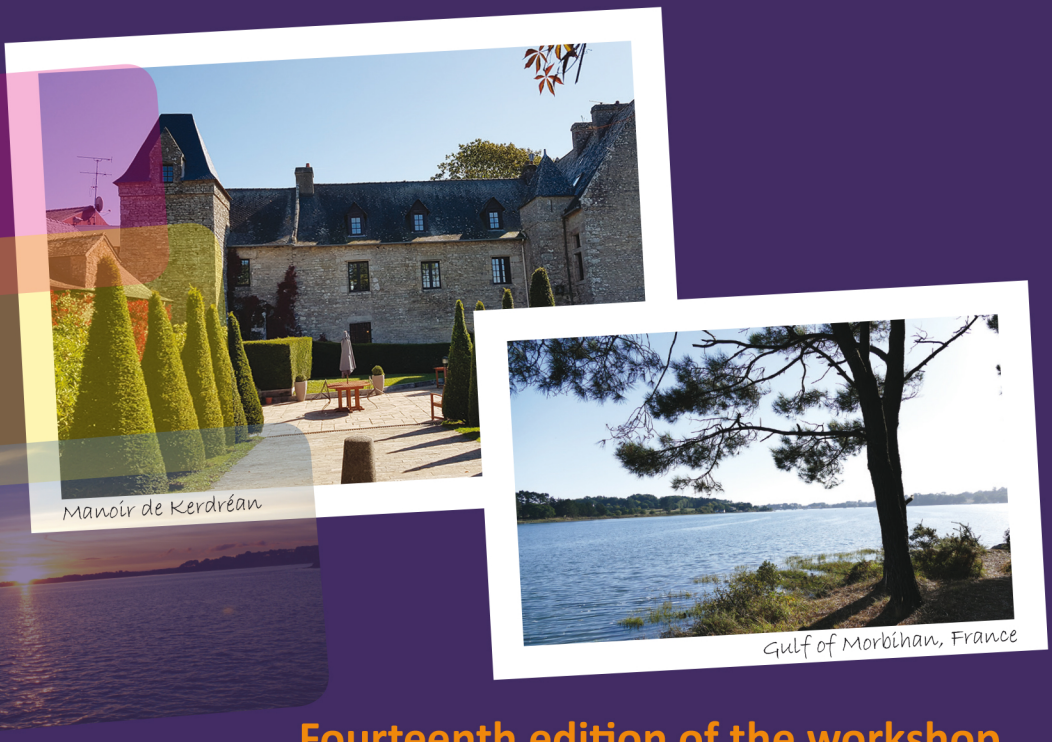
Tumour Targeting, Imaging, Radiotherapies

Cancéropôle grand ouest

Adaptation of the tumour and its ecosystem to radiotherapies:

Mechanisms, imaging and therapeutic approaches

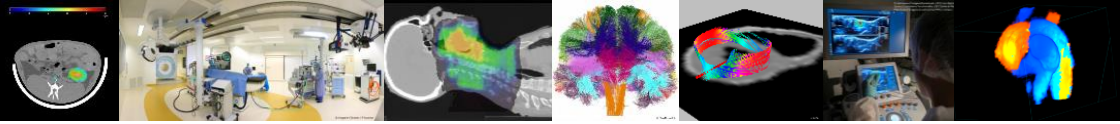


Fourteenth edition of the workshop

Manoir de Kerdréan, Le Bono, France

September 22nd- 25th, 2021

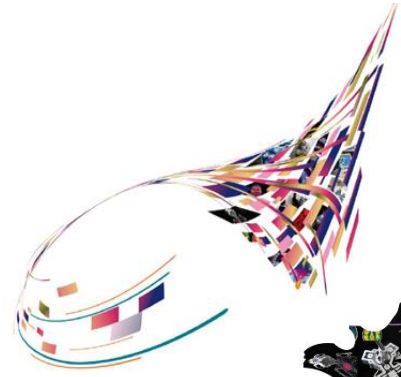
www.cgo-workshop-vecto.fr

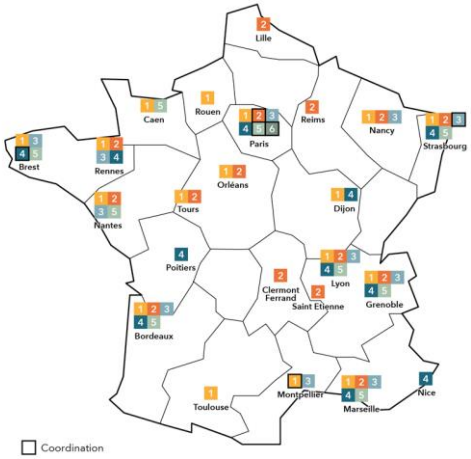


France Life Imaging

France Life Imaging (FLI) is a large-scale and distributed network of research platforms ensuring high technological innovation in *in vivo* biomedical imaging. It offers an open access to the academic, clinician and industrial community to state-of-the-art in-vivo imaging technologies and integrated services.

Coordinated by the CEA, **FLI** gathers more than 160 imaging facilities covering the French territory under the tutelage of the main French research organizations and universities: INSERM, CNRS, INRIA, Paris Saclay, Sorbonne Paris Cité, Bordeaux, Claude Bernard Lyon I, Aix Marseille and Grenoble Alpes universities.





1. Molecular imaging agents
2. Instrumentation and technological innovations
3. Interventional imaging
4. Multimodal image analysis and processing
5. Training
6. Management

National coordination

Vincent LEBON

Scientific coordinator

Régine TREBOSSEN

Executive coordinator

+33(0) 1 69 08 25 65

regine.trebossen@cea.fr

Training unit

Albertine DUBOIS

+33 (0) 1 69 08 54 88

albertine.dubois@cea.fr

LA LIGUE
CONTRE LE CANCER

MISSION AND GOAL

The French league against cancer, founded in 1918, is an independent NGO, exclusively funded by the public's generosity, which federates more than 640.000 members, 13.000 volunteers and 400 employees. All together, they are commited in four main fields : funding research, promoting screening and prevention, providing assistance to patients and addressing questions through advocacy.

MAIN FIELDS OF ACTIVITY

Four missions to fight cancer on all fronts :

- Providing significant fundings for cancerology research in France. The French league is the number 1 private and independent organization funding academic cancer research in France.

- Information on prevention and national screening campaigns.

- Actions for and with patients and their loved ones to support them during and after the disease.

- Advocacy for patients' rights and changes in the society knowledge of cancer.

Contact details :
LIGUE NATIONALE CONTRE LE CANCER
Federation head office
14, rue Corvisart - 75013 Paris
Tel. : 01 53 55 24 00 - www.ligue-cancer.net

S'INFORMER SUR LES CANCERS

Parce que la lutte contre la maladie passe aussi par une MEILLEURE COMPRÉHENSION des différents cancers, des moyens de prévention, de dépistage et de traitement, LA FONDATION ARC ÉDITE trois collections.

Sensibiliser et Prévenir

Pour se sensibiliser aux risques et à la prévention des cancers.

Comprendre et Agir

Pour s'informer sur la maladie et la prise en charge.

Mieux Vivre

Pour améliorer sa qualité de vie pendant et après la maladie.

Disponible gratuitement sur www.fondation-arc.org

La Fondation ARC, reconnue d'utilité publique, est 100 % dédiée à la recherche sur le cancer. Les ressources de la Fondation ARC proviennent exclusivement de la générosité de ses donateurs et testateurs.
Pour en savoir plus : www.fondation-arc.org

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

Société Française du Cancer

The Société française du Cancer, founded in 1906, is the oldest learned society on cancer.

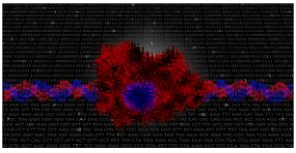
Training, information, expertise, these are the missions of our society which have been provided for more than a hundred years.
It publishes the **Bulletin du Cancer**, the only French-language oncology journal indexed in international databases, which has reached its 108th volume this year and is open to the entire Francophonie.

Every year, the French Cancer Society organizes a **high-level international scientific day, the Louise-Harel Day**, named after its founder, by inviting French and foreign researchers to discuss current topics.

The French Cancer Society also organizes an **annual training cycle at the interface between biology and the clinic** and aimed at fostering the mutual understanding of clinicians and researchers.

It publishes a collection of books on therapeutic innovation in oncology and has trained generations of oncology clinicians in clinical research.

In the areas of expertise of its members, it ensures **active participation in expert committees** set up by the public authorities, in particular within the framework of the National Cancer Institute.



Tel : 06 17 44 70 76
Mail : info@sfc.asso.fr

Société Française du Cancer

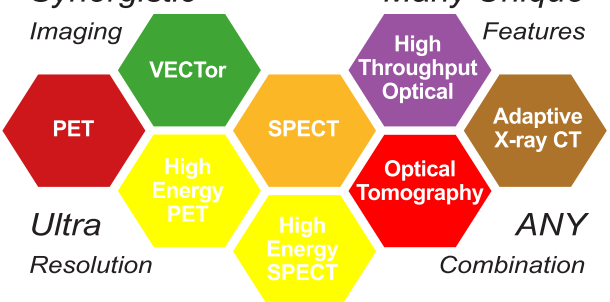
www.sfc.asso.fr

I tegrate dive si y

Labs
Making Molecular Imaging Clear

Synergistic Imaging

Many Unique Features



Ultra Resolution

ANY Combination

Breakthrough translational resolution:

- ✓ SPECT resolution down to 0.12 mm.
- ✓ PET resolution down to 0.55 mm.
- ✓ PET w/o positron rang e blurring for e.g. ^{89}Zr, ^{124}I, ^{82}Rb.
- ✓ Theranostic SPECT at <1 mm for all radiotherapy isotopes.
- ✓ Optical tomography at 1.5 mm in deep-tissue.
- ✓ In-vivo CT with down to 2.4 micron voxel resolution.

Higher sensitivity for 4D imaging:

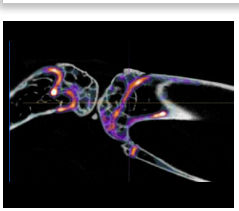
- ✓ Dynamic SPECT: up to 30kcps/MBq sensitivity.
- ✓ Dynamic PET w/o random coincidence noise.
- ✓ 3D/4D tomographic optical imaging.
- ✓ On-the-fly readout from fast rotating detectors on an autonomous CT imaging gantry.
- ✓ Dual-gated cardiac and respiratory acquisitions

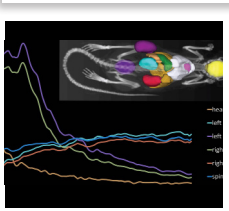
Unlimited theranostics research:

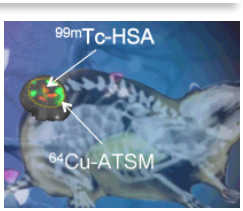
- ✓ All radiotherapy nuclide imaging at <1mm resolution
- ✓ Auger-electron emitters: e.g. ^{111}In, ^{123}I, ^{124}I
- ✓ Beta particle emitters: e.g. ^{177}Lu, ^{131}I, ^{188}Re
- ✓ Alpha particle emitters: e.g. ^{212}Pb, ^{225}Ac, ^{213}Bi, ^{209}At/^{211}At, ^{221}Fr, ^{223}Ra
- ✓ Direct radiotherapy imaging, w/o surrogate tracers
- ✓ Quantitative dosimetry

Multiple modalities working in unison:

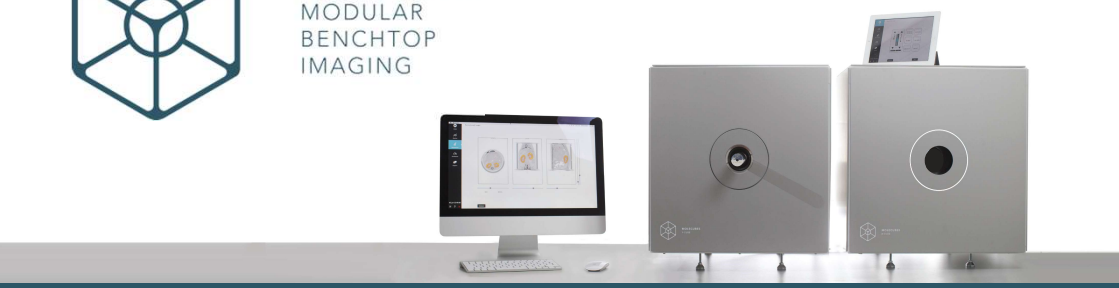
- ✓ One-to-one preclinical SPECT to clinical PET translation by simultaneous acquisition of coinjected tracers
- ✓ Simultaneous PET/PET and PET/SPECT with spatial and temporal co-registration.
- ✓ Single pass Optical to Nuclear PET/SPECT translation without animal shuttling.
- ✓ CT-guided 3D/4D Optical tomograpgy







MOLECUBES
MODULAR
BENCHTOP
IMAGING

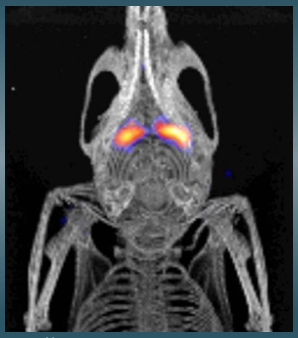


High-end | Modular | Benchtop | Software | Animal monitoring | Service

Customer testimonials

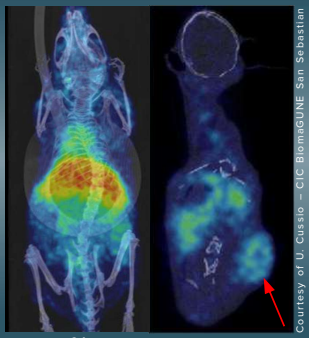
Prof. Tove Grönroos – Turku PET Centre, Finland:

"The CUBES have a very intuitive user interface and we are extremely pleased with the image quality. The X- and β-cubes have enabled us to significantly lower the radiation as well as the injected doses used for imaging mice and rats. The small sized cubes are easily located in our small imaging laboratory and furthermore, they can effortlessly be re-located e.g. in order to scan "dirty" animals. The communication with MOLECUBES is effortless and our suggestions for improvements are implemented quickly."



^{11}C-Raclopride MOUSE
Striatum

Scan code for more
MOLECUBES applications



Courtesy of U. Cussio – CIC BiomaGUNE San Sebastian

^{64}Cu-GNP MOUSE
Tumormodel

Prof. Joel Karp - University of Pennsylvania, USA:

"The clever design and excellent engineering made MOLECUBES an obvious choice for us. We are looking at long dynamic PET scans with various radiotracers produced from our local cyclotron. We appreciate the simple and intuitive user menu and operation of each CUBE both separately and together. It saves us time and allows multiple researchers to work simultaneously. They operate reliably from day to day allowing on time scheduling of studies from different UPenn research groups."

www.molecubes.com
MODULAR BENCHTOP IMAGING

info@molecubes.com

SIRIC ILIAD
Nantes - Angers

INSTITUT NATIONAL DU CANCER

Imaging and Longitudinal Investigations to Ameliorate Decision-making

Developing cutting edge research around

3 integrated research programs

Nuclear oncology :
Develop nuclear medicine tools to predict prognosis and develop innovative targeted and personalized therapies.

Functional cell oncology:
Develop functional personalized medicine tools by combining predictive algorithms and cellular tests.

Epidemiology, social sciences and public health:
Develop tools to identify and correct social inequalities and return to employment.

A unique research consortium

at the disciplinary crossroads

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Integrated Center for Oncology
Nantes / Angers - France

CHU ANGERS

Inserm
Institut national de la santé et de la recherche médicale

ARRONAX

CENTRALE NANTES

université angers

UNIVERSITÉ DE NANTES

ATLANPOLE
Land of innovation

Nantes Interdisciplinary Cluster for Translational Research in Nuclear Medicine

NExT
IRC TransForMed

4 main research expertises

Targeted therapy using alpha emitters and in particular astatine-211

Theranostic approach

Study of metabolism and tumor response

Basic and translational science task

5 research and training facilities

Production of radionuclides

Chemistry and radiopharmacy

Pre-clinical experimentation and clinical research

Non-living and living matter exposed to radiation

Training

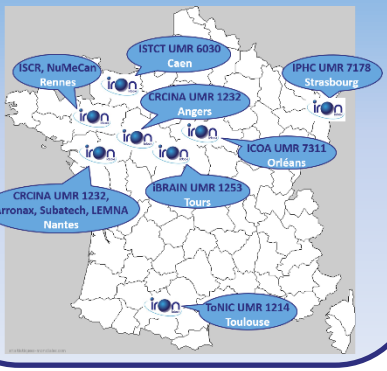
---

www.arronax-nantes.fr

Open to academic and industry

Innovative Radiopharmaceuticals in Oncology and Neurology
2012 - 2024

A national network of 11 research teams (≈160 scientists)



A national network of 5 cyclotrons

Highly innovative, translational and collaborative projects

Task Force 1	Task Force 2	Task Force 3	Task Force 4
Biology	Physics Chemistry Radiochemistry	Radiopharmacy Radiopharma-ceuticals	Clinic
M. Bernaudin (Caen) *M. Chérel (Nantes)*	G. Montavon (Nantes) *J. Vercouillie (Tours)*	M. Bourgeois (Nantes) *AS. Salabert (Toulouse)*	P. Payoux (Toulouse)

Translational Project 1 - Innovative theranostic radionuclide production and basic radiochemistry
F. Guérard - *F. Haddad - M. Pellicioli (Nantes, Strasbourg)*

TP2 - Predictive PET imaging in multiple myeloma C. Bodet-Milin - *T Carlier - S. Routier (Nantes, Orléans)*

TP3 - PET imaging in neurodegenerative diseases related to movement disorders P. Payoux - *S. Chalon (Toulouse, Tours)*

TP4 - PET imaging of neuroinflammation and inflammation in oncology
N. Arlicot - *S. Routier (Tours, Orléans)*

TP5 - Hypoxia-based theranostic approaches M. Bernaudin (Caen)

TP6 - Investigation of tumor and microenvironment responses after radionuclide therapy
E. Garcion - *M. Chérel - JF. Gestin - N. Lepareur (Angers, Nantes, Rennes)*

General objective

To reach the top level in Europe and worldwide for the development of radiopharmaceuticals in Oncology and Neurology through:

- **Multidisciplinary research in physics, chemistry, radiochemistry, nuclear oncology and neurology**
- **Finalized research on radionuclide and radiopharmaceutical production for imaging and therapy**
- **Translational research from molecule design to clinical trials**
- **Taking into account human and society factors related to medical innovation**
- **Ambitious teaching/training and technology transfer programs**

https://www.labex-iron.com/

Your preclinical research partner

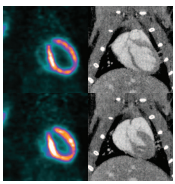
inviscan
imaging systems

IRIS and IRIS XL PET/CT

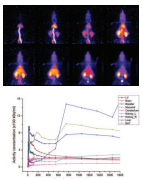
Ultimate preclinical PET/CT systems with bore size from 10 cm to 26 cm

- High performance
- High throughput
- Fully shielded
- Easy to use
- Cost-effective
- For rodents and non-human primates

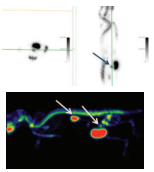
Cardiac PET/CT
Gated Imaging



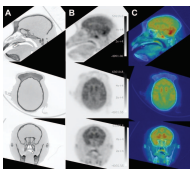
PET Dynamic
Imaging



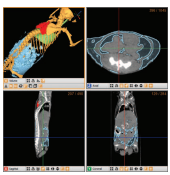
Mouse Prostate
PET Imaging
(Lesion < 1 mm)



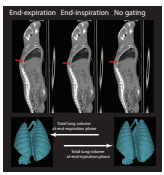
PET/CT FDG Brain Imaging
for Non-human Primate



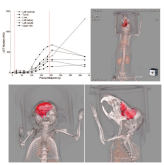
Mouse CT Imaging
Segmentation Of
Adipose Tissues



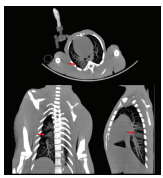
Mouse CT Lung
Imaging with Automatic
Software Gating



Dynamic 4D CT Imaging
for Mouse Glioma Model



CT Lung Imaging
for Non-human Primate



www.inviscan.fr **info@inviscan.fr**

"Adaptation of the tumour and its ecosystem to radiotherapies: Mechanisms, imaging and therapeutic approaches"

Organizing committee

Grégory Delpon	ICO, Saint-Herblain
Emmanuel Garcion	CRCINA, UMR 1232 INSERM, University of Angers
Jean-François Gestin	CRCINA, UMR 1232 INSERM, ERL CNRS 6001, University of Nantes
Mathieu Hatt	LaTIM, UMR 1101 INSERM, University of Brest
Vincent Potiron	CRCINA, UMR 1232 INSERM, University of Nantes & ICO, saint-Herblain
Latifa Rbah – Vidal	CRCINA, UMR 1232 INSERM ERL CNRS 6001, University of Nantes
Stéphane Supiot	CRCINA, UMR 1232 INSERM, University of Nantes & ICO, Saint-Herblain
Jessica Auffray	Cancéropôle Grand Ouest
Barbarella Speranza	Cancéropôle Grand Ouest
Françoise Léost	Tumour Targeting, Imaging, Radiotherapies network, Cancéropôle Grand Ouest

The organizing committee on behalf of the Canceropôle Grand Ouest and the "Tumour targeting, Imaging, Radiotherapies" network is glad to welcome you in Le Bono for a relaxed and productive meeting.

Program

Wednesday September 22nd

Registration opened at 17:30

18:30 **Opening of the Workshop**: Organizing committee

18:35 **Presentation of the « Tumour Targeting & Radiotherapies network » of the Canceropôle Grand Ouest**. **Dimitris Visvikis**, LaTIM, National Institute of Health & Clinical Sciences, Brest, **France**.

18:45 *sponsors communications*

Katarzyna Desrocques, **MOLECUBES**, Ghent, **Belgium**.
"MOLECUBES: High-end preclinical imaging PET, SPECT and CT systems for drug discovery and evaluation of new therapies"

Stéphane Supiot, ICO & CRCINA, Nantes, **France**.
Presentation of « La Société Française du Cancer »

19:00 Plenary conference:
Alexander Haug, Department of Nuclear Medicine, Medical University of Innsbruck, **Austria**.
"Clinical challenges and opportunities to reverse adaptation of the tumour and its ecosystem to radiotherapies".

20:00 *Dinner*

Thursday September 23rd

Session 1: Tumour adaptation to radiotherapies: biological aspects

8:30 – 9:00: Invited speaker: **Olivier Feron**, Cancer Translational Research Lab, Pole of Pharmacology and Therapeutics, Institute of experimental and clinical research, UCLouvain, **Belgium**.
"Getting Warburg to be right to improve radiotherapy efficacy"

9:00 – 10:00 **Ana Canha-Borges**, Institute of Investigation and Innovation in Health, University of Porto, **Portugal**.
"Dissect the tumor microenvironment to battle cancer radioresistance and immune escape"

Kristin Lode, Faculty of Health Sciences. UiT – The arctic University of Norway, Tromsø, **Norway.**
"Regulatory functions of cancer associated fibroblasts following radiation"

Luca Possenti, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, **Italy**.
"*In-vitro* microvasculature-on-a-chip to study biological alterations due to radiotherapy"

10:00 – 10:30 *Poster session & Coffee Break*

10:30 – 11:30 **Nolwenn Pasquet**, Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy group, GIP Cyceron, Caen, **France**.
"Overcoming hypoxia-induced radioresistance of glioblastoma cells by hadrontherapy"

Jia-Wei Chen, Namur Research Institute for Life Sciences (NARILIS), University of Namur, **Belgium**.
"Determination of genes implicated in the resistance to proton beam therapy during the treatment of glioblastoma"

Radu Marian Serban, Horia Hulubei National Institute for R&D in Physics and Nuclear Engineering (IFIN-HH, Magurele-Ilfov, **Romania.**
"Assessment of cellular response to internal radiotherapy delivered by Auger-electrons emissions"

11:30 -11:50 *sponsors communications*

Adam Badar– MILabs, Utrecht, **The Netherlands**.
"Synergistic Photon Tomography from 1eV to 1MeV: Integrated Ultra-High Definition PET, SPECT, Optical & X-ray CT"

Jacques Barbet, NEXT IRC Transformed & Cyclotron Arronax, Nantes, **France.**
"Arronax cyclotron: a unique facility for research and production of innovative radionuclides"

12:15 *Lunch*

Session 2: Tumour adaptation to radiotherapies: contribution of imaging

14:00 – 14:30: Invited speaker: **Heidi Lyng**, Oslo University Hospital, The Norwegian Radium Hospital, Department of Radiation Biology, Oslo, **Norway.**
"Hypoxia imaging and tumour adaptation to radiotherapies"

14:30 – 15:30 **Théo Bossis**, University of Paris-Saclay, CNRS/IN2P3, IJCLab, Orsay, **France.**
"A portable gamma camera for the optimization of the patient dosimetry in radioiodine therapy of thyroid diseases"

Cassandra Métivier, CHU Nantes, CNRS, Inserm, CRCINA, University of Nantes, **France**.
"*In vitro* and *in vivo* evaluation of a ^{64}Cu-radiolabelled anti-CD 138 antibody for Multiple Myeloma imaging and dosimetry"

Fatima-Azzahra Dwiri, Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy group, GIP Cyceron, Caen, **France**.
"Longitudinal and multiparametric study of radiotherapy toxicities on healthy brain in the rat"

15:30 – 16:00 *Coffee break*

16:00 – 17:20 **Jade Fantin,** Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy group, GIP Cyceron, Caen, **France**.
"Characterization of hypoxia in brain metastases from lung cancer: from the pre-clinical approach to the clinic "

Giula Fontana, National Center for Oncological Hadrontherapy (Fondazione CNAO), Pavia, **Italy.**
"Apparent diffusion coefficient and high b-value Diffusion-Weighted Magnetic Resonance Imaging as biomarkers for tumor response to re-irradiation with Carbon Ion Radiation Therapy for pelvic rectal recurrences: an explorative analysis"

Louis Marage, Centre Georges-François Leclerc, Dijon, **France**.
"Quantitative Magnetic Resonance Imaging during prostate radiotherapy treatment: preliminary study using a 0.35T MR-linac system"

Armend Jashari, Alma Mater Europaea Campus College "REZONANCA", Prishtine, **Republic of Kosovo.**
"^{99m} Tc-Tektrotyd, the first radiopharmaceutical for NETs diagnosis at the Nuclear Medicine Service in Kosovo"

19:00 *Dinner*

Friday September 24th

Session 3: Innovative radiation therapeutic strategies

8:30 - 9:00 Invited speaker: **Marie-Catherine Vozenin**, Department of Radiation Oncology, Department of Oncology, Lausanne University Hospital and Lausanne University, **Switzerland.**
"Irradiation at ultra high dose rate: from the FLASH effect to clinical translation"

9:00 - 10:20 **Thom Reuvers**, Department of Radiology & Nuclear Medicine, Department of Molecular Genetics, Erasmus MC, Rotterdam, **The Netherlands.**
"Adaptation of DNA damage repair using DNA-PKcs inhibitors as selective potentiation of peptide receptor radionuclide therapy"

Simone Kleinendorst, Department of Medical Imaging: Nuclear Medicine, Radboudumc, Nijmegen, **The Netherlands**.
"CAIX-targeted radionuclide therapy in immunodeficient and immunocompetent mouse models"

Magdalena Rodak, Institute of Nuclear Chemistry and Technology, Warsaw, **Poland**.
"Anti-HER2 2Rs15d nanobody labeled with 225Ac as a potential molecule for targeted alpha therapy"

Déborah Iglicki, Institut des Sciences Chimiques de Rennes - UMR6226 CNRS, University of Rennes, **France.**
"From Ouzo effect to combined chemo-radio-therapies"

10:20 – 10:50 *Poster session & Coffee Break*

10:50 – 12:30 **Marine Le Goas**, Faculté de Pharmacie, Université de Montréal, Québec, **Canada.**
"Improving systemic radiotherapy with radioenhancing nanoparticles"

Malak Sabbah, Laboratory of Oncology and Experimental Surgery, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, **Belgium**.
"Novel therapeutic combination strategies in non-BRAF mutant melanoma"

Julie Coupey, Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy group, GIP CYCERON, Caen, **France**.
"Investigating the interest of proton therapy to obtund radiation-induced lymphopenia in a context of brain tumour irradiation: a preclinical study"

Edoardo Mastella, CNAO, National Center for Oncological Hadrontherapy, Pavia, **Italy**.
"*In silico* feasibility study of carbon ion radiotherapy with simultaneous integrated boost (CIRT-SIB) for head and neck adenoid cystic carcinoma"

Paulina Apostolova, Faculty of medical sciences, Goce Delcev University, Stip, **Republic of North Macedonia.**
"Trastuzumab radioimmunoconjugates – promising strategy for selective anticancer therapy"

12:30 *Lunch*

Session 4: Learning and data driven techniques

14:00 – 14:30: Invited speaker: **Charlotte Robert,** Molecular radiotherapy unit, Inserm, Gustave Roussy, University of Paris –Sud, **France**.
"Radiomics for immune response characterization under RT treatment"

14:30 – 15:30 **Luis E. Ayala-Hernández**, Departamento de Ciencias Exactas y Tecnología Centro Universitario de los Lagos, Universidad de Guadalajara, Jalisco, **Mexico.**
"A mathematical model of the low-grade gliomas response to chemotherapy and radiotherapy: Therapeutic implications "

Beatriz Ocaña-Tienda, Mathematical Oncology Laboratory (MOLAB), Instituto de Matemática Aplicada a la Ciencia y la Ingeniería, Universidad de Castilla-La Mancha, Ciudad Real, **Spain**.
"Radiation necrosis vs progression in Brain Metastases treated with stereotactic radiosurgery: How to distinguish them using mechanistic mathematical models"

Dana Naser Tahboub, Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, **United Kingdom**.
"Spatial analysis of preclinical dynamic contrast-enhanced ultrasound (DCE-US) images for assessment of tumour response to radiotherapy"

15:30 – 16:00 *Coffee break*

16:00 – 17:00 **Vincent Bourbonne**, LaTIM UMR 1101 INSERM & Department of Radiation Oncology, University Hospital, Brest, **France.**
"Development and prospective validation of a spatial dose pattern based model predicting acute pulmonary toxicity in patients treated with volumetric arc-therapy for locally advanced lung cancer"

Guillaume Sallé, UMR 1101 Inserm LaTIM, UBO, IMT Atlantique & CHRU, Brest, **France.**
"Synthetic tumor insertion using one-shot generative learning for cross-modal image segmentation"

Yi-heng Cao, UMR 1101 Inserm LaTIM, UBO, IMT Atlantique & CHRU, Brest, **France.**
"Patient-specific 4DCT respiratory motion synthesis using generative adversarial networks"

17:00 Social event

Saturday September 25th

Session 5 : Futures challenges

9 :00 – 9 :30 Invited speaker: **Julie Nonnekens**, Department of Radiology & Nuclear Medicine, Department of Molecular Genetics, Erasmus MC, Rotterdam, **The Netherlands.**
"**Radiobiology of targeted radionuclide therapy: necessity and current challenges**"

9:30 - 10:00 **Mathieu Hatt**, LaTIM, National Institute of Health & Clinical Sciences, University of Brest, **France**.
"Data science and machine learning in radiomics: past, present, perspectives"

10:00 – 10:15 *Coffee break*

10:15 - 11:00 Round table on industrial point of view.

11:00 – 11:45 Focus on European policy in Oncology and elaboration of call of projects, **Emilie Floch**, European projects platform (2PE) – Brittany, Brest, France.

11:45 – 12:00 Awards.

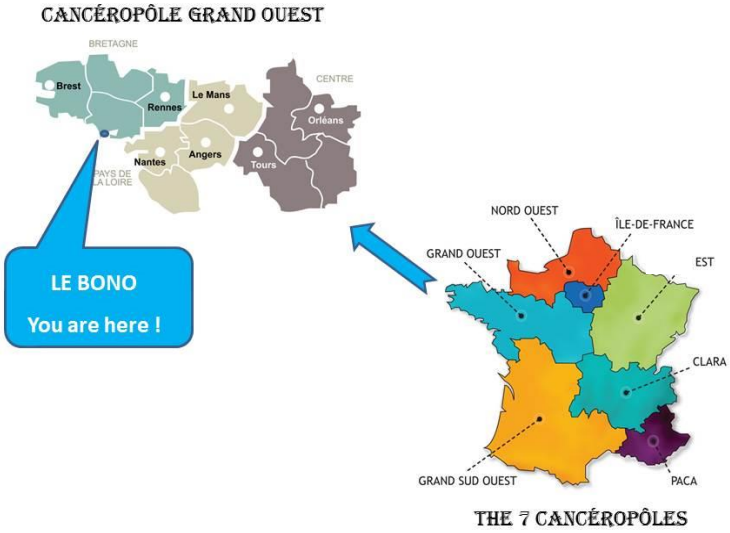
12:00 *Lunch*

13:00 *End of the workshop – Departure of the bus*

Presentation of the "Tumour Targeting, Imaging, Radiotherapies network"of the Cancéropôle Grand Ouest

Dimitris Visvikis, LaTIM, National Institute of Health & Clinical Sciences (INSERM), Brest, **France**.

The first "Plan Cancer" was launched in 2003 as an initiative to foster France's efforts in cancer management. One of the actions of the plan was the creation of 7 "Cancéropôles" with the mission of organizing cooperation in the field of translational research between laboratories and clinical departments within a large geographic area. The Cancéropôle Grand Ouest (CGO) covers today 3 of the 13 French Regions.



From the beginning, broad collaborative research projects were proposed and financed, some specific for each Cancéropôle depending on their domain of expertise, some more general. At the beginning there were two specific networks: "Marine products" and "Tumour targeting". Given that the initial “Plan Cancer” was maintained, in 2009 the “Tumour targeting” network became the “Tumour

Targeting and Radiotherapies" network to incorporate research teams working in the field of External Beam Radiotherapy and to acknowledge the significance of the research and clinical work carried out in radiotherapy in general, external or radionuclide-based, for cancer treatment within the borders of the CGO. The name of the network further evolved in 2019 to "Tumour Targeting, Imaging, Radiotherapies" in order to clearly mention the field of medical imaging that is one of the corner-stones of the network from the day of its creation. Our goal remains the development of an integrated, translational approach, recognizing the strong interest of bringing together scientists and physicians from diverse horizons to create synergies. "Tumour Targeting, Imaging, Radiotherapies" is today an interdisciplinary network, with about 250 members, 25 preclinical research teams and 15 clinical sites, and its activities span four interconnected research domains:

- **Concept of innovating agents and nanomedicines for imaging and therapeutic purposes**
  Innovations: targeting of novel pharmacological agents, iron chelators, interfering oligonucleotides, alpha emitters, positron-emitting radionuclides, theranostics.
- **Targeted therapies and radiotherapies for cancer: from animal models to clinical trials**
  Innovations: targeting the tumor environment, administration routes and biological barriers, spontaneous animal tumors, targeted alpha-radiotherapy, dose modulation, image-guided radiotherapy emitter for small animals, hypofractionated external beam radiotherapy, hadrontherapy.
- **Quantitative multimodal imaging and radiotherapies**
  Innovations: multimodal imaging, MRI/SPECT, MRI/PET, US, cell tracking, multiparametric imaging, prognosis models, image-guided radiotherapy, Monte Carlo dosimetry.
- **Biological response and targeted therapies**
  Innovations: radiobiology, combined treatments, synergistic effects, mechanisms of radiotherapy resistance (pO2, hypoxia), -omics (lipidomics, proteomics, transcriptomics, matrixomics, miRNomics…), development of predictive mathematical models.

The "Tumor Targeting, Imaging, Radiotherapies" network brings together various disciplines, such as Chemistry, Biology, Physics and Medicine.

More information: http://www.canceropole-grandouest.com/

“MOLECUBES: High-end preclinical imaging PET, SPECT and CT systems for drug discovery and evaluation of new therapies”

Katarzyna Desrocques, MOLECUBES, Ghent, **Belgium.**

MOLECUBES manufactures and sells high-end preclinical imaging PET, SPECT and CT CUBES, which enable researchers and laboratory scientists to achieve high quality images supported by fast and simple workflows. The X-CUBE, ɣ-CUBE and β-CUBE are the most compact micro-CT, micro-SPECT and micro-PET scanners in the field of molecular small-animal imaging. They are designed to work both as stand-alone units and in modular combinations.

MOLECUBES enables researchers in academia and industry to obtain high resolution images in vivo for their breakthrough research. In 5 years we grew from the innovative beginner to the market leader with a rapidly growing community of users thanks to exceptional performance and ease of use of our scalable benchtop setup.

At this year's workshop, we proudly present how our innovative scanners, our continuous technological developments and worldwide support of the imaging community have helped researchers in their search for new breakthroughs. A selection of recent applications will illustrate the use of systems in understanding of biological pathways, drug discovery and evaluation of new therapies.

"Clinical challenges and opportunities to reverse adaptation of the tumour and its ecosystem to radiotherapies"

Alexander Haug, Department of Nuclear Medicine, Medical University of Innsbruck, **Austria**.

Novel radionuclide therapies such as 177Lu-DOTATATE and 177Lu-PSMA have emerged important tools in oncologic treatment algorithms. Most patients are responding well to these treatments, but a minority of patients still are refractory to these treatments. This resistance can arise from various factors:

1 A lack of expression of the treatment target
2 Insufficient applied activity resulting in (too) low absorbed tumor doses
3 Radiation resistance of the tumor

Ad 1: A lack of target expression is precluding successful radionuclide treatment. The only way to deal with this issue is to try to enhance target expression by medical interventions. For both PSMA AND somatostatin receptors such approaches have been tried.

Ad 2: Dosimetry might help to overcome applying too low activities. However, some hurdles are still to be overcome.

Ad 3: Radiation resistance is a major obstacle for successful radionuclide therapy. Several attempts have been made to overcome radiation resistance. First, treatment with radio-sensitizing drugs has been combined with radionuclide therapy. Second, tumor hypoxia is a well-known mechanism for radio-resistance. Initial studies have tried to increase tumor oxygenation. Third, studies have explored the potential of combining radionuclide therapies with drugs, which inhibit DNA repair. An interesting approach might be treatment with FAPI-targeting radiopharmaceuticals, as tumor associated fibroblasts are a well-known cause for increasing treatment resistance of tumors.

"Getting Warburg to be right to improve radiotherapy efficacy"

Invited speaker: **Olivier Feron**, Cancer Translational Research Lab, Pole of Pharmacology and Therapeutics, Institute of experimental and clinical research (IREC), UCLouvain, **Belgium**.

The so-called "Oxygen Effect" documents that well oxygenated tumor areas respond to radiotherapy by up to a factor of three better than hypoxic areas. The O2 levels in a tumor are determined by the balance between vascular supply and consumption mostly via cell respiration. Misinterpretation of the Warburg effect led to make O2 consumption poorly contributing to the final tumor pO2 (the extent of angiogenesis and tumor perfusion through neo-formed blood vessels being the main factors). Otto Warburg actually found that as far as carbohydrate metabolism is concerned, cancer cells mainly depend on anaerobic glycolysis (i.e. glucose to lactate conversion even in the presence of oxygen). He further hypothesized that cancer is a disease of irreversibly damaged respiration leading to a model where dysfunctional mitochondria are a characteristic of cancer cells (forcing them to be dependent on glucose fermentation). Today we know that in a minority of tumors, primary mitochondrial defects are detectable mostly because of mutations in Krebs cycle enzymes. In most cancer cells, mitochondria actually represent a major hub for a variety of biosynthetic pathways and respiration is a major contributor to O2 deficiency in tumors.
Warburg was thus right claiming that glycolysis is largely anaerobic in cancer cells but the hypothesis of defective mitochondria was not correct for most tumors … except if we make it happen! Lately, drugs were indeed developed (or re-purposed) to block cancer cell respiration and/or oxidative metabolism and thereby make O2 more available to radio-sensitize tumors. This approach will be illustrated through recent progresses made with OXPHOS inhibitors and blockers of mitochondrial transporters.

"Dissect the tumor microenvironment to battle cancer radioresistance and immune escape"

Ana Canha-Borges[1,2]*, Flávia Castro[1,2]*, Ana Pinto[3]*, Filipa Trabuco[1,2], Catarina Barbosa[1,2], Olivier De Wever[4], Raquel Gonçalves[1,2], Eric Deutsch[5,6], Joana Paredes[1,7], Maria José Oliveira[1,2,8]

[1] i3S – Institute of Investigation and Innovation in Health, University of Porto
[2] INEB – Institute of Biomedical Engineer, University of Porto
[3] iBiMed – Institute of Biomedicine, University of Aveiro
[4] Laboratory of Experimental Cancer Research, Department of Radiation Oncology and Experimental Cancer Research, Ghent University
[5] Department of Radiation Oncology, Gustave Roussy, Paris-Sud University
[6] Paris-Sud University, Kremlin-Bicêtre Medical University
[7] IPATIMUP – Institute of Pathology and Molecular Immunology, University of Porto
[8] FMUP – Faculty of Medicine, University of Porto
**, Equally contributing first authors*

Triple-negative breast cancer (TNBC), characterized by the absence of estrogen, progesterone and human epidermal growth factor type 2 receptors expression, represents about 10-15% of all diagnosed breast tumors[1,2]. Despite being insensitive to target therapies, TNBCs are more radioresistant than other breast cancer subtypes, being significantly associated with higher risk of locoregional relapse following radiotherapy (RT) [3]. The lack of efficient therapeutic approaches prompted us to unveil the mechanisms underlying TNBC radioresistance, envisaging the disclosure of alternative therapies to improve the management of this poor prognosis tumor[3,4].

Importantly, genetic instability or clonal diversity cannot fully explain cancer cell radioresistance. For further elucidation, attention has also to be paid to other elements of the tumor microenvironment, also targets of irradiation, which modulate and are modulated by cancer cell response[5-7]. Our team explored the role of RT on macrophages and on their interaction with cancer cells. Interestingly, DNA damage induced by cumulative RT (2Gy/day, total 10Gy) led to the activation of pro-survival pathways, remaining irradiated macrophages viable and metabolically active. In addition, upon RT, macrophages polarized towards a pro-inflammatory-like profile, but still preserving their ability to stimulate cancer cell invasion and angiogenesis[8]. Noteworthy, cancer cell response to RT was

modulated by irradiated macrophages. While inducing apoptosis in radiosensitive cancer cells by promoting PARP and Caspase-3 cleavage, macrophages protected radioresistant cancer cells from death by inhibiting apoptosis and upregulating glucose transporters expression[9]. More recently, our team developed immunomodulatory nanoparticles, that in combination with RT, reduces mouse TNBC growth and lung metastases, by decreasing systemic and local myeloid cells[10,11].

Based on these strong evidences, we are now dedicated to unravel the role of macrophages and Tcells on the modulation of TNBC radioresistance, dissecting the associated molecular mechanisms. We believe that identifying novel targets to the development of more effective immunomodulatory therapies will improve patients outcome.

REFERENCES

[1] Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. (2016) Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol, 13(11): p.674-690. Doi: 10.1038/nrclinonc.2016.66.

[2] Denkert C, Liedtke C, Tutt A, von Minckwitz G. (2017) Molecular alterations in triple-negative breast cancer-the road to new treatment strategies. Lancet, 389(10087): p.2430-2442

[3] Langlands FE, Horgan K, Dodwell DD, Smith L. (2013) Breast cancer subtypes: response to radiotherapy and potential radiosensitisation. Br J Radiol, 86(1023): p.20120601. Doi: 10.1259/bjr.20120601.

[4] Eifel P, Axelson JA, Costa J, Crowley J, Curran WJ Jr, Deshler A, Fulton S, Hendricks CB, Kemeny M, Kornblith AB, Louis TA, Markman M, Mayer R, Roter D. (2001) National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer. J Natl Cancer Inst, 93(13): p.979-89. Doi: 10.1093/jnci/93.13.979.

[5] Mareel M, Oliveira MJ, Mandani I. (2009) Cancer Invasion and metastasis: interacting ecosystems. Virchows Arch, 454: p.599-622. Doi: 10.1007/s00428-009-0784-0.

[6] Barker HE, Paget JTE, Khan AA, Harrington KJ. (2015) The Tumour Microenvironment after Radiotherapy:
Mechanisms of Resistance and Recurrence. Nat Rev Cancer 15(7): p.409-25. Doi: 10.1038/nrc3958.

[7] Tommelein J, De Vlieghere E, Verset L, Melsens E, Leenders J, Descamps B, Debucquoy A, Vanhove C, Pauwels P, Gespach CP, Vral A, De Boeck A, Haustermans K, De Tullio P, Ceelen W, Demetter P, Boterberg T, Bracke M, De Wever O. (2018) Radiotherapy- Activated Cancer-Associated Fibroblasts Promote Tumor Progression through Paracrine IGF1R Activation. Cancer Res, 1;78(3):p.659-670. Doi: 10.1158/0008-5472.CAN-17- 0524.

[8] Pinto AT, Pinto ML, Cardoso AP, Monteiro C, Pinto MT, Maia AF, Castro P, Figueira R, Monteiro A, Marques M, Mareel M, Santos SG, Seruca R, Barbosa MA, Rocha S, Oliveira MJ.

(2016) Ionizing radiation modulates human macrophages towards a pro- inflammatory phenotype preserving their pro-invasive and pro-angiogenic capacities. Scientific Reports, 6: p.18765. Doi: 10.1038/srep18765.
[9] Pinto AT, Pinto ML, Velho S, Pinto MT, Cardoso AP, Figueira R, Monteiro A, Marques M, Seruca R, Barbosa MA,Mareel M, Oliveira MJ, Rocha S. (2016) Intricate macrophage-colorectal cancer cell communication in response to radiation. PLoS One, 11(8): p.e0160891. Doi: 10.1371/journal.pone.0160891.
[10] Castro F, Pinto ML, Silva AM, Pereira CL, Teixeira GQ, Gomez-Lazaro M, Santos SG, Barbosa MA, Gonçalves RM, Oliveira MJ. (2017) Pro-inflammatory chitosan/poly(γ- glutamic acid) nanoparticles modulate human antigen-presenting cells phenotype and revert their pro-invasive capacity. Acta Biomaterialia, 63: p.96-109. Doi:10.1016/j.actbio.2017.09.016.
[11] Castro F, Pinto ML, Pereira CL, Serre K, Barbosa MA, Vermaelen K, Gartner F, Goncalves RM, De Wever O, Oliveira, MJ. (2020) Chitosan/gamma-PGA nanoparticles-based immunotherapy as adjuvant to radiotherapy in breast cancer. Biomaterials 2020, 257: p.120218. Doi: 10.1016/j.biomaterials.2020.120218.

"Regulatory functions of cancer associated fibroblasts following radiation"

Kristin Lode[1], Rodrigo Berzaghi[1], Inigo Z. Martinez[1], Turid Hellevik[2]
[1] *Department of clinical Medicine, faculty of Health Sciences. UiT – The arctic University of Norway, Tromsø, Norway*
[2] *Department of Radiation Oncology, University Hospital of Northern Norway, Tromsø, Norway*

Background. Radiotherapy (RT) still represents a mainstay of treatment in oncology. Traditionally, the effectiveness of radiotherapy has been based on the killing potential of radiation over malignant cells, however, it has become clear that the therapeutic efficacy of RT also involves the activation of other cell types present in the tumour microenvironment (TME)[1]. As one of the major constituents of the TME, cancer-associated fibroblasts (CAFs) play central roles in cancer development at all its stages [2] and are recognised contributors of tumor immune evasion [3,4]. While some studies argue that RT affects CAFs negatively through growth arrest and impaired motility [5,6], others claim that exposure of fibroblasts to RT promotes their conversion into a more activated phenotype [1]. This study was undertaken to determine the effect of RT on CAFs regulatory function.

Methods. Human CAFs were isolated from newly excised non-small cell lung carcinoma tumour tissues by the outgrowth method, as previously described by our group [7]. CAFs were irradiated to study the general effect of radiotherapy (RT) on cultured CAFs. Tumour cells were co-cultured with irradiated or sham-irradiated CAFs prior to functional assays to study the proliferative and migratory rates of tumour cells, production of EMT associated markers. Co-cultures of tumour cells and CAFs were irradiated to study the potential radioprotective effect exerted by CAFs.

Results. Our data show that RT induced senescence in CAFs, and reduced proliferative and migratory capacity, without causing cell death. Expression of CAF specific markers FAP-1, FSP-1 and α-SMA remained unchanged following RT, whereas the expression of podoplanin was reduced following RT. Proliferative rates of tumour cells remained unchanged upon co-cultures with irradiated and sham-irradiated CAFs, whereas co-cultures with irradiated CAFs reduced EMT in an adenocarcinoma cell line. Clonogenic survival of tumour cells following RT remained unchanged in co-cultures with CAFs.

REFERENCES

[1] Chargari, C., Clemenson, C., Martins, I., Perfettini, J. L. & Deutsch, E. Understanding the functions of tumor stroma in resistance to ionizing radiation: Emerging targets for pharmacological modulation. *Drug Resist. Updat.* **16**, 10–21 (2013).

[2] Monteran, L. & Erez, N. The dark side of fibroblasts: Cancer-associated fibroblasts as mediators of immunosuppression in the tumor microenvironment. *Front. Immunol.* **10**, (2019).

[3] Yang, N. *et al.* Irradiated Tumor Fibroblasts Avoid Immune Recognition and Retain Immunosuppressive Functions Over Natural Killer Cells. *Front. Immunol.* **11**, 3567 (2021).

[4] Liu, T. *et al.* Cancer-associated fibroblasts: An emerging target of anti-cancer immunotherapy. *J. Hematol. Oncol.* **12**, 86 (2019).

[5] Wang, Z., Tang, Y., Tan, Y., Wei, Q. & Yu, W. Cancer-associated fibroblasts in radiotherapy: Challenges and new opportunities. *Cell Commun. Signal.* **17**, (2019).

[6] Rodriguez-Ruiz, M. E., Vitale, I., Harrington, K. J., Melero, I. & Galluzzi, L. Immunological impact of cell death signaling driven by radiation on the tumor microenvironment. *Nat. Immunol.* **21**, 120–134 (2020).

[7] Hellevik, T. *et al.* Cancer-associated fibroblasts from human NSCLC survive ablative doses of radiation but their invasive capacity is reduced. *Radiat. Oncol.* **7**, 59 (2012).

"*In-vitro* microvasculature-on-a-chip to study biological alterations due to radiotherapy"

L. Possenti[1,2,3], R. El Bezawy[4], T. Giandini[5], C. Stucchi[5], D. Petta[2], A. Cicchetti[1], V. Doldi[4], C. Candrian[2,6], M.L. Costantino[3], S. Bersini[2], C. Arrigoni[2], M. Moretti[2,6], T. Rancati[1]

[1] *Prostate Cancer Program, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan*

[2] *Regenerative Medicine Technologies Laboratory, Ente Ospedaliero Cantonale, Lugano*

[3] *Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Milan*

[4] *Molecular Pharmacology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan*

[5] *Medical Physics Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan*

[6] *Facoltà di Scienze Biomediche, Università della Svizzera Italiana, Lugano*

Introduction

Biological modifications after radiotherapy do not involve tumor cells solely but also the other components of the microenvironment. To accurately model in-vitro these phenomena, advanced models are required [1,2], leveraging 3D cell cultures, co-cultures techniques (among others). In this work, we considered the microvasculature (μVN), and we built an in-vitro model to recapitulate μVN irradiation on a chip.

Methods

The microfluidic chip was designed and produced by soft-lithography [3], using a 3D printed mold and plasma bonding. Such a device allows the 3D culture of endothelial cells to form μVN by a vasculogenic-like process. The μVN-on-a-chip was obtained co-culturing HUVECs and dermal fibroblasts in a fibrin gel for seven days. Samples were irradiated with doses ranging from 2 to 20 Gy (6 MV photons, dose rate 2.8 Gy/min, using a medical linear accelerator). After the irradiation, cell apoptosis and double-strand breaks (DSBs), which reflect DNA damage, were assessed by evaluating caspase-3 and γ-H2AX foci staining, respectively. Permeability tests were run to evaluate the endothelial barrier function.

Results

The μVN was successfully generated on a chip, obtaining a perfusable vascularized construct of 9 mm^3 (10x3x0.3 mm). Apoptosis quantification revealed a significant apoptotic fraction (e.g. 16% at 10 Gy) and a cell death-dose non-linear correlation. The DSBs increased linearly with the dose (max damaged fraction 46%).

Permeability tests revealed a decrease in the barrier function with increasing the dose, which is reflected by an increase of permeability to dextran by an order of magnitude (from 10-7 to 10-6 cm/s with 40kDa dextran).

Conclusions

We successfully developed a µVN-on-a-chip to study microvascular damage induced by IR. These findings validate the model to further characterize the microvasculature role in radiotherapy and defining its impact on treatment efficiency.

Funding

AIRC Investigator Grant IG21479 funded this study.

REFERENCES

[1] Possenti, L., Mecchi, L., Rossoni, A., Sangalli, V., Bersini, S., Cicchetti, A., Costantino, M. L., Candrian, C., Arrigoni, C., Rancati, T., & Moretti, M. (2021). Radiobiological Studies of Microvascular Damage through In Vitro Models: A Methodological Perspective. Cancers, 13(5), 1182. https://doi.org/10.3390/cancers13051182

[2] Guo, Z., Yang, C. T., Maritz, M. F., Wu, H., Wilson, P., Warkiani, M. E., Chien, C. C., Kempson, I., Aref, A. R., & Thierry, B. (2019). Validation of a Vasculogenesis Microfluidic Model for Radiobiological Studies of the Human Microvasculature. Advanced Materials Technologies, 4(4), 1–12. https://doi.org/10.1002/admt.201800726

[3] Chen, M. B., Whisler, J. A., Frose, J., Yu, C., Shin, Y., & Kamm, R. D. (2017). On-chip human microvasculature assay for visualization and quantification of tumor cell extravasation dynamics. Nature Protocols, 12(5), 865– 880. https://doi.org/10.1038/nprot.2017.018

"Overcoming hypoxia-induced radioresistance of glioblastoma cells by hadrontherapy"

PASQUET Nolwenn[1], VALABLE Samuel[1], TOUTAIN Jérôme[1], BERNAUDIN Myriam[1], PERES Elodie[1]

[1] *Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy Group, GIP CYCERON, 14000 Caen, France*

Hypoxia, well pronounced in glioblastoma (GBM; Bekaert *et al.,* 2017) is known to limit the efficacy of low-LET (linear energy transfer) ionizing radiations such as conventional radiotherapy using X-rays. Consequently, the hypoxia-induced radioresistance of cancer cells is a major problem in the curative treatment of GBM and therefore represents a poor prognosis factor.

The most radioresistant cells in a tumor mass could be the glioma stem cells (GSC) due to their quiescent state and the high efficacy of their DNA repair pathways. Moreover, the number of GSC increases after radiotherapy and is associated with the risk of recurrence. It has been recently proposed that this increase in GSC is related to the dedifferentiation of the tumor cells after X-ray irradiation. Hypoxia has been identified as a factor contributing to dedifferentiation of GBM cells into GSC. Nevertheless, the oxygen effect is less documented in a hadrontherapy context which is the originality of this project.

Here, we aim to evaluate *in vitro* whether high-LET particles, especially carbon ions and protons could overcome the contribution of hypoxia to radioresistance.

First, hypoxia-induced radioresistance was studied in two human GBM cells (U251 and GL15) exposed to X-rays or to carbon ions with increasing LET (28, 50, 100 keV/µm). The results demonstrate that, although carbon ions are more efficient than X-rays in GBM cells both in normoxia and hypoxia, hypoxia can influence carbon ions efficacy in a cell-type manner (Valable *et al.,* 2020). To go further in the characterization of this radioresistance, we studied the effect of carbon ions irradiation on the dedifferentiation phenomenon. Preliminary results showed that dedifferentiation of GBM cell seems be less pronounced with carbon ions compared to X-rays both normoxic and hypoxic conditions.

These results highlight the existence of hypoxia-dependent radioresistance to carbon ions depending on the GBM cells and we have to pursue these investigations with protons. Lastly, these results suggest that combined strategies, in particular targeting hypoxia could be interesting to study.

REFERENCES:
Bekaert *et al.,* 2017, Eur J Nucl Med Mol Imaging; 44(8):1383-1392.
Valable *et al.,* 2020, Cancers (Basel); 12(8):2019.

Ackowledgements:
CNRS, UNICAEN, Archade, ANR-10-EQPX1401, Région Normandie and the French State in the framework of the CPIER " Vallée de la Seine " 2015-2020 (HABIONOR project); 2020-22 (ARCHADE-CHOxTracc project co-funded by the Normandy County Council, the European Union within the framework of the Operational Programme ERDF/ESF 2014-2020).

"Determination of genes implicated in the resistance to proton beam therapy during the treatment of glioblastoma"

Jia-Wei Chen[1], Anne-Catherine Wera[1], Benjamin Le Calvé[1], Stéphane Lucas[2], Anne-Catherine Heuskin[2], Carine Michiels[1]
[1] Laboratory of biochemistry and cellular biology (URBC), Namur Research Institute for Life Sciences (NARILIS), University of Namur, Namur, Belgium.
[2] Laboratory of nuclear reaction analysis (LARN), Namur Research Institute for Life Sciences (NARILIS), University of Namur, Namur, Belgium.

Glioblastoma multiforme (GBM) is the most malignant and common form of primary brain tumors in adults. It accounts for more than 60% of all brain tumors and most of the patients affected by this type of cancer survive less than 2 years. The standard treatment for GBMs is composed of three steps: the surgical resection of the tumor, the combination of fractioned radiotherapy and temozolomide (TMZ) followed by adjuvant TMZ therapy[1]. Despite improvements in treatment modalities, curing GBM is still very challenging due to the tumor resistance against anti-cancer therapies. In this context, this project aims to identify genes involved in the resistance to GBM standard treatment in order to bypass the intrinsic resistance of cancer cells to treatment. The GeCKO v2 pooled single-guide RNA libraries[2] were used to conduct a genome-scale CRISPR-Cas9

screen in U87 cell line. After the transduction of pooled libraries, U87 cells were exposed to fractioned doses of X-rays combined with TMZ during 2 weeks in order to identify candidate genes upon which knockout selectively enhanced or reduced cell sensitivity to treatment. Genomic DNA of non-treated and treated cells was harvested and the lentiviral regions containing the sgRNA sequence were amplified by PCR for the subsequent Illumina sequencing. Screen analysis highlighted several potential target genes and groups of genes that are currently under validation. Finally, the implication of candidate genes in GMB resistance to combined treatment using proton irradiation will be assessed in comparison to X-rays.

REFERENCES

[1] Lee, C. Y. Strategies of temozolomide in future glioblastoma treatment. *Onco. Targets. Ther.* **10**, 265–270 (2017).

[2] Sanjana, N. E., Shalem, O. & Zhang, F. Improved vectors and genome-wide libraries for CRISPR screening. *Nature Methods* (2014).

"Assessment of cellular response to internal radiotherapy delivered by Auger-electrons emissions"

Radu Marian SERBAN[1,2], Dana NICULAE[1], Gina MANDA[3], Ionela Victoria NEAGOE[3], Maria-Roxana CORNOIU[1], Dragos Andrei NICULAE[4], Mihaela TEMELIE[1], Anca DINISCHIOTU[2]

1 Horia Hulubei National Institute for R&D in Physics and Nuclear Engineering (IFIN-HH), Radiopharmaceutical Research Centre, 30 Reactorului Street, Magurele-Ilfov, Romania

2 University of Bucharest, Faculty of Biology, 91-95 Splaiul Independentei, Bucharest, R-050095, Romania

3 National Institute of Research Developement in the Pathology Domain and Biomedical Science "VICTOR BABES", 99-101 Splaiul Independentei, Bucharest, Romania

4 University of Medicine and Pharmacy Carol Davila, Pharmacy Faculty, 37 Dionisie Lupu street, Bucharest, Romania

Increased specificity of internal radiotherapy and improved delivery methods are needed to foster this approach, especially when high LET emitting radioisotopes (alpha, Auger electrons or low energy beta) are employed. On the course of developing improved strategies for the treatment of cancerous tumours, the use of certain types of radiations to induce targeted cellular damage to the afflicted cells, and subsequently triggering cell death mechanisms, became outstanding. Radiolabelled biocompatible molecules, such as (poly)peptides or nanoparticles are being used to ensure that the tumour cells receives internally most of the radioisotope's linear energy transfer, thus having a lesser effect on surrounding healthy tissues.

Low energy Auger-electrons, emitted during electron-capture nuclear decay, short range penetrate the tissue (nanometres), therefore it's considered an excellent choice to induce cellular death in cancerous cells by damaging DNA structure, directly or through increased oxidative stress. Given the importance of copper ions in cellular division, especially in cancerous cells, we have chosen to use ^{64}Cu radioisotope.

We assessed *in vitro* the effects of ^{64}Cu radiation on different cancerous cell lines and one reference normal cell line, testing for radio-induced oxidative stress by measuring the GSH and MDA content, activation of certain gene involved in cells oxidative stress response and protection. Cellular viability was tested using the MTS and LDH assays. Morphological staining methods were used to determine the cell death by apoptosis or necrosis. Experiments indicate that cell lines with higher proliferation rate are more susceptible to cell death by apoptosis, as a result to incubation with $[^{64}Cu]CuCl_2$.

The results demonstrate the potential of short range, highly damaging radiation emissions to be used as internal radiotherapy agents, by contributing to the understanding of the involved mechanisms of biochemical processes within the tumour ecosystem.

Acknowledgements: This work was supported by a grant of the Romanian MCD/UEFISCDI project 64PCCDI/2018.

"Synergistic Photon Tomography from 1eV to 1MeV: Integrated Ultra-High Definition PET, SPECT, Optical & X-ray CT"

Adam Badar, MILabs, Utrecht, **The Netherlands**

In preclinical research we have dreamed about a 3D magnifying glass that would allow us to e.g. see various cell functions and structures in a dynamic 4D single scan, and map integrated detailed dynamics of e.g. contrast agents, tracers, pharmaceuticals, receptors and indicators of therapy response in tumors. To meet these and many other imaging needs we developed a user friendly fully integrated PET-SPECT-Optical-CT imaging platform (WMIC Commercial Innovation of the Year 2018) comprising: A) down to 0.12 mm SPECT & 0.6 mm PET resolution, proprietary sub-mm resolution positron-range free PET for e.g. 124-I, 76-Br, 82-Rb and 89-Zr. B) concurrent sub-mm multi-tracer PET and PET-SPECT C) sub-second dynamic PET & SPECT D) sub-mm resolution imaging of alpha and beta emitting pharmaceuticals E) ultra-high performance low dose X-ray CT, and F) Quantitative Fluorescence & Bioluminescence Tomography.

In this presentation this highly adaptive and versatile nuclear, optical and anatomical imaging platform will be explained along with many scientific applications contributed by hundreds of worldwide users.

www.milabs.com

MILabs
Making Molecular Imaging Clear

"Arronax cyclotron: a unique facility for research and production of innovative radionuclides"

Jacques Barbet, NEXT IRC Transformed & Cyclotron Arronax, Nantes, **France**.

The Arronax cyclotron is unique, by its energy, 70 MeV, its proton intensity (2 x 375 µA) and its ability to accelerate negative (H-, D-) and positive (H-H+, He2+) ions. Delivered on-site in 2008, it has been fully operational since 2011. Primarily dedicated to research in nuclear medicine and especially nuclear oncology through the production of a variety of radionuclides, it has also developed research activities in physics, radiochemistry and radiolysis, and radiobiology by offering a dedicated vault for inert and living matter irradiation with accelerated charged particles. It is one of a few sites in the world producing strontium-82 for routine clinical cardiology PET. It also produces copper-64 and astatine-211 on a regular basis for research and a series of radionuclides including scandium-44 and ruthenium-97. The productions of copper-67 and germanium-68 are under development, and Arronax is open to propositions to produce radionuclides of high scientific interest. Arronax also houses an Internal Pharmacy Annex of the Nantes University Hospital with the capability of producing radiopharmaceuticals for clinical research use. While Arronax has been the heart of many local collaboration projects and now of the NEXT IRC Transformed, it welcomes scientists who develop projects within its numerous application domains.
Please visit the Arronax web site at www.arronax-nantes.fr and do not hesitate to get in touch with it staff to see how Arronax can help you.

"Hypoxia imaging and tumour adaptation to radiotherapies"

Invited speaker: **Heidi Lyng**, Oslo University Hospital, Oslo, **Norway**.

Solid tumours generally shown regions with insufficient oxygen supply, defining them as hypoxic. Oxygen is needed for efficient cell kill with ionizing radiation (the oxygen effect), and hypoxia is associated with poor radiotherapy outcome in most cancer types. Emerging radiotherapy strategies, like proton therapy and combination therapies with radiation and hypoxia targeted drugs provide new opportunities to overcome the hypoxia barrier and improve therapeutic outcome. To implement such strategies in the clinic and identify patients with an expected benefit, medical imaging is an appealing approach. With imaging, information about the entire tumour is achieved and response to treatment can be recorded over time will high reproducibility.
Hypoxia varies considerably within and across tumours. Differences exist not only in prevalence but importantly, also in level, ranging from mild, almost non-hypoxic, to severe and anoxic levels. This heterogeneity shows transient and long-term changes as the cancer develops, creating a dynamic pattern of hypoxia levels that induces cellular responses and controls interactions between tumour cells, stroma and immune cells in the microenvironment. The radiosensitizing effect of oxygen as well as the effect of hypoxia-targeted strategies strongly depends on the hypoxia level. In this talk, I will briefly summarize how hypoxia modulates the biology of solid tumors and promotes radiotherapy resistance through other mechanisms in addition to the oxygen effect. I will further present a novel MRI-based method developed in our lab to image hypoxia levels, and discuss the potential of such imaging approaches in adaptive radiotherapy.

"A portable gamma camera for the optimization of the patient dosimetry in radioiodine therapy of thyroid diseases"

T. Bossis[1], M-A Verdier[2], L. Pinot[1], F. Bouvet[1], Y. Charon[2], T. Beaumont[3], D. Broggio[3], S. Lamart[3], O. Caselles[4], S. Zerdoud[4], L. Ménard[2]

[1] Université Paris-Saclay, CNRS/IN2P3, IJCLab, ORSAY, France,

[2] Université Paris-Saclay, CNRS/IN2P3, IJCLab, ORSAY, France and Université de Paris, IJCLab, ORSAY, France,

[3] IRSN, LEDI, FONTENAY-AUX-ROSES, France,

[4] IUCTO, ICR, TOULOUSE, France,

Molecular radiotherapy is an efficient treatment modality of benign and malign thyroid diseases. However, there is still a need to better assess the dose delivered to target tissues and organs-at-risk in order to optimize for each patient the activity to be administered according to the objectives of disease control (destruction of tumor residues, restoration of thyroid function or hypothyroidism) while maintaining the risk of toxicity at a justifiable level. In that context, our objective is to develop a high-resolution mobile gamma camera specifically designed to accurately measure the radiotracer biokinetics at the patient's bedside during treatment planning and therapeutic dose verification. A first feasibility prototype of the mobile camera with a 5x5cm^2 field of view was developed for the treatment of benign and malign thyroid diseases with ^{131}I, leading to promising results [1]. Its abilities to quantify homogeneous and heterogeneous activity distributions (such as nodules) was evaluated on 3D thyroid phantoms. The recovery coefficient achieved with a very simple quantification protocol was above 90% even for the smallest nodules. This relies both on the high spatial resolution of the camera, which reduces partial volume effect and leads to better ROIs definition and on its compactness, which offers the possibility to improve image resolution by reducing the distance and the angular view between the detector and the targeted structures. We are currently developing a new prototype for clinical use with extended field of view 10x10 cm^2. It consists of a 3D-printed parallel-hole tungsten collimator coupled to a 1 cm thick $CeBr_3$ scintillator, readout by an array of 6x6 mm^2 Silicon Photomultipliers. Preliminary results show an energy resolution of 7.1 % and a FWHM spatial resolution around 1 mm at 356 keV. A detailed description of the camera optimization (collimator and shielding design, intrinsic spatial performance, counting rate capabilities) will be presented.

REFERENCES
[1] C. Trigila, Development of a portable gamma imaging system for absorbed radiation dose control in molecular radiotherapy, These de doctorat, Université Paris-Saclay (ComUE), 2019.

"In vitro and in vivo evaluation of a ^{64}Cu-radiolabelled anti-CD 138 antibody for Multiple Myeloma imaging and dosimetry"

Cassandra Métivier[1], Patricia Le Saëc[1], Séverine Marionneau-Lambot[1], François Davodeau[1], Catherine Chauvet[1], Catherine Maurel[1], Peter O Hofgaard[2 3], Bjarne Bogen[2 3], Joëlle Gaschet[1], Raphaël Tripier[4], Férid Haddad[5], Michel Chérel[1], Nicolas Chouin[1,6], Alain Faivre-Chauvet[1], Latifa Rbah-Vidal[1].

[1] Université de Nantes, CHU Nantes, CNRS, Inserm, CRCINA, F-44000 Nantes, France

[2] Department of Immunology, Centre for Immune Regulation, Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

[3] KG Jebsen Centre for Influenza Vaccine Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

[4] UMR CNRS 6521 CEMCA, University of Brest, Brest, France.

[5] GIP Arronax, Saint-Herblain, France

[6] Oniris (Nantes Atlantic College of Veterinary Medicine, Food Science and Engineering), Nantes, France.

CD138 is a surface proteoglycan used as a target in multiple myeloma (MM) because of its high expression in myeloma cells. Recently, an anti-murine CD138 monoclonal antibody (9E7.4) radiolabelled with ^{64}Cu ([^{64}Cu]Cu-HTE1PA-9E7.4) has been tested as PET radiotracer in the 5T33 murine MM model, with promising results(1). The murine myeloma cell line, MOPC315.BM has been developed to better mimic the human disease, with bone marrow homing and damage when injected in Balbc/j mice.

In this project, we evaluated *in vivo* (PET imaging) and *ex vivo* biodistribution, pharmacokinetics and dosimetry of ^{64}Cu]Cu-HTE1PA-9E7.4 in balbc/J mice bearing MOPC315.BM tumour.

Methods:
First, CD138 expression in MOPC315.BM cells and 9E7.4 mAb specificity were validated by flow cytometry. Immunoreactivity of [^{64}Cu]Cu-HTE1PA-9E7.4 was determined using CD138-peptide-coated magnetic beads. PET imaging and *ex vivo* biodistribution studies using [^{64}Cu]Cu-HTE1PA-9E7.4 were performed at several times after tracer injection in mice bearing subcutaneous MOPC315.BM tumours. Finally, pharmacokinetics and dosimetry have been estimated based on biodistribution studies.
Results:
Flow cytometry results confirmed overexpression of CD 138 in MOPC315.BM cell line. Biodistribution results showed a progressive decrease in blood of [^{64}Cu]Cu-HTE1PA-9E7.4 from 20.3 ± 4.1% IA/g at 30 min to 3.5 ± 0.6% IA/g at 24 h p.i. and a specific tumour uptake from 30 minutes p.i (37.8 ± 4.4% IA/g) which increased up to 48 hours (> 50% IA/g at 24 h and 48 h p.i) was demonstrated. After 24 hours, PET imaging shows a high tumour to muscle ratio (55.1:0.4). Mean absorbed s.c tumour of 0.1 g was 0.6 Gy/MBq.
Conclusion:
This study supports the interest of [^{64}Cu]Cu-HTE1PA-9E7.4 in targeting CD 138 in the MM with a greater uptake in MOPC315.BM tumors than 5T33 tumors (13.6 ± 5.4 % IA/g at 24 h). The biodistribution study of the [^{64}Cu]Cu-HTE1PA-9E7.4 has predicted the biodistribution of [^{67}Cu]Cu-HTE1PA-9E7.4. Copper-67 is a radionuclide with a longer half-life than copper-64 that emits 100% of β^- radiation which promises an interest for a therapeutic application.

The TheraScCoop project is financially supported by the NExT "Nantes Excellence Trajectory" initiative (I-SITE call for projects), an action of the second Future Investments Program (PIA2) launched by the French State and implemented by the ANR (reference ANR-16-IDEX-0007). This initiative takes place in the Pays de la Loire region, in Nantes Métropole.

REFERENCES
[1] Navarro, A.S. et al. (2019) TE1PA as Innovating Chelator for 64Cu Immuno-TEP Imaging: A Comparative in Vivo Study with DOTA/NOTA by Conjugation on 9E7.4 mAb in a Syngeneic Multiple Myeloma Model. Bioconjugate Chemistry 30 : 2393-2403.

"Longitudinal and multiparametric study of radiotherapy toxicities on healthy brain in the rat"

Fatima-Azzahra Dwiri[1], Julie Bécam[1], Carole Brunaud[1], Laurent Chazalviel[1], Samuel Valable[1], Myriam Bernaudin[1], Elodie A. Pérès[1], Omar Touzani[1]

[1] *Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy group, GIP Cyceron, Caen, France*

Although radiation therapy (RT) improves patient prognosis with brain cancer, it also affects healthy brain tissue, a phenomenon recognized to induce irreversible cognitive deficits in long-surviving patients. Over the past fifteen years, quality of life of treated patients has taken greater importance in neuro-oncology and current clinical paradigm is to specifically target brain tumors while sparing surrounding healthy tissue. Thereby, new RT modalities have been developed, but scientific evidence is strongly needed to demonstrate their value in reducing radiation neurotoxicity. Most preclinical studies of brain damage after RT are performed in healthy animal models with whole-brain irradiation, not considering bystander effects induced by the tumor itself. Thus, this study aims to characterize the effects of targeted brain irradiation (TBI) on tissue integrity and cognition in healthy rat or bearing glioblastoma model.

Wistar rats were divided into control (CTL) and irradiated (IR) groups. Fractionated irradiation (30 Gy) was applied on the right hemisphere using a preclinical irradiator (X-RAD 225Cx). A battery of behavioral tests was performed longitudinally (6 months) to analyze short-term (Novel-Object-Recognition) and long-term (Passive-Avoidance) memories, spatial learning and reference memory (Morris water maze), locomotor activity (Actimetry) and anxiety-like behavior (Elevated-Plus-Maze). MRI analyses were also performed.

Studies in healthy rats have shown that long-term memory was not impaired in IR group unlike short-term memory compared to CTL. Irradiation induced a significant alteration of learning ability. No major difference in locomotor activity was found, but the exploration activity of IR rats was significantly higher. IR rats showed significant anxiety-like behavior. MRI did not show any radio-necrosis nor edema in IR group but a significant reduction of the irradiated hemisphere volume. These results show that TBI induces significant brain damage and cognitive deficits in rat. The same multiparametric study is currently underway in irradiated rats bearing glioblastoma in order to compare the neurotoxicity of radiation with those observed in healthy rats.

Acknowledgments: This study was co-funded by the Région Normandie, the European Union-Fonds Européen de Développement Régional (FEDER), the French State in the framework of the interregional development Contract "Vallée de la Seine" 2015-20 (Habionor) and 2018-21 (3R), the CNRS, the Université de Caen Normandie, the Ministère de l'Enseignement Supérieur et de la Recherche, the French National Agency for Research "Investissements d'Avenir" (ANR-11-LABEX-0018-01 and ANR-10-EQPX1401) and the Cancéropôle Nord-Ouest.

"Characterization of hypoxia in brain metastases from lung cancer: from the pre-clinical approach to the clinic "

Jade Fantin[1#], Aurélien Corroyer-Dulmont[1,2#], Samuel Valable[1], Jérôme Toutain[1], Sylvain Teulier[1,4], Céline Bazille[1,3], Jérôme Levallet[1], Méziane Ibazizène[1], Stéphane Guillouet[1], Cécile Perrio[1], Françoise Chapon[3], Guénaëlle Levallet[1,3], Myriam Bernaudin[1]

[#]equal contribution

[1] Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy group, GIP CYCERON, 14000 Caen, France

[2] Medical Physics Department, CLCC François Baclesse, 14000 Caen, France

[3] Department of Pathology, University Hospital of Caen, Caen, France

[4] Department of Pulmonology & Thoracic Oncology, University Hospital of Caen, Caen, France

Lung cancer patients frequently (40%) develop brain metastases (BM). Despite aggressive treatment including neurosurgery and external radiotherapy (RT), overall survival remains poor. The hypoxic intra-tumoral microenvironment generates expression of many genes, through the transcription factor Hypoxia-inducible Factors (HIFs), known to participate in tumor growth and resistance to RT making hypoxia a factor of poor prognosis. The purpose of this study is to further characterize the microenvironment of BM.

Hypoxia was evaluated in 28 BM biopsies from non-small cell lung cancer patients (NSCLC) using CA-IX and HIF-1α immunostaining (North-West-Committee-for-Persons-Protection-III N°DC-2008-588). HIFs and target genes were also studied *in vitro* on NSCLC tumors cells H2030-BrM3 (MSKCC, Dr Massagué, USA) in normoxic/hypoxic conditions (1% O_2). Hypoxia characterization by pimonidazole,

CA-IX, HIF-1α and HIF-2α was also performed in different rat BM models (H2030-Br3M and H1915 intracerebral injections into cortex and striatum, or H2030-Br3M intracardial injection) in nude rats. Additionally, [^{18}F]-FMISO-PET and oxygen-saturation-mapping-MRI (SatO2-MRI) were carried out in intracerebral BM models to further characterize tumor hypoxia and evaluate the potential of hypoxia-image-guided-RT (CENOMEXA#5065-#8941).
In patients, we showed that 78.6% of BM expressed CA-IX and that HIF-1α staining is observed where that of CA-IX is strong. *In vitro* studies also showed HIF-1α and HIF-2α expression in H2030-BrM3 cells and that hypoxia increased target gene expression (TUBB3, VEGF, GLUT-1, CCDN1, CA-IX). Moreover, in both intracerebral injection models (H1915 and H2030-BrM3), pimonidazole, CA-IX and HIF-1α were detected with a heterogeneity inter- and intra-metastasis. Multimodal imaging with [^{18}F]-FMISO-PET and SatO2-MRI confirmed that the microenvironment of H1915 and H2030-BrM3-derived BM is hypoxic. In the BM model induced by intracardial injection, we observed a positive staining for pimonidazole, HIF-1α, CA-IX, and for HIF-2α. These results highlight hypoxia as a hallmark of BM from lung cancer and that BM hypoxia could be further used to guide RT.

Funding: CNRS, UNICAEN, Région Normandie, Union Européenne-Fonds Européen de Développement Régional (FEDER) et l'Agence Nationale de la Recherche « Investissements d'Avenir » n°ANR-11-LABEX-0018-01 and n°ANR-10-EQPX1401.

"Apparent diffusion coefficient and high b-value Diffusion-Weighted Magnetic Resonance Imaging as biomarkers for tumor response to re-irradiation with Carbon Ion Radiation Therapy for pelvic rectal recurrences: an explorative analysis"

G.Fontana[1], A.Barcellini[1], D.Boccuzzi[1-2], S.Imparato[1], M.Pecorilla[1], A.Vai[1], V.Vitolo[1], D.Maestri[1], A. Ghirelli[1-3], P. Loap[1-4], L. Preda[5-6], G.Baroni[1-7], E.Orlandi[1]
[1]National Center for Oncological Hadrontherapy (Fondazione CNAO)
[2]Diagnostic Radiology Residency School, University of Pavia
[3]Radiation Oncology Residency School, Department of Radiotherapy, Istituto Oncologico del Veneto
[4]Radiation Oncology Residency School, Department of Radiation Oncology, Institut Curie

[5]*Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, Unit of Radiology, University of Pavia*
[6]*Radiology Unit, Fondazione IRCCS Policlinico San Matteo*
[7]*Department of Electronics, Information and Bioengineering, Politecnico di Milano*

Background: Carbon Ion Radiotherapy (CIRT) has proved to be effective, safe and feasible as re-irradiation of locally recurrent rectal cancers (LRRCs)[1-4]. Radiological features might be worthwhile in building a tailored treatment strategy optimizing the advantages of particles. In this context, Diffusion-Weighted magnetic resonance Imaging (DW-MRI) and the related Apparent Diffusion Coefficients (ADC), sensitive to tissue microstructural parameters, proved to be promising biomarkers of CIRT response[5-8].

Aim: To investigate the role of pre-treatment ADC and b=1000 smm^{-2} DW-MRI (b1000) in treatment response prediction of LRRCs re-irradiated with CIRT.

Material and Methods: Clinical and radiological data of 17 consecutive patients (age range: 34-78 years; M:F=16:1) re-irradiated with CIRT for LRRCs (11 pre-sacral, 5 perineal and 1 pre-coccygeal) were retrospectively analysed. Each relapse was manually contoured on pre-treatment b1000 and respective ADC. Median, inter-quartile, skewness and kurtosis were used to describe ADC and b1000 lesion histograms. According to radiological hallmarks, patients were stratified as 1-year-responder (R) and 1-year-non-responder (NR). Statistically significant differences of DW-MRI features were tested with non-paired Mann-Whitney U test (α=0.05). Receiver Operating Characteristic (ROC) analysis was performed on relevant DW-MRI features, and related Area Under the ROC Curve (AUC) was computed as a feature diagnostic accuracy indicator.

Results: All b1000 features and ADC kurtosis showed statistically significant differences between NR (6 patients) and R (11 patients) groups. Especially, b1000 median and inter-quartile and ADC kurtosis appear promising ($p<0.025$, AUC>0.8) in stratifying patients as NR (62.5 ± 23.9, 1.15) or R (34 ± 13, 0.44).

Conclusion: b1000 median and inter-quartile, as well as ADC kurtosis, showed remarkable potentiality of being a biomarker of CIRT response in LRRCs reflecting the worth of DW-MRI as a non-invasive approach to test tumour response. Further investigations should be carried out on a larger cohort of LRRC patients to confirm these results.

REFERENCES
[1] Barcellini, A et al. "Re-irradiation With Carbon Ion Radiotherapy for Pelvic Rectal Cancer Recurrences in Patients Previously Irradiated to the Pelvis." *In vivo (Athens, Greece)* vol. 34,3 (2020): 1547-1553. doi:10.21873/invivo.11944
[2] Cai, X et al. "The role of carbon ion radiotherapy for unresectable locally recurrent rectal cancer: a single institutional experience." *Radiation oncology (London, England)* vol. 15,1 209. 28 Aug. 2020, doi:10.1186/s13014-020-01653-w
[3] Shiba, S et al. "Prospective Observational Study of High-Dose Carbon-Ion Radiotherapy for Pelvic Recurrence of Rectal Cancer (GUNMA 0801)." *Frontiers in oncology* vol. 9 702. 31 Jul. 2019, doi:10.3389/fonc.2019.00702
[4] Habermehl, D et al. "Reirradiation Using Carbon Ions in Patients with Locally Recurrent Rectal Cancer at HIT: First Results." *Annals of surgical oncology* vol. 22,6 (2015): 2068-74. doi:10.1245/s10434-014-4219-z
[5] Preda, L et al. "Predictive role of Apparent Diffusion Coefficient (ADC) from Diffusion Weighted MRI in patients with sacral chordoma treated with carbon ion radiotherapy (CIRT) alone." European journal of radiology vol. 126 (2020): 108933. doi:10.1016/j.ejrad.2020.108933
[6] Preda, L et al. "MRI evaluation of sacral chordoma treated with carbon ion radiotherapy alone." Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology vol. 128,2 (2018): 203-208. doi:10.1016/j.radonc.2017.11.029
[7] Buizza, Get al. "Radiomics and Dosiomics for Predicting Local Control after Carbon-Ion Radiotherapy in Skull-Base Chordoma." Cancers vol. 13,2 339. 18 Jan. 2021, doi:10.3390/cancers13020339
[8] Franconeri, A et al. "Intravoxel incoherent motion as a tool to detect early microstructural changes in meningiomas treated with proton therapy." Neuroradiology, 10.1007/s00234-020-02630-6. 3 Jan. 2021, doi:10.1007/s00234-020-02630-6

"Quantitative Magnetic Resonance Imaging during prostate radiotherapy treatment: preliminary study using a 0.35T MR-linac system"

L. Marage[1], S. Rapacchi[2], P-M. Walker[1], M. Quivrin[1], E. Martin[1], G. Truc[1], A. Petitfils[1], J. Boudet[1], I. Bessières[1], L. Aubignac[1]
[1] *Centre Georges-François Leclerc, Dijon, France*
[2] *Aix-Marseille Univ, CNRS, CRMBM, Marseille, France*

The interest for MR-linac systems is growing for their capacity to gate radiative treatment of the moving lesion in real time, dramatically increasing the precision and range of external radiotherapy treatments. This real time gating is performed

by a Magnetic Resonance Imaging (MRI) device, providing high tissue contrast and fast non-ionizing imaging. Additionally, MRI can acquire quantitative images that measures the tissues relaxation times.

In the case of the prostate cancer, MR T_2 relaxation time has been used to help the detection of lesions [1]. The acquisition of quantitative MRI (qMRI) sequences right after the treatment fraction is possible with the MR-linac system. Thus, MR-linac could provide a better insight of the lesion microenvironment during the treatment and could show the inertia of this treatment. This is the purpose of this preliminary study.

A MR-linac system 0.35T MRIdian (ViewRay) was used. qMRI acquisitions were carried out on patients included in a clinical trial about hypo-fractioned external radiotherapy treatments of the prostate.

The qMRI protocol is an adaptation of the DESPOT method [2]. DESPOT is a fast qMRI method providing an estimation of the T_1, T_2, which was extended to also include T_2^* relaxation times. Quantitative tissues parameters are obtained as mappings from MR images using a homemade Matlab code.

The current results show a decrease of the T_2, an increase of the T_2^* and no effect of the T_1 during the treatment.

Further investigations on more patients are warranted to confirm the trends of relaxations times from the preliminary results. Seven patients have been scheduled to this day. Correlation with treatment side effect and biopsies will prolong this preliminary study.

REFERENCES

[1] Lee CH. Quantitative T2-mapping using MRI for detection of prostate malignancy: a systematic review of the literature. Acta Radiol 2019;60:1181–9. https://doi.org/10.1177/0284185118820058.

[2] Deoni SCL, Rutt BK, Peters TM. Rapid combined T1 and T2 mapping using gradient recalled acquisition in the steady state. Magn Reson Med 2003;49:515–26. https://doi.org/10.1002/mrm.10407.

"^{99m}Tc-Tektrotyd, the first radiopharmaceutical for NETs diagnosis at the Nuclear Medicine Service in Kosovo"

Armend Jashari[1, 2,4], Fakir Spahiu[3], Ismet Bajrami[3], Emilija Janevik-Ivanovska[1]

[1] *Faculty of Medical Sciences, Goce Delcev University Stip, Republic of North Macedonia*

[2] *Hospital and University Clinical Service of Kosovo-Shskuk*

[3] *Nuclear Medicine Department in Hospital and University Service of Kosovo*

[4] *Alma Mater Europaea Campus College "REZONANCA", Republic of Kosovo*

The new Radiopharmacy in Nuclear Medicine department in Hospital and University Service of Kosovo apply the policy that all products administered into the human body, especially the new ones are safe and show a constant high quality in producing the required effects.

Tektrotyd or HYNIC – (D-Phe[1,] Thyr[3]-Octreotide) trifluoroacetate (Polatom) radiopharmaceutical labelled with ^{99m} Technetium (^{99m}Tc) was used to identify medical problems related to overexpression of somatostatin receptors, particularly subtype 2 and, to a lesser extent subtypes 3 and 5.

A number of clinicopathological criteria proved to be used as predictors of malignant behavior of these tumors. Immunohistochemical markers for neuroendocrine tumors (NETs) include cell proliferation (Ki-67 index) and neuroendocrine markers such as chromogranin A (CgA).

^{99m} Tc-Tektrotyd is administered intravenously in a single dose after labelling of the kit using a sterile, oxidant-free sodium pertechnetate (^{99m} Tc) solution for injection (eluate of ^{99}Mo/^{99m}Tc radionuclide generator) in accordance with the instructions for preparation of the radiopharmaceutical and regular quality control after the labelling.

The goal of our presentation is to show the regular use of ^{99m} Tc-Tektrotyd as a part of our daily diagnostic procedures for (1) assessment of patients with NET and improve imaging, staging and follow up of oncological patients demonstrating carcinoid tumor patient management.

REFERENCES

[1]Sergieva S, Robev B, Dimcheva M, Fakirova A, Hristoskova R. Clinical application of SPECT-CT with 99mTc-Tektrotyd in bronchial and thymic neuroendocrine tumors (NETs). Nucl Med Rev Cent East Eur. 2016;19(2):81-7.

"Irradiation at ultra high dose rate: from the FLASH effect to clinical translation"

Invited speaker: **Marie-Catherine Vozenin**, Department of Radiation Oncology, Department of Oncology, Lausanne University Hospital and Lausanne University, **Switzerland.**

Radiation therapy is a cornerstone of cancer treatment used in over 50% of cancer patients. However, its efficacy remains suboptimal in the case of radiation-resistant tumors that relapse and ultimately undergo metastatic development. Therefore innovation is required to eradicate the primary tumor and improve the therapeutic outcome. Thanks to our pioneering work, which has now been reproduced by many other laboratories worldwide, ultra-high dose rate, FLASH-RT has now emerged as one of the most promising innovations in the field of radiation oncology, since it simultaneously controls tumor growth without normal tissue complications in experimental models and early clinical trials performed in domestic animals. Interestingly, the potential benefits of FLASH-RT might go beyond normal tissue protection and might allow the cure of tumors known to be resistant to radiotherapy delivered at conventional dose rates. Investigations of the physico-chemical and biological mechanisms involved in tissue response to FLASH-RT have been started that will be summarized in this talk. Limitations and perspectives will also be discussed.

"Adaptation of DNA damage repair using DNA-PKcs inhibitors as selective potentiation of peptide receptor radionuclide therapy "

Thom Reuvers[1,2], Julie Nonnekens[1,2]

[1] Department of Molecular Genetics, Erasmus MC Cancer Institute, Erasmus University Medical Center, 3000 CA Rotterdam, The Netherlands

[2] Department of Radiology and Nuclear Medicine, Erasmus MC Cancer Institute, Erasmus University Medical Center, 3000 CA Rotterdam, The Netherlands

Peptide receptor radionuclide therapy (PRRT), using [^{177}Lu]Lu-DOTA-(Tyr^3)-octreotate, is an FDA- and EMA-approved treatment modality for patients with somatostatin receptor subtype 2 (SSTR2) expressing neuroendocrine tumors (NETs). PRRT exerts its anti-cancer mechanism by octreotate binding to SSTR2, after which DNA damage, such as double strand breaks (DSBs), is induced during radioactive decay. Although PRRT has been shown to be effective, complete cure is rare. Cancer cells counteract PRRT by activating DNA repair via the DNA damage response (DDR). An attractive idea for improvement is therefore to combine PRRT with inhibitors of DDR proteins to inhibit damage repair, ideally increasing efficacy without adding toxicity.

We have conducted a high-throughput viability screen with 699 small molecule inhibitors of DDR proteins in combination with PRRT in two different SSTR2-positive cell lines to identify potential radiosensitizing compounds. Besides known radiosensitizers such as PARP1 and HSP90 inhibitors [1,2], we identified multiple inhibitors of DNA-PKcs, a central DDR protein involved in DSB repair, as one of the major hit classes. Using newer generation DNA-PKcs inhibitors AZD7648 and KU57788, using different viability, cell death and survival assays, we found a significant radiosensitizing effect in multiple NET and non-NET cell lines, while monotherapy toxicity was kept at a minimum. Moreover, we analyzed the nature of this therapy effect on cell cycle distribution using flow cytometry analysis and found that the combination therapy increases G2/M-checkpoint blockade. Analysis of DSB dynamics by 53BP1 immunofluorescent microscopy showed that DNA-PK inhibitors significantly increase the total level of DSBs over multiple days, indicating a severe deficiency in DSB repair.

Concluding, our data demonstrate that DNA-PKcs inhibition is an effective strategy for potentiation of PRRT in various NET models. Future work will include testing this combination therapy *in vivo* using different dosing schemes and investigation into NET-specific biomarkers to predict therapy efficacy.

REFERENCES
[1] Nonnekens J, van Kranenburg M, Beerens CEMT, Suker M, Doukas M, van Eijck CHJ, de Jong M, van Gent DC. Potentiation of Peptide Receptor Radionuclide Therapy by the PARP Inhibitor Olaparib. Theranostics 2016; 6(11):1821-1832. doi:10.7150/thno.15311.
[2] Hofving, T., Sandblom, V., Arvidsson, Y., Shubbar, E., Altiparmak, G., Swanpalmer, J., Almobarak, B., Elf, A., Johanson, V., Elias, E., Kristiansson, E., Forssell-Aronsson, E., & Nilsson, O. (2019). 177Lu-octreotate therapy for neuroendocrine tumours is enhanced by Hsp90 inhibition, Endocrine-Related Cancer, 26(4), 437-449. doi:10.1530/ERC-18-0509

"CAIX-targeted radionuclide therapy in immunodeficient and immunocompetent mouse models"

Simone Kleinendorst[1], Robin Merkx[1,3], Jan Bussink[2], Peter Mulders[3], Alfred Morgenstern[4], Frank Bruchertseifer[4], Peter Chandler[5], Michael P. Wheatcroft[5], Mark Rijpkema[1], Mark Konijnenberg[1], Egbert Oosterwijk[3], Sandra Heskamp[1]
[1]Department of Medical Imaging: Nuclear Medicine, Radboudumc, Nijmegen, The Netherlands;
[2]Department of Radiotherapy, Radboudumc, Nijmegen, The Netherlands
[3]Department of Urology, Radboudumc, Nijmegen, The Netherlands;
[4]European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany;
[5]Telix Pharmaceuticals Limited, Melbourne, Australia

Introduction
Radioimmunotherapy (RIT) using ^{177}Lu-labelled cG250, an antibody recognizing CAIX which is overexpressed by clear cell renal cell carcinoma (ccRCC) cells, demonstrated therapeutic efficacy in ccRCC patients, but haematotoxicity hindered further clinical implementation. An attractive approach to potentially improve efficacy and lower toxicity of RIT is the use of alpha-emitters, because of their high linear energy transfer and short path length. In this study we compare the therapeutic efficacy of [^{225}Ac]Ac-DOTA-hG250 (^{225}Ac-hG250) to [^{177}Lu]Lu-DOTA-hG250 (^{177}Lu-hG250) in immunodeficient mice. Furthermore, we set up two immunocompetent mouse models to evaluate the immunological and radiobiological effects of CAIX-targeted RIT.

Methods

Therapeutic efficacy was evaluated in immunodeficient BALB/c nude mice bearing subcutaneous CAIX-expressing SK-RC-52 xenografts treated with ^{225}Ac-hG250 (5, 15 or 25 kBq), ^{177}Lu-hG250 (13 MBq), or no treatment. For the setup of immunocompetent mouse models, Renca and CT26 cell transfected with human CAIX (Renca-CAIX and CT26-CAIX), were characterized *in vitro* for CAIX expression, internalization, and radiosensitivity. Furthermore, tumor growth curves and ^{177}Lu-hG250 uptake were evaluated in BALB/c mice.

Results

Treatment with 15 or 25 kBq ^{225}Ac-hG250 in immunodeficient mice resulted in tumor sizes comparable to ^{177}Lu-hG250-treated tumors at 150 days post-treatment (62.3 ± 79.9, 44.1 ± 19.7, and 44.0 ± 50.6 mm^3, respectively; $p = 0.745$) and significantly prolonged survival compared with non-treated mice ($p<0.05$). CAIX expression in SK-RC-52, Renca-CAIX, and CT26-CAIX cells was 807787, 251404, 340944 receptors/cell, respectively. All cell lines showed internalization of radiolabeled hG250. Renca-CAIX and CT26-CAIX cells were less radiosensitive than SK-RC-52 cells (2.1, 20.2, 16.7 % survival after 4 Gy, respectively). ^{177}Lu-hG250 tumor uptake in Renca-CAIX and CT26-CAIX was 24.0 and 11.1 %ID/g, respectively.

Conclusion

These results highlight the potential of ^{225}Ac-hG250 for ccRCC treatment. Further studies to validate therapeutic efficacy and study the radiobiological and immunological effects in immunocompetent mouse models are ongoing.

"Anti-HER2 2Rs15d nanobody labeled with ^{225}Ac as a potential molecule for targeted alpha therapy"

Magdalena Rodak[1], Yana Dekempeneer[2,3], Maria Wojewódzka[1], Tony Lahoutte[2,3], Frank Bruchertseifer[3], Alfred Morgenstern[3], Matthias D'Huyvetter[2,3], Marek Pruszynski[1]

[1]*Institute of Nuclear Chemistry and Technology, Warsaw, POLAND*

[2]*In Vivo Cellular and Molecular Imaging Lab, Vrije Universiteit Brussel, Brussels, BELGIUM*

[3]*Precirix NV/SA, Brussels, BELGIUM*

[4]*Joint Research Centre – Department for Nuclear Safety and Security, Karlsruhe, GERMANY*

Human Epidermal Growth Factor Receptor type 2 (HER2) overexpression leads to a more aggressive form of cancer, metastatic activity and chemo-resistance. In the case of epithelial derived tumors, intact monoclonal antibodies might not always be ideal vectors for targeted radionuclide therapy due to their slow pharmacokinetics. Therefore, nanobodies (Nbs) with their small size (~15kDa), nM-range affinity, low immunogenicity, rapid clearance from blood and ease of tumor penetration, might be attractive alternative. The aim of this study was to evaluate the therapeutic potency of an anti-HER2 Nb labeled with ^{225}Ac.

2Rs15d Nb was conjugated with *p*-SCN-Bn-DOTA, purified to obtain DOTA-2Rs15d, which was labeled with ^{225}Ac. Its binding specificity and affinity was evaluated on SKOV-3 (HER2+) cells, and its immunoreactive fraction (IF) by the Lindmo method. *In vitro* toxicity was assessed via clonogenic assays, while cell damage was evaluated using comet and γH2AX phosphorylation assays. Its biodistribution and tumor targeting capacity was assessed in SKOV-3 xenografted mice after which its therapeutic potential was compared to that of trastuzumab, and to a combination of both therapeutics, in a relevant mouse model for HER2+ metastatic cancer.

^{225}Ac-DOTA-2Rs15d was obtained with a radiochemical purity of ≥95% and bound specifically to HER2 with approximately 75% IF and a K_D of 3.50±0.17 nM. Toxicity studies demonstrated that ^{225}Ac-DOTA-2Rs15d significantly reduced the viability of SKOV-3 cells compared to controls. Tumor uptake of ^{225}Ac-DOTA-2Rs15d after i.v. administration in SKOV-3 xenografted mice was high and specific over time, with low uptake in additional organs and tissues, except for kidneys. ^{225}Ac-DOTA-2Rs15d was found to be therapeutically effective compared to control groups and to a clinically relevant trastuzumab regimen. A combination of three fractions of ^{225}Ac-DOTA-2Rs15d with trastuzumab was found most effective.

^{225}Ac-DOTA-2Rs15d showed strong therapeutic potential *in vitro* and *in vivo*, which supports its further development towards the clinic.

Acknowledgments: This work was supported by the National Science Center Poland under grant 2019/34/E/ST4/00080.

"From Ouzo effect to combined chemo-radio-therapies "

Déborah IGLICKI[1], Clément GOUBAULT[1], Ulrich JARRY[2,3], Pierre-Antoine ELIAT[4], Paul RETIF[5], Mégane BOSTOËN[2], Rémy PEDEUX[2,6], Thierry GUILLAUDEUX[2], Myrtil L. KAHN[7], Fabienne GAUFFRE[1] & **Soizic CHEVANCE[1]**

1. *Univ Rennes, CNRS, Institut des Sciences Chimiques de Rennes - UMR6226, Rennes, France.*
2. *Univ Rennes, CNRS, INSERM, BIOSIT - UMS 3480, LabCom Oncotrial, Biotrial Pharmacology, US_S 018, F-35000 Rennes, France.*
3. *Biotrial Pharmacology, Unité De Pharmacologie Préclinique, Rennes, France.*
4. *Univ Rennes, CNRS, INSERM, BIOSIT - UMS 3480, PRISM Bio-SCANS, F-35000 Rennes, France.*
5. *Unité de Physique Médicale, CHR Metz-Thionville, Ars-Laquenexy, France.*
6. *COSS (Chemistry Oncogenesis Stress Signaling)—UMR_S 1242, University of Rennes, INSERM, CLCC Eugène Marquis, F-35000 Rennes, France.*
7. *Laboratoire de Chimie de Coordination - UPR8241, CNRS, 205 route de Narbonne, Toulouse, France.*

Radiotherapy is widely used to treat cancers, especially certain aggressive or non-operable cancers. Although the potentiating effect of photonic radiation by high-Z nanoparticles has been demonstrated, the understanding of this effect is largely limited to the use of individual particles. At the same time, there is a real challenge in therapeutic innovation to develop objects that can be used to apply chemo- and radiotherapy simultaneously.

Thus, the ISCR has patented an efficient process for the elaboration of new type of capsules based on the Ouzo effect[1]. Hybrid capsules, called Hybridosomes®, are obtained by spontaneous emulsification in a THF/water/butylated hydroxytoluene (BHT) mixture. They consist of an inorganic shell of NP nanoparticles (gold, iron oxide, etc.) stabilized by a biocompatible polymer. These nanocapsules (D_H ~ 100 nm) have an internal volume allowing to load up to 170 $g.L^{-1}$ of hydrophobic molecule inside the nanocapsules [2]. The encapsulation process of Sorafenib has been successfully performed and will be extended to other active ingredients such as Paclitaxel and Osimertinib in order to develop applications in chemotherapy. Furthermore, tested in pre-clinical studies for the treatment of glioblastoma by radiotherapy, our Hybridosomes® have greatly improved the survival of mice. We are now interested in the evaluation of the combined chemo- and radio-therapeutic effect of drug encapsulating formulations (*in vitro and in vivo*).

Moreover, thanks to the computational and simulation tools developed at the CHR Metz-Thionville, we are interested in the effect of the organization of the gold nanoparticles envelope as well as their concentration and size on the dose deposition, in order to improve the radiosensitizing effect of our Hybridosomes®.

REFERENCES
[1] Brevet PCT/FR2016/053522 (18/12/2015); F. Sciortino *et al., ChemNanoMat,* **2016**, 2, 796; C. Goubault *et al., JCR* ***2020****, 324, 430.* C. Goubault *et al., JCIS* ***2021****, (accepted for publication JCIS-21-2172R2)*
[2] C. Goubault et al., *JCR* ***2020****, 324, 430.*
[3] **P. Retif** *et al., Theranostics.* **2015,** *5*, 1030-1144. S. Pinel *et al.,* Adv. Drug Deliv. Rev. **2019**, 138, 344 – 357

"Improving systemic radiotherapy with radioenhancing nanoparticles"

Marine Le Goas[1,2], Béatrice Cambien[3], Geraldine Carrot[2], Jean-Philippe Renault[2]
[1] Faculté de Pharmacie, Université de Montréal, Montréal, Québec H3C 3J7, Canada
[2] NIMBE, CEA, CNRS UMR 3685, Université Paris-Saclay, CEA Saclay, 91191 Gif-sur-Yvette, France
[3] Laboratoire TIRO, UMRE 4320, Université Côte d'Azur, CEA, 06107 Nice Cedex, France

The challenge for radiotherapy remains to deliver curative doses to tumor tissues while sparing sound ones. Hence the use of tumor-located radioenhancers is a promising way to improve the efficacy of radiotherapy[1]. High-Z materials have been known for several decades to amplify the damaging effects of both photon and ion radiations[2]. Various nanoparticles have already been developed to take advantage of this property, with gold and gadolinium amongst the most investigated elements[3]. Yet, most studies have dealt with external beam radiotherapies only.

Here, we provide a proof of concept for nanoparticle-based enhancement of systemic radiotherapy. We show how the use of polymer-grafted gold nanoparticles allows to reduce the dose of radioiodine (^{131}I) required to reach

curability. Both *in vitro* and *in vivo* assays demonstrated an enhancement of the killing potential of radioiodine in presence of these nanoparticles, which were otherwise proven as biocompatible and stable under irradiation[4,5]. Special attention was given to the colloidal stability of the particles in biological environments, and to their ability to diffuse in the tumor extracellular matrix, as both aspects may greatly affect their radioenhancement properties. The versatility of the polymer corona was shown to enable fine-tuning of the biological behavior of these hybrid particles[6,7].

REFERENCES
[1] D. Kwatra, A. Venugopal, S. Anant, *Translational Cancer Research* 2013, *2*, 330.
[2] K. Kobayashi, N. Usami, E. Porcel, S. Lacombe, C. Le Sech, *Mutation Research/Reviews in Mutation Research* 2010, *704*, 123.
[3] Z. Kuncic, S. Lacombe, *Phys. Med. Biol.* 2018, *63*, 02TR01.
[4] M. Le Goas, A. Paquirissamy, D. Gargouri, G. Fadda, F. Testard, C. Aymes-Chodur, E. Jubeli, T. Pourcher, B. Cambien, S. Palacin, J.-P. Renault, G. Carrot, *ACS Appl. Bio Mater.* 2019, *2*, 144.
[5] M. Le Goas, M. Paquet, A. Paquirissamy, J. Guglielmi, C. Compin, J. Thariat, G. Vassaux, V. Geertsen, O. Humbert, J.-P. Renault, G. Carrot, T. Pourcher, B. Cambien, *IJN* 2019, *14*, 7933.
[6] M. Le Goas, T. Roussel, M. Kalbazova, D. Carrière, E. Barruet, V. Geertsen, G. Fadda, F. Testard, G. Carrot, J.-P. Renault, *Journal of Materials Chemistry B* 2020, *8*, 6438.
[7] M. Le Goas, F. Testard, O. Taché, N. Debou, B. Cambien, G. Carrot, J.-P. Renault, *Langmuir* 2020, *36*, 10460.

"Novel therapeutic combination strategies in non-BRAF mutant melanoma"

Sabbah M[1], Krayem M[1], Najem A[1], Simon S[2], Vanderkerkhove C[2], Van gestel D [2], Awada A[3], Journe F[1], Van gestel D [2], Ghanem G [1]

[1] Laboratory of Oncology and Experimental Surgery, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium.

[2]Department of Radiation Oncology, Institut Jules Bordet, Université libre de Bruxelles, 1000 Brussels, Belgium.

[3]Medical Oncolgy Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium.

Metastatic melanoma is a mutinous disease, often requiring drug combinations. Several efforts were dedicated to prevent tumor growth and metastases in WT BRAF melanoma by targeting RTKs that regulate cell proliferation, invasion, and migration. Moreover, melanoma is commonly regarded as a radioresistant tumor entity and prescribed as an adjuvant treatment to reduce the risk of local and metastatic tumor recurrence. However, ionizing radiations activate RTKs that also regulate proteins involved in DNA repair mechanisms. In this study, we aimed to assess the benefit of combining RTK inhibition and radiotherapy in WT BRAF melanoma and depict the associated signaling pathways and DNA repair mechanisms.

Firstly, we found that RT upregulates mRNA and protein expression of several RTKs (EGFR, c-Met, IGF1R, and c-Kit) along with an increase in nuclear levels of EGFR and c-Met. Specific inhibition of RTKs resulted in a significant enhancement of melanoma radiosensitivity. Furthermore, we found an increase in the nuclear enzymatic activity of PARP under RT that can be reversed when combined with c-Meti. Of note, targeting PARP significantly enhances the radiosensitivity of melanoma cells. Interestingly, proximity ligation assay carried out on irradiated cells identified an interaction between c-Met and PARP suggesting promotion of c-Met translocation to the nucleus thus activating PARP and participating in melanoma radioresistance. Accordingly, targeting MET and PARP under radiotherapy resulted in a significant decrease in cell survival, and an increase in cell death and DNA damage compared to METi or PARPi alone combined with radiotherapy. Interestingly, in nude mice bearing melanoma xenografts, the triple combination mediates a synergistic effect on tumor growth inhibition and a potent control on tumor regrowth in all animals following the stop of the treatment.

Combining c-Met and PARP inhibitors with RT appears a promising therapeutic approach in WT BRAF melanoma and deserves further investigation.

"Investigating the interest of proton therapy to obtund radiation-induced lymphopenia in a context of brain tumour irradiation: a preclinical study"

Julie Coupey[1], Jérôme Toutain[1], Erika Hue[2], Charly Helaine[1], Jade Richard[1], Romaric Saulnier[3], Laurent Chazalviel[1], Marc Rousseau[4], Juliette Thariat[5], Samuel Valable[1], Marine M. Leblond[1]

[1] *Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy group, GIP CYCERON, 14000 Caen, France.*

[2] *LABÉO, Normandie Univ, Unicaen, BIOTARGEN EA7450, 14280 Saint-Contest, France.*

[3] *UMS 3408, UNICAEN, CNRS, GIP Cyceron, Bd Henri Becquerel, Caen, France.*

[4] *Université de Strasbourg, CNRS, IPHC UMR 7178, Strasbourg, F-67000, France.*

[5] *Laboratoire de physique corpusculaire UMR6534 IN2P3/ENSICAEN, France - Normandie Université, France.*

Although conventional radiotherapy based on X-rays improves brain tumour patient survival, it also leads to deleterious effects on the inflammatory component: enrichment of pro-tumour macrophages[1] as well as recruitment of myeloid cells at the tumour site and severe lymphopenia[2]. This radiation-induced lymphopenia and enrichment in protumoral macrophages in the tumour bulk could decrease the immunotherapeutic response and are associated to a poor prognosis[3]. Proton therapy has emerged as a new radiation strategy for brain tumours. Thanks to its precise dose deposition, it enables to spare healthy tissue and circulating leukocytes[4], and to its different biological effects on the irradiated tissue[5], it could result in less harmful effects for systemic inflammation[6]. In this project, we aim to evaluate if brain radiation with proton therapy is less deleterious for circulating leukocytes than conventional brain radiotherapy.

Tumour-free mice have been irradiated with X-rays (X-Rad 225 Cx GIP CYCERON, Caen) or proton beams (25MeV PRECy platform, Strasbourg). For each type of radiation, mice were divided according to radiation volume (whole-brain or hemisphere). Mice were irradiated twice a day (2.5 Gy/session) for four consecutive days. Blood samples were collected before, during and after radiation and circulating leukocytes were analysed by flow cytometry. First experiments confirmed the feasibility of the protocol.

Preliminary data showed that mice weight decreased after whole-brain radiation with X-rays but not with proton beams. Blood sampling confirmed radiation-induced lymphopenia after irradiation with X-Rays, whole-brain irradiation

inducing a more pronounced effect than hemisphere irradiation. Changes in leukocytes after proton-irradiation are under investigation but preliminary results suggest a conservative effect on leukocytes.
Proton therapy appears as a better radiotherapy option for brain tumour but its effects on inflammation remains to be further analysed.

Key words: *brain radiotherapy*, *proton therapy, lymphopenia*

REFERENCES

[**1**] Leblond, M. M. *et al.*, (2017) Oncotarget 8, no. 42, 72597-612. [**2**] Yovino, S. *et al.*, (2013) Cancer Invest. 31, no. 2, 140–144. [**3**] Grossman, S. A. *et al.*, (2011) Clinical Cancer Research 17, no. 16, 5473-80. [**4**] Hammi, A. *et al.*, (2020) Phys. Med. Biol. 65, no. 5, 055008. [**5**] Césaire, M. *et al.*, (2020) Bulletin du Cancer, 107, 7-8, 813-822. [**6**] Mohan, R. A. *et al.*, (2020) Neuro-Oncology, 284-294.

ACKNOWLEDGEMENTS

This project has received financial support from the CNRS through the 80|Prime program and Ligue Contre le Cancer. We also acknowledge the PRECy platform.

"*In silico* feasibility study of carbon ion radiotherapy with simultaneous integrated boost (CIRT-SIB) for head and neck adenoid cystic carcinoma"

E. Mastella[1], S, Molinelli[1], G. Magro[1], M. Bonora[1], S. Ronchi[1], R. Ingargiola[1], M. Ciocca[1], B. Vischioni[1], E. Orlandi[1]
[1]CNAO, National Center for Oncological Hadrontherapy, Strada Campeggi 53, I-27100 Pavia, Italy

Purpose: Simultaneous integrated boost (SIB)-intensity modulated radiotherapy (IMRT) is one of the major technical photon-based RT advances in the last 20 years [1]. In carbon ion radiotherapy (CIRT), a SIB approach has not been fully exploited so far. To our best knowledge, only Kawashiro et al. [2] Investigated a SIB treatment using CIRT for pancreatic cancer. The feasibility of a CIRT-SIB strategy for head and neck adenoid cystic carcinoma (ACC) patients was investigated in this study in order to improve treatment planning dose distributions.
Methods and Materials: CIRT plans of 10 ACC patients previously treated at CNAO with sequential boost (SEQ) irradiation and prescription doses of 41.0 Gy(RBE)/10

fractions to low risk (LR)-CTV plus 24.6. Gy(RBE)/6 fractions to the high risk (HR)-CTV were re-planned with two SIB dose levels to the LR-CTV: namely 48.0 Gy(RBE) and 54.4 Gy(RBE). While planning with SIB, the HR-CTV coverage had higher priority, with fixed organs at risk dose constraints among the SIB and SEQ plans. The homogeneity and conformity indexes were selected for CTV coverage comparison. The biological effective dose (BED) was calculated to compare the different fractionation schemes.

Results: Comparable HR-CTV coverage was achieved with the treatment approaches, while superior conformality and homogeneity was obtained with the SIB technique in both CTVs. With the SEQ, SIB48.0 and SIB54.4 the LR-CTV median doses were 50.3%, 11.9% and 6.0% higher than the prescriptions. Significant reductions of the median and near-maximum BEDs was achieved with both SIB dose levels in the LR-CTV.

Conclusions: The SIB approach resulted in highly conformal dose distributions with the reduction of the unintended dose to the LR-CTV. A prescription dose range for the LR-CTV will be clinically defined to offer tailored personalized treatments, according to the clinical and imaging characteristic of the patients.

REFERENCES

[1] F. De Felice et al., "Moderately accelerated intensity-modulated radiation therapy using simultaneous integrated boost: Practical reasons or evidence-based choice? A critical appraisal of literature," Head and Neck, vol. 42, no. 11. John Wiley and Sons Inc, pp. 3405–3414, Nov. 01, 2020, doi: 10.1002/hed.26400.

[2] S. Kawashiro et al., "Dose escalation study with respiratory-gated carbon-ion scanning radiotherapy using a simultaneous integrated boost for pancreatic cancer: Simulation with four-dimensional computed tomography," Br. J. Radiol., vol. 90, no. 1072, 2017, doi: 10.1259/bjr.20160790.

"Trastuzumab radioimmunoconjugates – promising strategy for selective anticancer therapy "

Paulina Apostolova[1], Marija Arev[1], Mila Ristova[1], Emilija Janevik - Ivanovska[1]

[1] *Faculty of medical sciences, Goce Delcev University, Shtip, Republic of North Macedonia*

Monoclonal antibody Trastuzumab is the first humanized approved antibody for tratment of HER-2 positive breast cancer. Led by its promising indication, we made further improvemetns to prepare freeze-dried immunogates with bifunctional chelators, ready to use kit formulation for radiolabeling.

Formulation of freeze dried immunoconjugates of trastuzumab was prepared after purification of commercially available drug, already used for treatment, using bifunctional chelating agent (BFCA) with acyclic (1B4M-DTPA) and macrocyclic (DOTA) structure.

A several chemical techniques have been used to determine the stability and retained immunoreactivity of the antibody in the formulated immunoconjugates and after their labelling with radioactive and non-radioactive isotopes.

The appearance of two bands of fragments in SDS-PAGE gels in lyophilized and labeled conjugates have shown retained secondary structure. The presence of characteristic amide bands in IR spectra and Raman spectra have indicated that all samples have retained native secondary structure. An average of 4.3-5.3 groups linked to the antibody determined by MALDI analysis helped in the decision of molar ratio Ab: BFCA and successful labeling.

Stability of freeze dried immunoconjugates (in molar ratio 1:20) were characterized by HPLC-UV and yield of labelling with ^{177}Lu and ^{90}Y by ITLC-SG.

According to all obtained results and previous experiens related to the freeze dried formulation of antibody conjugates, we have hope that this approach can give a distinctive contribution in the fields of radioimmunotherapy using beta emitters and alpha as well.

REFERENCES

[1] Sterjova M, Dzodic P, Makreski P, Duatti A, Risteski M, Janevik-Ivanovska E, Emilija (2019) *Vibrational Spectroscopy as a Tool for Examination to the Secondary Structure of Metal-labeled Trastuzumab Immunoconjugates.* Journal of Radioanalytical and Nuclear Chemistry, 320 (1). 209-218.

[2] Sterjova M, Dzodic P, Makreski P, Zivkovic J, Janevik-Ivanovska E, (2019) *Electrophoresis and Raman spectroscopy characterization of integrity and secondary structure of p-SCN-Bn-DTPA- and p-SCN-Bn-1B4M-DTPA-conjugated trastuzumab.* Farmacia, 67 (4).

“Radiomics for immune response characterization under RT treatment”

Invited speaker: **Charlotte Robert,** Molecular radiotherapy unit, Inserm, Gustave Roussy, University of Paris –Sud, **France**.

Radiomics is a field that has grown considerably in the last 10 years and refers to the high-throughput extraction of computational features from medical imaging data in order to develop machine learning models to answer to various classification and regression tasks in oncology. Originally developed for gene-expression characterization and survival prediction in radiation oncology, it is recently finding appealing applications, beneficiating from crucial new knowledges in this field. Indeed, recent studies have shown that radiotherapy acts as an in situ tumor vaccine, generating the release of tumor antigens and activating tumor-specific T cells during tumor cell death. Based on these results, numerous clinical trials are in progress to combine immunotherapy to radiation oncology, either to promote abscopal responses in metastatic patients, or as part of the treatment for locally advanced tumors. After a short reminder of the radiomics concept, this presentation will illustrate how radiomics can make possible the non-invasive characterization of the tumor microenvironment before and after radiotherapy and how these signatures can be integrated in a clinical workflow to personalize patient care.

"A mathematical model of the low-grade gliomas response to chemotherapy and radiotherapy: Therapeutic implications "

Luis E. Ayala-Hernández[1], Armando Gallegos[1], Philippe Schutz[2], Michael Murek[2], Juan Belmonte-Beitia[3] and Víctor M. Pérez-García[3]

[1]Departamento de Ciencias Exactas y Tecnología Centro Universitario de los Lagos, Universidad de Guadalajara, Enrique Díaz de León 1144, Colonia Paseos de la Montaña, C.P. 47460, Lagos de Moreno, Jalisco, Mexico.

[2]Universitätsklinik für Neurochirurgie, Bern University Hospital, CH-3010 Bern, Switzerland.

[3]Mathematical Oncology Laboratory (MOLAB), Instituto de Matemática Aplicada a la Ciencia y la Ingeniería, Department of Mathematics, E.T.S.I. Industriales, Universidad de Castilla-La Mancha, Avda. Camilo José Cela, 3, 13071 Ciudad Real, Spain.

Adult supratentorial WHO grade II diffuse low-grade gliomas (LGGs) are slow-growing primary brain tumors that are in general incurable due to their infiltrative nature. Treatment typically consists of surgery followed by observation, radiotherapy, chemotherapy, or chemoradiation. Temozolomide (TMZ) has demonstrated effectivity against low-grade gliomas [1]. There is evidence that the combination of chemotherapy and radiotherapy could be a beneficial strategy for the management of LGGs but their optimal use is still under study [2]. Because of the high cost, human effort, time and ethical issues involved in clinical trials and basic medical research, mathematical modeling and analysis can potentially contribute to the discovery of optimal cancer treatment delivery regimens [3,4]. However, although mathematical models have potential for the study of improved combination treatments, no studies have addressed computationally the best combination scheme of TMZ and RT for LGGs. We constructed a mathematical model describing the response of LGGs to combinations of TMZ and radiation therapy. Patient-specific parameters were obtained from longitudinal imaging data of the response of LGGs to both treatments. Computer simulations show that concurrent cycles of radiotherapy and temozolomide could provide the best therapeutical efficacy in-silico for the patients included in the study. This result was confirmed with a virtual clinical trial [5]. Thus, the proposed treatment schedule could be the basis for the care of LGGs with substantial survival benefits.

REFERENCES
1. Lombardi G, Barresi V, Castellano A, Tabouret E, Pasqualetti F, Salvalaggio A, et al. Clinical Management of Diffuse Low-Grade Gliomas. Cancers. 2020;12(10):3008.
2. Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Eng J Med. 2016;374(14):1344-55.
3. Malinzi J, Basita KB, Padidar S, Adeola HA. Prospect for application of mathematical models in combination cancer treatments. Inform Med Unlocked. 2021:100534.
4. Pérez-García VM, Ayala-Hernández LE, Belmonte-Beitia J, Schucht P, Murek M, Raabe A, et al. Computational design of improved standardized chemotherapy protocols for grade II oligodendrogliomas. PLoS Comput Biol. 2019 ;15(7):e1006778.
5. Ayala-Hernández LE, Gallegos A, Schucht P, Murek M, Belmonte-Beitia J and Pérez-García VM. Optimal combinations of chemotherapy and radiotherapy in low-grade gliomas: A mathematical approach. "Submitted to Journal of Personalized Medicine".

"Radiation necrosis vs progression in Brain Metastases treated with stereotactic radiosurgery: How to distinguish them using mechanistic mathematical models"

Beatriz Ocaña-Tienda[1], Julián Pérez-Beteta[1], David Molina-García[1], Odelaisy León-Triana[1], Estanislao Arana[2], Ana Ortiz de Mendivil[3], Beatriz Asenjo[4], David Albillo[5], Luis Pérez-Romasanta[6], Elisabet González-Del Portillo[6], Manuel Llorente[5], Natalia Carballo[5], Víctor M. Pérez-García[1]

1 Mathematical Oncology Laboratory (MOLAB), Department of Mathematics and Instituto de Matemática Aplicada a la Ciencia y la Ingeniería, Universidad de Castilla-La Mancha, Avda. Camilo José Cela, 3, 13071, Ciudad Real, Spain

2 Department of Radiology. Fundación Instituto Valenciano de Oncología, 46009, Valencia, Spain

3 Department of Radiology, Sanchinarro University Hospital, HM Hospitales, 28050, Madrid, Spain

4 Hospital Regional Universitario Carlos Haya, Málaga, Spain

5 MD Anderson Cancer Center, 28033, Madrid, Spain

6 Radiation Oncology Service, Salamanca University Hospital, 37007, Salamanca, Spain

Brain metastases (BM) are the most common intracranial tumor in adults with around 20% of cancer patients developing BMs. Stereotactic radiosurgery (SRS) is becoming increasingly used in the treatment of BM [1]. However, SRS leads

sometimes to radiation necrosis (RN), a transient adverse event appearing after irradiation, difficult to distinguish from tumor progression and observed in 5% to 25% of treated patients [2]. RN may resolves spontaneously, not requiring further work-up, while progression need additional treatment. Thus, distinguishing between RN and progression is clinically relevant in the management of BM.

Scaling laws (SLs) are simple mathematical models allowing to describe tumor growth [3]. We used SLs in this study to characterize the growth dynamics of BMs subject to different treatments. To characterize the dynamics, a growth factor, the scaling law exponent beta, was used. MR images of 382 patients (1050 BMs) were collected and 97 BMs satisfied the inclusion criteria of the study: availability of three sequential volumetric contrast-enhanced T1-weighted MR imaging, increasing volumes and no SRS for four months before the first measurement. MR images were semi-automatically segmented to compute volumes and the exponent beta for each BM.

There were significant differences ($p<0.005$) between patients experiencing RN and tumor progression after SRS. BMs grew faster, leading to super-exponential growth, when they developed RN. A simple mathematical model based on two differential equations accounting for the inflammatory response after RT accounted for the observed results, as it did a more sophisticate multivoxel mesoscopic stochastic tumor growth simulator incorporating more details of the tumor biology [4].

In summary we have shown that RN and tumor relapse have different growth patterns what may help in their differentiation in clinical settings. We have substantiated our findings using mechanistic mathematical models incorporating aspects of the tumor biology and inflammatory response.

REFERENCES

[1] L. M. Halasz, J. C. Weeks, B. A. Neville, N. Taback, and R. S. Punglia, “Use of stereotactic radiosurgery for brain metastases from non-small cell lung cancer in the United States,” Int. J. Radiat. Oncol. Biol. Phys., vol. 85, no. 2, pp. e109–e116, 2013, doi: 10.1016/j.ijrobp.2012.08.007.

[2] D. Lee, R. A. Riestenberg, A. Haskell-Mendoza, and O. Bloch, “Brain Metastasis Recurrence Versus Radiation Necrosis: Evaluation and Treatment,” Neurosurg. Clin. N. Am., vol. 31, no. 4, pp. 575–587, 2020, doi: 10.1016/j.nec.2020.06.007.

[3] V. M. Pérez-García et al., “Universal scaling laws rule explosive growth in human cancers,” Nat. Phys., 2020, doi: 10.1038/s41567-020-0978-6.

[4] J. Jiménez-Sánchez et al., "A mesoscopic simulator to uncover heterogeneity and evolutionary dynamics in tumors," PLOS Comput. Biol., vol. 17, no. 2, p. e1008266, Feb. 2021, doi: 10.1371/journal.pcbi.1008266.

"Spatial analysis of preclinical dynamic contrast-enhanced ultrasound (DCE-US) images for assessment of tumour response to radiotherapy"

Dana Naser Tahboub[1], Carol Box[1], Simon P. Robinson[1], Jeff Bamber[1] and Emma Harris[1]

[1] Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, United Kingdom

Early radiotherapy-induced changes in tumour vasculature may predict treatment response. Dynamic contrast-enhanced ultrasound (DCE-US) is a non-ionizing and low-cost imaging modality, ideal for longitudinal monitoring. The vascular radioresponse is spatially heterogenous, depending on vessel morphology[1] and local hypoxia[2]. DCE-US for assessing radiation response is explored in this preclinical study. Tissue vasculature was characterized using DCE-US perfusion metrics for a region of interest (ROI), subregions and pixels to investigate heterogeneity.

C33A cervical and LICR-LON-HN5 (HN5) head & neck cancer xenografts were treated with a single X-ray (220 kV) dose of 15, 20 or 25 Gy, or sham irradiated (n=4-6 per group). Tumour radioresponse was classified based on tumour regression and growth delay. A central plane of the tumour was imaged within 24 hours before and 48 hours after irradiation using Sonazoid™ microbubbles and the Aplio XG™ Toshiba scanner. The perfusion metrics calculated included area under the curve (AUC) and wash-out time (WOUT). The change in whole-tumour ROI and subregion metrics was determined, in addition to the change in the shape parameters of pixel-wise metric histograms.

Completely responding HN5 tumours had a greater decrease in whole-tumour AUC ($p=0.038$), while C33A complete responders had a greater decrease in WOUT ($p=0.016$) compared to partial responders. Highly perfused subregions in both HN5

and C33A tumours were more sensitive to the decrease in AUC (p=0.019 & 0.016, respectively). These results reflect a decrease in vascular volume, consistent with vascular disruption. The skewness of the WOUT histogram increased in C33A complete responders (p=0.029), shifting from slow to quick wash-out, implying disruption of areas of smaller tortuous vessels. This study demonstrates the potential of DCE-US to detect vascular changes related to radiotherapy outcome. Importantly, these changes occurred 48 hours after treatment, 4 days before detectable volume differences in C33A tumours.

REFERENCES
1. Chen, F.-H., et al., Radiotherapy decreases vascular density and causes hypoxia with macrophage aggregation in TRAMP-C1 prostate tumors. Clinical cancer research : an official journal of the American Association for Cancer Research, 2009. **15**(5): p. 1721-1729.
2. Schwartz, D.L., et al., HIF-1-dependent stromal adaptation to ischemia mediates in vivo tumor radiation resistance. Molecular cancer research : MCR, 2011. **9**(3): p. 259-270.

"Development and prospective validation of a spatial dose pattern based model predicting acute pulmonary toxicity in patients treated with volumetric arc-therapy for locally advanced lung cancer"

Bourbonne V.[1,2], Lucia F.[1,2], Jaouen V.[2,3], Bert J.[2], Rehn M.[1], Pradier O.[1,2], Visvikis D.[2], Schick U.[1,2]
1 Department of Radiation Oncology, University Hospital, Brest, France
2 LaTIM UMR 1101 INSERM, University Brest, Brest, France
3 Institut Mines-Télécom Atlantique, Brest, France

Introduction: (Chemo)-radiotherapy is the standard treatment for patients with locally advanced lung cancer (LALC) not accessible to surgery. Despite strict application of dose constraints, acute pulmonary toxicity (APT) remains frequent, and may impact patients' quality of life. In the present study, we aim to define spatial dose patterns and to validate our findings prospectively.
Methods: For the training cohort, we included all patients treated in our institution by VMAT for a LALC between 2015 and 2018. APT was scored according

to the CTCAE v4.0 scale. All dose maps were registered to a thorax phantom using a segmentation-based elastic registration. Voxel-based analysis was performed with a non-parametric permutation test producing a 3-dimensionnal significance map on which clusters of voxels that exhibited significant dose differences ($p < 0.05$) between the two toxicity groups (APT ≥ or < grade 2) were identified. A prediction model (Pmap-Model) was then built using a neural network approach and then applied to an observational prospective cohort. The model was evaluated using the Area under the curve (AUC) and the balanced accuracy (Bacc).

Results: 165 and 42 patients were included in the training and validation cohorts, with respective APT rates of 22.4% and 19.1%. In the training cohort, a cluster of voxels (Pmap-region) was identified in the lower right lung. In the training cohort, the Pmap-Model combining 11 features among which the mean dose to the Pmap-region resulted in an AUC of 0.99 and a Bacc of 99.2 using an 8% probability threshold. Using the same voxel cluster on the validation cohort, the Pmap-model resulted in an AUC of 0.81 and a Bacc of 82.0.

Conclusion: Our APT-prediction model was successfully validated in a prospective cohort treated by VMAT. Regional radiosensitivity should be considered in usual lung dose constraints, opening the possibility of easily implementable adaptive dosimetry planning.

"Synthetic tumor insertion using one-shot generative learning for cross-modal image segmentation"

Guillaume Sallé[1], Pierre-Henri Conze[1], Nicolas Boussion[1,2], Julien Bert[1,2], Dimitris Visvikis[1], Vincent Jaouen[1]

[1] *UMR 1101 Inserm LaTIM, UBO, IMT Atlantique, Brest, France*

[2] *CHRU Brest, Brest, France*

Introduction: Domain adaptation (DA) is typically required in machine learning when training and testing conditions differ. DA has recently raised much awareness in medical imaging with dedicated approaches based on image-to-image (I2I) translation models like CycleGANs. However, fine-scale details e.g. tumors may vanish during translation as I2I models learn a global intensity

mapping [2]. We propose a new method to maintain tumors during translation by inserting realistic tumors in the target domain using a single GAN model trained on a single image. We validate our model on cross-modal segmentation without target labels.

Method: We base our approach upon SinGAN, a multi-stage generative approach where patches of different scales are used to train a series of generators within a single 2D image allowing for various one-shot applications [3]. We propose for the first time to use this architecture for fake tumor insertion respecting the style of the target domain in volumetric images. We then exploit the synthesized images for cross-modal segmentation [4]. To this end, we learn a tumor-preserving mapping using the tumor-augmented dataset and use it to learn a better cross-modality mapping. Finally, translated images are used to train a deep segmentation network and compared to CycleGAN-based DA without tumor augmentation.

Experiments and results: We tested our method on the crossMoDa MR vestibular schwanomma segmentation challenge between labelled contrast T1-weighted and unlabelled T2-weighted images [4]. We obtained superior dice similarity coefficient (DSC) : 0.58±0.31 against 0.46±0.32 for baseline. In particular during validation, 9/32 patients had DSC>0.8 compared to only 3/32 for baseline.

Conclusion: We have proposed a realistic tumor insertion technique for 3D medical images using a SinGAN-based model requiring a single 2D image at the training stage. Preliminary results for cross-modal image segmentation demonstrate the interest of the proposed approach for tumor preservation in DA.

REFERENCES

[1] J.-Y. Zhu et al., “Unpaired Image-to-Image Translation using Cycle-Consistent Adversarial Networks,” in ICCV 2017

[2] J. Jiang and al., “Tumor-Aware, Adversarial Domain Adaptation fromCT to MRI for Lung Cancer Segmentation,” inMICCAI 2018

[3] T. R. Shaham et al., “SinGAN : Learning a Generative Model from a Single Natural Image,” in ICCV 2019

[4] https://crossmoda.grand-challenge.org/

"Patient-specific 4DCT respiratory motion synthesis using generative adversarial networks"

Yi-heng Cao[1], Vincent Jaouen[1], Vincent Bourbonne[1,2], Nicolas Boussion[1,2], Ulrike Schick[1,2], Julien Bert[1,2], Dimitris Visvikis[1]

1 UMR 1101 Inserm LaTIM, Université de Bretagne Occidentale, IMT Atlantique, Brest, France

2 CHRU Brest University Hospital, Brest, France

Introduction: Four-dimensional computed tomography (4DCT) imaging is used routinely for respiratory motion synchronized image acquisition in radiotherapy treatment planning [1]. However, such acquisitions lead to higher radiation exposure up to six times a standard 3DCT acquisition, due to longer acquisition times [2]. Recently, we proposed an image-to-image (I2I) generative adversarial network (GAN) model to synthesize realistic 4DCT images from static 3DCT imaging using an ensemble of I2I networks, each learning one respiratory phase-gated frame of the 4DCT acquisition [3]. The synthesized motion was however not patient-specific. In this work, we propose a new deep synthesis network to further condition the generated 4DCT to the actual patient's respiratory amplitude.

Material & Methods: We propose a novel I2I 3D GAN architecture conditioned both on 3DCT and breathing amplitude with a new latent-code injection mechanism based on an Adaptive Instance Normalization layer [4]. We evaluated our model using both synthetic 4D phantom images (balls, ellipsoids) with simulated motion (training: 800 images, testing: 200 images) as well as real clinical data (training: 26 patients, testing: 9 patients). Motion similarity between ground truth phases and synthesized images was assessed using the Absolute Percentage Volume Difference (APVD) in the lungs.

Results: Small motion recovery errors were observed between ground truth and synthesized images with an APVD of 4.3±2.0%, 5.9±5.2% for synthetic balls and ellipsoids respectively. In the clinical dataset, the APVD was reduced from 5.6% to 1.2% on average compared to differences between phases without correction, suggesting a good ability of the model in reproducing the actual patient phase.

Conclusion: These preliminary results demonstrate that realistic and patient-specific respiratory motion dynamics can be synthesized using the proposed novel I2I architecture. Future developments will exploit real external respiratory measurements to further assess clinical feasibility.

REFERENCES
[1] Fayad et al., “Generation of 4-Dimensional CT Images Based on 4-Dimensional PET–Derived Motion Fields,” Journal of Nuclear Medicine, vol. 54, no. 4, pp. 631–638, 2013
[2] J. de Koste et al., “Renal mobility during uncoached quiet respiration: An analysis of 4DCT scans,” International Journal of Radiation Oncology*Biology*Physics, vol. 64, no. 3, pp. 799–803, 2006.
[3] Jaouen et al., “4D respiratory motion synchronized image synthesis from static CT images using GANs,” in IEEE NSS/MIC, Manchester, United Kingdom, Oct. 2019.
[4] Huang et al. Arbitrary Style Transfer in Real-Time with Adaptive Instance Normalization. In IEEE ICCV, pages 1510–1519, 2017.

"Radiobiology of targeted radionuclide therapy: necessity and current challenges"

Invited speaker: **Julie Nonnekens**, Department of Radiology & Nuclear Medicine, Department of Molecular Genetics, Erasmus MC, Rotterdam, **The Netherlands.**

Targeted radionuclide therapy (TRT) is a form of anti-cancer therapy in which intravenously injected radiolabeled molecules (α- and β-particle emitters) localize to metastatic tumor sites to locally irradiate during radioactive decay, leading to tumor cell eradication. Even though patients benefit from the therapy, current TRTs function suboptimally due to over-treatment (toxicity) or under-treatment (no tumor regression), clearly illustrating the urgency for therapy improvement. So far, little is known about the biological effects of ionizing radiation (i.e. radiobiology) specific for TRTs and how these radiobiological effects relate to dose, dose rate and timing. Since these radiobiological effects are poorly understood, and rational design of new modalities based on underlying cellular mechanisms is therefore not possible. In contrast to TRT, radiobiological principles of external beam radiotherapy (EBRT) have been studied for decades and these principles contributed to breakthroughs in improving its effectiveness. Therefore, current application of TRT is guided by results from EBRT, however this evidently leads to suboptimal treatment regimens. EBRT relies on short term, high dose radiation with an external source, while during TRT, radiopharmaceuticals are targeted to cancer cells which result in long term, low-to-medium dose exposure during radioactive decay.

In this talk, I will discuss various in vitro and in vivo radiobiological effects of TRT (e.g. DNA damage repair kinetics) and compare these effects with EBRT. For TRT, the absorbed dose is traditionally calculated using the MIRD scheme in which the total number of disintegrations in a source region is taken into account, to calculate the average absorbed dose in the target region of interest. Currently, dosimetry is based on rough estimations of e.g. the shape of the tumor, while important parameters such as inhomogeneous dose distributions are mostly ignored. These models follow the concepts that have proven to be successful in EBRT, but are thus not accurate for TRT. I will discuss the implications of the radiobiological effects, cellular shape, and subcellular and intra-tumoral distribution parameters when predicting anti-tumor effects for TRT.

"Data science and machine learning in radiomics: past, present, perspectives"

Mathieu Hatt, LaTIM, National Institute of Health & Clinical Sciences, University of Brest, **France**.

Radiomics is a very active field of research with applications in most fields of medicine, including neurology, cardiology and of course oncology, its field of "birth". The development of radiomics over the last few years has been carried out while witnessing two important, almost simultaneous, evolutions: the first is related to standardization, thanks to the efforts of the community. Nowadays, studies are much more reproducible and comparable than in the past. The second is related to the use of machine and deep learning based techniques, that can facilitate or replace some or even all parts of the usual radiomics workflow, in order to improve the performance and effectiveness for practice use in routine clinical applications. However, for efficient translation of radiomics models into clinical aid decision systems, a number of challenges still have to be overcome, including but not limited to acceptability and interpretability, harmonization and robustness, as well as higher levels of proof. The talk will cover the history of radiomics, the benefit for machine and deep learning in that field, and the perspectives to come.

P1/
"Modulation of PD-L1 expression in HPV-driven and non-HPV-driven head and neck squamous cell carcinoma after X-ray irradiation"

Christoph Schifflers[1,2], Angelika B. Riemer[2,3*], Carine Michiels[1*]

[1] *Cell Biology Research Unit (URBC)—Namur Research Institute for Life Sciences (NARILIS), University of Namur, Namur, Belgium*

[2] *Immunotherapy and Immunoprevention, German Cancer Research Center (DKFZ), Heidelberg, Germany*

[3] *Molecular Vaccine Design, German Center for Infection Research, Partner Site Heidelberg, Heidelberg, Germany*

* *Equal contribution*

Head and neck squamous cell carcinoma (HNSCC) driven by high risk human papillomaviruses (HPV^+) is characterized by profoundly distinct molecular landscapes, as well as biological and clinical behavior, compared to non-HPV-driven (HPV^-) HNSCC [1]. For instance, HPV^+ HNSCC is more sensitive to radiotherapy than HPV^- HNSCC and usually associated with a better prognosis. Nevertheless, treatment strategies for both types of tumors are similar. At advanced stages or in recurrent settings, immune-checkpoint blockade (ICB) harbors the potential to promote systemic eradication of cancer cells, particularly in combination with radiotherapy [2]. However, this effect in response to ICB remains rare for reasons that are not fully elucidated yet. Higher expression of ICB target PD-L1 was shown to be associated with a better ICB response [3]. To what extent radiotherapy of HNSCC affects PD-L1 expression and potentially ICB response remains unknown.

Therefore, this study assessed the expression level of PD-L1 after X-ray irradiation in HPV-driven and non-HPV-driven HNSCC. The results indicate that PD-L1 appears to be expressed at higher levels at the cell surface of HPV^- compared to HPV^+ cells. While X-ray irradiation induces *PD-L1* overexpression and increased PD-L1 cell surface abundance in HPV^- cells, no significant increase in PD-L1 expression or cell surface abundance could be detected in HPV^+ cells. The investigation of the underlying mechanisms suggests that HPV interferes with DNA damage response-mediated regulation of *PD-L1* expression after X-ray irradiation. The relevance of this observation for ICB response remains to be assessed in a syngenic orthotopic mouse model of HPV^+ and HPV^- HNSCC treated with a combination of fractionated radiotherapy and ICB.

REFERENCES
[1] Chow LQM. Head and Neck Cancer. N Engl J Med. 2020 Jan 2;382(1):60-72. doi: 10.1056/NEJMra1715715. PMID: 31893516.
[2] Kumari S, Mukherjee S, Sinha D, Abdisalaam S, Krishnan S, Asaithamby A. Immunomodulatory Effects of Radiotherapy. Int J Mol Sci. 2020 Oct 31;21(21):8151. doi: 10.3390/ijms21218151. PMID: 33142765.
[3] Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, Soria A, Machiels JP, Mach N, Mehra R, Burtness B, Zhang P, Cheng J, Swaby RF, Harrington KJ; KEYNOTE-040 investigators. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet. 2019 Jan 12;393(10167):156-167. doi: 10.1016/S0140-6736(18)31999-8. Epub 2018 Nov 30. Erratum in: Lancet. 2019 Jan 12;393(10167):132. PMID: 30509740.

P2/
"Biological evaluation of innovative theranostic agents based on peptides-functionalized iron oxide nanoparticles for colon cancer"

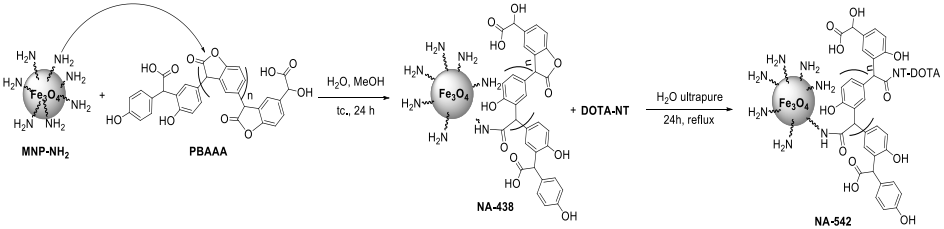
Livia E. Chilug[1], Radu A. Leonte[1], Ramona Dusman[1,2], Gina Manda[3], Rodica Turcu[4], Alexandrina Nan[4], and Dana Niculae[1]
[1] Horia Hulubei National Institute for R&D in Physics and Nuclear Engineering (IFIN-HH), Radiopharmaceutical Research Centre, 30 Reactorului Street, Magurele-Ilfov, Romania
[2] University Politehnica of Bucharest, Faculty of Applied Chemistry and Materials Science, 1-7 Gheorghe Polizu Street, Bucharest, Romania
[3]National Institute of Pathology "Victor Babes", 99-101 Splaiul Independentei Street, Bucharest, Romania
[4] National Institute for R&D of Isotopic and Molecular Technologies, 67-103 Donat Street, Cluj-Napoca, Romania

Iron Oxide nanoparticles have attracted great interest regarding their use for radionuclides delivery in nuclear imaging and therapy. Due to their large surface areas where multiple functional moieties can be incorporated, IONPs can bind several ligands like peptides for tumour-specific targeting. Among the different biocompatible polymers embedding carboxylic acid moieties, poly(benzofurane-co-arylacetic acid) provides the ability of covalent linkage to radioligands such as ^{64}Cu-DOTA-Bombesin and ^{64}Cu-DOTA-Neurotensin.

This study describes the labelling process of DOTA-NT(8-13), DOTA-BBN(7-14) radiotracers and further conjugation of poly(benzofurane-co-arylacetic acid)-Fe_3O_4 nanoparticles for *in vitro* assay of specific binding, uptake, and retention of the resulted nanostructures on colon cancer cells. The lactone ring reaction with terminal amino group of neurotensin/bombesin peptides was evaluated by FTIR, EDS coupled TEM/SEM and DLS to adapt the synthesis time to the half-life of radionuclide ^{64}Cu.

In vitro kinetic interaction of ^{64}Cu-DOTA-Peptide-Polymer-IONPs nanostructure with HT-29 and HCT116 colon cancer cells was evaluated using radioimmunoassay to determine the uptake time required for all the receptors to be saturated with the peptide-nanoparticle complex, also the percent of the incubated activity retained by the cells.

We obtained stable ^{64}Cu-labelled nanotracers, with >80% labelling yield. Following *in vitro* evaluation of both labelled peptides and ^{64}Cu-DOTA-Peptide-Polymer-IONPs nanostructures, the results highlighted the doubling of retained activity when IONPs were incubated. The results demonstrate the potential of nanoparticles to concentrate the radioisotopes with short-range radiation emissions, within the cancer cells, and promote them for further *in vivo* testing.



Acknowledgements: This work was supported by a grant of the Romanian Ministry of Research and Innovation UEFISCDI project number 64PCCDI/2018.

P3/

"Investigation of tumor and micro-environmental responses following the application of an innovative targeted radiotherapy in glioblastoma"

Loris Roncali[1], François Hindré[1-2], Franck Lacoeuille[1-2], Jean-François Gestin[3], Nicolas Lepareur, Michel Chérel[3], **Emmanuel Garcion[1-4]**

[1] CRCINA, INSERM, Angers University, Angers, France

[2] PRIMEX, SFR ICAT 132, Angers University, Angers, France

[3] CRCINA, INSERM, CNRS, Nantes University, Nantes, France

[4] PACEM, SFR ICAT 132, Angers University, Angers, France

[5] Comprehensive Cancer Center Eugène Marquis, Rennes, France,

Glioblastoma (GB) is the most common and aggressive tumor in the central nervous system. The standard first-line treatment is based on surgery followed by radiotherapy and chemotherapy (temozolomide). Despite this conventional combined approach patients have a median survival time of 15 months and GB remains an unmet medical need. Hence, loco-regional vectorized radiotherapy represents a promising option. Indeed, results from the laboratory have already shown the efficiency of lipid nanocarriers loaded with Rhenium 188 (a beta-emitter element) on the survival of rodent cancer models[1,2]. This kind of strategy has led to further developments toward possible clinical trials (DosiSphere, submitted Nanorad.01).

The next step here is to develop alpha radiopharmaceuticals based on Astatine 211 and to study the added value of such a strategy [3,4]. New radiopharmaceuticals will be developed by use of antibodies directed against heparane sulfate syndecan-1 (CD138) and the receptor CXCR4 (CD184) which are in the GB markers facing the tumor micro-environement, associated with malignant phenotypes, tumor progression and treatment resistance [5,6]. By use of *in vitro* and *in vivo* orthotopic dedicated models investigations will include study of targeting, clearance, bio-distribution and efficiency of these new radiopharmceuticals.

While focusing on tumor cell intrinsic responses, this work will also imply a thorough analysis of micro-environmental immune and inflammatory responses. For instance TAM populations can represent up to 50% of tumor mass[7] and their recruitment can be increased following internal radiation treatment [9]. As an initial focus, we produced some pivotal data on the polarization of tumor-associated

macrophages (TAM) in response to GB cells issued from patients (already exposed to radiations or not). Not only GB cell condition medium affect their anti-tumoral (M1) or pro-tumoral phenotype (M2) but those phenotypes affect responses to radiation [8]. This wok will allow better understanding in ^{211}At alpha therapy prior development of a FIH study.

REFERENCES
1. Vanpouille-Box, C. & Hindré, F. Nanovectorized radiotherapy: a new strategy to induce anti-tumor immunity. *Front Oncol* 2, (2012).
2. Vanpouille-Box, C. *et al.* Tumor eradication in rat glioma and bypass of immunosuppressive barriers using internal radiation with (188)Re-lipid nanocapsules. *Biomaterials* 32, 6781–6790 (2011).
3. Zalutsky, M. R. *et al.* Clinical experience with alpha-particle emitting 211At: treatment of recurrent brain tumor patients with 211At-labeled chimeric antitenascin monoclonal antibody 81C6. *J. Nucl. Med.* 49, 30–38 (2008).
4. Guérard, F. *et al.* Bifunctional aryliodonium salts for highly efficient radioiodination and astatination of antibodies. *Bioorg Med Chem* 25, 5975–5980 (2017).
5. Shi, S. *et al.* Syndecan-1 knockdown inhibits glioma cell proliferation and invasion by deregulating a c-src/FAK-associated signaling pathway. *Oncotarget* 8, 40922–40934 (2017).
6. Kioi, M. *et al.* Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma after irradiation in mice. *J. Clin. Invest.* 120, 694–705 (2010).
7. Kim, J. & Bae, J.-S. Tumor-Associated Macrophages and Neutrophils in Tumor Microenvironment. *Mediators Inflamm* 2016, (2016).
8. Martinez, F. O. & Gordon, S. The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep* 6, (2014).
9. Séhédic, D. *et al.* Locoregional Confinement and Major Clinical Benefit of ^{188} Re-Loaded CXCR4-Targeted Nanocarriers in an Orthotopic Human to Mouse Model of Glioblastoma. *Theranostics* 7, 4517–4536 (2017).

P4/
“Development of a new generation dosimeter simulator”

ALFAYTAROUNI Zeinab[1], NOEL GEORGES[2], EL BITAR Ziad[1]
[1] *Université de Strasbourg, CNRS, IPHC, 67000 Strasbourg, France*
[2] *Radiotherapy department, institut de cancérologie Strasbourg Europe (ICANS), 67200 Strasbourg, France*

In treatment planning systems (TPS), Monte Carlo simulations are used to predict the outcome of irradiation before it is carried out, which allows to adjust the irradiation parameters in order to have the requested biological effect.
The water cross sections used in these simulations has failed to model the ionization process, especially at low incident energy [1][2].
Thus, the main objective of our work is to calculate the ionization cross sections of complex biological molecules to improve simulations of biological damage induced by ionizing radiation and subsequently to establish efficient radiobiological TPS.
The calculation is done using a program that calculate the triple, double, simple and total ionization cross sections in the framework of the first-born approximation, with the distorted/coulomb and the Gaussian-centered molecular wave functions to represent the ejected electron and the target molecule respectively, and the plane wave to represent the incident and scattered electrons.
Triple Differential Cross Sections (TDCS) are validated for water and other complex molecules such as pyrimidine and tetrahydrofuran [3], and now we are calculating these TDCS for the DNA bases. The whole program is validated for the water molecule and we are working to extend it to more complex molecules. The Total cross sections of pyrimidine will be calculated.
These cross sections will be implemented in the Geant4-DNA software which allows the monitoring of particles in the material in order to estimate the different dosimetric quantities to improve the simulation of the radiation treatment.

REFERENCES

[1] P. Bernhardt and H. G. Paretzke, “Calculation of electron impact ionization cross sections of DNA using the Deutsch–Märk and Binary-Encounter-Bethe formalisms,” International Journal of Mass Spectrometry, vol. 223, pp. 599–611, 2003.
[2] Z. Francis, Z. El Bitar, S. Incerti, M. A. Bernal, M. Karamitros, and H. N. Tran, “Calculation of lineal energies for water and DNA bases using the Rudd model cross sections integrated within the Geant4-DNA processes,” Journal of Applied Physics, vol. 122, no. 1, p. 014701, 2017.
[3] L. MOUAWAD, "Monte Carlo simulations and a theoretical study of the damage induced by ionizing particles at the macroscopic scale as well as the molecular scale," Strasbourg, 2017.

P5/

"In silico feasibility study of carbon ion radiotherapy with simultaneous integrated boost (CIRT-SIB) for head and neck adenoid cystic carcinoma"

E. Mastella[1,*], S, Molinelli[1], G. Magro[1], M. Bonora[1], S. Ronchi[1], R. Ingargiola[1], M. Ciocca[1], B. Vischioni[1], E. Orlandi[1]

[1]CNAO, National Center for Oncological Hadrontherapy, Strada Campeggi 53, I-27100 Pavia, Italy

Purpose: Simultaneous integrated boost (SIB)-intensity modulated radiotherapy (IMRT) is one of the major technical photon-based RT advances in the last 20 years [1]. In carbon ion radiotherapy (CIRT), a SIB approach has not been fully exploited so far. To our best knowledge, only Kawashiro et al. [2] Investigated a SIB treatment using CIRT for pancreatic cancer. The feasibility of a CIRT-SIB strategy for head and neck adenoid cystic carcinoma (ACC) patients was investigated in this study in order to improve treatment planning dose distributions.

Methods and Materials: CIRT plans of 10 ACC patients previously treated at CNAO with sequential boost (SEQ) irradiation and prescription doses of 41.0 Gy(RBE)/10 fractions to low risk (LR)-CTV plus 24.6. Gy(RBE)/6 fractions to the high risk (HR)-CTV were re-planned with two SIB dose levels to the LR-CTV: namely 48.0 Gy(RBE) and 54.4 Gy(RBE). While planning with SIB, the HR-CTV coverage had higher priority, with fixed organs at risk dose constraints among the SIB and SEQ plans. The homogeneity and conformity indexes were selected for CTV coverage comparison. The biological effective dose (BED) was calculated to compare the different fractionation schemes.

Results: Comparable HR-CTV coverage was achieved with the treatment approaches, while superior conformality and homogeneity was obtained with the SIB technique in both CTVs. With the SEQ, SIB48.0 and SIB54.4 the LR-CTV median doses were 50.3%, 11.9% and 6.0% higher than the prescriptions. Significant reductions of the median and near-maximum BEDs was achieved with both SIB dose levels in the LR-CTV.

Conclusions: The SIB approach resulted in highly conformal dose distributions with the reduction of the unintended dose to the LR-CTV. A prescription dose range for the LR-CTV will be clinically defined to offer tailored personalized treatments, according to the clinical and imaging characteristic of the patients.

REFERENCES
[1] F. De Felice et al., "Moderately accelerated intensity-modulated radiation therapy using simultaneous integrated boost: Practical reasons or evidence-based choice? A critical appraisal of literature," Head and Neck, vol. 42, no. 11. John Wiley and Sons Inc, pp. 3405–3414, Nov. 01, 2020, doi: 10.1002/hed.26400.
[2] S. Kawashiro et al., "Dose escalation study with respiratory-gated carbon-ion scanning radiotherapy using a simultaneous integrated boost for pancreatic cancer: Simulation with four-dimensional computed tomography," Br. J. Radiol., vol. 90, no. 1072, 2017, doi: 10.1259/bjr.20160790.

P6/

"Apparent diffusion coefficient and high b-value Diffusion-Weighted Magnetic Resonance Imaging as biomarkers for tumor response to re-irradiation with Carbon Ion Radiation Therapy for pelvic rectal recurrences: an explorative analysis"

G.Fontana[1], A.Barcellini[1], D.Boccuzzi[1-2], S.Imparato[1], M.Pecorilla[1], A.Vai[1], V.Vitolo[1], D.Maestri[1], A. Ghirelli[1-3], P. Loap[1-4], L. Preda[5-6], G.Baroni[1-7], E.Orlandi[1]
[1]*National Center for Oncological Hadrontherapy (Fondazione CNAO)*
[2]*Diagnostic Radiology Residency School, University of Pavia*
[3]*Radiation Oncology Residency School, Department of Radiotherapy, Istituto Oncologico del Veneto*
[4]*Radiation Oncology Residency School, Department of Radiation Oncology, Institut Curie*
[5]*Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, Unit of Radiology, University of Pavia*
[6]*Radiology Unit, Fondazione IRCCS Policlinico San Matteo*
[7]*Department of Electronics, Information and Bioengineering, Politecnico di Milano*

Background: Carbon Ion Radiotherapy (CIRT) has proved to be effective, safe and feasible as re-irradiation of locally recurrent rectal cancers (LRRCs)[1-4]. Radiological features might be worthwhile in building a tailored treatment strategy optimizing the advantages of particles. In this context, Diffusion-Weighted magnetic resonance Imaging (DW-MRI) and the related Apparent Diffusion Coefficients (ADC), sensitive to tissue microstructural parameters, proved to be promising biomarkers of CIRT response[5-8].

Aim: To investigate the role of pre-treatment ADC and b=1000 smm^{-2} DW-MRI (b1000) in treatment response prediction of LRRCs re-irradiated with CIRT.
Material and Methods: Clinical and radiological data of 17 consecutive patients (age range: 34-78 years; M:F=16:1) re-irradiated with CIRT for LRRCs (11 pre-sacral, 5 perineal and 1 pre-coccygeal) were retrospectively analysed. Each relapse was manually contoured on pre-treatment b1000 and respective ADC. Median, inter-quartile, skewness and kurtosis were used to describe ADC and b1000 lesion histograms. According to radiological hallmarks, patients were stratified as 1-year-responder (R) and 1-year-non-responder (NR). Statistically significant differences of DW-MRI features were tested with non-paired Mann-Whitney U test (α=0.05). Receiver Operating Characteristic (ROC) analysis was performed on relevant DW-MRI features, and related Area Under the ROC Curve (AUC) was computed as a feature diagnostic accuracy indicator.
Results: All b1000 features and ADC kurtosis showed statistically significant differences between NR (6 patients) and R (11 patients) groups. Especially, b1000 median and inter-quartile and ADC kurtosis appear promising ($p<0.025$, AUC>0.8) in stratifying patients as NR (62.5 ± 23.9, 1.15) or R (34 ± 13, 0.44).
Conclusion: b1000 median and inter-quartile, as well as ADC kurtosis, showed remarkable potentiality of being a biomarker of CIRT response in LRRCs reflecting the worth of DW-MRI as a non-invasive approach to test tumour response. Further investigations should be carried out on a larger cohort of LRRC patients to confirm these results.

REFERENCES

[1] Barcellini, A et al. “Re-irradiation With Carbon Ion Radiotherapy for Pelvic Rectal Cancer Recurrences in Patients Previously Irradiated to the Pelvis.” *In vivo (Athens, Greece)* vol. 34,3 (2020): 1547-1553. doi:10.21873/invivo.11944

[2] Cai, X et al. “The role of carbon ion radiotherapy for unresectable locally recurrent rectal cancer: a single institutional experience.” *Radiation oncology (London, England)* vol. 15,1 209. 28 Aug. 2020, doi:10.1186/s13014-020-01653-w

[3] Shiba, S et al. “Prospective Observational Study of High-Dose Carbon-Ion Radiotherapy for Pelvic Recurrence of Rectal Cancer (GUNMA 0801).” *Frontiers in oncology* vol. 9 702. 31 Jul. 2019, doi:10.3389/fonc.2019.00702

[4] Habermehl, D et al. “Reirradiation Using Carbon Ions in Patients with Locally Recurrent Rectal Cancer at HIT: First Results.” *Annals of surgical oncology* vol. 22,6 (2015): 2068-74. doi:10.1245/s10434-014-4219-z

[5] Preda, L et al. “Predictive role of Apparent Diffusion Coefficient (ADC) from Diffusion Weighted MRI in patients with sacral chordoma treated with carbon ion radiotherapy (CIRT)

alone." European journal of radiology vol. 126 (2020): 108933. doi:10.1016/j.ejrad.2020.108933
[6] Preda, L et al. "MRI evaluation of sacral chordoma treated with carbon ion radiotherapy alone." Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology vol. 128,2 (2018): 203-208. doi:10.1016/j.radonc.2017.11.029
[7] Buizza, Get al. "Radiomics and Dosiomics for Predicting Local Control after Carbon-Ion Radiotherapy in Skull-Base Chordoma." Cancers vol. 13,2 339. 18 Jan. 2021, doi:10.3390/cancers13020339
[8] Franconeri, A et al. "Intravoxel incoherent motion as a tool to detect early microstructural changes in meningiomas treated with proton therapy." Neuroradiology, 10.1007/s00234-020-02630-6. 3 Jan. 2021, doi:10.1007/s00234-020-02630-6

P7/

"Delivery of a drug molecule to thyroid cancer cells via EGFR targeting"

Zehra-Cagla Kahvecioglu[1,2], Manon Bruynbroeck[1], Laetitia Gheysen[1,2], Fabrice Journé[2], Sophie Laurent[1,3], Sven Saussez[2], Carmen Burtea[1]
ZEHRACAGLA.KAHVECIOGLU@umons.ac.be
[1] *UMONS - General, Department of General, Organic and Biomedical Chemistry, NMR and Molecular Imaging Laboratory, Faculty of Medicine and Pharmacy, University of Mons*
[2] *UMONS - Human Anatomy and Experimental Oncology, Faculty of Medicine and Pharmacy, University of Mons*
[3] *UMONS - Center for Microscopy and Molecular Imaging (CMMI), Faculty of Medicine and Pharmacy, University of Mons*

The anaplastic thyroid carcinoma (ATC) is the most aggressive thyroid cancer and is characterized by a high mortality rate, occurring within 2-6 months from diagnosis. The current systemic treatment is based on conventional therapies. New molecular targeted therapies are explored and are aimed to limit the systemic effects [1,2].
Our strategy consists of bringing a PIP3-targeted therapeutic peptide (TP) (PIP3-P2 and P3 peptides) directly into the thyroid cancer cells thanks to a vector peptide (VP) targeted to EGFR (EGFR-P5 and P20 peptides). The TP and VP peptides were identified using the phage display technology.
The binding of VP to their target was evaluated by immunohistochemistry on biopsies of ATC, subsequent to the validation of total and phosphorylated EGFR

expression on the same cases. The staining of these biomarkers is important on all cases, which confirms the receptor overexpression and overactivation in ATC. The staining obtained with peptides is similar, which suggests their good specificity and affinity. Detection of total and phosphorylated EGFR on ATC cells (8505C) by immunofluorescence confirmed that peptides bind the receptor and act as non-competitive antagonists of EGF.
To evaluate the binding of TP to their target, they were detected on several cases of ATC. Before confirming their binding, the presence of PIP3 and phosphorylated AKT was validated by an important staining on all these cases, revealing their overactivation. The labelling observed with peptides is comparable to that of PIP3, suggesting that peptides bind this biomarker with good affinity and specificity. Aiming to evaluate the therapeutic efficacy of these peptides, apoptotic cell death was demonstrated by the immunofluorescent detection of activated caspase 3 on 8505C cells.
Finally, the most promising TP and VP were coupled via streptavidin and their efficacy was assessed by the detection of activated caspase 3 on 8505C cells. This peptide combination appears as promising since the mortality rate was 100% and the labelling was more localized implying that the VP delivers TP directly into the ATC cells.

REFERENCES
[1] Tiedje V et al. Endocr Relat Cancer. 2018;25(3):R153-R161. 10.1530/ERC-17-0435.
[2] Li Z et al. Exp Ther Med. 2019;18(4):2369-2377. 10.3892/etm.2019.7869.

P8/
"RADIOTRANSNET, the French Network for Preclinical Research in Oncological Radiotherapy"

E. Bayart[1], D. Azria[2], J. Balosso[3], M. Benderitter[4], E. Cohen-Jonathan Moyal[5], G. Delpon[6], E. Deutsch[7], M. Dutreix[8], T. Lacornerie[9], P.H. Romeo[10], V. Marchesi[11], P. Maingon[1,12].

[1] Société Française de Radiothérapie Oncologique, 47 rue de la Colonie, 75013 Paris, France

[2] Pôle Radiothérapie Oncologique, Institut régional du Cancer de Montpellier, 208 Avenue des Apothicaires, 34298 Montpellier, France

[3] Département de Radiothérapie, Centre François-Baclesse, 3 Avenue du Général Harris, 14000 Caen, France
[4] Institut de Radioprotection et de Sûreté Nucléaire, 31 Avenue de la Division Leclerc, 92260 Fontenay-aux-Roses, France
[5] Institut Universitaire du Cancer de Toulouse - Oncopôle de Toulouse – Centre de Recherche de Cancérologie de Toulouse - Avenue Irène Joliot-Curie, 31100 Toulouse, France
[6] Institut de Cancérologie de l'Ouest - Site Nantes Saint-Herblain - Bd J. Monod 44805 Saint-Herblain, France
[7] Département de Radiothérapie, Gustave Roussy, 114 Rue Edouard Vaillant, 94800 Villejuif, France
[8] Institut Curie, Centre Universitaire, 91405 Orsay Cedex, France
[9] Service de Physique Médicale - Centre Oscar LAMBRET - 3 Rue Frédéric Combemale, 59000 Lille, France
[10] CEA – DRF - Centre d'études de Saclay- 91191 Gif sur Yvette cedex, France
[11] Service de Physique Médicale - Institut de Cancérologie de Lorraine - 6 Avenue de Bourgogne, 54519 Vandœuvre-lès-Nancy, France
[12] Département de radiothérapie, GHU Pitié-Salpêtrière-Charles Foix, 47/83 bld de l'hôpital, 75013 Paris, France

The ambition of the RADIOTRANSNET network, launched by the INCa at the end of 2018, is to create a French research consortium dedicated to preclinical radiotherapy to foster scientific and clinical interactions at the interface of radiotherapy and radiobiology and to identify research priorities dedicated to innovation in radiotherapy. The activities of the network are organized around four major axes that are target definition, normal tissue, combined treatments and dose modelling. Under the supervision of the Scientific Council, headed by a coordinator designated by the SFRO and a co-coordinator designated by the SFPM, three leaders coordinate each axis: a radiation-oncologist, a medical physicist and a biologist, who are responsible for organizing a scientific meeting based on the consensus conference methodology to identify priority issues. The selected themes will be the basis for the establishment of a strategic research agenda and a roadmap to help coordinate national basic and translational research efforts in oncological radiotherapy. This work will be published and will be transmitted to the funding institutions and bodies with the aim of opening dedicated calls to finance the necessary human and technical resources. Thus, structuration of a

preclinical research network will allow coordinating the efforts of all the actors in the field and thus promoting innovation in radiotherapy [1].

REFERENCES
[1] RadioTransNet, the French network for preclinical research in oncological radiotherapy. Bayart E, Azria D, Balosso J, Benderitter M, Cohen-Jonathan Moyal E, Delpon G, Deutsch E, Dutreix M, Lacornerie T, Romeo PH, Marchesi V, Maingon P. Cancer Radiother. 2019 Oct;23(6-7):609-616. doi: 10.1016/j.canrad.2019.07.155.

P9/
"Theranostic evaluation of a copper-64 radiolabelled antibody in a mouse model of multiple myeloma"

Cassandra MÉTIVIER[1], Patricia LE SAËC[1], Séverine MARIONNEAU-LAMBOT[1], François DAVODEAU[1], Catherine CHAUVET[1], Catherine MAUREL[1], Peter O HOFGAARD[2,3], Bjarne BOGEN[2,3], Raphaël TRIPIER[4], Férid HADDAD[5], Joëlle GASCHET[1], Michel CHÉREL[1], Nicolas CHOUIN[1,6], Alain FAIVRE-CHAUVET[1], **Latifa RBAH-VIDAL**[1]

[1] Université de Nantes, CHU Nantes, CNRS, Inserm, CRCINA, F-44000 Nantes, France

[2] Department of Immunology, Centre for Immune Regulation, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[3] KG Jebsen Centre for Influenza Vaccine Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[4] UMR CNRS 6521 CEMCA, Université de Brest, Brest, France

[5] GIP Arronax, Saint-Herblain, France

[6] Oniris (Nantes Atlantic College of Veterinary Medicine, Food Science and Engineering), Nantes, France.

Introduction: In nuclear medicine, theranostics is based on the use of specific radiolabelled vectors, combining diagnosis by molecular imaging and targeted radionuclide therapy (TRT). Copper-64 (^{64}Cu) is an innovative radionuclide, which has decay properties suitable for PET imaging (*17.4% β^+ emission*) and potentially for TRT (*40% β^- emission*). This project aims to explore the theranostic potential of a radiolabelled anti-CD138 antibody (^{64}Cu-HTE1PA-9E7.4) in the MOPC315.BM mouse model of multiple myeloma (MM).

Methods: *Distribution* of ^{64}Cu-HTE1PA-9E7.4 was assessed by both *in vivo PET Imaging* and *ex vivo* Organ Counting at different times post-injection (p.i) to evaluate the cumulative radioactivity taken up by organs and tumors and perform dosimetric calculations. Then, a single and repeated injection TRT study was performed with activities ranging from 22 to 65 MBq. Therapeutic anti-tumour efficacy was determined by the survival of treated mice in comparison to controls. Daily monitoring of external signs of toxicity, and weekly monitoring of haematological and renal parameters were performed.
Results: The biodistribution of ^{64}Cu-HTE1PA-9E7.4 showed a favourable profile with specific targeting of CD138 positive cells as early as 30 min p.i. and reaching more than 50% ID/g of tissue by 24 h p.i. A single dose of 35 and 65 MBq increases the median survival of the mice (*32 days and 35 days respectively versus 28 days for controls).* Repeat dosing was significantly more effective with a median survival of 47 days for mice receiving 2 injections of 55 MBq. Also, 50% of the mice treated with two doses of 35 MBq were still alive at 80 days post-inoculation. *Mild* to *moderate* and *transient* haematological *toxicity* was *observed* at potentially therapeutic doses.
Conclusion: These promising results confirm the theranostic potential of ^{64}Cu-HTE1PA-9E7.4 in our preclinical model of MM.
Acknowledgments: *The "TheraScCoop" project is financially supported by the NExT "Nantes Excellence Trajectory" initiative (I-SITE call for projects), an action of the second Future Investments Program (PIA2) launched by the French State and implemented by the ANR (reference ANR-16-IDEX-0007). This initiative takes place in the Pays de la Loire region, in Nantes Métropole.*

P10/
"Effect of ultra-high dose rate protontherapy on zebrafish embryos"

Vincent Potiron[1,2], Gaëlle Saade[1], Charbel Koumeir[3], Arthur Bongrand[2], Daphnée Villoing[2], Noël Servagent[3], Stéphane Supiot[1,2], Ferid Haddad[3], Sophie Chiavassa[2], Grégory Delpon[2]
CRCINA, Inserm U1232, Université de Nantes, France
Institut de Cancérologie de l'Ouest, Saint-Herblain, France
SUBATECH, CNRS UMR6457, Université de Nantes, France

Ultra-high dose rate radiotherapy (UHDR), named FLASH-RT, holds great promise in reducing radiotoxicity. However, what parameters are required such as radiation type or dose rate remains uncompletely defined. Preservation of body length of zebrafish embryos (ZE) has been demonstrated after Flash-RT using electron accelerators. Nevertheless, whether proton accelerators can induce a Flash-mediated protection is controversial in the literature.

In this study, we explored the relative toxicity of protontherapy at various dose rates on zebrafish embryos. Embryos aged of 4 hours post-fertilization (4hpf) and 28 hpf were irradiated at doses of 6-8 Gy and 30-40 Gy with 68 MeV protons at 10 Gy/min or 7000 gy/sec. Survival, embryo length and curvature were determined as experimental readouts.

Irradiations of embryos at conventional dose rate led to reduction of body length and increased curvature. However, no statistical difference was found at UHDR protontherapy with 4-12 pulses spaced by 750µsec. Similarly, no protection of embryos was detected when irradiating with a single proton pulse, despite largely exceeding the usually well accepted threshold of 40 Gy/sec. Our data do not demonstrate a Flash-mediated protection for zebrafish embryos when using accelerated protons. Further experiments will have to re-investigate ZE effects at dose rates higher than 7000 Gy/sec.

Keywords : radiotherapy, proton, ultra-high dose rate, toxicity, zebrafish

Acknowledgments : this work was funded by Ligue contre le Cancer (VP), ICO translational (VP), IRC Transformed training grant (GS) and Inserm PCSI cancer (GD).

P11/
"Role of pericytes in the tumor response to radiotherapy"

Vincent Potiron[1,2], Luc Ollivier[1], Séverine Marionneau-Lambot[1], Vincent Libois[2], Manon Pietri[2], Delphine Caron[2], Sophie Chiavassa[2], Grégory Delpon[2], Stéphane Supiot[1,2]

CRCINA, Inserm U1232, Université de Nantes, France
Institut de Cancérologie de l'Ouest, Saint-Herblain, France

The vascular microenvironment influences the tumor response to radiotherapy (RT) by modulating oxygen level, among other mechanisms. Vascular destruction following irradiation is therefore expected to decrease radiotherapy efficacy through hypoxia. Yet, we have originally observed that conventional RT improves vascular function, accompanied by the recruitment of pericytes around tumor blood vessels (Potiron *et al*, PLoS One 8, 2013). Radiotherapy-induced vascular remodeling (RIVR) improves drug delivery (Potiron *et al*, Cancer Letters 457, 2019) and is visible upon various fractionation schedules (2-12 Gy/fraction, Clément-Colmou *et al*, Cancers 12, 2020).

In this study, we focused on the specific contribution of pericytes in the microenvironment and overall tumor response to RT. 4T1 orthotopic syngeneic mammary tumors were engrafted in Balb/c PDGFRβ-TK mice, in which pericytes (PDGFRβ+ cells) are conditionally eliminated with ganciclovir (GCV). Depletion of pericytes was validated using immunohistochemistry for α-smooth-muscle actin and desmin in the 2 µm lining CD31+ vessels. CD4, CD8 and Foxp3 were detected by multispectral fluorescence microscopy to measure immune T cell infiltration. Tumor growth and lung metastasis were evaluated in response to 2x12 Gy RT.

Ganciclovir at 50 mg/kg led to a 70% decrease of intra-tumoral pericytes. RT alone slowered tumor growth (median survival >36 days vs 19d for ctl and 21d for GCV ; $p<0.0001$). However, depletion of pericytes during irradiation did not modulate tumor growth (median survival > 36d). In addition, RT decreased the number of metastasis (ctl: 10.5 per lung ± 1.3, GCV: 13.2 ± 1.6, RT: 4.7± 0.7; $p<0.05$ vs ctl) but this was completely abolished upon pericyte depletion (RT+GCV: 14.1 ± 3.2; $p<0.05$ vs RT). Moreover, RT increased the ratio of effective (T CD8+) / regulatory (CD4-FoxP3+ and CD8-FoxP3+) T cells (ctl: 0.35 ± 0.06, GCV: 0.46 ± 0.11, RT: 0.69 ± 0.12; $p<0.05$ vs ctl) but depletion of pericytes counteracted this effect (RT+GCV: 0.33 ± 0.06; $p<0.05$ vs RT).

Overall, our results demonstrate that the recruitment of pericytes governs the anti-metastatic efficacy of irradiation.

Keywords : radiotherapy, pericyte, metastasis, blood vessel, immune cells

Acknowledgments : this work was supported by funding from Association pour la Recherche sur le Cancer (SS, VP) and Année Recherche from Univ. Brest (LO).

P12/
"Calibration of the zebrafish embryo model for radiotherapy TOXICITY"

Gaëlle Saade[1], Sophie Chiavassa[2], Arthur Bongrand[2], Daphnée Villoing[2], Charbel Koumeir[3], Noël Servagent[3], Ferid Haddad[3], Grégory Delpon[2], Stéphane Supiot[1,2], **Vincent Potiron[1,2]**

CRCINA, Inserm U1232, Université de Nantes, France
Institut de Cancérologie de l'Ouest, Saint-Herblain, France
SUBATECH, CNRS UMR6457, Université de Nantes, France

Ultra-high dose rate radiotherapy, named FLASH-RT, has recently emerged as a promising strategy to reduce RT toxicity. A great challenge of FLASH-RT is to identify the parameters allowing normal tissue protection, such as radiation type or dose rate. In this regard, there is a strong need for a biological model that offers ease of use for testing multiple conditions in a timewise and reproducible manner. The zebrafish embryo (ZE) is a non-autonomous transparent organism which allows rapid, cost-friendly testing of large numbers of individuals, thereby achieving high statistical power. FLASH protection has been demonstrated on ZE body length using electron accelerators. However, several conditions must be met to measure adequate responses, such as dose and larval stage.

In this study, we calibrated the dose and stage-dependent RT response of ZE. Survival, embryo length and curvature were determined as experimental readouts. Effects on cell proliferation and apoptosis were assessed by whole-mount immunohistochemistry for phospho-H3 and DNA cleavage.

The optimal doses to produce length and curving effects while maintaining survival of >80% were 6-8 Gy at 4 hpf and 30-40 Gy at 28 hpf. For embryos irradiated at 12 Gy, survival ranged from 40% at 4 hpf to 90% after 7 hpf, with corresponding increase in body length close to baseline at 9 hpf. Using different accelerators, no statistical difference was found between 225 kV photons and 68 MeV protons. Additionnally, we developped a simple methodology to assess the influence of hypoxia. Placing embryos in a closed tube allowed to reproducibly lower oxygen content with time and specifically impacted ZE response to irradiation, leading to increased RT-induced curvature and viability. At the cellular level, increasing doses of RT induced apoptosis and blocked proliferation.

These data provide valuable ressources for comparing multiple irradiation conditions in a reproducible manner across different laboratories, using amenable bench equipment.

Keywords : radiotherapy, zebrafish, ultra-high dose rate, toxicity

Acknowledgments : this work was supported by a IRC Transformed training grant (GS) and research funding from Ligue contre le Cancer (VP), Inserm PCSI cancer (GD) and ICO translational (VP).

P13/
"From Ouzo effect to combined chemo-radio-therapies "

Déborah IGLICKI[1], Clément GOUBAULT[1], Ulrich JARRY[2,3], Pierre-Antoine ELIAT[4], Paul RETIF[5], Mégane BOSTOËN[2], Rémy PEDEUX[2,6], Thierry GUILLAUDEUX[2], Myrtil L. KAHN[7], Fabienne GAUFFRE[1] & Soizic CHEVANCE[1]

1. *Univ Rennes, CNRS, Institut des Sciences Chimiques de Rennes - UMR6226, Rennes, France.*
2. *Univ Rennes, CNRS, INSERM, BIOSIT - UMS 3480, LabCom Oncotrial, Biotrial Pharmacology, US_S 018, F-35000 Rennes, France.*
3. *Biotrial Pharmacology, Unité De Pharmacologie Préclinique, Rennes, France.*
4. *Univ Rennes, CNRS, INSERM, BIOSIT - UMS 3480, PRISM Bio-SCANS, F-35000 Rennes, France.*
5. *Unité de Physique Médicale, CHR Metz-Thionville, Ars-Laquenexy, France.*
6. *COSS (Chemistry Oncogenesis Stress Signaling)—UMR_S 1242, University of Rennes, INSERM, CLCC Eugène Marquis, F-35000 Rennes, France.*
7. *Laboratoire de Chimie de Coordination - UPR8241, CNRS, 205 route de Narbonne, Toulouse, France.*

See the abstract page 54.

Last name	First name	Laboratory	City	Country	Mail
ABRUNHOSA	Antero	ICNAS/University of Coimbra	Coimbra	Portugal	antero@pet.uc.pt
ALFAYTAROUNI	Zeinab	Institut Pluridisciplinaire Hubert Curien , Université de Strabsbourg	Strasbourg	France	zeinab.alfaytarouni@iphc.cnrs.fr
APOSTOLOVA	Paulina	Laboratory for Radiopharmacy, Faculty of Medical Sciences	Stip	Rep. of North Macedonia	paulina.apostolova@ugd.edu.mk
AREV	Marija	Laboratory for Radiopharmacy, Faculty of Medical Sciences	Stip	Rep. of North Macedonia	marija.arev@ugd.edu.mk
AYALA-HERNANDEZ	Luis Enrique	Det. de Ciencias Exactas y Tecnología Centro, Universitario de los Lagos	Jalisco	Mexico	quique.a.h@hotmail.com
BADAR	Adam	MiLabs	Utrecht	The Netherlands	A.Badar@milabs.com
BARBET	Jacques	Cyclotron Arronax	Nantes	France	Jacques.Barbet@univ-nantes.fr
BAYART	Emilie	RadioTransNet	Paris	France	eb.radiotransnet@gmail.com
BORGES	Ana	i3S & INEB – Institute of Biomedical Engineer, University of Porto	Porto	Portugal	ana.borges@i3s.up.pt
BOSSIS	Théo	Université Paris-Saclay, CNRS/IN2P3, IJCLab	Orsay	France	theo.bossis@ijclab.in2p3.fr
BOURBONNE	Vincent	LaTIM, U 1101 INSERM, University of Western Brittany	Brest	France	vincent.bourbonne@chu-brest.fr
CAO	Yi-Heng	UMR 1101 Inserm LaTIM, Université de Bretagne Occidentale, IMT Atlantique	Brest	France	Yi-Heng.Cao@univ-brest.fr
CHEN	Jia-Wei	Namur Research Institute for Life Sciences (NARILIS), University of Namur	Namur	Belgium	jia-wei.chen@unamur.be
CHEREL	Michel	CRCINA, UMR 1232 INSERM, ERL CNRS 6001, University of Nantes	Nantes	France	Michel.Cherel@univ-nantes.fr
CHEVANCE	Soizic	ISCR UMR 6226 CNRS-UR1 - Equipe COrInt	Rennes	France	soizic.chevance@univ-rennes1.fr
CHILUG	Elana Livia	Horia Hulubei National Institute for R&D in Nuclear Physics and Engineering	Magurele-Ilfov	Romania	livia.chilug@nipne.ro
COUPEY	Julie	Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy group, GIP CYCERON	Caen	France	coupey@cyceron.fr
DELPON	Grégory	Institut de Cancérologie de l'Ouest	Saint-Herblain	France	Gregory.Delpon@ico.unicancer.fr
DESROCQUES	Katarzyna	MOLECUBES	Ghent	Belgium	katarzyna.desrocques@molecubes.com
DWIRI	Fatima-Azzahra	Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy Group, GIP CYCERON	Caen	France	dwiri@cyceron.fr

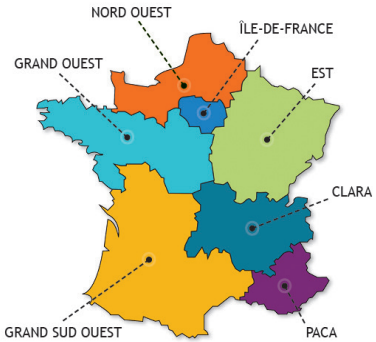
EL FAKIRI	**Mohamed**	University Medical Center Freiburg, Radiopharmaceutical Development	Freiburg	**Germany**	mohamed.el.fakiri@uniklinik-freiburg.de
FANTIN	**Jade**	Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy Group, GIP CYCERON	Caen	**France**	fantin@cyceron.fr
FERON	**Olivier**	Cancer Translational Research Lab, Institute of experimental and clinical research	Louvain	**Belgium**	olivier.feron@uclouvain.be
FLOCH	**Emilie**	Plateforme projets européens (2PE) - Bretagne	Brest	**France**	emilie.floch@2PE-bretagne.eu
FONTANA	**Giulia**	National Center for Oncological Hadrontherapy (Fondazione CNAO)	Pavia	**Italy**	giulia.fontana@cnao.it
GARCION	**Emmanuel**	Nantes-Angers Cancer Research Center, University of Angers	Angers	**France**	emmanuel.garcion@univ-angers.fr
GESTIN	**Jean-François**	Nantes-Angers Cancer Research Center, University of Nantes	Nantes	**France**	jfgestin@nantes.inserm.fr
HATT	**Mathieu**	LaTIM, U 1101 INSERM, University of Western Brittany	Brest	**France**	mathieu.hatt@univ-brest.fr
HAUG	**Alexander**	Department of Nuclear Medicine, Medical University of Innsbruck	Innsbruck	**Austria**	alexander.haug@meduniwien.ac.at
HESKAMP	**Sandra**	Dept of Medical Imaging – Nuclear Medicine, Radboudumc	Nijmegen	**The Netherlands**	Sandra.heskamp@radboudumc.nl
IGLICKI	**Déborah**	ISCR UMR 6226 CNRS-UR1 - Equipe COrInt	Rennes	**France**	deborah.iglicki@univ-rennes1.fr
JANEVIK-IVANOVSKA	**Emilija**	Laboratory for Radiopharmacy, Faculty of Medical Sciences	Stip	**Rep. of North Macedonia**	emilija.janevik@ugd.edu.mk
JASHARI	**Armend**	Faculty of Medical Sciences, Goce Delcev University Stip	Prishtine	**Republic of Kosovo**	armendjashari@yahoo.com
KAHVECIOGLU	**Zehra-Cagla**	Faculty of Medicine and Pharmacy, University of Mons	Mons	**Belgium**	ZEHRACAGLA.KAHVECIOGLU@umons.ac.be
KLEINENDORST	**Simone**	Department of Medical Imaging: Nuclear Medicine, Radboudumc	Nijmegen	**The Netherlands**	Simone.C.Kleinendorst@radboudumc.nl
LEFAUCHEUR	**Jean-Luc**	INVISCAN SAS	Strasbourg	**France**	jeanluc@inviscan.fr
LEOST	**Françoise**	Cancéropôle Grand Ouest	Nantes	**France**	francoise.leost@univ-nantes.fr
LE GOAS	**Marine**	Faculté de Pharmacie, Université de Montréal	Montréal	**Québec**	marine.le.goas@umontreal.ca
LEPAREUR	**Nicolas**	Centre Eugène Marquis	Rennes	**France**	n.lepareur@rennes.unicancer.fr
LODE	**Kristin**	Department of clinical Medicine, faculty of Health Sciences. UiT	Tromsø	**Norway**	kristin.lode@uit.no
LYNG	**Heidi**	Oslo University Hospital, The Norwegian Radium Hospital	Oslo	**Norway**	Heidi.Lyng@rr-research.no
MARAGE	**Louis**	Centre Georges-François Leclerc	Dijon	**France**	lmarage@cgfl.fr
MASTELLA	**Edoardo**	CNAO, National Center for Oncological Hadrontherapy	Pavia	**Italy**	edoardo.mastella@cnao.it

METIVIER	Cassandra	Nantes-Angers Cancer Research Center, University of Nantes	Nantes	France	cassandra.metivier@etu.univ-nantes.fr
NICULAE	Dana	Radiopharmaceutical Research Centre, IFIN-HH	Magurele	Romania	dana.niculae@nipne.ro
NOEL	Georges	Institut de Cancérologie de strasbourg Europe	Strasbourg	France	m.meyer@icans.eu
NONNEKENS	Julie	Dept. of Radiology and Nuclear Medicine, Erasmus	Rotterdam	The Netherlands	j.nonnekens@erasmusmc.nl
OCANA-TIENDA	Beatriz	Instituto de Matemática Aplicada a la Ciencia y la Ingeniería	Castilla-La Mancha	Spain	Beatriz.Ocana@uclm.es
OLIVEIRA	Maria José	i3S-Institute for Research and innovation in Health, University of Porto	Porto	Portugal	mariajo@ineb.up.pt
PASQUET	Nolwenn	Normandie Univ, UNICAEN, CEA, CNRS, ISTCT/CERVOxy Group, GIP CYCERON	Caen	France	pasquet@cyceron.fr
POSSENTI	Luca	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan & Politecnico di Milano	Milan	Italy	luca.possenti@istitutotumori.mi.it
POTIRON	Vincent	Nantes-Angers Cancer Research Center, University of Nantes	Nantes	France	Vincent.Potiron@univ-nantes.fr
RBAH-VIDAL	Latifa	CRCINA, UMR 1232 INSERM, ERL CNRS 6001, University of Nantes			latifa.rbah-vidal@univ-nantes.fr
REUVERS	Thom	Erasmus MC Cancer Institute, Erasmus University Medical Center	Rotterdam	The Netherlands	t.reuvers@erasmusmc.nl
ROBERT	Charlotte	UMR 1030 Radiothérapie moléculaire, Inserm, Gustave Roussy	Paris	France	CH.ROBERT@gustaveroussy.fr
RODAK	Magdalena	Institute of Nuclear Chemistry and Technology	Warsaw	Poland	magdalena.rodak22@gmail.com
SABBAH	Malak	Institut Jules Bordet, Université Libre de Bruxelles	Brussels	Belgium	Malak.sabbah@ulb.be
SALLE	Guillaume	UMR 1101 Inserm LaTIM, UBO, IMT Atlantique	Brest	France	guillaume.salle@univ-brest.fr
SCHIFFLERS	Christoph	Cell Biology Research Unit, Unamur	Heidelberg	Germany	christoph.schiffers@unamur.be
SERBAN	Radu Marian	Horia Hulubei National Institute for R&D in Physics and Nuclear Engineering	Bucharest	Romania	radu.serban@nipne.ro
SUPIOT	Stéphane	CRCINA, UMR 1232 INSERM, University of Nantes & ICO	Saint-Herblain	France	Stephane.Supiot@ico.unicancer.fr
TAHBOUB	Dana	Division of Radiotherapy and Imaging, The Institute of Cancer Research	London	United Kingdom	dana.tahboub@icr.ac.uk
VISVIKIS	Dimitris	LaTIM, U 1101 INSERM, University of Western Brittany	Brest	France	Visvikis.Dimitris@univ-brest.fr
VOZENIN	Marie-Catherine	Lausanne University Hospital and Lausanne University	Lausanne	Switzerland	Marie-Catherine.Vozenin@chuv.ch

Cancéropôle Grand Ouest

for accelerating translational cancer research

Since 2003, the cancéropôles have become part of the cancer research landscape in France enabling a better coordination of resources and means and breaking down barriers.
They give rise to large-scale research networks and infrastructures fostering interdisciplinarity.



The 7 regional or interregional hubs named cancéropôles bring together research units of scientific institutions (Inserm, CNRS, universities, Ifremer, …), university hospitals, comprehensive cancer centers, pharmaceutical companies and biotech players.

Their goals are mainly:

(1) **structure and coordinate research between institutions, at regional and inter-regional levels,**
(2) **define specific strategic orientations based on the fields of excellence of each Cancéropôle,**
(3) **create synergies with innovation and economic development stakeholders** and
(4) **ensure adequacy between regional and national R&D policies in oncology**, as promoted by the french National Cancer Institute (INCa).

High-level quality research projects supported by the INCa and the Ministry of Health through the cancéropôles networks should allow to better understand the molecular mechanisms involved in oncogenesis which is crucial to define new therapeutic targets and to develop innovative treatments for the benefit of all patients.



Cancéropôle grand ouest

www.canceropole-grandouest.com

Find and follow the news

of the Cancéropôle Grand Ouest on :

www.canceropole-grandouest.com

web

Join us on LinkedIn

web

Find us on facebook

web

twitter

Cancéropôle grand ouest

Tumour Targeting, Imaging, Radiotherapies

Workshop supported by :

FLi France Life Imaging

LA LIGUE CONTRE LE CANCER

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

SFC Société Française du Cancer

MOLECUBES MODULAR BENCHTOP IMAGING

MILabs Making Molecular Imaging Clear

SIRIC ILIAD Nantes - Angers

NeXT IRC TransForMed

inviscan Imaging systems

iron labex

Endorsed by ESTRO

www.cgo-workshop-vecto.fr