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# The Current Status and Future Outlook of FLASH RT Delivery Systems

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# Disclosures



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



# What is FLASH?

## Ultra-rapid radiation treatment (dose rate $> \sim 40$ 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)



# Why FLASH - Therapeutic index

## Holthusen's hypothesis

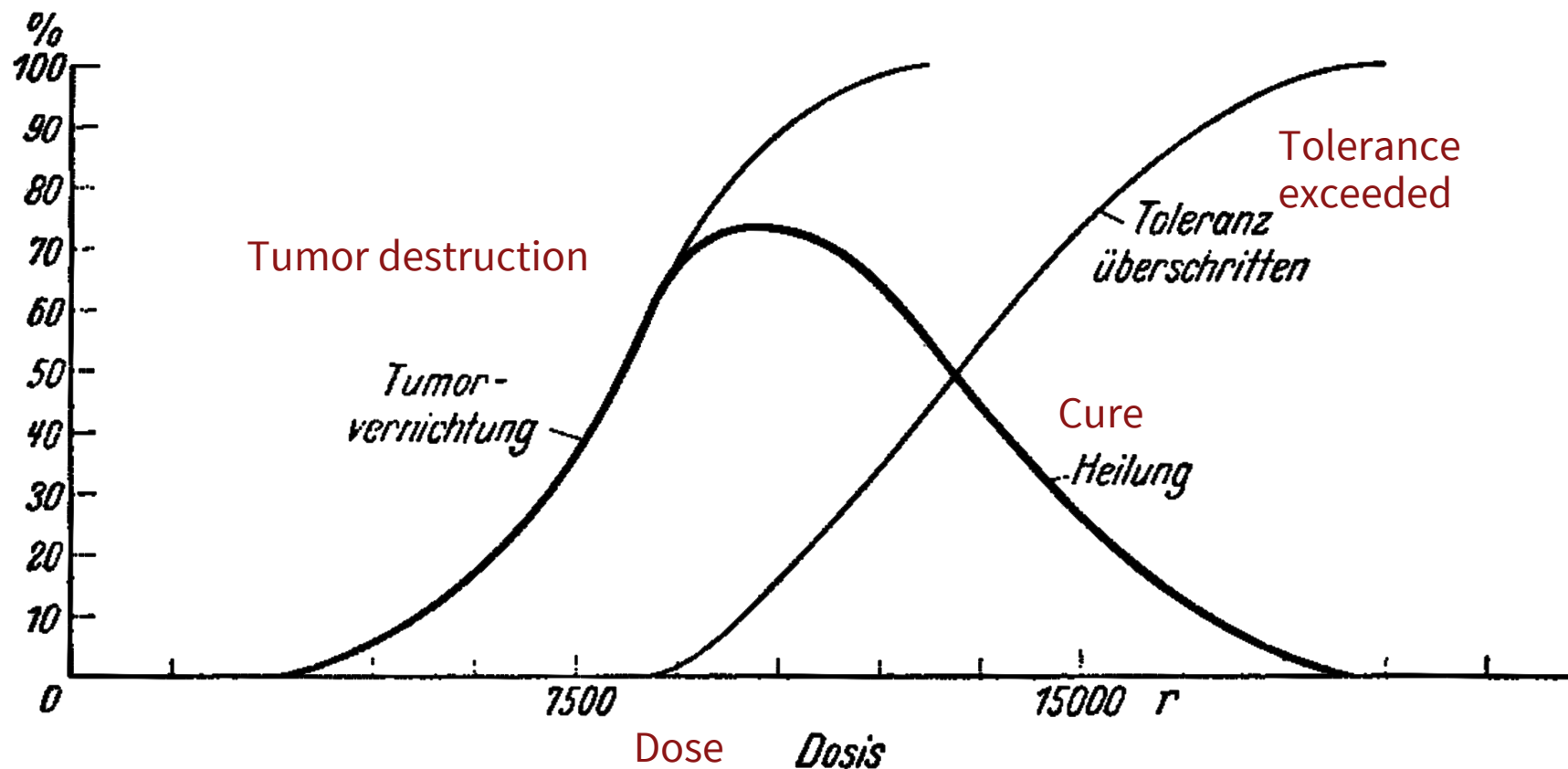


Bild 6.

Holthusen Strahlenther Onkol 1936



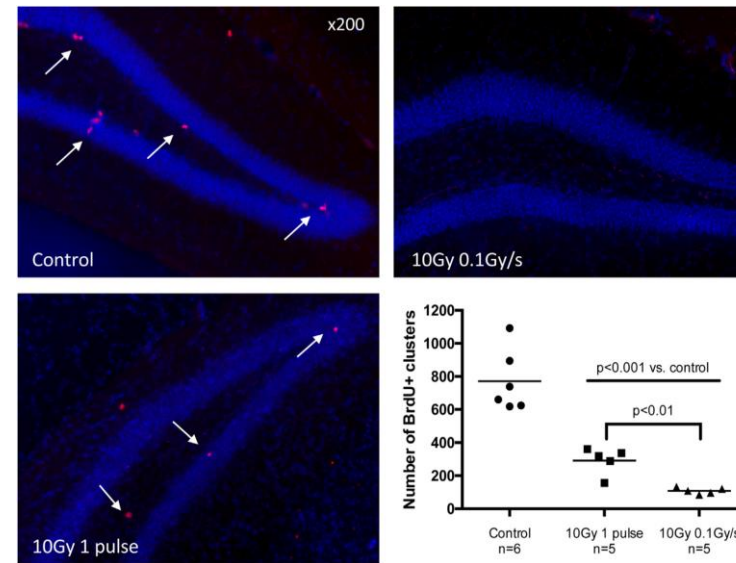
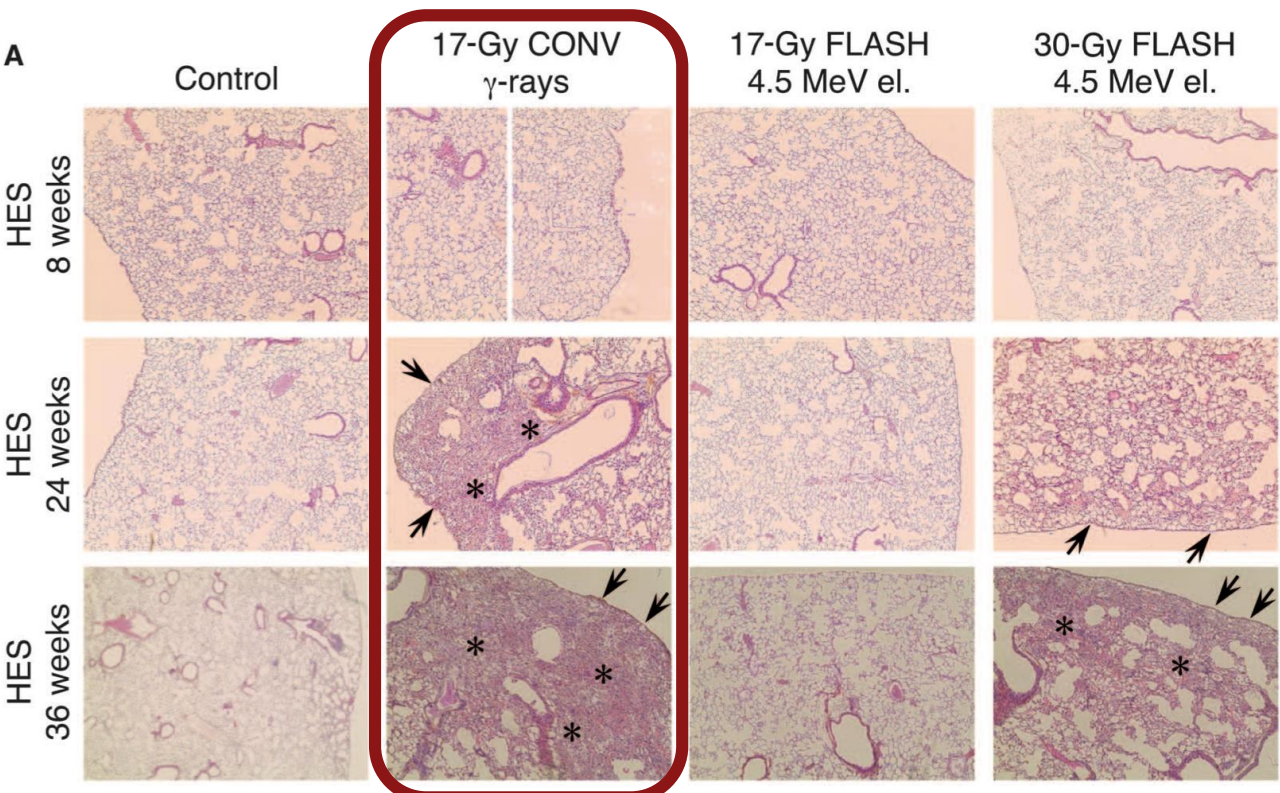


# Ultra-rapid "FLASH" RT: New biology

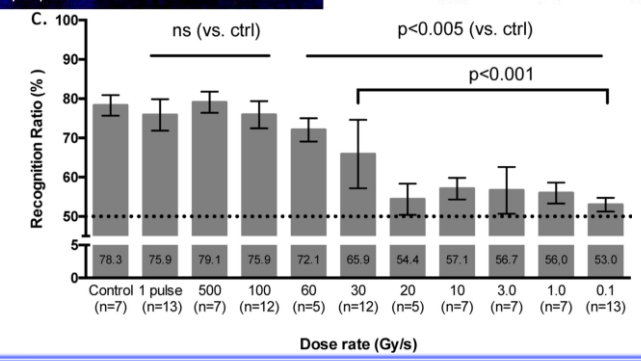
## Normal organ sparing

### Lung

### Brain



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



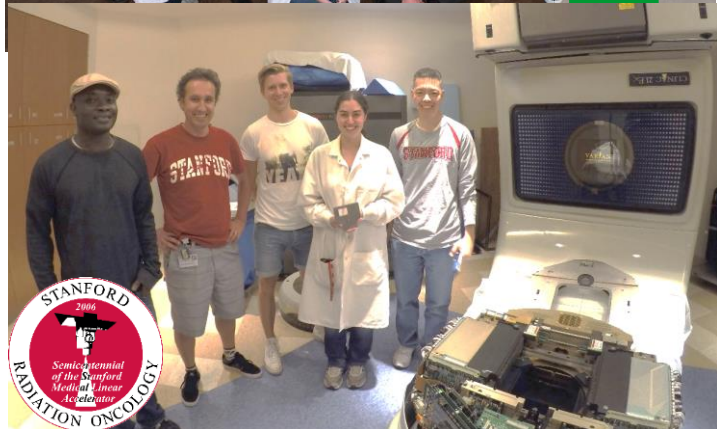
Montay-Gruel  
Radiother  
Oncol 2017

Favaudon Science Translat Med 2014



# 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

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

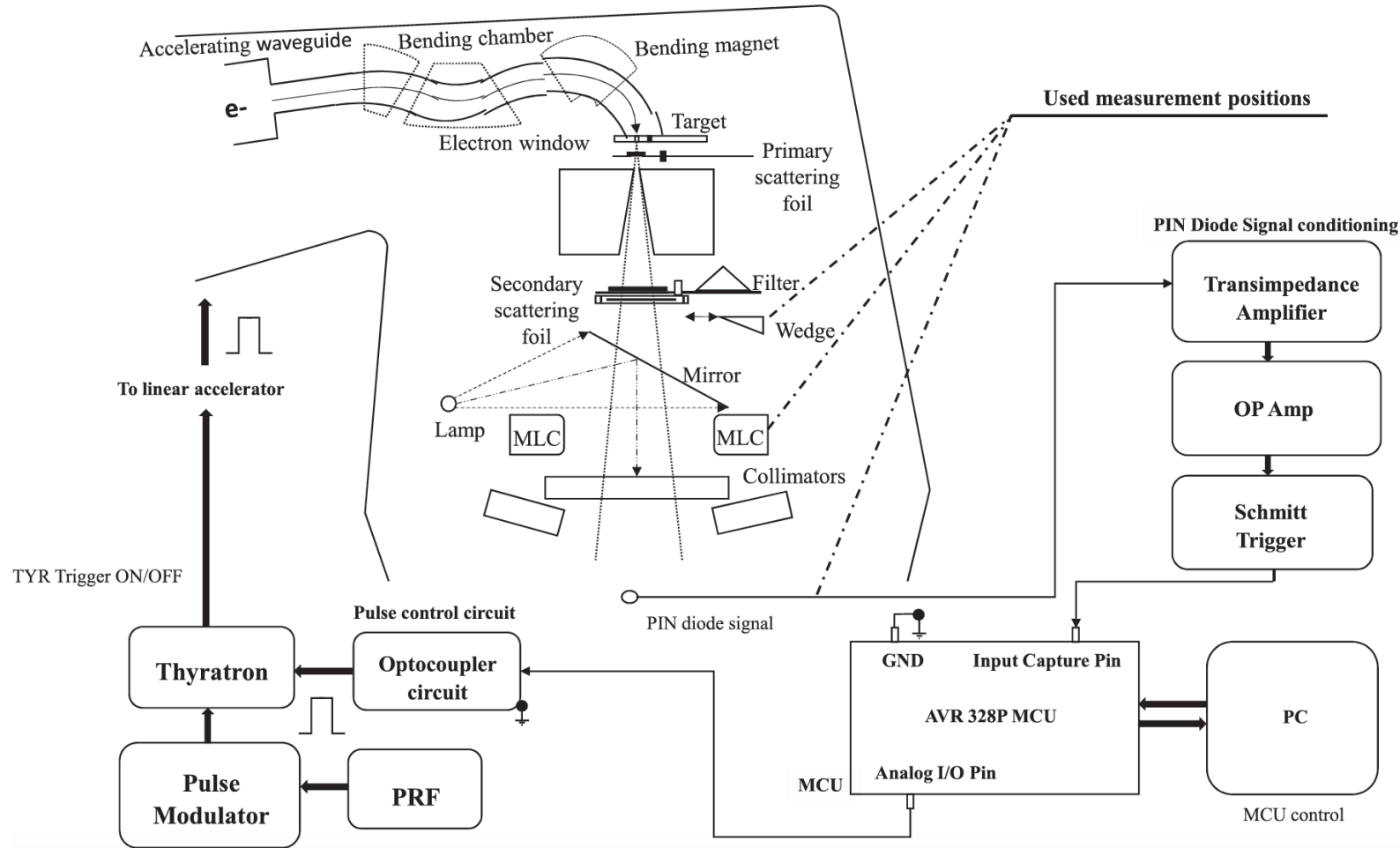


- Oriatron 6e
- Dose rates: few Gy/min - >1000Gy/s
- Wide range of parameters
- Gun current, pulse-repetition frequency, pulse width, and SSD
- Dosimetry characterized





# MeV electron FLASH -RT at Lund University



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

Lempart Radiother Oncol 2018







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# Proton FLASH RT at U Penn / Groningen

- IBA Proton RT
- March 2019 IBA announced first proton FLASH-RT at University Medical Center Groningen
- May 2020 – Mevion/Wash U announced 226Gy/s FLASH at Bragg peak using 230MeV proton beam





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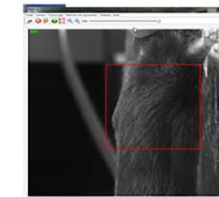
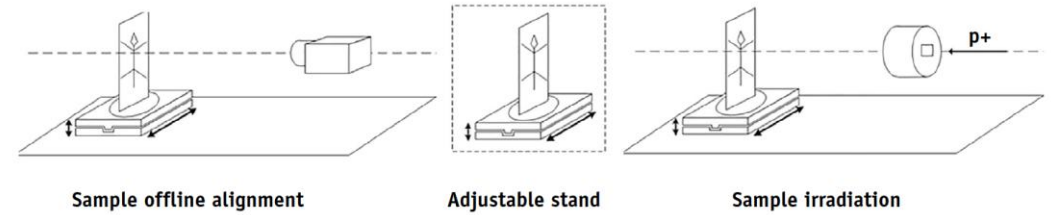
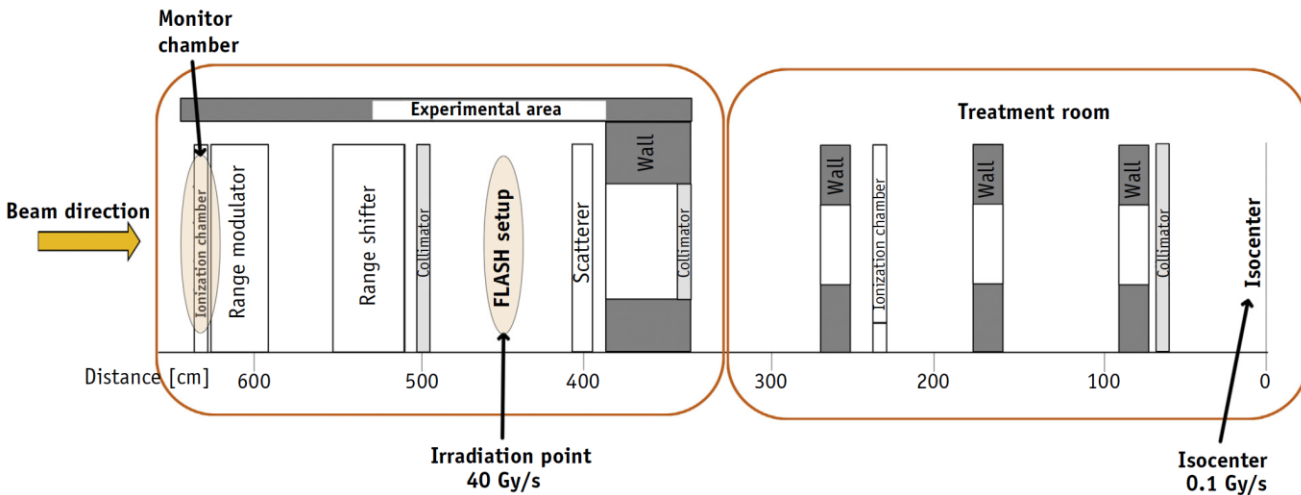
# Proton FLASH RT at U Maryland

- Varian FLASH Forward Consortium / U Maryland
- Modified clinical ProBeam
- FLASH (40Gy/s) vs conv proton RT (1Gy/s)
- 30% reduction in lung fibrosis with FLASH in mice
- Reduced incidence of skin dermatitis and improved overall survival in FLASH- vs conventionally-treated mice

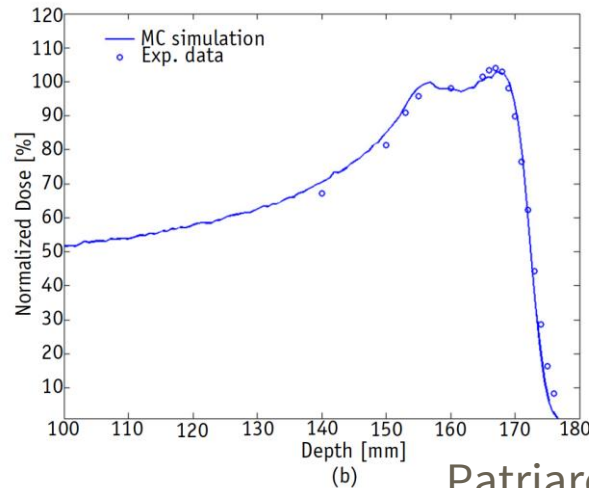
*Ghirdani Annual conference AACR 2019*



# Proton FLASH RT at Institut Curie



(a)



(b) Patriarca IJROBP 2018

- 138 MeV and 198 MeV:
- > 40Gy/s
- 3D printed Lucite ridge filter
- 2 cm spread-out Bragg peak
- Offline animal immobilization
- Camera alignment system
- Aperture for irradiation



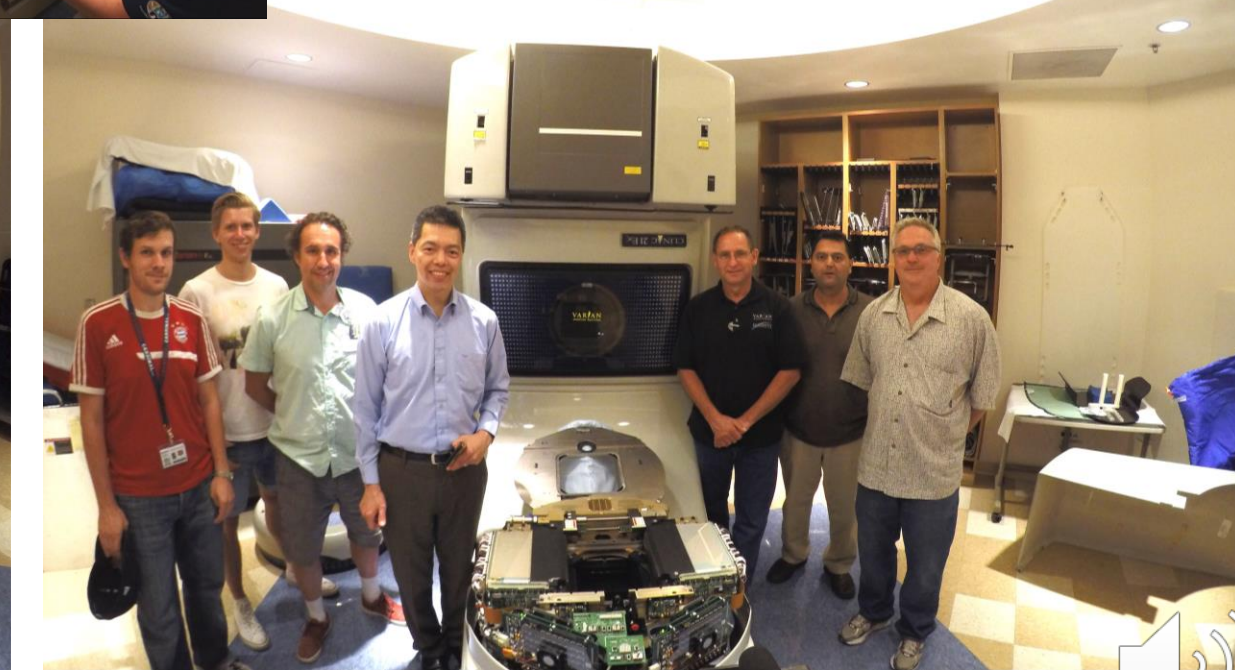
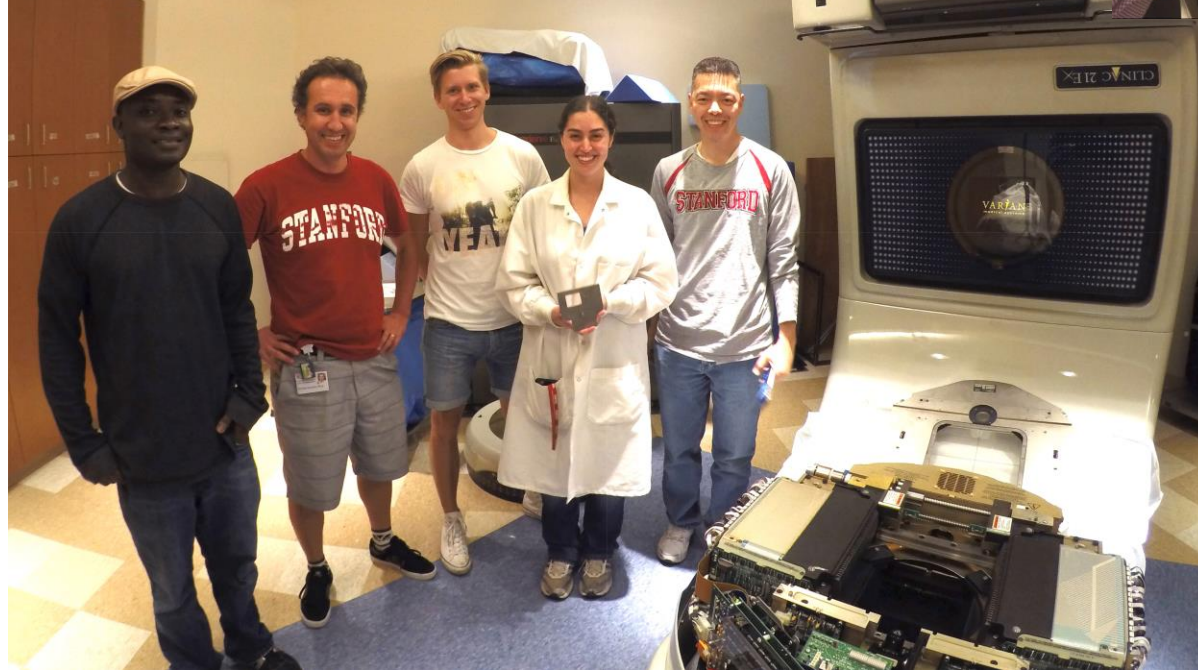
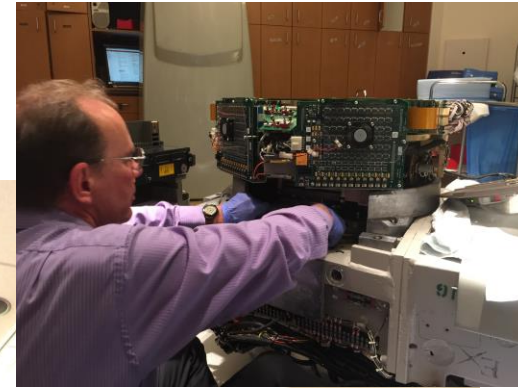
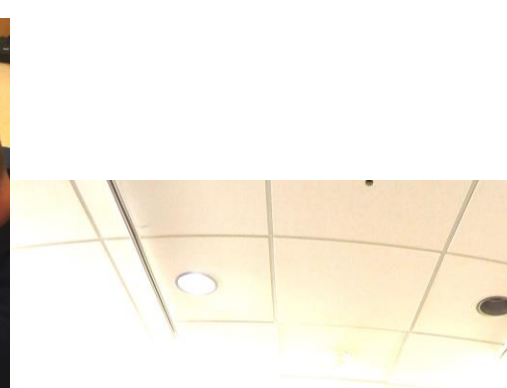
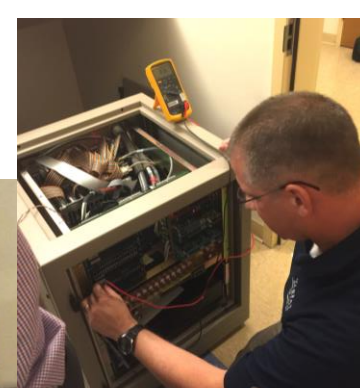


# FLASH experiments at Stanford and IU



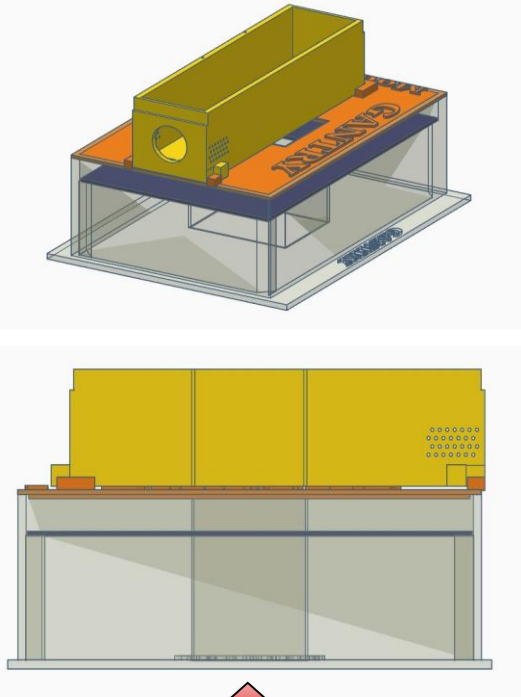
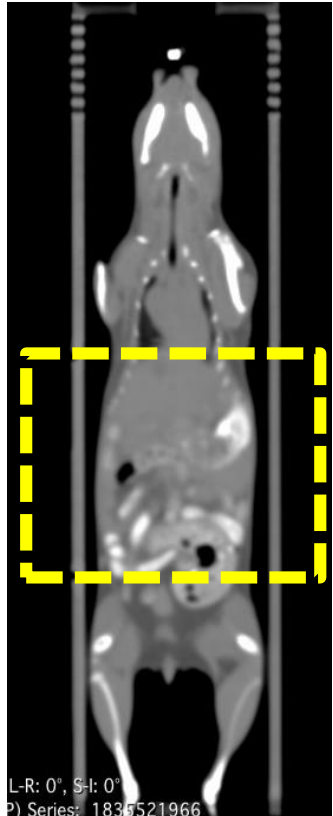
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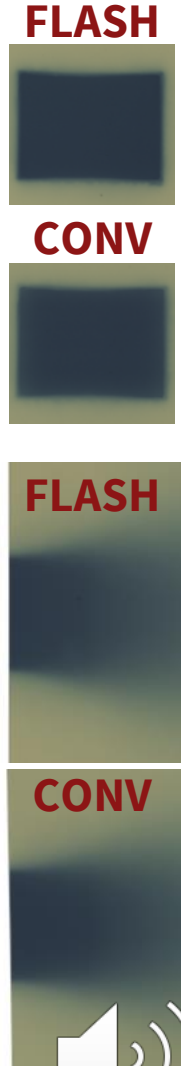
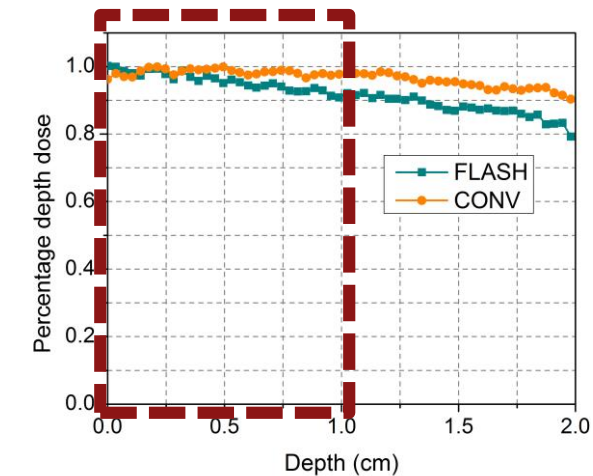
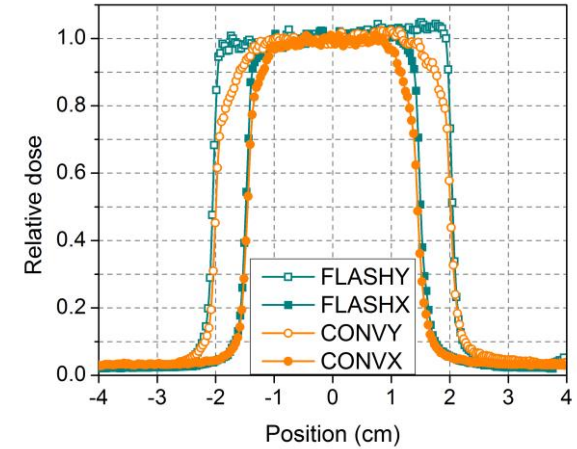




# FLASH total abdomen irradiation



~16 MeV FLASH e<sup>-</sup>



Levy/Rankin, Wang/Loo/Maxim Unpublished 2019



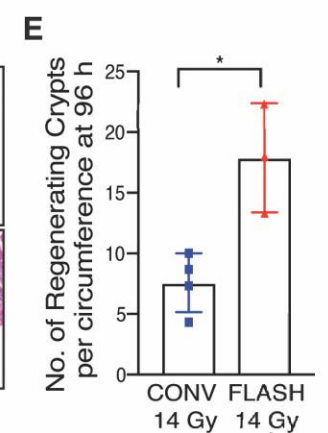
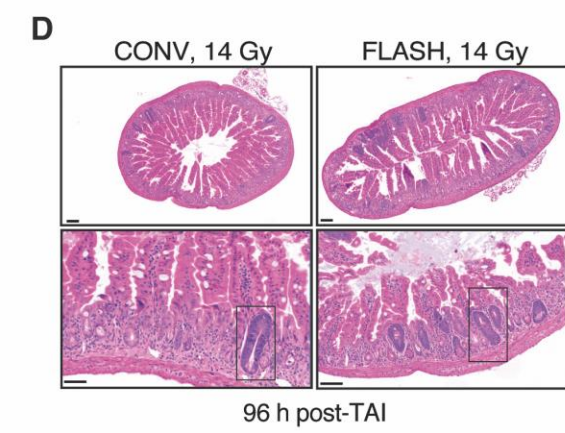
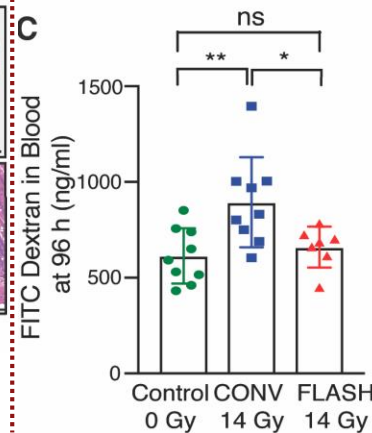
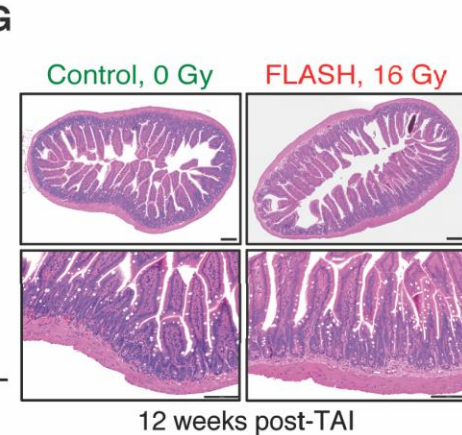
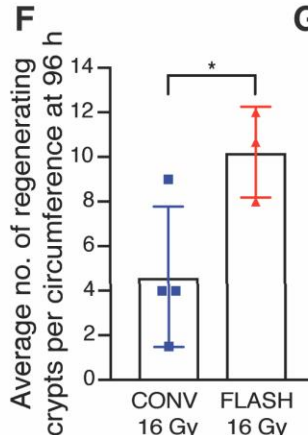
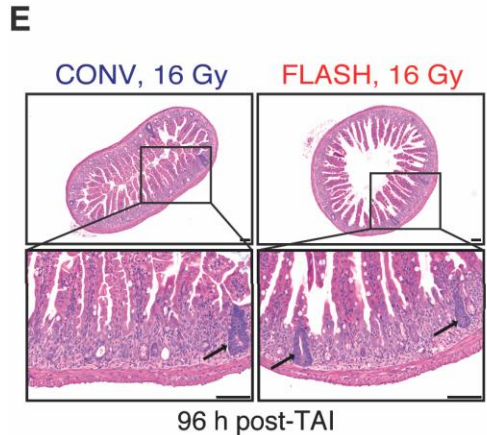
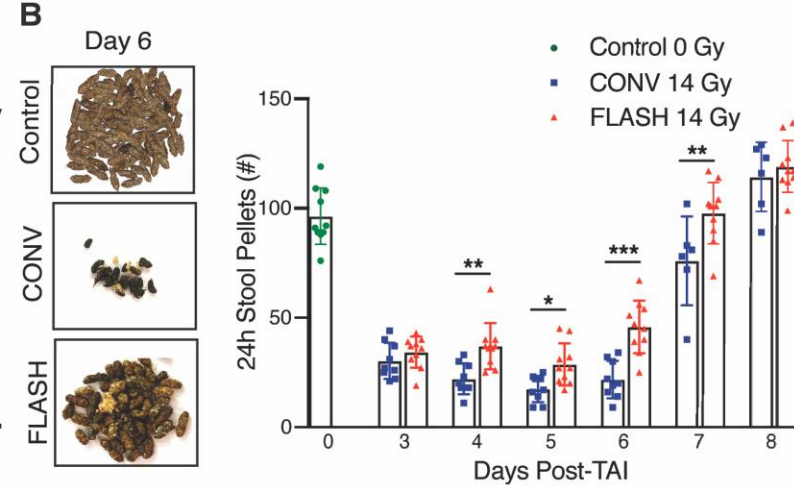
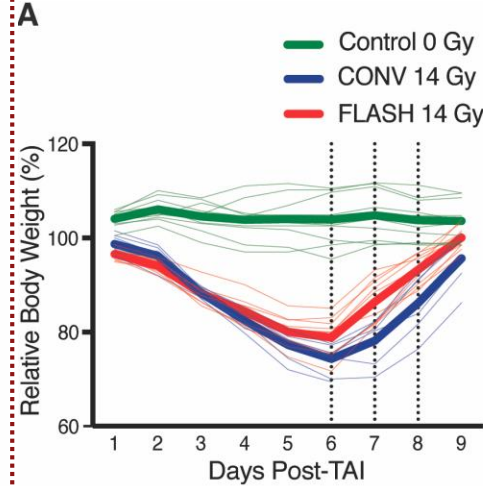
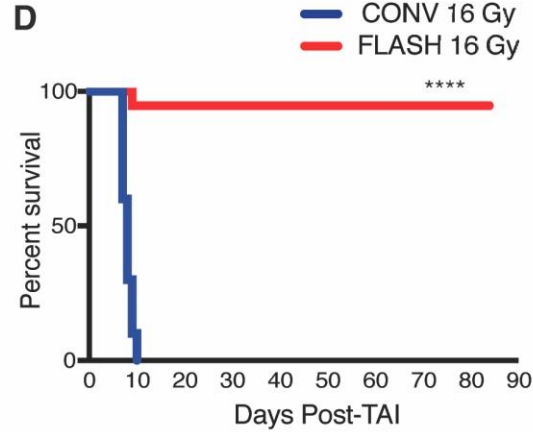
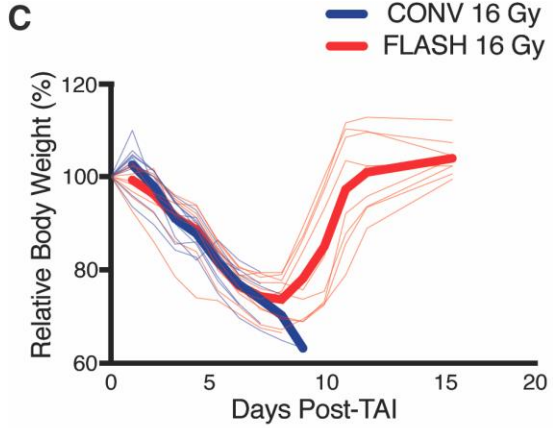
# FLASH total abdomen irradiation



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## 16 Gy (lethal dose)

## 14 Gy (sublethal dose)



**Normal female C57BL/6 mice**

Levy/Natarajan/Wang *bioRxiv* 2019

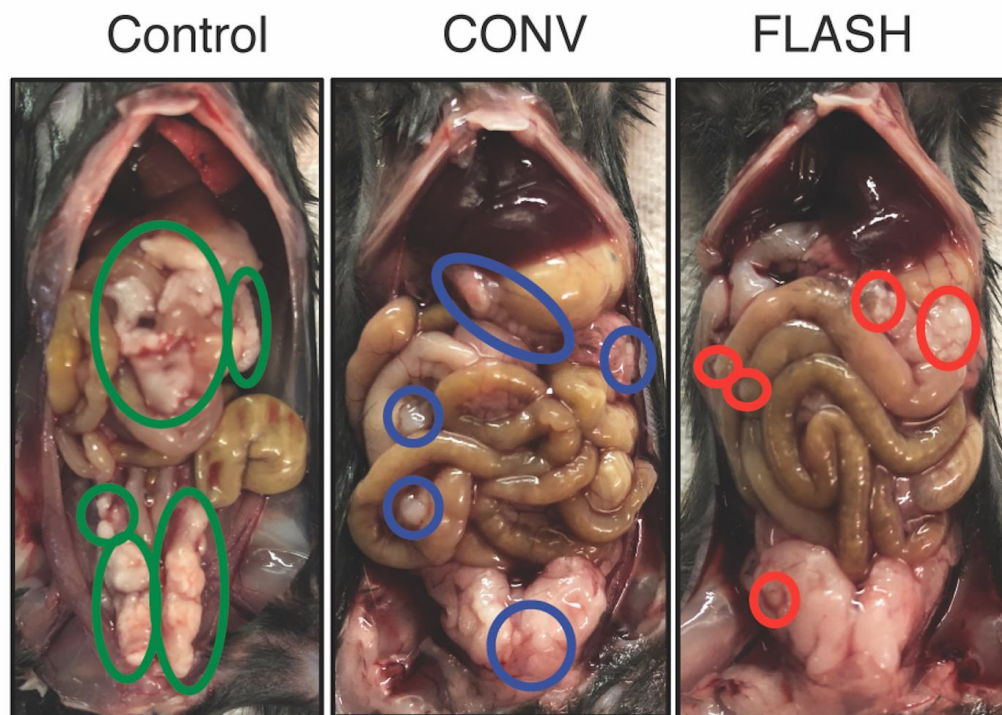




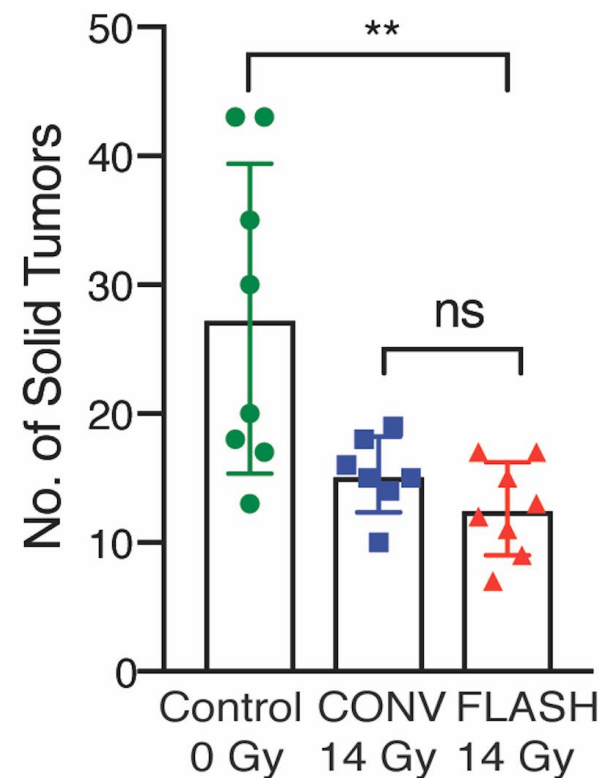
# FLASH total abdomen irradiation

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

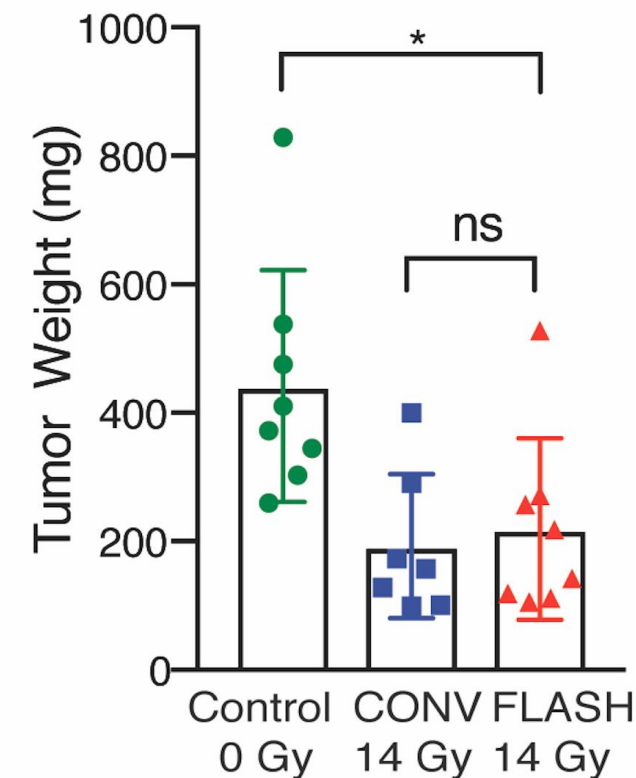
E



F



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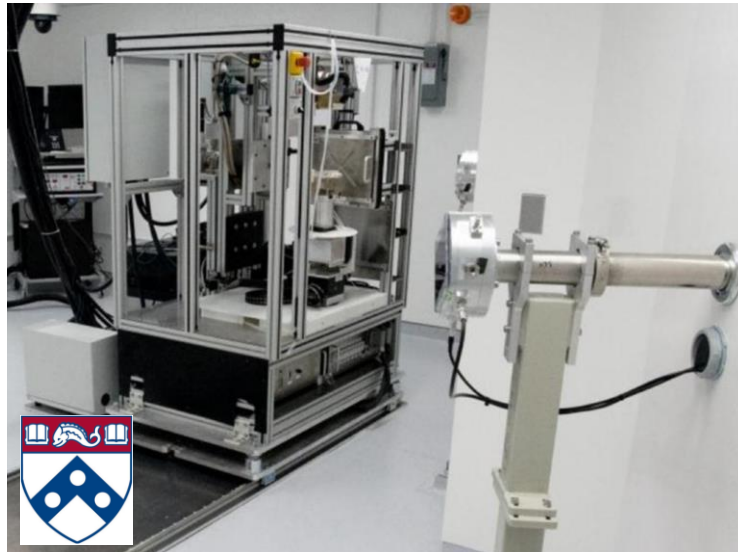
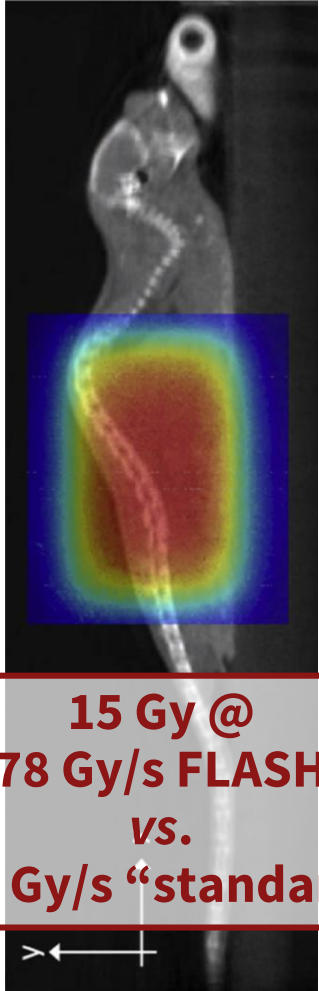


Levy/Natarajan/Wang *bioRxiv* 2019

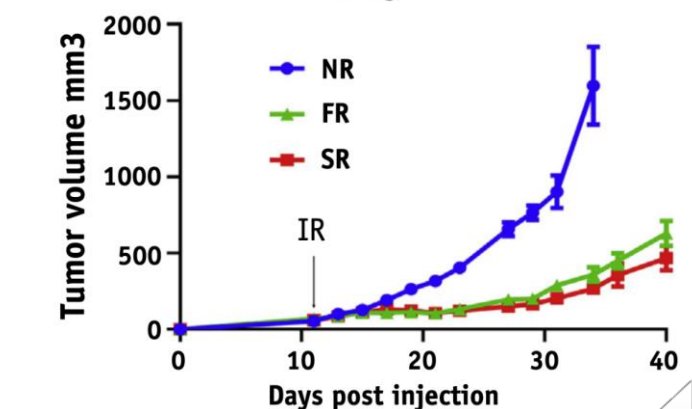
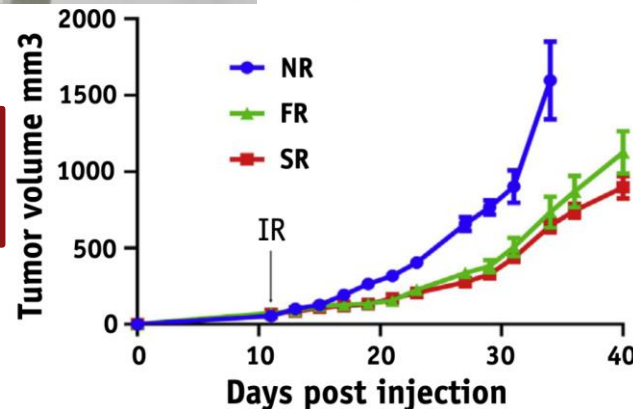
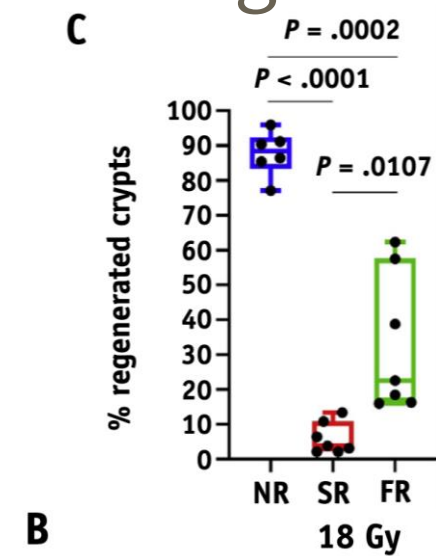
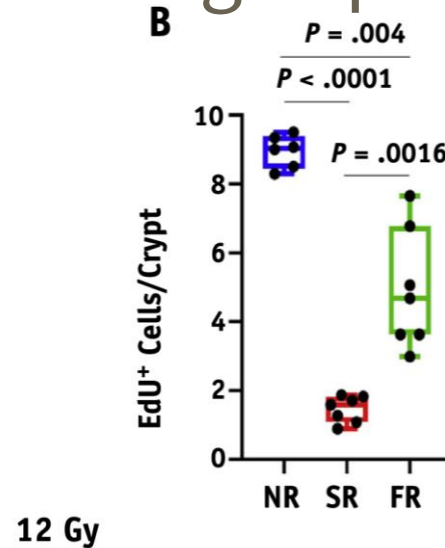


# FLASH proton total abdomen irradiation

Proton beam 230 MeV treating in plateau region



**MH641905 flank tumors**



Diffenderfer *IJROBP* 2020





# FLASH – Summary of biological findings

Compared to conventional dose rate irradiation, FLASH achieves:

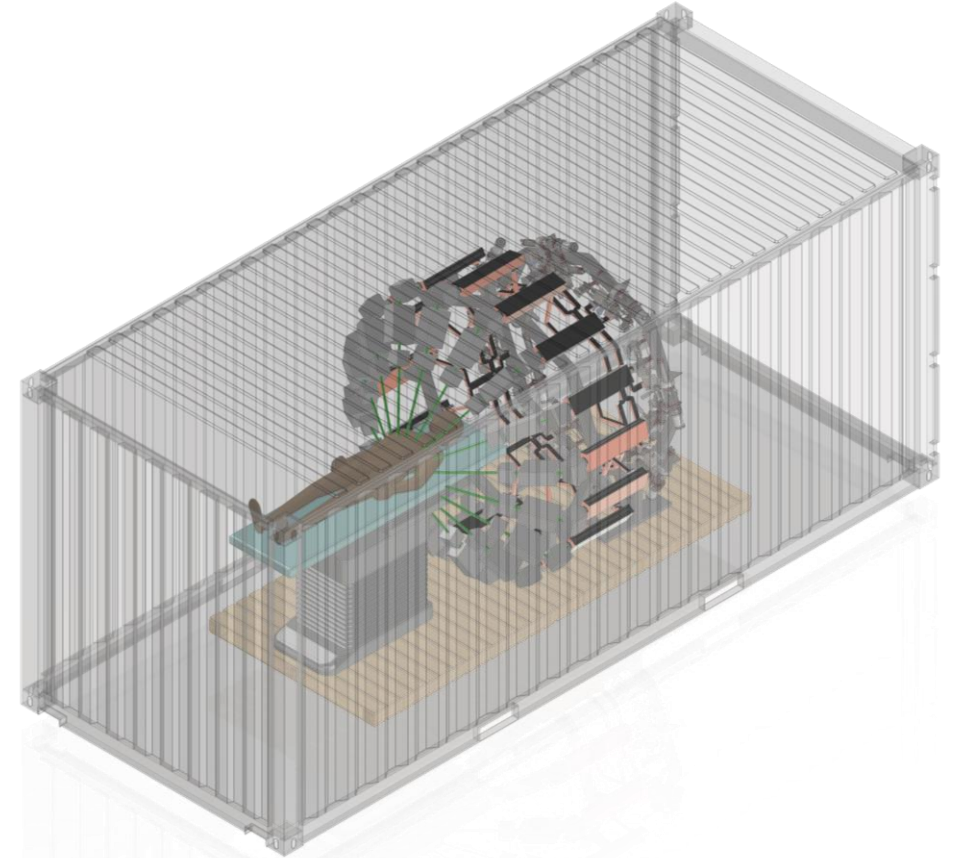
- Reduced normal tissue injury
  - Multiple organ systems: lung, brain, intestinal tract, skin
  - Multiple mouse strains, multiple species
- Equal or better tumor killing *in vivo*
  - Multiple tumor models





# PHASER: Next generation radiation therapy

## Pluridirectional High-energy Agile Scanning Electronic Radiotherapy (PHASER)



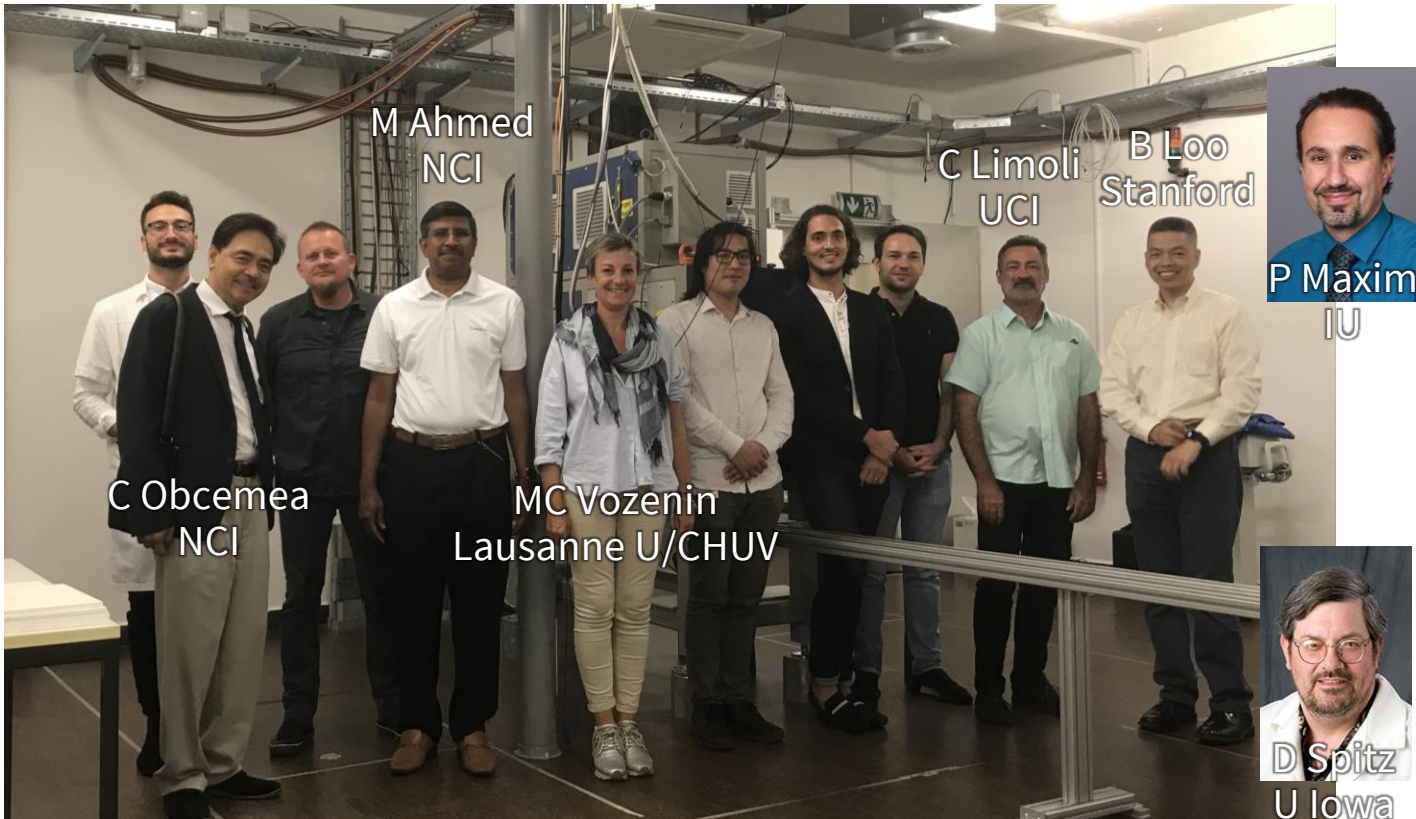
- **400X faster:** Freezes motion, ultimate precision
- **FLASH RT:** New biological advantages
- **Compact & economical:** Global access to RT



# Multi-center FLASH collaboration

## NCI program project grant proposal

- 4 projects on brain tumor and normal brain responses to FLASH, and mechanisms – led by Stanford, UCI, Lausanne U, and U Iowa
- 3 cores including FLASH irradiation infrastructure and neurocognition – led by Stanford/IU and UCI



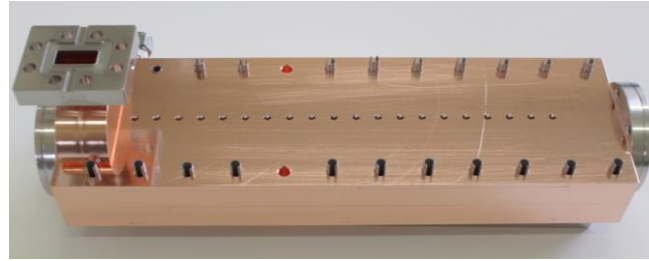
FLASH electron linac facility at Lausanne U/CHUV



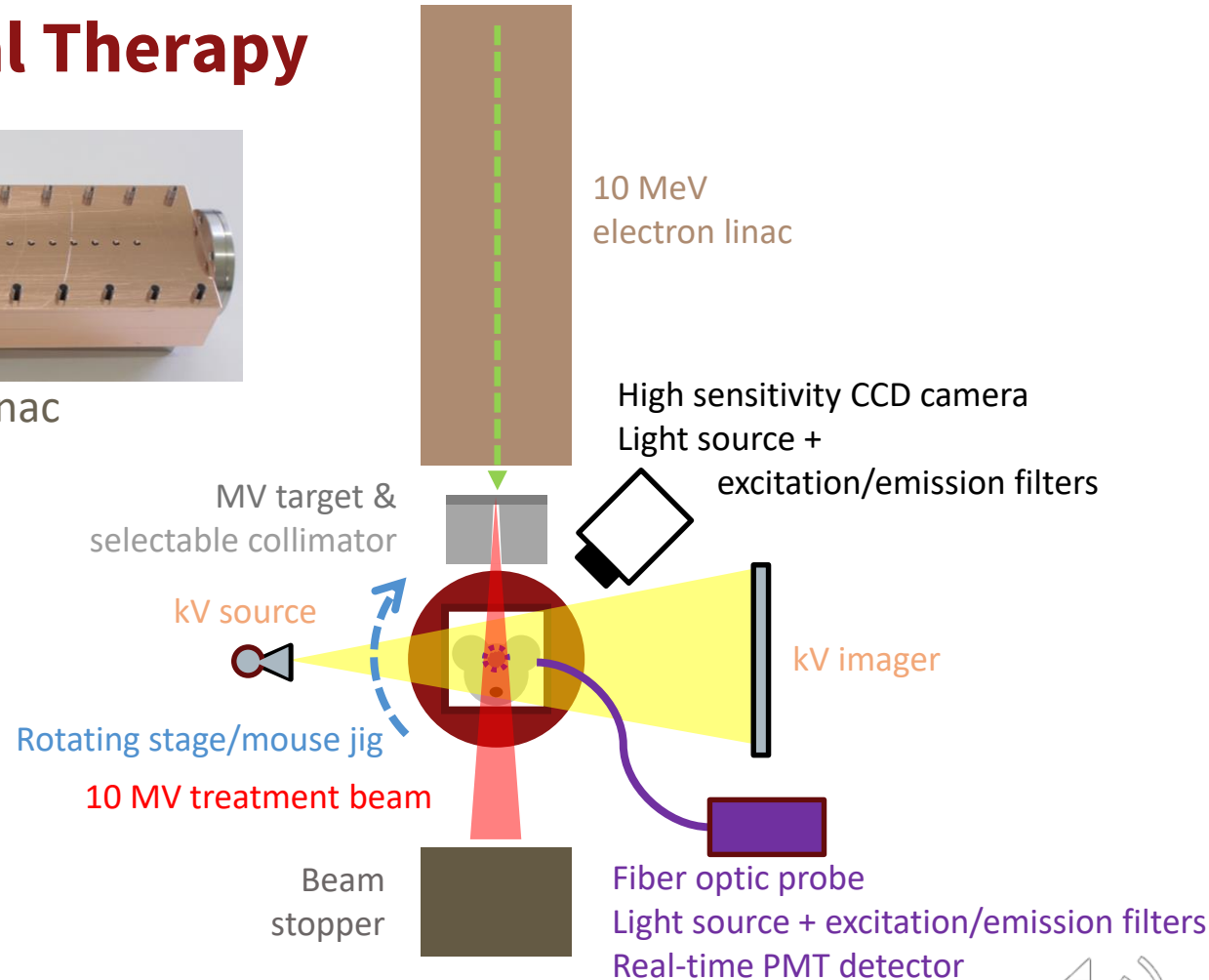
# Immediate next step: preclinical system

## FLASH Experimental X-ray Conformal Therapy (FLASH-EXaCT)

6MW commercial modulator/klystron



DRAGON linac



International collaboration:  
UC Irvine, Stanford Rad Onc/SLAC,  
Lausanne U/CHUV, Indiana U, U Iowa





# 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



# Supported by



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Dylan Yamabe  
Ryan Ko  
Emil Schueler  
Fred Lartey  
Nathaniel Scher  
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Anna Kim

Marjan Rafat

## **Medical Physics:**

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Amy Yu

## **Max Diehn Lab:**

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