Novel Ultrafast Transparent Online FLASH Monitor and Dosimeter

P. Friedman – *President & CEO, Integrated Sensors, LLC*

R. Schulte, V. Bashkirov – *Loma Linda University*

D. Levin, N. Ristow, C. Ferretti, D. Litzenberg – *University of Michigan*

Description

An Ultra-Fast & Transparent ("**UFT**") *large-area* *(26 cm x 30 cm)*, *real-time* beam monitor is being developed for all types of FLASH-RT and Particle Therapy (e.g., electrons, protons, alphas, carbon ions, photons and neutrons). The UFT beam monitor is based on two different novel, highly efficient, microcrystalline polymer & hybrid scintillators along with a number of system hardware / software innovations.

Proof-of-Concept was demonstrated in 2019. Phase-II from the National Cancer Institute (NIH) was initiated Sept 2021 for prototype development & demonstration.

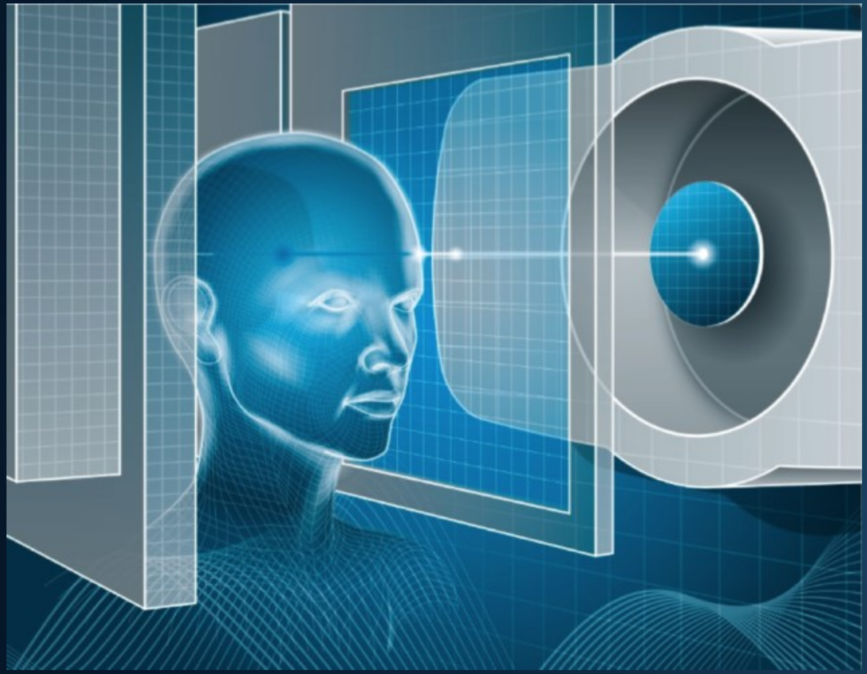
For FLASH-RT, the UFT beam monitor continuously analyzes the incident beam immediately in front of the patient every ***100 µs*** as the patient is irradiated.

Major Problem – Monitoring FLASH Delivery

- FLASH is ~ ***1,000* times faster** with order-of-magnitude higher dose (e.g., ≥ 20 Gy) than conventionally-fractionated RT (~ 2 Gy)

- FLASH dose is typically delivered in **≤ 0.5 sec**. For *proton*-FLASH the corresponding beam flux is ~ **10^{11} to 10^{12}** protons / cm^2 s

- Standard dosimetry methods are not fast enough and ***do not work*** at the radiation intensity of FLASH delivery



Solution

Integrated Sensors (I-S) **Breakthrough**: *Ultra-Fast & Transmissive* (UFT) beam monitor *technology*, *originally developed for nuclear physics*, can continuously analyze FLASH beam every **100 μs** as patient is irradiated, allowing ultra-high dosing with reduced toxicity resulting in better tumor response, making it an enabling technology for FLASH-RT.

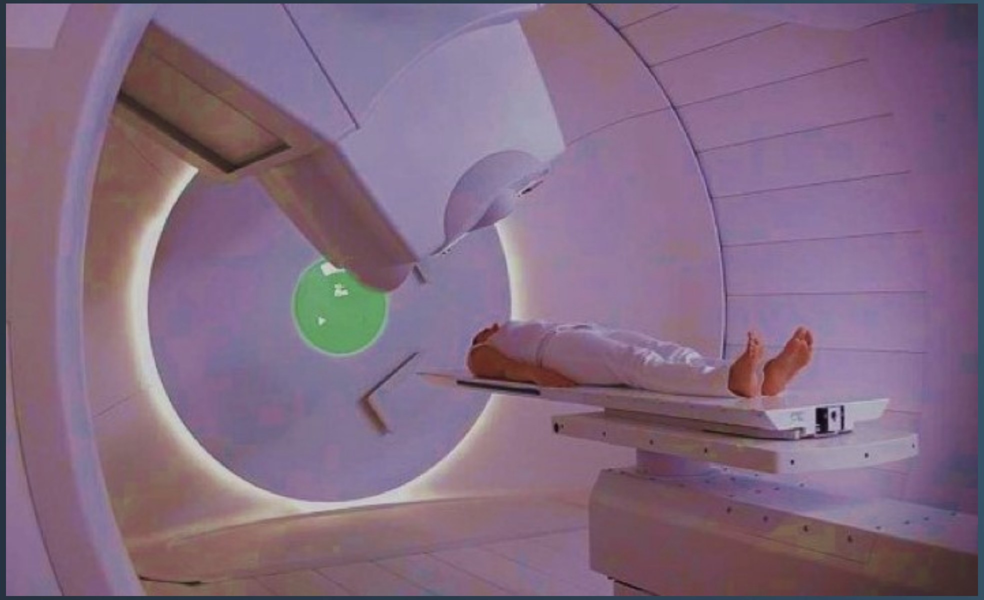
"At Varian, we are aware that dosimetry systems have to be developed that could resolve and monitor very short (microsecond) pulses of radiation with ultra-high dose rates. Your technology promises to fulfill that goal and would thus overcome this critical barrier."

Deepak Khuntia, MD (March 9, 2020)
Senior VP and Chief Medical Officer at Varian Medical Systems

I-S Competitive Advantages

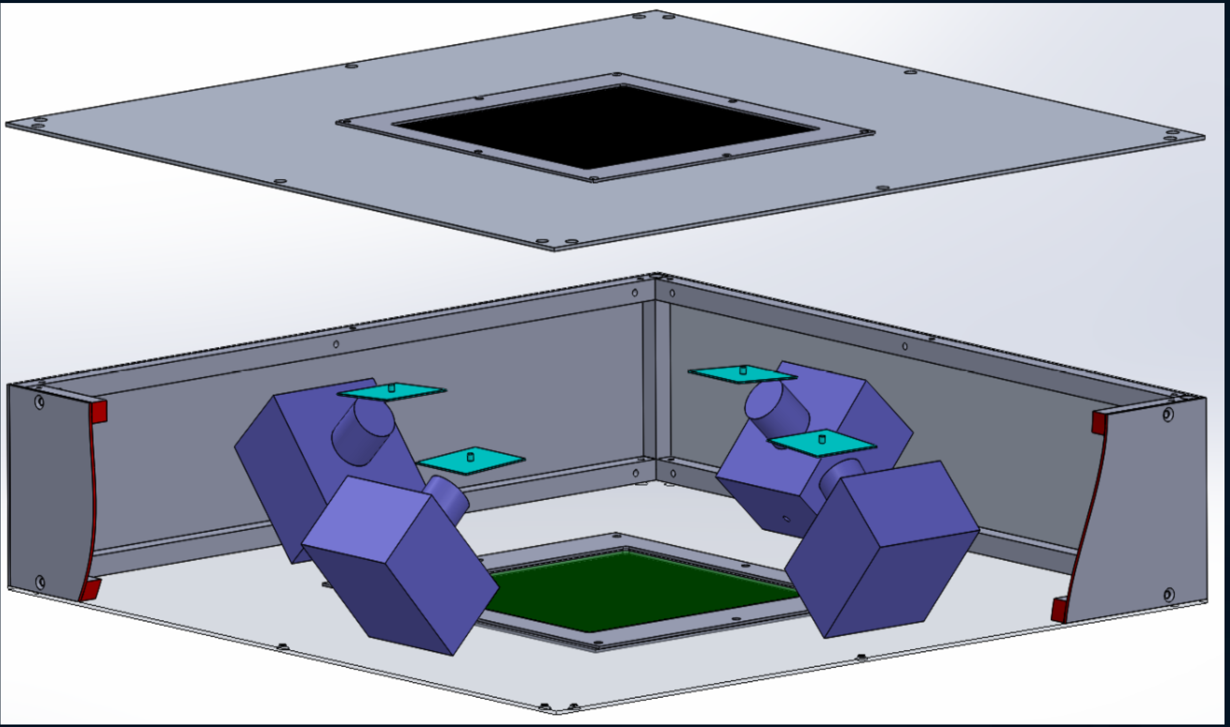
UFT beam monitor is a patented, enabling technology for FLASH-RT

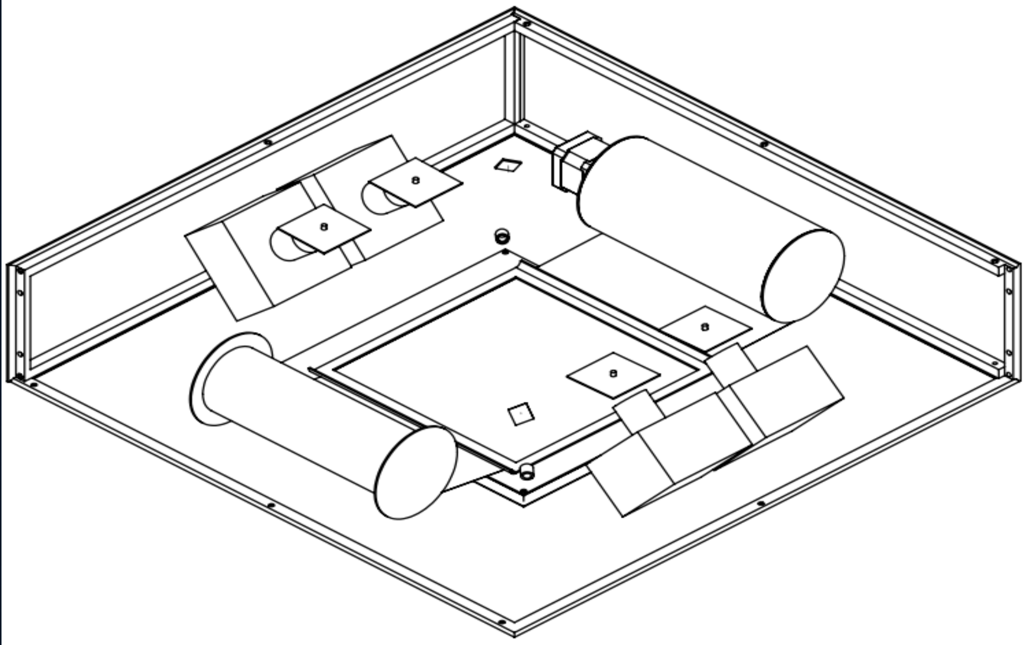
- Two New High Efficiency Scintillators
  - PM-scintillator (polymer) ultra-thin rolls
  - HM-scintillator (hybrid) highest efficiency
- Innovative UFT Patented Configurations
  - Ultra-fast beam analysis ~ **100 µs** *(continuous)*
  - Real-time dosimetry, beam position & shape
  - High spatial resolution (~ 10 – 100 µm)
  - Water-equivalent thickness about ~ 0.5 mm
  - Internal calibration
  - Multiple cameras & folded optics
  - Detector area: 26 cm x 30 cm (1st prototype)

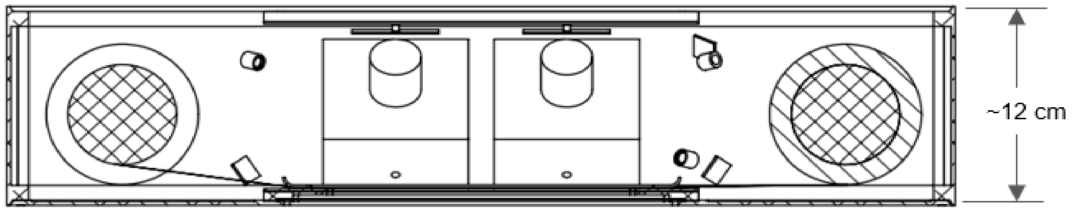


Many UFT Beam Monitor Configurations

Two examples with replaceable large-area (~ 26 x 30 cm) PM or HM scintillators







Real-time beam analysis & dosimetry with UV-LEDs and UV-photodiodes for internal calibration

Scintillator Rad Damage Test

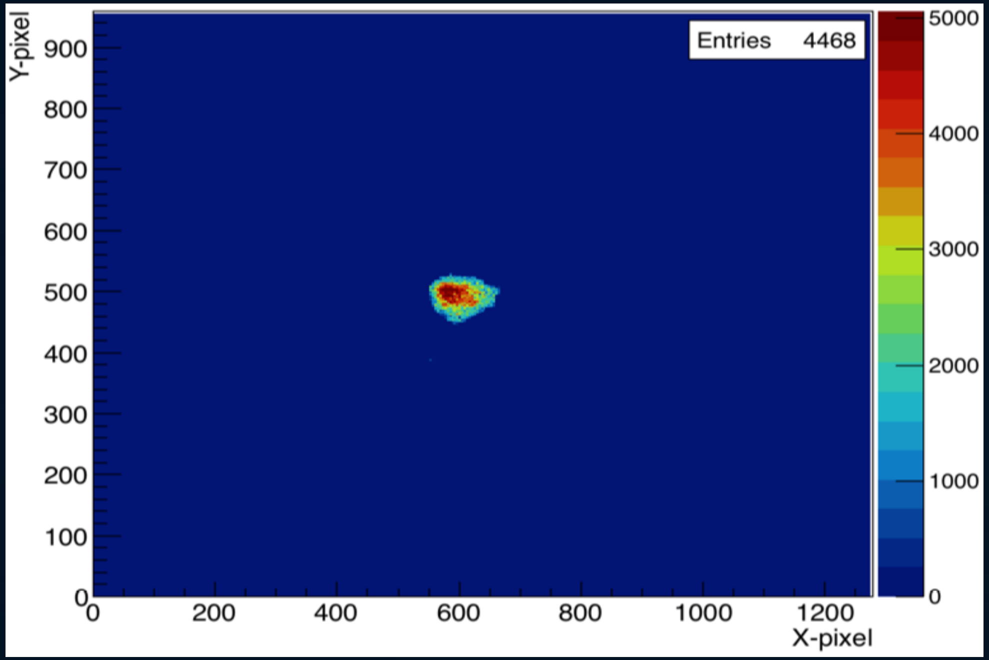
Univ. of Michigan proton beam *accelerated test* of 190 μm thick PM-scintillator

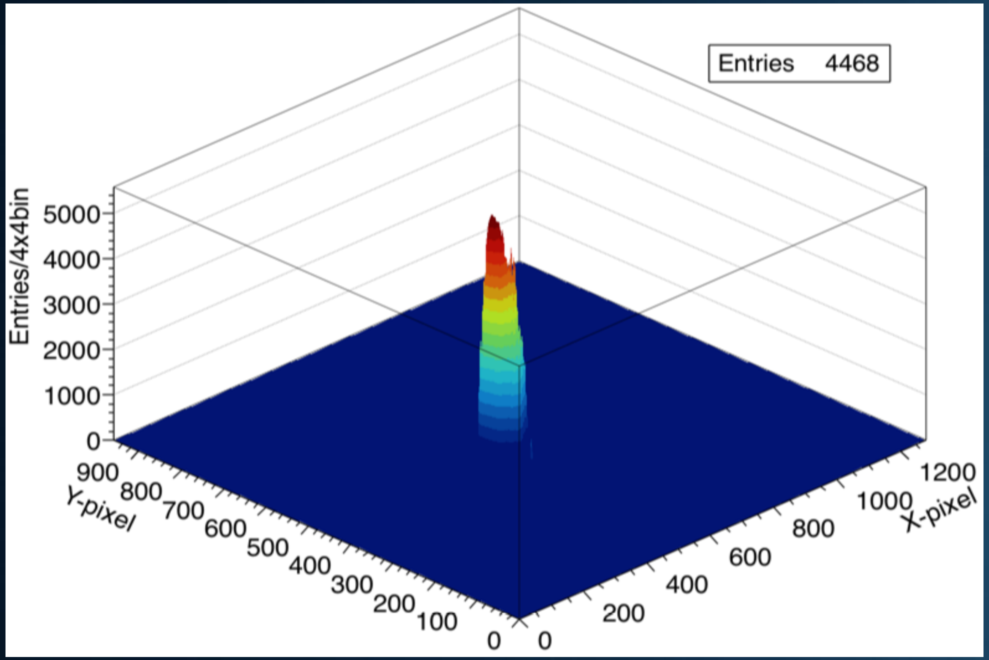
Dose Rate (kGy/s)	Beam Energy (MeV)	Total Dose (kGy)	PM-Scintillator Radiation Damage Observations
0.11*	5.4	**33**	**FLASH-RT**. No discoloration. **Minimal rad-damage, 60% recovery in 4 hours***
0.20*	5.4	**59**	**FLASH-RT**. No discoloration**. Minimal rad-damage, largely reversible***
3.3†	5.4	390	**Manageable rad-damage**. Very slight darkening that eventually disappeared†
9.2	3.0	490	Unacceptable rad-damage. No ablation but rapid fluorescence decrease
92	3.0	6,100	Slow surface ablation and immediate fluorescence decrease
460	3.0	15,000	*Immediate fast* surface ablation, burning hole through 60-70% of scintillator film
†Rate of 3,300 Gy/s with "manageable" rad-damage is well above that required for FLASH-RT			

***Radiation damage to scintillator per FLASH-RT treatment is ~ 0.001% (assuming FLASH dose delivered in 3 fractions of 7 Gy per fraction in 70 ms – i.e. dose rate of 100 Gy/sec). It would thus take ~ 1,000 patient FLASH treatments to degrade the scintillator response 1%. For conventional 2 Gy fractions, it would take ~ 3,500 patient treatments to degrade the scintillator signal response by 1%.**

PM-Scintillator Image at FLASH Dose Rate

Proton beam image (color coded) captured with *10 μs exposure * **using $200 camera**



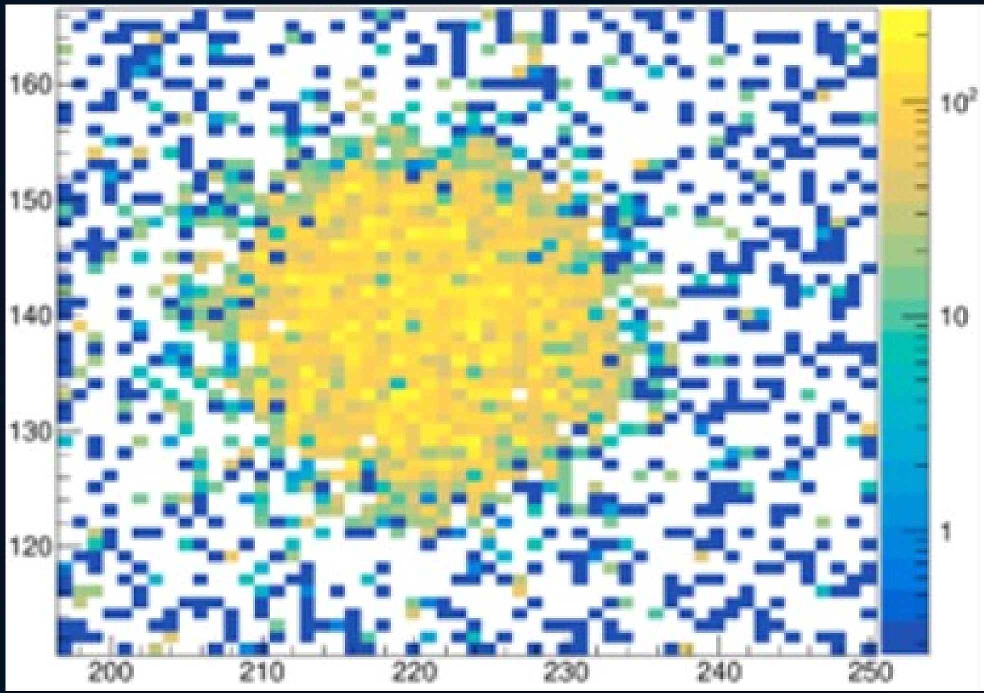


10 nA beam of 5.4 MeV protons moving at 80 mm/ms, through 190 μm thick PM-scintillator with diameter of ~2.5 mm. Particle flux corresponds to *FLASH dose rate of ~200 Gy/s.

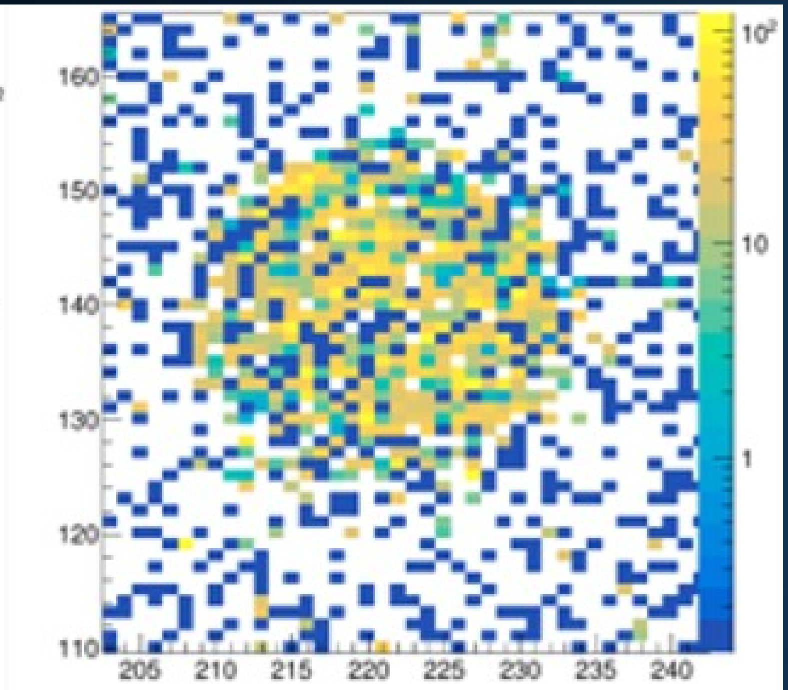
PM-Scintillator vs. BC-400

PM – scintillator ADC values ~ <u>250 counts</u> vs. BC-400 ADC values ~ <u>50 counts</u>

190 µm thick PM scintillator



200 µm thick BC-400



Identical setup for both scintillators – i.e., camera, optics and ^{90}Sr beta source (2 MHz / cm^2)

UFT Beam Monitor Performance

*Proton Beam Energy Loss through UFT Beam Monitor**

< 0.30 MeV at 70 MeV, **< 0.18 MeV** at 140 MeV, **< 0.14 MeV** at 210 MeV

*Beam Spread 70 cm Downstream from UFT Monitor Materials**

≤ 0.024 mm at 70 MeV, **≤ 0.006 mm** at 140 MeV, **≤ 0.003 mm** at 210 MeV

* *Calculated beam energy loss & lateral spread via TOPAS/Geant4 simulations*

$^{86}Kr^{+26}$ Beam on FRIB-ReA3 Beamline

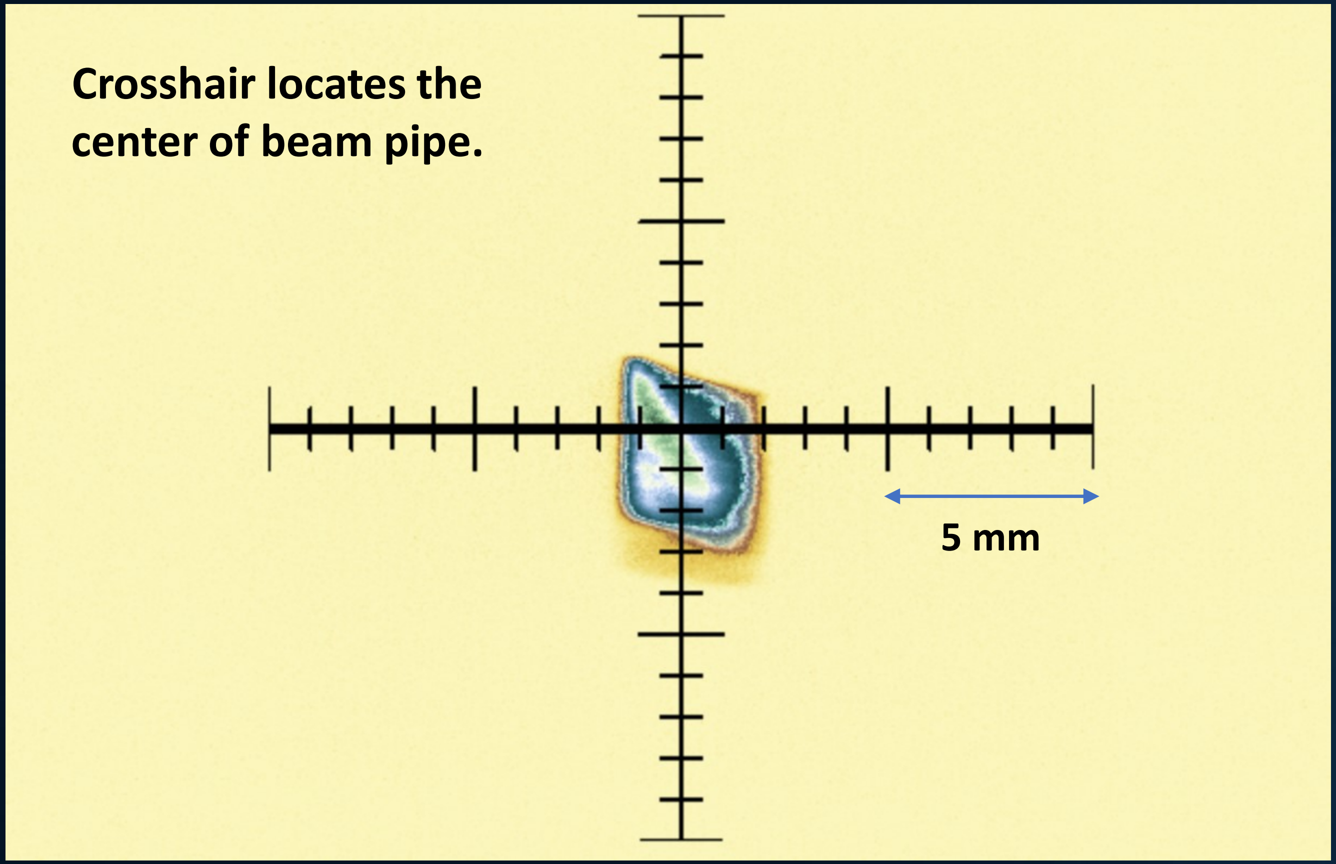
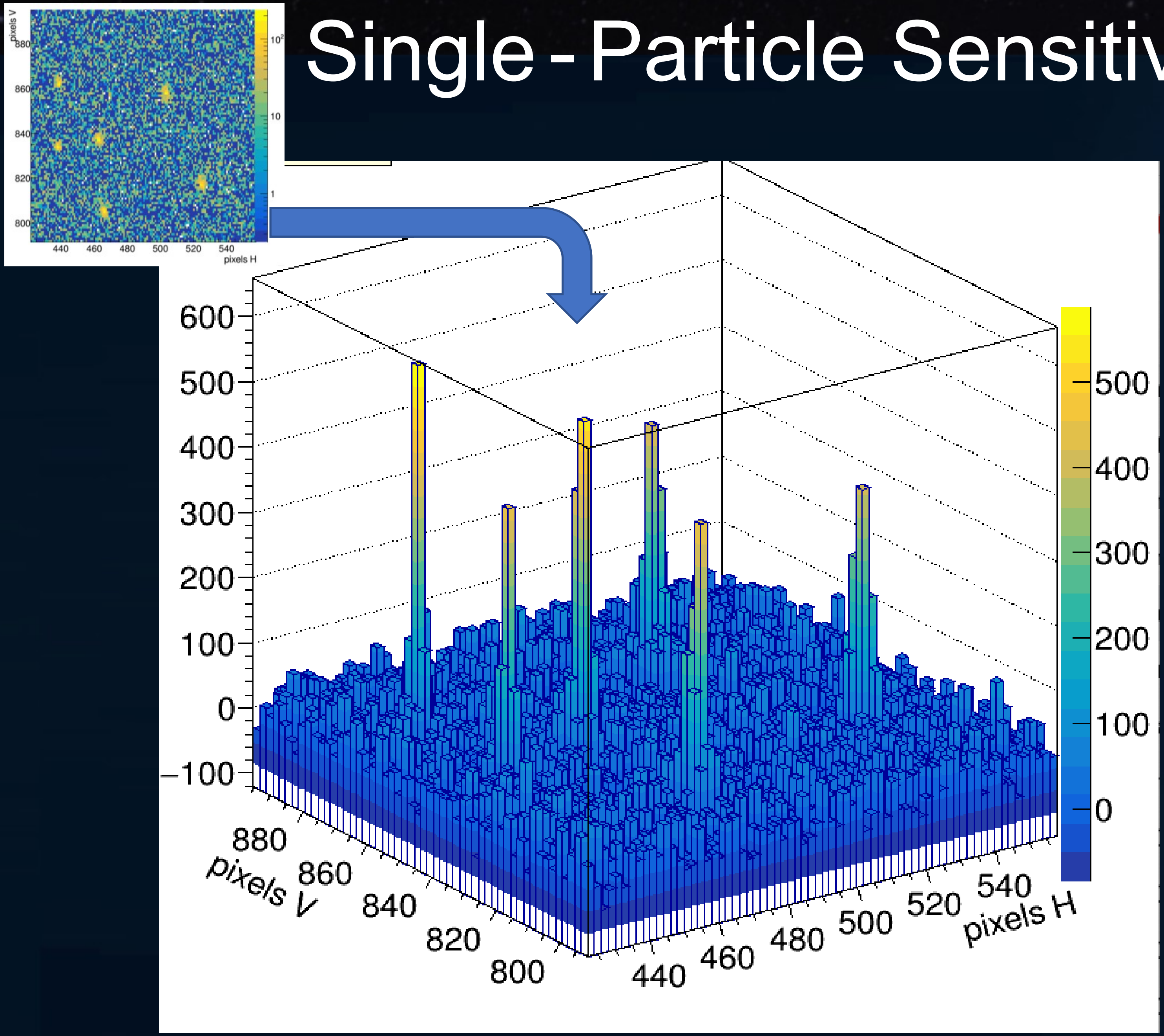


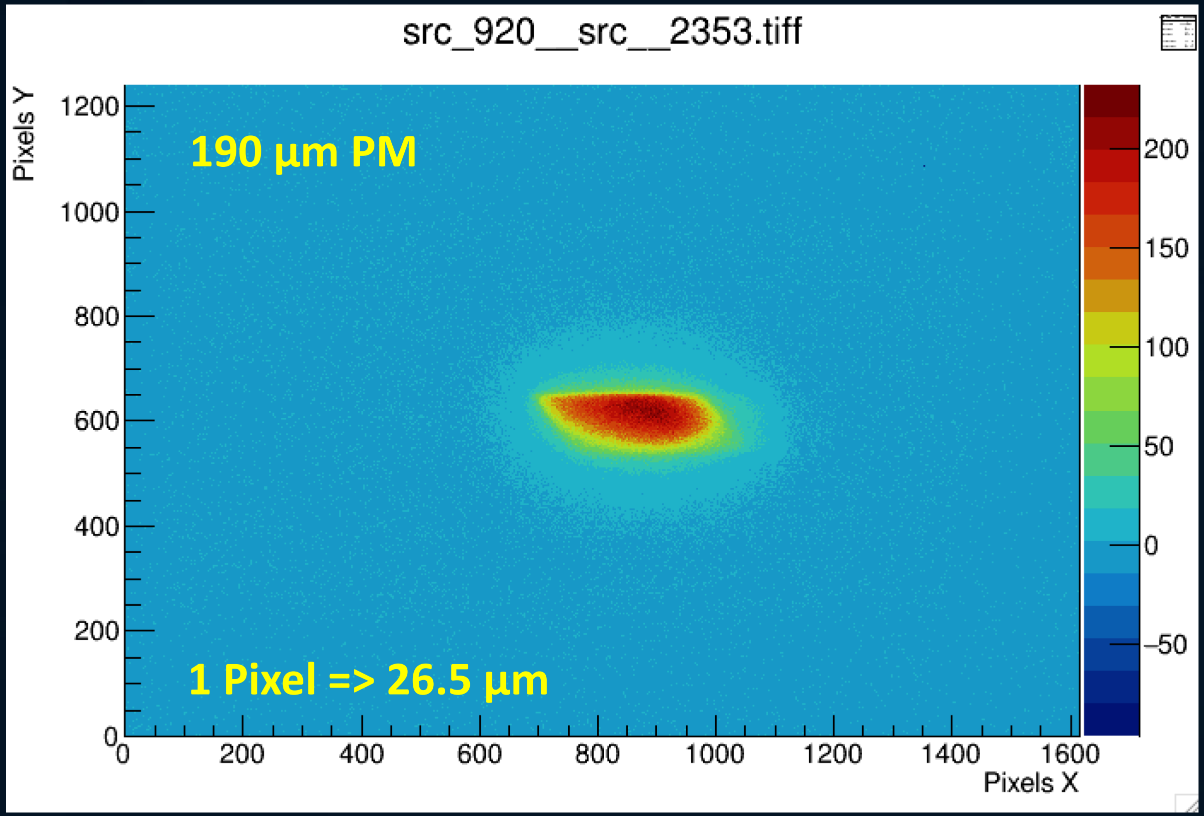
Image captured at DOE Facility for Rare Isotope Beams (FRIB) in **real-time** during tuning of beam of $^{86}Kr^{+26}$ particles (2.75 MeV/u) irradiating a 2x2 cm **HM** type scintillator at a rate of **5 x 10^4 pps**.

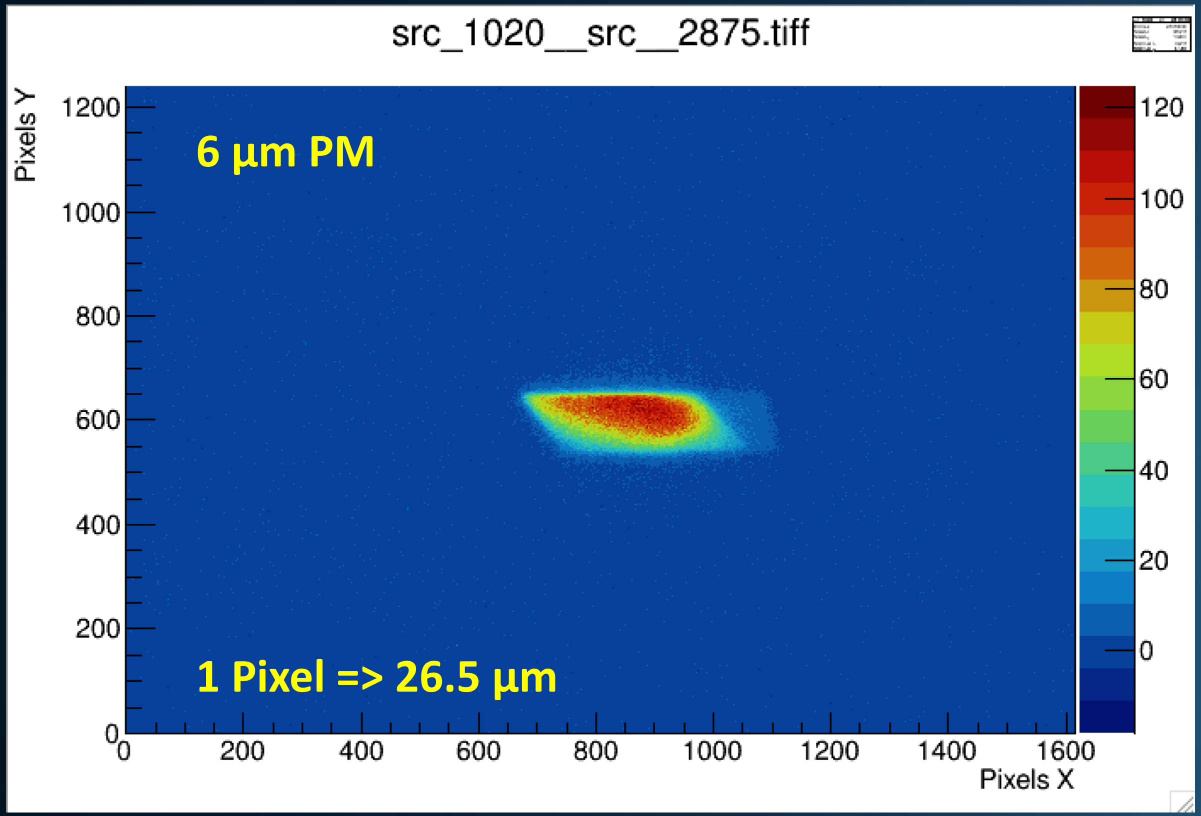
Single-Particle Sensitivity ($^{86}Kr^{+26}$)



Single particle capture at the FRIB of $^{86}Kr^{+26}$ irradiating our **HM** type scintillator at beam rate of 5-10 pps and particle kinetic energy of 236.5 MeV (i.e., **2.75 MeV/u**). Figure inset in upper left is initial 2D image. Enlarged image in center is the same figure and field-of-view, but shown as a 3D Lego plot with 2x2 binning (each binned pixel is 53 µm x 53 µm).

Beamline Images of $^{86}Kr^{+26}$





Above beamline images captured in real-time of same 2.75 MeV/u beam of $^{86}Kr^{+26}$ particles irradiating two different thickness 2x2 cm **PM** scintillators at a rate of **5.2 x 10^5 pps**. Image on Left was with **190 µm** thick **PM;** image on Right was with **6 µm** thick **PM** that transmits 75% of the beam. Z-bar intensity scale is different for the two images with max intensity of Left image twice that of Right image.

Interested / Collaborating Parties

(Academic – Government – Industry)

- Universities in U.S. & Europe
  (**UFT electron-FLASH test in 1Q22** at NDRL)
- NIH-NCI and DOE-NP/FRIB
  (e.g., DOE Facility for Rare Isotope Beams)
- Companies in U.S. & Europe
  (i.e., more than a half-dozen)

Product Applications

Medical: FLASH-RT & Advanced EBRT (Non-FLASH Dose Rate)

- **FLASH-RT** (electrons, protons, ions, photons / x-rays, neutrons)
- FLASH Intraoperative radiation therapy (Electron IORT)
- Synchrotron based Proton and Carbon-ion EBRT
- Boron Neutron Capture Therapy (BNCT – EBRT)
- Spatially Fractionated EBRT (Grid, Lattice, Minibeam, Microbeam)
- Beamline Monitoring (medical & scientific applications – e.g. **FRIB**)

Intellectual Property

- Company has 23 *issued* U.S. & foreign radiation detector patents (4 on FLASH-RT)
- Core patents issued for FLASH-RT beam monitoring system with broad claims
- Patented claims cover both the PM and HM scintillators
- Additional patent applications in process, including Continuations-in-Part (CIPs)
- Trade secrets also being utilized

Key Accomplishments

- *Proof-of-Concept* demonstrated for UFT beam monitoring system
- Scintillator radiation damage per FLASH-RT fraction is ~ 0.001%. It would take ~1,000 patient FLASH treatments to degrade the scintillator signal response by ~ 1%.
- Real-time UFT beamline monitor demonstrated for highly-ionized heavy particles over the range 10^6 to 10^1 pps at FRIB (Sept 2, 2021), but with rate capability from ~ 10^{13} to 10^1 pps
- NIH-NCI **$3.8M** in Phase-II SBIR Awards for development of EBRT / FLASH beam monitors
- DOE-NP **$1M** Phase-II SBIR Award for development of UFT-beam monitors for FRIB
- Collaboration with leading academic and research institutions involved in FLASH-RT

Conclusions / Summary

- Enabling technology for faster, safer & lower cost radiotherapy
- Technology protected and validated
- Development partners in place
- Non-dilutive financing leverage from NIH and DOE
- I-S is ready to commercialize the technology and is open to licensing, strategic partnerships, development agreements, equity investments, etc.