NAME	Current positions
VIVIEN, Denis March 4, 1966	➢ Professor of Cell Biology (Prof. Excellence Class 1 - CNU 44.3), Univ. Caen-Normandy, ➢ University Hospital Practitioner in Cell Biology (PUPH, PhD), Caen Hospital, Head of the Center for Biological Ressources (CRB-InnovaBIO) and Scientific Advisor Guichet for Innovation and Partnerships (CHU Caen). ➢ Senior Member IUF "Institut Universitaire de France" (2009) ➢ Director, INSERM UMR_S U1237 "Physiopathology and Imaging of Neurological Disorders" (phind.fr) (73 people) ➢ Scientific Director Blood and Brain @ Caen-Normandie Institute ➢ Scientific Director of the European Platform for Experimental Stroke (ESRP, esrp.fr), granted IBISA.

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Paris XI, Orsay University (Paris, France)	PhD	1992	Molecular and cell biology
Sloan Kettering Howard Hughes Institute (New York, U.S.)	Post-doctoral	1993-94	Cancer research/ molecular biology
Caen Normandy University (France)	HDR	1997	Neurosciences

Positions:

1993-94 - Research Associate, Sloan Kettering Cancer Center, Howard Hughes Institute, New York.
1995-01 - Assistant professor in molecular biology, Université de Caen Normandy
2001- - Full Professor in Neurosciences, Université de Caen Normandy
2004-05 - Vice-Director of UMR CNRS 6185
2005-08 - Director INSERM-Avenir "tPA in the working brain" award
2008-2017 - Director, INSERM UMR_S U919 "serine proteases and pathophysiology of the neurovascular unit"
2014- - Coordinator of the team FRM "Immunotherapy for Neurological Diseases" funded "Fondation pour la Recherche Medicale"
2017- - Director INSERM UMR-S PhIND "Physiopathology and Imaging of Neurological Disorders" (phind.fr), leader Team 1 "tPA and Neurovascular Disorders"
- Full Professor – University Hospital Practitioner in Cell Biology (PUPH, PhD), CNU 44.3, Caen University Hospital.
- Department of Clinical Research, head of the Center for Biological Ressources (CRB-InnovaBIO), Caen University Hospital and Scientific advisor Guichet Innovations and Partnerships, Caen University Hospital.
- Scientific Director of the Platform for Experimental Stroke Research (ESRP)
2019- - Scientific Director Blood and Brain @ Caen-Normandie Institute

Awards:

- Senior member of the Institut Universitaire de France (2009)
- Award: "medical innovation" (Fondation de France-Matmut), 2011
- Schlumberger Foundation prize for an innovative teaching aid called «Cérébro», 2012

- FRM group" by the French Medical Research Foundation, 2014-2017
- Rose LAMARCA Award for advance in translational research, 2016

Production

Results found:	210
Sum of the Times Cited:	9231
Average Citations per Item:	43,96
h-index:	**49**

Extraction SIGAPS te concernant 2016 – 2020.

Période : 2016 - 2020

Année	Total	A	B	C	D	E	NC
	Score						
2016	18	9	4	1	2	1	1
	276						
2017	20	9	4	3	2	1	1
	212						
2018	20	5	6	1	1	2	5
	153						
2019	10	4	3	3	0	0	0
	122						
2020	20	8	10	1	0	0	1
	259						
Total	88	35	27	9	5	4	8
	1022						

Previous experience in collaborative research

2005-10 : - Partner in the European consortium "Diagnosis In Molecular Imaging", FP6
2008-13 : - Group leader in the European consortium "Eurostroke", FP7
2008-13: - Workpackage leader in the European consortium "ARISE", FP7
2008-13: - Coordinator of the European consortium ERANET-Neuron "Protea", FP7
2010-19: - 12 ANR contracts
2013-17: - Partner European Marie Curie International Training Network "NeuroInflammation, FP7
- Partner of « MULTIPARTt » EU network, FP7
2015-20: - Team partner H2020, Medit-Ageing
2016-20: - Co-PI Netherland Stroke Program, CONTRAST
2016-20: - Partner RHU Marvellous and RHU on small vessels diseases (RHU: Hospitalo-Universitary Network, PIA-2)
2020-23. - Partner H2020 program, NeuroAtlantic, An Atlantic innovation platform on diagnosis and treatment of neurological diseases and aging - Partner, H2020, International Marie Curie Training Network, ENTRAIN, Neuroinflammation.
2020-25 - Partner RHU, "Booster" Acute phase of stroke, including a clinical trial on N-Acetyl-Cysteine (NAC), a program initiated from our own fundamental research (Circulation, 2017).
2020-25 - Partner H2020, Euronanomed III, PLATMED, Improving fibrinolysis for stroke.

Committee member:

2001-07 - Member of the CSS 1 « scientific council » INSERM, Neurosciences, Neurologie et Psychiatrie
2007-11 - section 69 (neurosciences) of the Conseil National des Universités (CNU)
2007-12 - section 1 "neurosciences, neurologie et neuro-psychiatrie" INSERM, CSS1
2012-16 - President of section 69 (neurosciences) of Conseil National des Universités (CNU)
2015-17 - Vice-president of the scientific committee of the new foundation "Recherche AVC", hosted by the - Fondation pour la Recherche Medicale (FRM)
2017-18 - Co-coordinator Scientific Pole Biology and Chemistry of Caen-Normandie-University
2013-19 - Vice-president (2 years) and President of the Committee for Biomedical Research and Public Health of the Caen Hospital
2013- - President of the Scientific council of the « Fondation Thèrèse et René Planiol »
2017-19 - President of the scientific committee of the new foundation "Recherche AVC", hosted by the Fondation pour la Recherche Medicale (FRM), Member of the scientific committee of the Fondation "Groupama"
2017- - Expert member of ITMO "Neurosciences, Neurologie and Psychiatrie", AVIESAN
2018- - Editorial: section Editor "Neuroscience" journal
2019- - In responsability of the Axis « Neurosciences », for the HCERES 2022 at the Caen-Normandie Hospital (with Pr O. Martinaud).
2020- - Expert ANR, "CES 14 – Physiologie et physiopathologie

List 5 of your most important publications.

Thiebaut AM, Gauberti M, Ali C, Martinez De Lizarrondo S, **Vivien D,** Yepes M, Roussel BD. The role of plasminogen activators in stroke treatment: fibrinolysis and beyond. **Lancet Neurol. 2018** Dec;17(12):1121-1132. Review. ***IF: 28.8 -*** doi: 10.1016/S1474-4422(18)30323-5

Martinez de Lizarrondo S, Gakuba C, Herbig BA, Repesse Y, Ali C, Denis CV, Lenting P, Touze E, Diamond SL, **Vivien D,** Gauberti M. Potent Thrombolytic Effect of N-Acetylcysteine on Arterial Thrombi. **Circulation**. **2017**, 15;136(7):646-660. ***IF: 23.05*** doi: 10.1161/CIRCULATIONAHA.117.027290

Fournier AP, Martinez de Lizarrondo S, Rateau A, Gerard-Brisou A, J Walder M, F Neurath M, **Vivien D**, Docagne F, Gauberti M. Ultasentitive Molecular Imaging of Mucosal Inflammation Using Leucocyte Mimicking Particles Targeted to MAdCAM-1. **Science Translational Med.** 2020 sous presse. **IF 17.5**

Aurelien Quenault, Sara Martinez de Lizarrondo, Olivier Etard, Maxime Gauberti, Cyrille Orset, Benoît Haelewyn, Helen C. Segal, Peter M. Rothwell, **Denis Vivien*,** Emmanuel Touze*, Carine Ali. ***** equal contribution. Molecular magnetic resonance imaging discloses endothelial activation after transient ischaemic attack. **Brain, 2017** 140(1):146-157 ***IF: 11.8*** doi: 10.1093/brain/aww260

Macrez R, Ortega MC, Bardou I, Mehra A, Fournier A, Van der Pol SM, Haelewyn B, Maubert E, Lesept F, Chevilley A, de Castro F, De Vries HE, **Vivien D,** Clemente D, Docagne F**.** Neuroendothelial NMDA receptors as therapeutic targets in experimental autoimmune encephalomyelitis. **Brain. 2016** Sep;139(Pt 9):2406-19.. ***IF: 11.8*** doi: 10.1093/brain/aww172

Lemarchand E, Maubert E, Haelewyn B, Ali C, Rubio M, **Vivien D.** Stressed neurons protect themselves by a tissue-type plasminogen activator-mediated EGFR-dependent mechanism. **Cell Death Differ. 2016** Jan;23(1):123-31. ***IF: 10.2*** doi: 10.1038/cdd.2015.76.

A/ Representative recent publications (10)

XXXX : PhIND's members

Thiebaut AM, Gauberti M, Ali C, Martinez De Lizarrondo S, Vivien D, Yepes M, Roussel BD. The role of plasminogen activators in stroke treatment: fibrinolysis and beyond. **Lancet Neurol. 2018** Dec;17(12):1121-1132. Review. ***IF: 27.1***

Martinez de Lizarrondo S, Gakuba C, Herbig BA, Repessé Y, Ali C, Denis CV, Lenting P, Touzé E, Diamond SL, Vivien D, Gauberti M. Potent Thrombolytic Effect of N-Acetylcysteine on Arterial Thrombi.. Circulation. 2017, 15;136(7):646-660. ***IF: 23***

Llovera G, Hofmann K, Roth S, Salas-Pérdomo A, Ferrer-Ferrer M, Perego C, Zanier ER, Mamrak U, Rex A, Party H, Agin V, Fauchon C, Orset C, Haelewyn B, De Simoni MG, Dirnagl U, Grittner U, Planas AM, Plesnila N, Vivien D, Liesz A. Results of a preclinical randomized controlled multicenter trial (pRCT): Anti-CD49d treatment for acute brain ischemia. **Sci Transl Med. 2015** Aug 5;7(299):299ra121. ***IF: 16.7***

Marcos-Contreras OA, Martinez de Lizarrondo S, Bardou I, Orset C, Pruvost M, Anfray A, Frigout Y, Hommet Y, Lebouvier L, Montaner J, Vivien D*, Gauberti M*. * equal contribution. Hyperfibrinolysis increases blood brain barrier permeability by a plasmin and bradykinin-dependent mechanism. **Blood. 2016** 17;128(20):2423-243. ***IF: 16.6***

Wyseure T, Rubio M, Denorme F, Martinez de Lizarrondo S, Peeters M, Gils A, De Meyer SF, Vivien D, Declerck PJ. Innovative thrombolytic strategy using a heterodimer diabody against TAFI and PAI-1 in mouse models of thrombosis and stroke. **Blood. 2015**;125:1325-32. ***IF: 16.6***

Aurélien Quenault, Sara Martinez de Lizarrondo, Olivier Etard, Maxime Gauberti, Cyrille Orset, Benoît Haelewyn, Helen C. Segal, Peter M. Rothwell, Denis Vivien*, Emmanuel Touzé*, Carine Ali. * equal contribution. Molecular magnetic resonance imaging discloses endothelial activation after transient ischaemic attack. **Brain (2017)** 140(1):146-157 ***IF: 11.8***

Leys D, Hommet Y, Jacquet C, Moulin S, Sibon I, Mas JL, Moulin T, Giroud M, Sagnier S, Cordonnier C, Medeiros de Bustos E, Turc G, Ronzière T, Bejot Y, Detante O, Ouk T, Mendyk AM, Favrole P, Zuber M, Triquenot-Bagan A, Ozkul-Wermester O, Montoro FM, Lamy C, Faivre A, Lebouvier L, Potey C, Poli M, Hénon H, Renou P, Dequatre-Ponchelle N, Bodenant M, Debruxelles S, Rossi C, Bordet R, Vivien D; OPHELIE investigators and the STROKAVENIR network. Proportion of single-chain

recombinant tissue plasminogen activator and outcome after stroke. **Neurology. 2016** 6;87(23):2416-2426. ***IF: 8.7***

Gakuba C, Gaberel T, Goursaud S, Bourges J, Di Palma C, Quenault A, Martinez de Lizarrondo S, Vivien D, Gauberti M. General Anesthesia Inhibits the Activity of the "Glymphatic System". **Theranostics. 2018** Jan 1;8(3):710-722. ***IF: 8.5***

Louessard M, Bardou I, Lemarchand E, Thiebaut AM, Parcq J, Leprince J, Terrisse A, Carraro V, Fafournoux P, Bruhat A, Orset C, Vivien D, Ali C, Roussel BD. Activation of cell surface GRP78 decreases endoplasmic reticulum stress and neuronal death. **Cell Death Differ. 2017** Sep;24(9):1518-1529. ***IF: 8.1***

Lemarchand E, Maubert E, Haelewyn B, Ali C, Rubio M, Vivien D. Stressed neurons protect themselves by a tissue-type plasminogen activator-mediated EGFR-dependent mechanism. **Cell Death Differ. 2016** Jan;23(1):123-31. doi: 10.1038/cdd.2015.76. ***IF: 8.1***

B/ Research monographs and any translations thereof

- Molecular Magnetic Resonance Imaging (mMRI). Maxime Gauberti, Antoine P. Fournier, **Preclinical MRI: Methods and Protocols**, Methods in Molecular Biology, vol. 1718, https://doi.org/10.1007/978-1-4939-7531-0_19, © **Springer** Science+Business Media, LLC 2018.

- Endoplasmic Reticulum Stress: an opportunity for neuroprotective strategies after stroke. Louessard M., Lemarchand E., Ali C., Roussel DB., Vivien D. Neuroprotective Therapy for Stroke and Ischemic Disease, **Springer, Editor, P.A Lapchak, 2017.**

- Orset C, Haelewyn B, **Vivien D**. Rodent Models of Stroke, Book chapter entitled: "**Thromboembolic stroke models"**. Humana Press Inc. 1607617498, Editor: Pr U. Dirnagl. 2010 and 2nd edition 2017.

- Macrez R, Gauberti M, **Vivien D**, Ali C: New thrombolytic agents. Tratamiento del ictus isquemico, Marge Medica Books, Barcelona, 2009; 59-77.

- **Vivien D**, Benchenane K, Ali C. Transforming growth factor-beta in brain functions and dysfunctions. Dans transforming growth factor-beta in cancer therapy, **The Humana Press Inc**., Totowa, 2008.

- Baron A, Ali C, **Vivien D**. Extracellular proteolysis and neurotoxicity. Fisiopatologia de la isquemia cerebral, **Marge Medica Books**, Barcelona, 2008.

C/ Ten representative recent invited talks (70) – seminars (50) above 120 these last 10 years

- **D. Vivien.** Giving New Life to Old Music: Novel Functions of tPA in the Neurovascular Unit. The Plasminogen Activation & Extracellular Proteolysis Gordon Research Conference 2018; - Four Points, Ventura, CA, USA.

- **D. Vivien,** The 24th congress of the ISFP Edinburgh, UK, September 3-7 2018. - joint meeting with the International Workshop on Molecular and Cellular Biology of Plasminogen Activation. tPA : from fibrinolysis to neurotransmission.

- **D. Vivien**, tPA is more than a fibrinolytic. Invited conference, International Stroke Conference (ISC) 2017, Houston, United-States, 22-24 Feb., 2017. Conf. 2: D. Vivien, Molecular MR imaging of neuroinflammation. Invited conference, International Stroke Conference (ISC) 2017, Houston, United-States, 22-24 Feb, 2017.

- **D. Vivien**, European Stroke Conference (ESOC), MR imaging of neuroinflammation, Pragua, 15-18 May, 2017

- **D. Vivien**, State-of-art: Stroke models: it is time for a compromise. ISTH-2017, 8-13 july 2017. Berlin, Germany Berlin ISTH.

- **D. Vivien**, Second symposium in Inflamamtion and Thrombosis, 31th March-April 1st 2016, **Vienna, Austria.**

- **Vivien D.,** tPA more than a fibrinolytic, **9th International Symposium on Neuroprotection and Neurorepair**, Leipzig, Germany 19-22 April 2016.

- **Vivien D.,** tPA, more than a fibrinolytic, International Chinese Stroke Conference. June 2016, **Beijin, China.**

- **D. Vivien**, Imaging of neurinflammation, **European Stroke Science Workshop**. Garmisch-Partenkirchen, Germany, 19-21 November 2015.

- **D. Vivien**. The Plasminogen Activation & Extracellular Proteolysis Gordon Research Conference 2014; - Four Points, Ventura, CA, USA, « Hot topics".

D/ Granted patents

- Patent TIE 08609 VIVIEN, Treatment of neurological and neurodegenerative disorders, inventors: D. Vivien, C. Ali, R. Macrez and KU Petersen, WO2011/023250, published 2001.

- Patent TIE13193, Novel antibody useful in neurological or neurodegenerative disorders. Filling 2014, Inventors: D. Vivien, F. Docagne, R. Macrez, KU Petersen, PCT/WO2014187879. Under license with a big pharma 2017 : the patent in United States Of America has been granted on 11 Sep 2018 with N° 10 072 077

- W02013/034710A1 / IND9470-US-PCD (2017). Mutated tissue plasminogen activators and uses thereof., 09/2012, Patented with Inserm-Transfert and under licence with Op2lysis

- Patent GB1404879.7; Dual targeting of TAFI and PAI-1, deposit 2014, Under license with Cobiores (UK)

- Imaging method for predicting the onset of multiple sclerosis
  WO 2017134178 A1 - cancelled

- Patent deposit in collaboration with UMR-S U 1048 Toulouse, use of pi3kc2β inhibitors for the preservation of vascular endothelial cell barrier integrity

- Two patents under deposit Inserm-transfert "Magnetic Particles Imaging" and "Physiomics", the three in the field of brain imaging and contrast agents.

Current grant supports:

NOM DU PROGRAMME		2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	Montant
ENTRAIN H2020 : Endothelial inflammation	PI: D. VIVIEN - M. RUBIO - C. ORSET (partner)					X	X	X	X				219 000
PLATMED H2020 Euronanomed, Biomimetic platelet-derived nanomedicines for treatment of thromboembolic stroke	PI: D. VIVIEN (partner)							X	X	X	X		188 000
NEURO ATLANTIC H2020 : Diagnosis and treatments of en urological disorders	PI: D. VIVIEN - C. ORSET (partner)					X	X						177 000
AGE WELL H2020 : MEDIT-Ageing	PI : G. CHETELAT partner D. VIVIEN			X	X	X	X						30 000
Europe CONTRAST : Experimental stroke models, precinical investigations	PI: D. VIVIEN (co-PI)				X	X	X	X	X				29 000
Europe WHRI : Molecular brain imaging	PI: D. VIVIEN (co-PI)			X	X								27 000
RHU MARVELLOUS : New imaging madalities for stroke and heart failures	PI: D. VIVIEN - C. ORSET (partner, WP leader)		X	X	X	X	X	X					438 000
RHU TRT CSVD : From Target identification to Nexte Generation Therapies for Cerebral Small Vessel Diseases (TRT cSVD)	PI: D. VIVIEN - C. ALI (partner)			X	X	X	X	X	X				147 000
RHU NAC : Acute phase of stroke	PI : D. VIVIEN - E. TOUZE - M. BOULANGER - M. GAUBERTI - S. MARTINEZ DE LIZARRONDO (partner, WP leaders)						X	X	X				935 000
ANR P2N : Perineuronal nets, tPA and stroke	PI: C. ALI - D. VIVIEN (PI)	X	X	X	X	X							149 000
ANR CYCLOPS : Cyclosporin and stroke, non human primates	PI: D.VIVIEN - C. ORSET - V. AGIN (partner, WP Leader)	X	X	X	X	X	X						35 000
ANR PIKSIP : Endothelial PI3K Kinase and stroke, Blood brain barrier opening	PI: D. VIVIEN (partner, WP Leader))		X	X	X	X	X						134 000
ANR PREDICT : Fast Ultrasoud Imaging to predict rupture of intracerebral aneurysms	PI: D. VIVIEN (PI)		X	X	X	X	X						222 000
ANR MRGLY : Imaging th glymphatic system	PI: D. VIVIEN (co-PI)			X	X	X	X	X					245 000
ANR MAD-GUT : Molecular Magnetic Resonnance Imaging of inflammation	PI: M. GAUBERTI - D. VIVIEN (PI)						X	X	X				250 000
ANR SMOG-1S : GDNF and ischemic stroke, brain protection	PI: C. ALI - E.TOUZE - D. VIVIEN (partner, WP leader)						X	X	X				170 000
ANR FLAMRING Unmasking thrombo-inflammation by in vivo molecular magnetic resonance imaging of von willbrand factor	PI: S. MARTINEZ (PI)							X	X	X			250 000
ANR PHYSIOMICS Development of a polydopamine hybridized Iron Oxide Mussel Inspired Cluster for molecular MRI	PI : T BOWNARD (PI)							X	X	X			214 000
ANR FlightClot. Targeted treatment of thrombotic diseases	PI: C. ORSET, D. VIVIEN (partner, WP Leader)							X	X	X			200 000
ANR BrainCam Permanent monitoring of the cerebral blood volume in the brain injured patient toward implantable ultrasensitive dop	PI : T. GABEREL (PI)							X	X	X			180 000
Regional Council / RIN RTPA EQUIPEMENT : tPA and brain functions	PI : D.VIVIEN - C. ALI (PI)			X	X	X							405 000
Regional Council / INSTITUT BB@C : Blood and Brain @ Caen-Normandie	PI : D. VIVIEN - E. TOUZE (PI)					X	X	X	X				1 500 000
Regional Council / FEDER FRM : tPA and brain functions, FRM team	PI: D. VIVIEN (PI)	X	X	X	X	X							96 000
Regional Council / MP12O : Molecular brain imaging - Magnetic Particle Imaging	PI: M. GAUBERTI - D. VIVIEN (PI)						X	X	X				250 000
Regional Council / RIN RTPA PERSONNEL : tPA and brain functions	PI: D.VIVIEN C.ALI (PI)			X	X	X							90 000
FRM : Tpa and brain functions, team FRM	PI: D. VIVIEN (PI)		X	X	X								300 000
AXA : ER stress, Tpa and stroke	PI: D. VIVIEN - B. ROUSSEL (PI)	X	X	X									70 000
FONDATION PLANIOL : ADAMTS-4 and an eurysms	PI: D. VIVIEN - C. ALI (PI)					X							17 000
FONDATION PLANIOL : Epidemiology of stroke	PI: M. BOULANGER - E. TOUZE (PI)			X	X	X							30 000
HYPPOLIA : Mutants of Tpa	PI: D. VIVIEN (PI)			X									6 000
LUNBECK : Experimental stroke models, preclinical investigations	PI: D. VIVIEN (PI)	X	X										28 000
Observatoire AVC : Observatoire AVC Normand	PI : E. TOUZE (PI)					X	X	X	X				1 100 000
PRIX LAMARCA : tPA and NMDA receptors	C. ALI - E. TOUZE - D. VIVIEN (PI)			X									17 000
EQUILYSE : Mutants of tPA	PI: D. VIVIEN - J. PARCQ (PI)			X	X	X							55 000

From 2017 to 2022, an INSERM Unit with 3 teams.

PHYSIOPATHOLOGY AND IMAGING OF NEUROLOGICAL DISORDERS "PhIND"

Team A: tPA and Neurovascular Disorders, Keywords: tissue-type Plasminogen Activator (tPA), NMDA receptors, Stroke, Neurovascular unit

Denis Vivien (March 4th, 1966), Professor in Cell Biology (PhD- PRE2), Hospital Practitioner (PU-PH), Caen-Normandy University since 1996, Caen Normandy Hospital from 2016. Senior member of the "Institut Universitaire de France" (2009)

Team B: Serine Proteases, Inflammation and Glial cells, Keywords: Multiple sclerosis, astrocytes, oligodendrocytes, serine proteases, inflammation

Fabian Docagne (June 16th, 1974), Research Fellow, CR INSERM since 2012 and DR2 INSERM since 2018

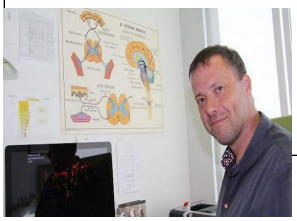
Team C: Multimodal Neuroimaging and Lifestyle in Ageing and Alzheimer's Disease, Keywords: ageing, Alzheimer's disease, multimodal neuroimaging, lifestyle, wellbeing

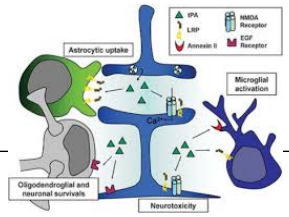
Gaël Chételat (January 8th 1976), Research Fellow, DR2 INSERM since 2002 and DR1 INSERM since 2019

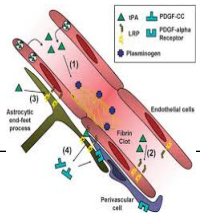
From 2022 to 2026, an INSERM unit with 2 teams

PHYSIOPATHOLOGY AND IMAGING OF NEUROLOGICAL DISORDERS "PhIND"

Team A: tPA and Neurovascular Disorders, Keywords: tissue-type plasminogen activator (tPA), NMDA receptors, Stroke, Neurovascular unit, theragnostic imaging





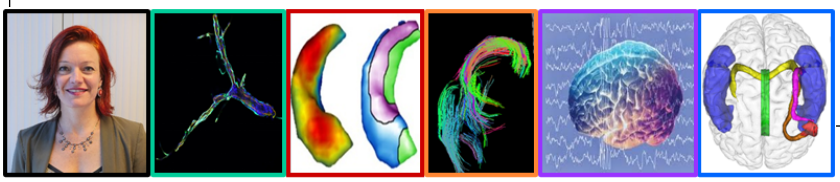


Director: Denis Vivien,

Deputy Director: Maxime Gauberti, MD-PhD, Caen – Normandy University, Resident

in radiology and endovascular radiology at Caen Normandy Hospital. CCA (2020) Inserm-Bettencourt.

Team B: Pathological mechanisms and lifestyle-based interventions in brain disorders, Keywords: neuroimmune disorders, sleep disorders, **alcohol use disorder**, **ageing**, **dementia, schizophrenia, physical activity**, **meditation**, affective disorders, non-pharmacological intervention, multimodal neuroimaging, cognition, neuroinflammation, Alzheimer's disease, multiple sclerosis, lifestyle, wellbeing.



Director: Gaël Chételat
Deputy Director: Géraldine Rauchs, CR1 INSERM.

Unit's workforce and means

Organization chart and human resources

TOP 20 publications (without reviews), PHIND – IF 2019

Team VIVIEN/GAUBERTI,
Team CHETELAT
Ex team DOCAGNE **(this team joins team Chetelat, Macrez joins Team Vivien/Gauberti)**

Martinez de Lizarrondo S, Gakuba C, Herbig BA, Repessé Y, Ali C, Denis V, Lenting P, Touzé E, Diamond SL, Vivien D, Gauberti M. Potent Thrombolytic Effect of N-Acetylcysteine on Arterial Thrombi. **Circulation**. 2017;136:646. **IF 23,603 citations: 31**

Marcos-Contreras OA, Martinez de Lizarrondo S, Bardou I, Orset C, Pruvost M, Anfray A, Frigout Y, Hommet Y, Lebouvier L, Montaner J, Vivien D*, Gauberti M* (*co-last authors). Hyperfibrinolysis increases blood-brain barrier permeability by a plasmin- and bradykinin-dependent mechanism. **Blood**. 2016;128:2423-2434. **IF 17,543 citations: 39**

Wyseure T, Rubio M, Denorme F, Martinez de Lizarrondo, Peeters M, Gils A, De Meyer SF, Vivien D, Declerck PJ. Innovative thrombolytic strategy using a heterodimer diabody against TAFI and PAI-1 in mouse models of thrombosis and stroke. **Blood**. 2015;125:1325-1332. **IF 17,543 citations: 28**

Fournier AP, Martinez de Lizarrondo S, Rateau A, Gerard-Brisou A, J Walder M, F Neurath M, Vivien D Docagne F, Gauberti M. Ultasentitive Molecular Imaging of Mucosal Inflammation Using Leucocyte Mimicking Particles Targeted to MAdCAM-1. **Science Transl. Med**. 2020 in press. **IF 16,304**

Llovera G, Hofmann K, Roth S, Salas-Pérdomo A, Ferrer-Ferrer M, Perego C, Zanier ER, Mamrak U, Rex A, Party H, Agin V, Fauchon C, Orset C, Haelewyn B, De Simoni MG, Dirnagl U, Grittner U, Planas AM, Plesnila N, Vivien D, Liesz A. Results of a preclinical randomized controlled multicenter trial (pRCT): Anti-CD49d treatment for acute brain ischemia. **Sci Transl Med**. 2015;7. **IF 16,304 citations: 108**

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Briens A, Gauberti M, Parcq J, Montaner J, Vivien D, Martinez de Lizarrondo S. Nano-zymography Using Laser-Scanning Confocal Microscopy Unmasks Proteolytic Activity of Cell-Derived Microparticles. **Theranostics**. 2016;6:610-626. **IF 8,579, citations: 10**

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de Flores R, La Joie R, Landeau B, Perrotin A, Mézenge F, de La Sayette V, Eustache F, Desgranges B, Chételat G. Effects of age and Alzheimer's disease on hippocampal subfields: comparison between manual and FreeSurfer volumetry. **Hum Brain Mapp**. 2015;36:463-474. **IF 4,746, citations: 56**

TOP 4 reviews

Thiebaut AM, Gauberti M, Ali C, Martinez De Lizarrondo S, Vivien D, Yepes M, Roussel BD. The role of plasminogen activators in stroke treatment: fibrinolysis and beyond. **Lancet Neurol**. Review 2018;17:1121-1132. **IF 30,039, citations: 11**

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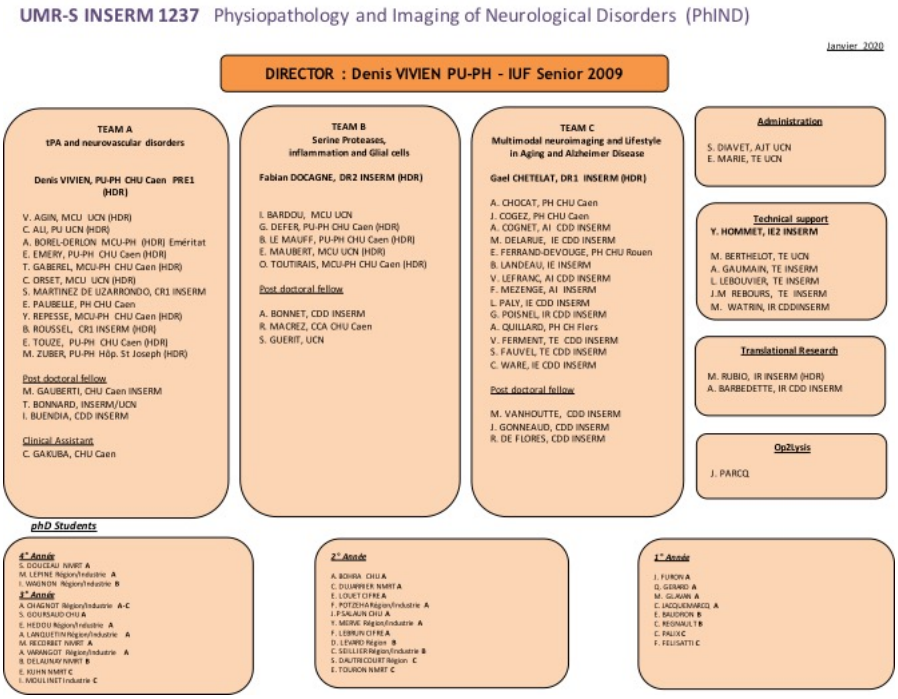
Current unit (2017-2021)



The current unit is composed of:

· 5 researchers with permanent positions (among which 2 INSERM director of research)

· 7 professors, 6 with functions at Caen-Normandie Hospital (PU-PH)

· 6 assistant professors, 3 with functions at Caen-Normandie Hospital (MCU-PH)

- 3 clinicians (PH)

· 20 technicians, among which 9 with permanent positions (6 INSERM and 3 Caen-University)

· 7 Post-docs

. 26 PhD students

Human Resource Evolution Since 2015

New appointments:

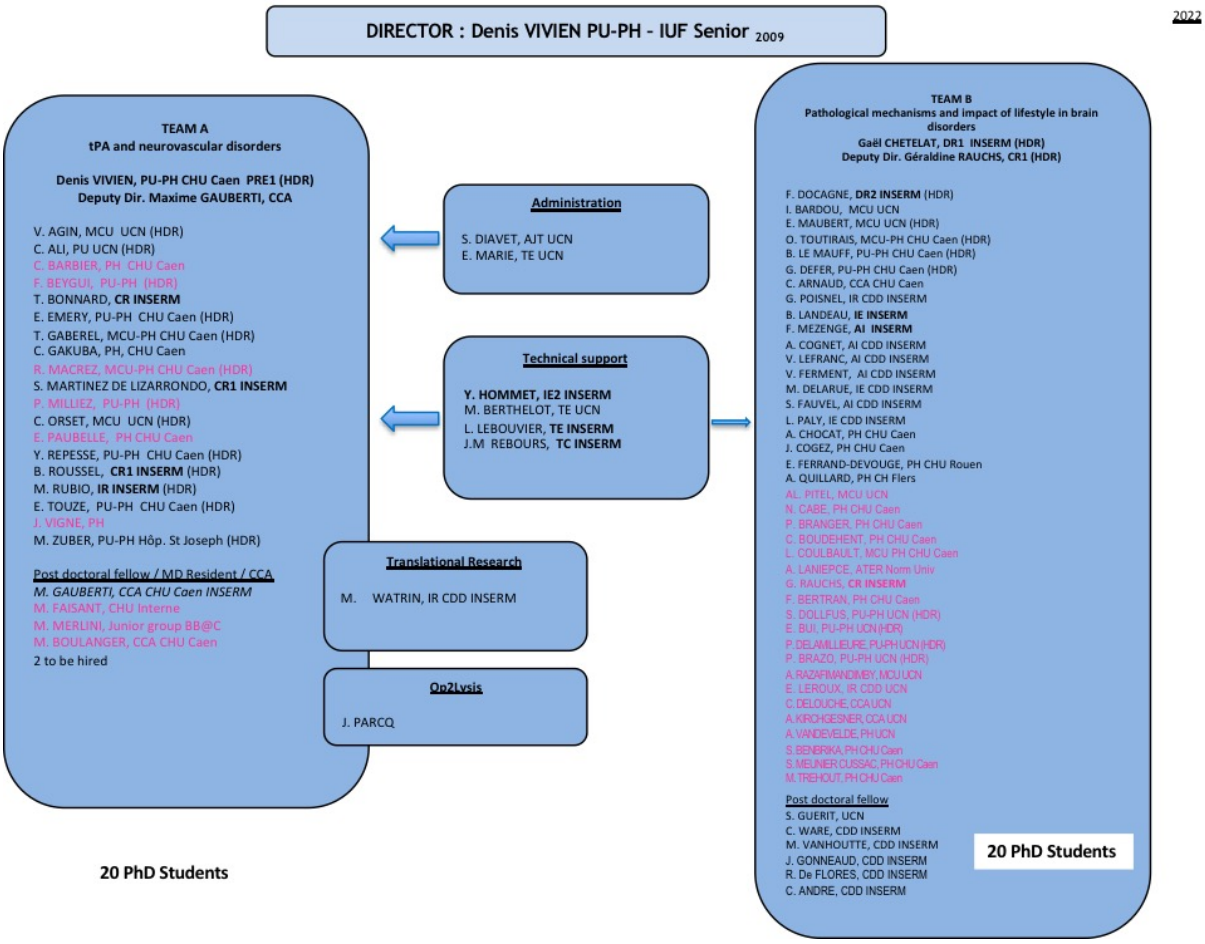
Roussel Benoit	Scientific Researcher, 1st class, INSERM, 2015
Sara Martinez De Lizarrondo	Scientific Researcher, 1st class, INSERM, 2017
Thomas Bonnard	Scientific Researcher, INSERM, 2019
Marina Rubio	Research Engineer, INSERM, 2018
Jean-Michel Rebours	Technician, INSERM, 2019
Marion Berthelot	Technician, University Caen Normandie (internal movement), 2019
Richard Macrez	MCU-PH (assistant professor, Caen-University-Hospital), 2020

Promotions:

Véronique Agin Promoted "Maîtres de Conférences hors classe", 2018

Carine Ali	Promoted PR1, 2019
Fabian Docagne	Promoted INSERM DR2, 2019
Eric Maubert	Promoted “Maîtres de Conférences hors classe”, 2019
Denis Vivien	Promoted PU-PH in cell biology at Caen University medical school and at Caen Hospital, 2016
Gaël Chételat	Promoted INSERM Director DR1, 2019
Yannick Hommet	Promoted INSERM “Ingénieur d’études”, 2018
Laurent Lebouvier	Promoted INSERM “Technicien Classe 1”, 2018
Florence Mézenge	Promoted INSERM “Assistant Ingénieur”, 2018

For the next contract, the unit will be organized as follows:



work forces

· 6 researchers with permanent positions (among which 2 INSERM director of research)
· 13 professors, 12 with functions at Caen-Normandie Hospital (PU-PH)
· 8 assistant professors, 4 with functions at Caen-Normandie Hospital (MCU-PH)
· 8 clinicians (PH)
· 12 technicians, among which 10 with permanent positions (5 INSERM, 3 Caen-University, 1 CHU)
· 12 Post-docs
. 40 PhD students

Scientific policy

The diverse areas of our expertise create a highly synergistic environment to promote:

- The development of innovative methods and investigation tools, focusing on molecular biology, cell biology, physiology, behavior, neuropsychology, and brain imaging;
- The application of these tools to push the boundaries of the study of the mechanisms underlying the functions and dysfunctions of the nervous system with a special interest for a set of common determinants of neurological and psychiatric disorders such as serine proteases (especially tPA), inflammatory processes, lifestyle and ageing;
- The interaction between basic research and clinical practice, with “bench to bed and bed to bench” approaches.

Our main objectives for the current program and the next program are:

- To decipher the molecular mechanisms through which serine proteases influence brain functions and dysfunctions.
- To determine how environment, life-styles and ageing influence brain functions and dysfunctions.
- To transfer our knowledge and tools to clinical applications, in the field of neurovascular, neuroinflammatory, neurodegenerative and mental disorders.

<u>For the previous evaluation, recommendations were very positive</u>:

For team A (D. Vivien): “*international reputation of PI, a very high capacity for structuring and research of funding. Extremely well structured and complete project combining molecular investigations to clinical research applications. Remarkable scientific production. The commission has no reservations about the quality of this team.*”

For team B (F. Docagne): “*small emergent team which displays all the conditions to develop high level research. The scientific project is highly innovant and original on the role of tPA in multiple sclerosis. The PI need to increase its international recognition*”. For Team C (G. Chételat): “*outstanding team in term of publications, of international recognition of the PI, of research of fundings. Very innovant project, well-coordinated and funded*”.

During the current contract, we have continued to focus our research topics, opening our research to its clinical aspects. The three teams have significantly increased their levels of publications and of international recognition. We expect to increase further these levels for the next contract (2022-2027), by strengthening our organization: the groups of Fabian Docagne (Team B) and Gaël Chételat will fuse and will be implemented by additional research groups (headed by Dr Géraldine Rauchs, CR1 Inserm; and Dr Anne-Lise Pitel, MCU (IUF junior) as well as the whole team of Pr Sonia Dollfus (former EA 7466) specialist of mental disorders). On the other hand, the group of D. Vivien (team A)

will be reinforced by Dr Richard Macrez (ER MCU-PH), a young neurologist - epidemiologist (Dr Marion Boulanger, CCA), a neuroradiologist (Dr Charlotte Barbier, PH), one young anathomo-pathologist (Dr Maxime Faisant), one your radiopharmacist (Dr Jonathan Vigne, PH), two cardiologists interested in the field of thrombosis and stroke of cardioembolic origins (Pr Farzin Beygui, PU-PH and Pr Paul Milliez, PU-PH) and Etienne Paubelle (PH) for the neurotoxicity of CAR-T.

Overall, these restructurations are adequate in the local strategy: at the academic level, the fields of neurosciences and brain imaging are leading research axes at Caen-Normandie university and Caen-University Hospital (HCERES program 2022); at the regional level, PhIND is the cornerstone of the recently created Blood and Brain @ Caen Normandie Institute, funded by the regional council of Normandie (BB@C, GIS: Inserm/Université Caen-Normandie/Hôpital Caen-Normandie). BB@C recruited a talented Junior team leader, Dr Mario Merlini, starting Oct-Nov. 2020, with a welcome pack of 435 KE for 3 years. Mario Merlini will be associated to UMR-S PhIND (team A), as a junior group, member of team A. Our plan is that this team will become independent as soon as possible (ATIP-Avenir …).

Presentation of the unit's research ecosystem

How has our Inserm unit been built-up and what is our projected evolution?

We are hosted at the "Groupement d'Intérêt Public" (GIP) Cyceron in Caen (Dir. Benoit Haelewyn), which includes one of the platforms benefiting from the national GIS-IBISA label, with a focus on *in vivo* imaging. There, we can perform investigations from molecular to integrated levels, thanks to an easy access to imaging equipment for animals and humans (two 7T and one 3T MRI, PET and micro-PET, NIRF, intravital two-photons microscopy, …), to core facilities (for molecular biology, cell biology, cell imaging, experimental surgery and in vivo imaging) and to an important animal facility (University Caen-Normandie). Our group has significantly contributed to the implementation of complementary technical infrastructures, via the acquisition of up-to-date equipment and know-how (Q-PCR, 2D-gel electrophoresis, gel-imager, lentiviral production, *in utero* electroporation, stereotaxic injection of adenovirus, bio-incubator, electroporator, confocal microscope, video-calcium imaging, STED confocal imaging, "spinning disc" epifluorescence imaging, « Imaris » software, laser doppler, doppler speckle, Fast-Ultrasound imaging...). We also benefit from common facilities for computer database, communication, health and safety**.**

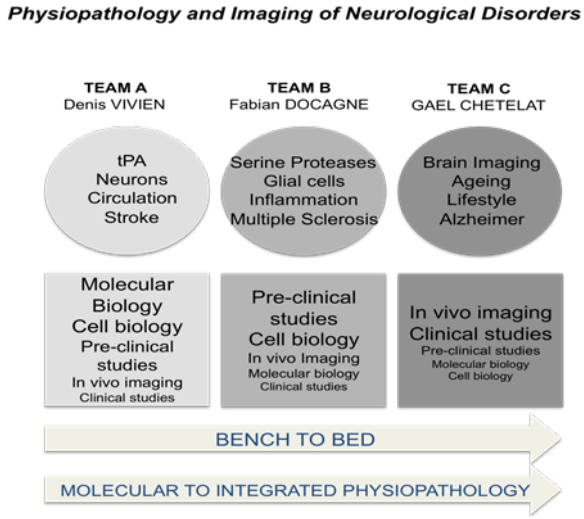
The INSERM Research Unit 919 (UMR-S U919 – 2012/2016) entitled « **Serine Proteases and Physiopathology of the neurovascular Unit (SP2U)",** was created in 2008 under the responsibility of Denis VIVIEN on the basis of the former INSERM AVENIR program entitled "**tPA in the working brain"** (2005). It then became the INSERM Research Unit 1237 (UMR-S U1237 – 2017-2021) entitled "**Physiopathology and Imaging of Neurological Disorders (PhIND)**».

From 2008 to 2012, the efforts of UMR-S U919 were focused on the mechanisms of action of the serine protease « **tissue-type plasminogen activator (tPA) » on neuronal functions and dysfunctions**, with a particular interest in stroke. These first 4 years corresponded to a pioneering and exploratory period. During this period, it became clear that tPA's functions in the nervous system were going far beyond neurons and that tPA should be considered at the interface between blood and brain. Indeed, tPA exerts pleiotropic effects throughout the nervous system, where it regulates important neuronal, glial and endothelial functions either independently or not of the conversion of plasminogen into active plasmin. The unit was renewed in 2012 (UMR-S U919). This time, our research became more translational thanks to clinicians of the Caen hospital who joined our lab. This led to a close collaboration with the departments of Neurology, Neurosurgery, Hematology,

Anesthesiology, Intensive Care Medicine, Emergency unit and Immunology. Accordingly, we developed a panel of research focusing on **neuroprotective and/or pro-fibrinolytic strategies** in stroke. This led, in parallel, to five **clinical trials**: KETA (combining rtPA-induced thrombolysis with a sub-anaesthetic dose of ketamine, interrupted), OPHELIE (aiming at determining the respective influence of sc-tPA and tc-tPA in stroke outcome, Leys et al., Neurology, 2016)), Rotem-predic (biomarkers for stroke, ongoing), FIVHeMA (PHRC-N - tPA for the drainage of intracerebral hematoma, ongoing) and N-Acetyl-Cysteine on stroke (RHU Booster, 2019 – funded, NAC-Safe / NAC-Efficacy). We then started working on new topics including **inflammatory processes** and **age-related brain dysfunctions**, still focused on the possible influence of tPA. We also developed original tools for molecular magnetic resonance imaging of endothelial adhesion molecules as a possible diagnosis of vascular suffering and/or neuroinflammation. In parallel, in partnership with the Caen Normandy University, we created a platform for **« Experimental Stroke Research »** (esrp.fr) granted by the GIS-IBiSA (since 2014).

Our current unit created in 2017 (UMR-S U1237) includes around 80 peoples with new permanent researchers and clinicians who joined us. **Fabian Docagne**, has setup his own team focused on serine proteases and neuroinflammatory processes. The opportunity for **Gaël Chételat** (formerly member of INSERM UMR-S U1077), expert in the field of human **brain imaging** to join our group, reinforced our translational strategy. Based on our background on **fibrinolysis and neuroinflammatory processes,** the « Etablissement Français du Sang, EFS » (French institute of blood), also member of AVIESAN, has become a partner of our unit, offering recurrent fundings. Thus, for the current five-years program, our unit is composed of the three following teams:

Team A: tPA and Neurovascular Disorders, Pr Denis VIVIEN (PU-PH)
Team B: Serine Proteases, Neuroinflammation and Glial cells, Dr Fabian DOCAGNE (DR2, INSERM)
Team C: Multimodal Neuroimaging and Lifestyle in Ageing and Alzheimer's Disease, Dr Gaël CHETELAT (DR1, INSERM)



As previously, our unit co-leads an **IBiSA platform "Experimental Stroke Research Platform**", (esrp.fr) a core facility of service, training and R&D in pre-clinical stroke research of international stature. Based on ESRP, we have created a "**Trademark" Strok@lliance**, which is a joined partnership between ESRP and the CRO Etap-lab. Based on our fundamental research, we are also at the initiative of a **startup project, Op2lysis**, now hosted at the GIP Cyceron. Op2lysis is developing a new treatment for hemorrhagic stroke, using a mutant of tPA developed within the lab. In addition to

the ongoing clinical trials (Rotem-predict, FIVHeMAH, RHU Booster-ACIST), we have setup an "**observatoire**" fully dedicated to stroke in Normandie (Normandie AVC) and a **medico-economic clinical trial** on the care organization for stroke (PRME – PRESTO). In parallel, we are coordinating **three bio-banks (Biostroke, Maestro and ADAMTS-4)** with the help of the "Centre de Ressources Biologiques" (CRB InnovaBIO, CHU de Caen, Resp. Pr Denis Vivien) for plasma and sera harvested from patients with a suspicion of stroke and/or Transient Ischemic Attack at the arrival at the Caen-Emergency Unit. Thanks to the RHU Booster we are member of a data bank for stroke brain imaging (ETIS) and a bio-bank for clots from stroke patients eligible to thrombectomy (Compot-clot).

For the next program (2022-2026), we expect to renew our INSERM Research Unit with the same title **"Physiopathology and Imaging of Neurological and mental Disorders (PhIND)"**, under the direction of Denis Vivien, but this time with two scientific teams:

- Team A "**tPA and neurovascular disorders**" will be renewed under its current form, with organizational modifications (Dir Denis Vivien – Deputy Dir. Maxime Gauberti)
- Teams B and C will fuse to set-up a new team entitled "**Pathological mechanisms and lifestyle-based interventions in brain disorders**" (Dir Gaël Chetelat – Deputy Dir. Géraldine Rauchs)

Importantly, by the end of 2021, CYCERON is supposed to evolve from a GIP to a University platform status, administered by Caen-Normandie University and dedicated to host biomedical research.

At the instigation of our INSERM-UNICAEN unit, a novel federative structure was created (inauguration Oct. 2019): the "**Blood and Brain @ Caen-Normandie Institute**" (BB@C Institute), funded by the Normandie Regional Council (3.2 MEuros for 4 years, 2019-2022) and the Fondation Groupama, under the scientific direction of Denis Vivien. BB@C was created as a GIS (Groupement d'Interêt Scientfique) with INSERM, Caen-Normandie University and Caen-Normandie University Hospital as founders (Oct. 2019).

For this new contract, we have seek advice from a **Scientific Advisory Board,** to evaluate our mid-term running contract (2017-2021) and our strategy for the next contract (2022-2026). This SAB visited us on October 9th 2019. It was composed of scientists of international caliber. See their evaluation below (section Program for 2022).

Catherine BELZUNG, Professor of Neurosciences, Université of Tours, senior member Institut Universitaire de France, Director UMR Inserm 1253 « Imagerie et cerveau »

Marie VIDAILHET, Professor of Neurology, hôpital Pité-Salpétrière, Paris. Director of an Inserm team at ICM "Institut du Cerveau et de la Moelle", Paris.

Jean-François DEMONET, Professor of the univerisity of Lausanne (UNIL), Chaire of excellence Leenaards and director of the « Centre Leenaards de la mémoire du CHUV ».

Pierre GRESSENS, Professor of neuropediatry, hôpital Robert Debré, Paris, Professor of neuropediatry "King's College of London", director UMR 1141, Inserm-Université Diderot, dir. RHU PROTECT, Co-director of the associated laboratory « Indian Institute of Sciences, Bangalore, Inde », Deputy director of the "Fondation PremUP", and vice-dean of the "UFR de Médecine Paris Diderot".

Research products and activities for the unit (team / theme)

Scientific track record

PRODUCTIONS - TEAM A (D. VIVIEN / M. GAUBERTI) (2015 TO NOW) (SEE COMPLETE LIST IN ANNEXE).

- 94 publications (5 are reviews), of which 51 with a member of Inserm UMR-S U1237 team A as either the first or the last author* (mean impact factor 7.23 including reviews and 6.37 excluding reviews, 6.65 with publications in collaboration). Publications with an IF>10: 8* + 3 (+2 reviews*); IF 8-10: 5* pubs (+1* review); IF 5-8: 13*+ 8 pubs (+2* reviews). *(this does not include papers published by the clinicians when related with their clinical activity)*
- 4 patents (2 under license) + 2 under consideration.
- 6 ANRs, 3 RHU, 2 H2020 programs
- 8 MEuro obtained (5 without the clinical trials)
- 6 clinical trials (Keta-Stroke, Ophelie, Rotem-Predict, FIVHeMAH, PRESTO, NAC-S and NAC-E^{RHU})
- 1 “Observatoire”; 3 “biobanks”
- 1 start-up created
- 1 plateform IBISA + Trademark “Strok@lliance”
- 1 Institute created GIS “Blood and Brain @ Caen-Normandie (BB@C)”
- 3 CR Inserm recruited

Main publications: Team A members are in bold / team B members underlined / Macrez R. from ex team B joins team A. (IF 2019).

Macrez R, Stys PK, **Vivien D,** Lipton SA, Docagne F. Mechanisms of glutamate toxicity in multiple sclerosis: biomarker and therapeutic opportunities. **Lancet Neurol. 2016** Sep;15(10):1089-102. Review. ***IF: 30.03 (collab. with team Docagne).***

Thiebaut AM, Gauberti M, Ali C, Martinez De Lizarrondo S, Vivien D, Yepes M, **Roussel BD**. The role of plasminogen activators in stroke treatment: fibrinolysis and beyond. Lancet Neurol**. 2018** Dec;17(12):1121-1132. Review. ***IF: 30.03***

Martinez de Lizarrondo S, Gakuba C, Herbig BA, **Repesse Y, Ali C**, Denis CV, Lenting P, **Touze E,** Diamond SL, **Vivien D, Gauberti M**. Potent Thrombolytic Effect of N-Acetylcysteine on Arterial Thrombi. Circulation. **2017**, 15;136(7):646-660. ***IF: 23.6***

Wyseure T, Rubio M, Denorme F, **Martinez de Lizarrondo S**, Peeters M, Gils A, De Meyer SF, **Vivien D,** Declerck PJ. Innovative thrombolytic strategy using a heterodimer diabody against TAFI and PAI-1 in mouse models of thrombosis and stroke. **Blood. 2015**; 125:1325-32. ***IF: 17.5***

Marcos-Contreras OA, Martinez de Lizarrondo S, Bardou I, Orset C, Pruvost M, Anfray A, Frigout Y, Hommet Y, Lebouvier L, Montaner J, **Vivien D*, Gauberti M*.** * *equal contribution*. Hyperfibrinolysis increases blood brain barrier permeability by a plasmin and bradykinin-dependent mechanism. **Blood. 2016** 17;128(20):2423-243. ***IF: 17.5***

Fournier AP, **Martinez de Lizarrondo S**, Rateau A, Gerard-Brisou A, J Walder M, F Neurath M, **Vivien D**, Docagne F, **Gauberti M**. Ultasentitive Molecular Imaging of Mucosal Inflammation Using Leucocyte Mimicking Particles Targeted to MAdCAM-1. **Science Transl. Med.** 2020 sous presse. ***IF 16,3***

Llovera G, Hofmann K, Roth S, Salas-Perdomo A, Ferrer-Ferrer M, Perego C, Zanier ER, Mamrak U,

Rex A, **Party H, Agin V**, Fauchon C, **Orset C,** Haelewyn B, De Simoni MG, Dirnagl U, Grittner U, Planas AM, Plesnila N, **Vivien D,** Liesz A. Results of a preclinical randomized controlled multicenter trial (pRCT): Anti-CD49d treatment for acute brain ischemia. **Sci Transl Med. 2015** Aug 5;7(299):299ra121. ***IF: 16.3***

Roth S, Singh V, Tiedt S, Schindler L, Huber G, Geerlof A, Antoine DJ, **Anfray A, Orset C, Gauberti M,** Fournier A**,** Holdt LM, Harris HE, Engelhardt B, Bianchi ME, **Vivien D**, Haffner C, Bernhagen J, Dichgans M, Liesz A. Brain-released alarmins and stress response synergize in accelerating atherosclerosis progression after stroke. **Sci Transl Med. 2018** Mar 14;10(432). ***IF: 16.3***

Llovera G, Benakis C, Enzmann G, Cai R, Arzberger T, Ghasemigharagoz A, Mao X, Malik R, Lazarevic I, Liebscher S, Erturk A, Meissner L, **Vivien D**, Haffner C, Plesnila N, Montaner J, Engelhardt B, Liesz A. The choroid plexus is a key cerebral invasion route for T cells after stroke. **Acta Neuropathol. 2017** Jul 31. 134(6):851-868. ***IF: 14,25***

Aurelien Quenault, Sara Martinez de Lizarrondo, Olivier Etard, **Maxime Gauberti, Cyrille Orset,** Benoît Haelewyn, Helen C. Segal, Peter M. Rothwell, **Denis Vivien*, Emmanuel Touze*, Carine Ali. *** equal contribution. Molecular magnetic resonance imaging discloses endothelial activation after transient ischaemic attack. **Brain, 2017** 140(1):146-157 ***IF: 11.3***

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Patents from 2015

W02013/034710A1 / IND9470-US-PCD (2017). Mutated tissue plasminogen activators and uses thereof., Patented with Inserm-Transfert and under license with Op2lysis

Patent GB1404879.7; Dual targeting of TAFI and PAI-1, deposit 2014, Under license with Cobiores (UK) 2017.
Imaging method for predicting the onset of multiple sclerosis - *WO 2017134178 A1 – "not maintained"*

Patent deposit in collaboration with UMR-S U 1048 Toulouse, use of PI3kc2β inhibitors for the preservation of vascular endothelial cell barrier integrity; 2018

Two patents under consideration at Inserm-transfert in the field of brain imaging and contrast agents; 2019

Key events

Striking facts (2015 - now) – Team A

A/ tPA SIGNALING AND NEW FUNCTIONS OF tPA

A.1/ tPA signaling *(Fig. 1)*

- We demonstrated that tPA is a ligand of the N-terminal domain of the mandatory GluN1 subunit of NMDA receptors (NMDAR) acting as a modulator of their dynamic distribution at the neuronal surface and subsequent signaling. This study allowed us to generate and characterize a monoclonal antibody (named Glunomab, patented ***PCT/WO2014187879***) to prevent the interaction of tPA with the GluN1 subunit of NMDAR and to identify the binding site of tPA to this GluN1 subunit of NMDAR (Lys 178) ***(Lesept et al., Cell Death Dis., 2016).***

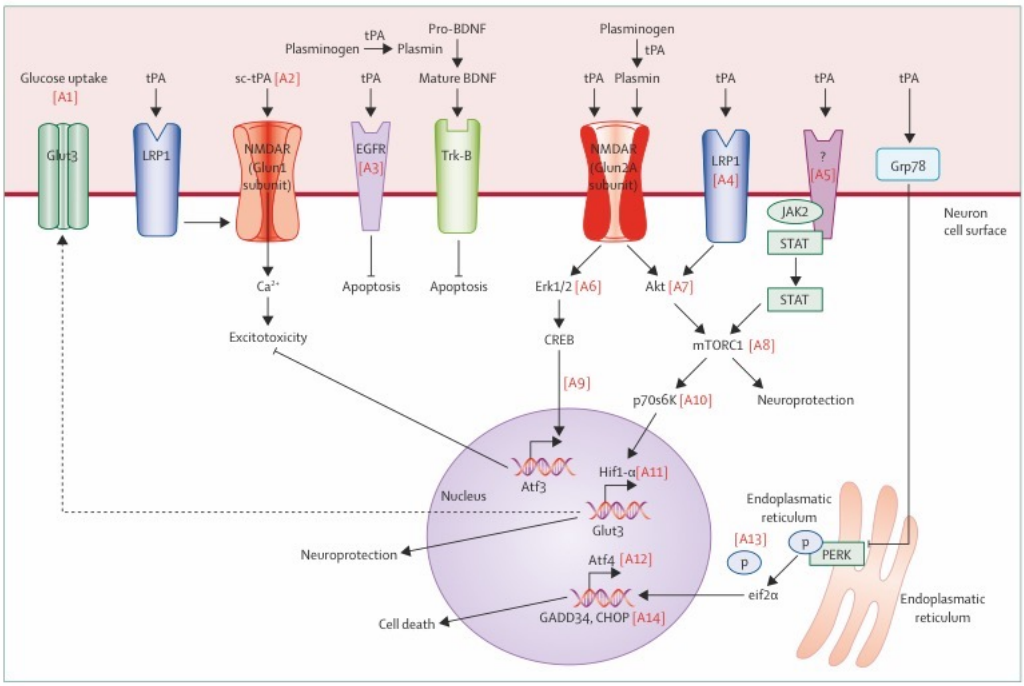
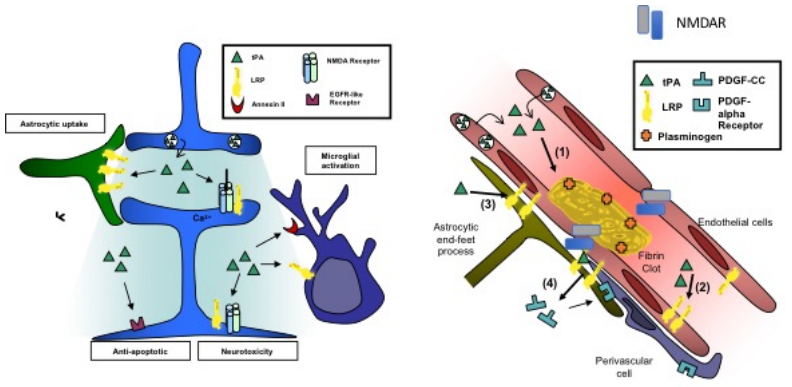


Figure 3: Pathophysiology of tissue-type plasminogen activators from in vitro studies and animal models

Thiebaut et al., Lancet Neurol., 2018 (review from team A)

- ➢ We have highlighted a new role and a therapeutic potential of the chaperone protein Grp78 as a membrane receptor of tPA capable to prevent from endoplasmic reticulum stress overactivation ***(Louessard et al., Cell Death Differ., 2017).***
- ➢ We have also demonstrated (collab. Team B, F. Docagne) that NMDARs expressed on endothelial cells are involved in the control of the transmigration of inflammatory cells across the blood-brain barrier (model of multiple sclerosis) through a mechanism dependent of tPA. ***(Macrez et al., Brain, 2016)***. tPA by interacting with endothelial NMDARs leads to Rho/ROCK mediated phosphorylation of myosin ***(Mehra et al., J. Neurosci., 2020)*** *(Fig. 2).*

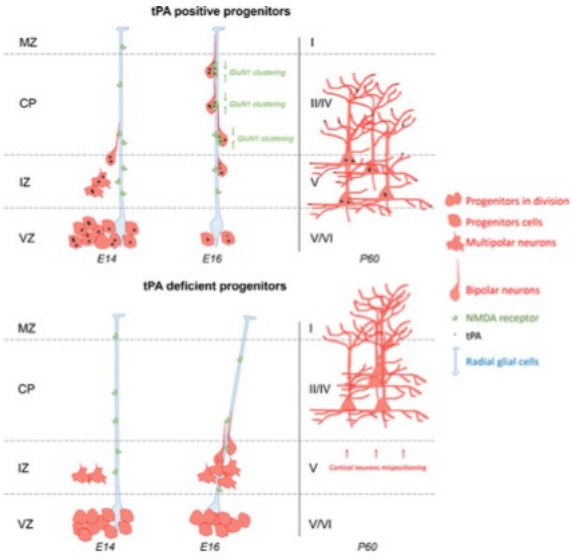


Modified from Vivien et al., JCBFM, 2011 review

Reijerkerk et al., J. Immunol., 2008
Reijerkerk et al., J. Neurochem., 2010
Macrez et al., Brain, 2016

A.2/ New functions of tPA

- ➢ We have reported for the first time that the lack of tPA, previously characterized as a neuromodulator and a gliotransmitter, leads to an altered cortical lamination in adult, through a mechanism dependent of NMDAR expressed at the surface of radial glial cells (RGC). These data provide the first demonstration that neuronal tPA ensures a proper corticogenesis by its ability to control NMDAR signaling in RGC ***(Pasquet et al., Cereb. Cortex, 2019).*** *Fig.3.*



Tissue-type plasminogen activator (tPA) plays a key a role in corticogenesis. Produced and released by neuronal progenitors, tPA promotes the maturation of radial glial cells (RGC) through activation of NMDAR expressed at their surface. The absence of neuronal tPA affects radial glial placement, orientation but not end- feet attachment over the pial surface. Accordingly, a global tPA deficiency or a conditional deletion of the neuronal tPA at E14 delayed neuronal migration mainly at E16. This delayed migration observed in the absence of neuronal tPA led to an altered lamination of cortical layers II–IV and V in adults.

- ➢ We have demonstrated that the tPA-dependent potentiation of NMDAR signaling in the entorhinal cortex controlled spatial memory (distal cues versus proximal cues) (***Hebert et al., Cereb. Cortex, 2017).*** (ongoing translational program with new team B)
- ➢ We have demonstrated that PAI-1 (type 1 Plasminogen Activator Inhibitor) was involved in depression-like behavior in mice, by a mechanism independent of tPA, involving the metabolism of serotonin. ***(Party et al., Acta Neuropathol. Comm., 2019).*** (ongoing translational program with new team B)
- ➢ We have demonstrated that ADAMTS-4, a desintegrin and metalloproteinase with thrombospondin motifs type 4, activated by tPA and plasmin, is a new marker of mature oligodendrocytes contributing to the myelination processes and thus to the control of motor capacities ***(Pruvost et al., Glia, 2017).***

B/ STROKE AND tPA

- ➢ We have further characterized our models of thromboembolic stroke in rodents, in term of responses to treatments, including fibrinolytics ***(Orset et al., Stroke, 2017)*** and anti-inflammatory drugs (***Llovera et al., Science Transl. Med., 2015; Drieu et al., Transl. Stroke Res., 2019; Drieu et al., JCI Insight, 2020***). *(Fig. 4)*

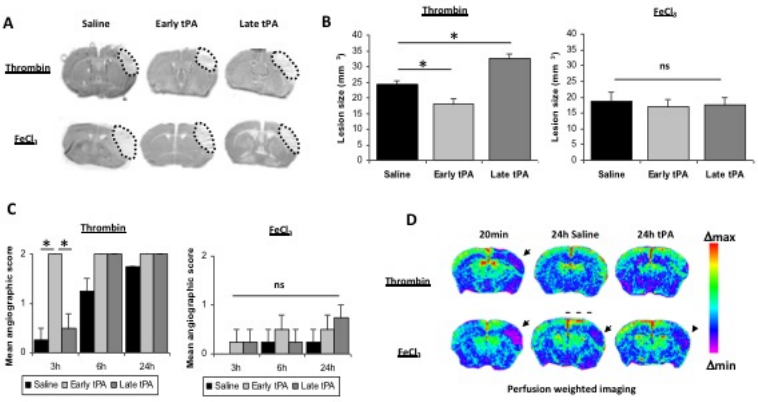
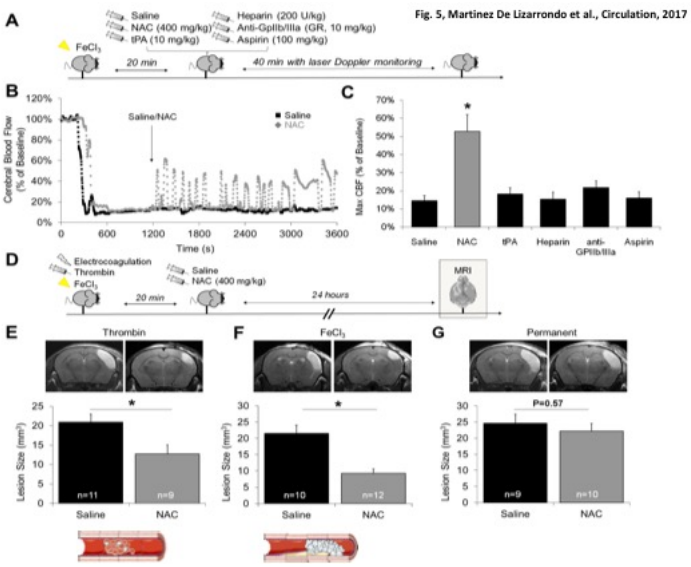


Fig. 4

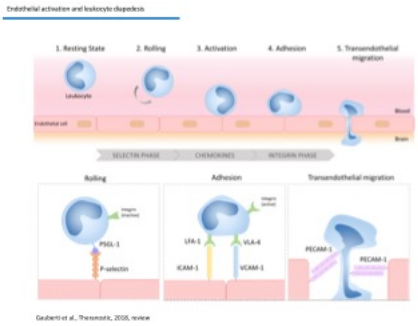
- We have demonstrated that tPA present in the bloodstream is a key player of the formation of intracerebral aneurysms (IAs) and thus that tPA should be considered as a possible new target for the prevention of IAs formation and rupture (***Labeyrie et al., Stroke, 2017*****).**
- We have demonstrated that strategies contributing to promote either endogenous production of tPA or its associated EGFR-linked signaling pathway may have beneficial effects following brain injuries such as stroke ***(Lemarchand et al., Cell Death Differ., 2016).***
- We have provided evidence of an efficient liver-driven clearance of tPA might influence the safety of thrombolysis after stroke ***(Lemarchand et al., Stroke, 2015).***
- We have demonstrated that a heterodimeric diabody targeting TAFI and PAI-1 (two main inhibitors of fibrinolysis) may have clear beneficial effects in a model of thromboembolic stroke, mimicking the clinical situation ***(Wyseure et al., Blood, 2015; Patented*** GB1404879.7 ***and licensed).***
- We have provided evidence that an innovative thrombolytic strategy using NAC is an effective and safe alternative to currently available antithrombotic agents to restore vessel patency after arterial occlusion ***(Martinez de Lizarrondo et al., Circulation, 2017).*** This leads to the recent funding of **the RHU Booster (2009)**, and the ongoing clinical trials NAC-safety and NAC-efficacy "EFFICACY OF N-ACETYLCYSTEIN WITH IV THROMBOLYSIS IN ACUTE ISCHEMIC STROKE (N-Acetyl Cysteine in Ischemic Stroke Thrombolysis)" *(Fig. 5).*

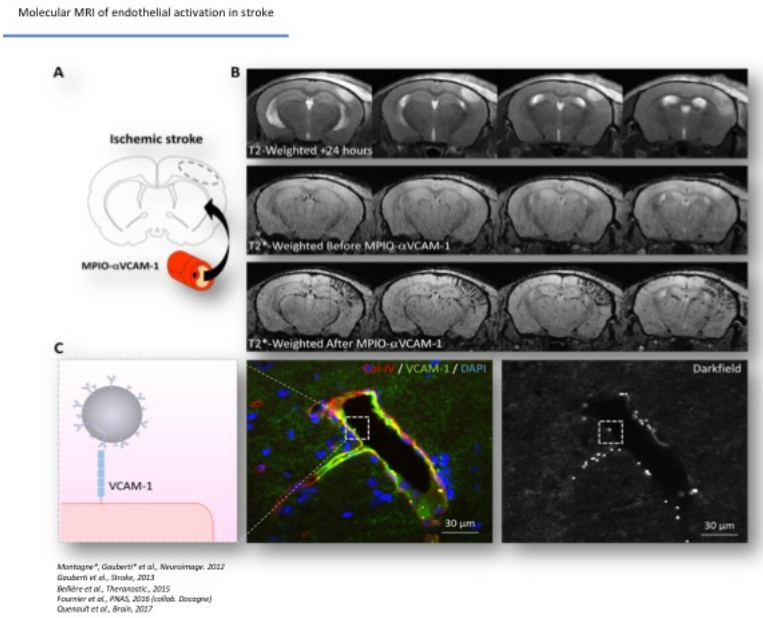


- ➢ We have demonstrated that the blockage of bradykinin B2 receptor may be a promising strategy to prevent the deleterious effects of hyperfibrinolysis on the homeostasis of the blood brain barrier **(*Marcos-Conteras et al., Blood, 2016).***
- ➢ We have confirmed in the context of stroke in Human, our previous *in vitro* and preclinical data demonstrating that the two forms of tPA, single chain tPA (sc-tPA) and two chain tPA (tc-tPA) display differential brain functions. ***(Bertrand et al., Cell Death Dis., 2015 ; Leys et al., Neurology, 2016).***
- ➢ We have demonstrated that a mutant of tPA, OpPA was a non-neurotoxic fibrinolytic agent for the drainage of intracerebral hemorrhages ***(Parcq et al., J. Cereb. Blood Flow and Metab., 2018) - Op2lysis is a startup hosted by the laboratory.***
- ➢ We have demonstrated the applicability and specificity of a method of nano-zymography using laser-scanning confocal microscopy to detect antigens and proteolytic activities of tissue-type plasminogen activator (tPA), urokinase and plasmin at the surface of microparticles (MPs). Furthermore, we were able to identify a subset of tPA-bearing fibrinolytic MPs using plasma samples from a cohort of ischemic stroke patients who received thrombolytic therapy and in an experimental model of thrombin-induced ischemic stroke in mice. Overall, this method is promising for functional characterization of cell-derived MPs ***(Briens et al., Theranostics, 2016).***
- ➢ We have setup a stroke registry, stroke cohort and stroke biobanks ***(Normandy-stroke, Biostroke, Maestro and ADAMTS-4).***

C/ BRAIN IMAGING *(Fig. 6 and 7)*

- ➢ Endothelial activation is a hallmark of cardiovascular diseases, acting either as a cause or a consequence of organ injury. To date, we lack suitable methods to measure endothelial activation *in vivo*. We have developed a magnetic resonance imaging (MRI) method allowing non-invasive endothelial activation mapping in the vasculature of the main organs affected during cardiovascular diseases. In clinically relevant mouse models (including systemic inflammation, acute and chronic kidney diseases, diabetes mellitus and normal aging), we have provided evidence that this method allowed detecting endothelial activation before any clinical manifestation of organ failure in the brain, spinal cord*, kidney, heart and intestine* with an exceptional sensitivity ***(Belliere et al., Theranostics, 2015; Gauberti et al., Theranostics, 2018 for review; Fournier et al., PNAS, 2017*; Fournier et al., Science Transl. Med., 2020 In press* - *Collab Team F. Docagne).***





- We have provided preclinical evidence that combining conventional magnetic resonance imaging with molecular MRI targeting endothelial P-selectin might aid in the diagnosis of transient ischaemic attack ***(Quenault et al., Brain, 2017).***
- We have investigated the effects of normobaric oxygen therapy (NBO) on T2*-weighted images in a pig model of ICH. Our data show that NBO makes disappear a peripheral crown of the hematoma, which in turn decreases the apparent volume of ICH by 18%. We hypothesized that this result could be translated to ICH in human, and subsequently could lead to inaccurate diagnostic ***(Goulay et al., J. Clin. Neurosci., 2018).***
- Solute transport through the brain is of major importance for the clearance of toxic molecules and metabolites, and it plays key roles in the pathophysiology of the central nervous system. This solute transport notably depends on the cerebrospinal fluid (CSF) flow, which circulates in the subarachnoid spaces, the ventricles and the perivascular spaces. We have provided evidence that the perinatal brain has non-optimal CSF flow and exit and, thus, may have impaired clean-up capacity ***(Di-Palma et al., Dev. Neurobiol., 2018).***
- We have also demonstrated that the parenchymal diffusion of small molecular weight compounds from the CSF is more active during wakefulness and that general anesthesia has a negative impact on the intracranial CSF circulation ***(Gakuba et al., Theranostics, 2018).***
- We have also demonstrated that he CSF actively extravasates in the brain parenchyma in the gyrencephalic brain, as described for the glymphatic system in rodent and that this parenchymal CSF circulation was severely impaired by SAH both in rodents and non-human primates ***(Goulay et al., Stroke, 2017).***

- We have setup a new methodology for in vivo hemodynamic brain imaging, Fast Ultrasound Imaging (fUS) (collaboration with M. Tanter, Paris). This methodology was applied to stroke, with the evidence that early fUS imaging (2 hours after stroke onset) was predictive of final outcomes, including lesion size at 24 hours and response to treatment (**Hingot V., Brodin C. et al., Theranostic, 2020)**.

Other importants facts

- Our team co-leads an **IBiSA platform "Experimental Stroke Research Platform**", (esrp.fr) a core facility of service, training and R&D in pre-clinical stroke research of international stature. ESRP transfers to the scientific community and industry the experimental models of stroke we develop in the unit. Based on ESRP, we have created a "**mark" Strok@lliance**, which is a joined partnership between ESRP and Etap-lab, a CRO.
- Based on our fundamental research, we are also at the initiative of a **startup project, Op2lysis**, now hosted at the GIP Cyceron. Op2lysis is developing a new treatment for hemorrhagic stroke, using a mutant of tPA we have developed.
- Six clinical trials conducted or ongoing: KETA-Stroke (interrupted), OPHELIE (closed-published), ROTEM-Predict (Ongoing), FIVHeMAH (PHRC-N - ongoing), PRESTO (PRME – ongoing), NAC RHU-Booster).
- One "observatoire" on stroke in Normandie "Normandie AVC", two biobanks on stroke "Biostroke" and "Maestro". One additional biobank on aneurysms is ongoing.
- Thanks to our recognized expertise in the fields of neurovascular (Team A), neuroinflammatory (Team B) and brain ageing research (Team C), we built an institute named GIS **"Blood and Brain @ Caen-Normandy (BB@C)"**, of which PhIND is a cornerstone (scientific director Denis Vivien).
- Recruitment of a Junior team leader (associated to team A - PhIND), Mario Merlini, inside of the Blood and Brain @ Caen Normandie Institute (BB@C), with welcome package of 435 KE for a 3 years. Our plan is that this team will become independent as soon as possible (ATIP-Avenir …).
- Two additional patents are under consideration (approved by Inserm-transfert) – "Physiomics" and "MPIO-PDA", two solutions for brain imaging and development of a start-up is on-going.

Full production: 2015-2020

PUBLICATIONS TEAM A: VIVIEN

Total number of publications: 94

Scientific articles with last authorship: 51

Scientific articles with first authorship: 43

Scientific articles with last, first or corresponding authorship (PDC): 65

2015

Chevilley A, Lesept F, Lenoir S, Ali C, Parcq J, Vivien D.Impacts of tissue-type plasminogen activator (tPA) on neuronal survival. **Front Cell Neurosci**. 2015;9:415. **IF 3,921**

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Conf. Seminar 2020

Planned reported

Stroke meeting Amsterdam

27 au 29 mai prochain j'organise le 27è workshop de l'international stroke genetics consortium, Debette Bordeaux

ESO summer school – Caen 2020 (24th-28th August 2020)
How to improve the thrombolytic effect of alteplase and to reduce the risk of bleeding, alteplase mutants?
Denis Vivien (Caen)

Neuroinflammation, All. Avril

Neurorepair Neuroprotection Berlin Oct

Conf. 1/ State of arts, **Gordon Conference of Plasminogen Activator**, Ventura, US, California, 9-14 feb, 2020

Sem.1/ Experimental Stroke models for the future, **Kupio, Finland, Charles River**, Jan. 8th, 2020

Conf. 2/ Translational stroke research, A new life for a old music, plenary lecture, The 2nd Annual Conference of the Society of Cerebral Small Vessel Diseases, **Chinese Stroke Association and**

Tiantan International Summit Symposium on Cerebral Small Vessel Diseases 2020 (SSVD-TSVD 2020), **Nov 20-21, Beijing, China.**

Conf. 3/ Les différents thrombi. **Société Française NeuroRadiologie, Paris, 16-17 Déc. 2020**.

Conf. 4/ Multicentric stroke preclinical trials. **Stroke CONTRAST Network, Amsterdam, Netherland, 10 Déc. 20210.**

Conf. Seminar 2019

Sem. 1/ **D. Vivien**, How experimental Stroke research could help stroke patients. Unité INSERM U1195 – Kremlin Bicêtre, Schumacher M – Benavides J – Diplôme Universitaire Neurovasculaire,. 15 mars 2019, Paris.

Conf. 1/ **D. Vivien**, Organisation et séminaire, 1er Atelier AVIESAN sur les accidents vasculaires Cérébraux – ITMO NNP, 26 mars 2019, esp. Van Gogh, Paris – Conf. 1 : Qu'avons nous appris des modèles animaux d'AVC ?

Conf. 2/ **D. Vivien**, Quelles nouvelles perspectives pour améliorer le reperfusion cérébrale post-AVC ? RENCONTRES TUC-GIHP-GACI, Cardiologie intervzentionnelle, de la thrombose et des urgences coronaires. Centre congrés Zalthabar,4 avril 2019, Paris.

Sem. 2/ **D. Vivien,** tPA more than a fibrinolytic ? Marseille, La timone, INSERM UMR-S U 1263 / INRA 1260, centre cardiovasculaire, 6 Mai 2019.

Conf. 3/ **D. Vivien,** Comment revisiter la pharmacie de l'hôpital dans le domaine neurovasculaire, Réunion Annuelle de l'Académie de Pharmacie (délocalisée à Caen), Caen, France, 15 Mai 2019.

Conf. 4/ **D. Vivien,** Neuro-prognostication in the Intensive Care Unit. Physiopathology of Stroke. June 20-21 2019, Paris, France.

Conf. 5/ **D. Vivien,** European Schoold of Radiology, Mechanical thrombectomy, Giving new life to old music: about the future of translational stroke research, June 26-28, 2019, Lille, France

Conf. 6/ **D. Vivien**, Serpin-2019 meeting. PAI-1 deficiency contributes to major depressive-like behavior, 19-22 Sept 2019, Sevilla, Spain

Conf. 9/ **D. Vivien**, 1st international congress of fast Ultrasound brain imaging. FastUltrasound imaging in diagnosis of stroke. Conf. Cargèse, France 28/10-01-11-2019.

Conf. 10/ **D. Vivien**, Blood and Brain interactions : the exemple of tPA ? pleanary lecture, EISC PARIS Orsay, France, 15 nov. 2019

Conf. 11/ **D. Vivien**, Stroke workshop, What we learned from experimental stroke models ?, Lund, Sueden. Nov. 21, 2019

Conf. 12/ **D. Vivien**, 7em rencontre du club Français des Plaquettes et des Mégacaryocytes Platelets or not Platelets, what is the question for stroke ?,Toulouse, France, 3-4 Déc. 2019

Conf. Seminar 2018

Conf. 1: D. Vivien, Plasminogen Activation and Extracellular Proteolysis, ***Gordon Research Conference,*** **February 11 - 16, 2018**, **Ventura, CA, US, Giving New Life to Old Music: Novel Functions of tPA in the Neurovascular Unit"**

Conf. 2 : D. Vivien, **Groupe jeunes de la société d'anesthésie et de réanimation (SFAR) pédiatrique.** II journée nationale, Caen 13 Avril 2018, Agents anesthésiques et développement cérébral.

Conf. 3. D. Vivien, **International meeting on Ischemia Reperfusion Injury in Transplantation, IMIRT** 2018, Poitiers, 19-20 Avril 2018. Whole body molecular résonance Imaging of inflammation.

Conf. 4. D. Vivien, **European Stroke Conference (ESOC), Goteborg, Sueden**, 15-18 Mai 2018. Integrating molecular imaging with other imaging technologies.

Conf. 5. **Key-Note Lecture by Denis Vivien** Contrast Collaboration for new treatment of acute stroke, Amsterdam; May 23th, 2018, Program contrast workshop; Amsterdam CONTRAST, Experimental stroke research on rodents especially outcome assessment and procedures without anesthesia.

Conf. 6: **Pr. Denis Vivien 2nd STROK@LLIANCE annual meeting ,** June 5th, 2018 – MAISON DE LA CHIMIE , Paris, Giving new life to old music about the future of translational stroke research

Sem. 1: **Toulouse, MP Gratacap**, UMR-s U1045, D. Vivien, tPA from synapses to neurovascular diseases, 11 july, 2018.

Conf. 7: **ISFP and Plasminogen Activator Workshop, 3-7 Edimburg 2018** – tPA more than a fibrinolytic.

Conf. 8: D. Vvien,– Recherche translationnelle sur les accidents vasculaires cérébraux. Ecole de **l'ITMO Neurosciences**, Bordeaux, France, 20-23 Oct. 2018

Conf. 9: D. Vivien, Molecular MR imaging of neuroinflammation. **X^{em} Neurorepair & Neuroprotection meeting, Dresden**, Germany, 9-11 Oct. 2018.

Conf. 10 : D. Vivien, tPA and brain functions. **GFHT-ISTH, 24-26 Oct. 20018, Marseille**, France

Conf. 11, D. Vivien, The glymphatic system on stroke, First French meeting on lymphatics, Rouen, 26 Nov. 2018

Conf. 12: D. Vivien, Physiopathology and imaging of neurological disorders, **IV UIMP-IBiS SCHOOL OF BIOMEDICINE** Mechanisms linking aging and vascular disease - Seville, 17-18 Dec 2018

Conf. Seminar 2017

Sem.1: **D. Vivien,** tPA from fibrinolysis to NMDA receptor signaling, 14 Fev 2017, **Hungarian Academy of Sciences**, Budapest, Hungaria.

Conf.1: D. Vivien, tPA is more than a fibrinolytic. Invited conference, International Stroke Conference (ISC) 2017, Houston, United-States, 22-24 Feb., 2017.

Conf. 2: D. Vivien, Molecular MR imaging of neuroinflammation. Invited conference, International Stroke Conference (ISC) 2017, Houston, United-States, 22-24 Feb., 2017.

Conf. 3: **D. Vivien**, European Stroke Conference (ESOC), MR imaging of neuroinflammation, Pragua, 15-18 May, 2017

Sem.2: **D. Vivien**, tPA more than a fibrinolytic? Bochum International Graduate School of Neurosciences, Germany, 22 May, 2017.

Conf. 4. **D. Vivien,** Molecular Imaging of Neuroinflammation after Stroke, 14th Interdisciplinary Cerebrovascular Symposium, June 28-30-2017, Montpellier, France

Conf. 5. **D. Vivien**, State-of-art: Stroke models: it is time for a compromise. ISTH-2017, 8-13 july 2017. Berlin, Germany Berlin ISTH

Conf. 6. **D. Vivien**, 28 ème Journée Scientfique de l'ANEBC, Bagnoles de L'Orne, 21-23 Sept. 2017. Bio C, Normandie. L'activateur tissulaire du plasminogène (tPA), une protéase vasculaire qui se dit être un neurotransmetteur ?

Conf. 7. **D. Vivien**, Studium Conference, The role of glycosylation on serpin biology and conformational disease, 2è-29 Sept. 2017, Orléans, France. Single chain versus two chain tPA from fibrinolysis to neuronal signaling.

Conf. 8: **D. Vivien,** MR Molecular Imaging of Inflammation. . 2e Congrés National d'Imagerie du Vivant, 8-9 Nov. 2017, Paris

Conf. 9: **D. Vivien**, How to improve the efficacy of tPA, Journée Internationale. / Société Française de NeuroVasculaire, SFNV, 15-17 Nov. 2017? Paris.

Sem. 3 D. Vivien. New thrombolytics for stroke. Ready for a clinical trial? Pamplona, Spain, CIMA research center. 23 Nov. 2017.

Sem. 4. D. Vivien., tPA More than a fiberinolytic ? Marseille, 18 Déc. 2017, Institut des Neurosiences de la Timone (F. Debarbieux)

Conf. Seminars 2016

Conf. 1 : **Vivien D**., Hyperfibrinolysis induces blood-brain barrier disruption by a plasmin-bradykinin dependent mechanism. **60th annual meeting of the society of Thrombosis and Haemostasis Research.** Munster, Germany, 17_20 fev, 2016

Conf. 2: **D. Vivien**, Second symposium in Inflamamtion and Thrombosis, , 31th March-April 1st 2016, **Vienna, Austria.**

Conf. 3: **Vivien D.** Neuroinflammation et traitements des Accidents Vasculaires Cérébraux. **20 èmes journée de la Société Française Neurovasculaire**, Paris 25-27 Nov, 2015.

Conf. 4: **Vivien D.,** tPA more than a fibrinolytic, **9th International Symposium on Neuroprotection and Neurorepair**, Leipzig, Germany 19-22 April 2016.

Conf. 5: **Vivien D.,** tPA, more than a fibrinolytic, International Chinese Stroke Conference. 24-26 June 2016, **Beijin, China.**

Sem. 1: **Vivien D.** tPA isoforms orchestrate neuronal survival. **Candiolo Cancer Institute, Candiolo, Turino**, Italy, Feb., 26th, 2016.

Sem.2: **Vivien D**. Preclinical stroke studies, time for a compromise, Invitation Arthur Liesz, Research Center for Alzheimer and Stroke, **Munchen,** 7-8 june 2016,.

Sem.3: **Vivien D.,** Molecular imaging of neuroinflammatory processes. Invitation, Rick Dkjuikensen, 13 June 2016, **Utrecht, Netherland.**

Sem.4: **Vivien D.,** tPA, from bench to bedside in the field of stroke. Tiantan Stroke Hospital., 26 june 2016, **Beijin, China.**

Sem.5: **Vivien D.,** Experimental Stroke Models, UFR de Pharmacie, 19 Sept. 2016, **Nancy, France.**

Sem.6: **Vivien D.,** What new in the field of the neuronal tPA? IRIB seminar., Invitation B. Gonzalez, 28 Sept. 2016, **Rouen, France**.

Sem 7: **Vivien D.,** Molecular Imaging of Neuro-Immune Interaction, Inserm U1028, Invitation FHU CHU Poitiers, Pôle Biologie Santé, Pr T. Hauet, **Poitiers** 28 Nov 2016..

2015

Sem. 3. D. >VivieConf 1: D. Vivien. L'activateur tissulaire du plasminogène entre fibrinolyse et neurotransmission, **Journées des Nouveautés de la Recherche Clinique**, Société Française de Neurologie. Institut de la Moelle et du Cerveau. Paris, 15-16 janvier 2015.

Conf 2: D. Vivien. Molecular magnetic resonance imaging of brain-immune interactions. Hot topics in Molecular Imaging, **9th winter conference of the European Society for Molecular** Imaging 2015, Les Houches, France, 01-06 Février 2015.

Conf 3: D. Vivien. Endovascular treatment for acute ischemic stroke, **11th International Conference on Cerebral Vascular Biology,** Paris, 6-9 july 2015.

Conf 4: D. Vivien. Qu'est-ce qu'un fibrinolytique au plan moléculaire ?, **Congrès National de la Société Française de Pharmacologie et de Thérapeutique**. Caen, 21-22 Avril 2015.

Conf 5: D. Vivien, Imaging of neurinflammation, **European Stroke Science Workshop**. Garmisch-Partenkirchen, Germany, 19-21 November 2015.

Conf 6: D. Vivien, How to improve stroke therapy : from bench to beside. **Journée recherche & santé, Accident Vasculaire Cérébral**. clinique physiopathologie, Aviesan, Paris, 24 novembre 2015.

Conf 7: D. Vivien, Inflamamtion et AVC, implication thérapeutiques. **20ème journée de la société Française de Neurovasculaire**. Paris, 25-27 November 2015.

Sém 1: D. Vivien. Imagerie moléculaire des accidents vasculaires cérébraux. **Séminaires de l'Institut Langevin**. Paris, 20 janvier 2015.

Sém 2: D. Vivien. tPA more than a fibrinolytic. **13eme cycle de séminaires de l'Hôpital Neurologique de Lyon**. Lyon, 26 mars 2015.

Sém 3: D. Vivien. tPA and synaptic plasticity. invited by Dr B. Gonzalez, Team ERI 28. INSERM. **Microvascular Endothelium and Neonate Brain Lesions. NeoVasc.** Rouen, 23 Février 2015.

Sém 4: D. Vivien. tPA more than a fibirnolytic. **4ème journée de l'IRIB, The Rouen Institute for Research and Innovation in Biomedicine**. 5 juin 2015.

Sém 5: D. Vivien. Essais précliniques muticentriques et Imagerie Moléculaire de VCAM-1 et p-selectin. **Journée scientifique du DHU Neurovasc** Paris, 20 mars 2015.

Sém 6: D. Vivien. co-organisation "The Neurovascular Unit in Health and Diseases ». **Atelier ITMO Neurosciences**. Paris, 26 mai 2015.

Sém 7: D. Vivien, tPA orchestrates brain fucntions. **IBiS**. Campus Hospital Universitario Virgen del Rocío Sevilla, Spain. November 5th, 2015.

RENSEIGNEMENTS CONCERNANT LE OU LES DIRECTEUR(S) DE THESE DEVANT OBLIGATOIREMENT ETRE TITULAIRE DE L'HDR

NOM prénom	% d'encadrement et nom du co-directeur ou co-encadrant	Type d'allocation [A]	Date d'inscription	Date de soutenance	Insertion Professionnelle [B]	Publications ou brevets [C]
LE BEHOT Audrey	100 % D. VIVIEN	Ministère	Octobre 2010	23/09/2013	- Ingénieur Registre AVC	58.69.87

BERTRAND Thomas	100 % D. VIVIEN	Région/ Inserm	Octobre 2010	06/01/2014	Post Doct France	43.62.74.88
GAKUBA Clément	100 % D. VIVIEN	CHU	Octobre 2010	05/01/2015	PH CHU Caen	5.10.22.24.70 .71.85.86
BRIENS Aurélien	F.DOCAGNE/D. VIVIEN (50/50)	Région/ Inserm	Octobre 2011	19/09/2014	Interne Cancéro Nantes	25.41.62.75
HEBERT Marie	V.AGIN/ D.VIVIEN (50/50)	Région/ Inserm	Octobre 2011	27/11/2014	Post Doct Etats Unis	2.18.21.39.49 .75.86.89
LEMARCHAND Eloïse	M.RUBIO/D. VIVIEN (50/50)	Région/ Inserm	Octobre 2011	08/12/2014	Post Doct UK	40.63.69.74
LESEPT Flavie	100 % D. VIVIEN	Région/ Industrie	Octobre 2011	04/12/2014	Post Doct UK	4.37.43.47.49 .59.62.74
GABEREL Thomas	E.EMERY /D. VIVIEN (50/50)	CHU Caen	Octobre 2011	07/04/2015	MCU-PH CHU Caen	5.10.19.24.70 .81.74.86.89. 98.99
LOUESSARD Morgane	D. VIVIEN/ ROUSSEL (50/50)	Région/ Inserm	Octobre 2012	13/11/2015	Post Doct Paris	4.20.39.47
PRUVOST Mathilde	100 % D. VIVIEN	Ministère	Octobre 2012	02/12/2016	Post Doct Etats Unis	13.27.28.36.75
CHEVILLEY Arnaud	100 % D. VIVIEN	Région/ Inserm	Octobre 2013	24/11/2016	Enseignement secondaire	26.37.39.43.59.62
GOULAY Romain	100 % D. VIVIEN	Région/ Inserm	Octobre 2013	08/12/2016	Post Doct Pays Bas	5.18.19.24.71 .74
PASQUET Nolwenn	D. VIVIEN/I. BARDOU (50/50)	Ministère	Octobre 2013	13/12/2016	Post Doct Lyon	4.24
ANFRAY Antoine	D. VIVIEN/ C.ORSET	Région/ Inserm	Octobre 2013	12/12/2017	Post Doct Etats Unis	1.7.39
ROSE Anna	AGIN /VIVIEN (50/50)	Fondation Alzeihmer	01/10/2015		Pas autorisée à soutenir	
LENOIR Sophie	VIVIEN	INSERM/ Région	01/10/2014 2018-10-07		Post Doc, Grenoble	2.3.43.59.62

A : Etablissement, Région 50% et co-financeur, Région 100%, CIFRE, salarié, Contrat, CEA, CNRS, INSERM, INRA, Entreprise….
B : Indiquer année par année les différents postes occupés (fonction, établissement ou entreprise) et connus à ce jour,
C : Indiquer la liste des auteurs, l'année, la revue en abrégé

1. **Doctorants en cours de formation :**

NOM prénom	**% d'encadrement et nom du co-directeur ou co-encadrant**	**Type d'allocation[A]**	**Date d'inscription**	**Publications ou brevets[B]**
CHAGNOT Sébastien	VIVIEN/ TOUZE (50/50)	INSERM/Région	01/09/2017	
VARANGOT Alexandre	VIVIEN	INSERM/Région	01/09/2017	3
YETIM Mervé	VIVIEN	Inserm/ Région Comue	01/09/2018	1

A : Etablissement, Région 50% en précisant le co-financeur, Région 100%, salarié, CIFRE, Contrat, CEA, CNRS, INSERM, INRA, Entreprise….
B : Indiquer la liste complète des auteurs, l'année, le nom de la revue en abrégé

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