

a transformational approach to precision, personalised particle-beam therapy



K. Long; 3 October, 2022, on behalf of the LhARA collaboration



The challenge

- **Cancer: second most common cause of death globally**
 - Radiotherapy indicated in half of all cancer patients
- Significant growth in global demand anticipated:
- Scale-up in provision essential:
- Radiotherapy indicated in half of all cancer patients
 Significant growth in global demand anticipated:

 14.1 million new cases in 2012 ---> 24.6 million by 2030
 8.2 million cancer deaths in 2012 ---> 13.0 million by 2030

 Scale-up in provision essential:

 Projections above based on reported cases (i.e. high-income countries)
 Opportunity: save 26.9 million lives in low/middle income countries by 2035

 Provision on this scale requires:
- **Provision on this scale requires:** \bullet
 - Development of new and novel techniques ... integrated in a
 - Cost-effective system to allow a distributed network of RT facilities

The LhARA initiative

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



LhARA initiative Programme org chart



The case for radiobiology

Relative biological effectiveness: Paganetti, van Luijk **Defined relative to reference X-ray beam** (2013) 2.0 SemRadOncol Known to depend on: Tumoui Bragg peak RBE Energy 1.5 Distal Ion species Relative dose fall-off Dose 1.0 LET **Dose spatial distribution** Proton **Dose rate** energy 0.5 Vitti & Parsons (2019) Cancers Tissue type Depth in tissue Dose [Gy] **Biological endpoint** р Yet: Ne Heavier – All *p*-treatment planning uses RBE = 1.1 Effective values are used for C⁶⁺ 4 0 RBE, 3 Maximise the efficacy of PBT now & in future: Systematic programme needed to develop full understanding of radiobiology 10 20 50 100 200 500 1.000 LET (keV/um)

 \bullet

ullet

Potential benefit of new regimens

FLASH

Conventional regime: ~2 Gy/min FLASH regime (p) : >40 Gy/s

Evidence of normal-tissue sparing while tumour-kill probability is maintained: i.e. enhanced therapeutic window

Time line:

- Reports: 2014 (e.g. Flauvadon et al, STM Jul 2014)
- Confirmation in mini-pig & cat: 2018 (Clin. Cancer Research 2018)
- First treatment 2019 (Bourhis et al, Rad.Onc. Oct 2019)





Potential benefit of new regimens

Worked example: micro beams

Conventional regime: > 1 cm diameter; homogeneous Microbeam regime : < 1 mm diameter; no dose between 'doselets'



Remarkable increase of normal rat brain resistance.

[Dilmanian et al. 2006, Prezado et al., Rad. Research 2015]

Dose escalation in the tumour possible – larger tumour control probability

Radiobiology in new regimens



In combination and with chemo/immuno therapies

Imperial College

Imperial College Healthcare

INFN

The Rosalind Franklin Institute

Partners

Corerain

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ССАР

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The LhARA collaboration's present mission

Develop LhARA, serving the ITRF, to:

- Explore the vast "terra incognita" of radiation biology
- Prove the feasibility of the laser-hybrid approach
- Lay the foundations for transformative ion-beam therapy
 - Highly automated, patient-specific; implies:
 - Triggerable source
 - Online imaging
 - Integrated fast feedback and control

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LhARA performance summary	
LhARA performance summary utw.2006.00431 12 MeV Protons 15 MeV Protons 127 MeV Protons 33.4 MeV/u Carbon	
Interformance summary Interformance summary	
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Laser-hybrid Accelerator for Radiobiological Applications

A novel, hybrid, approach:

- 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
 - Strong focusing (short focal length) without the use of high-field solenoid
- Fast, flexible, fixed-field post acceleration
 - Variable energy
 - Protons: 15-127 MeV
 - Ions: 5—34 MeV/u

LhARA Project Organisational Breakdown Structure





Schwoerer, H. et al., 2006; Nature, 439(7075).



Sheath acceleration
Laser incident on foil target:

Drives electrons from material
Creates enormous electric field

• Field accelerates protons/ions - Dependent on nature of target

Active development:

- Laser: power and rep. rate

Target material, transport

Laser-driven beams for rbio: example 1

<u>On Draco @ HZDR</u>

DOI: 10.1038/s41598-020-65775-7

- Draco:
 - Petawatt laser
 - E = 13 J, $\tau = 30 fs$, $3 \mu m$ FWHM
- Beam line:
 - Target Normal Sheath Acceleration (TNSA)

E 45

eter 40

diam 35

36am

- Pulsed solenoid focusing
 - 19.5T, 2 or 3 pulses/min.
 - S1, S2: 40 mm bore
 - Half angle acceptance 14°
- Measured transmission (18.6 MeV p)
 - 50.6% (dual solenoid)
 - 28.6% (single solenoid)



Laser-driven beams for rbio: example 2

<u>On BELLA @ Berkeley</u>

DOI 10.1038/s41598-022-05181-3

- Berkeley Lab Laser Accelerator (BELLA):
 - Petawatt laser
 - E = 35 J, $\tau = 35 fs$, 52 μm FWHM
- Beam line:
 - Target Normal Sheath Acceleration (TNSA)
 - Active plasma lens focusing
 - 1 mm diameter Ar gas filled capillary
 - 33 mm length
 - 13 mm behind the tape drive target
 - ~0.2% transport efficiency for protons with E > 1.5 MeV



Laser-driven proton/ion source

- Commercial laser:
 - Motivation: risk management



LhARA Capture

 "Electron-plasma" (Gabor) lens:
 Strong focusing exploiting electron gas in "Penning/Malmberg" trap







MQPI

Article Anomalous Beam Transport through Gabor (Plasma) Lens Prototype

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Abstract: An electron plasma lens is a cost-effective, compact, strong-focusing element that can ensure efficient capture of low-energy proton and ion beams from laser-driven sources. A Gabor lens prototype was built for high electron density operation at Imperial College London. The parameters of the stable operation regime of the lens and its performance during a beam test with 14 MeV protons are reported here. Narrow pencil beams were imaged on a scinilitator screen \mathcal{S} can downstream of the lens. The lens converted the pencil beams into rings that show position-dependent shape and intensity modulation that are dependent on the settings of the lens. Characterisation of the focusing effect suggests that the plasma column exhibited an off-axis rotation similar to the m = 1 diocotron instability. The association of the instability with the cause of the rings was investigated using particle tracking simulations.

Keywords: plasma trap; space-charge lens; beam transport; instability; proton therapy

1. Introduction

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Whyte, C. Anomalous Beam Transport through Gabor (Plasma) Lens Prototype. Appl. Sci. 2021, 17, 4357. https://doi.org/10.3390/ app11104357

Dascalu, T.S.; Bingham, R.; Cheung, C.L.; Lau, H.T.; Long, K.; Pozimski, L;

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One of the principal challenges that must be addressed to deliver high-flux pulsed proton or positive-ion beams for many applications is the efficient capture of the ions ejected from the source. A typical source produces protons with kinetic energies of approximately 60 keV [1–3] and ions with kinetic energies of approximately fraction of this divergent flux therefore requires a focusing element of short focal length. Proton - and ion-capture systems in use today employ magnetic, electrostatic, or radio frequency quadrupoles, or solenoid magnets to capture and focus the beam [26-81].

Laser-driven proton and ion sources are disruptive technologies that offer enormous potential to serve future high-flux, pulsed beam facilities [9–16]. Possible applications include proton- and ion-beam production for research, particle-beam therapy, radio-nuclide production, and ion implantation. Recent measurements have demonstrated the laser-driven production of large in fluxes at kinetic energies in excess of 10 MeV [17–20]. The further development of present technologies and the introduction for onvel techniques [21,22] makes it conceivable that significantly higher ion energies will be produced in the furure [13,25,24]. By capturing the laser-driven ions at energies two orders of magnitude greater than those pertaining to conventional sources, it will be possible to evade the current space-charge limit on the instantaneous proton and ion flux that can be delivered. While in some situations the high divergence of laser-driven ions have a to delive (22,26), for the tape-drive targets proposed for medical beams [16,20] it necessary to capture the beam using a strong-focusing element as close to the ion-production point as possible.



Beam envelopes Stage 1



- Propagation of "semi-realistic" source distribution:
 - Generated using SMILEI
 - Optimisation studies on going

Rapid, flexible acceleration for stage 2

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0.2 0.4 0.6 0.8 1 1.2 1.4 1.6

s [m]

- Fixed-field alternating-gradient accelerator (FFA):
 - Invented in 1950s
 - Kolomensky, Okhawa, Symon
 - Compact, flexible solution:
 - Multiple ion species
 - Variable energy extraction
 - High repetition rate (rapid acceleration)
 - Large acceptance
 - Successfully demonstrated:
 - Proof of principle at KEK
 - Machines at KURNS
 - Non-scaling PofP EMMA (DL)



-20 -25___

-10

-5

x [mm

-15

10

15



LhARA @ the Ion Therapy Research Facility



Access In Vivo End Rack Room 3 Station Control Water chiller Water chiller Room Fixed Field Accelerator In Vivo End Assembly Station Area 6 Area 5 High Energy Line & Cleanroom 32m 4.25m Area 4 Water Lift ater Plan Tank Acc. Room Target Laser Room Low Energy Line Control Heat Room 11 Outside Room Exchanger Pumps pen Areal Area 2 Area 3 N Area 1 Switchboard Meeting Fenced Area RF Room Transformer Room Rack Room Office Access 57m 15m N. Bliss (DL) **Ďraft** 72m Draft N. Bliss (DL) 45° Dipole Magnets (2) Quadrupole Magnets (6 Dipole Switching Magnet to FFA Octopole Magnets (2) RF Cavities (2) Gabor lenses (5) Target Chamber Abort line Beam Dumr Compressor Chamber 100 TW Laser Support & Alignment modules 1 California N. Bliss (DL) Draft

Proposal for LhARA contributions to Preliminary Activity and ITRF Preconstruction Phase



Finalised 01Jun22: <u>CCAP-TN-10</u>



The Laser-hybrid Accelerator for Radiobiological Applications R&D proposal for the preliminary, pre-construction phases

The LhARA collaboration

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Requested resources for 2-year preliminary phase; Identified need for further 3-year preconstruction phase

Preliminary & Preconstruction Phase proposal summary

ITRF timeline submitted to IAC, 15Jun21																								
	202	2	2	2023		2024		2025	5	202	6	202	27	2	028	2	2029		2030		203	1		
	Q2 (Q3 Q4 (Q1 Q	Q2 Q3	Q4 Q1	Q2 Q3	Q4 Q1	Q2 Q	Q3 Q4 C	Q1 Q2	Q3 Q4 Q	1 Q2	Q3 Q4	Q1 Q	2 Q3 Q4	Q1 0	Q2 Q3 (Q4 Q1	Q2 Q3	Q4 C	1 Q2	Q3 Q4	Q1	
Preliminary Activity (PA)							L.L.		بالسال	İ						İ		İ	<u> </u>	1.1				
Preconstruction programme																								
Facility construction					J		Įį				Stage	e 1					Stag	ge 2						
Facility exploitation																								
hARA Preliminary Activity and Pre-construction Phase: principal milestones																								
				LhA	ARA <mark>CDR</mark>																			
						Sta	ge 1 <mark>TDR</mark>																	
											Stage 2 <mark>TD</mark>	R												
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VP1: Project Management																								
LhARA CDR status updat	e																							
LhARA CD	R																							
	.1										_													
LhARA TDR	.2									_														
NP2: Laser-driven source																								
One-to-one simulation of proton source design	n					+				+		-												
Experimental demonstration of low repetition LhARA specification proton source	e																							
Experimentally motivated specification of LhARA lase	er																							
Experimental generation of stabilised 5 Hz bear	m																							
WP3: Proton and ion capture																								
Validation of Plasma simulation against Swansea Exp	t.				_)r	oli	m	in		rv	Λ	rti	vi
Next generation plasma lens testbench desig	;n						_													u	y	A		VI
Progress report - standalone plasma apparatu	JS										_						_		_	_	_			_
Ion focussing results and final plasma lens desig	'n														Wİ	н	st	ar	't (Da	:†(b	er	2
MPA: Ion acoustic doce manning	_															•••								
Preliminary Geant4 simulation	26											_		-										
Acoustic sensor array desir	'n																							
Preliminary report on reconstruction method	ds																							
LhARA ion acoustic test resul	ts																							
WP5: End-station development		_																						
Initial end station input	ts				_																			
End station desig	n									_														
Beam monitoring specificatio	in .										_													
End station and beam monitoring resul	ίS							-		_														
NDC: Eacility docian and integration	-																							
Interim report on design and integration LhADA COL						+						-												
Design and integration, LIARA CD	R																							
Design and integration, LIARA CD	1							-				-												
Design and integration hAPA TDP	22																							

Novel accelerator techniques







System: image processing fast feedback, control



62.4 MeV Protons (0.5% Energy spread) Measurements Corrected to PureWater

Fundamental biology & biochemistry



Conclusions

- Laser-driven sources are disruptive technologies ...
 - With the potential to drive a step-change in clinical capability
- Laser-hybrid approach has potential to:
 - Overcome dose-rate limitations of present PBT sources
 - Deliver uniquely flexible facility:
 - Range of: ion species; energy; dose; dose-rate; time; and spatial distribution
 - Be used in automated, triggerable system → reduce requirement for large gantry
 - Disruptive/transformative approach to "distributed PBT for 2050"
- By serving the ITRF, the LhARA collaboration now seeks to:
 - Prove the novel laser-hybrid systems in operation
 - Contribute to the study of the biophysics of charged-particle beams
 - Enhance treatment planning
 - Create novel capabilities to 'spin back in' to science and innovation







Hadron beams for radiation therapy



Robert R. Wilson



- Wilson, then at Harvard designing 150 MeV cyclotron:
 - Identified benefits and properties of proton beams for RT
 - Pointed out potential of ions (carbon) and electrons

Particle beam therapy today

Cyclotron based



Synchrotron based



Christie Hospital Manchester



Evolving state of the art



Many initiatives in Americas, Europe, Asia

Applications in biological research, ambition to push toward clinical application ...

Phys Lett A. (2002) 299:240-7. doi: 10.1016/S0375-9601(02)00521-2 Med Phys. (2003) 30:1660-70. doi: 10.1118/1.1586268 Med Phys. (2004) 31:1587-92. doi: 10.1118/1.1747751 Science. (2003) 300:1107-111 New J Phys. (2010) 12:85003. doi: 10.1088/1367-2630/12/8/085003 Phys Med Biol. (2011) 56:6969-82. doi: 10.1088/0031-9155/56/21/013 Appl Phys Lett. (2011) 98:053701. doi: 10.1063/1.3551623 Appl Phys Lett. (2012) 101:243701. doi: 10.1063/1.4769372 AIP Adv. (2012) 2:011209. doi: 10.1063/1.3699063 Appl Phys B. (2013) 110:437-44. doi: 10.1007/s00340-012-5275-3 Appl Phys B. (2014) 117:41-52. doi: 10.1007/s00340-014-5796-z Radiat Res. (2014) 181:177-83. doi: 10.1667/RR13464.1 Phys Rev Acceler Beams. (2017) 20:1–10. doi: 10.1103/PhysRevAccelBeams.20.032801 J Instrum. (2017) 12:C03084. doi: 10.1088/1748-0221/12/03/C03084 A-SAIL Project. (2020). Available online at: https://www.qub.ac.uk/research-centres/A-SAILProject/ Vol. 8779. Prague: International Society for Optics and Photonics. SPIE (2013). p. 216–25. Vol. 11036. International Society for Optics and Photonics. SPIE (2019). p. 93–103. Nuovo Cim C. (2020) 43:15. doi: 10.1393/ncc/i2020-20015-6 10th International Particle Accelerator Conference. Melbourne, VIC (2019). p. TUPTS005

I will not attempt a review, choosing instead to focus on opportunity

Variety of initiatives; some key examples

On PHELIX @ GSI

DOI: 10.1063/1.3299391 DOI: 10.1103/PhysRevSTAB.14.121301 DOI: 10.1103/PhysRevSTAB.16.101302 DOI: 10.1103/PhysRevSTAB.17.031302 NIMA 909 (2018) 173-176

- **PHELIX:** \mathbf{O}
 - Petawatt High-Energy Laser for Heavy **Ion EXperiments**
 - $E < 25 J, \tau = 500 fs, I > 10^{19} J/cm^2$
- LIGHT:
 - Target Normal Sheath Acceleration (TNSA)
 - Ion beam is collimated by a pulsed highfield solenoid
 - Phase rotation in RF cavity
 - Final focus with a second pulsed highfield solenoid

Capture



https://www.gsi.de/work/forschung/appamml/plasmaphysikphelix/experimente/light



Variety of initiatives; some key examples

On CLAPA @ Peking University

DOI: 10.1103/PhysRevAccelBeams.22.061302 DOI: 10.1103/PhysRevAccelBeams.23.121304

- Compact Laser Plasma Accelerator (CLAPA):
 - Petawatt laser
 - E = 1.3 J, τ = 30 fs, 5 μ m FWHM
- Beam line:
 - Target Normal Sheath Acceleration (TNSA)
 - Quadrupole triplet focusing

TABLE I. The CLAPA beam line parameters.											
Туре	Length	Aperture	Max B	# turns	Current						
Q1	100 mm	30 mm	5 KGs/cm	16	300 A						
Q2	200 mm	64 mm	2.5 KGs/cm	20	540 A						
O3	100 mm	64 mm	2.5 KGs/cm	20	540 A						

- Measured transmission:
 - 88% transmission through triplet
 - ±50 mrad collection angle @ 5 MeV









Extreme Light Infrastructure, Prague, Czech Republic:

- ELI Multidisciplinary Applications of laser-Ion Acceleration (ELIMAIA)
 - ELI MEDical and multidisciplinary applications (ELIMED)
 - ELIMAIA section dedicated to ion focusing, selection, characterization, and irradiation
 - Proton energies from 5 to 250 MeV transported to in-air section

ELIMAIA-ELIMED

Quantum Beam Sci. 2018, 2, 8; doi:10.3390/qubs2020008 Frontiers in Phys. Med. Phys. & Imag. – doi: 10.3389/fphy.2020.564907



