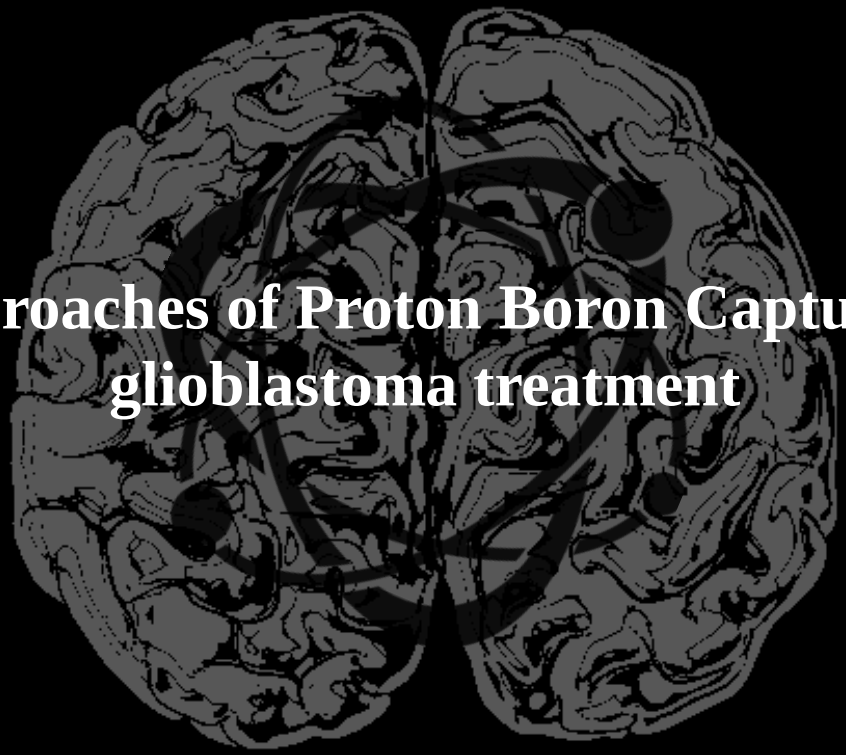
2nd International Workshop on Proton-Boron Fusion



Preclinical approaches of Proton Boron Capture Therapy for glioblastoma treatment

Dr. Filippo Torrisi
Ph.D. Biotechnology, University of Catania
Post-Doctoral Research Fellow - Fondazione Umberto Veronesi

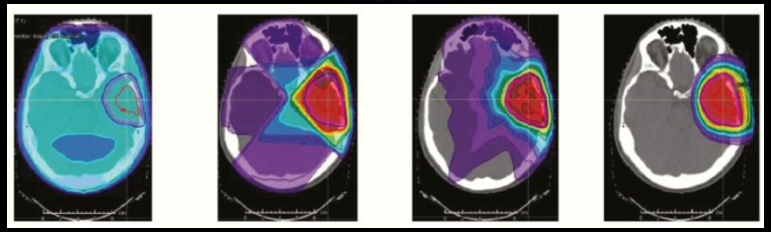
Radiation approaches in neuro-oncology

Advances in technological systems

Image-guided radiation therapy

Stereotactic radiosurgery

Intensity-modulated radiation therapy



2DRT 3DRT IMRT IMPT

radiation

MDPI

Systematic Review

Proton Therapy and Gliomas: A Systematic Review

Isabelle Chambrelant [1], Jordan Eber [1], Delphine Antoni [1], Hélène Burckel [2], Georges Noël [1,2,*] and Romane Auvergne [2]

[1] Paul Strauss Comprehensive Cancer Center, Institut de Cancérologie Strasbourg Europe (ICANS), Department of Radiation Oncology, Unicancer, 67200 Strasbourg, France; i.chambrelant@icans.eu (I.C.); j.eber@icans.eu (J.E.); d.antoni@icans.eu (D.A.)

[2] Paul Strauss Comprehensive Cancer Center, Radiobiology Laboratory, Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg University, UNICANCER, 67000 Strasbourg, France; h.burckel@icans.eu (H.B.); r.auvergne@icans.eu (R.A.)

* Correspondence: g.noel@icans.eu

Abstract: Background: Gliomas are primary cerebral tumors. Radiation therapy plays a key role in their treatment but with a risk of toxicity associated with the dose to and volume of normal tissue that is irradiated. With its precision properties allowing for the increased sparing of healthy tissue, proton therapy could be an interesting option for this pathology. Methods: Two reviewers performed a systematic review of original papers published between 2010 and July 2021 following PRISMA guidelines. We analyzed disease outcomes, toxicity outcomes, or dosimetry data in four separate groups: children/adults and individuals with low-/high-grade gliomas. Results: Among 15 studies, 11 concerned clinical and toxicity outcomes, and 4 reported dosimetry data. Proton therapy showed similar disease outcomes with greater tolerance than conventional radiation therapy, partly due to the better dosimetry plans. Conclusions: This review suggests that proton therapy is a promising technique for glioma treatment. However, studies with a high level of evidence are still needed to validate this finding.

Keywords: proton therapy; gliomas; brain tumors; outcomes; systematic review

check for updates

Citation: Chambrelant, I.; Eber, J.; Antoni, D.; Burckel, H.; Noël, G.; Auvergne, R. Proton Therapy and [illegible] Review. *Radiation* **2021**, *1*, 218–233. https://[illegible]/radiation1030019

Deepak K. et al., 2009.
M. Baumann et al., 2016

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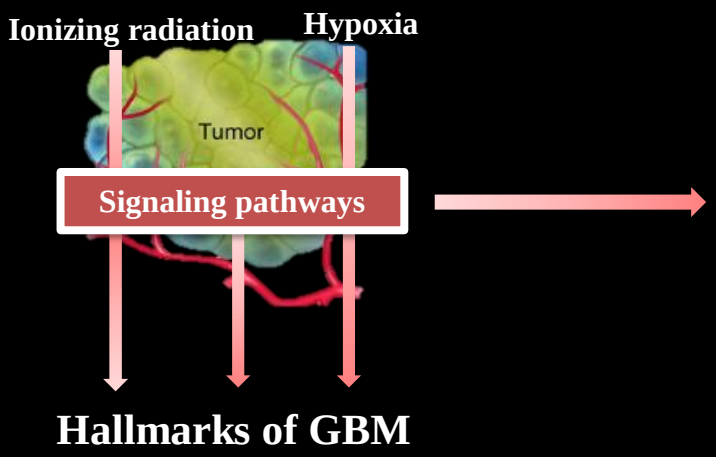
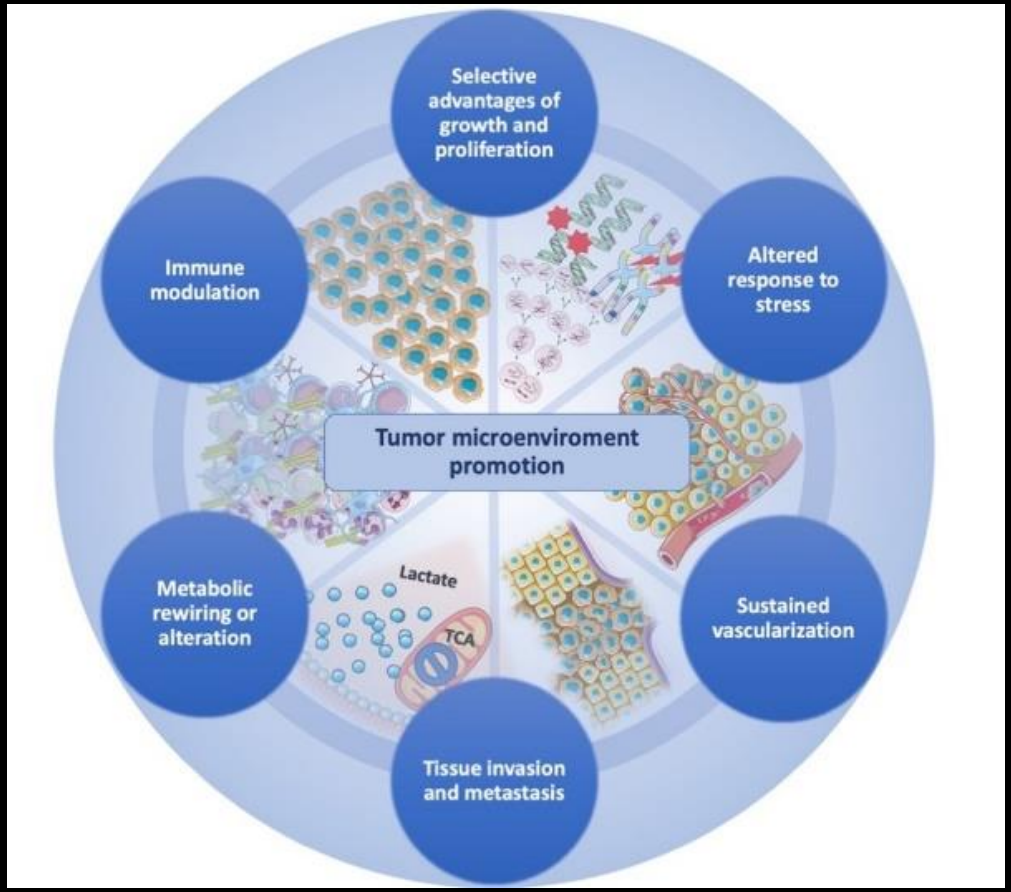
Glioblastoma aggressiveness and mortality

- **Delayed diagnosis and treatment**
- **High propensity for tumor recurrence**
- **12-18 months as average survival time (Stupp's regimen, since 2005)**





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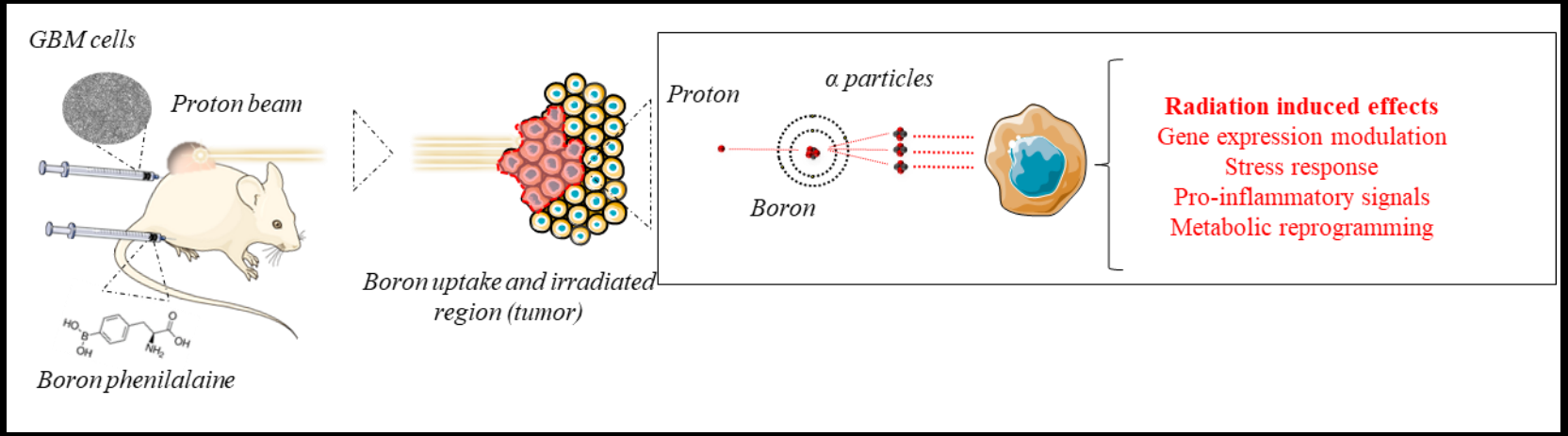
AIM

Proton Boron Capture Therapy for GBM treatment: first preclinical study



- **Multimodal imaging techniques**

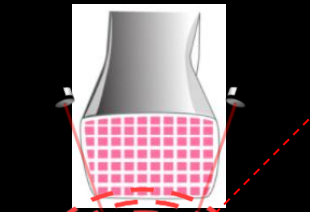
Ultrasound and photoacoustic imaging

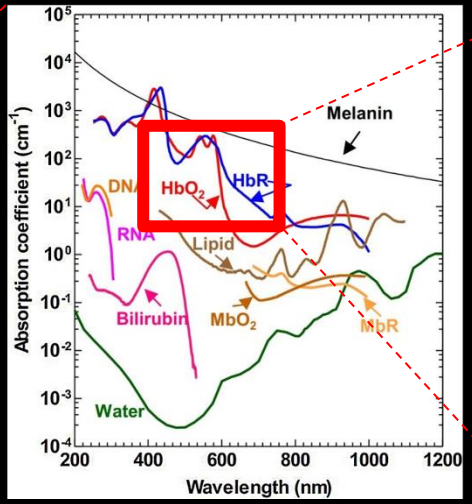
Micro positron emission tomography assisted scanning

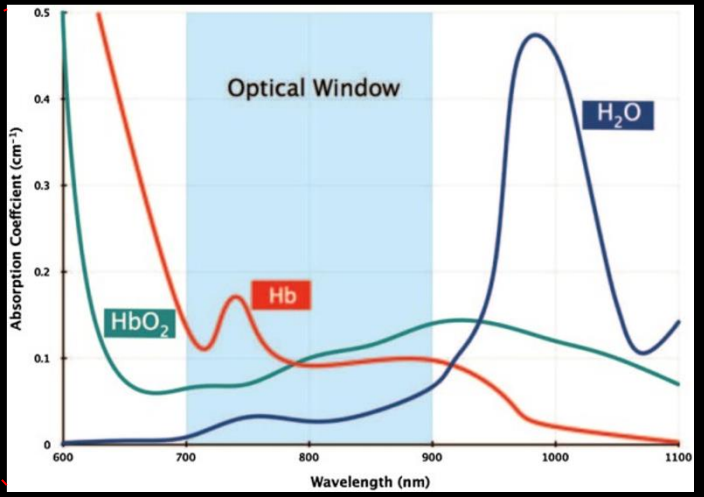
- **Pathological analyses associated to RNA-sequencing**

GBM preclinical model assessment by ultrasound and photoacoustic system

Transducer for US detection







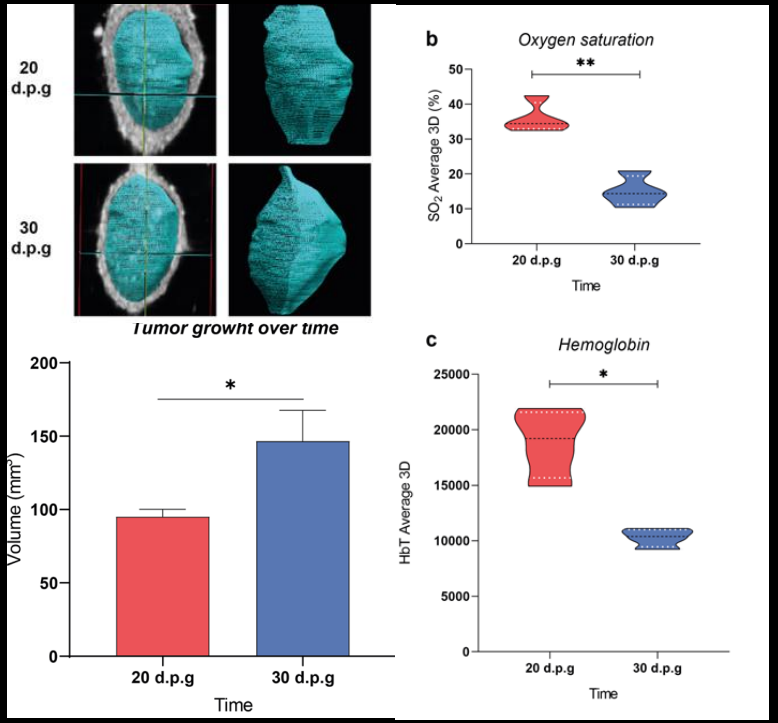
Oxygen saturation calculation

$$sO_2 = \frac{[HbO_2]}{[Hb] + [HbO_2]}$$

GBM preclinical model assessment by ultrasound and photoacoustic system

Tumor growth increased significantly comparing GBM xenografts model 20- and 30-days post graft (d.p.g.).

Hypoxia were found significantly increased over time



Cammarata, Torrisi, Vicario et al. submitted

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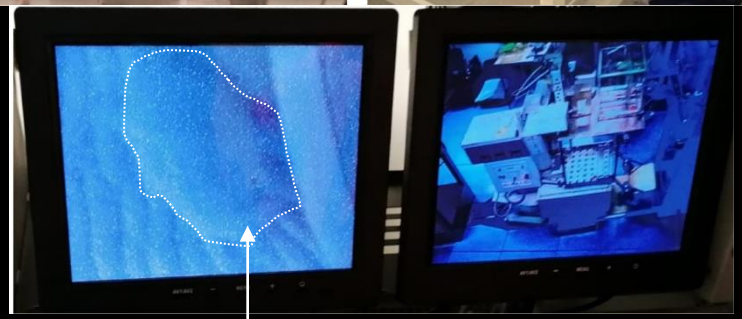
Proton beam irradiation on heterotopic GBM mouse model at INFN-LNS CATANA facility



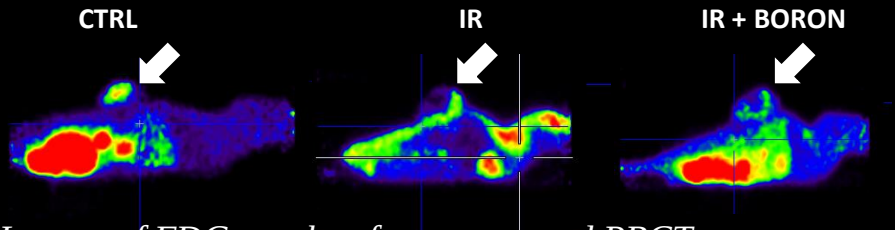
- Experimental depth dose distribution of protons for the SOBP creation.
- Light field allows the correct position of collimator at the specific site to be irradiated.
- A video camera allows the remote viewing to ensure that no movement occurs during irradiation.

Cammarata, Torrisi, Vicario et al. submitted

PBCT reduces total lesion glycolysis *in vivo*

ΔTLG indicate a reduction of metabolic activity with FDG decrease uptake in PBCT treated mice in comparison with mock proton and proton groups

TLG provides a simultaneous estimation of volumetric (MTV) and metabolic (SUV) information

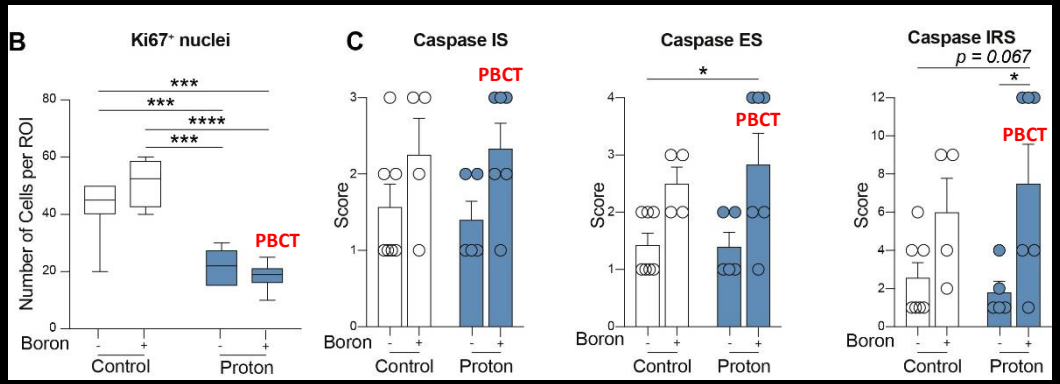


Images of FDG uptake after proton and PBCT treatment

$$\Delta TLG = \frac{TLG_{post} - TLG_{pre}}{TLG_{pre}} \times 100$$

Cammarata, Torrisi, Vicario et al. submitted

PBCT increases cell death

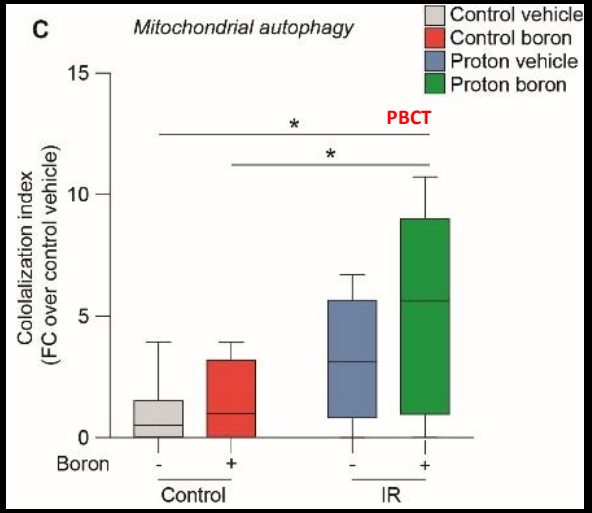


- No significative changes were reported between PBCT and proton groups considering Ki67 positive cells.
- Caspase intensity and immunopositive cells were found significant increased in PBCT groups

Cammarata, Torrisi, Vicario et al. submitted

PBCT increases mitophagy

- Interestingly significantly high levels of the structural protein of autophagosomal membranes (LC3B) in PBCT vs proton irradiated GBM were observed.
- Co-localization of autophagic signals with mitochondrial staining revealed that PCBT determined also a mitophagy response.



Cammarata, Torrisi, Vicario et al. submitted

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Differential gene expression induced by PBCT

- Functional enrichments analysis of differentially expressed genes with Venn diagrams revealed common genes able to regulate cellular processes.

- Specific biological pathways analysis reported down-regulation of cells survival, growth, and viability and an up-regulation of cell death

Upregulation in PBCT vs Control

- Apoptosis
- Necrosis

Upregulation in PBCT vs Control

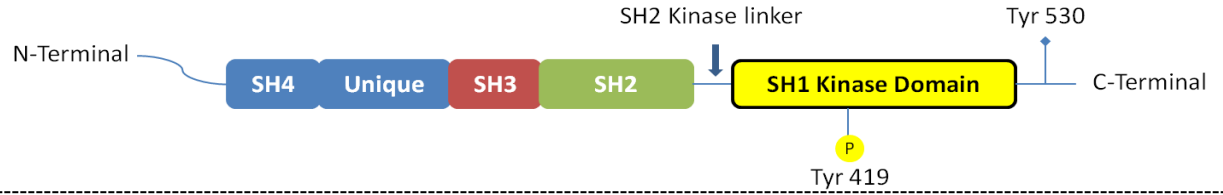
- Cell survival
- Cell viability

Cammarata, Torrisi, Vicario et al. submitted

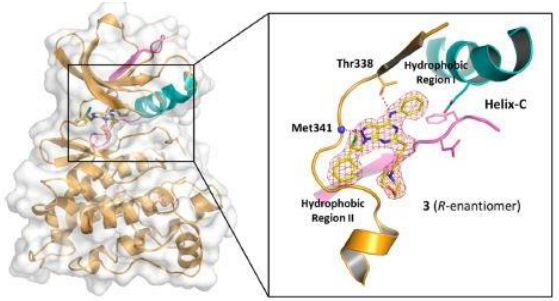
Summary of results

- PBCT increases efficacy of proton therapy in mouse model of GBM.
- Increased autophagy and mitophagy was observed in PBCT.
- High levels of autophagy may represent self-protective mechanisms for GBM cells.
- Reduced mitochondrial fitness are potential mechanisms underlying PBCT-induced effects.

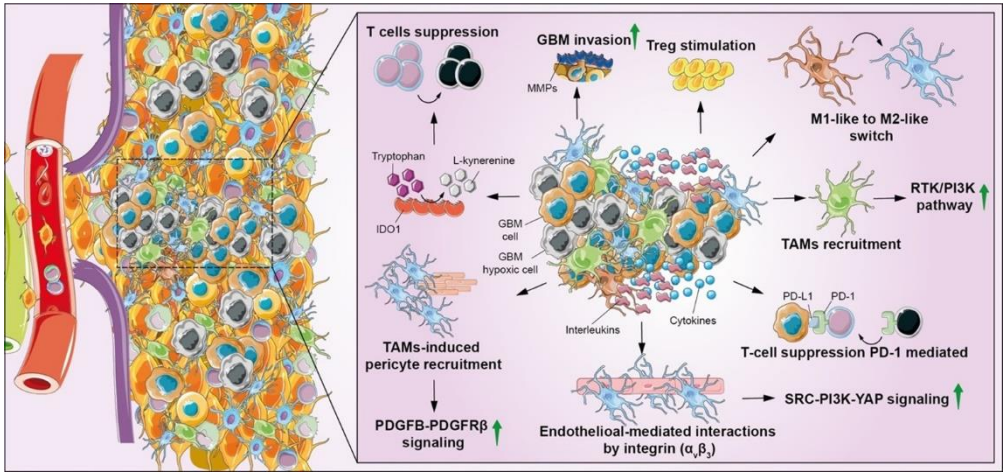
Perspectives
Molecularly targeted drugs and PBCT



Schematic representation of SRC structure.



Si306 + Boron



F. Torrisi et al., 2020
F. Torrisi et al., 2022

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