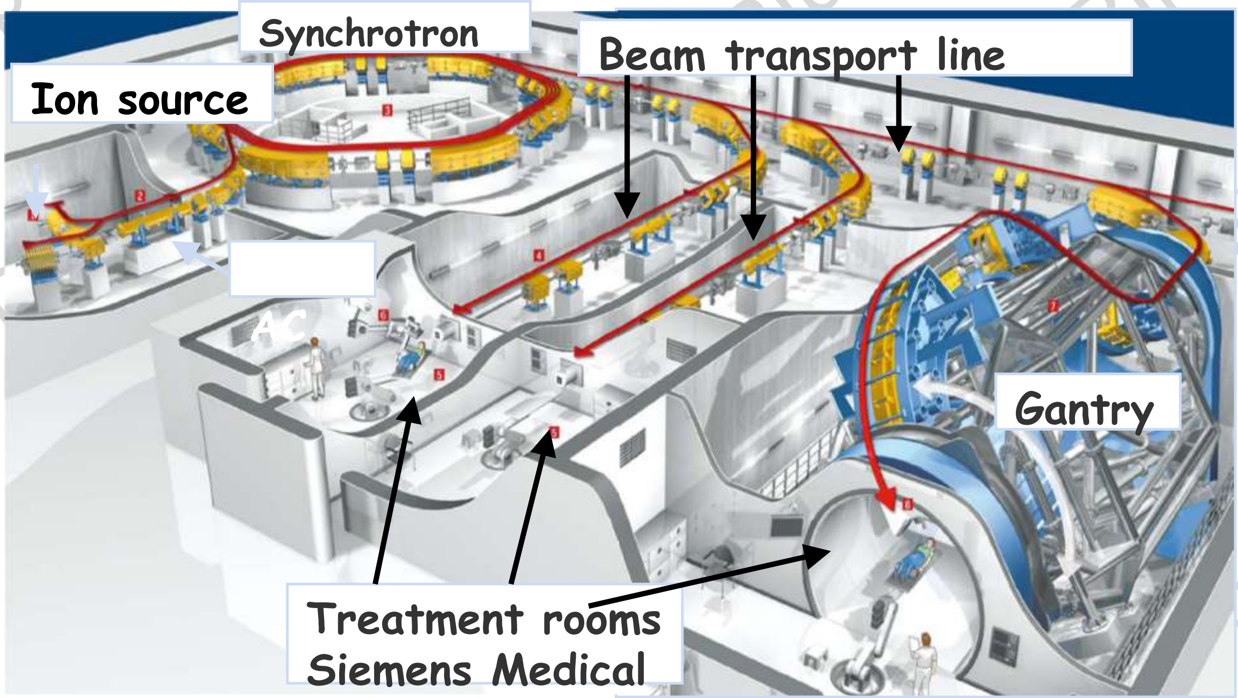
[1]



[2]

Large accelerators are necessary

- Heidelberg Ion-Beam Therapy Center (HIT)

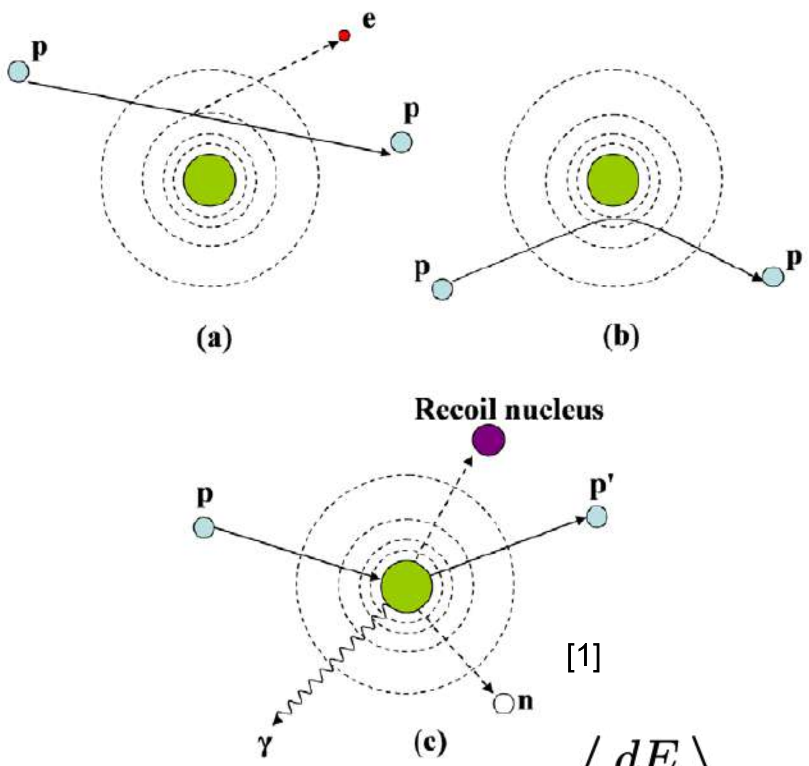


[1]

- First carbon facility with a gantry
- First patient treatment in 2009

[1] Universitätsklinikum Heidelberg – HIT Broschüre - HIT Ionentherapieanlage. Accessed from https://www.klinikum.uni-heidelberg.de/fileadmin/hit/dokumente/HIT_Broschuere.pdf on 12.02.2021

Particle dose (protons/ions)



[1]

(a) Coulomb scattering: proton kicks electron → energy loss

(b) deflection in the electrical field

(a) proton hits nucleus and is absorbed → secondary particles are created

- loss of energy mainly due to (a)
- described by Bethe-Bloch formula

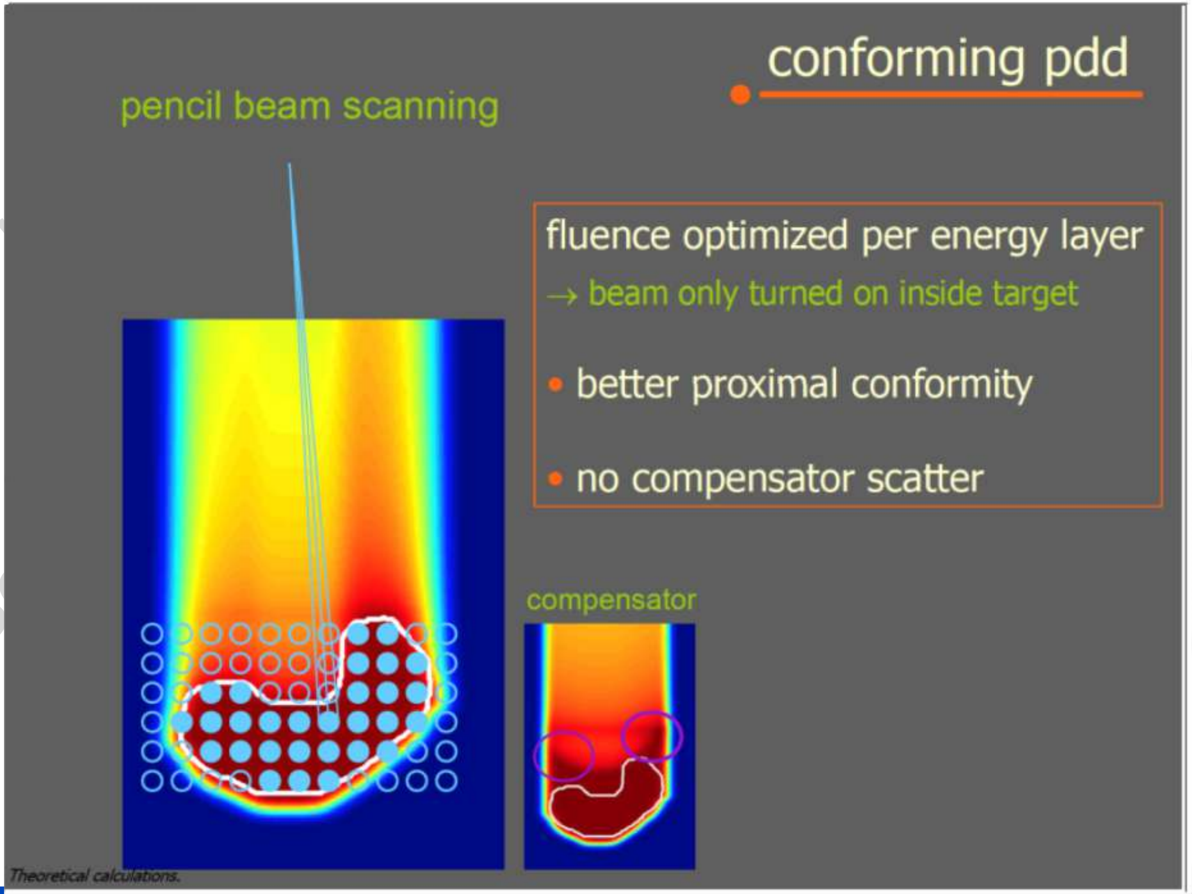
$$-\left\langle \frac{dE}{dx} \right\rangle = \frac{4\pi}{m_e c^2} \cdot \frac{nz^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0} \right)^2 \cdot \left[\ln\left(\frac{2m_e c^2 \beta^2}{I \cdot (1-\beta^2)} \right) - \beta^2 \right]$$

[1] Newhauser, D. W., & Zhang, R. (2015, April 21). The physics of proton therapy. 60(8). Physics in Medicine & Biology, p. 158.

Delivery Methods
Passive versus Pencil Beam Scanning

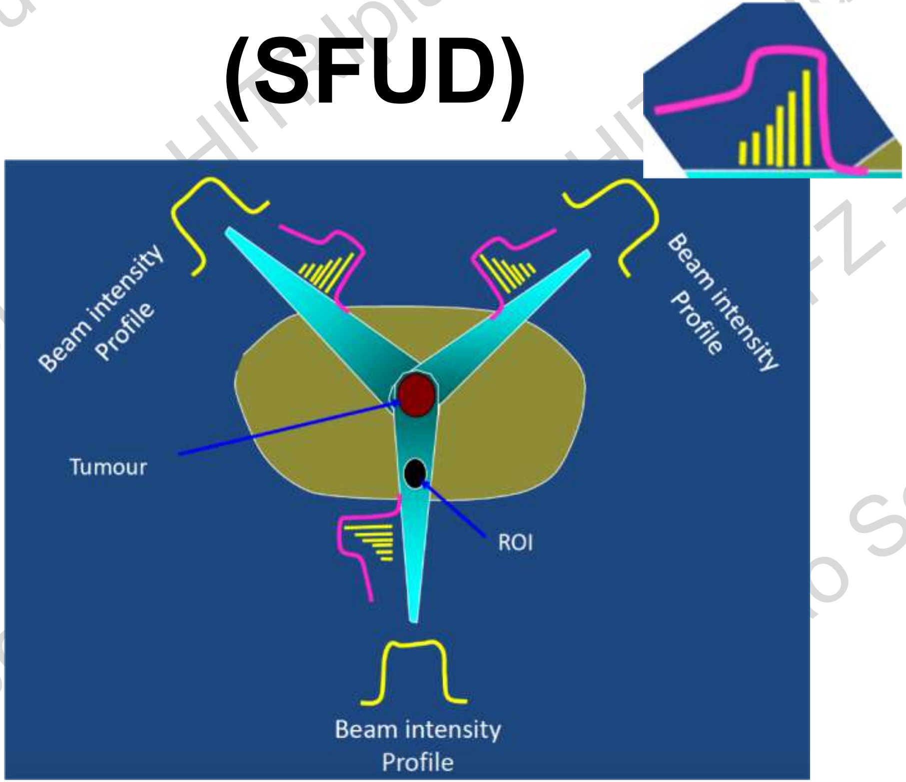
Massachusetts General Hospital (MGH)

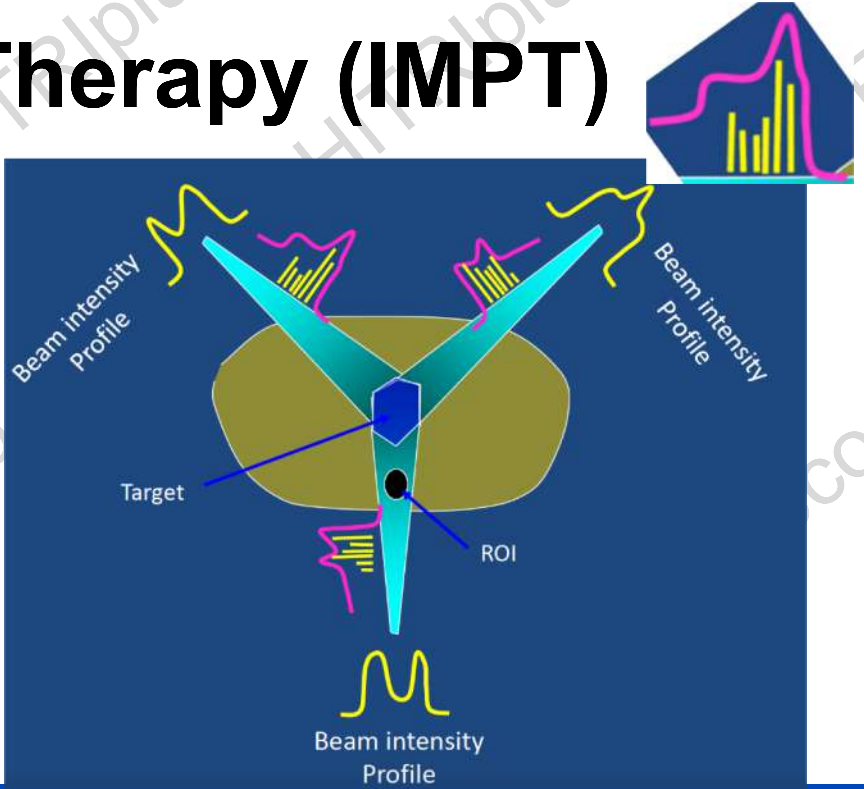
Passive Scattering and Pencil Beam Scanning (PBS)



Single Field Uniform Dose (SFUD)

Intensity Modulated Proton Therapy (IMPT)

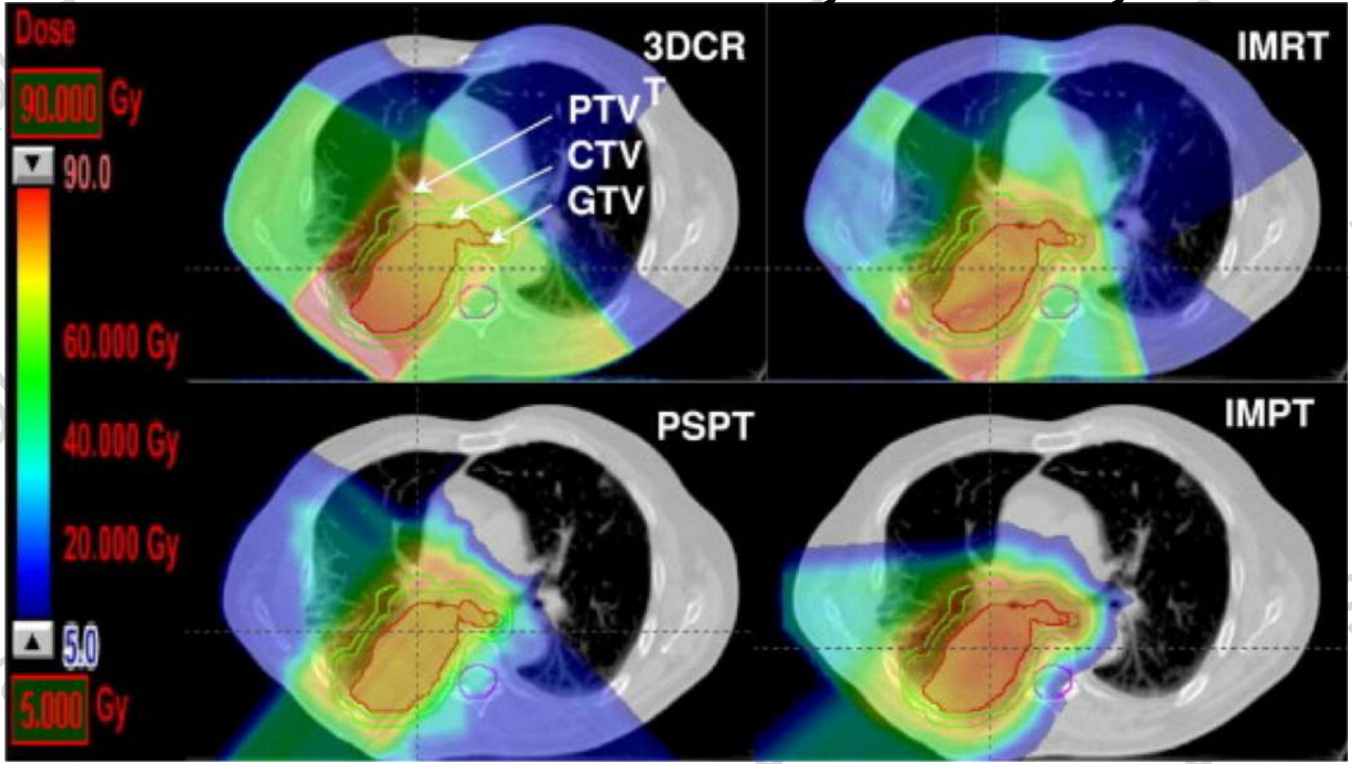




Potential of IMPT vs 3DCR, IMRT, PSPT

Photons

Protons

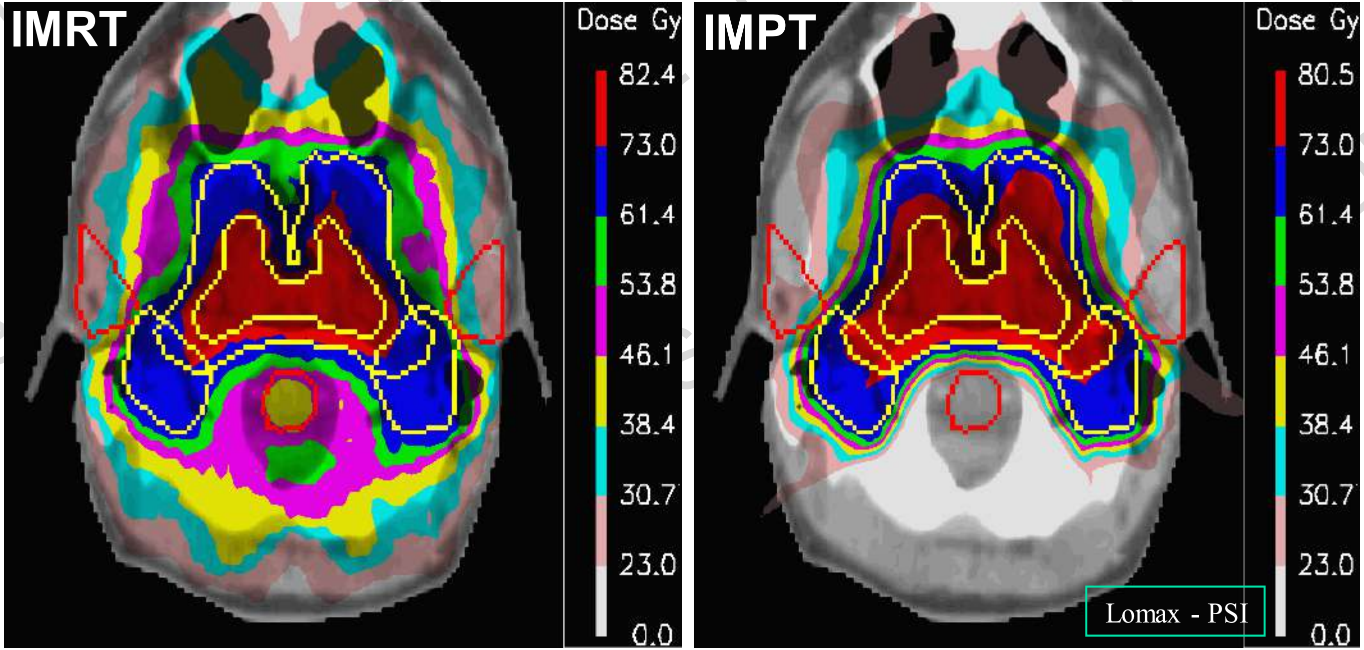


Courtesy of Radhe Mohan

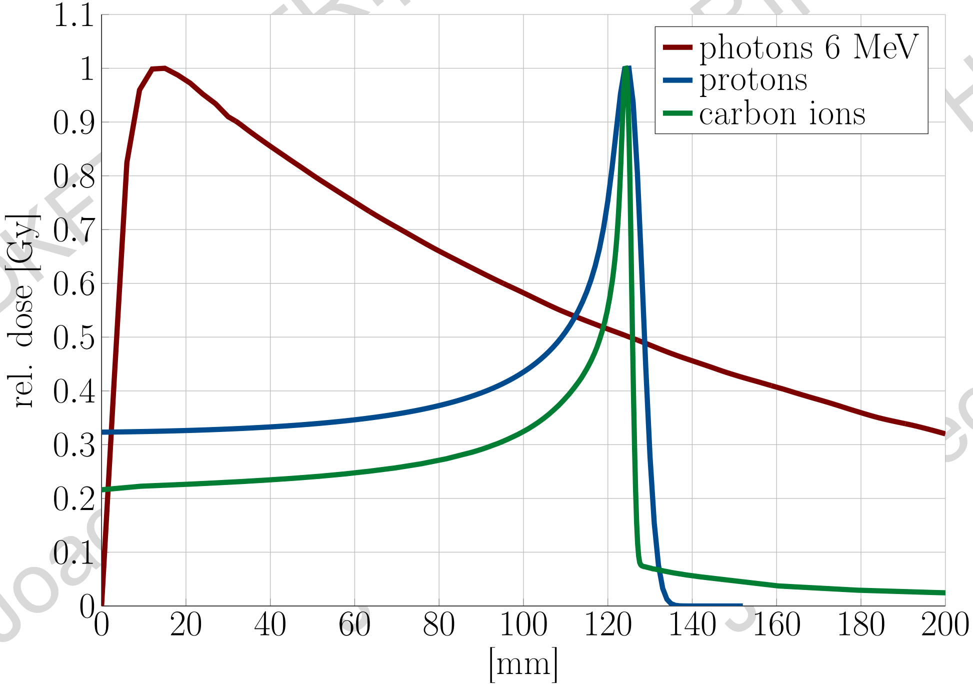
Proton Therapy Derives its Potential to Improve Clinical Outcomes from the Physical Properties of Protons

→“Compact” dose distributions

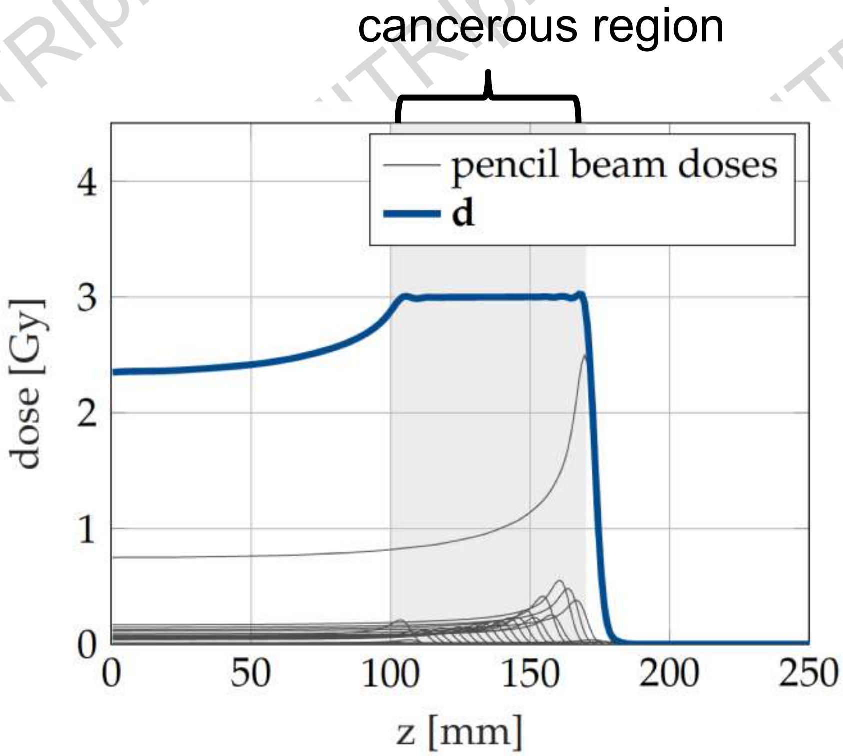
Nasopharynx Treatment Plans



Why bother with particle therapy?

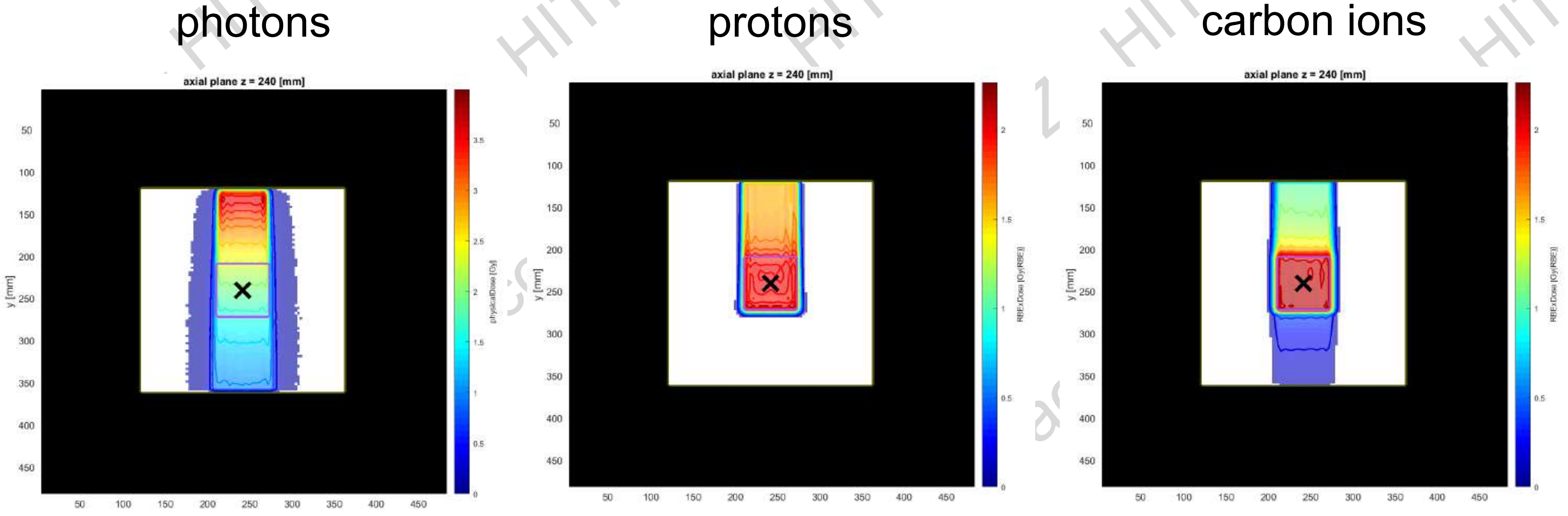


penetration depth



Why bother with particle therapy?

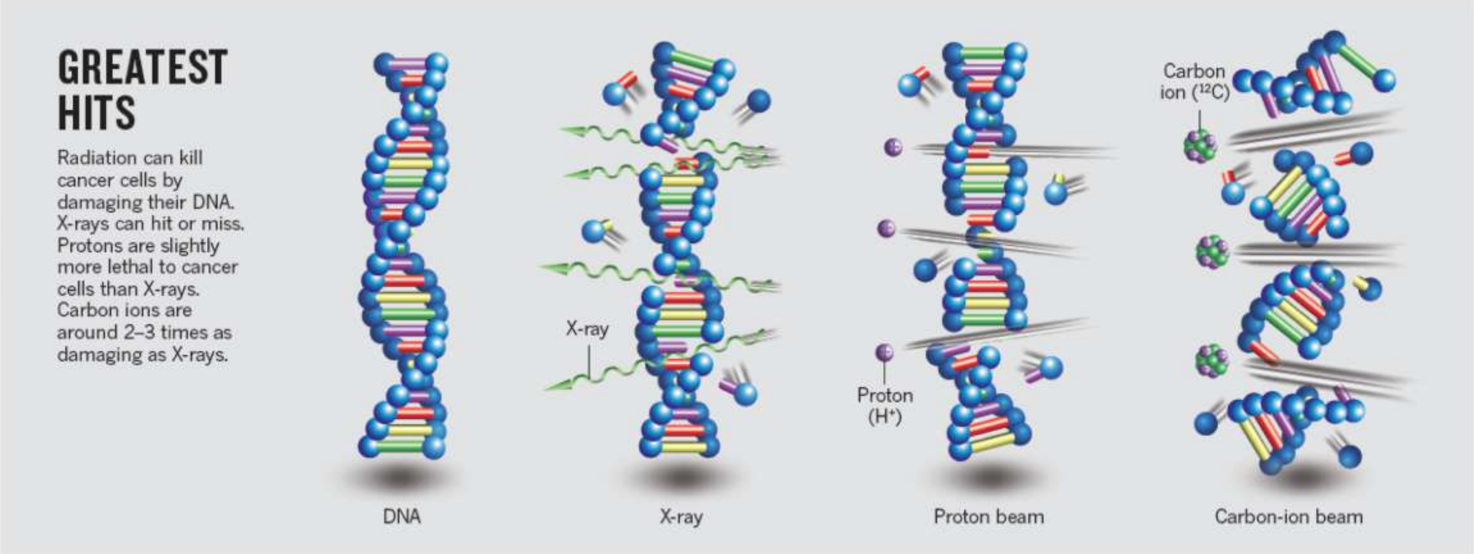
- We always risk damaging healthy tissue "on the way"...



.... but it looks quite good for a particle beam ☺

Why bother with carbon ions?

photons protons carbon ions



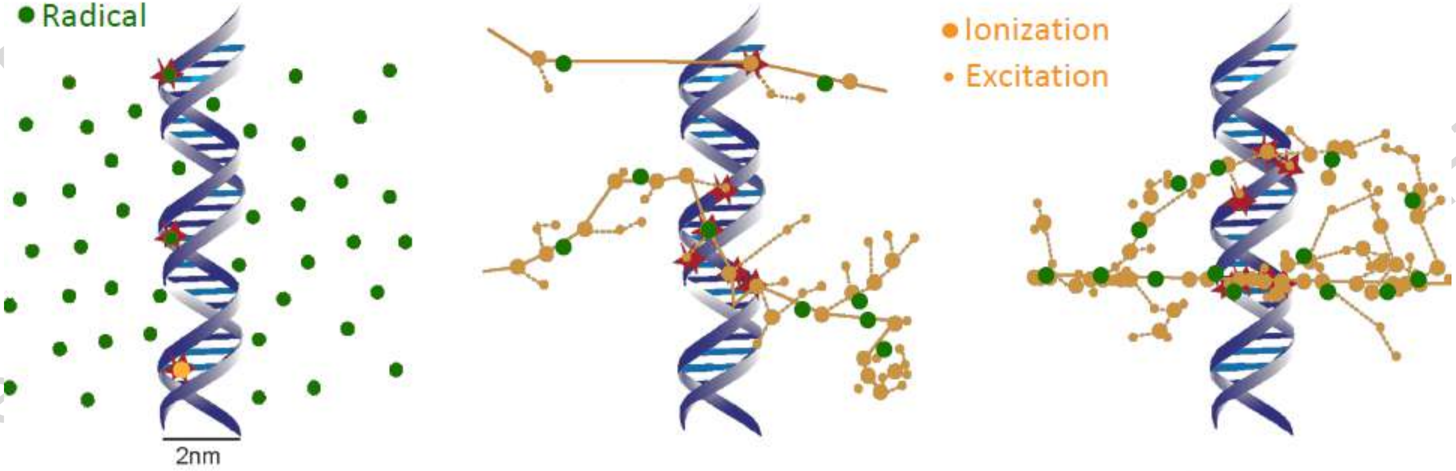
[1]

- Energy release is **localized** to a varying extent. ^{12}C is 12 times heavier than p^+
- Heavy ions generate locally more severe damage → more difficult to repair

[1] Marx, V. (2014, April 4). Sharp shooters. 508. Nature, p. 137.

DIRECT AND INDIRECT ACTION

The biologic effects of radiation result principally from damage to deoxyribonucleic acid (DNA), which is the critical target, as described



γ-radiation | Low LET radiation | High LET radiation

Low and homogeneous ionization density / radical production
→ Random distribution of indirect damage
→ Easier to repair by cell!

LET ↗

High and localized ionization density / (radical production)
→ Clustered/Complex DNA Damage
→ Very difficult to repair by cell!

FLASH Irradiation Protects Organs

FLASH Studies

Studies	1960s-70s		2010s-20s	
In-Vitro (2D Assay)	Town 1967 Berry 1969 Prempree 1969 Berry 1972 Weiss 1974 Purrott 1977	HeLa Cells HeLa and CHL Cells Human Lymphocytes HeLa and Murine Leuk. E.Coli B Cells Human Lymphocytes	Adrian 2019 Buonanno 2019	DU145 (Prostate) IMR90 (Normal Lung Fibroblasts)

FLASH Studies

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In-Vivo (Animal)	Hornsey 1966 Hornsey 1971	Mice/Whole Body (LD50/4) Mice/Whole Body (LD50/4)	Favaudon 2014 Zlobinskaya 2014 Montay-Gruel 2017 Beyreuther 2018 Vozenin 2018 Bourhis 2019 Montay-Gruel 2019 Pawelke 2021	Mice/Lung and HBCx-12A/Hep-2 Mice/FaDu Tumor Xenograft Mice/Brain Zebrafish Embryos Mini-Pig and Cat/Skin Human/Skin-Lymphoma Mice/Brain Zebrafish Embryos

FLASH Studies

Studies	1960s-70s		2010s-20s	
In-Vitro (2D Assay)	Town 1967	HeLa Cells	Adrian 2019	DU145 (Prostate)
	Berry 1969	HeLa and CHL Cells	Buonanno 2019	IMR90 (Normal Lung Fibroblasts)
	Prempree 1969	Human Lymphocytes		
	Berry 1972	HeLa and Murine Leuk.		
	Weiss 1974	E.Coli B Cells		
	Purrott 1977	Human Lymphocytes		
In-Vivo (Animal)	Hornsey 1966	Mice/Whole Body (LD50/4)	Favaudon 2014	Mice/Lung and HBCx-12A/Hep-2
	Hornsey 1971	Mice/Whole Body (LD50/4)	Zlobinskaya 2014	Mice/FaDu Tumor Xenograft
			Montay-Gruel 2017	Mice/Brain
			Beyreuther 2018	Zebrafish Embryos
			Vozenin 2018	Mini-Pig and Cat/Skin
			Bourhis 2019	Human/Skin-Lymphoma
			Montay-Gruel 2019	Mice/Brain
			Pawelke 2021	Zebrafish Embryos
Models OR Simulations	Town 1967	Experiment/Model	Pratx 2019	Model
	Berry 1969	Experiment/Model	Spitz 2019	Model
	Weiss 1972	Experiment/Model	Labarbe 2019	Model
	Weiss 1974	Experiment/Model	Abolfath 2020	Model
	Ling 1975	Model	Petersson 2020	Model (based on Adrian 2019)

Models Proposed to Explain FLASH

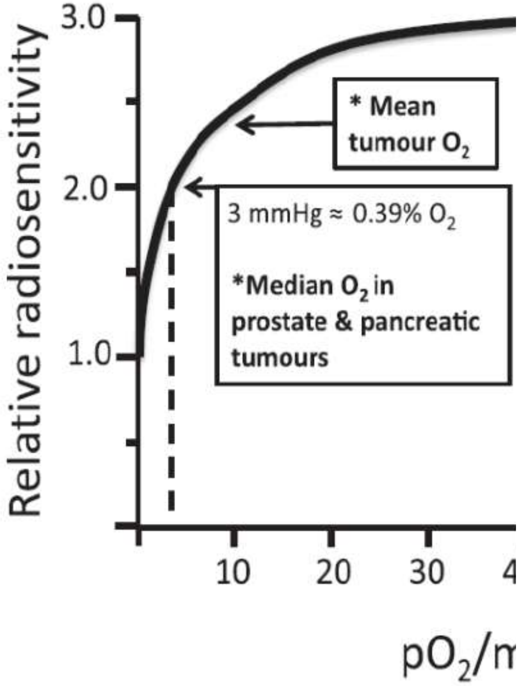
FLASH MODEL	1960s-70s	2010s-20s
Oxygen Depletion	Town 1967 Weiss 1974 Ling 1975 Purrott 1977	Favaudon 2014 Zlobinskaya 2014 Montay-Gruel 2017 Beyreuther 2018 Vozenin 2018 Adrian 2019 Buonanno 2019 Bourhis 2019 Montay-Gruel 2019 Petersson 2020 Pratx 2019 Pawelke 2021

FLASH Radiation

In-Vitro Studies

FLASH Irradiation of Cancer Cells 1960s-70s

Oxygen Enhancement Ratio (OER)



McKeown, Br J Radiol 2014; 87: 20130676

Radiation Clonogenic Assay: Survival Fraction vs Dose

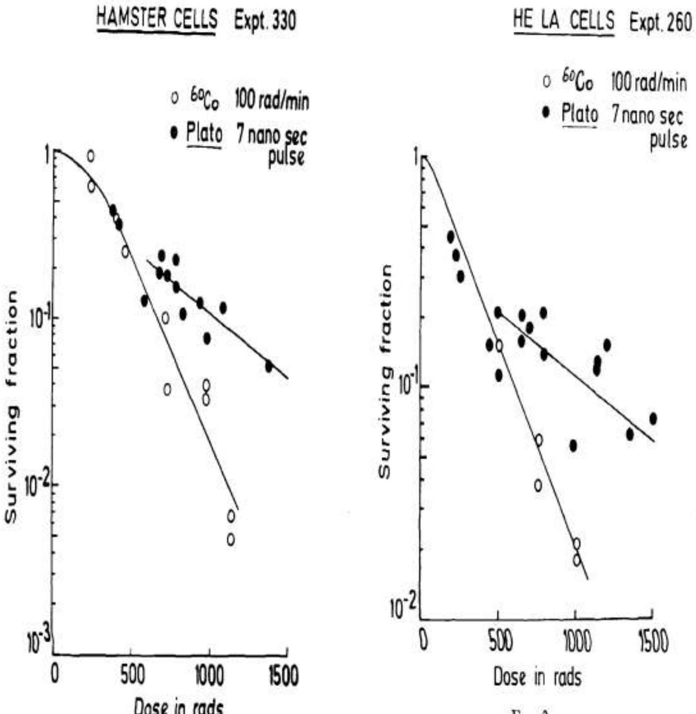


FIG. 2.

Berry et al, Br J Radiol 1969; 42 102-104

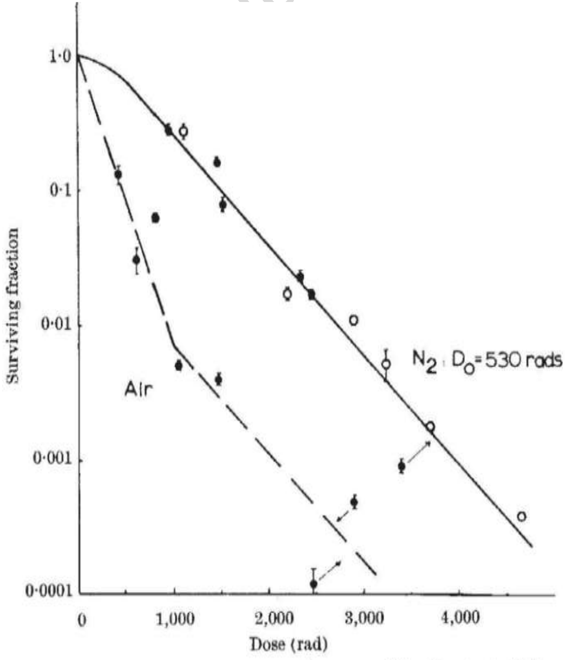


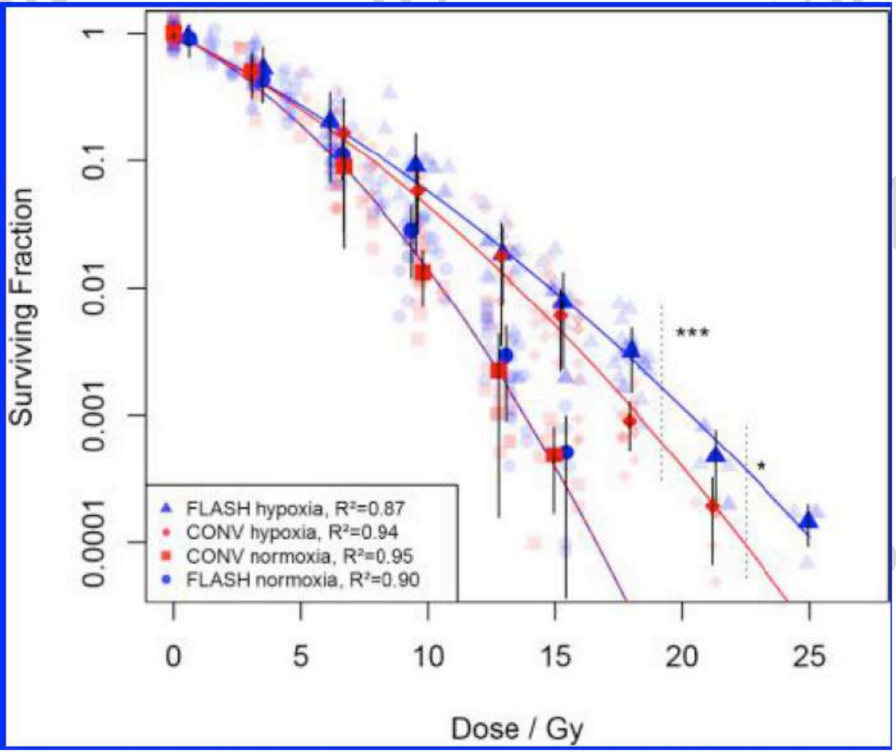
Fig. 2. HeLa cell survival curves under gas equilibration by bubbling air or nitrogen through the suspensions. The initial slope of the broken line is that of Fig. 1, and the second portion was drawn parallel to the nitrogen line. ●, One pulse; ○, two pulses.

Town et al, Nature 215 1967 847-848

FLASH Irradiation of Cancer Cells 2010s-20s

Radiation Clonogenic Assay: Survival Fraction vs Dose

2019 Prostate DU145



Adrian, Br J Radiol 2019; 93: 20190702

1967 Cervical HeLa

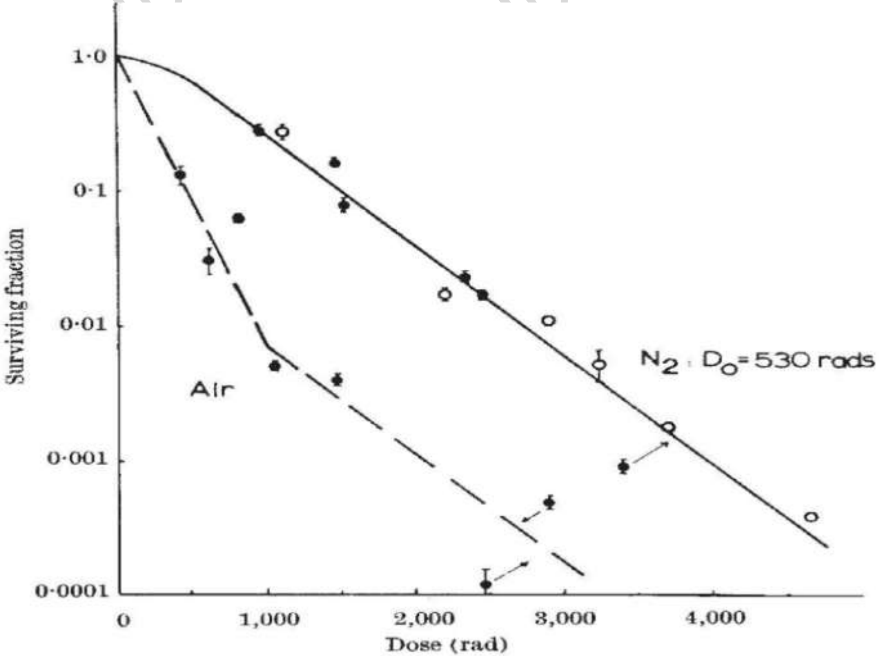


Fig. 2. HeLa cell survival curves under gas equilibration by bubbling air or nitrogen through the suspensions. The initial slope of the broken line is that of Fig. 1, and the second portion was drawn parallel to the nitrogen line. ●, One pulse; ○, two pulses.

Town et al, Nature 215 1967 847-848

FLASH Irradiation of Cancer Cells 1960s-70s

Minimum Dose
5-12 Gy

FLASH Rate
10^7 Gy/s

- Dose-rates higher than ~10^7 Gy/s and 5 – 10 Gy deplete cellular oxygen
- Some data suggesting changes at lower dose-rates (10^2 Gy/s for *in vivo* studies (FLASH Radiotherapy Normal tissue sparing)
- No data for high LET radiations

Authors (dates)	Experimental system	O...gen depletio... dose, etc.	Radiation type	Dose rate	P... ...ation
Town et al (1967) [2]	HeLa S-3 cells	Above 9 Gy exposu... effect lost for second pulse 2.5×10^{-3} s later	15 MeV electrons	3.5×10^7 Gy s^{-1}	1.3 μs
Prempree et al (1969) [3]	Human lymph...cyte chromoso...l aberratio...	Reduction in yield described	X-rays	4.8×10^8 Gy s^{-1}	n/a
Nias et al (1969) [4]	HeLa	7 Gy	...–14 MeV electron	$<1.8 \times 10^7$ Gy...	1 μs
Berry et al (1969) [5]	HeLa S-3o... and CHL-F	5–10 Gy for short pulses	...MV X-rays up; 3.7 MV X-rays:	10^9 Gy s^{-1}, up to 10^{10} ...y s^{-1}	7 ns pulse, 50 ns pulse
Berry et al (1972) [6]	2 HeLa li...s and m...ne leukae...a	5–10 Gy; partly hypoxic cells develop radiolo-gical hypoxia above 5 Gy	...0 KeV ...lectrons at ...ose rate	10^9 Gy s^{-1}	3 ns
Purrot et al (1977) [7]	Chromos...al aberrat...ns in huma... lympho...es	No increase in yield	...MeV electrons	5×10^6 Gy s...	1 μs
Ling et al (1978) [8]	CHO cells	12 Gy depletion dose; oxygen diffusion to single cells significant after 3×10^{-3} s	...ectrons	10^9 Gy s^{-1}	3 ns
Watts et al (1978) [9]	Cultured V-79 ...ls	Oxygen diffusion to single cells significant after $1–2 \times 10^{-3}$	400 keV electrons	10^9 Gy s^{-1}	n/a

CHO, Chinese hamster ovary; n/a, not ava...

Wilson et al 2012, BJR, 85, e933-39

FLASH: Reduces Normal Tissue Toxicity (2014)

- 4.5 MeV electron or γ-ray irradiated thorax of C57/B6 mice
- The two radiation qualities had similar effectiveness in lung fibrogenesis when delivered at the same conventional dose rate of 1.8 Gy min^{-1}.

Favaudon et al., Sci Trans Med 2014; Commentary in Durante et al., BJR 2018

Building Evidence for FLASH

Clinical Oncology 31 (2019) 407–415

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

ELSEVIER

Overview

Biological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: Sleeping Beauty Awoken

M.-C. Vozenin *†, J.H. Hendry ‡, C.L. Limoli §

*Laboratory of Radiation Oncology/CHUV, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
† Department of Radiation Oncology/Department of Oncology/CHUV, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
‡ Department of Medical Physics and Engineering, Christie Hospital, Manchester, UK
§ Department of Radiation Oncology, University of California, Irvine, California, USA

Received 27 February 2019; received in revised form 8 March 2019; accepted 12 March 2019

Table 1
In vivo studies of FLASH res[illegible]rious normal tissues

Dose (Gy) at conventio[illegible] dose rates	FLASH dos[illegible] rate (Gy/s)	Dose modifying factor	System	Anaesthetic	Assay	Reference
Normal tissues						
11.9	17–83	[illegible]13	Mouse intestine	Nembutal	LD50/5	[3]
14.7	70–210	[illegible]13–1.24	Mouse intestine	?	LD50/5	[14]
24	56–83	[illegible]	Mouse foot skin	Sodium amytal	Early and late reactions	[4]
50	17–170	[illegible]6	Mouse tail skin	None	Necrosis ND50	[5]
22–34	300	[illegible].36	Minipig and cat skin	General anaesthesia	Early and late reactions	[13]
15–17	40	[illegible]8	Mouse lung	Ketamine/xylasine/acepromazine	Fibrosis	[9]
10	$100–10^6$	1.4	Mouse brain	Isoflurane	Memory	[10] Montay-Gruel *et al.* (in revision)

Clinical FLASH Protons

- Manufacturers setting up clinical beams

iba

Flash Irradiation Delivered in a Proteus®ONE Treatment Room

Proton therapy / 11.06.2019

Successful Ultra High Dose Rate delivered at Isocenter in IBA's compact proton therapy solution

Louvain-la-Neuve, Belgium, 11 June 2019 – IBA (Ion Beam Applications SA), the world's leading provider of proton therapy solutions, is pleased to announce the first Flash irradiation in an IBA Proteus®ONE compact gantry treatment room at the Rutherford Cancer Centre Thames Valley in Reading, United Kingdom, on June 8, 2019. This represents another major milestone for IBA and its medical and research partners in their work to lead the development of Flash irradiation.

iba

University Medical Center Groningen, The Netherlands

Flash Irradiation Delivered in a Clinical Treatment Room

Proton therapy / 08.03.2019

Successful Flash Irradiation at Isocenter in IBA's Proteus® Solution Gantry Room

Louvain-la-Neuve, Belgium, 8 March 2019 – IBA (Ion Beam Applications SA), the world's leading provider of proton therapy solutions, is pleased to announce the first Flash irradiation in an IBA gantry treatment room at the University Medical Centre Groningen (UMCG) in The Netherlands. This achievement represents a major milestone in the work that IBA and its medical and research partners are engaged to bring Flash irradiation to clinical treatment.

FLASH Irradiation

Experimental Evaluation of Oxygen Consumption during FLASH Radiation in Photons, Protons and Carbon Ions.

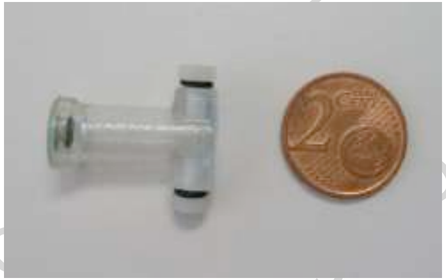
Jeannette Jansen, Raphael Skuza, Jan Knoll, Rachel Hanley, Francesca Pagliari, Stephan Brons, Elke Beyreuther, Jörg Pawelke, Joao Seco
Author address(es) here

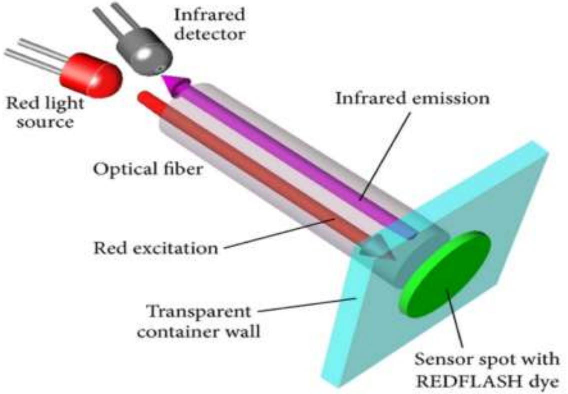
Version typeset November 3, 2020

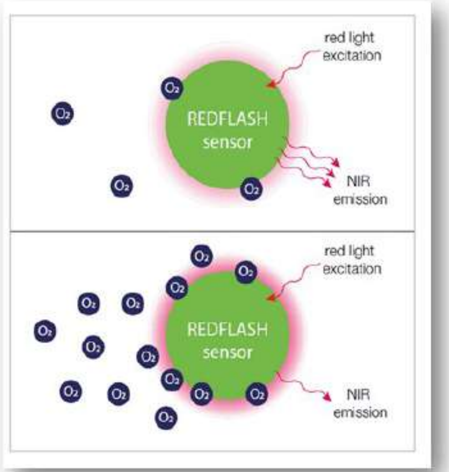
Author to whom correspondence should be addressed: Joao Seco. email: j.seco@dkfz-heidelberg.de

Measure Oxygen Consumption

- sealed water phantom
- optical sensor
- allows for non-invasive measurement
- suitable for all beam geometries

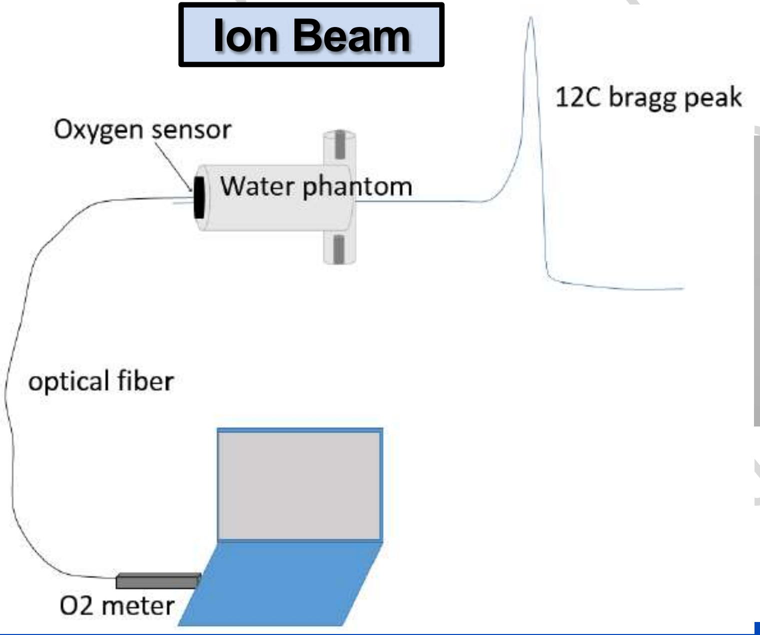


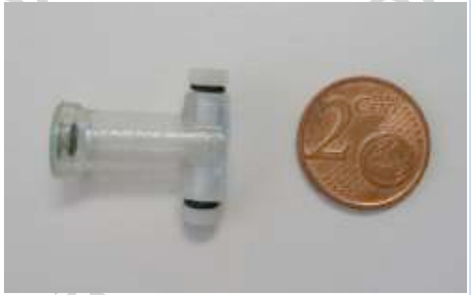


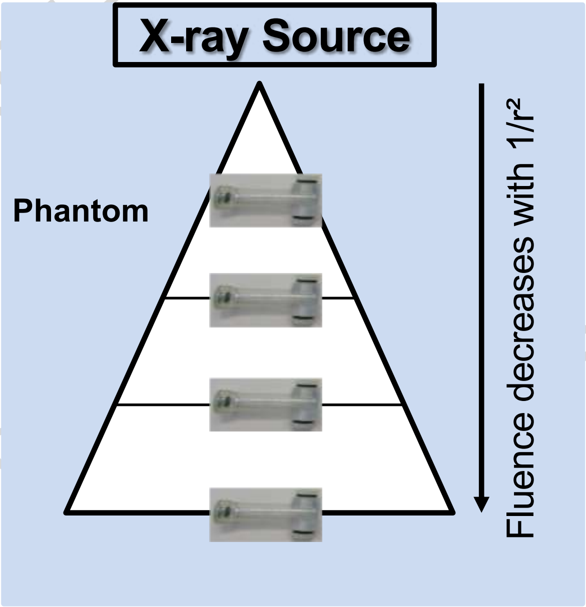


Oxygen Measurement: Oximeter

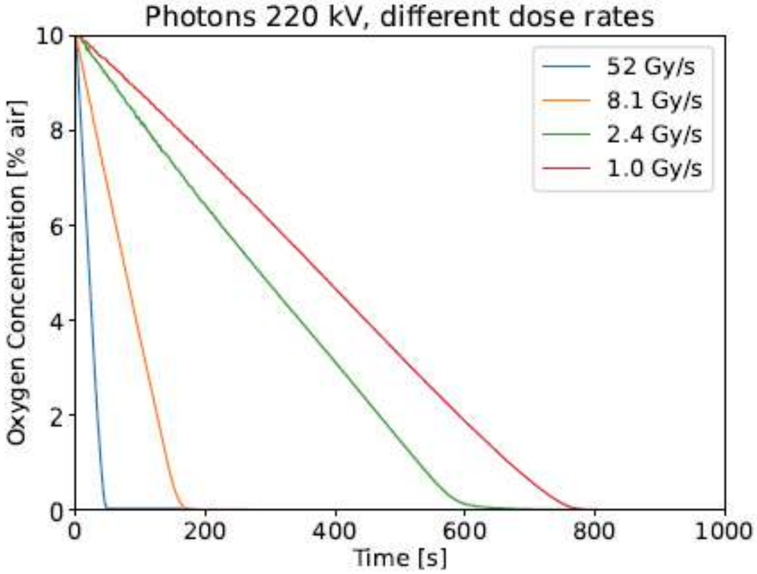
- sealed water phantom
- optical sensor
- allows for non-invasive measurement
- suitable for all beam geometries



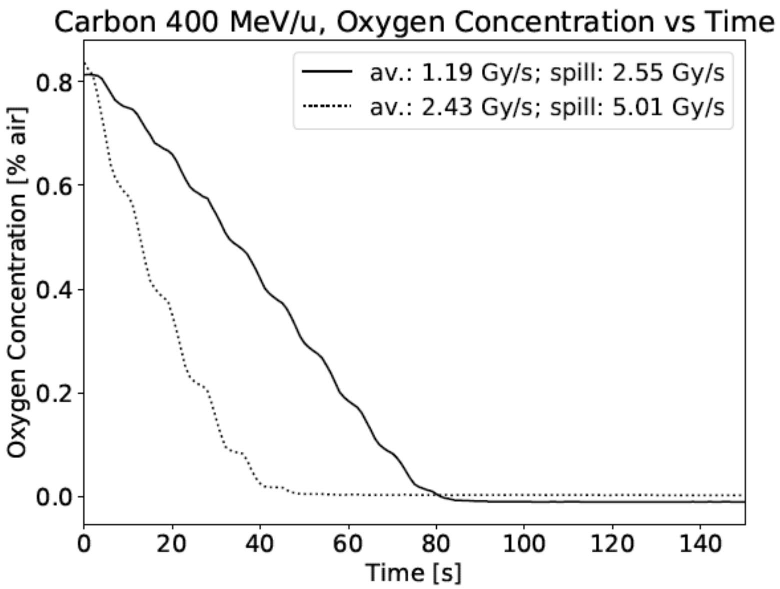




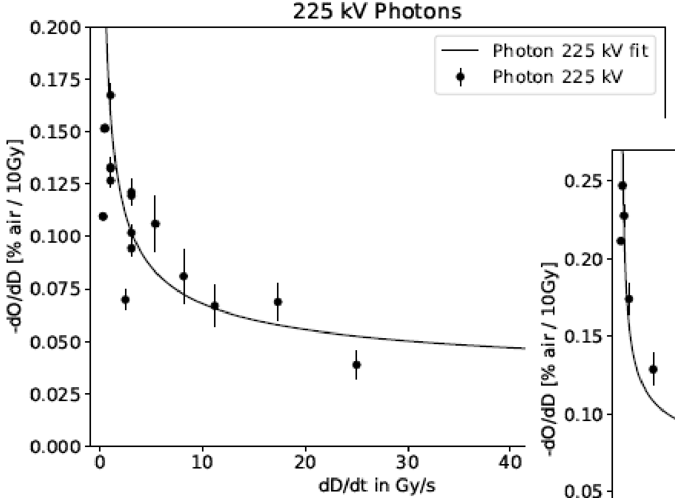
Oxygen Concentration for 220kV Photons

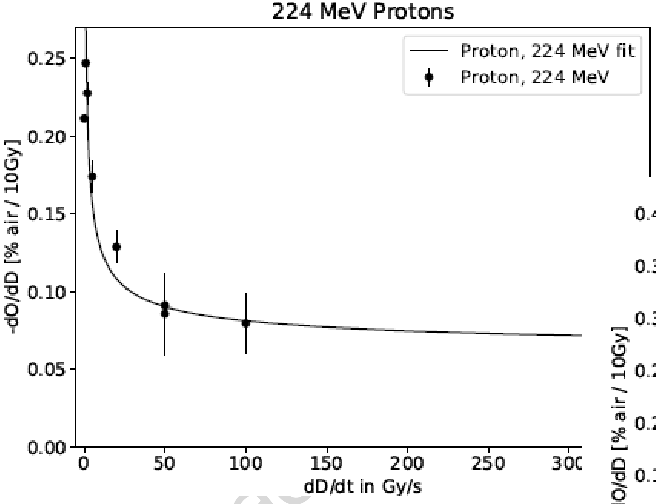


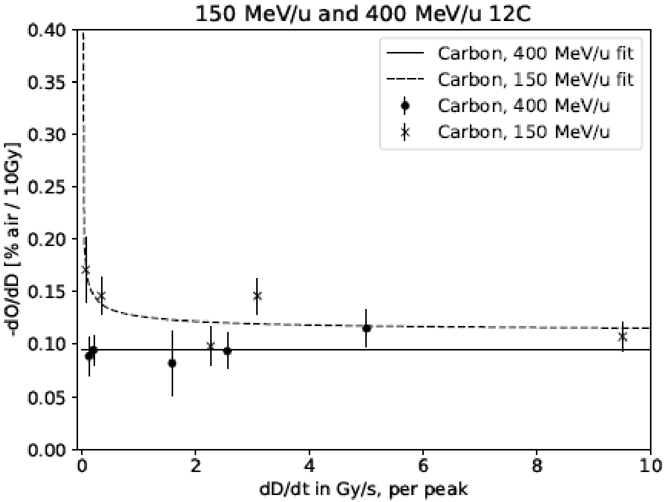
Oxygen Concentration for 400MeV/u Carbon Ions



Oxygen Consumption vs Dose Rate



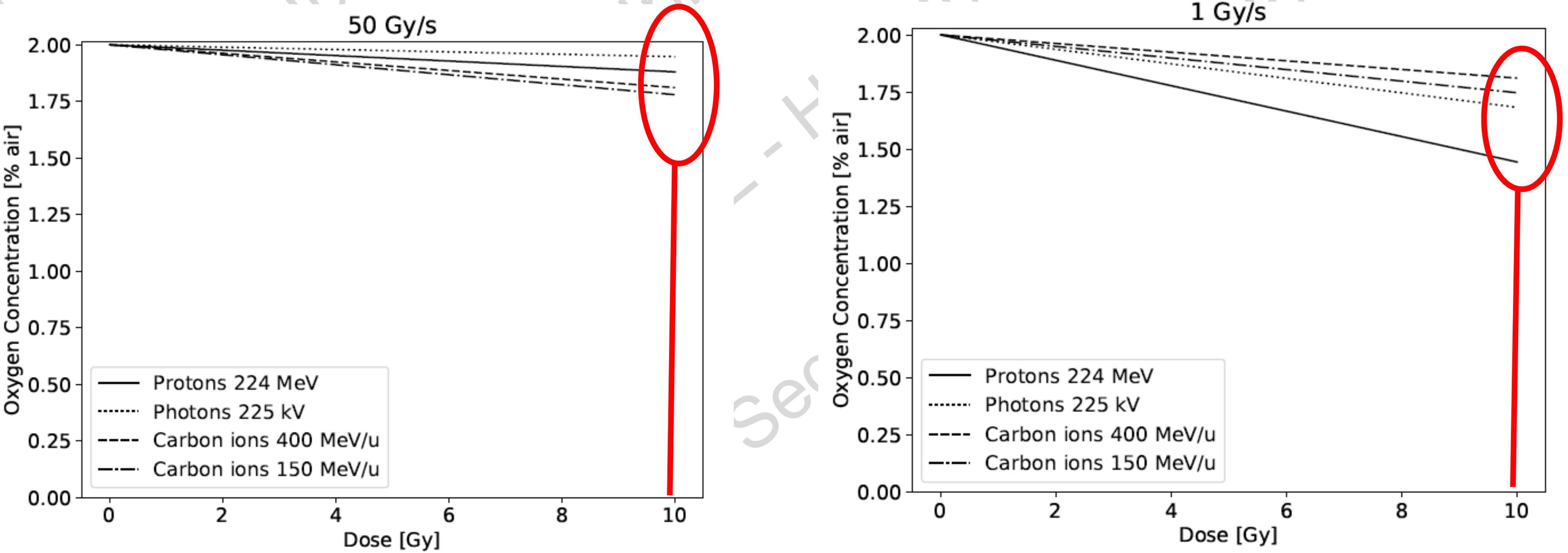




$$e^-_{aq} + e^-_{aq} + 2\,H_2O \longrightarrow H_2 + 2\,OH^-$$

$$e^-_{aq} + O_2 \longrightarrow O_2^{\bullet -}$$

Oxygen Consumption vs Dose



NO Oxygen Depletion @ 10 Gy

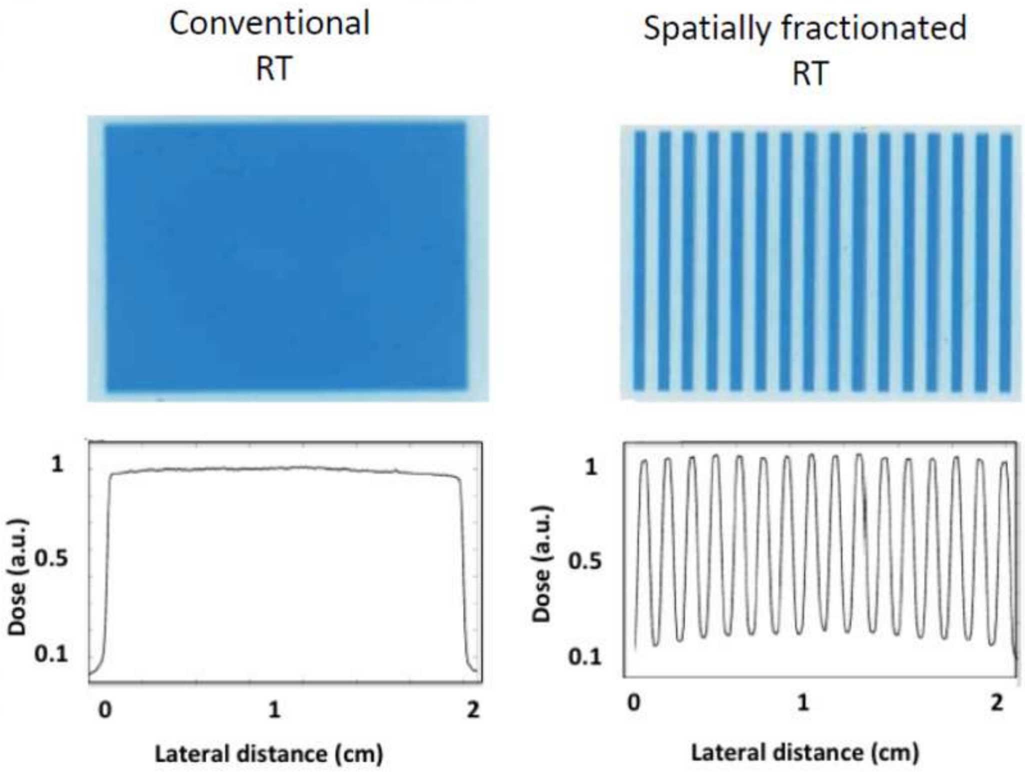
Physics Challenges in Proton Therapy

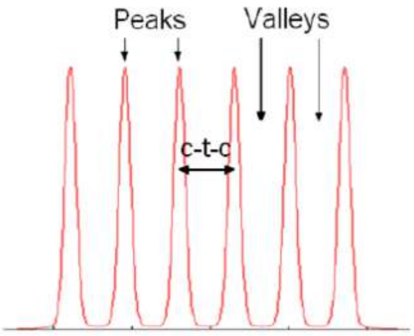
FLASH Irradiation:

- Why does FLASH protect organs and not affect tumor control?
- All clinical applications of FLASH have used 1 beam (e- or p+).
  How do we clinically implement FLASH with multiple beams?

Micro- and Mini-Beam Irradiation Protects Organs

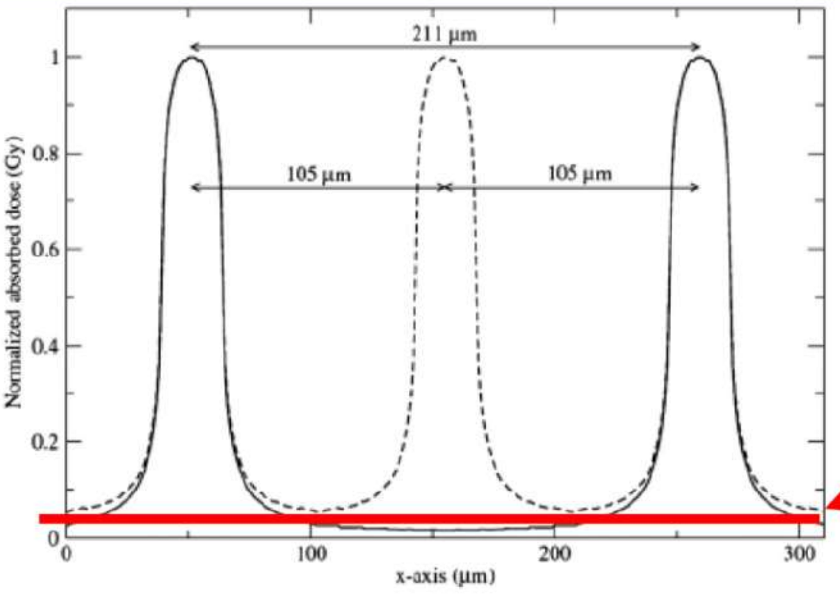
Micro- and Mini-Beam Irradiation





$$PVDR = \frac{D_{\text{peak}}}{D_{\text{valley}}}$$

MRT= extremely high doses delivered in spatially fractionated microplans



Tissue tolerance threshold dose for healthy tissue homogeneous irradiation

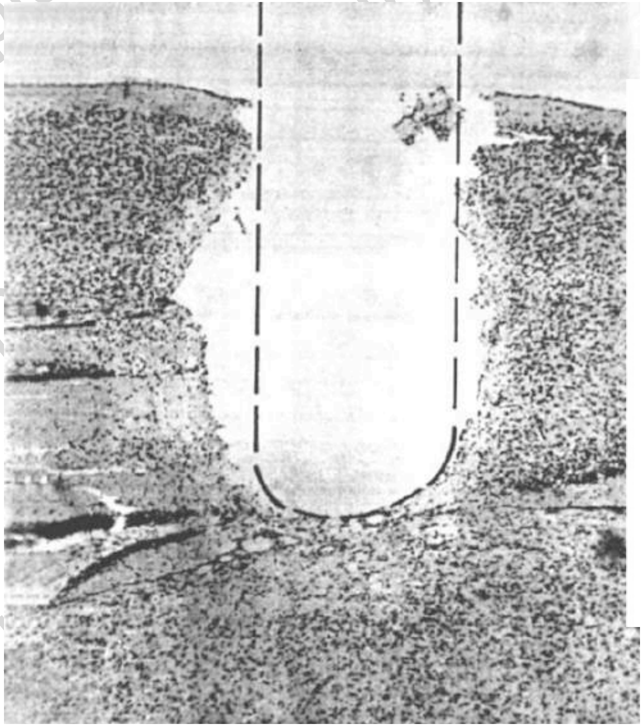
The dose in the valleys that creates a dose offset in the tissues, has to be below the tolerance threshold dose

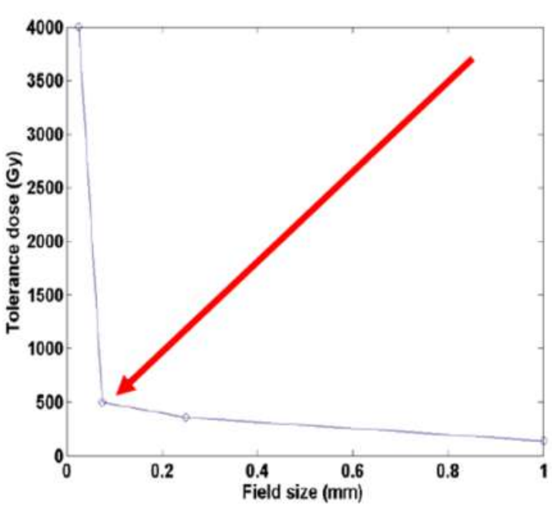
Dose Volume Effect

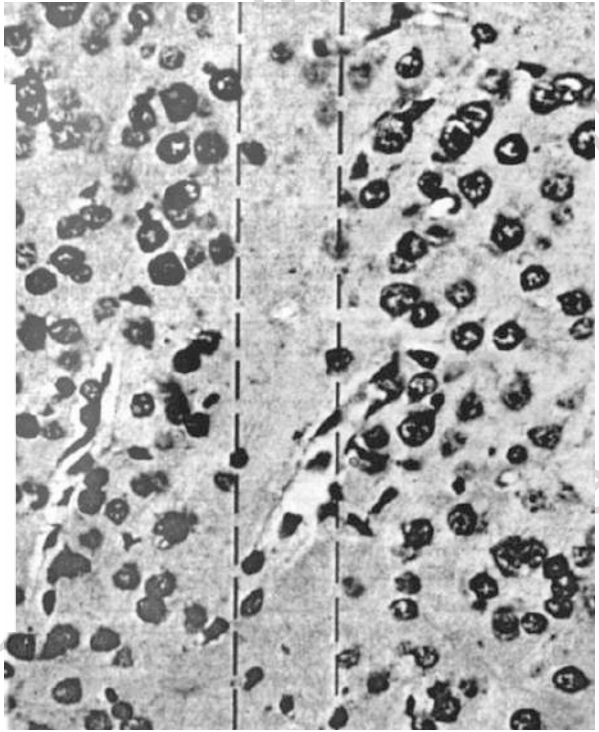
1mm

Mouse Brain
(visual cortex)

25μm





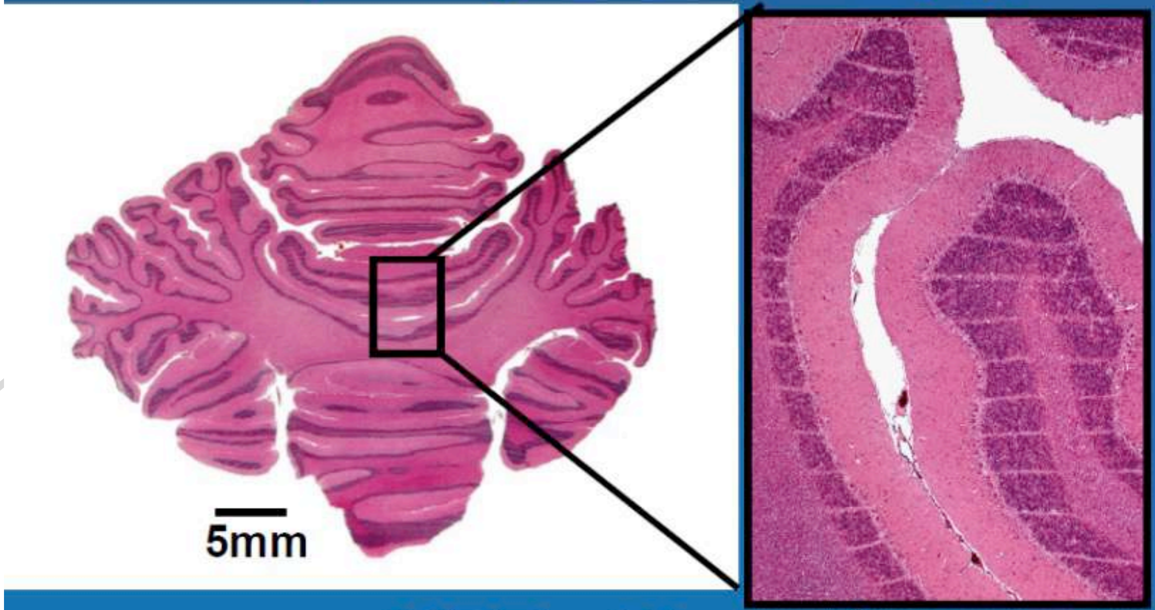


140 Gy

Zeman et al 1961
Radiat Res 15, 496

4000 Gy

Tissue sparing of MRT on piglet cerebellum



300 (625) Gy

25/200 μm ctc

MRT +15 months

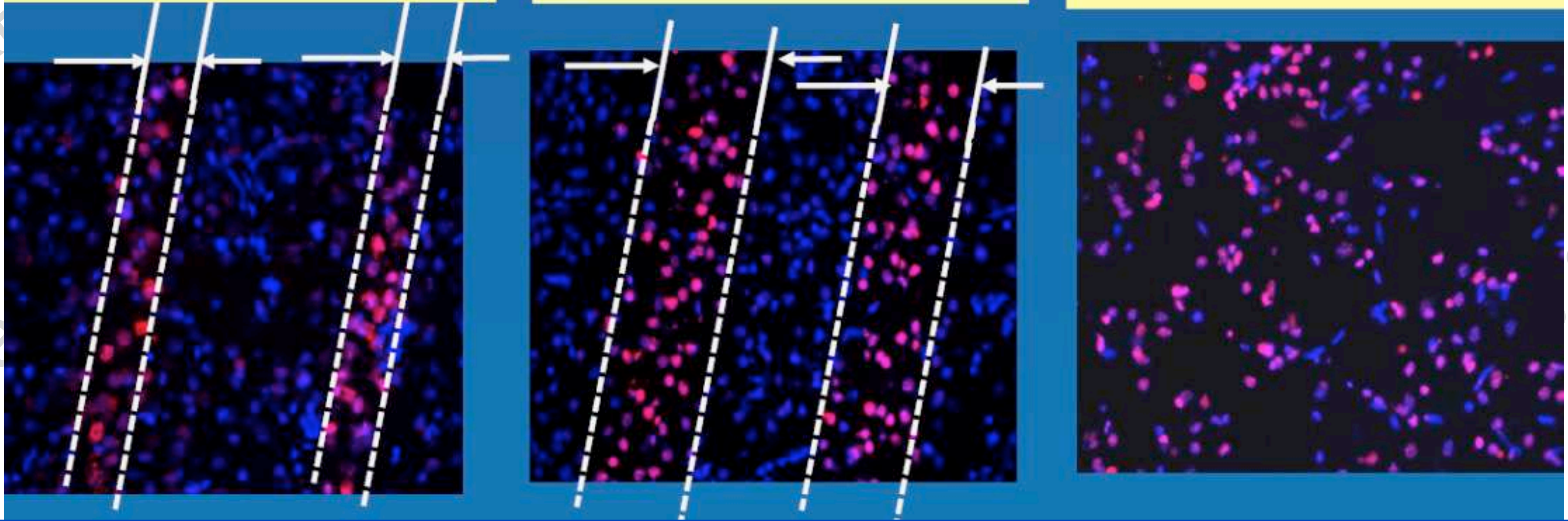
No tissue destruction. Normal appearance of brain and cerebellum

Animals (20 pigs) were kept alive for ~2 years.
No one animal showed CNS damage clinical signs

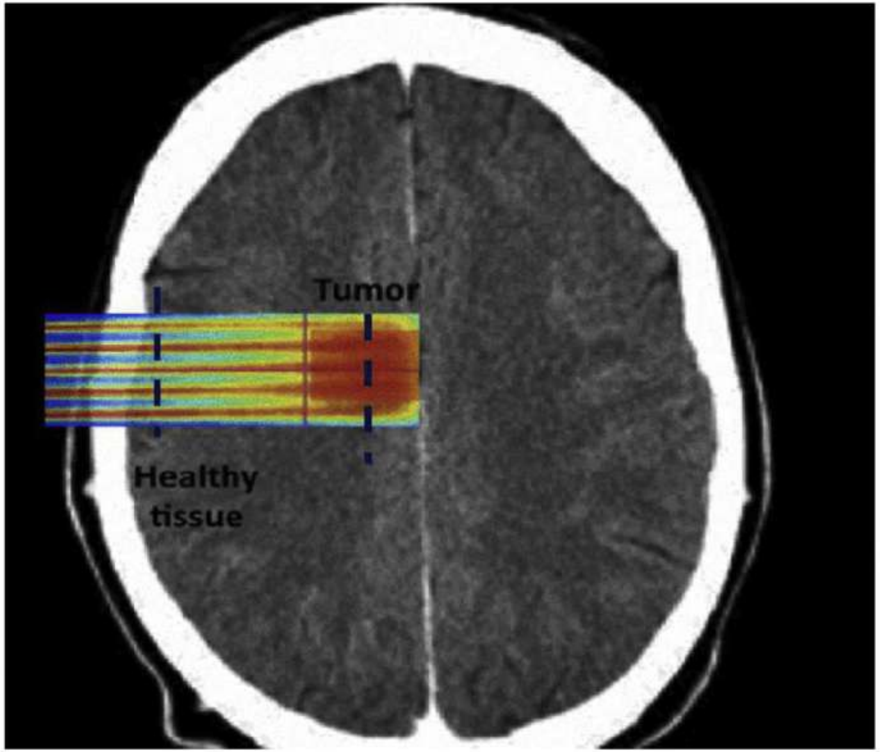
Sharp lateral dose fall off: rat brain

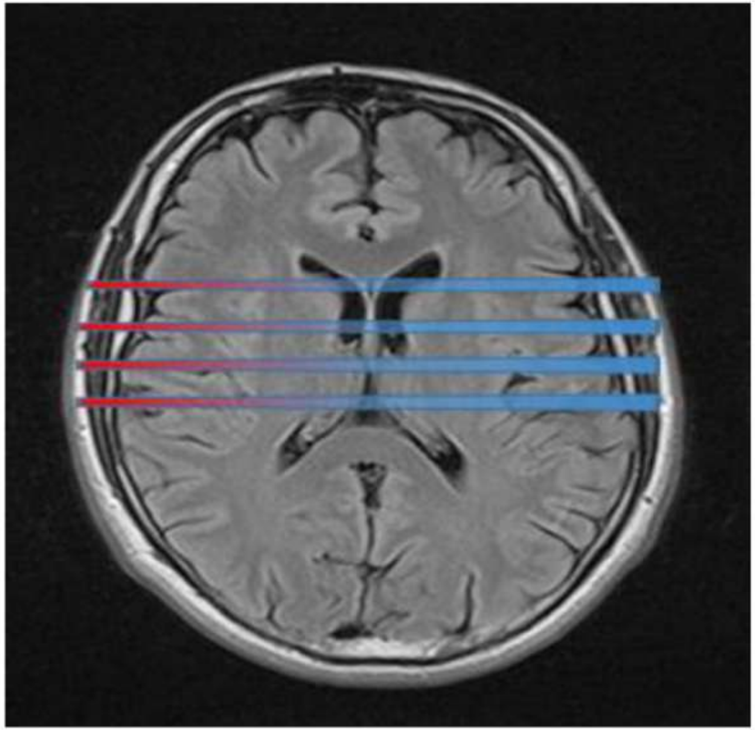
pH2Ax analysis (DNA Double Strand Breaks)

50 µm /200 µm c-t-c	100 µm /200 µm c-t-c	homogeneous



Possible Clinical Implementation





Proton Mini-beam in High-Grade Glioma

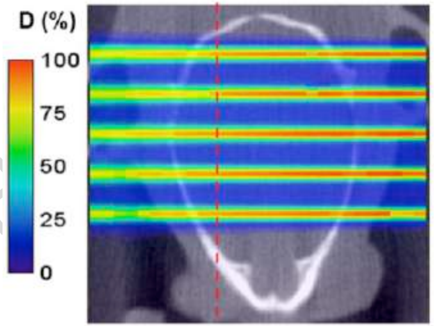
SCIENTIFIC REPORTS

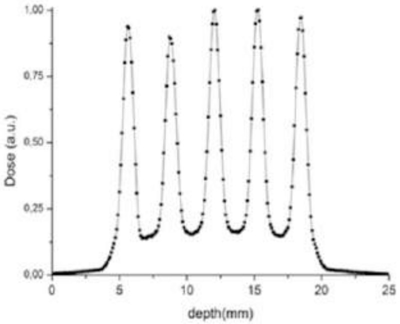
OPEN

Proton minibeam radiation therapy widens the therapeutic index for high-grade gliomas

: 11 July 2018
l: 26 October 2018
d online: 07 November 2018

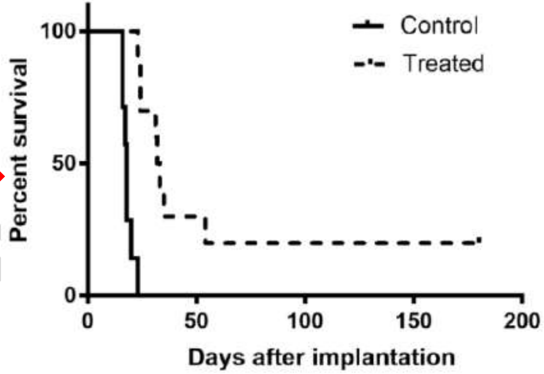
Yolanda Prezado[1], Gregory Jouvion[2], Annalisa Patriarca[3], Catherine Nauraye[3], Consuelo Guardiola[1], Marjorie Juchaux[1], Charlotte Lamirault[1], Dalila Labiod[4,5], Laurene Jourdain[6], Catherine Sebrie[6], Remi Dendale[3], Wilfredo Gonzalez[1] & Frederic Pouzoulet[4,5]





C-T-C = 3.2 μμ ορ 3200 μιχρο μετερ

Study groups	Sacrificed	MRI	Histology
Tumor bearing- rats, non-irradiated controls (n=7)	When endpoints reached	No	All
Tumor bearing- rats, pMBRT (n=9)	When endpoints reached or at the end of the study (6 months)	10 days after irradiation (n=5) Long-term survivals (n=2/9)	All
Normal rats, pMBRT (n=9)	If endpoints reached or at the end of study: 6 months (n=5) 12 months (n=4)	6 months (n=5) 12 months (n=4)	All
Normal rats, controls (n=4)	At the end of study	No	All



Chemical Model for Micro and Mini-Beams

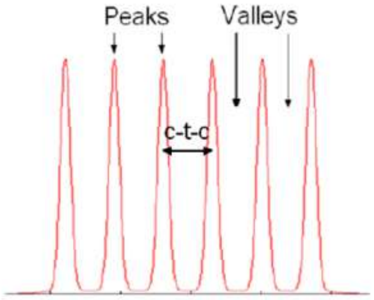
frontiers

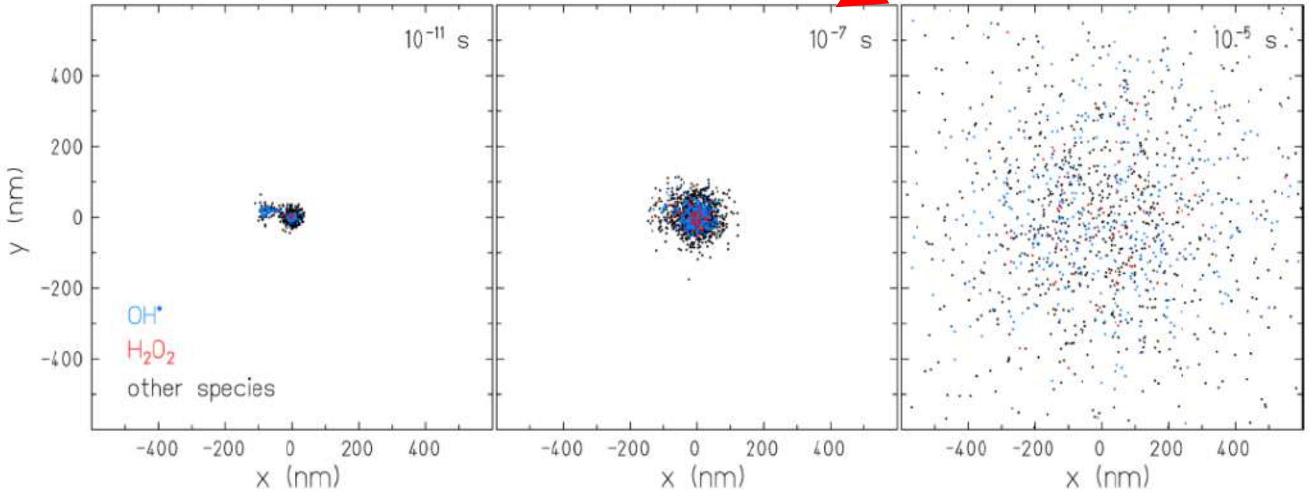
1

Proposal of a chemical mechanism for mini-beam and micro-beam efficacy

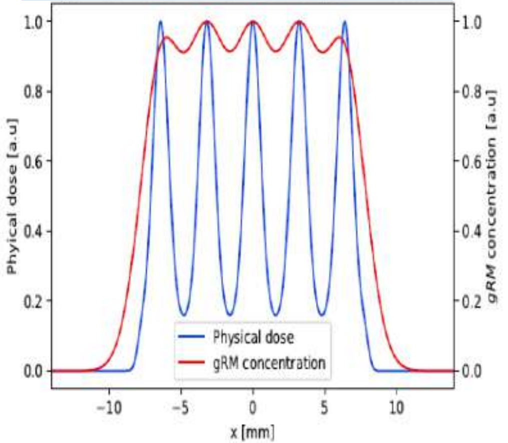
Riccardo Dal Bello[1,2,†], Tobias Becher[1,2,†], Martina C. Fuss[3], Michael Krämer[3] and Joao Seco[1,2,*]

$^{\bullet}OH$	H_3O^+	$^{\bullet}H$	H_2O
e^-	H_2	H_2O_2	OH^-
O_2	$^{\bullet}HO_2$	$^{\bullet}O_2^-$	HO_2^-

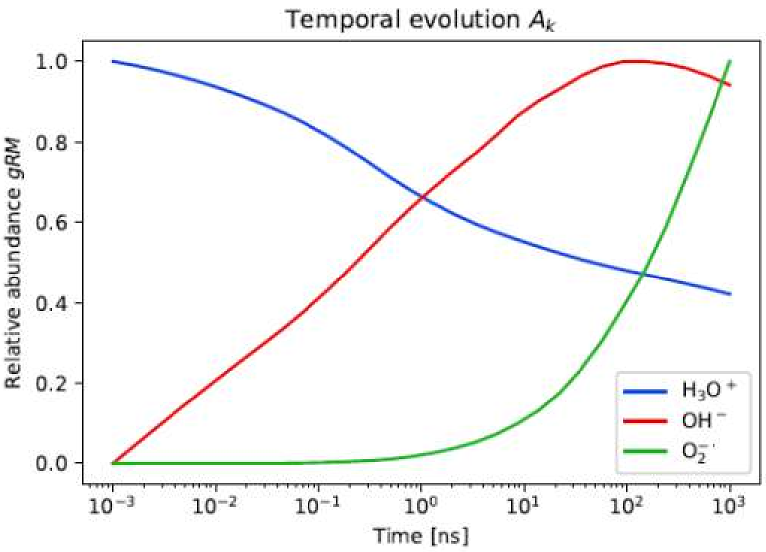


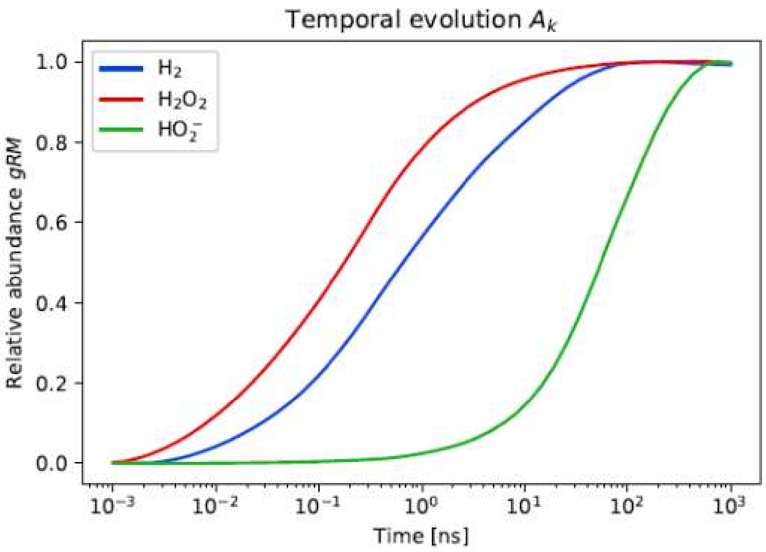


H2O2 Tumor Coverage



Chemical Model for Micro and Mini-Beams



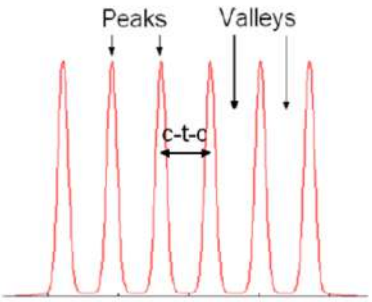


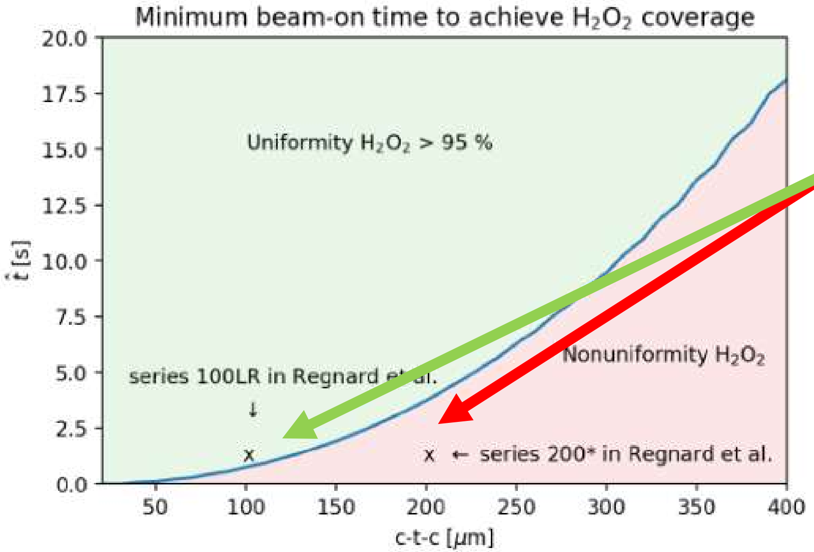
$^\bullet OH$	H_3O^+	$^\bullet H$	H_2O
e^-	H_2	H_2O_2	OH^-
O_2	$^\bullet HO_2$	$^\bullet O_2^-$	HO_2^-

Time to Achieve tumor Coverage with H_2O_2

	C-T-C distance	Model: Minimum Time to H_2O_2 Coverage	Irradiation time
Prezado (2018)	3200 μιχρο meter		2100 s
Dombrowsky (2020)	350 micro meter		300 s
Regnard 200* (2008)	200 micro meter		1 s
Regnard 100* (2008)	100 micro meter		1 s

$$\hat{t} = \begin{cases} 2120 \pm 240\ \text{s} & \text{for Prezado et al. [8]} \\ 13.9 \pm 1.5\ \text{s} & \text{for Dombrowsky et al. [6]} \\ 3.5 \pm 0.4\ \text{s} & \text{for } 200^{*} \text{ in Regnard et al. [9]} \\ 0.70 \pm 0.08\ \text{s} & \text{for 100LR in Regnard et al. [9]} \end{cases}$$





Physics Challenges in Proton Therapy

Micro- or Mini-beam Irradiation:

- **Micro-beams presently not possible with presently available commercial proton therapy machines.**
- **Mini-beams possible with new Pencil Beam Scanning systems, but new animal studies are needed to validate new model. A better understanding is needed of mechanism.**

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FLASH Irradiation:

- Why does FLASH protect organs and not affect tumor control?
- All clinical applications of FLASH have used 1 beam (e- or p+).
  How do we clinically implement FLASH with multiple beams?

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GOT IT?....... Questions??

DKFZ