Toulouse-Excellent Practice in Radiation Oncology and research

Pr Elizabeth Cohen-Jonathan Moyal MD, PhD

Head of the Radiation Oncology Department IUCT-O

Head of the INSERM RADOPT Team -CRCT-Toulouse

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Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

CRCT Centre de Recherches en Cancérologie de Toulouse ONCOPOLE

Radiation Oncology Department of Oncopole Claudius Regaud
Accelerators adapted to each disease or situation

3 Tomotherapies including 1 Radixact
Adaptive radiotherapy

2 Truebeam Novalis: brain Stereotactic irradiation (Brain; moving targets, cardiac..)

- Comparative dosimetry studies performed for the best choice of accelerator

2 Halcyon

- >3000 patients/ year
- 60 clinical trials)
- 8 Bunkers
- All brachytherapy technics

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Team RADOPT

E. Cohen-Jonathan Moyal

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Radiotherapy Optimization

Glioblastoma stem cells resistance

Study of brain tumors methylome profile

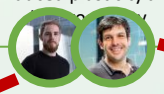
E. Uro-Coste
Y. Nicaise

Impact of pesticides exposure (SDHI) on chemo- radio- resistance

A. Le Naour
E. Abbey

A. Hagimont

Role of metabolism in Glioblastoma stem cells radio-induced plasticity and



A. Lemarie
T. Maillet

Impact of pesticides (SDHI) on mitochondrial metabolism of neural cells

Radio-induced trans-differentiation of Glioblastoma stem cells into endothelial-like

M. Courtade-Saïdi
S. Evrard
F. Arnauduc

Invasion capacity of Glioblastoma stem cells : analysis of involved mechanisms

C. Eva

C. Delmas

A. Modesto

Predictive response to immunotherapy and radio-chemo- therapy in esophageal carcinomas

Biomarker determination in patients treated by immunotherapy and radiotherapy

FGFR1 : new therapeutic target in Glioblastoma treatment

Glioblastoma stem cells resistance to Tumor Treating Fields (TTF)

P. Deshors
V. Gouazé-Andersson

Metabolic shift and radio-resistance of glioblastoma stem cells: patient validation

S. Ken
Z. Kheil

Artificial Intelligence Machine Learning

A. Berjaoui
L. Robinet

Prediction on MRI and biological multi-data of therapeutic response to radiotherapy, immunotherapy and TTF

Optimization of machine learning algorithms for image registration in radiotherapy

Ancillary Studies

Translational Research

L. Vieillevigne
A. Delbaere
H. Cherid

Modeling biological and physical effects of Ionising radiation & TTF at cellular and sub-cellular scales

Optimization of absorbed dose determinaton in external radiotherapy

L. Simon
S. BLas

Modeling of treating devices used in external radiotherapy

Medical Physics - Imaging

Esophageal Carcinomas

ToNIC Toulouse NeuroImaging Center UMR1214

A. Laprie Belongs to Team Devin Imaging, Neurotoxicity and Paediatric RT

INSTITUT NATIONAL DU CANCER · ARTC Association pour la Recherche sur les Tumeurs Cérébrales · Cancéropôle Grand Sud-Ouest · Fondation Recherche Médicale · Fondation ARC pour la recherche sur le cancer · arc · INSTITUT NATIONAL DU CANCER · Incyte · LA LIGUE CONTRE LE CANCER · SAINT EXUPÉRY · calmip · GEANT4-DNA · novocure · AstraZeneca · BAYER

Research and Innovation, Care, Quality

INSERM Team
Radiation Optimization
CRCT
(Biology, physics,TTFields
imaging, AI)

Imaging,
Neurocognition,
team1
TONIC

Radiation Oncology
department

Physics department

Quality
Weekly
Multidisciplinary
team meeting

Written radiotherapy and physics protocols for each disease

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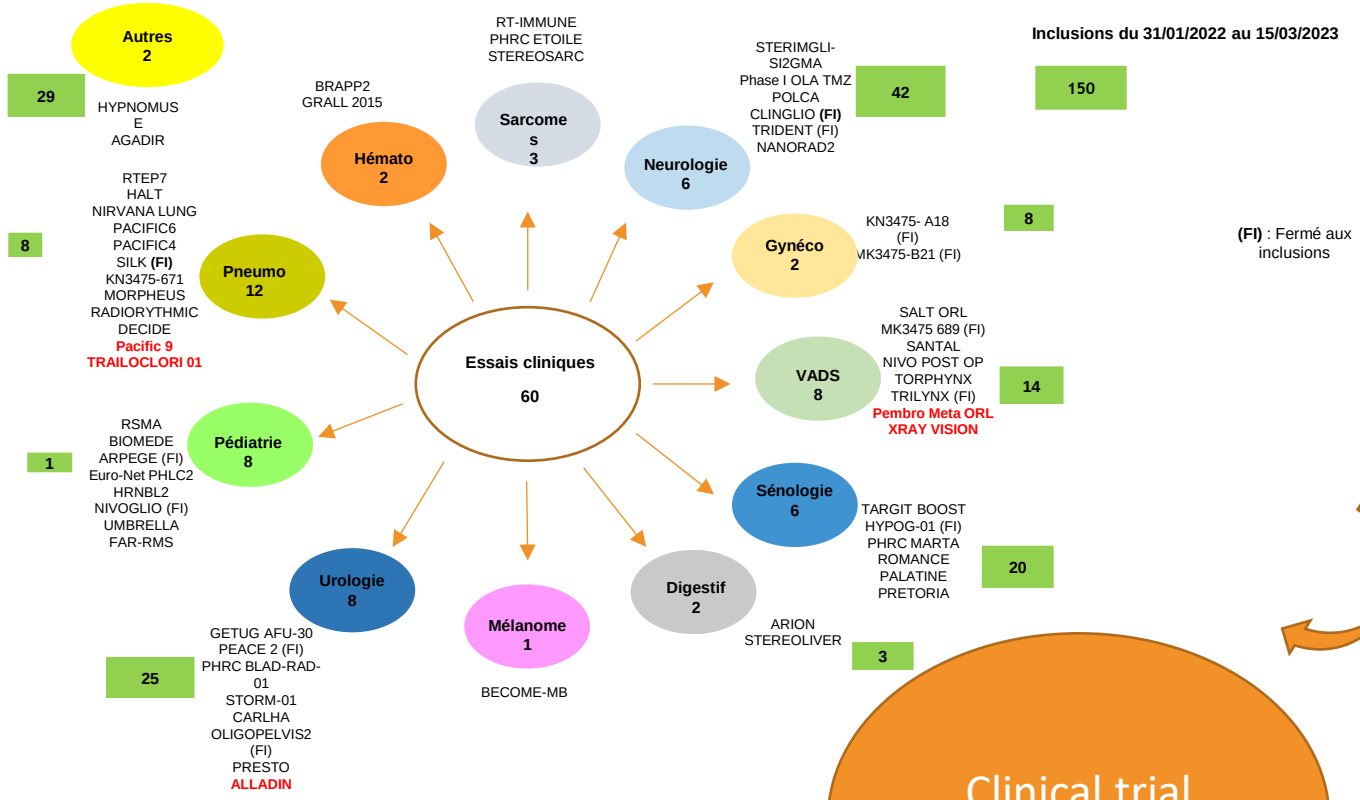
Clinical trials 2022

Radiation Oncology department



Physics department

Clinical trial Departement

1 Clinical research associate in the Radiation oncology department
(S Ochoa) in charge of all the technical duties for RT clinical trials and research (dosimetry , imaging transfers, doses in Crf..)

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Research in the Radiotherapy Departement IUCT-Oncopole

Overcoming biological tumor radioresistance (Team RADOPT, CRCT)

Better define the target to be irradiated (Teams RADOPT and TONIC)

Optimal dose delivery in heterogeneous systems Treatment modeling

Optimizing radiotherapy and patient care

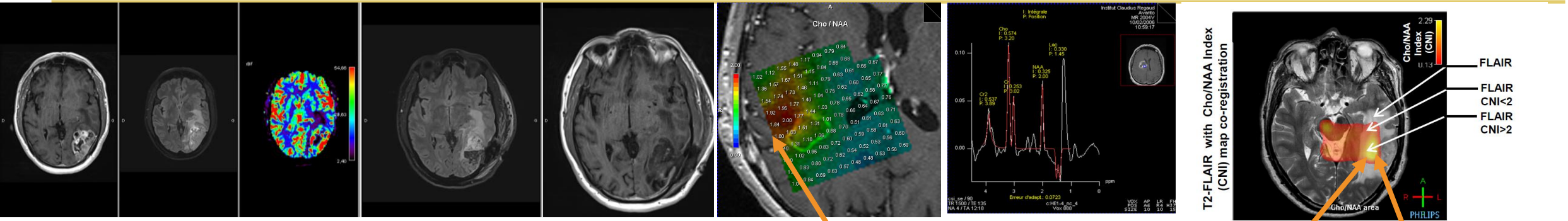
Assessing and reducing the toxicity of radiotherapyT (TONIC team)

Prediction of therapeutic response using biological and multi-data imaging analyses (Collaboration IRT Saint Exupéry; IRIT)

Machine failure prediction

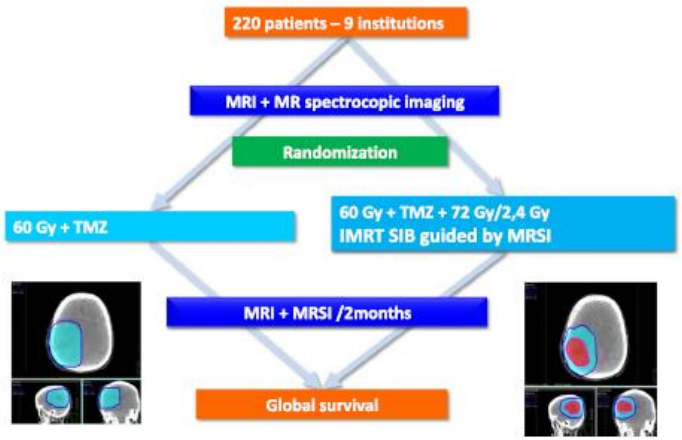
Optimizing scheduling of patients appointement on the machines

Better define the target to be irradiated; reduce toxicity

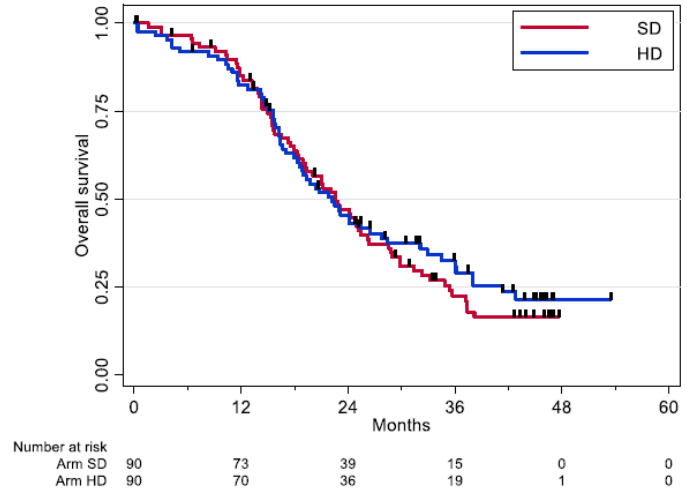


Predictive of the site of relapse after radiotherapy

Laprie…;Co*hen-Jonathan* Moyal Int J Radiat Biol Phys 2008



Laprie …Cohen-Jonathan Moyal BMC 2019



Laprie…Cohen-Jonathan Moyal , Neurooncology in revision 2023

Why?

Metabolic zone enriched in GB stem cells?

GB stem cells plasticity after radiotherapy ?

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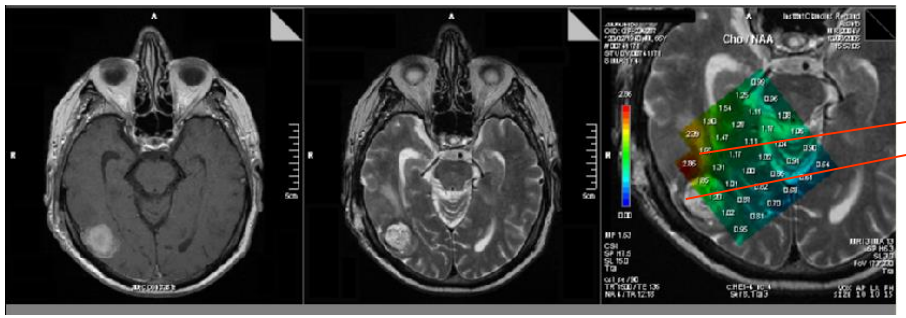
Understanding the mechanisms by which stem cells adapt to radiotherapy and predicting the relapse pathway of patients undergoing treatment

STEMRI trial

Stem cells: 

- Is the metabolic zone on MRI spectroscopy enriched in GBM stem cells?
- 16 patients; biopsies and resection guided by multimodal MRI and MRI spectroscopy



- Neurosphere formation kinetic
- RNASeq on bulk of each sample and on GSC extracted
- Stem cell characterization
- Radiosensitivity
- Co-registration of all MRI sequences (perfusion, diffusion, spectro) with tumor samples localizations

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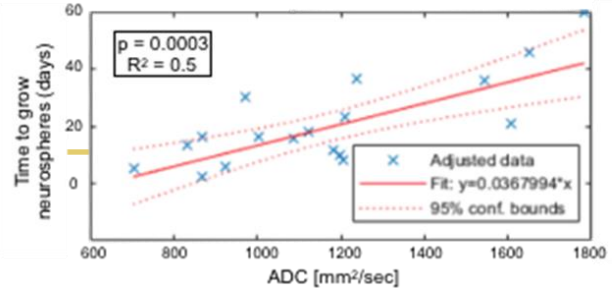
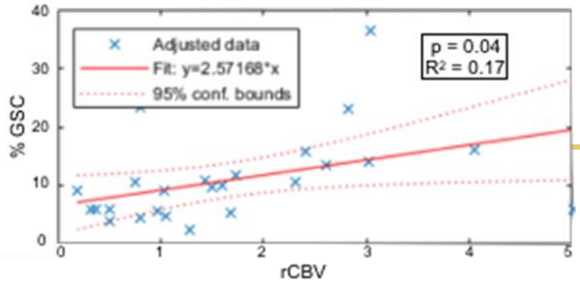
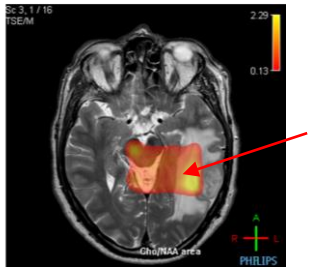
Enrichment in glioblastoma stem cells defined by by MRI spectroscopy and multimodal imaging





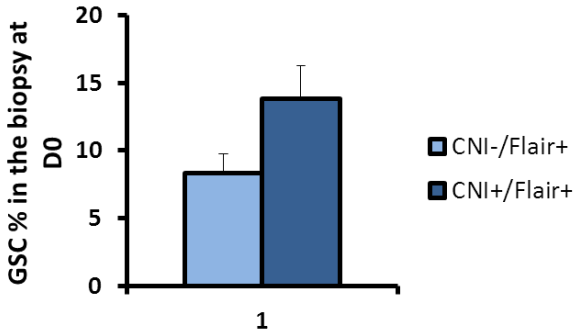
(Duval et al, Cancers 2022)

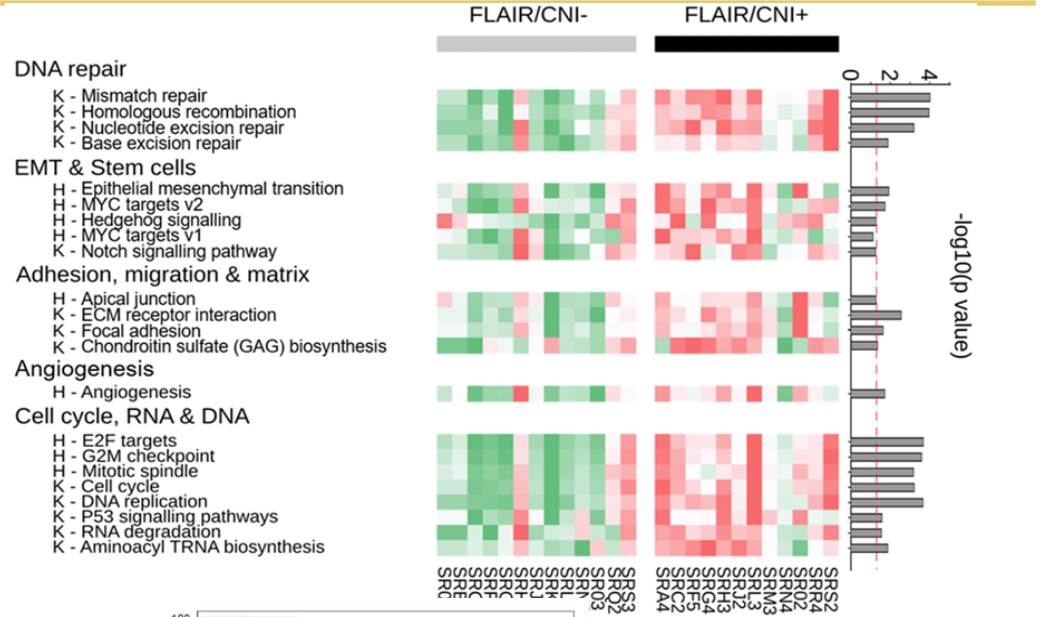


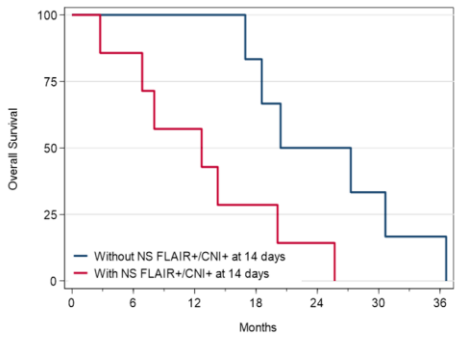
Inflitrative area : FLAIR

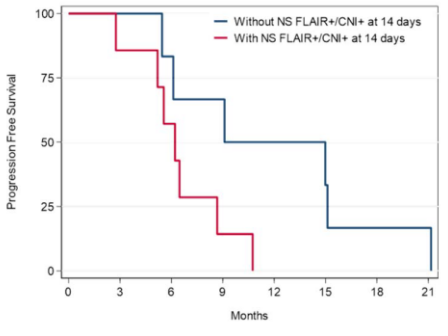
CNI-: Choline/NAA<2
CNI+: Choline/NAA>2

CNI+ metabolic zone : enriched in GSC





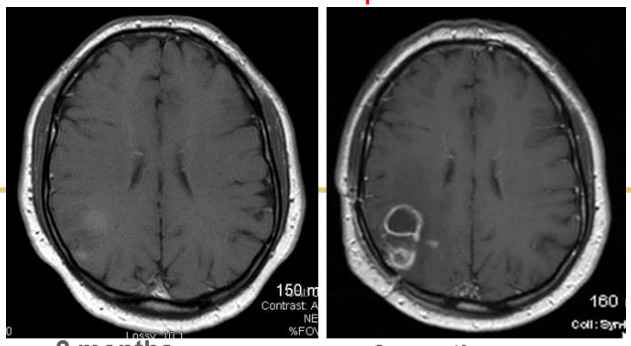




(Lemarié …Cohen-Jonathan Moyal , Science Advances in revision)

Radiation-induced plasticities mechanims

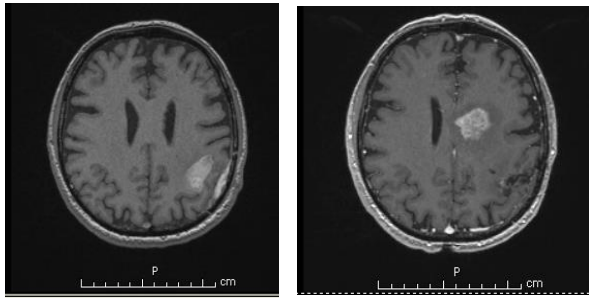
Local relapse



2 months after radiotherapy

9 months after radiotherapy

Distant Relapse

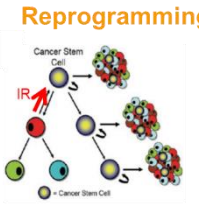


2 months after radiotherapy

8 months after radiotherapy

- Radiation-induced dedifferentiation through a Metabolic shift

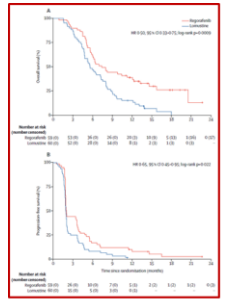
(Dahan et al, Cell death and Disease 2014)



National Program MSrGB

- Radiation-induced trans-differentiation into endothelial cells ? (Tie2; inhibited by Regorafenib)

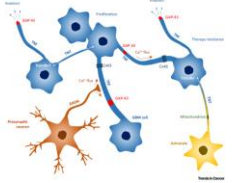
(Deshors et al, Cell Death Dis 2019; Deshors et al Cancers 2022)



(Lombardi, Lancet Oncol 2019)

- Radiation-induced GSC communication through Tunelling nanotubes

(Pinto G et al, Biochemical Journal 2021
Collab with Pr Zurzolo, Institut Pasteur)



- Radiation-induced migration of glioblastoma stem cells?

(Malric et al. Mol Cancer Res 2018;, Kowalski-Chauvel Cell Death Dis 2018; Boyrie et al, Oncotarget 2019; Kowalski-Chauvel et al Cancers 2020; Lacore et al, Cells 2022)

(Khalifa et al, Radiation Oncology 2017
Attal et al, J Neurooncology 2018)

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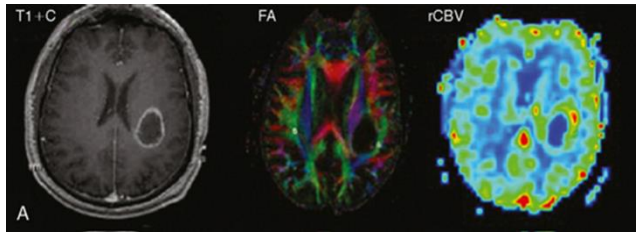
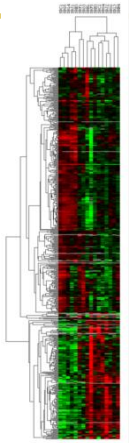
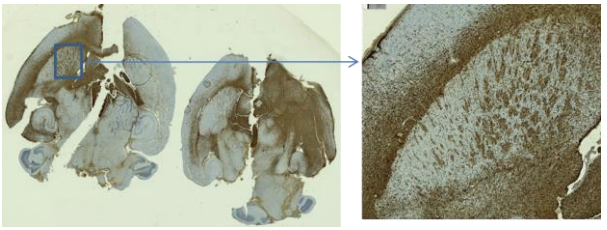
Could we predict such pattern of recurrence/agressivity and the biological pathway involved in such relapse pattern ?

On all the data from STEMRI trial

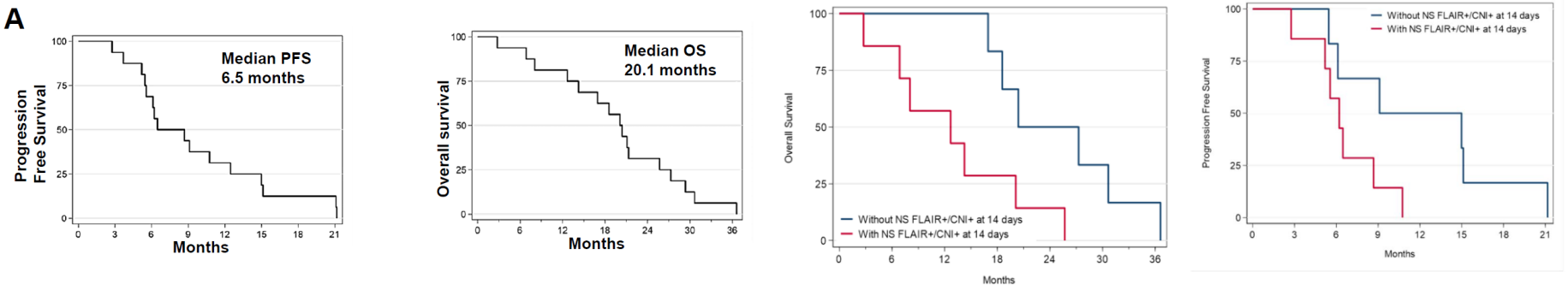
- **Bulk and stem cells RNA seq data**





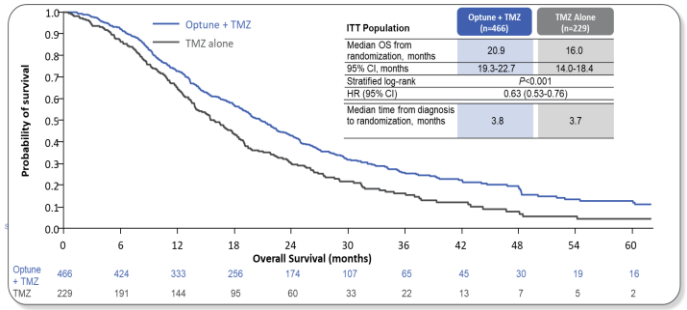


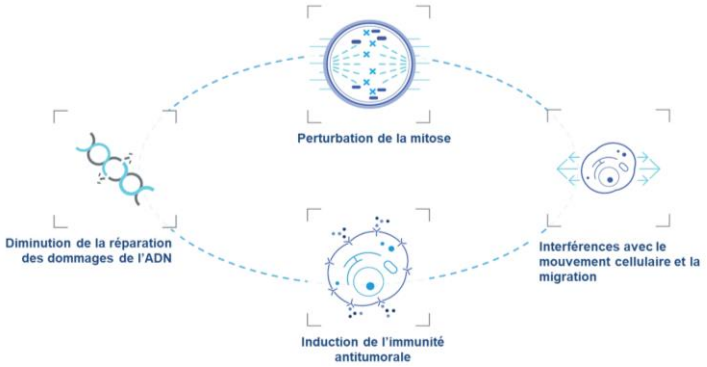
- **Before treatment and follow-up**
  - **STEMRI data (PFS; OS)**
- **All GSC implanted**



Prediction by Artificial Intelligence of relapse pattern and biological pathway involved in this relapse *Collaboration with Ahmad Berjaoui*

TTFields : another treatment in Oncology



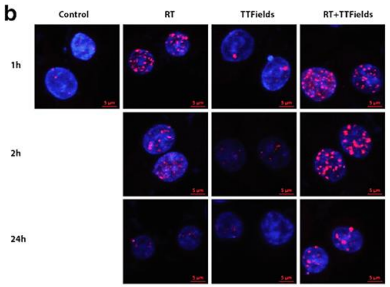


International TRIDENT trial

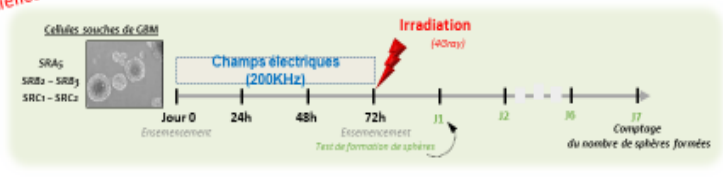
RT-Chimio-TTFields then TTFields vs RT-Chimio then TTFields

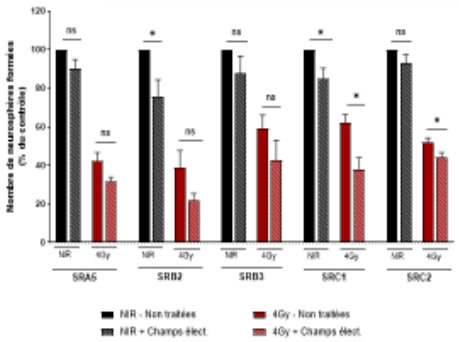
(Coordination France E Moyal)

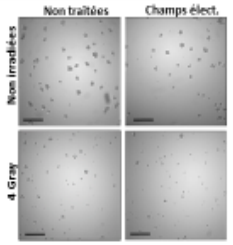
→ Clinical study validation of biological factors of resistance to TTFields (Exofields study, sponsor OCR)



Données confidentielles







→ Cible commune ?

(Brevet avec Novocure)

Mathematical modeling and optimization of the RT-TTFields association

(L Vieillevigne, A Delbaere, V Gouaze-Andersson)

Common Radioresistance and TTFields resistance mechanisms (Patent)

→ Clinical trial associating specific inhibitor of this resistance to Radiotherapy and TTFields

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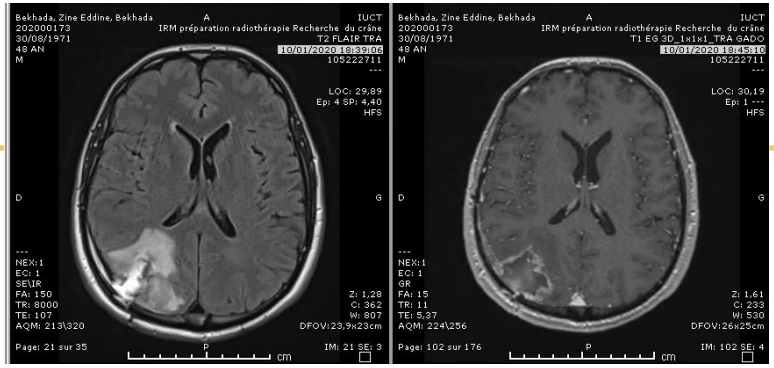
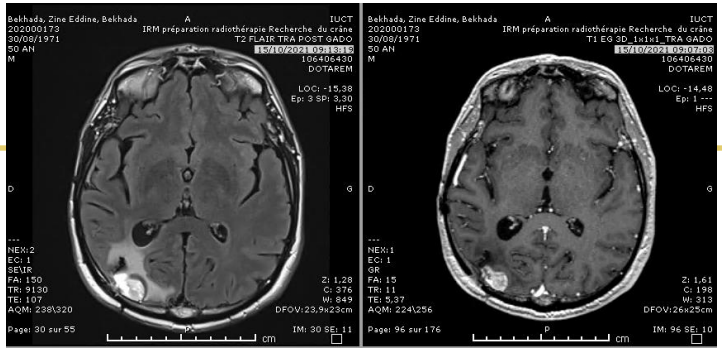
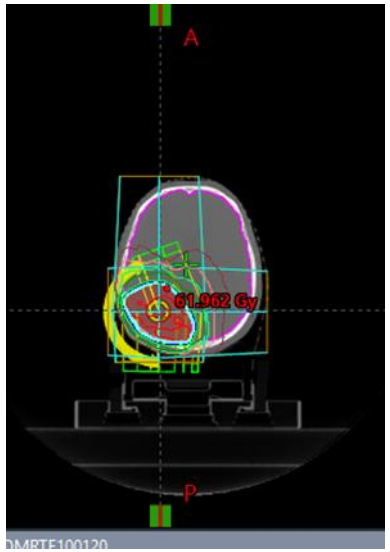
Recurrent tumor: re-irradiation and efficacy prediction (Glioblastoma)

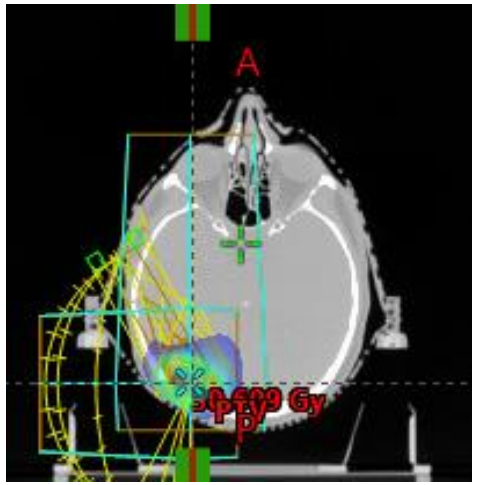




Fondation ARC pour la recherche sur le cancer

STERIMGLI clinical trial and national SIGN'IT program SI2GMA project





Hypofractionated Stereotactic Radiation Therapy (hFSRT) (3X 8 Gy; 3X 9 Gy)

N 34 patients

Arm A : standard arm
hFSRT

hFSRT
24 Gy, 3 fractions X 8 Gy (on 80%)

Day 1 RT | Day 3 RT | Day 5 RT

RANDOMIzATION 1 : 2

N 68 patients

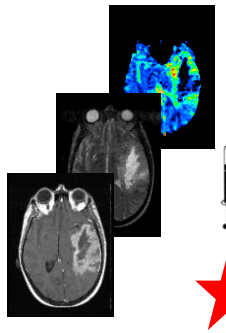
Bras B : experimental arm
hFSRT + durvalumab 1500 mg Q4W

hFSRT
24 Gy, 3 fractions x8 Gy

Day 1 RT | Day 3 RT | Day 5 RT

Perfusion de durvalumab 1500 mg Q4W
max 12 mois

W 0 D 1	w. 4 D1	w. 8 D 1	w. 12 D1	.... Q4W



(imaging analysis, cytokines, exosomes, tumor burden , immunomonitoring)

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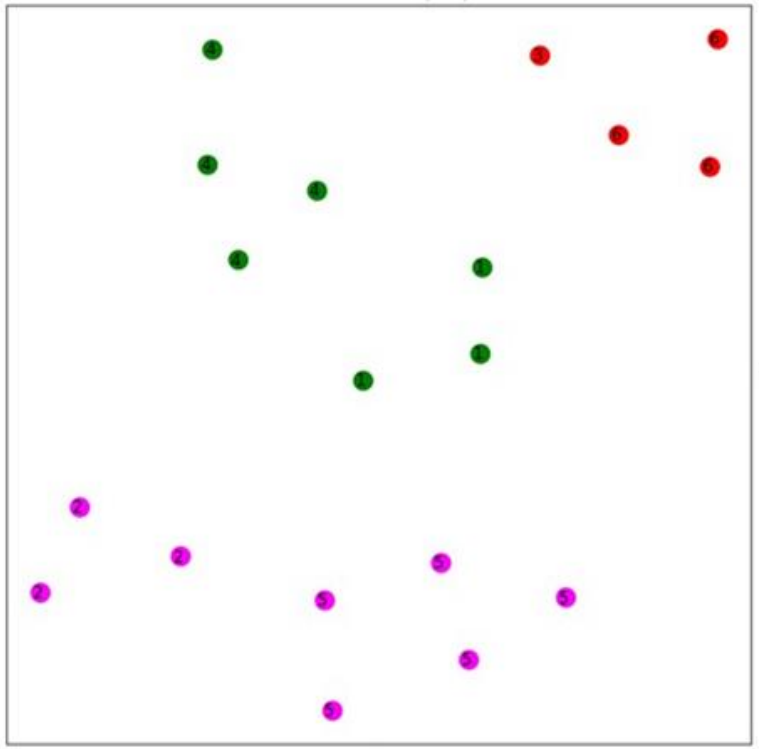
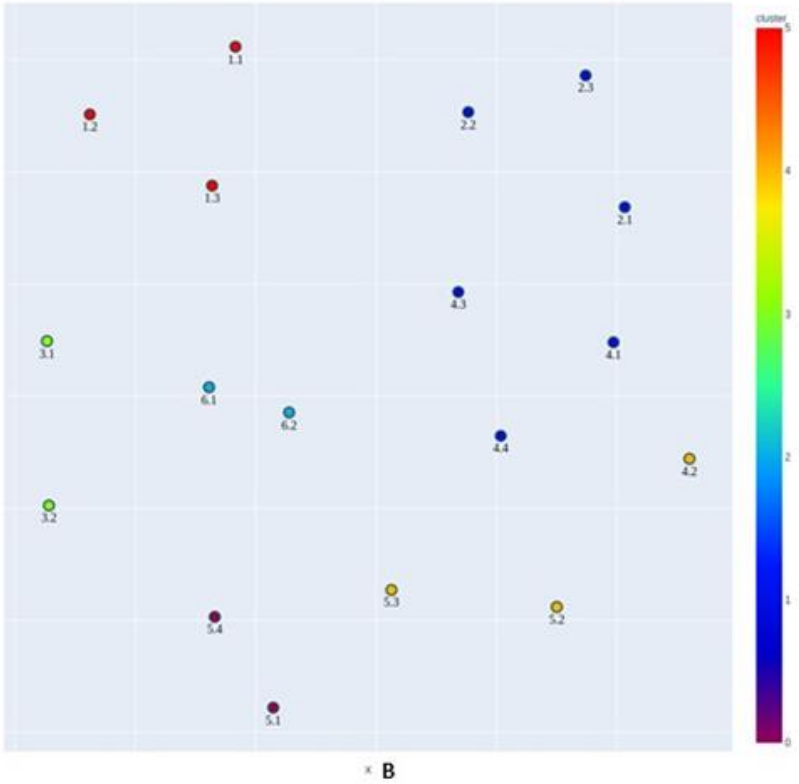
Artificial Intelligence prediction of therapeutic response including MRI, Cytokines and Neutrophils/Lymphocytes



A



B

Validation on the 100 patients included in the phase II

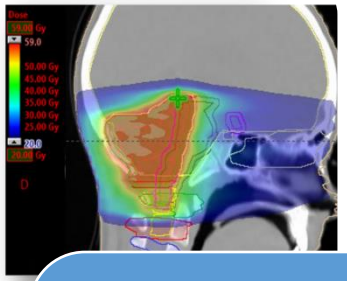
Ahmad Berjaoui

Lucas Robinet

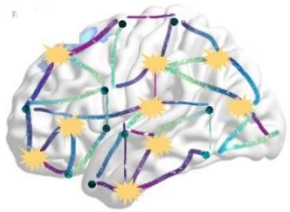
2nd prize-winner of the international Data Challenge Visiomel « Prediting Melanoma Relapse »

(Pouessel et al, The Oncologist 2023)
https://doi.org/10.1093/oncolo/oyad095

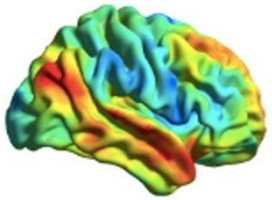
Preventing the sequelae of cerebral radiotherapy



60% cognitive deficits after treatment of brain tumors including radiotherapy ↓quality of life, ↓school, social and professional integration



Which structures are linked to memory deficits? What are the limiting doses to these organs?



IMPALA single-center Mr ROBOT study funded by PAIR Neurocognition and imaging

THINK Project

Multicentric clinical trials and basic research

Baudou et al, CTRO 2021
Troudi et al, Cancers 2022
Baudou et al, Radiother Oncol 2022
Baudou et al, EJPN 2023

How can Artificial Intelligence be used to optimize patient care in radiotherapy? One exemple

Help with patient planning on the machines

Context :
3000 patients/year
Which patient on which machine?
1 to 35 fractions/patient
Different techniques for different pathologies and situations
Different choice of machine for certain pathologies

AI program with Airbus industry

Faster and optimized care

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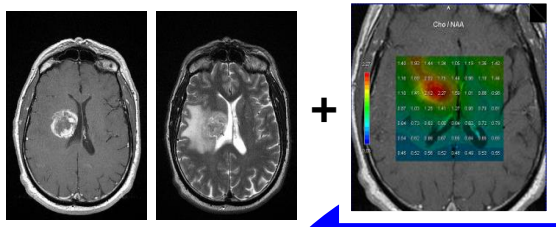
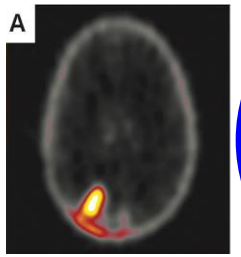
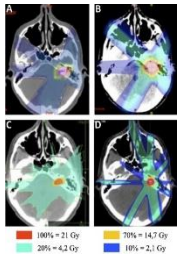
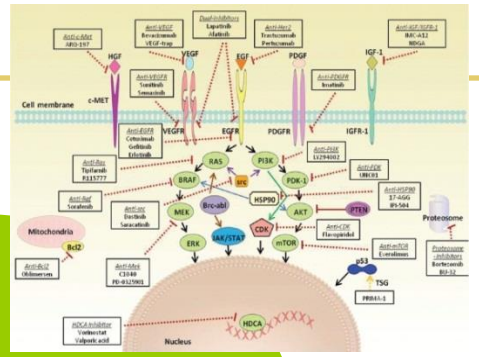
Conclusion: towards personalized radiotherapy treatments









Prediction: which treatment for whom? Artificial intelligence

Multimodal imaging

Inhibitors of biologic radioresistance mechanisms

AI tool for therapeutic planning

Toxicity prevention

Precision irradiation

Immunomodulation

TTFields

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Thanks to our patients and their families

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LA LIGUE CONTRE LE CANCER

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Thank you for your attention