

# EN HOPE SMART4CBT project

**E**ast **N**orth-**H**ematology **O**ncology  
**P**ediatric consortium offering research  
programs of **S**ocial sciences,  
**M**icroenvironment & multiomics  
**A**nalyses in **R**adio**T**herapy resistance **F**or  
**C**hildren **B**rain **T**umors

Natacha ENTZ-WERLE – Center Director – pediatric  
oncologist

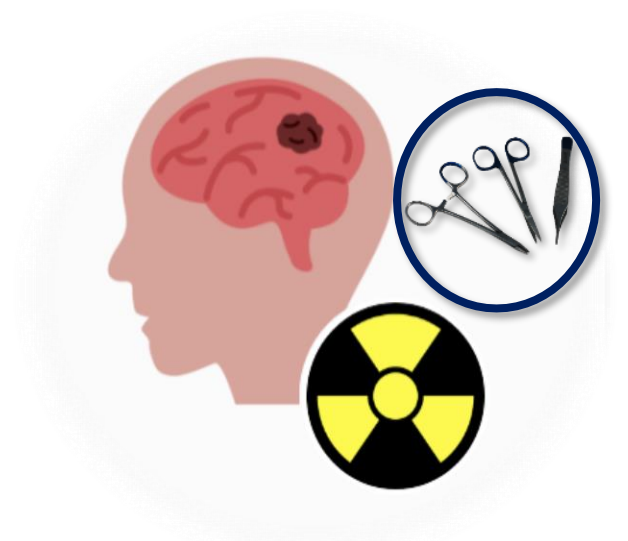
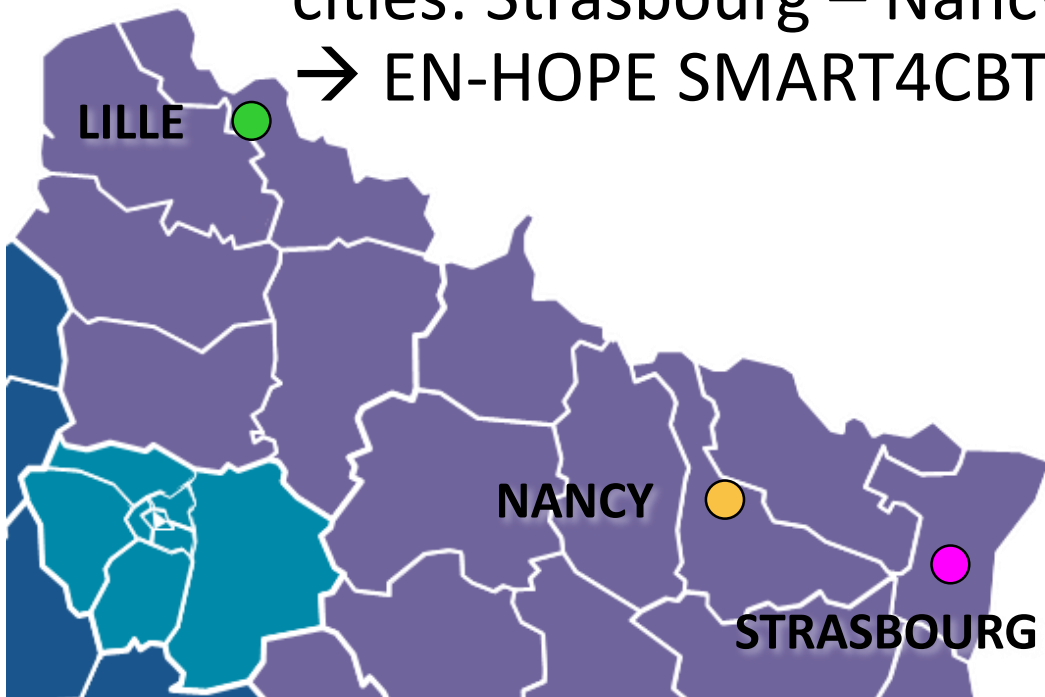
Chloé BERNHARD – Project Manager – pharmD, PhD  
University Hospital of Strasbourg



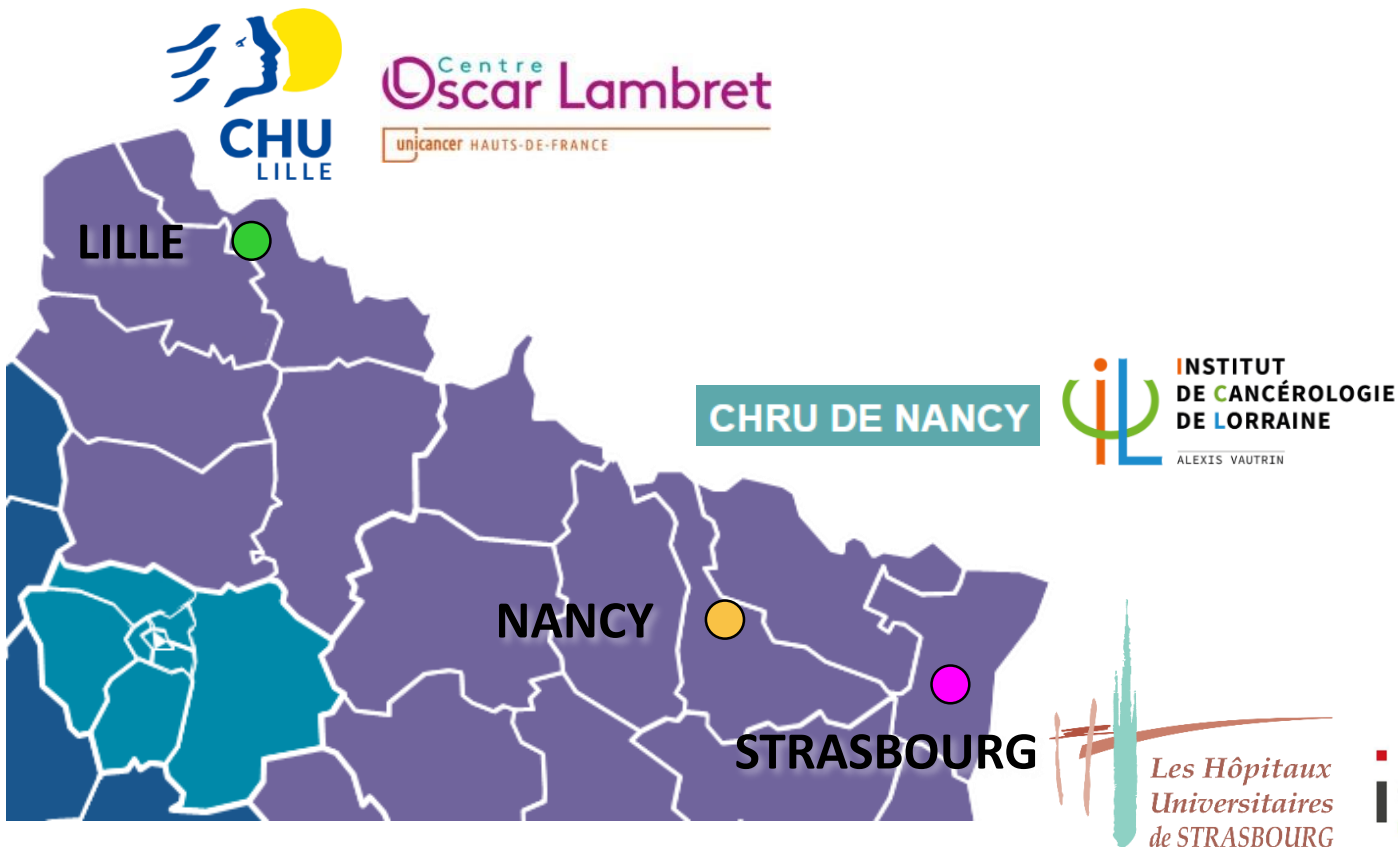
Organisation Inter Régionale de recours en hématologie-oncologie pédiatrique Hauts-de-France et Grand-Est

# EN-HOPE SMART4CBT

- Structuring of pediatric brain tumor research in Northern and Eastern France
- 20% of French patients are treated across the following three cities: Strasbourg – Nancy – Lille  
→ EN-HOPE SMART4CBT research consortium



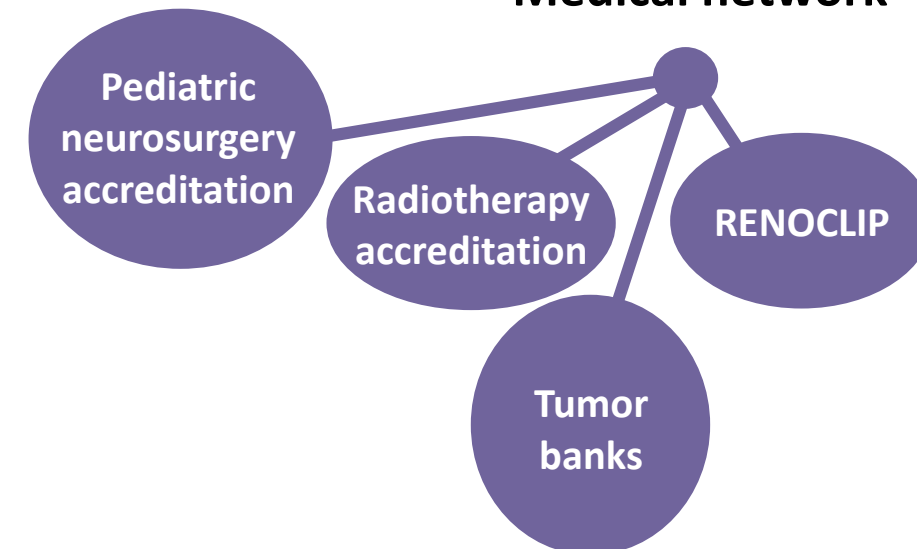
# EN-HOPE SMART4CBT consortium



- 7 pediatric neurosurgeons
- 3 distinct biobanks
- 3 neuropathologists
- 3 pediatric neuroradiologists
- 5 neuro-oncologists
- 3 pediatric radiotherapists



## Medical network



# EN-HOPE SMART4CBT consortium

SCALab  
SCIENCES COGNITIVES ET SCIENCES AFFECTIVES

IESEG  
SCHOOL OF MANAGEMENT

Laboratoire  
Paul Painlevé



Canther  
Cancer Heterogeneity, Plasticity  
and Resistance to Therapies

PRISM  
Inserm U1192



LILLE

Centre  
Oscar Lambret  
unicancer HAUTS-DE-FRANCE

CeREFIGE  
Centre Européen de Recherche en Économie Financière  
et Gestion des Entreprises

INSPIRE

CRAV

n-GERE  
nutrition-génétique et exposition  
aux risques environnementaux

IMoPA  
Ingénierie Moléculaire & Physiopathologie Articulaires

CHRU DE NANCY

INSTITUT  
DE CANCÉROLOGIE  
DE LORRAINE  
ALEXIS VAUTRIN

NANCY

STRASBOURG

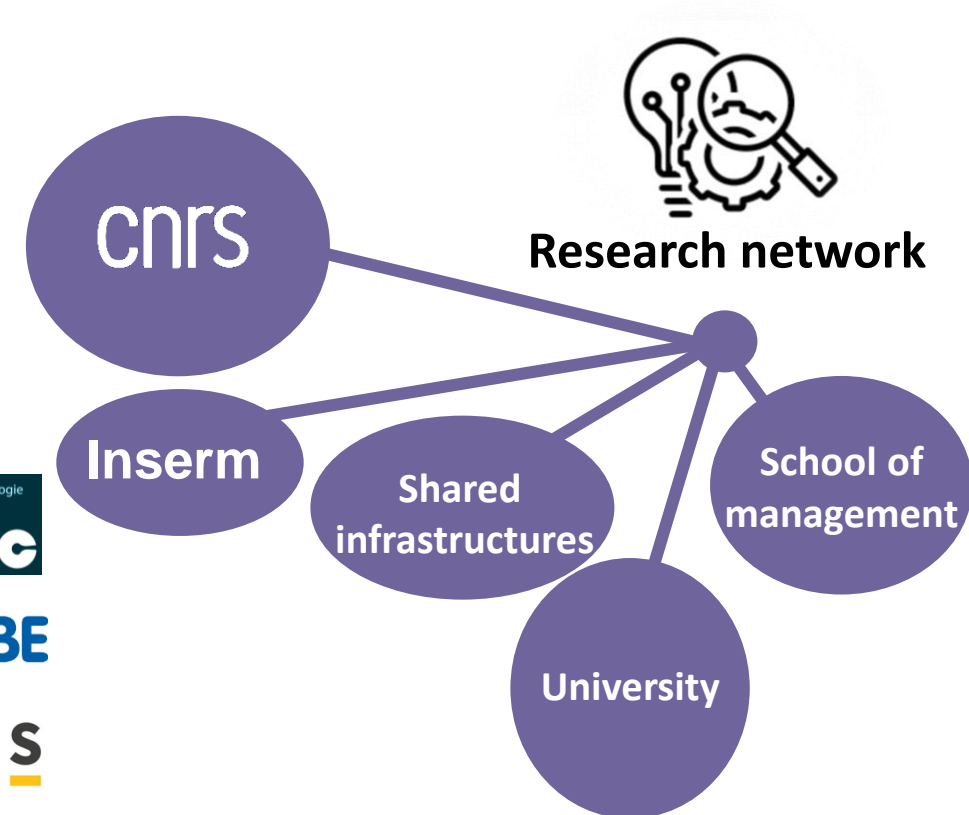
ONKO<sup>ST</sup>

Les Hôpitaux  
Universitaires  
de STRASBOURG

ibmc  
institut de biologie  
moléculaire et  
cellulaire

ICU3E

ICANS



# EN-HOPE SMART4CBT consortium



LILLE



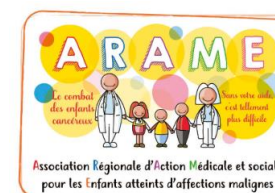
CHRU DE NANCY



NANCY

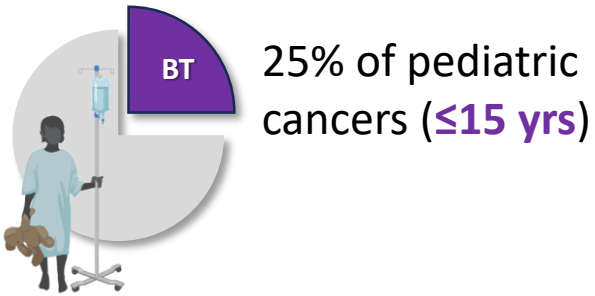


STRASBOURG

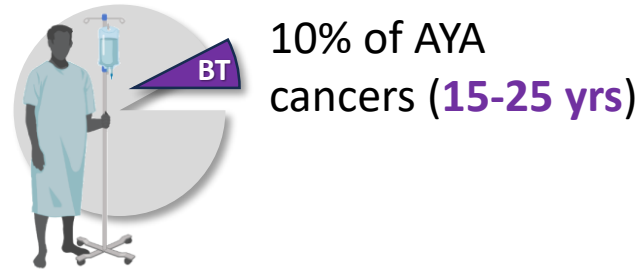




# Numbers in child/AYA brain tumors



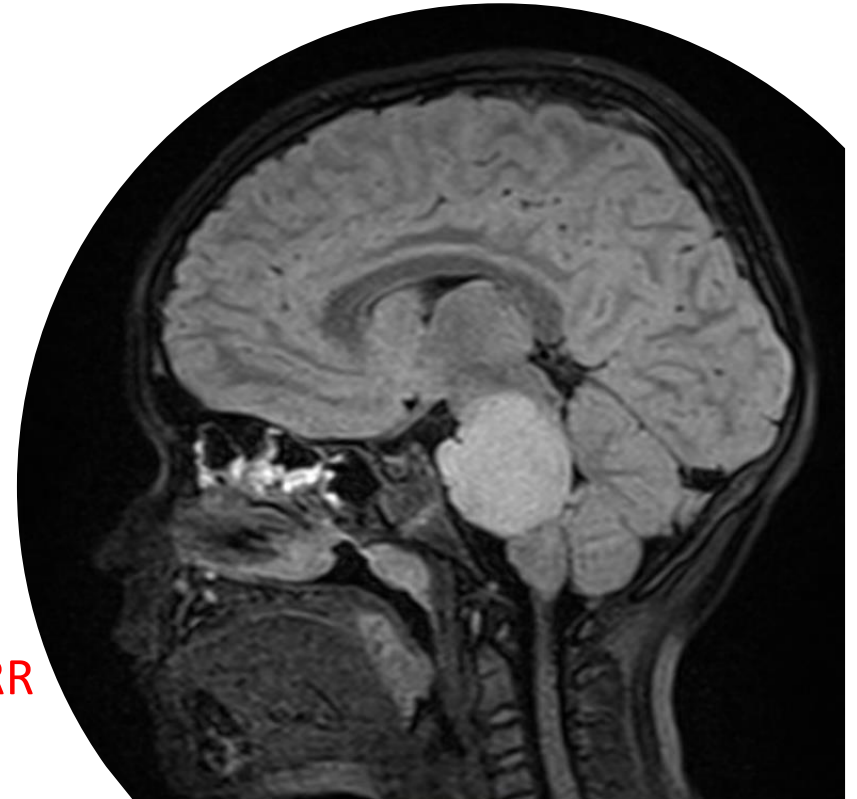
**brain tumors = second common cause of death in pediatrics/AYA**



15% medulloblastomas/  $\approx 40\%$  RR

15-18% HGG/  $\approx 90\%$  RR

6% ependymomas/  $\approx 20-40\%$  RR





A fundamental and translational research program encompassing the most aggressive **brain tumor** histo-types (high-grade gliomas, medulloblastomas and ependymomas), and their **radioresistance** (RR) mechanisms

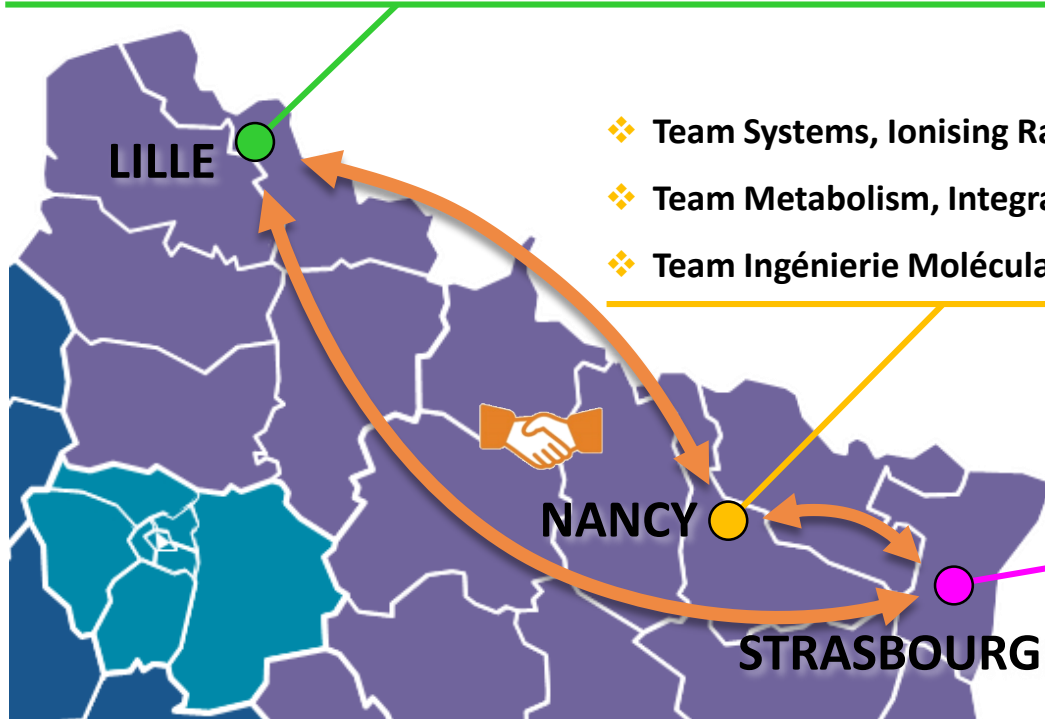
**From biology to clinics, studying tumor cell plasticity and heterogeneity and their role in radioresistance**

# Research teams

20 researchers  
14 clinicians-researchers  
4 clinicians  
8 engineers  
8 post-doctoral fellows  
14 PhD

❖ Team Cell Plasticity & Cancer - UMR Canther - UMR9020 CNRS – UMR 1277 Inserm

❖ 2 teams in Laboratory PRISM U1192 Inserm



❖ Team Systems, Ionising Radiation & Nanomedicine applied to Neuro-Oncology - CRAN UMR 7039

❖ Team Metabolism, Integrative genomics & Bioinformatics - NGERE UMR 1256 Inserm

❖ Team Ingénierie Moléculaire et Physiopathologie Articulaire (IMoPA) - UMR 7365

❖ Team ONKO3T - UMR CNRS 7021

❖ Team Radiobiology – UMR 7357 – ICube – Strauss Institute

❖ Team Metabolomics - UMR7357 – ICube - Strauss Institute

❖ Team Complex Systems and Translational Bioinformatics – UMR7357 - ICube

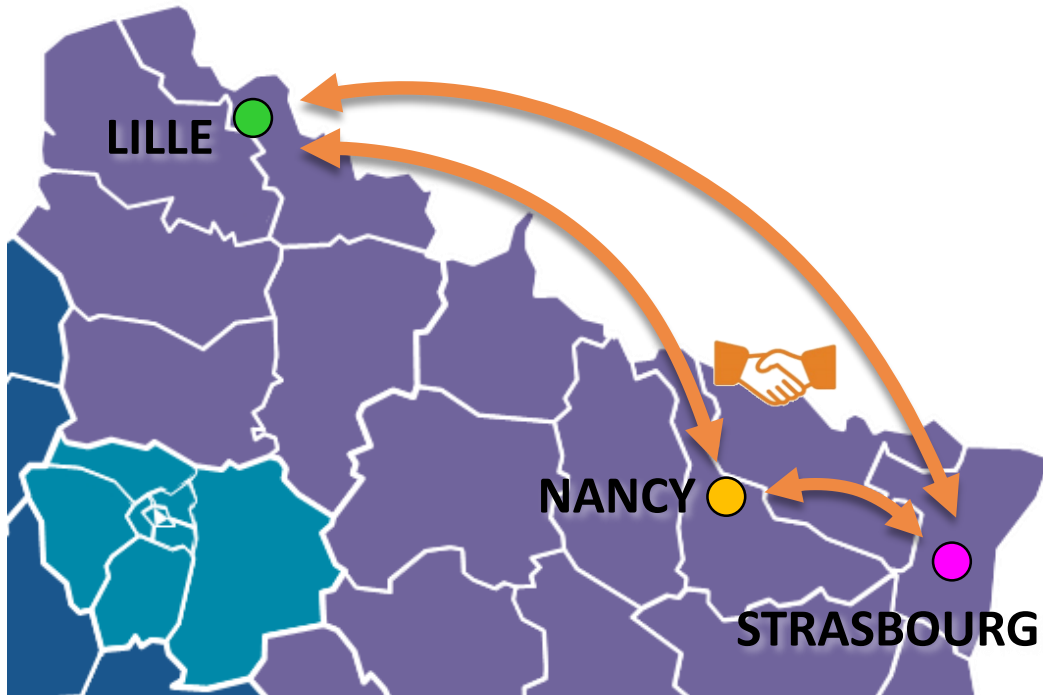
❖ Team Structure, dynamics and targeting of biomolecular machines - CNRS UPR 9002 – IBMC

❖ Team Immunology, Immunopathology and therapeutic chemistry – CNRS UPR3572 I2CT - IBMC



# Shared infrastructures

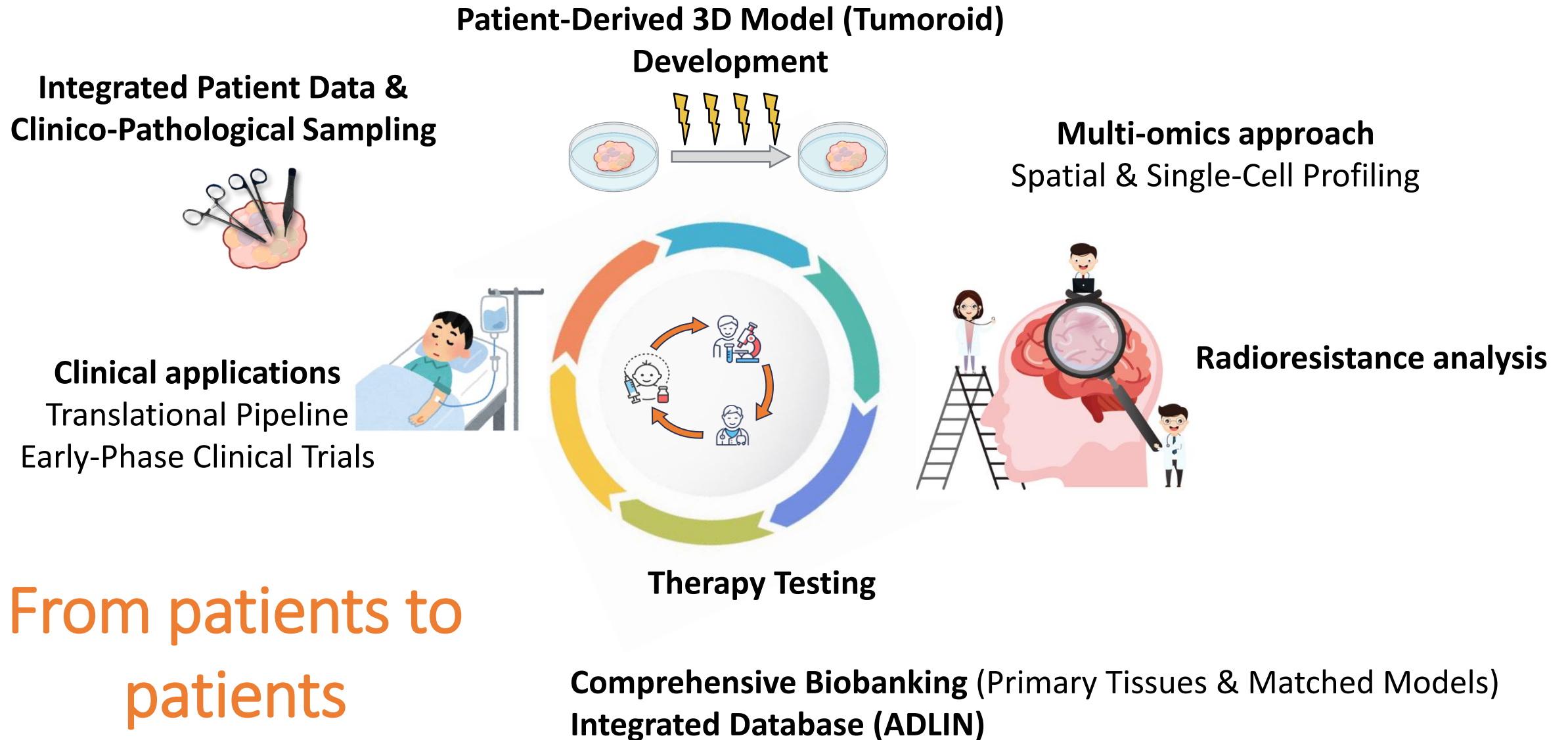
## Platforms:



- ① OrgaRES - organoids
- ② Platform for model irradiation in Strauss Institute
- ③ OptiRAD platform - irradiation
- ④ RISEst - Imaging
- ⑤ BICel platform - Imaging
- ⑥ GenomEast - molecular analyses (RNAseq and spatial RNAseq, epigenetics)
- ⑦ OrganOmics - organoids/molecular analyses (metabolomics and proteomics)
- ⑧ BIGEst - ICube platform - Bioinformatics and AI (artificial intelligence)
- ⑨ PHENOMIN-ICS - animal models

- ● ● **Biobanks** : structuration
- ● ● **Molecular departments**
- ● ● **Clinical research facilities**
- ● ● **Clinical departments**

# Workflow

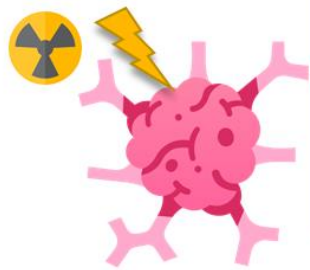




N. Entz-Werlé



S. Meignan



**WP1** : Identification of intrinsic and extrinsic alterations characterizing RR brain tumor (BT) cells.



C. Bund



M. Salzet



S. Martin



A. Furlan

**WP2** : Validation of the drivers involved in intrinsic and extrinsic resistance: from *in silico* to *in vitro* cross validation.



A. Simonetti



P. Chastagner

**WP3** : Therapeutic approaches targeting RR in *ex vivo* and *in vivo* BT models.



C. Pochon

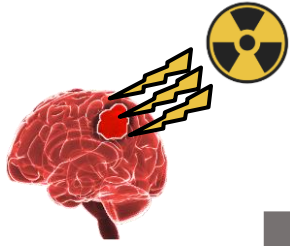


F. Sevrin

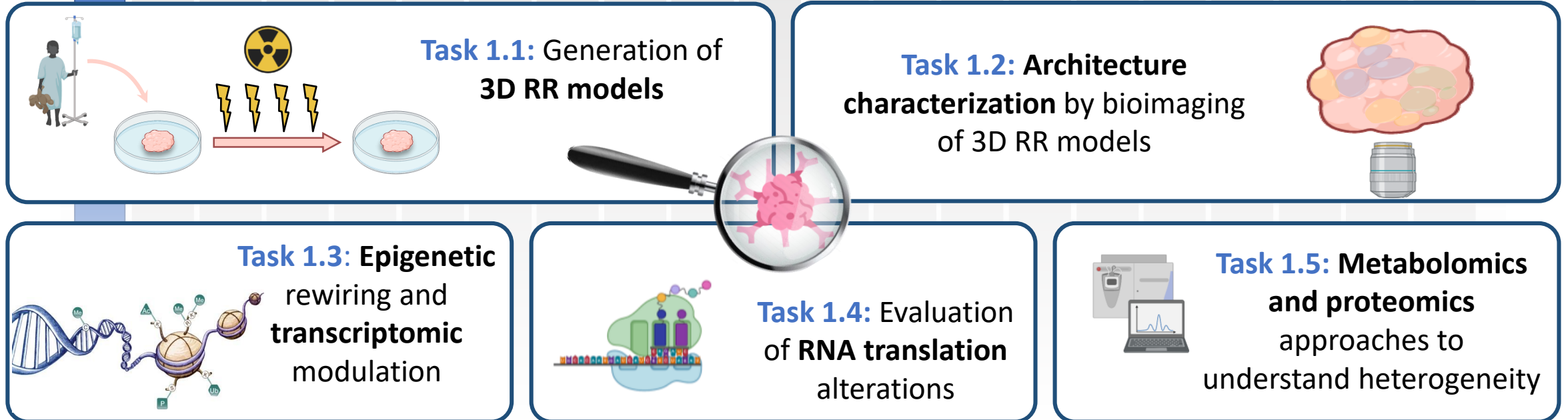
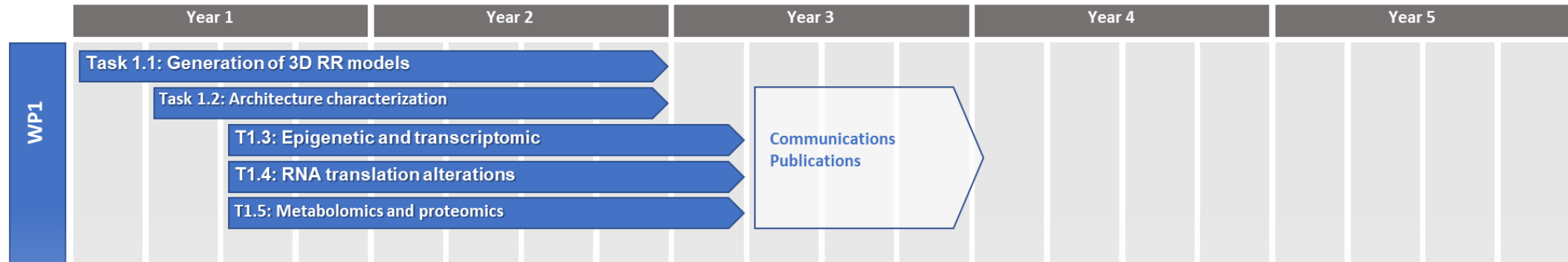
**WP4** : A patient operated WP: from biology to patient translation.



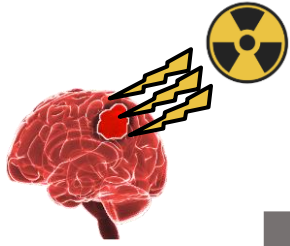
# WP1 Identification of intrinsic and extrinsic alterations characterizing RR brain tumor (BT) cells.



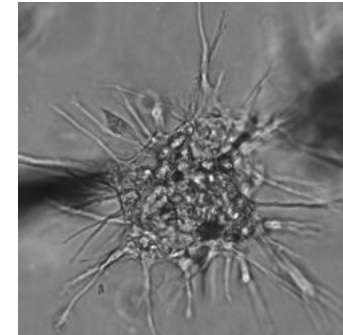
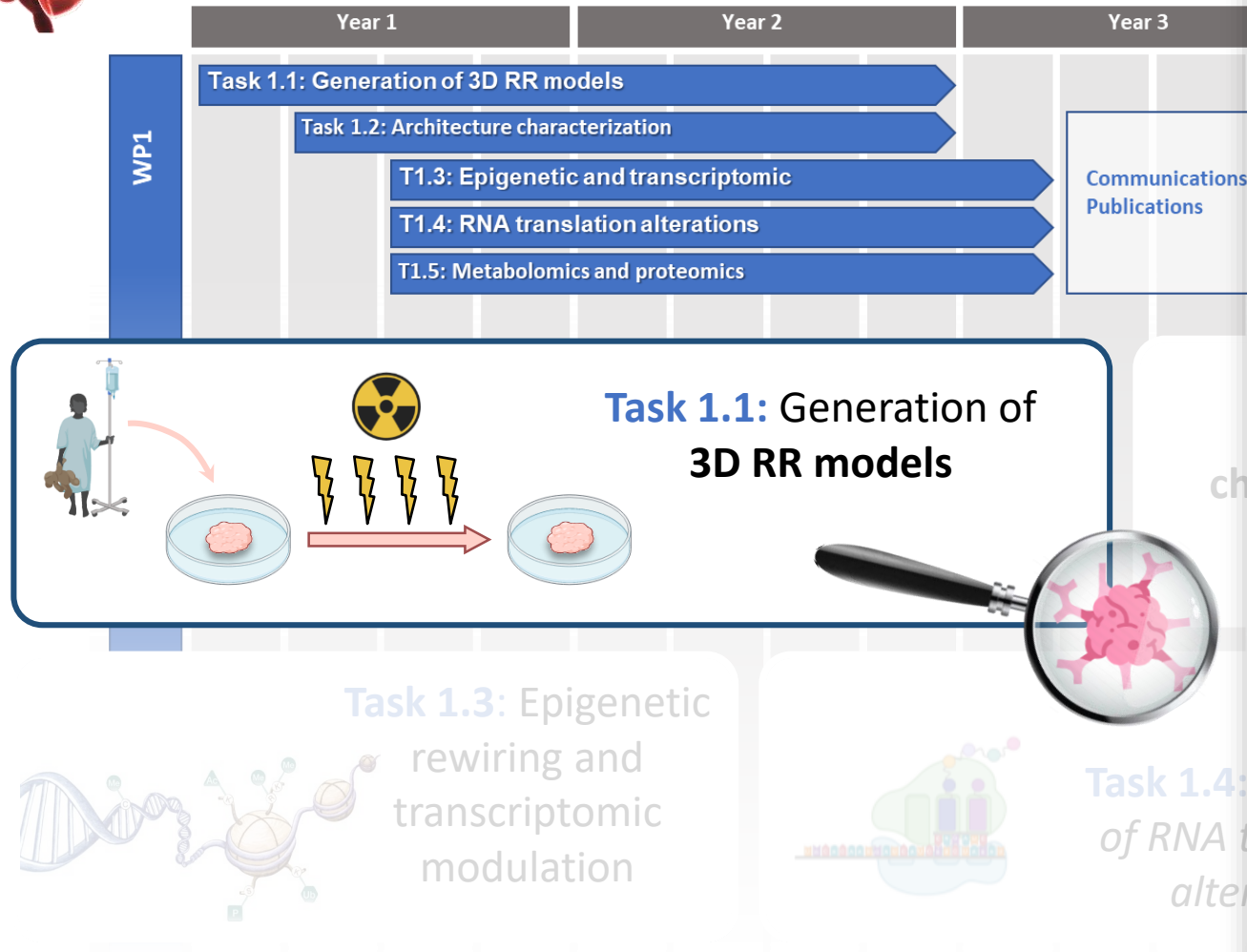
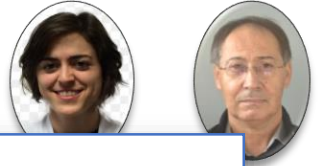
Leaders: **Caroline Bund (Strasbourg)/Michel Salzet (Lille)**



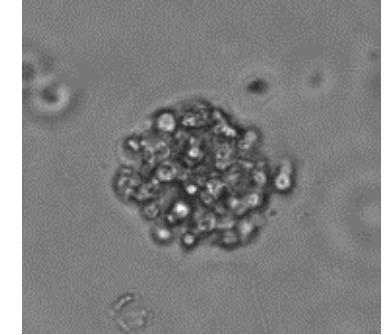
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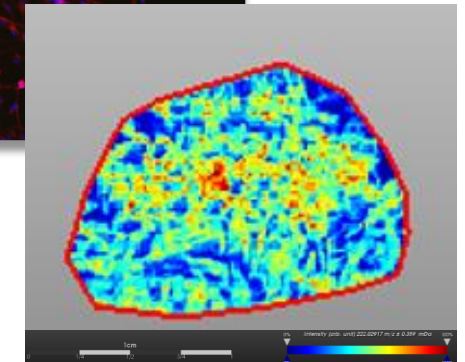
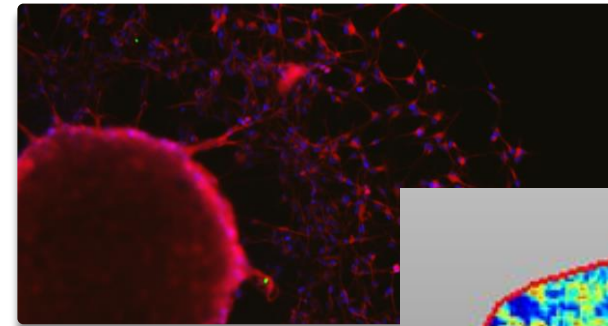
Leaders: **Caroline Bund (Strasbourg)/Michel Salzet (Lille)**



ependymoma organoid

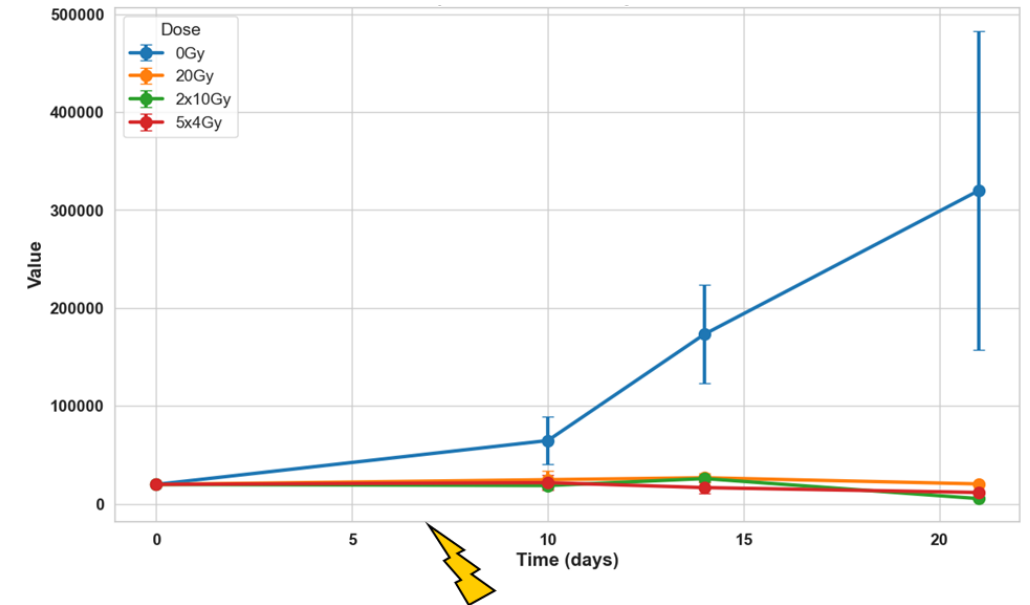
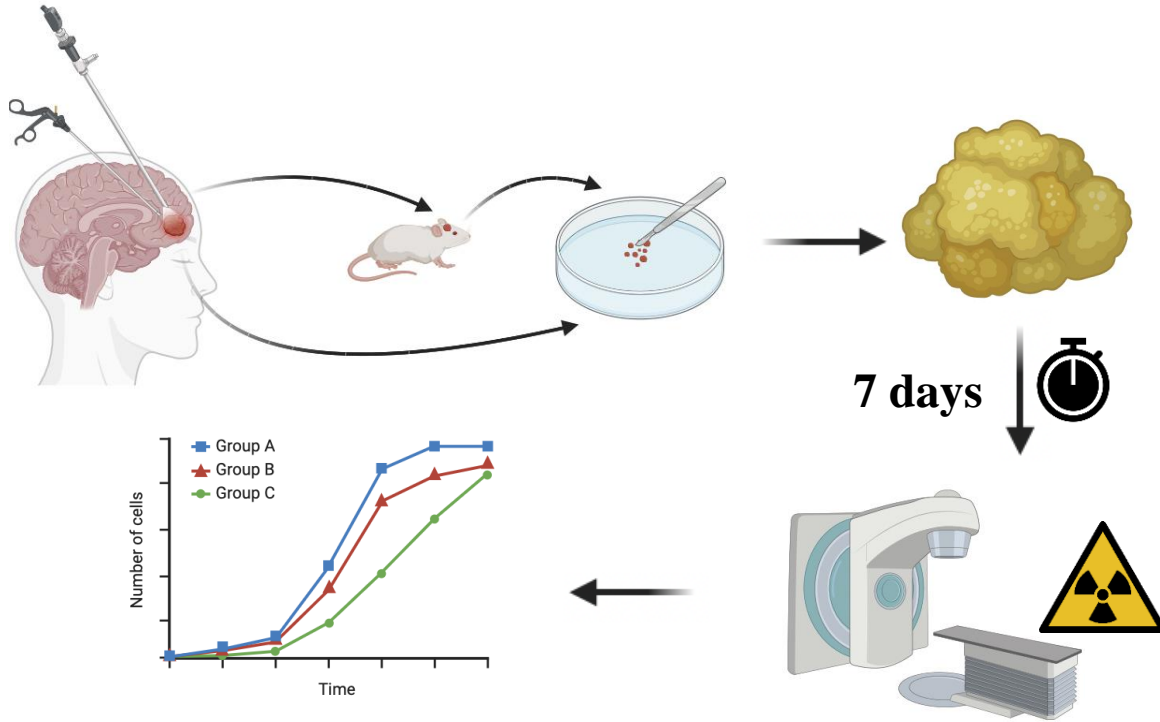


high-grade glioma organoid





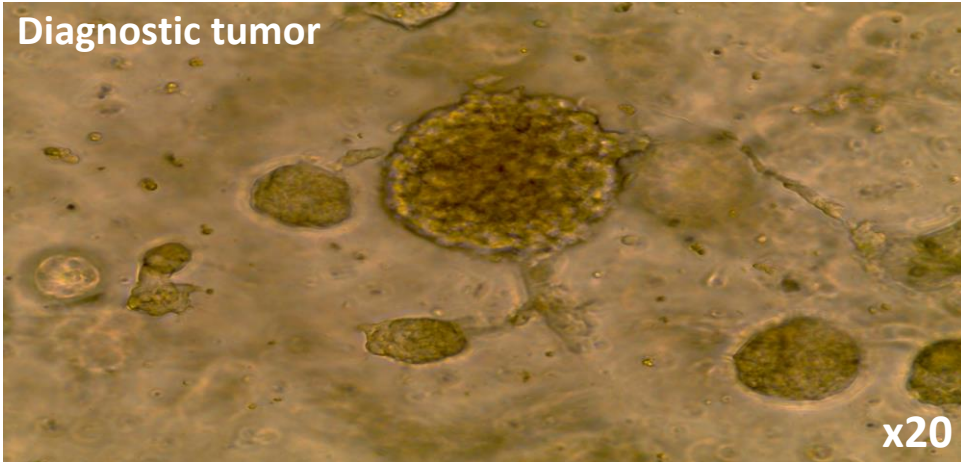
# First characterization of tumoroids models



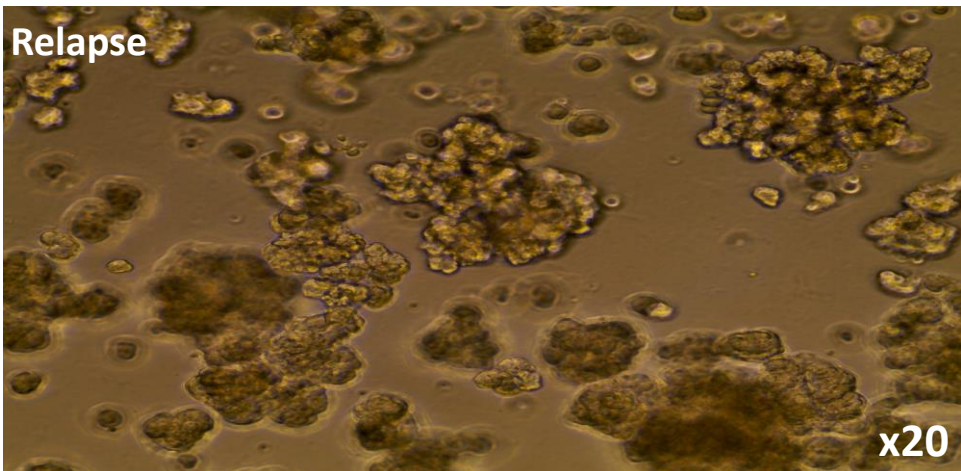
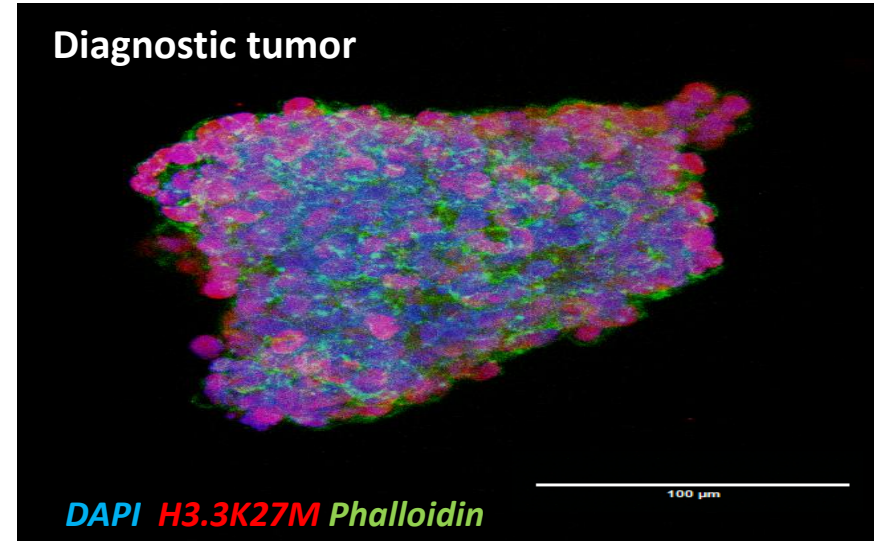


# First characterization of tumoroids models

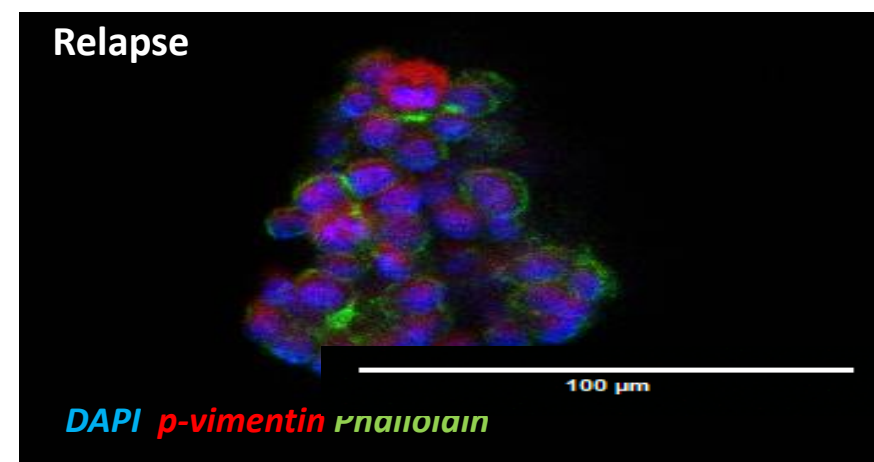
**DMG**



**DMG**

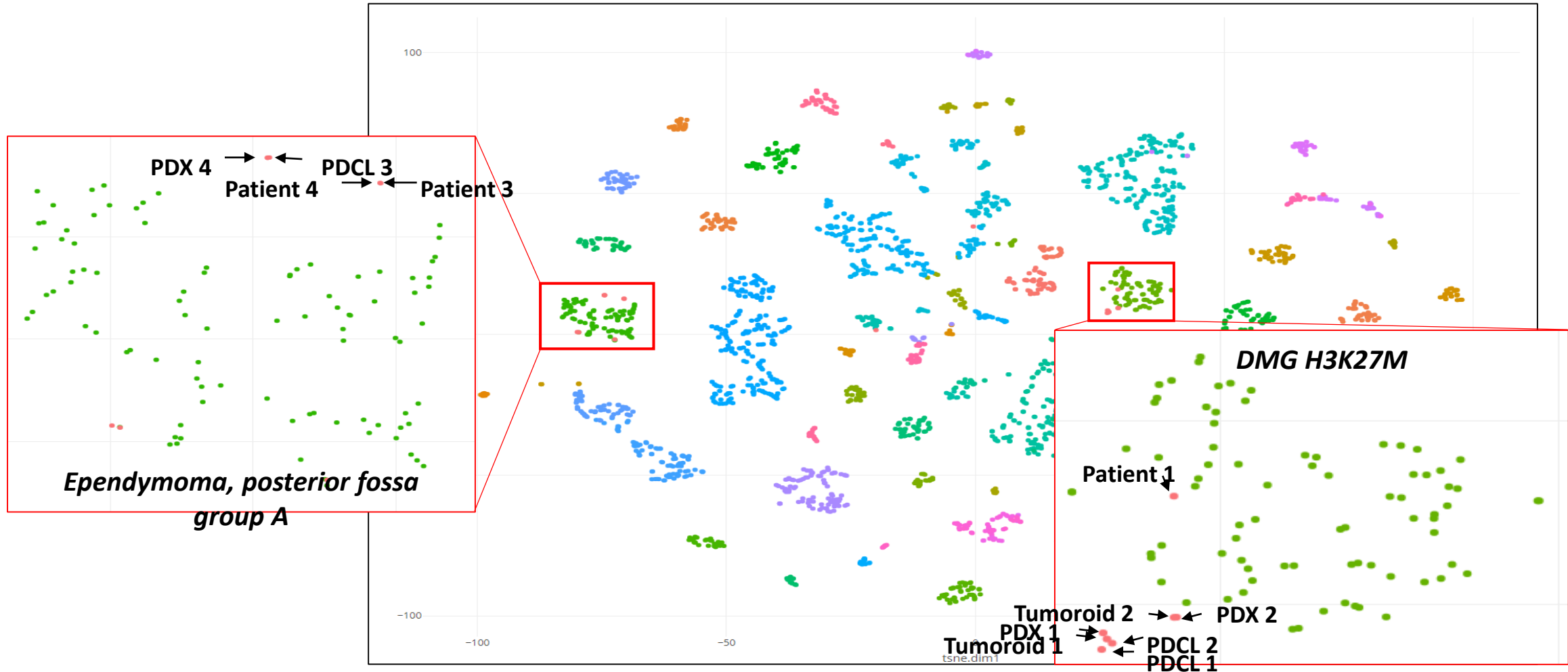


**Relapse**

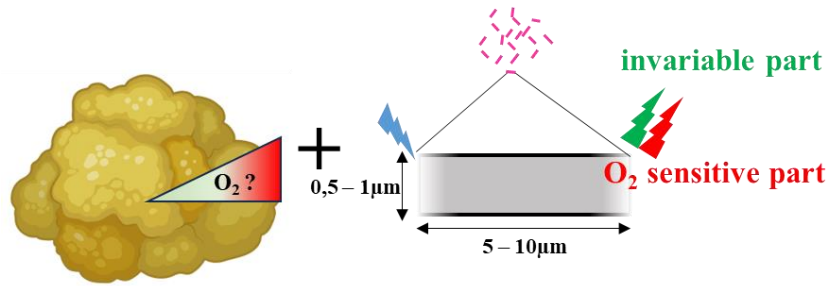


# First characterization of tumoroids models

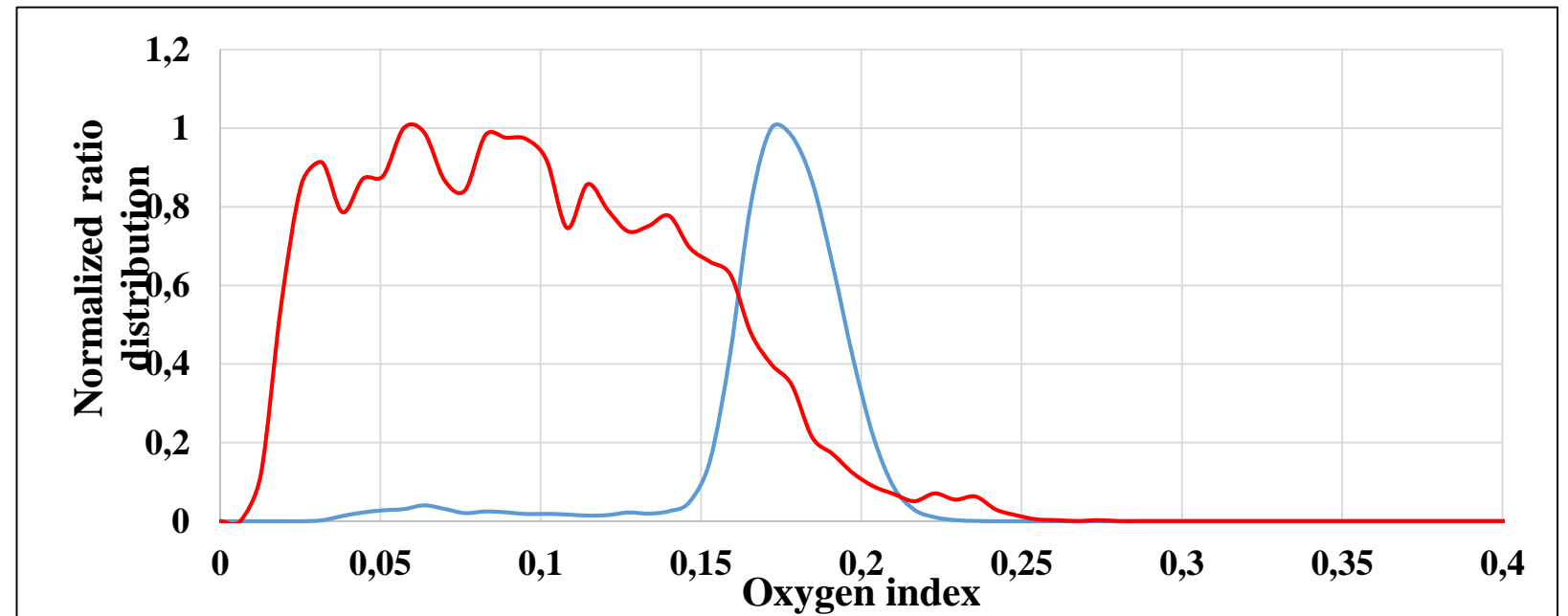
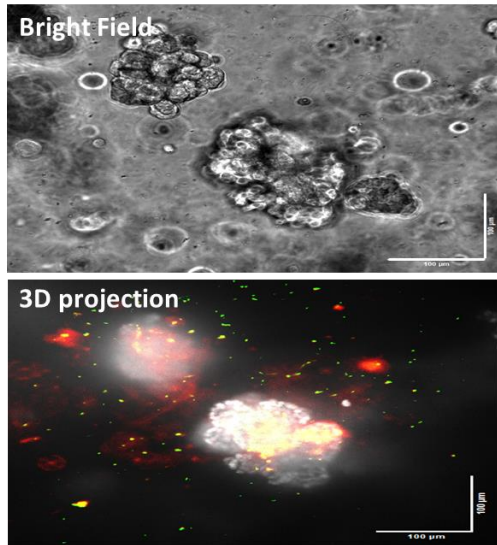
methylation analyses with methylEPIC 935k beadchip (Illumina)



# First characterization of tumoroids models



## Oxygen-sensitive nanorods

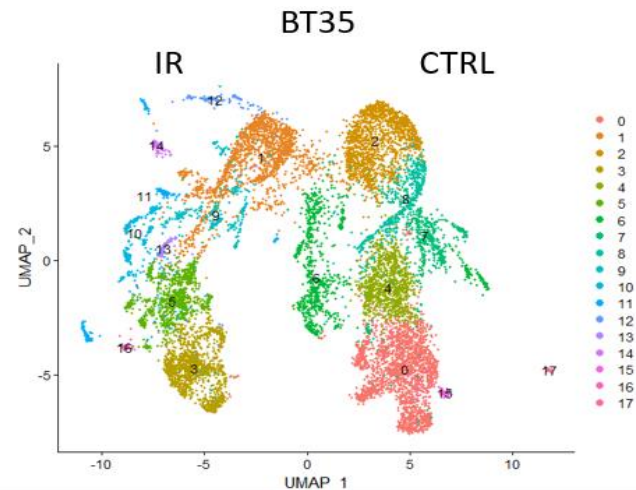


— Inside tumoroid  
— Matrix environment

# Characterization of RR models

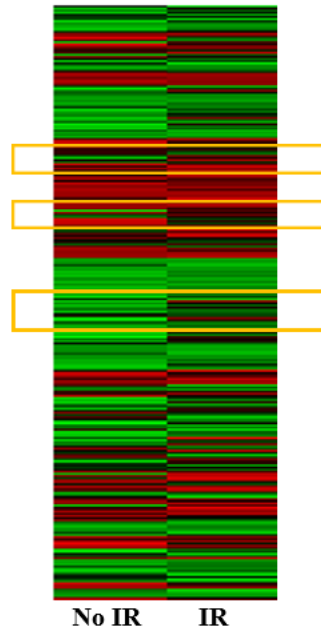
## Pre- vs. Post-irradiation results (5 x 2 Gy Stupp protocol)

sc transcriptomic

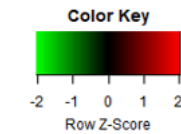
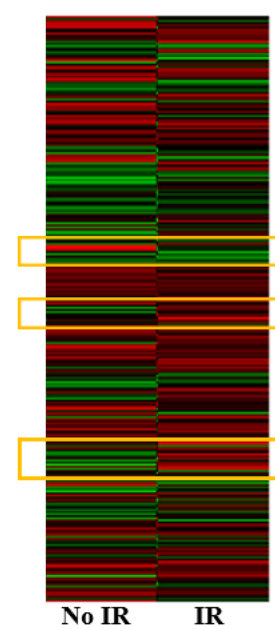


proteomic

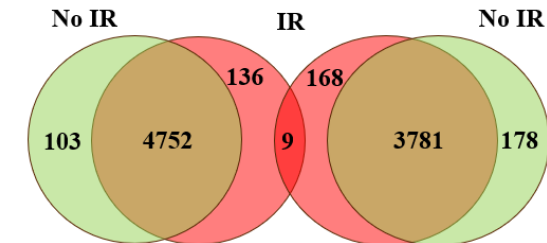
DMG diagnostic tumor



DMG relapse tumor



DMG diagnostic tumor

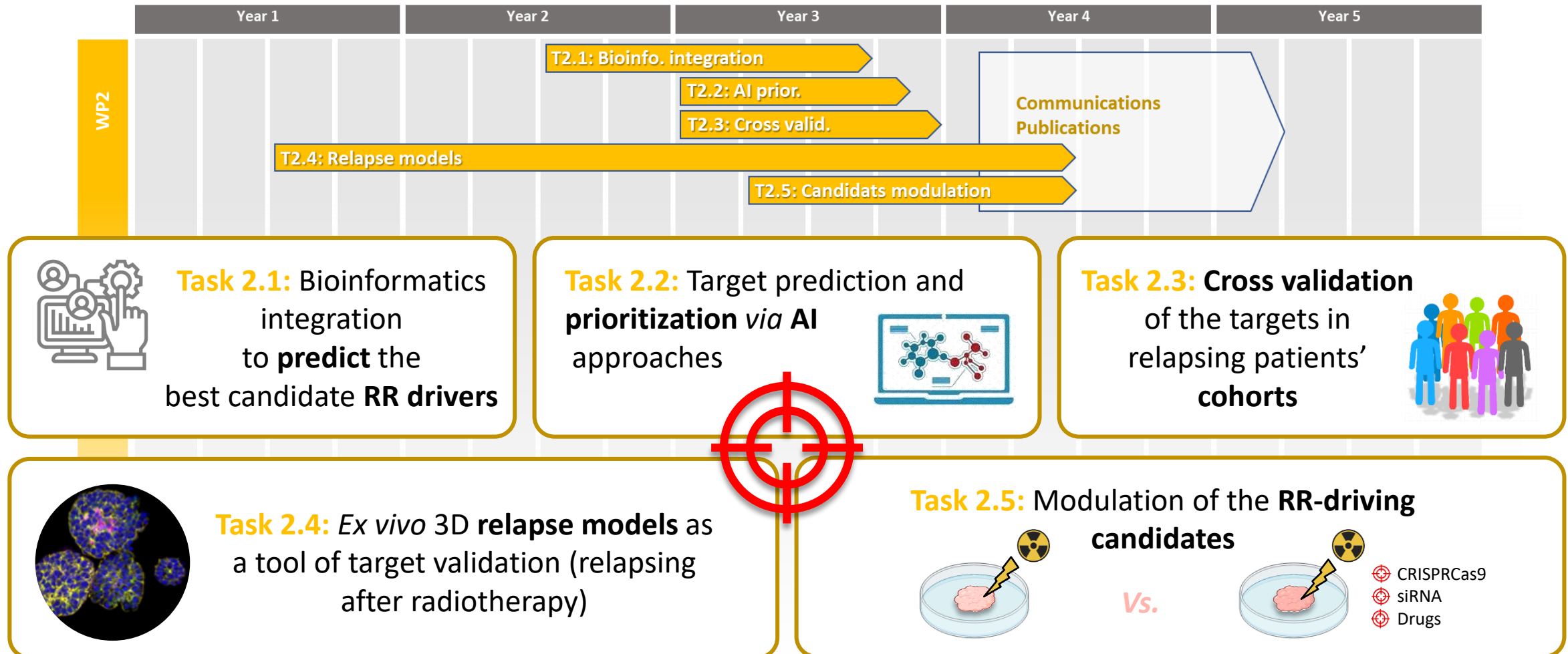


DMG relapse tumor

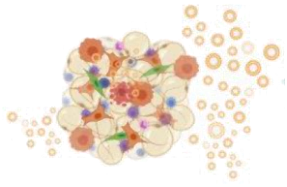
# WP2 Validation of the drivers involved in intrinsic and extrinsic resistance from *in silico* to *in vitro* cross validation.



Leaders: Sophie Martin (Strasbourg) / Alessandro Furlan (Lille)

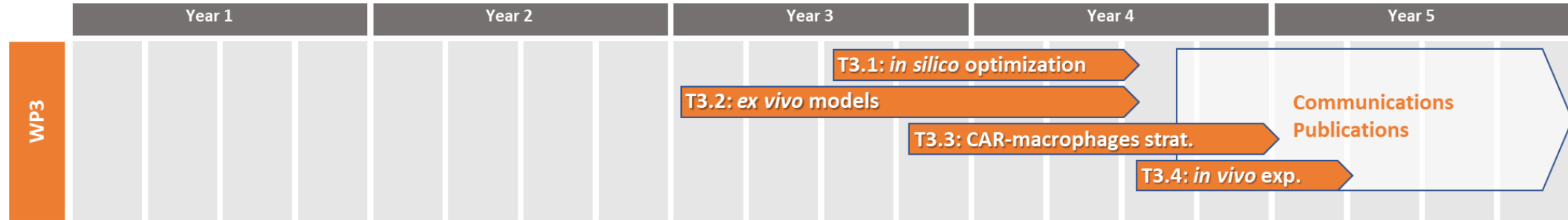




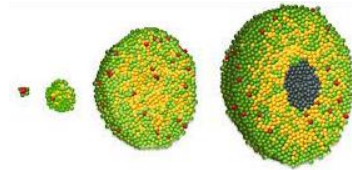


# WP3 Therapeutic approaches targeting RR in *ex vivo* and *in vivo* BT models

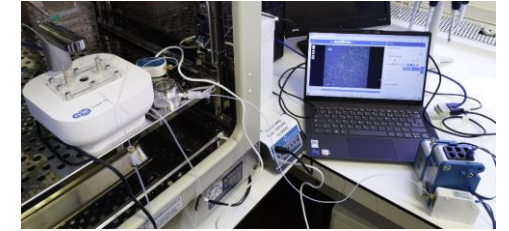
Leaders: Angelita Simonetti (Strasbourg)/Pascal Chastagner (Nancy)



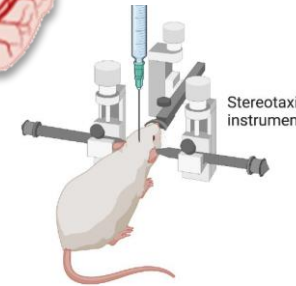
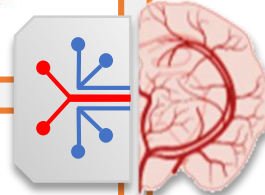
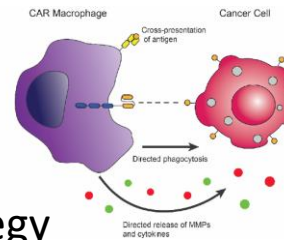
**Task 3.1:** *in silico* optimization of therapies used to target RR and their validation in 3D models



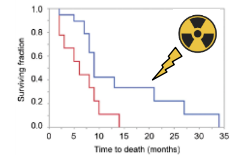
**Task 3.2:** Complexification of *ex vivo* validation models



**Task 3.3:** Understanding the macrophagic environment and exploiting CAR-macrophages strategy



**Task 3.4:** *in vivo* models to decipher radiopotential

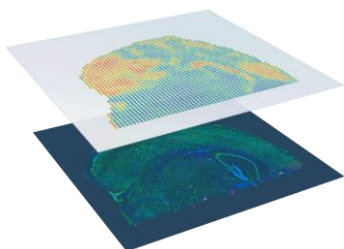
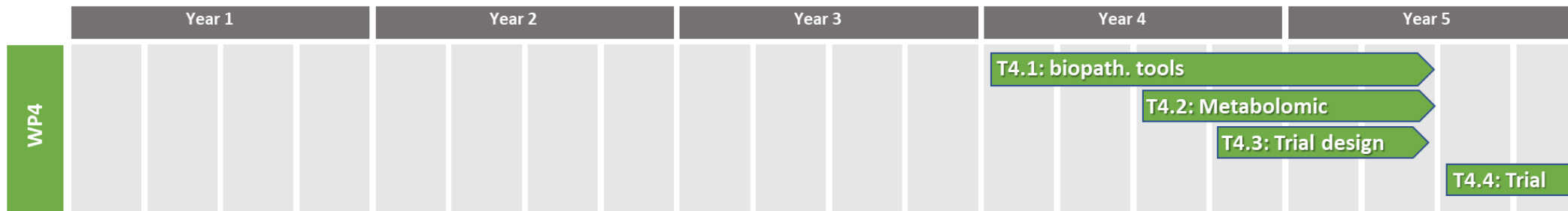




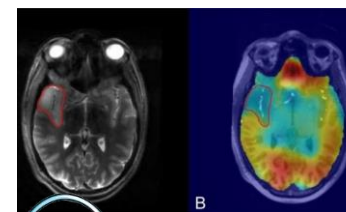


# WP4 A patient centered WP: from biology to patient translation

Leaders: Cécile Pochon (Nancy) and François Sevrin (Lille)



**Task 4.1:** Development of adequate tools to assess the predefined biomarkers and signatures in a biopathology approach



**Task 4.2:** Development of metabolomic or macrophagic biomarkers using metabolomic imaging



**Task 4.3:** Development of clinical trial designs serving our top drug(s)/radiotherapy combinations



**Task 4.4:** Trials development and options in direct link with investigation clinic structuration and platform for patient transfers

# EN HOPE SMART4CBT

