National Cancer Institute

Joint DCB / DCTD concept proposal:

Defining High-LET Radiation Molecular and Cellular Damage and Responses Relevant to Oncology

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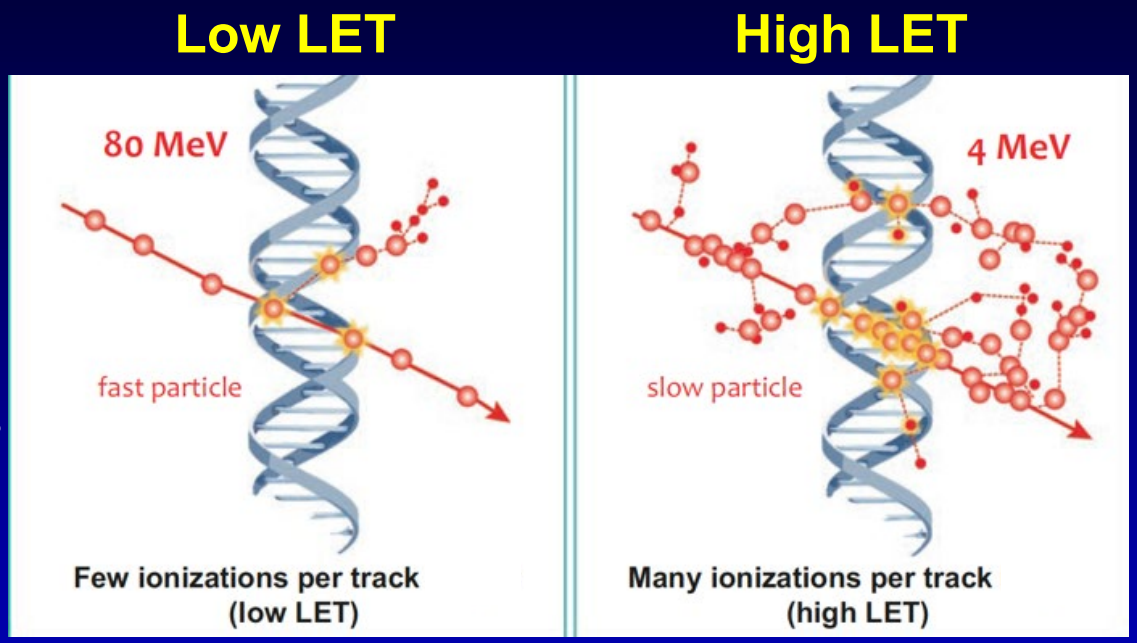
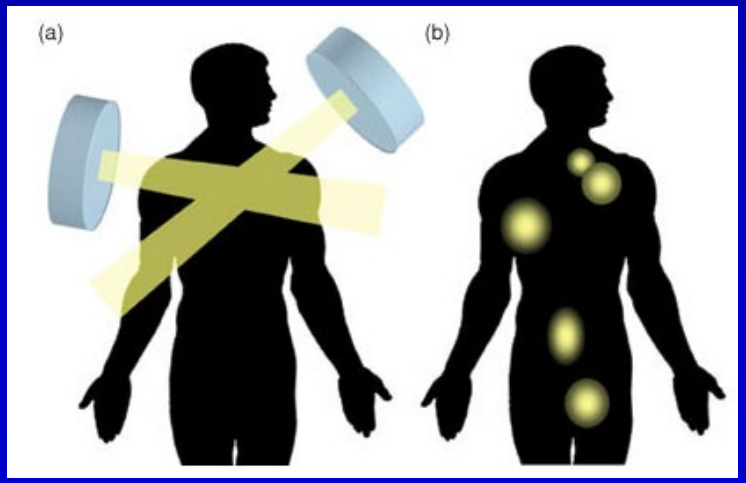
High Linear Energy Transfer (LET) Radiation

- High Relative Biological Effectiveness (RBE)
- More therapeutically effective in some cases
- More damaging to DNA and other macromolecules or cellular components
- Less impact of hypoxia



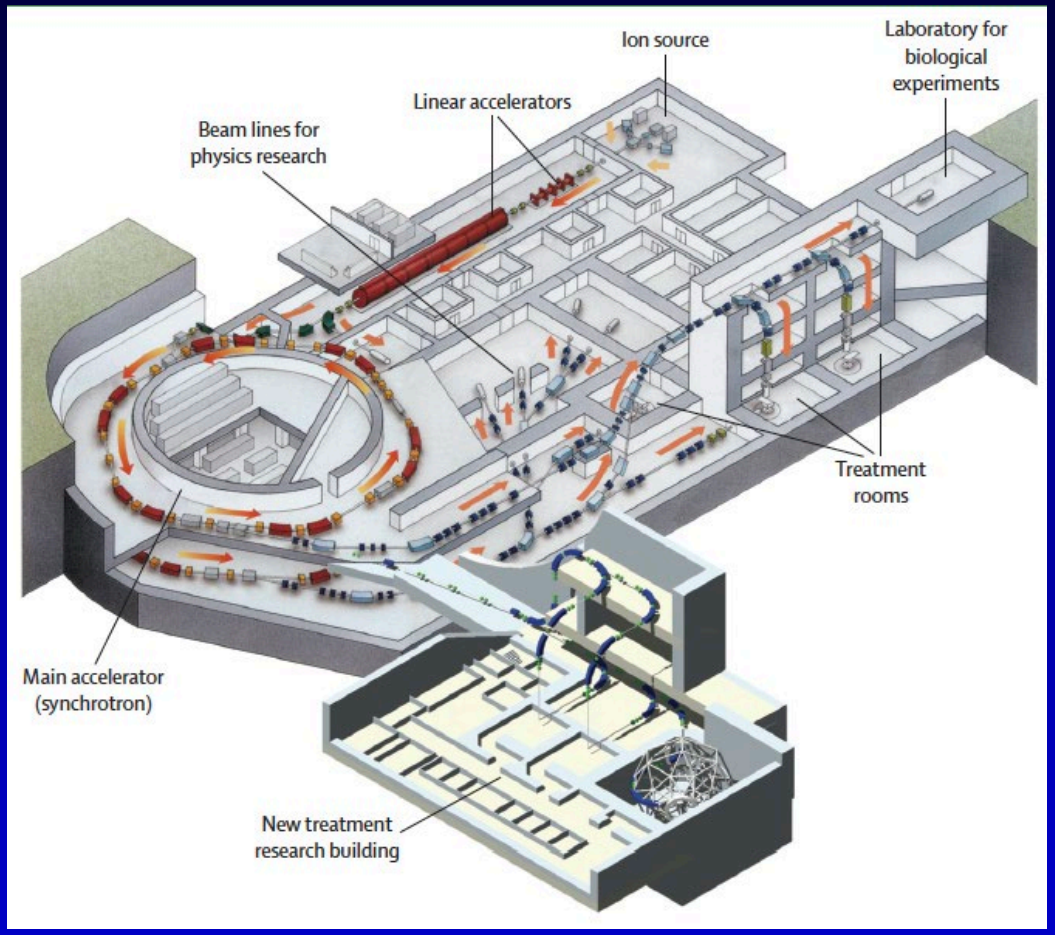


- Precise targeting to tumors
- Can be delivered by external sources or systemic radionucleotide therapy.
- In US only systemic radionucleotide therapy is available

Justification for Concept Proposal:

- Interest in High LET radiation for therapy (both targeted and systemic) is growing rapidly.
- The infrastructure for clinical particle therapy centers is costly and the justification for developing these centers needs to be based on firm scientific evidence of their utility.
- There are significant unanswered questions about the basic characteristics of the molecular damage caused by high LET radiation, its repair, and the cellular responses to this damage.
- Better understanding of the basic biology of high LET radiation is essential to inform future decisions regarding its application to cancer treatment

Barrier 1: Requirement for specialized external beam facilities



HIMAC Chiba, Japan
Carbon ion treatment

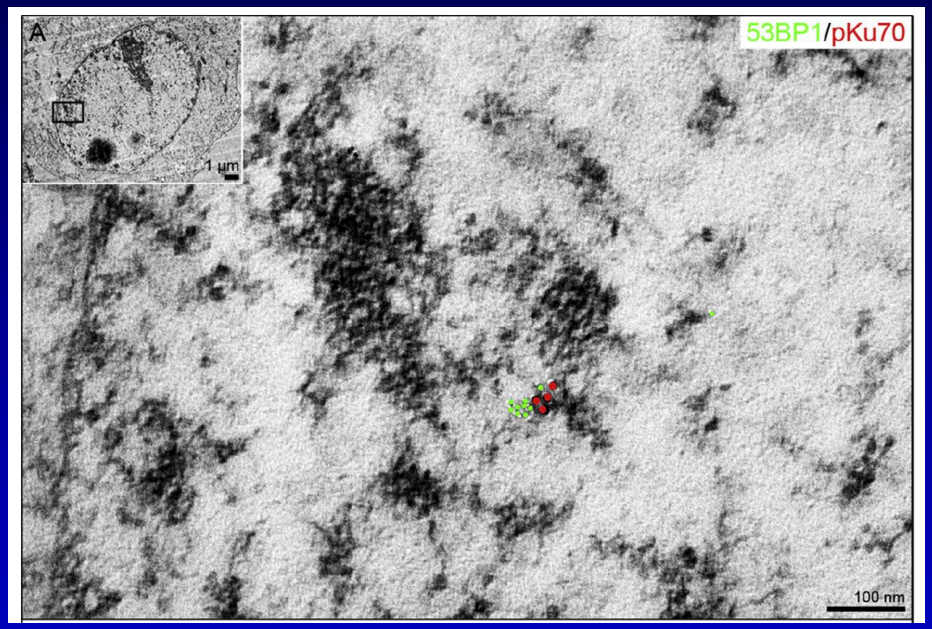
11 clinical sites (4 in Europe and 7 in Asia) none in the US

Barrier 2: Lack of understanding of how human cancer cells respond to therapeutic levels of high LET radiation

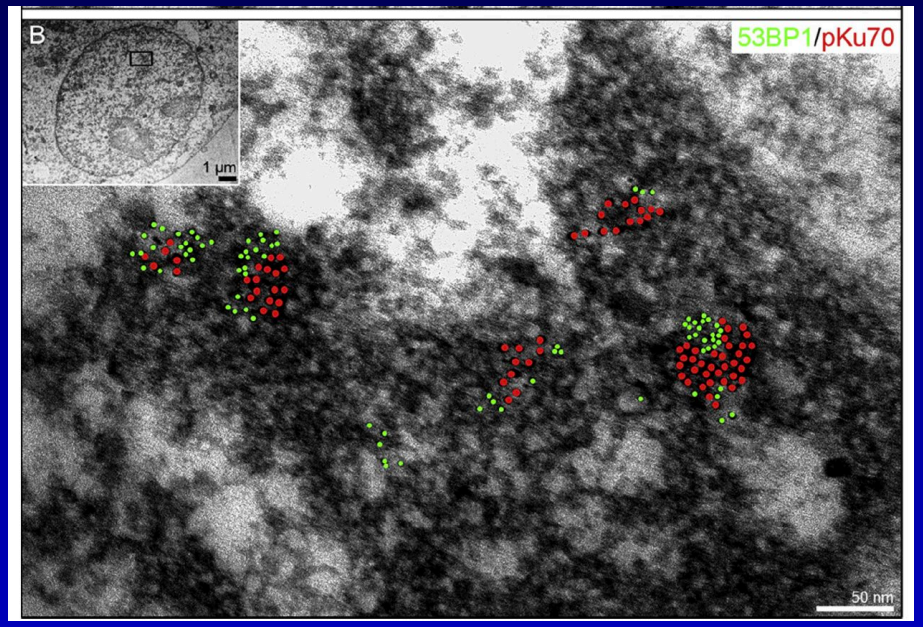
- How do tissues, cells, organelles, and macromolecules respond?
- Are there differences in tumor vs normal tissue?
- Are different DNA repair pathways activated under high LET?
- How are cell stress, death, and survival pathways impacted?
- What is the impact on innate immunity?
- What is the effect on the tumor immune microenvironment?
- Is there a different neoantigen spectrum?
- How can high LET and its effects be exploited for cancer therapy?

Example: DNA damage after high LET radiation

24 hours post low LET photon treatment



24 hours post high LET ion treatment



Y. Lorat et al. DNA Repair 28 (2015) 93–106

Residual 53BP1 and pKu70 Foci

- High-LET signature: Clustered DNA damage and chromosome breaks
- Evidence for biphasic DNA repair
- Different DNA repair pathways activated
- Link to G2/M checkpoint decay and mitotic replication

Workshops and Extramural input:

RFI: NOT CA-16-011
Input on a Particle Beam Facility for Radiotherapy-Related Cancer Research

WORKSHOPS:

- **Workshop on charged particle radiobiology (April 2016)**
- **Mechanistic links between the DNA-damage response network & immunogenic toxicity in transformed cells (August 2017)**
- **Utilizing the Biological Consequences of Radiotherapy in the Development of New Treatment Approaches (September 2017)**
- **Immunobiology of radiotherapy (June 2017)**
- **Workshops on Targeted Radionuclide Therapy (Nov. 2016 and April 2018)**

Research topics of interest

Chemistry of high LET damage to DNA, proteins and lipids
Macromolecular damage
Simulation of damage propagation

Biology of high LET DNA damage repair response
Recognition and processing of DNA damage induced by High LET irradiation
Targeting DNA repair pathways after high-LET irradiation
Impact on cell-innate immunity (e.g., cGAS Sting pathway)

Impact of high LET radiation on tumor vs normal tissues
Cancer cell stress responses
Inter- and intra-cellular damage signaling
Mitochondrial effects / Cell death pathways.

Impact of high LET radiation on immune response
Neoantigen shift
Immune microenvironment (TiME)

- Proposals must show relevance to cancer therapy and include study of particles from Helium to Carbon

NIH Portfolio (FY16-present):

Over 80 applications on or related to this topic NIH-wide.
The majority have been studying targeted radionuclide therapy (59 applications, 12 funded)

Fourteen applications studied various aspects of high LET beams that closely align to this FOA, including particle beam modelling and DNA damage repair. Of these three were funded.

In addition: Two planning grants (P20) were awarded and have been completed and a contract to compare Carbon to photon irradiation is being carried out through Einstein University in a Carbon facility in Shanghai.

None of the funded applications dealt with the underlying mechanisms of high LET-induced cell death or mechanisms of resistance in irradiated cells.

Concept Proposal FOA:

Request for Applications (RFA):

-Need for expertise in particle beam radiation, radiation chemistry, DNA damage repair and cell biology

-Need for SRO/ Program coordination and reviewer orientation to programmatic goals

-Special review criteria

-Propose review by NCI DEA

R01 and R21 applications eligible

Multi-PI requirement with clinician or clinical physicist / basic scientist collaboration

Foreign components encouraged

Anticipated Budget and Awards and Timeline:

Standard receipt dates, 3 per year

Anticipate funding 5 R01 and 2 R21's each year for 3 years

Budget estimated at $2.4M direct costs $3.84M total costs per year for new awards

The term of the FOA (2019-2021) will result in a maximum estimated total project cost of $31.65 M over 8 years.

Timeline:

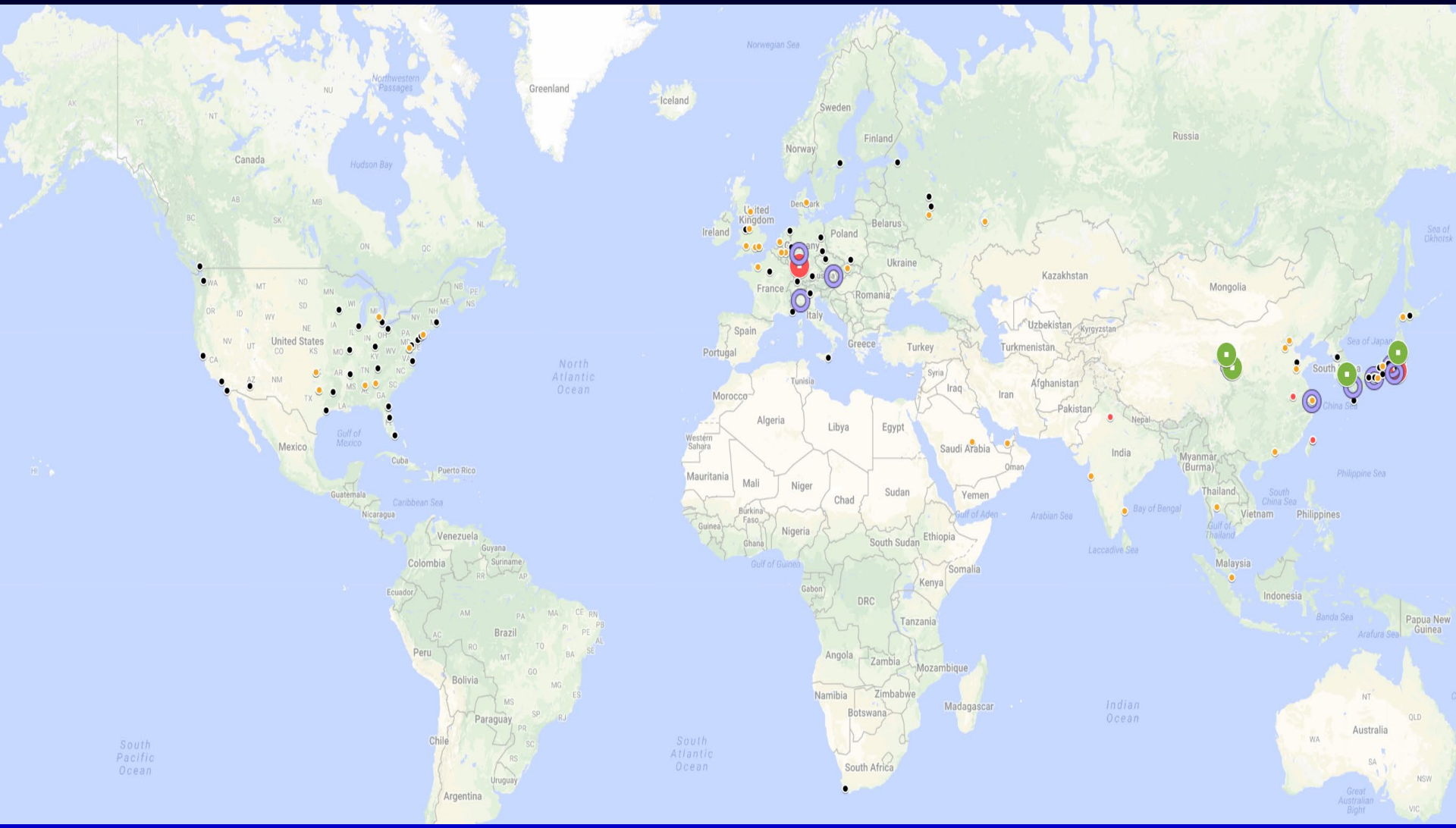
FOA to open 2019 and run through 2021

Anticipated first applications Fall 2019

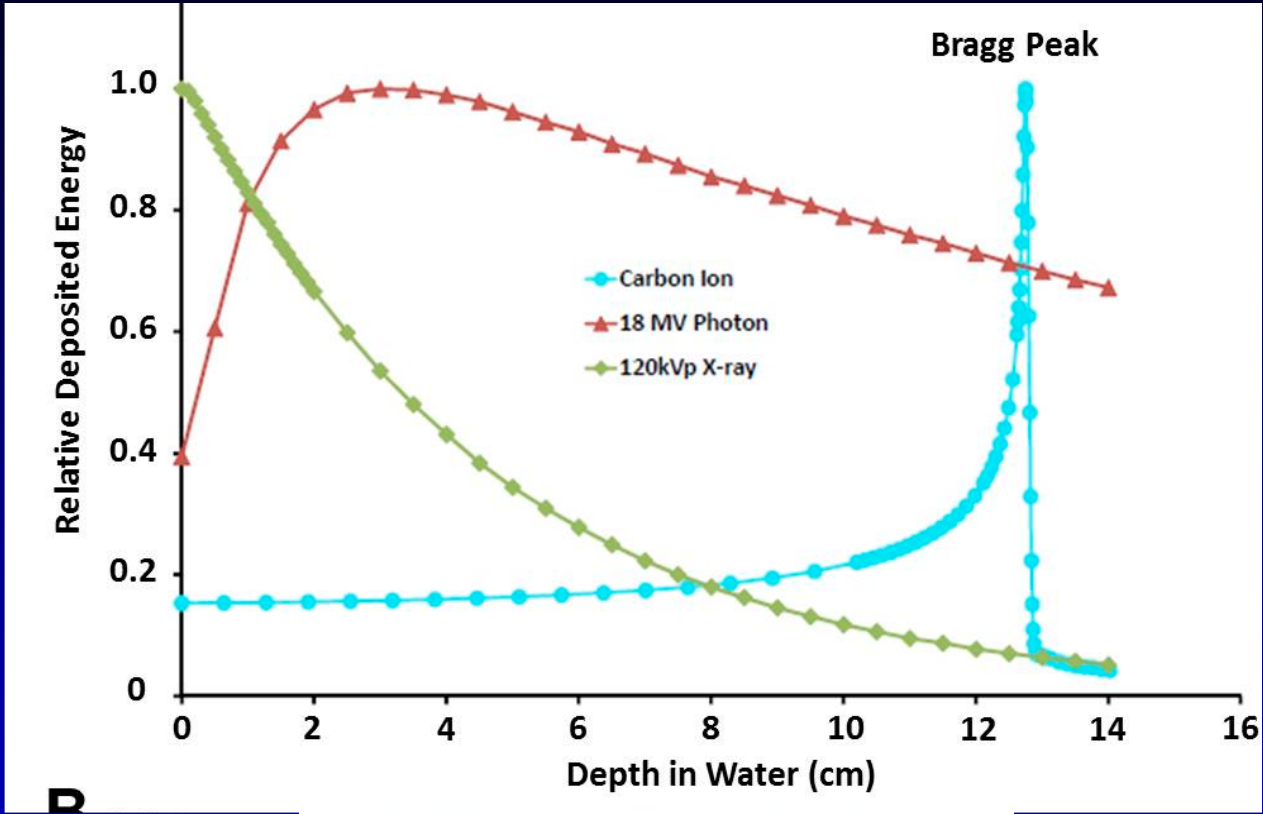
Funding start in FY2020, ending 2022

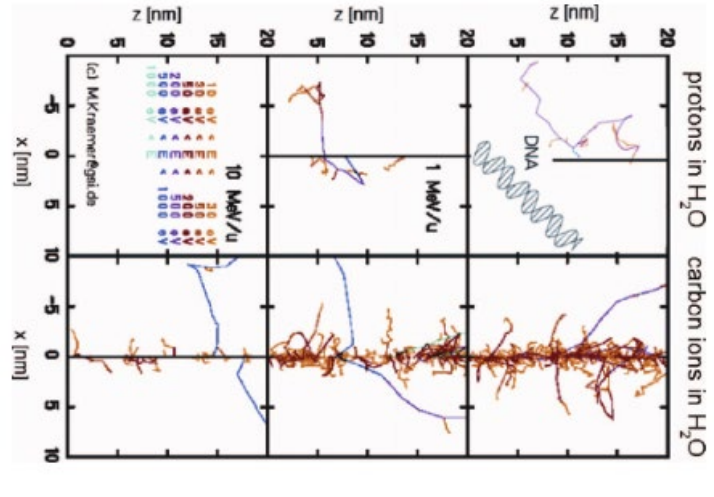
Back-up slides

Particle Therapy Centers world-wide

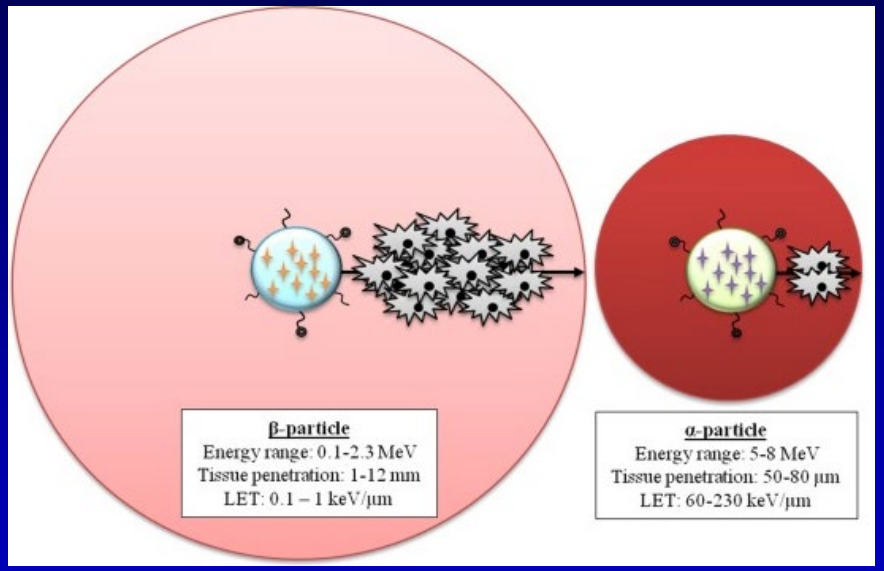


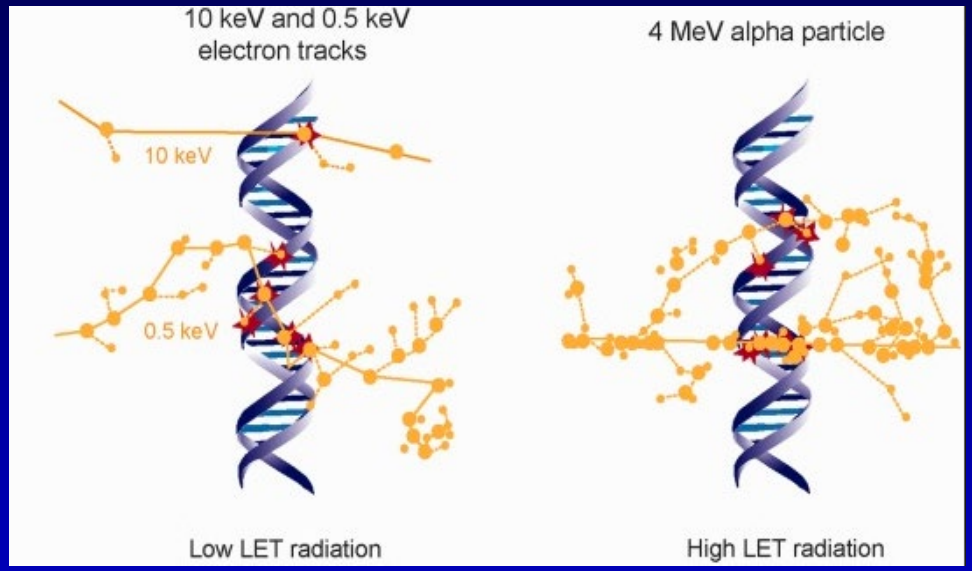
Depth-dose distribution of external beam radiation





Particles Emitted from Therapeutic Radionuclides

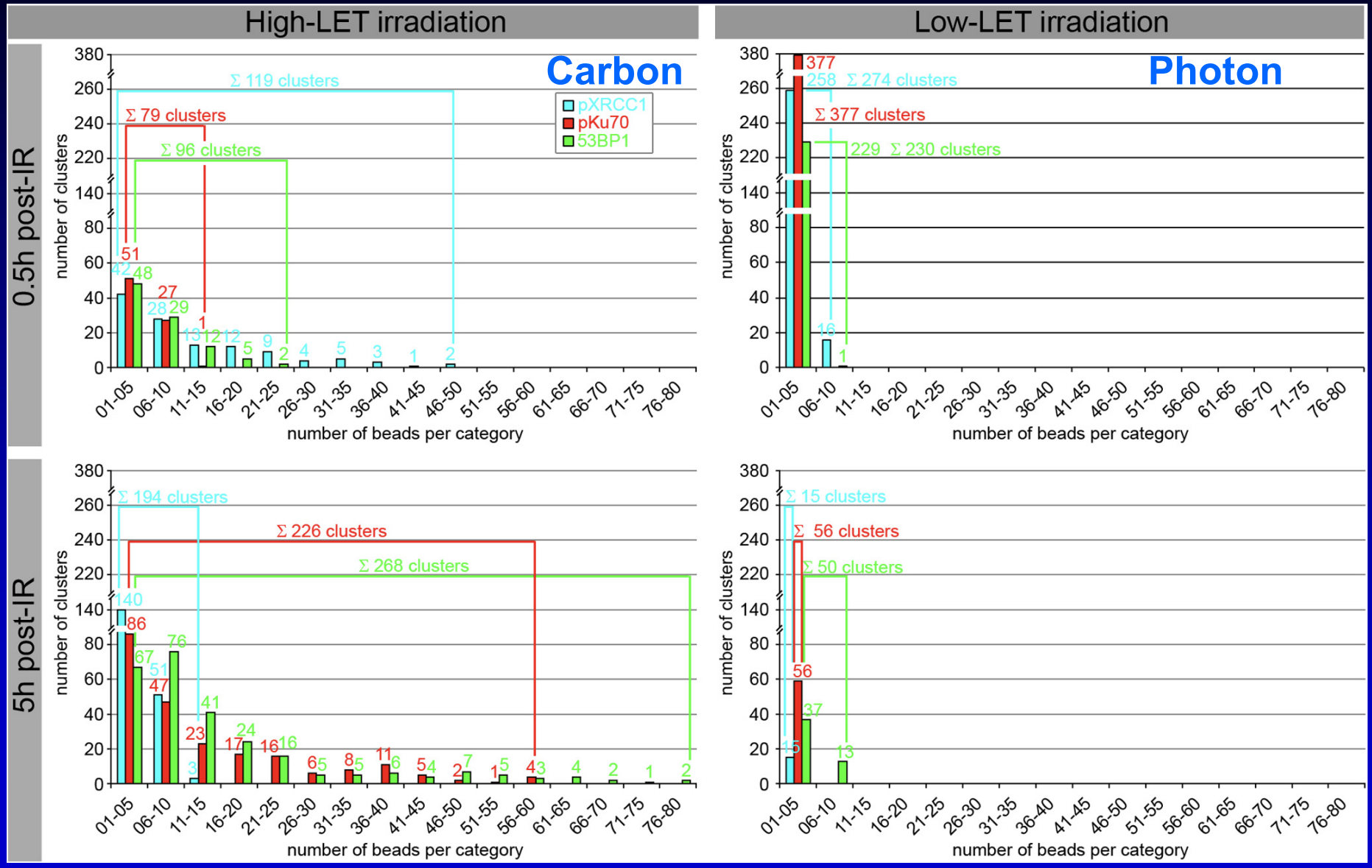




Difference in range

Differences in macromolecule ionization and damage

Quantitation of initial and residual DNA damage foci - High vs Low LET



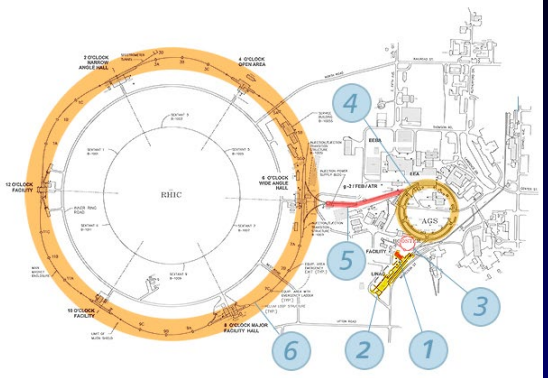
Y. Lorat et al. / Radiotherapy and Oncology 121 (2016) 154–161

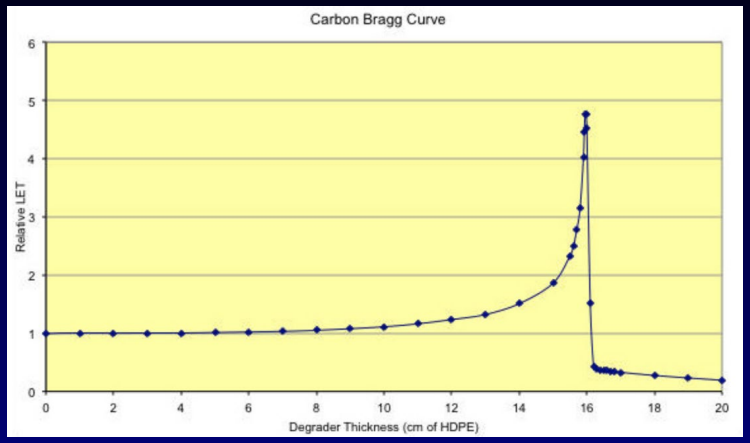
Via BNL website and links.

RHIC Accelerators

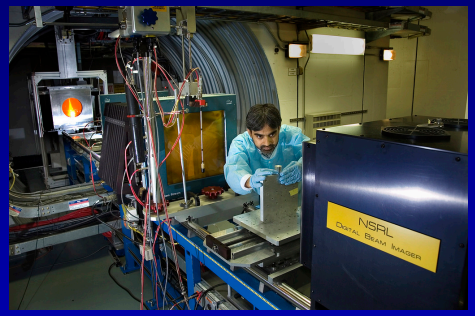
The Relativistic Heavy Ion Collider complex is actually composed of a long "chain" of particle accelerators

Heavy ions begin their travels in the Electron Beam Ion Source accelerator (1). The ions then travel to the small, circular Booster (3) where, with each pass, they are accelerated to higher energy. From the Booster, ions travel to the Alternating Gradient Synchrotron (4), which then injects the beams via a beamline (5) into the two rings of RHIC (6). In RHIC, the beams get a final accelerator "kick up" in energy from radio waves. Once accelerated, the ions can "orbit" inside the rings for hours. RHIC can also conduct colliding-beam experiments with polarized protons. These are first accelerated in the Linac (2), and further in the Booster (3), AGS (4), and RHIC (6).





Ion Species [1]	Max Energy [2] (MeV/n)	LET in H_2O at Max Energy (keV/micron)	Peak LET (keV/micron)	Range in H_2O (mm)	Maximum Intensity [3] (ions per spill)
H	2500	0.206	84.3	10490	2.2×10^{11}
He^3	1500	0.83	237	4170	0.6×10^{10}
He^4	1500	0.84	237	5550	0.6×10^{10}
Li^7	1500	1.8	375	4340	4×10^{9}
C^{12}	1500	7.55	922	1856	1.2×10^{10}
O^{16}	1500	13.4	1306	1391	0.4×10^{10}
Ne^{20}	1500	20.97	1637	1113	0.10×10^{10}
Si^{28}	1500	41.1	2519	795	0.3×10^{10}
Cl^{35}	1500	60.6	3046	674	0.2×10^{10}
Ar^{40}	1500	68	3268	687	0.02×10^{10}
Ti^{48}	1500	101.5	3924	552	0.08×10^{10}
Fe^{56}	1470	142	4706	449	0.2×10^{10}
Kr^{84}	383	403	6221	50	2.0×10^{7}
Zr^{91}	300	565	6904	29.3	1×10^{6}
Nb^{93}	300	594	6690	28.0	1×10^{6}
Xe^{132}	350	947.4	9788	30.7	5.0×10^{7}
Ta^{181}	342	1745	12300	22.7	3.0×10^{8}
Au^{197}	165	3066	13140	6.8	1×10^{8}
Th^{232}	217	3352	140.1	9.8	1×10^{7}



Potential therapeutic targets for combination with high-LET radiotherapy

- c-NHEJ - DNA PKcs inhibitors (in clinical trials)
- CDK inhibitors of the cell-cycle checkpoints

Phase-1

- Alt-NHEJ - polymerase Θ and PARP1 inhibitors (PARPi) – small-molecular inhibitors are in clinical use or clinical trials
- HR – ATM , ATR and Mre11 small-molecule , inhibitors at various stages of clinical trials
- *RAD52 mitotic salvage? – small-molecule*

Phase-2