FLASH Physics

Peter G Maxim, PhD
Department of Radiation Oncology
Indiana University School of Medicine

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Disclosures

- Employment – Indiana University School of Medicine
- Founder – TibaRay, Inc.

Outline

- Physics of FLASH RT
- Equipment used for FLASH RT
- FLASH RT - Preclinical evidence

What is FLASH?

Ultra-rapid radiation treatment (dose *rate* > ~40 Gy/sec)

How does it compare to conventional dose rate RT?

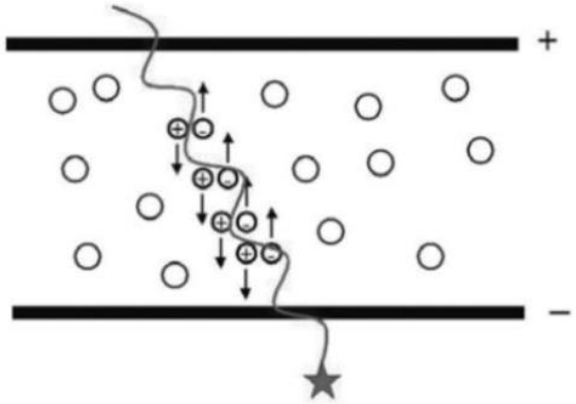
Varian TrueBeam dose rate (calibration conditions) = 24 Gy/min = 0.4 Gy/s

(at 10 MV FFF mode for an open field)

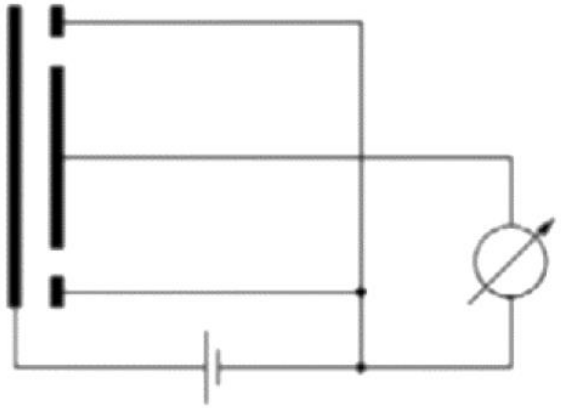
Varian TrueBeam dose rate (real world) = 10 Gy/min = 0.1667 Gy/s

(10 MV FFF **intensity modulated** plan)

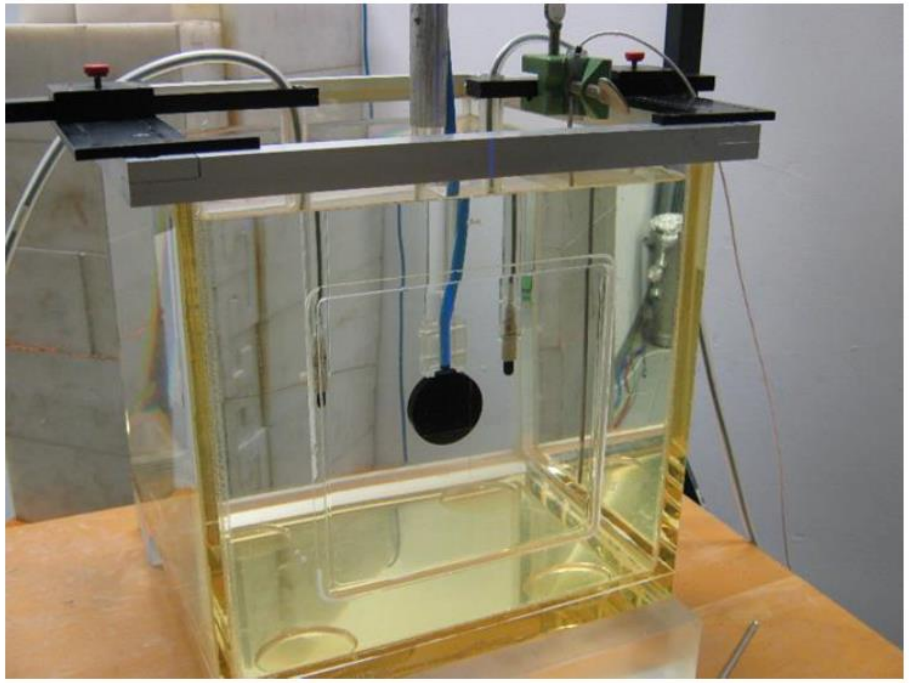
Dosimetry for conventional beams



ionizing radiation creates ion pairs



high voltage current



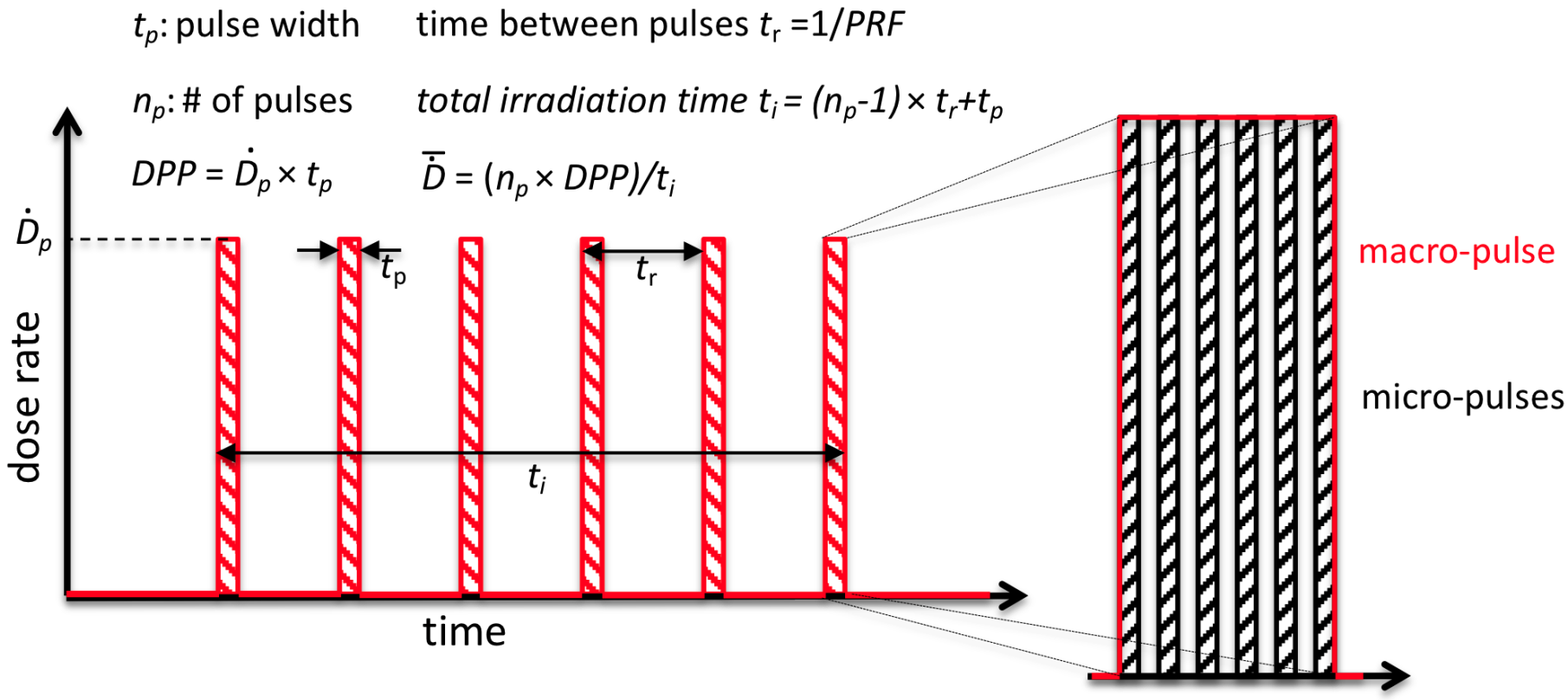
Plane-parallel ionization chamber in a water phantom (recommended for electron beams)

Codes of Practice:
Formalism for clinical reference dosimetry of high-energy electron beams (3 – 50 MeV)
→ IAEA's TRS 398, AAPM's TG-51, DIN 6800-2

Physics of FLASH RT

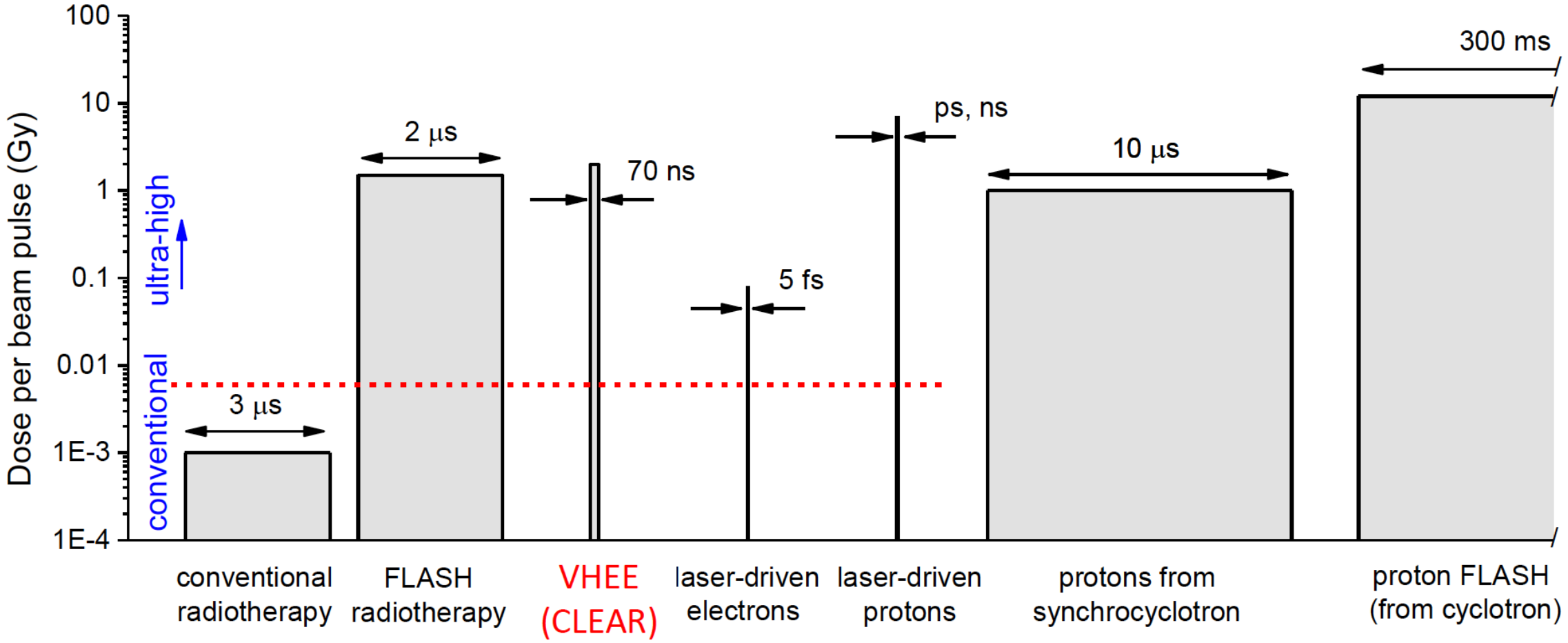
- Standard linac operation:
  - Dose or dose rate per pulse
  - Pulse frequency
  - # of pulses
  - Delivery time

What are the physical parameters to achieve the FLASH effect?

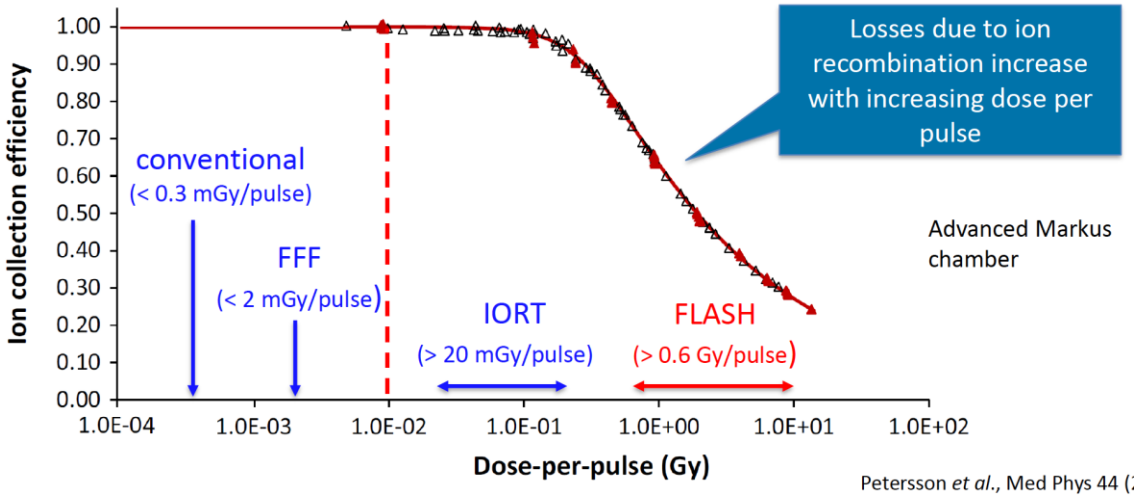


Esplen *et al.* PMB 2020

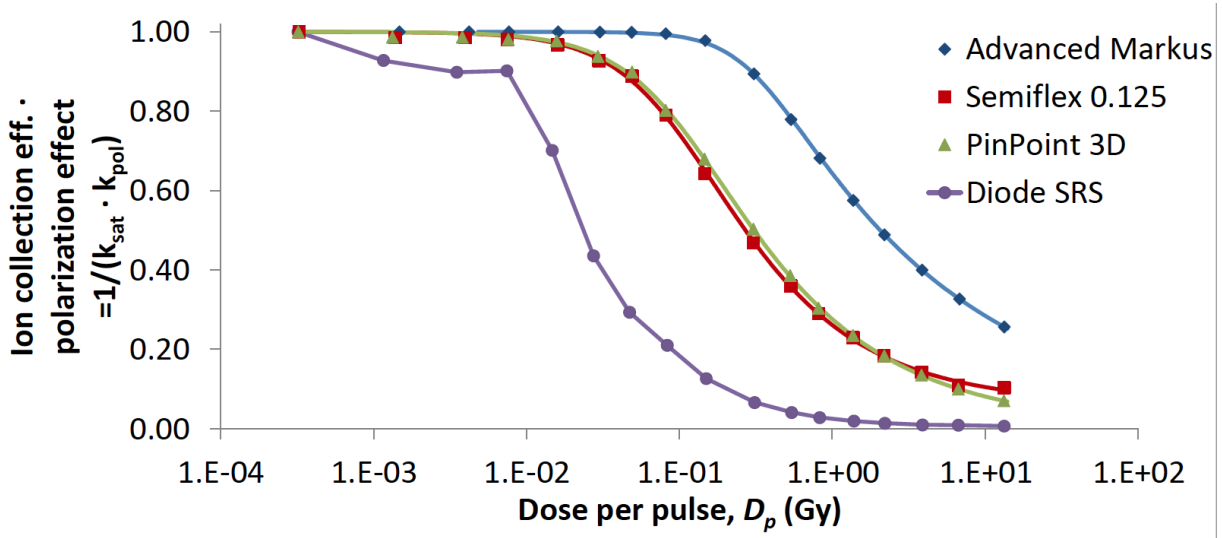
Physics of FLASH RT



Limitation of ionization chambers



Petersson *et al.*, Med Phys 44 (2017) 11
https://doi.org/10.1002/mp.12111



Petersson *et al.*
Unpublished

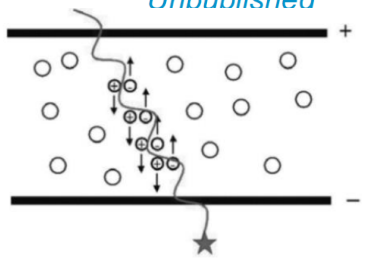
If an error is made in dosimetry, the difference in tissue response between conventional irradiation and ultra-high dose rate irradiation at apparently the same total dose may be due to this error and not due to the FLASH effect.

Tools and methods established in dosimetry for conventional RT are not suitable for FLASH-RT

no active dosimeters for real time dosimetry

no formalism (Codes of Practice) for reference dosimetry

no corresponding primary standard



high dose per beam pulse
→ high density of ion pairs
→ ion recombination
→ deviation from linear response

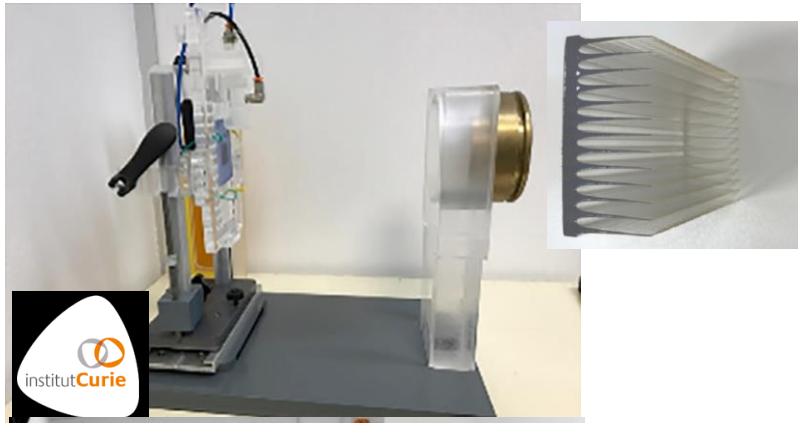
FLASH – Current technologies (preclinical)

MeV electrons at Lausanne U, Stanford, IU and Lund U

Synchrotron kV x-rays at ESRF (Grenoble)

Schüler *IJROBP* 2017
Jaccard *Med Phys* 2018
Montay-Gruel *Radiother Oncol* 2018
Patriarca *IJROBP* 2018
Kim *Phys Med Biol* 2019
Lempart *Radiother Oncol* 2018

>100 MeV protons at Curie, U Penn, Groningen



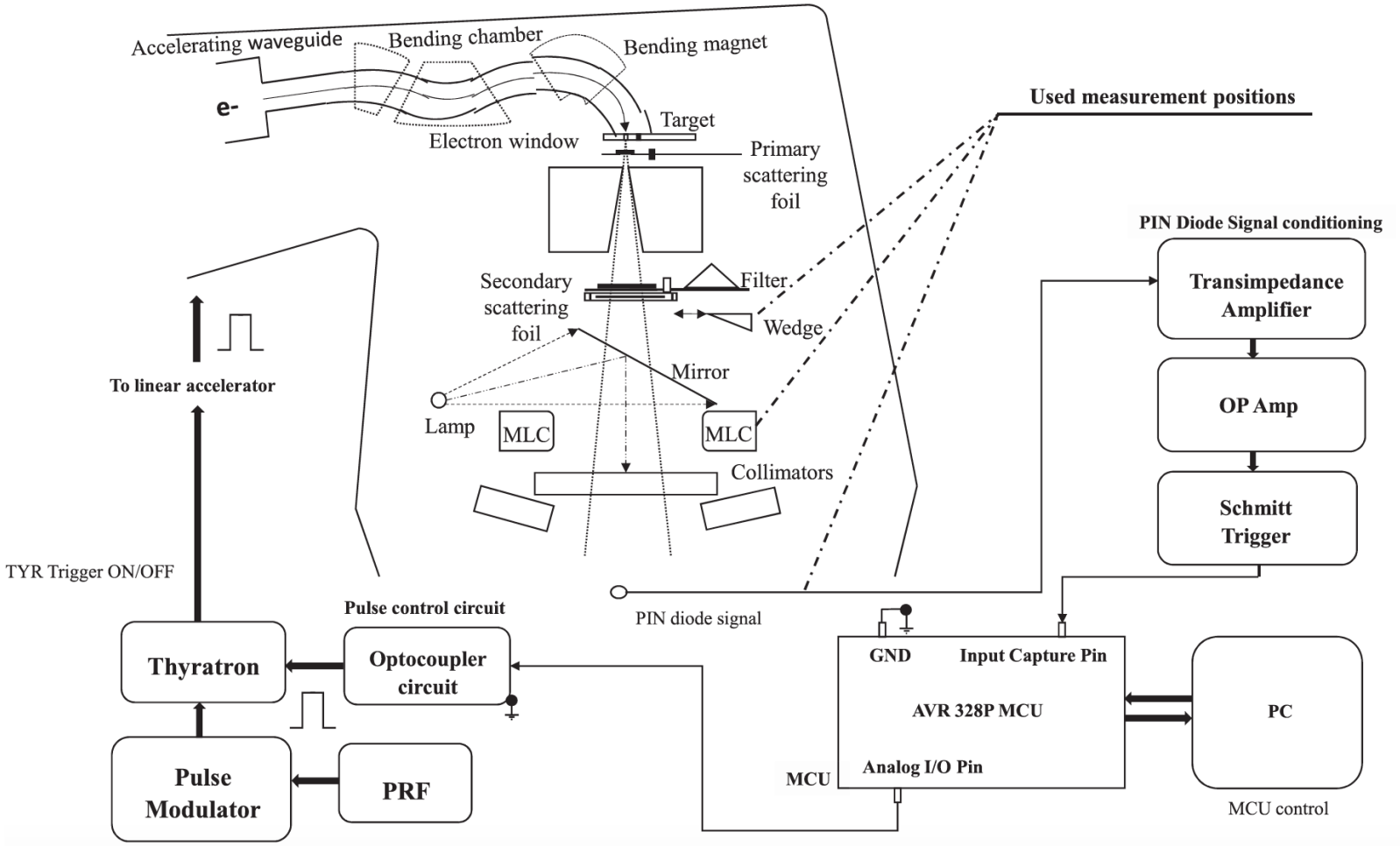
MeV electron FLASH -RT at CHUV

SLAC NATIONAL ACCELERATOR LABORATORY

Prototype 6 MeV electron Linac
PMB-Alcen, Peynier, France

- Oriatron 6e
- Dose rates: few Gy/min - >1000Gy/s
- Wide range of parameters
- Gun current, pulse-repetition frequency, pulse width, and SSD
- Dosimetry characterized

MeV electron FLASH -RT at Lund U



- Elekta linac:
- Clinical electron energies
- >1000Gy/s at short SSD
- Pulse by pulse control
- Diode signal amplified and counted by MCU
- Triggered thyratron
- Dosimetry characterized

Lempart *Radiother Oncol* 2018

Why FLASH - Therapeutic index

Holthusen's hypothesis

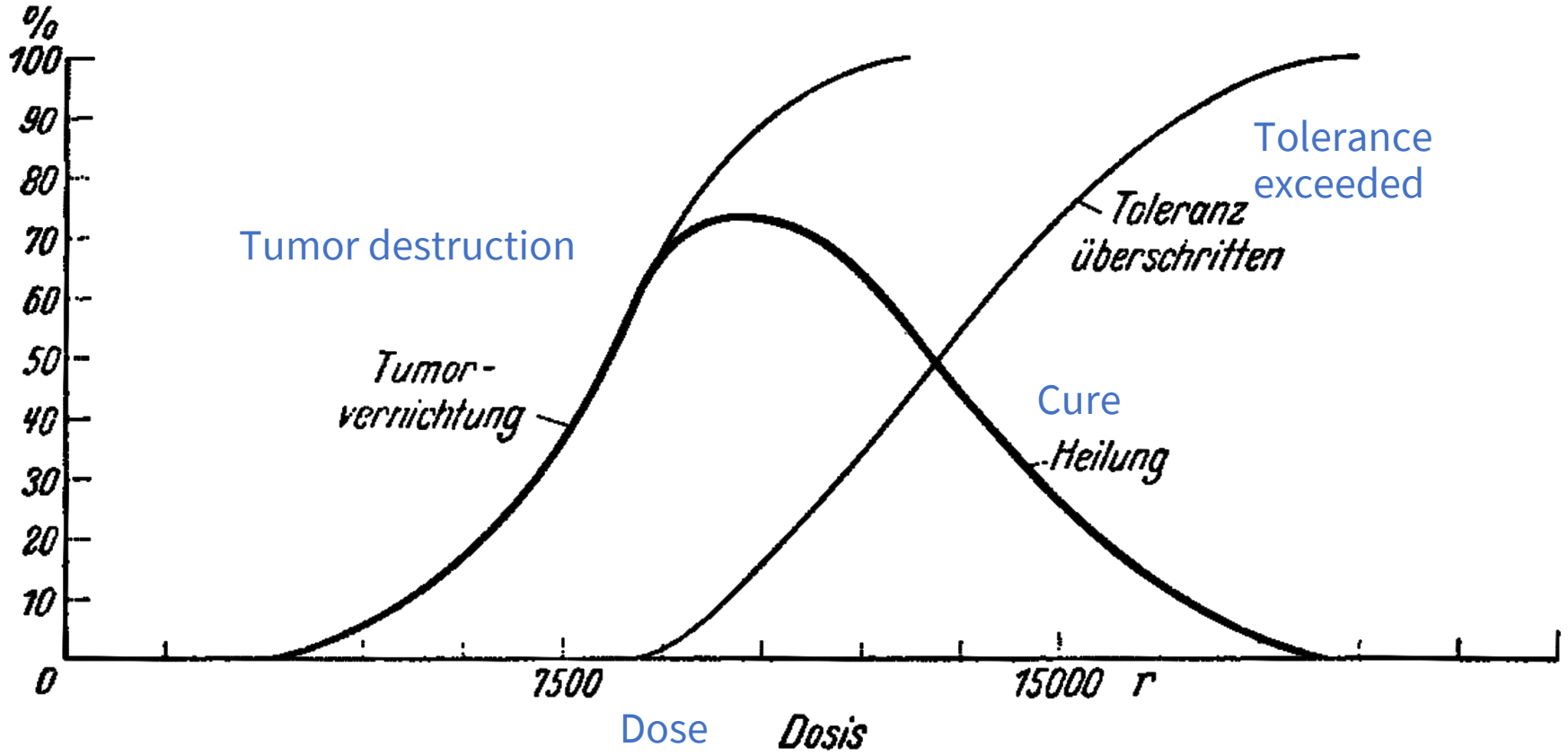


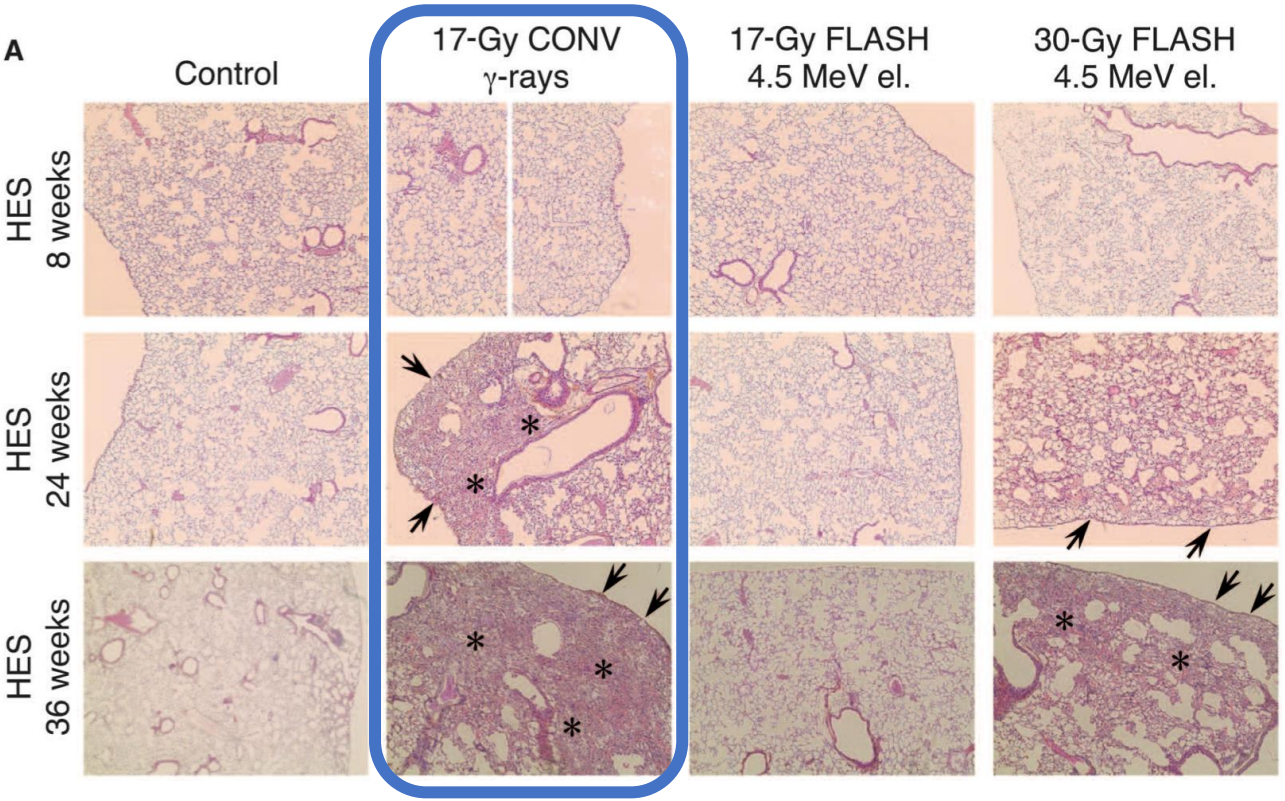
Bild 6.

Holthusen *Strahlenther Onkol* 1936

Ultra-rapid "FLASH" RT: New biology

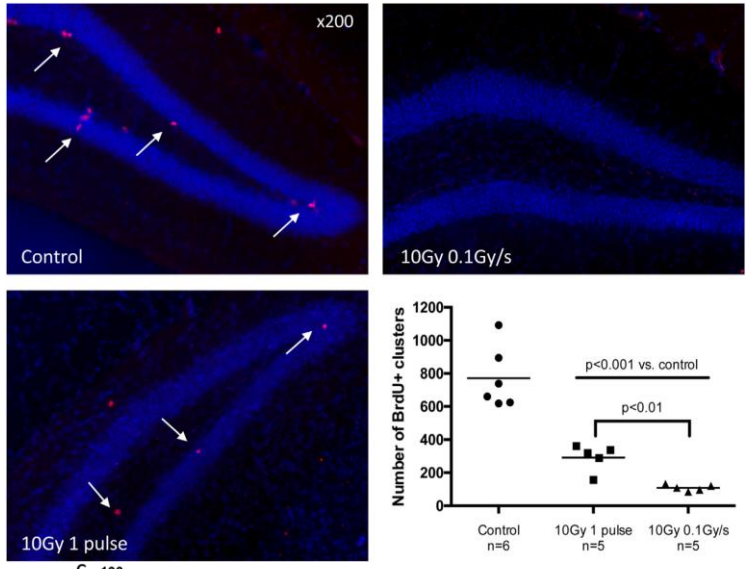
Normal organ sparing

Lung

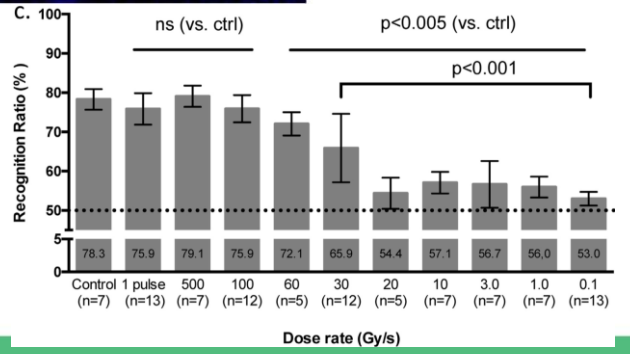


Favaudon *Science Translat Med* 2014

Brain



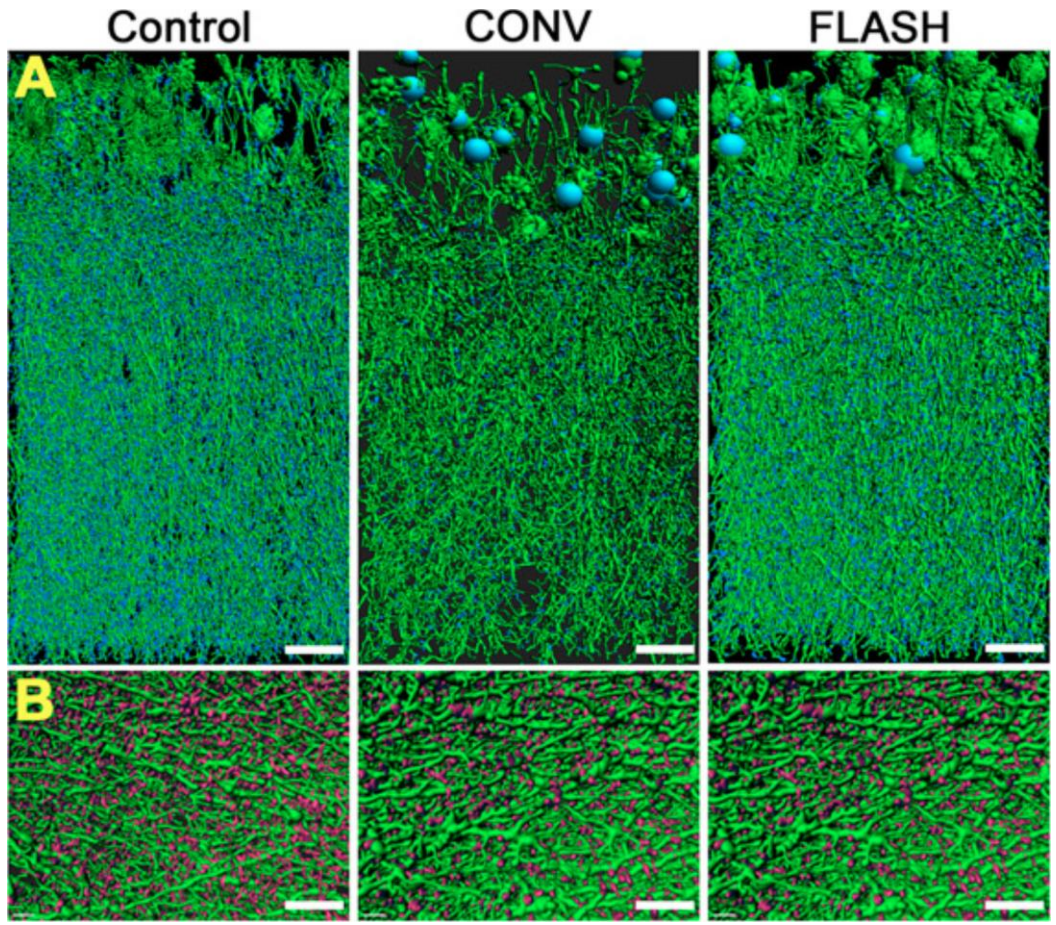
Hippocampal neurogenesis (BrdU) & memory (novel object recognition) 2 mo after 10 Gy WBI

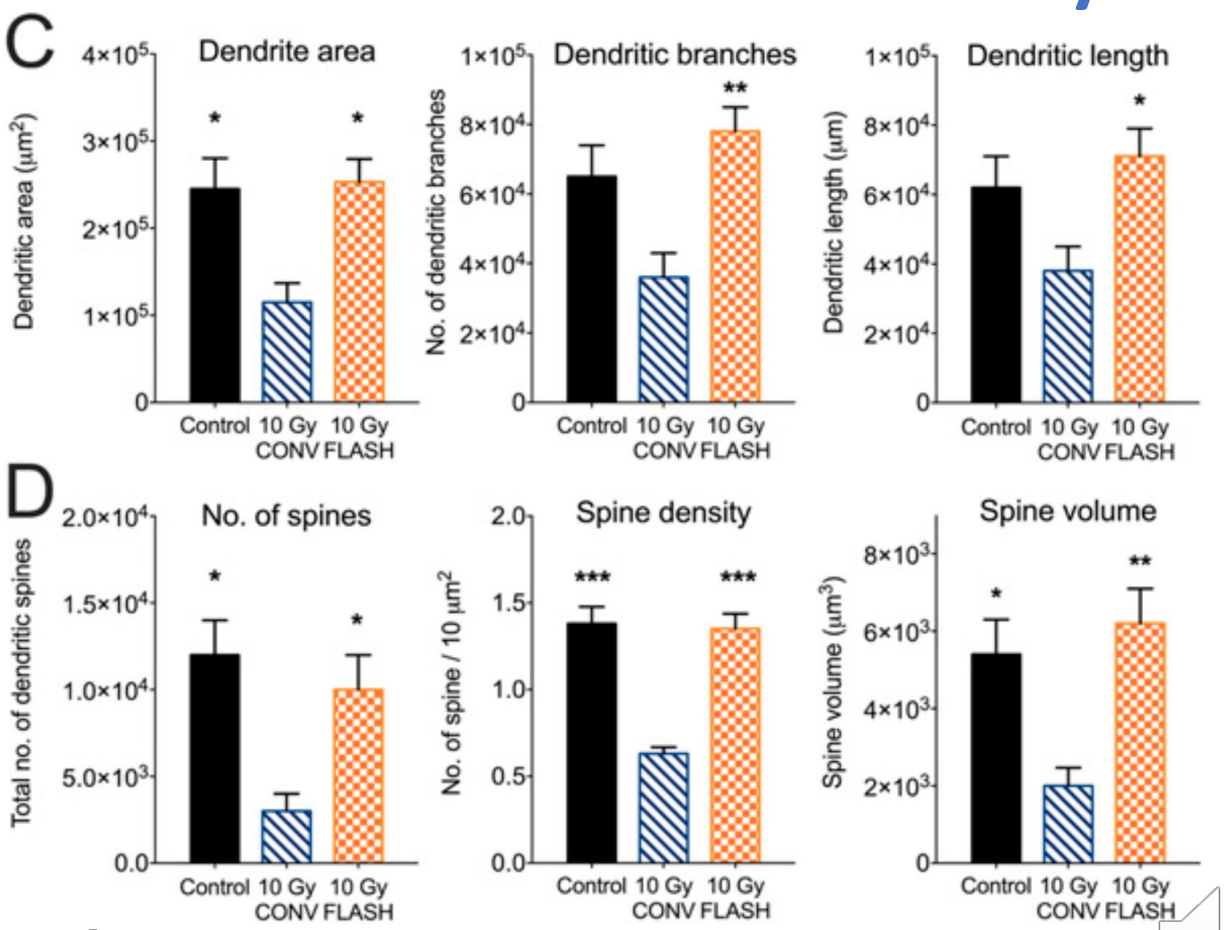


Montay-Gruel *Radiother Oncol* 2017

Ultra-rapid “FLASH” RT: New biology

Preservation of neuronal microanatomy





Montay-Gruel *PNAS* 2019

Ultra-rapid “FLASH” RT: New biology

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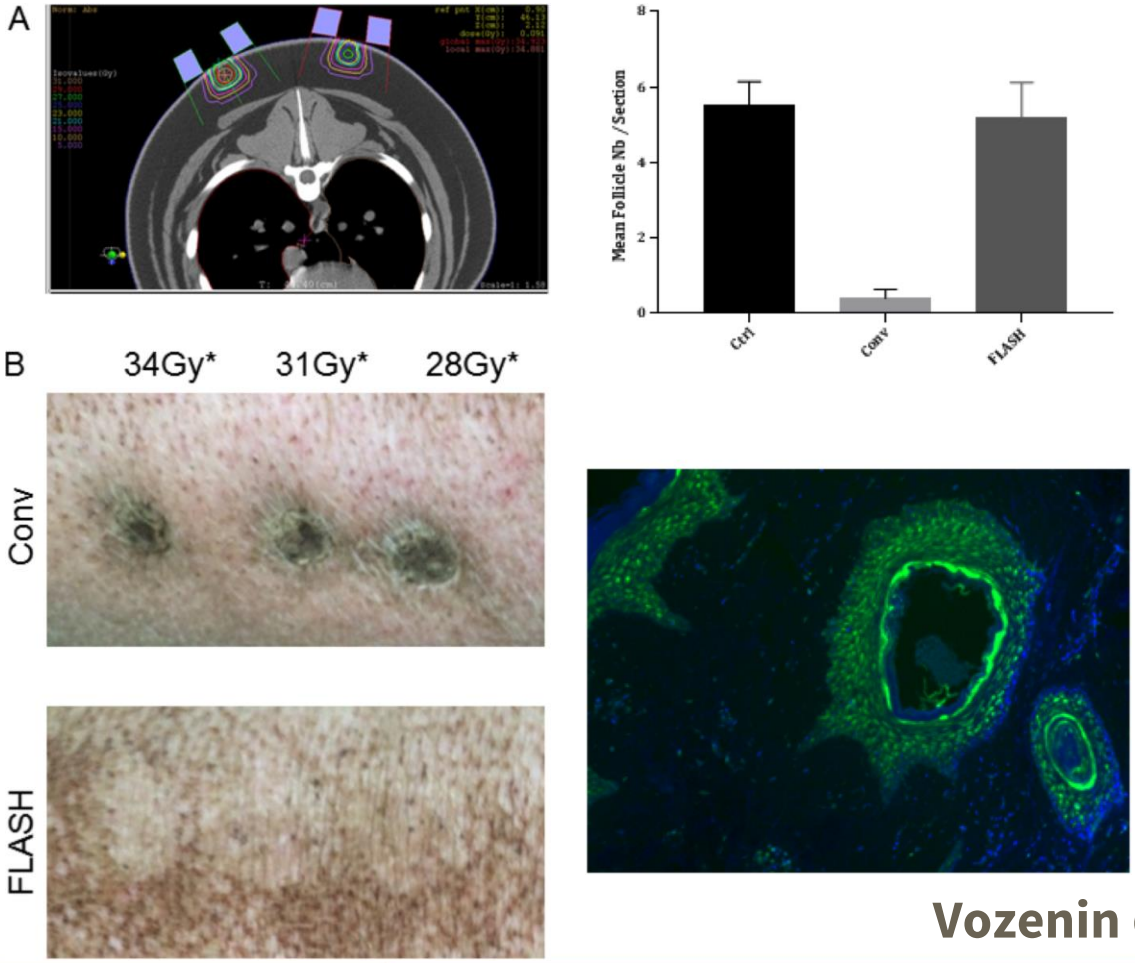
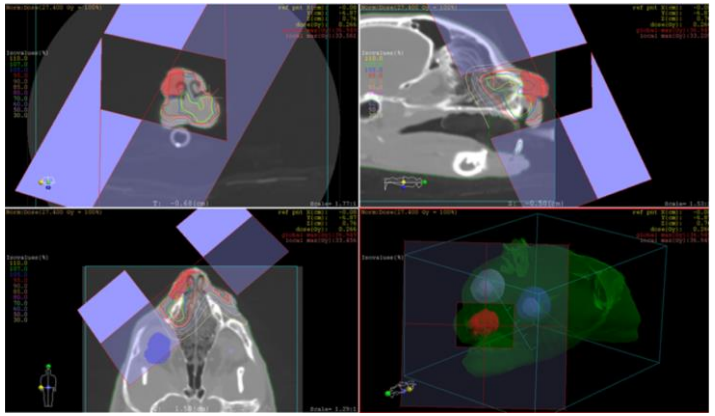
Skin sparing in mini-pig



Vozenin *Clin Canc Res* 2018

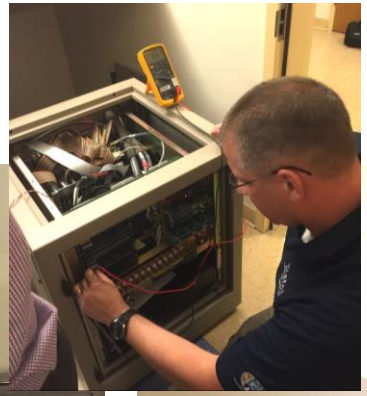
Therapeutic index in cat nasal cancer

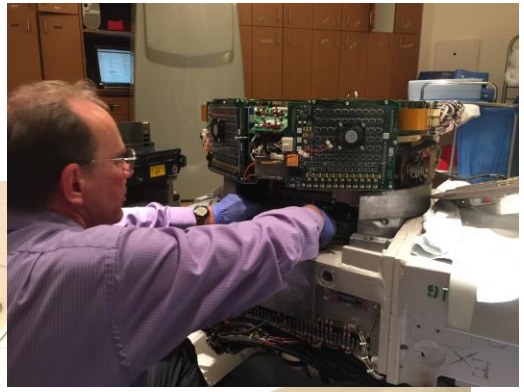


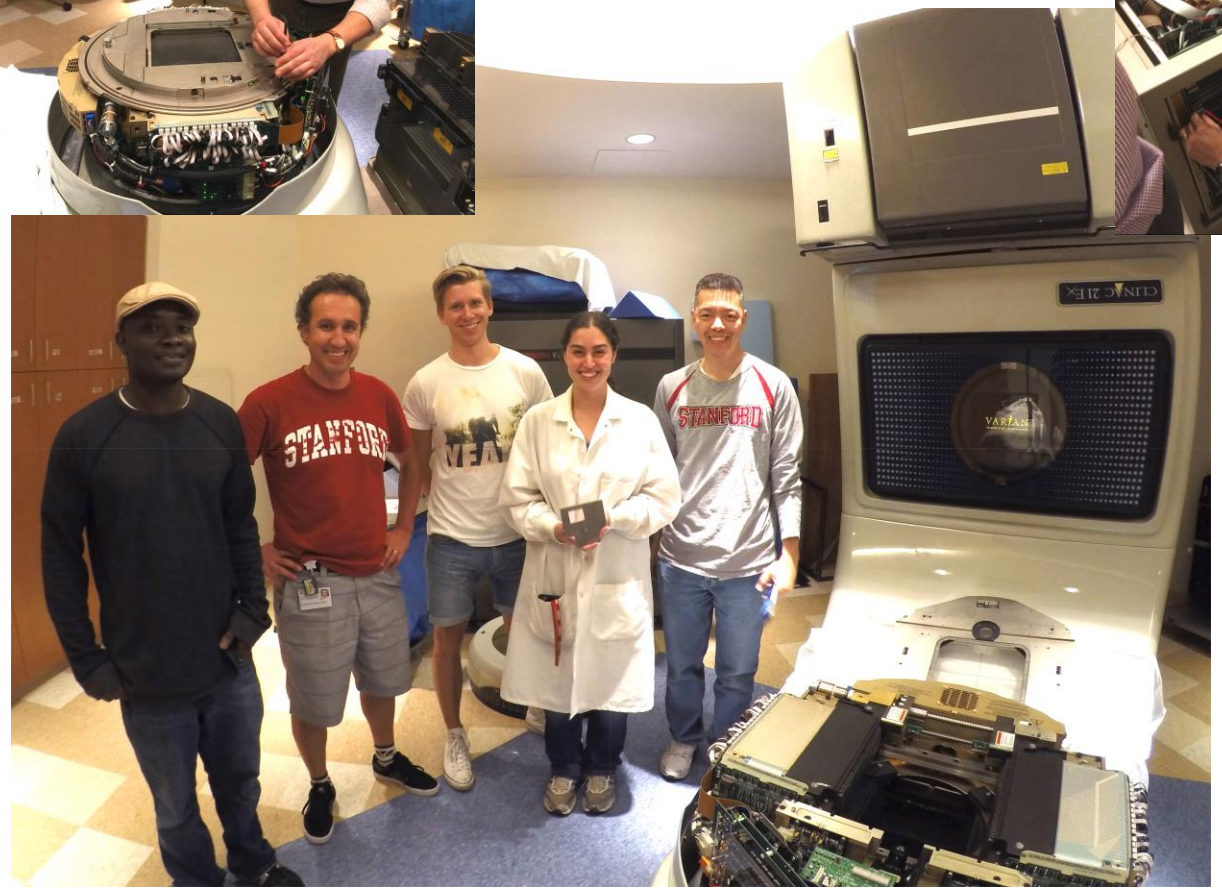
25-41 Gy single fraction to nasal squamous carcinoma:

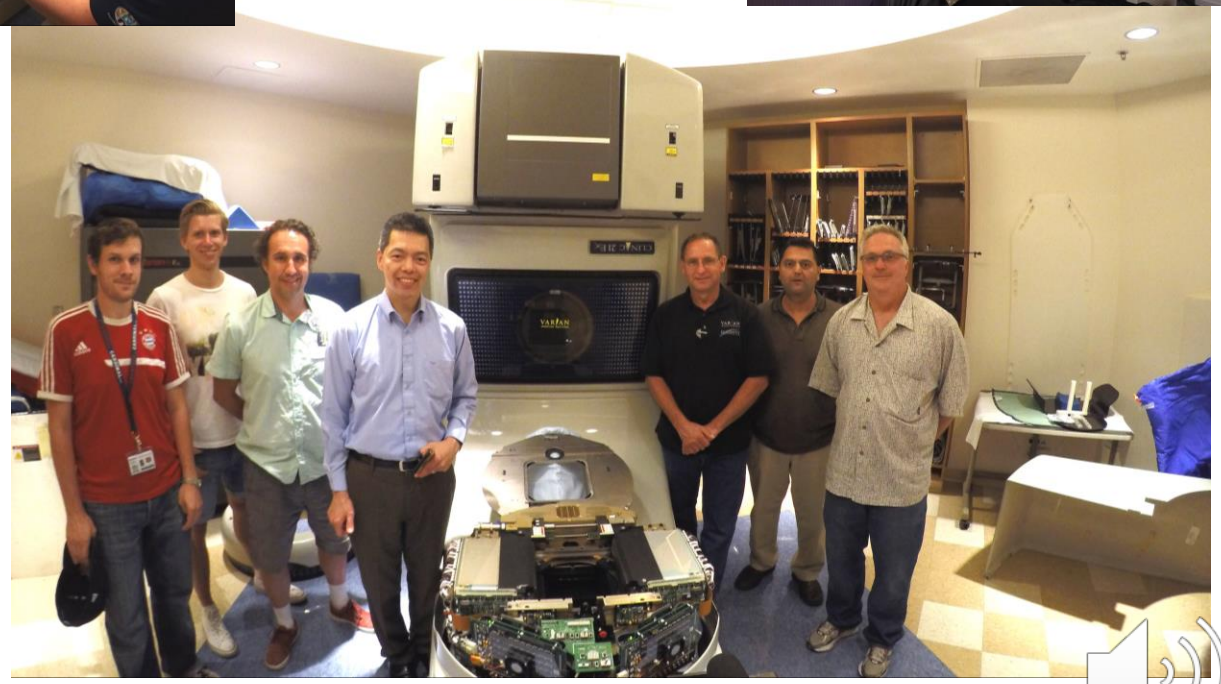
5 of 6 tumors controlled, minimal toxicity

FLASH experiments at Stanford and IU

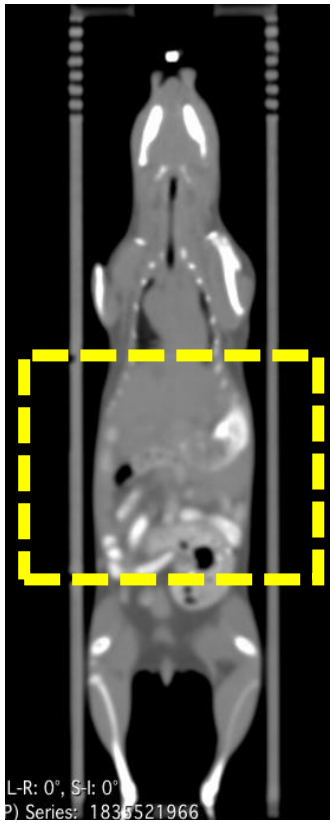


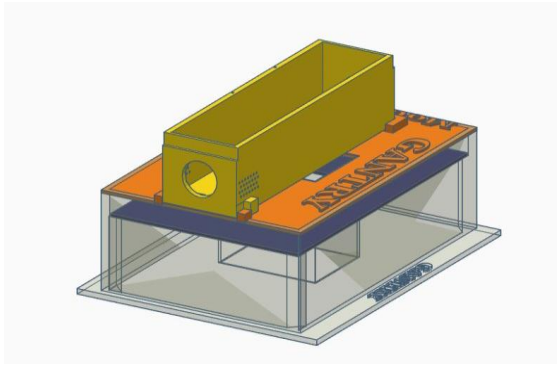


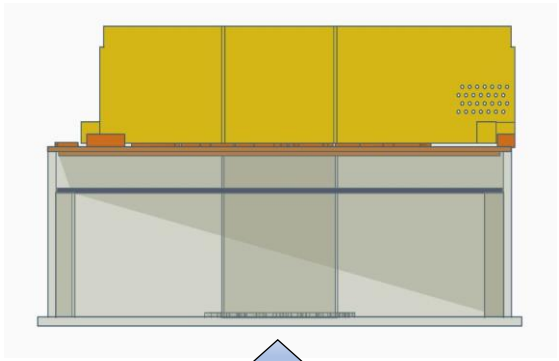




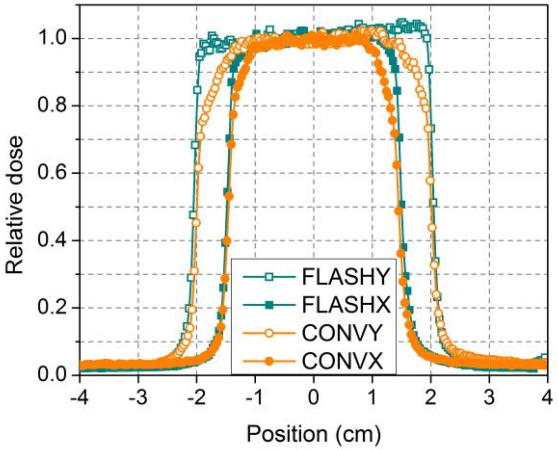
FLASH total abdomen irradiation

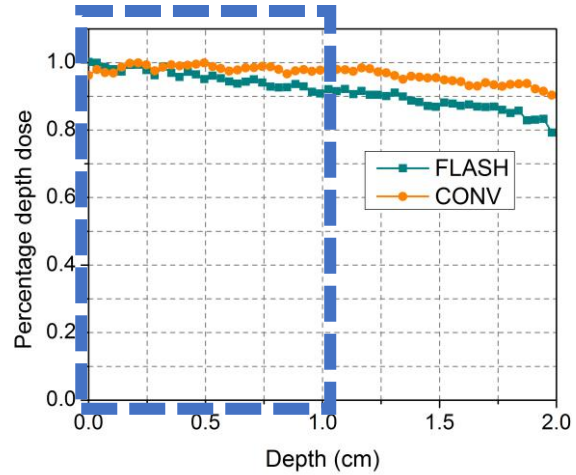






~16 MeV FLASH e⁻





Levy/Rankin, Wang/Loo/Maxim *Unpublished* 2019

FLASH total abdomen irradiation

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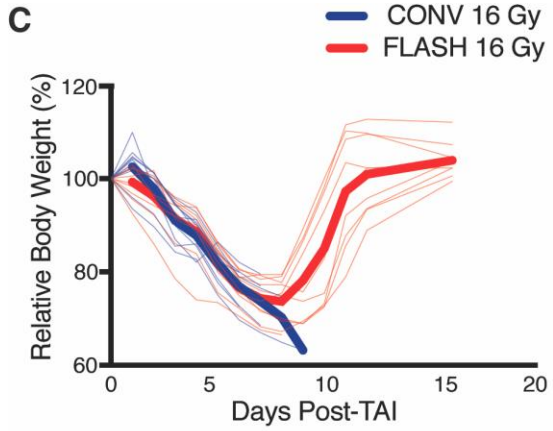
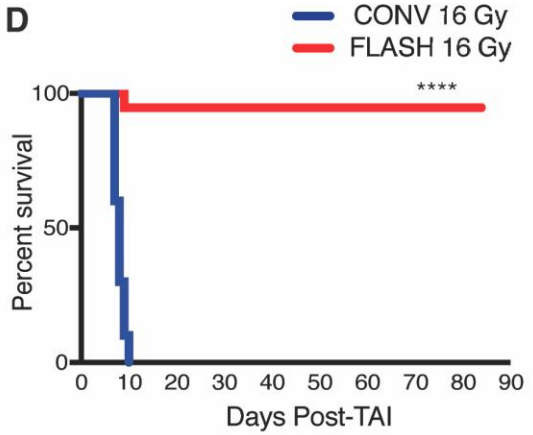
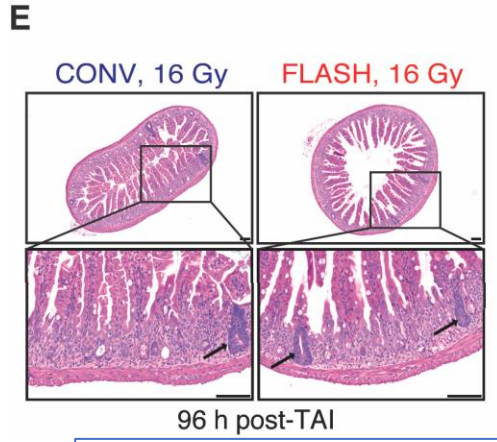
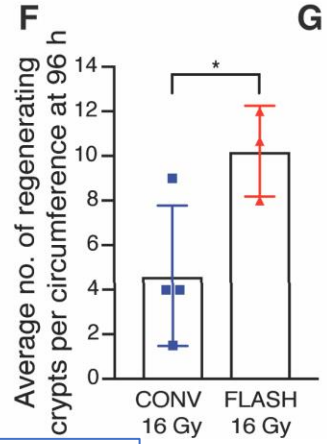
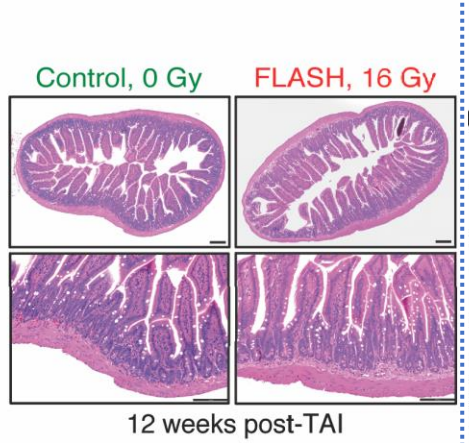
16 Gy (lethal dose)





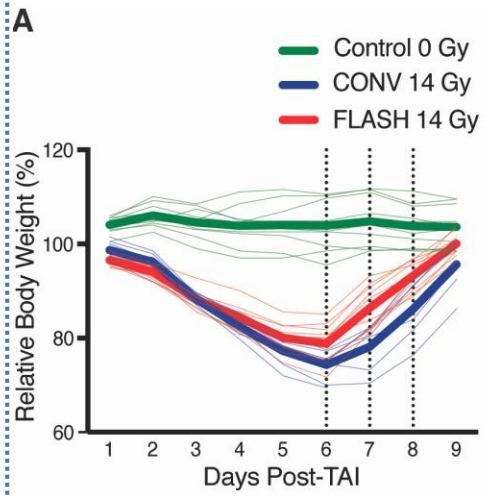


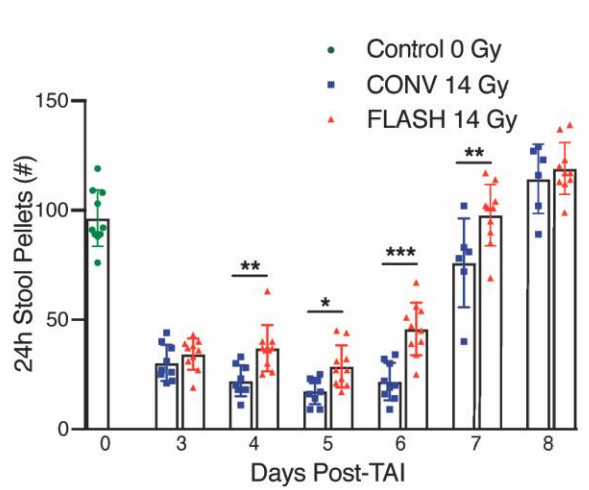


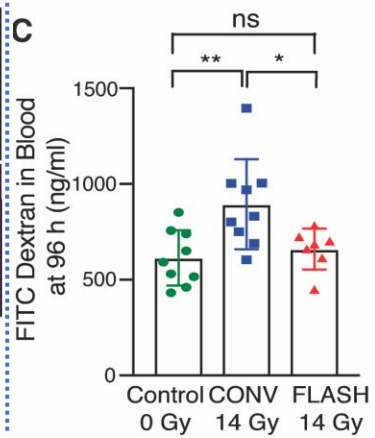


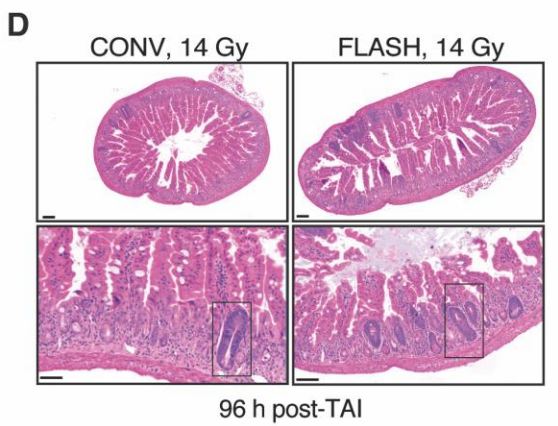
Normal female C57BL/6 mice

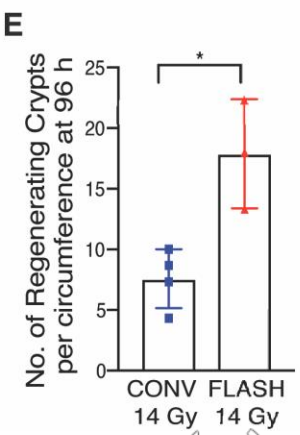
14 Gy (sublethal dose)







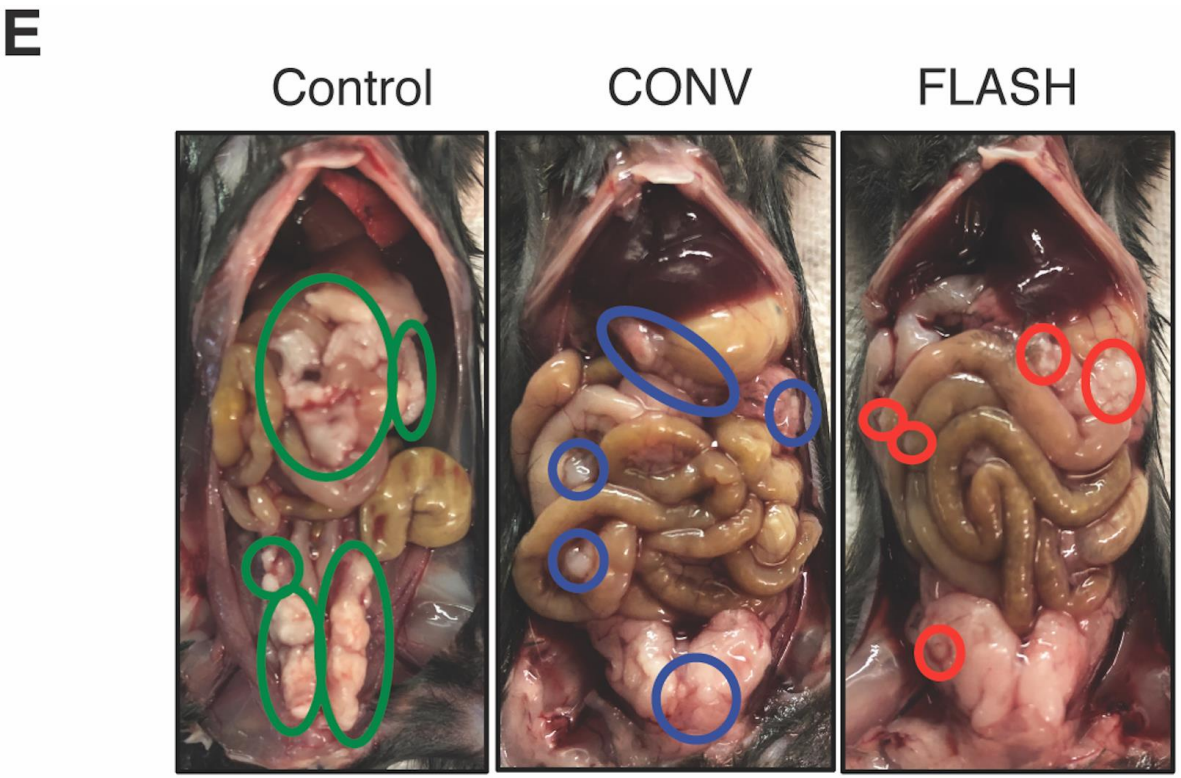


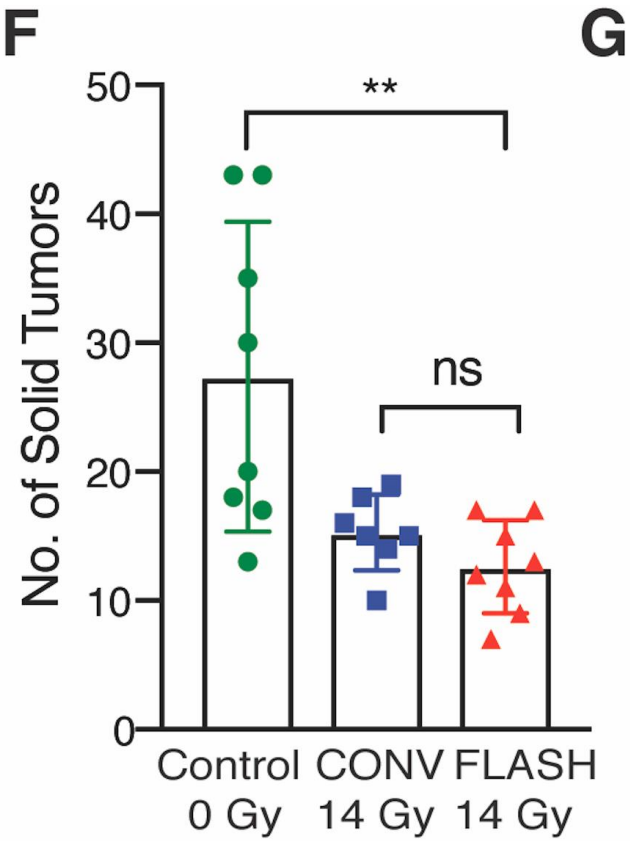


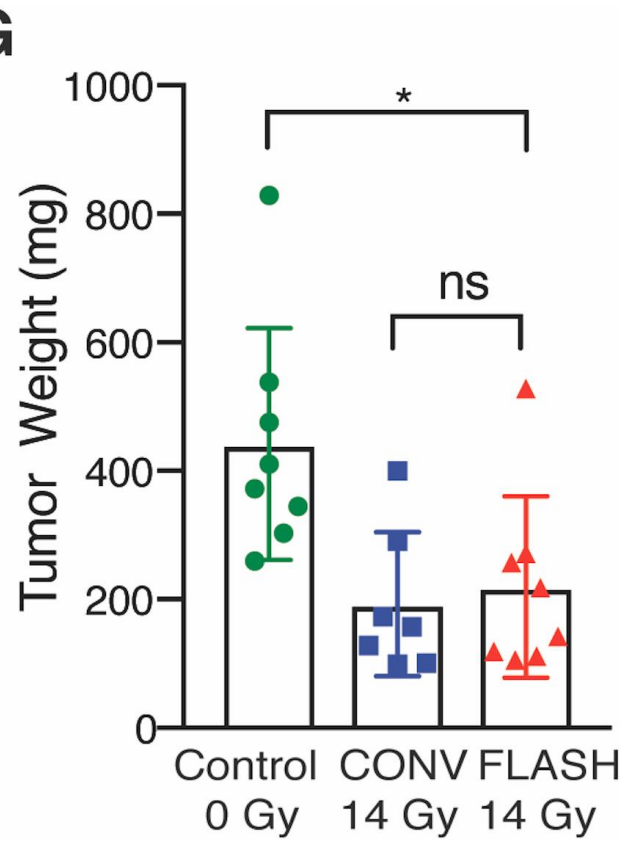
Levy/Natarajan/Wang *bioRxiv* 2019

FLASH total abdomen irradiation

Syngeneic orthotopic (peritoneal) ID8 ovarian cancer in C57BL/6



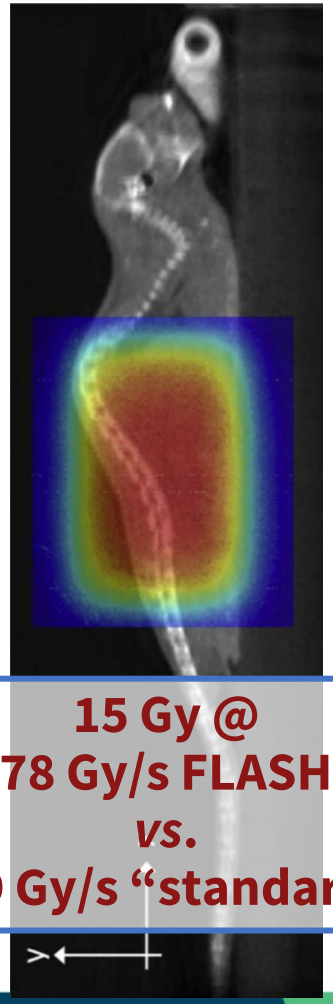




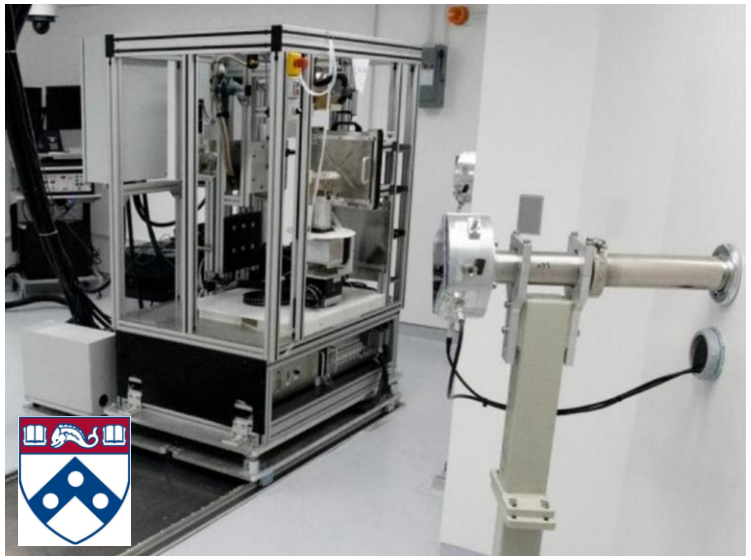
Levy/Natarajan/Wang *bioRxiv* 2019

FLASH proton total abdomen irradiation

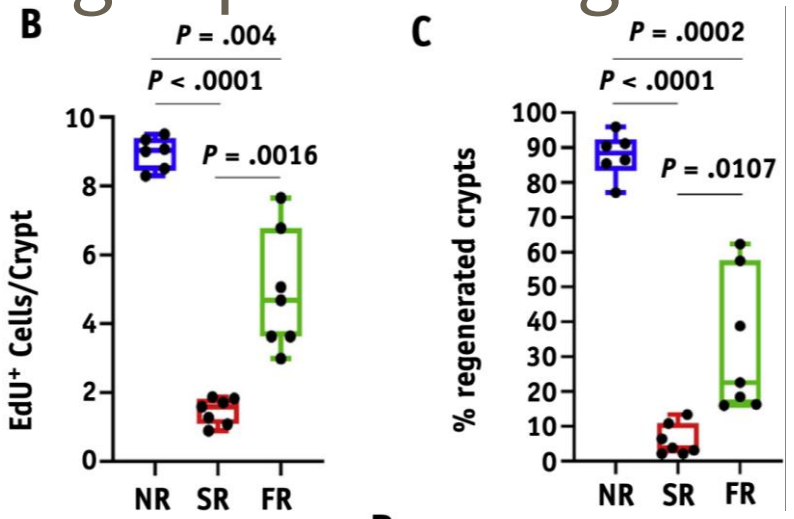
Proton beam 230 MeV treating in plateau region

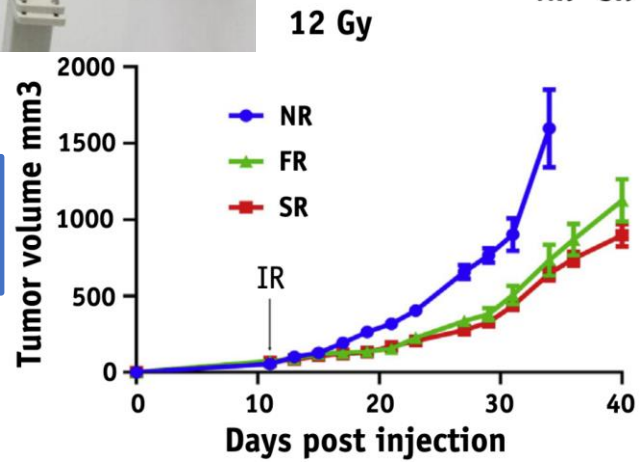


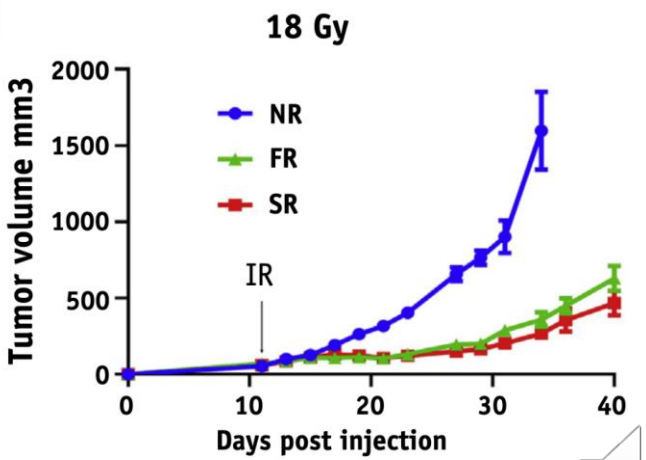
15 Gy @
78 Gy/s FLASH
vs.
0.9 Gy/s "standard"



MH641905
flank tumors





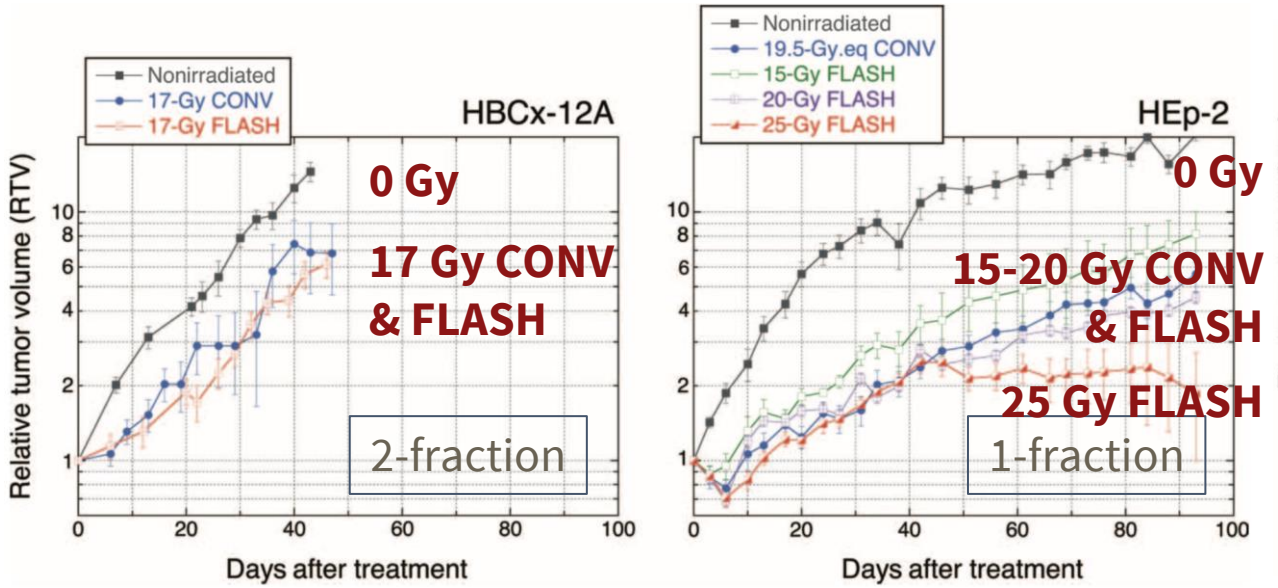


Diffenderfer *IJROBP* 2020

Ultra-rapid "FLASH" RT: New biology

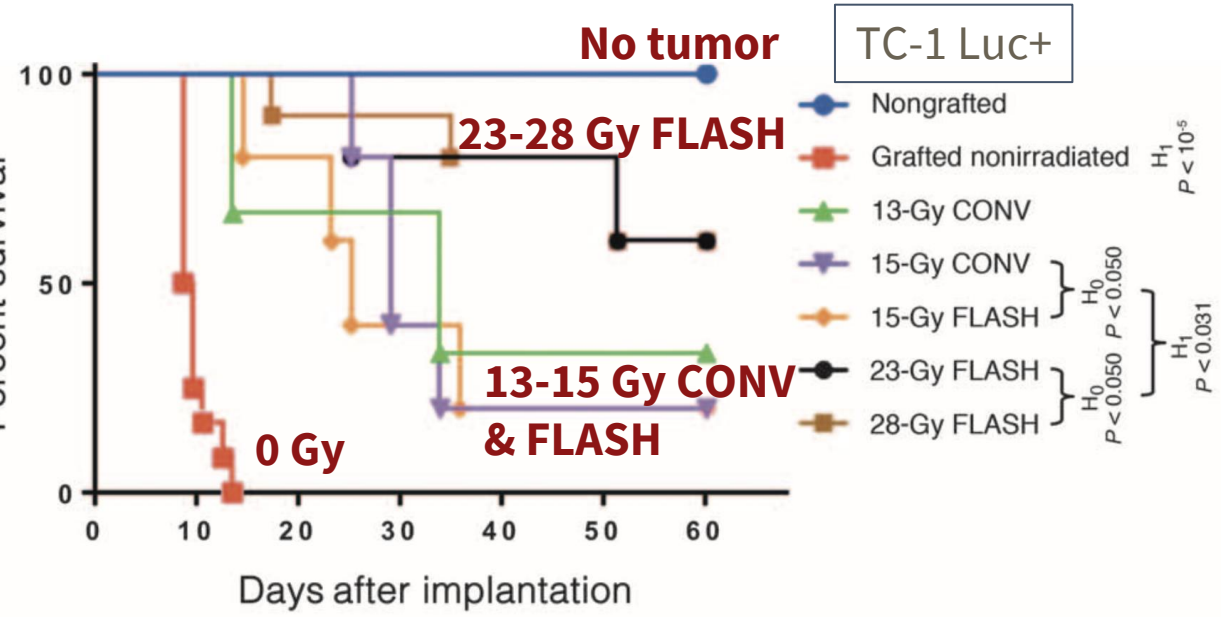
Tumor control isoeffectiveness

Subcutaneous



Human tumors in nude mice

Orthotopic lung



Syngeneic tumors in C57BL/6J mice

Favaudon *Science Translat Med* 2014

FLASH: potential mechanisms?

Ultra-high dose rate effects

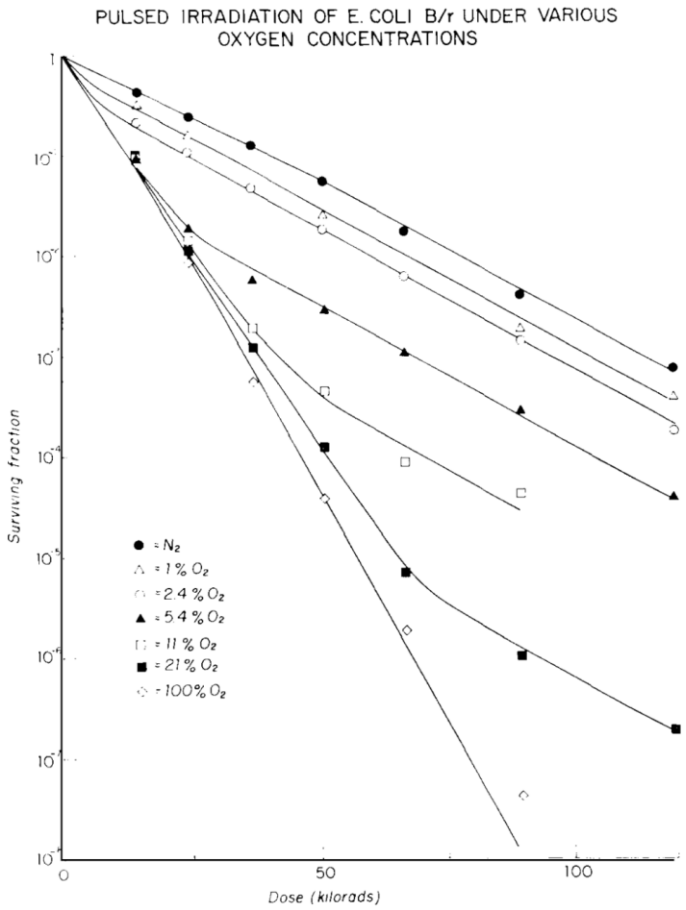


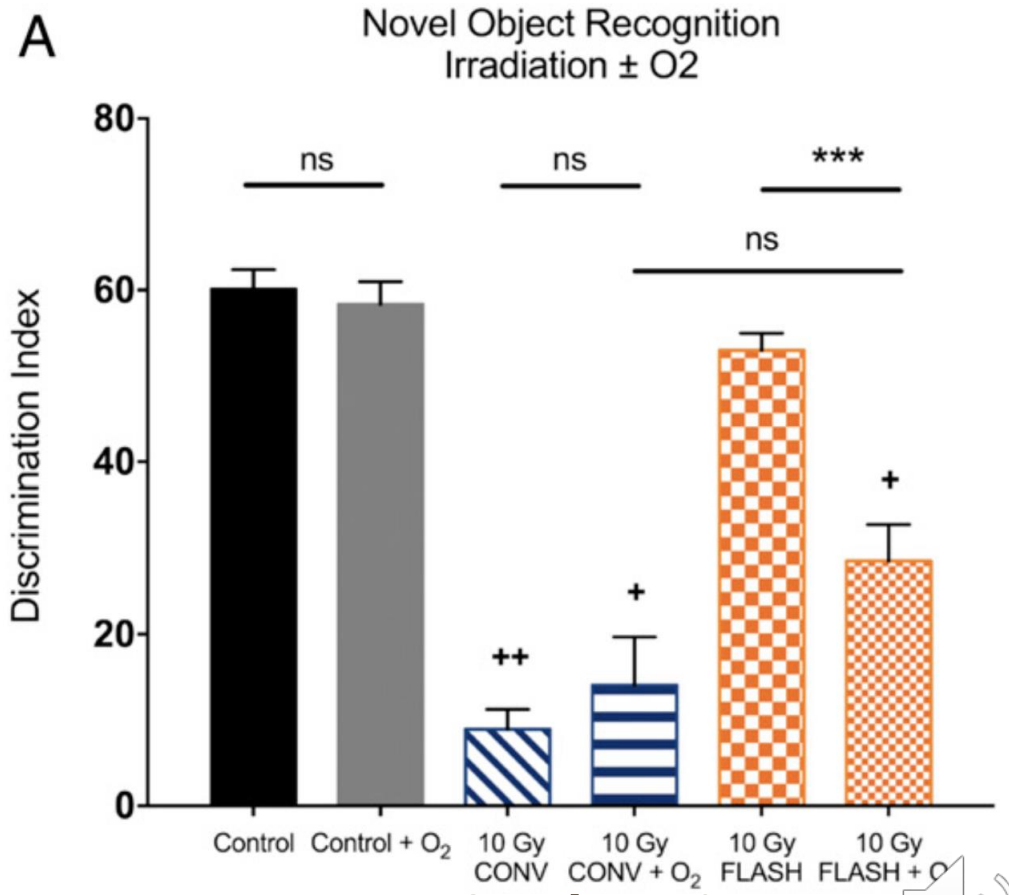
FIG. 2.
Survival curves for *Escherichia coli B/r* irriadated with single short (30 ns) pulses of electrons under various oxygen concentrations. Taken from Epp *et al.* (1968).

Hall *Br J Radiol* 1972

Extremely high dose rates of >10^9-10^{10} Gy/s produce less cell killing – related to radiochemical oxygen depletion

Modeling studies suggest same could happen at lower dose rates *in vivo*

Impact of oxygen breathing



Montay-Gruel *PNAS* 2019

FLASH – Summary of biological findings

Compared to conventional dose rate irradiation, FLASH achieves:

- Reduced normal tissue injury
  - Multiple organ systems: lung, brain, intestinal tract, skin
  - Multiple mouse strains, multiple species
- Equal or better tumor killing *in vivo*
  - Multiple tumor models

Take home points

- Ultra-rapid FLASH has shown the potential for increased therapeutic index for cancer therapy in multiple preclinical models
- Radically new technologies are being developed to deliver FLASH for general cancer radiotherapy indications
- There is much more to be studied biologically, technologically, and clinically

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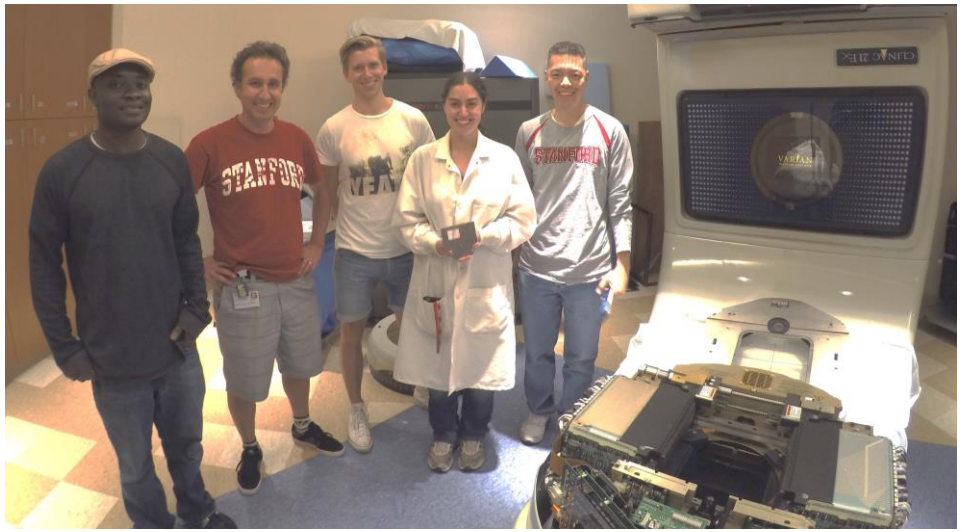
B Loo/P Maxim Lab:
Jinghui Wang
Rakesh Manjappa
Stavros Meleminidis
Dylan Yamabe
Ryan Ko
Emil Schueler
Fred Lartey
Nathaniel Scher
Duaa Al Rawi
Anna Kim
Marjan Rafat

Medical Physics:
Karl Bush
Amy Yu

Max Diehn Lab:
Jason Ross

Jianghong Rao Lab:
Xianchuang Zheng
Liyang Cui



Erinn Rankin Lab:
Stephanie Chow
Karen Levy
Joshua Eggold
Suchitra Natarajan
Phoebe Loo
Hussein Shehade

Ted Graves Lab:
Luis Soto

Richard Frock Lab:
Paul Barghouth

Quynh Le Lab:
Dhanya Nambiar
Hongbin Cao
Vignesh Viswanathan

Frank Longo Lab:
Danielle Simmons

Immunology:
Ed Engleman
Sam Strober
Suparna Dutt

Comparative Medicine:
Kerriann Casey

Guillem Pratx Lab:
Byunghang Ha
Syamantak Khan

MDACC:
Albert Koong
Chih-Chien Chou

Korea:
G-One Ahn (POSTECH)
Hak Jae Kim (SNU)

SLAC:
Sami Tantawi
Aaron Tremaine
Muhammad Shumail
Chris Nantista
Mark Kemp
Matt Franzi
Brandon Weatherford