Wave 4 STFC Preliminary Activity proposal form

Details and descriptions

Key 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)
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3. Which submission route are you using (Advisory Panel, internal, resubmission) etc.)?	Internal
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-beam therapy and the treatment of "hard-to-treat" cancer.	

Project description

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 with fewer 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 underlying IBT and which can be used to optimise radiation delivery in time, space, ion species, and energy spectrum, alone and in combination with new drugs. The project proposed here will create a facility to explore advanced radiotherapy, deliver 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 construction project 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).

Project description

Deliverables:

ITRF PA1 has defined a two-stage implementation scheme:

- Stage 1: proton beams with energies in the range 12 MeV to 15 MeV to the Low-energy *in-vitro* End Station;
- Stage 2: proton beams of 127 MeV and ion beams of 33.4 MeV/nucleon to the High-energy *in-vitro* and *In-vivo* End Stations.

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.

Management:

The management and governance structure of ITRF PA2 will build on the effective structure successfully employed in ITRF PA1. ITRF PA2 will be delivered by a project team that includes the Project Sponsor, the Project Scientist, and the Project Manager. Individuals will be appointed to these positions by the Executive Director for National Laboratories on the advice of the Advisory Board. The Project Board will co-opt additional expert representation as required.

The ITRF will be served by LhARA, the Laser-hybrid Accelerator for Radiobiological Applications. A consortium agreement will be established between STFC and the institutes that form the LhARA/ITRF collaboration by the end of July 2024. The agreement will define roles and responsibilities for the duration of the Preliminary Activity.

Route to full implementation:

Investment on the scale of the ITRF will require submission to the Infrastructure and Projects Authority (IPA) Gateway Review Process. Early in ITRF PA2, discussions with the IPA will be held to understand how to initiate the Process.

Infrastructure Fund investment need:

Realising the potential of the ITRF requires a multidisciplinary approach. The LhARA/ITRF collaboration is composed of clinical oncologists; medical, particle, plasma, laser, ultrasound, and optical physicists; accelerator, computer, and instrumentation scientists; radiobiologists, industrialists, and patient representatives. No one research council supports this diverse community. Insight into radiobiology and the planning and execution of the radiobiology programme will be provided by UK and international radiobiologists. Clinical horizon scanning will come from a UK and international clinical consortium with patient oversight and input from individuals and the charity Radiotherapy UK. The UKRI Infrastructure Fund is the ideal cross-council forum for investment in the ambitious scientific and technological programme required to deliver the ITRF.

No single STFC department encompasses the expertise needed to develop, implement, and operate the ITRF. Therefore, an inter-departmental approach has been adopted. Accelerator design, physics, and operations experience come from ASTeC and ISIS. CLF brings plasma physics knowledge, laser-driven particle acceleration experience, and high-power laser operations. PPD contributes instrumentation and detector expertise, data handing, automation and control, and modelling of the interaction of particle beams with matter. The Mary Lyon Centre will be essential in the specification and design of the *In-vivo* End station and the animal handling requirements and will play a critical role in the site study and building implementation plan. Hartree will provide the bridge to innovative treatment planning and dose calculation methods. Full engagement with TD and SCD will ensure the successful delivery and exploitation of the facility. Technology transfer, advanced manufacturing, and remote-operation expertise that reside in RAL Space and the ATC will also be of benefit.

Project description

6. Please describe the full infrastructure capability that this Preliminary Activity is exploring or working towards (800 words] – Please note this box expands as you type.

Research/innovation objectives:

Our vision is to enable a radical transformation in the clinical practice of ion-beam therapy. To realise this, the ITRF will:

- Provide a fully automated, highly flexible infrastructure to allow fundamental research at the tissue, cellular and DNA levels to understand the radiobiological impact of proton and ion beams generated by the laser-hybrid approach;
- Demonstrate the capability to deliver IBT therapy in completely new regimens by combining ion species from proton to carbon, exploiting hypo- and single-fraction, ultra-high dose rates, and novel spectral-, spatial- and temporal-fractionation schemes; and
- Establish the R&D programme required to make "best in class" treatments available to all patients. The envisaged system integrates patient, soft-tissue, and dose-deposition imaging with real-time treatment planning in an automated system that triggers the delivery of dose tailored in real time to the individual patient. It eliminates the need for conventional gantries, reducing the size and cost of a clinical facility and increasing patient throughput.

We have created the broad interdisciplinary collaboration required to realise our vision.

Research/innovation need:

In the UK, 1 in 2 people will develop cancer; globally, the present incidence of 17 million new cases per year will increase to 27.5 million per year by 2040. RT is used in the treatment of 50% of cancer patients and is responsible for 40% of cancer cures. The NHS long-term plan to diagnose cancer in the early, curative stage underscores an increasing need for effective RT treatment including IBT. LhARA will deliver beams with properties qualitatively and quantitatively different from what is available today, providing a new approach to the investigation of the biology of the enhanced effects of IBT at the tissue, cellular and molecular levels. These investigations will include study of the immune system, its stimulation by IBT and will lead to more effective treatments and cancer cures.

The use of novel beams with strikingly different characteristics reduces normal tissue damage in treatments that kill more tumour cells and stimulate the immune system, e.g. via ultra-high dose rate "FLASH" and "mini-beam" therapy. This, combined with personalised medicine based on the biology of individual tumours, now provides the impetus for the radical transformation of IBT that the proposed programme will provide. This has the potential to transform management of difficult to treat/less survivable cancers, the subject of the current HSC Select Committee inquiry into the Future of Cancer Care.

Target user base:

There is currently no infrastructure in the UK or overseas that can deliver multiple ion species over the range of conditions necessary to revolutionise biomedical research and cancer care. Our approach is transformational and distinguishes itself from other initiatives by:

- Providing in a single facility the capability to carry out biomedical research in completely new regimens by delivering ion species from proton to carbon, exploiting ultra-high dose rates and novel spectral-, spatial- and spectral-fractionation schemes; and
- Demonstrating in a single facility the technologies required to integrate patient, soft-tissue, and dose-deposition imaging with real-time treatment planning in an automatic system that triggers the delivery of dose tailored in real time to the individual patient.

The target user base is therefore composed of:

- Radiation biologists from the UK and overseas who seek the spatio-temporal flexibility required to elucidate the mechanisms that underpin the impact of ionising radiation on tissue;

Project description
• Pre-clinical researchers from the UK and overseas who are active in the development of new regimens for particle beam therapy; and • Medical physicists, engineers and others from the NHS, academia internationally, and industry who are working to improve instrumentation, diagnostics, computer and AI systems. The ITRF will become a national facility that serves as a key international centre of excellence. *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. *What success will look like after 5 & 10 years:* Five years after the start of ITRF PA2 our intention is that we shall have: • Production of a "prototypic" laser-hybrid demonstrator on an existing facility with critical radiobiological characterisation with results published in seminal papers; • Initiated, through the Gateway Review Process or otherwise, the ITRF construction project; and • Brought the programme addressing the technical risks to maturity. Ten years after the start of ITRF PA2 our intention is that: • Stage 1 of LhARA serving the Low-energy *in-vitro* End Station will be commissioned and in operation; and • Stage 2 of LhARA to serve the High-energy *in-vitro* and *In-vivo* End Stations will be commissioned and in operation.

Timing of Preliminary Activity	
7. When would the Preliminary Activity begin? Please highlight the year.	FY 2024/25
8. How many financial years would this project take? Please state this in whole numbers between 1-5. If the project will take over 5 years please state >5.	5
9. Is there likely to be an application for a second Preliminary Activity before that for a full infrastructure (if it is taken forward)?	No

The next two sections on project criteria and timings refer to the Full infrastructure capability this Preliminary Activity is exploring or working towards.

This will understandably be briefer and more uncertain than a full project template.

Project criteria

10. How has the research or innovation area been prioritised? Tick all that apply.	☒ Community engagement (e.g. Statement of Need, workshop) ☐ Infrastructure Roadmap theme or concept ☐ Council's strategy or equivalent ☐ Discipline or technology roadmap or strategy (e.g. European Strategy for Particle Physics) ☒ Government or UKRI strategy (e.g. UKRI strategic themes) ☐ Other

11. If relevant, comment briefly on how this has been done (50 words)

Selected by STFC in a previous round following committee review and supported by the MRC.
Workshops were held to seek a clinical consensus on what ion therapy provision is appropriate in the UK. The recommendations led to the proposal to develop the ITRF (published in *Br J Radiol* 2020; **93**: 20200247).

12. Outline the strategic drivers for the infrastructure project and how the project will help achieve the strategic goals (200 words)

The UKRI Opportunities Report highlights the need for improved health technologies. Previous UKRI investment resulted in the first demonstrated fixed-field alternating gradient accelerator, EMMA. EMMA is the basis of future machines for high intensity particle physics, neutron science, X-ray facilities such as the UK XFEL, and healthcare applications. The UK is at the forefront of this technology. Similarly, the UK has a leading role in the science of laser-plasma acceleration, holding the record for the proton energy produced using one of the most developed laser-plasma acceleration techniques. The proposed infrastructure is the first combined, multi-ion, high dose-rate laser-driven generation-and-acceleration facility. It will greatly surpass any existing infrastructure in the range and quality of the proton and ion beams that it will deliver. It will enable the first systematic *in-vitro* and *in-vivo* biological studies of multi-ion irradiation. There is broad global consensus of the need for such a facility, which would be complementary to lower-dose-rate systems, e.g. at Christie Hospital, UCL Hospital, MedAustron and elsewhere. The project will leverage not only the UK experience in core accelerator technologies, but benefit from close collaboration with NIMMS at CERN, spreading costs amongst our partners and de-risking the technical developments.

If this project contributes to achieving one or more of UKRI's strategic themes (i.e. where the outputs/outcomes/impacts could be additionally reported through the strategic themes programme of work), please indicate which theme and at which stage of the project

Preliminary Activity itself:	Resulting **Full infrastructure** project:
☐ Building a Green Future	☐ Building a Green Future
☒ Securing better health, ageing and wellbeing	☒ Securing better health, ageing and wellbeing
☐ Tackling infections	☐ Tackling infections
☐ Building a secure and resilient world	☐ Building a secure and resilient world
☐ Creating opportunities, improving outcomes	☐ Creating opportunities, improving outcomes

13. Describe the potential benefits/impacts of the project and risks of not doing the project
(300 words)

When thinking about risks, proponents should be as specific as possible to the infrastructure and avoid general statements such as "risk of not reaching 2.4% goal" which are relevant to all projects.

Benefits and impacts:

The ITRF will have an open-access user model. It will deliver world-leading research in the science and technology underpinning IBT. Every opportunity will be taken to generate clinical impact early, in areas such as instrumentation, diagnostics, automation, and simulation/treatment planning.

No existing infrastructure allows in-vitro and preclinical radiobiology studies. The ITRF will meet this need allowing future clinical trials to take place. Its exploitation will:

- Enable exploration of the vast "terra incognita" of the biological response to charged particle beams.
- Maximise the benefit from the UK's investment in PBT;
- Underpin the future of proton- and ion-beam therapy globally; and
- Enhance the UK's leadership in ion-therapy research.

The ITRF will complement existing UK capabilities. In the medium term, its multiple ion species beams, delivered at high dose rate in a wide range of spatial, temporal, and spectral distributions, will generate biological understanding, develop medical physics capability and expertise, and benefit the practise of radiotherapy. Long term, the technologies will revolutionise clinical capability. Spin off in other industries will enhance the UK science base. Commercial partnerships will ensure the UK becomes the global supplier of the clinical IBT systems of tomorrow.

Risks of failure to proceed:

Societal impact: Radical approaches rather than incremental change are needed to achieve the UK government's cancer treatment targets. Failure to proceed squanders previous investment in ITRF PA1. Without funding this next step, progress in understanding the underlying radiobiology and the development of the necessary skills and experience within the UK will be lost thereby jeopardising the overall NHS goal.

Economic impact: The UK has a world-leading track record in the relevant technologies. Without investment in the ITRF development, the opportunity to develop partnerships between the science base and industry to deliver the next generation IBT facilities is likely to be lost.

14. Describe how this is a step change (transformation) in capability and how it fits in the existing infrastructure landscape (200 words)

There is no current infrastructure in the UK or overseas that can deliver multiple ion species over the range of conditions necessary to revolutionise biomedical research. The ITRF makes the step necessary from today's lower-intensity capabilities (e.g. Surrey, Dalton Cumbria) and proton-only capabilities at (e.g. Clatterbridge, Christie, UCLH). A systems approach is taken to couple together the accelerator source with the dosimetry, delivery, and computing necessary for the next generation of treatment modalities. Proposals elsewhere seek to serve biomedical research (BIO-LEAR, GSI, ELIMEA/ELIMED). Our approach is transformational and distinguishes itself from other initiatives by:

- Providing in a single facility the capability to carry out biomedical research in completely new regimens by combining a variety of ion species from proton to carbon in a single fraction, exploiting ultra-high dose rates and novel spectral-, spatial- and spectral-fractionation schemes; and
- Demonstrating in an integrated facility the technologies required to combine patient, soft-tissue, and dose-deposition imaging with real-time treatment planning in an automatic system that triggers the delivery of dose tailored in real time to the individual patient.

Only UKRI can support an integrated project of this nature and foster a new interdisciplinary community across the research councils and their user bases.

15. Please briefly describe how the full infrastructure is likely to be delivered, e.g. competition followed by grant, by UKRI, a combination of grant and UKRI etc. Who are the likely beneficiaries (e.g. wide pool of possible applicants, limited number of applicants, a known beneficiary e.g. UKRI or international collaboration)	(100 words)
Full funding of the ITRF will require submission to the Infrastructure and Projects Authority (IPA) Gateway Review Process and we plan substantial engagement with the IPA during this project. The preliminary activity described here will create a construction plan, identify a suitable site, and deliver the first radiobiology results from a scaled down, proof-of-principle system. The activities undertaken will allow the selection and optimisation of suitable technologies for each aspect of this novel system. The project management structure builds in a multidisciplinary approach that ensures integration and decreases risks.	

Timings

Please provide timings for the Full infrastructure and describe any external drivers of timings.

16. Ideally when would the full project begin?	[ ] 2025/26 [ ] 2026/27 [*] 2027/28 [] 2028/29 [ ] 2029/30 [ ] 2030/31 [ ] 2031/32 [ ] 2032/33
17. How many financial years will it take to complete? Please state a number between 1 – 10.	4
18. If more than 10 years, specify:	

19. Brief explanation of why this project is timely if not already covered (100 words) If this has already been described, please signpost to the relevant answer.
The pressing research need for an ion-therapy research platform was established through peer-group consultation (BJR 93 (1116) 20200247). The LhARA/ITRF initiative now has significant momentum and breadth of engagement, e.g.: • CLF, CI, JAI, QUB, and Strathclyde collaborate on the laser-driven ion source; • The UK groups responsible for the ALPHA positron trap (Swansea, CI/Manchester) lead the plasma-lens development; • The FFA team now encompasses ASTEC, ISIS, JAI; and • Well-attended peer-group consultation meetings have attracted more than 50 researchers from the UK, Europe, and elsewhere. The LhARA/ITRF initiative now has significant international visibility, allowing the collaboration to discuss collaboration with key contributors to the field (e.g., HZDR, LMU, BELLA@Berkeley, and CERN).

20. Is there an <u>external</u> driver of decision timing?	☐ International agreement ☐ Commercial agreement ☐ Regulatory compliance ☐ Other ☒ No external driver
21. If there is an external driver, please state when a decision is needed by and explain why the timing is fixed. If you have selected a specific date driving the start of the project, please describe how flexible this is. Otherwise, we will assume that if we cannot award funding at this date, the project is not viable to be taken forward. **(100 words)**	

Costs

Cost tables for the Preliminary Activity.

The funding for the current preliminary activity ends 30 September 2024 and consequently funding is needed from October 2024. Without this the collaboration will struggle to keep staff greatly increasing the risks associated with the project.

Table 1. Preliminary Activity costs (£m)	Year					Total
	24/25	25/26	26/27	27/28	28/29	
Costs requested from Fund	2.7	4.9	5.2	5.2	3.5	21.5
Other funding agreed/anticipated						

Cost tables for the Full infrastructure that this activity would enable/is working toward.

22. Please name any other funders that may contribute to the full infrastructure.

If relevant, please list 2nd funder:		If relevant, please list 3rd funder:	
If relevant, please list 4th funder:		If relevant, please list 5th funder:	

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

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

24. b. Please complete the following table if it is likely that the project will attract other sources of funding.

Other funders (£m). Point estimates.	Year												Total
	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	Y9	Y10	Y11	Y12	
UKRI Infrastructure Fund (from TOTAL line in previous tables)													
Other UKRI funding													
Non-UKRI funding source(s)													
Total													

Project activities and high-level milestones for the Preliminary Activity

This is to help the Panel understand what the Preliminary Activity will do and how it is costed.

25. Please describe high level milestones and key deliverables of the Preliminary Activity (100 words)

The principal milestones for the proposed Preliminary Activity are:

1. Technical Design Report LhARA Stage 1 (TDR1) Month 15
2. LhARA laser-driven source specification Month 24
3. Standalone plasma lens early results Month 24
4. Site selection report Month 30
5. Radiobiology experiment initial results Month 36
6. Technical design review LhARA stage 2 (TDR2) Month 48

The milestones cover the major program risks in: system design (1&6), laser source performance (2) and capture lens capability (3) as well as the major decisions (4) and the key demonstration of capability (5).

26. Please complete the following table to provide a high-level costed breakdown of the different elements of the project being funded through the UKRI Infrastructure Fund.

You can delete rows as necessary.

Project Work Packages		Cost £m (to 1 decimal place)				
WP	High level description	Y1	Y2	Y3	Y4	Y5
1	Project management	0.1	0.2	0.3	0.2	0.1
2	Laser-driven proton and ion source	0.7	1.3	1.4	1.4	0.7
3	Proton and ion capture	0.6	1.1	1.1	1.1	0.5
4	Ion-acoustic dose-profile mapping	0.3	0.6	0.6	0.6	0.3
5	Novel end station development	0.3	0.6	0.7	0.7	0.3
6	Facility design and integration	0.6	0.9	0.9	0.9	1.5
7&8	Radiobiology expt & Clinician, patient, and public involvement	0.1	0.2	0.2	0.2	0.3
Total (UKRI IF contribution)		2.6	5.0	5.1	5.2	3.6

27. Please briefly describe how the Preliminary Activity will be delivered, e.g. grant to a single beneficiary / consortium, by UKRI, a combination of grant and UKRI etc. (100 words)

The resources granted by the UKRI Infrastructure Fund will be used to fund activities in the STFC Laboratory Departments ASTeC, CLF, Estates, ETC, ISIS, PPD, and TD. Grants will be issued to the institutes which are members of the LhARA/ITRF collaboration and are carrying out the research and development activities specified in the PA2 project plan. Responsibilities and deliverables will be defined though the consortium agreement will be established between STFC and the institutes that form the LhARA/ITRF collaboration by the end of July 2024.

Any other comments? [Optional]

28. Any other comments? Please use this field to include any additional information that you would wish the STFC review panels to receive (200 words)
Track-record: ITRF PA1 started in October 2022 with a budget of £2M over 2 years. The project is "green" on the STFC Project Risk register and has met all its principal milestones. Highlights of progress include: first measurements on SCAPA to benchmark 3D particle-in-cell (PIC) simulations of laser-driven proton production; detailed PIC simulations of the electron-plasma lens and initial benchmarking studies at Swansea; the design of a proof-of-principle experiment to demonstrate ion-acoustic dose-profile measurement; peer-group consultation meetings in the planned series by which the *in-vitro* and *in-vivo* end stations will be specified; development of a more flexible beam line to serve LhARA Stage 1; and initial engineering designs for the facility, building, and of the critical source and capture sections. *Net Zero:* The sustainability of the facility during construction and operation has been included in the design requirements from the start. Material choices for the shielding and the building are being discussed alongside technology choices for the accelerator facility. Key examples of technology choices that will reduce the carbon footprint of the facility in operation are the plasma lenses in the Stage 1 beam line and the fixed-field accelerator that will be used to boost the energy in Stage 2.