Projet “Tumeurs Cérébrales”
LAMC-INSERM U1029

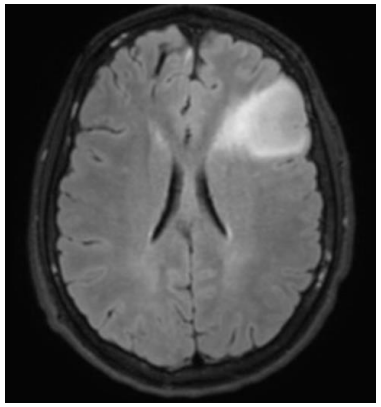
Prof Andreas Bikfalvi

Tumeurs du Cerveau

Tumeurs cérébrales primitives(TCP)
(Gliomes, Meningiomes, Meddulloblastomes etc)

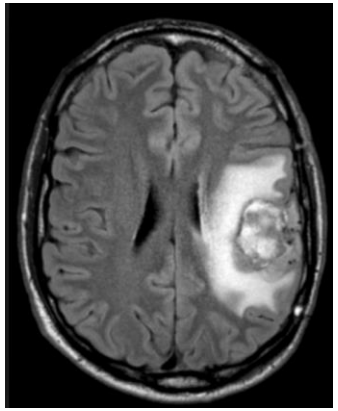
Gliomes

Gliomes de bas grade



15 -30 % des TCP
Population plus jeunes
Evolution plus lente
(> 6 ans)

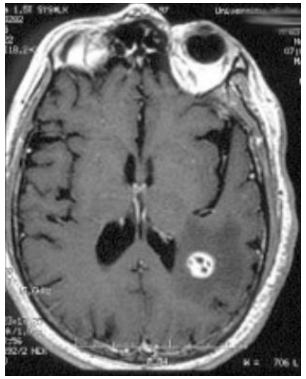
Gliomes de haut grade (Glioblastomes)



14,9 % des TCP, 55 % des Gliomes
Population plus âgée
Evolution rapide
(14,6 mois survie moyenne,
30 % à 2 ans)

Tumeurs cérébrales secondaires (TCS)

Métastases cérébrales de tumeurs solides d'autres organes (Cancer du sein et poumon, mélanome, lymphome etc.)



25-50 % des tumeurs du cerveau
24-45% de tous les patients avec cancer

Team « Tumeurs Cérébrales » U1029

Andreas Bikfalvi Pr
Clotilde Billottet (MCU)
Thomas Daubon (Post-doc)
Virginie Dinet (CR INSERM)
Céline Leon (IGE)
Nadège Pujol (Tech)
Students (3)
Post-docs (2)

1/ Projets fondamentaux et précliniques

2/ Projets translationnels

4/ Modèles disponibles

5/ Structuration future de la neuro-oncologie

I. Projets Fondamentaux

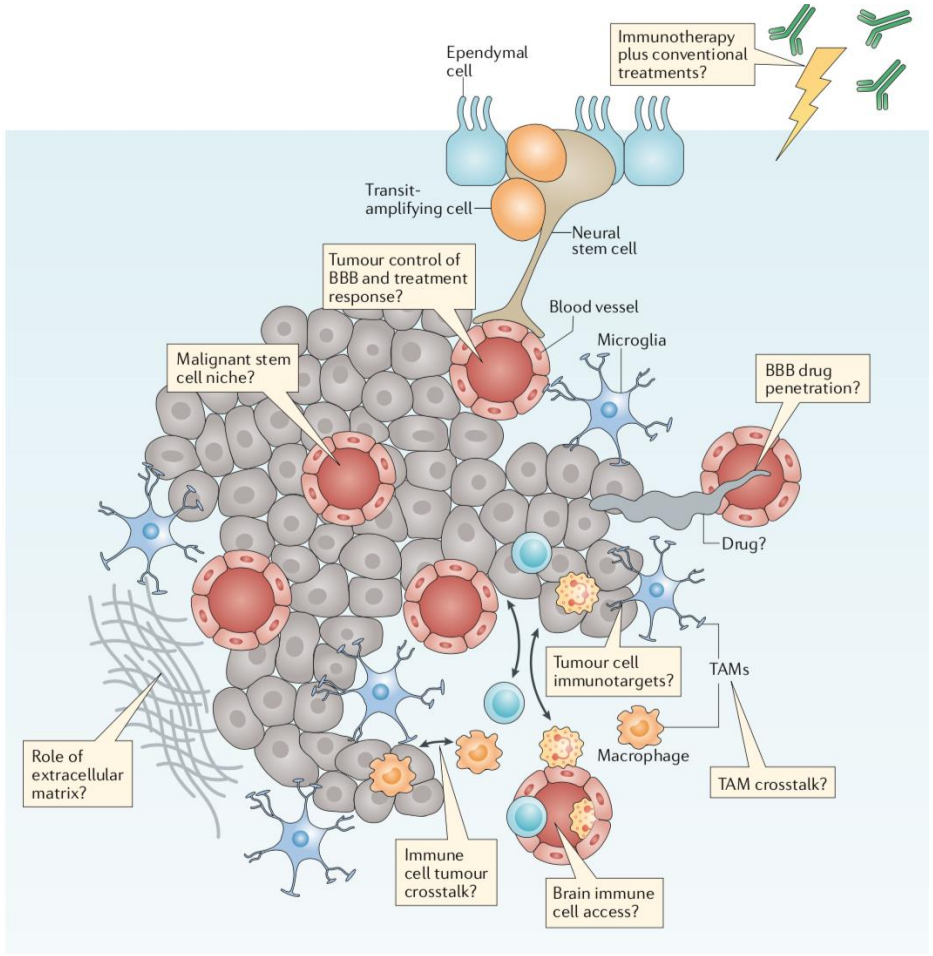


Fig. 4 | **The brain tumour microenvironment and treatment.** Brain tumours typically comprise a complex mixture of malignant cells and a great variety of nonmalignant cells. These include immune, vascular and nonmalignant brain cells,

- **- Chimiokines CXCR3-LRP1**

-> Mécanismes fins

->Validation dans une cohorte plus large de patients

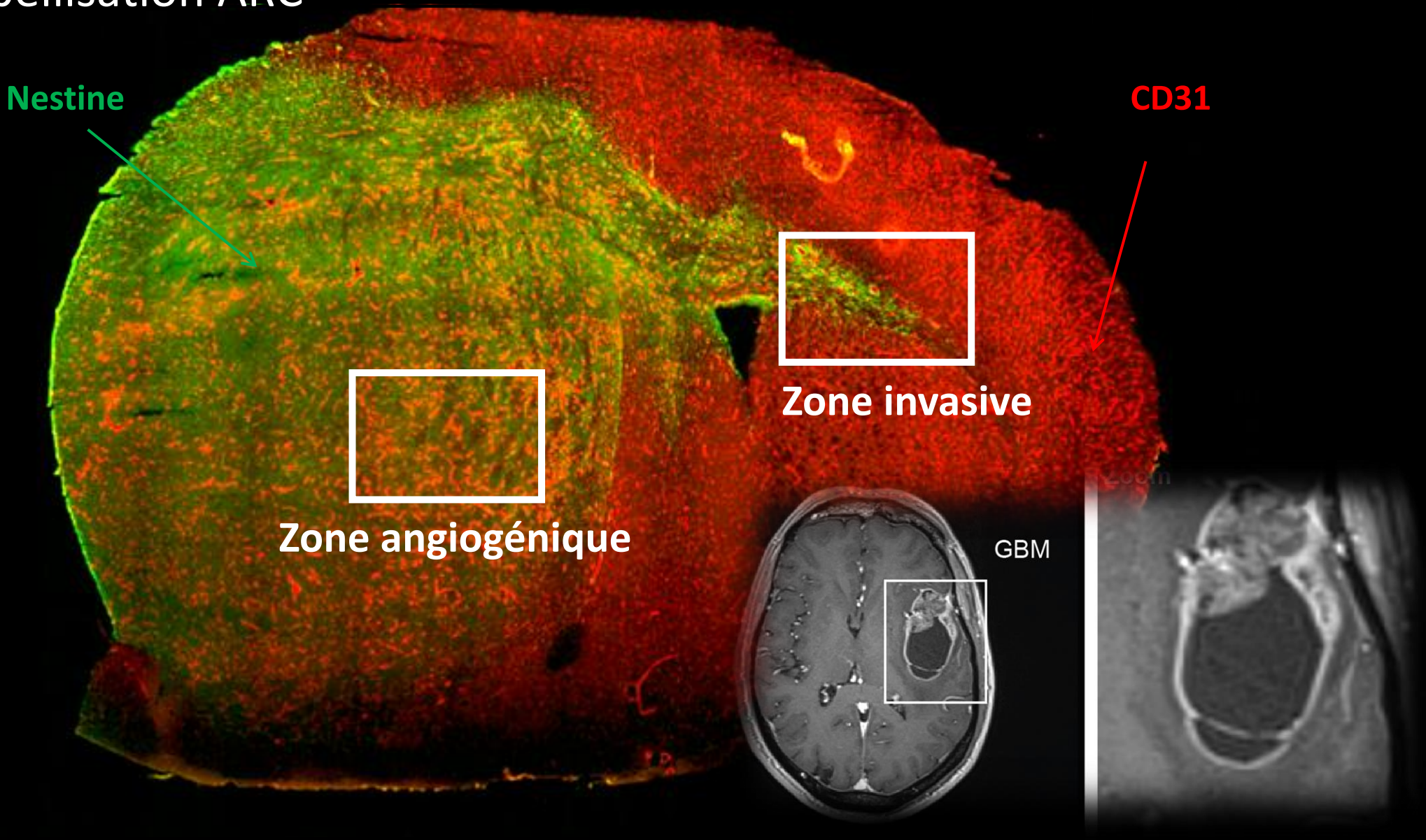
->Développement d'un inhibiteur spécifique/ non toxique/hydrophile de CXCR3

- **- Matrice et GBM**
- **- Génomique et protéomique de l'invasion tumorale**
- **- Phosphatases et molécules de guidage**
- **- Métabolisme et invasion**

Challenges to curing primary brain tumours.
Aldape et al Nat Rev Clin Oncol. 2019 Feb 7.
doi: 10.1038/s41571-019-0177-5

Glioblastome (GBM)

Labellisation ARC



Chimiokines et GBM

nature COMMUNICATIONS

Altmetric: 1 Citations: 1 More detail »

Article | OPEN

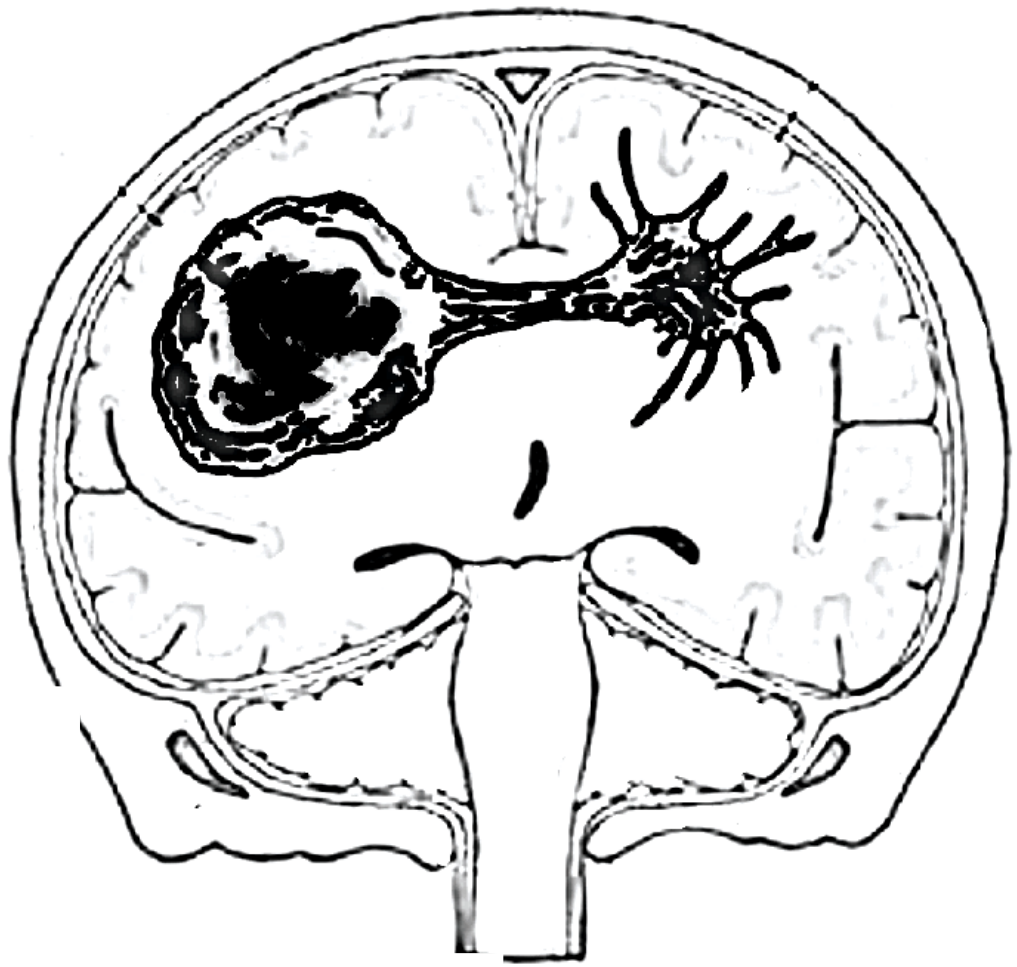
The role of CXCR3/LRP1 cross-talk in the invasion of primary brain tumors

Kevin Boyé, Nadège Pujol, Isabel D Alves, Ya-Ping Chen, Thomas Daubon, Yi-Zong Lee, Stephane Dedieu, Marion Constantin, Lorenzo Bello, Marco Rossi, Rolf Bjerkvig, Shih-Che Sue, Andreas Bikfalvi ✉ & Clotilde Billottet ✉

Nature Communications **8**,
Article number: 1571 (2017)
doi:10.1038/s41467-017-01686-y
Download Citation

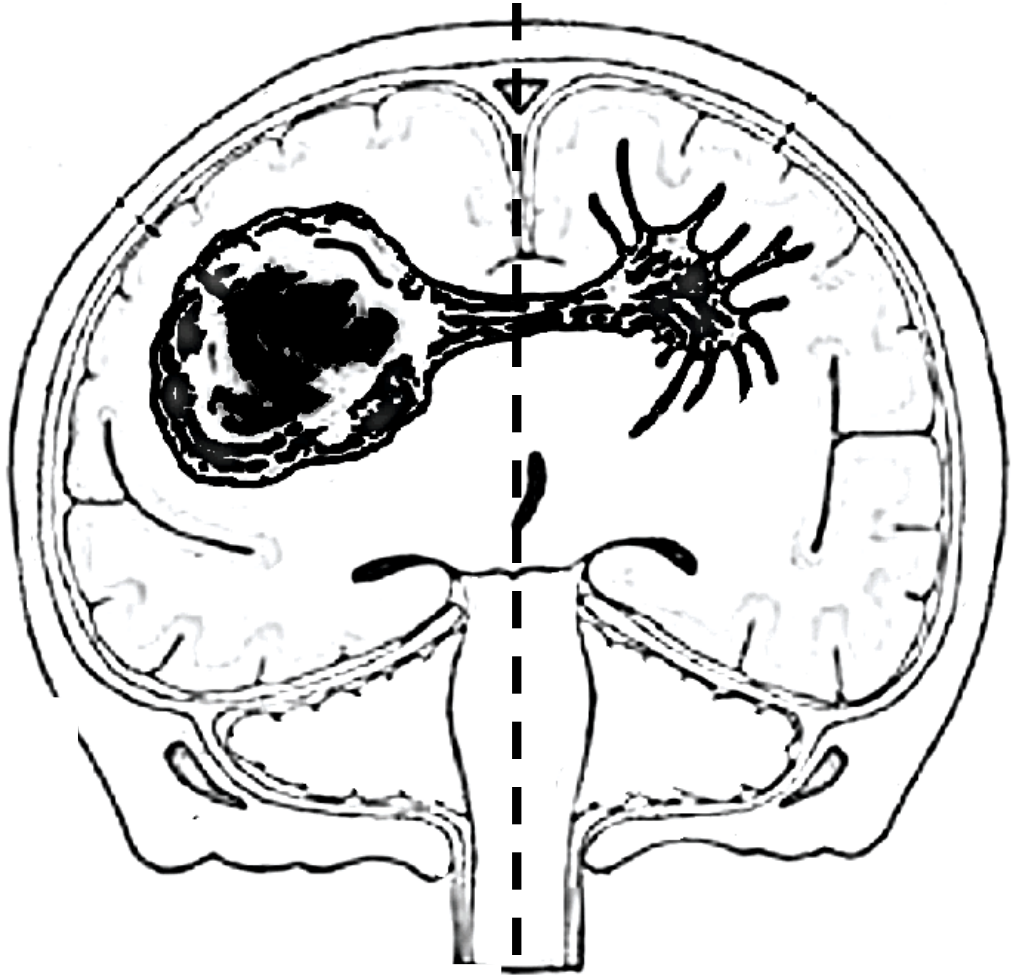
Cell signalling | CNS cancer | Oncology

Received: 01 January 2017
Accepted: 10 October 2017
Published online: 17 November 2017



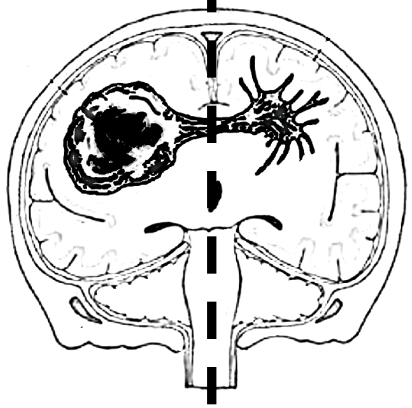
Angiogenic

Invasive



Angiogenic

Invasive



Extracellulaire

PS372424
CXCL10
CXCL4L1

SCH546738

Activation

LRP1

CXCR3-A

I
II
III
IV

αq/αi

β

γ

GDP

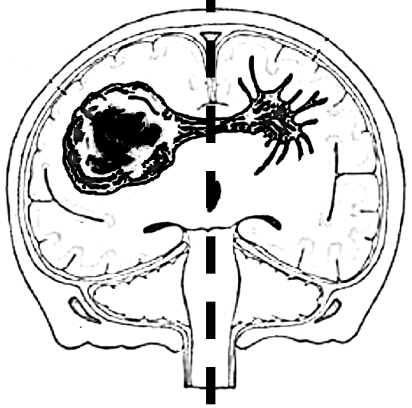
GTP

Flux Ca2+

MAPK/ERK

Intracellulaire

Angiogenic



Invasive

Extracellulaire

Si LRP1
RAP

PS372424
CXCL10
CXCL4L1

SCH546738

Inhibition

Activation

LRP1

CXCR3-A

I
II
III
IV

αq/αi

β

γ

GDP

GTP

βγ

Flux Ca2+

MAPK/ERK

Internalisation

Endosome de recyclage

EEA1

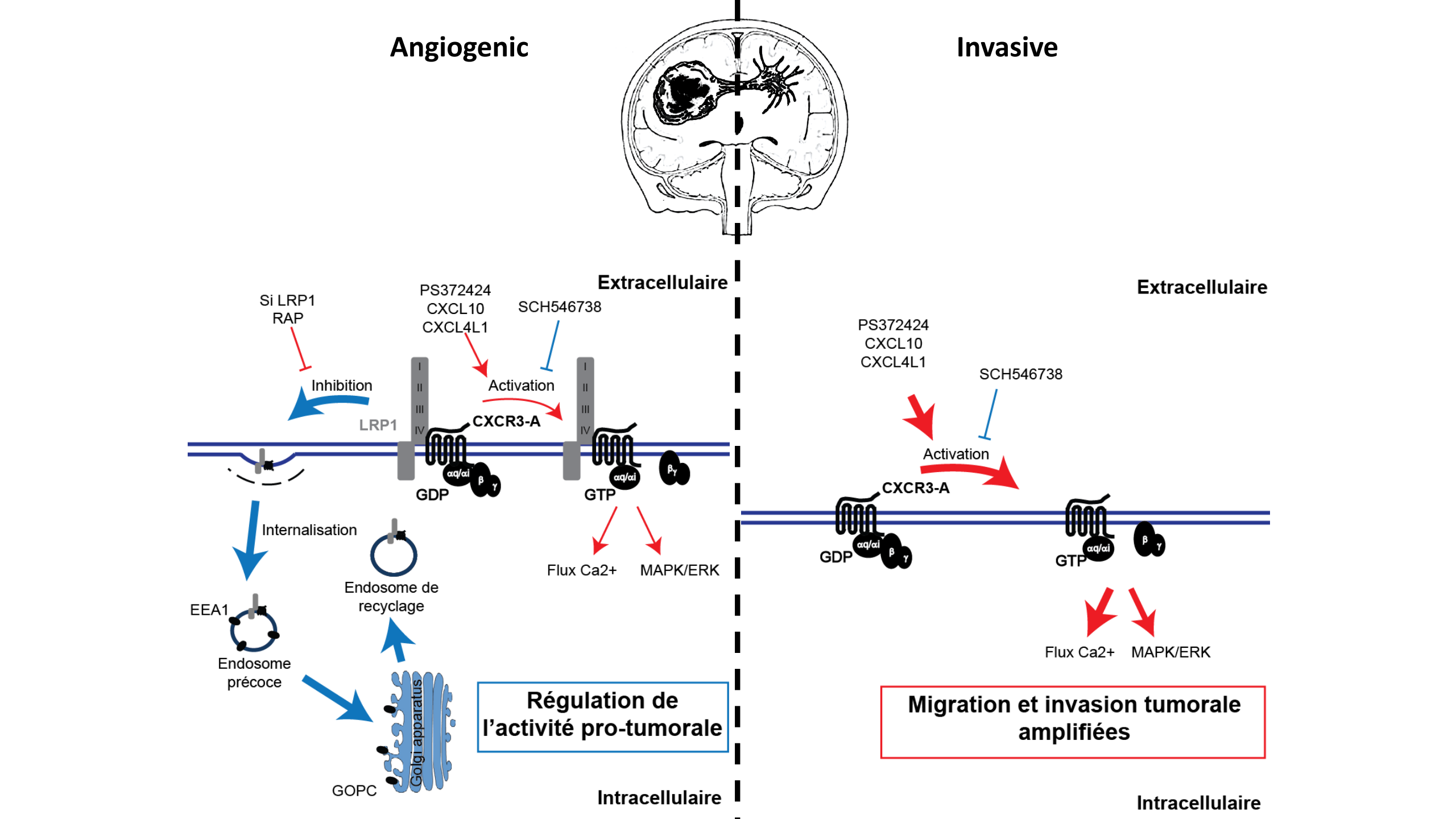
Endosome précoce

Golgi apparatus

GOPC

Régulation de l'activité pro-tumorale

Intracellulaire


Angiogenic
Invasive
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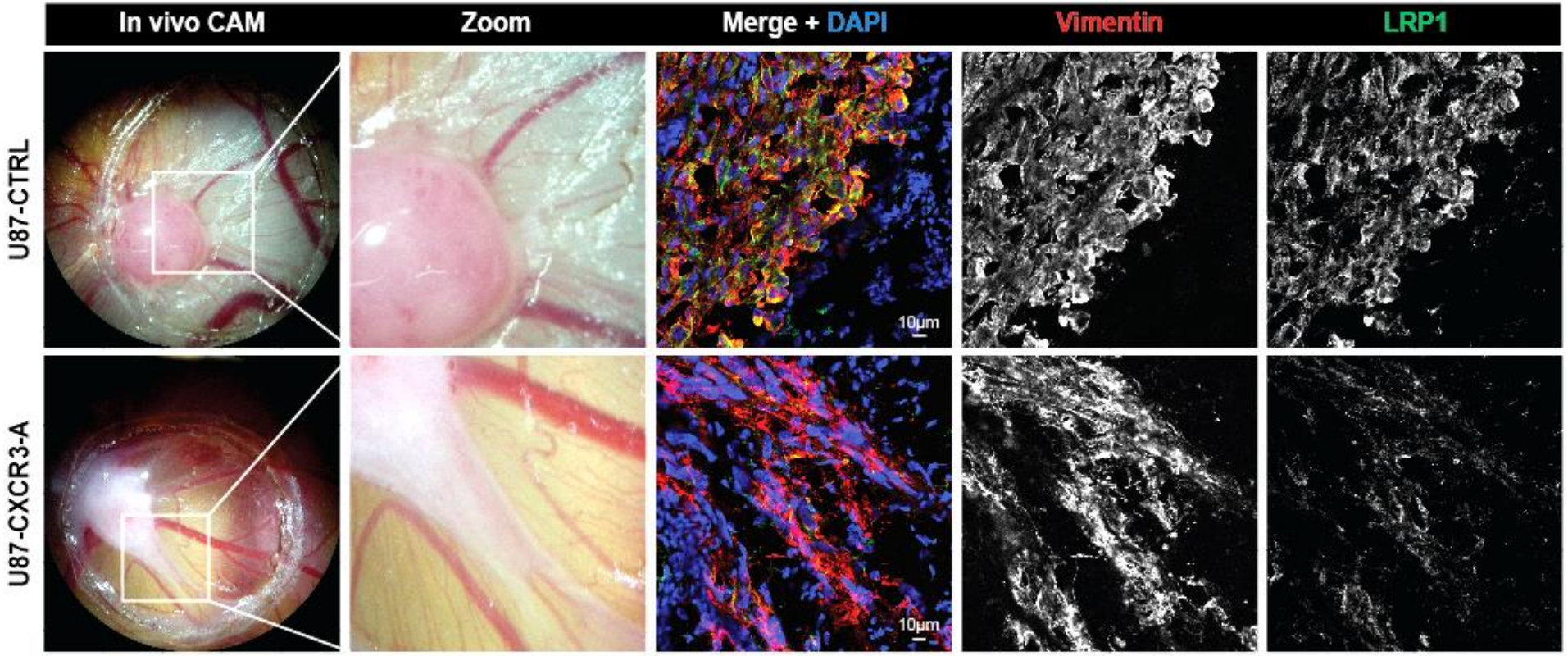
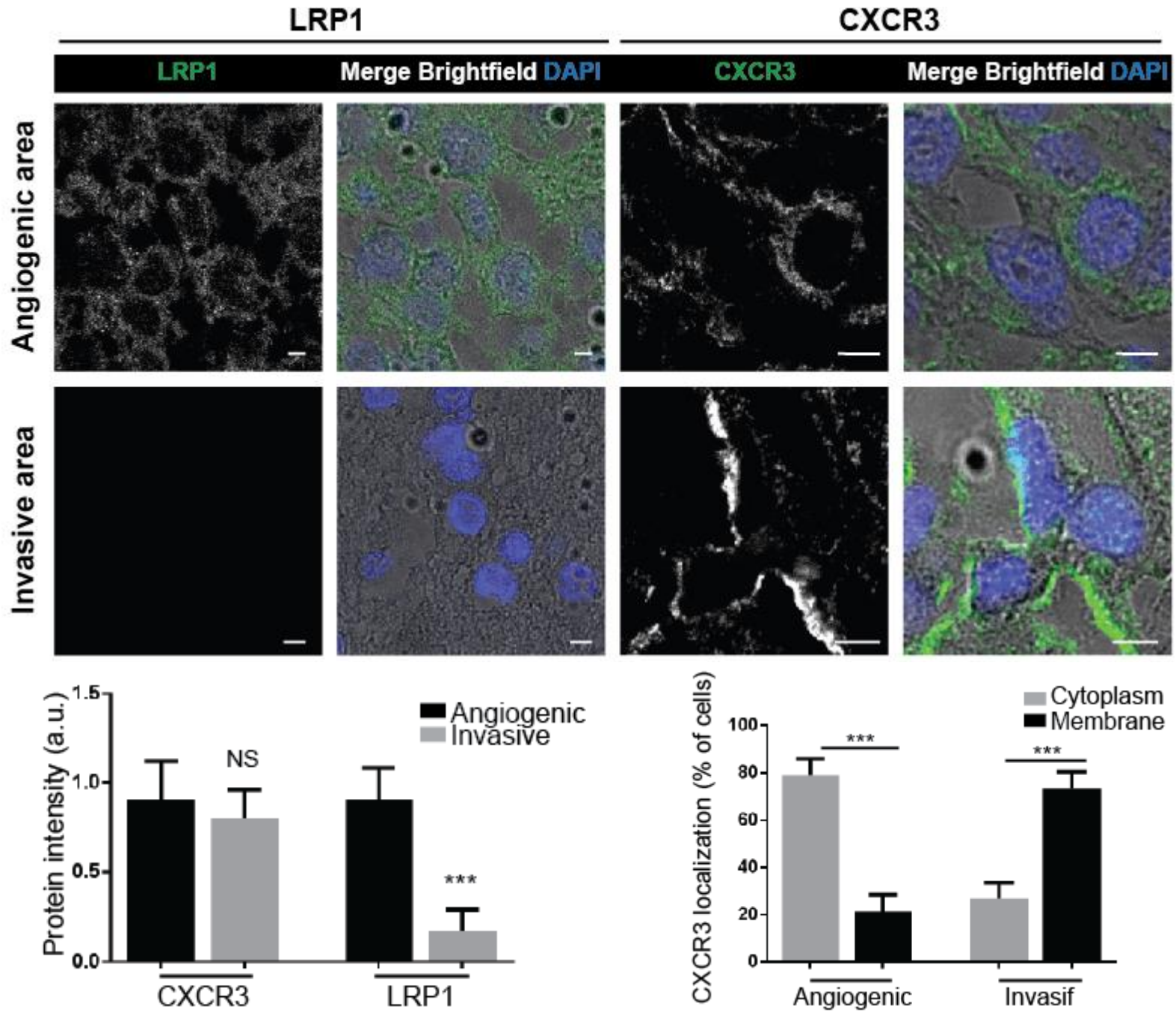
MAPK/ERK
Internalisation
Endosome de recyclage
EEA1
Endosome précoce
Golgi apparatus
GOPC
Régulation de l'activité pro-tumorale
Intracellulaire
Migration et invasion tumorale amplifiées

LRP1 is downregulated in invasive areas



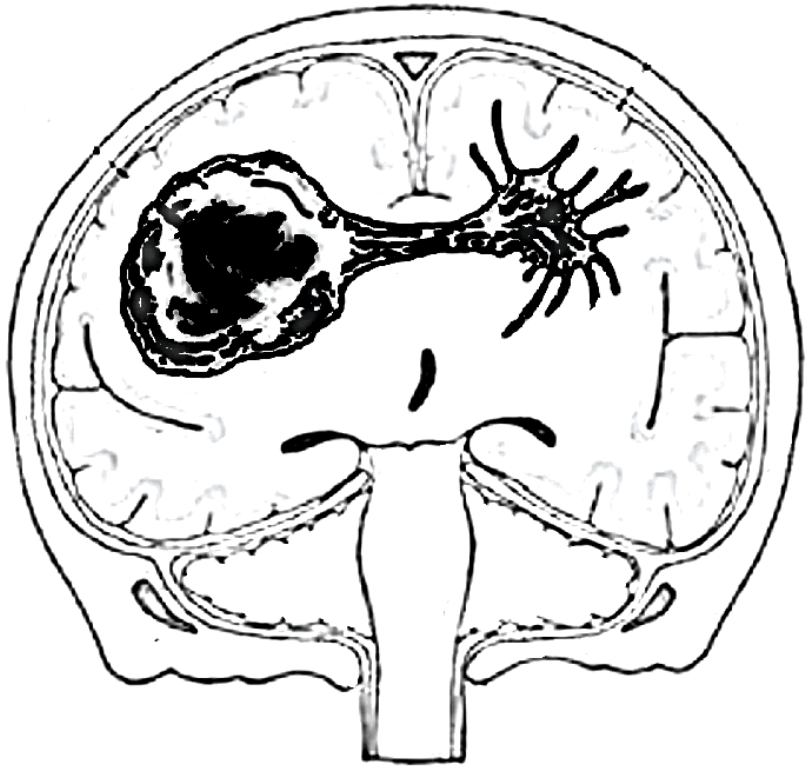
Boyé K et al. Nature communication. (2017)


LRP1
CXCR3
LRP1
Merge Brightfield DAPI
CXCR3
Merge Brightfield DAPI
Angiogenic area
Invasive area
Protein intensity (a.u.)
1.5
1.0
0.5
0.0
NS
***
Angiogenic
Invasive
CXCR3
LRP1
CXCR3 localization (% of cells)
100
80
60
40
20
0
***
***
Cytoplasm
Membrane
Angiogenic
Invasif

CXCR3-A regulateur majeur de l'invasion des glioblastomes

LRP1 inhibits CXCR3A-induced infiltration **but** LRP1 is downregulated in invasive areas

How can we develop new therapeutic strategy ?



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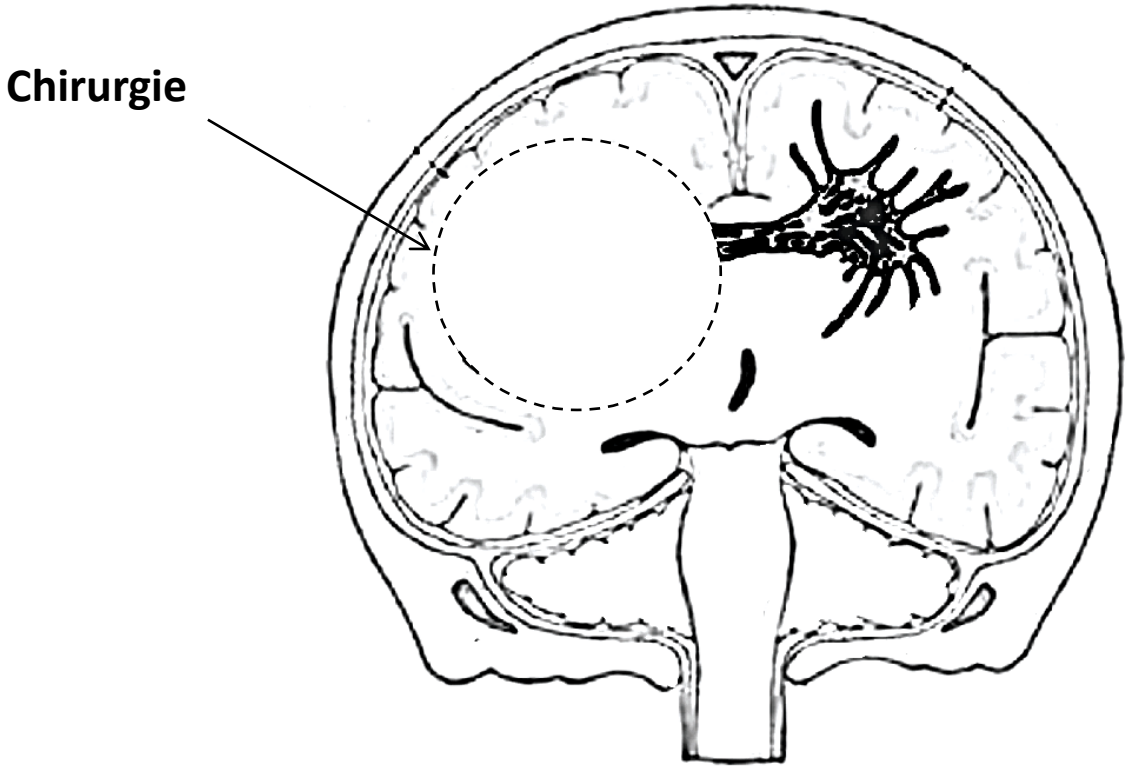

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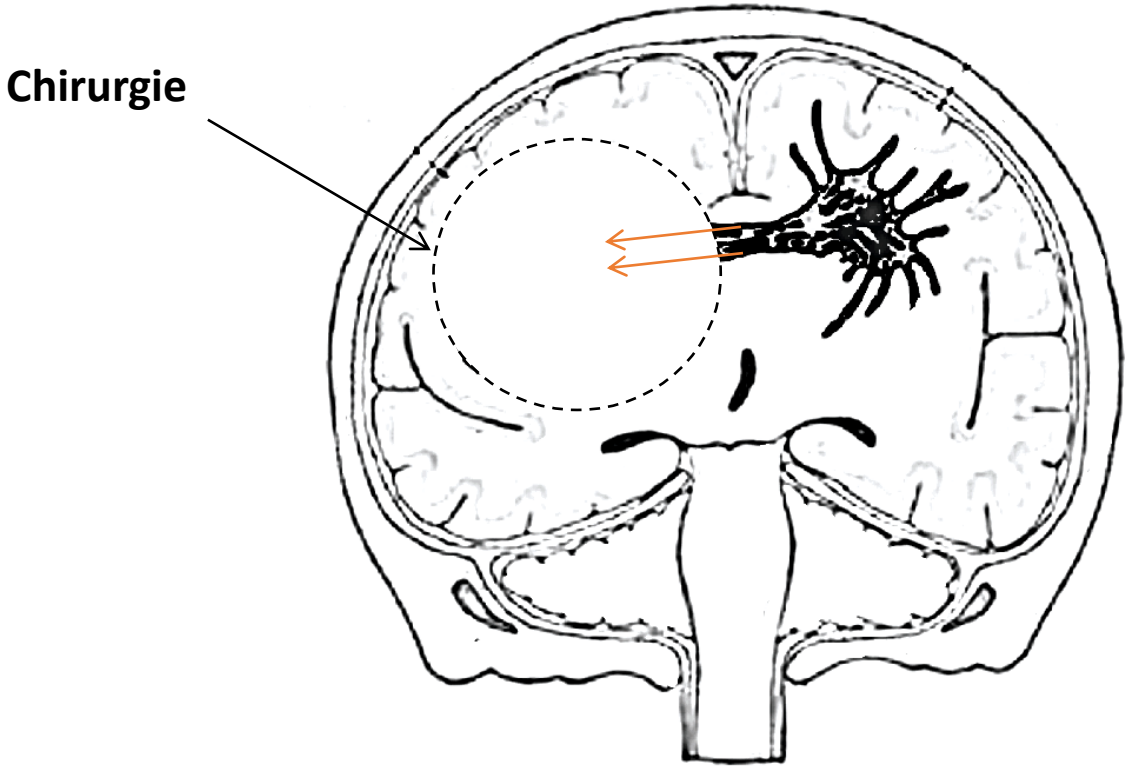

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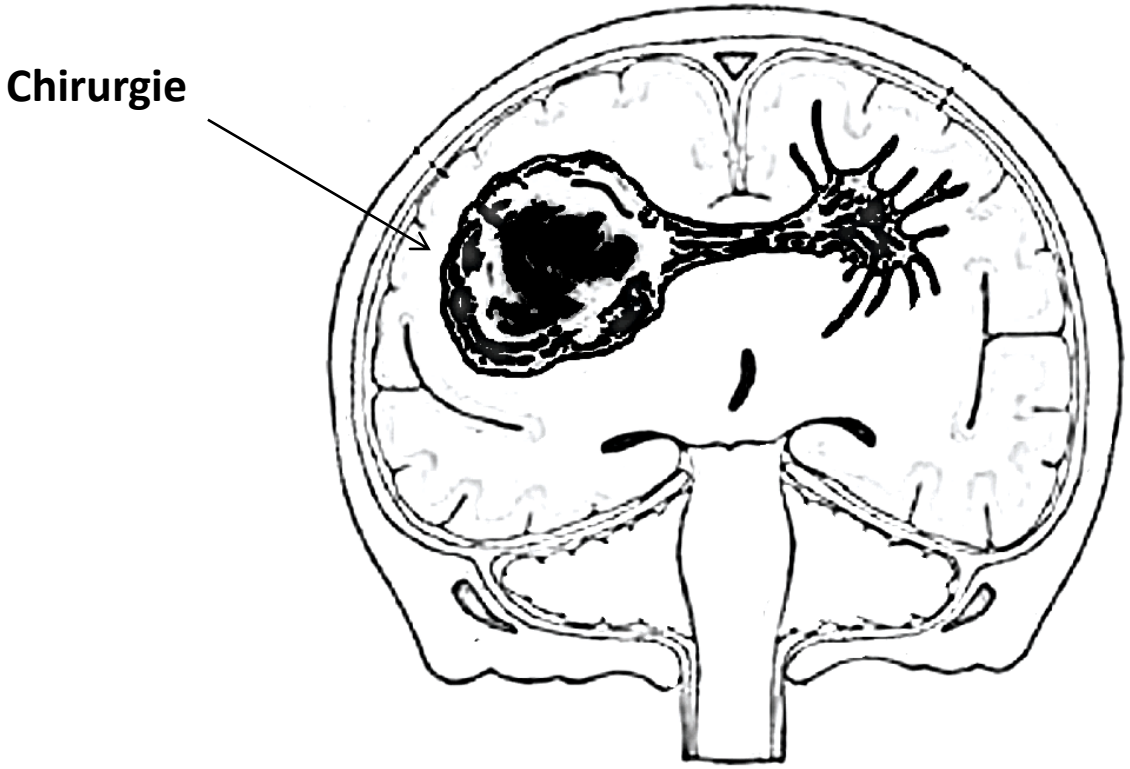
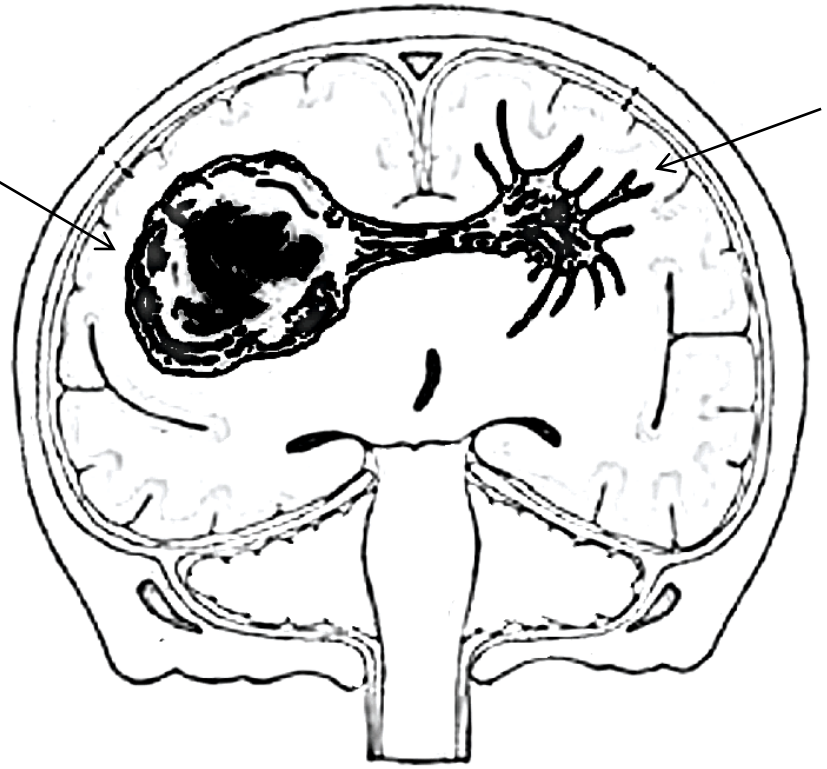


CXCR3-A regulateur majeur de l'invasion des glioblastomes

LRP1 inhibits CXCR3A-induced infiltration **but** LRP1 is downregulated in invasive areas

How can we develop new therapeutic strategy ?

Chirurgie



Inhibition de l'invasion médiée par CXCR3-A

nature COMMUNICATIONS

Altmetric: 1 Citations: 1 More detail »

Article | OPEN

The role of CXCR3/LRP1 cross-talk in the invasion of primary brain tumors

Kevin Boyé, Nadège Pujol, Isabel D Alves, Ya-Ping Chen, Thomas Daubon, Yi-Zong Lee, Stephane Dedieu, Marion Constantin, Lorenzo Bello, Marco Rossi, Rolf Bjerkvig, Shih-Che Sue, Andreas Bikfalvi & Clotilde Billottet

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Articles

Pre

Oligomerization State of CXCL4 Chemokines Regulates G Protein-Coupled Receptor Activation

Ya-Ping Chen†, Hsin-Li Wu†, Kevin Boyé§ǁ, Chen-Ya Pan†, Yi-Chen Chen†, Nadège Pujol§ǁ, Chun-Wei Lin†, Liang-Yuan Chiu†, Clotilde Billottet§ǁ, Isabel D. Alves ǁ⊥, Andreas Bikfalvi*§ǁ, and Shih-Che Sue*†‡

†Institute of Bioinformatics and Structural Biology and ‡Department of Life Science, National Tsing-Hua University, Hsinchu, Taiwan

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ACS Chem. Biol., **2017**, *12* (11), pp 2767–2778

DOI: 10.1021/acschembio.7b00704

Publication Date (Web): September 25, 2017

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Cite this: *ACS Chem. Biol. 12, 11, 2767-2778*

RIS Citation GO

SCIENTIFIC REPORTS

OPEN

Received: 23 May 2017
Accepted: 21 August 2017
Published online: 06 September 2017

Ligand activation induces different conformational changes in CXCR3 receptor isoforms as evidenced by plasmon waveguide resonance (PWR)

K. Boyé[1,2], C. Billottet[1,2], N. Pujol[1,2], I. D. Alves[2,3] & A. Bikfalvi[1,2]

Cancer Research

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Molecular and Cellular Pathobiology

Dual Roles for CXCL4 Chemokines and CXCR3 in Angiogenesis and Invasion of Pancreatic Cancer

Cathy Quemener, Jessica Baud, Kevin Boyé, Alexandre Dubrac, Clotilde Billottet, Fabienne Soulet, Florence Darlot, Laurent Dumartin, Marie Sire, Renaud Grepin, Thomas Daubon, Fabienne Rayne, Harald Wodrich, Anne Couvelard, Raphael Pineau, Martin Schilling, Vincent Castronovo, Shih-Che Sue, Kim Clarke, Abderrahim Lomri, Abdel-Majid Khatib, Martin Hagedorn, Hervé Prats, and Andreas Bikfalvi

DOI: 10.1158/0008-5472.CAN-15-2864 Published November 2016

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-08480-y OPEN

Matrice et GBM

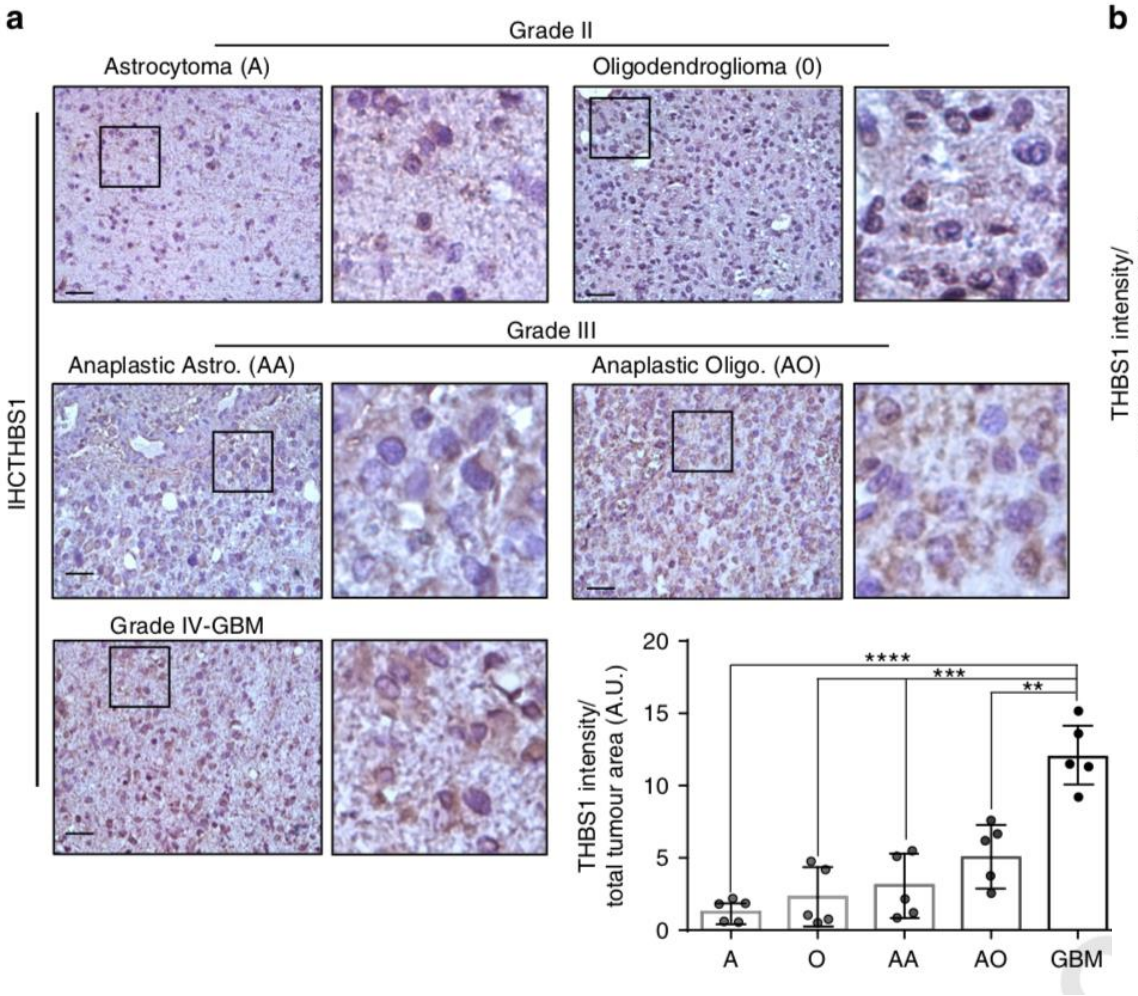
Deciphering the complex role of thrombospondin-1 in glioblastoma development

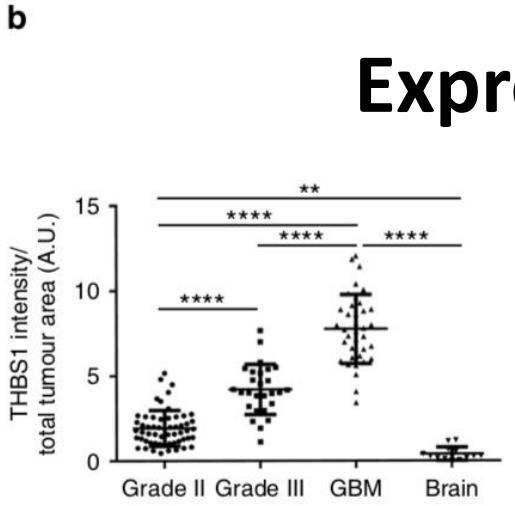
Thomas Daubon[1,2,3], Céline Léon[1], Kim Clarke[4], Laetitia Andrique[1], Laura Salabert[1], Elodie Darbo[5], Raphael Pineau[6], Sylvaine Guérit[1], Marlène Maitre[7], Stéphane Dedieu[8], Albin Jeanne[8,9], Sabine Bailly[10], Jean-Jacques Feige[10], Hrvoje Miletic[2,11], Marco Rossi[12], Lorenzo Bello[12], Francesco Falciani[4], Rolf Bjerkvig[2,3,13] & Andréas Bikfalvi[1]

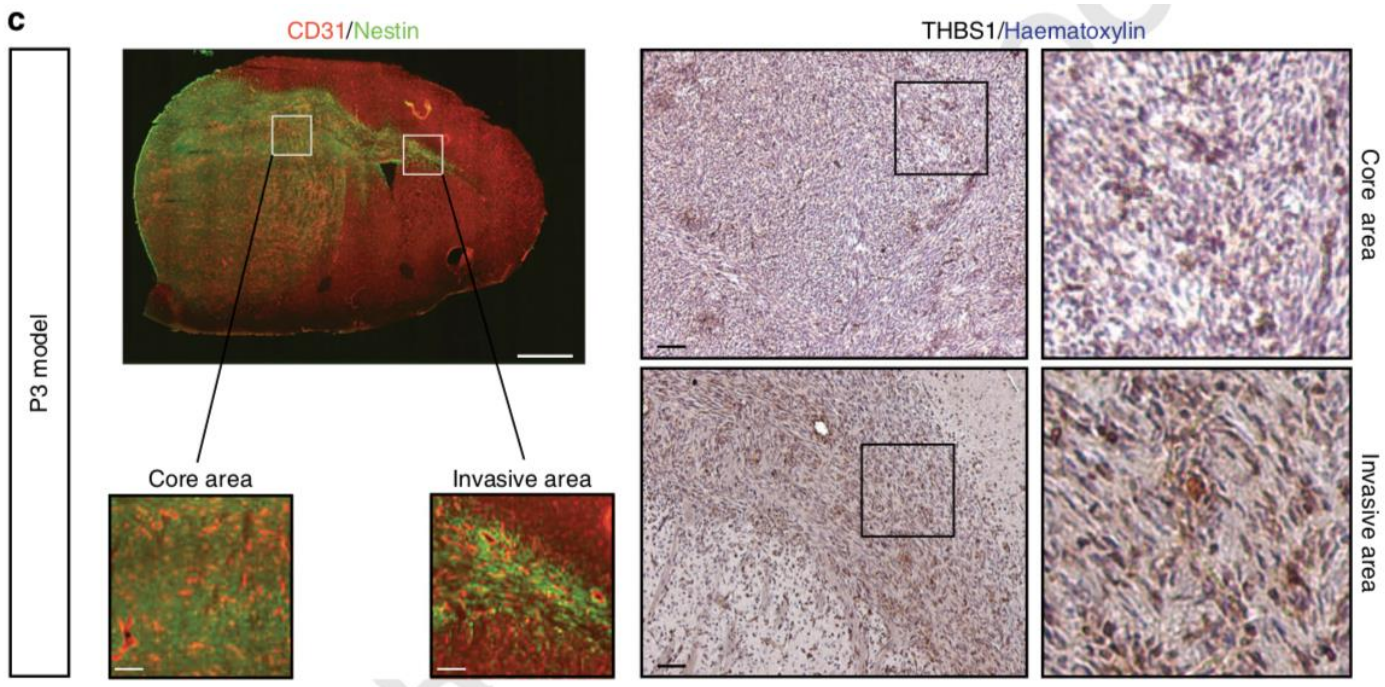
Published online March 8, 2019

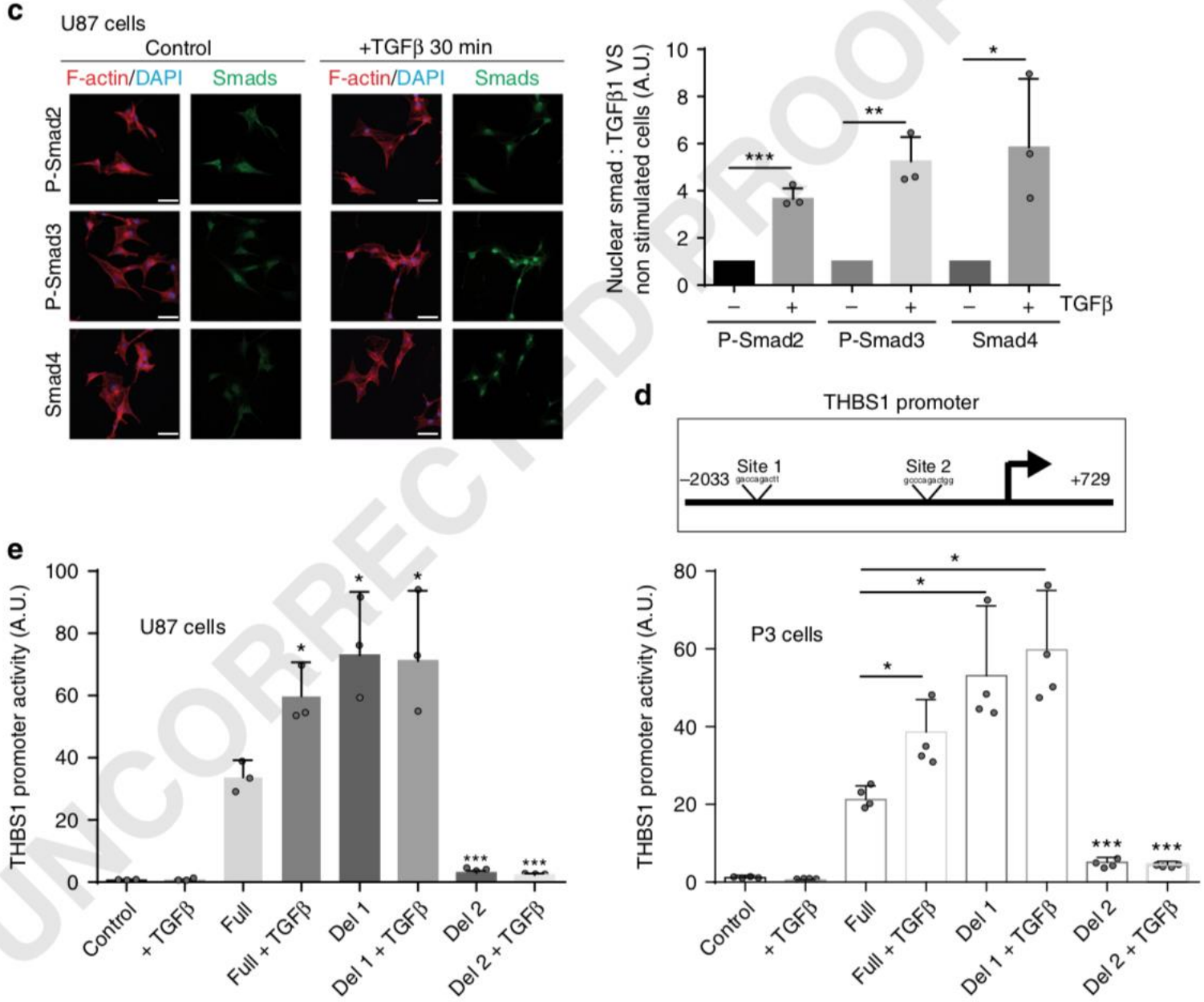
We undertook a systematic study focused on the matricellular protein Thrombospondin-1 (THBS1) to uncover molecular mechanisms underlying the role of THBS1 in glioblastoma (GBM) development. THBS1 was found to be increased with glioma grades. Mechanistically, we show that the TGFβ canonical pathway transcriptionally regulates THBS1, through SMAD3 binding to the THBS1 gene promoter. THBS1 silencing inhibits tumour cell invasion and growth, alone and in combination with anti-angiogenic therapy. Specific inhibition of the THBS1/CD47 interaction using an antagonist peptide decreases cell invasion. This is confirmed by CD47 knock-down experiments. RNA sequencing of patient-derived xenograft tissue from laser capture micro-dissected peripheral and central tumour areas demonstrates that THBS1 is one of the gene with the highest connectivity at the tumour borders. All in all, these data show that TGFβ1 induces THBS1 expression via Smad3 which contributes to the invasive behaviour during GBM expansion. Furthermore, tumour cell-bound CD47 is implicated in this process.

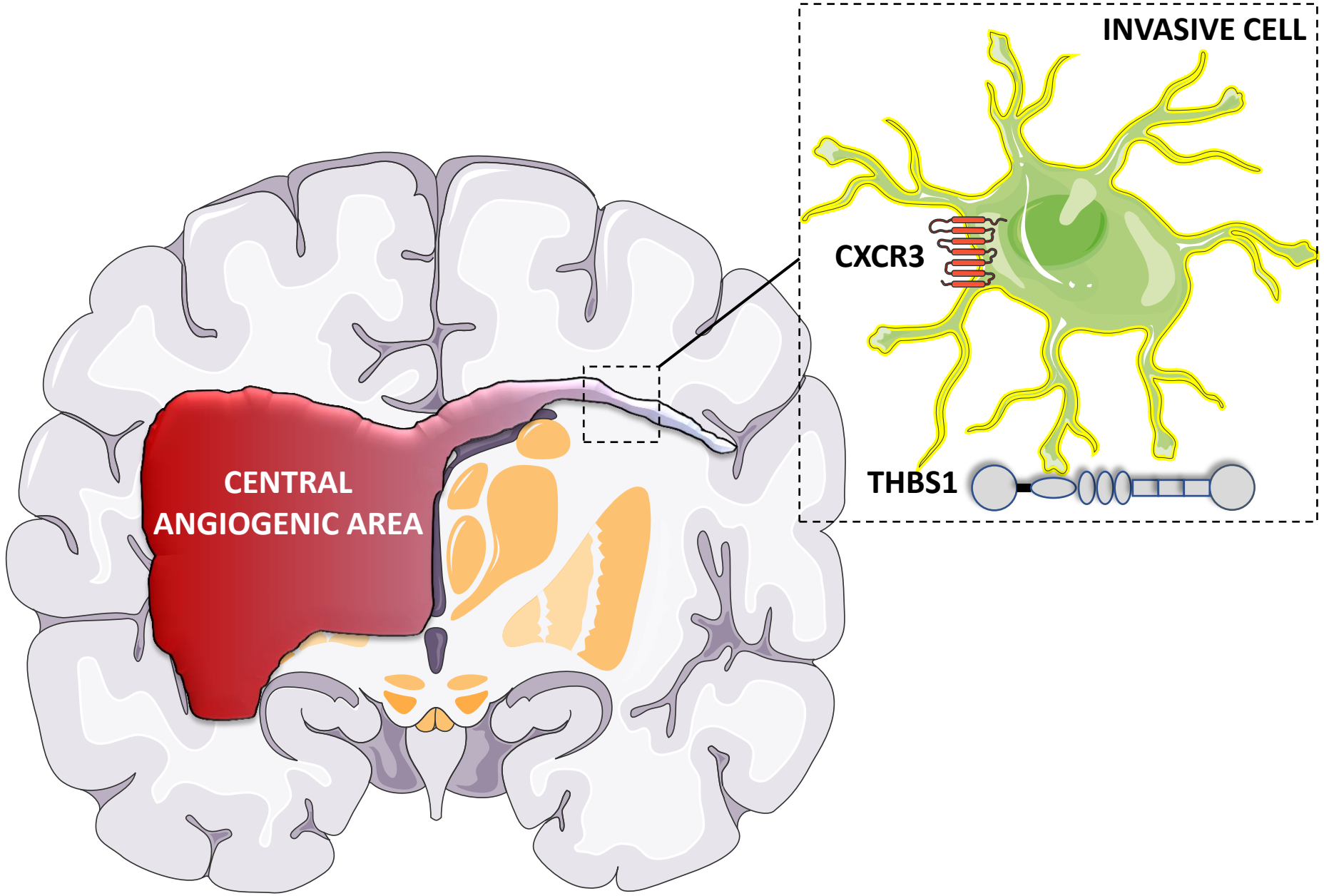
Expression of TSP1 in GBM










INVASIVE CELL
CXCR3
THBS1
CENTRAL
ANGIOGENIC AREA

Partners

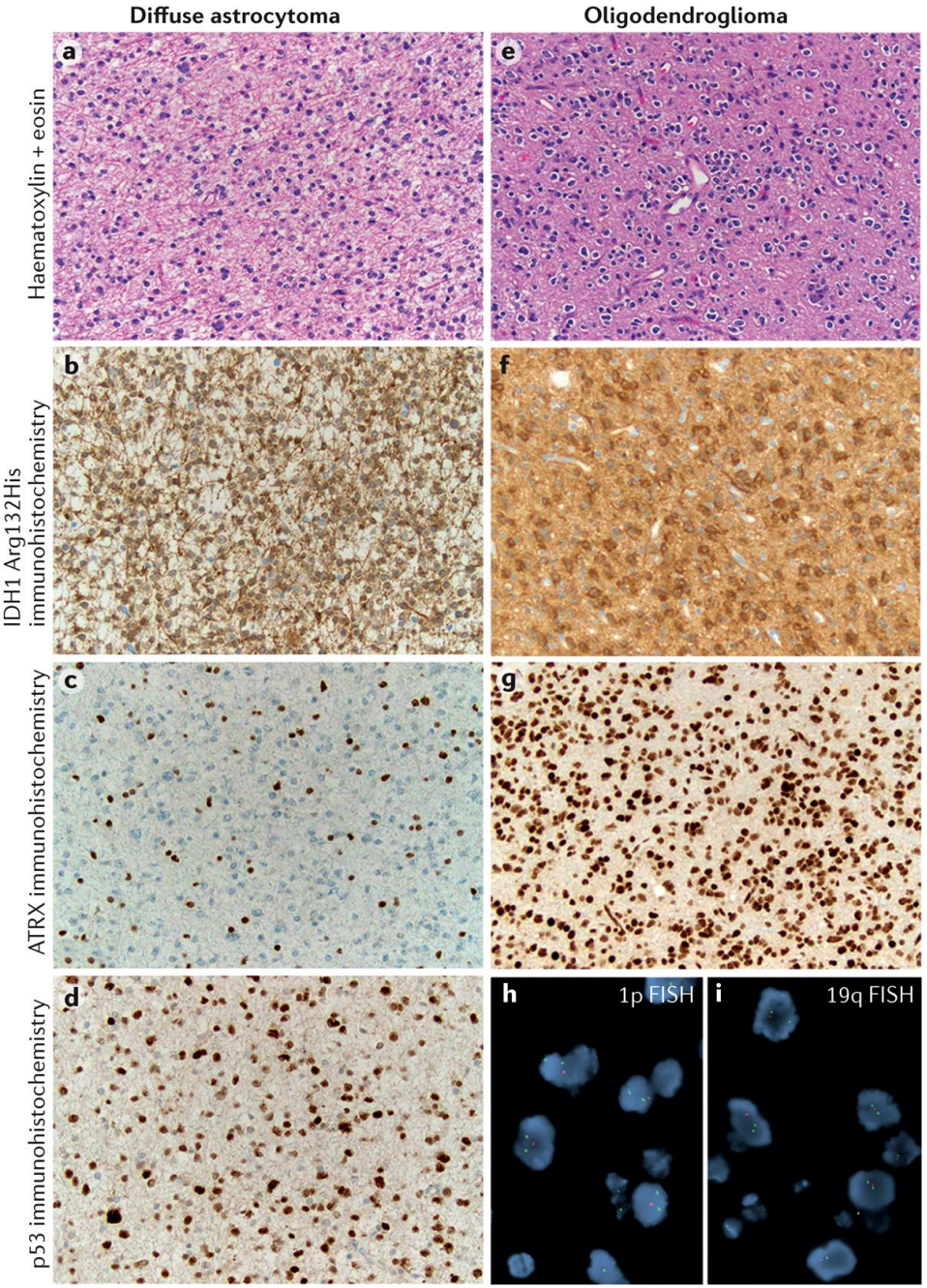
- **International:**

R. Bjerkvig & S. Niclou (NorLux Laboratory)
L. Bello (Humanitas, Milan)
F. Falciani (Univ Liverpool)
SC Sue (NTHU, Taiwan)
M Tremblay (McGill Montreal)

° **Bordeaux:**

M. Nikolski (CBIB)
I. Alves (CBMN)
Oncoprot (F.Saltel, etc…)
Bordeaux Imaging Center BIC
P. Nassoy (Institut Optique)
Neurocentre Broca (V Nagerl, nouveau)
C. Bronnimann (intratecal treatment strategy)

° **France**: Réseau préclinique ANOCEF



Buckner, J. *et al.* (2017) *Nat. Rev. Neurol.* Nature Reviews | Neurology

II. Projet Translationnel

GLIOMES DE BAS GRADE

Population plutôt jeune

Tumeur très infiltrative mais à évolution lente

Absence d'angiogenèse prononcée

Traitement actuelle : Chirurgie, Radio et Chimiothérapie (Temozolamide ou PCV (procarbazine, CCNU, Vincristine)

Importance de la chirurgie: EOR (Etendue de la résection)

Problème:

Cependant groupes de patients à évolution rapide !

https://www.fondation-arc.org/projets/predire-evolution-gliomes-bas-grade-pour-ameliorer-prise-en-charge

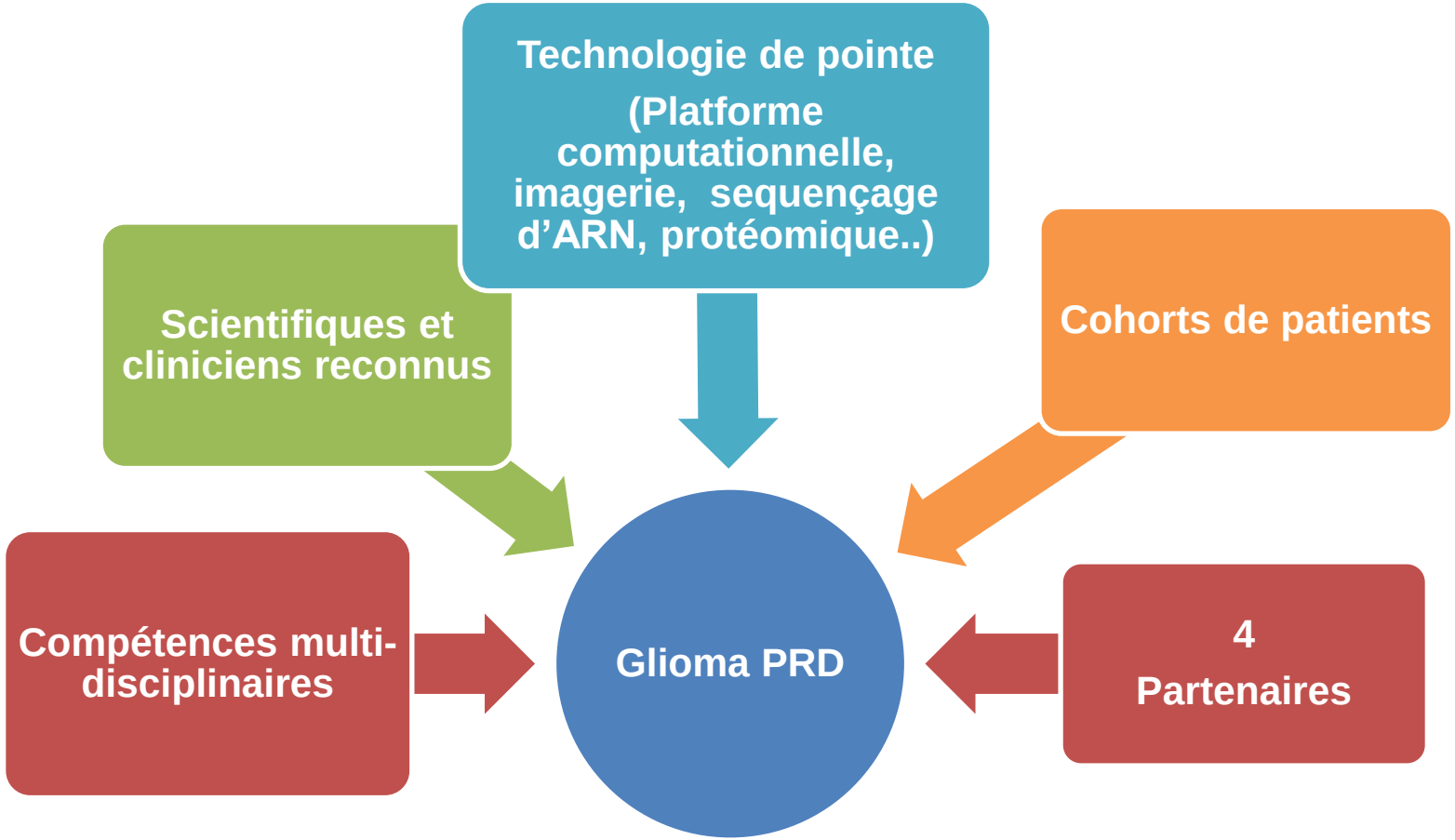
Projet Européen Transcan (ERA-NET) - ARC

Consortium Européen France, Italie, Norvège

Associant: Biologistes, médecins, bioinformaticiens/ biostatisticien et mathématiciens

But:

Elaboration d'algorithmes de prédiction pour prédire l'évolution



TRANSCAN-2

ERA-NET: Aligning national/regional translational cancer research programmes and activities

TRANSCAN-2

GLIOMA-PRD

Reserved Area

Abstract 14 November 2017 Hits: 1096

Title: Multi-parametric analysis of the evolution and progression of low grade glioma

Project Coordinator:
Andreas BIKFALVI (France) University of Bordeaux, Pessac

Project Partners:
Lorenzo BELLO (Italy) IRCCS Humanitas Research Hospital, Rozzano, Milan
Olivier SAUT (France) INRIA, Talence
Rolf BJERKVIG (Norway), University of Bergen, Bergen

TRANSCAN-2 News

Fourth Joint Transnational Call 2017 (JTC 2017)

on: Translational Research on Rare Cancers

12 projects selected for funding

visit the page

https://www.transcanfp7.eu/index.php/abstract/glioma-prd.html

1 • LE CONSTAT

Parmi les tumeurs cérébrales les plus courantes, il est difficile de distinguer celles qui risquent d'évoluer rapidement pour devenir agressives de celles qui évoluent très lentement.

2 • LE PROJET SÉLÉCTIONNÉ PAR LA FONDATION ARC

À partir des données cliniques, moléculaires et d'imagerie de plus de 150 patients, le projet de quatre équipes coordonné par le Professeur Andreas Bikfalvi (Bordeaux) vise à développer un modèle de prédiction de l'évolution des tumeurs cérébrales les plus courantes, les gliomes de bas grade.

3 • L'ESPOIR

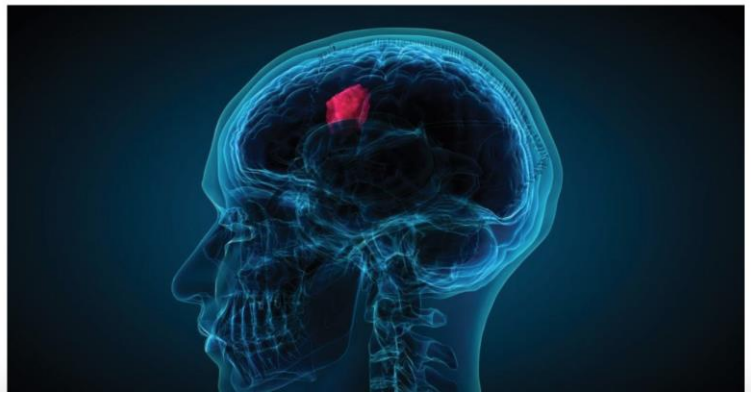
À terme, ce projet devrait permettre d'améliorer, dès le diagnostic, la prise en charge des formes les plus agressives de ces cancers qui touchent particulièrement les jeunes de moins de 30 ans.

Projet GLIOMA PRD - réseau européen ERA-NET TRANSCAN-2
Participation Fondation ARC : **550 000€** sur 3 ans

http://maraisondedonner.fondation-arc.org

Multi-parametric analysis of the evolution and progression of low-grade glioma

19th July 2018



https://www.scitecheuropa.eu/analysis-evolution-low-grade-gliomas/88086/

Partenaires

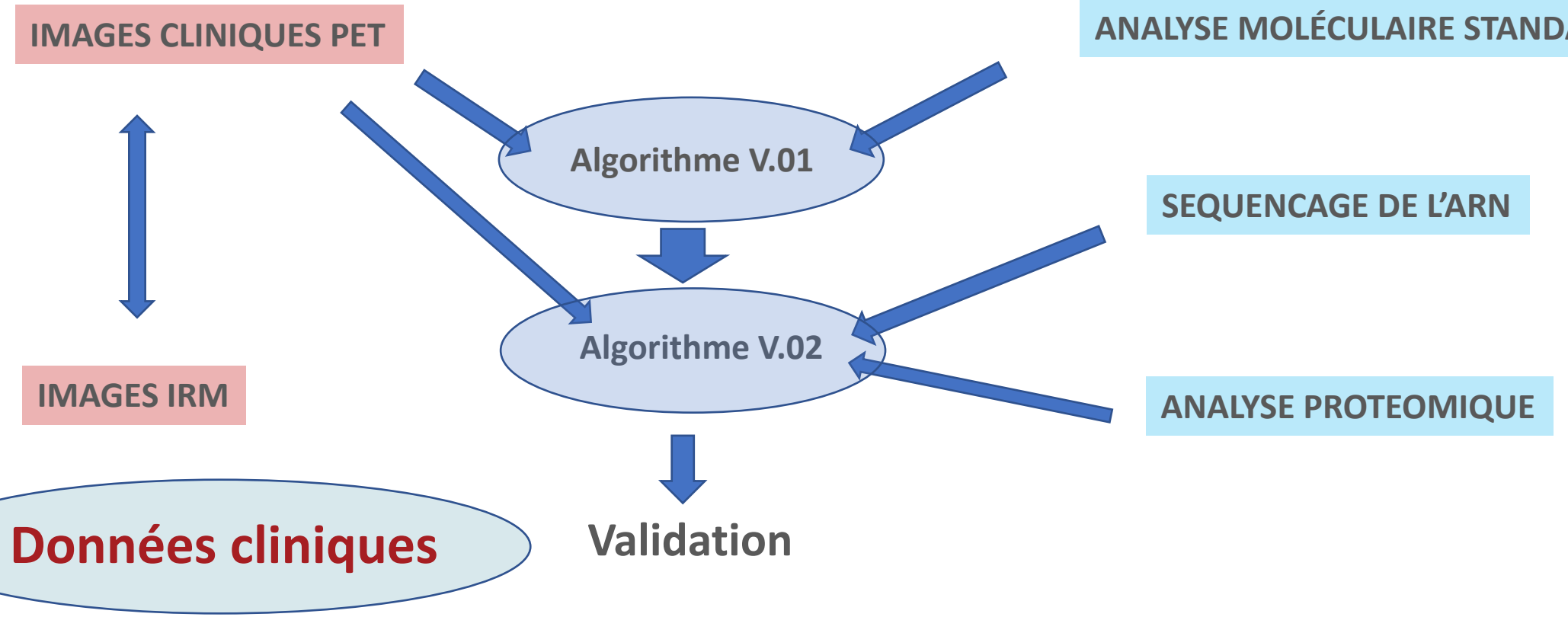
- Andreas Bikfalvi, Directeur LAMC-INSERM U1029 coordinateur
- Lorenzo Bello, Directeur Departement de Neuro-oncologie, Humanitas, Université de Milan
- Olivier Saut, Directeur d’équipe MONC, INRIA, Bordeaux
- Rodolphe Thiebaut, Directeur SISTM, INRIA Bordeaux
- Rolf Bierkvig, Directeur du Jebsen Brain Tumor Research Center, Dept de Biomedicine, Univ Bergen

STRATEGIE

IMAGES CLINIQUES

ECHANTILLONS DE PATIENTS

Echantillons PET chaud (diffus) v PET froid
Zones PET chaud (ponctuées/»spots») v PET froid



Données cliniques

III. Modèles

-Modèles implantatoires orthotopiques

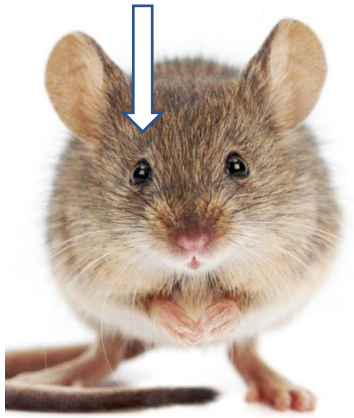
-Modèles syngéniques ou xénogreffe

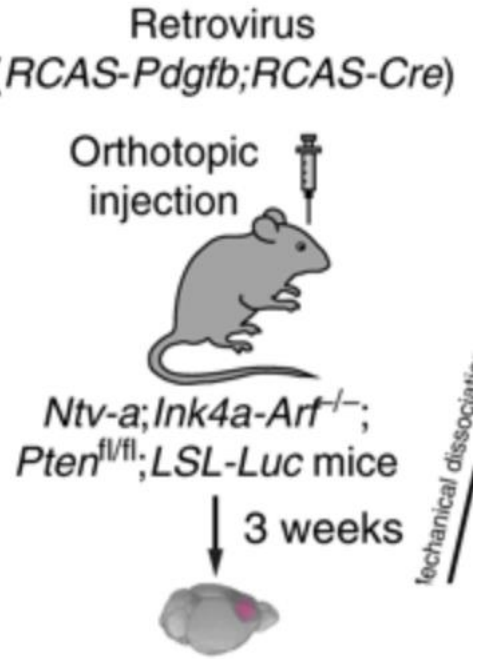
-Implantation de suspension cellulaires

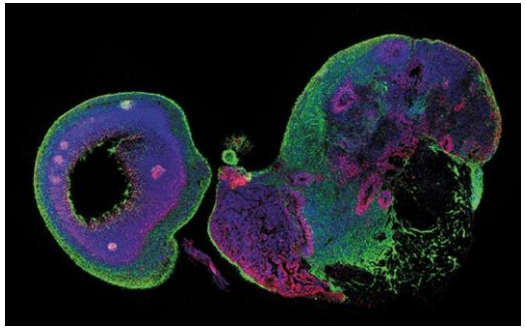
-Implantation de sphéroides

-Souris génétiquement modifiées

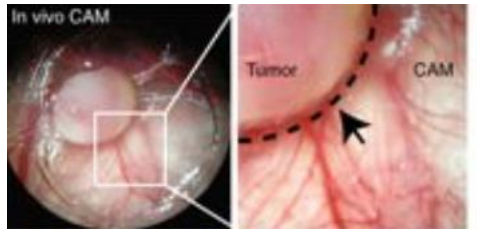
-Organoides *in vitro*







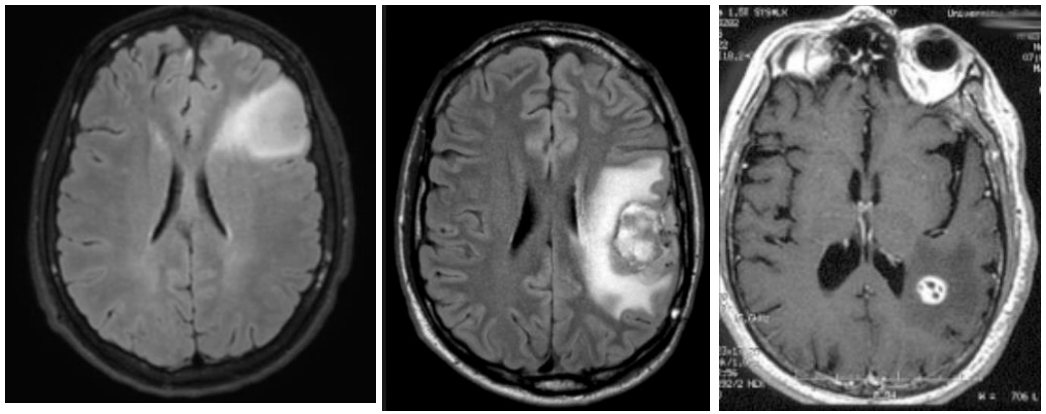
Organoides complexes



Modèle de l'embryon de poulet

IV. Structuration future sur Bordeaux

- Création d'un laboratoire spécifique de Neuro-Oncologie
- Tumeurs cérébrales primitives et secondaires (métastases cérébrales)



A.Bikfalvi MD PhD Pr
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POSITION PAPER

Challenges to curing primary brain tumours

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Abstract | Despite decades of research, brain tumours remain among the deadliest of all forms of cancer. The ability of these tumours to resist almost all conventional and novel treatments relates, in part, to the unique cell-intrinsic and microenvironmental properties of neural tissues. In an attempt to encourage progress in our understanding and ability to successfully treat patients with brain tumours, Cancer Research UK convened an international panel of clinicians and laboratory-based scientists to identify challenges that must be overcome if we are to cure all patients with a brain tumour. The seven key challenges summarized in this Position Paper are intended to serve as foci for future research and investment.

Challenges to curing primary brain tumours.
Aldape et al Nat Rev Clin Oncol. 2019 Feb 7.
doi: 10.1038/s41571-019-0177-5

Challenge 1: redesign research pipeline

Challenge 2: use neuroscience research

Challenge 3: understand the TME

Challenge 4: develop preclinical models

Challenge 5: drugging complex cancers

Challenge 6: precision medicine

Challenge 7: reduce treatment for some