Design Study for an Ion Therapy Research Facility

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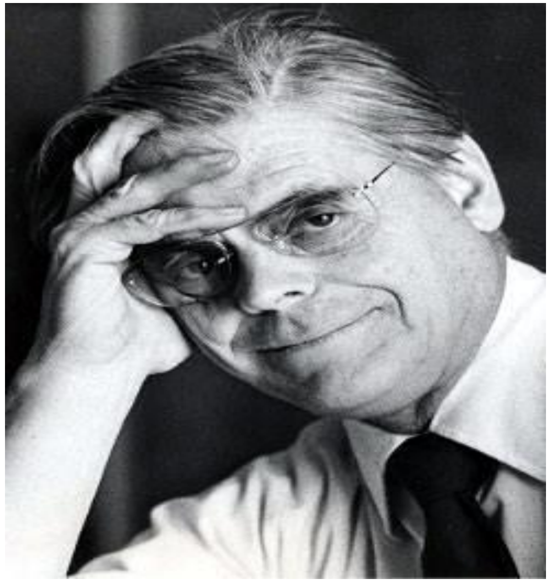
STFC Daresbury Laboratory
Accelerator Science and Technology Centre

6th June 2023
ARR Glasgow

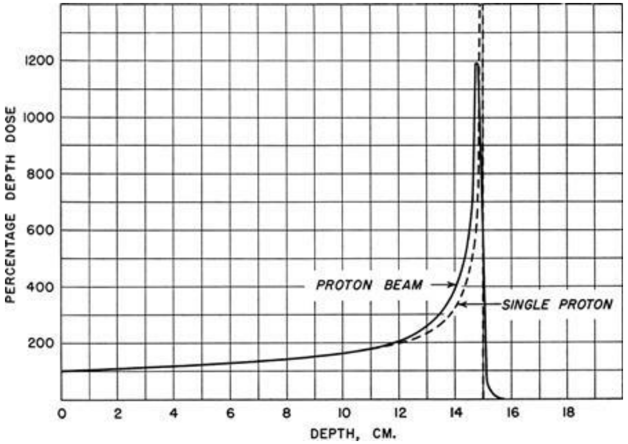
(The work of many people is shown in these slides – I've tried to acknowledge it all!)

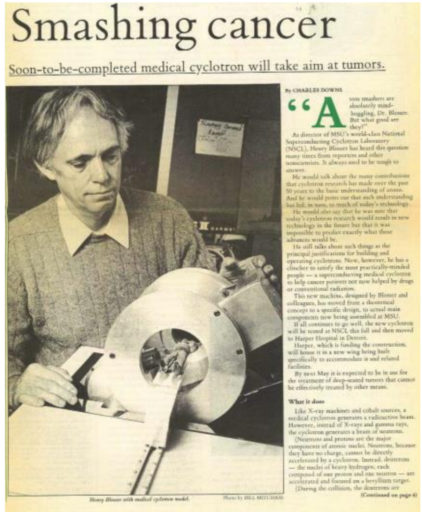
From physics to clinic



Robert R Wilson "*Radiological Use of Fast Protons*". Radiology **47** (5): 487–491. November 1946. doi:10.1148/47.5.487

$$-\frac{dE}{dx} = \frac{4\pi}{m_e c^2} \cdot \frac{nz^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0}\right)^2 \cdot \left[\ln\left(\frac{2m_e c^2 \beta^2}{I \cdot (1-\beta^2)}\right) - \beta^2\right]$$





Smashing cancer

Soon-to-be-completed medical cyclotron will take aim at tumors.

By CHARLES DOWNS

"Atom smashers are absolutely mind-boggling, Dr. Blosser. But what good are they?"

As director of MSU's world-class National Superconducting Cyclotron Laboratory (NSCL), Henry Blosser has heard that question many times from reporters and other nonscientists. It always used to be tough to answer.

He would talk about the many contributions that cyclotron research has made over the past 50 years to the basic understanding of atoms. And he would point out that such understanding has led, in turn, to much of today's technology.

He would also say that he was sure that today's cyclotron research would result in new technology in the future but that it was impossible to predict exactly what those advances would be.

He still talks about such things as the principal justifications for building and operating cyclotrons. Now, however, he has a clincher to satisfy the most practically-minded people — a superconducting medical cyclotron to help cancer patients not now helped by drugs or conventional radiation.

This new machine, designed by Blosser and colleagues, has moved from a theoretical concept to a specific design, to actual main components now being assembled at MSU.

If all continues to go well, the new cyclotron will be tested at NSCL this fall and then moved to Harper Hospital in Detroit.

Harper, which is funding the construction, will house it in a new wing being built specifically to accommodate it and related facilities.

By next May it is expected to be in use for the treatment of deep-seated tumors that cannot be effectively treated by other means.

What it does

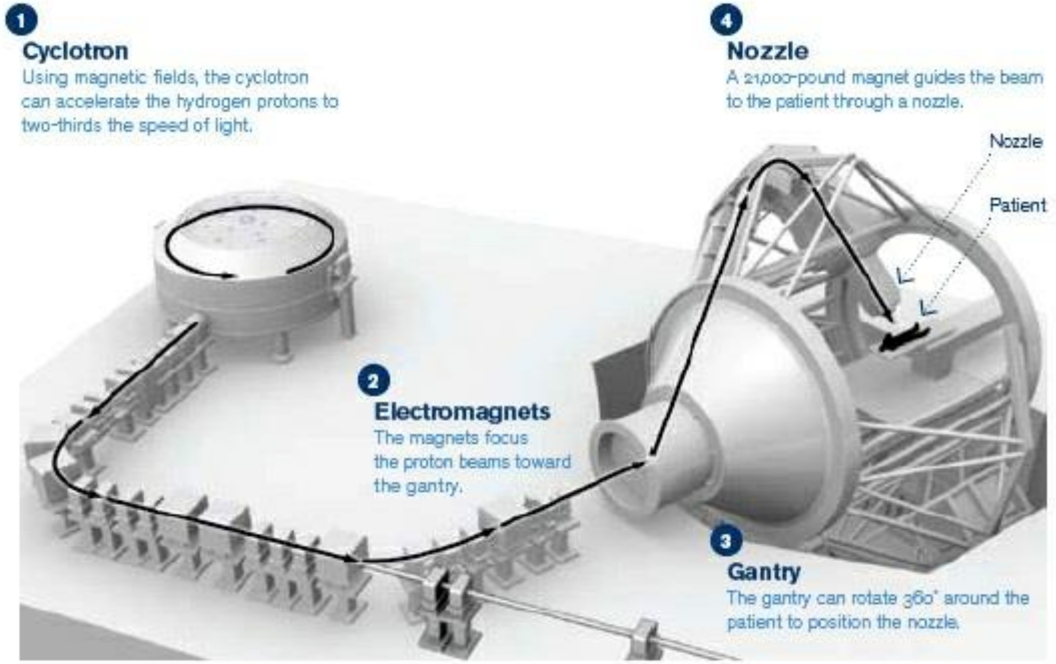
Like X-ray machines and cobalt sources, a medical cyclotron generates a radioactive beam. However, instead of X-rays and gamma rays, the cyclotron generates a beam of neutrons.

(Neutrons and protons are the major components of atomic nuclei. Neutrons, because they have no charge, cannot be directly accelerated by a cyclotron. Instead, deuterons — the nuclei of heavy hydrogen, each composed of one proton and one neutron — are accelerated and focused on a beryllium target.

(During the collision, the deuterons are

(Continued on page 6)

Henry Blosser with medical cyclotron model. Photo by BILL MITCHAM



1 Cyclotron
Using magnetic fields, the cyclotron can accelerate the hydrogen protons to two-thirds the speed of light.

2 Electromagnets
The magnets focus the proton beams toward the gantry.

3 Gantry
The gantry can rotate 360° around the patient to position the nozzle.

4 Nozzle
A 21,000-pound magnet guides the beam to the patient through a nozzle.

Siemens/Varian

Mevion

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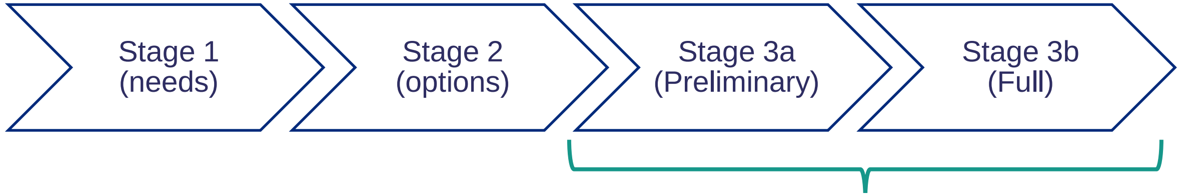
Technology > Experiment > Infrastructure > Clinic

UKRI, STFC, ASTeC and Infrastructures

- STFC Strategic Framework:
  - ‘giving priority to infrastructures that support the science mission needs’
  - ‘ensure that critical technologies are developed for future infrastructures’
  - ‘provision and operation of research facilities in… …any area of UKRI’s activity’

- UKRI Infrastructure Fund:
  - ‘aimed at supporting significant investments that enable a step change in research and innovation infrastructure’
  - New build, upgrades, or decommissioning

  - Full Project or Preliminary Activity

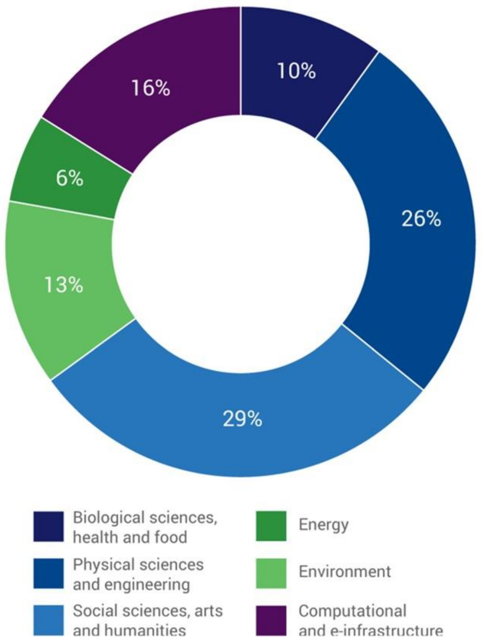

Stage 1
(needs)

Stage 2
(options)

Stage 3a
(Preliminary)

Stage 3b
(Full)

Infrastructure Fund eligibility



Over **500** nationally and internationally significant infrastructures

A breadth of expertise: **92%** work across more than one topic domain

Three quarters work with UK business and **42%** with public policy organisations

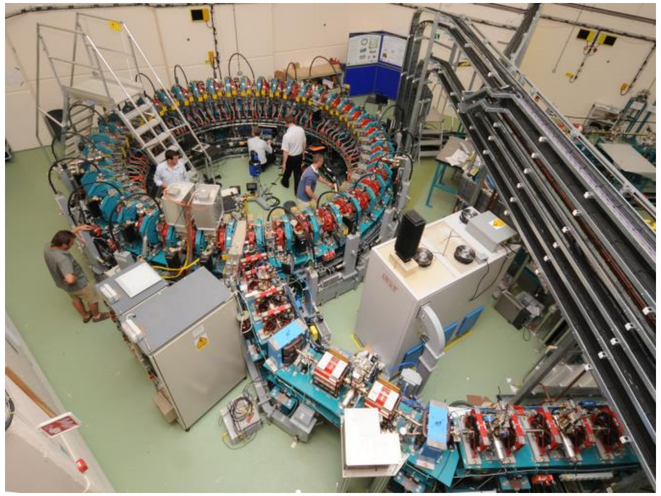
Infrastructures employ just under **25,000** staff

- UKRI Infrastructure Projects:
- 32 Full Projects
- 9 Preliminary Activities – ASTeC pivotal in 1/3 of PAs
- Total investment 481M 2022-2025
- Includes projects such as DIAMOND-II, SKAO, Hyper-K

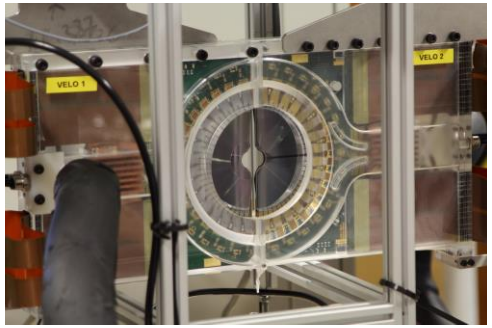
- Accelerator Science and Technology Centre (100 staff)
- Science and Technology Facilities Council (1900 staff)

- ‘Coordinates research and development of national infrastructures’

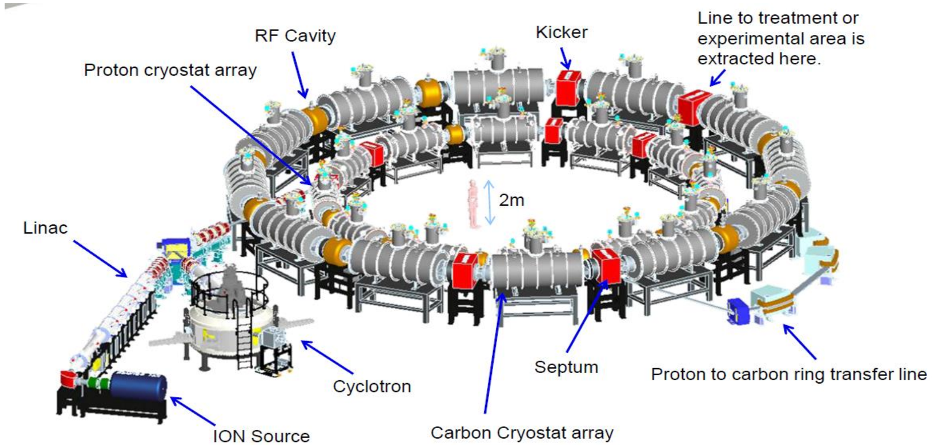
Developing New Capabilities



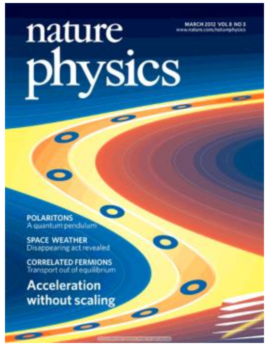
EMMA demonstrator (2012)

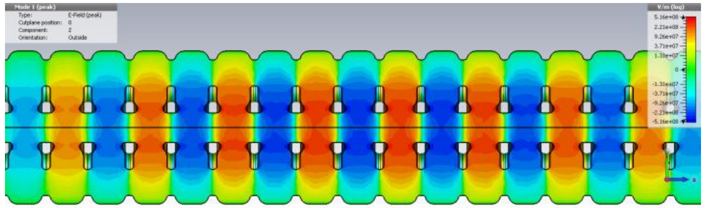


Diagnostic instrumentation (ULiv/CCC)



PAMELA design study (2013)





PROBE high-gradient proton linac (ULan/UMan)

www.oma-project.eu

Christie research beamline (2019)

Partnership between National Lab, academic groups, and clinical

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Protons in the UK

- 1989: Clatterbridge UK world's 1st hospital proton therapy centre (62 MeV, ocular); 100 patients/year
- 2007: NRAG report 'Radiotherapy: developing a world class service for England' recommends proton facilities
- 2007: Cancer Reform Strategy
- 2008: Proton Overseas Programme; 1102 patients (2008 – 2018)
  https://doi.org/10.1016/j.ijrobp.2020.07.2456
  https://doi.org/10.1016/j.clon.2018.02.032
- 2012 NHS Strategic Outline Case
- 2015: Full Business Case approved for 2 NHS centres
- 2018: NHS Christie 1st patients – seen as a big success story
- 2021: NHS UCLH 1st patients

Clatterbridge – 62 MeV Scanditronix cyclotron
Basis for much UK technology and clinical-related research

Christie – 250 MeV Varian cyclotron
+ unique research beamline

Protons in UK:
- Evidence-based
- Intention to cure
- Emphasis on children, young adults (<25), adults with rare tumours

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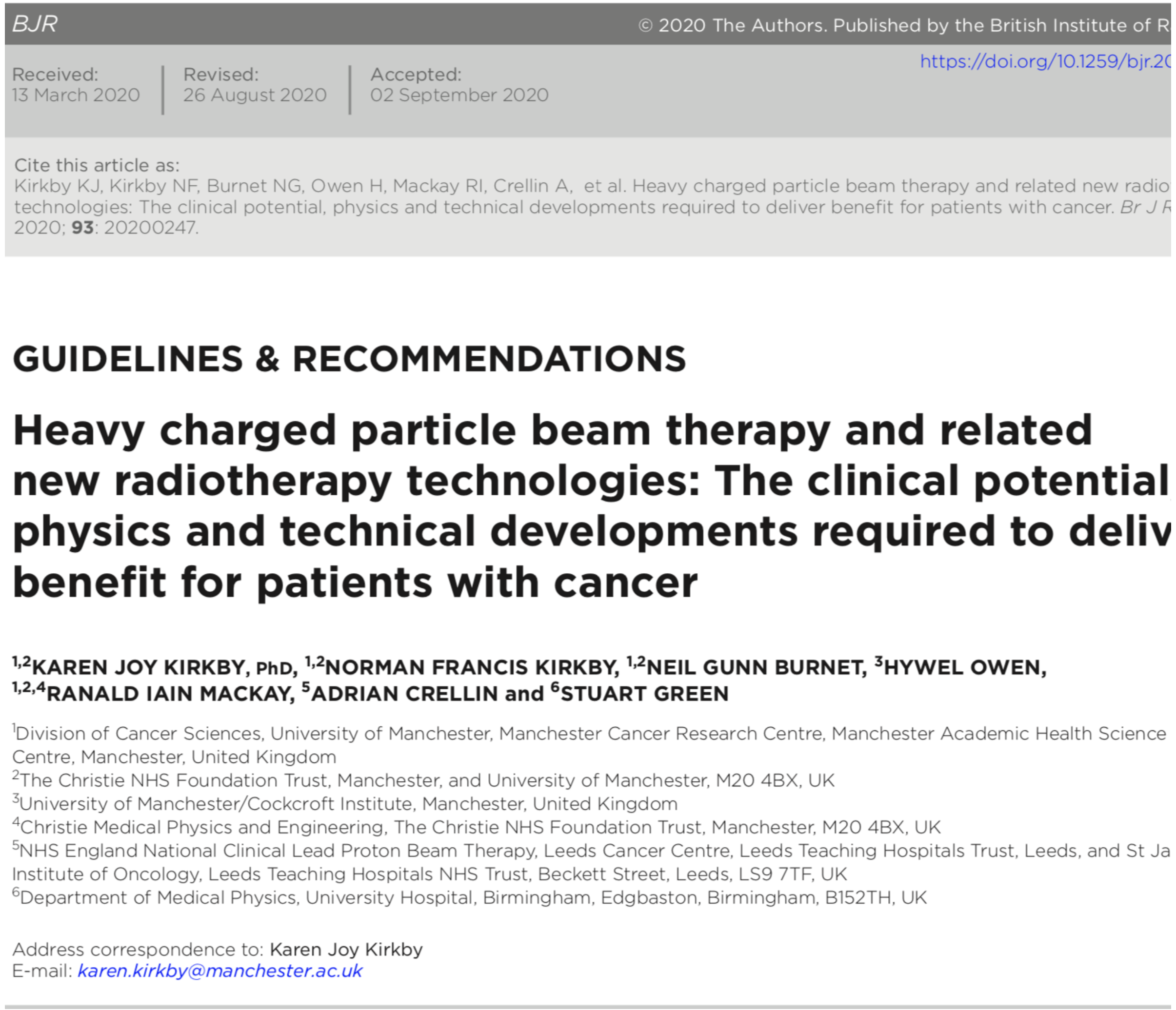
The Path to Ions

- Various prior projects, including EU networks on particle therapy and STFC/EPSRC networks on proton therapy
- Outline proposals c. 2015-2017
- Key meeting 2019 > BJR paper 2020

- Need to learn from the past
- Overseas referral programme gave UK PBT experience
- Finding a window and a USP – take opportunity
- Need for basic science to underpin future of ion therapy



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GUIDELINES & RECOMMENDATIONS

Heavy charged particle beam therapy and related new radiotherapy technologies: The clinical potential physics and technical developments required to deliv benefit for patients with cancer

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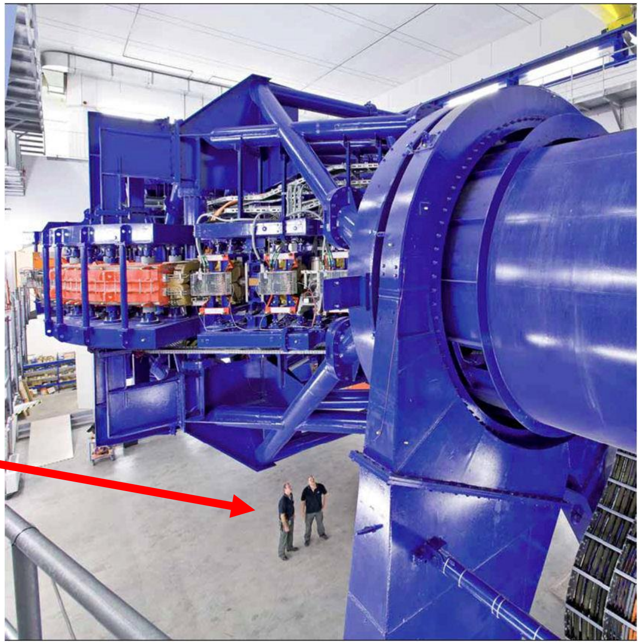
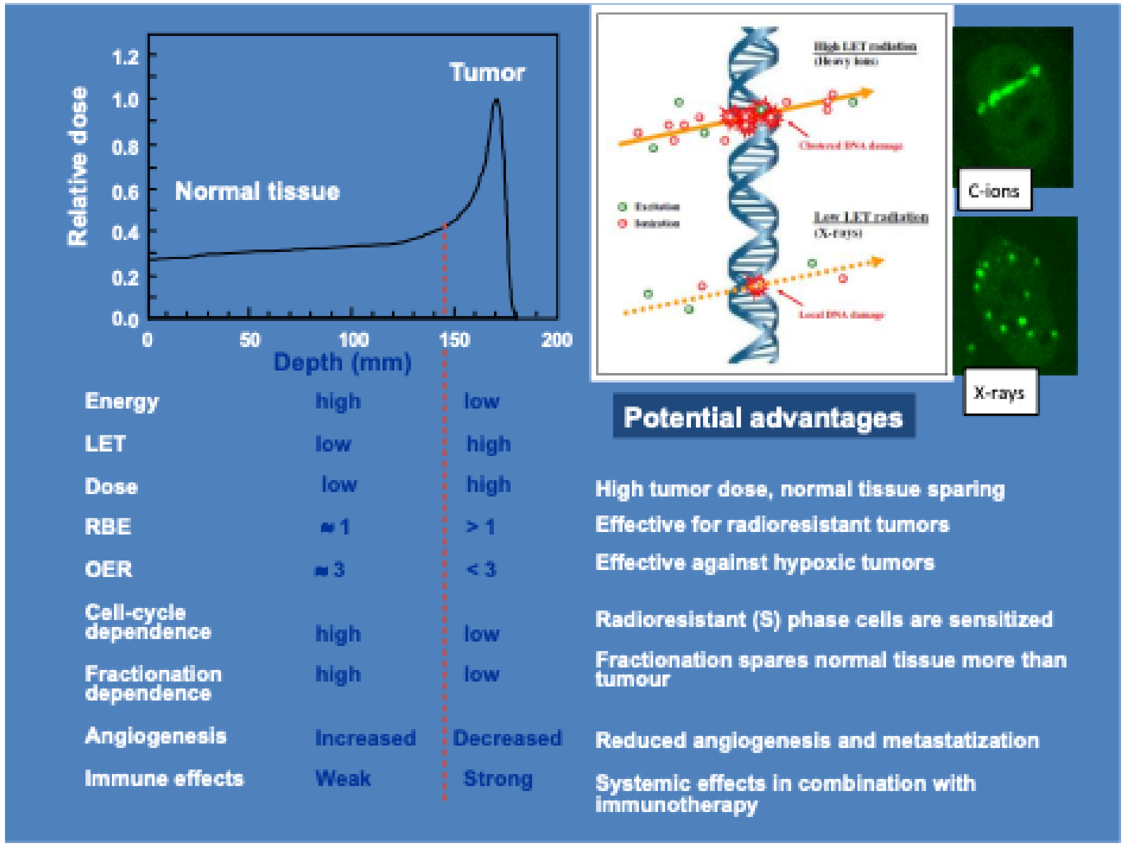
- https://doi.org/10.1259/bjr.20200247

Use of (Heavy) Ions

- Tinganelli and Durante *Cancers* 2020, *12*(10), 3022; https://doi.org/10.3390/cancers12103022
- Is there a clinical need?
- ‘Cancers of unmet need’

- BUT…
- Need to reduce size and increase capability





			Potential advantages
Energy	high	low	
LET	low	high	
Dose	low	high	High tumor dose, normal tissue sparing
RBE	≈ 1	> 1	Effective for radioresistant tumors
OER	≈ 3	< 3	Effective against hypoxic tumors
Cell-cycle dependence	high	low	Radioresistant (S) phase cells are sensitized
Fractionation dependence	high	low	Fractionation spares normal tissue more than tumour
Angiogenesis	Increased	Decreased	Reduced angiogenesis and metastatization
Immune effects	Weak	Strong	Systemic effects in combination with immunotherapy

- Japan: 6 centres
- China: Shanghai
- Germany: HIT; MIT (GSI He trials)
- Austria: MedAustron
- Italy: CNAO
- USA: NAPTA (led UCSF), NPTRC (led UTSW) design studies: Mayo Clinic & Hitachi to build a C centre
- Other centres proposed world-wide. A number being proposed in Europe (NIMMS, SEEIST)

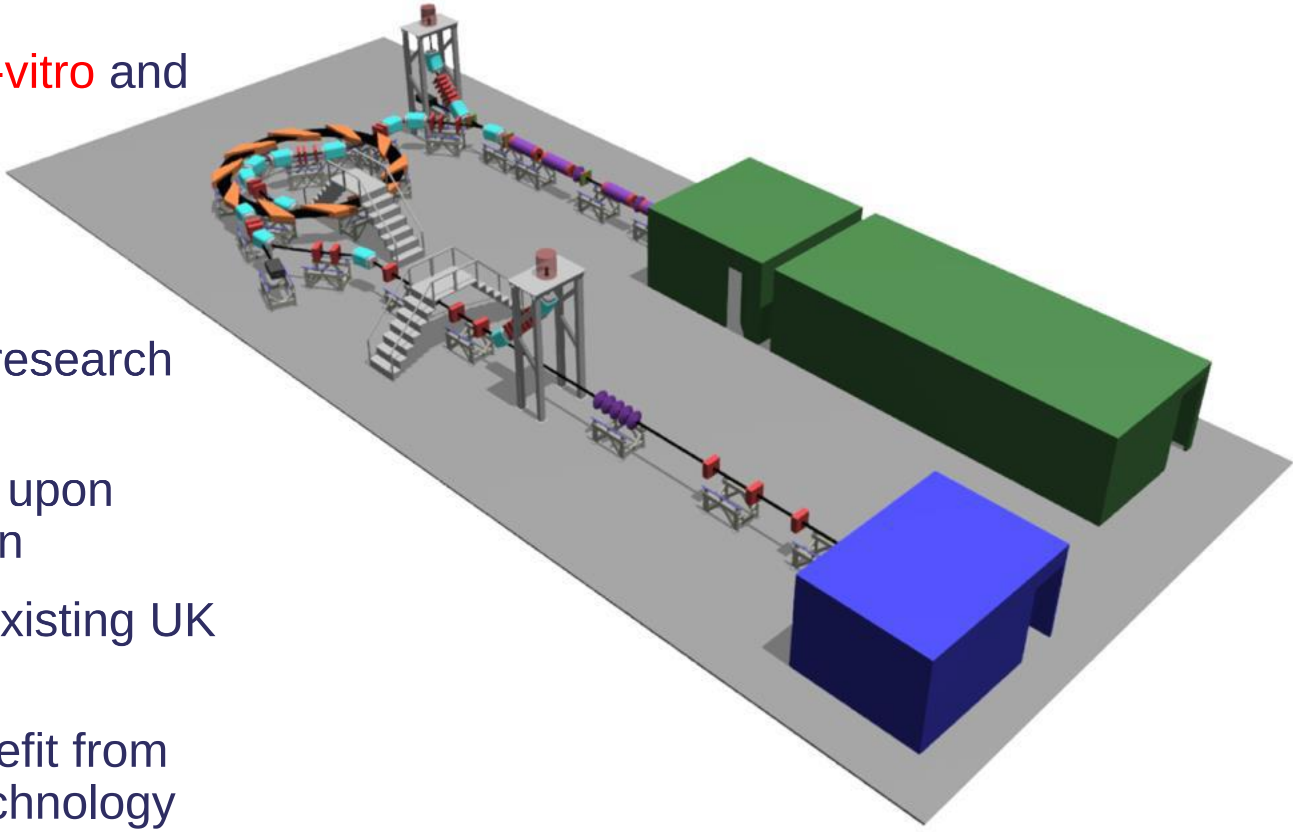
Ion Therapy Research Facility – an ambition for new capabilities

HOW

- A compact, single-site national research infrastructure delivering very high dose rates and other unique (spatial and temporal features)
- Protons and beyond, at energies sufficient for both in-vitro and in-vivo studies

WORK PLAN

- Conceptual design of layout, cost and operation of a research facility
- Develop innovative laser-plasma technology, building upon world-leading expertise within the LhARA collaboration
- Develop innovative end-station designs, building on existing UK expertise in proton radiobiology research
- Collaborative agreement with CERN allows us to benefit from enormous experience and expertise in accelerator technology and successful projects

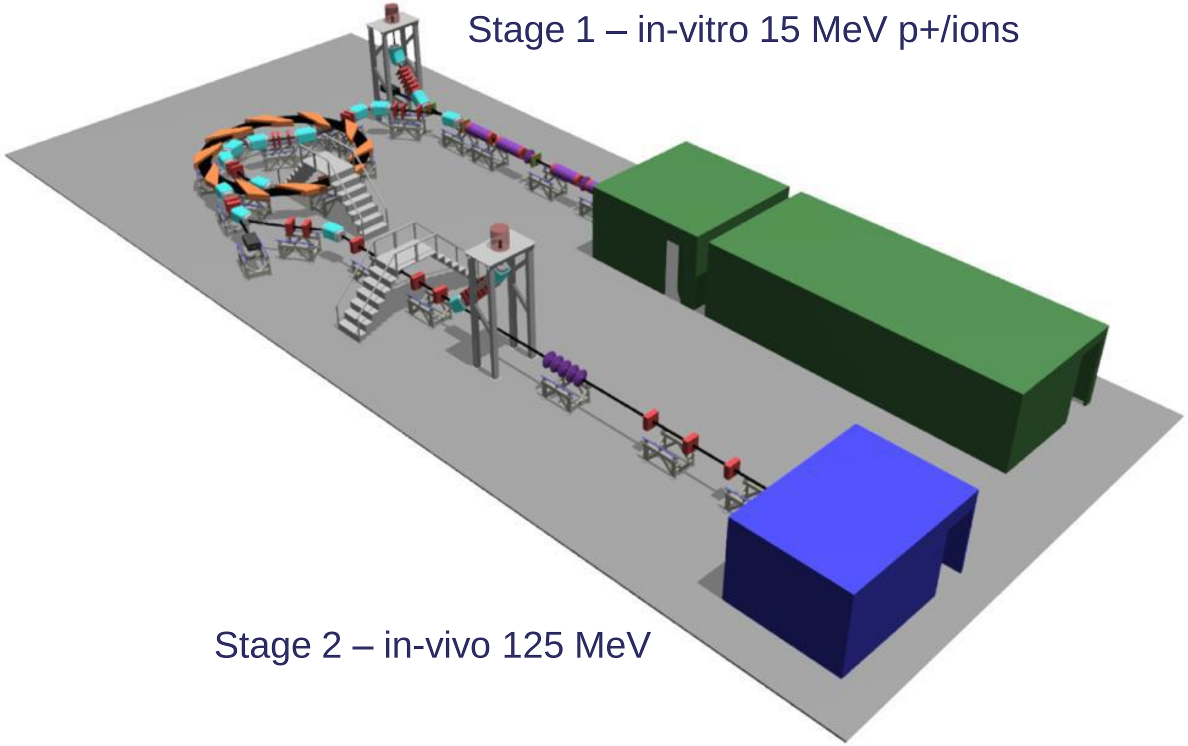


What is the Ion Therapy Research Facility?

- A medium-scale, single-site research facility c £50M envelope
- Multi-ion delivery p/He/C/N,O…
- Depth suitable for in-vitro and in-vivo studies
- High dose rate, suitable for FLASH >40 Gy/s

- Two technology choices:
  - Very high dose rate plasma/FFAG. Several novel technologies require demonstrations
  - Conventional technology – likely synchrotron

- The facility must provide user research programme for future ion treatments in the UK
- The facility may act as a testbed for the required technologies for future UK Clinical Research and Treatment Facility (CTRF)
- In parallel, there are other technology developments (NIMMS etc.)



Stage 1 – in-vitro 15 MeV p+/ions

Stage 2 – in-vivo 125 MeV

LhARA baseline design:
https://www.frontiersin.org/articles/10.3389/fphy.2020.567738/full

LhARA performance summary

arXiv:2006.00493

	12 MeV Protons	15 MeV Protons	127 MeV Protons	33.4 MeV/u Carbon
Dose per pulse	7.1 Gy	12.8 Gy	15.6 Gy	73.0 Gy
Instantaneous dose rate	1.0×10^9 Gy/s	1.8×10^9 Gy/s	3.8×10^8 Gy/s	9.7×10^8 Gy/s
Average dose rate	71 Gy/s	128 Gy/s	156 Gy/s	730 Gy/s

ITRF Research Need:
- Ion biology not yet well understood
- Likely benefits from heavier ions
- Clinical choice will require understanding of effects in tumour and normal tissue
- Ultimately might require individual patient research

Partner/Collaborating Organisations

- STFC (BID, ASTeC*, TD*, ISIS, CLF, PPD*)
- John Adams Institute/Cockcroft Institute
- University of Birmingham*
- Imperial College (Physics*, Computing, Aeronautics, Surgery and Cancer)
- Imperial College Healthcare Trust*
- Lancaster University*
- University of Liverpool (Physics*, Sys Mol Biol)
- University of Manchester (Physics*, Cancer Sciences*)
- University of Oxford (Physics, Materials, Oncology)
- QU Belfast*
- RHUL*
- University of Surrey
- Swansea University
- UCL *
- University of Strathclyde*
- Christie Hospital
- Clatterbridge Cancer Centre

- Institute of Cancer Research*
- Rosalind Franklin Institute
- National Physical Laboratory

- CERN
- INFN Catania
- Leo Cancer Care
- Maxeler Technologies Limited
- Corerain Technologies (China)
- Institut Curie
- Netherlands Cancer Institute
- Hampton University
- Stanford University
- Cyril & Methodius University (N Macedonia)

Neil Burnet (Adv committee chair)

Massimo Noro (Project Sponsor)

Key People:
Karen Kirkby (UMAN)
Jason Parsons (BIRM)
Amato Giaccia (Oxford)
Ken Long (Imperial)
Neil Bliss (STFC)
Colin Whyte (Ustrath)

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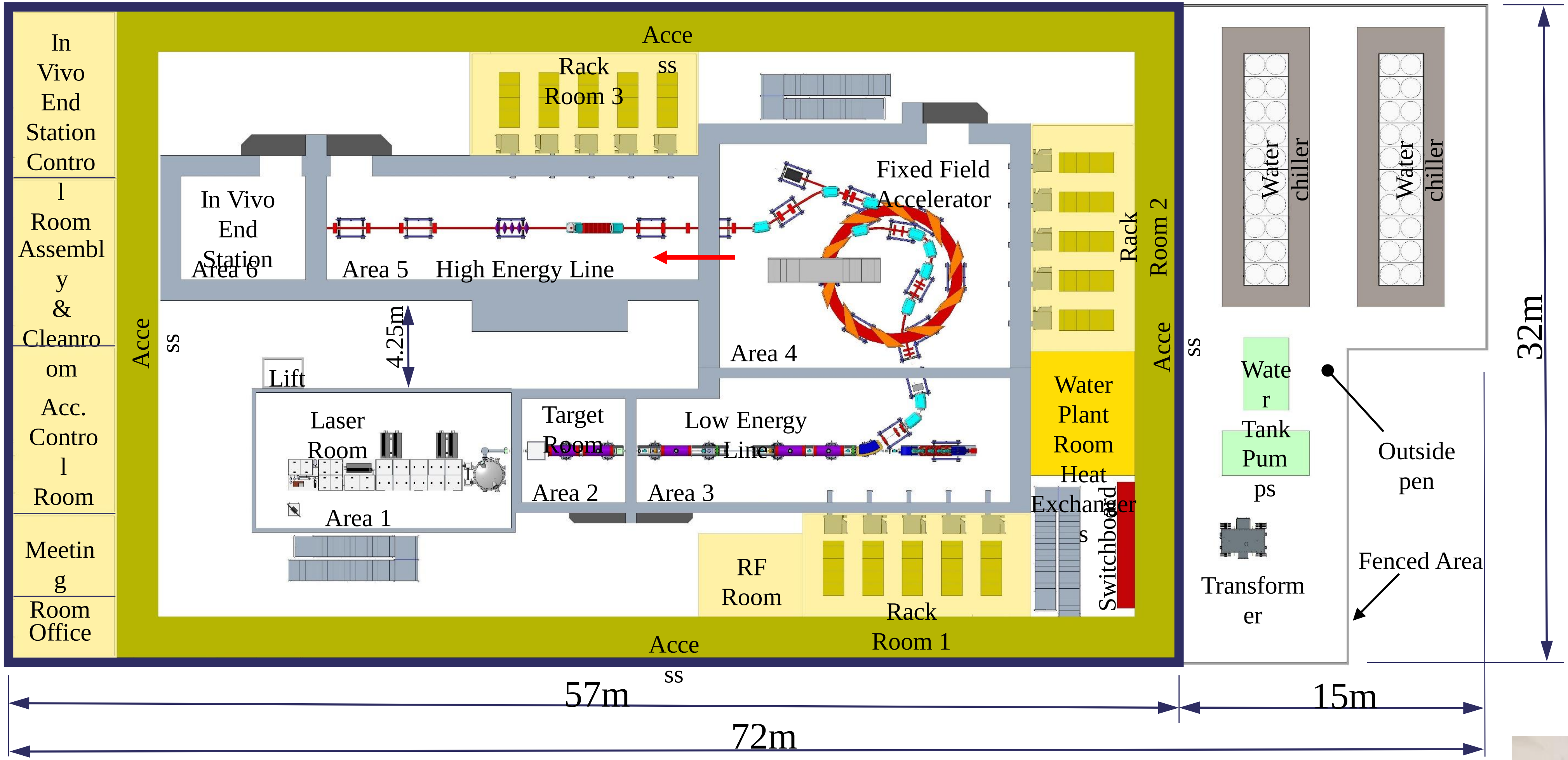
Some possible research directions

- Characterising biophysical effects of high dose rate ions cf conventional using different models.
- Assessing the impact of oxygenation on DNA damage and immune responses to different temporal and spatial patterns
- Identify the impact of genetic mutations where ion beams would be effective
- Study the impact of ultra-high dose rate and spatial forms of delivered ions using in-vivo mouse models, examining clinically relevant fractionation schedules

- Technical advantages of pulsed beams:

- Beam is flexible, accessible and with high throughput (unlike clinical facilities)
- Ions delivered in very short pulses and high repetition rates – a challenge and an opportunity
- Ability to deliver p/C etc at different energies and LET
- Potential for live cell imaging

ITRF (LhARA) Pre-Conceptual Layout



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What are we offering?

Unique beams:

- Triggerable, max rate 10 Hz
- Arbitrary structures
    - E.g. pump probe
- Minimum bunch lengths:
    - 10 ns at Low-energy *in-vitro* end station
    - 40 ns at High-energy *in-vitro* and *In-vivo* end stations
- Dose distribution:
    - Low-energy *in-vitro* end station:
        - Quasi uniform over 3.5 x 3.5 cm^2
        - Spot to be studied
    - High-energy *in-vitro* and *In-vivo* end stations:
        - Spot ~1 mm
        - Uniform distribution over circle with diameter 1—3 cm
    - Production of "more conventional" parameters to be studied

End stations must maximise scientific return:

- Extended uninterrupted operation:
    - *In vitro:* 16—24 hours
    - *In vivo:* maximum consistent with animal welfare
- Advanced, time resolved (<0.1s) instrumentation

Vision:

Transform clinical practice of proton/ion-beam therapy by creating a fully automated, highly flexible system to harness the unique properties of laser-driven ion beams

- Present-day ion technology delivers moderate dose rates
- Recent progress in plasma acceleration techniques offer path from FLASH (c. 100 Gy/s) to 'ultra FLASH' (>10^6 Gy/s)
- Plasma/FFA acceleration also offers pathway to more compact facilities in the future – need to examine this
- UK is world-leading in plasma acceleration and FFAs.
- Like AI, plasma accelerators are 'on the cusp'

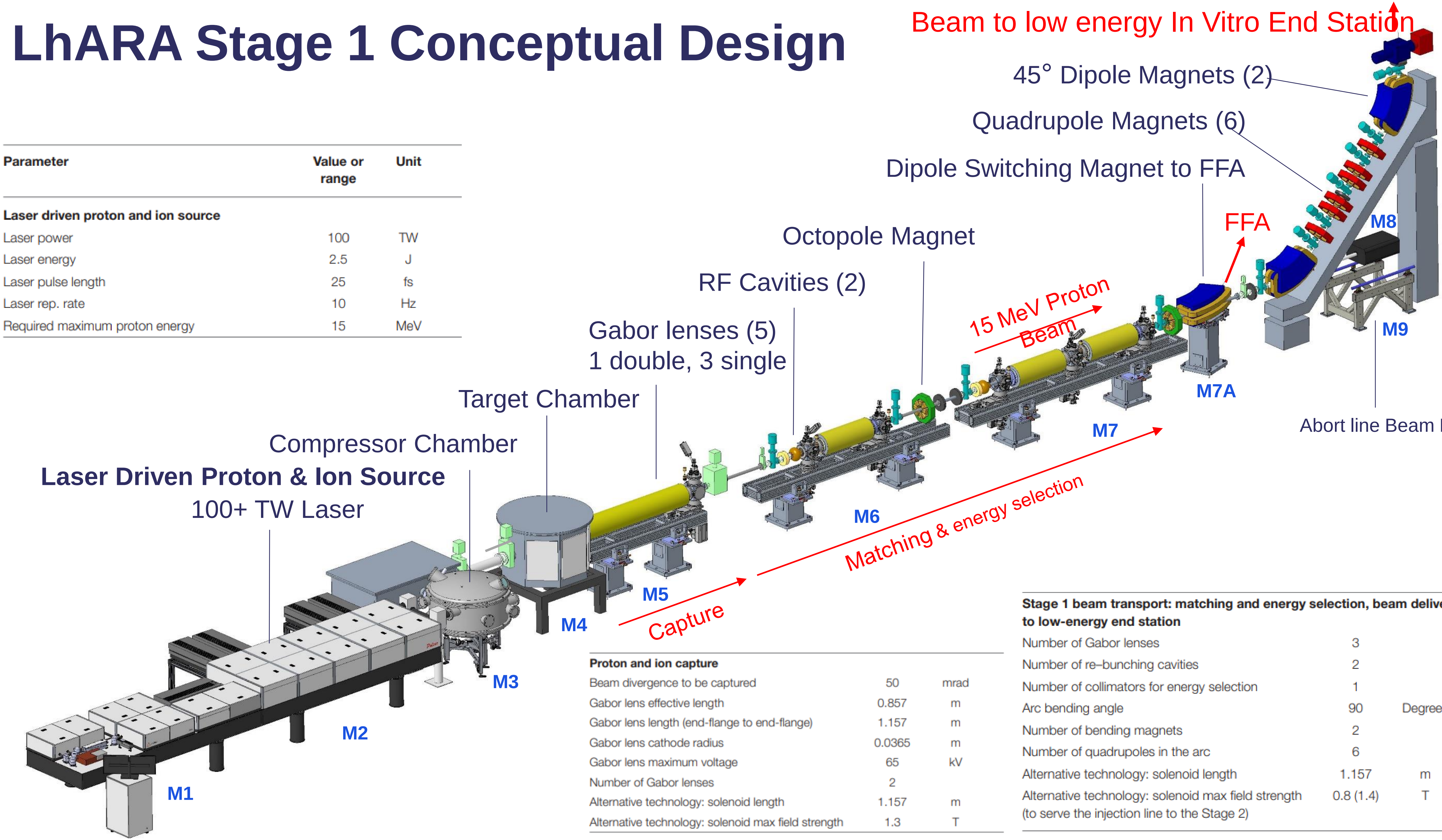
- BUT: can we make a match with our user community?

What do we need?

- Input and collaboration!
- 6 months into our 2-year preliminary activity
  - Seeking to engage more with possible users
  - Define experimental needs, including dosimetry and
  - Match ‘user pull’ with ‘technology push’
  - Understand the sample handling and regulatory issues ready for the next stage
- CDR > TDR > construction; 7 years
- Help to define our experimental programme at the 2nd peer-group consultation: https://indico.stfc.ac.uk/event/780/ (University of Birmingham)

LhARA Stage 1 Conceptual Design

Parameter	Value or range	Unit
Laser driven proton and ion source		
Laser power	100	TW
Laser energy	2.5	J
Laser pulse length	25	fs
Laser rep. rate	10	Hz
Required maximum proton energy	15	MeV



Beam to low energy In Vitro End Station

45° Dipole Magnets (2)

Quadrupole Magnets (6)

Dipole Switching Magnet to FFA

FFA

Octopole Magnet

RF Cavities (2)

15 MeV Proton Beam

Gabor lenses (5)
1 double, 3 single

Target Chamber

Compressor Chamber

Laser Driven Proton & Ion Source

100+ TW Laser

Abort line Beam Dump

Matching & energy selection

Capture

Proton and ion capture		
Beam divergence to be captured	50	mrad
Gabor lens effective length	0.857	m
Gabor lens length (end-flange to end-flange)	1.157	m
Gabor lens cathode radius	0.0365	m
Gabor lens maximum voltage	65	kV
Number of Gabor lenses	2	
Alternative technology: solenoid length	1.157	m
Alternative technology: solenoid max field strength	1.3	T

Stage 1 beam transport: matching and energy selection, beam delivery to low-energy end station		
Number of Gabor lenses	3	
Number of re–bunching cavities	2	
Number of collimators for energy selection	1	
Arc bending angle	90	Degrees
Number of bending magnets	2	
Number of quadrupoles in the arc	6	
Alternative technology: solenoid length	1.157	m
Alternative technology: solenoid max field strength (to serve the injection line to the Stage 2)	0.8 (1.4)	T

LhARA Stage 1

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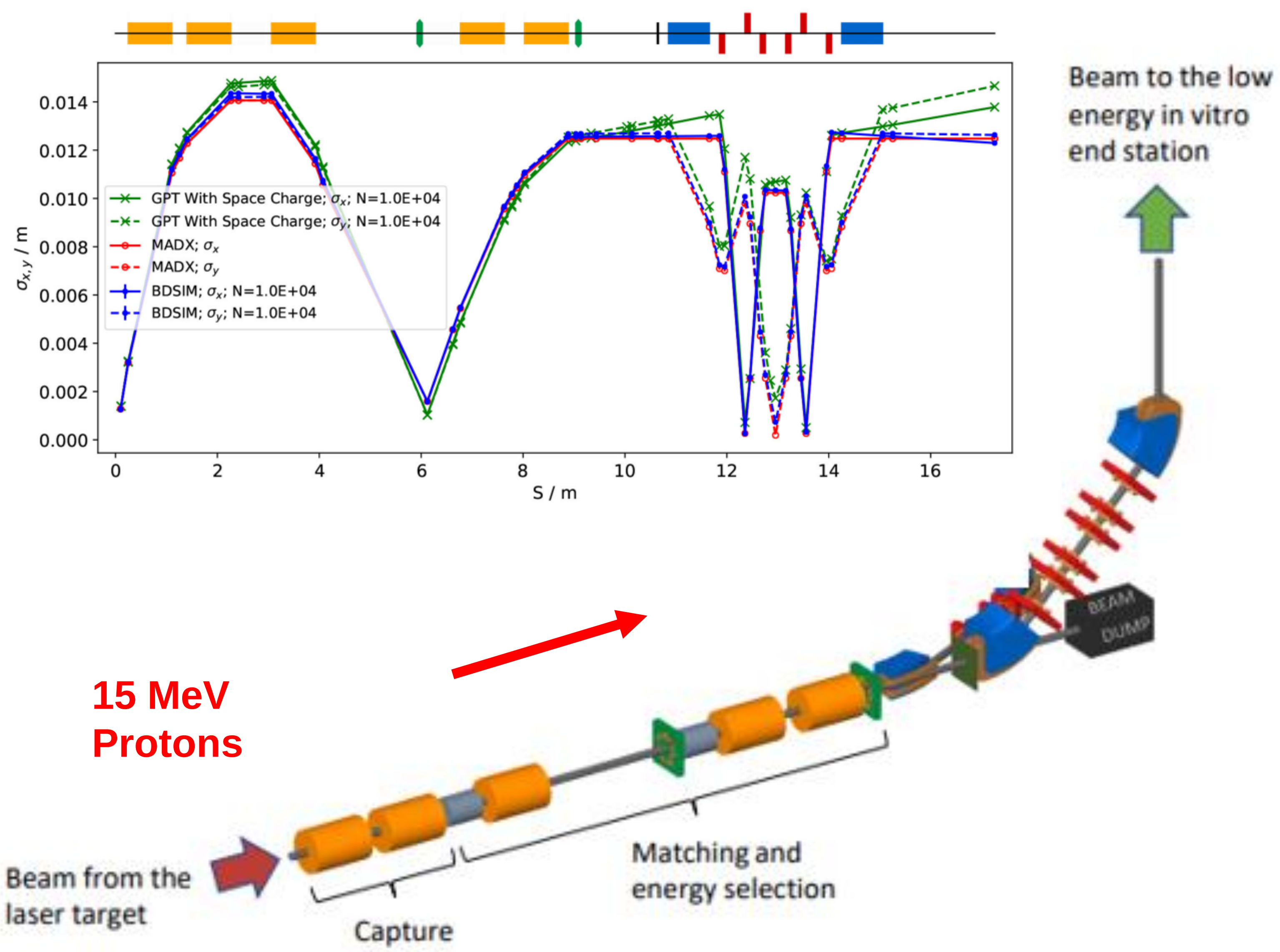

15 MeV Protons

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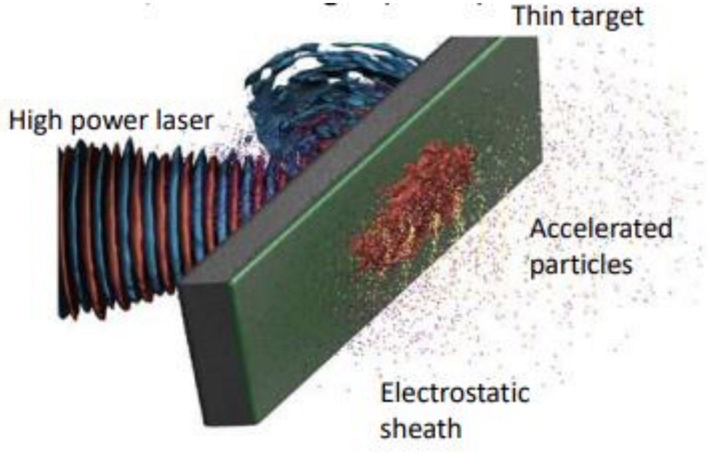
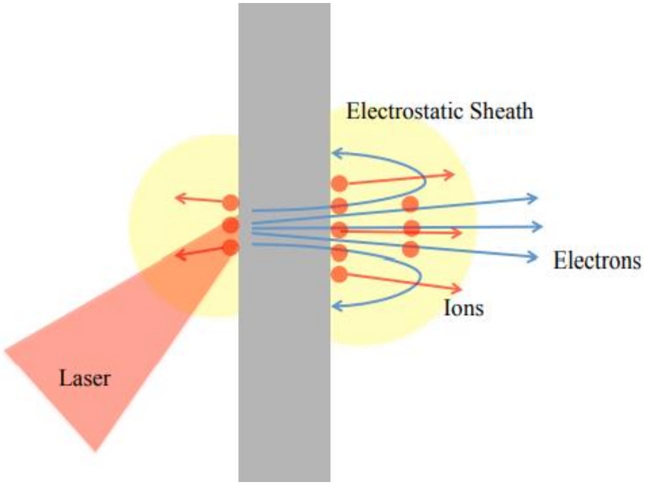
https://www.frontiersin.org/articles/10.3389/fphy.2020.567738/full

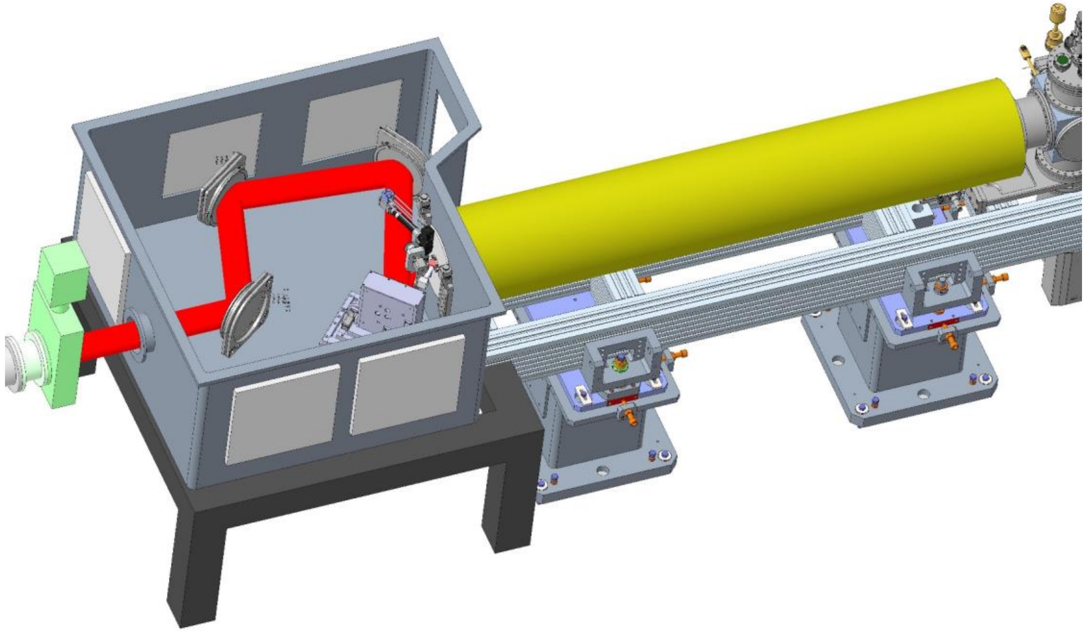
Laser Driven Proton & Ion Sources

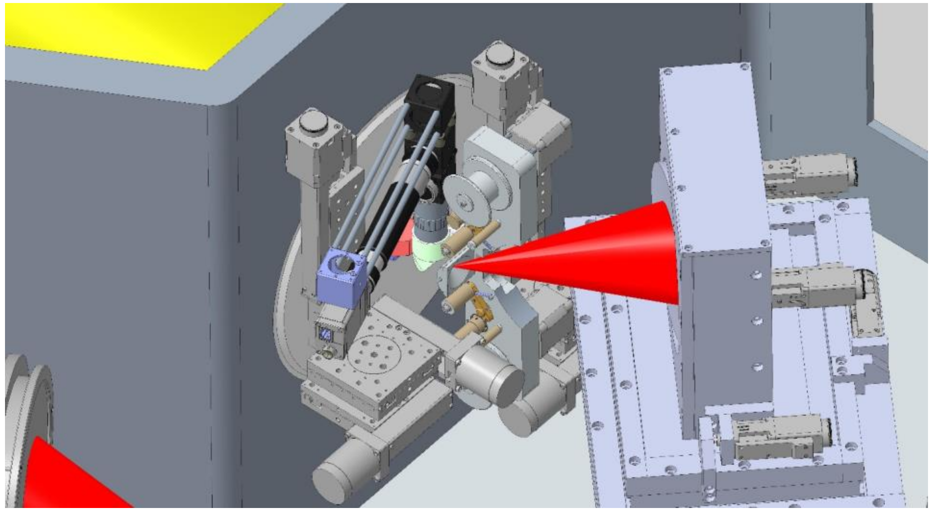
- TNSA (Target Normal Sheath Acceleration) is basis for particle production
- Target and capture both elements of study in ITRF programme
- UK has world-leading research groups in this area
    - Including holding the world record for laser-produced proton energy
- Significant installed infrastructure across several UK labs able to be used to progress the understanding and design of the ion source.



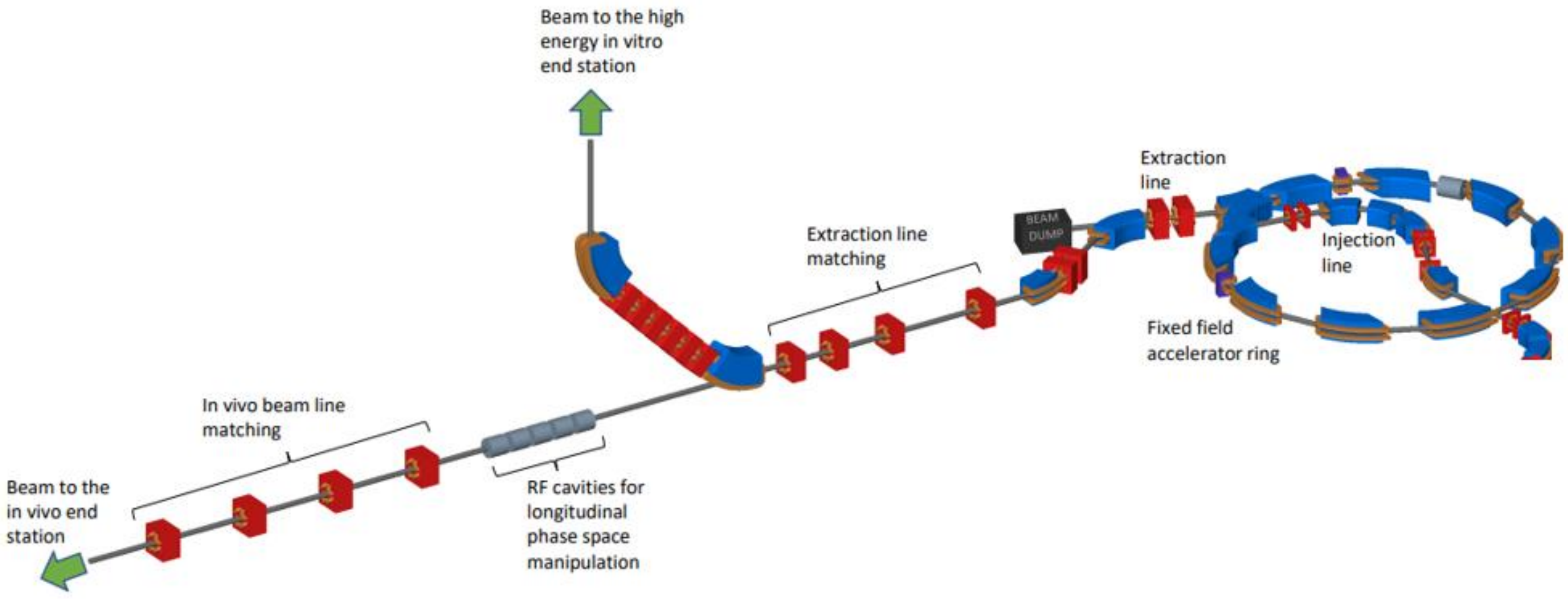


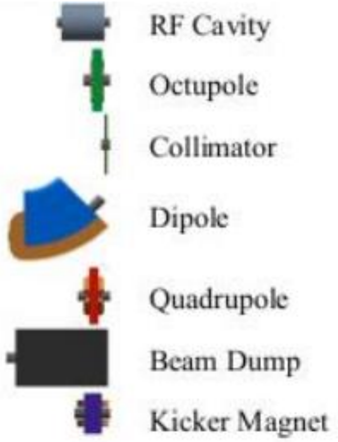
Target

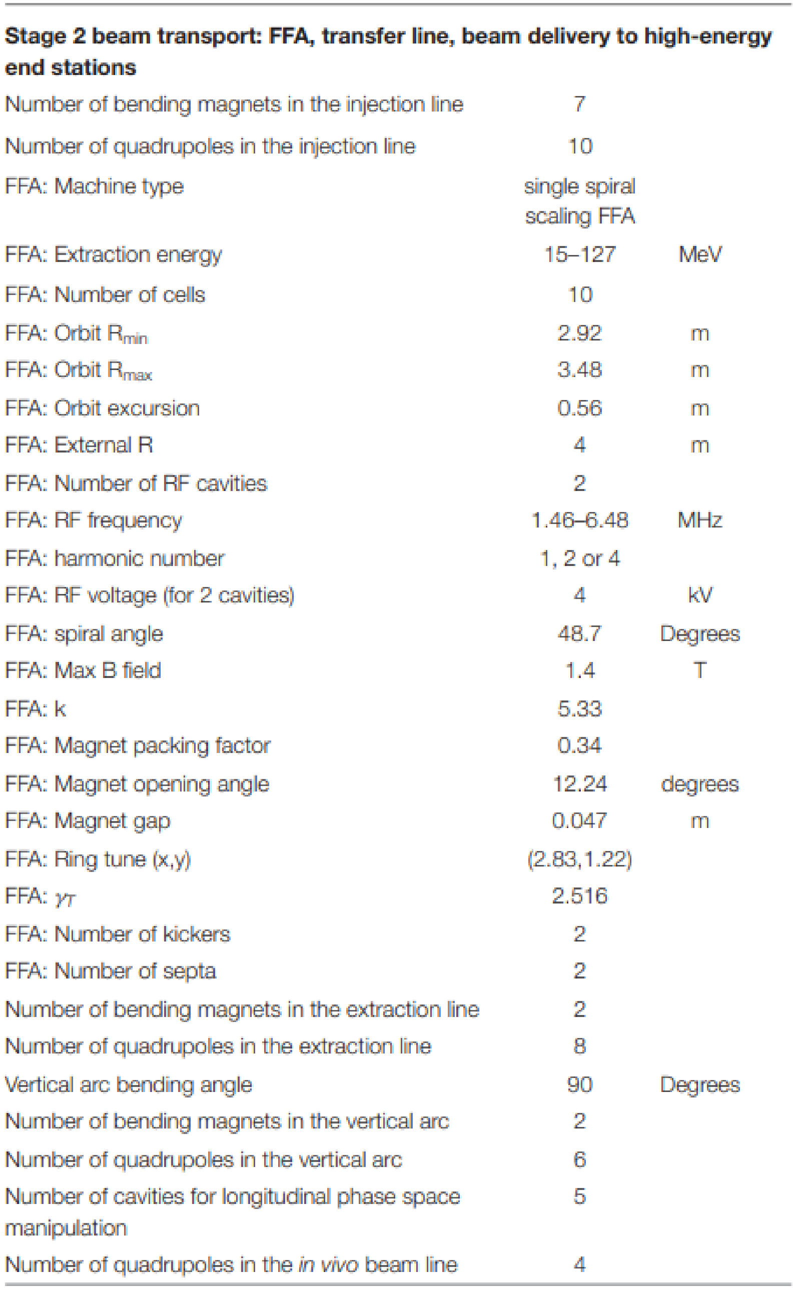




LhARA Stage 2







Stage 2 beam transport: FFA, transfer line, beam delivery to high-energy end stations		
Number of bending magnets in the injection line	7	
Number of quadrupoles in the injection line	10	
FFA: Machine type	single spiral scaling FFA	
FFA: Extraction energy	15–127	MeV
FFA: Number of cells	10	
FFA: Orbit R_{min}	2.92	m
FFA: Orbit R_{max}	3.48	m
FFA: Orbit excursion	0.56	m
FFA: External R	4	m
FFA: Number of RF cavities	2	
FFA: RF frequency	1.46–6.48	MHz
FFA: harmonic number	1, 2 or 4	
FFA: RF voltage (for 2 cavities)	4	kV
FFA: spiral angle	48.7	Degrees
FFA: Max B field	1.4	T
FFA: k	5.33	
FFA: Magnet packing factor	0.34	
FFA: Magnet opening angle	12.24	degrees
FFA: Magnet gap	0.047	m
FFA: Ring tune (x,y)	(2.83,1.22)	
FFA: γ_T	2.516	
FFA: Number of kickers	2	
FFA: Number of septa	2	
Number of bending magnets in the extraction line	2	
Number of quadrupoles in the extraction line	8	
Vertical arc bending angle	90	Degrees
Number of bending magnets in the vertical arc	2	
Number of quadrupoles in the vertical arc	6	
Number of cavities for longitudinal phase space manipulation	5	
Number of quadrupoles in the *in vivo* beam line	4	

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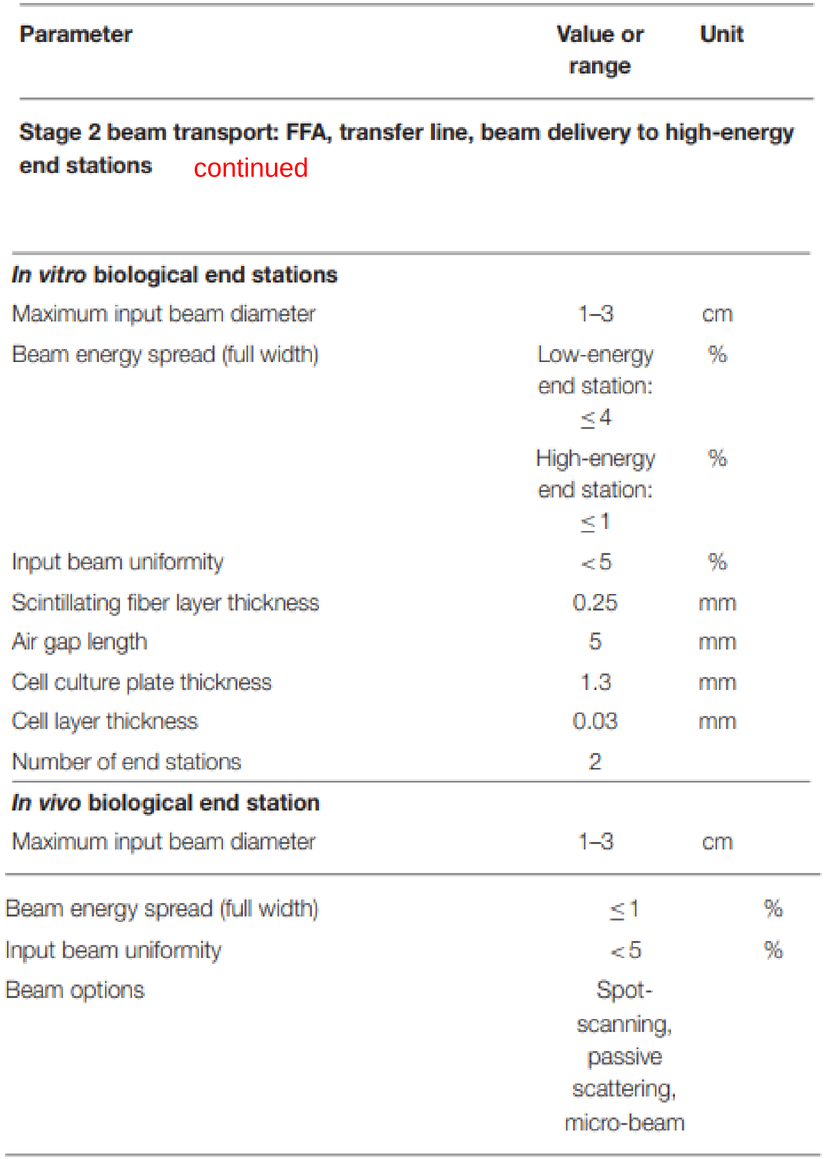
In vitro and In vivo Parameters (LhARA)

- Three biological end stations (two in vitro and one in vivo)
  - Low energy in vitro – proton beams between 12 – 15 MeV
  - High energy in vitro – proton beams between 15 – 127 MeV ion beams (including C6+) up to 33 MeV/u
  - High energy in vivo – proton beams between 15 – 127 MeV – ion beams (including C6+) up to 33 MeV/u
- Two in vitro end stations – high and low energy
  - Located within a state-of-the-art laboratory, fully equipped with various work spaces
  - Irradiation of a wide range of biological models (2D cell monolayers and 3D spheroids/patient-derived organoids)
  - Investigate a myriad of biological end points (clonogenic survival, spheroid/organoid growth, angiogenesis, inflammation)
  - Additional capabilities include hypoxia studies (0.1 – 1 % oxygen) and high-throughput screening (compound drug libraries, siRNA/CRISPR- Cas9)
- One high energy in vivo end station
  - Located on the ground floor in the accelerator complex



Parameter	Value or range	Unit
Stage 2 beam transport: FFA, transfer line, beam delivery to high-energy end stations continued		
***In vitro* biological end stations**		
Maximum input beam diameter	1–3	cm
Beam energy spread (full width)	Low-energy end station: ≤ 4	%
	High-energy end station: ≤ 1	%
Input beam uniformity	< 5	%
Scintillating fiber layer thickness	0.25	mm
Air gap length	5	mm
Cell culture plate thickness	1.3	mm
Cell layer thickness	0.03	mm
Number of end stations	2	
***In vivo* biological end station**		
Maximum input beam diameter	1–3	cm
Beam energy spread (full width)	≤ 1	%
Input beam uniformity	< 5	%
Beam options	Spot-scanning, passive scattering, micro-beam	

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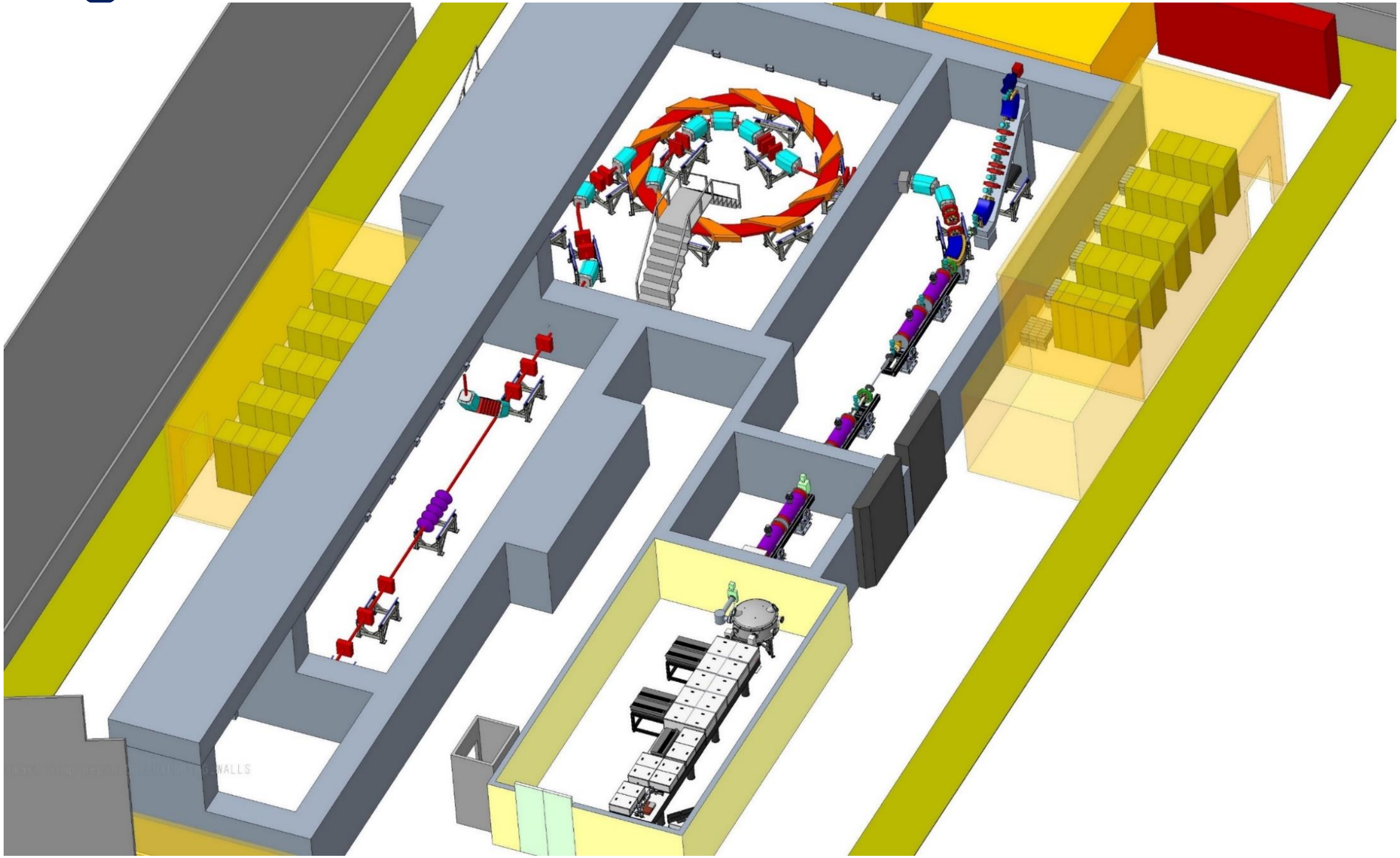
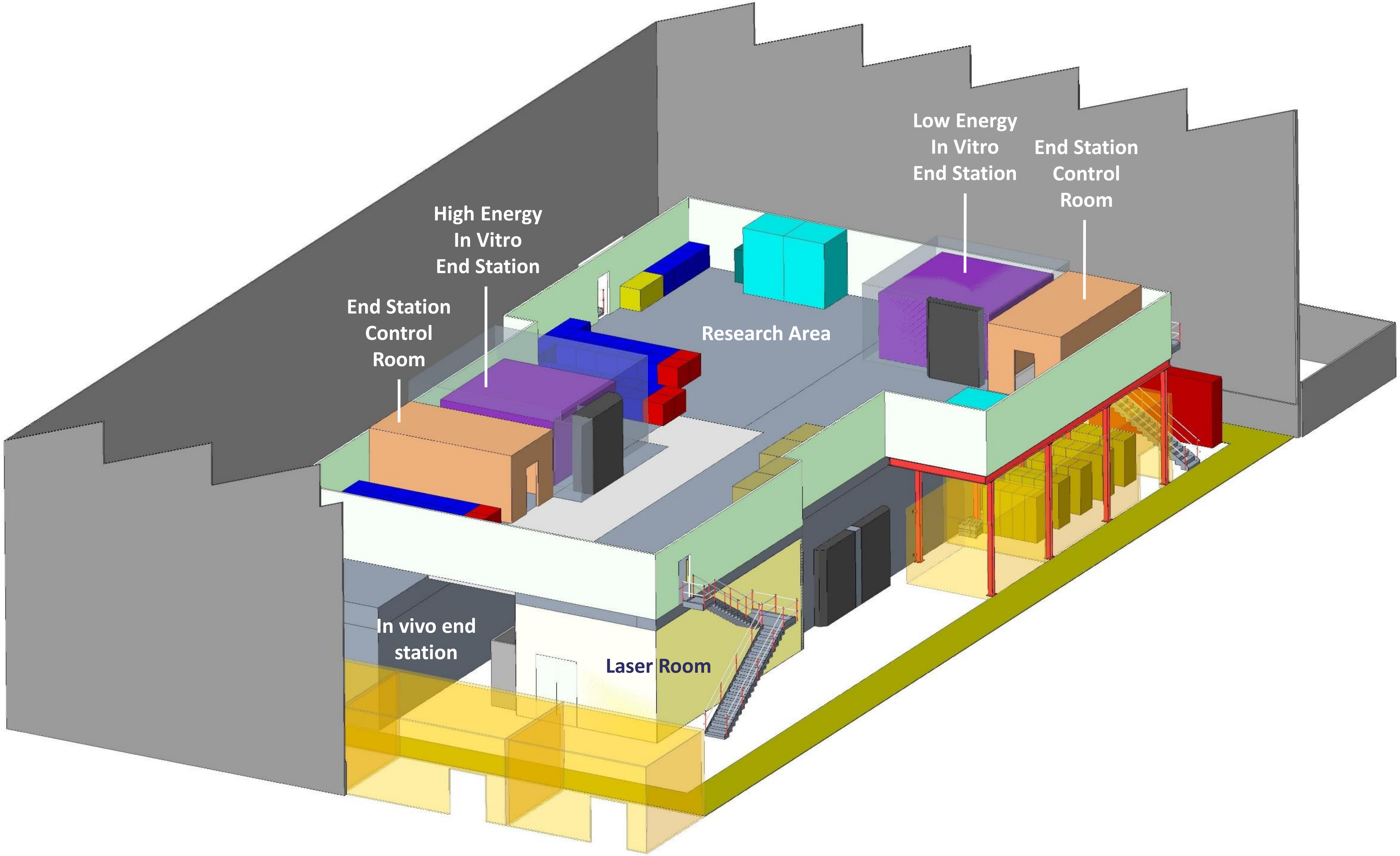
Daresbury Laboratory

Visualising ITRF



(STFC-TD Engineering)

Building Concept Design showing the Research Area on the 1st floor



Read More about ITRF/LhARA

- https://doi.org/10.1259/bjr.20200247
- https://www.frontiersin.org/articles/10.3389/fphy.2020.567738/full
- IAPC'23 (https://www.ipac23.org/preproc/index.html):
    - MOPL176, TUPA060, THPL106, THPM066, THPM083

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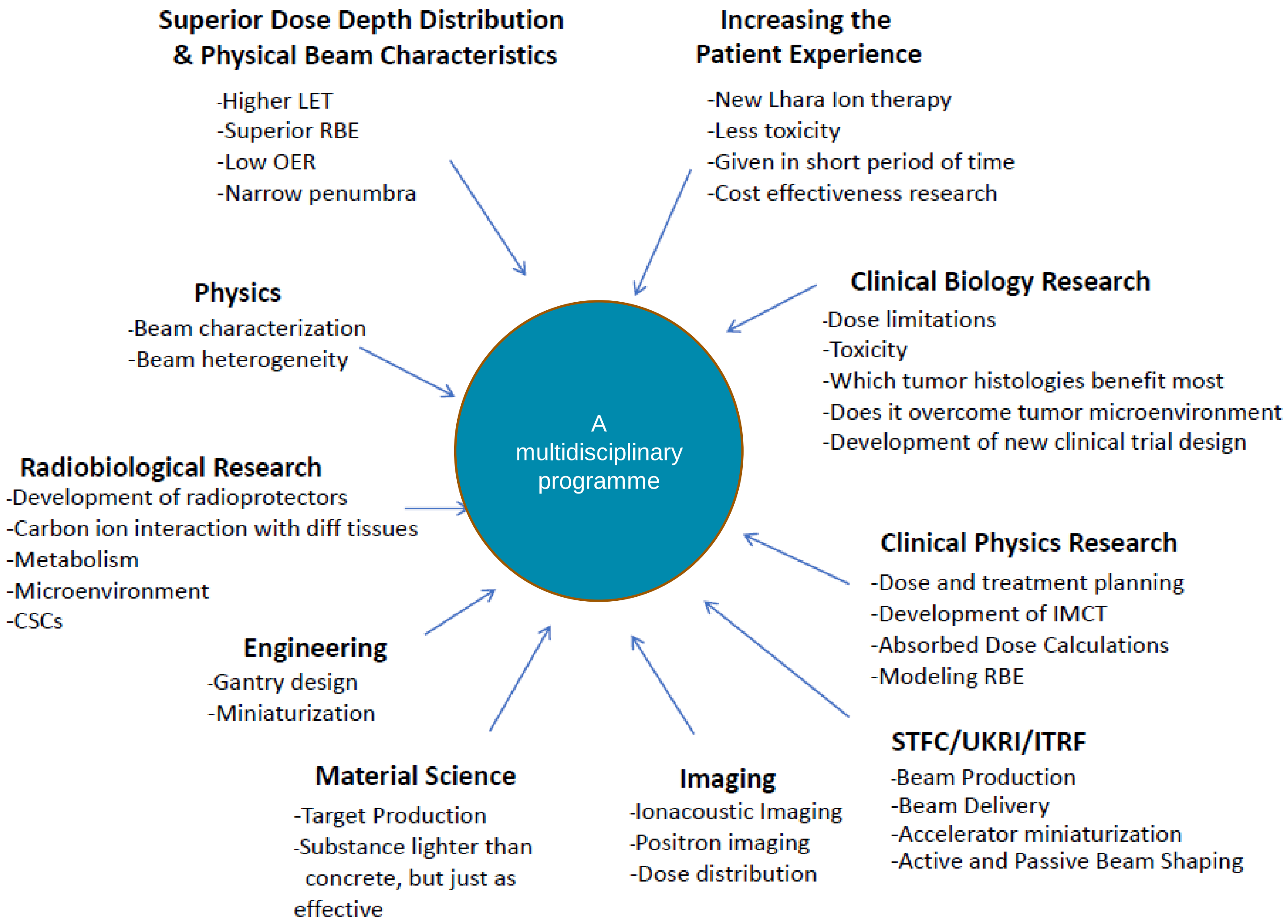

A multidisciplinary programme

Superior Dose Depth Distribution & Physical Beam Characteristics
-Higher LET
-Superior RBE
-Low OER
-Narrow penumbra

Increasing the Patient Experience
-New Lhara Ion therapy
-Less toxicity
-Given in short period of time
-Cost effectiveness research

Physics
-Beam characterization
-Beam heterogeneity

Clinical Biology Research
-Dose limitations
-Toxicity
-Which tumor histologies benefit most
-Does it overcome tumor microenvironment
-Development of new clinical trial design

Radiobiological Research
-Development of radioprotectors
-Carbon ion interaction with diff tissues
-Metabolism
-Microenvironment
-CSCs

Clinical Physics Research
-Dose and treatment planning
-Development of IMCT
-Absorbed Dose Calculations
-Modeling RBE

Engineering
-Gantry design
-Miniaturization

Material Science
-Target Production
-Substance lighter than concrete, but just as effective

Imaging
-Ionacoustic Imaging
-Positron imaging
-Dose distribution

STFC/UKRI/ITRF
-Beam Production
-Beam Delivery
-Accelerator miniaturization
-Active and Passive Beam Shaping