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The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

Dosimetry for advanced radiotherapy approaches using particle beams with ultra-high pulse dose rates (UHPDR) in the EMPIR UHDpulse project

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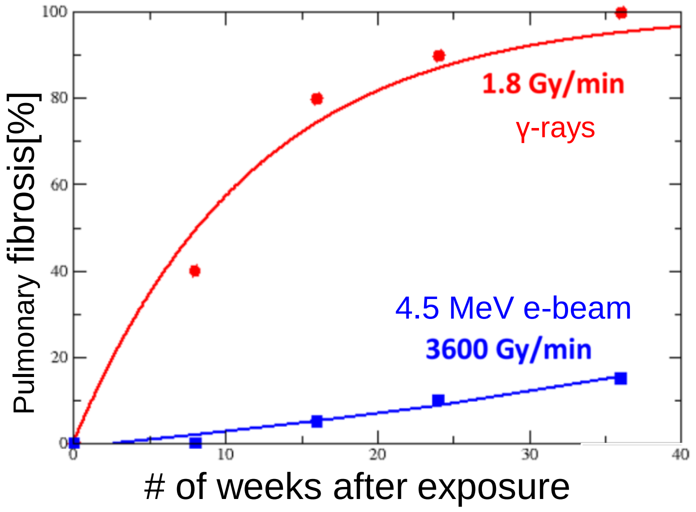
PTCOG 2020, 13-14 September 2020

PTCOG 2020 Online

Outline

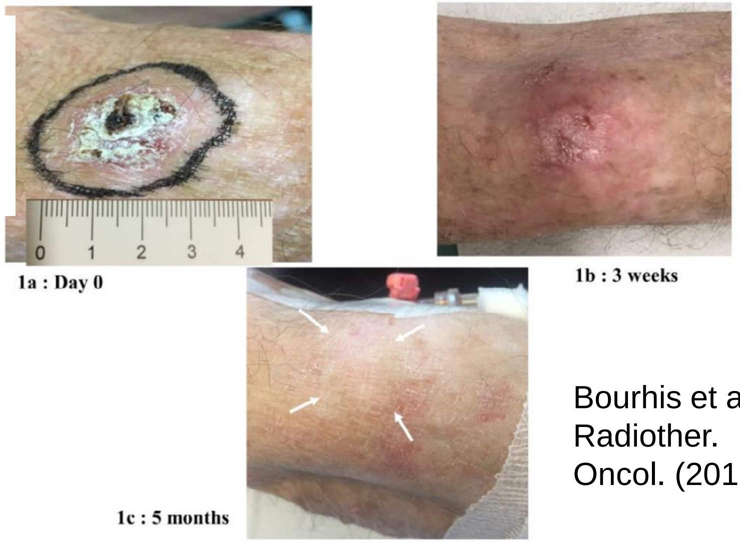
- Interest in UHPDR RT
- Challenges of dosimetry of UHPDR beams
- The EMPIR UHDpulse project
- First results
  - ionization chamber dosimetry in UHPDR VHEE beams
- Conclusions

Why are we interested in UHPDR RT?



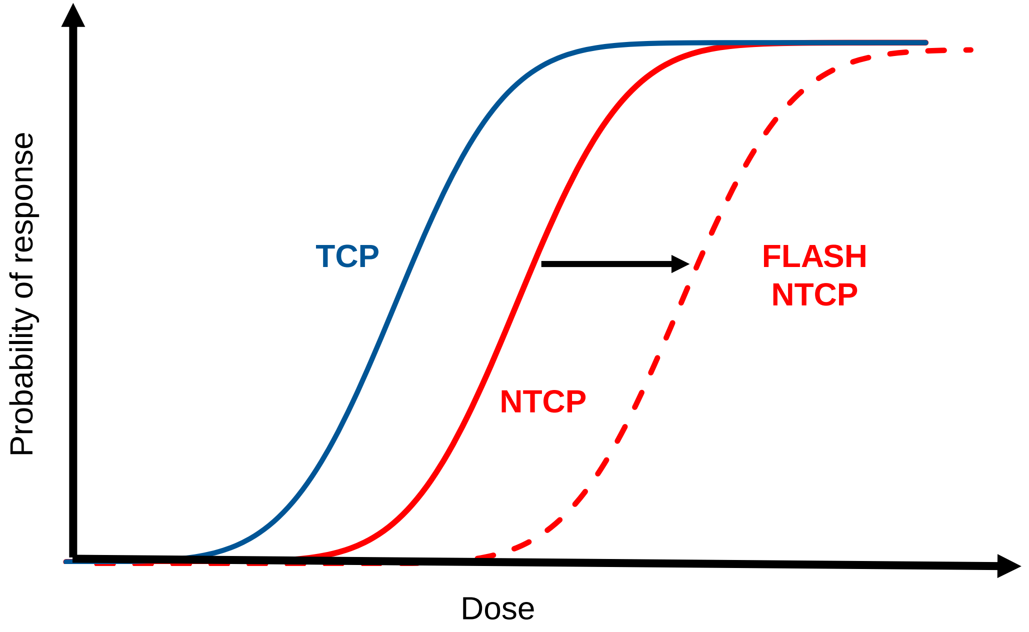
Favaudon, *et al.* *Sci Transl Med* 2014; **6**

- subcutaneous lymphoma
- delivery: 10 pulses (1 us) in 90 ms with 1.5 Gy/pulse



Bourhis et al., Radiother. Oncol. (2019)

FLASH effect!



Review of FLASH studies (Wilson et al. Frontiers in Oncology 2020)

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Summary of irradiation parameters and outcomes for in vivo studies investigating the FLASH effect

normal tissues

In vivo studies			Irradiation delivery technique			
Model	**Assay**	**FLASH dose modification factor (Bold if > 1)**	**Total dose (Gy)**	**Dose rate (Gy/s)**	**Pulse rate (Hz)**	**Modality of radiation**
Zebrafish embryo (16)	Fish length	**1.2–1.5**	10–12	10^6–10^7	Single pulse	Electron
Zebrafish embryo (29)	Fish length, survival, and rate of oedema	1	0–43	100	0.106 × 10^9	Proton
Whole body irradiation of mice (34)	LD50	**1.1**	8–40	17–83	400	Electron
Thoracic irradiation of mice (10)	TGFβ signaling induction	**1.8**	17	40–60	100–150	Electron
Thoracic irradiation of mice (18)	Number of proliferating cells, DNA damage, expression of inflammatory genes	**> 1 Significant Differences**	17	40–60	100–150	Electron
Abdominal irradiation of mice (33)	Survival	< 1 Significant Difference	16	35	Likely 300	Electron
Abdominal irradiation of mice (12)	LD50	**1.2**	22	70–210	100–300	Electron
Abdominal irradiation of mice (17)	Survival, stool formation, regeneration in crypts, apoptosis, and DNA damage in crypt cells	**> 1 Significant Differences**	12–16	216	108	Electron
Whole brain irradiation of mice (25)	Novel object recognition and object location tests	**> 1 Significant Differences**	30	200, 300	108, 180	Electron
Whole brain irradiation of mice (13)	Variety of neurocognitive tests	**> 1 Significant Differences**	10	5.6·10^6	Single pulse	Electron
Whole brain irradiation of mice (14)	Novel object recognition test	**> 1 Significant Differences**	10	30–5.6·10^6	100 or single pulse	Electron
Whole brain irradiation of mice (8)	Novel object recognition test	**≥ 1.4**	10	5.6–7.8·10^6	single pulse	Electron
Whole brain irradiation of mice (24)	Novel object recognition test	**> 1 Significant Difference**	10	37	1,300	X-ray
Total body and partial body irradiation of mice (32)	TD50	1	3.6–28	37–41	1,388	X-ray
Thoracic irradiation of mice (11)	lung fibrosis, skin dermatitis, and survival	**> 1 Significant Difference**	15, 17.5, 20	40	?	Proton
Irradiation of mouse tail skin (49)	Necrosis ND50	**1.4**	30 and 50	17–170	50	Electron
Irradiation of mouse skin (27)	Early skin reaction score	**1.1–1.6**	50–75	2.5 mean, 3 × 10^4 in the pulse	23–80	Electron
Irradiation of rat skin (26)	Early skin reaction score	**1.4–1.8**	25–35	67	400	Electron
Irradiation of mini-pig skin (15)	Skin toxicity	**≥ 1.4**	22–34	300	100	Electron

tumour tissues

In vivo studies			Irradiation delivery technique			
Model	**Assay**	**FLASH dose modification factor (Bold if > 1)**	**Total dose (Gy)**	**Dose rate (Gy/s)**	**Pulse rate (Hz)**	**Modality of radiation**
Thoracic irradiation of orthotopic engrafted non-small cell lung cancer (Lewis lung carcinoma) in mice (36)	Tumor size and T-cell Infiltration	**> 1 Differences in tumor size (significant) and T-cell infiltration**	18	40	?	Proton
Thoracic irradiation of orthotopic engrafted mouse lung carcinoma TC-1 Luc+ in mice (10)	Survival and tumor Growth Delay	1	15-28	60	100–150	Electron
Abdominal irradiation of mice (17)	Number of tumors, tumor weights	1	12–16	216	108	Electron
Whole brain irradiation of nude mice with orthotopic engrafted H454 murine glioblastoma (8)	Tumor Growth Delay	1	10–25	2.8–5.6·10^6	Single pulse	Electron
Local irradiation of subcutaneous engrafted Human breast cancer HBCx-12A and head and neck carcinoma HEp-2 in nude mice (10)	Tumor Growth Delay	1	15–25	60	100–150	Electron
Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (8)	Tumor Growth Delay	1	0–35	125–5.6·10^6	100 or single pulse	Electron
Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (19)	Tumor Growth Delay	1	10–30	125–5.6·10^6	100 or single pulse	Electron
Local irradiation of subcutaneous engrafted Human hypopharyngeal squamous cell carcinoma ATCC HTB-43 in nude mice (35)	Tumor Growth Delay in irradiated Mice and RBE	1	20	0.008 mean, ≈10^9 in pulse	<< 1	Proton
Treatment of locally advanced squamous cell carcinoma (SCC) in cat patients (15)	Tumor response and survival	1 Similar response as in published studies with CONV-RT	25–41	130–390	100	Electron
Treatment of CD30+ T-cell cutaneous lymphoma T3 N0 M0 B0 in human patient (9)	Tumor response	1 Similar response as previous treatments with CONV-RT	15	167	100	Electron

Challenges of dosimetry of UHPDR beams

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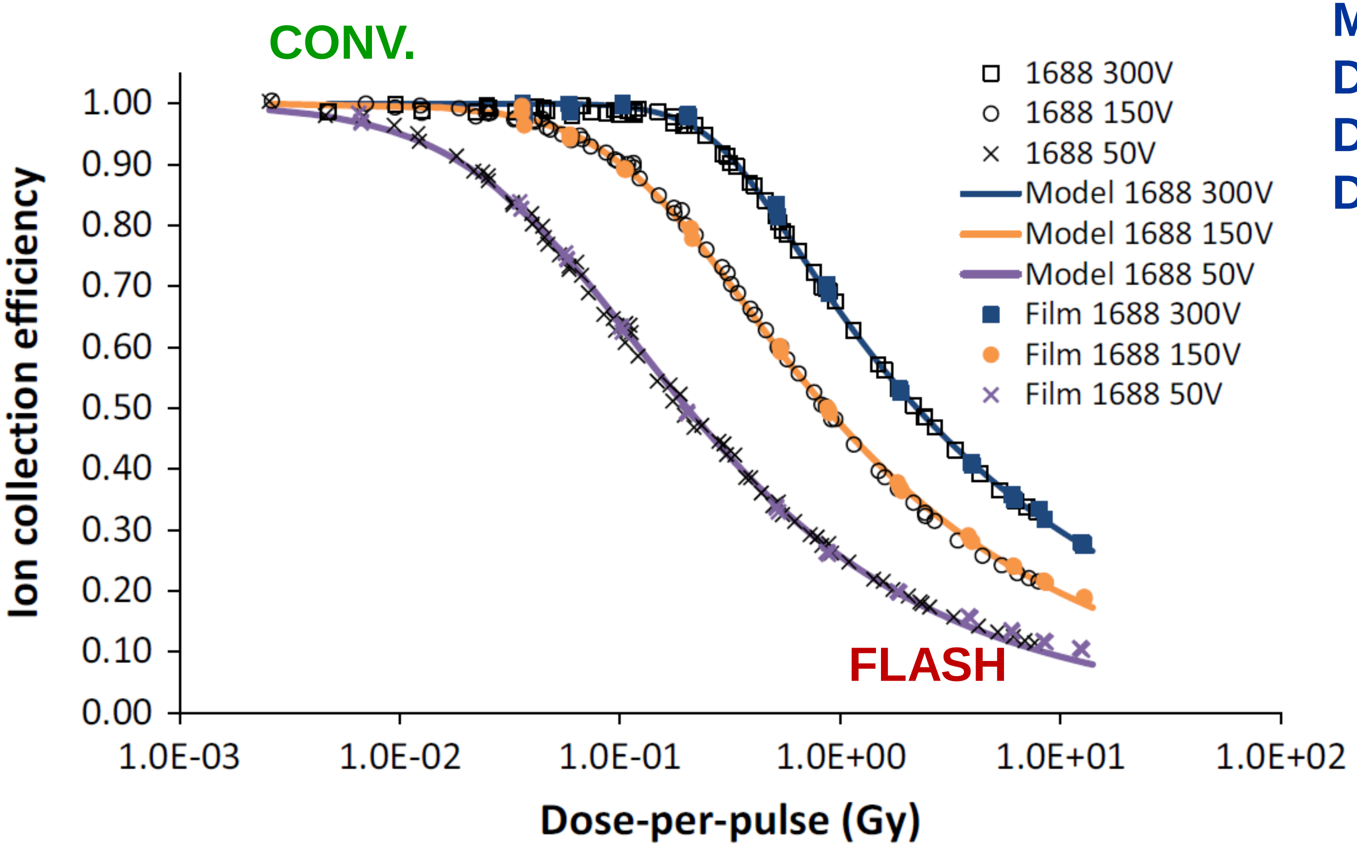
Loss of collection efficiency in IC



Petersson et al., Med Phys 44 (2017) 1157

	CONV.		FLASH
Mean dose rate →	0.05 Gy/s	*vs*	40-1000 Gy/s
Dose per pulse →	0.3 mGy	*vs*	1-10 Gy
Dose in a pulse →	10^2 Gy/s	*vs*	10^6 Gy/s
Delivery time →	few min	*vs*	<1s

NEW DOSIMETRY TOOLS & METHODS NEEDED

USE THE RIGHT TOOL FOR THE RIGHT JOB

EMPIR UHDpulse project

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EMPIR Call:	2018 / Health (JRP)
Coordinator:	Andreas Schüller (PTB)
Duration:	2019-2022
Start:	1. Sept. 2019
Funding:	2.1 M €

Topic: tools for traceable dose measurements for:

- **FLASH radiotherapy**
- **VHEE radiotherapy**
- **laser driven medical accelerators**

UHDpulse

***UHDpulse**: Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates*

5 National Metrology Institutes
leading in the field of dosimetry

3 academic hospitals
pioneers in FLASH-RT

3 universities
experts in detector development
pioneer in laser-driven beams

3 national research institutes
pioneer in detector development
pioneer in laser-driven beams
dosimetry expert

1 European research institute
laser-driven beam research

5 companies
expert in detector development

NMI's

- PTB Physikalisch-Technische Bundesanstalt Braunschweig und Berlin — WP6 (coordin.)
- NPL National Physical Laboratory — WP1
- METAS — WP2
- CMI Czech Metrology Institute — WP5 (impact)
- Central Office of Measures

Irradiation facility provider

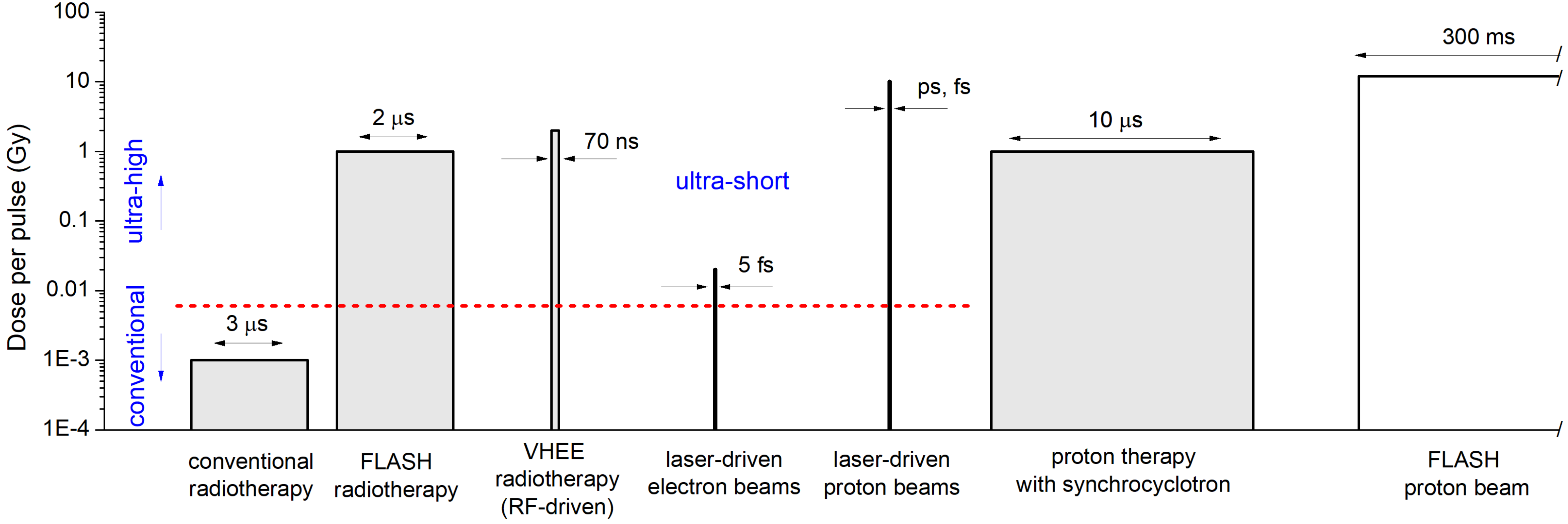
- CHUV Centre hospitalier universitaire vaudois — WP3
- institut Curie
- eli beamlines
- Nuclear Physics Institute of the CAS public research institution
- Queen's University Belfast
- HZDR Helmholtz Zentrum Dresden Rossendorf

Radiation detector developer

- ADVACAM Imaging the Unseen — WP4
- CSIC, cnm Centro Nacional de Microelectrónica
- USC Universidade de Santiago de Compostela
- Politecnico Milano 1863
- Carl von Ossietzky Universität Oldenburg
- iba, varian, lpc caen, Sun Nuclear corporation, PTW

http://uhdpulse-empir.eu/

Beams with ultra-high pulse dose rates



Courtesy of A. Schueller

UHDpulse EMPIRE project: WPs

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WP1: Primary standards

- Definition of reference conditions
- Reference radiation fields
- Adapting primary standards (water calorimeter, Fricke dosimeter)
- Prototype graphite calorimeters for laser-driven beams

WP2: Secondary standards, relative dosimetry

- Transfer from primary standards
- Characterizing established detector systems
- Formalism for reference dosimetry for future Code of Practice

WP4: Detectors and methods outside primary beam

- Active detection techniques for pulsed mixed radiation fields of stray radiation
- Methods with passive detectors

WP3: Detectors for primary beam

- Novel and custom-built active dosimetric systems
- Beam monitoring systems

First experimental results: UHPDR VHEEs

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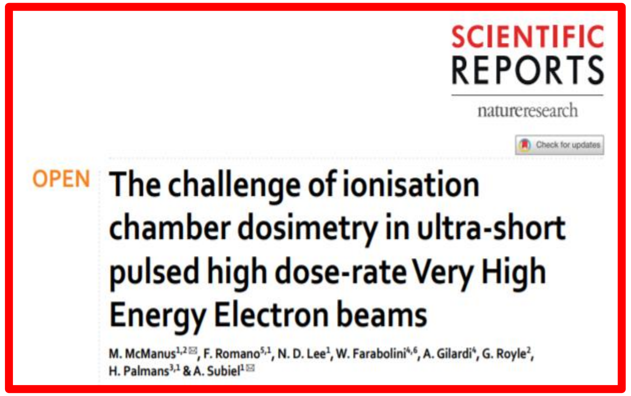
OBJECTIVE: To study ion collection efficiency as a function of dose-per-pulse at instantaneous dose rates 5.0×10^6–3.1×10^8 Gy/s for VHEE beams (→ energies suitable for deep-seated tumours)

- BEAM PARAMETERS: 200 MeV, x and y σ of 5 mm, ΔE between 0.25 and 6.5%
- side-by-side measurements: **PTW Roos** chamber and NPL's **graphite calorimeter**
- quantification of the recombination factor $k_{s,abs}$ for the Roos chamber for a range of collecting voltages: 75 V – 600 V


SCIENTIFIC REPORTS
natureresearch
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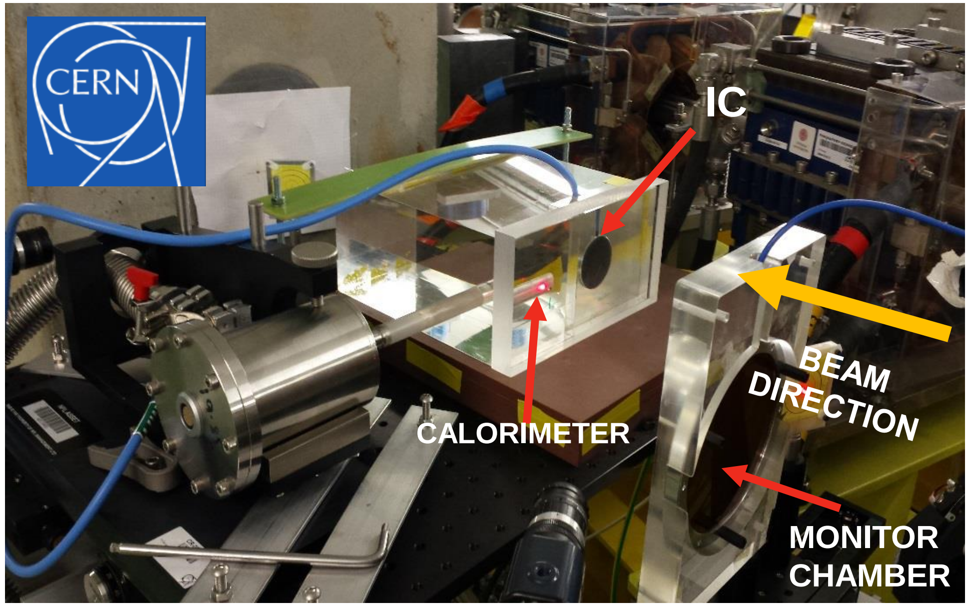
OPEN
The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate Very High Energy Electron beams
M. McManus[1,2], F. Romano[3,1], N. D. Lee[1], W. Farabolini[4,6], A. Gilardi[4], G. Royle[2], H. Palmans[5,1] & A. Subiel[1]

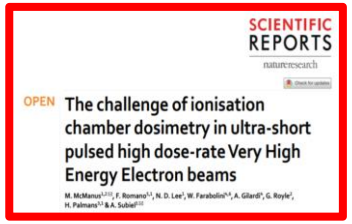


The test-stand at the CLEAR facility, with the calorimeter, ion chamber and monitor chamber placed along the beam line with the beam travelling from right to left.

Nominal Beam Charge (nC/pulse)	Dw,cal (Gy/pulse)	ks,abs			
		75 V	200 V	350 V	600 V
0.05	0.03	1.3	0.98	0.89	0.78
0.2	0.20	3.41	1.87	1.56	1.14
0.25	0.14	2.46	1.33	2.05	-
1	0.67	6.00	3.07	2.12	1.58
2.2	1.25	8.80	4.12	2.80	1.94
3	1.95	11.96	5.67	-	2.58
4.5	2.63	14.99	6.87	4.59	3.07
6	3.66	18.94	8.54	5.63	3.81
7.5	4.12	19.54	8.77	5.69	3.74
9	4.56	21.38	9.30	5.99	4.23
10.5	5.26	22.99	9.95	6.50	4.24

$$k_{s,abs} = \frac{D_{w,cal}}{M k_{pol} k_{TP} k_{Q,Q_0} N_{D,w,Q_0}}$$

Results cont.

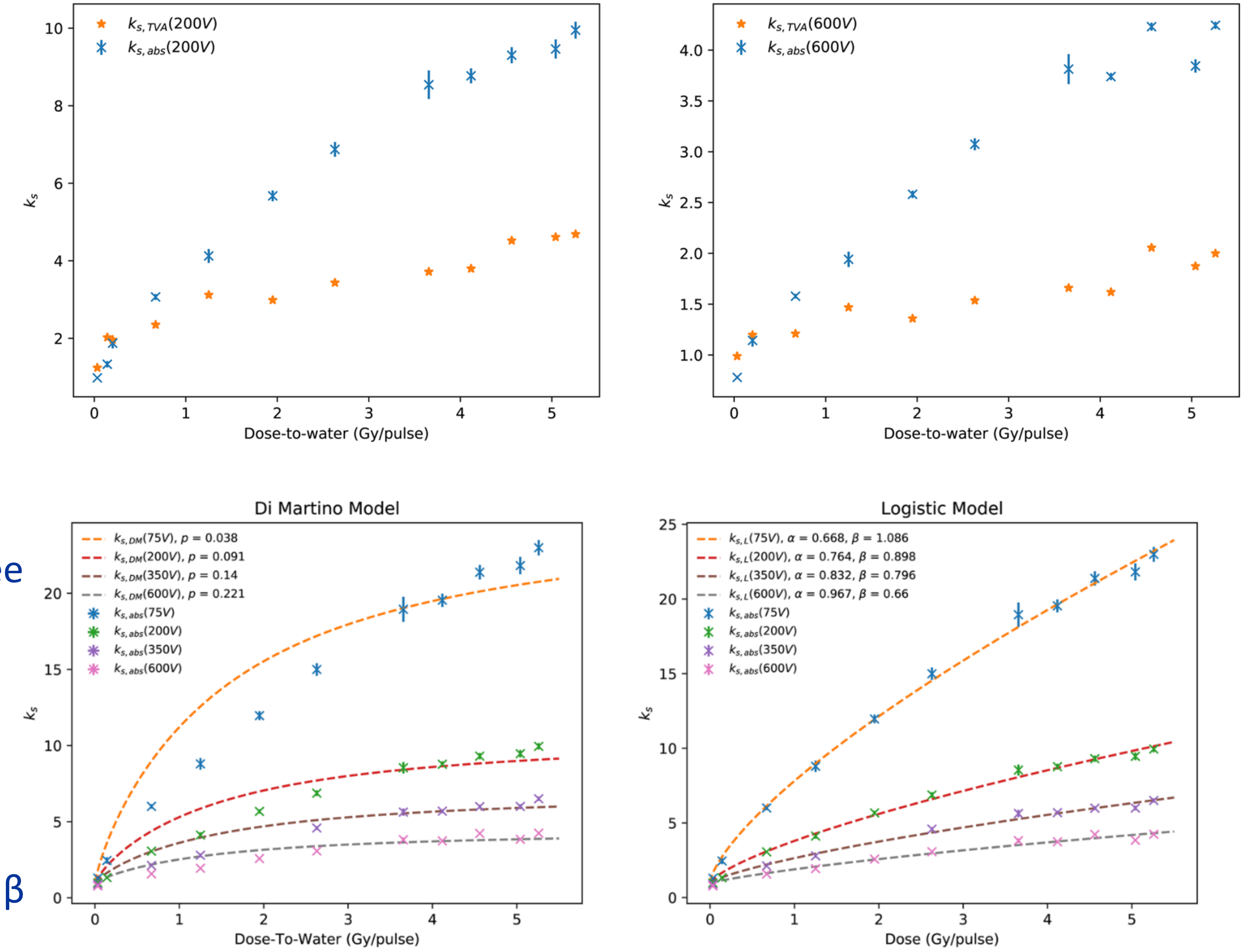

SCIENTIFIC REPORTS
natureresearch

OPEN The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate Very High Energy Electron beams

M. McManus, F. Romano, N. D. Lee, W. Farabolini, A. Gilardi, G. Royle, H. Palmans & A. Subiel

- k_s up to 10 (V = 200V) → collection eff. 10%
- k_s up to 4 (V = 600V) → collection eff. 25%
- $k_{s,abs}$ compared with $k_{s,TVA}$ (two-voltage method)

- Available recombination models include Boag's free-electron fraction models (Boag 1996)
- By optimising the free-electron fraction parameter in these equations, we were able to determine a best fit of our data.
- All analytical models of Boag and Di Martino show similar predictions of the recombination factor and estimations of the free electron fraction
- Analytical (Boag 1996, Di Martino 2005) and logistic (Petterson 2017) models tested
- The logistic model from Petersson shows the best fit to data over the whole dose-per-pulse range, however this model has no physical meaning and simply relies on two fitting constants α and β



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Conclusions

- Tools and methods established for dosimetry of conventional RT sources are not suitable for UHPDR beams
- Challenges of dosimetry for ultra-high pulse dose rate to be addressed within EMPIR UHDpulse project
- Metrological and validated tools will be provided to support accurate preclinical studies and to enable future clinical applications for UHPDR beams

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Thank you for your attention

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This project has received funding from the EMPIR programme co-financed by the Participating States and from the EU Horizon 2020 research and innovation programme.