New approaches in radiotherapy

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Current radiotherapies

➢ "Conventional" radiotherapy (> 95%)

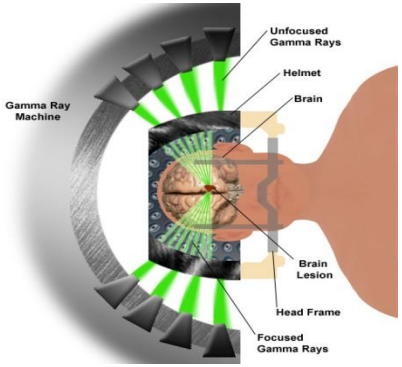
- **Particles**: X-rays 6-25 MV (every tumors), electrons 3-18 MeV (surface tumors)
- **Machines**: clinical electron accelerators with multileaf collimator and embedded imaging systems
- **Time fractionation**: 2 Gy/session, 5 session/week
- **Dose**: 40-70 Gy
- **Dose rate**: 30-70 mGy/s
- **Field sizes**: 2 - 40 cm²

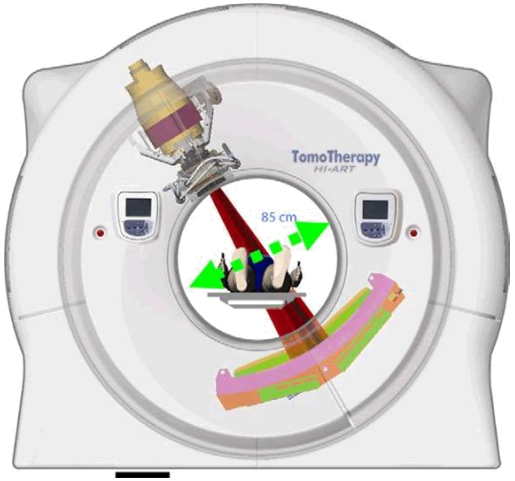




Standard clinical accelerator with embedded imaging systems

Gamma knife radiosurgery

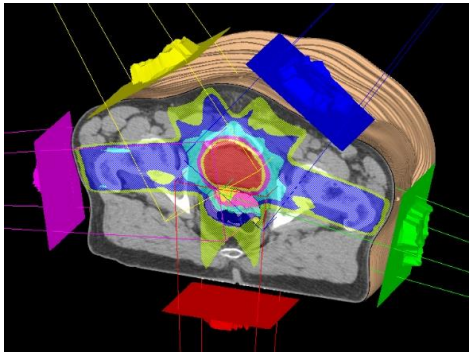




Tomotherapy

Cyber-knife





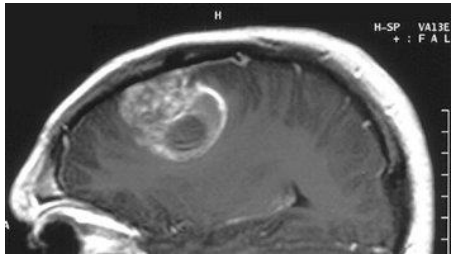
Intensity-modulated irradiation

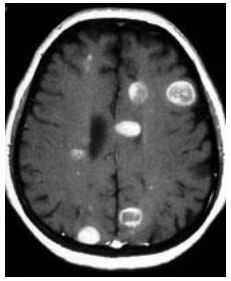
→ Objectives: large dose in tumor, low doses in healthy tissues

Current radiotherapies

➢Limitations:

- The toxicity to healthy tissue limits the dose
- In particular for very radioresistant, bulky and diffuse cancers *(glioblastomas)*, or non-localized tumors *(multiple metastasis)*





➢How to improve the treatment?

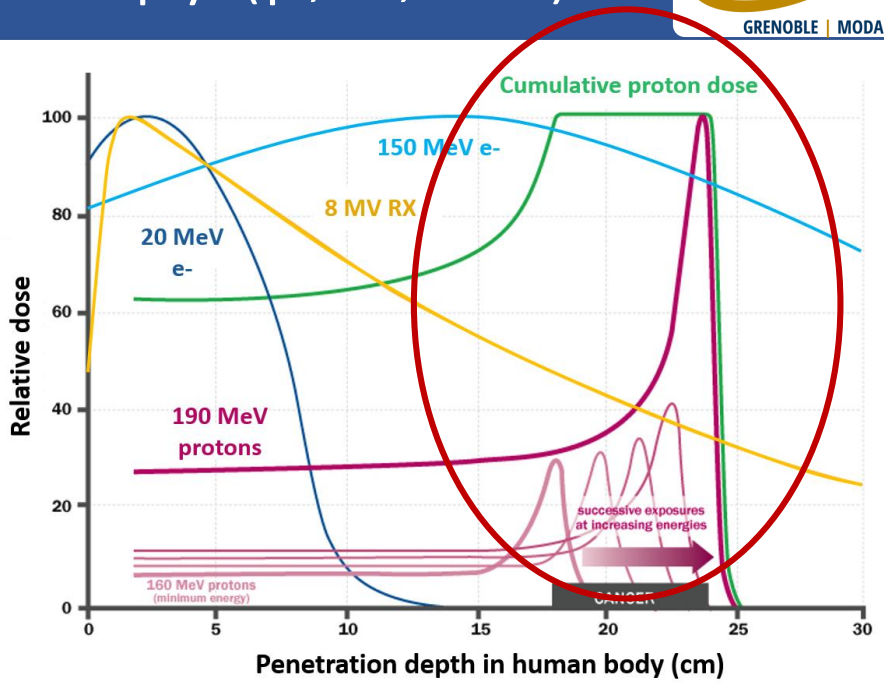
- Induce a more efficient tumoral irradiation
  - Particle: hadrontherapy (p, α, ^{12}C, ions)
  - Targeted radiotherapy: BNCT, nanoparticles, radionuclides…
- Preserve the healthy tissues:
  - Particle/energy: hadrontherapy, very high-energy electrons (VHEE)
  - Dose delivery mode: spatial fractionation of dose (beam size < mm), “FLASH” irradiation (very high dose rate)

→ Play on physical parameters to induce a different biological effect

Different particles: Hadrontherapy (p, α, ^{12}C)

➢In clinics: *(cf. presentation of J. Thariat)*

- ~1% of RT indications
- 3 protontherapy (PT) centers in France: CPO (Orsay), CAL (Nice), Archade (Caen)
- 1 He/C-ion center: planned for 2025 in Archade (Caen)



➢Physical and biological efficacy:

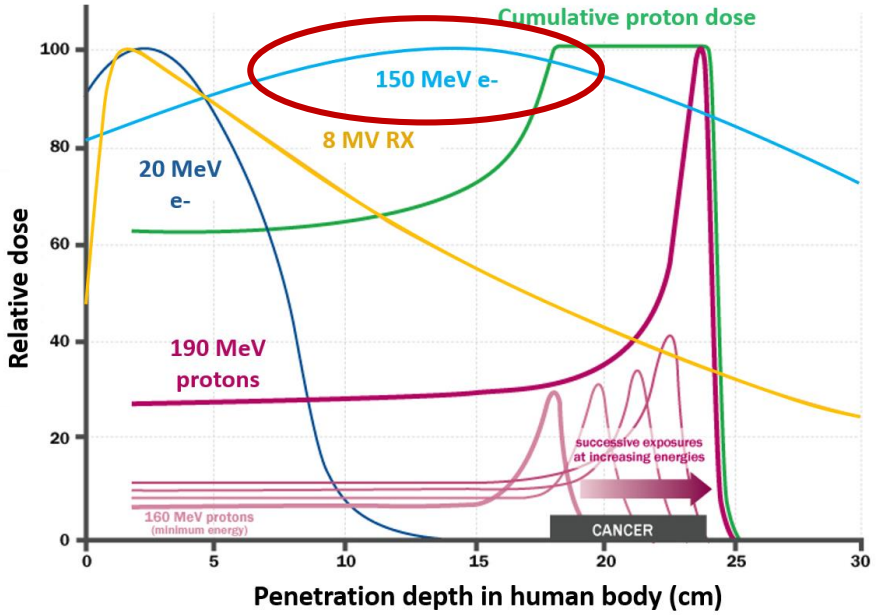
- Finite range of primary beam
- Higher dose in the tumor (Bragg peak)
- High Linear Energy Transfer (LET) → high Relative Biological Effectiveness (RBE)

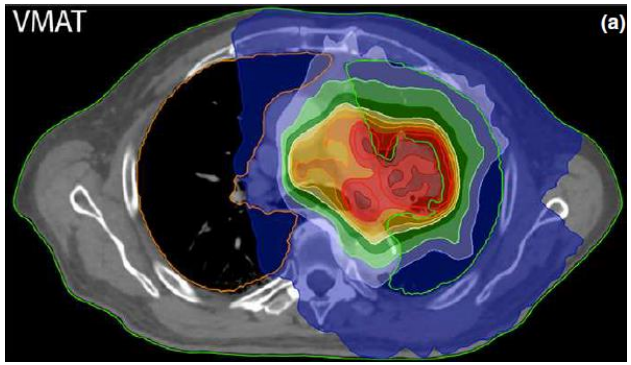
➢Current challenges:

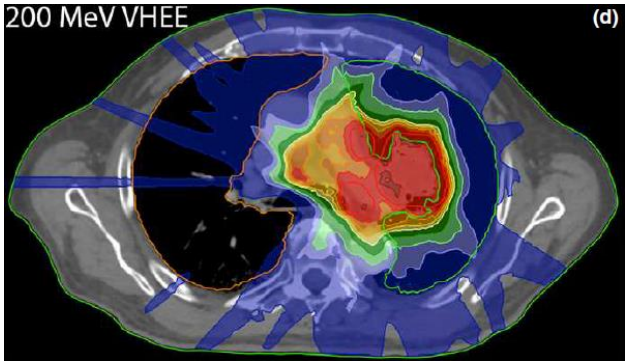
- Radiobiology of ions: need for hadronic research platforms
- Optimization: enhancement of therapeutic index (anti-tumor effect vs toxicity).
- Online quality control of ion beams *(cf. presentation of E. Testa)*

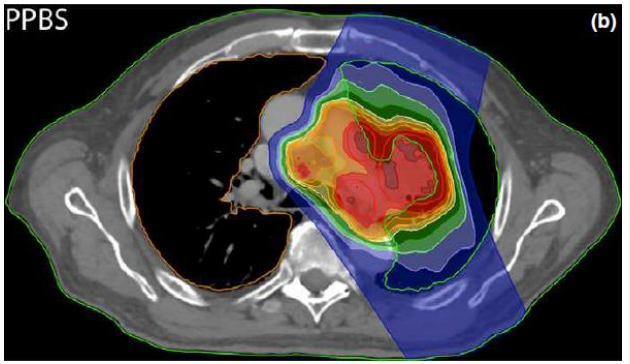
Different particles: VHEE (50-250 MeV)

- Advantages vs MV photons
  - Flatter depth dose profile: deep tumors
  - Relative insensitivity to heterogeneities
  - Magnetic collimation
  - "Flash" dose rate accessible
- Advantages vs protons
  - Potential reduced cost, compactness and beam shaping
- Current challenges:
  - Radiobiology of VHEE and pulsed-regime unknown
  - Reliable VHEE dosimetry protocols (potential ultra-short pulses, high-dose rates)









Clinical case VHEE compared to VMAT → Better protection of OAR (prostate, Lung, brain, H&N…) Schuler et al. 2017

New delivery mode: FLASH therapy

➢Very-high dose rates (> 40 Gy/s) protect normal tissues:

- Favaudon *et al.* 2014: observed **lower normal tissue toxicity** (lung fibrosis) using high-dose rate e- beam (> 40 Gy/s) with **similar tumor control** to conv. (~0.03 Gy/s)
- FLASH-effect confirmed with e-/photon beams in several *in vivo* experiments. **First patient treated** in Lausanne *(Bourhis et al. 2019)*.
- Recently demonstrated with **scattered proton beam** *(Diffenderfer et al. 2019)*.

➢What is needed to have a "Flash" effect ?

- Dose-rate > 40 Gy/s – up to ~MGy/s
- Irradiation < 100-200 ms
- Minimum dose per fraction > 4 Gy

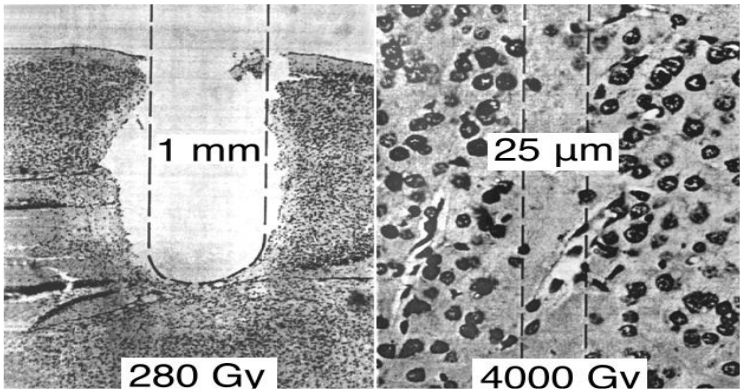
➢Challenges/Questions:

- Limits of physical parameter's impact on FLASH biology: pulse duration/intensity, mean or instantaneous dose-rate, beam size…
- Chemical and biological mechanisms of FLASH-effect ?
- Is it observable *in vitro* ?
- Adapted dosimetry solutions for very-high dose rates needed

New delivery mode: Spatially fractionated RT

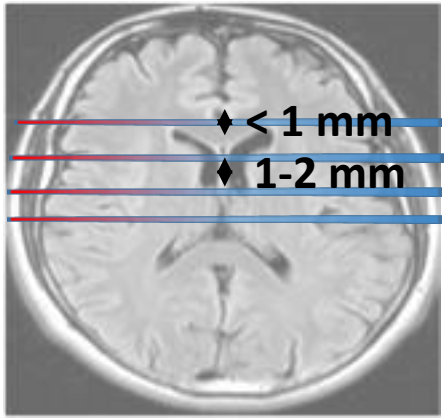
➢Principle:

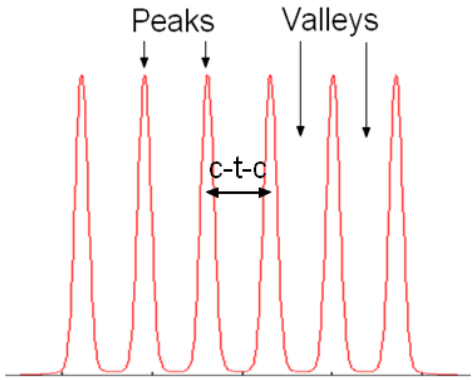
- Combines **submillimetric beam sizes** with **spatial fractionation of the dose**



Dose-Volume effect (Zeman et al. 1959)

+





Heterogeneous dose profiles

- Beam < 200 µm (MRT, synchrotron) ; 400-700 µm (MBRT, accessible clinical facilities)
- Remarkable **increase of the dose tolerance** in normal tissues
- Equivalent **tumor control** efficiency

➢Challenges/developments:

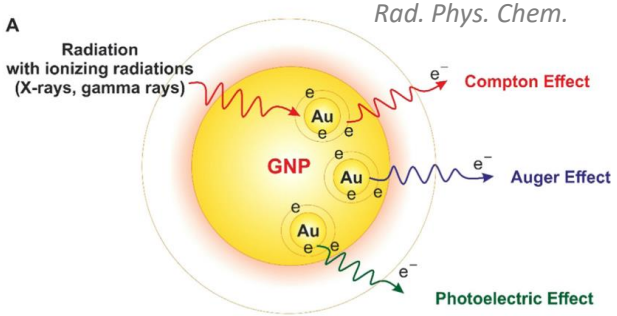
- Explore the *terra incognita* of influence parameters
- Biological processes induced in normal and cancerous cells/tissues ?
- Reliable dosimetry protocols for very small beams

Targeted therapies: nanoparticles (NP)

➢ Metallic / Oxide NP can enhance radiosensitization of RT:

- First showed by Hainfeld *et al.* in 2004: GNP + RX
- Confirmed in numerous studies with different NP/beams
- 2 clinical trials in France: AGuIX® (Gd), NBTXR3® (Hf oxide)

Borran et al., 2018. Rad. Phys. Chem.



➢ High complexity to optimize NP-based treatments

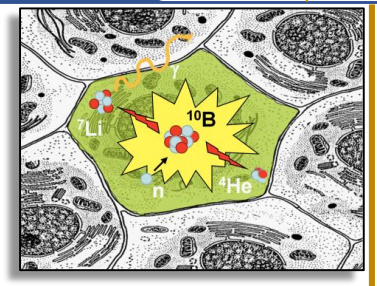
- **Radiosensitization is cell-line and NP-type dependent**: need for standardization
- Treatment efficacy may depend on tumor targeting and cell-uptake
- Macroscopic dose-enhancement cannot explain alone observed biological effects.

➢ Challenges / questions:

- How to improve targeting of tumor cells ?
- Key parameters for NP-radiosensitization ?
- Question of pertinent subcellular target ?
- Physical, chemical and biological mechanisms involved in NP-radiosensitization ?
- Biological-dose modeling: need nanometric precision and adapted biophysical models

Targeted therapies: boron-enhanced therapies

➢ Boron Neutron Capture Therapy (BNCT): $^{10}B(n,^{7}Li)\alpha$



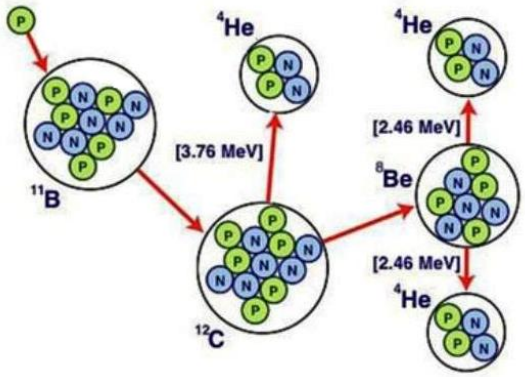
Natural (20%) or enriched boron isotope, delivered in cancerous cells (BPA or BSH)

$$^{10}B + n_{th} \rightarrow [11B]^{*} \quad \begin{cases} \xrightarrow{6\ \%} {}^{4}He + {}^{7}Li \quad (2{,}79\ MeV) \\ \xrightarrow{94\ \%} {}^{4}He + {}^{7}Li \quad (2{,}31\ MeV) + \gamma\ 0{,}48\ MeV \end{cases}$$

- BNCT efficacy relies on local emission of high-LET ions: destruction limited to the cell
- Several clinical trials *(Barth et al. 2012)*: promising results for GBM and recurrent H&N

➢ Proton-Boron Fusion Therapy (PBFT): $^{11}B(p,\alpha)2\alpha$

- New proposition to enhance anti-tumor effect of protontherapy using natural boron *(Yoon et al. 2014).*



➢ Challenges/developments:

- Improve selectivity of boron-carriers
- Access to in-hospital epithemal neutron-beams
- Modeling: nanometric precision and biophysical models needed + reaction cross sections

Prospective: ADOC proposal

➢ Common questions and technical needs to answer it:

- Understand underlying mechanisms
- Access to research platforms
- Specific modeling to drive experiments

} Competences of in2p3 teams, with close interdisciplinary collaborations

➢ Proposal of project's structuration on innovative RT addressing « Dose-enhancement and optimization of cell-destruction » (ADOC)

Initiated by Y. Prezado (Inst. Curie) & G. Montarou (LPC-Clermont). Contribution of IN2P3 teams from CENBG, IP2I, IPHC, LPC-Clermont, LPC-Caen, LPSC, Subatech…

- Objective of moving toward radiobiological, preclinical or clinical purposes
- Still under construction and discussion…

➢ Overview of contributions proposed:

- Provide **fully instrumented ion-beam (p, α) platforms** to allow preclinical proof of concepts for **FLASH-RT** *(Subatech, IPHC, LPC-Caen)*
- Improve **biological mechanisms understanding** of **targeted RT** and **hadrontherapy** *(IP2I, CENBG, LPC-Clermont)*
- Improve **modeling of targeted RT** *(LPC-Clermont, CENBG, LPSC-IP2I)*
- Explore influence parameters for new **dose-delivery approaches** *(I. C., LPSC, IPHC, Subatech)*
- Optimize **Boron-Enhanced Therapies** *(LPSC, LPC-Clermont)*

Dosimetry for FLASH

LPC Caen: S. Salvador, J.M. Fontbonne, J. Thariat

➢ Dedicated detector for ultra-high dose rate beam monitoring:

- **Specific design for monitoring of new electron-accelerator** to be installed at Inst. Curie/CPO for FLASH experiments.
- Phd Thesis started in sept. 2019

➢ Needs:

- Dose rate: up to 1 MGy/s
- Real-time monitoring
- Reproducible meas., independent of machine setting
- 2D beam profile and positioning
- Absolute dose calibration *(few % on dose uncertainty)*
- Minimal beam perturbation

➢ Medium-term prospect (1-3 years):

- Determination of best design & conception
- Implementation on machine with industrial partnership

➢ Long-term prospect (3-10 years):

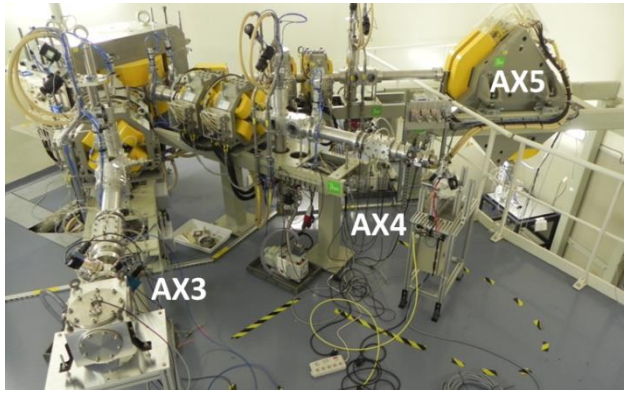
- Application to other beam energy/type: in particular, for monitoring of FLASH p/α beams of ARRONAX/PRECy platforms
- Development of a 5 MeV FLASH photon machine!

Adapting hadronic platforms for FLASH

Subatech/Arronax: A. Guertin, F. Haddad, C. Koumeir, V. Métivier, F. Poirier, N. Servagent

➢ ARRONAX (Nantes):

- **Beams:** proton (30-70 MeV), deuton (15-35 MeV) & alpha (68 MeV)
- **Pulsed beams:** duration µs to ms, spaced from ~100 ns to s
- **Dose rate**: few Gy/min to 1 MGy/s
- **Irradiation**: plateau – SOBP,
- in vitro & in vivo experiments



➢ Future developments:

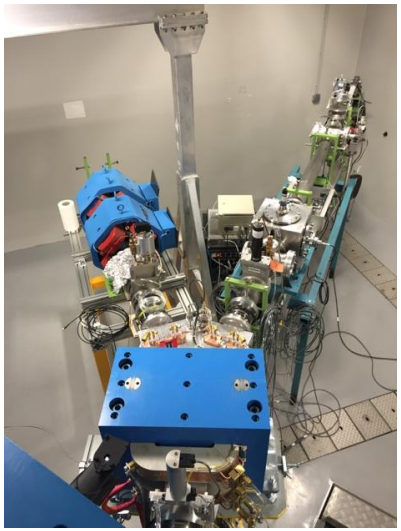
- Toward Flash proton/α for *in vivo* irradiation
- Improved dosimetry for low-energy ion beams:
  - **Transparent detectors for online beam profile/flux** (diamond *(LPSC collab.)*, polymers…)
  - **Range-meas. with µm precision**: based on Bremsstrahlung or UV radiation emission *(cf. E. Testa presentation)*
  - **LET determination** combining detection (ultra-thin semi-conductor), cross section meas. (keV-MeV) and modeling to determine **dose in biological material**.
- Will benefit from developments of LPC-Caen for very high-dose rate detection

Adapting hadronic platforms for FLASH

IPHC: M. Rousseau et al.

➢PRECy (Strasbourg)

- **Beams:** proton (0-25 MeV)
- **Pulsed of continuous beams**
- **Dose rate**: few 0.1 Gy/min to 50 Gy/s
- **Irradiation**: plateau – SOBP, field 2-20mm -> to be extended 50mm
- in vivo & in vitro exp. with designed sample support



➢Future Developments:

- Toward Flash proton (> 100 Gy/s) irradiation:
  - R&D for measurement of high-intensity in air
- Will benefit from developments of LPC-Caen for very high-dose rate detection
- Development of alpha-irradiation:
  - Through (p,α) conversion reaction: tests on ^{7}Li and ^{12}C targets ➔ dose rate ~1Gy/min

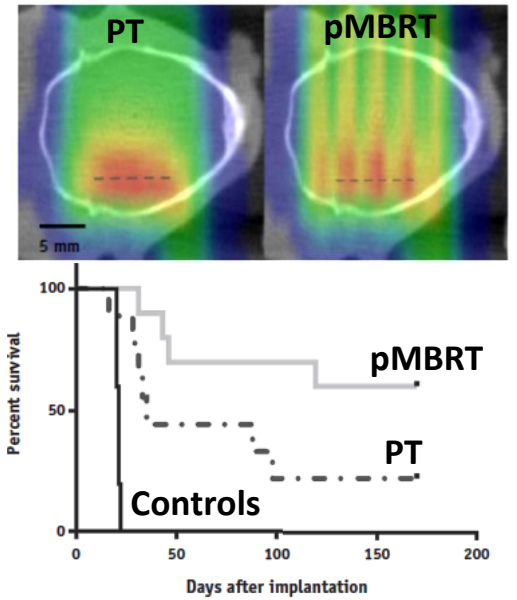
→ Objectives of both platforms: enable within 3 years FLASH-p/α irradiation, with modeling and dosimetry support, to start biology experimental program.

Spatially fractionated radiotherapy (SFR)

Institut Curie: Y. Prezado et al. ; LPSC: R. Delorme ; Work initiated at IMNC

➢ Proton minibeams (pMBRT): toward clinical trials

- Remarkable normal-tissue tolerance, tumor-control similar or better PT *(Prezado et al. 2017,18,19, ERC)*
- Systematic characterization of parameters of influence:
  - Temporal fractionation, multiple beam incidence
  - Full or partial fractionation
  - Mechanism in normal & cancer cell/tissue/microenvironnement
- Adaptation of dose-calculation and protocols for clinics



➢ Exploration of heavy-ion MBRT (^{12}C, ^{16}O, ^{20}Ne, ^{40}Ar, ^{56}Fe)

- *In vitro* and dosimetry experiments planned in Japan (NIRS)
- Biological dose modeling of heavy-ion MBRT (G4-DNA/Gate + MKM or NanOx)

➢ Exploration of VHEE RT

- Evaluation of dosimeter's response under e- beams (high dose rate & Laser-plasma)
- *In vitro* experiments planned in VHEE Laser-plasma beams *(LOA collab.)*
- Monte Carlo characterization of VHEE beams and potential use for SFR

Hadronbiology & Targeted therapies (Nanoparticles)

IP2I – Team PRISME- RCM: C. Rodriguez-Lafrasse et al.

(cf. C. Rodriguez-Lafrasse presentation)

➢Hadronbiology & Innovative RT:

- **Produce biological data for simulation** implementation (*NanOx*) for ion-beams (p, α, ^{12}C), BNCT, targeted nuclide therapies. *(cf. M. Beuve presentation)*
- **Demonstrate ion-beam superiority to conv. RT** at molecular level: **new paradigm "Bombardier furtif" effect** *(Wozny et al. 2019)* **potentially explaining RBE of ions**:
  - Confirm this effect with other beam and cell types
  - Study protein metabolism response (stress granules, proteasome, reticulum stress)
- Inter-cellular signaling (bystander effect, exosomes)
- Biological effects of the combination of immunotherapy and hadrontherapy

➢Nanoparticle radiosensitization:

- Development of **new generation of AGuIX® NP** *(Phd thesis underway)*
  - Influence of high-Z element modification (Bismuth / Yttrium)
  - Surface modification (Nanobodies)
- Study of radiosensitization mechanisms implying extra-nuclear cell organelles (mitochondria, endoplasmic reticulum…)

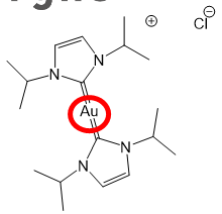
➢Prediction of tumor response to radiotherapy

Nanoparticles and Mitochondria

LPC-Clermont-pôle PPSE: P. Vernet et al.

➢ Development of new NP targeting mitochondria:

- Target mitochondria through biochemical properties *(N-heterocyclic carbenes)* and deliver gold into mitochondria



Develop new nanoparticles

- Not limited to high Z compounds
- Combination of **various metals compounds**
  * Doped metals

Develop new functionalization

- To innovate in chemical functionalization
- To **target specific cellular compartments**
- To **follow** in cellulo location

Explore new combination of NP and ionizing radiations

- **NP and hadrontherapy**: Understand the observed enhancement
- Various energies : **3 MeV to 230 MeV**

Modeling dose deposit in subcellular compartments

- **Combine super-resolution microscopy, chemical imaging** (AIFIRA, ESRF) **with dose deposit modeling**
- Effect of chemical induced reactions
- Effects of induced modifications of the NP (ligands,…..)

Partnership between various scientific fields: chemists; physico-chemists; physicists; biologists

Metal-oxide Nanoparticles

CENBG – team IRIBIO: H. Seznec et al. *(cf. P. Barberet presentation)*

➢ Understand mechanisms of radiation on metallic/oxide NP :

- *In-vitro* evaluation of toxicity and NP-induced radiosensitization: Need for **quantification of intracellular localization of NP** as a function of NP-type and cell-type

➢ Development of irradiation and analysis tools on AIFIRA platform:

- Specific protocols for sample preparation
- **Irradiation**: microbeam (1.5 µm) of 3 MeV proton
- **Micro-chemical analysis**: element quantification, cell homeostasis, Physico-chemical alterations
- Provide data for code parametrization & validation (Geant4)



➢ Interest in studying and develop new probes:

- E.g. extra-nuclear cell mechanisms analysis (*as mitochondria, reticulum stress)*

➔ Common developments/interests with LPC-Clermont and IP2I

- Quantification and localization of NPs (NP-type/cell line)
- Radiosensitization NP function of Z/surface functionalization
- Study NP-induced extra-nuclear mechanisms
- Provide data for code parametrization & models

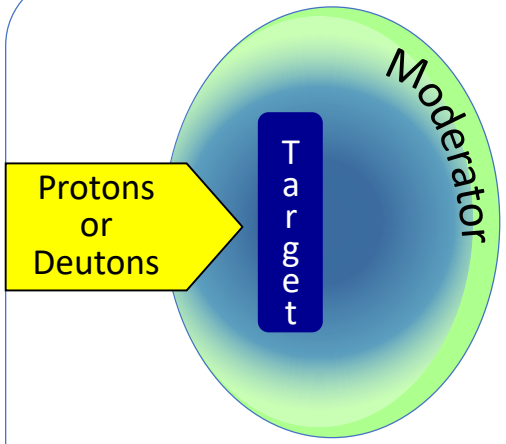
} Toward standardized database

Accelerator-based Neutron Capture therapy (AB-NCT)

D. Santos, V. Ghetta, M. Hervé (PhD), J. Giraud, J-F. Muraz, N. Sauzet, LPSC (IN2P3)-Grenoble, J-L. Coll, L. Sauzet, IAB (Inserm)-Grenoble

➢Work in Progress:

- Liquid lithium target (Patent FR1906353)
- Be target developed with innovative internal regeneration: thermic tests
- Development of an optimized moderator
- Characterization of the neutron fields produced (**MIMAC-FastN**)
- New proposed epithermal limits optimizing based on MC simulations
- Active phantom for BNCT and PBFT data measurements



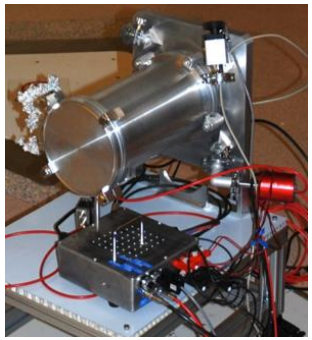
Thermal neutron field at tumor depth
> 10^9 n/cm^2/s

Define a device that produces low energy neutrons and continuously supports a power of 15-30 kW over a few cm2. The best candidates are:

LITHIUM + Proton from 1,9 MeV
BERYLLIUM thin layer + Deuton 1,5 MeV

➢Medium/long term scientific objectives:

- Demonstration of the robustness of the targets developed (Be and Liquid Lithium)
- Validate the dose deposited by an integrated mass of ^{10}B in the active phantom after the developed moderator
- Contribution to the definition and construction of an AB-BNCT demonstrator in France.



MMAC-FastN

Experimental measurements of PBFT reaction

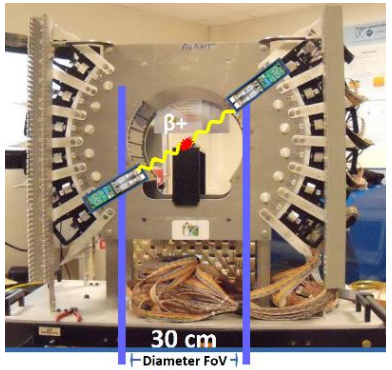
Common work between LPC-Clermont (G. Montarou, F. Martin) and LPSC (D. Santos et al.)

➢ Problem of differences between exp. And simulated data:

- Radiosensibilization demonstrated on ^{11}B-charged cells (Cirrone et al. 2018)
- Production reaction alphas poorly understood / implemented in MC codes

➢ Preliminary exp. performed at CAL (Nice, p 65 MeV):

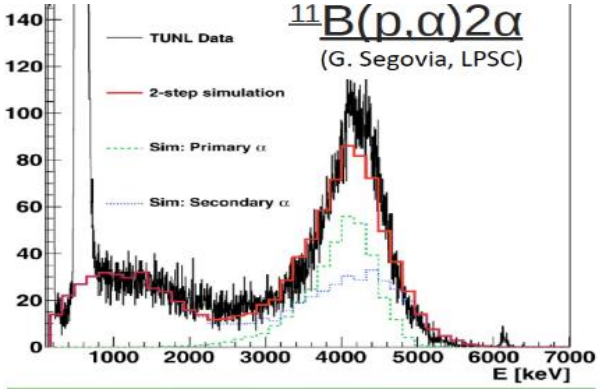
- Try to detect the prompt-gamma emission (719 keV) with the **DPGA** detector *(LPC-Clermont) :* non conclusive results



➢ Mid-term perspective:

- Improvement of reaction simulation p + ^{11}B -> 3 α and microdosimetric local dose calculation
- Experimental measurement of α production rate using **MIMAC-FastN** active phantom
- Experiment with MIMAC-FastN+DPGA → Precise measurement of the Bragg peak in target

Modeling of α spectrum



Conclusions

- Several in2p3 teams work at improving innovative RT approaches based on:
  - New particle type: hadrontherapy, VHEE
  - Dose-delivery modes: FLASH, SFR
  - Targeted therapies: Nanoparticles, BNCT
- A common motivation: go toward radiobiological and clinical applications, through several developments:
  - Irradiation, instrumentation and analysis tools: allowing radiobiological experiments
  - Understanding of physical, chemical and biological mechanisms: experiments and modeling
  - Characterizing and optimizing new approaches
- ADOC: proposed new MP to structure projects under these objectives
  - Already common perspectives identified, still work to do on structuration
- Multidisciplinary activities with multiple competences:
  - Experimental and numerical physics, biology, chemistry, clinics…
  - Need for recognition of these multidisciplinary activities by IN2P3

Backup

Les grandeurs physiques nécessaire pour la dosimétrie

- Plusieurs grandeurs physiques sont nécessaires pour la dosimétrie :

Dose (Gy)= Ø [cm^{-2}]×S(E) [$MeV.cm^2.g^{-1}$] ×1,6×10^{-10}
(définition de la dose physique)

Ø: la Fluence (déterminée par mesure)

S(E): le pouvoir d'arrêt (déterminé souvent par simulation)

Le **parcours** des ions dans la cible irradiée (déterminé par mesure et/ou simulation)

- Les méthodes de mesure conventionnelles sont adaptées pour les faisceaux médicales de haute énergie.

- Dans le cas de faisceau de basse énergie (un à quelques dizaines de MeV/u), ces méthodes sont peu précises et perturbent le faisceau incident.

Mesure du flux incident en ligne + profil

- Détecteurs transparents (quelques µm équivalent d'eau) sont nécessaires à développer (diamants, polymères…?).

Mesure du parcours

- Besoin de mesurer le parcours avec une précision de l'ordre de µm
- Développement d'un système de détection des rayonnements de freinage et des photons UV-visible émis par le milieu irradié (en cours).

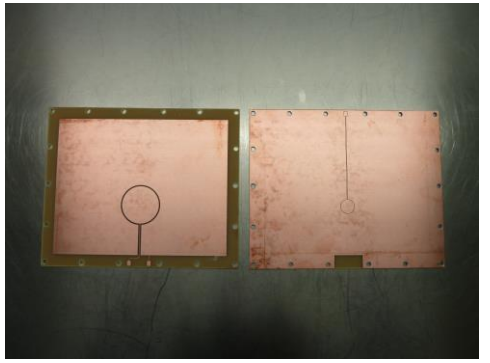
Mesure du TEL dans les tissus biologiques

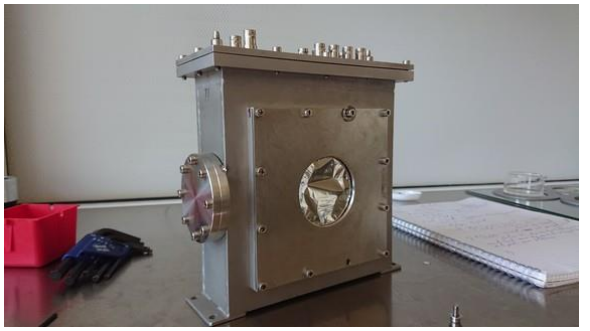
- Le TEL peut être mesuré par exemple avec un semi-conducteur ultra mince puis ramené à l'eau à travers l'épaisseur équivalent.
- Il est intéressant de ramener la dose au milieu biologique:
  - Une connaissance parfaite des mécanismes de l'interaction des ions avec les molécules biologiques, comme des bases de la molécule d'ADN, est nécessaire.
  - Il est important de mesurer, avec des faisceaux d'ions dans la gamme keV – à quelques 10 MeV/u les sections efficaces d'ionisation totales avec les molécules d'intérêt biologique

DOSION:

- Activités 2018: Vers les hautes et très hautes intensités

  - Développement d'une nouvelle chambre, prévue pour les très hauts débits :
    - Chambre intégrale avec gap réduit (800 microns contre 3 mm)
    - dessinée pour des flux pouvant atteindre 5 Gy dans un pulse de 2,2 µs
    - Développement et tests menés auprès du Kinetron d'Orsay, avec de premiers résultats encourageants





  - Une éventuelle suite sera réalisée au sein d'un nouveau projet
    - Intégration dans un nouveau MP plus clinique?

Radiobiologie Cellulaire et Moléculaire
Pr Claire Rodriguez-Lafrasse
UMR 5822 – IP2I

Hadronbiologie

Irradiations **protons** 3MeV : Radiograff ; **alpha** : ARRONAX, Nantes ;
Ions carbone : GANIL, Caen - INFN, Italie- NIRS/HIMAC, Japon

Données biologiques pour la simulation (Nanox®) et dosimétrie biologique

Compréhension de l'EBR : spécificités de la réponse tumorale aux ions de TEL élevé (paradigme de l'effet « bombardier furtif »)

Physique Cancer ClinNanox, Cancéropôle CLARA, LabEx PRIMES

Radiosensibilisation par nanoparticules

Preuve de concept de l'effet radiosensibilisant des NP AGuIX® sur culture cellulaire 3D et souris nude avec xénogreffe tumorale de chondrosarcome *ANR CHONDRAD*

Prédiction de la réponse tumorale à la radiothérapie

Culture *ex-vivo* de biopsies de tumeurs ORL et détermination de biomarqueurs (profils d'expression génique Nanostring®) ;
Isolement caractérisation des cellules tumorales circulantes. *Cancéropôle*

2015 -2019 : 31 Articles / 54 Communications / 3 Thèses

Perspectives

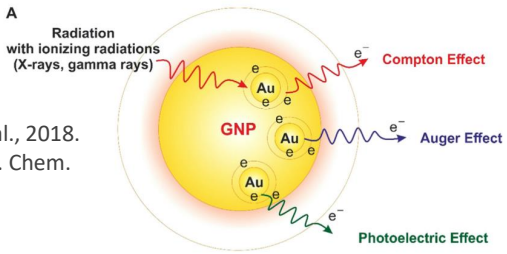
- **Radiothérapies innovantes**
  - Données biologiques pour la simulation (protons, hélium, ions carbone, BNCT, targeted-radionuclide therapies)
  - Paradigme du bombardier-furtif : réponse du métabolisme protéique (granules de stress, protéasome, stress du réticulum)
  - Signalisation inter-cellulaire (effet bystander, exosomes)
  - Effets biologiques et pré-cliniques de la combinaison de l'immunothérapie à l'hadronthérapie
- **Radiosensibilisation par nanoparticules**
  - Développement d'une nouvelle génération d'AGuIX®
    - Modification du cœur (Bismuth / Yttrium)
    - Modification de la surface (Nanobodies)
- **Prédiction de la réponse tumorale à radiothérapie**
  - Rôle prédictif des cellules tumorales circulantes dans la non-réponse au traitement des tumeurs ORL
  - Etude randomisée ions carbone/ radiothérapie standard dans une cohorte de 250 patients atteints de sarcome : étude ancillaire radiobiologique (expression de biomarqueurs protéiques et géniques)

Radiosensitization through nanoparticles

Key questions for radiosensitization development

How to specifically target tumor cells?	How to increase locally dose deposit?	What would be a good subcellular target for radiosensitization	What is the key mechanism of this radiosensitization?

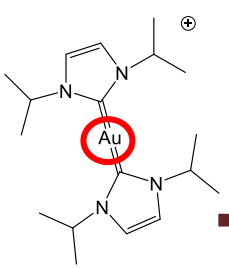
Some answers



Borran et al., 2018. Rad. Phys. Chem.

- Choice of high Z compounds → increase dose deposit during X rays treatment
- Proper choice of size → to promote EPR effect
- Targeting nucleus or structure with key molecules such as DNA
  - Interest for mitochondria

N-heterocyclic carbenes



Target mitochondria through biochemical properties and deliver gold into mitochondria

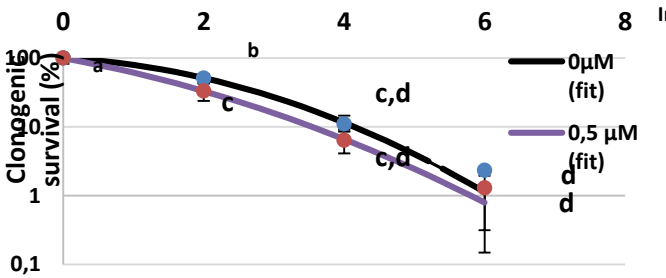
Taggart *et al. Cancer Nanotechnology* 2014, 5:5
http://www.cancer-nano.com/content/5/1/5

Cancer Nanotechnology
a SpringerOpen Journal

RESEARCH Open Access

The role of mitochondrial function in gold nanoparticle mediated radiosensitisation

Laura E Taggart[1], Stephen J McMahon[1], Fred J Currell[2], Kevin M Prise[1] and Karl T Butterworth[1*]



Potential of mitochondrial targeting to improve radiosensitization

What next?

Key points to focus on:

Develop new nanoparticles

- Not limited to high Z compounds
- Combination of various metals compounds
  * Doped metals

Develop new functionalization

- To innovate in chemical functionalisation
- To target specific cellular compartments
- To follow in cellulo location

Explore new combination of NP and ionizing radiations

- NP and hadrontherapy
  * Understand the observed enhancement
- Various energies : 3 MeV to 230 MeV

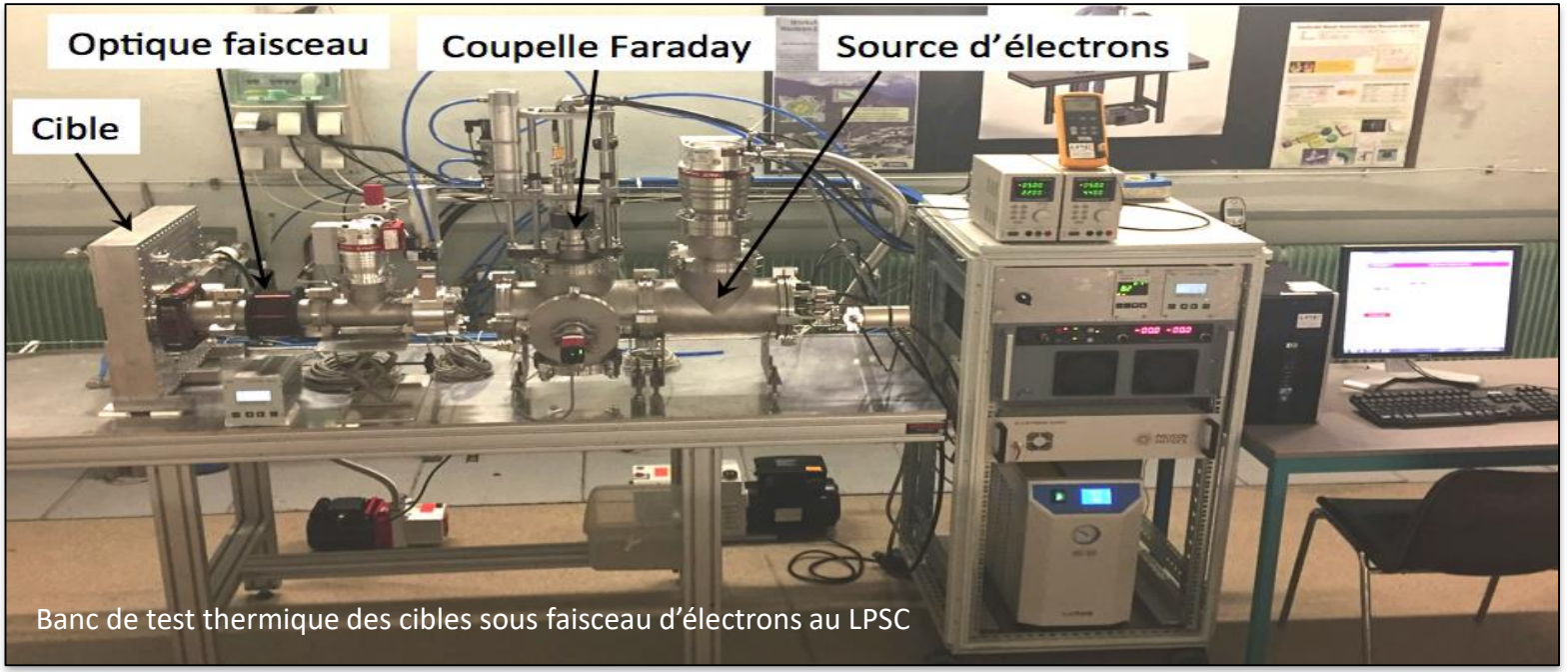
Modeling dose deposit in subcellular compartments

- Explore the local enhancement dose from physical reactions
- Combine super-resolution microscopy, chemical imaging (AIFIRA, ESRF) with dose deposit modeling
- Effect of chemical induced reactions
- Effects of induced modifications of the NP (ligands,.....)

Partnership between various scientific fields: chemists; physico-chemists; physicists; biologists

Travaux encours de développement actuellement au LPSC (IN2P3):

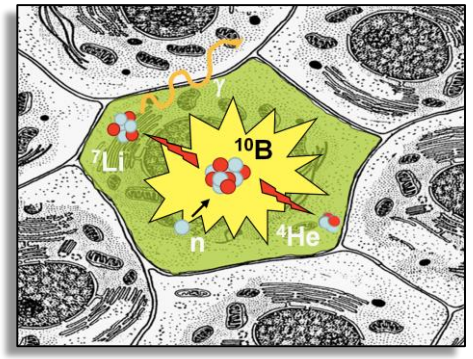
- Cible lithium liquide (Brevet FR1906353)
- Cible Be en couche mince avec régénération interne
- Développement des dispositifs de modération adaptés (Beam Shape Assembly (BSA))
- Caractérisation des champs neutroniques produits au niveau de la cible et après modération (MIMAC-FastN)
- Nouvelles limites épithermiques proposées optimisant la dose sur la tumeur et minimisant la dose secondaire
- Fantôme actif pour la BNCT et la PFBT (Proton Fusion Boron Therapy)



Banc de test thermique des cibles sous faisceau d'électrons au LPSC

Thérapies par Capture Neutronique basées sur Accélérateur (AB-NCT)

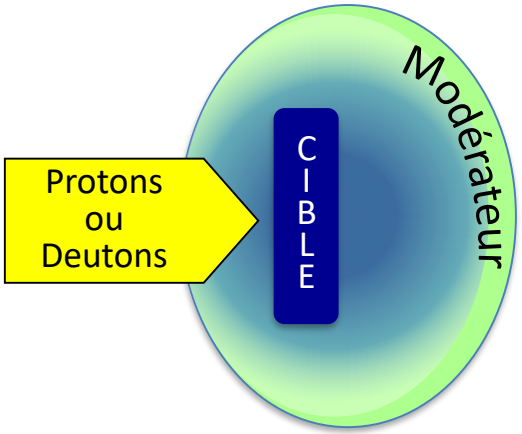
D. Santos, V. Ghetta, M. Hervé (PhD), J. Giraud, J-F. Muraz, N. Sauzet, LPSC (IN2P3)-Grenoble, J-L. Coll, L. Sauzet, IAB (Inserm)-Grenoble



Isotope naturel du Bore (20%) fixé sur les cellules cancéreuses par BPA ou BSH

$^{10}B + n_{th} \rightarrow [11B]^*$

- 6 % → $^{4}He + {}^{7}Li$ (2,79 MeV)
- 94 % → $^{4}He + {}^{7}Li$ (2,31 MeV) + γ 0,48 MeV



Champ neutronique thermique au niveau de la tumeur
> 10^9 n/cm^2/s

Définir un dispositif qui produise des neutrons de basse énergie et supporte en continu une puissance de 15-30 kW sur quelques cm^2.
Les meilleurs candidats sont :

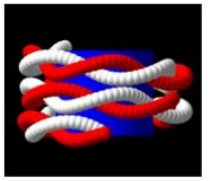
LITHIUM + Proton à partir de 1,9 MeV
BÉRYLLIUM couche mince + Deuton 1,5 MeV

Objectifs scientifiques à moyen et long terme :

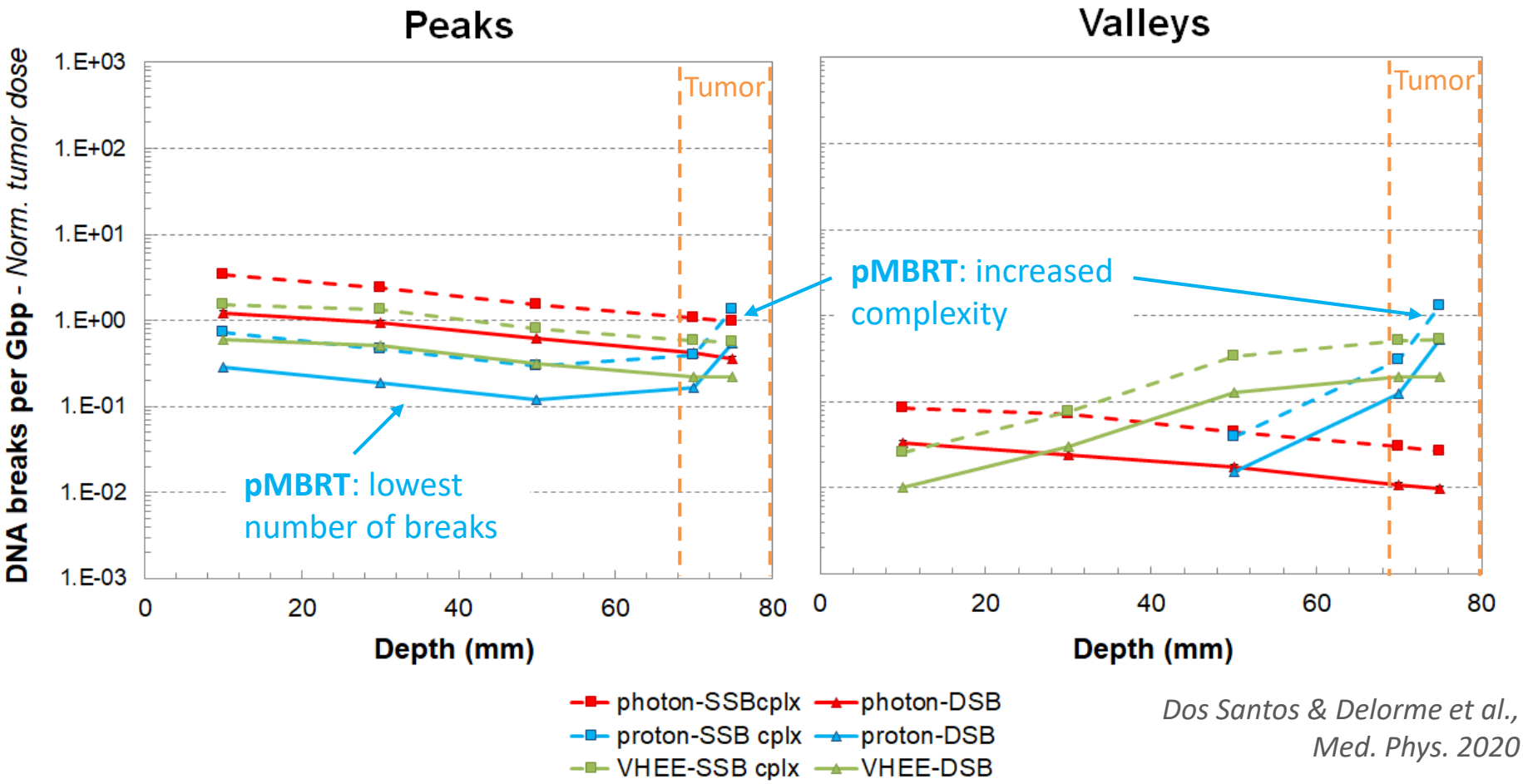
- Démonstration de la robustesse des cibles développées (Be et Lithium liquide)
- Développement des modérateurs innovants
- Validation complète de la dose déposée par 100 µg de ^{10}B en utilisant les modérateurs développés et le fantôme actif fourni par MIMAC-FastN
- Contribution à la définition et à la construction d'un démonstrateur d'AB-BNCT en France en collaboration avec les équipes intéressées (physiciens, biologistes, chimistes, médecins) qui cherchent à pratiquer la BNCT comme radiothérapie innovante et à développer de nouveaux vecteurs du bore.

Nanodosimetry: direct DNA for RX, VHEE and p MBRT

Number of DNA breaks normalized for a same dose of 1 Gy at 7.5 cm:

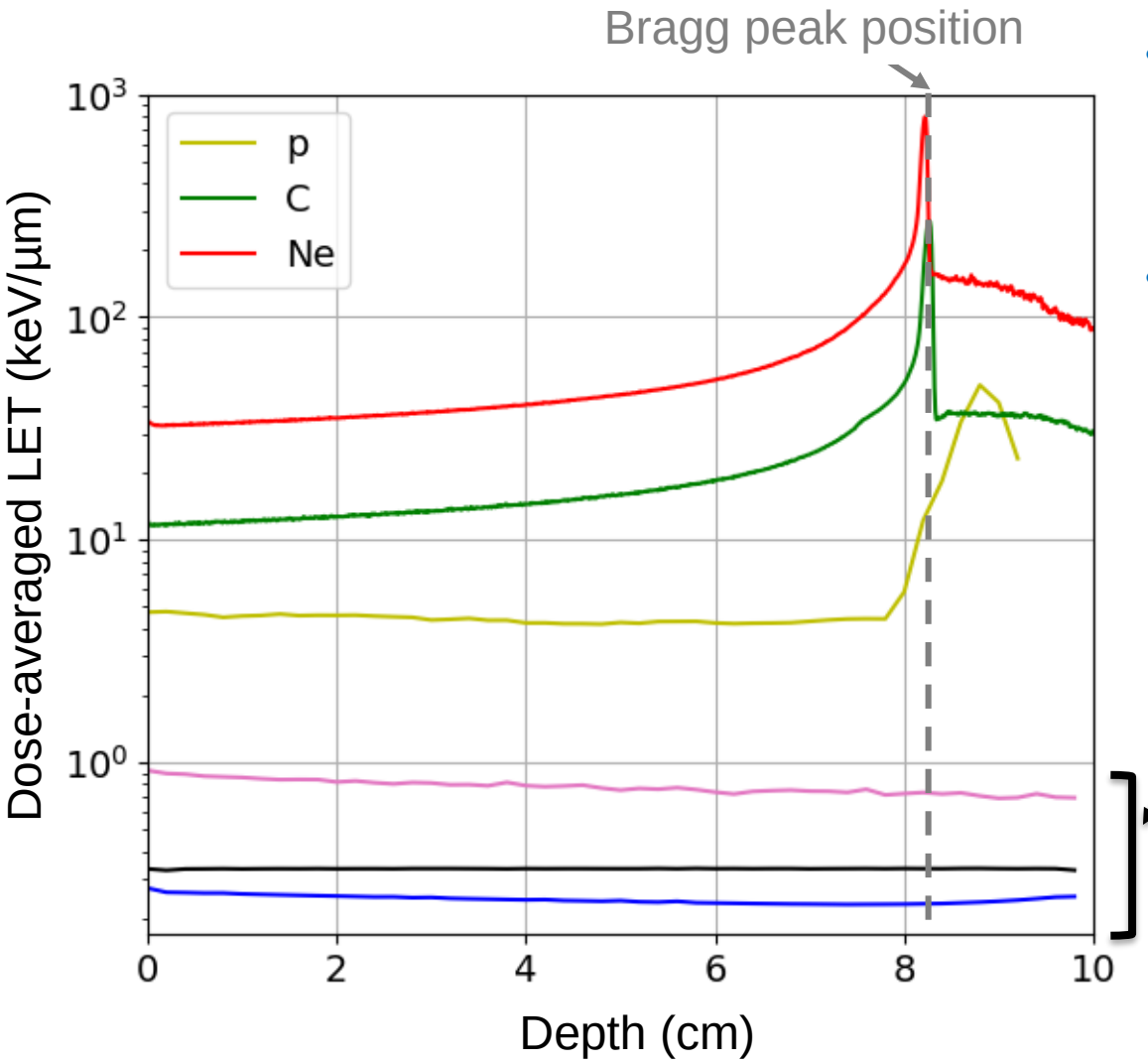


➔ **SSBcplx** (1.5-5%) and **DSB** (0.5-2%) **maximum at proton Bragg peak.**

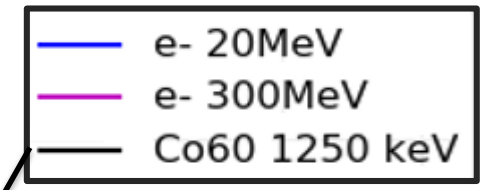


Dos Santos & Delorme et al., Med. Phys. 2020

Dose-averaged LET: $\overline{L_d}$



- *VHEE located between the proton and photon/low-energy e- in terms of $\overline{L_d}$*
- *The $\overline{L_d}$ values for VHEE (and e-/photons) constant with depth in contrast to ion beams.*

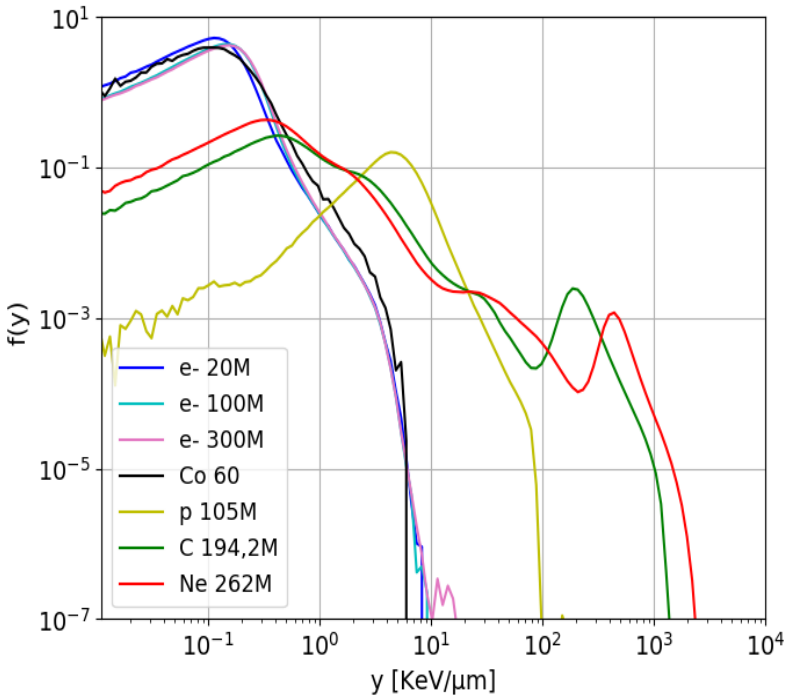


Entrance comparative factors:

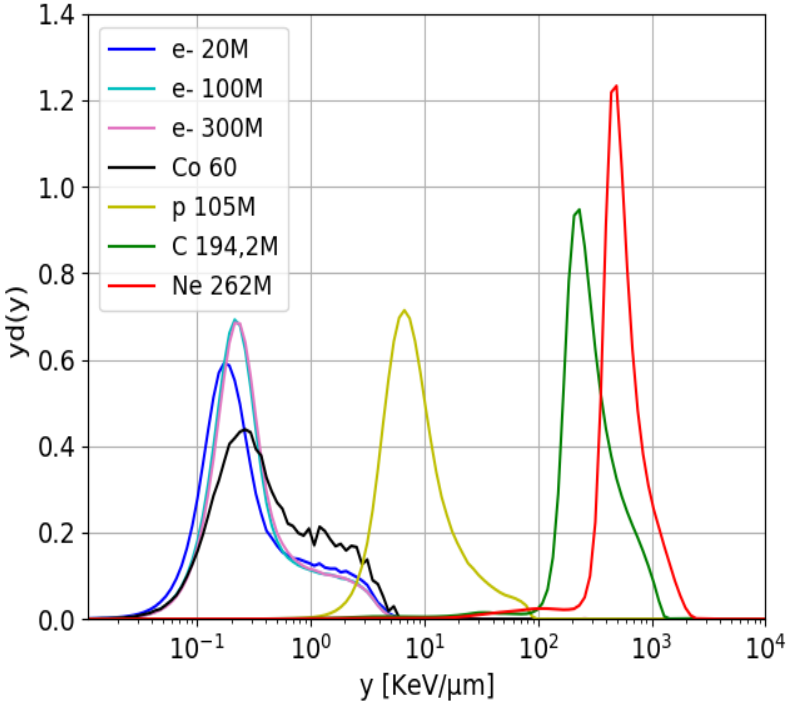
VHEE / Carbons = 0,05
VHEE / Protons = 0,2
VHEE / e- 20MeV = 3,2
VHEE / Photons = 2,6

Microdosimetric approach: $f(y)$ and $yd(y)$

$f(y)$ spectra at Bragg-peak position : frequency of occurrence of events



$yd(y)$ spectra at Bragg-peak position: Contribution of events to the dose



Aggressiveness of events at the cell nucleus scale

No significant differences between photons and all energies of electron beams with the microdosimetry formalism.

→ *Needs for experimental data…*

Spatial Fractionation of Dose

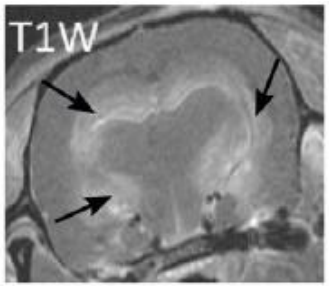


Microbeam radiation therapy (25-100 µm beams) born at synchrotrons

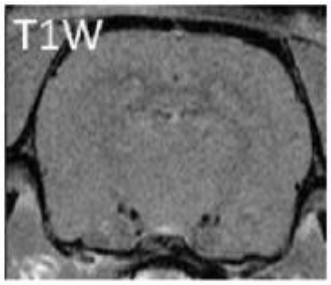
Toward "clinics" using Mini-Beam Radiation Therapy (MBRT, 400-700 µm beams)

- ✓ **Experimental evidences with Photon MBRT:** Prezado et al.
  - Remarkable increase of the rat brain dose tolerance (up to **100 Gy/session**), against lethal dose at **20 Gy** in standard irradiation → 2015, 2017
  - Life span increase in 9L gliosarcoma-bearing rats, interlaced MBRT (100 Gy) →2012
- ✓ **Experimental evidences with Proton MBRT*:***
  - Remarkable tissue-sparing with pMBRT irradiation →Pr2017
  - Tumor regression on RG2 glioma bearing rats with fully fractionated pMBRT 2018

Standard protontherapy (~25Gy)



Proton MBRT (~25Gy)



Non-irradiated

