RADIO ONCOLOGIE

FLASH RADIATION THERAPY – CURRENT STATUS AND THE WAY TO THE CLINIC

LATEST RESULTS AND ADVANCES TOWARDS CLINICAL FLASH-RT

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Joint AAPM/COMP Meeting
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Latest results and advances towards clinical FLASH-RT

Latest preclinical results on the brain

Glioblastoma and cognition

Juvenile model to foresee medulloblastoma treatment

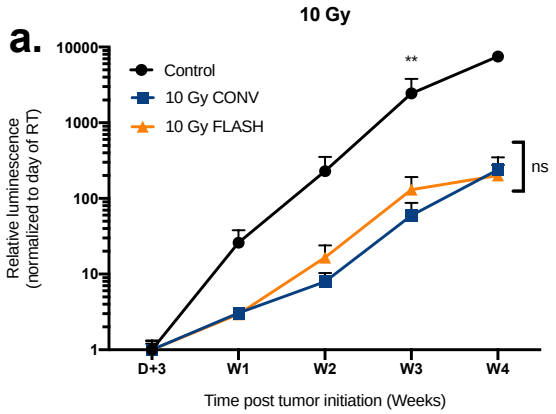
Clinical transfer

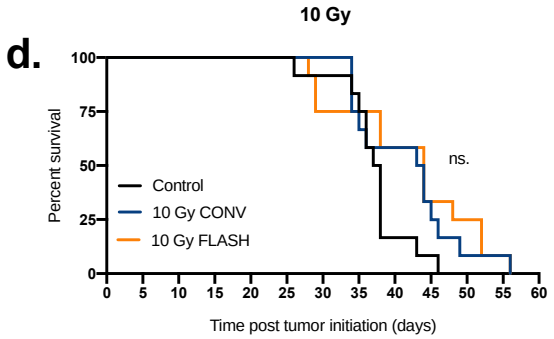
Which beam parameters ?

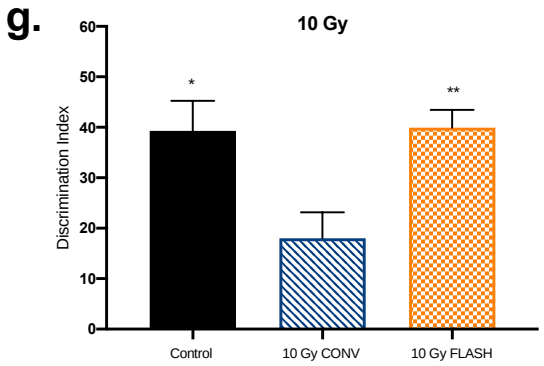
Which technology with electrons ?

What are the challenges ?

FLASH-RT is efficacious against GBM and protects the brain functions

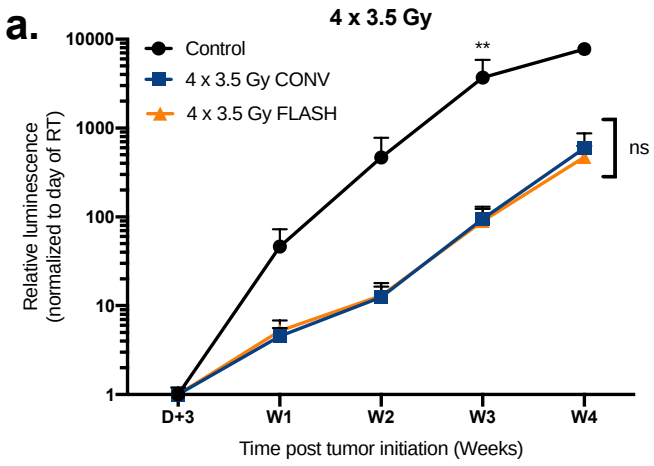


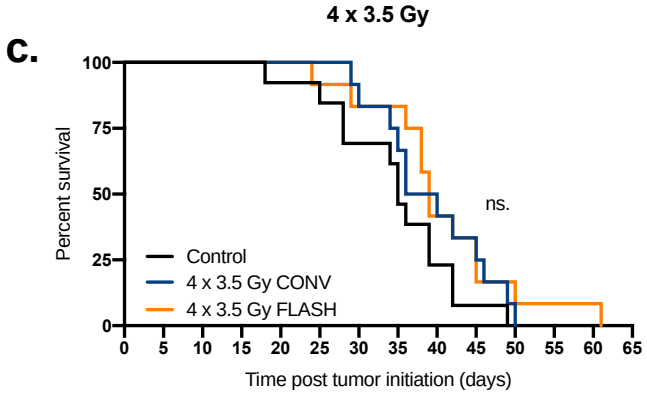


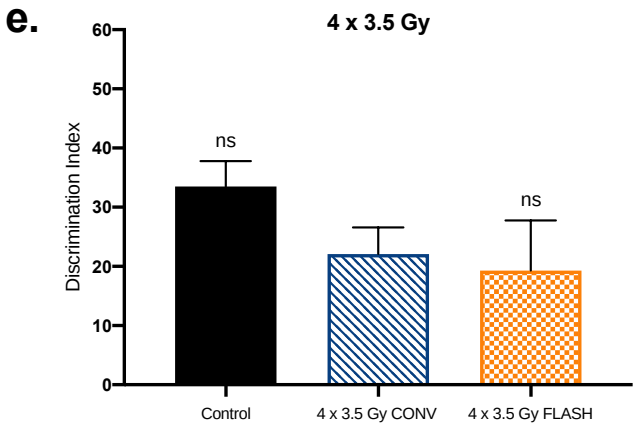


Montay-Gruel et al (in revision)
Please do not circulate

Towards hypo-fractionation ?







Montay-Gruel et al (in revision)
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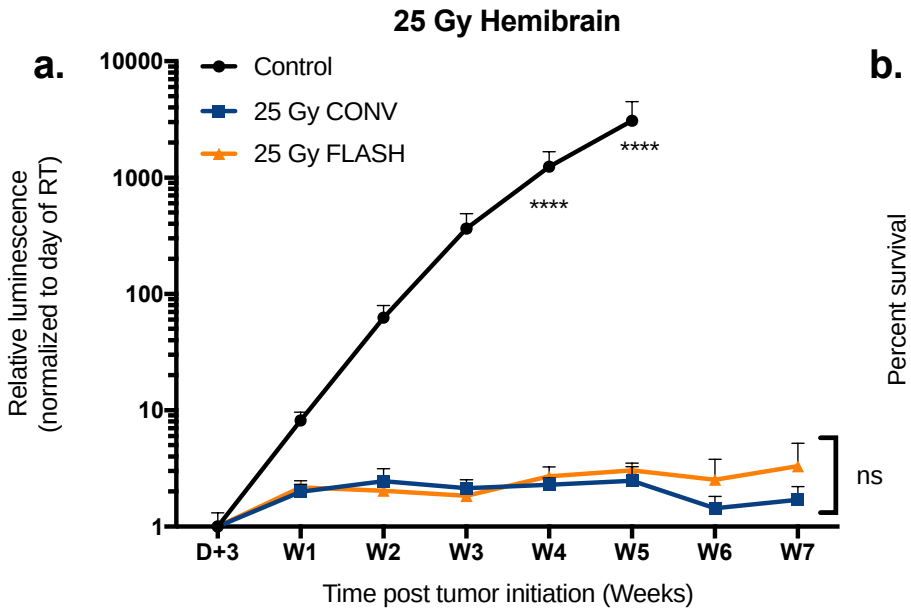
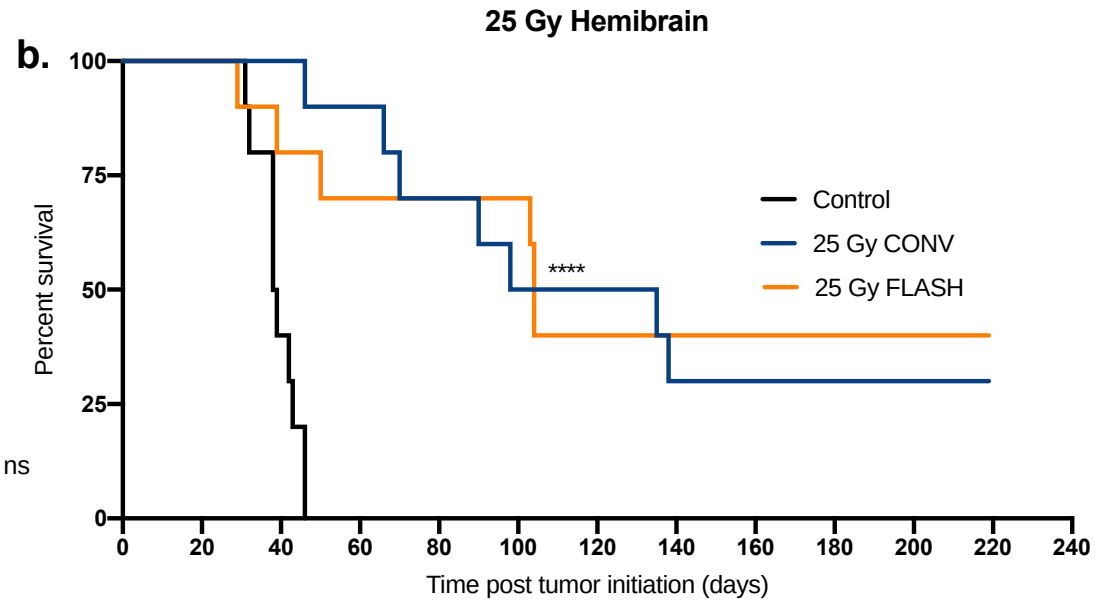
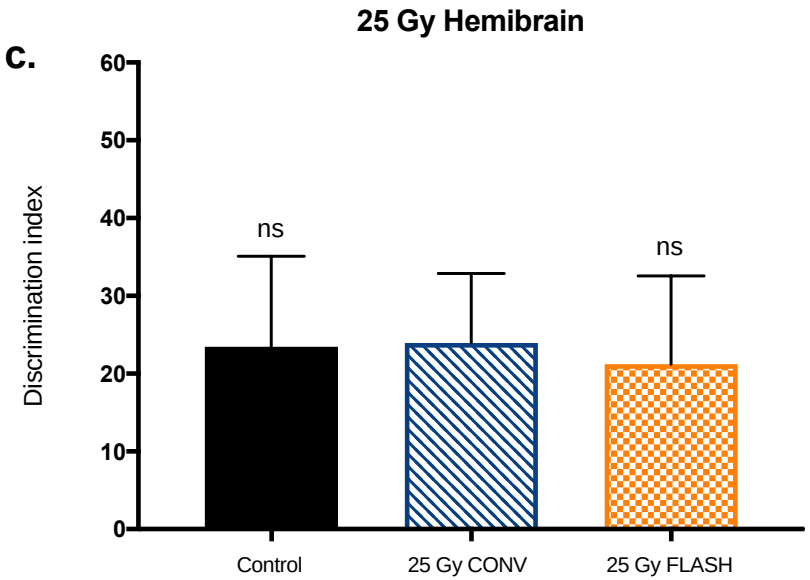
What about complete tumor control ?







Montay-Gruel et al (in revision)
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Advantages of protecting the normal tissue

Medulloblastoma patients

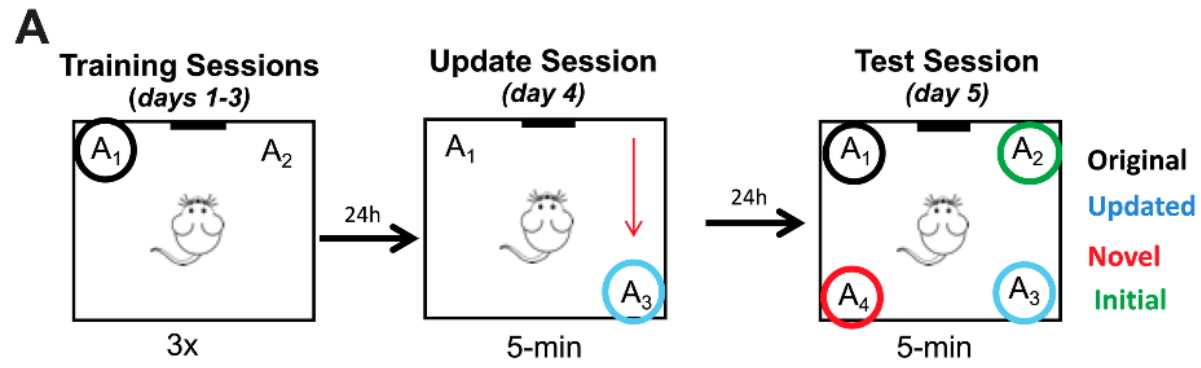
→ Long term survival achieved >80% pediatric cases
→ Surgery followed by cranio-spinal RT + chemo

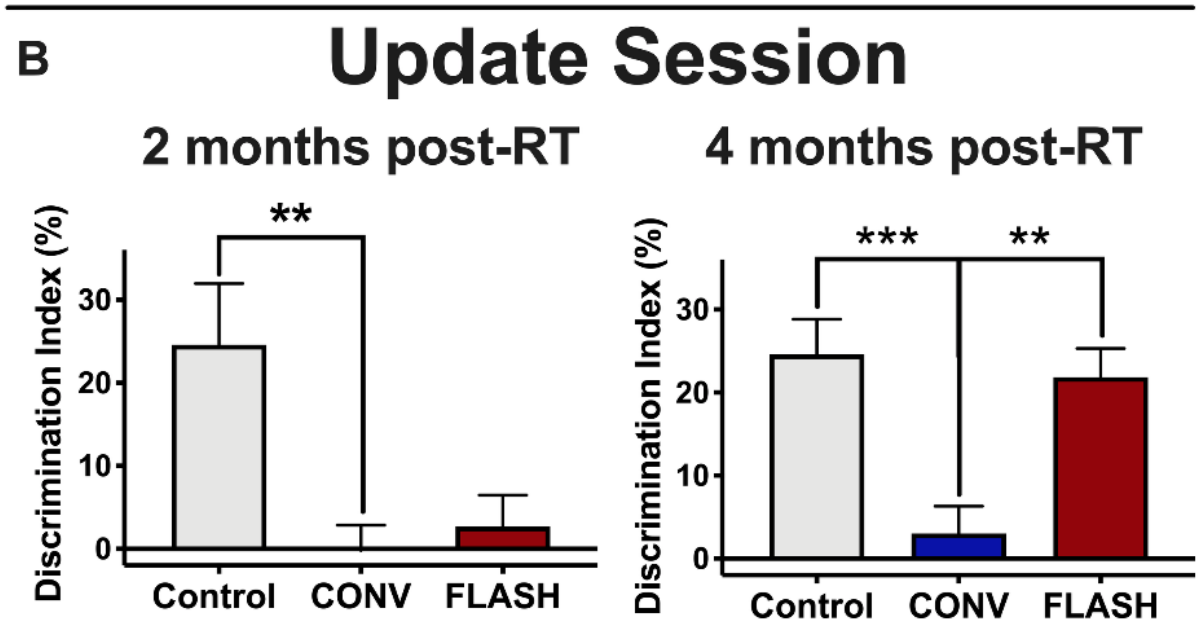
→ Significant impairments
cognition,
mood disorders,
endocrine dysfunction,
cerebrovascular complications

WBRT 8 Gy FLASH / CONV-RT
3 week old pups
Congnitive investigation

Alaghband et al (Cancers, 2020)

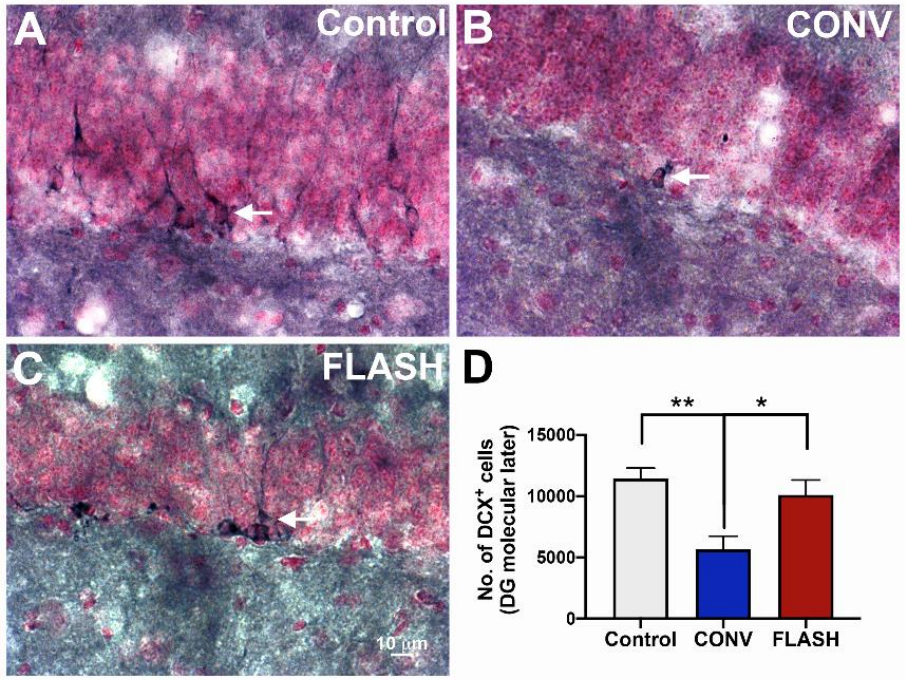
Conservation of complex congnitive functions in young animals

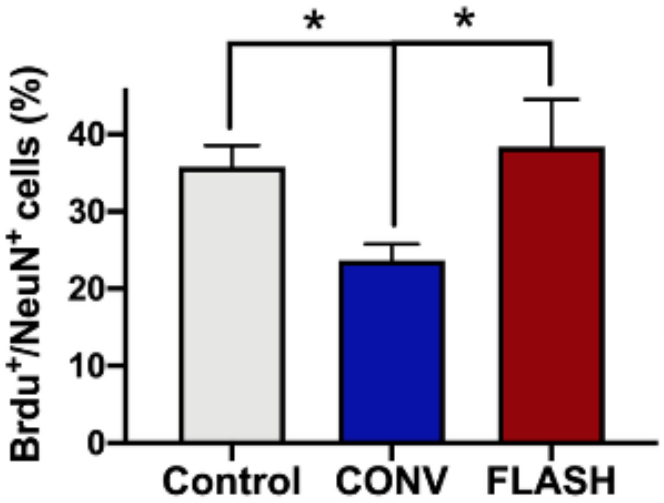




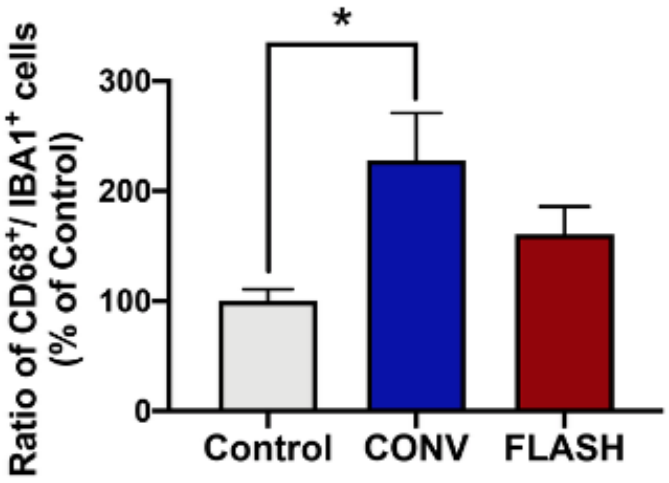
Cellular preservation

Absence of neurogenesis impairment

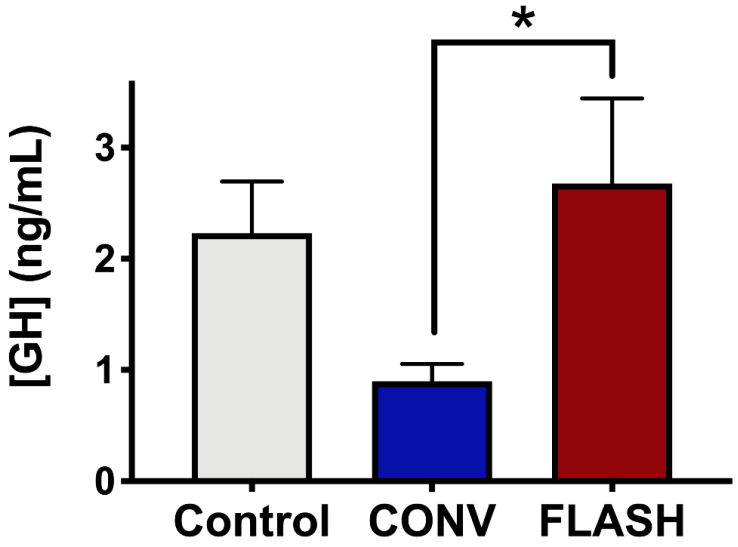




Absence of neuroinflammation

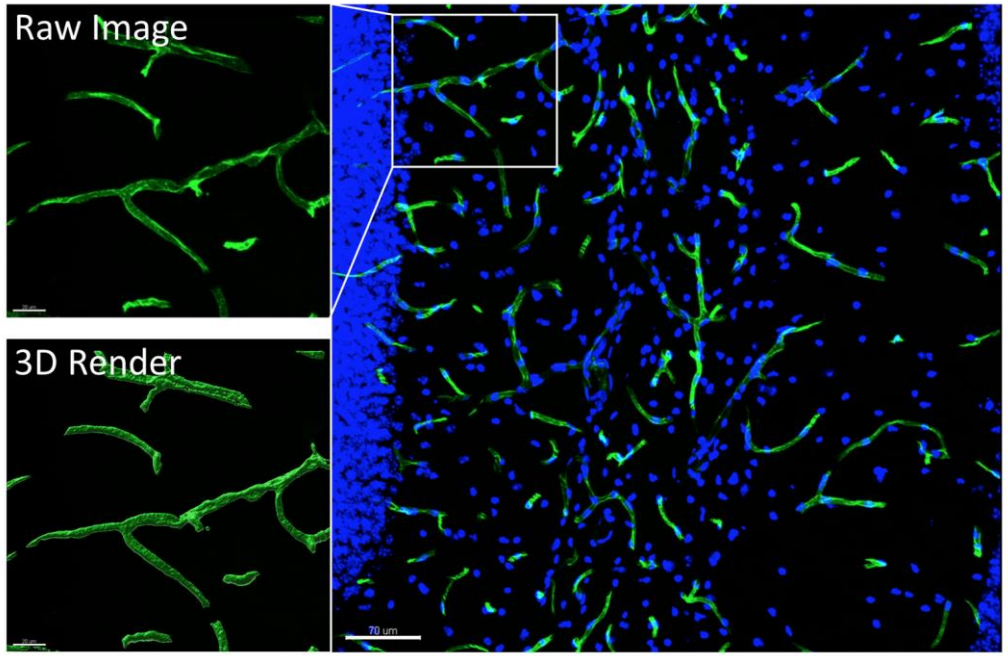


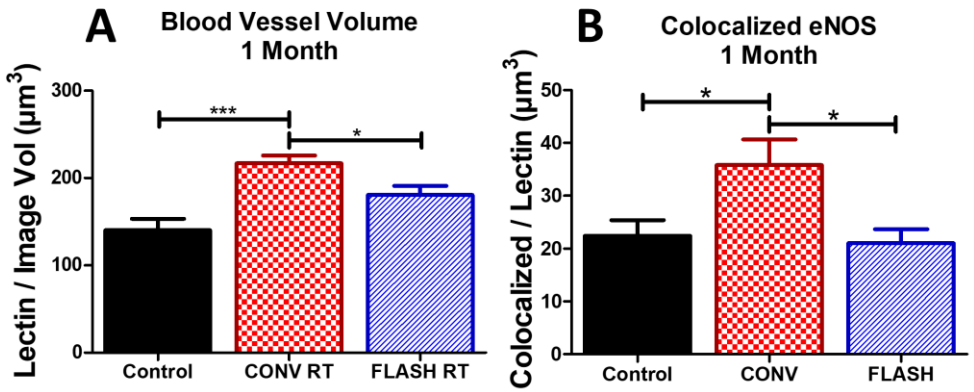
Preservation of the endocrine system



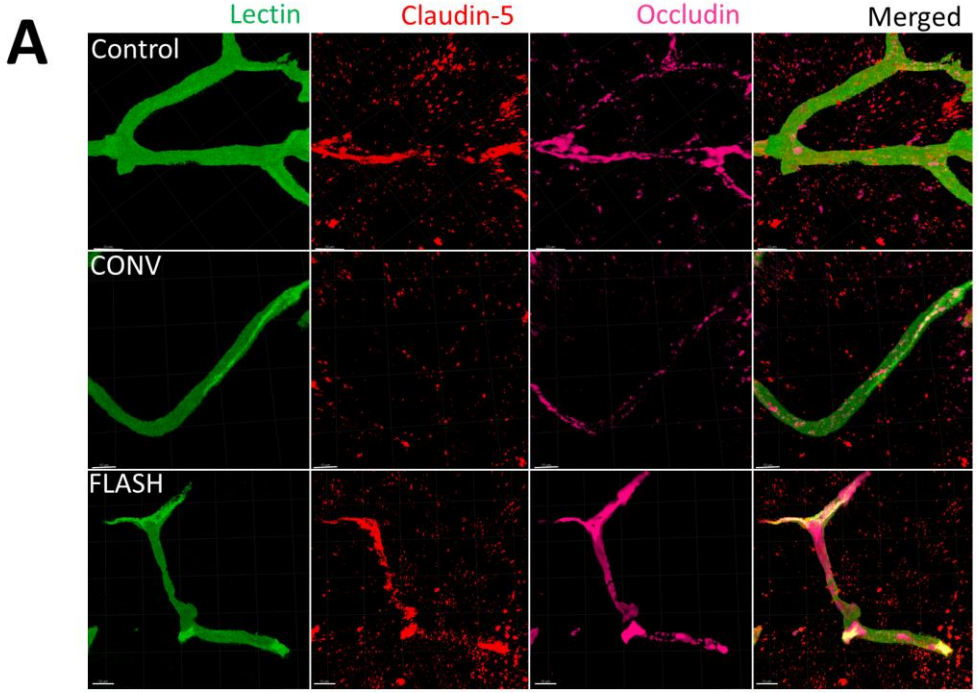
Alaghband et al (Cancers, 2020)

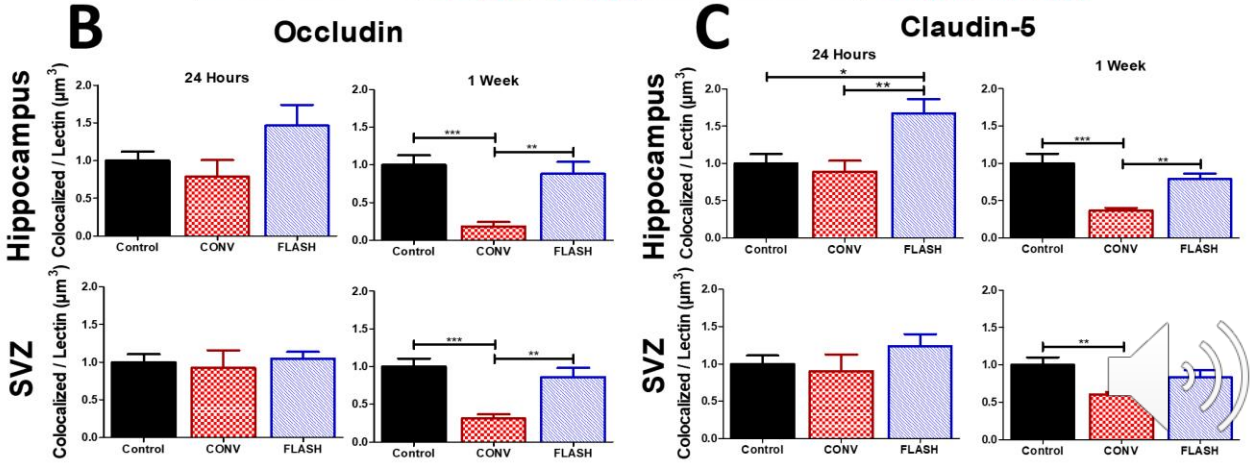
Integrity of the adult cerebrovascular system after FLASH-RT





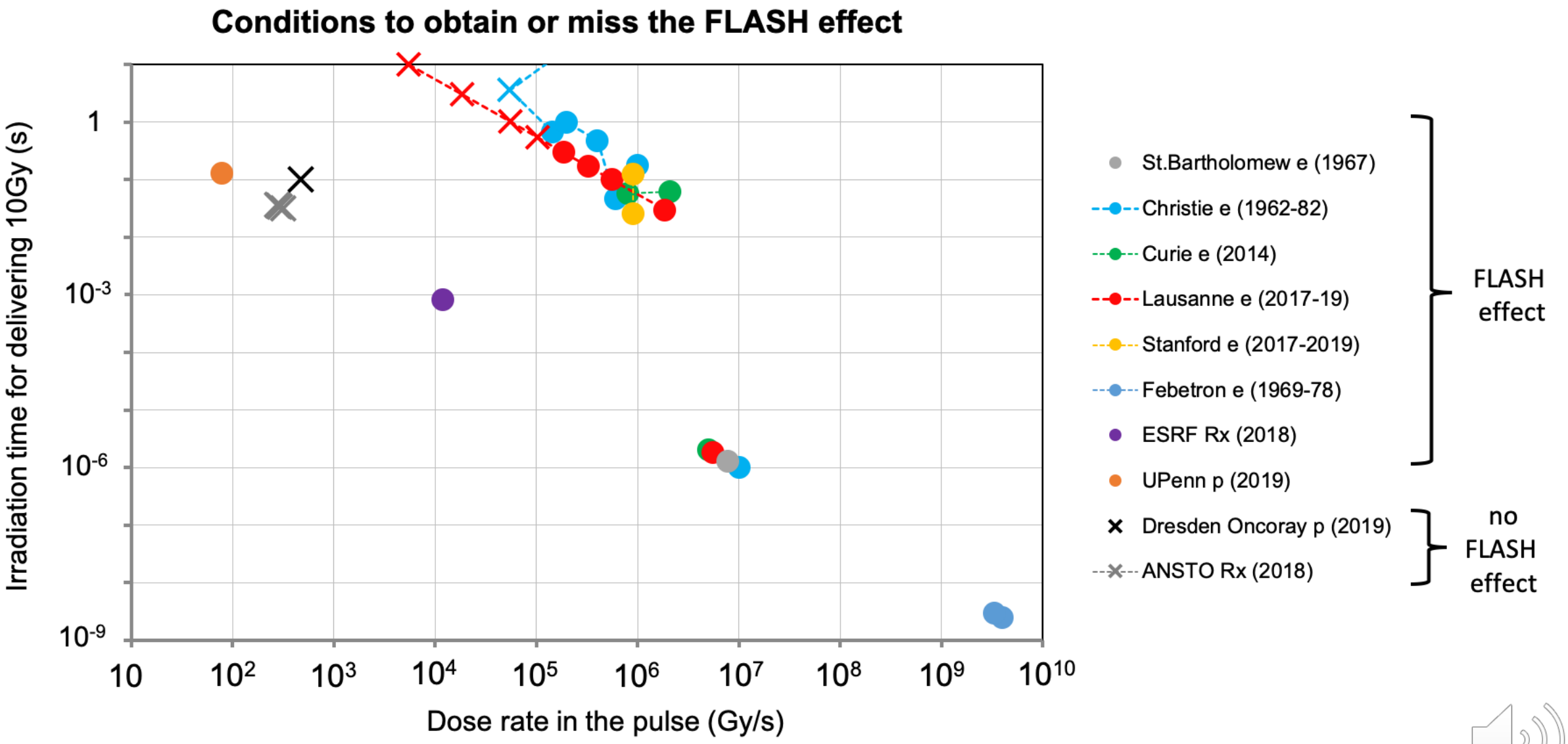
Preservation of tight junctions





Are electron beams suitable to transfer FLASH-RT to the clinics ?
What are the challenges ?

What do we know about the optimal parameters to obtain the FLASH effect ?



Bourhis et al (Radiother&Oncol 2019)
Montay-Gruel et al (in revision)

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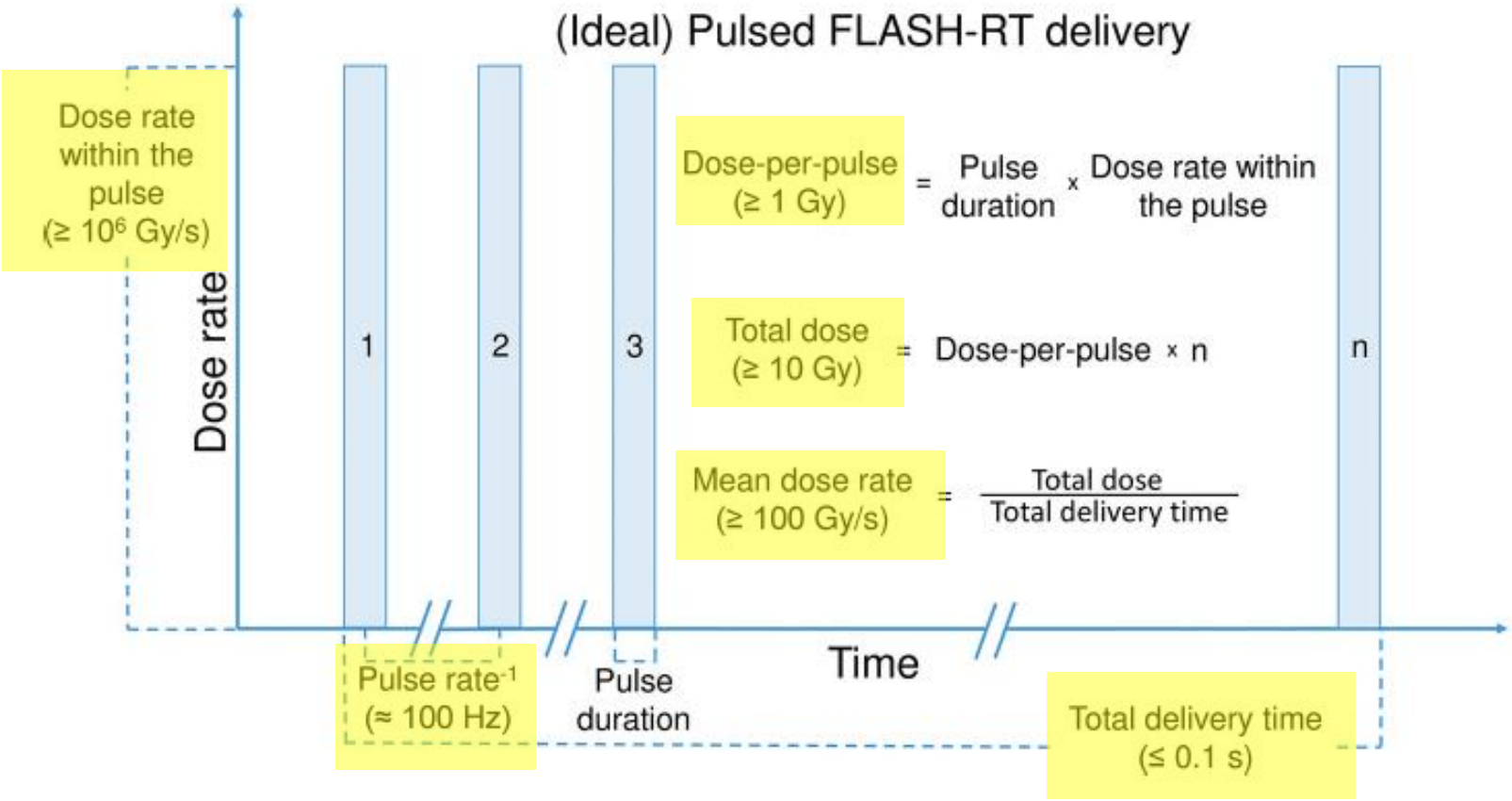


FIGURE 1 | (Ideal) Pulsed FLASH-RT delivery. A schematic view of a pulsed beam delivery, specifying some parameters which seems to be important for inducing the FLASH effect.

Wilson et al (Frontiers in Oncology, 2020)

Which technologies are currently available for a clinical transfer ?

What are the challenges ?

TABLE 3 | Some relevant advantages and disadvantages of current and prospective FLASH radiotherapy sources (color coded by radiation modality).

Radiation source	Modality of radiation	Advantages (+)	Disadvantages (–)	Currently available for FLASH-RT clinical studies, with which main limitations?
Conventional electron linear accelerator (10, 14, 66, 67)	1–25 MeV Electrons	Inexpensive. Minor beam size limitation.	Poor depth penetration. Wide penumbra.	Yes, Limited to treating superficial tumors.
Very High Energy Electron linear accelerator (68, 69) or Laser plasma accelerators (70, 71)	100–250 MeV Electrons	Good depth penetration. Electromagnetic steering and focusing. Not sensitive to tissue heterogeneity.	Low pulse rate (1–10 Hz) for Laser plasma accelerators. Limited beam size.	No
Laser plasma accelerators (75)	1–45 MeV Protons	Compact design possible. Electromagnetic steering possible.	Poor depth penetration. Low pulse rate (1–10 Hz). Very sensitive to tissue. heterogeneity. Higher LET in Bragg peak. Beam contamination. Stability issues. Limited beam size.	No
Cyclotrons, synchrotrons or Synchrocyclotron (11, 76)	100–250 MeV Protons	Good depth penetration. Electromagnetic steering possible. Limited dose-bath. Electromagnetic steering.	Large expensive sources. Sensitive to tissue heterogeneity. Higher LET in Bragg peak. Beam scanning or scattering required to cover target volumes	Yes, FLASH effect might be lost with beam scanning and/or higher LET.
X-ray tube (72)	50–250 keV X-rays	Inexpensive. Compact design.	Very limited depth penetration. Limited beam size. High entrance dose.	Yes, Limited to treating small and very superficial tumors.
Synchrotron (24, 32)	50–600 keV X-rays	Microbeam Radiation Therapy possible.	Very large. Very expensive. Limited depth penetration. Very limited availability. Limited beam size requires scanning of sample/target.	Yes, Very limited availability.
Electron linear accelerator with high density target (20)	6–10 MV X-rays	Good depth penetration. Narrow penumbra. Minor beam size limitation.	Multiple beam angles required.	No

Wilson et al (Frontiers in Oncology, 2020)

External beam RT with 5-6 MeV LINAC is suitable for superficial skin tumor treatments

CLINICAL CANCER RESEARCH

Clinical Trial Brief Report

The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients

Marie-Catherine Vozenin, Pauline De Fornel, Kristoffer Petersson, Vincent Favaudon, Maud Jaccard, Jean-François Germond, Benoit Petit, Marco Burki, Gisèle Ferrand, David Patin, Hanan Bouchaab, Mahmut Ozsahin, François Bochud, Claude Bailat, Patrick Devauchelle, and Jean Bourhis

First in Human

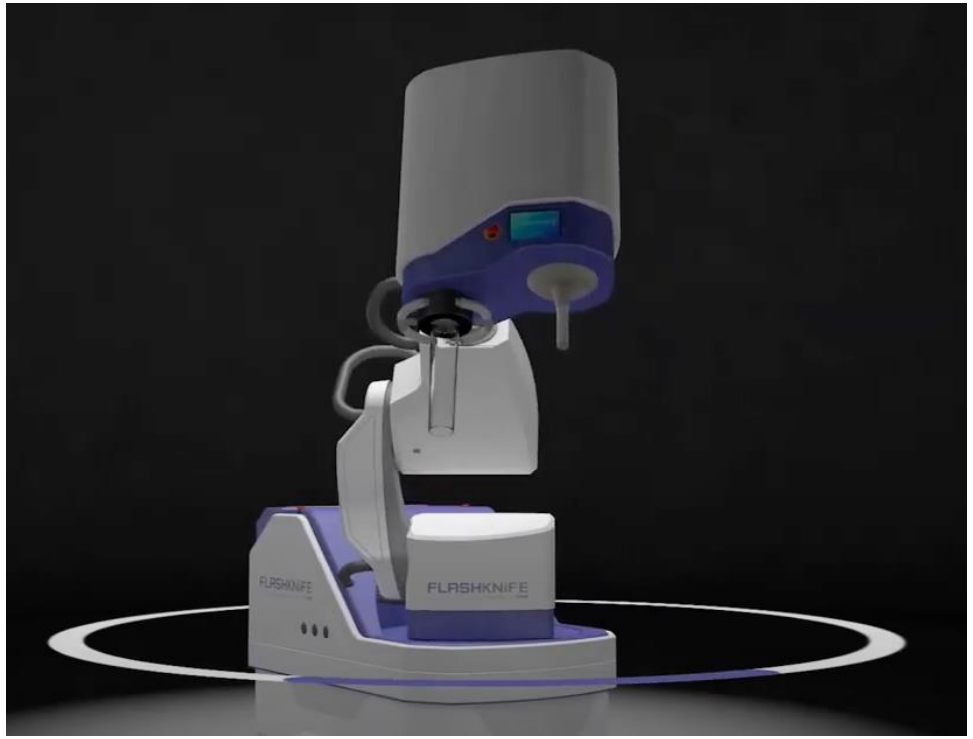
Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

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

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

Intra Operative RT will overstep the depth penetration challenge associated with electron beams



Relatively high single doses
Access to deeper tumors
Extremely fast beam-on time : advantage for surgery
Protection of the surrounding normal tissues

Multiple clinical applications

Conclusions

More and more preclinical data showing in different models

- Protection of the normal tissues: from cellular effect to organ function
- Efficacious anti tumor effect with single doses or hypo fractionated regimen

Current studies are aiming at defining the optimal parameters to reach the FLASH effect

- Mean dose rate
- Instantaneous (intra-pulse dose rate)
- Pulse repetition (frequency)
- Dose per pulse
- Total dose
- Total delivery time

Clinical tranfer is *almost* ready, with challenges yet to overcome (electrons)

- Penetration in the tissue (possibility of IORT or superficial tumors with EBRT)
- No available VHEE technology available yet

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Animal Facilities of Epalinges and Irvine

National Institute of Neurological Disorders and Stroke

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