

# Proton Therapy: Highlights of Inspire project: advances in Proton therapy

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University of Manchester/ The Christie NHS Foundation Trust

Cockcroft Institute



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# Disclosures

- Member Varian FlashForward™ consortium
- Varian Framework Agreement



# Thank you

- Invitation to speak
- Colleagues in INSPIRE
- International Advisory Committee, Ethics Committee, User selection panel
- EU for funding INSPIRE
- PO and reviewers
- Wonderful Project Managers  
Helena Kondryn, Rebecca Parker



# Collaborations

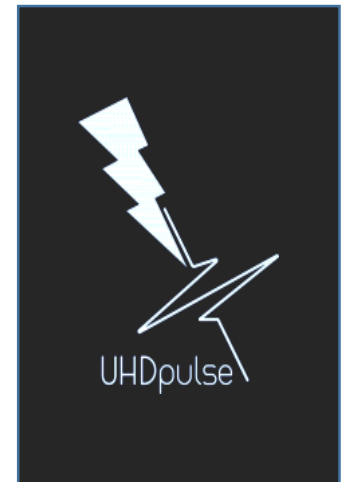
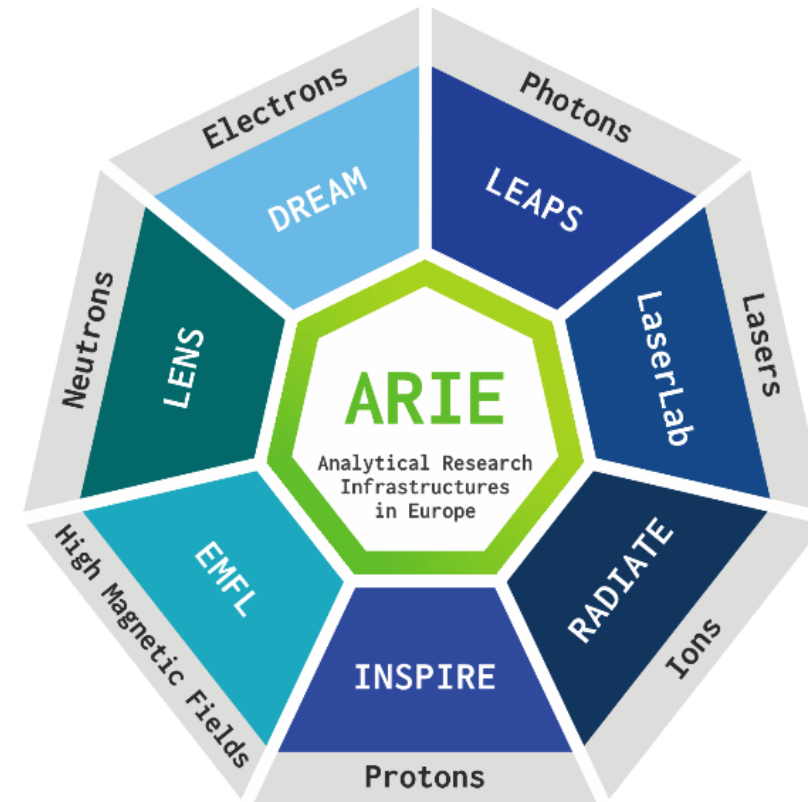
## ARIE PUBLICATIONS



<https://doi.org/10.5281/zenodo.4049768>



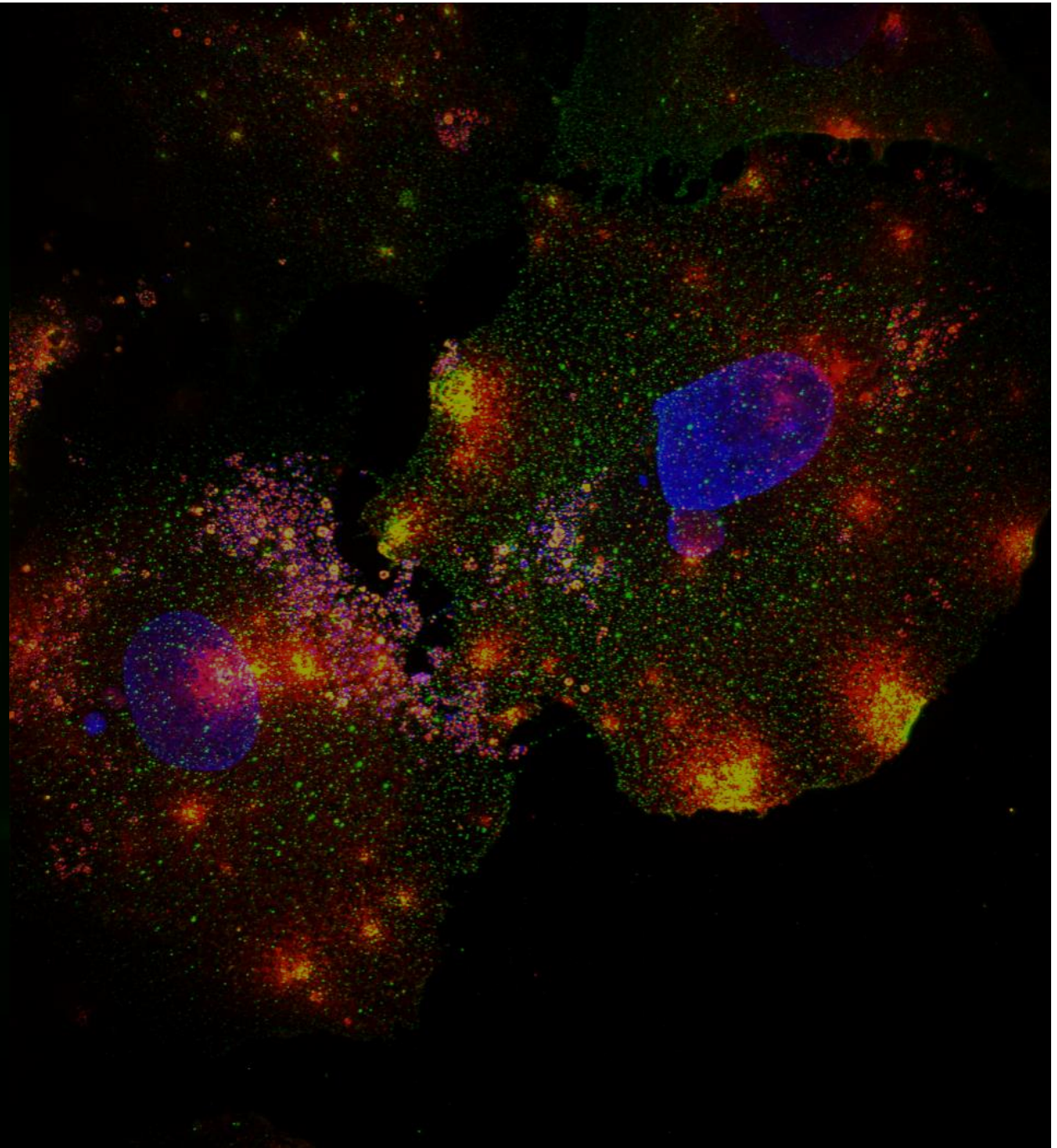
<https://doi.org/10.5281/zenodo.4049719>





# Contents

- What is Inspire
- Transnational Access
- Networking Activities
- Future





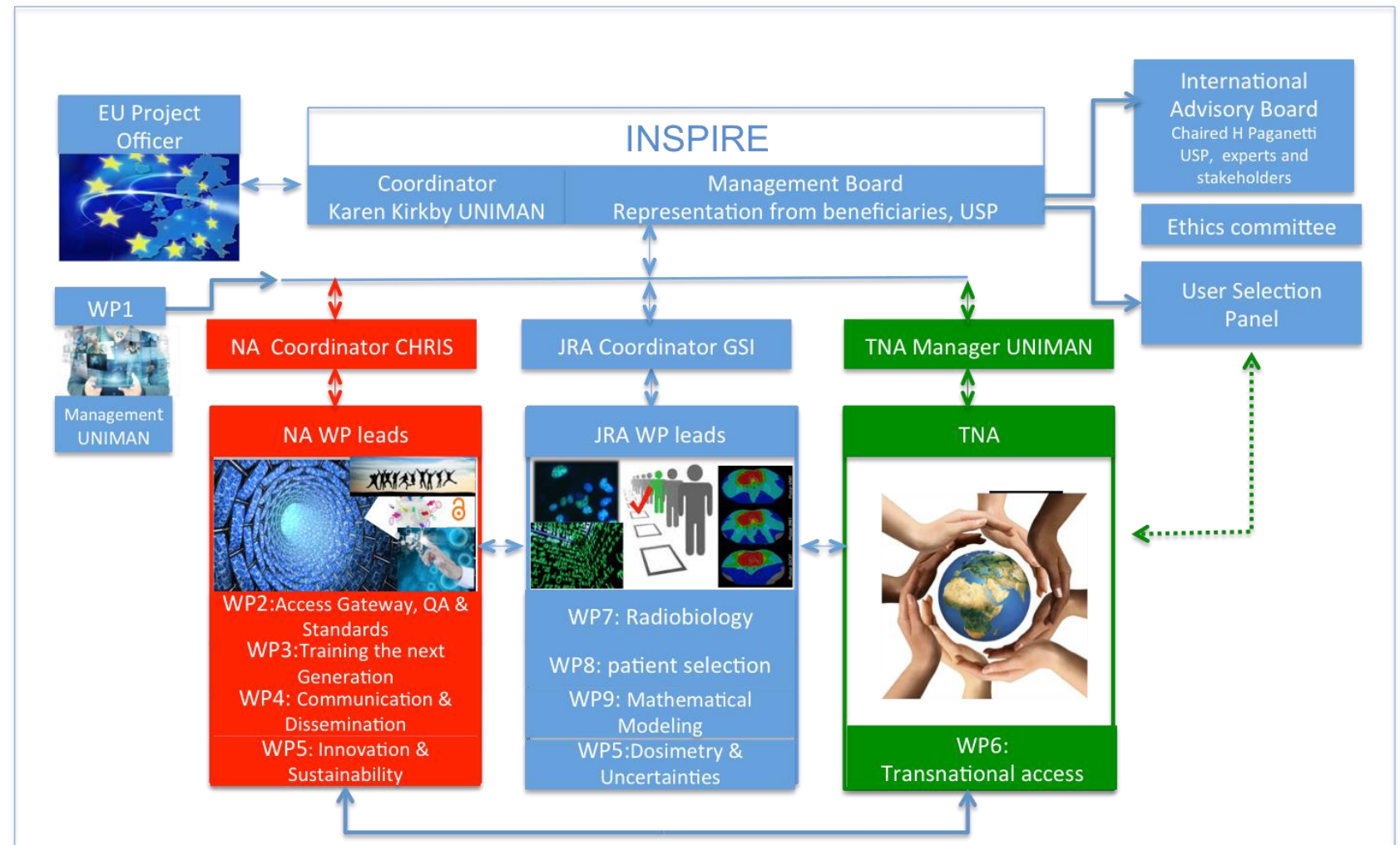
# What is INSPIRE?

- €5M (Coordinated by Manchester)
- Integrating proton research across Europe (now contains heavy ions GSI, KVI)
- 17 partners
- Networking, Transnational Access, Joint Research Activities
- 11 TNA providers
- 12 PBT centres; national hubs
- Industry Varian and IBA involvement
- <https://protonsinspire.eu>

the project  
vide an  
urope through



- Management WP1
- Networking WP2-5
- TNA WP6
- JRA WP7-10





# Transnational Access

Access to research rooms in PBT clinical facilities

”Clinical beams” in a research environment

Gantries

Fixed beamlines

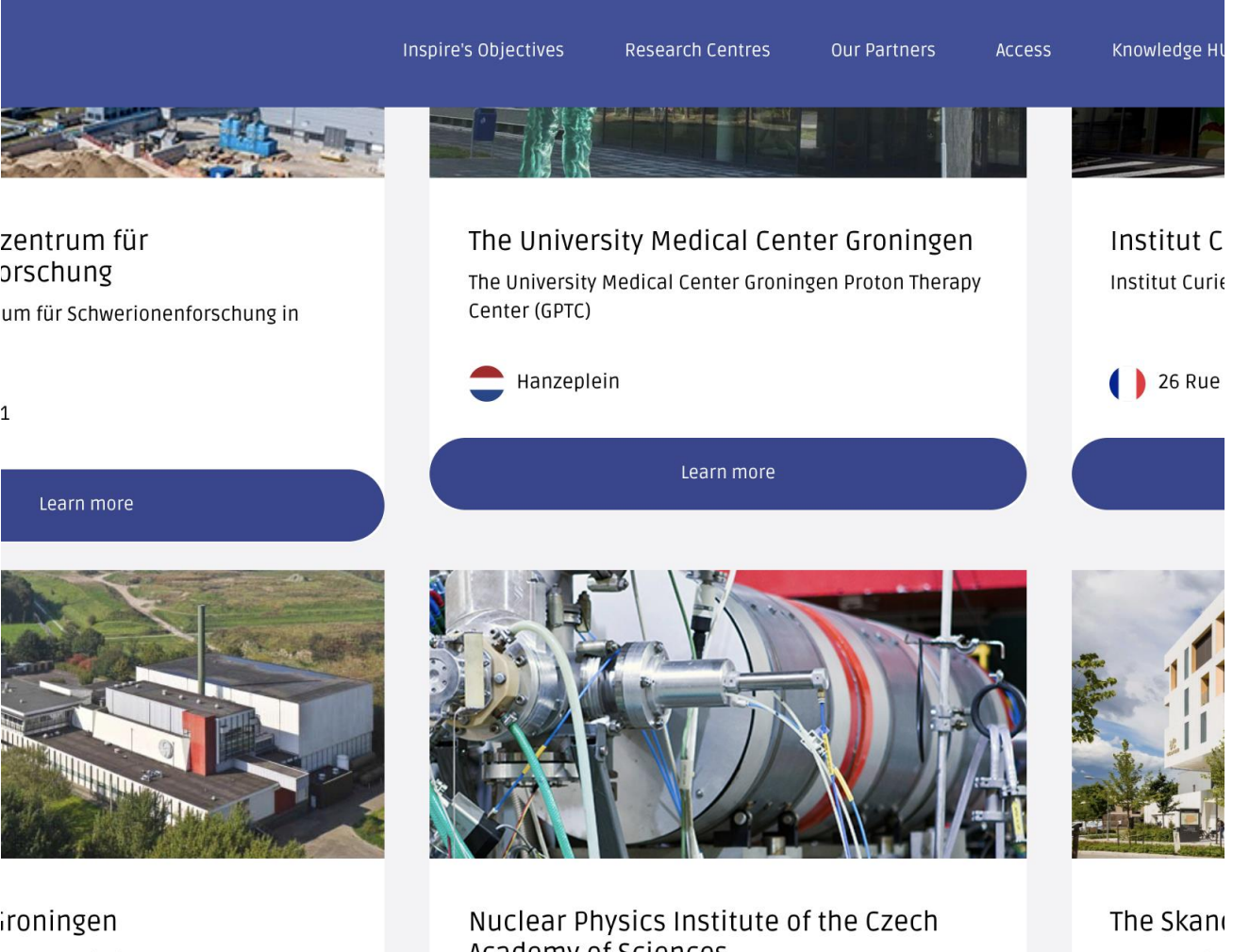
With or w/o scanning nozzle

Some became operational during INSPIRE

Late due to Covid-19

Range of ions GSI and RUG (now part of UMCG)

Apply via the website



The screenshot shows a website interface with a dark blue navigation bar at the top containing the following links: Inspire's Objectives, Research Centres, Our Partners, Access, and Knowledge Hub. Below the navigation bar is a grid of six facility cards. Each card features a header image, a title, a brief description, a location icon and name, and a blue 'Learn more' button. The visible cards are:

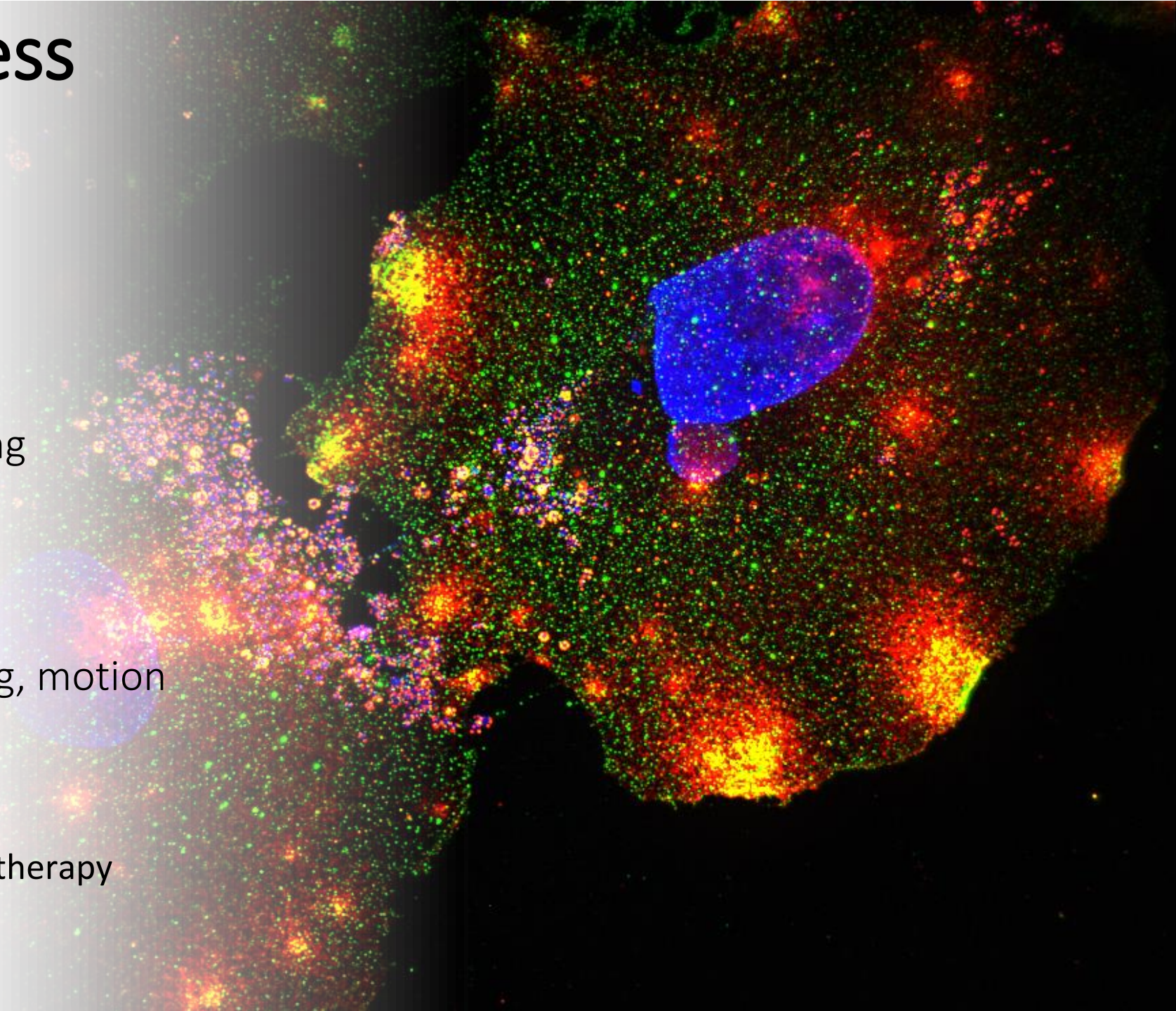
- Card 1:** Header image of a construction site. Title: "zentrum für Forschung". Description: "um für Schwerionenforschung in". Location: "1".
- Card 2:** Header image of a person in a green protective suit. Title: "The University Medical Center Groningen". Description: "The University Medical Center Groningen Proton Therapy Center (GPTC)". Location: "Hanzeplein".
- Card 3:** Header image of a building entrance. Title: "Institut C". Description: "Institut Curie". Location: "26 Rue".
- Card 4:** Header image of a large industrial building. Title: "Groningen".
- Card 5:** Header image of a large cylindrical particle accelerator component. Title: "Nuclear Physics Institute of the Czech Academy of Sciences".
- Card 6:** Header image of a modern building. Title: "The Skan".





# Transnational Access - Capabilities

- Radiobiology
  - Cells 2D and 3D, tissue plants
- Proton CT
- Detector design and testing
- Pan – European studies
  - Radiobiology
  - Metrology
  - phantoms
- Range verification, imaging, motion management
- New technologies
  - FLASH
  - Spatially fractionated radiotherapy





# Transnational Access - Capabilities































- Radiobiology
  - Overview of INSPIRE centers' capabilities to perform *in vitro* and *in vivo* experiments with proton beams



## REVIEW ARTICLE

Front. Phys., 06 October 2020 | <https://doi.org/10.3389/fphy.2020.565055>

## Mapping the Future of Particle Radiobiology in Europe: The INSPIRE Project

 Nicholas T. Henthorn<sup>1,2†</sup>,  Olga Sokol<sup>3†</sup>,  Marco Durante<sup>3,4\*</sup>,  Ludovic De Marzi<sup>5</sup>,  Frederic Pouzoulet<sup>6</sup>,  Justyna Miszczyk<sup>7</sup>,  Pawel Olko<sup>7</sup>,  Sytze Brandenburg<sup>8,9</sup>,  Marc Jan van Goethem<sup>8,9</sup>,  Lara Barazzuol<sup>9,10</sup>,  Makbule Tambas<sup>9</sup>,  Johannes A. Langendijk<sup>9</sup>,  Marie Davidkova<sup>11</sup>,  Vladimír Vondráček<sup>12</sup>,  Elisabeth Bodenstein<sup>13</sup>,  Joerg Pawelke<sup>13,14</sup>,  Antony J. Lomax<sup>15,16</sup>,  Damien C. Weber<sup>15,17,18</sup>,  Alexandru Dasu<sup>19,20</sup>,  Bo Stenerlöv<sup>20</sup>,  Per R. Poulsen<sup>21</sup>,  Brita S. Sørensen<sup>21</sup>,  Cai Grau<sup>21</sup>,  Mateusz K. Sitarz<sup>21</sup>,  Anne-Catherine Heuskin<sup>22</sup>,  Stephane Lucas<sup>22</sup>,  John W. Warmenhoven<sup>1,2</sup>,  Michael J. Merchant<sup>1,2</sup>,  Ran I. Mackay<sup>1,2,3</sup> and  Karen J. Kirkby<sup>1,2</sup>

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1,970  
TOTAL VIEWS

Am score 4

View Article Impact



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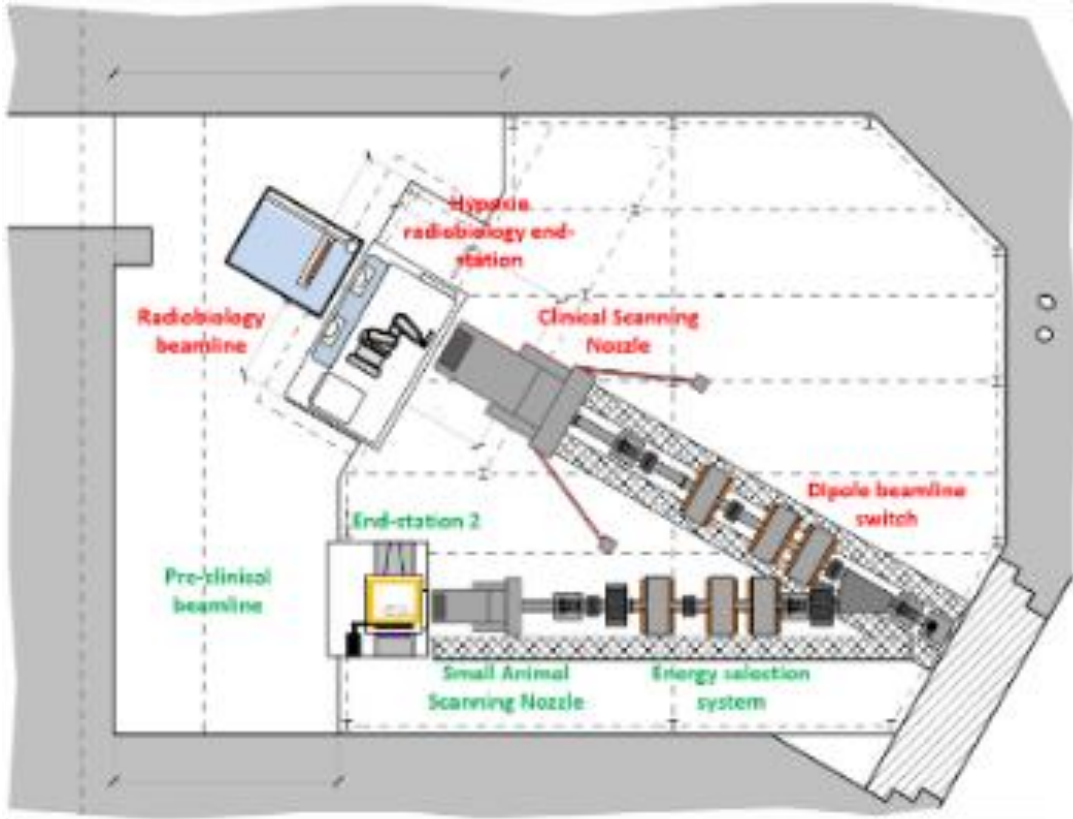
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# PBT Research room: design



Mike Merchant



Mike Taylor

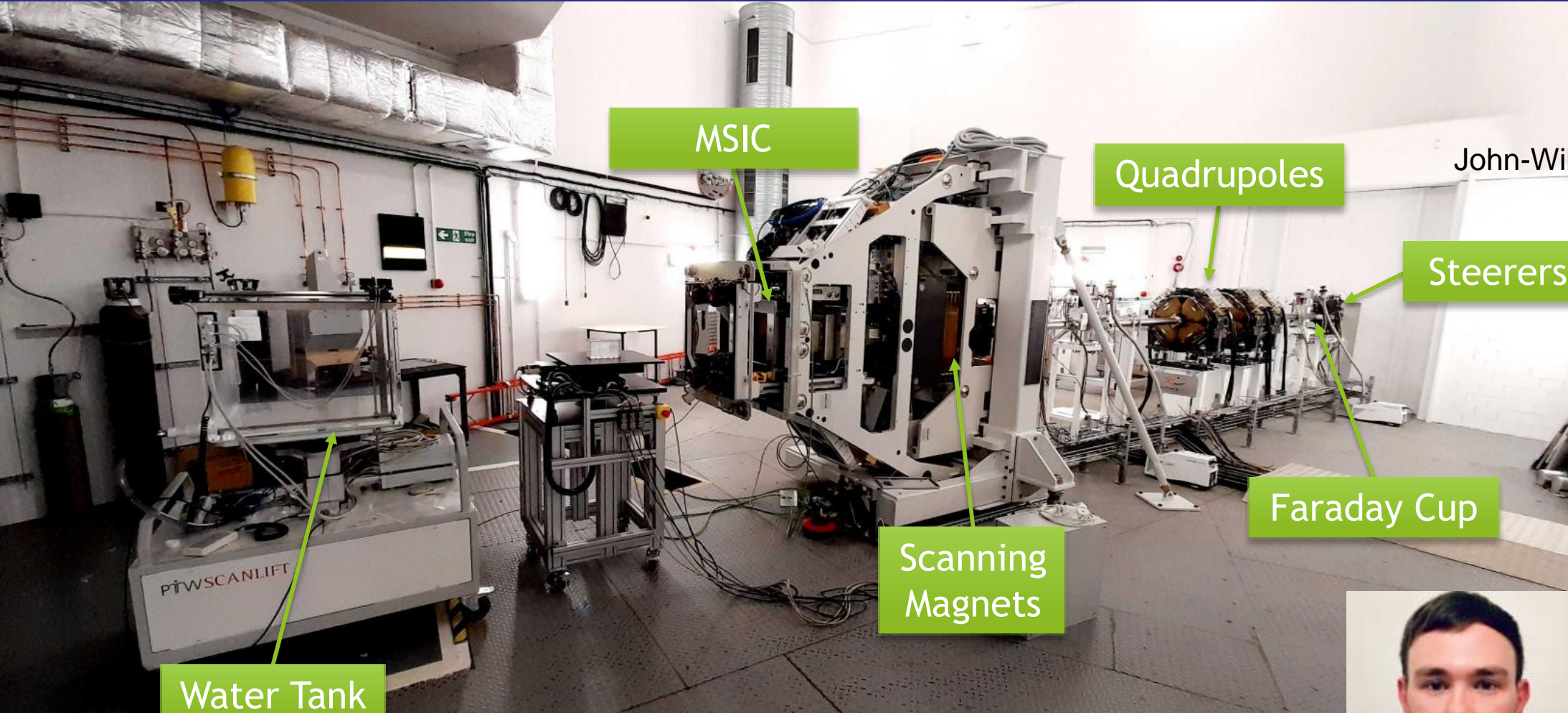


Hywel Owen

- Flexible design
  - Floor
  - Water
  - Electricity
  - Earthing
- Radiation protection
  - Infrastructure
  - Beam lines
  - End Stations
  - Clinical nozzle



# PBT Research room: Beamline A



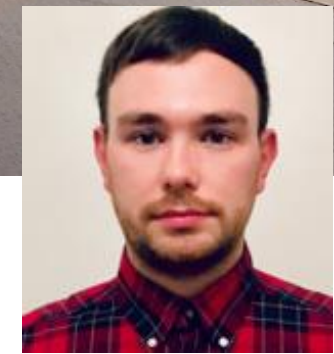
John-William Warmenhoven



Nick Henthorn



Sam Ingram



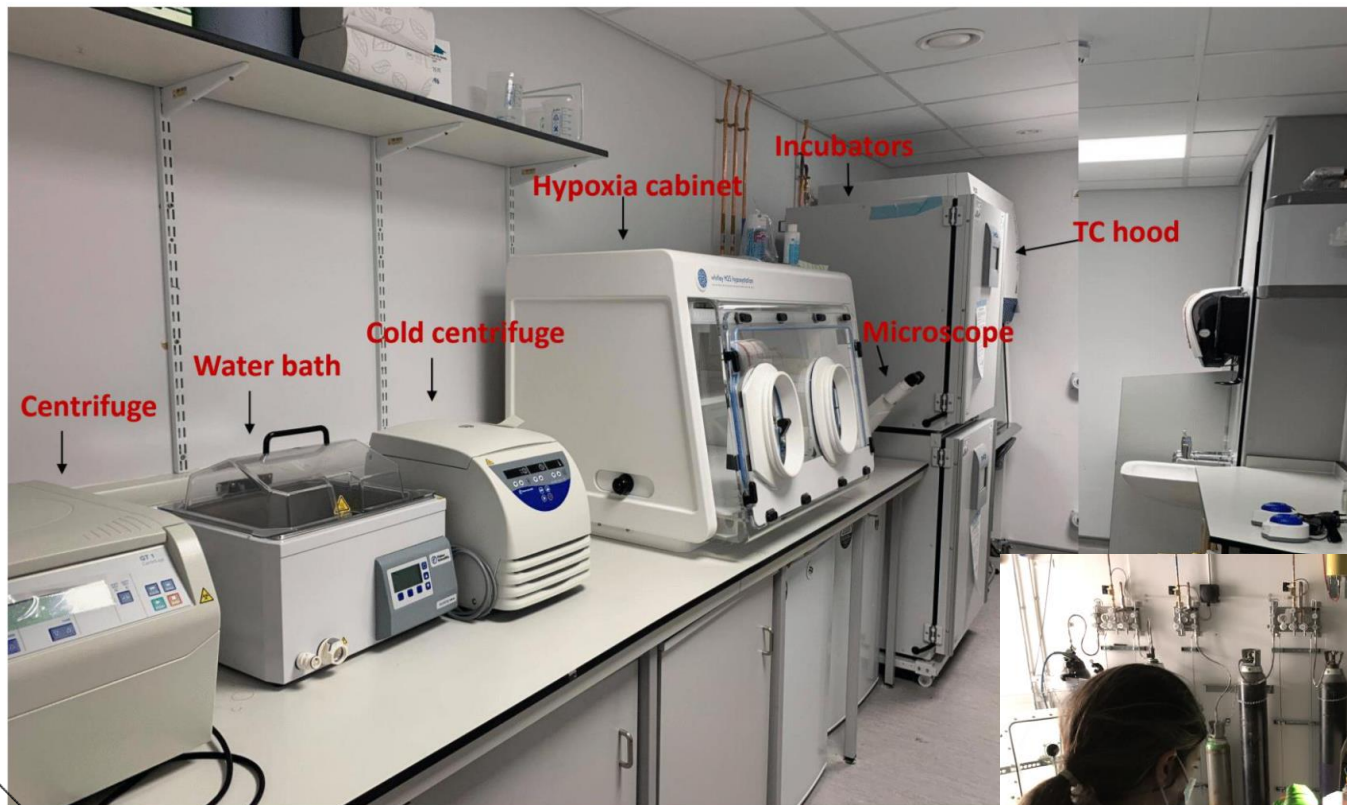
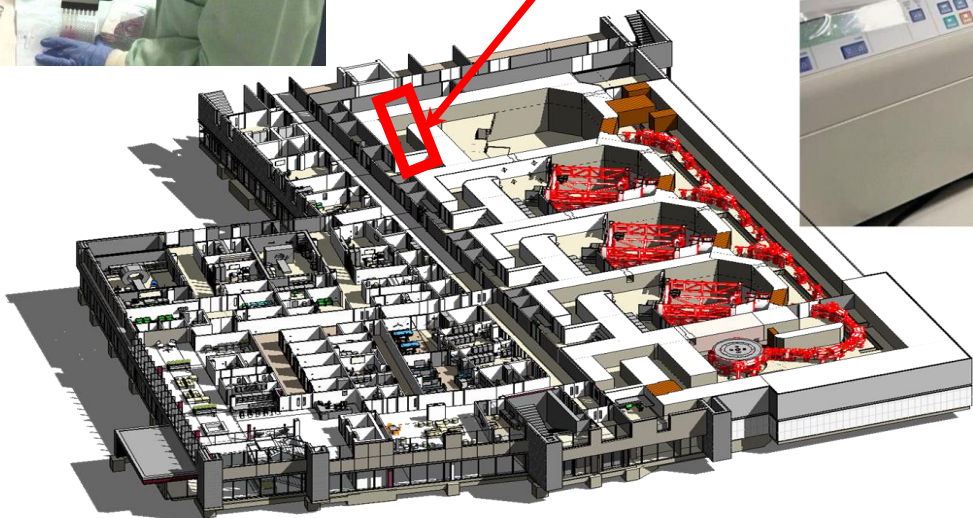
Sam Manger



# PBT Research room: Bio Prep room

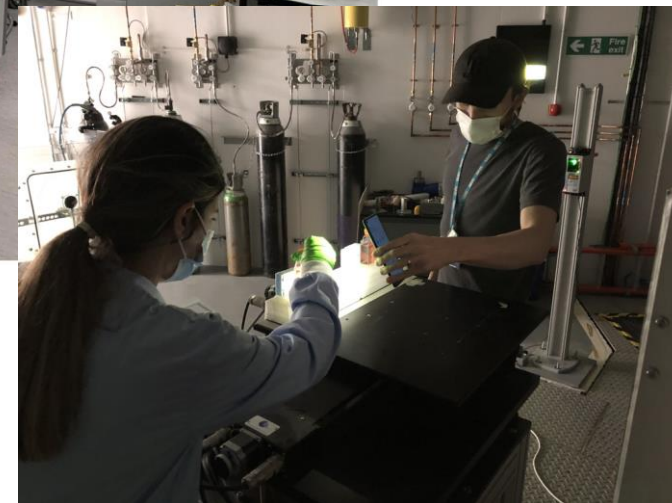


The Christie  
Charitable Fund



Live cell imaging system

EVOS m7000



# End Stations: Hypoxia; high throughput end station



## Environmental Control

- **O<sub>2</sub>**: 0.1% - ambient
- **CO<sub>2</sub>**: 0% - 20%
- **Temperature**: ambient +4°C - 45°C
- **Humidity**: ambient – 100%

## Irradiation:

- 20 x 20 cm scanning area
- 6-axis robot: 30s between sample
- 36 sample hotel
- Automated liquid handling for 96-well plates
- Scattered dose to hotel at worst 1.27 mGy/Gy
- Conventional; FLASH

## Example experiment:

- 56x Samples, 300 Gy delivered, 2 hours



# Ultra high dose rate FLASH

MANCHESTER CANCER RESEARCH CENTRE



MANCHESTER CENTRE

## A DAY IN THE LIFE....

“On the night of 25th February 2021 members of the University of Manchester PRECISE group and The Christie Medical Physics and Engineering set out to deliver the first Ultra-High Dose Rate (UHDR) proton beams into the Stoller Research Room of the Proton Beam Therapy Centre.....”

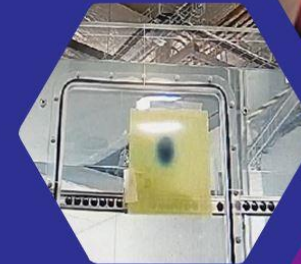
Jack Aylward,  
Postgraduate Researcher  
Research Group: PRECISE

Sam Manger @spmng

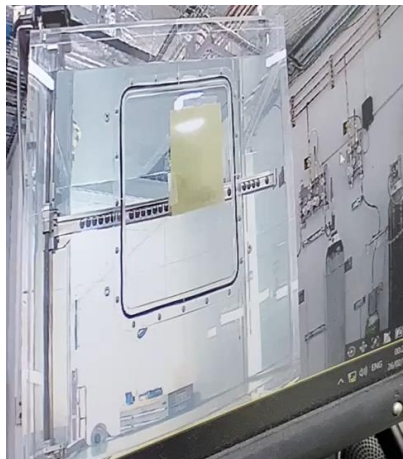
A Manchester bee drawn with the proton FLASH beam at the end of the night in the @Proton\_Research research room 🐝 Thanks to Nick Henthorn, @mike\_merchant, @ranmackay, @jackdaylward and @SamPIngram for work on FLASH these last two weeks 🐝



9:52 AM · Aug 6, 2021 · Twitter for iPhone



Training and Education Newsletter  
Autumn/Winter 2021



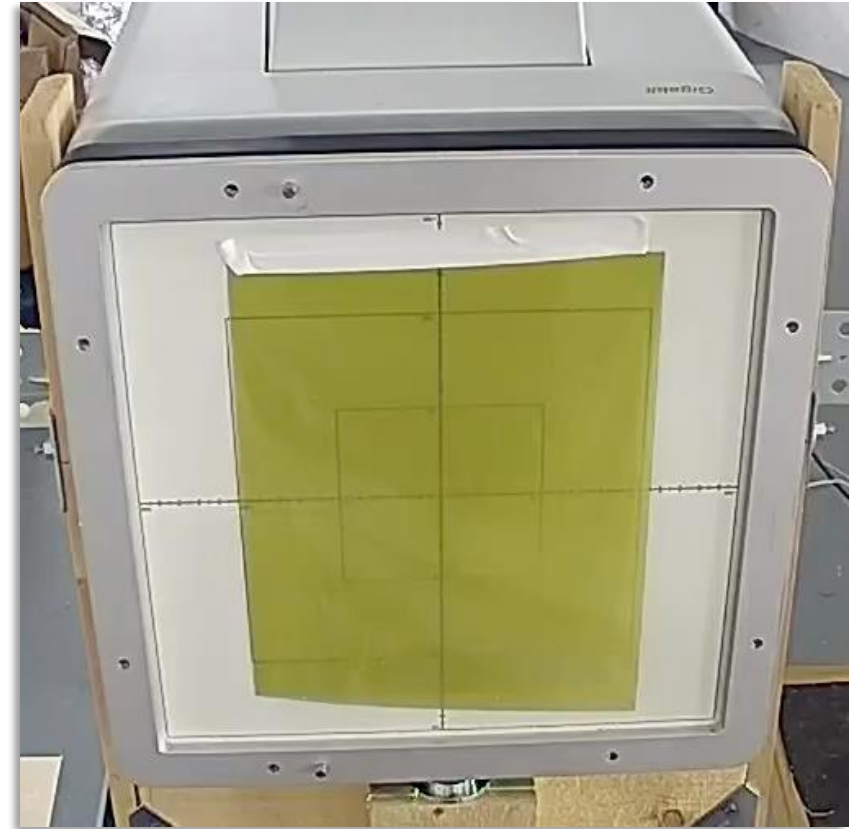
Standard Operation ( $\leq 2$ nA at nozzle)		
Energy (MeV)	Minimum Nozzle Current (nA)	Maximum Nozzle Current (nA)
70	0.0025	0.41
244	0.52	2.0
FLASH Operation		
Energy (MeV)	Maximum Nozzle Current (nA)	Dose Rate (Gy/s)
244	88	175

# FLASH: *Scanning Test*

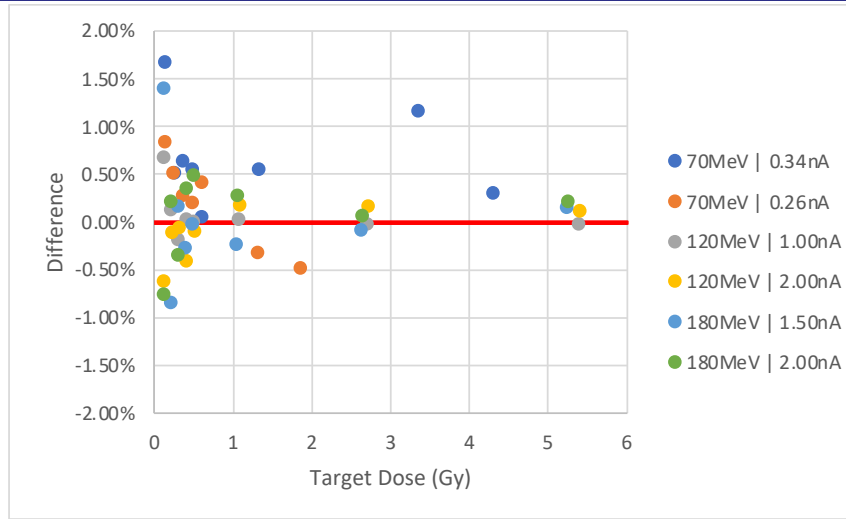
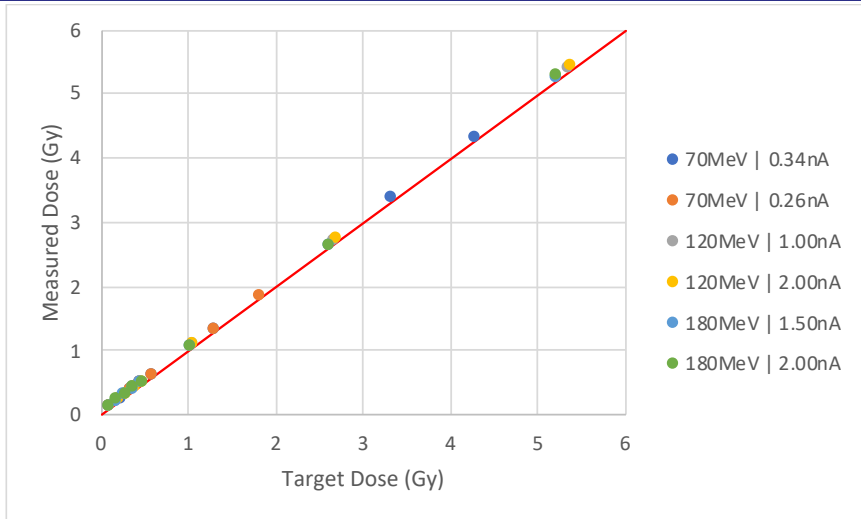
**Conventional**



**FLASH**



# Beamline A – CONV & FLASH dosimetry

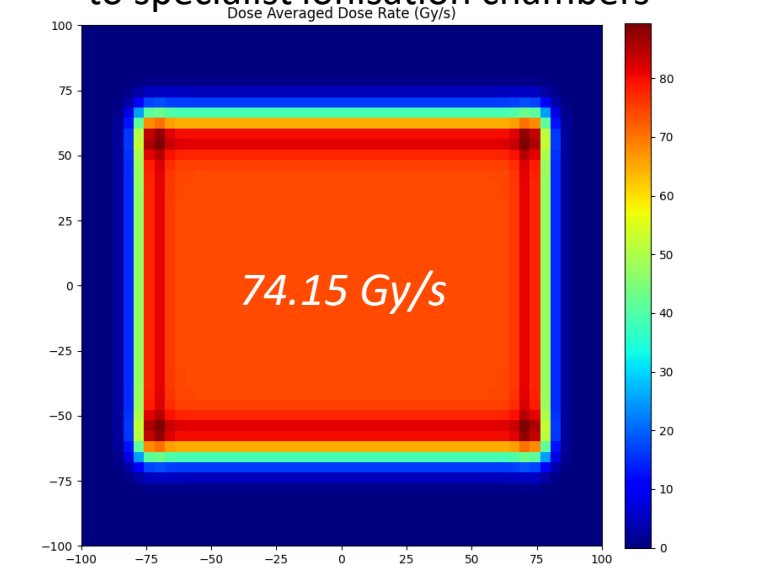
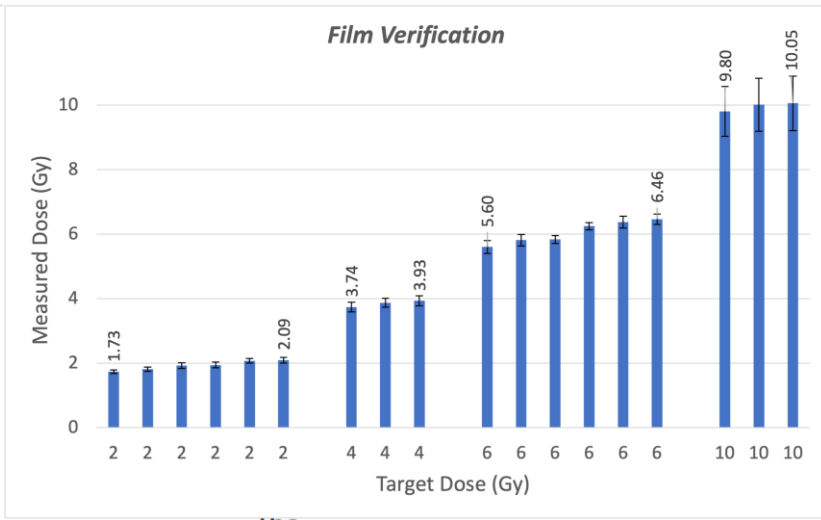
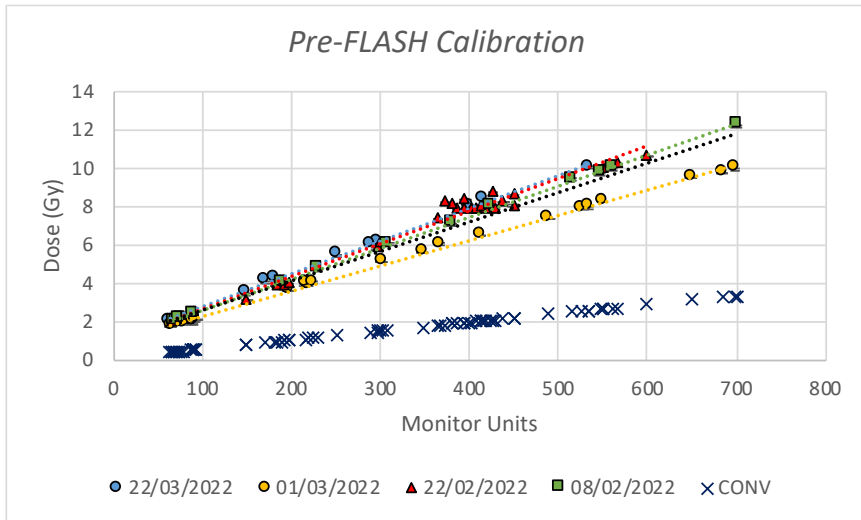


## Conventional

- $\leq 2$  Gy/min
- Comparable dose accuracy and reproducibility to clinical service

## FLASH

- $\geq 40$  Gy/s
- Increased dosimetric uncertainty compared to conventional (~5%)
- Competitive performance compared to specialist ionisation chambers



# Beamline B – Developing a preclinical beamline

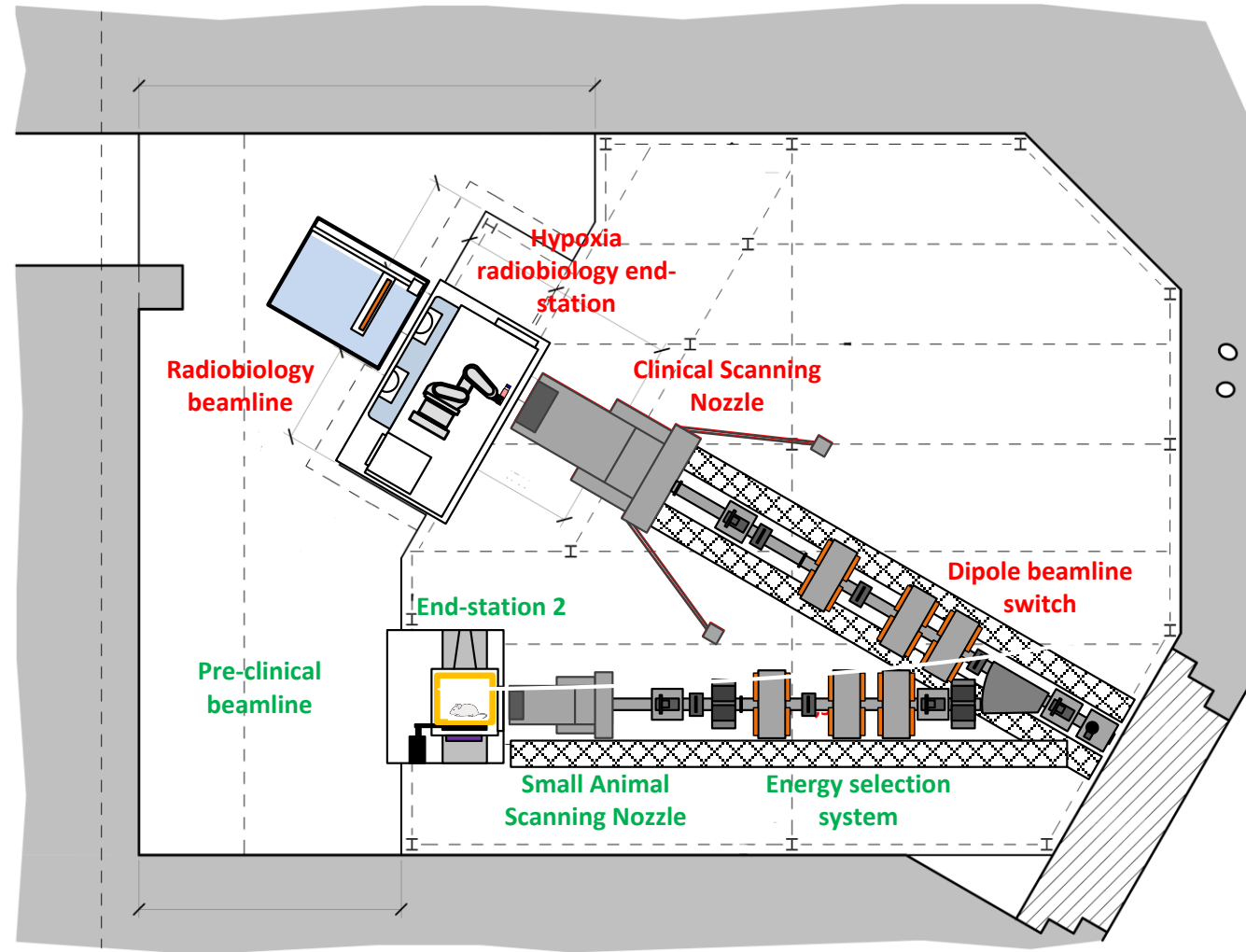
Pre-clinical beamline  
in design & evaluation  
phase

Design aims:

1 mm  $\sigma$  spot

3 cm x 3 cm scanning  
area

Imaging capability –  
Xstrahl SAARP



Beamline A:

Built and commissioned.

Specifications

70 – 245 MeV

5.5 mm  $\sigma$  spot

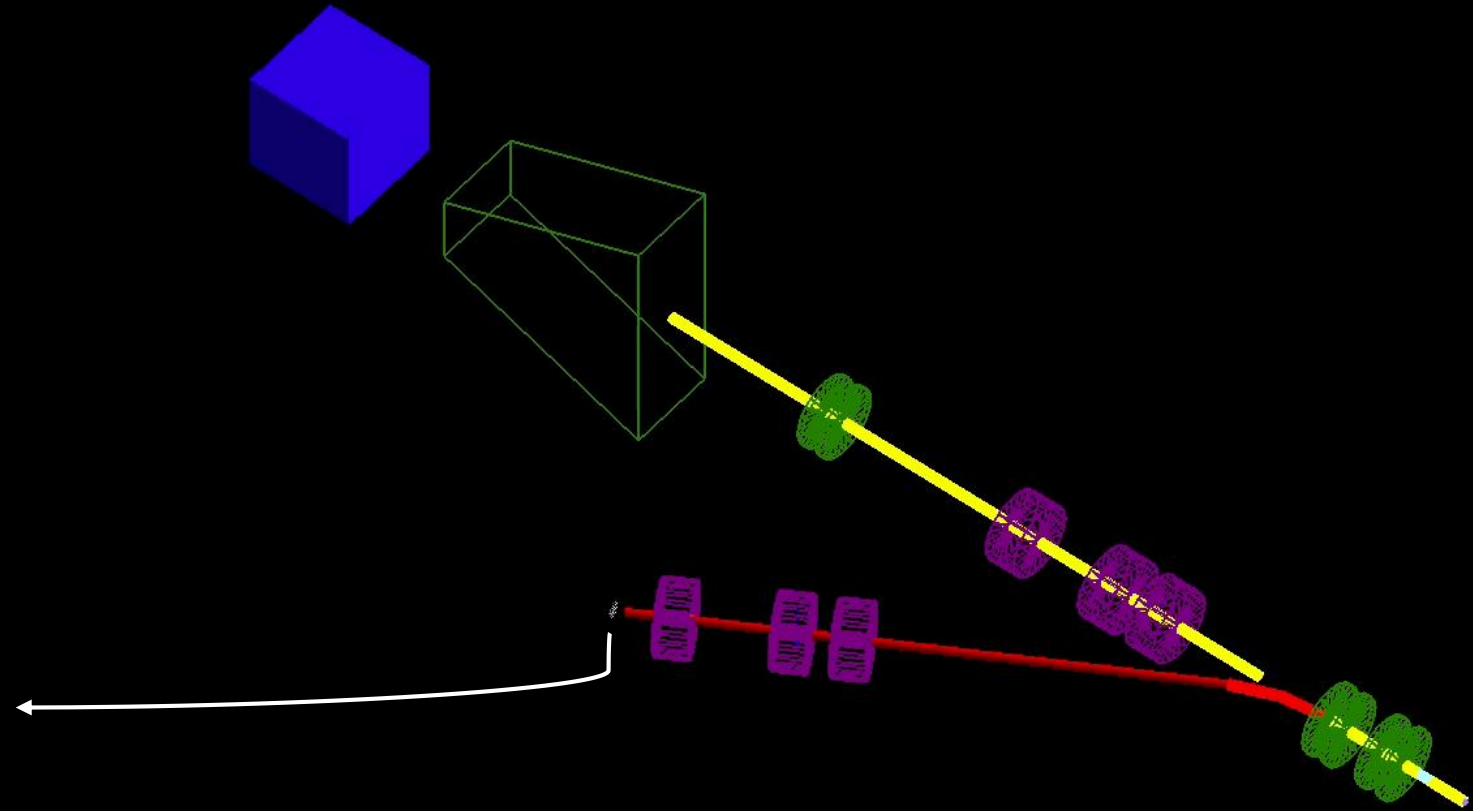
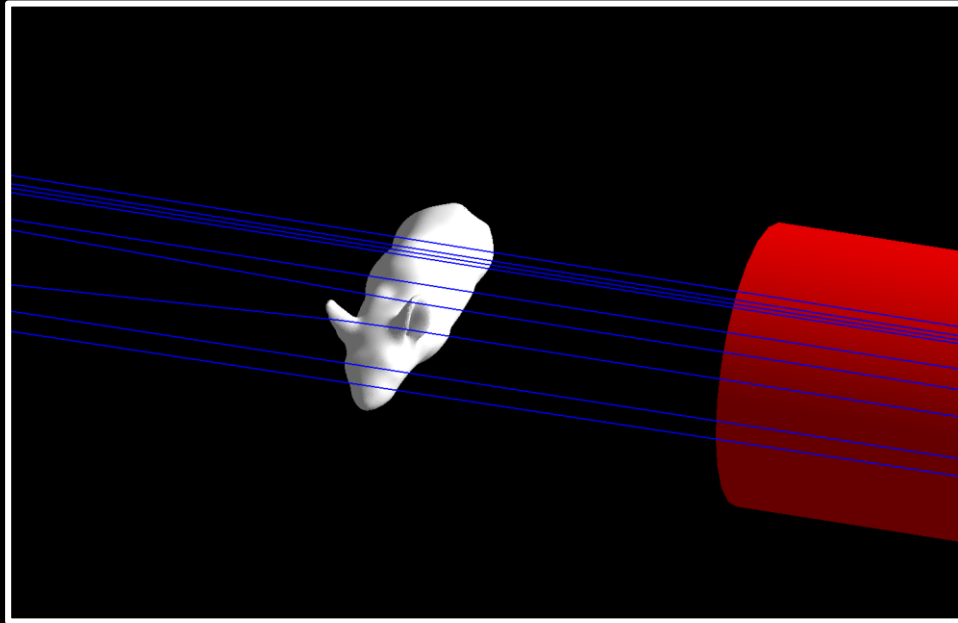
30 x 40 cm scan area

- Automated Proton Hypoxia Endstation
- Can deliver FLASH beams



# Beamline B – Developing a preclinical beamline

- Monte Carlo model of pre-clinical beamline
- Optimising beamline layout and components
- Investigating beam optics and potential capabilities



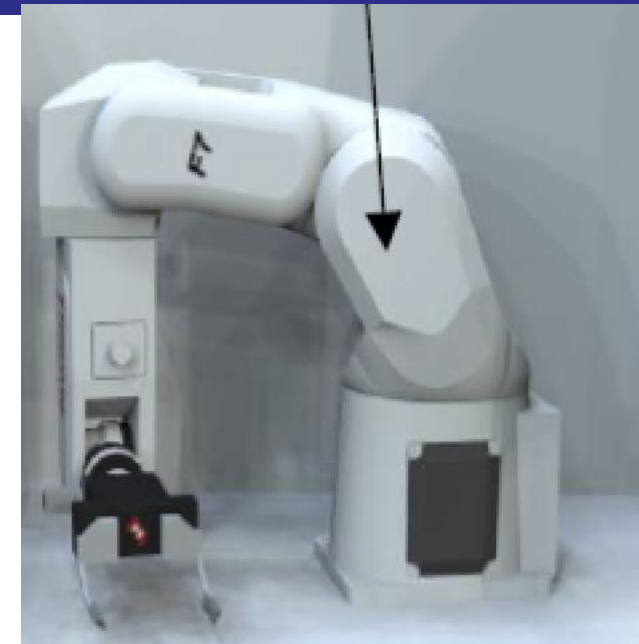
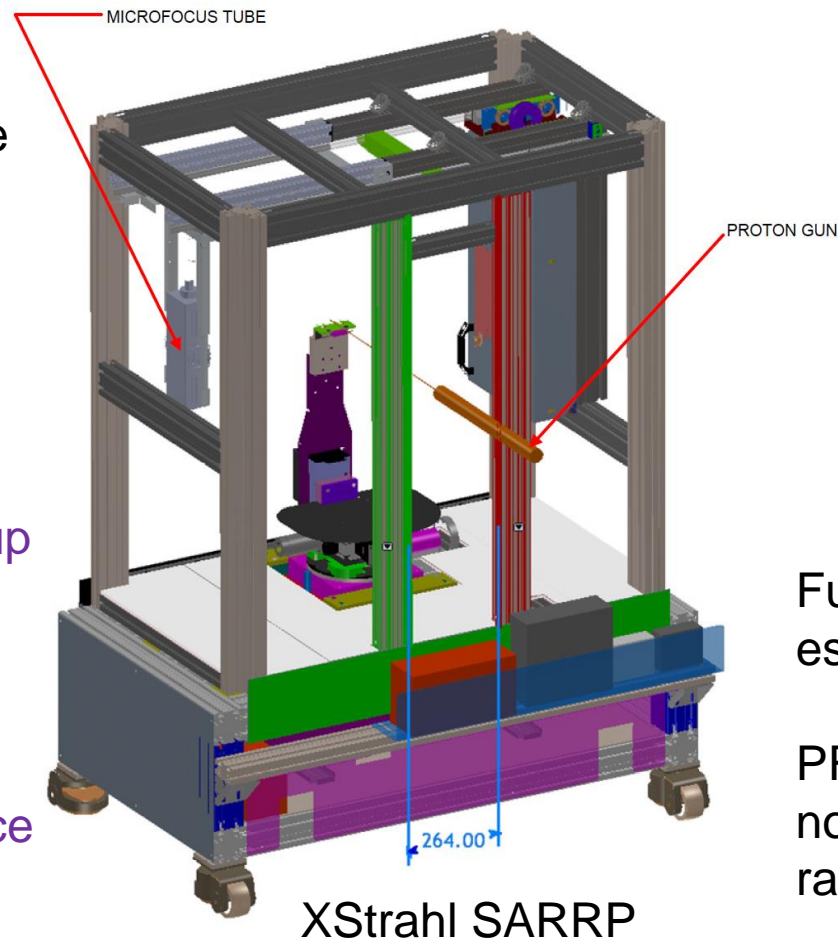
# Pre-clinical Beamline End-station Automation

End-station design investigating automation solutions.

High throughput and high repeatability are central to design philosophy.

The consequence of not completing an experiment with animals is higher than *in vitro* radiobiology.

- Experimental requirement to irradiate up to 14 animals per session.
- 4 hours max beam-time per night, including set-up, dosimetry tests, and mitigation for any cyclotron maintenance etc



Full automation from the control room essential especially for FLASH.

PRECISE has experience developing novel automation solutions for radiobiology.



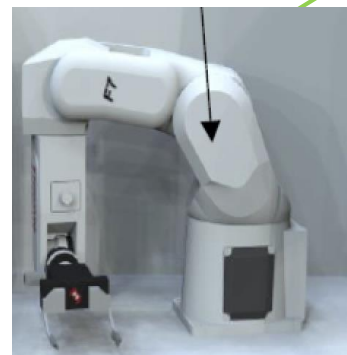
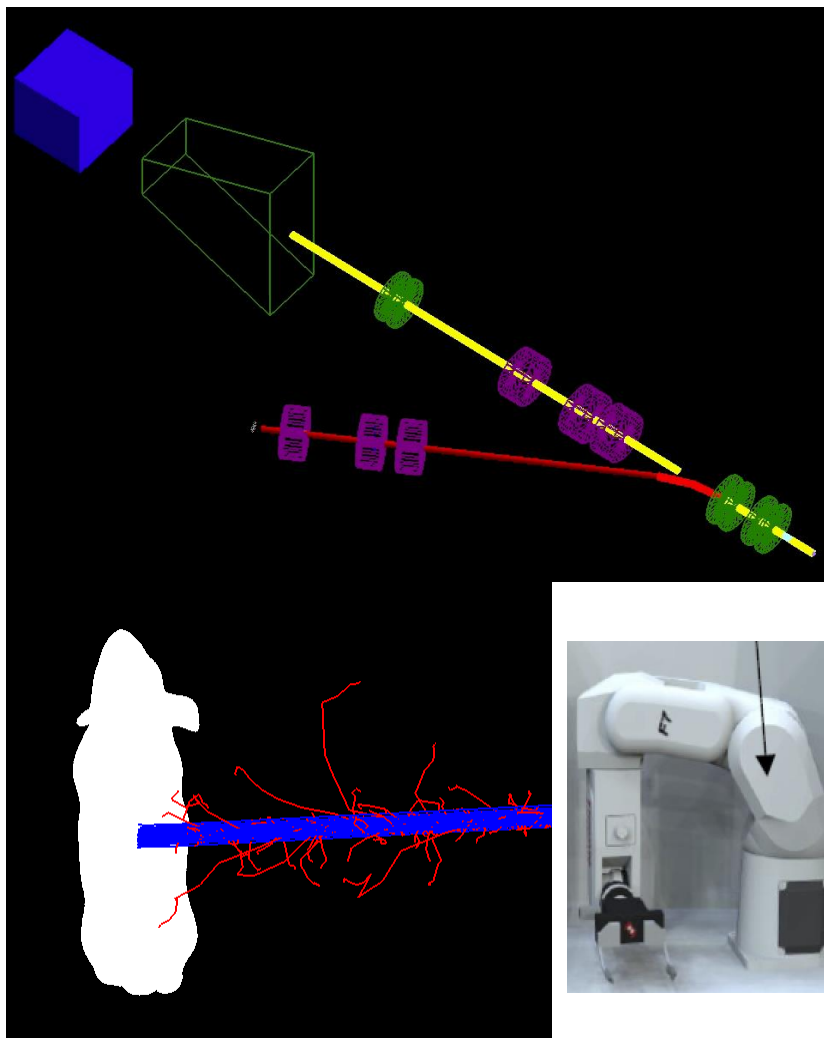
# Pre-clinical beamline B development

## Pre-clinical Beamline

- 1 mm  $\sigma$  spot, 3 cm x 3 cm scanning area
- Flash capable (Bragg peak) [1 MeV – 65 MeV]
- Working with Cockcroft Institute (Prof R Appleby)

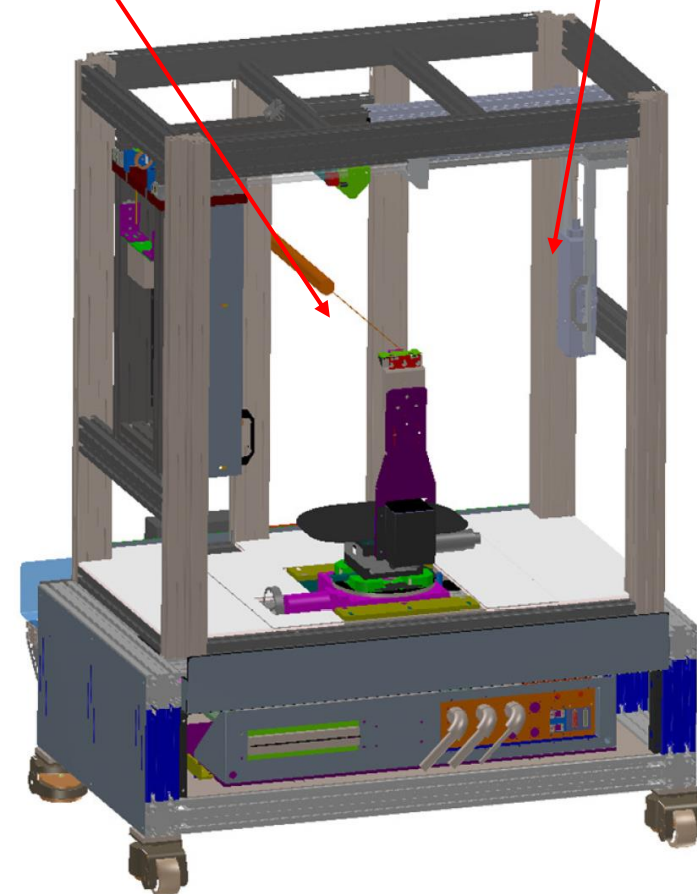
## Timeline

- **Now**, Design development consultation with suppliers (XStrahl, SigmaPhi), Safety and Licences evaluation
- **Sep 2022**, Formal procurement
- **March 2023**, Begin modifications to RR
- **June 2024**, Install, Commission
- **March 2025**, First experiments



Proton nozzle

Microfocus X-ray imaging

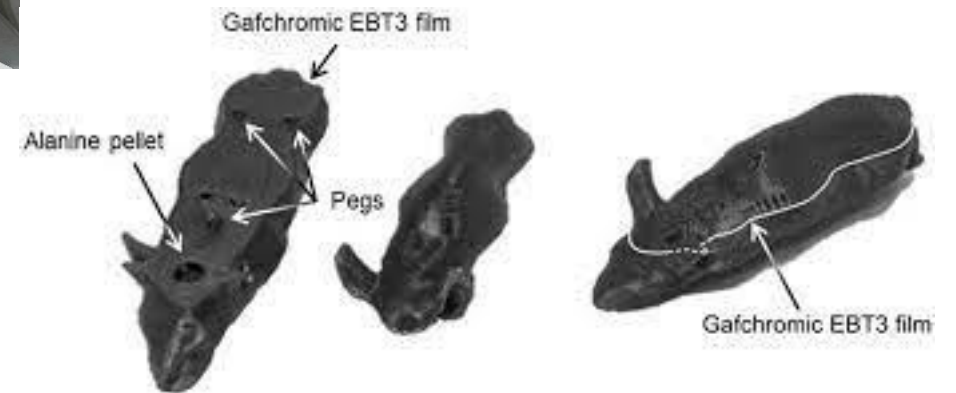
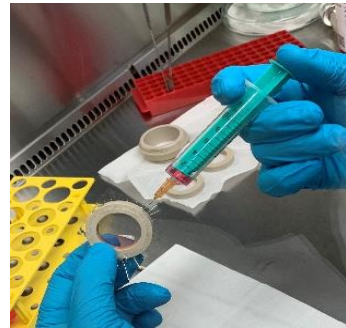


XStrahl SARRP  
Proton Platform

**NHS**  
The Christie  
NHS Foundation Trust

# Transnational Access – expanding capabilities through JRA

- Hypoxia
  - Across a range of different oxygen tensions
  - Compact hypoxia chamber (patent)
- Building a Flash capability
- Zoomorphic phantoms
- Animal irradiation on gantries (patent)
- Software
- Databases
- Drug delivery nano-peanuts (patent)



# Networking

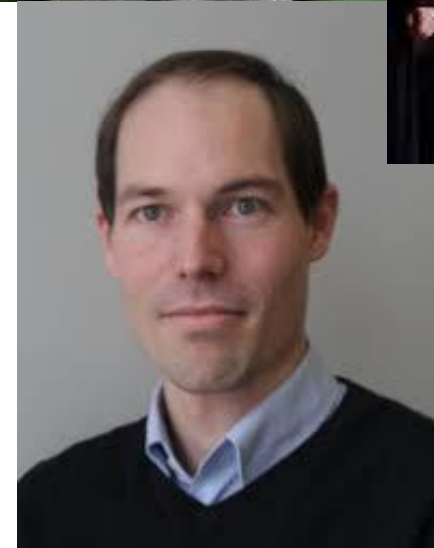
## WP2 QA and Standards

- Joint collaborative projects for benchmarking
  - Radiobiology Olga Sokol GSI
  - Dosimetry Marie Davidkova NPI-CAS
  - RBE and LET Armin Luhr Dresden

## WP4 Public Engagement and outreach

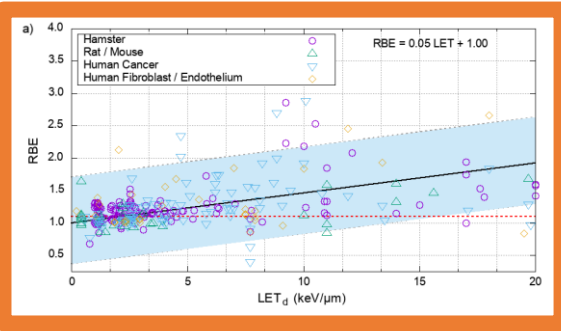
## WP5 Innovation and Sustainability

- Innovation Gateway
  - Example of very successful project Varian



# The INSPIRE Experiment

## A Fair Test

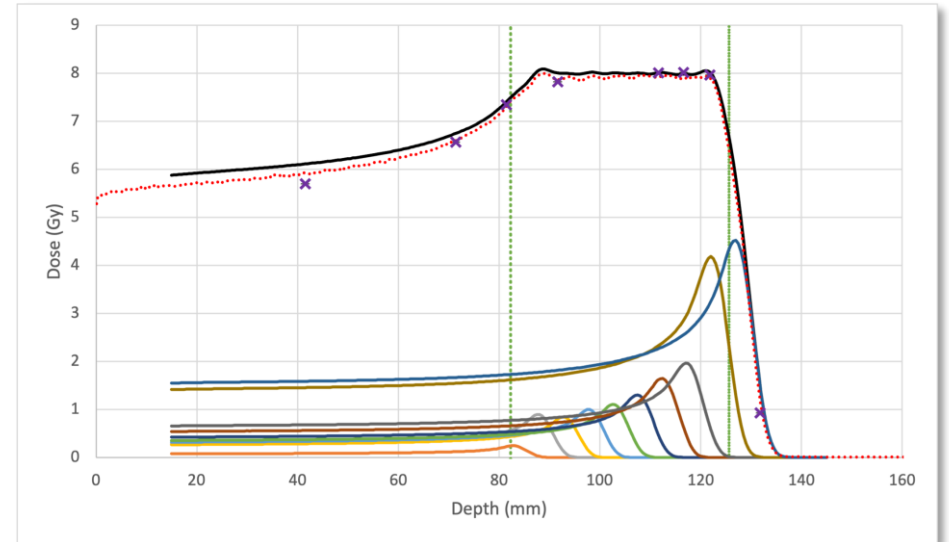
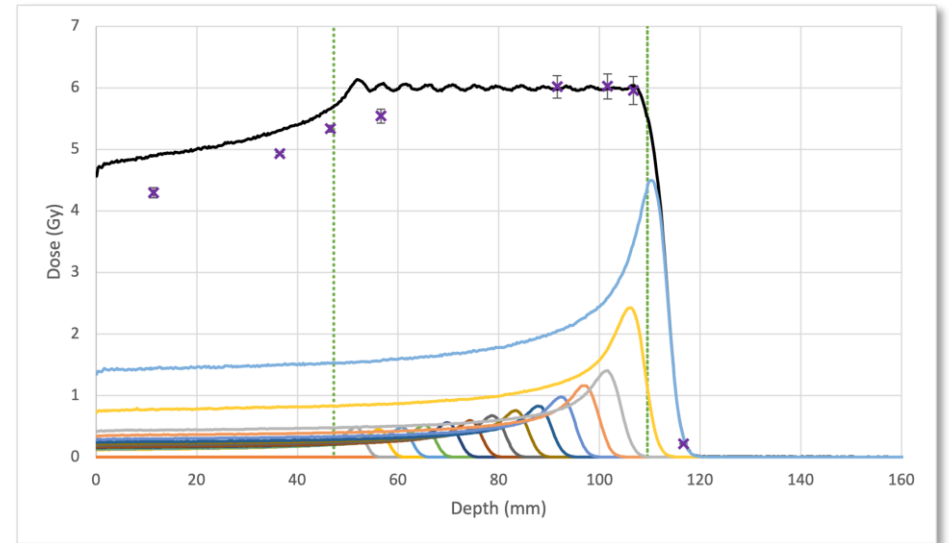


Parameters*	Geometry A	Geometry B
Target area size, mm (x, y, z)	60 x 80 x 60**	60 x 80 x 40**
Target center position, mm (z)*	80	105
Physical dose in the target, Gy	6	8

- ☐ Same geometry
- ☐ Same cell-line (V79)
- ☐ Same beams (sort of)
- ☐ 9 Institutes:

KVI, Groningen; OncoRay, Dresden; Skandion, Uppsala; NPI-CAS, Prague; IFJ-PAN, Krakow; AU, Aarhus; IC, Paris; GSI, Darmstadt; UoM, Manchester



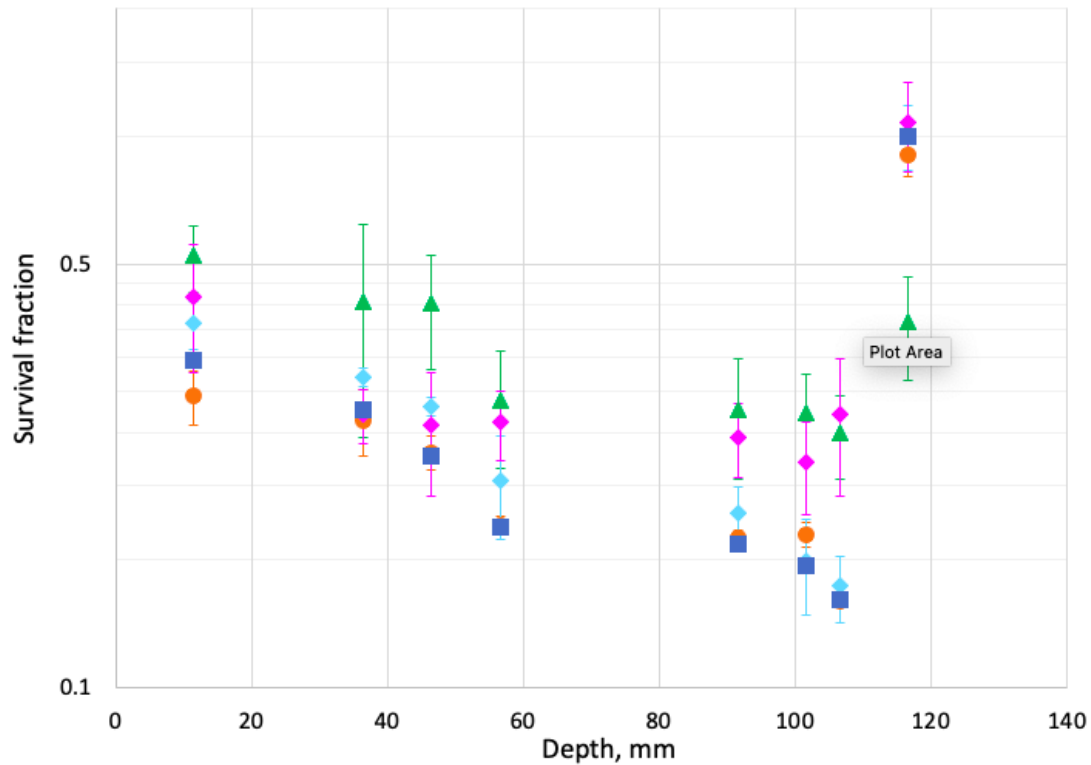


# The INSPIRE Experiment

## Preliminary Results

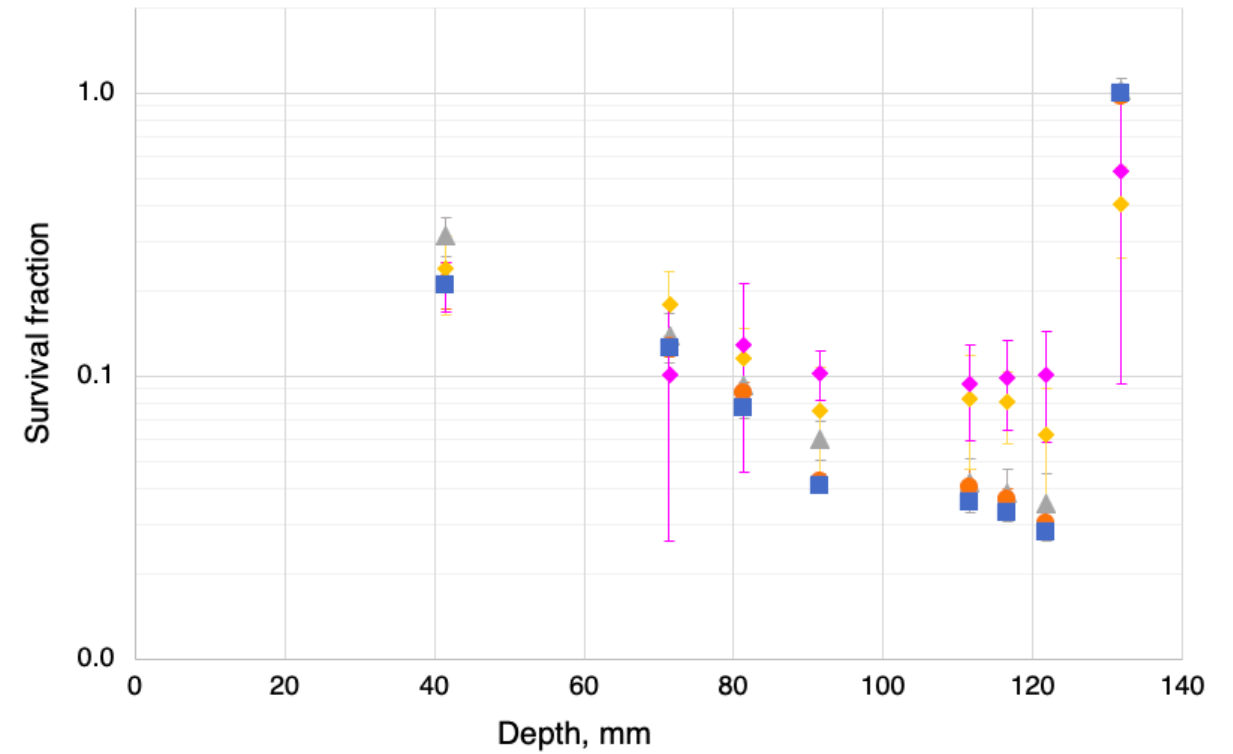
### 6Gy SOBP

Center 2   Center 4   Center 5   Center 6   Estimated



### 8Gy SOBP

Center 1   Center 2   Center 3   Center 6   Estimated



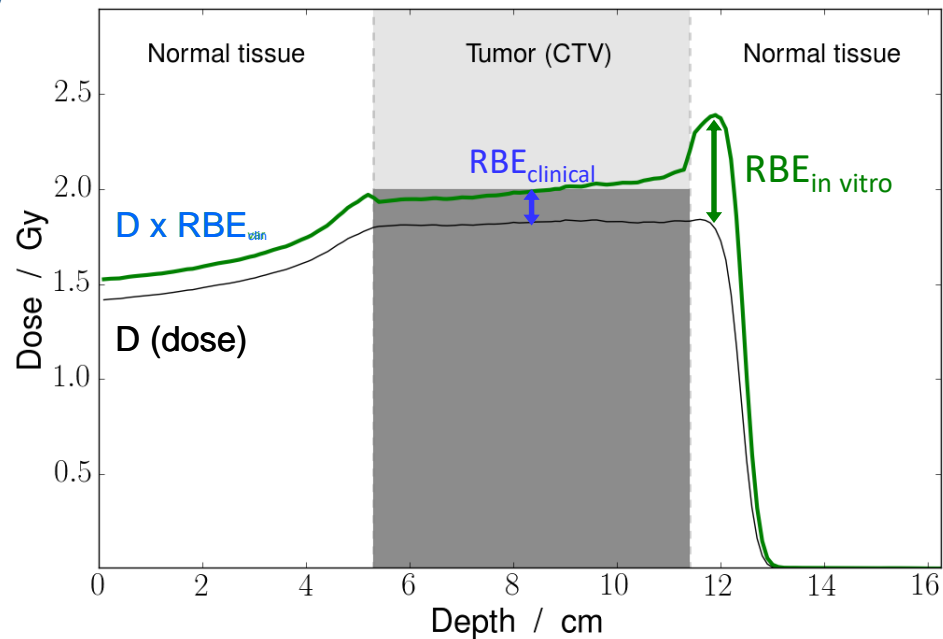
# WP2 and WP9 Benchmarking RBE & LET

- RBE varies with LET
- Compare and harmonise LET calculations
- 9 INSPIRE partners
- Centre TPS with centre beam model
- Constant and variable RBE
- Water phantom
- Patient cases



# European framework for RBE calculation in patients WP9, WP2

## Motivation



- **Clinical practice:** protons are 10% more biological effective than photons ( $RBE = 1.1$ )
- **Research finding:** varying RBE as a function of dose and linear energy transfer (LET)

## Problems

- Center-specific RBE modelling
  - LET calculation not
  - Variable RBE modeling
- Impacts quality of patient treatment and comparability of clinical outcome data

## Aims

- Towards variable RBE-modelling in clinical proton therapy
- Harmonizing LET definition and calculations in Europe
- Compare and harmonize clinical RBE-modelling in Europe



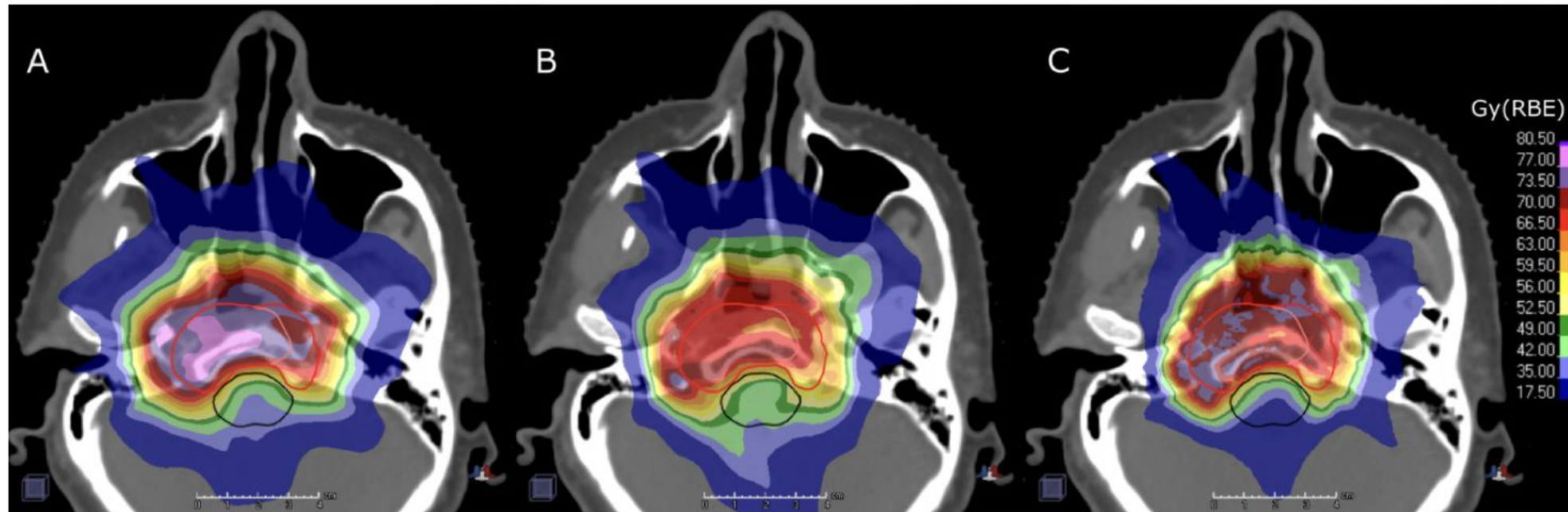
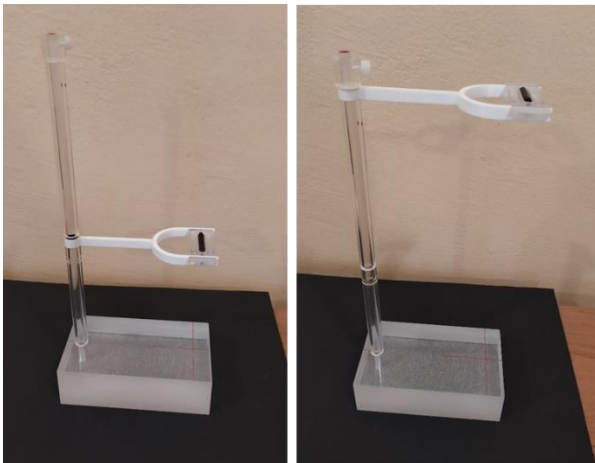
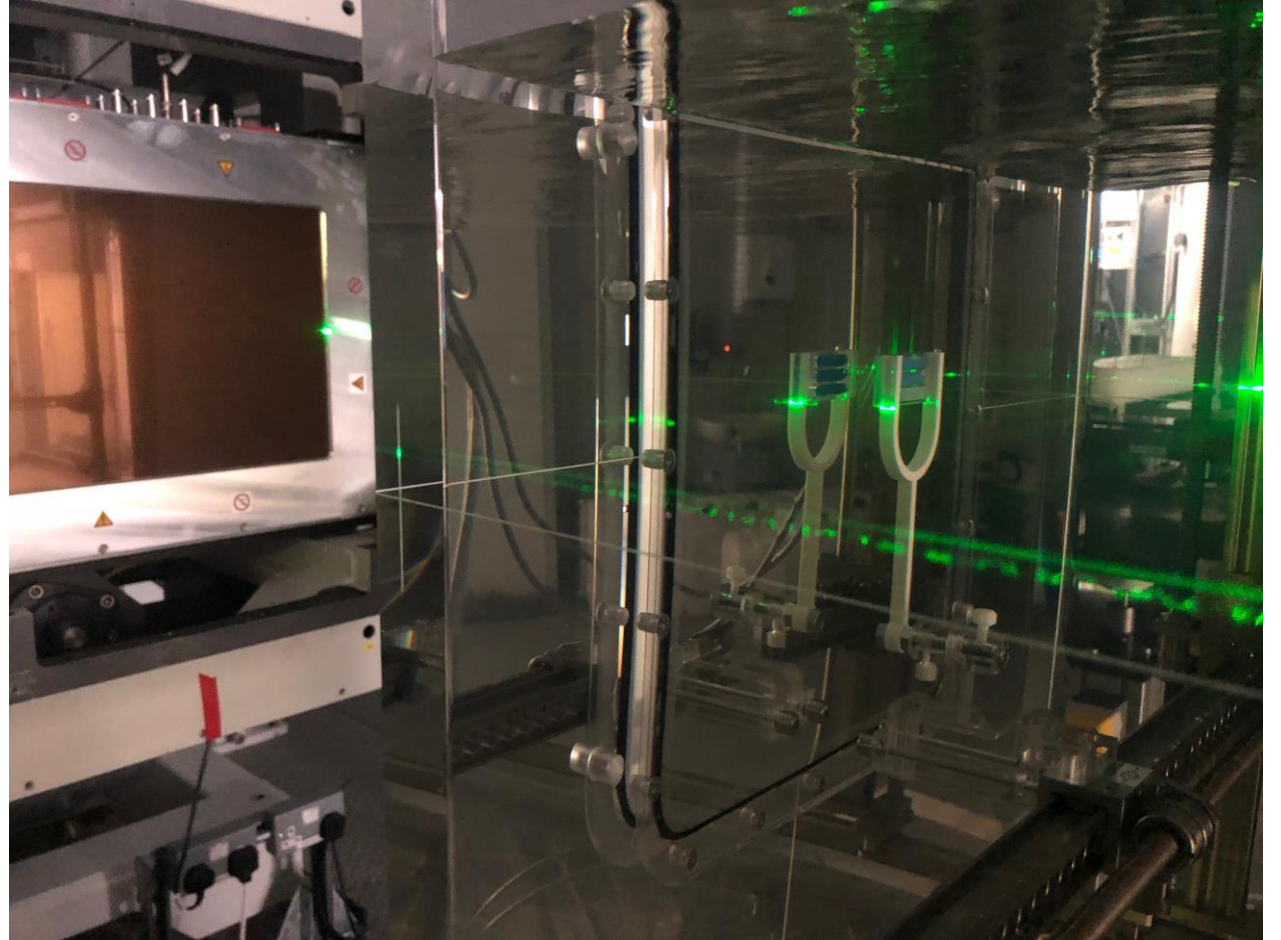


Figure 1: Dose distributions for the base of skull case from each centre using their centre-specific variable relative biological effectiveness (RBE) models: A) McNamara model with  $\alpha/\beta=2\text{Gy}$  everywhere, B) Wedenberg model with  $\alpha/\beta=10\text{Gy}$  in the clinical target volumes (CTV) and  $3\text{Gy}$  elsewhere, C) McMahon model without  $\alpha/\beta$  dependency. Prescription dose was  $57\text{ Gy(RBE)}$  to the CTV (darkred) and  $70\text{ Gy(RBE)}$  to the CTVboost (lightred) in 33 fractions and planned as simultaneous integrated boost. Brainstem: black.

# WP2 and WP10 Dosimetry Audit

- 7 INSPIRE partners + EURADOS WG9
- Special assembly for positioning in water phantom
- Thermoluminescent (capsules with TLD powder)
- Alanine pellets
- Radio-photoluminescent detectors
- On gantry and in front of horizontal beam line







17 November 2020

## Funding available for the PSI Winter School for Protons - Jan 2021

The PSI Winter School will be taking place virtually this year. The course will cover a range of topics related to Proton Therapy and has internationally renowned speakers. This is a great opportunity for physicians and physicists to learn more about

[Read More](#)

3 November 2020

## Research during corona crisis at GSI

TNA progress update from GSI.

[Read More](#)



### Inside this issue:

Welcome	1
Upcoming events	1
INSPIRE Fellows Training Course	2

### NEWSLETTER

Issue 4. Winter 2020



## InspireProject

Infrastructure in Proton International Research

### Welcome and update

As we move into 2021, the INSPIRE Consortium are looking back at the achievements from the past year. **TNA** User Groups continued to submit applications this year for TNA and INSPIRE has now received over 33 requests for access. Many of these experiments have

an international survey to gain an insight into how adults are selected for Proton Therapy across Europe. The eight partners in WP9 (Mathematical Modelling and Simulation) have formed a European network to simulate biological effects (LET, RBE) of PBT and WP10 (Dosimetry, Robustness & Uncertainties) have worked

2021. We are pleased to announce that the INSPIRE joint led conference 'Flash Radiotherapy and Particle Therapy' will take place in December 2021. Click [here](#) for details.



# Public Engagement and Outreach

- Open Nights programme at IFJ-PAN have continued, despite Covid-19
- Now online and attracted even more participants 1000 in the case of IFJ-PAN.





# Science Museum: Cancer Revolution



# Knowledge Hub and Fact Sheets

- Links to information materials in various languages on partner sites :

## Germany

Universitätsklinikum Carl Gustav Carus  
Klinik und Poliklinik für Strahlentherapie und Radioonkologie  
Direktorinnen: Prof. Dr. med. Mechthild Krause, Prof. Dr. med. Dr. Esther Troost



Patienteninformation und Einwilligungserklärung: Protonen- vs. Photonentherapie

**- Patienteninformation zur Protonentherapie bei noch fehlendem wissenschaftlichen Nachweis einer Überlegenheit gegenüber der Standard-Photonentherapie -**

Sehr geehrte Patientin, sehr geehrter Patient,

wir möchten Sie über Ihre weitere Behandlung im Rahmen der Strahlentherapie informieren. Am Universitätsklinikum Dresden, Klinik und Poliklinik für Strahlentherapie, wird seit Ende 2014 zusätzlich zu der weltweit üblichen Photonentherapie (ultraharte Röntgenstrahlen) eine Strahlentherapie mit Protonen angeboten. Die Behandlung mit Protonen ist weltweit nur an wenigen Standorten verfügbar, in Deutschland kann die Behandlung neben Dresden nur noch an derzeit drei weiteren Standorten durchgeführt werden.

## UK



**brainstrust**  
the brain cancer people

## Sweden



Så här går en behandling till

Protonstrålning går till på samma sätt som annan strålbehandling. Patienten får ligga sig på ett behandlingsbord och placeras med hjälp av



De patienter som bor för långt från Uppsala för att kunna åka hem mellan behandlingarna bor ofta på Hotel von Kraemer, som ligger i samma byvägad som kliniken. Barnfamiljer har

## France



### L'enseignement

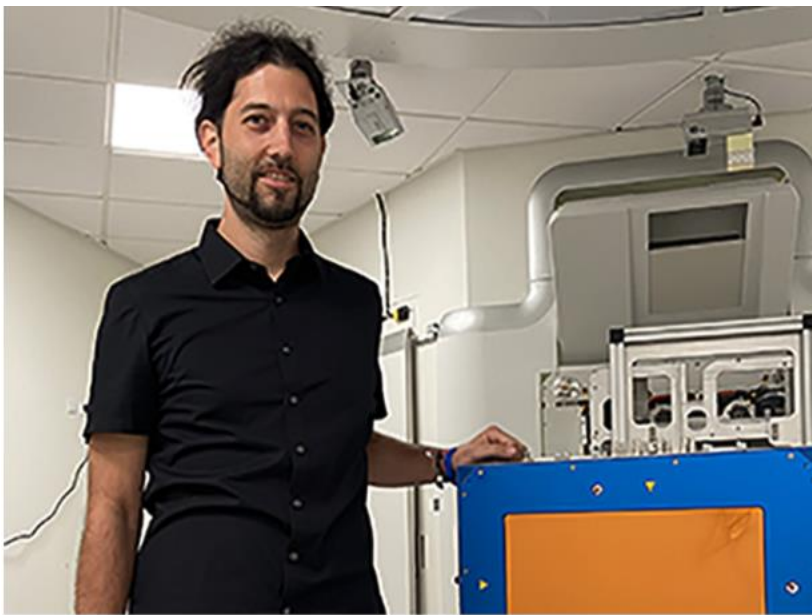
La diffusion des savoirs pour faire progresser la recherche et la médecine est une composante essentielle de la mission de service public de l'Institut Curie, œuvrant dans la lutte contre les cancers.

### Chiffres-clés de l'Ensemble Hospitalier

2100 professionnels de santé  
13 500 patients pris en charge  
170 000 consultations





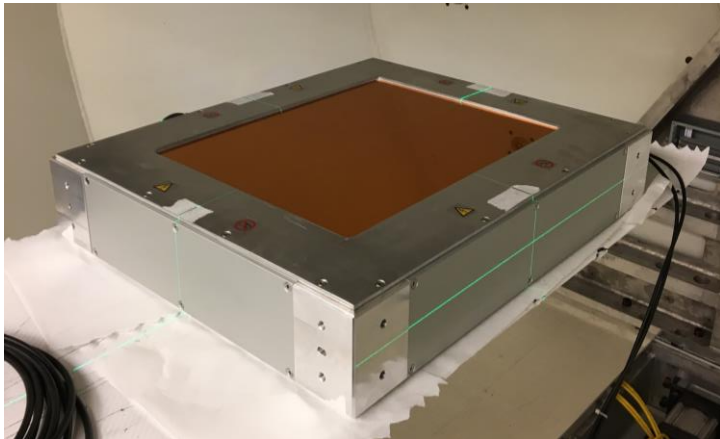


30 September 2021

## An Industry Academic Partnership Yields Fruit - An Ultra-High Dose Rate Beam Monitoring Tool for FLASH Trials

Varian, supported by the INSPIRE Project, partners with two members of the FlashForward Consortium to test novel ionization chamber for FLASH research.

[Read More](#)



WP5 Innovation Gateway: Pathfinder

Worlds first PBT FLASH trial FAST01, Cincinnati

Commercial research product FLEX developed

Clinical prototype being tested Aarhus

Varian and PTW-Freiburg, (UHDpulse) on FLASH dosimetry equipment

GSI Darmstadt and THM Gießen 3D printed range modulators FLASH Bragg peaks

INSPIRE is funded from the European Union's Horizon 2020 Research and Innovation Programme, under Grant Agreement no. 730983



# WP5 – Innovation and Sustainability: Example: Golden ticket ADVACAM

- Working with EMPIR project UHDPulse
- New detector from AVACAM Czech republic, measurement of stray radiation
- At Dresden measurements in a water phantom dose rates 1 Gy/min to FLASH dose rates of 150 Gy/s
- Extended range of proton beam current available at Dresden from 2-300 nA to 0.001 -500nA



MiniPIX TimePIX3



AdvaPIX TimePIX3



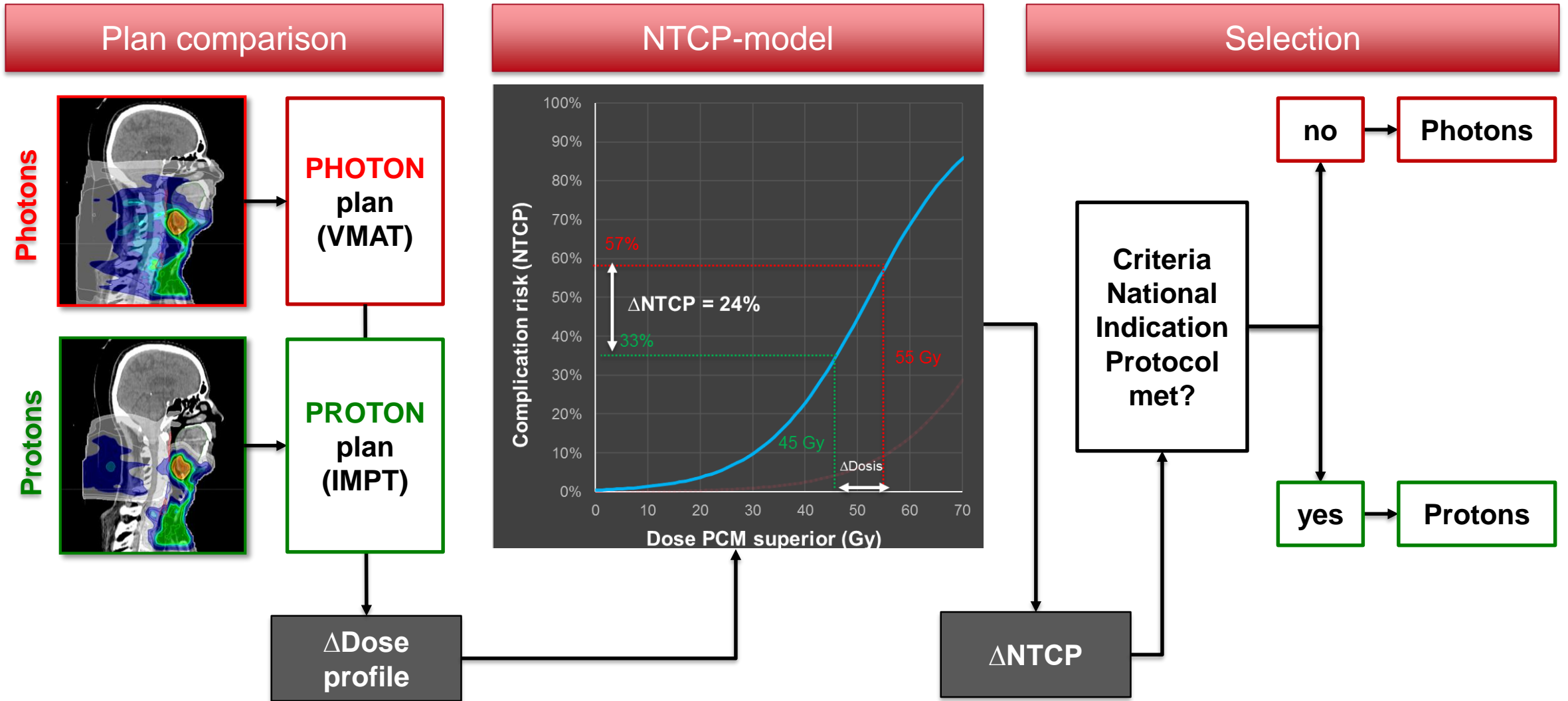
*Single chip Timepix 3  
pixel detectors  
(each pixel records  
deposited energy)*

Prototype FLEX  
MiniPIX TimePIX3



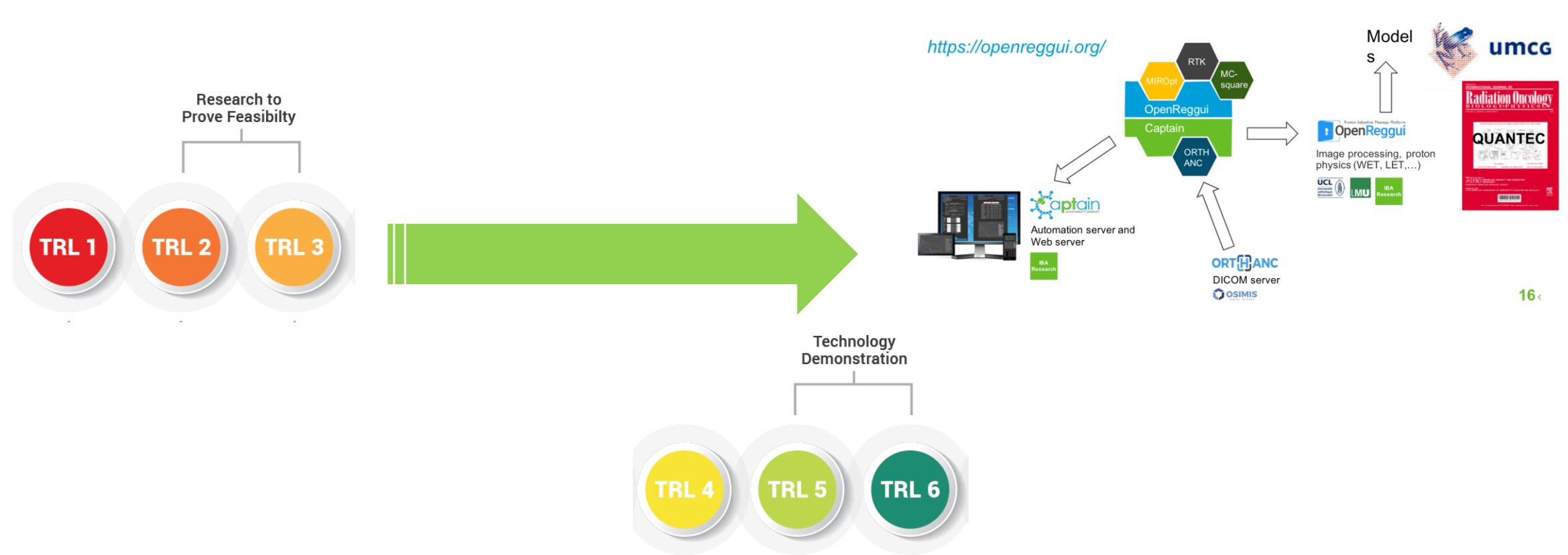


# How does model-based selection work?



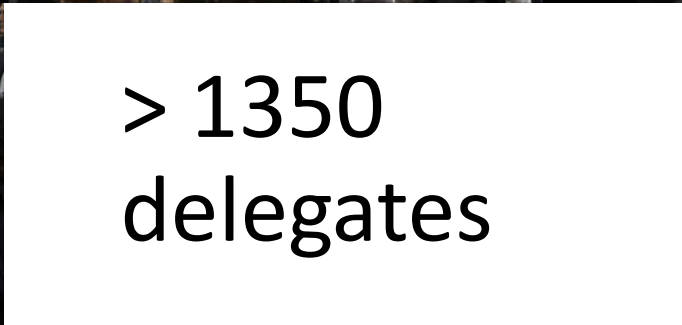
# WP5 – Innovation and Sustainability: Example: Integrating Cultures, KE, Pathfinder IBA

- Uses research from WP8 to develop a NTCP database 3 TRLs





# PTCOG June 2019



> 1350  
delegates





# FRPT: Flash Radiotherapy & Particle Therapy



- Working with Kenes and international leaders in the field
- > 700 participants
- 40 countries
- **Next meeting 29 Nov-2 Dec 2022 Barcelona**
- Special edition Green Journal
- In person & virtual
  - Building and operating a PBT centre
  - FLASH
  - Spatially fractionated radiotherapy
  - Protons & Ions (INSPIRE, HITRIplus)
- Modalities, mechanisms and the clinic
- 3 webinars – Proton FLASH 10<sup>th</sup> June
- Green conference



New horizon in  
therapy & treatment

# FRPT

FLASH  
RADIOTHERAPY  
& PARTICLE  
THERAPY

# 2021

VIENNA & ONLINE

1-3 DECEMBER 2021

FRPT 2021



FRPT-Conference.org

# Future

- Collaboration
- Increase TNA capacity
- Move closer to the clinic
- Working with industry
- Personalizing treatment
  - Outcomes: clinical outcomes, eproms
  - Wearables: real time monitoring
  - Involving patients in decision making
  - Digital biomarkers, learning from particle physics and astronomy communities
  - Integrating with imaging
- Next generation clinical trials
  - Paediatric & rare tumours so pan European approach needed
- Health research
  - Who benefits most from PBT and how are they chosen
  - Health inequalities
  - Impact of Covid



canSERV







Thankyou

Colleagues in INSPIRE

# Thankyou to a brilliant group of people

## The PRECISE Group

Ran MacKay  
Norman Kirkby  
Neil Burnet  
Mike Merchant  
Mike Taylor  
Helena Kondryn  
Rebecca Parker  
Adam Aitkenhead

Adam Aitkenhead  
Amy Chadwick  
Elham Santina  
Tom Mee  
Nickolay Korabel  
Sam Ingram  
Sam Manger  
Noemie Defourny  
John-William Warmenhoven  
Nicholas Henthorn  
Emma Biglin

Ed Smith  
Beth Rothwell  
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Danni Love  
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Mat Lowe



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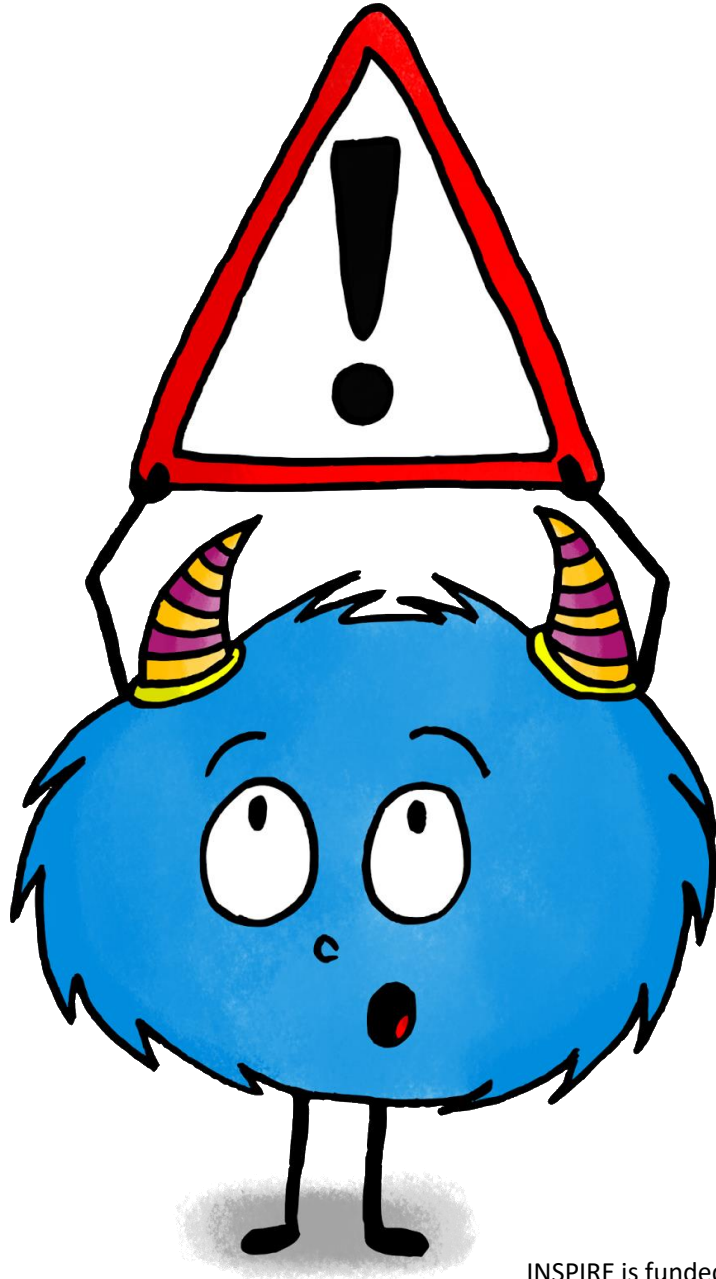


Questions?

# Thank you for listening







"This material was prepared and presented within the HITRIplus **Specialised Course on Heavy Ion Therapy Research**, and it is intended for personal educational purposes to help students; people interested in using any of the material for any other purposes (such as other lectures, courses etc.) are requested to please contact the authors ([karen.kirkby@Manchester.ac.uk](mailto:karen.kirkby@Manchester.ac.uk)).

