Anti-VEGF alter cognitive functions and the CA1-CA3 hippocampal activity in mice: the first reported chemofog with a targeted cancer therapy

Hélène Castel

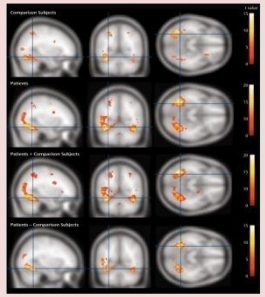
Lab DC2N, Team astrocyte and Vascular Niche
U982 Inserm, IRIB, University of Rouen, France

Chemotherapy-2015-04th-06th August, Valencia, Spain

Interdisciplinary program: Interface between Cancer and Neurosciences

http://www.france5.fr/sante/

Cognitive impairments
Functional Imaging



Researcher,
B. Giffard, Normandy, France
Inserm U1077

Clinical Protocols
Cognitive Function
Fatigue
Quality of life

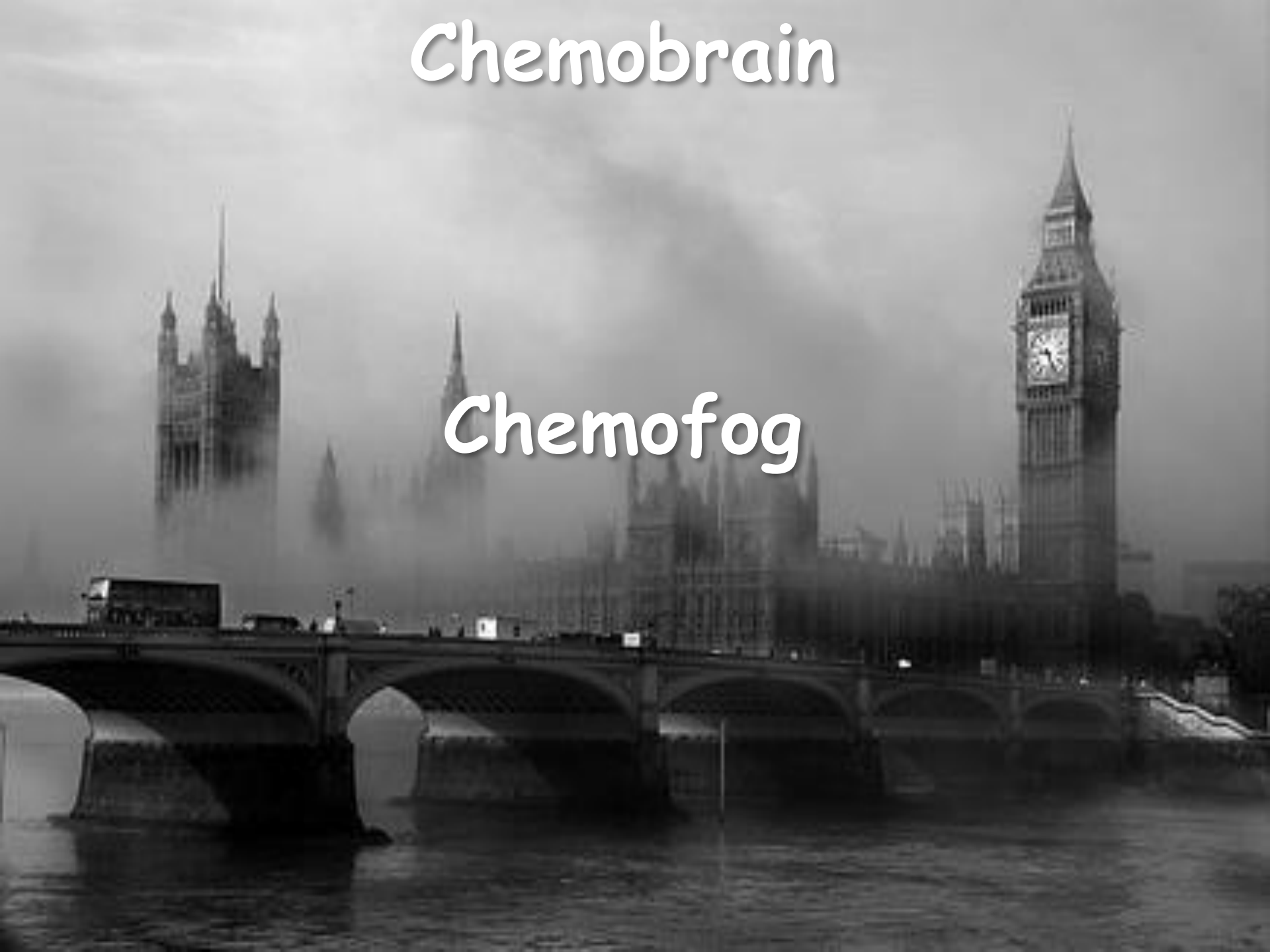
Animal Models-
Brain mechanisms

Oncologists , psychologists
F. Joly, Normandy, France
O. Rigal, J Lefel, Normandy, France

Researcher, Neurosciences
H. Castel, Normandy, France
Inserm U982

Elderly Patients

Cancéropôle Nord-Ouest


Chemobrain
Chemofog

Cognitive functions after cancer, What patients report…

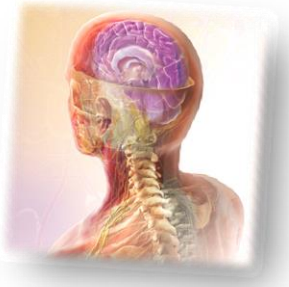
« I am confused, I want to do everything at once, and can not hold me, I lose my items, I even put my laptop in the fridge for example!

« I struggle to name people and things that I know them very well

« I do not know what I'm doing! Yesterday in the same day I cleaned chicken legs with dish soap, then in the afternoon I put my clothes in the freezer compartment!

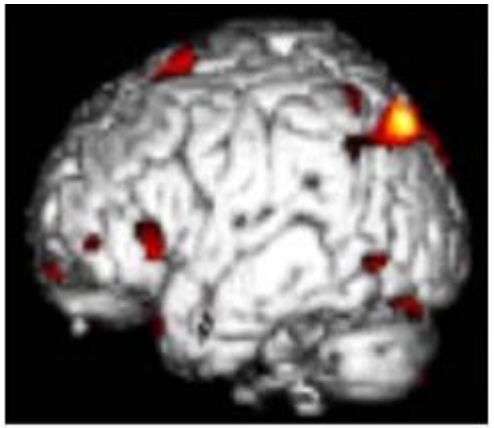
« I have huge doubts about my abilities since the end of treatment, look at how I wrote "painting" the other day

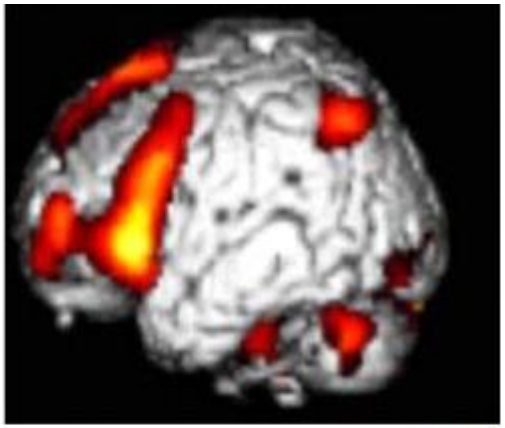
…Woman interviewed after breast cancer and chemotherapy

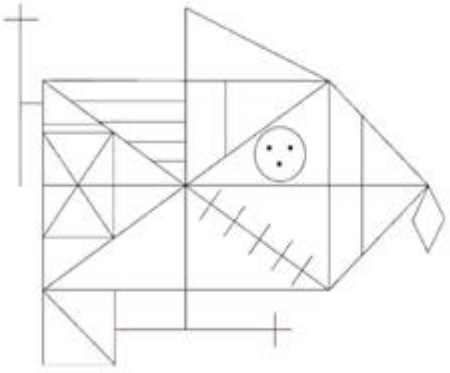


Neurotoxicities and chemotherapies : « Objective » cognitive troubles

Control **Chemotherapy** **Complex draw of Rey**







(Silverman, et al. 2007)

PET-scan associated to a short term memory task :
5-10 years after treatement

- Alteration of performances
- Modification of cerebral blood flow/cerebral activity

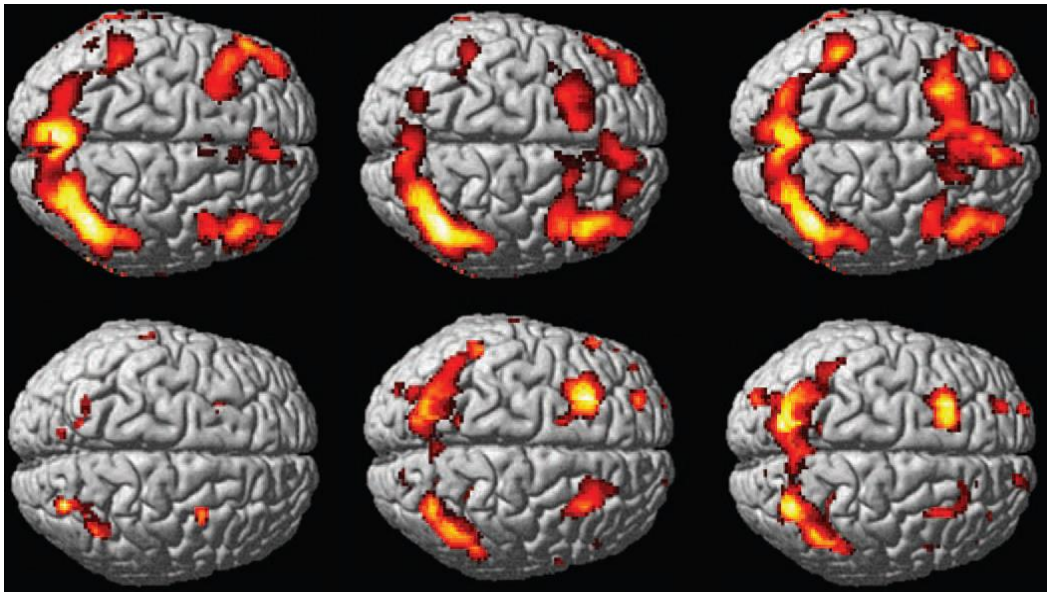
Activity → Frontal cortex and cerebellum

Activity → Parietal cortex

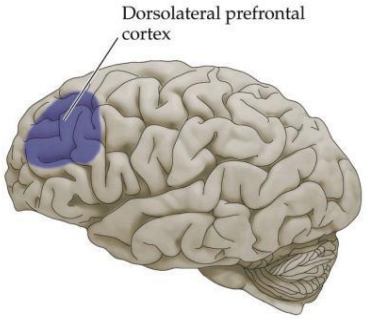
Role of chemotherapy: the story of the two homozygous twins

Cancer/chemotherapy

Control



1-back ***2-back*** ***3-back***



Ferguson et al., 2007

n-back test : Executive functions

One-back test – P R M **M** Y D **D** R P R

Two-back test – A C M **C** Q P C X R **X**

Three-back test – A B C M R **C** Q **R**

- **Low efficacy = deficit**
- **Cerebral fatigue**

The fog and fatigue of CHEMOBRAIN - CHEMOFOG in cancer survivors

Myelin damage

Stress

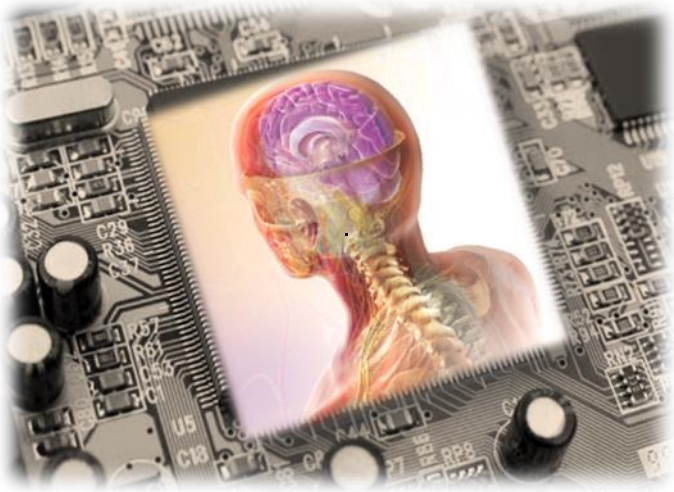
Anxiety

Neurotoxicity

Emotions

Fatigue

Aging



Depression

Cognitive reserve

Brain blood barrier

Vascular lesions

Inflammation

Hormones

Anemia

Metabolism

Secondary organ toxicity

Cancer | Chemotherapy | Targeted Therapy

icctf international cognition and cancer taskforce

- **Neurocognitive evaluation guidelines**
- **Clinical networks**
- **Imaging procedures**
- **Rehabilitation**

Chemotherapy-2015-04th-06th August, Valencia, Spain

The fog and « fatigue » of Chemobrain in animal models: Chemotherapy

- Direct **role on cognition**: learning and memory deficits and/or executive function impairments

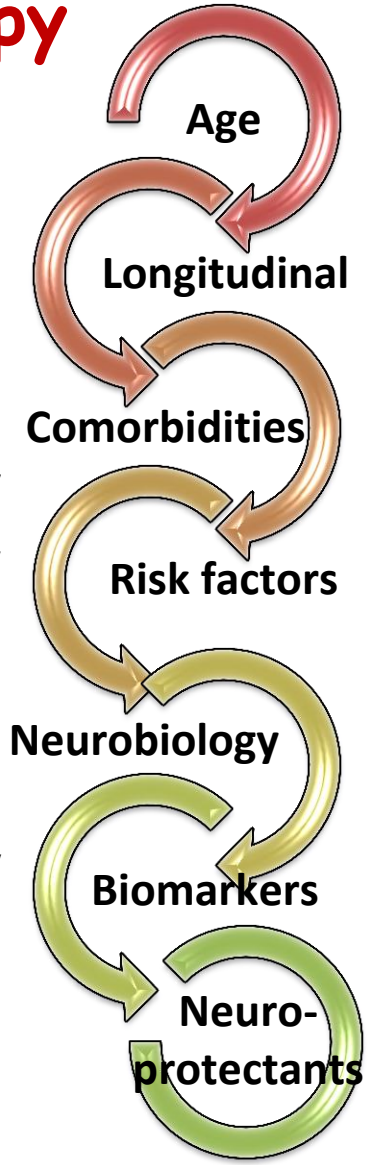
  Metotrexate alone (Madhyastha et al., 2002; Seigers 2008, 2009); 5-FU alone (Mustafa et al., 2008; Fardell et al., 2012), combination including 5-FU or metotrexate (Winocur, 2006; Gandal et al., 2008; Foley et al., 2008; Liedke et al., 2009; Walker et al., 2011), cyclophosphamide, doxorubicine, cytocine arabinoside or tiotTEPA (Konat et al., 2008, MaclLeod et al., 2007, Li et al., 2008; Mondie et al., 2010; Yang et al., 2010)...**or no effect** *(Fremouw et al., 2011).*

- Highlight **neurobiological mechanisms**

  Decreased cell proliferation, alteration of neuromediators, Neural progenitor cells, oligodendroglial precurors (Dietrich et al., 2006; Han et al., 2007), hippocampal and sub-ventricular zones , Hypothalamic functions (Weymann et al., 2013)

- Testing neuroprotectants and **prevention** of cognitive deficits

  Donepezil, fluoxetine, physical activity, glucose (Elbeltagy et al., 2009; Lyons et al., 2011; Winocur et al., 2011; Fardell et al., 2012; Dubois et al., 2014)

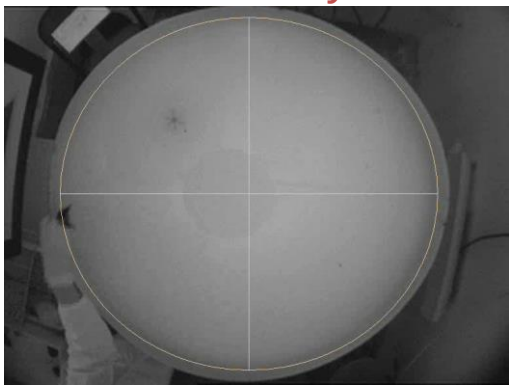


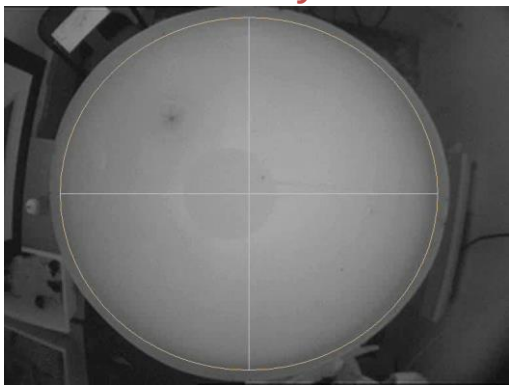
Effects of 5-FU on cognitive functions in young and aged mice

Dubois et al, Neuropharmacology, 2014a

The Morris water maze test

1st Day — Learning test — 4th Day

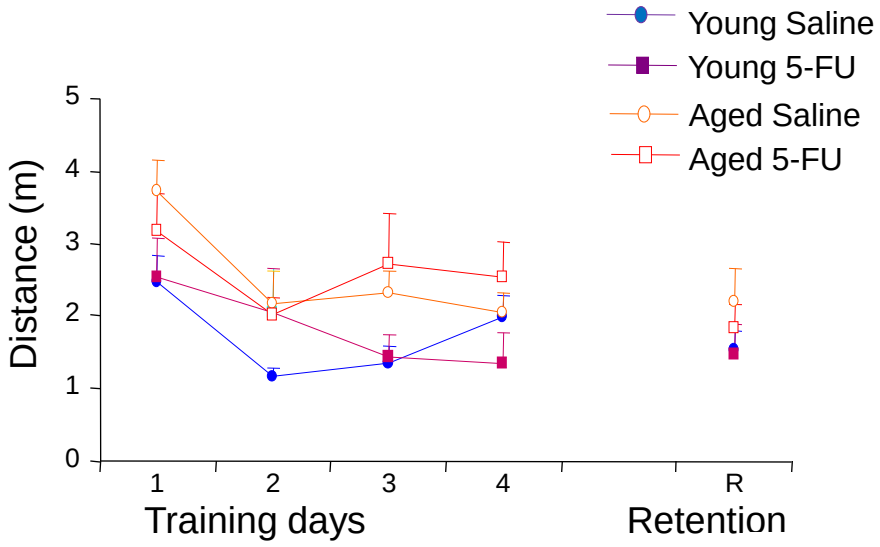




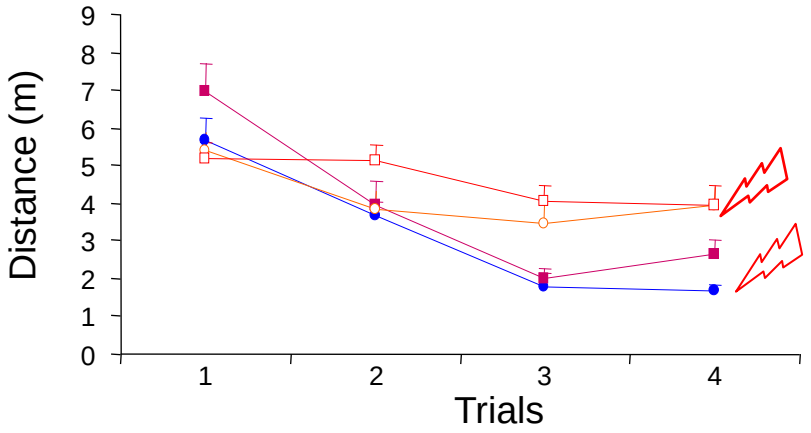
Transfer test

Spatial learning and memory

Learning plasticity



Treatment effect: *



Effects of 5-FU in learning plasticity in young and aged mice

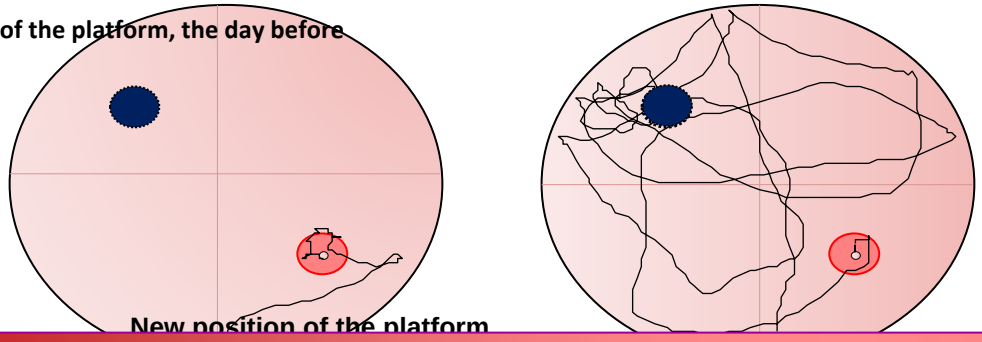
Dubois et al, Neuropharmacology, 2014a

Occupancy plots : Strategy to find the platform!

Young Saline

Young Saline

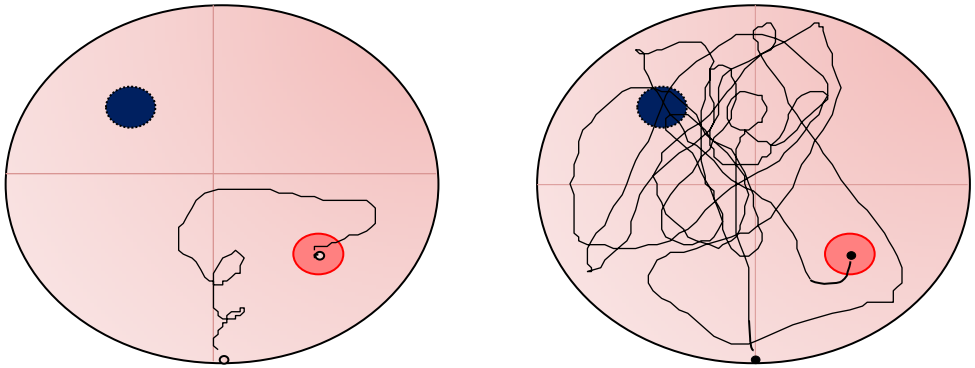
Young 5-FU



5-FU alters behavioral flexibility: Adaptation to novelty

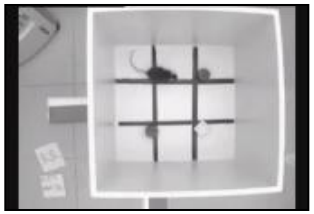
Aged Saline

Aged 5-FU

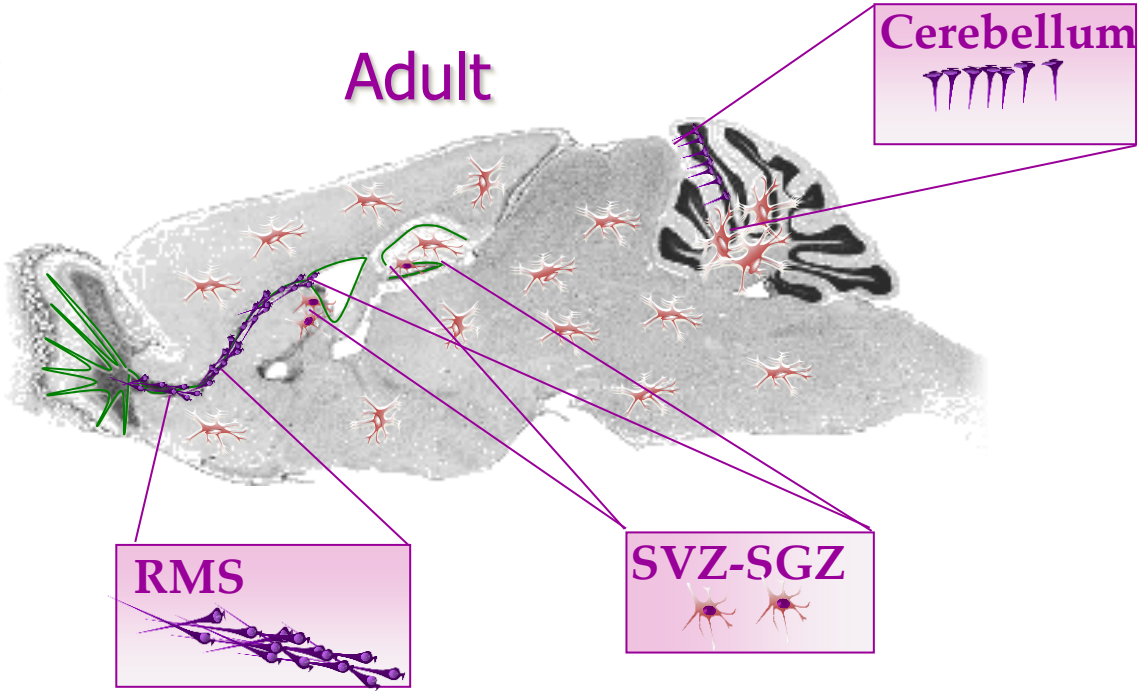


Chemotherapy alters neural progenitor division?

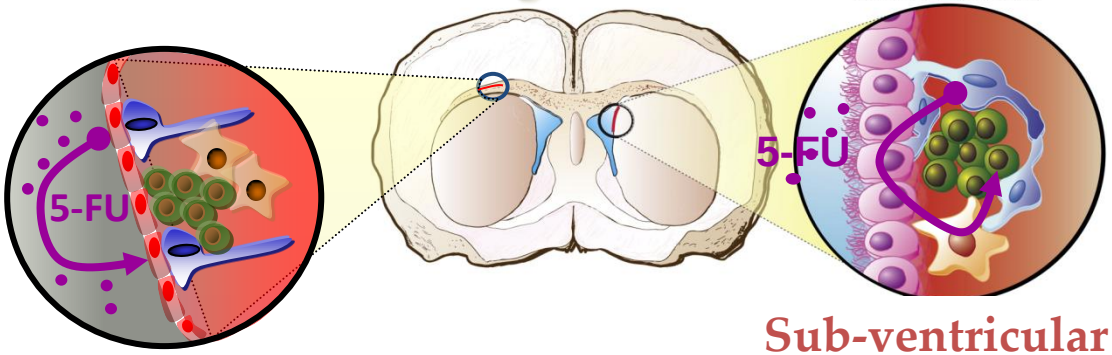
Hippocampus and prefrontal cortex



Adult



Neurogenic niches



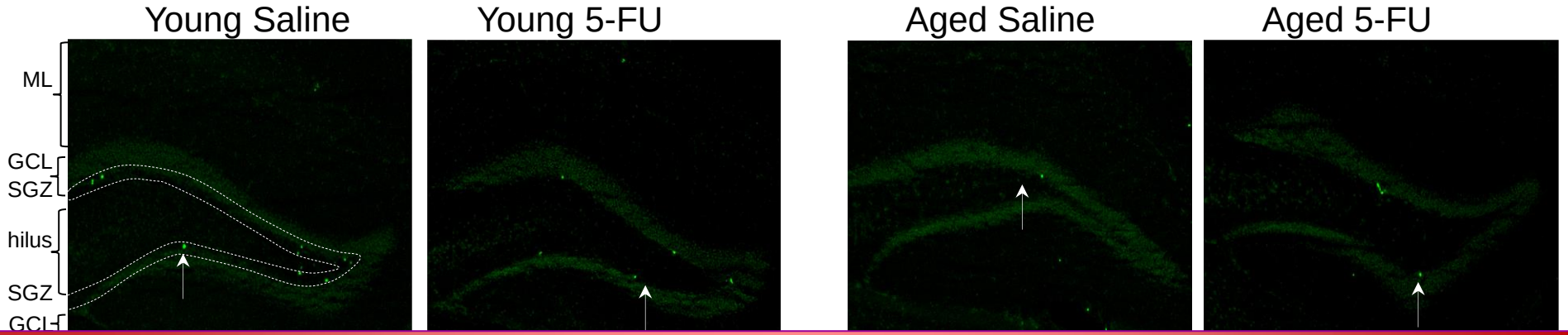
Sub-granular zone

Sub-ventricular zone

5-FU and hippocampal cell proliferation in young mice

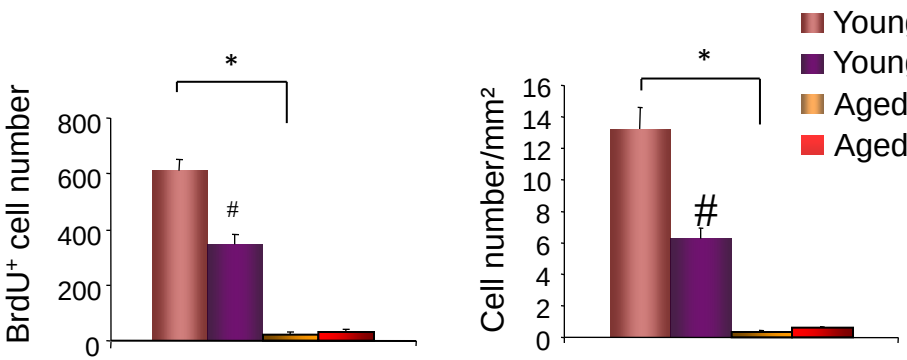
Dubois et al, Neuropharmacology, 2014a

In vivo proliferating cells in the hippocampus

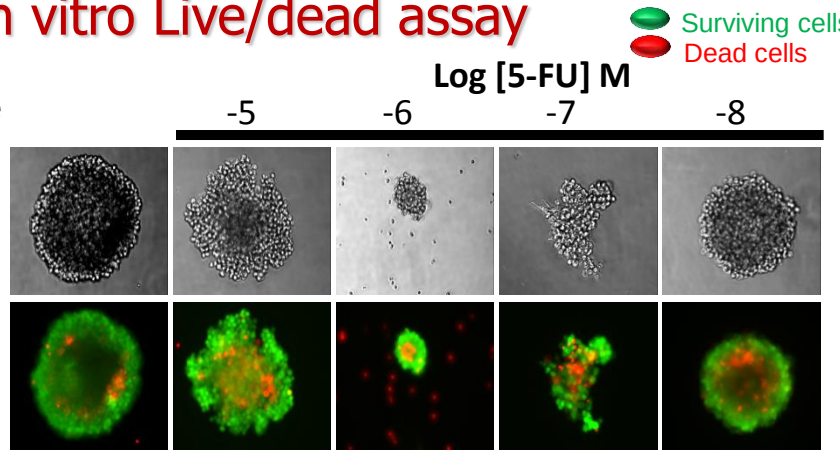


Specific link between behavioral flexibility and neurogenesis?

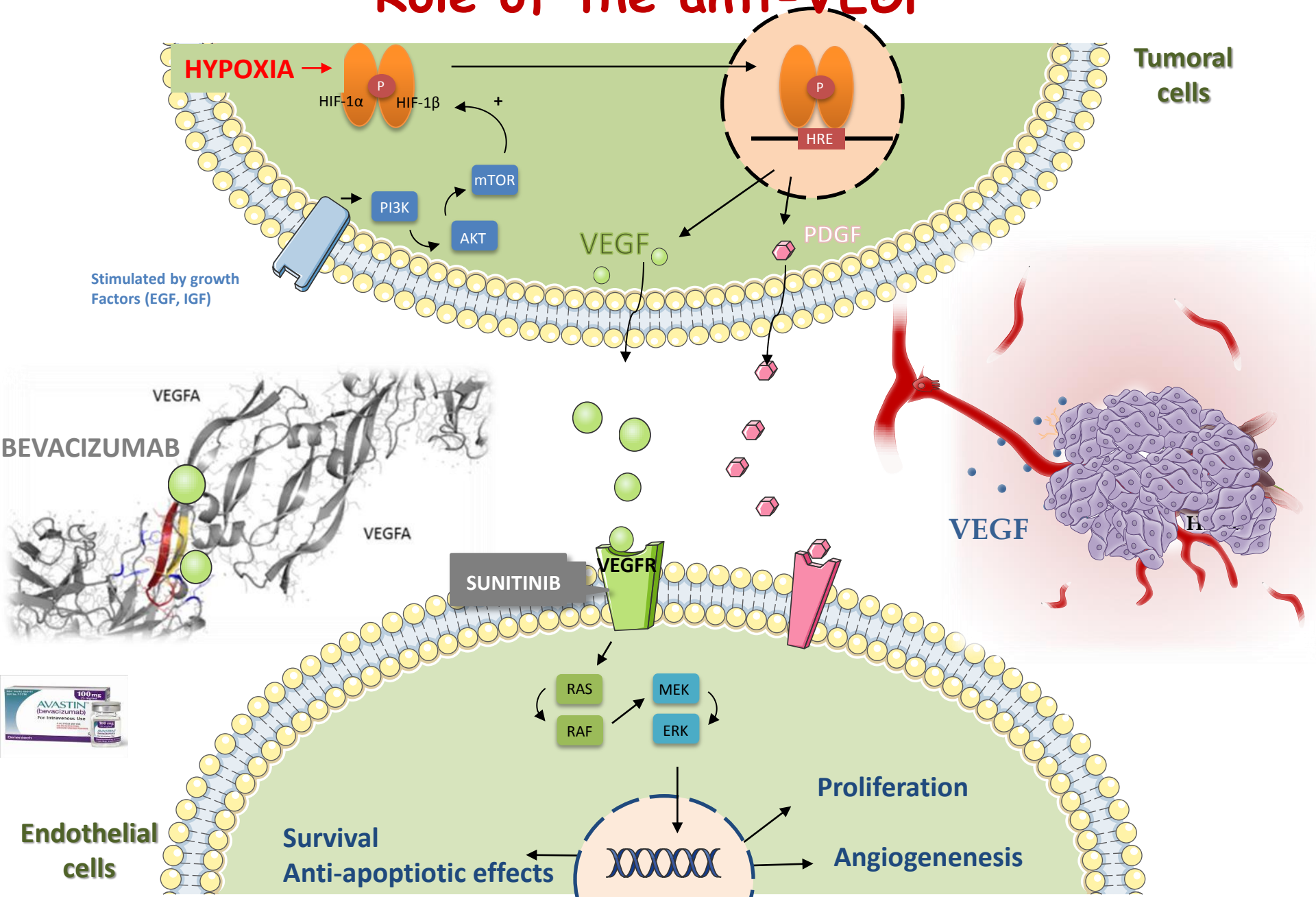
Subgranular zone of the hippocampus



In vitro Live/dead assay



Does targeted therapy also induce chemofog? Role of the anti-VEGF



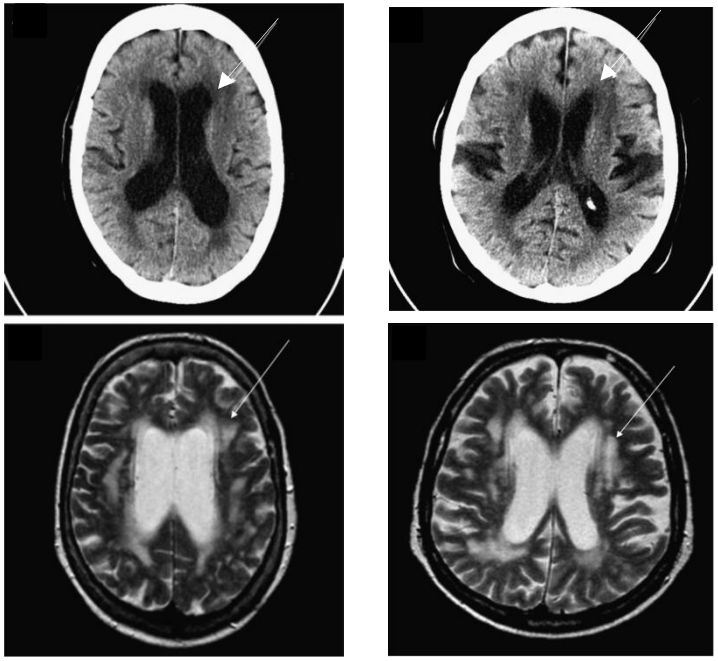
CNS effects of anti-VEGF: Leuco-encephalopathy in peripheral cancers

Renal cancer

Sunitinib
(50 mg/day)

Pet-Scan

MRI



Van Der Veldt *et al.*, 2007

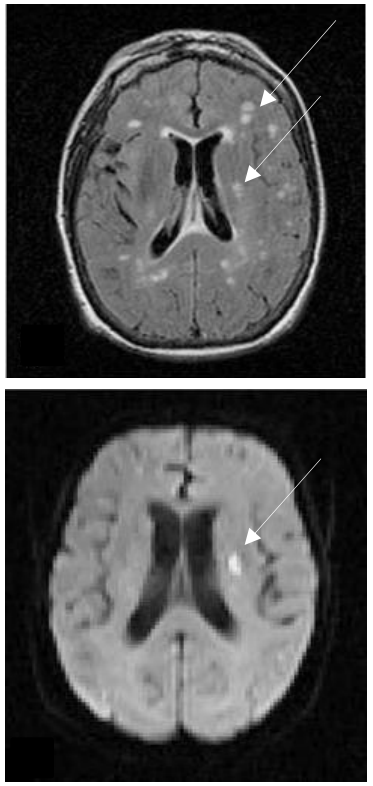
- **Verbal deficits**
- **Confusion**
- **Temporal Dysorientation**
- **Motor (walking) troubles**
- **Letargy**
- **Hypokinesia**
- **Cognitive troubles**

Breast cancer

Bevacizumab
(15 mg/m2/day)

FLAIR

MRI diffusion



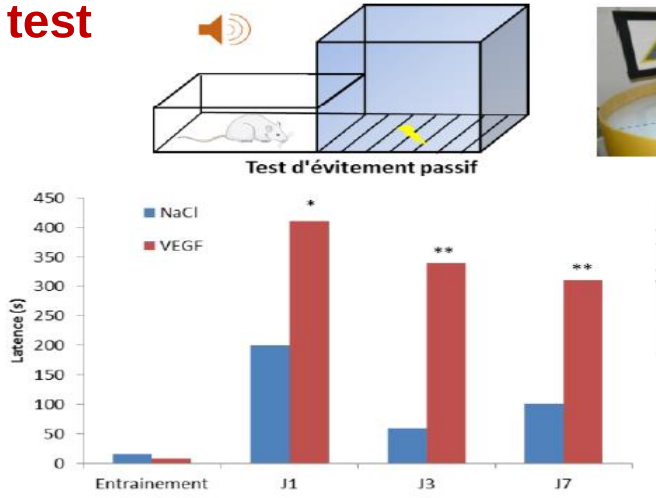
Kleinschimdt DeMasters *et al.*, 2009

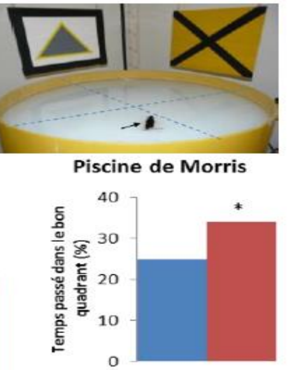
- **Dysorientation**
- **Attentional deficits**
- **Deficits of short-term memory**
- **Motor (Walking) troubles**

Major effects of VEGF on cognition: Information from animal models

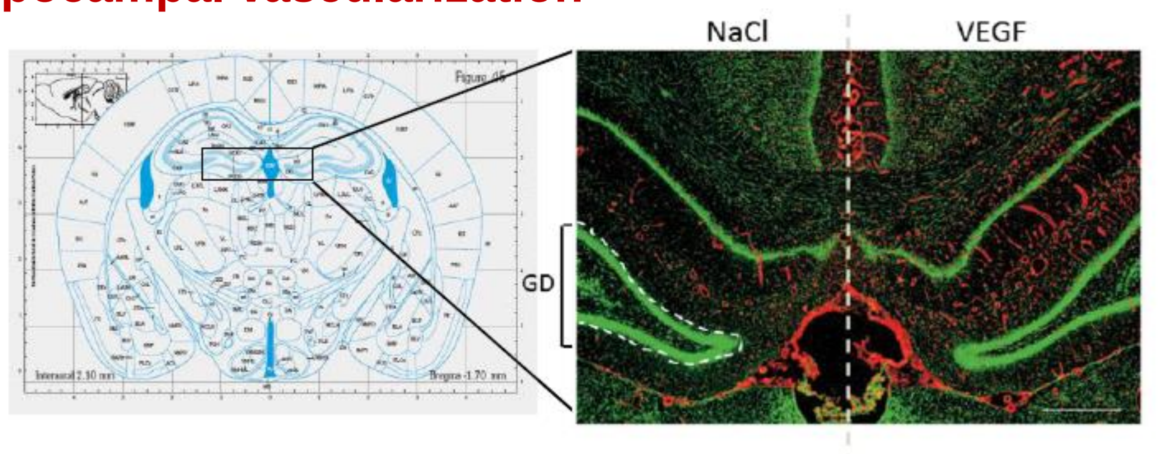
Behavioral tests: passive avoidance test and Morris Water maze

VEGF injected into the brain parenchyma

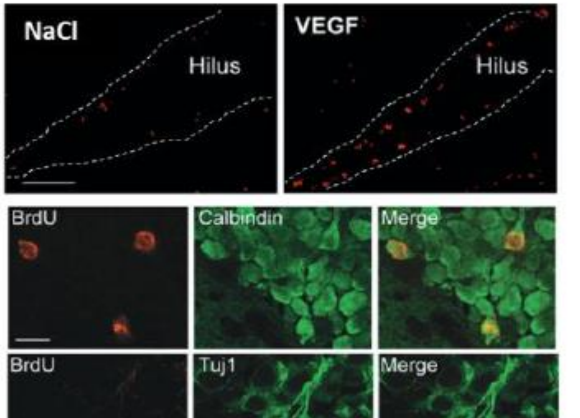




Hippocampal vascularization



Neurogenesis



VEGF on memory, neurogenesis and brain vascularization

Direct impact of anti-VEGF cancer therapy on cognitive functions and brain plasticity?

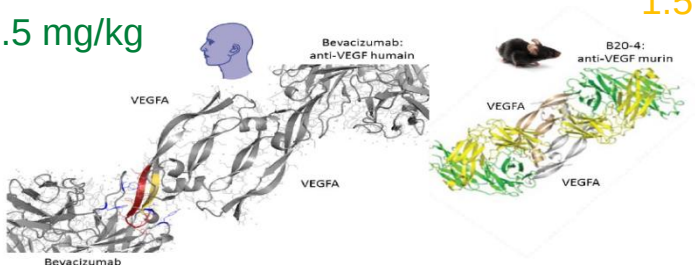
Saline

Bevacizumab

1.5 mg/kg

B-20.4.1.1

1.5 mg/kg



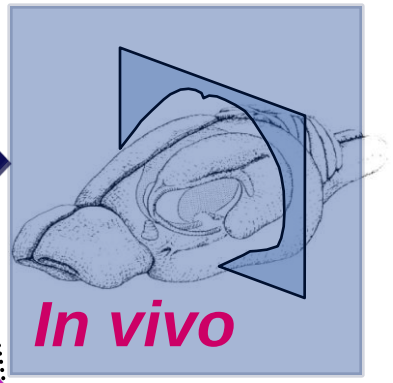
➔ MTA with Genentech/Roche

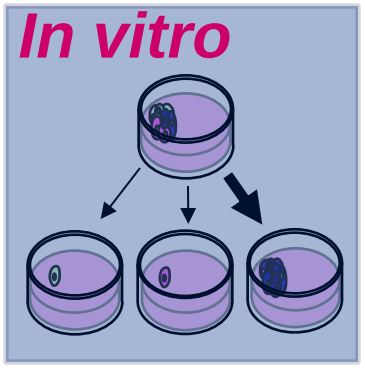
➔ MTA with Genentech/Roche

Mice arrival

J0 J4 J8 J12 J16 J20 J26

IP injections





Anxiety

Depressive-like

Spatial learning

Spatial memory

Flexibility

Spontaneous activity

Exploration

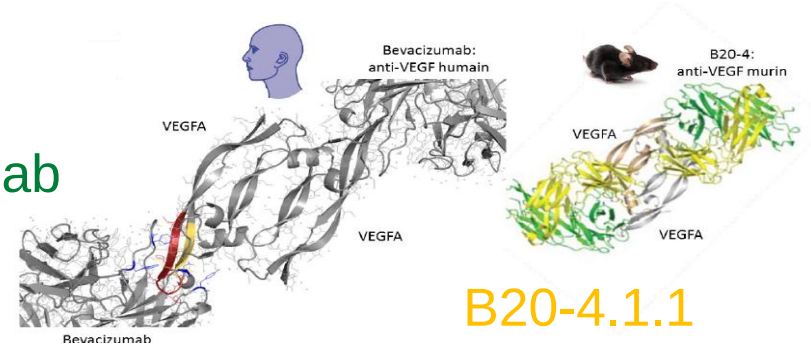
Reactivity to novelty

BrdU

Weight evolution during treatment with anti-VEGF

Dubois et al, submitted

Bevacizumab



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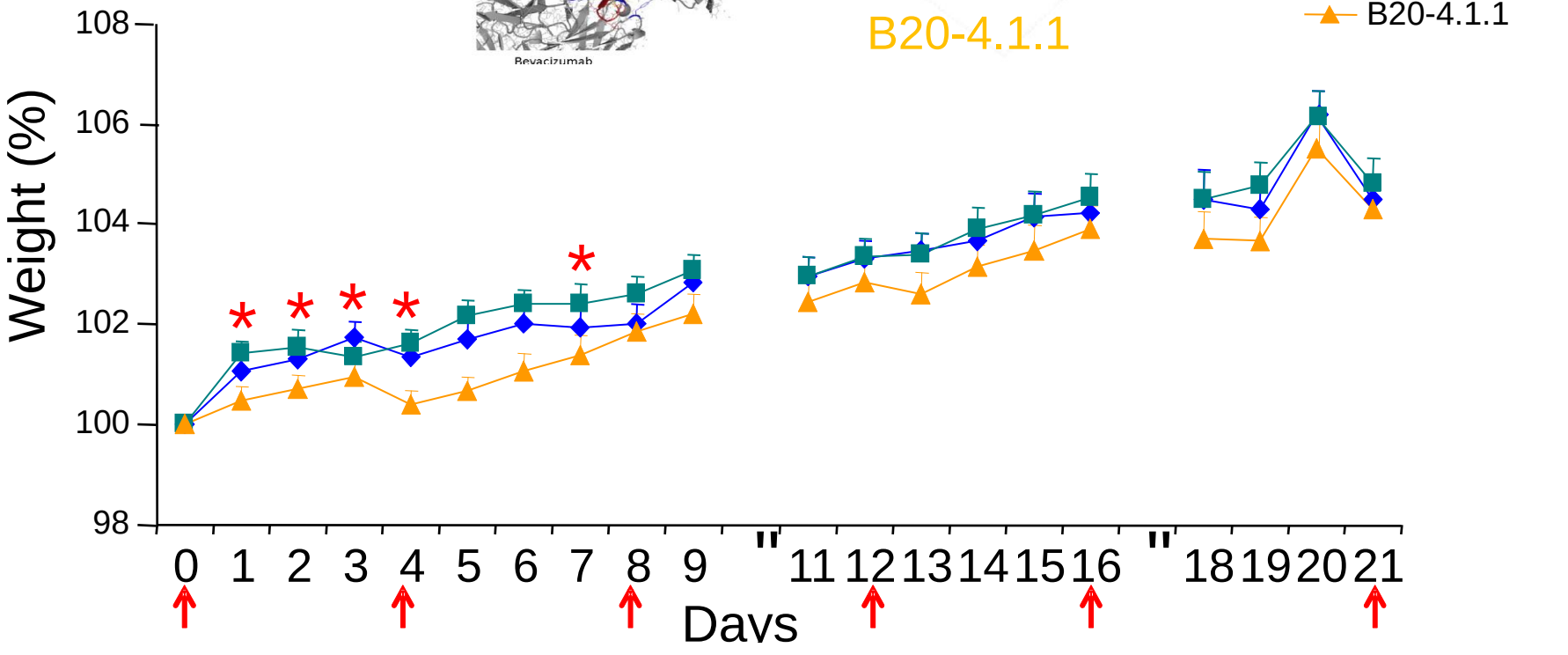
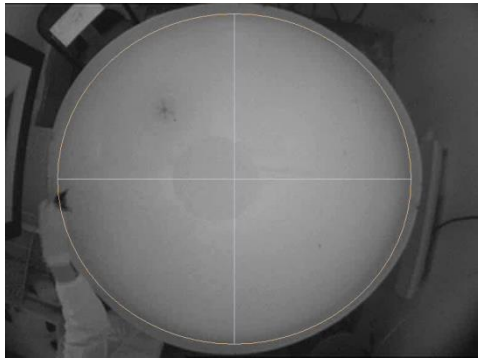


Effect of anti-VEGF on spatial learning and memory

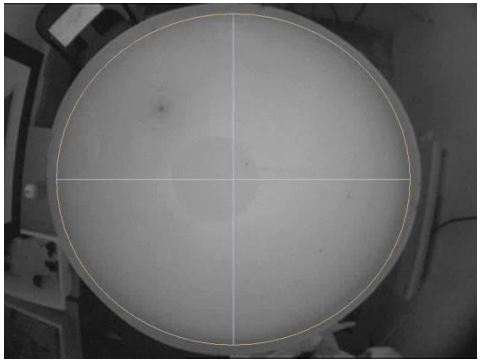
The Morris water maze test

Spatial learning and memory

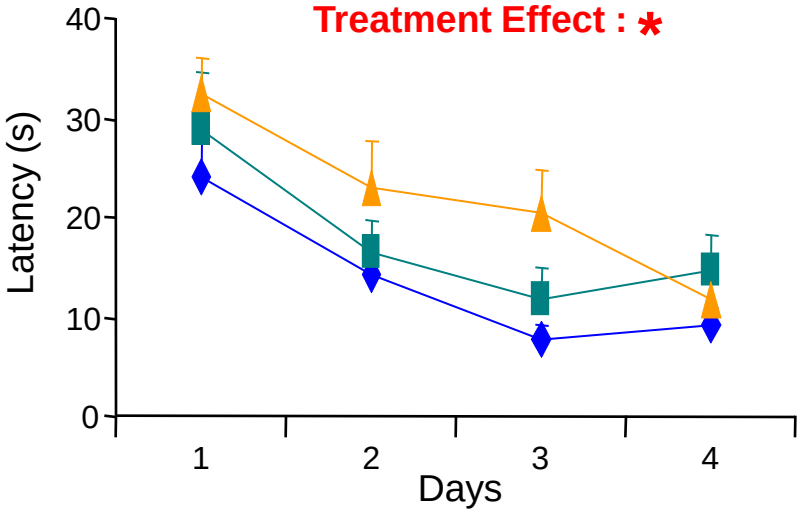
1st Day

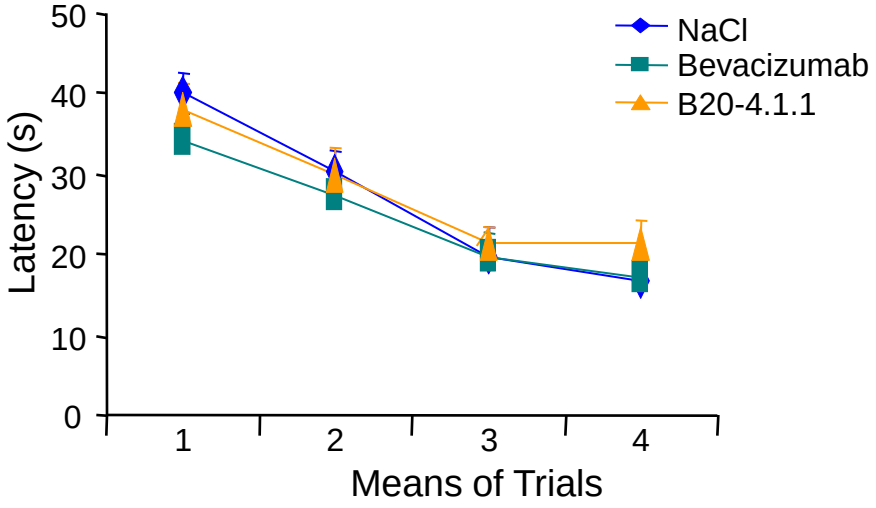


4th Day



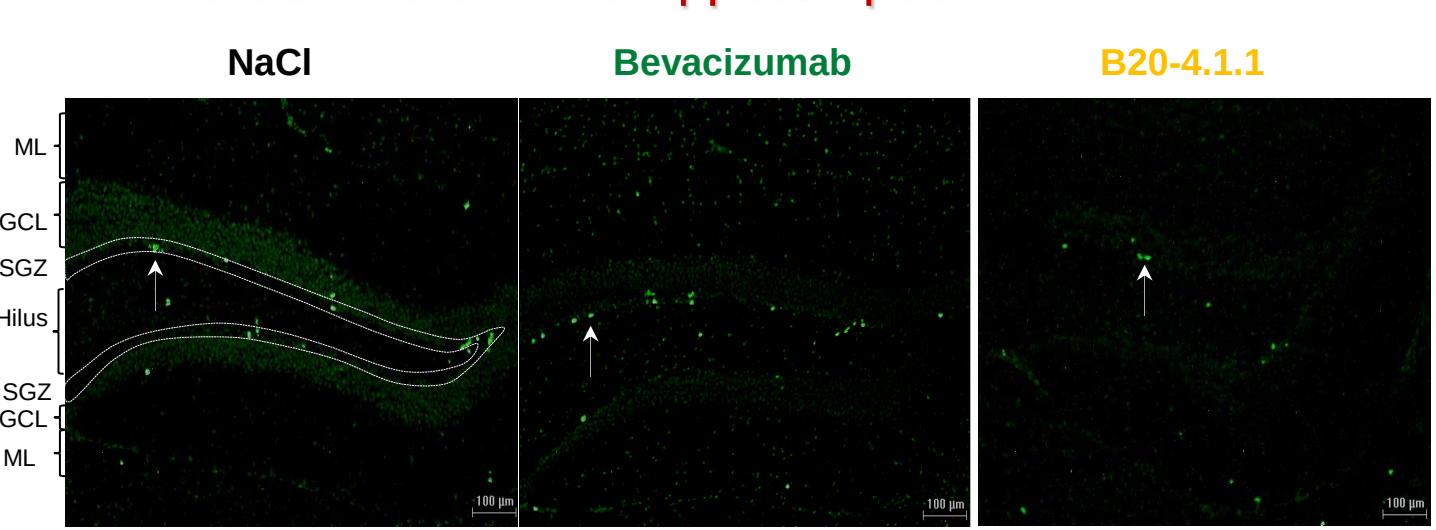
Behavioral flexibility

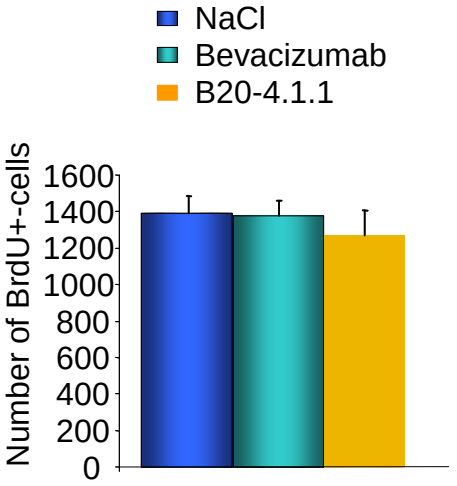




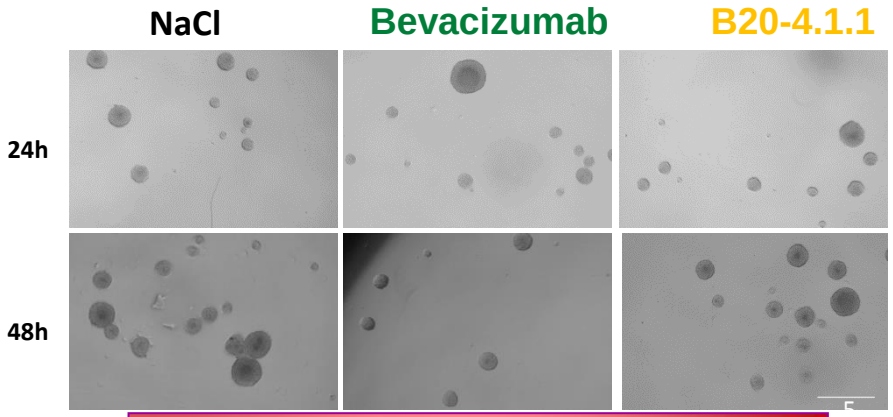
Anti-VEGF and hippocampal cell proliferation?

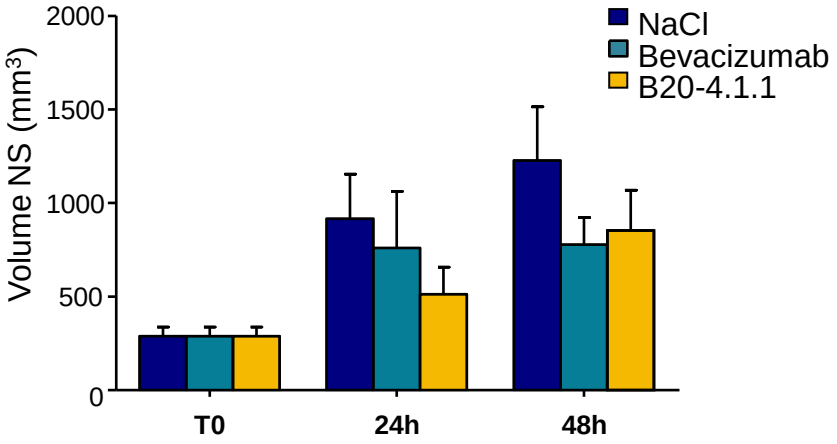
In vivo BrdU+ cells in the hippocampus





In vitro Neural stem cells

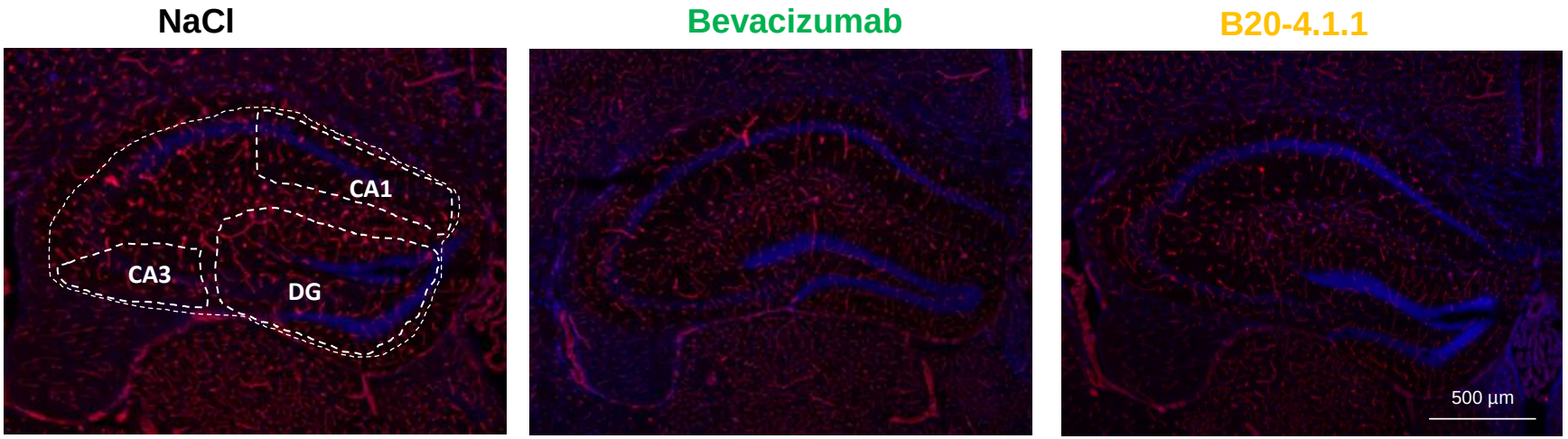


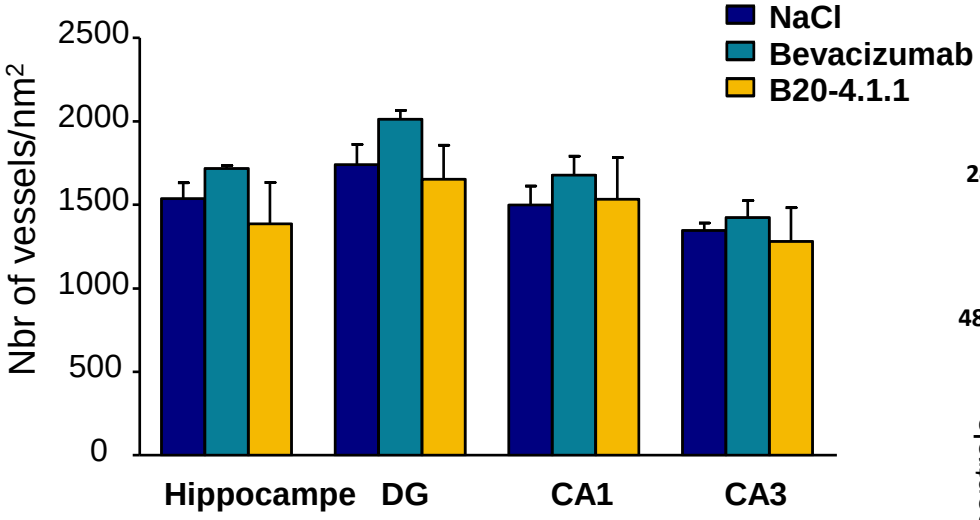


NO significant effect

Anti-VEGF on hippocampal vascularization

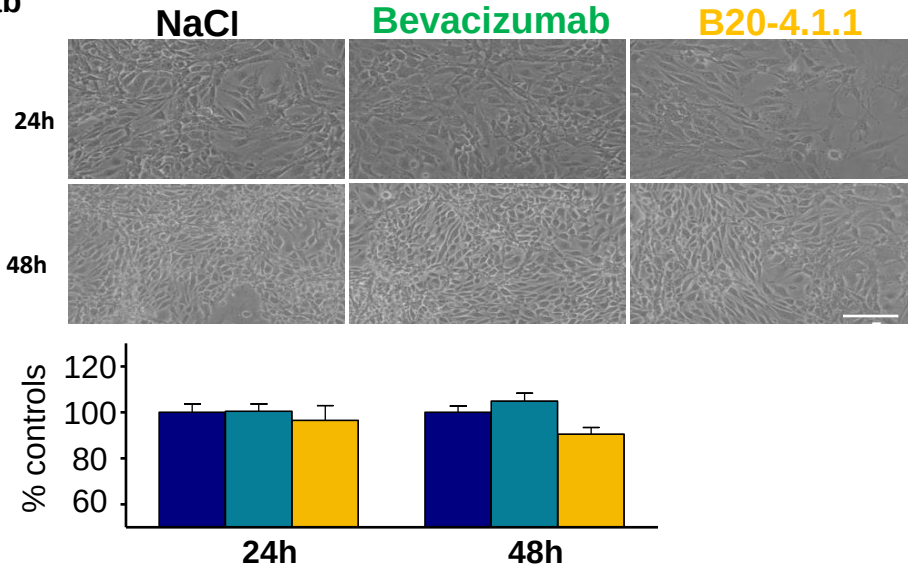
In vivo Collagen IV^{+}-components in the hippocampus



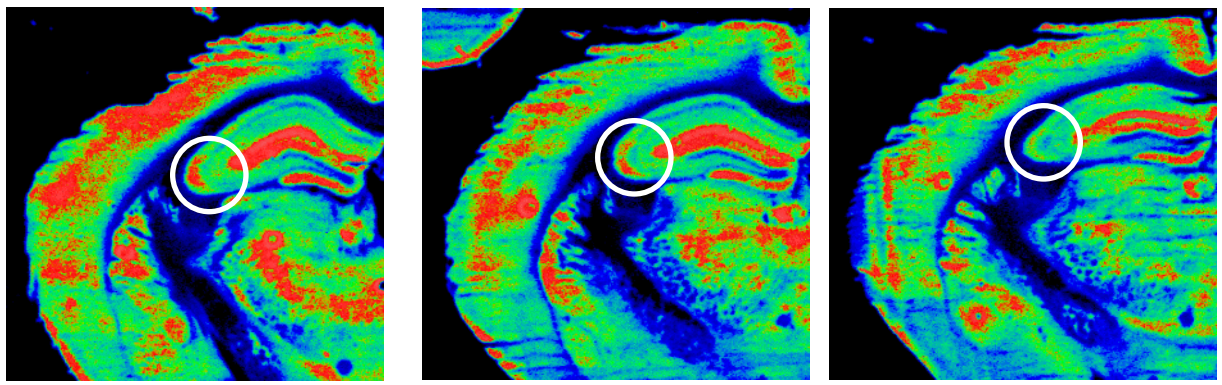


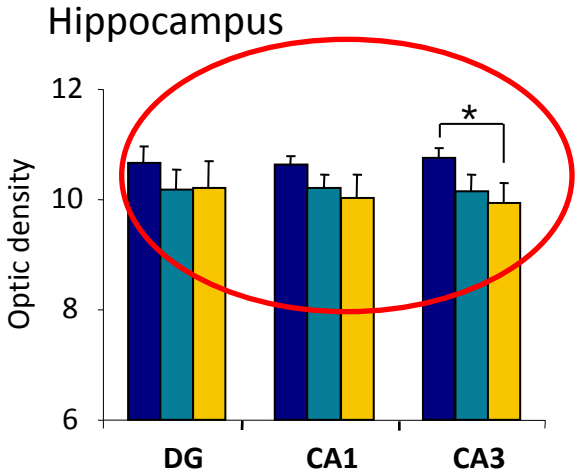
NO significant effect

In vitro endothelial cell proliferation

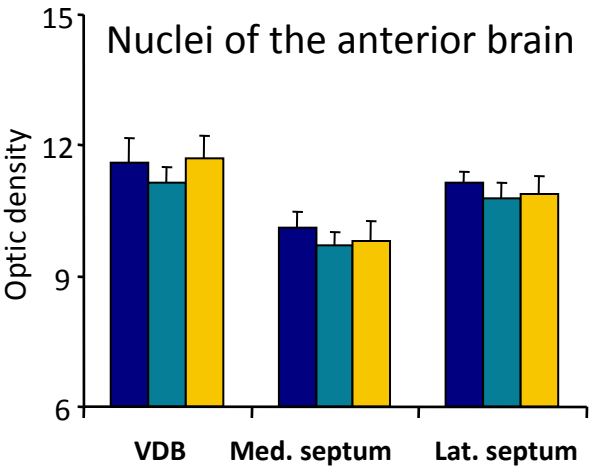


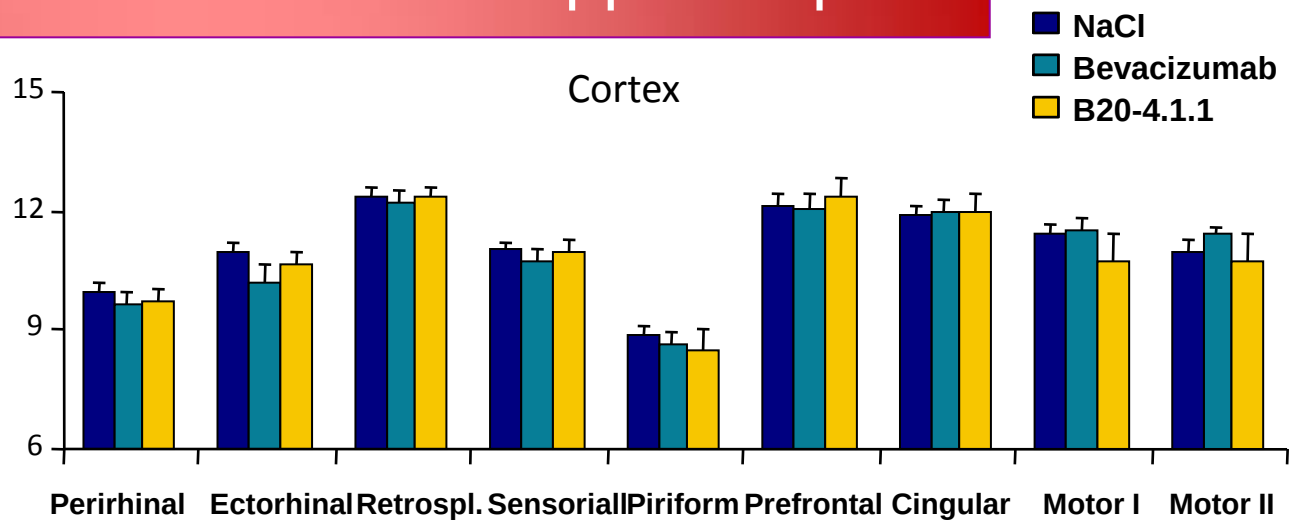
Brain metabolic activity: cytochrome oxidase





Selective alteration of the CA3 area hippocampus

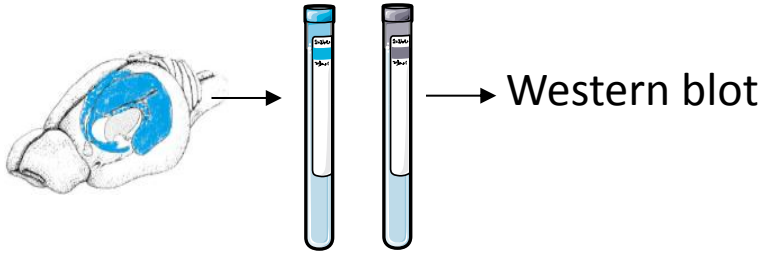


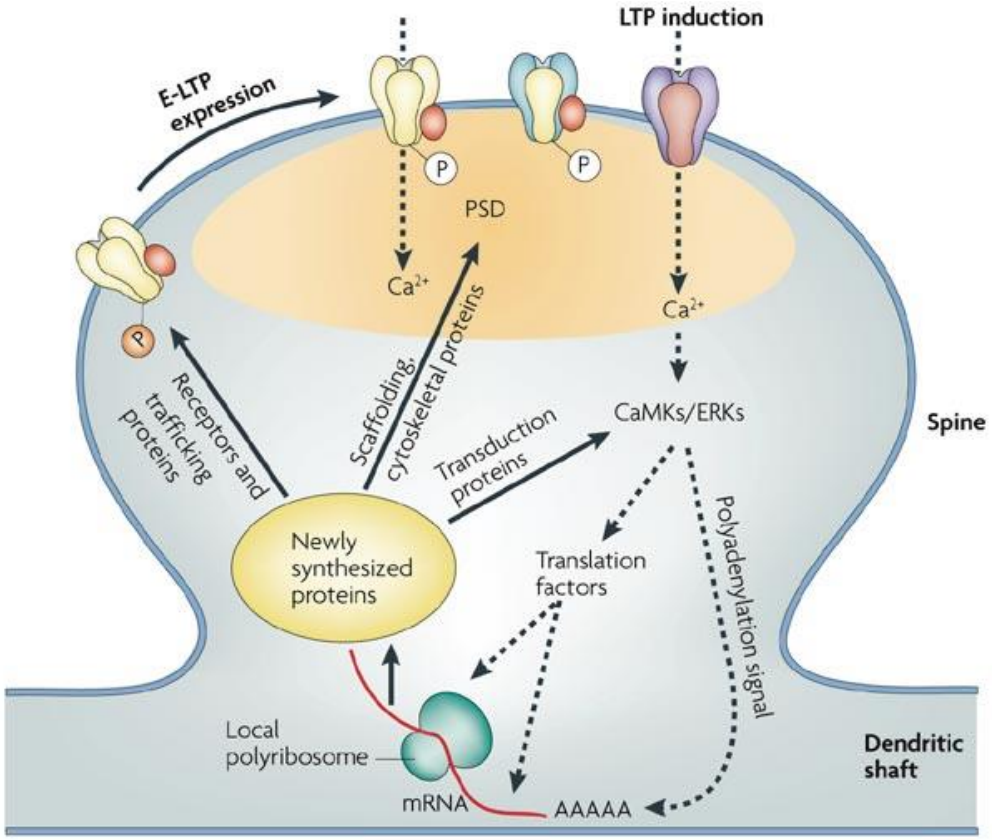


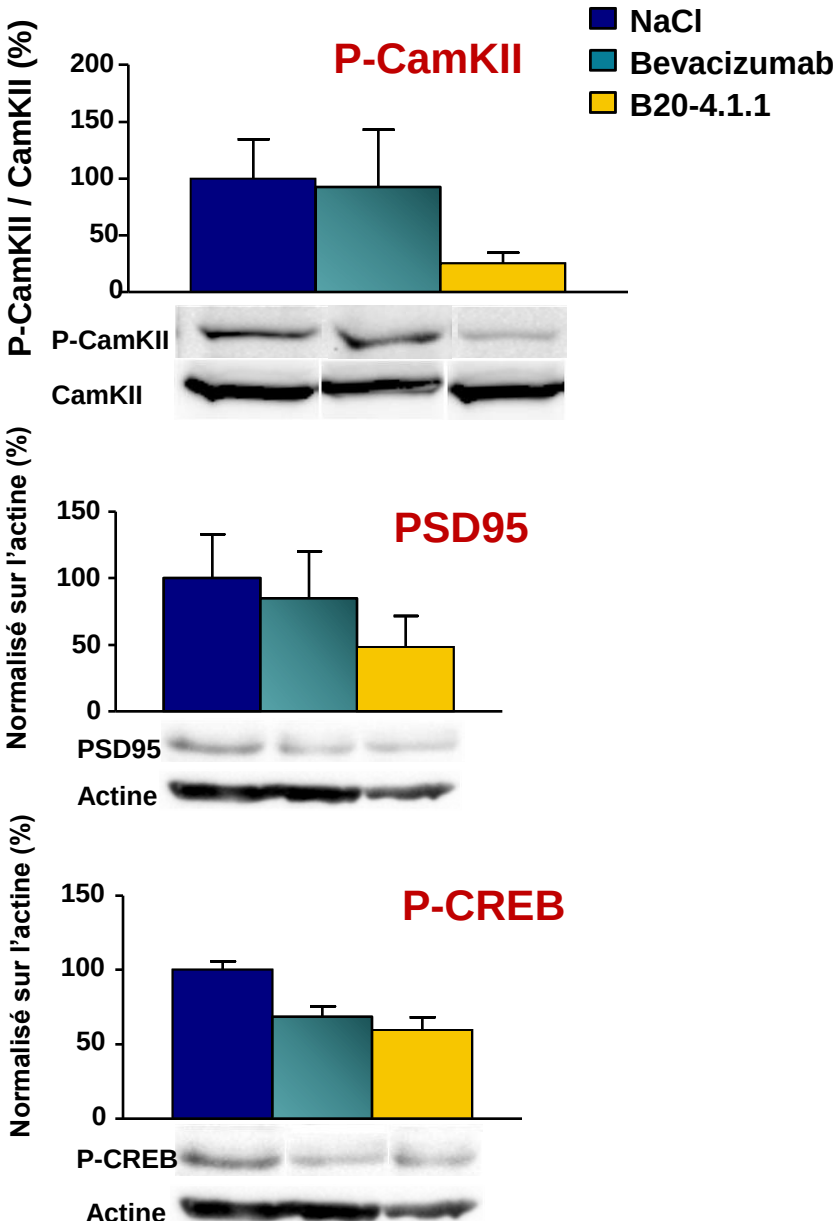
DG, dentate gyrus;
VDB, nucleus of the vertical diagonal band of Broca;
med., median ;
lat., lateral

Retrospl., retrosplenial cortex ;
Prefrontal, prefrontal median cortex (prelimbic – infralimbic);
Motor I, primary motor cortex;
Motor II, secondary motor cortex

CA3 and long-term potentiation (LTP)- learning







In conclusion

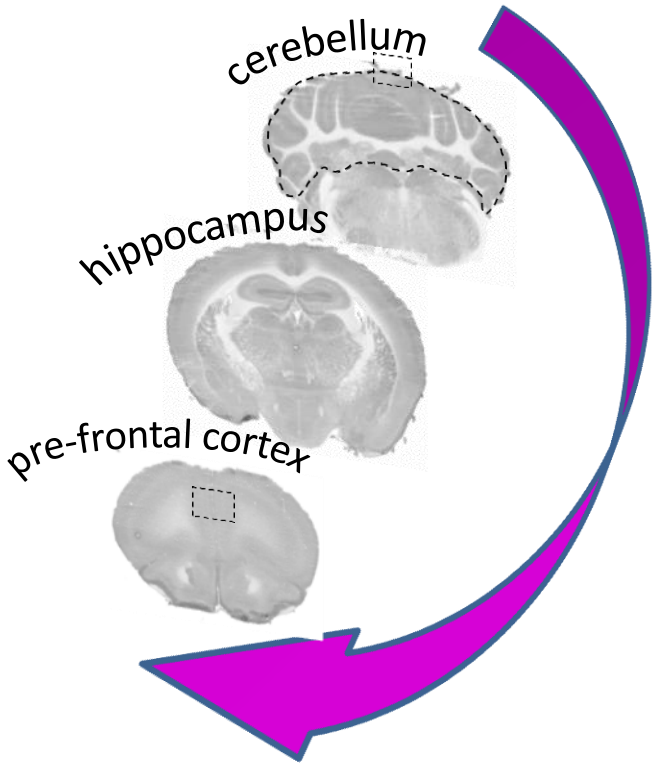
- **Chemotherapy**

Behavioral flexibility and decrease of hippocampal cell proliferation

- **Bevacizumab**

Learning memory and long-term potentiation

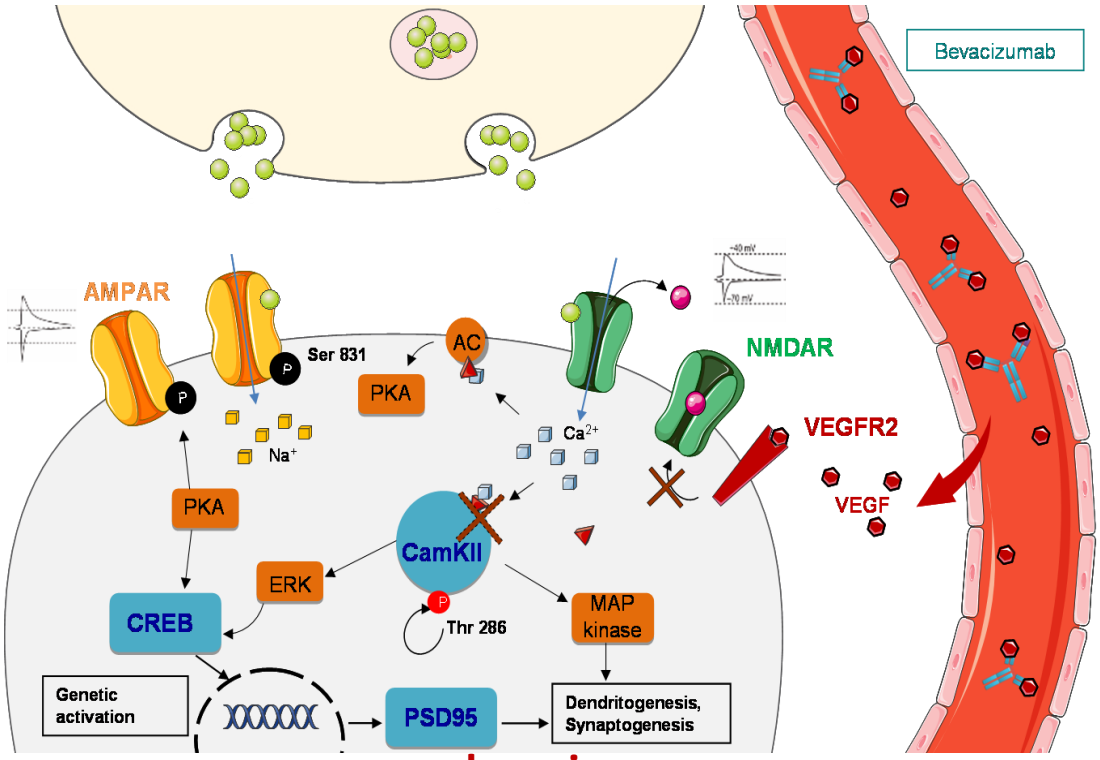
neurogenesis



Behavioral flexibility

hippocampus

Long-term potentiation



learning

International platform « Cancer and Cognition »

Our goal: rely on our multidisciplinary expertise when assessing the influence of cancer and cancer treatments on patient cognitive function.

A daunting challenge: Oncology patient management has improved in the last few years. There have never been so many drugs for personalized treatments. New treatments are often taken by the oral route and concern an increasing number of patients.
The impact of these therapies on patient care is therefore a key issue. Patient complaints (both during and after treatment) and studies confirm the clinical reality represented by cognitive issues and how toxic chemo-therapy is to the brain, even in the absence of brain tumors.
Initial results tend to demonstrate that new targeted therapies - angiogenic inhibitors in particular - can also affect cognitive functions.

"Today, we can model any treatment scenario, from animal models to patients, and help identify effective prevention strategies."

Pr Florence Joly, M.D., Ph.D., Medical Oncologist
Supervisor of the Cancer and Cognition Platform

A remarkable undertaking

The Cancer and Cognition platform consortium engages the different sites of the Cancéropôle Nord-Ouest as well as a number of partners.

Cancéropôle Nord-Ouest

Inserm Unit U982 "Neuronal and Neuroendocrine differentiation and communication", Rouen
Inserm Unit U1086 "Cancer and Prevention", Caen
Inserm Unit U1077 "Neuropsychology and functional neuro-anatomy of the human memory", Caen
Centre François Baclesse / CHU, Caen
Centre Henri Becquerel /CHU, Rouen
Institut Jules Bordet, Bruxelles
CHU, Amiens

Partnerships *(teams, groups, drug companies)*

Special partnerships have been established with teams specialized on brain tumors

UMR 6301 CNRS-CEA-UCBN "Therapeutic Strategies and Imaging for Cerebral and Tumour Pathologie (ISTCT)", Caen

Hôpital de la Pitié Salpêtrière, Paris
Ecole Normale Supérieure, Cachan
Hôpital du Val de Grace, Paris
GREC-Onco
OncoNeurotox, Paris
UMR 8257 COGNAC G, Paris
PSY-NCA, Rouen

Partners

Gustave Roussy, Paris
Centre Antoine Lacassagne, Nice
Centre Paul Strauss, Strasbourg
CHU, Strasbourg

Platforms

Cyceron, Caen
Pissaro, Rouen
Primacen, Rouen
SCAC, Rouen

Task Forces

ICCTF
EORTC

Oncology intergroups

Unicancer
Groupe GINECO
EANO
ANOCEF
SNLF

Physicians, oncology intergroups, researchers and drug companies.

Contact us: www.canceretcognition.fr

Plateforme
Cancer et Cognition
Cancéropôle Nord Ouest

Cancer and Cognition

Cancer and cognition is the first French platform for studying and assessing the impact of cancer and its treatments on cognitive functions.

Coordinated by the Cancéropôle Nord-Ouest

Contact us:
www.canceretcognition.fr

International platform « Cancer and Cognition »

Created by the Cancéropôle Nord-Ouest, the Cancer and Cognition platform targets French networks in Cancerology, oncology intergroups, academics researchers and drug companies.

Our consortium, the only one of its kind, includes expert oncologists, neuropsychologists, neuro-imaging specialists and neurobiologists.

Pioneer

Since 2010, our teams have been rising to the challenge of putting the cognitive impairment associated with cancer and cancer treatments in the scientific spotlight. Our model applies an innovative approach that associates clinical studies, neuropsychology, neuro-imaging, animal models and biostatistics.

At your service

For the drug industry

We develop partnerships by ensuring the use of preclinical models. We advise you on the tools to use for ancillary studies and help you to design and analyze studies on cognitive impairment.

For oncology intergroups

We offer dedicated cognition studies in addition to your clinical studies. We also offer tests for preclinical animal studies.

An innovative approach using 4 complementary areas of expertises

Clinical *Pr F.Joly*

Would you like to know the impact of drugs, medicine or treatment strategies on cognitive functions during your trials?

Our services:

- **Evaluation of cognitive impairment** during clinical trials
- **Design of clinical studies** on cognitive impairment
- **Studies among targeted groups** such as elderly patients
- **Brain imaging** (MRI, PETScan)

Preclinical and Biomarkers *Dr H. Castel*

Do you think that animal modelling is an innovative tool for assessing the neurobiological mechanisms of cancer and cancer therapies?

Our services:

- **Detection of biomarkers** in animal models and patients
- **Design of protocols for behavioural studies** in animals to determine the mechanisms of new therapies
- **Evaluation of parameters** that could lead to cognitive impairment, assistance in understanding the physiopathology of neurological changes in patients...
- **Brain imaging in animal models**

Neuropsychology *I. Léger and Dr B. Giffard*

Do you think it is essential to have integrative neuropsychology tools and to understand the functional abnormalities as well as the anatomical effects of cancer and cancer treatments?

Our services:

- **Testing: standardised cognitive** testing that is adapted to a given situation
- **Functional imaging:** examination of functional signs of cognitive impairment using fMRI and PET Scan, identification of pathophysiological processes, study of relationships between different types of brain impairment...

Biostatistics *Dr N. Heutte*

In your studies, do you wish to use a methodology to assess neuropsychological functions?
Take advantage of our dedicated biostatistics expertise

Our services:

- **Support for and/or drafting of statistical methodology** in study protocols according the approved study design
- **Assistance in submitting projects** for call of proposals
- **Support for and/or writing of statistical analysis plans and results interpretation**

Contact us: www.canceretcognition.fr

http://www.cancerandcognition.com
helene.castel@univ-rouen.fr

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Aknowledgments

Astrocyte and Vascular Niche team

Permanent staff members

Dr Hélène CASTEL (CR1 Inserm)[1]
Dr M-Christine TONON (DR2 Inserm)[2]
Pr Pierrick GANDOLFO (PU)[3]
Dr Fabrice MORIN (MCU)[4]
Pr François PROUST (PU-PH)[5]
Dr Vincent COMPÈRE (PU-PH)[6]
Dr Emmanuel GERARDIN (PU-PH)[7]
Dr Laurence DESRUES (IRE CNRS)[8]

Postdoctoral fellows

Dr Céline Lecointre (INCA)
Dr Martine DUBOIS[9] (Novartis)
Dr Mohamad EL-AMKI[10] (Haute-Normandie; Seinari)
Dr Pierre-Olivier GUICHET[11] (Région Haute-Normandie)

CDD

Nicolas PERZO[12] (IE Inserm, PeReNe Network)

Graduate students

Pierre-Mikael COLY[13] (Ministry Allocation)
Jane-Eileen JOUBERT[14] (Région Haute-Normandie Allocation)
Vadim LE JONCOUR[15] (ATER)

Master students

Antoine ARRICHIELLO[16]
Thomas CLAVIER[17]
Benjamin QUIGNON[18]