



Lecture 21

#### Laser-hybrid Accelerator for Radiobiological Applications (LhARA)

#### **JAI Student Design Project 2023-2024**

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Accelerator Physics Graduate Course John Adams Institute for Accelerator Science 22 November 2023

Perspectives on laser-driven sources for particle beam therapy

#### **CHALLENGES AND OPPORTUNITIES**

# Radiotherapy; the challenge

- Cancer: second most common cause of death globally
  - 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:
  - Development of new and novel techniques ... integrated in a
  - Cost-effective system to allow a distributed network of RT facilities

# The benefit of particles

- Maximise therapeutic benefit by:
  - Maximising damage to tumour
  - Minimising damage to healthy tissue



- X-ray therapy:
  - Modality used in most radiotherapy
  - Dose falls exponentially with depth
  - Proximity of sensitive organs limits dose to tumour



#### **Particle-beam therapy**



#### Proton and ion-beam therapy:

- Bulk of dose deposited in Bragg peak
- Significant normal-tissue sparing (entry)
- Almost no dose beyond the Bragg peak

## The need for a step-change in capability

- Growing recognition of benefits of PBT worldwide:
  - 70 PBT centres in operation;
     40 under construction
- 'Incremental' development of technique
  - Existing suppliers
  - New initiatives



#### Exciting indications of benefits of novel beams ...

## Particle beam therapy today

#### Cyclotron based



Synchrotron based



#### **Christie Hospital Manchester**



# **Beam delivery**



#### **PSI** gantry

- Engineering tour de force!
- 360-degree irradiation
- At a price:Size, complexity, maintenance

#### The Typical Ion Source

Every ion source basically consists of two parts:

1. Ion production inside a plasma

2. Beam extraction from the plasma

# **Particle source**



- Limited by extraction voltage
- Instantaneous flux (current or dose):
  - Determined by acceptance of first accelerator structure

S. Laurie

Limited by mutual repulsion of protons (ions) ... "space-charge effect"

# The technological challenge

- Cancer is the second leading cause of death globally (WHO)
   Radiotherapy indicated in half of all cancer patients
- Growing requirement for radiotherapy:
  - High-income countries: anticipate significant growth in demand
  - Low/middle income countries; enormous unmet need:
    - Opportunity to save ~30 million lives by 2035
- Scale-up in provision essential:
  - Requires:
    - Development of new and novel techniques ... integrated in a
    - Cost-effective system to allow a distributed network of RT facilities

The Laser-hybrid Accelerator for Radiobiological Applications (LhARA)

## RADIOBIOLOGY



# The case for fundamental radiobiology

Relative dose

- 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





# Biological impact from the physics of ionisation

- **Low-LET radiation:** 
  - *Repairable* single/double strand breaks
- High-LET radiation:
  - Complex DNA lesions
    - Multiple DNA pathways
    - More difficult to repair
    - Enhances cell death



Control

0

Hours post-IR

- Programmatic approach:
  - Dynamic studies of impact of radiation
  - Interpret with advanced computer models (e.g. G4DNA)

### A complex, multi-facetted problem



# **Radiobiology in new regimens**

#### Worked example: FLASH

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

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

#### Time line:

- Initial 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)





Prezado; 13Nov19

## **Radiobiology in new regimens**

#### Worked example: micro beams

Conventional regime: > 1 cm diameter; homogeous 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 tumor control prob.

### Laser-driven sources are disruptive

I will argue that laser-driven sources have the potential to:

- Create the capability to deliver particle-beam therapy in completely new regimens
  - Flexibility!
    - Combine a variety of ion species in a single treatment fraction, exploiting ultra-high dose rates in novel spatial- and spectral-fractionation schemes
- Make "best in class" treatments available to the many
  - Automated, triggerable system  $\rightarrow$  remove requirement for large gantry:
    - System incorporating dose-deposition imaging in fast feedback-and-control system; track movement, deliver dose at optimum tissue alignment

# THE IN-PRINCIPLE ADVANTAGE OF THE LASER-DRIVEN SOURCE

Perspectives on laser-driven sources for particle beam therapy



 $\bullet$ 

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

## Advances

(2018)9:724 DOI: 10.1038/s41467-018-03063-9





- Ultrathin foil irradiated by "long", linearly-polarised laser pulse
- **Mechanism:**  $\bullet$ 
  - Radiation-pressure/target-normal sheath acceleration
  - High-energies confined to narrow angular range by radiation-induced transparency

# Advantages

- Protons (and ions) produced at "high energy":
  - e.g. 15 MeV  $\rightarrow$  250 times energy of conventional proton source
    - High energy substantially reduced impact of space charge
      - Allows evasion of instantaneous dose-rate limitation of today's sources
- Pulsed operation "natural":
  - Discharge sources are DC; accelerator imposes time structure
  - Pulsed operation determined by laser:
    - A triggerable, "on demand", source
- Critical issues:
  - Efficient capture of divergent, high-energy ion flux
  - Transformation of captured flux into useful beam



**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





## 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 ...

## **Opportunity; a hybrid approach**

- Create protons (ions) at "modest" energy:
   Consider 10–15 MeV; high flux, "plateau" region
- Capture and manipulate proton (ion) flux:

Inject into post accelerator for biomedical application



High Energy Density Physics 37 (2020) 100847

#### Laser-hybrid Accelerator for Radiobiological Applicatons

• Vision:

LhARA will be a uniquely-flexible, novel system that will:

- Deliver a systematic and definitive radiobiology programme
- Prove the feasibility of the laser-driven hybrid-accelerator approach
- Lay the technological foundations for the transformation of PBT
  - automated, patient-specific: implies online imaging & fast feedback and control
- Ambition:
  - Develop:

necessary techniques, technologies, and systems

- Exploit:

system approach to novel bring techniques into clinical practice as they mature

– Integrate:

production prototypes in a production system for radiobiological research

– Engage:

industry and clinical PBT centres

during development of techniques, technologies, and systems





#### Perspectives on laser-driven sources for particle beam therapy



#### Laser-hybrid Accelerator for Radiobiological Applications

#### <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
  - 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: 5—34 MeV/u

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Edited by Saplanza University of Rome, Italy Reviewed by: Lorenzo Meri Investiv of Naples Federico II. Itely

Gluseppe A. Pablo Cirrone, aboratori Nazionali del Sud (NFN), Italy \*Correspondence: Ait Kuna a.kurup@imperial.ac.uk <sup>†</sup>Present address

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Samey, Landan, United Kingdom, <sup>19</sup> STFC Daresbury Laboratory, Liverpool, United Kingdom, <sup>10</sup> Leo Cancer Care, London, United Kingdom, <sup>10</sup> Corealn Technologies, Shenzhen, China Erontiare in Otucir The "Laser-hybrid Accelerator for Radiobiological Applications," LhARA, is conceived

as a novel, flexible facility dedicated to the study of radiobiology. The technologies demonstrated in LhARA, which have wide application, will be developed to allow particle beam therapy to be delivered in a new regimen, combining a variety of ion Citation: species in a single treatment fraction and exploiting ultra-high dose rates. LhARA will be a hybrid accelerator system in which laser interactions drive the creation of a large flux of protons or light ions that are captured using a plasma (Gabor) lens and formed into a beam. The laser-driven source allows protons and ions to be captured at energies significantly above those that pertain in conventional facilities, thus evading the current space-charge limit on the instantaneous dose rate that can be delivered. The laser-hybrid approach, therefore, will allow the radiobiology that determines the

response of tissue to ionizing radiation to be studied with protons and light ions using a wide variety of time structures, spectral distributions, and spatial configurations at instantaneous dose rates up to and significantly beyond the ultra-high dose-rate "FLASH" regime. It is proposed that LhARA be developed in two stages. In the first stage, a programme of in vitro radiobiology will be served with proton beams with energies between 10 and 15 MeV. In stage two, the beam will be accelerated using a fixed-field

(LhARA) Conceptual Design Repor

#### The LhARA collaboration

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# Laser-driven proton/ion source

- Advantage:
  - Enormous proton/ion flux at 10—15MeV in tiny (30 fs) pulse at 10 Hz



- Requirement:
  - Efficient capture, focusing, selection and manipulation of divergent ion beam



#### Posocco, Pozimski

# Beam capture/production principle

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







MDPI

#### Article Anomalous Beam Transport through Gabor (Plasma) Lens Prototype

Toby Nonnenmacher <sup>1,\*</sup>, Titus-Stefan Dascalu <sup>1,\*</sup>, Robert Bingham <sup>2,3</sup>, Chung Lim Cheung <sup>1</sup>, Hin-Tung Lau <sup>1</sup>, Ken Long <sup>3,4</sup>, Jürgen Pozimski <sup>3,4</sup> and Colin Whyte <sup>2</sup>

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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 1.4 MeV protons are reported here. Narrow pencil beams were imaged on a scintillator screen 67 cm 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 = 1diocotron 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

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Transport through Gabor (Plasma) Lens Prototype. Appl. Sci. 2021, 11, 4357. https://doi.org/10.3390/ app11104357

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1. Introduction 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 typically below 120 keV [4,5]. At this low energy the mutual repulsion of the ions causes the beam to diverge rapidly. Capturing a large 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 [2,6-8].

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 laserdriven production of large ion fluxes at kinetic energies in excess of 10 MeV [17-20]. The further development of present technologies and the introduction of novel techniques [21,22] makes it conceivable that significantly higher ion energies will be produced in the future [13,23,24]. 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 ion beams can be reduced [25,26], 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.



#### **Energy collimation**

#### LhARA Stage 1 beamline





**±2**%

- + Flat initial energy profile 15  $MeV\pm15\%$
- 3 collimators
  - **1.** Energy collimation (at beam focus, controls energy spread)
  - 2. Beam shaping
  - 3. Momentum cleaning (removes energy tails)



#### Beam Size Evolution Comparison



- Ideal beam simulation repeated but included nozzle and other collimators.
- Space charge effects included for both beams.
- For energies 14.7 < KE < 15.3 MeV



## LhARA – Stage 2

- In-vitro radiobiology using animal models:
  - Post-acceleration required
- Baseline:fixed field accelerator:
  - x3 increase in momentum
    - 15 MeV protons accelerated to 127 MeV
    - 3.8 MeV/u carbon 6+ ions accelerated to 33 MeV/u



## **Fixed Field Accelerator**

- Bending magnetic fields do not vary in time.
  - Rapid acceleration.
- Alternating gradient gives strong focussing.
- Very large acceptance.
  - Useful, e.g. to accelerate muon beams.



- Advantages over conventional medical cyclotron
  - Variable energy operation without energy degraders
  - Operation with different ions
  - Multiple extraction ports

# **FFA potted history**

- Early 1950s, FFAG developed independently:
  - Japan by Tihiro Ohkawa
  - US by Keith Symon
  - Russia by Andrei Kolomensky.
- The first prototype was operated in 1956
  - Jones, Terwilliger, Technical Report MURA-LWJ/KMT-5 (MURA-104), April 3, 1956.



The Michigan Mark I FFA 400KeV electron accelerator Not much activity until first proton accelerator in 2000 the first operational FFA.



500 keV Proton proofof-principle FFA at KEK.



Kyoto University FFA for **ADSR** 



**PRISM muon beam** phase rotation demonstration ring at Osaka.



**EMMA at Daresbury** 

# Rapid, flexible acceleration for stage 2

Ē

0.2 0.4 0.6 0.8 1

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 pop, EMMA, at DL



0.25

1.2 1.4 1.6



#### FFA for acceleration in LhARA – Stage 2

- Baseline: x3 increase in momentum
  - 15 MeV protons accelerated to 127 MeV
  - 3.8 MeV/u carbon 6+ ions accelerated to 34 MeV/u





#### LhARA performance: doses and dose rates

LhARA performance summary				<u>arXiv:2006.00493</u>
	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	$1.0  imes 10^9$ Gy/s	$1.8 imes10^9\mathrm{Gy/s}$	$3.8 imes10^8{ m Gy/s}$	$9.7 imes10^8\mathrm{Gy/s}$
Average dose rate	71 Gy/s	128 Gy/s	156 Gy/s	730 Gy/s

Perspectives on laser-driven sources for particle beam therapy

#### CONCLUSIONS

# 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"
- 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





# Acknowledgements





#### **JAI Training**





#### **Foundation of the JAI Programme**





#### **Accelerator Design Project**

- Accelerator Design Study for
  - Electron SPS: 2020-2021
  - FCC-ee Booster Ring: 2021-2022
  - FCC-ee Positron Damping Ring: 2022-2023
  - Design work consisted of study of the lattice, magnet systems and RF cavities.

"The design project significantly contributes to the value of a PhD at the JAI and is a very effective learning tool ... it played an essential role in helping me to find a postdoc."

"To me, the design project was by far the best part of the course. It puts the material taught into context and bridges the gap between lectures ... and a DPhil project ... ."



Accelerator Design Studies for the FCCee Positron Damping Ring and Transfer Line

John Adams Institute Student Design Project 2023





FCC-ee Positron Damping Ring Design Report published on CDS (10.17181/CERN.E06E.3CHI)

Students delivered JAI Seminar on 9 March 2023.



Student Poster at FCC Week, London June 2023







#### **Studies for Stage 1**

- Gabor Lens
  - Study particle production/focusing from source
- Optics Studies
  - Optimisation of lattice (phase space, final focusing for beam spot)
- Magnet Design
  - Optimise dipole and quadrupole magnets (sustainable designs).
- RF System
  - Design of RF system.

Many thanks to Prof. Ken Long / Imperial College London for the slides on LhARA.

London

OXFORD

