Projet Emblématique

Programme SESAME

PRAE: Platform for Research and Applications with Electrons

PRAE collaboration

Imagerie et Modélisation en Neurobiologie et Cancérologie

Institut de Physique Nucléaire

Laboratoire de l'Accélérateur Linéaire

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Seminar at IHEP/UCAS, March 23, 2018

Sergey Barsuk, LAL Orsay

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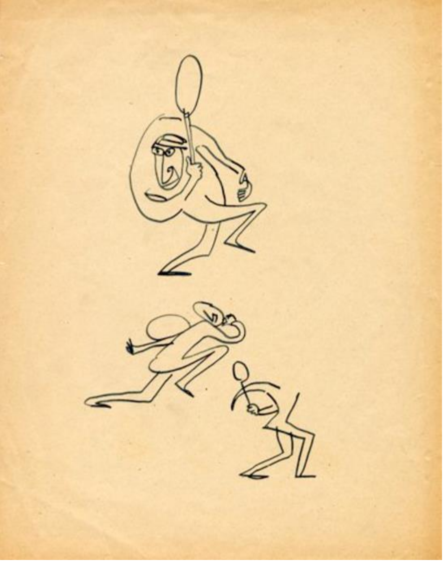
- **PRAE: the multi-disciplinary site** based on the **high-performance electron beam** with the energy of **70 MeV** (intermediate PRAE version) and **140 MeV** (designed PRAE version). Infrastructure and PRAE design allows an upgrade to 300 MeV.

- Mutually linked **axes of PRAE:**

  - **Accelerator: construction of the machine** to **service** other axes with the beam of required performance; **accelerator R&D**
  - **Nuclear physics/nucleon structure**: **proton charge radius measure**
  - **Radiobiology:** new approaches in radiobiology; promising for IMRT (Intensity Modulated Radiation Therapy), radiobiology studies
  - **Instrumentation R&D**: versatile instrumentation **platform**

- Re-use of the **unique site of the former Linear Accelerator** and its infrastructure

- Start of the operation foreseen in 2020-2021.



Bruno Touschek

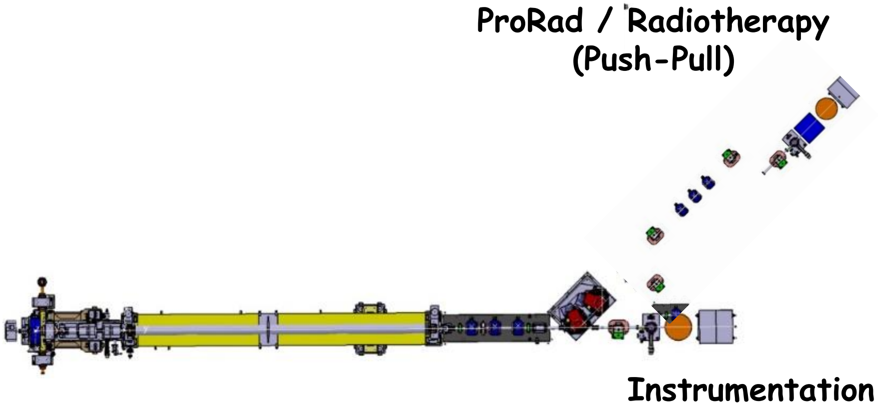
PRAE accelerator

- *Principle goal:* ***core accelerator construction / application***
- *Other studies: R&D high-gradient RF, large intensity dynamic range BPMs, R&D on other accelerator applications*
- *Training of engineers and technical staff*

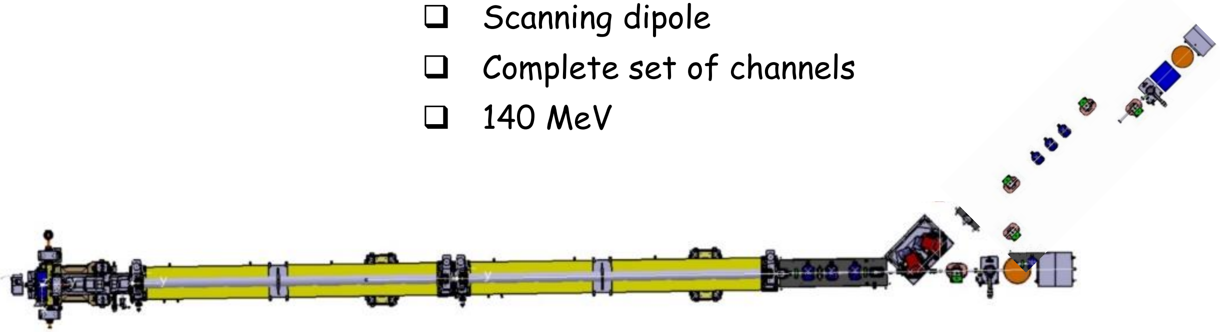
PRAE accelerator: phases of construction

Beam parameters	phase A (B)
Energy, MeV	50-70 (100-140)
Charge (variable), nC	0.00005 – 2
Normalized emittance, mm.mrad	**3-10**
RF frequency, GHz	3.0
Repetition rate, Hz	**50**
Transverse size, mm	**0.5**
Bunch length, ps	**< 10**
Energy spread, %	**< 0.2**
Bunches per pulse	1

- **Phase A:** RF gun at 50 Hz; 50-70 MeV, two lines:
  - Direct for Instrumentation
  - Deviated: magnetic chicane for ProRad and radiobiology in mode “Push-Pull”



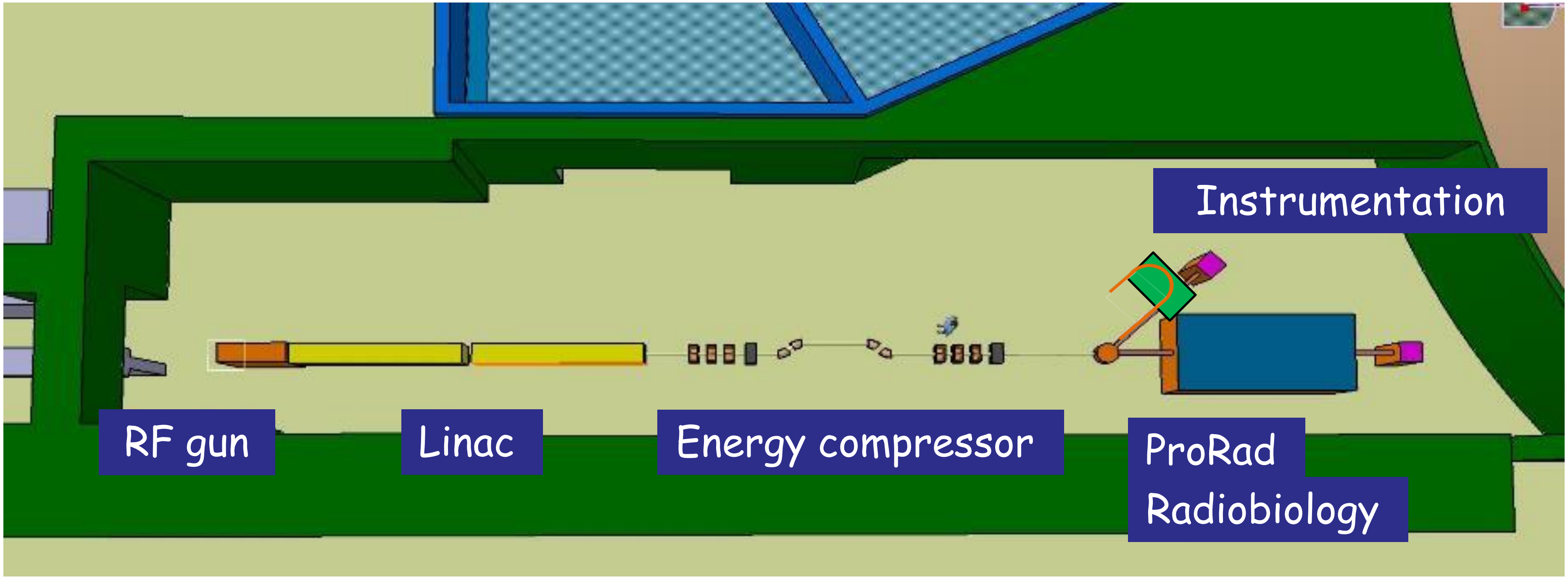
- **Phase B:**
  - Spectrometer for Instrumentation line
  - Scanning dipole
  - Complete set of channels
  - 140 MeV



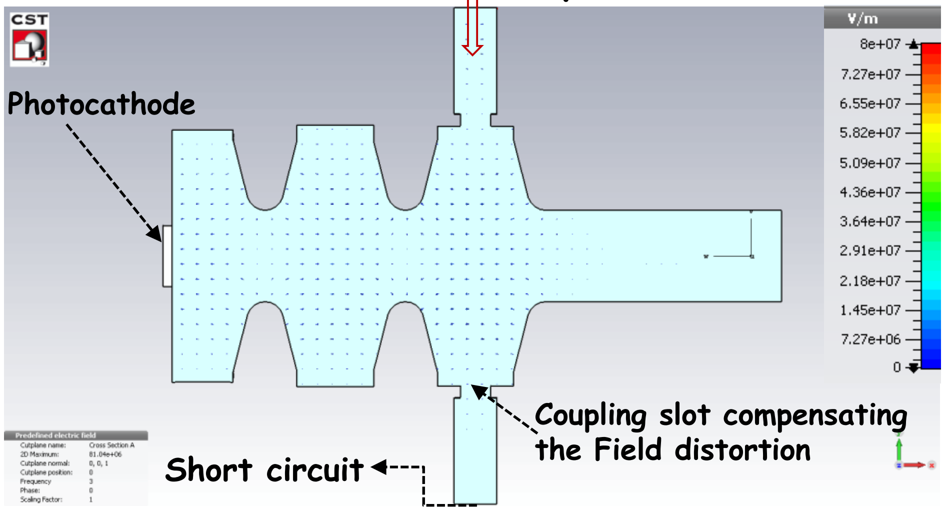
Platform for Research and Applications with Electrons

PRAE

PRAE accelerator: schematic outline



Accelerating gradient (TM_{010} _ π mode):
80 MV/m at P_{in}=5 MW

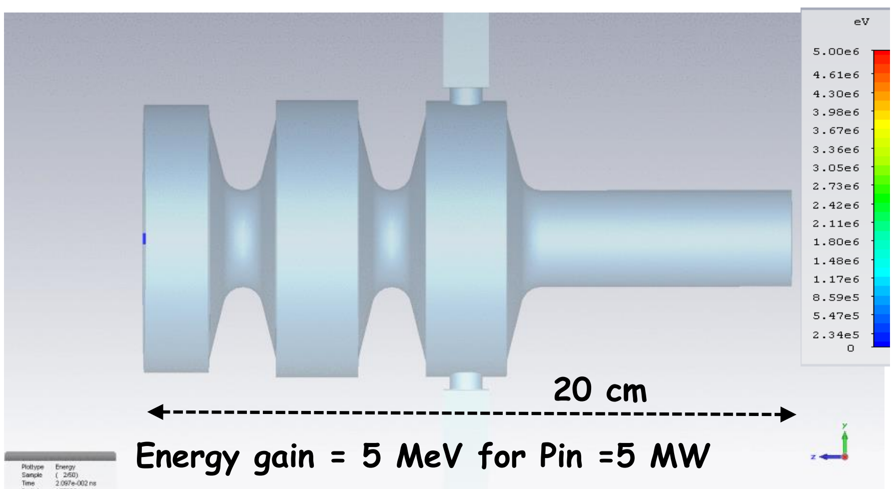


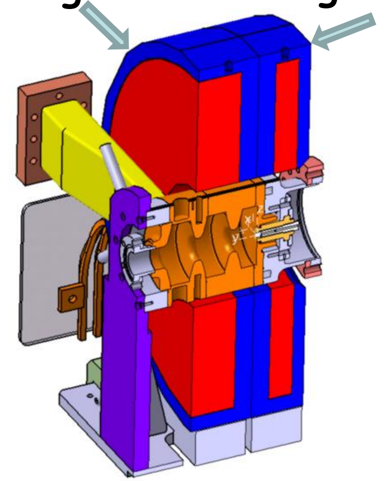
Photoinjector specification

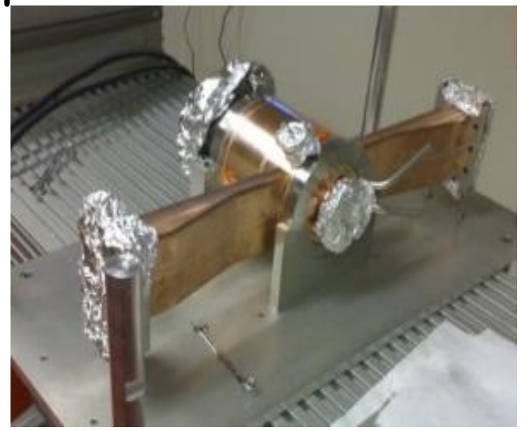
Operation frequency	2998,55 MHz (30°C, in vacuum)
Charge	1 nC
Laser wavelength, pulse energy	266 nm, 100 μJ
RF Gun Q and Rs	14400, 49 MΩ/m
RF Gun accelerating gradient	80 MV/m @ 5 MW
Normalized emittance (rms)	4.4 π mm mrad
Energy spread	0.4 %
Bunch length (rms)	5 ps

2.5 cells RF gun designed and produced at LAL for ThomX

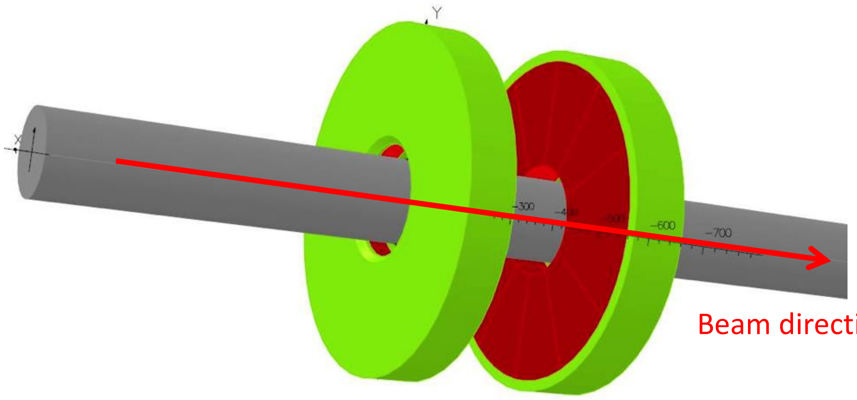
CST-Particle in cells, simulation results

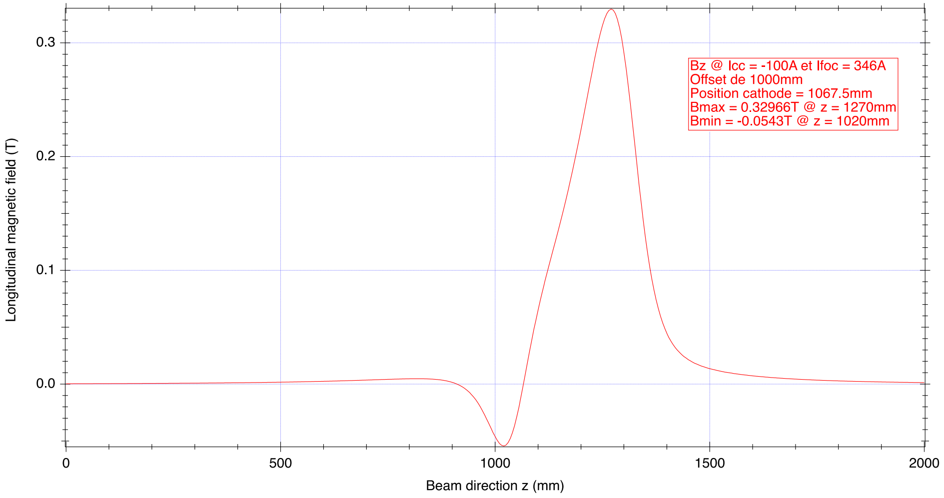






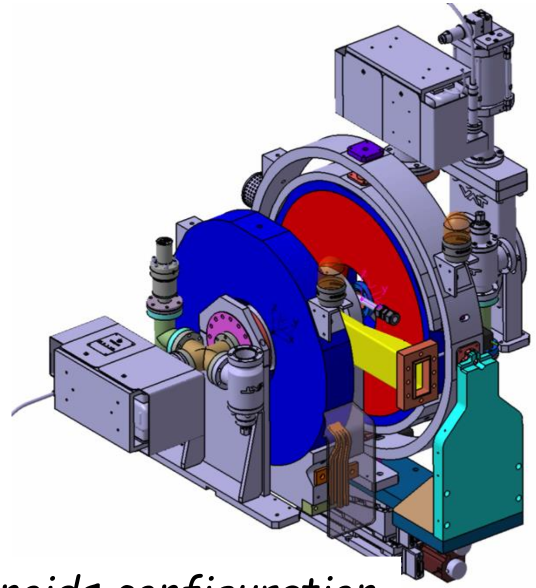
Based on ThomX RF Gun configuration





bobine de contre champ	Pour 4 galettes de 21 spires conducteur 6x6t4 2 circuits d'eau courant de 400A			
	pression (bars)	10	15	20
	puissance (W)	12025	11518	11239
	échauffement (°C)	56.91	43.79	36.58
	débit total (l/min)	3.03	3.78	4.41

bobine de focalisation	Pour 8 galettes de 21 spires conducteur 6x6t4 4 circuits d'eau courant de 400A			
	pression (bars)	10	15	20
	puissance (W)	24051	23036	22478
	échauffement (°C)	56.91	43.79	36.58
	débit total (l/min)	6.07	7.55	8.82



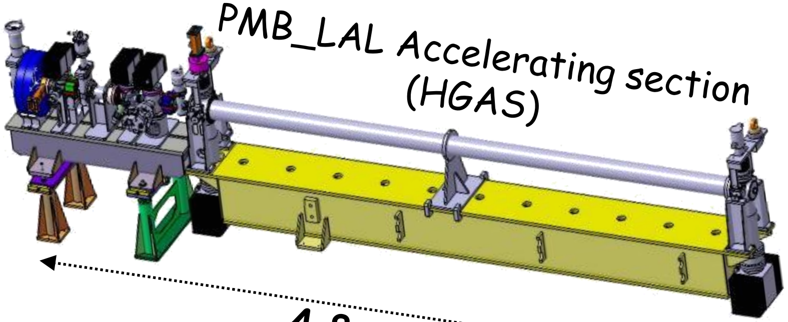
Solenoids configuration

High-gradient linac: LAL - PMB research collaboration

- **High-gradient S-band compact accelerating structure** development (collaboration with industry):

  Development of high-gradient S-band TW accelerating structure (HGAS)

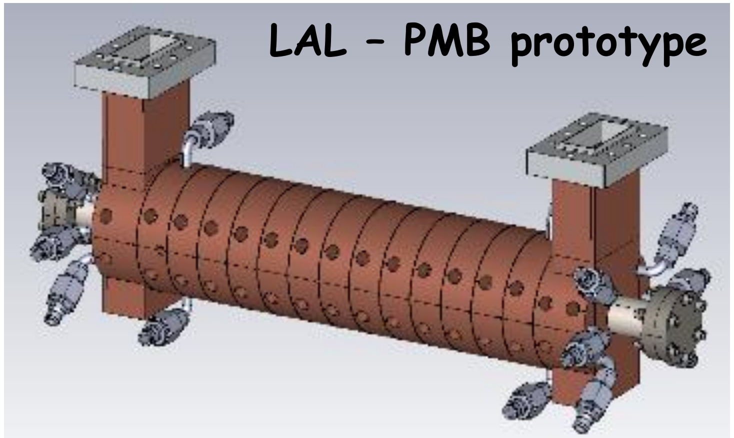
  duration: 2014 - 2018 (4 years)



HGAS Technical specification:

Structure	Disk-loaded
Operation mode or phase advance	2π/3
Operation Frequency	2998,55 MHz (30°C, in vacuum)
Accelerator type	Quasi constant gradient, travelling wave
Accelerating Field for an input peak power of 22 MW	25 MV/m (peak value)
Energy gain for an input peak power of 22 MW	65 MeV (only HGAS)
Quality factor Q	> 14000
Number of cells	94 + 2 coupler cells
Flange to flange length	3,47 m

M. EL Khaldi, L. Garolfi,"RF DESIGN OF A HIGH GRADIENT S-BAND TRAVELLING WAVE ACCELERATING STRUCTURE FOR THOMX LINAC", IPAC2015,
M. EL Khaldi, J. Bonis, A. Camara, L. Garolfi, A. Gonnin, "ELECTROMAGNETIC, THERMAL AND STRUCTURAL DESIGN OF A THOMX RF GUN USING ANSYS", Proceedings IPAC2016



- RF design has been performed & main requirements accomplished
- Prototype mechanical drawings

- Aluminum prototype fabrication is finished (check out & validation of all technical choices) → not validated.
- Low power tests and thermal analysis completed
- Copper prototypes will be constructed in order to validate the fabrication process
- High power tests of the Copper prototype will be done in collaboration with the IFIC HG-RF lab.
- Beam dynamics simulations of the accelerating section are underway using ASTRA and RFTrack (benchmarking)

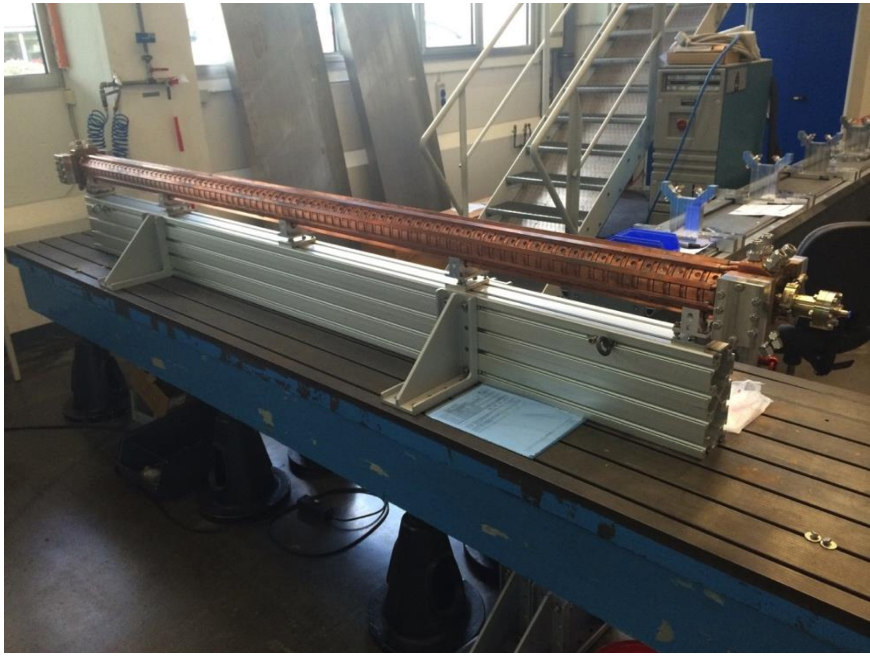
High-gradient linac: RI company

TW S-Band structures from RI

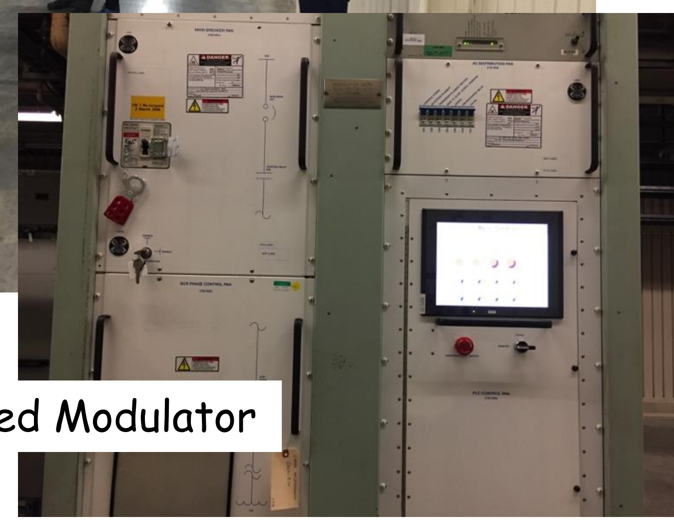
research instruments

Parameter	Value
Length	3.5m
Number of Couplers + Cells	1+96+1
Type	Constant gradient
Phase Advance	$2\pi/3$
Frequency	2998.55 @ 30° C
Pulse Width	3μs
Repetition Rate	50Hz
Max. input Power	40 MW
Max. average power	5 kW
Guaranteed unloaded energy gain	>65MeV

- SLAC-type structures
- Constant gradient
- Race track coupler for quadrupole compensation
- BIG Splitter for dipole compensation
- 2 RF loads



- **RF powering:** Second generation SLAC **modulator** from S-band old 30 GeV linac being recuperated



Refurbished Modulator

❑ **RF powering:** the klystron characteristics

Klystron Specifications:
Frequency Functioning mode : Pulsed
Repetition Rate : 50 Hz
Beam Pulse Width (mid-height) : ≥ 6,5 μS
RF Pulse Width (flat top) : ≥ 4,5 μS
Peak RF output power: ≥ 45 MW
Average RF output power : ≥ 10 kW
Nominal beam voltage : 305 kV
Nominal beam current : 340 A
Micro-perveance : 2
Efficiency (@ saturated RF output power) : ≥ 43%
Gain (@ saturated RF output power) : ≥ 47
Bandwidth -1dB (@ saturated RF output power): ≥ 8 MHz
RF input power : ≤ 500 W
Nominal load VSWR : ≤ 1.1:1
Sustainable load VSWR : ≥ 1.35:1

Communications & Power Industries
microwave power products division

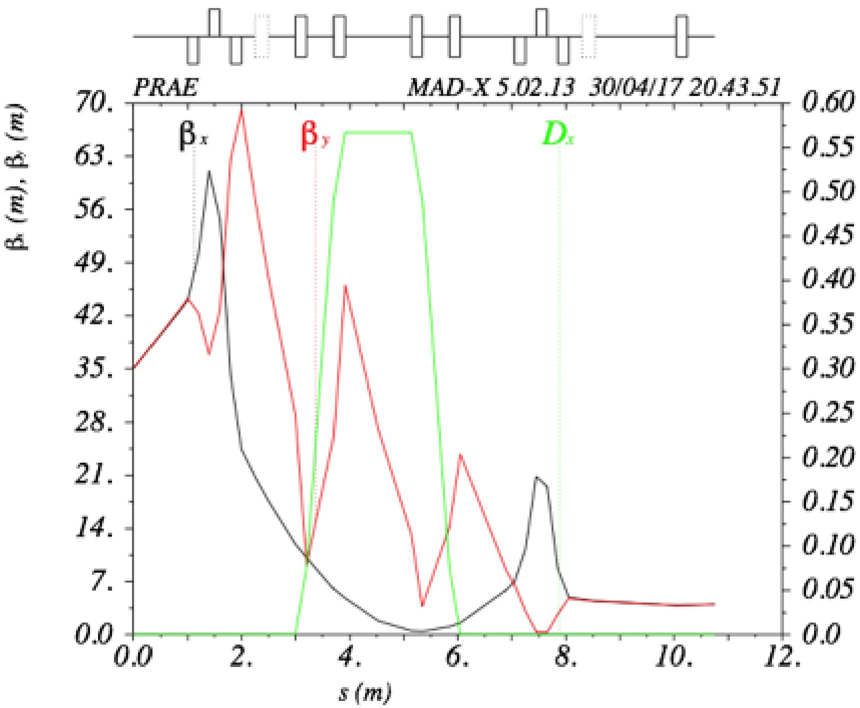
Focusing Electromagnet:
Coils : high impedance

Connections:
RF Input : Type N
RF Output : WR284 with crush-seal vacuum flange LIL type (use of SF6 acceptable with pressurization between 2,4 bar and 3,1 bar)

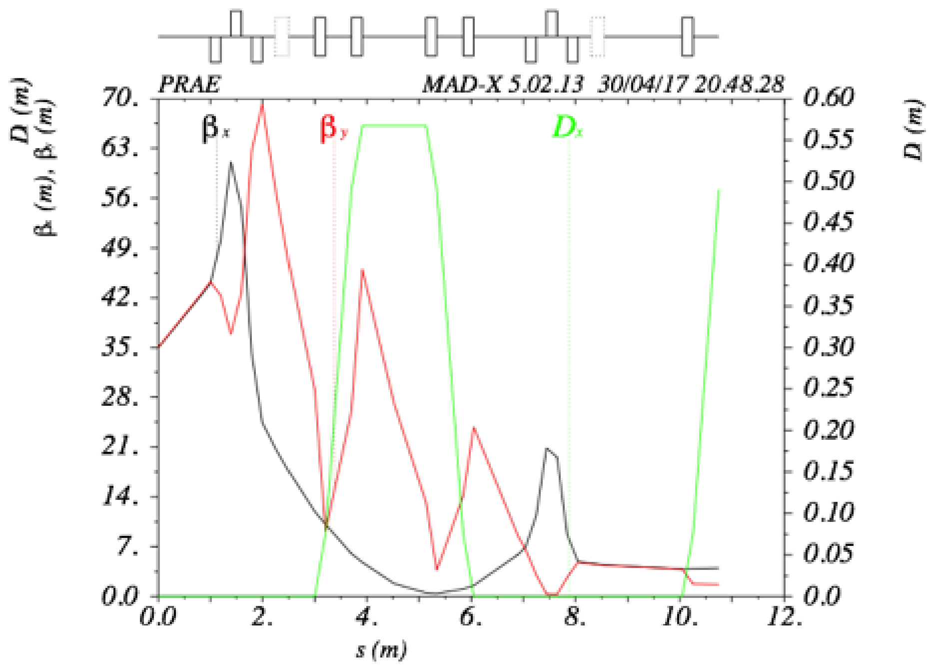
Tank oil with functionalities adapted to SLAC modulator

Platform for Research and Applications with Electrons

- Two triplets, flexible final conditions, with Energy compression System (ECS) in the direct line and a dedicated Beam Energy Measurement in the deviated line.

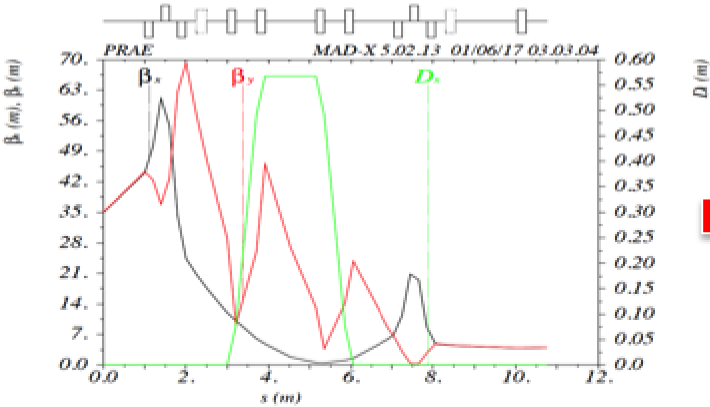


Direct line:
ProRad and Radiobiology



Deviated line:
Instrumentation

ECS dipoles (150 MeV)



Initial parameters :

σ_x = 6.53mm => $\pm 8\sigma_x$ = 105mm

σ_y = 1.43mm => $\pm 10\sigma_y$ = 30mm

Deviation angle = 45°

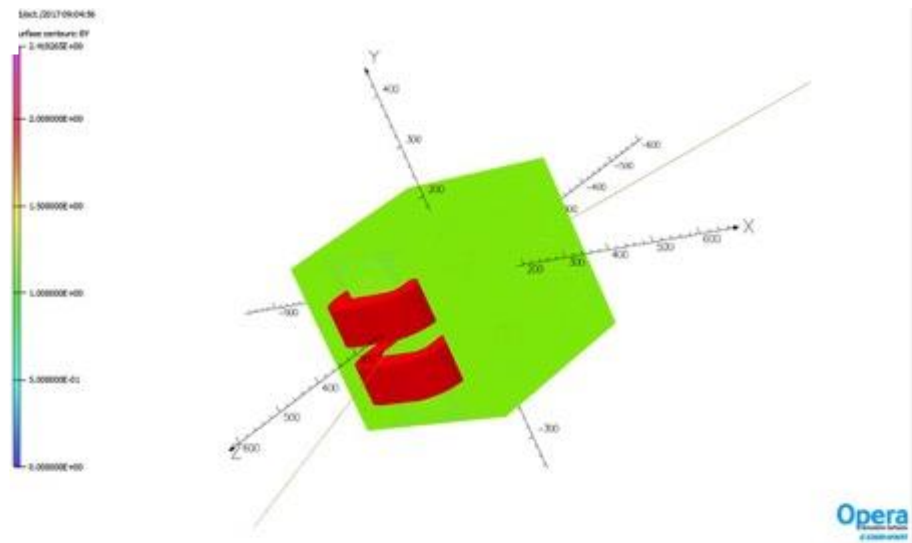
E = 150MeV

GFR = ± 15mm

Gap = 40 mm

Main parameters of the yoke @ 150 MeV

Gap (mm)	40
Center magnetic field (T)	1,0643
Curvature radius (°)	45
Pole width (mm)	120
Pole height (mm)	90
Yoke length (mm)	347
Yoke thickness (mm)	350
Chamfer entrance/exit (mm)	10*10



Main parameters of the coil @ 150 MeV

Ampere-turns	18000
Number of double pancakes vertical	6
Number of double pancakes horizontal	10
Number of turns	60
Current (A)	300
Conductor size (mm)	7*7
Cooling diameter conductor size (mm)	4
Number of circuits	4
Current density (A/mm2)	8,28
Conductor length (m)	78,00
Résistance/magnet (ohm)	3,85E+01
Voltage drop/magnet (V)	23,08
Power/magnet (kW)	6,92
Number of cooling circuits	4
Water temperature rise (°C)	6
Pressure drop (bar)	7
Flow rate/magnet (l/mn)	2,24
Cooling water speed (m/s)	2,97
Reynolds number	0,03

B1 = 1,0643 T

Homogeneity = 5.10^{-4} in the GFR

Magnetic length = 383 mm

- ❑ Pre-design is finished

Initial parameters :

R = 20mm

k = 28m^{-2}

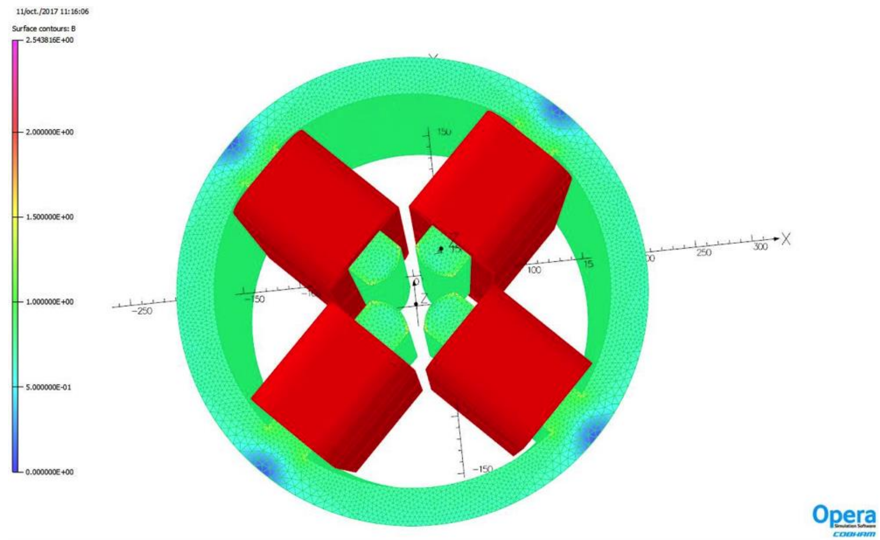
E = 150 MeV

Main parameters of the yoke @ 150 MeV

Gap (mm)	40
Center magnetic field gradient (T/m)	14,6059
Pole width (mm)	40
Pole height (mm)	120
Yoke length (mm)	300
Yoke thickness (mm)	190
Chamfer entrance/exit (mm)	0

Main parameters of the coil @ 150 MeV

Ampere-turns	2400
Number of double pancakes vertical	12
Number of double pancakes horizon	20
Number of turns	240
Current (A)	10
Conductor size (mm)	2*5
Current density (A/mm2)	1,00
Conductor length (m)	194,00
Résistance/magnet (ohm)	3,26E-01
Voltage drop/magnet (V)	13,04
Power/magnet (kW)	0,13



Integrated magnetic field B2 = -0.07063 T.m

Magnetic gradient G = -14.6059 T/m

Magnetic length = 366 mm

Main harmonics :

B6/B2 = -10,6

B10/B2 = 1,1

B14/B2 = 1,85

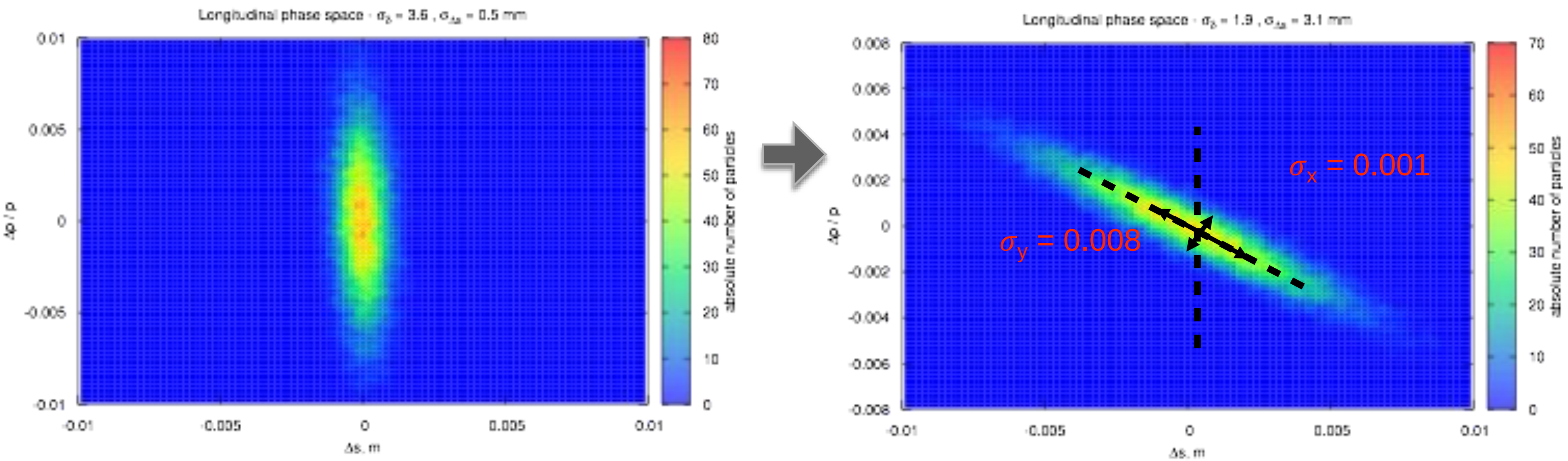
- Pre-design is finished. Need to optimize coils.

Initial parameters

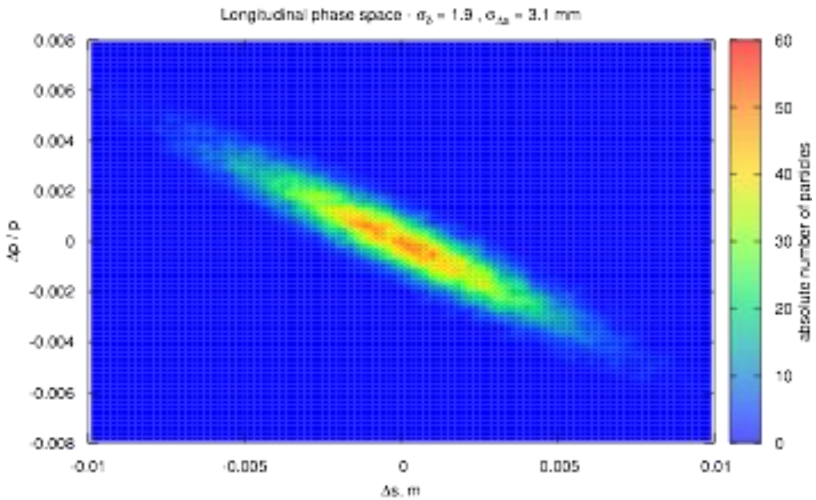
- Beam energy: 70 MeV
- Emittance: 5×10^{-8} m
- Bunch length: 3 mm
- Energy spread: 2×10^{-3}
- $\beta_{x,y}$ = 35 m
- α_x = -4.24
- α_y = -4.34
- D_{xy} = 0.0

Initial distribution

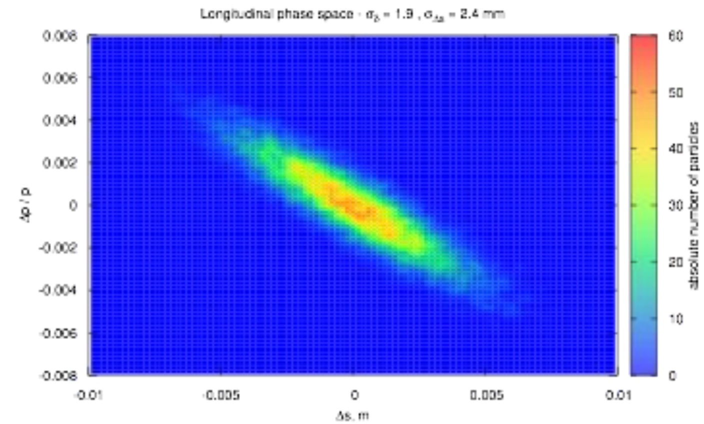
- Transverse distribution generated with 2 Gaussians, which are then rotated to simulate the energy chirp at the end of the linac, tracking with MadX-PTC in a first stage, further simulation taking into account CSR and wakefields under study.



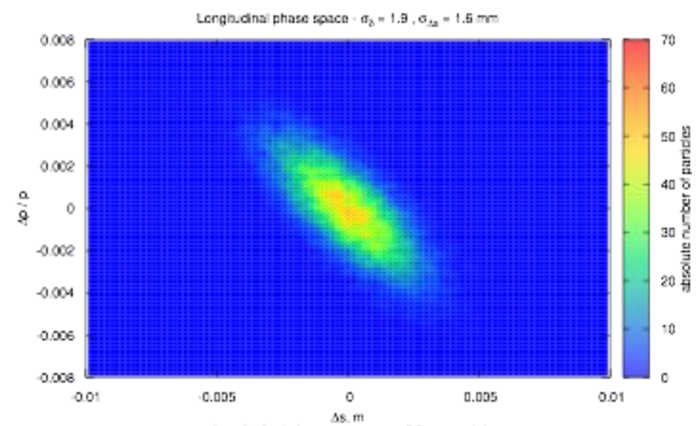
Bunch propagating through the chicane



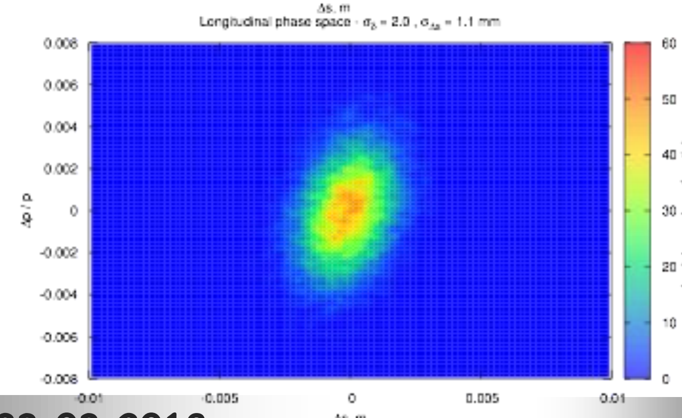
30^0



45^0



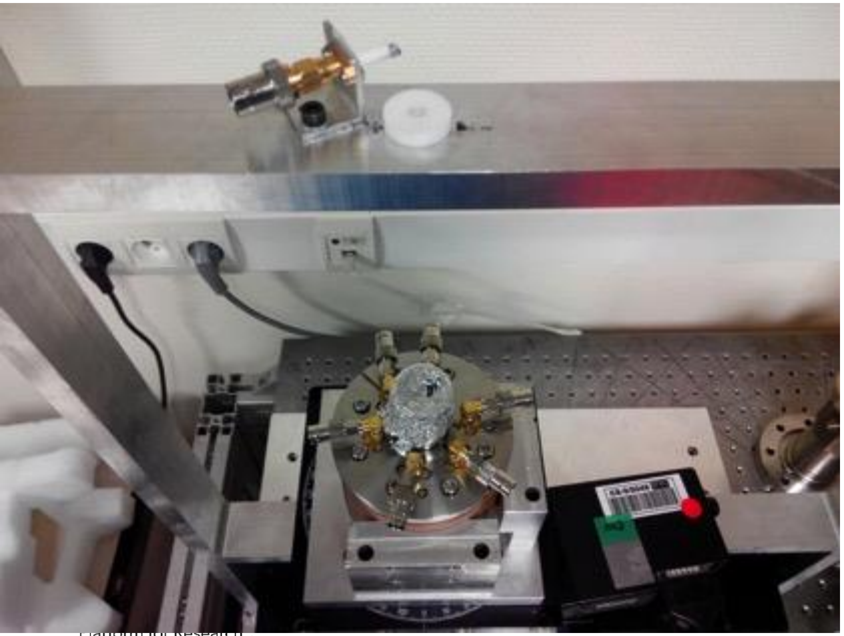
60^0

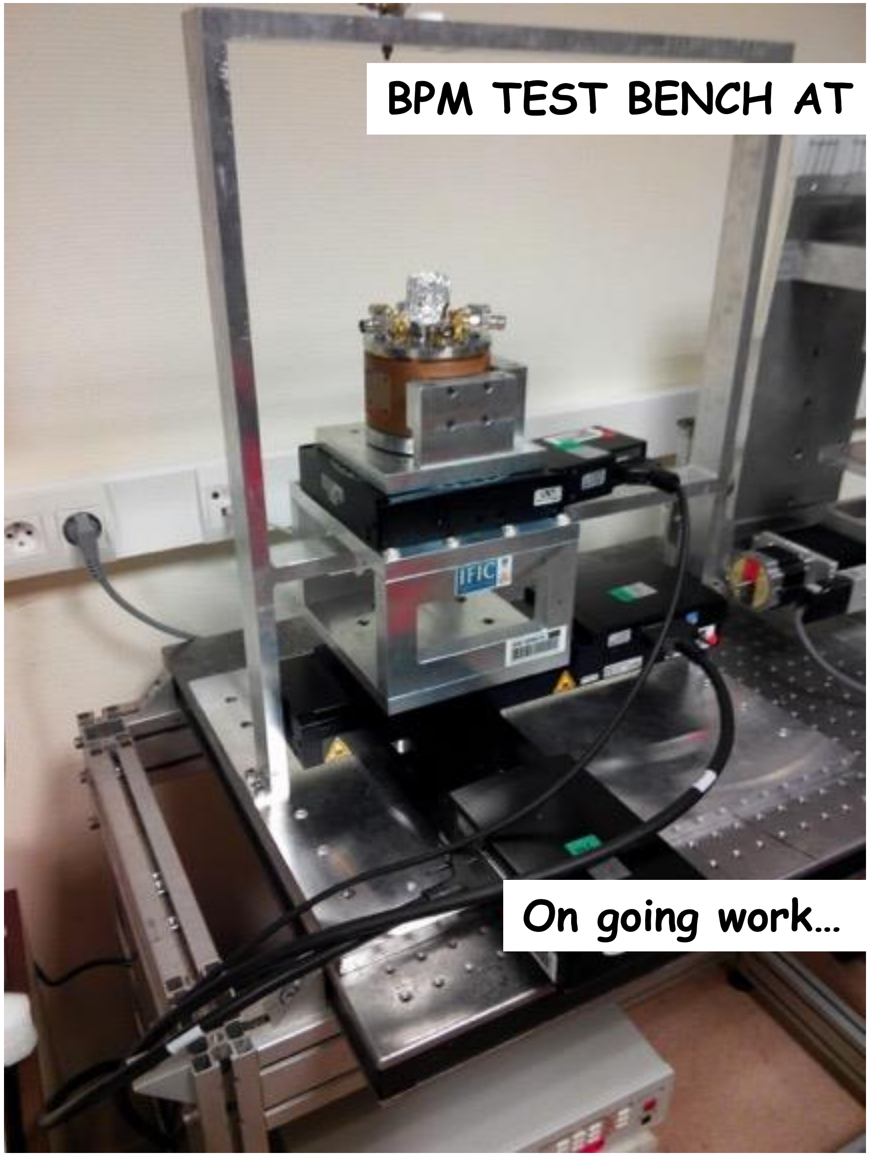


Different angles 30^0, 45^0, 60^0 considered

Inductive BPMs recuperated from CTF3, tests at IPNO in collaboration with BI-CERN

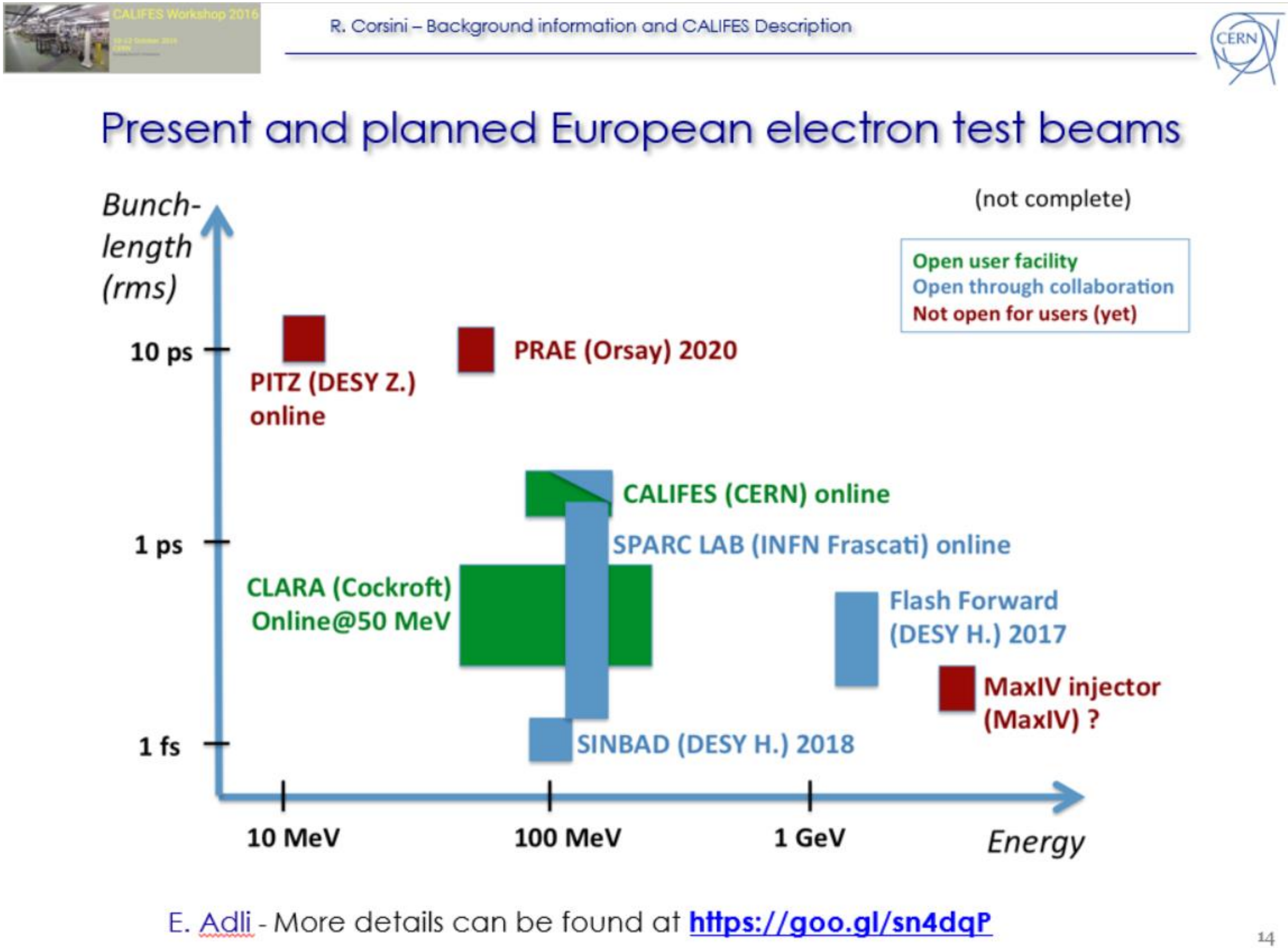
INDUCTIVE BPM





BPM TEST BENCH AT IPNO

On going work…


CALIFES Workshop 2016
R. Corsini – Background information and CALIFES Description
CERN
Present and planned European electron test beams
(not complete)
Bunch-length (rms)
Open user facility
Open through collaboration
Not open for users (yet)
10 ps
1 ps
1 fs
PITZ (DESY Z.) online
PRAE (Orsay) 2020
CALIFES (CERN) online
SPARC LAB (INFN Frascati) online
CLARA (Cockroft) Online@50 MeV
Flash Forward (DESY H.) 2017
MaxIV injector (MaxIV) ?
SINBAD (DESY H.) 2018
10 MeV
100 MeV
1 GeV
Energy
E. Adli - More details can be found at https://goo.gl/sn4dqP
14

Bruno Touschek

Nuclear physics / nucleon structure

- *Principle experiment:* ***proton charge radius measurement, 30-70 MeV***

Platform for Research and Applications with Electrons

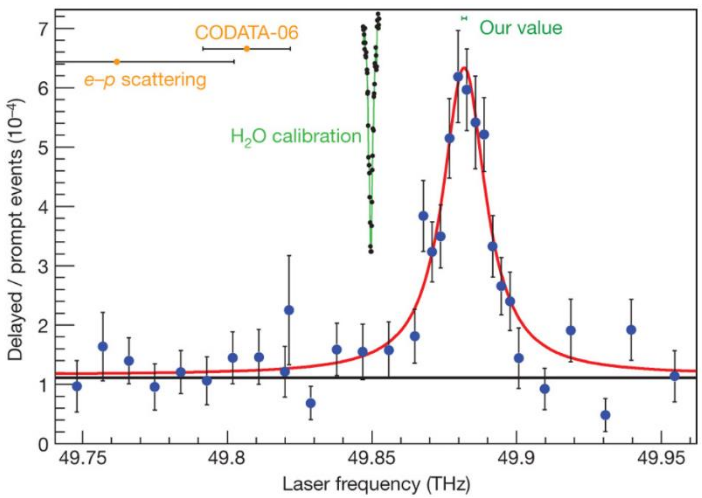
- Determination of the proton charge radius from
  muonic hydrogen Lamb shift
  significantly differs from that using
  electronic hydrogen Lamb shift and **electron scattering**.

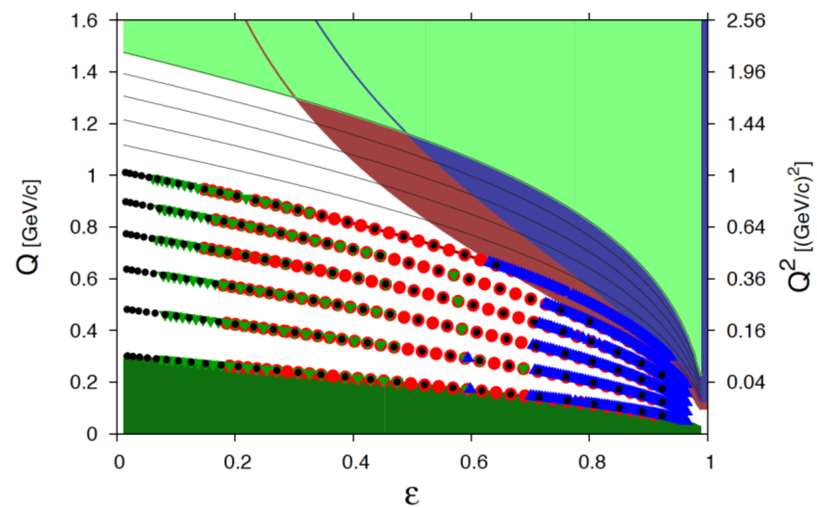
R. Pohl et al. Nat. 466 (2010) 213

J.C. Bernauer et al. PRL 105 (2010) 242001

Mesure of Lamb shift **2S->2P** in muonic atom

Mesure of G_E**(p)** in elastic ep diffusion.





$$E_{nl} \sim -\frac{R_\infty}{n^2} + \delta_{l0}\frac{r_p^2}{n^3}$$

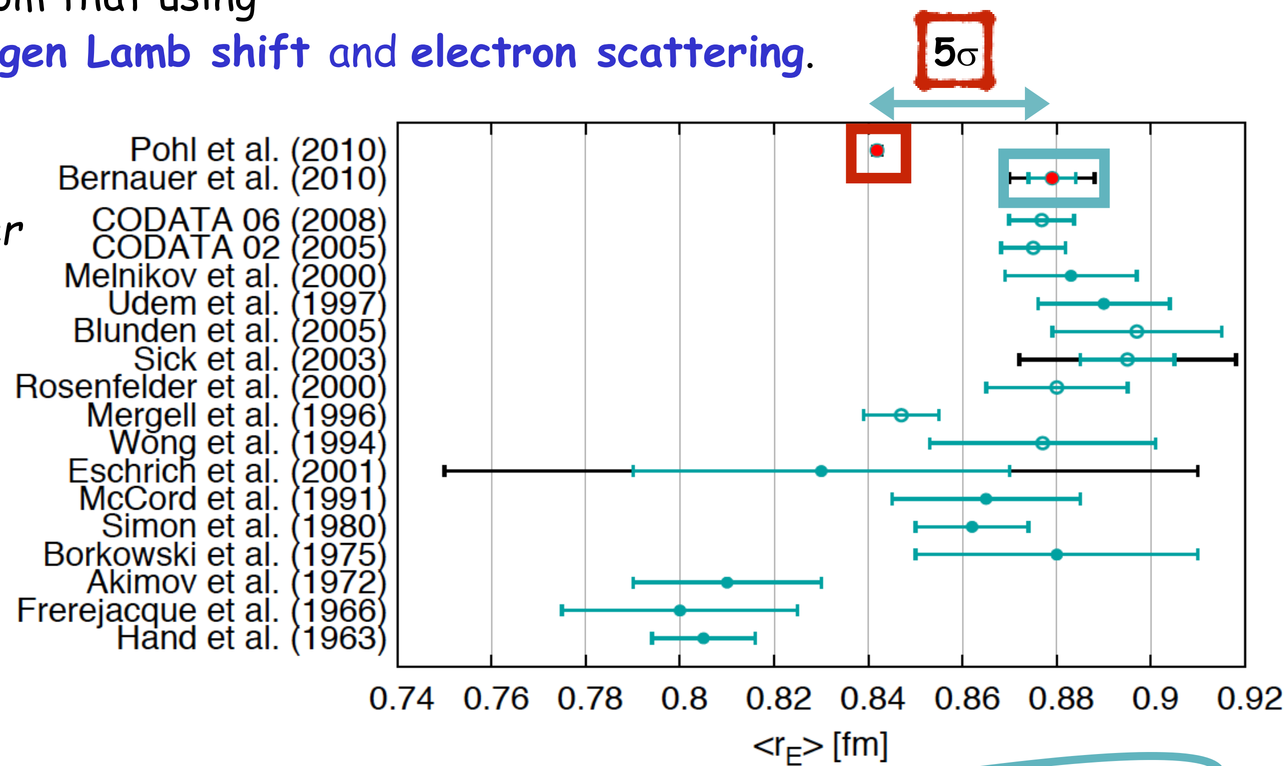
$$< r_p^2 > = -\frac{6(\hbar c)^2}{G_E(Q^2)} \frac{\partial G_E(Q^2)}{\partial Q^2}\Bigg|_{Q^2=0}$$

- **Model dependence** on proton structure corrections (polarisability, **2γ**) ?
- Shift of **Rydberg** constant ?

- Radiative effets and 2γ exchange ?
- Wrong determination of r_p ?

- Determination of the proton charge radius from
  muonic hydrogen Lamb shift
  significantly differs from that using
  electronic hydrogen Lamb shift and **electron scattering**.

*The **proton** looks smaller*
*to **muons***
than
*to **electrons**.*



r_p = 0.84184±0.00067 fm

Direct measurement
(10 times more precise)

$$r_p = \sqrt{< r^2 >} = \sqrt{-6 \frac{\partial G_E^2(Q^2)}{\partial Q^2}\Big|_{Q^2=0}}$$

r_p = 0.87900±0.00800 fm

Indirect measurement
(extrapolation of FF data to Q^2 =0)

- Search for **explanations from experimental issues, theory, …** : Underestimated uncertainties / Bad radius determination / Lepton non-universality / New force/particles / Novel hadronic physics / …

- Problem maybe related with

B physics anomalies: experimental results ≠ SM predictions!

charged current SM tree level

$$R_{D^{(*)}} = \frac{BR(B \to D^{(*)}\tau\nu_\tau)}{BR(B \to D^{(*)}\mu\nu_\mu)}$$ 3.9σ

$$\frac{BR(B_c \to J/\Psi\tau\nu_\tau)}{BR(B_c \to J/\Psi\mu\nu_\mu)} = 0.71 \pm 0.17 \pm 0.18$$

13 Sept. 2017
LHCb result
~2 σ

FCNC - SM loop process

P_5' in $B \to K^*\mu^+\mu^-$ (angular distribution functions) 3σ

$$R_{K^{(*)}} = \frac{\Gamma(B \to K^{(*)}\mu^+\mu^-)}{\Gamma(B \to K^{(*)}e^+e^-)}$$

in the dilepton invariant mass bin
$1\ \mathrm{GeV}^2 \le q^2 \le 6\ \mathrm{GeV}^2$ ~4σ

Muon anomalous magnetic moment

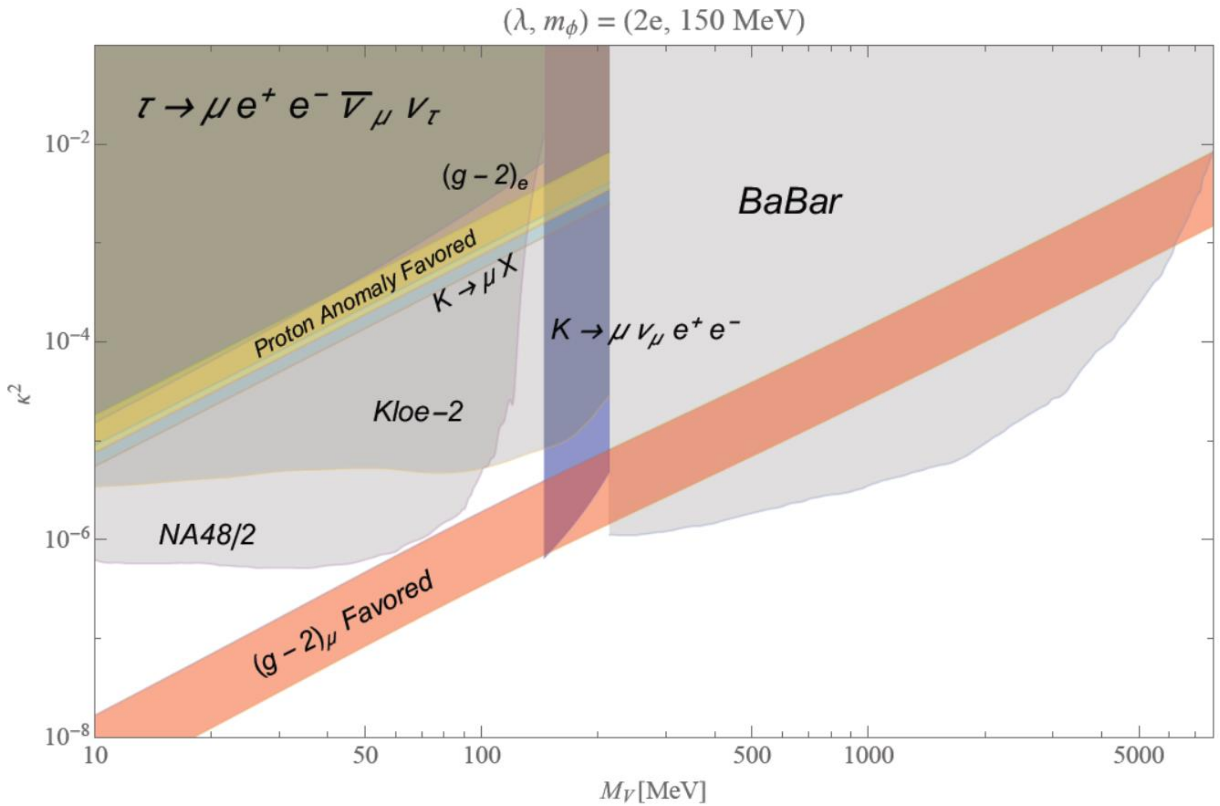
$$a_\mu^{\mathrm{exp}} = 1.16592080(63) \times 10^{-3}$$
$$a_\mu^{\mathrm{SM}} = 1.16591803(70) \times 10^{-3}$$

$$\Delta a_\mu = (2.8 \pm 0.9) \times 10^{-9}$$
~3σ

S. Fajfer

Model of DM (F. C. Correia, S. Fajfer, arXiv:1609.0860, Batell et al., arXiv:1103.0721):

- ❑ V is the gauge boson, neutral under the SM gauge group and charged under $U(1)_d$
- ❑ κ is a mixing angle between dark boson and photon



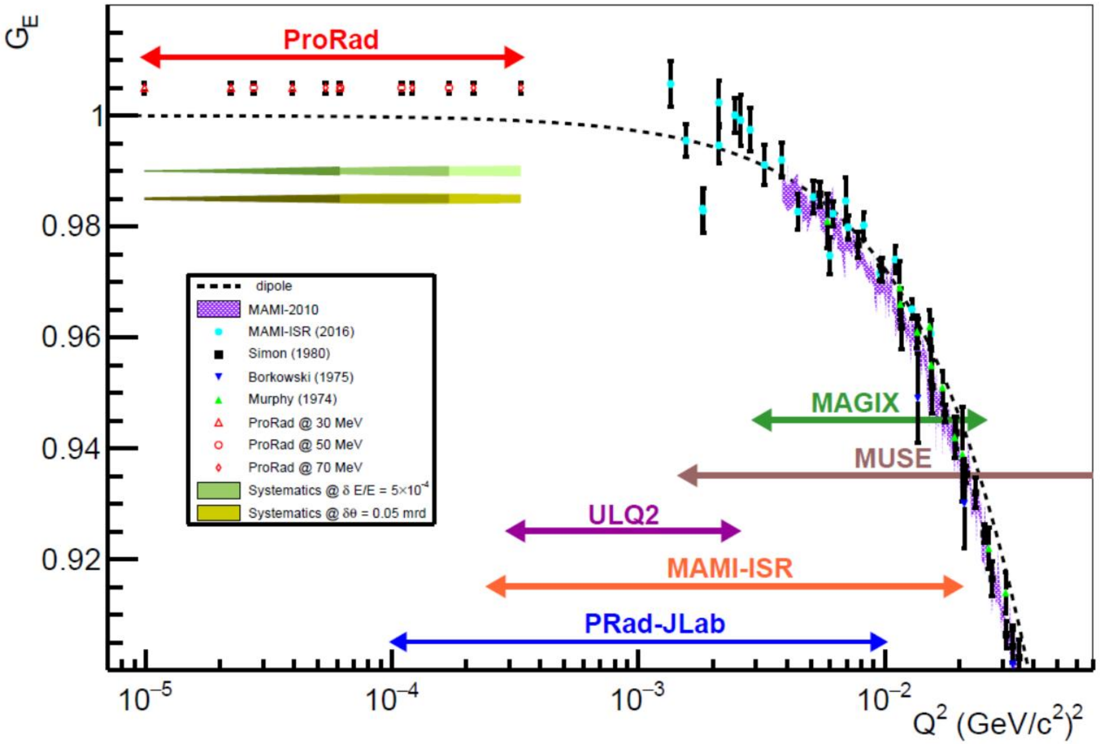
- ❑ Colour areas are excluded (for proton charge radius and $(g\text{-}2)_\mu$ yellow and red are favored)!

Platform for Research and Applications with Electrons

- The **ProRad** experiment at **PRAE** aims at accurate measurements (≤1%) of the electric form factor of the proton $G_E(Q^2)$ at **very low** four-momentum transfer **Q^2**.

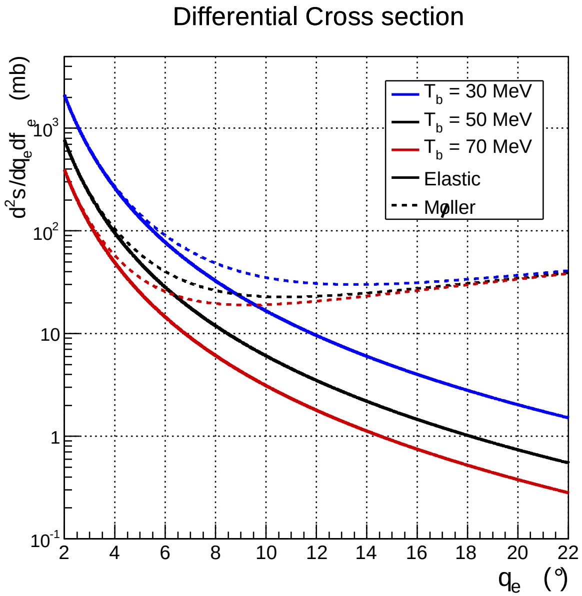
$$\frac{d^2\sigma}{d\Omega} \equiv \left.\frac{d^2\sigma}{d\Omega}\right|_{Mott} G_E\left(Q^2\right) \Rightarrow r_p^2 = -\frac{6\hbar^2}{G_E(0)} \left.\frac{\partial G_E\left(Q^2\right)}{\partial Q^2}\right|_{Q^2=0}$$

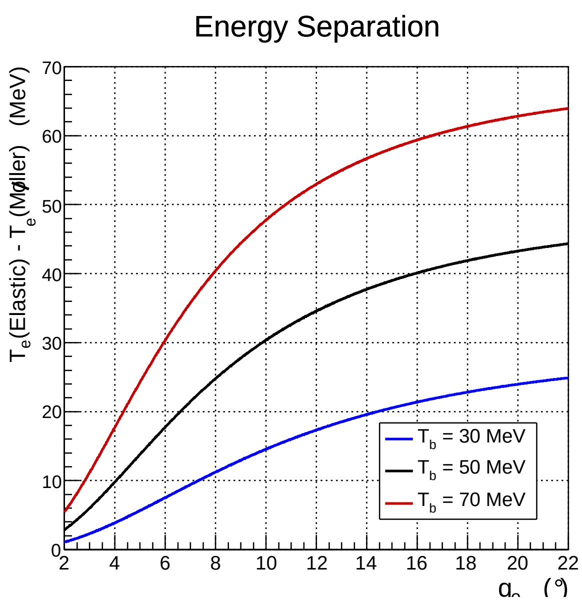
A linear region in the FF: extrapolation with no dependence on non-linearities



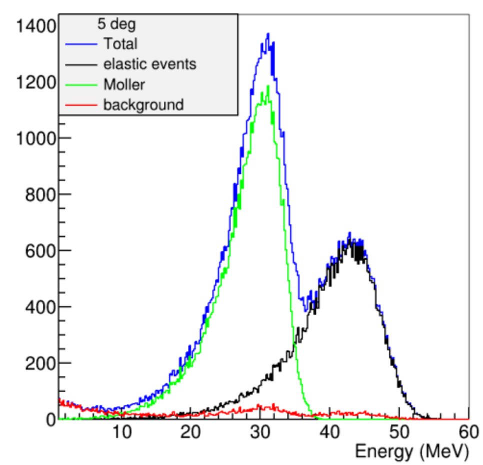
- Measurements in the **unexplored** Q^2-range **1.5×10^{-5} – 3×10^{-4} $(GeV/c^2)^2$** will **constrain** the **Q^2-dependence** of **G_E** and the **extrapolation to zero** important for the determination of the **proton charge radius**.

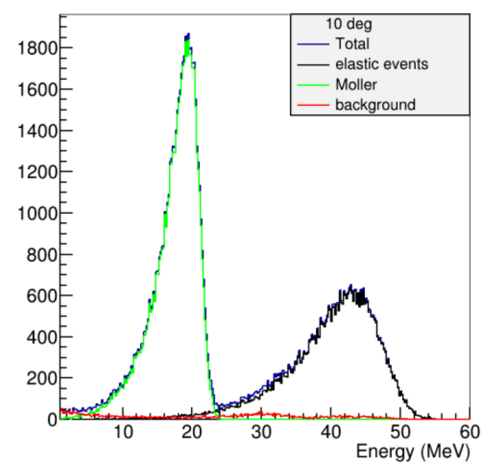
- Any **deviation** from **1** would indicate **genuine novel effects**.





- Measurements of the **ep elastic** scattering between **5°** and **15°** (5 angle points) at 3 different beam energies, and in **absence** of any **magnetic field** (and **tracking system** ?).
- The **energy deposit spectra** in calorimeter allow separation between **elastic** and **Møller** electrons





- Absolute **normalization** from **simultaneous** measurement of **ep elastic** and **ee Møller** within the **same detector** using scattered electron kinematic separation.
- Precise **beam**:

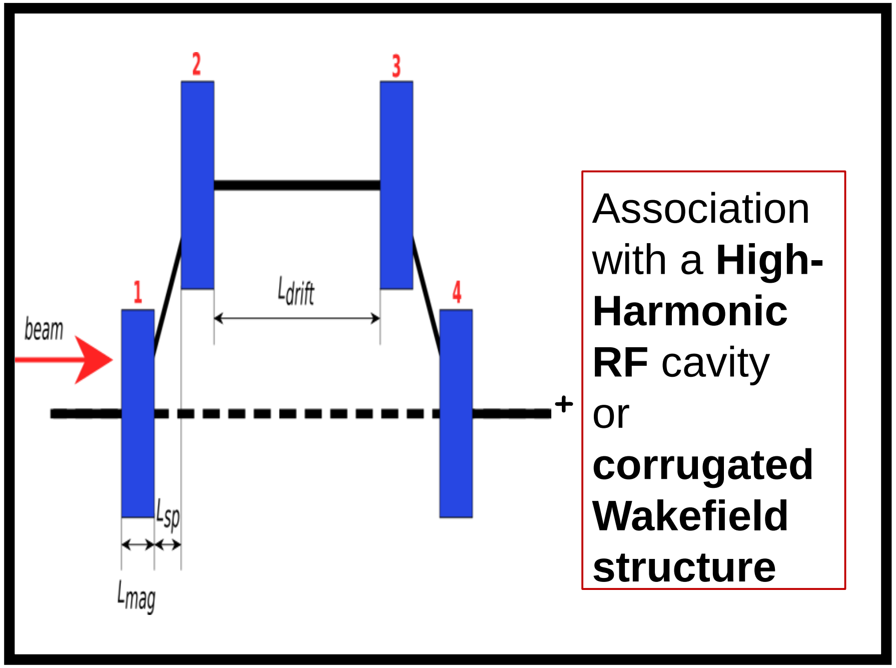
  $\Delta E/E = 10^{-3}$, $\sigma_{x,y} < 0.5$ mm, $\Delta\theta < 1$ mrad

with Electrons

- High precision beam: **Reduced energy dispersion δP/P = 5x10^{-4}**
- Precise knowledge of the beam energy **δE/E = 3x10^{-4}**
- A stable target
- Optimized measurement of the scattered electron energy and position

$$E = \frac{c}{\theta}\int Bdl = \frac{c}{\theta} I_B$$

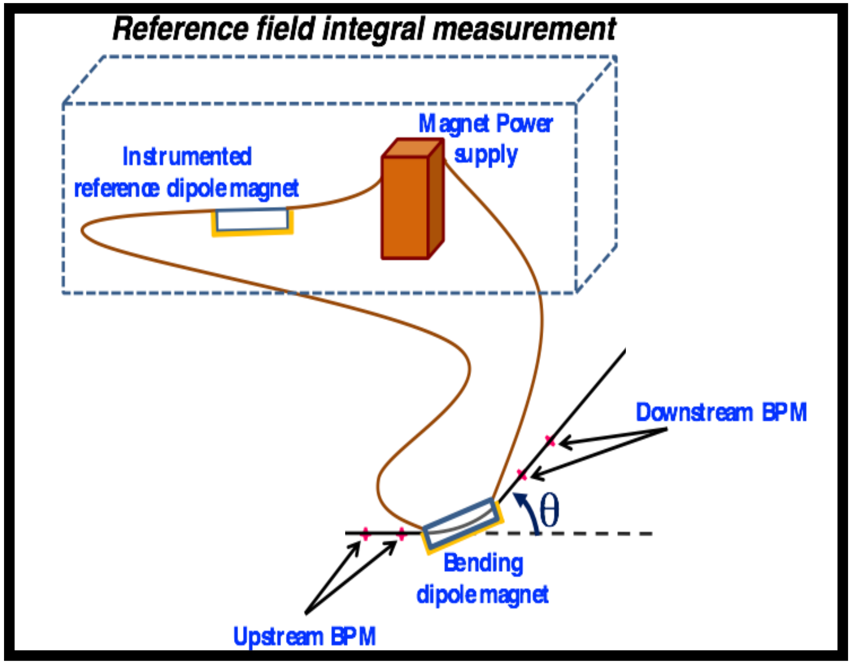
Energy compression

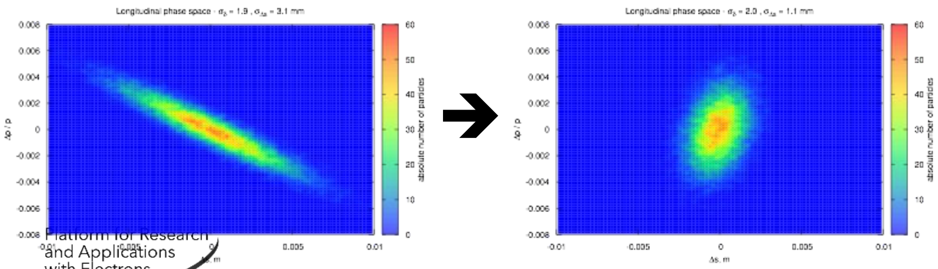


Association with a **High-Harmonic RF cavity** or **corrugated Wakefield structure**

\+

Beam energy measurement





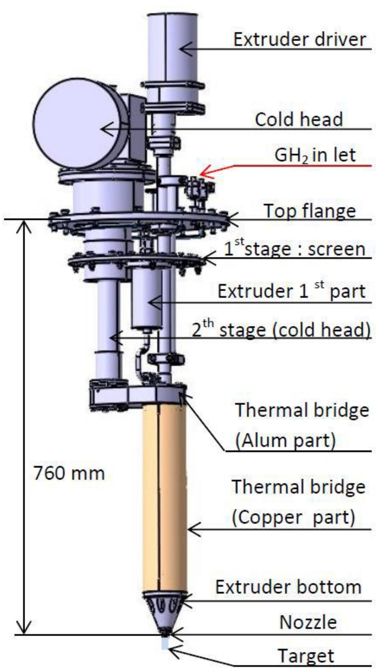
$$\frac{\delta I_B}{I_B} = \frac{\delta\theta}{\theta} = 2\times10^{-4}$$

- Selection of reliable target of acceptable cost: **CHyMENE film** (CEA Saclay), **solid wire** from techniques of droplet beam (Frankfurt am Main University), …

J.-M. Gheller et al. AIP Conf. Proc. 1573 (2014) 58

A. Gillibert et al. EPJA 49 (2013) 155

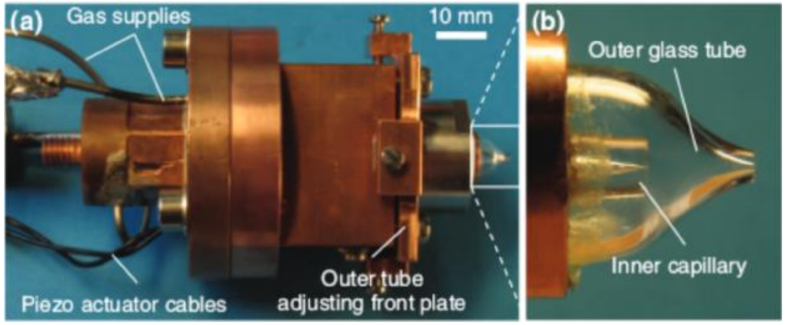
Cryogenic system in the cryostat



CHyMENE

Bi-national ANR proposal with Francfort University submitted.

Droplet Sream



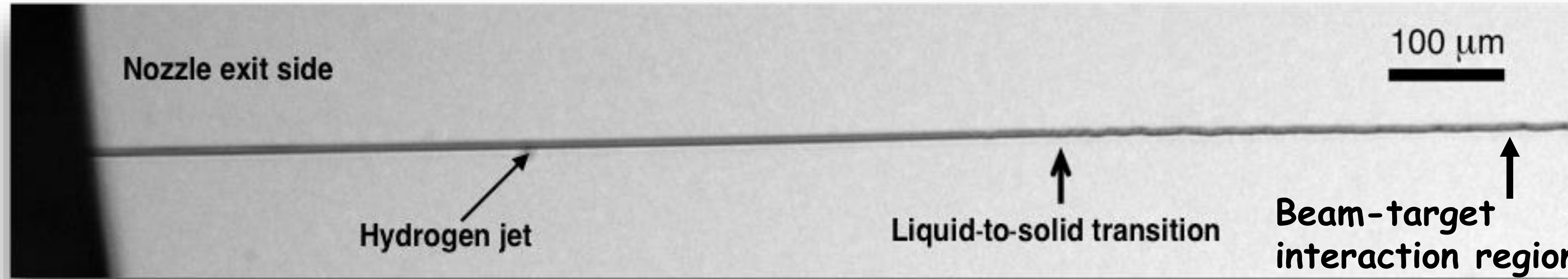
R.A. Costa Fraga et al. Rev. Sci, Inst. 83 (2012) 025102

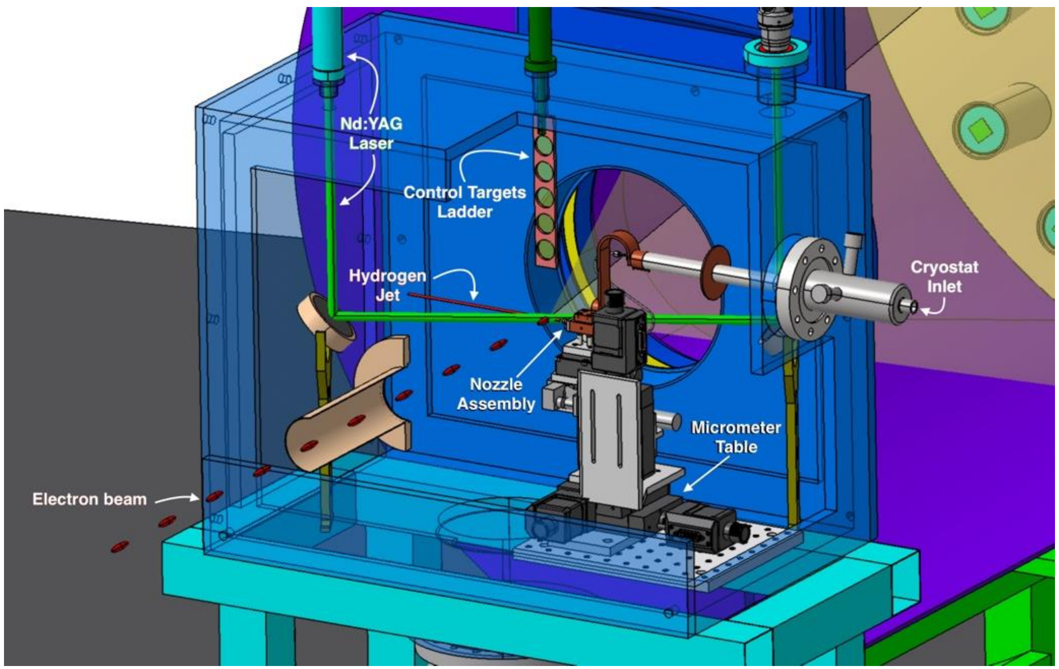
- Hydrogen film of **50-200 μm** produced via extrusion technique.
- Adaptation needed to achieve ~**20 μm**.

- Complementary system based on **conventional solid targets** for beam control and check for systematics effects.

Requirements:

A very stable, windowless, and self-replenishing target of 15 μm diameter



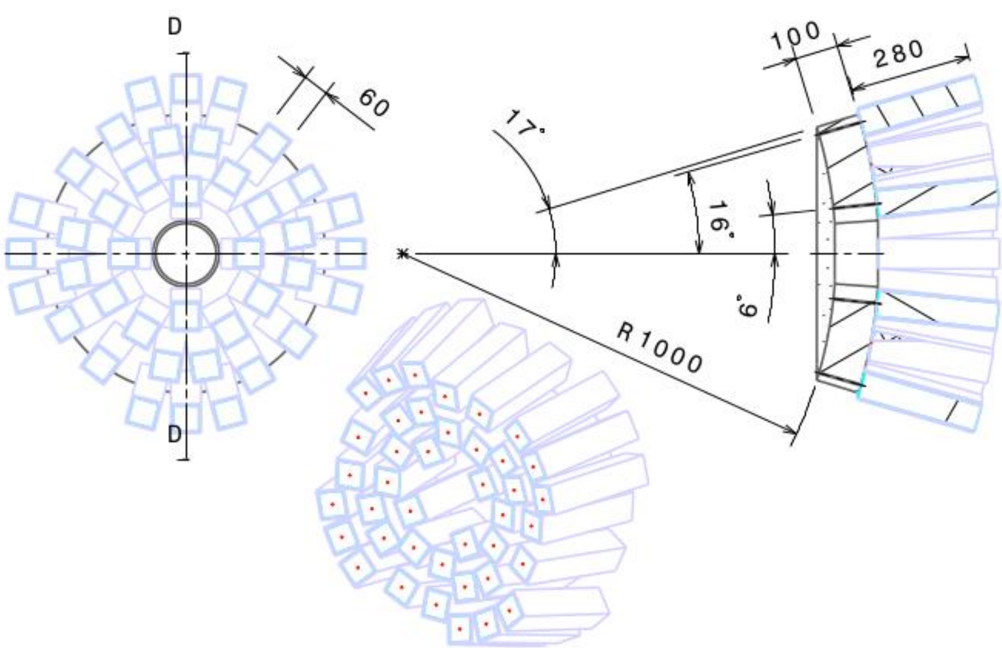


Ultra cold liquid technology developed at Frankfurt University

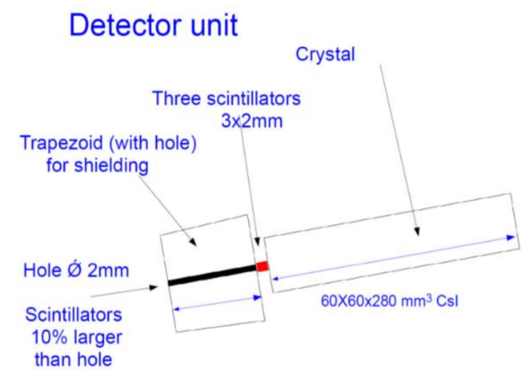
GOETHE UNIVERSITÄT FRANKFURT AM MAIN

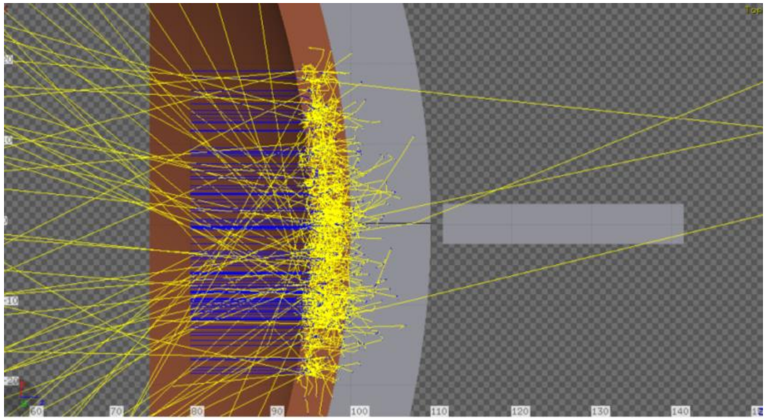
R.A. Costa Fraga et al. Rev. Sci, Inst. 83 (2012) 025102

- Conceptual studies with GEANT4 and FLUKA to **optimise detector configuration for small diffusion angles**.
- BGO crystals for energy measurements and fiber tracker to measure position
- Studies of **system mechanics**.



Cristaux de 6 cm + 5 mm de boitage
Inclinaison angulaire = 6° - 8.5° - 11° - 13.5° - 16°





Platform for Research and Applications with Electrons

Bruno Touschek

Radiobiology

- *Principal goal* : ***explore new original approaches in radiotherapy***
- *Other studies : promising for IMRT, radiobiology studies*

Platform for Research and Applications with Electrons

New approaches in radiotherapy

- Radiotherapy (RT) is one of the most frequently used methods for **cancer** treatment
- Treatment of some **radio resistant tumors, pediatric cancers** and tumors close to a delicate structure (i.e. spinal cord) is currently **limited**
- The main challenge is to find **novel** approaches to increase normal tissue resistance
- Standard RT restricted to the few temporal and spatial schemes, dose rates, broad field sizes: mainly photons, 2 Gy/session, 1 session/day, 5 days/week, dose rates ~ 2 Gy/min, field sizes > cm2, homogeneous dose distributions

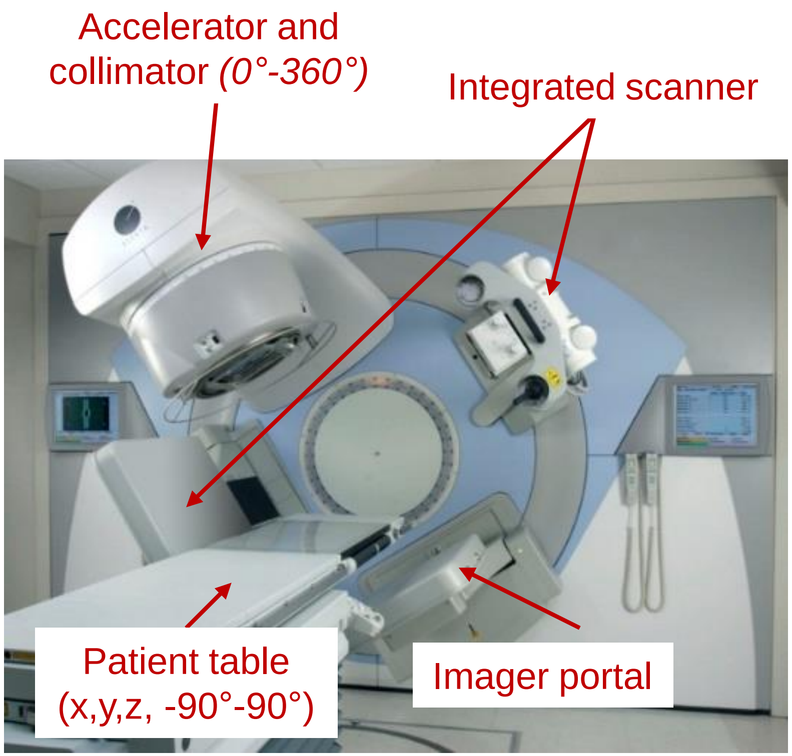
Possible strategy to spare normal tissue: VHEE

- Different particle types: very **high energy electrons** (VHEE)
  - At hospitals mainly photons (6-18 MV) and electrons (2-25 MeV) are used.
  - *Compared to clinical electron beams*: longer **penetration depth**; reduced **lateral scattering** (transversal widening → sparing normal tissues).
  - *Compared to photons*: **scans** possible → advantageous for image-guided energy- and intensity-modulated radiation therapy.
  - *Compared to protons*: greater **precision** of the beam, lower accelerator **cost**; less **radioprotection** issues.
  - *Biological advantages to be established !*

- Conventional radiotherapy
  - X-rays: 6 - 18MV (tumors of all types)
  - Electrons: 3 – 18 MeV (surface treatment)
  - Machines: electron linear accelerators + multi-lame collimators *(1-4 M€)*
  - Syst. quality control & imagers : advanced

  - Dose rate: **30-70 mGy/s**
  - Time fractionation: 2 Gy/session, 5 sessions/week, total dose: 40-70 Gy
  - Field sizes: 4 cm² – 40 cm²

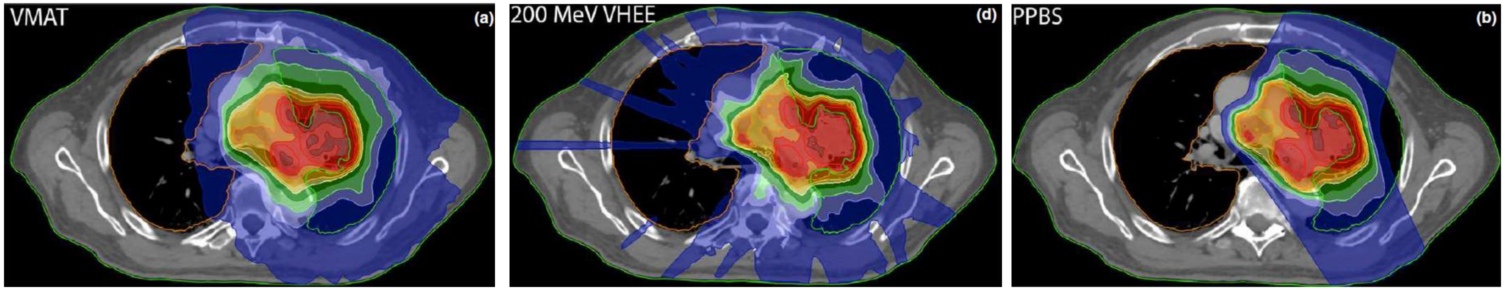
  - Many items become « conventional »: experience 60 years in dosimetry, clinical effect of X-rays, dose control …



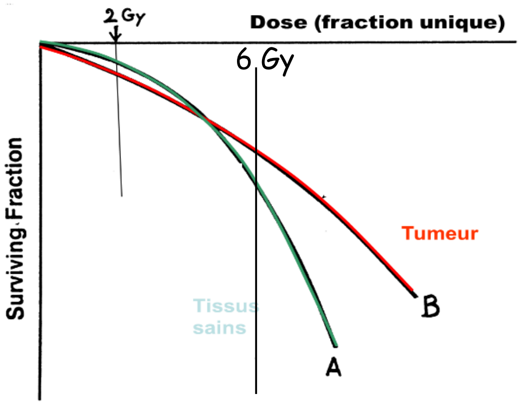
Conventional e- accelerator (X-rays 6-18 MV)

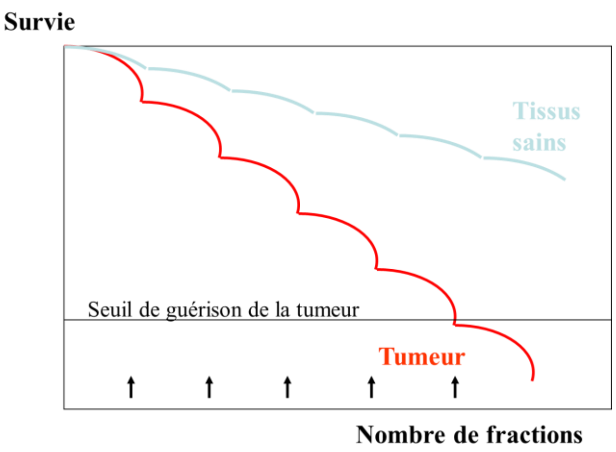
- Different effect for tumor and healthy tissues with:
  - **Ballistic precision**/ anatomic restrictions

Lung tumor : comparison X-ray, VHEE, & protons
Schuler, 2017 (Stanford)



    - Limits: precision of tumor limits, organ movements / repositioning errors, machine cost.
  - **Dose deposit shape & time fractionation**
    - For the same total dose, biological efficiency differs according to dose/session, total number of sessions (fractionation) and treatment time (staggering)
    - Allows reparation of radiomolecular lesions and tissue repopulation
    - Allows tumor reoxy-genation: reduces radioresistance of tumors

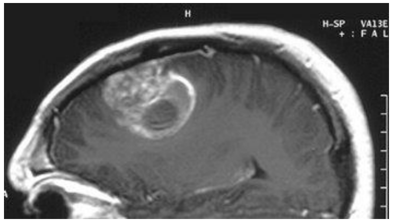




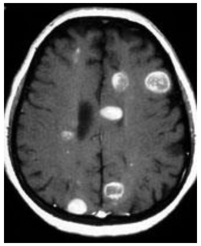
  - **Pharmacomodulation**: combination of radiotherapy with chemotherapy, specifically acts on the cells of rapid proliferation (particularly tumors)

- Limits of conventional radiotherapy

Resistant, voluminous and diffuse cancers (glioblastomes)



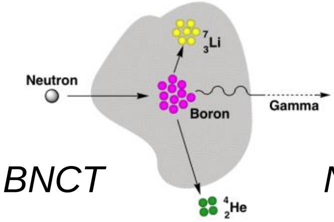
Non-localized tumors (multi-métastases)



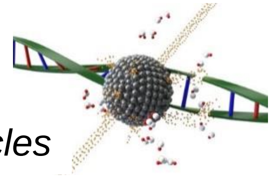
- Precision of tumor limits, organ movements, patient repositioning errors
- Toxicity to healthy tissues limits the dose

- How to improve the treatment?
  - Induce more effective tumor irradiation → e.g. **hadrontherapy**, **combined therapy** with nano-particles/chemical agents

Combined therapies

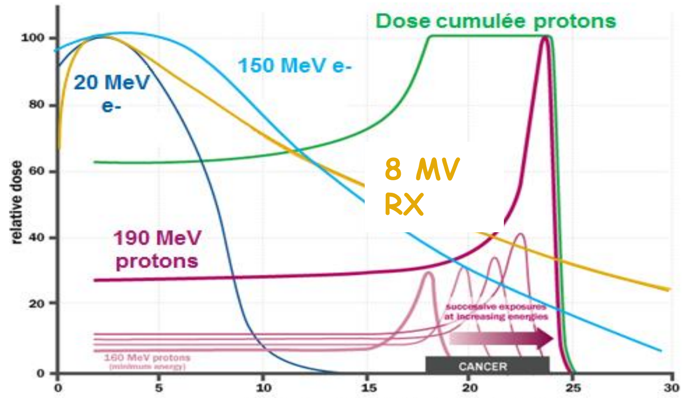


BNCT



Nanoparticles

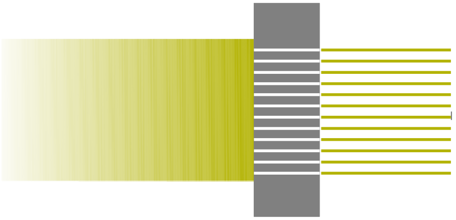
Different particles/energies

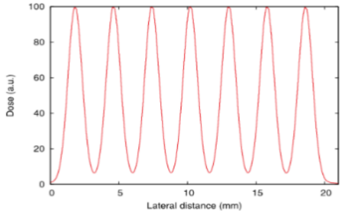


Penetration depth in the human body (cm)

  - Preserve healthy tissues via dose delivery mode: **microbeams & FLASH**

***FLASH therapy**, very high dose rate > 40 Gy/s (conventional 0,03 Gy/s)*

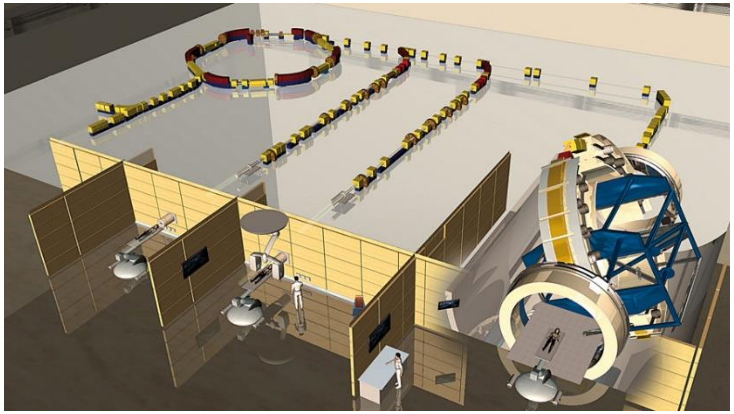




Spatial fractionation of the dose

X-rays, hadrons, VHEE

- Impact of cost and congestion on the number of patients treated



Hadrontherapy center in Heidelberg
(~Ten in the world, ~100 M€)

VHEE ?
(~10 M€ ?

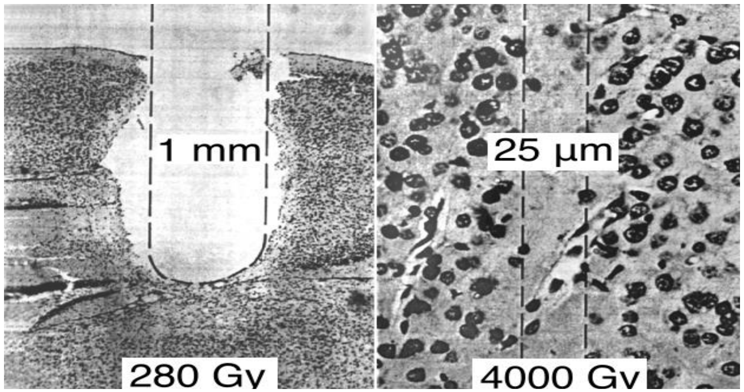
Standard medical accelerator
(~ 500 in France, ~1-4 M€)

→ Challenge for quality control of the dose

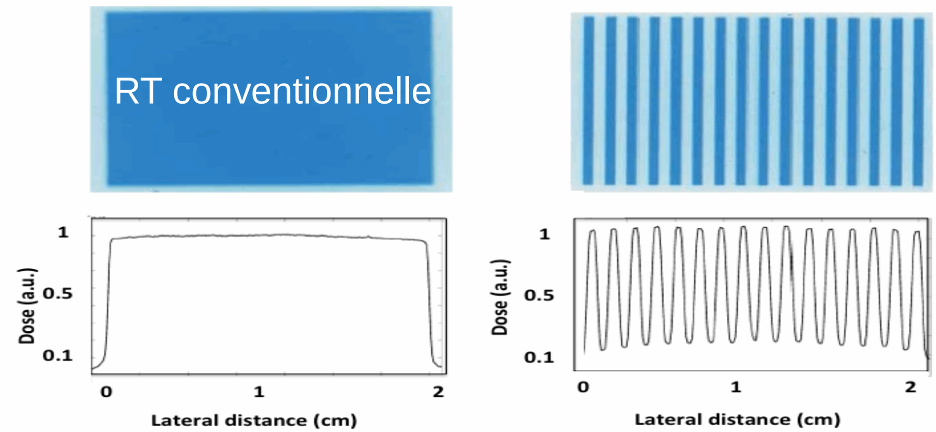
- **VHEE beams: avantages vs protons**
  - Cost and beam handling, more compact accelerators
  - For our applications: very small beam sizes (<1mm)

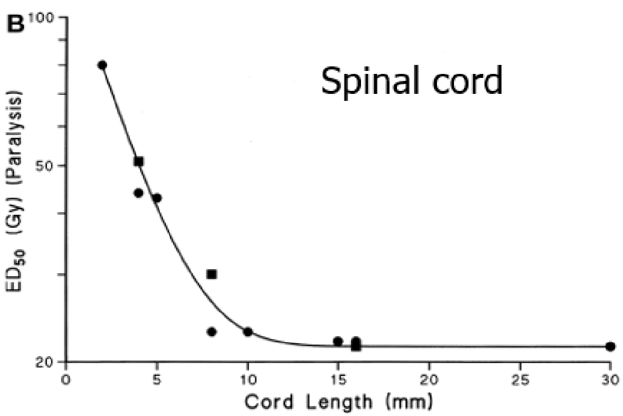
- Spasial fractionation of the dose and mini-beams

Very small field sizes (< 1 mm^2) + Spasial fractionation of the dose

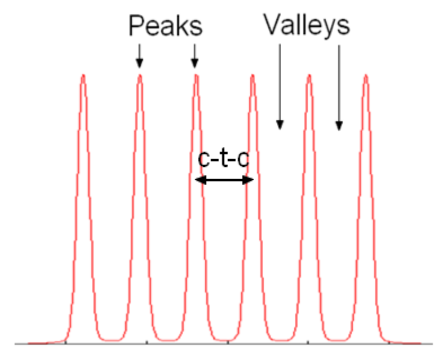


Zeman et al., Science (1959)





Hopewell et al., Radioth. Oncol. (2000)



$$PVDR = \frac{D_{\text{peak}}}{D_{\text{valley}}}$$

↗ PVDR = ↗ tolerance of healthy tissue

↘ D_{valley} to ensure tissue integrity

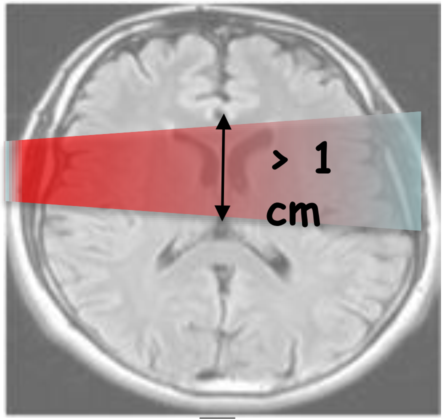
Dose-volume effect: the smaller the field is, the higher dose tolerance of healthy tissues

Platform for Research and Applications with Electrons

NARA: Spatial fractionation of the dose

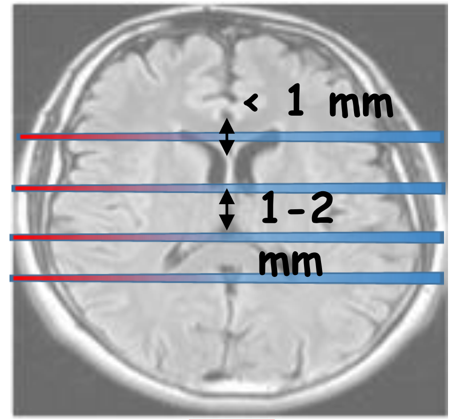
Standard radiotherapy

Large field sizes
(> 1 cm^2)
+
Homogeneous dose



Lethal dose > *20 Gy*

Fractionated radiotherapy: *x-rays mini-beams*

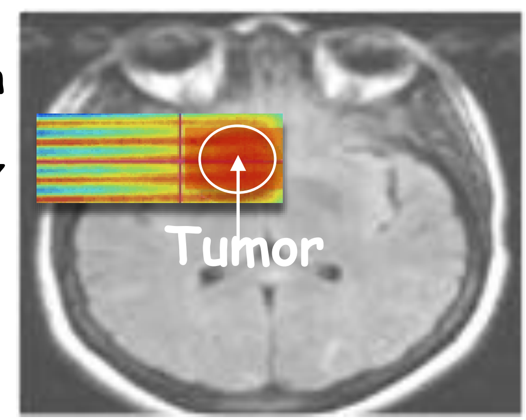


Small-size beams spaced by the zones of low dose
+
Heterogeneous dose

Biological mechanisms still poorly known

- ❑ Remarkable increase in brain tolerance (100 Gy/session) *Prezado et al. 2015*
- ❑ Possible dose increase → better tumor control

- ❑ « Protective » effect of healthy tissues reproduced with **proton mini-beams** + tumor control increased with proton mini-beams compared to standard proton treatment Prezado et al. 2017



Radiobiological effect of spatial fractionation :

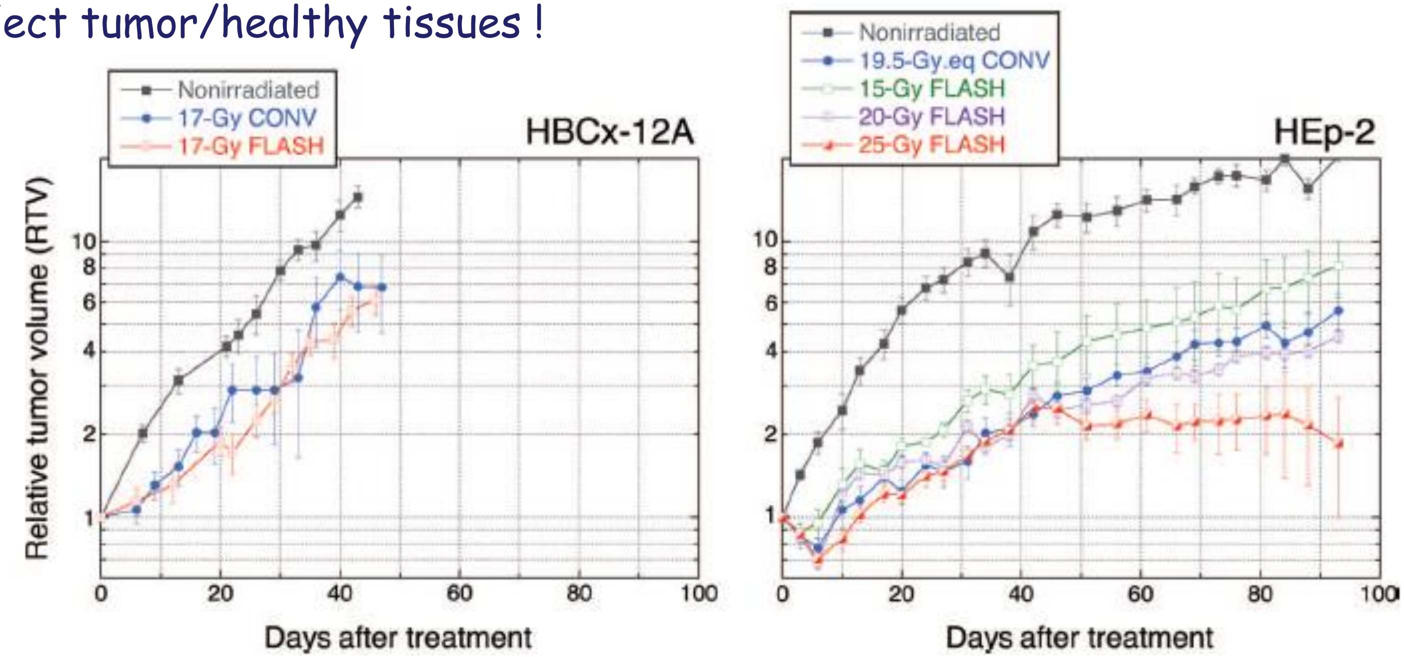
- ❑ Cell repair and repopulation of zones « valley » → zones « peak »
- ❑ Differential tissue effect between vascularization « immature » (tumor type, reparation --) and « mature » (healthy tissues) *Bouchet et al.*

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

2014

Vincent Favaudon,[1,2*] Laura Caplier,[3†] Virginie Monceau,[4,5‡] Frédéric Pouzoulet,[1,2§]
Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2‖]
Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2]
Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]

- Appearance of Pulmonary Fibrosis on mice:
  - Starting from **15 Gy** in CONV mode **(0.03 Gy/s)**.
  - No fibrosis appearance in FLASH mode **(40 Gy/s)** up to **20 Gy** + Protection of **muscles** and epithelial cells (skin, membranes…)
  - Xenograft tumors on nude mice: **same tumor control** for CONV & FLASH
  - → different effect tumor/healthy tissues !

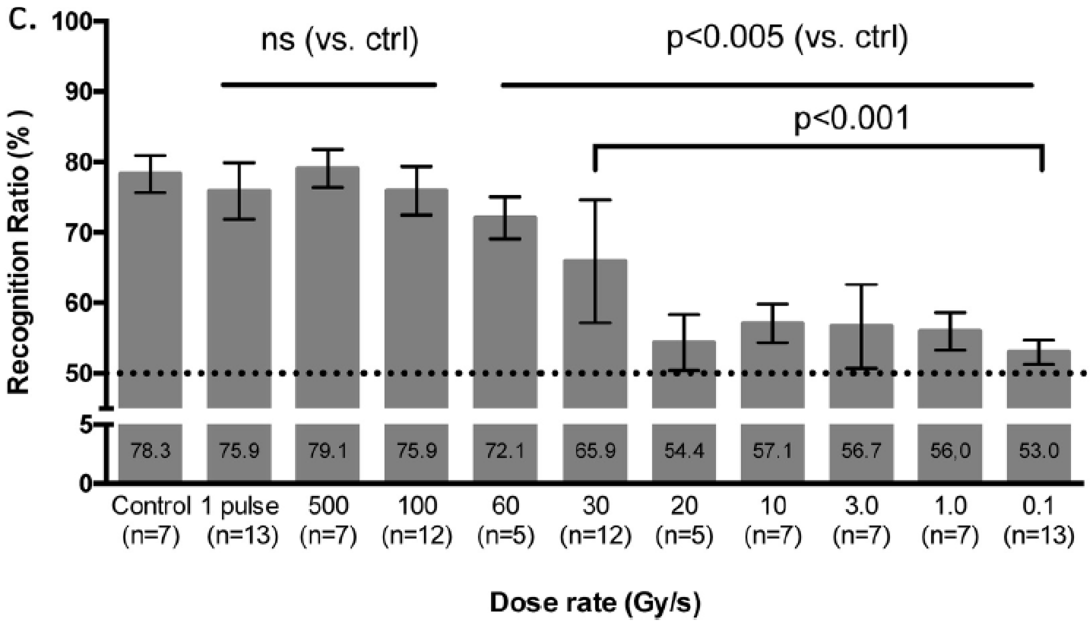


Platform for Research and Applications with Electrons

Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s

2017

Pierre Montay-Gruel [a,b,1], Kristoffer Petersson [c,1], Maud Jaccard [c], Gaël Boivin [a], Jean-François Germond [c], Benoit Petit [a], Raphaël Doenlen [d], Vincent Favaudon [b], François Bochud [c], Claude Bailat [c], Jean Bourhis [a,1], Marie-Catherine Vozenin [a,*,1]



Limit of a good effect at 100 Gy/s
(or < 100 ms)

+ No effect if < 4 Gy unique dose

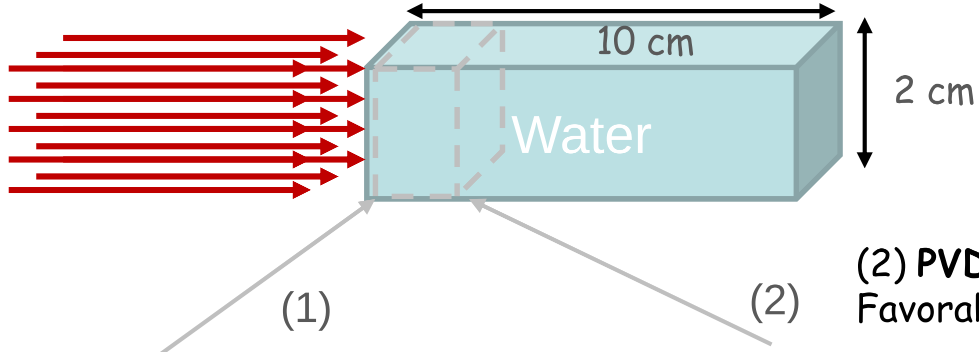
- Effect on the brain 50 Gy in FLASH mode equivalent to 10 Gy in CONV mode.

→ **Biological effect ? Some oxygen process occuring very fast… (?)**

- Beam at PRAE
  - ✓ Small beam-size: 250 µm < σ < 2 mm
  - ✓ Energies: 70 – 140 MeV
  - ✓ Small divergence: 0.1 – 0.4 mrad
  - ✓ Dose rate: 0.035 Gy/s – 40 kGy/s *

*depending on σ, Q

- First simulations to optimize the beam for VHEE:

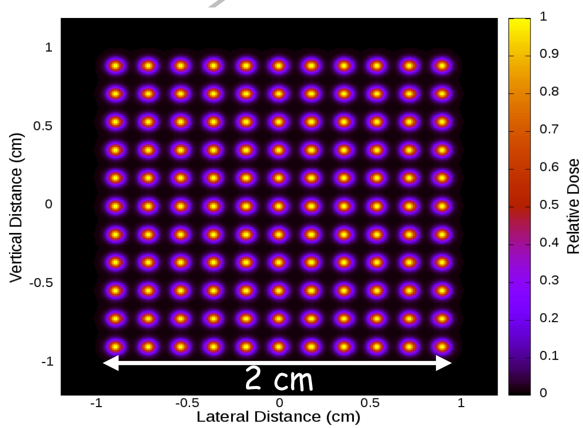


(2) **PVDR = 1**,
Favorable for tumor control

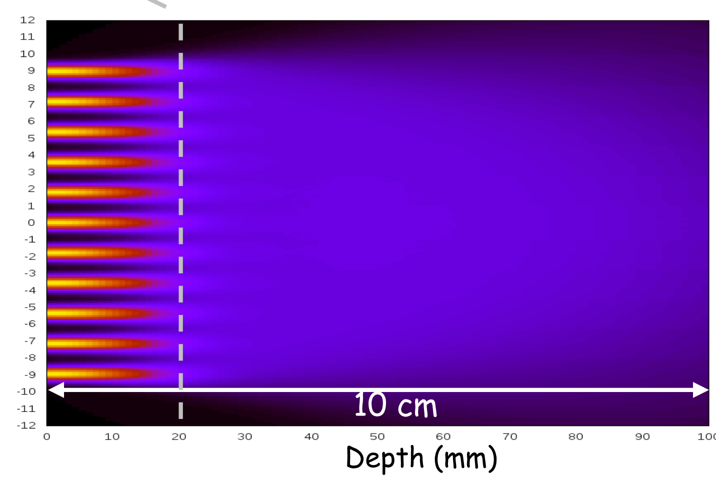
Example: 70 MeV, σ~250 µm

(1) PVDR = 20,
important spatial dose fractionnation

$$PVDR = \frac{D_{\mathrm{peak}}}{D_{\mathrm{valley}}}$$



dose fractionation at the entrance



dose homogeneisation with depth

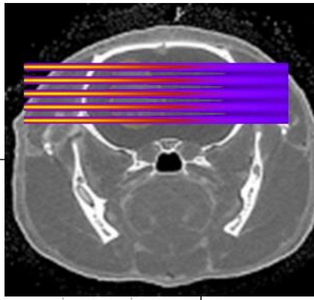
Platform for Research and Applications with Electrons
PRAE

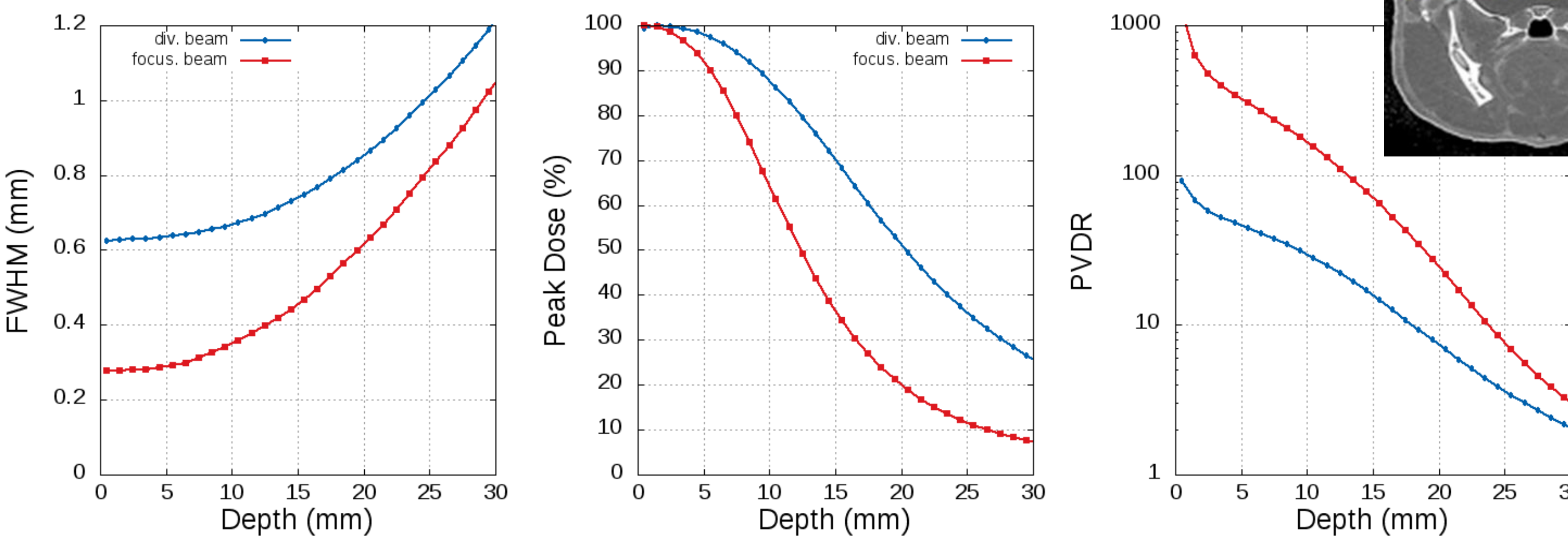
❑ **Beam size (FWHM) and dose rate at the phantom entrance** *(Gy/s , voxel 0.1x0.1x1mm^3)*:

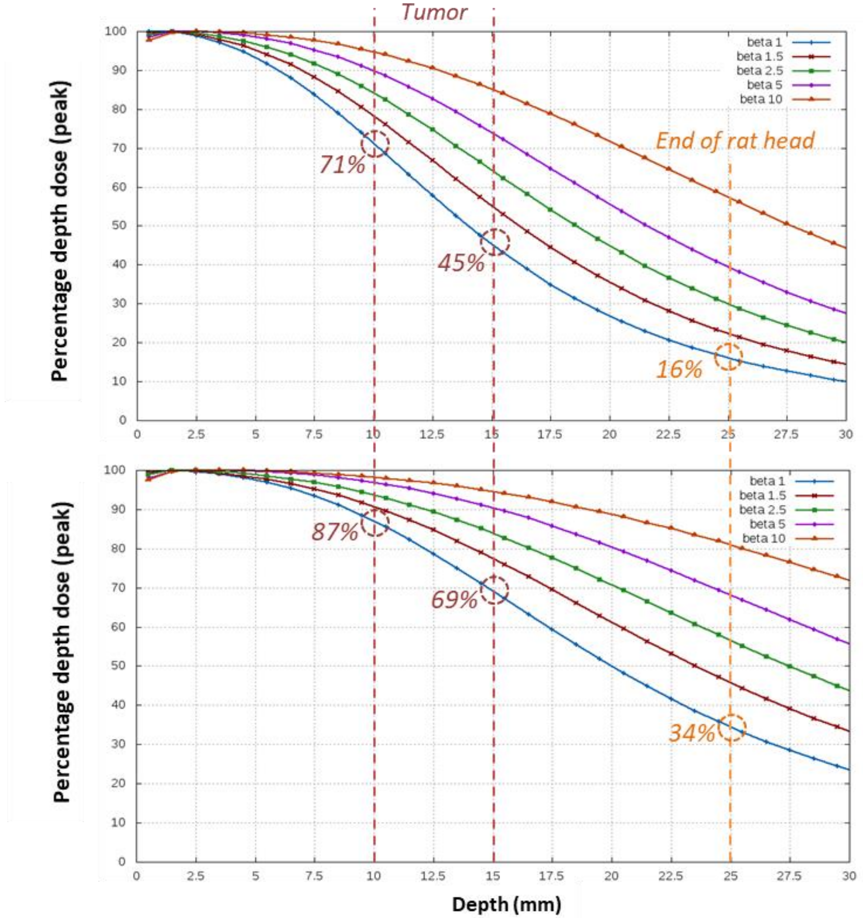
Energy	Beta/AG (cm)	FWHM	BWF	1 pC	2 nC
70 MeV	Beta1 – 10 cm	650 µm	1.15	18 Gy/s	36 kGy/s
	Beta 1 – 100 cm	11 mm	20	0.05 Gy/s	110 Gy/s
	Beta 120 – 100 cm	12 mm	2	0.037 Gy/s	70 Gy/s
140 MeV	Beta1 – 10 cm	600 µm	1.03	23 Gy/s	46 kGy/s
	Beta 1 – 100 cm	6 mm	9	0.25 Gy/s	500 Gy/s
	Beta 120 – 100 cm	6.1 mm	1.06	0.2 Gy/s	400 Gy/s

**Conventional = 0.033 Gy/s*

❑ PRAE settings: beam pipe window – 10 cm of air – 3 cm depth in phantom

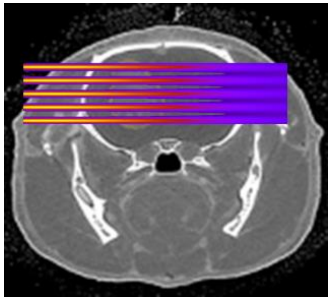






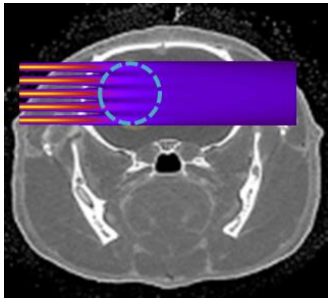
70 MeV

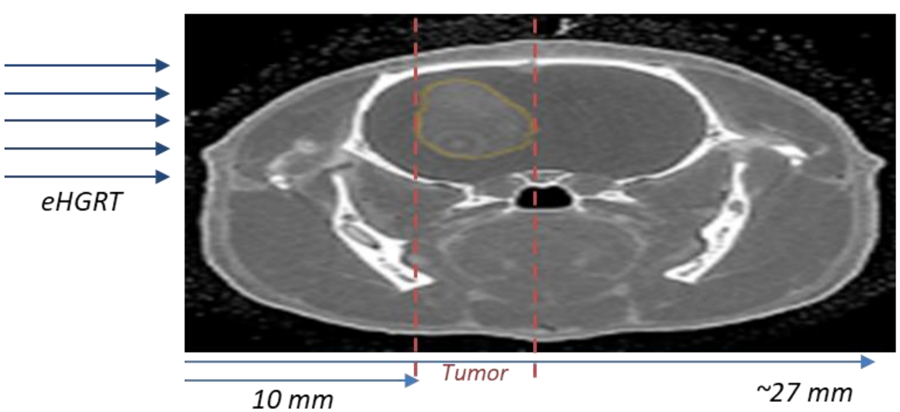
140 MeV



With 140 MeV, σ 250 µm (*SFR*):
- submillimetric over all depth
- dose sufficiently large to control a tumor

With 70 MeV, σ 350 µm (partial SFR)
- submillimetric < 10 mm
- dose homogeneous in tumor



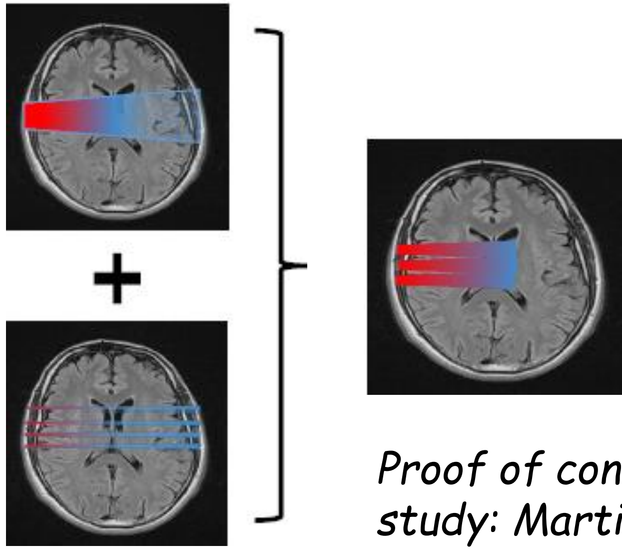


Example of rat head with a brain tumor
-
Typical depth of interest

- **High Energy Electron Grid Therapy (eHGRT):**

Very high energy electrons (VHEE)

Spatial fractionation of the dose (MBRT)

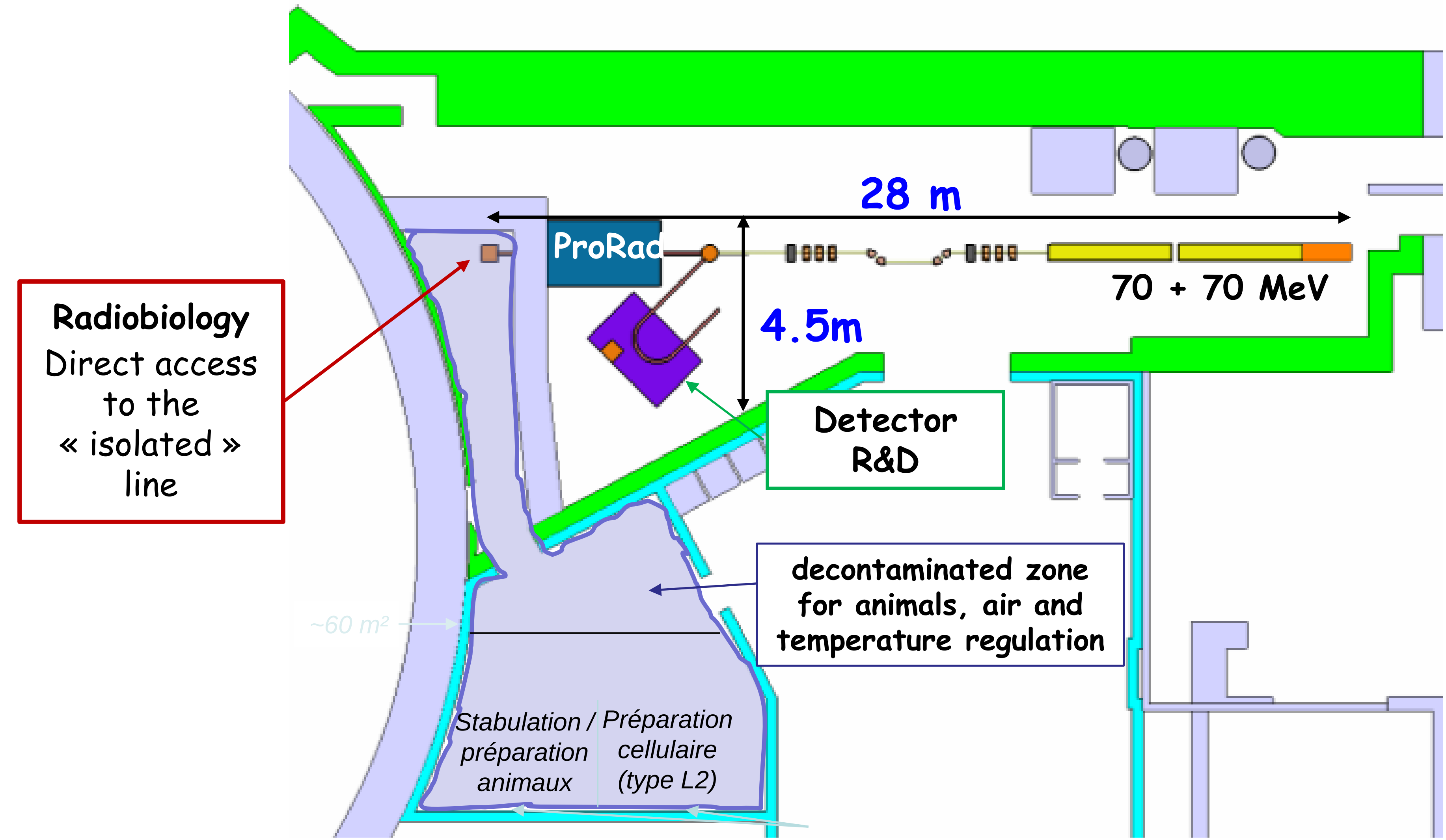


eHGRT: novel approach to spare normal tissue at the entrance with a quasi homogeneous dose distribution in the tumor

Proof of concept with dosimetric Monte Carlo study: Martinez and Prezado, Med. Phys. 2015

- **To be studied on the PRAE radiobiology line:**
  - *Experimental dosimetry for very small field sizes*: with radiochromic films and microdiamond detector
  - *Monte Carlo dose calculation*: beam characteristics for eHGRT, validation of experimental dosimetry, dose calculation for radiobiology studies
  - *Radiobiology studies on cells and small animals*: confirmation of the hypothesis of high normal tissue resistance
  - Relative Biological Efficiency (RBE) of VHEE with respect to photons
  - « FLASH » effect
  - Online imaging/control

Experimental area



Preparation hall for biological experiments (animal room by Curie Institute)

Bruno Touschek

Instrumentation R&D

- *Principle goal is to construct versatile tool for detector R&D and tests:* ***deliver calibrated beam with adjusted and known kinematics and number of electrons per sample***

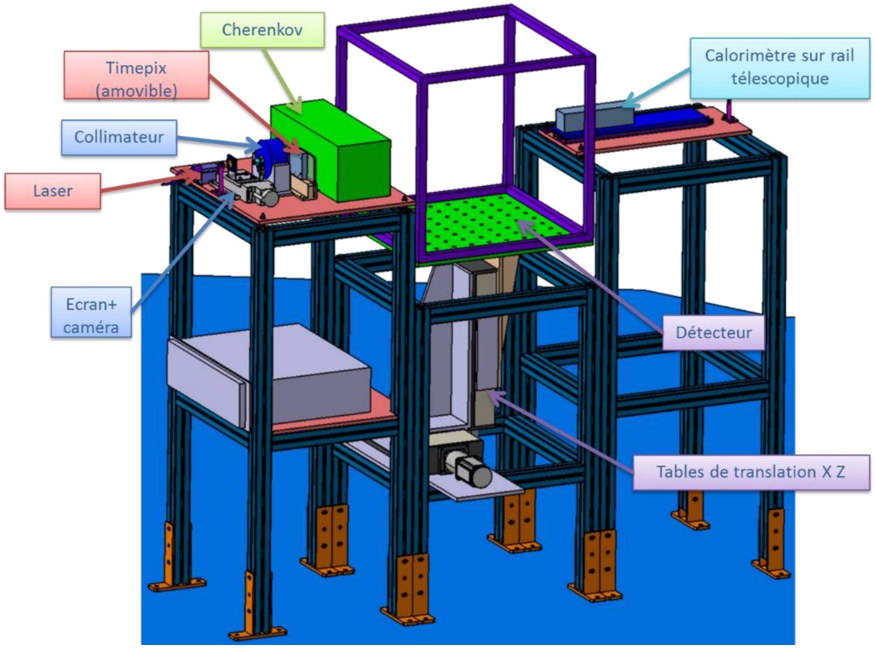
Platform for Research and Applications with Electrons

- **Fully-equipped versatile tool for precision instrumentation R&D based on high-performance electron beam**
- Excellent technical performance
  - **Timing** reference, < 10 ps bunch length
  - **Charge accuracy**, RMS < 2×10^{-3}
  - Low straggling (energy >> 1 MeV)
- High-performance, remotely controlled tools
  - **Beam position, profile and monitoring**
  - 60 digitization channels for users on NARVAL-based **data acquisition**
  - Motorized **moving table for scans**, accuracy < 500 μm
- No need to place the detectors in vacuum

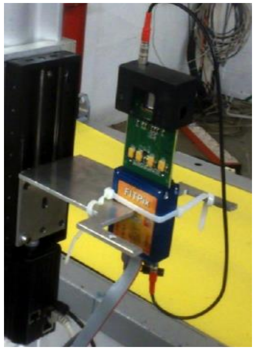
Measure the time, charge and imaging performance of particle detectors

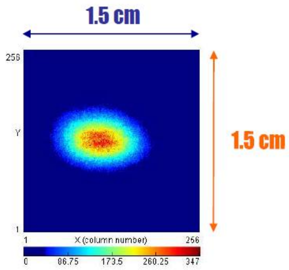
→ *Calibration for charge, trigger, tracking detectors*

Instrumentation R&D at PRAE



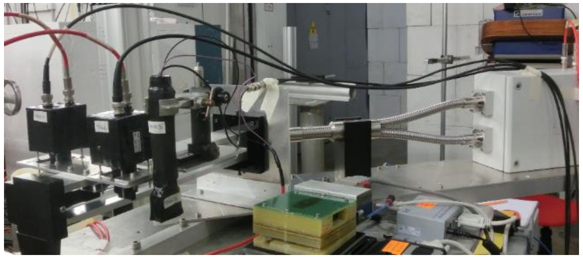
Timepix detector for precision spot measurement

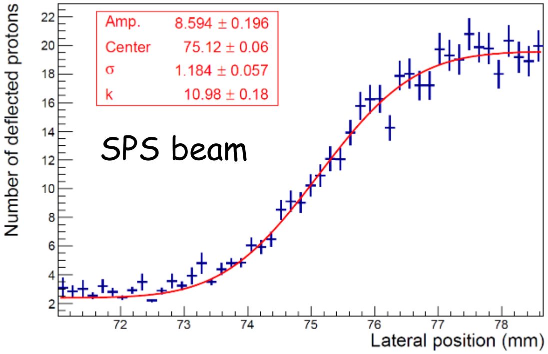




Cherenkov quartz counter for intensity monitoring

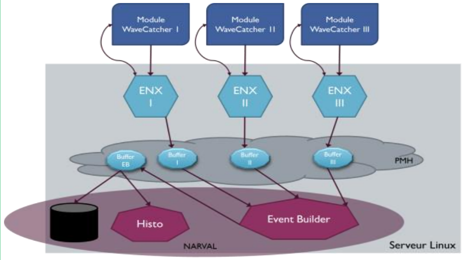
2 channel Cherenkov counters (LAL) tested at BTF (Frascati); installed in the SPS (CERN) beam pipe





DAQ + slow control

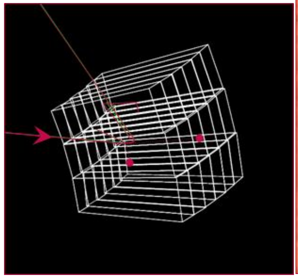
- 60 user digitization signals (WaveCatcher)
- DCOD = NARVAL + ENX



Participation of
Centre de Sciences Nucléaires et de Sciences de la Matière

Calorimeter for energy monitoring

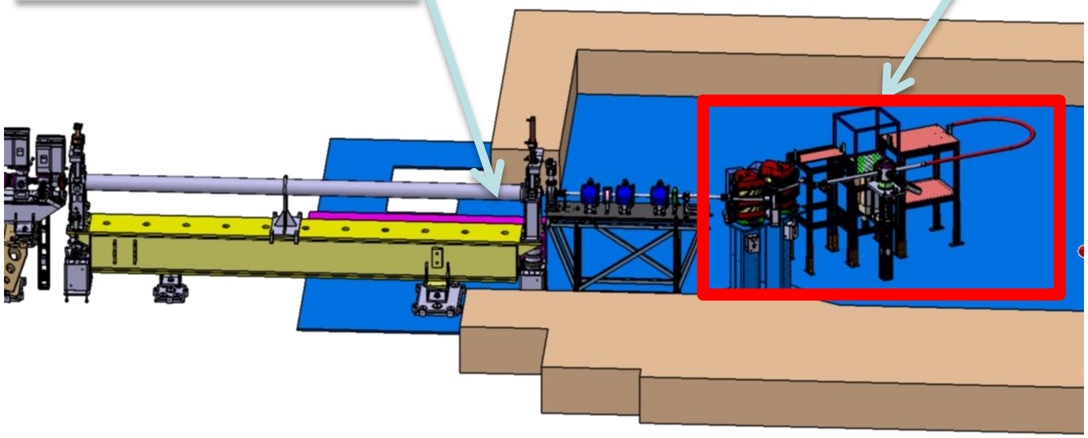
BGO scintillator crystals in compact matrix geometry

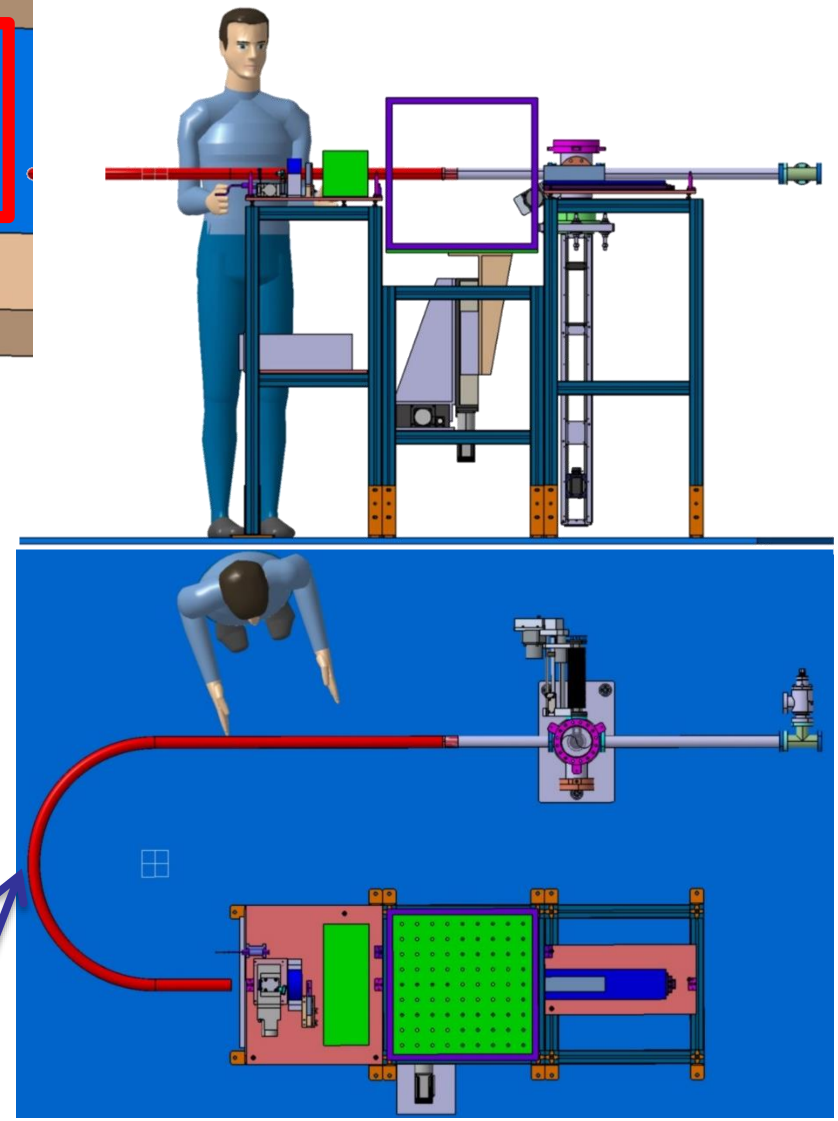


Example of a calorimeter realized at IPN

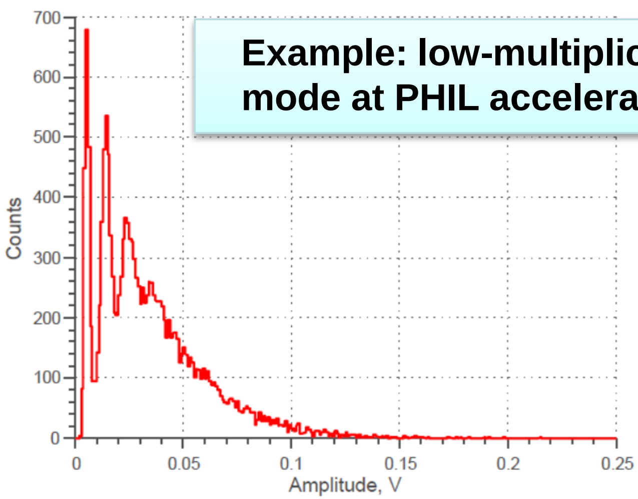
Ligne accélératrice

Plateforme



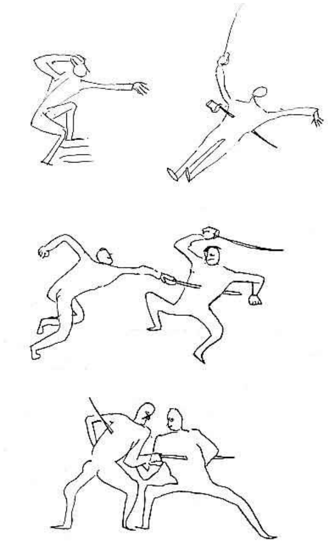


Example: low-multiplicity mode at PHIL accelerator



SPECTROMETER

Platform for Research and Applications with Electrons

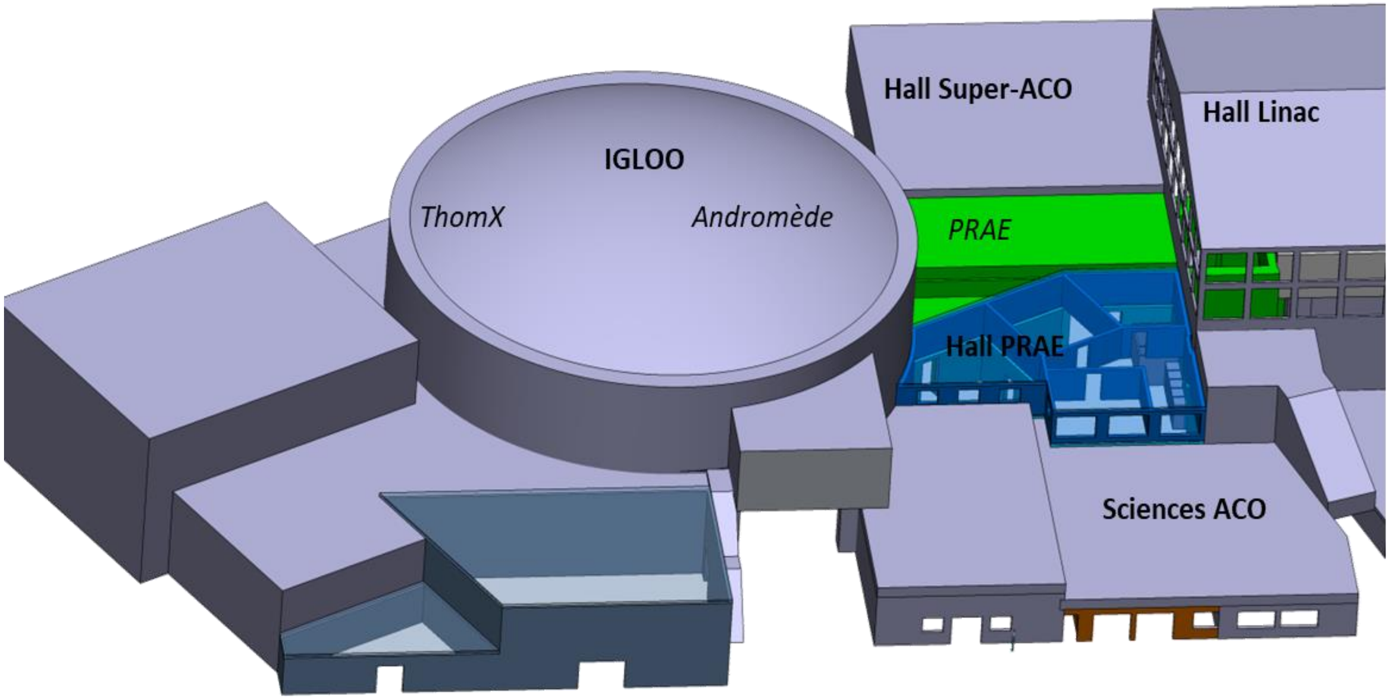


Bruno Touschek

PRAE site

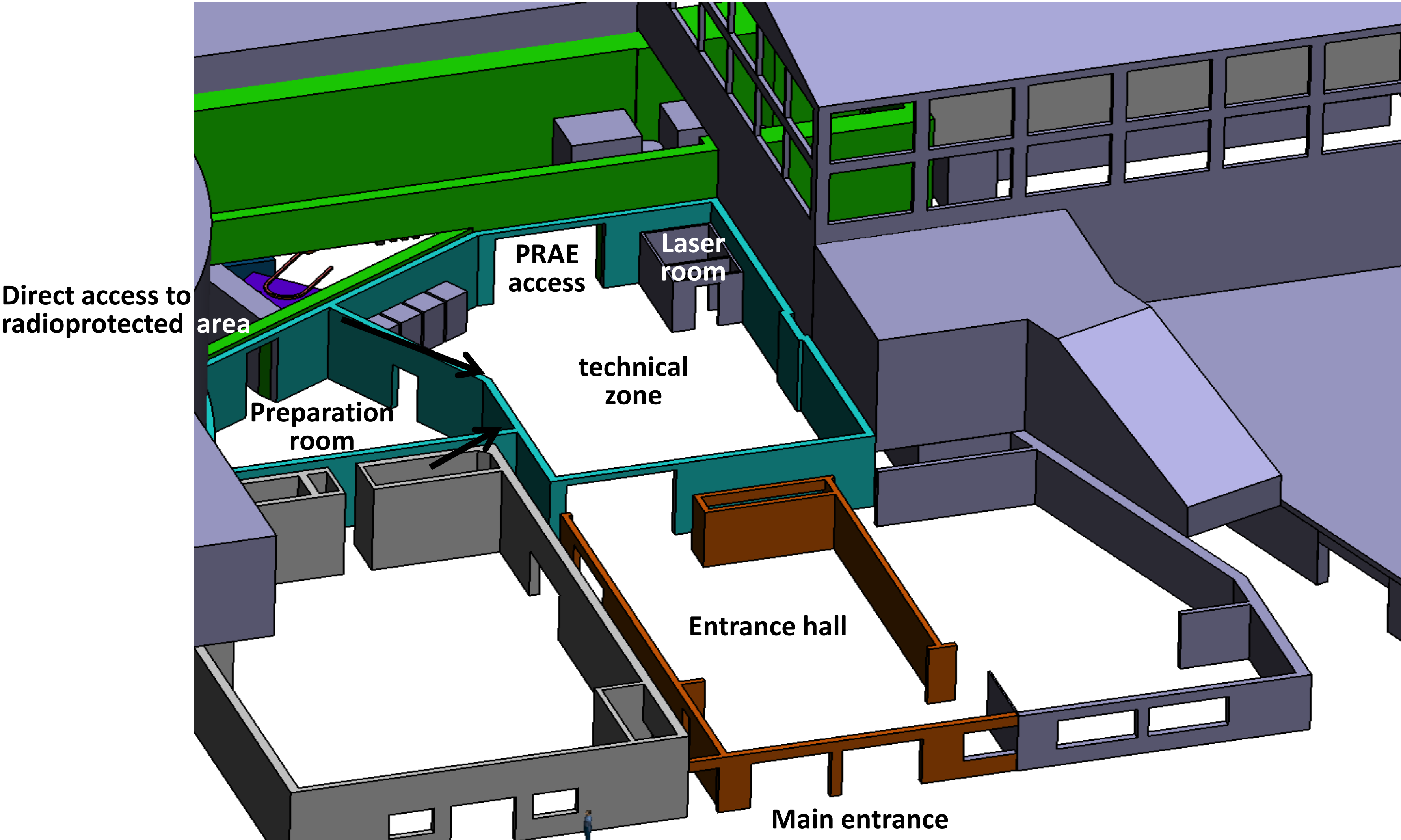
Future PRAE site: IGLEX complex

- PRAE experimental hall - existing structure, locked and radio-protected site



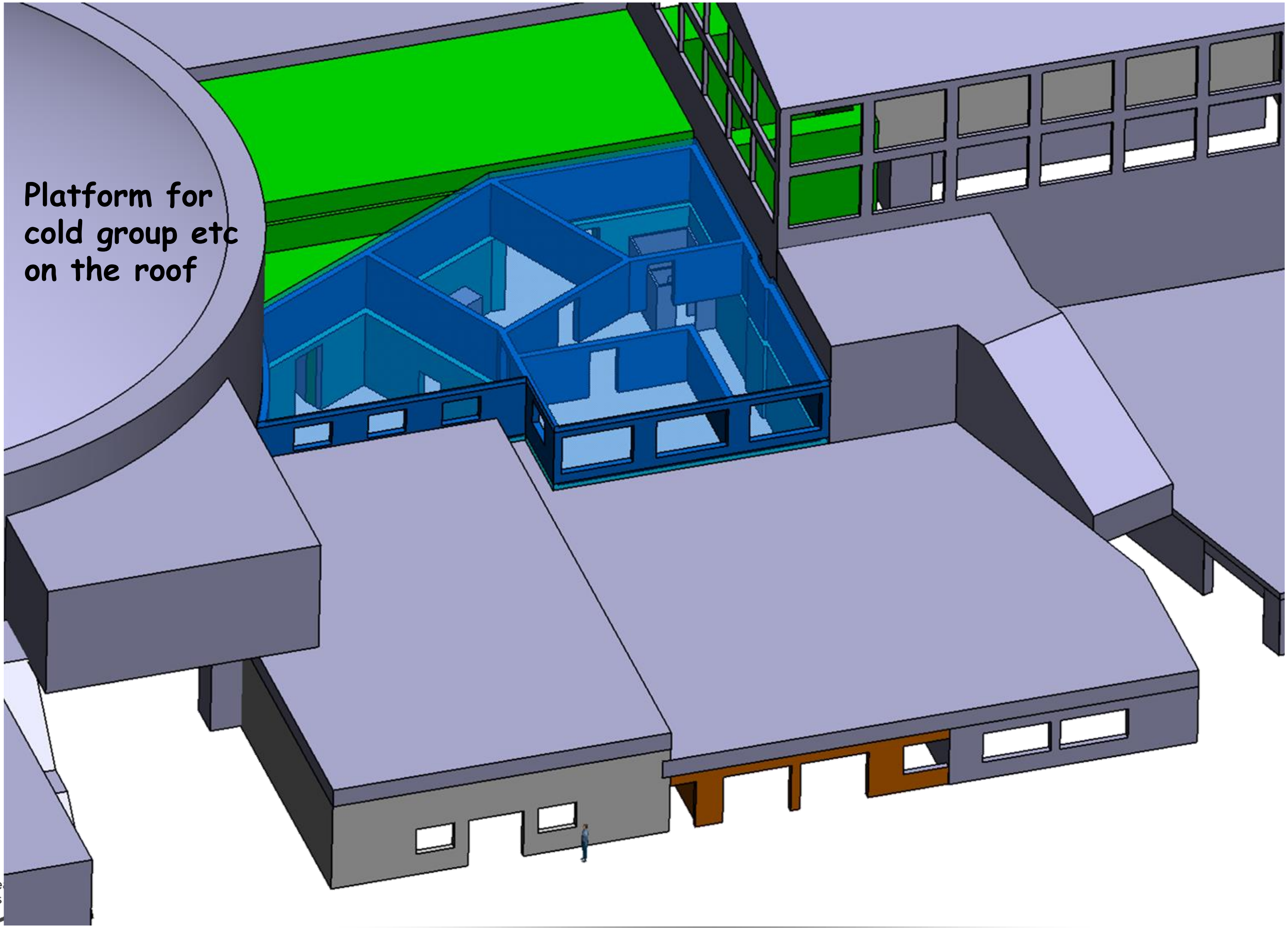
Ground floor of new building

Ground surface : 290 m²



1st floor of new building

- Control and acquisition room
- Additional equipment



- PRAE is a new project for science, R&D and applications based on **complementary expertise of major Orsay laboratories**.
- Construction of the **multi-disciplinary PRAE site – Subatomic physics, Radiobiology, Instrumentation R&D and Accelerator** – is centered around the **new high-performance electron accelerator**.
- We expect a start of the main PRAE program in 2020-2021.
- The PRAE collaboration is open to new groups:

YOU ARE WELCOME TO JOIN !

Bruno Touschek

Platform for Research and Applications with Electrons

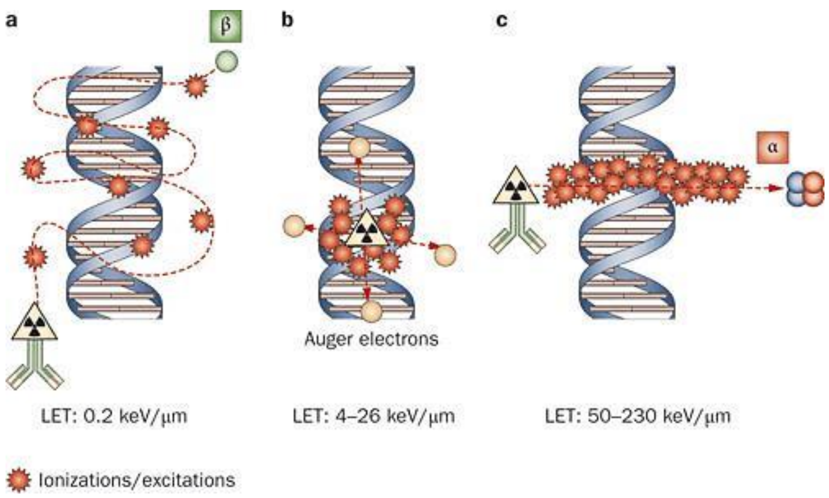
PRAE

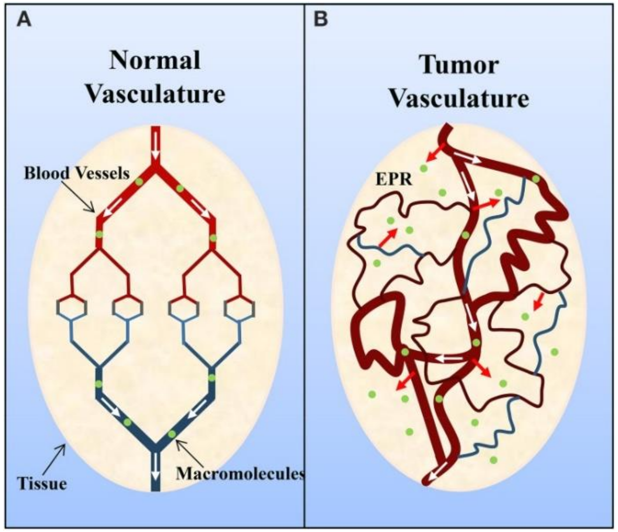
Backup

(this worksheet is now protected, please contact Erik Adli if you have modifications/corrections.)	EUROPE (only primary beams)									
Name	**CALIFES**	**CLARA**	**FlashForward**	**Sinbad**	**PITZ**	**SPARC_LAB**	**Max IV injector**	**PRAE**	**RADEF (clinac)**	**FLUTE**
Country	Switzerland	UK	Germany	Germany	Germany	Italy	Sweden	France	Finland	Germany
Laboratory	CERN	Daresbury	DESY, Hamburg	DESY, Hamburg	DESY, Zeuthen	INFN, Frascati	Max IV	Orsay, France	Jyväskylä	KIT
Type of facility	TBD	Test facility for UKFEL R&D	DESY tests of PWFA	Adv. accel. research	Photo-inj test facility	Adv. accel. research	Part of Max IV. Ideas (but no funding) to create a 3 GeV ebeam test facility	Multi-disiplinary	Medical linac (?)	THz tests
Online when?	Online	Jan 2017 (50 MeV)	mid-2017	2018 ?	Online	Online	Linac under final commissioning. Parameters as expected when fully commissioned.	2020 ?	online	online (?)
Energy	130-200 MeV (60 with upgrade)	50 MeV (Jan 2017) 250 MeV (Sept 2019)	1.25 GeV	100 MeV	25 MeV	150 MeV	3 GeV	65 MeV	<= 20 MeV	41 MeV
Energy spread	< 1 MeV FWHM (< 0.2 % rms)	25 to 100 keV rms	0.10%	< 0.3% (low charge, peak	<0.5%	0,1%	<0.05% + chirp	0.2 % rms		
RF Frequency	3 GHz	3 GHz		3 GHz	1.3 GHz	2.856 GHz	3 GHz	3 GHz		
Rep. rate	1 or 5 Hz (25 Hz with upgrade)	100Hz at 250MeV, 400Hz at 100MeV	10 Hz	10 - 50 Hz	10 Hz	10 Hz	10 (100) Hz	50 Hz		10
Time structure	1.5 GHz, or single bunch	single bunch	single or double bunch	single bunch	up to 600 bunches at 1 MHz rep rate	single bunch or up to 4 bunches at 1 THz rep rate		single bunch		single bunch (?)
Bunch length	4 ps FWHM (~ 500 um rms)	35 fs to 1.9ps FWHM	10-500fs	sub-fs - 2 fs (low charge)	Flat top, 2ps rise/fall time; 22ps FWHM	30 fs - 5 ps	10-500 fs	10 ps		1 - 300 fs
Charge per bunch	10 pC to 0.5 nC (for < 30 bunches)	25 to 250pC	250 pC	0.5 pC - 20 pC for fs bunc 1 nC possible	20 pC to 4 nC	0.1-0.8 nC	20-200 pC	sub pC - 2 nC		1 - 3000 pC
Trans. emittance Normalized	3 um for 0.05 nC bunches, 20 um for 0.4 nC	0.5 to 1.0um	2 um	< 0.5 um	0.6 um for 1 nC	1 um	< 1um	3 - 10 um		

Platform for Research and Applications with Electrons

- **« Biological » dose vs. « physics » dose**
  - Molecular scale:
    - LET: ionisation density
    - Reparation mechanisms …
  - Cellular / tissue scale
    - Cellular regulation
    - Vascularisation…

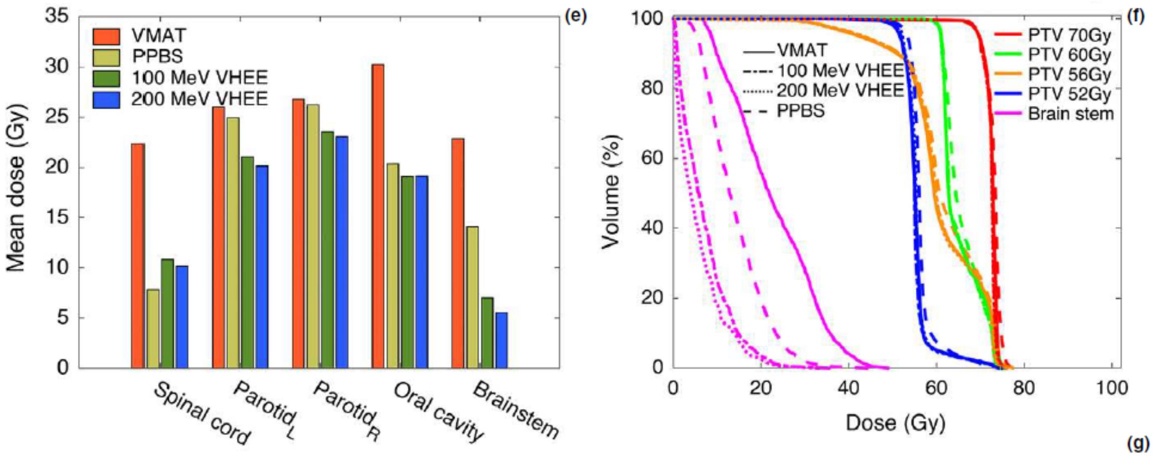




- Optimize physics parameters to induce different biological response
  - Particles
  - Dose delivery mode: temporal, spatial

- **Objective: favorable difference between healthy tissue and tumor**

Avantages VHEE, hétérogénéités, cas cliniques



(g)

VMAT				PPBS				100 MeV VHEE				200 MeV VHEE			
$\bar{D}_{Body}(Gy)$	CI_{100}	CI_{50}	HI	$\bar{D}_{Body}(Gy)$	CI_{100}	CI_{50}	HI	$\bar{D}_{Body}(Gy)$	CI_{100}	CI_{50}	HI	$\bar{D}_{Body}(Gy)$	CI_{100}	CI_{50}	HI
9.5	1.03	12.56	0.082	7.9	1.13	12.17	0.10	8.5	1.09	11.75	0.084	8.4	1.08	11.51	0.084

$CI_{100} = V_{100\%}/V_{PTV}$ $CI_{50} = V_{50\%}/V_{PTV}$ HI = (D2-D98)/D50

Fig. 6. Treatment plan comparison, HNC. Treatment planning comparison between VMAT, PPBS, 100 MeV VHEE, and 200 MeV VHEE plans. (a–d) Coronal images through PTV for the different modalities, (e) mean doses to the spinal cord, parotid glands, oral cavity, and brain stem, (f) dose volume histogram for the PTVs and brain stem, and (g) mean integral body dose, conformity index, and homogeneity for the different modalities. [Color figure can be viewed at wileyonli-

Schuller 2017: comparaison VHEE vs protons et photons, H&N cancer

DesRosiers et al. 2008 : hétérogénéité

Agnese Lagzda : avantage hétérogénéités