Institute of radiation physics, Switzerland

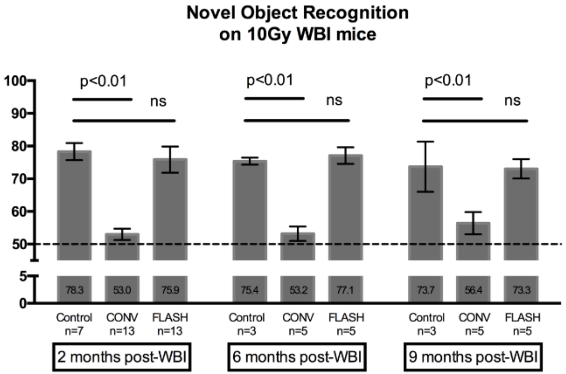
Introduction to FLASH-RT

C. Bailat, PhD
Radiometrology group leader

FLASH-RT in short: Irradiation at ultra high dose-rate increases the differential response between normal and tumour tissue

Flash

Conventional



Record 1 of 12
Title: The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients
Author(s): Vozenin, MC (Vozenin, Marie-Catherine); De Fornel, P (De Fornel, Pauline); Petersson, K (Petersson, Kristoffer); Favaudon, V (Favaudon, Vincent); Jaccard, M (Jaccard, Maud); Germond, JF (Germond, Jean-Francois); Petit, B (Petit, Benoit); Burki, M (Burki, Marco); Ferrand, G (Ferrand, Gisele); Patin, D (Patin, David); Bouchaab, H (Bouchaab, Hanan); Ozsahin, M (Ozsahin, Mahmut); Bochud, F (Bochud, Francois); Bailat, C (Bailat, Claude); Devauchelle, P (Devauchelle, Patrick); Bourhis, J (Bourhis, Jean)
Source: CLINICAL CANCER RESEARCH **Volume:** 25 **Issue:** 1 **Pages:** 35-42 **DOI:** 10.1158/1078-0432.CCR-17-3375 **Published:** JAN 1 2019
Accession Number: WOS:000455001100007
PubMed ID: 29875213
Author Identifiers:

Author	Web of Science ResearcherID	ORCID Number
Petersson, Kristoffer		0000-0003-0300-5790
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Vozenin, Marie-Catherine		0000-0002-2109-8073
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Record 2 of 12
Title: X-rays can trigger the FLASH effect: Ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice
Author(s): Montay-Gruel, P (Montay-Gruel, Pierre); Bouchet, A (Bouchet, Audrey); Jaccard, M (Jaccard, Maud); Patin, D (Patin, David); Serduc, R (Serduc, Raphael); Aim, W (Aim, Warren); Petersson, K (Petersson, Kristoffer); Petit, B (Petit, Benoit); Bailat, C (Bailat, Claude); Bourhis, J (Bourhis, Jean); Brauer-Krisch, E (Brauer-Krisch, Elke); Vozenin, MC (Vozenin, Marie-Catherine)
Source: RADIOTHERAPY AND ONCOLOGY **Volume:** 129 **Issue:** 3 **Pages:** 582-588 **DOI:** 10.1016/j.radonc.2018.08.016 **Published:** DEC 2018
Accession Number: WOS:000452272800026
PubMed ID: 30177374
Author Identifiers:

Author	Web of Science ResearcherID	ORCID Number
Serduc, Raphael	D-6398-2017	0000-0003-3294-8544
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Montay-Gruel, Pierre-Gabriel		0000-0003-0623-1355
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Vozenin, Marie-Catherine		0000-0002-2109-8073

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Record 3 of 12
Title: High dose-per-pulse electron beam dosimetry: Commissioning of the Oriatron eRT6 prototype linear accelerator for preclinical use
Author(s): Jaccard, M (Jaccard, Maud); Duran, MT (Duran, Maria Teresa); Petersson, K (Petersson, Kristoffer); Germond, JF (Germond, Jean-Francois); Liger, P (Liger, Philippe); Vozenin, MC (Vozenin, Marie-Catherine); Bourhis, J (Bourhis, Jean); Bochud, F (Bochud, Francois); Bailat, C (Bailat, Claude)
Source: MEDICAL PHYSICS **Volume:** 45 **Issue:** 2 **Pages:** 863-874 **DOI:** 10.1002/mp.12713 **Published:** FEB 2018
Accession Number: WOS:000424809700036
PubMed ID: 29206287
Author Identifiers:

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Petersson, Kristoffer		0000-0003-0300-5790
Bailat, Claude		0000-0002-0386-4782

ISSN: 0094-2405
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Record 4 of 12
Title: Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s
Author(s): Montay-Gruel, P (Montay-Gruel, Pierre); Petersson, K (Petersson, Kristoffer); Jaccard, M (Jaccard, Maud); Boivin, G (Boivin, Gael); Germond, JF (Germond, Jean-Francois); Petit, B (Petit, Benoit); Doenlen, R (Doenlen, Raphael); Favaudon, V (Favaudon, Vincent); Bochud, F (Bochud, Francois); Bailat, C (Bailat, Claude); Bourhis, J (Bourhis, Jean); Vozenin, MC (Vozenin, Marie-Catherine)
Source: RADIOTHERAPY AND ONCOLOGY **Volume:** 124 **Issue:** 3 **Pages:** 365-369 **DOI:** 10.1016/j.radonc.2017.05.003 **Published:** SEP 2017
Accession Number: WOS:000412383700004
PubMed ID: 28545957
Conference Title: 15th International Wolfsberg Meeting on Molecular Radiation Biology/Oncology
Conference Date: JUN 17-19, 2017
Conference Location: SWITZERLAND
Author Identifiers:

Author	Web of Science ResearcherID	ORCID Number
Bailat, Claude		0000-0002-0386-4782
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Vozenin, Marie-Catherine		0000-0002-2109-8073
Bochud, Francois		0000-0003-2076-0296
Bourhis, Jean		0000-0001-5162-1171
Petersson, Kristoffer		0000-0003-0300-5790

ISSN: 0167-8140
eISSN: 1879-0887

Record 5 of 12
Title: Hopes of high dose-rate radiotherapy
Author(s): Fouillade, C (Fouillade, Charles); Favaudon, V (Favaudon, Vincent); Vozenin, MC (Vozenin, Marie-Catherine); Romeo, PH (Romeo, Paul-Henri); Bourhis, J (Bourhis, Jean); Verrelle, P (Verrelle, Pierre); Devauchelle, P (Devauchelle, Patrick); Patriarca, A (Patriarca, Annalisa); Heinrich, S (Heinrich, Sophie); Mazal, A (Mazal, Alejandro); Dutreix, M (Dutreix, Marie)
Source: BULLETIN DU CANCER **Volume:** 104 **Issue:** 4 **Pages:** 380-384 **DOI:** 10.1016/j.bulcan.2017.01.012 **Published:** APR 2017
Accession Number: WOS:000398022000011
PubMed ID: 28283183
Author Identifiers:

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Romeo, Paul-Henri	L-5989-2017	0000-0002-8294-0367
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ISSN: 0007-4551
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Record 6 of 12
Title: High dose-per-pulse electron beam dosimetry - A model to correct for the ion recombination in the Advanced Markus ionization chamber
Author(s): Petersson, K (Petersson, Kristoffer); Jaccard, M (Jaccard, Maud); Germond, JF (Germond, Jean-Francois); Buchillier, T (Buchillier, Thierry); Bochud, F (Bochud, Francois); Bourhis, J (Bourhis, Jean); Vozenin, MC (Vozenin, Marie-Catherine); Bailat, C (Bailat, Claude)
Source: MEDICAL PHYSICS **Volume:** 44 **Issue:** 3 **Pages:** 1157-1167 **DOI:** 10.1002/mp.12111 **Published:** MAR 2017
Accession Number: WOS:000397870800032
PubMed ID: 28094853
Author Identifiers:

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Bochud, Francois		0000-0003-2076-0296
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Bourhis, Jean		0000-0001-5162-1171

ISSN: 0094-2405
eISSN: 2473-4209

Record 7 of 12
Title: High dose-per-pulse electron beam dosimetry: Usability and dose-rate independence of EBT3 Gafchromic films
Author(s): Jaccard, M (Jaccard, Maud); Petersson, K (Petersson, Kristoffer); Buchillier, T (Buchillier, Thierry); Germond, JF (Germond, Jean-Francois); Duran, MT (Duran, Maria Teresa); Vozenin, MC (Vozenin, Marie-Catherine); Bourhis, J (Bourhis, Jean); Bochud, FO (Bochud, Francois O.); Bailat, C (Bailat, Claude)
Source: MEDICAL PHYSICS **Volume:** 44 **Issue:** 2 **Pages:** 725-735 **DOI:** 10.1002/mp.12066 **Published:** FEB 2017
Accession Number: WOS:000397401800038
PubMed ID: 28019660
Author Identifiers:

Author	Web of Science ResearcherID	ORCID Number
Bochud, Francois		0000-0003-2076-0296
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Bailat, Claude		0000-0002-0386-4782
Bourhis, Jean		0000-0001-5162-1171

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Record 8 of 12
Title: Electron dosimetry with Gafchromic EBT3 films: energy and dose rate dependence
Author(s): Jaccard, M (Jaccard, M.); Petersson, K (Petersson, K.); Buchillier, T (Buchillier, T.); Germond, JF (Germond, J.-F.); Ramiro, TD (Ramiro, T. Duran); Vozenin, MC (Vozenin, M.-C.); Bourhis, J (Bourhis, J.); Bochud, F (Bochud, F.); Bailat, C (Bailat, C.)
Source: STRAHLENTHERAPIE UND ONKOLOGIE **Meeting Abstract:** 9.4 **Volume:** 192 **Issue:** 11 **Pages:** 848-849 **Published:** NOV 2016
Accession Number: WOS:000387198700054
Conference Title: 2nd Joint Meeting of the SASRO/SGSMP
Conference Date: AUG 25-27, 2016
Conference Location: Sursee, SWITZERLAND
Conference Sponsors: SASRO, SGSMP
ISSN: 0179-7158
eISSN: 1439-099X

Record 9 of 12
Title: Absolute dosimetry with EBT3 Gafchromic films in a pulsed electron beam at high dose-rate
Author(s): Jaccard, M (Jaccard, M.); Petersson, K (Petersson, K.); Buchillier, T (Buchillier, T.); Bailat, C (Bailat, C.); Germond, JF (Germond, J. F.); Moeckli, R (Moeckli, R.); Bourhis, J (Bourhis, J.); Vozenin, MC (Vozenin, M. C.); Bochud, F (Bochud, F.)
Source: RADIOTHERAPY AND ONCOLOGY **Meeting Abstract:** EP-1494 **Volume:** 119 **Pages:** S690-S690 **DOI:** 10.1016/S0167-8140(16)32744-X **Supplement:** 1 **Published:** APR 2016
Accession Number: WOS:000463117902411
ISSN: 0167-8140
eISSN: 1879-0887

Record 10 of 12
Title: The Advanced Markus ionization chamber is useable for measurements at ultra high dose rates
Author(s): Petersson, K (Petersson, K.); Jaccard, M (Jaccard, M.); Buchillier, T (Buchillier, T.); Bailat, C (Bailat, C.); Germond, J (Germond, J.); Vozenin, M (Vozenin, M.); Bourhis, J (Bourhis, J.); Bochud, F (Bochud, F.)
Source: RADIOTHERAPY AND ONCOLOGY **Meeting Abstract:** PO-0798 **Volume:** 119 **Pages:** S373-S373 **DOI:** 10.1016/S0167-8140(16)32048-6 **Supplement:** 1 **Published:** APR 2016
Accession Number: WOS:000463117901239
ISSN: 0167-8140
eISSN: 1879-0887

Record 11 of 12
Title: Potential of FLASH irradiation to minimize the incidence of radio-induced damage and fibrosis to normal lung in a mouse model
Author(s): Fouillade, C (Fouillade, Charles); Verrelle, P (Verrelle, Pierre); Vozenin, MC (Vozenin, Marie-Catherine); Favaudoni, V (Favaudoni, Vincent)
Source: JOURNAL OF THORACIC ONCOLOGY **Volume:** 11 **Issue:** 2 **Pages:** S5-S5 **Supplement:** S **Published:** FEB 2016
Accession Number: WOS:000427344900007
ISSN: 1556-0864
eISSN: 1556-1380

Record 12 of 12
Title: Ultrahigh dose-rate, "flash" irradiation minimizes the side-effects of radiotherapy
Author(s): Favaudon, V (Favaudon, V.); Fouillade, C (Fouillade, C.); Vozenin, MC (Vozenin, M.-C.)
Source: CANCER RADIOTHERAPIE **Volume:** 19 **Issue:** 6-7 **Pages:** 526-531 **DOI:** 10.1016/j.canrad.2015.04.006 **Published:** OCT 2015
Accession Number: WOS:000364108500028
PubMed ID: 26277238
Conference Title: Proceedings of the Societe Francaise de Radiotherapie Oncologique (SFRO) 26th Annual Meeting
Conference Date: OCT 08-10, 2015
Conference Location: Paris, FRANCE
Author Identifiers:

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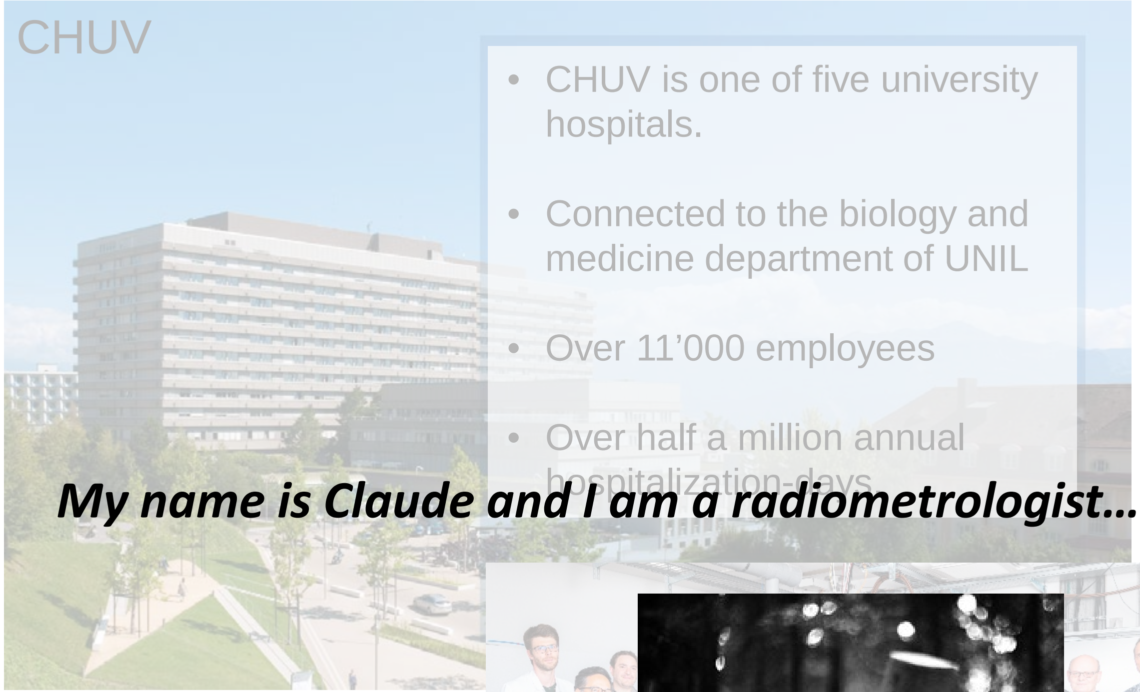
- one of five university hospitals.
- Connected to the biology and medicine department of UNIL
- Over 11’000 employees
- Over half a million annual hospitalization-days.

Institute of Radiation Physics (IRA)

IRA: ~60 Collaborators

IRA provides expertise in:

- **Medical physics**
- **Radiation protection**
- **Radiochemistry**
- **Radiopharmacy**
- **Radiometrology**



CHUV

- CHUV is one of five university hospitals.
- Connected to the biology and medicine department of UNIL
- Over 11’000 employees
- Over half a million annual hospitalization days

My name is Claude and I am a radiometrologist…

Who can’t predict the weather

Institute of Radiation Physics (IRA)

IRA: ~60 Collaborators

IRA provides expertise in:

- **Medical physics**
- **Radiation protection**
- **Radiochemistry**
- **Radiopharmacy**
- **Radiometrology**

Metrology is the science of measurement

Measurement requires common knowledge

Need to share a common perception of what is meant by expressions such as meter, kilogram, liter, watt, etc.

Confidence is vital in enabling metrology to link human activities together across geographic and professional boundaries.

Metrology is the science of measurement

→ SI

https://www.bipm.org/en/measurement-units/

The International System of Units (SI)

→ The recommended practical system of units of measurement is the International System of Units (*Système International d'Unités*), with the international abbreviation **SI**.

The SI is defined by the **SI Brochure**, which is published by the BIPM.

In a landmark decision, Member States voted on 16 November 2018 to revise the SI, changing the world's definition of the kilogram, the ampere, the kelvin and the mole.

This decision, made at the 26th meeting of the General Conference on Weights and Measures (CGPM), means that from 20 May 2019 all SI units are defined in terms of constants that describe the natural world. This will assure the future stability of the SI and open the opportunity for the use of new technologies, including quantum technologies, to implement the definitions.

The seven defining constants of the SI are:

- the caesium hyperfine frequency $\Delta\nu_{Cs}$;
- the speed of light in vacuum c;
- the Planck constant h;
- the elementary charge e;
- the Boltzmann constant k;
- the Avogadro constant N_A; and
- the luminous efficacy of a defined visible radiation K_{cd}.

The SI was previously defined in terms of seven base units and derived units defined as products of powers of the base units. The seven base units were chosen for historical reasons, and were, by convention, regarded as dimensionally independent: the metre, the kilogram, the second, the ampere, the kelvin, the mole, and the candela. This role for the base units continues in the present SI even though the SI itself is now defined in terms of the defining constants above.

Metrology covers three main tasks:

1. The definition of internationally accepted units of measurement,

The SI base units:

Base quantity		Base unit	
Name	**Typical symbol**	**Name**	**Symbol**
time	t	second	s
length	l, x, r, etc.	metre	m
mass	m	kilogram	kg
electric current	I, i	ampere	A
thermodynamic temperature	T	kelvin	K
amount of substance	n	mole	mol
luminous intensity	I_v	candela	cd

Metrology covers three main tasks:

1. The definition of internationally accepted units of measurement

Derived quantity	SI coherent derived unit [a] Name	Symbol	Expressed in terms of other SI units	Expressed in terms of SI base units
plane angle	radian [b]	rad	1 [b]	m/m
solid angle	steradian [b]	sr [c]	1 [b]	m^2/m^2
frequency	hertz [d]	Hz		s^{-1}
force	newton	N		$m\ kg\ s^{-2}$
pressure, stress	pascal	Pa	N/m^2	$m^{-1}\ kg\ s^{-2}$
energy, work, amount of heat	joule	J	N m	$m^2\ kg\ s^{-2}$
power, radiant flux	watt	W	J/s	$m^2\ kg\ s^{-3}$
electric charge, amount of electricity	coulomb	C		s A
electric potential difference, electromotive force	volt	V	W/A	$m^2\ kg\ s^{-3}\ A^{-1}$
capacitance	farad	F	C/V	$m^{-2}\ kg^{-1}\ s^4\ A^2$
electric resistance	ohm	Ω	V/A	$m^2\ kg\ s^{-3}\ A^{-2}$
electric conductance	siemens	S	A/V	$m^{-2}\ kg^{-1}\ s^3\ A^2$
magnetic flux	weber	Wb	V s	$m^2\ kg\ s^{-2}\ A^{-1}$
magnetic flux density	tesla	T	Wb/m^2	$kg\ s^{-2}\ A^{-1}$
inductance	henry	H	Wb/A	$m^2\ kg\ s^{-2}\ A^{-2}$
Celsius temperature	degree Celsius [e]	°C		K
luminous flux	lumen	lm	cd sr [c]	cd
illuminance	lux	lx	lm/m^2	m^{-2} cd
activity referred to a radionuclide [f]	becquerel [d]	Bq		s^{-1}
absorbed dose, specific energy (imparted), kerma	gray	Gy	J/kg	$m^2\ s^{-2}$
dose equivalent, ambient dose equivalent, directional dose equivalent, personal dose equivalent	sievert [g]	Sv	J/kg	$m^2\ s^{-2}$
catalytic activity	katal	kat		s^{-1} mol

Metrology covers three main tasks:

1. The definition of internationally accepted units of measurement,

   the meter.

2. The realization of units of measurement by scientific methods,

   the realization of a meter through the use of laser beams.

→ Primary measurements (another subject by itself!)

Metrology covers three main tasks:

1. The definition of internationally accepted units of measurement,

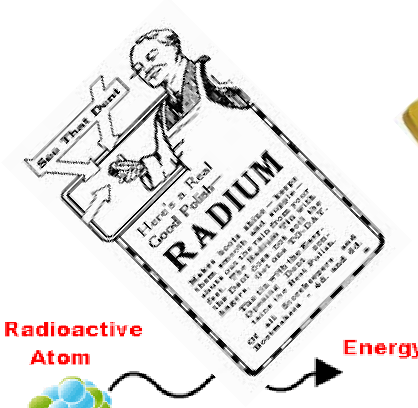
2. The realization of units of measurement by scientific methods,

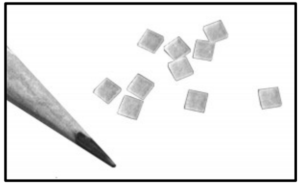
3. The establishment of **traceability** chains in documenting the accuracy of a measurement,

And then comes the BIPM …. The umbrella organization!

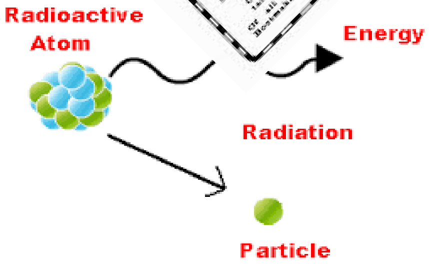
BIPM: bureau international des poids et mesures

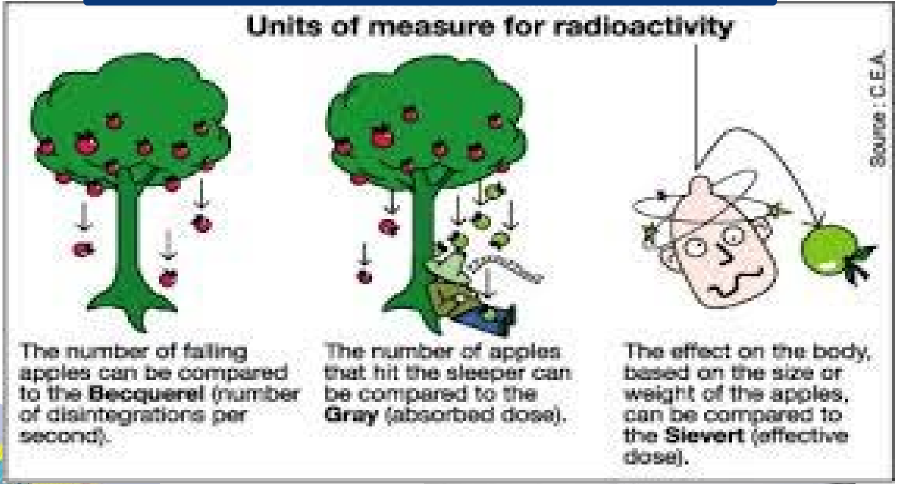
RADIOMETROLOGY

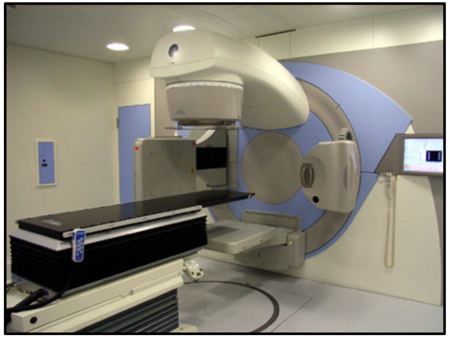


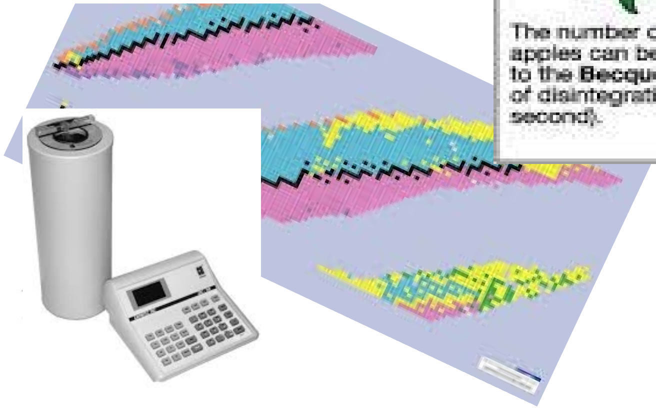


Bq Gy Sv

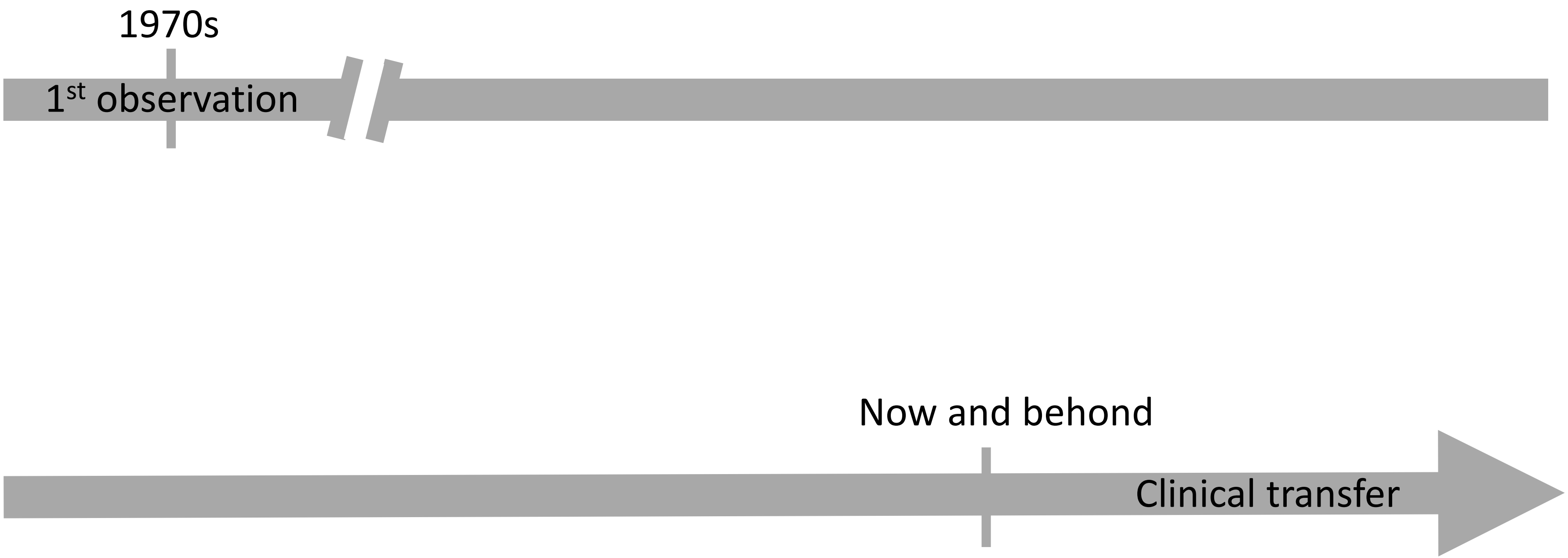






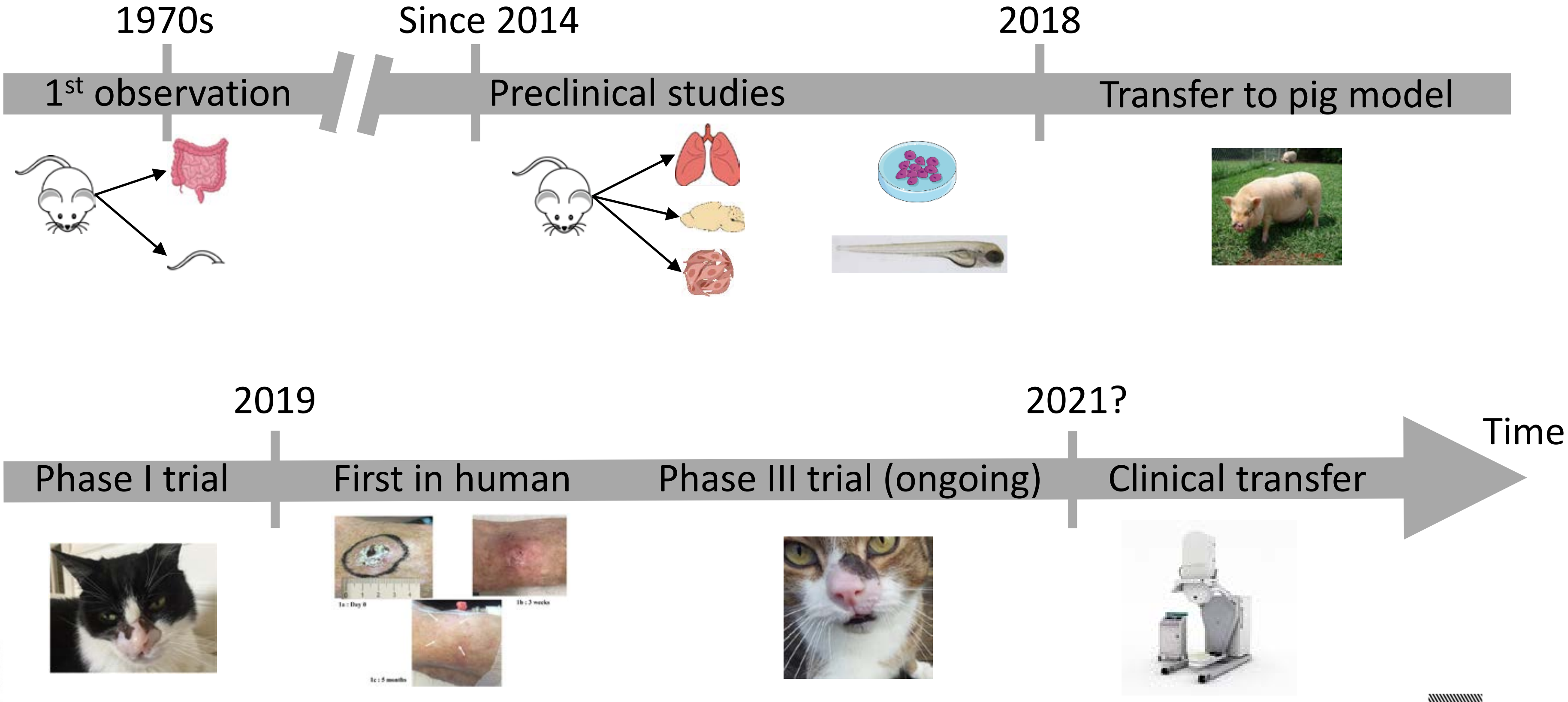


History of FLASH radiotherapy (FLASH-RT)?

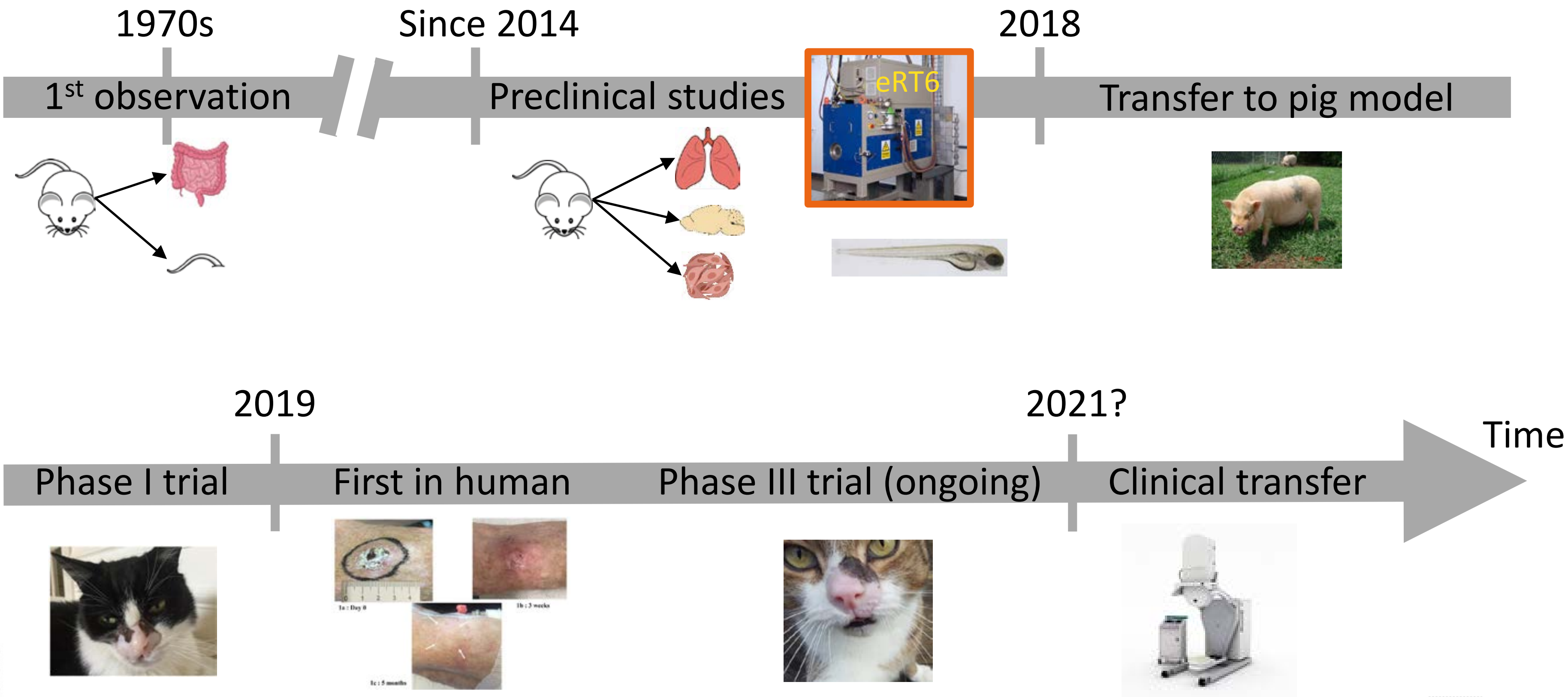


→ **TIMELINE**

FLASH-RT timeline: from effect to RT

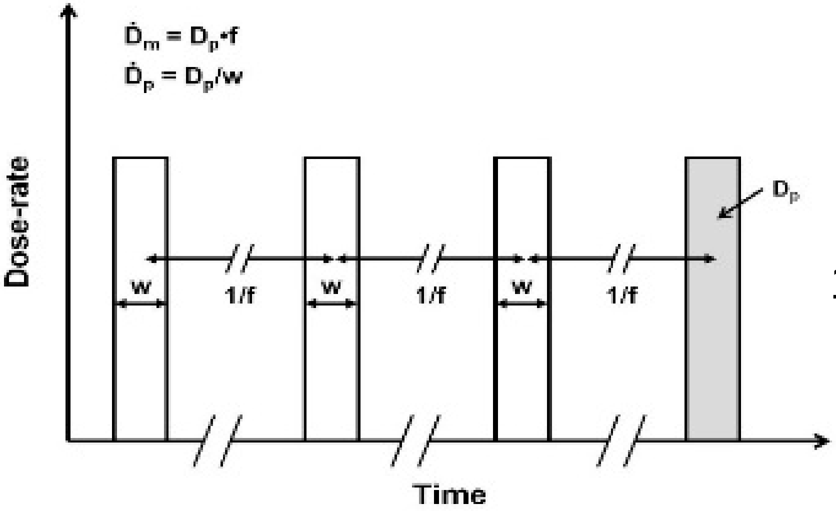


FLASH timeline



- 4-6 MeV electron beam
- Pulsed e-beam of high intensity with some flexible parameters

eRT6: **pulsed** 6 MeV e-beam of **high intensity** with some flexible parameters



1/f >>>> w

w	pulse width	$0.5 - 2.2\ \mu s$
f	pulse repetition frequency	$10 - 200\ Hz$
$\dot{D}_p$	dose-rate in pulse	$10^3 - 5 \cdot 10^6\ Gy/s$
$D_p = \dot{D}_p \cdot w$	dose per pulse	$10^{-3} - 10\ Gy$
$\dot{D}_m = \dot{D}_p \cdot w \cdot f$	mean dose-rate	$10^{-2} - 1000\ Gy/s$

Flash parameters vs conventional

TABLE I. Parameter definitions and corresponding dose-rates (at a SSD of 1 m and at the depth of dose maximum in water) of the Flash and Conv functioning modes of the eRT6.

	Flash	Conv
GT (V)	300	100
w (μs)	2.2	1.0
f (Hz)	200	10
$\dot{D}_m$ (Gy/s)	200	0.05
$\dot{D}_p$ (Gy/s)	4.5×10^5	4.9×10^3

EFFECT   NO EFFECT

Time to deliver 20Gy   ~200 ms (μs)   ~500 sec (8 min)

Flash parameters vs conventional

TABLE I. Parameter definitions and corresponding dose-rates (at a SSD of 1 m and at the depth of dose maximum in water) of the Flash and Conv functioning modes of the eRT6.

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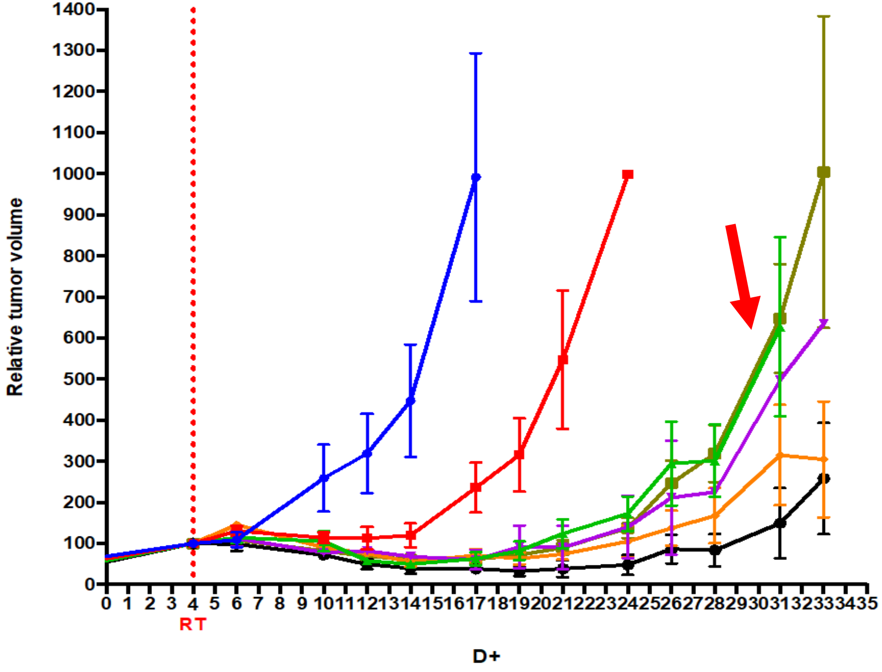
EFFECT NO EFFECT

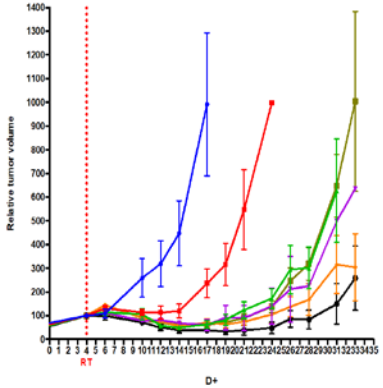
WHAT DOES IT MEAN?

Time to deliver 20Gy

canton de vaud

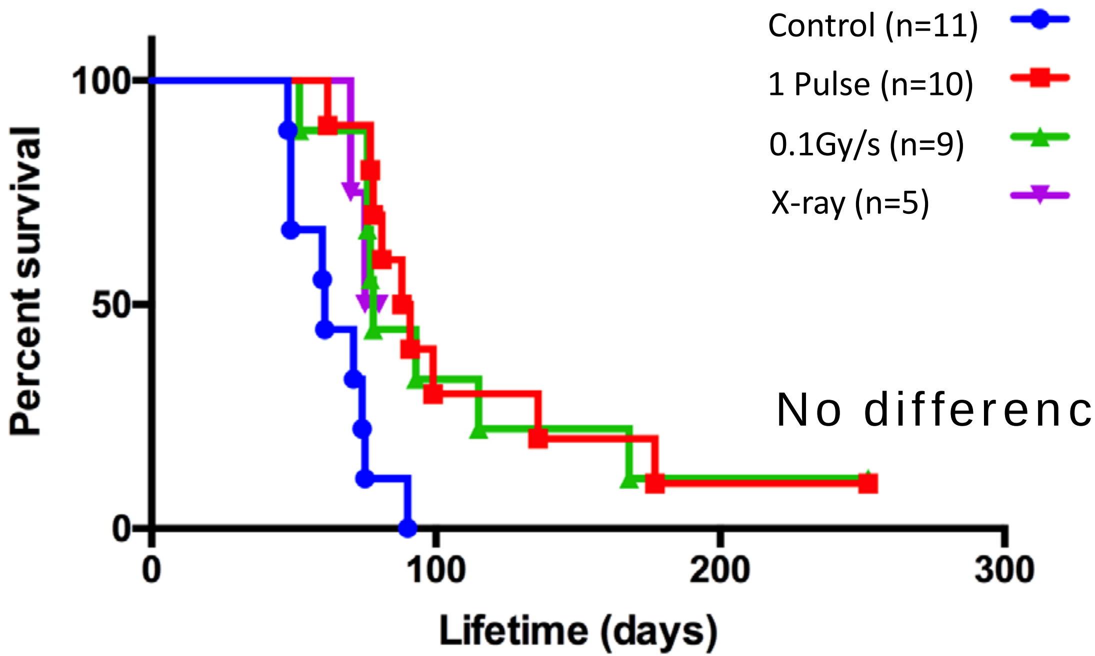
Tumor growth: 10 Mio cells engrafted in mice



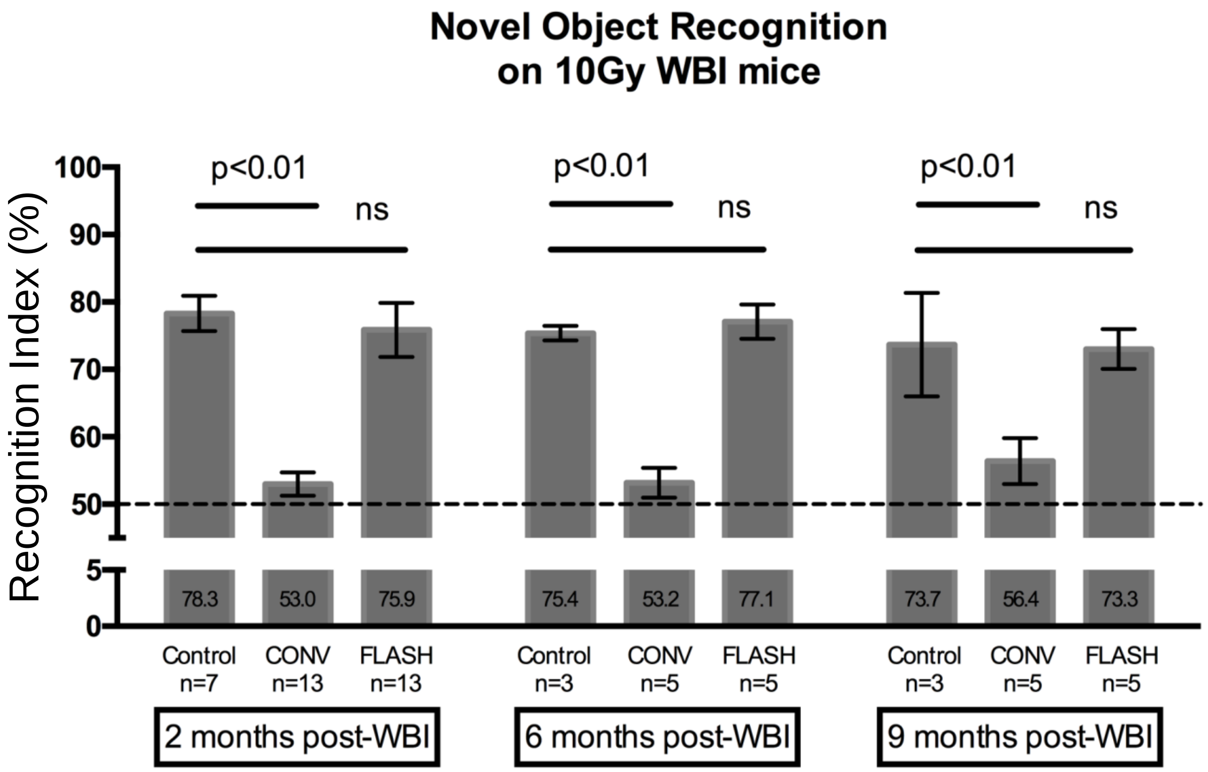


No clear difference

Mice survival: Glioblastoma; 15 Gy WBI

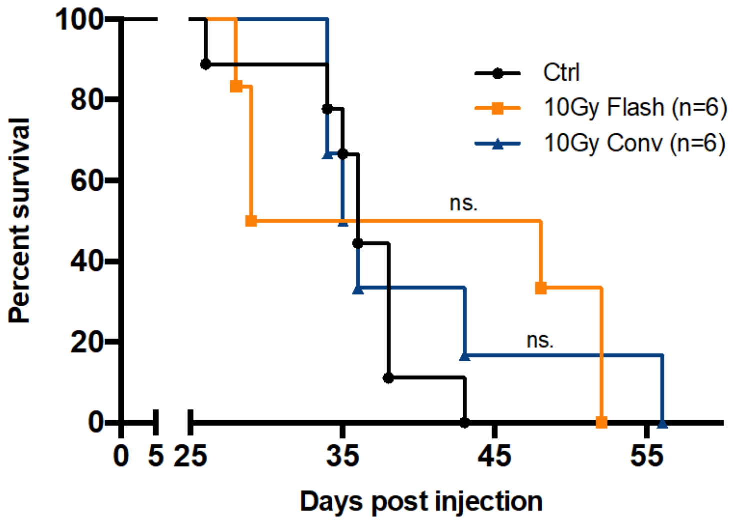


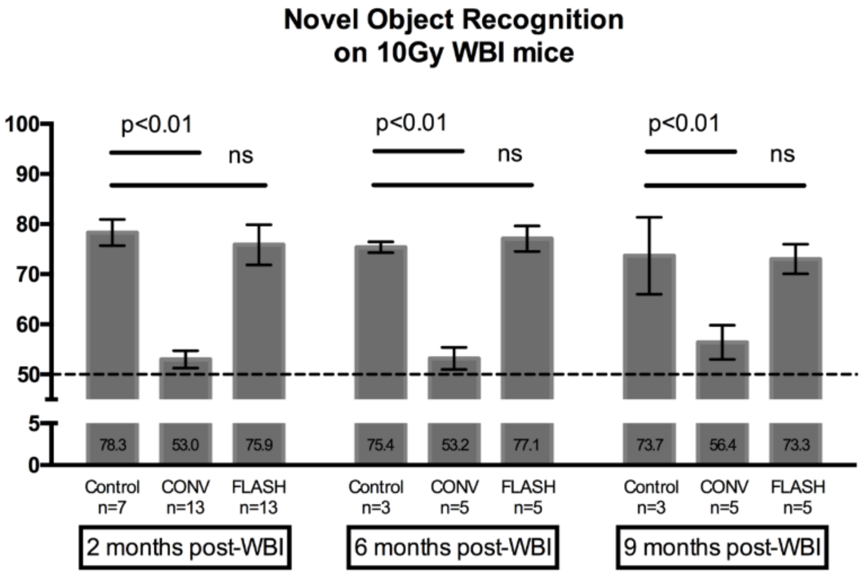
No difference in survival



Clear difference!

Survival is the same using Flash-RT or conventional RT, BUT **cognitive abilities are preserved**.

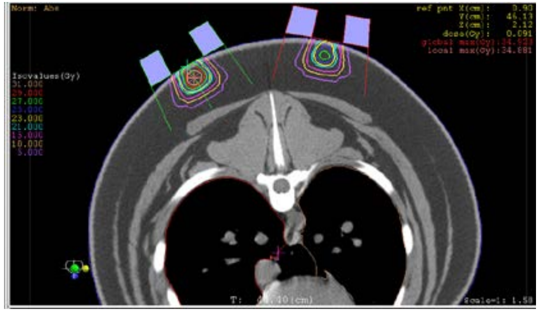




Treatment of Cats patient using Flash-RT

- Good tolerance of Flash-RT (single dose ~30 Gy)
  - Only mild acute reactions
  - Irreversible alopecia
  - Percentage Survival fraction of 84% at 1 year

MC Vozenin, P De Fornel, K Petersson, V Favaudon, M Jaccard, JF Germond, B Petit, M Burki, G Ferrand, D Patin, H Bouchaab, M Ozsahin, F Bochud, C Bailat, P Devauchelle and J Bourhis, "The Advantage of Flash Radiotherapy Confirmed in Mini-Pig and Cat-Cancer Patients." , Clinical Cancer Research 2018



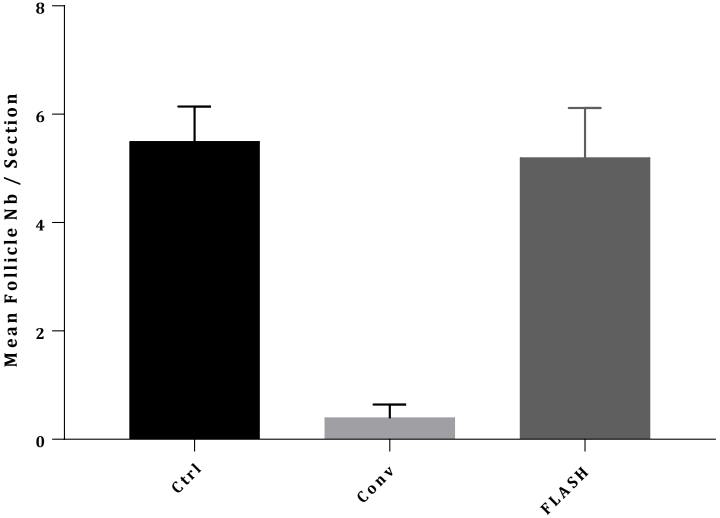
FLASH effects found in mini-pig

Conventional irradiation induces necrosis at same dose.

34Gy 31Gy 28Gy

Conv

FLASH



MC Vozenin, P De Fornel, K Petersson, V Favaudon, M Jaccard, JF Germond, B Petit, M Burki, G Ferrand, D Patin, H Bouchaab, M Ozsahin, F Bochud, C Bailat, P Devauchelle and J Bourhis, *"The Advantage of Flash Radiotherapy Confirmed in Mini-Pig and Cat-Cancer Patients." , Clinical Cancer Research 2018*

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Introduction – FLASH-RT

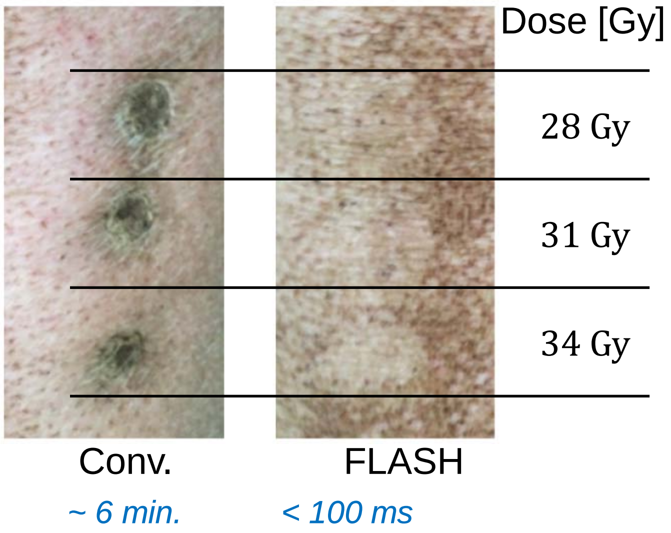
Differential response between normal and tumour tissue increased at ultra-high dose-rates :

- Healthy tissue protection compared to conv. RT
- Equivalent tumor control than in conv. RT

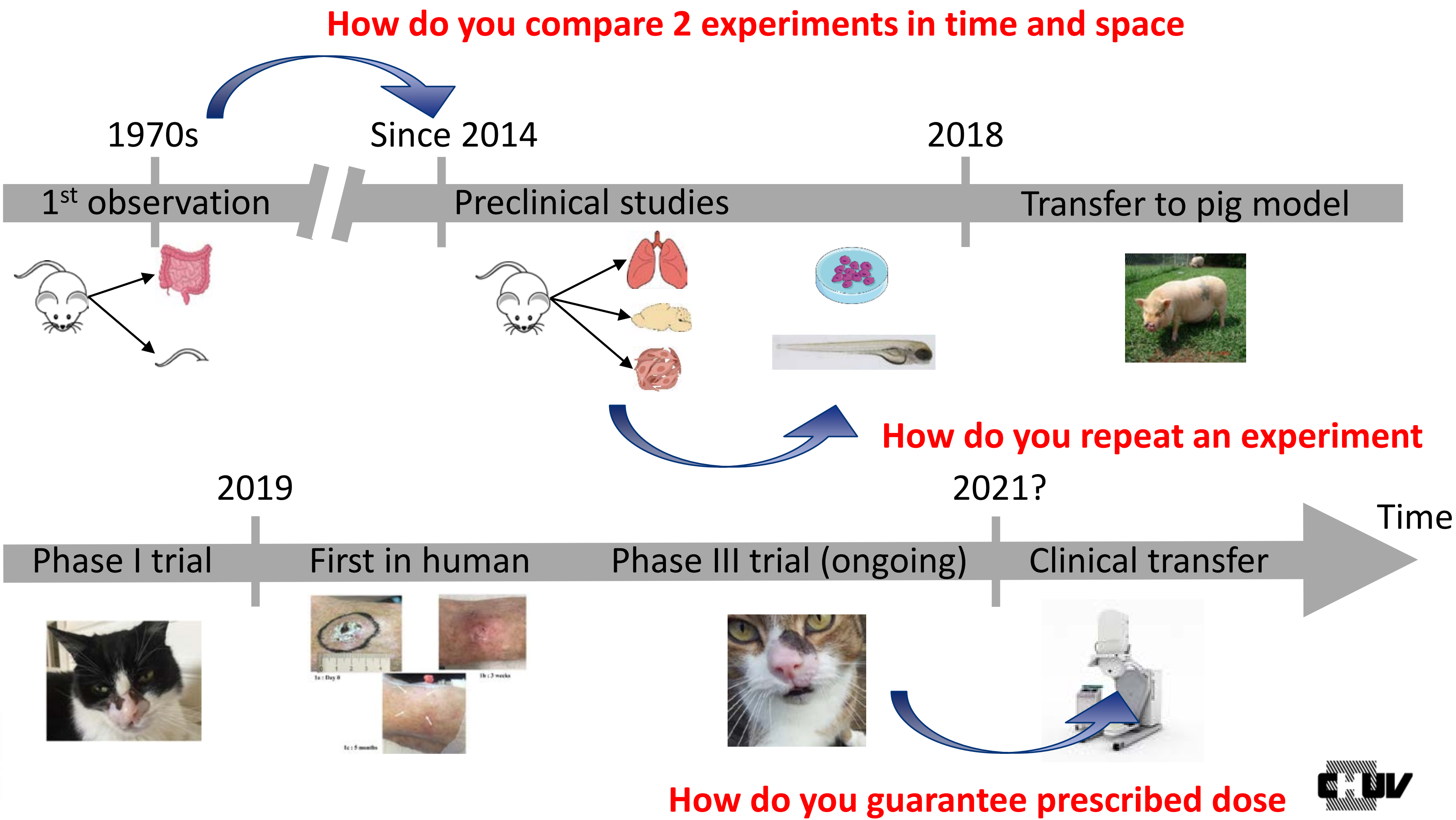
Short treatment time also offers motion management and an increased patient comfort.

First patient treated in 2018 (CD30+ T-cell cutaneous lymphoma).

J. Bourhis et al (2019)



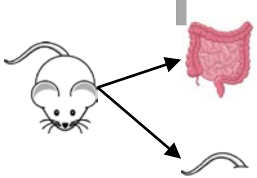
Vozenin et al (2018)


How do you compare 2 experiments in time and space
1970s
Since 2014
2018
1st observation
Preclinical studies
Transfer to pig model
How do you repeat an experiment
2019
2021?
Time
Phase I trial
First in human
Phase III trial (ongoing)
Clinical transfer
How do you guarantee prescribed dose

How do you compare 2 experiments in time and space

1970s — Since 2014 — 2018

1st observation | Preclinical studies | Transfer to pig model

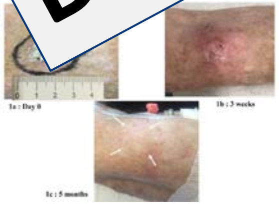


Dosimetry/traceability

How do you repeat an experiment

2019 — 2021?

Phase I trial | Phase III trial (ongoing) | Clinical transfer → Time



How do you guarantee prescribed dose

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CHUV

The narrative is set after the facts….. We had to work in the dark for some years….

First some pre-clinical irradiation examples

Dosimetry for Cats – Phase 3 randomized trial

Dosimeters positioning

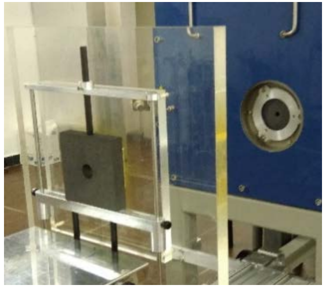
34 Gy single fraction
RT FLASH

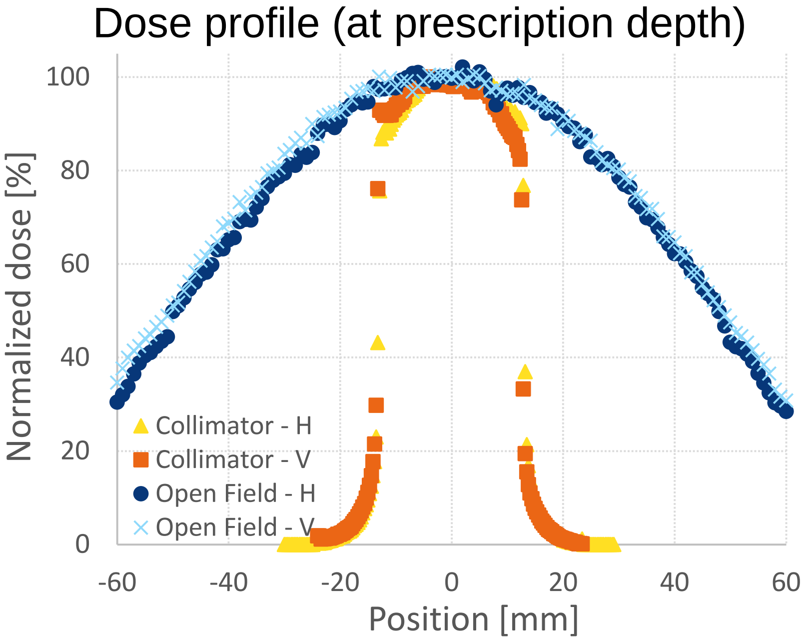
14 months post-RT
Vozenin et al. 2018

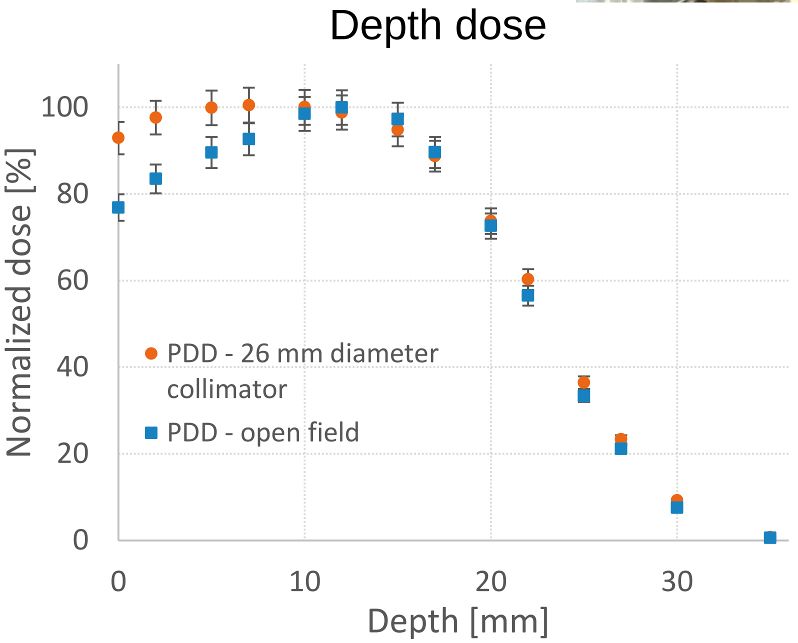
Patient positioning

Beam characterization

Example : carbon collimator (26 mm diameter)







Jorge et al (2019)

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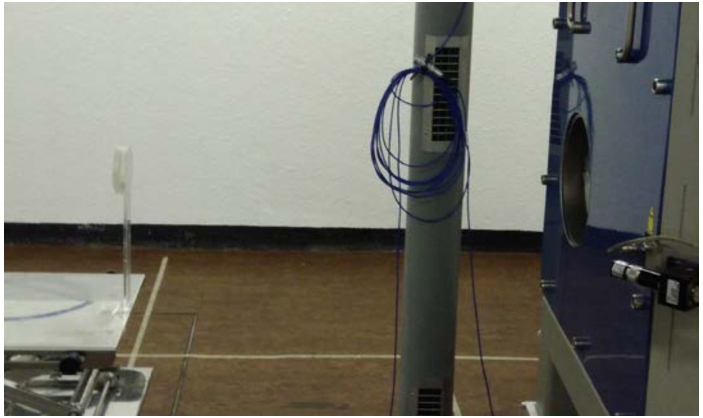
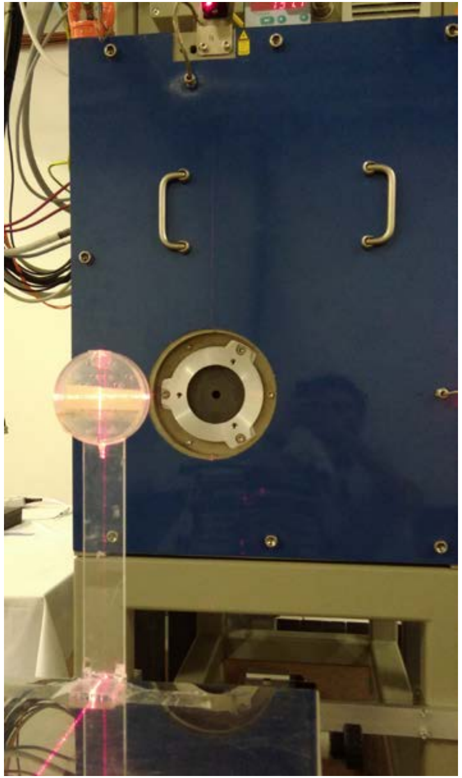
Mice total body irradiations (TBI)

Dosimetric preparation performed using TLD and water (~mice) inside the box.

Prescribed dose [Gy]	**Delivery time [ms]**	***R***
4	20	0.96

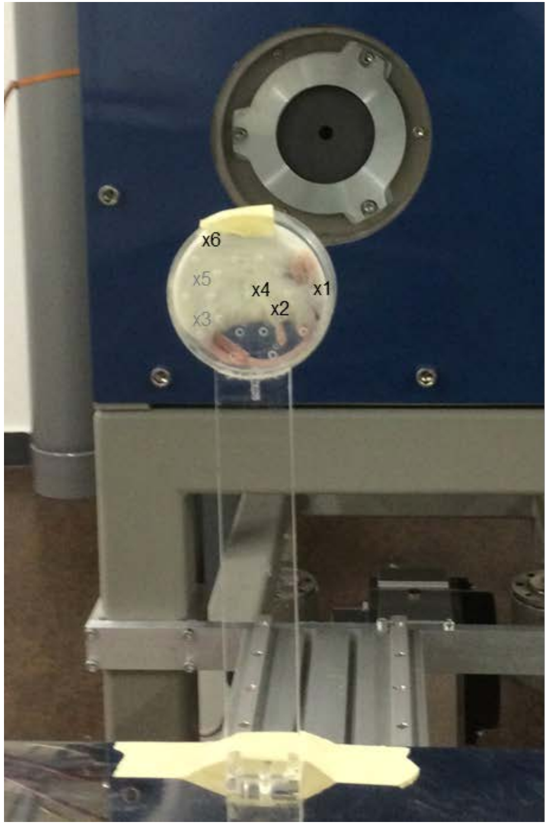




Mice total body irradiations (TBI)

Dosimetric validation performed using TLD and MOUSE inside the box.

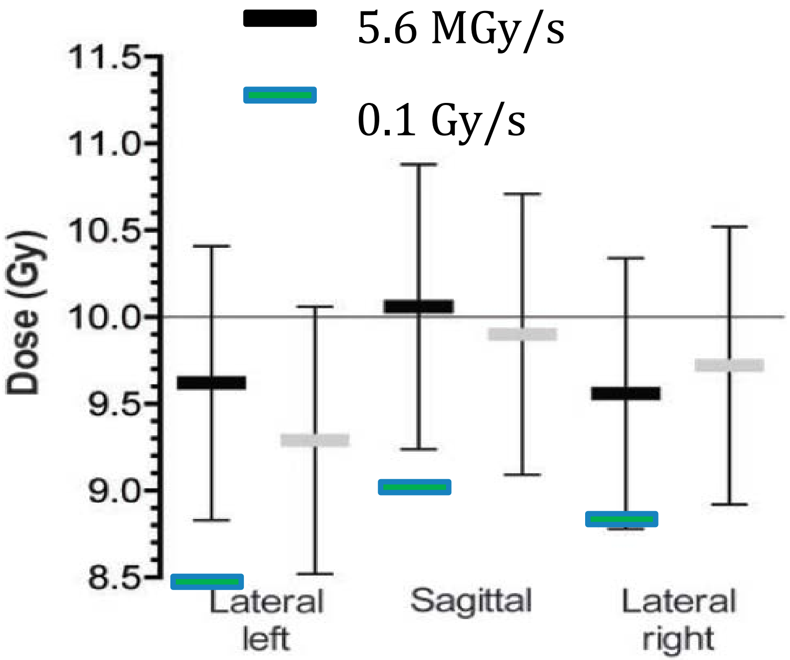
Prescribed dose [Gy]	Depth [cm]
8	1.5

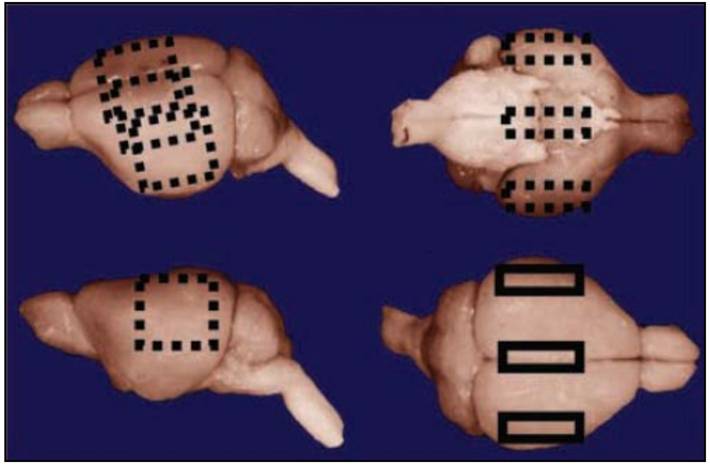


X1: TLD head (between skin and skull)
X2: TLD front leg exit (between skin and muscle)
X3: TLD back leg entrance (between skin and muscle)
X4: TLD thorax (between skin and ribs)
X5: TLD under the gut (in the abdominal cavity)
X6: TLD back (between skin and spinal cord)

	Flash	Conv
X1 at 3 mm	6.58	6.48
X2 at 16 mm	7.25	7.10
X3 at 1 mm	6.32	6.96
X4 at 7 mm	7.87	7.36
X5 at 10 mm	8.37	7.53
X6 at 3 mm	6.7	Not done

TLD in mouse brain



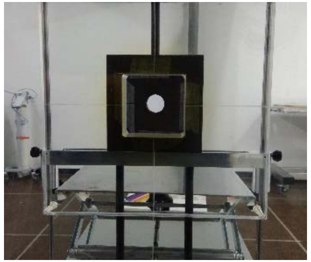


- Prescribed dose: 10 Gy
  → 10 Gy in the central part
- Sligthly less on the sides
- Similar values in both modes

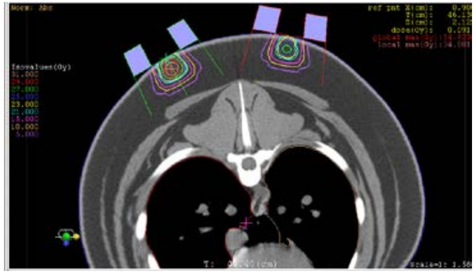
Mini-pig

Dosimetric preparation performed with a alanine pellets at the surface of a solid water phantom.

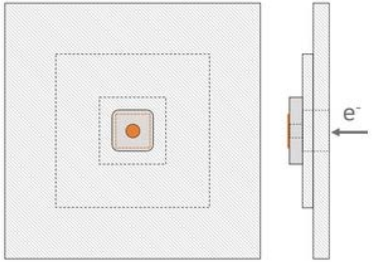
View from the exit of the accelerator



Prescribed dose [Gy]	Delivery time [ms]	*R*
28	90	1.079



Treatment plan



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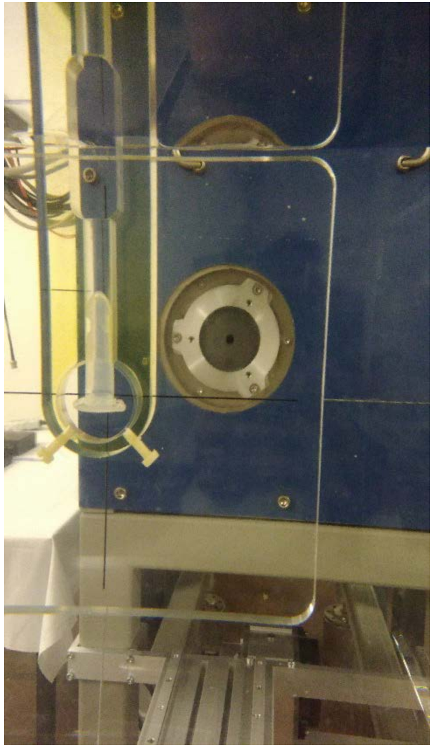
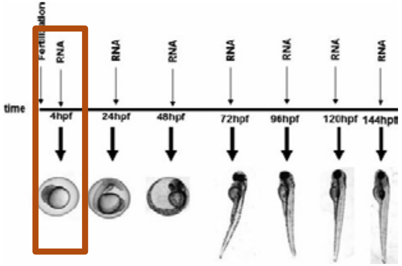
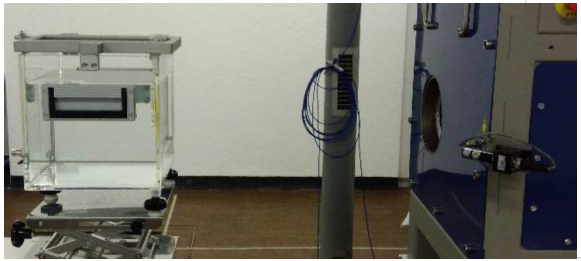
Zebrafish embryos

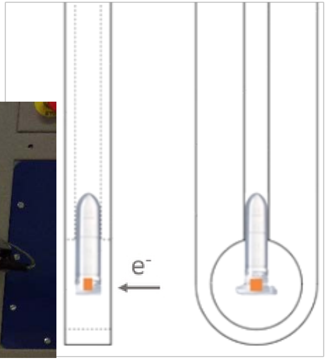
Dosimetric preparation performed with a wrapped TLD inside the 2ml Eppendorf tube.

Prescribed dose [Gy]	Delivery time [ms]	*R*
8	0.002	1.039







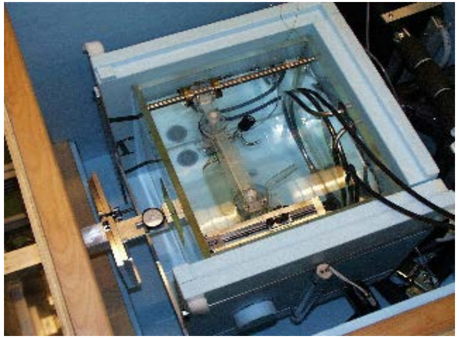


The dosimetry relies on adequate detectors and traceability.

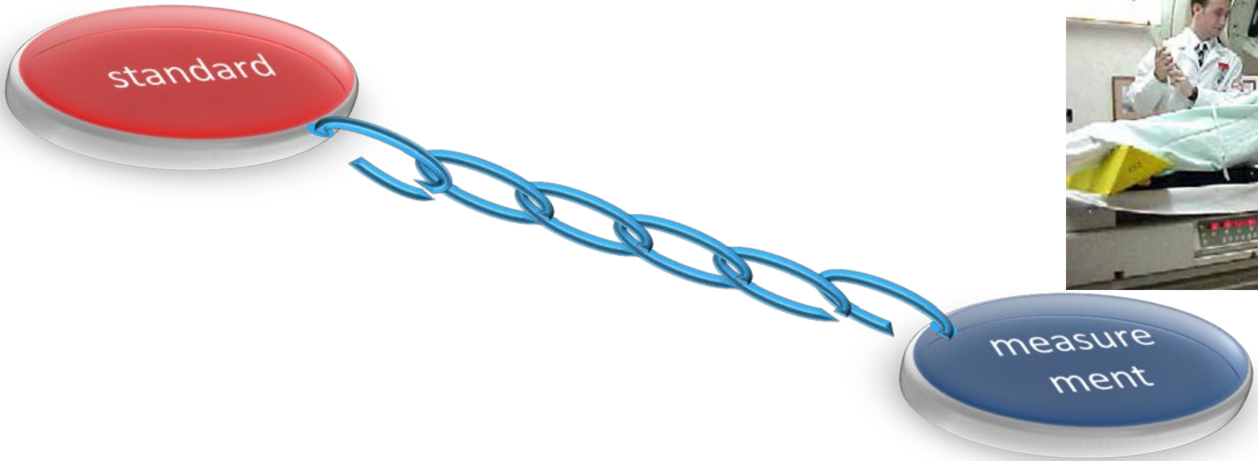
Adequate → ~5 % uncertainty

Traceability → if one wants to compare across users and/or sites

How is the traceability chain from primary to absorbed dose to water for a specific organ in external beam radiotherapy?

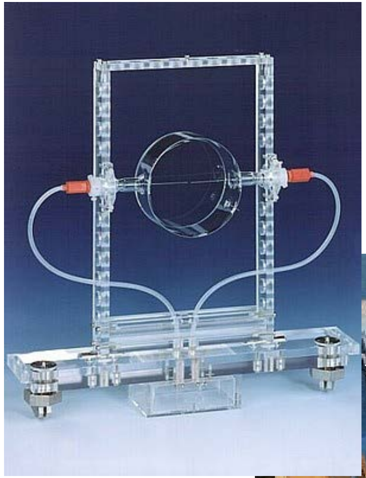


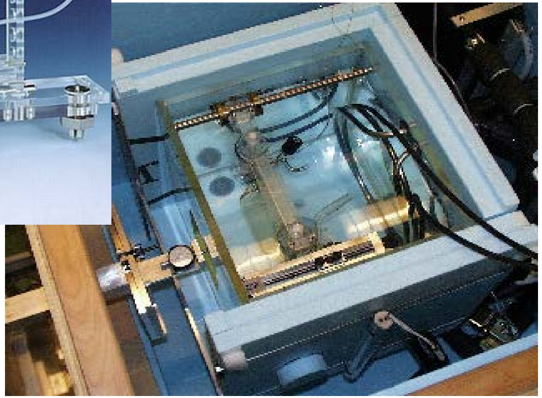
~6 steps of the traceability chain



traceability chain for external beam radiotherapy

1) Primary standard



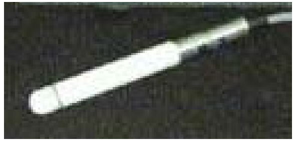


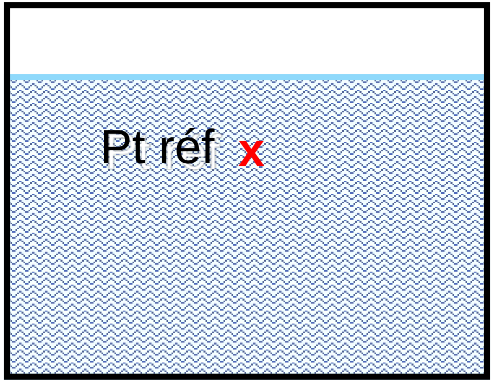
Cont.	High energy XR	High energy electrons	Brachy therapy
1	0.9 %	1.0 %	1.6 %

Water calorimeter for example

1) Primary standard

2) Secondary standard

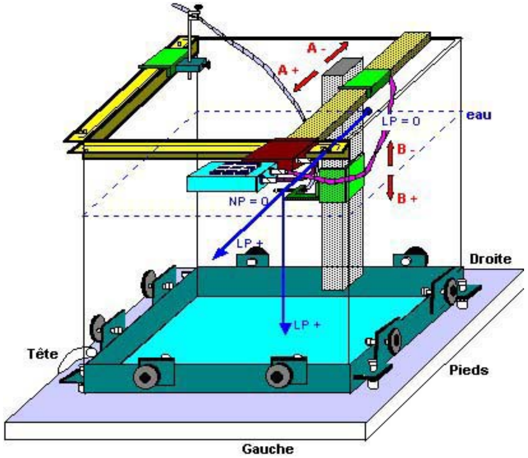




Cont.	High energy XR	High energy electrons	Brachy therapy
1	0.9 %	1.0 %	1.6 %
2	1.1 %	1.4 %	1.4 %

Local reference conditions

1) Primary standard
2) Secondary standard
3) Local conditions



Cont.	High energy XR	High energy electrons	Brachy therapy
1	0.9 %	1.0 %	1.6 %
2	1.1 %	1.4 %	1.4 %
3	1.7 %	1.4 %	1.7 %

For example:
Depth → use of percentage dose depth curves (PDD);
Energy → beam quality correction factor (N_Q)

1) Primary standard

2) Secondary standard

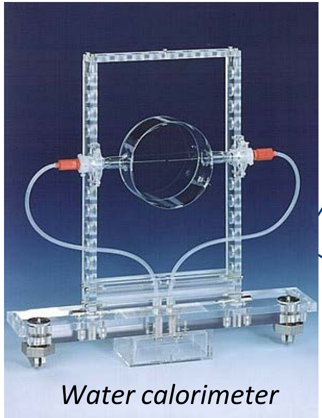
3) Local conditions

…………..

Cont.	High energy XR	High energy electrons	Brachy therapy
1	0.9 %	1.0 %	1.6 %
2	1.1 %	1.4 %	1.4 %
3	1.7 %	1.4 %	1.7 %

→ Uncertainty budget

Primary standard



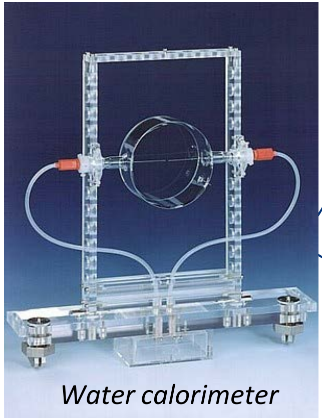
Water calorimeter

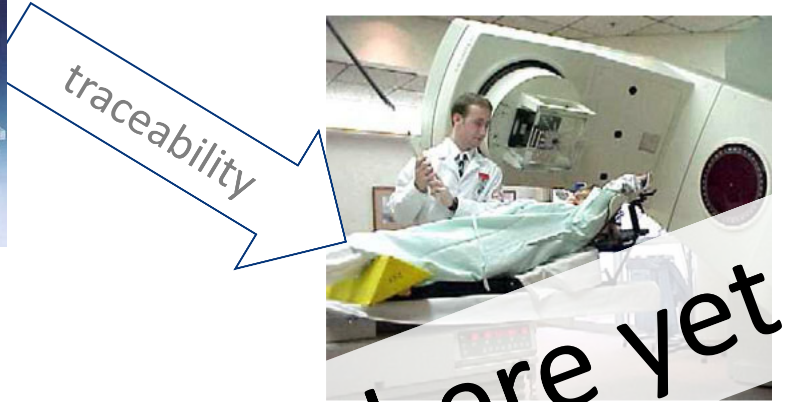
traceability

Cont.	High energy XR	High energy electrons	Brachy therapy
1	0.9 %	1.0 %	1.6 %
2	1.1 %	1.4 %	1.4 %
3	1.7 %	1.4 %	1.7 %
4	2.9 %	n.a.	n.a.
5	3.0 %	2.1 %	11.5 %
6	2.0 %	n.a.	n.a.
Total	**5.0 %**	**3.1 %**	**12 %**

→ Uncertainty budget

Primary standard





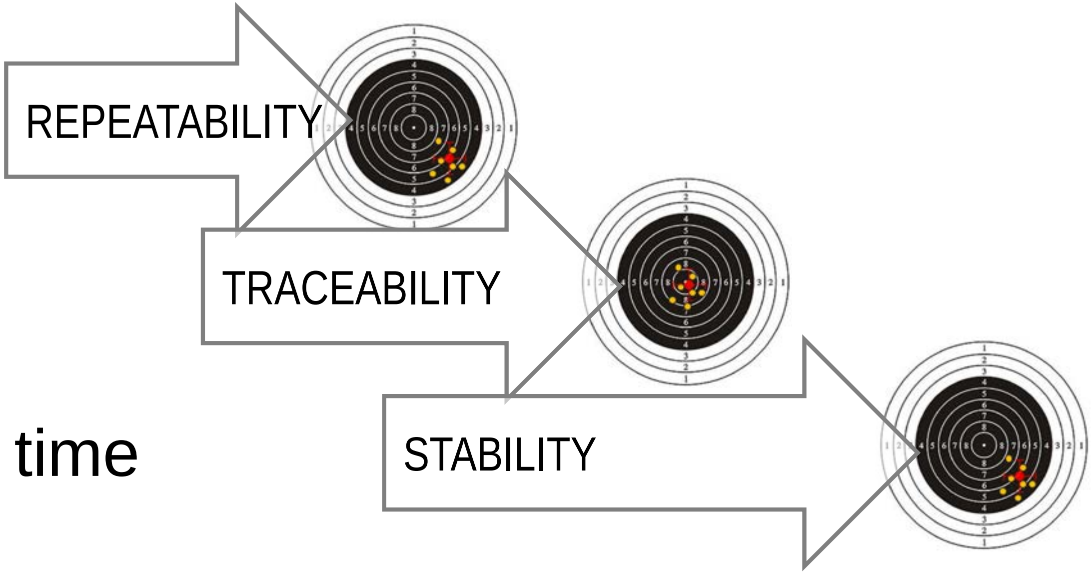
Cont.	High energy XR	High energy electrons	Brachy therapy
1	0.9 %	1.0 %	[illegible]
2	1.1 %	1.4 %	1.4 %
3	1.7 %	1.4 %	1.7 %
4	2.9 %	n.a.	n.a.
5	3.0 %	2.1 %	11.5 %
6	2.0 %	n.a.	n.a.
Total	**5.0 %**	**3.1 %**	**12 %**

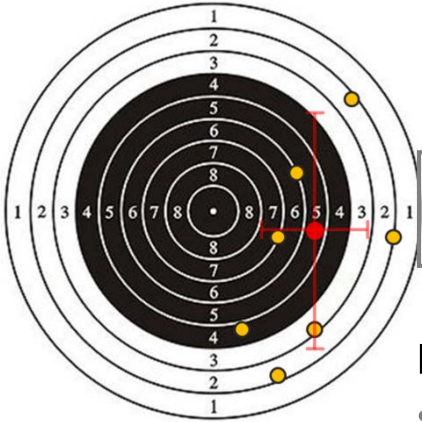
We are not there yet for FLASH-RT

Our Goals for a safe use of FLASH-RT:

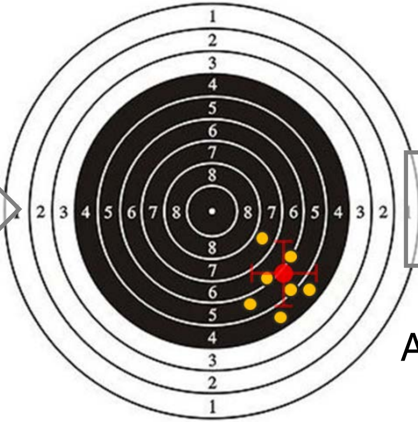
Ensure a reliable **and** accurate **dose delivery**

- Reliable
- Accurate
- Reproducible vs time





REPEATABILITY



RELATIVE DOSIMETRY

- Time resolution
- Response to beam parameters
- Energy response

TRACEABILITY

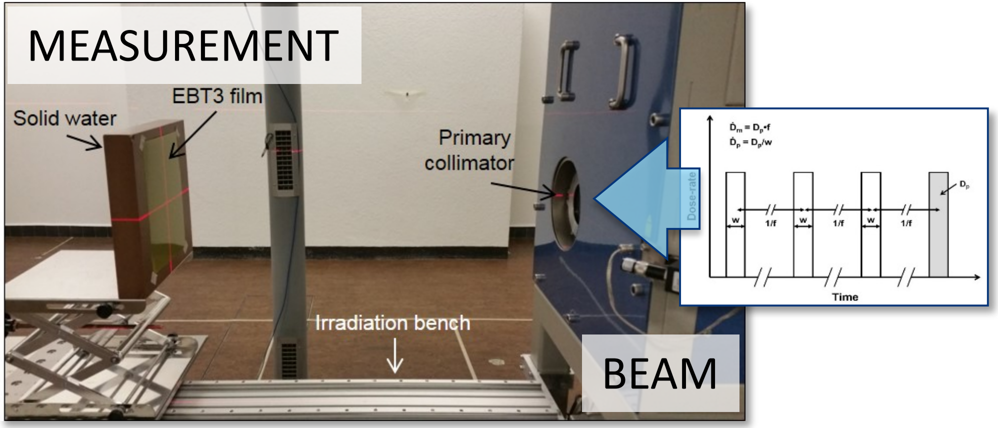
ABSOLUTE DOSIMETRY:

Calibration traceable to international standards (primary meas., NMI).

STABILITY

RELATIVE STABILITY

- short (minutes)
- medium (hours)
- long (days)



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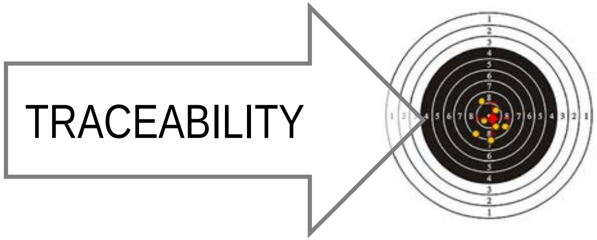
Ensure a reliable and accurate dose delivery

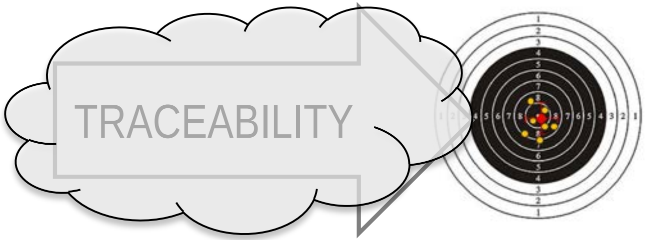
- Reliable
- Accurate
- Reproducible vs time



→ Agreement accross various locations

Ensure a reliable and accurate dose delivery

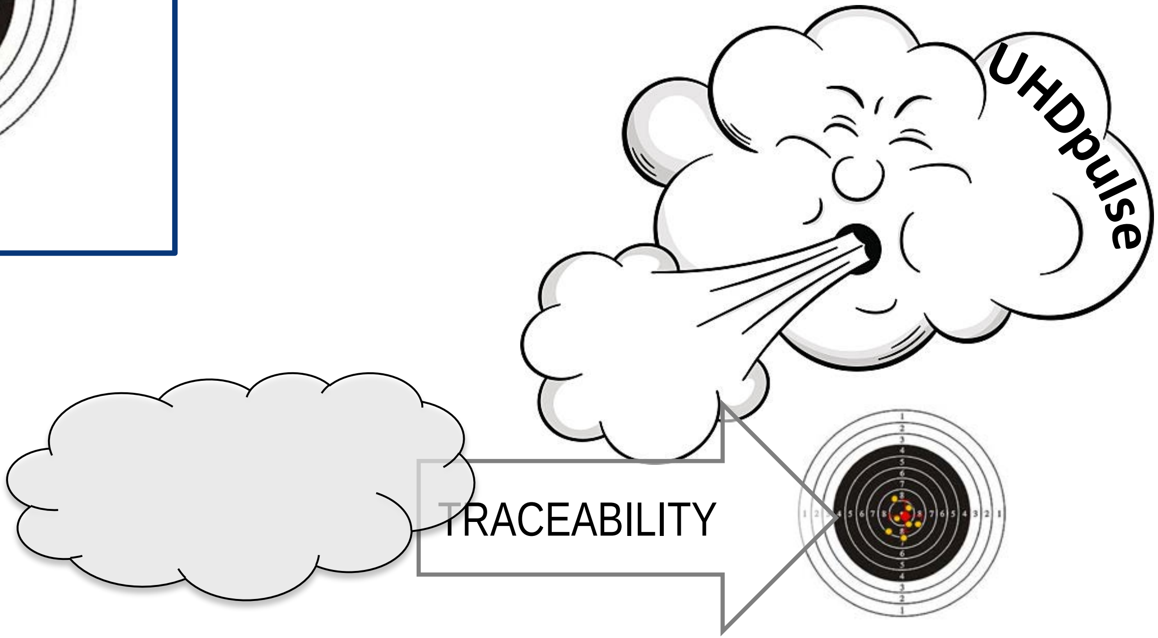
- Reliable
- Accurate
- Reproducible vs time



EMPIR project UHDpulse

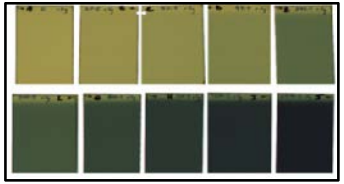
“Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates”

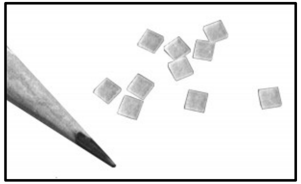
- Reliable
- Accurate
- Reproducible vs time

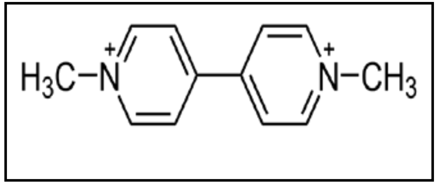


- Beam is not **standard** (dose rate, field size, …)
  → no primary standard, no commissioning protocol, etc etc etc!!!

- Need to adapt our methodology established using conventional LINACs.

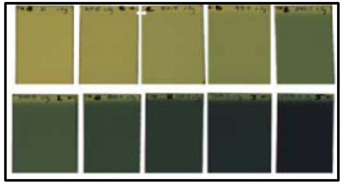


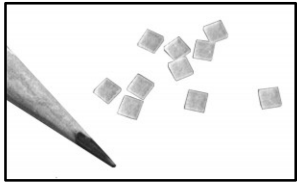
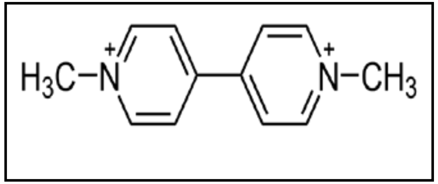




Five different dosimeters:

- Films
- Ionization chamber
- Thermoluminescent dosimeter (TLD)
- Methyl viologen
- Alanine



Five different dosimeters:

- Films
- Ionization chamber
- Thermoluminescent dosimeter (TLD)
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- Alanine

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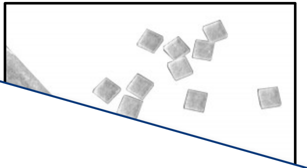
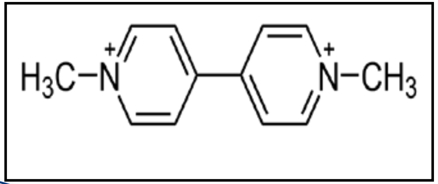
CHUV





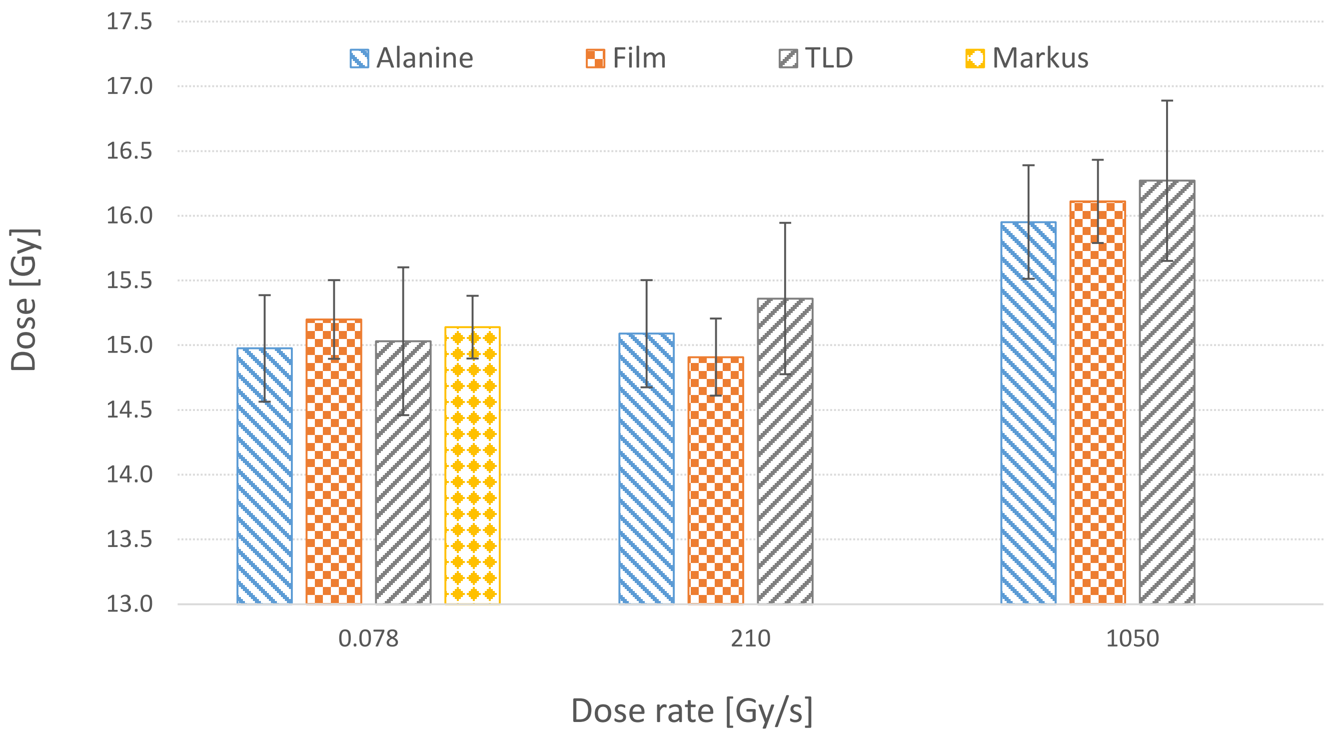
Fiv

- Them
- Methyl viologen
- Alanine

Our strategy:

- **5 different detecting principles**
- **The dose rate dependency must be different**
- **Start with reference conditions (conventional LINAC) and extrapolate to Flash**

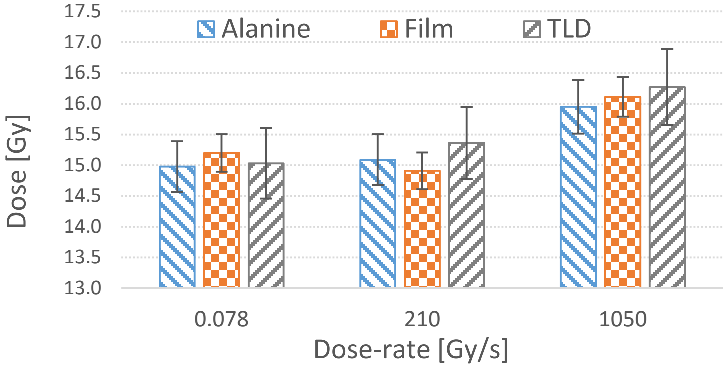
Redundancy of dosimetric measurements ⇨ traceability



Agreement within 3 % for FLASH and within 2 % for CONV

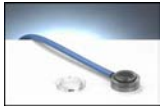
Dose-rate independent

- Radiochromic films 
- TLD 
- Alanine 

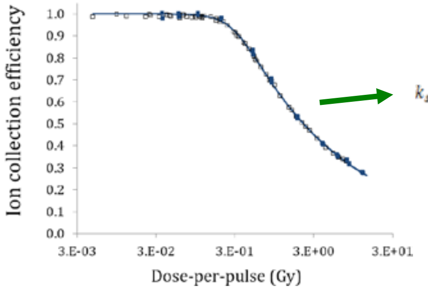


Jorge et al, Radiother. Oncol. (2019)

Dose-rate dependent

- Ionization chambers
  - Advanced Markus 

High dose-per-pulse → Saturation



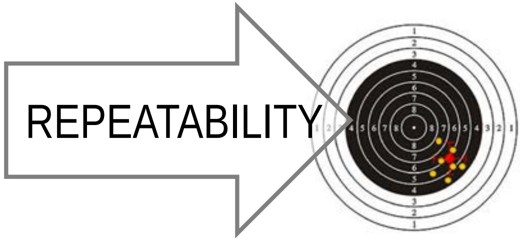
$$k_s = \left(1+\left(\frac{D_p[mGy]}{U[V]}\right)^a\right)^b$$

Petersson et al, Med. Phys. (2017)

Our Goals for a safe use of FLASH-RT:

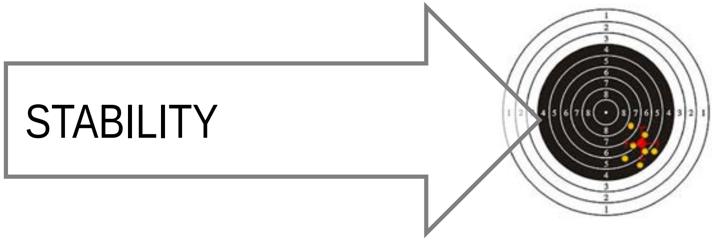
Ensure a reliable **and** accurate **dose delivery**

- Reliable



- Accurate

- Reproducible vs time



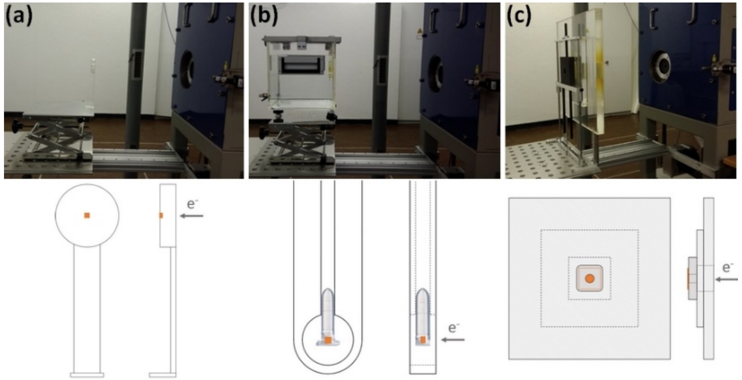
Dosimetric procedure for UHDR-RT

Procedure developed for three setups :

a) PMMA box (mice)

b) Water Tank (zebrafish)

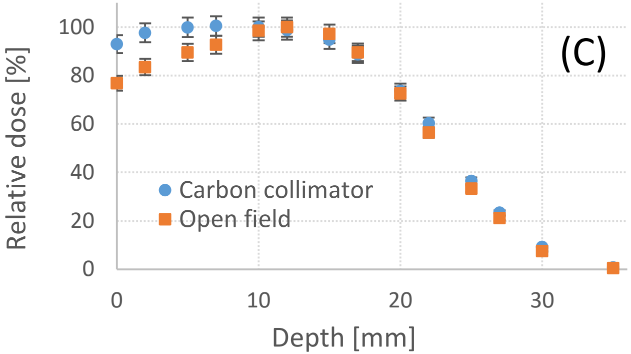
c) Collimator (mini-pig)



Differences between setups :

- Depth
- SSD
- Collimators
- Surrounding matter
- Field size

Out of reference conditions



Uncertainty 15 % → 3 %

Jorge et al, Radiother. Oncol. (2019)

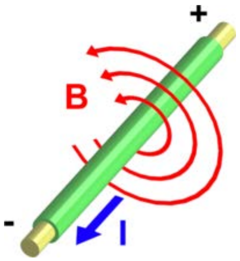
- Our framework suffers from a major drawback:
  - We are monitoring the beam before and after irradiation, but not during!!!

- We insure an adequate beam output repeatability, but still, s… happens!

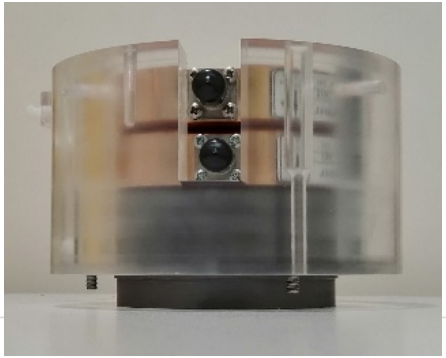
- On conventional LINACS: semi-transparent ionization chamber
  - 👎 for FLASH…. Saturation → non linearity

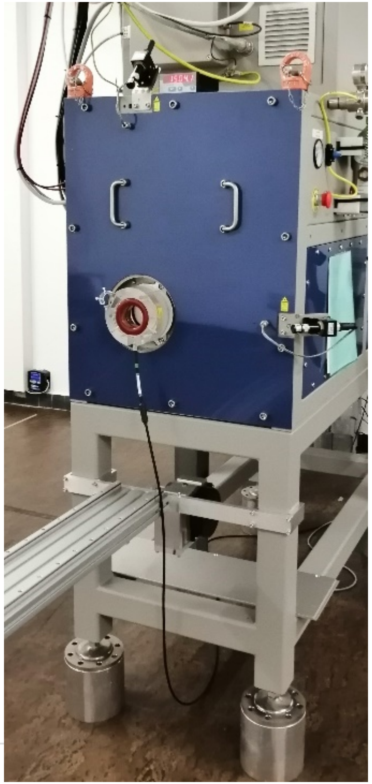
… and now what??

- Beam monitored by measuring the charge/current



- Two AC Current Transformers (ACCT):
  - CONV - 10 mA full scale
  - UHDR - 300 mA full scale

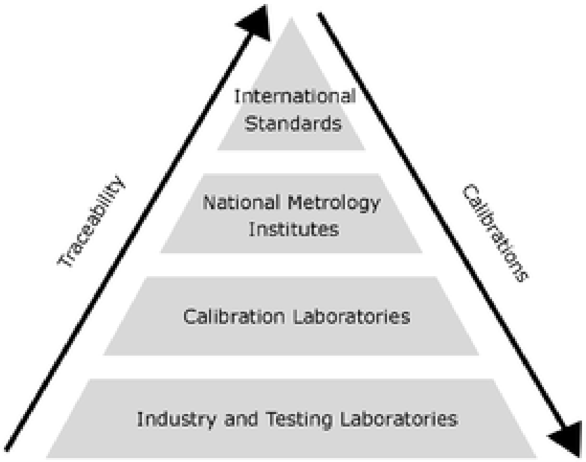




General strategy we adopted (*recipe for non-disaster*)

- Listen to users (especially if there are not physicists….)
- Take your validated tools
- Move stepwise away from reference conditions and document
- Use redundant techniques
- Use various detecting principles
- Move one parameter at a time and document

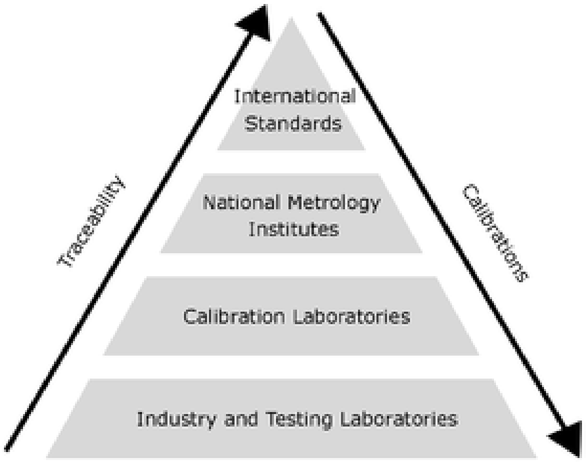
METROLOGY means traceability



Traceability refers to an unbroken chain of comparisons relating an instrument's measurements to a known standard.

How do we build a chain of traceability?

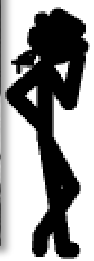
METROLOGY means traceability



Traceability refers to an unbroken chain of comparisons relating an instrument's measurements to a known standard.

How do we build a chain of traceability?

...backward in fact



Building a chain of traceability

International prototype

Primary national standard

Secondary standards

Working standards
-
Calibrations → instruments

Highest level of accuracy

↓

Lowest level of accuracy

Building a chain of traceability

International prototype

Primary national standard

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Working standards
-
Calibrations → instruments

Highest level of accuracy

Lowest level of accuracy

Preclinical FLASH-RT

Building a chain of traceability

International prototype

Primary national standard

Secondary standards

Working standards
-
Calibrations → instruments

Highest level of accuracy

Lowest level of accuracy

Needs to set this value pragmatically (level of the investigated effect, tools, time, …)

U = ?

Preclinical FLASH-RT

Building a chain of traceability

International prototype

Primary national standard

Secondary standards

Working standards
-
Calibrations → instruments

Highest level of accuracy

↓

Lowest level of accuracy

U about 5 %

Preclinical FLASH-RT

canton de vaud

CHUV

Building a chain of traceability

International prototype

Primary national standard

Secondary standards

Working standards
-
Calibrations → instruments

Highest level of accuracy

Lowest level of accuracy

SIR

?

UHDpulse

U ~ 2-3 %

Calibration lab, NMI, ...

U ~ 5-10 %

Preclinical FLASH-RT

Now what….

Radiometrologists are still improving dosimetry (UHDpulse project)

Radiobiologists are still designing experiments to test FLASH effects in various locations

Radiochemists and physicists are designing experiments to understand the FLASH effect

Beam physicists are designing new irradiation facilities

Physicists are designing detectors

And companies are writing patents to make money…..

Whole Brain Irradiation (WBI)
Conventional dose rate RT vs. FLASH-RT

Flash is really a flash

Conventional dose rate RT	**FLASH-RT**
Dose delivered in **minutes**	Dose delivered in about **0.1 seconds**

Questions?