INSPIRE

Karen Kirkby
Richard Rose Chair in Proton Therapy Physics
University of Manchester / The Christie NHS Foundation Trust

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

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

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InspireProject

Collaborations

ARIE PUBLICATIONS


ANALYTICAL RESEARCH INFRASTRUCTURES IN EUROPE

A KEY RESOURCE FOR THE FIVE HORIZON EUROPE MISSIONS

JOINT POSITION PAPER

FINAL RELEASE 16 SEPTEMBER 2020

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

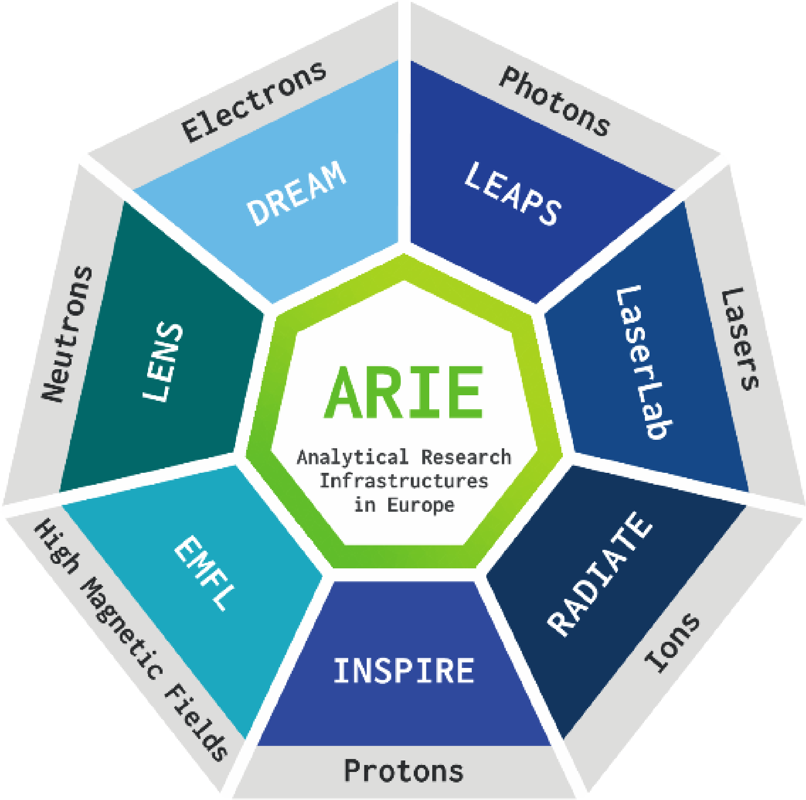

ANALYTICAL RESEARCH INFRASTRUCTURES IN EUROPE

VIRAL AND MICROBIAL THREATS

JOINT POSITION PAPER

16 SEPTEMBER 2020

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



UHDpulse

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Overview

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

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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

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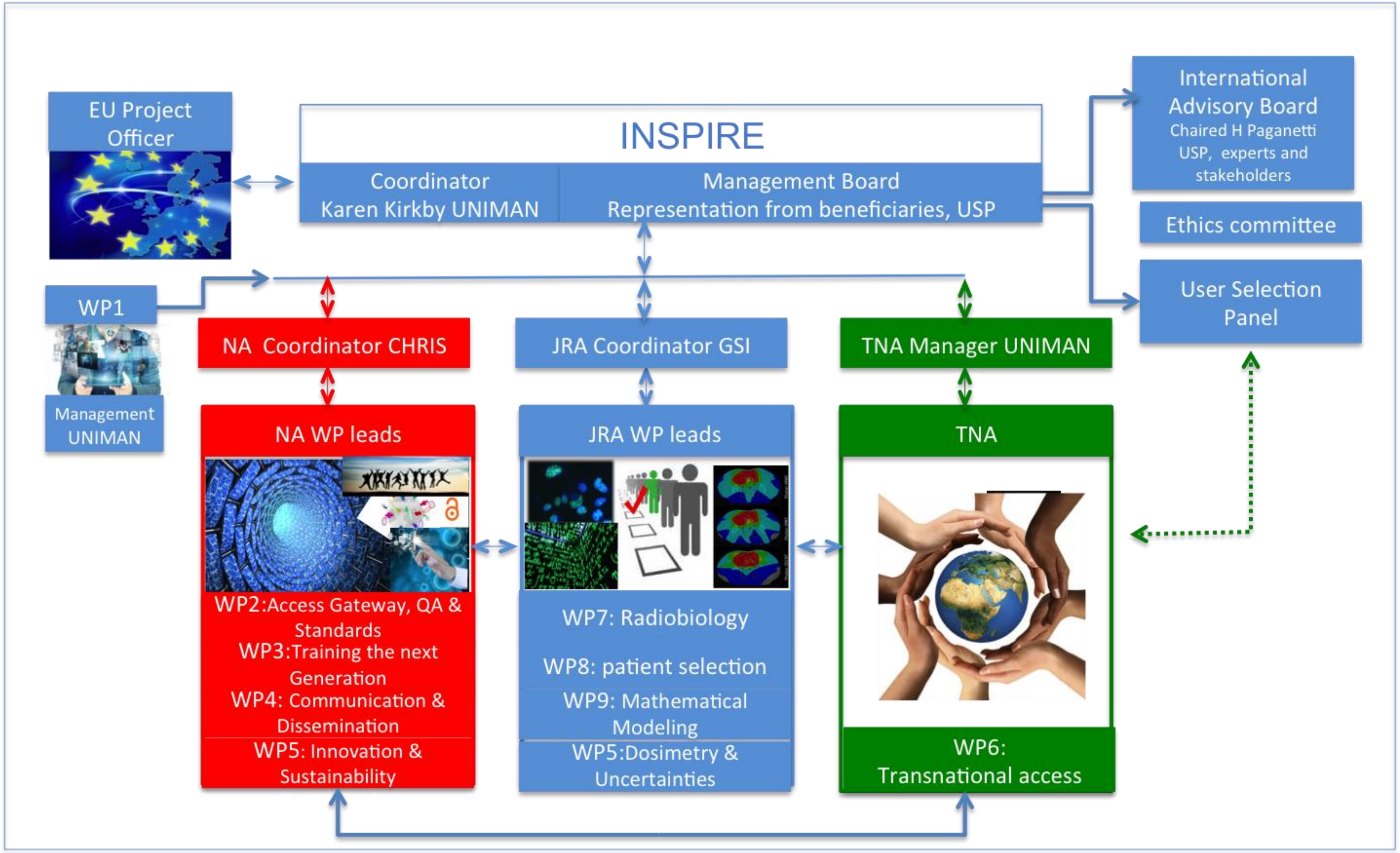
- Management WP1
- Networking WP2-5
- TNA WP6
- JRA WP7-10



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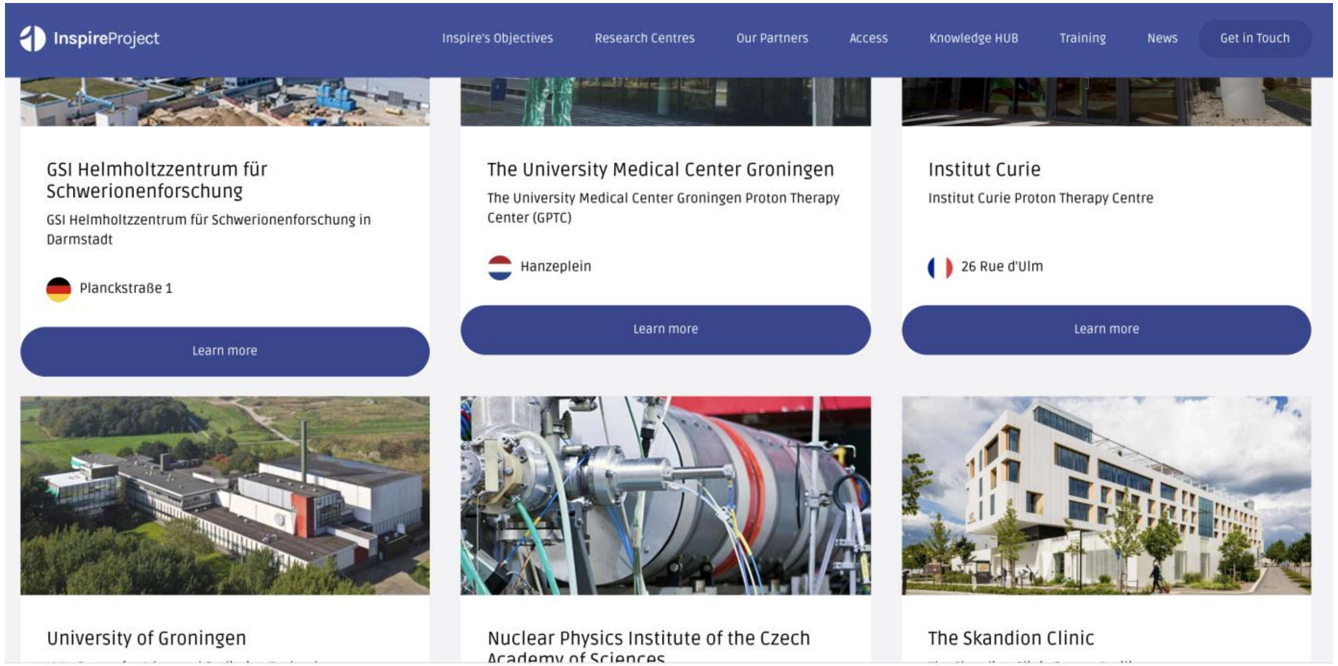
Transnational Access

- Access to research rooms in PBT clinical facilities
- ”Clinical beams” in a research environment
- Gantries
- Fixed beamlines
- W or wo 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



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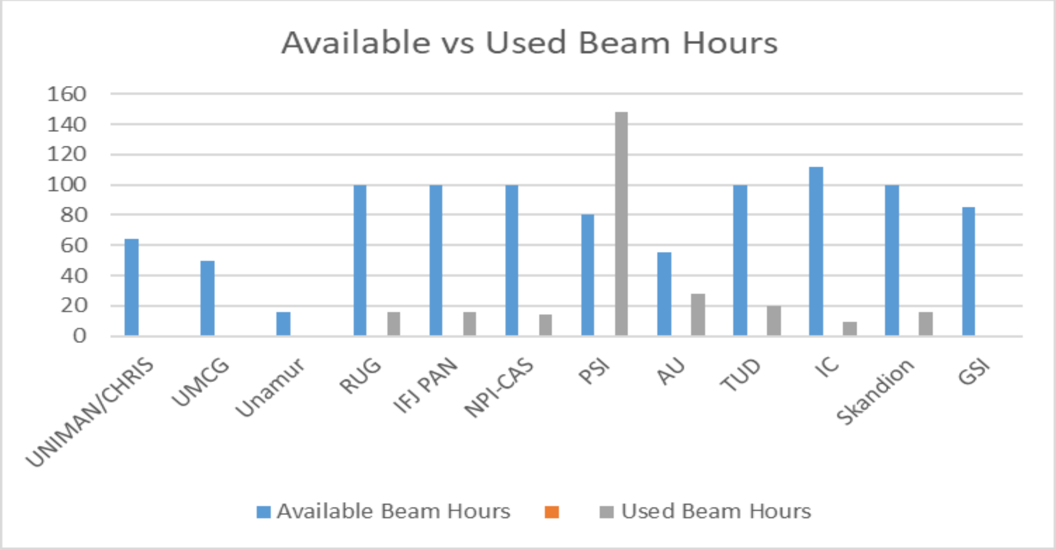
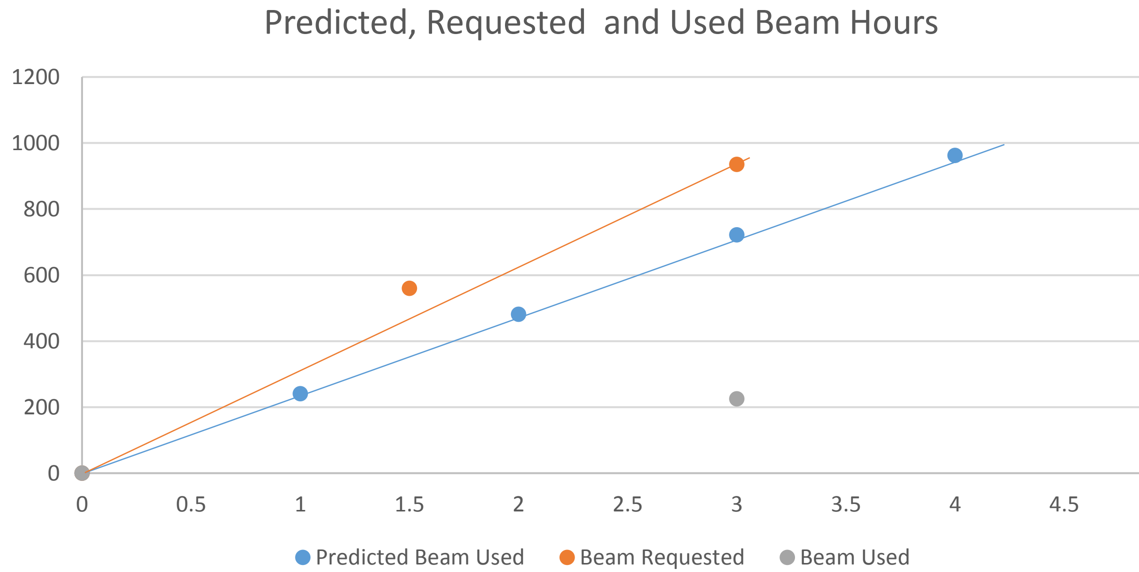
Transnational Access - Capabilities

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





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Transnational Access - Capabilities

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- 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[1,2†], Olga Sokol[3†], Marco Durante[3,4*], Ludovic De Marzi[5], Frederic Pouzoulet[6], Justyna Miszczyk[7], Pawel Olko[7], Sytze Brandenburg[8,9], Marc Jan van Goethem[8,9], Lara Barazzuol[9,10], Makbule Tambas[9], Johannes A. Langendijk[9], Marie Davídková[11], Vladimír Vondráček[12], Elisabeth Bodenstein[13], Joerg Pawelke[13,14], Antony J. Lomax[15,16], Damien C. Weber[15,17,18], Alexandru Dasu[19,20], Bo Stenerlöw[20], Per R. Poulsen[21], Brita S. Sørensen[21], Cai Grau[21], Mateusz K. Sitarz[21], Anne-Catherine Heuskin[22], Stephane Lucas[22], John W. Warmenhoven[1,2], Michael J. Merchant[1,2], Ran I. Mackay[1,23] and Karen J. Kirkby[1,2]

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frontiers in Physics

REVIEW
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OPEN ACCESS

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Specialty section:
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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)

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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

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Radiobiology WP2 and WP7

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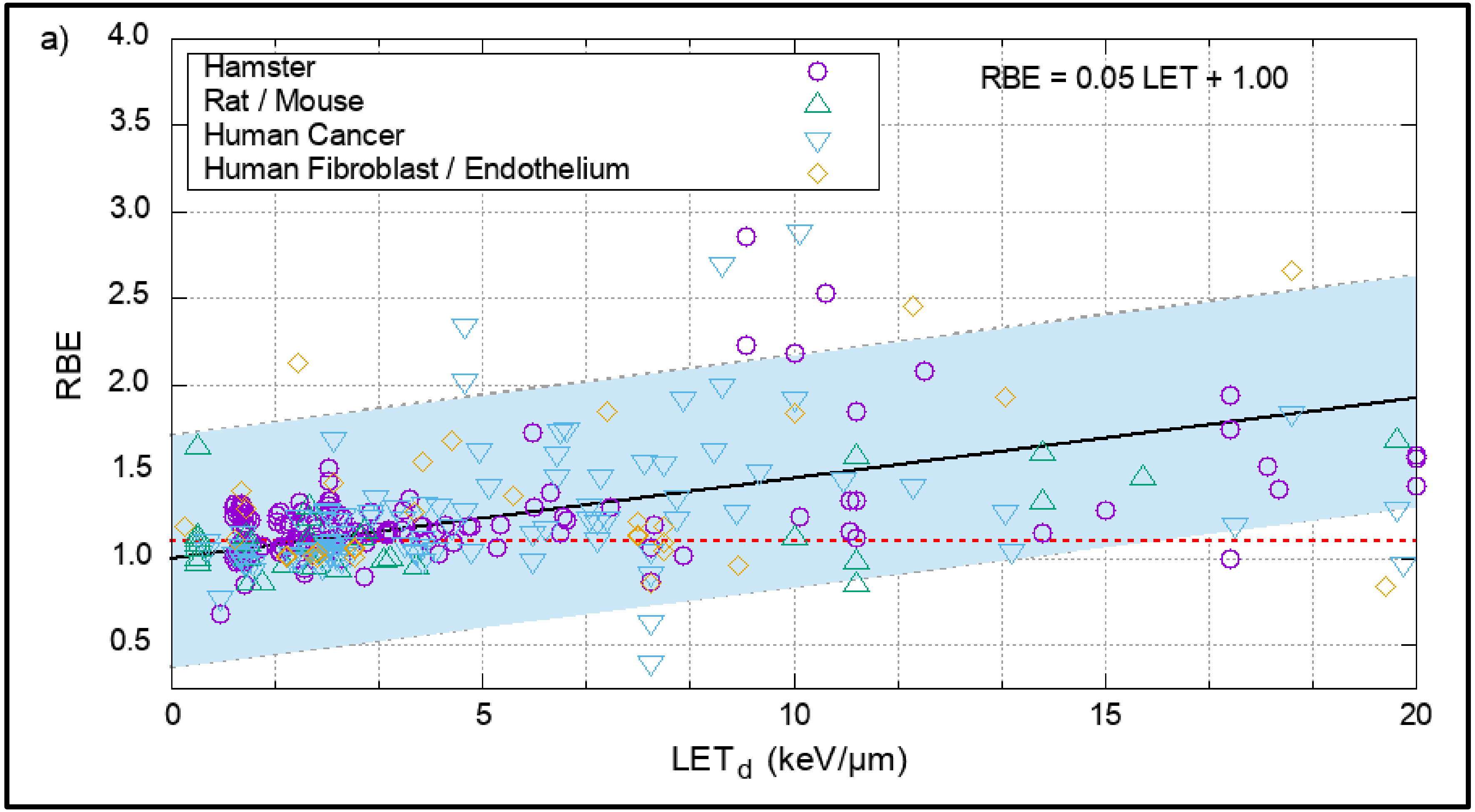

Data from: Paganetti, PMB, 2014

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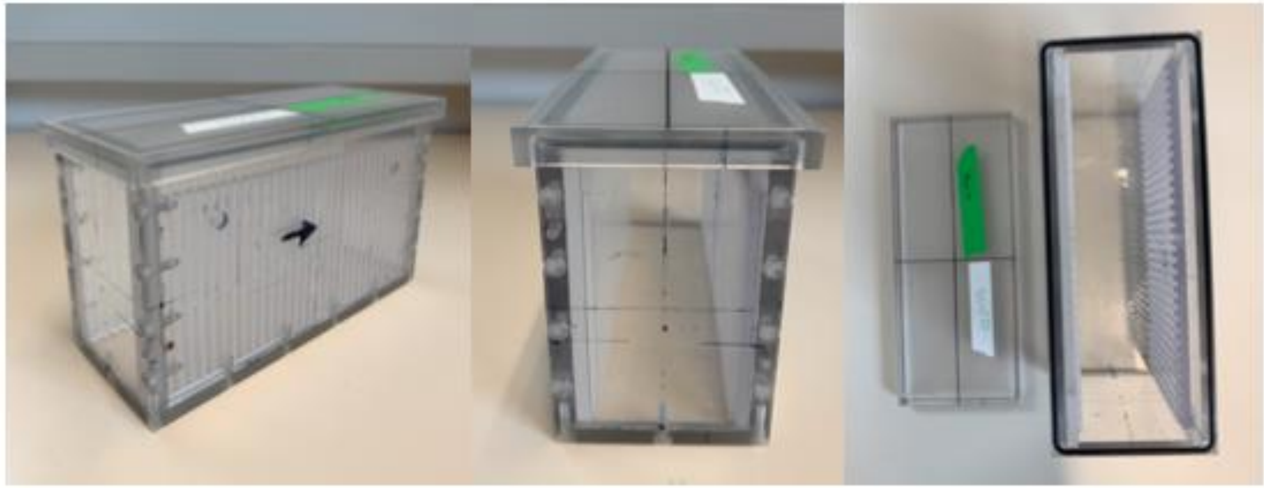
Inter-Comparison

A fair test…



Sharing the same geometry & cell-line (V79)

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

Sharing the 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

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The Experiment

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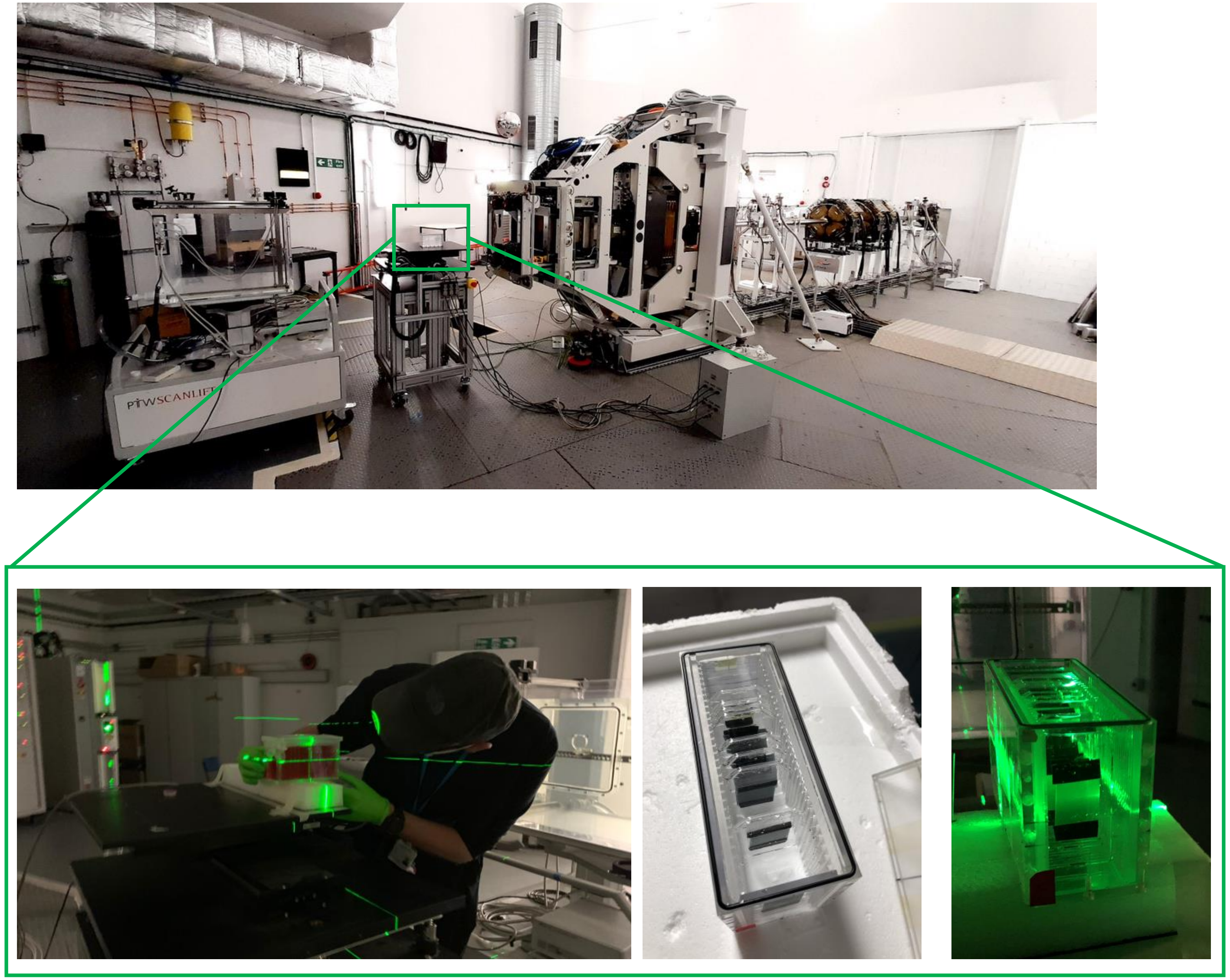

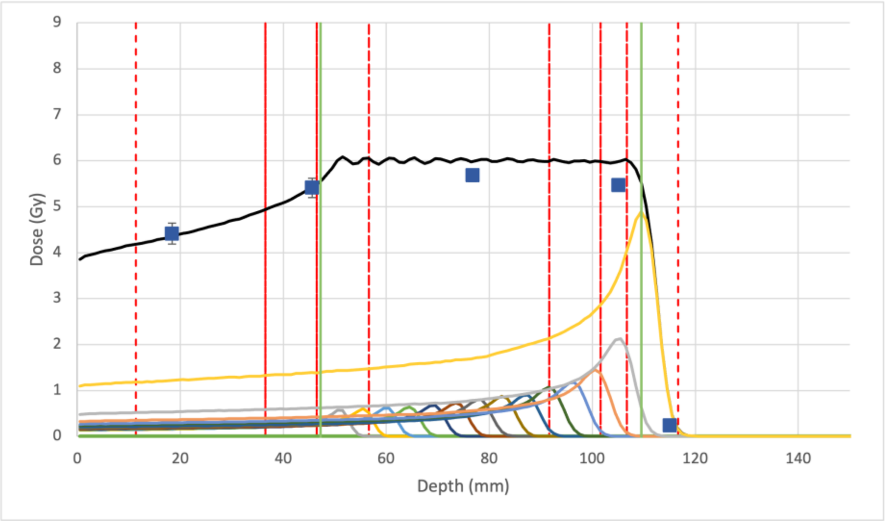

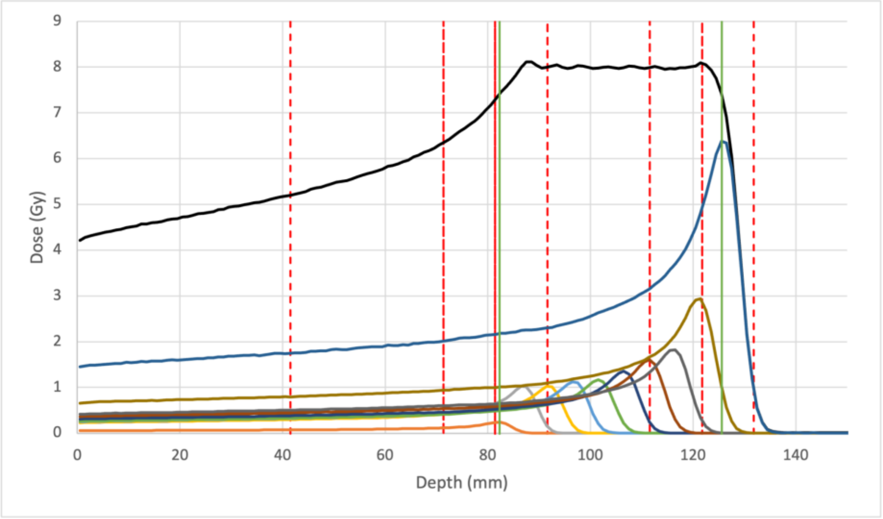

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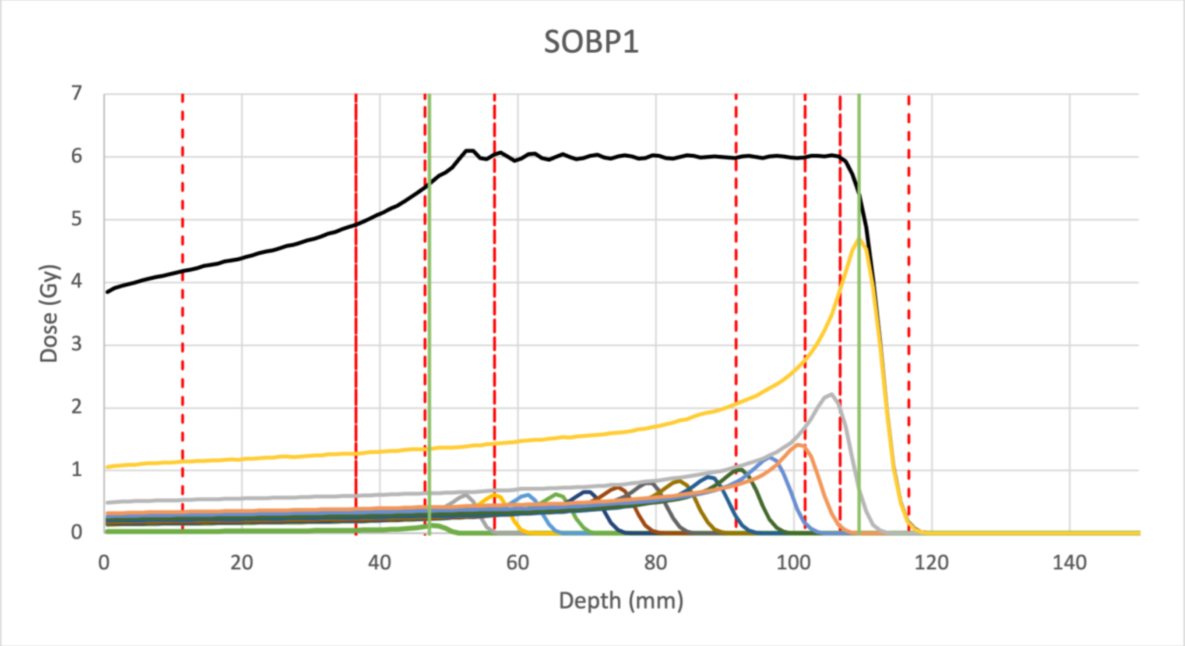
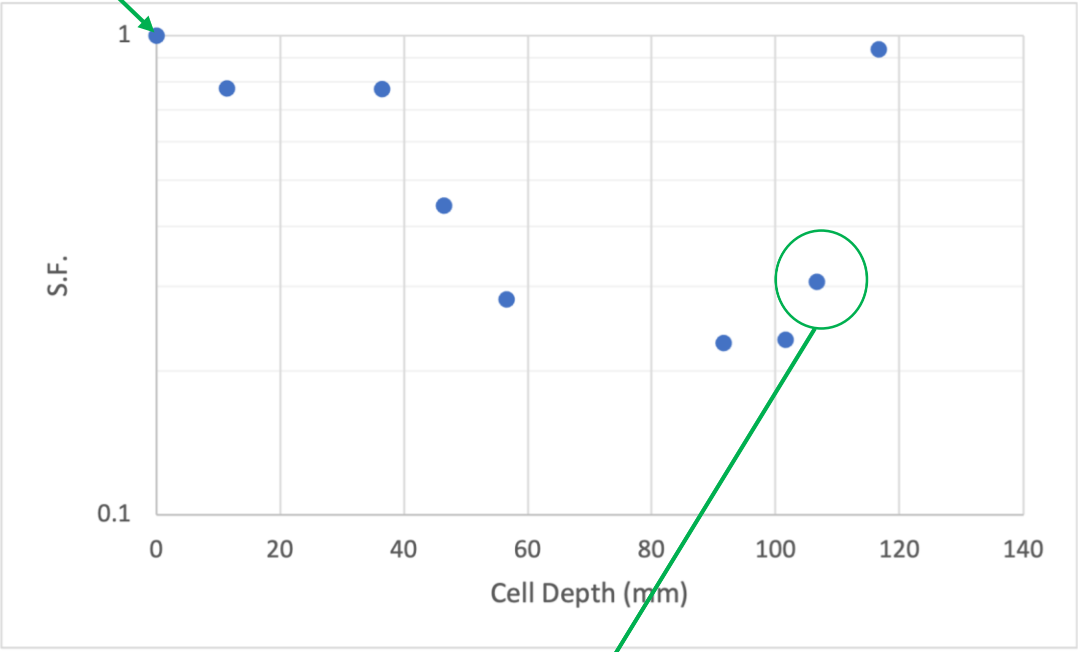
Results

So Far…

Control





Energies: 82.0 -> 126.3 MeV

Expecting to see a "spiked" decrease in S.F due to increased LET
Possible "overshoot"

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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

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European framework for RBE calculation in patients WP9, WP2

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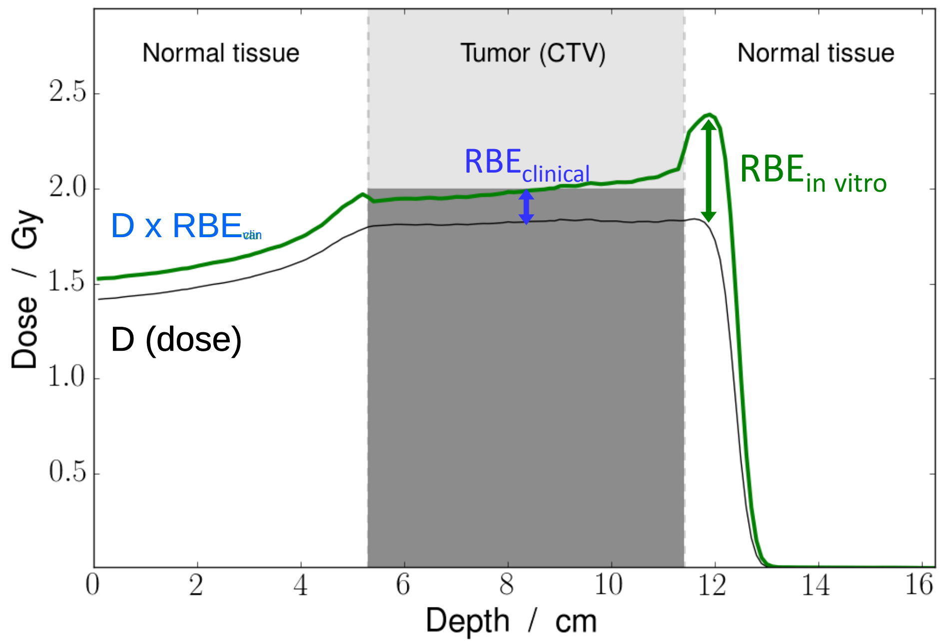
Motivation



- **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 comparibility 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

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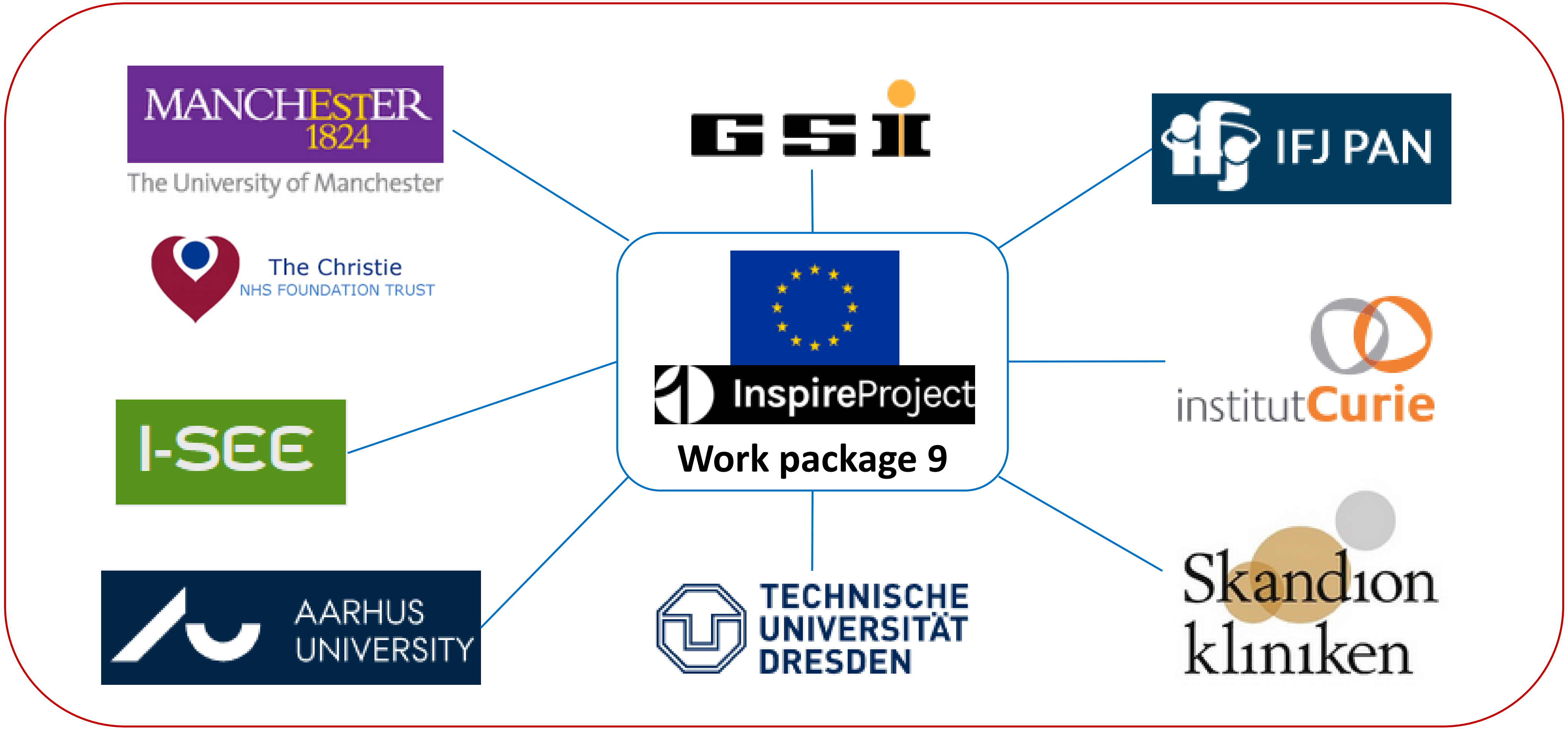
INSPIRE participants



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P1: Simulation techniques at European proton centers

Calculation algorithm for LET	Simulation environment
Monte Carlo	RayStation
	TOPAS
	GATE
Analytical Codes	Eclipse
	FRoG
	TRiP98

LET Scoring Methods used *
Primary Protons
All protons
Ions with Z=1
All primaries and secondaries

* Centers are capable of track- and dose-averaging

→ *Various algorithms, simulation tools, treatment planning software and LET scoring are used*

→ *Need for common European framework for simulation of biological effect of proton therapy*

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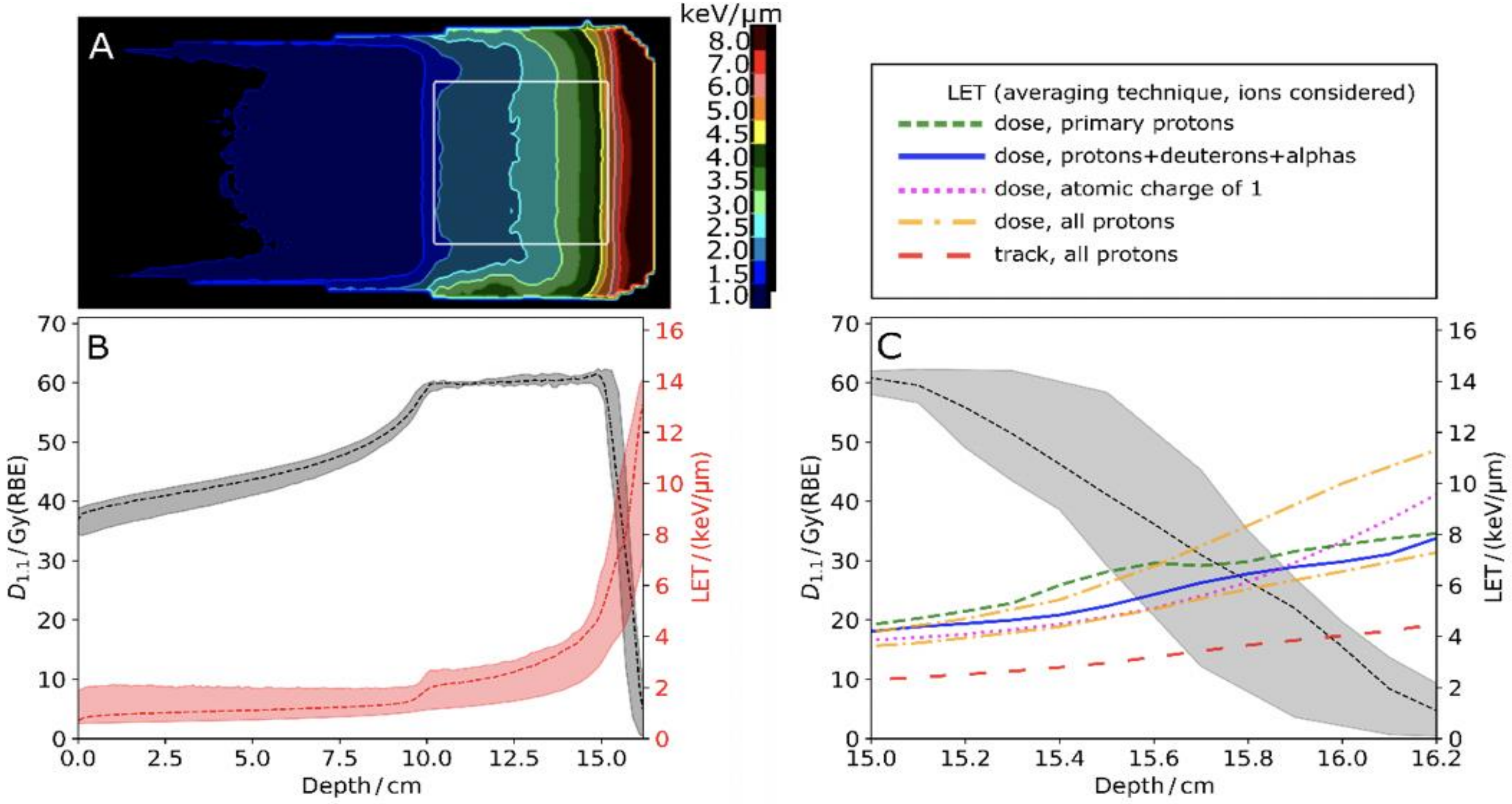

Figure 2: A) Example of a linear energy transfer distribution (LET, dose-averaged, all protons), corresponding to the dose distribution in Figure 1A. Line profiles of the six institutions along beam central axis are depicted in B) for biologically equivalent dose with relative biological effectiveness of 1.1 ($D_{1.1}$, grey, upper) and non-harmonized LET distributions (red, lower). Median (dashed) $D_{1.1}$ and LET are shown together with their minimum and maximum values (shaded area) showing inter-institutional variability between the six institutions. C) Magnification of the distal area in B) with a detailed depiction of LET line profiles for all six institutional non-harmonized LET calculations.

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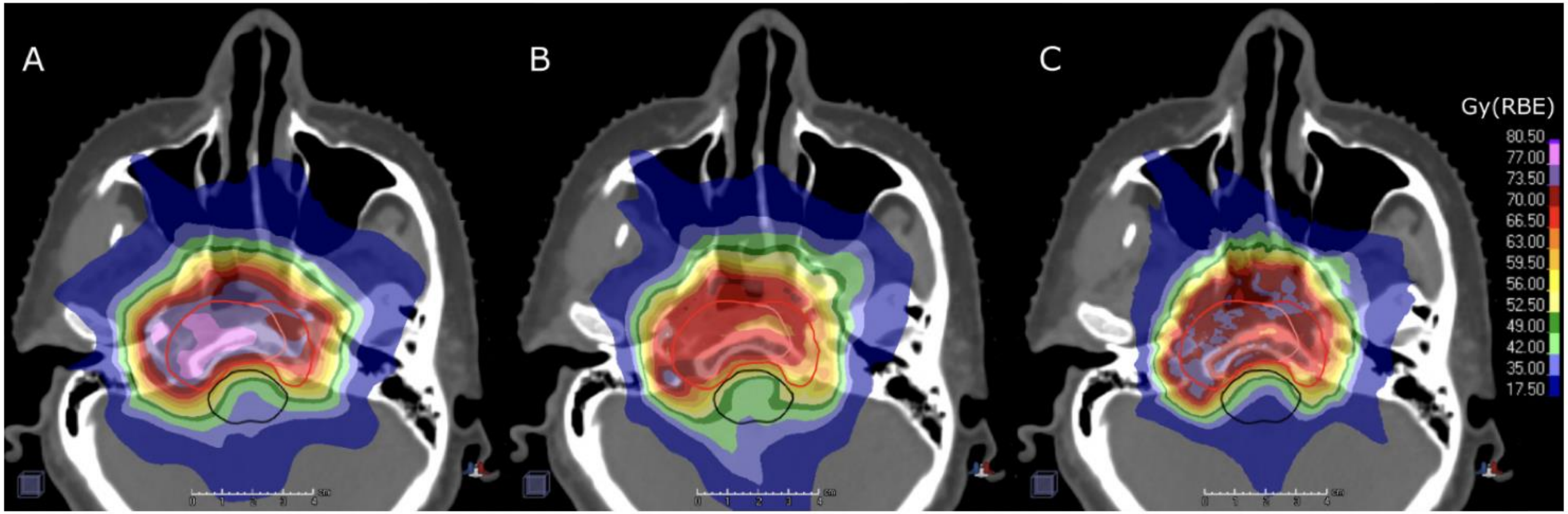

Figure 1: Dose distributions for the base of skull case from each centre using their centre-specific variable relative biological effectiveness (RBE) models: A) McNamara model with α/β=2Gy everywhere, B) Wedenberg model with α/β=10Gy in the clinical target volumes (CTV) and 3Gy elsewhere, C) McMahon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

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WP2 and WP10 Dosimetry Audit

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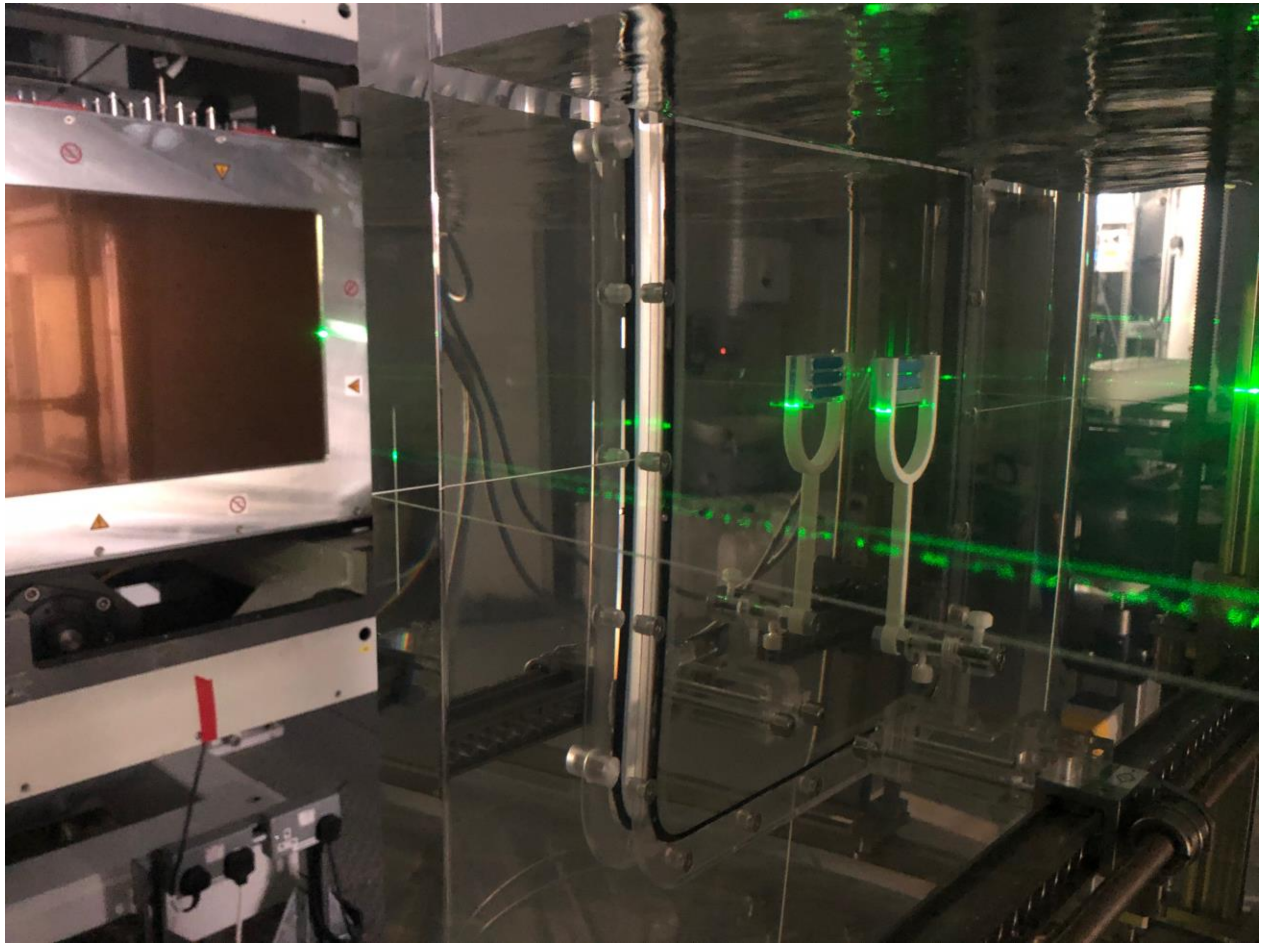
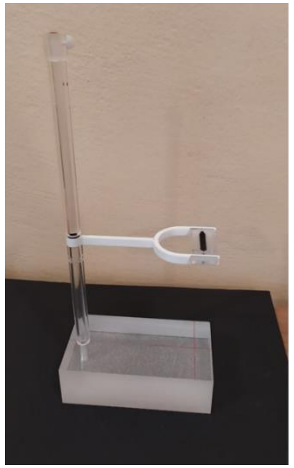
- 7 INSPIRE partners + EURADOS WG9
- Special assembly for positioning in water phantom
- Thermoluminescent (capsules with TLD powder)
- Alanine pellets
- Radio-photoluminescent detectors
- On gantry and infront of horizontal beam line





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News & Newsletters

InspireProject

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 abou

Read More

3 November 2020

Research during corona crisis at GSI

TNA progress update from GSI.

Read More

NEWSLETTER

Issue 4. Winter 2020

InspireProject

Infrastructure in Proton International Research

Welcome and update

Inside this issue:

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.

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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.

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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

Universitäts Protonen Therapie Dresden

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

Sweden

Så här går en behandling till

Protonstrålning går till på samma sätt som annan strålbehandling. Patienten får lägga 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 byggnad 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

2 100 professionnels de santé
13 500 patients pris en charge
170 000 consultations

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WP5 – Innovation and Sustainability: Example: Pathfinder project

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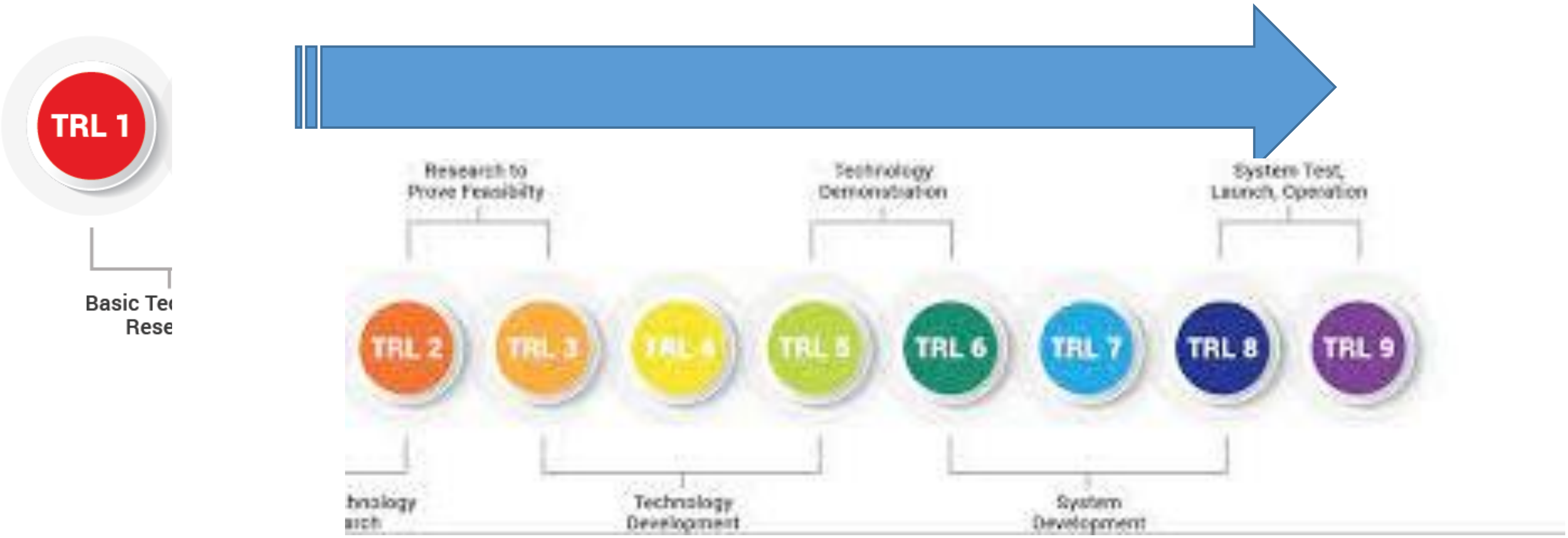
- JRA in WP10
- Worlds first PBT FLASH trial FAST01, Cincinnati
- Commercial research product FLEX developed
- Clinical prototype being tested Aarhus
- Varian and PTW-Freiburg, (UHDpulse) on FLASH dosimetry equipment
- GSI Darmstadt and THM Gießen 3D printed range modulators FLASH Bragg peaks



WP5 – Innovation and Sustainability: Example: Golden ticket ADVACAM

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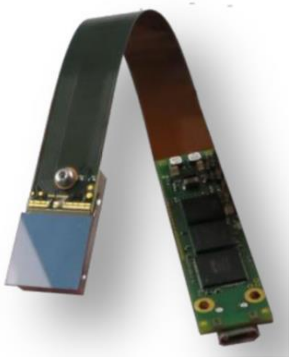
- Working with EMPIR project UHDPulse
- New detector from AVACAM Czech republic, measurement of stray radiation
- At Dresden measurements in a water phantom dose rates 1 Gy/min to FLASH dose rates of 150 Gy/s
- Extended range of proton beam current available at Dresden from 2-300 nA to 0.001 -500nA

MiniPIX TimePIX3

AdvaPIX TimePIX3

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

Prototype FLEX MiniPIX TimePIX3



ADVACAM
Imaging the Unseen

UHDpulse

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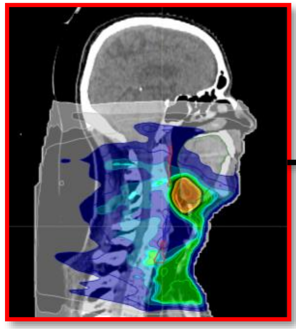
How does model-based selection work?

umcg

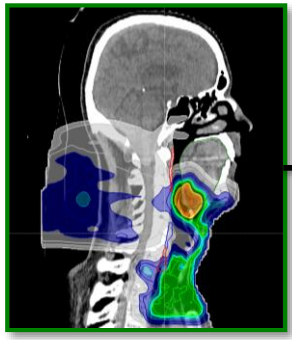
Plan comparison

Photons



PHOTON plan (VMAT)

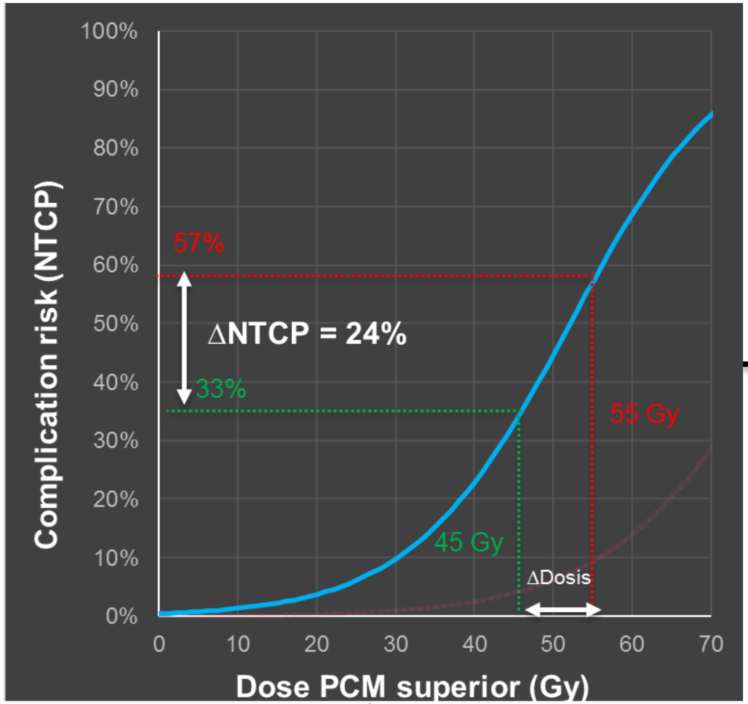
Protons



PROTON plan (IMPT)

ΔDose profile

NTCP-model



ΔNTCP

Selection

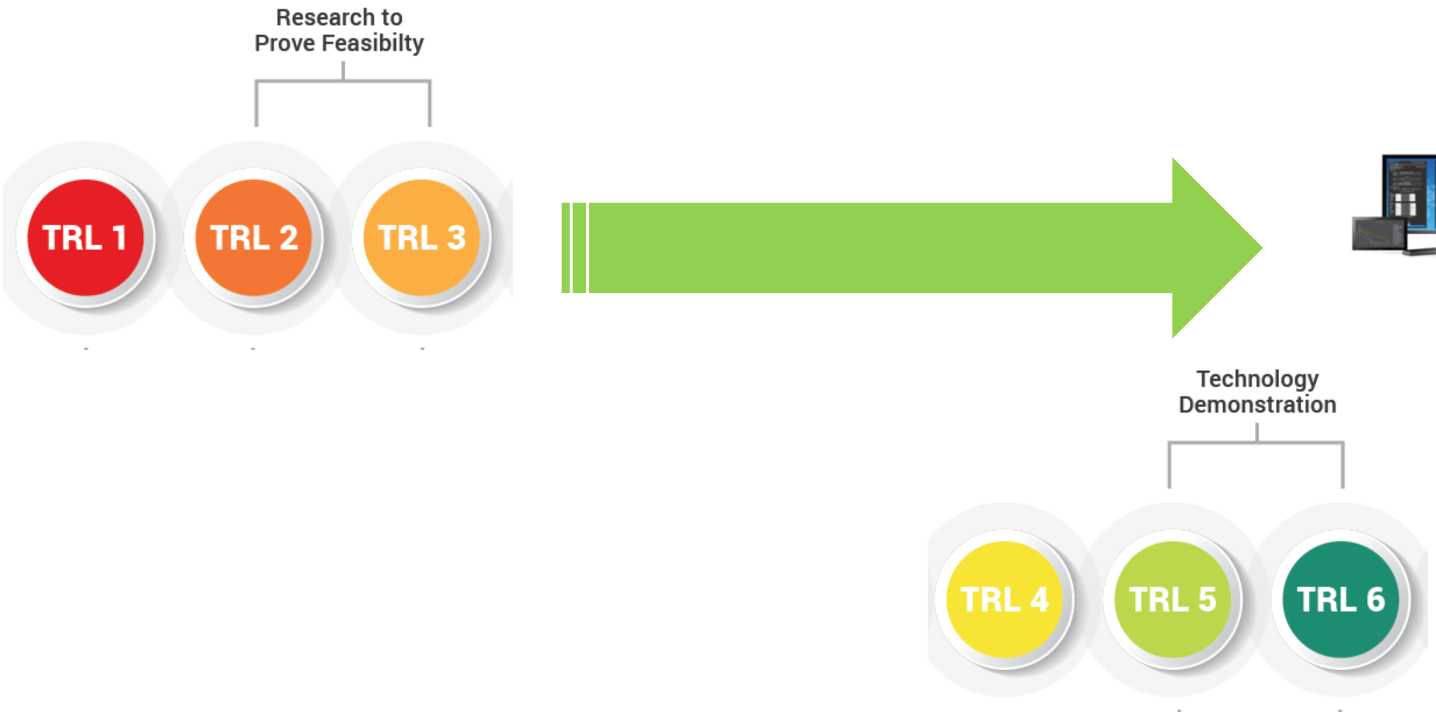
Criteria National Indication Protocol met?

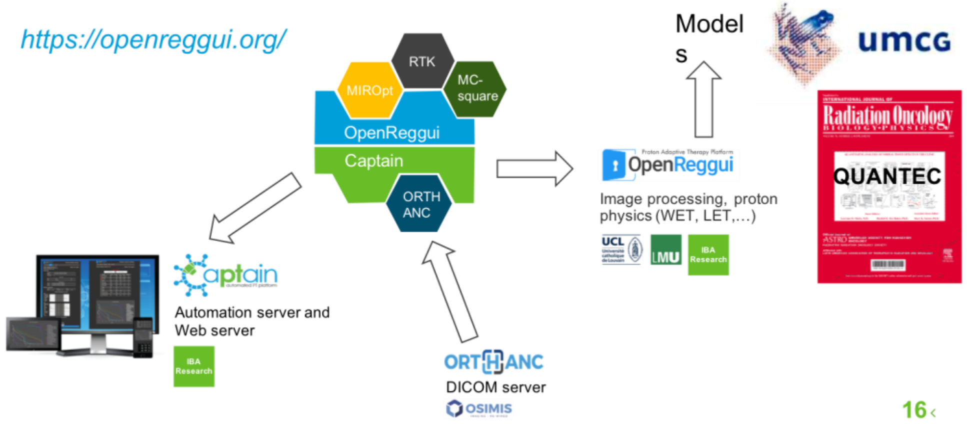
no → **Photons**

yes → **Protons**

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

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





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PTCOG June 2019

InspireProject

> 1350 delegates

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New horizon in therapy & treatment
FRPT
FLASH RADIOTHERAPY & PARTICLE THERAPY
2021
VIENNA & ONLINE
1-3 DECEMBER 2021
FRPT 2021
KENES GROUP
NHS The Christie NHS Foundation Trust
MANCHESTER 1824 The University of Manchester
Biophysics
CHUV
EMPIR
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Future

- 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

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Cancer Mission recommendations

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relevant Ris	BBMRI	EATRIS	ECRIN	ELIXIR	INFRAFRONTIER	EU-OPENSCREEN	Euro-BioImaging	EMBRC	Instruct	INSPIRE
Cancer Mission recommendations										
1 UNCAN.eu – Understand Cancer	~687 human biobanks & linked data - ELSI/GDPR compliant samples/data access - biomedical/big data expert networks	Access to 110 translational research institutions, of which many designated cancers centres, 26 institutions form the EATRIS Oncology Task Force - validated PDX models and advanced screening models (organoid, 3D cultures) with primary cells and translational experise to study the tumour microenvironment with selected markers and immune monitoring platform.	multinational cohorts (either retrospective through transnational cohort integration, or prospective cohort) supporting patient stratification based on –omics data generation and biomarker profiling. Identification of homogenous clusters of patients through biomarker profiling provides key information of the mechanisms of disease – not only on the tumor characteristics, but also on the tumor microenvironment or the host's response to tumor.	ELIXIR's data infrastructure can facilitate knowledge generation and sharing of data enabling better understanding of cancer.	- Dedicated Cancer Resources and Services page - Cancer Resource for choosing genotyped EMMA mice strains for cancer research - 13 curated & annotated cancer disease models for different cancers - mice studies (user projects) on different cancers	Development of highly selective chemical tool compounds to understand mechanism of action of novel cancer targets	- Advanced biological and biomedical imaging modalities to investigate disease mechanisms from a cellular to whole organ level such as DNA replication and repair, immune response, tumour cell metabolism, cell migration - Any aspect related to the biology of tumor cells, the characterization of the tumour microenvironment, the identification of new therapeutic targets, and validation of molecular mechanisms of action, involves heavy imaging (from super-resolution microscopy to advanced real-time and non-	- Model organisms for understanding cancer mechanisms. Models also relevant for cancer related topics such as immune responses, cell repair, and insights into diagnosis and treatment of cancer	contribution and access to cancer-related biomolecular structures and tools to help understand structure/function relationships. Infrastructure in use to support cancer projects (currently represent ~30% of all projects supported.	INSPIRE has provided access for cancer researchers across Europe to the research rooms in proton therapy centres and also to 2 research infrastructures which allow the effects of heavier ions to be investigated through TNA. Through its JRA INSPIRE has further developed its cababilities including a clinical prototype to measure FLASH doses and dose-rates, working with industrial partners (in INSPIRE) and metrology partners via EMPIR project UHDPulse. A model to select which patients might benefit most from proton therapy has been developed in INSPIRE. As has a European benchmark for describing LET and RBE, incorporating these parameters in to clinical treatment planning systems and correlating their effects with clinical patient outcomes. intercomparison experiments to measure these effects in a vitro in a 3D phantom are ongoing
2 polygenic risk scores	- Genomic data from biosamples & linked clinical, phenotype, pathology scans, other omics data; - generation of virtual cohorts; - data deposition (as a part of data return principle) to enrich existing data resources in the biobanks; - data QA;	Framework for assuring quality/reproducibility of WGAs studies, e.g., through ring testing programmes. Assessment of clinical relevant PGRS with access to patient cohorts (e.g. breast, prostate, colon cancer) and linked to immunophenotyping and		Support the data management of the research programme, ensuring research results are stored safely, securely and sustainably in databases, and available for re-use by others where appropriate. Harmonisation of software and			- Population-based imaging to be developed based on non-invasive medical imaging technologies to enable screening as part of the assessment of the polygenic risk scores predictive value - Development of methods to assess long-			Through its TNA INSPIRE is collaborating with the UK RAPPER study and the international genomics consortium to study the normal tissue genetic determinents for patient response and radioosensitivity to proton therapy. Initial studies will be for patients with Chordoma and Chrondrosarcoma and correlating results with clinical outcomes, initially at PSI and Christie. Studies are also being undertaken to study the effects of high LET regions on normal tissue and OAR in treatment plans and how such plans can be optimised to improve short and long term

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Thank you for listening

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