Conclusion and Future Perspectives

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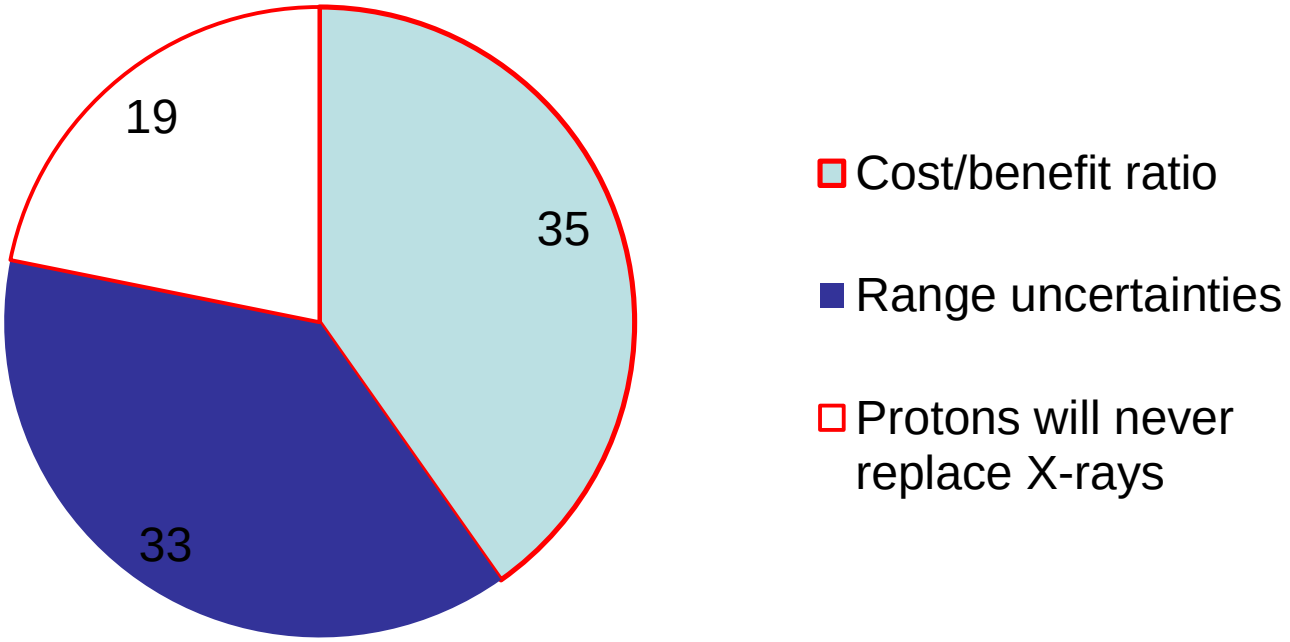
University of Liverpool / Cockcroft Institute

Look into the future

- Workshop at Archamps, June 2018
- indico.cern.ch/event/682210
- Where do we want to go next?

AAPM poll, August 2012

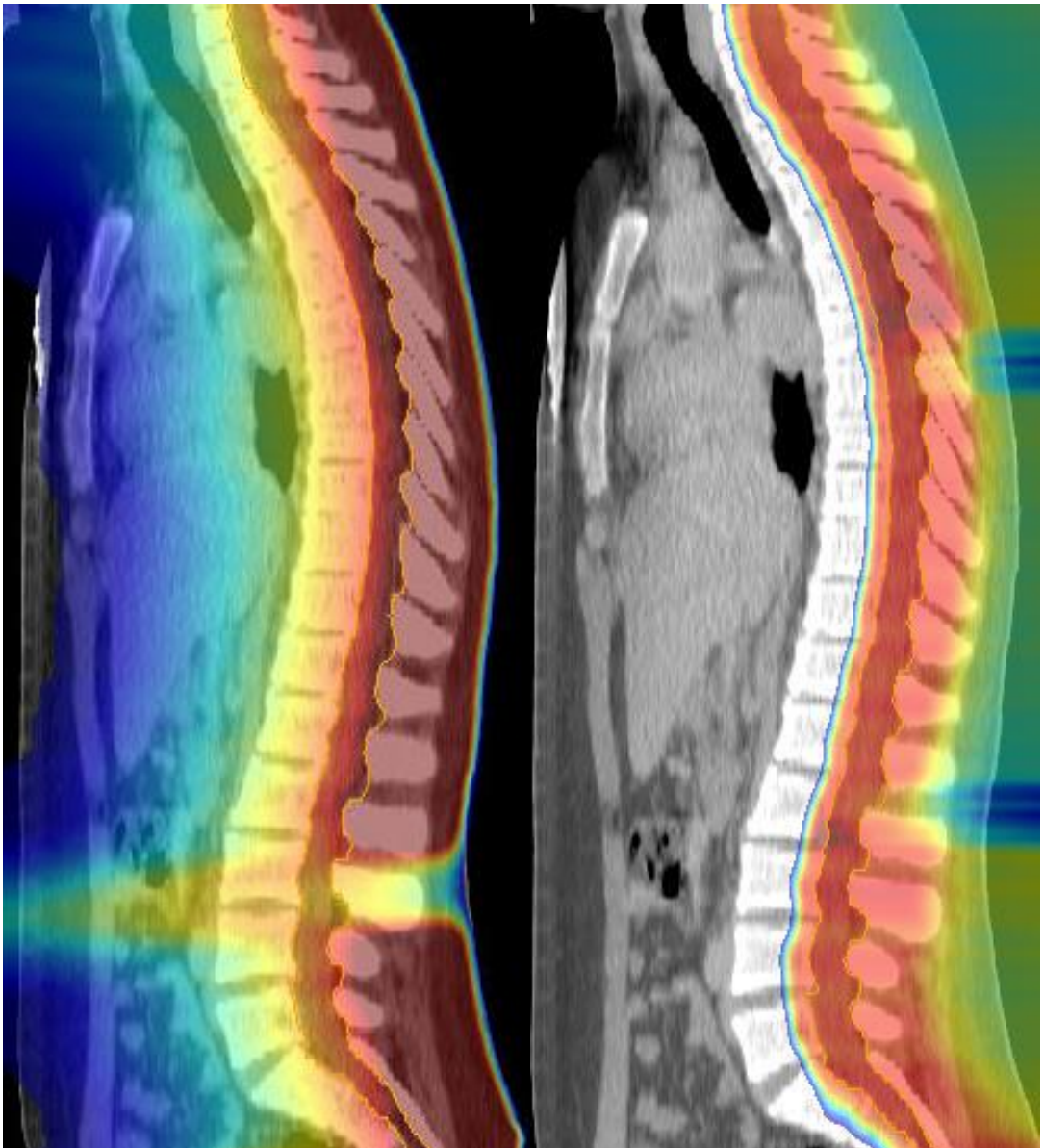
What is the main obstacle to proton therapy replacing X-rays?

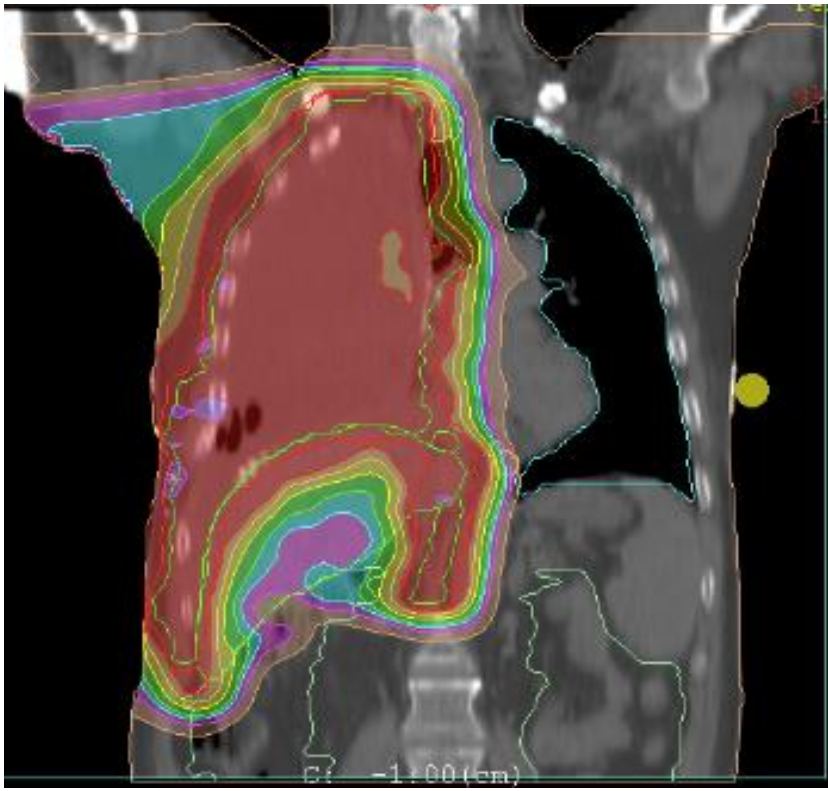


Slides courtesy M. Durante, GSI

Protons stop...

X-rays **Protons**

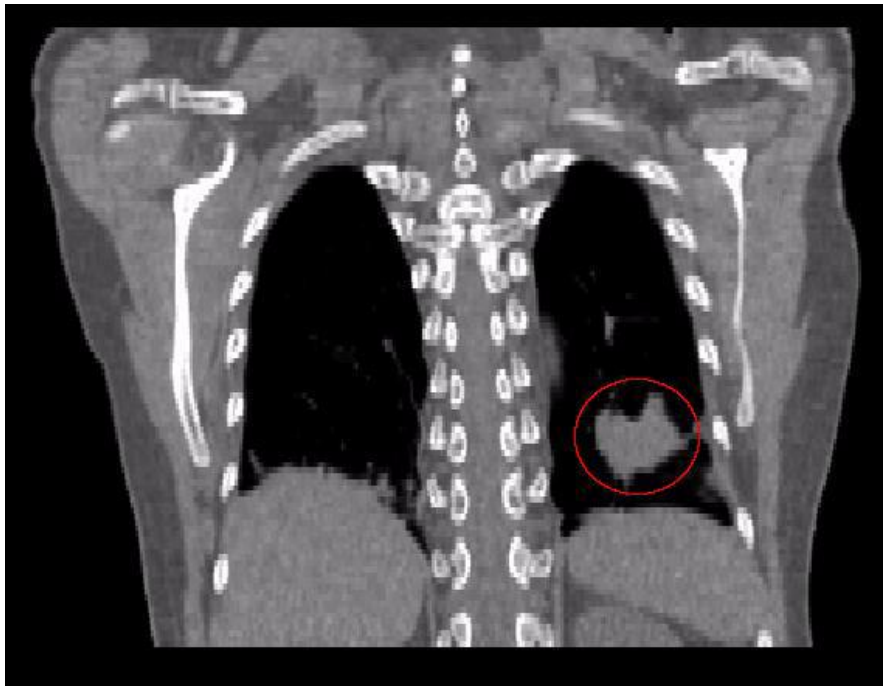




Courtesy of Marco Schwarz

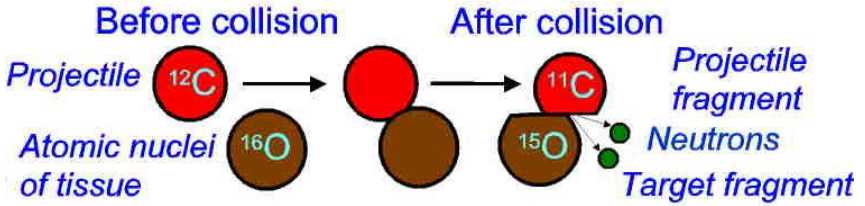
Treating moving targets

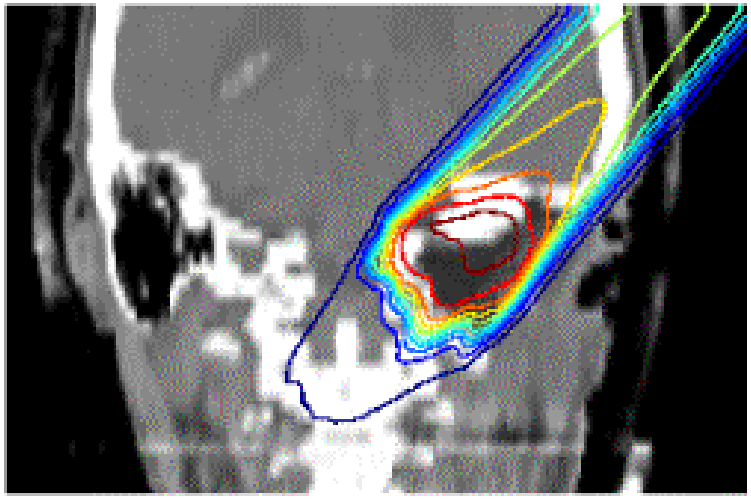
Courtesy of Christian Graeff, GSI, Germany



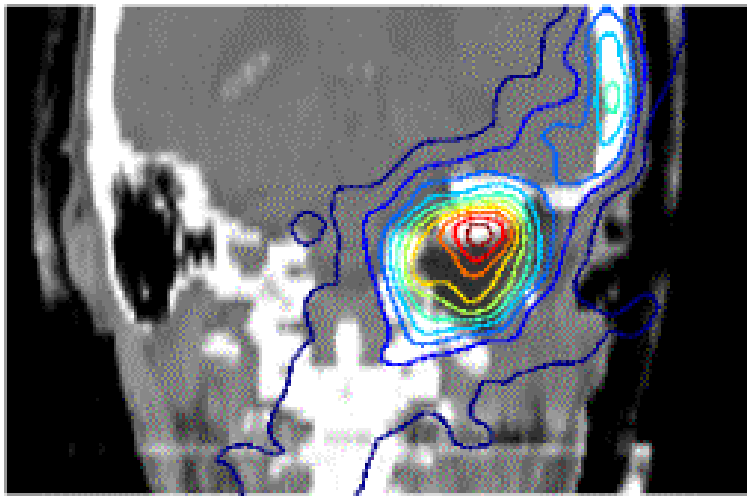
- **Motion**: Geometric miss of target
- **Range changes**: Position of Bragg Peak under motion
- **Interplay**: Interference between scanning and tumor motion
- **Current solution**: ITV, rescanning
- **Future**: 4DTP, online tracking

In situ control with PET

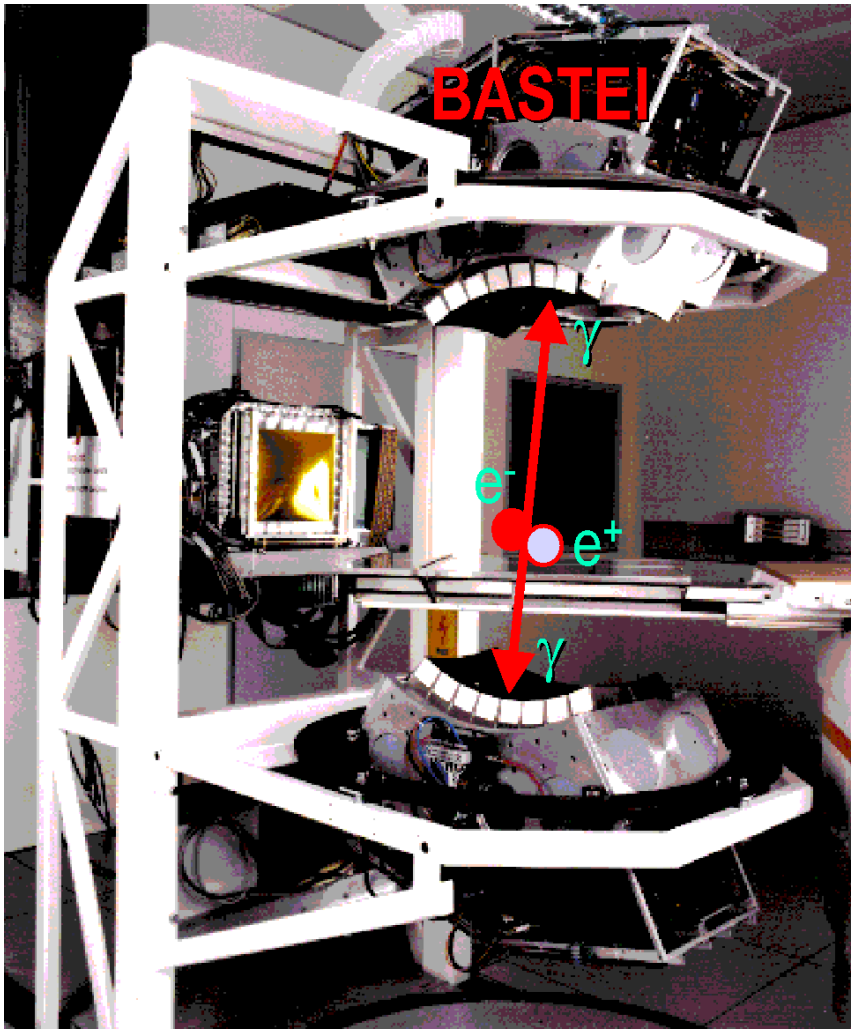




dose plan



measured

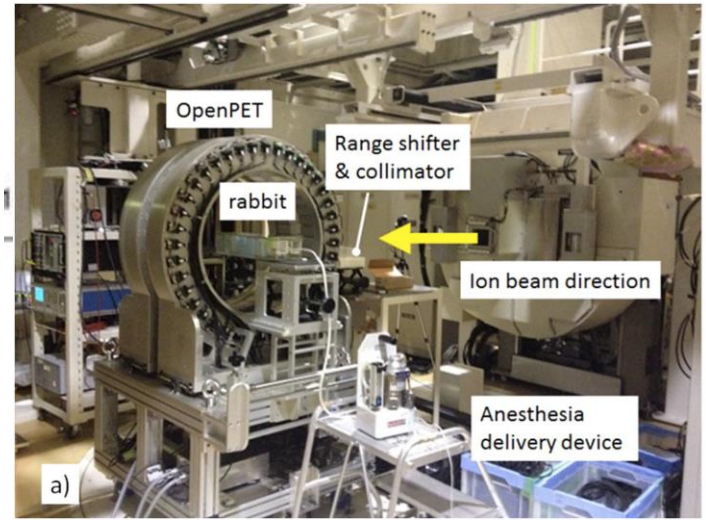


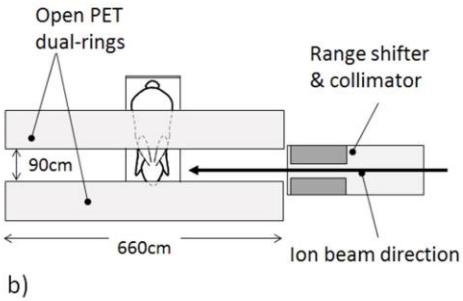
Courtesy of Wolfgang Enghardt, HZDR, Dresden

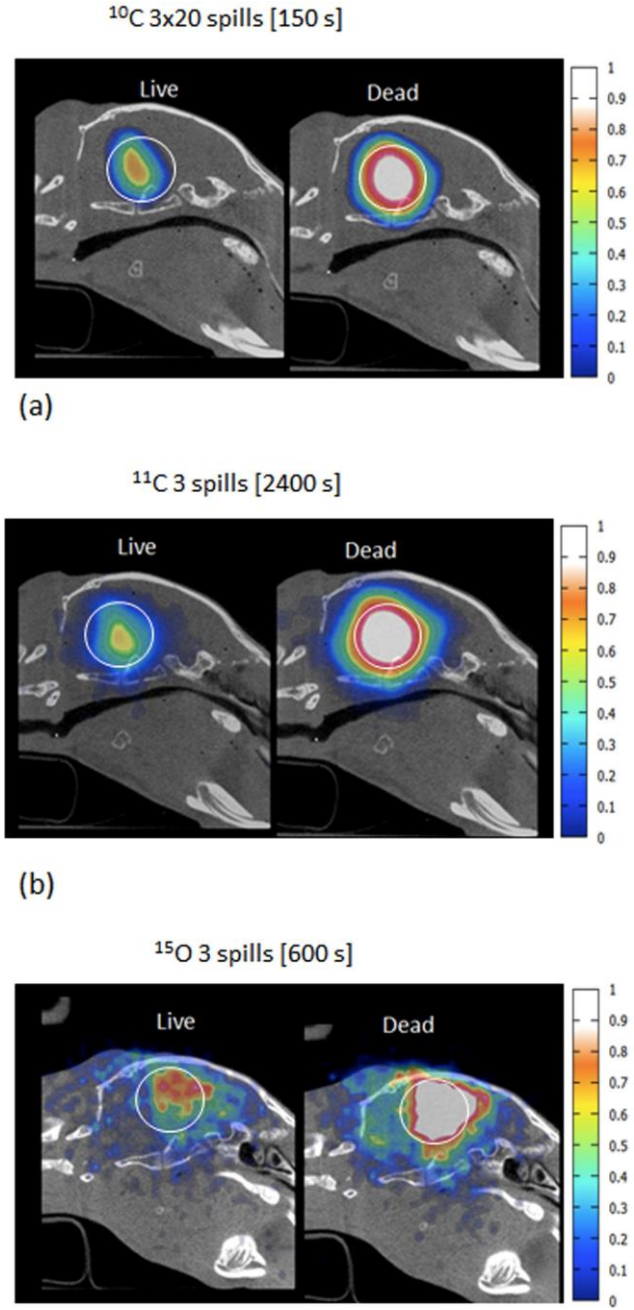
Future: imaging with RIB

Positron-emitting accelerated ion	Half-life (min)
^{10}C	0.32
^{11}C	20.3
^{15}O	2.04

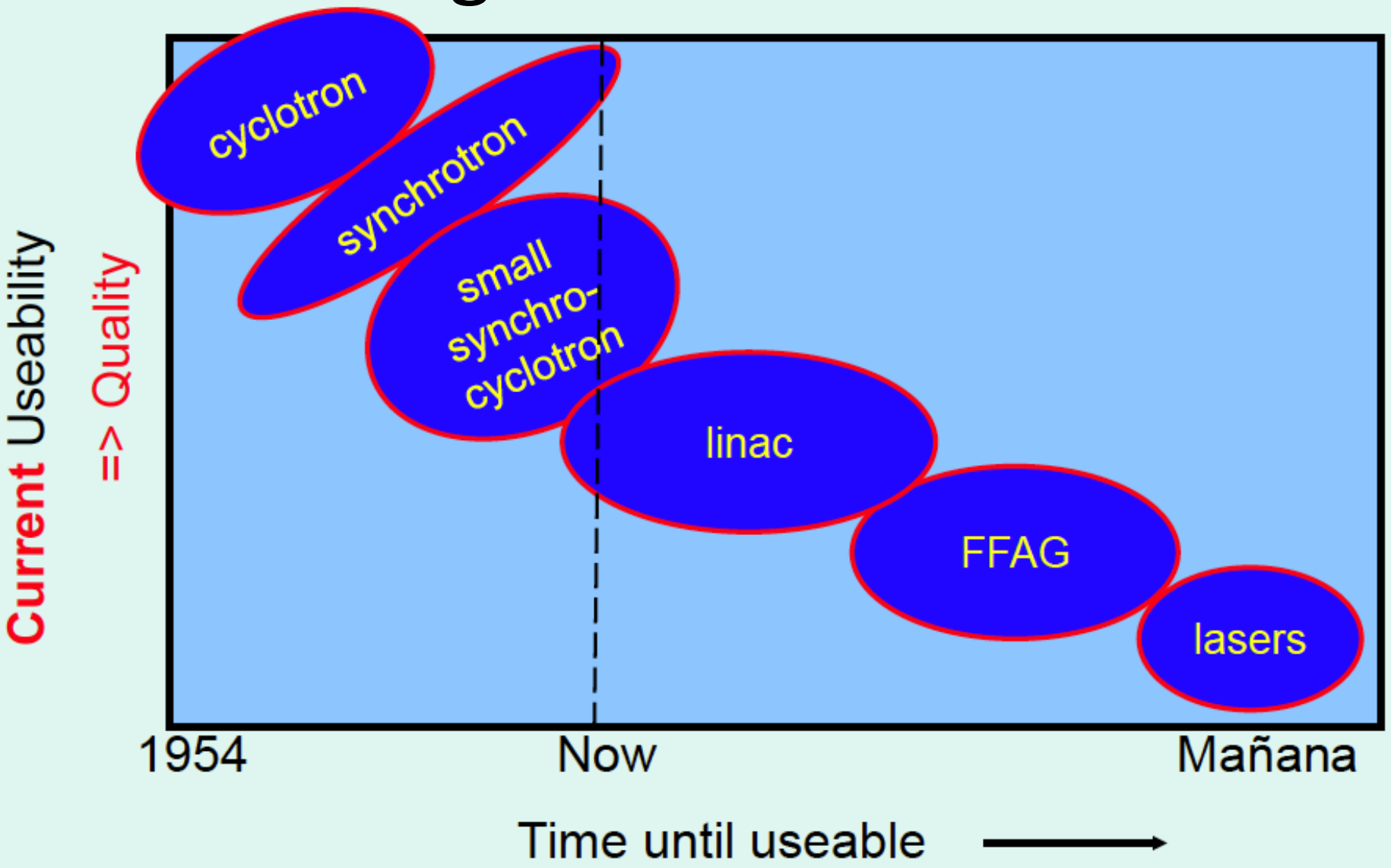
Chie Toramatsu et al *Biomed. Phys. Eng*. 2018







Reducing costs: accelerators



Courtesy of Marco Schippers, PSI

This is happening today in the market

IBA/SHI – 250 Ton **Isochronous** Cyclotron

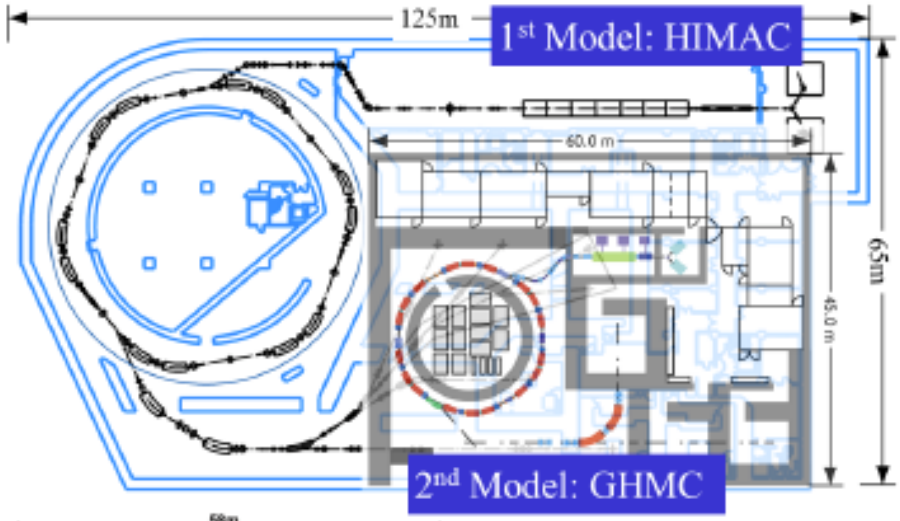
Varian – 90 Ton **Isochronous** Cyclotron

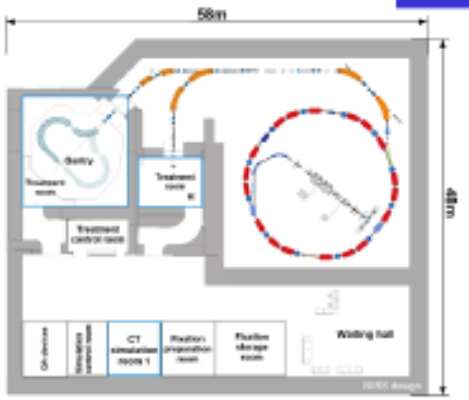
IBA – 60 Ton **Synchrocyclotron**

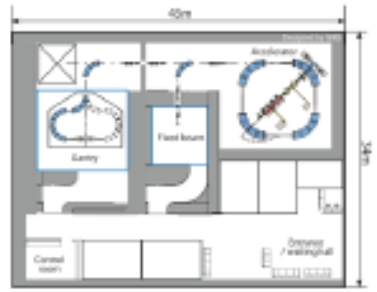
MEVION – 15 Ton **Synchrocyclotron**

NIRS HIMAC

Plan of Miniaturizing Machine







Courtesy of Dr. Kojii Noda

Convincing the non-believers: phase-III clinical trials

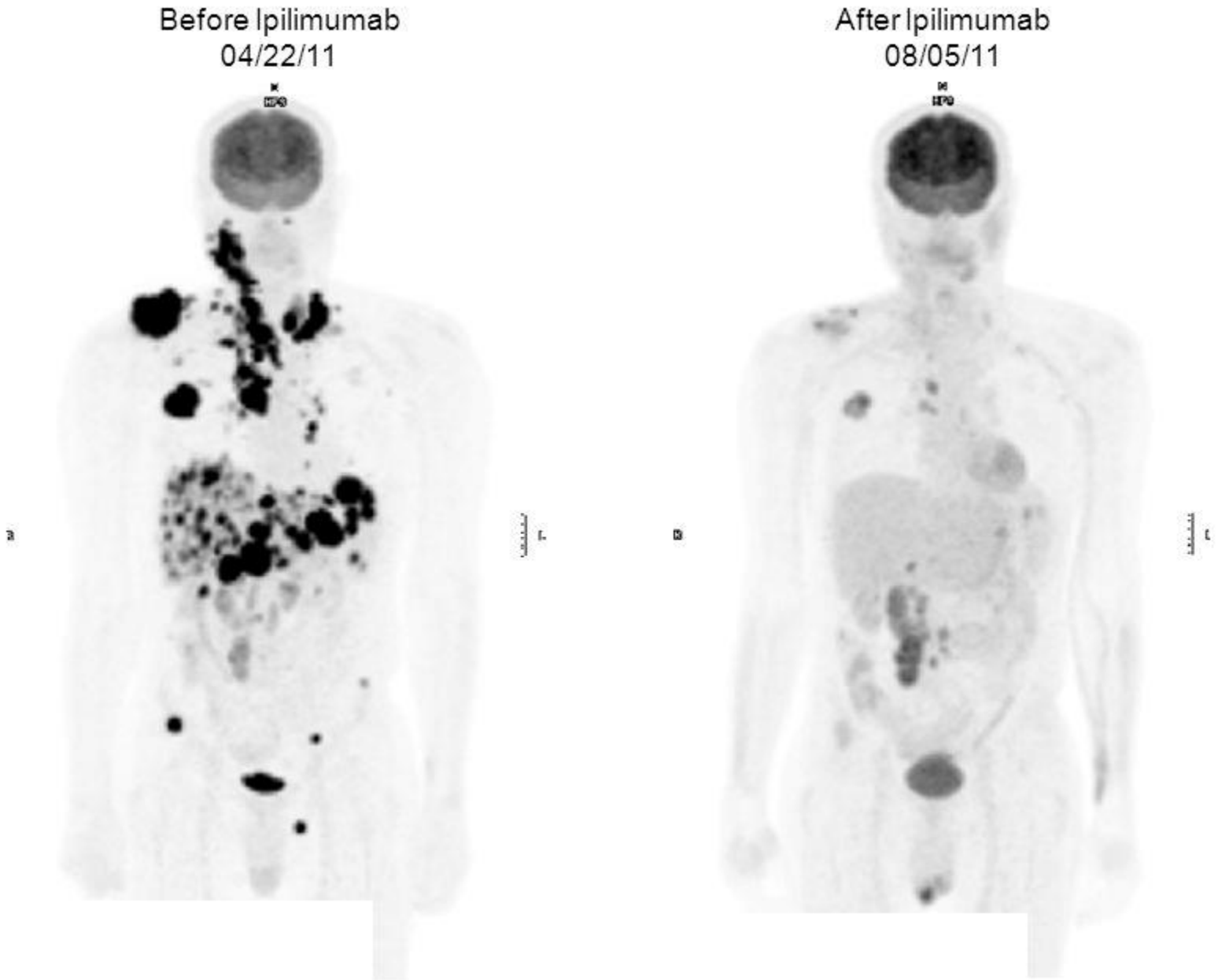
Table 1 | Ongoing randomized clinical trials comparing different radiation modalities for the same disease

Study	Institution	Phase	Condition	Radiation arm 1	Radiation arm 2
R03CA188162: IMPT vs IMRT	MDACC	III	Oropharyngeal cancer (head and neck cancer)	Protons*	X-rays*
PARTIQoL (NCT01617161): proton therapy vs IMRT	MGH	III	Low-risk or intermediate-risk prostate cancer	Protons	X-rays
NCT01512589: proton-beam therapy vs IMRT	MDACC	III	Oesophageal cancer	Protons*	X-rays*
RADCOMP (NCT02603341): pragmatic randomized trial of proton vs photon therapy	PTCORI	III	Post-mastectomy stage II or III breast cancer	Protons	X-rays
NRG BN001: dose-escalated IMRT or IMPT vs conventional photon radiation	NRG Oncology	II	Newly diagnosed glioblastoma	Protons*	X-rays*
NRG 1542: proton radiation vs conventional photon radiation‡	NRG Oncology	III	Hepatocellular carcinoma	Protons	X-rays
NCT01182753: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Low-grade and intermediate-grade chondrosarcoma of the skull base	Protons	Carbon ions
NCT01182779: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Chordoma of the skull base	Protons	Carbon ions
CLEOPATRA (NCT01165671): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Primary gioblastoma	Protons*§	Carbon ions*§
IPI (NCT01641185): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Prostate cancer	Protons	Carbon ions
ISAC (NCT01811394): proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	II	Sacrococcygeal chordoma	Protons	Carbon ions
ETOILE (NCT02838602): carbon-ion radiotherapy vs IMRT	Lyon University Hospital, France	III	Radioresistant adenoid cystic carcinoma and sarcomas	Carbon ions	IMRT
BAA-N01CM51007-51: prospective trial of carbon-ion therapy vs IMRT	NCI	I/III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*
CIPHER: prospective multicentre randomized trial of carbon-ion radiotherapy vs conventional radiotherapy	UTSW	III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*

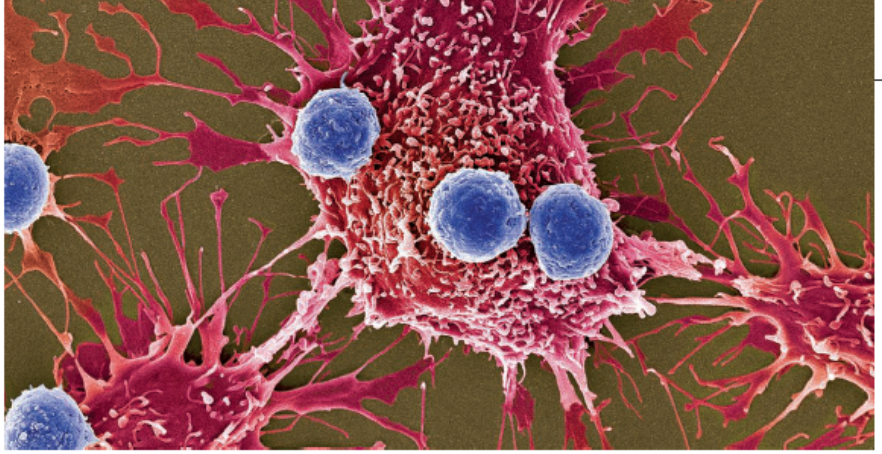
Durante *et al.*, *Nat. Rev. Clin. Oncol.* 2017

The big question: shall we need radiotherapy *at all* in the future?

Metastatic Melanoma Response to Ipilimumab



Courtesy of Dr. Paolo Ascierto, Istituto Pascale, Naples, Italy



A class of drugs meant to help unleash T cells (blue) on cancer cells (red) stumbled in a recent trial.

Science
5.16.2018
AAAS

BIOMEDICINE

A new cancer immunotherapy suffers a setback

An exciting drug failed in a large trial, triggering a retreat and raising questions about the field's frantic pace

By **Ken Garber**

The surprising failure last month of a large clinical trial of a promising cancer immunotherapy drug from the biotech company Incyte has quickly reverberated across the pharmaceutical industry. Three companies have canceled, suspended, or downsized 12 other phase III trials of the compound, epacadostat, or two similar drugs, together slated to enroll more than 5000 patients with a variety of advanced cancers.

The companies say they aren't dropping the potential drugs, designed to unleash the immune system on cancer cells by blocking an enzyme called indoleamine (2,3)-dioxygenase (IDO). But the retrenching suggests that the frenzy to combine novel drugs with the wildly successful immunotherapies known as checkpoint inhibitors is outpacing the science (*Science*, 23 March, p. 1346). The IDO strategy, says neuroimmunologist Michael Platten of the University of Heidelberg in Germany, "has been moved to ran-

The results from smaller, phase II trials don't always predict how a cancer drug will do in a randomized phase III trial. But the epacadostat data "were pretty compelling," says Yale University immuno-oncologist Mario Sznol, who expected to see some benefit to patients. (Sznol was not involved in

Mass exodus

Three companies have suddenly suspended, canceled, or downsized 13 trials of indoleamine (2,3)-dioxygenase inhibitors (in combination with drugs called checkpoint inhibitors).

COMPANY	DRUG	CANCER
Incyte (nine trials)	epacadostat (INCB24360)	Melanoma, lung, head and neck, urothelial, kidney
Bristol-Myers Squibb (three trials)	BMS-986205	Melanoma, lung, head and neck
NewLink Genetics (one trial)	indoximod (NLG8189)	Melanoma

treated? "You could go through the whole list of reasons," Sznol says.

The field still generally agrees that IDO makes sense to target, in combination with checkpoint inhibitors. Those drugs release a molecular brake on tumor-killing immune T cells. But the unleashed cells then stimulate the production of IDO, which, in a negative feedback loop, shuts them down again. IDO does this mainly by indirectly activating a protein inside immune cells called the aryl hydrocarbon receptor (AHR). Suppressing IDO should therefore make checkpoint inhibitors work better.

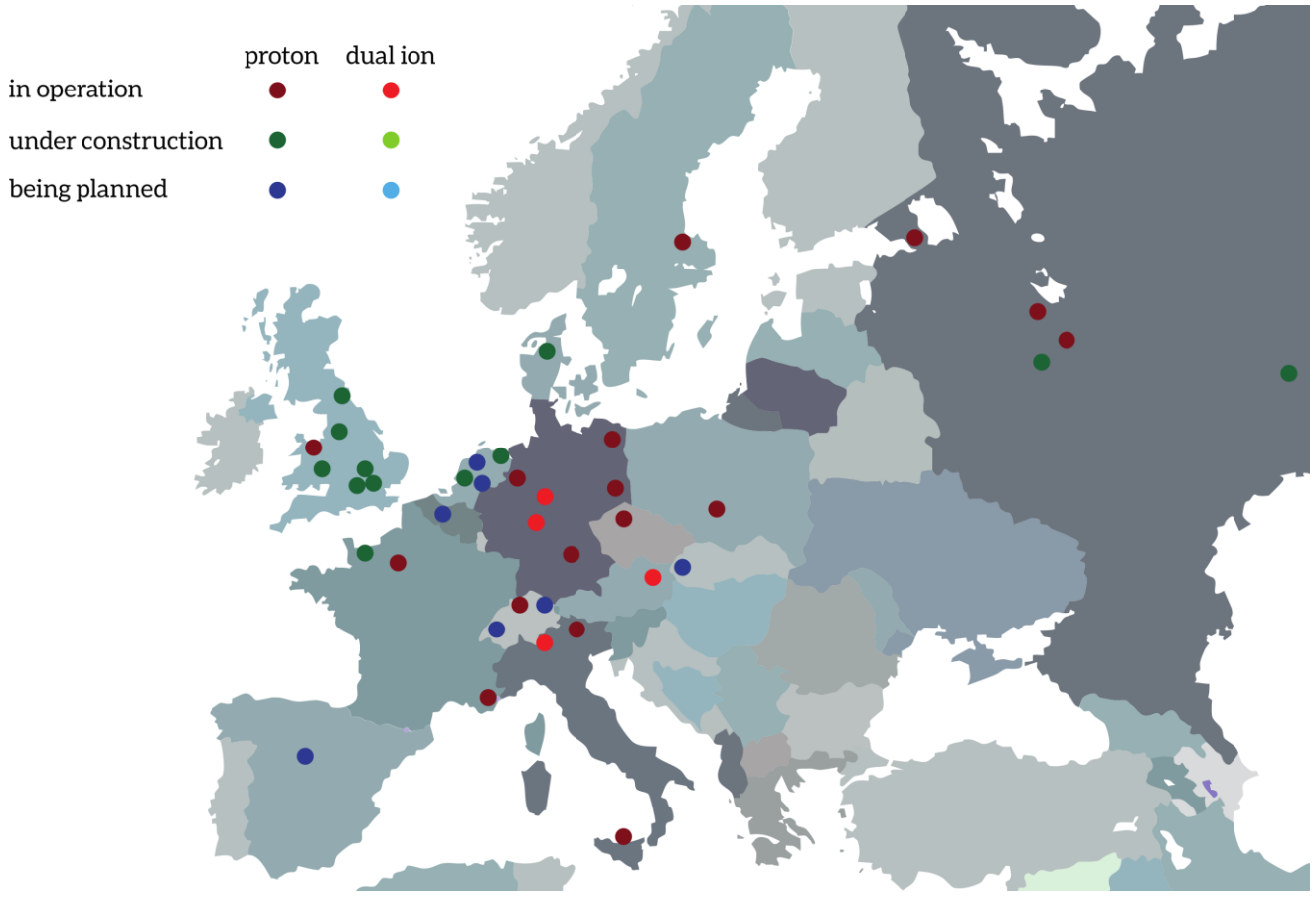
But much about IDO remains unknown, Platten says. Exactly how IDO stifles the immune system is unresolved, nor is it clear which immune cells are most involved, he says. Even the idea that IDO blunts the antitumor effects of checkpoint inhibitors is suspect. "The evidence that this is really happening in the clinical situation ... is very slim," Platten says.

The drug, not the target, might be the problem. Some IDO inhibitors bind the AHR and thus could suppress the immune system, the opposite of the drug's intent. NewLink Genetics reports that its drug does activate the AHR, but in a way that it still believes promotes a strong immune response against tumors. Both Incyte and Eli Lilly and Company say their drugs do not affect the AHR.

Levi Garraway, Eli Lilly's senior vice president of oncology global development and medical affairs in Indianapolis, says that going forward the company will try to select patients who are most likely to respond to IDO inhibitors, using unspecified biomarkers. At a recent cancer meeting, immuno-oncologist Tom Gajewski of the University of Chicago in Illinois noted that biomarker analysis in the IDO trials has been "lagging." The epacadostat trial failure, he added, is "a good wake-up call to make sure all the boxes are checked" for new combination therapies. But companies may still be tempted to press ahead with limited data. "There can be a sense of, 'I'd better act now.'"

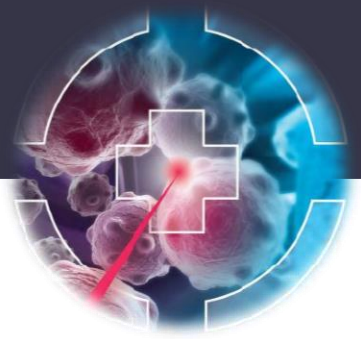
Proton therapy facilities

- Existing/planned proton facilities in Europe

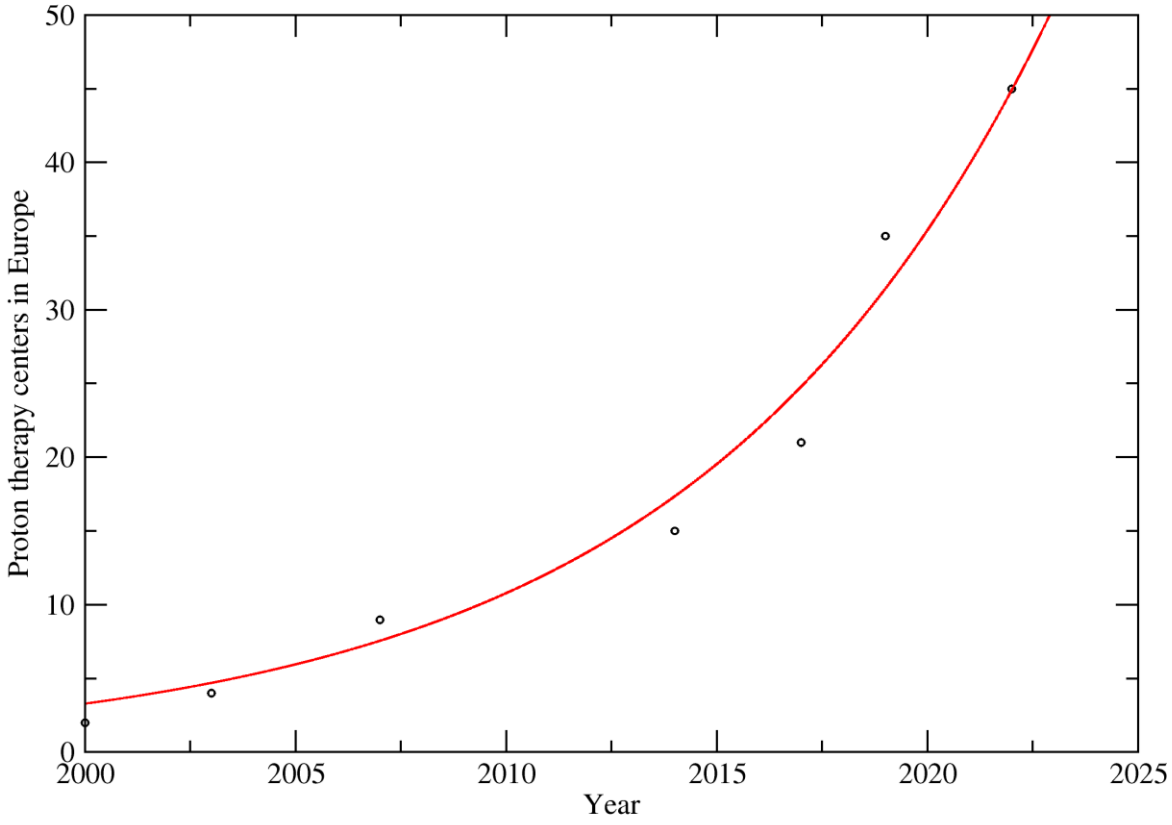


Source: CERN

Proton therapy facilities



- Number of proton facilities in Europe



New therapy centres

Basic concepts for a

SOUTH-EAST EUROPE

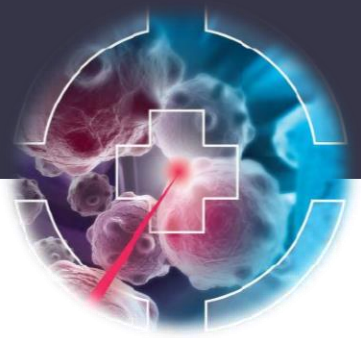
INTERNATIONAL INSTITUTE FOR

SUSTAINABLE TECHNOLOGIES

(SEEIIST)

January 15, 2018

Funding opportunities

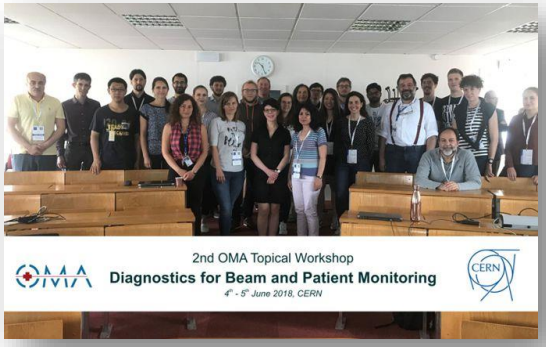


- Medical R&D
- Technology transfer developments
  - ATTRACT
  - EIC
  - MSCA individual Fellows
  - ERC
  - Etc

- Brexit?

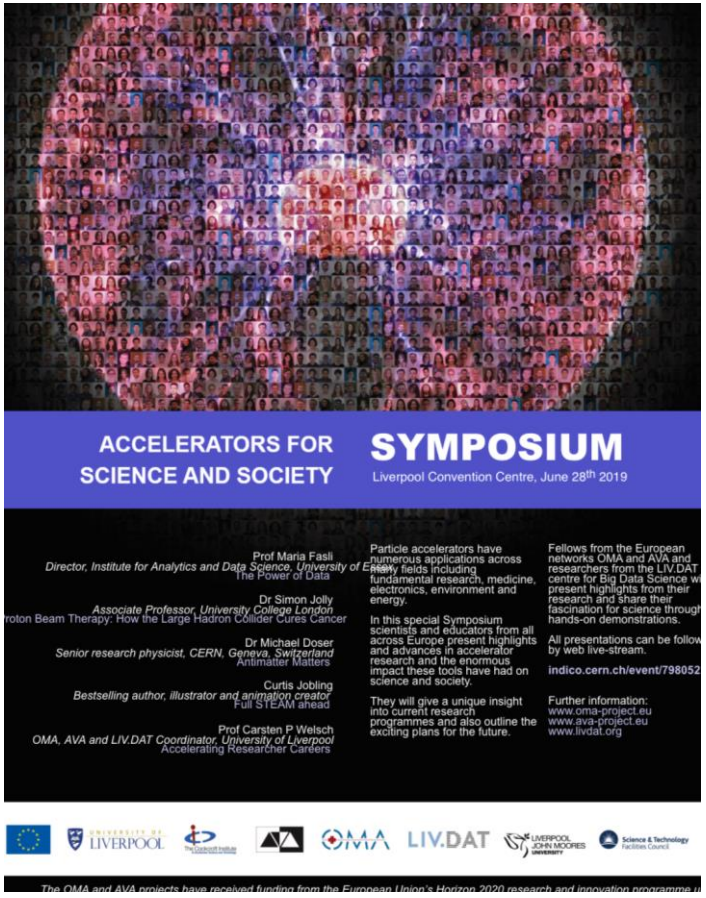
OMA Events

- International Schools on medical accelerators and Monte Carlo simulations;
- Topical Workshops on focused research topics – all material available online;
- Symposium and Final Conference this year to engage wider community and general public.



Symposium

- 28 June 2019 in Liverpool, UK
- indico.cern.ch/event/798052/
- Talks via live-stream
- Join in! Participate via social media



Conference

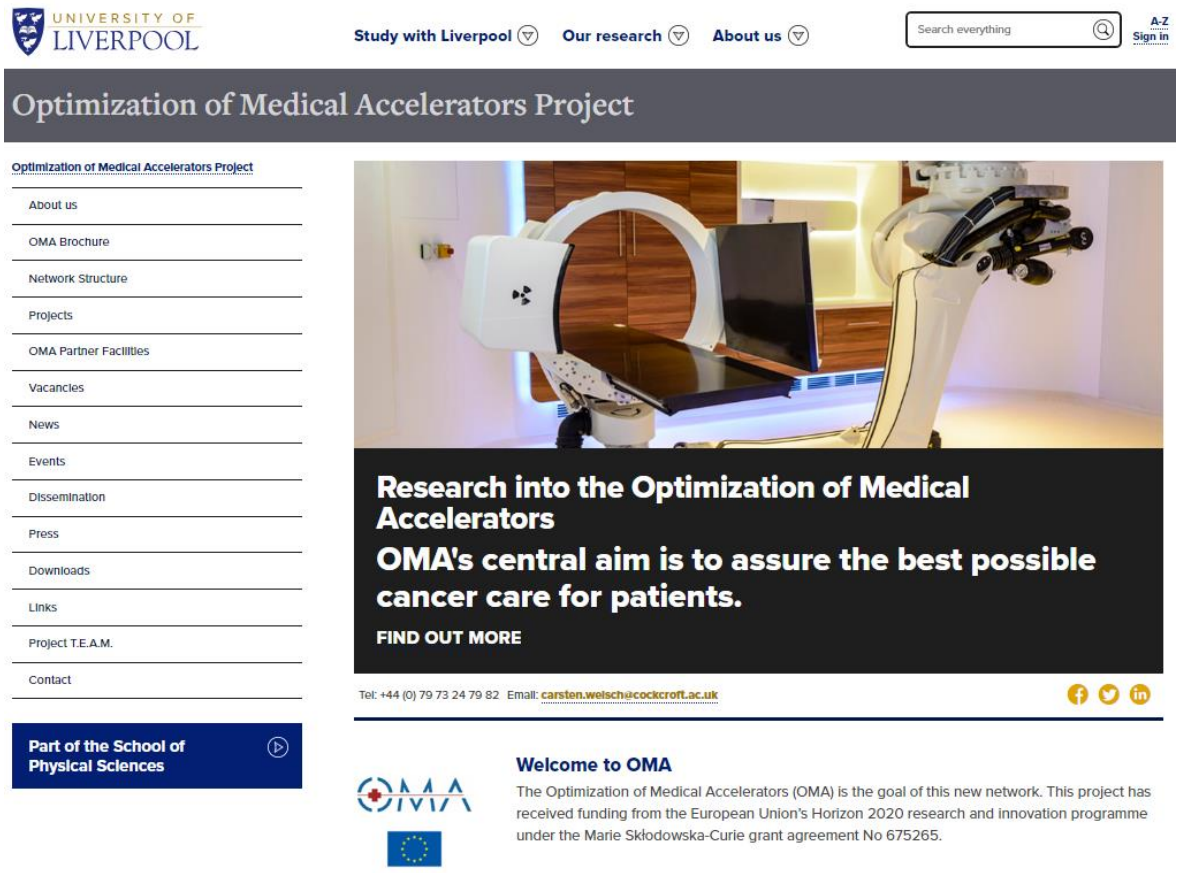
- International conference on particle therapy
- Seville, Spain
- 4-6 September 2019

- indico.cern.ch/event/803528/

- Contributed talks, poster session, proceedings

Project Web Site

- URL: (http://www.)oma-project.eu



Summary

- Future of particle therapy will depend on solution of technical issues (eg online imaging, range uncertainty) and decreasing cost/benefit ratio
- While industry is progressing in reducing size and costs, no major breakthroughs in past 20 years
- Good time to establish R&D programs – huge expertise in OMA – this School highlighted many of the needs
- Opportunities everywhere: national funding, KT, EIC, H2020 Design studies, etc.

Exciting field – still a LOT to be done.

I look forward to seeing you at next OMA events.