Treating cancer with radiation:
a new approach with FLASH Therapy

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@ Lausanne University Hospital (CHUV) Switzerland
Cancer cure in 2021?

Cancer 2.7 M cases / year in UE

Cure 65%

Failure 35%

Local 1/3

Metastases 2/3

Unmet clinical need
How do we fight cancer?

- Surgery
- Radiotherapy
- Chemotherapy / homonotherapy
- Molecular targeted
- Immunotherapy
What is FLASH therapy?

= a new way of delivering radiotherapy
« FLASH » is a biological observation

= A reduction of radiation toxicity to normal healthy tissues, while maintaining a similar effect on tumors

when comparing ultra-high to conventional dose rates
Historical perspective

FLASH sparing of normal tissues
Recognized in the 1970's ...

1st Description
Town et al


2014
1st tumors
Prof Vozenin

2018
1st patient
Bourhis et al

2020
1st clinical trials
Until 1982:

Dose for inducing tail necrosis in mice

Flash dose rates

FLASH sparing effect on normal tissues was recognized
2014 Re-discovery …

1) Sparing normal tissues

2) No sparing of tumors

Favaudon & Vozenin
What is the magnitude of the sparing effect on normal tissues?
FLASH is consistently associated with a relative sparing of normal tissues (compared to normal radiotherapy):

1) in several types of tissues (brain, skin, lung, GI ...)

2) in several animal species (cat, mouse, pig, Z-fish)

3) with several types of beam and energy (electrons, X-rays, protons)

4) across a few Institutions (Europe, USA)
Results of the CHUV were first confirmed @ Stanford University

“... Pre-clinical data indicate a marked reduction of normal tissues side effects while maintaining the destruction of tumor cells.

This could revolutionize the field of radiation oncology ...”

Pr. Billy LOO MD PhD,
Thoracic radiation oncology program
Stanford Cancer Institute

* Experimental Platform for Ultra-high Dose Rate FLASH Irradiation of Small Animals Using a Clinical Linear Accelerator, IRO. Juin 2016. Bill Lou, (Stanford University
Example N° 1: FLASH effect on the skin (Pig)

(skin of a pig, @ 9 months post-RT)
Example N°2 in normal brain (mice)

Montay-Gruel Radiother Oncol 2017
FLASH versus Normal RT in mouse brain

Less inflammation

Blood vessel protection

Protection of juvenile brain
What is the effect of FLASH on tumors?
So far ... no sparing effect for tumors with FLASH-RT:

1) in mouse: breast, H/N, glioma, lung, GI xenografts and orthotopic models

2) in a phase I veterinarian clinical trial in SCC of cat-patients
High cure rate in cat cancer patients
(a veterinarian clinical trial @ CHUV)

6 cats with spontaneous cancers treated with FLASH

- Minimal mucosal toxicity swallowing preserved
- 84% tumor control rate at 1 year

Vozenin et al Clinical Cancer Research 2019
How does it work?
Potential mechanisms?

Lower production of H2O2/contribution of O2
(Montay-Gruel, 2019; Adrian, 2019)

Lower level of persistent DNA damages and senescent cells
(Fouillade, 2019)

Metabolism including redox (Spitz, 2019)

Inflammation/Immune system
(Favaudon, 2014; Montay-Gruel, 2019; Simmons, 2019; Diffenderfer, 2019)

Signaling pathways/Stem cells protection

Vascular protection
(Montay-Gruel, 2020; Allen, 2020)
Mechanisms? Some level of O2 dependency

Hyper-oxygenation with carbogen breathing abolishes the FLASH effect
FLASH-RT spares lung basal stem cells *in vitro*

- Increased proportion of remaining of human basal stem cells after FLASH-RT
Are there potential limitations for clinical use?
How high should be the dose rate to observe a FLASH effect?

(for small volumes / with electrons)

Possible: 30-40 Gy/s (Favaudon et al 2014)

Likely: > 100-150 Gy/s (Montay-Guel et al 2017)

Reproducible: Dose / pulse (> 1.5 Gy and very few pulses)

Dose rate in the pulse (>= 10^6 Gy/s)

Overall time (< 100 ms)

Potential limitations for the clinical translation?

The experimental conditions to observe a FLASH effect were essentially:

- **Small** volumes of normal tissues (a few cc)
- **Mainly** (but not only) with **single** dose (7-10 Gy or higher)
- Overall Treatment Time < 100-200 ms
Is the magnitude of the benefit clinically meaningful?

Example for the pig’s skin:

Conventional

- 25 Gy, no necrosis
- 28 Gy
- 31 Gy
- 34 Gy

FLASH

- 28 Gy
- 31 Gy
- 34 Gy, no necrosis

(Potential DMF between 1.25 and 1.36)

(late effects @ 9 months post-RT)
... Clinical translation

is ongoing ...
Great interest in the radiation oncology community

1) Promising, reproducible and consistent pre-clinical observations

2) Potentially **less toxic, more efficient treatments for the radio-resistant tumors**

3) Numerous projects initiated worldwide
For clinical translation: additional safety measures are needed...

(ex @ CHUV :)

Pre-treatment

Treatment

Dosimetry check

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<td>14.9</td>
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Independent pulses and time counter device for beam stopping
First treatment of a patient with FLASH
(CHUV, Oct 2018)

Multiresistant T cell lymphoma

150 Gy/s
Overall time 90 ms

Feasible
Safe

(Bourhis et al 2019)
FLASH with Protons (broad beam)

Varian and the Cincinnati Children's/UC Health Proton Therapy Center Announce Initial Patient Treated in the FAST-01 First Human Clinical Trial of FLASH Therapy for Cancer

- First patient in the world to participate in a clinical trial of FLASH therapy
- Physicians and researchers at Cincinnati’s Children’s/UC Health Proton Therapy Center are using a Varian ProBeam® proton therapy system modified to deliver radiation treatment at ultra-high dose rates
- Therapy delivers radiation at ultra-high dose rates up to 100 times faster compared to conventional radiation therapy
Transfert clinique au CHUV (I)

FLASH-Mobetron

Only for superficial skin cancers
First Investigational Trials Planned with Mobetron FLASH HDR

Lausanne University Hospital Clinical Translation Initiatives:

**Impulse Trial:**
Phase I dose escalation study for multiresistant melanoma skin metastases (Mobetron-FLASH @ CHUV)

- Classical 3 x 3 dose escalation: 22 Gy to 34 Gy
- First cohort: Small fields (< 30 cc)
- Second Cohort: Larger fields (30-100 cc)

**Primary Endpoint**: DLT / MTD with independent blinded photograph review

**Status**: Enrollment expected to start in 2020

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**NMSC Trial:**
Randomized phase II trial for BCC and SCC of the skin (Mobetron-FLASH @ CHUV)

- FLASH with Electrons single dose 22 Gy
- Randomisation volumes < 30 cc
- SOC 5 x 7 Gy

**Primary Endpoint**: composite (toxicity / tumor control) with independent blinded review

**Status**: Enrollment expected to start in 2021

Courtesy of Prof. Jean Bourhis
Transfert clinique @ CHUV (II) : intra-operative FLASH-THERAPY

With
Pr Simon,
Pr Demartines,
Pr Mathevet

For cancers not amenable to
A complete resection
What about large tumor volumes and deep seated tumors?

- **Unmet clinical need**: this is where we have most of the tumor failures …

- **So far no FLASH** pre-clinical data mimicking these clinical situations

- **No FLASH** irradiating device is currently **available** : technical challenges

- **FLASH characteristics may not help** for its use in such large volumes?
Next step: CHUV-CERN project

For deep seated tumors

Lausanne University Hospital and CERN collaborate together on a pioneering new cancer radiotherapy facility

Lausanne University Hospital (CHUV) and CERN, in Switzerland, are collaborating to develop the conceptual design of an innovative radiotherapy facility, used for cancer treatment. The facility will capitalise on CERN breakthrough accelerator technology applied to a technique called FLASH radiotherapy, which delivers high-energy electrons to treat tumours. The result is a cutting-edge form of cancer treatment, highly targeted and capable of reaching deep into the patient’s body, with less side-effects. The first phase of the study comes to a conclusion this September.

In radiotherapy, the FLASH effect appears when a high dose of radiation is administered almost instantaneously — in milliseconds instead of minutes. In this case, the tumour tissue is damaged in the same manner as with conventional radiotherapy, whereas the healthy tissue appears to be less affected, meaning that less side effects are expected.
CERN-CHUV collaboration

- CHUV and CERN are actively collaborating on the realization of a clinical FLASH facility for large, deep-seated tumors.
- We have worked intensively and are now confident that the facility is feasible and are establishing the design.
- We are now working towards the next steps of the project, with the target of a clinical facility.

The remarkable connection between CLIC and FLASH

Both need:
- Very intense electron beams
  - CLIC – to provide luminosity for experiments
  - FLASH – to provide dose fast for biological FLASH effect
- Very precisely controlled electron beams
  - CLIC – to reduce the power consumption of the facility
  - FLASH – to provide reliable treatment in a clinical setting
- High accelerating gradient
  - CLIC – fit facility in the Geneva area and limit cost
  - FLASH – fit facility on a typical hospital campus and limit cost of treatment
CLIC technology for a FLASH facility being designed in collaboration with CHUV

Treat large, deep-seated tumors in FLASH conditions. Uses 100 MeV-range electrons and optimized dose delivery. Compact to fit on a typical hospital campus.
Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species

Pierre Montay-Gruel, Munjal M. Acharya, Kristoffer Petersson, et al
FLASH therapy CERN–CHUV project

Construction of the prototype

Installation 2023

First patient 2024-25

Glioblastome = cancer profond

ISREC & BILTEMA Foundations
Conclusions

1) FLASH:
   - Increases the **differential** effect between normal tissues & tumors
   - Operates at **high dose / fraction**, delivered in few **milliseconds**
   - Mechanisms?

2) Clinical translation:
   - Optimal parameters for obtaining a FLASH effect **in large fields needs to be investigated**
   - Both FLASH & high conformal delivery are needed: **technical challenges (CERN +++)**
Remerciements

L’équipe FLASH therapy du CHUV

Pr Vozenin
(cheffe de laboratoire)

Pr Bochud et l’IRA

UNIL & CHUV : Pr P Eckert, Mr O Peters, Pr JD Tissot, Pr PF Leyvraz,
DO : Pr Coukos, Pr Kandalaft & l’équipe du CTE
Sponsors : ISREC & Fondation Biltema, Fondation CePO, Fond’Action, FNS, ANR, PO1, Fondation CHUV
Partenaires : PMB, CERN, IntraOp, RaySearch
Recherche de nouveaux partenaires en cours pour le projet CERN-CHUV
<table>
<thead>
<tr>
<th>Device</th>
<th>Mbetron (IntraOp)</th>
<th>Otalron eRT6 (PMB Alcen)</th>
<th>Kinetron (CGRMeV)</th>
<th>Modified Elekta</th>
<th>Modified Varian (Sordina)</th>
<th>Novac7</th>
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<tbody>
<tr>
<td>Reference</td>
<td>This publication</td>
<td>Jacqard 14, Petersson 26</td>
<td>Lansonneur 16</td>
<td>Lempart 16</td>
<td>Schuler 6,17</td>
<td>Felici 25</td>
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<td>Available beam energy [MeV]</td>
<td>6 and 9</td>
<td>6</td>
<td>4.5</td>
<td>10</td>
<td>9, 16 and 20</td>
<td>7</td>
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<td>Maximum average dose rate [Gy/s]</td>
<td>≥ 700 @ 6 MeV</td>
<td>1000</td>
<td>NA*</td>
<td>≥ 300</td>
<td>74 @ 9 MeV</td>
<td>540</td>
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<tr>
<td></td>
<td>≥ 800 @ 9 MeV</td>
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<td>300 @ 16 MeV</td>
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<td></td>
<td></td>
<td>200 @ 20 MeV</td>
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<td>Maximum dose per pulse [Gy]</td>
<td>&gt; 8 @ 6 MeV</td>
<td>10</td>
<td>1</td>
<td>1.9</td>
<td>1.67 @ 16 MeV</td>
<td>18.2</td>
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<tr>
<td></td>
<td>&gt; 9 @ 9 MeV</td>
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<td></td>
<td></td>
<td>1.85 @ 20 MeV</td>
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<tr>
<td>Max. beam size @ max. dose rate [cm]</td>
<td>4 @ 90%</td>
<td>NA</td>
<td>NA</td>
<td>2 (5% flatness)</td>
<td>1 (90% isodose)</td>
<td>0.5 (FWHM)</td>
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<td>Short term stability [%]</td>
<td>0.8</td>
<td>&lt; 1</td>
<td>NA</td>
<td>1 to 4***</td>
<td>NA</td>
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<tr>
<td>Long term stability</td>
<td>1.8 @ 6 MeV</td>
<td>4.1%</td>
<td>NA</td>
<td>NA</td>
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<td>2.3 @ 9 MeV</td>
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* NA: data not available; ** during 10 mins; 7 to 11 for > 10 mins