The CHUV-CERN collaboration to design and construct a high-energy electron FLASH therapy facility

Introduction

- A very hot topic in radiation oncology is so-called FLASH therapy which involves delivering an entire radiation treatment in a few hundred ms or less, as opposed to minutes, and in one or few fractions.
- This fast delivery can reduce toxicity to healthy tissue while maintaining tumor control expanding the parameter space for treatment – more in a moment.
- Another trend in radiation oncology is a renewed interest in VHEE (Very High Energy Electron) therapy.
- In parallel universe, major developments in accelerator technology have occurred in linear collider projects, relevant for this story, CLIC…

Introduction

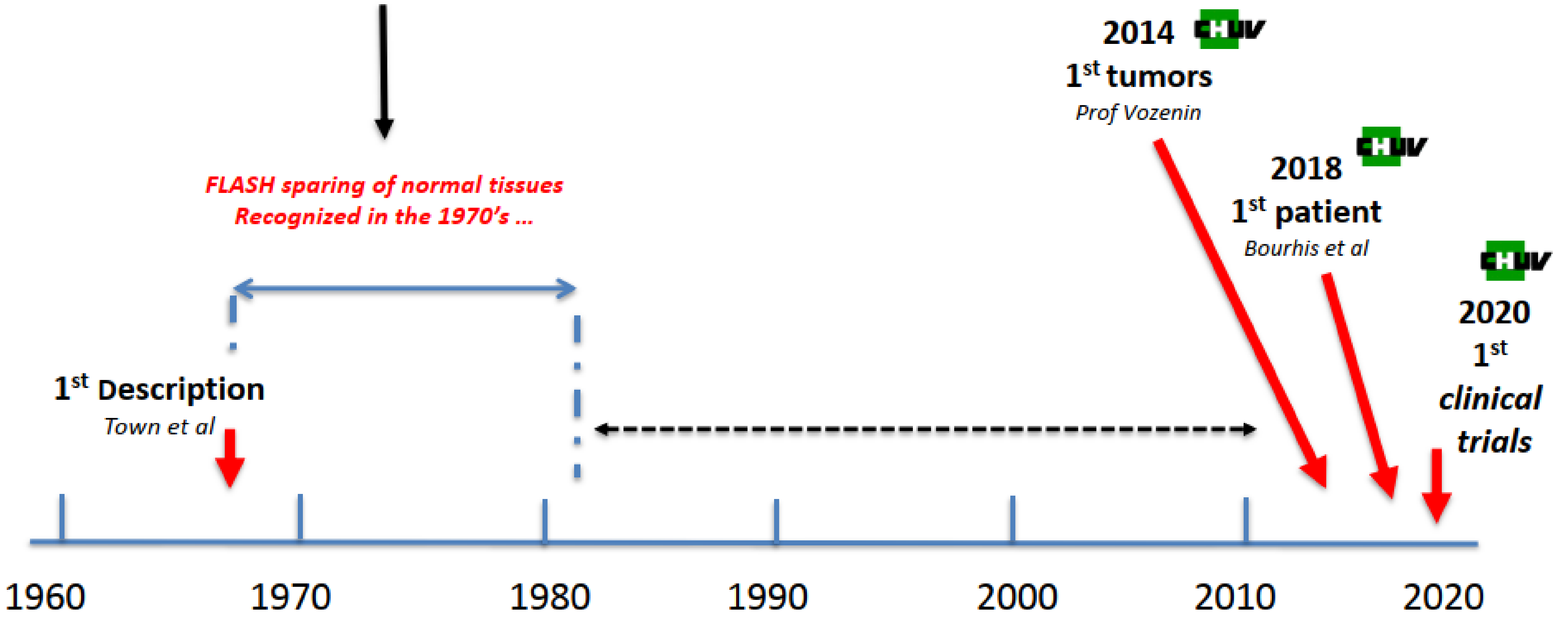
I will describe to you today a project which draws together these different themes, in a collaboration between CHUV (Centre Hospitalier Universitaire Vaudoise, Lausanne Hospital) and CERN to build a clinical FLASH-capable facility for treatment of large, deep-seated tumors using high-energy, 100 MeV-range, electrons accelerated with CLIC-developed technology.

Outline

- Some history and the CHUV clinical FLASH program – I will use slides from Prof. Jean Bourhis
- The CHUV-CERN collaboration
- Brief CLIC introduction
- Introduction to the accelerator part of the facility

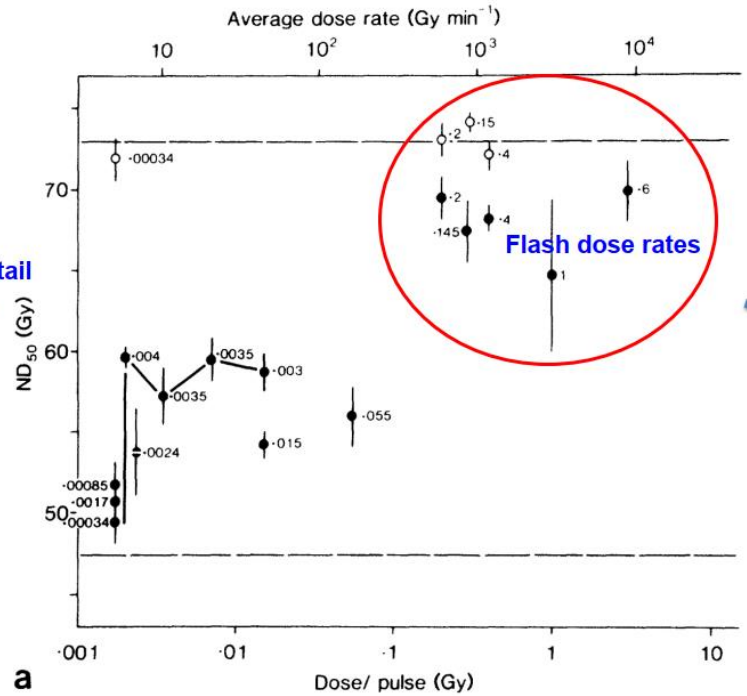
FLASH goes way back

Historical perspective



Until 1982 :

Dose for inducing tail necrosis in mice



Jolyon H. Hendry
1982

FLASH sparing effect on normal tissues was recognized

2014 Re-discovery …

1) Sparing normal tissues

2) No sparing of tumors

Favaudon & Vozenin

RESEARCH HIGHLIGHTS

IN BRIEF

RADIOTHERAPY

FLASHing tumours

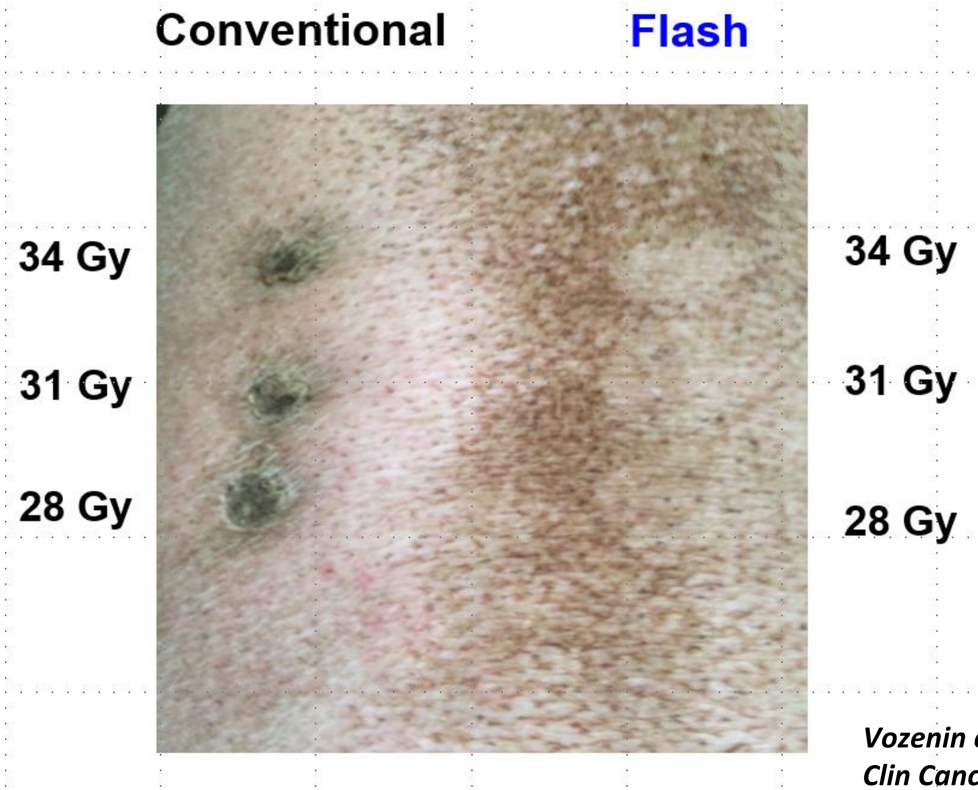
A new study in mice suggests that radiation delivered in short pulses at ultrahigh dose rates (FLASH) is as effective against lung tumours as conventional protracted single lower dose rates and has fewer side effects. Using both orthotopic lung tumours in immunocompetent mice and human lung tumour xenografts in nude mice, Favaudon *et al.* showed that FLASH irradiation caused less lung fibrogenesis and less apoptosis in normal tissue than conventional radiation. Although this technique was only tested in one tumour type, it suggests that delivery methods are crucial to minimizing radiation treatment side effects, and it has implications for therapeutic protocols.

ORIGINAL RESEARCH PAPER Favaudon, V. *et al.* Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci. Transl Med.* **6**, 245ra93 (2014)

NATURE REVIEWS | CANCER VOLUME 14 | SEPTEMBER 2014

Visually

Illustration of the Flash-RT effect in pig :
A major decrease of radiation side effects



Vozenin et al
Clin Cancer Res
2018

Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com
ELSEVIER

Original Article

Treatment of a first patient with FLASH-radiotherapy

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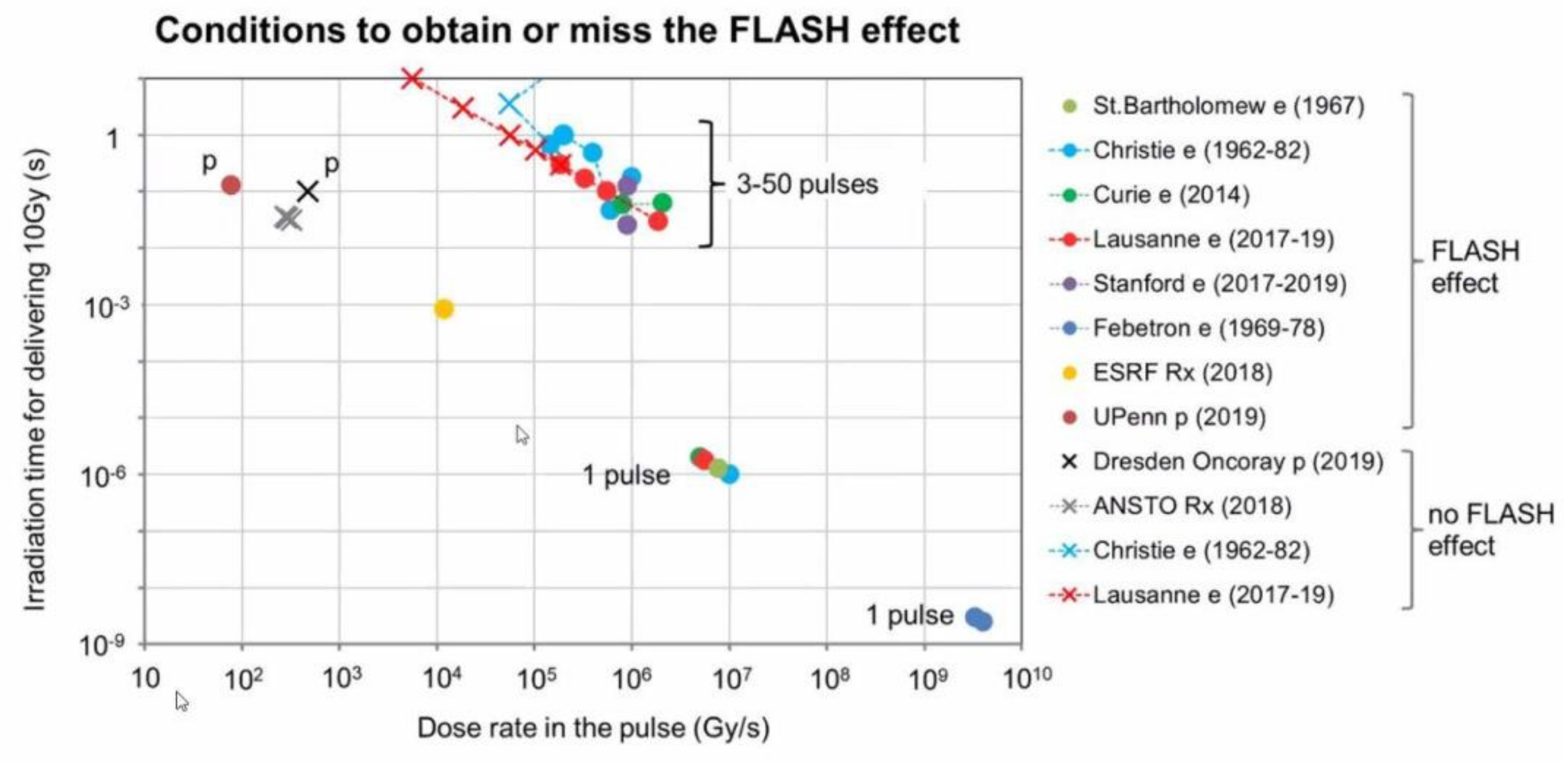
[a] Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [b] Radiation Oncology Laboratory, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [c] Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne; and [d] Department of Dermatology, Lausanne University Hospital and University of Lausanne, Switzerland

Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

First human patient – skin cancer treated with 10 MeV-range electrons



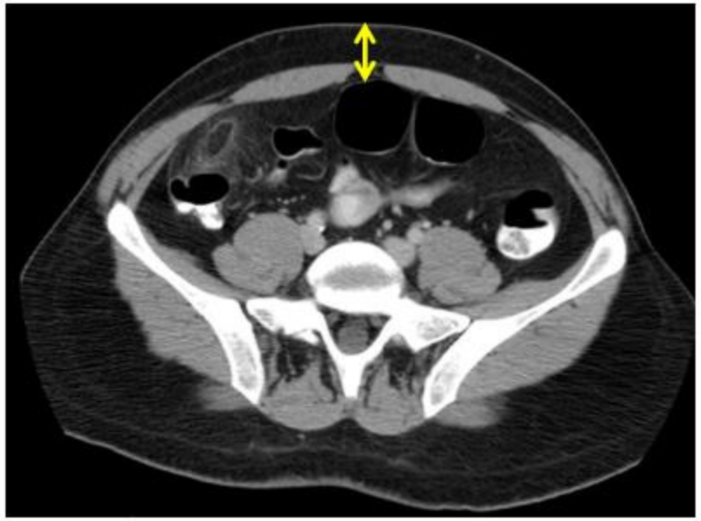
Apparently no dependence on type of radiation – what matters is time structure.

JF Germond, CHUV

Transfert clinique au CHUV (I)

FLASH-Mobetron

Only for superficial skin cancers



Press release — Lausanne, Switzerland & Sunnyvale, USA, June 18 2020

IntraOp and Lausanne University Hospital Announce Collaboration in FLASH

A collaborative R&D agreement will advance FLASH radiotherapy for cancer patients

The Lausanne University Hospital (CHUV) and IntraOp Medical Corporation have announced a research and development collaboration to accelerate the development of FLASH radiotherapy toward first human trials.

Transfert clinique @ CHUV (II) : intra-operative FLASH-THERAPY

With
Pr Simon,
Pr Demartines,
Pr Mathevet

For cancers not amenable to
A complete resection

t-

What about large tumor volumes and deep seated tumors ?

- **Unmet clinical need :** this is where we have most of the tumor failures …
- **So far no FLASH** pre-clinical data mimicking these clinical situations
- **No FLASH** irradiating device is currently **available** : technical challenges
- **FLASH characteristics may not help for its use in such large volumes ?**

The CHUV-CERN collaboration

- From a few coincidences then follow up discussions (a story for another day) CHUV and CERN realized that electron linac technology developed for CLIC could be the basis for a facility for treating large, deep-seated tumors in FLASH timescales – extending CHUV's clinical translation program.
- An extremely dynamic collaboration started in early 2019 to make a conceptual design of such a facility. This design is now done, feasibility OK and we have a good idea of the critical areas.
- CHUV succeeded in finding a donor to fund the construction of the facility.
- The project officially started on 1 September 2022, and ramp-up – as a collaboration, at CHUV and at CERN – is now underway.
- Participation of an industrial partner is planned and investigation and discussions are underway.

Working title:

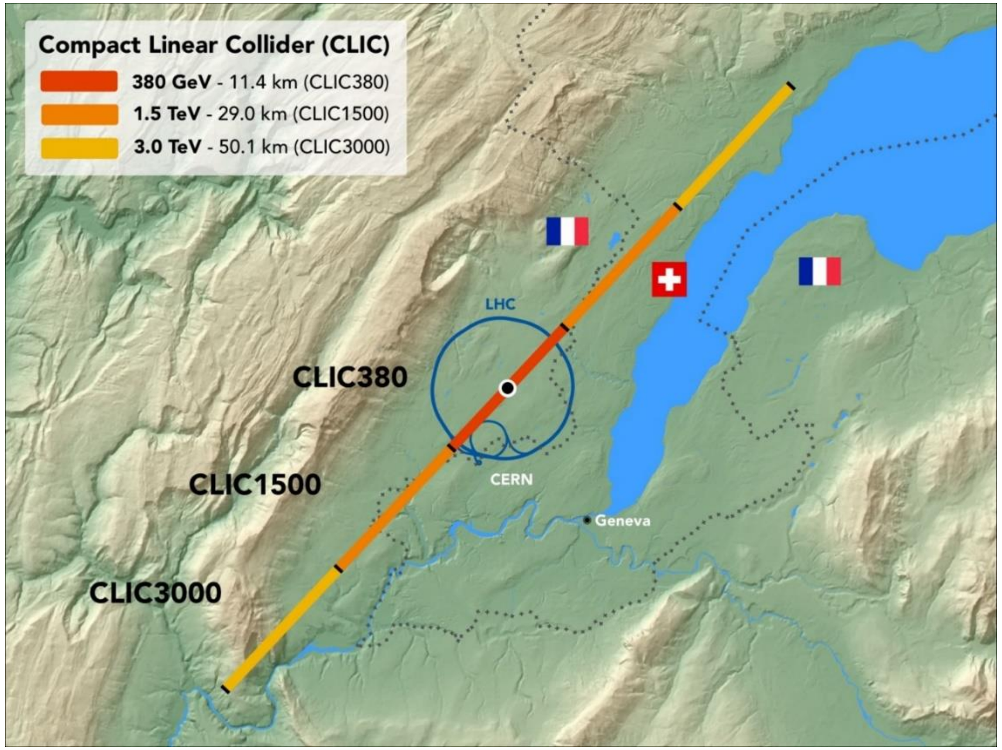
The DEFT (Deep Electron FLASH Therapy) facility

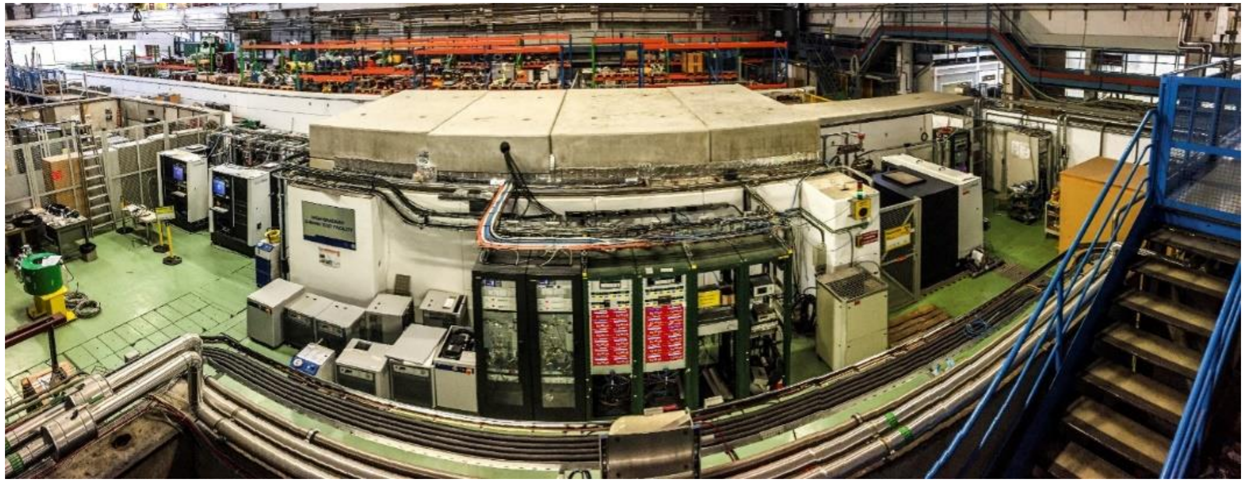
Deft, *adjective*

neatly skilful and quick in one's movements.
"a deft piece of footwork"
demonstrating skill and cleverness.
"the script was both deft and literate"

The CLIC heritage

Very broadly, the DEFT accelerator is a combination of the CLIC main linac, XBoxes, CTF2,3 and CLEAR. It draws on both simulation tools and hardware developed for CLIC,





CLIC CDR https://clic-study.web.cern.ch/content/conceptual-design-report and update https://clic-study.web.cern.ch/content/updated-baseline-document

CLIC technology transfer

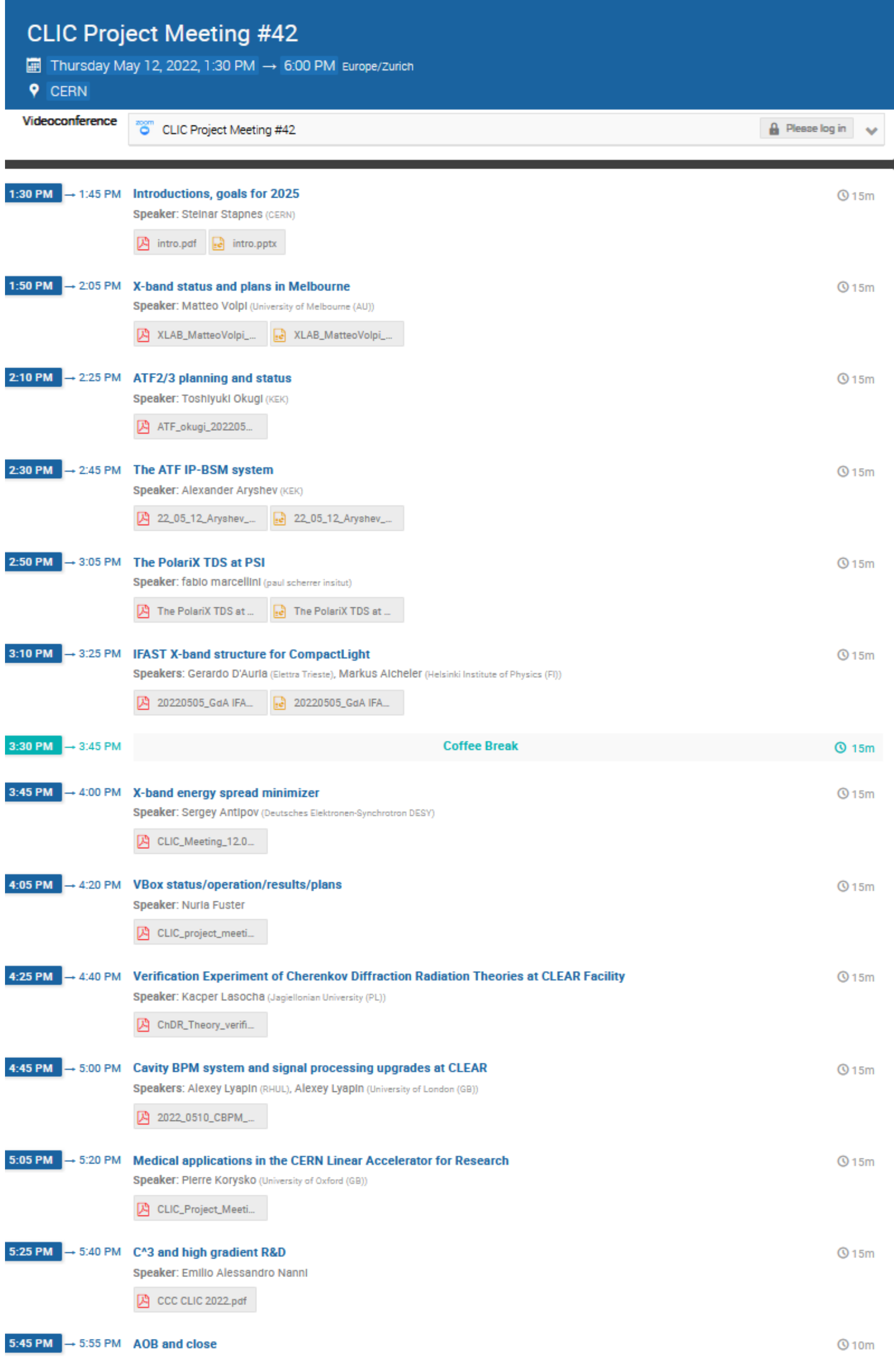
An important priority for the CLIC study has been to help promote the use of X-band and high-gradient technology in diverse applications.

The objectives are to:

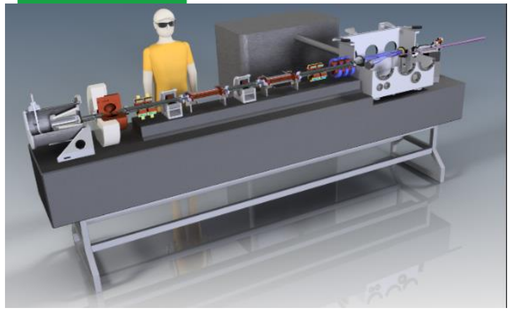
- expand the high-gradient community,
- broaden the technical base,
- add to resources beyond those currently available
- and provide a near-term return on the investment in the technology development we have made.

See for example

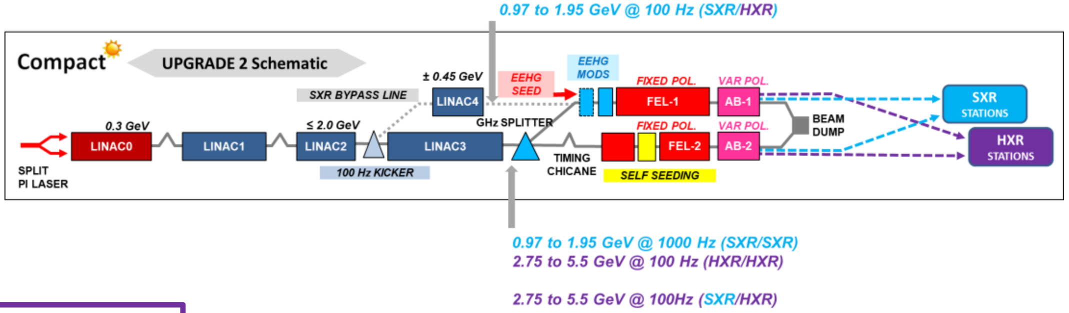
https://indico.cern.ch/event/1147007/



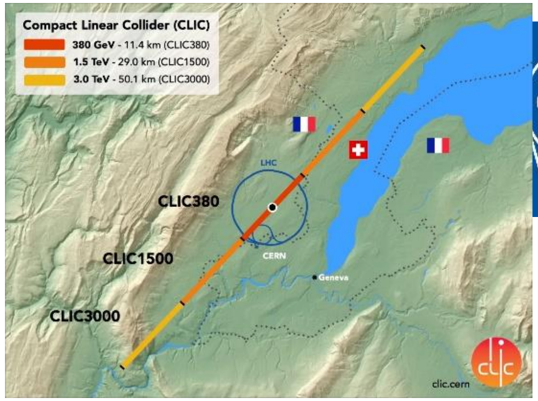
X-band and high-gradient applications overview



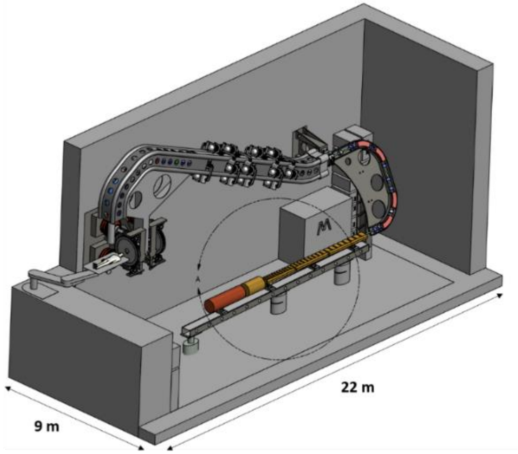
Light source - Inverse Compton Scattering Source



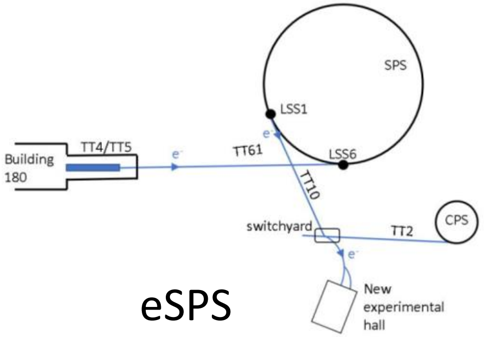
Light source - XFEL



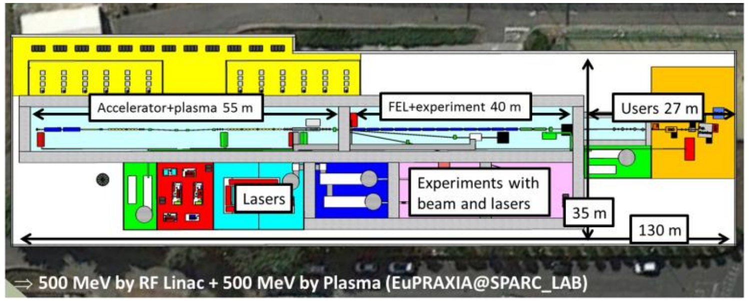
Linear collider



Medical applications

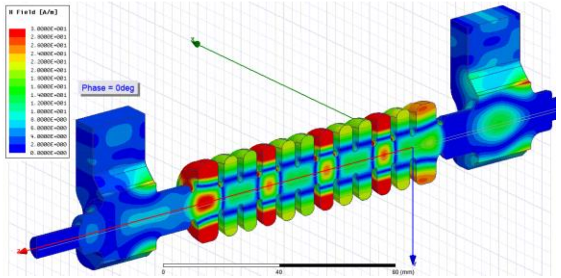


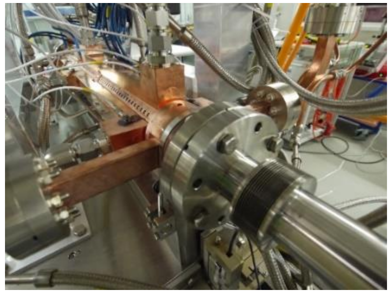
eSPS



⇒ 1 GeV by high gradient RF Linac only (EuSPARC)

GeV-range research linacs





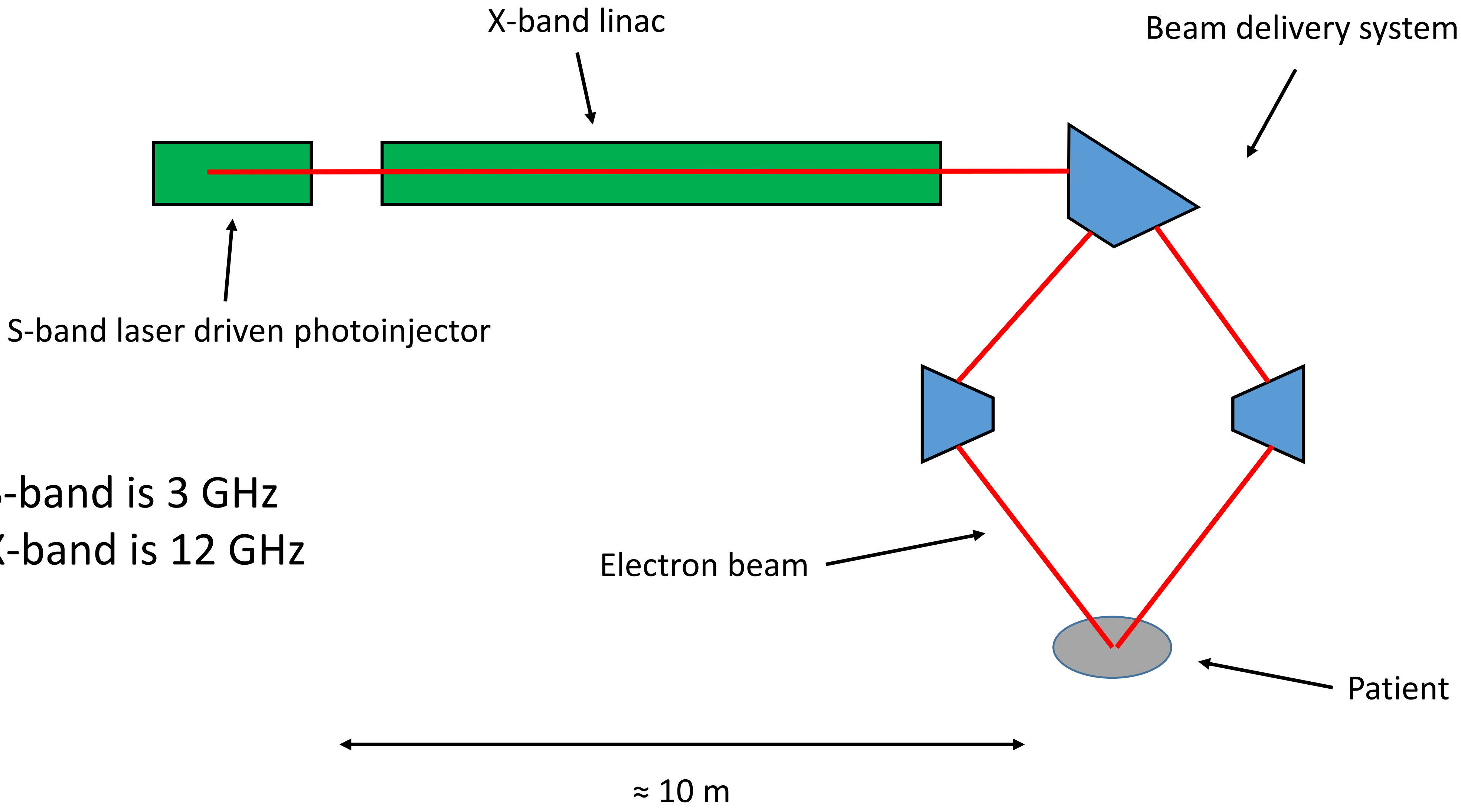
Beam manipulation

Working environment

Let me be clear, I will be vague

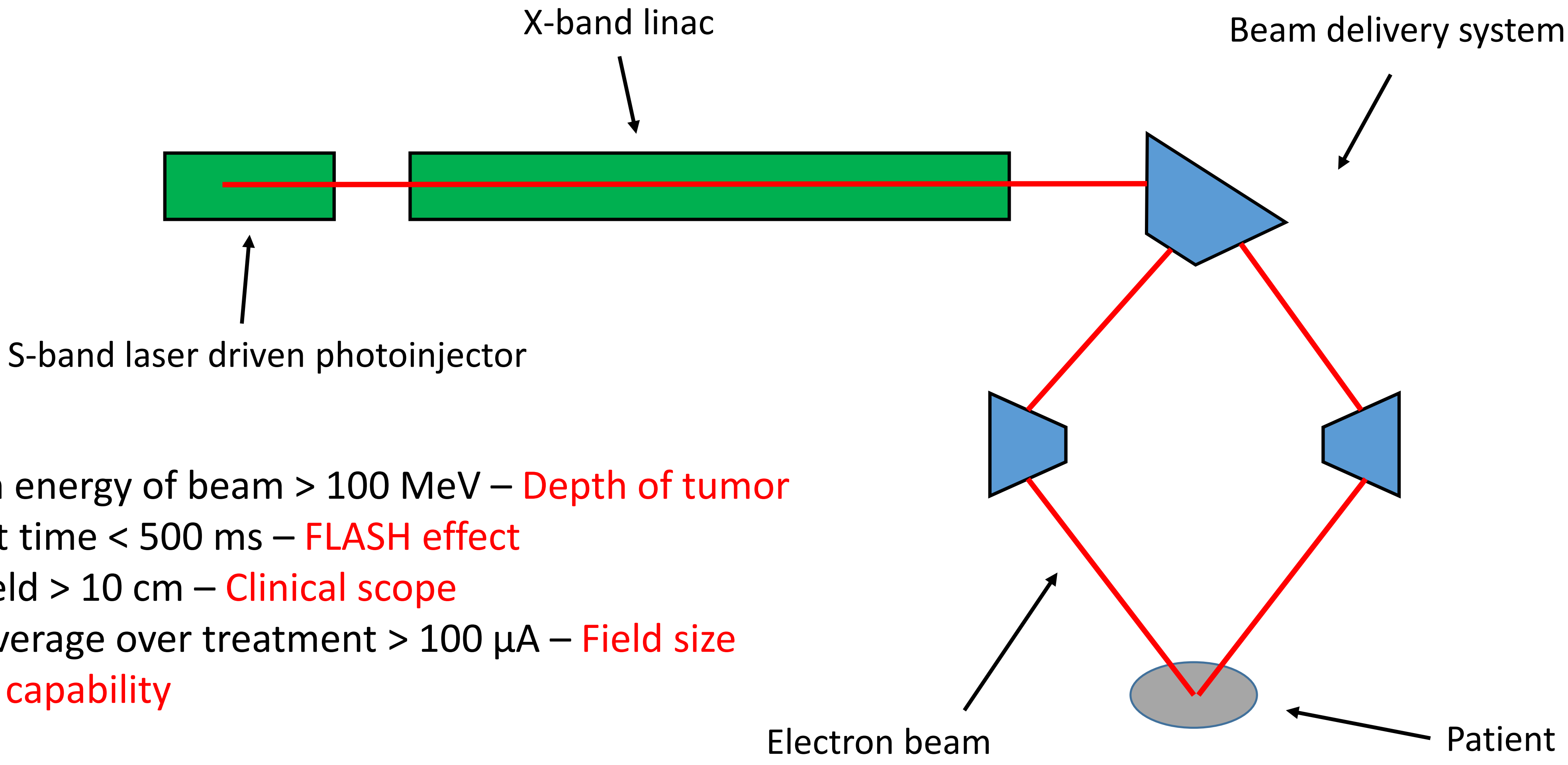
…about many aspects of the project. I apologize, but the medical world is complicated to navigate.
Still I hope to give you a good idea about the basic principles of our facility and an insight into the technology that makes it happen.

Layout



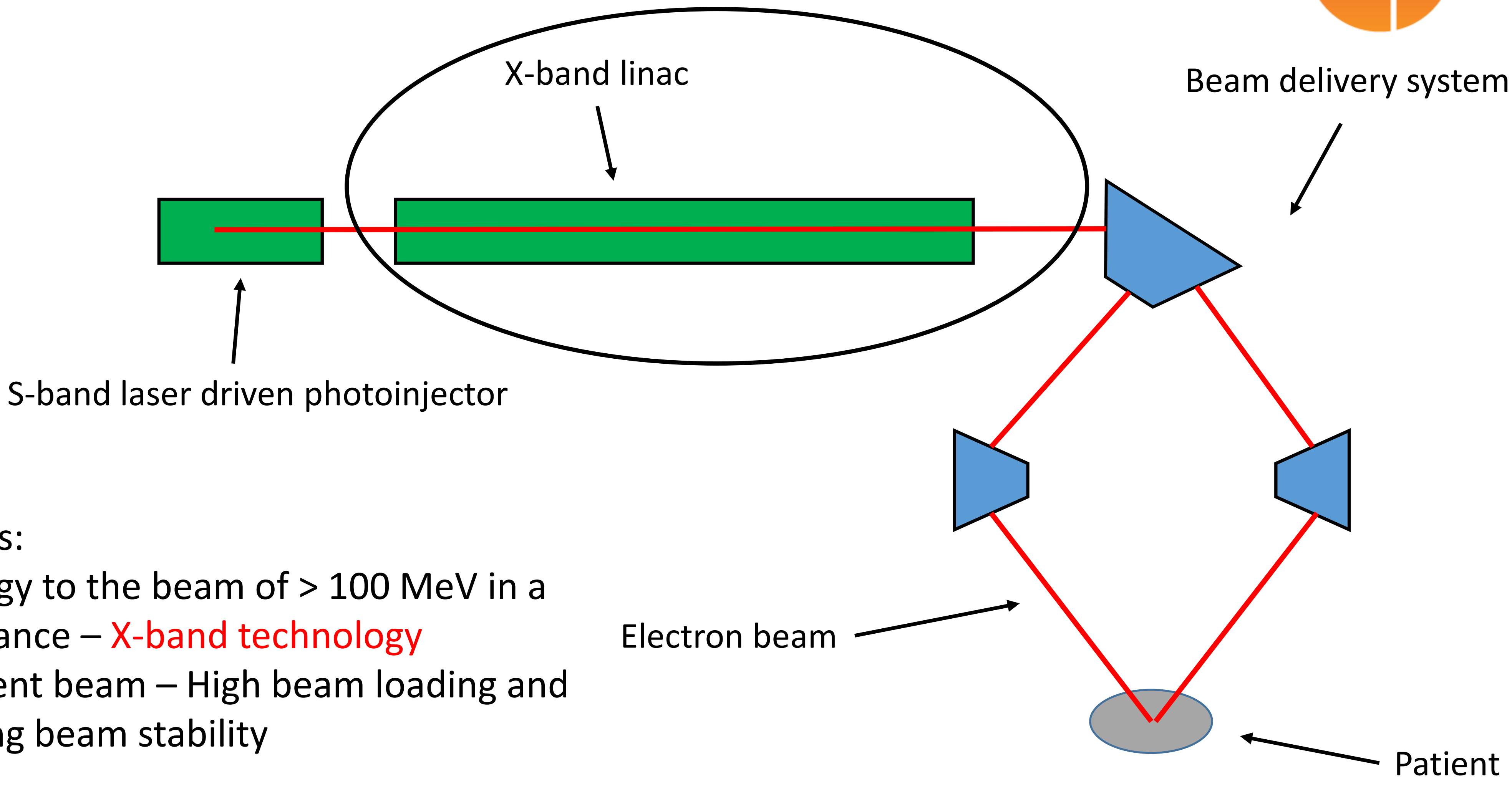
S-band is 3 GHz
X-band is 12 GHz

Basic parameters



- Maximum energy of beam > 100 MeV – Depth of tumor
- Treatment time < 500 ms – FLASH effect
- Largest field > 10 cm – Clinical scope
- Current average over treatment > 100 µA – Field size over time capability

Starting in the middle – the X-band linac

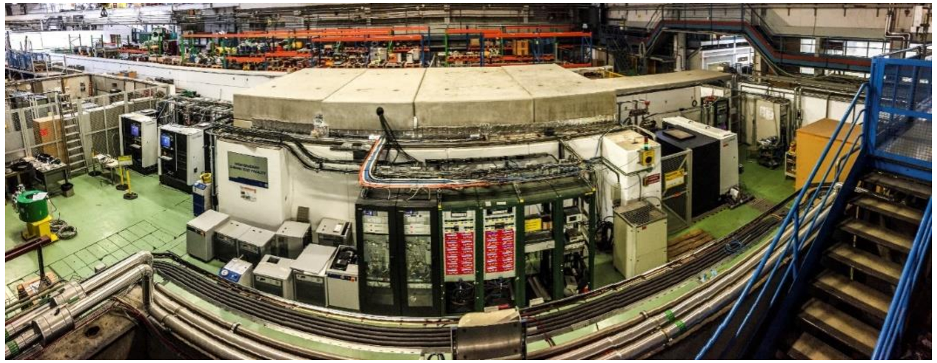


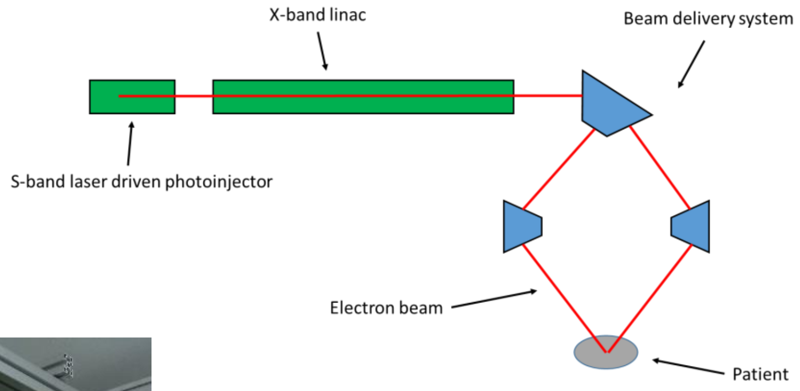
Critical issues:

- Give energy to the beam of > 100 MeV in a short distance – X-band technology
- High current beam – High beam loading and challenging beam stability

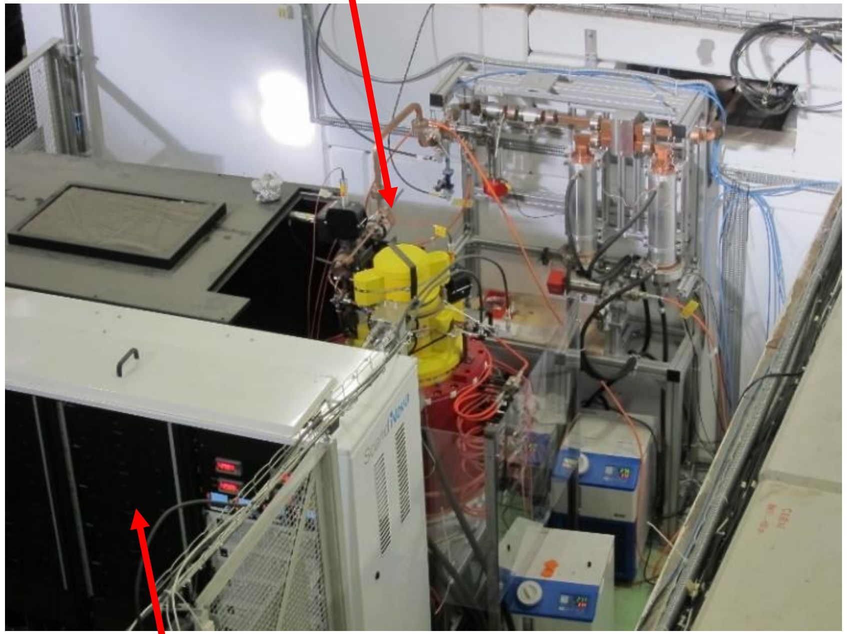
X-band linac hardware

Based on CLIC accelerating structures and XBox test stands.

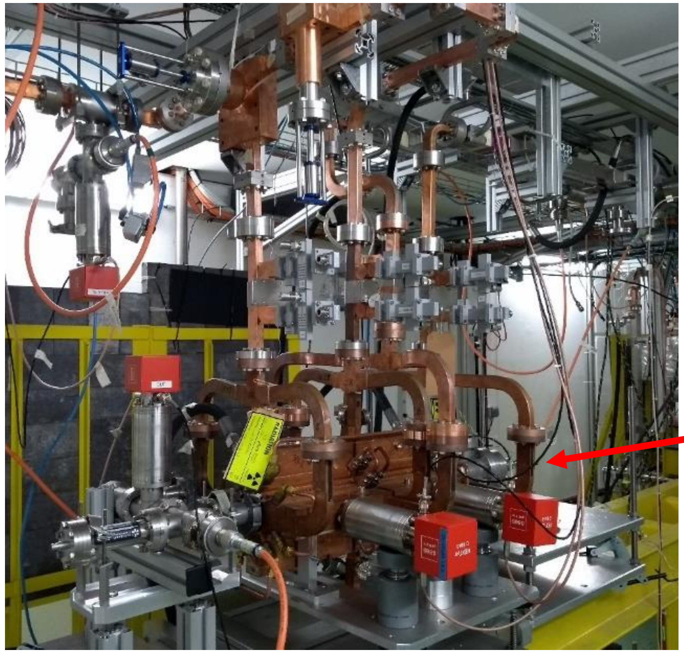




CPI 50 MW klystron

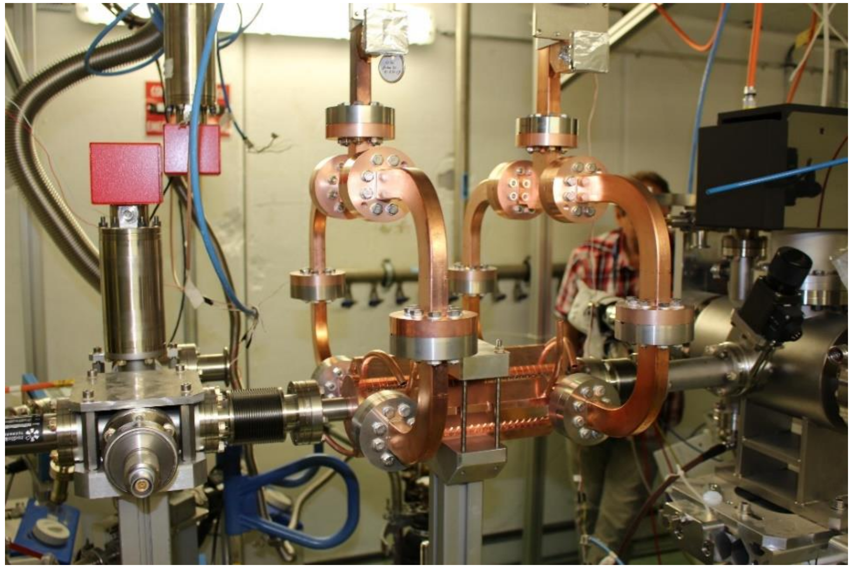


Scandinova solid state modulator

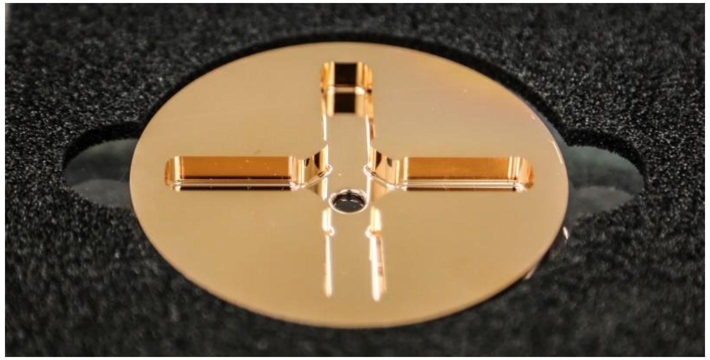


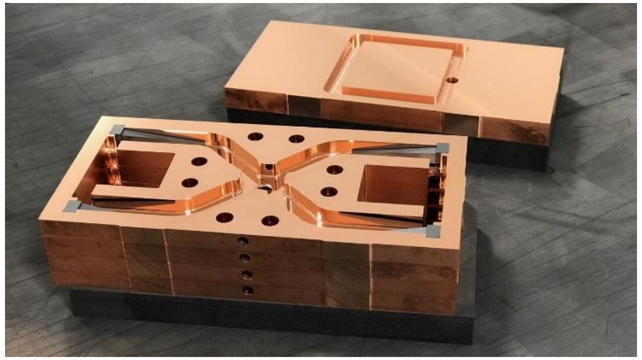
Prototype CLIC accelerating structure

X-band accelerating structures

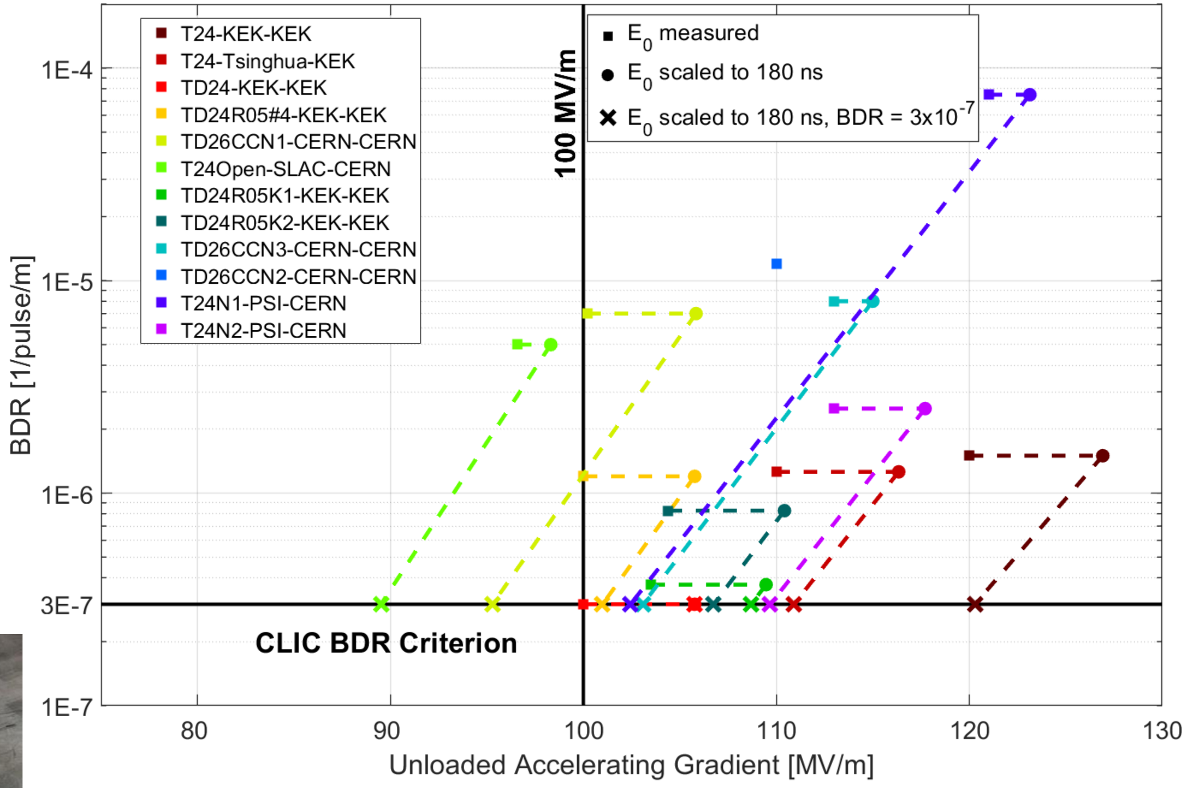


Test structure





Assembly methods



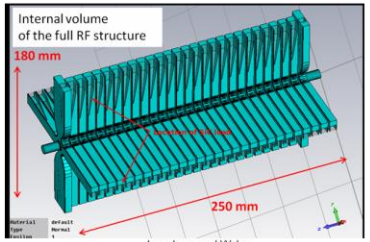
Achieved accelerating gradients in tests

X-band accelerating structures

High-current beam requires Higher-Order-Mode suppression for beam stability, just like CLIC

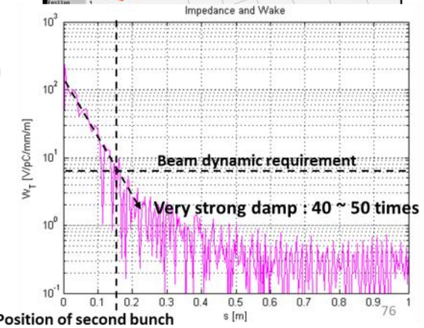
Transverse long-range Wakefield in CLIC-G structure

Structure name	CLIG-G TD26cc
Work frequency	11.994GHz
Cell	26 regular cells+ 2 couplers
Length (active)	230mm
Iris aperture	2.35mm - 3.15mm



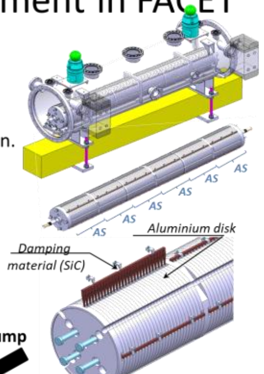
transverse long-range wakefield calculation using Gdfidl code:

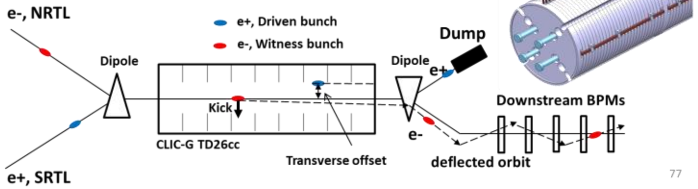
Peak value :
250 V/pC/m/mm
At position of second bunch (0.15m):
5~6 V/pC/m/mm
Beam dynamic requirement:
< 6.6 V/pC/m/mm



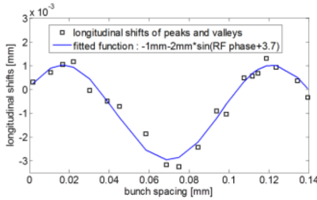
Direct wakefield measurement in FACET

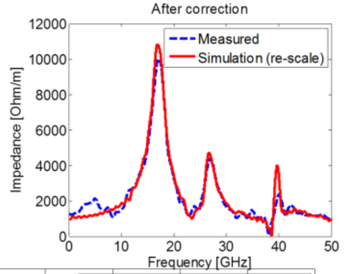
- Prototype structure are made of aluminium disks and SiC loads (clamped together by bolts).
- 6 full structures, active length = 1.38m
- FACET provides 3nC, 1.19GeV electron and positron.
- RMS bunch length is near 0.7mm.
- Maximum orbit deflection of e- due to peak transverse wake kick (1mm e+ offset): 5mm, BPM resolution: 50um

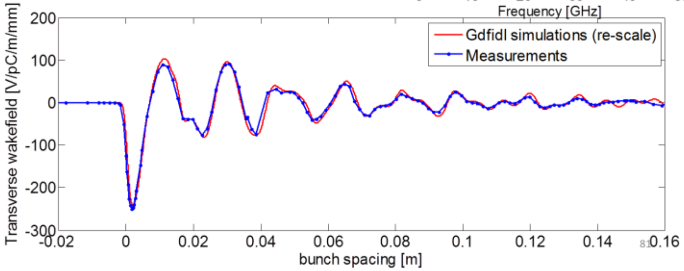


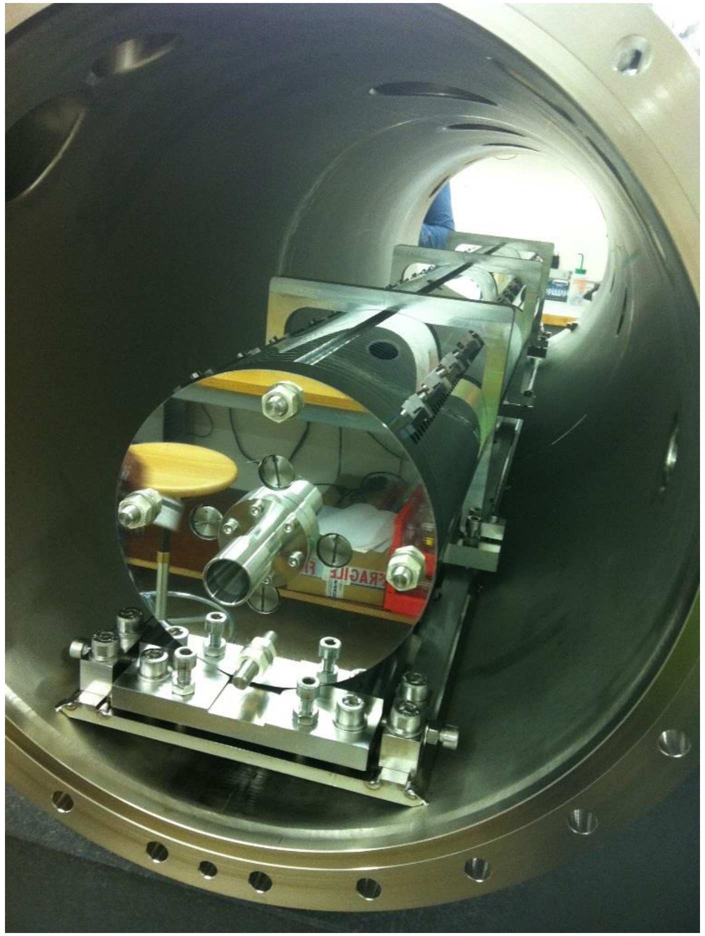


Timing correction



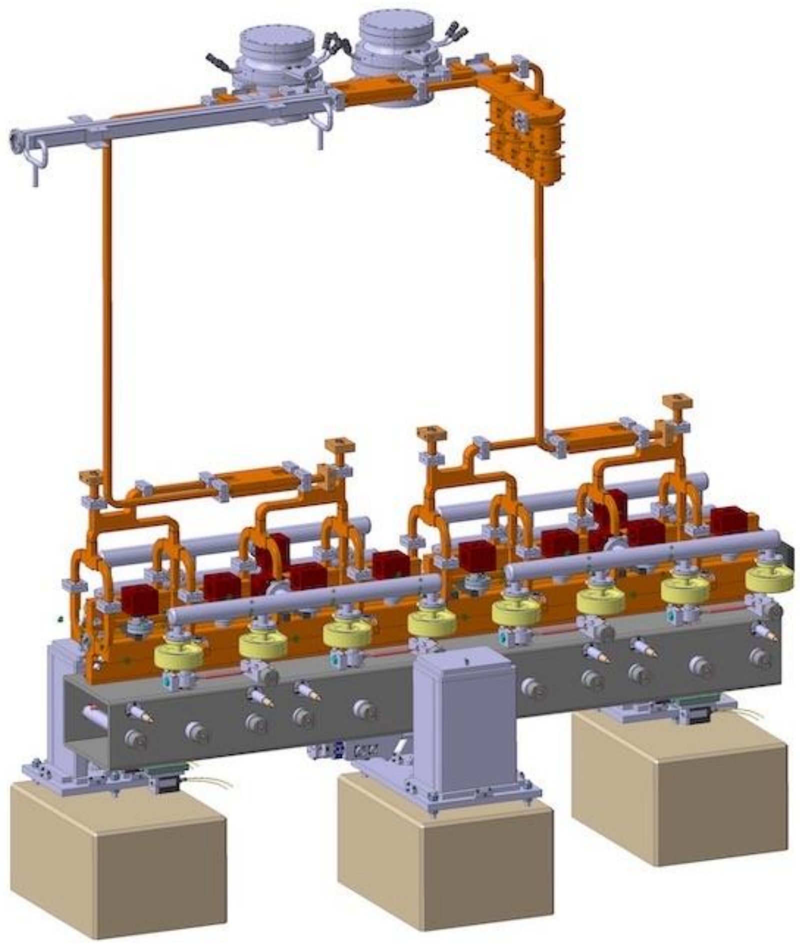


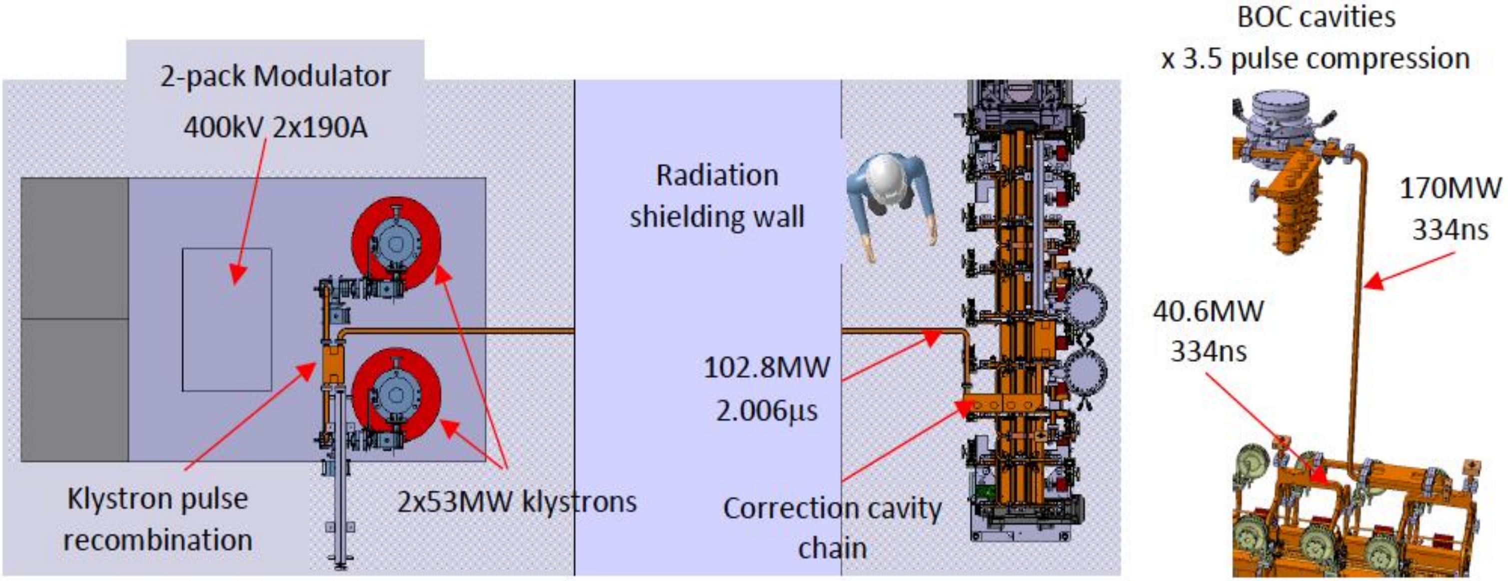




https://doi.org/10.1103/PhysRevAccelBeams.19.011001

CLIC klystron-based rf module



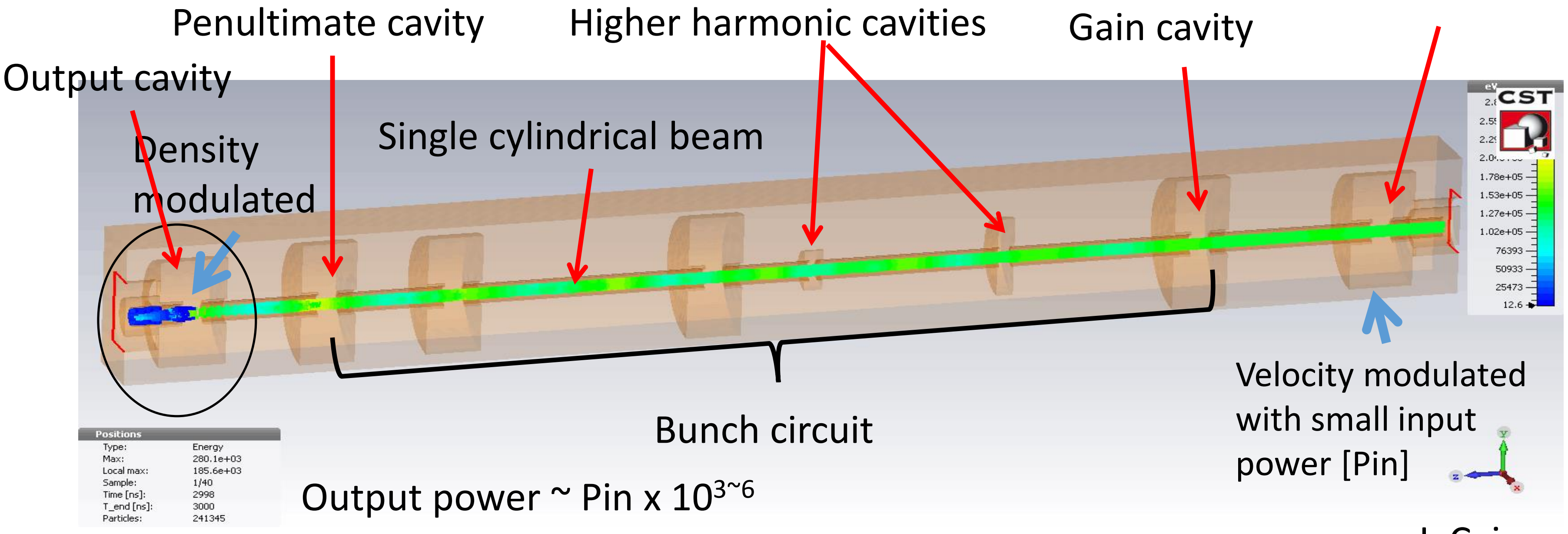


CLIC has as a baseline two-beam RF power generation, but we have also studied a klystron-based version.

- 160 MeV energy gain
- 2 m long
- 1 A beam current
- (round numbers)

High-efficiency power source development

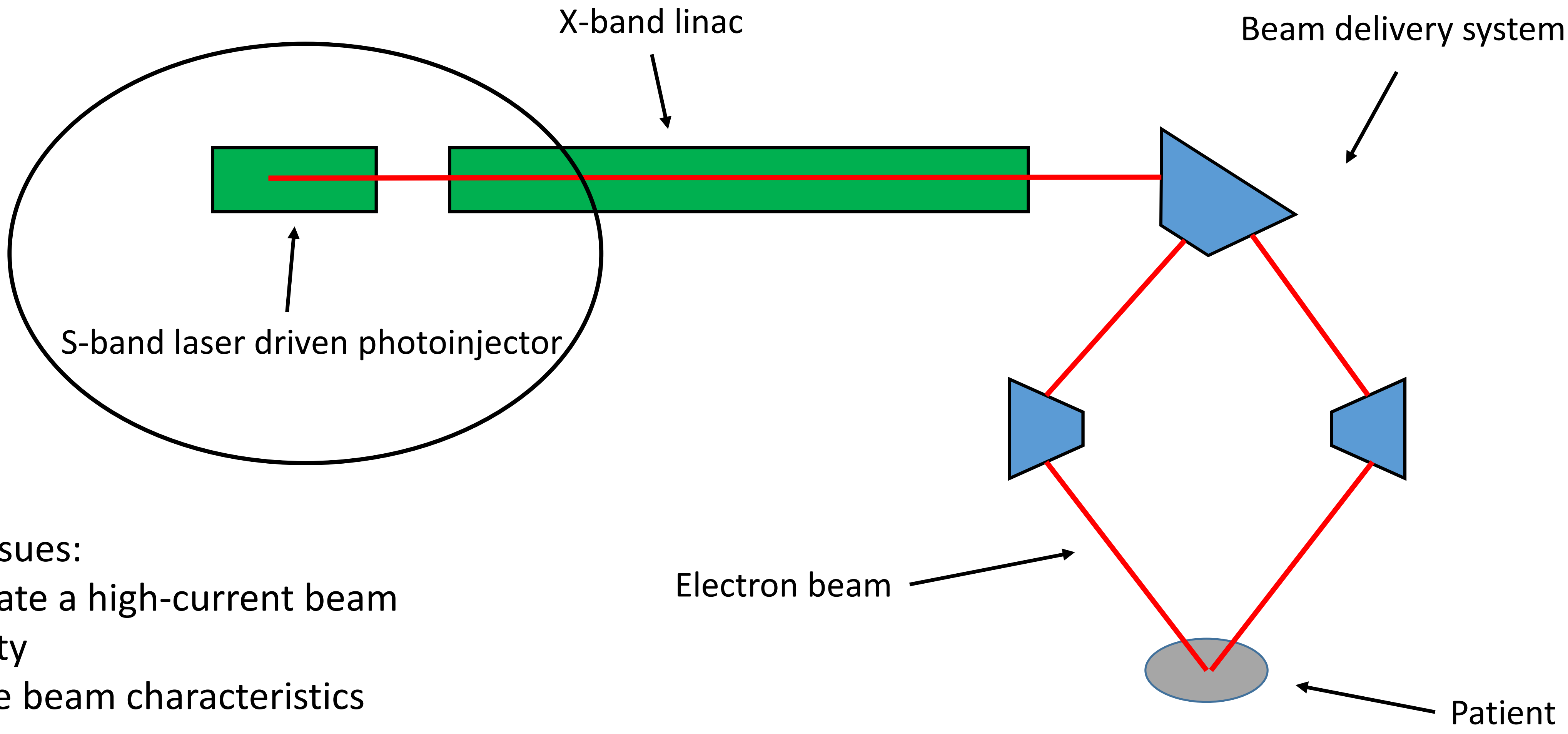
Existing commercial CPI 50 MW klystron in XBox-2



J. Cai

New high-efficiency design fully simulated 36 to 68 % electronic efficiency.
Improves performance and lowers cost for DEFT.

The S-band photoinjector



Critical issues:

- Generate a high-current beam
- Stability
- Precise beam characteristics

Laser-driven RF photoinjectors

Laser-driven RF photoinjectors are a commonly used device to provide well controlled electron bunches in a wide variety of linacs including XFELS, Inverse Compton Sources, ERLs, linear collider related test facilities etc.

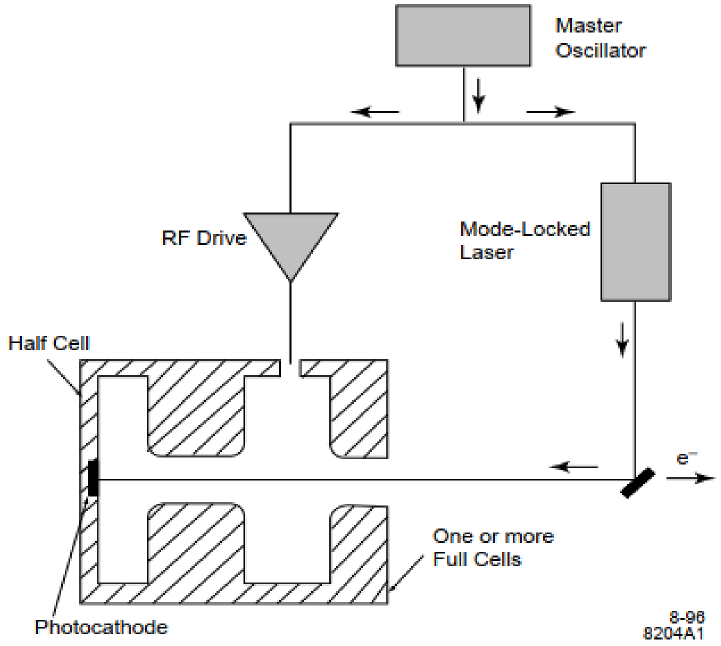
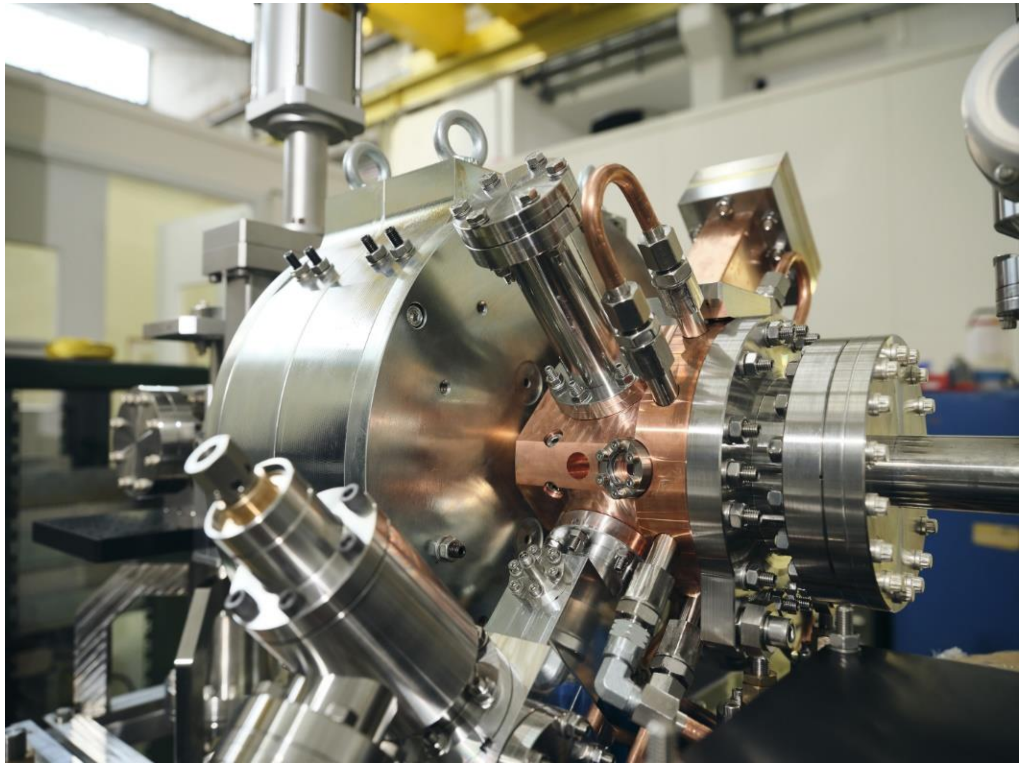


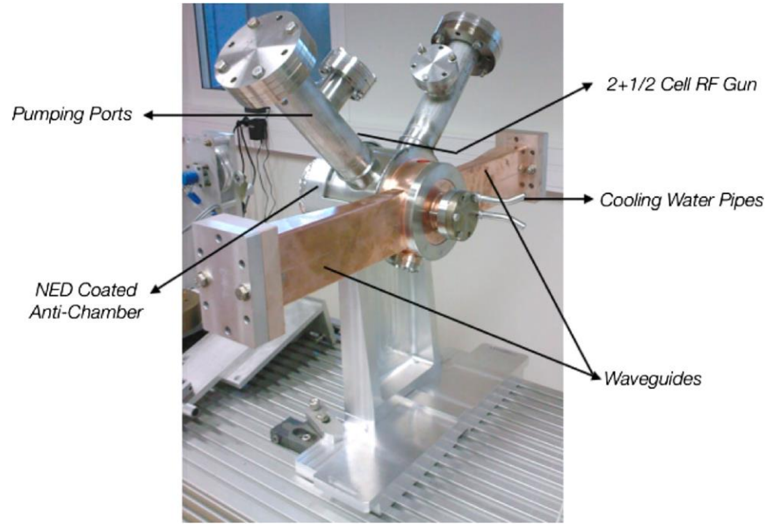
Fig. 1. Principal components of an rf photoinjector.

From J.E. Clendenin, LINAC96



2021 - New CLEAR gun from INFN Frascati

PHIN gun – high-current operation



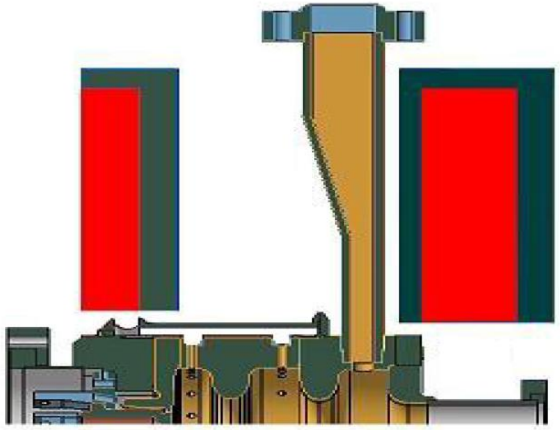
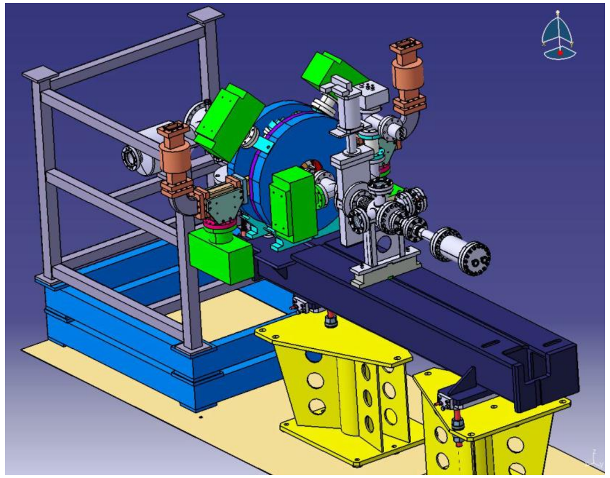


Figure 2: cut in the horizontal plane of the technical drawing of the photo-injector. Red blocks are coils.



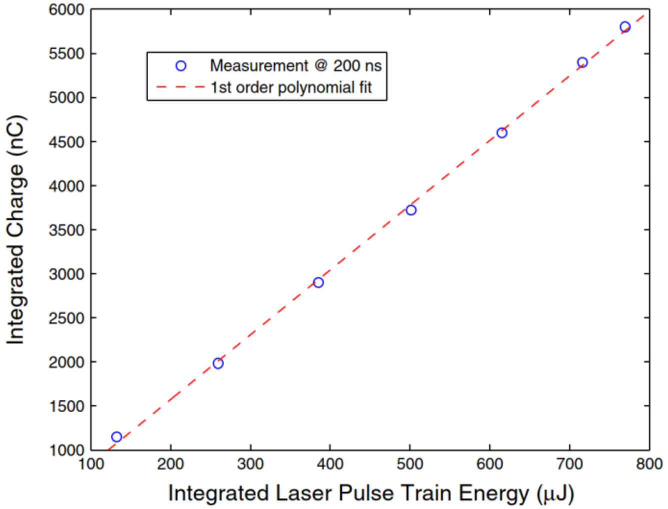
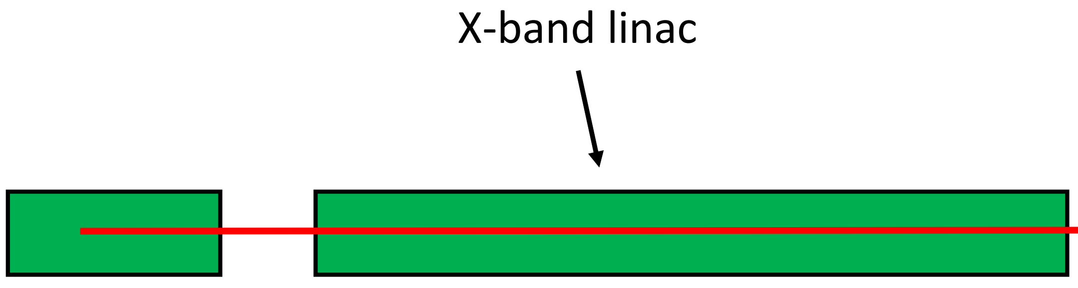


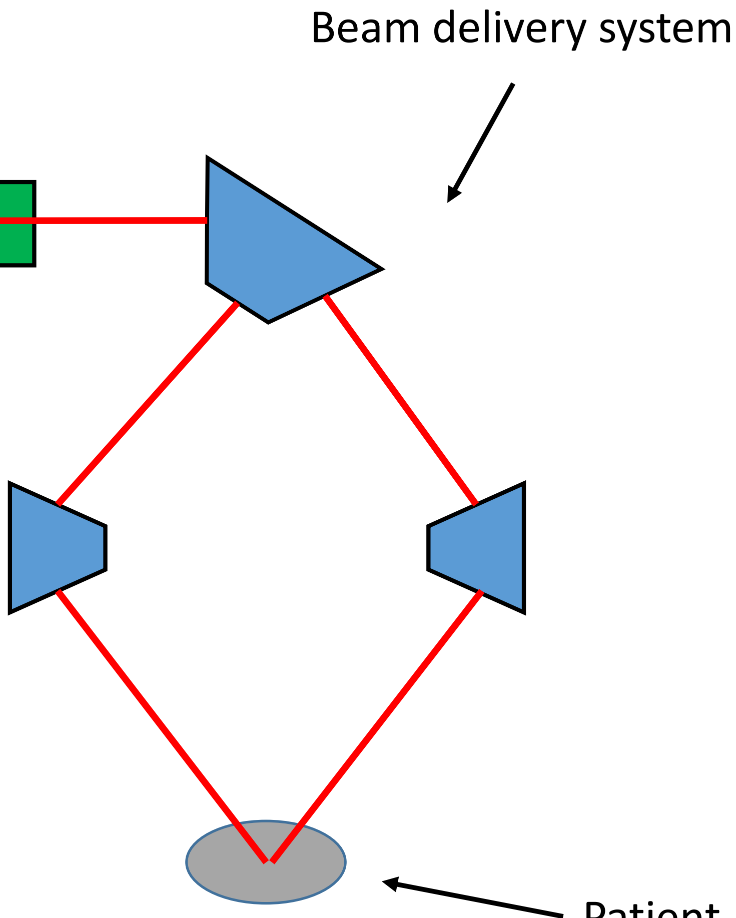
TABLE IV. The specifications for the PHIN photoinjector in comparison with the achieved values during the short intermittent runs between 2008–2011.

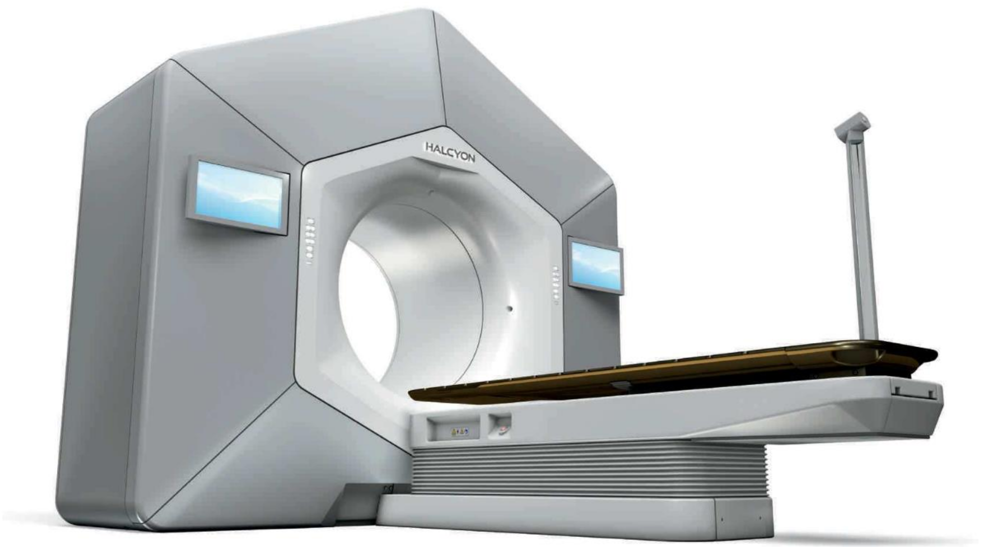
Parameter	Specification	Achieved
Laser		
UV laser pulse energy (nJ)	370	400
Micropulse repetition rate (GHz)	1.5	1.5
Macropulse repetition rate (Hz)	1–5	1
Train length (ns)	1273	1300
Electron beam		
Charge per bunch (nC)	2.33	8.1@50 ns 4.4@200 ns
Charge per train (nC)	4446	5800
Bunch length (ps)	8	6.5
Current (A)	3.5	6.6
Transverse normalized emittance (mm mrad)	<25	14
Energy spread (%)	<1	0.7
Energy (MeV)	5.5	5.5
Charge stability (%, rms)	<0.25	0.8
rf gun		
rf gradient (MV/m)	85	85
Quantum efficiency (%)	3	3–18

https://doi.org/10.1103/PhysRevSTAB.15.022803

The beam delivery system



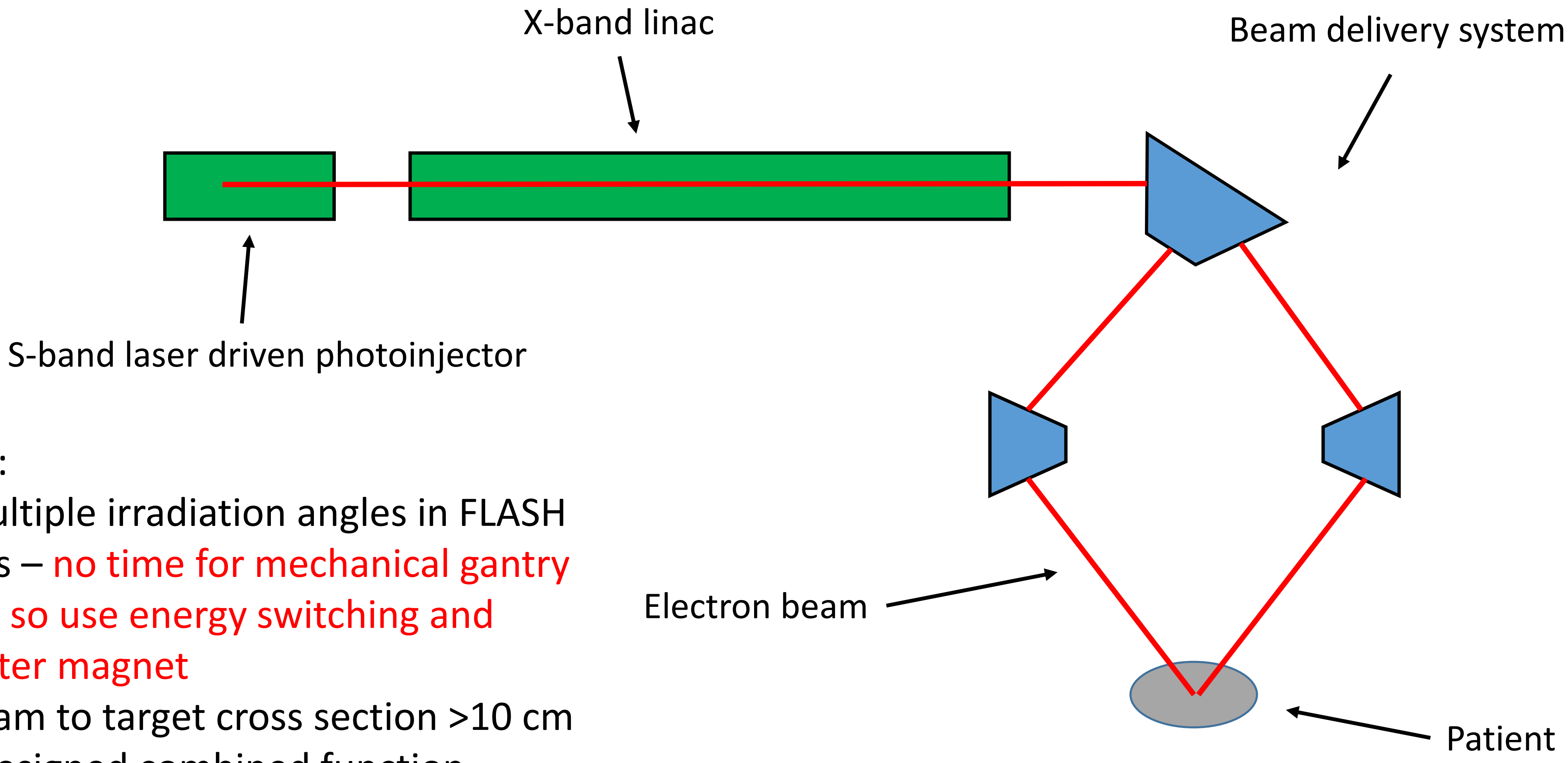




XRay therapy system
from https://www.varian.com/en-ch

(not same scale)

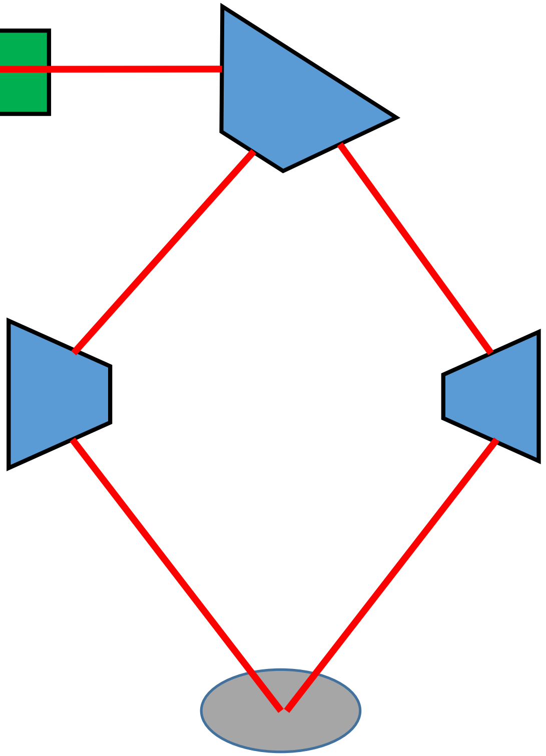
The beam delivery system



Critical issues:

- Provide multiple irradiation angles in FLASH sub-100 ms – no time for mechanical gantry movement so use energy switching and spectrometer magnet
- Expand beam to target cross section >10 cm
- Specially designed combined function separator magnet.

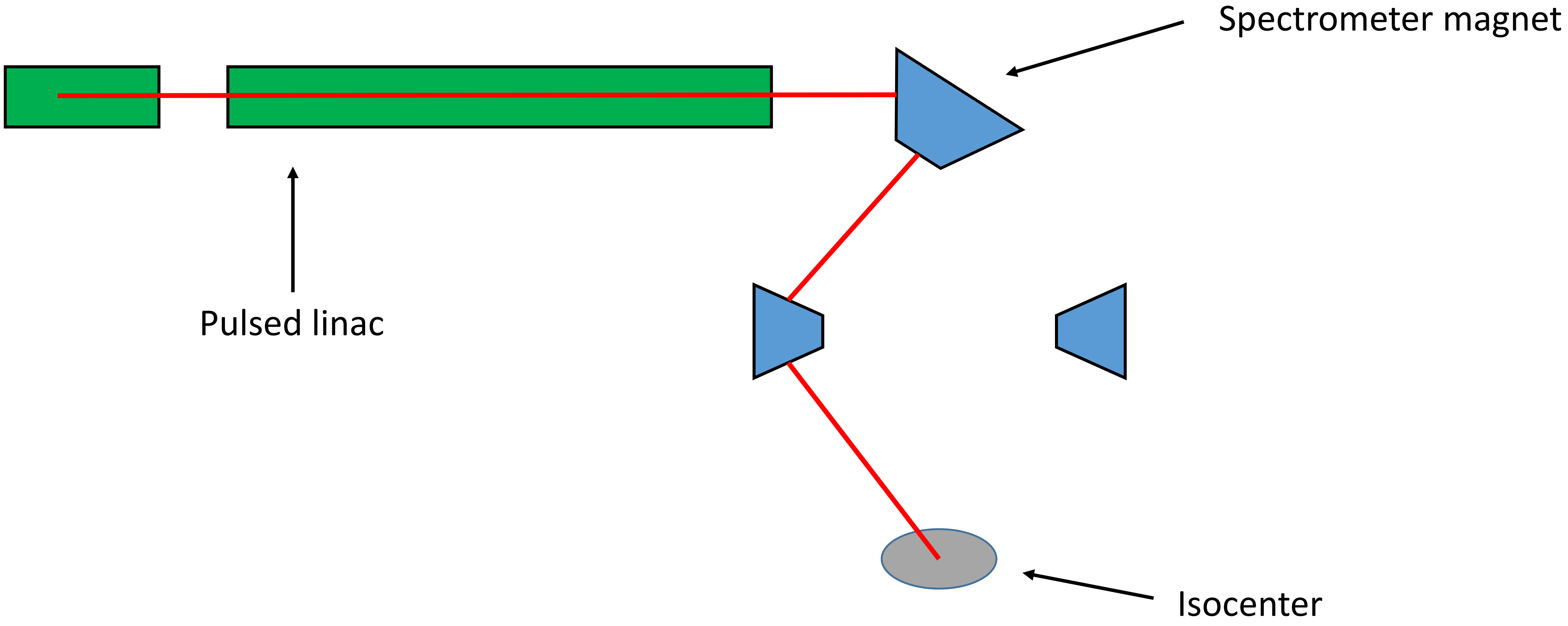
Pulsing and energy modulation



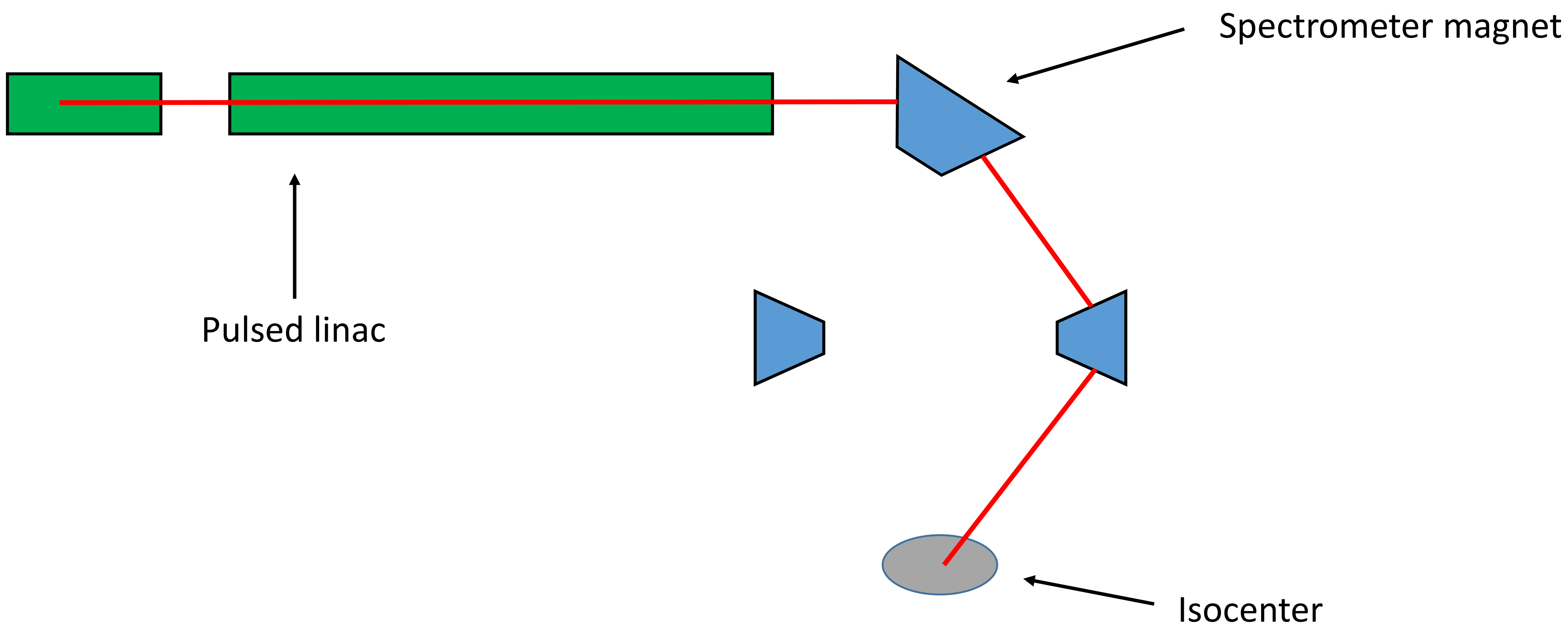
LINAC2

XBox-3 high-gradient test stand. Klystrons operate at 400 Hz, alternatively powering two test slots at 200 Hz.

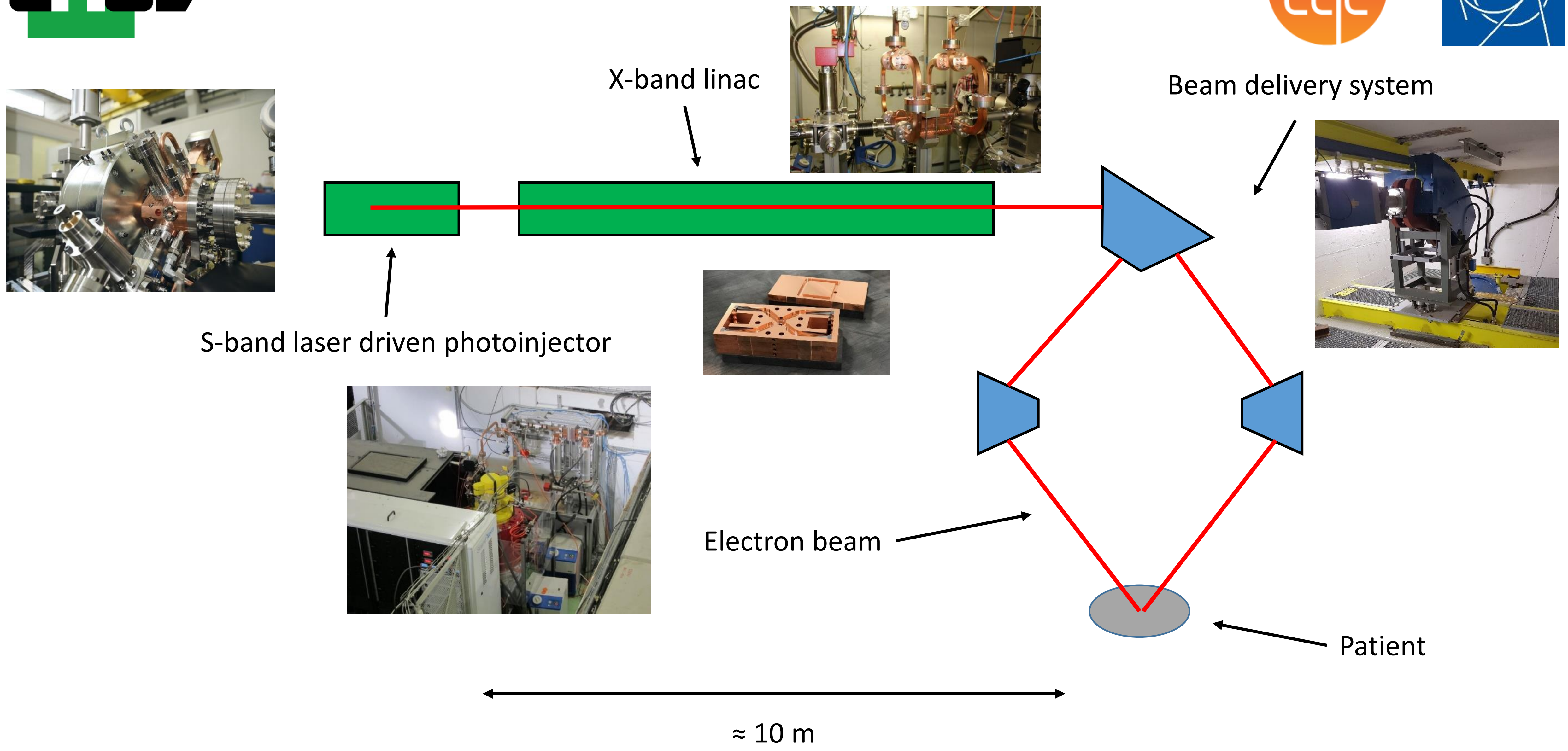
Energy E_1



Energy E_2

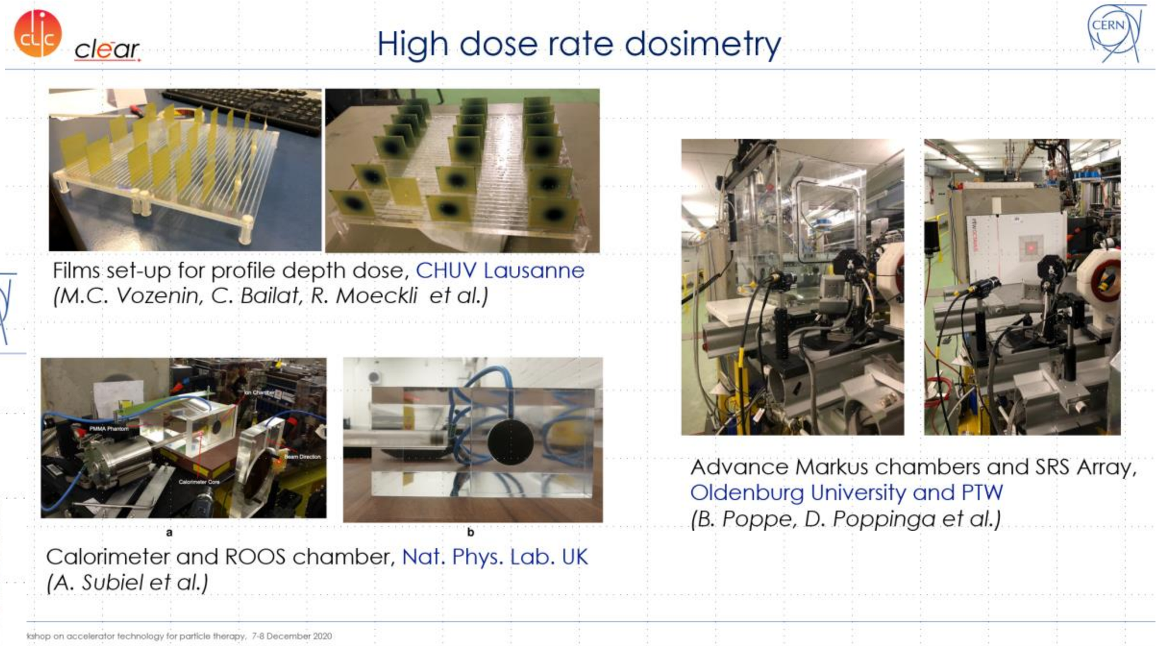


The overview again



In parallel – Active VHEE and FLASH program in CLEAR

CLEAR – 60-220 MeV electron linac user facility serving many communities. Beam diagnostics, THz, plasma acceleration, irradiation and VHEE (Very High Energy Electron) medical.

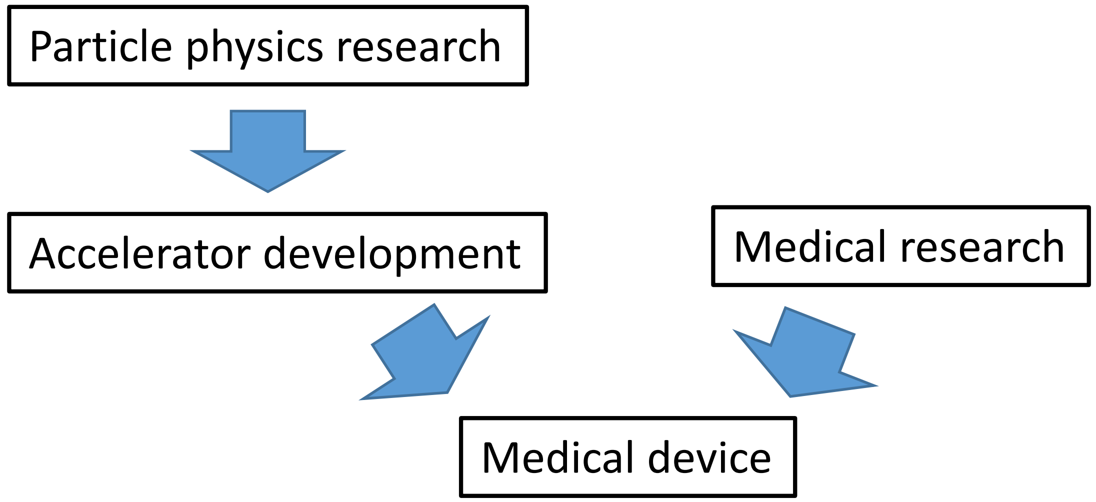


Example of FLASH studies in CLEAR

Conclusions

We are benefiting from a remarkable confluence of a major development in radiation therapy with the fruition of a significant advance in accelerator technology.

The project represents an excellent example of knowledge transfer between fields.



Thank you for your attention!

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