



# **Overview of ITRF/LhARA**

Laser-hybrid Accelerator for Radiobiological Applications to serve the Ion Therapy Research Facility





#### K. Long, 26 April, 2024

### Our mission is to:

- Deliver a systematic and definitive radiation biology programme
- Prove the feasibility of laser-driven hybrid acceleration
- Lay the technological foundations for the transformation of PBT
  - automated, patient-specific proton and ion beam therapy



# What is LhARA?

### <u>A novel, hybrid, approach:</u>

- Laser-driven, high-flux proton/ion source
  - Overcome instantaneous dose-rate limitation
    - Capture at >10 MeV
  - Delivers protons or ions in very short pulses
    - Bunches as short as 10-40 ns
  - Triggerable; arbitrary pulse structure
- Novel "electron-plasma-lens" capture & focusing

5—34 MeV/

- Strong focusing (short focal length) without the use of high-field solenoid
- Fast, flexible, fixed-field post acceleration
  - Variable energy
    - Protons: 15-127 MeV
    - lons:

LhARA performance summary								
	12 MeV Protons	15 MeV Protons	127 MeV Protons	33.4 MeV/u Carbon				
Dose per pulse	7.1 Gy	12.8 Gy	$15.6\mathrm{Gy}$	73.0 Gy				
Instantaneous dose rate	$1.0  imes 10^9$ Gy/s	$1.8 imes10^9{ m Gy/s}$	$3.8 imes10^8{ m Gy/s}$	$9.7 imes10^8{ m Gy/s}$				
Average dose rate	71 Gy/s	128 Gy/s	156 Gy/s	730 Gy/s				



# **Radiobiology in new regimens**

T. Schneider, C. Fernandez-Palomo, Annaïg Bertho et al.



### Dose escalation in the tumour possible – larger tumor control prob.

Beam

# **Proton FLASH data review**

#### J. McGarrigle

Frontiers | Frontiers in Oncology

To appear in



- Study impact of beam parameters in vitro & in vivo
- Overall picture somewhat unclear
- Continuing analysis of impact on LhARA specification

#### J. McGarrigle

# **SFTR data review**





- Study impact of beam parameters on effect in vivo
- Seeking now to pursue experimental programme

# Impact on specification of LhARA?

- Initiative to build-up evidence base leading to prioritised parameter set underway:
  - Measurements:
    - At Birmingham MC-40 cyclotron
    - Later at SCAPA (see later)
  - Simulation/study:
    - TOPAZ-nBio
- Develop programme to build:
  - Evidence base and understanding
  - Collaborations with biologists
  - Provide basis for prioritised beam/instrumentation specification





Puerta/Prezado

# **Radiobiology in new regimens**





and with chemo/immuno Therapies

Source: Expert Rev Proteomics © 2013 Expert Reviews Ltd

## Status: resources

### 2-year Preliminary Activity – Project start 01Oct22



#### To serve ITRF: 2 + 3-year project in 6 work packages:

#### 1. Project Management

- 2. Laser-driven proton and ion source
- 3. Proton and ion capture
- 4. Real-time dose-deposition profiling
- 5. Novel, automated, end-station development

6. Facility design and integration

#### First two years of "Five-year plan" CCAP-TN-10

# **Progress: design & integration: Stage 1**



#### T.J. Kuo K. Long J. Pasternak R. Razak W. Shields

### Activation study:

 $\circ$ 

- Ongoing contract with TUVSUD; seek to determine:
  - Required shielding thickness and building constraints
  - Guidance on operation method
  - Guidance on material use & activation

N. Bliss, A. Goulden, C. Hill, H. Owen, C. Whyte 10

#### N. Dover

T.S. Dascalu

## R&D objectives:

- "Full-scale" tests in conditions approaching LhARA specification
- LhARA-focused diagnostic and targetry development
- High-repetition rate, automation and longevity studies
- Accurate numerical modelling 3D simulation codes





Realistic, 2-stage simulation on ARCHER2 using accurate "pre-plasma" profile

**Progress: source** 

Study proton production as a function of angle of incidence, spot size, proton-layer thickness

Seek to benchmark against data



Laser-solid interaction beamline B1 in Bunker B.



## **Experiments at SCAPA**







R. Gray

# **Progress source:** diagnostics & high rep-rate **Diagnostics**

#### Absolute calibration and dose linearity scan



Energy dependent emission scan

### *High-rep rate / longevity ...* **Experimental R&D at ICL - Initial results**



- Preliminary experiments run at 5 mJ level (without final amplifier)
- Continuous operation at 100 Hz for 10s minutes
- · Plasma formation, x-ray generation (and debris production!) observed

O. Ettlinger, N. Xu, Z. Najmudin



90 mJ of laser energy, 30 fs pulse width at 100 Hz Predicted maximum proton energies ~ few MeV Semi-continuous access allows long term R&D into technical issues in stabilisation, debris, targetry, etc

#### N. Dover, O. Ettlinger, N. Xu, Z. Najmudin

### Scintillators: key for high rep rate operation

- **Dedicated calibration effort led by** N. Dover (ICL):
  - **Birmingham MC40 cyclotron**

# **Progress: design & integration: Stage 1**

#### M. Maxouti, N. Dover, K. Long

## Standardised TNSA source



### Impact: look at entrance to arc:



### Important for (e.g.) activation calculation

### W. Shields, J. Pasternak, K. Long Revised Stage 1 baseline



### 7 Gabor lens adopted

- Greater flexibility
- Drifts longer:
  - Diagnostics
  - Shielding
- Gabor lens/solenoid focusing equivalence



## **Progress: capture**

- Key issues:
  - Electron density, plasma stability
- Measurements on Penning-Malmberg trap at Swansea University
  - "Moving potential well" capture
  - "Rotating wall" to "spin-up" plasma to gain stability



- Ongoing campaign:
  - Already significant increase in hold time and plasma density
  - Next steps:
    - Improved diagnostics
    - Numerical analysis to interpret and optimise experiments

Future plan: K. Long, C. Dyson (PhD from Oct24)

## **Progress: real-time dose measurment**



# **Progress: real-time dose measurment**



<u>M.</u> <u>Maxouti,</u> C. Bird, O. Jeremy, K. Ladhams, K. Long, D. Nardini

Infinite

bandwidth

### **Optical Reconstruction**





Relative Geant4 energy depositions





<u>P. Hobson,</u> B. Cox, J. Bamber

#### 17

# **Progress: Stage 2: injection & FFA magnet**

## Injection-line update



**Resign revision encorporates:** 

- Shielding, collimation & diagnostics
- Continued design effort:
  - Match to FFA cell requirements
  - Study & mitigate space charge
- BDSIM model now synced with accommodates:
  - Vacuum valves, diagnostics, shielding shutters, correctors ...



#### **Emerging collaboration with ISIS u/g team**



# **Progress: consultation & end-station**

- Peer-group consultation:
  - 1. Stage 1 in vitro & 2 in vivo
  - 2. Focus on Stage 1 in vitro
  - 3. Focus on Stage 2 in vivo
  - Beam-line diagnostics:
    - Gas-jet (Liverpool): tested at DCF
  - Seek increasing engagement with more novel techniques:
    - Initiated "ART" meeting series

Conclusions and recommendations documented at: https://ccap.hep.ph.ic.ac.uk/trac/browser/LhARA/Governa nce/ProjectManagementBoard/LhARA-Gov-PMB-2023-04

to be updated!

Wave 4 STFC Preliminary Activity proposal form

Details	and	descr	ip	tior	1
---------	-----	-------	----	------	---

ĸe	y information	
1.	Name of project (and acronym or short name if relevant)	Ion Therapy Research Facility (ITRF) Preliminary Activity 2
2.	(a) Lead contact	Amato Giaccia (amato.giaccia@oncology.ox.ac.uk)
		Kenneth Long (k.long@imperial.ac.uk)

(b) STFC contact Massimo Noro (massimo.noro@stfc.ac.uk)

### 3. Which submission route are you Internal using (Advisory Panel, internal, resubmission) etc.)?

4. One-line description of the Preliminary Activity (22 words)

The ITRF will be a unique radiobiological research facility exploiting technologies that can transform ion-bea
and the treatment of "hard-to-treat" cancer.

Pro	iect	descri	ntion
	,	acsen	0.000

5. Summary of the Preliminary Activity (800 words) – please note this box expands as you type.

#### Background:

Conventional X-ray therapy (RT) is needed in 40% of cancer cures but some tumours are radioresistant and difficult to treat and cure. In Ion Beam Therapy (IBT), X-rays are replaced by energetic particles such as carbon ions. The physics of IBT allows the dose to be more precisely localised in the tumour and IBT causes significantly more direct, difficult to repair, DNA damage and stimulates a robust immune response. As a result, more tumours will be cured and variables are bust immune response.

repair, DNA damage and stimulates a robust immune response. As a result, more tumours will be cured and side effects. However, IBT has yet to reach its full potential.

Globally, there is no facility that can be used to explore the fundamental biological processes underlyin which can be used to optimise radiation delivery in time, space, ion species, and energy spectrum, alo combination with new drugs. The project proposed here will create a facility to explore advanced radiothera new cancer treatments fit for 2050 and beyond, and make the UK a leader in the global fight against cancer.

#### Objectives:

The Preliminary Activity (ITRF PA2) proposed here will complete the design and planning of the ITRF constructi

to create the world-leading, compact, single-site research infrastructure that will deliver the multidisciplinary programme necessary to:

- Elucidate radiobiological mechanisms that underpin the clinical efficacy of particle therapy;
- Generate the accelerator, diagnostic, imaging, and computing technologies required to transform the clinical practice of IBT; and
- Deliver the capability to provide IBT in completely new regimens by combining ion species from protons to carbon exploiting ultra-high dose rates and novel spectral-, spatial- and temporal-fractionation schemes.

The design, specification and planning carried out within ITRF PA2 will build on the complete Conceptual Design Report that is the principal deliverable of the current ITRF Preliminary Activity (ITRF PA1).

#### The deliverables for ITRF PA2 are:

- Technical Design Reports for the staged implementation of the facility;
- A site study leading to site selection and building implementation plan; and
- A proof-of-principle demonstrator system at an existing pulsed-laser facility.

#### Engagement:

To ensure direct engagement of the target user community, members of the leadership team are drawn equally from the biomedical and natural science communities. On the biomedical side, key leadership positions include LhARA/ITRF collaboration Co-Spokesman, A. Giacca (Director Oxford Institute of Radiation Oncology), Institute Board Co-Chair, Y. Prezado (CNRS Institute Curie), Biological Science Programme Manager, J. Parsons (Birmingham, Vice-Chair of the Association for Radiation Research), and Impact; Clinical and Industrial Programme Manager, P. Price (Imperial, Chair Radiotherapy UK). The biological and medical communities are also strongly represented on the PA1 oversight and advisory bodies.

23. a. Complete the following table for UKRI Infrastructure Fund requirements, noting that costs are only approximations at this stage.

Infrastructure Fund requirement	Year								Tabal				
(£m) Point estimates.	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	Y9	Y10	Y11	Y12	Total
Project costs	22	50	81	50	22								225
TOTAL	22	50	81	50	22								225



1

## Feedback on PA2 proposal to STFC Visions Team



#### UKRI Infrastructure Fund: Wave 4 Preliminary Activities

The STFC prioritisation process for Wave 4 preliminary activities of the UKRI Infrastructure Fund began in early 2023 with an invitation to the PPAN Advisory Panels and internal STFC departments to identify and submit proposals for consideration.

STFC received thirteen Preliminary Activity proposal submissions, seven of which were resubmissions from previous waves of the STFC prioritisation process. Initial feedback from the STFC Visions Panel was provided for all proposals in August, focusing on the potential for delivery of a step change in capability and the strategic drivers of the projects.

Following incorporation of feedback, the proposals were assessed by both STFC Science Boards, PPAN and Facilities & Laboratories, and resulting recommendations were provided to STFC Council for consideration alongside the proposals. STFC Executive Board then considered all advice to agree the final outcomes of the prioritisation process.

Unfortunately, the ITRF Preliminary Activity proposal was not selected by STFC for submission to Wave 4 of the UKRI Infrastructure Fund. More detailed proposal feedback focused solely on the outcome of the prioritisation process is provided below.

#### ITRF: Ion Therapy Research Facility- Preliminary Activity 2

The ITRF proposal illustrated the high impact potential of the project, and it was recognised that the full infrastructure could deliver a large step change in capability for the UK. The proposal was considered ambitious and a good fit to the Infrastructure Fund. However, the project fit within the international landscape was unclear and the proposal would have benefitted from focusing on the specific strategic cirkives of the project.

The proposal clearly displayed the project's potential for broad reach beyond one discipline, but the level of engagement of potential partners for the preliminary activity and the potential target community for the full infrastructure were unclear from the proposal.

Although the proposal was ambitious, it was considered to be lacking in evidence and clarity across a few areas; the progress of the first preliminary activity could have been more prominent, the physics case for progressing the project made clearer, and the leasibility of the proposal more clearly justified. It was noted that the proposal would have benefitted from providing information on the proposed approach to achieving the listed deliverables.

Overall, the proposal was not considered suitable for submission to Wave 4 of the UKRI Infrastructure Fund, but discussions are ongoing within STFC and in co-ordination with the ITRF team.

### Broad support

- High impact potential
- Could deliver step change
- Potential for broad reach
- Ambitious

### But not selected

- Fit with international landscape unclear
- Potential for target community unclear
- Progress of first preliminary activity unclear (but only 9 months into 2 year project when written)

### Now seeking access to bridging funds

# Structuring the bridging activity

Define bridging programme to optimise delivery of:

- Biology/proof-of-principle programme
- R&D programme to address key project risks
- Strategic partnerships

Radiobiological experimentation and modelling		WP A.7 - Radiobiology Experiment		
	WP A	WP A.4 - Ion acoustic dose measurement		
		WP A.5 - End station and novel diagnostics		
		WP A.2 - Source for Radiobiology Expt		
ITRF/LhARA R&D	WP B	WP B.6 - FFA feasibility study		
		WP B.2 - Source		
		WP B.3 - Capture		
РМ	WP C	WP C.1 - Proj Man		
		WP C.8- Outreach & Engagement		

- Development of radiation biology programme:
  - At existing facilities:
    - Novel (e.g. laser driven)
    - Conventional

### • LhARA proof-of-principle experiment:

 CW: "... include as many of key LhARA elements as possible ..."



### Biological measurement programme & proof-of-principle experiment

"WP7", led by J. Parsons Increasingly import aspect of the programme going forward



## **Conclusions**

- Significant progress in ITRF/LhARA:
  - Beamline design and optimisation
  - Engineering, initial studies of FFA magnet
  - Initial characterisation of laser-driven source
  - Progress on understanding and stablisation of plasma for Gabor lens
  - Design of ion-acoustic proof-of-principle experiment
  - Peer-group consultation leading to specification of end-station
- Looking forward:
  - Recognition of importance of development of biological programme:
    - First steps in design and specification of proof-of-principle experiment as part of broader radiation-biology programme
  - Project programme for Bridging Period now being developed
- Exciting programme, but, clear need to <u>make the case!</u>



## $\Rightarrow$ compact, uniquely flexible facility





Access

In Vivo

# The case for fundamental radiobiology

- Relative biological effectiveness:
  - Defined relative to reference X-ray beam
  - Known to depend on:
    - Energy, ion species
    - Dose & dose rate
    - Tissue type
    - Biological endpoint
- Yet:
  - p-treatment planning uses 1.1
    - Effective values are used for C<sup>6+</sup>
- Maximise the efficacy of PBT now & in the future:
  - Require systematic programme to develop full understanding of radiobiology





# **Progress: selected engineering highlights**



## **Progress capture**



Progress on Plasma lens development (13<sup>th</sup> February 2024)

## **Progress: capture**

## Preliminary results (October 2023)







Progress on Plasma lens development (13th February 2024)

## **Progress capture**

## Rotating Electric fields / Rotating wall





https://alpha.web.cern.ch/science/rotating-wall





A six-segment rotating wall electrode is used to control plasma radii. The relative phase of the signal applied to each sector of the electrode is labelled.

This gives a rotating electric field perpendicular to the axis of symmetry of the plasma.

Solution The electric field induces an electric dipole moment in the plasma, leading to plasma compression.

#### Progress on Plasma lens development (13th February 2024)

## **Outreach & engagement (WP8); progress to date**

### **Communication Strategy**

- **Public:** LhARA Website strategy devised for web development, management/domains/social media/LinkedIn for public and patient engagement
- Public engagement events: Planning for Great Exhibition and Royal Society Exhibition 2025
- Media: Mentioned as future innovation in cancer care on Radio4 Today podcast Feb 2024
- **Parliamentary**: Mentioned in UK Radiotherapy ten year Vision documents launched at HOC Feb 2024. Meetings being planned with Scottish SNP science spokesman Carol Monaghan and Shadow science minister Chi Onwurah. Planned to be included in future Westminster MedTech commission .

### Stakeholder engagement

- Discission with MRC, the Radiotherapy UK charity and NGO-Global Coalition for Radiotherapy on engaging national and international clinical colleagues and radiobiology community, patients and the radiotherapy industry in parallel.
- International workshop of clinical/biologists planed for Q3 2024

### **Professional Bodies Engagement**

• Links with IPO via Richard Amos and arranging engagement with other professional bodies

### **MRC Engagement**

• Work started to engage MCR in biological/translational clinical areas

#### **International Engagement**

- LMU, HZDR, CNRS/Institute Curie
- CERN
- ELI/ELIMED

### Multiple ion source & capture





Fundamental radiobiology